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Ralph B. Arlinghaus, PhD

Interview # 52

Interview Session One: 21 March 2014

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Chapter 00A
Interview Identifier

T.A. Rosolowski, PhD:
00:02
I am Tacey Ann Rosolowski. Today is the 21st of March, 2014, and today I'm in the Life Sciences Plaza, on the ninth floor, in the Department of Translational Molecular Pathology. Did I get that right?

Ralph B. Arlinghaus, PhD:
00:17
Yes.

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T.A. Rosolowski, PhD:
00:19
I did? Good. Interviewing Dr. Ralph Arlinghaus for the Making Cancer History® Voices Oral History project run by the Historical Resources Center at MD Anderson Cancer Center in Houston, Texas. Dr. Arlinghaus came to MD Anderson in 1969 – is that correct, 1969?

Ralph B. Arlinghaus, PhD:
00:36
Correct, yes.

T.A. Rosolowski, PhD:
00:37
Okay, and you were a faculty member or a Chief of the Section of Environmental Biology?

Ralph B. Arlinghaus, PhD:
00:44
I was a faculty member in the Department of Biology …

T.A. Rosolowski, PhD:
00:47
Department of Biology.

Ralph B. Arlinghaus, PhD:
00:47
… and a Chief of the Section of Environmental Biology.

T.A. Rosolowski, PhD:
00:51
Okay, great. So, that's how. Alright, that's why I got those things together. And, today he's Professor in the Department of Translational Molecular Pathology in the Division of Pathology and Laboratory Medicine.

Ralph B. Arlinghaus, PhD:
01:11
Correct.

T.A. Rosolowski, PhD:
01:12
And Dr. Arlinghaus also holds the Hubert L. Stringer Chair in Cancer Research.

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Ralph B. Arlinghaus, PhD:
01:16
Correct.

T.A. Rosolowski, PhD:
01:17
Great. Today is the first interview session, we have two of them planned, and I want to thank you, Dr. Arlinghaus, for devoting the time …

Ralph B. Arlinghaus, PhD:
01:26
You're welcome.

T.A. Rosolowski, PhD:
01:26
… to this project.

Ralph B. Arlinghaus, PhD:
01:27
You're welcome.

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Chapter 01
Key Research on ABL Kinases
A: The Researcher;

Story Codes
A: The Researcher;
A: Overview;
A: Definitions, Explanations, Translations;
B: Devices, Drugs, Procedures;
C: Professional Practice;
D: Understanding Cancer, the History of Science, Cancer Research;
D: On Pharmaceutical Companies and Industry;
C: Discovery and Success;

T.A. Rosolowski, PhD:
01:27
I know you ran down from the twelfth floor from your labs so I'm sure I'm interrupting you.

Ralph B. Arlinghaus, PhD:
01:32
No, I — I knew you were coming so I finished up. I was reading this. One of the things I do is try to catch up with experts in the field of areas that I work in. And, there was a mini review that I'm reading and I just made copies of this mini review and gave to my four people who work in my lab: trainees, PhDs.

T.A. Rosolowski, PhD:
01:57
And what's the review of?

Ralph B. Arlinghaus, PhD:
01:58
It's *Structure and Dynamic Regulation of ABL Kinases*.

T.A. Rosolowski, PhD:
02:04
Wow. Okay. So, you kind of scour the literature and then pass the…

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Ralph B. Arlinghaus, PhD:
02:08
Yes, I'm always interested

T.A. Rosolowski, PhD:
02:08
… strategic things on.
Ralph B. Arlinghaus, PhD:
02:09
This is a mini review compendium put out every year by the Journal of Biological Chemistry. So, I often leaf through this thing, and the first article in here was something I'm going to end up studying.

T.A. Rosolowski, PhD:
02:24
Wow. That's very cool.

Ralph B. Arlinghaus, PhD:
02:25
Because it's got lots of data that I'm familiar with but not some of the details and I've already learned some things.

T.A. Rosolowski, PhD:
02:32
Wow. So this is like a brand new project that you're planning on taking on.

Ralph B. Arlinghaus, PhD:
02:35
Well, let me tell you. Maybe I'm jumping the gun here but I'm studying the role of Janus kinase 2 in chronic myeloid leukemia and I'm kind of known in that small segment of science for that discovery. And, MD Anderson, by way of Jorge Cortez, a leukemia physician here, will be running a human — actually two human trials which is based on my discovery which began in 19 — I'll have to go to my CV, but I think it's 1995. So I started working on Janus kinase 2. The reason I bring that up is this protein called ABL kinase --we have a paper submitted for publication and it's in minor review. That ABL kinase that you and I have activates the Janus kinase 2 kinase. Activates it. That means that ABL does something to the Janus kinase to make it active. Many enzymes and kinases are dormant until acted upon to make the kinases functional for usually a short period of time.

T.A. Rosolowski, PhD:

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04:00
And the ABL kinase – I'm just checking back in my notes to make sure I have consistency here – so that's ABL, all capitals?

Ralph B. Arlinghaus, PhD:
04:06
Yes.

T.A. Rosolowski, PhD:
04:07
Okay. And the Janus kinase, I don't think I've encountered that one before. How do you spell the Janus part of that?

Ralph B. Arlinghaus, PhD:
04:12
Janus is J-A-N-U-S, Janus kinase.

T.A. Rosolowski, PhD:
04:17
Kinase.

Ralph B. Arlinghaus, PhD:
04:17
It's named after a Greek god that had two heads.

T.A. Rosolowski, PhD:
04:20
The two faces. That's right, I remember that.

Ralph B. Arlinghaus, PhD:
04:21
That's right. Two faces, you're right.

T.A. Rosolowski, PhD:
04:22
Why is it called after that particular god?

Ralph B. Arlinghaus, PhD:
04:25

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Well, because Janus kinase, when it was first discovered – I forget the name of the person who published first on Janus kinases – he noted that the structural entities of Janus kinase 2, argued that they had two catalytic domains like, the Janus, the two-head, two-face god.

T.A. Rosolowski, PhD:
04:51
Right.

Ralph B. Arlinghaus, PhD:
04:52
So it had two — most kinases, protein kinases, have one catalytic domain. Janus kinase has two and …

T.A. Rosolowski, PhD:
05:07
And do they function very differently or …

Ralph B. Arlinghaus, PhD:
05:08
They do.

T.A. Rosolowski, PhD:
05:09
They do, very differently.

Ralph B. Arlinghaus, PhD:
05.09
They do.

T.A. Rosolowski, PhD:
05:10
So …

Ralph B. Arlinghaus, PhD:
05:10
In fact, the one controls the other.

T.A. Rosolowski, PhD:
05:12
Oh, wow.

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Ralph B. Arlinghaus, PhD:
05:14
We now know.

T.A. Rosolowski, PhD:
05:14
Interesting. Hmm.

Ralph B. Arlinghaus, PhD:
05:15
It's not my work but others have shown that.

T.A. Rosolowski, PhD:
05:19
Well, I'm glad you mentioned that and that we kind of dived in because one of the things that I wanted to ask you about - because as I mentioned to you before I turned on the recorder, I interviewed pathologists before, but I've never interviewed a molecular pathologist. And so, can you tell me what you do as a molecular pathologist that makes you unique?

Ralph B. Arlinghaus, PhD:
05:39
Well, pathologists – and I'm probably not going to do justice to this – they examine tissue and slides and they are looking at the tissue level with microscope, looking at the cells within the tissue. A molecular pathologist like me – I started this department in 1986, I guess, '86. I heard people like myself who was interested in understanding the molecular details of what goes on inside the abnormal cell and how that differs from normal cells. So, you know, in pathology, they look at cells and they identify abnormal cells. We use special techniques to break open the cells to then analyze these various factors inside the cells, and how those factors interact with one another inside the cell, in normal cells and in cancer cells, or in my case, leukemia cells.

So, that has led — I don't want to overstate my role in Gleevec. Gleevec is a major targeted therapy for chronic myeloid leukemia discovered by Brian Druker in Oregon. And, that drug is not chemotherapy. It targets the ABL kinases which are actually fusion proteins, hybrid proteins, in chronic myeloid leukemia. So …

T.A. Rosolowski, PhD:
07:31
So, you say it's not chemotherapy because it actually ….

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Ralph B. Arlinghaus, PhD:
07:35
It's therapy, its targeted therapy.

T.A. Rosolowski, PhD:
07:37
It's targeted therapy.

Ralph B. Arlinghaus, PhD:
07:38
When I think of chemotherapy, and I'm not a physician**,** I think of things like 5-fluorouracil …

T.A. Rosolowski, PhD:
Right

Ralph B. Arlinghaus, PhD:
07:47
… which is — targets a lot of nucleic acids …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
07:50
… in normal cells.

T.A. Rosolowski, PhD:
07:51
So, it infuses everything.

Ralph B. Arlinghaus, PhD:
07:52
It changes — changes lots of things in the cell.

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:

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07:55
And very toxic. So chemotherapy in general, you can take eight to 10 weeks if you're a cancer patient. If you take it longer, it's lethal.

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
08:05
So Gleevec, being targeted therapy, affects one or two things inside the leukemia cell and it's not toxic to any great extent so people can take Gleevec and have been taking Gleevec for five, six, seven, eight years.

T.A. Rosolowski, PhD:
Wow.

Ralph B. Arlinghaus, PhD:
08:24
And there — and it maintains the leukemia in a dormant state, so to speak. It doesn't cure the disease, but it maintains the disease in a quiescent state. So, that's targeted therapy. You're — you're inactivating a key factor in the cancer.

T.A. Rosolowski, PhD:
08:51
Now, am I assuming correctly that you had a contribution to discovering how Gleevec could be applied in the leukemia cell?

Ralph B. Arlinghaus, PhD:
09:00
I did.

T.A. Rosolowski, PhD:
09:01
Can you tell me about that?

Ralph B. Arlinghaus, PhD:
09:01

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Well, there were trials run on Gleevec in patients so I developed a method to measure quantitatively levels of the BCR-ABL protein – I'll have to get to that for you but – in chronic myeloid leukemia, there's an abnormal chromosome that develops, fuses parts of BCR to parts of ABL to give you a hybrid gene, BCR-ABL, that produces a hybrid protein that you and I and other healthy people do not have. So that BCR-ABL leukemia protein, when it forms in the right cell in leukemia patients, will cause chronic myeloid leukemia.

T.A. Rosolowski, PhD:
09:58
So, the protein – what does the protein actually do? Is it does that lead to the --

Ralph B. Arlinghaus, PhD:
10:04
See, your cells are full of protein that are kind of doing all the heavy lifting inside the normal cell, carrying out things like -- this is not a good example now, but what comes to my mind is insulin. Insulin is a protein and what does insulin do to control blood sugar? It's very complicated. It's not my field, but we could talk about it a long time. But, the insulin gene doesn't do much for you but the messenger RNA for insulin and then the protein that's produced from the messenger RNA produces the insulin protein, which is doing all the work for us, to keep us with reasonable levels of in our blood, in our cells. So, proteins are the functional entities that carry out different things inside cells or between cells. Genes encode for those and that's very important. But, the genes are not, in general, functional entities like proteins. Protein is actually and so, as a molecular pathologist, we want to understand what these various catalysts, these various proteins, these various enzymes, what they do normally in your blood cells and mine, and what they do in the leukemia cell, and how that differs. And then, we want to find out, 1), how to -- how to detect that abnormality – abnormal protein – and how to neutralize it or make in inactive. So, molecular pathology is looking at the functional parts of leukemia or cancer cells, the proteins to try to describe how they interact with the cellular machinery inside the cell, how they interact with other normal proteins, how they alter other normal proteins and that — all those process — processes contribute to how the BCR-ABL oncoprotein, leukemia protein, causes leukemia. What Brian Druker did many years ago now, working with Novartis, a pharmaceutical company. is ---

T.A. Rosolowski, PhD:
12:54
Excuse me. Do you mind if I shut the door to make sure?

Ralph B. Arlinghaus, PhD:
12:55.6

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You can go ahead and shut it. Sorry

T.A. Rosolowski, PhD:
12:57.9
I got it. Little more noise control

Ralph B. Arlinghaus, PhD:
12:58.4
You can --- what Druker did — Brian Druker did was work with Novartis with their — they had a compound which was the forerunner of Gleevec, and he studied this compound in cells from patients that had leukemia, chronic myeloid leukemia, not just any leukemia, but chronic myeloid leukemia. And he studied that compound that they made and showed that it should be useful to kill chronic myeloid leukemia cells without having much effect on cells that have the forerunner of the BCR-ABL protein, called ABL, we talked about here. That ABL protein is in you and I and under certain conditions, Gleevec can inhibit ABL. So as I understand it, Novartis didn't want to develop this drug compound that they developed because they were afraid it would be too toxic. Because not only would it inhibit or block the BCR-ABL enzyme, it would also block the normal ABL enzyme, creating lots of side effects. Well, it turns out that the level of their compound needed to block BCR-ABL was lower in concentration than what it took to inhibit ABL. So in other words, there was a low enough concentration of their drug, they could block BCR-ABL activity but not ABL activity. And that --- of course, Druker didn't know that but he eventually found that out.

T.A. Rosolowski, PhD:
14:52
But it opened the gateway to ---

Ralph B. Arlinghaus, PhD:
14:53
So it opened the gate ---

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:
14:54
--- and plus they started treating patients in trials and some of those trials were done here at MD and I was asked – that's how we got into this – I was asked because they paid me a little money from the trial – very little – to analyze blood fractions, some blood from chronic myeloid leukemia patients treated with Gleevec and what happens to the leukemia cells.

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T.A. Rosolowski, PhD:
How interesting.

Ralph B. Arlinghaus, PhD:
15:24
So I was kind of the — I had an advanced technique to analyze leukemia cells and determine whether they would be alive or dead.

T.A. Rosolowski, PhD:
Interesting.

Ralph B. Arlinghaus, PhD:
15:33
And so, I — that was my mini role.

T.A. Rosolowski, PhD:
Yeah, yeah. But a role.

Ralph B. Arlinghaus, PhD:
15:38
But, yeah, and this ---

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:
15:41
So what I found out is when you use Gleevec, the BCR-ABL protein cell disappeared, and I found by my assay they died. They underwent cell death.

T.A. Rosolowski, PhD:
15:59
That must have been an amazing moment to discover that.

Ralph B. Arlinghaus, PhD:
16:05
Well, Druker already knew that ---

T.A. Rosolowski, PhD:

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Yes.

Ralph B. Arlinghaus, PhD:
16:07
--- but I had a different assay that sort of confirmed that.

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:
16:13
So again, a very small role.

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:
16:16
I didn't do the pioneering work that Brian Druker did. I am not going to detract from what he did. So I was one of the many players.

T.A. Rosolowski, PhD:
16:26
Yeah. Over and over again, people have emphasized to me how many contributors there are to discover ---

Ralph B. Arlinghaus, PhD:
16:31
That's right.

T.A. Rosolowski, PhD:
16:31
--- discoveries of this kind

Ralph B. Arlinghaus, PhD:
16:32
I was one of the many contributors ---

T.A. Rosolowski, PhD:

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Yeah.

Ralph B. Arlinghaus, PhD:
16:35
--- played an interesting important problem.

T.A. Rosolowski, PhD:
16:37
Yeah. Well, thank you for telling me that. And that does kind of orient me better as we go ahead kind of talking about how your career evolved.

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Chapter 02
A Death Inspires a Career Change and a Commitment to Leukemia Research
A: Joining MD Anderson/Coming to Texas;

Story Codes
C: Evolution of Career;
A: Professional Path;
A: Personal Background;
A: Joining MD Anderson;
A: The Researcher;
A: Professional Path;
C: The Life and Dedication of Clinicians and Researchers;
C: Human Stories;
C: Discovery and Success;

Ralph B. Arlinghaus, PhD:
16:47
Right. Well, I should tell you more.

16:50
I mean --- in 1967, my first wife – I'm now remarried, years later – died of chronic myeloid leukemia in 1967. I had three children – she and I did. I decided-- I was working at a U.S. government laboratory in Long Island ---

T.A. Rosolowski, PhD:
17:23
Was that Plum Island?

Ralph B. Arlinghaus, PhD:
17:24
Yes, ma'am.

T.A. Rosolowski, PhD:
17:25
Yeah. So from — in 19 — from the Plum Island Animal Disease Laboratory from 1965 to 1969.

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Ralph B. Arlinghaus, PhD:
17:31
That's where I worked, yes, ma'am.

17:33
And I decided that I was going to stop working on viruses that cause foot and mouth because there's this terrible disease that killed my first wife. I decided I was going to focus all my scientific brain on trying to do something about that disease, which at that time, it was only known that there was an abnormal chromosome. It was called the Philadelphia chromosome which my — my wife's blood cells had that abnormal chromosome. Mine don't, yours don't, normal people don't. Only those that have CML have this abnormal chromosome. And so, I wanted to know more about what that chromosome encoded for and how its expression in normal blood cells converted them to leukemia cells. So that was in 1969. And I didn't have a clue, nor did anybody else of what the molecular details of CML was about. And many people contributed since then an understanding of what happens in a chronic myeloid leukemia cell, including me but, not just me.

19:08
So what I'm trying to emphasize, that I gave up my lifetime job at Plum Island, because you know you're — like to have GS ratings, and I have a GS 15 or 16 I don't remember

T.A. Rosolowski, PhD:
19:22
What does that mean – GS rating?

Ralph B. Arlinghaus, PhD:
19:24
Government Service ---

T.A. Rosolowski, PhD:
Oh, okay.

Ralph B. Arlinghaus, PhD:
19:26
--- rating of 15 or 16, and I was paid a very good salary and a lifetime job and my wife just died and I start scouring the country for places to work on cancer. And one of the places I looked at was MD Anderson because a former colleague of mine – he and I trained together in Lexington, Kentucky. During the time I was a trainee, that would be from '61 to '65. His name was Joe [Joseph] Schaeffer. He worked at MD Anderson. And I called him, I said, look, "I'm interested in changing jobs, changing career. I want to find out if MD Anderson has some — some

openings for people like me who was looking for a faculty to work on chronic myeloid leukemia. I didn't have a clue how I was going to work on it because nobody else did. But I was going to start." And he got me set up with the Department Chair. He was in the Department of Biology. The Department Chair's name was Felix Haas. They had a very strong scientific department at MD Anderson --- Department of Biology. And so, I was invited down to give a talk. I gave a talk on what I did on foot and mouth disease virus, and told them I wasn't going to work on foot and mouth disease virus, I was going to work on leukemia somehow, somewhere. And, Dr. Haas — generally, when you hire somebody as an academic scientist, you hire them and they bring and they bring a whole set of technology with them ---

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
21:19
--- to work on a project that they're working on --- wherever they were. I told them something different. I was not going to — I couldn't work on foot and mouth disease virus at MD Anderson; that's forbidden by federal law. You could only work on foot and mouth disease virus at Plum Island Animal Disease Laboratory.

T.A. Rosolowski, PhD:
21:34
Because of the quarantine issues.

Ralph B. Arlinghaus, PhD:
21:36
Because of the quarantine issues.

T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
21:38
Because the State of Texas is full of cattle. And, boy, I would go to jail in a hurry if I was working with foot and mouth disease virus anywhere in the U.S., let alone Texas. So, Dr. Haas had faith in me and he hired me, and he helped me, he gave me money from his sources to get me started.

T.A. Rosolowski, PhD:
22:01

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What did he — how did you present yourself? You know, because obviously the institution had a reason to have faith in you. I mean, what did you tell them you were bringing to them?

Ralph B. Arlinghaus, PhD:
22:12
Well, first of all, Joe Schaeffer knew me and Joe was an employee, an Assistant Professor at MD Anderson so he sort of spoke for me. That's one. And plus, when he and I worked together at the Lexington, Kentucky Medical School, I did some – what words can I use – some very important work that led to important findings that were published in high-class --- of which I was the first author. So I was the lead scientist breaking new ground in this particular area called protein synthesis. And — so then, I was hired at Plum Island to continue those studies to understand how the proteins of foot and mouth disease virus were and how they were assembled to make viral particles. So I was doing at the time when I took that job, when my wife was already diagnosed and ill. She and I, with our three children moved to Long Island. She lived about 30 months, she died, and I decided I was going to work on leukemia and stop working on viruses and take my protein expertise, my ability to study how proteins function and what they affect and how they change other proteins. I tried to take that to work on leukemia. And I published some important papers in Lexington. He could open my CV, Dr. Haas, and see I published some high-level, high impact publications.

T.A. Rosolowski, PhD:
Sure.

Ralph B. Arlinghaus, PhD:
24:13
And I was the leader. So I went to Plum Island and I published another high impact paper about foot and mouth disease. So it looked like I was doing important things at Plum Island after done — doing important things on a completely different subject at Lexington, Kentucky.

T.A. Rosolowski, PhD:
24:38
Now, was there something about — I mean, obviously, you were demonstrating a deep understanding of protein functionality at this time but maybe also, were you developing a kind of research approach or — I mean, I'm just trying to think of other kinds of things ---

Ralph B. Arlinghaus, PhD:
24:55
Well, I think I think he had faith in me that I was successful in a very high-level way in Lexington ---

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T.A. Rosolowski, PhD:
25:03
And that you could be adaptable.

Ralph B. Arlinghaus, PhD:
25:04
— and then I was very successful to some degree at Plum Island in publishing a high impact paper. So it looked like Arlinghaus was productive, published good science papers that were read by people in the field. So, when I said I wanted to work on leukemia at the MD Anderson Cancer Center, he had faith in me. And I — so my background, my track record, my productivity gave me support. Plus, Joe Schaeffer knew me quite well, can vouch for my leadership role at the University of Kentucky.

T.A. Rosolowski, PhD:
25:50
Well, it sounds like it was an excellent connection ---

Ralph B. Arlinghaus, PhD:

It was.

T.A. Rosolowski, PhD:
25:53
--- that was made there.

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Chapter 03
Initial Research with Viruses and Proteins: Slow Progress on the Gag-Pol Protein
A: The Researcher;

Story Codes
A: The Researcher
C: Evolution of Career;
A: Professional Path;
A: Overview;
A: Definitions, Explanations, Translations
C: Discovery and Success;
C: The Professional at Work
B: MD Anderson Impact
D: Understanding Cancer, the History of Science, Cancer Research

Ralph B. Arlinghaus, PhD:
25:54
You know, from my point of view, I had no idea – and I told Dr. Haas this – I had no idea of how to attack the problem of chronic myeloid leukemia. We didn't know the proteins that were involved, so ---

T.A. Rosolowski, PhD:
26:11
So, how did you start?

