

# **Dr. Isaiah Fidler, DVM, Ph.D.**

Interview #3

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## **Dr. Isaiah Fidler, DVM, Ph.D.**

Interview #3

### **Interview Profile**

#### **Interview Information:**

Two interview sessions: September 26 and 27, 2011

Approximate total duration:

Interviewer: Tacey A. Rosolowski, Ph.D.

For a CV, biosketch, and other support materials, contact:

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#### **About the Interview Subject:**

Dr. Isaiah J. Fidler (b. Jerusalem, Israel, 1936) was recruited to MD Anderson in 1983 to establish the Metastasis Research Laboratory. He is the Director of the Metastasis Research Laboratory in the Dept of Cancer Biology. He is a Professor in the Department of Cancer Biology with a joint appointment in the Graduate School of Biomedical Sciences.

#### **Major Topics Covered:**

Personal and educational background

The “seed and soil” theory; theory of cancer as a regulated, predictable process

The practice of basic and translational research

**University of Texas MD Anderson Cancer Center  
Making Cancer History Voices® Oral History Project**

**Research Medical Library: Historical Resources Center**

ORIGINAL Interview Profile: Dr. Isaiah Fidler, DVM, Ph.D.

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

Date: Updated 4/18/2014 (originally submitted, 4 October 2011)

During this interview conducted over two sessions on September 26 and 27, 2011, Dr. Isaiah J. Fidler (b. Jerusalem, Israel, 1936), focuses on the contributions he has made to advancing research on metastasis. Tacey A. Rosolowski is the interviewer. The interview takes place in Dr. Fidler's office in the Smith Research Building on the MD Anderson South Campus. Dr. Fidler came to MD Anderson in 1983 to establish the Metastasis Research Laboratory. On display in his office are numerous awards and memorabilia, including the microscope he used when conducting his first studies on metastasis and a first-edition book by the 19<sup>th</sup>-century pathologist, Stephen Paget, who articulated the "soil and seed" theory that Dr. Fidler continues to champion as he studies interactions between differentiated cancer cells and the body sites in which they produce metastasis. Dr. Fidler is very skillful at explaining complex molecular and physiological processes. He also offers many insights into the creative process of scientific discovery, often weaving in bits of wisdom taken from eclectic sources.

Dr. Fidler is the Director of the Metastasis Research Laboratory in the Dept of Cancer Biology. He holds the R.E. "Bob" Smith Distinguished Chair in Cell Biology. He is a Professor in the Department of Cancer Biology with a joint appointment in The Department of Cancer Biology in the Graduate School of Biomedical Sciences. Dr. Fidler is known as the 'father of modern cancer metastasis research,' and his numerous award include: the Lifetime Achievement Award from Nature Publishing (2010); the President's Award from MD Anderson (2007); the American Cancer Society Distinguished Service Award (2004); the 22<sup>nd</sup> Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research (1999). He was made an Honorary Member of the Japanese Cancer Association in 2007. He also received The Israel Cancer Association Award Presented by the President of Israel, the honor he says is the most meaningful to him.

In this interview, Dr. Fidler discusses his research in detailed terms, bringing great passion to the conceptual bases of his experiments: the "seed and soil" theory and the notion that cancer is a regulated and even predictable process. He discusses how his discoveries foster hope that more therapies will be discovered. He also comments on his own approaches and thought processes, providing insight into the practice of basic and translational researchers.

## **Dr. Isaiah Fidler, DVM, Ph.D.**

Interview #3

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## **Dr. Isaiah Fidler, DVM, Ph.D.**

Interview #3

### **Segment Summaries**

Interview Session 1: 26 September 2011

Segment 00A  
*Interview Identifier*

Segment 01  
*From Veterinary Medicine to Cancer Research*  
A: Professional Path  
[01:17]

Story Codes  
A: Personal Background  
A: Inspirations to Practice Science/Medicine  
A: Military Experience  
A: Experiences re: Gender, Race, Ethnicity  
D: The History of Health Care, Patient Care  
A: The Researcher  
D: Understanding Cancer, the History of Science, Cancer Research

In this Segment, Dr. Fidler talks about his youth in Israel, the decision to study veterinary medicine that brought him to the United States in 1958, and the later events that inspired his shift from veterinary medicine to the study of cancer in humans. In 1961 he received his B.S. in Veterinary Medicine at Oklahoma State University, Stillwater, Oklahoma. Dr. Fidler was awarded his Doctorate in Veterinary Medicine from the same institution in '63. He describes the difficulties of setting up a veterinary practice upon returning to Israel, where pet owners chose to terminate the lives of even beloved pets much more quickly than they do today. "I didn't work so hard to become an executioner," he recalls, explaining decisions that took him from private practice, to pharmaceutical research, and eventually back to the U.S. for a fellowship at the University of Pennsylvania Veterinary School, where his work on animals with cancer sparked his passion for problems of metastasis. After receiving a fellowship that enabled him to conduct basic research at the U. Penn. Medical School, he was advised to apply to the Department of Pathology, where many scientists were conducting research on metastasis. He received his Ph.D. in (human) Pathology from the University of Pennsylvania Medical School (Philadelphia) in '70. There he framed the basic question that would govern his career: how cancer moves from the primary tumor via the circulatory system to create secondary tumors and ultimately the metastases that are still the primary killers of cancer patients. After receiving his Ph.D., he went to work in the Department of Pathology in the U. Pennsylvania Dental School with a Luther Terry Fellowship(late '70).

Segment 02

*A New World of Research at University of Pennsylvania: Focusing a Research Career*

A: The Researcher

[19:50]

Story Codes

A: The Researcher

A: Overview

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

A: Definitions, Explanations, Translations

A: Career and Accomplishments

C: Discovery, Creativity and Innovation

C: Professional Practice

C: Evolution of Career

Dr. Fidler details how he began to look more deeply into the question of cancer cell differentiation, a groundbreaking discovery that was ultimately published in *Nature*. (Dr. Fidler shows the interviewer a Plexiglas containing a unit he invented to facilitate injection of cells into the tail veins of up to 100 mice per hour, underscoring the resourcefulness that a researcher had to have to move ahead quickly with a study.) Through this success, he was recruited to join the National Cancer Institute at Frederick, Maryland. His wife-to-be, Margaret Kripke, known for her pioneering work in photoimmunology, was also hired in a concurrent recruitment, and he describes how Dr. Kripke challenged him with the question that inspired a new line of research: “How do you know whether the cells you are culturing from a line are a selection or an adaptation?” His discovery that the differentiation of metastasis cells is a priori “revolutionized the world,” he states, noting that “you cannot treat a heterogeneous disease with homogeneous therapy” –the origin of individualized therapy. Dr. Fidler then explains connections between Paget’s “seed and soil” theory and his next experiments with transplanting metastatic cells between the organs of mice.

Segment 03

*Metastasis: A Regulated Process*

A: The Researcher

[46:39]

Story Codes

A: The Researcher

A: Career and Accomplishments

C: Discovery, Creativity and Innovation

A: Definitions, Explanations, Translations

A: Influences from People and Life Experiences

C: Professional Practice

C: Evolution of Career

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

D: On Research and Researchers

A: Character, Values, Beliefs, Talents

Dr. Fidler begins this segment by explaining that, in contrast with the prevailing belief (in the 70s) that cancer is the “ultimate expression of cellular anarchy” and that metastasis is random, his work has shown that cancer is a regulated process along every step of the way; similarly,

metastasis is predictable. In response to a question about why scientists held (and still hold to) these conventional assumptions about cancer, Dr. Fidler notes how difficult it can be for a scientific community to accept innovative ideas. He then talks about significance of training clinicians in research and the basic sciences.

Segment 04

*Reflections on Research; Becoming a Citizen; Influences: Words of Wisdom*

A: Personal Background

[13:12]

Story Codes

A: Personal Background

A: Influences from People and Life Experiences

A: Character, Values, Beliefs, Talents

In this character-revealing segment, Dr. Fidler talks about his ability to think outside the box. He recalls becoming a citizen and some of the cross-cultural challenges he faced. He recalls family members who influenced his independent thinking. He reflects on the contributions he has made to his field and the influence of Dr. Judah Folkmann on his thinking.

He ends this session by talking about the implications of his discoveries for research, its links to the current push for individualized care. He also questions how quickly they have been translated into therapies that will benefit patients.

Interview Session Two: 27 September 2011

Segment 00B

*Interview Identifier*

Segment 05

*Recent Research: A Focus on Brain Metastasis*

A: The Researcher

[00:19]

Story Codes

A: The Researcher

A: Definitions, Explanations, Translations

A: Overview

A: Inspirations to Practice Science/Medicine

C: Professional Practice

A: Career and Accomplishments

C: Discovery, Creativity and Innovation

A: Influences from People and Life Experiences

B: Industry Partnerships

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

D: On Research and Researchers

A: Character, Values, Beliefs, Talents

Dr. Fidler discusses his research focus for the last four years: brain metastasis. He emphasizes that very few researchers focus on brain metastasis, largely due to the complexities presented by the blood-brain barrier. Dr. Fidler explains that the blood-brain barrier is already compromised in metastasis, a fact that has implications for treating as well as studying the condition. He discusses his work on astrocytes, which protect tumor cells from chemotherapy, until he and his group discovered a drug (now patented) that interrupts the astrocyte's protective activity.

#### Segment 06

##### *Brain Metastasis: Activating the Body's Capacity to Heal Itself*

A: The Researcher

[26:14]

#### Story Codes

A: The Researcher

A: Definitions, Explanations, Translations

A: Overview

C: Professional Practice

C: Discovery and Success

A: Career and Accomplishments

C: Discovery, Creativity and Innovation

A: Influences from People and Life Experiences

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

D: On Research and Researchers

A: Character, Values, Beliefs, Talents

Dr. Fidler begins this segment by noting his roles as the president of the International Differentiation Society and as the youngest president of the American Association for Cancer Research. He talks about how leadership of professional societies. He then returns to a discussion of the mechanisms of brain metastasis. He notes that the death of his friend, Judah Folkman, led him to re-evaluate his life and step down from his administrative responsibilities, a move that left him with more time to think about his research and investigate the role of astrocytes. He believes that intervening in the role of astrocytes in interacting with the genetics of metastatic cells has implications for treatment of many different diseases as well as other forms of cancer. He then turns back to a discussion of his work on activating macrophages to attack metastasis, quoting from "The Doctor's Dilemma," a play by George Bernard Shaw (1911), to dramatize that the body has all it needs to cure itself: "Nature has provided in the white corpuscle... a natural means of devouring and destroying all disease and germs.... Drugs are a delusion."

#### Segment 07

##### *Translational Research at MD Anderson*

A: The Researcher

[60:23]

#### Story Codes

A: Joining MD Anderson

A: Professional Path



A: Contributions to MD Anderson

B: MD Anderson History

A: The Researcher

B: Multi-disciplinary Approaches

A: Career and Accomplishments

A: Service Beyond MD Anderson

B: Beyond the Institution

A: Personal Background

Dr. Fidler explains that changes at NCI had threatened to limit his research freedom and motivated his move in 1983 to MD Anderson, where collaboration with clinicians was fostered: his main goal at that time was to understand metastasis at a clinical level. He speaks about his work training clinicians, many of whom now work at MD Anderson. In the final fifteen minutes of the session, Dr. Fidler tells an amusing anecdote about how he came to occupy the R.E. "Bob" Smith Distinguished Chair in Cell Biology (as his wife, Margaret Kripke was simultaneously offered the Vivian Smith Distinguished Chair in Cell Biology). He describes his relationships training Japanese and Korean clinicians, and notes that the work at MD Anderson he is most proud of is training the next generation. He closes with an anecdote about his most significant award, though he also quotes words attributed to King Solomon: "Don't do things for the sake of an award."

## Isaiah J Fidler, DVM, PhD

Interview Session 1 – September 26, 2011

### 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.

**The views expressed in this interview are solely the perspective of the interview subject. They are not to be interpreted as the official view of any other individual or of The University of Texas MD Anderson Cancer Center.**

### Chapter 00A

#### Interview Identifier

#### *Tacey Ann Rosolowski, PhD*

[00:00]

All right. I'm Tacey Ann Rosolowski interviewing Dr. Isaiah Fidler 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. Fidler is the director of the Metastasis Research Laboratory in the Department of Cancer Biology at MD Anderson. He holds the R. E. Bob Distinguished Chair in Cell Biology. And he is a professor in the Department of Cancer Biology. He has a joint appointment with the Department of Cancer Biology in the Graduate School of Biomedical Sciences. The interview is taking place in Dr. Fidler's office in the Smith Research Building on the MD Anderson South Campus. This is the first of two planned interview sessions. Today is September 26th, 2011. The time is about ten after 2:00. Thank you for devoting your time to this interview and to the oral history project, Dr. Fidler. I wanted to start, as I mentioned earlier, with some general personal background, and then move into the history of your career. So please tell me where you were born and when and where you grew up.

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Interview Date: September 26, 2011

## Chapter 1

### A: Educational Path From Veterinary Medicine to Cancer Research

#### Story Codes

- A: Personal Background
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- D: The History of Health Care, Patient Care
- A: The Researcher
- D: Understanding Cancer, the History of Science, Cancer Research

#### *Tacey Ann Rosolowski, PhD*

I wanted to start, as I mentioned earlier, with some general personal background, and then move into the history of your career. So please tell me where you were born and when and where you grew up.

#### *Isaiah J Fidler, DVM, PhD*

[01:17]

I was born in Jerusalem in 1936. I grew up in Jerusalem until I was 13. And then I left Jerusalem to go to high school, agricultural high school, in a small village in Israel, where I graduated in 1955. This was at the time the top high school in Israel, and difficult. But I had to grow up really rapidly, since I was not growing up at home.

#### *Tacey Ann Rosolowski, PhD*

[02:08]

You were not growing up at home?

#### *Isaiah J Fidler, DVM, PhD*

[02:09]

No. I grew up in a dormitory in that high school, about three hours' drive from Jerusalem.

#### *Tacey Ann Rosolowski, PhD*

[02:18]

What was the name of the town?

#### *Isaiah J Fidler, DVM, PhD*

Pardess Hanna.

#### *Tacey Ann Rosolowski, PhD*

[02:20]

Pardess Hanna?

#### Commented [T1]:

In this Segment, Dr. Fidler talks about his youth in Israel, the decision to study veterinary medicine that brought him to the United States in 1958, and the later events that inspired his shift from veterinary medicine to the study of cancer in humans. In 1961 he received his B.S. in Veterinary Medicine at Oklahoma State University, Stillwater, Oklahoma. Dr. Fidler was awarded his Doctorate in Veterinary Medicine from the same institution in '63. He describes the difficulties of setting up a veterinary practice upon returning to Israel, where pet owners chose to terminate the lives of even beloved pets much more quickly than they do today. "I didn't work so hard to become an executioner," he recalls, explaining decisions that took him from private practice, to pharmaceutical research, and eventually back to the U.S. for a fellowship at the University of Pennsylvania Veterinary School, where his work on animals with cancer sparked his passion for problems of metastasis. After receiving a fellowship that enabled him to conduct basic research at the U. Penn. Medical School, he was advised to apply to the Department of Pathology, where many scientists were conducting research on metastasis. He received his Ph.D. in (human) Pathology from the University of Pennsylvania Medical School (Philadelphia) in '70. There he framed the basic question that would govern his career: how cancer moves from the primary tumor via the circulatory system to create secondary tumors and ultimately the metastases that are still the primary killers of cancer patients. After receiving his Ph.D., he went to work in the Department of Pathology in the U. Pennsylvania Dental School with a Luther Terry Fellowship (late '70).

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**Isaiah J Fidler, DVM, PhD**

[02:22]

Pardess P-A-R-D-E-S-S Hanna H-A-N-N-A.

**Tacey Ann Rosolowski, PhD**

[02:29]

Thank you. I'm sorry. I read that your father died in the Israeli war of independence when you were 12.

**Isaiah J Fidler, DVM, PhD**

[02:38]

My father was killed.

**Tacey Ann Rosolowski, PhD**

[02:40]

He was killed.

**Isaiah J Fidler, DVM, PhD**

[02:42]

In the army in 1948 in the war.

**Tacey Ann Rosolowski, PhD**

[02:45]

And you were 12 years old at the time?

**Isaiah J Fidler, DVM, PhD**

[02:47]

That's right.

**Tacey Ann Rosolowski, PhD**

[02:49]

And I read somewhere that you said you felt that you assumed a role as the man of the house or head of the household. Is that correct?

**Isaiah J Fidler, DVM, PhD**

[02:59]

No, not exactly. But I became the big brother to my little brother. And had to take care of him. He still claims I take care of him, but it's not true.

**Tacey Ann Rosolowski, PhD**

[03:11]

It's not true.

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**Isaiah J Fidler, DVM, PhD**

[03:13]

He's still my little brother.

