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LOWY: "OUR PATIENTS ARE COUNTING ON US, AND WE MUST NOT LET THEM DOWN" — NCI FREDERICK LAB TAKES AIM AT COVID-19

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For more information, please contact Gina Mallozzi, Physician Recruiter at (207) 661-2092 or gmallozzi@mainehealth.org.

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LOWY: "OUR PATIENTS ARE COUNTING ON US, AND WE MUST NOT LET THEM DOWN"

NCI FREDERICK LAB TAKES AIM AT COVID-19

By Matthew Bin Han Ong

NCI's Frederick National Laboratory for Cancer Research has launched three initiatives focused on SARS-CoV-2:

- Identifying genetic determinants of SARS-CoV-2 susceptibility and outcomes at the Cancer Genomics Research Laboratory,
- Testing and validating serologic assays for SARS-CoV-2 in the Serology laboratory of the Vaccine, Immunity, and Cancer Program, and
- High-throughput screening for small molecule inhibitors of SARS-CoV-2 proteins, with technology developed by the RAS Initiative.

"We think that it was built for a situation like this, where speed, flexibility, and expertise are critical to addressing such a deadly public health threat," Douglas Lowy, NCI principal deputy director, said April 9 in an emergency virtual meeting of the NCI Board of Scientific Advisors and the National Cancer Advisory Board.

"Of course, what we are doing at the Frederick Lab—even more broadly across NCI—is only part of a truly massive global effort to understand, control, and overcome the pandemic.

"No one research group, institution or country can do this alone, but because of what we're trying to do, I like to think that we are trying to take a massive mountain, an infectious threat as large as Mount Everest, and, ultimately, be able to subdue it into a molehill that, with vigilance, can be restrained and tamed."

The National Institute of Allergy and Infectious Diseases has used the Frederick National Lab to respond to other epidemics, including SARS in 2003, Ebola in 2013, and Zika in 2015. NIAID is sponsoring a trial of the antiviral agent remdesivir, which was originally developed for treatment of Ebola and Marburg virus infections.

Remdesivir, a nucleoside analog that functions as an RNA chain terminator, was subsequently found to inhibit replication of other RNA viruses, including coronaviruses. The drug, made by Gilead Sciences, is the focus of multiple trials worldwide and is closely watched by the public health and financial communities.

Earlier this week, *The New England Journal of Medicine* published a paper on remdesivir. At this writing, the market is moving in part as a result of a news report based on fragmentary information from the University of Chicago cohort in two Gilead phase III studies.

"No one research group, institution or country can do this alone, but because of what we're trying to do, I like to think that we are trying to take a massive mountain, an infectious threat as large as Mount Everest, and, ultimately, be able to subdue it into a molehill that, with vigilance, can be restrained and tamed."

As data accumulate, Gilead is scaling up production of the drug, with a target of more than 1 million treatment courses by December.

"We have proactively and rapidly scaled our supply chain," the company said in a recent statement. "As of late March, using the active ingredient we already had in our inventory, we have increased our supply to more than 30,000 patient courses of remdesivir on hand, assuming a 10-day course of treatment for patients. As new raw materials arrive over the next few weeks from manufacturing partners around the world, our available supply will begin to rapidly increase.

