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Chapter 00A

Interview Identifier

Tacey A. Rosolowski, PhD
[00:00:00]
All right, and we are recording. So, I'm Tacey Ann Rosolowski, and today is February 23, 2015. The time is about fourteen minutes after two in the afternoon. And today we're on the twentieth floor of Pickens Academic Tower in the Office of the President, and I'm interviewing Ronald DePinho, MD Anderson's fourth full-time president for the Making Cancer History Voices Oral History Project run by the Historical Resources Center at MD Anderson Cancer Center in Houston, TX. Dr. DePinho came to MD Anderson in September of 2011. He is also professor in the Department of Cancer Biology, if that it correct.

Ronald DePinho, MD
[00:00:43]
Correct.
Tacey A. Rosolowski, PhD
[00:00:45]
All right, great. This session is being held in a conference room, and it is the first of what I hope will be a number of planned sessions, if you have the time in your extraordinarily busy schedule. Also present is Brette Peyton, who is sitting in on the interview. So, I wanted to thank you, Dr. DePinho, for making time for this today.

Ronald DePinho, MD
[00:01:04]
It's my pleasure. I love telling the story of MD Anderson.
Chapter 01
From an Early Interest in Biology to a Fascination with Developmental Processes
A: Educational Path;

Tacey A. Rosolowski, PhD
[00:01:07]
Well good! And I hope telling your story, too, which from my background research is equally fascinating. So I wanted to begin really with chronological beginning and just asking, where were you born and when? And tell me a little bit about your family of origin.

Ronald DePinho, MD
[00:01:23]
Well, I'm the son of Portuguese immigrants that were uneducated who came to this country to have a better life for themselves and their children. I was born in The Bronx in New York City, and grew up most of my life in and around New York City, Westchester, and was instilled with the values of education, altruism, of service, and high ethical behavior.

Tacey A. Rosolowski, PhD
[00:01:57]
Tell me your parents' names.

Ronald DePinho, MD
[00:01:59]

Tacey A. Rosolowski, PhD
[00:02:05]
And what really happened in family life to help instill those values? What did your parents do?

Ronald DePinho, MD
[00:02:11]
Well, they led by example. My father, who grew up very poor, deeply religious, was very interested in helping his family and helping others, came to this side of the earth and tried to make a living so that he could support the family back home. And when he finally realized the
American Dream and had a stable living, he spent a lot of his time helping others who were in disadvantaged situations around the world—identifying families, sponsoring them to the United States, supporting them in ways by putting them, giving them housing or giving them a job and enabling them to get the start that he got and the chances that he got. And so I grew up in a household where there was always some stranger in our kitchen, where he was trying to help and move along, and he was a really remarkable human being in that regard. And my mom was just a wonderful housewife who devoted her full energies to helping him and our family at large, and really kept us healthy, happy. We were expected to work very hard. We had jobs from when we were twelve years old and onward. And at the same time, we were expected to do well in school, and essentially contribute to society.

**Tacey A. Rosolowski, PhD**

[00:03:45]

Tell me about your educational background a little bit. And what I'm interested in here is kind of when did you kind of know that you had gifts that were going to be really important in your life?

**Ronald DePinho, MD**

[00:03:59]

Well I'm not too sure about the gift part, but I'm a very hard worker. My um—I went to Catholic grade school, and was instilled with the core values of discipline, courtesy, respect, humility, I think which has served me over the years. And then when to a Catholic, all-boy high school, where they had a dean of discipline.

**Tacey A. Rosolowski, PhD**

[00:04:28]

Wow. (laughs)

[00:04:30]

**Ronald DePinho, MD**

That, you know, provided an additional level of structure, shall they say, for my adolescent years.

**Tacey A. Rosolowski, PhD**

[00:04:36]

Can I interrupt you just for a second? What was the name of your grade school?

**Ronald DePinho, MD**

[00:04:40]

Saint Dennis Grade School in Yonkers, and Mount Saint Michael in the Bronx. And, you know, these were schools that my parents had to scrape together their resources to be able to support their children and what they thought would be a better education environment. So it was a real
struggle for them, they had to work very hard so that they could support our education, and that was mission number one for them.

**Tacey A. Rosolowski, PhD**

[00:05:09]
Was that unusual among your parents' peers, to be so interested in spurring the education of their children?

**Ronald DePinho, MD**

[00:05:17]
I think everybody believes that education is important, but I would say that my parents really valued, at a very, very high level, not just getting an education, but harnessing one's full potential, so the expectations were very high. And so, you know, it was expected that you would do well, and that you would do so in a respectful and humble way, but that you were going to try your best. And that was, you know, permeated the entire household, and it was expected over the years, that we would behave in that way. And what was remarkable about my parents is that they never expected us to be any one profession in particular. All they wanted us to do was to do well, and to achieve our potential and pursue those dreams they felt would be fulfilling for us. And that was a very remarkable aspect of their approach to raising us.

**Tacey A. Rosolowski, PhD**

[00:06:26]
What was their education level?

**Ronald DePinho, MD**

[00:06:29]
They were not educated.

**Tacey A. Rosolowski, PhD**

[00:06:32]
Yeah, that's actually a common story.

**Ronald DePinho, MD**

[00:06:32]
They had rudimentary schooling back then in Portugal, but it was a very poor country with minimal resources. They knew how to read and write, but they taught themselves for the most part. In fact, my mom learned English by teaching us, you know, or by doing our homework with us.
Oh wow.

**Ronald DePinho, MD**

She couldn't speak English when she got to this country. So then, high school was interesting. In high school, I started to get into sports like most young boys, and took my biology class in sophomore year, and opened up my first frog, and was fascinated by how all of this might work. And that sparked my lifelong interest in biology and medicine. And then around that time, I read this book, The Making of a Surgeon, and that also gave me insights into medicine that I found fascinating, and I loved people, and I wanted to combine a profession that connected with the human element and the science, the biology part. And that's why I thought medicine would be a great — great opportunity for me. So from that point on, I was very interested in pursuing science, and ultimately medicine. I then went to Fordham University, and I studied both biology and art history. I was very interested in art history and history in general.

**Tacey A. Rosolowski, PhD**

Why did you choose Fordham?

**Ronald DePinho, MD**

Fordham had a really exceptionally good biology curriculum. It was Jesuit training; they were really exceptional in education. And also they had one of the best art history departments in the country, so it was a really nice mix.

**Tacey A. Rosolowski, PhD**

Where did that interest in art history come from?

**Ronald DePinho, MD**

You know, I'm not sure, but I think it was — I loved history, and I loved viewing history through the lens of art, and I was also fascinated with great artists like Leonardo da Vinci, who combined both science and art in really powerful ways. And it was very natural back then for the great artisans to also be engineers, or mathematicians, or scientists.

**Tacey A. Rosolowski, PhD**

It wasn't any division between disciplines.
And for me it seemed very natural. And, so I was very interested in both, but obviously focused most of my energies on the biology, because I wanted to get into medical school.

Tacey A. Rosolowski, PhD
[00:09:16]
Right.

Ronald DePinho, MD
[00:09:17]
And then from Fordham University, I then went on to go to Albert Einstein College of Medicine, where I was really very, very excited and in awe of the field of medicine, and how just complex the human body was, and its physiology, and learning about how diseases unfold, learning about how to manage diseases. It was something that was a real passion for me.

Tacey A. Rosolowski, PhD
[00:09:]
Why did you elect to go to Albert Einstein?

Ronald DePinho, MD
[00:09:54]
Well, it was an area — well I was very interested around that time in neuroscience, and that was one of the great institutions in neuroscience. I wanted to stay in New York. And I was interested in pursuing that path, which I've continued on throughout my career, to a certain extent. I worked in both neurodegeneration and in cancer, and so that was always very fa — the brain was always a fascination for me.

Tacey A. Rosolowski, PhD
[00:10:24]
When did that start?

Ronald DePinho, MD
[00:10:26]
I think it was just a natural evolution, it wasn't any seminal event. But it was — the things that fascinated me throughout my career were things related to development, how is it that a single-cell organism becomes a multi-cellular complex organism? That goes through all of these complex developmental decisions to become this, this, this organism. And then, reciprocally, how those processes can go awry in congenital defects, birth defects, and so on.

Later on, I became interested in the intersection between development and cancer, because I had this hypothesis that a cancer cell, amongst its many biological attributes that it
needs to acquire, commandeers the developmental processes that are normally well controlled during development, but that they are co-opted to make a cancer cell immature and embryonic-like so that it grows and develops and maintains this relatively immature state. So those paths have crossed.

And then the other big question that I was always fascinated with was the whole issue of how information is stored in the central nervous system, the complexity of the brain. So those problems always fascinated me. And then again, my interests evolved more towards neurodegeneration, aging, and the intersection of aging and neurological problems. And then also, cancer, and how cancer is intimately linked to aging. That's where most of my career has focused on, that intersection between those two.
Chapter 02

Deciding to Focus on the Molecular Basis of Disease

A: The Researcher;

Story Codes
A: The Researcher;
A: Professional Path;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;
A: Definitions, Explanations, Translations;

Tacey A. Rosolowski, PhD
[00:12:21]
Well, did the first stirrings of those interests — I mean, was that an intellectual interest, or were there some personal things going on that also helped kind of direct you towards those big issues?

Ronald DePinho, MD
[00:12:31]
Well, the first major career transition for me, from a directional standpoint, came when I was — after medical school, when I was doing my internship and residency at Columbia Presbyterian. I was still very enthusiastic and interested in medicine, but I became increasingly frustrated by my inability to understand, on a fundamental level, what these diseases were all about. And not just managing them or attenuating their course, their natural history, but actually curing them, as we did with antibiotics and infections. And many of those diseases were also called idiopathic diseases — that is, we didn't really understand their causation — and it wasn't enough for me to just rattle off facts. I really wanted to understand the underpinnings of those diseases on a molecular level. So I became interested in pursuing a scientific as well as medical path, because I wanted to go to the laboratory and understand what made these diseases tick, and hopefully that new insights would illuminate new therapeutic approaches that would cure these diseases, and not just simply manage them. So that was a major turning point in my career, where I pivoted to include science as well as medicine. And then I — after my residency, internship and residency, instead of pursuing a sub-specialty and continuing my medical training in that path, I instead enlisted full-time into a laboratory and learned how to do science. And it was a very exciting time because the laboratory that I joined was one of the leading laboratories in immunology and in cancer, exploiting the power of molecular biology, recombinant DNA technology, cloning, and sequencing genes. These were very heady days for medicine, because we could actually see the genes for the first time, clone them, manipulate them, and start to understand them. So it was a very, very exciting time in science and in medicine. Of course, it would be many decades before we would be able to harness the full knowledge and potential of that technology into
medicines that would impact these diseases. But nevertheless, the seeds were planted, and it was a major turning point for science.

Tacey A. Rosolowski, PhD
[00:15:16]
Who were you working with at that time?

Ronald DePinho, MD
[00:15:18]
That was Fred Alt, a very famous professor at Columbia. He later went to Harvard. And he was really one of the great leaders in the new field of molecular immunology, and he had discovered many of the molecular rules, biological rules by which immune cells govern the development of immune responses.

Tacey A. Rosolowski, PhD
[00:15:47]
And what were you doing working with him?