**Tacey Ann Rosolowski, PhD**

[03:14]

Yeah. Well, older siblings take care of their younger siblings.

**Isaiah J Fidler, DVM, PhD**

[03:17]

Yeah, he was six years younger than me.

**Tacey Ann Rosolowski, PhD**

[03:19]

That's a big difference.

**Isaiah J Fidler, DVM, PhD**

[03:19]

But he was six years old at the time.

**Tacey Ann Rosolowski, PhD**

[03:23]

When you went to the agricultural school, was that where you got a sense that you be involved in veterinary medicine?

**Isaiah J Fidler, DVM, PhD**

[03:32]

Well, the truth is I wanted to become an MD. But at the time there was a sense in the land of Israel, the emerging country, that we have too many doctors and too many lawyers and we need to go back to the land. So my compromise was well, then I will study veterinary medicine. Which as you will see as we go on was -- I regret it. But in any event, I went -- when I graduated from high school, I then served mandatory two and a half years in the army.

**Tacey Ann Rosolowski, PhD**

[04:16]

From '55 to '57?

**Isaiah J Fidler, DVM, PhD**

[04:18]

To '57. And that time, I had received a fellowship, a full scholarship, to go to the University of Arizona in Tucson, Arizona by the Buffalo Oil Company of Tulsa.

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**Tacey Ann Rosolowski, PhD**

[04:37]

What made you apply for that? How did that come about?

**Isaiah J Fidler, DVM, PhD**

[04:41]

I heard about it indirectly, and I applied, and my grades were good. My recommendations were high.

**Tacey Ann Rosolowski, PhD**

[04:51]

Why is it that you wanted to leave Israel for your higher education?

**Isaiah J Fidler, DVM, PhD**

[04:55]

Because there was no veterinary school in Israel. You could either go to Europe or the United States. And United States always attracted me. What we heard and read. The land of opportunity. In the high school English was the second language. At home both my mother and father graduated from English colleges. So English was spoken constantly. English was not a problem for me. My accent turned out to be a problem. But not my ability to converse, to write, to read. In fact it was much higher, still is, than the average American. So going to the United States was easy. If I had to go to a school in Germany and learn German or to Sweden and learn Swedish it would have been something I did not want to do. Or Italy or Spain. So in any event I went to school in Arizona. And after six months I realized that there were a handful of -- just a handful of veterinary colleges in America. And I learned very quickly that even if I would get straight As at the University of Arizona, it would not get me into one of those restricted colleges. Because first, I was a foreign student, and second, I was out of state, and Arizona, especially Tucson, did not have a veterinary school, or even a medical school. And my first choice really was Davis, California to go to school, because other Israelis were there. But when I went for an interview, it became very clear that it would be extremely difficult for me to transfer from Arizona to University of California. So the Buffalo Oil of Tulsa, the scholarship followed me to Oklahoma State University in Stillwater, Oklahoma. A university that had a veterinary school. Not a medical school, but a veterinary school. And I was led to -- they explained to me that with very hard work and good grades I had a good chance of making it to the veterinary school. And indeed that was the case. I worked my butt off to get As and Bs. I think I had one B in my career. And it was not in English, it was in something else. Don't ask me what, but it was -- I had like almost straight four point. Three nine something. And I was accepted to the veterinary school. And spent four years in Stillwater, Oklahoma going to veterinary school. And when I graduated I decided -- I was married and decided to return to Israel to practice veterinary medicine. But I was spoiled. Most veterinarian in Israel worked for an organization almost like a union. Like a health care organization for animals. But I was growing up in America, and I believed in independence, and opened a private clinic. And fortunately one of my uncles let me rent a small apartment for me in his building, so I could open a clinic. And I literally starved, because at that time pets were very rare. People did not make the money they make now. To have a pet was a great luxury. And at the time when an individual brought a sick animal to a veterinarian there were two questions. "What's wrong with my animal, doc, and how much will it cost to cure the animal?" And

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quite a few with tears in their eyes said, "It's too expensive, can you put the animal to sleep?" And I thought I didn't go to school for four years and work so hard to become an executioner. So I accepted a half day job in a drug company. The son of the president of the company and I were in the army together, and that's how you build relationship. And he said, "Why don't you come work in our company?" "What are you going to do with a veterinarian?" He said, "We're interested in developing veterinary pharmaceutical." "Well, well. And maybe I can help." So for several years I had my clinic and I had a half day job with the drug company that paid my rent basically. But I still was very frustrated because my education was not -- I was not working seriously as a veterinarian. Being married to an American lady, we returned to her hometown which is Philadelphia. And I applied for a position at the University of Pennsylvania School of Veterinary Medicine. And although I graduated several years earlier I figured that I shouldn't shoot for the stars. So I took a year of a fellowship. And fortunately -- and decided to really practice surgery at the University of Pennsylvania, which was at the time -- maybe still is, I don't know -- but at the time was the most advanced veterinary school in America.

**Tacey Ann Rosolowski, PhD**

[11:57]

I just want to interrupt you for a second because I'm curious. What were the pharmaceuticals that you were working on when you were back in Israel? And why didn't that satisfy you?

**Isaiah J Fidler, DVM, PhD**

[12:09]

Because I was not a pharmacist. And I wanted to practice with animal, not to help run, make sure that experiment done on animal by somebody were done correctly. At the time I was an idealist. And I'm glad I was. But any event, came back to Pennsylvania. And was very fortunate to work with a genius by the name of Robert Brodey B-R-O-D-E-Y. Robert Brodey specialized in surgical oncology. Not just surgery but literally just surgical oncology. And took me under his wing. And the fellowship ended up, and I joined the faculty. And really we only operated on animal that had cancer. Now there were three things that bothered me. The first is people brought sick -- we got only those dogs and cats the local veterinarian could not handle. Which means we got the tough cases. Second, the cost was not that major a problem, because at the university this was not a practice that had to -- it's hard to explain. It was not a practice that had to be considered on income, but rather on advancing the field, etc. We had other sources to support surgery and animal care, etc. What was frustrating me the most was the fact that we were operating on animal that were dying of cancer anyhow. And they were not dying of the primary tumor. They were dying of tumor that spread -- by the time we saw the animals, a year or two after the local veterinarian resected the mammary cancer, resected the melanoma on the skin, the animals were dying from metastases, from cancer that spread to the lung, to the liver. At the time I didn't realize it, to the brain. That was extremely frustrating because what do you do about cancer that spread? That's the major cause of death from cancer at the time and still is. Individuals, human beings, don't die of primary tumors by and large. We're not talking about brain tumors. We're talking about breast and lung and bone and kidney, colon cancer, prostate cancer. Surgeon can handle the primary tumor. But the major cause of death from cancer is when cancer spread to other site and goes in distant organs, in lymph nodes, in lung, in the bone, in the brain. And these growth are called metastases.

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**Tacey Ann Rosolowski, PhD**

[15:35]

Now I read a note in one of the articles that the University of Pennsylvania Medical School -- you got your PhD in pathology there in 1970 --

**Isaiah J Fidler, DVM, PhD**

[15:45]

I will get there in about three minutes.

**Tacey Ann Rosolowski, PhD**

[15:47]

OK. Well, I just wanted to ask. I read that it was unusual in the '50s that they were -- when they -- in the '50s they were studying metastasis and invasion, it was quite unusual. And so I just was wondering --

**Isaiah J Fidler, DVM, PhD**

[15:59]

That's right.

**Tacey Ann Rosolowski, PhD**

[15:59]

-- when you mentioned that, if you could address that.

**Isaiah J Fidler, DVM, PhD**

[16:01]

Yeah I will. So I always kept complaining, complaining, complaining. And finally the dean of the veterinary school, Dr. Marshak, Robert Marshak, called me to his office and told me he was tired of my complaining. If you were not recording it, I will tell you, he said, "Complain, stop bitching already." But in any event complaining. And he told me that there was a very interesting program that I should apply to. And that was called the Luther Terry Fellowship. Luther Terry T-E-R-R-Y. Now Luther Terry, MD was the surgeon general at the time. And he was very very supportive and interested in MDs, DVMs, doctor of veterinary medicine, and DMD, doctors of dentistry, who had a clinical background to go back to research. The reverse in other words. He wanted more clinicians to do basic research. And you applied to the Luther Terry Fellowship and if you received it you can then go to graduate school, where your tuition is paid, plus at the time -- we don't need to -- I will tell you that the Luther Terry Fellowship was probably twice more money to survive on than what I was getting at the veterinary school. So it was really attractive. But it was identical to MD, DMD and DVM. It did not discriminate. So maybe for MD it was not that high. But for me it certainly was.

**Tacey Ann Rosolowski, PhD**

[17:57]

Was it unusual not to discriminate between those three degrees?



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**Isaiah J Fidler, DVM, PhD**

[18:02]

Usually MDs receive more. Their salary is more competitive, higher than veterinarian. Even now at MD Anderson. But in any event. It depends. If you don't like it you go to private practice, what does veterinarian make, and what does a cosmetic surgeon make? OK, think about it.

**Tacey Ann Rosolowski, PhD**

[18:22]

Oh sure but --

**Isaiah J Fidler, DVM, PhD**

[18:23]

This guy Brown, OK, is a super billionaire. He works on a little hand. If he worked on the paw of a dog he wouldn't be able to pay a lawyer to get -- never mind.

**Tacey Ann Rosolowski, PhD**

[18:36]

I'm just thinking in the context of --

**Isaiah J Fidler, DVM, PhD**

[18:38]

At the time it was unusual. But that was the greatness of the surgeon general. Now I don't say that they gave just as many fellowships to veterinarians as they give to dentists and to MDs. I think it depended on the applicant. What is your background? What letter of recommendation do you have? What grade did you make in school? And are you going to graduate school because you're a clinical failure? If you were a clinical failure, to send you to graduate school is an escape. Was not the case. You had to be a real success in the clinic. So the dean wrote a letter that I wish I had. I told the dean, "My mother would love you for that." It was a really strong letter. And I received the Luther Terry. And in my memory as I said, I crossed the street and entered a new world. The medical school and veterinary. This is the medical school. This is the veterinary school. Just across the street. And I've not been to veterinary medicine ever since.

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**Chapter 2**  
**A: The Researcher**  
**A New World of Research at University of Pennsylvania: Focusing a Research Career**

Story Codes

- A: The Researcher
- A: Overview
- D: Understanding Cancer, the History of Science, Cancer Research
- A: Definitions, Explanations, Translations
- A: Career and Accomplishments
- C: Discovery, Creativity and Innovation
- C: Professional Practice

C: Evolution of Career

**Tacey Ann Rosolowski, PhD**

[19:50]

What was the world that opened up?

**Isaiah J Fidler, DVM, PhD**

[19:52]

World that opened up was that there was virtually no research at the veterinary school. No basic research. I did clinical research. I wrote several papers about the incidence of breast cancer in dogs and how old are the dogs, what strain they are, reviewed records and wrote papers. OK? But if I wanted to do tissue culture, whatever, there wasn't such a thing. And it was recommended to me to interview specifically in the department of pathology, which in fact had individual who were very interested in metastases. And my mentor was the late Irving Zeidman. All of these individuals are no longer with us unfortunately. Z-E-I-D-M-A-N. Irving Zeidman and Charles Breedis and others have written many many papers on cancer metastasis. They were pathologists. The other area of heavy heavy study in metastasis was in Pittsburgh by the surgeon Fisher, Bernard Fisher, who is still with us, thank God. He's in his mid 90s. We still correspond. And there was also Leonard Weiss, W-E-I-S-S, Leonard, at Buffalo, New York, oh, God, the cancer center in Buffalo.

**Tacey Ann Rosolowski, PhD**

[21:36]

Roswell.

**Isaiah J Fidler, DVM, PhD**

[21:39]

Roswell Park. So these were the three areas of cancer metastasis research. Irving Zeidman took me, and it was amazing. I used to come at -- I'm used to 7:00, 7:30 to work. And these prima donnas, the pathology, show to work at 9:00. And they sat around drinking coffee. Arguing with each other till 10:00, etc. And I had my lunch with them when they had breakfast. But in any event, the question that

**Commented [T2]:** Dr. Fidler details how he began to look more deeply into the question of cancer cell differentiation, a groundbreaking discovery that was ultimately published in Nature. (Dr. Fidler shows the interviewer a Plexiglas containing a unit he invented to facilitate injection of cells into the tail veins of up to 100 mice per hour, underscoring the resourcefulness that a researcher had to have to move ahead quickly with a study.) Through this success, he was recruited to join the National Cancer Institute at Frederick, Maryland. His wife-to-be, Margaret Kripke, known for her pioneering work in photoimmunology, was also hired in a concurrent recruitment, and he describes how Dr. Kripke challenged him with the question that inspired a new line of research: "How do you know whether the cells you are culturing from a line are a selection or an adaptation?" His discovery that the differentiation of metastasis cells is a priori "revolutionized the world," he states, noting that "you cannot treat a heterogeneous disease with homogeneous therapy" -the origin of individualized therapy. Dr. Fidler then explains connections between Paget's "seed and soil" theory and his next experiments with transplanting metastatic cells between the organs of mice.

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came up. I wanted to know. We knew that tumor cells to get say from the breast cancer to the lung or to the brain, there were many publication on that, have to enter the bloodstream. Otherwise how do they get there? Or the lymphatics. So either the lymph vessels or the blood vessels. They had to circulate through the body. And what I wanted to know is how many cells can enter the circulation and how many cells survive in the circulation to give rise to the distant metastasis. At the time what I decided to do, and after consultation with many, was to take a mouse tumor, a mouse melanoma, which has never been in culture before by the way, I was the first one to put it in culture. Egotistical, I labeled it B16F for Fidler. Nobody knows. I keep telling people who lecture me about B16. I laugh. I say, "Do you know what the F stand for?" And they don't but that's OK.

***Tacey Ann Rosolowski, PhD***

[23:43]

I'm curious why no one had cultured it before.

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**Isaiah J Fidler, DVM, PhD**

[23:45]

Because nobody worked with the cell. The way you transferred tumor was from animal to animal to animal to animal. There was no -- at the time there were no laminar flow cabinets where everything is sterile. We had to work in a cabinet with UV light to kill the bugs at night. And in the summer you couldn't culture anything because you'll have bacteria and mold contamination. And we had to wash our hands with iodine. I mean for months my hands were brown all the time. And then another fellow in pathology who is no longer with us, John Kreider, a human pathologist who then went to do research, OK, so he had his clinical background, and he was researching alongside me. Was hired by NASA to help them with some mice that were -- to analyze tissue from mice that they were going to send to space. So he goes to NASA around Philadelphia, and he comes back and he says, "I can't believe what I just saw. I saw this cabinet where there is airflow that keeps all the bugs out. And they did it so they can assemble parts for the space that will be dust-free, bug-free, mold-free." So he contacted the company and said, "Will you give me a unit? I want to see if I can do tissue culture in it." That was the first tissue culture cabinet. Now there must be hundreds of millions of those. And John never got a patent on his idea, which is a mistake. But in those days we didn't think patent. Today everything is patent, patent. "Do you have a patent?" "No." "Then you are a loser." But at the time we only thought about knowledge. So tissue culture became, at least at the University of Pennsylvania in our department, we had two units that were given to us. Gift. They were \$50,000 then. Today they're a few thousand, nothing. They build so much. And started culturing cells. And talking, talking, talking to other people. And there was another fellow who was a radiotherapist who also had a Luther Terry. So we like had a Luther Terry brunch club if you know what I mean, talking to each other. And he said, "If you can label the DNA of the cells, label it with an isotope called -- that has iodine-125 in it. And as long as the cells are alive, they emit a signal for the I-125, which is a gamma emitter. And that gamma emitter is very strong. So if you take a lung or liver and you put it in a tube the emission will go through and you can measure it. If it was an alpha emitter or beta emitter, you have to make jelly out of it, which is impossible. And as long as the cell is alive they'll emit that from the DNA. Once the cell is dead, the DNA will break down. The I-125 will disappear in the urine, and that's it. So if you have a high count you have live cells, and a low count low cells. And you can run alongside, and you know exactly how many cells are in the animal." I said, "Oh, I love you for that." And I did the first experiment with -- iododeoxyuridine I-125. That's too complicated. I-125-emitting DNA. And showed that after one month, OK, of all the cells that are introduced to the animal, maybe 0.01% survive. Now I will tell you it's even less than that because we can do more sensitive things. But at the time I couldn't. And shown also another interesting thing. That initially we injected the cells into the tail vein of the mouse. Initially there were counts everywhere. But ultimately when the animal died the melanoma was only in the lung. Not in the liver, not in the kidney, not in the bone. We couldn't find tumor residues. But initially they were everywhere.

**Tacey Ann Rosolowski, PhD**

[28:55]

Did you have any suspicion of such results when you --

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**Isaiah J Fidler, DVM, PhD**

[28:57]

No.

