

William Plunkett, Ph.D.

Interview #35

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William Plunkett, Ph.D.

Interview #35

Interview Profile

Interview Information:

Three interview sessions: 25 March 2013, 10 April 2013, 8 May 2013
Total approximate duration: 6 hours and 30 minutes
Interviewer: Tacey A. Rosolowski, Ph.D.

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About the Interview Subject:

William Plunkett, Ph.D. (b. Boston, 4 May 1943), came to MD Anderson in 1975 as an Assistant Biochemist in the Department of Developmental Therapeutics. He joined the faculty of that Department as an Assistant Professor later that year. He is now a full professor in the Department of Experimental Therapeutics and has a joint appointment in the Department of Leukemia. Dr. Plunkett's research has focused on the study of the cellular mechanisms of tumor viability. He has examined the roles of nucleoside analogues, fludarabine and gemcitabine, as well as mechanisms of cell apoptosis. His translational collaborations result in innovative strategies to kill tumor cells. He is a co-director of the Moon Shot Program devoted to Chronic Lymphocytic Leukemia.

Since 2008 Dr. Plunkett has served as Deputy Chair of the Department of Experimental Therapeutics. Prior to this, from 1993–2004 he served as Chief of the Section of Cellular & Molecular Pharmacology, Department of Experimental Therapeutics, then as the Department's Director of Research Development from 2005–2008.

Major Topics Covered:

Personal and educational background

View of history of biomedical sciences; evolution of team science

Research: nucleoside analogues; gemcitabine, fludarabine; mechanisms of cell death, DNA repair

Research collaborations: with Pharma; importance of collegiality; inter-disciplinary discussions

The CLL Moon Shot Program

The Department of Developmental Therapeutics

Memories of Emil J Freireich, MD

The Department of Experimental Therapeutics: origin of; strategic plan for; training initiatives; department culture

MD Anderson's Conflict Resolution Process

Research Integrity Officer: roles; cases, research issues; ethics

MD Anderson executive leadership: views on

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Original Interview Profile #35: William Plunkett, Ph.D.

Submitted by: Tacey A. Rosolowski, Ph.D.

Date revised: 9 July 2014

Dr. William Plunkett, Ph.D. (b. Boston, 4 May 1943), Deputy Chair of the Department of Experimental Therapeutics, is interviewed over three sessions (approximately 6 hours 31 minutes). Dr. Plunkett came to MD Anderson in 1975 as an Assistant Biochemist in the Department of Developmental Therapeutics and joined the faculty of that Department as an Assistant Professor later that year. He now holds the Barnts Family Distinguished Chair for Cancer Research as well as a joint appointment in the Department of Leukemia. The interview sessions take place in Dr. Plunkett's office on the South Campus of MD Anderson. Tacey A. Rosolowski, Ph.D. is the interviewer.

Dr. Plunkett received his B.S. in Biology and Chemistry from Springfield College, Springfield, MA (1965) and his Ph.D. in Biochemistry from the University of Massachusetts, Amherst (1970). He went on to a Research Fellowship in Physiology at the Marine Biological Laboratory, Woods Hole, Massachusetts (6/1967–9/1967), a Postdoctoral Fellowship in Therapeutic Research at the University of Pennsylvania in Philadelphia (1970–1971), and then took a position as a Research Associate in Microbiology at the University of Colorado Medical Center, Denver (1972–1975). Since coming to MD Anderson, Dr. Plunkett's work has focused on the study of the cellular mechanisms that control tumor viability, using this knowledge to develop innovative strategies to kill tumor cells. From 1993–2004 he served as Chief of the Section of Cellular & Molecular Pharmacology, Department of Experimental Therapeutics, then as the Department's Director of Research Development from 2005–2008, prior to his role as Deputy Chair.

Dr. Plunkett has been elected the chairman of the Gordon Research Conference on Purines & Pyrimidines, and as President of the Graduate Faculty of the University of Texas Graduate School of Biomedical Sciences. He is the recipient of the Service to Mankind Award from the Leukemia Society of America, the Faculty Achievement Award for Clinical Research from M. D. Anderson Cancer Center, and the 1st Sowell-Huggins Professorship in Cancer Research from the University of Texas Graduate School of Biomedical Sciences.

In this interview, Dr. Plunkett goes into detail about the evolution of his investigations into the cell mechanisms of tumors. He begins with his work on the nucleoside analogues fludarabine and gemcitabine, which are taken up into tumors cells, then interfere with their DNA synthesis, eventually killing those cells. He also discusses his recent work on apoptosis, the intrinsic mechanisms by which a tumor cell programs its own death.¹ His discussion of research reveals his own attitudes toward collaborative work: Dr. Plunkett frequently notes that collaboration and collegiality can advance scientific work. Dr. Plunkett is also a keen observer of institutional change he explains the processes by which divisions and departments have been reorganized

¹ The multi-disciplinary (and translational) nature of Dr. Plunkett's work (as well as periodic institutional restructuring) resulted in his connection with a number of different departments: Developmental Therapeutics, Chemotherapy Research, Medical Oncology, Clinical Investigation, Experimental Therapeutics, and Leukemia.

and changed under different leadership. Dr. Plunkett also explains his recent role as MD Anderson's Institutional Research Integrity Officer (and comments on ethical issues within the institution). Also explains his role as co-director of the Moon Shot Program devoted to Chronic Lymphocytic Leukemia under Dr. Ronald DePinho.

William Plunkett, Ph.D.

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William Plunkett, Ph.D.

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Segment Summaries

Interview Session One: 25 March 2013

Segment 00A
Interview Identifier

Segment 01
A Time of Change in the Sciences
A: Educational Path

Story Codes
A: Character, Values, Beliefs, Talents
A: Personal Background
A: Professional Path
A: Inspirations to Practice Science/Medicine
A: Influences from People and Life Experiences
A: The Researcher
C: Evolution of Career
D: On Research and Researchers
D: The History of Science, Cancer Research

Dr. Plunkett briefly sketches his family history. (His father was a research technician at a metals laboratory in Milton, Massachusetts, and Dr. Plunkett still has a titanium chalice his father made for him.) He then discusses his educational path, beginning with his undergraduate years at Springfield College, where he heard Dr. Frances Crick speak about DNA. He explains his decision to focus on biochemistry when he was in graduate school at Amherst and describes the vibrant atmosphere of experimentation during this period when the biological sciences were in ferment. Dr. Plunkett then describes how the evolving science of molecular biology spurred the understanding of genetics.

Segment 02
Focusing a Research Career
A: The Researcher

Story Codes
A: The Researcher
A: Professional Path
C: Formative Experiences

A: Influences from People and Life Experiences
A: Definitions, Explanations, Translations
C: Professional Practice
C: The Professional at Work
C: Evolution of Career
C: Mentoring
D: On Research and Researchers
D: The History of Science, Cancer Research

In this segment, Dr. Plunkett talks about key events that focused his research career, beginning with a competitive summer research fellowship in Physiology he was able to secure at the Biological Laboratory at Woods Hole, Massachusetts. He describes the cutting edge work being done and the mentorship he received. He goes on to talk about several mentors who had an impact on his career including Seymour Cohen (Univ. of Pennsylvania) and Bud Moner at Amherst who was very open to Dr. Plunkett's interest in purifying and classifying enzymes. He gives a portrait of Seymour Cohen, giving a brief history of how Cohen moved from U. Penn to the University of Colorado Medical Center in Denver, inviting Dr. Plunkett to join him. Dr. Plunkett next describes the work he conducted in Colorado on nucleoside analogues (offering a definition of these molecules) and noting other researchers influential in this research area at the time.

Segment 03

An Interest in Therapeutic Applications and a Job Offer from J Freireich

A: Joining MD Anderson/Coming to Texas

Story Codes

A: The Researcher
A: Professional Path
A: Overview
A: Definitions, Explanations, Translations
C: Funny Stories
C: Joining MD Anderson
C: Portraits
B: MD Anderson History

Dr. Plunkett begins this segment explaining the growth of his interest in therapeutic applications of biochemistry. He defines nucleoside analogues, the focus of his research throughout his career.

Dr. Plunkett describes how Dr. Cohen brought an influential researcher in for a site visit: this was how Dr. Plunkett met Emil J Freireich [Oral History Interview] from MD Anderson and, during their brief interaction, received an invitation to come and work at MD Anderson. Dr. Plunkett describes Dr. Freireich's skills as an analytical listener, going on to explain the structure of the Department of Developmental Therapeutics and Dr. Freireich's role as one of its founders and a mentor to an entire generation of scientists.

Dr. Plunkett next explains some bureaucratic obstacles that had to be dealt with before he could be hired at MD Anderson. He also sketches the institutional restructuring that took place in 1983 under the leadership of Dr. Charles LeMaistre and observes that this move allowed clinical people to move into more leadership roles.

Segment 04

Basic and Clinical Researchers in Conversation at MD Anderson

A: The Researcher

Story Codes

A: The Researcher

A: Professional Path

A: Overview

A: Definitions, Explanations, Translations

C: Funny Stories

C: Joining MD Anderson

C: Portraits

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

C: MD Anderson Past

C: Collaborations

D: On Research and Researchers

Dr. Plunkett discusses the position of basic scientists in an institution where clinical investigators have more of a voice. He lists the series of individuals who have headed the Division of Medicine and sketches the history of the Department of Experimental Therapeutics. He notes that he and his colleagues have never had a department leader from the basic sciences who would make the cases on their behalf. He then sketches the evolution of the relationship between basic and clinical researchers, beginning in '75, when Dr. Emil Freireich established the weekly meeting of specialties (sometimes with 40-50 people) to discuss how to treat solid tumors, hematologic malignancies, and other cancers. He describes the (sometimes emotional) character of the meetings. He tells an anecdote about the role of statisticians in presenting analysis of data. He notes that the meetings influenced the design of investigations and led Dr. Michael Keating to set up a database for the Department of Leukemia. Dr. Plunkett then talks about how basic and clinical scientists worked together, first describing the receptive mindset necessary for collaboration. He demonstrates with an example from studies of drugs to treat hematologic malignancies. Dr. Plunkett describes how much more easily scientists could get research proposals approved in the seventies. Then he explains the symbiotic relationship between basic and clinical researchers, where clinicians need a basic science foundation to confirm their clinical findings (giving clinical research "street cred").

Segment 05

Working on Nucleoside Analogues

A: The Researcher

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

- B: Institutional Mission and Values
- B: MD Anderson Culture
- C: Professional Practice
- C: The Professional at Work
- C: MD Anderson Past
- C: Collaborations
- D: On Research and Researchers

Dr. Plunkett begins the story of his research on nucleoside analogues. He first mentions the collegial environment that Dr. Emil Freireich established in the Department of Developmental Therapeutics and how this encouraged basic and clinical scientists to work together, extending laboratory findings to patients. He collaborated with Drs. Michael Keating and Freireich on pharmacokinetic profiles of leukemia treatment with various drugs (ARA-C Cytarabine was the first studied) and explains that Dr. Ken McCready helped them acquire leukemia samples. He defines pharmacokinetics and pharmacodynamics. (He explains Dr. Kenneth McCready's work on intracellular metabolism and the recovery of leukemia cells.) He then begins to talk specifically about his own work, noting his prior research in Colorado that focused on Fludarabine in B-cell malignancies. He then explains the impact of nucleosides on DNA replication, RNA metabolism, and DNA modifications that silence gene expression.

Dr. Plunkett describes how to go about designing translational research projects and the need for researchers to know "two languages" to do this. First the scientist must understand how cancer functions to maintain its replication capacity. By learning the mechanism of action, the scientist is then positioned to ask what cells would be susceptible to intervention. He gives examples of two studies that come from this kind of questioning. He then reviews what translational research can accomplish and notes his ongoing activities with the Department of Leukemia –necessary so he can keep up his understanding of the clinical dimension of his research studies.

Segment 06

A: The Researcher

Drug Studies (and How Collegiality Can Move Them Along)

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

B: Industry Partnerships

D: On Pharmaceutical Companies and Industry

C: MD Anderson Past

C: Collaborations

D: On Research and Researchers

Dr. Plunkett describes his work on Fludarabine and his discovery that it was effective on Chronic Lymphocytic Leukemia, resulting in a treatment that is now standard of care. He explains that he first acquired Fludarabine via his professional networks (with colleagues sometimes passing packets of drug samples for study at a conference), a resource that has continued to bring him new compounds, such as Clofarabine. Dr. Plunkett stresses how important it is to maintain collegial relationships with colleagues across institutions. He then talks about academic institutions are doing much less drug development now than in the past.

Segment 07

Co-Director of the Leukemia Moon Shots Program

A: The Administrator

Story Codes

A: The Researcher

A: Overview

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

C: MD Anderson Past

C: Collaborations

C: Discovery and Success

Dr. Plunkett notes that Dr. Ronald DePinho's has given drug development a central place in his leadership mission, bringing in a team of people devoted to this research initiative. He explains that shares directorship of the Leukemia Moon Shots Program with Dr. Michael Keating and lists the four promising areas of research that they were unable to pursue before (because of lack of resources) and that have now been funded. Four clinical trials of patients with chronic lymphocytic leukemia focus on Ibrunitib and its effects on a signaling pathway never before investigated. He describes those trials and finishes this segment with some comments on the effectiveness of fludarabine-Cytosan-rituximab in extending leukemia patients' lives.

Interview Session Two: 10 April 2013

Segment 00B

Interview Identifier

Segment 08

Working with Fludarabine; The Importance of Extra-Institutional Connections and Ethics

A: The Researcher

Story Codes

A: The Researcher

A: Overview

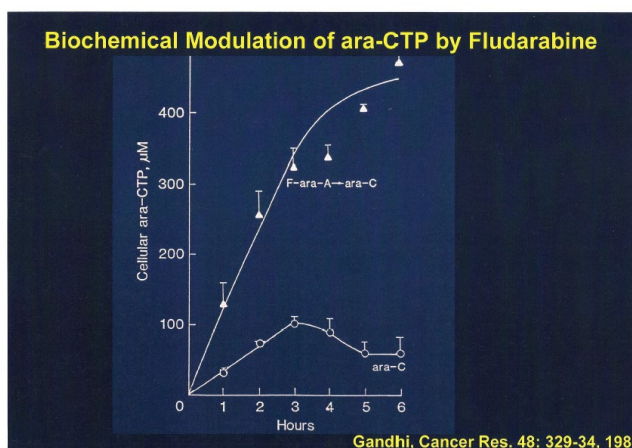
A: Definitions, Explanations, Translations

B: MD Anderson History
 B: Multi-disciplinary Approaches
 B: Institutional Mission and Values
 B: MD Anderson Culture
 C: Collaborations
 C: Professional Practice
 C: The Professional at Work
 B: Industry Partnerships
 D: On Pharmaceutical Companies and Industry
 C: MD Anderson Past
 C: Collaborations
 D: On Research and Researchers
 D: Business of Research
 D: Understanding Cancer, the History of Science, Cancer Research
 D: Ethics
 A: Professional Values, Ethics, Purpose

Dr. Plunkett reviews the history of his work with Fludarabine and focuses specifically on how connections with colleagues at other institutions helped drive his research. He begins by explaining how fortunate he has been to have connections with chemists and biochemists at other institutions who were very willing to provide substances for investigations to anyone who was interested. He explains how John Montgomery provided Fludarabine, a gesture that led to a ten year investigation of its action. Dr. Plunkett also mentions the work of MD Anderson graduate student, Peng Huang, who pursued these mechanisms and developed the knowledge base that led to combining the drug with others.

Dr. Plunkett explains that the process of acquiring drugs for study is quite different now, as pharmaceutical companies (and their legal advisors) control research very tightly. Dr. Plunkett explains that this new system curtails imagination and the researcher's freedom to pursue ideas in different directions. "Pharmaceutical companies write the prescription" for studies, Dr. Plunkett notes, and this is "not the spirit of science we want anyone to be pursuing." Dr. Plunkett next explains the conclusions about Fludarabine that Dr. Huang established and then discusses the two investigative lines this work gave rise to. Dr. Varsha Ghanda took up one investigative line, pairing Fludarabine with Cytarabine. He discusses results of this study (published in 1988), referring to a graph (provided below). Combining Fludarabine and Cytarabine (ara-CTP) was the front line work in treating certain cohorts of patients with myeloid leukemia. A third element is now being added to the mix, Myelotarg, an antibody that creates even better results.

Dr. Plunkett next explains the rationale for selecting patients for the Fludarabine/Cytarabine study: a cohort that was doing the best on what was available at the time. He outlines the ethical dimensions of clinical trials. He then summarizes his ethical values as a basic researcher: "Truth above everything," the gold standard for reproducibility. He next comments on his 5-year role as Research Integrity Officer, noting that many case investigated reveal honest errors. He explains how errors can occur, noting a common



discrepancy between data and the visual figures used to summarize data: he explains an imaging analysis software currently in use to locate discrepancies.

Segment 09

The CLL Moon Shot Program

B: An Institutional Unit

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Collaborations

A: The Administrator

C: Professional Practice

C: The Professional at Work

C: Discovery and Success

C: Patients, Treatment, Survivors

B: MD Anderson Snapshot

B: MD Anderson Impact

B: Institutional Processes

Dr. Plunkett begins by explaining how Dr. Huang's discoveries provided the basis for the CLL Moon Shots Program established under Dr. Ronald DePinho. He explains that Dr. Huang's work began with the hypothesis that the repair of DNA in a cancer cell "could be our friend" if that repair included a compound, such as Fludarabine, that would ultimately inhibit the cell's ability to function. He notes that this has set a standard of care for CLL and that remission rates have gone over 70%. Next he describes how that foundational work opened up investigative areas now included in the Moon Shots Program. Data managers have noticed that survivors of this treatment are developing secondary malignancies at a higher rate. Investigations are now focusing on biologically based strategies, asking How does CLL arise (a pathogenesis question) and What keeps it going (a question about pathophysiology). He describes the studies currently underway that address these questions from different perspectives. Next Dr. Plunkett explains how the CLL Moon Shot Program is structured and how the individual studies prioritized. He notes that patients today are very aware of CLL therapies and shop for treatment armed with information they have acquired from blogs and online sources. He explains the long and short-term aims of the CLL Moon Shots program.

Segment 10

Team Science and Training Team Scientists

A: The Administrator

Story Codes

A: The Researcher

D: On Research and Researchers

A: Overview

D: Understanding Cancer, the History of Science, Cancer Research
B: Multi-disciplinary Approaches
B: Institutional Mission and Values
B: MD Anderson Culture
C: Collaborations
A: The Administrator
C: Professional Practice
C: The Professional at Work
C: Discovery and Success
A: The Educator
B: MD Anderson Culture
C: Understanding the Institution

Dr. Plunkett begins this segment by observing that his entire career has been based on the team science approach. He also explains that team science is very valued (its importance underscored by the NCI) but the model of the PI on grants is still based on the independent researcher as are many parameters used in academic institutions to award promotion and tenure and even laboratory space. (Dr. Plunkett notes that institution presidents Dr. John Mendelsohn and Dr. Ronald DePinho are both team scientists.) Dr. Plunkett next talks about training students and young faculty for team science, noting that his laboratory is a magnet for people who want to learn “Hypothesis Testing in the Clinic,” as the Department of Experimental Therapeutics described its translational research approach.

Dr. Plunkett explains that he selects new students and faculty based on their fit with the culture of the laboratory and Department. He also notes that the culture of collegiality and sharing can spread to other departments. He talks about a graduate student with a degree in philosophy whom he took on trial and who ended up working as a research nurse and phlebotomist in Leukemia.

Segment 11

Mentoring, Education, and Team-Science Culture

A: The Administrator

Story Codes

D: On Mentoring
A: The Educator
A: The Administrator
A: The Mentor
C: Mentoring
B: Education
C: Portraits
B: MD Anderson Culture
C: The MD Anderson Ethos
C: Diversity at MD Anderson
C: Understanding the Institution
A: Professional Values, Ethics, Purpose
B: Institutional Mission and Values

Dr. Plunkett explains that he believes in mentoring by example as well as the importance of determining when young people are ready to absorb information about getting promoted. He

gives the example of challenges confronting fellows who wish to advance as MD Anderson faculty and speaks at length about the successes of Dr. Varsha Gandhi. He also cites the importance of public exposure and the significance of the firm, “white knuckle handshake” that is so important in American culture. Next he talks about the Department’s mentoring programs for young faculty, headed up by Dr. Varsha Gandhi.

To underscore his philosophy of active mentoring, Dr. Plunkett says, “This discussion [meaning the interview] is the only time this door is closed.” He articulates his belief that working in a laboratory is mentoring and he also notes that the Department’s Journal Clubs and research meetings offer mentoring opportunities (and this is not the case in all MD Anderson departments). These large, collegial meetings model for trainees how “we can work together.”

Dr. Plunkett comments on the career paths of physician scientists and notes that the Department does not see many medical fellows. He then explains that his commitment to teaching comes from the desire to create a new generation of scientists. He notes that he has stayed committed to his field because of his successes in creating end products (both knowledge and treatment). He has oriented his laboratory toward clinically relevant questions that can be answered.

Segment 12

Research with Gemcitabine

A: The Researcher

Story Codes

A: The Researcher

D: On Research and Researchers

D: On Pharmaceutical Companies and Industry

A: Overview

A: Definitions, Explanations, Translations

B: Multi-disciplinary Approaches

C: Collaborations

D: Understanding Cancer, the History of Science, Cancer Research

Dr. Plunkett tells the story of the contributions his laboratory made to demonstrating the efficacy of the drug Gemcitabine. He first notes that he had many friends in pharmaceutical companies in the early 1980, among them Gerald Grindy at Eli Lilly, where Gemcitabine was being developed. He explains that he was asked to work with Gemcitabine because of its structural similarity to Cytarabine, a drug he had formerly worked on. He recalls the speed—a few months—with which the lab showed that Gemcitabine had metabolic effects, specifically inhibiting ribonucleotide reductase. Paul Heinemann made the observations on the metabolic mechanisms by which Gemcitabine was retained in cells of circulating leukocytes. This became a multi-billion dollar drug for Eli Lilly, approved for use in solid tumors. Dr. Plunkett explains that a cultural/political gap between researchers and management of large corporations made it difficult for Gerald Grindy to convince Lilly to keep supporting the drug. The drug’s further possibilities have not been investigated.

Dr. Plunkett then observes that the high cost of drug research often causes projects to be dropped if preliminary results do not lead in predicted direction. He explains the importance of conducting rational tests of hypotheses and of reporting negative results.

Segment 13

Exploiting Cell Death Mechanisms and DNA Repair to Kill Tumor Cells

A: The Researcher

Story Codes

A: The Researcher

D: On Research and Researchers

D: On Pharmaceutical Companies and Industry

A: Overview

A: Definitions, Explanations, Translations

B: Multi-disciplinary Approaches

C: Collaborations

D: Understanding Cancer, the History of Science, Cancer Research

C: Discovery and Success

Dr. Plunkett tells the story of his most recent (and very gratifying work) on mechanisms of cell death (apoptosis) and Imatinib, the “poster child” of targeted therapy. He explains that CLL cells are reliant (“addicted”) on several proteins for their survival, one of which is very short-lived so if one can block its production, all CLL cells will die. Dr. Cortez and Kartajian demonstrated the Imatinib results. This work also gave rise to a different strategy for CLL, one not aimed at damaging DNA, but at getting cells to kill themselves. Dr. Plunkett next describes a project that returns to nucleoside work, based on a compound much like Cytarabine. This story involves a Japanese scientist, Kira Matsuka, who provided Dr. Plunkett with CNDAC (2'-C-cyano-2'-deoxy-1-beta-D-arabino-pentofuranosylcytosine). Dr. Plunkett worked on the mechanism of action independent of support while Dr. Kartajian studied the drug in acute myeloid leukemia in patients older than 70, and a multi-center phase three trial is now in progress.² Dr. Liu Xiaojung in Experimental Therapeutics is conducting studies of the drug's mechanism of action. He has found that the drug targets a single break in the DNA strand, and was active in patients who could not repair double strand breaks. They have identified a cohort that lacks part of a gene that leads to the inability to make double strand breaks. The drug enables these patients to make double-strand breaks (which means they will then be able to benefit from nucleoside treatment that introduces cancer-damaging agents into DNA as it is repaired). Dr. Plunkett confirms that this has been one of the most satisfying studies, as it brings his basic laboratory research into molecularly targeted individualized research. He then lists other disease cohorts that might benefit from this kind of strategic approach.

² Dr. Plunkett expands on a related drug produced by Cycacel, a company mentioned in the interview session:

“The compound that Cyclacel has in clinical trial is an orally-available pro-drug called sapacitabine. We don't use it in the lab because it requires metabolism to generate the parent nucleoside, CNDAC. This, by the way, is also in clinical trial at MDACC in acute leukemias (Kantarjian). It is administered parenterally (intravenous), and provides some flexibility in dosing compared to sapacitabine. Further, Sankyo made the pro-drug sapacitabine from CNDAC. The clinical results were first reported in phase 1 clinical trials, the purpose of which is to determine safety, although we always look for clinical activity. These were in solid tumors (lung, colon breast, etc.) of patients who had failed many prior therapies. These were conducted mostly by Sankyo Pharmaceuticals, who later dropped the compound (then known as CS-682). After Cyclacel licensed the drug from Sankyo and re-named it sapacitabine, Dr. Kantarjian tested sapacitabine in acute myeloid leukemia in a phase 1 trial; there were responses, including complete remissions. This progressed to a phase 2 trial, and some combination trials before the current phase 3 trial was designed and initiated.” (From Email correspondence, 12 April 2013).

Interview Session Three: 8 May 2013

Segment 00C

Interview Identifier

Segment 14

Developmental Therapeutics and the Origin of The Department of Experimental Therapeutics

B: An Institutional Unit

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

C: Portraits

B: MD Anderson Culture

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

C: Collaborations

B: Institutional Processes

A: Joining MD Anderson

To tell the story of how the Department of Experimental Therapeutics evolved, Dr. Plunkett begins with Dr. R. Lee Clark, who recognized the “two major forces in chemotherapy,” Dr. Emil Frei, III and Dr. J Freireich, who came to MD Anderson and created the Department of Developmental Therapeutics. Dr. Plunkett explains that these two researchers were some of the first to apply combination treatments for leukemia, and their work showed the first remissions (eventually with over 80% of pediatric patients reaching long-term survivorship). Dr. Frei left the institution in 1972, leaving Dr. Freireich to head the Department. Dr. Plunkett emphasizes that Dr. Freireich brought together researchers from many fields who had a collaborative or a translational-research mindset: Developmental Therapeutics was a “rockin’ place,” says Dr. Plunkett, and he explains the mixture of people from different disciplines who came together. Dr. Plunkett then describes how Dr. Freireich could handle over thirty research projects simultaneously. He then tells an anecdote about preparing a grant proposal in two weeks, eventually being awarded funds that effectively provided his start-up funds when he arrived at MD Anderson.

Segment 15

Reorganizing Developmental Therapeutics: The Challenge of Naming Experimental Therapeutics

B: Institutional Change

Story Codes

A: The Researcher

A: Overview

B: Obstacles, Challenges

B: Controversy

- B: MD Anderson History
- B: MD Anderson Culture
- B: Multi-disciplinary Approaches
- B: Institutional Mission and Values
- C: Collaborations
- B: Institutional Processes
- B: Growth and/or Change
- D: On Research and Researchers
- D: Understanding Cancer, the History of Science, Cancer Research

Dr. Plunkett begins this segment by explaining how MD Anderson was restructured when Dr. Charles LeMaistre replaced R. Lee Clark as president of the institution. Under Dr. Clark, the “medical enterprise” was divided between the Division of Medicine and Developmental Therapeutics. Dr. LeMaistre wanted to use organ sites as a principle of reorganization, so the faculty in Developmental Therapeutics were reorganized according to medical oncology principles. Dr. Plunkett explains that Dr. Krakoff was named head of the Division of Medicine (now the Division of Cancer Medicine) and oversaw the change. He describes what happened to the basic scientists during this process. Dr. Plunkett joined the Department of Chemotherapy Research. He describes how Dr. J Freireich was relieved of his administrative duties after receiving an Outstanding Investigator Award. He then notes that with this reorganization, basic scientists didn’t have administrative representation that understood their issues and subject matter. The situation became worse, he explains, when Dr. Bast took over from Dr. Krakoff as head of the Division of Medicine. Dr. Plunkett goes on to explain changes in the leadership of the Division of Medicine (up to 1998) and several name changes of the department (Department of Medical Oncology, Department of Clinical Investigation), noting that there was no structure for creating collegiality among basic scientists.

Dr. Plunkett then explains that the Department of Clinical Investigation (including the Section of Cellular and Molecular Biology) begged Dr. Bast to rename the department because the name completely misrepresented the faculty’s activities, making it difficult to secure grants. (The Department was renamed in 1998.)

Dr. Plunkett explains more leadership changes after 1998. Dr. Hong became head of the Division of Medicine, which was renamed ‘the Division of Cancer Medicine,’ and the Department of Experimental Therapeutics undertook a search for a full time chair. Dr. Plunkett notes that Bioimmunology merged with Experimental Therapeutics, and Dr. Ruben Lotan served as ad interim chair. Dr. Plunkett then explains the reasons why Dr. Hong removed physicists from the Department eight years ago, going on to note some additional changes of leadership.

Segment 16

The Department of Experimental Therapeutics: a Strategic Plan for the Department

B: Building the Institution

Story Codes

- A: The Administrator
- A: The Researcher
- C: Professional Practice
- C: The Professional at Work
- C: Collaborations
- C: Leadership

- B: Obstacles, Challenges
- B: MD Anderson History
- B: MD Anderson Culture
- B: Multi-disciplinary Approaches
- B: Institutional Mission and Values
- C: Collaborations
- B: Institutional Processes
- B: Growth and/or Change

Dr. Plunkett explains that the Department of Experimental Therapeutics was located on the MD Anderson's main campus until January of 2010, when the Department began its move to South Campus. The increase in space is an advantage, he explains, but the new location also presents several challenges. For example, the Department uses primary materials from leukemia patients, located on North Campus, and distance and transportation have created a problem, resulting in a slowdown of research. The Department's faculty made many suggestions for the design of their South Campus space, but very few were followed. Dr. Plunkett reviews the pros and cons, then explains at length how the new space presents a real challenge collaborative work, collegiality, and interaction. Dr. Plunkett explains that, as a result, Dr. Garth Powis (Chair of the Department) had an idea to create a strategic plan to answer the question, "How do we make this a department that will represent us?" Dr. Plunkett chaired the strategic plan committee, and he explains the initiatives they undertook as a result of the process: identifying opportunities for sharing equipment; establishing goals for mentoring junior faculty, associate professors and post-docs; creating a team-taught course on mechanisms of cancer therapeutics to give the Department more institutional exposure. He lists activities held to increase social opportunities and collegial interaction.

Segment 17

Faculty Senate and the Revised Conflict Resolution Process

A: The Administrator

Story Codes

- A: The Administrator
- C: Professional Practice
- C: The Professional at Work
- C: Leadership
- B: Obstacles, Challenges
- B: MD Anderson History
- B: MD Anderson Culture
- B: Institutional Processes

Dr. Plunkett talks about his administrative roles within the institution, touching briefly on his role as Director of Research for Experimental Therapeutics (2005-2008), then discussing his role in revising the grievance process for the faculty. He explains that the Faculty Senate identified the problem: a lack of defined pathways for grievance, and this led to Dr. John Mendelsohn creating "The Blue Ribbon Panel for Peer Review and Conflict Resolution," a 12-15 person panel. He explains the problems with the existing grievance process, then lists the three options the panel set in place to create a rational set of steps to resolve conflict. 1) Conferring with the Ombudsman, 2) Working with a professional mediator, 3) Presenting conflict to a faculty panel. Dr. Plunkett talks about the main sources of conflict for the faculty.

Segment 18

Conflict of Interest: MD Anderson Faculty and Presidents

B: Overview

Story Codes

A: The Administrator

C: Professional Practice

C: The Professional at Work

C: Leadership

B: Obstacles, Challenges

B: MD Anderson History

B: MD Anderson Culture

B: Institutional Processes

C: Ethics

D: On Ethics

Dr. Plunkett explains that in the nineties, conflict of interest became such a prevalent issue at the institution that a Conflict of Interest Committee was convened (in 1996) with president Dr. John Mendelsohn's backing. After Dr. Stephen Tomasovic stepped down as the first committee chair, Dr. Plunkett took on that role. At the time, conflict of interest was dealt with by "collegial agreement" involving no legal assistance. The Committee wrote a formal policy that was adopted. Dr. Plunkett explains the conflict of interest issues arising because of John Mendelsohn's role in developing the drug Cetuximab (as well as the concurrent problems arising because he was involved with Enron.) Dr. Plunkett describes the impact of the conflict of interest policy. He describes how conflict of interest can arise for clinical faculty in an environment where pharmaceutical companies "had been overtly attempting to buy physicians." Conflict of interest can arise sometimes for translational researchers, he explains, but doesn't really affect basic scientists. Dr. Plunkett then talks about the restrictions in place to prevent conflict of interest then extends the discussion to the current president, Dr. Ronald DePinho. He notes that MD Anderson was ahead of other institutions in creating formal policies to address conflicts of interest.