Ronald DePinho, MD
[00:15:50]
Well, when I was also doing my residency, and working in the lab, one of the other areas that he was interested in other than immunology — so I did some research in immunology — he was also beginning to clone new oncogenes, cancer genes. This was a time when the field of immunology, molecular oncology, was beginning. And we were beginning to discover, as a field, some of the very first genes that were altered and cancer, that were either translocated, or mutated, or many copies were there. And Fred discovered gene amplification, that is, you having a single gene with an abnormal number of copies because they became amplified. And he subsequently discovered a very important cancer gene, which is amplified at the genetic level that causes it to be over-produced, in a rare childhood cancer called neuroblastoma. And that was one of the first oncogenes to be discovered, and a lot of my effort was focused on taking advantage of this new recombinant DNA capability to discover new oncogenes and tumor suppressor genes. So these were really exciting times, because we were now able to identify these genes that were fundamental to the development to the pathogenesis of cancer. Of course, back then we were just dealing with the tip of the iceberg of cancer genes, and later on I'll tell you about some of the work we had done with the cancer genome and some of the work we were involved in there.

So from there I — having learned the basics of how to be a scientist and having training in medicine — I started my independent career back at Albert Einstein College of Medicine. And I was particularly interested in using genetically engineered mouse models to understand complex biological processes. Now, keep in mind that back then, it was the era of reductionism.
That is, we tried to use very simple systems, like cells in a petri dish, to understand complex biological processes. Or we were in search of that one gene that was important for a particular biological process, or a disease. And the reality is, this vision that was just intuitive to me, that these diseases would be polygenic, and that they would involve many different processes. And so — and I felt that for us to truly understand these diseases, and these complex biological processes, that we had to exploit the experimental merits of an organism that could be genetically manipulated and that was reasonably close to humans, and that's why I focused on mouse models. To be able to then bring my knowledge in medicine, and my comfort in dealing with, you know, physiology and anatomy from my physician background, to bringing the molecular biology skills to genetically engineer mice, so that I can reproduce mice that have deleted genes, or over-expression of certain genes, to ask, in an in vivo context, what function might they serve. And that was a very exciting time as well. Because now for the first time, we had the technology that enabled us to genetically manipulate the genes of a mouse in, you know, a very complex physiological setting, and ask fundamental questions about the function of genes. So that was an advantage that I had because I was able to bring my knowledge of physiology, anatomy, medicine, together with the scientific knowledge that I had. And as a result, I became very interested in trying to ask questions like, well, how did these oncogenes, these cancer genes, influence the developmental biology of a cancer cell? How did they control cell division? And a variety of other biological processes. So it's an anti-reductionist, to a certain extent, I was trying to understand and embrace complexity and the interaction between genes and biological processes.

*Tacey A. Rosolowski, PhD*

[00:20:39]
Do you think that shift away from reductionism has been completed at this point in oncology?

*Ronald DePinho, MD*

[00:20:45]
I think so. I think that now folks are very interested in integration of very large data sets of different types, and that is the norm now. At the end of the day, you do really have to understand the individual parts. But what's critically important is to understand the interaction between those parts, and how they cooperate or counter any biological process — cooperate with each other or counter each other in biological processes.
Chapter 03

Work on Telomeres Leads to an Interest in Aging and Cancer

A: The Researcher;

Ronald DePinho, MD

[00:20:45]

So then, from there, I started working more on cancer. I was more interested in the basic processes of development and the role in cancer. And as we began to develop mouse models to understand cancer genes, these animals began to develop cancer themselves, and I began to investigate cancer in the context of these complex model organisms. And there again, I had the advantage of having this background in medicine, and I was able to understand complex phenotypes that these animals were developing. That, then, you know, turned to a really seminal moment for me, and had a very significant change in the direction of my research, which was that when these animals were genetically engineered with the genes that were found in human cancers, they developed cancers, but they didn't develop the same type of cancers that humans did. Now, most folks would say, "Well, I guess mice aren't good models for human disease." My response was that perhaps if I can understand the cross-species difference, I might illuminate what's going on in humans, and the types of cancers that humans develop as they age are known as epithelial cancers — colon cancer, breast cancer, prostate cancer — as opposed to blood and soft tissue cancers which are more pediatric in their distribution. Yet mice develop mostly blood and soft tissue cancers. So I was very, very struck with how that difference could be. And for a lot of reasons, I focused in on telomeres, which are the structures at the ends of chromosomes. These were different in mice and humans, and telomeres function to maintain the integrity of the chromosomes. And as we age in humans — but not in mice — these telomeres erode, and eventually they lose that capping function, and it creates a period of instability, genomic instability, that then fuels the development of changes that can lead to cancer. And this happens predominantly in epithelial cells, and is a major mechanism, we now know, to be operative in the development of the major cancers that affect humans. So what we did was to engineer mice to have telomere dysfunction, like humans do. And when we did that, the mice developed a humanized tumor spectrum, and that then lead to one of the important discoveries that my lab made, which is to help us understand why aged individuals develop cancer, and why they develop the cancers they do, and why do those cancers merge with radically altered chromosomal aberrations that what are seen in humans, but not necessarily in mice. And so that
began my life-long interest in understanding the interaction between aging and cancer, understanding the aging process itself — which I felt that if I could understand it, I would be able to not only deal with the aging process per se, but potentially reduce the incidents of age-related diseases, like Alzheimer's and cancer. And at the same time, study cancer to understand at the same time how is it that we could ultimately control it.

And so we began to develop many models of human disease in the mass, with that new knowledge of how to engineer mice in a way that faithfully recapitulated the human situation. And that lead to many animal model systems that are now in use today that allows us to use those models to understand the fundamental development of these cancers, the genes that are involved in those cancers, and now the ways that we can potentially use therapeutics to impact those cancers.

Tacey A. Rosolowski, PhD
[00:25:45]
Just for clarity, can you give me an example of how one of those models has been used to understand human disease?

Ronald DePinho, MD
[00:25:55]
Sure. So, one of the discoveries that we made was to develop an animal model for melanoma, which is a lethal skin cancer. And in melanoma, there's a gene, or a pathway that's activated almost universally. And this gene, the RAS oncogene, was a gene that we put into mice to have it expressed in melanocytes, against the backdrop of a tumor suppressor gene that we also worked on that we showed was a tumor suppressor. And when we combine those two, the mouse — we developed the first mouse model for melanoma. That then led to opportunities to study that disease more effectively. However, RAS itself, which is a really important gene, wasn't therapeutically targetable — it’s a non-druggable target. So what we did was to ask a very basic question, and that is, if a gene causes cancer in a fully established cancer, when you've developed many, many other mutations, is it still important, is it still rate limiting, and if you were to target that therapeutically, would it impact on the cancer? So no one had ever asked that question before. Folks assumed that a gene that was important in the genesis of a cancer remained important for the maintenance of that cancer. However, in the life history of that cancer cell, they may accumulate myriad other mutations that may make that initial inciting alteration irrelevant. So, so we developed this concept for tumor maintenance, that is, is it a tumor maintenance gene? And we used this approach called inducible genes, where we can turn genes on and off by simply giving a chemical in the drinking water — that is, you can engineer a gene that can be turned on and off like a light switch in a particular cell — with the addition of doxycycline, it’s an antibiotic. And so it's engineered — it's an engineered gene — so it allows you to turn this gene on. When you turn it on, they get melanoma. And then in a fully established melanoma, we have the opportunity then to flip the switch off and ask, what
happens? And what happened was, the tumor was, went away completely. It was regressed. So it proved that RAS was not only important for the development of the cancer, but remained important to maintain the cancer. We then had this idea that if you had that platform, then you can take cells before you flip off the RAS gene, and ask, can you complement the RAS oncogene? Are there surrogates of RAS activity, other genes that are in a pathway, that if you were to now constitutively express those genes, would you be able to maintain the tumor after you've flipped off the RAS oncogene? So this is a concept — this idea of looking for component pathways has been around for decades, but it would've never been used in mammalian systems. It was used in simple model systems like yeast and [inaudible]. And that allowed us to identify many new therapeutic points of attack that have since entered into the clinic in the form of drugs, new drug development — that is, a focus on these targets that could essentially replace RAS and be formidable targets in their own right, yet the difference is that they're druggable. And as a result of that, I started a biotechnology company; it was the first one that I started. And the reason that I got involved in that area is that as an academic, I can only bring things so far. And by working with the private sector in this new concept called tumor maintenance, that I would be able to attract new investments that could take my idea into the clinic, so I realized that was another very important path through which discoveries get converted into things that could help patients.

_Tacey A. Rosolowski, PhD_
[00:30:36]
Which one of the companies —

_Ronald DePinho, MD_
[00:30:38]
That was AVEO.

_Tacey A. Rosolowski, PhD_
[00:30:40]
AVEO. And is that an acronym, or —

_Ronald DePinho, MD_
[00:30:43]
No.

_Tacey A. Rosolowski, PhD_
[00:30:44]
And where did the name come from?

_Ronald DePinho, MD_
[00:30:46]
It was invented by somebody in the company.

_Tacey A. Rosolowski, PhD_

[00:30:48]

Oh, OK. It's kind of a pretty, melodic name. (laughs)

_Ronald DePinho, MD_

[00:30:50]

Yeah. So that was an interesting experience because I got to learn how to translate discoveries into new drug development opportunities for patients. And that led to the development of a number of drugs that have now moved into clinical development, so I'm very proud of that.

And then from there, let's see — so getting back to the sequence of my career. So I was at Albert Einstein, I began to work on cancer using genetically engineered models. I was very interested in translating that knowledge, hence the entrepreneur aspect of my career —

_Tacey A. Rosolowski, PhD_

[00:31:44]

Can I ask you quickly, where did that entrepreneurial spirit come from, do you think? I mean, that takes sort of a different skill set than —

_Ronald DePinho, MD_

[00:31:52]

Well, I was very fortunate to have mentors, because I was not just interested in studying problems, getting back to my residency, I was interested in converting knowledge into things that would help people. And so everything I've done has been about that. What can I do to move the needle on the disease and reduce pain and suffering? And so, I reached the point where I said, well I have all of these really great discoveries, but how do you then move things forward, so that you can really have this be translated into something that would make an impact? And so I was fortunate to be around individuals that had done that, and they recognized the value of my discoveries, and wanted us to move that into the private sector, and the rest is history.

_Tacey A. Rosolowski, PhD_

[00:32:42]

So who are some of those influential folks, and how did they help you out?

_Ronald DePinho, MD_

[00:32:46]

Well, I had many throughout my entire career, and some of them were in my personal life, and some of them were in my professional life. But one of the — obviously my father has had a profound impact on my life, and I'll get to him a little bit later. I was fortunate to have teachers
who really took the time to help and develop me at the right time — not just teaching, but giving me advice as a child, and so on. And I had a great English teacher, Mr. Vallar — V-A-L-L-A-R — who really somehow recognize potential in me in high school and wanted to support me and help me.
Chapter 04
*Martial Arts: A Mind/Body Practice that Feeds Success*

A: Personal Background;

Story Codes
A: Character, Values, Beliefs, Talents;
A: Personal Background;
A: Influences from People and Life Experiences;
C: Portraits;
C: Formative Experiences;

*Ronald DePinho, MD*
[00:32:46]
I also started training in martial arts in high school and Kang Ik Jo, or that's the way you say it in Korean, so it's Ik Jo Kang — A-I-K, second name J-O, last name K-A-N-G. He was a very gifted individual, gifted teacher, who taught me martial arts, which is really built on this philosophy of respect, courtesy, humility, and discipline. You know, you can do anything that you set your mind to, mind and body and emotion all working towards goals. So that really helped me tremendously in school, helped me focus my mind. It’s something that I really rely on to this day, the attributes that I got there. So that was a hugely, hugely seminal event in my personal life, because it really gave me a really strong foundation. I’d say my father gave me the core values, and this gave me the ability to — gave me the inner strength to be able — and courage to be able to pursue really hard problems.

*Tacey A. Rosolowski, PhD*
[00:34:43]
Why didn't you consider really focusing on more of a team sport? For example, football, baseball.

