

Robert Bast, MD

Interview One - July 7th, 2014

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 A. Rosolowski, PhD

[00:03]

All right, the counter is moving, so we are officially recording. (laughter) So I am Tacey Ann Rosolowski, and this morning I'm interviewing Dr. Robert C. Bast for the Making Cancer History Voices Oral History Project run by the Historical Resources Center at MD Anderson Cancer Center in Houston, Texas. Dr. Bast came to MD Anderson in 1994 to head the Division of Cancer Medicine. He also joined the faculty as internist and Professor of Medicine in the Department of Experimental Therapeutics. Dr. Bast was division head until the year 2000 when he became vice president for the Office of Translational Research, a position he occupies today. This interview is being conducted in Dr. Bast's office in the Office of Translational Research on the eighth floor of Pickens Tower on the main campus of MD Anderson, and this is the first of two planned interview sessions. And today is July 7th, 2014. The time right now is 9:40.

So I wanted to thank you, Dr. Bast, very much for giving your time to the project. We really appreciate it.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Robert Bast, MD

[01:06]

It's a pleasure to talk with you.

Interview Session: 01
Interview Date: July 7, 2014

Chapter 01
A: Educational Path
Early Opportunities to Focus on Research

Story Codes

A: Personal Background;
A: Professional Path;
A: The Researcher;
C: Professional Practice;
C: The Professional at Work;
A: Inspirations to Practice Science/Medicine;
A: Influences from People and Life Experiences;
A: Character, Values, Beliefs, Talents;

Tacey A. Rosolowski, PhD

[01:08]

And I'm really looking forward to hearing about your work in translation, which is obviously so key to the identity of MD Anderson. But first, why don't we just start in the traditional oral historical place, and if you could tell me when you were born, and where, and where you grew up.

Robert Bast, MD

[01:26]

Great. I was born on December 8th, 1943, in Washington, DC, but grew up across the river in Arlington, Virginia. And it was a very fortunate place to live, because we were close to the nation's capital, with all of its educational opportunities, providing an appreciation for politics and international affairs that I probably wouldn't have obtained in other areas.

Tacey A. Rosolowski, PhD

[01:50]

So you were steeped in that pretty early then?

Robert Bast, MD

[01:52]

Yes, that's right. And fortunately, there was a lot of medical research activity around the Washington area. I had started with science fair projects in junior high school and then in high school, and when I was a sophomore in high school, I had worked with Dr. Robert Patnode who was a microbiologist at the Veteran's Administration Hospital in Washington, in tuberculosis research. I'd read a Scientific American article about bacterial mutation, and the selection of

Interview Session: 01

Interview Date: July 7, 2014

pre-existing antibiotic resistant bacterial mutants versus the adaptation of bacteria to survival in the presence of antibiotics. With Bob Patnode's training, I set up a laboratory in our basement. My father had helped me to construct an incubator. We used to keep the E. coli cultures in our refrigerator—

Tacey A. Rosolowski, PhD

[02:44]

You were a nerd. (laughter)

Robert Bast, MD

[02:46]

(laughter) I was definitely a nerd. And almost certainly, still am. But, I was a well-rounded nerd who played the lead in our high school's version of Arthur Miller's All My Son's, sang in the school choir and served as VP of our student council.

Tacey A. Rosolowski, PhD

[02:50]

That's—so you obviously had science in your family.

Robert Bast, MD

[02:54]

My grandmother was a nurse, but we didn't have any scientists or physicians. I was particularly fortunate to be able to work with Bob Patnode at the VA Hospital. He really taught me how to plate bacteria and to count them, and was very generous with his time in introducing me to research.

Tacey A. Rosolowski, PhD

[03:20]

So tell me, how old were you at this time? You said you were in junior high?

Robert Bast, MD

[03:23]

I would have been a sophomore in high school.

Tacey A. Rosolowski, PhD

[03:26]

Oh, okay.

Tacey A. Rosolowski, PhD

[03:27]

—so that would have been about, fifteen, sixteen?

Interview Session: 01
Interview Date: July 7, 2014

Robert Bast, MD

[03:29]

Yes. It was amazing to have experience real science at that age.

Robert Bast, MD

[03:32]

Fortunately, I was able to work at the VA for several summers during college, and also worked at the FDA's [Food and Drug Administration] research facility.

Tacey A. Rosolowski, PhD

[03:43]

Wow, that's amazing.

Robert Bast, MD

[03:44]

So, me being in the Washington area was just a tremendous help, and had a lot of good and different experiences.

Tacey A. Rosolowski, PhD

[03:52]

Now, as you look back on that time, you know, what was it about those experiences? What kinds of, like perspectives, or gifts did it start to develop in you at such an early age?

Robert Bast, MD

[04:07]

I guess one thing that was really important was gaining respect for data. You really had to believe what your experiments told you. And also, that the people I worked with - Bob Patnode and then Dorothy Heilman, and Bill MacFarland - were all scientists who really were very respectful of data. I was shocked to learn later in life, when I went to Harvard [Medical School], that many scientists were as, or more interested in the concept, rather than the data.

Tacey A. Rosolowski, PhD

[04:43]

Interesting.

Robert Bast, MD

[04:44]

I think it gave me a respect early on for having to accept the results that your experiments gave you.

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[04:54]

Even if it contraindicated your concept.

Robert Bast, MD

[04:57]

Even if it negated your favorite hypothesis.

Tacey A. Rosolowski, PhD

[05:01]

Right, interesting.

Dr. Robert Bast

[05:03]

Each of these mentors had incredible integrity. I think they exemplified how scientists ought to behave toward each other. They emphasized how you really need to respect not only your own work, but that of other investigators. And they were involved in medical, and to some extent in translational research, although that was far before the days of translational research. That term wasn't coined for a while to come.

Tacey A. Rosolowski, PhD

[05:41]

Right.

Robert Bast, MD

[05:42]

But obviously with something like tuberculosis research, you want to be able fight infection more effectively, using new antibiotics, and the like. But they were also very much interested in the immunity that tuberculosis evoked. And that proved to be useful in later studies of cancer that I performed as a pre-doctoral and postdoctoral fellow.

Tacey A. Rosolowski, PhD

[06:08]

Let me just make a couple notes here.

Robert Bast, MD

[06:14]

Subsequently, I'd gone to college at Wesleyan University, majored in biology and minored in religion, and then had attended Harvard Medical School. After two years, I'd taken out a couple

Interview Session: 01

Interview Date: July 7, 2014

of years to work at Mass General Hospital. They had a program at that time where you could actually spend time studying in depth a research topic, and I was again, fortunate to work both in pathology and immunology research. That was valuable in a lot of different ways. I had worked with Hal Dvorak, who had just come back from serving as a postdoctoral fellow in Bethesda, at the National Institutes of Health. Hal was interested in a phenomenon called “cutaneous basophil hypersensitivity.” Some years later, he had gone on to identify and clone “vascular permeability factor” that turned out to be the same molecule as vascular endothelial growth factor.

Tacey A. Rosolowski, PhD

[07:19]

Oh, interesting.

Robert Bast, MD

[07:20]

So he was one of the co-discoverers of VEGF/VPF, along with Napoleone Ferrara.

Tacey A. Rosolowski, PhD

[07:25]

Wow, so you were brushing shoulders with some people doing really foundational work, yeah.

Robert Bast, MD

[07:30]

Yeah, for sure, and obviously, Harvard sets a pretty high standard for science in general. But the pathology department was particularly good place to spend two year, because I had a chance to do surgical pathology and postmortem exams, and learned enough about reading slides to be dangerous.

Tacey A. Rosolowski, PhD

[07:46]

Mm-hmm, mm-hmm. (chuckles)

Robert Bast, MD

[07:47]

This had provided a background to think about cancer and other conditions in three dimensions, considering cancer not only as isolated cells in a Petri dish, but also in the context of blood vessels, stroma, and immunocytes that make up tumors.

Tacey A. Rosolowski, PhD

[08:10]

I have a number of follow-up questions I want to ask, but the first one I want to jump on is that, a comment you made learning to think about things in three dimensions. Do you meant—mean

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

that very literally in a visual way that you see it?

[08:22]

Dr. Robert Bast

Yes.

Robert Bast, MD

During the same two years I had the time to read through Harrison's Textbook of Internal Medicine. I never would have had the time to do that during regular medical school rotations. In the laboratory, I finished two original papers that were published in the Journal of Experimental Medicine. In the evenings once a week I cared for live patients in the outpatient clinic with John Stoekle a consummate internist. Perhaps most important, I had also met my wife of 43 years, who worked in the same laboratory.

Tacey A. Rosolowski, PhD

[09:00]

Oh, wow.

Tacey A. Rosolowski, PhD

[09:02]

Now tell me about—just want to jump back and find out about that decision to go to Wesleyan. How did you choose your undergraduate institution?

Robert Bast, MD

[09:18]

Well, I wanted to go to a liberal arts college.

Tacey A. Rosolowski, PhD

[09:23]

Why was that?

Robert Bast, MD

[09:25]

I thought it was important not just to learn science, but to understand history, government, economics, and religion as well as literature and the arts. Although in all candor, one of my high school fraternity brothers had gone to Wesleyan a year before and liked it, influencing my choice of Wesleyan over Princeton and Dartmouth. In retrospect, it was a good decision. At the time, I had some doubts about my choice. One of my favorite stories came from Vic Butterfield, then Wesleyan's President, who addressed the freshman class shortly after our arrival. He had said, "Gentlemen (Wesleyan was not yet co-ed), at alumni reunions I often encounter a somewhat inebriated alumnus who tells me 'Vic, my years at Wesleyan were the best years of my life'.

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

Gentlemen, I submit to you that if these are the best years of your life, either you or Wesleyan have failed.”

Tacey A. Rosolowski, PhD

[10:43]

(laughter) That is a good comment! Now, tell me—

Robert Bast, MD

[10:48]

So, at the time, I'm not sure that it was the most enjoyable experience, but it did awaken me to issues of social justice and civil rights and prepare me for five decades of life-long learning. An introductory course in Art History, for example, stimulated a life-long interest in art. Over the years, I have been fortunate to visit many of the buildings and paintings in that course.

Tacey A. Rosolowski, PhD

[11:09]

Oh, interesting. Yeah.

Robert Bast, MD

[11:11]

During my freshman year, I was one of 20 students who participated in a curriculum that included Philosophy, led by an Aristotle Scholar, History led by a Marxist historian and Literature led by a Pulitzer Prize winning poet. For the year, we read books and wrote papers, rather than participating in usual courses. This was a great experience that guided my reading over many years.

Tacey A. Rosolowski, PhD

[11:47]

Do you think it also, I mean, I'm just speculating here, and you tell me if I'm wrong, but, I mean, it sounds like you have an interest in connecting information across fields. And, you know, even from Humanities, from sciences and outside of the sciences. And I'm wondering if that comes with your abilities as a Translational Researcher to work in interdisciplinary ways, you know, kind of in between the cracks, if you will, of the boundaries that divide conventional fields. I'm mean, I'm wondering if that makes any sense to you?

Robert Bast, MD

[12:21]

Yes, perhaps so.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[12:22]

Mm-hmm.

Robert Bast, MD

[12:23]

One example of those kind of connections is found in a short, thin book by Jay [Jacob] Bronowski called *Science and Human Values* that I read early on. Bronowski analyzed Leonardo da Vinci's *Portrait of a Woman with an Ermine*, suggesting that the expression on the ermine's face was very similar to the expression on the woman's face, and that a great deal of scientific thinking depends upon recognizing such similes. I'm not quite sure how that applies to all translational pursuits, but it does make a connection across the arts and sciences.

Tacey A. Rosolowski, PhD

[13:07]

But it made sense to you.

Robert Bast, MD

[13:08]

It does make sense, in terms of how scientific research is conducted.

Tacey A. Rosolowski, PhD

[13:14]

Interesting. Interesting. I wanted to ask you about your religion minor. How did you select—I mean, it sounds like you were really interested in art. Why wasn't art your minor? (laughter)
Why religion?

Robert Bast, MD

[13:26]

We had some great religion professors at Wesleyan. I was particularly interested in the history of religion and how theology interacted with historical influences from outside the Church, particularly the Renaissance and Reformation, a particularly interesting area.

Tacey A. Rosolowski, PhD

[13:58]

I wanted to, again, just touch on that 3D comment you made, because I'm always surprised at how the medical fields really do select for visual thinkers, and how, in subtle ways, that influences or enables what they do. So, I'm curious. I mean, do you see, when you're thinking out these very complex dynamic systems, do you see them in three dimensions in your own mind? Does that help you figure them out?

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

Robert Bast, MD

[15:08]

Yeah, I think cartoons are very helpful. Also estimating orders of magnitude are very helpful too. Not all people think about how many nanometers are involved in the spatial arrangement of a particular molecule. I also find cartoons helpful in dissecting mechanisms.

Tacey A. Rosolowski, PhD

[15:29]

Interesting. Do you see them in color? Or, is it black and white?

Robert Bast, MD

[15:32]

Color.

Tacey A. Rosolowski, PhD

[15:33]

Color? Cool! Yeah. Jordan Gutterman doesn't. (laughter) Which is funny, because he's really a colorist in his painting.

Robert Bast, MD

[15:42]

Yeah, absolutely.

Interview Session: 01
Interview Date: July 7, 2014

Chapter 02
A: Professional Path
Integrating Research and Clinical Practice

Story Codes

A: The Researcher;
A: The Clinician;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
A: Influences from People and Life Experiences;
C: Patients;
C: Discovery and Success;
A: Definitions, Explanations, Translations;

Tacey A. Rosolowski, PhD

[15:46]

Well, tell me about the next step, after Wesleyan.

Robert Bast, MD

[15:51]

After Wesleyan, I had gone to Harvard Medical School which I thoroughly enjoyed. After completing the first two pre-clinical years, I had the opportunity to spend two years in the Pathology Department at MGH [Massachusetts General Hospital] before completing medical school. Ben [Benjamin] Castleman [MD] was the head of Pathology at that time, and he was one of the truly great pathologists. Training in pathology helped me to not only think in three dimensions, but also to understand that anatomy and pathophysiology of disease. Very often, if you're trained only as an internist, and you don't necessarily visualize the organs and tissues that are affected by disease.

Tacey A. Rosolowski, PhD

[16:22]

Right.

Robert Bast, MD

[16:24]

And then, I returned to finish up my clinical years at Harvard.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

[16:31]

So, how did that work? You were in med school for how long? And then took time—

Robert Bast, MD

[16:35]

Well, it was two years, and then two years and two years. So—

Tacey A. Rosolowski, PhD

[16:37]

Okay.

Robert Bast, MD

[16:39]

—I finished medical school in six years.

Tacey A. Rosolowski, PhD

[16:40]

I see. So that two years out, it wasn't an official part of your program? You chose to stop for a time?

Robert Bast, MD

[16:48]

Well, no, it was an official part of the program. I wrote an honors thesis—

Tacey A. Rosolowski, PhD

[16:53]

Oh, I see. Okay. Interesting.

Robert Bast, MD

[16:55]

—out of that. So, I was still technically in medical school.

Tacey A. Rosolowski, PhD

[16:59]

Right. So, you were basically—I mean, just tell me, I'm interpreting that this was basically your way of making the medical—putting a research stamp on medical school? Was that really what it was, or—

Robert Bast, MD

[17:09]

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

The two years were great preparation for practicing medicine and for research. I always both really enjoyed clinical medicine and really enjoyed research.

Tacey A. Rosolowski, PhD

[17:16]

Mm-hmm?

Robert Bast, MD

[17:18]

And I think that this was a way to actually get in greater depth, and to provide preparation in research, between the two years I had spent at MGH working with Hal Dvorak and the three years that I subsequently spent at NIH. I had about five years of lab research experience.

Tacey A. Rosolowski, PhD

[17:35]

Oh.

Robert Bast, MD

[17:37]

I know there's no exact formula for this, but whether you earn a formal PhD or work in the laboratory as an MD, you need to gain enough research experience to actually become funded and prepare for a career in research, it generally takes about five extra years of research activity.

Tacey A. Rosolowski, PhD

[17:57]

Mm-hmm?

Robert Bast, MD

[17:59]

After graduating from Harvard Medical School, I had then survived an internship, at Johns Hopkins [University].

Tacey A. Rosolowski, PhD

[18:03]

Yeah, I noticed this—

Robert Bast, MD

[18:05]

Those were the days when you spent two nights on and one night off.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[18:08]

Oh, so that's the survival part. That's brutal!

Robert Bast, MD

[18:06]

That's the survival part.

Tacey A. Rosolowski, PhD

[18:09]

Oh, wow.

Robert Bast, MD

[18:11]

Johns Hopkins was, again, in retrospect, a great experience, but there must be an even better way to become a physician! One of the positives about two nights on and one night off is that you spend long hours with patients, and you really watch from minute to minute how a disease can rapidly progress. Not only do you learn to integrate all of the details of care for each patient, but also, you get a sixth sense for when somebody's really sick. That sort of sixth sense has served well for decades after internship.

Tacey A. Rosolowski, PhD

[18:50]

Mm-hmm.

Robert Bast, MD

[18:52]

Having cared for patients at Harvard with Dana Farber [Cancer Institute], the Brigham and Women's, Johns Hopkins, Duke [University] and here, one of the common denominators of all four places, although there certainly are differences as well, is that there's a fierce dedication to exceptional patient care. Certainly at Johns Hopkins, it was almost fanatic.

Tacey A. Rosolowski, PhD

[19:13]

Really?

Robert Bast, MD

[19:15]

Which I think is a very good kind of fanaticism.

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[19:16]

Hmm. Now, obviously you were doing some—it sounded like you were working with oncology patients. And when did the oncology piece enter your professional life?

Robert Bast, MD

[19:30]

Well, it's tough to say, although my mother had developed breast cancer when I was ten or eleven, and fortunately was cured by surgery. I had also worked with Bill MacFarlane, a hematologist-oncologist at the VA [Veterans Administration] Hospital, during college. Most of his patients had leukemia, rather than solid cancers. So my first interaction with cancer patients would have been during summer jobs in the early 1960's.

Tacey A. Rosolowski, PhD

[20:16]

Very early.

Robert Bast, MD

[20:16]

—with leukemia patients early on.

Tacey A. Rosolowski, PhD

[20:18]

Wow.

Robert Bast, MD

[20:19]

Being interested in immunology initially, I was very much interested in the possibility of using immunotherapy to control cancers more effectively.

Tacey A. Rosolowski, PhD

[20:33]

When did that idea start to occur to you, do you think?

Robert Bast, MD

[20:36]

That would have been, again, in high school and college.

Tacey A. Rosolowski, PhD

[20:40]

Really, in early, early times. Wow, that's amazing. So, you were very focused. I mean, it just

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

worked that you retract pretty—

Robert Bast, MD

[20:48]

Yeah, it's, you know, it's very fortunate I'm very focused.

Tacey A. Rosolowski, PhD

[20:52]

Yeah. (laughter)

Robert Bast, MD

[20:52]

You know, those are opportunities that wouldn't be available if you were living in a different part of the country.

Tacey A. Rosolowski, PhD

[20:57]

Absolutely. And it sounded like you—

Robert Bast, MD

[20:58]

Or in a rural area.

Tacey A. Rosolowski, PhD

[21:00]

And you were just put in the way of really key people who helped you consolidate this path.

Robert Bast, MD

[21:04]

Yes, exceptional mentors who really were dedicated to helping younger people, too, which is, again, really special.

Tacey A. Rosolowski, PhD

[21:12]

Yeah.

Robert Bast, MD

[21:13]

I mean, that's something I've tried to do in return over the years.

Interview Session: 01

Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[21:18]

Right. That pipeline, as people call it.

Robert Bast, MD

[21:18]

Yes.

Tacey A. Rosolowski, PhD

[21:20]

Yeah. Is there anything else you want to say about your formal medical training, the residency on out?

Robert Bast, MD

[21:29]

After internship, I spent three years at the National Cancer Institute (NCI) working with Herb Rapp [PhD] and Bert Zbar [MD] who were interested in guinea pig models for immunotherapy. Here's where my early experience with mycobacteria at the VAH proved particularly valuable. Herb and Bert were using a tuberculosis vaccine, an attenuated strain of bovine tuberculosis, called Bacillus Calmette-Guerin [BCG]. They injected BCG directly into the transplants of liver cancers growing on the flanks of guinea pigs. Not only the transplanted cancer regressed when exposed to the intense inflammatory granulomatous response to the BCG, but also lymph node metastases regressed. Following BCG-induced tumor regression, animals were resistant to subsequent re-challenge with transplants of the same cancer, but not to other cancers, so they were specifically immune to their cancer. After I joined their group, we tried to use other bugs like *Listeria monocytogenes* with similar results in mice. At that time, there was a lot of clinical research going on with BCG worldwide injecting living BCG vaccine directly into metastases from cutaneous cancers like melanoma. Some investigators scratched BCG into the skin, to see if that would control cancer body-wide.

Tacey A. Rosolowski, PhD

[23:10]

Mm-hmm?

Interview Session: 01
Interview Date: July 7, 2014

Chapter 03

A: The Researcher

A Review of MD Anderson Research in the Early Seventies and a Discussion of Clinical Trials

Story Codes

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

D: The History of Health Care, Patient Care;

C: On Research and Researchers;

A: The Researcher;

A: Overview;

A: Definitions, Explanations, Translations;

Robert Bast, MD

[23:11]

During my years at NCI, I got a chance to write a review for the New England Journal [of Medicine] on “BCG and cancer”. About half of the article talked about the poor quality of the trials in those days at MD Anderson—I think it was my karma to spend a couple of decades here.

Tacey A. Rosolowski, PhD

[23:33]

(laughter)

Robert Bast, MD

[23:33]

And clearly over the years, MD Anderson’s become a whole lot more critical in its clinical trials.

Tacey A. Rosolowski, PhD

[23:38]

Now, tell me about that, I mean, because, you know, around what year was this?

Robert Bast, MD

[23:46]

This would have been between ’72 and ’75.

Tacey A. Rosolowski, PhD

[23:55]

Interview Session: 01

Interview Date: July 7, 2014

So, what was it that you saw at that time? You know, because obviously, I've been interviewing people who are talking about research at that time. And there's, you know, people talk about controversies over clinical trials, and how do you set up—how do you design research, and all that. So, what were you seeing as a reviewer, an outside reviewer, of what was happening at the research, here?

Robert Bast, MD

[24:16]

In the 1970's, it was becoming apparent that you really did need to do randomized phase III clinical trials, at least to resolve some questions regarding the efficacy of treatment. There are great cycles of belief in this area. It was clear that you could really delude yourself with single-arm trials, comparing their outcomes to historical controls. Obviously, if you're treating bacterial pneumonia with penicillin for the first time, you may or may not need historical controls. But the results of BCG and cancer were much more subtle.

Tacey A. Rosolowski, PhD

[24:49]

Mm-hmm.

Robert Bast, MD

[24:50]

By and large, the original trials at Anderson at that time were often single-armed, and their results not sufficiently dramatic to base future treatment on those anecdotes. As an aside, now with some of the targeted therapies, we are coming back to a point where single-arm phase II trials make a lot more sense than they used to for understanding which patients are most likely to respond.

Tacey A. Rosolowski, PhD

[25:19]

Really?

Robert Bast, MD

[25:21]

If you have to do a randomized study, you've got to be sure to include patients who are most likely to respond to the targeted therapy.

Tacey A. Rosolowski, PhD

[25:38]

So, just so I understand, I mean, there's maybe a subtlety here I'm missing. You know, what, exactly, is it about targeted therapy that suits that approach to a single-arm trial?

Interview Session: 01

Interview Date: July 7, 2014

Robert Bast, MD

[25:51]

In concurrently controlled, randomized clinical trials, you try to make both the experimental and the control group exactly equal, or as nearly equal as possible for all parameters that could influence prognosis. So, you try to treat the average patient. In the case of targeted therapy, you're attempting to identify those individuals who are uniquely suited to respond to a particular drug, and you're trying to match targeted therapies to the molecular abnormalities of the particular patient's cancer.

Tacey A. Rosolowski, PhD

[26:24]

Interesting.

Robert Bast, MD

[26:24]

Under those circumstances, if you can find enough patients who have exactly the same abnormalities in their cancers, then you might think about randomizing as a final step in the approval of a targeted drug use in the community. Outcomes for some of the targeted therapies, however, can be dramatic. With EGFR [Epidermal Growth Factor Receptor] inhibitors in metastatic lung cancer, survival beyond two years is being observed frequently, while two year survivors were uncommon with conventional chemotherapy. With Gleevec and other Abl inhibitors, patients with chronic myelogenous leukemia (CML) are likely to be cured.

Tacey A. Rosolowski, PhD

[27:06]

Interesting. Now, does that shift, or does that nature of targeted therapy and the type of research that's suited to it, does that make it easier to fund, easier to generate support for it? You know, what's the larger impact?

Robert Bast, MD

[27:24]

In terms of the—

Tacey A. Rosolowski, PhD

[27:24]

Or, cheaper to run, I should say, might be the first based question.

Robert Bast, MD

[27:31]

Well, there certainly are adaptive trials with Bayesian design that are more efficient, and where

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

you're predicting your expected outcome and adjusting your parameters as you go to figure out whether the trend is or isn't affected.

Tacey A. Rosolowski, PhD

[27:58]

Well, I—from my own reading, and granted, you know, limited understanding of this issue of research design, it sounds like randomized clinical trials, they're large, they're multi-institution, often to be really, really credible. And they're consequently extremely expensive to run.

Robert Bast, MD

[28:16]

Yes.

Tacey A. Rosolowski, PhD

[28:17]

And so, I'm wondering if targeted therapy, given that it doesn't require randomized trials, has certain advantages in terms of, you know, economics of research, basically.

Robert Bast, MD

[28:29]

Yes. Some randomized clinical trials will still be required, but we must choose them wisely. Single arm trials used strategically will help us to plan Phase III trials more strategically with a higher probability of success and that would impact on their cost-effectiveness.

Tacey A. Rosolowski, PhD

[28:35]

I see. I see.

Robert Bast, MD

[28:38]

For Food and Drug Administration approval of most targeted drugs, you really do still need a randomized study. Ideally, you want a randomized study that just includes the people who are most likely to respond.

Tacey A. Rosolowski, PhD

[28:55]

And that sounds like it would be a challenge, given the specificity of the patients that are being treated.

Robert Bast, MD

[29:02]

Interview Session: 01
Interview Date: July 7, 2014

And it would certainly require collaboration between multiple institutions for Phase II studies, even with a population of patients as large as MD Anderson's, where we see 30,000 new patients a year.

Tacey A. Rosolowski, PhD

[29:13]

Wow.

Robert Bast, MD

[29:14]

Patients with almost every molecular abnormality, as well as every kind of cancer, walk through our doors every day. That's one of the tremendous advantages of an institution like our own, where at least for Phase I and Phase II studies, we can complete trials in a timely manner just with our own patient population.