Segment 19

Research Integrity Officer

A: The Administrator

Story Codes

A: The Administrator

C: Ethics

D: On Ethics

A: Overview

A: Definitions, Explanations, Translations

B: Building/Transforming the Institution

D: On Research and Researchers

D: On Leadership

D: On Mentoring

C: Professional Practice

C: The Professional at Work

C: Leadership

B: Obstacles, Challenges

B: MD Anderson History
B: MD Anderson Culture
B: Institutional Processes
C: Personal Reflections on MD Anderson
C: Giving Recognition
A: Professional Values, Ethics, Purpose

Dr. Plunkett explains how he assumed the role of Research Integrity Officer and describes his responsibility to address allegations of research falsification, fabrication, or plagiarism. He explains that the Office of Research Integrity was created by an unfunded mandate from the NIH and the Department of Public Health: the Office of Research Integrity answers to these government bodies via the Provost. Dr. Plunkett explains that suspicions about infraction are brought to the Office's attention confidentially and usually by an anonymous complainant. He explains the three-phase process used to address the allegations: evaluation, inquiry via a panel, and formal intervention. Eight cases were investigated in 2012. Dr. Plunkett distinguishes between research integrity issues and research ethics issues that are referred to the Ombudsman or the Provost. In general, he says, people are sloppy and what looks like research misconduct generally comes about through careless errors made while acquiring and handling data. Dr. Plunkett explains that researchers who have been subjected to scrutiny by the Office of Research Integrity often spur their colleagues to be more careful. He also describes an ad hoc, virtual community of data analysts, who scrutinize data made public for errors.

Dr. Plunkett expresses how honored he feels to have the confidence of the Faculty and to have been asked to serve the role of Research Integrity Officer. He notes the bond that grows between individuals who serve on panels or committees that deal with integrity issues.

Segment 20

Skills and Support for New Research

A: The Researcher

Story Codes

A: Character, Values, Beliefs, Talents
A: Overview
A: Definitions, Explanations, Translations
A: The Researcher
C: Patients
C: Professional Practice
C: The Professional at Work

Dr. Plunkett observes that he is not often required to develop new skill sets, as he does not work in the lab anymore. He more often develops new ideas and exercises his skills of data interpretation. He then observes that the MD Anderson Core Facility offers basic services to researchers at the institution and serves as a pool of laboratory skills. He notes that Dr. Ronald DePinho is head of a grant that includes many Cores and Programs, and that received a rating of "exceptional" from the review committee.

Segment 21

MD Anderson Presidents

B: Key MD Anderson Figures

Story Codes

C: Portraits
B: MD Anderson History
B: MD Anderson Culture
C: Professional Practice
C: The Professional at Work
A: Influences from People and Life Experiences
C: Understanding the Institution
B: Growth and/or Change
B: Controversy

In this segment, Dr. Plunkett sketches his view of the MD Anderson presidents, noting that Dr. Charles LeMaistre [Oral History Interview] was separated from the Faculty by a “layer of VPs.” Dr. John Mendelsohn [Oral History Interview], in contrast, was responsive to the Faculty: his was part of the Department of Experimental Therapeutics and lectured in the Department’s lead course. Dr. Plunkett says that Dr. Ronald DePinho has been outgoing with his Town Halls. Dr. DePinho’s Moon Shots have brought together diverse groups of people. Dr. Plunkett says he expects that the difficulties with Dr. DePinho’s leadership will smooth out.

Segment 22

J Freireich’s Impact and A Career Commitment to Collaborative Work

A: View on Career and Accomplishments

Story Codes

C: Portraits
B: MD Anderson History
B: Multi-disciplinary Approaches
A: Overview
A: Definitions, Explanations, Translations
A: The Researcher
B: MD Anderson Impact
C: This is MD Anderson
C: Discovery and Success
B: Multi-disciplinary Approaches

Dr. Plunkett begins this segment with comments about contributions made by J Freireich. He notes that Dr. Freireich made his own work possible: his work opened a new era in studying leukemia cells and that some of the most exciting work is still based on his pioneering advances. As an example, Dr. Plunkett talks about the efforts to determine the mechanisms that create a specific genetic lesion’s drug sensitivity. He notes that work on cellular pharmacology enabled him to interact with clinical colleagues and trainees, collaborations that increased cross-department trust and established Dr. Plunkett’s lab as the “go-to” resource for questions about specific compounds. He explains that the laboratory continues to generate hypotheses and study the susceptibility of cancer cells. He describes how blocking protein synthesis can lead to tumor-cell death, leading in turn to tumor lysis syndrome, where the body responds to the rapid death of a tumor.

Looking back at the path of his career, Dr. Plunkett says he is particularly thankful to have trained in the basic sciences and then progress to clinical applications. He notes that MD Anderson gave him the luxury of extending his work to clinical investigations and being recognized for his contributions. Once again, he credits Dr. J Freireich for bringing different specialties together in collaborative situations. At the end of the interview he speaks about Dr. Michael Keating's role in building philanthropic support, "the glue for national and international collaboration."

William Plunkett, PhD

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About transcription and the transcript

This interview had been transcribed according to oral history best practices to preserve the conversational quality of spoken language (rather than editing it to written standards).

The interview subject has been given the opportunity to review the transcript and make changes: any substantial departures from the audio file are indicated with brackets [].

In addition, the Archives may have redacted portions of the transcript and audio file in compliance with HIPAA and/or interview subject requests.

Chapter 00A

Interview Identifier

Tacey Ann Rosolowski, PhD

0:00:01.4

Terrific. All right, I've got really good sound levels. I'll start with the identifier, and then we're ready to roll. I'm Tacey Ann Rosolowski interviewing Dr. William Plunkett at the University of Texas MD Anderson Cancer Center in Houston, Texas. This interview is being conducted for the Making Cancer History Voices Oral History Project run by the Historical Resources Center at MD Anderson. Dr. Plunkett came to MD Anderson in 1975 as an assistant biochemist in the Department of Developmental Therapeutics, and he joined the faculty of that department as an assistant professor later that year. He is now Deputy Chair of Developmental Therapeutics and holds the Barnts Family Distinguished Chair for Cancer Research. Dr. Plunkett also holds a joint appointment in the Department of Leukemia. He serves as an associate vice president of Research Integrity and is the—is that correct, or is it Institutional Research Integrity?

William Plunkett, PhD

0:00:58.1

Associate Vice President, Research Integrity.

Tacey Ann Rosolowski, PhD

0:01:01.6

He is the Institutional Research Integrity officer. He was recently designated a co-leader of the

Moon Shot Program devoted to chronic lymphocytic leukemia. This interview is taking place in Dr. Plunkett's office on the South Campus of MD Anderson. This is our first of two planned interview sessions, and today is the 25th of March, 2013. The time is about 2:42, and thank you, Dr. Plunkett, for agreeing to do this interview.

William Plunkett, PhD

0:01:31.4

You're welcome. Just one correction on your lead-in. We're in the Department of Experimental Therapeutics now, although I was recruited here into the Department of Developmental Therapeutics.

Tacey Ann Rosolowski, PhD

0:01:46.3

I was going on automatic pilot when I read that. Just before we turned on the recorder, we talked about that separation, yes. Thank you for pointing that out.

Chapter 1

A: Educational Path

A Time of Change in the Sciences

Story Codes

A: Character, Values, Beliefs, Talents

A: Personal Background

A: Professional Path

A: Inspirations to Practice Science/Medicine

A: Influences from People and Life Experiences

A: The Researcher

C: Evolution of Career

D: On Research and Researchers

D: The History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

0:01:46.3+

Okay, well, I wanted to begin with some basic background questions, so if you could tell me where you were born and when and where you grew up.

William Plunkett, PhD

0:02:06.5

I was born in Boston, Massachusetts, on May 4th, 1943. I grew up in Milton, Massachusetts, a suburb of Boston.

Tacey Ann Rosolowski, PhD

0:02:19.1

And was anyone else involved in the sciences in your family?

William Plunkett, PhD

0:02:23.8

I think later in my dad's career he was employed as a research technician in a metals laboratory.

Tacey Ann Rosolowski, PhD

0:02:35.4

Metals laboratory.

William Plunkett, PhD

0:02:36.1

It was called Norton. I can't remember the full name of the thing, but it was metals. I can remember they particularly played a strong role with titanium, and they were producing the nose

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cones of some of the rockets that were produced. I have a titanium chalice at home that he made for me.

Tacey Ann Rosolowski, PhD

0:02:58.8

How neat! So that work came home and was part of your home life. When did you first get the sense that you were going to be going into the sciences as well?

William Plunkett, PhD

0:03:11.5

I think my freshman year in college. I went to [Springfield College](#) in western Massachusetts and I enrolled there as a—I think it was a physical education major. I quickly realized taking college classes and biological sciences—that this was intriguing to me, and before the year was out, I had changed my major to biology, I believe.

Tacey Ann Rosolowski, PhD

0:03:40.9

And what was it that intrigued you so much?

William Plunkett, PhD

0:03:44.5

Learning about plants and about animals and cells, and at the time, it was very topical. I'd say that several years into my undergraduate education my genetics professor, Dr. Jean Ross, took us all fifteen miles south to Mount Holyoke College to hear [Dr. Francis Crick](#), the recent recipient of a Nobel Prize, at that time, for the discovery of the structure of DNA. That certainly was inspiring. I recently had the opportunity to revisit with Dr. Ross that event. She was quite surprised. She probably didn't recognize me at my forty-fifth college reunion. She was there, and I recognized her. We were all invited to stand up and say what we're doing and so forth. I noted to the audience the inspiring role that she had played in my interest in biology.

Tacey Ann Rosolowski, PhD

0:05:00.1

That must have really meant a lot to her, I'm sure.

William Plunkett, PhD

0:05:02.2

I think it did.

Tacey Ann Rosolowski, PhD

0:05:04.3

When did you make the decision to do graduate work, and what was the first area you thought about working in?

William Plunkett, PhD

1:56:59.7

Well, I think I made the decision to do graduate work when I was probably a junior or a senior in college looking forward to graduate school. I didn't go very far. I went to the University of Massachusetts at Amherst, which is about 30 miles north of Springfield, and there I was accepted on a teaching fellowship which paid my salary of \$2,200 a year.

Tacey Ann Rosolowski, PhD

0:05:51.0

This was in the late '60s.

William Plunkett, PhD

0:05:54.2

Right. That was 1965. My wife and I were married three days before I started that. I was in a department of zoology, which we defined as being everything from hunters and trappers to grinders and finders. This would be known as ecology on the former. Biochemistry was a budding area at the time, an emerging area at the time, and I was in that latter area. The decision was to become biochemical. I sought out a strong biochemical laboratory and pursued my dissertation purifying two enzymes that are important in processing the precursors of nucleic acids, nucleotides, and that was at a time when nucleotide analogs were becoming notable in cancer therapy.

Tacey Ann Rosolowski, PhD

0:07:12.0

Now, if you look back on this period, I'm always so struck when I talk to individuals of your generation, because you went through really the formative educational period during this time when things were really exploding in the sciences and in medicine. It's hard for me to even grasp. I ended up going to college in 1973, and of course I learned about DNA, but for some reason I always thought, "Gosh, this has always been around," but that wasn't true. In fact, this info had come in. I'm curious; as you look back on this time, what was it about that zoology department that was so broad and probably would be broken up now? What about all the things you were exposed to? How did that explosion of information influence you in your decisions?

William Plunkett, PhD

0:08:05.5

One thing, it probably prolonged my graduate education by at least a year, because I was interested in many things and kept taking courses. That's not something that we see in graduate students—at least in the graduate school of biomedical sciences now.

Chapter 2

A: The Researcher

Focusing a Research Career

Story Codes

A: The Researcher

A: Professional Path

C: Formative Experiences

A: Influences from People and Life Experiences

A: Definitions, Explanations, Translations

C: Professional Practice

C: The Professional at Work

C: Evolution of Career

C: Mentoring

D: On Research and Researchers

D: The History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

0:08:21.6

What were some of the areas that you were exploring?

William Plunkett, PhD

0:08:25.8

Well, there was a time when my mentor came into the laboratory, and I was there at night, which was our custom. We had seminars at night, and you could work at night and so forth, as well as regular hours. It's a matter of how, I think, all of the graduate students that I knew at that time practiced and learned. When my mentor came into the laboratory and found me doing something completely different that had never been done in that laboratory but had been published two years earlier in the literature, and I was reproducing it, he gave me a talking to and told me to focus and get to work on something that's going to get me out of graduate school.

Tacey Ann Rosolowski, PhD

0:09:17.7

What was the experiment you were running?

William Plunkett, PhD

0:09:19.1

Oh, it was something about using drosophila larvae and exposing them to a hormone and seeing what we now know as gene expression start, and that was shown as puffs in the chromosomes of the larvae, in the salivary glands. Once you learned about how to do that biology—and I was using drosophila or had access to that from local laboratories—it was a fairly easy experiment to do. But it was at a time when I could take all of the biochemistry courses—the biochemistry

professors—and a few were located as a section in the chemistry department. There was no Department of Biochemistry. Our Department of Zoology was starting to recruit people with biochemical backgrounds, so we can really learn from them. But with the diversity of courses that were there, I was taking Comparative Anatomy, Protozoology. My research subject was protozoan, microbiology, and really there was no such thing as cell signaling at the time or more directed molecular biological things. It was at a time when the book *Phage and the Origins of Molecular Biology* was published, which was stimulatory to many people who read it with—well, I read it with a great deal of interest and enthusiasm, understanding how molecular biology was evolving or coming out of the genetics that was involved with the coming together of the understanding of DNA, the function of DNA, how information went out from the genome into RNA to be made into protein, how that could be explored in bacteria and in part in bacteria phage and the regulation of it. That was the era at the time, and there weren't very many laboratories in my locale that were practicing that, but I was really fascinated by it.

Tacey Ann Rosolowski, PhD

0:12:10.0

So you generated it yourself.

William Plunkett, PhD

0:12:12.1

The interest I generated, yeah, but I think a key point—people always ask about what are key points in your career that really influenced you to go in a particular direction or fired you up to be able to make a career out of whatever we're doing now. This, for me, was a summer course that was quite competitive to go into—to be accepted in at the [Marine Biological Laboratory](#) in Woods Hole, Massachusetts—and it's called the physiology course. They still teach it there, and many people who are notable in their careers subsequently had trained there. That certainly was the case with me, where we would go to lectures in the morning and then work the rest of the day and night in the laboratories, which were pretty crude at the time, being a laboratory that was built in the nineteenth century. But nevertheless, we were all in it together, and the mentors, who you'd spend two weeks with—four different mentors over two-week periods—knew what was going on, and they knew how to set things up so that students would learn. It was terrific.

Tacey Ann Rosolowski, PhD

0:13:45.5

What was the focus of that particular course?

William Plunkett, PhD

0:13:51.4

It was modern-day—really contemporary biology, and it played off on the work that I had been reading about. For instance, one mentorship was done with [Sydney Brenner](#), who subsequently was the recipient of a Nobel Prize. He was quoted in his autobiography as saying it was his second Nobel Prize; they just forgot to give him the first one. (laughter) And there is a lot of credibility to that. He was an amazing person. Also Seymour Cohen, who discovered, among

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other things, that phage can produce virus-induced enzymes that when viruses infect cells—and these were bacteria phages infecting bacteria—produced enzymes. It seems so logical now, but he discovered the first couple of those that were there. He was a biochemist who had a strong background with people who were nucleic acid biochemists before him, and he certainly instructed us in a rigorous way of pursuing biochemistry and being rigorous in thinking, in experimental design, in interpretation of data. It was with Dr. Cohen that I was fortunate enough to do my postdoctoral work.

Tacey Ann Rosolowski, PhD

0:15:43.0

Before I talk about him, you had mentioned a mentor before when you were at Amherst, and I'm wondering who that was.

William Plunkett, PhD

0:15:53.7

Oh, it was John Moner, Bud Moner—M-O-N-E-R.

Tacey Ann Rosolowski, PhD

0:15:59.3

And tell me about him. How was he influential to you?

William Plunkett, PhD

0:16:04.8

He was tolerant. (laughter)

Tacey Ann Rosolowski, PhD

0:16:07.7

He's the one that came in and told you to—

William Plunkett, PhD

0:16:12.7

He provided gentle direction, but he also let me do my own thing. The work that I was engaging in and wanted to pursue, of purifying and characterizing enzymes, was—it was topical at that time, but it wasn't something that the laboratory was actively engaged in, so I had to do a lot of bootstrapping around to, first of all, get firsthand knowledge of the appropriate techniques and then equipment to really pursue that. He let me do that. He was interested in studies involving regulation of cell division. I would have done well to have pursued those as well. I'm interested in that now, but it's a different sense.

Tacey Ann Rosolowski, PhD

0:17:10.9

Tell me about—let's see. You finished up at the University of Massachusetts Amherst in 1970, and then you went to your postdoc program in therapeutic research. How did that all happen?

William Plunkett, PhD

0:17:27.4

Well, just something more about Dr. Cohen. He had traditionally been in the biochemistry department at the University of Pennsylvania. I believe he was there for twenty-four years. But he'd always wanted to—I mean, other than the work that I mentioned about these virus-induced enzymes, he had an interest in therapeutics. For instance, his laboratory—he was the one who discovered—who revealed—the mechanism of action of a drug that's widely used today, [5-fluorouracil](#), as inhibiting the activity of the enzyme [thymidylate synthase](#). He also worked with an MD Anderson faculty member, Colleen Moore, who was a member of this department at one time—she's retired for quite a few years now—to show that another prominent therapeutic that's used largely in acute myeloid leukemia called cytarabine—the mechanism of that was not as proposed against the enzyme ribonucleotide reductase, but rather it was against the enzyme responsible, a set of enzymes responsible—for replicating DNA, DNA polymerase. Dr. Moore together with her colleague here, Dr. Robert Hurlbert, discovered the first mammalian ribonucleotide reductase, and this is a target of several effective cancer therapeutics now and widely recognized.

Tacey Ann Rosolowski, PhD

0:19:24.1

So you had contact with some pretty key people early on who were interested in therapeutic applications of this knowledge.

William Plunkett, PhD

0:19:34.0

Yeah, I digressed a little bit, but Dr. Cohen was, I think, in his earlier times, not an easy person to get along with in perhaps a collegial sense and certainly in a mentorship sense. I was told, being one of his latter trainees, that he had mellowed greatly and that I was quite fortunate at that time or times were different than they had been in the laboratory in the '50s, not so very long before I arrived there. But we used to joke about if you do well the first half year, you get Sunday afternoon off or something.

Tacey Ann Rosolowski, PhD

0:20:26.9

Did he steer you into a direction, or was that influential?

William Plunkett, PhD

0:20:29.8

In his personal manner, I think he convinced the administration of the University of Pennsylvania that he should have his own department, and he became chair of that department. That's the Department of Therapeutic Research. It was separate. I'm not sure whether he recruited some of the people who were in there, the professors who were in there, but he had maybe four professors and their laboratory staff involved in that. That was the Department of

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Therapeutic Research. I was only at Penn in that capacity for 15 months when Dr. Cohen announced that he wanted to be closer to having an influence on the development of new therapeutic approaches and that he was moving his laboratory to the University of Colorado in Denver. Let me be sure of that. It's the University of Colorado Medical Center in Denver. I was invited to join them there. There were other people who were invited who couldn't go, but I was very interested in pursuing that, and it was an active laboratory.

Tacey Ann Rosolowski, PhD

0:22:19.0

I was going to say, so you made that move in 1972, from '72 to '75.

William Plunkett, PhD

0:22:25.4

December '71, so 15 months of being there, and I was the last one to go, so I closed down the laboratory. He pointed out I made the error of packing—because I drove out the equipment in a U-Haul, and I packed the equipment in first and then followed it with my personal effects from my home. Of course, the place where we had rented in Colorado wasn't quite ready, so I couldn't unpack my personal effects to get at the laboratory equipment, which slowed down reassembling that portion of the laboratory.

Tacey Ann Rosolowski, PhD

0:23:17.4

One of those interesting flow chart problems.

William Plunkett, PhD

0:23:20.0

Yes, not something that you think about. You want your home to be the last to go. That was a very productive time.

Chapter 3

A: Joining MD Anderson/Coming to Texas

An Interest in Therapeutic Applications and a Job Offer from J Freireich

Story Codes

A: The Researcher

A: Professional Path

A: Overview

A: Definitions, Explanations, Translations

C: Funny Stories

C: Joining MD Anderson

C: Portraits

B: MD Anderson History

C: Understanding the Institution

B: Building/Transforming the Institution

B: Growth and/or Change

C: Discovery and Success

Tacey Ann Rosolowski, PhD

0:23:33.1

Tell me about the work you were doing that time.

William Plunkett, PhD

0:23:36.7

What we were trying to do was work on therapeutics. These were nucleoside analogues, and that's important because I pursued that general area for—I still pursue that area.

Tacey Ann Rosolowski, PhD

0:23:57.3

Could you briefly tell me what that means? I'm saying it because these oral history interviews are going to be heard by a wide range of people, including non-specialists, so it'd be really helpful to get that.

William Plunkett, PhD

0:24:11.9

Okay. The nucleic acids, DNA and RNA, are comprised of basic components known as nucleotides, and there are four or five natural nucleotides that occur in DNA and RNA. They vary slightly, so a therapeutic approach that was adopted and essentially we were responsible for growing out further was to follow the lead of [Gertrude Elion and George Hitchings](#) who received the Nobel Prize for their leading work in 1988 with nucleobase analogues, just a portion of them. That laboratory then was interested in pursuing a—let me start again. There are two general forms of nucleotides. One is called a pyrimidine, of which cytarabine is an example. Another one

is a purine-based nucleoside, so we were interested in working out a purine-based nucleoside on the hypothesis that this may also be effective as the first fluorouracil, and then cytarabine, which is a nucleoside, was effective in cancer therapeutics.

Tacey Ann Rosolowski, PhD

0:25:53.8

This may be a very messy question to ask, but what's the significance of the difference between these two types?

William Plunkett, PhD

0:26:00.3

Well, they could be like families. When you think of DNA as being double-stranded and held together by hydrogen bonds between the bases, one base is a pyrimidine. The other base is a purine, and those hydrogen bonds, each one of them comes in essentially two varieties. They hydrogen bond, and so this approach was termed by Elion and Hitchings as antimetabolites, meaning they're slightly different than normal metabolites, and the working hope is that they will have therapeutic efficacy.

Tacey Ann Rosolowski, PhD

0:26:51.4

Now, I didn't ask you about your own specific developing interest in therapeutic applications. Do you feel it was because of the environment you were in educationally, or is there something that was growing in you intellectually or in some other way to say, "Yeah, I want to work on an area that can have a human application?"

William Plunkett, PhD

0:27:18.3

Well, there are several driving forces. If you just take the intellectual approach, yes, I knew what nucleoside analogs were when I was a graduate student, and I felt that I wanted to pursue that. That's the reason I went to Cohen's lab. He had several projects, and one was involved with nucleoside analogs. Then he left that for me to pursue. Others had followed it before and to grow that out in mammalian cell systems. You have to remember, in the early '70s there weren't very many cell lines available, and many of them were for mice. That is essentially what we were working on, and we pursued that. We were trying to show how these compounds work in the cell, what the mechanism of action is, which is a constant theme through our research in my laboratory now—mechanisms of action, mechanism-based rationale for particular lines of investigation. We were successful in showing that a particular form of this class of compounds can get into a cell and hypothesizing that it may be a useful new therapeutic.

Dr. Cohen was, I would say, a famous scientist. He was a member of the [National Academy of Sciences](#), and it was not infrequent that he would have other important and notable scientists or people in general coming through the laboratory. He'd introduce them to us, and some people we would know and other people we'd have to go—you couldn't google them at the time, of course.

You'd have to ask Seymour. This is really a turning point where one day Dr. Cohen was bringing a visitor through the laboratory that I didn't visually recognize, and he came up to me. I was at the laboratory bench, and he said, "Plunkett, tell Dr. [Emil J] Freireich what you're doing." I introduced myself to Dr. Freireich [Oral History Interview], who apparently was there on a site visit of a grant that was being reviewed. And Dr. Freireich being Dr. Freireich, you can explain something clearly to him—and he was involved in this area—he immediately gets it and asks hard questions back. Within, I would say, five minutes—they don't take a lot of time with postdocs in the laboratories—he said, "Really, you should come to Houston. We'll give you a job." And that's the part that when I say that to postdocs and so forth they don't believe it. It's one of those moments. Within a relatively short time—it was a period of, I think, six months—of wrapping up in Denver the work that I had been doing in the laboratory with Dr. Cohen, I moved to Houston. I then worked directly with Dr. Freireich, who had a very impressive section in the Department of Developmental Therapeutics, the pharmacology section, and that was headed by a very famous and wonderful person, Dr. Ti Li Loo. Dr. Loo, in his own right, was a famous cancer compound pharmacologist. That was a wonderful section to work in.

Tacey Ann Rosolowski, PhD

0:32:03.9

Tell me a little bit more about the connection that you established with Dr. Freireich, because you mentioned, maybe before we had the recorder on, that he was one of your mentors.

William Plunkett, PhD

0:32:18.4

Well, we adopted him as our mentor, whether he acknowledges that or not. Really, he had a tremendous influence on a whole generation of people, of scientists and clinical researchers, who went on to really distinguish themselves here and elsewhere after they left Developmental Therapeutics. Within a few years of my arriving, I realized—because the department administrator at the time told me that there were sixty-three faculty members in the Department of Experimental Therapeutics. This is the department that Dr. Freireich was the chair of. Essentially, he and Dr. Emil Frei III had set up this department. They had been recruited here by Dr. [R. Lee] Clark. In 1972 Dr. Frei left after seven years and went to Harvard and became physician-in-chief at the [Dana-Farber Cancer Center](#). With the sixty-three slots that were available—that is full-time—we call it FTEs—I was told that there were five that were actually funded. Everything else was on so-called soft money, where we would have to get funding for our own salaries, and I would say that probably no more than 20% were laboratory scientists. The rest were clinical researchers, and so they don't understand the undertaking to obtain those salaries. There was a time at which at that time funding was possible through a mechanism called program project grants, which exists today, but at the time they were much larger than the program projects that we know today. For instance, Dr. Freireich was the principal investigator of two program projects and then subsequently a third one that he had running in parallel. He was the PI of three program projects, so we would participate in that, individual investigators with individual projects, as many as eleven or thirteen projects on each grant.

Tacey Ann Rosolowski, PhD

0:35:13.3

When you came in 1972—no, I'm sorry.

William Plunkett, PhD

0:35:18.7

It was '75.

Tacey Ann Rosolowski, PhD

0:35:19.6

In 1975 you came as an assistant biochemist.

William Plunkett, PhD

0:35:27.2

As an assistant professor.

Tacey Ann Rosolowski, PhD

0:35:28.2

Oh, you were?

William Plunkett, PhD

0:35:29.3

There is an interesting story about that. Dr. Ti Li Loo adhered to protocol, and at the time Dr. [Robert] Hickey was the vice president under Dr. Clark. He brought me up to Dr. Hickey's office and introduced me to Dr. Hickey and told him that I was the new assistant professor of Biochemistry. Dr. Hickey didn't even look at me. He looked right at Ti Li, and he said, "No way," at which time I thought I was going through the floor. Then he went on to explain or ask if I had been introduced to Dr. Darrell Ward, who was the chairman of the Department of Biochemistry at the time. Developmental Therapeutics was a separate department. There was this partitioning between academic titles, particularly with disciplines associated with academic titles, and having the departments that may be named in those disciplines, such as Biochemistry, over that title. So I might have been Assistant Professor of Developmental Therapeutics, for instance, or Pharmacology or something. But in any event, Dr. Ward was a wonderful man and chairman in addition to being a terrific scientist. I went down and spoke with him, and then everything was smoothed out, but it was quite a startling introduction for me.

Tacey Ann Rosolowski, PhD

0:37:23.7

Did you end up retaining the title of biochemist in Developmental Therapeutics?

William Plunkett, PhD

0:37:28.0

I think it became pharmacologist, assistant pharmacologist.

Tacey Ann Rosolowski, PhD

0:37:34.1

Now, were these kinds of details—when you look back at them—were these purely administrative details which had to do with territories in this evolving institution, or what was that about?

William Plunkett, PhD

0:37:51.0

I think it was administrative territories. I'm not sure whether Dr. Hickey was playing up his role as vice president and protecting Dr. Ward from having somebody given the name of his discipline, but there were times when it seemed uncertain. It always seemed inappropriate, as it does now, to be Professor of Medicine, yet I'm in the Division of Cancer Medicine, and happily I'm Professor of Experimental Therapeutics. But once the Department of Developmental Therapeutics was subdivided into mainly medical departments with the basic scientists who were in that department being brought into a new department that Dr. [Irwin] Krakoff, who was the first head of the division—hmm, he may not have been the first head of the Division of Medicine, but he became head of the Division of Medicine, and then these organ site departments evolved from that. And interestingly enough, it was the many members of the Department of Developmental Therapeutics that became chairs of those departments.

Tacey Ann Rosolowski, PhD

0:39:41.5

Let me make sure I understand this restructuring. I was going to say the clinical departments broke off. And the organ departments were a subset of that? Is that how I'm understanding?

William Plunkett, PhD

0:39:53.8

The clinical departments were really formulated. I think there was a Division of Medicine, and then there was a Department of Developmental Therapeutics, and those were combined. But then defined departments arose in this Division of Medicine, and that's when it was under Dr. [Irwin] Krakoff. That was 1983, so it was under Dr. [Charles] LeMaistre [Oral History Interview] that that occurred.

Tacey Ann Rosolowski, PhD

0:40:28.8

What do you think was the effect of that?

William Plunkett, PhD

0:40:32.0

Well, it depends on whom we're speaking of. I think it gave many developing clinical researchers an opportunity to become leaders and work their way into leadership positions. I'm talking about Dr. [Gabriel] Hortobagyi [Oral History Interview] and Dr. [Maria] Cabanillas that

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were formally in Lymphoma, Dr. [Robert] Benjamin, Melanoma/Sarcoma. There was recruitment for the head of—so then the people in the hematologic malignancies became the Department of Hematology, and then within several years, because we have such a large group, that was divided into Leukemia, Lymphoma/Myeloma, and at the time Bone Marrow Transplantation and Stem Cell at the present time. Those are three separate departments. So what happened to the basic scientists then? Dr. Krakoff said he's going to start a department that he would chair in addition to being the head of the Division of Medicine, and we're going to call that Chemotherapy Research. Then with regard to titles, I may have been Associate Professor of Chemotherapy Research.

Tacey Ann Rosolowski, PhD

0:42:15.1

But that didn't happen.

William Plunkett, PhD

0:42:17.5

I don't know. I can't remember. I think I just ignored that because Dr. Krakoff was here for 10 years in that capacity and was replaced by Dr. Robert Bast, and Dr. Bast said he wanted a different administrative designation for the people in our department. What the people in Chemotherapy Research had been was now going to be Clinical Investigations. Then I would have been Associate Professor of Clinical Investigations in 1993. You see, for me it's a progression of Dr. Freireich, who is a very busy person with all these faculty members and has a focus certainly in the clinic; Dr. Krakoff, who was less busy and who had been involved in drug development from the clinical side mainly at Memorial Sloan Kettering before he was recruited here; Dr. Bast, who was of course a clinical researcher being involved in an expanding administrative structure in the Division of Medicine, being a department chairman; and then subsequently, Dr. Bast was replaced by Dr. [Waun] Ki Hong [Oral History Interview], who has no background, by his own admission, in laboratory science, but he's head of the division which then became Cancer Medicine. Then our department was under ad interim leadership with Dr. Zahid Siddik. It was ad interim at that time. Then our department, by vote of the faculty, we didn't want the name Clinical Investigation. We came up with Experimental Therapeutics because we couldn't use the name Developmental Therapeutics, which had applied broadly. That's a name that Dr. Frei and Dr. Freireich created when they came from the NCI.

Tacey Ann Rosolowski, PhD

0:45:15.7

I think I recall Dr. Freireich telling me you didn't know why they called it that. It just sounded good at the time.

William Plunkett, PhD

0:45:23.3

Yeah, they created it, and now the NCI, of course, has a developmental therapeutics section. I was always under—up until 19—I'm trying to remember now. I'll get it straight later. Up until

the middle—oh, so Dr. Bast had been chair of our department at that time, so each time our department changed its name— There was one time when Dr. Krakoff was trying to be chairman of two departments, Medical Oncology and Chemotherapy Research, but he was told, “No, you can’t be chairman of two departments.” Then we became the pharmacology section in the Department of Medical Oncology. That was before Dr. Bast. We had never, by our view—that is my colleagues and I involved in this group—really had a leader of our department who would sit at the table as a basic scientist and make the case on our behalf. Rather, we always felt that we pretty much had to go it alone.

Chapter 4

A: The Researcher

Basic and Clinical Researchers in Conversation at MD Anderson

Story Codes

A: The Researcher

A: Professional Path

A: Overview

A: Definitions, Explanations, Translations

C: Funny Stories

C: Joining MD Anderson

C: Portraits

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

C: MD Anderson Past

C: Collaborations

D: On Research and Researchers

C: Discovery and Success

D: Understanding Cancer, the History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

0:46:56.1

Let's get into a question that—actually, before you summarized it in that way, I was feeling like it was emerging, which is as you were observing when you came in '75 and this evolving situation, what was the relationship between the basic scientists and the clinical researchers?

William Plunkett, PhD

0:47:17.4

That's really an interesting situation. When I came here, I didn't know what to think when Dr. Freireich, for whom I had a lot of affinity because of his responsibility in getting me here in the first place, said, "Well, we're going to have two or three meetings a week, and we're all going to get in the room together." And by "we" he meant the basic scientists who may be there and all of the clinical researchers who were involved. We'd be talking about different questions in solid tumors, in hematologic malignancies, and in drug development and pharmacology all in this same group. I took the positive view and would sit close to a—there was no question about sitting close. It was crammed.

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Tacey Ann Rosolowski, PhD

0:48:21.3

How many people were in this gathering?

William Plunkett, PhD

0:48:24.4

There may be forty or fifty in a relatively small room with people standing or not being able to get in if you came late.

Tacey Ann Rosolowski, PhD

0:48:34.4

How long did they last?