*Ronald DePinho, MD*
[00:34:49]
You know, at that time in high school, I was interested in less about sports per se, I did all that, but I was more interested in something that was going to go beyond physical activity. I was interested in something that would bring both mind and body development. And the two things I could think of was dance, and martial arts. And I don't think I'd ever be able to (laughter) — my friends would never, you know, they would tor — I would be tortured. So, skip that one. And I was very fortunate in that I had this instructor, and his school ended up dominating US competition in the 1970s, so this was a serious, you know, effort. And he was — he really trained some of the best competitors in the country.
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Interview Date: February 23, 2015

Tacey A. Rosolowski, PhD
[00:35:51]
Was that also a kind of spiritual practice for you?

Ronald DePinho, MD
[00:35:53]
Absolutely. No — the reason that martial arts has been enduring for 3,000 years is because it does something very fundamental to your mind, your body, and your emotions. And that's the — it's that process of development and integration across those three spheres that makes martial arts so enduring. It is not about kicking and punching. It's about developing a better social being, inner and outer. And, you know, helping you develop yourself to the maximum potential possible. That's why it's so enduring. And you see transformations occurring in all individuals that really are in a good school, that really put their mind to that.

Tacey A. Rosolowski, PhD
[00:36:37]
Can you tell me — what were some of the transformative, what was a transformative moment for you during that training? I mean, you know, you start out with something like that and you're a total neophyte. You don't know what you don't know. When did you realize, wow, this is an important path, much more so than I ever knew?

Ronald DePinho, MD
[00:36:55]
You know, it's a gradual process. It's like, you know, your development as a person when you're becoming a young adult, and so on. But what was remarkable to me was the ability to concentrate, and this really helped me in school. But previously, you know, I'd be able to sit down for half an hour, forty-five minutes, and, you know, not get up and be able to focus on the task at hand. And after training in martial arts, for me to be able to sit down for four or five hours and focus was something that was recognize — recognizing that that was now possible, and how rapidly that occurred, as an example. The amount of just discipline that one develops is pretty remarkable as well. So those were some of the early indications that this was something that was going to lead to a personal transformation, and it happens to everybody. It's a remarkable structure that develops, you know, individuals into their full potential. The other was being able to perform under pressure. You could imagine being in competition, and I was a pretty weak kid, I didn't have any natural athletic ability, and I was put in situations where I was in front of folks that were world champions. And it helped me — and I was a very shy child, very little confidence — and that experience taught me, gave me the courage to be able to pursue things and do things, you know, on a more significant scale, in front of many people. Where in the past, I would never be able to do it — stage fright, and things of that nature. It's true for many kids, and was certainly the case for me. And that gave me the confidence I needed in myself to be able to apply myself and do so in a setting of extreme high stress, in front of many
people, some of who could impact your health and well-being. (laughter) So those were clearly formative days as a kid.

_Tacey A. Rosolowski, PhD_
[00:39:22]
Sounds like an amazingly exciting time, really.

_Ronald DePinho, MD_
[00:39:24]
Yeah, it was a great experience. I got to see the United States and travel, and we did very well in competition. He was a gifted teacher, and we applied ourselves.

Then, you know, so that was Kang Ik Jo. And then — and during my internship or residency, I became very close with [Kaise Aloquady?] — I'll get you the spelling on this later — he's a professor at Columbia, and he gave me the courage to pursue a scientific career after my residency and training. Because there's a certain hackneyed path, you know, that one pursues when you go through your training. And this was, you know, folks back then didn't do this. For a physician to pivot strongly towards a scientific career, back then. Now it's more commonplace with MD/Ph.D. programs. Back then it was a big risk. But he gave me the courage to pursue that path, and I did, and that allowed me to have — be a physician-scientist, as opposed to one or the other.
Chapter 05

*Developing an Industry-Informed Approach to Research;*

**B: Building/Transforming the Institution;**

Story Codes
A: The Researcher;
A: Entrepreneur, Biotechnology;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
A: Personal Background;
A: Professional Path;
A: Inspirations to Practice Science/Medicine;
A: Influences from People and Life Experiences;
C: Formative Experiences;
C: Discovery, Creativity and Innovation;

Tacey A. Rosolowski, PhD
[00:40:48]
Was anyone even coining that term [physician-scientist] at the time, or translational research?

Ronald DePinho, MD
[00:40:43]
It was just beginning actually. Physician scientist — that was part of the inaugural class of the National Institutes of Health for the physician scientist award. So this was now recognizing that you needed to train physicians who knew science, so that you can bridge bench and bedside. The word translation was just beginning to be uttered, because there was a continental divide between the laboratory and the clinic. And there was very little cross-pollination that occurred between those worlds. And it was — yet it recognized that if we're really going to impact on disease, we had to begin to bridge that valley of death between those two worlds. And so then, I be — that's the space that I was in. I really wanted to bridge those two worlds, and be really strongly grounded in science, but with that medical background. Always do things that were clinically relevant, asking clinical questions, through the lens of this science, this new scientific ability that we had with recombinant DNA, genetically engineered models, and so on. So then the next significant mentor that I had were two scientific mentors, when I entered into the science world, that was Matty Scharff, a professor at Albert Einstein, and Fred Alt, who was my main post-doctoral advisor. They had a very profound impact on my scientific maturation, and they were role models, not just for me, but for many around the world. They were truly special individuals.
Tacey A. Rosolowski, PhD
[00:42:22]
What did you learn from them?

Ronald DePinho, MD
[00:42:44]
Well, from Fred I learned how to ask important questions, not the next question, but to pursue
the big question, and to design experiments that — and use whatever sophisticated technologies
were needed to get at the answer. What I learned from Matty, was that experiments were only as
good as your controls, and also that communication was very important, both written and verbal.
And the ability to communicate effectively allowed you to, first of all, talk about your science
and gain addition support, recruit people to your lab, but also get the world excited about science
and medicine and the opportunities therein. So they were very different from each other, but I
really was very fortunate to have those two as mentors. They guided my professional
development quite significantly.

And then getting back to my father, a profound impact on my career occurred when he
passed away from cancer. This was in the late 1990s. And to that point, I was studying aging
and cancer, but on a very, very fundamental level — genetic level, biological processes. And
focusing on that, you know, elegant study, with some translational interest. But his death made
me recognize that while these discoveries might be elegant, they had very little utility unless they
were converted into drugs, devices, diagnostics, that could bend the arc of this disease. And so I
felt powerless that, you know, I was unable to help my hero, even though I was studying cancer,
that there just wasn’t enough knowledge. So I began to intensely focus on cancer at that point,
and to always try to ask, "How can my science impact on the human situation?" So that led to
the one example that I gave — AVEO, other companies I was involved in that led to diagnostics
or led to other drugs, and so that allowed me to help either my own science or the science of
others to move forward into new drugs and diagnostics that could really help folks, and I’m very
proud of that part of my life.

At that point, in my career, recognizing that I needed to focus on cancer, the Harvard
system was beginning to organize all of their institutes behind the Dana Farber Harvard Cancer
Center. And in this development, they were able to bring together almost 1,000 investigators
throughout the Harvard system to focus on cancer. So I said, I want to be part of that. So I was
recruited to Dana Farber, where I was able to hone my interests in cancer and interact with that
broader community. And the first thing that I did was to organize an effort at Harvard on G.I.
cancers. My dad died of colon cancer. And so I helped organize efforts for — in colon cancer,
G.I. cancer in general, and pancreas cancer. And I was able to bring groups together to write —
to do program project grants, centers of excellence grants, [inaudible] grants, the G.I. cancers
became part of the program at the Dana Farber Harvard Cancer Center core grant and that led to
a lot of interest across many groups to begin to move the needle on those diseases. And there's
been a lot of progress since. I'm very proud of that. In addition, while at Harvard, beginning to learn about what it took to develop drugs, and what it took to do good science behind that drug development, I realized that the discoveries in the laboratory and academic setting, and drug development in pharma, and then later on clinical development, the drugs were highly compartmentalized, fragmented, siloed. And it was clear that for us to develop new drugs against the right disease and through the right clinical trials, that we had to organize and integrate those worlds into one holistic, integrated effort. So we started the Belfer Institute for Applied Cancer Science. This was a novel organizational construct where we would bring together scholars interested in fundamental mechanisms, with individuals that could do more industrial scale biology and using model systems to test drugs and hypothesis, and drug developers who could make drugs against those targets, and then go back to the scholars to validate the mechanism or not. But also bring in the clinical trialists so that we could understand, what is the ultimate clinical trial going to be to prove this in a human, in a cancer? So that, then, was essentially my interest in trying to pull together these different worlds that I had, which was basic science, my knowledge now of drug development as a result of the entrepreneurial experience, and then later on the clinical activities which represented my medical background, and trying to bring them together in a parallel fashion, as opposed to this relay race of handing the baton off and not necessarily getting that synergy you need to have understanding and expertise to be able to iteratively move a particular opportunity forward into a drug development endpoint.

**Tacey A. Rosolowski, PhD**

[00:49:08]

Give me an example of how that worked at Belfer. I mean, obviously this whole experience with the Belfer Institute became a pattern on which you expanded to then bring the MD Anderson. So give me a portrait of kind of how that worked at the institute level.

**Ronald DePinho, MD**

[00:49:24]

So what we did — at that time it was really exciting because the Human Cancer Genome Project — which I had the privilege of being the co-chair of the external advisory board for that project — was just getting underway. And we, even before that, my lab and other labs were focusing on what appeared to be a treasure trove of new cancer genes. And the Human Cancer Genome Project has since allowed us to recognize that we were dealing with the tip of the iceberg in terms of the genes that cause cancer; that we now have a pretty good understanding, a more complete atlas of the genes that are abnormal in cancer. So, at that point, we developed a pipeline that allowed us to take those new genes that were being discovered with genomic science, and functionalize that information to say, yes, they are in fact a validated gene, and to develop the strategies that would allow us to then develop the drugs against those genes, and test them in sophisticated model systems, and do so on an industrial scale. That is, individual labs, it was clear, were not sufficiently resourced, nor had the capabilities to systematically convert that
into an endpoint that would be useful. And they tended to occur in a Brownian Way, through collaboration — you know, collaborate, lab A will collaborate with lab B and bring the ball down the field a little bit further down the field, then lab B will collaborate with lab C or D. You know, it kind of works in this more haphazard fashion. Here what we did was organize ourselves, in a way that would allow us to develop systematic translation of discoveries and integrate knowledge and disciplines across that developmental process. And so, since we have that, that enabled us to then work productively with the private sector, because now we could go to Merck, we could go to a [Synochem?] event and establish tactical relations with them that allowed them to develop the drugs, because they were the best in the world at developing drugs, and our developing capabilities were still vestigial, so we did these alliances where we would bring the biology and the clinical insight, and they would bring the drug development expertise. And those were very exciting collaborative relationships that allowed us to bring in resources and at the same time work more productively and help pharma develop drugs and programs that, you know, are still in development.

_Tacey A. Rosolowski, PhD_

[00:52:20]
Did it take some effort to kind of convince people of that vision? I mean I'm thinking that sometimes there's a view of academics, for example, that they work in a certain way, that the industry may be like, OK, they're not so concerned about stakeholders. So what was the process of communicating?

_Ronald DePinho, MD_

[00:52:39]
It was not easy, because it was a cultural transformation as anything else. Because for many, many centuries, academia celebrated the individual, yet we were clearly moving into an area where we needed to do more team science to be able to help patients, so that was different. Working productively with pharma in a way that allowed us to preserve our research integrity, and maintain our focus on the elemental truth of a biological process, and to validate targets, validate drugs against those targets, develop experiments that will allow us to very, very directly address the critical clinical questions that would emerge — those were all new. And it required organizing ourselves in a way that allowed us to bring together those different disciplines seamlessly. And that proved to be quite successful, but it was a learning process, because it's a lot easier to do the things that academia's been great at doing, which is, you know, you pursue questions, you get grants, you publish papers, you train the next generation, and that's great. And I love that. And we support that here at MD Anderson, and we celebrate it. But it's also important to recognize that we have a solemn responsibility to convert knowledge into things that make a difference. You know, the famous quote, "Discovery is not enough. We must do. We must apply." That's something that has been a big focus for myself and my career and the kinds of programs that I've tried to organize.
What were some of the big lessons learned through those years at Belfer as you were beginning to get that engine — because that's a word you've used, the engine of discovery — how to get that on track?

