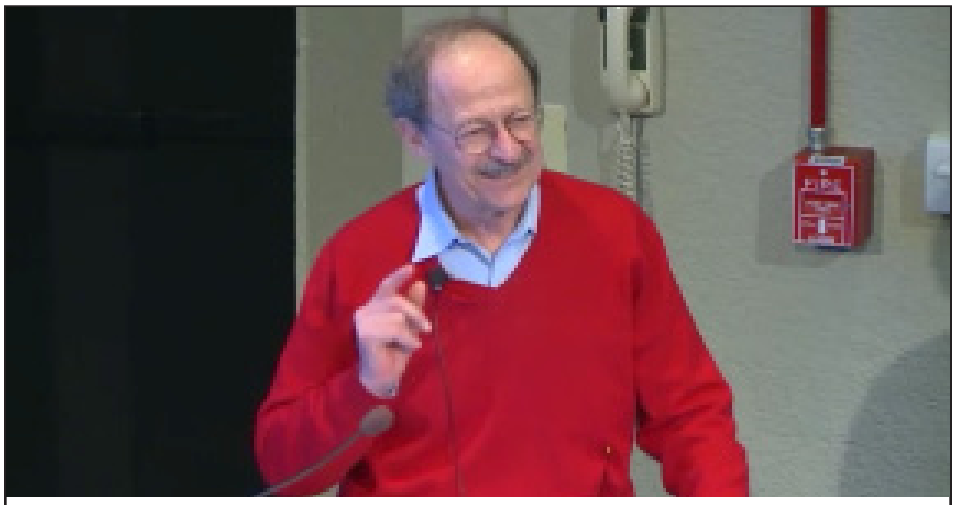
THE CANCER LETTER

March 27, 2015 • www.cancerletter.com • Vol. 41 No. 12



"All Pull; No Push"—Varmus Describes his Reasons for Leaving In Farewell Town Hall

By Conor Hale

In a farewell town hall meeting March 24, NCI Director Harold Varmus reflected on statements he made during his first day on the job, July 12, 2010, summarizing the proceeding four-and-three-quarter years; listing goals met and lamenting work left unfinished.

After Varmus steps down March 31, he will be replaced by Deputy Director Douglas Lowy, who will become the acting director.

Varmus's remarks ranged from his reasons for leaving NCI—"All pull; no push"—to the accomplishments of the institute during his tenure, and lessons learned from obstacles unforeseen.

(Continued to page 2)

Guest Editorial

How the Lung-MAP Clinical Trial is Responding to Changing Science

By Roy S. Herbst, David Gandara and Vassiliki Papadimitrakopoulou

When the Lung Master Protocol clinical trial (Lung-MAP or S1400) [1] was launched in June 2014, the goal of this first-of-its kind trial was simple: find effective treatments for seriously ill patients suffering from a specific type of lung cancer.

(Continued to page 12)

In Brief

FDA's Richard Pazdur Named by Fortune As One of 50 "World's Greatest Leaders"

RICHARD PAZDUR was chosen by **Fortune** magazine as one of 50 of the "world's greatest leaders."

(Continued to page 19)

Varmus Describes His Reasons For Leaving in NCI Town Hall

(Continued from page 1)

Varmus discussed his Provocative Questions initiative and sequestration; the RAS initiative and the Frederick National Lab; as well as the formation of the National Clinical Trials Network and the completion of the National Lung Screening Trial.

Varmus organized the talk around five points, comparing the institute's state today to what he encountered in 2010.

- What he proposed to do, and what he did.
- What he proposed to do, but feels he did not finish.
- What he should have envisioned, but didn't.
- Unforeseeable crises, and the institute's reactions.
- The future of the NCI and its role in the research community—either immediately, in the hands of soon-to-be Acting Director Lowy, or in the years to follow.

"Ambitions that I set on July 12, 2010, don't seem long ago to me," Varmus said.

"On day one, at that first town hall, I said I was arriving for four reasons. One, is it's a great time to lead the nation's cancer research effort. And indeed it was, and is still a great time. Second, I had what I call institute director's envy when I was director of NIH.

"I saw these institute directors having all the fun running the science, and I was going down to the department and Capitol Hill and having a pretty boring time. And I say it's still true that one should have envy of institute directors. Institute directors have a great job. Sometimes I feel I have envy of division directors who are even closer to the science, but I doubt I'll come back as division director. But you never know.

Editor & Publisher: Paul Goldberg
Associate Editor: Conor Hale
Reporter: Matthew Bin Han Ong

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.

"The third reason I gave was that I had, and have, a lot of affection for the NIH. That's true. I became a scientist here under the influence of my pal Ira Pastan, sitting right there. I love this place and I still do.

"Fourth, I said, 'You know, I'm finished at Sloan Kettering—I need a job.' This is a job."

Varmus presided over consolidation of the clinical trials system to create the National Clinical Trials Network.

"The first thing that I said on day one was that we need to fix the clinical trial system, it wasn't a hard thing to say because we recently had a report from Institute of Medicine pointing out they were serious problems," Varmus said. "I won't list those, but those of you close to this know what those were.

"It's been reorganized in a way that is much simpler, more efficient, and is linked. We have the major parts of the National Clinical Trials Network… It is linked much more closely to the community centers and the cancer centers that are NCI-designated.

"We have become much better poised for doing molecularly based trials. We have shielded the system from the budget cuts that many other parts of our budget had to sustain…This has not been an easy road—we have had bricks thrown at us along the way."

The budget crunch NCI endured on his watch presented challenges: "Though NCI kept up the number of grants over these last years, we know that there is real discomfort in the scientific community," Varmus said. "That crunch has created a hypercompetitive atmosphere. It has occasioned a loss of nerve among many of our investigators, especially our extramural investigators. It has contributed to a declining appeal of research careers at a time when cancer science is the most exciting I've seen it."

The Outstanding Investigator Award could provide some relief, as well as emphasizing the people that make up the research community instead of simply the projects.

"Applications are under review as I'm speaking this very day," he said. "Those applications are to acquire grants that are intended to provide large and stable—and by stable, I mean seven-year funding—to our very best investigators; about 50 awards per year. So in that sense it's probably a pilot."

The budget woes hit the NIH Clinical Research Center.

"I have come to appreciate how difficult it is to manage a research hospital which has inevitably rising fixed costs at a time when budgets are shrinking," Varmus said. "And as result we have a clinical center which I believe is extremely vulnerable to decline and even failure.

"I think there are many things that we can try to do

to save what is historically one of the great institutions on this campus. It is the symbol of what NIH [is capable of] to the many members of Congress who have increased our appropriations in the past.

"And it also represents a place where the fulfillment of our dream of taking basic science and making it a valued contributor to how we improve the health of the nation and the world, all these things can be fulfilled here. We need to pay a lot of attention to that."

NCI has been in a "durable drought." The institute's appropriation is lower than the day he started: "We are now $177 million below where we were the year I arrived. Don't put that on my tombstone," Varmus said. "Furthermore, we had a demoralizing shutdown as a result of appropriations.

"I also said on day one, we're going to have to try and do better with what we have while working and hoping for better economic times. And we need a better job shepherding the considerable funds that we already have. We do have a budget that can round off to $5 billion; that's a lot of money.

"I'm proud of having said that. That was before I had learned of Lord Rutherford's dictum: 'Gentlemen we have run out of money. It's time to start thinking.' That's been my mantra for several years, and I think in general, as a group, we have been thinking about how to use our funds in the best possible way."

Varmus described a recent Capitol Hill event run by the American Cancer Society and Stand Up to Cancer:

"We had many hundreds of people jamming the floor and listening to members of Congress get to the microphone and talk about how important cancer research is.

"But the majority of those folks said, I would love to see cancer cured. I love the NIH. Cancer is a terrible disease. And then they sat down.

"Only a few said I have proposed a bill—as Rep. Rosa DeLauro (D-Conn.) has, along with Rep. Peter King (R-N.Y.) and [Rep. Brian Higgins (D-N.Y.)] that will restore money lost in sequestration, and bring us back in buying power to where we were in 2003. That would have big effect.

"There is a big distinction between people who speak who speak to repairing the wounds of the last 12 years of budgeting, and those who are paying lip service to the idea that cancer is a bad disease, we ought to get rid of it."

NCI is more than a funder of medical research. It has the ability to bring together—and energize--the scientific community. "In 2010, on day one, I said that 'scientific thought begins with individual scientists, but depends and depends strongly on community of scientists who share, who validate and who expand ideas,'" Varmus said. "I have always been strenuous in my insistence that we do the most that we can to insure to access to data, to publications and to our scientific materials.

"I also think we need to attend carefully, in thinking about the community of scientists, to the mood of the community and to the individuals who make it up. That means both inside and outside the NIH, these folks are the NIH's number one asset.

"The things that need to be attended to if we're going to take their mood high despite fiscal constraints are the fairness of peer review, the kinds of grant mechanisms with we offer to support their research activities. We need to keep an eye on the demographics of our scientific community—who is getting grants and when—how long people are allowed to age before being given free rein to exercise their imaginations?

Varmus said he is looking forward to life in New York.

"We soldiered on and did good work, had fun, and I'm looking forward, of course, to one of the things that I anticipate with great pleasure—spending more time supervising my laboratory work a little more closely, and being more deeply engaged than this job allows me to be."

The video of his March 25 town hall is available on the NIH Videocast website. The recording of his day one town hall meeting, July 12, 2010, is available here.

A transcript of Varmus's remarks follows:

Ambitions that I set on July 12, 2010, don't seem long ago to me. We will call that "day one." I will be quoting from things that I said, recorded verbatim by the NIH and probably by The Cancer Letter.

First, before we get into that analysis, let me answer a question that needs to be gotten out of the way. There is a question that I get asked: Why are you leaving? Let me try to quickly answer that.

On day one, at that first town hall, I said I was arriving for four reasons. One, is it's a great time to lead the nation's cancer research effort. And indeed it was, and is still a great time. Second, I had what I call institute director's envy when I was director of NIH.