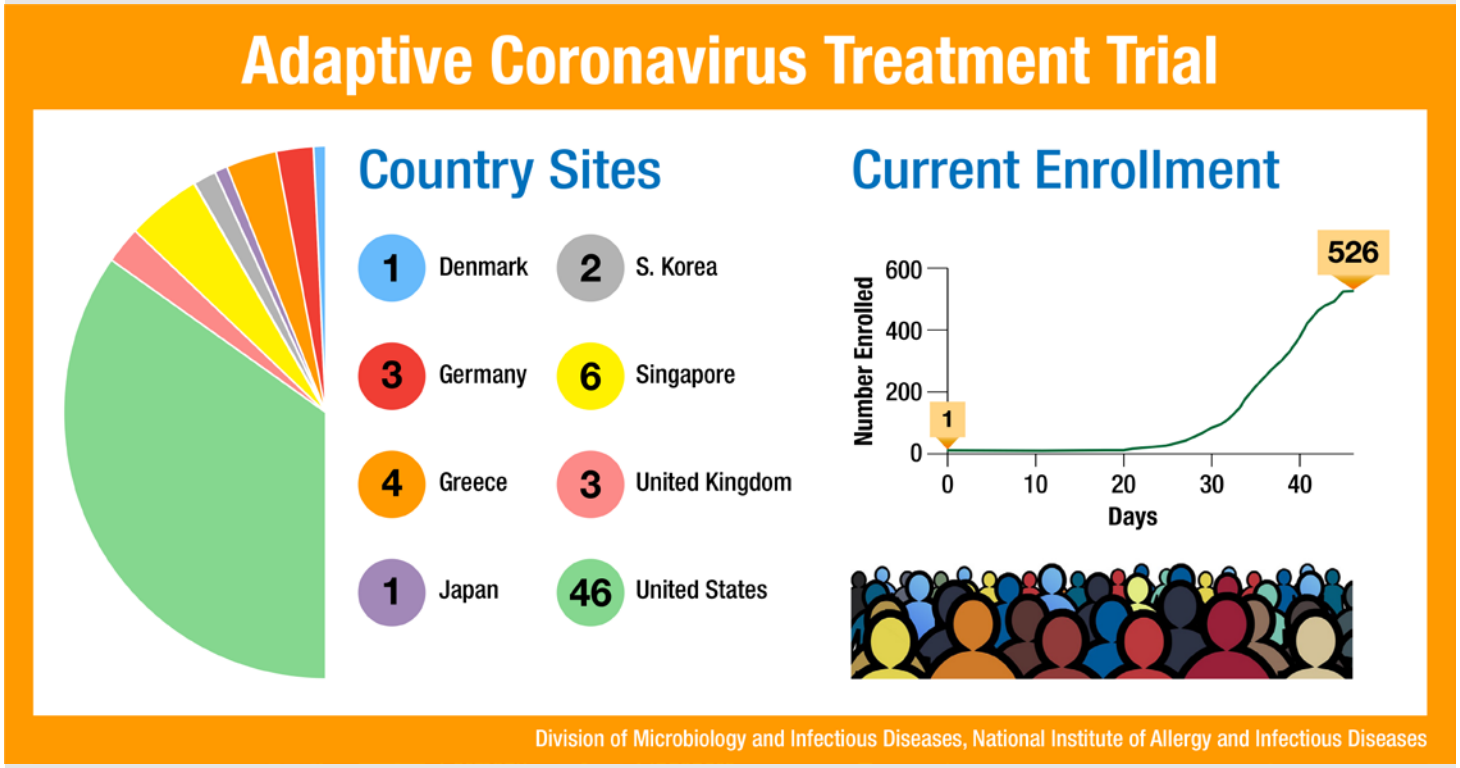
"Every day we are improving processes, shortening timelines and increasing volumes as we work to bring remdesivir to patients as soon as possible. Our goal is to produce a total of:

- More than 140,000 treatment courses by the end of May,
- More than 500,000 treatment courses by October,
- More than 1 million treatment courses by December,
- Several million treatment courses in 2021, if required."

The NIAID global therapeutic trial of remdesivir in COVID-19 patients has, to date, enrolled over 500 patients in eight countries: Denmark, South Korea, Germany, Singapore, Greece, the United Kingdom, Japan, and in the United States, Lowy said at the BSA and NCAB meeting.

The Adaptive COVID-19 Treatment Trial is scheduled to be completed on April 1, 2023. While it appears the trial has exceeded its accrual goal of 440 patients, it's unclear whether enrollment would be defined as completed, as per protocol. Preliminary results are expected later this spring.

Lowy's remarks to BSA and NCAB follow:



Ned [Sharpless, NCI director], thanks for reviewing some of the responses that we have made at NCI and the extraordinary efforts extramurally during this really terrible time.

I want to really tell people that Ned has not only been working 24 hours a day, so we know that he's been working hard. But let me assure you, he has also been working smart and he is everywhere trying to, essentially, deal simultaneously with the ramifications of the COVID-19 epidemic, as well as being able to continue cancer research.

I am going to be focused on three different projects that are being conducted largely at the Frederick National Laboratory, because I think that they exemplify our ability there to change things pretty rapidly. For those of you who may not be entirely familiar with the Frederick National Laboratory, it was established in 1971 by the National Cancer Act and it's the only one of the 42 Federally Funded Research and Development Centers in the United States that is dedicated to biomedical research.

The Frederick National Lab is sponsored by the NCI, but it's operated by a private contracting firm, Leidos Biomedical Research, and Ethan Dmitrovsky, whom many of you know from his time at Dartmouth and then at MD Anderson. He's the head of the Frederick National Laboratory. So, a lot of cancer research is performed at the Frederick National Lab and includes lots of different things, from large scale genomic and proteomic studies, to advanced biomedical computing research.

The lab also anchors many NCI initiatives, such as the RAS Initiative and the Cryo-Electron Microscopy Facility. I'm not going to talk specifically about the Cryo-EM Facility, but that facility, which is for the exclusive use of the extramural community, is being made available for investigators who want to solve Cryo-EM problems related to the COVID-19 epidemic.

The Frederick National Laboratory houses two current Good Manufacturing Practice facilities that produce experimental treatments for first-in-human clinical trials.

