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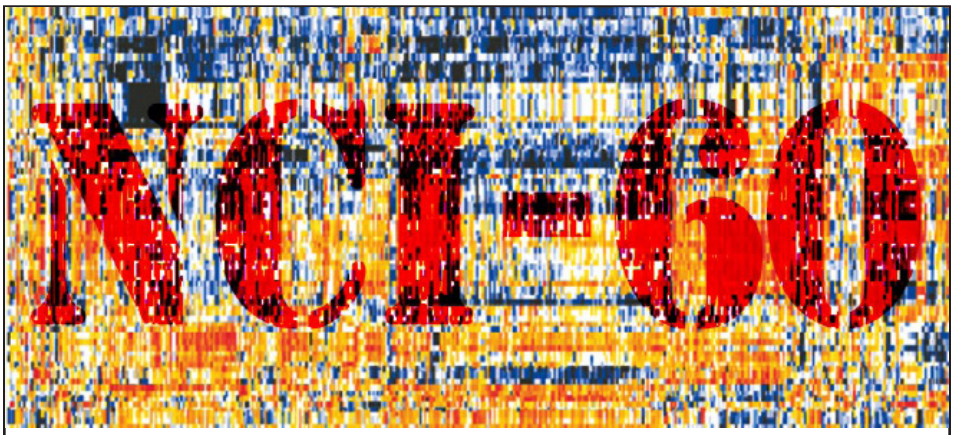

NCI Developing Mouse Models To Succeed NCI-60 Cell Lines

By Matthew Bin Han Ong

The NCI-60, a panel of 60 cancer cell lines that have become the Rosetta Stone for the development of anticancer drugs, may be entering its twilight years as NCI develops new, and more expansive, patient-derived xenografts, or PDX models.

For over 25 years, the NCI-60, a set of about a dozen tissue types—leukemia, non-small cell lung, small cell lung, colon, CNS, melanoma, ovarian, renal, and breast—have been used to perform initial screens on over 100,000 compounds.

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Conversation with The Cancer Letter

Doroshow: Evidence Suggests PDX Models Come Closer to Simulating Human Cancer

NCI is developing patient-derived xenograft mouse models as a potential substitute for the NCI-60 cell lines, a standard screen which experts say can no longer keep up with advances in cancer research and targeted molecular therapy.

(Continued to page 5)

Slamming the Door

Part VI: The Provost's Choice

By Paul Goldberg

After my conversation with Gilman, I called MD Anderson and asked to talk with somebody about the $18 million grant for a biotech incubator.

First, folks at the press shop told me that they view the controversy arising from the application as CPRIT's problem.

Let's see: the wife of president of MD Anderson gets a grant seemingly out of turn, causing a political disaster, and this is not an MD Anderson problem?

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NCI Developing Mouse Models To Replace NCI-60 Cell Lines

(Continued from page 1)

In the 1980s, the panel became the first tool to provide the answers to a fundamental problem in oncology: since growing implanted tumors in mice was too slow a process, how can experimental drugs be tested without subjecting patients to toxicity and risk?

When the NCI-60 was established, it became the standard procedure for researchers who wanted to test anticancer agents in highly controlled laboratory experiments. The panel removed patient-to-patient variability, and it was comprehensive: researchers could blast it with an array of drugs and identify which cell lines were responding.

Today, many experts say that cancer research has advanced beyond the capabilities of the screen—burgeoning data on cancer subtypes and targeted therapies mean that the old menu of NCI-60 cannot address the rapidly expanding range of research questions.

"Over the past five to 10 years, many large cancer centers and other organizations have assembled large collections of human cell lines for testing in a variety of different ways," said James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis and deputy director for clinical and translational research.

"It became clear over that time frame that it really would be a good idea, in order to better understand molecular heterogeneity across diseases, for the NCI to start considering what we should do going forward regarding the use of the NCI-60 cell line panel.

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"There are many strengths to the NCI-60; it also has weaknesses. Among those weaknesses is the fact that there are no pancreatic cancer cell lines. There are also only a limited number of hematological malignancies represented," Doroshow said to The Cancer Letter.

A conversation with Doroshow appears on page 1.

Doroshow is leading an effort to develop up to 1,000 new PDX models at the institute using NSG mice, a strain of immunodeficient inbred mice created by The Jackson Laboratory. He estimates that NCI has developed close to about 300 models, but will only make available 50 to 100 xenografts in the first release early this summer."

"These initial models will have passed NCI's quality-control procedures, and the rest will be available as soon as they pass those procedures," Doroshow said.

"It became clear that using a recently developed new strain of immunologically compromised mice—so-called NSG mice—one could use tumors, either biopsies or surgical samples, and have a higher "take rate" for developing xenografts directly from patients," Doroshow said.

"And so, we began to think about how we might change our procedures. Could we test drugs and provide resources to investigators more effectively, both in the context of xenograft testing, and with respect to the NCI-60 and other cell lines?"

The new patient-derived models repository, or PDM, may take years to fully develop, Doroshow said. NCI has no immediate plans to stop distributing the NCI-60, contrary to a Feb. 17 article in Nature announcing NCI's decision to "retire" the panel.

"It will take, almost surely, at least one to two more years to have sufficient number of cell lines and then to do the validation and quality control studies in terms of drug sensitivity testing, to be even in the position to consider whether or not what was developed is ready to allow us to begin to phase out the NCI-60," Doroshow said.

"It could be a year, it could be two years, it could be more. It really depends on the pace with which we'll be able to develop the lines and extensively test and validate the results in terms of drug sensitivity."

Data on the NCI-60 will remain publicly available on NCI's Cell Miner website, even if the panel is phased out in the future.

"Sometimes people don't realize something about the NCI-60 panel; while the number of cell lines is clearly smaller than many other large collections, the number of chemicals and drugs, which have been tested across those 60 cell lines is really unparalleled,"

Doroshow said.

"The wealth of this information, including the fact that all of those cells have had very extensive molecular characterization performed, makes the data quite valuable. We will absolutely maintain access to all of that information indefinitely."

NCI-60 Not Representative of Tumors in Vivo

The rationale for expanding NCI's set of cell lines to encompass some subtypes of cancer that weren't well represented before is convincing, said Keith Baggerly, a professor in the Department of Bioinformatics and Computational Biology at MD Anderson Cancer Center.

"The NCI-60 was and is a standard panel," Baggerly said to The Cancer Letter. "For example, we might want to look at more melanoma cell lines that have BRAF mutations where we have a drug for it. We might want to look, if possible, more at breast cancer cell lines that aren't just breast cancer—they're triple-negative, or ER+ or whatever—basically, broken down by subtypes we know exist, and have different treatment outcomes.

"Some of those are partially represented in the NCI-60, but by no means all, so there is a definite argument for expanding."

Baggerly's work with cell lines exposed Anil Potti's fraudulent genomic research at Duke University.

"I'm very familiar with this, because this was the story being sold as part of the Potti fiasco," Baggerly said. "They said, 'We looked at this panel of cell lines, and what we've been able to do, is for this drug, given that we know which cell lines responded and which do not, we will use the information from those cell lines to identify a molecular signature of response. By looking at a patient sample, we can tell whether they have that signature or not, we can tell whether this patient will respond to this drug.'

"Now, it didn't work, and actually, there has been a lot of effort trying to use these cell lines to predict patient response, and that has not produced a great deal of success. The first of which is because these 60 cell lines are from 11 different tissue types. You're expecting that drug sensitivity to be associated with a change that is so big, that it is large relative to the scale of difference between different tissue types. That's a pretty big jump, so the fact that you've got a mix of tumor types in there makes that hard."

The NCI-60 was established as a screen in the late 1980s—by the Developmental Therapeutics program at NCI—under the hypothesis that cell lines would represent their tissues of origin in terms of response to compounds tested.

While still useful, researchers say the NCI-60 cell lines on plastic are not representative of real human tumors in vivo, and that limits their reliability in studies that aim to predict clinical activity.

Researchers have been aware of the limitations of the NCI-60 for more than 10 or 15 years, Doroshow said.

"People have known this for a long time," Doroshow said. "It has been clear for at least that period of time, perhaps much longer, that once you keep a cell line, whether it's human or mouse or whatever, in passage for years on plastic, it's not that it changes all of its characteristics, but it certainly changes many characteristics that are different from the tumor from which it originated.

"The question was, 'What are we going to do about it?'"

In a return to early efforts aimed at propagating cancer cells outside the human body, the answer might come from mouse models.

"I would say that there is accumulating evidence from biological, pharmacological, and drug efficacy studies that show that these models can mirror the human condition," Doroshow said. "Give me another year before I'm sure. I'm close to being sure, but I think that the community would say that there are still additional questions to be answered."

Pros and Cons

Cell lines grown on plastic have a lot of deficiencies, said John Weinstein, professor and chair of the Department of Bioinformatics and Computational Biology at MD Anderson.

