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IMPACT FACTOR MANIA AND PUBLISH-OR-PERISH MAY HAVE CONTRIBUTED TO DANA-FARBER RETRACTIONS, EXPERTS SAY

Learning from past errors (and misconduct) in cancer research

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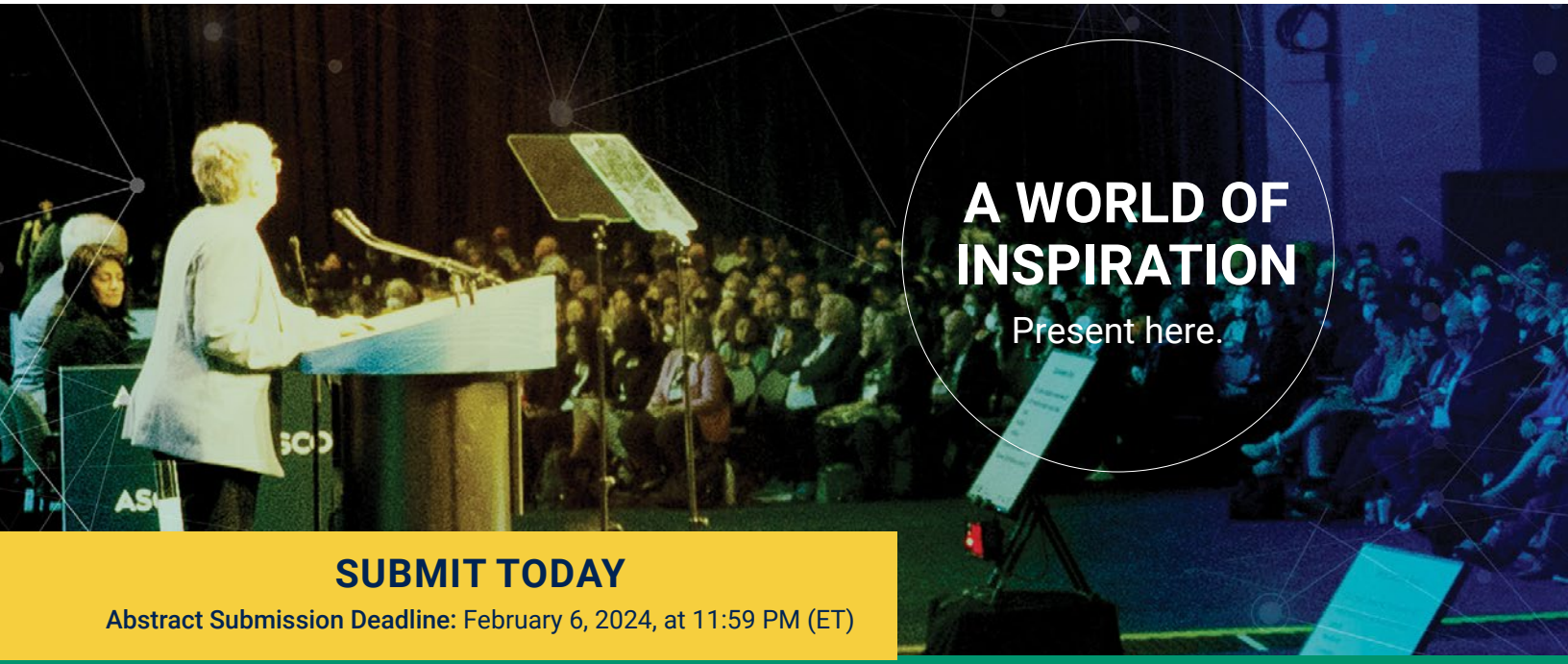

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In this issue

Impact factor mania and publish-or-perish may have contributed to Dana-Farber retractions, experts say

Learning from past errors (and misconduct) in cancer research

By Jacquelyn Cobb

More than a decade ago, Glenn Begley and Lee Ellis published a paper with astounding findings: of 53 "landmark" studies, only six, or 11%, were reproducible, even with the same reagents and the same protocols—and even, sometimes, in the same laboratory—as the original study.

Begley's and Ellis's classic paper, published in *Nature*, gave rise to a movement that captured the attention of the uppermost crust of biomedical research.

Then NCI Director Harold Varmus, for example, focused on the paper—and the broader problem of reproducibility—at a 2013 meeting of the National Cancer Advisory Board (*The Cancer Letter*, Dec. 3, 2013). In 2014, Francis Collins and Lawrence Tabak, then-director and then-deputy director of NIH, outlined the institute's plan to address the issue of reproducibility in biomedical research. Journals and funding agencies took action. Declarations, meetings, and reports suddenly materialized, and research funders rapidly responded.

Fast forward to February of 2024. Dana-Farber Cancer Institute is sorting through the 50-or-so papers with alleged evidence of image discrepancies. Biologist Sholto David brought attention to the papers on the blog For Better Science Jan. 2 (*The Cancer Letter*, Jan. 26, 2024).

So, what, if anything, has changed? Is it possible that a decade after the breast beating over Ellis's and Begley's findings research institutions continue to crank out irreproducible results? Does the incentivization structure of academic oncology continue to reward errors and research misconduct?

"There are so many people out there who are doing anything they can to get a paper in *Nature*, including falsifying data, choosing the best blot—do you choose the average western blot or the western blot which shows the best results, even through other western blots may be more modest? That's just our culture," Ellis, professor of surgery in the Department of Surgical Oncology at MD Anderson Cancer Center, said to *The Cancer Letter*.

"Any institute—and especially esteemed institutes like Harvard, there is pressure to publish in order to get through graduate school or to get a good job as a postdoc in a competitive world where funding gets tougher and tougher over time. Trainees need to have a big time publication(s) in order to advance in their careers," said Ellis, who is also the Ruben Distinguished Chair in Gastroenterology Cancer Research at MD Anderson and vice chair of Translational Medicine at SWOG Cancer Research Network.

Begley and Ellis are not involved in Dana-Farber's investigation of the disputed papers.

Concerns of research integrity are not unique to Dana-Farber. Sholto David has also written blog posts about Memorial Sloan Kettering surgeons.

"It's a cultural problem within the scientific community," Begley said. "The institutions that pretend they don't have poor quality research are deluding themselves. Every major institution has it."

At least six of the U.S. News's top ten cancer centers retracted at least one paper last year alone, according to the Retraction Watch database, the largest collection of retractions currently available. Retraction Watch's database was acquired by CrossRef in Sept. 2023.

Begley commends Dana-Farber for accepting responsibility.

"Dana-Farber really should be applauded for doing this. Not criticized," Begley said. "It's not something that we want to happen, but when it does happen, the institutions that take it seriously and deal with it really should be trumpeted. I don't know how we best applaud them, but they should be applauded in some fashion, because there are many institutions where it's happening.

"Other institutions just sweep it under the carpet and refuse to acknowledge that it's really going on."

The process of correcting the record continues, Dana-Farber officials said to *The Cancer Letter*:

> All the relevant papers for which Dana-Farber has primary responsibility are in varying stages of our process of review, which could include corrections or retractions. Moving as quickly as possible to correct the scientific record is important and a common practice of institutions with strong research integrity processes at which basic research is conducted.
>
> If a correction or retraction is necessary, it is submitted to the relevant journal, each of which has a different process to review, accept and publish.
>
> A separate, concurrent process on how errors occurred is ongoing. It bears repeating that the presence of image discrepancies in a paper is not evidence of an author's intent to deceive. That conclusion can only be drawn after a careful, fact-based examination, which is an integral part of our response.

"[Harvard] dealt with this quite swiftly," Ivan Oransky, co-founder of *Retraction Watch*, editor-in-chief of *The Transmitter*, and Distinguished Journalist in Residence at New York University's Carter Journalism Institute, said to *The Cancer Letter*. "When you compare this

response to other institutions, even recently, it's lightning-fast. And, in fact, it's lightning-fast compared to how Harvard has dealt with things in the past, which may reflect an evolution.

"One thing that's really noteworthy is the lack of drama. At no point have I seen any statements from Harvard or any of the people involved either out-and-out denying that there's anything going on or trying to lash out at Sholto David, or anyone else that has been commenting on it. I shouldn't have to say that that's refreshing and positive. That's just how it should be. But that sure as hell isn't how recent cases have gone.

"I think we should give credit where credit's due in terms of lack of drama, apparently lack of retaliation, and relative swiftness."

Investigators were unable to reproduce their own findings

Begley's doubts about the reliability of high-profile findings crept in during his years at Amgen Inc.

Between 2002 and 2012, in his role as vice-president and global head of hematology and oncology research at Amgen, Begley was building the Hematology and Oncology Research Therapeutic Area. Naturally, he was scanning the literature for novel, preclinical research that could reveal "actionable" targets that could be used in cancer treatment.

"So, of course, we were following the literature closely, and when something came up that was new, we would try and repeat it internally," Begley said. "When we couldn't, our standard operating procedure was to contact the researchers and ask if an Amgen scientist could go into their lab and watch them do the experiments.

"People were very generous and allowed us to do that, so long as we signed a confidentiality agreement."

Amgen scientists would typically ask the researchers to repeat their experiment in a blinded fashion.

"So, the researchers didn't know if they were looking at their positive controls or at their test sample or at their negative controls," Begley said. "And when they did that, they were unable to reproduce the findings that they'd published. The original investigators, in their own lab, using their own reagents, were unable to reproduce their own findings. That was, frankly, shocking to me."

As a result of those confidentiality agreements, Amgen cannot reveal the laboratories that were unable to reproduce their own work when the experiments were performed blinded.

"I don't think any of those papers have since been retracted, but because of the confidentiality agreement I cannot [identify them], nor can I disclose who those investigators were, but some of them actually subsequently did disclose themselves."

The Begley and Ellis collaboration began when they were connected by colleagues at MD Anderson.

"When I was at Amgen, I called Lee, because he'd been talking at many of the conferences about the slow translation of basic research into clinical work," Begley said. "And I said, 'Lee, this is part of the problem; we can't actually reproduce the work that's being published by the academics. It's not as though industry is deliberately trying to be difficult. When we dig into it, we just can't find it.'"

Together, they wrote what Ellis describes as "a treatise on the world of cancer and how it needs to be fixed."

The *Nature* article was influential. Ellis recalled the traction it made, over a decade ago, with Harold Varmus, Francis Collins, and leaders from other NIH institutes weighing in.

"We all sat around the table. Glenn and I went to the NIH when we met with nearly all of the NIH leadership, including Harold Varmus, who was head of the NCI and a Nobel Prize winner; Francis Collins, who was head of the NIH.

"We sat around a large table in the director's conference room and discussed issues with research integrity. We didn't present a slide program, but we had great discussions and we could see that it "opened the eyes" of NIH leadership. I think this meeting made an impact."

On perverse incentives

Intense pressure to "publish or perish" is not conducive to the goals of rigor and reproducibility, *Retraction Watch*'s Oransky said.

"All of this—whether it's error or out-and-out misconduct—the root is 'publish or perish.' I've only become more and more convinced of that over time," Oransky said. "I had some at least open-mindedness about it when Adam [Marcus] and I launched *Retraction Watch* in 2010. But by now, we're both quite convinced of that."

Ellis uses the previously-coined term "impact factor mania" when describing this disorder.

"Impact factor mania is doing whatever it takes to get over the hump to make it sensational. People want to quote studies in *Nature* or *Science* or *Cell* rather than the less 'elite' journals," Ellis said. "The desire to publish in the journals with the highest impact factors is just being human, but it's not being ethical. You're doing your best to advance your own

career. You're doing your best to get noticed in the world of cancer research.

"The system does not work in favor of reporting everything truthfully; if you don't publish in *big time* journals, you're not going to get a great academic appointment or get promoted. We're creating our own discourse and we're creating our own environment where we tend to publish what the principal investigator or institute or journal editor *wants* you to publish, rather than sometimes having a flaw, an unanswered question, or an imperfect story. And let me tell you, cancer is imperfect and constantly evolving; therefore, you don't see the same gene signature every single time."