**Tacey Ann Rosolowski, PhD**

[28:57]

-- began these tests? No.

**Isaiah J Fidler, DVM, PhD**

[28:58]

No, of course not. I had no -- I just -- I couldn't believe that every cell will survive, because then patient would not survive five or six years sometimes. Today in 2011, there's a big deal about circulating tumor cells, etc. And I say, "Why don't you read the literature? You will see that just because they circulate doesn't mean that they're going to survive and kill the patient." But in any event the finding was so startling that I was told, "Why don't you write your thesis based on one experiment?" So I wrote my thesis. It's still there. And it's the record. It's the shortest thesis ever written at the University of Pennsylvania. Let me see if I can find it. Well, it's one of those. By the way we didn't have computer. Everything had to be typed. No, that's not it. That's my graduates list. That's old, that's another one. It looks just like that. Mine is thin. All of these are my graduate student who wrote theses. I'm sorry.

**Tacey Ann Rosolowski, PhD**

[30:30]

No. That's fine.

**Isaiah J Fidler, DVM, PhD**

[30:32]

Here it is.

**Tacey Ann Rosolowski, PhD**

[30:35]

That's great. With photos and everything.

**Isaiah J Fidler, DVM, PhD**

[30:40]

Yeah. Anyhow. And I say in 1970 I'm deeply in debt to the member of the department, Dr. Irving Zeidman, John Kreider for his initial suggestion which have encouraged me to undertake the work, that's laminar airflow, financial support to the predoctoral fellowship from USPHS and my patient people, my wife and two children. Because to do that in a year and a half, I worked a long time. But anyhow, I was told, "Present it." And I finished my PhD in a very short time, like in two years or two and a half years. And I insisted that my degree would be in human pathology, not veterinary but human pathology, since I was in the human, in Penn Medical School. I wanted to stay in the department of pathology at the medical school. But the young chairman of the department, Peter Nowell, who should have received the Nobel Prize for his work --

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***Tacey Ann Rosolowski, PhD***

[32:05]

What did he work on?

***Isaiah J Fidler, DVM, PhD***

[32:06]

He worked on leukemia. He showed the leukemia starts from a single cell. In any event told me, "No, you cannot stay here, because there'll always be a suspicion that you're not independent. You must leave." But I didn't want to leave Philadelphia. I already had a little home, etc. So I heard that the dental school is interested in recruiting me. And I went, had lunch with the dean, and over lunch I told him what it would take to recruit me. And when he said yes to everything I thought I should have asked for more. But anyhow I went to the department of pathology at the dental school, University of Pennsylvania. So here I am, a veterinarian who graduated from veterinary school, medical school, and now I'm in the dental school.

***Tacey Ann Rosolowski, PhD***

[33:13]

So that was shortly after 1970 or that was 1970?

***Isaiah J Fidler, DVM, PhD***

[33:16]

That was the end of '70, beginning of '71. And then I decided to look deeper into the finding. Just a few cells survive to give rise to metastasis. And the serious question of the day was are they different from all the cells that didn't survive. That's a selection process? Or is it adaptation? So I did -- now it looks like a simple experiment. At the time it was very unusual. I injected -- don't remember, 10,000, 20,000 cells into a mouse. And the mouse developed let's say ten isolated colonies in the lung. Since they were black, it was very easy to find them. Very carefully dissected those metastases. And put them in tissue culture and grew a culture out of them. And injected that culture into the tail vein of another syngeneic, in other words genetically identical, mouse. So there would not be immune rejection.

***Tacey Ann Rosolowski, PhD***

[34:47]

Can I ask what the significance of the tail vein is?

***Isaiah J Fidler, DVM, PhD***

[34:51]

It's the easiest vein to reach in a mouse. They have a huge vein. For me. Now we can inject carotid artery and things, but you need a microscope for that. The tail vein I could, when I was good I could do probably 100 an hour.

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**Tacey Ann Rosolowski, PhD**

[35:12]

So it took a lot of hand skills too.

**Isaiah J Fidler, DVM, PhD**

[35:15]

Yeah but I invented this thing. I didn't take a patent on it unfortunately but this was the original. You put a mouse here. And here's the tail, OK?

**Tacey Ann Rosolowski, PhD**

[35:33]

For the recorder, we're looking at a Plexiglas container for a mouse.

**Isaiah J Fidler, DVM, PhD**

[35:37]

Yeah but this was even easier. You just put the mouse, hold the tail, and you inject.

**Tacey Ann Rosolowski, PhD**

[35:42]

Oh I see. So and then it just stabilizes the mouse, keeps it from squirming.

**Isaiah J Fidler, DVM, PhD**

[35:45]

When you collect. This is a sieve like tea. You collect your lesions from the lung. You take a syringe and you grind them. They come out as groups of cells. And you put that in culture. So at the time you had to be very resourceful to do your own things. Otherwise waiting for others to invent things for you would take too long. In any event I've done it several times. And every passage it was clearly more and more and more metastases in the lung. So after a few passages the whole lung was black. And it was very clear that I'm selecting for more and more and more malignant cells. This was published in Nature, made a big noise. And then there were many other. Obviously I'm giving you one major experiment. But at the time I probably published 20 papers. Not just on that but many other things.

**Tacey Ann Rosolowski, PhD**

[36:59]

What were some of the related things you're doing? Because I was really interested in the array of studies that you did.

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**Isaiah J Fidler, DVM, PhD**

[37:05]

In the array for example it became very clear that cells that circulate and survive do so because they can clump together. You have a clump, the internal cell will survive the bumps of the circulation. But the clump didn't have to come just from tumor, tumor, tumor. We have shown that the clump could be lymphocytes that bind to the tumor cell and don't kill it or platelets. A platelet is a cell that's supposed to block hemorrhage when it happens. Unfortunately clumps of platelets can lead to a lot of problems in the human. Including -- trying to think how to say it in simple language. When platelet clump in the brain, they lead to total disaster. In the heart they can lead to cardiac failure. So on and so forth. We found that tumor cell clump with platelets. A colleague at the medical school asked me to help him to inject mice because he said that the best way to treat to prevent platelets from clotting is a simple aspirin. And Gabriel Gasic in fact published that paper, thanked me for injecting mice for him. But in any event showing that aspirin can reduce metastasis. You know that today aspirin is being recommended to individuals who have had heart failure, brain problem, etc. Simple aspirin.

**Tacey Ann Rosolowski, PhD**

[38:58]

The idea that it's a blood thinner.

**Isaiah J Fidler, DVM, PhD**

[39:00]

Well, it prevent platelets from clumping. So that was the lymphocyte story. I worked on that. I have a very small group at the time. I wasn't that advanced. But we were recruited. Margaret Kripke, who was -- and I were married, and we were recruited -- well, we were not married yet. But we were looking at a place to go together. She was at University of Utah. And I was at University of Pennsylvania. And we had two independent recruitments simultaneously to a new program that opened at Frederick, Maryland. By the National Cancer Institute. And the director of the program, who's still one of our dearest friends, Michael Hanna H-A-N-N-A, from Oak Ridge, Tennessee became the director of the program. He recruited Margaret because he knew her work. And she's the one that showed that UV light is immunosuppressive. Margaret was the chairman of immunology here. She became the executive vice president and the provost of the institute. When she retired DuBois took over. It was her. She did it all. But in any case we were recruited to go to Maryland. And about that time she challenged me and she said, "OK, so how do you know whether the cells that you are culturing from the lung, how do you know whether it's selection or adaptation?" And I said, "Not only don't I know what you mean, I don't even know what's the difference between the two. So give me -- I'm just a dumb veterinarian. I'll go read about it." So I read, read, read. And I told her, "I still don't know how to do it." And she said, "You have to do the Luria-Delbruck fluctuation analysis." OK, Luria-Delbruck, which nobody knows who they are. Just shows you. They received the Nobel for medicine. In 1938, '39 they were interested in resistance of bacteria to antibacterial agent. By now you know don't use penicillin, it's a waste of time, but at the time it was the cure. But there were always -- at the beginning it looked great. And all of a sudden you have a resistant strain in tissue culture. Was that strain resistant a priori? You just killed all the sensitive? And that one bacteria that was resistant now grows up? Or was the drug mutagenic? The drug created DNA infidelity or DNA failure or DNA genetic alteration and the drug created the



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resistance? What Luria-Delbruck did then. They took bacteria, microorganisms. And cloned them. They took a single bacteria per dish. And they grew cultures. Each one originating from a single bacteria. They had thousands of these dishes. And they flooded them with antibacterial agent. And they showed conclusively that in some dishes every bacteria was killed, every mold was killed. And in few, none were killed. And they were not exposed to the same drug, different application, but only once. In other words, the resistance preexisted. That's called a fluctuation analysis. Since in my selection experiment that I published in Nature I did it six times, maybe it just was that the procedure that I'm using, the tissue culture, the sieve, somehow I'm mutagenizing the cells. So what Margaret and I did, for which we received every conceivable prize you can think of. We did the first to my knowledge fluctuation analysis with mammalian cells. We took this melanoma. We isolated single cell from the culture. And we grew cultures from single cells and injected ten mice from each culture. And each one came from a single cell. And with other cells, with others, we injected a mix, the parental. Well, the parental injected to 80 mice gave average number of metastases. Eight, nine, ten, between eight and 12, eight and 12, some eight, some 12. But the median was not significantly different. But when we injected cells that all were derived from this single cell or that single cell or that, some gave no metastases whatsoever. Some gave 200. Some gave 50. The variation was enormous. In other words, this proved that some cells in the tumor are metastatic and the majority are not. And we never played the game of again, again. They all were given the same chance. Once. It was published in Science and was immediately accepted to my great surprise and really in my opinion revolutionized the world. Because for the first time it said the tumors are heterogeneous. In other words they don't consist of cells that are all alike. Tacey, you know what it means in 2011 that when you talk about individualized therapy, genetic therapy, bullshit therapy, some cells will respond and some cells will not. You cannot treat a heterogeneous disease with homogeneous therapy. The two words are not parallel. It has to be combination against this, against that. By now there are thousands and thousands of papers. I'm sorry. My eye is killing. Thousands of papers about heterogeneity for cell size, cell shape. Making enzyme this and enzyme that. And this protein and that protein. When you look carefully, you see that the world is very heterogeneous. So that really made a significant significant sort of revolution in the field.

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**Chapter 3**  
**A: The Researcher**  
**Metastasis: A Regulated Process**

Story Codes

A: The Researcher  
A: Career and Accomplishments  
C: Discovery, Creativity and Innovation  
A: Definitions, Explanations, Translations  
A: Influences from People and Life Experiences  
C: Professional Practice  
C: Evolution of Career  
D: Understanding Cancer, the History of Science, Cancer Research  
D: On Research and Researchers  
A: Character, Values, Beliefs, Talents

[46:39]

**Tacey Ann Rosolowski, PhD**

So the prevailing idea at the time about cancers were that they were -- all of the cells in a tumor were similar.

**Isaiah J Fidler, DVM, PhD**

[46:47]

No. But nobody could prove that they were not similar.

**Tacey Ann Rosolowski, PhD**

[46:51]

That they were not. OK.

**Isaiah J Fidler, DVM, PhD**

[46:53]

In fact people treated at the time cancer as cancer of this. Cancer is a disease.

**Tacey Ann Rosolowski, PhD**

[47:00]

A big C, yeah.

**Isaiah J Fidler, DVM, PhD**

[47:01]

Yeah. I'm telling you now. And we can talk about it tomorrow, another date. Maybe I should show you some pictures tomorrow.

**Commented [T3]:** Dr. Fidler begins this segment by explaining that, in contrast with the prevailing belief (in the 70s) that cancer is the "ultimate expression of cellular anarchy" and that metastasis is random, his work has shown that cancer is a regulated process along every step of the way; similarly, metastasis is predictable. In response to a question about why scientists held (and still hold to) these conventional assumptions about cancer, Dr. Fidler notes how difficult it can be for a scientific community to accept innovative ideas. He then talks about significance of training clinicians in research and the basic sciences.

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**Tacey Ann Rosolowski, PhD**

[47:13]

Sure.

**Isaiah J Fidler, DVM, PhD**

[47:14]

Cancer of the breast. If it grows in the breast or if it metastasize to the bone or the brain or the liver are four different diseases in the same patient. They're not the same. So to even say breast cancer, thinking that -- and I say, "Where is it growing?" Because of the next chapter that I'll come to right now. So the next big challenge was OK, the tumors are growing in the lung. The lung is not tissue culture. It's not plastic. It has lots of cells. The lung, if you're a pathologist, I can show you lung, I can show you liver. They're different organs. Don't they have to say something about it? And I then realized that King Solomon -- if you know who he was -- supposedly according to my tradition the wisest man that ever lived -- said a few things. And one of the things upon his deathbed. He said, "There is nothing new under the sun." He was very disillusioned. He thought that his big brain is going to discover new things. And he concluded that everything that he thought about somebody else thought about before. So working about the organ environment as we'll call it now, came to my attention that in 1892 a British pathologist by the name of Stephen Paget in Lancet issue number one, 1892, yeah, wrote a phenomenal paper called On the Seed and Soil Hypothesis. And Paget said when a seed goes to soil it will germinate if the soil is fertile. It will not germinate if the soil is not fertile. But not all seeds will germinate even in fertile soil. He was a botanist, OK? I always when I lecture about that, I'm going to do it in Boston in about two weeks, I say that you know when I was in Frederick, Maryland I used to buy Burpee seeds for Big Boy tomatoes. And I have a picture of me with a tomato that was like two pounds. Was a huge tomato. And I buy the same seeds. \$1.25 packet of seed. Put them in Houston. I get a six-foot weed. Because the soil and the climate here are not what the tomato needs. Weeds love Houston. But not tomatoes. You want to grow tomatoes, you got to go and buy a bag of garden soil and you know what I mean.

**Tacey Ann Rosolowski, PhD**

[50:19]

Yeah I do.

**Isaiah J Fidler, DVM, PhD**

[50:20]

OK. So began to read with my English postdoc Ian Hart I-A-N H-A-R-T. Ian Hart. About the Paget work. And reading other reviews discovered that a very influential person in America, name of Ewing, E-W-I-N-G.

**Tacey Ann Rosolowski, PhD**

[50:57]

James Ewing.

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**Isaiah J Fidler, DVM, PhD**

[50:57]

James Ewing. In fact dismissed the Paget hypothesis and said that patterns of metastases can be explained merely on the vasculature. And Paget wrote something fascinating. He studied thousands of patient records. Among which were thyroid carcinoma. And Paget said, "How can you explain the thyroid carcinoma metastasize preferentially to bone?" Bone. Thyroid to bone. There is a direct connection? Cannot be. OK. But he didn't say that, because he didn't know Ewing in 1929 is going to dismiss. So anyhow Paget was dismissed literally. And Ian Hart and I decided to do -- now, even now, it looks like a very sophisticated type of experiment. So we took the lung and kidney and ovary from one-day-old mice. And implanted them into the leg muscle of adult animals. Because it was ovary it was all done in female mice. So it wouldn't be male-to-female rejection. And two weeks later when the wound - - you open the muscle, you put the organ, and you close. Being two surgeons, for us it wasn't a big deal. And two weeks later we injected the mice when the wound completely healed with melanoma intravenously. Into the tail vein. Where the tumor reach, OK? Will reach the right heart, go into the lung, oxygen comes into where the CO2 goes out, oxygen comes in, and everything goes to the left heart, and from the left heart you go to the body, and that's the cycle. So the first major organ they will encounter after the heart when you put them into the vein will be the lung. And we said the following. If metastasis merely can be explained on the circulation, then the mice will have tumors in the natural lung but not in the implanted lung in the leg. And not in the kidney, not in the ovary. If, however, Paget is correct, that there is some synergy, some magic, between the interaction of the tumor cell and the organ environment, we will expect to see tumors in the natural lung, of course we're putting them there, but if he's correct we will see it growing in the lung in the leg but not in the kidney or in the ovary. And that's exactly what happened.

**Tacey Ann Rosolowski, PhD**

[54:27]

It seemed like James Ewing's was a real mechanical understanding of body systems, and Paget's was --

**Isaiah J Fidler, DVM, PhD**

[54:33]

It's OK. It's 1929. Paget was a little more advanced.

**Tacey Ann Rosolowski, PhD**

[54:38]

Yeah. They had a much more organic understanding of how --

**Isaiah J Fidler, DVM, PhD**

[54:41]

Paget. OK. I can show you two people in 2011 that still think like they're in the Middle Ages. What can I do? OK? Arbitrary, OK? He was the chairman of a department and what he said everybody agreed with him.

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**Tacey Ann Rosolowski, PhD**

[54:59]

Which one? Ewing?

**Isaiah J Fidler, DVM, PhD**

[54:59]

Ewing.