One is for NCI and the other is for NIAID, and NIAID and NCI are the major users of Frederick. Let me turn briefly to a discussion of NIAID. They have helped to support and lead clinical trials in two therapies that proved to be particularly effective for treating Ebola infections, including a monoclonal antibody that, actually, was developed and manufactured by NIAID's vaccine

HIV: Genetic polymorphisms of CCR5 receptor can increase or decrease risk of infection and rate of disease progression

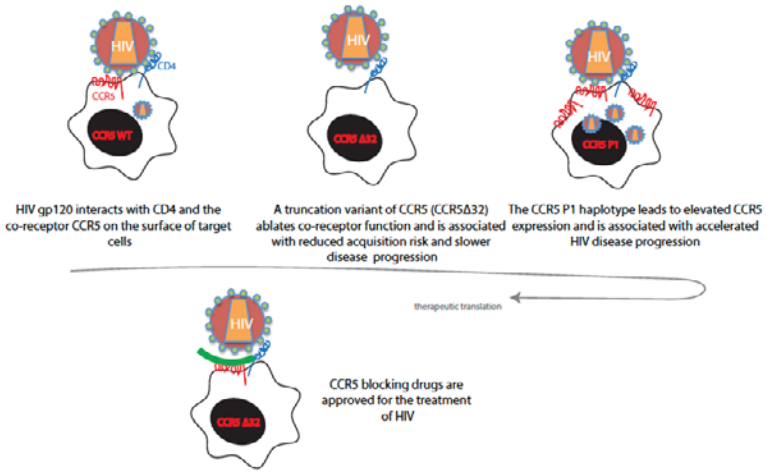


Fig. 1 CCR5 is a key co-receptor for HIV entry. CCR5Δ32 individuals in whom CCR5 expression is lost have reduced HIV acquisition risk and disease progression while individuals with the CCR5P1 haplotype have higher CCR5 expression and accelerated disease progression. These and other observations led to drugs that block CCR5, which are licensed for the treatment of HIV

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Naranbhai & Carrington, Immunogenetics, 2017 9

research center through the Frederick National Laboratory.

With the current epidemic, they have stood up a clinical trial of remdesivir, and for those of you who don't know about it, it's a nucleoside analog, which is an antiviral that functions as an RNA chain terminator.

It was originally developed for treatment of Ebola and Marburg virus infections, but it was subsequently found to inhibit replication of other RNA viruses including coronaviruses. The next slide shows you the patient accrual for the remdesivir trial sponsored by NIAID, but stood up by the Frederick National Laboratory.

The request came from NIAID at the end of January and the trial was started at the end of February. And, as of a few days ago, there were more than 500 patients enrolled in the trial.

The majority of the patients come from the United States, but they are scattered throughout other parts of the world, patients who also are enrolled in this international trial.

So, having heard a bit about NIAID, let me tell you about three different projects which the NCI has begun largely, although not exclusively, at the Frederick National Laboratory. And I think about this as pivoting some cancer research activities at Frederick to the SARS-CoV-2 research.

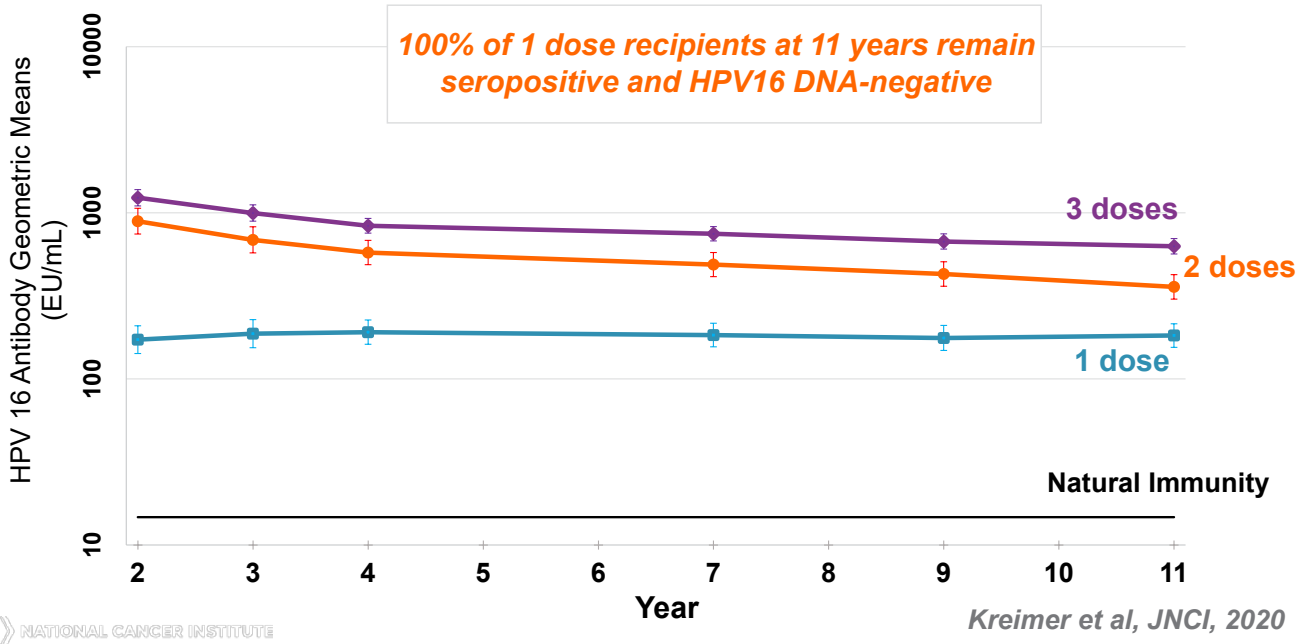
Genetic determinants

The first project that I'll mention is identifying genetic determinants of SARS-CoV-2 susceptibility and outcomes. The second is testing and validating serologic assays for SARS-CoV-2, and the third is high-throughput screening for small molecule inhibitors of SARS-CoV-2 proteins.