Incentive structures encourage research misconduct at every level—from journalists to journals, Begley said.

"Many editors send papers out for review because they come from famous labs and they want those papers in their journals—not because the work is necessarily good, but because they come from a prestigious institution or someone that's got a good reputation," Begley said. "They think that publishing those papers means that the advertisers are more likely to use their journal because they're more likely to be read.

"Journalists, many of whom don't have formal scientific training, often simply put papers in the press because of the sexy title or the catchy abstract, or because it comes from a famous group," Begley said. "So, everyone has a part to play. The more you think about it, the more perverse incentives there are within the system."

Begley isn't looking for villains.

"It's not about academics being bad, it's about the incentives that we've put in place to try and encourage people to do things that don't necessarily square with robust reproducible science," Begley said. "That's really the message that I've been trying to convey. It's not as though I'm anti-academic. I'm not; I spent more than 20 years in academia myself, but it's more about the perverse incentives that we've got. We shouldn't, but we treat a paper that's published in one of the highly cited journals as though it's fact.

"I would hate for this to come out saying academia is wrong. That's not the truth. But it's the perverse incentives that we put in place that really lead people astray."

> "The institutions that pretend they don't have poor quality research are deluding themselves. Every major institution has it."
>
> – *Glenn Begley*

This culture sets off reverberations that harm research and researchers, Raymond N. DuBois, director of the MUSC Hollings Cancer Center and executive chairman of the board of The Mark Foundation for Cancer Research, said to *The Cancer Letter.*

"The biggest damage done by publishing disputable data is that as other researchers read these reports and assume they're accurate, they begin designing their own experiments based on unreliable data. They end up wasting valuable time, money, and resources," he said. "Which can have a multiplier effect, because young scientists in their labs go off on misguided tangents that could cause a crucial setback to their careers.

"We have a responsibility to ensure that data in the literature has high integrity and is reproducible. Otherwise, there will be a delay in moving the field forward. Ultimately, patients and science in general will suffer."

What's changed?

Problems with reproducibility usually affect basic science, but these issues sometimes spill over into the clinic.

In 2010, NCI eliminated a biomarker test from an ongoing phase III clinical trial that was studying an omics-based biomarker developed at Duke University.

The study—CALGB-30506 (LMS, Lung Meta-Gene Score) Trial—aimed to evaluate the prognostic value of the LMS test. (However, in the cooperative group trial patients weren't being assigned to treatment groups based on the test).

After NCI discovered that the test was based on corrupted data and therefore had no merit, the institute pulled it completely from the trial (*The Cancer Letter,* May 14, 2010).

This happened amid a larger set of issues that were covered closely by *The Cancer Letter.*

The controversy is remembered largely because a prominent genomics researcher, Anil Potti, who played a key role in developing the biomarker test at Duke University, falsely claimed to have been a Rhodes Scholar.

However, the central question was far more significant: At what point are omics tests results ready to be evaluated in patients?

Lisa McShane, associate director of the Division of Cancer Treatment and Diagnosis and head of the Biometric Research Program at NCI, said the Duke case was an important landmark in establishing the need for rigor in omic studies.

Said McShane:

> Omics technologies were emerging as a powerful research tool in the early 2000s. Some research findings were developed into omics-based clinical tests proposed for incorporation into clinical trials where they would be used to guide treatment for individual patients. Some cases of premature advancement of omics-based tests to use in clinical trials came to light, including the flawed omics-based tests developed by the Potti/Nevins team at Duke University.
>
> Concerns began to arise more generally about rigor and reproducibility in this arena and led to calls for examination of the field of translational omics.
>
> The Institute of Medicine conducted a study to review the field and formed the "Committee on the Review of Omics-Based Tests for Predicting Patient Outcomes in Clinical Trials," which published a landmark report.
>
> Simultaneously, the National Cancer Institute was also observing a troubling lack of rigor and reproducibility in research that it was reviewing that utilized these powerful omics technologies.
>
> A major focus of the concern at that time was tests for which high-dimensional omics data were processed by a mathematical algorithm to produce a multivariate score or classifier that was intended to predict patient outcome or response to therapy; we referred to these broadly as "omics predictors."
>
> Motivated by our own experiences and the deliberations of the IOM committee, the NCI convened a workshop to bring together scientists and stakeholders who had an interest in this area of research to stimulate community dialogue.
>
> As a byproduct of the workshop, a group was formed to develop a checklist aiming to operationalize the principles set forth in the IOM report and the NCI workshop discussions.
>
> The goal was to provide a convenient checklist to remind researchers developing omics predictors of best practices so that they might avoid common pitfalls and increase chances of successful clinical translation.
>
> Considerations include defining specimen requirements, ensuring robust and analytically valid omics assays with well-documented technical protocols, use of proper statistical and computational approaches for developing and validating "locked down" predictors, choice of study designs appropriate for establishing clinical utility of candidate predictors, and abiding by ethical and legal requirements.
>
> The biggest change is an increase in the types of omics technologies and their greater penetration into research and clinical laboratories.
>
> Consequently, there are more users, particularly more inexperienced users, of these technologies. Free software to analyze omics data and build omics predictors is also more widely available.
>
> My perception is that the research community has learned how to better scrutinize evidence presented in support of an omics predictor, especially when claims of its performance look "too good to be true."
>
> While we don't want the field to be viewed with pure cynicism, a healthy level of scrutiny should help to raise the standards for omics research in general, with respect to quality, rigor, transparency, and reproducibility.
>
> As omics predictors, or any other biomarker-based tests, move closer to the clinic, the stakes become higher. Patients are relying on these tests that guide clinical care to perform well, just as new drugs must be adequately evaluated for safety and effectiveness before they reach the clinic.
>
> Our hope is that the omics checklist is a useful tool to aid in evaluating readiness of an omics-based test for clinical use.

Documents produced as a result of what is still colloquially known as "Pottigate" include the NCI "Omics Checklist" and the report by what was then the Institute of Medicine (*The Cancer Letter*, Jan 23, 2015; Feb. 7. 2013; Oct. 22, 2010).

Said McShane:

Since 2012, many research funding agencies have changed their guidelines and are taking the issue of research reproducibility more seriously, Begley said.

The criteria by which NIH reviewers are now asked to evaluate the scientific merit of a grant application include

components that address reproducibility, rigor, and transparency, and NIH now offers related guidance for would-be grantees.

Some of the leading highly-cited journals also made commitments to enhance reproducibility. *Nature* abolished their word limit in their methods section in 2013 to "more systematically ensure that key methodological details are reported." *Science* and *Science Translational Medicine* followed suit shortly after.

"When I first published the paper in 2012, I received threats and abuse," Begley said. "Now, when I give talks on this subject, scientists no longer challenge the idea that many publications in highly cited journals are misleading. Instead of challenging that, they now ask 'What should we be doing about this?'"

The number of retractions has grown dramatically since 2010, according to *Retraction Watch*'s Oransky.

"One thing that's changed is the growth in retractions; right? So, that's actually been pretty dramatic," Oransky said. "When we launched, there were about 400 retractions per year from journals. In 2023, there were more than 10,000. A big jump, one that is much larger than you would expect if you just said it's because there are more papers being published. That would account for a doubling or tripling maybe, but not a 25-fold increase."

The errors were always there, but nobody was looking, Oransky said.

"With scientific misconduct and errors, when no one's looking for it, which was essentially the case until quite recently, it looks like it doesn't exist," Oransky said. "You had people getting up in front of Congress in the 1980s saying it doesn't exist, telling Al Gore when he was in Congress that scientific misconduct basically doesn't happen—'Don't worry about this.'

"Until people started looking in any systematic way—I wouldn't even say it's systematic yet—but until people started looking in a large-scale way, it's not surprising they didn't find anything, But now that they are, we really need to take it seriously."

Oransky compares the uptick in public scrutiny to a cancer screening test.

"It's a lot like a cancer screening test, which, of course, readers of *The Cancer Letter* are more than familiar with," Oransky said. "The facts of the matter are: If you use a screening test, you will find more cases. Are those real cases? That's something we have to work out."

Oransky said he believes that at least 2% of published papers should be retracted. Currently, the estimate of papers retracted stands at 0.2%.

A paper published in *PLOS Medicine* in 2009 reported that an estimated 1.97% of scientists anonymously admitted to having fabricated, falsified, or modified data or results at least once.

"That's been replicated," Oransky said. "In fact, often, people find more than 2%."

Steps to ensure rigor and reproducibility

In separate interviews, Ellis, Begley, DuBois, and Oransky suggested strategies to help investigators avoid their names appearing on the dreaded websites, which include *Retraction Watch*, *PubPeer*, and *For Better Science*.

1. Read papers before you cite them

People typically cite papers without actually reading them, Begley said.

"They read the title of the paper or the abstract, but they don't actually read the paper itself," he said. "If you read a paper, you can tell whether or not the work is robust or not."

Blinding and randomization are the gold standard to ensure scientific rigor, Begley said.

"So, the first thing I do when I'm reading a paper is to see whether or not it was blinded," Begley said. "I search for the word blind, then I search for the word random, to see if the animals were randomized in the studies. And most papers, that's not the case. That makes the work suspect.

"If it's not blinded and you've got subjective endpoints, people are going to see what they want to see. The whole reason we have blinding—justice is supposed to be blind—is so that we just make judgments based on the facts, not on what we want it to be."

Scientists are quick to dismiss this tip, Begley said.

"When I give a talk, I say one of the things that we as scientists should do is read papers before we cite them. And the audience always laughs," Begley said. "They think it's a joke; it's not a joke. They know it's not true. They know that people just cite papers primarily because they're citing people who are famous. They know that if they don't cite those famous people, they might get punished in the future or whatever. But that's not why we should cite papers. We should cite papers because they're good quality work."

Young researchers are especially vulnerable.

"Again, it's these perverse incentives—people, especially young people, are scared that if they don't cite the work of a senior scientist, when they submit their paper to be published, it may not get published because they failed to cite the leaders in the field," he said.

2. Review your lab's raw data weekly: The good, the bad, and the ugly

Ellis reviews his lab's raw data every week, and encourages others to do the same.

"One thing that needs to be in place is that principal investigators, or leaders of the lab, need to see data every week," Ellis said. "There may be a week that you go to a meeting or something like that, that's fine. But we need to keep track of data in real time and not just wait until somebody hands you a draft paper without seeing its evolution over time. A PI should be involved in all of his/her lab's research from start to finish. When you have a lab of 26 people, you see their data once every six months, maybe. So, you can't just wait for a *Nature* paper to fall on your desk. You need to see it in real time."

"That's why with my laboratory, even in this crazy era, even if I'm out of town, we'll have a lab meeting. I'll look at the data every single Wednesday morning from 9:30 to 11:00 a.m."

MUSC's DuBois agrees.

"I can give you my perspective, being the PI of my own laboratory," he said. "What I do is to review the raw data during my weekly laboratory meetings. Postdocs and students present their data, and we review it carefully. Sometimes, this leads to additional experiments that confirm or disprove the results. It is important to examine all the data carefully before it gets curated into a slide presentation.

"Before we even consider starting to write a manuscript, I take the responsibility to examine the raw data generated at the bench and confirm that it truly represents the results we use to make our conclusions."

It's important to create an honest lab environment, Ellis said.

"The lab needs to know that you're being transparent and you want to see the real data, not just the best data," he said. "I've trained a bunch of people, and they all know we're going to meet on Wednesdays and we're going to show data, and I want to see the good and the bad."

3. Keep each other accountable

Data collection processes need to incorporate checks and balances, Ellis said.

"When you go back and harvest tumors from animals, there should be three people there," Ellis said. "One person taking care of the mouse, one person who's a scribe, and another person to help wherever the help is needed.