William Plunkett, PhD

0:48:36.6

They were typically noontime meetings. Bring your own lunch. But I would sit next to somebody who I knew so I could ask questions about, “What the heck does that acronym mean?” or, “What are we talking about here?” and try to figure out what’s going on with medical oncology and hematologic malignancies. You just have to feel comfortable, I felt, with asking those questions rather than sitting there continually not learning.

Tacey Ann Rosolowski, PhD

0:49:16.0

What was the atmosphere in those? What were the kinds of questions that people took on?

William Plunkett, PhD

0:49:23.4

Spontaneous at any time. When I came for a formal interview and seminar the first time before being formally invited to join the department Dr. Loo brought me into the seminar room, and he said, “Now, Dr. Freireich will sit right here in the very front row, and he’ll ask you questions at any time.” Having been with Dr. Cohen for the previous four-and-a-half years, I thought, “Well, I’m used to that,” and it didn’t bother me at all. I think it didn’t bother me. It only bothered me when Dr. Freireich would ask me a question about my research that I hadn’t thought of myself and hadn’t considered, or you can put it more closely in the context of therapeutics. I looked at them as really effective learning sessions from a very positive point of view, and why not be positive?

Tacey Ann Rosolowski, PhD

0:50:35.5

Were they very contentious? I was talking to Dr. Hortobagyi recently about these multidisciplinary meetings that they were setting up in Breast Medical Oncology, and he said there were some real tussles during those, which were productive.

William Plunkett, PhD

0:50:50.3

In DT, right, there were for sure.

Tacey Ann Rosolowski, PhD

0:50:53.5

What were some of the issues that were colliding, and then what positives came out of those?

William Plunkett, PhD

0:51:03.8

There were also statisticians there, and sometimes the discussions about how to analyze clinical data in particular, you'd really get a course in applied statistics as to why—Dr. Freireich is quite knowledgeable about statistical methods. The major person at the time was Edmund Gehan, G-E-H-A-N, and he had very different demeanor—very calm and wants to explain it to you, quite academic in going at things, whereas Dr. Freireich usually had an opinion and could think moves ahead of you in terms of the conversation and was ready to go on with it and wondering why you hadn't caught up. Sure, they were emotional, because we were at a time when they could be emotional, because we were at a time when everybody wanted to make progress in cancer therapeutics, and it was frustrating that we were at a place where we didn't have the tools, we didn't have the drugs, we didn't have the knowledge to be able to go forth and do that. We were making up investigational designs of our own means. For instance, [Michael] Keating [Oral History Interview] was instrumental in setting up a database for the Leukemia Department. That was patients who are entered, what their diagnosis is, how they were treated, and then that was complemented with laboratory-medicine-type things like chromosome analysis, where their chromosome breaks, deletions and so forth. The leukemia group used that to develop an approach of seeking prognostic factors. That is elements other than, say, blue eyes or black hair or something or other that would give you some idea about how the patient is going to respond, prior treatments, duration of response to prior treatments, if any, and then the chromosome analysis came into it. Then they developed and together they published—I think it was 1983—Michael Keating published as first author a paper which I think was the first paper—he had to fight to get this published on prognostic factors. Now, or not long after that, you can't publish a paper without prognostic analysis. What the heck does it all mean in the setting of our patients?

Tacey Ann Rosolowski, PhD

0:54:39.8

Just so I'm connecting the dots correctly, are you saying that that kind of flow chart of activities came from the point of discussions in these meetings with Developmental Therapeutics?

William Plunkett, PhD

0:54:57.4

I think definitely it did, because if we didn't have any better drugs or if we only had a few drugs to compare, then what's the basis for comparison? What brings into account all of the information that we have at hand? That was the sort of thing that Michael Keating systematized,

and he, together with Ed Gehan and Terry Smith, his assistant, really put that into play in employing a system called [Cox modeling](#) of prognostic factors. We didn't have anything other than what we had, but what they did was to create a new system of looking at what we did, what we had.

Tacey Ann Rosolowski, PhD

0:55:51.6

How did those conversations two to three times a week have an impact on your work?

William Plunkett, PhD

0:56:00.8

Well, I learned about statistical analysis of things. At the time, we were treating mice, and I learned about how to go about analyzing the results in a more effective fashion. It showed me the passion people brought to their daily job description, to their work, and it's most impressive. You try to work on something that somehow can be useful or can make a difference, and that's the sort of thing that I really was impressed with about how people who are treating— My colleagues who were treating patients were so impassioned about finding a solution to problems, and even small advances, when you can document them, were important and followed. When large advances occurred—I mean—it was not uncommon to say, “Well, okay, this is frontline office practice. Now let's get something that's better.” Then if it's approved and it's an office practice, they don't need to come to MD Anderson to get that treatment. That's not always the case in leukemias where they need really intensive treatment, but it is the case, say, when you're talking about Dr. Hortobagyi. The frontline therapies that were conceptualized and proved in his developmental area, some of which are still in play today and used today, can be used in aligned hospitals, primary referral centers.

Tacey Ann Rosolowski, PhD

0:58:07.5

Is there anything else you wanted to say about the relationship between basic scientists and clinical scientists during this time?

William Plunkett, PhD

0:58:13.6

Yeah, I think we felt—and “we” may not have been a large group. You have to have the mindset for making it work. There were some basic scientists who stuck to the laboratory and didn't participate in these types of activities, but you're interviewing me, and for me it's the sort of openness and receptivity of new ideas. And you have the reciprocity of that—of people trying out ideas on me, which is still not uncommon and very much appreciated. We work very closely together. We used to call it “hypothesis testing” in the clinic because—this is a different area of my research that Dr. Freireich enabled that I can talk about at another time, but we were able, in the hematologic malignancies where it's possible, to obtain primary tumor cells through the blood and then study them in the laboratory and study drug metabolism and drug effects—that is,

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pharmacology and pharmacodynamics in the laboratory. We were able to come up with answers relatively quickly, or you can ask questions relatively quickly.

Another thing that we encountered is that, in an earlier time, writing and having a protocol approved for use in clinical trials was not as involved and tedious a proposition as it is today. I'm sure Dr. Freireich has told you about the days of one- or two-page consent forms and protocols that were ten pages long and so forth. If you're discussing something, a hypothesis, a discussion leads to, "Hey, what about this?" or, "What about that?" The clinical researchers can actually write a protocol and enact it in the clinic before I could get into the laboratory with an appropriate model system to investigate it. But it was the sort of thing that people thought, "That's an idea worth trying," and they could try that in the clinic and have a protocol written before I could publish what the rationale for the protocol was really.

Tacey Ann Rosolowski, PhD

1:01:21.9

And certainly there are time advantages to that.

William Plunkett, PhD

1:01:28.7

These are people who want to treat their patients with something more effective than what they had.

Tacey Ann Rosolowski, PhD

1:01:33.0

Sure. I'm wondering in terms of the doing of science, how do you evaluate that?

William Plunkett, PhD

1:01:40.3

Oh, well, that's on a different level, because in order to have the resources to do what I've been alluding to—or I'll get to describing it perhaps—with clinical samples, you really have to have a basis in basic science—a support basis in basic science. What that means is having an NCI or an NIH grant for individual investigators. They're known as R01 or "R oh one," as it's usually pronounced. That's an investigator-initiated grant. So that type of thing, or something that independently you're pursuing laboratory research on a more basic level, although it's not uncommon to say, "Yeah, I'm going to do this and try to understand how this compound is metabolized by cells, how it kills cells," but then say, "Well, it can have use in clinical trials." And after some time of doing this and actually showing that what we have in the laboratory can be brought into the clinic and investigated, because we're working in hematological malignancies that have that hypothesis testing in the clinical situation, then you get the street cred or credibility with the groups that review your applications for the next study sections. That's something that you maintain in parallel with other proposals that may go in, and actually, I have been the principal investigator on R01 grants that included clinical trials. It's still that way in spores and in program projects. They're always directed towards some sort of therapeutics, but

in R01s—it's unusual, but I have an R01 now that's supporting a clinical trial that my colleague Bill Wiedra and I put together based on laboratory work here in my lab.

Chapter 5

A: The Researcher

Working on Nucleoside Analogues

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

C: MD Anderson Past

C: Collaborations

D: On Research and Researchers

C: Discovery and Success

D: Understanding Cancer, the History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

1:04:14.4

Let's start with that story of your research. How would you like to go about that?

William Plunkett, PhD

1:04:23.5

From the beginning.

Tacey Ann Rosolowski, PhD

1:04:24.6

Okay, let's start at the beginning then.

William Plunkett, PhD

1:04:28.4

(laughter) You're going to have to phrase this—well, it starts with Dr. Freireich.

Tacey Ann Rosolowski, PhD

1:04:35.6

It all goes back to Dr. Freireich.

William Plunkett, PhD

1:04:37.4

So much does. Well, with the collegial environment that he established in the Department of Experimental Therapeutics of having laboratory scientists and clinical researchers together, speaking with one another, listening to one another, it really opened up the opportunities for endeavors that would extend from the laboratory into the clinic. This really started from very early on in my experience, where we would be getting samples into my laboratory to test the hypothesis that we had already established in the laboratory. For instance, I think Dr. Keating and I co-authored a paper—essentially it was a laboratory paper—using primary leukemia cells—and Dr. Freireich was a co-author as well—that in 1980 published in *Cancer Research*. It took a while to get going because we didn't have a means of getting regular samples or multiple samples, although there weren't any stringent prohibitions of that or stipulations. In a clinical protocol, essentially you had to get physician approval, but I think the person who really facilitated that in the Department of Developmental Therapeutics—it was the section of leukemia, and Dr. Kenneth McCredie was the head of that. He was the one who really took over and enabled our ability to get samples, speaking with the head of Laboratory Medicine at the time, Dr. [J.M.] Trujillo, and coming to an agreement of how we could get six, eight, ten samples on an individual in order to put together a pharmacokinetic profile.

Tacey Ann Rosolowski, PhD

1:07:11.6

Can you explain to me what that is, pharmacokinetic profile?

William Plunkett, PhD

1:07:16.0

Yeah. Let's start with some definitions that may be helpful. *Pharmacokinetics* is what the body does to the drug. That is, it accepts it. It metabolizes it. It eliminates it over time, so it's a concentration in time. *Pharmacodynamics* is what the drug does to the body. That's response. You're killing tumor, its toxicity. You're killing more than tumor; it may be affecting normal cells. It may be that you're killing so much tumor that it has an adverse effect on the body because of it upsetting body chemistry. This is called [tumor lysis syndrome](#). Those are generally the two areas.

The thing that really—and at its height, Dr. [Kenneth] McCredie had enabled, in his position as head of the section of leukemia, our ability to obtain leukemia cells when patients were receiving therapies, and we would process those cells as we would cells from tissue culture or cultures in the laboratory and then be able to analyze the metabolites. Really, it was the first time that this had been done in intracellular metabolism. And because the compound that you give to the patient is not the really active compound, it has to be metabolized to an active compound by phosphorylation. So we were able to analyze the phosphorylated metabolites and relate it to patient response.

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Tacey Ann Rosolowski, PhD

1:09:18.7

And what was the compound that you were studying at this time?

William Plunkett, PhD

1:09:23.0

There has been a line of them, but the earliest one was cytarabine or Ara-C, but cytarabine is how it's known. Then going back to my time when I met Dr. Freireich in Colorado, I was working on a strategy that didn't directly but indirectly led to the development and evaluation here of a major drug called fludarabine, and that's widely used in B-cell malignancies. Although it has similar mechanisms of action of cytarabine, the pharmacology is different in the cell, and the mechanisms of action are different enough so that it's a whole different set. Where cytarabine affects myeloid leukemia, fludarabine affects mainly lymphoid leukemia, and that's the lead drug in CLL.

Tacey Ann Rosolowski, PhD

1:10:37.3

You began that work with fludarabine in Colorado, and was that one of the first projects you took on here?

William Plunkett, PhD

1:10:44.6

I began the work that led to that, because I was trying to put two drugs together. The primary drug was going to be degraded by the body, and we were putting together an inhibitor of that degradation process and administering them together and showing, at least in mice, that it had an advantage.

Tacey Ann Rosolowski, PhD

1:11:09.1

I was going to ask you about the whole issue of research design and how you actually decide to sequence these studies in a way that will build up that knowledge about how those mechanisms work. It sounds like it's a real art, actually.

William Plunkett, PhD

1:11:28.6

Well, yeah. You have to be receptive to something new, and you certainly expect something new pretty much as a challenge. Right now there are, I think, fourteen essentially [nucleoside analogues](#) that are approved for use in cancer, and I think we've been able to identify at least nine different mechanisms of action among those.

Tacey Ann Rosolowski, PhD

1:11:59.1

What do they do exactly?

William Plunkett, PhD

1:12:00.6

They do different things. Probably the major class of nucleoside analogues affects DNA replication, but others are incorporated into RNA, and they affect RNA metabolism. I think the earliest one, fluorouracil, is metabolized in the cell, and it inhibits a key enzyme that makes a key normal metabolite, thymidylate synthase, but 5-fluorouracil monophosphate inhibits thymidylate synthase. That's the mechanism that Dr. Cohen had worked out. There are others that affect chemical modification of the DNA that will silence genes—these have been appreciated in the last decade—called epigenetic modifiers. They will block the modification which normally would occur when cells replicate, and they add new nucleotides and are going to be modified, but that process of modification is blocked, and therefore, the genes are expressed differently. The modification usually silences the expression of the gene, but this allows the genes to be expressed. That's a therapeutic approach.

Tacey Ann Rosolowski, PhD

1:13:47.9

How do you go about designing a study that will demonstrate those kinds of arrays of effects?

William Plunkett, PhD

1:13:59.3

Well, a couple of things. From our early assumption that we were doing hypothesis testing in the clinic grew into translational research in the popular press and application in terms of drug development, so we accept that translational research. But if you take it literally, a translator is a person or instance where you have to know two languages. You've heard about where I got my introduction to medical oncology language, and that was in the workshops of Dr. Freireich. I appreciate that, so then you maintain an interest in that, and as an extension of that there is an understanding of what makes a cancer cell a cancer cell. This is both the ideology of the disease and, in a more general term, its pathophysiology. Although those two terms may be different, there may be something that causes a cell to be cancerous, and then that causes the cell to act in a particular way. What we're trying to do, rather than being in cancer prevention—which is extremely important and a difficult field to pursue—is to understand what the cancer cell now has to do and how it functions in order to maintain its replication capacity for growth, the lack of differentiation, so that it doesn't differentiate its cells. It typically will not be growing if these were associated. Then try to attack that. Sometimes you learn what the mechanism of action is, and then you bring that to the point of asking yourself and your colleagues, well, which cells would be particularly susceptible to this?

For instance, we've worked out a mechanism of action now of yet another nucleoside analog. I've only named a couple, but there is a line of them. This nucleoside analogue, when incorporated into DNA, it doesn't inhibit DNA replication, but rather it permits it. But because the modification on it is of a chemical nature, it causes the DNA to break, and it's difficult to repair that and then another subsequent successful replication to get a double-strand break.

By example, we asked what disease would be challenged to repair double-strand breaks. We can identify now a cohort of patients with chronic lymphocytic leukemia who lack a key enzyme because of a deletion and a mutation that eliminates the function of this key enzyme called ATM. In model systems, cells that lack that enzyme and further down in the process that that enzyme initiates are synthesized thirty to 100-fold to this drug. What that means is—the drug is called sapacitabine. In that patient cohort it would be selected for the tumor. Presumably at concentrations that would kill the tumor—pharmacology concentrations that would kill the tumor—you'd have less of an incidence of harming the most sensitive, normal cells. That's one thing that we're pursuing now, and that's the thing that Bill Wierda and I, less than a year ago, initiated a clinical trial supported by an R01 grant that we competed for. Then the progression is understanding how the drug works, what it does to the cell, thinking about which cells may be sensitized to this, and then bringing it on into that cohort of patients in a clinical trial support by some laboratory rationale.

Another example, in addition to this ATM—and this is being pursued—is to treat patients who lack another enzyme in this same DNA repair pathway called BRCA1 and 2 that are associated with predisposition to breast cancer and ovarian cancer. The company that's sponsoring this is trying that at the present time, but it's based on the rationale that we developed for the mechanism of action of the compound.

Tacey Ann Rosolowski, PhD

1:20:19.7

Interesting.

William Plunkett, PhD

1:20:21.7

For a laboratory scientist, this is the ultimate. That is, you do something in the laboratory that can be applied to the clinic, but really, the ultimate for us is yes, to do that, but then be part of the analysis of how it works in the clinic. That's part of the hypothesis testing in the clinic approach

Tacey Ann Rosolowski, PhD

1:20:59.1

I see how those conversations with clinicians and being immersed in both languages is really, really important to make this happen, absolutely.

William Plunkett, PhD

1:21:09.3

Now, you noted that I may have a joint appointment in the Department of Leukemia, so regularly I will go to two or sometimes three Leukemia Department meetings a week—administrative meeting and research meeting and grand rounds. There are others associated with grants that I share with my colleagues in Leukemia—[SPORE grant](#), PL1 grants.

Tacey Ann Rosolowski, PhD

1:21:38.5

So this is all part of sustaining that immersion part.

William Plunkett, PhD

1:21:41.3

Yes, the fun. When we were talking, walking up here, having to drive up there in order to conduct that where I used to walk two buildings away, this takes another hour out of my day just going to one meeting.

Tacey Ann Rosolowski, PhD

1:21:57.7

Just for the recorder, we were commenting earlier on the fact that this interview is taking place on South Campus, which is a couple miles away from the MD Anderson main campus, so there is the transportation issue and lack of casual, spontaneous coming across of colleagues and exchange of ideas. I was asking you about how the distance affected the workplace.

William Plunkett, PhD

1:22:21.8

It's a very real occurrence, and it takes the sting out of having to spend an extra hour getting myself up there and getting back and getting back to what I was doing here.

Chapter 6

A: The Researcher

Studies with Fludarabine and Other Drugs (and How Collegiality Moved Them Along)

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

B: Industry Partnerships

D: On Pharmaceutical Companies and Industry

C: MD Anderson Past

C: Discovery and Success

C: Collaborations

D: On Research and Researchers

D: Understanding Cancer, the History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

1:22:35.6

Would you continue with the story of—? I interrupted you with a request for some of those definitions. I wanted to make sure we got back on track with the story, the evolution of your research, because you were at starting to work with fludarabine, and then you started to explain what nucleosides do, and then we talked about research design. We were still pretty early in the process.

William Plunkett, PhD

1:23:11.0

Happily, and somewhat unexpectedly to me, fludarabine proved to be quite effective in a disease that had no real effective treatment prior to that. That was chronic lymphocytic leukemia where, at best, the agent that was approved for that disease gave maybe a 5% complete remission rate, whereas under Dr. Keating's direction in development of fludarabine, it produced a 25% complete remission rate. That was really a major breakthrough. So my question—my hesitation—about using fludarabine in that disease was that the disease is largely quite indolent. The cells aren't growing, dividing, at least the ones we could see in the blood. We know now that the cells, where they are nurtured and sustained in the lymph nodes and to some extent in the

bone marrow, have a lot more rapid turnover. I still don't think that that's the whole reason why fludarabine was as effective as it was, but it's a point for—

Tacey Ann Rosolowski, PhD

1:24:42.7

What do you suspect?

William Plunkett, PhD

1:24:45.2

Well, lymphoid malignancies are known to have a very effective DNA repair capacity, and one hypothesis is that this is a nucleoside that gets incorporated into DNA. Unlike Ara-C or some that came after Ara-C, it is really very effective as a single drug at blocking DNA replications. We've shown that in the laboratory biochemically. The hypothesis is that when DNA repair takes place, damaged nucleotides are removed, and then new nucleotides are inserted in a repair patch. What we're thinking is that perhaps fludarabine may be incorporated into DNA at that point and cause some damage to the DNA just because of endogenous events that are going on in the cell and because cancer cells may be unstable anyway. That may be elevated. But it leads to a rationale for a combination that also became a standard of care, and that was intentionally take a compound of the class of compounds that was only minor, had only minor effectiveness, and what it does is it forms an adduct on the DNA, and it stimulates repair. The hypothesis is maybe fludarabine is acting, at least in part, normally because of normal DNA repair. Why don't we antagonize that and really make the cells repair their DNA? We would devise an experimental design first in the laboratory and then in the clinic to give the cells the fludarabine and active metabolite accumulated. We could demonstrate that and then damage the DNA, because the DNA damage is repaired within two to four hours. It's quite rapid. So if the active metabolite is there, the hypothesis was it would be incorporated into repairing DNA and cause, let's say, bad things to happen to the cell, signaling that would lead to cell death, in better terms. When that was compared in three large, randomized clinical trials elsewhere, that was shown to be the case—that fludarabine and Cytosan were more effective than fludarabine alone.

So sometimes something new comes along, and you're hoping that it will be advantageous. Again, this was the case with the monoclonal antibody rituximab that was really thought to be more effective in lymphomas because on the outside of the cell membrane the target to which that is directed is more prevalent than in CLL. In fact, treating CLL with that, the response rate is less than 10%. The complete response rate is less than 10%, but when we combine that with fludarabine-Cytosan then the response rate went from 35% to over 70%. That was a major eye-opener. That was done because of the availability of monoclonal antibodies. I don't work in that field, but I certainly appreciate it, and that's the standard of care now by a very large clinical trial.

Tacey Ann Rosolowski, PhD

1:29:14.0

Where would you like to go next with this story?

William Plunkett, PhD

1:29:19.6

Do you want to talk about other nucleosides?

Tacey Ann Rosolowski, PhD

1:29:22.3

Yeah, I have the three main areas of your work here that came from the documents that you provided me before so that I would prep for this, which was the CLL and—

William Plunkett, PhD

1:29:35.3

Let me drop back a little bit to tell you where the fludarabine came from. Dr. Freireich, his approach to developing new therapeutics was to speak to experts in the world, and some of the experts were known to form a cluster and lead disciplines at the [Southern Research Institute](#). One of those people led the chemistry area. His name was John Montgomery, and it was Montgomery who synthesized fludarabine originally. He had tried it, as he told me. Dr. Freireich shares his friends, and he introduced me early on to Dr. Montgomery and Dr. Montgomery's colleagues as well. I was very fortunate in being in this company. Dr. Montgomery had tried this on one schedule in tumor-bearing mice and wasn't impressed with the activity and put it on the back shelf of his chemistry lab and moved on. I can move on to where he went. So when he saw the results of the work that we were doing by inhibiting an enzyme that limited the action of a drug that we were working on, a compound that we were working on, arabinosyl adenine, Ara-A, he said, "Well, putting that together with the idea that one modification that became fludarabine, it's a fluorine, blocked this degradation procedure in another set of nucleosides." What he was saying is if you had a compound with a fluorine on here—he said, "We have that," then brought it out and they did the first experiment at Southern Research with a reprint of their—actually it preceded two months ahead of this correspondence. It preceded two months of the publication of this paper. John sent me an envelope, no MTA or anything, with sixty-three milligrams of the compound that eventually became fludarabine. He said, "I know you'll know what to do with this."

Tacey Ann Rosolowski, PhD

1:32:14.6

That's a neat story. That's a very neat story.

William Plunkett, PhD

1:32:17.6

It's true.

Tacey Ann Rosolowski, PhD

1:32:21.4

And the fortuitousness of bringing you together with them and all of that.

William Plunkett, PhD

1:32:28.4

Well, you can extend it in somewhat of a decade jump, because one of my graduate students—during a tutorial, I put them on a project saying, Can fludarabine be degraded in a particular way? We were able to show that some bacterial enzymes would degrade this compound that he had used, that this fludarabine really wasn't very susceptible to that. But it still had a noticeable degradation pattern to this particular enzyme, a different degradation pattern. What John did then was—so we asked him about other compounds that he might have made that would be resistant to this type of degradation. In fact, it generated a product that was toxic. That, for a while, really concerned us, because it was not incorporated into DNA. It was incorporated into RNA. It was not specific for tumor. He went back, and he said, "Well, I've made all of these compounds with double modifications. Let's try this one." When he saw our publication, he said, "Well, that could be a problem." And by the way, the person who did that, the graduate student who did that, is Peng Huang, who is currently a professor in the Department of—it just became Translational Molecular Pathology. He had done the work that published the paper that influenced John Montgomery, by John's citations and conversations, to go back and try these other compounds. He selected one, and again, he had his own publication and then sent me a package with the compound in it.

Tacey Ann Rosolowski, PhD

1:34:49.2

What was that?

William Plunkett, PhD

1:34:49.9

It's called clofarabine. I had another graduate student who pursued mechanism of action of that, and people at Southern Research worked out a second mechanism of action, and I think they're both in play in the treatment of disease. It was approved for pediatric leukemias, and we're using it currently in adult myeloid leukemias. I think we've caught on. That's the idea of being colleagues with people who want to share knowledge, who are very outgoing. These people at Southern Research would publish at their own expense and distribute to Dr. Freireich and other colleagues at large what their laboratory findings were, because they were working on government grants, and these things were distributed, and it was known they would write that. You'd get a letter from John Montgomery or Frank Schabel, who was in experimental therapeutics, working with testing anti-tumor activity in animals, or Howard Skipper.

Tacey Ann Rosolowski, PhD

1:36:21.5

How frequent is that kind of interaction now?

William Plunkett, PhD

1:36:25.9

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I think beneficiaries of that interaction are more likely to carry it on. The association with people who are making compounds in an academic research environment—I think they all had appointments at the University of Alabama. But the association with drug development coming out of academics is diminishing. I don't see the opportunity for pursuing that. I've had other people, colleagues and friends of Montgomery, who actually came up and didn't tell me what it was but put a package in my pocket at [AACR](#) with a structure on it that said, "I'll tell you about this. Why don't you investigate that?" I know, looking at the structure, I would have an idea about what to do. This was Roland Robins, who was a very productive, famous chemist from, I think, Brigham Young University.

Tacey Ann Rosolowski, PhD

1:37:45.6

Why was he more circumspect about passing this on?

William Plunkett, PhD

1:37:49.6

He wasn't circumspect. He was just quite willing because he knew it would be investigated in our laboratory, whereas his laboratory didn't have the same capacity, and our laboratory had had productivity.

Tacey Ann Rosolowski, PhD

1:38:04.7

I was picking up on that because he had drawn it instead of telling you what it was.

William Plunkett, PhD

1:38:07.9

Oh, no. It's just that at some of these AACR mixers you don't get a chance to speak to a person in a quiet room, and where they do find you it's noisy, and that's the fastest way to get things done. There are some other things that are more drawn out. We were the first laboratory outside of Eli Lilly to have what became gemcitabine. Within seven months, I had two posters standing at AACR—that was three months lead time to get the data—and then subsequently published, I think, the first six papers on its mechanism of action and two clinical pharmacology papers, one with Jim Abbruzzese, which was adopted as the schedule to go—he's the head of Gastrointestinal Oncology here. He was an assistant professor at the time.

Tacey Ann Rosolowski, PhD

1:39:14.7

What was the name of that drug again?

William Plunkett, PhD

1:39:16.5

Gemcitabine. It's a nucleoside analogue. It just went off patent with Lilly. They were doing about six billion dollars a year, they were telling me. It's widely used in solid tumors. And then the one

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that I described to you with regard to the pathophysiology of the disease not having a DNA repair mechanism was given to me by a colleague, or a person with whom I knew from meetings and we knew through the literature—one another—from Japan, from Sapporo, the island of Hokkaido. It was Akira Matsuda. He said, “Would you be interested in studying this?” I said, “Yes.” And he said, “Would it be helpful if I gave you what we think will be the active metabolite?” I said, “Yes.” He said, “The person who actually synthesized this is trained as a chemist, but he wants to learn some biochemistry. Would you be interested in training him?” I said, “Yes.”

Tacey Ann Rosolowski, PhD

1:40:34.1

So you got the compound, the metabolite, and the person.

William Plunkett, PhD

1:40:38.0

Right. And he paid for the person.

Tacey Ann Rosolowski, PhD

1:40:40.1

Wow, that is true collegiality.

William Plunkett, PhD

1:40:44.7

It is. Those are examples. With gemcitabine, just to back up that story, I had a colleague there who had been in academic research and was one of the first of our generation to go into pharmaceutical research when they were deciding that they really wanted to grow out cancer drug programs. This was in the early '80s, and his name was Jerry Grandey, G-R-A-N-D-E-Y. Jerry was a different guy. He really developed the Eli Lilly drug development program from the start, including design of the laboratories and what would be included and so forth. They built a large building. There was always some contention between Jerry and the rest of the Lilly group that he really had to work hard to get his program to go. He says, “Well, I have one that you're really going to like,” and then I'd see him six months later, and he'd say, “Boy, it's coming close,” and then sooner or later— The only one with an MTA was Eli Lilly—the material transfer agreement, which is compulsory now, but this is in the end of 1986. He received the drug here, and they were going to start a clinical trial, and that's the drug that went on. But finally, he came across and made sure that our lab was the laboratory that got the drug, and it's in no small part due to our previous track record with cytarabine, fludarabine, and other compounds I've mentioned.

Tacey Ann Rosolowski, PhD

1:42:56.0

What was this drug he sent?

William Plunkett, PhD

1:42:57.8

Gemcitabine.

Tacey Ann Rosolowski, PhD

1:43:05.6

We only have about a few more minutes until the end of the session. I'm wondering how you would like to close at this point. Do you want to talk about another study? Or I have a couple questions about pharmaceuticals.

William Plunkett, PhD

1:43:23.1

I've been making up my own questions. (laughter)

Chapter 7

A: The Researcher

Co-Director of the Leukemia Moon Shots Program

Story Codes

A: The Researcher

A: Overview

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

C: MD Anderson Past

C: Collaborations

C: Discovery and Success

D: Understanding Cancer, the History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

1:43:24.8

No, that's fine. I'm just curious about the observation you were making that you're seeing less and less of drug development in academic situations. There are a lot of issues that have come up for many institutions about institutions developing their own drugs and then what do you do with marketing them. What do you do with all kinds of ethical and other kinds of responsibility issues? I'm curious maybe how you want to frame what some of those issues are that are arising now.

William Plunkett, PhD

1:44:06.9

Well, that's really the flagship of Dr. [Ronald] DePinho's approach is to develop. He's brought in a large team of experienced people, and they're well resourced, and they're looking at targeting new areas for the development of therapeutics. These people are experienced. Dr. DePinho and his team are experienced at this. They set up several pharmaceutical companies on their own and participate in others. Certainly it's a different approach from Anderson. He's the first person to say, "Yeah, we're going to try this approach. This is the time to do it, and we have to marshal the resources to enable this." This is the background of the rationale, as I understand it, for the Moon Shot program. We're off and going. The Moon Shots were announced. The initial areas of emphasis were announced on September twenty-first, and early in February. Then he announced those areas, after narrowing down their focus to something that would be most immediately effective or brought into play. There are some areas of research that take a long time to bring about, but he was asking for some of the things that had some immediacy to them in turning out results. Each of the Moon Shots contributed one or two of those areas and then prioritized which projects would go forward, and that's the process that we're in now. And

believe me, that is an everyday effort, particularly the way I see it, as the co-leader with Dr. Keating of CLL Moon Shot. We're on something every day. Our group meets every week, at the least once, at Thursday noontimes, and there are other times when other meetings are needed, including scheduled meetings with Moon Shot steering committees.

Tacey Ann Rosolowski, PhD

1:46:52.7

It's a huge endeavor. How are you breaking it down?

William Plunkett, PhD

1:46:58.8

We're focusing on our most promising—what we see as our most promising area to go. It's something that we had wanted to do. It's something that we didn't have the resources to explore fully, although there is pharmaceutical support for the clinical trials that are ongoing or about to start. But being able to resource and then conduct clinical trials that will be complementary to the clinical outcome, to really give us a large-scale body of knowledge to know why things happen the way they did and perhaps, when needed, to indicate how they might be better brought forward.

Tacey Ann Rosolowski, PhD

1:47:55.7

What are the dimensions of the studies that you're undertaking right now?

William Plunkett, PhD

1:48:00.4

There are four clinical trials that are being conducted or will be conducted. One is directed at patients who have not been treated before but have indications, cytogenetic indications, of being our most difficult to treat, where we're least successful, and they have the shortest survival time. They lack function in this regulatory protein p53. It's only the patients with cytogenetic indicators of that situation that will be entered on that protocol. Another one is one which is an academic study, but we're really studying the growth rate of CLL cells and then treating them with this drug. I should have started with all four protocols are focused on a single drug that's active and apparently effective on a component of a signaling pathway that hasn't been investigated before. It's a new approach to treatment of CLL, and I think this deals with the pathophysiology of the disease. It's a signaling pathway which, when active evidence indicates, sustains viability of the cell and maybe stimulates growth of the tumor cell.

Tacey Ann Rosolowski, PhD

1:49:51.4

What is the drug?

William Plunkett, PhD

1:49:52.1

The drug is called [ibrutinib](#), and the basis for that is it targets an enzyme in this pathway called Burton's tyrosine kinase, so it's tailored to be associated with that.

Tacey Ann Rosolowski, PhD

1:50:11.5

You were saying that this academic study looks at the growth rate of CLL cells.

William Plunkett, PhD

1:50:16.6

Right, yes, it does, and it's by treating them with a non-therapeutic diagnostic agent called a radionuclide. Essentially, it's heavy water. It's deuterium instead of hydrogen. It's an isotope of hydrogen. This will label the nucleic acids, and by using spectroscopic methods, mass spectroscopy, you're able to tell when the cell—knowing when the patients drink this heavy water and you'll know when the cell was born, and then once the patient stops drinking it, you'll know the rate at which it goes away as being prevalent in the DNA of these patients. It's a procedure that was first brought forth in a consortium which Dr. Keating and I, Dr. Wierda, Dr. [Varsha] Gandhi are all members. Keating and I are all charter members. It's centered around a program project grant focused on CLL. The unusual aspect is that each project is in a different cancer center located around the United States and in London. But we each have different specialties, disciplinary focus. There is genetics, immunology, drug development, a couple of drug development projects here and at Ohio State, and transplant strategies that go forward, and of course, as they say, clinical centers. Together we developed a cell bank repository that's located in San Diego, where the PI of the grant is located. It now has samples from over 15,000 patients. Many of these samples are longitudinal over time, and this will give us an opportunity to investigate genetic changes and changes in general and an actual unnatural history of the disease.

