5-7-2014

Wai-Kwan Alfred Yung, MD, Oral History Interview, May 7, 2014

Wai-Kwan Alfred Yung MD
The University of Texas MD Anderson Cancer Center

Tacey A. Rosolowski PhD
The University of Texas MD Anderson Cancer Center

Interview Session: 02
Interview Date: May 7, 2014

Chapter 00B
Interview Identifier

Tacey Ann Rosolowski, PhD
00:00.0
So --- I will --- Alright. Now we are at the official beginning of the interview.

Wai-Kwan Alfred Yung, MD
00:06:4
The official beginning. Okay.

Tacey Ann Rosolowski, PhD:
00:09:5
And we we're at about 12:38 when we started and now at we're about 12:42

Wai-Kwan Alfred Yung, MD
00:17:8
Alright.

Tacey Ann Rosolowski, PhD
00:18:0
And today I'm on the 7th Floor of the Faculty Center at M --- the main campus of MD Anderson in the Department of Neuro-Oncology, interviewing Alfred Young, Chair of the Department, as he has just been describing. So thank you for making time.

Wai-Kwan Alfred Yung, MD
00:34:5
You're welcome.

Tacey Ann Rosolowski, PhD
00:35.1
We were --- We were talking about how busy you are because you were in the midst of a search for a new chair.

Wai-Kwan Alfred Yung, MD
00:39.2
Well, I have nothing to do with the search.

Tacey Ann Rosolowski, PhD

00:41:2
Yeah.

Wai-Kwan Alfred Yung, MD
00:41.5
I'm --- I'm busy because of the many projects that we're doing.

Tacey Ann Rosolowski, PhD
00:50.5
Okay. Gotcha.

Wai-Kwan Alfred Yung, MD
00:51.9
And today's my, you know, day that I meet with my Lab people.

Tacey Ann Rosolowski, PhD
00:54:6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
00:56:3
But then we also, you know, working on a big Moon Shot proposal to try to get brain tumor into the Moon Shot world, you know.

Tacey Ann Rosolowski, PhD
01:07.7
01:25:5
Well, let me ask you what you would like to do now. We could continue talking about your administrative role as Chair, or would you like to talk about your research? We ha --- Because we really haven't done that in depth so far. Where --- What's kind of on your mind to explore today?

Wai-Kwan Alfred Yung, MD
01:28.4
Well, I can d --- I mean I can do anything, you know.

Tacey Ann Rosolowski, PhD:
01:30.9
Okay.

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Wai-Kwan Alfred Yung, MD
01:31.4
you --- you want to do whatever you want to follow the --- the trail that we've followed before.

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Chapter 06
Looking at Chromosomal Patterns in Brain Tumors; Chromosomal Heterogeneity, Chemo-Sensitivity, and EGFR
A: The Researcher;

Story Codes
A: The Researcher;
A: Overview;
A: Definitions, Explanations, Translations;
D: Understanding Cancer, the History of Science, Cancer Research;
B: MD Anderson History;
B: Multi-disciplinary Approaches;
C: Discovery and Success;
C: The Professional at Work;
D: Understanding Cancer, the History of Science, Cancer Research;
B: MD Anderson Impact;
B: Institutional Mission and Values;

Tacey Ann Rosolowski, PhD
01:37.1
Well why don't we talk about your research then? Because we --- we had talked a little bit last time about you coming to MD Anderson. You talked about your dreams for making Neuro-Oncology really a clinical piece of what MD Anderson could offer. And but we didn't talk about --- And you talked about how you set up your lab and then moved it to the main campus but we really didn't talk about the projects you were working on and the evolution of your own research. So I'd really like to --- to get that story.

Wai-Kwan Alfred Yung, MD
02:09.4
Well when --- When I was a fellow at --- at Memorial Sloan-Kettering I started on a project with --- with Dr. Joan Shapiro at that time at Memorial. We started a project looking at the question of heterogeneity.

Tacey Ann Rosolowski, PhD
02:34.4
Okay.

Wai-Kwan Alfred Yung, MD
02:36.1

Recognizing that, you know, brain tumor is not a, you know, homogeneous tumor

Tacey Ann Rosolowski, PhD
02:45.7
Hmm

Wai-Kwan Alfred Yung, MD
02:46.2
Like a liquid tumor like leukemia or lymphoma. You know, brain tumor is like other solid tumor, breast cancer, lung cancer, it is very heterogeneous.

Tacey Ann Rosolowski, PhD
02:58.1
Hmm

Wai-Kwan Alfred Yung, MD
02:58.5
with --- with multiple populations. So we started a project back then looking at chromosomal pattern back, but back then in 19 in the --- in the late 1970's, you know, molecular genetic is coming online. And --- and, you know, genetics is starting with looking at karyotyping and looking at chromosome changes, chromosome gain, chromosome loss. And that is --- that was the time that, you know, in the brain tumor world we start --- with in terms of karyotyping begin --- began to identify some chromosomal change in brain tumor, including gaining chromosome 7 and loss of chromosome 10. These ---

Tacey Ann Rosolowski, PhD
03:58/2
04:00.5
Wha --- What is the significance of those?

Wai-Kwan Alfred Yung, MD
04:00.9
The --- These are the work done at Duke, you know, and also with Joan Shapiro. The --- The significance of chromosome changes is that you cannot --- you can use those changes as a marker

Tacey Ann Rosolowski, PhD
04:12.5
Uhm.

Wai-Kwan Alfred Yung, MD
04:14.6
for the tumor, you know, and also identify the m --- you know, clones of cells with a different chromosome pattern. So in fact, we di --- we did a project like th --- just like that in terms of looking at one patient's tumor, how many different clones of cells are there are and what kind of chromosome, you know, pattern those clones of cells, you know, display.

Tacey Ann Rosolowski, PhD
04:48.9
And what did you find?

Wai-Kwan Alfred Yung, MD
04:50.2
And we find that, you know, from one tumor have many different clones and each clone has its own chromosome --- basic chromosome pattern. Changes in chromosome. And that's --- I think that is --- is --- you know we ---- we start working on this question of how does the chromosome pattern influence the sensitivity of the cell to different drug? You know, using drug sensitivity again as a, you know, functional characteristic of the cell in relationship with --- with the chromosome pattern. Th --- Later on, now a day we don't talk about chromosome pattern now. Now we talk about genes. What gene **colony (5:34)** with sensitivity, what drug?

Tacey Ann Rosolowski, PhD
05:38.2
And what ca---

Wai-Kwan Alfred Yung, MD
05:39.2
So that was the very beginning, so it is kind of, you know, early development on precision medicine _____ **(5:48)**. But the crude assay at that time is looking chromosome change.

Tacey Ann Rosolowski, PhD
05:53.6
And what caused that wh --- you --- when you talked about used to talk about chromosome patterns and now you talk about genes, what caused that shift in vocabulary? It was a conceptional shift or ---

Wai-Kwan Alfred Yung, MD
06:04.5
Well, because, you know, with the --- with the development of, you know, molecular genetics and molecular biology, you know, the technology advanced a lot. It was to look at, you know, the gene structure. We have the total number of genes in a human genome change in number,

you know. Until the human genome project is completed, then there is a --- a better understanding of how many genes is in the human genome. And how many genes is in the enti --- the 22 chromosomes. So early days, you're only looking at chromosome pattern and --- and --- and you can look at the character of the chromosome by different band, we call chromosome banding. And --- And we don't have the knowledge of the gene yet at that point. But later on when the tech --- technology develops and now we start sequencing, you know, the chromosome or the DNA in the chromosome and now you are able to --- to really identify the gene and location of the gene and the structure Of the gene, whether it is normal or mutated or lost. So you evolve from a big picture of chromosome to the final picture of gene. And then also, you know, the structure of the gene that is involved. Exon, you know, non --- you know, the space between the exon --- intron and exon. And --- And all these just keep develop where we find with the technology coming up, you know.

Tacey Ann Rosolowski, PhD
08:05.4
Uh-hmm. So this is really the development of an entirely new field.

Wai-Kwan Alfred Yung, MD
08:09.3
There's the development of an entirely new field in --- in, you know, genetics into molecular genetics and with molecular biology. And now, you know, we're in the area of genomic medicine. You know, the application of the geno --- genomic knowledge into --- into the clinic and prescribing medicine according to the --- to the genetic makeup of the disease.

Tacey Ann Rosolowski, PhD
08:39.1
Uh-hmm.

Wai-Kwan Alfred Yung, MD
08:39.9
So my first project in really looking at, you know, heterogeneity in terms of, you know, the technique that we will have at that time _____ **(8:48)** is --- is chromosome pattern. And --- And chemosensitivity. Then later on, you know, we --- when I moved to Anderson, we started looking at then --- then we beginning to --- again the --- the field developed that now we recognize there are some growth factors that you know, are important in the, you know, in the growth potential of these cells. And the first growth factor receptor that was identified is important to brain tumors is epidermal growth factor receptor. You know, so

Tacey Ann Rosolowski, PhD
09:31.5
And that's the EGFR.