"As with every drug screening methodology, there are pros and cons as to what they provide and what they don't provide," Weinstein said to The Cancer Letter. "Most of the NCI-60 colon cancer lines are, in fact, quite coherent in their patterns of response. However, that is not the case for breast. We now understand that breast cancer consists of several diseases that are really no more like each other than if they came from different organs.

"There is value to what exists currently, but the PDX models are more immediately related to what goes on in clinical tumors. I might well have made the same decision [to use PDX models over cell lines] if it's a question of doing one or the other."

Weinstein was a part of a group of scientists that developed the NCI-60 system as it now functions.

"In 1991, I realized we could also use 'clustered heat maps,' which we introduced for the purpose, to predict the mechanisms of action of unknown

compounds by seeing how their patterns of activity fit in with those of over 100,000 other compounds tested," Weinstein said.

Other researchers who played major roles included: Kenneth Paull, former chief of the Information Technology Branch in the NCI Division of Cancer Treatment and Diagnosis; Robert Shoemaker, chief of the NCI Screening Technologies Branch; Tito Fojo, now a professor of medicine at the Columbia University Medical Center; William Reinhold, head of the Genomics and Bioinfomatics Group at the NCI Center for Cancer Research; and Yves Pommier, chief of the NCI Laboratory of Molecular Pharmacology.

Weinstein calls the NCI-60 a "60-square chess board" that played an important role in the development of bioinformatics and large-scale molecular profiling.

"The critique that the NCI-60 cell lines are not fully representative of human tumors in the patient is certainly correct," Weinstein said. "However, what they do provide is signatures of response, even if those signatures may represent different biology and pharmacology from what pertains in vivo. That information has been used by chemists and biologists over the 25-year period. Because the cells have not changed their properties much over the history of the screen, they provide coherent molecular and pharmacological databases.

"For example, if one tests a new compound in the NCI-60, its signature across the 60 cell lines can be compared with signatures of the more than 100,000 tested compounds to find those that are most similar—and therefore likely to have the same mechanisms of action and resistance. That analysis can be done using Kenneth Paull's COMPARE program or our methods based on clustering."

At the time, Weinstein realized that those signatures of response would be more powerful if the cells were profiled more broadly on the molecular level—RNA, DNA and protein.

"So I met with Bruce Chabner, the NCI clinical director at the time, and challenged him to list the genes that he would like to see characterized in the NCI-60," Weinstein said. "To my surprise, a week later, he sent me a list. That was the beginning of the NCI-60 molecular profiling project, headed by William Reinhold in my laboratory.

"It was the first large, public molecular profiling project on cancers. It provided a template for the Cancer Cell Line Encyclopedia, the Genomics of Drug Sensitivity in Cancer project, and other such programs. The CCLE and GDSC include lots of cell lines but, so far, only a modest number of drugs have been tested against them; the NCI-60 includes only a modest number of cell lines, but over 100,000 drugs tested."

Doroshow: PDX Models Stable and Sustainable

When the PDM repository is established, NCI will only distribute PDX tumor samples that have gone through no more than two or three passages, or cycles of propagation in mice.

"It's been clear for a couple years that once these tumors grow, after they first come from a patient, the characteristics are stable for about two, or three at most, passages in animals," Doroshow said. "It usually takes about four or five months or more to grow the tumor the first time and to grow up again takes, as it's passed from one animal now to another after the initial implantation takes on the order of six weeks to 12 weeks.

"What we are doing is banking tissues after no more than two or three passages. And that's what we will use for distribution."

It is unclear how much of the tumors' molecular characteristics will be lost in long-term passage.

"We suspect that they will lose some, and so we're basically trying to develop our systems so that what we give investigators are really early passage tumors," Doroshow said. "So as to make sure that the tumors are quality controlled and that they will grow when we send them to investigators, we will not distribute tissues that have been passed for years."

PDX tumors can be produced on a large scale, Doroshow said.

"A tumor will grow in the NSG mouse on average 65 to 70 percent of the time—we call it a 'passage zero' tumor that is implanted directly from patient materials," Doroshow said. "We can dramatically expand the number of animals implanted, which then gives us, in P2 or exponentially in P3, a much larger number of animals, from which we harvest tumors. It is from those animals that we can produce tumor fragments that can be molecularly characterized and stored.

"We can actually end up with hundreds and hundreds of individual vials of tumor that we know are going to be sufficient to regrow if you take them out of the freezer and send material to another laboratory.

"We have a set of standard operating procedures for banking early passage material that we can use

to restock the material that's going to be used for distribution."

The primary drawback of the PDX model is that immunotherapies are difficult to test on immunodeficient mice, Doroshow said.

"The immunological issue is of major consequence, because we would desperately like to have models that could be used to test these wonderful new immunotherapeutic approaches, and to be able to study combinations of immunotherapies with small molecules, and combinations of the immunotherapies themselves," Doroshow said.

NCI's new repository would include models for rare tumor subtypes, including adult sarcoma—a disease with limited therapeutic options and few readily available models.

"Our goal is to provide a repository that has a sufficient number of models so that we begin the process of representing the high degree of heterogeneity that exists as well as the wide range of molecular subtypes of tumors that exist in the real world," Doroshow said.

"I can't tell you that I know, unequivocally, how large, but I know that we need to be substantially larger than we are now, so that we can adequately provide resources for studying a wide range of malignancies.

"I think that's an important role for NCI to try to, wherever we can, facilitate the development of models for these diseases that really haven't been developed. And I think that's one of the things we can do, if we're successful, is to provide models for many of these underrepresented areas."

Conversation with The Cancer Letter

Doroshow: PDX Models Can More Closely Mirror Cancer

(Continued from page 1)

"The goal is to try to understand whether these new models will be more successful in providing a better reflection of the underlying biology in the context of the clinical history and treatment history of patients from whence the tissues came," said James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis and deputy director for clinical and translational research.

"We hope to be able to open the repository for distribution with somewhere between 50 and 100 xenografts in the first release. And we hope to have those available sometime early this summer.

"It will take, almost surely, at least one to two more years to have sufficient number of cell lines and then to do the validation and quality control studies in terms of drug sensitivity testing, to be even in the position to consider whether or not what was developed is ready to allow us to begin to phase out the NCI-60."

Doroshow spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: *There has been some talk about NCI's plan to retire the NCI-60 cell lines and replace them with PDX models. What is NCI's thinking on this?*

James Doroshow: Over the past five to 10 years, many large cancer centers and other organizations have assembled large collections of human cell lines for testing in a variety of different ways. It became clear over that time frame that it really would be a good idea, in order to better understand molecular heterogeneity across diseases, for the NCI to start considering what we should do going forward regarding the use of the NCI-60 cell line panel.

There are many strengths to the NCI-60; it also has weaknesses. Among those weaknesses is the fact that there are no pancreatic cancer cell lines. There are also only a limited number of hematological malignancies represented. So we started considering how we might provide better service to the community in terms of drug screening, by developing in vitro models that were more relevant.

Approximately three to four years ago, the first publications appeared demonstrating that there were some new techniques for developing human cell lines. One was the Georgetown technique for producing conditionally reprogrammed cell lines; the other, developed by Hans Clevers, is a methodology for producing organoid cultures. Both of these technologies suggested that one might be able to be more successful in terms of turning tumor biopsies and surgical samples into cell lines that more accurately represented the molecular characteristics and clinical characteristics of the patients from whom those cell lines were developed.

At the same time, it became clear that using a recently developed new strain of immunologically compromised mice—so-called NSG mice—one could use tumors, either biopsies or surgical samples, and have a higher "take rate" for developing xenografts directly from patients. And so, we began to think about how we might change our procedures. Could we test drugs and provide resources to investigators more effectively, both in the context of xenograft testing, and with respect to the NCI-60 and other cell lines?

So we began to develop our capacity to produce

patient-derived xenografts. The idea at the time, and I think it has proven to be a good one, was to determine whether or not it was possible for the material that you could get from a single patient—we started using biopsies taken from patients in my clinic at the NIH clinical center, but then it broadened out—could we get enough material to at the same time produce a cell line and a xenograft from each patient?

The idea was that if we were successful, then perhaps having both kinds of models available with the appropriate level of clinical annotation that hasn't been routinely available in the past in terms of cell lines that you can buy—would it be possible to do screening in vitro, and then immediately go and study in vivo the solid tumor model made from the same patient's tumor. Could that speed up the drug development process, and more importantly, better reflect the clinical situation than current models that we had been using?

In addition, my colleagues at the NCI, from the Division of Cancer Biology, suggested that: If we are going to try to produce new tumor cell lines, and we were getting clinical biopsies or surgical material, would it be reasonable to at the same time to try to separate from tumor cells the cancer-associated fibroblasts, because we know that those cells dramatically affect the growth of tumors in vivo. No repository of such cells exists, to the best of my knowledge. If we were separating the tumor cells from the fibroblasts, perhaps we should purify both populations to be able to give them to investigators to better understand the interactions between the tumor microenvironment and the tumor cells themselves.