Tacey Ann Rosolowski, PhD

1:52:57.9

How many patients are you—? It's 15,000 patients?

William Plunkett, PhD

1:53:02.6

No, no. I'm just saying where the heavy water—it grew out of that. It was conceptualized in the [CLL Research Consortium](#), CRC. Another one compares the activity of ibrutinib to a recently approved monoclonal antibody, [ofatumumab](#). The drug that I referred to earlier with reference to fludarabine that was the only drug that was used in treatment of chronic lymphocytic leukemia is called [chlorambucil](#), and it's still the only one that's approved for frontline treatment of CLL practically. I think it's grandfathered. But the FDA considers activity versus chlorambucil when it's considering how it will rule on the use of drugs in clinical usage. There is an ibrutinib versus chlorambucil clinical trial that will start as well.

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Tacey Ann Rosolowski, PhD

1:54:24.7

And the fourth one?

William Plunkett, PhD

1:54:26.5

One was ofatumumab versus ibrutinib, heavy water, and then the p53 protocol. Those are the four trials that are in our flagship project. Each of those trials has laboratory correlative investigations, and we're preparing to conduct those so that we'll have as full a picture as possible as to what the effectiveness of the interesting new compound is and as a family. There is already a second generation of a compound that targets the same Bruton's tyrosine kinase. There are more on the way, other compounds that interact with other elements, other components of this B-cell signaling pathway. That's the key thing.

Tacey Ann Rosolowski, PhD

1:55:28.6

Well, we're at 3:35, so why don't we close off for today, and we can resume next time.

William Plunkett, PhD

1:55:34.1

Let me just say that some of the interest in this compound is driven by the fact that the therapeutic that's being used does not damage DNA, and because of the success that we've had with the fludarabine-Cytosan-rituximab protocol, we have patients who are long-term survivors. Now, 40% over that have survived more than 10 years, but we've noticed the incidence of second malignancies among these individuals previously. If you're not successful at maintaining response, then you'd never see those second malignancies now. Because of that success, the way we interpret it, we are, so we're concerned about agents that damage DNA. These agents don't interact with DNA. That's part of the enthusiasm for pursuing this new target. Now I accept your—

Tacey Ann Rosolowski, PhD

1:56:37.5

Cool. That's very cool. Thank you for adding that piece.

William Plunkett, PhD

1:56:47.2

Yeah, it might get lost.

Tacey Ann Rosolowski, PhD

1:56:50.1

Well, I'm turning off the recorder now at 3:37, and thanks so much for your time today.

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William Plunkett, PhD

1:56:57.9

My pleasure.

1:56:59.7 (End of Audio Session 1)

William Plunkett, PhD

Interview Session 2: April 10, 2013

Segment 00B

Interview Identifier

Tacey Ann Rosolowski, PhD

0:00:00.6

Well, let me put on the identifier at this point. We are recording. It is 1:41. I am in the office of Dr. Bill Plunkett. Today is April 10, 2013, and we are starting our second session. So thanks again for taking the time to do this.

Chapter 8

A: The Researcher

Working with Fludarabine; the Importance of Extra-Institutional Connections and Ethics

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Collaborations

C: Professional Practice

C: The Professional at Work

B: Industry Partnerships

D: On Pharmaceutical Companies and Industry

C: MD Anderson Past

C: Collaborations

D: On Research and Researchers

D: Business of Research

D: Understanding Cancer, the History of Science, Cancer Research

D: Ethics

A: Professional Values, Ethics, Purpose

Tacey Ann Rosolowski, PhD

0:00:00.6+

And you had said that you wanted to start off this session going back and picking up a bit on—to elaborate a bit more on the story of the development of your research and to mention at least one key colleague that you had not been able to mention last time. So I will just turn it to you and let you continue with your story.

William Plunkett, PhD

0:00:47.0

Okay. All right. Chronologically, I think I have mentioned that we have been very fortunate—I have been very fortunate to have friends and colleagues at a distance outside of MD Anderson who are synthetic organic chemists or were in drug development who were very generous in providing or making sure that some compounds of interest that we could work on constructively came to my laboratory. One of these people was Dr. John Montgomery from the Southern Research Institute in Birmingham, Alabama.

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Tacey Ann Rosolowski, PhD

0:01:25.6

Yes, you did mention him last time.

William Plunkett, PhD

0:01:27.2

Yes, and Dr. Frank Schabel. So they were—through my relationship with Dr. Freireich, who was very supportive—and these people have a shared mindset of sharing information and data and ideas with colleagues such as me or everyone who will listen. And then they also share resources. So Dr. Montgomery generated a drug, which came to be known as fludarabine, and provided it to me directly as soon as their first publication was accepted—not how he looked back at the documentation. It was accepted, not published. It came in an envelope. There was no material transfer agreement or anything like that. So I set to work on that with people and trainees in the laboratory investigating it. It was probably—almost ten years. It went into the clinical trials, and then it became clear that we had new ways to determine more precisely mechanisms of action. And then a young trainee named Peng Huang—he was a graduate student in my group. He decided he was going to pursue these mechanisms of action as part of his dissertation, and he was spectacularly successful generating several highly cited and notable papers which were correct in assigning different mechanisms of action to fludarabine. This really provided the knowledge and indeed inspiration to try to use fludarabine in multiple ways other than just giving it alone rather than—have a rationale for combinations. So he called this mechanism-based rationale for combinations. That is applied generally, but it was applied specifically with this.

Tacey Ann Rosolowski, PhD

0:03:55.4

Now, Dr. Huang was a fellow at the time?

William Plunkett, PhD

0:03:57.2

He was a graduate student.

Tacey Ann Rosolowski, PhD

0:03:58.7

A graduate student?

William Plunkett, PhD

0:03:59.3

Yes.

Tacey Ann Rosolowski, PhD

0:03:59.5

Okay. Okay. And is that—? That is a common kind of process where—I mean—I am trying to

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get a sense of whether the setting that you are describing with this collegiality with scientists outside the institution and then bringing in substances and handing them off to people inside—is that still the way it works?

William Plunkett, PhD

0:04:24.0

Well, largely no.

Tacey Ann Rosolowski, PhD

0:04:25.3

Okay. What has changed?

William Plunkett, PhD

0:04:28.8

Most of the development of new agents—certainly those that are going into the clinic—95% I have heard tell come from pharmaceutical companies, and they are curtailed or advised by a group of legal experts to place restrictions on the use and availability of compounds. This is part of the material transfer agreement. But it is also—they do this in part because the Food and Drug Administration—our FDA—asked them questions about what possible adverse effects they have noted in the development of a drug when they are applying for approval of the drug for use in human beings. And they are duty-bound to report this. So they do not—so then it is the pharmaceutical company's approach then to really maintain very close control over what might happen with their compound that they are going to be—have to report on—even report what other laboratories have done with it. And so if there is something that is adverse to—or it could be questioned as producing an adverse event in humans, then typically the FDA would ask them to explain it or investigate it further. It is more of an inconvenience and certainly an expense—and time is expensive—for them. So time is critical because they only have a certain clock going on the patent rights to a compound.

Tacey Ann Rosolowski, PhD

0:06:20.1

What has been the impact of that change on the careers of students—graduate students—and then more established professionals?

William Plunkett, PhD

0:06:32.0

Well, I think it curtails imagination and pursuing things in different directions. It leads to—in my view of my experience and viewing the experience of others—a prescription that comes from the pharmaceutical company to you can do these experiments, and this is going to be your objective. So it is almost as though you know what the result is that you are going to get, and you do determinations. So this is not the spirit of science that we want our graduate students, our trainees on any level, or particularly ourselves to be practicing rather than to—you know—we would pursue ideas and formulate hypotheses from those ideas and then test those hypotheses

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with experimentation. That is the way we go after it. So one of the two major directions that fludarabine took coming up from these mechanisms-of-action studies that Dr. Huang did—he is now a professor at MD Anderson, and he has an endowed position as well.

Tacey Ann Rosolowski, PhD

0:08:05.1

Wow.

William Plunkett, PhD

0:08:05.2

He graduated in 1990. So one was the realization that fludarabine—the metabolite of fludarabine—the triphosphate—would inhibit a key enzyme in the metabolism of the precursors of nucleic acids but particularly DNA, so this ribonucleotide reductase. Then another trainee in the laboratory, Dr. Varsha Gandhi, who was a postdoc in the lab—

Tacey Ann Rosolowski, PhD

0:08:43.8

I am sorry. His first name again is—?

William Plunkett, PhD

0:08:45.4

Her name is Varsha.

Tacey Ann Rosolowski, PhD

0:08:46.9

Varsha?

William Plunkett, PhD

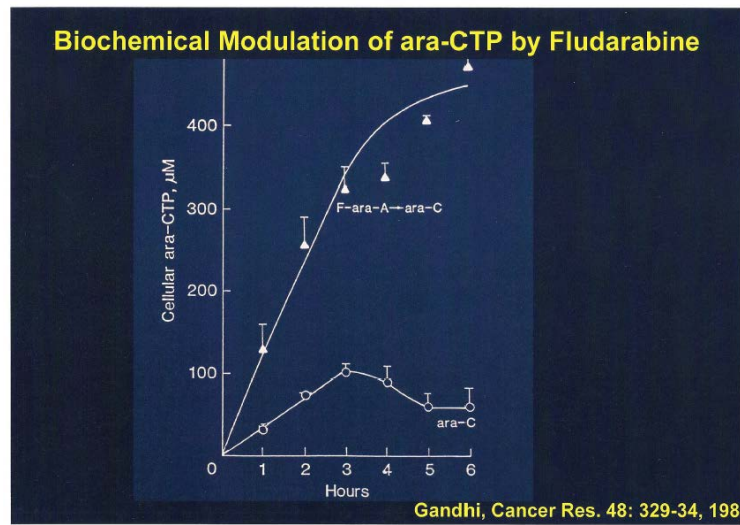
0:08:47.2

V-A-R-S-H-A. She developed the idea of using fludarabine to inhibit ribonucleotide reductase, and thereby that would cut off some of the production of metabolites that would compete with the activation and activity of a second drug which was fully established in acute myeloid leukemia called cytarabine. And to my pleasure and amazement, her first experiments showed that that would be the case. And in this case—here you can see this—this is what it is alone, and this is what it is with fludarabine. So there is about a five-fold increase in the ability to accumulate the active metabolite in tumor cells as this goes.

Tacey Ann Rosolowski, PhD

0:09:55.7

And just for the record, I want to say Dr. Plunkett is showing me a graph of the results [see page below]. Would it be possible to just get a screenshot of that to provide with me—? That would be great.



William Plunkett, PhD

0:10:04.8

Sure.

Tacey Ann Rosolowski, PhD

0:10:05.6

I will email you to remind you about that.

William Plunkett, PhD

0:10:07.4

I can print it off for you.

Tacey Ann Rosolowski, PhD

0:10:08.6

Great.

William Plunkett, PhD

0:10:10.6

I have been invited to a meeting in Italy on—the title is “New Drugs in Hematology,” and they have asked me and a colleague, Michael Keating, to go back and review the oldest drug in hematologic malignancies, which happens to be fludarabine.

Tacey Ann Rosolowski, PhD

0:10:32.1

Now, can I ask you why that request was made? Why do they want that historical overview?

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William Plunkett, PhD

0:10:38.7

I think they have to fill an 8:00-9:00 slot on a Saturday morning. No, actually, it is the last morning of the meeting, and they figure the old gomers will show up.

Tacey Ann Rosolowski, PhD

0:10:52.6

Here I thought you would give me some great history-of-science reason.

William Plunkett, PhD

0:10:59.1

No, it is—I am not sure why, although we know these people who are inviting us obviously, and they know that individually and together we can tell a good story. So it's easy going after about three days of meetings, where newer things are being presented. In fact, I told Keating that I—well, yeah, we will show the structure—

Tacey Ann Rosolowski, PhD

0:11:32.9

Great. Thank you.

William Plunkett, PhD

0:11:33.0

—of this drug, and then we will talk about the new stuff. But he said, “No, no.” He wants to go back and illustrate that.

Tacey Ann Rosolowski, PhD

0:11:44.2

I mean, intellectually, what is the value, do you think, of—?

William Plunkett, PhD

0:11:49.4

Well, essentially, it is understanding where these things came from. I mean, there are so many people—you know—so for instance, I have mentioned Dr. Freireich before. He appears permanently in the beginning of our talk because it was essentially the precursor to fludarabine that I was working on as a postdoc when he came through that laboratory and asked me to tell him what I was doing. Then he offered me a job on the spot.

Tacey Ann Rosolowski, PhD

0:12:20.9

Right.

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William Plunkett, PhD

0:12:21.8

So—

Tacey Ann Rosolowski, PhD

0:12:24.3

I wanted to ask—

William Plunkett, PhD

0:12:25.4

So let me just—

Tacey Ann Rosolowski, PhD

0:12:26.3

Sure.

William Plunkett, PhD

0:12:28.7

—just say that putting these—we worked it out—Varsha—Dr. Gandhi and I worked this out so that—what exactly the schedule should be and the doses or the concentrations—in vitro and doses in people—should be to maximize this effect that you are looking at of an increased amount. This is the same—this is the metabolite of this drug, but all you are doing is adding this. Okay? And you are adding the fludarabine to it. You are not adding any more of this, but what you do is you have got more of the active metabolite. And that is not achievable by adding more of this.

Tacey Ann Rosolowski, PhD

0:13:16.8

Interesting. So then it just turbo charges it.

William Plunkett, PhD

0:13:20.6

Yeah. So then this combination of fludarabine and cytarabine has gone on to be widely used around the world as a combination, but it is also frontline at MD Anderson in several protocols. I was watching Dr. [Hagop] Kantarjian present a lecture, and he is showing this curve of what the survival of this particular myeloid leukemia cohort—it is called transcription-factor driven AML, and it is identified by particular chromosomal abnormalities—and showing how it used to be so dreadful. Then with the addition of the start with fludarabine and cytarabine, and then addition of another drug, now it is incredibly impressive. It is above 90% over a period of years—survival.

Tacey Ann Rosolowski, PhD

0:14:35.5

And what is this third drug that is being added now?

William Plunkett, PhD

0:14:39.2

It is an antibody. It has one of these crazy names, but it had been known as Mylotarg—M-Y-L-O-T-A-R-G. It has a DNA intercalating agent in it.

Tacey Ann Rosolowski, PhD

0:15:04.2

So you were saying that this is being used in several MD Anderson protocols. And that means that these are investigative studies that are confirming—

William Plunkett, PhD

0:15:12.3

Well, the addition of the new compound is an investigative study bringing it on. The key thing here, and just to go back to get the full story of bringing it in to this cohort of patients, is that those are the patients who did the very best, whose survival rate was the most favorable on the therapies that we had at the time. Our rationale collectively—and talking collegiately with my clinical colleagues and ourselves—was to say, well, if we really want to know how good fludarabine and cytarabine are as a combination, we should try it in the patients who do the best—our most favorable patients. So the way you do that in an ethical way is you build in stopping rules based on—that is, you would stop the protocol—based on prior results, expected results, if they were treated with the standard therapy. Then you would stop the protocol if you didn't meet or exceed those, but in fact it exceeded it essentially at every time point and every look, and it just went on to not look back. And this is what we have been using now probably for close to twenty years.

Tacey Ann Rosolowski, PhD

0:16:36.7

Wow. So when was this work done by Dr. Gandhi and yourself? When did—?

William Plunkett, PhD

0:16:43.3

Well, her earlier work—this founding experiment that I showed you here is 1988, and it was in clinical trials. In 1993 and 1991, we published in—I think—in *Clinical Cancer Research*, and in 1993 we published in the *Journal of Clinical Oncology*.

Tacey Ann Rosolowski, PhD

0:17:09.9

I have had conversations with a number of people about the ethical dimensions of clinical trials. It just was reminding me that that procedure of running experiments with patients who are doing the best was something that was done very early at MD Anderson. The concerns about endangering patients that were doing well were something that kind of flowed through

discussions at the institution about doing clinical research. So I am wondering if you could talk a little bit more about how you see the ethical dimensions of clinical trials.

William Plunkett, PhD

0:17:47.3

Well, of course I am not involved in the responsibility of treating patients. I participated in the discussions, but I am certainly respectful of the consequences and the responsibilities of my clinical colleagues. So to come to the approach of building in very strong stopping rules, which would be what might be expected as the trials went forward—that is, by the time you enter—let's say—for example—if you enter five patients on this new protocol, and what you would expect if those patients had been treated on an older protocol is that six of the—about three of the five would have responded with complete remission. So then if you've got any fewer than that at that point, then you have to stop and stop the protocol and readjust so that those patients won't be at risk in bringing it forward in that fashion. But it is over longer periods of time—say, like at six months. But there are different guidelines. One is initial response, and another one is duration of initial response. So a large number, maybe as expected or greater than expected, may respond. But if they don't stay in remission for as long as expected then that would be a negative result because to stop the protocol and reassess—

Tacey Ann Rosolowski, PhD

0:19:41.1

What are some of—I mean—obviously the ethical considerations are really different for basic scientists versus clinical researchers. I am wondering how you would articulate your value system in your research practice.

William Plunkett, PhD

0:20:02.7

Well, sure. We try to do the right thing.

Tacey Ann Rosolowski, PhD

0:20:08.3

And that means?

William Plunkett, PhD

0:20:10.1

Well, that means a truth above everything. Always—you are always being truthful and reporting what you do not what you had hoped to do and so forth in terms of—if you are going to report that you did the experiment three times when this is the average of the result or representative of the result, you better have done the same experiment three times, for instance. So that pretty much has been a gold standard for reproducibility. You get that, and then average the results, and it's expected. There will be variability in biological systems. So that is credibility when you see error bars that show very little variability—that raises a red flag. Why would that be? That's chemistry. That's not biology. Chemistry, you can be quite precise.

Tacey Ann Rosolowski, PhD

0:21:13.7

Oh, okay. Interesting. Have there been any issues in your field that have caused you—I mean—I am thinking ethical issues in your field that have caused you to reflect on that in any kind of way or sort of recommit to this issue of truth above anything? I am just curious. I mean, I am not asking you to tell tales. This is a complicated field with—and as the stakes for doing work and succeeding get even higher, I think temptations are there.

William Plunkett, PhD

0:21:47.4

Well, there is that little line in my curriculum vitae that says I am the Institutional Research Integrity Officer, and that certainly has caused me to think. It's helped me become more aware of what the very specifics are that are demanded by the literal letter of the law and the difficulties that people encounter when—either by honest error, which is—it is an occurrence whenever people are involved there will be errors, and most of them are honest errors. We find, in my experience of being in this position over a period of five years now, little evidence of deliberate misrepresentation or manipulation of data. It is usually, well, what would be considered honest error. If it happened in my laboratory, I would call it sloppiness or carelessness, I guess, it would be. You may read the test, but you don't look at the figure, and you realize that the pictures have been duplicated by error—by mistake—you know when you have a panel of, say, micrographs or something and tissue sections. That is the most common thing, and they were our people in the community—scientific community—who are surveying the scientific community, who have image analysis software. And the literature is being scrutinized more intensively than ever. The errors are most frequently—this type of error which eventually can be investigated and shown by going back to original notebooks, original data—the experiment was done, the data are there—and showing that it was a mistake in the construction of the figure. That is our experience.

Tacey Ann Rosolowski, PhD

0:24:17.8

Interesting. Well, thanks for letting me derail you from your story. I just wanted to pick up on—I am aware that I did that.

Chapter 9

B: An Institutional Unit

The CLL Moon Shot Program

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Collaborations

A: The Administrator

C: Professional Practice

C: The Professional at Work

C: Discovery and Success

C: Patients, Treatment, Survivors

B: MD Anderson Snapshot

B: MD Anderson Impact

B: Institutional Processes

William Plunkett, PhD

0:24:29.0

No, that is okay. Actually, this is the outline for the talk that I am going to be giving in Bologna, so I have a little bit of a guideline to keep me in order. Right. So, let us go back to Dr. Huang's discoveries of the mechanisms of action of fludarabine. What this also showed is that it would be an effective inhibitor of repair of DNA damage. So then we developed a hypothesis that repair of DNA damage, which had always been thought to be the enemy of DNA-damaging agent chemotherapy, could actually be our friend. These compounds have to be—fludarabine has to be incorporated into DNA. The way that particular damage is repaired is by cutting out—excising the damaged portion of DNA, and then resynthesizing it. So if the active form of a nucleoside analogue is present at the time that is going on, then it may be incorporated into the DNA and even worse things can happen to the cell if you do not have a specific inhibitor of this type of DNA repair for the imaging agent. But fludarabine serves that purpose.

Tacey Ann Rosolowski, PhD

0:26:02.9

And what does happen to the cell?

William Plunkett, PhD

0:26:05.4

Well, then the cell struggles with—probably at the time of they are replicating DNA—it struggles to do it with fidelity. Then other sensors recognize the lesions in DNA. Then they either signal for—try to repair that, but fill in that. Then these sensors may signal for the death of the cell. That is a common mechanism by which we say teleologically that the cell has to die because it is damaged. You would not want it to go on and replicate itself with being a—with infidelity in that fashion. So it goes through a cell death process actually. This is part of what we were presenting at the AACR this—two days ago.

So that rationale was brought forward, and you may recognize, or I will tell you, that many of the cells in the tumor are not replicating their DNA. So a drug, like a nucleoside analogue, that has to be incorporated into DNA in order to be active, to do damage, would not be eligible because there is no DNA replication going on. But when it is used in combination with a DNA damaging agent which initiates this repair, removal, and re-synthesis of DNA, it may be incorporated. And because of its properties, one of which Dr. Huang demonstrated, once it gets into DNA it is very difficult to get it out of DNA. Then what we think of as—that could compromise the viability of the cells.

Fludarabine was brought forward clinically by Dr. Keating in B-cell lymphoid malignancies. His focus was on chronic lymphocytic leukemia. So after discussing and planning on how this might go, then he ran a clinical protocol of a DNA-damaging agent and fludarabine in sequence. First you make sure that the active form of the nucleoside fludarabine is there, and then you damage the DNA. Then you've got better clinical responses. And that reads out that way. So subsequently, that has formed the nucleus of—it became the gold standard for treatment—just that combination—the DNA damaging agent and fludarabine. But then subsequently, an antibody has been added to that, and the response rate has gone over 70%. Complete remission rate has gone over 70%. That has been validated in a large, randomized trial and shown to be preferable to the two-drug combination. Not only that, it is the first time that a real survival advantage has been shown in chronic lymphatic leukemia. So that is part of the basis for our CLL Moon Shot.

Okay, so that has been brought forward in that way. Dr. Keating and I are the leaders, although everybody—we have maybe fifteen nuclear people in the Moon Shot, and we are all very active. Dr. Keating and I do more of the administrative responsibility and sort of front man the ship, but that does not speak to really the contributions in bringing it forward—that designation.

Tacey Ann Rosolowski, PhD

0:30:45.6

Now, last time you talked about the four clinical areas of clinical investigation that are going to take place under the Moon Shots for leukemia. I am curious about what this foundational work with fludarabine and this other agent establish. What do you hope—? Where are you hoping to go from there?

William Plunkett, PhD

0:31:07.8

Okay.

Tacey Ann Rosolowski, PhD

0:31:08.3

What was promised?

William Plunkett, PhD

0:31:08.9

Yeah. Well, it is a little bit of a turnaround, because I have been speaking of damaging DNA and blocking DNA repair. When people do not live very long, you cannot see, perhaps, what might be the consequences of that until the therapy becomes so effective that people are—a substantial portion—30-40%—are living ten years or longer. Then what we are noticing and the data managers are noticing is that our former patients are getting secondary malignancies, and it is secondary malignancies at a higher rate than what the average population—those malignancies arising in the population that did not have CLL, and we have not treated with this. So then you say, “Well, likely this could be therapy-related induction of malignancies.” So what we are trying to do then is to go away from the strategies that have brought us to where we are to a more biologically based therapy—knowing more about how chronic lymphocytic leukemia arises and that’s the pathogenesis of it, and what keeps it going, which is the path of physiology of the disease.

It’s difficult at the present time to target pathogenesis, so many of our strategies then are aimed at the pathophysiology. So for instance, there are—the newest therapy that has received conditional approval from the FDA is aimed at the B-cell’s signaling pathway. And with therapies that have been seen—that have been tried—targeting two elements of this B-cell signaling pathway, then they seem to be giving more favorable results, or as favorable results as we might get, with what we call chemoimmunotherapy. That is the drugs plus the antibody, okay? So going ahead with that and exploring that, and then we will see how—combinations are under investigation. Some combinations do involve cytotoxic drugs, but not as much as previously. But that is what we are thinking is that we should be developing therapeutic regimens that go away from the cytotoxic chemotherapy which has a relatively less specificity and is not aimed at either what causes the disease or what, in particular, keeps the disease spreading and is responsible for the survival of the disease.

Another example of the pathophysiology of the disease that is being targeted is a family of proteins that are highly expressed in CLL that they keep the cells surviving. They’re pro-survival proteins of the Bcl2 family. Specific drugs have been made elsewhere to interfere with their functions, and those are under investigation here. When these drugs were applied to cells in—CLL cells in the laboratory and in the initial studies in patients, they seem to be quite active and quite specific for CLL.

We have another strategy that we have developed here that is aimed at the same family of drugs. Based on what we have learned and know about their metabolism—they turn over quite rapidly—our strategy has been to transiently block the synthesis of these compounds although it may affect the synthesis of many proteins. The hypothesis that is being bored out now is that chronic lymphocytic leukemia, in a sense, requires the constant presence of these proteins in order to stave off cell death mechanisms. The transient depletion of those proteins over a period of only as little as eight to twelve hours results in onset of irreversible cell death processes. That is your apoptosis process. So that is specifically aimed at the pathophysiology of the disease.

Tacey Ann Rosolowski, PhD

0:37:10.8

Interesting. And so those trials are also part of the CLL Moon Shot program? Or is that separate?

William Plunkett, PhD

0:37:18.1

In large, they are. The way that the CLL Moon Shot program is being brought forward at these initials stages is that we have identified flagship protocols or approaches that we want to pursue first. These are the ones that are either the most—appear to be most promising or most urgent to pursue, most likely to produce results that will be important for the future of medical management of CLL, in our case. So we are just focused on that. And then subsequently, they will come up with other Moon Shot proposals. That is the subject of our discussions tomorrow. That is, the CLL group is discussing what is going to be next. So we have one proposal that deals with that, and we have the second flagship protocol that our cell therapy group has brought forward. But that can't be implemented immediately with as much intensity as the one that we are focused on.

See, the agent—the center—that this is centered on is an inhibitor of this Bruton's tyrosine kinase, and it is controlled by a pharmaceutical company. The pharmaceutical company has delineated in part with our input into the design and evaluation for clinical trials. But those trials are open and ongoing, so you can't hesitate or the multicenter trials—three of the four are multi-centered trials, so if they are not done by us, they will be done by others. But as it's turning out, we have the patients—the patient population—that would accrue on those trials, and we expect to enter the majority of the patients on each of the three trials that I am speaking about and all of the patients on the fourth trial. We will then be seen—we see ourselves as the leaders in that respect, although some people have similar views of themselves. But we have a large number of patients who are very aware of new developments in the field of CLL therapies—totally Internet savvy. They will come with a sheath of papers saying, “Your protocol is this, and a different medical center is that, and what is the difference?” and really shopping to find the drug that they feel that they should be treated with based on blogs and websites and news releases as they come available.

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Tacey Ann Rosolowski, PhD

0:40:31.1

Has that had an influence on the trials themselves, or what's the impact of that patient savvy?

William Plunkett, PhD

0:40:47.3

Well, it is attractive to us if we have access to the compounds. We have extremely effective referral systems and networks that let it be known, so there will be a group of patients who have been screened. Their medical condition makes them eligible for entry onto the protocol, and they will be lined up as slots become available.

Tacey Ann Rosolowski, PhD

0:41:15.9

So it just eases the process—speeds the process, I guess.

William Plunkett, PhD

0:41:19.9

It does, yeah.

Tacey Ann Rosolowski, PhD

0:41:22.1

Now, what is the time frame that you are looking at for this Moon Shot program? Are there different time frames for them? How did that all work?

William Plunkett, PhD

0:41:35.4

Well, each—yes, there were different time frames. This is the short-term time frame. There are longer-term time frames in terms of, say, just understanding the genetics, how the genetic changes influence the progress of the disease. These are longitudinal studies—over time—some of which can be done by samples that we have in our archives and tissue banks. In others, we may want to be prospective. In a longer time frame, understanding of the basis for, or the etiology of, CLL—what drives that—then that would be a basis for prevention strategies that would be brought forward in the future. But those—that whole time frame is under consideration. Dr. DePinho has asked us to think on those terms, although in these initial stages of the Moon Shot, we are being asked to focus on short-term goals.

Tacey Ann Rosolowski, PhD

0:43:04.0

One of the things I have been thinking about is this whole issue of the team science that the Moon Shots has really formalized in a big way. I'm wondering if you can talk about the challenges of that, the benefits of doing science in that particular way, and since you are in a leadership role with one of these projects, what it means to lead individuals.

William Plunkett, PhD

0:43:35.7

I would say that what we have been discussing provides evidence for my evaluation that my whole career as an independent investigator has been influenced by and certainly benefitted from a team science approach. I came here and very quickly recognized the potential for interacting with my clinical colleagues to be able to generate information that otherwise was not available anywhere initially about how drugs are metabolized in tumor cells during therapy. This is in leukemia. This is something that is possible. Then a subsequent step is understanding how the tumor cells respond to those drugs. That could be associated with either a response or resistance. Those are questions that are just fascinating to me to try to tackle, to approach. It is just interesting that you come here at this time. Sorry. So this is—I have this quote from Louis Pasteur, and it deals with applied research and basic research. And so this is—I do not have the year on this, but obviously it is a century old. He says, “To the individual who devotes his or her life to science, nothing can give more happiness than when the results immediately find practical application. There are not two sciences. There is science and the application of science, and the two are linked as the fruit is to the tree.” That is where I have chosen to do my research, at that level. So there will be—you know—it is a spectrum of how you want to approach things. And it is partitioning in part— Understanding the mechanism of action at a molecular level of a particular drug is pretty basic, and how cells respond to that. But on the other hand, the response curves that our colleagues read out by having the faith in our experimental rationale and preliminary of the results that we have generated, models that are credible with regard to the disease, and then writing a protocol and testing it in patients is about as good as it gets for laboratory people.

Chapter 10

A: The Administrator

Team Science and Training Team Scientists

Story Codes

A: The Researcher

D: On Research and Researchers

A: Overview

D: Understanding Cancer, the History of Science, Cancer Research

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

B: MD Anderson Culture

C: Collaborations

A: The Administrator

C: Professional Practice

C: The Professional at Work

C: Discovery and Success

A: The Educator

B: MD Anderson Culture

C: Understanding the Institution

Tacey Ann Rosolowski, PhD

0:46:51.6

Do you think that there are different mindsets or perspectives between people who gravitate toward these more collaborative models of research versus those who choose to take a more independent route? I am thinking about this in the context of—it seems from the conversations I've had with people, when you entered the field in the '70s and certainly in the '60s, the assumption was that the scientist operated independently. Then there were those among you who chose to get into multidisciplinary or translational research interaction, whereas now, a number of years later, it is an expectation that you are going to do science as a team whether or not you may have been prepared to do that.

William Plunkett, PhD

0:47:40.9

Well, not always.

Tacey Ann Rosolowski, PhD

0:47:42.0

Not always?

William Plunkett, PhD

0:47:42.9

I think there is a— So what you are describing is the traditional view of the individual who runs

his or her research laboratory establishment and is the driving force on the discoveries that are made. That is the principle investigator of the investigator initiated grant request—R01. It has been recognized by the NCI, as you suggested in general, that team science is valued, and the contributions of team science—where it comes into play—is valued. So then you get the multi-PI grant requests. The grant is what enables you to do your research and follow your hypotheses and test them. That is not the end point. The testing of the hypothesis is the end point. Still, the overall—so this is the basis for promotion and, of course, for tenure. Are you the first author or the last author? And as you move on in your career, it is thought that you should be last author and your trainees should precede you on the authorship list. So each of the last two presidents, for sure, have emphasized the importance of team science. Dr. DePinho, no less, and he is certainly the paradigm of a very top laboratory scientist bringing it into animal models in a very molecular and defined way. Dr. [John] Mendelsohn had a track record of trying to develop—be involved in patient treatment directly but also bringing things to the clinic. But he was very supportive of team science and recognizing that.

We have awards now, so let's just say at the AACR meeting there is an award for team science. I think it's in its sixth or seventh year of being awarded. The head of our division of cancer medicine, Dr. Huang, is an extremely strong advocate of team science. He created an award for team members in the Division of Cancer Medicine—now over 300 faculty members—who participate in this. And in fact, the CLL group—not all of whom, as in the Division of Cancer Medicine—won that award last year.