**Tacey Ann Rosolowski, PhD**

[55:00]

Ewing.

**Isaiah J Fidler, DVM, PhD**

[55:01]

And Stephen Paget was the son of one of the most famous surgeons in England. And was always living in the shadow of his father. I'll show you in a minute why I mean that. But in any event, we also used in that publication, we also used radioactive labeled cells. And we showed that just as many cells reached the kidney implant as reached the lung implant, but they only grew in the lung and not in the kidney. So it's not getting there. That paper was published so rapidly, I thought ooh. And many years later Nature had their review of the field of cancer or what did they call it, milestone in cancer research. And number one milestone in fact was to reinvigorating the seed and soil. That seeds are unique and the soil is unique. And they fully gave me and my people the credit for everything I told you so far.

**Tacey Ann Rosolowski, PhD**

[56:22]

Can I ask you? The papers were accepted just with light speed. What about a more general acceptance of the ideas that you were putting out?

**Isaiah J Fidler, DVM, PhD**

[56:31]

It took a lot. It took a lot to. It's now accepted completely. But it was not easy to convince individual but --

**Tacey Ann Rosolowski, PhD**

[56:41]

What was the resistance about?

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**Isaiah J Fidler, DVM, PhD**

[56:43]

It was not convenient. Today when I say that tumor cells are clonal -- because that's what we wrote -- and there were progenitor cell for metastases. Today you can read papers. Clonal, progenitor, stem cell. OK. They give it different name but it's same idea. Seed. Paget called it a seed. I called it a progenitor. Organ microenvironment. Niche. Host factors. It's all the same. But everybody feels like they have to reinvent the wheel. That's another thing that Solomon said.

**Tacey Ann Rosolowski, PhD**

[57:32]

I'm just struck that in so many fields there's a natural resistance to change and --

**Isaiah J Fidler, DVM, PhD**

[57:39]

But that's human nature.

**Tacey Ann Rosolowski, PhD**

[57:42]

Yeah. But it's frustrating.

**Isaiah J Fidler, DVM, PhD**

[57:42]

So I want you to see that.

**Tacey Ann Rosolowski, PhD**

[57:44]

So what's this?

**Isaiah J Fidler, DVM, PhD**

[57:46]

A good friend after I gave a lecture. A friend said to me, "You will enjoy it more than I would." So he sent it to me. The memoirs and letters of Sir James Paget. That's the father of Paget, OK?

**Tacey Ann Rosolowski, PhD**

[58:00]

Oh. That's the father, yeah.

**Isaiah J Fidler, DVM, PhD**

[58:01]

And guess who wrote it? He was the father, OK? James Paget. Stephen wrote --

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**Tacey Ann Rosolowski, PhD**

[58:10]  
Stephen wrote it.

**Isaiah J Fidler, DVM, PhD**

[58:11]  
Stephen wrote it. Dedicated by permission to the Queen, Alexandra. These memoirs, Paget's, etc. Stephen --

**Tacey Ann Rosolowski, PhD**

[58:24]  
So a biography of his father.

**Isaiah J Fidler, DVM, PhD**

[58:25]  
And as I leafed through this book, this falls out. My dear pater, we are sending you with our love the collected essays, OK? They make a goodly volume, etc. This was written in 1902.

**Tacey Ann Rosolowski, PhD**

[58:47]  
Just for the recorder, I'm seeing that these are two blue handwritten sheets that fell out of the book. Stephen Paget, wow. He penned those.

**Isaiah J Fidler, DVM, PhD**

[58:56]  
Well, here he says, "Talking of moping, do you know the story of the little girl who was horribly disappointed because her baby brother could not talk? They said, 'Why, dear, he won't begin to talk till he's a year old.' And she said, 'Well, they told me at Sunday school that God cursed the day he was born.'" Job. Excuse me. Job cursed the day he was born. "With best love to Betty. And affectionately yours. Stephen Paget. My dear pater." Isn't that nice?

**Tacey Ann Rosolowski, PhD**

[59:41]  
Yeah.

**Isaiah J Fidler, DVM, PhD**

[59:42]  
Anyhow.

**Tacey Ann Rosolowski, PhD**

[59:43]  
What a treasure --

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**Isaiah J Fidler, DVM, PhD**

[59:44]

Yes, it is, I'll keep it.

**Tacey Ann Rosolowski, PhD**

[59:46]

-- this is. It really is a treasure.

**Isaiah J Fidler, DVM, PhD**

[59:47]

I only have two books of my --

**Tacey Ann Rosolowski, PhD**

[59:49]

There it is, one of two books on your desk. What's the other book?

**Isaiah J Fidler, DVM, PhD**

[59:51]

Other one is *The Talmudic Anthology: Tales and Teachings of the Rabbis*. Which from time to time -- I tell you that there is nothing new under the sun. Anyhow. A man should not say, "I will study in order to attain the degree of a rabbi." He should study for the love of it and the honor will come at the end as of the by-product. The Bible said it differently. The Bible says, "Don't do good things in order to be rewarded. Do good things --"

The recorder is paused.

[00:00]

**Tacey Ann Rosolowski, PhD**

Now it seems to be happy again. So we had the recorder off for about five minutes, ten minutes, where we were looking at some pictures of tumors and visual summaries of some of Dr. Fidler's experiments. And we were talking about the idea of -- well, your conclusion, your belief that there's no such thing as cellular anarchy. There's just --

**Isaiah J Fidler, DVM, PhD**

[00:33]

No, no, I said that metastasis, when I started my research the prevailing viewpoint was that metastasis is the ultimate expression of cellular anarchy. Because the process of the pathogenesis of metastasis was not clearly delineated. And what we have done now, we know every step in the process that a cell must complete to leave the primary tumor and grow at a distant site. And it doesn't appear to be an anarchy at all. It's a very very regulated process. And it's regulated by tumor cells interacting with host factors at every step of the way.



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**Tacey Ann Rosolowski, PhD**

[01:32]

Can you describe? I'm sorry. Go ahead.

**Isaiah J Fidler, DVM, PhD**

[01:34]

The other thing that I stated. At the computer -- at the microscope side, was that at the time that I started my research the prevailing viewpoint was that metastasis was a random process. And I never understood why a process could be called random when you predict the outcome. In other words, oncologists clearly know that if a patient has pancreatic carcinoma the tumor will metastasize to the liver. In renal cancer metastasis will occur to the lung and the bone. In glioblastoma there is no metastasis. Ovarian cancer primarily metastasizes in the peritoneal cavity. And I can go on and on. Breast cancer metastasizes to the lung, liver, bone and brain. Thyroid carcinoma metastasize only to bone primarily. There are some exception of course to everything I tell you. Melanoma is the real -- how shall I say -- highway thief, because it can grow anywhere. Melanoma is the most vicious tumor I know. But today and yesterday a good oncologist know precisely where to look for metastasis of a given tumor. Once the pathologist confirms the tumor. If they don't know the pathologist will tell them. If it's colon cancer you look at lymph node and liver before you search in the brain and the lung. How can you say that when you can predict the site of metastasis a metastasis is random? If it was random, you say, "I'm sorry, Mr. So-and-so, you have a tumor. And where it will go I have no idea." That's what random means. If you have no idea, you don't belong in the field. People don't come to you to hear "I have no idea." You can say the truth is some tumors cannot be treated, some can. But "I have no idea," then where were you in medical school? Where were you in fellowship? I mean playing golf? What do you mean you have no idea? We all know. So why was it such resistance to admit that metastasis is not random? When you began to read the literature, you see that the first one who said that metastasis is not random was Stephen Paget. Or maybe even before him. I could not search before. Most of that literature is in German. I don't read German.

**Tacey Ann Rosolowski, PhD**

[04:42]

Do you know where the -- what's your suspicion about where the resistance came from? I mean why just keep mouthing those words?

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**Isaiah J Fidler, DVM, PhD**

[04:53]

Because tomorrow we'll talk about brain cancer more as an example for the seed and soil. And you hear "The blood-brain barrier prevents me from doing thing." Even this morning I heard it. I said, "There's no such thing in cancer. Here's the proof." Said, "But that's a small molecule." I said, "Small, large, it doesn't matter." Data should speak, not suspicions. When you don't have data you have suspicion. Now you can quote me on what I'm going to tell you now that's mine. When a scientist says "I believe" means they don't have data. "I believe" belongs in church or synagogue. In science you either know or you don't know. What you believe is irrelevant. The minute you say "I believe" means you don't have data. So you have to believe. Or "I speculate." "I have a hypothesis." That's OK. Because you can test a hypothesis. But how can you test "I believe"? You either believe in God or you don't. I mean I'm not going to convince you. There's no way to convince you. If I could everybody would know. At the time with metastasis was a lot "I believe." You go to meeting, you hear what people believe. They believe in this, they believe in that. They were frustrated because there were no answers. And very few people worked in the field. Very few. Even now. I would say there's no more than 1,000 people in the world that work on metastasis, the number one killer.

**Tacey Ann Rosolowski, PhD**

[06:42]

Killer. That's amazing.

**Isaiah J Fidler, DVM, PhD**

[06:45]

And there is 10,000 working on signals. OK? On this receptor. That receptor. Gene analysis. I don't know. 20,000, 100,000. But on biology, on real pathology, there's very few. Because it's complicated. Makes life difficult. And unfortunately in research if you don't do popular things you may not get a grant. I encountered it myself when I had a new -- I at my stage. If I have a hypothesis I don't get it from thin air. I based on something. I said a hypothesis. Why tumors in the brain are resistant. And I went, wanted some seed money. They said, "Where are your data?" I said, "If I had data, I don't need you. What do I need you? For seed money. I had data, I'd go to a drug company." Which I did. But Paget was so revolutionary, was so -- and even today when you go around and ask graduate student, or ask the fellow that write paper, look at publication. I'll take you one paper after another. Look at the -- here. We are now submitting this paper to -- our own paper. We're submitting this paper. It will come out in PNAS about microarray to study transcriptome of metastasis. There's lots of authors on this paper. I only edited part of it. Because a lot of it I really don't even -- you see the famous tumor in the ear, etc., etc. 2009, 2002, 2008, 2003, 2005, '94. Ooh that's an old one. 2003, 2003, 2001, 2009, 2008, 2006, 2007, 2002, 2011, 2004, 2002, 2002, 2005. The world doesn't exist before. If you published 15 years ago nobody knows who you are. That's the way it goes. And with PubMed you rarely go beyond five years.

**Tacey Ann Rosolowski, PhD**

[09:38]

PubMed?

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***Isaiah J Fidler, DVM, PhD***

[09:39]

PubMed, publication med. PubMed. So if I say to somebody -- I do when I teach graduate student. Now I'm going to Harvard to teach. OK? And just for fun I said, "Luria-Delbruck. Show of hands. You know who I'm talking about." Nothing. They received the Nobel for medicine. I said, "Don't feel bad. When you receive Nobel for medicine five years later nobody will know who you are anyhow." So it's only famous for five years. Your mother and father will say all the time, but anybody else on the street doesn't know who you are. But there is such -- how shall I say it -- a pouring of information now that it's impossible to read everything. But at the time it wasn't. You see? There were a few journals that -- in my field there were three or four journals we published in. That's it. And everything had to be typed by hand. You had to be very careful. It's not like a computer, you can change things and move things. You want to redo it, you just redo it in five -- everything, secretaries hated you. You brought them handwritten. And "Why don't you type it?" "I don't know how to type." And on and on.

***Tacey Ann Rosolowski, PhD***

[11:16]

I'm thinking too of that Luther Terry Fellowship and I just wondered if that was unusual to try to encourage people to go from clinical --

***Isaiah J Fidler, DVM, PhD***

[11:24]

Very very very very unusual. Very unusual. Look, the president of MD Anderson is a phenomenal scientist but he doesn't have a PhD, he's an MD. He decided he's going to go into science. He's lucky. He's very lucky. Many people in the clinical area are MD/PhD but they did their PhD in two years at Yale, Columbia. And now it's almost giving you a gift of a PhD. But they didn't do fellowship. They didn't do postdoctoral fellowship. I have trained more than 180 people by now. Many of them were MDs who had even a PhD. Never mind names. And came to me for two years just to learn how to do things. Because in two years what do you do? You just write a thesis. Luther Terry was revolutionary. Paget was revolutionary. We're only mentioning people who really moved the field. And it was unconventional thinking. Even today you will hear that breast cancer is spread by the lymphatics and this tumor spread by the veins. Give me a break. Some tumors don't grow in lymph node. Fibrosarcomas. It doesn't mean they don't penetrate veins. I can deposit them in the lymph node. They will not grow.

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**Chapter 4**  
**A: Personal Background**  
**Reflections on Research; Becoming a Citizen; Influences: Words of Wisdom**

**Story Codes**

**A: Personal Background**

**A: Influences from People and Life Experiences**

**A: Character, Values, Beliefs, Talents**

[13:12]

**Tacey Ann Rosolowski, PhD**

What do you think gave you the ability to do that kind of unconventional thinking?

**Isaiah J Fidler, DVM, PhD**

[13:24]

I often wonder. I guess I just in general -- thinking I always am outspoken. Many people don't like it. Thinking out of the box. Want to be different, that's all. And I always think -- you have children?

**Tacey Ann Rosolowski, PhD**

[13:48]

No.

**Isaiah J Fidler, DVM, PhD**

[13:50]

You remember yourself as a child?

**Tacey Ann Rosolowski, PhD**

[13:53]

Yeah.

**Isaiah J Fidler, DVM, PhD**

[13:54]

What was the first question you asked your parents? A real question. "Tacey, wash your hands." What did you say?

**Tacey Ann Rosolowski, PhD**

[14:04]

Why. Of course.

**Isaiah J Fidler, DVM, PhD**

[14:05]

Ah. Why.

**Commented [T4]:**

In this character-revealing segment, Dr. Fidler talks about his ability to think outside the box. He recalls becoming a citizen and some of the cross-cultural challenges he faced. He recalls family members who influenced his independent thinking. He reflects on the contributions he has made to his field and the influence of Dr. Judah Folkmann on his thinking. He ends this session by talking about the implications of his discoveries for research, its links to the current push for individualized care. He also questions how quickly they have been translated into therapies that will benefit patients.

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***Tacey Ann Rosolowski, PhD***

[14:06]

Yes.

***Isaiah J Fidler, DVM, PhD***

[14:07]

Not how.

***Tacey Ann Rosolowski, PhD***

[14:08]

No.

***Isaiah J Fidler, DVM, PhD***

[14:09]

Not what.

***Tacey Ann Rosolowski, PhD***

[14:09]

No.

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**Isaiah J Fidler, DVM, PhD**

[14:10]

Not when. All these are techniques. Why. That's the question a child asks. Why. Give me a reason. And maybe they were patient with you. "Because you have dirt on your hand." Why. "Because if you don't do that I'm going to take something to you." And I said, "OK, OK, OK." My father used to say, "You want why? Why. I'm tired of you asking questions." The why is the question in medicine. Why is there metastasis? Not how. When. If. Seventeen different ways of doing a technique. I'm not a technocrat. Very bad in that. But why leads to a hypothesis. And I was fortunate that I could in my first research position in the dental school, they gave me a goodly amount of money to come and do research. So I could do all those things. Get my preliminary data. Now go write grants. At the time NCI did a smart thing. When I came to MD Anderson I was at NCI. And I had to write proposal for -- they encouraged us to think, don't compete with everybody else, do something great, etc., wonderful. But when we came to MD Anderson we became regular citizens. And NCI began something that I thought was a phenomenal advance called Outstanding Investigator Award. Outstanding Investigator Award, you had to really compete for that. They didn't give it to everyone. You had to be moving earth and shaking in your field. But if you received it you were not allowed to compete for any other grants. And I'm one of the very few who was able to renew it. And I had it for 15 years. I think it was \$600,000 a year. But I could not write an R01 or P01. This is it. Many of my colleagues said they don't want it because they have three R01s, they can get \$1 million. I said, "But then you're wasting your time writing grants." "We don't care." And then a lot of people began to complain. "What is different than us?" And instead of saying, "We only have about 20 of them, and we recognize our best scientists like that," said OK, and they folded. That's what governments do. So that also encouraged people to think unconventionally. Not to be afraid. We had meetings. We had arguments, etc., etc. I think that's the reason.

**Tacey Ann Rosolowski, PhD**

[17:33]

Couple of just questions to pick up details. What year did you become a citizen?

**Isaiah J Fidler, DVM, PhD**

[17:39]

Gee. That's a tough one. Probably around 1960.

**Tacey Ann Rosolowski, PhD**

[17:58]

Was that a big deal to change citizenship?

**Isaiah J Fidler, DVM, PhD**

[18:01]

No, because I did not lose my Israeli citizenship. US and Israel recognize dual citizenship. So when I'm in Israel I enter on Israeli passport. When I'm in America on an American passport. Were I required to give up it would have been difficult. But --

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**Tacey Ann Rosolowski, PhD**

[18:25]

You didn't have to confront that.