"If you have one person do it, who knows what kind of results you're going to get? So, I think you need to have three people back there. When you're looking at preclinical studies, it would be really hard to falsify data, or just to choose the best data, when you have three people there, rather than just a single person."

Once again, establishing a culture of rigor in the lab is important—especially in the era of team science.

"While as the lab leader, I'm not in there sacrificing mice, my team is," Ellis said. "That's why I think you have to have a whole team and you have to set a tone for the laboratory."

4. Pursue only high-performing experiments, or be willing to publish negative studies, or both

Implicit in "publish or perish" is "publish negative results and perish."

"There are funding issues," Ellis said. "I mean, in the current culture, if you only publish negative studies in preclinical models that are seen as "suboptimal and not reflective of human cancer", then you have a failed lab where you haven't discovered anything. There are cultural issues."

Negative findings are to be expected as experiments get more complex, Ellis said.

"Every time you take a step from a preclinical, whether it's cell culture to a mouse model, to a better mouse model, etc., every time you go one step to the next, expect to lose 50% efficacy," Ellis said. "You have perfect conditions for these cell lines, the RAS status, the BRAF status, the P53 status. But, in humans, you've got immune cells and you've got fibroblasts and you've got drug delivery issues.

"In every step for drug development, expect a drop in your hopeful outcomes by about 50% along the way, which means you have to have really robust findings to begin with. By the time you get to the clinic with patient heterogeneity and tumor heterogeneity and various sites of metastasis, you're not going to get a standard error that's going to be 0.1%. Especially in this era, we should be shooting high.

Despite the stigma in academic oncology, negative findings are useful for the research community.

"You want to get your paper into *Nature* rather than an open access journal where you pay to publish," he said. "I just published in *PLOS One*. I wanted to get the paper out there. It was an important paper. It was about two drugs that, in combination, looked good in vitro, but they didn't do anything in vivo; therefore it's not going to go to a clinical trial. So, it was important to get this solid data out there, even though it was negative. But we thought that it was im-

portant to share this finding and get it out there. My lab did the right thing.

"I like to think that I stick by my principles and I practice what I preach."

"Having a paper that reports negative data, I'm proud to talk about that, because as a clinician who's vice chair of SWOG, an NCI sponsored clinical trial group, I want to know what *doesn't* work," Ellis said. "We have so many options these days that if somebody did a well-done study and it's negative, it absolutely should be published. But that's not going to get a lot of citations and it's not going to help you get promoted.

"Suppose a PI did not have a good hypothesis or their hypothesis was wrong, there's nothing wrong with that. You need to have a place to publish the negative study."

"It is a long process"

Despite DuBois's commitment to checking his lab's raw data, new technologies pose new challenges.

"I think before the digital age, it was a lot easier to monitor this from just looking at films from blots and other data generated in the lab," DuBois said. "But now, there are so many ways to manipulate images using sophisticated software platforms, making it much easier to cobble very compelling figures together."

The field can call on new technologies to help mitigate these problems, DuBois said.

"I don't know what the ideal solution is, but it's probably something that could be addressed by the National Academy of Medicine or an agency that brings in all the experts—those in AI, the coders, and others—and tries to develop a rapid screening process for manuscripts to ensure that no manipulation of the data has occurred," he said.

"If a group could come together—and I'm not an expert in image analysis or certainly not an expert in software development—but these groups could come together and see if there could be an effective solution created."

Team science introduces more opportunity for error.

"One thing that's changed is that if you look at the authorship on a lot of these papers, there are multiple authors and sometimes multiple institutions involved," DuBois said. "I think there is a rush to try to get these impactful papers out as quickly as possible. So, I think some of the raw data may not be accessible to all the authors; they don't get to examine it. It just gets plugged into the paper without somebody really looking it over and making sure that it's all reliable with high integrity. I think the papers are bigger, they're longer, with more supplemental data.

"So, because of the size of the research team, I think that may have led to some of this because whoever the appointed lead author is may not be monitoring all of that data as carefully as needed. Some labs have become huge, so PIs, in that situation, are really focused on overseeing the grant portfolio and raising money, philanthropic support, and other administrative duties. So, they may lack the time needed to review all of the raw data."

Even in the Collins-Varmus era, there was talk of transitioning away from the version of the biosketch which allowed for an infinite citations list, opting instead to highlight an applicant's most impactful papers and their role in the study.

"What I'd love to see happen is for everybody to stop using publications and citations as the only coin of the realm," Oransky said. "I might even like to get rid of that currency altogether. There are some really good ideas about that. And again, that's a root cause problem that is often the hardest to get at."

Begley said he hopes that junior researchers will bring about cultural change in academia.

"The younger scientists see this as a more important problem than the laboratory heads," Begley said. "There is reason to be optimistic that there will be change as they assume leadership positions.

"I hope we will see evidence of this in the next few years as there are fewer publications of poor quality appearing in the literature. But it is a long process, that begins with the grant reviews, but then the research typically takes several years and the publications then appear 1-2 years later, but I remain optimistic that the changes that have already happened will have an important impact."

> "When you compare this response to other institutions, even recently, it's lightning-fast. And, in fact, it's lightning-fast compared to how Harvard has dealt with things in the past, which may reflect an evolution."
>
> – *Ivan Oransky*

REGULATORY NEWS

FDA tells sponsors of CAR T-cell therapies to add boxed warning about secondary T-cell malignancies

By Alexandria Carolan

FDA has directed the sponsors of CAR T-cell therapies to place boxed warnings on their products to indicate that the agents may cause secondary T-cell malignancies.

The agency said it decided to require the warning after its investigation found that 22 of more than 34,000 people treated with this class of drugs, called BCMA-directed or CD19-directed autologous chimeric antigen receptor cell immunotherapies, developed such secondary malignancies.

The findings triggered the agency to issue a series of letters to the sponsors of all CAR T-cell therapies on the market:

- Yescarta (ciloleucel), sponsored by Kite,
- Carvykti (ciltacabtagene autoleucel), sponsored by Janssen Oncology and Legend Biotech,
- Abecma (idecabtagene vicleucel), sponsored by Bristol Myers Squibb,
- Breyanzi (lisocabtagene maraleucel), sponsored by BMS,
- Kymriah (tisagenlecleucel), sponsored by Novartis.

The agency states that since these agents were approved, it has "become aware of the risk of T-cell malignancies, with serious outcomes, including hospitalization and death, following treatment with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies."

The letter continues:

> FDA identified postmarketing adverse event and clinical trial reports describing occurrence of mature T cell malignancies, including CAR-positive tumors, following treatment with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies.
>
> For additional information please see CBER safety communication titled, "FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies," and a posting at July - September 2023 | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) | FDA for BCMA- or CD19directed genetically modified autologous T cell immunotherapies.
>
> We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.
>
> Furthermore, we consider the serious risk of T cell malignancy to be applicable to all BCMA- and CD19-directed genetically modified autologous T cell immunotherapies.

FDA also sent a letter directing Kite to update the safety information for Tecartus (brexucabtagene autoleucel).

However, this change states that patients treated with Tecartus haven't been diagnosed with T cell malignancies.

FDA is requiring the companies to respond within 30 days.

Oncologists who spoke with *The Cancer Letter* do not anticipate that these new boxed warnings will have a profound impact on patient care.

CAR T-cell therapy is an important treatment option for patients with several high-risk lymphoid malignancies, said Ruben Mesa, president and executive director of Atrium Health Levine Cancer, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, said to *The Cancer Letter.*

"Given the significant and unique clinical benefit of CAR T in high-risk lymphoid neoplasms, we do not envision changing our utilization of these treatments at this point, but will be monitoring CAR T recipients closely," Mesa said. "We have a very active program across both main campuses of our NCI Comprehensive Cancer Center."

FDA previously stated that the benefits of these therapies "continue to outweigh their potential risks for their approved uses."

Most physicians were already discussing the risk of secondary malignancies with their patients, said Helen Heslop, director of the Center for Cell and Gene Therapy at Baylor College of Medicine, Texas Children's Hospital and Houston Methodist.

Heslop is also a professor in the departments of medicine and pediatrics, section of Hematology-Oncology and Dan L Duncan Chair at Baylor College of Medicine. She is the leader of cancer cell and gene therapy at Dan L Duncan Comprehensive Cancer Center.

"It was always a theoretical but low risk with current vectors that the CAR could insert in a place where it caused a malignancy," she said to *The Cancer Letter.* "And it is not yet clear if the CAR insertion or genetic changes the patient already had caused the malignancy in these cases."

Those treated with CAR T-cell therapy often already received other treatments—chemotherapy, radiotherapy, or transplants—which can cause secondary malignancies as well, Heslop said.

"It was a conversation oncologists would have always had, but now there'll just be some additional information from the FDA report to discuss," she said.

Secondary malignancies associated with treatment with CAR T-cell therapy are rare.

"If you consider how many commercial CAR T-cell products have been given, which are over 34,000 since they've all been approved, it's a low incidence," Heslop said. "There are a few caveats there, in that not all the cases may have been reported to the FDA."

The first CAR T-cell therapies were approved in 2017, and so there hasn't necessarily been enough time for long-term follow up, she said.

Additional research is needed, Mesa agreed.

"I hope more will be discovered on the pathophysiology of these CAR T emergent T-cell neoplasms that may allow us to decrease this risk further in the future," he said.

Long-term follow-up care is important, Heslop said.

"I'd encourage people to enroll these patients in the Center for International Blood and Marrow Transplant Research Registry," she said. "In transplant we've learned a lot from long-term follow up data, and I think we can hopefully do the same in cell therapy to get much more accurate information to give to patients."

Ultimately, these boxed warnings don't change the risk-benefit of CAR T-cell therapy, she said.

"It's obviously something you've got to talk to patients about, but I think the benefits of CAR T-cell therapy for all the current commercial indications outweigh the risks," she said.

"Given the significant and unique clinical benefit of CAR T in high-risk lymphoid neoplasms, we do not envision changing our utilization of these treatments at this point, but will be monitoring CAR T recipients closely."

– *Ruben Mesa*

BLACK HISTORY MONTH

Video series uses storytelling to increase diversity in clinical trials: "Having a seat at the table is essential"

By Amy Lacey, VCU Massey Comprehensive Cancer Center

Sheldon L. Holder knew he wanted to pursue a career in medicine in the second grade, thanks to a career day at his school on the island of Bermuda.

Trailer for The Color of Cancer, a video series by Sheldon Holder.

Working in a doctor's office in high school officially set Holder on the path. He then decided to become a physician-scientist his freshman year at Oakwood University, a Historically Black College and University (HBCU) in Huntsville, AL after witnessing upperclassmen conduct research.

But now storytelling is where Holder, assistant professor of pathology and laboratory medicine at The Warren Alpert Medical School of Brown University, found a new niche for the accrual of a more diverse patient population in clinical trials.

The Color of Cancer is a video series Holder launched with funding he received in 2021 from the Robert A. Winn Diversity in Clinical Trials Award Program (Winn Awards).

"Rhode Islanders who have had cancer or family members who have had cancer tell their story about cancer. We film it, we archive it," said Holder, who is also the associate director for diversity, equity and inclusion at Legorreta Cancer Center at Brown University.

The Winn Awards program was established in 2020 with a $100 million pledge by the Bristol Myers Squibb Foundation (BMSF) to increase diversity in clinical trials and transform the clinical research landscape.

"It's important for the science," said Holder. "We want to make sure our treatments, our regimens are effective in all people."

Holder graduated from the Winn Career Development Award (Winn CDA) in November 2023; the two-year program is designed for early-stage investigator physicians from diverse backgrounds and physicians who have demonstrated a commitment to increasing diversity in clinical research.

As part of his Winn CDA project, Holder created a community advisory board to guide his outreach. It is composed of residents from across Rhode Island who represent various professions and backgrounds, with a focus on "everyday" residents.