I saw these institute directors having all the fun running the science and I was going down to the department and Capitol Hill and having a pretty boring time. And I say it's still true that one should have envy of institute directors. Institute directors have a great job. Sometimes I feel I have envy of division directors who are even closer to the science, but I doubt I'll come back as division director. But you never know.

The third reason I gave was that I had, and have, a lot of affection for the NIH. That's true. I became a scientist here under the influence of my pal Ira Pastan, sitting right there. I love this place and I still do.

Fourth, I said, "You know, I'm finished at Sloan Kettering—I need a job." This is a job.

Now I'm departing, but not because any of what I have mentioned is no longer true, but because first my real home is in New York City, not in D.C. Wife, sons, home and much more. Second, it's good, healthy to integrate your life and your work and I have been far from integrated over the last five years. I have taken over 200 rides on the Amtrak 185 on Monday mornings. Enough.

Third, we have gotten a lot done; it's a pretty good time to leave. You never can have satisfaction in the job in the sense of everything is done; a lot of stuff is in progress, and I'll come back to that a little later. And fourth, I have a job waiting for me in New York, so that's good.

All pull; no push.

So let me say something about how I'm going to organize our little discussion: five big organizational points.

I'm going to talk about five things. First, what I promised to do or to try to do on day one, July 12, 2010, and what we did. Second, what I proposed to do, and didn't get done. And fortunately that list is pretty small. A little bit of editing there, but still, pretty small.

Third I'll talk about what we did, and I should have anticipated, but I didn't.

Fourth, I want to talk about what I couldn't have foreseen, because a lot of jobs these jobs are unforeseeable, and there are events that hit you and you have to respond and you could not have guessed they would happen.

And fifth, I have to spend couple of times talking about what I hope Doug, and his colleagues, and the people that come after Doug, need to do to keep this operation running as well as currently is.

So first, before we get to that list of five, I need to say something about the budget. When I first came to NIH as director someone said to me that appropriation is the lifeblood of federal agencies. Indeed that's true.

On day one I said, quote, "Just because I was here when the NIH budget started to double, don't expect me to produce budget magic. Things will probably be tough for a while."

Well, that was a grand understatement.

So we have had a durable drought and we have actually lost money, 6 percent during sequestration, a little here and there. We are now $177 million below where we were the year I arrived. Don't put that on my tombstone. Furthermore, we had a demoralizing shutdown as a result of appropriations.

I also said on day one, we're going to have to try and do better with what we have while working and hoping for better economic times. And we need a better job shepherding the considerable funds that we already have. We do have a budget that can round off to $5 billion; that's a lot of money.

I'm proud of having said that. That was before I had learned of Lord Rutherford's dictum: "Gentlemen we have run out of money. It's time to start thinking." That's been my mantra for several years, and I think in general, as a group, we have been thinking about how to use our funds in the best possible way.

Ambitions Set on Day One

So, number one: what did I propose to do, and what we did.

Notice "we," nothing I'm going to talk about here was done solely by me. I was here, I get some credit for it, but these are all group efforts. I take responsibility for the statements on day one, but the follow-up has to do with the concerted effort made by all of you.

So the first topic of six I want to mention briefly—this will be superficial but hopefully clear.

The first thing that I said on day one was that we need to fix the clinical trial system, it wasn't a hard thing to say because we recently had a report from Institute of Medicine pointing out they were serious problems. I won't list those, but those of you close to this know what those were.

And as I said day one, quoting again, "the first thing we need do is repair some of the things that are obviously dysfunctional in the system, the first is the clinical trial system."

I have to give explicit thanks here, not going to mention all that many names today—boring for the audience—but Jim Doroshow, Jeff Abrams, Barry Kramer and many others deserve special credit for bringing the former cooperative group system and the long list of community centers for doing clinical trials work, into one big organization with some important components. It's been reorganized in a way that is much simpler, more efficient, and is linked. We have the major parts of the National Clinical Trials Network. That is the acronym. It is linked much more closely to the community centers and the cancer centers that are NCI-designated.

We have become much better poised for doing molecularly based trials. We have shielded the system from the budget cuts that many other parts of our budget

had to sustain.

We built a centralized institute review board, we subjected everybody in the system to reporting requirements, through clinicaltrials.gov, and other things to make sure get the results of all trials into the public domain.

This has not been an easy road—we have had bricks thrown at us along the way. But I think, without being overly dependent on the words of W., mission has been achieved in this domain. And this is going to be important, because it's going to have a major role in the way we transform clinical care, by precision medicine, in the way which we respond to the other Institute of Medicine report on precision medicine, and now the president's initiative on precision medicine.

The second thing I would like to mention is something that got accomplished is the way in which we support our talented individuals.

On day one, I said the following: "There are lots of good reasons to support teams of scientists, and I will be supporting many. But we have to remember that the great achievements in science, that I'm aware of, have almost always begun with an individual scientist."

The budget crunch that we've have been experiencing the last several years at the NIH generally has affected many more people than I expected to be effected and for a much longer time. Though NCI kept up the number of grants over these last years, we know that there is real discomfort in the scientific community.

That crunch has created a hypercompetitive atmosphere. It has occasioned a loss of nerve among many of our investigators, especially our extramural investigators. It has contributed to a declining appeal of research careers at a time when cancer science is the most exciting I've seen it.

We have limited the amount of time that our best investigators—or any investigators—have for doing creative thought and a private relaxed session.

I tried with my colleagues in the extramural world, Drs. [Shirley] Tilghman, [Marc] Kirschner and [Bruce] Alberts, to summarize some of these in an essay that we published in the Proceedings of the National Academy of Sciences last year and the four of us have been working on these problems independent of my NIH role for some time.

Among our suggestions in that article were recommendations on how to improve the welfare and sustained support; the environment in which our best scientists do their best work. And I think the general notion that something needs to be done is permeated widely in the NIH , the NIH is taking a NIH -wide role in trying to emphasize people as much as or more than we emphasize projects in the review of applications for support.

I would like to think, in fact I would contest strongly, that NCI has been a leader in that effort and in many ways. The Outstanding Investigator Award is perhaps our flagship enterprise in that regard.

Applications are under review as I'm speaking this very day. Those applications are to acquire grants that are intended to provide large and stable, and by stable, I mean seven-year funding, to our very best investigators; about 50 awards per year. So in that sense it's probably a pilot. Particularly indebted to Dinah Singer for helping push this through and for many others who contributed to thinking about how this new award would be constructed.

We have other awards under consideration to try to improve the way which people are trained, the way they're supported, the way they envision careers in science.

We have one award that would be given to our best graduate students to move them quickly through Ph.D. program and move into post-doctoral situations of great distinction without pause.

We have an award that would dignify position of staff scientists, not just at the NIH, where I think it already is a pretty dignified position, but in the extramural community by emphasizing people who spend careers working in labs run administratively by others, or people who work in core facilities or who serve the entire institution.

These two new awards have been approved by our Board of Scientific Advisors and we simply await a stamp of approval from NIH central. I hope that's forthcoming soon.

The third thing we have done is to think how appraisal is done, if you make awards to people who are being judged by past performance as well as by the projects they propose.

This should not be done by seeing if they have published in journals with single-word names, but instead by evaluating their productivity in a more subjective, thorough and profound way, and we have helped devise a new biosketch that is now taken on by all of NIH. This is going to make the evaluations we expect, better.

The next topic to mention briefly is the place we have had success is in the realm of building institutional and agency collaborations.

So to go back again to day one, I said to a group approximating this one, "the NCI needs to be not just proud and alone and fighting its own wars, but working with the other institutes and centers the FDA and the CDC.

We have to recognize we cannot succeed in controlling cancer without strong connections in industry."

I mention a couple of ways I believe that's come further down the road toward fruition. First, we have had success with industry to get early stage drugs for some new trials. For example, the famous MATCH trial that is open to all with advanced refractory cancer, which genomic analysis of their cancer genome will be matched by use of new targeted therapies, has been assisted dramatically by the congenial relationship the NCI had with drug companies.

We had a good relationship with the Center for Medicaid Medicare Services, because they have been involved, for example, in approving lung cancer screening with helical CT scanning, I'll come back to that later.

We have had more and better relations with the FDA across a wide spectrum of activities ranging from tobacco control—Bob Croyle had major influence in acquiring fiscal support from the FDA for the tobacco centers we have been establishing—and efforts to define how we're going to use combination therapies, which are one of the next great things, I believe, in cancer research.

Specifically in this domain of the FDA, I remind you in 2010 on day one, I said specifically the cancer drug approval and regulation need to be readjusted to a modern era, in which there is genetically based selection of therapies. And indeed the FDA's efforts under [Commissioner Margaret] Hamburg—who coincidentally is also leaving government this week—in applying what she calls regulatory science, to these new kinds of testing and using diagnostics tools that weren't available until recently, has been critical in trying to develop the kinds of care that will exist once we identify useful drugs under trials like MATCH and others that are also based on genetic criteria.

The next topic is one I'm sure most of you could predict: Provocative Questions.

So on day one I said that we have to admit to ourselves that we haven't succeeded in controlling cancer to the extent that I believe is possible and we need to ask ourselves why we haven't succeeded, and how we think about the scientific problems we're trying to solve how we frame questions we're trying to answer. For example, why does a cell become dependent on a mutant cancer gene or what accounts for well-established association between obesity and certain cancers.

I went on to say I'm going to stage a series of meetings inviting people from across a range of disciplines an across the country, across the world, to try to establish a list of provocative unanswerable questions—sorry, provocative answerable questions! It may seem to be unanswerable even today, but at least provocative, that will help our scientists think about the next steps ought to be.

And as this process evolves I began to realize that we were creating a new way how we fund science, not by top-down elucidation of problems that people haven't solve or by just allowing everybody to give free range of imagination which some ways would be ideal, but by getting the community of sciences together with those who administrate the NCI to come up with a list of provocative questions that we could all discuss and some could be elected as topics for grants.