We have been working for about three years; however, we've taken in many more tumor samples for the last year and a half, and have been relatively successful in producing both the solid xenografts and cell lines and fibroblasts to try to develop this repository.

The goal is to try to understand whether these new models will be more successful in providing a better reflection of the underlying biology in the context of the clinical history and treatment history of patients from whence the tissues came.

MO: *What is the timeline on the NCI-60 and the new models?*

JD: One of the issues involved in doing all of this is the extensive quality control procedures that we've developed and that we go through both for the solid tumor models and the cell lines—because the notion is that, if we're going to be in the business of distributing these materials to investigators, we want to be very sure of what it is that we are producing and distributing. As well, it's not just the cells and the xenografts that we're distributing; we're also conducting baseline studies of the whole exome sequences of these materials.

We're also doing RNA-seq and a variety of other tests, so that when we go live and when individuals ask to obtain these materials from us, they will be able to select from a menu of models on our website, and they'll be able to look at the time that the models are available, we hope, at the whole exome sequence data and the RNA expression data to choose what models they want to work with. All of this will be provided as part of the package in the repository. Of course, it takes time to do all that testing, which we don't do until the models have been certified and quality controlled.

We hope to be able to open the repository for distribution with somewhere between 50 and 100 xenografts in the first release. And we hope to have those available sometime early this summer. There will be a certain number of tumor cell lines and fibroblast cell lines that we will also make available at that time. I don't know exactly how many we will make available yet, but what will happen is, once we start the process of distribution, as the models, in real time, become certified, they will go up on this website, and we will be able to distribute them to the community. It will take, almost surely, at least one to two more years to have sufficient number of cell lines and then to do the validation and quality control studies in terms of drug sensitivity testing, to be even in the position to consider whether or not what was developed is ready to allow us to begin to phase out the NCI-60.

It could be a year, it could be two years—it could be more. It really depends on the pace with which we'll be able to develop the lines and extensively test and validate the results in terms of drug sensitivity.

MO: *What are the implications of this transition for cancer researchers everywhere? What is your message to academic investigators and drug developers?*

JD: Sometimes people don't realize something about the NCI-60 panel. While the number of cell lines is clearly smaller than many other large collections, the number of chemicals and drugs, which have been tested across those 60 cell lines, is really unparalleled.

There are over 100,000 molecules that have been tested, and essentially, all or much of that information is publicly available. The wealth of this information, including the fact that all of those cells have had very extensive molecular characterization performed, makes the data quite valuable. Again, all of that information is publicly available.

We will absolutely maintain access to all of that information indefinitely. My colleague in the NCI

intramural program, Dr. Yves Pommier [chief of the Developmental Therapeutics Branch at the NCI Center for Cancer Research] has worked very hard with the Division of Cancer Treatment and Diagnosis to develop a really easy to use website that gives you much of the molecular characterization data for these cell lines: mutational profiles, RNA expression, many other things that have been done and stored.

What investigators very commonly do is, if they come upon a new gene that they don't know much about and want to study, or that they think might be interesting, they'll go to that website—we call it the Cell Miner website—and they'll query the database to find out: are there cell lines that have already been studied that have high levels of expression, or not, of that gene? Then, great, I can now find exactly what cell lines I want to use without having to search randomly and looking for these kinds of profiles.

So that's very useful, and it's a very cool piece of software that Dr. Pommier has developed, and that NCI provides as a service. That's going to continue.

What we hope to transition to is actually utilizing more highly clinically annotated cell lines for testing so that we can help the extramural community address clinical issues in drug development that depend on a knowledge of the molecular characteristics of the tissues under study. As one aspect of the whole issue of precision oncology, we need to basically have resources and reagents and cell lines and tissues available where it is known, in advance, what their molecular characteristics are, so you can more easily figure out in what tissues and in what cells you should study your question.

If you can obtain information that will focus your investigations, because you can go through a website to quickly say: "Oh, I'm studying gene X, look, that's really common in, say, breast cancer, or colon cancer, and common in these particular cell lines. In advance, I know I don't have to search or buy a lot of cell lines that are irrelevant to my studies. I can go specifically after what I'm interested in and hopefully speed up the timeframe required and the ability to answer the question."

MO: *And you're hoping to eventually achieve all of this with the PDX model?*

JD: We call it the PDM repository—Patient-Derived Models repository. There will be times when people will want tumor cell lines. There will be times when they will want actual tumors that they can put into immunocompromised mice to test in vivo. They might actually start with the cell lines, get a result, and then want to test it in vivo, and then hopefully be able to do it with tissues that may not be identical, but are much more closely matched than what they're able to do now.

MO: *When did researchers or NCI start realizing that the old tumor cell lines have become significantly different from their original states?*

JD: That kind of knowledge, that human cell lines, not just the NCI-60—we're talking thousands of cell lines that the ATCC (American Type Culture Collection) has in its repository or others have used—has been known for certainly more than 10 or 15 years. It has been clear for at least that period of time, perhaps much longer, that once you keep a cell line, whether it's human or mouse or whatever, in passage for years on plastic, it's not that it changes all of its characteristics, but it certainly changes many characteristics that are different from the tumor from which it originated.

So the whole point of this endeavor—and I want to make it very clear, this is not just an endeavor that the NCI is involved in. There is a big effort to develop an ovarian cancer PDX program; it's the largest in the world, at the Mayo Clinic, for example. And Memorial Sloan Kettering is developing a large program. There are other large institutions, such as Jackson Laboratories, that have led the way in the development of PDX models. We are all trying to do this because we want models, acknowledging that they are certainly not perfect, that are better than what we've been using before. That would obviously be helpful. Novartis and other pharmaceutical companies also have large libraries of these models that they use for their drug development activity, without question.

People have known this for a long time. The question was, "What are we going to do about it?" These new methods of developing organoids and conditionally reprogrammed cell lines which are different kinds of tumor cell cultures, are only, as I said, three or four years old.

MO: *In your work at NCI on the new and upcoming PDX models, what have you learned about two things, specifically: stability of the cells over time, and then sustainability—can it keep up with commercial demand in the future?*

JD: We're not doing this, of course, for commercial demand. It's not that we won't provide models to industry. We will. They are obviously capable of producing these models themselves. Our real goal in providing these models is to assist academic investigators. Obviously, there are institutions that have the capacity to do these things themselves—that's wonderful and we are highly supportive of that—but there are other cancer centers

that perhaps don't have the resources to do this, and we think that it would be very useful for the NCI to be able to provide these kinds of reagents and resources to investigators throughout the country to facilitate their work.

What we know—and I want to make sure that you understand I'm not saying anything that I'm personally taking credit for—it's been clear for a couple years that once these tumors grow, after they first come from a patient, the characteristics are stable for about two, or three at most, passages in animals.

It usually takes about four or five months or more to grow the tumor the first time and to grow up again takes, as it's passed from one animal now to another after the initial implantation takes on the order of six weeks to 12 weeks. After about three passages, the amount of human stroma—connective tissue, not tumor cells—with those tumors starts to be replaced by mouse connective tissue and stroma. And so most investigators—and we include ourselves in that category—if we're trying to develop a repository, what we are doing is banking tissues after no more than two or three passages. And that's what we will use for distribution.

So as to make sure that the tumors are quality controlled and that they will grow when we send them to investigators, we will not distribute tissues that have been passed for years. We don't know how much in the way of their molecular characteristics they will lose after long-term passage. We suspect that they will lose some, and so we're basically trying to develop our systems so that what we give investigators are really early passage tumors.

MO: *So you're saying that after the second or third passage, chimerism is an issue?*

JD: Well, yes. It's not chimerism in terms of the tumor. It's basically the human tumor microenvironment: the inflammatory cells, the immune cells, whatever had been there that came with the biopsy or the surgical sample. Those cells tend to be replaced by passages three, four, and five with mouse equivalents. And so that's why we hope to be able to grow and have been successful so far, enough tumors and bank enough early passage tissue to supply the extramural community with early passages of the tumors.

MO: *I've learned that before in vitro cell lines were established, scientists put them in mice first. Then they realized that it was more logistically convenient to grow cells in vitro. I know you said they are not for commercial demand, but how do the PDX models compare? How is it going to be sustainable, in that regard?*

JD: A tumor will grow in the NSG mouse on average 65 to 70 percent of the time—we call it a "passage zero" tumor that is implanted directly from patient materials. And then we take tumors from the mice where, initially, the tumor successfully grew, and we pass those into a much larger number of so-called "passage 1" or P1 animals. When it becomes clear that most of the P1 tumors are growing, we can start to do our complete quality assessment procedures. But also, we can dramatically expand the number of animals implanted, which then gives us, in P2 or exponentially in P3, a much larger number of animals, from which we harvest tumors. It is from those animals that we can produce tumor fragments that can be molecularly characterized and stored.