The board, which meets about every other month, suggested a video campaign to reduce stigmas and improve low levels of medical trust associated with cancer and clinical research. There are plans to release seven testimonials sequentially on the web experience.

> "[We need to] be able to identify where there are disparities that need to be addressed, how we can address them, what are the reasons they exist in the first place and why it's important that we address them."
>
> *– Sheldon L. Holder*

"The Color of Cancer has resulted in several personal interactions with cancer survivors and their families," Holder said. "Additionally, several cancer survivors have connected with each other. We have also seen support from local charities. Moreover, there appears to be a growing interest in the Color of Cancer within the community and growing interest in the Legorreta Cancer Center."

To further dialogue created by the Color of Cancer, Holder also started the Cancer Talk Cafe.

"[Legorreta Cancer Center has] events in the communities, target communities, where people from the community can come and, in an informal way, talk with our oncologists and our administrators at the cancer center," Holder described. "Not a lecture, not a sign-up drive, but really just to come and talk and get to know us."

While Holder's time with the Winn CDA has ended, he is determined to advance work started with the Color of Cancer. He is currently seeking additional funding for the initiative and in his lab that studies novel targets for cancer therapy, with a particular focus on PIM1 Kinase as a therapeutic cancer target.

"I am continuing to conduct open clinical trials and develop new clinical trials," Holder said. "I am also enthusiastically participating in the development and establishment of the Historically Black College and University Cancer Trials Consortium (HBCU-CTC). I believe the HBCU-CTC will revolutionize the ability to bring clinical trials to communities of color."

He added, "It requires a team. It's a lot of work, a lot of effort to recruit and enroll people in clinical trials."

While Holder also maintains an active genitourinary oncology clinic, he will explore opportunities to integrate clinical trials in the greater conversation about social drivers of health and cancer inequity.

"[We need to] be able to identify where there are disparities that need to be addressed, how we can address them, what are the reasons they exist in the first place and why it's important that we address them," said Holder.

Holder said Winn's work has inspired him. Winn, for whom the awards are named, is the director of the Virginia Commonwealth University (VCU) Massey Comprehensive Cancer Center in Richmond, VA. Winn is a leader in integrating a community-to-bench model for a new generation of cancer centers.

Looking to Winn's career focus, Holder has a better understanding of the value community members place on research when they are involved in the process.

"He gives you energy, gives you a will to want to do this work to make a bigger impact," Holder said about Winn. "You need someone at the table who knows what the needs are, what the problems are and how we can better change the way we conducted ourselves in the past to improve accrual of people of color in clinical trials. Having a seat at the table is essential to helping to solve this problem in impactful ways."

This story is part of Winn's ongoing coverage as guest editor of the Cancer History Project during Black History Month. A full list of his past coverage appears on page 26.

The Robert A. Winn Diversity in Clinical Trials Award Program aims to train, develop and mentor more than 308 diverse and community-oriented clinical trialists and 308 medical students by 2027 through the Winn CDA and Robert A. Winn Clinical Investigator Pathway Program. The program is supported by BMSF, Gilead Sciences and Amgen. VCU and the American Association for Cancer Research are implementation partners. Implementation collaborators include Conquer Cancer, the American Society of Clinical Oncology Foundation and the American Heart Association.

> "You need someone at the table who knows what the needs are, what the problems are and how we can better change the way we conducted ourselves in the past to improve accrual of people of color in clinical trials."
>
> – *Sheldon L. Holder*

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NCI Outstanding Investigator Award (with up to $600,000 a year) goes to 17 scientists

By Jacquelyn Cobb

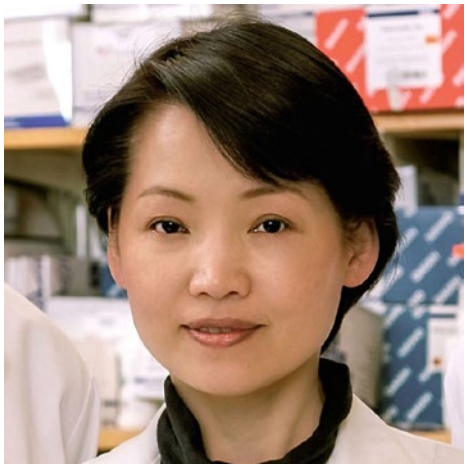
Seventeen scientists have received NCI's 2023 Outstanding Investigator Awards, with up to $600,000 in direct costs per year over six years.

The Outstanding Investigator Award supports accomplished leaders in cancer research who are providing significant contributions toward understanding cancer and developing applications that may lead to a breakthrough in biomedical, behavioral, or clinical cancer research.

Candidates for the OIA must be nominated by their applicant organization which should consider nominating meritorious mid-career, women and under-represented minority candidates.

Additional eligibility criteria can be found on the NCI website.

The most recent NCI Outstanding Investigator Award recipients are:



Jean J. Zhao, PhD
Professor of biological chemistry and molecular pharmacology,
Harvard Medical School;
Dana-Farber Cancer Institute

The Zhao Lab investigates the signaling networks regulating cellular processes in cancer, examining how these signals affect tumor, immune, and stromal cells. Their research aims to elucidate mechanisms of immune evasion, therapy resistance, and metastasis.

Ongoing projects focus on deciphering how PI3K/PTEN signals control immune responses in prostate and breast malignancies. They are also unraveling how immune activity influences targeted therapy effectiveness in cancer. Additionally, they investigate how breast tumors spread to the brain and pursue therapeutic approaches to treat brain metastases.

By applying their expertise in signal transduction and pharmacology to genetically engineered mouse models (GEMMS) and patient-derived xenografts (PDXs), the lab conducts multi-omics and mechanistic analyses. This enables comprehensive understanding of tumorigenesis, immune evasion, and therapeutic resistance to significantly advance cancer biology and immuno-oncology.

Craig B. Thompson, MD
Member,
Cancer Biology and Genetics Program,
Department of Medicine,
Memorial Sloan Kettering Cancer Center

There has been a renewed interest in how oncogenic driver mutations and tumor suppressor losses contribute to cancer-associated alterations in cellular metabolism. Through their research, the Thompson Lab is exploring the hypothesis that glutamine-dependent mitochondrial glutamate accumulation provides the cell with an intracellular reserve of reduced nitrogen that can be directed toward mitochondrial support of de novo polyamine production, amino acid biosynthesis, and glutathione generation.

In addition, the Thompson Lab is studying how the differential fates of mitochondrial glutamate are regulated by growth factors, as well as by oncogenes and tumor suppressors. While the normal pool of mitochondrial glutamate is fed by extracellular glutamine uptake, the Thompson Lab plans to test whether the combination of lactate and ammonia that accumulates in the tumor microenvironment (TME) under nutrient-poor conditions can be utilized to restore mitochondrial glutamate and cytosolic glutamine to levels that support adaptive translation and cell survival.

The results will aim to clarify how cancer cell avidity for nitrogen is satisfied based on nutrient availability and the presence of specific oncogenic mutations and tumor suppressor losses. The insights gained will help to shape new approaches for the diagnosis and treatment of cancer.

Kimberly Stegmaier, MD
Professor of pediatrics,
Harvard Medical School;
Vice chair of pediatric oncology research,
Ted Williams Chair,
Dana-Farber Cancer Institute;
Co-director, Pediatric Hematologic Malignancy Program,
Boston Children's Hospital and Dana-Farber Cancer Institute

Despite progress in understanding the molecular basis of childhood malignancies, cancer remains a leading cause of

disease-related death in children. Moreover, childhood cancers continue to be treated with old approaches, including cytotoxic chemotherapy, radiation, and surgery, each with associated morbidities.

The Stegmaier laboratory will address the fundamental challenge of improving treatments for children with cancer with more tumor targeted drugs. They will focus primarily on fusion-driven pediatric cancers of high unmet need, such as acute myeloid leukemias (AMLs) and the solid tumor Ewing sarcoma. Stegmaier and her team propose a multipronged strategy—the direct targeting of oncogenic fusions, the targeting of highly vetted non-oncogene liabilities, and the discovery and targeting of regulators of immunotherapies. They will focus on targets involved in gene regulation such as transcription factor fusions, transcriptional co-activators/repressors, and chromatin regulating complexes, which have emerged from their screening efforts.

They will pioneer strategies of targeted protein degradation to validate and mechanistically dissect the role of these targets in tumor maintenance and to develop inhibitors/degraders that will ultimately inform new therapies.

Ross L. Levine, MD
Senior vice president for translational research, Memorial Hospital; Laurence Joseph Dineen Chair in Leukemia Research, Member, Human Oncology and Pathogenesis Program, Attending physician, Memorial Sloan Kettering Cancer Center

Genetic and functional data have demonstrated the importance of somatic mutations in signaling effectors and in epigenetic modifiers in the pathogenesis of myeloproliferative neoplasms (MPN) and acute myeloid leukemia (AML). However, the mechanisms by which these two classes of leukemia disease alleles cooperate to induce transformation, and how coordinated mutations in signaling pathways and in epigenetic regulators affect the response to targeted therapy, has not been fully explored.

Through their work, the Levine Lab plans to investigate how mutations in signaling effectors cooperate with mutations in epigenetic regulators to induce myeloid transformation, and how these mutations influence the response to targeted therapies. The Levine Lab will then extend their studies to investigate whether combination therapeutic approaches can achieve increased efficacy in models of MPN and AML.

The long-term goal of their research is to characterize novel mechanisms by which oncogenic disease alleles cooperate to induce leukemogenesis, and to create novel combination strategies that can be investigated in the clinical context. The Levine Lab will use a combination of genetically accurate animal models, epigenomic studies in murine models and patient samples, and preclinical therapeutic studies aimed at rational design of combination therapeutic strategies.

Timothy C. Wang, MD
Chief, Division of Digestive and Liver Diseases, Silberberg Professor of Medicine, Co-leader of the Tumor Biology and Microenvironment Program, Herbert Irving Comprehensive Cancer Center, Columbia University

The Wang Lab seeks to investigate the role of nerves and other stromal cells in the development of digestive cancers, including stomach, esophageal, colon, and pancreas. The Wang Lab will build on previous work that suggests that GI cancers arise from tissue stem cells, and that stromal niche elements can regulate stem cells, and that by inhibiting stromal cells in the microenvironment, it may be possible to inhibit the development of tumors.

Marcel R.M. van den Brink, MD, PhD
Principal investigator, medical oncologist, President,
Deana and Steve Campbell Chief Physician Executive Distinguished Chair,
City of Hope National Medical Center

The gut microbiota consists of a community of diverse microbes and has many effects on human (patho)physiology. Microbiome composition has been associated with many diseases, but causal inference is often lacking.

Over the last several years, the van den Brink Lab has focused on the role of gut microbiota in outcomes of allogenic hematopoietic cell transplantation (allo-HCT) and immunotherapy. In their new research, the van den Brink Lab plans to improve cancer immunotherapy by targeting the intestinal microbiome based on preclinical and clinical studies.

The van den Brink Lab will accomplish this through the development of a new pipeline for microbiome analysis, as well as preclinical and clinical projects regarding intestinal microbiome and CAR T-cell therapy, new techniques to analyze the effects of diet and drugs on the intestinal microbiome, and preclinical and clinical studies regarding immune modulation by bile acids.

Results from the research will aim to inform the future development of clinical trials to test therapeutic strategies to enhance efficacy and decrease toxicity in patients receiving cancer immunotherapy, such as CAR T-cell therapy and allo-HCT.

Jeffrey S. Miller, MD
Deputy director, Co-Leader Immunology Program,
Masonic Cancer Center,
University of Minnesota

During the last 25 years, the Miller Lab has led clinical efforts to develop novel natural killer (NK) cell immunotherapy strategies to treat cancer by advancing lab-based discoveries in the areas of NK cell and interleukin (IL)-15 biology. The Miller Lab has found that exposure to cytomegalovirus (CMV) induces a population of NK cells with potent immune and anti-tumor function that are marked by the expression of the NKG2C activating receptor that recognizes HLA-E, which is overexpressed on many solid tumor cancers.