Tacey A. Rosolowski, PhD

[29:37]

Well, thanks. I'm sure we'll talk a lot more about this, because obviously your office is intimately involved in—

Robert Bast, MD

[29:54]

Yeah, absolutely.

Tacey A. Rosolowski, PhD

[29:54]

—defining exactly these questions. (laughing)

Interview Session: 01

Interview Date: July 7, 2014

Chapter 04

A: The Researcher

Studies of C. Parvum and a Screening Test for Ovarian Cancer

Story Codes

A: The Researcher;

C: Discovery and Success;

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

D: The History of Health Care, Patient Care;

C: On Research and Researchers;

A: Overview;

A: Definitions, Explanations, Translations;

C: Discovery and Success;

B: MD Anderson Impact;

Robert Bast, MD

[29:58]

Picking up the narrative, though, after finishing three years at the National Cancer Institute, I headed back to Boston and was a resident at the then Peter Bent Brigham (now the Brigham and Women's Hospital), working with Marshall Wolf, the head of their house staff training program, who, I think, in retrospect, was a great influence. He is a remarkable clinician; probably one of the best clinicians I've ever met. But he also was an incredible mentor and a wise leader. While he believed in tough love, he was incredibly supportive of young physicians who wanted to take different and diverse career paths. Two years ago, he actually had about 1,000 of his former trainees come back for a celebration. He's still going strong as an internist in the Boston area, and he's retired from heading up the house staff. But he has had individuals who ended up going into international medicine, one graduate headed the FDA, others excelled as leaders in academic medicine and in more traditional research. As an aside, Marshall made heading a house staff training program a respected position. In the mid 1970's, heading the house staff for a few years was considered a "stepping stone" to becoming a chair of medicine or a deans. Marshall was one of the first people at a major training program who made this role a "destination", rather than a stepping stone. And so, he really impacted the lives of a very large number of very able young doctors.

Tacey A. Rosolowski, PhD

[32:06]

Interview Session: 01
Interview Date: July 7, 2014

Wow.

Robert Bast, MD

[32:08]

Yeah.

Tacey A. Rosolowski, PhD

[32:08]

That's pretty—

Robert Bast, MD

[32:09]

I spent a year at the Brigham and then spent a year at the Dana Farber Cancer Institute as a fellow. In those days, there was short-tracking, where you could finish an internal medicine residency and sub-specialty training in less time. As I had had about five years away from traditional clinical training in the laboratory, that made a huge amount of sense at the time. In 1977, I became an Assistant Professor at the Dana Farber Cancer Center. And at that time, I was looking for ways that you could apply what I had learned from Herb Rapp and Bert Zbar with their intratumoral injection of immunostimulants to a different kind of cancer where we could treat visceral metastases, and not just cutaneous lesions.

So, one of the things that occurred to me was that ovarian cancer ought to be that kind of disease, because you can imagine putting immune—bacterial immunostimulants in the abdominal cavity, where much of the spread of ovarian cancer is on the surface of the bowel, or the internal surface of the abdominal wall, and where you might have the bugs actually direct contact the cancer. And fortunately, Bob Knapp [MD] and Ross Berkowitz [MD] were working with a mouse model for ovarian cancer, where they could inject cells in the peritoneal cavity where the tumor would block the lymphatics and diaphragm in the mice producing ascites. Rather than living BCG, they had injected heat-killed *Corynebacterium parvum* (now called Propionibacter) into the abdominal cavities of mice with intraperitoneal transplants of a mouse ovarian cancer.

C. parvum had only a modest effect on cancer growth, but if you added a rabbit antibody made against antigens on the surface of the mouse ovarian cancer cells, you could have dramatically greater antitumor activity. As I was joining the faculty at Dana Farber, Bob Knapp and I joined forces, and we had labs right next to each other, and we shared technicians. In my first project, I explored the mechanism underlying the dramatic interaction between the antibody and *C. parvum*. And it turned out that the intraperitoneal *C. parvum* attracted macrophages and other white blood cells into the abdominal cavities of the mice and activated them for cancer cell killing. These activated leukocytes could then kill the antibody coated tumor cells through the mechanism of antibody dependent cellular cytotoxicity (ADCC).

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[34:54]

I think I'm missing the name of that other compound, C. parvum?

Robert Bast, MD

[34:57]

Yes, Corynebacterium parvum, C-O-R-Y-N-E-B-A-C-T-E-R-I-U-M.

Tacey A. Rosolowski, PhD

[35:04]

You spelled that really fast. Too fast for me. Okay, once more, please?

Robert Bast, MD

[35:06]

C-O-R-Y-N-E-B-A-C-T-E-R-I-U-M, bacterium parvum.

Tacey A. Rosolowski, PhD

[35:16]

Got it. Thank you very much.

Robert Bast, MD

[35:19]

In the days before the term Translational Research had been coined, we decided to translate this approach directly to the clinic. Burroughs-Wellcome Pharmaceuticals was evaluating C. parvum in clinical trials at that time. We performed the first trial testing intraperitoneal injection of C. parvum into patients with small volumes of residual tumor on the peritoneal surface that had failed initial conventional chemotherapy. This created substantial inflammation and abdominal pain, but 5 of 11 patients (45%) had objective responses. Two patients had complete responses that lasted for a year.

Tacey A. Rosolowski, PhD

[36:05]

Wow.

Robert Bast, MD

[36:06]

So, it looked like it was a good start. But if we were going to exactly mimic the mouse model, we needed an antibody against human ovarian cancer. And making rabbit antibodies against human tumor cells was more of a challenge. Two or three years earlier, [Georges J. F.] Kohler

Interview Session: 01

Interview Date: July 7, 2014

and [Cesar] Milstein had developed the monoclonal antibody technology. We were the first to apply that technology to developing antibodies against ovarian cancer. We immunized mice with human ovarian cancer cell lines and fused their spleen cells with mouse myeloma cells producing immortal “hybridoma” clones that would continue to produce unlimited quantities of a single antibody that reacted against ovarian cancer cells. The 125th promising hybridoma that we developed against ovarian cancer (OC) was designated OC125 and this antibody recognized an ovarian cancer associated cancer antigen (CA) designated CA125.

Tacey A. Rosolowski, PhD

[37:00]

Okay.

Robert Bast, MD

[36:59]

And we had started to—

Tacey A. Rosolowski, PhD

[37:04]

And that was in 1983?

Robert Bast, MD

[37:05]

No, actually, this was more like 1978 or '79.

Tacey A. Rosolowski, PhD

[37:08]

Oh, okay. Mm-hmm.

Robert Bast, MD

[37:09]

It took a little while to develop a blood test for that.

Tacey A. Rosolowski, PhD

[37:11]

Got you. Okay.

Robert Bast, MD

[37:13]

We developed OC125 in '78 or '79, and then we published that in the Journal of Clinical Investigation in 1981. And then, found that the CA125 antigen recognized by OC125 was shed

Interview Session: 01

Interview Date: July 7, 2014

from the surface of ovarian cancer cells. And that CA125 might not be an optimal target for therapy, because the antibody might complex with the antigen in the blood stream or abdominal cavity, the immune complexes might be cleared in the liver and spleen and insufficient amounts of antibody might reach cancer cells. Bob and I attempted to make lemonade out of lemons. If OC125 detects shed antigen, maybe we could use it for a blood test. Vince Zurowski had been working with monoclonal antibodies at a small start-up called Centocor in an incubator facility in the University of Pennsylvania. Vince had collaborated with Jack Wands at the Mass General Hospital to develop a serum hepatitis test. Using their newly gained knowledge with monoclonal immunoassays, Vince and Tom Klug helped us develop an assay for CA-125.

Fortunately, we had a bank of serum that had been collected by other investigators at the Dana Farber. Using these samples, we were able to test, retrospectively, a number of patients with ovarian cancer. CA-125 was elevated in more than ninety percent of patients with ovarian cancer, and could be elevated in other kinds of cancers, but not as frequently. Levels of CA125 tended to track the course of the disease. Before that time, there really wasn't a blood test for it that would track the course of ovarian cancer. And so results with our new assay were published in the New England Journal in 1983, and as it turned out, we expected that within a short period of time that an even better blood test would be developed, but now, thirty-some years later, it still is not—we still haven't found one that's better.

Tacey A. Rosolowski, PhD

[39:32]

Really? Wow. So, that's really been a durable discovery.

Robert Bast, MD

[39:37]

Yes, it's been used worldwide for monitoring hundreds of thousands of patients with known ovarian cancer. But we've been trying to use CA125 to develop a test for early detection.

Tacey A. Rosolowski, PhD

[39:58]

Certainly. I'll just pause the recorder.

[The recorder is paused.]

Tacey A. Rosolowski, PhD

[00:00:00]

Return us to record, here.

Robert Bast, MD

[00:00:04]

Yes.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Interview Session: 01
Interview Date: July 7, 2014

Chapter 05
A: The Researcher
Developing Tools to Monitor and Screen for Ovarian Cancer

Story Codes

A: The Researcher;
C: Discovery and Success;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
C: On Research and Researchers;
A: Overview;
A: Definitions, Explanations, Translations;
C: Discovery and Success;
B: MD Anderson Impact;

Tacey A. Rosolowski, PhD

[00:00:03]

Okay, I just had the recorder off briefly, as Dr. Bast took a phone call. But we are back recording at twenty minutes after ten. So, what's the next part of—we're into your research story, here, which is exciting. So—(laughter)

Robert Bast, MD

[00:00:22]

Soon after the CA125 assay was developed, we had the opportunity to test serum from a patient, who had a completely different illness, acquired hypo-gammaglobulinemia.

Tacey A. Rosolowski, PhD

[00:00:37]

Could you repeat that one, please?

Robert Bast, MD

[00:00:37]

Yeah. Acquired, A-C-Q-U-I-R-E-D, hypo, H-Y-P-O, gamma, G-A-M-M-A, globulin, G-L-O-B-U-L-I-N, emia, E-M-I-A.

Tacey A. Rosolowski, PhD

[00:00:51]

Emia, oh, globulinemia. Okay. Got you.

Interview Session: 01

Interview Date: July 7, 2014

Robert Bast, MD

[00:00:56]

Yes, a disease that was treated with immunoglobulin injections, so that her physicians had been saving her serum to measure immunoglobulin levels. While being treated, the patients had developed ovarian cancer. So, it was possible to go back and determine whether her levels of CA125 had been elevated prior to the time that the cancer was diagnosed clinically.

Tacey A. Rosolowski, PhD

[00:01:22]

Mm-hmm?

Robert Bast, MD

[00:01:24]

And when we broke the code, we found that the CA125 started to go up linearly on a log scale for about ten to twelve months prior to the development of the clinical disease. After cytoreductive surgery, CA125 went down, and when she had chemotherapy, it went down even further. But it really looked like that there was lead time. So, working with Steve Skates [PhD] and Nina Einhorn [MD] in Stockholm, and ultimately then with Ian Jacobs [MD] in London, it's been possible to see whether CA125 would be useful for early detection of ovarian cancer. Steve had developed an algorithm that would plot the course of CA125 over time, and to see whether any rise was something you'd worry about a lot or worry about a little, and where you could set each patient's individual baseline. With that "ROCA" algorithm it was possible to identify patients with ovarian cancer even within the normal range of CA125. If CA125 levels went up, an ultrasound was performed. If the ultrasound was abnormal, surgery was performed. So, there have been several studies of that over the years in Stockholm and in London, and for the last thirteen or fourteen years, there have been two studies going in parallel, a very large study in the UK of 200,000 women—

Tacey A. Rosolowski, PhD

[00:03:10]

Wow.

Robert Bast, MD

[00:03:11]

—which the results should be back late this year or early next. And that's large enough to determine whether there's really a survival or mortality advantage to screening, which will be very important. With Karen Lu here at MD Anderson, we've been working with a much smaller study including 5,000 women, here in Houston, and in Dallas, Des Moines, Iowa, Providence, Rhode Island and Morristown, New Jersey. With this smaller group, we can still determine the specificity of the screening strategy and how many operations will be required to detect each

Interview Session: 01

Interview Date: July 7, 2014

case of ovarian cancer. One of the challenges with ovarian cancer is that it is neither common, nor rare. The prevalence in women who are over fifty and are at greatest risk of developing ovarian cancer is about one in 2,500. So, you've got to have high sensitivity to detect the early stage of disease, but you've got to have very high specificity, like, 99.7 percent, just to have ten operations for each case of ovarian cancer detected. Both in the UK study and in the NROSS study that we've coordinated here at Anderson, we only did three to four operations for each case of ovarian cancer detected.

Tacey A. Rosolowski, PhD

[00:04:39]

Really?

Robert Bast, MD

[00:04:38]

So, the specificity of putting together the algorithm with ultrasound is quite high, and it would be practical. So, if the UK study actually shows that there is a survival advantage, or better yet, a mortality reduction, we've shown that that's practical here in the United States, and get exactly the same answer in terms of specificity. A lot of our research has been dedicated to trying to improve on CA125, and we found three other blood tests, or at least two other blood tests for sure, that give you a slight improvement over CA125. But it would need a much more sensitive early detection system, so we're focusing a lot of our efforts these days on autoantibodies that can develop—a patient can develop antibodies against her own ovarian cancer. Antibodies against the p53 protein show up a year or more before detection of the disease. This only detects 20-25% of patients, so we need additional autoantibodies. We currently have been looking for autoantibodies against ovarian cancer with a chip that has 17,000 human proteins produced by Origene, and—

Tacey A. Rosolowski, PhD

[00:05:55]

Produced by?

Robert Bast, MD

[00:05:56]

It's a company Origene, O-R-I-G-E-N-E. And what's special about the chip is that these are human proteins expressed in human cells, so you get the right folding and the right glycosylation, and that consequently, the right epitopes for autoantibodies. And with that, we got more than a couple hundred candidates that would show up a year before the detection of disease by CA-125, so we're currently trying to improve on that. The other thing that's encouraging these days in terms of early detection is that I've been working with a company, a small startup company in New Mexico that has a SQUID detector. This is a superconductive quantum

Interview Session: 01

Interview Date: July 7, 2014

interference detection. And that's a very sensitive way to measure magnetic fields. It's so sensitive, you can actually measure the magnetic fields around synapses in the brain.

Tacey A. Rosolowski, PhD

[00:06:57]

Wow.

Robert Bast, MD

[00:06:58]

But if you have magnetic ferritin nanoparticles attached to antibodies that react specifically with ovarian cancers, you can detect perhaps as few as 105 ovarian cancer cells.

Tacey A. Rosolowski, PhD

[00:07:18]

So, how does it work? Do you have to attach a nanoparticle to the cancer, and then you see—

Robert Bast, MD

[00:07:25]

No, this would be attaching the nanoparticle to the antibody, then injecting the antibody either intravenous or intraperitoneally, having the antibodies stick to the cancer cells. And as long as the antibody's in the circulation, you don't get any signal. And as soon as it lines up on the surface of the cancer cell, you reinforce the effect. And so, you get a delay in relaxation of a magnetic pulse measured by Superconducting Quantum Interference Detection (SQUID). With John Hazle here at Anderson, we have a SQUID machine on south campus, and we're trying to see if that fact is going to be as good as it's supposed to be, in terms of detecting that in the cells. The current screening trials in the UK and at MD Anderson use rising CA-125, followed by ultrasound. A significant limitation of this approach is that ultrasound is not optimally sensitive, and as many as one third of ovarian cancers are now thought to arise, in the fallopian tube.

Robert Bast, MD

[00:08:39]

The ultrasound really doesn't detect those fallopian tube cancers. And it also is not able to see cancers much smaller than a millimeter or two. And with this SQUID technique, presentably, and it should be possible to see much smaller deposits of cancer either in the ovary or in the fallopian tube. But we need to find out if that, in fact, is the case. So, we're trying to improve the first stage of early detection with other blood tests, or for other antigens, and also trying to improve the second step of that with something that's much more sensitive than ultrasound, is the SQUID technology.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

[00:09:24]

So, is this SQUID machine, is it like an MRI? The whole body goes into it? Or—

Robert Bast, MD

[00:09:30]

Well, currently, it's on a much less grand scale. It's basically a detector with liquid helium that is over a platform. And currently it's about mouse size for the prototype.

Tacey A. Rosolowski, PhD

[00:09:49]

Oh, because it's on mice right now?

Robert Bast, MD

[00:09:50]

This is on mice.

Tacey A. Rosolowski, PhD

[00:09:52]

Okay. I was getting overly excited and thinking we were at clinical trials.

Robert Bast, MD

[00:09:54]

Well, there's no reason why you couldn't scale this up. And the nice thing is, it's not exactly the imaging, it's a detector. So, you could actually take this, even the machine we have now and focus—and if you had a patient with rising CA-125 or rising antibodies, and you couldn't see anything on ultrasound or CT or MRI, you could imagine injecting the antibody with antibody-coated ferritin nanospheres, coming back several hours later, and just putting the probes over one or the other ovary, and to see if you've, in fact, got a delay in the relaxation of magnetic pulse.

Robert Bast, MD

[00:10:33]

So, you wouldn't really have to see a shape of an ovary, just to know whether the nanoparticles are localized there.

Robert Bast, MD

[00:10:37]

And so, that, we're currently evaluating that, as well. So, when we're doing this, we've been doing this with the support of the NCI Specialized Program of Research Excellence (SPORE), but we're also incorporating this in the moon shot. So, this is one of the areas where the moon shot's been a tremendous element.

Interview Session: 01

Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[00:11:02]

Maybe you mentioned this, but I kind of missed it in all the detail that was coming at me. What are the nanoparticles made of? And what is their special sensitive—how do they—why is it that particle, kind of particle, that's being used to detect?

Robert Bast, MD

[00:11:19]

Well, basically it's iron containing particles that are coated with polyethylene glycol and antibodies. The iron can be magnetized. The SQUID measures quite precisely the time for relaxation of the magnetic particles to occur back to baseline.

Tacey A. Rosolowski, PhD

[00:11:46]

Okay. Wow. Really, really interesting. So, I mean, given that this is part of the Moon Shot, that means that there is a hope that there would be a fairly short timeframe to get results from this. So, how do you see it transpiring? What are you looking for in terms of results?

Robert Bast, MD

[00:12:11]

Well, certainly in terms of the, if the autoantibodies were affected, you would require probably in the next year, or at the most, two, to try to identify the optimal panel of autoantibodies, and to verify those with other databases.

Tacey A. Rosolowski, PhD

[00:12:29]

And are you—

Robert Bast, MD

[00:12:30]

And other serum banks.

Tacey A. Rosolowski, PhD

[00:12:31]

And I'm just saying, are you—now, I just want to make sure I understand where the antibodies are coming in, because I may have missed that detail. So, is this—so, please explain that.

Robert Bast, MD

[00:12:46]

The antibodies, of course, are present in serum, so that in addition to protein antigens being shed

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

into serum, you can also find antibodies in serum. But it looks now as if those might be increased a whole year, before the CA-125 starts to elevate. We need to confirm that for sure. But if that, in fact, pans out with multiple serum samples from multiple serum bags, you can image incorporating that in an algorithm that can then be used in the same population where we've been using CA-125, and the same 4,000 women, we could put that in to be sure that we're not going to see too many false positives, so people are getting ultrasounds, or even worse, getting surgery that they didn't need.

Tacey A. Rosolowski, PhD

[00:13:31]

So, you kind of get a triple or quadruple process, where you're looking for the proper antigen, the one that emerges as being, you know, very sensitive, and then C-25, unless that's made obsolete by the antigen. Then—

Robert Bast, MD

[00:13:46]

Yes, and probably, realistically, it's going to be pick up the cases that CA-125 misses.

Tacey A. Rosolowski, PhD

[00:13:50]

And then the next phase would be either ultrasound, and/or SQUID detection.

Robert Bast, MD

[00:14:10]

Yes, exactly.

Tacey A. Rosolowski, PhD

[00:14:11]

So, you've got kind of like four tools.

Robert Bast, MD

[00:14:13]

And this SQUID probably is a three to five year project—

Tacey A. Rosolowski, PhD

[00:14:14]

Okay.

Robert Bast, MD

[00:14:16]

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

If it continues to be promising, we'll know within the year whether this is as good as it promises to be, at least in terms of imaging, or in terms of detecting ovarian cancers in mice.

Tacey A. Rosolowski, PhD

[00:14:28]

Interesting. Okay. So that's, like, I mean, pretty amazing from when you first started working with ovarian cancer, where there was just nothing, to suddenly all of these tools.

Robert Bast, MD

[00:14:37]

CA125 has also been used to detect disease recurrence. It has also been used as part of tests to identify women with pelvic masses, who need to be referred to a gynecologic oncologist for specialized surgery. And so, it's been used in several different ways.

Tacey A. Rosolowski, PhD

[00:15:11]

Interesting. Wow.

Interview Session: 01
Interview Date: July 7, 2014

Chapter 06

A: The Researcher

Increasing Patients' Sensitivity to Taxol; Understanding the Function of ARHI (DISRAS3) and Autophagy

Story Codes

A: The Researcher;

C: Discovery and Success;

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

D: The History of Health Care, Patient Care;

C: On Research and Researchers;

A: Overview;

A: Definitions, Explanations, Translations;

C: Discovery and Success;

B: MD Anderson Impact

Robert Bast, MD

[00:15:13]

In addition to early detection, for many years our laboratory pursued the idea of labeling or conjugating antibodies with the toxic A chain of ricin, a poison from castor beans, to try to deliver ricin A chain just to ovarian cancers and not to normal tissues. Radionuclide conjugates can also be delivered to ovarian cancer cells for very local radiotherapy. We were able to show that there was additive anti-tumor activity when ricin A chain conjugates and radionuclide conjugates were administered together.

Tacey A. Rosolowski, PhD

[00:15:53]

Now, just so I'm understanding, this is the RAS? Am I hearing you properly? Because these are technical terms I may not have actually heard before. I mean, I may have read them. Is this what you're—

Robert Bast, MD

[00:16:03]

Not really Ras. Antibodies were directed against cell surface proteins on breast and ovarian cancer cells.

Tacey A. Rosolowski, PhD

[00:16:18]

Oh, interesting.

Interview Session: 01

Interview Date: July 7, 2014

Robert Bast, MD

[00:16:19]

Over the last 10-15 years, we've focused our research in two additional areas: making paclitaxel (Taxol) chemotherapy more effective by modulating the sensitivity of ovarian cancer cells to the drug; and studies of ARHI (DIRAS3) an imprinted tumor suppressor that modulates cell growth, motility, autophagy and tumor dormancy.

In the first area, we have studied more than a dozen kinases that regulate primary resistance to paclitaxel that is present before treatment with the drug. Knocking down each of these kinases has increased the drug's effect on ovarian cancer cells. The most interesting has been SIK2. Ahmed Ahmed [MD, PhD], a postdoctoral fellow in our laboratory, had found that SIK2 was elevated in about thirty percent of ovarian cancers and that its overexpression was associated with a poor prognosis. SIK2 was required for the splitting of centrioles during cell division. When he knocked down SIK2, cancer cells became polyploid with more than two copies of each gene in each cancer cell. Knockdown of SIK2 enhanced sensitivity to paclitaxel. These observations formed the basis of a paper in Cancer Cell.

Rationale for these studies goes back to a clinical trial that was done when paclitaxel was first being developed for ovarian cancer. The GOG [Gynecological Oncology Group] 132 clinical protocol tested cisplatin alone to paclitaxel alone, to a combination of paclitaxel and cisplatin in patients who had just had primary surgery for ovarian cancer, but had a very poor prognosis, because there was still a large amount of cancer that could not be resected. Seventy percent of patients responded either to platinum or to platinum plus paclitaxel, but only forty-two percent of patients responded to paclitaxel alone. In two of three large studies, patients lived longer with carboplatin and paclitaxel than with paclitaxel alone. Consequently we give all ovarian cancer patients carboplatin and paclitaxel, but no more than half of the patients benefit from the paclitaxel. There are two ways to improve care: one is to try to get a better predictive test to determine who does or does not respond to paclitaxel; the second is to make ovarian cancer cells more sensitive to the drug, so that we could raise that forty-two percent to a much higher number. And so we have identified kinases that regulate sensitivity to paclitaxel. Currently we are evaluating 14 kinase candidates funded by a grant from CPRIT [Cancer Prevention Research Institute of Texas]. One of the most promising targets is SIK2 and a small company named Arien has made an orally available inhibitor of the kinase. ARN3236 is a drug that inhibits growth of 80% of the ovarian cancer cell lines tested and that enhances sensitivity of ovarian cancer xenrafts to paclitaxel. So, this drug or one similar to it may actually be evaluated in clinical trials in the next year or two.

Tacey A. Rosolowski, PhD

[00:20:13]

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

Mm-hmm.

Robert Bast, MD

[00:20:15]

The third area that we're involved in is in understanding the function of a gene that was originally called NOEY2 (Normal ovarian epithelium Yinhua-Yu 2), then ARHI (Aplasia Ras Homology I) and most recently DIRAS3. (laughter) So, maybe for today's discussion, we'll call it DIRAS3.

Tacey A. Rosolowski, PhD

[00:20:43]

DIRAS3, yeah.

Robert Bast, MD

[00:20:45]

But ARHI is more in the literature.

Tacey A. Rosolowski, PhD

[00:20:47]

Okay.

Robert Bast, MD

[00:20:50]

This gene is expressed by normal ovarian epithelium, but down-regulated in about sixty percent of ovarian cancers. DIRAS3 is also down-regulated in breast cancer, lung cancer, prostate cancer, pancreatic cancer, liver cancer and thyroid cancer. So, what we're discovering in ovarian cancer might have much broader applicability. When you re-express DIRAS3 at physiologic levels, you inhibit proliferation. You inhibit motility. We've gone in the mechanisms of both of those. But most interesting, we've found that DIRAS3 induces a process called autophagy, and establishes tumor dormancy. We have genetically modified ovarian cancer cells, so that we can increase the levels of DIRAS3 with doxycycline. In culture, re-expression of DIRAS3 kills ovarian cancer cells within 3 days. But in xenografts in immunosuppressed nude mice, re-expression of DIRAS3 doesn't kill cancer cells. They just sit there. And when you take the mice off of the doxycycline, the DIRAS3 goes back down in the cancer, the tumor xenografts grow out like nothing has happened. So, we've got a way to control dormancy. Dormant cells also undergo a process of autophagy or self-eating. If we inhibit autophagy ovarian cancer cells grow out more slowly and if we increase autophagy to a point where cancer cells die, the mice are cured.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

[00:22:37]
Please.

Robert Bast, MD

[00:22:37]
Straight technical material or some explanations.

Tacey A. Rosolowski, PhD

[00:22:42]
I mean, a mixture helps, actually.

Robert Bast, MD

[00:22:42]
Okay.

Tacey A. Rosolowski, PhD

[00:22:42]
Because it is a varied audience for the material.