We can actually end up with hundreds and hundreds of individual vials of tumor that we know are going to be sufficient to regrow if you take them out of the freezer and send material to another laboratory. One of our quality control steps is to show that if we've frozen something for a period of time, we can take it out of the freezer and regrow the tumor.

If we can't, we will not send it to investigators. So you can geometrically increase the amount of material you need, as long as you retain a sufficiently large amount of earlier passage material. So we have a set of standard operating procedures for banking early passage material that we can use to restock the material that's going to be used for distribution.

MO: *Would you say that it's established, or there is a consensus that the PDX model is a lot more representative of tumors in their natural states compared to traditional cell lines?*

JD: I would not use the word "established." I would say that there is accumulating evidence from biological, pharmacological, and drug efficacy studies that show that these models can mirror the human condition. Give me another year before I'm sure. I'm close to being sure, but I think that the community would say that there are still additional questions to be answered.

MO: *This might be one of the additional questions: what measures do you have to show that these new PDX models are more representative of real human tumors than the in vitro cell lines?*

JD: I think that's apples and oranges, because we don't have the clinical data associated with most of the cell lines that have been used routinely in the past that would allow for direct comparisons. We don't know what those older cell lines were sensitive

to or resistant to when they came from the patient. We know now because they've been tested against so many different drugs.

I'll just quote from a talk that I heard from a Mayo Clinic investigator just two weeks ago. When they develop their ovarian cancer models from patients undergoing surgery, they know that many, if not most, of those women, by the time the model is established, will have already been treated with platinum or taxanes or other standard chemotherapy. They then can go back, because the patients have all been consented to do this, and say, "Okay, we know that on average, somewhere between 60 and 80 percent of women with stage III ovarian cancer will get an initial response to chemotherapy." That's well known. So the question then is, "In the patients where we grew a model, we'll know nine months after they gave us tissue for this model, whether or not they responded or didn't respond in real life to these drugs. Then if the models are treated with those same drugs, the responses in the animals can be retrospectively correlated with what happened to that patient's tumor growing in the patient.

And when they do that, it's not perfect, but they get a very high level of correspondence between what they observe initially in the patient and what they observe when they give the same drugs to the animals bearing that patient's model tumor. It's not 100 percent, but it's pretty good.

MO: *What other drawbacks might the PDX model have?*

JD: These are pretty clear. The number one drawback that I think most people would tell you is a consequence of using immunologically incompetent mice. Although this enhances the tumor take rate, this makes it very difficult, if not impossible, with the NSG mice as they are usually produced, to test immunotherapies.

So there is considerable effort going on in a variety of different institutions to try to figure out a sustainable way to reintroduce at least part, or parts, of human immune systems into these animals so that you could use the system to test all the new immunotherapies that are being developed. A lot of interest, some success, but there's a lot of experimentation to be done to understand if that's going to be possible and how that could best be done. The other drawback is—there's no question—these mice are very expensive.

I would say that those are the two biggest issues, but the immunological issue is of major consequence because we would desperately like to have models that could be used to test these wonderful new immunotherapeutic approaches, and to be able to study combinations of immunotherapies with small molecules, and combinations of the immunotherapies themselves. But until we overcome and learn how to best recreate a partial immune system in these animals, that's going to be a limitation.

MO: *When the day does come, when NCI has sufficient data on PDX models to justify phasing out the NCI-60, what steps might NCI be taking to help researchers cope with the transition?*

JD: We would, of course, not do this without providing a very substantial lead-time to the community, informing investigators about how this transition might occur, and developing a specific transition plan. As you know, one of the biggest issues with the current process is that people send us material for testing, which we do without charge. This is why so many molecules have been tested in the NCI-60 panel in the first place.

We will develop a substitute process for helping the community. Again, there are lots of chemists who routinely send us molecules for testing. We would like to be able to continue to offer that service to the extramural community with a new set of cell lines. We will have to develop the process to be able to do that, but this will be far in advance of any phase out. We actually hope to have services that we will make available to the extramural community that are far superior to what we offer now.

MO: *Do you think NCI's PDX registry will eventually become one the most comprehensive in the U.S.? Is that a goal?*

JD: Our goal is to provide a repository that has a sufficient number of models so that we begin the process of representing the high degree of heterogeneity that exists as well as the wide range of molecular subtypes of tumors that exist in the real world.

I can't tell you that I know, unequivocally, how large, but I know that we need to be substantially larger than we are now, so that we can adequately provide resources for studying a wide range of malignancies.

I do want to mention that one of our goals is to not only have a large number of models representing the heterogeneity in molecular subtypes, but also to try to go after relatively rare tumor subtypes. We made a special effort in the first two years to go after adult sarcoma samples, which are hard to grow, and are not readily available.

I think that's an important role for NCI to try to, wherever we can, facilitate the development of models for these diseases that really haven't been developed. And I think that's one of the things we can do, if we're

successful, is to provide models for many of these underrepresented areas.

MO: *How much funding is NCI allocating towards this effort?*

JD: This is a significant effort. It's a several-million-dollars-a-year effort. It takes money to do two things: we have to help acquire the tissues, because it costs money to do biopsies, and then it takes money to actually produce the models. What we have done is, rather than put a lot of new money into this, we have basically reallocated, stopped a variety of projects that we were previously doing, so that we could more carefully focus in this area. It's certainly several million dollars a year.

MO: *Will NCI be having conversations with any other parties outside NCI about the development of these PDX models? Is anyone else beyond NCI involved organizationally?*

JD: Number one, we're having a workshop at the end of March, which Dr. Dinah Singer [director of the NCI Division of Cancer Biology] and I organized. We've got about fifty investigators coming. Many of the world's experts in this area will be there to provide input as to how we ought to utilize and further develop this activity. We're hopeful that, with that input, we will be able to devise ways to expand this activity into collaborations across the extramural community.

MO: *Did I miss anything? Is there anything else that you'd like to address?*

JD: I have a clinic in the NIH Intramural Program that has been helpful in many ways, but it does not have a large throughput of patients. We would never have gotten to where we are now without the collaboration of over a dozen NCI-designated cancer centers as well as, importantly, our community affiliates, our NCORP sites.

We've obtained blood samples and tissues from many of our colleagues across the country. Again, we're not a large volume cancer center, we don't have 20,000 new cancer patients coming to Bethesda every year. But our networks have many patients who have been willing to provide tissue specimens with which we have been able to develop this repository.

I'd just like to express my appreciation to all of the cancer center directors, the directors of their tissue acquisition facilities, and the PIs of the NCORP sites, including minority NCORP sites, that have helped us, and I hope will continue to help us acquire the tissues that allow us to make these models. And we hope to give the models back soon, providing them to the community that has helped us produce them in the first place. I think that's really important.

Slamming the Door

Part VI: The Provost's Choice

(Continued from page 1)

DePinho was initially silent on the controversy, but after the Houston Chronicle published a hard-hitting editorial that laid out a series of questions about the grant, he responded with a letter that portrayed the central question in the controversy as a "difference of opinions."

"Some may choose to call our proposal 'research,'" he wrote in a letter submitted to the newspaper. "We call it business, and we are confident Texans will be the beneficiaries in the future. As one who has worked in the laboratory and the clinic and founded multiple biotechnology companies, I have learned that academic discoveries will only benefit patients if they are converted into approved commercial products."

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In an off-the-record conversation, our first, Gilman told me that the proposal wasn't reviewed by the MD Anderson provost, Ray DuBois.

This was surprising, because the role of the provost is to promote the academic mission of an institution. The rule of thumb in academic medicine is that the provost gets to sign off on any grant application that contains a budget. Plus, Gilman knew of only one way a grant application could be submitted to CPRIT, and that was through the portal, and at MD Anderson there was no way to do this except through the provost's office.

When I asked MD Anderson press office folks to give me someone to talk to, I got DuBois.

I understood that DuBois was in an unsustainable situation, and felt bad about pressing him on whether he reviewed the Chin grant proposal. The guy had enough troubles. Alas, I had to do it.

With my tape recorder rolling, DuBois and I engaged in an awkward verbal dance:

"I guess we should first establish whether the incubator proposal went through your office," I said.

There was silence. I could tell that DuBois was trying to decide what was more important to him: his good name or his job.

That pause was telling. I knew he would choose his good name. A liar wouldn't have required a pause.

"The incubator proposal was a joint effort with Rice [University], and my understanding is that it went

through the Rice [provost's] office in terms of being submitted, along with the Rice proposal."

A smoke screen. DuBois was buying time. Of course, he knew that I would follow up.

"So it didn't go through your office?"

"We have an office of grant administration and an office of grants and management, and since this was a joint effort with Rice, the institute team worked directly with the provost at Rice. I assumed that it was routed through the grants office at Rice, since it was a collaborative effort with them. However, I have not checked directly with Rice on this issue."

This had to be the truth, with a light smoke screen of caveats to quell anxiety, with an "I assume" thrown in.

"It did not go through the MD Anderson provost? That's unusual; isn't it?"