Ralph B. Arlinghaus, PhD:
26:16
Well, I wasn't a physician so I couldn't work with patients who had chronic myeloid leukemia. I was a scientist. So I started working on viruses that cause leukemia in mice. Not chronic myeloid leukemia. (Phone rings) Excuse me.

T.A. Rosolowski, PhD:
Sure.

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Ralph B. Arlinghaus, PhD:
26:35
Reminding me to make sure I see you, I think.

T.A. Rosolowski, PhD:
(laughter)

Ralph B. Arlinghaus, PhD:
26:42
No, that's something else. Okay, so — anyway, I had to bide my time while the field helped me focus my attempts on CML. So I did. I picked an area that dealt with leukemia, but in mice. And, it's a widely studied technology. There were two famous NIH scientists, Frank Rauscher and Jim Maloney. Each of them discovered a mouse leukemia virus named after them, the Maloney leukemia virus after Jim Maloney, who I never met, and Frank Rauscher, the Rauscher leukemia virus. Both of them cause in appropriate mouse — mice strains. So ---

T.A. Rosolowski, PhD:
27:40
And when was that discovery made? I mean, was that before you came to MD Anderson or ---

Ralph B. Arlinghaus, PhD:
27:45
Oh, yes.

T.A. Rosolowski, PhD:
27:45
Okay. okay.

Ralph B. Arlinghaus, PhD:
27:46
Oh, yes.

T.A. Rosolowski, PhD:
27:47
I'm just trying to get the timing.

Ralph B. Arlinghaus, PhD:
Yeah.

T.A. Rosolowski, PhD:

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Yeah. Okay.

Ralph B. Arlinghaus, PhD:
27:49
So, those discoveries were made years before I sort of landed at MD Anderson.

T.A. Rosolowski, PhD:
27:54
Right. So that's – hence, kind of gave you the opening.

Ralph B. Arlinghaus, PhD:
27:57
So I was able to get a — there were leukemia cells from the mice that were sick with Rauscher leukemia virus. And I got those cells from a colleague — one of my colleagues — I don't even remember who gave them to me – but wrote an email — wasn't an email then. I wrote a letter and said, and I am going to start working with Rauscher leukemia and I understand you have this cell line from these sick mice. The cells were growing culture and you could start getting to study the molecular events in these cells that grow in plastic dishes. That's where I started. Had no relationship to chronic myeloid leukemia.

T.A. Rosolowski, PhD:
28:53.
By just looking at the function ---

Ralph B. Arlinghaus, PhD:
28:54
But, as I always did even as a Ph.D. student, I made discoveries that made me — one discovery that made me famous in a small area. I always found something unique and interesting to publish. And, with those cells from Rauscher leukemia virus mice, I chose to try to understand what proteins were made in the leukemia cells that led to the production of Rauscher leukemia virus particles that were released into the media on which the cells were grown. So, in the culture media, those leukemia cells, they were Rauscher leukemia particles. I wanted to know how — what proteins were involved in creating the particles, hoping that I would identify a leukemia-causing protein for Rauscher leukemia. And after a number of years getting funded, I understood how — what proteins were being made, some of them very interesting, how they were being made. So, for example, the reverse transcriptase, have you ever heard of it? Probably not.

T.A. Rosolowski, PhD:
30:33

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I've heard of it but I don't – I mean, as a word.

Ralph B. Arlinghaus, PhD:

Yeah.

T.A. Rosolowski, PhD:
30:37
I don't understand what it is.

Ralph B. Arlinghaus, PhD:
30:38
Reverse transcriptase was discovered by Dave Baltimore and Howard Temin as an enzyme present in these particles, like Rauscher leukemia or Maloney leukemia virus and others. And I studied in part how the reverse transcriptase in the cells from Rauscher leukemia virus infected mice, which I could grow in bottles. I studied how the reverse transcriptase was made. And of course, I discovered something interesting and it turns out that, back then, that was able — allowed me to publish a high impact paper. Now I'm at MD Anderson, so although I didn't publish anything on CML, my first papers were on the proteins made in Rauscher leukemia virus-infected cells.

T.A. Rosolowski, PhD:
31:42
What was the discovery that you made?

Ralph B. Arlinghaus, PhD:
31:45
Well, it turns out that – I have to think about how to tell you --- Rauscher leukemia virus contains what we call a genomic RNA of about 8,000 nucleotides. Others in the field about the same time I was doing my work, found out that there were three genes encoded by that 8,000 nucleotides present in the Rauscher leukemia virus particle. One of them was a protein that encoded for this — the structural entities that packaged the viral RNA, this 8,000 nucleotide viral genome, as we called it. And then, there was a second protein which was involved– I have to think of the name of the protein because it's been 20 years – it's called the Pol gene. The Pol gene, after studying how the Pol gene proteins were made on ribosomes and found that the Pol gene was translated into two entities – the core proteins which I talked about, and then the Pol gene protein. They were fused in a protein which I called Gag-PolI initiated that term because normally, proteins that are made in cells are made as individual units so DNA polymerases are coded for by gene and DNA polymerase, and there will be a messenger RNA protein A polymerase, the messenger RNA gets on ribosomes, and the ribosome translate the coding

sequence for the DNA polymerase, and you form the DNA polymerase protein. Well, the Pol protein was made as a hybrid called Gag-Pol.

T.A. Rosolowski, PhD:
34:24
That's G-A ---

Ralph B. Arlinghaus, PhD:
34:25
G-a-g. That terminology was instigated or identified or first used by David Baltimore who got a Nobel Prize for discovering reverse transcriptase, so --so, I was the first to show that the Pol gene, or the reverse transcriptase protein, was not made on ribosomes as a single but as a Gag-Pol protein.

T.A. Rosolowski, PhD:
34:51
Now, what would the implications of that be? How would that be connected to abnormal function, related to leukemia?

Ralph B. Arlinghaus, PhD:
34:58
Well, at the time, we didn't but it turns out the Gag proteins play a role in packaging the viral genomic RNA, so when the virus is assembling, the Pol — the Gag proteins sort of wrap up the viral RNA, the genome as we call it, as it encoded for these three genes that package the viral RNA. But, remember the — you don't know, but the reverse transcriptase was encapsulated inside of that package. So, making a Gag-Pol protein allowed the Gag proteins to associate with the other Gag proteins that are made separately from – it's complicated, I'm sorry.

T.A. Rosolowski, PhD:
35:45
No, no. I'm just trying to visualize it …

Ralph B. Arlinghaus, PhD:
35:46
Okay, I know.

T.A. Rosolowski, PhD:
35:47
… because it sounds like it's making a sort of bomb.

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Ralph B. Arlinghaus, PhD:
35:49
Well, Gag — the Gag — the Gag gene is — is the — I said 8,000 nucleotides form up the viral RNA. The first 3,000 nucleotides enc — encode for a precursor protein called – I'm going to lose you, I'm sorry about it — it — it encodes for Gag — for the Gag proteins which were called — and still are, Cor p15, p12, p30, and p10. Those four proteins wrap up the viral RNA and form a particle that — that's going to be in the virus. But if you wanted to get the Pol protein in there, the reverse transcriptase, it's very important — if you wanted to get that inside the virus particle, it makes a lot of sense to make a Gag-Pol hybrid protein. So, when you made a Gag-Pol protein, it gets packaged in the viral particle with the 15, 12, 30, and 10 Gag proteins. And then now, you've encapsulated not only those proteins but you've encapsulated the Pol protein. So, you've got that now inside the viral particle. Now, the third protein encoded for by the viral genome are envelope proteins. Two proteins that form spikes on the surface membrane of the particle. So the particle – if I think of it — is too simplistic– as – as a — as a ball. Inside the ball there is this core. Inside the core, there's the viral genome packaged by these four structural proteins and the reverse transcriptase. Then that's all packaged by a membrane which had envelope proteins – we call them envelope – surface projections that form the surface of the Rauscher viral particle.

T.A. Rosolowski, PhD:
Wow.

Ralph B. Arlinghaus, PhD:
37:51
Very complicated.

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:

So …

T.A. Rosolowski, PhD:
37:55
I mean, I'm starting to get an appreciation of the — I mean, I'm — I — I'm just — my mind's kind of being boggled at all …

Ralph B. Arlinghaus, PhD:
38:05

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I'm sure it is.

T.A. Rosolowski, PhD:
38:05
Well, all of the …

Ralph B. Arlinghaus, PhD:
38:06
I've dumped a lot on you, I know.

T.A. Rosolowski, PhD:
38:08
No, no, no. And, that's fine. But — but — but I'm trying to translate this information back to your lab, you know, the steps, the kind of breaking it down, breaking it down, how do we look at each piece, each mechanism, then figure out how it all works together.

Ralph B. Arlinghaus, PhD:
38:24
Most enzymes are made up several polypeptides and each polypeptide is encoded by a single messenger RNA and they self-assemble. That's another story we're not going to talk about. So, in the case of the Rauscher virus and many of the other viruses, the proteins for the 15, 12, 30, and 10 are made as a one –which I termed – polyprotein which will then slice at the appropriate sites to give you four proteins. Po — one polyprotein is made from the viral genomic RNA on ribosome to give you something which — which I named as PR 65 Gag. It's — it's 65,000 molecular weight protein encoded for what Baltimore termed as a Gag gene. Remember, it's — the leukemia virus genome has got the Gag gene, the Pol gene, and the envelope gene. The envelope gene, the surface proteins; the Pol gene, the enzymatic activity, that's involved in reverse transcription; and then the Gag proteins made on packaging the viral genome. So …

T.A. Rosolowski, PhD:
39:35
So — I mean, it's kind of amazing because it's actually producing leukemia, in a way.

Ralph B. Arlinghaus, PhD:
39:43
Well, that's another story now. I never did find a leukemia-causing protein …

T.A. Rosolowski, PhD:
39:48
Oh, you didn't?

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Ralph B. Arlinghaus, PhD:
39:49
… made by the Rauscher leukemia virus genetic information. It wasn't there.

T.A. Rosolowski, PhD:
39:52
It wasn't there.

Ralph B. Arlinghaus, PhD:
39:55
I only found p15, p12, p30, and p10, the four Gag gene proteins, the reverse transcriptase, and the two envelope proteins that form spikes on the surface of the particle.

T.A. Rosolowski, PhD:
40:12
Now, what does that particle do?

Ralph B. Arlinghaus, PhD:
40:14
Which — which one?

T.A. Rosolowski, PhD:
40:15
The — the one that's being packaged with these three proteins.

Ralph B. Arlinghaus, PhD:
40:17
It — it packages the — the viral inside the Rauscher and the Moloney leukemia viruses. Like all retroviruses, they have two copies of the viral coding RNA – two, not one. And, it's still being studied why there are two. But — so that 15, 12, 30, and 10 interaction of those four proteins, packages these two RNA's inside that core protein structure which then surrounded by a membrane were the envelope proteins. Remember, the four core proteins also had the — the Gag-Pol. And Pol encodes the activity to make a — a DNA from RNA. You know, in molecular biology – DNA encodes RNA, and RNA encodes for protein. But, with the discovery of the reverse transcriptase by Dave Baltimore, Nobel laureate; Howard Temin, Nobel laureate, published a paper of the same year --I forget which year. So, they found that there's an enzyme in these leukemia virus particles that makes DNA from RNA. Now, DNA encodes for RNA and RNA encodes for protein. But here, for the first time in the scientific universe, there's an enzyme encoded for by these leukemia virus particles which are called retroviruses and it had an

enzyme called reverse transcriptase that made DNA from RNA. And for that, Dave Baltimore, still alive; and Howard Temin – I think he is gone – got the Nobel prize — shared the Nobel prize for that. So, what I was doing was studying how the reverse transcriptase was made in these leukemia virus-infected cells, and what I became known for, because there's a — so, this genomic RNA is at one end the ____ 42:52.8 codes for p15, p12, p30, and p10. Then, we later found out there's a stop codon them. That doesn't mean much to you. But, it tells the ribosome to stop translating.

43:08
Ribosomes translate the information in the RNA into the protein sequences for p15, for p12, p30, and p10. But then, there's a — a series of two codons that say, stop putting amino acids in, there's — this – I don't know if you know how protein synthesis occurs but that's it. I'm dumping a lot on you right now.

T.A. Rosolowski, PhD:
43:36
That's okay. I mean, one — one thing I'm — I'm curious about is when you — as you were beginning to assemble this knowledge of all of these details, you know, how was your mind working to think about, okay, here's the implications. You know, here's how I'm going to take this information and then move closer to my goal of addressing CML?

Ralph B. Arlinghaus, PhD:
43:57
Yes. Well, see, I had a big disappointment because I couldn't find a leukemia-causing protein …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
44:05
… in the Rauscher leukemia virus encoded proteins in the cell. So, I said either I'm stupid and I miss it, but it turns out here – and I'll throw you a curve now --the field, not me, not Arlinghaus. The field discovered that they are two types of leukemia or cancer-causing viruses – ones that were slow-acting, and ones that were fast-acting. The fast-acting ones encoded for a cancer-causing protein. The slow-acting ones did not and cause leukemia in another way. Now, remember – so here's another curve I'm throwing at you – when these viruses, these retroviruses that were being studied by people like me, when they enter a cell and convert the cell to an infected cell, those leukemia viruses, they make a DNA copy with reverse transcriptase. That DNA copy is integrated or inserted into the chromosome's DNA of the cell at random. So, the

slow-acting leukemia viruses like Rauscher inserted their DNA, the viral DNA, made in the core particle inside the infected cell, that viral DNA was then integrated or inserted into the cellular DNA of the nucleus of the cell and very rarely, it inserted at a place that there was a gene that could cause cancer.

46:03
So, in my case, the Rauscher leukemia virus did not encode a cancer gene but encoded a — a mechanism to activate a cancer gene present in the cell that's to be infected. But, that didn't happen, you know, when the virus integration occurred, it didn't happen every time because the — the viral DNA was inserted at various parts in chromosomes in the normal cell and only when it inserted nearby a — a gene we now call cancer genes, did that cause leukemia. So …

T.A. Rosolowski, PhD:
46:44
Interesting.

Ralph B. Arlinghaus, PhD:
46:45
… the virus never carried a leukemia-causing protein, it carried a mechanism to activate a cellular
present in the infected cell nuclei.

T.A. Rosolowski, PhD:
46:58
Now, as I'm kind of — first of all, how — what's the span of time that it took you to kind of do all of these studies after you got here at MD Anderson on this particular subject ____ (over-talking)

Ralph B. Arlinghaus, PhD:
47:09
Well, I had worked …

T.A. Rosolowski, PhD:
47:10
… on the Rauscher.

Ralph B. Arlinghaus, PhD:
47:11
I — I — I worked three years on a virus much like foot and mouth disease but wasn't. So, I had to start somewhere that I knew. And then, I wrote grants to try to get me started on working on

leukemia. Once I got the cells from a that were from Rauscher leukemia virus-infected mice, I started writing grants to National Cancer Institute to be — to go — begin the — my — my long journey …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
47:46
… to try to understand how chronic myeloid leukemia was caused. And …

T.A. Rosolowski, PhD:
47:54
Now…

Ralph B. Arlinghaus, PhD:
47:54
… let's say I reached the point where Felix Haas got tired of funding me because I got a grant to study the foot and mouth disease-like virus, but then I started writing grants on how viruses like that would cause a slow cancer. And, most of those grants were not funded. So, I — I thought that I'd reached a roadblock and I was going to fail. Even though I learned a lot about how Rauscher and Moloney leukemia virus made their proteins but I didn't know anything about how they caused leukemia because that — that process of genetically inserting viral DNA in chromosomes wasn't well understood for some time. So, I — I was almost — Felix Haas had me in after one year of not bringing any grants and gave me a warning. He says, "I'm not going to give you a salary increase. You're not bringing in any money." He was telling me…

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:
49:24
… I'm on my last legs.

T.A. Rosolowski, PhD:
49:29
I — I — obviously I want to ask you what happened next but I wanted to go back a little bit because the first thing that was striking me as you're telling the story is how — it seems like the story couldn't happen today. I mean, if a faculty member came …

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Ralph B. Arlinghaus, PhD:
49:46
Probably not.

T.A. Rosolowski, PhD:
49:47
And, it — it — it just seemed like an incredible opportunity …

Ralph B. Arlinghaus, PhD:
49:50
It took a lot of faith of Felix Haas …

T.A. Rosolowski, PhD:
49:51
Right.

Ralph B. Arlinghaus, PhD:
49:53
… to give me a start, and he ran out of faith …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
49:54
… and he …

T.A. Rosolowski, PhD:
But …

Ralph B. Arlinghaus, PhD:
49:56
… almost terminated me.

T.A. Rosolowski, PhD:
49:57
But, but the fact was they — they did take you on, they allowed you this freedom that seemed very unusual, and a great — an amazing opportunity for you to expand in an entirely new direction. And, I guess the other question that I had in my mind is when you arrived at MD

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Anderson, who were you working with? You know, who were you — who were you connecting with?

Ralph B. Arlinghaus, PhD:
50:20
I built a team of people, thanks to Felix Haas.

T.A. Rosolowski, PhD:
50:24
And, who were these people that ____ (over-talking)

Ralph B. Arlinghaus, PhD:
50:25
They were the young post-doctoral fellows the same people I have working with me now.

T.A. Rosolowski, PhD:
50:28
Oh, really! Wow.

Ralph B. Arlinghaus, PhD:
50:29
They're not the same people, they're different people. Because we're talking many years ago. They're off having their own lives, they've got their own jobs. So, I — I trained new people brainwashed them into what I think was going on in a leukemia cell. And, I never did find that leukemia protein because it didn't exist. But then, something happened at the NIH level …

T.A. Rosolowski, PhD:
50:54
Yes.

Ralph B. Arlinghaus, PhD:
50:54
… that saved me.

T.A. Rosolowski, PhD:
50:55
What was that?

Ralph B. Arlinghaus, PhD:

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50:56
It had — had nothing to do with me but they started what was called the Virus Cancer Program. And Jim Moloney started that program and that …

T.A. Rosolowski, PhD:
51:07
I'm sorry, the Virus Cancer Program?

Ralph B. Arlinghaus, PhD:
51:09
Virus Cancer Program.

T.A. Rosolowski, PhD:
51:11
Okay, thank you.

Ralph B. Arlinghaus, PhD:
51:12
And, I started writing grants to the Virus Cancer Program, talking about my mission that I was on and what I wanted to study eventually, and …

T.A. Rosolowski, PhD:
51:29
What year was this that this was started? The Virus Cancer Program? What year?

Ralph B. Arlinghaus, PhD:
51:34
Oh …

T.A. Rosolowski, PhD:
51:36
Just ballpark.

Ralph B. Arlinghaus, PhD:
51:37
I'm bad about this, I'm sorry.

T.A. Rosolowski, PhD:
51:38
That's okay. I'm just thinking ballpark. Must have been in the early seventies.

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Ralph B. Arlinghaus, PhD:
51:42
No, late seventies.

T.A. Rosolowski, PhD:
51:43
Late seventies. Okay.

Ralph B. Arlinghaus, PhD:
51:45
I remember …

T.A. Rosolowski, PhD:
___ (over-talking)

Ralph B. Arlinghaus, PhD:
51:46
… I occupied most of the early seventies accumulating this data …

T.A. Rosolowski, PhD:
Really.

Ralph B. Arlinghaus, PhD:
51:50
… about how — how this — the — the viral proteins were made and how they assembled in the virus particles and the — the Gag-Pol protein …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
52:01
… which made me famous because the first time ever – and I probably didn't make this clear – I — I predicted that there is a — a Gag-Pol protein and that when you translated it on ribosomes, you would mostly make Gag then it would stop translating. And then, it would bypass the stop codon and keep translating to give you a Gag-Pol protein. So, I proved that and published some very high impact papers in – two papers in *Cell*, and …

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T.A. Rosolowski, PhD:
52:36
You know, because the other thing that's striking me is as you're describing this, it is really building an entirely new field. You know …

Ralph B. Arlinghaus, PhD:
52:44
Yes.

T.A. Rosolowski, PhD:
52:44
… that seems like that's what in progress. What happened …

Ralph B. Arlinghaus, PhD:
52:47
I'm not the only one.

T.A. Rosolowski, PhD:
No,

Ralph B. Arlinghaus, PhD:
52:49
A lot of us …

T.A. Rosolowski, PhD:
52:50
Absolutely.

Ralph B. Arlinghaus, PhD:
52:50
.. and I'm going to tell you about an important discovery that allowed me to continue and to work directly on CML.

T.A. Rosolowski, PhD:
52:57
Well, I'm …

Ralph B. Arlinghaus, PhD:
52:57

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With help from the Virus Cancer Program.

T.A. Rosolowski, PhD:
53:00
And, well, why don't you tell me about that? And so, what happened — what was the next step?

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Chapter 04
Leaving MD Anderson for Industry: Research into Hybrid Proteins with Tyrosine Kinase Activity
A: The Researcher;

Story Codes
A: The Researcher;
C: Evolution of Career;
A: Professional Path;
A: Overview;
C: Discovery and Success;
A: Definitions, Explanations, Translations;
C: The Professional at Work;
D: Understanding Cancer, the History of Science, Cancer Research;
A: Finance, Entrepreneur, Biotechnology;

Ralph B. Arlinghaus, PhD:
53:06
Well, because — because I looked like I was going to fail at MD Anderson, I took a job with Johnson & Johnson …

Ralph B. Arlinghaus, PhD:
53:18
… and helped start up a company in San Diego.

T.A. Rosolowski, PhD:
53:23
Okay. This was in 1983.

Ralph B. Arlinghaus, PhD:
53:27
Yes.

T.A. Rosolowski, PhD:
53:29

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1983. Okay. Because, yeah, because I — I had noticed that you were away from the institution for three years.

Ralph B. Arlinghaus, PhD:
53:32
I went there because Johnson & Johnson agreed not only to — to have them — me help them develop their company, but allowed — but give me money to support my leukemia research.

T.A. Rosolowski, PhD:
53:48
Now, can I ask you just a kind of a …

Ralph B. Arlinghaus, PhD:
53:49
So, in other words, I don't take the job in La Jolla, in California, unless Johnson & Johnson agrees that they're going to give me money to develop their company but also give me money to develop my research on chronic myeloid leukemia.