Through their work, the Miller Lab plans to develop novel strategies to specifically target solid tumor malignancies by testing new induced pluripotent stem cells (iPSC) edits that facilitate homing and migration, overcome hypoxia, and promote survival after adoptive transfer in patients with solid tumor malignancies. To enhance the specificity and anti-tumoral activity of iPSC derived NK cells (iNK) cells, the Miller Lab has developed a camelid nanobody specific for B7-H3, an immune checkpoint protein, that serves as the engager of a novel chimeric antigen receptor (CAR).

In addition, the Miller Lab will compare these CAR iNK cells using the same CAR edited into an iPSC-derived T cell. The impact of these investigations is to develop novel off-the-shelf immune cell therapies with the potential to change standards of cancer care.

M. Celeste Simon, PhD, MS
Arthur H. Rubenstein, MBBCh Professor,
Scientific director,
Abramson Family Cancer Research Institute,
Associate director, Shared Resources,
Abramson Cancer Center,
University of Pennsylvania

The most common kidney cancer subtype is clear cell renal cell carcinoma (ccRCC), which accounts for approximately 75% of all cases. Multiple therapies are now available to ccRCC patients, including anti-angiogenic VEGF/receptor tyrosine kinase inhibitors, immune checkpoint blockade, mTORC1-based drugs, and a novel HIF-2a inhibitor. However, not all patients respond to

these treatments and five-year relapse rates now approach 40%, where many of these cases develop metastases.
Through their work, the Simon Lab has generated copy number variation, transcriptomic, and metabolomic data to identify multiple metabolic pathways that are universally altered in ccRCC tumors. The findings of the research conducted by the Simon Lab have been extended to other cancers such as hepatocellular carcinoma (HCC) and soft tissue sarcoma (STS), which appear to engage in highly similar metabolic reprogramming.

To continue these advancements, Simon and her team will investigate how consistent metabolic adaptations within the tumor parenchyma impact stromal components. A principal conceptual innovation of their recent work is the demonstration that multiple metabolic networks are consistently altered (approximately 100%) in genetically diverse cancers like ccRCC, HCC, and STS, and the identification of novel, highly feasible therapeutic strategies.

Ralph J. DeBerardinis, MD, PhD
Professor, Children's Research Institute, UT Southwestern Medical Center; Investigator, Howard Hughes Medical Institute

Metabolic reprogramming is a hallmark of malignancy and potential source of therapeutic targets. Recent studies indicate that metabolic liabilities change as cancer progresses, meaning pathways most relevant to advanced cancers may not be apparent in locally invasive, treatment-naïve tumors at the site of origin. With this knowledge, the DeBerardinis Lab developed an approach to probe the metabolic network of intact human tumors by infusing patients with stable isotope-labeled nutrients during tumor resection or biopsy.

To aid in their work, DeBerardinis and his team propose three directions. First, examine how mitochondrial metabolism stimulates metastasis to identify discrete metabolic dependencies that could be safely targeted in patients. Second, develop a series of approaches to discover new metabolic liabilities in human tumors. Third, use the orthogonal approach of studying human inborn errors of metabolism (IEMs) to discover why some metabolic anomalies prime cells to become malignant.

Altogether, DeBerardinis and his team hope these efforts will build on their long-standing productivity in human cancer metabolism by uncovering new mechanisms governing the metabolic basis of cancer progression and producing new methodologies to understand and treat lethal malignancies.

Paul J. Hergenrother, PhD
Kenneth L. Rinehart Endowed Chair in Natural Products Chemistry, Professor, Department of Chemistry, Carl R. Woese Institute for Genomic Biology, Deputy director, Cancer Center at Illinois, University of Illinois at Urbana-Champaign; Director, NIH Chemistry-Biology Interface Training Program

The clinical success of Gleevec (imatinib) two decades ago appeared to usher in a new era for cancer treatment, whereby a molecular defect in a patient's tumor was known and could be exploited with a selective drug. However, the progress of traditional drug discovery in this realm suggests new approaches are needed to fully realize the potential of targeted therapy for oncology.

Through their work, Hergenrother and his team have developed a discovery platform—from compound synthesis, to cell culture evaluation, target identification, sophisticated animal models, and translation—that has resulted in four novel cancer drugs licensed and moving toward cancer patients in 15 years.

In their continued research, the Hergenrother Lab will create an unprecedented collection of compounds biased for anticancer activity. In doing this work, Hergenrother and his team will

help the field realize the full potential of personalized medicine for cancer.

Charles G. Mullighan, MBBS (Hons), MSc, MD
Member, St. Jude faculty,
Deputy director, Comprehensive Cancer Center,
Co-leader, Hematological Malignancies Program,
Medical director, St. Jude Biorepository,
William E. Evans Endowed Chair,
St. Jude Children's Research Hospital

Acute leukemia is the commonest childhood tumor and a leading cause of cancer death in the young. The goal of research of the Mullighan laboratory is to use integrated genomic discovery, experimental modeling and therapeutic development to identify and characterize the genomic drivers of disease, mechanisms of resistance to therapy, and to develop new treatment approaches.

The research program will build upon prior discoveries to pursue several conceptually and technically innovative areas central to advancing cure rates for these diseases, including: the mechanistic basis of enhancer deregulation in leukemia; the role of genomic drivers such as activation of BCL11B in lineage ambiguous leukemia; the mechanistic role and potential for therapeutic targeting of LMO2/STAG2 alterations in leukemia; and the mechanistic role and potential for therapeutic targeting of fusion oncoprotein-mediated liquid-liquid phase separation.

The Mullighan laboratory will develop innovative protein degradation approaches using molecular glues to degrade hitherto intractable cancer drivers of high-risk leukemia.

Titia de Lange, PhD
Leon Hess Professor,
American Cancer Society Professor,
Head, Laboratory of Cell Biology and Genetics,
Director, Anderson Center for Cancer Research, Rockefeller University

Numerous recent whole-genome sequencing (WGS) studies have revealed that most cancer genomes carry a remarkable level of structural changes, affirming the need to understand how this genome instability arises. In their work, the De Lange Lab will focus on how telomeres affect tumorigenesis with emphasis on the two major contributions of telomeres in cancer: the telomere tumor suppressor pathway and telomere-driven genome instability.

To gain deeper insights into the telomere tumor suppressor pathway, De Lange and her team will determine how telomere length is regulated. Following a recent demonstration that cancer cell lines with short telomeres are exceptionally sensitive to loss of the telomeric factors CST and TRF1, De Lange and her team will determine the mechanistic basis of these vulnerabilities in hopes that their insights may point to new treatments.

The De Lange Lab aims to derive deep insights into how cancer genomes are altered, with the overarching goal of providing oncologists with information that can inform their decisions on diagnosis, treatment, and prevention.

Jeanne S. Mandelblatt, MD, MPH
Professor of oncology,
Georgetown University

By 2030, three-quarters of the 22 million U.S. cancer survivors will be 65 years and older, and the number of older Hispanic and Black survivors will have grown three times faster than White survivors. These shifting demographics are a driving crisis in cancer care due to a lack of evidence to guide care for older survivors.

The Mandelblatt Lab plans to shift how cancer disparities are approached by providing a mechanistic understanding of the role of cellular aging in the relationships between social determinants of health and survivorship outcomes. The Mandelblatt Lab will use a conceptual model that integrates a multi-level disparities framework with oncology and geroscience.

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The primary goals of the Mandelblatt Lab are to discover cellular aging processes in large cohorts of older Black, Hispanic and White survivors that explain relationships between health determinants and quality of life; define mechanistic pathways suggested by cohort results; and test the impact of interventions targeting those pathways in a preclinical model of cancer survivorship. The work of Mandelblatt and her team will support efforts to tailor clinical care for the burgeoning older minority survivor population and will aim to transform how we approach cancer disparities in the context of aging.

Thomas F. Gajewski, MD, PhD
AbbVie Foundation Professor of Pathology,
Professor of medicine,
Professor, Ben May Department for Cancer Research,
University of Chicago

Novel immunotherapies for cancer are having a major clinical impact, in particular anti-PD-1 monoclonal antibodies (mAbs). However, our understanding of the mechanisms that explain why a subset of patients responds to these therapies while other patients do not remain incomplete. Prior data discovered by the Gajewski Lab suggested that a baseline T cell-inflamed tumor microenvironment is a predictive biomarker for response to anti-PD-1.

The overall hypothesis of the Gajewski Lab is that germline polymorphisms in the host, genomic features of the tumor cells, and the composition of intestinal microbiota can influence the extent of a spontaneous T cell response against a patient's tumor, which in turn will determine the likelihood of response to immunotherapy. While the work of the Gajewski Lab thus far has focused on melanoma, genomic data have indicated that many of the same principles apply to multiple additional cancer types.

Gajewski and his team identify candidate therapeutic targets from patient material, create mouse preclinical models to study mechanism, then use those data to prioritize new treatment strategies to expand immunotherapy efficacy further.

Riccardo Dalla-Favera, MD
Percy and Joanne Uris Professor of Clinical Medicine,
Professor of pathology and cell biology, genetics and development, and microbiology and immunology,
Institute for Cancer Genetics,
Director, Institute for Cancer Genetics,
Columbia University

Diffuse large B cell lymphoma (DLBCL), the most common lymphoma, is incurable in approximately 30% of patients and, despite recent advances in CAR T-cell therapies, remains a significant clinical challenge. One barrier to rationally targeted new therapies is the remarkable heterogeneity of these tumors, which leaves as many as 20% to 50% of cases unclassified based on cell-of-origin or more recent genetic-based classifications.

In their recent work, the Dalla-Favera Lab found that regions corresponding to active super-enhancers (SEs) are highly and specifically hypermutated in 97% of DLBCL cases, as compared to the same loci when not active as SEs. Through their research, Dalla-Favera and his team hope to identify and mechanistically dissect the top recurrently mutated/functionally relevant SEs and associated target genes. In addition, Dalla-Favera and his team aim to gain a better understanding of the role of the glucocorticoid receptor pathway, which appears to be commonly targeted by the SE hypermutation mechanism, as well as by direct coding mutations, in normal B cell biology and lymphomagenesis.

The Dalla-Favera Lab anticipates that this new layer of genetic alterations will identify novel mechanisms of dysregulation for known oncogenes, as well as new dysregulated genes and pathways, with implications for precision classification and therapeutic targeting of DLBCL.

Peter A. Jones, PhD, DSc (hon)
Chief scientific officer,
Van Andel Institute

The mammalian de novo DNA methyltransferase, DNMT3A, is essential for postnatal development of the brain, control of body size and regulation of hematopoiesis. Mutations in the DNMT3A gene are commonly found in age-associated clonal hematopoiesis of indeterminant potential and are drivers for certain leukemias, which reinforces the importance of understanding how the enzyme functions in living cells.

Although we know how DNMT3A methylates naked DNA, less is known about how this occurs in the context of nucleosomes. The Jones Lab will utilize biochemical, cryo-EM, cellular and mouse studies to gain a more precise understanding of how DNA methylation works in the context of chromatin. They also will leverage recently developed techniques to explore the role of a truncated isoform, DNMT3A2.

In addition, the Jones Lab will study the prevalence of hemimethylation in cancer cells and investigate its effects on binding of other transcription factors and chromatin structure, due to differential binding in asymmetric cell divisions in cancer cells. Through their work, the Jones Lab hopes to answer critical questions that will advance cancer research and inform improved treatments.

William G. Kaelin Jr., MD
Sidney Farber Professor of Medicine,
Harvard Medical School;
Dana-Farber Cancer Institute;
Investigator, Howard Hughes Medical Institute

VHL tumor suppressor protein (pVHL) inactivation is the usual initiating truncal event in clear cell renal cell carcinoma (ccRCC), the most common form of kidney cancer. pVHL forms a ubiquitin ligase that targets the hypoxia-inducible factors (HIF) transcription factor for degradation.