Let me go through them one at a time. We're going to talk about identifying genetic determinants of susceptibility and outcomes. This is under the auspices of the Cancer Genomic Research Laboratory headed up by Stephen Chanock and largely staffed by people who are from the Frederick National Laboratory.

The goals of this project is to rapidly identify variants which could identify lead to targets for therapy, insights into the biology of COVID-19 pathogenesis, and use for screening and public health. And it really will be using genome-wide association studies, or GWAS studies, looking for single nucleotide polymorphisms or mutations. A very important principle of everything that is done at the Frederick National Laboratory related

Stable HPV16 serum antibodies 11 years after one dose of the bivalent HPV vaccine (post-hoc analysis)



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Kreimer et al, JNCI, 2020 14

to the COVID-19 epidemic is that the information that data will immediately be shared with the community.

The next slide tells you about really two things. The first is that the COVID-19 epidemic probably has much more in common with HIV, where you have a single etiologic agent than with cancer, which is such a complicated situation, and where GWAS analyses have not yielded quite the same degree of insight that have been seen with HIV.

The second reason is, that Mary Carrington did pathbreaking HIV research—and she is part of the Frederick National Laboratory, but also affiliated with the Center for Cancer Research—and this slide is taken from a recent review, where she talks about the different mutations that there are with CCR5, which is the main receptor by which HIV binds to T-cells and gets into them.

Her laboratory identified the so-called delta 32 mutation, which greatly reduces your risk of infection. But the research related to CCR5 has identified mutations that decrease risk and increase risk of infection and rate of disease progression, and, ultimately, has also led to the development of inhibitors for CCR5 interaction that have been FDA approved.

I now just want to tell you very briefly about the three cohorts that are going to be followed.

One is an Italian epidemic cohort, this is in collaboration with NIAID, and it's likely to be skewed to patients who have a poor outcome, because of how poorly so many people have done in Italy.

A second project is through the NIH Clinical Center, and this is in collaboration with the Genome Research Institute as well as NIAID, and it is centered at the moment at the clinical center, but it is planned to be able to be expanded to extramural centers. And when that expansion is available, we hope to go out to different centers and make people aware of it.

The third is a longitudinal cancer cohort, and Jim Doroshow is going to discuss that in some detail. But this cohort will be looking at infections focused on cancer patients, which, of course, are a group that is of increased risk for poor outcomes. But we expect that the cohort will include patients with a benign course, in addition to those with poor outcomes, and there will be detailed prospective information.

Convert part of HPV serology lab to SARS-CoV-2 serology

- A collaborative research effort with several labs: NIAID, CDC, Mt. Sinai, others
- **Shorter term goals:** 1) Characterize performance of different serologic assays, correlate with neutralization assays, understand possible cross-reacting sera from prior to epidemic; 2) correlations with serologic tests submitted to FDA
- **Longer term goals:** Understand implications of being seropositive (e.g., resistance to reinfection), duration of seropositivity
- **Cohort oriented research projects:** COVID-19 longitudinal trial of cancer patients (to be discussed by Dr. Doroshow), others

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And we hope that it will be possible to identify through the genome-wide association studies mutations that are associated with increased risk of poor outcome and others of a decreased risk of a poor outcome.

Serologic assays

The second project that I want to discuss is the serology assay. And before I get to that, I want to show you that this is really a highly specialized program, which has been used up to now primarily for HPV serology. And it is headed up by Ligia Pinto, who's the director of the Vaccine, Immunity and Cancer Program.

Ligia's serology laboratory is multifaceted and is involved in collaborations with extramural HPV vaccine community, supporting vaccine trials sponsored primarily by NCI, and, also, is the HPV Serology Standardization Initiative for the World Health Organization and it is jointly supported with The Bill and Melinda Gates Foundation.

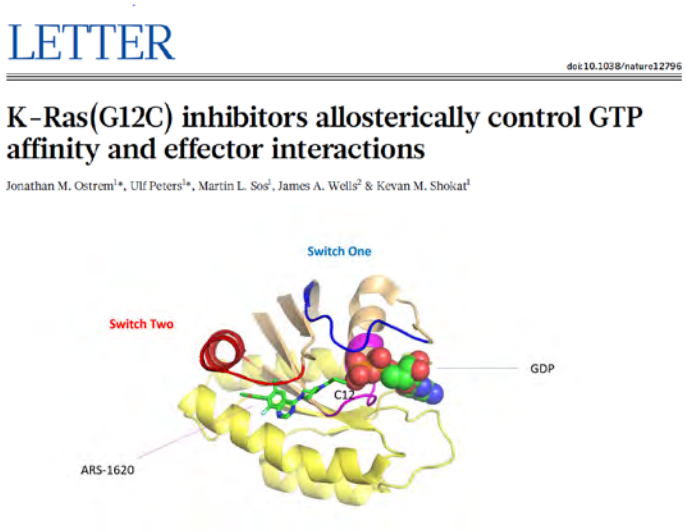
This shows you data from Ligia's serology laboratory, which was published six weeks ago from the Costa Rica Vaccine Trial. These are post hoc data, but they show that, over an 11-year period, that the young women who were immunized with just one dose of the GlaxoSmithKline HPV vaccine, their antibody levels to HPV-16 remained high throughout this 11-year period.