Wai-Kwan Alfred Yung, MD
09:32.8
EGFR

Tacey Ann Rosolowski, PhD
09:33. 4
09:33.7
Yeah. Okay.

Wai-Kwan Alfred Yung, MD
09:35.2
Now EGFR is

Tacey Ann Rosolowski, PhD
09:35.0
And you --- is --- your lab identified that, or

Wai-Kwan Alfred Yung, MD
09:38.1
No. Our lab did not identify that. The EGF receptor is --- is identified by --- by, I don't remember. Actually, Dr. Mendelson is --- is very essential in th --- in the work of EGF receptors functioning in cancer.

Tacey Ann Rosolowski, PhD
09:56.2
Uh-hmm.

Wai-Kwan Alfred Yung, MD
09:57.5
But I don't remember who discovered the EGF receptor.

Tacey Ann Rosolowski, PhD
10:03.2
And I noticed as I was doing the background that EGFR comes up a lot in describing your focus. So you eventually began to work with that.

Wai-Kwan Alfred Yung, MD
10:12.8
I wou --- We --- We --- We spent a lot of time working on EGF receptor and the --- the protein that stimulates EFG receptors. And --- And then in --- in the --- you know, when my lab first

established and come over, you know, we moved the lab to Anderson in '83 and then we --- we recruited a scientist, Peter Steck, to join us. Peter --- Peter joined --- was at Anderson already. He finished his post doctoral fellowship with Dr. Nicholson --- Nicholson and looking for a staff position and --- and I created a --- a scientist faculty position for him and he joined us. And --- And, so we work on EGF receptor together but he's also a --- a protein chemist, you know, so

Tacey Ann Rosolowski, PhD
11:12.5
So he's a PhD.

Wai-Kwan Alfred Yung, MD
11:13.4
He's a PhD.

Tacey Ann Rosolowski, PhD
11:14.5
PhD. Uh-hmm.

Wai-Kwan Alfred Yung, MD
11:14.8
11:
He's a scien --- scientist to run EGF receptor together with --- and then at the same time he started a --- a --- a project of, you know, trying to --- to look at the observation of loss of chromosome 10 in these brain tumors. Glioblastoma cell. And --- And what's behind this loss

Tacey Ann Rosolowski, PhD
11:44.0
Hmm.

Wai-Kwan Alfred Yung, MD
11:44.3
of chromosome 10. Especially, there is a piece of chromosome 10 that is missing in many tumors and he wanted to identify what gene is located in that pie --- that piece of chromosome 10. And --- And, the thinking at that time is that, you know, when you have gene that is missing, that --- that is a tumor suppressive gene that --- that now plays a role in --- in preventing cancer development. But, then when you miss that tumor suppressive gene then

Tacey Ann Rosolowski, PhD
12:20.3
Uh-hmm.

Wai-Kwan Alfred Yung, MD
12:21.0
You know, the cell becomes malignant. So --- with a long story, it takes awhile for him to --- but he started with a technique of somato --- somato-cell fusion and --- and tried to reidentify this in bits --- bit by piece of the chromosome and --- and

Tacey Ann Rosolowski, PhD
12:38.5
Hmm.

Wai-Kwan Alfred Yung, MD
12:40.0
Identify the gene ____ **(12:40).** But eventually in 1997, you know, we --- we sequenced and --- and --- and discovered the --- the PTNG ---- PTNG.

Tacey Ann Rosolowski, PhD
12:55.5
Hmm.

Wai-Kwan Alfred Yung, MD
12:56.7
But there is a com ---, you know, --- competing lab in Columbia that is also working on the same --- same gene and that --- they're proving in --- in Columbia by Ramon Parsons. And, we ended up actually announced the --- the --- the discovery together.

Tacey Ann Rosolowski, PhD
13:22.6
Hmm.

Wai-Kwan Alfred Yung, MD
13:23.4
You know, the two labs announced the discovery together.

Tacey Ann Rosolowski, PhD
13:25.6
Oh wow.

Wai-Kwan Alfred Yung, MD
13:27.2
We --- At Anderson we id --- we call the gene as MMAC1. MMAC1, you know, stands for Mutated Multiple Advanced Cancer, because Peter was able to show that --- that missing gene

the P10 ge --- the missing gene --- missing chromosome 10 is involved in not only glioblastoma but also involved in advanced breast cancer.

Tacey Ann Rosolowski, PhD
13:53.4
Oh, wow.

Wai-Kwan Alfred Yung, MD
13:54.6
and prostate cancer. That's why --- he used the term --- he quickly named it as MMAC, but Dr. Parsons' group named it PTEN --- PTEN because it's on chromosome 10.

Tacey Ann Rosolowski, PhD
14:14.2
Hmm.

Wai-Kwan Alfred Yung, MD
14:16.1
And --- And I think that --- that PTEN was adopted as the --- as the official name of that gene.

Tacey Ann Rosolowski, PhD
14:22.8
Right.

Wai-Kwan Alfred Yung, MD
14:24.4
But the --- the function of PTEN gene is intimately related to an enzyme called --- PI3 kinase --- PI3 kinase and it's also --- and PI3 kinase is linked with EGF receptor function. So, that's why we --- we --- we started with EGF receptor work and then Peter

Tacey Ann Rosolowski, PhD
14:52.7
Hmm.

Wai-Kwan Alfred Yung, MD
14:53.7
branched off to look at, you know, tried to clone the gene of PTEN and then so from that point on with all that really worked on a goal, the function of the PTEN gene and how it's length with growth factor receptor activity in --- in brain tumor. That has been the line of research that now we follow.

Tacey Ann Rosolowski, PhD
15:17.8
Uh-hmm.

Wai-Kwan Alfred Yung, MD
15:19:0
)
From 1997 onward. Unfortunately, Peter died in 1999 from a massive heart attack, you know.

Tacey Ann Rosolowski, PhD
15:26.9
Hmm. That's a loss.

Wai-Kwan Alfred Yung, MD
15:36.3
So --- So it is a big loss.

Tacey Ann Rosolowski, PhD
15:37.3
Uh-hmm.

Wai-Kwan Alfred Yung, MD
15:38.3
I took over some of his work, but, I mean I'm not since I --- I wear two hats at that time trying to be a physician scientist, run the lab as well as run the clinic. So, we --- we take a more translational direction trying to look at the function of the, you know, --- the PTEN regulated PI3 kinase pathway and how it influence cell growth and how we can --- how we can int --- you know, inhibit this function. And --- And you know, inhibit cell growth. So we took the e --- the --- the lab takes on a more translational direction instead of a basic science direction.

Tacey Ann Rosolowski, PhD
16:34.0
Now I wanted to ask you about that, because, you know, we talked about how you --- your work and just you professional life has been evolved during the creation of entirely new fields and translational --- the translational approach has been part of that. And one of the things I've been interested in asking people about in these interviews is what is really the history of translational research? You know, what did translational research, how are pe --- how were people thinking about it i --- in the early days and how has it developed? How has it changed or become more complex. So that --- I --- you know, you'll have to tell me what the evolution has been.

Wai-Kwan Alfred Yung, MD
17:16.8
It's --- That's a interesting question. Because, I think you could get different answers from different people.

Tacey Ann Rosolowski, PhD
17:23.8
Yeah.

Wai-Kwan Alfred Yung, MD
17:24.8
I --- I mean is --- if I look back as, you know, in --- in --- in cancer research as well as you know, --- you know, medical research, you know, even when I was, you know, very active in terms of st --- study section review of giving out grants, you --- in --- in th --- back then in the '70s and '80s very strong emphasis on basic science. So, that's the time that we're developing fundamental knowledge of disease and the biology of the disease and --- and there's a lot of emphasis on understanding the biology in the very fund --- basic levels. Cellular level, organ --- organ level. And so, you know, basic science is --- is the foundation of the knowledge.

Tacey Ann Rosolowski, PhD
18:37.4
Uh-hmm.

Wai-Kwan Alfred Yung, MD
18:40.0
And the clinical --- clinical research come along in a --- you know, you're looking at clinical research. Besides understanding the anatomy and the cause of the disease is, you know, the treatment of the disease. And, the treatment of the disease, especially in the cancer world, is really, you know, besides radiation therapy and surgery, chemotherapy the use of drug came pretty much after the second World War.

Tacey Ann Rosolowski, PhD
19:20.3
Uh-hmm. Yeah.

Wai-Kwan Alfred Yung, MD
19.22.0)
I mean I think when you look at the history of development and even at Anderson using, you know, --- Dr. Freireich (19:28) and Emil Frei, these are people who are really champions and the forefathers of developing chemotherapy

Tacey Ann Rosolowski, PhD
19:38.2
Uh-hmm.

Wai-Kwan Alfred Yung, MD
19:38.2
Using a drug for cancer treatment.