**Isaiah J Fidler, DVM, PhD**

[18:27]

The US has recognized dual citizenship with quite a few countries. Israel is one of them. Britain is another. France.

**Tacey Ann Rosolowski, PhD**

[18:36]

Have you encountered -- was it difficult for you when you came to this country? Were there a lot of intercultural issues that you had to deal with or challenges?

**Isaiah J Fidler, DVM, PhD**

[18:49]

Yeah of course. It was a different culture, different language. Everything was different, especially in Arizona, Oklahoma. I went to Stillwater, Oklahoma, a town of 20,000 people, and 30,000 students. Jerusalem was so far more advanced than Stillwater, Oklahoma. It was a tiny little community. You could walk from end to end. And I went with a good friend of mine. I used to go to church on Sunday because I was -- sort of wanted some religious experience. The closest synagogue was in either Tulsa, Oklahoma City. The food was different. Language was not a problem, because again my English background was so strong. My accent was a problem. I was inducted to the hall of fame of Oklahoma State, and as I received it I told them that when I first arrived I still remember going to eat grilled cheese sandwich which is my -- only thing we could afford. Was delicious. I cannot find that grilled cheese taste again. It probably was the cheapest cheese possible and smeared with some who knows what. It was not butter. But anyhow. And the lady. I said, "Can I have a grilled cheese sandwich?" And she looks at me, says, "Oh you must be a foreigner." I didn't know what she was talking about. I went home, and I look in the dictionary. Fern F-E-R-N. God, that's a plant. Why is she calling me a plant? Then I realized that in Oklahoma fern is a foreigner. And after that everything was OK. I said, "For them to call me a foreigner was a distinct --" everybody's laughing. But it was true. I had to get used to the accent there. I don't know. When I left home at the age of 13 to go to a dormitory, so that prepared me not to be home. I was in the army for two years. That was not home. And then I came to the States. It was just a continuation of being on my own. That's another thing maybe that I was never afraid of. Is to be on my own. Whether I like it or not that's my life. I had to trust myself.

**Tacey Ann Rosolowski, PhD**

[21:45]

And trusted yourself about your scientific directions as well.

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**Isaiah J Fidler, DVM, PhD**

[21:49]

Well, I imagine so. I don't know if it's here. I carry some principle with me. That's not it. Michael Crichton. There's no such thing as consensus science. If it is consensus it's not science. If it is science it's not consensus. Period. But here are the three principles that I read to students. Only two things are infinite. The universe and human stupidity. And I'm not sure about the former. That's Einstein. I don't know the key to success. But the key to failure is trying to please everyone. But this is the best one. If you're looking for a helping hand you'll find it at the end of your arm. That's my grandmother.

**Tacey Ann Rosolowski, PhD**

[22:48]

That's your grandmother.

**Isaiah J Fidler, DVM, PhD**

[22:49]

Yeah.

**Tacey Ann Rosolowski, PhD**

[22:49]

Yeah. So that independence thing was --

**Isaiah J Fidler, DVM, PhD**

[22:52]

No, I mean she --

**Tacey Ann Rosolowski, PhD**

[22:52]

-- there in the family.

**Isaiah J Fidler, DVM, PhD**

[22:53]

-- used to -- it was -- she didn't even have to say it anymore. She just went like that. Means go do it yourself.

**Tacey Ann Rosolowski, PhD**

[23:01]

Go do it yourself.

**Isaiah J Fidler, DVM, PhD**

[23:02]

Grandma, can I have that? She said.



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**Tacey Ann Rosolowski, PhD**

[23:04]

Go do it yourself.

**Isaiah J Fidler, DVM, PhD**

[23:05]

Yeah. You want to do it, do it.

**Tacey Ann Rosolowski, PhD**

[23:07]

That's great.

**Isaiah J Fidler, DVM, PhD**

[23:08]

I'm not going to do it for you. So you learn after a while to be totally independent. Then as you get older you realize that there's no such thing as independent. You're dependent all the time. You just don't know it. It's the seed and soil hypothesis. Seeds are not independent. Soil is not independent.

**Tacey Ann Rosolowski, PhD**

[23:30]

Interdependent.

**Isaiah J Fidler, DVM, PhD**

[23:32]

If you ask what makes -- if you really study the biology of a lung you realize how it's regulated by protein that are made by everywhere. If you look at all this complicated diagram of protein and this, and looks like a highway in Los Angeles, OK, but when push comes to shove it's not that complicated. It's just that we don't understand.

**Tacey Ann Rosolowski, PhD**

[23:59]

I'm curious on how quickly your research was so -- so revolutionized the field. How quickly were some of these principles taken up and applied to actually intervene in patients' lives?

**Isaiah J Fidler, DVM, PhD**

[24:21]

I don't know how to say it politely. Probably within a decade. But I don't think people gave credit. If you say, "Tumors are biologically heterogeneous," people will say, "Of course they are." "Who was the first to show it?" "Nobody." It's like Luria-Delbruck, same thing, I realize that that's the way the world is. And they remember who invented a drug, but the principle I'm not sure. If I asked you who got the Nobel for better understanding of the AIDS virus, about two years ago it was the hottest thing. And Robert Gallo didn't get it and this one in France got it. And today both of them go to the movies, they pay the same ticket. So I don't know. The question of heterogeneity has influenced the field a lot. The

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fact that metastases are not random greatly influenced the field. But whether it was taken to patients. In principle yes, in practical I don't know how to tell you. The fact that tumors in different organs within same patient are different is beginning to penetrate now. And the fact that right now at MD Anderson there's a big push for what is called individualized therapy. How do you explain individualized therapy? What's the need? Why do we need individualized therapy if all tumors are alike? If all tumors are one big C, we need one drug and that's it. For years we were looking for the miracle drug. It's not there. OK, so all colon cancer. Colon cancer is different than prostate, and prostate different than melanoma, etc., right? But now I'm telling you that not all colon cancer are alike, and not all breast cancer are alike. Some have a receptor for erbB-positive and some are erbB-negative. So even breast cancer are not alike. And now when we're publishing that gene expression of breast cancer cells growing in different organ are absolutely unique to the organ, then the treatment has to be directed to where the tumor is growing.

**Tacey Ann Rosolowski, PhD**

[27:37]

To the soil.

**Isaiah J Fidler, DVM, PhD**

[27:37]

To the soil. So that's another complexity. Is that convenient? No. So we have to finish. But I'll tell you -- I'll have to leave in a minute. Surgeons understood that for many years. I'm a surgeon. We refer. For example, a patient that has breast cancer and the tumor metastasize in the lung, and surgical approach is determined to be useful. A thoracic surgeon will operate on the lung. But if the tumor is in the bone it won't be the thoracic surgeon. It will be an orthopedic surgeon. If the tumor is in the brain no thoracic surgeon will do neurosurgery. Go to the neurosurgeon. So here three surgeons could work on the same patient. If surgery was determined to be an approach to therapy. Where we got spoiled is radiotherapy. You can radiotherapy here, here, here. It's the same person. But what about oncologists? And you see in oncology you have a breast cancer specialist, and they'll treat the patient regardless of the organ. Eye cancer specialist. Melanoma specialist. I say, "Folks, keep in mind you're treating different disease." "Well, what would you like us to do?" "Well, if it metastasize to the brain, let a neuro-oncologist handle it. Regardless of where the tumor originated from, it's growing in the brain." And you'll see tomorrow the brain is a very unique microenvironment. I could give you the same story on the bone, on the liver. But I'll choose the brain because that's where I've dedicated the last four years of my life to. And on and on and on. So hopefully that concept, that the microenvironment alters the behavior of the cell. There is adaptation there. And if we can treat the microenvironment we may be able to have one therapy for a single organ. And that's what the late Judah Folkman -- you know his name, Folkman -- was advocating when he talked about the issue of angiogenesis. Oxygen. This is something we published. Oxygen can only diffuse about 100 micrometer from the blood vessel. And here we published an interesting paper. Excuse me, my back. We published an interesting paper some time ago. Maybe I took it out. Anyhow we took a clinical specimen and measured dividing cells and dead cells' distance from the nearest capillary. All dividing cells were 60 to 80 micrometers from blood vessels, and all dead cells were 140 and further from the blood vessel. Oxygen only diffuses 100 micrometers. And with all due respect to the world, without oxygen there's no life. So tumor cells that couldn't get sufficient oxygen died of hypoxia. OK? So Judah said that unless the tumor develops blood vessels it cannot increase in size.

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Because of this finding that we had. He was absolutely correct. But you know what objection angiogenesis had? What trouble he had? He was almost thrown out of Harvard because he was so unconventional. He was a pediatric surgeon. Let him go back to surgery. And the senior faculty at Harvard were livid with him. The dean appointed, gave him tenure. He was assistant professor. He says, "I'd like to protect you," and gave him tenure as associate professor like that. So the rest will know that he is sacrosanct, leave him alone, he's thinking out of the box. I really wanted Judah to come here for a year when I was the chairman for so many years. "I give you a nice office. Come and escape." They were attacking him again and again. When he talked about antiangiogenesis therapy. And today you have thousands of people working on it. He was the first to say. He was correct. If you attack the stroma, if you know how to attack an endothelium, the blood vessel cell, whether the oxygen is being given to a sarcoma, melanoma, carcinoma doesn't matter. They all need oxygen. Attack the stroma. And my conclusion was from the Paget in 1980. The conclusion from the Paget was that metastases occur only when the seed and the soil are compatible. Completely agree with him. Attack the soil, because it's the same. Much easier. That's what we are doing now for the brain. OK?

**Tacey Ann Rosolowski, PhD**

[33:54]

Well, let's stop for today, and I'll let you go. Thank you very much for your time today.

**Isaiah J Fidler, DVM, PhD**

[34:00]

You're very --

End of session one.

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***Isaiah J Fidler, DVM, PhD***

Interview Session Two: 27 September 2011

Chapter 0

Interview Identifier

***Tacey Ann Rosolowski, PhD***

OK, let me just -- today this is Tacey Ann Rosolowski interviewing Dr. Fidler for the Making Cancer History Voices Oral History Project. Today is our second session. It is September 27th, and the time is just about five after 2:00.

***Isaiah J Fidler, DVM, PhD***

[00:19]

Thank you.

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## Chapter 5

### A: The Researcher

#### Recent Research: A Focus on Brain Metastasis

##### Story Codes

- A: The Researcher
- A: Definitions, Explanations, Translations
- A: Overview
- A: Inspirations to Practice Science/Medicine
- C: Professional Practice
- A: Career and Accomplishments
- C: Discovery, Creativity and Innovation
- A: Influences from People and Life Experiences
- B: Industry Partnerships
- D: Understanding Cancer, the History of Science, Cancer Research
- D: On Research and Researchers
- A: Character, Values, Beliefs, Talents

#### *Isaiah J Fidler, DVM, PhD*

[00:19]

So the finding that the organ microenvironment influences the behavior of cancer had a significant influence on the design of animal models to study a cancer. Basically that development of what you call orthotopic models or models in the correct organ environment versus ectopic which means incorrect. Ectopia is incorrect, orthotopia is correct. Came from the observation that when we wanted to study the biology and metastasis of colon cancer we received a specimen from surgery. And the question was can we design an animal model that will predict whether the specimen that we receive are going to produce metastasis or not a year or two or three later in a patient. And if we could then the advice will be "Why don't you do a very aggressive therapy? Because this cancer will metastasize and it will be a disaster two years, four years down the line." And we literally did close to 80 or 90 different specimen. And not in single one did we see a metastasis when we implanted it into a mouse that had no immune system, so it couldn't reject it. The problem was we injected it, like anybody else, under the skin. And it's very easy to do. And all these tumors, whether they were metastatic in the patient, we even had example of already metastases that theoretically should have metastasized in the mouse. They did not. They grew locally into a quite large tumor where we either had to surgically resect the tumor or simply sacrifice the mouse. But we never found metastases. And then it dawned on me that perhaps injecting tumors under the skin is not exactly the correct model. And we began to inject human colon cancer cells into the cecum or appendix of a mouse. Into the wall of the cecum. The cecum in a mouse is almost equivalent to the appendix of man. And to my great surprise the tumors grew locally and produced metastases.

#### *Tacey Ann Rosolowski, PhD*

[03:16]

Can I ask you how you came up with the idea to shift procedures?

**Commented [T5]:** Dr. Fidler discusses his research focus for the last four years: brain metastasis. He emphasizes that very few researchers focus on brain metastasis, largely due to the complexities presented by the blood-brain barrier. Dr. Fidler explains that the blood-brain barrier is already compromised in metastasis, a fact that has implications for treating as well as studying the condition. He discusses his work on astrocytes, which protect tumor cells from chemotherapy, until he and his group discovered a drug (now patented) that interrupts the astrocyte's protective activity.

***Isaiah J Fidler, DVM, PhD***

[03:21]

Well, I began to think about Paget seed and soil. I said, "Subcutaneous is the wrong soil." And colon cancer in patient, we don't see under the skin. We see it in the colon. And we then followed with renal cancer in the kidney. Pancreatic cancer in the pancreas. Lung cancer in the lung. Breast cancer in the mammary fat pad or breast of mice. And in all those examples malignant tumors were distinguished from nonmalignant by the fact that they produced metastases. The implication of that orthotopic model was enormous, because the subcutaneous tumors by and large were very sensitive to chemotherapy, but the same tumor growing in the correct organs were not sensitive. And once again patient who have kidney cancer, they don't have it growing in the skin. And whether the tumor in the skin is sensitive or not to chemotherapy is irrelevant because you never see it. You see it in the kidney. You see it metastasize to the lung and so on. And when we duplicated the correct organ environment we found that we were mimicking the resistance or we were duplicating, a better word, the clinical situation. So again this microenvironment, seed and soil, was translated to something extremely practical. That is can you predict the metastatic potential of individual cancers from patient and can you predict the therapeutic sensitivity or resistant.

***Tacey Ann Rosolowski, PhD***

[05:21]

Why were the cancers that ended up in the organs themselves so resistant to chemotherapy?

***Isaiah J Fidler, DVM, PhD***

[05:29]

Well, there are many explanations for that. And I want to focus on the last four years of my research. And there is a personal reason why I became so committed to work on brain metastases, and I don't want to discuss it. It was not -- it was a death in the family from brain metastases. And when I realized that in the United States almost 250,000 patients are going to die a year from brain metastases, 50% to 60% of all lung cancer patient, which is the most common cancer now, will develop brain metastases, 25% of breast cancer, 20% of melanoma, I can go on and on and on. It's very difficult to diagnose brain metastases because you depend on MRI and CT, etc. And you cannot identify tiny little lesions. They have to be of a certain size. And it's not like mammography where you do it routinely, or colonoscopy, or prostate examination, which are very relatively easy to do. And consequently in the majority of patients if you don't treat them, the median survival after diagnosis is one to two months. 250,000 people. Actually it's 230,000. Well, OK, close. And with chemotherapy, surgery, radiotherapy and on and on and on we can increase survival to a median of four to six months. But that's about it. Very few - - out of 250,000 or 230,000, I can't think of a number of survivors. And yet when you read the literature you see that very few people, very few laboratories work on brain metastases. Very few. In the world I'd say -- in therapy yes, because they have no choice. But research, pure research, maybe ten.