T.A. Rosolowski, PhD:
54:04
Was this a, you know, kind of a leave of absence from MD Anderson?

Ralph B. Arlinghaus, PhD:
54:09
No, I resigned.

T.A. Rosolowski, PhD:
54:10
You resigned. Okay.

Ralph B. Arlinghaus, PhD:
54:11
I was never coming back because, you know, I — I had — I had to move on to try to find out how to get — start working on chronic myeloid leukemia.

T.A. Rosolowski, PhD:
54:22
What was it that — what made you make the decision to resign?

Ralph B. Arlinghaus, PhD:

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54:28
I wasn't getting money from NCI to fund my leukemia research so I said, well, I've got to get it from somewhere. So, I convinced J&J — they wanted me to develop their company. I said, well, I'll come to California but only if you promise to give me money to support my research and allow me to attract trainees and pay them so that I can do that leukemia research at Johnson & in La Jolla.

T.A. Rosolowski, PhD:
55:01
So, tell me about — first of all, what — what were you doing for them. Because I had down Vaccine Development Director.

Ralph B. Arlinghaus, PhD:
55:08
Well, they — there was a — a guy at Scripps Clinic named Richard Lerner.

T.A. Rosolowski, PhD:
55:14
And then, you were a visiting investigator at Scripps Clinic and Research …

Ralph B. Arlinghaus, PhD:
55:18
I also had a …

T.A. Rosolowski, PhD:
55:18
… Foundation.

Ralph B. Arlinghaus, PhD:
55:19
… NCI grant …

T.A. Rosolowski, PhD:
Oh, okay.

Ralph B. Arlinghaus, PhD:
55:21
… so I worked …

T.A. Rosolowski, PhD:

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Mhmm.

Ralph B. Arlinghaus, PhD:
55:22
… I worked for Johnson & Johnson at their building in La Jolla. It was a rental facility.

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
55:28
Then I worked at Scripps on my grant, working on one of these rapidly acting cancer genes called Moss (55:34).

T.A. Rosolowski, PhD:
Oh, okay.

Ralph B. Arlinghaus, PhD:
55:37
Because I didn't know about the gene that caused CML.

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
55:42
But — so I had a grant that I brought with me from MD Anderson. I did get funded but I got promised to have much more resources from J&J in addition to this grant from the National Cancer Institute, and that allowed me to hire people at J&J to help me investigate chronic myeloid leukemia.

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
56:06
And there were physicians here – one guy named ____ 56:08 who was working on chronic myeloid leukemia and he agreed to send me cell lines — cell lines is too strong — cells from

chronic myeloid leukemia patients, packaged them up in dry ice, ___ 56:31 frozen send them to La Jolla. He and some of his people came to La Jolla. I trained them how to do some of the assays so that they could do it here. But it was all J&J …

T.A. Rosolowski, PhD:
56:44
All J&J money. Okay. Why did Johnson & Johnson agree to do that, do you think?

Ralph B. Arlinghaus, PhD:
56:51
Because they wanted to hire me to develop their company on synthetic peptide vaccines.

T.A. Rosolowski, PhD:
Okay. So …

Ralph B. Arlinghaus, PhD:
56:58
And I was — my CV looked the best and they decided that I could — I could make Johnson & Johnson a lot of money to a peptide vaccine.

T.A. Rosolowski, PhD:
57:12
What were these va — peptide vaccines supposed to do?

Ralph B. Arlinghaus, PhD:
57:15
Well, I'll give you an example. Hepatitis B, serious human virus, causes hepatitis, which is liver disease and leads to liver cancer.

T.A. Rosolowski, PhD:
57:32
And – I'm sorry, what - hepatitis C?

Ralph B. Arlinghaus, PhD:
57:34
Hepatitis B.

T.A. Rosolowski, PhD:
57:35
Hepatitis B. Okay.

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Ralph B. Arlinghaus, PhD:
57:37
Dick Lerner at Scripps got a — a bunch of money from J&J on this peptide vaccine concept.

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
57:45
So, it was Lerner who convinced J&J to hire me because he knew about my work with Gag-Pol and all the proteins encoded for by leukemia. He knew about that exquisite work – exquisite may be too strong - …

T.A. Rosolowski, PhD:
58:03
Sounded pretty exquisite to me.

Ralph B. Arlinghaus, PhD:
58:03
It — it was. And he knew — he knew me. He knew I was productive. It's like Joe Schaeffer, when I got hired at MD Anderson, he told Felix Haas this guy, Arlinghaus, is going to make things happen. And I did. And when I went to California to work for J&J, Dick Lerner, who knew my papers, convinced them, 1) to hire me to come to California; 2) to work on his peptide vaccine. So, we hired seven or eight Ph.D. scientists to work on these peptide vaccine, for hepatitis, for influenza. None of that worked out. It was all failure. Not because of what I did; because there was a flaw that Lerner didn't recognize. And, how am I going to explain that flaw to you?

T.A. Rosolowski, PhD:
59:00
That's going to be your challenge.

Ralph B. Arlinghaus, PhD:
59:09
When you inject a fragment of a protein called a peptide. Proteins – let's say, hemoglobin in your cells, your liver cell and mine – they have a 12,000 molecular weight protein. There's an alpha chain and a beta chain. They come together to form hemoglobin. That 12,000 molecular weight protein is a protein that has 120 amino acids. Lerner thought you could make a 10-amino

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acid fragment of globin, inject it into mice, rabbits, humans, and make a antibody that would neutralize hemoglobin.

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
59:46
Although he didn't talk about hemoglobin. He was doing it with viral proteins. But, the point is he — he had this concept that if you had a small chunk of viral protein and you made it chemically in a lab, that if you immunize an animal, that small chunk of protein would make an antibody which would then recognize proteins made or secreted by the virus …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:00:17
.. and it would be useful to neutralize the virus. But, it turns out what Lerner failed to recognize, I didn't know, I learned it for him and told him about it, is that these peptide vaccines — I can't use more words you don't know of – had limited — if it's a 10-amino acid peptide compared to a 120-amino acid protein, the number of sites that an antibody would tightly bind to would be three or four for the 10-amino acid peptide. But it would be ten times that for the whole protein. And, it turns out that the affinity of antibodies for their proteins requires multiple binding sites in the target protein. And peptides didn't identify those other – let's say, three – 25 different binding sites. They only identified a few so your antibodies only detected a small portion of the viral protein.

T.A. Rosolowski, PhD:
1:01:35
That's a great explanation …

Ralph B. Arlinghaus, PhD:
1:01:37
And it didn't bind very tightly …

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:

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1:01:38
… so it was — what we call low affinity. So it turned out there were no peptide vaccines, we didn't make one. No one else made one. Other people tried. That's failed technology because of not understanding that you couldn't use short peptides as antigens to — to – what shall I call it – to — to – looking for a word – you couldn't use short peptides that may represent 5% of the amino acids of the total protein to accomplish, to allow the immune system to decorate all the sites. It would only to decorate those sites that were in the short peptides. And you needed all the sites to be decorated by antibodies.

T.A. Rosolowski, PhD:
1:02:33
Makes sense. Good explanation. Thank you.

Ralph B. Arlinghaus, PhD:
1:02:36
And we didn't know it back then.

T.A. Rosolowski, PhD:
1:02:37
Yeah, you didn't know it. But it seems like you had to go thro — go through that process …

Ralph B. Arlinghaus, PhD:
1:02:41
That's right.

T.A. Rosolowski, PhD:
1:02:42
… to figure it out.

Ralph B. Arlinghaus, PhD:
1:02:42
That's right. Because what we got were antibodies that recognized the peptide, but antibodies that only poorly recognized the viral protein.

T.A. Rosolowski, PhD:
10:02:53
So, that's what you were doing for Johnson & Johnson …

Ralph B. Arlinghaus, PhD:

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1:02:55
Johnson & Johnson.

T.A. Rosolowski, PhD:
1:02:56
… so what were you doing in your CML …

Ralph B. Arlinghaus, PhD:
1:02:58
Well, when — when I moved to Johnson & Johnson, a paper by now a colleague called John Groffen – G-r-o-f-f-e-n, John Groffen and his wife, Nora Heisterkamp, published a paper that said that – thinking of the words – that — they were studying the structure of this abnormal ABL protein present in cells like Rauscher leukemia virus and — and Moloney leukemia virus, and now in patients with CML. What they found was that there was a gene called ABL, this genome, reading this mini review about that's fused. Remember CML is a disease where you've got part of the ABL gene fused to part of the BCR gene. And so, Groffen found out that — that hybrid chromosome produced a hybrid messenger RNA made up of sequences from BCR and ABL gene, and that — and then to produce a protein that was made up of ABL sequences and BCR sequences. So, it was a BCR-ABL protein and that protein was made in every CML patient that he examined. So, I wrote ____ 1:05:01 and asked him to send me cell lines or cells from patients with CML to see if I could detect that abnormal ABL protein using sophisticated peptide technology that I learned about from Lerner, make short peptides, make antibodies, and those antibodies would see that short peptide and would see it to some degree in the protein itself. So — so, I used that technology to identify and publish a paper that in CML cells, there was a protein that had sequences from the ABL protein and sequences from the BCR protein, leading to the conclusion that it was a BCR-ABL protein. And more than that, identify that BCR-ABL protein as a tyrosine kinase that had activity in and of itself, that was always active in itself. So that finding was made possible by Groffen and his wife, Nora Heisterkamp.

T.A. Rosolowski, PhD:
1:06:21
And her name, Hiserkamp?

Ralph B. Arlinghaus, PhD:
1:06:24
Heisterkamp

T.A. Rosolowski, PhD:
1:06:24
Heister — H-e-i- …

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Ralph B. Arlinghaus, PhD:
1:06:25
H-e-i-s-t-e-r-k-a-m-p.

T.A. Rosolowski, PhD:
1:06:28
… k-a-m-p. Okay, thank you.

Ralph B. Arlinghaus, PhD:
1:06:30
Nora Heisterkamp.

T.A. Rosolowski, PhD:
1:06:30
Nora. Great. Alright, thank you.

Ralph B. Arlinghaus, PhD:
1:06:34
So, in any event, all the science we all do in our field, what — whatever we're working on, it's all built on discoveries from other people.

T.A. Rosolowski, PhD:
1:06:43
Sure. Now, this — I mean, leading up to the tyrosine kinase activity, because that, as I learned from background research for other folks that I've — I've prepared to interview. I mean, that — that's a word that's come up in terms of signaling pathways and crosstalk ….

Ralph B. Arlinghaus, PhD:
1:07:05
That's right.

T.A. Rosolowski, PhD:
1:07:05
… and all the receptor sites.

Ralph B. Arlinghaus, PhD:
1:07:06
That's right.

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T.A. Rosolowski, PhD:
1:07:08
So, is that adding a new dimension to your work at this point, or …

Ralph B. Arlinghaus, PhD:
1:07:11
Yes.

T.A. Rosolowski, PhD:
1:07:11
… were you ___

Ralph B. Arlinghaus, PhD:
1:07:12
Yes.

T.A. Rosolowski, PhD:
1:07:12
Okay. So this added an entirely new …

Ralph B. Arlinghaus, PhD:
1:07:14
I knew that the BCR-ABL hybrid protein was a tyrosine protein kinase. That means it — it bound ATP and took the phosphate from ATP and put it on target proteins.

T.A. Rosolowski, PhD:
1:07:28
Now, could you tell me now, given what you've learned since then, what is the role of those protein products in that transfer of phosphates, what's the role of that in cancer?

Ralph B. Arlinghaus, PhD:
1:07:48
Well, I mentioned this two-faced god called Janus. Well, as — as a — as a young assistant professor at MD Anderson, I recognized what was known in the field by a guy named Jim Iley, again standing on the shoulders of — of these great giants. Jim Iley found out, along with many others 25 years ago, that Janus kinase is — plays a very important in blood cells for making more blood cells and making blood cell proteins. So, I reasoned that the BCR-ABL oncoprotein causing leukemia in blood cells — affecting blood cells would probably partner with Janus kinase, and that — that guess in 1995 turns out to be correct in 2011. So, my — my papers have

led to this scenario. That the Philadelphia chromosome forms, we don't know how, by accident, fusing parts of BCR and parts of ABL to give you this hybrid, this has a eternally active tyrosine kinase from the active ABL sequences in the BCR-ABL. And, now we know that that sequence, that kinase, is one of the things it does is activate, turn on Janus kinase 2 in CML cells. And then, we published that Janus kinase 2 activates the RAS and PI 3 kinase pathways in leukemia.

T.A. Rosolowski, PhD:
1:09:55
I'm sorry, P — P …

Ralph B. Arlinghaus, PhD:
1:09:55
RAS, R-A-S…

T.A. Rosolowski, PhD:
Mhmm, and …

Ralph B. Arlinghaus, PhD:
1:09:59
… and PI 3 kinase pathways in leukemia cells. And use — people used to think was BCR-ABL kinase that did that but it was actually Janus kinase that did it because BCR-ABL kinase was necessary to activate Janus kinase so it could do that.

T.A. Rosolowski, PhD:
1:10:19
And so, these are all pathways that are essential.

Ralph B. Arlinghaus, PhD:
1:10:20
Quarter after two. Okay.

T.A. Rosolowski, PhD:
1:10:25
We're good?

Ralph B. Arlinghaus, PhD:
1:10:25
We're good.

T.A. Rosolowski, PhD:

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1:10:26
Okay.

Ralph B. Arlinghaus, PhD:
1:10:26
So far.

T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
1:10:28
Forty-five minutes. I'm talking too damn much.

T.A. Rosolowski, PhD:
1:10:31
No, that's fine. We have another session scheduled so, you know, we're — we're good.

Ralph B. Arlinghaus, PhD:
1:10:34
Okay, alright.

T.A. Rosolowski, PhD:
1:10:35
It — it will take whatever time it takes. No problem.

Ralph B. Arlinghaus, PhD:

Yeah.

T.A. Rosolowski, PhD:
1:10:39
So, am I correct in understanding that these — these different functions, you know, one step to the next step, to this next step, to this next step …

Ralph B. Arlinghaus, PhD:
1:10:49
Yes.

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T.A. Rosolowski, PhD:
1:10:50
… are all involved in keeping that leukemia cell active …

Ralph B. Arlinghaus, PhD:
1:10:54
Yes.

T.A. Rosolowski, PhD:
1:10:55
… keeping it dividing, keeping it …

Ralph B. Arlinghaus, PhD:
1:10:56
Keeping it alive.

T.A. Rosolowski, PhD:
1:10:57
Keeping it alive. Okay. So, they're all — it's basically part of the, you know, life function, if you will, …

Ralph B. Arlinghaus, PhD:
1:11:03
It is.

T.A. Rosolowski, PhD:
1:11:04
… of the cancer cell. So, do you — were you able to discover precisely what roles these serve inside the cancer cell?

Ralph B. Arlinghaus, PhD:
1:11:14
Others have done that. Like the RAS pathway …

T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
1:11:17

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… and what it does in normal cells as well as cancer cells. That was done by others.

T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
1:11:23
The PI 3 ki — I just learned how CML cells, which were known to have activated RAS pathway, activated PI 3 kinase pathway — I learned how that came about. That's because BCR-ABL activated JAK 2 …

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
1:11:40
… and then JAK 2 phosphorylated a site on tyrosine that led to activation of the RAS and PI 3 kinase pathways. That's what's in that leukemia paper in 2011.

T.A. Rosolowski, PhD:
1:11:54
Interesting.

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Chapter 05
Leaving Johnson and Johnson to Return to MD Anderson
A: Joining MD Anderson/Coming to Texas;

Story Codes
A: The Researcher;
A: Joining MD Anderson;
A: Professional Path;
B: Institutional Politics;
C: Evolution of Career;
C: Controversies;
D: Business of Research;
D: The History of Health Care, Patient Care;

Ralph B. Arlinghaus, PhD:
1:11:57
So, I need to back up a little bit and — and say Dr. Demakowski, who didn't want me to be at MD Anderson – that's my words, not his - but …

T.A. Rosolowski, PhD:
1:12:09
Dr. De – Demakowski?

Ralph B. Arlinghaus, PhD:
1:12:10
He was the one that was Chairman of the Department of Virology who was studying leukemias including chronic myeloid leukemia. He thought that I shouldn't be competing with him and I convinced him that my work would be so much different than his work, that I would be adding to his work, not competing with it. And, he finally signed off on the piece of paper for the Committee that decided that this new faculty member called Ralph Arlinghaus could then begin to work on leukemia using his methods.

T.A. Rosolowski, PhD:
1:12:45
Now, was — was this kind of discussion with Dr. Demakowski, was that when you first came to MD Anderson?

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Ralph B. Arlinghaus, PhD:
1:12:53
First.

T.A. Rosolowski, PhD:
1:12:53
Okay, okay. So, there was some concern about overlap …

Ralph B. Arlinghaus, PhD:
1:12:56
There was.

T.A. Rosolowski, PhD:
1:12:56
… of territory at that point.

Ralph B. Arlinghaus, PhD:
1:12:57
There was.

T.A. Rosolowski, PhD:
1:12:58
Yeah.

Ralph B. Arlinghaus, PhD:
1:12:59
He was protecting his territory.

T.A. Rosolowski, PhD:
1:13:00
Sure. So …

Ralph B. Arlinghaus, PhD:
1:13:03
Remember at the time, he was also claiming that there was a human cancer virus which he named ESP 1 after his trainee, Elizabeth Priory, ESP 1, that turned out to be published papers – I have to be careful now – was on the wrong track, let's put it that way. And, that was ess — that was essentially found out by others, not me, because I wasn't working on human CML. I didn't have to work on CML. I had to work on Rauscher leukemia virus …

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T.A. Rosolowski, PhD:
1:14:00
Right. Sure.

Ralph B. Arlinghaus, PhD:
1:14:01
… because I knew what to do there so I had to — wait Groffen and Heisterkamp in the early eighties to tell me about …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:14:07
… the — the Gag B — I mean, the BCR protein that was fused to Gag.

T.A. Rosolowski, PhD:
1:14:16
So, the story you were telling earlier is, you know, kind of fleshing out your work when you were in California. So, this — that span of time was 1983 to 1986.

Ralph B. Arlinghaus, PhD:
1:14:28
Right.

T.A. Rosolowski, PhD:
1:14:29
So, what made you come back to MD Anderson?

Ralph B. Arlinghaus, PhD:
1:14:34
Interesting story. I had never planned to come back.

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
1:14:38

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Not because I didn't like MD Anderson but I figured I had a lifetime job with J&J, they were going to pay me …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:14:44
… then we were going to have to write another grant again. Okay. Then something bad happened to J&J. You can read about it. Somebody in Chicago opened up a Tylenol bottle took out the Tylenol and put cyanide in them, five or six capsules, put the cap back on, put it back on the shelf, and then, I think two people died of cyanide poisoning, blamed on Tylenol bottles from J&J.

T.A. Rosolowski, PhD:
1:15:19
And this was in the …

Ralph B. Arlinghaus, PhD:
1:15:21
This has got to be now …

T.A. Rosolowski, PhD:
1:15:21
… sometime …

Ralph B. Arlinghaus, PhD:
1:15:24
… '84, '85.

T.A. Rosolowski, PhD:
1:15:25
Yeah, I remember that story.

Ralph B. Arlinghaus, PhD:
1:15:27
I don't think those people ever have been caught, whoever did that. But, J&J decided that we couldn't afford to keep a guy like Arlinghaus and his team to work on other things. We need to protect our Tylenol product line, we need to make other product lines to make money because

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we're losing money. Because now, 100,000 people every month were buying Tylenol and now …

T.A. Rosolowski, PhD:
1:16:01
Yeah, I remember the stories …

Ralph B. Arlinghaus, PhD:
1:16:02
Not many …

T.A. Rosolowski, PhD:
1:16:02
… about it. Yeah. People were scared.

Ralph B. Arlinghaus, PhD:
1:16:05
Scared.

T.A. Rosolowski, PhD:
1:16:05
They were.

Ralph B. Arlinghaus, PhD:
1:16:06
And, J&J lost a lot of money and a lot of business. And they came to us in California and said, "You guys have to start working on generating new products." I didn't tell them right away. I — I said to the — they brought a new guy in from Israel and I said to him, "You know, this is new territory for me. I'm — I'm in the discovery business, I'm not in product development." I — I don't — I don't even know if I could do it. I probably could. But I don't want to do it. So, I started looking for a job. I didn't tell them that. I started looking for a job and I almost went to Abbott. I made three trips to Abbott in Chicago. They wanted to hire me.

T.A. Rosolowski, PhD:
1:16:50
And, Abbott is …

Ralph B. Arlinghaus, PhD:
1:16:51
Abbott Laboratories.

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T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
1:16:53
Famous pharmaceutical company.

T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
1:16:55
Florida, Baton Rouge, New Orleans. I looked at jobs to leave and go back to academia. Instead of having a research institute, Scripps Clinic, associated with J&J. And, I was walking in the hallway of my lab in California and the guy — the pathologist there named Bob Nakamora. I didn't know him very well but he knew me because of my – what do you call it – whatever the — localized fame, you know. I am not — I wasn't a famous man. I was well known in some areas, right. So, he said, "Hey," something like this: "Hey, Arlinghaus, you want to go back to Texas?" I said, "What's the deal?" He said, "Well, MD Anderson is looking to hire somebody and shall I give them your name?"

T.A. Rosolowski, PhD:
Wow.

Ralph B. Arlinghaus, PhD:
1:17:56
And I sa — I said — "Bob," I said, "That would — that would be great." Because the cyanide thing, Tylenol had already gone underway and our budget was collapsed …

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:
1:18:10
… and they wanted me to work on things that I didn't want to work on. I spent all my years — I was going to work on what I wanted to work on. That's not because I was egotistical. Because, all my training led me to somewhere. I was on a mission, remember? I wanted to cure CML, which I haven't, still haven't. But, that's what I wanted to do. I didn't want to make drugs for J&J. So, I left and went back to MD Anderson.

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T.A. Rosolowski, PhD:
1:18:36
So, how did that happen? Who — who did you contact about this new position …

Ralph B. Arlinghaus, PhD:
1:18:40
Dr. Patakis …

T.A. Rosolowski, PhD:
Okay.