It was important to get this stated clearly, on record.

"We do process a lot of CPRIT grants that go to the scientific review panel," DuBois continued. "This is a new mechanism—the RFA just came out several months ago—and that was apparently the preferred mechanism. I believe the institute team had worked closely with CPRIT in formulating their application, and I think this was the preferred route."

Again, DuBois was saying, artfully but clearly, that he had nothing to do with it. That took courage.

"Preferred by whom?" I asked. "I would have thought that because this proposal has a budget, and the budget is an MD Anderson budget, you would have been given the opportunity to review it."

By now, I realized that DuBois was slowly starting to welcome the opportunity to state and restate publicly that he had nothing to do with this.

"Well, we do joint grants with a lot of other institutions. A lot of that comes as a subcontract. That is the mechanism used when we have multi-investigator grants that are led by some of these other institutions. You would have to ask CPRIT to understand that mechanism."

Since there were surely handlers on the line, or at least in the room, DuBois needed to make another half-hearted attempt at obfuscation.

"I was thinking more in terms of an MD Anderson question, I would have thought it would have gone through your office," I repeated, mostly because I could, to see how far DuBois would go. "I'm just surprised it didn't. Are *you* surprised it didn't?"

"Well, I don't know if I'm surprised, but this is the way that CPRIT and the individuals working on the incubator proposal worked it out."

I decided to signal to DuBois know that I understood his predicament.

"I'm just trying to establish which questions you are able to answer, because if it didn't go through your office…"

"It really didn't go through my office. That was the route that it took. I haven't discussed that with the CPRIT individuals, or people at Rice, or others."

That was a good one… True, DuBois hadn't spoken with CPRIT *individuals* (plural), but he had spoken with one *individual* (singular), and that individual's name was Al Gilman, when Gilman called informally to find out why CPRIT had received a major proposal in a manner that bypassed DuBois and the official portal used for submission of applications. Of course, DuBois couldn't have known that I knew this, and, of course, I was in no position to tell him.

Since DuBois seemed amenable to having the truth pulled out of him in conversation, I decided to ask him about his role in dealing with potential conflict of interest issues at MD Anderson.

I knew he was the guy in the middle, the official designated to say No to Lynda Chin.

"Wouldn't everyone's life be easier if Lynda Chin were working at, say, Baylor?" I asked.

"There was recognition by the University of Texas System and the executive vice chancellor, [Kenneth] Shine, when Lynda came on board of the potential conflicts of interest when you have a department chair in the institution and her husband as the president. You always worry about potential conflicts of interest, but we've tried to put things in place to alleviate those conflicts.

"And Lynda actually reports directly to Dr. Ken Shine. She doesn't report to Ron or to me—it's set up so that she reports to Dr. Shine.

"Obviously Dr. Shine and I confer on things and make sure that we are all on the same page. But that reporting relationship was set up from the very beginning, when Ron and Lynda came on board.

"The UT System has set up a sort of system-wide review panel made up of individuals from across the university system to look at those conflicts, to make sure that there is no problem there."

How would a group of this sort be able to handle conflicts on day-to-day basis?

I briefly considered following up, but decided to leave DuBois alone on this. However, I couldn't resist asking him about the Moon Shots.

"One other question, that I guess would fall under

your purview, is, with the teams of [MD Anderson] scientists now looking for five cancers to cure, or at least make a big dent in, it feels like you can't come up with a plan like that without restructuring an entire institution. And how is that working out?"

Here again, DuBois danced a lackluster jig, but told the truth. The idea was DePinho's, he said.

"There is a lot of excitement at the institution about using that approach," he said. "Clearly that is something that Ron brought here with his vision. And I would hate to speak for him, but clearly I do represent the institution, and the idea of selecting some higher priority areas is the idea of bringing a really comprehensive, multidisciplinary team together to try to tackle some of the issues related to individual cancers.

"What we've been doing so far is spending a lot of time bringing groups of MD Anderson faculty and staff together to talk about what it would take in some of these areas to really have a maximal impact.

"It's a different way of thinking about tackling these problems in academic centers around the country. We set up individual experiments to answer pretty

low-level questions about different types of cancers and different issues related to cancer biology. It's a very iterative process that depends on what the individual experimental results are from point A—and then the next experiment you design is to get to point B.

"This is actually taking a much broader look at these problems and trying to understand what it is about a certain type of cancer that we don't know. Something that, if we did know, we'd be able to make a transformative impact in. It's a difficult process.

"Typically, our faculty and others, and other cancer centers around the country, haven't thought about tackling the problem this way. So, clearly, we are still in the phase where we're developing our plans of attack and evaluating our strengths in different areas and in different types of cancers, and where we would be able to have the most impact in terms of the low-hanging fruit.

"We are sort of in the development phase of thinking about this. We're trying to formulate these questions and we haven't really gotten to the point where we've put a whole team together or selected individual types of cancers that we want to attack.

"I guess the simple answer is yes. It's a different way of thinking about things. I think it has the potential to be transformative—if we can get the right teams together and select the truly most impactful questions to answer.

"It's exciting to think about a single institution having such major impact on the disease. So there is enthusiasm across the campus. Individual faculty members are becoming involved in the strategic planning sessions.

"I have to be honest, we don't know exactly what to expect, because we've never done something like this before. But it could be transformative."

DuBois kept going, making more and more distance between himself and DePinho.

"It's quite different," he said about the Moon Shots. "I can't take any credit for the idea, because it's really Ron's idea, but I think it has a lot of potential if we select the right areas and are able to formulate the most needed questions."

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In an interview in January 2016, MD Anderson Executive Chief of Staff Dan Fontaine said a simple bureaucratic error was to blame for the manner in which MD Anderson Institute for Applied Cancer Science's grant proposal was submitted:

"Let me give you the benefit of both my view at the time, and also looking back on it. And there's some similarity between those two.

"I was always somewhat surprised that what really kind of appeared to be a clerical processing error between Eric Devroe [IACS executive director for

strategic alliances], who had recently been recruited, and [Jerry] Cobbs [CPRIT chief commercialization officer], on how to get the materials up to CPRIT, turned into as big of a deal as it did.

"Obviously, as it turned out, there were other facts at play. There were things that were going on that we didn't have anything to do with. But I remember at the time being somewhat struck by the fact that this was the first time we submitted a commercialization grant. And so, admittedly, and I think this came out in some of the stories that I was interviewed for.

"When we go back and look at it, we had not put the proposal through Ray DuBois's office, but when you look back and you look at the request for application, this being an incubator infrastructure that had called for a business plan—business plan sort of things usually came through my part of the institution, and in those days, even research budgets and grant budgets were also handled by our research finance group, which was in a reporting relationship with the CFO, as well as a dotted-line-reporting relationship to Ray DuBois.

"So, to me, the fact that it had not gone through Ray's office did not seem like that big of a deal, for that reason. But also, one of the things that never seemed to get mentioned in the dialogue back then, was that the application is only step one of the process.

"Once the application meets with a positive determination, and the grant is going to be awarded, there's a whole contracting process that goes on between the institution and CPRIT—and so certainly we would have gotten down into the details of the budgeting at that point in time. So I found that to be curious.

"The second thing was, as you know, because you reported on it, Eric [Devroe] had transmitted the material directly to Cobb at Cobb's suggestion. And I was always struck by the fact that if there was something wrong with that, then CPRIT would have easily said: You didn't put it through the right way. It has to be put through our portal."

I asked Fontaine whether, with the benefit of 20/20 hindsight, the application should have gone through the provost.

"Frankly, through 20/20 hindsight, if it had to be put through the portal, the only guy that knew how to do that was [Wesley] Harrott, who worked in DuBois's office, and we would have sent it through Wes through the portal and, two clerical mistakes made by a young guy working for IACS wouldn't have turned into what it did," Fontaine said.

"I think I may have made this comment to you and [Houston Chronicle reporter] Todd [Ackerman] both when I was interviewed, once this occurred. We looked at the process and said, 'If there's going to be more applications of a commercialization nature, it's probably for it better to go through both. But our thinking at that time was that it would go through the provost's office largely to go across Wes Harrott's desk, so it could go through the portal. Because it seemed that going through the portal was the most important thing to do, out of what we had learned."

Though the CPRIT grant was awarded, the money never changed hands.

"At the time that the consternation and the questions were being raised, things seemed to be going about internal workings at CPRIT that we were not a privy to," Fontaine said.

"It still became apparent that there was at least one constituency within CPRIT that felt like even though the RFA had specifically said that it was going to go through the commercial review group, that it needed to go through both the commercial review group and the scientific group.

"If the process was going to change to do that, we felt that it was important to be very clear that we were happy to let the process take place a second time and have whatever we had submitted go through both review processes.

"So we wrote a letter, as you may recall, to CPRIT and we suggested two things: kind of belt-and-suspenders. We said that, number one, whatever additional review process you want it to go through, please have it go through. And if there's questions raised, if there's more scientific information that is wanted, since this is supposed to be a business plan—if there's more scientific information that is wanted, we would be happy to supplement that as requested. So we would be happy to do whatever additional review process CPRIT wanted to do at that point in time.