Ronald DePinho, MD

Well, it was first of all very important to develop strategies that people felt they would all be respected for their contributions. That was important because academia wasn't set up that way. So we worked very hard on that, to make sure that we gave attribution to those that were contributing. There was also the challenge of accountability. The notion here was that it wasn't enough to just be active, that results mattered. And that we were getting resources and we had milestones and goals that we had to achieve that was also different, and that required an understanding of, you know, the whole concept of to whom much is given, much is expected. That was also important. That was also challenging for academics that were interested in just the sole pursuit of knowledge, which is important, that leads to Nobels, that has cured many diseases, and we don't want to change that. But we wanted to add a dimension of get the job done, of accountability. And that was also a learning curve as well. And then there was the communication — communicating what the construct was all about. It was first and foremost about the patient, about impacting on the problem, and using all the different component parts so that everybody was putting their oar in the water and rowing in the same direction, be it the academic, the drug developer, the private sector, the government. You know, we were all going to try to organize ourselves in a direction that would make sense for patients and do so more quickly. So those were all things that allowed us to, you know, develop this construct, which was a great learning process and it proved to be very successful. And it was a construct that made me realize that we could expand and export that further. Think of the 1980s, when we had translation. The word translation was new, and it took us twenty years before translation became very systematic and ingrained in our academic culture, where it was celebrated. When you think about applied science, which is this integration and directiveness of how we convert knowledge into practical endpoints, that's something that is also new, and I think requires an evolution of understanding, so that we can more effectively empower such a system to acknowledge, reward individuals that are participating in this, and to enable us to track the resources that are needed, which oftentimes dwarf that of individual science activities and so on. But the returns for these are great, and we've already seen those returns.

Tacey A. Rosolowski, PhD

We're almost out of time for today, and I don't want to intrude on the rest of your afternoon, so is this a good stopping place?
Interview Session: 01
Interview Date: February 23, 2015

Ronald DePinho, MD
[00:58:24]
I think just to continue this one point for a few minutes.

Tacey A. Rosolowski, PhD
[00:58:28]
Sure.
I think that the next question is the MD Anderson part of this. And, you know, I was very happy at Harvard in the Belfer Institute, collaborating and coordinating with the private sector to advance medicine for patients, and fulfilling a role in my collaboratory environment, training some really gifted folks who have since gone on to have really exceptional careers. And when the opportunity came for this position, I recognized that MD Anderson was a unique institution, in that it already had this culture of collaboration and collegiality. It had a critical mass of both basic translational, as well as clinical, science. It had a global reach, so that if things were discovered, it would maybe be more — it would be easier to facilitate the exporting of that knowledge to parts, other institutions around the world, other parts of the world. And so, in arriving here, and recognizing the excellence and potential of the institution, I thought about where the field was in terms of its conceptual maturity — Cancer Genome Project, knowledge of how the immune system works, and other major advances in the technology of genome sequencing, cognitive computing, the ability to manipulate genes at will, genetically engineered models that have matured — all of those things were converging at a time when the institution, the field, was poised to seize the moment and apply that knowledge more vigorously. And that's one of the things that inspired me about this place. I recognized the tremendous potential that it held to be the leader in taking all of this amazing knowledge and converting it into new drugs, new diagnostics, new standards of care for patients, as well as prevention and early detection strategies. So that then led to the launch of the Cancer Moon Shots Project, which had several basic elements. One was getting back to the accountability and the goal-oriented aspect. It was about reducing cancer mortality. That was the main metric through which we judged success. The projects would be projects that would be resourced enabled. A lot of times our projects are resource limited and we shorn our projects into what we can afford. This was, we were going to try to do the right thing and try to get the right resources. We were going to bring together the disciplines needed to be able to accomplish the goal. There was also going to be a backbone of directed activity in the form of platforms like the one I described earlier, the Belfer Institute,
which was only for drug development, but we were going to develop this for other aspects of what was needed to get the job done. And that related to work and big data and analytics, it related to cancer control and prevention, which involved policy education services, of course drug development and diagnostics that can detect cancer earlier, things of that nature. So there, in those platforms, you have more professional staff that are now poised to work with the scholars here to be able to more systematically drive these unprecedented opportunities that we have in medicine, because of the science of the last decades, to more rapidly accelerate declines in cancer mortality and save lives. And, you know, we have had a number of cancers, a number of projects that have gotten started. We've seen some progress that has been very exciting in a few of them. So this is another area where, you know, no one's done this before, and we're trying to organize ourselves and learn as we go to make it more effective. But we're doing something that no one's tried before, and it's enabling us to apply a new dimension to our capability. It doesn't replace what we have done, but it adds this new dimension so that we can more reliably move the ball down the field to help patients.

_Tacey A. Rosolowski, PhD_
[01:03:34]
Well I thank you for your time today, Dr. DePinho.

_Ronald DePinho, MD_
[01:03:36]
Thank you very much.

_Tacey A. Rosolowski, PhD_
[01:03:37]
Yes, and I am turning off the recorder at about nineteen minutes after three.
Ronald DePinho, MD

Interview Session Two: 18 June 2015

Chapter 00B
Interview Identifier

Tacey A. Rosolowski, PhD
[00:00:00]
All right, our counter is moving. I'm Tacey Ann Rosolowski and today is June 18, 2015. The
time is about ten minutes after ten. And today, I'm on the twentieth floor of Pickens Academic
Tower, in the Office of the President, interviewing Dr. Ronald DePinho for our second session
together. So I wanted to thank you for making time in your busy schedule.

Ronald DePinho, MD
[00:00:25]
Good morning.

Tacey A. Rosolowski, PhD
[00:00:26]
And also wanted to note that Brette Peyton is also present for this interview session.
Chapter 07

A Complex Economic Environment Presents Challenges to an Academic Medical Center

B: Institutional Change;

Story Codes
A: The Leader;
A: Overview;
B: MD Anderson Mission and Values
B: MD Anderson Culture;
B: The Business of MD Anderson;
B: The MD Anderson Brand, Reputation;
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: Fiscal Realities in Healthcare;

Tacey A. Rosolowski, PhD
[00:00:26]
So, I wanted to start today with the comment that I've heard from a number of people at the institution, which is that MD Anderson has always managed to have the right president for its historical moment. And one of the things that, of course, has been going on in the past number of years and when you took on the institution, was enormous changes in the economy of healthcare. So, I wondered if we could start with your perspective on that general context, and then kind of get into more of what you've been working with at the institution, kind of transforming the institution to meet those challenges. So talk to me about that a bit.

Ronald DePinho, MD
[00:01:16]
Well, this is a time of change; it’s a time of not simply economic change, but also opportunities for good change. And so, you know, much of the national debate has focused on the Affordable Care Act and trying to bring the uninsured into the system, trying to move our healthcare system to a more evidence-based, quality-based, outcomes-based efficient healthcare delivery system, as opposed to the reactive, provider-centric, disease care system that we have. And so those are forces on the healthcare system that address those critical gaps in our healthcare delivery, but also the burden of the cost of disease from an economic standpoint on the nation, as well as from
a health and productivity standpoint for its citizens. And so, we need to do better. And so, this has been a major push. And so, what has been going on in healthcare, is to try to drive unnecessary costs out of the system by having a, let's say, a more quality-based delivery activities, and not necessarily based on simple activities — fee-for-service related activities. And so, this is all good, because it provides us with opportunities to make sure that we're delivering, you know, the best care possible to the right patient in the right context. So that's been very, very helpful. At the same time, academic medical centers have a very complex mission, in that we're not simply delivering care, but we're also attempting to drive new standards of care and training the next generation. And so, these economic forces on the healthcare system are also operating on these key academic medical centers, leaders in their field, which are responsible for improving health through science and through education. So, the pressures that are on academic medical centers as a result of the economics and the diminished reimbursement is one that is a key issue that we have to pay attention to as we make these changes. And so, we — and other academic medical centers — anticipate about a twenty percent-plus decline in reimbursement through the end of the decade. So if you look at those economics, and you look at the fact that our costs are going up, our patients are increasingly more and more complicated, and they require significant care, that these are challenges that require us to evaluate how is it that we can maintain our financial vigor so that we can maintain our mission of research, exceptional care, and driving new standards of care as well as education and prevention through a variety of different strategies.

And so, one of the things that we've been doing here is to look at the economics of the institution to try to maintain our costs and do things more effectively and efficiently. Through, for example, electronic health record, activities that will make us more effective and efficient. At the same time, we are developing a strategy to increase our network throughout the United States. This also provides us with increased patient volumes that allow us to impact on patients, but also provide us with additional sources of revenue. We are working very hard and trying to enhance the effectiveness and impact of our faculty, so that they'll be more competitive for extramural grants. This includes the development of platforms that enable them to move their discoveries further down the field so that they can have higher-impact science coming out of their labs and out of the clinics. We are developing collaborate alliances with the private sector, including Biopharma, so that we can secure resources through those relationships, but also provide opportunities for increased drugs for our patients that are failing standards of care. We have enhanced dramatically our ability to secure philanthropic funds, and through a variety of novel strategies that include international fundraising, cause marketing, e-philanthropy, to name a few. So as we look at the economics and through the lens simply of clinical revenue, it's clear that we needed to diversify our revenue stream in the way that I just mentioned. Finally, as a result of our development of the Moon Shots and the platforms where we had the ability to mature ideas and assets — drugs, diagnostics — more than most academic institutions, we've been able to realize significant new sources of revenue through our intellectual property.
Chapter 08
The Moon Shots Program: Concept, Operations, Some Results
B: An Institutional Unit;

Story Codes
B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
B: MD Anderson Snapshot;
B: MD Anderson Impact;
B: Institutional Processes;
B: Devices, Drugs, Procedures;
B: MD Anderson Mission and Values
B: MD Anderson Culture;
C: Understanding the Institution;
C: The Institution and Finances;
C: Research, Care, and Education;
B: Industry Partnerships;
C: Discovery and Success;

Tacey A. Rosolowski, PhD
[00:07:40]
I wanted to go on and talk a little bit more about the Moon Shots, if that's OK. And I wanted to
start with when you decided on that particular metaphor for this enormous push and this way of
intellectually organizing this new initiative at MD Anderson.