Ralph B. Arlinghaus, PhD:
1:18:41
… who was Chairman of the Division of Pathology before — that was before pathology merged with lab medicine, remember? We had the Division of Surgery, and the Division of – I can't even think of all the names of these Divisions – but you — you know them better than I do. But, anyway, there — there turned out there was a Division of Lab Medicine and a Division of Pathology, and Patakis, who's a great guy, hired me to come back to MD Anderson and they formed a new department …

T.A. Rosolowski, PhD:
1:16:15
So, …

Ralph B. Arlinghaus, PhD:
1:19:15
… in 1986 called the Department of Molecular Pathology. I named it. And that's what I wanted to do. I wanted to study — hire people that would study the — the molecular details of various cancers. I couldn't cover them all …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:19:30
… but I was going to try to get the best people on the planet …

T.A. Rosolowski, PhD:

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Mhmm.

Ralph B. Arlinghaus, PhD:
1:19:35
… to come work in our department, get grant support, and study whatever they want to study on how … I hired a guy – he's now full professor - ____ 1:19:48 works on reactive oxygen and its — its involvement in — in cancer. So, they brought us in and others I hired from Harvard …

T.A. Rosolowski, PhD:
1:20:08
So, can I ask you — I mean, you must have had some interesting conversations with people in 1985 or '86 when you thinking about coming back. They say, "Hey, Dr. Arlinghaus, I mean, you … you …

Ralph B. Arlinghaus, PhD:
1:20:20
They said …

T.A. Rosolowski, PhD:
1:20:21
… you're back."

Ralph B. Arlinghaus, PhD:
1:20:22
____ (over-talking) they said, "What the hell are you leaving the glory land of southern California to come back to — are you crazy?" No, they would say things like that to me.

T.A. Rosolowski, PhD:
1:20:31
Yeah, that's interesting.

Ralph B. Arlinghaus, PhD:
1:20:33
I would smile and say, "Well …

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:

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1:20:36
… things changed." I — maybe if I got to know them better, I'd tell them a little bit about the cyanide deal, …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:20:41
… you know, and if — if not — if we didn't get that deep, I wouldn't mention it …

T.A. Rosolowski, PhD:
Sure.

Ralph B. Arlinghaus, PhD:
1:20:45
… and …

T.A. Rosolowski, PhD:
1:20:45
Sure. Now, …

Ralph B. Arlinghaus, PhD:
1:20:48
.. I'd still be at J&J if somebody hadn't put Tyl — cyanide in Tylenol. Because they liked me and they liked what I did. We used to — there were people that worked for Dick Lerner, they were doing projects that didn't work out and I found out what they were doing — not me. The team that I hired …

T.A. Rosolowski, PhD:
Mhmm.

Ralph B. Arlinghaus, PhD:
1:21:10
… were all legitimate Ph.D. scientists. We were — we were known for being – trying to think of the words – good scientists, honest, straightforward, tell it like it is. And, I did. And — so the people at J&J, they liked me. So, if somebody didn't put cyanide in Tylenol, I'd probably still be there. I'd be in New Jersey doing some administrative job I don't want to do. And I probably would have said no, I don't want to do it.

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T.A. Rosolowski, PhD:
1:21:51
So, when you came back in 1986, how — what did you see about the institution. How had it changed in those few years …

Ralph B. Arlinghaus, PhD:
1:21:57
Well, first of all, I came back as Chair.

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:22:02
Now, they had a search committee to find a new Chair of the Department of Tumor Virology which was formed up, and I was second in line. And I want — the — the head of research didn't like me at MD Anderson. So he, when the — the first candidate finally turned him down, the second candidate was in-house, Ralph Arlinghaus, he disbanded the search. And, he had a meeting …

T.A. Rosolowski, PhD:
1:22:29
And this was Frederick Becker at the time.

Ralph B. Arlinghaus, PhD:
1:22:30
Yes, it was. I wasn't going to use his name …

T.A. Rosolowski, PhD:
1:22:32
I — I've interviewed him, yeah.

Ralph B. Arlinghaus, PhD:
1:22:35
But …

T.A. Rosolowski, PhD:
1:22:36

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Sorry, I didn't …

Ralph B. Arlinghaus, PhD:
1:22:36
That's alright. No, that's fine. I just don't like to — I don't like to …

T.A. Rosolowski, PhD:
1:22:40
Yeah.

Ralph B. Arlinghaus, PhD:
1:22:41
… I don't like to talk bad about people.

T.A. Rosolowski, PhD:
01:22:42
Well, I mean, these kinds of, you know, butting of heads is normal in big institutions, too.

Ralph B. Arlinghaus, PhD:
1:22:49
So, he did some very important things for this institution and so — anyway, Mickey LeMaistre bypassed Fred Becker and hired a new Chair in his division of research that was Ralph Arlinghaus and Fred Becker would not give me the chance to compete for a job three years earlier.

T.A. Rosolowski, PhD:
Interesting.

Ralph B. Arlinghaus, PhD:
1:23:14
So, I didn't say a thing to him. I didn't smile. I just kept my head down, got my appointment, got my positions through Fred Becker from Mickey LeMaistre and so, I bypassed Fred Becker.

T.A. Rosolowski, PhD:
1:23:29
So this — so Dr. LeMaistre was very, very supportive of …

Ralph B. Arlinghaus, PhD:
1:23:32

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Oh, yeah.

T.A. Rosolowski, PhD:
1:23:32
… what you were doing.

Ralph B. Arlinghaus, PhD:
1:23:32
Oh, yeah. I'll never forget when I resigned at the budget meeting, when I was Acting Chair of the Tumor Virology Department, and when they had the — I'll never forget it — neither will LeMaistre, they were done with all the budget information, I was Acting Chair, and I said, "Are we done? I don't want to break up your …" I said, "I want to tell you one more thing." I said, "I'm going to resign next month." And I told them what I was doing, going to work for J&J, starting a new lab out there, new company, start — continue the work on leukemia there. And – I don't want to embarrass LeMaistre – but his face turned the pinkest pink. I'm not — I don't see pink very well but he was shocked. And clearly didn't want me to leave. He didn't say it, because Becker is in the room, right? So, Becker is just happy as all get out, because what he told me, "Arlinghaus, since — since ___ candidate left, there's nothing for you here at MD Anderson." And I took him at his word and there wasn't.

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:24:41
And I found a good job somewhere else …

T.A. Rosolowski, PhD:
Sure.

Ralph B. Arlinghaus, PhD:
1:24:43
… to do what I wanted to do, somewhere else. And so, when Patakis must have went to LeMaistre – and I don't know what was said – but I got everything I wanted, and more, to come back. I didn't burn any bridges when I left. I didn't say bad things to Becker, I still don't. He — he — he's in my department. I'm no longer Department Chair but I treated him well.

T.A. Rosolowski, PhD:
Yeah. Yeah.

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Ralph B. Arlinghaus, PhD:
1:25:10
I did.

T.A. Rosolowski, PhD:
1:25:11
Well, I mean, it's like a family. You got live together.

Ralph B. Arlinghaus, PhD:
1:25:14
You know, I wasn't about to — I don't have time ...

T.A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD:

… for that.

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Chapter 06
The New Department of Molecular Pathology
B: Building the Institution;

Story Codes
A: The Administrator;
C: Leadership;
B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
B: Obstacles, Challenges;
B: MD Anderson Culture;
A: The Researcher;
C: Discovery and Success;

T.A. Rosolowski, PhD:
1:25:18
Sure. Sure. I — I'm also wondering, too — I mean, the creation of this department, because — I'm — I'm always, you know, always interested in how — why new departments are formed at the time they are. I mean it seemed like, par — in part, it was to create a space for you where you had an administrative role …

Ralph B. Arlinghaus, PhD:
1:25:40
That's true.

T.A. Rosolowski, PhD:
1:25:41
… an administrative ___.

Ralph B. Arlinghaus, PhD:
1:25:42
And I could have accepted and left it at that …

T.A. Rosolowski, PhD:
1:25:43

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Sure.

Ralph B. Arlinghaus, PhD:
1:25:43
… but I told them what else I wanted to do. I wanted to …

T.A. Rosolowski, PhD:
1:25:44
And, what was that?

Ralph B. Arlinghaus, PhD:
1:25:46
Well, I wanted to study the molecular mechanisms of how cancer cells became cancer at the level of proteins. Because remember, the proteins are the — they do all the heavy lifting in cells. Hemoglobin binds oxygen in red cells, and without hemoglobin, you wouldn't be alive. You and I wouldn't be talking if we didn't have hemoglobin. So, the protein, hemoglobin, is critical for red cell function. So, all cancer cells have critical changes that makes them into cancer cells. I wanted 100 people to find those critical proteins and identify them diagnostically and therapeutically.

T.A. Rosolowski, PhD:
1:26:29
Were there other departments of molecular pathology at cancer centers?

Ralph B. Arlinghaus, PhD:
1:26:33
Oh, in other cancer centers, yeah. The one in Pittsburgh.

T.A. Rosolowski, PhD:
1:26:35
Okay. There's one in Pittsburgh.

Ralph B. Arlinghaus, PhD:
1:26:36
There was, at the time. Yeah.

T.A. Rosolowski, PhD:
1:26:38
Because I'm trying to get a sense of, you know, …

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Ralph B. Arlinghaus, PhD:
1:26:40
There weren't many.

T.A. Rosolowski, PhD:
1:26:40
… what was going on in the field, you know. Was the time ripe, you know, with all of this research coming out, for suddenly departments to start forming and ____ (over-talking)

Ralph B. Arlinghaus, PhD:
1:26:48
I — I was criticized by pathologists, you're not doing pathology. This is not pathology …

T.A. Rosolowski, PhD:
1:26:52
Why did they say that?

Ralph B. Arlinghaus, PhD:
1:26:52
… here at MD Anderson.

T.A. Rosolowski, PhD:
1:26:53
Why did they say that?

Ralph B. Arlinghaus, PhD:
1:26:55
Well, they didn't have the vision. The vision is not looking at cells but examining what's going on in the cells, from a cancer point of view. They didn't have that vision. But, it didn't bother me. I didn't care what — that kind of criticism never bothered me.

T.A. Rosolowski, PhD:
1:27:16
Is that something that you found you had to keep explaining over the years?

Ralph B. Arlinghaus, PhD:
1:27:21
No.

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T.A. Rosolowski, PhD:
1:27:22
No.

Ralph B. Arlinghaus, PhD:
1:27:23
No. They finally got it.

T.A. Rosolowski, PhD:
1:27:25
How long did that take?

Ralph B. Arlinghaus, PhD:
1:27:31
I don't know. I never keep track of that. I don't know.

T.A. Rosolowski, PhD:
1:27:33
I'm curious because it — I mean, it just seems like a real mind shift — mind set shift.

Ralph B. Arlinghaus, PhD:
1:27:38
Well, first of all, when I came here, I didn't have any grant support and I wrote — every grant I wrote to the National Institutes of Health, I got funded. So, I ended up with five — six grants from NIH. So, that got a lot of people off my back.

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:27:52
I was treated very well by the study sections at NIH because of my past productivity …

T.A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD:
1:28:04
… discovering the activity of the BCR-ABL oncoprotein while I was at J&J.

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T.A. Rosolowski, PhD:
1:28:08
Yeah, I mean, that kind of credibility goes a long way ____ (over-talking)

Ralph B. Arlinghaus, PhD:
1:28:14
Well, I mean, I — I made things happen.

T.A. Rosolowski, PhD:
1:28:16
Sure. Absolutely. So, tell me about this vision you had for this department, you know, hiring, as you said, you know, the best people on the planet to study the mechanisms of proteins and how they — they lead to cancer. How did you go about creating that here? In this department?

Ralph B. Arlinghaus, PhD:
1:28:33
Well, I had to get positions given to me and Dr. LeMaistre gave me faculty positions, not too many, and then I had to beg LeMaistre to give me more, to hire more people. We never had a big department and we were never very large. Cancer therapeutics, like 25 faculty members. We — we've never been over 10, so … I wasn't into just quantity,I was interested in quality.

T.A. Rosolowski, PhD:
1:29:05
Who were the people you hired and why did you hire them?

Ralph B. Arlinghaus, PhD:
1:29:10
Well, some people I inherited, but I didn't take all the people I inherited. I said, no, this is not going to work out. I'm going to end up firing them sooner or later so I don't want to take them in the first place. So there was Dr. Kwoh, who was — who I inherited. Dr. Sen, who I inherited. And then, I hired Dr. Mani from Harvard.

T.A. Rosolowski, PhD:
1:29:39
And that's M-a-n-i?

Ralph B. Arlinghaus, PhD:
1:29:40

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M-a-n-I, yeah. He's on stem cells in cancer. And, Dr. Wong, I inherited – I didn't inherit him. He was an outstanding Fellow in — in — in another department and he was looking for a faculty position, and I read his papers and I really liked what I saw.

T.A. Rosolowski, PhD:
1:30:05
What were you looking for?

Ralph B. Arlinghaus, PhD:
1:30:07
Well, in his case, I was looking about how he was going to — to advance the field of understanding cancer cells, what happens inside cells. And, he was working on — excuse me, I just got the hiccups – he was working on reactive oxygen. I know you don't know anything about that but … it turns out cancer cells produce reactive oxygen. Oxygen is a mutagen and the progression of cancer cells which is — that's the bad thing about cancer — cancer – you get the cancer tumor and then it keeps changing --mutagenesis. And the reason is, mutagenesis is this reactive oxygen that's produced by cancer cells …

T.A. Rosolowski, PhD:
1:31:00
How interesting. I didn't know

Ralph B. Arlinghaus, PhD:
1:31:02
… and Pei Wong uncovered many of the mechanisms of this — this production of reactive oxygen.

T.A. Rosolowski, PhD:
1:31:12
Hmm. Amazing. Hmm.

Ralph B. Arlinghaus, PhD:
1:31:5
He's a really brilliant guy. Full professor now. I hired him as an assistant professor from another department, Khow from another department.

T.A. Rosolowski, PhD:
1:31:25

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What were some of the other qualities you were looking for as you were recruiting to create this new department?

Ralph B. Arlinghaus, PhD:
1:31:32
I — I wanted vision and creativity. See, some people had departments here at MD Anderson and everything revolved around their work. I was not interested in having a bunch of people working on my projects. I wanted them to develop a unique set of research problems that were their own, not mine. I didn't want them to depend on me so when I failed, they would still be strong. So, I had all these strong people that developed under me and they were — most of us, we were all funded independently. There wasn't a pyramid of grant support like in some departments here. There was a whole variety of grants being approved and funded based on the — the people that were — that I hired that built their own pyramid, so to speak.

T.A. Rosolowski, PhD:
1:32:38
In their own, in their own arena.

Ralph B. Arlinghaus, PhD:
1:32:39
Their own structure

T.A. Rosolowski, PhD:
1:32:39
Their own arena, yeah.

Ralph B. Arlinghaus, PhD:
1:32:40
Their own arena.

T.A. Rosolowski, PhD:
1:32:42
How has that evolved over the years? I mean, that's 1986 …

Ralph B. Arlinghaus, PhD:

Well …

T.A. Rosolowski, PhD:

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1:32:48
You came back, so …

Ralph B. Arlinghaus, PhD:
1:32:49
Well, now — but now, I'm gone, right? So, it's no longer Chair, stepped down two years ago – I was asked, I didn't volunteer.

T.A. Rosolowski, PhD:
1:33:03
Can you tell me why that was?

Ralph B. Arlinghaus, PhD:
1:33:09
I probably don't know the whole story. I — I — I don't know if I can answer that question. But, I do know — I knew that they were making up my mind and it was time to step away. So, I stepped away. You know, if they don't want you …. it's pretty obvious what you have to do.

T.A. Rosolowski, PhD:
Yeah. I'm sure it.

Ralph B. Arlinghaus, PhD:
1:33:37
So, I did. Of course, I was, what, 75? I'm 79 now, and mentally still going strong for my own stuff and … Actually, it didn't bother me. It actually relieved me. I didn't have — I got the same salary. I asked them, "Are you going to cut my salary?" And it took me a while to find out but they didn't cut my salary. So I'm — I'm being treated very well. Except, some people thought it was my time – I'm not going to mention who – thought it was my time to step aside. And, hey, I didn't say you can't do that to me. I just said, okay, what's the timeframe?

T.A. Rosolowski, PhD:
1:34:23
Sure. So, over the course of that time as Chair, what do you feel you accomplished in — as — in the department?

Ralph B. Arlinghaus, PhD:
1:34:33

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I hired people like Tim McDonald, like ___ Mani, like Pei Wong, ___ Sen, who developed our own strong laboratories. And, Chen Kwoh. So, I had labs that could stand on their own, and if I died the next day, it wouldn't matter. They'd still be strong and had their own money for their own grants, so I built a very strong funded department, maybe – I — I don't know this – maybe one of the best funded basic science departments in the institution for years, because I hired strong people on their own that weren't dependent on Ralph Arlinghaus. They were their own pillars of strength and ideas.

T.A. Rosolowski, PhD:
1:35:32
How did you continue — I mean, once you hired these creative and strong people, how did you continue as a leader of this department? How did you continue to support that creativity and encourage it?

Ralph B. Arlinghaus, PhD:
1:35:50
I tried to continue to raise money for the budget, and things started to go — go downhill in that regard and I'm not going to say why. I could tell you why but, I don't think I can tell you the story is true, but …

T.A. Rosolowski, PhD:
1:36:14
Well, if you ____ (over-talking)

Ralph B. Arlinghaus, PhD:
1:36:15
It was — it was — I did a very non-political thing as an editor of a journal and the — I'm going to say – you can't use this.

T.A. Rosolowski, PhD:
Do you want me to turn off the recorder?

Ralph B. Arlinghaus, PhD:
1:36:33
Yes.

T.A. Rosolowski, PhD:
Okay.

[The recorder is paused.]

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T.A. Rosolowski, PhD:
0:00:03.7
Alright I'm turning the recorder back on after about a four-minute pause and you --- we were talking about how you continue to nurture the department and support these really strong people, talked about f --- you know generating funds. There was a kind of a difficult dry period that ensued. How did you ride that out?

Ralph B. Arlinghaus, PhD:
0:00:25.2
Well the people themselves --- are getting good support from themselves, but again I wasn't helping them through getting money from the institution in general ways and --- and that may have been the beginning of the end for me when I was asked to step down. So --- But they were still doing well, but they lacked some of the what we call "core facilities" that other departments had.

T.A. Rosolowski, PhD:
0:00:55:3
Okay.

Ralph B. Arlinghaus, PhD:
0:00:56.7
So we're totally being overlooked despite suc --- success of the individuals.

T.A. Rosolowski, PhD:
0:01:03.1
Now let me ask you …

Ralph B. Arlinghaus, PhD:
0:01:04:02
And maybe, the people I reported to said, "Well, this is not going to stop so we've got to get somebody else."

T.A. Rosolowski, PhD:
0:01:16.3
Right. So kind of to save the department there was a change of leadership.

Ralph B. Arlinghaus, PhD:
0:01:20.6

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So I think that's probably true.

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Chapter 07
Translational Research in the Department of Molecular Pathology (Now the Department of Translational Molecular Pathology)
A: The Researcher;

Story Codes
A: The Researcher;
A: Definitions, Explanations, Translations;
D: On Research and Researchers;
C: The Professional at Work;
D: Understanding Cancer, the History of Science, Cancer Research;
B: MD Anderson Culture;

T.A. Rosolowski, PhD:
0:01:27.8
Now when you came on, you --- the department was called --- was originally called Molecular Pathology.

Ralph B. Arlinghaus, PhD:
0:01:39.9
Correct.

T.A. Rosolowski, PhD:
0:01:40.1
When was the name Translational Molecular Pathology created?

Ralph B. Arlinghaus, PhD:
0:01:44:1
The new department chair was appointed in 2012.

T.A. Rosolowski, PhD:
0:01:48.2
Okay so that was when the new department chair came in.

Ralph B. Arlinghaus, PhD:
0:01:50.1
The new department chair changed it to Translational Molecular Pathology.

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T.A. Rosolowski, PhD:
0:01:55.0
And I'm sorry, I --- I don't know who the no --- new chair is.

Ralph B. Arlinghaus, PhD:
0:01:58.8
His name is Ignacio Vestuba. He was a patholog --- He was a pathologist, full professor at MD Anderson, and he got a job to go somewhere else and somebody didn't want him to go somewhere else. So they appointed him as chair of this department and he's been chair and I think he's doing a reasonably good job. It's early, but he treats people well. He treats me well.

T.A. Rosolowski, PhD:
0:02:30.9
Well I wanted to ask you about the translational piece because I mean that's certainly an important word here at MD Anderson, you know, the translational research. What can you tell me about how --- what --- your feelings about how your work evolved in the direction of translational research.

Ralph B. Arlinghaus, PhD:
0:02:49.9
Well, as I said to Dr. Vestuba, we're already translational molecular pathology. So I think, you know, I was working with leukemia docs. Moni was working with breast cancer docs to try to develop new ther --- new diagnostics, new therapies. So I said, we were all redoing it so it fits perfectly well. That's what I said.

T.A. Rosolowski, PhD:
0:03:13.7
How do you define that term? And how do you --- how do you see your work fitting into that category?

Ralph B. Arlinghaus, PhD:
0:03:19.9
So Molecular Pathology, if you want to be strict, you can say that's just studying molecular mechanisms with not a --- not a directive to --- towards finding a new diagnostic or a new therapy. Translational molecular pathology would be making these discoveries with the goal of helping the cancer patient. In other words. --- But we always did. I always --- I --- I'll tell you that the two technical trials running --- that are going to be run or recruited for by Dr. Cortez in Department of Leukemia based on my Jak2 studies in chronic myeloid leukemia. So I've played

a critical role in those studies because other people publish with me and they have advanced the field more than I could have done alone.

T.A. Rosolowski, PhD:
0:04:13.5
Now were these …

Ralph B. Arlinghaus, PhD:
0:04:14.6
And some of those advancements were particularly appropriate for running a --- a --- another trial on female patients that are resistant, not responding well, to Gleevec:
Imatinib) and the other TKIs. So that's one trial.

T.A. Rosolowski, PhD:
0:04:38.2
Now when you have set up your studies, I --- I'm trying to get a sense of how like what --- what a model of a translational study would be. You know somebody sets out to say, "Okay I'm going --- I'm going to embark now on a translational study." How --- How would you go about setting that up?

Ralph B. Arlinghaus, PhD:
0:04:55.6
Well I'll give you my model and we can talk about several. So my model was to understand what goes on in leukemia cell, identify the key factors, Janus kinase 2 and then identify ways to block that key factor so that we can kill leukemia cells and not kill normal cells. That's essentially what we want to do.