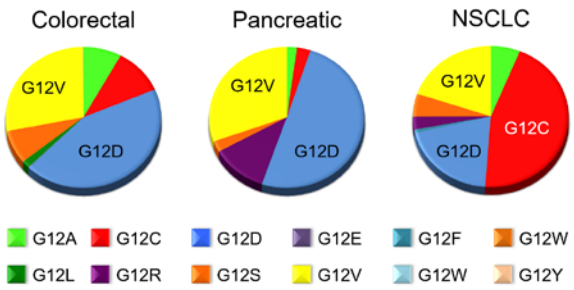
And I should also point out again, post hoc analysis, all of these women, none of them have been infected with HPV-16, in contrast to the control. And this has led to a large clinical trial in Costa Rica to test the hypothesis that one dose of the vaccine will be able to provide strong long-term protection against the HPV types targeted by the vaccines.

So, the notion is to convert part of the HPV serology lab to focus on SARS-CoV-2 serology. And this is a collaborative research effort with multiple laboratories, NIAID, CDC, Mount Sinai, and other academic laboratories—and the interaction, cooperation has simply been phenomenal.

The short term goals are to characterize performance of different serological assays and to correlate them with neutralization assays, so we can also understand possible cross reacting sera from prior to the epidemic. This will be important because, as most of you are aware, the notion of getting people back to work, a particularly attractive group would be those people who are antibody-positive, and so, it's critically important to make sure that

Development of RAS G12C mutant allele-specific inhibitors that attach covalently (tethered) to Cysteine-12 mutation





Channing Der

the people who are antibody positive, these are not false positives.

Because of the interactions that we are having with various parts of the U.S. government, as well as amazing cooperation through NCI cancer centers and Ned's initiative, the FDA has asked us if we would essentially help to validate the serological tests that have been submitted to the FDA. That is in progress, but I want to reiterate, it's being done as a wide collaborative in Denver.

Longer-term goals will be to understand the implications of being seropositive. We think that people are going to be resistant to reinfection, but we don't know for a fact that that is the case, and this will be a critically important issue.

Another issue is the duration of seropositivity. And then, longer-term, to participate just for the serology effort in some of the longitudinal efforts, particularly for the cancer patient effort to be discussed by Dr. Doroshow.

Small molecule inhibitors

The third and last topic is the high-throughput screening for small-molecule inhibitors and the technology, actually, was developed by the RAS Initiative. So, Kevan Shokat and his colleagues at UC San Francisco, back in 2013, essentially recognized that you could attach, covalently, to cysteines to make subhydro bonds with small-molecule inhibitors. And his laboratory focused on RAS glycine-12 cysteine mutant alleles.

This is a relatively common mutant allele in non-small cell lung cancer, but uncommon unfortunately, in this context in colorectal cancer and pancreatic cancer. The next slide shows you that a number of different pharmaceutical companies have taken this idea and developed inhibitors against G12C.

Early phase trials have been completed, they have been quite encouraging, and phase II and ultimately phase III trials are going to be ongoing. And we hope that this will end up leading to improved outcomes, at least for the subset of patients with mutant KRAS who have the G12C mutation.

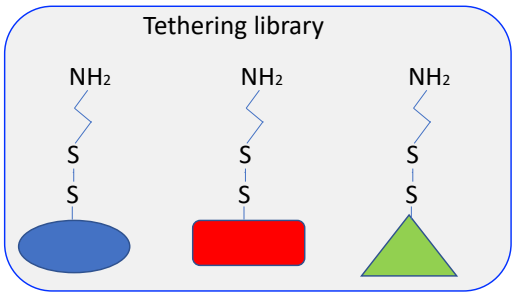
So, this approach can be used not just for G12C, but actually for any situation where there is a pocket that might be targeted with a small inhibitory molecule, providing that there is a cysteine adjacent to that pocket. And in the figure it shows the cysteine and then under reducing conditions, you get the subhydro groups connecting to each