Robert Bast, MD

[00:22:47]
Autophagy is a mechanism that's used by normal cells as well as cancer cells to survive when they are starving without adequate amino acids or adequate glucose. During autophagy, vesicles formed within the cells that surround mitochondria, bits of endoplasmic reticulum, and high molecular weight proteins. Vesicles carrying this intracellular cargo then fuse with lysosomes. They autophagolysosomes then become acidified, activating proteases and lipases that break down proteins and lipids to amino acids and fatty acids which provide energy for starving cells. In the short run, this provides a protective mechanism that saves cancer cells, but prolonged autophagy will kill cancer cells.

Tacey A. Rosolowski, PhD

[00:23:59]
Mm-hmm.

Robert Bast, MD

[00:24:00]
Chloroquine can block autophagy functionally by neutralizing the contents of autophagolysosomes so that the proteases and lipases are no longer active. You still have the autophagic vesicles, but they're just not producing fatty acids and amino acids that are need for energy to maintain the viability of starving cancer cells. And so, but if you feed chloroquine to

Interview Session: 01

Interview Date: July 7, 2014

mice with xenografts that are dormant, you have increased DIRAS3 chloroquine. You markedly delay the outgrowth of tumors. Similarly, we found in cell culture that autophagic cells died, but if you restored some of the growth factors in the xenograft environment, you can partially rescue the autophagic cancer cells in culture. If you add antibodies against these growth factors to the culture, you don't rescue them anymore. If you treat mice with antibodies against VEGF [Vascular Endothelial Growth Factor], against IL8 [Interleukin-8], and also against the receptor for IGF [Insulin-like growth factor receptor], you can cure a fraction of mice, completely inhibiting the outgrowth of the dormant cells.

Tacey A. Rosolowski, PhD

[00:25:28]

Wow.

Robert Bast, MD

[00:25:28]

So, we've discovered a couple of different ways to eliminate dormant cells; one would be chloroquine, although chloroquine, clinically, is, there are a number of toxic side effects. Hydroxychloroquine is another possibility.

[00:25:53]

Robert Bast, MD

[00:25:57]

You could imagine, again, translating this work to try to eliminate dormant cells in ovarian cancer patients, because at the present time, about half to two thirds of patients with ovarian cancer after chemotherapy will have a normal CA-125 and PET CT. But if you perform "second look" surgery after chemotherapy, about half of those patients will have small nodules of cancer that are destined to grow back. Over the last 20 years, few second look operations have been performed as there was no curative therapy for persistent disease, but we are considering reinstating "second looks" as part of the Moon Shot project at MD Anderson. Years ago, many second look procedures were performed at [Memorial] Sloan Kettering [Cancer Center]. From their pathology archives, we've obtained samples of tumor from primary cancers and from the second looks after platinum based therapy. Only 20% of the primary cancers had ARHI-positive autophagic cells, whereas 80% of the second looks contained numerous ARHI-positive autophagic cells consistent with our model for tumor dormancy.

Tacey A. Rosolowski, PhD

[00:27:18]

Mm-hmm. Mm-hmm.

Robert Bast, MD

[00:27:19]

It looks like our model with our inducible cell lines and xenografts actually mimics what's

Interview Session: 01

Interview Date: July 7, 2014

actually happening in ovarian cancer patients. So, we have a really exciting opportunity to functionally inhibit autophagy and eliminate dormant cancer cells, with drugs like chloroquine and hydroxychloroquine, or new agents that are being developed or to eliminate growth/survival factors that are required to keep the autophagic cells from self-destructing after consuming their own body parts.

Tacey A. Rosolowski, PhD

[00:28:04]

Right, right. Because how do you, I mean, how does—how do you force the autophagic cells to target the cancer cells?

Robert Bast, MD

[00:28:14]

Well, it turns out that the cancer cells are autophagic.

Tacey A. Rosolowski, PhD

[00:28:17]

Okay.

Robert Bast, MD

[00:28:18]

Themselves.

Tacey A. Rosolowski, PhD

[00:28:20]

Right, okay.

Robert Bast, MD

[00:28:21]

And it looks like at least our experiments so far point to the fact that you've got to have autophagy to maintain dormancy.

Tacey A. Rosolowski, PhD

[00:28:30]

So, so the ARHI is actually specifically linked to the autophagy of the cancer cell?

Robert Bast, MD

[00:28:39]

Yes.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[00:28:39]

And no other kinds of cells?

Robert Bast, MD

[00:28:38]

Well, no, to normal cells, as well.

Tacey A. Rosolowski, PhD

[00:28:41]

Oh, okay.

Robert Bast, MD

[00:28:43]

But presumably, the cancer cells depend more on autophagy than most normal cells.

Tacey A. Rosolowski, PhD

[00:28:48]

Interesting. Oh, okay.

Robert Bast, MD

[00:28:49]

And so, for—

Tacey A. Rosolowski, PhD

[00:28:50]

So for especially—so that's the sort of shift between cancers providing their own energy sources, and then going to needing angiogenesis to be fed by the blood supply?

Robert Bast, MD

[00:29:01]

Yes, because the other thing about the small nodules on the peritoneal cavity that you can find at second look surgery is that they're usually very poor in blood vessels. So, these cells are almost certainly nutrient deprived and likely to be autophagic.

[00:29:10]

Tacey A. Rosolowski, PhD

[00:29:14]

Okay. Oh, interesting. Wow!

Robert Bast, MD

Interview Session: 01

Interview Date: July 7, 2014

[00:29:17]

We are also doing some more fundamental research. Zhen Lu [MD], an assistant professor, and Margie Sutton, a graduate student, in our lab are looking at the importance of more fundamental mechanisms related to DIRAS3 (ARHI). Mouse cells can undergo autophagy, but they don't have DIRAS3.

Tacey A. Rosolowski, PhD

[00:29:45]

Hmm.

Robert Bast, MD

[00:29:45]

Mice split from the human lineage about sixty million years ago. Pigs and cows are on the human side; they have DIRAS3, but mice don't. Mice and humans do have DIRAS1 and 2, and Margie is looking at the possibility that DIRAS1 and 2 may be doing for mice what DIRAS3 is doing for humans in terms of mediating autophagy. Another discovery that she has made is that DIRAS3 binds to Ras, and so we're looking at the possibility that we might have a Ras-specific inhibitor. So far there's no drug that actually specifically targets Ras.

Interview Session: 01
Interview Date: July 7, 2014

Chapter 07

A: The Researcher

Rapidly Changing Science and the Pressure to Publish in High-Impact Journals

Story Codes

A: The Researcher;

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

D: The History of Health Care, Patient Care;

B: MD Anderson Culture;

C: Professional Practice;

C: The Professional at Work;

C: On Research and Researchers;

B: MD Anderson Impact;

Tacey A. Rosolowski, PhD

[00:30:41]

I have kind of a—just, I'm going to throw this question out here, and see what happens. (laughter) You know, obviously, in order to come to these exciting conclusions, and, you know, these systems are moving together, and wow, we have, you know, a possibility to intervene in the cancer system at this particular point, you have to have this extremely elaborated understanding of many, many different types of mechanisms within the body. So, my question is, and I guess it's basically the collaboration-translation question, how do you go about establishing the conversations and assembling the people with the specific brain power needed to make that field of knowledge happen?

Robert Bast, MD

[00:31:38]

Yes, one of the things I've realized over the years is that science is changing so rapidly, that it's almost all continuing medical education.

Tacey A. Rosolowski, PhD

[00:31:51]

Hmm, interesting! (laughter)

Robert Bast, MD

[00:31:50]

One of the strengths of MD Anderson, is that there are other scientists here who are

Interview Session: 01

Interview Date: July 7, 2014

knowledgeable about almost any particular area within our institution. These days, people collaborate nationally and internationally. There usually are experts in most of these areas right within our institution, which is one of the tremendous advantages of a really large cancer center, like our own. You also have the opportunity to attend very specialized conferences to learn about areas like autophagy.

Tacey A. Rosolowski, PhD

[00:32:36]

Mm-hmm.

Robert Bast, MD

[00:32:38]

Over the years, I've really had to learn almost all of the current recombinant DNA techniques that have been developed since I finished my formal training. Fortunately, there are people in our laboratory who are quite competent in this. But again, it really requires, as you're suggesting, a team, if not a village, that actually can encompass all of the different techniques, let alone all the concepts that are involved in dissecting these really complex cancer-related systems.

Tacey A. Rosolowski, PhD

[00:33:15]

Mm-hmm. Do you feel, I mean, there used to be this kind of image of the lone genius researcher, you know, who kind of hold up and had a big ego, you know, obviously that's no longer the case.

Robert Bast, MD

[00:33:33]

There still may be a few of those around.

Tacey A. Rosolowski, PhD

[00:33:34]

Well, and I guess that's kind of the question I'm asking. I mean, is there a personality type that's attracted to translational, you know, are there certain characteristics that you really need to have as a thinker, as a social personality, that suits you to this kind of work, and that creates a culture of translational?

Robert Bast, MD

[00:33:57]

Yes, there are some translational challenges. One of the verities, although this may be changing to some extent, is that it is difficult to publish translational research in the very highest impact journals.

Interview Session: 01

Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[00:34:15]

Really?

Robert Bast, MD

[00:34:17]

And the flipside to that is that these days, even for Cell, Nature and Science, you get extra credit, for having clinically relevant figures in papers. But in terms of purely translational research, that has not been attractive to a number of the highest impact journals.

Tacey A. Rosolowski, PhD

[00:34:43]

And why is that?

Robert Bast, MD

[00:34:45]

I don't know, but over the last 40 years, the very highest science hasn't necessarily emerged from hospitals or cancer centers. The mechanistic studies that are given the highest respect don't necessarily take into account the heterogeneity from patient to patient, or from cancer to cancer. There's the abstract principle that should apply to everything, and then there's clinical medicine where the differences are really important from individual to individual.

Tacey A. Rosolowski, PhD

[00:35:55]

Yeah. I mean, a number of people that I have spoken with have, you know, talked about—I mean, some people have been pretty blunt and said that clinical medicine is just a poor handmaiden, that it's just not as supported or respected, and it's difficult to get funding. You know, and so that question of what is—because, you know, all science takes place in a political and social context. And it is very influenced by all of those factors, and economics as well is tied up with them. So, you know, what is that? You know, what does that add up to?

Robert Bast, MD

[00:36:44]

Yes.

Tacey A. Rosolowski, PhD

[00:36:46]

You know, how does that influence what research gets done, how it gets done, how the findings are disseminated, you know, which obviously has been one of its impacts.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Robert Bast, MD

[00:36:58]

Well, again, there are many translational journals that have intermediate impact, and so it's not a question of whether this gets published, it's more a question of where it gets published.

Tacey A. Rosolowski, PhD

[00:37:09]

Where. Yeah.

Robert Bast, MD

[00:37:10]

For PhD post-doctoral fellows to get a tenure track job on a faculty at a decent institution, they need high-impact papers somewhere on their CV to justify their hiring. There is incredible competition these days for employment.

Tacey A. Rosolowski, PhD

[00:37:34]

Mm-hmm.

Robert Bast, MD

[00:37:35]

And we've trained probably more PhDs than we can utilize.

Tacey A. Rosolowski, PhD

[00:37:41]

Oh, really?

Robert Bast, MD

[00:37:44]

In terms of jobs. About the only place that has excess capacity for hiring these days is in China.

Tacey A. Rosolowski, PhD

[00:37:48]

Really?

Robert Bast, MD

[00:37:49]

Yeah.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

[00:37:50]

Well, I didn't realize that there was a glut—

[00:37:51]

Robert Bast, MD

[00:37:53]

Yes, but glut may be too strong a word.

Tacey A. Rosolowski, PhD

[00:38:00]

Mm-hmm.

Robert Bast, MD

[00:38:00]

But there's certainly an excess.

Tacey A. Rosolowski, PhD

[00:38:02]

Okay. I mean, I'm just surprised to hear that, because I guess I was making an assumption based on the comments that there were a lack of physicians, that there would also be a lack of researchers, or—

Robert Bast, MD

[00:38:17]

No.

Tacey A. Rosolowski, PhD

[00:38:17]

Not at all.

Robert Bast, MD

[00:38:18]

And certainly in terms of PhD investigators, this relates to the fact that we've been the graduate school for the world for the last fifty years or so.

Tacey A. Rosolowski, PhD

[00:38:27]

Oh, really? Okay.

Robert Bast, MD

Interview Session: 01

Interview Date: July 7, 2014

[00:38:28]

So, a number of very able people come from China, India, or other countries to join students and postdoctoral from the United States. So, there's a very large number of able people competing for the same jobs.

Tacey A. Rosolowski, PhD

[00:38:48]

Right. Right.

Robert Bast, MD

[00:38:49]

And I think we've had very little birth control on the number of students recruited to graduate schools.

Tacey A. Rosolowski, PhD

[00:38:53]

Yeah, well, and it happens. I mean, there's always a lag time with academia response to reality of the kind of market needs.

Robert Bast, MD

[00:39:01]

Yes, and I think it's probably only been in the last five years or so, I'm sure somebody saw this coming. But it's only been the last five years or so that you've seen more of this in Science and Nature.

Interview Session: 01
Interview Date: July 7, 2014

Chapter 08

A: The Researcher

Research to Develop a Big Picture of Ovarian Cancer; Creating a Collaborative Laboratory Environment

Story Codes

A: The Researcher;
A: Overview;
A: Definitions, Explanations, Translations;
C: Discovery and Success;
C: Professional Practice;
C: The Professional at Work;
C: Leadership;
C: Mentoring;
B: MD Anderson Culture;
B: Multi-disciplinary Approaches;
C: Understanding the Institution;

Tacey A. Rosolowski, PhD

[00:39:10]

Interesting. Well, my question kind of derailed you from your story about the research. I'm just wondering if there are other areas that—we haven't really talked about the epithelial ovarian cancer.

Robert Bast, MD

[00:39:30]

Well, there's—most of the ovarian cancers are epithelial ovarian cancers.

Tacey A. Rosolowski, PhD

[00:39:34]

Okay. So, this was the immune stimulants. Have we fully covered that? You mentioned some of them.

Robert Bast, MD

[00:39:39]

Yes, immunostimulants were important in the early days of my own work . Over the years, our group has really gotten much more into cell biology—

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[00:39:46]

Cell biology.

Robert Bast, MD

[00:39:49]

—of ovarian cancer, and modulating drug sensitivity.

Tacey A. Rosolowski, PhD

[00:39:55]

Okay. Let's see, now, with the—I'm just going to run through, I may have used slightly different language to describe the various areas of your research, and so I need to kind of connect the dots. We certainly—just to make sure we've covered all the areas. So, we've talked about the detection and the screening and the biomarkers. We talked about the autophagy, and ARHI. I'm wondering, because I have down here, too, it's marked as 2011, the models of personalized care for patients with ovarian cancer? Have we—I don't know if that's, like, a code that you're not recognizing. (laughter)

Robert Bast, MD

[00:40:34]

No, clearly that's an interesting—one of the things that our group has done over the years has been, tried to pull together an overview of all of the ovarian cancer research—

Tacey A. Rosolowski, PhD

[00:40:46]

Oh, okay.

Robert Bast, MD

[00:40:46]

—that is being done both in the laboratory and the clinic, and written the ovarian cancer chapter for the last editions of John Mendelsohn [MD]'s book, *Molecular Biology of Cancer*. To get the bigger picture, with both the forest and the trees has been one of our goals over the years. To some extent, that gives you leads about what other targets might be exploited.

Tacey A. Rosolowski, PhD

[00:41:15]

Mm-hmm. And so, I mean, tell me about that. Are there themes that are emerging from that, big picture?

Robert Bast, MD

Interview Session: 01

Interview Date: July 7, 2014

[00:41:23]

For ovarian cancer, for sure. About eighty or ninety percent of epithelial ovarian cancers are so-called high grade, the cells look more abnormal under the microscope; about ten percent are low-grade cancers. With high grade cancers, there are a couple of major changes. Almost all of them have mutations of p53. Currently, we don't have many strategies for targeting mutant p53, new work suggests that small molecule drugs can normalize the conformation of mutant p53. Abnormalities of the PI3 kinase pathway occur in forty percent to fifty percent of ovarian cancers. Only about fifteen percent of ovarian cancers have mutations of BRCA that are inherited, but forty percent of ovarian cancers have abnormalities of DNA repair mimicking BRCA mutation. Gordon Mills [MD, PhD], and others are trying to target PI3 kinase or BRCA-ness, with different drugs or combinations of drugs. Combinations of drugs against these targets maybe more effective than individual agents.

Tacey A. Rosolowski, PhD

[00:43:23]

Mm-hmm.

Robert Bast, MD

[00:43:24]

I have headed the NCI sponsored Ovarian Specialized Program of Research Excellence (SPORE) at MD Anderson for the last fifteen years and we're in the process of renewing that grant again this year. Most of the high grade ovarian cancers are driven by the amplification of genes, where you've got too many copies of the normal DNA. Low grade ovarian cancers are driven by mutations, most frequently of Ras, but also of PI3 kinase and PTEN. Many of the targeted therapies are most successful where there are mutations, or where there's a translocation involved. Targeting amplified genes has been more difficult. So, ovarian cancer, in that regard, is probably the next frontier.

Tacey A. Rosolowski, PhD

[00:44:36]

Hmm. I'm curious, when you came to the institution in, let me think, '94, I think it was—

Robert Bast, MD

[00:44:49]

Mm-hmm.

Tacey A. Rosolowski, PhD

[00:44:49]

—yes, remembering, and set up your laboratory, did you bring part of your laboratory with you?

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

Robert Bast, MD

[00:44:57]

I did.

Tacey A. Rosolowski, PhD

[00:44:56]

Your personnel? And so, I mean, it's obvious that you're, you know, you have a very strategically established laboratory army, if you will.

Robert Bast, MD

[00:45:08]

It's a pretty small army, but...

Tacey A. Rosolowski, PhD

[00:45:11]

Well, but, you know, obviously, you're talking about, you know, you've got this dimension that's kind of looking at the big picture, then you've got these people who are really looking at very detailed dimensions of pathways and mutations. So, I'm curious, you know, how did your own strategies for setting up a lab evolve over time? Or, is that not the best way to ask the question?

Robert Bast, MD

[00:45:41]

No, it's a very good question. I'm just trying to think of the right answer. .

Tacey A. Rosolowski, PhD

[00:46:09]

Mm-hmm.

Robert Bast, MD

[00:46:10]

But I guess one thing is that our laboratory has done has been to jump on new technologies over the years.

Tacey A. Rosolowski, PhD

[00:46:17]

Mm-hmm?

Robert Bast, MD

[00:46:18]

Interview Session: 01

Interview Date: July 7, 2014

Discovering CA125 depended on developing the OC-125 antibody which, in turn, depended upon Kohler and Milstein's earlier studies that developed the monoclonal technology. Our discovery of ARHI, again, depended upon the precursor of gene expression array analysis. When compared to normal ovarian epithelium, ARHI is the most down-regulated gene on gene expression array analysis. SIK2 was discovered by using high throughput SIRNA screens, which, again, is a relatively new technology. So, that's been a big component.

Tacey A. Rosolowski, PhD

[00:47:07]

Mm-hmm.

Robert Bast, MD

[00:47:07]

Also, our laboratory has been very collaborative. A lot of the work that we've published is multi-authored and multi-laboratory, realizing that if we're going to get those done most effectively, then doing that with other people who have different expertise, has been helpful.

Tacey A. Rosolowski, PhD

[00:47:29]

Mm-hmm. Mm-hmm.

Robert Bast, MD

[00:47:30]

Within our lab, we have depended upon faculty members and post-doctoral fellows. Over the last several years I have just gotten seriously involved in the Graduate School of Biological Sciences, creating a curriculum and program in Clinical and Translational Research with Khandan Keyomarsi and colleagues at UT Health. Over the last three years, Margie Sutton has been our first graduate student. Research assistants have also been very important and included as authors on our papers.

Tacey A. Rosolowski, PhD

[00:48:02]

Mm-hmm.

Robert Bast, MD

[00:48:03]

Over the years, we've had several real superstars pass through our laboratory. Ian Jacobs was a little farther along in his career, when he came to visit our laboratory at Duke [University]. In 2000 Ian had started the 200,000 women UKCTOCS trial in the UK, and then served as Dean at the University College London Medical School, and then had been provost at the University of

Interview Session: 01

Interview Date: July 7, 2014

Manchester. Now, he's going to be president at the University of New South Wales, in Sydney, Australia. He really has had a very effective administrative, as well as scientific career. He's also highly respected in GYN Oncology in the UK and in Europe as past president of the British Society of Gynecologic Oncology.

Andy Berchuck [MD], who is now head of GYN Oncology at Duke, joined forces with our lab while he was on the junior faculty at Duke. Andy's insights and drive were a tremendous help to our lab.

Ahmed Ahmed is another extremely talented person who was a postdoctoral fellow. Ahmed had started the SIK2 studies, which ended up in Cancer Cell. He is now full professor of Gynecologic Oncology at Oxford. So, we've had some really incredible people come through.

Tacey A. Rosolowski, PhD

[00:49:51]

Mm-hmm.

Robert Bast, MD

[00:49:52]

Over the years, however, I've realized that's only a fraction of the people whom we've trained have remained in full time research. One of the things that I've tried to do more is to identify people for our laboratory who really have a future. So often, if in training people from other countries who go home to their hospital, they're never really given the opportunity to do enough research to really have an impact. Coming to the US for a year or a year and a half doesn't really prepare them adequately for what they're going to do, and then they're not given the opportunity to really do laboratory-based or translational research when they get home. So, I've been trying harder to find people with a different trajectory.

Tacey A. Rosolowski, PhD

[00:50:41]

Mm-hmm. Right.

Robert Bast, MD

[00:50:42]

Tacey A. Rosolowski, PhD

[00:50:46]

Mm-hmm. Mm-hmm.

Robert Bast, MD

[00:50:47]

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

The success of our laboratory depends upon having really great junior faculty members like Zhen Lu. Finding technicians who are really professional and competent provides some continuity. Post-doctorate fellows come and go over a two or three year period.

Tacey A. Rosolowski, PhD

[00:51:24]

Right. Right.

Robert Bast, MD

[00:51:28]

As an aside, what sort of answers have you gotten to that question from other people?

Tacey A. Rosolowski, PhD

[00:51:34]

I think it's the first time I've asked it directly, frankly. Some people have kind of spontaneously talked about it, you know? But I was just curious, because you had added—the reason I asked the question is that you had, you know, talked about wanting to bring in this, you know, 20,000 foot view, or I can't remember how you phrased it, exactly, and it just seemed like a very, you know, precise moment. Like, okay, now we're going to add this dimension to the laboratory, because it's needed. So, I was wondering, you know, if you had kind of a philosophy of setting up a lab, or a strat—or a larger path?

Robert Bast, MD

[00:52:10]

That is really two different, but related questions.

Tacey A. Rosolowski, PhD

[00:52:14]

Mm-hmm?

Robert Bast, MD

[00:52:16]

One is what you do with your laboratory, once it's set up. The other is, what kind of people do you select for your laboratory?

Tacey A. Rosolowski, PhD

[00:52:21]

Exactly.

Robert Bast, MD

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

[00:52:22]

And what are the criteria for them?

Tacey A. Rosolowski, PhD

[00:52:24]

Right. Right. And I think it's also an evolving question of—because, you know, people in any position change over time. And Mien Chie Hung [Oral History Interview] was telling me about the importance of the journal club, and the way he has set up what the journal club looks like, because it's sort of a practice pad for looking at the state of the field, you know? And so, that's a very intentional decision about what he wants his laboratory to provide, training-wise. So, I just—and that was a new idea for him, basically.

Robert Bast, MD

[00:53:00]

Yes.

Tacey A. Rosolowski, PhD

[00:53:01]

You know, now I'm going to do this as an educator, as a leader, or as an administrator, you know, as a leader of a lab. So, I was just kind of curious about your decisions in these areas.

Robert Bast, MD

[00:53:10]

Each Monday, we have had a lab lunch where people present their developing papers. We also have had guest speakers in the same forum. Most recently, our guest speakers have been interested in autophagy and/or ovarian cancer. We have also started an autophagy journal club for the Houston community.

Tacey A. Rosolowski, PhD

[00:53:53]

Oh, really?

Robert Bast, MD

[00:53:55]

Yes, Margie Sutton, a graduate student in my laboratory is taking the lead in doing that. There are a number of people here at MD Anderson who are interested in autophagy. So, I think we'll see how the experiment works, but my guess is, we'll probably find an opportunity to share our work in progress.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

[00:54:11]
Right.

Robert Bast, MD

[00:54:12]

We also have another data session each Friday for our lab and then spend at least a half an hour, if not more, with each one of our trainees during the week, to make plans for their next experiments and papers.

Tacey A. Rosolowski, PhD

[00:54:40]

Hmm, which is kind of incredible, because, you know, your busy-ness level has increased, and people's workloads in general has increased, and often those training moments, or mentoring moments, are cut back.

Robert Bast, MD

[00:54:53]

Sure.

Tacey A. Rosolowski, PhD

[00:54:52]

You know, out of necessity. But you've gone against the grain, and now—(laughing)

Robert Bast, MD

[00:54:58]

It's the one thing that we can't [inaudible], at least not often.

Tacey A. Rosolowski, PhD

[00:55:02]

Oh, that's funny! Do you need to stop a little bit early today?

Robert Bast, MD

[00:55:06]

No, 11:30 will be fine.

Tacey A. Rosolowski, PhD

[00:55:07]

It'll be fine? Okay, just wanted to check with you about that.

Interview Session: 01
Interview Date: July 7, 2014

Chapter 09

A: Joining MD Anderson/Coming to Texas

Experience at Duke and Coming to MD Anderson to Build Research

Story Codes

A: Professional Path;
A: Joining MD Anderson;
A: Overview;
A: The Administrator;
B: MD Anderson History;
C: Understanding the Institution;
D: On Texas and Texans;
B: MD Anderson Culture;
B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
B: Critical Perspectives on MD Anderson;

Tacey A. Rosolowski, PhD

[00:55:07]+

I mean, since we're on the topic, I wanted to ask you, you know, how do you think your own kind of personae as an administrator, you know, and as a leader, both in the lab and in the institution has evolved? When did you first understand that you were interested in becoming more involved with administrative issues, and with taking the leadership role?

Robert Bast, MD

[00:55:35]

My first real administrative experience was at Duke. In 1984, I'd been at the Dana-Farber Cancer Center in Boston for seven years and had just become an associate professor at Harvard. At Duke I had the opportunity to codirect the division of Hematology-Oncology and to be Clinical Director for the Duke Comprehensive Cancer Center. Within three years I became director of the Duke Comprehensive Cancer Center which turned out to be a lot of fun. There had been one previous director, Bill [William] Shingleton [MD].

[00:56:17]

Tacey A. Rosolowski, PhD

Interview Session: 01

Interview Date: July 7, 2014

[00:56:54]

Now, just thinking back to that time, why were you recruited to that position? What did you offer the institution at the time?