The work of the Kaelin Lab has contributed to the development of vascular endothelial growth factor (VEGF) inhibitors/HIF-2 inhibitors for ccRCC, and 2-HG inhibitors for IDH mutant leukemia. In addition, the Kaelin Lab has identified new potential SL interactors for VHL (CDK4/6 and ITGAV) and mutant IDH (DHODH and GSK3b), and plan to conduct further validation and mechanistic studies. Additionally, the Kaelin Lab embarked on SL screens in Drosophila fly cells as paralog compensation may cause false negatives in genetic screens with human cells.

The Kaelin Lab created an "up" screen for chemicals and gene knockouts that can degrade a protein of interest and used it to discover that Spautin-1 is a cereblon-independent IKZF1 degrader and are pursuing the underlying mechanism. Research conducted by Kaelin and his team found that HIF-2 drives the expression of many endogenous retroviruses, some of which can be translated and presented as HLA-bound peptides. However, the researchers plan to continue examining additional ccRCC cell lines and tumors for such peptides and whether they are immunogenic.

IN THE ARCHIVES

CANCER HISTORY PROJECT

Past Black History Month coverage from guest editor Robert A. Winn

GUEST EDITOR
BLACK HISTORY MONTH

Robert A. Winn, MD
Director and Lipman Chair in Oncology, VCU Massey Comprehensive Cancer Center, Senior associate dean for cancer innovation, Professor of pulmonary disease and critical care medicine, VCU School of Medicine

This month, Robert A. Winn returns to his role as guest editor of *The Cancer Letter* and the Cancer History Project during Black History Month.

In his day job, Winn is the director and Lipman Chair in Oncology at VCU Massey Comprehensive Cancer Center, senior associate dean for cancer innovation, and professor of pulmonary disease and critical care medicine at VCU School of Medicine.

As we welcome Winn to this role, the Cancer History Project is taking a look back at his work as guest editor—beginning in the summer of 2020, through now.

Robert Winn, Otis Brawley: "I could have been George Floyd"
Aug. 6, 2020

Walter Lawrence, 95, reflects on the National Cancer Act, medicine, social justice, COVID-19, and Richmond's vanishing monuments
Aug. 6, 2020

Lori Pierce: Therapies are of no use when patients can't get off work to be treated
Feb. 19, 2021

Kunle Odunsi: 50 years from now disparities—and metastatic disease—will be gone
Feb. 26, 2021

Wayne Frederick on the legacy of LaSalle Leffall, Jr. – The Cancer History Project
Feb. 4, 2022

Harold Freeman, father of patient navigation, on cutting the cancer out of Harlem
Feb. 11, 2022

Edith Mitchell on her path from Tennessee farm to becoming a cancer doctor and brigadier general
Feb. 18, 2022

Black History Month panel: "We need to talk about justice"
Feb. 25, 2022

Otis Brawley & Robert Winn discuss the killing of Tyre Nichols and the power dynamics in policing—and health care
Feb. 3, 2023

Richard Silvera is bridging advocacy and research through the Robert A. Winn Diversity in Clinical Trials Award Program
Feb. 3, 2023

MSK's Vickers: "We've been seen as exclusive and selected. I want to broaden that aperture for the organization."
Feb. 17, 2023

'The house that Jack built': remembering Howard University's Jack E. White
Feb. 24, 2023

This column features the latest posts to the Cancer History Project by our growing list of contributors.

The Cancer History Project is a free, web-based, collaborative resource intended to mark the 50th anniversary of the National Cancer Act and designed to continue in perpetuity. The objective is to assemble a robust collection of historical documents and make them freely available.

Access to the Cancer History Project is open to the public at CancerHistoryProject.com. You can also follow us on Twitter at @CancerHistProj, or follow our podcast.

Is your institution a contributor to the Cancer History Project? Eligible institutions include cancer centers, advocacy groups, professional societies, pharmaceutical companies, and key organizations in oncology.

To apply to become a contributor, please contact admin@cancerhistoryproject.com.

IN BRIEF

C. Norman Coleman receives Henderson Lifetime Achievement Award

C. Norman "Norm" Coleman has received the 2023 D.A. Henderson Lifetime Achievement Award, bestowed by the Administration for Strategic Preparedness and Response in the U.S. Department of Health and Human Services.

The award, presented by the assistant secretary of ASPR, Dawn O'Connell, recognized Coleman's accomplishments and commitment to medicine, science, public health, and health security.

This is ASPR's premier award, recognizing a person's outstanding contributions to public health and health security. D.A. Henderson is recognized for leading the global efforts to eradicate smallpox.

This award was established and posthumously awarded in 2019 to him because he was instrumental in establishing the office that eventually became ASPR following Sept. 11 and the anthrax attacks in 2001.

Coleman is recognized for his efforts as a radiation oncologist to build, promote, and enhance the United States's preparedness for radiological and nuclear incidents, building a network of colleagues and organizations across government, academia, industry, and health care systems.

When the Sept. 11 terrorist attacks led to increased efforts to mitigate risk to civilian populations from potential radiation exposure from high consequence radiological and nuclear events, he assembled a group of radiation, biology, and oncology experts to identify gaps in knowledge, which led to the current HHS Radiological and Nuclear medical countermeasure programs in both NIH and ASPR and the development of medical and public health operational plans for preparedness and response.

He serves on committees and working groups relating to medical preparedness for radiological and nuclear events. In response to the March 2011 Fukushima nuclear disaster, Coleman worked directly in Japan with the U.S. Ambassador and Japanese leaders to provide expertise in managing the incident.

For this work, he received the premier award for career federal employees, the Samuel J. Heyman Service to America Medal ("Sammie") for Safety, Security and International Affairs. These awards are considered the "Oscars" of public service.

In 2013, he founded the International Cancer Expert Corps, and still serves as the organization's senior scientific advisor. He is the associate director of the Radiation Research Program, Division of Cancer Treatment and Diagnosis, at NCI, and he is a senior investigator, Experimental Therapeutics Section (laboratory) at the Radiation Oncology Branch, Center for Cancer Research at NCI. Coleman continues to work with ASPR as a senior medical advisor.

David Pfister to step down as chief of the Head and Neck Oncology Service at MSK

David Pfister, chief of the Head and Neck Service at Memorial Sloan Kettering, has decided to step down from this role after more than 20 years of leadership. He will remain in the position until a successor has been selected.

Pfister was the inaugural chief of the Head and Neck Service at Memorial Sloan Kettering Cancer Center. The unit, one of the first of its kind, was created in 2004. An expert in the management and

research of head and neck tumors, Pfister is a leader, investigator, and clinician who made important contributions in the development of combined modality, "organ preservation" treatment programs that are now standard of care alternatives to radical surgery to preserve function and cosmesis without compromising survival.

Pfister has served Memorial Sloan Kettering for over 30 years. He arrived at Memorial Sloan Kettering as a medical oncology fellow and then joined the faculty in 1989.

Under his leadership and fostering of multidisciplinary collaborations, the Head and Neck Service grew beyond the historic emphasis on upper aerodigestive tract cancers, to include NCI-supported research and clinical programs in thyroid, salivary gland, and non-melanoma skin malignancies.

Pfister has also served MSK in other leadership capacities, most notably as associate deputy physician-in-chief for strategic partnerships. Related to that role, he is chief of oncology for MSKCC's collaboration with Jamaica Hospital Medical Center/MediSys, a safety-net hospital in Queens, with the intent of growing the oncology program there and improving the outcomes of cancer care for the community it serves.

Pamela Kunz named editor-in-chief of new *JCO Oncology Advances*

Pamela Kunz was named editor-in-chief of *JCO Oncology Advances*, a new open-access journal published by The American Society of Clinical Oncology.

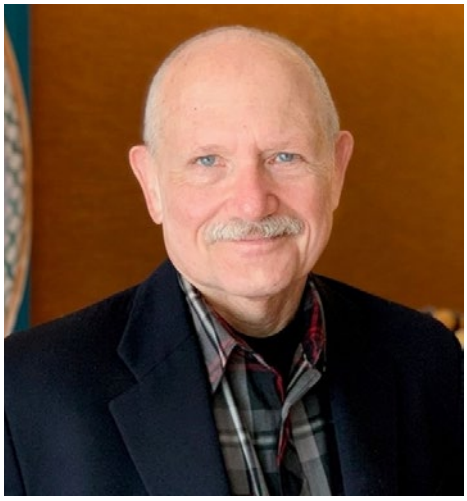
Kunz leads the Center for Gastrointestinal Cancers at Smilow Cancer Hospital and Yale Cancer Center and is also the division chief of GI Medical Oncology at Yale. She is an associate professor of internal medicine, specializing in medical oncology, at the Yale School of Medicine.

JCO OA aims to foster interdisciplinary collaboration and make oncological insights freely accessible, supporting the global effort to improve patient outcomes.

"Leading as the first editor-in-chief of *JCO Oncology Advances*, I am committed to shaping this platform into the foremost oncology open-access journal," Kunz said in a statement. "By publishing a wide array of content, we aim to engage a diverse audience, encompassing academics, community practitioners, international colleagues, and patient partners."

"Our accessible online format empowers us to be innovative, agile, and impactful, extending our reach far beyond conventional boundaries." The journal will open for submissions in Spring of 2024. Learn more on *JCO Oncology Advances*.

Michael Lotze named editor-in-chief of SITC's *Journal for ImmunoTherapy of Cancer*



Michael T. Lotze was named editor-in-chief of Society for Immunotherapy of Cancer's official journal, *Journal for ImmunoTherapy of Cancer.*

Lotze has worked in the field of immunology and clinical medicine for over 30 years and is a long-time SITC member and past president, attending his first meeting in 1989.

In addition, Sjoerd H. van der Burg, was promoted and appointed to the role of deputy editor-in-chief for *JITC*. He served as interim deputy editor-in-chief over the past year.

James L. Gulley was *JITC*'s interim editor-in-chief for the past year and will continue to serve in such capacity.

MD Anderson designated IAEA Collaborating Centre to focus on improving radiation, radiology and nuclear medicine

MD Anderson Cancer Center has signed an agreement with the International Atomic Energy Agency to become an IAEA Collaborating Centre.

Working together, MD Anderson and the IAEA aim to enhance radiation oncology, radiation physics, radiology, nuclear medicine, and nutrition globally. MD Anderson will be the first IAEA Collaborating Centre in the United States focused on health care.

"Our years of work with the IAEA and now being named a Collaborating Centre, exemplifies our commitment to advancing global efforts in cancer research, treatment and education," Peter WT Pisters, president of MD Anderson, said in a statement. "This collaboration underscores our dedication to fostering international collaborations that accelerate progress, particularly in low- and middle-income countries, where radiation treatment and diagnostic imaging capabilities are least accessible."

The IAEA has six decades of experience helping countries take action against cancer, and also cooperates with the World Health Organization and other agencies within the United Nations system.

An IAEA Collaborating Centre is an IAEA Member State institution that focuses on research, development and training and which has been designated by the IAEA to support its programmatic activities by implementing an agreed work plan.

As of January 2024, 71 active IAEA Collaborating Centres worldwide operate in areas related to the safe, secure and peaceful application of nuclear science and technology.

The Imaging and Radiation Oncology Core Houston in the Department of Radiation Physics at MD Anderson has provided several international member states of the IAEA with quality assurance services, including audits, training, and research.

Additionally, training and expert missions have been conducted by teams from radiation physics, radiation oncology, imaging physics, diagnostic imaging and others.