Evaluating several KRASG12C inhibitors in US-based clinical trials

Agent(s)/Mechanism	Phase	Company	Setting	N of pts
AMG 510 (+/− PD1/L1)/KRASG12inhibitor	1/2	Amgen/Carmot Therapeutics	AMG 510 monotherapy in KRASG12C advanced solid tumors and in combination w/PD1/L1 in KRASG12C advanced NSCLC	158
MRTX 849/KRASG12inhibitor	1/2	Mirati	MRTX 849 in KRASG12C advanced solid tumors	200
ARS-3248 (JNJ-74699157)/KRASG12inhibitor	1	Wellspring Biosciences and Janssen	ARS-3248 (JNJ-74699157) in KRASG12C advanced solid tumors	140
LY3499446/KRASG12inhibitor +/− abemaciclib, cetuximab, erlotinib vs docetaxel (phase 2)	1/2	Eli Lilly and Company	Advanced solid tumors including NSCLC and CRC	230

Nagasaka et al, Cancer Treat Rev 2020

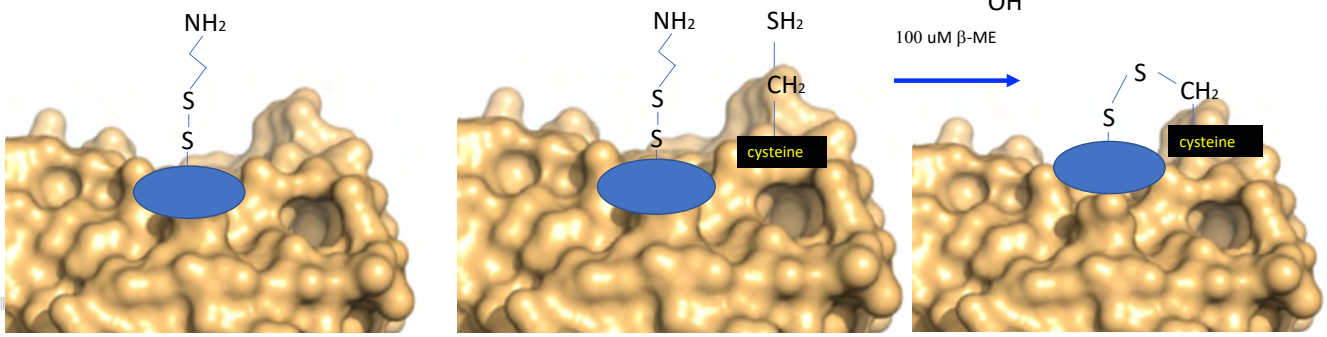
Tethering can identify fragment binding pockets adjacent to cysteines



TETHERING: Fragment-Based Drug Discovery

Daniel A. Erlanson, James A. Wells, and Andrew C. Braisted

Sunesis Pharmaceuticals, Inc., 341 Oyster Point Boulevard, South San Francisco, California 94080; email: erlanson@sunesis.com; jaw@sunesis.com



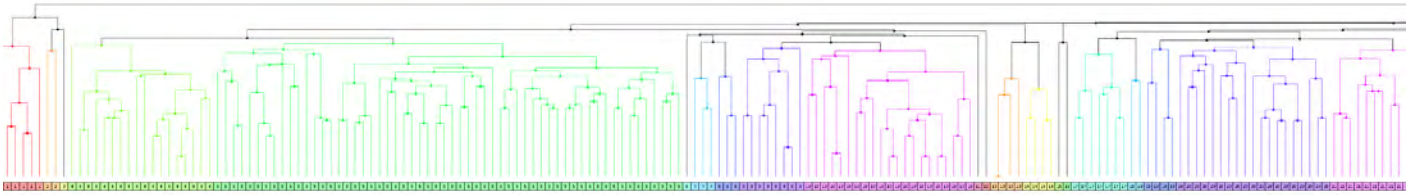
FNL Disulfide tethering library

Assessed library of 13,000 carboxylic acid building blocks – compounds selected through computational analysis based on R-group diversity:

- k-mean clustering (Lloyd's algorithm)
- Hierarchical clustering (Tanimoto similarity metric)
- Diversity-based selection (Soergel distance metric)

Total = 1158 unique disulfide fragments

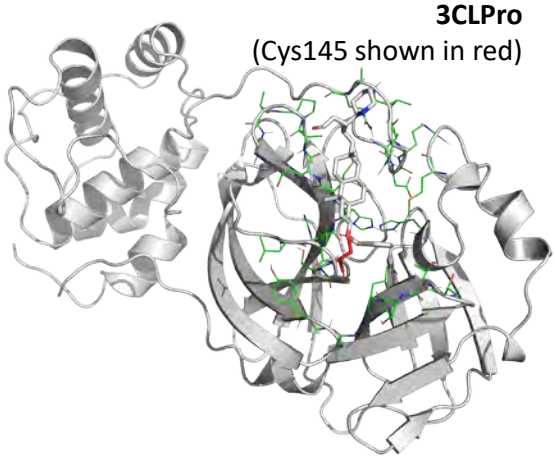
- Good fragment-like properties (MW <300, ClogP ≤ 3, $_n$(H-bond donors/acceptors) ≤3 etc.)
- Minimal overly complex molecules
- Exclusion of compounds with unnecessary stereochemistry (e.g. racemizable groups)
- Exclusion of PAINS / reactive groups