Robert Bast, MD

[00:57:01]

I suspect that Duke was very much interested in immunology, with my experience up to then had been with monoclonal antibodies, both the diagnostic and therapeutic side of their application. Also, I think that they saw a need for more rigor in science among their medical oncologists. Duke, overall, had some great scientists, like Bob [Robert] Lefkowitz [MD] who just won the Nobel Prize a couple of years ago. The leaders at Duke saw the need for more peer-funded laboratory-based oncology research. They did have some industry-sponsored clinical research there, but it was not on a par with clinical investigation in cardiology or neurology.

Tacey A. Rosolowski, PhD

[00:57:54]

Mm-hmm.

Robert Bast, MD

[00:57:56]

So, I think they saw that there was a need for a modernization, if you will, and a more rigorously academic atmosphere in that part of the medical center. Two or three years after arriving at Duke, Bill Shingleton retired, and became the Cancer Center director. Duke was a “matrix” center, rather than a “free-standing” cancer center, like MD Anderson. All of the Cancer Center members at Duke had been recruited into different departments within the Medical School such as Surgery, Medicine, Microbiology, whatever. Actually, most of the sixty or so Cancer Centers are matrix centers. Perhaps nine or ten are free-standing, like MD Anderson. So, that took a fair amount of diplomatic skill to work with the sundry department chairs to bring together the Center. Bob [Robert] Bell [PhD], our deputy director, had done a lot of work with cell growth regulation. Together we built a really effective team that recruited more Cancer Center members and constructed more buildings and renewed the “Core” grant twice. We actually doubled the Cancer Center membership and increased fund raising.

Tacey A. Rosolowski, PhD

[00:59:17]

Mmm.

Robert Bast, MD

[00:59:18]

So, I think it encouraged a lot of collaboration that didn't exist before. We renewed the NCI Core grant a couple of times for that.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Tacey A. Rosolowski, PhD

[00:59:28]

Mm-hmm?

Robert Bast, MD

[00:59:30]

And I think, and I noticed on your list that you'd mentioned, you know, why did you come to MD Anderson, or why did you leave Duke specifically?

Tacey A. Rosolowski, PhD

[00:59:38]

Yeah, I was going to get to that question.

Robert Bast, MD

[00:59:38]

Bob and I had taken a matrix cancer center about as far as you can go.

Tacey A. Rosolowski, PhD

[00:59:44]

Mmm.

Robert Bast, MD

[00:59:46]

The opportunity to work in a center like MD Anderson that is dedicated just to cancer, where you didn't have to justify that cancer is really an important problem relative to heart, kidney or lung disease, was something that seemed to be very attractive at the time.

Tacey A. Rosolowski, PhD

[01:00:07]

So, how did you come to MD Anderson? How did that recruitment take place?

Robert Bast, MD

[01:00:13]

Irv [Irwin] Krakoff [MD], was retiring, and MD Anderson carried out a lengthy national search to find his successor. David Hohn [MD] was vice president of clinical affairs, and was leading that search. Certainly Mickey LeMaistre [oral history interview] had a lot to do with my decision to come to MD Anderson. This was an opportunity, to lead a remarkable group of exceptional people. As Cancer Center Director, you led by persuasion. That was true at MD Anderson as well, but the members of the Division of Medicine had a direct reporting

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

relationship. And so, this was an interesting opportunity to accomplish even more.

Tacey A. Rosolowski, PhD

[01:00:53]

Who contacted you first?

Robert Bast, MD

[01:00:57]

I think it was David, I could be mistaken.

Tacey A. Rosolowski, PhD

[01:01:00]

David Hohn? Mm-hmm. Did you think about it for more than two minutes? (laughter)

Robert Bast, MD

[01:01:04]

For sure. I was looking at other opportunities at the same time.

Tacey A. Rosolowski, PhD

[01:01:10]

Uh-huh, okay.

Robert Bast, MD

[01:01:11]

At City of Hope and other places.

Tacey A. Rosolowski, PhD

[01:01:13]

Okay.

Robert Bast, MD

[01:01:14]

Over the last twenty years, MD Anderson has grown stronger and stronger. It has always been known for its exceptional clinical care. We've always had a fraction of really great scientists on our faculty, but twenty years ago, MD Anderson was not nearly so strong in translational and laboratory-based research, as it is today.

Tacey A. Rosolowski, PhD

[01:01:42]

Mm-hmm.

Making Cancer History®

Interview Session: 01
Interview Date: July 7, 2014

Robert Bast, MD

[01:01:44]

Having written my article on BCG and cancer, I certainly wondered whether I could, in fact, have a role in strengthening our research efforts.

Tacey A. Rosolowski, PhD

[01:01:58]

Right.

Robert Bast, MD

[01:01:57]

Fortunately, Irv Krakoff had made a huge difference over the previous ten years, increasing the rigor of clinical trials, and their review, and having established a really effective infrastructure. Now, coordination of clinical trials research is all coordinated centrally by Aman Buzdar [oral history interview], but it used to be based in the Division of Medicine. When I came here, the Division of Medicine included both what is now Internal Medicine Specialties and Cancer Medicine both of which were smaller at the time, but it was still pretty good-sized operation.

Tacey A. Rosolowski, PhD

[01:02:30]

If we can, in the minutes that we've got left, when you were, you know, coming down to Houston, what did you, at that point, see as the challenges that you were stepping into?

Robert Bast, MD

[01:02:47]

Why don't we start with the opportunities, one of the things that really impressed me about MD Anderson was the notion that almost anything is possible. Again, it's a Texas philosophy. The cancer focus, as I mentioned, was really important as well. There clearly was a great strength here in clinical investigation. But it seemed to me there was an opportunity to build up translational research as well, where I could make a distinctive contribution.

Tacey A. Rosolowski, PhD

[01:03:44]

Mm-hmm?

Robert Bast, MD

[01:03:46]

There was also a great opportunity in education. I headed the medical oncology fellowship program at Duke and was awarded a couple of NCI T32 training grants. When I first arrived at

Interview Session: 01

Interview Date: July 7, 2014

MD Anderson our fellows were not always on an academic track. Almost none of our trainees were primarily from the United States. There's been a tradition At MD Anderson of launching incredible careers for fellows who were first educated outside of our country. Gabe [Gabriel] Hortobagyi [MD], Chris Logothetis are some of the best examples, but a whole bunch of oncologists have done exceptionally well and made major contributions to patient care, research and teaching, not having come from the United States. But we had not competed very effectively for the best domestic trainees and very few fellows had ever published a paper before joining our fellowship.

Tacey A. Rosolowski, PhD

[01:04:49]

Wow.

Robert Bast, MD

[01:04:50]

Of greater concern, we had very few people who ended up going on into academia. And at the end of the day, many became fine practitioners in the community, but did not contribute to research.

Tacey A. Rosolowski, PhD

[01:04:59]

Yeah, that issue you were talking about earlier, even within your lab, identified people who were really going and take the experience, and then have an impact on research.

Robert Bast, MD

[01:05:07]

Yes.

Tacey A. Rosolowski, PhD

[01:05:09]

Yeah.

Robert Bast, MD

[01:05:09]

One of the accomplishments of which I'm most proud from my years in the Division of Medicine, was getting the fellowship program off the ground. Building on that base, [Waan] Ki Hong [MD] has taken the program much farther. When I moved from the Division to become VP for Translational Research in 2000, the 33 fellows recruited between 1998 and 2000 had published 124 papers before joining the program and included 9 M.D.-Ph.D.'s and 3 chief residents. Fellows were recruited from residency programs at the Beth Israel-Deaconess Hospital

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

in Boston, New England Medical Center, U. of Pennsylvania, Maryland, Virginia, Duke, Vanderbilt, U. of Alabama, Washington University, Mayo Clinic, Colorado, UCLA, UCSD and Scripps as well as the Baylor College of Medicine, U.T. Southwestern and the University of Texas Health Science Center Houston. This was a diverse group as well. Between 1994 and 2000 there were 3 African-American, one Native American, 8 Hispanic and 24 Asian-American medical oncology fellows trained at M.D. Anderson. Among fellows completing the program in 2001 and 2002, 19 of 23 pursued academic careers. This provided a foundation for Ki, who has done so exceptionally well to build up the fellowship program even farther. So, we had built the fellowship program purposefully over six years. We'd sent out letters to chairs of medicine at all medical schools describing the improvements in training, letting them know that it's a new day at MD Anderson, and we're really interested in developing careers of young people for academic medicine.

Tacey A. Rosolowski, PhD

[01:06:24]

Interesting.

Robert Bast, MD

[01:06:24]

And so, I think that has made a difference for the institution over the years.

Tacey A. Rosolowski, PhD

[01:06:31]

Mm-hmm. Would you like to stop for today, and—

Robert Bast, MD

[01:06:35]

I think this would be a good time to break.

Tacey A. Rosolowski, PhD

[01:06:37]

Time. Okay, great. Great. Well, thank you very much!

Robert Bast, MD

[01:06:39]

You're welcome! I hope this is the sort of thing you were looking for.

Tacey A. Rosolowski, PhD

[01:06:41]

Making Cancer History®

Interview Session: 01

Interview Date: July 7, 2014

It is precisely the sort of thing we were looking for, so I thank you for working with my program, here. And I am turning off the recorder at twenty-seven minutes after eleven.

Robert Bast, MD

Interview Two - July 24, 2014

Chapter 00B **Interview Identifier**

Tacey A. Rosolowski, PhD

[00:00:00]

All right. So we are recording. And it is twelve minutes after 9:00. And today is the 24th of July, 2014. And I am in the office of the vice president of translational research talking to Dr. Robert Bast. This is our second session. So thank you very much again for making time amidst all the grant writing and the busy schedule to talk about this.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 10
B: Building the Institution
The Office of Translational Research: Building Collaborations

Story Codes

B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
B: Institutional Processes;
B: MD Anderson Culture;
A: Overview;
B: MD Anderson History;
C: Discovery and Success;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;

[00:00:00]+

Tacey A. Rosolowski, PhD

We were strategizing a bit before the recorder turned on and decided to tell the story of this office today. So I wanted to ask you. How did MD Anderson make the decision to establish this office? What was the history of that? And why in 2000?

Robert Bast, MD

[00:00:47]

MD Anderson has been a comprehensive cancer center designated by the National Cancer Institute since the 1960s I believe, perhaps even earlier. And Fred Becker [oral history interview], who was our vice president for research for many years, had coordinated the submission of the core grant that is tied to NCI designation. This is a grant that's awarded to about sixty centers around the country. And for us most recently it's been about \$10 million a year that's dedicated to supporting shared resources. Over the three grants that we have renewed, more than \$150 million has been brought to MD Anderson. But you have to score well on a core grant in order to become an NCI-designated cancer center. Obviously, it's unthinkable that MD Anderson wouldn't be an NCI-designated cancer center, but we have to maintain a core grant in order to do that.

Tacey A. Rosolowski, PhD

[00:01:43]

Go through the hoops. Right.

Interview Session: 02

Interview Date: July 24, 2014

Robert Bast, MD

[00:01:43]

So in 2000 when I moved from the head of the Division of Medicine to create the Office of Translational Research. Fred Becker had just retired or was retiring and it was necessary to find a new office to write and administer the Core grant. When I was at Duke as head of the cancer center there I had twice renewed our core grant. So this was familiar territory. One of the first responsibilities of the Office of Translational Research was to oversee the shared resources that were part of the core grant and then to prepare each Core grant for John Mendelsohn.

Traditionally, the head of the cancer center writes and institutions core grant, but needless to say, Dr. Mendelsohn had a few other things to do. So our office had both written that grant and then taken care of the shared resources for him.

Tacey A. Rosolowski, PhD

[00:02:40]

I just want to ask you a question because it sounds to me like the shared resources are the hard material that really supports an entire culture of activity. So I wanted to ask you about what that looked like in 2000 and maybe even how you saw that evolve from the time you arrived.

Robert Bast, MD

[00:03:03]

The shared resources were already well developed in 2000. And there are several kinds of shared resources. Some of those really stood and still stand on their own. For example the office that takes care of clinical research is really its own office in terms of the approval and record keeping for our clinical protocols. But is also a part of the NCI core grant. Similarly, veterinary medicine here has become extremely well developed over the years with departments not only here on the main campus, but also at Smithville as well as at Bastrop. And so those really have a life of their own, but again are components of the core grant. And then there are instrumental shared resources like flow cytometry and gene sequencing and the like that really did not have—or reported to Fred's office and subsequently reported to ours. So we do a couple of things. For those smaller resources we've managed to be sure that they're financially solvent and that they have the instrumentation that they need and the proper management and the like. However, in terms of biostatistics, bioinformatics, veterinary medicine, and clinical research, we integrate their efforts into the core grant, but they really have their own management. So it's a matrix of activities. And with that over actually now the fourteen years or so that we've been coordinating that, we have developed new shared resources. We've improved the instrumentation within some of the existing resources. For example within flow cytometry they now have a CyTOF machine, which can measure 100 different parameters of a given cancer cell. Mike Andreeff has been marvelous in putting together the resources for that.

Interview Session: 02

Interview Date: July 24, 2014

In terms of the core grant itself, we managed to improve that substantially. When these core grants were first instituted, MD Anderson had a substantial amount of support from the state and our need for this incremental support was not seen as a priority. And so when I had started with the office in 2000 we had a core grant renewal that was I guess scheduled for 2003. And we were able to actually increase the number of dollars coming to Anderson over 5 years from about \$27 million to \$45 million, i.e, by about two thirds. Subsequently, we've renewed the core grant twice again. And the last time they had an old grading system and we got an outstanding on that, which is the highest grade you could get. And this time in 2013 we got an exceptional. And it's really a tribute to all of the research that's ongoing here at MD Anderson and also all the efforts of the people who are working with the shared resources. But at least we've been able to represent those effectively to peers who have to review these. I served on the parent committee for this activity that reviews all the different grants ultimately. So I think MD Anderson clearly is if not the most effective cancer center, it's clearly one of the top two or three. And it's been very important I think to all of us that that's recognized outside of Houston.

Tacey A. Rosolowski, PhD

[00:06:59]

So that piece with the great research going on but then representing it to the outside, is that one of the main functions of this office?

Robert Bast, MD

[00:07:09]

It is. And also we're probably the only office where all of the research in MD Anderson comes together, because we not only have to write a grant every five years, but we also have to submit non-competing renewals each year. Overall, we have nineteen different programs—there are basic science programs like immunology and carcinogenesis and the like, there are other translational programs at each of the disease sites like breast cancer and gastrointestinal cancer and leukemia, and then there are disciplinary translational programs like radiation oncology or stem cell transplantation, and finally population-based programs with behavioral science, molecular epidemiology and chemoprevention. The strength of these nineteen programs really determines the priority score of the entire grant and the need for the shared resources that are actually what these grants support. So not only every five years but every year for the noncompeting renewals of these grants we receive information about all of the research that's ongoing at MD Anderson and we integrate that so that if you want to know what's actually happening with research, we're a source of information for that that integrates the activities across the institution.

Tacey A. Rosolowski, PhD

[00:08:42]

I was going to ask. So that information is not only obviously extremely useful for bodies outside

Interview Session: 02

Interview Date: July 24, 2014

the institution, but is this a way for researchers within MD Anderson to communicate or have information about one another, to find out about collaborations?

Robert Bast, MD

[00:08:59]

It is. One of the things that we established over the years is a faculty information system. We'd actually been the catalyst to get all of the faculty CVs on a single computer platform. They're redoing that now. Oliver Bogler is in the process of trying to find another even more effective platform for the faculty CVs. But for the last ten years if you were interested in aurora kinase, any faculty member could type "aurora kinase" into it and then get not only the previously published papers of each faculty member, but the papers that were in press that showed up on CVs or the abstracts that would be dealing with aurora kinase. So it's been a resource for bringing faculty members together.

One of the goals of the cancer center programs is to encourage collaboration, not only within programs but between programs as well. We've tried to facilitate that in addition.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 11
B: Building the Institution
Training Physician-Scientists at MD Anderson

Story Codes

B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;
D: Business of Research;
D: Women and Diverse Populations;
C: The Life and Dedication of Clinicians and Researchers;
A: Overview;
B: Industry Partnerships;
D: On Pharmaceutical Companies and Industry;
C: Discovery and Success;
C: Healing, Hope, and the Promise of Research;

Tacey A. Rosolowski, PhD

[00:10:05]

So to go back when you stepped into the role, what did you feel was your mission and the stated mission for the new office?

Robert Bast, MD

[00:10:15]

Well, our mission was and is to facilitate translational research. Translational research goes on all over MD Anderson. Each department really has a translational component, some more than others. And so the responsibility for that is centered in each department and clinical center. The purpose of this office is to facilitate those activities. We've done that in several different ways. We've also expanded our role in shared resources to include not only the shared resources that are partially funded from the core grant, but also the instrumental resources that are shared by different departments outside of the core grant. That's been more developed over the last two or three years since Ron DePinho became president. We're also working with the shared resources in each of the centers that John Mendelsohn established. In Alan McClelland and Kat Hale, we've got two people who really are experts in the management of shared resources. They're able to use that expertise not only in the core grant and in the center shared resources but also most recently Alan has begun to help out with the moon shot platforms in terms of being sure that they're being run optimally. So a portion of our office facilitates programmatic activities

Interview Session: 02

Interview Date: July 24, 2014

and keeps track of the programmatic activities around MD Anderson scientifically, and we also help with the shared resources.

Early on we began to work with multi-disciplinary research programs. Now that's a euphemism for program project grants (P01s) from NCI, and also Specialized Programs of Research Excellence (SPOREs) from NCI. And SPOREs have really become a house specialty. Because we're so large and so deep and have four or five investigators who are funded from other mechanisms for research in ovarian cancer or in lung cancer or in other areas, we'd started I guess more than fifteen years ago in a collaboration with UT Southwestern with John Minna and Jack Roth. John is from UT Southwestern and Jack of course had headed thoracic surgery here. They developed a joint SPORE, but that the principal investigator was from UT Southwestern. Our ovarian SPORE was the first SPORE to actually be developed here, to come from MD Anderson. We had collaborators at UCSF and the like over the years, but that was our first.

Over the years we've actually had at peak at about thirteen SPOREs. I think we're back to six now. And there are only about sixty SPOREs nationally. So it's been up to twenty percent of the national SPOREs. Each of those grants in the past has contributed up to \$3 million annually. They're down to \$2.3 million a year total cost, but it is still a major source of funding for translational research. The purpose of those grants is purely translational. You have to have four or more projects that take an idea from the laboratory to the clinic and ideally back again within five years. And that's been a very successful program that fortunately has recently been renewed at a national level by NCI.

We also have had a number of program projects. Some are more translational than others, but we have established a system where we could provide seed money to encourage investigators here at MD Anderson to get together to establish a track record for collaboration and for publication of preliminary data they need for successful applications to the National Cancer Institute either for program project grants, P01s, or for SPOREs. And with the institution of the Cancer Prevention and Research Institute of Texas there are also multi-investigator awards for CPRIT. So as the going has gotten tougher for funding in Bethesda particularly for P01s, it's been possible to compete successfully within the state for the multi-investigator awards using the same mechanism.

These MRPs involve \$250,000 over two and a half years and it's a competitive program. We usually have—you can award two to three of these a year. And we usually get about five to seven applications for each one that we can award. And it's evaluated by a faculty committee

Interview Session: 02

Interview Date: July 24, 2014

that we coordinate. And basically these are awarded based on what the perception is of the probability of getting funded after a year or two if the people are working together and developing the preliminary data that they need and the like.

And so it's been a remarkably successful program. We've invested about \$8 million of institutional funding in that and we've received more than \$120 million of NIH and CPRIT funding for those awards. And it's ongoing. It's still I think a very effective program. So that's one of the ways that we've facilitated translation.

Another has been to work on career development for translational scientists. We've done that in two different areas. One is for physician scientists. And there had been a physician scientist program that had started just—I guess actually we really formalized the physician scientist program within our office.

Tacey A. Rosolowski, PhD

[00:16:25]

When did that program begin?

Robert Bast, MD

[00:16:27]

Probably around 2000. It was very shortly after our office was formed. And obviously again there had been physician-scientists at MD Anderson long before that and there had been people training to be physician scientists. But this really brought together a formal program where we could support two or three of our best and brightest young MDs or MD/PhDs to do laboratory-based research with eighty percent dedicated time and still be in the clinic at least twenty percent of the time and in the case of the surgical physician scientists, usually a little bit more than that.

With that program we've actually had forty-one physician scientists that have been supported across seven divisions. So this has not just been medicine where many of the physician scientists nationally are found, but in surgery and radiation oncology, cancer prevention and pediatrics, internal medicine, pathology, lab medicine. We've not been totally successful. Three physicians—we evaluate this each year. Three were actually terminated and four resigned to pursue opportunities at other institutions. And currently six are in the program and there have been twenty-eight graduates. The purpose of the program is actually for people to get their own individual investigator funding either from NIH or from the American Cancer Society. More than 80% of graduates have obtained an R01 or equivalent.

Interview Session: 02

Interview Date: July 24, 2014

Tacey A. Rosolowski, PhD

[00:17:55]

People have said—a number of people that I’ve interviewed have talked about the challenges of supporting a career that is bifurcated in that way. How do you see the challenges? What are the obstacles for someone who wants to take on a physician scientist pathway?

Robert Bast, MD

[00:18:17]

You’ve got to do two or three things at the same time really well. Not just being a really competent compassionate clinician, but also being a really cutting-edge scientist who’s completely up to date in what’s going on in increasingly complex fields. But it’s also having a life in addition to that. Increasingly over the last twenty or thirty years people have been “working to live” rather than “living to work”. And I certainly come from a generation of kamikaze physician-scientists who would walk through walls to be able to do their research. But I think that increasingly life balance is becoming an important issue. And I think it’s particularly acute for women because if you want to have a family there’s a time limit on that. And consequently recruiting and supporting careers of women physician scientists has been all the more important. Fortunately, this is one of the few places on earth where you can do that effectively. But it’s still a national and international problem because you really need to be fully trained in medicine and fully trained in research. At this point MDs who get their first grant on the average get that grant at age forty-three.

Tacey A. Rosolowski, PhD

[00:19:43]

That’s late.

Robert Bast, MD

[00:19:45]

It is. And PhDs are a couple years younger than that. But that’s late too. And basically the career path for physician-scientists would be twelve years of grade school, four years of college, four years of medical school, and if they get a PhD during medical school that’s at least three more years, sometimes more. And then usually residency training, depending on your specialty, requires anywhere from three to five years. Subspecialty training in medical oncology, for example, is another three years. Generally you still need a postdoctoral fellowship or instructorship. There’s no hard and fast rule, but in general if somebody’s going to be effective in the laboratory and be able to get their own grants, on average you have to have about five years of laboratory-based experience. You can do that by earning a PhD. You can do that by pre- and postdoctoral fellowships. But you need to be able to write important papers with mentors to establish your reputation. You need to have been in labs long enough to know how to do experiments and how to interpret them and also you need to have read enough articles and be

Interview Session: 02

Interview Date: July 24, 2014

familiar enough with the areas to be able to have ideas that are worth funding. And all of that takes about five years of laboratory time.

Tacey A. Rosolowski, PhD

[00:21:16]

Is there also a dimension of the physician scientist—because there's so much collaborative work and listening to people in other fields and being able to interact effectively with other vocabularies of science, do you find that there's a skill set or personality type that is more successful than others or that is more attracted to that career path than others?

Robert Bast, MD

[00:21:46]

There are a variety of different kinds of people who end up as physician-scientists. Increasingly there has been more team science in translation perhaps than other areas. But there certainly are people who have individual laboratories as physician scientists that are pretty insular. So, you have posed a great question, but I think it's difficult to generalize. A lot of basic scientists are excited by the possibility that their fundamental observations might help people. By and large physician-scientists are motivated in Texas parlance from the get-go in terms of wanting to see science help people and to learn from patients and their body fluids and biopsies how to make more effective treatments. So it's the Arrowsmith approach. There's a long tradition of course that goes back 100, 150 years for physician scientists in medical history. The majority of Nobel Prizes in medicine went to physician scientists until about fifty years ago. That trend has really changed. And now the majority of Nobel Prizes are awarded to PhDs working in the laboratory rather than to translational investigators.

Tacey A. Rosolowski, PhD

[00:23:28]

What created that change?

Robert Bast, MD

[00:23:28]

Well, certainly science has gotten a whole lot more exciting. And very often it's necessary to spend full time in the laboratory to understand and to develop that science. Too, the reward system has been directed toward understanding general principles and truly novel ideas rather than to work out the nuts and bolts of how you help individual people, each of whom can be quite different. Dealing with the individuality of medical practice and dealing with the generality of basic laboratory science are the challenges of translational research. Putting those two things together is the goal.

Interview Session: 02

Interview Date: July 24, 2014

One of the things we've worked out in the last five years is a course in Translational Cancer Research for the Graduate School of Biological Sciences (GSBS). That's a course that I put together and has only a few different lecturers, rather than the usual fifteen different lecturers per course, to achieve a bit more continuity. The classes include graduate students, clinical fellows, postdoctoral fellows and junior faculty. The initial lecture concerns enough tumor biology to understand the principles that underlie translation. Then we've looked at how you develop conventional drugs, how you develop targeted therapies, how you develop molecular diagnostics, and how you put molecular diagnostics and therapeutics together for personalized or precision therapy. Then we consider what academe does best, what pharma does best, what NCI does and what the FDA does and the like, hopefully to provide the nuts and bolts of how the system actually operates, and to provide a way for potential physician-scientists and clinician-investigators and translational PhDs to navigate that system going forward.

We have also established a new GSBS Clinical and Translational Sciences program with Khandan Keyomarsi and some co-conspirators in UTHHealth. Over the years and we finally managed to formalize the courses and get approval from Austin and the like for a brand-new program.

I had mentioned translational PhDs. If you look at the statistics for physician-scientists over the last thirty years, the number of docs in the United States over the last thirty years has about trebled to 900,000, mostly from immigration, because only recently have we begun to increase the number of graduates of US medical schools. But there are people from all over the world who've wanted to come to practice medicine in the United States. And because there have been a lot of hospitals that have training programs, some with medical schools, some without, it's been possible for foreign-educated physicians to get training in the US and then join our physician force.

The number of physician scientists for clinical research, for laboratory research, not just for cancer but for heart disease and neurosciences and endocrinology and the rest of medical disciplines, has been about 15,000 for the last thirty years. So, less than two percent of physicians have been involved in full-time academic research in the laboratory and in the clinic. And depending on how you count it could be down as low as 13,500 now. So physician-scientists and clinician-investigators are a shrinking or at least a barely stable labor force.

One of the realities is that we're going to need to have PhDs who want to work in translational science both as leaders and as members of groups who really understand enough medicine to recognize an unmet medical need, and enough whole-person biology to be able to function in

Interview Session: 02

Interview Date: July 24, 2014

translational science.