***Tacey Ann Rosolowski, PhD***

[08:13]

The difficulty level is preventing people or --

***Isaiah J Fidler, DVM, PhD***

[08:15]

It's the difficulty level and the point, the strong belief that something called the blood-brain barrier which I'll explain in a minute is the culprit. The blood-brain barrier consists of blood vessels that are very tightly attached surrounded by other cells called pericytes and astrocytes. And the role of the blood-brain barrier in the brain is to prevent toxic substances from entering the brain, to protect our neurons. Because our neurons don't divide. If we're going to start losing neurons, it's irreversible loss, it's not like skin cells or lung cells, colon cells that constantly are replaced. Neurons are not replaced. So we have protection called the blood-brain barrier. The thing is that in primary tumors of the brain like glioblastoma and in metastases a very telling symptom is headache. And turns out that these patients have edema in the brain. Edema means that the vessels are leaky. I can tell you clinically the blood-brain barrier when you would diagnose metastases is leaky. It cannot be intact. But we did a lot of experiments. You can inject fluorescent material into mice. And check whether the fluorescent material is inside the vessel or outside the vessel. And in a normal brain it always is retained in the vessels. In the brain metastases that we establish it leaks out. Now oh, 20, 25 years ago, a neurosurgeon by the name of Gabi G-A-B-I Schackert S-C-H-A-K-E-R-T Schackert came to do a fellowship with me. And she introduced me to brain metastases. At the time I was working with colon cancer and prostate cancer and pancreatic cancer and ovarian cancer. You name it. And it was one thing. OK, brain metastases. And then there was another fellow came from Japan to continue her work. But it wasn't that captivating. I don't know how to explain it. It was difficult. And I said, "OK, fine." But she developed a method to introduce tumors through the carotid artery which is right here to the brain of mice. And we published, I don't know, half a dozen to a dozen paper on models for brain metastases. And we have shown in these metastases that there were the same cell melanoma injected into the brain was resistant to chemotherapy, the identical clone injected subcutaneously was sensitive. In the lung it was sensitive. But in the brain it was resistant. But I attributed it to the blood-brain barrier. So the chemotherapy can reach the tumor in the skin and in the lung, but not in the brain. But as I said, a few years ago it became very clear that that prevailing viewpoint of the field is absolutely wrong. And again similar to what I told you, how can metastases be random? If you can predict metastases. But it took me quite a few years to reach that conclusion. What are they talking about that metastasis is random? You can predict it. It's a contradiction in terms. Same thing here. If a patient has edema, cerebral edema, what are you telling me about the blood-brain barrier? There is edema for God's sake. So we had to look at something else. And here circumstantial evidence became extremely strong. And that is that any wound in the brain, any lesion, any inflammatory change in the brain involves a cell of the microenvironment called astrocyte. Astro like the ballplayer that don't know how to play ball. Astrocyte C-Y-T-E-S. These stromal cells of the brain's job in physiology is fascinating. They send a process to the blood vessel and another process to a neuron. And they transfer nutrients from the blood to the neuron, glucose, galactose. They participate in signal transmission. They do all the -- practically they help neuron do their job, etc. But they're the main support cell of neurons. When metastases or primary tumor grow in the brain, we found -- I had a slide given to me by Dr. Ken Kenneth Aldape A-L-D-A-P-E. A neuropathologist, or head of neuropathology. And we're looking at the slide. And here is lung cancer metastases to the brain. And it's surrounded by huge number of activated or angry astrocytes. And I say to Ken, it's true story, "What is that?" He said, "Well, these are astrocytes surrounding tumor." And I say, "Is that new?" He said, "No. Everybody knows it." "So how come it's not published?" He said, "Everybody knows it."

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**Tacey Ann Rosolowski, PhD**

[14:41]

When you say activated or angry what do you mean? What is it doing?

**Isaiah J Fidler, DVM, PhD**

[14:44]

They express a certain protein so we --

**Tacey Ann Rosolowski, PhD**

[14:46]

I see.

**Isaiah J Fidler, DVM, PhD**

[14:46]

-- call them activated astrocyte.

**Tacey Ann Rosolowski, PhD**

[14:47]

I see.

**Isaiah J Fidler, DVM, PhD**

[14:48]

If you look at the normal brain the astrocytes are there attaching every neuron. But they don't express the protein. Only when there is hypoxia. Any stress in the brain would lead to expression of this protein called GFAP. Doesn't matter. It's too complicated. But the astrocytes are activated. Well, I'm looking at that and I'm saying to my fellows, "Go ahead, and let's produce this model in the brain of a mouse." And we inject lung cancer, breast cancer, melanoma into the brain of mice. And what do you know? They're surrounded by angry or activated astrocytes. I began to think about it. What does it mean? Well, if the astrocytes were anticancer, there'll be no cancer. The fact that they are interacting with all the tumor cells could be two things. Either they are neutral, they don't do anything, or God help us, they enhance cell growth, because their job is wound healing in the brain. I didn't tell you at all about 15 years that I spent on macrophages. But we're going to leave it alone. These are the cells that enhance wound healing in the body. And they're also -- they can do everything under the sun. The phagocyte. Everything.

**Tacey Ann Rosolowski, PhD**

[16:30]

And this was the research that basically enlisted their aid. To activate the macrophages so that they would attack. Both benign and malignant cells.



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**Isaiah J Fidler, DVM, PhD**

[16:39]

Right, right. So anyhow, we began to be very interested. And Robert Langley L-A-N-G-L-E-Y isolated mouse astrocytes and gave us a nice cell line and when Sun-Jin Kim who did all the work, Sun-Jin J-I-N Kim K-I-M. Sun-Jin Kim cocultured tumor cell and astrocytes, to make the story short, tumor cell were protected from chemotherapy. And we showed that the astrocytes must touch the tumor cells. You can separate them by a membrane. You can do all kind of things. Unless an astrocyte put an end foot on a tumor cell, the tumor cell is not protected. Well, remember, the astrocyte have an end foot on a blood vessel cell, an end foot on a neuron. They don't talk in -- they touch everything. Well, if they touch a tumor cell, tumor cell is going to be protected. And we looked at every conceivable mechanism, and the most fascinating thing is when we looked at growth of lung cancer or breast cancer or melanoma with astrocytes, versus fibroblasts, we saw that when they grow with astrocytes, there are more than 250 genes common that are upregulated in all the cell line. So the astrocyte, well, they can upregulate 2,000 in this. But there were almost 250 genes that in every cell line the same genes were upregulated. Among them were three survival genes. So these survival genes or antideath genes resulted from the interaction of this so-called stromal cell with the tumor cell. And the tumor cells are resistant to chemotherapy. We submitted the paper for publication. And a reviewer said, "You didn't prove anything. Knock those genes down and show me that the tumor cells are now sensitive." Well, Sun-Jin and colleague discovered something very interesting. If you knock one gene, the cells are still protected. Any one of these three genes as a single gene, they're still protected. But when we knocked out all three of those genes, OK, the tumors became sensitive to chemotherapy. And we did something else. Again Dr. Aldape gave us clinical specimen of multiple tumors from patient brain metastases. In every case those genes are expressed in the metastases in patient. Now we did it in mice. Turn it off. You'll excuse me.

**Tacey Ann Rosolowski, PhD**

[20:16]

I will pause the machine.

**Isaiah J Fidler, DVM, PhD**

[20:17]

This is my wife.

The recorder is paused.

**Tacey Ann Rosolowski, PhD**

[20:21]

OK. We're resuming recording at 2:25 after Dr. Fidler took a brief phone call.

**Isaiah J Fidler, DVM, PhD**

[20:28]

The fact that astrocytes protect tumor cell leads to a simple conclusion. Role of astrocytes in the brain is to support and protect neurons. Unfortunately they don't distinguish between a tumor cell and a neuron. They'll do it to any cell they touch. But it indicates again the relative importance of the organ microenvironment on cells' growth and survival. I told you that previously we injected lung cancer into the lung of a mouse or to the brain. In the lung it's sensitive to chemo. In the brain it's not. Well, there

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are no astrocytes in the lung. There are astrocytes in the brain. Damage to the lung occurs every day of our life. And it's being repaired. It's not -- obviously total damage is a disaster. But every day you damage your lung when you breathe the air in Houston, OK? And it's repaired with alveolar macrophages. Here we go to the macrophage. But damage to the brain is almost irreversible, OK? Because the only cell that will divide will be the stromal cell, not the neurons. And we lose neurons all the time. That's why I don't remember names. But if I wish I knew how to revive neurons so we will never grow old. But the blood-brain barrier and the astrocytes' function in physiology is to protect the neurons from damage from circulating toxic molecules. Well, tumor cells need oxygen. Tumor cell need nutrients. And they release a molecule that -- all tumors in the brain we published release molecule called vascular endothelial growth factor or VEGF. VEGF was identified years earlier as vascular permeability factor. So when cells release that molecule, endothelial cell become not as tight, and things become porous, and things leak out. In edema. It leads to edema. And when you flood the tumor with oxygen and with nutrient, the tumor will grow better. It doesn't depend on blood vessels. But when that happen, the astrocyte goes berserk. And it becomes activated. Because it means there's something wrong. There is stress. I'm sorry to make a movie out of it. But I don't know how to explain it any better. There's a knee-jerk reaction here. They become stressed. And when they're stressed their job is to protect, to protect, to protect. And they're so stupid they don't know if you are protecting neurons or tumors. And unfortunately they protect everything alike. And that's why tumor cells are insensitive or resistant to chemotherapy. Now we have a patent on that now. Because we know the pathway by which astrocytes activate those genes. I can describe it. It's too sophisticated in a way. But I don't know what else to tell you.

**Tacey Ann Rosolowski, PhD**

[24:25]

I'd like to hear.

**Isaiah J Fidler, DVM, PhD**

[24:25]

How to do it. The signal that astrocytes send to tumor cell to say, "Upregulate these genes," or they send it to neuron, is called endothelin-1, ET-1. Now the signal has to bind to a receptor. And the way I explain to my graduate student the relationship of a signal, a receptor and activation of a receptor is very simple. You take a key, that's the signal. You put it in a keylock, in a keyhole, excuse me, that's the receptor. Now you got to have the right key to go into the receptor but sometimes you can put anything you want. You can put a toothpick in it. But in order to turn the keylock and open the gate or the door, the key and the keylock must be absolutely matched, and you have to turn the key, and that's called phosphorylation. You activate the receptor. And if the receptor is not activated, the door will not be opened, and it doesn't matter whether you stick the key in the key, you look stupid when you just stand there with the key, and then you realize, "Oh my God, I put the wrong key in the wrong keyhole." If you can stop the key from turning over, nothing else will fall down. We're working with a small company in Switzerland. This is really just for you. Not -- OK?

**Tacey Ann Rosolowski, PhD**

[26:13]

Shall I turn this off?

***Isaiah J Fidler, DVM, PhD***

[26:14]

No. I'm just telling you. Don't -- and we found that a drug that inhibits phosphorylation of the endothelin receptor which was developed to lower blood pressure can prevent the astrocytes from upregulating those genes. We wrote a patent on that and MD Anderson now has a patent together with the company. But it was our, my idea to do that, OK? In fact the company didn't think that -- I said, "I'd like to try it," and they said, "Go ahead." I think they thought I was out there in left field. And I told my friends, "Don't turn down my intuition, it's pretty good." "No, no, no." Said, "Fine, then I'll do it on my own. I don't need your money to do it." So it was our idea, and it works. So I say to you we have done therapy experiment in mice. And I present it now in many many symposia where I'm invited, and I end up by saying, "If you're a mouse that has brain metastases, come to me. I'll cure you." Not therapy. Cure. In human we need to do clinical trials. And clinical trials are planned for the near future. And you're going to say again, "Well, what gave you the idea?" Well, one and one and one is three. If you believe in the principle of the seed and the soil, then who cannot believe in that? Just ignorant people. Absolute ignorant. Don't have to understand metastases, have to understand medicine. You really think that muscle and the kidney are the same? Probably some people maybe. You really think that the brain and the colon is the same? Maybe in some. But these are distinct organ with distinct molecule, with distinct cell. Yes, we all evolve from two cells. But that's called differentiation.

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## Chapter 6

### A: The Researcher

#### Brain Metastasis: Activating the Body's Capacity to Heal Itself

##### Story Codes

- A: The Researcher
- A: Definitions, Explanations, Translations
- A: Overview
- C: Professional Practice
- C: Discovery and Success
- A: Career and Accomplishments
- C: Discovery, Creativity and Innovation
- A: Influences from People and Life Experiences
- D: Understanding Cancer, the History of Science, Cancer Research
- D: On Research and Researchers
- A: Character, Values, Beliefs, Talents

[26:14]

#### *Isaiah J Fidler, DVM, PhD*

Incidentally, Tacey, I was the president of the International Differentiation Society because of my -- I don't know what to call it. At the time revolutionary strong opinion about differentiation. But it was only logical. And the fact that tumors also differentiate, but at a marginal level. Because some are metastatic, some are not. We talk about that, the other thing is that I'm very proud to tell you I'm the youngest at the time president of the American Association for Cancer Research. No one has ever been elected younger than me. So I keep telling them I want respect because I'm the youngest. Now I'm probably the oldest member.

#### *Tacey Ann Rosolowski, PhD*

[29:29]

Well, congratulations on that.

#### *Isaiah J Fidler, DVM, PhD*

[29:30]

Thank you. But I was the youngest at the time.

#### *Tacey Ann Rosolowski, PhD*

[29:33]

And that was because of your advocacy for differentiation and this new line?

**Commented [T6]:** Dr. Fidler begins this half-hour segment by noting his roles as the president of the International Differentiation Society and as the youngest president of the American Association for Cancer Research. He talks about how leadership of professional societies. He then returns to a discussion of the mechanisms of brain metastasis. He notes that the death of his friend, Judah Folkman, led him to re-evaluate his life and step down from his administrative responsibilities, a move that left him with more time to think about his research and investigate the role of astrocytes. He believes that intervening in the role of astrocytes in interacting with the genetics of metastatic cells has implications for treatment of many different diseases as well as other forms of cancer. He then turns back to a discussion of his work on activating macrophages to attack metastasis, quoting from "The Doctor's Dilemma," a play by George Bernard Shaw (1911), to dramatize that the body has all it needs to cure itself: "Nature has provided in the white corpuscle... a natural means of devouring and destroying all disease and germs... Drugs are a delusion."

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**Isaiah J Fidler, DVM, PhD**

[29:38]

No, no, no, differentiation came much later. No, I was really active and very vocal. And I gave great lectures and told jokes and people liked me and they voted for me. It's a democracy. The vote for president, you open, there are five candidates. And people, three or four candidates. And all the members vote. And because I give keynotes they know who I am. And others, maybe they don't. It's just like running for president. They look at the debate. You give a good debate, they think you're a great president. Well, never mind. I'm not a liberal anymore, so I will keep my mouth shut. A great debater doesn't necessarily make a great president. But I was very young when I was the president and very radical in many ways.

**Isaiah J Fidler, DVM, PhD**

[30:35]

How so? In what way were you radical? Now as you look back.

**Isaiah J Fidler, DVM, PhD**

[30:40]

In what way is that we were dependent at the time on a handout from the government to public Cancer Research. OK? And the handout ended. And everybody said, "What are we going to do?" "What do you mean, what are you going to do, we're going to have a fee, you want to publish, you pay for it, like any other journal." "Nobody will submit." I said, "You don't understand. We're going to make it so exclusive, everybody would die to publish in now. Because we will be the expensive journal."

**Tacey Ann Rosolowski, PhD**

[31:14]

What was the journal you were --

**Isaiah J Fidler, DVM, PhD**

[31:15]

Cancer Research.

**Tacey Ann Rosolowski, PhD**

[31:16]

Cancer Research.

**Isaiah J Fidler, DVM, PhD**

[31:17]

Guess what? I was right. We made it exclusive. By saying no more anybody can. You have to pay. Now people who couldn't pay would write a nice letter. And there will be a committee that will say, "Look, this particular person is." But there is a pay charge in every decent journal.

**Tacey Ann Rosolowski, PhD**

[31:44]

I didn't know that in the sciences that was the case.

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**Isaiah J Fidler, DVM, PhD**

[31:45]

Oh sure.

**Tacey Ann Rosolowski, PhD**

[31:46]

In the humanities that doesn't happen.

**Isaiah J Fidler, DVM, PhD**

[31:47]

Sure.

**Tacey Ann Rosolowski, PhD**

[31:48]

Yeah I didn't know.

**Isaiah J Fidler, DVM, PhD**

[31:48]

Sure.

**Tacey Ann Rosolowski, PhD**

[31:49]

What are the fees like?

**Isaiah J Fidler, DVM, PhD**

[31:50]

I don't remember. But whatever they were, we became self-sufficient. And I also insisted that we raise the -- when you go to an annual meeting it used to be practically giveaway. "What do you mean giveaway? Other societies charge a fee to attend, we will also charge a fee." "Nobody will come." I said, "They'll come, don't worry." And they did. But anyhow, the point of the matter is that the brain story illustrates everything. Cells that reach the brain are different cells than reach the lung, etc. Those that can interact favorably with the microenvironment will survive to grow. Those who cannot interact will die. But we can go deeper than that to say that metastatic cell -- I used to say usurp but most Americans don't know what usurp is so I say exploit. Usurp is being used more in England than in the United States. I like the word --

**Tacey Ann Rosolowski, PhD**

[33:06]

It's a --

**Isaiah J Fidler, DVM, PhD**

[33:07]

-- usurp.

***Tacey Ann Rosolowski, PhD***

[ 33:07]

-- better word, I think. It's a better word. It's different than exploit.