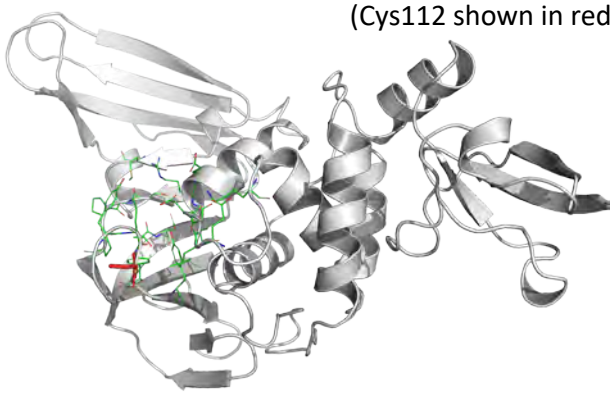
Hierarchical clustering example (different clusters represented by color)

3CLPro and PLPro: Two SARS-Cov-2 protease targets involved in viral life cycle

3CLPro
(Cys145 shown in red)

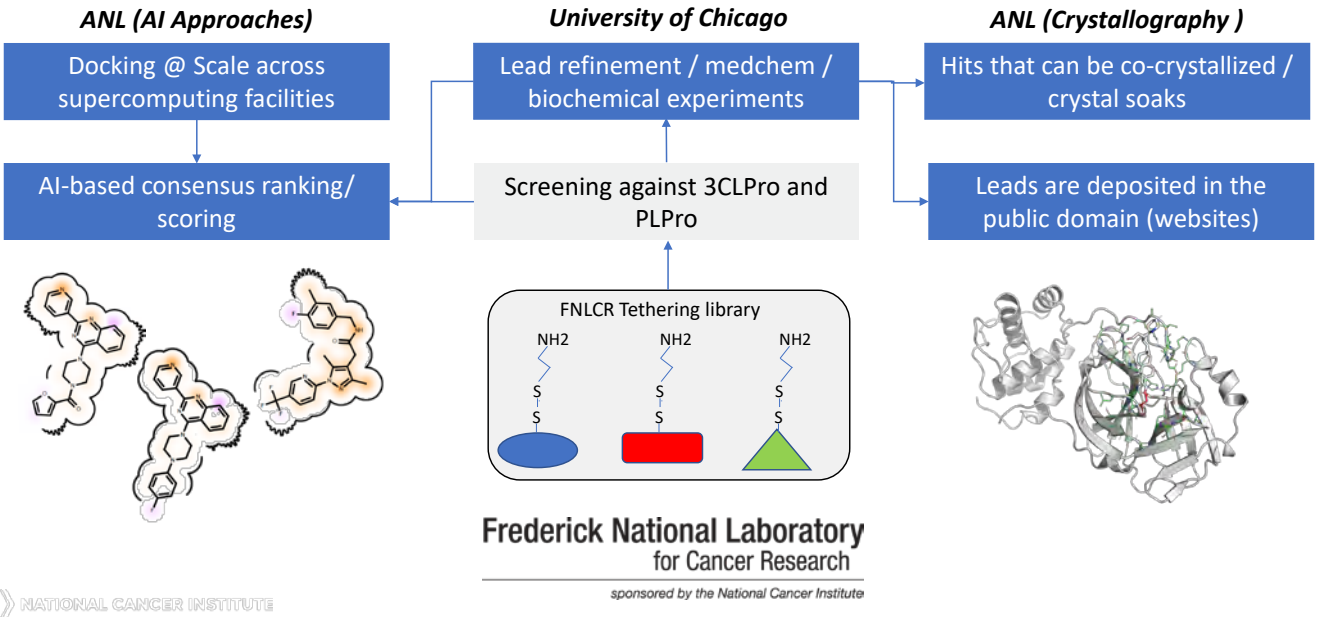


PLPro
(Cys112 shown in red)



- Both proteins have at least 10 exposed cysteine residues that can be targeted for covalent inhibition
- Covalent inhibitors can have better antiviral activity
- AI-methods provide rapid "leads" that can test for inhibition across both targets

Iterative design: Argonne National Laboratory (ANL), FNLCR, and University of Chicago



other, forming the covalent bond and the inhibitor bound to this.

For the FNL disulfide tethering library, David Turner at the Frederick National Laboratory in the RAS Initiative has been the major person to take essentially 13,000 of carboxylic acid building blocks and essentially to screen them, so that you screen out undesirable characteristics and screen in more desirable characteristics.

And reduce this, then, to a library that's about 10% that of the original library, about 1,200 unique disulfide fragments. And what's shown with a hierarchic clustering is that this library is quite diverse.

So, colleagues at the Argonne National Laboratory, the Department of Energy in Chicago have been essentially identifying with the two proteases encoded by the coronavirus that they have adjacent exposed cysteine residues to the areas where there might be a binding pocket for an inhibitor. And so, the Frederick National Laboratory is going to take its tethering library and screen the tethering library for such possible inhibitors.

So, once the lead compounds are identified, medicinal chemists at the University of Chicago are going to essentially be optimizing this, going to, also at the Argonne National Laboratory, to use artificial intelligence for further optimization. And then, it will be in vitro inhibition against the proteases, and, ultimately, interference with infection by the authentic coronavirus.