When I was going through medical school forty years ago at Harvard, PhDs who were earning their degrees from the medical school spent the first two years taking all of the medical school courses. Consequently, they were exposed to anatomy, histology, pathology, physiology, bacteriology, pharmacology, and more. With developments in science over the last forty years, there's so much more to learn about molecular genetics and cell biology that the curriculum has changed. But it's swung almost totally in the opposite direction, where there's almost no pathophysiology or human biology.

One of the things we're trying to do with the graduate portion of the Clinical and Translational Science program is to provide a crash course in human pathobiology. There's a new revamping of this GSBS curriculum this year which involves basically a very thorough cell biology course for the first semester to be sure everybody in the Graduate School is on the same page and has the same background. Second semester for the students who are interested in clinical and translational sciences we're going to have a pathobiology course with a month or two of pathology and normal tissue histology and organ structure. And then go through each kind of disease: heart disease, lung disease, GI disease, and the rest, talking a little bit about cancer for sure. We will provide a general idea of what can go wrong with each one of those organs, but also pick out a couple of the best examples where molecular medicine has informed more effective diagnosis or treatment in each of those areas. Hopefully, that will begin to provide some medical background. In the second year there are programs like "Translational Cancer Research" and "Bench-to-Bedside and Back" that will provide translational expertise. We are also planning a "Clinical Oncology" course where we would discuss lung, breast and colon cancer and cancers at other sites, providing a clinical description of each form of cancer as well as the molecular genotypes and phenotypes and where we are with targeted therapy at different disease sites. So hopefully in that if a PhD graduate student is interested in pursuing that we can provide some of the background for doing that. In addition, graduate students would shadow clinicians to learn how medicine is practiced and to begin to recognize unmet needs.

Tacey A. Rosolowski, PhD

[00:30:42]

One of the themes that I've been observing as I've talked to people, and this conversation that we've been having about training has addressed it, is how—people were reflecting back on strategies in Developmental Therapeutics for example and how do we approach a clinical question, how do we start to address this clinical need. There wasn't really a model. There was well, we'll just try. And then we'll go back and evaluate what worked. We'll try everything and then evaluate what worked. But then it seems that what's emerging now is much more of a

Interview Session: 02

Interview Date: July 24, 2014

formalized approach. How do we understand a model of what translational research might look like? And it sounds enormously complicated from what you're describing. And I'm wondering. Do you see it that way? I mean is there a model to be taught? Is it a style of thinking? Is it an approach that each person makes their own because of their own cluster of interests and expertise? How does that work at the training level?

Robert Bast, MD

[00:31:49]

One of the things that we're trying to accomplish with these individual courses and with the overall program for both MDs and PhDs is not only to focus on the laboratory-based problem with which they're often dealing, but also to develop a reflex to identify the path you would need to take to move that observation to help people in the clinic, and to know what the steps would be, and to anticipate with whom you'd have to work and collaborate, what you'd have to negotiate in terms of intellectual property and working with biotech or with pharma or whatever. At MD Anderson we now have the capacity thanks to the IACS [Institute for Applied Cancer Science] of being able to take a drug all the way to the clinic, if necessary. But even IACS seeks to partner at some point with pharma companies that can help facilitate drug development and to pay for clinical trials.

Tacey A. Rosolowski, PhD

[00:32:51]

I haven't heard that word before, IACS. What is that?

Robert Bast, MD

[00:32:53]

IACS is the Institute for Applied Cancer Science. When Ron and Lynda Chin were at the Farber they recruited Giulio Draetta to head the Belfer Institute. When Ron and Lynda moved here they brought the Belfer with them. It's now the IACS on the South Campus.

Tacey A. Rosolowski, PhD

[00:33:14]

Okay, I'd never heard that acronym.

Robert Bast, MD

[00:33:16]

And that means that we have the ability to develop drugs in house. A lot of it is done through outsourcing. We've got seventy pharma professionals who are developing drugs and biologicals, but most institutions don't have that capacity. Even here the IACS has a finite capacity and so I think it's very important for all investigators to understand how you get from a laboratory observation to a clinical advance and also how you actually take advantage of clinical material to

Interview Session: 02

Interview Date: July 24, 2014

study human biology.

One of the challenges is to have effective models for human disease. And this isn't just in cancer, but across the spectrum of human illness. Genetically engineered mouse models have helped and are increasingly useful, but only some of those actually mimic precisely the genetic changes that occur in humans and in human cancer. Pharma tries very hard to identify drugs that will be effective in the clinic. They're pretty good at identifying toxicities. About eighty percent of the time or more we can figure out that a drug will be toxic and not take it to the clinic. So very few drugs actually flunk out on toxicity during phase I trials.

For cancer drugs, only one in twenty drugs introduced into the clinic turns out to be approvable by FDA, if all potential indications are considered. At best, it is one in eight if only the primary indication is considered. The FDA is not to blame. If anything, the FDA has relaxed its standards a bit with some of the targeted therapies. They used to require an overall survival advantage. Now three or four months of improvement in progression-free survival, without any overall survival will get approval for one of the new targeted therapies. So I don't think that one in twenty can be blamed on the FDA. The real problem is that we don't have the preclinical models to be able to predict clinical activity, i.e., which drugs are going to work more effectively. So, developing predictive models is a huge need in translational research.

With that batting average the pharmaceutical companies are having real challenges. Every time you hear about a merger of a pharmaceutical company. That has happened a lot in the last ten years. When you merge you can lose up to a quarter of the value of both companies.

Tacey A. Rosolowski, PhD

[00:35:40]

Really.

Robert Bast, MD

[00:35:41]

Mergers are used by Pharma to acquire new drugs and capabilities, but also to cut down on the labor force. Largely because they have to invest in seven drugs to get the eighth, the drugs are priced at an outrageous level. Progress is slow and the future of the companies are uncertain. So at a time when the National Institutes of Health is suffering from the crossfire of the ideologic gridlock we've got in Washington these days, the pharmaceutical companies are also struggling. And if you actually look at the numbers, about seventy percent of all the investment in cancer research is from pharma. Much of that investment is in moving things from the lab to clinic and

Interview Session: 02

Interview Date: July 24, 2014

then developing drugs of course. And not so much on the basic side of what you need to know in order to be able to identify the targets. I think that's one of the areas where academe can help hugely and I know Ron DePinho really sees this very much the same way. Our deep understanding of cancer biology should drive our identification of targets at which we should aim. If you find the right targets, pharma is remarkably good at making molecules that would inhibit those. Some targets aren't druggable, but increasingly many are.

And so with that I think one of the things we really need to do in academe and places like MD Anderson is to understand the molecular, cellular and clinical biology of cancers, what is actually going wrong in different cancers even in the same organ or the same apparent histology, and to try to develop the combinations of drugs that you need.

It's also obvious that with targeted therapies, with a few notable exceptions like chronic myelogenous leukemia, one drug isn't going to do it. You're going to need combinations, and then the right combinations will differ from person to person. Working out the ground rules for that is obviously one of the challenges we're facing in translational medicine here and elsewhere. And I think increasingly that's going to be true for diseases other than cancer as well.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 12
A: Overview
The Moon Shots Program and a Model of Translational Research

Story Codes

A: Overview;
A: The Researcher;
C: Discovery and Success;
C: Healing, Hope, and the Promise of Research;
B: Multi-disciplinary Approaches;
C: Understanding the Institution;
D: On Research and Researchers;

Tacey A. Rosolowski, PhD

[00:38:00]

Is there a unique way? You talked earlier about how research at MD Anderson has always had this translational flavor to it. And I'm wondering if there is a unique way that MD Anderson trains people or if there's an MD Anderson model of translational research. Is there something that's unique to the culture here?

Robert Bast, MD

[00:38:29]

Well, the culture here really has evolved. I think in truth there's been much more of an emphasis on clinical research traditionally at MD Anderson. As we may have talked about in the last interview the tradition has not always had the most rigorous standards. I mentioned to you that I wrote a review article for the New England Journal on "BCG and Cancer". A large part of that was the fact that we weren't doing very carefully controlled trials at Anderson. And again the whole issue of controlling trials is really contextual. If you've got something that's dramatically effective like penicillin for pneumonia, you may not need a randomized controlled clinical trial to prove that it is useful. Similarly, with some of our targeted therapies, if you're looking at a very small subset of people and they respond dramatically and they live for two years rather than for two months, whether you really need a controlled randomized trial for that isn't clear.

For some of the combinations of conventional drugs that we were working on thirty or forty years ago, you needed randomized controlled trials to be sure that you were helping somebody. And so with that Irv Krakoff who had done a huge amount here not only to improve the infrastructure for clinical trials but also to improve the rigor of those trials and to make our

Interview Session: 02

Interview Date: July 24, 2014

institution respected nationally and internationally for the clinical research that was ongoing.

For translation, there certainly has been translation that goes back a ways in the history of MD Anderson, but it's really been in the last twenty years that we've begun to emphasize that more. And I think in fairness that's true nationally. I talked about CA125 and trying to translate a mouse model directly to the clinic. In the 1970s I don't think anybody had yet coined the term "translational research", or if they had it wasn't widely used. So that whole idea of there's a method or methods to try to move something from the lab to the clinic and back again, and there are better and worse ways to do that, had not really been thought deeply.

And so at MD Anderson we've seen more translational investigators recruited here and more investigators have been in working between the lab and the clinic. And that's really the key. Not just doing clinical empirical research, but trying to understand the mechanisms that are involved in what's going wrong in a particular person's cancer, and then developing your therapies based on that in the lab.

Tacey A. Rosolowski, PhD

[00:41:12]

I was wondering. You said over the last twenty years. What was it that was happening twenty years ago that shifted that emphasis into this?

Robert Bast, MD

[00:41:23]

Well, I think in part it was the new people who came here. Certainly something I tried to contribute to the Division of Medicine at the time was the recruitment of Gordon Mills and a number of younger investigators who have changed the culture. Most importantly, John Mendelsohn's recruitment here, a little less than twenty years ago, was very important, because John supported translational pursuits as did Margaret Kripke. They were both extremely helpful. Much of our progress depends upon whom you recruit. A number of the department chairs within medicine and surgery and others really saw the need and the importance of that.

So people like Chris Logothetis recruited Wadih Arap and Renata Pasqualini, two of our exceptional translational investigators. Hagop Kantarjian recruited John Pierre Issa. The group in neuro-oncology recruited faculty who were passionate about impacting glioblastoma based on laboratory models. But you can tick off most of the departments here that began to recruit laboratory and clinically-based investigators supported by John and Margaret and the upper administration. I think that was very important.

Interview Session: 02
Interview Date: July 24, 2014

Tacey A. Rosolowski, PhD

[00:42:53]

I'm just looking at some of the other areas to touch on.

Robert Bast, MD

[00:42:58]

I guess the other thing we might come back to—although I think this has been a really helpful conversation – is the physician-scientist program. One of the accomplishments of which I am most proud is the really outstanding young physician-scientists whom we have recruited. In the early days, these were faculty who had already been recruited to MD Anderson for whom we were able to free up eighty percent dedicated time to work in the laboratory. More than eighty percent of those individuals have earned their individual investigator grants and almost all of them have stayed in research.

Something like twenty-seven of the twenty-eight have remained in academe. And one of them who left now heads a thirty-member team at Amgen in cardiovascular research. So they have really stayed the course and continued to contribute. Also if you look at their achievements, they've published more than 2,000 peer-reviewed articles. And about fourteen percent of these articles have an impact factor greater than ten. About ten percent have an impact factor greater than five.

Our graduates have been awarded \$25 million in grants. In the last 2-3 years with Ron DePinho's and Ethan Dimitrovski's interest in physician scientists—both of course are physician-scientists - we have begun recruiting physician-scientists from outside the institution. So we now have some incredible young people like Cullen Taniguchi, who's going to be joining us. It took us a while to get CPRIT to get back in business and to help augment his recruitment package. Cullen is absolutely amazing. He graduated summa cum laude from Occidental, then was a Rhodes Scholar and completed an MD/PhD at Harvard Medical School, and trained in radiation oncology at Stanford. He has already published a number of high impact papers, and is poised and destined to make real and unique contributions to radiation oncology. He's trying to understand radiation damage to normal organs like the intestine and has already discovered ways to keep the intestine from being damaged so that you can control the local growth of pancreatic cancers using radiation therapy. He has studied hypoxia at a very fundamental level, but is also focused on improving treatment of patients with pancreatic cancer.

Tacey A. Rosolowski, PhD

[00:46:13]

Interview Session: 02

Interview Date: July 24, 2014

Talk to me about what happened with Dr. DePinho's arrival. What did that add, change to the course of translational that had already been well established here under John Mendelsohn?

Robert Bast, MD

[00:46:25]

Well, I think John in addition to having been very supportive of recruitments of translational investigators had also begun the Center's program as well. A number of those Centers, including the Institute for Personalized Cancer Therapy, are very translationally oriented. Some of them are more basic. But there's a translational component of most of the Center. The Centers further helped improve the translational environment.

Ron's Moon Shots project has stimulated some of the most direct translation we've had. It's been a real game changer in terms of applying what we know in the laboratory to actually helping people in a finite period of time. We're already beginning to see some of the outcomes of that, for example in the breast and ovarian moon shot project for high grade serous ovarian cancer patients and for the triple-negative breast cancer patients. They're doing genome sequencing but also particularly looking at BRCA1 and BRCA2 even if there's not a strong family history. And they're actually identifying a number of people who have mutations of those genes who you might not have predicted from families.

They've also started to treat patients with ovarian cancer much more consistently. Anil Sood has convinced all 26 different doctors within GYN oncology to join in a common protocol for new ovarian cancer patients. Every ovarian cancer patient now gets a laparoscopy, rather than an open operation as a first step. Using a rigorous method that involves two or even three docs they score the estimated difficulty of completely removing all of the cancer up front.

I don't think we talked about this last time, but it turns out that GYN oncologists believed for decades that if you could take out most of the cancer but not all you really benefit the patient. And that belief for ovarian cancer differs from the management of almost every other solid tumor.

Even in ovarian cancer, when you can get all the cancer out patients will do the best with subsequent chemotherapy. If you're starting from trying to get rid of microscopic cells with your chemotherapy, those are the patients you cure, or at least live a lot longer. Only about a third of the patients can be completely cytoreduced if you don't select up front.

Interview Session: 02

Interview Date: July 24, 2014

With this laparoscopic algorithm, surgeons can identify women whose cancers are most likely to be completely resectable up front. It turns out more than ninety percent of cancers can be completely removed by this technique. Those patients who are predicted not to be resectable are given three or more cycles of chemotherapy and then resected. More than eighty percent of those patients are now resectable. So instead of a 30% of patients with complete resections, you have more than 80%.

Whether this will translate into the same sort of survival advantages that is seen in the one third of unselected patients who were completely resected up front still remains to be seen. With the new protocol, the investigators are getting tissue in the bank from patients before they're treated in 120 cases over the last fourteen or fifteen months. We're also going to have that as a group which we can use as a control to see if we do other things differently.

One of the things we're working on at the moment is not completely finalized. As part of the Moon Shot and the Ovarian SPORE we are beginning to do "second look" operations with laparoscopy for each patient as well after chemotherapy. Twenty five years ago gynecologic surgeons did that a lot, when we were developing intraperitoneal therapy or early immunotherapy. After initial surgery and chemotherapy, another operation was performed to see if there's any cancer left. With the most sensitive imaging and with normal CA125s, still about half the patients will have tiny microscopic bits of tumor on the surface of the intestines or abdominal wall if you look for it.

The problem was for many years there just wasn't anything to do that was different and that would have made a difference in survival. So in routine practice, people have gotten away from that. But I think now with some of the work that I may have described last week with getting rid of dormant cells and the rest, we're planning protocols for the new SPORE to try to use anti-autophagic therapy to get rid of the dormant cells. And so if we do second looks and they're positive then patients would end up on a protocol of that, probably hydroxychloroquine as a starter, and then perhaps more sophisticated work as the preclinical studies develop.

Patients with negative "second looks" would be offered immunotherapy so that there would be a treatment based on the second look operation for everyone who participated in the new trail. We can compare how well each group does to the 120 patients who've been pretty rigorously treated in a very uniform way. But that kind of organization just never existed at MD Anderson, or likely at any other Cancer Center.

Interview Session: 02

Interview Date: July 24, 2014

The Moon Shot has created the hope and expectation for funding for these sorts of research protocols. The Moon Shot program has catalyzed our faculty to imagine new approaches and challenged them to get things together to do research that would improve survival within the next five to ten years, rather than someday. That is the sense of direction and urgency that Ron has brought to the institution.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 13
B: Overview
The Moon Shots Program; Genomic Medicine

Story Codes

B: Critical Perspectives on MD Anderson;
A: Overview;
A: Definitions, Explanations, Translations;
C: Healing, Hope, and the Promise of Research;
C: Discovery and Success;

Tacey A. Rosolowski, PhD

[00:52:38]

What's been controversial about the Moon Shots? What's been really successful and what have been the lessons learned in these past years? Or things that maybe were perfectly designed immediately but now you learned something, you can go forward.

Robert Bast, MD

[00:52:59]

I think there's huge skepticism on the land that you can intentionally do much to accelerate progress. The National Cancer Act of 1979, declared war on cancer, which it wasn't. Over the last four decades it is a half full or half empty track record depending on your outlook. Clearly things are much, much better for many cancer patients now than they were in 1979 [1971]. Adding adjuvant chemotherapy to surgery and radiation therapy has now cured seventy percent of all breast care patients. I wish it were 100 percent. Particularly for patients with node-positive disease, the statistics are dramatically better now. In testicular cancer ten or twenty percent of people used to survive. Now it's greater than ninety percent. And similarly things like chronic myelogenous leukemia, which was chronic but was lethal. Now people are living up to a decade and longer by taking a pill a day and most are probably cured.

So there's been huge progress. The trouble is it's never enough and it's never fast enough from a patient's perspective. So there are relatively few people who believe that additional investment will bring more rapid progress. So you've got to overcome that skepticism. As the Moon Shots mature, positive outcomes will help to change that attitude.

I think one of the concerns, which was not a fair criticism, was that Moon Shots were being built

Interview Session: 02

Interview Date: July 24, 2014

on the backs of the clinicians who had to work harder. As I understand it, almost all the moon shot money has come from philanthropy. So that really was a misperception. Preventing misperceptions like that is always difficult.

The Moon Shots have not been as controversial as some of the other initiatives in asking clinicians to work harder to make up for perceived financial downturns that were not as severe as predicted. Any miscalculations were not so much from Ron, but ultimately he's the president. You have to take responsibility for all of the institution. From the business side there also seemed to be the belief that we could increase the targets for clinicians and that they would gladly contribute to that year in, year out, without changing the infrastructure, without motivating people, and without explaining why all this is really important and having them really buy into greater sustained effort. This may be one of the causes for some of the concerns that have been raised.

I guess my own view on this is that things are dramatically better over the last six months. I'm a medical oncologist and a perpetual optimist, but I think there's evidence for that. Ron has really chosen wisely in people like Ethan Dmitrovsky, who is caring, transparent, fair, honest, and I think is being increasingly perceived that way as Provost, which is a huge help. Certainly Helen Piwnica-Worms is marvelous. She's just another great recruit as is George Wilding.

Getting Tom Buchholz to head the clinics was another wise choice. He is a person who's hugely respected, and also really understands and appreciates and values the academic side of MD Anderson. We are not just a clinical operation. The clinical enterprise is hugely important, but it's not the only reason we're here. Choosing Tom to lead that has been another great move. So I think we're headed toward smoother waters with any amount of luck. It is important though to really empower our people in the trenches and also to have them believe that they're being heard. We now have people in place who are doing that. I think that's going to be very helpful.

Tacey A. Rosolowski, PhD

[00:57:30]

Yeah. And the institution has certainly gone through some rough waters. Thinking too with the moon shots, I mean I pick up statements here, statements there. But it sounded as though this concentrated organization focused on specific cancers purified or intensified what people were already doing. And then putting a very short time limit on it added additional pressure. And I'm wondering how has implementing that gone. And what are some lessons learned? What are some things that have worked really well? Where are some things that have emerged that needed a slightly different organization to go forward and create this pattern again?

Interview Session: 02

Interview Date: July 24, 2014

Robert Bast, MD

[00:58:19]

Well, again I'm most familiar with the breast and ovarian work, which I think has gone very extremely well. I think it's gone well because people like Anil Sood have really taken the time. Karen Lu, much to her credit, as the new head for GYN oncology has been very supportive of this through retreats to get consensus. People raise their concerns, to talk that through, to try to figure out, develop even better protocols in the process, and really to get buy-in from everybody, so they're just not being told to do something but they really want to do it because they've bought into it and it's their project. I think that's good practice in general. But I think it's been particularly effective there.

Tacey A. Rosolowski, PhD

[00:59:05]

What were some concerns that people were raising?

Robert Bast, MD

[00:59:10]

I wasn't part of those retreats, so I can't tell you directly. My guess is that we had a lot of particularly more established faculty members who want to do their own thing for patient care. Often that has been really good patient care, but if you want to do research I think you can have both. You can have really good patient care and also be consistent practices, provided that you attain consensus, and also be willing to make exceptions for individual patients to best meet their needs. There needs to be a mechanism for making those exceptions, if there's a really good reason. And so I think those things worked out well.

As I have a particular interest in diagnostics, one there are projects in some of the other Moon Shots, where people haven't really thought through the steps that you need to validate some of the diagnostic predictive biomarkers. For some of the other disease sites there are a number of biomarker projects that were simply up there on the board that were suggested and are good ideas but really thinking through all the steps that you'd need to do to get there hasn't been accomplished yet. In part we've talked about the possibility of getting a coach or resident expert in diagnostics for the moon shots and for the institution. That's still a work in progress.

Tacey A. Rosolowski, PhD

[01:00:41]

It sounds as though the Moon Shots have created an opportunity to really look at a number of different patient care practices as well as research practices and see well, how do they mesh, where are we missing certain steps. Is that correct?

Interview Session: 02

Interview Date: July 24, 2014

Robert Bast, MD

[01:00:59]

It is, although I think that each one of the different disease sites has approached that in a little different way and I don't think there's been a consistent approach either suggested or taken. The plans and progress for each Moon Shot have been presented repeatedly to inside and outside groups for input to be sure that what was being done made sense. The Moon Shots have and should be driven in large part by the research opportunities that were out there on the therapeutic side. For example in the Breast and Ovarian Moon Shot, PARP inhibitors have been effective not only for women who have germline mutations of BRCA1 and BRCA2, but for a much larger group of people whose cancers for other reasons have problems repairing DNA. And so there's been a large emphasis on identifying the drugs that you need to mix with PARP inhibitors to be even more effective.

So that part of the agenda has been driven by the opportunities that are out there. Same thing for ibrutinib, an inhibitor of Bruton's tyrosine kinase, for the Chronic Lymphocytic Leukemia Moon Shot. That is the drug of the year, if not of the decade, for CLL. A lot of the work is being driven by that opportunity.

Tacey A. Rosolowski, PhD

[01:02:33]

One thing that—a word that has come up over and over is genomic. And I'm curious. How do you define genomic medicine and then place it within the context of translational research and then personalized care?

Robert Bast, MD

[01:02:54]

I guess in its narrowest sense genomics has often meant deep sequencing of DNA. Increasingly most investigators also worry about expression of coding and non-coding RNA and the epigenetic regulation of DNA and histones, as well as proteomics - both defined signaling proteomics that Gordon Mills does and mass spec proteomics. So it's really putting together what's known at multiple levels of regulation within the cell what's different about a cancer cell from a particular patient from normal cells. For personalized therapy, investigators are using these omic technologies to identify drugs that would target either those abnormal molecules or something downstream of those molecules and/or the other pathways that are causing resistance to inhibiting that particular molecule.

The challenge, in my view, is to get the clinical side of this together. Certainly you can do a

Interview Session: 02

Interview Date: July 24, 2014

pretty good job of identifying targets with cell lines and xenografts, but again to make sure that that actually works in patients the way you hope it will, and also to get the biopsies from patients before, during and after treatment so you can actually sort out why they're becoming resistant to a drug is extremely important. Again we're working on methods to do that and ways to pay for it. But that's I think been a lot of the challenge. If we're going to make decisions that affect patient care based on molecular changes in their cancers, laboratory testing must be done under CLIA-approved conditions. Again this is very expensive and a lot of work to develop these assays under CLIA-approved conditions, even when you can cover the expense.

Tacey A. Rosolowski, PhD

[01:04:55]

What is it that makes them so challenging and expensive?

Robert Bast, MD

[01:05:00]

The CLIA law requires that you do the tests at a dedicated facility, that you measure standards before, during, and after the assays, and that you show the rigor of the tests in terms of day-to-day variation and within-assay variations. For some of these new tests, that's a lot of work, and that costs time, effort and large sums of money. This means very high charges for new tests. Whether a new predictive test will be reimbursed is always a question. MD Anderson has set up committees to look at what's ready for prime time and what's not, as well as ways to fund some of these tests that are needed. But it's a work in progress. It's a huge work in progress. This really falls very heavily on our Pathology Division and which is very busy in the first place. So it's been an extra stress I think for them. Stan Hamilton has done an extraordinary job as leader of this division.

Tacey A. Rosolowski, PhD

[01:06:12]

So it sounds to me—what's the relationship between—because there's an Institute of Genomic Medicine now. And what's the relationship between that institute and your office? And do you oversee those grants?

Robert Bast, MD

[01:06:27]

The Genomic Institute, as I understand it, is one of the Centers that sets its own agenda for sequencing. Sequencing across MD Anderson involves many different groups. Helen Piwnicka-Worms has brought together faculty from North and South Campus to see how much gene sequencing we needed institutionally, how much we should have here and how much we should outsource, determining how many more sequencers we really need. It's obviously an important question. Through the core grant we have gene sequencing for the individual investigators who

Interview Session: 02

Interview Date: July 24, 2014

might not fit into the Genome Institute or the IPCT or routine patient care in the CLIA facility.

Tacey A. Rosolowski, PhD

[01:07:36]

When I was speaking with John Mendelsohn he was talking about the challenge of collaborating with people across the institution to enroll their patients in protocols that take periodic sequences to profile a tumor over the course of an individual disease. Would the ideal be for information acquisition to do as much gene sequencing as possible? I mean is that the ideal? Or is there some other model that's in mind that would really work to create a bank of information for the institution?

Robert Bast, MD

[01:08:13]

Well, as I'm sure John mentioned, until gene sequencing gets even less expensive, there's a balancing act between how deeply you sequence and what you can afford. Like computers, with every passing year, sequencing the whole genome has become less and less expensive, but this is still in the thousands of dollars, I believe. It will necessary to find ways to pay for gene sequencing, perhaps from philanthropy in the short run, but certainly from third parties in the long run. The most important genes to sequence are those for which we have drugs. And that's been the strategy so far, to try to develop a panel of genes that would match up with the kinds of drugs that we're testing in the clinic to find which patients would be candidates for treatment.