Tacey Ann Rosolowski, PhD
19:40.5
Uh-hmm

Wai-Kwan Alfred Yung, MD
19:40.8
Before that is surgery, radiation. And --- and so clinical research really is --- is totally separate from the fundamental basic research. The laboratory knowledge accumulate in the laboratory --- in the structural level and, you know, cellular level under --- understanding protein and understanding DNA and those are all fundamental development. And there's no improvements into the clinic because the clinic research is interaction back in behind. In --- and so the --- the two directions really dev --- develop independently of each of other

Tacey Ann Rosolowski, PhD
20:27.9
Hmm.

Wai-Kwan Alfred Yung, MD
20:29.2
for a long time until --- until, you know, probably I would say late '80, early '90 when --- when --- when --- when the two sides start talking. The clinical people and the basic science people talking. There are more physician scientists. You know, people like, you know MD, PhDs --- that or MD with P --- MD PhD to s --- to start with thinking about we need to bring the clinical question into the lab.

Tacey Ann Rosolowski, PhD
21:07.8
Uh-hmm.

Wai-Kwan Alfred Yung, MD
21:08.1
And take the lab observation back into the clinic. And --- And that's where, you know, the way translation research come up is we need to bring some more of the clinical observation into the

lab, you know, as our scientists, you know, how --- what do you think about this ob --- clinical observation and how do we, you know, sort of like, you know, we see when we --- when we take the cell and we treat it with this drug and it is not working. Well, why is it not working? Or we use this drug for this group of patient and it's not working, well why is not working? And we take that question to the lab and say can you help us answer why I treat this tumor with this drug and it not working. And then the people in the lab start saying well let's create some --- some model system.

Tacey Ann Rosolowski, PhD
22:05.5
Uh-hmm.

Wai-Kwan Alfred Yung, MD
22:06.6
Can we --- Can we isolate the cell from this tumor or the cell **(22:10)**. Can we, you know, make --- make a tumor --- similar tumor in the animal, in the mouse, in the dog so that we can study the tumor in mouse and dog.

Tacey Ann Rosolowski, PhD
22:22.1
Now what ---

Wai-Kwan Alfred Yung, MD
22:22.5
That's where they're at beginning of translational

Tacey Ann Rosolowski, PhD
22:25.9
Uh-hmm.

22:26.4
research.

Tacey Ann Rosolowski, PhD
22:28.1
Now what was happening at MD Anderson in the '90s --- in the late '90s that made it more attractive, necessary, to have those conversations?

Wai-Kwan Alfred Yung, MD
22:41.8
I --- I think we in the --- well when I came to Anderson in '81 --- between '81 and '85, you

know, that's when, you know, Nic --- [Garth] Nicholson, Fidler --- Dr. [Isaiah Joshua] Fidler, Dr. [Margaret] Kripke, joined MD Anderson. And I --- I would say, you know, they bring in the --- the more translational branch --- more translational research.

Tacey Ann Rosolowski, PhD
23:34.8
Hmm.

Wai-Kwan Alfred Yung, MD
23:35.5
into it --- into MD Anderson. And --- And this --- at the --- at the time that we are also --- Anderson is really developing clinical research.

Tacey Ann Rosolowski, PhD
23.51.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
23:55.5
And with under --- under the group with --- with at that time we called Developmental Therapeutics. You know, with Dr. Freireich and his group.

Tacey Ann Rosolowski, PhD
24:09.5
Uh-hmm.

Wai-Kwan Alfred Yung, MD
24:11.2
And then later on Dr. Krakoff came in to con --- to continue with --- with that development of emph --- elevating the sophistication and the level of clinical research. And then in the laboratory, Dr. Becker would bring in people like Nicholson, Fidler, Kripke and other people. I think from the beginning --- in the beginning of the '80s maybe even the '90s, Anderson is --- become the fore --- forerunner in more applied, more transitional laboratory usage. And I think we remain the leader in that transition as opposed to, you know, institutions like Rockefellers and Memorial Sloan-Kettering and they have, you know, they started with a strong focus on the basic issues. They have a separation from clinic to basic _____ (25:28), but at Anderson even I came in and joined in the '80s --- early '80s and mid '80s we start with focus on the translational issues and clinical research.

Tacey Ann Rosolowski, PhD
25:43.5

Hmm. Hmm. Now wh --- in the '80s when you were beginning this project looking at heterogeneity and, you know, unraveling this whole

Wai-Kwan Alfred Yung, MD
25:56.2
Uh-hmm.

Tacey Ann Rosolowski, PhD
25:57:4
--- all these mechanisms involved with PTEN, how were --- I mean it seemed from the very beginning that just thinking about that research --- you were posing research questions that had clinical implications from the very beginning.

Wai-Kwan Alfred Yung, MD
26:14.3
Uh-hmm.

Chapter 07
Research Pathways and Research Issues that Emerge from EGFR Work
A: The Researcher;

Story Codes
A: The Researcher
A: Definitions, Explanations, Translations
C: The Professional at Work
D: Understanding Cancer, the History of Science, Cancer Research
C: Controversies
D: Ethics
A: Activities Outside Institution;
B: Beyond the Institution;
C: Healing, Hope, and the Promise of Research;

Tacey Ann Rosolowski, PhD
26:15.2
Now how did that research lead to other projects --- well maybe I should ask you first, what were some of the key findings that you've made with that research about the epider --- epidermal growth factor receptor and with PTEN that have taken a turn into affecting patient care with therapies?

Wai-Kwan Alfred Yung, MD
26: 40.1
Well I --- I think the research in epidermal growth factor functions in brain tumor and --- led to,

you know, many clinical trials.

Tacey Ann Rosolowski, PhD
26:53.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
26:54.1
You know, foll --- actually following the --- the --- the timeline of dev --- the development of epiderm --- EGF receptor inhibitor and EGF receptor antibody.

Tacey Ann Rosolowski, PhD
27:09.3
Hmm.

Wai-Kwan Alfred Yung, MD
27:09.7
in --- in --- in cancer research. And so the --- the laboratory study that we do in our laboratory and other labs in the brain tumor world actually convinced, you know, several drug companies to give us EGF receptor inhibitor.

Tacey Ann Rosolowski, PhD
27:31.0
Hmm.

Wai-Kwan Alfred Yung, MD
27:31.7
to --- to --- to treat brain tumor in the glioblastoma patient. We did not see a who --- un --- un --- unfortunately it is not highly active, you know, in --- in --- in glioblastoma, you know. But it was also not very active in other cancer until the --- the --- the, you know, development of molecular biology and --- and molecular genetic, you know, when we start matching the genetic changes

Tacey Ann Rosolowski, PhD
28:14.0
Hmm.

Wai-Kwan Alfred Yung, MD
28:14.8
To the reason of responding or not responding and --- and the lung cancer people is able to identify the mutation --- specific mutation in the EGF receptor gene. Spec --- that match with

sensitivity to the EGF receptor inhibitor. I mean that's the time --- when --- when we start identify as this specific mutation in the --- in the kinase domain of the --- of the EGF receptor gene that is present in the higher frequency in Asia --- you know, Asia population in Asian man and woman than Caucasian. And there is a discrepancy of that gene mutation

Tacey Ann Rosolowski, PhD
29.00.6
Hmm.

Wai-Kwan Alfred Yung, MD
29:01.0
20% --- 20% in --- in --- in Asian population and only 5% in --- in Caucasian and --- and those who carry this mutation is highly sens --- highly responsive or sensitive to the EGF receptor inhibitor. They --- th ---- so that again takes a long time when we go to that stage of now we're able to match the gene mutation with sensitivity drug.

Tacey Ann Rosolowski, PhD
29:31.2
Can I just ask you bec ---

Wai-Kwan Alfred Yung, MD
29:32.8
And brain tumor does not have that mutation

Tacey Ann Rosolowski, PhD
29:35.0
Hmm.

Wai-Kwan Alfred Yung, MD
29:35.6
Unfortunately.

Tacey Ann Rosolowski, PhD
29:36.3
Right.

Wai-Kwan Alfred Yung, MD
29:36.9
There is very low frequency with --- with in --- that's why right now up to this time, almost 20 years now, we still have not really increased the responsiveness of brain tumor patients to EGF receptor inhibitor.

Tacey Ann Rosolowski, PhD
29:51.2
Uh-Hmm.

Wai-Kwan Alfred Yung, MD
29:51.1
We have some clue but we ha --- we are not there yet.

Tacey Ann Rosolowski, PhD
30:00.3
____, I was just going to ask you that question about the time. You know, 20 years, looking at this one problem. I mean this may be a naïve question, but are you --- if you --- the persistence question. You know, why --- what is that you are unraveling that gives you the sense that

Wai-Kwan Alfred Yung, MD
30:23.4
30:23:6
Well --- I --- I think that

Tacey Ann Rosolowski, PhD
30:25.0
Eventually there will be

Wai-Kwan Alfred Yung, MD
30:25.6
What the --- the --- the so --- I mean --- if I look at, you know, the question of, you know, are you disappointed that after that many years of focusing on EGF receptor for brain tumor we still have not find a --- a

Tacey Ann Rosolowski, PhD
30:45.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
30:46.7
--- a --- a, you know, solution or we have not find a hit to really in --- increase the responsiveness of the tumor to EGF receptor. I am --- I am disappointed for that end, but I am not disappointed because of focusing on EGF receptor also unraveled all the parallel relationship discovering other pathways.