T.A. Rosolowski, PhD:
0:05:17.3
So it's ba --- it starts with a hypothesis.

Ralph B. Arlinghaus, PhD:
0:05:20.1
Yes.

T.A. Rosolowski, PhD:
0:05:20.5
And the aim, the purpose.

Ralph B. Arlinghaus, PhD:

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0:05:21.8
That's right. And that turned out to be successful. There is a new FDA approved drug for Janus kinase 2. So the leukemia doc Cortez is going to combine that with Glivec. We --- We found --- This person that I worked with, found out that if you --- the patients are resistant to Gleevec or Imatinib, but if you combine that with a Jak2 inhibitor, that changes things and allows the combination to be more effective in killing leukemia cells than either inhibitor alone.

T.A. Rosolowski, PhD:
0:06:01.2
Now do you find for your …

Ralph B. Arlinghaus, PhD:
0:06:03.4
Surprise and don't understand why the ….

T.A. Rosolowski, PhD:
0:06:05.8
Sorry, I didn't mean to cut you off.

Ralph B. Arlinghaus, PhD:
0:06:07.2
No, that's okay. So we don't know why that happens but the --- the reason trials are going to be run is because we found out in cell culture, this lady that I collaborated in Vancouver found this out. And she found out first you combine Jak2 inhibitor with Gleevec-like drugs, the combination is better than any one alone for killing off leukemia cells and not normal cells. She did that, but only because I introduced her to Jak2.

T.A. Rosolowski, PhD:
0:06:42.7
Interesting. Yeah.

Ralph B. Arlinghaus, PhD:
0:06:44.1
So I'm a co-author on that paper.

T.A. Rosolowski, PhD:
0:06:46.5
Now are your collaborators primarily basic scientists?

Ralph B. Arlinghaus, PhD:

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0:06:50.9
Yes.

T.A. Rosolowski, PhD:
0:06:51.2
Okay, so you don't collaborate with clinicians or what's your relationship?

Ralph B. Arlinghaus, PhD:
0:06:55.4
I don't object to that but …

T.A. Rosolowski, PhD:
0:06:59.1
It's not how you work?

Ralph B. Arlinghaus, PhD:
0:07:01.5
No, it's not that. They --- They --- You can't do --- You can't do experiments with patients. You have to do it from cells from patients. Right. You can work with cells from patients, but you can't do experiments on patients. FDA doesn't like that, right?

T.A. Rosolowski, PhD:
0:07:21.8
Well, I guess the reason I'm asking the question, I'm thinking of a conversation that I had with Mien-Chie Hung [oral history interview] who was saying, you know, he gets a lot of ideas about cancer problems from talking to clinicians and so --- and that helps feed his research and it seems --- I --- I mean I'm not sure if this is the case, but it seems to me like ….

Ralph B. Arlinghaus, PhD:
0:07:42.4
No I think that's a good strategy. But in --- in --- in …

T.A. Rosolowski, PhD:
0:07:44.5
Just that's not your strategy?

Ralph B. Arlinghaus, PhD:
0:07:45.3

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In my case, my focus is much more defined. I'm not working on breast cancer, prostate cancer, lung cancer, brain cancer. Many of those cancers, they don't have a lot in common except they are cancer, but I'm working focused pretty --- on not all leukemias, chronic myeloid leukemia.

T.A. Rosolowski, PhD:
0:08:06.4
Okay so….

Ralph B. Arlinghaus, PhD:
0:08:09.3
So I don't need --- I hear --- I hear the things about chronic myeloid leukemia by reading the papers and journals and so I don't have --- I don't need help from clinicians about what I'm going to do next, because I see it from the literature. Not that I wouldn't take it from clinicians I just --- they're --- they're learning from me. They're ---

T.A. Rosolowski, PhD:
0:08:35.6
Well I'm not --- I'm not saying there's a right or a wrong way. I'm trying to understand like what are the different models.

Ralph B. Arlinghaus, PhD:
0:08:38.3)
No I think his way --- If I were studying all the fields of cancer I would take that same approach that he's taking.

T.A. Rosolowski, PhD:
0:08:48.2
I mean I just --- it's --- the --- it's interesting.

Ralph B. Arlinghaus, PhD:
0:08:50.8
It's a good one. It's a good approach.

T.A. Rosolowski, PhD:
0:08:51.6
Yeah. And it seems --- And it's interesting because being translational research is so complicated because of the range of issues that it has to encompass and it's unique goals and so it --- I've been interested to --- to talk to people about how they understand how to create a model or an approach to --- to reach those --- those goals which is changing things for patients.

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Ralph B. Arlinghaus, PhD:
0:09:17.3
I think for Mien-Chie Hung [oral history interview] model is a good one if you're running a department that's studying cancer in general. But I --- again, I --- I don't --- I don't direct the people that I hire as faculty. I hire them because they have expertise on their own. They're going to generate their --- their ideas and their models to treat their --- to get their grant support to study their version of cancer. So

T.A. Rosolowski, PhD:
0:09:46.6
So there's quite a variety in your --- within this department

Ralph Arlinghaus
There is

T.A. Rosolowski, PhD:
9:53.5
then of people's approaches to the prob --- the issue of translational research and you go about doing it.

Ralph B. Arlinghaus, PhD:
0:09:56.7
There is.

T.A. Rosolowski, PhD:
0:09:57.3
Very interesting.

Ralph B. Arlinghaus, PhD:
0:10:05.2
And I think another reason that I was asked to step aside was because they wanted to recruit a chair where they could get space for a new chair. And if they had a new chair there would be a package for that new chair which would include space, resources whereas an old chair not likely to get that new --- new package.

T.A. Rosolowski, PhD:
0:10:28.8
Right. Sure.

Ralph B. Arlinghaus, PhD:

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0:10:30.5
Have to leave and go somewhere else.

T.A. Rosolowski, PhD:
0:10:32.5
Well, we're almost out of time for today and this feels like maybe a good place to stop. Is that okay?

Ralph B. Arlinghaus, PhD:
0:10:39.4
That's --- yeah, sure.

T.A. Rosolowski, PhD:
0:10:40.3
Alright. Great. Well thank you for your time today Dr. Arlinghaus.

Ralph B. Arlinghaus, PhD:
0:10:43.9
Alright. I probably talk too much but that's --- I hope it was informative.

T.A. Rosolowski, PhD:
0:10:47.2
Not at all. Yes. No. Very informative. Very interesting. And I am turning off the recorder at about 2:58.

Ralph B. Arlinghaus, PhD:
0:10:54.2
Okay. Sounds good.

T.A. Rosolowski, PhD:
0:10:54.4
Thank you very much.

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Chapter 00B
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T. A. Rosolowski, PhD:
0:00:03.1
Alright. So now we are recording and today is the 2nd of April 2014. The time is about 11 minutes after 1 and I'm in the Life Sciences Building on Holcombe Boulevard interviewing Dr. Ralph Arlinghaus. This is our second session. Thanks for making time in your schedule for me again. I appreciate that. And we dove right into talking about your research last time so --- and we kind of skipped over some background information so I wanted to go and pick that up today.

Ralph B. Arlinghaus
0:00:35.8
Okay.

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Chapter 08
Discovering a Talent for Laboratory Research and an Early Research Success
A: Educational Path;

Story Codes
A: Personal Background;
A: Influences from People and Life Experiences;
A: The Researcher;
C: Evolution of Career;
A: Character, Values, Beliefs, Talents;
C: Portraits;
D: Understanding Cancer, the History of Science, Cancer Research;
C: Discovery, Creativity and Innovation;
A: Definitions, Explanations, Translations;
C: Professional Practice;
C: The Professional at Work;

T. A. Rosolowski, PhD:
0:00:36.3
And so I wanted to ask you where were you born and when? If you would share your birthdate with me?

Ralph B. Arlinghaus:
0:00:45.2
Let's see. So, when I left MD Anderson, I of course took a job with Johnson & Johnson in Lahoya and they had me help them start up a company. I think I covered some of that and then I also brought a grant with me from MD Anderson. I was working on …

T. A. Rosolowski, PhD:
0:01:12.6
Actually we --- we did talk about this last time. Your --- Your movement yeah to --- and I kind of wanted to go back in time a little bit if you don't mind and talk about your --- your early background. Where you were born and then your family history. Yeah. Just because we're --- we're interested in getting a biographical picture of you, too.

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Ralph B. Arlinghaus:
0:01:29.6
I was born in Newport, Kentucky in 1935 and …

T. A. Rosolowski, PhD:
0:01:34.0
And what's your birthdate?

Ralph B. Arlinghaus:
0:01:35.3
08/16/1935. August 16, 1935.

T. A. Rosolowski, PhD:
0:01:39.4
Thank you. Okay. Is that a small town? Newport?

Ralph B. Arlinghaus:
0:01:42.2
Newport is a --- is a small town in northern Kentucky across the Ohio River from Cincinnati, Ohio. So Cincinnati is big, Newport is small. And, uh, It's a nice --- It was a nice little town, but it went through some cleanup issues. It used to be a big gambling --- a big gam --- a gambling place. Wide open place.

T. A. Rosolowski, PhD:
0:02:10.4
Interesting. Now what about your family? Was anybody in your family involved in the sciences at all?

Ralph B. Arlinghaus:
0:02:17.6
Oh no. No. My --- My mom and dad went to Catholic schools in either northern Kentucky or Cincinnati and I think my mom went to the third grade and my dad probably about the same. My mother ended up because she was one of 11 and her father wasn't doing so well. Her father was in --- My mom's father was in the grain business who I never knew and then when automobiles came --- came out, feeding horses grain to pull your wagon around or your buggy, wasn't available. So his business went --- went downhill. So --- So I think my mother was third or fourth grade. She went to work.

T. A. Rosolowski, PhD:
0:03:06.2

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Wow. That's pretty amazing.

Ralph B. Arlinghaus:
0:03:08.4
In what you might call a sweatshop.

T. A. Rosolowski, PhD:
0:03:09.5
Wow. That's amazing.

Ralph B. Arlinghaus:
0:03:11.3
She called it piece work. Where you make --- you make a skirt, you got a nickel. You make a pair of pants, you got another nickel. And you work 10 hours a day and …

T. A. Rosolowski, PhD:
0:03:23.5
Now what's your family background in terms of --- are you of an immigrant background?

Ralph B. Arlinghaus:
0:03:29.1
My --- My --- My parents were born --- My mother was born in Kentucky --- northern Kentucky. My father was born in Cincinnati. Their parents came over from Germany.

T. A. Rosolowski, PhD:
0:03:42.6
Okay. That's very common it seems with the --- the generation that comes over you know works really hard so the next generations can have an education.

Ralph B. Arlinghaus:
0:03:58.3
And my mom and dad they worked very hard because he was one of 12. She was one of 11. She was the youngest of 11. He was the oldest of 12 and they had to bring money in. So that the family had enough to eat, I guess.

T. A. Rosolowski, PhD:
0:04:18.1
So how --- Did you go to work at an early age? How --- What was the balance of work and education?

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Ralph B. Arlinghaus:
0:04:22.4
My --- My --- My dad was a --- He was blind from birth. So he was employed as a baker in Newport, Kentucky for the same bakery shop. I don't know, 40 years and my mother had odd jobs in addition to being a housewife and taking care of five children. So she would --- she'd clean doctors' offices. So they --- they had a hard time. So when I was --- reached high school age my mother was a very strict Catholic. And she said "Ralph, you're going to have to go to a Catholic school. Not to the public school in Newport. I don't want you going there. So you're going to have to go to the Roman Catholic school, but they have --- you have to pay tuition and we don't have the money for that. So you need to get a job." So I was like 12 years old, right? So I got a job at a pharmacy working afternoons. Three to five afternoons a week and went to --- went to Catholic high school. And worked at that same place when I went to college. The only one of our family that went to college --- went to university.

T. A. Rosolowski, PhD:
0:06:00.3
And you went to the University of Cincinnati, right?

Ralph B. Arlinghaus:
0:06:03.2
That's correct.

T. A. Rosolowski, PhD:
0:06:04.5
And you got your BS in 1957.

Ralph B. Arlinghaus:
0:06:06.7
That's correct. So I had to pay my way through that. So at that same pharmacy that I worked all through high school, I worked that same pharmacy all through university studies.

T. A. Rosolowski, PhD:
0:06:21.7
So what did you do in work at the pharmacy and is that why you ended it?

Ralph B. Arlinghaus:
0:06:26.1
I was a clerk.

T. A. Rosolowski, PhD:

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0:06:23.6
You were a clerk?

Ralph B. Arlinghaus:
0:06.:25.8
I was a clerk. I was a soda fountain clerk.

T. A. Rosolowski, PhD:
0:06:29.2
Oh, yeah? So why did you select to go? I --- I mean I'm just thinking you worked at a pharmacy and you ended up going into pharmacy.

Ralph B. Arlinghaus:
0:06:35.3
That's right. I did.

T. A. Rosolowski, PhD:
0:06:35.5
So what was that about?

Ralph B. Arlinghaus:
0:06:39.0
Well, I mean --- I mean our edu --- the family and --- our education in our family was minimal, right? So I --- if I was going to able to go to college and I wanted to because my mother stressed education. Although she never went passed the third grade, she said "You need to get educated." And so she pushed me, pushed me, and pushed me to get education. So --- So I didn't want to go to a liberal arts school at University of Cincinnati. I picked College of Pharmacy because I was working in the --- the pharmacy and I knew something about pharmacists. so I was --- I got into the College of Pharmacy because I was a very good student at the Catholic high school that I went to and was like third or fourth in my class. I don't remember. But --- So --- So I went to that University of Cincinnati and it was a small college of pharmacy that wasn't part of the university. It used to be called Cincinnati College of Pharmacy and I entered in, what is that --- 50 --- '53 September and I'm trying to think. So in '54 the College of Pharmacy merged. Or --- Merged is probably too strong a word. Became part of the University of Cincinnati. The Dean of the College of Pharmacy --- The Cincinnati College of Pharmacy, just a small school, somehow managed to convince the un --- the big university to take the College of Pharmacy as part of one of their --- their colleges. And that was a big deal for the College of Pharmacy. And --- So the second year of College of Pharmacy I went to the University of Cincinnati and took courses with all of the --- all of the --- all of the big college courses unlike the College of

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Pharmacy. So it's a new world for me. I did pretty well my first year but I did extremely well the third --- second, third, and fourth year at the university.

T. A. Rosolowski, PhD:
0:09:01.6
Interesting. Yeah. So what --- what did you --- what were the courses you really gravitated for and how did you see your own abilities developing? Because that must have been an amazing, you know, here is an emersion in a whole new world.

Ralph B. Arlinghaus:
0:09:14.3
Well first of all you know we were in very small classes at College of Pharmacy, maybe 70 people. Like my organic chemistry course in the second year of College of Pharmacy at the university there was probably 600 people. The instructor, his name was Ian McGregor, spoke with a microphone in this big auditorium and I thought, man, I'm --- I'm not going to make it. But, uh --- So it turns out he gave very tough exams and I finished the exams. I was one of the few that finished. And I was --- my class average in that course was something like in the mid-90s and the average for the class was the mid-60s, maybe mid-50s.

T. A. Rosolowski, PhD:
0:10:02.6
So you'd really found your element.

Ralph B. Arlinghaus:
0:10:07.0
So I --- A lot of people didn't like me. I blew the curve so to speak. But I --- I have to tell you that I wasn't sure I was going to make it through school so I studied all the time. I didn't have a car. So I had to take a bus to go from Newport, go to the bus terminal in Cincinnati, walk from the bus terminal to another bus stop, take a street car to the College of Pharmacy, and then later take a --- take a street car or bus to what's called Clifton Area of Cincinnati where the university was. So --- So I worked at that College of Pharmacy and so I was working probably 20 hours a week and taking a four --- a full course load. Back then a full course load was 18 hours and I ended up Valedictorian in my class at the College of Pharmacy so --- because I was I don't know. I remembered everything I read and

T. A. Rosolowski, PhD:
0:11:21.8
Yeah you kept at it.

Ralph B. Arlinghaus:

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0:11:22.2
I asked questions and on exams I wrote it all down.

T. A. Rosolowski, PhD:
0:11:25.3
Did you love it?

Ralph B. Arlinghaus:
0:11:29.9
I --- That's too strong a word. I knew it was a means to an end. Because I --- I knew I wanted to get a college degree and after I found out I was so talented in getting grades --- in getting good grades and I decided I was going to get my Master's degree. And I made that decision in the senior year of college. I went on and got my Master's degree.

T. A. Rosolowski, PhD:
0:11:57.4
And that --- you got that in 1959.

Ralph B. Arlinghaus:
0:12:00.3
Right. And then I decided well people told me that after the Master's degree you don't want to stop here. You're --- you're doing well and I had a good advisor who was the Dean of the College of Pharmacy, a guy name Joseph Kowaliski
0:12:13.3) and Dr. Kowaliski
0:12:15.7) was a --- really a good mentor for me and so I --- he helped me get into the graduate program of Arts & Sciences at the University of Cincinnati. The Master's degree was in the College of Pharmacy. They had their own Master's program. So then I got a degree --- a Ph.D. degree and …

T. A. Rosolowski, PhD:
0:12:45.2
And that was in 1961 in Biochem.

Ralph B. Arlinghaus:
0:12:47.6
Yes. Yes. And …

T. A. Rosolowski, PhD:
0:12:53.0
What was your --- your Ph.D. research?

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Ralph B. Arlinghaus:
0:12:58.4
That's another interesting story. For me interesting. I --- When --- I was part of the medical school faculty. I was not the faculty. I was --- my advisor was a medical school faculty member and he was studying the structure of collagen. And --- Yes, so I --- they accepted me into their laboratory and I --- I was asked to sequence collagen. Now back then it wasn't known, but collagen is not one long polyprotein. It's three long polyproteins. We called them alpha, beta, and gamma. I don't know what they're called now but --- and there --- so sequencing them was not --- not going to be easy. And I didn't know that. I was naïve and so I took on that project and the guy before me who got his Ph.D., he had purified lots of fragments of collagen and he had them stored in a freezer. I don't know if you remember the Evenflo baby bottles.

T. A. Rosolowski, PhD:
0:14:28.9
No, I don't. No.

Ralph B. Arlinghaus:
0:14:30.1
Well, Evenflo was one of the first to make bottles with nipples to feed babies, right, and back when I was growing up and so we had these 4 ounce Evenflo bottles. There must have been 25 of them in this freezer --- chest freezer and my advisor said, "Well, I want you to sequence all of those peptide fragments of collagen and I picked the first one out." and got my Ph.D. on that first one and why. Well, back then this department --- this laboratory was kind of behind times. I didn't know that, but I would go to the library and look at modern methods which were not available in that department. So the first baby bottle, I thawed it out and using techniques I was taught by my advisor, it looked like a dipeptide, two amino acids, based on his methods. And I was reading in the library and there was a group at Rockefeller called Moore & Stein, very famous for developing methods to separate all 20 amino acids from proteins on a single analysis which happened to be something called column chromatography. So the --- So it was a setup that wasn't available in this laboratory --- in this department. So according to Moore & Stein from Rockefeller's PNAS paper I needed a 4 foot 1 cm diameter glass column and put a resin called Dowex-50, pack that resin into this column that went from here to the floor.

T. A. Rosolowski, PhD:
0:16:33.5
Wow so about six feet? Eight feet?

Ralph B. Arlinghaus:
0:16:35.6

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Well maybe four or five feet. And then --- then it had to be jacketed and run at 37 degrees. So I had to --- I went and scrounged up a water bath and a heater that would maintain the water bath at body temperature and I got a pump from a hardware store. Pumped the water out of that bath into the column jacket and so essentially made my Moore & Stein column as they described it in their PNAS paper. So then I --- I'll never forget this --- I did all 20 amino acids like Moore & Stein, mixed --- made an artificial mixture. You know hydroxyprolene, prolene, glycine, phenylalanine, the list goes on. You mix them all together --- put them all together and then put them on as a mixture on the column and got 20 peaks just like Moore & Stein. And I could identify which was phenylalanine, which was tyrosine, which was lusein, which was isolusein by their appearance, their elution from the column.

T. A. Rosolowski, PhD:
0:17:50.2
How amazing.

Ralph B. Arlinghaus:
0:17:51.7
So there --- these 20 peaks that always eluded in the same position and the two amino acids I was in --- I was interested in --- Sorry I have this partial in my mouth. I had a tooth pulled. Waiting to have another one drilled up in there. But anyway, so two amino acids I was interested in based on the analysis from my advisor was glycine and hydroxyprolene. So I knew from my analyses from Moore & Stein, where each one of those amino acids should emerge. So I put the dipeptide hydrolysis where you fragment the --- you use hydrochloric acid, put it in a CO_2 110 degrees overnight, break the tube open, evaporate down the hydrochloric acid and then you have your amino acids as free amino acids and as --- as my advisor said, "Well, you get two amino acids." Well, that's when things changed. The --- His analysis said it was two amino acids, glycine and prolene. My analysis said it was glycine, hydroxyprolene and something that wasn't part of the 20 amino acids. In other words, a new peak. A new --- What appeared to be a new amino acid. So the title of my thesis was "A New Amino Acid of Collagen".

T. A. Rosolowski, PhD:
0:19:25.9
Wow. So that was a really significant discovery.

Ralph B. Arlinghaus:
0:19:30.5
Yeah for a --- for a guy that just got off the turnip truck, yeah.

T. A. Rosolowski, PhD:
0:19:37.2

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Yeah. I mean I'm seeing too you know just that very story because you were stressing last time you know how you always had like a --- you know, a good intuition about where to find interesting results and also a real independence. You know doing your own research, putting that together and that shows there --- right there in that story.

Ralph B. Arlinghaus:
0:19:54.5
You see this --- this guy that was my mentor was behind times. Well he didn't know it. Then I knew it. After I went to Moore & Stein, ran the column and figured out that his two amino acids was really three amino acids, one of which didn't match with any of the peaks of Moore & Stein. So I knew I had something new. At least I believed that. He didn't believe me. He made me run it many times and I got the same results.

T. A. Rosolowski, PhD:
0:20:24.3
Did he --- He eventually did believe you?

Ralph B. Arlinghaus:
0:20:26.2
He finally had to believe me.

T. A. Rosolowski, PhD:
0:20:26.5
He finally had to believe you. Yeah.

Ralph B. Arlinghaus:
0:20:29.3
And then I crystallized this new amino acid.