Secondly, we also suggested that we would even allow CPRIT to hold the money in escrow for a year to see what kind of milestones we hit with progress on the grant.

They wrote us back, and said we'll put it through the additional review process, thank you very much, and we're not going to make you put it in escrow for a year because once we've gone through the reward process, we will make the award immediately.

"And I think it was a letter from [CPRIT Executive Director] Mr. [Bill] Gimson that said that. So at that point in time, we anticipated that there would be some sort of additional review process. As it turned out, I think in looking back, other things and other controversies at CPRIT began to arise. To my knowledge, they never put it through an additional process. To my knowledge, they never notified us whether they were going to put it through an additional process or not. We never resubmitted, because there was never an RFA or any communication to us.

"I know there were a couple of instances when we may of contacted them and said is there anything else—but, you'll recall shortly after that, the controversy grew to the point that the granting was stopped at some point in time. There were directives, etc. And we never got beyond that point. We never resubmitted; they never re-reviewed. And funds never changed hands."

Would MD Anderson officials have handled this matter differently today?

Was there a lesson to be learned?

"Well, hindsight being 20/20, I wouldn't have had two clerical errors made.

I didn't think it was a big deal at the time—still don't think it's a big deal; don't think it's what led to

anything else that went on with CPRIT," Fontaine said. "Obviously, as you know, the story took a completely different direction with a company that they had funded, Peloton, leading to further things that took place—including a criminal trial, where eventually there was an acquittal, by an Austin jury, of Cobb.

So in looking back, a couple of clerical errors. If I could do it differently, we would have understood the process a little bit better for commercialization grants. We would have submitted it through the portal. I don't know that DuBois's office would have had a lot to say one way or another.

"I suspect, given the way that Ray and I worked, he would have said, "Hey Dan, this looks like a business plan—could either you or your folks look at it?"

I don't know that that would have happened, but it seems to be the most logical thing that would have gone on. Ray and I worked closely on a number of different things in those days. But other than submitting it through the portal, I'm not sure I would have done anything different.

"Other than it going across Ray's desk and through Wesley's operation, I don't know that I would have done anything else differently, and I don't think we would have submitted anything else differently based upon what was in the request for applications at that point in time, which was calling for a business plan for infrastructure."

Indeed, submission through the portal was a requirement, and there is no question that DuBois would have demanded that this be done. In the process, the application would have been reviewed, to make sure that it contained all the information CPRIT required.

"As it turns out, having the benefit of 20/20 hindsight, if it had been successfully granted, and if we had gone through negotiations with CPRIT, I'm sure because in those days CPRIT was doing this and I think they'd still be doing it: When they give a grant they talk about whether or not—usually there's a term in there that if there's commercialization that comes out of the grant, CPRIT wants some way of retrieving their funds.

"In retrospect, not having to have CPRIT involved in some of our financial decisions for some of our commercializations that are coming up may prove to be to our financial advantage. It may be the least expensive $20 million that we ever turned down.

"There's just no way of telling that. It all depends on some of the commercialization opportunities that are going to come out of IACS in the future."

The question of how much money is coming through IACS—both costs incurred and revenues generated—warrants an examination.

Indeed, I recently filed a request for information under the Texas open records law.

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Bypassing the provost of your own institution is puzzling and unusual in the extreme.

"If a provost has heartburn about something, you want to hear it," Arthur Caplan, the Sidney D. Caplan Professor of Medical Ethics in the Department of Medical Ethics and Health Policy at the University of Pennsylvania, said to me at the time. "If you have animal experimentation or phase I research, you need to involve all the university and hospital officials that need to be aware be aware.

"You put the institution at risk when you go off course in terms of regular review procedures."

In a situation where a husband and wife team is employed in key positions at the same institution, the provost should play a more significant role, especially when research on human subjects and animals is involved.

A situation where a nepotism issues can arise requires more scrutiny rather than less scrutiny. "You can say, we would normally take it though the provost, but we are going to do something extraordinary because of a concern about a nepotism issue," Caplan.

Additional review is needed in case a provost is unable to say No to the president. "In any case, it's a mistake not to let the provost sign off on the institution's portfolio," Caplan said. "If they want to have a special committee look into conflicts of interest, I have no issue with that, but they should not reach out of the standard pattern.

"That creates the worst appearance."

But there was something else he said: "You can quote me on this: This is not going to end well."

I refrained from using this line in my story.

Next Week: Conversations with DePinho

National Academy of Medicine Publishes Report on Categorizing Different Ovarian Cancers

Ovarian cancer should not be categorized as a single disease, but as many different cancers involving the ovary, according to a report published by the National Academy of Medicine.

Questions remain on how and where various ovarian cancers arise, said the report that also presents research opportunities for reducing the number of women who are diagnosed with or die from ovarian cancers. Roughly two-thirds of women are diagnosed at an advanced stage when the cancer has already spread beyond the ovary, of which less than 30 percent survive past five years. The report was also sponsored by the Centers for Disease Control and Prevention.

"When we look at ovarian cancers at the molecular level, we can see that many of these tumors arise in other organs or cell types and then metastasize to the ovary," said report co-author Kunle Odunsi, deputy director and chair of gynecologic oncology at Roswell Park Cancer Institute.

"This is a striking finding that changes our fundamental understanding of ovarian cancer, but it also underscores how much we have yet to learn about ovarian cancer subtypes and their progression."

Furthermore, researchers do not have a complete understanding of how each subtype of ovarian cancer progresses, the report said. The committee publishing the report recommended that researchers and funding organizations design and prioritize research agendas to take into account the different ovarian cancer subtypes, and a top priority in research should be to determine the cellular origins and how the disease develops.

A family history of ovarian cancer, specific inherited genetic mutations, and certain hereditary cancer syndromes have strong links with risk for ovarian cancers. The BRCA1 and BRCA2 genes, also associated with increased risk for breast cancer, are among the most recognizable ovarian cancer risk-related genes, the committee said, and that multiple professional groups recommend all women diagnosed with an invasive ovarian cancer receive genetic testing and counseling.

The committee called for the development and implementation of strategies to increase genetic counseling and testing as well as testing relatives for known inherited genetic predispositions to the disease. Researchers, clinicians, and commercial laboratories should also determine the analytic performance and clinical utility of testing for other gene mutations beyond BRCA1 and BRCA2, the committee said.

"The study reinforces the need for genetic counseling and testing," said Odunsi. "Every woman with ovarian cancer should be referred for genetic counseling and potential testing. This has implications for identifying risk for other family members and for therapy selection. There are new treatments available to women with mutations in genes responsible for inherited predisposition to ovarian cancer."

Regarding screening, current imaging technologies are effective at detecting pelvic masses but are limited in their sensitivity to detect small, early lesions, the report said, but current screening methods have not had a substantial impact on overall death rates for general or high-risk populations. The committee recommended that researchers and funding organizations focus on the development and assessment of early detection strategies that extend beyond current imaging technologies and biomarkers.

The committee also found considerable variability in the quality of care provided to women with ovarian cancers nationwide. Several organizations have developed national standard-of-care guidelines for the assessment and treatment of women with both newly diagnosed and recurrent ovarian cancers, but less than one-half of women with ovarian cancer receive such care.

Being treated by a gynecologic oncologist and having treatment in a high-volume hospital or cancer center are the two most significant predictors of whether a woman with ovarian cancer will receive the appropriate standard of care and have better health outcomes, but access to such care can be a challenge, the report said. To reduce disparities in care, the committee recommended that clinicians and researchers investigate methods to ensure the consistent implementation of current standards of care – such as access to specialists, surgical management, a chemotherapy regimen, and universal genetic testing.

The full report, Ovarian Cancers: Evolving Paradigms in Research and Care, is available from the National Academies Press.

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Funding Opportunity

FDA Providing $2 Million for Natural History Studies in Rare Diseases

By Sarah Pavlovna Goldberg

FDA will provide $2 million in two to five research grants for the study of the natural history of rare diseases. The objective of the grants is to expedite the development of products for these conditions.

The Feb. 29 announcement marks the first time FDA will provide funding through its Orphan Products Grants to collect data on the progression of specific rare diseases in individuals over time.

Rare diseases, as defined by the Orphan Drug Act, are diseases that have a prevalence of less than 200,000 persons in the U.S. Altogether, about 7,000 known rare diseases affect approximately 30 million Americans.

The studies will focus on characterizing the natural history of the diseases, identifying subpopulations, developing and showing the validity of clinical outcome measures, biomarkers and companion diagnostics.

Information on the progression of many rare diseases is often unavailable. Natural history is the course a disease takes from the time immediately prior to its inception, progressing through a pre-symptomatic phase and different clinical stages, to a final outcome in the absence of treatment.