This has been very successful in the community. We have had workshops, issued grants in response to questions listed as granting opportunities. We have had terrific teams of scientists and program officers here who enthusiastically embraced this concept under the leadership of Ed Harlow, to whom I'm very grateful for his passionate embrace of this concept.

But it is to be said, that while we issued a lot of grants and have been spending a lot of money, whether this concept actually is going to produce results that are different from what we would have had without this initiative. Too early to say. But I hope that in coming years there's attempt to evaluate whether this approach is important.

Many institute directors have considered taking on something like this, and I think if we're doing this experiment we need to try to analyze the results. Not just by looking at what's been done, but trying to think about whether something we did in putting this together was important in obtaining the outcomes that we obtained.

This item here has to do with quite few acronyms, only couple of which are here, with the intellectual infrastructure in which we work.

On day one I said, "I want to acknowledge everything we do with the NCI is not about biological mechanisms. We need to do certain kinds of collecting of obvious things, epidemiological information, disseminating knowledge, carrying out our training programs, and gathering scientific information so that we know how to gather together, such as The Cancer Genome Atlas project."

So that quotation is meant to say is that as a categorical institute devoted to study of one disease unlike other places like National Institutes of General Medical Sciences, we need support not just individual investigator-initiated grants, but also programs and centers, strengthening intellectual infrastructure, gathering various kinds of information, guaranteeing

continued success of our centers, building team science, building informatics and support science, and so forth.

And there's remarkable examples, The Cancer Genome Atlas project which was already mentioned, the similar project for pediatrics which is called TARGET, an acronym I can never define. We need to finish jobs and basically we're nearly done with that.

They are forming the components of this precision medicine initiative that you have been hearing about and importantly the constellation of activities that are intended to build the informatics infrastructure has led to creation of new center, the Center for Cancer Genomics, which was pioneered by Barbara Wald, while she was on sabbatical from Cal Tech a few years ago, and brilliantly led by Lou Staudt who is here in the front row, and I'm very grateful to them for that.

The way we build infrastructure with computational tools has been a contentious one over the years at the NCI, but I'm happy to say that by bringing Warren Kibbe here from Northwestern. We have reinvented the Center for Bioinformatics and Information Technology, and that's now doing great work and carrying out pilot experiments with computation and participating with the Center for Cancer Genomics in other ways of bringing genomic information about cancer together with clinical information.

We also paying attention to cancer centers, recognizing that they are an essential feature, the backbone of the NCI investment in extramural research.

We have tried to encourage them by rearranging the way in which they receive their budgets, making it more dependent on current priorities rather than historical performance. Making financial incentives undertake new actions through supplementary funding, giving them a bigger role in setting the tone of how we do research more generally, by encouraging ways for them to share their results and participate in our global health activities I will mention in a moment.

So, something about global health. On day one I said that we need to expand the range of what NCI does, developing programs that are suitable for improving health in poor countries through tobacco control, vaccination against oncogenic viruses, and other things.

The first year I was here, we spent time putting together a Center for Global Health and we were able to entice Ted Trimble, whose familiarity was not in deep in the broad realm of global health, as in doing international clinical trials, and Ted is taken on this charge admirably for building a new center, for coordinating the activities already ongoing across the NCI, and for making the center well known internationally as a place to go for learning how to put together a systematic program to improve cancer outcomes throughout the world.

So planning developing national cancer programs, building partnerships between our cancer centers and places abroad with resources and the will to undertake an assault on cancer has been central to what the Center for Global Health, with its relatively small budget, has been trying to do.

The emphasis has been tobacco, on certain vaccines like human papillomavirus vaccine, engaging our NCI-designated cancer centers in this fight against cancer worldwide, building national cancer plans in places like Mexico, Indonesia, Turkey, India, China, and others and building networks to study specific diseases particularly prevalent in poor countries.

Work Left Unfinished

So enough of unmitigated success—let me talk about things that were more problematic, especially what I propose to do and feel I didn't get done.

I want to emphasize one very brief thing that has a big potential here for us to do something really critical for NCI, NIH and the world. And that is to address some of the problems in the Mark O. Hatfield Clinical Research Center.

So to go back to day one, what I said on that occasion was one of my goals is to improve the utilization of the Mark O. Hatfield Clinical Research Center. All well and good, but I believe I strongly overestimated how much intrinsic capacity there was at the center to overcome its problems.

I thought that the intrinsic appeal of this newly constructed, beautiful center, with its great staff, rich history, and in combination with the new Lasker scholars program which provided basically tax-free program for investigators who want to devote all their time to clinical activities would be unparalleled and irresistible, but in fact it has not been very successful in recruiting new clinical scientists, don't know why that is.

Mike Gottesman and I have been in conversations, we don't fully understand this. Nor did I think we would have that much trouble in fixing the finances of the clinical research center. But I have come to appreciate how difficult it is to manage a research hospital which has inevitably rising fixed costs at a time when budgets are shrinking.

And as result we have a clinical center which I believe is extremely vulnerable to decline and even failure. As we have come to realize the depth of this problem, many of my fellow institute directors and Francis Collins have pooled our energies and in conjunction with the energy of John Gallin and Mike

Gottesman to try to do something about this.

I sense a new level of energy trying to confront the problem the clinical center is having, I can't—I don't have time today to spell out what I think specifically can be done. I think there are many things that we can try to do to save what is historically one of the great institutions on this campus. It is the symbol of what NIH can do to many members of Congress who have increased our appropriations in the past.

And it also represents a place where the fulfillment of our dream of taking basic science and making it a valued contributor to how we improve the health of the nation and the world, all these things can be fulfilled here. We need to pay a lot of attention to that.

The Potential of the Frederick National Lab

Number three: what we did, and should have envisioned, but didn't at the time. So this is an interesting topic.

On day one, in 2010, I mentioned the following: I'm going to be paying attention to the pipeline of therapeutics, while I visit Frederick over the next couple of weeks.

Now I have to confess I didn't really know what Frederick was. I knew where it was, but I didn't know much about what was going on up there, because it is complicated.

We have a third of the intramural program, we've got pieces run by various divisions, and we have laboratory activities in various kinds. But we put lot of energy into this, first developing at the suggestion of the National Cancer Advisory Board, an advisory board of distinguished people dedicated solely to paying attention to Frederick.

One of the first things we did is a little anatomy. What's up there? Let's define components.

Then let's name something which is incredibly important, that is original laboratory work being done under contract at Frederick and call the Frederick National Lab for Cancer Research.

It forms an obvious analogy with a very strong national labs run by department of energy, they are very ambitious, they have academic connections. I think the name itself has mattered here.

We coincidentally opened a new building that was nearly constructed by the time I got here and that new building has been a forceful influence in building the new programs there. We recruited more external advisors to join the group.

We have encouraged building some of the scientific base over the traditional laboratories like Nanotechnology Characterization Lab to make more potent than they already were.

Importantly we have begun major initiatives. The one most people know about is the RAS initiative, and I was able to recruit Frank McCormick at UCSF to come and run that, and that's inspired consideration of other initiatives yet to be named. But there's an active seeking of additional things that might be done on this potent element which we have contract program, with its inherent flexibility that are not often exercised to do things that flexibility can allow us to do more forcefully.

So, the fourth element is to remind you what I could not have foreseen, and this encompasses good things and bad. Things just happen that we had to respond to, and I think have responded to reasonably well. I'm going the look at those in two categories: things that provided some angst and discomfort, and some things that made us all feel good.

One of the first things I learned only about a month after I started is that while we're all excited about using genomics and other omics in clinical medicine, there are some pretty severe dangers illustrated by a really outlier episode that occurred at one of our great academic centers, indeed one of our NCI cancer centers, in which the use of omics in clinical trial was inappropriate. It was not an NCI trial but still an NCI center; that mattered to us.

But we were able to make good use of that very unfortunate example by having the Institute of Medicine do a report on the use of omics in clinical medicine. That was a very useful outcome, but also was a way of presaging the more widespread concerns about non-reproducible results in NIH-supported research, and needed in general biomedical research.

There are now NIH-wide responses to reproducibility problems, but our schooling in that matter of reproducibility, through this and other misadventures, has put us in a unique position in providing solutions, checklists, training programs and other things to the NIH-wide community.

The other thing that of course has been problematic, that I alluded to before, is the unexpected depth of fiscal woe and duration. I certainly would never have expected there would be sequestration, or that the sequestration would not spare places like the NIH, but I was wrong about that.

But there were good things as well, and unexpected moments, for example, the announcement the National Lung Screening Trial had come to a positive outcome, with this new screening method

proving that we can reduce mortality from lung cancer in a selected group of high risk patients by about 20 percent. And that led to other things to do working with agencies like CMS and FDA and others, to be sure that once the U.S. Preventative Services Task Force has given a favorable rating to this new method, that things can be put in place for the nation. And now insurers under Obamacare, that is all insurers, and Medicare, as well, as a result of the opinion by the Center for Medicare and Medicaid Services—there are down sides of methodology, obviously a very large number of false positive readings but we have worked with the Foundation for the NIH with and Paula Jacobs and others in the NCI to put together a prize competition to develop algorithms that are more adept at distinguishing pathology from artifacts in the reading of the films produced by helical CT scanning.

The Future

Finally a few things about what I hope that Doug and colleagues and their successors will take on. And take on over at least the next few years, and hopefully the years to succeed those.

Let me mention quickly in three broad categories. The first has to do with what I repeatedly alluded to, the need for NCI to act as an agent that brings together communities of scientists, maintains their spirit and sets their moral standards and their intellectual excitement at high levels.

In 2010, on day one, I said that "scientific thought begins with individual scientists, but depends and depends strongly on community of scientists who share, who validate and who expand ideas."

I have always been strenuous in my insistence that we do the most that we can to insure to access to data, to publications and to our scientific materials.

And I hope to continue the efforts to make data more useful and accessible through the initiatives I mentioned earlier, through the Center for Cancer Genomics, the genetic data commons, the cloud pilot exercises being carried out by Warren and his colleagues, to our affiliation with a new alliance, the Global Alliance for Genomes and Health and through the NIH-wide big-data-to-knowledge initiative BD2K.