I think it is extremely important, although there are vestiges of the evaluation system when it comes to promotion and tenure that calls people back to the age-old idea that the R01 grant is the coinage of the academic realm. I am quite familiar with that on—in our evaluation of laboratory research space, one of the first things that is asked is, if the person is a professor, does that professor have two R01 grants or equivalents—that is, an investigated or initiated grants as a means of evaluating that start for accomplishment of pursuing research. So it certainly is there, but I am sure that every year either the provost or the president speaks to the Promotion and Tenure Committee and says, “We really value team science. We value education.” And then somehow the committee needs—is hearing that message and going forward with it.

Tacey Ann Rosolowski, PhD

0:52:22.3

I want to ask you about training people to do team science, but I know that maybe we can reserve that for another time, because I know you are very—another part of this—of the interview—because I know you are very interested in teaching.

William Plunkett, PhD

0:52:36.9

Yes.

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Tacey Ann Rosolowski, PhD

0:52:36.9

Unless you want to talk about it now?

William Plunkett, PhD

0:52:37.6

Well, that is a magnet for people coming to this laboratory—my laboratory.

Tacey Ann Rosolowski, PhD

0:52:42.3

Oh, okay.

William Plunkett, PhD

0:52:43.8

Always had been, but we would go to—we would present data at national or international meetings illustrating interdisciplinary approaches to therapeutics. We initially called it—when I started with Dr. Freireich’s enthusiasm and Dr. McCreadie’s enthusiasm behind this, we called it “hypothesis testing” in the clinic. And then it became—those very activities became known as translational research, where they stand today.

Tacey Ann Rosolowski, PhD

0:53:23.7

Now, I’m sorry. I think I missed—what is the formal status of this? Is it—?

William Plunkett, PhD

0:53:29.0

It is what we do.

Tacey Ann Rosolowski, PhD

0:53:30.4

Okay. So it’s not like a name of a particular training program. It’s just the entire philosophy.

William Plunkett, PhD

0:53:34.2

No. It’s what we call it. Right.

Tacey Ann Rosolowski, PhD

0:53:35.4

It’s the philosophy of the entire department.

William Plunkett, PhD

0:53:36.8

Well, see, when we started it—when we started with it, I am sure there were people who were

taking samples from individuals, but certainly we systemized it in a—over a pharmacologic time span and had access to tumor cells that had not been done in leukemia and then brought that forward. Then people wanted to learn that. So a lot of my initial trainees, many of them coming from Europe and Japan, came here at the urging of their mentors to learn how to participate in that.

Tacey Ann Rosolowski, PhD

0:54:24.3

Now, you've talked about the intellectual dimensions of that in our last conversation and reviewed some of those principles today as well, but I'm wondering what other kinds of skills are required for a scientist to really be able to participate completely successfully in team science? Because it seems like there are some—maybe on a personal scale of—well, I don't want to put the words in your mouth. You're the one who has grappled with these issues. What have you seen, and how have you facilitated that process?

William Plunkett, PhD

0:54:57.9

Well, I think that—well, you've hit that right. It extends from a laboratory—outside the laboratory—to colleagues that you wish to interact with. It is exceedingly important, and I always emphasize, particularly in the laboratory, where I can really do something about it is the fit of people to our laboratory and our culture.

Tacey Ann Rosolowski, PhD

0:55:33.0

How would you describe that culture?

William Plunkett, PhD

0:55:36.9

That it is friendly and congenial and collaborative and interacting. People interact and help their colleagues without asking for direct payback with authorship. I mean, when we recognize that that is justified, fine, but if you are dealing with a technique, it is a technique. If it is sharing reagents, it is that. And we have that sort of culture. That culture exists between laboratories, and when you have it going in your own laboratory, I have seen that it spreads to other laboratories around to you. Not that it may not and not that they don't have that sort of environment themselves, but we benefit from it because this is assistance that spreads down the hallway or assistance that people, colleagues, wherever, when they know one another, will help with one another. And I find people coming back to the laboratory with new ideas, new results that I hadn't known that they were pursuing. I like to have people do their own thing, and then we come and discuss it with the original data. Not always; it depends. It is based on the individual.

Tacey Ann Rosolowski, PhD

0:57:12.1

What qualities do you look for when someone comes and expresses an interest in becoming—being a trainee in this lab—in the system of labs?

William Plunkett, PhD

0:57:23.6

Well, certainly earnestness in terms of they are not just here for a salary and that they want to be here to develop their careers and do something with their careers. You know, it is practically every day that you have inquiries coming in on the Internet—you know—“I have read all of your papers, and I am very impressed,” and so forth. And, “I would like to be able to work in your neurology experiments,” with which of course I have nothing to—but they are just sending off a form letter. You talk with colleagues, and they will get a same letter. That is just—people just spotting around the whole institution regardless and without being specific as to what their background is and so forth.

On the other hand, one of my very best technical assistants ever came to me with—she had a degree in philosophy, and her dad happened to be on faculty. She was really determined that this was something that she wanted to grow out and then look towards maybe a nursing career or something. I said, “No, no. You do not have any background in this.” She said, “Well, I will be taking courses in biology.” Okay, that is good; you go take them. She was so insistent that I said—finally I said, “Okay, we are going to try this for a month with the tacit agreement that if it doesn’t work out you’ll leave.” I told you what the endpoint is. She was just determined to make it work.

So you have ways of taking fluid out of containers and so forth. They are called pipettes. And I found in her—and people do not think about—they come in one, five, and ten, and so forth, in different areas. Now we are down in very small quantities as well. I looked in her notebook at a time when she first left to go to nursing school. I looked in her very beginning notebook, and she says, “Well, the five millimeter pipette is the one with blue on it.” What was I dealing with?

Tacey Ann Rosolowski, PhD

1:00:06.1

But she obviously had it; she had something.

William Plunkett, PhD

1:00:07.9

Yes. Yes, she really did. She did get a nursing degree, and she came back as—in our lab—as a research nurse. But it is not really doing what the job description of research nurse at MD Anderson describes, and it is not the pay that MD Anderson research nurses get. She worked directly with patients and was certified as a phlebotomist and so forth and had a very good bedside manner and rapport. Taking blood samples at the time was a major part of the job description as well as working up those blood samples in the laboratory for the various biochemical analyses. Eventually she went and became part of the leukemia section, and she trained the next one—the next person who took over that position. The next person already was a

nurse, but she was from China, so she couldn't be certified in Texas because her nursing degree was three years behind. Subsequently she realized that if she were certified in California, which did not have this three-year time period—California and Texas had reciprocity, so she went back door on that. She is a nurse in the leukemia department now—research nurse.

Chapter 11

A: The Educator

Mentoring, Education, and Team-Science Culture

Story Codes

D: On Mentoring

A: The Educator

A: The Administrator

A: The Mentor

C: Mentoring

B: Education

C: Portraits

B: MD Anderson Culture

C: The MD Anderson Ethos

C: Diversity at MD Anderson

C: Understanding the Institution

A: Professional Values, Ethics, Purpose

B: Institutional Mission and Values

Tacey Ann Rosolowski, PhD

1:01:43.3

I wanted to ask you, too, about Doctors Huang and Gandhi.

William Plunkett, PhD

1:01:47.2

Yes.

Tacey Ann Rosolowski, PhD

1:01:47.6

Because it seems the very fact that you wanted to tell their particular research stories—I was curious if you had a mentoring kind of role with them?

William Plunkett, PhD

1:01:59.3

Yes. Sure.

Tacey Ann Rosolowski, PhD

1:02:00.9

Maybe you could tell me about that and what you think are the important qualities of a mentor, particularly in a very multidisciplinary, team-oriented context such as this.

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William Plunkett, PhD

1:02:13.2

Well, I think mentoring—one, I believe in mentoring by example, but on the other hand, understanding when people are ready to know the things about their academic environment other than research and making that available to them and letting them know how certain procedures work. For instance, in promotion, how do you get promoted from being a postdoc to the next step and the next step? And how do you get on to faculty? That is certainly one of the most difficult tasks for a trainee here is to be trained in a laboratory at MD Anderson and then come on to faculty in a research position.

Tacey Ann Rosolowski, PhD

1:03:06.1

What are the impediments there that have to be—?

William Plunkett, PhD

1:03:07.7

They think, well, if they have Plunkett, they do not need X or Y if they are doing the same thing. So what they have to do is learn how to—is propose to do something different than Plunkett and add other value. Although they have the value of having trained in this laboratory environment and been productive here, for sure, because those two certainly were very productive—is that—then I have to—what I have done is to allow them to start off on individual areas that they can identify as their own, that's not me. I'm not a member. I'm not participating on their publications. With Dr. Huang, he was recruited into another department. It was a completely different project from what I was directly working on, although I was particularly interested in what he is doing. He just took the whole project with him, and that has become the foundation of his research for which he is internationally renowned right now.

Tacey Ann Rosolowski, PhD

1:04:26.2

It kind of reminds me of what you did when you were in Philadelphia or working—I am sorry. I am forgetting—

William Plunkett, PhD

1:04:32.4

Yes, Philly and then Colorado.

Tacey Ann Rosolowski, PhD

1:04:33.8

Yes. I was saying, yes, this person thought, “Well, you’re kind of out there doing your own thing, but he let you do it.”

William Plunkett, PhD

1:04:39.9

Oh, yeah. That's my graduate guy.

Tacey Ann Rosolowski, PhD

1:04:42.6

Yes.

William Plunkett, PhD

1:04:44.5

Well, maybe that was influential.

Tacey Ann Rosolowski, PhD

1:04:45.8

Yes, well, that importance of being allowed to—

William Plunkett, PhD

1:04:49.5

Well, if you have the curiosity—this was her, Varsha's, own curiosity. She put the experiments together and then came to me with that. That is why we call it the founder experiment. Of all of that work that came through —

Tacey Ann Rosolowski, PhD

1:05:07.9

I mean, that is really—

William Plunkett, PhD

1:05:08.5

And we both take pride in it.

Tacey Ann Rosolowski, PhD

1:05:10.3

—independent spirit—you know—really a kind of courage to go off and trying to forge ahead.

William Plunkett, PhD

1:05:16.1

Well, she was just ready to start at the time. But subsequently, because she is so accomplished and so fluent and recognized as a leader in areas that she seeks to pursue, she wasn't all that greatly differentiated from me, but she had the—certainly she had the opportunity to speak at meetings where groups from MD Anderson might be speaking at meetings. People could hear her, listen to her answers to questions, speak with her, totally—it is—and she just has that very pleasant, outgoing spirit. She is not shy to introduce herself and develop her own career in that

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way. She was the one I was telling you about, who was the example now of the white-knuckle handshake, to illustrate to our trainees how you greet people when you meet them.

Tacey Ann Rosolowski, PhD

1:06:29.4

Why do you think that is so important?

William Plunkett, PhD

1:06:31.4

It is an American trait, and you are living in America, so get with it. It lets people know that you are—that you appreciate what is American, whereas other cultures either do not have handshakes or do not participate the way Americans do.

Tacey Ann Rosolowski, PhD

1:07:00.8

And just for the recorder, we were talking before the recorder was on about the prevalence of the very soft, unassertive handshakes as a greeting and how that can really put people off.

William Plunkett, PhD

1:07:15.4

Yes.

Tacey Ann Rosolowski, PhD

1:07:15.9

Put Americans off, yes.

William Plunkett, PhD

1:07:18.9

Yes. Dr. Gandhi is known as the knuckle cracker.

Tacey Ann Rosolowski, PhD

1:07:24.8

Well, good for her.

William Plunkett, PhD

1:07:26.1

Well, when you meet her, you wouldn't think that at first. Similarly, Dr. Huang—there is no question when you shake hands with him you are going to be looking at him.

Tacey Ann Rosolowski, PhD

1:07:41.2

That's good?

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William Plunkett, PhD

1:07:41.6

Yes.

Tacey Ann Rosolowski, PhD

1:07:41.7

Are there any other—because you shepherded these individuals from trainee status—from fellow graduate student status into faculty. What about young faculty who come here? What kind of mentoring do they need?

William Plunkett, PhD

1:08:01.2

Well, so we are aware of that. Our department is—Experimental Therapeutics—is pretty much top heavy with people in the higher ranks—professors. When we set out a strategic plan when Dr. [Garth] Powis came here originally, I was the Director of Research at the time and chaired the Strategic Plan Committee. One of the appointments was an education program, and that focused largely on graduate education, but it had elements of mentorship in it. Then Dr. Gandhi became head of the faculty development in education. It was she who really grew out the mentorship in the Department of Experimental Therapeutics, designed it in collaboration and so forth, but she was obviously the director of it.

So we have a mentorship program that goes from—that takes in junior faculty, non-tenure track or research faculty, appointment faculty, and also the junior faculty who are tenure track or associate professors. They speak with the—their mentors are—they choose their mentors from within the department. I think there may be some who choose mentors outside of the department who will participate in this. They just sit down once a year—I think it is once a year—and have these discussions. How are you doing? Are you on track?

You may not know, but there is a policy for junior faculty development, assistant professor development. It is that they will get a mid-tenure track review. So at three to four years, are you on target? Are you doing the right things? Do you need to do something else to make sure that you are successful in reaching the next step in your career? This is meant to align with that, and this will be more frequent in leading up to it. But you point to that, and this is what you need to do. It's letting people know what the expectations are in terms of the faculty.

Now, Dr. Gandhi also set up a postdoctoral mentoring program and developed a notebook of all useful information of, okay, now you are a postdoc. This is where you are supposed to be working to get your—whatever your career is going to develop into, at least initially. So it provides a mentorship for postdoc. So postdocs then go and speak with faculty members. They have to speak with their own faculty as well, but it is clear that they are welcomed. The NCI is saying that each institution has to have a postdoctoral mentoring awareness if not a particular program. That was coming forward in our institution under Dr. [Stephen] Tomasovic, when he was the senior vice president for Academic Affairs. I am not exactly sure what happened to that.

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I haven't seen it. I think perhaps we are—lately, I think we are able to pursue our postdoctoral mentoring program as a—in separate paths if that is active. There was some thought that our program might serve as a template for the development of a broader implementation of a postdoctoral mentoring program because the graduate students are mentored on a regular basis—every six months by committee—so they have—depending on where they are on their progression towards their degree.

Tacey Ann Rosolowski, PhD

1:12:17.8

Just as you are describing the way this program has been formalized, it already sounds a little bit different than kind of the classic model of mentoring, which is—you know—someone who pops into somebody's office on a regular basis to ask a question.

William Plunkett, PhD

1:12:36.4

Yes, I'm going to address that.

Tacey Ann Rosolowski, PhD

1:12:37.8

I'm wondering what your observations are about how mentoring has changed just because of the increase in responsibilities and the time stress and all of that?

William Plunkett, PhD

1:12:52.4

Well, personally, this discussion is the only time this door is closed. Otherwise it's always open. I encourage my trainees to come by when they have something to talk about. Preferably they make an appointment, but I don't have set appointments with them at particular times each week. Pardon me; this is—

Tacey Ann Rosolowski, PhD

1:13:21.1

Should I pause the recorder for a sec? Okay.

William Plunkett, PhD

1:13:28.7

So part of the laboratory environment is also part of the—I think—part of the mentoring, and that is you try to make information available in a transparent manner—you know—appropriately. There are some things that some people would benefit from and some people—and some things that other people do not need to know. We do this on a weekly basis in a lab group. Dr. Gandhi and I have lab groups that traditionally have met together. At one time, when Dr. Huang was in association with us, as he was on faculty as well, we would meet as a whole group and there would be other PIs from—coming—when we were in the north campus—

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bringing their students in who wanted to participate in journal clubs and research meetings and things.

Tacey Ann Rosolowski, PhD

1:14:24.2

And the subjects of discussion would be? I mean, just generally, what—?

William Plunkett, PhD

1:14:28.2

Well, Journal Club you present—the individual—and we all participate—faculty as well—select a journal article. It becomes available as a PDF file to everybody in the group, and the responsibility is to read it, to be familiar with it, and then be prepared to—the presenter will present it, and then try to elicit discussion from that. So you're hearing some new research every week. It's not just what you're doing on your lab bench.

Tacey Ann Rosolowski, PhD

1:15:04.0

Right. And then there is all the critical skills and learning the vocabulary to communicate with other specialties and all that.

William Plunkett, PhD

1:15:09.1

Right. So then there is the second aspect of it, and that's the research meeting, and we hold those together as well. It's part of the same meeting. It's when a—then it will be a trainee who will present his or her research so other people in the lab will know what is happening. So we are—our laboratory is open among people, about one another, about what we all are doing, what the hypothesis is, and what we are pursuing. I would say that that is not the way in some laboratories. Some laboratories are just so large it is impossible. Some laboratories are designed so that you are going to work on this, and do not talk to anybody else about it. So I think not participating in the latter sort of activity—I haven't found it necessary, and I certainly don't find it desirable. The meeting is a way of letting students know—trainees know—that this is the way that we can all know what is going on and potentially help one another, and it provides an opportunity for the extension of that collegial—building collegiality among the group. When there is somebody who comes in who messes up an instrument and doesn't get it fixed, it becomes apparent immediately because people know. It's not sign up lists.

Tacey Ann Rosolowski, PhD

1:16:48.3

There is again that culture of the group working.

William Plunkett, PhD

1:16:49.6

Yes. Right. And there will be this buzz and—

Tacey Ann Rosolowski, PhD

1:16:55.1

A little group enforcement there.

William Plunkett, PhD

1:16:56.5

Yes. And then somebody will come in here.

Tacey Ann Rosolowski, PhD

1:17:02.0

All right. Well, thank you for again digressing on that. That was important. Is there—?

William Plunkett, PhD

1:17:07.2

That is very—that has been very important to me, and it is an element that I think we share with the people that we collaborate with.

Tacey Ann Rosolowski, PhD

1:17:18.0

Is there more that you would like to say about the training initiatives? Have we kind of hit on the high points of that for you?

William Plunkett, PhD

1:17:29.4

I have tried to. In the past we have had medical fellows, but we do not see medical fellows so much now. I am not sure whether it is the prevalence of physician-scientists having laboratories and they can—they have a closer presence with medical fellows, and therefore they can speak an extended language that would extend into the clinic and allow them to participate in that fashion. That is probably good for the fellow; it could be. But we do not have the experience of having those—the fellows in the lab. Actually, the fellows that I had in my lab, they were pretty highly awarded and honored outside of here, so I wasn't unhappy about what their experience had been. Then they went on to get good positions outside of Anderson after, I think, going to faculty first and then going elsewhere.

Tacey Ann Rosolowski, PhD

1:18:42.7

So providing solid training.

William Plunkett, PhD

1:18:45.4

Yes. That is what we try to do.

Tacey Ann Rosolowski, PhD

1:18:48.4

What about the physician-scientists? A number of people have just kind of almost looked despairing when they speak about the burdens placed on physician-scientists—a kind of do-it-all. I'm wondering if you have that perspective as well that it's—that in a sense—do you feel the institution is as well set up as it might be to support a physician—career development as a physician-scientist?

William Plunkett, PhD

1:19:17.6

Well, I think opportunity is here, but there are competing responsibilities that are placed on physician-scientists. You know, one—surprisingly—might be you try to didactically educate them, and they have to go to courses and courses, whereas you are thinking they might be in the clinic or they might in the laboratory or they might be writing or this type of thing. So there are so many things that they are responsible to do that probably—almost certainly—are well intended. I think the success of our medical fellowship program is just astounding. They are at the very top in terms of our fellows being recognized by national societies and given awards in career development and so forth. So whatever they are doing, I think they are probably doing a good job of it.

Tacey Ann Rosolowski, PhD

1:20:27.5

Is there anything else you want to comment on about training and—?

William Plunkett, PhD

1:20:33.5

Well, I think it is a tough row to hoe. You read letters. You read publications that say, “Is the physician-scientist an endangered species?” Those have been coming out for a couple of decades now. It is very difficult—very difficult to fulfill—both as a trainee and practice as a faculty member—to fulfill the responsibilities of a physician-scientist and maintain a high-level, competitive laboratory and be able to fulfill your clinical responsibilities, which at Anderson frequently is clinical research. So it requires writing protocols and so forth and trying to take observations from your laboratory, other laboratories, and to test them in the clinic. It's really—when it works it's quite exciting and, I'm sure, quite rewarding, even without working on it directly in the clinic, although we have laboratory collaborative investigations going on in many protocols that we have initiated and that we are participating in that are exceedingly, I feel, really rewarding for myself and for other people. As I have mentioned, that is why some people have wanted to come and train or get the opportunity to do that here and then take it away and do it someplace else.

Tacey Ann Rosolowski, PhD

1:22:11.5

I noticed in your background materials you note a couple of times that you are very, very

committed to education and to training. I'm wondering—it may seem obvious—why? What has driven that commitment for you?

William Plunkett, PhD

1:22:27.8

Well, somebody has to supersede us. I mean, after all, we're—you can't train or bring up the next generation if you're standing in your way. That is the idea of people who are experienced not taking up every opportunity that comes along even though you may be qualified for it. It is the same idea of let's not see the same hands all the time. I am absolutely certain that we, as a country and the world, really need a new generation of scientists coming along, and I am seeing more and more here, for sure—trainees from other countries. Many of them stay here and are great contributors, and that is fine, but I would like to be able to impress our own—I do not have anything really to do with getting, say, Texans or Americans to go into a particular area, but you just have to make the area as good as you can and as attractive as you can and participate in whatever means that—whatever you do to make it seem like—make people understand what a fulfilling experience it could be on many levels. That's how I feel about the opportunity that I have had here.

Tacey Ann Rosolowski, PhD

1:24:14.8

What in particular has kept you so committed—has kept you in your field? What is it that has driven you?

William Plunkett, PhD

1:24:22.3

Well, now, it's success and progress in the end product, really. It's having—with a few colleagues—having made personal commitment to contribute. Let's be realistic and appropriately modest to contribute to the cure of a particular disease. If you see other opportunities to contribute anywhere else, that is fine. I am happy to participate in that. But I want to have—I am looking at an end product now, particularly since I am near the end of my career and certainly in running a research laboratory, that I think—I don't know—I don't have any particular plans. But you have to—you don't want to look back and say, "Gee, I wish I had planned that." So I am going to act that way. I have oriented my laboratory more towards overtly clinically relevant questions to answer—things that could be directly applied to clinical aspects.

Chapter 12

A: The Researcher

Research with Gemcitabine

Story Codes

A: The Researcher

D: On Research and Researchers

D: On Pharmaceutical Companies and Industry

A: Overview

A: Definitions, Explanations, Translations

B: Multi-disciplinary Approaches

C: Collaborations

D: Understanding Cancer, the History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

1:25:46.7

It sounds like a good moment to maybe go back to your research story.

William Plunkett, PhD

1:25:51.1

Okay. All right.

Tacey Ann Rosolowski, PhD

1:25:53.8

If you would like to do that.

William Plunkett, PhD

1:25:54.3

Well, I am not sure if I mentioned in addition to fludarabine there is one other drug that our group played a substantial role in developing. The drug now is known as gemcitabine—G-E-M-C-I-T-A-B-I-N-E. I may have mentioned colleagues and friends in pharmaceutical companies. One who was in academics—and I knew him the—and went to pharmaceutical companies in the early 1980s was Gerald Grindey. There was a time when several of my friends were recruited—or the pharmaceutical companies were recognizing the potential benefit for developing oncology drugs. They needed to do—have a setup for doing that within their organization. So that involved maybe—largely it was drug discovery at the time, because specific targets weren't known as they are today and how to bring it through testing and presentation to the FDA for use in—for evaluation in humans. Grindey was the person that was chosen by Eli Lilly. He took the job there, and they built a beautiful facility at Eli Lilly. This was their first initiative in oncology. One of his colleagues there was a synthetic organic chemist, and his compounds were being tested as antivirals. They recognized in the screen that no viruses were growing up, but when they looked closely at the plates they realized all the cells were dead. So Grindey said, "Give me that. That is

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not so much an antiviral, but it is an anticancer drug—a potential anticancer drug.” So he took it. They worked on it for some time, a couple of years, and then after some going back and forth with him we had—because of prior work that we had done with this drug cytarabine, which is structurally related and likely metabolically related, that we had done and worked on in the clinic as well, they came to make an agreement with us that my laboratory would be the first that would receive this drug. Lily was clearly going to develop it in the clinic, and it was in the clinic within a year. Here was where the first patient was given a dose of gemcitabine.

Dr. Abbruzzese and Dr. [Martin] Raber [Oral History Interview] were the PIs on that protocol. Dr. Abbruzzese is now head of GI Oncology. So really we were set up to investigate this. It was a matter of giving it to one postdoc who was really in hyper speed in terms of knowing what to do, seeing an opportunity when it presented itself, and a couple of really experienced technical people in the laboratory. I think we had that in September 1986, and abstracts for the AACR meeting were due in late November. We had two abstracts in there at that time. It was presented at the AACR meeting in 1987. It was quite clearly something that was really different, particularly this postdoctoral fellow, Volker Heinemann, who subsequently went back to Germany. He is a leader there now.

Tacey Ann Rosolowski, PhD

1:30:34.6

I am sorry; his last name was?

William Plunkett, PhD

1:30:35.5

Heinemann—H-E-I-N-E-M-N-N. He was really quite a thoughtful man, and he came up with—over a period of two years—came up with some—he made observations that led him to think about how this possibly could be.

Tacey Ann Rosolowski, PhD

1:31:11.7

I am sorry; what exactly would it do that was so different?

William Plunkett, PhD

1:31:16.3

Structurally it is different, and that was exciting. It was the second drug of this particular class of drugs that I am speaking of—pyrimidine nucleoside analogues—and I think also Grindey had done some hyping around the community and wouldn't let anybody have it at the time.

Tacey Ann Rosolowski, PhD

1:31:40.8

Right.

William Plunkett, PhD

1:31:44.8

And it also—our group had a reputation for doing this type of investigation. We had a fairly complete story and a couple of posters just with posters, and then the manuscripts and publications followed in 1988. Then it was going into clinical trials. So it is interesting to know this about the different properties, particularly if properties are different than what has come before about a new agent as it goes into clinical trial. Then you can have the opportunity to look for—in this case, it was being evaluated in solid tumors. So we are evaluating its metabolism in the surrogate endpoint of circulating the peripheral blood in mononucleosis cells, meaning the lymphocytes. That followed shortly—but I was getting to the point that he came up with a series of metabolic pathways and mechanisms by which this—the active metabolite of this drug—of gemcitabine—was retained in the cell for much longer than anything that had been seen before, which has implications for scheduling. That is, if the active metabolite is there, you do not have to give it again soon, then a series of things about how it influenced—how the metabolites of gemcitabine influenced the zoned success. It is called self-potential.

Tacey Ann Rosolowski, PhD

1:33:40.2

Interesting.

William Plunkett, PhD

1:33:42.1

It also was an inhibitor of this enzyme that I mentioned with regard to fludarabine—ribonucleotide reductase. We showed that first, and then, terrific, biochemists at MIT showed by mechanism that it actually killed the enzyme. It alkylated the enzyme. So the enzyme had to be resynthesized. It is not just inhibiting it transiently and going away. Likely that has something to do with its clinical activity, it seems.

I am telling you the story because it is something that made it, and it made it big in the sense that it became a multibillion dollar drug for Eli Lilly. The synthetic organic chemist who made it got his one dollar. It was a real struggle for Dr. Grindey to maintain it on track to make sure that the company kept supporting it.

Tacey Ann Rosolowski, PhD

1:34:50.9

Really? Why?

William Plunkett, PhD

1:34:54.5

You know. That's a question that can be asked of any management team or any company large or small—"Why did you do this?" They have their own rationale for doing things or what they want to bring forward, and somehow they hire people who are experts in mechanism or metabolism and evaluating it in an animal model, and yet they want to make their own decisions

at the management level. I was certain that this was going to be a terrific anti-leukemia drug simply because of its mechanism and the way it was metabolized. We evaluated it in some leukemia models, and oh yeah, sure. I told Grindey—well, you can—don't expect too much out of a solid tumor. So it became approved in solid tumors. It is widely used as much for its contributions to the activity and combinations as to its relative lack of toxicity. That's something that can be combined with many things. But it shares this attribute that I spoke about with fludarabine that if you administer it with a DNA-damaging agent, it's likely to be incorporated into DNA and then inhibit that repair process. Those mechanisms-based combinations were widely placed, and that was the idea was—that you give the drug first, and you give the DNA-damaging agent. It was being developed at a time when DNA-damaging agents were widely used in solid tumors. They still are. It's because they are effective. It isn't because we don't want to get rid of them or replace them with biological. That's the whole thing about targeted therapies. So that turned out to be very productive.

So just to go back to how we got to where we were, and perhaps the answer to your earlier question, Volker worked out the metabolism work, but it was Peng Huang, again, who insisted on staying on for a couple of years as a postdoctoral fellow because he wanted to work on this. He wanted to work in something that was more clinically related than he thought—that the fludarabine work that he had done. He worked out the whole biochemical mechanisms at how the thing actually gets incorporated into DNA and how it works at that level. It is a widely cited publication that he came up with. Let's say it was a contribution that has not—that has largely not been extended, and it certainly hasn't been corrected. That's an important thing when you publish is to publish the right stuff. Get it right the first time.

Tacey Ann Rosolowski, PhD

1:38:35.1

I was having a conversation yesterday with someone who was saying in the current research climate where there is so much pressure the consequences for taking time and going down a blind alley or having something that doesn't fail can be—having an investigation that “fails” or does not pan out can be pretty catastrophic. I'm wondering if you agree with that. And if you do, what kind of impact does that have on the frame of research questions?

William Plunkett, PhD

1:39:10.5

It depends on what path you are going down. If you are doing a clinical trial, we recognize that so many drugs are tested and so few are approved that it has got to be happening all the time. The point is that you ask your question, and you get your answer. Sometimes the answer is no. It is like prayers. So in terms of following a laboratory research program, first of all, it will almost always be supported. So somebody has looked at it and thought it was a pretty good idea. So if you're asking the right questions and then you find that the preliminary results that you have didn't lead to the endpoints that you had predicted—hypothesize would happen—then if you have a rational test of the hypothesis, I think that that is—and you have given it a fair shake that can be published. You will find people, of course, who will—say, editorial board meetings—it is

important to know what didn't work and why it didn't work and we should have a special section. But I don't think it really ever happens that they have a special section, although sometimes negative results do get reported. Generally, that is the repository of lower-level journals with lower citation indexes. It is a self-fulfilling prophecy. If you have a negative result, it is not going to be cited very often.

Tacey Ann Rosolowski, PhD

1:41:16.1

Right.

William Plunkett, PhD

1:41:18.3

But it is important to report that, particularly the clinical initiatives.

Chapter 13

A: The Researcher

Exploiting Cell Death Mechanisms and DNA Repair to Kill Tumor Cells

Story Codes

A: The Researcher

D: On Research and Researchers

D: On Pharmaceutical Companies and Industry

A: Overview

A: Definitions, Explanations, Translations

B: Multi-disciplinary Approaches

C: Collaborations

D: Understanding Cancer, the History of Science, Cancer Research

C: Discovery and Success

Tacey Ann Rosolowski, PhD

1:41:28.7

What is the next step in the research story you wanted to tell?

William Plunkett, PhD

1:41:38.7

Where I am now?

Tacey Ann Rosolowski, PhD

1:41:39.0

Yes.

William Plunkett, PhD

1:41:42.0

Well, I am not sure if we have discussed this about the different mechanisms for activating cell death or activating apoptosis.

Tacey Ann Rosolowski, PhD

1:42:00.0

No, we really didn't.

William Plunkett, PhD

1:42:02.0

We had talked—

Tacey Ann Rosolowski, PhD

1:42:03.2

I do want to make sure we know—recognize the time at this point. I am sorry; it is almost 3:30. So I wanted to make sure that we are not abusing your time.

William Plunkett, PhD

1:42:12.5

No, my time is okay, endless. We have had an initiative to think that if there are proteins that the tumor cell really requires for viability, survival, and propagation, that if you deprive the cell of those proteins, then bad things will happen to the cell—the tumor cell. Presumably that would be specific to the tumor cell—this is part of the hypothesis—and it is phrased in terms of in the last decade addicted to this protein. A tumor cell, in order to survive, is addicted to it. So with these CLL cells that I had mentioned earlier, it is thought, or it is phrased, that they are addicted to the presence of pro-survival proteins. And if you decrease those pro-survival proteins, then death processes ensue very rapidly.

Tacey Ann Rosolowski, PhD

1:43:15.7

Can I ask you a question? You said a couple of times, “the way it is phrased is.” I was wondering why you said it that way. Maybe it is just your style of expression, but I am wondering is it important how the hypothesis is raised?

William Plunkett, PhD

1:43:31.1

Well, when you use a word like “addicted” people have certain expectations about it. When it was first published in 2002—that was formulated and brought forward—it was, “Oh yeah, yeah.” But people recognize that this is really—that some cells really have a requirement for this, and it is part of their pathophysiology. If you take it away, then they are not going to do well in the end. It is also recognized what the molecular mechanism is for the onset of cell death. That happens quite quickly.

We have a couple of ways of decreasing this. It is not specific. We brought this on in the face of a success of imatinib at the same time, in the same disease, which is—this is the poster child of targeted therapy, and it is directed at CML. It is brilliant. It works so well, and it has been perfected with—or extended so that there are now four or five other compounds in that family which address deficiencies that the original drug, imatinib, had ways to get around resistance mechanisms. We pursued this, and in discussions with our colleagues—Dr. [Jorge] Cortes and Dr. Kantarjian in the Department of Leukemia—we designed or hypothesized clinical trials that might test this.

The idea is that the critical protein in chronic myeloid leukemia is relatively short-lived, and if we blocked the production of that protein, even for a short period of time, then those cells might die. At that time—quite soon after we had made this proposal, imatinib became approved. Then

the detection of the disease was not on the basis of I can see the cells in a blood cell smear, but rather it was a molecular detection. You would know patients—we know patients are relapsing on the basis of a molecular test, and you never see a tumor cell. We can know—we can predict what is going to happen, so you can tell about earlier relapse. It was those patients who were relapsing who then were evaluated on this—with this compound that did this. Subsequently, Dr. Cortes and Dr. Kantarjian pursued this and pursued it, and this fall the drug that we had hypothesized and they had brought into clinical trials—we had shown the laboratory research—was approved by the FDA for imatinib-type therapy resistant disease. That is satisfying.