Ronald DePinho, MD
[00:08:00]
Well it — yeah, first of all was inspired by the fact that this is an extraordinary institution with
tremendous potential and a global reach, with the capacity to take on bold initiatives, and it has
done that repeatedly throughout its history. Secondly, we have a really extraordinary game-
changing advances in both technology and our understanding in cancer at this particular moment
in time. And so, the ability to really seize the moment and drive those discoveries and exploit
those technologies in ways that were unimaginable just a half-dozen years ago, is also important
to appreciate. The concept of saying we're going to do a Moon Shot — Moon Shot, Manhattan
Project, Human Genome Project — all of these projects are goal-oriented projects. And in each
project, there was a clear goal. And in this case, the goal is reducing cancer mortality as rapidly
as possible, and as significantly as possible, through projects that get nominated within the next
ten years. And very similar to what Kennedy [John F.] said, "We're going to go to the moon and
come back," he didn't specifically prescribe how we're going to get there, but he recognized that
Interview Session: 02
Interview Date: June 18, 2015

we were on the precipice of technology and understanding of rocketry and material sciences and computer science and so on, that it was possible if we put our minds and will to that task. And so, in a similar way, we've done that repeatedly throughout our history with the Manhattan Project, with the Moon Shot, with the Human Genome Project. Seemingly impossible projects, but on the precipice of, you know, being in a position to actually do it, but it would require the ingenuity, the will, the drive, and the resources and focus in a goal-oriented way, as opposed to just simply thinking about the next experiment. The other aspect of this is that for all of those projects, it required multidisciplinary activities. So if you look at the Manhattan Project, if you just had theoretical physicists, or bomb makers, or material scientists, or engineers, you wouldn't get there. It required a, you know, village of capabilities. So in the same way, with our Moon Shots initiative, we recognized that we were gonna have to have policies, education, new therapies, diagnostics, and a variety of different strategies that were going to impact on mortality statistics down the road. So prevention, early detection treatment, and so on, were all gonna be important in launching this. And by the very definition of that, would require multidisciplinary capabilities. The other things that we learned about the Manhattan Project and the Moon Shot initiative, again drawing from that inspiration, is that you really needed to have those that were discovery-oriented, and highly creative — your scholars, your theoretical physicists, for example — and at the same time, you needed folks who were gonna get the job done, the engineers. And that's in a sense, we've embodied that in the context of the Moon Shots through the collaborative nature of having all of our academic scholars work closely with industry-seasoned individuals that work in our platforms that are the equivalent of the engineer part. So there's the discovery part and the do part, and so on. And so I think that all of those analogies were all drawn from the Moon Shot, the Manhattan Project, and so on.

Tacey A. Rosolowski, PhD
[00:11:57]
I've talked to some people who really appreciate the fact that it doesn't have a military - it's not a war on cancer. People said they're really tired of the military metaphors, and that this has a different feel, and also something that the public can understand very easily. I wondered if issues like that were part of your thinking at all in choosing this.

Ronald DePinho, MD
[00:12:21]
Well, you know, we recognized — we wanted something that folks could understand through something that captured the imagination of the public in the past. So, you could've picked Manhattan Project or the Moon Shot. Each of those had a sense of urgency. They were goal-oriented, they were milestone-driven, they were multidisciplinary, and so on. So that was one of the things actually labeled it. If we'd simply said, "We're gonna go flagship projects that are gonna reduce cancer mortality," that would not help the public understand what we were trying to do and the scope of which we're trying to — the scope of the problem, and also the opportunity. The other aspect is that, if we had something that was understandable and
inspirational, we would get the support of the public through new philanthropy, and we've been very successful in that regard, recognizing that when I came in, we were at the tail end of the most significant capital campaign at the institution. And so, in the wake of any large campaign, there's donor fatigue, and so, you know, it really required something extraordinary for folks to say, you know, I think that this is incredibly exciting, the resources that I have committed to the institution have provided us a foundation and put us in this position, but now we really want to actually get the job done. And folks recognized that this was, you know, an opportunity, that the field was presenting itself, and that MD Anderson was well positioned as the NASA for cancer science and cancer care. And so that then proved to be true. That proved to be very successful. Since we launched — since the end of the last campaign, we've raised about $600 million in philanthropy. And then as a result of the platforms that we've developed, we've since raised a few hundred million dollars already in IP strategic alliances and so on, which may grow significantly as milestones unfold.

*Tacey A. Rosolowski, PhD*  
[00:14:50]  
I'm sorry, what does IP mean?

*Ronald DePinho, MD*  
[00:14:51]  
Intellectual property.

*Tacey A. Rosolowski, PhD*  
[00:14:52]  
Oh, OK.

*Ronald DePinho, MD*  
[00:14:55]  
And this, you know, will obviously put more fuel in the rocket for us to get there.

*Tacey A. Rosolowski, PhD*  
[00:15:00]  
Who were some of the people that you sat down with when you were strategizing — you know, choosing this label?

*Ronald DePinho, MD*  
[00:15:08]  
Well the label, I think, came from myself. But the concept of how to go about and do it engaged about 600, beginning with disease leaders and the cancer center core grant. So we have a core grant in which we have various disease leaders, and so I was very lucky in that I was able to just go to those disease leaders and say, you're already charged with the responsibility of leading this
particular disease, and this area, I want you to lead think tanks to figure out, you know, if we were gonna do this, how would we do it? And what would the projects look like? And I gave some guiding principles. Had to be goal-oriented, not just simply the next experiment. Had to impact on mortality. Had to bring in whatever disciplines were needed, so it had to be very inclusive, and it had to be technology-enabled and identifying what those gaps might be — in drug development, diagnostic development, intellectual, the information technology platforms — things of that nature. And so that's how we put it together, and it was very easy to do, because we had the framework from the cancer center core grant, so we really got off to a running start.

Tacey A. Rosolowski, PhD
[00:16:40]
Now, I know we spoke last time - when we spoke last time, you gave some examples of how this all functioned. But I wondered if we could revisit that, because — remind me when you sent out this request to the disease leaders to present these proposals.

Ronald DePinho, MD
[00:16:56]
It was early on in my tenure. So I think the earliest discussions that we had were within about — within six months of my arrival. I did want to study the institution and see if my impressions were, in fact, accurate, that we had a very collegial, multidisciplinary culture here, that people were really interested in solving big problems, and that we had infrastructure and resources and talent to be able to do that. And all of those boxes were checked. So in the first six months, it was more assessment. And then, there was another six months of thinking behind this, in terms of, you know, what are the cancers and what are your best ideas, and do you have a team that we could deploy to get this started, all of those things. And then we did an external and internal review of that peer review of the projects of the diseases -

Tacey A. Rosolowski, PhD
[00:18:07]
To see how effective and how promising it would be?

Ronald DePinho, MD
[00:18:09]
Yeah, there were two dozen internal/external peer peers that reviewed us, that that was important and that that then led to the first half-dozen cancers, and amongst those cancers, prioritization of about a dozen major projects, major flagship projects. And we got off and running as a result of that. In the first year we spent most of our time on building platforms, building teams. So we didn't expect any major projects, but we were fortunate getting some early wins right out of the gate.

Tacey A. Rosolowski, PhD
Interview Session: 02
Interview Date: June 18, 2015

[00:18:45]
Now describe to me these platforms for the record.

Ronald DePinho, MD
[00:18:50]
So in academic medicine, we discover. But the discovery and its conversion into something that makes a difference in patients requires a different set of capabilities to, let's say, convert a target in cancer as a result of some genetic mutation, into a drug that is tested pre-clinically and then eventually advanced into the clinic, right? And so, the discovery is key, but the ability to then convert that discovery into something that will make a difference for patients, is something that academia typically doesn't do. And we sort of leave that up to the private sector to do that — biotechnology, or the government in terms of policies or educational systems in the media in terms of education, and so on. And so, what we decided to do was to establish that directional capability within the academic setting. So this is very novel, it's perhaps the most novel aspect of the approach, which is that we would have scholars, but we would also bring in individuals largely from industry that were capable of understanding how to convert an idea into something that would make a difference for patients. That something could be a drug, it could be a diagnostic, it could be a new policy through legislative activity, or it could be educational curriculum in K - 8 that would influence children to lead healthier lifestyles for decades to come, and so on and so forth. Those kinds of capabilities, which are embodied in approximately ten platforms, are typically not resident within an academic organization. Some components of that are, but not in the way that we've organized it, nor at the level of, let's say, sophisticated structure, governance, critical mass, and resources. So these are very, very significant engines that are responsible for driving knowledge to these clinical endpoints. And we have websites, you know, video clips of what these platforms are, if you needed more information.

Tacey A. Rosolowski, PhD
[00:21:42]
Yeah, I've had a little bit of a look at them. I wanted to kind of get your take for the record. And also, I mean this — I mean, as you mentioned, it's a novel, very unusual way of setting up, or contextualizing discovery within something that has not appeared within academic medicine before. What are some lessons you learned in setting up this process? We're coming up on the anniversary of the Moon Shots, as Brette reminded me a while ago. But what about this process has been an education for you?
Chapter 09
A Brief History of Translational Medicine
A: Overview;

Story Codes
A: Overview;
D: On Research and Researchers;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
D: The Healthcare Industry;
D: On Pharmaceutical Companies and Industry;

Ronald DePinho, MD
[00:22:16]
Well, I'll answer that. But I think it's important to appreciate that at various points in the history of academic medicine, we've gone through very similar transitions. So in the late 1980s, we began to think about translation. So, up until that point, basic discovery in the laboratories and what was going on at the clinic was very, very separate. It was a true continental divide between those two activities. And, in fact, when we began to talk about, "Well, how can we convert this science into something that would matter for patients?" The basic scientists - the vast majority of them were saying, "I'm here to pursue truth and knowledge. I shouldn't be asked to think about application." And so, there was a real cultural difference between those two domains. And it took about fifteen years before that was fully embraced, and in fact, held on the highest levels of esteem and respect within the medical community, and the life sciences in general. And it took that time to really get us to the point where we were mature enough. And now, almost any basic scientist will want to ask the question, "Well, what is my very basic science work mean for disease, pain and suffering, and so on?" So I think that's been a major transition. And I would say that we're at a very similar point where we don't do a great job in translating ideas systematically. So you have to ask yourself, "Well why is that?" And you know, we have the light on the private sector to take the ball down the field, to a certain extent. But the private sector can't quite do it in the way that it needs to be done, and so you can look at the gap analysis and ask the question, "What do you need to ensure that ideas really reach those endpoints that matter for patients."

Tacey A. Rosolowski, PhD
[00:24:52]
Why doesn't the private sector do it so well?

Ronald DePinho, MD
Well, they're driven by a different set of motivations, right? You know, they're interested in market share shareholder value, and so on. Our shareholders are the patients, making a difference for humanity. And of course, Biopharma and biotech do that in the end, they help alleviate pain and suffering through the good work they do. But they're not going to, say, focus on prevention. How do you, you know, enact new legislation and new curriculum for kids, you know, and so on. So that's something that we need to recognize. Similarly, early detection of cancer. They may not be as motivated to work in those areas, because the return on investment wouldn't be as high; rare cancers, including pediatric cancers, and so on and so forth. So there are things that we, I feel, have a responsibility to follow through on, and to make sure that we're helping all patients that are afflicted with this disease, and so on. In terms of the lessons that were learned, I would say that the most important is — and this is true for change in general — that we needed to do a better job in communication. That, you know, like with any idea, the idea can bring excitement, but it can also bring confusion and anxiety, because change is not easy for the majority of individuals. It's — we're wired to, you know, gravitate towards the known, and not the unknown, although some of us are wired to pursue, you know, those frontiers. So I think that there needed to be more effective communication, and it's very challenging in an institution of 21,000 people with over 1500 faculty at the time that have many different interests. Of course, united by the mission of Making Cancer History. But you know, the approach in academic medicine has been small teams, individual science, which has made us great and has been very effective and we're not changing that. But the idea that we're adding a new dimension of capability, just like in the 1980s we added a new dimension called translational medicine — with something that we needed to do a better job.
Chapter 10

*Lessons Learned from the First Years of the Moon Shots*

**A: The Administrator;**

Story Codes
A: The Administrator;
A: The Leader;
B: Building/Transforming the Institution;
A: Obstacles, Challenges;
C: Professional Practice;
C: Leadership;
D: On the Nature of Institutions;

**Ronald DePinho, MD**

[00:24:54]

So I'd say one important lesson would've been you can’t communicate enough to get people to understand what it is and what it isn't and so on. As folks have gotten to understand it, and most importantly, vision is one thing, but results are another. That as you begin to see the philanthropic success, the IP success, which is external validation, the increased number of grants that are now more competitive, the increased quality of the publications that we have, and most importantly, the results that we've been able to produce, it has, I think, galvanized a significant fraction of the institution and our supporters. And at the same time, we have tried to become more inclusive and engaging. And this past year, we called for proposals for a new set of Moon Shots — pilot Moon Shots — that were initiated. And those have now undergone their first year of review for the potential to scale to the next level, which would be a full Moon Shot. So —

**Tacey A. Rosolowski, PhD**

[00:29:07]

What are some of the areas that you're anticipating adding to the Moon Shots?