In 2010, on day one, I said that 'scientific thought begins with individual scientists, but depends and depends strongly on community of scientists who share, who validate and who expand ideas.'

"I have always been strenuous in my insistence that we do the most that we can to insure to access to data, to publications and to our scientific materials.

I also think we need to attend carefully, in thinking about the community of scientists, to the mood of the community and to the individuals who make it up. That means both inside and outside the NIH, these folks are the NIH's number one asset.

The things that need to be attended to if we're going to take their mood high despite fiscal constraints are the fairness of peer review, the kinds of grant mechanisms with we offer to support their research activities. We need to keep an eye on the demographics of our scientific community—who is getting grants and when—how long people are allowed to age before being given free rein to exercise imaginations?

We need to keep special tabs on the bureaucracy, though we can't always do anything about it except rant and rave.

I hope that, perhaps in the coming years, people can do more than I was able to do, to get relief from restrictions on travel and meeting attendance and other things that should not be restrictions on hardworking scientists.

I enjoyed working with the leaders of our intramural program, Drs. [Robert] Wiltrout, [Lee] Helman and [Stephen] Chanock to get relief for some things, but I would say our success rate is small, and I hope Doug will have greater success in this venue.

Second major category of things that I hope he and his colleagues will be thinking about has to do with finishing difficult jobs that we made progress on, but haven't completed.

The top of my own list, because it's been so difficult emotionally and arithmetically have been fixing the budgets for the cancer centers, and that will happen the next couple of months. We've been re-evaluating some of the things we tried to re-evaluate, and I'm a believer in bringing in outsiders to give us advice. Doug is too.

But now we have a group that's working the question of how best to support translational science, including the SPORE program, and that will be a contentious report. I hope we can learn and improve the way we operate as a result.

The third has to do with approval for getting good career-shaping awards. I mentioned earlier to facilitate and expedite training of young investigators, especially the very best, and to give honor to staff scientists.

I'm concerned about possible declines in our commitment to basic science in the NIH in general and NCI specifically. And I hope that will be an effort to watch for possible declines in the number of applications we receive and the way in which

people attempt to describe their work, in a way that doesn't necessarily always lead to a claim that this has translational potential, instead let's say that this has the potential to solve difficult, enduring questions in the basic science of how cancer arises and how we might better control it.

I feel we have not paid as much attention as we might to workforce diversity. We have done some, I think more can be done here—I look to Doug and his colleagues in the future.

I know that we're putting together to better assess the portfolio of ongoing work, on health disparities—local, national and international, and I look forward to hearing more about that.

The third category is more stylistic and perhaps humorous, but what I said on day one still applies. These are useful rules: A) when you report something please don't refer to an abstraction like the department or building one or the White House, refer instead to people who are behind those statements.

Second, let's try to avoid the classical NIH retort which I have been hearing since 1993, when a suggestion is made: "We're already doing it." Because we're usually not.

Third, promote greater informality. I wore a tie on day one. I'm much more relaxed today. I hope you're all feeling that informality has grown and will continue to grow as a mark of the way in which we operate.

Fourth thing is to minimize the use of clichés and euphemisms. I tried to define as many acronyms on slides as I could on the way through, as an object lesson in defining the acronyms, and hope you will do that too.

And of course, this list would be incomplete without saying: never use impact as a verb. Not so successful in controlling that, I have to say.

This is not about individual thank yous. I'm grateful to everybody on this campus, and elsewhere—my advisory groups other places around here made my nearly five years here very pleasurable.

But I do need to single out a few, my two most-trusted, highest-ranking deputies, Drs. Lowy and Doroshow, who have been at my side—two legs of the troika—for the last four years or so, and without them life would have been a lot less fun and a lot less productive.

A good word to Francis Collins who agreed the take on this peculiar dance in which we reversed roles, he used to be an institute director under my directorship; it's been the other way around since then. And I will not pretend we never had any disagreements, but they resolved amicably and everything was always conducted on a level of scientific and rational discussion and I'm very pleased that Francis is willing to take on the potentially complex task of working with someone who used to be in the flip relationship.

I have been welcomed, I feel, by my fellow institute directors, I'm grateful to all them but especially Tony Fauci who has been willing to have a weekly conversation with me about matters from trivial to profound, and giving me common sense/common sensical advice how to cope with the bureaucracy that I had come to enjoy being without during my 10 years at Sloan Kettering.

Critical to my life on a day-to-day basis have been two people in my office, Joy Wiszneauckas and Mieko Togashi, without whom I'm going to suffer in months to come. I will be relieved not to have a little schedule that's got 15 appointments during the day.

Organizing my life more generally will be left to myself, and that will be a little more problematic.

I'm grateful to my lab members who threw a picnic party today, who have seen much less of me in person than I would have liked. Not sure that made them happy or unhappy.

But nevertheless we soldiered on and did good work, had fun and I'm looking forward of course to one of the things that I anticipate with great pleasure, spending more time supervising my laboratory work a little more closely and being more deeply engaged than this job allows me to be.

Last but not least, I want to issue a shout out to my wife Constance Casey who is making a rare appearance in the DC area, for her indulgence of allowing me to do this for four-and-three-quarters years. It's not been easy on her, at least not as easy as it's been on me.

So at this point I'm happy to take few questions before we wrap it up and adjourn for some refreshment.

Questions? Comments? I hasten to say comments, but questions? Marston Linehan!

LINEHAN: I've got a question for you.

You've have been director of NIH, now of course director of NCI, and you talked about importance of basic science and everything—and I've always felt personally that we would never make progress, and I'm a little biased, but we're never going to make progress without physician-scientists. So for all the young people that work with us, I always ask the same

question, can I do this on the outside? What is the future for this? Can I outside NIH—so what do you think? There's a lot of stresses and concerns.

But I still feel that's a critical thing to us.

What do you think about future of physician scientists?

VARMUS: It's interesting because across the biomedical research enterprise we know we have a tremendous overabundance of people who are trained with Ph.Ds. to do biomedical research.

In fact, if you enter graduate school today to get a Ph.D. in our fields, chances are one-in-ten that you will do what your mentor does—that is run a large laboratory in an academic institution. But the outcomes for physician-scientists are quite different. Physicians that choose to do science have a much better chance of succeeding.

One of the reasons many of them choose not to do that is because they have the lucrative and stimulating and emotionally gratifying option of just practicing medicine, participating in a few clinical trials, and not getting deeply engaged in the research that requires raising major resources.

That being said, I think we have a wide range of people who are trying to increase the options and attractions of doing research as a physician-scientist, Robert Tijan who runs the Howard Hughes Medical Institute has recently opined on this. I think there are a lot of good opportunities to get trained to do that.

That's one of the reasons why it worries me that, despite the complaints I hear from some physician-scientists who are trying to run a research program while also serving their own institution as a physician two or three days a week in hospital clinics, that we have hat not had huge number of outstanding applicants from other institutions to come here as Lasker scholars—with the tenure track appointment, six years of support, no requirement to do service, and the option of going back to the extramural community with two years of support. It just seems like a program very well-suited to attract people of the kind you're concerned about into the system.

The other thing that's being done that I think is a related issue, that is graduate programs that make people into clinically informed, but scientists who are not clinicians. I think that is a valuable way to begin to deal with the fact that a lot of our Ph.Ds. don't know very much about cancer at as a clinical phenomenon.

At Sloan Kettering, for example, one small advertisement to a place I have left behind by several years, we started a graduate program of cancer biology in which all the students get clinical exposure, have a clinical mentor, know about cancer as a disease, but primarily getting Ph.Ds. in bench science. I think we need to think about other ways to attract people into a field which has produced folks like you, and emphasize excitement of doing clinical research on cancer at a time when the fruits of our laboratory work—genomics and proteomics and understanding of signaling pathways, and new ways to think about immune responses to cancer—are fundamentally changing clinical research making it much less empiric and much more evidence based.

JENNIFER LOUKISSAS: So next week we have this event taking place on PBS which I know you're aware of, the Emperor of All Maladies will be on. It seems like a good opportunity for cancer research and cancer treatment to raise awareness, and I was wondering what hopes you have for the aftermath or any kind of legacy.

VARMUS: I don't know about aftermath and legacy, I know a lot about the show, I think it will be terrific visual experience—two hours a night, on Monday, Tuesday, and Wednesday—don't make dinner dates, I'm not making any. Or order in.

Of course there will be DVD set, or record it if you are more in depth than I am in operating my entertainment center. It will be inspiring. To tell you about how medical care is given to cancer patients, will tell you about the basic science, history of cancer, advocacy. [Siddhartha Mukherjee] himself remarkable gave lecture in this room not too long ago, at my invitation. I think it will teach people a lot about the history of cancer research, how difficult it is, how much progress we have made, where the opportunities are.

You will see many examples of people being treated under circumstances where hope is higher than ever, but death comes all too often. Whether it will affect the kind of problems that Marston was raising, I don't think in any measurable way.

It's going to be good learning experience, it will make conversations with your friends stimulating because people will be asking you what your experiences are like, and I think it will help to buttress support for cancer research more generally.

I have to say though that I was recently at an event run by the American Cancer Society and Stand Up To Cancer in the Cannon caucus room just last week and we had many hundreds of people jamming the floor and listening to members of Congress get to the microphone and talk about how important cancer research is. But the majority of those folks said, I would

love to see cancer cured. I love the NIH. Cancer is a terrible disease. And then they sat down.

Only a few said I have proposed a bill—as Rep. Rosa DeLauro (D-Conn.) has, along with Rep. Peter King (R-N.Y.) and [Rep. Brian Higgins (D-N.Y.)] that will restore money lost in sequestration, bring us back in buying power to where we were in 2003. That would have big effect.

There is a big distinction between people who speak who speak to repairing the wounds of the last 12 years of budgeting, and those who are paying lip service to the idea that cancer is a bad disease, we ought to get rid of it.

Dr. Lowy, now I'm worried!