T. A. Rosolowski, PhD:
0:22:33.4
And I'm sorry, what was the name of the new amino acid?

Ralph B. Arlinghaus:
0:20:35.8
Well what's in collagen is 4-hydroxyprolene. As I found out and that's the title of my thesis, "3-hydroxyprolene – A New Amino Acid of Collagen." So I crystallized that peak and going around to the chemistry department which I said I was --- those people knew me because I was an item. I --- I got --- I got the highest grades and I was just kind of from the moon, I guess. I don't know. Something --- Somebody --- Some young man that was very unusual. So I got a lot

of cooperation and I got in contact with some of the people that did physical chemical studies, crystallized this purified amino acid and between that and this physical chemistry stuff, I said it's 3-hydroxyprolene. And then we --- we made 3-hydroxyprolene in the chemistry lab and compared what eluded from the --- the so-called tripeptide that was in collagen. Compared it on the Moore & Stein column and the chemically made 3-hydroxyprolene co-eluded --- co-emerged with the --- the --- the unknown 3-hydroxyprolene that eluded from the column.

T. A. Rosolowski, PhD:
0:22:08.8
Hmm.. Now your next move was to --- to get some …

Ralph B. Arlinghaus:
0:22:11.3
So that --- So I got out in two years.

T. A. Rosolowski, PhD:
0:22:13.6
You got out in two years?

Ralph B. Arlinghaus:
0:22:14.1
Because --- I have to say it. I was the most advanced person in that department and they knew it and then I knew it.

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Chapter 09
Fellowships and More Creative Research
A: Professional Path;

Story Codes
A: Influences from People and Life Experiences;
A: The Researcher;
C: Evolution of Career;
C: Portraits;
A: Character, Values, Beliefs, Talents;
C: Discovery, Creativity and Innovation;
C: Professional Practice;
A: Definitions, Explanations, Translations;
D: Understanding Cancer, the History of Science, Cancer Research;
C: The Professional at Work;

T. A. Rosolowski, PhD:
0:22:25.4
So what was your next move?

Ralph B. Arlinghaus:
0:22:27.2
Well, with the help of somebody who wanted me in his lab as a Post Doc after my Ph.D. I can't remember his name and I should because he helped me a lot. I don't know why he took an interest in me. So he got me uh connected with several very competent high-level researchers and I wrote letters, sent them my CV, sent them a brief copy of my thesis so I could argue, you know, here I did something that was unique and real. And so that --- so there was a --- you know, again growing up in northern Kentucky there was a very well-known biological chemist named Richard Schweet. He had moved from northern California a couple years earlier, I didn't know that, but he was looking to hire postdoctoral fellows.

T. A. Rosolowski, PhD:
0:23:34.2
And you said Richard Schweet?

Ralph B. Arlinghaus:

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0:23:35.6
Schweet. S-c-h-w-e-e-t. Schweet.

T. A. Rosolowski, PhD: 0:23:35.7
Gotcha

Ralph B. Arlinghaus:
0:23:40.3
And Schweet --- I interviewed with Dick Schweet in Lexington. I was in Newport, Cincinnati. Lexington is about 80 miles. I made that trip down there. I got married in 1957, married Barbara, my wife and so she agreed. She said let --- let's go to Lexington. So anyway we had two children while I was in graduate school so we --- Barbara and the two kids and I, we moved to Lexington in 1961 of September or October. I don't remember. And then I worked in Schweet's lab for four years. Got a Fellowship from the America --- National Cancer Institute to support my salary for two years while I was Post Doctoral Trainee for Dick Schweet and then got a Fellowship from the American Cancer Society. Again, these are competitive awards that you had to write up a project and so I got --- I got these two awards that paid my salary. So Schweet didn't have to pay me, so he was very happy with me. He could have labor that --- researcher that didn't take any of his money.

T. A. Rosolowski, PhD:
0:24:57.5
So what was the project that --- what were the projects you were working on that got you NCI money?

Ralph B. Arlinghaus:
0:25:05.7
The --- The --- The money I got at Schweet's lab that I got a Fellowship was --- Dick Schweet was a guy that worked for a fellow named Henry Borsick and Henry Borsick was a guy at Cal-Tech that studied hemoglobin synthesis in red cells. As you may or may not know, your red cells and my red cells when you take them out or rabbits or mice or whatever the red cells produced predominantly one protein. That's hemoglobin. So Dick Schweet was studying how hemoglobin was made not in whole cells, not in rabbit reticulocytes but in what he called "cell free systems" that made protein on ribosome. And eh --- he was trying to study the mechanism of peptide bond formation on ribosomes which nobody at the time knew but which I figured out. It was believed at the time, remember protein-like hemoglobins got two, an alpha chain and a beta chain. The two alpha chains and two beta chains come together to form hemoglobin and hemoglobin in your red blood cells exchanges oxygen. When you breathe in, hemoglobin binds oxygen and releases CO_2.

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T. A. Rosolowski, PhD:
0:26:45.4
As I recall, it's a very sort of convoluted --- that the chains are very convoluted to create that little pocket in the center that binds the oxygen.

Ralph B. Arlinghaus:
0:26:56.3
Oxygen or CO_2. So --- So he --- So Dick Schweet was interested because that --- at that time it was thought that --- See ribosomes relatively speaking are big structures and protein chains are small things being produced on this big structure so it was widely believed at that time, we're talking --- when did I publish that paper? 1964. In 1962 it was widely believed that the ribosome, which bound messenger RNA, assembled the amino acids along the ribosome in long stretches which are --- then the amino acids were linked together to form large segments of in this case the globin chain. And finally the complete 120 amino acids of globin were made on the ribosome and released. That's what --- That's what the current dogma believed with very little evidence. So what I found is that it was really quite different from that. It was --- Now I have to explain. Amino acids bind to ribosomes not as amino acids but as aminoacyl-tRNA. You've heard of transfer RNAs?

T. A. Rosolowski, PhD:
0:28:23.2
Mmmhhmm.

Ralph B. Arlinghaus:
0:28:24.3
Transfer RNAs transfer the amino acid from the milieu to the ribosome where they bind the messenger RNA and so it turns out what we found with the help of a guy named Joe Schafter and with the help of Dick Schweet, he played some role in this, that there's essentially a three step model. The ribosome bound two aminoacyl-tRNAs, amino acid 1 and amino acid 2. They got linked. Amino acid 2 linked to amino acid 1 and now it was part of the zone transfer RNA 2. Then transfer RNA 2 moved to a site to allow another transfer RNA to come in for the third amino acid.

T. A. Rosolowski, PhD:
0:29:18.2
So a very complicated process.

Ralph B. Arlinghaus:
0:29:19.3

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And then they link to form a trimer and then that --- that trimer has a --- has a transfer RNA, three amino acids on transfer RNA move to a site and then found another transfer RNA with a fourth amino acid which then linked to form a tetramer, four amino acids on the transfer RNA that was incoming. And then --- Then --- So there was a --- there was a binding step and a --- a step where the transfer RNA translocated to a --- what's called the acceptor site. This is in textbooks. And it came from the work I did in the Schweet's lab. So I worked out how peptide bonds are formed on ribosomes as a graduate --- as a Post Doctoral Fellow. So I became from, let's call it pretty well-known at The University of Cincinnati for new amino acids in collagen, definitely at the medical school, to somebody nationwide that was known for understanding how proteins were made on ribosomes by this two --- two step model. Bind to transfer RNAs, amino acid links to form a dimer peptide then a shift of the dimer peptide transfer RNA allowing the third transfer RNA to come. That was validated by others and I became famous. Famous in the world of biochemistry, you know, for a little while. Perhaps famous is too strong a word. What's the --- Well-known as a Post Doctoral Fellow. I gave a talk at Atlantic City after I submitted an abstract on this. I'll never forget. It was in this big auditorium in Atlantic City and that's where a lot of the what we call _____
0:31:15.0) meetings used to be held and I had to get --- stand up on the stage and give a talk. But I wasn't --- I wasn't afraid and I wasn't even nervous. I was confident because I knew what no one else in that room knew. How these proteins were made on ribosomes and I was going to tell them about it and I felt very confident.

T. A. Rosolowski, PhD:
0:31:40.1
Wow. What a great feeling.

Ralph B. Arlinghaus:
0:31:41.8
Well I wasn't nervous. I wasn't shy although I was a very quiet young man growing up and didn't blow my own horn so to speak. So I --- I had a little bit of fame. Let's call it a little bit of fame. And uh . . .

T. A. Rosolowski, PhD:
0:32:02.7
That's great. A very gratifying feeling to have an impact on a field like that and really make a contribution.

Ralph B. Arlinghaus:
0:32:07.0
It was. And I realized that --- like I realized when I got the 95s on an exam that everybody else or most everybody else flunked, I knew that I was I don't know what's the word? I had ability. I

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had knowledge. I had creativity. I knew that. And that showed up again in the mechanism of peptide bond formation on ribosomes. That was the title of my paper published in Poseidon's National Academy of Science with Dick Schweet and Joe Schafer.

T. A. Rosolowski, PhD:
0:32:40.2
Where do you think that creativity comes from? You know like …

Ralph B. Arlinghaus:
0:32:46.7
That's a very good question. I don't know if I can give you a good answer except I was always at the forefront of the literature in the area that I was working on. So I was very knowledgeable about the latest techniques and I had some luck. Sometimes it's luck when you make a discovery. So --- But I was simple minded in many ways. I --- I did things in a straightforward manner that gave me surprises, but part of the luck and those surprises I believed them and it allowed me to take it further and understand things that no one else could understand because they didn't use the methods that I used.

T. A. Rosolowski, PhD:
0:33:49.2
Well I was struck that there have been a few times in our conversation, you know, this time and our last session too where you said this was the dogma, you know. and it seemed like you went in and you weren't blinded by the dogma. You looked for something else.

Ralph B. Arlinghaus:
0:34:01.1
I wasn't. Not that I didn't believe it but I was always open minded. I had a guy that taught me biochemistry in the College of Pharmacy. His name was Gill Schmidt and he taught me that. To always be aware of things may be a little different than you learn in the textbook and he was right. And so I took advantage of that and was lucky enough to make discoveries that I was able to publish and so …

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Chapter 10
A Critical Point in a Career: Crisis and Key Decisions
A: Personal Background;

Story Codes
A: Character, Values, Beliefs, Talents;
A: Personal Background;
A: Professional Path;
A: Inspirations to Practice Science/Medicine;
D: On Research and Researchers;
A: Obstacles, Challenges;
A: Contributions;
A: Activities Outside Institution;
A: Career and Accomplishments;

T. A. Rosolowski, PhD:
0:34:41.3
Yeah. So what happened next? You had the research fellowships and then …

Ralph B. Arlinghaus:
0:34:45.8
Well anyway, I left. [I was] at Schweet's lab and I started looking for a job, because now I was -- and I had offers to go to several different medical schools as an assistant prof, as assistant professor. But again my shyness or my, what to call it, maybe insecurity. I don't know. I still had some of that coming from a small town, small school, not a very educated environment. So I didn't know if I could compete, even though I made this marvelous discovery about how peptide bonds were formed on ribosomes. I was still a little bit unsure of myself. So I happened to go to a Gordon conference. I don't know if you know what those are. Dick Schweet sent me to talk about this work on how peptide bonds are formed, and I'm thinking about this. I'm thinking about what part of the story I want to tell you about that. My mechanism of how peptide bonds were formed on ribosomes was so new that when I presented this story, there were other young post docs in that meeting one of which was a very aggressive. I would call him mean. But anyway, he took me to task to grill me thinking that I made all this stuff up, although he never said that. And so I dealt with him and I met a guy at Gordon conference who was Director of Research at Plum Island Animal Disease Laboratory and I didn't have to write grants to do research there. So I made a mistake in my career. Instead of following up my discovery in Dick

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Schweet's lab on how peptide bonds were formed on ribosomes --I should have had the confidence to go to The University of Florida or The University of Indiana, which I could have gone to as assistant professor tenure track. I took a safe route and I went to this animal disease laboratory at Plum Island to work on foot and mouth disease virus. Completely changed. Completely changed, and helped those people do modern molecular biology at Plum Island. That was like a --- What's that? What do we say? Big fish in a little pond. Whereas at Schweet's lab I was a fish in a very, very big pond some of which didn't believe what I did and it took several years of people publishing my work to find out what I did was correct, and that felt very good when other people would list the Arlinghaus paper as being correct. This is how peptide bonds --- how proteins are made on ribosomes.

T. A. Rosolowski, PhD:
0:38:08.1
That must have been a very complicated time. I mean have the feeling as though you had this strength and confidence in your laboratory creativity and your abilities, but then there was this other piece. How do I work in the academic world? How do I negotiate that?

Ralph B. Arlinghaus:
0:38:23.8
Well see, in the academic world, people are always doubting new discoveries, and there I was making a new discovery, this postdoc from Schweet's lab. And, you know, I got plenty of opportunities to go follow that up. But after getting beat up at this Gordon conference by this postoc who --I don't even remember his name and whatever-- but eventually he found out he was way off base . So I, you know, that's the way science is. If you make a ver --- if you're really ahead of your field, you're going to get criticized, and the doubting Thomases will come in and create doubts about your work, and that's what happens. It still happens. It happens all the time if you're that far ahead.

T. A. Rosolowski, PhD:
0:39:18.6
What did your mentors say at the time? I mean did they --- were they concerned that you were making this decision?

Ralph B. Arlinghaus:
0:39:23.9
No. Because I had another postdoc in the lab that I reproduced my results.

T. A. Rosolowski, PhD:
0:39:28.5

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No, no. I don't mean did they not believe. I mean when they saw you making a decision to go to Plum Island as opposed to taking an academic position, did any of them say, Hey wait a minute. I'm worried that maybe you're making the wrong decision?

Ralph B. Arlinghaus:
0:39:39.9
Well something else happened in my life at that time. My third child was delivered in February of 1966 and my wife Barbara developed chronic myeloid leukemia. She delivered him having chronic myeloid leukemia. We didn't know that, but her --- but I was the happiest guy in the world because I had two girls and had a baby boy. Barbara and I were happy. But the next morning I found out she had chronic myeloid leukemia, a lethal disease. So then that's another reason I didn't want to gamble and go to some tenure track position. So I decided to take the safe route, take a government job in a government laboratory to work on foot and mouth disease virus. In retrospect, it was a mistake but it was the safe route.

T. A. Rosolowski, PhD:
0:40:30.5
Yeah at the time.

Ralph B. Arlinghaus:
0:40:31.3
And other people --- other professors at The University of Kentucky they understood that because it was --- it was a disaster for me and for my wife, who lived 30 months and died.

T. A. Rosolowski, PhD:
0:40:48.3
Oh, my gosh, wow. And you talked last time about how that really transformed your career at that point.

Ralph B. Arlinghaus:
0:40:52.5
It did. It did. Yeah. So anyway I did some --- published some nice papers at Plum Island and then Barbara died of CML and I --- I think I told you I decided I was going to work on chronic myeloid leukemia.

T. A. Rosolowski, PhD:
0:41:15.0
And when did she die?

Ralph B. Arlinghaus:

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0:41:16.3
She died in 1967 of October. I had three children, single.

T. A. Rosolowski, PhD:
0:41:24.9
Very hard. Very, very hard.

Ralph B. Arlinghaus:
0:41:26.5
Working two jobs and wrote a science paper while I was at Plum Island on work I was doing on foot and mouth disease virus. So it was so important that I was able to publish in Science. So I always did things that were unique, you know? So in any event I think that brings us back to …

T. A. Rosolowski, PhD:
0:41:54.0
Yeah, kind of back to the MD Anderson part.

Ralph B. Arlinghaus:
0:41:55.3
I went to MD Anderson and worked on _____ 0:41:57.6) leukemia virus and made some pioneering discoveries there. So what I'd like to say to you is, every place that I've worked I made unique, reproducible, exciting, new findings and that led me to where I am. I'm still doing it.

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Chapter 11
Research Projects: Working on an HIV Vaccine; Lipocalin 24p3; How CML Causes Uncontrolled Growth of Blood Cells
A: The Researcher;

Story Codes
A: The Researcher;
C: Evolution of Career;
A: Character, Values, Beliefs, Talents;
C: Discovery, Creativity and Innovation;
C: Professional Practice;
B: MD Anderson Impact;
A: Definitions, Explanations, Translations;
D: Understanding Cancer, the History of Science, Cancer Research;
C: The Professional at Work;

T. A. Rosolowski, PhD:
0:42:18.5
Now last time you talked about going to Johnson & Johnson and then your return as Department Chair to MD Anderson in 19 --- in 1986 and you talked some about the work that you did but we --- we didn't really get caught up with your --- your more current research. So maybe you'd like to tell me a bit about that.

Ralph B. Arlinghaus:
0:42:38.9
Yeah.

T. A. Rosolowski, PhD:
0:42:40.8
We talked about the ABL kinases. We talked about your work on vaccines at the --- at Johnson & Johnson.

Ralph B. Arlinghaus:
0:42:46.4

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See at Johnson & Johnson I was asked to work on HIV.

T. A. Rosolowski, PhD:
0:42:52.6
Oh, okay. You hadn't mentioned that part. Yeah.

Ralph B. Arlinghaus:
0:42:56.4
So I start working on vaccine strategies for HIV and it became clear at the time that antibody mediated vaccines for HIV were not protective. Still the case. There is no effective vaccine for HIV. I proposed that to make an effective vaccine that you had to make fragments of HIV proteins and induce killer T-cells. I became a self-made immunologist, if you will, while I was out there in California. I kep --- always kept learning and so my method, which I still believe in that method --and nobody's taken me up on it, although I do have a patent application issued on that strategy. Basically the strategy is --- is induce killer T-cells to kill the infected cells, because the antibody mediated inactivation of HIV wasn't working. So I wanted --- My patent talks about an antibody-negative approach to an HIV vaccine and that's never really --- never been disproved but other people have taken up that mantra, but there isn't an HIV vaccine that's killer T-cell only. And what's the reason for that? At the time --- this is going to get pretty deep for you. At the time, we were using short fragments of proteins to induce killer T-cells in mice and rabbits. That approach was faulty, because if you want to be --- have a protective approach, either antibody binding to the proteins or killer T-cells, lysine HIV infected cells or flu infected cells. You have to generate a response that sees many parts of the proteins in question and not just short peptides, which only activate the immune system with one or two sites on a peptide. So that was the faulty scenario. That was --- That was a false lead for me. So I --- I got a grant to study this from NIH and I didn't get very far for reasons I just told you. So --- But remember when I came back to MD Anderson, I came back working on HIV and chronic myeloid leukemia and I decided I couldn't be in both camps. So I turned over my HIV work to my postdoc. His name is Jacob Sastry [phonetic, ?Jagannadha K. Sastry, PhD,? 0:46:33.0]. He's a full professor in another department. He took and ran with that and is studying various aspects of HIV immunology and I got out of the HIV business to focus on chronic myeloid leukemia.

T. A. Rosolowski, PhD:
0:46:55.8
I was just noticing that in 2005 you made a discovery about lipocalin 24P3 which …

Ralph B. Arlinghaus:
0:47:05.7
24P3, yeah.

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T. A. Rosolowski, PhD:
0:47:06.8
Yeah which is using killer cells.

Ralph B. Arlinghaus:
0:47:10.1
We're still working on that. Still working on that. So we published an important paper on that so we could show in mouse models that if you could --- What we found is leukemia cells, CML cells induced lipocalin 2 formation and caused its secretion from the cell into the environment. We showed in this 2008 *Oncogene* paper that if you knocked out the lipocalin 2 gene and induced leukemia in mice, that didn't make lipocalin 2. The disease was --- was disabled. So what the steps of CML leukemia are is --- see what happens in people that get leu --- CML or most other leukemias, the bone marrow and spleen get replaced by leukemia cells. Our data, which we published using this knockout model, that if you removed, not inhibited or reduced, but removed lipocalin 2 from the environment that _____ 0:48:40.6) can no longer induce in its cells lipocalin 2 and could no longer secrete it. Then those leukemia cells did not cause leukemia in mice over many, many weeks. So wh --- why is that lipocalin 2 so important? Lipocalin 2 was first published by one of the people who advanced the field of lipocalin 2. His name is Michael Green. He sent me the CDNA to start working on lipocalin 2. He found out that lipocalin 2 kills normal T-cells and B-cells in mice and humans. So our data argued that chronic myeloid leukemia cells induce secretion of lipocalin 2 into the environment to kill normal spleen cells to make room in the spleen to allow the leukemia cells to overgrow the spleen, to kill bone marrow cells to allow the leukemia cells to overgrow. Because we showed the leukemia cells could not compete with normal cells to outgrow and overgrow cells in the bone marrow and spleen.

T. A. Rosolowski, PhD:
0:50:06.0
Yeah, that is a really different theory then. It pushes ce --- normal cells out of the way.

Ralph B. Arlinghaus:
0:50:12.0
In fact it's killing them with lipocalin 2.

T. A. Rosolowski, PhD:
0:50:15.6
Really interesting. Wow.

Ralph B. Arlinghaus:

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0:50:17.5
I'm very proud of that work.

T. A. Rosolowski, PhD:
0:50:18.3)
Yeah. Fascinating.

Ralph B. Arlinghaus:
0:50:19.8
And I'm still working on it.

T. A. Rosolowski, PhD:
0:50:21.4
So what are the --- what are the directions you're working on now with it?

Ralph B. Arlinghaus:
0:50:25.2
With lipocalin 2? Well, it took a while to come to the next part but it --- it's not published so it's --- this is hypothesis now. It appears that the host supplies lipocalin 2 just as the leukemia cells produce lipocalin 2, that both steps are necessary for stable leukemia. So it's not just the leukemia cells that are producing lipocalin 2, but it looks like its these normal bone marrow cells that go to the tumor sites --not published-- secrete lipocalin 2. So, for example, when leukemia has to spread to the spleen, something has to go into the spleen to prepare the way for the leukemia cells to overgrow it. And that turns out that there are normal cells that sort of partner with the leukemia cells to --- in this case, kill normal spleen cells to make space for the leukemia cells to grow. Leukemia cells are doing its part, but these other cells are also participating. So it's much more complicated than just the leukemia cells producing this killer molecule, because it looks like normal immune cells, which go to the site and also assist in that killing normal cells.