**Ronald DePinho, MD**

[00:29:12]

Well, the new — the new cancers, which we can give you the list, include cancers like colorectal cancer, pancreas cancer, glioblastoma, brain cancer, HPV-associated cancers, certain forms of lymphoma, there may be one other. And those are added on to the ones that we had previously. And it's a reflection of the fact that the program's working, it's breaking new ground, it's enabling people to do things that they couldn't have done previously, and it provides them with resources to do those flagship projects that their collective wisdom has said, these are the best projects that we can do, but we don't have the technological support, we don't have the monetary support, we don't have the multidisciplinary teams to do it, so this organizational construct has enabled us to
do something we couldn't have done easily in the past.
Tacey A. Rosolowski, PhD

[00:30:17]
You mentioned results, and I wonder if you could take me through a project that is yielding some really interesting results.

Ronald DePinho, MD

[00:30:25]
Well, we have a couple of really astounding results. One — perhaps the best and the most unexpected is in ovarian cancer. And in ovarian cancer, when a patient presents, patient undergoes surgical intervention, most disease is fairly advanced, and what you try to do is you try to eliminate as much gross disease as possible, achieve what's called R-0 status. And about twenty percent of patients in the field are able to achieve that level of status, at the time of closure no gross disease that could be observed. And then those patients go through systemic therapy, and about eighty percent of those patients do extremely well at five years — very good prognosis. On the other hand, at the time of closure, if you have R-1 or higher disease — you have some residual disease that you can see — those patients do very poorly. And in fact, R-1, -2, -3, or -4, it's as if you never had surgery. So those patients do very poorly, with about a twenty percent survival rate at five years. And so, this was an example of two different groups coming together around a woman's cancer Moon Shot, so over 100 investigators, clinicians, scientists, got together in both breast and ovarian cancer. In breast cancer, the way that they had done it for the last couple of decades, which has driven the enormous survival statistics for breast cancer, is if you have large disease, you first undergo a few rounds of systemic therapy. Then you do your surgery. And then you continue with your systemic therapy. That has led to tremendous increase in survival. So when the ovarian cancer folks were starting to communicate
with the breast cancers — and they don't normal go to the same meetings and so on — they began to question, "Why are we doing this way? There has not been an increase in survival of ovarian cancer since the 1970s — why are we doing it this way?" So they got together and they developed what they call the Anderson Algorithm. And what they do is, two surgeons get together, do a laparoscopy, if the patient is deemed surgically acceptable, that patient undergoes surgery, followed by systemic therapy as usual. However, if they agree that the patient cannot achieve R0 status at that point, then what they do is they go through three rounds of chemotherapy before surgery. And in those cases they went from twenty percent to eighty-eight percent R-0 status. That's an astounding result. We don't yet know if that's going to translate into increased survival, but we full anticipate that it will, and it could save thousands of lives per year. There are 14,000 deaths from ovarian cancer per year. So that's an example. And frankly, if that's the only success that we had in the Moon Shot initiative, you know, we hope that it's going to be a lot more, but I think that's going to be a really exciting opportunity. The other exciting thing about the Moon Shot initiative is that in the context of ovarian cancer, when you isolate — when you have the laparoscopy, and you say I can't achieve R-0 status, you can isolate tissue and cells from the peritoneum at that point. And then, when the patient is undergoing their three rounds of chemotherapy, you can also add a novel agent, to see if you can improve still further the ability to impact on the disease. And then at the time of surgery, you can harvest tissue again, and cells, and see how the drug did, the new drug. So this will dramatically accelerate our ability to assess the utility of new drugs in the pipeline for ovarian cancer through what we call "window of opportunity" trials. So even if this leads to a marginal increase in survival as a result of the algorithm itself, which I believe it will have a significant impact on survival — but even if its marginal, just that framework allows us to drive a significant number of compounds into and through ovarian cancer trials that could have a profound impact on developing new standards of care, and dramatically accelerate progress. So that was one example. The other example that I think is gonna be equally impactful relates to prevention. And here's an example where we have a lot of scholars and prevention that say, we are going to, you know, discover what causes cancer, and we're going to push information out there in hopes somebody is going to be inspired enough to develop a new policy, or K - 12 curriculum, or educate the public, all right. And it happens to a certain extent, but not as much as one would imagine. So we developed — one of the platforms we developed was a cancer control platform. And in this platform we brought individuals expert in legislative affairs, education, and in services. And in the context of this, what we have learned is that when you bring those prevention scholars and disease experts, in let's say melanoma, where we know UV is a major instigator of melanoma later in life, that it then enables us to bring that knowledge through the capabilities of a legislative affairs expert in the cancer control platform of professional and legislative activity that don't normally interact with the prevention folks, but here they are — the scholars plus these professionals in the platform are able to say, "What can we do from a policy standpoint that would impact on the exposure of children to harmful UV, which we know to be a major cause decades later of melanoma?" And so we — one of the first states, as a result of this platform, to enact tanning bed legislation. There are now eleven states that protect children from
the harmful effects of tanning beds, which are a major cause of harm and skin cancer, melanoma, and so on. And now we're working with fifteen other states as well, and this legislative session to try to drive tanning bed legislation as well. In addition, we've signed an agreement with the CATCH [Coordinated Approach To Child Health?] program, which is the program that focused on K - 8 education for obesity, profoundly impactful and success program in obesity, and we're working with them and in the 9,000 schools that they're in to try to develop curriculum that would teach children about, you know, what they can do to protect themselves from UV, or from tobacco use, and so on and so forth. So these are examples where two plus — one plus one equals eight. You know, where you have the scholars and the disease experts coming together with the platform professionals to be able to enact policy, education, and so on. So those are two significant success stories. Just heard on the way over here that the governor just signed the health bill which includes HPV legislation, which will help us further educate the community on the benefits of vaccination of children for HPV, which is a major opportunity for preventing a cancer from happening in the first place.

[00:38:48]
Chapter 12
Reflections on the Need to Support Both Team Science and Individual Investigators

Ronald DePinho, MD
[00:39:00]
Well, I think that science in general has gotten extremely complicated. And it requires many different technologies and disciplines to understand and answer, you know, big, big problems, big questions. So, you know, the shining example of this was Watson and Crick and the discovery of DNA. It was two authors on that 1953 paper. And then in the year 2000, when the Human Genome Project was published in Nature and in Science, there were hundreds and hundreds of investigators that were authors on that paper. And so, it just takes a village to be able to tackle the big problems - technology, knowledge, and so on. And so, folks recognize that, and so even my own career, in the 1990s I had five RO1 grants. These are investigator-initiated grants that are about specific problems in a single lab, typically. And ten years later, I had one RO1 and four multi-investigator grants that I was part of. And so, my own career was a reflection of the evolution from single investigator-initiated activities to multi-investigator. At the same time, it's important that we support those individual investigators. Those are the individuals that, through pursuing very fundamental concepts and thinking deeply about a very specific problem, you know, are going to break new ground and teach us things that we can't yet imagine — the Noble Prize-winning results. A good example of this is Jim Allison, who was my first recruit when I came here. Jim, in the 1990s, asked the question of how the immune system as regulated, and whether or not those regulatory switches are relevant to cancer. He discovered a brake on the immune system, he developed a drug to deactivate the brake, and that knowledge has now been converted into new classic drugs that when given to patients with advanced...
cancers, reawakens the immune system, and in a good fraction of patients, they have curative results, you know, really durable responses, no evidence of disease many, many years out. So that's an example where you want to foster that individual science, but there are times — and the Moon Shots is reflected in this — where you reach a point where you have a "line of sight," you know where you need to go, and it becomes more reduction of practice, and that typically requires large teams that are adequately resourced, and that are technology enabled.

_Tacey A. Rosolowski, PhD_
[00:42:14]
I've noticed too, in speaking with people, that it also takes a different kind of skill set. I mean, a number of the investigators that I've interviewed talk about how their careers began with the single investigator model but then transformed, talked about having to learn how to open their minds to a new language. You know, a new way of organizing concepts and paradigms to communicate with people who would be potential collaborators. And that can be a very new activity for a lot of people who have been raised in a — you know, come to their professional lives under a different system.

_Ronald DePinho, MD_
[00:42:50]
That's true, but I would say that that evolution has been ongoing and steady over the last twenty-five years. I think this is something that, you know, folks from the very beginning, as graduate students or clinical trainees, learn that they have to work in the context of multidisciplinary teams. I mean the clinical researchers have known this for a very long time that it takes a very large number of individuals to do clinical trials. You need to bring together interventional radiologists, molecular pathologists, surgeons, imaging experts, oncologists, scientists, to be able to do a clinical trial. And so it has been the norm in clinical research for a while. I think what you're beginning to see is increasingly, on the science side, more and more multi-investigator type initiatives. You're seeing those initiatives cross institutional boundaries, where you have multiple institutions that are working together to take on these problems. There aren't too many institutions like MD Anderson that have this critical mass, and you, in many cases, can find a lot of capabilities here within our walls. But even our problems, you know, could be enhanced still further by multi-institutional initiatives.

_Tacey A. Rosolowski, PhD_
[00:44:20]
Are you considering any of those now, or anything like that —

_Ronald DePinho, MD_
[00:44:22]
The Moon Shots, you know, are scaling to global projects. So, one in particular is our early detection of lung cancer, which is in the lung cancer Moon Shot. There, we are working with
many institutions in our global program in other countries, in particular, China, Brazil, Germany, where we have institutions that are gonna be enlisting patients into a clinical trial that will try to design a simple blood test as well as CT scanning to look for early stage cancers in the lung, which is, they're highly curable relative to the ones that are more advanced. So that's an example, and in fact this Sunday, the Vice Premier of China is coming, and that's one of the topics that will come up. They're very excited that we've launched this major project that will hopefully save many lives through early detection of lung cancer, which is a big problem in China, because of the tobacco use and the pollution.
Excuse me. I wonder if you could talk a little bit about, sort of next steps in developing faculty initiatives, developing support for faculty.

Well, it's something that we've focused on continually. We have arguably the most supported faculty in the United States of any academic medical center. And we do this through philanthropy, through a fiscally healthy institution where we can plow back our resources to support our faculty. But as importantly, developing the infrastructure that allows them to carry out their great capabilities from developing new ORs that allow our great surgeons and interventional radiologists to do their work, pioneering work in surgery, or the Institute for Personalized Cancer Therapy, the Zayed Building, which will allow us to harness the potential of precision medicine and developing the infrastructure and genomics, proteomics, metabolomics, and data aggregation systems and big data platforms that allow us to learn from every patient and drive our science and our impact as rapidly as possible through those initiatives. It's also about mentoring — mentoring our faculty. So we have launched a new mentoring project that have been enabled us to ensure, particularly those at the beginning stages of their career, understand what they need to do to create and impactful and sustainable career. And another thing that we've done is to open up more grants that are peer reviewed, that provide our faculty with more opportunities to launch pilot projects. And so we have launched the Clark Fellows Program, which is a competitive program that allows our faculty to write proposals that are, again, peer reviewed externally. And this enables our faculty to have access to more resources to drive their specific science. And then, of course, the Moon Shots has brought in new philanthropies for projects that support our faculty as well as the platforms, which enable our faculty to, you know, realize more impact.
[00:48:40]
We're almost at eleven o'clock and I know that you needed to stop early today, so I wanted to thank you for your time this morning.