"Rare diseases are often poorly understood," Gayatri Rao, director of the FDA Office of Orphan Products Development, within the Office of Special Medical Programs, said in a statement. "Not understanding how a rare disease progresses is often a major obstacle in the development of life-saving medical products. Information about a disease's natural history can aid in clinical trial design, identify study endpoints and lead to faster, better trials—hopefully leading to new and effective diagnostics and treatments."

The grants will provide:

• A maximum of $400,000 in total costs per year for up to five years for prospective natural history studies involving clinical examination of affected individuals.

• A maximum of $150,000 in total costs per year for up to two years for retrospective natural history studies (i.e., chart review) or survey studies (i.e., questionnaire).

Congress appropriates funding for the study of rare diseases. FDA uses these funds for this new Orphan Products Natural History Grants Program as well as the existing Orphan Products Grants Program for clinical trials. The program has provided over $350 million to fund more than 570 new clinical studies and has supported the marketing approval of more than 55 products since its creation in 1983.

Grant applications are due by Oct. 14, 2016. Funding for grantees is expected to begin in March 2017.

In Brief

Massagué Wins Pezcoller-AACR International Research Award

JOAN MASSAGUÉ received the International Award for Cancer Research, presented by the **Pezcoller Foundation** and the **American Association for Cancer Research**.

Massagué is director of the Sloan Kettering Institute and Alfred P. Sloan Chair at Memorial Sloan Kettering Cancer Center. He will be presented the award at the AACR annual meeting in New Orleans next month.

Massagué, who is also a professor at Weill-Cornell Graduate School of Medicine Sciences, is being recognized for his discoveries in TGF-β biology, now considered fundamental to the understanding of cellular physiology.

His efforts delineated the TGF-β signaling pathway and its mechanism of action from receptor activation to the regulation of key target genes. Furthermore, his studies demonstrated how TGF-β can be both a tumor suppressor and promoter of metastasis.

Massagué will present his lecture, "Latent Metastasis," April 17, during the annual meeting.

The Pezcoller Foundation-AACR International Award for Cancer Research was established in 1997 to annually recognize a scientist who has made a major scientific discovery in basic cancer research or who has made significant contributions to translational cancer research.

Massagué has been an active member of the AACR since 1990. He served on the AACR Board of Directors from 2009 to 2012, and is currently a scientific editor of Cancer Discovery.

He has been recognized with myriad honors throughout his career, including the 2009 AACR G.H.A. Clowes Memorial Award, the 2008 AACR Distinguished Lectureship in Breast Cancer Research, the Pasarow Prize, and the Frontiers Prize in

Biomedicine from the BBVA Foundation, and elected membership to the National Academy of Sciences and National Academy of Medicine, and the Spanish Royal Academies of Medicine and of Pharmacy. Before joining the faculty at Memorial Sloan Kettering in 1989, he was an associate professor of biochemistry at the University of Massachusetts Medical School.

DAVID WEINER was named executive vice president of **The Wistar Institute**, director of the Vaccine Center, and the W. W. Smith Endowed Chair in Cancer Research.

Weiner will also contribute tumor immunology-focused research as a professor in Wistar's Translational Tumor Immunology program. Previously, Weiner was a professor of pathology and laboratory medicine at the University of Pennsylvania School of Medicine.

"David will bring to Wistar a 30-year career of groundbreaking achievements and unprecedented innovation that have revolutionized the way we think about vaccines for disease prevention as well as cancer vaccines for treatment," said Dario Altieri, Wistar president and CEO.

"I very much look forward to working with David and embrace his clear vision for immunology, virology and vaccine research to shape the future of Wistar science in solving some of the most complex biological problems in infectious diseases."

Weiner was elected as a fellow to both the American Association for the Advancement of Science in 2011 and the International Society for Vaccines in 2012. He is the recipient of the NIH Director's Transformative Research Award and received the Vaccine Industry Excellence Award for Best Academic Research Team in 2015 at the World Vaccine Congress.

Weiner was honored with the prestigious Hilleman Lectureship in 2015 at the Children's Hospital of Philadelphia Grand Rounds session and received a Stone Family Award from Abramson Cancer Center for his work on DNA vaccines for cancer immune therapy.

DOUGLAS LEVINE was named director of the Division of Gynecologic Oncology at the Laura and Isaac Perlmutter Cancer Center at **NYU Langone Medical Center**, effective May 15.

Levine joins NYU Langone from Memorial Sloan Kettering Cancer Center, where he served as an attending physician and head of the Gynecology Research Laboratory.

He also served as a translational scientist on many national clinical trials determining what genomic alterations are associated with response to targeted therapies. There, he helped discover universal mutations in SMARCA4 that drive small cell carcinoma of the ovary.

Levine has been active within the NIH-sponsored Cancer Genome Atlas project. He serves as co-chair of the ovarian, endometrial, and uterine carcinosarcoma disease working groups and provides a translational focus to the genomic analyses of these projects. In addition, Levine is a member of the Scientific Advisory Committee of the Ovarian Cancer Research Fund, the Clearity Foundation, and the Honorable Tina Brozman Foundation, and has authored or co-authored more than 150 peer-reviewed publications and two textbooks.

He has been awarded the American Congress of Obstetricians and Gynecologists Mentor Award; served as co-chair of the American Association for Cancer Research Special Conference on Ovarian Cancer; received the 2013 Foundation for Women's Cancer Excellence in Ovarian Cancer Research Prize; and was recently named the assistant dean of the Department of Defense Ovarian Cancer Academy.

LAUREN STREICHER joined **Northwestern Medical Group** as medical director and gynecologist for Northwestern Medicine's Center for Sexual Health, anticipated to open in late 2017.

Streicher is an associate clinical professor of obstetrics and gynecology at Northwestern University Feinberg School of Medicine.

Streicher has appeared in numerous national and local media outlets discussing all aspects of women's health and is a recurring contributor on The Today Show, ABC-7's Windy City Live, The Steve Harvey Show, The Dr. Oz Show and The Meredith Vieira Show. She is the author of two books: Sex Rx: Hormones, Health and Your Best Sex Ever (2014) and The Essential Guide to Hysterectomy (2004 and 2013). Streicher is also a blogger for EverydayHealth.com.

Streicher is a fellow of the American College of Obstetricians and Gynecologists; a diplomat of the American Board of Obstetrics and Gynecology; and a member of the Sexual Medicine Society of North America, Inc., the International Society for the Study of Women's Sexual Health, the Scientific Network on Female Sexual Health and Cancer, and the Association for Gynecologic Laparoscopy. She is also a certified menopause practitioner of the North American Menopause Society.

MICHAEL BUKOSKY was appointed chief operating officer of **USMD Holdings Inc**., and will oversee daily operations of therapeutic, diagnostic and centralized services, including hospital services, cancer treatment centers, clinical and pathology labs, imaging, human resources, contracting, revenue cycle, marketing and communications and IT.

Bukosky will retain his position as president of USMD Physician Practice Management, in which he oversees operations of USMD's Physician Practice Management group, comprising nearly 50 clinics and more than 250 physicians and associate practitioners.

Prior to joining USMD, Bukosky served as chief executive officer of University of Louisville Physicians, the largest multi-specialty physician practice group in Louisville. Before that, Bukosky was executive vice president and chief administrative officer of Carle Clinic Association in Urbana, Ill.

Bukosky is active in the American Medical Group Association, a trade association representing more than 160,000 physicians. He has served as a board member since 2005 and served as the organization's chairman of the board, secretary and treasurer.

THE INTERNATIONAL CANCER GENOME CONSORTIUM authorized its 1,000th user, giving them access to the Consortium's Controlled Access datasets.

ICGC datasets that catalogue tumor-specific mutations are unrestricted and freely available to the scientific community. However, the consortium developed an authorization process to distribute clinical and inherited genetic data associated with unique individuals in order to minimize the risk of identification of donors based on computer analyses of demographic, clinical or genetic data.

Controlled Access datasets are scientifically valuable in revealing potential diagnostic, prognostic or drug-response biomarkers that could inform cancer treatment decisions, according to the ICGC. ICGC Controlled Data users are mainly from North America (49 percent), Europe (33 percent) and Asia (14 percent). The proportion of academic to industry users is approximately 87 percent to 13 percent.

IBM and the **New York Genome Center** will collaborate on a comprehensive and open repository of genetic data to accelerate cancer research, using Watson technology. The collaboration was announced at the White House's Precision Medicine Initiative Summit.

IBM and the center will build the capacity to house the contributed data, train Watson's cognitive computing capabilities for genomic analysis, and enable the center's member institutions and other research collaborators to sequence and analyze tumor DNA and RNA.

In the first phase of the project, the two organizations will examine genetic information from 200 cancer patients to compare how different types of sequencing might impact possible treatment options, examining whole genome and whole exome sequencing as well as clinical panels currently in wide use.

Sequencing and clinical data will be fed into Watson to accelerate and focus reviews of massive amounts of medical evidence to help identify existing drugs that may be candidates to target patients' cancer-causing mutations.