There are other groups like Foundation Medicine, a private sector group in the Boston area, who will perform whole genome sequencing or will sequence ten times as many genes as most of these panels involve. Clearly it will be crucial to be able to save and to share the data that's obtained not only within the institution but to develop ways to do that that protect patient confidentiality across institutions, because particularly for these rarer abnormalities you've simply got to. Even here where we see 30,000 new patients a year we're not going to see enough of every subset to be able to make conclusions about how reliable these correlations really are.

So one of the things Steve Friend was talking about at AACR this year was the importance of figuring out ways to share data. And it is a very important need for the scientific community at the moment. And perhaps even ways to share data before it's published. That's even more of a challenge.

Tacey A. Rosolowski, PhD

[01:10:20]

Interesting.

Interview Session: 02

Interview Date: July 24, 2014

Robert Bast, MD

[01:10:24]

This is driven by the fact that if you look in different databases for what's abnormal in adenocarcinoma of the lung you won't always get consensus and particularly won't get consensus if you look for prognostic subgroups within ovarian cancer or breast cancer or whatever. And in part this is related to the fact that you've got 26,000 genes on a gene expression array and you've got 50 patients or 100 patients. And just by chance alone you can find something that will fit your data. Different groups doing the same experiment will find different genes that fit their data. So the way to get around that is to have much larger databases and analyze those using similar techniques.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 14
B: Building the Institution
Working with Pharma; Supporting Innovation; Attracting Philanthropic Dollars

Story Codes

B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
B: Obstacles, Challenges;
B: Industry Partnerships;
B: Beyond the Institution;
D: On Pharmaceutical Companies and Industry;
B: Philanthropy, Fundraising, Donations, Volunteers;

Tacey A. Rosolowski, PhD

[01:11:20]

You've touched a number of times on this important collaboration between academic medical centers and pharmaceutical companies. But I know that you've worked through this office to create a number of partnerships. And I wonder if you would talk about those. There's EMD Serono, Incorporated and—

Robert Bast, MD

[01:11:41]

Sure. And actually with John Mendelsohn our office coordinated partnerships with a number of different companies. Ultimately, there were a half a dozen strategic alliances with pharmaceutical companies that included master agreements to resolve IP issues ahead of time so that contracts and protocols could proceed promptly.

Tacey A. Rosolowski, PhD

[01:12:24]

And by IP you mean intellectual property.

Robert Bast, MD

[01:12:27]

Yes. Exactly. We also resolved how we could use the biopsy or surgical specimens from the clinical trials for other research here. And we had to work out different agreements with each different company about how to do that. But established agreements you could then have a contract that did not require any additional legal review or at least minimal legal review. Any

Interview Session: 02

Interview Date: July 24, 2014

delay in getting the contract up and running, was avoided. Strategic alliances had been created with AstraZeneca Pharmaceuticals, Glaxo Smith Kline, Exelixis, Roche and EMD Serono to accelerate the development and evaluation of new drugs. Each strategic alliance involved a master contract that settled legal issues for up to 10 years, multiple investigator initiated projects to support pre-clinical and clinical research, as well as semi-annual meetings between the faculty at M.D. Anderson and the scientists and clinical investigators.

Some companies, like AstraZeneca, actually contributed \$1 million a year or so to projects by MD Anderson faculty that were chosen by mutual agreement. Overall, our office have obtained \$34 million in supplementary funding from Pharma. With Astra-Zeneca, 10 fold growth in annual contracts was observed after initiation of the Strategic Alliance.

A number of interesting things came out of those Strategic Alliances over the years. We had one administrative experiment with AstraZeneca to see whether we could start a first-in-human trial without delay. There can be months of delay between when a drug is available to be tested in patients after approval of the trial by the FDA and actually getting it into the first patient. In the Strategic Alliance with Astra-Zeneca, we sat down with Razelle Kurzrock when she was here and with representatives of AZ and tried to figure out if we could completely eliminate the delay in initiating a trial by overcoming administrative barriers.

Tacey A. Rosolowski, PhD

[01:13:50]

And that was successful?

Robert Bast, MD

[01:13:54]

It was. It was also really interesting because we found that although the processes with AstraZeneca for getting drugs up and running and the steps at MD Anderson were different, the process was the same and in that both organizations tended to do things sequentially. Until the IRB had signed off a clinical protocol, our financial people wouldn't take a look at it, because it might change. If both IRB and financial review were performed in parallel you could go back and adjust, saving substantial time.

Similarly, AstraZeneca tended to wait for the IND to actually be signed off by the FDA before they shipped drug from the UK, sometimes requiring days to a week to clear customs. There's nothing improper about having the drug waiting AZ facilities in Delaware and shipping overnight to Houston. So by processing in parallel and communicating more effectively we treated a patient on a Phase I trial within 48 hours—

Interview Session: 02
Interview Date: July 24, 2014

Tacey A. Rosolowski, PhD

[01:14:49]

Oh my gosh.

Robert Bast, MD

[01:14:50]

—of the IND being signed off. We were trying for 24 but—

Tacey A. Rosolowski, PhD

[01:14:55]

And IND? I'm sorry.

Robert Bast, MD

[01:14:57]

Investigational new drug.

Tacey A. Rosolowski, PhD

[01:15:00]

Investigational.

Robert Bast, MD

[01:15:01]

That's the license to actually start to do clinical trials.

Tacey A. Rosolowski, PhD

[01:15:05]

That's interesting. It's really a communication about workflow and just institutional processes.

Robert Bast, MD

[01:15:11]

And having a champion in each place, if something got stuck, to get it unstuck. And one of the things Aman Buzdar has been working on over the last four or five years is try to make that much more universal and not just for one time only but try to remove some of these other barriers. And [Waun] Ki Hong [Oral History Interview], who'd been a vice provost for clinical research for a year or so, again spent a lot of that time trying to get that process accelerated.

There are other glitches, different departments within MD Anderson tack on different levels of administrative costs to pay their departmental employees, which drives the pharmaceutical companies crazy. We're trying to make that more uniform as well. It's a controversial area, but

Interview Session: 02

Interview Date: July 24, 2014

that's the sort of logistic problem that Ki and several of the other people have been working on.

Tacey A. Rosolowski, PhD

[01:16:00]

So was this a pilot project to see how it worked?

Robert Bast, MD

[01:16:08]

Yes, this was a pilot project. We actually published it in the Journal of Clinical Oncology with Razelle Kurzrock as an example for how to do that. With Ron's arrival, he appropriately realized that this is a huge area that deserved its own office and identified Ferran Prat, who's doing a great job coordinating our strategic alliances with pharma. We're still helping whenever we can from a distance, but Ferran is now the champion of the pharmaceutical alliances.

Tacey A. Rosolowski, PhD

[01:16:50]

I've been amazed at the themes that have come up with people talking about working with pharmaceutical companies in the '60s or '70s. A world of difference with now.

Robert Bast, MD

[01:17:02]

I guess there are a lot of observations that came out of the work that we did with different companies. First of all each pharmaceutical company has its own culture. Each company is relatively unstable in its own way. There is a tremendous amount of shifting of individuals at least in the mid levels from one company to another. Certainly at MD Anderson we have people join and leave our faculty, but in academe it's at a much slower pace and a much smaller fraction of people.

Tacey A. Rosolowski, PhD

[01:17:37]

Does that mean that you may have a champion who's then gone after a certain period of time?

Robert Bast, MD

[01:17:41]

Yes, but the other experience we had was to have a champion in one company become our champion in the next company. So it works both ways.

Tacey A. Rosolowski, PhD

[01:17:50]

Interesting.

Interview Session: 02

Interview Date: July 24, 2014

Robert Bast, MD

[01:17:51]

Transparency and secrecy varied greatly between companies. Some companies would tell you what they're planning to do for the next five years and you could even find it on their Web site. Others are very secretive about current and future plans. Again it seems to be an individual cultural characteristic. I think another issue is that oncology is only one of many areas that are being developed within companies. Decisions about supporting trials of cardiovascular or neurologic drugs may result in downregulating or even eliminating oncology programs. Merck has had a very strong pipeline. They were developing a world network in oncology, and turned on a dime and eliminated it about two years ago.

Tacey A. Rosolowski, PhD

[01:18:37]

And why was that?

Robert Bast, MD

[01:18:39]

Apparently related to their view of what the future of oncology medicine was for Merck. So I don't know all the details. But that's again the kind of behavior that drives academics crazy. But it is a fact.

Tacey A. Rosolowski, PhD

[01:18:59]

Yeah, it's a reality. Let's see. I'm just looking at some other names, things that haven't come up. I have a name written down here. I actually have a question mark after it. So I better ask this question. The Office of Technology Discovery. Is that something within—what is that?

Robert Bast, MD

[01:19:19]

That's our technology transfer office, and that's in charge of patenting and licensing all of the inventions at MD Anderson. Let me back up. Within our office Oli Wenker, Stan Tucker, and Luetta Allen had substantial experience in technology development. Working collaboratively and in parallel with our technology transfer office, they had established an Office of Technology Discovery to encourage disclosure of new inventions and to counsel faculty members in developing drugs and markers that could be patented or licensed. Some 1497 faculty contacts over 7 years facilitated more than 200 invention disclosure reports and the formation of 81 project teams. A Technology Review Committee was established that awarded grants totaling \$1.97 million to support 32 projects averaging \$61,594 to improve in-house inventions with focused development plans and timelines. From these projects, 9 patents were filed, 10 inventions were licensed, 5 startup companies were formed, and \$6.1 million was returned to

Interview Session: 02

Interview Date: July 24, 2014

MDACC from license and royalty income, SBIRs and other grants. Over the last two or three years since Ron's arrival, the IACS as covered drug development really well so we have another mechanism for developing new ideas.

Tacey A. Rosolowski, PhD

[01:21:16]

I wanted to ask you too about the Commonwealth Foundation grant. Could you tell me about that? What the scope was.

Robert Bast, MD

[01:21:26]

The Goodwin family from Richmond created the Virginia Commonwealth Foundation. Bill and Alice Goodwin and their family have provided some very generous grants to MD Anderson that have made a real difference. Our office had coordinated the preparation of those grants and the administration of them as well. The Marcus Foundation and Bernie Marcus had provided grants for clinical research as well. Maurie Markman had initially administered those but with Maurie's departure we had also helped coordinate them. And again they've been very generous and have permitted us to do clinical trials that we wouldn't otherwise have been able to do. Over the years, we have helped to obtain and facilitated the distribution of \$30 million in philanthropy for our faculty, with another \$25 million gift in negotiation.

Tacey A. Rosolowski, PhD

[01:22:19]

Was there a special interest in particular kinds of clinical trials that were supported?

Robert Bast, MD

[01:22:21]

Both groups gave us pretty broad mandates—they wanted innovative trials that wouldn't have otherwise been done. I think both foundations ultimately had pretty similar desires. In terms of exactly what was done that was pretty much left up to our best judgment.

Tacey A. Rosolowski, PhD

[01:22:40]

And what was supported through those grants?

Robert Bast, MD

[01:22:42]

Renata Pasqualini and Wadih Arap had a peptide that had an address label that would stick just to the blood vessels serving the tumor rather than to other blood vessels in the body. And they were able to actually deliver those to prostate cancer cells in the bone marrow and show that they

Interview Session: 02

Interview Date: July 24, 2014

could get there, killing prostate cancer cells

Certainly there were other projects where people were using inhibitors that would affect two different components of tumor blood vessels. The smart bombs project which was with the neurosurgeons and neurooncologists where they had viruses that were injected right into brain tumors. And it would infect brain tumors selectively because of the genetic wiring of the brain tumor, and not the normal brain tissue. They've actually gotten a remarkably high response rate to those. Plus people are going strong a couple years later you never would have expected.

So there was some really innovative research but can perhaps come up with a more complete list. Those were some of the highlights.

Tacey A. Rosolowski, PhD

[01:24:15]

Now why wouldn't that research have been supported in other ways?

Robert Bast, MD

[01:24:20]

The tumor seeking peptides and viral therapy would be too much of a financial risk for pharma. In some cases the drug company would be willing to provide a drug for a clinical trial against different components of blood vessels but the development of these novel peptides that just stick to the inside of blood vessels might be something that biotech companies would eventually pick up on. But we've been through a time as you probably are aware over the last five to ten years when even venture capitalists have become risk-averse and where they've really wanted to derisk projects before they would take them on. And also had incredible expectations of twentyfold return on investment within the next two years. And the sorts of things that work in—novel approaches to cancer research don't usually work that way. Certainly the "smart bombs" for brain tumors did have funding from NCI and from the Brain SPORE, but it's never enough, particularly for clinical trials. Perhaps aware that NCI funding has been flat for ten years. That means that NCI funding has lost twenty percent of its value through inflation. In addition with the craziness of the last year we lost five percent more with sequestration overnight. So that funding is down about twenty-five percent. And so for a SPORE project if there are four projects it's about \$200,000 a year. When you start doing operations for brain tumors and brain tumor research, even the clinical costs of that becomes prohibitive. So the foundations have been able to cover some of the clinical costs, the SPOREs some of the preclinical activities. And so without all of those components you just couldn't do the trials.

Tacey A. Rosolowski, PhD

Interview Session: 02

Interview Date: July 24, 2014

[01:26:21]

What proportion—how important are philanthropic dollars to this office?

Robert Bast, MD

[01:26:28]

Most of the \$8 million for the MRP seed money for P01s and SPOREs that I mentioned ultimately comes from philanthropy through the institution.

Tacey A. Rosolowski, PhD

[01:26:39]

Really? Wow. Now is this something that you work with development on getting?

Robert Bast, MD

[01:26:44]

We've worked with development certainly on these two grants that we just mentioned. The University Cancer Fund includes institutional funds for which our office applies for the MRPs and the rest. But I think the ultimate source of those funds is philanthropy.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 15
B: Building the Institution
The Office of Translational Research: Growth Areas

Story Codes

B: Education;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;
C: Discovery and Success;
D: Technology and R&D;
C: Mentoring;
C: Leadership;

[01:26:44]+

Robert Bast, MD

Getting back, there's one other area that we didn't cover in terms of career development. And that was the clinician investigators. This is the flip side of the physician scientist program. And that's a program for clinician-investigators. We've three times renewed a K12 grant from NCI to rain senior fellow and junior faculty members. Instead of being eighty percent in the laboratory doing clinically relevant research as physician scientists would be, clinician investigators spend seventy-five percent of their time doing clinical research. The endpoint here is to develop their own investigator-initiated clinical trials that ask a question so that no matter how the trial turns out, positive or negative, you get information that you need to plan the next trial, a so-called hypothesis-driven trial. Twenty-three scholars that have been part of this program.

The K12 grand that funds them is from the National Cancer Institute, but that only pays about seventy-five K of the physician's salaries. The difference from the actual salary, depending on your subspecialty, is huge, so that the institution really has picked up the difference to make seventy-five percent dedicated time for each of the clinicians who've been part of this.

Tacey A. Rosolowski, PhD

[01:28:33]

How long has that program been in existence?

Robert Bast, MD

[01:28:36]

Again, just about the duration of our office, fourteen or fifteen years. We've got five clinician-

Interview Session: 02

Interview Date: July 24, 2014

investigators currently in our program and eighteen graduates. Ninety-four percent have stayed in academe and one of the “drop outs” is actually founding a Phase I clinical trials unit for Sarah Cannon, which technically is a private group, but will be doing clinical trials.

And most of these investigators have remained at MD Anderson. Seven are still assistant professors, and six have been promoted to associate professor, and four to professor. Seven are currently pursuing degrees and three have obtained either a master’s or a PhD. Altogether they’ve published more than 370 peer-reviewed publications and again with reasonable impact factors.

Graduates have obtained \$28 million in contract funding, but I think most importantly have had really productive careers in clinical research studying cancers at several different disease sites. The program has included medical, surgical and radiation oncologists. Clinician-investigators are crucial to translational science.

Tacey A. Rosolowski, PhD

[01:30:04]

And I noticed I mean both among this group and the other training program you were talking about earlier a pretty high percentage stay at MD Anderson. Is that a surprise to you?

Robert Bast, MD

[01:30:16]

No, it’s a great place.

Tacey A. Rosolowski, PhD

[01:30:19]

Yeah. Well, and I’m curious. It certainly maximizes the investment.

Robert Bast, MD

[01:30:23]

Increasingly too we have seen more senior people recruited away. When I first came to MD Anderson twenty years ago that didn’t happen nearly so often. But increasingly we’ve got really great people from MD Anderson who have become leaders at other institutions. You think of Roy Herbst and Lajos Pusztai are at Yale where Roy heads translational research and Lajos heads their breast cancer program. Fadlo Khuri is at Emory where he is currently head of their oncology department. Wadih Arap and Renata Pasqualini are now leaders at the New Mexico Cancer Center. Jean Pierre Issa now heads the Fels institute in Philadelphia. So we’ve got a number of people who have gone to other institutions in a good way, not because they were disgruntled with MD Anderson, but just because they had an opportunity to really lead

Interview Session: 02

Interview Date: July 24, 2014

something important at other outstanding institutions.

Tacey A. Rosolowski, PhD

[01:31:31]

What about the leadership piece? Because you've talked about setting in place the planes of professional information that are needed simply to practice at the bench or to practice in the clinic and make the connections between the two. But what about emerging into a leadership role in the field? To what degree is this office involved in helping facilitate that in these careers?

Robert Bast, MD

[01:32:02]

There are several answers. We just submitted a K12 grant renewal and one of the initiatives we've identified moving forward is to provide formal leadership training for the trainees. MD Anderson has two appropriate programs in which scholars can participate. We're also developing what we have called a "Master Class" for the clinician investigators in the K12 program where senior leaders in clinical investigation at MD Anderson and elsewhere are invited to share their secrets and their wisdom about how they have made career decisions, deal with pharmaceutical companies, choose projects, how they got to where they are, and what problems they've overcome, and what they found most difficult or least difficult in all that. So we're trying to do that as well.

Scientific leadership is also important. For both physician scientists and clinician investigators the oversight committee has an annual committee meeting to review progress. I've found over the years that really wasn't enough. So every four months or so I get together with each scholar individually and provide a second layer of mentorship. We have individual mentors both laboratory and clinical for each scholar. But it is important for someone to make sure that the physician scientists and clinician investigators are actually meeting with their mentors, that they're getting their dedicated time and have clear goals and timelines for papers and grants.

We've also helped to get small committees together to review grant applications or revisions to grant applications. I think that's helped that as well. But increasingly in terms of mentorship we've become much more proactive in advocating for people as potential leaders to be sure that they meet other people in their chosen field. Also that we propose them for awards as soon as it's appropriate, both for career development awards outside of the institution and actually. With Liz Travis [oral history interview] we've established an institutional committee to propose people for awards more aggressively. That's actually paid off remarkably well. Also working with Helen Piwnica-Worms we've got another committee coordinated by Nancy Hubener in my office to try to increase our batting average in getting really prestigious career development awards for our faculty. Also working with Ki, and others, we have been successful in getting

Interview Session: 02

Interview Date: July 24, 2014

MD Anderson candidates elected to the American Society for Clinical Investigation, the American Association of Physicians and to fellowship in the AAAS.

Tacey A. Rosolowski, PhD

[01:35:28]

What are next steps for this office? I mean I know you're hanging on with the immediate steps. You've got a lot going on right now. But I mean in terms of planning for—

Robert Bast, MD

[01:35:40]

Well, I think in terms of growth areas, clearly to keep pace with emerging technologies is going to be crucial to maintain state-of-the-art shared resources. New gene editing techniques for example have been developed with CRISPR-Cas9. One of our problems this week is try to figure out how to invest in new technologies most efficiently and most effectively.

So there's an ongoing process not just in keeping our current shared resources well managed but actually trying to identify what is the next frontier. And does shared instrumentation make sense?

And also Alan McClelland has recently just taken on doing this with the Moon Shot platforms. Obviously each of the platforms does its own thing. But he's providing a second layer of review if you will to be sure that there aren't needs for the platforms that aren't being met within the moon shots program. So that's part of where we're headed.

In terms of our educational programs—we want to develop the Clinical and Translational Science program in the GSBS. And we need to be sure that both the graduate and post-graduate programs are optimal. But we're going to have to have I think a substantial role in that. We also need to put together a new "Clinical Oncology" course for the second year as well.

Interview Session: 02
Interview Date: July 24, 2014

Chapter 16

A: A View on Career and Accomplishments

Thoughts about Training as a Physician-Scientist; A Review of Good Colleagues

Story Codes

A: Personal Background;
A: Career and Accomplishments;
A: Professional Path;

Tacey A. Rosolowski, PhD

[01:38:47]

When you look back at your own career and formation as a physician scientist, I mean what do you wish you had had?

Robert Bast, MD

[01:39:00]

First of all I think as a physician scientist I've been really fortunate because I had access to training very early on. I think I mentioned it started in high school and through college. I had some great mentors. Like Hal Dvorak when I took two years out from medical school and Herb Rapp and Bert Zbar as a postdoc.

And also the opportunities really to do things that I really enjoyed doing and were hopefully productive as well for the last forty-five years or so. So in terms of things that I really missed, I think that that's probably a pretty short list.

I think it would have been good to have had more rigorous training earlier on I think in scientific methodology. I think I learned about hypotheses relatively late. And if I'd had a formal MD/PhD I might have learned about those a little bit earlier. As it was, I think my two years out for pathology and cellular immunology at MGH and my three years as a postdoc at NCI were remarkably productive times. And I'm not sure that I would have had the opportunities if I'd done a routine MD/PhD with it.

But I think one of the things that would have been helpful would have been to have really been trained a little more in how really basic scientists think. And that would have really been useful.

Interview Session: 02

Interview Date: July 24, 2014

I guess too one of the challenges has been to balance science and administration and clinical medicine. I care for patients every week. It basically keeps me grounded and reminds me every week why I'm doing research and administration to make progress as rapidly as possible. I really enjoy caring for patients. So it's something I've done for my whole career, although in a relatively limited role. I've depended upon physicians' assistants like Lee Daly at Duke and nurse clinicians like Mary Hernandez here at MD Anderson, who are just wonderful individuals and who have permitted me to practice without malpracticing. With their collaboration it's been possible to maintain a medical practice. And certainly some of the things that I value the most are the interactions with patients that I've had over the years.

I think the other—and certainly administratively we created the Office of Translational Research to meet the needs that we've seen around the institution. We've been fortunate to be given support to do that from John Mendelsohn and Margaret Kripke and more recently by Ron DePinho and Ethan Demitrovsky. I believe that we've been able to return a lot of value to the institution in the process. But all of that obviously takes some time and attention.

In the Office of Translational Research, I've been blessed by people like Jene Reinartz, Ruby Robinson and Nancy Hubener and so many others who have contributed to our office over the years. All have been really well trained and have been able to work independently. I've been able to work as a coach sharing a vision and suggesting things from time to time and being a counselor to be sure that things are on track. So we've got a very mature office who really are professionals, which has been a tremendous help.

But having said that, the amount of time that I've spent in research has varied hugely. And I think it really has only been in the last five years or so that I've religiously spent a lot more time working with my laboratory.

I've been blessed over the years with a few really outstanding postdoctoral fellows who have made a difference. Technically I guess Ian Jacobs was more of a young visiting investigator than a postdoctoral fellow in our lab at Duke. But he's gone on to do that UKCTOCS trial that we talked about before and is going to be president of the University of New South Wales in Sydney starting in January, after being a most successful provost at Manchester. So again he's just gone to a stellar career.

Interview Session: 02

Interview Date: July 24, 2014

Andy Berchuck was a junior faculty member at Duke, and Andy has gone on to become head of GYN oncology and president of the Society of Gynecologic Oncology and the rest, and again really an exceptional person.

And Ahmed Ahmed is a recent postdoctoral fellow that worked with our lab who's a professor at Oxford now. So we've had some really exceptional people. I guess I've mentored a huge number of clinical fellows over the years and have had some great clinical fellows I've worked with both at Duke and MD Anderson.

But I think I guess one semiregret is that we haven't had even more really outstanding postdoctoral fellows. Paying more attention to my laboratory, might have aided and abetted that.

Tacey A. Rosolowski, PhD

[01:44:41]

Is there anything else you'd like to add at this point?

Robert Bast, MD

[01:44:43]

No, I don't think so. I think we covered almost all the things our office has done today.

Tacey A. Rosolowski, PhD

[01:44:49]

Good. Well, we have a few minutes left, but we can certainly close off at this point and then hopefully we can schedule another time for additional questions.

Robert Bast, MD

[01:44:59]

Great. That would be super. At least after that next grant gets out.

Tacey A. Rosolowski, PhD

[01:45:05]

Well, thank you very much for your time this morning, Dr. Bast. I really appreciate it.

Robert Bast, MD

[01:45:08]

You're welcome.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 02

Interview Date: July 24, 2014

[01:45:10]

And I'm turning off the recorder at 10:57.

Robert Bast, MD

Interview Session Three: 18 December 2014

Chapter 00C **Interview Identifier**

Robert Bast, MD

[00:00:00]

Sounds good.

Tacey A. Rosolowski, PhD

[00:00:01]

All right.

Tacey A. Rosolowski, PhD

[00:00:03]

All right, so I've pushed record. And the counter is moving. And today is December 18th, 2014. The time is 2:27. And I'm Tacey Ann Rosolowski. And today I'm on the eighth floor of Pickens Tower in the Office of Translational Research, interviewing Robert C. Bast, who's the vice president of that office. And this is our third session together. So, thanks again for making time for this interview.

Robert Bast, MD

[00:00:32]

Tacey, it's a pleasure.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 17

B: Building the Institution

The Office of Translational Research: The Multi-disciplinary Research Program

Story Codes

B: Building/Transforming the Institution;

B: Multi-disciplinary Approaches;

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

C: The Institution and Finances;

C: Research, Care, and Education;

Robert Bast, MD

[00:00:32]

We—I think you had mentioned a few minutes ago the MRP [Multi-disciplinary Research Programs].

Tacey A. Rosolowski, PhD

[00:00:36]

Yes.

Robert Bast, MD

[00:00:36]

We developed the Multi-disciplinary Research Programs project some ten years ago, to support investigators at MD Anderson who wanted to come together to prepare a successful application for a multi-investigator award, either at the National Cancer Institute [NCI], or more recently at CPRIT [Cancer Prevention and Research Institute of Texas]. The NCI multi-investigator awards include the Specialized Programs of Research Excellence (SPOREs) and the Program Project grants (P01s); and the CPRIT awards a Multi-Investigator Research Award (MIRA). In each of these awards, there are three or more projects that are much like individual investigator R01 grants, but they fit together, and there's synergy between investigators working together on a similar project with a single theme. In addition, there are often Cores for administration, pathology, or statistics. These tend to be good sized grants in the range of \$10M over 5 years, although they've been capped in recent years, and even reduced with some of the cutbacks in Washington. Given the size of our faculty and the fact that we're deep and broad in a number of areas, we've competed particularly well for multi-investigator grants.