***Isaiah J Fidler, DVM, PhD***

[33:10]

They usurp physiological mechanism for their own gain. I say now exploit the host cells for their own gain. And what else can you talk about than astrocytes. Look what they do. They allow you to grow and they protect you from destruction by toxic substances which will reach the tumor cell and the neurons because the blood-brain is leaky. So it's a perfect example for the seed and the soil. Once again. And it says the following. If you want to treat melanoma in the brain and you go for genes of melanoma, if you want to treat colon cancer in the brain, they do make brain -- lung, breast, you name it, you have to have six different treatments. But if you think, "If I can interfere with those astrocytes." OK, the astrocyte so far react the same whether you're colon cancer, breast cancer, lung cancer. They don't care. If they touch you they send a signal. You upregulate genes. Now we only looked at three. But I already told you we know 250. And in fact because of other reasons -- oh it's over there. Never mind. I have a list of all the genes that they upregulate. And my God, it gives idea for many other diseases to control by the same mechanism. So if you target the astrocytes, if you target the microenvironment, you don't only rely on targeting the seed. You target the soil and the seed. You will have twice. Not twice, I shouldn't say. Say 20 times better chance, because it's highly synergistic. It's not one and one. When you target this and that it's not this, it's like you're covering your bases. And if you do the model correctly, the orthotopic, you understand the seed and soil. If you look at metastases different than the primary tumor, you understand the tumors are heterogeneous. If you speak now about individualized therapy you understand there's no such thing as the big C, all cancers are alike. And just logic, OK? If you look at fact A and fact one and one have to be two. It cannot be seven or cannot be zero. Now some people go one and one is seven, and they are so futuristic that they don't know how to prove the point. But the majority of people say one and one is one, and they're afraid to fail. And if you're afraid to fail you don't try big things. You try, you move in small steps. So you wouldn't be exposed to ridicule if you fail. It's called insecurity. And I figured what happened really was that I was in California asleep ready to give a talk at 10:00 in the morning. And the phone rang at 5:00 in the morning, woke me up. It was a friend of mine, Robert Kerbel from Toronto, who called because he thought -- with cell phone you don't know where people are. He thought I was in Houston. It's 7:00 in the morning. To tell me that a good friend of ours, Judah Folkman, died the night before at the Denver airport. Judah was on his way from Boston to one of the meetings in the mountains. And had a heart attack at Denver. I think what happened was he probably was late. He was rushing. He forgot that Denver is 5,500 feet over sea level and not Boston. And didn't have enough oxygen. I don't know. Something happened to him and he died. And it really depressed me because I was doing about the same thing. Running all over. I came back and met with Dr. Mendelsohn and I told him that I'm going to be -- we just celebrated my 70th birthday and had a huge symposium in Houston for 45 years to my work in metastasis. And it was a really major major international symposium that Dr. Mendelsohn was kind enough to finance. It was a big success. Really major. All my graduate students, all my fellows came for one day, and then three days' meeting, with everybody leading in the field came to give a talk. And among them was Judah Folkman. And where are they? To the reception here. President and Mrs. Bush came to the reception. See that over there.

***Tacey Ann Rosolowski, PhD***

[39:10]

Oh yes.

***Isaiah J Fidler, DVM, PhD***

[39:13]

Says, "To Josh." And blah blah blah. I'll tell you about it in a minute. About this insane man who was jumping out of airplanes when he's 70. But anyhow he and his wife came to the reception. And it was wonderful. But Judah was there. And then two months later he's dead. So I came back from California. And I told John that I'm really -- I'm too busy. I'm a chairman of a department now for -- I don't know, 40 years. I'm in charge of a building. I'm in charge of animal facility. I have to do my own work. And I have three grandchildren, I have a wife, I have a farm, I have a horse. I don't have time to do anything. So two choices. Either I completely retire or he will allow me to step down from my administrative responsibility so I can only quietly do research. And he was kind enough to say the latter is OK. So Dr. Lee Ellis fortunately took over as interim chairman. Doing a fabulous job. Lee is one of my fellows. He's a professor of surgery and cancer biology. And he is also directing the metastasis program now. And I was allowed -- I don't go to meetings anymore for example. No more meeting. No more. And if I want I go. But I don't have to do all the administration. And it simply allows more time to think. And when you see those astrocytes, you have to think. What are they doing? They don't kill the tumor, or the tumor wouldn't be there. I already told you that. They either do nothing -- but there's no such thing as doing nothing. If a cell does nothing, the cell would have been eliminated, whether you believe in creation or evolution, it's a constant changing area. On my own I keep telling people who don't believe in evolution, believe in creation, that say, "Read the first chapter in the Bible. What do you mean you don't believe? Day one this was done, day two this, day three. And it's in the correct order. How did they know 4,000, 5,000 years ago the correct order?" I said, "Now you're going to argue with me about a day?" I said, "That's a day in the life of God. Do you really know? Before man was created, this is a day. A day of God is a day of man? How about if it's a billion and one year? How about if it's infinite? There's no such thing as time? A day in the life of God. So how old is God? 400 years old? 70 years old by your -- what are you talking about? There's no such thing as time." So they ask me, "You believe in evolution? You believe in creation?" I believe in everything. Believe means you don't have data. It's easy to believe. What do you mean I believe? Yeah of course I believe. You look and you say, "What do they do?" Well, maybe they protect. And you do some experiment. You make a hypothesis. And God almighty, all of a sudden you have a molecule. Now if I did it 40 years ago I would never have a molecule. Because we were not that sophisticated. And 40 years from now the work today is going to look primitive. You really think we reached the end of the road? Come on. I have a computer. I don't know how to use it. But look at the screen I have. I put a slide on this microscope and it shoots into the computer and I can manipulate. I can do this. Oh my God. Look down there. You see that, Tacey? That's my fellow computer from Department of Pathology, University of Pennsylvania. They gave it to me as a gift. This is it.

***Tacey Ann Rosolowski, PhD***

[43:53]

That's it, that microscope.



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***Isaiah J Fidler, DVM, PhD***

[43:54]

Yeah it's like a \$350 microscope today. I worked more hours on that than on this fancy one that is like \$5,000, \$6,000, \$7,000. I learned more from that. Sit in a dark corner quietly, looking, looking, looking, looking. Trying to figure what does it mean. When I ask questions people will say, "Don't nag us. Go read a book." You had to do it yourself. There was no such thing as people taking -- nobody -- just learn for yourself. I think that what we know now is a fraction of what we're going to know years from now. But logic is going to remain. And yes we're going to have 500,000 new molecule. But what they do and how they do unless you have a certain hypothesis and logic we will never know. There'll be a list of molecules. So what? So what do they do? We cloned the human genome, didn't we? It cost us who knows how many billions of dollars. Are we any closer to curing disease? It's not how, when, what, it's why that is the central question. OK. Let me tell you a little bit about macrophages, OK?

***Tacey Ann Rosolowski, PhD***

[45:21]

OK, OK.

**Isaiah J Fidler, DVM, PhD**

[45:23]

Now I became fascinated with macrophages. I had to give it up. We used to be called the M&M laboratory, macrophage metastasis. And the reason I became fascinated with macrophages was because they were -- again when you looked at a tumor you always see macrophages. Turns out that macrophages participate in wound healing. And they produce -- a good friend called Nathan N-A-T-H-A-N wrote in 1980 a review listing 120 proteins that macrophages make. Today it's probably 2,000. I mean that's all we knew then but today we -- it's an independent cell. It's like an animal inside our bloodstream. One cell can do everything. It's amazing. And they always participate in infection. They are the phagocytic cell. You have a bacteria, they'll eat it. Digest it and spit out protein. You have a virus infection. They'll take care of it. They don't need antibiotics, they don't need anything. This is a fantastic play that Bernard Shaw wrote called *The Doctor's Dilemma*. In here. So in this play that he wrote there is an argument about modern technology versus the old stuff. "Drug can only repress symptoms. They cannot eradicate disease. The true remedy for all diseases is nature's remedy. Nature and science are at one, Sir Patrick, believe me. Though you were taught differently. Nature has provided in the white corpuscle as you call them, in the phagocyte as we call them --" these are macrophages "-- a natural means of devouring and destroying all disease germs. There is at bottom only one genuinely scientific treatment for all diseases. And that is to stimulate the phagocytes, stimulate the phagocytes. Drugs are a delusion. Find the germ of the disease. Prepare from it a suitable antitoxin. Inject it three times a day, quarter of an hour before meals, and what is the result? The phagocytes are stimulated. They devour the disease, and the patient recovers. Unless of course he's too far gone. That I take it is the essence of Ridgeon's discovery." This is a play that Bernard Shaw wrote. Copyright 1911. OK, so at the time I became aware of individual who were injecting BCG. That's a form of tuberculosis bacteria. Bovine tuberculosis bacteria. To stimulate the immune system. And there were multiple multiple publications that BCG can eradicate cancer. But nobody knew the mechanism, etc. And we began to look into BCG and macrophages and tissue culture in animal. But it was very clear that is an unbelievably primitive way to do it. And of course BCG had the downside that it was an infectious agent. It gave a lot of inflammation. Animal were dying from it if you were not careful. And so I was complaining about it in one meeting. And I was approached by a brilliant man by the name of Lajos L-Y-O-S Tarcsay T-A-R-C-S-A-Y. And Lajos tells me, "I work in Ciba-Geigy in Basel. And we have something called muramyl dipeptide. Muramyl dipeptide is in essence -- is a molecule that is BCG, only we reduced it to the real molecule." BCG was all everything, like a vegetable soup. If you want one you -- the problem with muramyl dipeptide as I discovered was that it goes in and is gone in a matter of a few minutes. So they produced something called MTP-PE, muramyl tripeptide phosphatidylethanolamine, MTP-PE, you don't need to know more than that. And what happened was that it had phosphatidylethanolamine is a phospholipid. And we began to encapsulate it. I had help from George Poste P-O-S-T-E. George became the president of -- oh God. I'll remember. A big drug company in Philadelphia. One of my closest friends, I don't remember the company he ran. But anyhow. Smith Kline & French. But at the time he was at Roswell Park. And at Roswell Park was the creators of something called liposomes or liposomes. They were little structures from phospholipids that now they're called nanoparticles. Now they gave a big name. New liposomes. And if you can encapsulate liposomes with MTP-PE and inject them, macrophages will go berserk. They're going to eat it. Because their job is to phagocytose any garbage in the bloodstream. And they did. And when they did they became very angry. When they became angry they began to make cytotoxic molecule. Second thing that was found is that macrophages' job in the body, physiological role, is to phagocytose dead red cells. Old red cells. Red cells live to about 100, 120 days. And then they'll

be removed and new red cells will come in. And there's the cycle. How do macrophages distinguish an old red cell from a young red cell? Well, turns out that the membrane of a red cell has three phospholipids, like any other cell. And one phospholipid called phosphatidylserine S-E-R-I-N-E is only exhibit on the inner leaflet. The double leaflet in the membrane. Only inside. When the red cell is old, somehow it flips. And PS comes to the outside. And it's negatively charged. A macrophage says, "Oh, phospholipid serine, we're going to eat you." And they eat the red cell. Any cell that has phosphatidylserine on the outer leaflet, they're going to recognize. And all tumor cells have PS on the outer leaflet. Normal cells don't. Except when you get to be old, when they're going to die, and they will take you out. So tumor cells have negatively charged membrane. And macrophages bind to the tumor cell. But they're too big to eat and too many of them. Red cell is tiny little thing. The tumor is like a watermelon. This is like a tiny little egg. So they can eat lots of red cells, they can eat platelet, but they cannot phagocytose tumor cells. They're going to die. But if they have MTP-PE when they bind to a tumor because of PS, they inject toxic molecule into the tumor cell. Tumor cell is going to die. And we published huge number of papers showing that this is how you activate macrophages to kill all kind of tumor cell. Whether benign or malignant, etc. Well, while I'm in Frederick, Maryland a brilliant young pediatric oncologist joined my group. Her name is Genie Kleinerman. Genie with a G. Eugenie or Genie Kleinerman. Genie Kleinerman is now the chair of pediatrics at MD Anderson. And she began to work with the liposomes, MTP-PE on tumors that are growing in the bone. Great result in mice. So she began to collaborate. She came here to MD Anderson with me and stayed with the project on macrophages, macrophages, macrophages. I literally yielded it to her because it was too much for me, and I wanted to focus on my metastasis. And she began to collaborate with another fellow who worked with me. Now he is the chair of veterinary oncology at University of Wisconsin. His name is Greg MacEwen. M-C-E-W-E-N MacEwen. The late Greg MacEwen. Unfortunately he died very young. And Greg was working on dogs that have spontaneous osteogenic sarcoma which is a disease in children where there's literally no treatment once the tumor metastasize to the lung. At the time she began to work on it, the treatment was to amputate the leg, on and on and on. But if the tumor metastasize to the lung, chemotherapy postponed inevitable death. And all these years she'd been working on getting MTP-PE in liposome to the clinic. And I'm happy to tell you that a few months ago she came here. And a big smile on her face. That it was approved in France and Italy a long time ago. But now England, Ireland, Scotland, practically Europe has now accepted it as the treatment for osteogenic sarcoma in addition to chemotherapy. It's not to substitute for. Chemotherapy can do so much obviously. But now they're using this to finish the job.

*Tacey Ann Rosolowski, PhD*

[57:40]

To augment it.

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**Isaiah J Fidler, DVM, PhD**

[57:41]

Right. So what started as a simple observation that macrophages will eat any garbage they want and they'll eat liposome MTP-PE and we can work with mice, then it went to dogs, then it went to tissue culture, then to children. Now it's clinically approved in Europe. Why it's not approved in America, talk to Genie. I don't know. The FDA is still resisting but all Europe said, "Of course." So they're doing it. For many years there was a problem because Ciba-Geigy became Novartis, Novartis dropped the project, and why they dropped the project -- I suspect, I don't know -- because osteogenic sarcoma is one of those orphan diseases. And if it was for lung or breast or colon everybody would be jumping on it. But osteosarcoma in children is an orphan disease. So not too many companies are interested. And a tiny company bought the rights to it, and they are producing the liposome. And hopefully now that it's approved it will be tried for many other cancers for which there is no chemotherapy. The macrophages couldn't care less. They'll kill you because you express negatively phospholipid phosphatidylserine on your outer leaflet. So that was again the example of host factor that can really work against tumor. Of course today with immunotherapy that has been revived. It was very popular. Then it disappeared. And now we understand better. Immunotherapy is now coming back to the front. But Bernard Shaw said it very well. "Activate the phagocyte. Drugs are a delusion." There's no heterogeneity for the macrophage. "You express a negatively charged, we're going to eat you." And old cells that are senescent, this is the recognition of senescence, is negatively charged membrane. Now why do tumor cells that divide all the time express senescence phenotype I don't understand. I don't really care. They do, and that's the story with macrophage. OK.

**Tacey Ann Rosolowski, PhD**

[60:18]

Shall we take a -- stop for a moment?

**Isaiah J Fidler, DVM, PhD**

[60:21]

Yeah please.

## Chapter 7

### A: The Researcher

#### Translational Research at MD Anderson

##### Story Codes

A: Joining MD Anderson

A: Professional Path

A: Contributions to MD Anderson

B: MD Anderson History

A: The Researcher

B: Multi-disciplinary Approaches

A: Career and Accomplishments

A: Service Beyond MD Anderson

B: Beyond the Institution

A: Personal Background

#### *Tacey Ann Rosolowski, PhD*

[60:23]

OK. OK. We're going to shift gears just a little bit and go back in time. I wanted to ask you how you came to join MD Anderson. Why you left the NCI institute in Frederick.

#### *Isaiah J Fidler, DVM, PhD*

[60:39]

Dr. Frederick Becker who was the vice president for research at the time approached both Margaret and I with the opportunity to move to MD Anderson. I was to head a department called cell biology, which then the name would change to cancer biology. And Margaret the department of tumor immunology. With NCI there was a shift in the director of the NCI. And with that shift our ideal condition in Frederick, which was do the best research you can, began -- they called me in, and they were going to tell me what area I should focus on. And I indicated that that is unacceptable, because when I was recruited from University of Pennsylvania one thing that was ironclad guarantee was that I could write my own grant. In other words if I wanted -- as long as I'm funded for decent project, if I want to work on metastasis, it's metastasis, and not work on tomatoes and cucumbers. And there began to be a shift that said at NCI that the people in Frederick ought to do projects rather than research. So the offer of Dr. Becker came at just the right time. In fact we negotiated one weekend and that was it.

#### *Tacey Ann Rosolowski, PhD*

[62:31]

This was in 1993.

#### *Isaiah J Fidler, DVM, PhD*

[62:32]

Right.

**Commented [T7]:** Dr. Fidler explains that changes at NCI had threatened to limit his research freedom and motivated his move in 1983 to MD Anderson, where collaboration with clinicians was fostered: his main goal at that time was to understand metastasis at a clinical level. He speaks about his work training clinicians, many of whom now work at MD Anderson. In the final fifteen minutes of the session, Dr. Fidler tells an amusing anecdote about how he came to occupy the R.E. "Bob" Smith Distinguished Chair in Cell Biology (as his wife, Margaret Kripke was simultaneously offered the Vivian Smith Distinguished Chair in Cell Biology). He describes his relationships training Japanese and Korean clinicians, and notes that the work at MD Anderson he is most proud of is training the next generation. He closes with an anecdote about his most significant award, though he also quotes words attributed to King Solomon: "Don't do things for the sake of an award."