VANTAGE ONCOLOGY LLC will be acquired by **McKesson Specialty Health**. Vantage is a provider of radiation oncology, medical oncology, and other integrated cancer care services.

"We are excited about what Vantage can accomplish as part of the McKesson platform," said Michael Fiore, chief executive officer and co-founder of Vantage. "By joining together, we will be able to offer an exceptionally broad set of services to patients and physicians, and strengthen our leadership in community-based oncology and value-based cancer care."

Vantage Oncology was founded in October 2002 and was based in California. It will continue to operate independently until the deal is closed.

Drugs and Targets

Imbruvica Granted 5th Approval, For First-Line CLL Patients

FDA approved Imbruvica (ibrutinib) as a first-line treatment for patients with chronic lymphocytic leukemia.

The approval is based on data from the randomized, multi-center, open-label phase III RESONATE-2 trial, which evaluated the use of Imbruvica versus chlorambucil in 269 treatment-naïve patients with CLL or small lymphocytic lymphoma aged 65 years or older. The data were previously presented at the annual meeting of the American Society of Hematology in December 2015 and also published in The New England Journal of Medicine.

Imbruvica is jointly developed and

commercialized by Pharmacyclics LLC, an AbbVie company, and Janssen Biotech Inc.

Imbruvica is now approved to treat CLL patients regardless of their treatment history, as well as to treat high-risk CLL patients with del17p. This is the fifth treatment indication for Imbruvica.

RESONATE-2 showed Imbruvica significantly improved progression-free survival and overall response rate compared to chlorambucil in treatment-naïve patients aged 65 or older with CLL or small lymphocytic lymphoma. The data indicated an 84 percent reduction in the risk of death or progression in the Imbruvica arm versus the chlorambucil arm (HR=0.161 [95% CI, 0.091-0.283]). Median PFS was not reached for Imbruvica, versus 18.9 months for chlorambucil (95 percent CI: 14.1, 22.0).

Health Canada approved Opdivo injection (nivolumab), the first and only immuno-oncology therapy approved in Canada for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy.

The approval was made under the Health Canada Priority Review process, after having met the criteria of substantial evidence of clinical effectiveness providing an improved benefit/risk profile over existing therapies. The data to support the approval was based on CheckMate-017 and CheckMate-057 trials and both phase three trials were stopped early when an independent data review showed evidence of superior overall survival in patients receiving Opdivo over chemotherapy treatment.

The results of the CheckMate-017 trial demonstrated superior overall survival in previously treated metastatic, squamous-cell NSCLC compared to chemotherapy, with a 41 percent reduction in the risk of death.

Opdivo-treated patients lived 3.2 months longer, with the median OS at 9.2 months in the Opdivo arm (95% CI: 7.3, 13.3) and 6.0 months in the docetaxel arm (95% CI: 5.1, 7.3). A one-year OS rate showed survival was almost double of that compared to docetaxel chemotherapy, 42 percent (n=135, 95% CI: 34-50) vs 24 percent (n=137, 95% CI =17-31).

In CheckMate-057, Opdivo demonstrated superior overall survival in previously treated metastatic non-squamous NSCLC compared to chemotherapy, with a 27 percent reduction in the risk of death. Opdivo-treated patients lived 2.8 months longer, with the median OS at 12.2 months in the Opdivo arm (95% CI: 9.7, 15.0) and 9.4 months in the docetaxel arm (95% CI: 8.0, 10.7). The overall survival rate at one year was 51 percent (95% CI, 45 to 56) with Opdivo and 39 percent (95% CI, 33 to 45) with docetaxel.

Treatment-related adverse events occurred less frequently with Opdivo than docetaxel. The most frequently reported drug-related AEs were fatigue, nausea, rash and decreased appetite in patients treated with Opdivo.

Opdivo was first approved in September 2015 for the treatment of adult patients with metastatic BRAF V600 wild-type melanoma. Opdivo currently has regulatory approval in 46 countries including the U.S., Japan, and in the European Union.

FDA granted orphan drug designation to the WT1 cancer vaccine developed by SELLAS Life Sciences Group for the treatment of patients with malignant pleural mesothelioma.

SELLAS recently reported positive results of a phase II trial of its WT1 vaccine in MPM patients, showing that overall survival improved and progression-free survival doubled. Based on these findings, SELLAS intends to initiate a phase IIb/III trial of its product candidate in patients with MPM by the third quarter of this year.

"We are thrilled with the progress of our WT1 vaccine program, which has received two orphan designations in the last two months and is advancing into pivotal studies in AML and in MPM patients in 2016, as well as further phase II studies including in multiple myeloma, ovarian cancer, glioblastoma multiforme, and a series of genetically defined cancers in a basket-trial design," said Angelos Stergiou, chairman and CEO of SELLAS.

The European Medicines Agency granted an Orphan Drug Designation to venetoclax, an investigational, oral B-cell lymphoma-2 inhibitor, for the treatment of acute myeloid leukemia. Venetoclax is being developed by AbbVie in partnership with Genentech and Roche.

The EMA previously granted Orphan Drug Designation to venetoclax for the treatment of chronic lymphocytic leukemia. Orphan Designation is granted to therapies aimed at the treatment, prevention or diagnosis of life-threatening diseases that affect no more than five in 10,000 persons in the European Union and for which no satisfactory therapy is available.

"There have been very few treatment advances for patients with AML who are older than 60, the

patient population that is most often affected by this aggressive and life-threatening cancer," said Michael Severino, executive vice president of research and development and chief scientific officer at AbbVie.

FDA recently granted venetoclax both Breakthrough Therapy Designation and Orphan Drug Designation for the treatment of patients with AML. The FDA has also granted venetoclax Breakthrough Therapy Designation for the treatment of CLL in previously treated patients with the 17p deletion genetic mutation and in combination with rituximab for the treatment of patients with relapsed/refractory chronic lymphocytic leukemia.

Additionally, venetoclax recently received validation from the EMA for its Marketing Authorization Application for the treatment of CLL patients with 17p deletion or TP53 mutation, as well as acceptance by Health Canada for the New Drug Submission for the treatment of patients with CLL who have received at least one prior therapy, including patients with 17p deletion.

The BCL-2 protein prevents apoptosis of some cells, including lymphocytes, and can be over expressed in some cancer types. Venetoclax is designed to selectively inhibit the function of the BCL-2 protein. Venetoclax is currently being evaluated in phase III clinical trials for the treatment of relapsed/refractory CLL, along with studies in several other cancers.

FDA and the European Medicines Agency have both granted Orphan Drug Designation to FLAG-003 for the treatment of glioma, sponsored by FLAG Therapeutics.

Orphan status is granted by the FDA to promote the development of products that demonstrate promise for the treatment of rare diseases, those which affect fewer than 200,000 Americans annually. Orphan drug designation entitles FLAG Therapeutics to seven years marketing exclusivity following product launch in the United States and 10 years marketing exclusivity in the EU, and enables the company to apply for research funding, tax credits, a waiver from FDA user fees, and access to the central authorization procedure within the European Union.

FLAG-003 is a small molecule which exerts both cytotoxic and cytostatic activity due to two mechanisms of action. It possesses cytotoxic anti-tubulin activity by binding to the colchicine site of tubulin causing microtubule depolymerization. It also possesses anti-angiogenic activity through binding and inhibition of RTK receptor tyrosine kinase activity.

Merck KGaA, Pfizer and Verastem entered into an agreement to evaluate avelumab, an investigational fully human anti-PD-L1 IgG1 monoclonal antibody, in combination with Verastem's VS-6063, an investigational focal adhesion kinase inhibitor, in patients with advanced ovarian cancer.

Avelumab is currently under clinical investigation across a broad range of tumor types. The phase I/Ib clinical trial is expected to begin in the second half of 2016. Financial terms of the agreement have not been disclosed.

"Recent research shows that FAK inhibitors could be beneficial in combination with immuno-oncology agents. We are excited to be working with MerckKGaA, Darmstadt, Germany, and Pfizer to build upon the early clinical signals observed in patients with ovarian cancer receiving combination therapy with VS-6063," said Robert Forrester, Verastem president and CEO.

NanoString Technologies Inc. entered into a collaboration agreement with Merck, through a subsidiary, to develop and commercialize a novel diagnostic assay to predict response to Keytruda (pembrolizumab), Merck's anti-PD-1 therapy.

Under the terms of the collaboration agreement, NanoString will be responsible for seeking regulatory approval for and commercialization of the diagnostic test. NanoString will be eligible to receive up to $24 million for technology access and near-term milestones, in addition to development funding and other potential regulatory milestone payments.

Previously, the companies had engaged in a research collaboration to develop an assay to evaluate the potential to predict benefit from Keytruda. The expanded collaboration is for the development and commercialization of the selected gene expression signature on NanoString's nCounter Dx Analysis System as a diagnostic assay to predict response to Keytruda in multiple tumor types.