Tacey Ann Rosolowski, PhD
31:16.0
Right

Wai-Kwan Alfred Yung, MD
31:17.4
other linkage to

31:18.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
31:19:7

to the PI3 kinase pathway to other growth factor. I mean, it open up an --- a --- a whole, you know, line of research to look at, you know, what propelled glioblastoma cell growth. What propelled glioma cell growth. Because the same --- the same question is being asked in different tumor types of glioblastoma, even in the brain tumor world, glioblastoma, astrocytoma**,** oligodendroglioma, and we got different laboratory stuff, building models to look at this question.

Tacey Ann Rosolowski, PhD
32:00.1
Uh-hmm.

Wai-Kwan Alfred Yung, MD
32:02.6
What is the role of growth factor in these ___ ____ **(32:00)?** What is the role of signal pathway? And --- And that really generated a whole new line of research

Tacey Ann Rosolowski, PhD
32:21.9)
32.22.0
Uh-hmm.

Wai-Kwan Alfred Yung, MD
32:23.0
Of --- and we bring in all this complicated pathway and --- of course --- I can --- we also benefit greatly, you know, when NCI and NIH, you know, decided to develop, you know, the genome Atlas for cancer

Interview Session: 02
Interview Date: May 7, 2014

Tacey Ann Rosolowski, PhD
32:45.1

The gene ---

Wai-Kwan Alfred Yung, MD
32:46:1
After they --- after --- after --- you know, in the mid '90s, the NIH --- was it --- was it the mid '90s or late --- yeah late '90s I think. I don't remember when the project began. NIH and NCI decided to, you know, follow the success of sequencing the entire human genome, the entire mouse genome, and --- and start asking the question well can --- can we sequence cancer genomes. And --- and there was --- actually there was big debate whether NIH will spend time and effort to try to sequence

Tacey Ann Rosolowski, PhD
33:46.3
Hmm.

Wai-Kwan Alfred Yung, MD
33:46.9
the cancer genome because cancer is such a complicated disease and such a dynamic disease and it keeps changing. Cancer is not a static process. You know, --- we --- but we --- but we all known that when --- when cancer --- cancer can present in a early stage, late stage, you know, early malignancy, late malignancy and so there is a dynamic change of cancer. Can you really sequence the genome in a dynamic disease as opposed to the human normal gene that is static.

Tacey Ann Rosolowski, PhD
34:24: 8
34:25.2
Uh-hmm.

Wai-Kwan Alfred Yung, MD
34:25.2
The normal. It doesn't ch --- when it changes it changes in a small way _____ **(34:30)** and --- and they identify disease in that small way.

Tacey Ann Rosolowski, PhD
34:33.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
34:34.6
But cancer keeps changing. So there was a big debate. The --- The cancer people win and say we will learn something

Tacey Ann Rosolowski, PhD
34:42.0
Uh-hmm.

Wai-Kwan Alfred Yung, MD
34:44:0
But let's sequence gene and NIH invest --- invest, you know a big chunk of money into sequencing it and it caused the --- the cancer genome Atlas project. And they select three cancers as a pilot and glioblastoma was selected as one of the three cancers besides squamous cell carcinoma of the lung and --- glioblastoma, squamous cell carcinoma of the lung, and what is the third one? Is it ovarian cancer? I think it is ovarian cancer.

Tacey Ann Rosolowski, PhD
35:25.6
Ovarian?

Wai-Kwan Alfred Yung, MD
35:26.2
Yeah.

Tacey Ann Rosolowski, PhD
35:26.7
UIh-hmm.

Wai-Kwan Alfred Yung, MD
35:27.4
And that's the pilot. And --- And so

Tacey Ann Rosolowski, PhD
35:32.8
What's your view of the value?

Wai-Kwan Alfred Yung, MD
35:34.7
We --- actually at MD Anderson is one of the tissue supplier --- the tissue supply --- brain tumor tissue as well as all the other lung cancer tissues and ovarian cancer tissue to --- to --- to the

project of the TCGA. But we have high quality tissue, you know, for them to do the sequencing. So we are the tissue supplier and then we also participate wit**h ____ (35:58**

Tacey Ann Rosolowski, PhD
36:00.1
And TGCA that stands for

Wai-Kwan Alfred Yung, MD
36:04.3
T is The, C Cancer, G --- G is Genome

Tacey Ann Rosolowski, PhD
36:09.2
Oh.

Wai-Kwan Alfred Yung, MD
36:09.4
A Atlas. So, its --- so TCGA

Tacey Ann Rosolowski, PhD
36:13.1
There we go.

Wai-Kwan Alfred Yung, MD
36.15.7
The Cancer Genome Atlas. And that actually evolved into an --- into the TCGA**,** the ____ is a US effort **(36:22).**

Tacey Ann Rosolowski, PhD
36:26.3
Hmm.

Wai-Kwan Alfred Yung, MD
36:27.1
And that evolved into an international effort called ICGC. International Cancer Genome Consortium.

Tacey Ann Rosolowski, PhD
36:45.3
How have --- have you benefited? Has your work benefitted in any way from this project?

Wai-Kwan Alfred Yung, MD
36.49.6
I think so. Yeah. We --- We --- We benefit I think not only our work at Anderson or my work and I'm intimately involved with the TCGA effort for brain tumor.

Tacey Ann Rosolowski, PhD
37:00.3
Uh-hmm.

Wai-Kwan Alfred Yung, MD
37:01.5
I'm involved in --- in --- because we --- we then from sequencing glioblastoma then we convince you know TCGA to also improve lower grade brain tumor. So, we have basically two projects. One with the high grade glioblastoma and then the lower grade tumor and I was involved in both projects.

Tacey Ann Rosolowski, PhD
37:27.7
So if you're

Wai-Kwan Alfred Yung, MD
37.28.4
37:35.5
So we benefited greatly because the knowledge --- really we define how we look at the --- the tumor.

Tacey Ann Rosolowski, PhD
37:36.0
How so?

Wai-Kwan Alfred Yung, MD
37:36:4
):
Not on --- Not only from the morphology side. I mean in the past we defined a tumor by, you know, this is --- this tumor comes from astrocyt --- astrocytoma. This tumor comes from oligodendroglioma --- is oligodendroglioma from oligodendrocyte. And this tumor comes from astrocyte and is a lower degree of malignancies because not that many cells are dividing and not that many blood vessels, so it's astrocytoma grade 2.

Tacey Ann Rosolowski, PhD

38:05.3
Hmm.

Wai-Kwan Alfred Yung, MD
38:06.3
Lots of cells dividing a lot of blood vessels as --- in astrocytoma grade 3. There is a lot of dead tissue necrosis, so it is glioblastoma. It's all based morphology. Now that we go into the molecular area we start looking at well this group of tumor had EGF receptor mutation. This group of tumor has NF1 mutation and this group of tumor has different mutation and --- and the meaning of this mutation and how do we --- and so we're now actually building a so-called molecular classification besides, you know, being parallel to the histologic classification. And in the future de --- we believe that the molecular classification will tell us a lot more how to treat these tumors. Then purely histologic classification because each histologic classification had multiple molecular subgroup.

Tacey Ann Rosolowski, PhD
39:10.4
Now how have you finessed the problem of can --- of these cancers being so dynamic? You know, are you taking samples longitudinally? So h ---

Wai-Kwan Alfred Yung, MD
39:21.5
And so now, is --- that's a very good question too. You know, it's --- that is --- that is a fundamental question. Can we understand the evolution of a tumor as it develops, as it's being treated, and in the different stages of treatment how does the cancer change? It is a much difficult question to answer for solid tumor than in liquid tumor.

Tacey Ann Rosolowski, PhD
39:48.9
Hmmm.

Wai-Kwan Alfred Yung, MD
39:49.9)
40:39.3
The liqui --- you know, leukemia you can actually --- is not --- it is much less invasive to the patient to draw blood in different stages of the tumor. But being a solid tumor depending on the location of the tumor is much more difficult to get tissue in different stages. For example in brain tumor where is the most --- being the most difficult location. Trying to --- to get a piece of the tumor is n --- is pretty invasive. You have to open the brain to get a piece of tissue. Even if --- if you can do a needle biopsy you still need to drill a hole and stick a needle into the brain passing through normal brain to get to the tumor to get a piece, so its not a --- not a simple

innocuous procedure. You cannot do it --- you certainly cannot do it many times

Tacey Ann Rosolowski, PhD
40:40.9
Hmm.

Wai-Kwan Alfred Yung, MD
40:41.5
as opposed to draw blood many times. So we are pretty limited in how many times we can sample the tumor. In the beginning of treatment, during treatment, or after treatment. It's not like leukemia when you get the blood easy or even malignant melanoma like in the surface of the --- the skin you can ta --- take a nip without that much damage or that much trauma to the patient. You know, you can take a snip of the --- of the tumor in the beginning, you know, one week after treatment and one month after treatment is still kind of on the surface you can, you know --- and the brain I cannot tap the brain weekly or monthly.