LOWY: I would like to tell you first what I learned on day two.

VARMUS: Uh-oh.

LOWY: Don't tell us that you want to have fewer people get cancer and those who do get cancer will do better so that they don't die. Tell us how we're going to do that as well as support basic research.

Harold, you have done an amazing job for the last four and a half years. It's been a privilege to be able to work with you. Your dedication and your commitment is really something. I realize you don't like this kind of hagiography, but you deserve it and much more.

VARMUS: Thank you, Doug.

That seems like a promising moment in which to say we're at the end of the article. There are refreshments, which amazingly enough are offered for free! So one final gesture supported by unnamed donor to whom I'm terribly grateful. And thank you very much for coming.

Guest Editorial

How Lung-MAP Responds To Changing Science

(Continued from page 1)

Lung-MAP is unique—a biomarker driven, multi-drug, multi-arm, study design, using a targeted screening approach, with state-of-the-art genomic profiling of neoplastic cells to match patients with sub-studies testing investigational new drugs and immunotherapies, based on their unique tumor profiles.

The matched drug treatments are designed to target genomic alterations driving the growth of the cancer.

Lung-MAP was conceived with the premise that new ways of thinking were required to advance drug-biomarker combinations for lung cancer.

It had become clear that the old paradigm of "all comer" phase III trials was largely unproductive, with few drugs making it through the approval process, and those that did weren't having a major impact. It was anticipated early on that an essential component of the project would be the ability to rapidly adapt to changes in the therapeutic landscape, including changes in standards of care.

This vision has never been clearer than these past weeks with the approval of nivolumab (Opdivo) in the second line therapy of squamous cell lung cancer (SCC), the same research space occupied by Lung-MAP (The Cancer Letter, March 6).

While the rapid approval of nivolumab represents success for an exciting new therapy, we still have much to learn. Immunotherapies, including nivolumab, have

already shown extraordinary benefit in melanoma, renal cancers, other lung cancers, and other tumor types, but we do not know which patients benefit most and why the majority of patients do not respond.

If we knew how to characterize patients in advance for a predictive biomarker to these checkpoint immunotherapies, we could select those most likely to benefit while sparing others, thus providing a more cost-effective approach tailored to best suit each patient. This now becomes an added charge of the Lung-MAP drug development team.

The Lung-MAP drug selection committee recognized the promise of immunotherapies as treatments for lung cancer when it chose an investigational immune therapy from AstraZeneca/MedImmune to be part of the inaugural launch of the trial. Utilizing the inherent flexibility of the Lung-MAP study design, the study team responded rapidly to the new approval of nivolumab by implementing appropriately responsive and timely modifications. A new amendment will make the trial open to second- or more line therapy, allowing for nivolumab prior to the trial. The trial will add pre-screening of patients while receiving first-line therapy to facilitate and expedite enrollment upon progression

Recent Changes to Lung-MAP (amendment pending)

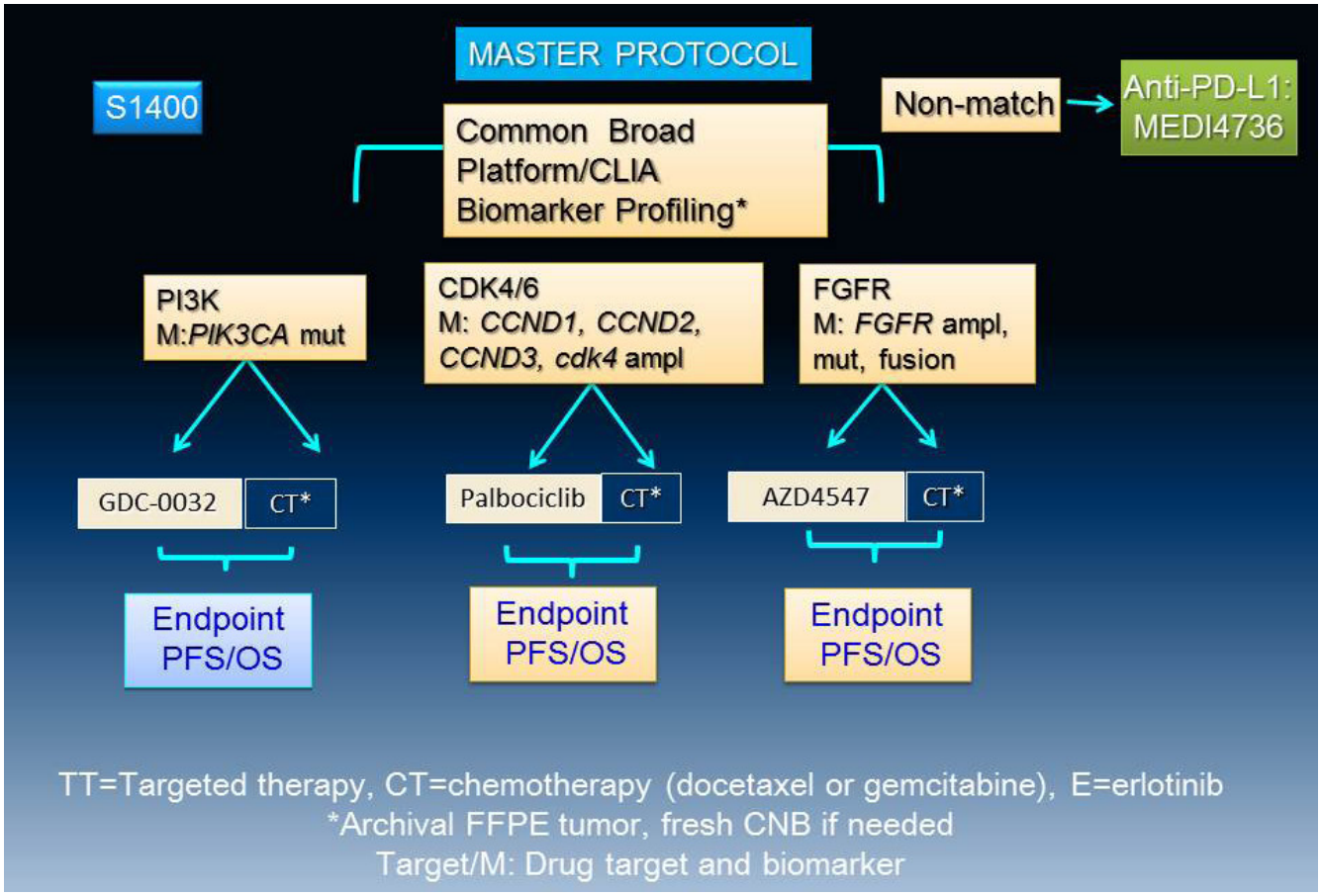
- Eligibility has changed from exclusively second-line therapy to second- or more line therapy
- Pre-screening, while patients receive first line therapy has been added to boost accrual
- The unmatched arm will no longer be a randomized arm- patients will be treated with MEDI-4736
- New arms are being investigated

In addition to immunotherapies, the development of drugs targeting specific genetic alterations that may drive cancer progression continues to be a highly promising area of research. We can now sequence every gene in a tumor including the 25,000 protein coding genes, providing the opportunity to use this information for drug development. This is amazing technology and science, but its application is still emerging and the challenges are multifold—and include issues such as limited knowledge of the distribution of a particular genetic alteration in the patient population and/or the low frequency of these alterations that make recruitment and study conduct difficult in the traditional clinical trial setting.

In lung SCC, the Cancer Genome Atlas (TCGA) and similar studies have detected a significant number of these rare somatic gene mutations/amplifications, some of which are targetable by investigational agents, and so we have developed a study design in lung SCC for development of targeted drugs that uses information available from genome sequencing studies for identification of patient sub-populations, provides access to the large patient population that can be reached through the NCI, Clinical Trials Network (NCTN), and provides a regulatory pathway for the targeted drugs.

The conduct of Lung-MAP relies on close collaboration (a public-private partnership) among the NCI and NCTN (spearheaded by SWOG), the pharmaceutical industry, the Foundation for the NIH (FNIH), Friends of Cancer Research, advocates, and FDA. This Master Protocol will improve genomic screening of SCC patients for clinical trial entry, and improve time lines for drug-biomarker testing, allowing for inclusion of the maximum numbers of otherwise eligible patients. The sub-studies are based on the same protocol, and so all the drugs are tested in a consistent, comparable manner. Some patients will have tumors bearing more than one relevant biomarker; they will be assigned to sub-studies based on a pre-defined algorithm that facilitates even enrollment across all sub-studies. Further, a "non-match" sub-study, *i.e.*, a study of a promising investigational drug that does not target biomarkers in the other sub-studies will be open to accrual throughout the trial, ensuring that all enrolling patients receive treatment on protocol.

Lung-MAP provides an efficient path for FDA-approval for targeted drugs and their companion diagnostic biomarkers; that is, a drug that shows evidence of efficacy (increased PFS) in phase II moves directly into the phase III registration setting, incorporating the patients from phase II. This reduces time, resources, and patient numbers needed to accomplish the ultimate goal of bringing novel agents to the clinic. The duration for each sub-study is expected to range from two to seven years through phase III, each sub-study will require approximately



300 to 400 patients to complete phase III; these are relatively short durations and small patient numbers. The primary objectives for phase III are to determine if there is a statistically significant difference in OS and to determine if there is both a clinically meaningful and statistically significant difference in PFS. The choice of PFS as a co-primary endpoint for phase III was made in collaboration with NCI and FDA, based on the well-known difficulties in obtaining non-confounded OS in trials in advanced lung cancer.