Ronald DePinho, MD
[00:48:48]
You're very welcome.

Tacey A. Rosolowski, PhD
[00:48:50]
I really appreciate it. And I am turning the recorder off at 10:59.

Tacey A. Rosolowski, PhD
[00:48:53]
Thank you very much.
Ronald DePinho, MD

Interview Session 3: 2 July 2015

Chapter 00C
Interview Identifier

Tacey A. Rosolowski, PhD
[00:00:00]
All right, we are recording. And the time is about twelve minutes after 10 a.m. It is the second of July 2015. I'm Tacey Ann Rosolowski and I am in the President's - the conference room in the President's Office for my third session with Dr. Ronald DePinho. So thanks very much for making time for me this morning.

Ronald DePinho, MD
[00:00:22]
My pleasure to be here.

Tacey A. Rosolowski, PhD
[00:00:24]
Also wanted to note that Brette Peyton is also present for this interview session.
Chapter 14
An Entrepreneurial versus Academic Mindset
A: Overview

Story Codes
A: Entrepreneur, Biotechnology;
A: Overview;
D: On Pharmaceutical Companies and Industry;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
C: Healing, Hope, and the Promise of Research;
D: On Research and Researchers;

[00:00:24]+

Tacey A. Rosolowski, PhD
Well, I wanted to start today in a little bit different place. I — When I was doing my background reading, I came across a phrase that you used to describe yourself, "the serial entrepreneur." I was wondering if you could talk a little bit about the difference in mindset between an entrepreneur and sort of traditional academic mindset that does research.

Ronald DePinho, MD
[00:00:55]
Well, it's an interesting question. So, I think the distinguishing feature of this, as an entrepreneur, is to try to understand how best to reduce something to practice. So, it's converting ideas and discoveries into practical endpoints via diagnostics, therapies, or other aspects that could impact on the human condition. And in order to make that happen, an entrepreneur has to be able to bring together business development strategies, scientific — as well as clinical — development strategies, financing of those opportunities, being able to bring together multidisciplinary teams from different sectors in order to bring it all together so that you can have an engine that can effectively support financially, operationally, and conceptually, the ability to go from idea to a practical product. And so it's a different set of capabilities than academia, which is focused more on discovery. Of course, you have to bring different elements together, so that you can understand the complexity of biology or any other area of scientific discipline. But it — it more's focused on idea generation and trying to illuminate biological complexity, as opposed to applying that information.

Tacey A. Rosolowski, PhD
[00:02:43]
Interview Session: 03  
Interview Date: July 2, 2015

Where do you think you gained the ability to do that? What is it in your experience or inside you that provided you with the ability to create that particular kind of innovation?

**Ronald DePinho, MD**

[00:02:57]
I don't know if it's specific to me, but I would say in general, entrepreneurs are driven by a passion to apply their discoveries in a way that impacts on the human condition. I think that's a common theme that you see throughout, because it's very hard to do, and you have to be extremely driven and passionate. It also - there is a certain level of risk that one is willing to take because the path to realizing the full potential of any discovery is very, very uncertain. And so, there's a very high level of risk-taking that's needed that you're willing to commit your time, your energy, to something that has a high probability of failure, and feel comfortable with that. I think entrepreneurs are also very oriented towards the possible, as opposed to why things won't work. So it's kind of the cup half-full type of orientation where you're always trying to think about the most positive outcome of any particular opportunity. And so, you need that, you have to be able to have that vision, drive, passion and courage to be able to carry this out.

**Tacey A. Rosolowski, PhD**

[00:04:32]
Is there any connection with your, your practice of martial arts?

**Ronald DePinho, MD**

[00:04:29]
I wouldn't say — no, I think they're different. I think that certainly my martial arts has helped me in the sense that it's given me a lot of physical and mental endurance. It does teach you to confront a challenge, which is at every corner when you're trying to do something entrepreneurial. There's a tremendous number of roadblocks. If it were easy, anyone would do it. It would be relatively straightforward. So I think that martial arts has given me the fortitude — the emotional, intellectual, and physical fortitude to be able to take on those types of challenges. It also teaches you a tremendous amount of humility, and that I think helps a great deal, because you have to understand that you don't know all the things that you need to know in order to be able to create a viable and sustainable company, that you have to bring others with significant talent and background to bring to bear on that entity so that it can become successful, because it's essentially a multi-organ system that allows you to go forward. So humility figures very, very prominently into that — discipline, things of that nature.

**Tacey A. Rosolowski, PhD**

[00:06:13]
Are there any generational differences — I mean, I'm wondering if young scientists coming up now kind of embrace an entrepreneurial perspective more easily than individuals educated say, twenty years ago.
Ronald DePinho, MD
[00:06:26]
I think there's no question. I think that more, increasingly so from what I have experienced in the last thirty years that I've been in science, thirty-plus years, is that you've gone from very early on - this was at the dawn of the biotech era when we had recombinant DNA technology - so Genentech, Amgen, all of these companies were just being formed at the time my career was starting, the first few years of my career. There was a complete lack of understanding in general as to what the private sector was doing in academia. No one really talked about it, it wasn't any training, it wasn't necessarily supported. You know, you pursued an academic career, that was your, you know, pure path towards research, teaching, clinical activities, and things of that nature. And then you had this other parallel universe in the healthcare ecosystem that related to taking ideas and bringing them forward through largely large Biopharma. And then, you know, a number of very creative individuals came together across the divide in academia and venture capital and there's some specific individuals — if you'd like, I can name them.

Tacey A. Rosolowski, PhD
[00:08:00]
Sure.

Ronald DePinho, MD
[00:08:01]
But Herb Boyer [Herbert W. Boyer] who was a founder of Genentech, the UCSF investigator. And on the other side, you had Brook Byers of Kleiner Perkins [Kleiner Perkins Caufield Byers], for example, who saw the opportunities of recombinant DNA technology, and then launched what became Genentech. And there are many other examples like this. And so that provided opportunities for there to be some early successes in recognizing that, in order for us to fully realize the potential of any discovery that we're making in the laboratory, that you really had now a new engine for applying that knowledge into something that could impact on the human situation. And so that, then, continued to grow and develop, particularly in certain areas of the country where there was increasingly an aggregation of knowledgeable academics and venture capitalists, as well as large Biopharma that began to coalesce, and increasingly created more and more opportunities for discoveries begin converted into these impactful endpoints. And so that's sort of where we are.

So I think, now, you've gone to a point where there's significant recognition that in order for us to help patients, we have to have different components of the ecosystem come together and work collaboratively in order to bring that forward. So you have your academic discovery engine, you've got your venture capital and biotech engine, which is high-risk and takes these early stage ideas and tries to create some early proof-of-concept, and then you've got your large Biopharma, which are engines for development and commercialization, supporting clinical trials,
and all of those coming together to be able to really more systematically convert that to things that help patients. And then internally at MD Anderson, we're adding a new organizational construct, in which we're taking discovery to a slightly more mature endpoint in the clinical path toward reducing to practice, you know, these discoveries, and so our Institute for Applied Cancer Science, for example, is creating opportunities for us to bring the ball down the field a little bit further, and so that we can then hand it over to the private sector at a higher level of validation. That, we think, is gonna help patients as well.
Interview Session: 03
Interview Date: July 2, 2015

Chapter 15
The Institute for Applied Cancer Science: A Unique Organizational Construct the Unites Academia and Industry

B: Building the Institution;

Story Codes
A: The Leader
A: The Administrator
A: Entrepreneur, Biotechnology;
B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
C: MD Anderson Impact;
B: Institutional Processes;
B: Devices, Drugs, Procedures;
B: MD Anderson Culture;
C: Discovery and Success
B: MD Anderson Product Development and IP
C: Healing, Hope, and the Promise of Research;
B: Institutional Mission and Values
C: Research, Care, and Education;

Tacey A. Rosolowski, PhD
[00:10:54]
Actually the Institute for Applied Cancer Science was my next topic I wanted to talk about. So, could you tell me, that the — it was established in 2011, became operational at the very beginning of 2012, so tell me a bit about setting that up here. What was the process?

Ronald DePinho, MD
[00:11:12]
Well, actually the seed for this really started about twelve years ago at Harvard, where as a result of my experience in biotech, consulting for large pharma, and working in academia, I felt that we were not quite in synch with being able to convert really great ideas into drug development endpoints.

Tacey A. Rosolowski, PhD
[00:11:34]
Where were some of the problem points at that time?

Ronald DePinho, MD
Interview Session: 03
Interview Date: July 2, 2015

[00:11:36]
Well, the simple fact that ninety-five percent of drugs that are entering into phase one clinical trials are failing indicates that there is potential room for improvement. And then if you ask why you fail, part of the reason why there was failure is that, at the pre-clinical phases, there wasn't enough validation of the target, or the drug against the target, in good models systems to give you the visibility you needed as to how to design the right clinical trials. And so we thought that that was one contributing factor. There are others, which we can talk about. But, that was a fundamental issue. And then if you ask, "Well, why aren't we validating?" Part of it relates to the fact that in academia, we don't have the resources, or the time or the right people to be able to do the industrial-level validation of our ideas. There's a different threshold for getting something published in a journal, versus having something being stringently validated enough that you know exactly how to prosecute that opportunity. And so, biotech is the next step in the relay race, but they are very resource constrained, and they can only laser focus on taking that idea and trying to move it down the field as efficiently as possible from a capital standpoint. So they're not well equipped to be able to do the deep biological analysis, again needed for validating that point. So what we did, was we decided to bring together professional drug developers, folks that are dedicated towards deep biological validation and sophisticated model systems, and collaborate with your scholars in the laboratories, and bring the clinical experts into the process early, who are only brought into the process at the very last part of the relay race, when clinical trials are ready, but to bring the disease in sight from those clinicians, the biologists, together with the academic scholars, and professional drug developers, to see if we can't do a better job in identifying great targets, validating those targets, generating drugs against those targets, and generating enough knowledge so that we have a clear clinical hypothesis so we would know in what few patients we would be able to test that drug and would we have a thumbs up or thumbs down, as opposed to the randomized phase three clinical trials which can sometimes involve hundreds, if not thousands of patients, and take a very long process. So, kill early, devalidate at the pre-clinical phase, try to illuminate the path at the early stage clinical phase, so that in a relatively short period of time, you have a very, very clear idea of what you're going to go after. So we've developed that organizational construct. It's allowed us to not only develop our own internal drugs, but because we have a professional staff, its allowed us also to work more productively with drugs, programs that are from pharma and biotech, because we have individuals with a lot of experience internally now that can work with the private sector to also provide opportunities to enhance their probability of success, which again will be good for patients. So I think it’s been a very successful program. At Harvard, we didn't have the drug development; we just had the deep biology and the clinical insight. But here, at MD Anderson, we've brought all of those elements together, plus strong business development, which is allowing us to really bring the ball down the field and have the launch point into the private sector be one that's more productive ultimately for patients and for, you know, those ideas.

Tacey A. Rosolowski, PhD
[00:15:46]
Now you mentioned a few minutes ago that there were some other points of failure within the original model. Would those be relevant to talk about?

**Ronald DePinho, MD**

[00:15:55]

No — I think those are most relating to the fact that in 2003, part of the reason we were failing is we didn't know enough. So now we know more, you know, just because the field is advanced. But what I described was an organizational problem, not so much a conceptual gap. Right? So what we did is, we [inaudible]. And now that we have both the conceptual, you know, strength and insight, coupled with this organizational construct, we are doing very well and providing new opportunities for drug development and bringing those opportunities to a higher point of visibility.