Tacey Ann Rosolowski, PhD
41:25.0
Yeah.

Wai-Kwan Alfred Yung, MD
41:25.5
Without a lot of damage. So it's a lot more

Tacey Ann Rosolowski, PhD
41:27.9
So

Wai-Kwan Alfred Yung, MD
41:28.4
It's a lot more difficult to answer that question but that's what we want to a --- wh --- that's what we are doing.

Tacey Ann Rosolowski, PhD
41:33.7
Um-hmm. So

Wai-Kwan Alfred Yung, MD
41:34.0
Want to do, yeah.

Tacey Ann Rosolowski, PhD
41:34.2
How are you deciding the timing of the samples since you have these limitations?

Wai-Kwan Alfred Yung, MD
41:40.9
It's again --- it is --- it is difficult. I mean I think wha --- what we can do --- right now we're actually only limited to the first piece

Tacey Ann Rosolowski, PhD
41:55.6
Uh-hmm

Wai-Kwan Alfred Yung, MD
41:56.0
To make the diagnosis that you have the tumor or the second piece when the tumor comes back and we need to remove the tumor, you know, to --- you know, either for needle diagnosis or we need to remove it to decompress the brain so to --- you know, to relieive symptoms.

Tacey Ann Rosolowski, PhD
41:16.7
Uh-hmm.

Wai-Kwan Alfred Yung, MD
42:16.9
You know so a second surgery is to --- to --- and that --- and we're --- you know, I --- I don't think, you know, we can really take biopsy when the patient is doing well from treatment and stable and you say I'm going to stick a needle into your brain now and get a biopsy even though we, you know, it's --- it's two months after the treatment or three months after the treatment and you're doing well, the tumor is stable and you don't need it, you know, we just want to have a piece of the tumor to study it.

Tacey Ann Rosolowski, PhD
42:53.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
42:55.5
Not only insurance will not pay for it.

Tacey Ann Rosolowski, PhD

42:57.8
Right.

Wai-Kwan Alfred Yung, MD
42:59.1
The patient probably don't want to subject that risk, right? Because it's high risk.

Tacey Ann Rosolowski, PhD
43:05.1
Right.

Wai-Kwan Alfred Yung, MD
43:06.2
So that's a --- right now it's a big limitation for us to answer the question of how brain tumor evolves and respond to treatment.

Tacey Ann Rosolowski, PhD
43:11.9
Uh-hmm. Sounds like a classic ethical issue too.

Wai-Kwan Alfred Yung, MD
43:17.4
Yeah.

Tacey Ann Rosolowski, PhD
43:17.6
Yeah. I mean there are a lot of controversy around the whole thing.

Wai-Kwan Alfred Yung, MD
43:21.4
--- controversy. Yeah.

Tacey Ann Rosolowski, PhD
43:22.4
Yep. Yep.

Wai-Kwan Alfred Yung, MD
43:23.5
But we need to be able to do that in order

Tacey Ann Rosolowski, PhD

43:25.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
43:26.0
You know --- you know then --- because we do --- we do know that even though we have a good understanding of the --- of the molecular profile or the genetic profile of the tumor in the beginning. Once we treat with radiation or with drug, that structure, that profile, changes. Because we are disturbing with the --- with the --- with the treatment modality with radiation or the drug we are disturbing that.

Tacey Ann Rosolowski, PhD
43:55.6
Wow.

Wai-Kwan Alfred Yung, MD
43:56.0
The genetic pattern.

Tacey Ann Rosolowski, PhD
43:57.3
That is a real gap in knowledge

Wai-Kwan Alfred Yung, MD
44:00.3
Yeah. And then when we --- when we try to propose a --- a new treatment when the tumor grows after the first set of treatment

Tacey Ann Rosolowski, PhD
44:08.4
Uh-hmm

Wai-Kwan Alfred Yung, MD
44:08.9
If we base on the profile here, we're proba --- is wrong is because that profile is changed by the treatment.

Tacey Ann Rosolowski, PhD
44:17.2
Right. Interesting.

Wai-Kwan Alfred Yung, MD
44:17.4
44: 19.7
And --- And we need to have a new profile.

Tacey Ann Rosolowski, PhD
44:19.9
Uh-hmm.

Wai-Kwan Alfred Yung, MD
44:20.8
Wh ---, you know, in that new tumor.

Tacey Ann Rosolowski, PhD
44:24.1
Uh-hmm.

Wai-Kwan Alfred Yung, MD
44:25.6
And --- And treatment needs to be based on that new profile. Leukemia can do that. Malignant melanomas do it easier and even breast cancer can do it easier at least, but brain is very difficult.

Tacey Ann Rosolowski, PhD
44:41.4
Hmm. Hmm.

Wai-Kwan Alfred Yung, MD
44:43.9
Yeah.

Making Cancer History®
Interview Session: 02
Interview Date: May 7, 2014

Chapter 08
Brain Tumor Research: Translational Studies in Progress and the NCI Study Section
A: The Researcher;

Story Codes
A: The Researcher;
A: Overview;
A: Definitions, Explanations, Translations;
A: Activities Outside Institution;
D: Understanding Cancer, the History of Science, Cancer Research;
D: On Research and Researchers;
D: On Pharmaceutical Companies and Industry;
B: Industry Partnerships;
C: Leadership;
D: On Research and Researchers;

Tacey Ann Rosolowski, PhD
44:46.1
What are some of the other research projects that you worked on?

Wai-Kwan Alfred Yung, MD
44:50.9
Well, besides the laboratory stuff, I --- I --- you know sort of --- I mean I said I am translational guy then I take --- I also, you know, led several teams in terms of developing clinical trials. Clinical research, you know, in the clinic, you know, in the clinic. So I was ver --- I was very involved in the --- in Ni --- NCI --- with NCI in st --- study section for research and then I was involved in the study section that is awarding clinical research, you know. And I was involved --- I was involved in our TOG designing clinical trials for brain tumor. I lead a consortium. You know, NCI developed a --- a --- in the mid '90s and late '90s NCI wanted to develop several groups of centers to do brain tumor research in a Phase 1 and Phase 2 setting. So I led one of those consortiums, put a field center together

Tacey Ann Rosolowski, PhD
46:06.4
Hmm.

Wai-Kwan Alfred Yung, MD
46:06.8
to develop clinical trials in the ea --- you know, early phase, clinical trial. Phase 1 and Phase 2

clinical trials studying new drugs. And that's when we study these EGF receptor, inhibitors and new --- new drugs like temozolomide and other drugs.

Tacey Ann Rosolowski, PhD
46:25.3
What were some of the challen ---

Wai-Kwan Alfred Yung, MD
46:26.5
And then actually I led to --- led the big group of people doing st --- clinical trial on temozolomide that led to registration of temozolomide.

Tacey Ann Rosolowski, PhD
46:35.9
Temozolomide

Wai-Kwan Alfred Yung, MD
46:37.3
Yeah. T-E-M-O-Z-O-L-O-M-I-D-E and the trade name is Temodar, T-E-M-O-D-A-R.

Tacey Ann Rosolowski, PhD
46:53.1
Hmm.

Wai-Kwan Alfred Yung, MD
46:54.1
And that's they're approved --- the drug tests approve of **TVM (46:55)** in 1997.

Tacey Ann Rosolowski, PhD
47:03.1
So it was the trials that you put together that confirmed the --- the usefulness of this drug.

Wai-Kwan Alfred Yung, MD
47:07.7
___ ____ ___ (47:07) Yeah.

Tacey Ann Rosolowski, PhD
47:09.2
Wow. I was going to ask you with your involvement of putting together these consortia, you know, working with different institutions, have there been some special or unique challenges that arose with setting up these translational projects?

Wai-Kwan Alfred Yung, MD
47:32.8
In --- It --- It is always a challenge in trying to really get a group of, you know, highly intelligent, highly driven people together to march to the same drum or to move in the same direction. So that is always a challenge --- that's a challenge. That is also a, you know, rate limiting factor for move --- for --- for advance. So, I mean, my observation in working with, you know, dif --- different consortium is that we really need to be able to enable and encourage, you know, people who are willing to work together and work together. I don't think we can please everybody and I don't think that we can force unwilling participants to participate in the same level. So --- So --- I --- I --- think the challenge for us really is for us to build a team with people willing to work together. And we al --- we --- we need to build teams with different focus.

Tacey Ann Rosolowski, PhD
49:11.5
Uh-hmm.

Wai-Kwan Alfred Yung, MD
49:12.2
You know, so that we can divide up the tasks into the multiple teams.

Tacey Ann Rosolowski, PhD
49:21.6
Are you observing that younger generations of people are maybe more willing to work on teams than older generations? Is --- I mean is there any trend like that that you're noticing?

Wai-Kwan Alfred Yung, MD
49:33.5
Well I think the younger generation is more willing because I think the younger generation is, you know, is more cognizant of the interdependence of --- of --- the research arena that we are. I mean, we are --- in --- in --- in the --- in the --- in the new, you know, world of research is that --- is such a complex problem we're faced with that if --- without working with each other with a larger --- larger group of people you cannot make anything happen.