T. A. Rosolowski, PhD:
0:52:22.6
So the question of --- is how the leukemia cells are harnessing or co-opting the activity of those normal cells to partner --- make them come into partnership.

Ralph B. Arlinghaus:
0:52:31.9
Well I don't know the answer to that. I don't know the answer.

T. A. Rosolowski, PhD:
0:52:35.7

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Yeah. How interesting. How scary.

Ralph B. Arlinghaus:
0:52:39.1
It is. So you think of the normal host as being able to repress.

T. A. Rosolowski, PhD:
0:52:44.2
Absolutely.

Ralph B. Arlinghaus:
0:52:44.6
But in this case our data says at some point for either breast ca --- we've done it in breast cancer models mouse and CML mouse models --that the host also produces lipocalin 2, which plays a role in the progression of the disease. I don't like that result, but that's the way it is. So how they partner, how they communicate, the breast cancer cell or the leukemia cell, I don't know the answer to that. But you know when a tumor forms there's a --- generally speaking there's a tumor, what could we call it, a tumor environment and that environment is invaded by normal bone marrow cells some of which are meant to kill the tumor. Others like these cells I was talking about are supplying lipocalin 2 to help out in the breast cancer formation or the leukemia formation. That's the way it looks right now.

T. A. Rosolowski, PhD:
0:54:05.4
So very, very complicated process.

Ralph B. Arlinghaus:
0:54:08.3
Yes ma'am.

T. A. Rosolowski, PhD:
0:54:08.6
Very complicated process.

Ralph B. Arlinghaus:
0:54:10.9
I haven't published this so you --- this is hypothesis yet. The data that says the normal cells that move to the tumor mark environment and produce lipocalin 2 is true in my lab.

T. A. Rosolowski, PhD:

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0:54:24.7
Very, very interesting. So what other projects are you working on?

Ralph B. Arlinghaus:
0:54:31.2
Well I'm still working on chronic myeloid leukemia. In the mid-1990s I published a paper. I'm trying to --- Where was it published? I have to look it up. I can look it up for you now, but it was in 1995 and I was interested --- Remember chronic myeloid leukemia takes over the blood cell and causes the blood cell to grow uncontrol --- out of control? I wondered what that must mean, since again, I would call it unique thinking. That must mean BCR-ABL leukemia cells need help from the host and it turns out that leukemia cells have a protein. When you --- when you put the oncoprotein into leukemia cells they produce this protein called Janus kinase 2.

T. A. Rosolowski, PhD:
0:55:43.2
You talked about that last time.

Ralph B. Arlinghaus:
0:55:44.3
And Janus kinase 2 is a major factor in how the cells make more copies of themselves if they are blood cells. So Janus kinase 2 is a major contributor to making blood cells. So I started thinking in 1995 that maybe BCR-ABL cooperates with jak2 to cause the disease, and that guess turns out to be right, because I published several papers along the way. The latest one in 2013 --- 2011 says that Janus kinase 2 and BCR-ABL function together to [?dry?] the leukemic phenotype in CML cells. So if you will remember the Philadelphia chromosome? I told you about that? Philadelphia chromosome forms just by mistake in people who have CML. That means the end of chromosome 9 and the end of chromosome 22 --- I think I said this last time. I don't know if I did or not.

T. A. Rosolowski, PhD:
0:56:57.5
I don't know if you did.

Ralph B. Arlinghaus:
0:56:58.6
The end of 9 and 22 exchange. So now the end of 9 is on 22 and the end of 22 is on 9. That hybrid chromosome produces this hybrid protein called BCR-ABL. BCR is from chromosome 22 and ABL is from chromosome 9. Make a hybrid BCR-ABL protein. So that event is --- is

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critical for the deed but --- but then we've just found, again not published, that the BCR-ABL oncoprotein activates Janus kinase 2 to become --- to do what it does. Now remember Janus kinase 2, like all cellular enzymes, are usually silent, and they become activated from signals generally from outside the cell. But in the case of CML, BCR-ABL is activating Janus kinase 2 inside the leukemia cell constantly. Constantly driving jak2 to do things, to make more leukemia cells and have leukemia cells --- leukemia cells spread to other parts of the body. So some of this is published. The latest was 2013 in a leukemia journal. So …

T. A. Rosolowski, PhD:
0:58:32.7
Quite the puzzle to unravel.

Ralph B. Arlinghaus:
0:58:34.5
So what I've found now, and haven't published, is that BCR-ABL phosphorylates --- Does that term mean anything to you? --- phosphorylates jak2.

T. A. Rosolowski, PhD:
0:58:45.3
I recognize the term.

Ralph B. Arlinghaus:
0:58:46.4
It's a --- It's --- It modifies jak2. It's puts a phosphate on one of the tyrosines in jak2 that activates jak2. So jak2 is silent. Then BCR-ABL activates it, but it turns out that a normal ABL protein, again not published, --- the normal ABL protein activates jak2 in a normal situation. So jak2 in normal blood cells uses normal ABL to activate it. Again, under very highly controlled system, but when BCR-ABL becomes eternally activated in that cell, it's always phosphorylating and activating jak2. So jak2 is always on, always doing things. Whereas in you and I our jak2 is active, silent, active, silent. You need more blood cells? Jak2 is active. You don't need any more? Jak2 is shut off. So that control mechanism in CML doesn't exist. It's out of control. So we have preliminary data. What residue in jak2 is phosphorylated by either normal ABL kinase or the hybrid BCR-ABL kinase? So that's the next paper I want to publish --- that --- that site, that BCR-ABL or ABL phosphorylates. Then I want to work on how does that phosphorylation event activate jak2? How does it make jak2 from an inactive enzyme to an active enzyme? That will be a next step. So if I can get grant support, I know what I'll be working on two years from now. I just need to train people to do my experiments.

Chapter 12
Reflections on a Research Style; Collaborating with Clinical Trials

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A: The Researcher;

Story Codes
A: The Researcher;
B: MD Anderson Impact;
A: Overview;
A: Definitions, Explanations, Translations;
D: Understanding Cancer, the History of Science, Cancer Research;
C: The Professional at Work;
A: Character, Values, Beliefs, Talents;
C: Discovery, Creativity and Innovation;
C: Discovery and Success;
C: Collaborations;
B: Multi-disciplinary Approaches;
D: On Research and Researchers;
D: Understanding Cancer, the History of Science, Cancer Research;
D: Business of Research;

T. A. Rosolowski, PhD:
1:00:43.4
So I'm starting to get a sense of how, once you get an image of the basic territory of these mechanisms, you unravel a little bit, and then you start to foresee, okay well, here's where the next --- you know the next piece might form, if I can figure that out. Then the next piece, and the next piece. So I'm just trying to get a sense of it.

Ralph B. Arlinghaus:
1:01:05.2
No, that's a good explanation. So I'm uncovering --- it's like an onion. I'm peeling back an onion one layer at a time to make discoveries. What's underneath that layer?

T. A. Rosolowski, PhD:
1:01:17.7
What's underneath or inside or in between?

Ralph B. Arlinghaus:
1:01:20.1
Yeah.

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T. A. Rosolowski, PhD:
1:01:20.9
Yeah. Yeah. Really, really fascinating.

Ralph B. Arlinghaus:
1:01:22.3
So I'm not --- you know, I'm not a genius. I'm just a very logical investigator who --- who follows intuition and guesses about what to do next, like in 1995. How does chronic myeloid leukemia take over blood cells? Well it must somehow control a ve --- a factor that's involved in making more blood cells, a normal factor, and that's janus kinase 2. That was 1995. I'm pa --- I published my first jak2 paper in 1996 --- no I'm sorry, 2006. Then 2011, 2013. So, I mean but the critical site was back in 1995. It was a guess. It could have been wrong, right?

T. A. Rosolowski, PhD:
1:02:27.3
Sure.

Ralph B. Arlinghaus:
1:02:27.6
I could have been following a lost leader and wasting my time and postdocs' time, but I wasn't.

T. A. Rosolowski, PhD:
1:02:35.6
Well I'm also seeing how in --- and this is kind of-- My interest in the way I put together, or when someone is telling me about what they do, how I put it together. You know, like how --- because the question I'm always asking myself when I sit down with an individual like you is, how do you do what you do? It's quite simply how --- how do you make it work?

Ralph B. Arlinghaus:
1:02:59.0
First you have to have the drive to do it.

T. A. Rosolowski, PhD:
1:03:00.9
Sure. Absolutely.

Ralph B. Arlinghaus:
1:03:01.9

Because there's a lot of failure along the way. False leads, mistakes, people that don't work well with you or for you. You know, whenever you work with people, you know, we're imperfect, all of us. So sometimes things don't work as smoothly as they should. So anyway --- so --- but I'm driven, right? When you have a wife and have three children and she dies you want to do something about it. This is serious and became very serious for me in 1967.

T. A. Rosolowski, PhD:
1:03:40.3
And it seemed too that you, you know, harnessed your --- your abilities to take on the challenge of learning work in a new field or in a new area so that you would move in and use the tools that you could pick up from that to further your own goals.

Ralph B. Arlinghaus:
1:03:58.5
People used to ask me, "Arlinghaus, why did --- why did you work on _____ 1:04:04.0) leukemia virus and now you don't work on it anymore?" and "Why are you working on --- on CML now?" I just didn't share with them what I've shared with you, that I'm on a mission. I just --- I just didn't feel comfortable doing that. So I always had a --- I had a goal. I wasn't sure I was going to get there but I always had in mind what I need to do so.

T. A. Rosolowski, PhD:
1:04:36.2
And where do you feel you are with that mission now?

Ralph B. Arlinghaus:
1:04:40.3
Well, let me tell you. They're running a human trial on CML. A guy named Jorge Cortez. He's a leukemia physician. I had to interchange with him about some of my work and I had a suggestion with --- thanks to a colleague of mine in Vancouver _____ 1:05:04.8). She helped me a lot. So I suggested to Jorge, how ---- you might have a better way to treat CML patients, and that was based on another collaborator _____ 1:05:27.6), which we published together on jak2. I suggested to Dr. Cortez that there --- there's a paper --- there's a paper published not too long ago. I'm writing my grant, and I just had this reference out. Anyway, there's a paper published by a guy named Mahon. Here it is. It's in 2010 *Lancet*. Very high impact journal. "Discontinuation of Imatinib in Patients with Chronic Myeloid leukemia Who Have Maintained Complete Molecular Remission for at Least Two Years". It's a prospective [study] of a stopped treatment. So he's doing it, and some of his patients stayed off of imatinib for some time. Some relapsed. So I suggested to Cortez and Dr. Kantarjian --- not Kantarjian, Dr. Champlain-- that instead of just treating them with imatinib, treat them with a combination of imatinib and periodically with an inhibitor of jak2. They're going to do that trial on patients that have reached

this point. But what you don't know is, I've worked out a method. You know imatinib is so effective at removing disease. Let me explain it to you this way. A chronic myeloid leukemia patient, when he comes to the doctor, in their body they have 10^{12} leukemia cells. That's an estimate. 10^{12}. 10^{3} is a thousand --- 6 is a million, 9 is a billion, 12^{th} is a trillion. They have a trillion leukemia cells in their body. Now imatinib has done a great job in getting rid of most of them, but it doesn't get rid of all of them. When --- Wh --- Perrotti published in another paper, the paper by Neviani in 2013, I'm co-author.[1] There's a reservoir in CML patients. A population of cells that are resistant to this imatinib drug. In other words they're not killed like the normal CML cells. So this reservoir of resistant cells is always there. What Perrotti found with my help is that reservoir contains a high level of jak2 kinase and a very low level of BCR-ABL kinase. So the thing that's driving that reservoir cell is jak2. So as I said to Dr. Cortez, let's change this strategy and instead of just treating with imatinib, treat periodically with jak2 inhibitor because one of the problems with jak2 inhibitors at this state --- current date --- is because jak2 plays such a critical role in normal blood cell production that it can be toxic.

T. A. Rosolowski, PhD:
1:09:15.3
I was going to ask you why periodically with jak2?

Ralph B. Arlinghaus:
1:09:18.1
Periodic to relieve the toxicity. So they're doing that. Cortez is doing that on --- so I have to tell you now these patients that have complete remission I used --- I developed an assay to help a person like Cortez determine whether a patient is in complete remission. Because remember in the old days it used to be when you dropped a log of leukemia cells that was considered remission, but you had eleven logs of leukemia cells still there. Didn't know it at the time.

T. A. Rosolowski, PhD:
1:09:57.0
Now I don't know what a log is.

Ralph B. Arlinghaus:
1:09:58.9
Well it's a mathematical term.

---

[1] Oaks JJ, Santhanam R, Walker CJ, Roof S, Harb JG, Ferenchak G, Eisfeld AK, Van Brocklyn JR, Briesewitz R, Saddoughi SA, Nagata K, Bittman R, Caligiuri MA, Abdel-Wahab O, Levine R, Arlinghaus RB, Quintas-Cardama A, Goldman JM, Apperley J, Reid A, Milojkovic D, Ziolo MT, Marcucci G, Ogretmen B, Neviani P, Perrotti D. Antagonistic activities of the immunomodulator and PP2A-activating drug FTY720(Fingolimod, Gilenya) in Jak2-driven hematologic malignancies. Blood 122(11):1923-34, 9/2013. e-Pub 8/2013. PMCID: PMC3772499.

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T. A. Rosolowski, PhD:
1:10:00.0
Okay.

Ralph B. Arlinghaus:
1:10:01.6
So --- So --- It's a way to count cells. You could count them by one to a million or you could do one times 10^6. So you take ten --- ten multiply it times itself six times that --- that becomes a million. So it's an abbreviate way. So that's six logs. So in people that have 12 logs, they have 10 multiplied by itself 12 times. That's the number of leukemia cells. That's a tremendous number. So I developed this assay to monitor the number of leukemia cells and I could get down to a reduction of five logs and they use such a test to monitor CML patients that are being treated with imatinib. So many of the ones that Cortez --- many of the ones --- some of the ones that Cortez has that have reduced in leukemia cells, here's numbers you can understand, a trillion-fold. So they have one trillionth the number of leukemia cells, but they still have a lot of leukemia cells. They still have 10^9.

T. A. Rosolowski, PhD:
1:11:23.4
The numbers are staggering. I mean you really have to get your head around a different scale.

Ralph B. Arlinghaus:
1:11:27.6
When --- When I get cancer, I'm not going to have just a few cancer cells. I'm going to have millions and now I have to find a way to heal them and not our normal cells. Well imatinib is pretty good at that. It's not chemotherapy. It's targeted therapy. So now what I want to do is treat these people which have virtually undetectable by my assay …

T. A. Rosolowski, PhD:
1:11:54.5
Shall I pause the recording while you answer your phone?

Ralph B. Arlinghaus:
1:11:57.3
Yeah go ahead. I don't know who this would be.

T. A. Rosolowski, PhD:
1:11:57.7

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Okay, I'm pausing the recorder at 2:23.

[The recorder is paused.]

T. A. Rosolowski, PhD:
00:11.0
We are back on record here, at 2:26, after just a quick break.

Ralph B. Arlinghaus, PhD:
00:16.2
So, where did I stop …

T. A. Rosolowski, PhD:
00:18.1
So, well, you were talking about doing the assessments or the creating the assay to determine the levels of this reservoir of ….

Ralph B. Arlinghaus, PhD
00:25.7
Yes, ….

T. A. Rosolowski, PhD:
00:26.0
… of cells that ….

Ralph B. Arlinghaus
00:26.9
… so, I hope he's going to start sending me patients' cells …

T. A. Rosolowski, PhD:
00:28.7
… right.

Ralph B. Arlinghaus, PhD
00:29.9

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… so that I can measure that reservoir as it's periodically treated. Now, whether they'll do that or have someone else do it, it doesn't matter to me. What matters if the patients can reach a point they don't have to pay a hundred dollars a day for their medication.

T. A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD
00:46.7
But, they've got a life ahead of them because of that hundred dollars a day. So… And, then, there's a second lady that I work with. The first one was this guy, Neviani, in --- in Ohio, he's now in ____ Sound 1:01. This lady helped me a lot.

T. A. Rosolowski, PhD:
01:09.5
This is Minh Chen?

Ralph B. Arlinghaus, PhD
01:11.8
No, it's the last author.

T. A. Rosolowski, PhD:
01:13.0
The last author…

Ralph B. Arlinghaus, PhD
01:13.5
Xiaoyan Jian.

T. A. Rosolowski, PhD:
01:14.5
Xiaoyan Jian

Ralph B. Arlinghaus, PhD
01:15.5
Pronounced "Jong."

T. A. Rosolowski, PhD:
Yeah.

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Ralph B. Arlinghaus, PhD
01:17.1
Anyway, I'm a co-author on that paper.

T. A. Rosolowski, PhD:
01:24.0
"Targeting Primitive Chronic Myeloid Leukemia Cells by Effective Inhibition of the New AHI …. AHI-1-BCR-ABL-JAK2 Complex."

Ralph B. Arlinghaus, PhD
01:35.1
That's right.

T. A. Rosolowski, PhD:
01:35.6
Yeah. And published in 2013.

Ralph B. Arlinghaus, PhD
01:39.1
Right.

T. A. Rosolowski, PhD:
01:39.5
Yeah, okay. Just for the record, I mean for the record.

Ralph B. Arlinghaus, PhD
01:41.2
So, anyway, what she's discovered in here is that when you combine JAK-2 inhibitors with imatinib, it makes JAK-2 more effective. She doesn't know why that is. I know why that is. I know why that is. I'm going to publish a paper on it.

T. A. Rosolowski, PhD:
How interesting. Okay.

Ralph B. Arlinghaus, PhD
02:06.1
That's because imatinib inhibits BCR-ABL which inhibits the production of activated JAK-2. And the JAK-2 inhibitor inhibits the activated JAK-2. So we have two --- two things operating on JAK-2. One preventing its imatinib, and the other inhibiting once --- once it gets formed. So, she doesn't know why that allows one to use a lower dose of JAK-2 inhibitor, which is very

important because JAK-2 inhibitor, will of --- inhibit normal blood cell formation, which would be toxic so you want to get the dose …

T. A. Rosolowski, PhD:
02:51:1
Exactly.

Ralph B. Arlinghaus, PhD
02:51.7
… as low as you can.

T. A. Rosolowski, PhD:
02:52.7
Yep. Interesting.

Ralph B. Arlinghaus, PhD
02:53.0
And I know why that is so I hope to publish a paper on that. But …

T. A. Rosolowski, PhD:
02:58.4
Any other research projects that you want to report on right now?

Ralph B. Arlinghaus, PhD
03:06:4
I'm still working on lipocalin-2, as I mentioned, and the --- the host role in that --- working on JAK-2 and CML. Working on what ABL or BCR-ABL does to activate JAK-2 and why phosphorylation of that one site activates JAK-2. So, those are kind of some of the things I want to do. And I hope to be able to help these physicians who are doing trials. Now, there are two trials that will be affected by my work. The one based on this guy's study, Mayhon [phonetic], where they're going to combine JAK-2 inhibitor periodically …

T. A. Rosolowski, PhD:
Right.

Ralph B. Arlinghaus, PhD
03:50.8
… with imatinib. And the other one I haven't told you about is based on this lady's work ….

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T. A. Rosolowski, PhD:
03:55:5
Okay.

Ralph B. Arlinghaus, PhD
03:57:1
… if you combine JAK-2 inhibitor with imatinib, you're going to ….

T. A. Rosolowski, PhD:
04:01.1
Dr. Jian's work.

Ralph B. Arlinghaus, PhD
04:02:1
… make --- make JAK-2 more potent or more effective at lower dose and that will be very useful.

T. A. Rosolowski, PhD:
04:10:1
So, it's taken a significant amount of time for your discoveries to kind of reach the clinical ….

Ralph B. Arlinghaus, PhD
04:16.8
That's right.

T. A. Rosolowski, PhD:
04:17:2
… clinical effectiveness.

Ralph B. Arlinghaus, PhD
04:18.3
And when you think of 1967, nobody knew any of this.

T. A. Rosolowski, PhD:
04:20.7
That's right. That's right. It's amazing.

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Ralph B. Arlinghaus, PhD
04:22.:3
So I had --- with others, break ground and make discoveries. But there's a whole group of people who've contributed. Like … all this information about JAK-2, I --- I had nothing to do within the normal situation, how it functions.

T. A. Rosolowski, PhD:
04:39:2
So, it's just creating this foundation. Because you --- I mean, I've talked to a number of people and --- and it's been a funny process for me, because I went to college in 1973 and, of course, I had all the info about DNA, and I had --- was dating a guy who was in biochem and, I had no idea this was all new. You know, that this was kind of groundbreaking research and this was formation of an entirely new field. I mean, you were there at the forefront of the --- the creation of an entirely new field of study.

Ralph B. Arlinghaus, PhD
05:07:9
That's right.

T. A. Rosolowski, PhD:
05:08:9
And now, we're seeing --- now we're seeing results. Now.

Ralph B. Arlinghaus, PhD
05:12:9
So --- so, I'm still following the discoveries that I made and …

T. A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD
05:19:6
… taking them to the next step.

T. A. Rosolowski, PhD:
05:21:6
Step by step.

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Ralph B. Arlinghaus, PhD
05:22.4
I don't know how long I'll be able to do that, because I'm writing this grant as ---- I've got all this paperwork, spread all over … I'm writing a grant trying to get funded when my grant in 2015 –July-- runs out. Am I going to be able to accomplish that? I have no idea. Getting funded by the National Cancer Institute or any agency is extremely difficult.

T. A. Rosolowski, PhD:
05:47:0
Yeah. I've --- a number of people have been talking about how the money situation is getting tighter and tighter.

Ralph B. Arlinghaus, PhD
05:51:1
That's right. Mainly because there are so many people trained. So now, the number of Ph.D.'s studying this area or any area has probably quadrupled. Because we are training more Ph.D.'s all the time and they're going out and working, at least some of them. So, we're training competitors.

T. A. Rosolowski, PhD:
06:10:3
Yeah. It's a catch-22, isn't it?

Ralph B. Arlinghaus, PhD
06:15:4
That's true. So…

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Chapter 13
A View of MD Anderson Presidents
B: Key MD Anderson Figures;

Story Codes
C: Portraits;
B: MD Anderson History;
B: MD Anderson Culture;
B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;
A: Personal Background;
B: Institutional Politics;
B: Controversy;
A: Character, Values, Beliefs, Talents;
C: The Professional at Work;
C: Leadership;
C: Giving Recognition;

T. A. Rosolowski, PhD:
06:19:2
Well, I wonder, if we're --- if you've kind of finished up talking your research, if you could talk a little bit about the institution that --- do you have anything more to add …

Ralph B. Arlinghaus, PhD
06:27:9
Yeah, I can …

T. A. Rosolowski, PhD:
06:28:2
… about the institution?

Ralph B. Arlinghaus, PhD
06:30:3
… I can. There's been four presidents, you know.