Interview Session: 03

Interview Date: December 18, 2014

The Multi-disciplinary Research Project program was developed to provide \$250,000 to groups of investigators who wanted to come together over a two-and-one-half-year timeframe, to develop the preliminary data, establish firm collaborations, and publish joint papers that would support a successful application. Overall, we've invested about \$8.7 million in MRPs to investigators at MD Anderson and we've received about \$136 million in awards. So that's about a sixteen-to-one return on investment. In recent years, the pay lines have decreased, particularly from NCI awards. Since 2007, it's still been a ten-to-one return on investment. With MRP support, we've competed successfully for five SPOREs and nine P01s, and then a number of individual investigator grants that have been funded as spinoffs from those.

So I think it's been a successful project, and it's really been a tribute to our investigators. If you give them a chance to develop new ideas and to—then to work together, they're very good at it.

Tacey A. Rosolowski, PhD

[00:03:31]

So what kind of support does the program offer to make these groups of investigators so successful at winning this—these awards?

Robert Bast, MD

[00:03:39]

Simply offering the opportunity to have in-house funding for these grants brings people together. We've developed a Multidisciplinary Research Awards Committee (MRAC) which includes faculty from a variety of different disciplines and with diverse interests that provides peer review for these awards. The idea is to try to identify a group of investigators and a group of projects with ideas that are sufficiently promising, that they stand a high chance of receiving federal or state peer-reviewed funding at the end of two and a half years or less. Our office has also helped investigators develop Specialized Programs of Research Excellence, or SPORE awards. We provide common boilerplate about institutional facilities and instrumentation and the rest. We also proactively coach faculty and staff on how to submit these, and how to package them, and provide them with previous grants that investigators have submitted from here, so they've got a model to work from. Al [Wai-Kwan Alfred] Yung and more recently, Jeff [Jeffrey N.] Myers have been the co-chairs of the MRAC committee, which judges the MRPs. We generally meet with people who are thinking of applying for MRPs. I've served on many if not all of the SPORE internal advisory boards and a lot of the internal P01 advisory boards, as well. There are usually are both internal advisor and external advisors who meet with each SPORE or P01 each year.

Tacey A. Rosolowski, PhD

[00:05:10]

Interview Session: 03

Interview Date: December 18, 2014

Have you felt that what the funding groups are looking for has changed substantially in, say, the last seven to ten years? And so, investigators are kind of having to regroup a bit?

Robert Bast, MD

[00:05:24]

In terms of these multi-investigator awards, not so much. Although I think the SPOREs have become more insistent on being able to take a project from the laboratory to the clinic within a five-year timeframe, or from the clinic and back in a five-year timeframe. That's always been a stipulation for the awards, but I think it's been taken much more seriously in recent years. With the pay lines as low as they are, less than ten percent of these multi-investigator awards are being funded and the number of SPOREs has actually been reduced from about sixty or sixty-five to fifty-five, the competition has become much more intense. As these are judged by study sections of mortals, sometimes the judgments are much more idiosyncratic, not just for the multi-investigator awards but for individual investigator awards. Our peer-review system has generally worked best when there were twenty-to-thirty percent of the grants funded. At that point, the individual opinions and tastes don't weigh quite so heavily. But to get one of these grants funded, you'd have to have two or three peer-reviewed reviewers, or peer reviewers, who would agree that this is something that ought to be funded. And getting that kind of agreement across the scientific community is sometimes difficult.

Tacey A. Rosolowski, PhD

[00:06:50]

Mm-hmm. Now I've spoken with some individuals in the course of the interviews who've reflected on the fact that funding is not only less available, but the funding that is available has become more conservative.

Robert Bast, MD

[00:07:01]

Mm-hmm.

Tacey A. Rosolowski, PhD

[00:07:01]

Would you agree with that?

Robert Bast, MD

[00:07:03]

Yes, certainly as a gross generalization I think that that is true. Having all the preliminary data in place and doing incremental rather than really truly innovative high-risk approaches has been rewarded. Although, I guess in fairness to point out CPRIT has high-risk, high-reward grants, where they have been willing to fund some projects that are not incremental. And I think that's

Interview Session: 03

Interview Date: December 18, 2014

very positive. There are also the R21 grants at NCI which are intended to be more innovative. And I think, to some extent, they are.

Tacey A. Rosolowski, PhD

[00:07:46]

Mm-hmm. Now what is this office's philosophy or approach to the range of investigations that might be available. That—you know, as they span conservative to more innovative, more risky, do you have a stance on that?

Robert Bast, MD

[00:08:04]

Not really. We provide advice when asked to about all kinds of projects. At least in terms of our internal peer review for seed funding I don't think that they have really discouraged innovation, quite the opposite. When you're talking about a pilot project, you've got two and a half years to find out whether this is going to work out or not. So the time frame has been really helpful. One of the funding mechanisms that's needed across the institution is to have grants specifically designed for discovery. We have IRG [Institutional Research Grant] grants for individual investigators—\$50,000 to get an individual investigator—toward an individual investigator application. But we don't have any funding source that would encourage people to look for synthetic lethality between genes. To some extent, some of the SPOREs and some of the Moon Shot programs have provided funding for that. But in terms of just competitive, pre-peer-review grants, that's one of the gaps that could well be filled.

Tacey A. Rosolowski, PhD

[00:09:21]

Mm-hmm. Is that something that this office has been working on, or thinking about to address?

Robert Bast, MD

[00:09:26]

This is certainly something that we've been mentioning at (laughs)—to the people who make decisions about where our money should be invested. One of the things we're currently working on is this strategic plan, as you know, across the institution. And there's a—one niche of that is translational research. And one of the things we're certainly discussing in that context is how we can encourage true innovation and discovery, and what the mechanisms could be that would be most effective to support that among our faculty.

Tacey A. Rosolowski, PhD

[00:10:05]

Thank you.

Making Cancer History®

Interview Session: 03

Interview Date: December 18, 2014

Robert Bast, MD

[00:10:07]

Yeah.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 18

B: Building the Institution

As Head of the Division of Cancer Medicine: Building MD Anderson's Academic Programs and Research Focus

Story Codes

A: The Administrator;

B: Institutional Mission and Values;

B: Building/Transforming the Institution;

B: Education;

C: Understanding the Institution;

B: MD Anderson History;

B: Growth and/or Change;

B: MD Anderson Culture;

B: Institutional Mission and Values;

Tacey A. Rosolowski, PhD

[00:10:08]

Now, as I mentioned before we started the recorder, we did not talk in our previous sessions about the time that you spent between 1994 and 2000 as head of the Division of Cancer Medicine, and also as chief of the Division of Medical Oncology. So I was—

Robert Bast, MD

[00:10:27]

Actually, Experimental Therapeutics.

Tacey A. Rosolowski, PhD

[00:10:29]

Oh, I'm sorry.

Robert Bast, MD

[00:10:29]

Chair of Experimental Therapeutics.

Tacey A. Rosolowski, PhD

[00:10:32]

Oh, okay, wow. I'm sorry. I don't know where I got that. (laughter) Thank you.

Interview Session: 03

Interview Date: December 18, 2014

Robert Bast, MD

[00:10:36]

There is a very small Division of Medical Oncology at UT Health's [University of Texas Health] Science Center.

Tacey A. Rosolowski, PhD

[00:10:43]

Oh, okay.

[00:10:43]

Robert Bast, MD

At that time, they did not have a competing activity with MD Anderson. The position and title at UT Health went along with being head of the Division of Medicine at MD Anderson.

Tacey A. Rosolowski, PhD

[00:10:55]

Okay, so that's where that came from.

Robert Bast, MD

[00:10:57]

Yeah.

[00:10:57]

Tacey A. Rosolowski, PhD

It wasn't pure fantasy on my part. (laughter)

Robert Bast, MD

[00:10:59]

No, no. That's—it—

Tacey A. Rosolowski, PhD

[00:11:01]

Thank you.

Robert Bast, MD

[00:11:01]

[inaudible]

Tacey A. Rosolowski, PhD

[00:11:02]

Interview Session: 03

Interview Date: December 18, 2014

I was worried. All right. Well, we didn't have an opportunity to talk about that particular period of time.

Robert Bast, MD

[00:11:07]

Okay.

Tacey A. Rosolowski, PhD

[00:11:08]

So I was wondering if you could maybe tell me some of the highlights of what you felt you accomplished during the time when you were head of the Division of Cancer Medicine.

Robert Bast, MD

[00:11:18]

Surely. Well, we talked before about being at Duke and heading up the Cancer Center there.

Robert Bast, MD

[00:11:27]

And I'd been co-chair of their division of hematology and oncology and headed the Cancer Center there for about seven years. And it was a matrix center, unlike MD Anderson, which is a free-standing cancer center. There we had done a lot of the things that you can do with a matrix center. We'd increased the philanthropy several-fold, although it was very modest by MD Anderson standards. We had put up new buildings, increased the membership, and increased peer-reviewed funding. We'd also built a section for experimental oncology that my colleague, Bob [Robert M.] Bell, had headed, so that we could actually recruit individuals directly to Duke for cancer-related activities, which is not the case at many centers that are matrix centers. Having accomplished about as much as I knew how to in that context, when there was an opportunity to lead a division at arguably the world's leading cancer center, that was a very good reason to move to Houston, and decision that I've never regretted.

At that time there was just one Division of Medicine. Subsequently, in 2000 or 2001, the Division of Medicine was split into a Division of Internal Medicine Specialties and a Division of Cancer Medicine. Over the previous six years, the Division of Medicine had grown substantially. At one time, the whole of Internal Medicine Specialties was just one department in the Division of Medicine. Obviously, it had much more room to grow, and reorganizing that was exactly the right thing to do.

Tacey A. Rosolowski, PhD

[00:13:14]

Why was that? I mean, it's always a question of why these big reorganizations are undertaken.

Interview Session: 03

Interview Date: December 18, 2014

[00:13:20]

Robert Bast, MD

The Division of Medicine had just grown substantially and Internal Medicine Specialties had a distinct role of providing general medical and supportive care for cancer patients, whereas the Division of Cancer Medicine provided chemotherapy and developed new treatments for different forms of cancer. I don't have the exact numbers of faculty members, but the Division of Medicine had grown by more than a third. The unit of organization within MD Anderson is the department and the Department of Internal Medicine had sections of cardiology, pulmonary, infectious disease and others. If you want to get a real leader to head those sections it's really tough, because sections don't have any formal status. By creating a Division of Internal Medicine Specialties, you could appoint department chairs for each of these sub-specialties and each department would include a reasonable number of faculty. For example, we must have more than a dozen infectious-disease people and that is within the range of at least some other departments at MD Anderson.

As the faculty grew institutionally, it made a lot of sense to split off a new division. Bob [Robert F.] Gagel became the first division head of Internal Medicine Specialties. The new Cancer Medicine still had at least ten departments, which I think have grown to sixteen. So we've had a general increase in all of our clinical divisions, but it's been particularly true for those two.

As we had discussed earlier, one of the things that we accomplished over the six years with the division was to build their educational programs, particularly the medical oncology fellowship program. When I first moved here, we had some really fine young people in training, but very few of them had actually gone to medical school in the United States. Many had come from South America or from Europe or from Asia, and had been twice trained in medicine, and then came here for their oncology fellowships. Almost none of our fellows had published a paper before they got here. I don't think we had had any MD PhDs apply to the program. We tried to change that. Marty [Martin N.] Raber [Oral History Interview] and then Rick [Richard] Pazdur had worked directly in leading the fellowship program. After my arrival, as we discussed previously, we had written to all the chairs of medicine at all of the medical schools and explained that life was different, and that our medical oncology fellowship program was a major priority at MD Anderson. We asked that they counsel their most promising graduates of their medical residency programs to consider MD Anderson as the place to get their oncology training.

Tacey A. Rosolowski, PhD

[00:16:24]

Interview Session: 03

Interview Date: December 18, 2014

So this was kind of part of that period when MD Anderson was really trying to build up its reputation as having a strong research component. Because I know many people have said, over and over, that there was this—this was considered to be a real gap.

[00:16:40]

Robert Bast, MD

Yes, I think that's true. And also, many fine young people came here to train, but the majority of graduates at that time wanted to go into community practice. We've really missed an opportunity, not only here but at most academic institutions, to encourage people who do want to practice in the community to maintain a commitment to research lifelong. Probably ninety-eight percent of the oncologists are in the community rather than at medical centers like this. All have been through academic training programs both in internal medicine and medical oncology. Many of them have felt that they weren't respected by academe, because they wanted to go into practice in the community. That's a huge mistake, for starters.

But we've missed the opportunity to really convince them that it's—that it's not just enough to go out and earn a living and care for people, but you've got to have a commitment to research, in clinical research, in the community, and that important—by supporting—by participating in trials that you can do in the community, and by referring patients to centers, at least for a portion of their care, so that they can participate in clinical trials. For whatever reason, we've not succeeded in getting that kind of commitment. And there certainly are some people in the community who do clinical research, but it's a minority. And it should be the majority.

Tacey A. Rosolowski, PhD

[00:18:43]

What is the obstacle there? Is it ignorance? What is going on?

Robert Bast, MD

[00:18:49]

I'm sure it's multi-factorial. I don't have a comprehensive list of factors and I'm sure that it also hasn't been studied very thoroughly.

[00:19:01]

Robert Bast, MD

[00:19:02]

It is difficult to find interviews and data regarding why physicians go into practice as opposed to stick with academic pursuits. On the positive side, some physicians really just enjoy taking care of patients, and, conversely, don't enjoy writing papers or applying for grants. Very often these days—it's been true for a long time—physicians take out huge loans for undergraduate school or for medical school. And as a resident or intern you don't get a salary that's adequate to pay those back. By the time many oncologists finish a fellowship program, they have not only a

Interview Session: 03

Interview Date: December 18, 2014

spouse but kids. Being able to support your family has become a real priority, understandably enough. Salaries in the community are at least twice what we can pay in academe. MD Anderson is something like seventy-fifth percentile in academic institutions, so we pay people pretty well by academic standards. But that is not nearly what a busy oncologist can make in the community.

In terms of having time for research in community practice, often medical oncologists will join practices where there's already a large patient base and where they need to see twenty or twenty-five patients every day with one afternoon off a week, in order to be able to earn the salary that they've been promised or they have a contract where their ultimate compensation really depends upon how many patients they see. With a busy practice, the amount of time left for research is limited. In academic institutions like MD Anderson, we subsidize research quite heavily. Almost all of the people who are investigators on clinical trials have their institutional salary paid, and not paid by the contracts for the trials that they're conducting. Also, we often don't have enough support for research nurses and data managers. That does largely come from contracts and rarely—and at least occasionally from grants. A substantial chunk of the true costs of doing clinical trials are subsidized either directly or indirectly by the institution. And in many practices in the community, there's not the same level of financial commitment for infrastructure support to conduct clinical trials.

In community practice there's not a lot of time to sit and talk with patients about their alternatives for clinical trials, let alone write a clinical trial. And—but also that there isn't the research nurses and the data managers paid by the practice to actually do interact with patients. There are some practices and groups like US Oncology, which do some research for sure.

[00:22:18]

Tacey A. Rosolowski, PhD

I'm sorry, what was the name of that?

Robert Bast, MD

[00:22:20]

US Oncology. It's a group of about 1,000 oncologists, mostly medical spread across the nation. Texas Oncology is the local branch of US Oncology. From the numbers I have heard, they enter no more than five or six thousand patients on clinical trials nationally. Last year, MD Anderson put at least 12,000 to 14,000 patients on trial with a much smaller number of medical oncologists on the faculty. So, by and large, it's been difficult to do research in the community.

The other thing is, increasingly, the kind of research that you can do in the community has really

Interview Session: 03

Interview Date: December 18, 2014

been late-stage phase II trials and phase III trials. If you need intensive monitoring or if you need biopsies, or any kind of monitoring of heart function or other thing on an ongoing basis, that's been really difficult to accommodate in the community. We're really the only kind of organization that could do that.

Over the six years when I led the Division of Medicine, the medical fellowship program evolved. In the final year, the majority of the thirteen graduates took academic jobs. Most had published papers before they arrived at MD Anderson for training. A third to one-half were MD PhDs. Importantly, we were beginning to compete for the best fellows with the Dana Farber Cancer Institute, Memorial Sloan Kettering, Johns Hopkins and other major institutions. Like Ki [Waun Ki] Hong [Oral History Interview], of course, who became head of the Division of Cancer Medicine after that, built on the start that we had made and took it a couple of levels higher, doing a wonderful job with the fellowship program.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 19

B: MD Anderson Culture

The Culture of Research at MD Anderson

Story Codes

- A: The Administrator;
- B: Institutional Mission and Values;
- B: Building/Transforming the Institution;
- B: Education;
- B: MD Anderson History;
- B: Growth and/or Change;
- B: MD Anderson Culture;
- B: Institutional Mission and Values;
- C: The Institution and Finances;

Robert Bast, MD

[00:22:20]

We recruited some exceptional faculty into the Division of Medicine during those years. Between 1994 and 2000, more than 60 new faculty members were recruited, including physicians, physician-scientists and scientists from Harvard, Tufts, Memorial Sloan-Kettering, Johns Hopkins, NCI, U.T. Southwestern, UCSF and the Burnham Institute. Gordon [B.] Mills is one of the people who we had recruited. With Chris Logothetis, we had recruited Wadih Arap and Renata Pasqualini. With Hagop Kantarjian, we recruited Jean Pierre Issa from Johns Hopkins. With Dick Champlin, we recruited Jeff Moldrem who has developed truly novel immunotherapies. Bob Wolf was recruited from Duke and Bob has had a great impact on the fellowship program and on our clinical effort in pancreatic cancer research. In addition, had recruited some very effective chairs of different departments, although a number of them were inherited from Irv [Irwin] Krakoff's administration, where they had been heads of sections. Just before Irv stepped down they converted those to department chairs. One of the critical decisions a year or two into my six years here was to decide whether to let all of those appointments stand. And, ultimately, I thought that most of them had been really chosen wisely, and did that.

Many things went quite well in the Division of Medicine. Between 1994 and 2000, the number of new patients cared for by members of the Division increased 46% to more than 10,000 per year. Grants and contracts increased 77% from \$26 to \$46 million per year. Our goals included: 1) orienting the division to succeed financially in meeting the challenges of managed care, 2)

Interview Session: 03

Interview Date: December 18, 2014

supporting reorganization of clinical care from a purely departmental structure to multidisciplinary disease sites, 3) enhancing both thematic and disease oriented clinical and translational research, and 4) integrating the division through more effective communication.

One of the challenges, though, with an organization like MD Anderson is that you really have a culture that's been developed over the last forty or fifty years, and a number of people have spent their entire careers here for that time. So, changing that culture is a challenge. In retrospect, I should have spent a lot more time studying the MD Anderson culture in my early days here, to understand the expectations of the faculty. I came to appreciate that those weren't necessarily the expectations that I'd run into at Harvard or Duke. Although there's much in common between the three institutions, there are some real differences as well. One of the things that's true about the Farber and Johns Hopkins and MD Anderson is that patient care is an ultimate priority, and that people at all three of those institutions believe fervently in putting patients first, and doing everything they possibly can do improve their lives. And so, that's a common value.

But in terms of academics, I suspect that Ron [Ronald] DePinho may have made similar observations in recent years, the things that drive people at the Farber may not necessarily be exactly the same things that motivate people here. Clinical investigation is a lot more important at MD Anderson. Holding multiple grants in each laboratory for basic and translational research is a necessity at Harvard or Duke, but not necessarily an expectation here. Aspiration to higher impact papers has become a cultural value at MD Anderson, but was not necessarily the norm two decades ago. Harder science and high impact publications has long been a given in the Harvard medical community. Under John Mendelsohn's leadership, there's been tremendous evolution in translational science, and I think our office has helped with that. John's efforts have, however, been critical.

I think, too, that building up more and more physician-scientists has been important. And again, we've had physician-scientists at MD Anderson for decades, but that community has grown in recent years.

Tacey A. Rosolowski, PhD

[00:28:12]

But I—

Robert Bast, MD

[00:28:13]

In the Division of Medicine we had recruited and supported physician-scientists. As VP for Translational Research I've had the opportunity to mentor physician-scientists across the institution. Ron [DePinho [Oral History Interview]] and Ethan [Dimitrovsky [Oral History Interview]] have supported the program with a new position each year and have encouraged a national search for the very most promising scholars. With Khandan Keyomarsi, and others, as

Interview Session: 03

Interview Date: December 18, 2014

we had discussed, we've been trying to develop PhDs who have enough understanding of human biology and of clinical medicine to be effective in translational research.

Tacey A. Rosolowski, PhD

[00:29:20]

Right. Dr. Bast, I wonder if I could close the office door—

Robert Bast, MD

[00:29:24]

Sure.

Tacey A. Rosolowski, PhD

[00:29:24]

—in case we have background noise from the hall?

Robert Bast, MD

[00:29:27]

Sure.

Tacey A. Rosolowski, PhD

[00:29:27]

All right, thank you. And I'm also really interested and glad that you raised the issue of culture. And you had anticipated a question, because I was wondering, you know, the ways in which your activities as head of the division had kind of prepared the soil, in a certain way, for more work in that area as—when you—as you took on the vice-president role of Translational Research. And I'm wondering if you could comment a little bit more on kind of how you negotiated the culture at MD Anderson? And, you know, now, in retrospect, what were you coping with, culturally speaking, when you arrived? And, maybe, what might you have done differently, and how have things changed?

Robert Bast, MD

[00:30:15]

Yes. I had watched other heads of medicine at other institutions try to centralize some of the activities of evaluating faculty members, set agendas for research and raise expectations for clinical productivity. MD Anderson has had some pretty independent leaders at the departmental level. Having made the decision that the section heads in Irv Krakoff's administration would become chairs, to have worked through them more effectively would have been a whole lot more successful. That approach is not without its challenges as all of the chairs are adults with well-developed ways of thinking and coping. To change the overall culture, working through leaders who have created that culture or been raised in it is a particular challenge.

Interview Session: 03

Interview Date: December 18, 2014

John Mendelsohn's arrival was an important event at MD Anderson. David Hohn was VP for Clinical Affairs at that time. In contrast to John, David felt that we were about to go under with managed care, and that we really should batten down the hatches, get more efficient, become more cost-conscious, and contract in size. With David's inspiration, I tried some methods to see if people could, at least on paper, earn back a portion of their salary in terms of the amount of work that they were doing. We never got down to RVUs [relative value units], but basically, in terms of the patient care and developing metrics, that turned out to be about 180 degrees from what most MD Anderson faculty were expecting at the time. What David perceived at the time was that we were in much more trouble than we really were and John, ultimately, decided to grow his way out of whatever financial challenges we were facing. And it worked. At the time, the faculty was hardly ready to think about getting more efficient, or metricizing their activities. Even today there is substantial push back.

If in fact our revenues do decrease by twenty-five percent over the next five years—which is one of the things that concerns everyone at present—we're going to be faced with an external reality with which we will have to cope. What we needed to do then was to convince the faculty that there really was a problem, that our existence really was being threatened, and that we had to change our ways if we were going to survive. And as it turns out, fifteen years ago that really wasn't the case. My guess is, this time it probably is.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 20

A: The Administrator

Accomplishments as Division Head and Observations about Leadership and Mentoring

Story Codes

A: The Administrator;

A: The Leader;

A: The Mentor;

A: Career and Accomplishments;

B: MD Anderson Culture;

C: Leadership;

C: Mentoring;

C: Giving Recognition;

Tacey A. Rosolowski, PhD

[00:35:11]

Other accomplishments that you feel you were able to move ahead with during your time as division head?

Robert Bast, MD

[00:35:17]

I think we also managed to begin to bring people together across departmental lines, in terms of learning about clinical research protocols and as VP for Translational Research our office has tried to extend that to communication across divisions. In the last three years, I think we've seen a number of other leaders really step up and start to organize things across the different disciplines, across the different departments and Cancer Center programs. While that's something that we began, it's been further developed by [Waun] Ki [Hong]. I think one of the things that I most appreciate Ki's leadership in Cancer Medicine is his ability to negotiate some of the same challenges that I faced. Ki really created a sense of appreciation for all of the administrators and all of the staff and he developed formal mechanisms for recognizing their contributions. Ki put a lot of energy into that, which was really well-founded. And I think it helped morale hugely, not just in the faculty, but in the entire organization.

Ki really had grown up with MD Anderson, and knew all of the department chairs and most of the faculty from way back. The fact that he had gained the trust of the faculty with whom he worked helped a lot. Also, I think Ki had the ability both to be feared and loved. That's another lesson that I learned:

Interview Session: 03

Interview Date: December 18, 2014

you've got to be feared at least a little. (laughs)

Tacey A. Rosolowski, PhD

[00:37:20]

Interesting. Hm. Is there anything else that you'd like to say about that period as division head, and how it kind of prepared the ground for the work you've been doing as VP of Translational?

Robert Bast, MD

[00:37:37]

First of all, I actually enjoyed working with the faculty and staff in the division and I've enjoyed working with translational research more directly. I was, and am, really inspired by the faculty members, nurses and staff who contributed to patient care, as well as to research. In leukemia, Hagop [M.] Kantarjian has been an exceptional leader, having inspired his department to produce more than a thousand papers and to become the leading clinical research and patient care center in leukemia worldwide. He has mentored and developed the careers of dozens of faculty including Jorge Cortes and Susan O'Brien. It's just an exceptional group of physicians. And I think one of the things that I've come more and more to appreciate over the last couple of decades is just what an extraordinary group of faculty and staff are here at MD Anderson.

Before I led the Division of Medicine, I don't think I appreciated how much time you could spend on conflict resolution. (laughter) Some people are really good at that. I'm not sure I'm one of those, although I'm probably better than I used to be.

Tacey A. Rosolowski, PhD

[00:38:55]

Why did you enjoy being division head so much?

Robert Bast, MD

[00:38:58]

Well, I think it gave you a window on just some really amazing people. There certainly were many cases where we really did help solve individual problems or provide support that people needed. One of the challenges of being division head, at least the way it was structured fifteen years ago, was that there wasn't much wiggle room in terms of authority over how you spent money. It wasn't delegated. I'm not sure it's delegated yet, but by and large, in terms of really helping individual programs or individual investigators, the funds really weren't held at the divisional level to the extent that you could help them financially. Obviously, there were other ways you could help. And I think you explore those other mechanisms as an administrator with advice, recommendations, promotion and the like.

During that six years, I really did enjoy mentoring when given the opportunity. And that's

Interview Session: 03

Interview Date: December 18, 2014

certainly something that has continued during the last fifteen years in the, certainly, the Physician-Scientist Program and the K12 Clinician Investigator Program. I'm particularly gratified when department chairs or whomever drop by to see what I think about the problems that they are solving. Over the last few years, I hope that I have helped some younger faculty and staff to be even more effective as well.

Tacey A. Rosolowski, PhD

[00:40:26]

What do you think—what is your particular approach to mentoring? I mean what is it that you bring to that relationship?