Tacey Ann Rosolowski, PhD

1:47:05.0

Yeah. No kidding.

William Plunkett, PhD

1:47:08.5

So that is an approach that doesn't involve a nucleoside analogue. The name of that compound, if I didn't mention it is—the pharmaceutical company named it omacetaxine.

Tacey Ann Rosolowski, PhD

1:47:22.3

Omacetaxine—O-M-O-C-Y-T-A-X—.

William Plunkett, PhD

1:47:27.5

No, there is no Y. It is an S-I— So we have a different strategy that will go after that in a different disease. We can do that in a different way with chronic lymphoid leukemia—CLL. We know that one of the survival proteins that keeps—that that disease requires is a protein called MCL1. It has a very short-lived transcript. So this is the first news out of the DMA. You make a transcript, and then that is translated into protein. So both—there are degradation signals in the transcript—the RNA transcript—of MCL1, and there are degradation signals in the primary sequence of the protein that give it a very short, rapid turnover. So the fact that this was really required for CLL cell viability and the rapid turnover made it an ideal candidate for this strategy of transiently inhibiting the expression of this. So, of course, it is the antithesis of targeted chemotherapy, because with imatinib, you are targeting essentially one *uncA* gene target that is different in the tumor. Many cells may have this. You may be inhibiting the synthesis of many proteins, albeit transiently—and I am talking about a few hours—but there is a selectivity in the sense that the tumor cells require it. Normal cells do not appear to require it. Most normal cells do not appear to require it. Then it has the properties of being able to—of turning over rapidly. So it lends itself to a strategy in which these types of drugs which are—the drugs themselves are eliminated rapidly once they are infused. So if you infuse them over a continuous infusion of a few hours and then stop, the drug itself goes away, which allows recovery of synthesis. The point is you want to match the time at which synthesis is inhibited to the time at which it takes for the

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critical protein to decrease below the threshold levels that will trigger cell death and then stop your infusion. That is what we are working on figuring out now.

Tacey Ann Rosolowski, PhD

1:50:39.8

Is it—I mean, this seems like kind of a paradigm shift. You know, it is a completely different way of approaching—

William Plunkett, PhD

1:50:49.2

Yes.

Tacey Ann Rosolowski, PhD

1:50:49.9

Well, I'm just trying to think of is that—? Is it difficult when you have worked for so long with one kind of strategy to kind of see it from a new point of view and come to something that is really a completely different basis?

William Plunkett, PhD

1:51:07.1

It is difficult for the funding agencies to see it that way. So we have been going along—

Tacey Ann Rosolowski, PhD

1:51:13.4

The cynical approach.

William Plunkett, PhD

1:51:15.0

Yeah. Yeah. Well, everything is difficult with funding now. It doesn't make any difference whether you're totally brilliant and on target with the party line or whether you are, as you say, running in opposition to that. At least we have an example now. And with publications which are pretty thorough, we have literature out there that backs up what we have said. We have done a couple of clinical trials to—and we can demonstrate that this is happening in the tumor cells during therapy and related to clinical response.

One of the difficulties has been pharmaceutical company continuity. A pharmaceutical company would be taken over, and new management does not see the urgency with this compound. A pharmaceutical company has limited resources, has to make a decision, and does not renew their license with a compound. Those are things that the candidates in this—candidate compounds—have faced that we have been involved with. So we are picking up the flag with a different company now and a compound that is very similar and going forward with that. They already ran a clinical trial here in myeloid leukemia. I think the one that they are proposing to run—it is already through the IRB and the CRC here. Our initiating here has the highest level of promise.

Again, that is something that is not aimed at damaging DNA per say, but rather it is aimed at encouraging the cell to kill itself by prescribed mechanisms. That process appears to be pretty much irreversible once it is initiated. It is right over the cliff. That is one thing that goes away from the nucleoside analogues.

The only thing that I would want to end on with the research is—it actually brings me back to a nucleoside analogue. I didn't think that this would happen, but some time ago I had a friend who—this is a synthetic, organic chemist in Japan—who was aware of the work that our laboratory had done and some of the training that we had done with Japanese students—trainees—who almost always returned to Japan, and he said, “Well, I have this new compound. It is of a class that you are familiar with. It is not totally unlike cytarabine or gemcitabine, but I think it works by a different mechanism.” He had hypothesized the mechanism by which it would work before he made it. This man is a smart cookie—Tomohiro Matsuda. He had hypothesized that before he made it, made it, did a little bit of laboratory work that was consistent with his hypothesis, but he really needed it tested in a cell system, so he wrote me and asked me if I would be interested in evaluating it. I expressed interest. He said, “Well, it would be helpful if I gave you authentic active metabolite,” which he did. Then he said, “Well, the person who participated in the synthesis of this compound is a synthetic, organic chemist, but he wants training in a biochemical and pharmacology laboratory.” So I said, “Sure.” Not only that, he paid for everything, which is not uncommon, because frequently academic laboratories are paired with pharmaceutical companies, and the pharmaceutical companies will support the training of a young PhD student, say, in a laboratory—my laboratory in this case—and then with the expectation that that person will go back and work for the pharmaceutical company. That will be his job. That is essentially the way it worked out.

So we worked through that, and he worked through two papers and came out with evidence of what Dr. Matsuda's—that supported Dr. Matsuda's hypothesis. Thereafter, the pharmaceutical company that was bringing this forward really didn't—the findings in the clinic did not live up to their expectations, and they dropped the compound. I lost sight of it. I didn't know where the heck it was. Then it came on to my—I recognized that a small pharmaceutical company in Scotland had picked it up. The company's name is Cytocell. When I looked it up, I found out that the vice president for research was a good friend of mine—had been a good friend of mine. He had worked in the United States in academics and then in drug development in pharmaceutical companies for years, and he returned to his native country and took up that position. This is another totally brilliant person—the sort of person you like to work with. So I called him. I said, “Bob, I understand that you have this compound.” He said, “You know, I was thinking of you.” I said, “Well, okay, let's do it.” So I was trying to get him to have his company run a clinical trial in leukemia here, which we were successful at because they—previously it had been evaluated in solid tumors and really hadn't shown very much. So I was working on mechanism of action in the compound independent of—this was—all of this work has been independent of any pharmaceutical support other than the fact that the postdoc was paid originally by that. I was having people in the laboratory working on mechanism of action of that, and Cytocell was pursuing it. They were pursuing it in solid tumors, but they also decided to

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sponsor a trial that Dr. Kantarjian headed in acute myeloid leukemia and myeloid dysplastic syndrome. That went forward quite quickly and demonstrated activity in those diseases. It was published in the *Journal of Clinical Oncology*—a high profile journal.

Then a second trial was started, and this is Dr. Kantarjian's specialty. He understands when he sees something different in the clinic and something worthwhile pursuing. So I was encouraged just by his actions in pursuing this. We ran a second clinical trial on that in a different patient population—on an older patient population which is known to be not tolerant or not fit, as it would be said, of standard of therapies that would be useful or effective in younger patients with those diseases, just as a generality—people over 70. So that was published last year or this year.¹

Tacey Ann Rosolowski, PhD

2:00:10.6

So positive results or—?

William Plunkett, PhD

2:00:11.6

Yes, with similar results. So at the same time, while that was ongoing, we knew what the results of—how those results were going to turn out. So the pharmaceutical company decided, well, we're going to try to—we are going to talk to the FDA and design a Phase III study. This is a multi-center trial that would show that it might be better than an approved drug in AML, and then this is the basis for approval. So the registration trial is ongoing. Okay, so that is clinical research, but where laboratory research meets clinical research is our mechanism of action studies that were headed by Dr. Liu here—L-I-U—Xianojun—X-I-A-O-J-U-N—Xianojun.

Tacey Ann Rosolowski, PhD

2:01:10.9

X-I-A-O—?

¹ Dr. Plunkett expands on a related drug produced by Cycacel, a company mentioned in the interview session:

“The compound that Cyclacel has in clinical trial is an orally-available pro-drug called sapacitabine. We don't use it in the lab because it requires metabolism to generate the parent nucleoside, CNDAC. This, by the way, is also in clinical trial at MDACC in acute leukemias (Kantarjian). It is administered parenterally (intravenous), and provides some flexibility in dosing compared to sapacitabine. Further, Sankyo made the pro-drug sapacitabine from CNDAC. The clinical results were first reported in phase 1 clinical trials, the purpose of which is to determine safety, although we always look for clinical activity. These were in solid tumors (lung, colon breast, etc.) of patients who had failed many prior therapies. These were conducted mostly by Sankyo Pharmaceuticals, who later dropped the compound (then known as CS-682). After Cyclacel licensed the drug from Sankyo and re-named it sapacitabine, Dr. Kantarjian tested sapacitabine in acute myeloid leukemia in a phase 1 trial; there were responses, including complete remissions. This progressed to a phase 2 trial, and some combination trials before the current phase 3 trial was designed and initiated.” (From Email correspondence with the Interviewer, 12 April 2013).

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William Plunkett, PhD

2:01:12.9

J-U-N-E.

Tacey Ann Rosolowski, PhD

2:01:13.9

J-U-N-E.

William Plunkett, PhD

2:01:15.0

L-I-U. She has pursued that now for six years and come up with four or five publications that clearly indicate that this acts like no other nucleoside has acted before. What it does is that it shows that not only does it act by the hypothesis that Dr. Matsuda said it would act, which was to bring it to a single break in the strand of DNA, But then when we matched it to biology—this is where medicinal chemistry meets biology—when we matched it to the appropriate biology, she showed that it was active in patients who, in cells that could not repair, double-strand breaks and showed how double-strand breaks could arise.

So there are cohorts of patients, both solid tumor and hematological malignancies, that are known to lack the ability to repair double-strand breaks—these key proteins. We have identified some in chronic lymphocytic leukemia who lack one copy of—there is a deletion of the chromosome. They lack one copy of the gene. And in a substantial cohort—we do not know how many right now—the second allele of the gene is mutated. So that would be known as a double hit or a lack of—loss of heterozygosis, but it means you don't have that gene function anymore in those tumor cells, so they can't repair double-strand breaks. This drug does make double-strand breaks, so my colleague Bill Weir and I, in Leukemia, wrote a series of grants and finally got an R01 funded to support the clinical trial of this in patients who have that signal lack of a single allele. They have the deletion, which can be identified by cytogenetic analyses. Those patients are eligible for it. It's our laboratory responsibility to find out whether the residual allele is functional or not.

Then the outcome of the trial, it's working with—our statistical colleagues worked out a design of the trial so that if we estimate that as many as 40% to 50% of the patients lack total function, then we need so many patients in the trial, and it will come out with or without and what the different responses will be. So that is ongoing now, and that is one of the most satisfying things. Well, what that really does is bring our laboratory research out of the more empirical. I know it will kill the cell era and into the area of molecularly targeted for individualized medicine or for personalized research, because you know that the patients— What it could mean is if patients with the lack of function of these particular proteins respond more favorably than the ones who have the protein that can do the repair, then it can mean you can establish a test in a pathology lab to determine whether that protein is functional in anyone and then select those individuals for treatment. Excuse me. So that is really okay. I like that too.

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Tacey Ann Rosolowski, PhD

2:05:22.7

Yes, I could see that. Wow. So that really is a kind of culmination of the whole translational journey.

William Plunkett, PhD

2:05:29.5

Right. It is.

Tacey Ann Rosolowski, PhD

2:05:30.8

It really is.

William Plunkett, PhD

2:05:31.1

Yes. And then the second thing is, what about other disease cohorts that lack that? Well, it turns out that in a couple of cancers in women—ovarian cancer and in breast cancer—it is known that particular proteins BRCA1 or 2 is deficient, and it is a familial sort of thing—largely it is familial. The cells that lack that protein can't repair double-strand breaks. So what I was discussing yesterday was a clinical trial that came from our hypothesis that was done someplace else—done at Dana-Farber. The principle investigator there presented the Phase I results in just trying to find the right dose that is safe, but also looking at—always look at responses. Then I was to get up—I did get up and ask to discuss the mechanisms and rationale for it, which I did. So it is a terrific day, except for this cough. I think I went through it so fast that the cough didn't catch up with me.

So that really drew a lot of attention—a lot of people paying attention to that about how it would work, what patient—I mean, those are only two of the cohorts that we can identify who may have that deficiency. And I think if—so of course it was the same pharmaceutical company that was supporting that clinical trial. It was all based on the mechanism work that Xiaojun had done here and published as they knew about that, and I had spoken with them before. They were quite happy with the outcome. I think they were happy that they did it because they have limited financial resources. But I think the fact that they are presenting it now may help their case in venture capital and the registration trial that Dr. Kantarjian is heading up—multi-centered trial—hopefully will have a favorable outcome to it. So that would certainly bring in resources that would allow them to pursue it—pursue other initiatives.

Tacey Ann Rosolowski, PhD

2:08:17.5

Yes. Success breeds success. I wanted to ask, too, the last name of your friend Bob who is at Cytocell.

William Plunkett, PhD

2:08:26.0

I just thought about it. I'll get it for you.

Tacey Ann Rosolowski, PhD

2:08:29.5

You will get it for next time. Sure. Well, do you want to end on this high note?

William Plunkett, PhD

2:08:33.6

Jackson.

Tacey Ann Rosolowski, PhD

2:08:34.5

Bob Jackson. Okay—Scotland—great. Is it okay to close off for today? Are we—?

William Plunkett, PhD

2:08:41.7

If you would like, yes. That is fine.

Tacey Ann Rosolowski, PhD

2:08:43.1

Okay. That's great.

William Plunkett, PhD

2:08:44.6

No that—

Tacey Ann Rosolowski, PhD

2:08:48.6

It's a great story.

William Plunkett, PhD

2:08:49.0

That's fine.

Tacey Ann Rosolowski, PhD

2:08:50.0

Yes. Well, thank you very much.

William Plunkett, PhD

2:08:53.7

You're welcome.

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Tacey Ann Rosolowski, PhD

2:08:54.0

I'm glad we had a chance to talk about this—you know—really great trial.

William Plunkett, PhD

2:08:58.7

Yes, well, it's really current with me.

Tacey Ann Rosolowski, PhD

2:09:01.3

Yes.

William Plunkett, PhD

2:09:02.6

And I'm certainly—well, we are well supported for pursuing these things now. So that's the plan for the immediate future.

Tacey Ann Rosolowski, PhD

2:09:12.6

That's great. That's great.

William Plunkett, PhD

2:09:15.4

Just taking care of doing that.

Tacey Ann Rosolowski, PhD

2:09:19.0

Well, thank you. And I'm turning off the recorder at 4:51.

William Plunkett, PhD

2:09:24.0

Okay.

2:09:25.4 (End of Audio Session 2)

William Plunkett, PhD

Interview Session 3: May 8, 2013

Chapter 00C **Interview Identifier**

Tacey Ann Rosolowski, PhD

0:00:00.9

Let me just put on the identifier. Actually, I will—I'm putting the identifier on even though we're a little bit into the interview time here. I'm Tacey Ann Rosolowski, and I am in SCRB Four of the Research Park, interviewing Dr. Bill Plunkett for our third session. Today is May 8, 2013, and the time—the formal start of the interview—is 1:48. So we were strategizing a bit on how to cover today's questions and thought that it would be appropriate to talk about the history of the development of the Department of Developmental Therapeutics, which then morphs, and one of the things that came out of that was the [Department of Experimental Therapeutics](#)—your department. So where would you like to start to tell that story?

Chapter 14

B: An Institutional Unit

Developmental Therapeutics: the Origin of the Department of Experimental Therapeutics

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

B: MD Anderson History

C: Portraits

B: MD Anderson Culture

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

C: Collaborations

B: Institutional Processes

A: Joining MD Anderson

Tacey Ann Rosolowski, PhD

0:00:00.9+

So we were strategizing a bit on how to cover today's questions and thought that it would be appropriate to talk about the history of the development of the Department of Developmental Therapeutics, which then morphs, and one of the things that came out of that was the [Department of Experimental Therapeutics](#)—your department. So where would you like to start to tell that story?

William Plunkett, PhD

0:00:59.8

Well, I think I'd just start as others could also tell it with the origins of the Department of Developmental Therapeutics, and that began with [Dr. \[R. Lee\] Clark](#)—a great visionary who recognized two major forces in the development of chemotherapy were [Dr. Emil Frei III](#)—known as Tom Frie—and [Dr. Emil Freireich](#)—known as J. He recruited Dr. Frei in 1965, and Dr. Frei then recruited Dr. Freireich to be the head of Hematological Malignancies—excuse me, so Dr. Frei created the Department of Developmental Therapeutics and probably in concert with Dr. Freireich with whom he had worked very closely at the [National Cancer Institute](#) before they both came here.

Tacey Ann Rosolowski, PhD

0:02:21.2

Let me just also say that it's maybe serendipity, but Dr. Frei passed away last Tuesday, I believe it was. Yes.

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William Plunkett, PhD

0:02:30.1

I understand. Right.

Tacey Ann Rosolowski, PhD

0:02:32.9

Yes. Well, I'm just saying it for the record.

William Plunkett, PhD

0:02:36.6

Yes, so Frei and Freireich, for a while then at the NCI and during their time here, were closely associated as both their names imply and their focus and attention to developing better patient care—better treatment. In 1972, Dr. Frei was recruited away to what was then the Sidney Farber Cancer Institute and became later the [Dana-Farber Cancer Institute](#) where he spent the rest of his career and—as you say—recently passed away. Dr. Freireich then went on to become the head of Developmental Therapeutics. He was the chairman. This was really distinguished by his initiative to have clinical researchers of many specialties and organ site specialties together in the same room with scientists who were developing a mind towards what we now call translational research. Many of us considered ourselves basic scientists but then looked towards applications in the clinic.

Tacey Ann Rosolowski, PhD

0:04:25.5

Where do you think Dr. Freireich developed that sort of mindset himself?

William Plunkett, PhD

0:04:34.5

I think he saw it as a means of assisting in the overall mission—the goal of the mission of developing effective therapeutics for patients. Together Dr. Frei and Dr. Freireich—probably with a few other individuals—were the first to employ combinations of therapeutic agents in the treatment of hematological malignancies—notably in the treatment of acute lymphoblastic leukemia—showed the first long-term remissions in response to combination chemotherapies, and that has been developed over the years by others now such that more than 80% of the patient population with acute—generally pediatric population—can expect to be long-term survivors on the order of as if they never had cancer. Quite an accomplishment. They have been recognized for that. They shared the [Lasker Award](#), which is a prestigious award, and also they shared the first—I'm not sure if it's NCI. I think it's an [NIH Alumni Award](#) as the distinguished alumni, and they were the first two recipients—that is, together—of that award. I know that's certainly something that Dr. Freireich is very proud of—quite pleased at that recognition.

The Department of Experimental Therapeutics was really quite a rocking place because it was a place where controversy rose to the surface, and it was expressed, and no assertion went unchallenged. I can remember when I interviewed here. The person who was—[Dr. Ti Li Loo](#)

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who was one of the early recruits to the Department of Developmental Therapeutics said, "Well now, Dr. Freireich will sit right in front, and he'll interrupt you and ask you questions during your talk," and Dr. Loo thought that that was rude. It might've been unusual, but coming from the background that I came from—training with [Dr. Seymour Cohen](#)—it was nothing new to me. Dr. Freireich always had interesting and incisive questions. I always thought if the speaker is good enough to explain something completely different or unfamiliar to Dr. Freireich in a clear sense, Dr. Freireich is able to ask an incisive question to the speaker, frequently setting them back on their heels. He's a master.

Tacey Ann Rosolowski, PhD

0:08:02.1

That's a great way to drive thought process.

William Plunkett, PhD

0:08:04.1

Yes! Well, that was in part his goal, but we had such a mixture of people in different disciplines, including basic science. Basic science of statistics was very important because that played a—that was brought in and made to play a key role in the development of the analysis of clinical trials. I know Dr. Keating would tell you that [Dr. \[Edmund\] Gehan](#), who was one of the first recruits that led the statistical group—that he was instrumental in driving the design of protocols.

Tacey Ann Rosolowski, PhD

0:08:57.2

How do you spell his name, Gehan?

William Plunkett, PhD

0:08:59.0

G-E-H-A-N

Tacey Ann Rosolowski, PhD

0:09:04.5

Thank you.

William Plunkett, PhD

0:09:04.8

And [Dr. \[Gerald\] Bodey](#) [Oral History Interview] was just outstanding in infectious diseases, [Dr. \[Evan\] Hersh](#) in immunology and immunologic approaches to diseases. Dr. McCreadie was a trainee of Dr. Freireich's who went on to lead the leukemia section. The Department of Developmental Therapeutics had probably, in the early 1980s, numbered more than sixty individuals—sixty faculty members. I could always remember being impressed or—yeah, impressed—when I was told that although they had sixty faculty members there, fifty-five of us were getting our entire salary off of grants. This was not a common occurrence at this time, and it wasn't a common occurrence in the rest of the institution, so we were a self-propagating and

sustaining group of people. And certainly you had to learn how to write a grant effectively. I would say—I was speaking with Dr. Freireich about a month ago and just going back over those early times. He was the leader of an original program project grant here in Developmental Therapeutics, and I believe it had eleven different projects, so that is quite large. It was large for the time, but it's unheard of now. I think they restrict them to no more than six projects. Then he got a second program project of the same size, and then some years later—while still having those two—received a third program that I was a member of. I had a project on each of these—the third project—and mainly directed towards hematological malignancies at this point.

Tacey Ann Rosolowski, PhD

0:11:21.2

So he was managing over thirty at once.

William Plunkett, PhD

0:11:23.5

It was incredible—incredible—that sort of thing. So that being just an anecdote is that when—I think I mentioned to you how I came to be at MD Anderson, and that is Dr. Freireich came through the laboratory one time, being shown through as a guest where I was doing a postdoc. I was asked to tell him what I was doing, and he was sufficiently impressed with that to say right at the moment, "You should come to Houston. We will give you a job." I mean, that's quite remarkable, and you can see the postdocs. When I tell that here, their pupils dilate. So when I came—

Tacey Ann Rosolowski, PhD

0:12:13.3

Gone are those days!

William Plunkett, PhD

0:12:13.9

Yeah. Right. So it was actually Dr. Ti Li Loo who was head of the pharmacology section. At that time, it was one department, many sections, and we were a section of maybe seven or eight people including [Dr. \[DahHsi\] Ho](#) to whom I just referred before we started. So we had discussed this and grants and when would I be expected to get a grant and so forth. I walked in, and apparently he hadn't been expecting me. It was December first. I thought he had been expecting me, but those were the days of letters and so forth. He says, "Oh, you're here. Where's your grant?" He says, "This [P01](#) is being competed in fourteen days. You need to have the grant in." So I said hi to everybody and went to the library for the next fourteen days and wrote a project. It was a modest project. It seemed to be well received by the—at that time—a site-visiting committee. It used to be that the grant reviewers would come to the institution. That's no longer the case. It was well received, and at the end of all of the presentations, there was an executive meeting, and we were asked to wait until the executive meeting was over. I was really taken aback when they said, "Plunkett, the site-visiting committee would like to speak with you," and the chairman of the site-visiting committee—I'm trying to remember his name but—said to

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me, "We appreciated your presentation, but we don't think you can do this project." I started putting together the reasons why I thought I would be able to do it, and then he says, "Oh, well, let me be clear. We don't think you can do it with this budget. Go back to your office and write a bigger budget." That hasn't happened again.

Tacey Ann Rosolowski, PhD

0:14:39.7

I bet.

William Plunkett, PhD

0:14:41.1

So—

Tacey Ann Rosolowski, PhD

0:14:42.6

Interesting.

William Plunkett, PhD

0:14:43.7

As it turned out, the grant was funded, and I had a grant account by September after coming here on December first. It was really a fortunate situation for me in terms of starting up my laboratory, because my startup package consisted of an inverted microscope, an incubator, and a laminar flow hood; that was it and then some space. That's what I had. Today you think in terms of millions of dollars' worth of startup packages for some recruits, but that was a different time.

Chapter 15

B: Institutional Change

Reorganizing Developmental Therapeutics: Naming Experimental Therapeutics

Story Codes

A: The Researcher

A: Overview

B: Obstacles, Challenges

B: Controversy

B: MD Anderson History

B: MD Anderson Culture

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

C: Collaborations

B: Institutional Processes

B: Growth and/or Change

D: On Research and Researchers

D: Understanding Cancer, the History of Science, Cancer Research

Tacey Ann Rosolowski, PhD

0:15:33.2

As you look back over the history of the department, what were some key moments of growth or change?

William Plunkett, PhD

0:15:43.3

Okay, so when we come up to a large department, there was a change when Dr. LeMaistre had taken over from Dr. Clark. He decided that what he wanted to do was restructure the medical enterprise. It had been either the Major Department of Medicine or the Division of Medicine and then Developmental Therapeutics. Relatively, it was a small number of faculty relative to what we have today. But he wanted to restructure it into organ-site specific departments—breast cancer, lung cancer, GI, GU, and so forth. So what happened was that he took the faculty in Developmental Therapeutics and merged those faculties on the basis of organ-site specificity into a series of medical oncology-type departments. There was a Department of Medical Oncology. So then I went from—so then what do you do with the basic scientists under those circumstances? Well, we became under—so [Dr. \[Irwin\] Krakoff](#) was named as the head of—then it was the Division of Medicine; now it's the Division of Cancer Medicine. Dr. Krakoff oversaw this reorganization, and it wasn't popular with everybody. We became a new department with several new recruits which we really welcomed. So this is called the Department of Chemotherapy Research. That was the second department that I was in, and Dr. Krakoff became the chairman of that. Others can tell you more about how things proceeded, but I think centrally that coincided with Dr. Freireich receiving an outstanding investigator award.

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With a title—a name like that—to the award, you can imagine the egos that applied for that. He got it on the first round.

Tacey Ann Rosolowski, PhD

0:18:17.3

Wow.

William Plunkett, PhD

0:18:18.8

So with that, it was our impression—which was solidified by seeing the letter that he wrote to Dr. Freireich—that he wanted to give him more opportunity to pursue his research interests, so he was leaving him of his administrative responsibilities. And it's an understatement to say that that was not popular with Dr. Freireich, in particular. So—

Tacey Ann Rosolowski, PhD

0:18:52.2

Why was that?

William Plunkett, PhD

0:18:53.3

Well, because he was used to being in charge and directing a large and very effective and creative constituency.

Tacey Ann Rosolowski, PhD

0:19:04.4

Do you think there were ulterior motives to that as well?

William Plunkett, PhD

0:19:07.3

It would only be speculation. I think that maybe that's the way that people saw the future of a large cancer hospital would be. There aren't very many cancer centers that are stand-alone cancer centers. Most of them are matrix associated with a medical school, and your primary appointment will be in the medical school, and, oh, by the way, you're part of the cancer center. That's the way things have clearly developed. So that cooked along under Dr. Krakoff's direction.

Tacey Ann Rosolowski, PhD

0:19:53.0

Can I ask you—you said there was the question about, "What happens to the basic scientists?" Did you feel as though—? How did basic scientists fair with that reorganization?

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William Plunkett, PhD

0:20:04.9

Dr. Krakoff had, I believe, at the time, approaching 130 faculty members in the Division of Medicine, and we were eleven or twelve in the Division of Medicine, so he was responsible for all of those people; but he was our department chairman. So we felt as though we didn't have people who would have their feet in the same fire in terms of being basic scientists and competing for grants and thinking in terms of different subject matter of thinking, particularly the ones who weren't so oriented towards becoming involved in clinical therapeutics and evaluation of things. So you feel left out, and it became even worse when [Dr. \[Robert\] Bast](#) took over from Dr. Krakoff. So the answer to your question is we felt as though we didn't a full-time department chairman, and the department chairman that we had wasn't of our lineage. Okay?

Tacey Ann Rosolowski, PhD

0:21:27.9

Yes.

William Plunkett, PhD

0:21:29.4

If you want to pursue that, then in ten more years, Dr. Krakoff retired, and [Dr. \[Martin\] Raber](#) [Oral History Interview], who had been a fellow when I first came here—in fact, I think I'm a co-author on one of his first papers. We get along just famously. Marty Raber took over as ad interim division head, and he became ad interim chairman of our department. Let me just put a little spike in there. Somewhere along the line, there had been a Department of Medical Oncology, and Dr. Jim Neidhart had been recruited to be head of that. That went along for about five years, and then he was recruited to the University of New Mexico, and Dr. Krakoff said, "Well okay, I'm going to be chairman of Chemotherapy Research and Medical Oncology." That's when people above Dr. Krakoff said, "No, you can't be chairman of two departments." So then we became a section in the Department of Medical Oncology, and Dr. Krakoff became head of the Division of Medicine and chairman of the Department of Medical Oncology. So we were then a section known for being a department. Dr. Krakoff ostensibly then is still our department chair under those circumstances, and that went along for a while.

Then Dr. Krakoff retired, and Dr. Raber took over at an ad interim phase of probably no more than a year before Dr. Bast was hired as head of the Division of Medicine. Of course, with each successive recruitment, people were looking for more resources—recruits are looking for more resources. So then the number of faculty in the Division of Medicine grew, and Dr. Bast—although he tried and he had a laboratory background—he still was viewed as a part-time department chairman by the faculty, and he gave us the name of Clinical Investigations. So that's the fourth administrative structure that I had been in. So here I am applying to basic science study sections that review my grants, and I'm from the Department of Clinical Investigations, and that was raised on some of the evaluation sheets. People just didn't understand.

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Tacey Ann Rosolowski, PhD

0:24:26.0

So explain the issue to me there.

William Plunkett, PhD

0:24:27.9

The issue is you're proposing to do basic science, but you're seen as being an administrative structure that isn't labeled as doing basic science when you have the name Clinical Investigations.

Tacey Ann Rosolowski, PhD

0:24:48.5

It's labeled as clinical. Okay, okay. So actually a disconnect between what you do and what you're named. Interesting. What were some other issues that arose under that kind of structure or in your relationships with these various heads who didn't quite get what your stakes were and your issues were?

William Plunkett, PhD

0:25:11.5

Well, part of it is a perception for me, because I've been very fortunate pretty much all along in being able to have proposals funded, and I remained funded and pretty much an independent entity and didn't really need to—you would like to have a— It's the collegial environment that you can see in basic science departments where they have their own seminar series, they have their research meetings and their own group, and you bump into people close by in a break room or in the corridor, and you can speak the language of your work and what you're doing. But that's not the case in the situation that we were in—collectively, "we." So eventually the department implored Dr. Bast to give us a different name, and we chose the Department of Experimental Therapeutics—the faculty did.

Tacey Ann Rosolowski, PhD

0:26:32.6

How did they set on that name?

William Plunkett, PhD

0:26:36.2

Well, it represents what we thought we did, and we were pretty sure we wouldn't be allowed to use the name Developmental Therapeutics. That's fine. If you look recently, we've gone through a situation of developing an educational program in the graduate school, and we call it the Experimental Therapeutics Program. And the dean was thinking, "Well, that's not a proper discipline like physiology and pharmacology and so forth," and we are saying, "Look, people are not attracted to pharmacology and physiology. They want to go to more contemporary names, and that's why places all over the country are using them." When you google experimental therapeutics, you come up with practically a department of experimental therapeutics at every

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cancer center. We weren't unique, although we hadn't done that exercise when we were arriving at the title.

Tacey Ann Rosolowski, PhD

0:27:40.3

Well, it's almost like the—

Tacey Ann Rosolowski, PhD

0:27:44.3

Those old categories of looking at biological processes through narrow lenses weren't working anymore. It was more defining a type of approach rather than this more traditional—this is the structure we study. This is—

William Plunkett, PhD

0:28:00.7

The walls came down because—and you have to be able to be flexible, and the collaborations are terrific. The opportunities are terrific for people who want to take advantage of them. So people who would call themselves pharmacologists were trained in the principles of that or weren't trained in, more formally, the principles of biochemistry and, more contemporarily, the principles of and practice of molecular biology. We do many of those things—draw upon techniques and procedures and knowledge of each field in order to push our own work forward. I don't feel any sort of—departmental boundaries are administrative tools now. I don't feel that many of our faculty can be defined by departmental names.

Tacey Ann Rosolowski, PhD

0:29:15.8

What was the effect that you noticed of the new name? Did it create a kind of new consciousness in the department? Did it open up other opportunities?

William Plunkett, PhD

0:29:26.7

With that, shortly thereafter, Dr. Bast took a vice president position of vice president of translational research, so there was another recruitment effort, and [Dr. \[Waun Ki\] Hong](#) [Oral History Interview] was recruited as the head of the Division of Medicine, which was renamed the Division of Cancer Medicine. That's where it is now. That was about twelve years ago. Subsequently, with Dr. Bast no longer being our department chairman, then we had a plebiscite within the department and elected our own department chairman ad interim.

Tacey Ann Rosolowski, PhD

0:30:19.1

Oh, I should—I didn't ask you. What was the date when the Department of Experimental Therapeutics received its new name?

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William Plunkett, PhD

0:30:30.3

Of course, it had always been that with us, but it has to go through these various things in order to name a department in a University of Texas System situation. But I think it was close to 1998, 1999, and it went as the Department of Experimental Therapeutics under Dr. Bast. Dr. Bast also included people in our department that were very different than what we do, including clinicians, the gynecological oncologists—there were three of them given a primary appointment in our department, and there were other people who wouldn't seem to fit.

Tacey Ann Rosolowski, PhD

0:31:28.3

Why did he do that?