Tacey Ann Rosolowski, PhD
50:24.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
50:27.2
As opposed to in the past when we're just in the beginning, I can just focus on my own world

and I really don't need a whole lot of help to know how this protein works if I am smart enough to figure out some of the new techniques of doing it I can do it all myself. But now is a new --- the technology is so advanced. A lot of technology developed that one --- one group or one person is going to master the various areas and it's just not possible. And also in terms of looking at a bigger picture of understanding how cells grow, understanding how cells move, understanding the --- the effect of the environment versus the effect of the cell itself. I mean the --- these are big questions. And it --- it really required a whole team of people to work together. And I think that realization brings people **looking (51:32)** So I think the team science is better recognized and --- and by nature you have to work in a team.

Tacey Ann Rosolowski, PhD
51:46.6
Hmm. I --- in my background research I noted a couple of studies. And I don't know if these are very significant --- significant enough to spend time on today. One of those, the Phase 2 study for BKM --- BKM 120 for patients with recurrent glioblastoma. That was part of the P13K pathway. Was that worth

Wai-Kwan Alfred Yung, MD
52:20:6
Well, that, I mean

Tacey Ann Rosolowski, PhD
52:21.3
talking about or ---

Wai-Kwan Alfred Yung, MD
52:22.9
That --- that clinical trial is --- is pretty unique because, you know, that clinical trial is developed based on a lot of laboratory data that was generated in my lab as well as --- as with --- with --- with the company in Nevada who developed the drug BKM 120 and it also illustrates the difficulty for a small cancer like GBM**,** glioblastoma or for _____ other small cancer like thyroid cancers or sarcoma to get attention from Biotech or ____ **(53:11**) whose main goal is to really make sure they have a --- a drug that makes money.

Tacey Ann Rosolowski, PhD
53:20.5
Right. Yep.

Wai-Kwan Alfred Yung, MD
53:20.7
Right. So the pharmaceutical companies are really almost always focused on big cancer so that

they --- they can have a big market.

Tacey Ann Rosolowski, PhD
53:30.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
53:32.6
Small cancer is --- never --- always ---, but you know, people --- you know --- they're so --- so we work very hard to develop in the clinic --- the preclinical data and work with a company you know to get a drug in the lab to do some preclinical study and our lab is very interested in PTEN and PI3 kinase so --- so I established some relationship with --- with Nevada and was able to get some of their, you know, new drug early on to --- to --- work in the lab

Tacey Ann Rosolowski, PhD
54:10.4
So

Wai-Kwan Alfred Yung, MD
54:11.2
____ ___ **(54:11)** the PI3 kinase. So we develop those preclinical data for this drug BKM 120.

Tacey Ann Rosolowski, PhD
54:17.6
So how did you convince then that it was worth their effort to do

Wai-Kwan Alfred Yung, MD
54:21.7
Well we

Tacey Ann Rosolowski, PhD
54:21.8
This study?

Wai-Kwan Alfred Yung, MD
54:22.1
--- we generate the dat and lo --- and --- and --- and --- and we show them that this drug had a level --- a certain level activity in this --- in cell line that we generated as well as seeing mouse and --- and we worked with them, you know, work with the company, you know to compare data with their own in-house data snd, you know, then they would --- you know, after we have enough data generated we said okay so --- the --- the --- there is something there that we can we

can --- we can take --- take a stab at this.

Tacey Ann Rosolowski, PhD
55:02.2
Uh-hmm. So is ---

Wai-Kwan Alfred Yung, MD
55:03.9
So we develop a f --- a clinical trial after they finish their Phase 1 all solid tumor trial knowing how much drug to use and then we develop a Phase 2 trial. But thi --- the --- we can only get that Phase 2 trial, you know, approved by them because we have pre-clinical data to convince them that it is a worthwhile attempt.

Tacey Ann Rosolowski, PhD
55:28.0
Great. Yep.

Wai-Kwan Alfred Yung, MD
55:28.5
You know --- you know.

Tacey Ann Rosolowski, PhD
55:29.3
Yep. So is the assumption --- I mean I'm kind of thinking about your description of this in parallel with what you were saying earlier about the growth factor research that --- is Novartis and are you assuming that even though this is a small cancer what you will you will learn will have implications well beyond.

Wai-Kwan Alfred Yung, MD
55:52.5
Definitely. I think, what you learn ---I th --- and this is one of the emphasis' that actually Anderson, you know, is driving and can be --- is --- is to --- to tell the pharmaceutical industry that we have enough expertise here that we can partner with them early on in development of drugs for different cancer types used. You know, we can work with them early one to get the drug from them and utilize our laboratory and preclinical, you know expertise to generate the --- the --- what we call the pre-clinical data to --- to --- what work, what does not work and how it works and how it did not work. And --- and w --- with those knowledge we can, you know, have a m --- a --- a more careful way of designing the clinical trial and speed up the clinical trial development. I mean, this is exactly the --- the line of thinking that Dr. DePinho is, you know, is advancing, you know. And --- And I think for a small cancer like brain tumor it is even more important for us to really be able to have established relationship early, you know to --- to get

those data because those data can be --- can be used to really convince the --- the --- the industry to say this drug may pay a little for this cancer and this cancer has a critical need for new drug.

Tacey Ann Rosolowski, PhD
57:47.5
Uh-hmm.

Wai-Kwan Alfred Yung, MD
57:49.0
And there may be a --- a small --- it's just a --- it is a small investment that may have very important implications.

Tacey Ann Rosolowski, PhD
57:57.1
Uh-hmm.

Wai-Kwan Alfred Yung, MD
57:57.9
While you are investing in breast cancer well invest a little to brain tumor. There is --- you know.

Interview Session: 02
Interview Date: May 7, 2014

Chapter 09
The Challenges of Glioblastoma; Lessons from MD Anderson's Moon Shot Program; No Low-Hanging Fruit for Neuro-Oncology Research
A: The Researcher;

Story Codes
A: The Researcher;
A: Overview;
A: Definitions, Explanations, Translations;
C: Professional Practice;
C: The Professional at Work;
D: On Research and Researchers;
B: Critical Perspectives on MD Anderson;
A: Definitions, Explanations, Translations;
D: Understanding Cancer, the History of Science, Cancer Research;
D: The History of Health Care, Patient Care;
B: Building/Transforming the Institution;
B: Multi-disciplinary Approaches;
B: Growth and/or Change;

Tacey Ann Rosolowski, PhD
58:05.0
Uh-hmm. Well, thinking too of what you said earlier about PTEN that --- and --- and that the --- the work that you were doing on those related pathways that it hasn't had the dramatic effect on glioblastoma, but it had some for lung cancer.

Wai-Kwan Alfred Yung, MD
58:22.1
Uh-hmm.

Tacey Ann Rosolowski, PhD
58:22.6
So there are --- you know, there can be collateral

Wai-Kwan Alfred Yung, MD
58:25.8
____ (58:25) collateral

Tacey Ann Rosolowski, PhD

58:27.2
Right. Very interesting. I had wanted to ask you what makes glioblastoma and glioblastoma multiform such challenging cancers? Because I read that --- somewhere that you had said how difficult they are to treat.

Wai-Kwan Alfred Yung, MD
58:46.1
Well, I think it's a challenge in many ways. One --- One is the --- the --- the degree of heterogeneity is very high.

Tacey Ann Rosolowski, PhD
58:571
58:57.3
Okay.

Wai-Kwan Alfred Yung, MD
58:58.0
You know. And two is we still, you know --- and --- and --- and we do not have enough understanding of the --- the intricate interaction among different signals. Signals of growth. Signals of migration. Because brain tumor is a very mobile tumor. It moves around the brain. Bu --- And we also do not understand enough why glioblastoma do not metastasize to the lung and to bone but

Tacey Ann Rosolowski, PhD
59:42.2
Hmm.

Wai-Kwan Alfred Yung, MD
59:42.6
--- only move around in the brain. The other challenge we have about difficulty is because the brain --- the tumor in the brain is --- is --- is a, you know, occupies different location in the brain but the surrounding brain is a very sensitive organ and it's not very forgiving when we start treating the tumor at the same time effecting the brain. So the --- the --- the therapeutic index or the tolerance of the brain to the --- to the treatment is not very high. So we damage the brain very frequently when we try to treat the tumor. So that's a limitation as opposed to free standing tumor that --- that surrounding tissue is more tolerant to the tumor and we have that problem.

Tacey Ann Rosolowski, PhD
1:00:43.0
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:00:43.5
The other problem we have is delivering of the drug to brain is limited by the protecting --- protective mechanism of the blood/brain barrier. Many drugs that's --- that is effectively treating cancer in the lung, in the liver, or in the breast do not the cross blood/brain barrier and cannot

Tacey Ann Rosolowski, PhD
1:01:06.8
Hmm.