Robert Bast, MD

[00:40:36]

Having made a fair number of mistakes over the years, I can sometimes share firsthand experience. In Boston faculty were most respected for what they discovered and thought and wrote. Respect for your brilliance and accomplishments was really the currency of the realm. At MD Anderson and most other places on the planet, it's really relationships with other people that are valued your mutual trust and appreciation for each other's contributions. And those contributions may or may not end up in Nature, Science, or Cell, but can also be contributions to patient care or to translation.

You had asked about mentorship, you need to find out where people want to go, what's really motivating them, and what it will take to fund their real destination. In terms of the Physician Scientist Program, some nuts-and-bolts things that are important. The program provides eighty percent-dedicated time for research. And it's really important that that happens and that clinical responsibilities are not expanded. So one of the mentoring functions is to be sure that mentees are getting the time that they need and aren't being required to do one more clinic each week or another month on service. I think that has helped.

Another important part of mentoring is to be sure that mentees really have game plans that are both long-term and short-term. They need to be thinking concretely about their next paper and about what the specific aims are going to be on their next grant. You also have to seek balances. You've got to be sure that people are enjoying life, they're enjoying their families and doing the things the things that they really need to do.

There are a number of people at MD Anderson who've traditionally worked very hard, and put in very long days. Certainly Ki Hong was one of the best examples of that. And I think if you're going to succeed in medicine, that's still important. When I was going through school and thereafter, many of us had a kamikaze approach that would walk through walls to develop a new idea, to create a new concept, or to help care for a patient. You'd come in whenever and

Interview Session: 03

Interview Date: December 18, 2014

wherever it was needed. Overall, I think that that's changed, although I'm still inspired by some of our fellows at LBJ [Lyndon B. Johnson Hospital Oncology Service]. About five years, one of our fellows came in to do an extra clinic the week before he was supposed to go on vacation to see his patients ahead of time so that they didn't have to be seen by somebody else who didn't understand what was going on.

So there are still some physicians who really are fanatics about practicing medicine, which is great. In general, many younger people these days want to have some sort of balance in their life. There probably are some young physicians who live to work rather than work to live, but the extremes are not as extreme as they used to be. If we are going to reduce cancer to less of a problem sometime soon, it's going to take a lot of effort and some sacrifice to accomplish that, but everybody's got to set their own balance in terms of how they contribute to that goal.

Tacey A. Rosolowski, PhD

[00:44:47]

It's kind of like that advice that you get on an airplane, to, you know, put your air mask on before you help the person next to you. (laughter) You know, if you don't take care of yourself, you're not going to be able to make headway for the benefit of other people.

Robert Bast, MD

[00:44:58]

Yes that's important.

Tacey A. Rosolowski, PhD

[00:45:02]

Is there anything else that you'd like to say about what you were able to achieve as division head, or anything else?

Robert Bast, MD

[00:45:13]

[phone rings] The—let's see. This may be one of those things that I need to give some thought to and fill in some—fill in some gaps. Excuse me.

Tacey A. Rosolowski, PhD

[00:45:22]

Sure, shall I pause the recorder?

Robert Bast, MD

[00:45:23]

Yeah, why don't you pause it. Oh, it looks like somebody got that.

Making Cancer History®

Interview Session: 03

Interview Date: December 18, 2014

Tacey A. Rosolowski, PhD

[00:45:26]

Okay.

Robert Bast, MD

[00:45:26]

It's good. But I may—I may need to give that some thought.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 21

B: Key MD Anderson Figures

John Mendelsohn and Ronald DePinho

Story Codes

C: Portraits;

C: Leadership;

Tacey A. Rosolowski, PhD

[00:45:31]

Mm-hmm, okay, that's fine. I'm trying to see what else I've got on the list here. I was going to ask—you've talked some about John Mendelsohn, and about Ronald DePinho. And I wanted to ask you about, you know, these kind of big leaders at MD Anderson, and what you feel the mark—the mark that they've made. And I know that Dr. DePinho is fairly early in his presidency, but, you know, maybe observations on what you see evolving at MD Anderson under his leadership.

Robert Bast, MD

[00:46:08]

Sure, I'll give it a shot anyway. As I've mentioned to you before, John Mendelsohn is one of my heroes. I think that he really is a superb leader. Over the fifteen or so years that he was president, John grew MD Anderson into the footprint that exists today. He accomplished that in some pretty turbulent times. About five years after he arrived at MD Anderson, as you recall, the Enron crisis occurred. I think you know that he was genuinely innocent of any wrongdoing in that, but he had served on their Board and survived as head of MD Anderson. Over the years, John and Ann were able to bring together the Houston community and had exceptional rapport with the Board of Visitors. He had a vision for actually growing the institution in size, and growing MD Anderson out of whatever dangers we faced financially.

John was not only a champion for research, he had deep respect for patient care and realized that our clinical enterprise must be strong. He understood the importance of surgery as an important front door for the institution. He recruited strong clinicians and expanded translational research. If he had a challenge, it was in recruiting basic scientists. At least until recently, we had no members of the National Academy. John had tried diligently to recruit National Academy members here, but was not able to accomplish that. We had only a couple of members of the IOM [Institute of Medicine].

With Ron's arrival, our representation in the NAS and IOM have changed pretty dramatically.

Interview Session: 03

Interview Date: December 18, 2014

Jim [James P.] Allison, a member of the NAS, was recruited early on and is very likely to win a Nobel Prize. Ron became a member of the NAS and Lynda the IOM. Craig Jordan, another NAS member was recruited last year. Gigi Lozano, Helen Piwnicka-Wurms and David Piwnicka-Wurms have been elected to the IOM (NAM). Academy membership certainly isn't the only factor by which a cancer center should be judged. But if we're really going to be the best cancer center on the planet, we need respected basic scientists. With Ron's leadership we're evolving in that direction.

A number of other investigators have been recruited at a more junior level. Andy Futreal has enhanced our expertise in genomics and has been amazingly collaborative. John Tainer is a World-class structural biologist. Giulio Draetta has led the IACS, providing the ability to develop drugs in house.

I think, also, that despite some of the controversy and grief in the first year or two, recently Ron has recruited several exceptional lieutenants —with Ethan Dimitrovsky, as Provost, who's a person of incredible integrity, Helen Piwnicka-Wurms, as Vice Provost for Science who's an absolute marvel and George Wilding Vice Provost for Multidisciplinary and Clinical Research who has great administrative experience. Moving Tom [Thomas A.] Buchholz to head the clinics was another important and positive appointment. Ron now has people around him now who really make good decisions and really care for the community. Given enough time, Ron's team will turn around the issues of morale that we've been reading about in the Cancer Letter.

I think, too, that a lot depends on the new chairs and division heads that are being recruited. I think one thing that, I guess, that—another facet of this is, it's really great to see how both John Mendelsohn and Ron have supported Liz [Elizabeth] Travis and others in changing the fraction of women who are in leadership roles at Anderson. That's gone from about fifteen percent to thirty percent or so, over the last six or seven years, which is clearly a step in the right direction.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 22

B: Building the Institution

The Moon Shots Program and Its Impact

Story Codes

B: Building/Transforming the Institution;

B: Discovery and Success;

C: Discovery, Creativity and Innovation;

B: Multi-disciplinary Approaches;

B: Controversy;

B: MD Anderson Impact;

B: Institutional Processes;

B: Devices, Drugs, Procedures;

B: Institutional Mission and Values;

B: MD Anderson Culture;

Robert Bast, MD

[00:46:08]

The Moon Shots have been controversial, but I think that that's one of the most important things that's happened at MD Anderson in the last twenty years. This is Ron's signature experiment and something I don't think John ever would have done. Ron's unique personality and vision that set the challenge to find things that can be done in the next five years that are going to change the status of practice. There aren't very many places like MD Anderson on the planet. And to challenge us to the Moon Shots was a very important thing to do. Ron had to convince the other ninety percent of faculty who aren't directly involved in the Moon Shots that they're also important. But I think that the Moon Shots experiment is just extraordinary, and I think it's beginning to pay off.

There really are concrete examples already where the Moon Shots are working. "Scope and Score" for ovarian cancer has increased the complete resection rate of ovarian cancer from about a thirty percent to > eighty percent which is likely to impact on survival and change the practice of gynecologic oncology. Figuring out how to make practical early detection of lung cancer is another area that Ron has supported. Restricting access of teens to tanning apparatus is another initiative. I think Ron will use the Moon Shots as a pulpit to change the approach to cancer prevention, detection and treatment nationally and internationally. That's an audacious vision, but I think it's very important that somebody have an audacious vision.

Tacey A. Rosolowski, PhD

Interview Session: 03

Interview Date: December 18, 2014

[00:52:34]

How does that—the Moon Shot experiment—I'm now trying—kind of forming this question in my head. Because, I mean, obviously it's a different way of doing research. And, you know, there's a certain population at MD Anderson that is involved in that, and a much greater population that isn't. In terms of that experiment, you know, from your position as someone who has developed research, what are the lessons that are being learned from this model of doing research, and how to make it really effective in an institution?

Robert Bast, MD

[00:53:06]

Yes, more people have been involved in the Moon Shots than you might think. For example, the Ovarian and Breast Moon Shot is only one of a dozen or so that are up and running at the present time. We had 150 people on a Saturday for a retreat two years ago to plan projects. The HPV Moon Shot, which involves head and neck and cervical cancer, brought out more than one hundred people for a similar retreat. The challenge is to convince the clinicians in the trenches that they're contributing to that too, and it's their Moon Shot as well as the laboratory-based folks and the physician-scientists.

Part of the challenge, as everyone as acknowledged, is that physicians really are being asked to do more and more clinically.

Tacey A. Rosolowski, PhD

[00:55:12]

What might be a solution to that problem, or a way of thinking about it differently?

Robert Bast, MD

[00:55:16]

People like Tom Buchholz are absolutely key to this. Because if they're perceived as actually listening, and if they're people who can be trusted, as I think Tom is, that that's going to help hugely. Do you know Joe [Joseph] Simone?

Tacey A. Rosolowski, PhD

[00:55:40]

No, I haven't met him.

Robert Bast, MD

[00:55:41]

He's a very wise fellow. He was the head of St. Jude's for a while, and was—

[00:55:46]

Interview Session: 03

Interview Date: December 18, 2014

Tacey A. Rosolowski, PhD

Oh, okay. I don't know the name.

[00:55:47]

Robert Bast, MD

—and also has been physician-in-chief at Memorial Sloan-Kettering and headed clinical research at the Huntsman Cancer Center. Joe is certainly one of the philosophers of the oncologic community. He has drafted a number of maxims. His first maxim is, “Great institutions don’t love you back.” (laughs) And the second maxim is, “First-rate people hire first-rate lieutenants. Second-rate people hire third-rate lieutenants.” (laughter) I think there are some other maxims, but those are the two I remember most frequently.

Tacey A. Rosolowski, PhD

[00:56:22]

And they ring so true.

Robert Bast, MD

[00:56:25]

Somehow we need to establish that our institution really does care. That is one of the things that Ethan and Helen and George are trying so hard to accomplish, with the Clark/Sanger Scholars and their other initiatives. A lot of their retention efforts for appropriate reasons aren't widely understood or publicized. Thee crucial factor in the long run is having the right department chairs who are in tune with the senior leadership. That's an achievable goal, and there are a lot of different ways to achieve it.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 23

A: The Researcher

Writing a Guidebook on Translational Research

Story Codes

A: The Researcher;

A: The Educator;

B: Industry Partnerships;

D: On Pharmaceutical Companies and Industry;

D: Business of Research;

B: MD Anderson Culture;

Tacey A. Rosolowski, PhD

[00:58:03]

If it's okay, I wanted to shift gears and ask you about your book.

Robert Bast, MD

[00:58:09]

Okay. Just about to return to it.

Tacey A. Rosolowski, PhD

[00:58:13]

Oh, cool.

Robert Bast, MD

[00:58:14]

So—but that's my—that's my goal for the next six months to get that done. .

Tacey A. Rosolowski, PhD

[00:58:52]

Mm-hmm. So what's the scope of the book? Because if—the subject, of course, is translational research. And what's the theme you're taking?

Robert Bast, MD

[00:58:59]

It's a guidebook for young people about how translational research is actually conducted. I don't know if we've covered this territory before, but the first couple of chapters are to provide enough background in translation—in tumor biology and immunology to understand the examples that are provided in the rest of the book. I'd like this to be something that a PhD graduate student could read and understand enough of the medicine to understand how things are accomplished.

Interview Session: 03

Interview Date: December 18, 2014

And you've—generally talk about how drugs have been developed and how targeted therapy does or doesn't differ from that. How biological therapies are different from just conventional small molecular weight drugs. Then the book discusses how molecular diagnostics have been developed and how they've been used, and how you bring those together to personalize therapy and/or to make precision medicine. And what the role of academe has been in that, and what it could be, as well as what pharma has done, and the predicament that pharma is currently in. And that—also, what the role of government has been. And, again, where we are this week in terms of the gridlock in Washington, and how that's impacting on our—what we can do scientifically. And also, the idea of—the FDA and regulation, and, you know, where that's—has been headed. And to talk about career development in translational research, and what the many roles are on translational teams. And then what are the numbers of physician-scientists and clinician-investigators, and the other activities that make up part of translational research. And then talking about the community, and how we need to figure out how to relate this to the community in several different ways. First of all, to have enough patients to actually move forward, and to—and to test and to validate our approaches for predicting who will respond to which drugs, and what it's going to take to be able to do that. And also, ultimately, educating the community in how you use targeted therapy, because we're rapidly getting beyond just the usual algorithm that NCCN [National Comprehensive Cancer Network] puts out about how you treat a particular kind of lung cancer. And increasingly, as we have to go to combinations of targeted therapies to get decent, long-lasting responses, we're going to have to have something more than the annotation on reference laboratories, tests, to help. So it's going to be—there's going to have to be some sort of informatics—some sort of consultative services between medical centers like MD Anderson and the community.

It's interesting that there's some solutions to that in this whole Apollo program. I don't know if you've heard about that, but one of the things—one of the other things that Ron has championed with Andy [Andrew] Futreal and others, has been the development of intelligent, or artificial intelligence, to provide a patient-care tool. Apollo is starting with leukemias and myelodysplastic syndrome syndromes [MDSs], but then moving to melanoma and, hopefully, to lung cancer and ovarian cancer and the like. So, trying to take advantage of all of our information here about how different patients respond to different drugs, but also how clinicians make decisions based on the information that's in front of them. With the hope that you may—you know, usually we report out our results in terms of technical papers, or applying for grants, or getting drugs to a point of approval. This would really be providing aids in medical-diagnosis decision making that could come straight from MD Anderson, taking advantage of experience with patients.

But I think—I think the—now there's sort of—there's a whole bunch of different suggestions that I'm trying to get across in the book. But one of them certainly—and this is one of Ron's favorite topics—that we need to get academe and pharma and biotech working much more

Interview Session: 03

Interview Date: December 18, 2014

collaboratively than we have in the past. You know, there's really been a chasm and a huge amount of distrust in—between the two groups, as well as the issues of conflict of interest and the like. Pharmaceutical companies are sometimes altruistic, but their fundamental function is to earn money for their stockholders. And their vision of how you do that, even for oncology, in the past has been to get a blockbuster drug that will bring in billions of dollars a year while it's still on patent, and to move on.

Increasingly, pharma is not being very effective. In part, it's related to the fact we don't have a lot of great preclinical models for predicting who will and won't respond in the clinic to different drugs. At present, several hundred million dollars are invested to get a drug ready for clinical trials. It then takes several hundred million more dollars to get it through the necessary trials. Only one out of eight oncologic drugs that enters clinical trials actually gets approved by the FDA. It's not because the FDA [Food and Drug Administration] is being too harsh. The FDA, if anything, is being more lenient these days. They're approving drugs if they'll significantly prolong progression-free survival by two or three months. In the past, they'd insisted on an increase in overall survival by at least that much or more. The lack of approvals are largely because the companies think they'll be—drugs will be effective, and seven times out of eight they're wrong.

And one way, perhaps, to improve that batting average is to use all we know about cancer with our deep biology to choose the right targets. Pharmaceutical companies are really good at making drugs if they know what they're supposed to make a drug against. And the trouble is that they've just guessed wrong way too often in terms of the targets that they're targeting.

Academe could help hugely in choosing the right combination of targets. The IACS ought to have a better track record than one-in-eight, and we'll find out. It's, again, an experiment, but it's an experiment that's really worth doing. If you look at where all the money comes from for cancer research, about seventy percent of it's from pharma. But it's not for the kind of fundamental research that you need to do. That, unfortunately, has got to come from the government and, to some extent, maybe \$3 billion or so from foundations and the like. And then, also, from the profit margins from clinical care, which is what we do here. But, you know, pharma is the 2,000-pound gorilla when it comes to funding sources. So if pharma were convinced that they could trust the data that comes out of academe—and often they don't—that you could imagine some of the more fundamental research could be funded. It would be in the interest of the pharmaceutical company to find out what they really ought to be making drugs against, and certainly in the interest of investigators here. But it would take more of the Moon Shot attitude and culture to make that really work.

With declining support for research, we're going to have to choose our experiments and projects more wisely. On the clinical side, there are some clinical protocols that are “me too,” and there

Interview Session: 03

Interview Date: December 18, 2014

are other clinical protocols that are really working with innovative drugs. And if they worked, they'd end up in the *New England Journal*, or they'd end up in the *Journal of Clinical Oncology*. Not because—some academic artifact, but because they're really going to help people, and they would change practice.

In mentoring young people, I try to encourage them to really think hard about, if this experiment really worked *Journal of Clinical Oncology* because you're going to spend two years of obtaining a drug, writing and executing a protocol. If the drug really worked, what would you have accomplished? Where could you publish it? How much of a chance would it stand to really help people?

Another facet of the book addresses how we can to stabilize the physician-scientist pool. But that's still not going to be enough. We've got to figure out how to utilize intelligent PhDs who want to do translational research. And we've got to have job opportunities for them at the end of the day. To some extent, that's in pharma. But to some extent, it must also be in academe—that there should be career paths for those individuals. With regard to the community, groups like *US Oncology* have got to become more effective in conducting clinical trials. We need to try harder to instill the idea that even when you go into community practice, you're still an investigator, you're still a researcher at some level, doing something. And try to improve those statistics. Only four percent of the patients in private practice go onto any kind of a clinical research protocol. And then, only four percent of the patients overall end up on clinical protocols at all, even when you count the medical centers. So it's a real challenge.

We need to figure out ways to communicate the new knowledge now that it's becoming so complex. Because if it takes a billion dollars and up to twelve years for a new drug that is approved once out of eight times to see the light of day, the outrageous costs for all of the targeted therapies these days were trying to make up for the batting average of seven out of eight failures.

Tacey A. Rosolowski, PhD

[01:12:12]

Sure, well, it sounds like—it sounds like a very, very broad meditation, as well as, you know, practical information on the field of translational research and its context, economically and educationally.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 24

B: MD Anderson Culture

Establishing a Habit of Translational Thinking

Story Codes

A: The Researcher;

A: The Educator;

B: MD Anderson Culture;

C: Education at MD Anderson;

B: Institutional Mission and Values;

Robert Bast, MD

[01:12:24]

Yes, Khandan Keyomarsi and I, with collaborators at UT Health have been putting together a graduates program in Clinical and Translational Science. This includes not only a graduate program for PhDs, but also master's and PhD degrees for MD's who've finished their medical training. For both groups, the challenge is to develop a translational habit of thinking. So that, if you make a discovery in the laboratory, you don't just stop there and figure out what journal you're going to send it to, but ask yourself, okay, if this is really going to impact on better diagnosis or treatment or both, what would I have to do to get there? One of our jobs as an institution is to provide an environment where it's possible to make that kind of translation possible. It means getting the right people. It means giving them enough time. It means having focused programs of smart investment, in terms of getting their potential discoveries to a point where they can be picked up by biotech or pharma or diagnostic companies. IACS is one great example of how that could work for pharmaceutical products.

Tacey A. Rosolowski, PhD

[01:13:51]

But it sounds as though fostering that translational habit of thinking, you know, really is embedding a different kind of element in the culture. I mean, it's an—the theme has been there since the very beginning, but it sounds as though, you know, making it very pervasive is really, really key.

Robert Bast, MD

[01:14:12]

We need to plan clinical trials so that no matter how a trial turns out, it tells you what you need to do with the next trial. We need to take into account the heterogeneity of cancer. Some investigators have to be discovering new genes that are driving cancer at the most fundamental level. Other investigators have to be working with pharmaceutical companies to see if they can

Interview Session: 03

Interview Date: December 18, 2014

find the right inhibitor for combinations of different agents. We need to figure out what combinations make sense for different patients.

Interview Session: 03

Interview Date: December 18, 2014

Chapter 25

A: Personal Background

Photography, Basketball, and Advisor to the V Foundation for Cancer Research

Story Codes

A: Personal Background;

A: Contributions;

A: Activities Outside Institution;

Tacey A. Rosolowski, PhD

[01:16:33]

I don't think I have anything else to ask right now.

Robert Bast, MD

[01:16:37]

Good, well let me take—

Tacey A. Rosolowski, PhD

[01:16:38]

Except, maybe (laughs)—

Robert Bast, MD

[01:16:41]

What's that?

Tacey A. Rosolowski, PhD

[01:16:42]

Just—I mean, nothing—nothing from the—I know, we're almost finished. But I wanted to ask you just a completely different kind of question.

Robert Bast, MD

[01:16:48]

Okay.

Tacey A. Rosolowski, PhD

[01:16:48]

Which is:

do you have any hobbies (laughter) or interesting things that you do that maybe no one else knows, but would—

Interview Session: 03

Interview Date: December 18, 2014

Robert Bast, MD

[01:16:55]

My wife and I really enjoy traveling, and my hobby is travel photography. We enjoy the symphony, and the Houston Grand Opera. Actually, I'm addicted to The Teaching Company and to Duke Basketball. (laughter) The Teaching Company is a group in Northern Virginia. And they go all over the country looking for the best lecturers in anything. They record courses of 24-48 lectures on DVDs and CDs for all of the sciences, geology and the like. Courses include music, art history, philosophy, religion, history and economics. I listen to the CDs commuting and watch the DVDs. So I've taken more than 100 of these courses.

Tacey A. Rosolowski, PhD

[01:18:16]

Wow.

Robert Bast, MD

[01:18:16]

But it—which is a lot of fun [inaudible].

Tacey A. Rosolowski, PhD

[01:18:18]

Is there one you really enjoyed that kind of surprised you, that you enjoyed it?

Robert Bast, MD

[01:18:22]

Most of the courses are interesting. The only one that I didn't enjoy was Philosophy of Science.

Tacey A. Rosolowski, PhD

[01:18:37]

Oh, really? (laughs)

Robert Bast, MD

[01:18:37]

It was incredibly dry and very abstract. It didn't seem to me to capture the real issues.

On the other hand, Duke Basketball has become a passion. My wife and I were at Duke for ten years. As I think I mentioned before, I headed up the Cancer Center there for about seven of those ten years. And it took us a while to realize that couldn't have dinner parties on the nights of the Duke games. (laughter) But then, about three years into my experience at Duke, they used to save tickets for the governor for the Duke-UNC [University of North Carolina] game. And the governor couldn't get there, so I got this call about four o'clock on a Saturday afternoon:

Interview Session: 03

Interview Date: December 18, 2014

“Do you want to come to the game?” So I ended up going to Cameron Indoor Stadium where it was ninety degrees and ninety decibels. I got thoroughly hooked. And you know you have it bad when you start watching all the other ACC [Atlantic Coast Conference] games, and then watching the PAC-10 [Pacific-12] to find out how the tournament’s going to turn out.

But I’ve worked with the V Foundation for more than twenty years. Jim [James] Valvano was a basketball coach at NC [North Carolina] State. And he had won the NCAA championship in 1983 against the University of Houston in a buzzer-beater. ESPN keeps showing the clip where he’s running around the floor trying to find somebody to hug. (laughs) Jim became athletic director at NC State, and his kids actually got caught, literally, selling their sneakers. And so, he was fired but ended up as a color announcer on ESPN [Entertainment and Sports Programming Network] and did a remarkably good job. He was a really passionate and interesting guy. He had developed cancer and it turned out that his family had a BRCA mutation but he did not know about. Jim had an unknown primary cancer and he was treated initially at Sloan-Kettering because he worked in New York. His family was still in North Carolina, so he came back to Duke. His personal doc was Joe Moore, who was one of my colleagues at Duke. At the time, I was the Cancer Center director, so I got to know the Valvanost. Just before Jim died, Jim gave an amazing speech at the ESPY awards.

Tacey A. Rosolowski, PhD

[01:20:55]

Uh-uh.

Robert Bast, MD

[01:20:55]

It’s on YouTube, but it’s also on the V Foundation website, as well. But it was just an amazingly human speech. Jim chose his college roommate who had just sold his dot-com to head up the board, and asked Joe and myself to join the Board as well. I’ve been head of the V Foundation Scientific Advisory Committee for two decades. We’ve raised about \$120 million, and that’s been leveraged into about a \$1 billion in grants by funding young investigators as well as translational science awards. The V Foundation has an annual wine event in Napa, which has raised about half of the total funds. We have our scientific advisory board do part of their work on that weekend, so it’s got to be the most popular scientific advisory board on the planet. (laughter) Mike [Michael] Krzyzewski have been part of the board, as well. Coach K, the legendary Duke coach, has been part of their organization, as well. So, we’ve managed to watch all the Duke basketball games we could find. Tonight they’re playing UConn [University of Connecticut], (laughter) which I trust will be on the air. So, those are my secrets.

Tacey A. Rosolowski, PhD

[01:22:22]

Interview Session: 03

Interview Date: December 18, 2014

Those are good secrets. Thank you for sharing them. Is there anything else you'd like to add?

Robert Bast, MD

[01:22:27]

No, I don't think so. At least not at the moment.

Tacey A. Rosolowski, PhD

[01:22:29]

Great.

Robert Bast, MD

[01:22:29]

Let me—let me take a look at the transcript and let me do some editing, and let me—I can perhaps put in some additions.

Tacey A. Rosolowski, PhD

[01:22:36]

Sounds good.

Robert Bast, MD

[01:22:36]

If there's things that I've left out.

Tacey A. Rosolowski, PhD

[01:22:37]

Well, I thank you, very much, for your time today, Dr. Bast.

Robert Bast, MD

[01:22:40]

You're welcome. Well, thank you. It's been much more enjoyable than I expected. (laughter)

Tacey A. Rosolowski, PhD

[01:22:44]

Well, I'm glad to hear that. It is—it is an investment of time, so I do appreciate it.

Robert Bast, MD

[01:22:50]

Yes.

Tacey A. Rosolowski, PhD

Making Cancer History®

Interview Session: 03

Interview Date: December 18, 2014

[01:22:50]

Well, I'm turning of the recorder at 4:50.

Robert Bast, MD

[01:22:54]

Great.

Tacey A. Rosolowski, PhD

[01:22:54]

Thank you, very much.