MD Anderson aims to expand its support of IAEA through a jointly developed work plan that includes:

- Training and educational activities in radiation oncology, radiation physics, radiology, nuclear medicine and nutrition.
- Technical expertise and assistance in expanding scientific and technical capabilities in radiotherapy and radiology.
- Research collaborations, for example, quality assurance of dosimetry auditing methodologies.
- Collaboration in the Rays of Hope initiative of the IAEA through Anchor Centres.
- Participation in the cost-free experts program of the IAEA through the provision of technical experts.

36 early-career investigators receive ASH 2024 Scholar Award

Thirty six early-career investigators received the the American Society of Hematology 2024 Scholar Awards.

The ASH Scholar Award supports early career investigators dedicated to careers in hematology research as they transition from training programs to careers as independent investigators.

Each Scholar Award provides $100,000 for the Fellow level, $125,000 for the Fellow to Faculty Scholars level, and $150,000 for the Junior Faculty level. The program funds hematologists in the United States and Canada who conduct basic, translational, and clinical research that advances the understanding and treatment of blood disorders.

"The ASH Scholar Award offers crucial support, resources, and mentorship to emerging scholars during their transition from training to establishing independent careers as investigators in hematology," 2024 ASH President, Mohandas Narla, of New York Blood Center Enterprises, said in a statement. "Through this award, ASH recognizes their remarkable contributions and acknowledges their potential to transform the field."

The 2024 Scholar Awards recipients are:

Basic/Translational Research Fellows:

- Joshua Brandstadter, University of Pennsylvania
- Nicoletta Cieri, Dana-Farber Cancer Institute
- David Glass, Fred Hutchinson Cancer Center
- Xu Han, Case Western Reserve University School of Medicine
- Mariia Kumskova, The University of Iowa
- Kentson Lam, University of California San Diego
- Pengfei Liang, Duke Medical Center
- Xinjian Mao, Stowers Institute for Medical Research
- Jeremy Meier, The University of North Carolina
- Caner Saygin, The University of Chicago
- Michael Tassia, Johns Hopkins University

Basic/Translational Fellow to Faculty Scholars

- Andres Chang, Winship Cancer Institute of Emory University
- Saravanan Ganesan, Weill Cornell Medicine
- Sascha Haubner, Memorial Sloan Kettering Cancer Center
- Yafeng Li, The University of Texas Southwestern Medical Center
- Erin Parry, Dana-Farber Cancer Institute

Basic/Translational Research Junior Faculty Scholars

- Robert Bowman, University of Pennsylvania
- Francesca Ferraro, Washington University in St. Louis
- Harinad Maganti, Canadian Blood Services
- Linde Miles, Cincinnati Children's Hospital
- Patrizia Mondello, Mayo Clinic
- Zuzana Tothova, Dana-Farber Cancer Institute
- Kim Vanuytsel, Boston University Chobanian & Avedisian School of Medicine / Boston Medical Center
- Aaron Viny, Columbia University Irving Medical Center
- Albert Yeh, Fred Hutchinson Cancer Center

Clinical Research Fellow

- Michelle Lee, Massachusetts General Hospital

Clinical Research Fellow to Faculty Scholars

- Christopher Su, University of Washington / Fred Hutchinson Cancer Center

Clinical Research Junior Faculty Scholars

- Ghaith Abu Zeinah, The NewYork-Presbyterian Hospital / Weill Cornell University
- Susanna Curtis, Icahn School of Medicine at Mount Sinai
- Natalie Grover, The University of North Carolina
- Swetha Kambhampati, City of Hope National Medical Center
- Madhavi Lakkaraja, Fred Hutchinson Cancer Center
- Ang Li, Baylor College of Medicine
- Reid Merryman, Dana-Farber Cancer Institute
- Melody Smith, Leland Stanford Junior University
- Shaina Willen, University of California Davis Medical Center

ASH Scholar Awards are made possible through support from the ASH Foundation as well as from the corporate community, individual donors, and funds committed by the Society. AstraZeneca sponsors this award.

ASH commits approximately $13 million annually in support of the careers of the next generation of leaders in the field of hematology through the society's awards and career development programs.

FUNDING OPPORTUNITIES

DoD Lung Cancer Research Program anticipated funding opportunities for FY24

The FY24 Defense Appropriations Act provides funding for the Lung Cancer Research Program to support innovative, high-impact lung cancer research.

The managing agent for the anticipated funding opportunities is the CDMRP at the U.S. Army Medical Research and Development Command (USAMRDC).

The LCRP is providing the information in this pre-announcement to allow investigators time to plan and develop ideas for submission to the anticipated FY24 funding opportunities. This pre-announcement should not be construed as an obligation by the government.

The FY24 LCRP funding opportunity announcements for the award mechanisms will be posted on the Grants.gov website. Pre-application and application deadlines will be available when the announcements are released.

A pre-application is required and must be submitted through the electronic Biomedical Research Application Portal.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Subcutaneous Opdivo shows noninferiority vs. intravenous Opdivo in advanced or metastatic RCC

The phase III CheckMate -67T trial, evaluating the subcutaneous formulation of Opdivo (nivolumab) co-formulated with Halozyme's proprietary recombinant human hyaluronidase (rHuPH20) (herein referred to as "subcutaneous nivolumab") compared to intravenous Opdivo in patients with advanced or metastatic clear cell renal cell carcinoma (ccRCC) who have received prior systemic therapy, demonstrated noninferiority for the co-primary endpoints of Cavgd28 (time-averaged Opdivo serum concentration over 28 days) and Cminss (trough serum concentration at steady state) compared to IV Opdivo.

Subcutaneous nivolumab displayed noninferior objective response rate as assessed by Blinded Independent Central Review vs. IV Opdivo. These results were featured in a late-breaking oral presentation (Abstract #LBA360) at the American Society of Clinical Oncology 2024 Genitourinary Cancers Symposium Jan. 25-27.

Opdivo is sponsored by Bristol Myers Squibb.

"Having the option to administer immunotherapy subcutaneously could undoubtedly reduce the treatment burden that patients diagnosed with cancer currently face, as well as help maximize efficiencies within healthcare systems," Saby George, professor of oncology and medicine and director of Network Clinical Trials, Department of Medicine, Roswell Park Comprehensive Cancer Center, said in a statement.

One injection that can be given in under five minutes and, in some cases, outside of the infusion center, George said.

In the CheckMate -67T trial investigating subcutaneous nivolumab (n=248) vs. IV Opdivo (n=247) in patients with advanced of metastatic ccRCC:

- Cavgd28: Noninferiority of subcutaneous nivolumab to IV Opdivo was shown for the time-averaged serum concentration over the first 28 days, with a geometric mean ratio of 2.098 (90% Confidence Interval [CI]: 2.001 - 2.200).
- Cminss: Noninferiority of subcutaneous nivolumab to IV Opdivo was shown for the minimum serum concentration at steady state, with a geometric mean ratio of 1.774 (90% CI: 1.633 - 1.927).
- ORR: Noninferiority was also seen in the key powered secondary endpoint of ORR by BICR, with subcutaneous nivolumab demonstrating an ORR of 24.2% vs. 18.2% with IV Opdivo (Relative Risk Ratio [RR] 1.33; 95% CI: 0.94 to 1.87).
- PFS: Median PFS by BICR with subcutaneous nivolumab was 7.23 months and 5.65 months with IV Opdivo.

The safety profile of subcutaneous nivolumab was consistent with the IV formulation. Incidence of local injection site reactions with subcutaneous nivolumab was 8.1%. Additionally, reactions were low grade and transient.

Global cancer burden grows amid mounting need for services

The World Health Organization cancer agency, the International Agency for Research on Cancer, has released the latest estimates of the global burden of cancer.

WHO also published survey results from 115 countries, showing a majority of countries do not adequately finance priority cancer and palliative care services, as part of universal health coverage.

The IARC estimates, based on the best sources of data available in countries in 2022, highlight the growing burden of cancer, the disproportionate impact on underserved populations, and the urgent need to address cancer inequities worldwide.

In 2022, there were an estimated 20 million new cancer cases and 9.7 million deaths. The estimated number of people who were alive within five years

following a cancer diagnosis was 53.5 million. About one in five people develop cancer in their lifetime, approximately one in nine men and one in 12 women die from the disease.

The global WHO survey on UHC and cancer shows that only 39% of participating countries covered the basics of cancer management as part of their financed core health services for all citizens, 'health benefit packages' (HBP). Only 28% of participating countries additionally covered care for people who require palliative care, including pain relief in general, and not just linked to cancer.

The new estimates available on IARC's Global Cancer Observatory show that 10 types of cancer collectively comprised around two-thirds of new cases and deaths globally in 2022.

Data covers 185 countries and 36 cancers.

Lung cancer was the most commonly occurring cancer worldwide with 2.5 million new cases accounting for 12.4% of the total new cases. Female breast cancer ranked second (2.3 million cases, 11.6%), followed by colorectal cancer (1.9 million cases, 9.6%), prostate cancer (1.5 million cases, 7.3%), and stomach cancer (970 000 cases, 4.9%).

Lung cancer was the leading cause of cancer death (1.8 million deaths, 18.7% of the total cancer deaths) followed by colorectal cancer (900 000 deaths, 9.3%), liver cancer (760 000 deaths, 7.8%), breast cancer (670 000 deaths, 6.9%) and stomach cancer (660 000 deaths, 6.8%).

Lung cancer's re-emergence as the most common cancer is likely related to persistent tobacco use in Asia.

There were some differences by sex in incidence and mortality from the global total for both sexes. For women, the most commonly diagnosed cancer and leading cause of cancer death was breast cancer, whereas it was lung cancer for men. Breast cancer was the most common cancer in women in the vast majority of countries (157 of 185).

For men, prostate and colorectal cancers were the second and third most commonly occurring cancers, while liver and colorectal cancers were the second and third most common causes of cancer death. For women, lung and colorectal cancer were second and third for both the number of new cases and of deaths.

Cervical cancer was the eighth most commonly occurring cancer globally and the ninth leading cause of cancer death, accounting for 661 044 new cases and 348 186 deaths.

It is the most common cancer in women in 25 countries, many of which are in sub-Saharan Africa.

Through the scale-up of the WHO Cervical Cancer Elimination Initiative Striking cancer inequity by Human Development Index (HDI), global estimates reveal inequities in the cancer burden according to human development. This is particularly true for breast cancer.

In countries with a very high HDI, one in 12 women will be diagnosed with breast cancer in their lifetime and one in 71 women die of it. By contrast, in countries with a low HDI; while only one in 27 women is diagnosed with breast cancer in their lifetime, one in 48 women will die from it.

WHO's global survey of HBPs also revealed significant global inequities in cancer services.

Lung cancer-related services were reportedly four to seven times more likely to be included in a HBP in a high-income than a lower-income country. On average, there was a four-fold greater likelihood of radiation services being covered in a HBP of a high-income than a lower-income country.

The widest disparity for any service was stem-cell transplantation, which was 12 times more likely to be included in a HBP of a high-income than a lower-income country.

Anti-cancer compound goes beyond current BTK inhibitors in CLL, other blood cancers

Researchers have identified a next-generation BTK degrader that could help overcome treatment resistance in chronic lymphocytic leukemia and related blood cancers.

The findings, published in the journal *Science*, could offer a therapeutic option for CLL patients whose tumors become drug-resistant or are unresponsive to frontline treatment. Targeting Treatment Resistance in Chronic Lymphocytic Leukemia.

"This new compound not only inhibits the cellular molecule BTK, but goes further by taking aim at the target and destroying it," Justin Taylor, Sylvester Cancer Center hematologist-researcher and the study's senior author, said in a statement. "It's a new and exciting drug class called BTK degraders."

Patients diagnosed with CLL are often prescribed BTK inhibitors. But some patients develop drug resistance, thereby limiting their therapeutic options.

Currently approved drugs like ibrutinib work by inactivating the cellular molecule called BTK (Bruton's tyrosine kinase). Ibrutinib and other approved inhibitors don't destroy their targets. Instead, they bind to them and modulate activity.