Wai-Kwan Alfred Yung, MD
1:01:07.8
get to the brain. And so we --- we cannot treat, you know, a tumor in the brain like glioblastoma or even metastasis in the brain in the same level of effectiveness with the same drug that --- that is active for lung cancer or breast cancer because it just doesn't go to the brain. So delivery of --- of the --- of the treatment is a hurdle for --- for brain tumor also.

Tacey Ann Rosolowski, PhD
1:01:37.4
So I am dying to ask. How do you deliver the drugs in that situation?

Wai-Kwan Alfred Yung, MD
1:01:42.9
Well, you know, --- I mean --- so you have to really work on --- number one there is a way to make the drug cross blood/brain barrier.

Tacey Ann Rosolowski, PhD
1:01:51:6
Hmm. Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:01:52.2
Smaller molecule or molecule that is more lipid soluble. You know, react with the --- with the cell membrane and can jump past the blood/brain barrier. They are people who try open the blood/brain barrier by heat, by wave and follow by infusion. There are different ways of doing that. E --- you know, --- mechanical way op --- open the blood/brain barrier has --- has a limitation of also exposing normal brain to the toxic drug ___ ____ **(1:02:27)**

Tacey Ann Rosolowski, PhD
1:02:28.8
Right.

Wai-Kwan Alfred Yung, MD
1:02:30.3
So --- And the --- the --- the other --- the other challenge we face in --- yeah --- we know there's ways to make the drug cross the blood/brain barrier, but in some situations you do want --- you do not want the brain --- you do not want the drug to cross the blood/brain barrier. For, you know because, --- you know, for a long time the pharmaceutical companies think we really don't want the drug to cross the blood/brain barrier because we're treating lung cancer and we're treating breast cancer. We don't want the drug to cross

Tacey Ann Rosolowski, PhD
1:03:02.6
Right.

Wai-Kwan Alfred Yung, MD
1:03:02.8
the blood/brain barrier to cause toxicity in the brain.

Tacey Ann Rosolowski, PhD
1:03:04.8
Right. Right.

Wai-Kwan Alfred Yung, MD
1:03:06.1)
1:03:48.3
So they deli --- they --- they would rather see the drug do not cross the blood/brain barrier so that they can treat the system --- systemic organ effectively without hurting the brain. But the other side of the coin is those drugs, even those highly effective in breast cancer and lung cancer, is no good for us --- for to treat brain cancer so --- so we --- even though you may share the same mechanism of kill betw --- you know, between the cancer in the breast or the cancer in the brain I cannot us --- you cannot use that drug. It doesn't _____ **(1:03:46)** --- so we have to redefine a way to modify that drug

Tacey Ann Rosolowski, PhD
1:03:49.1
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:03:49.5
To make it cross the blood/brain barrier. Alright.

Tacey Ann Rosolowski, PhD
1:03:55.9
Are there any other research related projects that you'd like to talk about?

Wai-Kwan Alfred Yung, MD
1:04:08.5
Well I mean, I think, at this stage I --- I, you know --- I am working with, you know, several brain tumor foundations to re --- to --- to foster, you know collaboration within, you know, the brain tumor community.

Tacey Ann Rosolowski, PhD
1:04:30.1
Hmm.

Wai-Kwan Alfred Yung, MD
1:04:30.5
So that we have a, you know, unifying, you know, effort of identifying, you know, a way that we really can advance the treatment for brain tumor. T--- So I'm working with brain tumor founda --- with the Bra --- The Brain Tumor Society. And we want to establish a --- a national network as well as, you know, working with several groups to develop an international network so that we can do, you know, collaborative research to move things faster by --- by involving, you know, more groups working together. Which is not --- I mean, I think, you know, the same kind of thinking, you know, stand up to cancer is the same thing as getting people hi --- a --- a group of experts and people working --- can work together to really focus on

Tacey Ann Rosolowski, PhD
1:05:40.6
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:05:41.3
one direction. And I think that in the ____ (1:05:44) working with the --- The Brain Tumor Society to really foster that kind of national initiative. And we --- we want to have, of course, locally at Anderson, the Brain Tumor Center, the Brain Tumor Group, Neurosurgery, Neuro-Oncology, Neuropathology, Radiation and really --- really working together to really --- to again put our --- put our experts together, you know, to form --- the --- the Moon Shot Team to --- to really make a strong and concerted effort to --- to --- to change the --- the --- the --- the landscape --and upwardly some strong impact. We are --- We are really in need of some new drug. But right now in t --- in the brain tumor world in glioblastoma we only have two drugs that is specifically approved.

Tacey Ann Rosolowski, PhD
1:06:44.8
What are those?

Wai-Kwan Alfred Yung, MD
1:06:44.9
for this disease besides radiation. BCNU and temozolomide.

Tacey Ann Rosolowski, PhD
1:06:54.9
B-C-N-U?

Wai-Kwan Alfred Yung, MD
1:06:55.9
U and temozolomide.

Tacey Ann Rosolowski, PhD
1:06:57.6
Yeah.

Wai-Kwan Alfred Yung, MD
1:06:58.3
And the third one approved for recurring disease is bevacizumab or Avastin. So in total we have three drugs --- drugs that's approved for --- for glioblastoma. Two for newly diagnosed disease and one for recurrent disease.

Tacey Ann Rosolowski, PhD
1:07:22.5
Are there specific drugs on the horizon that

Wai-Kwan Alfred Yung, MD
1:07:27.2
Close to being, no.

Tacey Ann Rosolowski, PhD
1:07:28.6
Really? What's the impediment? The blood/brain barrier is one.

Wai-Kwan Alfred Yung, MD
1:07:33:3

Blood brain/barrier, the really strong resistant ____ **(1:07:37)**

Tacey Ann Rosolowski, PhD
1:07:37.9
Hmm.

Wai-Kwan Alfred Yung, MD
1:07:38.4
Of the --- of the tumor.

Tacey Ann Rosolowski, PhD
1:07:40.0
Wow.

Wai-Kwan Alfred Yung, MD
1:07:40.8
I don't think that there is one drug close to approval right now.

Tacey Ann Rosolowski, PhD
1:07:43.8
Wow. Why is the glioblastoma so resistant?

Wai-Kwan Alfred Yung, MD
1:07:47.8
I don't know.

Tacey Ann Rosolowski, PhD
1:07:48.7
That's part of what you're figuring out.

Wai-Kwan Alfred Yung, MD
1:07:50.3
That's what we're trying to figure out. Trying to figure out. But I sa --- I must say though I think, you know --- you know, I'm certainly very --- I mean over the years at Anderson, you know, I'm very appreciative in terms of the kind of investment the institution is --- has placed in o --- in brain tumor --- in the brain tumor group. And we have the largest brain tumor group in the country and probably the world because --- and --- and --- and this is the investment that started with Dr. [Charles] LeMaistre [Oral History Interview] and continued with Dr.[John] Mendelson [Oral History Interview] and now continuing with Dr. [Ronald] DePinho [Oral History Interview].

Tacey Ann Rosolowski, PhD
1:08:45.9
Tell me about the Moon Shots platform for glioblastoma.

Wai-Kwan Alfred Yung, MD
1:09:00.7
1.9
Well we don't have it yet.

Tacey Ann Rosolowski, PhD
1:09:02.2
Oh, really.

Wai-Kwan Alfred Yung, MD
1:09:03.3
We're not --- We are not, I mean --- as you know, the --- the six cancers that we've included in the Moon Shot, you know, initiative is melanoma, prostate, CML, AML, ovarian and woman cancer. The six cancers.

Tacey Ann Rosolowski, PhD
1:06:36.7
I had forgotten that glioblastoma was not part of it.

Wai-Kwan Alfred Yung, MD
1:06:38.6
Glioblastoma is not part of it.

Tacey Ann Rosolowski, PhD
1:09:39.8
Right.

Wai-Kwan Alfred Yung, MD
1:09:41.4
We --- The institution is, you know --- is going to extend, you know, ne --- this year --- is going to extend to include more cancer. So the Brain Tumor Group is, you know, working to put together a proposal.

Tacey Ann Rosolowski, PhD
1:10:03.1
Hmm. And what are your strategies for putting that together?

Wai-Kwan Alfred Yung, MD
1:10:13.9
I --- It, you know --- I think we --- we certainly want --- is looking at, you know, the --- the expertise that we have in terms of drug development and also, you know, immunotherapy. Brain tumor is --- especially glioblastoma, you know, has some prior success in ap --- in applying immunotherapy to this disease and there has --- and also with the institutional immunotherapy platform that really opened up many --- many opportunities

Tacey Ann Rosolowski, PhD
1:10:55.3
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:10:57.2
to utilize that to attack brain tumors so we --- we are looking at how to really look both at new drug, signal transduction drug, cytotoxic drug, and immunotherapy how it amplifies each other.

Tacey Ann Rosolowski, PhD
1:11:13.9
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:11:14.5
You know, that's going to be, you know the --- the --- the strategy. We also have developed a --- I think I forgot to mention actually one of the other projects that we developed internally is a oncolytic virus

Tacey Ann Rosolowski, PhD
1:11:31.7
Hmm.