Another aspect of Lung-MAP is that it *can adapt to new research findings rapidly*. That is, new sub-studies enter the trial on a rolling basis as sub-studies close, or relevant drug-biomarker pairs with sufficient proof-of concept become available. Each sub-study functions autonomously and opens and closes independently and is analyzed independently of the other sub-studies. In fact we have already seen this in action during the first six months. It is expected that four to seven sub-studies will be running simultaneously throughout the duration of Lung-MAP. Currently, four are underway: 1) AstraZeneca/MedImmune MEDI4736 (anti-PD-L1) vs. docetaxel as the non-match sub-study; 2) Genentech GDC-0032 (PI3K inhibitor) vs. docetaxel; 3) Pfizer palbociclib (CDK4/6 inhibitor) vs. docetaxel; and 4) AstraZeneca AZ4547 (FGFR inhibitor) vs. docetaxel. We have closed one of the initial sub-studies, rilotumumab vs. erlotinib because the manufacturer, Amgen, withdrew the drug from its phase III study in gastric cancer on observation of toxicity that was not outweighed by efficacy. Clearly, as nivolumab becomes second line standard of care therapy for lung SCC, changes are being made to the current non-match arm, which is an investigational immunotherapy affecting the PD-1/PD-L1 pathway, and consideration will also be given to changes in the control arm for other sub-studies. In the short term we are planning a non-randomized assignment to single agent MEDI4736 in the unmatched arm. These changes will ensure continued viability and even enhance accrual.

As noted above, identifying which patients will respond best to a drug is one of the critical challenges for oncology drug development. Lung-MAP is approaching this by matching drugs to specific genomic alterations. Because a broad NGS platform is being used, there will be opportunities to do exploratory studies with the NGS results and clinical outcomes, as

well as with tissue and blood that will be banked. This could help refine the definition of responders.

We have not yet seen results from the analysis of nivolumab biomarker data, but we expect that these data (e.g., PD-L1 expression) could also identify a subset of patients with a high response rate. Our recent paper[4] demonstrated that using IHC and testing immune cell PDL1 we could develop a highly predictive biomarker for MPDL3280 response—while also working to better understand the mechanism of activity. Other groups are doing the same and the availability of tissue for the biomarker analysis will be a key aspect of the Lung MAP. In fact we have a great opportunity in this tissue-based study for biopsies pre- and post-treatment to better understand mechanism of effect and to design appropriate combination therapies.

Lung-MAP will evolve given the recent data, and as previously planned for. In addition to the changes detailed above, we are now planning new sub-studies of additional targets in advanced lung SCC, other promising drugs and drug combinations for the targets evaluated in the first phase to replace drugs as they leave the trial, and additional immunotherapy and other strategies for the non-match sub study. Candidate drugs are evaluated by a multidisciplinary drug selection committee using specific criteria such as demonstrated biologic activity against the target associated with a proposed predictive biomarker(s); well-understood mechanism of activity against the target; evidence of clinical activity in cancer, particularly in SCC (e.g., phase I responders); manageable toxicity as a monotherapy and/or in combination with chemotherapy; and practical dosage regimens that are acceptable to the patient and clinician. A PARP inhibitor sub-study will enter Lung-MAP this summer, and we recently have been considering immunotherapy combinations and several drugs with kinase targets.

The best is yet to come…

The authors are co-principal investigators of the Lung-MAP trial as well as members of its oversight and drug selection committees. Herbst is the chief of medical oncology and associate director for translational research at Yale Cancer Center. Gandara is director of the Thoracic Oncology Program at UC Davis, and Papadimitrakopoulou is a professor in the Department of Thoracic/Head and Neck Medical Oncology at MD Anderson Cancer Center.

REFERERENCES

1.) Herbst RS, Gandara DR, Hirsch FR, Redman MW, LeBlanc M, Mack PC, Schwartz LH,Vokes E, Ramalingam S, Bradley JD, Sparks D, Zhou Y, Miwa C, Miller VA, Yelensky R, Li Y, Allen JD, Sigal EV, Wholley D, Sigman CC, Blumenthal GM, Malik S, Kelloff GJ, Abrams JS, Blanke CD, Papadimitrakopoulou VA. Lung Master Protocol (Lung-MAP)-A biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. Clin Cancer Res. 2015 Feb 13. pii: clincanres.3473.2014. [Epub ahead of print]

2.) Kim ES, Herbst RS, Wistuba, II, Lee JJ, Blumenschein GR, Jr., Tsao A, et al. The BATTLE trial: personalizing therapy for lung cancer. Cancer Discov. 2011;1(1):44-53.

3.) Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharm Ther. 2009;86(1):97-100.

4.) Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528):563

17% of MD Anderson Faculty Signed Petition Disagreeing with Faculty Senate Exec. Committee

By Paul Goldberg

About 17 percent of the faculty members at MD Anderson Cancer Center signed a petition that disagreed with the institution's Faculty Senate in its efforts to step in and improve morale at the Houston-based institution.

The Faculty Senate recently sent out a letter requesting that the UT System officials and the Board of Regents "provide guidance" to the MD Anderson administration "in establishing milestones and timelines to implement measures to improve the morale of the faculty and the general health of the Institution" (The Cancer Letter, Feb. 20).

Responding to this appeal for help from Austin, three former chairs of the Faculty Senate who now hold administrative positions launched a petition stating that the position taken by the Executive Committee of

the Faculty Senate "cannot be said to reflect the full feelings of the faculty at large, and was not in the best interest of this institution, the faculty, the staff, the Faculty Senate, and most importantly the people who entrust us with their lives today and those whom our research will help in the future."

In a letter that accompanied the petition, the three former Faculty Senate chairs wrote:

"It was conveyed to us that a number of senators believe that the Executive Committee of the Faculty Senate (ECFS) actions did not accurately reflect what they understood to have occurred in November 2014. We also heard from many faculty members at large who believe it does not fully represent their true sentiments nor is it a comprehensive depiction of the current environment."

At MD Anderson, where morale of the faculty has been measured on multiple occasions with similar results, the survey was an effort to pose the question in an inversely different way: How many people *support* the administration and *disagree* with the Faculty Senate?

The three former Faculty Senate chairs announced the results in an email blast March 23:

"Dear Colleagues,

"We would like to thank all of you who signed the petition in support of our institution. We believe that transparency applies to all, and below are the results of the petition:

"Overall, 270 faculty signed the petition; this represents 17% of all faculty members. Among them, 84% are front line faculty, while 16% hold some level of administrative appointment. Clinical and research faculty comprised 66% and 34%, respectively. All academic ranks were represented with 45% at the rank of full professor, 23% associate professor, 26% assistant professor and 6% instructors.

"Despite attempts by some to slant the petition as taking sides, the wording of the petition was clearly in support of our institution as a whole and for open, transparent, and constructive dialogue between faculty and administration to fulfill our mission. We agree with Chancellor McRaven, who, in his recent visit to our Faculty provided a similar voice of support for our institution. He clearly outlined that each one of us as a faculty member is a leader and that the future of our institution is ours to mold. We sincerely hope that all of us will work within our institution to make it a better place.

"If you have constructive ideas or suggestions, we encourage you to bring them forward to your chair, division head, faculty leadership or the faculty senate representative from your area. Arthur Ashe once said, 'Start where you are, use what you have, and do what you can.' Only by looking forward and working together openly and honestly will we be able to realize the true potential of this great institution."

The petition was launched by:

- **JB Durand**, Faculty Senate Chair, 2012-2013
- **J. Jack Lee**, Faculty Senate Chair, 2004-2005
- **Paul Mansfield**, Faculty Senate Chair, 2003-2004

MD Anderson has 1,700 faculty members.

Critics—including eight past chairs of the Faculty Senate—described the petition as a "loyalty oath." (The Cancer Letter, Feb. 27)

"As former chairs, we are disheartened and dismayed at the precipitous decline in faculty morale that has occurred at MDACC under the current executive leadership," the past chairs wrote in an email distributed to the faculty on Feb. 26. "We are further troubled by the continuing loss of outstanding long-term senior faculty from MDACC, an exodus that many have attributed to current administrative policies."

The debates over how the best way to take the pulse of the faculty has been largely settled last week, when the UT System Chancellor William McRaven declared to the cancer center's faculty that he believes that the bonds of trust at MD Anderson have been broken.

McRaven called for joint governance, stating that he will be working closely with both the Faculty Senate and the administration as they seek to forge a viable relationship (The Cancer Letter, March 20).

Republican Budgets Propose $5 Trillion Cut, On Top of Sequestration, Through 2025

By Matthew Bin Han Ong

The Senate passed its 2016 budget early Friday morning in a marathon voting session—an event called "vote-a-rama" in Washington-speak—that split along party lines with a 52-46 Republican margin.

The Senate budget resolution would slash $5.1 trillion in federal spending over the next decade, mirroring the resolution passed by the House 228 to 199 March 25, which cut spending by $5.5 trillion over the next nine years.

Both budgets agree on keeping sequestration cuts in place, and on repealing the Affordable Care Act.

Over the next month, lawmakers would have to negotiate a joint resolution, which would require the Senate and House to reconcile their contradictory plans for Medicare.

The Senate budget supports the White House request to find $430 billion in savings for Medicare; the House resolution proposes partial privatization of Medicare by converting it into a premium support system.

In summary, the Senate budget would cut $4.3 trillion in mandatory spending and $97 billion from discretionary programs.

The 10-year spending plans for both budgets call for even deeper cuts to non-defense domestic programs than was agreed to in the 2011 Budget Control Act, said Jon Retzlaff, managing director of science policy and government affairs at the American Association for Cancer Research.

"We are extremely concerned about both the House and Senate budget resolutions, which would make things exceeding difficult for the appropriators on Capitol Hill to provide budget increases in FY 2016 and beyond for our nation's national priorities, including the life-saving cancer research and biomedical science supported by NCI and NIH, as well as FDA, which is increasingly using a variety of innovative regulatory tools to increase the pace and quality of new cancer drugs reaching patients," Retzlaff said to The Cancer Letter.

"The bottom line is that these House and Senate budget resolutions underscore the need for the White House and Congress to reach a broader budget deal to replace sequestration and raise the spending caps that are currently handcuffing our policy makers from investing in these critical federal agencies (NIH, NCI, and FDA) that are so effective in leading our nation's efforts to improve health and treat disease."

These cuts would further erode federal investment in biomedical research, said Carrie Wolinetz, president of United for Medical Research.