For example, ibrutinib and other inhibitors bind to the BTK enzyme that acts to keep B cells alive in leukemia. The drugs quell BTK activity, leading to B-cell death in CLL and other blood malignancies.

For this study, Taylor and colleagues, including first author Skye Montoya, a graduate student in his research lab, Omar Abdel-Wahab, from Memorial Sloan Kettering Cancer Center, and other collaborators assessed the new compound in laboratory studies and a phase I clinical trial involving patients with tumors that had become drug-resistant or were unresponsive to therapy.

Developed by Nurix Therapeutics, the compound, called NX-2127, is constructed with two modules—one that binds to BTK and another that degrades and eliminates it. Thus, the term BTK degrader.

The researchers reported that NX-2127 efficiently destroyed its cellular targets in both petri dishes and patient cells.

"More specifically, this compound destroyed BTK cells in tumors resistant to currently used BTK inhibitors, while shrinking tumors in 11 of 14 CLL patients participating in our study," Abdel-Wahab, who was co-corresponding author with Taylor, said in a statement.

One patient, in particular, had an impressive response to this BTK degrader, Taylor and Abdel-Wahab noted. The elderly man had been on pirtobrutinib for two years, but became resistant to it as well as other therapies, leaving him with no other conventional options.

However, while taking NX-2127 during the trial, his symptoms and quality of life improved to where he no longer needed transfusions for anemia, they said.

Overall, 41% of CLL patients responded to NX-2127 and the elderly man was still responding favorably to the drug.

Additionally, the research showed that drug resistance can occur when BTK acquires mutations that give it an entirely new function. These mutations cause BTK to operate as a "scaffold" that recruits other cellular molecules to keep B cells alive.

Most importantly, NX-2127 appears to overcome resistance caused by virtually all of the BTK mutations identified to cause resistance to available BTK inhibitors.

Taylor believes that BTK degraders have the potential to treat other B-cell malignancies or even autoimmune conditions such as multiple sclerosis. He and his colleagues, including Alvaro Alencar, Sylvester hematologist-researcher and contributing study author, are now enrolling patients in another study testing a more potent and selective BTK degrader, NX-5948, also from Nurix.

Protein identified as a potential biomarker and therapeutic target for aggressive neuroendocrine carcinomas

UCLA Health Jonsson Comprehensive Cancer Center researchers have identified a protein, UCHL1, in highly aggressive neuroendocrine carcinomas and neuroblastoma that could potentially be used as a molecular biomarker for diagnosing these cancers and predicting and monitoring responses to therapy.

The team also found that using a UCHL1 inhibitor, either alone or in combination with chemotherapy, significantly delayed the growth and spread of neuroendocrine carcinomas and neuroblastoma in pre-clinical models.

"Our study demonstrates the therapeutic potential of targeting UCHL1 and its utility as a detection tool in neuroendocrine carcinomas and neuroblastoma in pre-clinical models creating a critical translational link between the study and the diagnosis and treatment of patients with these malignancies," Tanya Stoyanova, associate professor of molecular and medical pharmacology and

urology at the David Geffen School of Medicine at UCLA and senior author of the study, said in a statement.

"In addition, we also revealed a detailed mechanism of action of UCHL1 and its role in regulating protein stability and nuclear import of proteins that regulate gene expression," first author Shiqin (Laura) Liu, a postdoctoral fellow in Stoyanova's laboratory, said in a statement.

Neuroendocrine carcinomas, such as neuroendocrine prostate cancer and small-cell lung cancer, start in the cells that release hormones into the body and can develop in different organs, including the prostate and lung.

Though they're not the most common type of cancer in those organs, cancers of this type often have a poor prognosis and limited therapeutic options. Current therapies for these cancers include combinations of chemotherapy, radiation and immunotherapy.

However, depending on the stage and risk groups, these treatments only extend patients' survival for a few months, emphasizing the need for better therapeutic targets and minimally invasive approaches to diagnosing these malignancies.

To identify druggable targets for neuroendocrine carcinomas and neuroblastoma, researchers first analyzed publicly available proteomics data and identified UCHL1 as one of the top druggable proteins.

The team then investigated UCHL1 levels in tissues from patients with various types of neuroendocrine carcinomas and found elevated levels of UCHL1 in neuroendocrine prostate cancer, lung carcinoid, small cell lung cancer, neuroblastoma, and other neuroendocrine neoplasms.

This suggested that UCHL1 may be a common target for drug development in neuroendocrine cancers based on its higher expression in these tumors compared to non-neuroendocrine tissues.

The team then tested the therapeutic potential of blocking UCHL1 in pre-clinical models of neuroendocrine carcinomas and neuroblastoma.

This research can help guide the development of new minimally invasive blood-based tests to detect and monitor responses to therapies in patients with neuroendocrine carcinomas, such as highly aggressive neuroendocrine prostate cancer and small cell lung cancer, as well as neuroblastoma.

This research also lays down the foundation for new clinical trials to test the inhibition of UCHL1 as a new treatment approach that could potentially help reduce deaths associated with the aggressive disease.

The study was published in the journal *Cell Reports Medicine*.

Rice study finds checkpoint inhibitor that could help treat breast cancer bone metastases

Rice University researchers in the lab of chemist Han Xiao have identified a promising new immunological pathway to treat stubborn bone tumors, one of most prevalent forms of metastases in breast cancer patients.

"There are now several immunotherapies that can potentially benefit breast cancer patients with metastases, but they aren't effective in patients with bone tumors," Yixian Wang, a Rice graduate student in the Han lab, and a lead author on a study published in *Proceedings of the National Academy of Sciences*, said in a statement.

While checkpoint inhibitors are effective for many patients, they do not work for everyone—and clinical trials have shown little to no response when used to treat bone metastases.

Xiao, associate professor of chemistry, biosciences, and bioengineering at Rice, said he and his team wanted to find another pathway that might be more effective in obliterating these stubborn bone metastases.

"We thought there must be another novel checkpoint axis we could target for the breast cancer cells in bone," Xiao said. "And we discovered a unique glyco-immune checkpoint axis in bone metastases that involves a protein called sialic acid-binding Ig-like lectin (Siglec)-15. We learned that it suppresses immune cells in the bone."

After noting that there was a significant upregulation of Siglec-15 in the tumor microenvironment in bone tumor samples from breast cancer patients, Xiao and colleagues demonstrated that this receptor plays an important role in hiding bone tumors from the immune surveillance.

"Current FDA-approved checkpoint inhibitors are mediated by protein-protein interactions that suppress immune cells," Xiao said. "Siglec-15, however, is a glyco-immune checkpoint inhibitor. Instead of binding to a protein, Siglec-15 binds to the sugars you find on the cell surfaces—and that's how it can suppress the immune system. "This is an entirely new type of immune checkpoint that offers great promise for future treatment for bone cancers."

Xiao's team conducted several cell culture experiments to study Siglec-15 interactions in the bone tumor microenvironment. They learned it is involved in crosstalk between tumor cells and important immune cells like T-cells and macrophages, as well as bone-specific cells, osteoclasts.

"You can find these glycolipids and glycoproteins on all cells—and we know they play an important role in immune modu-

lation," said Xiao. "These findings offer us an opportunity to study these glyco-immune checkpoint inhibitors more in depth and identify those that can help bone tumors stop evading immune recognition."

But simply modulating the behavior of Siglec-15 may be enough to treat bone metastases. When the team injected a monoclonal antibody that targets Siglec-15 into an animal model of metastatic breast cancer with bone tumors, they were able to trigger a powerful immune response. In fact, the researchers saw the tumors diminish after only one or two doses of the antibody therapy.

DRUGS & TARGETS

Abecma receives positive CHMP opinion in MM indication

The Committee for Medicinal Products for Human Use of the European Medicines Agency has recommended marketing authorization approval of Abecma (idecabtagene vicleucel; ide-cel) for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

The European Commission, which has the authority to approve medicines for the European Union, will now review the CHMP recommendation.

Abecma is sponsored by Bristol Myers Squibb.

The CHMP adopted a positive opinion based on the final progression-free survival (PFS) analysis from the pivotal, phase III, open-label, global, randomized, controlled KarMMa-3 study evaluating Abecma compared with standard combination regimens in adults with relapsed and refractory multiple myeloma after two to four prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody, which are the three main classes of therapy (triple-class exposed) in multiple myeloma, and who were refractory to their last regimen.

Results recently presented at the American Society of Hematology annual meeting in December 2023 showed, at a median follow-up of 30.9 months (range: 12.7-47.8), Abecma significantly improved PFS compared with standard regimens, with a median PFS of 13.8 months vs. 4.4 months (HR:0.49; 95% CI: 0.38-0.63), representing a 51% reduction in the risk of disease progression or death with Abecma.

Results for the key secondary endpoint of overall response rate showed the majority of patients (71%; (95% CI: 66-77) treated with Abecma achieved a response, with 44% (95% CI: 38-50) achieving a complete response or stringent complete response. In comparison, less than half of patients (41%; 95% CI: 34-51) who received standard regimens achieved a response, with 5% (95% CI: 2-9) experiencing a complete response or stringent complete response.

European Commission authorizes Omjjara in anemia indication

The European Commission has granted marketing authorization for Omjjara (momelotinib), a once-a-day, oral JAK1/JAK2 and activin A receptor type 1 (ACVR1) inhibitor.

Omjjara is the first authorized medicine in the EU for disease-related splenomegaly (enlarged spleen) or symptoms in adult patients with moderate to severe anemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

About 40% of patients have moderate to severe anemia at the time of diagnosis with myelofibrosis and nearly all patients are estimated to develop anemia over the course of the disease.

Myelofibrosis patients with anemia require additional supportive care, including transfusions, and more than 30% will discontinue treatment due to anemia. Patients who are transfusion dependent have a poor prognosis and shortened survival.

The authorization of Omjjara is based on the MOMENTUM pivotal phase III trial and a subpopulation of adult patients with moderate to severe anemia (hemoglobin <10 g/dL) from the SIMPLIFY-1 phase III trial.

MOMENTUM was designed to evaluate the safety and efficacy of Omjjara versus danazol for the treatment and reduction of key manifestations of myelofibrosis in an anemic, symptomatic, JAK inhibitor-experienced population. SIMPLIFY-1 was designed to evaluate the efficacy and safety of Omjjara versus ruxolitinib in myelofibrosis patients who had not received prior JAK-inhibitor therapy.

NCI TRIALS

NCI Trials for February 2024

The National Cancer Institute approved the following clinical research studies last month.

For further information, contact the principal investigator listed.

Phase II - EAY191-E5
A Randomized Phase II Study of AMG 510 (Sotorasib) with or Without Panitumumab in Advanced Solid Tumors: A ComboMATCH Treatment Trial

ECOG-ACRIN Cancer Research Group
Spencer, Kristen Renee
(212) 731-6667

Phase II - EAY191-N5
A Randomized Trial of Neratinib, A Pan-ERBB Inhibitor, Alone or in Combination with Palbociclib, a CDK4/6 Inhibitor, in Patients with HER2+ Gynecologic Cancers and Other Solid Tumors: A ComboMATCH Treatment Trial

NRG Oncology
Mahdi, Haider Salih
(412) 641-5609

Phase II - NRG-GY033
A Phase II Study of Androgen Receptor (AR) Inhibition by Darolutamide in Combination with Leuprolide Acetate and Exemestane in Recurrent Adult-Type Ovarian Granulosa Cell Tumor

NRG Oncology
Hopp, Elizabeth
(414) 805-6606

Phase II - NRG-HN011
A Randomized Phase II Study of Nivolumab Versus Nivolumab and BMS-986016 (Relatlimab) as Maintenance Treatment After First-Line Treatment with Platinum-Gemcitabine-Nivolumab for Patients with Epstein-Barr Virus-Associated Recurrent/Metastatic Nasopharyngeal Carcinoma (REMAIN)

NRG Oncology
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