William Plunkett, PhD

0:31:29.2

Well, I'm not sure. I can't say, but it's an administrative sort of thing. If you can't get along with one group, then here's a group that will take you. It won't make any difference or something—except to the people who are looking around and saying, "What's our entity?"

Tacey Ann Rosolowski, PhD

0:31:49.1

So how did things change when Dr. Hong took over as head?

William Plunkett, PhD

0:31:54.0

Before long—let's see, probably two or three years—we were pushing for a nationwide search for a full-time chair, and that was going pretty much in fits and starts and not very effectively. We didn't think that the institution had made a strong commitment of space. We remained spread out in various places, and then Dr. Hong decided, "Well, what I have here is a group of—" okay, so you have two mixtures; one was Bioimmunotherapy, and the other one was Experimental Therapeutics. And we had the predominance of laboratory scientists, although we had clinicians in there, and Bioimmunotherapy had mainly clinicians, although I think there were a few basic scientists in there as well. What he says is, "Well, we are going to put them all together, and you can figure out what your name is going to be." I mean, we wanted to stick with Experimental Therapeutics, and eventually that won the day. I can't remember how exactly that was decided. The leadership that Dr. Hong chose—ad interim again—he removed Dr. Siddik as ad interim chair, so he had no further administrative responsibilities. He removed [Dr. Moshe Talpaz](#) as chartered chair. He was a chairman of Bioimmunotherapy. He said, "You are no longer chairman of Bioimmunotherapy. We are going to have some new leadership." So Dr. Hong then put in [Dr. Reuben Lotan](#) as the ad interim chair. Ruben had worked with Dr. Hong for many years. I think he was acknowledged by the faculty, and certainly demonstrated it during his tenure as ad interim chair, as being fair, wise, and evenhanded, and tragically, a couple of years ago, he died. He had a catastrophic motorcycle accident and was recovering and then died

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suddenly, so he's a great loss to the institution. But in that role, he was selfless in standing in as ad interim chair to foster this diverse group of faculty.

The second step that Dr. Hong said is, "Look, the clinicians who are in Bioimmunotherapy and maybe the clinicians who are associated with Experimental Therapeutics might do better—might do more work,"—that's how it could be translated— "see more patients if they were in a different department." So some people came out and went into—so the physicians were all removed from the department. We had no per se practicing physicians in the department, although we have a couple of MDs at the present time. That was almost eight years ago. Then there was a search—

Tacey Ann Rosolowski, PhD

0:35:44.6

So that would've been right around the time when there was a big financial ruckus?

William Plunkett, PhD

0:35:49.7

That was 2003, and then there was a search for a department chair, and that produced [Dr. \[Garth\] Powis](#). We were in the North Campus probably for five years, still a diaspora of—it can't be a diaspora if you are never together, I think.

Tacey Ann Rosolowski, PhD

0:36:20.8

Your hearts are together.

William Plunkett, PhD

0:36:21.2

We're all out there, a universe of individual laboratories. Several of us had laboratories, two people together and so forth, but we were spread out in four or five different buildings on the North Campus, and then they built this building.

Chapter 16

B: Building the Institution

The Department of Experimental Therapeutics: A Move, Challenges, A Strategic Plan for the Department

Story Codes

A: The Administrator

A: The Researcher

C: Professional Practice

C: The Professional at Work

C: Collaborations

C: Leadership

B: Obstacles, Challenges

B: MD Anderson History

B: MD Anderson Culture

B: Multi-disciplinary Approaches

B: Institutional Mission and Values

C: Collaborations

B: Institutional Processes

B: Growth and/or Change

Tacey Ann Rosolowski, PhD

0:36:39.5

How did you, during that time, maintain a sense of group identity? How did you manage that, because it seems as though some of it existed?

William Plunkett, PhD

0:36:48.8

Well, that gets to how Dr. Powis sought to pursue a strategic plan that we put together. I chaired the committee that did the strategic plan. It was really a committee effort, but I'm just saying that I know about it pretty well, and I know what parts were filled with it.

Tacey Ann Rosolowski, PhD

0:37:12.4

Do you want to talk about that or—?

William Plunkett, PhD

0:37:14.3

Oh, we can go back to it. We were on the North Campus there until January 2010, and then people started moving in here. My lab and Dr. Gandhi's lab were the last labs to move. Both of our laboratories do a lot of research in relation to the clinics. A large part of our experimental

material is primary leukemia material, and being displaced down here was predicted to and has put a big slowdown on our—inconvenience to our capabilities and our functioning.

Tacey Ann Rosolowski, PhD

0:38:21.0

Where does that come from? I mean, what practically is the problem with getting you your samples, given the distance?

William Plunkett, PhD

0:38:28.2

Well, we take—in some cases, you take many samples and given the—it's not only samples. Dr. Gandhi and I are both involved in a lot of ongoing administrative aspects of the institution, and 98% of those meetings are held on the North Campus for which we—the shuttles are better, but you can't—when they run—when you get into them, they're okay, but you may have to wait twenty minutes before you can get into one. So that's twenty additional minutes to that, so we just maintain a parking area up there. We pay and drive to the meetings. We drive together and bring friends or colleagues and so forth. Things start before the shuttles start, and things end after the shuttles stop. And there will be days when as many as three trips will be made. We figure it's almost an hour extra round-trip, going back and forth and then going to get to a meeting. We are less effective because of that.

That being said, the laboratory space is terrific laboratory space. I think the only complaint I would have—not so much about the space but the interstitial space—that my senior trainees all have their—junior faculty, non-tenure track faculty—research faculty appointments, they're called now. That's their title. They all have offices, and they're on the other end of the building. They are in SCRB Four, and this office is in SCRB Three, so if I want to see somebody—that is, face-to-face—somebody has to walk. It's not like—so things are different than when they used to be more compact, but they would say that it's—they like having an office. Well, that's good for you. I would say I was a tenured associate professor, and I was still sharing an office that's the size of theirs, but things change.

Tacey Ann Rosolowski, PhD

0:41:02.8

Was there—what was the process of designing South Campus, and did you know what your space was going to be? Was there any input that you folks were asked to offer?

William Plunkett, PhD

0:41:18.2

We had people—I wasn't personally involved in that, but we had faculty members that were responsible—put faculty members on the committee—very attentive to it, knowledgeable, making suggestions about how the building would be designed, and very few of those suggestions were followed. For instance, we have a meeting room—the largest meeting room in the building holds sixty people. When we were on the North Campus, we routinely had between

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110 and 130 at our weekly seminars. That's not going to happen anymore. Well, part of it is the people who would come to those seminars, some of them are still up there, and they don't want to come down here, or they would be asked to take a shuttle with all of the same consequences in order to do that. So the net effect is—for the people who were used to living or working on the North Campus—we've lost what we consider to be valuable contact and opportunities for interaction with our colleagues who remain there, and that's just the way this. It's real. I can go and stand at an appropriate spot in the [Pickens Tower](#) where people cross on the third floor, and I know people will be coming by there. Then I will bump into people, or people will come by, and they will stop and talk and so forth. I always appreciate it and put it into the time accounting when I'm going there because it's part of the collegiality of things. We no longer have a faculty dining room—a common place—where faculty can get together for some informal get-togethers. That's now becoming clinical area and so forth. We don't have a cafeteria in either of these two buildings. There is a little snack bar that you can walk up to and take away a cup of coffee or a prepared sandwich.

Tacey Ann Rosolowski, PhD

0:43:36.4

Is there a generational difference in perceiving that? I mean, does the older faculty perceive that loss? Do you see that trainees and younger generations also feel something is missing because they've never—?

William Plunkett, PhD

0:43:51.6

No. They just feel that—they've never experienced it other than to say, "Boy, I wish we had a place to sit down and chat." But some of them have their own offices, and they've built out enough space around here where they presume people are going to get together in rooms—little rooms and areas.

Tacey Ann Rosolowski, PhD

0:44:10.9

Or where they are seeing the seating areas.

William Plunkett, PhD

0:44:12.6

But largely, I don't see that being used on a regular basis.

Tacey Ann Rosolowski, PhD

0:44:17.9

They are awfully gold-fishy feeling. I mean, the seating areas have a lot of space around them, and when people walk by, they can see you. It doesn't have the feel of a coffee shop or a restaurant where people tend to gather. .

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William Plunkett, PhD

0:44:33.0

Well, I think the answer is in what we can observe in their use, because I observed that they are rarely. You'll find one person sitting in a little—what they call literally—a huddle room designed for four or five.

Tacey Ann Rosolowski, PhD

0:44:51.9

Wow.

William Plunkett, PhD

0:44:54.1

It's nice. You have Wi-Fi and everything. We have a satellite library in this building, which is convenient. I think it's convenient for students who come and attend courses here. Our courses are given here now not on the North Campus; that's a convenience. We have our own—we are sponsoring an academic program for the graduate students; that's good.

Now, to get to a point of—I think, if I remember correctly, you brought up, "How do you get a feeling of community if you are so separated apart?" Early on in the first year, Dr. Powis set about coming up with a strategic plan on how we should conduct ourselves as a department. He created that, and he gave me the title of Director of Research, which I don't need. People direct their own research, so it doesn't really ring with me. But when you know what the job description is, then you can try to do what is expected—and chairing the strategic plan of getting the faculty together and decide, "What the heck is it that we need, and how do we make this a department that would represent us?" So one thing was pulling together with the faculty and trying to have shared equipment. Well, it's hard to have shared equipment when you're all spread out in different areas, and ironically, that goal didn't really carry over when we got down here with two and a half floors that are relatively centralized. So I think the new leadership—ad interim leadership of the department under Dr. Gandhi—is going to try to bring that back and really designate that we need to share our equipment and welcome colleagues, and perhaps that would help us be more collaborative or at least communicative.

Tacey Ann Rosolowski, PhD

0:47:31.3

What are some other—?

William Plunkett, PhD

0:47:33.0

Other things would be, say—education turned out to be the largest one, and that was grown out actually—we had set out some bullet points of things that we could do in terms of mentoring and mentoring at different levels, and that was given to Dr. Gandhi. She has had the title of Director of Education and Faculty Development. Now that, I think, was a solid title, and boy, she really filled that role. So it was she who had developed our seminar series to the level that I expressed

before of having large numbers of people attend on a regular basis. Certainly Dr. Powis—when it was appropriate in the fiscal time—provided the resources to support it with more than coffee but pastries and so forth, and we didn't see many people walking in to pick up a pastry and walk out.

Tacey Ann Rosolowski, PhD

0:48:43.7

Oh, free food!

William Plunkett, PhD

0:48:44.8

Whatever! Yeah, I know. Sure. Of course, I've had students tell me, "If they're not serving breakfast, I'm not getting up." "Okay, we know where you stand, and good luck with your career." No, but what I wanted to emphasize is Dr. Powis accommodated that, and then he also accommodated the development of this course, Mechanisms of Cancer Therapeutics. This had been a course that had been offered years before, but it wasn't well supported—team taught—and the leader of it had left. So it was sort of in demise. And Varsha Gandhi really—with an organizing committee to provide background on a little bit of vision and ideas and so forth—that group came up with a new course—that is, revitalized the course under the same title, Mechanisms of Cancer Therapeutics. So that allowed our department to be identified with that course because many of the team-taught lecturers came from the department, although not all. I would point out that [Dr. \[John\] Mendelsohn](#) [Oral History Interview] had his primary appointment in our department, and he still lectures to this day.

So Varsha had grown that out. She had grown out the seminar series, and then she started in on the mentoring aspects of it. We focused first on mentoring junior faculty. These are non-tenure track faculty, and we included associate professors as well—to assign them or have them pick a senior member of the department. Our department had been going for a long time, so we were predominantly senior and had few in the lower ranks. But then we had a little bit of recruitment, and that filled out some of the lower ranks and so forth. Also the research faculty appointment—what we call junior faculty, who are not on tenure track—then those individuals probably who are most in need of mentoring and some direction in their career, otherwise they will just go from postdoc to postdoc to postdoc. But there have been things to cause decision points in postdoctoral careers now—a five-year limit and then you have to have a new job description. It is either a classified title or an academic title, and you have to have been achieving at a level that would justify an academic title. So that was put in place, and then finally, a postdoctoral mentoring committee group was formed. The postdocs were given their own identity with being able to have their own social events, and Dr. Powis supported that. These are from chairman's funds, I assume, and also academic endeavors of, I'm thinking, a journal or a research club. I'm not certain about that.

One other thing that was Dr. Powis' idea was to have two things to bring the department together. One was to have socials of different laboratories. He would sponsor a social at a restaurant, sort

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of a happy hour-type environment with hors d'oeuvres and a bar. He would pick up the tab for that. He'd have three departments at a time go, and they wouldn't be—he knew that they weren't best friends, but they were people who would benefit from getting to know one another. He chose the departments who would go on each endeavor, and I think people really liked that.

Tacey Ann Rosolowski, PhD

0:53:41.1

Is that still—is that ongoing?

William Plunkett, PhD

0:53:43.3

It hasn't been since—I think the last one was not a year ago. It was less than a year ago. He was trying to bring that back up, but then I think he had the realization that he was probably going to be leaving the institution and was paying less attention to the department in that formal sense. So the second way to bring the department together was with a—I think it's called a—it's a meeting that's put on by the classified laboratory personnel—that would be research assistants, not to say technicians. They get together, and they put on their own program. They will talk about things that they know, like what technique is new in our laboratory, and then you can learn about this. That's, of course, over lunch, and the department would sponsor lunch. This was Dr. Powis' idea.

Then once a year, he would sponsor an ice cream social in the spring where you get together and there you go—so you're together. It's everybody in the department. Then the department also sponsors a Thanksgiving party which is potluck. It's always fun to get different cuisines and so forth. It was those types of efforts. I think it may have worked best when we were here, now that we're here and really are together, but the ironic thing is you have to go over to South Campus Research Building Two in order to get a room large enough to get the entire department together. You can't do it in your building.

Tacey Ann Rosolowski, PhD

0:55:54.4

That's really—that's bizarre.

William Plunkett, PhD

0:55:56.0

Yes. Well, we had all sorts of schemes. I mean, just having a covered walkway to go to SCRB Two. No, if a hurricane comes, then it will be ruined. Well, they put things out here, and a little wind came through and blew one of the larger umbrellas down that we had out over the tables out here. That wasn't Powis' idea. The institution wouldn't sponsor anything like that.

Tacey Ann Rosolowski, PhD

0:56:28.8

Can you tell me what your responsibilities were when you were the director of Research?

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William Plunkett, PhD

0:56:35.2

Well, I'm head of the strategic plan for the department, and then when [Dr. \[Elizabeth\] Grimm](#) went into a different—she got a different responsibility. She is serving as deputy director of Research, deputy head of the Division of Cancer Medicine for Research, so she replaced Reuben Lotan when he retired. She went on to that, and I became deputy department chair.

Tacey Ann Rosolowski, PhD

0:57:09.8

Okay.

William Plunkett, PhD

0:57:10.1

After that, there really wasn't much activity. Although it sounds like a nice title, it really didn't have much to do other than—I think I probably served as, in some way, a history book for Dr. Powis, and this is why it is the way it is, and this is how it came to be and so forth, to provide a little bit of perspective. He's been around in leadership positions, so he could appreciate it, but I don't think it was all that much of a help to him, and I wasn't given any particular assignments. I had plenty of other administrative assignments that—

Chapter 17

A: The Administrator

Faculty Senate and the Revised Conflict Resolution Process

Story Codes

A: The Administrator

C: Professional Practice

C: The Professional at Work

C: Leadership

B: Obstacles, Challenges

B: MD Anderson History

B: MD Anderson Culture

B: Institutional Processes

Tacey Ann Rosolowski, PhD

0:57:58.6

What are some of those roles that you served where you feel you did make a leadership impact?

William Plunkett, PhD

0:58:08.9

At one time we had a—the faculty senate was acutely aware of the lack of defined pathways in which faculty who were unhappy with their situation could really voice that and it could be addressed in a collegial fashion. So Dr. Mendelsohn convened what he called a blue-ribbon panel for peer review, and I think—I'm not sure that “grievance” was in that title. I think it was—we used “conflict resolution” because it was basically about conflict resolution as it's known to ombudsman and to people who mediate conflicts and so forth. It's a more positive term than the grievance, and I don't think we chose to use that again in re-titling the policy. That was an interesting experience because there were probably twelve or fifteen people on the committee, and Dr. Mendelsohn chose people who had opinions, which is helpful. It's just a matter of getting organized.

Tacey Ann Rosolowski, PhD

0:59:49.1

What were some of the conversations like? I mean, what was the process?

William Plunkett, PhD

0:59:51.6

First of all, you have to let everybody vent—this is my view of it. You spend about three quarters of an hour doing that or just listening to it, and then you say, “Well, okay. Here are some ideas for going forward. Here's what we want to do and objectives that we want to achieve, and we don't want this to take six months. We don't even want it to take—we don't want it to take that long.” So people agreed that they would get together as a committee and

meet twice a week. This is—I've never heard of that since or before. That is what we would have to do. The administrative lead on that was [Susan Gilbert](#), and she had some really clear thinking about what the problems were and how to go about addressing the problems and making progress and the—

Tacey Ann Rosolowski, PhD

1:01:00.4

What were the problems?

William Plunkett, PhD

1:01:01.6

The co-chair of that—I was the chair of it, but they named a co-chair. I don't know whether that is unique to MD Anderson. I've been a co-chair a couple of times, so we've had them a couple of times. [Joe B.] Bill Putnam was very—he was a thoracic surgeon, and he also was clear-thinking and quite reasoned in his thought processes and the way he expressed himself, so he was very helpful in the overall process.

Tacey Ann Rosolowski, PhD

1:01:35.7

What were the problems that you identified? What were the bumps in the system that was in place?

William Plunkett, PhD

1:01:42.9

Well, the grievance sort of thing sort of ended up as a face-to-face confrontation in front of a grievance panel. If you have a faculty member who may be a junior and has a grievance against the department chairman, and the department chairman controls space, salary, and promotion and is probably more eloquent in being able to conceptualize and express the feelings, then that seems to be a mismatch. That didn't seem to work, and the faculty always seemed to lose. That was one of the things that had people upset, and I think this is really spearheaded by thoughts that were coming from the faculty senate, because the faculty senate, I think, had been entitled or had been given the responsibility of maintaining what was then known as the grievance policy. I can't remember exactly how it all played out, but what happened here with us is to rationalize—essentially, if we were in conflict with somebody, how would you best like it resolved? What steps would you take? So we came up with a three-step process: The first step was the ombudsman. You go to a knowledgeable, trained person—knowledgeable about the institution and the institution ways. It really grew out. I think we have five—recently, they had as many as five people in the ombudsman's office for the institution, not just for the faculty. But we were focused on faculty, and we recommended that an ombudsman be identified and sanctioned and that the ombudsman would be independent, not reporting to anybody. But the way ombudspersons operate is they don't take notes and they don't give advice or direction; they just listen. It's more like the Socratic method of just asking questions and trying to get people to arrive at conclusions that may be conciliatory or resolve the conflict, and you may do it with one

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individual, one participant at a time or two together. That's their way of doing it. So this was facilitated by asking truly a great man in this field, [Judge Frank Evans](#) from the [South Texas College of Law](#) downtown. This is the man who created right turn on red. Now how controversial could that be, and he also made left turn into a one-way street on red.

Tacey Ann Rosolowski, PhD

1:05:14.3

That's also good, yes.

William Plunkett, PhD

1:05:15.3

People don't know about that one. But he runs a—the South Texas College of Law conducts training classes in conflict resolution, and they go for a week. It turned out that our choice in ombudsperson—actually, he took that course, and then he became our choice as an ombudsperson. But he became interested in it in the process of being on the committee that I'm speaking of; this is [Bill Brock](#). He had been a full-time faculty member, and he has subsequently gone to half time in this function. He was the initial ombudsperson, and then as the responsibility grew, they brought in a full-time person, and she recruited at least two more people to assist with Bill. I think that's on the tenth floor of the Pickens Tower. They have this suite of rooms where people can come in, speak confidentially, and exit by a private exit. They really have it set up well. The last I heard, they had seen more than 300 cases in a year in terms of speaking with people and so forth and counseling people.

Tacey Ann Rosolowski, PhD

1:06:49.1

What are the other two steps? Oh, I'm sorry.

William Plunkett, PhD

1:06:50.0

So then the second step, failing ombudsman discussion—then if that doesn't resolve it, then we proposed that we would have a professional mediator come in to mediate the discussion or the conflict between individuals. I'm not sure if that ever was practiced. It just may have been too impractical for the institution to put into place. The third step, which has been practiced—and I think it was practiced—they used to have a conflict resolution oversight committee. I think probably it went out of business somewhere during [Dr. \[Margaret\] Kripke's](#) [Oral History Interview] tenure, but she used to participate in that actively. The third one was a faculty panel. It's a faculty panel, and each participant in this process—not the panel but the people in conflict—then would have the opportunity to submit in paper a writing of what their arguments were. The panel would review it and give them a judgment on that—make a recommendation to the president. We had at least one open house on this—that is, among the faculty. You go down to the Hickey Auditorium—large auditorium—and let the faculty come and present the ideas and answer questions, let them ask questions and so forth. So essentially what you're doing is vetting

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the potential policy and incorporating ideas upon further discussion and so forth and bringing it out. It went to various committees, and it became policy.

Tacey Ann Rosolowski, PhD

1:09:00.3

Is there primarily promotion and tenure issues to the faculty?

William Plunkett, PhD

1:09:06.5

Not really.

Tacey Ann Rosolowski, PhD

1:09:07.9

There's not really.

William Plunkett, PhD

1:09:08.8

No. It's all confidential. I didn't participate in things up to—when you're thinking of what generated the need for this, I don't recall promotion and tenure being key issues. You know of situations where it's the department chairman's prerogative not to recommend the person, but the person still has to be put up to be reviewed by the promotion and tenure committee. That's part of the P&T policy so that he or she can just choose not to endorse the candidate, but when the time comes, it has to happen.

Tacey Ann Rosolowski, PhD

1:09:53.6

What were some of the other areas of need—I mean—without breaking any kind of confidentiality but—?

William Plunkett, PhD

1:10:00.1

Well, authorship is one, how you divide the money on grants and those types of things, and intellectual property to some extent. I mean, I get people who come into me now as research integrity officer here, and I'll recommend that this is an ethics issue. It's not research integrity. There's no plagiarism, falsification, or fabrication here. It's a you-think-somebody's-done-you-wrong-type thing, and that's a research ethics thing, so I send them the ombudsman, which maybe doesn't satisfy a lot of people.

Tacey Ann Rosolowski, PhD

1:10:41.0

Interesting.

William Plunkett, PhD

1:10:42.5

Still, people feel strongly about their intellectual property or their creativity.

Chapter 18

B: Overview

The Conflict of Interest Committee

Story Codes

A: The Administrator
B: Building/Transforming the Institution
C: Professional Practice
C: The Professional at Work
C: Leadership
B: Obstacles, Challenges
B: MD Anderson History
B: MD Anderson Culture
B: Institutional Processes
C: Ethics
D: On Ethics
B: Controversy

Tacey Ann Rosolowski, PhD

1:10:46.8

Sure. Do you want to talk about your role on the Institutional Research Integrity—?

William Plunkett, PhD

1:10:55.7

Let me say one other thing. You asked where I might have had an impact. This policy that I'm speaking of is on the books. It's part of the institutional policy. In the, I think, late middle 1990s, Congress recognized that giving money to their—through the NIH, taxpayer money is being awarded to institutions. A couple of incidents came up nationwide that showed a conflict of interest, and it was perceived that people really had to manage—that's the euphemism—their potential conflicts of interest. That is, if you are the PI on a clinical protocol, you shouldn't be on the lecture scheme for that company who is sponsoring the drug and so forth. That's one example.

But on the other hand, there are conflicts of commitment. So in that sense, where do you spend your time? Do you spend your time with MD Anderson, or do you spend your time out on the road and where? Recently, it's been brought up and emphasized again; it's the clinical faculty that generates 85% of the revenue for the institution, so that was no small factor in trying to draw faculty back into the institution and limit the number of administrative days away that our faculty could take. The limit now is thirty days, and it's been set at that limit since we first wrote the policy. Okay?

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Tacey Ann Rosolowski, PhD

1:13:12.2

Okay.

William Plunkett, PhD

1:13:13.1

The first chairman of the committee was [Steve Tomasovic](#) [Oral History Interview], whom you know. He went on to be senior vice president for Academic Affairs, but he was—

Tacey Ann Rosolowski, PhD

1:13:26.7

Just so I know what committee we're talking about—

William Plunkett, PhD

1:13:28.5

Oh, it's Conflict of Interest Committee. It was mandated that each institution receiving its federal funds for research should have a Conflict of Interest Committee. Steve was the first chair, and he chaired it for two years, and then subsequently they offered the chair to Dr. [Andrew] von Eschenbach, but he was going to have too many responsibilities because he was rising to vice president for something. They had several names—chief executive. I'm not sure what he was, but he was succeeded by Dr. Kripke, who became vice president for Research and—

Tacey Ann Rosolowski, PhD

1:14:21.7

Academic Affairs?

William Plunkett, PhD

1:14:23.5

Possibly. So [Dr. von Eschenbach](#) couldn't take it. Then they offered it to another person who had been on the committee for two years, and he was deciding he had too many things to do because he's getting ready—he's the chair of Medical Physics. Then he decided he wouldn't take it. I was the third in line, and I said, "Well, okay." And at that time, we were operating on a collegial agreement of, "We know something wrong when we see it. We want to do well and have our colleagues do well," but we had absolutely no legal assistance there. That turned out to be 1996, when I took over that responsibility, coinciding with Dr. Mendelsohn coming to the institution. I think he caught me on his first official day as president and came up and told me how important this was, that the committee really needed some assistance. We got an administrative officer, administrative help, and then assistance with that, and then we also had two legal consults, one of whom is still with the institution in some capacity. So that was quite helpful.

Then it was decided that we need really need to write a fulfiller policy, and that was [Mr. \[Dan\] Fontaine's](#) initiative. It was the mandate to the committee, and he said that he would assist the

committee doing that. So I was asked to stay on for another year as chair. I served two years as chair, and that is when the conflict of interest policy came into being and became institutional policy. Then happily I rotated off of the committee.

After about three years, the problem arose within the institution and outside that—it was widely known and applauded that Dr. Mendelsohn had participated in creating a new therapeutic agent. That was cetuximab—monoclonal antibody directed at a growth-factor receptor. But then it was revealed—and I can't remember exactly how it came to light—that more than 100 patients had been treated on the cetuximab protocols, and they had not been notified that Dr. Mendelsohn had a financial interest in the development of this. This is before it was approved. That resulted in a big brouhaha—that is, notoriety of the wrong kind. It was at the same time that Enron was having problems and so forth. So that just seemed to build on one another because Dr. Mendelsohn was involved in standing a committee with Enron as well, and we were wondering, "What is he doing there?" But he was very proactive in formulating a committee. This was chaired by Paul Mansfield, who is now vice president for clinical something. He was from Thoracic Oncology as well.

So Paul convened this committee, and he was head of the Conflict of Interest Committee at the time, but they asked me to be on this blue-ribbon committee because of the experience that I had had in the formulation of the first iteration of the policy. Then Paul, after whatever time—I'm not sure if he had spent two years as chair of the committee—likely. He's very contributory of his time and very thoughtful in directing this committee. He rotated off. Then the committee's work was just about done, but the committee's recommendation had to be codified into making the new policy. So then I became chairman of the Conflict of Interest Committee again, and that was with the help of the committee and Mr. Fontaine's direction and guidance that we generated a new conflict of interest policy. That had been in existence until two years ago when it was updated—and updated not because of things that were happening at Anderson that we had overlooked but rather changes in federal laws and guidelines that had to be accommodated in our institutional policies. So those are things that I look back upon as administrative contributions to the institution.

Tacey Ann Rosolowski, PhD

1:20:18.3

What was the impact of that conflict of interest policy and how—?

William Plunkett, PhD

1:20:23.4

Well, there were people—so let's talk about conflict of commitment. Then there were people who were practicing taking many more days than thirty away. For instance, at UT Austin, faculty can take one day a week away from their offices, and it's viewed in the context of, "Well, they're going out and making contacts with industry and contacts with commercial concerns and bringing that back, and the institution will be stronger and perhaps enriched because of these contacts that they can make with that time." I've heard that explained in that way.

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I've already explained Anderson's view on people being away, and Anderson's isn't the most restrictive. For instance, Mayo Clinic is only a little bit more than half of what MD Anderson has—the time that they get away. So if you invite a speaker to come to MD Anderson, they probably want to speak Monday morning and be back there Monday afternoon because they—I think their time away is eighteen days a year—administrative time. You have vacation time, which you accrue otherwise, but we have faculty—and I myself have been involved in things that you would consider normal academic functions, going to meetings. I have a colleague who had been chair of a major conference, and she had to take vacation time in order to do that, being on a study section—that is, you're not only donating your time being away, but you donate a heck of a lot more time reviewing grants before you get to go away. But because of the administrative-time-away strictures of 30 days, that time wasn't available, so you have to take vacation time in order to accommodate yourself.

Tacey Ann Rosolowski, PhD

1:22:22.9

Can you see—do those days represent something different for clinicians than basic scientists? Because they've drawn a clear link between the revenue-generating powers of clinicians—these would be the institution. How does that work with the activities of basic scientists and what that—?

William Plunkett, PhD

1:22:44.3

Well, it's imposed—it's imposed, but my view is that basic scientists benefit greatly at MD Anderson largely due to the efforts of our clinical research colleagues. I have no problem with it in many ways, so I think that it makes it a stronger institution and we all benefit. That's something that might be explained in a different way—that the basic laboratory research faculty shouldn't have such a restriction—but I can live with it, and I don't hear much in the way of argument about it.

Another thing about conflict of interest that largely affected the clinical faculty, sometimes people would be on the panels sponsored by drug companies that would be going to different institutions or different small groups of probably medically related things and speaking about their aspects of a particular drug or therapy or device, that sort of thing. So the policy now has cut back on the ability to do that. Some institutions have cut it out altogether.

Tacey Ann Rosolowski, PhD

1:24:31.4

What's your view of that?

William Plunkett, PhD

1:24:35.4

I think that the pharmaceutical industry overtly had been attempting to buy clinicians—not only in academic institutions such as our own but certainly private doctors—to influence them into

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using and prescribing their products. I mean, how else can you explain a paid trip for your family to Hawaii to participate maybe in a talk group or think tank?

Tacey Ann Rosolowski, PhD

1:25:23.0

How does that affect the basic researchers? Are there instances?

William Plunkett, PhD

1:25:26.3

Well, pretty much not much. There are some instances—people who are involved in translational research. Companies will like to have the credibility of having a basic science background to what they are doing, so people who are involved in what is called translational research would occasionally get invited to these meetings. I've had that experience. But now the strictures are everywhere. The pharmaceutical companies have to publish who they pay. That goes for honoraria. So I understand the Conflict of Interest Committee is going down the list, looking for MD Anderson faculty and making sure that they have disclosed what they are doing and what they are being paid for. The requirements as they were set out—and I think they continue to be—are that you cannot earn outside of your MD Anderson employment more than 50% of your MD Anderson salary from all institutions and not more than all payers—outside employment—and not more than 25% from any single payer. It's a judgment call. Do we think that that's unreasonable? There are people who can go out and earn lots more than that now, but that's what the policy is, and it applies to everybody. I think the opportunity to participate in that applies more to physicians who have a much more direct role with pharmaceutical companies. Where it might affect basic scientists is with equipment, but you buy a piece of equipment, you're good. You don't need to buy anything more.

Tacey Ann Rosolowski, PhD

1:27:34.9

What are the concerns? I mean, it may seem obvious, but maybe it isn't? I mean, what are the concerns when these kinds of relationships are established, and then you factor in patients and research?

William Plunkett, PhD

1:27:47.8

Well, it's a judgment thing, and you can't be the PI of a clinical protocol if you're financially involved with the sponsor of the protocol. That's it. If you are a co-investigator, you may participate, but your participation with the sponsor has to be declared on the informed consent. You have to disclose it to the people who are being affected so they can use their judgment in terms of whether you would advise them fairly to go on this protocol versus that protocol co-appointed in leukemia. I think, in beginning drug protocols, we may have fifteen protocols that may apply to patients in a particular category, literally. It's really competitive for patients there. So you can see how that might come into play, but I don't see it coming into play with my

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clinical colleagues. You write the eligibility rules, and you go by the eligibility rules, and there is oversight for that as well with the IRBs. I mean, the auditing these days is thorough.

Tacey Ann Rosolowski, PhD

1:29:28.2

Yes, I've heard people express it otherwise. Would you like to say more about conflict of interest? I'd like to hear next about the research integrity role.

William Plunkett, PhD

1:29:43.0

Well, I would say that the conflict of interest policy that we had originally written and then extended—and it extended to the point where Dr. Mendelsohn's agreement that the management committee would not be involved financially with any company with which MD Anderson does business. That is part of the basis for the discussion that's gone on with regard to Dr. DePinho and his role. He discloses to the Board of Regents and the vice chair for Health Affairs and the Board of Regents, and so then—they knew coming in that that would be an issue with him and with his relationship with the institution and the perception of the faculty. It was the first thing that Dr. [Kenneth] Shine brought up when he introduced Dr. DePinho as the lone, final candidate in May, two years ago. It clearly was on the mind of the people who were involved in that because it was different, and we had come through the problems that were associated with Dr. Mendelsohn. So it certainly was different, and my understanding is Dr. DePinho is divesting himself—going off of boards and divesting himself or placing his holdings in blind trusts, and those were things that were recommended from the beginning by the Conflict of Interest Committee.

Tacey Ann Rosolowski, PhD

1:31:33.4

So the Conflict of Interest Committee had gotten involved from the very beginning, when he was a candidate?