"While we applaud the Senate Budget Committee's call for strong funding for medical research in its FY16 budget resolution, the proposed $236 billion cut to non-defense spending over ten years would make needed increases nearly impossible," Wolinetz said in a statement. "Reduced and inconsistent spending at the National Institutes of Health has devastating implications for our health and the economy.

"The House Budget Committee›s FY16 budget resolution drastically reduces non-defense discretionary spending by $759 billion over ten years and, as such, would significantly impede our ability to advance science and combat disease. As a nation, we cannot continue to erode non-defense discretionary funding levels and by association the National Institutes of Health budget which, when measured against the rising cost of conducting research, has been slashed by 22 percent between 2003 and 2013. We urge Congress to boost NIH funding to save and improve patient's lives, increase economic growth and restore our nation's place as the world leader in biomedical research."

The proposed cuts are counterproductive, said Research!America President and CEO Mary Woolley.

"The House and Senate FY16 budget proposals call into question our nation's commitment to medical innovation," said Woolley in a statement. "Are we willing to delay the discovery, development and delivery of lifesaving therapies and cures because of insufficient funding, or will we choose to accelerate the pace of medical progress?

"The proposed cuts for discretionary programs are counterproductive given health threats like cancer, Alzheimer's, Ebola, mental illness and diabetes afflicting millions of individuals close to home and abroad. Policymakers must work towards lifting sequestration and assigning a higher priority to medical research and innovation. Too many lives hang in the balance."

House Votes to Repeal Sustainable Growth Rate; Senate Delays Action

By Matthew Bin Han Ong

The House voted 392-37 to approve legislation that would eliminate the Sustainable Growth Rate, a method currently used by the Centers for Medicare and Medicaid Services to control spending by Medicare on physician services.

While the House voted on March 26, the Senate adjourned for spring recess without acting on the bill.

Physicians are now faced with the prospect of a 21 percent cut in Medicare reimbursement when the current SGR payment patch expires next week on March 31.

"ASCO is extremely disappointed that the Senate failed to act on the Medicare Access and CHIP Reauthorization Act of 2015 (H.R. 2)," the society said in a statement. "Over the next two weeks, ASCO will continue to urge the Senate to pass H.R. 2 immediately upon its return. President Obama supports the bill and is expected to sign the legislation into law."

The SGR formula has called for drastic reductions in physician payments in 2002, resulting in 17 expensive payment patches, ASCO said.

"Although the current SGR patch expires on March 31, the Center for Medicare & Medicaid Services has the ability to hold claims for 10 business days," ASCO said in a statement. "The hold claim period will

begin on April 1, 2015 and last through April 14, 2015. All claims for services delivered on or before March 31, 2015 should be paid under normal procedures."

Senate Majority Leader Mitch McConnell (R-Ky.) said the Senate will wait more than two weeks before acting on SGR, according to Reuters.

"They can handle a two-week gap here," McConnell said after the Senate vote-a-rama that ended on March 27. "We'll turn to it very quickly when we get back. I think there's every reason to believe it's going to pass the Senate by a very large majority."

The delay would not cause doctors to see lower Medicare payments due to the lag time in the normal processing of payments, McConnell said in the Reuters report.

The bill would restore stability in one of cancer care's most vital programs, said ASCO CEO Allen Lichter.

"We applaud the House of Representatives for passing legislation that eliminates the Sustainable Growth Rate formula and takes a giant leap toward meaningful and urgently needed Medicare physician payment reform," Lichter said in a statement. "Cancer incidence among Medicare beneficiaries is expected to increase by 67 percent by 2030, and maintaining a fundamentally flawed payment system could compromise healthcare access for this growing patient population.

"This bill would finally eliminate the perennial threat and uncertainty that the SGR has created for oncology practices across the country. It would also put in place important incentives to encourage the delivery of high quality care, and provide resources to enable practices to move toward alternative payment models."

Report: 2 in 5 Cancer Patients Concerned About Bankruptcy

Out-of-pocket costs for health care remain a top concern for many people living with cancer, according to a report by the Cancer Support Community, an international nonprofit.

The study, "An Insight into Patient Access to Care in Cancer," surveyed 511 cancer patients, 480 of whom live in the U.S. Nearly 90 percent of the respondents were women, and nearly two-thirds were between the ages of 45 and 64.

The study found that, despite advances made in health care reform, nearly 50 percent report paying more for health care over the past 12 months, and out-of-pocket medical costs remain a top concern for many.

Regardless of whether respondents indicated that they liked or did not like their health insurance, the top three concerns were out-of-pocket costs for premiums, co-insurance, and co-pays for medications.

"People are making decisions like consumers in a situation where the clinical stakes and the potential suffering of patients is substantial," said John Sprandio, a specialist in hematology and oncology in Philadelphia. "In general, health care reform is working well for some, and not as well for others."

Specifically, among those who said that they did not like their coverage, 58 percent had concerns about their premiums, 67 percent had concerns about their coinsurance and 54 percent had concerns about copay costs for medications.

Furthermore, two in five patients said they were seriously or very seriously concerned about potentially bankrupting their family with medical costs.

Additionally, 71 percent reported not receiving social and emotional support services during their cancer experience, which could have prevented some trade-off decisions, such as skipping doses of medications or missing medical appointments, according to CSC.

In patients for whom [health care reform] is working well, there are still bumps in the road," said CSC CEO Kim Thiboldeaux. "While the Affordable Care Act has brought health care access to people with preexisting conditions, such as cancer, who were previously denied coverage, there is still work to be done to ensure high-quality, affordable care for all people with cancer."

The full report is available here.

Pitt, Carnegie Mellon and UPMC Form Big Data Alliance

Three Pittsburgh institutions—Carnegie Mellon University, the University of Pittsburgh, and the University of Pittsburgh Medical Center—are pooling their electronic medical records to form the Pittsburgh Health Data Alliance.

The alliance is funded by UPMC and designed to support applied research and commercialization, along with basic foundational research in medicine and computer science. UPMC Enterprises, the commercialization arm of UPMC, will lead the effort.

"We are unlocking the potential of data to tackle some of our nation's biggest challenges: raising the quality and reducing the cost of health care. Not only will this effort benefit patients, but it also will accelerate Pittsburgh's revitalization," said UPMC CEO Jeffrey Romoff.

The alliance will include two research and development centers: the Center for Machine Learning and Health, led by founding director Eric Xing, a CMU professor in the Department of Machine Learning; and the Center for Commercial Applications of Healthcare Data, led by Michael Becich, chair of the Department of Biomedical Informatics at the University of Pittsburgh. Scientists from all three institutions will participate in the work of each center.

"The complementary strengths of the alliance's partner institutions will allow us to re-imagine health care for millions of people in our shared, data-driven world," said Subra Suresh, president of CMU. "Through this collaboration, we will move more rapidly to immediate prevention and remediation, further accelerate the development of evidence-based medicine, and augment disease-centered models with patient-centered models of care."

The new research centers will be funded over the next six years by UPMC and will benefit from several hundred million dollars in existing research grants at all three institution, according to a statement.

The centers will work to transform data into new technologies, products and services to change the way diseases are prevented and how patients are diagnosed and treated.

"Through this partnership, our brilliant scientists at Pitt and CMU will have unprecedented resources for turning their innovative ideas into products and services that can truly better the lives of patients and society," said Patrick Gallagher, chancellor of the University of Pittsburgh. "The knowledge created here will result in the spin-off of many new companies and thousands of new jobs over the next decade."

The CMLH will work on challenging problems at the intersections of health care and machine learning. Data from sources as varied as electronic medical records, genomic sequencing, insurance records and wearable sensors will be utilized to directly improve health care.

The CCA at the University of Pittsburgh will research and invent new technology for potential use in commercial "theranostics" and imaging systems for patients and doctors. Theranostics combines diagnostic and therapeutic capabilities to develop individualized therapies.

These technologies will be based on intelligently engineered big data solutions. Some areas of focus for CCA will be: personalized medicine for understanding diseases such as cancer and various lung disorders; genomics and imaging data; and methods for data capture and health care analytics.

In Brief

Pazdur Named One of 50 "Worlds Greatest Leaders" By Fortune Magazine

(Continued from page 1)

"Rarely does one hear anybody celebrate the FDA," Pazdur's profile reads. "But lately the agency's gatekeeper for cancer drugs is getting nearly universal praise for his effort to speed promising medications to market. In 2014 the FDA approved the greatest number of novel drugs in almost 20 years. Under Pazdur's leadership, says Len Lichtenfeld of the American Cancer Society, 'the FDA has been more responsive to the needs of cancer patients.'"

Pazdur is the director of the FDA Office of Hematology and Oncology Products. The full list of the 2015 leaders is available here.

JACK GAULDIE was named vice president of research of the **Research Institute of St. Joseph's Healthcare Hamilton**.

Gauldie is a distinguished university professor of pathology and molecular medicine at McMaster University. He is also director of the Institute for Molecular Medicine and Health. St. Joesph's is the university's academic hospital partner.

His primary area of focus has been gene therapeutics involving molecular manipulation for the treatment of diseases including cancer, arthritis and chronic lung diseases.

Gauldie previously served on advisory boards for the Canadian Institutes for Health Research, and is currently chair of the advisory board of the Ontario Research Fund.

He has received awards from the Canadian Medical Association, the Canadian Society of Clinical Chemists, and the Canadian Society for Immunology.

ELIZABETH JAFFEE was awarded the 20th annual AACR-Joseph H. Burchenal Award for Outstanding Achievement in Clinical Cancer Research by the **American Association for Cancer Research.**

Jaffee is deputy director of the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University. The award will be presented at the AACR's 2015 annual meeting, in Philadelphia April 18-22.

She was recognized for her contributions to cancer immunology in both the pre-clinical and early clinical settings. Her work in immunotherapies for

breast and pancreatic cancers has been influential to the discovery and development of new and effective cancer treatments. She is also recognized for her mentorship of researchers and clinicians.