Wai-Kwan Alfred Yung, MD
1:11:32.9
Project, that I also have a part of it. It's --- Dr. Juan Fueyo is --- is one of the researchers in ou --- in our department that --- that he took the --- the --- the --- the --- the flu --- the influenza virus --- the adenovirus. They did a piece of the genome. They did 24 base pair from the genome. And, you know, according to --- to the discovery of Dr. Frank McCormick we deleted the 24 --- he deleted the 24 base pair and created a virus called Delta 24. With the deletion of that 24 base pair the virus only replicates in dividing cells but would not --- would not divide until --- until resting cell like normal neuron and normal astrocyte. So we make the virus only

kill tumor and not affecting the brain. And we --- we, you know, developed --- that --- that virus in the laboratory. We showed that the working animal model and we also had a grant from the --- from the NIH, from NCI to do all the preclinical studies that required by the FDA. And we get a grant from the Marcus Foundation, you know, with Dr. Bass' help to ----. And we finish the Phase 1 clinical trial to show very interested in activity in this virus. And --- And --- And so this is homegrown viral therapy direction. We call viral or viral therapy

Tacey Ann Rosolowski, PhD
1:13:26.1
Yeah. Interesting.

Wai-Kwan Alfred Yung, MD
1:13:27.1
That will be integrated into the Moon Shot.

Tacey Ann Rosolowski, PhD
1:13:29.4
Hmm. What's you impression of the way the Moon Shots Program has been structured with it --- with it --- it's very different as I understand.

Wai-Kwan Alfred Yung, MD
1:13:50.6
It's very different. I --- I think, you know, the idea --- the idea that we should look at a disease in a very focused fashion and we also invest, you know --- you know, in a very high level and sort of like, you know, we must land on the moon. So we must make something happen. We've done put a lot of resources, put a lot of talent, and put a lot of research to make something happen. I think that's the right concept --- great concept. I don't think, you know --- without --- without that kind of, you know, investment you will make things happen slowly. With that kind of --- say I'm going to make a concentrated effort and I'm going to make big effort, big investment and put a lot of talents in it and w --- we'll make things happen fast. The question really is how selective we want --- can we really use the same strategy to many, many different cancers.

Tacey Ann Rosolowski, PhD
1:15:08.6
Hmm.

Wai-Kwan Alfred Yung, MD
1:15:09.6
Or we have to select --- be selective --- and if we have to be selective, how do we select?

Tacey Ann Rosolowski, PhD
1:15:24.8
I'm wondering too at a practical level since this is such a different way of putting together research. I can imagine there are some people who are glad in a certain way not to be part of the first Moon Shots and maybe to be applying in the second wave because they can kind of look at well that didn't work so well maybe thi --- I mean, were there lessons learned? Are there lessons that you learned by observing that first couple of years of Moon Shot so that you can tweak what you're imaging is going to happen with glioblastoma?

Wai-Kwan Alfred Yung, MD
1:16:02.1
Well I --- I think there is a lot of lessons learned.

Tacey Ann Rosolowski, PhD
1:16:04.8
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:16:05.2
And I observe it is, you know, whether you --- you know, whether we have over promise the community and the speed of things. And --- And --- And where the lesson learned in terms of how fast that we --- we can develop the infrastructure to support it. You know, how easy and how difficult to put the team together to make the team work together. You know, I think there's a lot of lessons learned in that.

Tacey Ann Rosolowski, PhD
1:16:46.5
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:16:47.0
You know, and of course I think, you know we can --- ____ ___ **(1:16:51),** you know, just like you said, that people may feel that it's better not to be in the first wave because, you know, more is given and more is demanded. You know.

Tacey Ann Rosolowski, PhD
1:17:03.9
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:17:04.8

If you're in the first wave you need to deliver quickly.

Tacey Ann Rosolowski, PhD
1:17:07.8
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:17:08.9
You know, you may not be --- I mean that's also what Dr. DePinho's emphasis is to say, you know, let's focus on something that has low-hanging fruit.

Tacey Ann Rosolowski, PhD
1:17:18.9
Right.

Wai-Kwan Alfred Yung, MD
1:17:19.3
When you do not have the low-hanging fruit

Tacey Ann Rosolowski, PhD
1:17:21.5
Uh-hmm.

Wai-Kwan Alfred Yung, MD
1:17:21.9
9.3
You know, you're not going to be able to deliver, you know, in the first few --- first three years.

Tacey Ann Rosolowski, PhD
1:17:29.5
9.7
Right.

Wai-Kwan Alfred Yung, MD
1:17:32.7
But the lesson also can be learned in what is low-hanging fruit.

Tacey Ann Rosolowski, PhD
1:17:38.5
I hadn't actually thought of that question. Yeah. Interesting. Is there is any low-hanging fruit or what is the low-hanging fruit in the arena of glioblastoma?

Wai-Kwan Alfred Yung, MD
1:17:54.4
We don't have low-hanging fruit.

Tacey Ann Rosolowski, PhD
1:17:56.5
Yeah. I kind of thought that might be your answer.

Wai-Kwan Alfred Yung, MD
1:17:57.6
Because if I --- if I define low-hanging fruit by something that I can change the survival of the brain tumor patient, you know, in a big way in the --- in the three year span, we don't have anything. If we define it just such a rigid way. If I --- If I'm defining it the --- if there --- is there a drug, is there a treatment, or is there an understanding of the biology that will allow me to save twice as many people in the next three years, I don't.

Tacey Ann Rosolowski, PhD
1:18:43.3
Hmm.

Wai-Kwan Alfred Yung, MD
1:18:43.8
To be honest, I don't.

Tacey Ann Rosolowski, PhD
1:18:45.0
Uh-hmm. So what is the fruit that y ---

Wai-Kwan Alfred Yung, MD
1:18:48.5
Do I have anything --- Do I have anything that I can move --- that'll move the response rate, you know, 10%, 15%. Yes, we have leads to work on. And then some of the immunotherapy, you know, antibody that we can get a hold on and we can --- we have opportunity there. Virus, opportunity there. Combination of several drugs will get --- you know, it's possible we learn more about those drugs. So, in --- in a way if we m --- if we're looking at, you know, --- it --- in the baseball analogy we're looking for a second base hit.

Tacey Ann Rosolowski, PhD
1:19:36.8
Hmm.

Wai-Kwan Alfred Yung, MD
1:19:38.0
We may --- We have. If we're looking for home run, we don't.

Tacey Ann Rosolowski, PhD
1:19:49.5
Well we're at two o'clock now and I --- I know you're a very busy person right now. So, is there is anything else you'd like to add for our session today?

Wai-Kwan Alfred Yung, MD
1:20:00.3
It's --- It's --- So no, I don't have anything that I am --- I --- I am. --- Now let me ask you, _____ **(1:20:06)** If you look back in the last session, I don't know whether you have really, you know, looked at the transcripts or any

Tacey Ann Rosolowski, PhD
1:20:16.5
That hasn't been transcribed yet.

Wai-Kwan Alfred Yung, MD
1:20:16.5
or --- or **just ____ ____ (1:20:16**

Tacey Ann Rosolowski, PhD
1:20:18.6
I --- I'm --- going by my notes.

Wai-Kwan Alfred Yung, MD
1:20:19.1
___ _____ ___ **(1:20: 19)** the mental, go back mentally to what we talk about from the last time, but I was --- I mean I was even less --- I mean I --- I actually have much better idea around this session.

Tacey Ann Rosolowski, PhD
1:20:34.5
Oh, okay.

Wai-Kwan Alfred Yung, MD
1:20:35.5

Then the last session.

Tacey Ann Rosolowski, PhD
1:20:36.1
Yeah.

Wai-Kwan Alfred Yung, MD
1:20:36.5
which, you know --- so I don't know what --- if you think back if there's anything that you want to go back. Any --- Any questions or anything that you want to go back

Tacey Ann Rosolowski, PhD
1:20:47.0
Nothing.

Wai-Kwan Alfred Yung, MD
1:20:47.0
that --- that we talked about last --- in our last session.

Tacey Ann Rosolowski, PhD
1:20:49.4
Nothing emerged. I mean --- I --- I, you know, as you notice I take a lot of notes and so I --- I typed all those up and I reviewed them. And if --- if things spring to mind that looked like they were kind of holes, I didn't come across any. I mean, I'll do the same with this session and we can follow --- we can fill in. We do have another session.

Wai-Kwan Alfred Yung, MD
1:21:08.1
Okay.

1:21:08.3
scheduled. And I did want to say that after I looked at my notes from last time, you gave a beautiful, beautiful explanation of the impact of the move from departments to divisions in the institution. It was just really great. It was a great explanation of that piece of MD Anderson history. So I wanted to thank you for that. It was really terrific. Well I look forward to talking to you again next time.

Wai-Kwan Alfred Yung, MD
1:21:34.2
Okay. Good. Good. Good.

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Tacey Ann Rosolowski, PhD
1:21:35.2
Alright. And I am turning off the recorder at about three minutes after two.

Wai-Kwan Alfred Yung, MD
1:21:39.3
Great.