**Tacey A. Rosolowski, PhD**

[00:16:38]

Now, from a slightly different perspective of organization, how is the institute related to the other institutes and centers at MD Anderson? How did you visualize that?

**Ronald DePinho, MD**

[00:16:49]

Well these are institution-wide. They initially were focused on high priority projects that related to the Moon Shots, because that's how we got the Moon Shots going, by having these platforms really be focused on being able to enhance what we thought would be the best ideas in each of these different areas. And indeed, a number of the drugs that we've developed are going to be applied for Moon Shot-related cancers. And that has helped a great deal, and it's also provided the resources to be able to do that. But these institutes that we've established are, you know, institution-wide, and in fact, even relatively early beyond the Moon Shot projects per se, the professional drug developers within the Institute for Applied Cancer Science met with many dozens of investigators. I think initially in the first year, they met and reviewed fifty different research projects here at MD Anderson, looking for opportunities for them to be able to help those projects going on in the labs and establishing collaborations with those labs to enable their ability to bring those ideas into drug development endpoints. And I think of the fifty, there were three that were identified as high priority and two of them have already been licensed for, you know, for development by the private sector.

**Tacey A. Rosolowski, PhD**

[00:18:27]

Now I noticed when I went to the web page for the Institute that it mentioned, you know, orphaned diseases and, you know, meeting unmet needs. And I'm wondering — that sounded — I put that in the context of a conversation we had in one of our previous sessions that one of the benefits of academia is that it could address — it had the leeway to address certain needs that
would not be financially viable for the private sector. So I'm wondering, in terms of that transitional structure, the institute being between private and academic, what are some of the - what are some of the things that academia brings, the academic mindset brings to this whole mix?

**Ronald DePinho, MD**

[00:19:12]

Oh, it brings much. I think that's another aspect that I think adds value to what we're doing. First and foremost, our shareholders are the patients, so we will pursue opportunities that will save lives. Of course, we'd like to save as many lives as possible, so there is, you know, an interest in trying to go after bigger cancers, only because they're bigger problems and more people are suffering. But clearly, we will pursue ideas — good ideas — that will ultimately impact. So we have less of an orientation towards only focusing on quote large markets, and we will go after rare cancers, and we have some examples of that. Secondly, in academia, we can afford to take risks. If we fail and we devalidate something, we continue to exist as an institution. Whereas if you're in biotech, it would be an existential event. And so that is another difference. Another is that we have patience — that is, when things get complicated in pharma, in the private sector, they tend to be dropped, terminated, iced, put on a shelf. But for us, we may continue to, you know, try to figure it out. And we have some — one celebrated example of that where multiple pharma actually failed to reach — go past a hurdle, and we were successful in figuring it out, but it took a lot of patience and collaboration with the investigators and laboratories and that, then, ultimately led to the breakthrough that allowed us to develop a new class of drugs.

**Tacey A. Rosolowski, PhD**

[00:20:58]

And what is that class of drugs?

**Ronald DePinho, MD**

[00:21:01]

It's a drug that is focused on the mitochondria, which is the powerhouse of the cell. It's called an OXPHOS [oxidative phosphorylation] inhibitor and there were simple cross-species differences between mice and humans, and all of the drugs were developed without recognition of that, and so when the drugs were developed in mice, they didn't have the side effects, because of metabolism of that drug was different. Whereas in the context of humans, and soon as those class of drugs enter into early stage clinical trials, they ended up failing because the toxicity was too high. So when we generated drugs, we generated drugs that had similar characteristics in both human and mouse cells, and then brought those forward into clinical trials.

**Tacey A. Rosolowski, PhD**

[00:21:50]
And what kinds of disease does this particular class of drug address?

**Ronald DePinho, MD**
[00:21:54]
A wide variety. It's a very exciting new class of drugs and that's why there's been interest in trying to develop this class, but it's a drug that targets the metabolism of cancers, which are rewired differently. And that class of drugs is applicable to AML [adult acute myeloid leukemia], which is a really virulent leukemia that causes a lot of death. And that's one of the Moon Shots, an example of the synergy, actually, in the clinicians in the Institute of Applied Cancer Sciences because we weren't thinking of leukemia, and it's because we were interacting with the clinicians that we thought of it and we pursued it and it ends up being the top one. So an example of bringing groups together that don't normally coexist.

**Tacey A. Rosolowski, PhD**
[00:22:47]
Yeah. And it's interesting you can't plan it ahead of time. It's like, bang, there's an emergence of information.

**Ronald DePinho, MD**
[00:22:49]
Yeah. It's the power of collective wisdom and multidisciplinary interaction. Not unlike the five men with the element. So that's one cancer, another cancer happens to be pancreas cancer, but there are others. That's going to be a new opportunity for us.
Tacey A. Rosolowski, PhD
[00:23:29]
I wanted to talk a bit about the financial picture that this new focus creates, because research is really expensive to run, I mean this demands a lot of resources, space, equipment. How have the financial needs of MD Anderson to support this kind of research changed, expanded?

Ronald DePinho, MD
[00:23:32]
Well, I think that as a result of inspiring our supporters with the Moon Shots, that's provided us with additional capital, philanthropy that has allowed us to jumpstart all of these platforms, the Institute for Applied Cancer Science being one of ten. And these platforms, professional platforms, that are really focused on delivery as opposed to simply discovery, but working together with the discoverers really was supported initially through philanthropy. And the ideas that have result — as a result of having these engines in place that will now become more competitive for grants and contracts; grants from the federal government, NIH grants or foundations or with pharma we'll have more clinical trials, and things of that nature. That'll bring in revenues. And then also because of what we're creating, some of it may become valuable through intellectual property rights, and then that will provide for longer-term sustainability, but those dollars are typically not seen at the front end. They tend to occur later, but when they do occur, it creates the potential for an evergreen situation. So it's sort of, the business model is front-ended with philanthropy, then bridged, to a certain extent, with grants and contracts, and then at the back end begin to realize, you know, the return on investment from
Tacey A. Rosolowski, PhD
[00:25:15]
The next thing I wanted to talk about is the business development piece. Now there's business development, there are international partnerships doing —

[00:25:25]

Ronald DePinho, MD
Who do I have now? [To another speaker.]

[00:25:24]

Speaker 3: It's — yeah, we need to wrap up shortly.

Tacey A. Rosolowski, PhD
[00:25:28]
OK. OK let me just pause for a second while we strategize. I'm sorry, you said it's novel and doesn't exist, meaning —

Ronald DePinho, MD
[00:25:34]
This particular organizational construct is not present in any other academic institution.

Tacey A. Rosolowski, PhD
[00:25:42]
Really?

Ronald DePinho, MD
[00:25:27]
There are elements of this. There's some drug development, there's some biological capability, and of course, there's clinical trials, but bringing it all together in the way that we have, we're the pioneers for this new organizational construct.

Tacey A. Rosolowski, PhD
[00:26:06]
What do you think the impact of that will be? I mean, beyond having an impact obviously on cancer and patients, but —

Ronald DePinho, MD
Well I think if this construct proves to be effective, and proves to be sustainable, and proves to reduce the rate of failure in cancer drug development, I believe that others will be inspired to pursue the same organizational construct. Of course, in order to do that, you need significant resources. You need the talent to be able to do it. And you have to have the critical mass that we have here at MD Anderson, which is a lot of good science, a fantastic clinical trials engine, and the resources and infrastructure to be able to do the drug development.

_Tacey A. Rosolowski, PhD_

Let me just pause the recorder.

All right, so we're back recording again after about a five-minute break. And I wanted to talk about the whole business development piece. Exploring other kinds of avenues for revenue generation beyond intellectual property. What has been your vision to develop that particular capacity within the institution? Sort of exploring more innovative ways of generating revenue from MD Anderson talent.

_Ronald DePinho, MD_

Well I think relatively early on in my tenure here, as in the first week, looking at the declining NIH budget and the decline in reimbursement, it was clear that we needed to diversify our revenue stream, and great opportunities to maintain our mission through other sources. And so, we did many things to enable that. The first is to enhance our philanthropic capabilities through a variety of strategies, beginning first with integration of marketing communications and development so that they can work more synergistically to enhance the reputation of the institution, get more folks to understand our mission, and potentially help us help others through supporting us. And so we did a variety of different strategies that expanded our reach internationally and nationally, and also engaged other mechanisms for fundraising that include cause marketing, e-philanthropy, international philanthropy, and so on. And so that's proving to be successful, and we anticipate that that will continue to grow because we helped so many and our reputation is truly global and we have a singular focus, so people identify with the concept of Making Cancer History.

The other area for opportunity relates to our clinical operations where we had opportunities to spread our knowledge throughout the United States and around the world, and through those mechanisms, enhance our patient volumes so that we can maintain our revenues,
and at the same time, help more people, especially folks that could not come to MD Anderson. So we reached across to other like-minded institutions that were interested in elevating their quality of care, and in doing so it provided expanded opportunities for us to make an impact on the disease, beyond Houston but also enhance our financial stability. Then also and the — on the faculty side, we have invested in our faculty quite significantly, in terms of recruitment but also in terms of building infrastructure to make our faculty more competitive for grants, contracts, clinical trials. And so that has also proven to be quite effective, and it’s enabled us to bring new dollars in from foundations and from the NIH. And so that's been another strategy. And also related to that are investments in the graduate school, in our trainee programs, so that we'd have really talented kids coming into our labs and our clinics to enhance that capabilities of our brilliant faculty. In addition, we are as a result of the platforms that we've created, it has created opportunities for more mature product development, which realizes higher returns from an IP licensing standpoint, and that has provided us with additional revenue streams. Last year we ranked number one in the country in deals and alliances of any institution in the country, ahead of Stanford and MIT. So that's proving to be successful. Also enhancing our business development and intellectual property offices that enable us to have more sophisticated contracting and deal-making capabilities that also allow us to strike more robust deals so that we can get a higher return on the investments that we're making in our institution.

And then finally we are developing a platform that brings together smartphone connectivity, cloud, and cognitive computing so that we can potentially reach many patients throughout the United States and around the world through those technologies, which may provide additional financial opportunities.
Interview Session: 03
Interview Date: July 2, 2015

Chapter 17
MD Anderson Poised at the Threshold of Opportunity
B: Institutional Mission and Values;

Story Codes
B: MD Anderson Impact;
B: Institutional Mission and Values;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
C: Healing, Hope, and the Promise of Research;
C: This is MD Anderson;

Tacey A. Rosolowski, PhD
[00:32:07]
Well I know we have to close off in just a few minutes here, so I wanted to ask you, is there anything else you would like to add at this point about your vision for the institution and its future?

Ronald DePinho, MD
[00:32:18]
Well, you know, I'm very excited and honored to be here. This is an institution that is the most impactful cancer science and cancer care institution in the world. As such, there's a tremendous responsibility to harness the full potential of that institution, and I think we are — we have the best faculty, we have committed staff, we have a lot of supporters outside of the institution as well, legislative, philanthropic, and other, that are providing us with an opportunity to really make an impact on the problem. That, coupled with the fact that the field is at a true turning point in its knowledge of what causes cancer, what maintains cancer, and the technologies that we have to be able to analyze a person’s cancer and their response to therapies — all of those things together are providing us with an opportunity to prevent the disease, to detect the disease much earlier, when the chances figure is greatest, or to definitively treat it and cure it and maintain the quality of life in ways that we unimaginable just a few years ago. So we're at this real threshold of opportunity, and MD Anderson, I believe, is better positioned than any other institution in the world to participate in that revolution of science and care.

Tacey A. Rosolowski, PhD
[00:33:47]
Well thank you very much for your time this morning, Dr. DePinho.

Ronald DePinho, MD
[00:33:52]
You're very welcome.

*Tacey A. Rosolowski, PhD*

[00:33:53]
And I am turning the recorder off at about 10:52.