Jaffee, who is also the Dana and Albert "Cubby" Broccoli professor of oncology at the Johns Hopkins University School of Medicine and co-director of the Skip Viragh Center for Pancreas Cancer, the Gastrointestinal Cancer Program, and the Cancer Immunology Program and Immunology and Hematopoiesis Division, will present her lecture, "Immunologic Treatments for Pancreatic Cancer: Current and Future Strategies," on April 21.

She is credited with opening the door to immunotherapy as a potential treatment for pancreatic cancer. Her research includes testing one of the earliest therapeutic pancreatic cancer vaccines, GVAX, in 1997. She has also shown that mesothelin is a viable target for therapeutic vaccines and adoptive therapy for pancreatic cancer. She recently led a phase II trial that showed that a GVAX prime and Listeria Monocytogenes vaccine boost improved overall survival for patients with pancreatic cancer; this approach was recently granted breakthrough status by FDA.

Jaffee is currently leader of the Stand Up To Cancer-Lustgarten Foundation Dream Team: Transforming Pancreatic Cancer to a Treatable Disease. The team is conducting combination clinical trials and establishing biomarkers of tumor microenvironment reprogramming. The trials focus on novel immune-suppressive pathways within the tumor, either in combination with a T cell-activating vaccine or chemotherapy.

She also currently serves on the AACR board of directors, as chair of the Cancer Immunology Working Group, and as co-chair of the Immunology Program Committee at this year's annual meeting. Additionally, she is deputy editor of Cancer Immunology Research and has been active in AACR mentoring programs, including those as part of the Women in Cancer Research Working Group.

JIMMIE HOLLAND will receive a Women of Influence Award from the **T.J. Martell Foundation**.

Holland is the Wayne E. Chapman Chair in Psychiatric Oncology at Memorial Sloan Kettering Cancer Center.

The New York foundation also presented awards to Delilah, a radio personality; Natalie Morales, host of NBC's Today Show; Latonya Crisp-Sauray, of the New York City Transit Union, Local 100; Elaine Turner, a designer; Kelly Turner, CFO of SESAC; and JuE Wong, CEO of StriVectin.

The award ceremony will be hosted by actress and radio personality Robin Quivers May 1 in New York, and will include a reception and silent auction.

"I am extremely excited about our third Women of Influence Awards in New York. The event brings together such amazing women to bond and learn about healthy living, breast cancer and ovarian cancer awareness and prevention and to celebrate women's achievements," said Laura Heatherly, CEO of the foundation. "This event will raise vital funds for the T.J. Martell Foundation's breast cancer and ovarian cancer research programs."

THE GAIRDNER FOUNDATION announced the winners of the **2015 Canada Gairdner Awards**, recognizing medical discoveries from around the world.

The awards provide a CAD $100,000 prize to each scientist for their work. The awards will be presented at a dinner in Toronto on Oct. 29, as part of the Gairdner National and Student Outreach Programs, a two week lecture series given by Canada Gairdner Award winners at more than 22 universities from St John's to Vancouver.

The selections for the Canada Gairdner International Awards, recognizing individuals from various fields for seminal discoveries or contributions to medical science, are:

Lewis Cantley, director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College and NewYork-Presbyterian Hospital; Margaret and Herman Sokol Professor in Oncology Research; and professor of cancer biology in medicine at Weill Cornell—"for his discovery of PI 3-Kinase, a critical component of the cell signaling machinery that plays a key role in normal functions of proliferations and growth and is de-regulated in diseases such as cancer and diabetes."

Michael Hall, professor, Biozentrum University of Basel, Switzerland—"for his discovery of the nutrient activated protein kinase TOR and elucidation of its central control of cell growth, critical to development and aging and widely implicated in cancers, diabetes, cardiovascular and immune diseases."

Lynne Maquat, director of the Center for RNA Biology: From Genome to Therapeutics; professor of biochemistry and biophysics at the University of Rochester School of Medicine and Dentistry; and the

J. Lowell Orbison Endowed Chair—"for the discovery of the mechanism that destroys mutant messenger RNAs in human cells, nonsense-mediated mRNA decay, which is critically important in both normal and disease states."

Yoshinori Ohsumi, honorary professor at the Frontier Research Center of the Tokyo Institute of Technology—"for pioneering the molecular elucidation of autophagy, an essential intracellular, degradation system and when disordered, is linked to many diseases including neurodegeneration, cancer, and infection."

Shimon Sakaguchi, distinguished professor and vice director of the Laboratory of Experimental Immunology at the WPI Immunology Frontier Research Center at Osaka University—"for his discovery of regulatory T cells, characterization of their role in immunity and application to the treatment of autoimmune diseases and cancer."

The Global Health Award, recognizing someone who is responsible for a scientific advancement that has made a significant impact on health in the developing world, was awarded to **Peter Piot**, director of the London School of Hygiene & Tropical Medicine and professor of global health—"for his co-discovery of the Ebola virus, his many contributions to HIV/AIDS research and his extraordinary leadership in the global response to the HIV/AIDS epidemic, especially in Africa."

The Wightman Award, given to a Canadian who has demonstrated outstanding leadership in medicine and medical science throughout his/her career, was awarded to **Janet Rossant**, chief of research at The Hospital for Sick Children in Toronto—"for her outstanding scientific contributions to developmental biology and for her exceptional international leadership in stem cell biology and policy-making, and in advancing research programs for children's illnesses."

BLOOMBERG PHILANTHROPIES, in partnership with the Australian government, launched **Data for Health**, a $100 million initiative that will enable 20 low- and middle-income countries to improve public health data collection.

The Data for Health initiative seeks to provide governments, aid organizations, and public health leaders with tools and systems to better collect data and use it to prioritize health challenges, develop policies, deploy resources, and measure success. Over the next four years, Data for Health aims to help 1.2 billion people in 20 countries across Africa, Asia, and Latin America.

In addition to improving the recording of births and deaths, Data for Health will support new mechanisms for conducting public health surveys. These surveys will monitor major risk factors for early death, including non-communicable diseases.

With information from these surveys, illness caused by day-to-day behaviors such as tobacco use and poor nutrition habits can be addressed. Data for Health will take advantage of the widespread use of mobile phone devices in developing countries to enhance the efficiency of traditional household surveys, which are typically time-consuming and expensive.

To assist governments with translating data into policy change, Bloomberg Philanthropies will support training programs for local officials that are led by organizations specializing in data use. This training will enable officials to better interpret data and use it to inform program and policy decisions.

The initiative's program partners include the University of Melbourne, the CDC Foundation, Union North America, and the World Health Organization.

Drugs and Targets

CHMP Grants Positive Opinion For Gardasil 9 HPV Vaccine

The European Committee for Medicinal Products for Human Use granted a positive opinion for Gardasil 9, the first nine-valent HPV vaccine.

The opinion recommends marketing authorization for active immunization of females and males from the age of 9 years against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types and genital warts (Condyloma acuminata) caused by specific HPV types.

The CHMP's positive opinion comes after the recent approval of Gardasil 9 granted by FDA.

Gardasil 9 includes the greatest number of HPV types in any available HPV vaccine. Seven high-risk HPV types, HPV 16, 18, 31, 33, 45, 52 and 58, cause approximately 90 percent of cervical cancer cases and approximately 80 percent of high-grade cervical lesions (cervical precancers, defined as CIN 2, CIN 3 and AIS) worldwide. The two remaining types, HPV 6 and 11, cause 90 percent of genital wart cases.

The CHMP opinion was granted following review of the results from an international clinical program that began in 2007 and included seven trials that evaluated more than 15,000 individuals.

The European Medicines Agency granted Orphan Drug Designation to Reolysin, for the treatment of ovarian, fallopian tube and primary peritoneal cancers.

"This is the second jurisdiction where we have gained Orphan Designation for the use of Reolysin in the treatment of these gynecological cancers and our first grant in the European Union," said Brad Thompson, president and CEO of Oncolytics Biotech Inc., the drug's sponsor.

The EMA grants Orphan Designation to medicines intended to treat, prevent or diagnose life threatening and debilitating disease, with a prevalence no greater than five in 10,000 in the EU, and where no satisfactory method of treatment, prevention or diagnosis exists, unless the proposed medicine offers a significant benefit to those with the condition. Following Orphan Designation, sponsors can access a number of incentives including protocol assistance, market exclusivity for a ten-year period following approval and potential fee reductions.

Teikoku Pharma USA submitted a New Drug Application to FDA for Docetaxel Injection Concentrate, Non-Alcohol Formula, for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer.

"Docetaxel Injection Concentrate, Non-Alcohol Formula offers an alternative to patients who might experience an adverse reaction to currently marketed docetaxel formulations due to alcohol sensitivity and those who simply prefer an alcohol free product." said Paul Mori, executive vice president and chief operating officer at TPU.

On June 20, 2014, the FDA issued a drug safety warning about docetaxel formulations. This communication indicated that docetaxel formulations, which contain alcohol, might cause patients to experience intoxication during and after treatment. The current available docetaxel formulations, including the brand Taxotere, range in alcohol content from 2.0 to 6.4 grams in 200 mg dose.

Rich Pharmaceuticals Inc. published a letter of intent with **Khon Kaen University** in Thailand to conduct clinical trials using Rich's molecule therapy RP-323 in treating AML patients.

Presently, the university has four research centers of excellence and 23 research groups doing clinical research across numerous disease states with emphasis in conducting oncology clinical trials.

The commencement of the clinical studies is conditioned upon establishing a budget and timeline for the studies, and the execution of a definitive clinical study agreement with the Faculty of Medicine at Khon Kaen University. The clinical studies are estimated to include 36 patients at three separate sites.

"As we move closer to beginning our AML clinical program, we are continuing to work diligently in securing additional principal investigators in the United States and finalizing our IND submission to the FDA," said Ben Chang, CEO of Rich Pharmaceuticals.

RP-323 is a phorbol ester, which induces differentiation and/or apoptosis in multiple cell lines and primary cells, activates protein kinase C, and modulates the activity of multiple downstream cell signaling pathways, including mitogen-activated protein kinase pathways.