William Plunkett, PhD

1:31:38.2

No, no. That was from 2000—the first policy.

Tacey Ann Rosolowski, PhD

1:31:41.5

Oh, I see. Right. Okay, I understand what you're saying now.

William Plunkett, PhD

1:31:45.9

Sorry I wasn't clear on that.

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Tacey Ann Rosolowski, PhD

1:31:47.2

No, that's okay. It's interesting to see how the issues have exploded.

William Plunkett, PhD

1:31:59.3

But we have the feeling—we certainly had the feeling when we first came out with the conflict of interest policy. Then it had been redone to include Management Committee and given some more breadth, so we were way ahead of other institutions. Paul Mansfield and I went to meetings for Conflict of Interest, Inc., or whatever, and we expressed what MD Anderson does. People would say, "Wow. That's really forward-looking," and so forth. I've heard that from people who are involved in the administration now of the conflict of interest policy as well as in our administration. I think we were on the right path, and it's my understanding that the recent changes are just adjusting to the outside exigencies.

Tacey Ann Rosolowski, PhD

1:33:04.0

What's your view of the dilemma that Dr. DePinho and [Lynda Chin](#) are in right now? I mean, do you think it was fully a known quantity given that they had disclosed a lot of their holdings upfront, or do you think they have moved into a different kind of situation with conflict of interest, or is it not conflict of interest?

William Plunkett, PhD

1:33:26.4

Well, we knew that the—it is the conflict of interest policy that the Management Committee—Dr. DePinho—and the people who hold that office wouldn't have financial interests in anything that MD Anderson might do business with. But there is also a policy for a waiver in there, and that, to my understanding, is what Dr. DePinho was exercising and thinking that—bringing forward. So it caused—when that became known locally and nationally through sources, then press—then that invited other opinions—expert opinions that have been involved in COI, and some of them differed with having a waiver—just the existence of that—because it's from academic sources and so forth. As Steve Stuyck used to say, if there is a problem, you just be transparent. I think his statement was, "Get it out. Get it all out, and get it out now." It's always seemed like a good policy to me. To have things come out slowly just makes it more difficult.

Tacey Ann Rosolowski, PhD

1:35:08.5

Many fires along the way.

Chapter 19

A: The Administrator

Research Integrity Officer

Story Codes

A: The Administrator

C: Ethics

D: On Ethics

A: Overview

A: Definitions, Explanations, Translations

B: Building/Transforming the Institution

D: On Research and Researchers

D: On Leadership

D: On Mentoring

C: Professional Practice

C: The Professional at Work

C: Leadership

B: Obstacles, Challenges

B: MD Anderson History

B: MD Anderson Culture

B: Institutional Processes

C: Personal Reflections on MD Anderson

C: Giving Recognition

A: Professional Values, Ethics, Purpose

William Plunkett, PhD

1:35:14.2

So we go to research integrity?

Tacey Ann Rosolowski, PhD

1:35:16.2

Or are there other kinds of initiatives that you would like to talk about?

William Plunkett, PhD

1:35:21.1

Well, these three are big ones? When you look at my CV, you can see that there's probably three pages single-spaced of committees that I have participated in, so I've had substantial experience.

Okay, conflict of interest. In thinking back about it, I knew that there was something to deal with research integrity and it was managed by [Dr. \[Leonard\] Zwelling](#) when he was vice president for Research Administration because I believe I had been on one committee that had some oversight of research integrity issues, although I can't recall specifically what those had

been. It was after [Dr. \[Raymond\] DuBois](#) was appointed provost, when Dr. Kripke retired. I hadn't met him personally, and we hadn't had any conversations. When I got the email, "Dr. DuBois would like to meet you in this room at this time on this day"—so I walk in the room, and I think there were five people in there, all men and a woman. Maureen Cagley was the woman who assisted Dr. DuBois and now serves the same position with [Dr. \[Thomas\] Buchholz](#). The other people all had dark suits on, and there was one empty chair around the table. There was literally a pile of papers in front of that, and I looked at that. The guy sitting in the chair next to me was Dan Fontaine with whom I had worked, as I mentioned to you, with conflict of interest. He looks at me, and he says, "Bill, you think something is coming your way?" Dr. DuBois said, "Please sit down."

That was in November 2007. I was not expecting this, and there really wasn't anybody mentioning, "Well, why don't you just take a week and think about it." I've had the experience that I've never heard those words around here. So I walked out of there with my stack of papers to read about conflict of interest and so forth, and a new partner, who was Wes Harrott. He is the executive director of Research Administration. I don't believe I'd ever met him before. So Dr. [Leonard] Zwelling was removed from his vice president position, and another vice president of Research Administration was appointed. Wes took over the direction of that and I think other groups which had really become—the group under Research Administration had become quite large. They were split into separate areas, each with their own director or manager or an appropriately titled individual. I think there were maybe five or six different areas that could have found their origins in Research Administration under Zwelling.

Tacey Ann Rosolowski, PhD

1:39:22.6

Can I ask you, how did Research Administration—? Maybe this is too big a question. You can tell me. We can save it till later. How did Research Administration evolve? I mean, it sounds like it's pretty complex, maybe cumbersome, and not unexpectedly given how research is positioned in this institution.

William Plunkett, PhD

1:39:44.4

I think there are a number of pressures. I know Dr. Zwelling very well. He has been a member of—we've been a member of the same department since he came here in 1984, I believe. He is still a member of our department. His explanation was it was a response to pressures from the legal side and from the regulatory side of more things that MD Anderson was responsible for and had to do in order to comply with regulations that were being promulgated on an unfunded mandate basis. Conflict of interest is one of those, and research integrity is another one. I mean, that doesn't even start to approach the clinical aspects of the regulation and the oversight of the—whatever goes into—however, the IRB is separate and an independent entity, but there has to be communication with the IRB. That responsibility also fell to that office. I never knew what drove it, and I haven't heard Len say really what resulted in him, as he would say, being fired

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from that position but only the result of what's happened and is a Balkanization of the efforts. That's one way of saying it.

Another way of saying it is you make it more concise and responsive or whatever—agile. He certainly drew a lot of attention, because Dr. Zwelling is very—he's clear-thinking. He understands what the policies are—what the rules are, as it would be—and he holds people to it. But he is also a strong, strong proponent of being transparent. This is why things are happening, and if you need an opinion, ask the people who are affected—that type of thing. So in any event, I ended up—so Wes is still—we consider ourselves partners on this. He does have legal assistance, and one of those people helps me on an as-needed basis.

Tacey Ann Rosolowski, PhD

1:42:42.2

So what are your roles?

William Plunkett, PhD

1:42:44.1

Well, the oversight of Research Integrity is to react to allegations of falsification, fabrication, and plagiarism. My role is not as an investigator or a snoop or to go out and look for that but to wait until those allegations come to us, pretty much. And then the role is like a fireman going down the fire pole trying to—you're reactionary to it. You react to it.

There are three phases of that, and one is an evaluation of the evidence, which I usually do by myself, or Wes—if he has time—will look at things. If it seems that there's credibility to allegations, then we would move to what's called an inquiry, where several people—it can be a faculty panel. It has been faculty panel. Or it can be Mr. Harrott, his legal counsel, and me just looking at things, interviewing respondents and rarely claimants. Most of the claims are anonymous. Most of the allegations come in anonymously.

There is an Office of Research Integrity at the Public Health Service, and we answer to them. The way the system was set up is that, first of all, there's going to be an Office of Research Integrity, but then, of course, Congress isn't going to fund them to go out to every research institution that receives funding from the Public Health Service. So then it becomes the unfunded mandate—unfunded by NIH to the Public Health Service—that every institution receiving funds shall have a point man, as it would be—an Institutional Research Integrity Officer; that's my title—to respond to these on behalf of the institution. I answer to the provost—work with the provost more recently.

What we're doing now is they've just come up with a new policy meeting. Instead of every month, it's every other month. Thank you very much. It goes with a cloak of confidentiality. This is implicit in this to preserve the reputations of those who are maybe respondents but the allegations are unfounded. Sometimes you can't prevent that—knowledge of it—because anonymous respondents or even known claimants will broadcast their allegations.

Let me just backtrack for a minute. There is the evaluation of evidence, an inquiry, and then if there is really thought that this is not right, it either falls into the fabrication, falsification, or plagiarism. Then you can go to a formal investigation, and there are time limits for this which can be extended. But there is a full way that you go about doing this and replying. We've developed at least a speaking relationship with the people at the Office of Research Integrity, so we can give them a call and say, "Well, what do you think about this?" Typically what they would say is, "Well, why don't you write it out in a letter and send it to us, and then we'll tell you what we think about it," and that type of thing. But we do get guidance. Some people are less formal than that, and I value that. Typically the people with more experience in the Office of Research Integrity—I had one terrific experience in the genre. They had a research integrity officer boot camp, so we had three days of speaking with, listening to, and being lectured to by people who are really experienced in this field and some of the people who were there in 1987 when the office was created, and it was a terrific experience. Of course, we had an opportunity for socializing some as well, so you really get the feeling that you know who you're calling up and speaking to. At least for them, it's on a first name basis, so that's of considerable assistance.

Tacey Ann Rosolowski, PhD

1:48:16.5

How many cases have you seen per year?

William Plunkett, PhD

1:48:20.1

Last year, it was probably eight real RI issues. I've probably had as many research ethics times when you sit down and try to counsel people about what they're doing, and on occasion, it goes around. And finally, it goes to the provost and so forth, and then they go through the grievance process.

Tacey Ann Rosolowski, PhD

1:48:56.5

Are there any themes that you see? I mean, I know you can't speak about individual cases but—

William Plunkett, PhD

1:48:59.6

Yeah. No, no, no. People are sloppy, and it's careless error. It's a pejorative term, but people know what you're talking about. It's things where a figure has accidentally been used twice. So the question immediately is, "Show me all of the data from the experiment and the evidence that you actually did the experiment and that you misplaced a figure—you used a figure twice where you should've used the figure that wasn't included." It's a matter of—this arises due to data handling, data management once you get the data acquisition, and to some extent the governance of the data. That's the largest problem is people make mistakes.

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Tacey Ann Rosolowski, PhD

1:50:09.2

Interesting.

William Plunkett, PhD

1:50:11.9

The lengths to which you have to go to really let them prove it—have them prove it and then you—because I'm always responsible not only to Dr. Buchholz at the provost but also to the Office of Research Integrity, so I have to write it up so that they will accept it and not come back with other questions. Sometimes you can just say, "Well, this is what happened, and that's what happened, and we saw this," but on the other hand, there have been occasions where they want to see the original data. There have been occasions where they do some analysis of the original data, saying, "This is what we're talking about." But those analysis procedures sometimes can be refuted by original data that shows that, "Look, when you blow this up in Photoshop, it distorts it. It doesn't really give you a clear view," and when you look at the original data, then the respondent is validated, and the allegations are denied.

Tacey Ann Rosolowski, PhD

1:51:33.3

Is there a place—? How would I want to ask this question? I mean, it seems if it's an issue of sloppiness or carelessness that there are places much earlier in the process where there could be intervention or checking. Is that a training issue? Is it a quality-control-in-the-lab issue?

William Plunkett, PhD

1:51:56.3

I think it's a human nature issue. People want to get things out—want to get things published. The senior investigator who is responsible for it may read the figure legends but doesn't look closely at the figures, assuming that they're okay. But knowing who is sitting across the table from me, the respondents, when they are sitting there and you show them what the problem is, they can see it right away. Then it comes to, "Do you have the data?" and to be able to refute it with the data, and then you just say it's honest error. So that's really the fourth outcome is that you may go through this process, and there may be a finding of a research misconduct issue, but much more likely honest error is the explanation or the conclusion.

Tacey Ann Rosolowski, PhD

1:53:06.7

And that's a hard way to learn that lesson, isn't it?

William Plunkett, PhD

1:53:10.0

It is, but as I started off with transparency and "get it out there" and so forth, people do well when they recognize that there is a problem. Maybe there has been an error or they can't find the original data. Some people who turn out to be respondents will bring—they will read their blogs

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now that indicate people with—and driving the blogs are some people who probably don't have a day job who are just sitting there with image analysis software, looking for duplication within a publication. I've seen these duplications come in one paper and another paper—it's the same figure—and of this type of thing. So there are people out there who are driving it and coming in with these things that most often can be explained as honest error, but boy, it's a real time sink for me. It takes a lot of time to get around to doing this and insert these responsibilities in with other things that I'm supposed to be doing.

Tacey Ann Rosolowski, PhD

1:54:34.6

How much longer are you going to be—?

William Plunkett, PhD

1:54:36.0

That's the thing that I didn't ask Dr. DuBois when I walked out of there with those papers. What's the time?

Tacey Ann Rosolowski, PhD

1:54:47.2

Not a minor detail. We've actually run over time. Thank you very much. But I have just a few more questions. We could do it now or—okay.

William Plunkett, PhD

1:55:01.2

Why don't you go ahead?

Tacey Ann Rosolowski, PhD

1:55:02.4

Okay. Was there anything in addition that you wanted to say about Research Integrity aside from you don't know when it will be over?

William Plunkett, PhD

1:55:11.3

I don't know. I think it's one of these boots-on-feet-first things. It seems like all of our faculty are working on overdrive, and you give them something that is not of their immediate concern—like something like this—and it's something they're not really experienced or schooled in and looking at it, and when it's explained, they're onboard, but they're not the discoverers or the real critics of it. So that's one reason that Wes Harrott, our legal assistant, Patrick Hanley, and I have really gone to looking at it ourselves. If I'm capable of evaluating the evidence, I do it myself. If I'm not—and you really need somebody who is an expert at it and try to walk them through it and what they're looking for and what alternative explanations there may be.

Tacey Ann Rosolowski, PhD

1:56:28.6

Does having a board of that kind, you think, sharpen people up if they are aware that there is somebody who is going to be—there's a chance that their work will be under that kind of scrutiny?

William Plunkett, PhD

1:56:41.6

Sure, I think it does, but what really sharpens people up is being under that scrutiny. It's the sort of thing of whether they've seen the light or felt the heat—it's both. These people come back, and they will write these policies for their labs. Or when they have administrative responsibilities in their departments or even divisions, they'll say, "This is the way we're going to keep records from now on," and so forth. I've been impressed with that.

Tacey Ann Rosolowski, PhD

1:57:19.7

That's great. I mean, I was just thinking as you were talking about how this honest error—I mean, "honest error"—it's such an innocence there, and to have someone go through that ringer of having their work—of having to go through that process, that would be just devastating to some people.

William Plunkett, PhD

1:57:38.5

People come in thinking the very worst about when you say research misconduct or research integrity. No scientist—nobody—wants to have themselves or their work questioned in that way.

Tacey Ann Rosolowski, PhD

1:57:58.3

No, no. I mean just—

William Plunkett, PhD

1:58:01.3

The times when you see any sort of evidence of tampering or manipulation with data are vanishingly rare. The time-consuming thing is working through the process that we have to work with.

Tacey Ann Rosolowski, PhD

1:58:21.2

And then it's great that the people who have unfortunately been through that process are publicizing the fact that taking some precautions and being careful along the way can prevent that.

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William Plunkett, PhD

1:58:33.0

I don't think they publicize that they've been through it, but what they do is they act accordingly. They act out.

Tacey Ann Rosolowski, PhD

1:58:39.9

To build it in, to build it into—yeah, because it just seems—what a potential waste of a career and a waste of time.

William Plunkett, PhD

1:58:47.9

Yes.

Tacey Ann Rosolowski, PhD

1:58:51.4

Were there any other—you mentioned the three big roles that you had—administrative roles—and then with this, is there anything else administrative?

William Plunkett, PhD

1:59:00.0

This is included—the conflict resolution, the conflict of interest, and research integrity. It has a theme in my experience through that. So it's a job description that I assumed when I had really no formal experience in there, so it's all been a learning process outside of what I do in the other portion of my life here.

Tacey Ann Rosolowski, PhD

1:59:33.5

Was there a particular reason why you were drawn to these kinds of ethical integrity issues?

William Plunkett, PhD

1:59:39.4

Well, I was given a letter saying, "Dr. Mendelsohn would like you to do this, do that, and Dr. DuBois would like to meet with you."

Tacey Ann Rosolowski, PhD

1:59:50.2

So you were tasked with it? It wasn't—

William Plunkett, PhD

1:59:51.4

Right. It's a tasking. I haven't sought any of this.

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Tacey Ann Rosolowski, PhD

1:59:55.1

Okay.

William Plunkett, PhD

1:59:59.2

But in a way, it's an honor to be sought for these things that are not regular and not easy.

Tacey Ann Rosolowski, PhD

2:00:10.1

Why do you think they tasked you in particular for these roles?

William Plunkett, PhD

2:00:14.5

More recently because of experience and longevity. I've been in the faculty for a long time. What I'm told is that faculty members have confidence in me because I've been in the spotlight for a while off and on. I've been on the Promotion and Tenure Committee three times, chaired it once. There are other things that are important and unimportant to faculty. I've been on so many committees that that's how I, of course, get to know other people. I've chaired search committees most recently for senior vice president for Academic Affairs. Those are not easy times. Really a lot of thought goes into that when people are really engaged, and my experience has been that your personal and professional relationship goes to a different level after you've been through that together.

Tacey Ann Rosolowski, PhD

2:01:42.2

You mean a committee of this kind?

William Plunkett, PhD

2:01:43.6

Yes.

Tacey Ann Rosolowski, PhD

2:01:44.0

And how so?

William Plunkett, PhD

2:01:45.7

Well, people recognize commitment and integrity and focus and willingness to speak your mind and defend what you say. That's the coinage of our academic environment. The coinage of the research realm is the R01 grant. That's an investigator-initiated grant. It's always good to have a couple of those.

Chapter 20

A: The Researcher

Skills in Developing New Ideas; Support for New Research

Story Codes

A: Character, Values, Beliefs, Talents

A: Overview

A: Definitions, Explanations, Translations

A: The Researcher

C: Patients

C: Professional Practice

C: The Professional at Work

Tacey Ann Rosolowski, PhD

2:02:24.0

I just wanted to ask you a couple of general questions, and some of these come from some of the interests from faculty development, actually. I was wondering as you—what happened to—? What you would call—identify as your research skill set? When you talked about the mentoring that you got when you were in those early programs, and have the changes in technology and the approach required you to develop new skill sets, what are those?

William Plunkett, PhD

2:03:03.7

How do you turn it on? I really enjoyed working at a laboratory bench and participating in hands-on research and being able to take trainees and show them how to do it and work together with them to overcome problems of a technical nature or explain the rationale behind that, and I can still explain most of the rationale and how things work. But I don't work in the laboratory, and that, I think, is a price that many of us pay when we become involved with—particularly with administrative responsibilities, but also, if you are successful in writing—in coming up with new ideas and new ideas that are fundable, which means you have to write grants. And overseeing publications, that takes a lot of time. It takes you away from being able to physically work in the laboratory. Technology will come, and I will see a result and know how to interpret it, but I wouldn't know how to take the cells and grind them up and achieve that result in a concentration and time and pH manner.

Tacey Ann Rosolowski, PhD

2:05:01.8

What about the interpretive skills? How have those evolved, you think, over the years?

William Plunkett, PhD

2:05:07.5

Experience and going over it with—you read papers, and you listen to people interpret their

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results in meetings and so forth, and you work with that. You learn. I learned as people came into the laboratory and started doing techniques that I had never done before, and there were some times when I would flatter myself to think that I was contributing something by asking a question. "Have you considered the pH of your buffer? Do you really know what the heck you're doing when you're looking for particular protein with particular properties?"—that sort of thing. So many things now are in kits, and it's one kit serves all purposes. Either you don't have the opportunity to fashion something in a very specific way—

Tacey Ann Rosolowski, PhD

2:06:19.0

What do you mean when you say "kits?"

William Plunkett, PhD

2:06:21.3

Oh, well, if you want to determine a protein concentration, you pay so much money for some commercially produced kit. You drop your sample in, and it will give you the results—for antibodies, for instance. That's a major portion of a lot of the biological research that's done. "Well, it's \$235." "Okay. Well, we'll get another antibody." "Well, I need five." "Okay." So people aren't making their own antibody. There are companies—if you have something for which there isn't—so I just used this example on antibody. They'll make it for you if you want to make a peptide, nucleic acid synthesis, nucleic acid sequencing, all those things. So at MD Anderson, we have a terrific set of cores—core facilities—that work on a fee-for-service basis that really function at a high level and enable us—all of the faculty—to do things that would take us a long time and a lot of expense, if ever, to utilize. But that is what the core grant is about and the programs that use them. And we just learned that we received on our latest grant—Dr. DePinho is head of the grant. It has many cores and many programs, and it received an exceptional rating, which is just what it says—exceptional. There may be a handful of institutions out of the seventy or so cancer centers that have core grants that receive that type of a rating.

Tacey Ann Rosolowski, PhD

2:08:23.8

And tell me what that means?

William Plunkett, PhD

2:08:26.2

That means you're going to get your money that you asked for.

Tacey Ann Rosolowski, PhD

2:08:28.7

Okay, so I mean—

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William Plunkett, PhD

2:08:29.3

So then it means—it's the highest rating.

Tacey Ann Rosolowski, PhD

2:08:31.3

It's the highest rating. Okay. And that's for the research design?

William Plunkett, PhD

2:08:33.2

There are places that have—I don't—I'm not sure if that will ever be advertised per se, but I know one cancer center that puts it on their logo that they're exceptional rated and so forth—advertise themselves as such. It's competitive, because patients can read the Internet and do, and they will come with a sheaf of papers that they've have printed out and downloaded and so forth and wanting to know about protocols. Many of them are very well informed—particularly those who come to tertiary care centers like this.

Tacey Ann Rosolowski, PhD

2:09:12.7

It's all promotional, and it's all—

William Plunkett, PhD

2:09:17.0

Distance doesn't really mean anything if their life is on the line. They're looking for a particular—the literature has convinced them that "this is what I need to be treated with." They now know their molecular readout of whatever it may be or a prognostic factor and indicators, and they'll come in and tell you.

Chapter 21

B: Key MD Anderson Figures

MD Anderson Presidents

Story Codes

C: Portraits

B: MD Anderson History

B: MD Anderson Culture

C: Professional Practice

C: The Professional at Work

A: Influences from People and Life Experiences

C: Understanding the Institution

B: Growth and/or Change

B: Controversy

Tacey Ann Rosolowski, PhD

2:09:42.5

I just had—there's sort of one question area that we haven't really covered yet, and that was your observations about the different presidents that you've worked with, and I'm wondering if you can tell me what you think their leadership styles were like and—

William Plunkett, PhD

2:10:00.6

Well, actually I was here—I've been here under all four of them only briefly—maybe four years under Dr. Clark. But I am happy to say—well, certainly I knew him, and there were signs that he recognized me. He would occasionally come by and say, "What are you working on?"—that type of thing. But then administration grew out, and then with Dr. LeMaistre, you would have less personal contact. At big seminars and meetings, he'd know who we were and particularly with the clinical staff faculty. But that's just my perception.

There is another layer of vice presidents that are in there and other higher-ups that come closer to the faculty. I think it's a matter of managing the growth of the institution. I think Dr.

Mendelsohn was most relational with the faculty, particularly when he came here. He would come to department meetings. He was always going to seminars, coming in to seminars and seeing what's going on. I mean, I really had a sense that he was participating in the academic environment. As I told you, as a member of our department, we asked him if he would lecture in our lead course, and yes, he did. That's the sort of persona that he put out there. I think probably with time and increasing responsibilities, that aspect of it—that is, he had so many things to do and attend to. But my feeling was that he was quite responsive to the faculty.

For instance, that's where this faculty peer review and grievance and conflict resolution came from. He appointed, what he called, a blue-ribbon committee—you call them all blue ribbons

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with the important ones to him—to deal with something that the faculty Senate was grouching about. He had some interactions with the faculty Senate over one issue or another issue that eventually was resolved. But he was right there interacting with people.

Dr. DePinho has been here less than two years, but he has been outgoing in the sense of putting on his town hall meetings, trying to cover different aspects of the environment and the responsibilities of MD Anderson with the clinical responsibilities, addressing research that's going to be a—when we get the new provost on board, it's my understanding that there's going to be an institution-wide evaluation of the strengths and weaknesses of our research programs here. He is, I think, almost certainly driving it. But look at the [Moon Shots](#). He's really had that vision to push that forward. I think some of it—there was a perception that maybe he was writing the lecture before he gave it every time—that it wasn't all planned out. He's reacting to things that may have been unforeseen, but it's a very large undertaking and diverse—diverse among the groups that are involved in that. But it's going. The Moon Shots have startup funding now, and there are concrete plans underway for getting the philanthropy-seeking machine in order.

As I think I said, I was just at [Lecture Tube](#), an infomercial to the development office, yesterday with Dr. Keating. They are very responsive. So time will tell with that. There have been sometimes these ups and downs that you can look at on a month-by-month basis, smooth out over time. I expect that that will happen with Dr. DePinho—some of the things that he's faced and gone through inside and outside of institution.

Segment 22

A: View on Career and Accomplishments

J Freireich's Impact; A Career Commitment to Collaborative Work

Story Codes

C: Portraits

B: MD Anderson History

B: Multi-disciplinary Approaches

A: Overview

A: Definitions, Explanations, Translations

A: The Researcher

B: MD Anderson Impact

C: This is MD Anderson

C: Discovery and Success

B: Multi-disciplinary Approaches

Tacey Ann Rosolowski, PhD

2:15:41.7

As you look back, what are the things you would identify as those initiatives or contributions that you are most pleased to have given to the institution?

William Plunkett, PhD

2:15:53.8

Well, I wouldn't be commenting on that if it weren't for the opportunity that I was given by Dr. Freireich. He is, without question in my mind, the reason for—the whole basis for great advancements that were made and mentoring, training, influencing a whole generation of cancer researchers. I certainly was one of them.

One of the opportunities that I had was to pioneer evaluating how drugs affect primary leukemia cells from patients during therapy. That opened up a whole new era that really isn't matched anywhere else on a pharmacologic basis. We pursued a class of compounds, but we were quite familiar with that. I can't say that I'm unhappy that I've moved on to some other things, but I still work on that aspect.

I think some of the most exciting work that I'm doing—that the whole laboratory is doing—is based on that genetic basis of being able to identify a genetic lesion in a cohort of individuals that is sensitized to a drug. We figured out the mechanism of action of that drug and why it should be sensitized. So we've been able to identify patients and designed a clinical protocol for that and actually got an R01 grant to support the clinical protocol with my colleague [Bill Wierda](#). So that's very satisfying.

That whole idea of developing the cellular pharmacology work—that was different everywhere from anything, and it really created an interaction between myself and my clinical colleagues and in my trainees. People have grown on to come onto faculty—have this trust. We feel like we are a go-to laboratory for questions that could be asked about compounds from our clinical colleagues—certain classes of compounds. But we are still coming forward with hypotheses of knowing how a drug works, knowing what the susceptibility of a cancer cell may be—that is, the pathogenesis, pathophysiology of a cancer cell.

Just last fall, we had developed this hypothesis, done it in model systems in laboratory, worked together with our colleagues in the Leukemia Department to develop clinical protocols that would test it. This was chronic myeloid leukemia that was resistant to these new tyrosine-kinase inhibitors. They were new ten years ago, but the resistance developed, and what you could see now is a predictable way. But this drug acts in a different way, and it was approved by the FDA on the basis of being effective in tyrosine-kinase-resistant CML. Now, what more could you ask for?

Tacey Ann Rosolowski, PhD

2:20:16.3

Is this the Brutyn's?

William Plunkett, PhD

2:20:18.1

No, that's not a Brutyn. This is called omacetaxine. It's an old drug. We knew how it worked and had to learn about the biology to figure out what biology would be susceptible to it because it blocks the generation of proteins. If you can do that transiently and if the proteins turnover rapidly, then it has a biological effect. That's something that we brought it to—I think the mechanism by which it acts—you can't patent a mechanism, but you can be happy that it's validated. The mechanism by which it acts fits this disease well, and we're opening another protocol in a disease that has another set of proteins that turnover very rapidly that are required for survival and proliferation of the cancer. If you bring them down—even only transiently—by blocking protein synthesis, then the cells induced cell death themselves, so much so that when you use compounds that act by this general mechanism, you would think it would be total body malaise if you are blocking protein synthesis or blocking RNA synthesis. But the selectivity comes from—this is probably more than hypothesis now. I think it's real. The selectivity comes from the fact that the target tumor cells really need the proteins that are being affected, and other cells don't need it, at least so much. The initial response had been a syndrome or a symptom called [tumor lysis syndrome](#), and that is you get the death of so much tumor so fast that the body can't handle the cytokines that are released from those cells and the imbalance of blood chemistry.

Tacey Ann Rosolowski, PhD

2:22:46.4

Interesting.

William Plunkett, PhD

2:22:47.2

And they have to go—and it's so specific for the tumor. So then now we are in the phase of, okay, how do I rein this in and make it manageable?

Tacey Ann Rosolowski, PhD

2:23:02.3

That's amazing.

William Plunkett, PhD

2:23:03.7

Yeah, it is. I think it's terrific. It's great for—but to have—the effect on me is to have been trained really in the basic science environment, progressively thinking about going more and more to the clinic until that became possible when I came here. You still have to have the support for your basic science, and you have to do the basic science underpinning for that. We do that, but then you have the luxury of extending that into clinical investigations and getting recognized for it, at least by your colleagues, and getting credibility, at least when you apply for support of a clinical protocol. But we are going to do the correlative studies. We are supporting research nurses and so forth—the whole thing. It doesn't sound like basic science to me.

Tacey Ann Rosolowski, PhD

2:24:20.4

No. It's a great flowering of an original set of interests.

William Plunkett, PhD

2:24:28.1

It is. Right. Yeah, who would've thunk it? So I'm happy with what I'm doing. I wish I could do more of it and expand further and have more proficiency and more of the contemporary things that are needed to do research, but that's what core facilities are for. And in the context of the Moon Shot, that's what the platforms are for is to further the technical needs of answering questions and doing research that are associated with what a particular Moon Shot is proposing to do. It is very focused. Having those capabilities really allows you to use your imagination and say—you don't have to really say—"What if?" because you can see how you can do it. Because with the facilities that we have with the cancer center core grant and the platform facilities that are only now being developed, you can see that there is probably not much that lies beyond your reach once you achieve the appropriate degree of organization and infrastructure to support the whole breadth of what you wish to accomplish—or tasked, as it is, with a hypothesis. When we started this cellular pharmacology thing, we always used to call it hypothesis testing in the clinic, and then all of a sudden, this term "translational research" came up around, and I guess that's us.

Interview Session: 3

Interview Date: May 8, 2013

Tacey Ann Rosolowski, PhD

2:26:23.5

I guess it is. It sounds like it.

William Plunkett, PhD

2:26:27.2

But the key thing about translational research, and before you hang that shingle outside your office, you have to remember that a translator speaks both languages. That is the one key thing that Dr. Freireich could enable us to do is all be together, and you are only limited by your ability or willingness to ask the person sitting beside you, "What the heck does that mean?" when you are in the clinic context and to reply accordingly to somebody who doesn't know what's going on with basic science sort of thing. We really came together that way. So it's not as though—at that time, we didn't have many physician-scientists, and that's probably one of the most difficult job descriptions to fulfill effectively. But we can work together as teams with respect and inter-reliance on one another.

Tacey Ann Rosolowski, PhD

2:27:37.4

Is there anything else that you would like to add?

William Plunkett, PhD

2:27:41.0

I can't think of it after that. I think that's—the collegiality of it all is really terrific.

Tacey Ann Rosolowski, PhD

2:27:49.1

That's been a theme throughout your interview—building that and enjoying the benefits of it.

William Plunkett, PhD

2:27:51.8

Oh, well, I'm happy that came across. Well, the other thing is that we try to teach that to our trainees. We have a laboratory where—or laboratories that work together—where outliers are recognized pretty quickly or outside of collegiality and respectful of one another.

Tacey Ann Rosolowski, PhD

2:28:25.5

Any further comments?

William Plunkett, PhD

2:28:27.6

I think that's it.

Interview Session: 3

Interview Date: May 8, 2013

Tacey Ann Rosolowski, PhD

2:28:28.5

Okay. Well, thanks very much for the time taken for the interview, Dr. Plunkett. I appreciate it very much.

William Plunkett, PhD

2:28:30.9

Well, you're welcome. You're welcome. Please, do speak with Dr. Keating.

Tacey Ann Rosolowski, PhD

2:28:35.8

I will.

William Plunkett, PhD

2:28:37.5

He has a remarkable history of having been a fellow here. He certainly has been a leader throughout his years. He is a leader internationally. He is known to his patients as "the guy who gives and leaves big hugs." He has a remarkable insight. He started an endeavor here that now—over the last, I think, eight years—has provided a conduit for the desire of patients to provide funding and philanthropy, potentially to their own benefit—patient-funded research—and funnel that into laboratories and sometimes clinics, but mainly laboratories, that are committed to doing something in that direction within two or three years. He has disbursed nearly 20 million dollars over that period of time, really, as an accelerant, but it's the facilitating glue for national and international collaborations—just good fellowship and collegiality and trust. So that's something that we've valued, and those are the people who have been included.

Tacey Ann Rosolowski, PhD

2:30:24.9

He sounds like a key person to talk to.

William Plunkett, PhD

2:30:26.9

Yeah, he is, and he's the chair of the Scientific Advisory Board. That determines where the grants go, which means they don't come here. That's a conflict of interest.

Tacey Ann Rosolowski, PhD

2:30:41.4

Well, I'm turning off the recorder now at 4:18. Thank you again.

William Plunkett, PhD

2:30:46.8

You're welcome.

2:30:48.2 (End of Audio Session 3)