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T. A. Rosolowski, PhD:
06:32:0
Yeah, and …

Ralph B. Arlinghaus, PhD
06:32:4
Dr. Clark, Dr. LeMaistre [oral history interview], Dr. Mendelsohn [oral history interview], and now Dr. DePinho [oral history interview].

T. A. Rosolowski, PhD:
06:37:9
And, huge growth of the institution. I mean, tell --- tell me about your observations about the leaders. What do you think their impact has been?

Ralph B. Arlinghaus, PhD
06:46:0
I was very impressed with Dr. Clark. He --- he hired me back in --- whenever that was --- 1969, yeah.

T. A. Rosolowski, PhD:
06:55:8
Tell me your impressions of him.

Ralph B. Arlinghaus, PhD
07:00:1
Hard-driving man, but was interested in the sciences. Was the clinic ---- you know, he was a surgeon. He was a surgeon. So, not only was he a surgeon, he was actually interested in what I was doing. I think I told you about Demakowski [phonetic] and that mess. Did I tell you about that?

T. A. Rosolowski, PhD:
07:18:6
A little bit, yeah.

Ralph B. Arlinghaus, PhD
07:19:0
How I had to …

T. A. Rosolowski, PhD:
07:19:5

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Yeah.

Ralph B. Arlinghaus, PhD
07:19:7
… fight my way to get approval back at that time as new faculty were coming in --had to get approval work on an area that I wanted to work on, and Dr. Demakowski [phonetic] was blocking them.

T. A. Rosolowski, PhD:
07:31:3
Right, yeah.

Ralph B. Arlinghaus, PhD
07:32:2
We had to convince him I wouldn't compete with him. I would add to what he was doing.

T. A. Rosolowski, PhD:
07:38:0
And Dr. Clark ….

Ralph B. Arlinghaus, PhD
07:39:2
Dr. Clark was …

T. A. Rosolowski, PhD:
07:39:5
… supported you.

Ralph B. Arlinghaus, PhD
07:40:9
… supported me a hundred percent.

T. A. Rosolowski, PhD:
07:42:5
Why --- what do you think --- I mean, I always struck that people describe how visionary he was. What do you think gave him that --- why do you think a surgeon, you know, who had that ability to say, yeah, this field, this field, this field, let's --- let's add them to the mix.

Ralph B. Arlinghaus, PhD
08:02:9

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I can't speak for him, but I --- I would set --- my guess is that he realized that surgery wasn't the only answer. We had to generate a lot of new knowledge, and he wanted to be part of that by forming this Cancer Institute in which faculty members like myself would come in to unravel some of the mysteries of what causes cancer. And I think he appreciated that very well. That's the reason he did what he did, was to form MD Anderson. So, he was a true visionary, in my opinion.

T. A. Rosolowski, PhD:
08:47:8
Tell me about your impressions of Dr. LeMaistre.

Ralph B. Arlinghaus, PhD
08:51:7
Dr. LeMaistre helped me a lot. He helped me. He was very sad that I left and went to California. He didn't tell me he was sad. I could read it on his face when I told him I was going to resign.

T. A. Rosolowski, PhD:
09:01:6
Yeah, you mentioned that meeting.

Ralph B. Arlinghaus, PhD
09:02:7
Yeah. And he was sad --- and he helped me come back. This is the part we need to water down, and Dr. Becker was not involved in my recruitment. He was the Vice President for research and he recruited all of the researchers. But, he didn't recruit me. Dr. LeMaistre did.

T. A. Rosolowski, PhD:
09:22:2
What do you think --- what --- what was the --- the connection you had with Dr. LeMaistre that made him support your work? What do you think that --- what did he see in you?

Ralph B. Arlinghaus, PhD
09:37:4
I can't give you an answer about that, but I used to attend these Monday morning meetings that all Department Chairs used to attend, and I used to speak up. I didn't speak up often but when I spoke up, it was --- it was meaningful. And one time, I spoke up and he followed --- wow --- he followed me out of the --- the big auditorium, he said, "Dr. Arlinghaus, thanks for your comment." Wow.

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T. A. Rosolowski, PhD:
10:08:4
So, he really appreciated your viewpoint …

Ralph B. Arlinghaus, PhD
10:12:6
He did.

T. A. Rosolowski, PhD:
10:12:7
… and your take.

Ralph B. Arlinghaus, PhD
10:13:1
And I didn't say much. I wasn't a …

T. A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD
10:14:3
… Department Chair. I was kind of third tier down. And a vice president, so …. People above the vice presidents --and then … I was small potatoes but I --- I only spoke when I had something to say. And ….

T. A. Rosolowski, PhD:
10:32:5
Amazing that he bothered …

Ralph B. Arlinghaus, PhD
10:34:2
Yeah.

T. A. Rosolowski, PhD:
10:34:5
… to thank you. Yeah.

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Ralph B. Arlinghaus, PhD
10:26:8
And when I left, he didn't like it …

T. A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD
10:38:6
… because of that. And he made sure I could get back in, and he knew (this is what you have --- can't put in the book) Becker blocked my growth.

T. A. Rosolowski, PhD:
10:48:2
Yeah. You know, those things happen at institutions

Ralph B. Arlinghaus, PhD
10:51:2
And that's the reason I left.

T. A. Rosolowski, PhD:
10:53:8
Those things really happen

Ralph B. Arlinghaus, PhD
10:54:0
And he wanted to make sure if I wanted to come back, I could get back in. Gave me a big start package. Becker had nothing to do with it. Becker was probably --- I couldn't be in Becker's office but I would say he was very angry that day when I was hired in his research division ….

T. A. Rosolowski, PhD:
11:15:3
Interesting.

Ralph B. Arlinghaus, PhD
11:15:6
… without his …

T. A. Rosolowski, PhD:
11:17:2

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Without his approval.

Ralph B. Arlinghaus, PhD
11:17:7
So in a way, I quietly – what's the word – overcame that block. I didn't go to LeMaistre and pound on the table: this guy, Becker, look at what he's doing to me. I just quietly said, look, I've found a job in California and I'm going to start up a company.

T. A. Rosolowski, PhD:
11:39:6
Right. Right, I've got to take an alternative route. It's not happening here.

Ralph B. Arlinghaus, PhD
11:43:9
I didn't --- I didn't burn any bridges.

T. A. Rosolowski, PhD:
Yep, yeah.

Ralph B. Arlinghaus, PhD
11:47:9
To this day --Becker was in my office right before you saw him.

T. A. Rosolowski, PhD:
11:49:9
Yeah, yeah. I saw him out in the hall actually.

Ralph B. Arlinghaus, PhD
11:50:7
He's always coming in to talk to me.

T. A. Rosolowski, PhD:
11:52:6
Yeah, yeah. Well, it means it paid off not to burn those bridges.

Ralph B. Arlinghaus, PhD
11:55:6
Well, I didn't --- I didn't --- there were times when I became Department Chair, I could have been negative towards him, an important time. But I chose not to do that. Or, in street fighting where I grew up, not to get even.

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T. A. Rosolowski, PhD:
12:14:9
Were you a street fighter as a kid? Did you have to take care of yourself?

Ralph B. Arlinghaus, PhD
12:24:0
I had to take care of it, but I was --- I --- I didn't like to fight. I was --- I usually broke up fights and got hurt because of it.

T. A. Rosolowski, PhD:
12:35:5
Interesting. Yeah, yeah.

Ralph B. Arlinghaus, PhD
12:40:5
Yeah. I was --- my mother's son.

T. A. Rosolowski, PhD:
12:45:1
What does that mean?

Ralph B. Arlinghaus, PhD
12:50:6
You'd have to know my mom.

T. A. Rosolowski, PhD:
12:51:3
Yeah.

Ralph B. Arlinghaus, PhD
12:53:2
You'd have to be flying at the speed of light now, because she's dead.

T. A. Rosolowski, PhD:
12:55:9
Yeah. Yeah, she sounds like she had a big influence on you with her support ….

Ralph B. Arlinghaus, PhD
13:00:0

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She did.

T. A. Rosolowski, PhD:
13:00:4
… of your education, and …

Ralph B. Arlinghaus, PhD
13:00:5
She did.

T. A. Rosolowski, PhD:
13:01:7
… yeah.

Ralph B. Arlinghaus, PhD
13:03:2
For a third grader.

T. A. Rosolowski, PhD:
13:04:0
Yeah. Her name?

Ralph B. Arlinghaus, PhD
13:05:9
Loretta. Loretta Francis.

T. A. Rosolowski, PhD:
13:09:9
And your dad's name?

Ralph B. Arlinghaus, PhD
13:15:1
Elmer Theodore, blind.

T. A. Rosolowski, PhD:
13:18:7
Yeah, that --- that really struck me when you said that. I mean, how amazing that he worked all those years, was an ind --- independent person, I assume.

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Ralph B. Arlinghaus, PhD
13:26:4
Yeah, he was head foreman …

T. A. Rosolowski, PhD:
13:28:0
Yeah. Wow.

Ralph B. Arlinghaus, PhD
13:19:3
… and he did everything by memory.

T. A. Rosolowski, PhD:
Wow.

Ralph B. Arlinghaus, PhD
13:31:2
So, I probably got my good memory from my father.

T. A. Rosolowski, PhD:
(laughter). Ah, there you go. Yeah

Ralph B. Arlinghaus, PhD
13:38:9
So I have to tell you. So, I told him I got my Ph.D. I graduated, my wife was with me, Barbara, who's now dead but… I said, well --- well, Dad, I got my Ph.D. degree, I'm --- I'm a Doctor of Philosophy. My father looked at me and said, "I have a question for you, Ralph. Can you write prescriptions?" I said, "No, I'm not an M.D." ….

T. A. Rosolowski, PhD:
Yeah.

Ralph B. Arlinghaus, PhD
14:03:3
… and he looked at me, he said, "What good is it?" (laughter)

T. A. Rosolowski, PhD:
14:05:7
Gee. Yeah.

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Ralph B. Arlinghaus, PhD
14:13:7
Some could say he's right but ….

T. A. Rosolowski, PhD:
14:15:3
Yeah.

Ralph B. Arlinghaus, PhD
14:15:8
… that's the way he felt.

T. A. Rosolowski, PhD:
14:17:2
Yeah. Well, it's funny. You know, my …

Ralph B. Arlinghaus, PhD
14:18:6
The practical side, he couldn't appreciate what I was going to do, right.

T. A. Rosolowski, PhD:
14:23:1
Right.

Ralph B. Arlinghaus, PhD
14:23:7
But he didn't know what I was going to do at that time …

T. A. Rosolowski, PhD:
14:25:6
Sure.

Ralph B. Arlinghaus, PhD
14:26:1
… because Barbara was still alive.

T. A. Rosolowski, PhD:

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14:27:5
Yeah. I think that's --- you know, there are stories from my family, too, because …

Ralph B. Arlinghaus, PhD
14:33:1
Sure.

T. A. Rosolowski, PhD:
14:33:3
… you know, my father's side of the family is immigrant family and for the generation that went on and got a lot of education, their parents and …

Ralph B. Arlinghaus, PhD
14:39:9
Sure.

T. A. Rosolowski, PhD:
14:41:2
… they didn't understand.

Ralph B. Arlinghaus, PhD
14:42:6
Yeah.

T. A. Rosolowski, PhD:
14:42:8
They couldn't appreciate what …

Ralph B. Arlinghaus, PhD
14:43:6
So, my mom had vision like that. She said – I think I told you – she said, get educated, all the education you can get and it will help you.

T. A. Rosolowski, PhD:
14:52:9
Yeah. And you did.

Ralph B. Arlinghaus, PhD
14:55:8

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I did.

T. A. Rosolowski, PhD:
14:56:3
Yes, you did.

Ralph B. Arlinghaus, PhD
14:57:8
I did.

T. A. Rosolowski, PhD:
14:58:9
Tell me about Dr. Mendelsohn.

Ralph B. Arlinghaus, PhD
15:01:9
Ah, another thing you can't put in the book.

T. A. Rosolowski, PhD:
15:05:6
Well, I will pause the recorder then.

[The recorder is paused.]

Ralph P. Arlinghaus
0:00:00.0
No, you can put that recorder on

Tacey Ann Rosolowski:
Okay.

Ralph P. Arlinghaus
0:00:00.2
I'm going to say nice things about him _____ 0:00:03.0 and Dr. Mendelsohn first of all was an excellent scientist. He developed a new drug to treat cancer patients which is a remarkable achievement. Many of us as researchers want to do that. And also none of us do that. He was able to do that. So he is an exceptional researcher and he added to the strength of this institution

and hired good people and I think I'll stop there. I think you can turn it off if you want and I can say the next part. I think I told you.

[The recorder is paused.]

Ralph P. Arlinghaus
0:00:00.0
Yeah, we can

T. A. Rosolowski, PhD:
0:00:04.0
Okay. Okay. So we're back after another quick pause, just a couple of minutes.

Ralph P. Arlinghaus
0:00:05.2
Hey, Dr. DePinho is, of all the four presidents, he is the most knowledgeable of the cancer research part of the business that we all do. And he has hired some really outstanding people in the short time he's been here. So I think the institution will grow under him. And I wish him well. You know, I don't --- I'm no longer department chair so I don't interact with him, and he was trained under a guy that learned their stuff from Rauscher at leukemia virus research. So Dr. DePinho has met me and brought this up as he has otherwise been here. So …

T. A. Rosolowski, PhD:
0:00:55.5
Right

Ralph P. Arlinghaus
0:00:57.1
So anyway. So that work is sitting in journals, but some people remember it. And his advisor that he trained under …

T. A. Rosolowski, PhD:
0:1:03.6
Yeah. Was part of that world…

Chapter 14
A Memorable Student and Advice to Students/Professionals

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A: View on Career and Accomplishments;

Story Codes
C: Portraits;
A: Personal Background;
A: Character, Values, Beliefs, Talents;
C: The Professional at Work;
C: Giving Recognition;
C: Mentoring;
C: Professional Practice;
C: The Professional at Work;
C: Collaborations;
A: Overview;
A: Definitions, Explanations, Translations;
A: Career and Accomplishments;

Ralph P. Arlinghaus, PhD:
0:01:09:3
I remember. So I think we would do well together if I was a department chair, but my time is over, which I don't like. But I had some good ideas about who're other good people to hire, but that parts gone. I've done my part and I wish MD Anderson well. It's a good institution. I've certainly thrived because of it for most of the years and I feel fortunate to be able to come here and do well and to be promoted up the ranks. I do I feel blessed and although my discoveries drove the process, because I wasn't a politician.

T. A. Rosolowski, PhD:
0:02:02.0
Right. Right

Ralph P. Arlinghaus, PhD:
0:02:04.9
My wife, both of them, said you don't speak enough about what you do. I said, "Well, I'll leave my work to speak for itself." And Barbara used to say, "That's a mistake." And Kathy says the same thing. Anyway, I did alright. I did alright. I'm very pleased --- pleased with the people I've trained. Pleased with the people that helped me as trainees and I had a graduate student that I maybe didn't mention to you. As my --- one of the first graduate students. He was Saudi Arabian. Did I talk about him? I've had probably 25 graduate students who've trained and got

their Master's or PhD's. Gazi Jamjune (phonetic, 0:02:55.0) was his name, a Saudi. He got his Master's at University of California and came to the graduate school here at Biomedical Sciences and had they --- they had these --- all the faculty had what are called tutorials to give a graduate student a chance to have a look at the lab they may want to get their work done, PhD work on. And Gazi got a Master's at University of California in Santa Barbara, from a wealthy Saudi, brilliant, brilliant, brilliant. I never learn from graduate students in the way I learned from him. He had the big picture. He had the small picture. Gazi Jamjune. He was quite a guy. He helped me a lot. And his --- and the performance of his research while he was in my lab. And, of all the other 25, there are a few I could mention, but not like him. He was brilliant. He was good with his hands. He was good with his brain.

T. A. Rosolowski, PhD:
0:04:29.2
What did you learn from him?

Ralph P. Arlinghaus, PhD:
0:04:41.4
Methods to make --- better methods. I used to marvel because he developed certain methods to examine things in my lab, and I watched and learned from him in that regard. That added to my knowledge about methods. You know, when I was a graduate student, they were using paper chromatography to analyze the composite of a peptide, and I went to the library. Gazi did that in modern way. So, for example, we used to --- we used to analyze --- I have to remember back. It now has been 15 years ago. I just lost the --- we used to analyze --- I don't know why I just lost it. But we used to analyze --- Ah --- And we used to fractionate proteins on what are --- these columns. I talked about the Moore & Stein column that was very long. We'd run buffer through that at 35 degrees --body temperature-- and collect fractions, maybe 100 fractions. Analyze each fraction. He used to run what are called 'analysis of proteins' on tube gels. So we'd put the mixture of the cell proteins on the top of a tube that long [gestures], using electrophoresis to drive the proteins through the tube and separate them by size. So we used to then push the tube out of the ---- the gel out of the tube and slice it with a razor blade and analyze each slice. He came to me and he said, "I looked this paper up." He did what I used to do. He looked this paper up and he found out that, instead of running tube gels --separating proteins within in the tube, run a slab gel and you could put your fraction on a --well, on a slab that had 10 --- potentially 10 tubes, 10 lanes. And you could develop that slab, because using radioactive at the time. Using sophisticated radioactive method. Again, he got that from the library. So my lab became --- so everybody in the lab learned those techniques from Gazi and they became more productive because they didn't have to cut 100 fractions --- a tube that is cut into 100 fractions and analyze each tube. We could do it on one slab gel. And you'd put a film over it and instantaneously develop the x-ray film and see the fractions...

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T. A. Rosolowski, PhD:
0:07:51.9
So amazing

Ralph P. Arlinghaus, PhD:
… on the film.

T. A. Rosolowski, PhD:
0:07:53.6
So amazing, amazing efficiency.

Ralph P. Arlinghaus, PhD:
0:07:55.0
So he taught me a lot. Plus he helped me decide on this --- I don't know if I told you or not. Anyway, so it turns out in the Rauscher leukemia virus they had this 8,000-nucleotide genome coding for essentially three proteins. And ribosome got onto the end of that messenger RNA and translated the first third called the gag protein –protein that encapsulated the viral genome and reverse transcriptase. Then the rest of it was not known how it got translated into protein, although the coding information was there. It was not known how the ribosomes got past that block, and I figured out that if wa --- because other people in yeast genetics were showing that there was special transfer RNAs that allowed the ribosome to bypass the stop codon. So, the gag gene has all the codes for the various amino acids, then the ribosome comes across this stop codon. Well in yeast genetics, there are transfer RNAs that would bind to that stop codon and put an amino acid there and allow the ribosome to continue translating into the pol. So you got a gag-pol protein, and that made me again in a very small world famous for a little while, right?

T. A. Rosolowski, PhD:
0:09:46.5
What did Gazi [phoneatic] add to that?

Ralph P. Arlinghaus, PhD:
0:09:48.2
Discussions, talking

T. A. Rosolowski, PhD:
0:09:51.0
So helped you.

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Ralph P. Arlinghaus, PhD:
0:09:52.6
He didn't provide the incentive, but he was one of the few people that could --- we could discuss things like that and he didn't say, "Well, I don't believe" or "I don't". Probably not giving him enough credit right now, but again it has been so long ago. But he was a confidant as a graduate student. It was unheard of.

T. A. Rosolowski, PhD:
0:10:16.3
Very, very unique

Ralph P. Arlinghaus, PhD:
0:10:18.5
For me it is still unheard of

T. A. Rosolowski, PhD:
0:10:19.9
Very unique. Wow. That sounds like he was creative in a similar way to you, so you make a good…

Ralph P. Arlinghaus, PhD:
0:10:21.6
Very creative
T. A. Rosolowski, PhD:
0:10:24.4
Good symbiotic unit there

Ralph P. Arlinghaus, PhD:
0:10:27.7
We were a good match. We were.

T. A. Rosolowski, PhD:
0:10:29.6
Yep.

Ralph P. Arlinghaus, PhD:
0:10:30.6
And I was fortunate to have him in my life.

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T. A. Rosolowski, PhD:
0:10:35.6
Is there anything else you would like to add, Dr. Arlinghaus? I don't have any more real questions to ask.

Ralph P. Arlinghaus, PhD:
0:10:41.1
I had a good career here. Could have done more, but I did the best and maybe even better than I thought, so I'm very pleased. I'm not unhappy with my career, although I missed some opportunities, not by any fault, it's just ….so there's so many mysteries when you attack a research problem and you're just not [reading] enough. You don't read enough. You don't see what the other pe --- other people in the field are doing. You might read it, a few of the papers, but you don't read enough and it's even worse now. Because of the number of papers coming out in chronic myeloid leukemia. So I get this thing I get every month. There's a computer program that looks at all the CML papers and I get --- I get to read them now, but that wasn't available two years ago or one year ago. So I can see other people who publish papers in journals I never heard of. That's what it takes to make progress. And the opportunities I missed because I don't know.

T. A. Rosolowski, PhD:
0:12:07.8
Right. Right. So what --- based on that, what advice do you have for people doing research now in your field?

Ralph P. Arlinghaus, PhD:
0:12:26.4
Work hard. Be honest. Only publish things you believe. Don't be false. You have to publish facts and findings so that they can use those facts and findings to build on. 'Cause you're going to use facts and findings from other people to build on. So, but I don't know how you would instill intuition. I don't know how you do that. Or mission-driven. If it a hobby, I don't know if it's good enough. You can't say that to a young assistant professor, because they're brilliant in a way that I'm not, and so I always tell them you've got to make happen. You've got to get bright people around you. You've got to educate bright people. You've got to listen to what they say because sometimes you may be wrong. So I, as I say, I'm blessed.

T. A. Rosolowski, PhD:
0:14:04.7

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So anything else you would like to add.

Ralph P. Arlinghaus, PhD:
0:14:08.1
Sorry it's over.

T. A. Rosolowski, PhD:
0:14:16.0
We've leave it there, Dr. Arlinghaus. Thank you. I'm turning off the recorder at 3 p.m.