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**Tacey Ann Rosolowski, PhD**

[62:33]

OK. And what did MD Anderson want to achieve by bringing you here and also Dr. Kripke? What was the reasoning?

**Isaiah J Fidler, DVM, PhD**

[62:42]

Well, they wanted to increase basic research. At the time there were only three departments doing basic research. And now they would have five departments. And research that were not especially -- both metastasis and tumor immunology was to increase the research at MD Anderson.

**Tacey Ann Rosolowski, PhD**

[63:17]

What made you take his offer? Why did you? I mean I understand why you left NCI. But why did you decide to come here? What did it offer?

**Isaiah J Fidler, DVM, PhD**

[63:25]

Because I wanted to work in an institute where I could directly talk to the clinical individual. Especially the surgeons and pathologists. Remember, I was a surgeon before I received a degree in pathology. And there were several surgeons here that I knew personally. I knew some pathologists. And I was assured that collaboration is a key factor in survival at MD Anderson. I like that a lot.

**Tacey Ann Rosolowski, PhD**

[64:01]

So what were your goals when you first started? And how did some of those collaborations take shape?

**Isaiah J Fidler, DVM, PhD**

[64:13]

My goal was to understand metastasis more on the clinical level than on the mouse or tissue culture level. How the goal became actual is that I began to work with some of our surgeons. I had a joint appointment in department of urology until last year. And the chair of urology was a new chair by the name of Andrew von Eschenbach. And Andy actually even came to Frederick to make sure that he and I could work together. He sent fellows immediately, fellows to my laboratory, to learn animal models. And we began to work on kidney cancer and prostate cancer almost within a month after I arrived. I also worked with Dr. Jessup J-E-S-U-P, Kim Jessup, on colon cancer. These are individual that I knew from national and international meetings and visitors to Frederick. They came to Frederick. We knew them, they knew us.

**Tacey Ann Rosolowski, PhD**

[65:39]

So how did the clinical collaboration work out? Maybe you could just explain how what you were doing had an effect on how --

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**Isaiah J Fidler, DVM, PhD**

[65:50]

Well, I trained -- many many clinicians who are at MD Anderson now in fact trained in my laboratory. And hopefully -- right now I mentioned Lee Ellis. Colin Dinney, who is the chair of urology, trained with me. I have 130 of those, I don't want to start naming. But hopefully when they look, when they wrote grant, when they looked at their own clinical research, the principle that they gained were the shining light to proceed. I mean they spent two to three years with me, I hope they learned something. And they did.

**Tacey Ann Rosolowski, PhD**

[66:38]

So there's a kind of synergy between the lab experience and then the clinical experience.

**Isaiah J Fidler, DVM, PhD**

[66:42]

Absolutely. Because I was very interested in -- I always considered myself to be a translational researcher. I'm not one who works on a single molecular pathway in tissue culture. If you find it, you do it in an animal, then you move on, you move on, spontaneous tumor. You go to the clinic. Developmental therapeutics, etc. Which were very strong here. I wanted to learn from them, and I did.

**Tacey Ann Rosolowski, PhD**

[67:15]

Can you tell me when -- could you tell me a bit about the history of the metastasis research laboratory? When did it start? And how did it --

**Isaiah J Fidler, DVM, PhD**

[67:28]

It started with my coming to MD Anderson.

**Tacey Ann Rosolowski, PhD**

[67:33]

And you founded it right away.

**Isaiah J Fidler, DVM, PhD**

[67:34]

Yeah.

**Tacey Ann Rosolowski, PhD**

[67:34]

It was your working space.

**Isaiah J Fidler, DVM, PhD**

[67:37]

It's my work.

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**Tacey Ann Rosolowski, PhD**

[67:38]

And how is --

**Isaiah J Fidler, DVM, PhD**

[67:38]

My work is on metastasis.

**Tacey Ann Rosolowski, PhD**

[67:38]

Yeah, yeah. And so how did it grow and evolve?

**Isaiah J Fidler, DVM, PhD**

[67:42]

Well, it started with a single laboratory. And then it became -- oh probably ten, 15 years ago we were the first center in MD Anderson was metastasis center. But we didn't receive support, financial support from MD Anderson. It was all take care of yourself. Remember what my grandmother told me. "You want a helping hand, you do it yourself." We had seminar series. We had grants. People joined it if they were interested. Many, most of the members or many were clinicians. Because that's what they encounter every day in the clinic.

**Tacey Ann Rosolowski, PhD**

[68:34]

When did it change? When did it become a part of MD Anderson that was actually supported by the institution?

**Isaiah J Fidler, DVM, PhD**

[68:43]

Mostly when Dr. Ellis took over.

**Tacey Ann Rosolowski, PhD**

[68:45]

OK. And why did that change happen under him?

**Isaiah J Fidler, DVM, PhD**

[68:48]

Because Dr. DuBois, there was a new type of administration with Dr. DuBois, Dr. Mendelsohn. Maybe -- no. Actually I received funding for two years before. The last two years we received funding from MD Anderson. But the help came in multiple different ways. I was allowed to fundraise. When Margaret and I first arrived, this building is called the R. E. Bob Smith Building. And we met with Mrs. Smith because Mr. Smith who was the owner of the Astros by the way died many years previously. And we met with her several times. And there's a cute story about that, that finally I said, "You know that it would be very nice if you could do something for MD Anderson." And she said, "What is that?" I said, "Well, one thing, you can donate a chair." And she said, "Well, OK, we can give the Bob Smith Chair." I said, "No. That's not good enough. I want a chair named after you." "I cannot do that." "Why not? Why not,



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Vivian?" Said, "It's not appropriate to have a chair called the Vivian Smith Chair. Has to be R. E. Bob." I said, "Well, in that case you can donate two chairs, one to me and one to Margaret." About a week later Dr. LeMaistre had a letter. "Dear Dr. LeMaistre, enclosed is a check. I want you to buy a love sofa for Josh and Margaret." True story. "But if a love sofa is not appropriate, buy them two chairs." It's true story. So I had the Distinguished Bob Smith and Margaret had the Distinguished Vivian Smith. Then we prevented both of us to the foundation. We presented work year in and year out. For the last God knows how many, I don't know, 28, 29 years, I had money from the Smith Foundation. But that money has been dedicated to graduate studies. It pays the tuition of students who are in the -- ten student in immunology and ten student in the metastasis area. We had that. We had other donors' money. I was allowed to at the time with Dr. LeMaistre, I could go bang on doors, OK? They took me to give lecture, things like that. It did change in the last few years with the administration. Didn't want people to ask for individual donor money. Everything had to go to MD Anderson. And that's when our location, two centers, became a reality. By then they had 20, 30 centers. Before as I said there was one. I started the center concept.

**Tacey Ann Rosolowski, PhD**

[72:49]

What are the pros and cons of that in your mind? That change in structure.

**Isaiah J Fidler, DVM, PhD**

[72:57]

OK, I'm not going to comment on that. I told you that's just not -- it's irrelevant. I'm no longer the director of the center. I'm no longer a chairman. I'm very happy with where I am. I can do what I want. Besides, we have a new president, and we'll see what he does.

**Tacey Ann Rosolowski, PhD**

[73:18]

I wanted to ask you -- let me just see here.

**Isaiah J Fidler, DVM, PhD**

[73:23]

I need to ask you a question. The only thing you didn't ask me, the size of my shoes. Why is it so detailed, for God's sake? I mean how many people are you interviewing?

**Tacey Ann Rosolowski, PhD**

[73:38]

Right now the list is 33, and there --

**Isaiah J Fidler, DVM, PhD**

[73:41]

33, everybody four hours, who's ever going to listen to that?

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**Tacey Ann Rosolowski, PhD**

[73:49]

Well, here, let me -- well, I guess I'll leave this on record. It's part of an ongoing oral history project that's being run by the Historical Resources Center. And like a lot of oral history projects, there's a sense that there's a mission. Who's going to be listening to this? There'll be scholars. There'll be in-house people. And there'll be the public. So there's a desire to collect information in a whole variety of areas to serve different kinds of audience needs.

**Isaiah J Fidler, DVM, PhD**

[74:20]

Well, I provided you I think more stimulating stories as to centers and things like that. Let it be. I mean ask the boring people those kind of questions. If they don't have good stories to tell, let them answer these kind of questions. For me, I'm not interested in that.

**Tacey Ann Rosolowski, PhD**

[74:39]

Well, I wanted to ask you though about some of the teaching and training. I notice some interesting connections that you have with other institutions. You got an award from the Japanese Association for Metastasis Research. And I know that you had a research center named after you in Shanghai and I was -  
-

**Isaiah J Fidler, DVM, PhD**

[75:01]

I don't know about this research center in Shanghai. They sent me a letter. They asked me whether I will agree. And I said sure, you know. And whether they named it or not I have no idea.

**Tacey Ann Rosolowski, PhD**

[75:13]

So but what of the Japanese association?

**Isaiah J Fidler, DVM, PhD**

[75:15]

The Japanese is real and the Korean is real. I have trained a very large number of Japanese scientists and some of them have risen in their own universities to dean and president, department chair. So my relationship with Japan is absolutely correct. George Poste and I, he's from England, I'm from Israel, were sent by the NCI as the first representatives to Japan to start connection. I thought it was a riot. Very funny that an Israeli and an Englishman are representing America. But that's the land of opportunity, isn't it? I have no very strong relationship also training fellows, scientists, physicians, clinicians from Korea. And of course I've trained people from China. And several from European and many many Americans. Yes, there are two foreigners who are members of this society, that's Bruce Chabner and myself.

**Tacey Ann Rosolowski, PhD**

[76:38]

How did that start?

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**Isaiah J Fidler, DVM, PhD**

[76:42]

Well, the president of the society, the late president of the society, trained with both of us. And he pushed for it, they will accept foreigners, and he is the president. It worked. And again I was the very first foreigner to keynote the Japan Cancer Meeting many years ago. 1991. I remember because I was on crutches and my daughter took me to Japan. Again it's because I trained Japanese scientists. I enjoy Japanese culture. I think they're great. I learned a lot from them. And as the man who invited me to keynote said, it shows. You treat us with -- he said, "You treat us with respect." OK? Which means it shows. In English we'll say, "It shows."

**Tacey Ann Rosolowski, PhD**

[78:01]

I was wondering if your experience coming to another country and adjusting to that --

**Isaiah J Fidler, DVM, PhD**

[78:06]

Oh sure.

**Tacey Ann Rosolowski, PhD**

[78:07]

-- had an influence on your ability to interact.

**Isaiah J Fidler, DVM, PhD**

[78:09]

Oh sure, of course. Of course. I have great understanding and sympathy for people who arrive here and are lost. And what's important.

**Tacey Ann Rosolowski, PhD**

[78:25]

Like having that experience, that intercultural experience, can help you in another intercultural context.

**Isaiah J Fidler, DVM, PhD**

[78:31]

Let me ask you a question. Ask me a question when you stop recording. I'll tell you the advice I give everyone who doesn't know the language.

**Tacey Ann Rosolowski, PhD**

[78:41]

OK. What do you feel are -- maybe you've implied the answer to this question in some that you've already said about the host environment. But what do you feel needs to be done next in the field?

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**Isaiah J Fidler, DVM, PhD**

[79:08]

We need to understand the pathways by which tumor cells interact with the environment, by which the environment influence tumor cells. And identify pathways that are perhaps unique to interaction of tumor with the environment, not normal cell with the environment, and interfere with that. Because that would be a nice way to get rid of tumor cells. We're very lucky in the brain that we can interfere with the way astrocytes interact with tumor cells. But I have big news for you. That's -- we're interfering also with how they interact with the neurons. The difference is that neurons don't divide. And tumor cells do divide. So if we give an antiding agent like temozolomide, a drug, you cannot kill cells that don't divide, only cells that divide. And only cells that divide are tumor cells. So whether the neurons express, don't express resistance molecule, at this stage it's not critical. It could be that in clinical trial that would take two, three years it will become critical. But as I said, if you're a mouse I know what to do.

**Tacey Ann Rosolowski, PhD**

[80:34]

Let me just ask you a couple other questions, because I know that we're running out of time here. Of all of the work that you've done at this institution, what are you most proud of?

**Isaiah J Fidler, DVM, PhD**

[80:58]

Well, influencing the next generation.

**Tacey Ann Rosolowski, PhD**

[81:04]

And what work do you hope they will carry on?

**Isaiah J Fidler, DVM, PhD**

[81:08]

Logic. As we say, don't look for the drug under the lamppost. You know what I'm talking about? Remember this gum that used to have cartoons?

**Tacey Ann Rosolowski, PhD**

[81:22]

Bazooka.

**Isaiah J Fidler, DVM, PhD**

[81:23]

The Bazooka. Somebody showed me a Bazooka cartoon. A man standing under a lamppost. And his friend says, "What are you looking for?" "My wallet." "Where did you lose it?" He said, "Down the road." "Why are you looking here?" "Because here there is light." So I don't want them to look under the light. I want them to follow logic, think about it, make a hypothesis and test it. And if you don't succeed, make another hypothesis. Not the end of the world.

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**Tacey Ann Rosolowski, PhD**

[81:54]

Don't be afraid of failure.

**Isaiah J Fidler, DVM, PhD**

[81:55]

But if you are afraid of failure you'll never have success. And remember Grandma [Stern, Rebecca Stern]. "If you're looking for a helping hand you'll find it at the end of your arm." Don't expect the world to give you the solution to problem. Go find them for yourself. And share. Be ready to share. Don't be selfish. If you found something that is good, share it with other collaborator.

**Tacey Ann Rosolowski, PhD**

[82:33]

You've been given a lot of honors and awards. Some of them you have mentioned. Some of them are the Charles LeMaistre Outstanding Achievement Award in Cancer, the Lifetime Achievement Award from Nature Publishing. You have had a lectureship named after you, the Isaiah J. Fidler Lectureship in Cancer Metastasis Research. The American Cancer Society Distinguished Service Award. Any number of others. Is there one of those or maybe one that I haven't mentioned that means more to you than others? And why would that be?

**Isaiah J Fidler, DVM, PhD**

[83:08]

The last one you get is the one that means something. No, I really -- it's very nice to get awards, and it's very -- I would be a hypocrite if I said that they don't mean anything. Of course they do. But I also believe in what King Solomon said. "Don't do things for the sake of an award. Do things for the sake of doing things." I told you my story that nobody knows who Luria and Delbruck are, and they got the best, they got the Nobel. Nobody knows who they are. And believe me, when they go to buy a hamburger, they pay just as much as you and I. There's one, however, that I must say that was very important to me. And that's when I got a prize from the president of Israel. It's hanging on the wall. And my mother was in the audience. Because when I received the award I said that I want to thank somebody who always told me that I didn't know what I was doing. "Mother, please stand up." And she did, and she waved to the crowd. And she was so proud.

**Tacey Ann Rosolowski, PhD**

[84:34]

That's wonderful. I'm trying to find -- I have that on my list somewhere. What was the name of that award? The E. G. Rosenblatt Award for Scientific Achievement?

**Isaiah J Fidler, DVM, PhD**

[84:45]

No.

**Tacey Ann Rosolowski, PhD**

[84:48]

Ah, yes.

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**Isaiah J Fidler, DVM, PhD**

[84:59]

Just the president of Israel award. Appreciation, gratitude for your contribution to fight against cancer worldwide, 2002. From the Israel Cancer Association.

**Tacey Ann Rosolowski, PhD**

[85:13]

Israel Cancer Association.

**Isaiah J Fidler, DVM, PhD**

[85:17]

It's not -- some awards give you money, and some give you this, and some give you that. This one gave me my mother in the audience. She wasn't in any other award. And here she was. When I asked her to stand up, that was it.

**Tacey Ann Rosolowski, PhD**

[85:34]

Is there anything else that you'd like to add?

**Isaiah J Fidler, DVM, PhD**

[85:39]

No. I'm happy that we have spent three hours yakking or four hours or whatever. And I hope I gave you enough material. And I hope that you'll edit it. Because a lot of it is repetitive.

**Tacey Ann Rosolowski, PhD**

[85:55]

I think it was a -- I really enjoyed talking to you. And I was --

**Isaiah J Fidler, DVM, PhD**

[85:59]

Thank you.

**Tacey Ann Rosolowski, PhD**

[85:59]

-- very interested too. Thank you very much for spending the time.

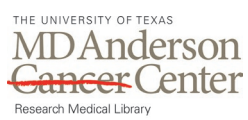
**Isaiah J Fidler, DVM, PhD**

[86:02]

You're welcome. OK.

**Tacey Ann Rosolowski, PhD**

[86:04]



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Interview Session: 02  
Interview Date: 27 September 2011

I'm turning off the recorder at about 3:30.  
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