So, I've tried to give you a smattering of what is being done at the Frederick National Laboratory, and we think that it was built for a situation like this, where speed, flexibility, and expertise are critical to addressing such a deadly public health threat.

Of course, what we are doing at the Frederick Lab—even more broadly across NCI—is only part of a truly massive global effort to understand, control, and overcome the pandemic. No one research group, institution or country can do this alone, but because of what we're trying to do, I like to think that we are trying to take a massive mountain, an infectious threat as large as Mount Everest, and, ultimately, be able to subdue it into a molehill that, with vigilance, can be restrained and tamed.

Our patients are counting on us, and we must not let them down.

Doroshow: NCI to accrue patients for COVID-19 longitudinal cohort

Ongoing trials see significant decrease in accrual

By Matthew Bin Han Ong

NCI is building a nationwide cohort of cancer patients with COVID-19 at over 1,000 sites across the institute's clinical trials networks and at NCI-designated cancer centers.

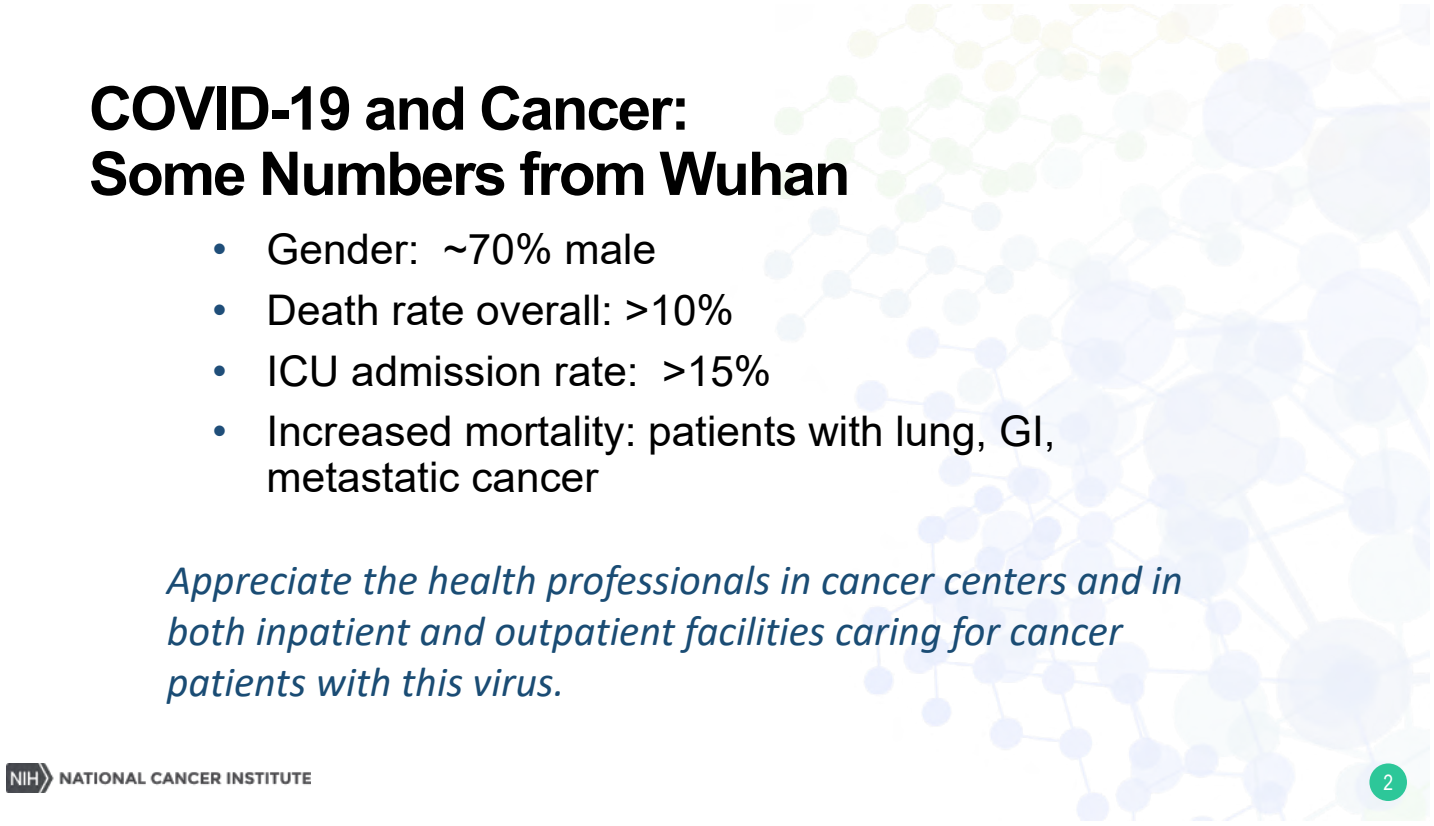
Patient accrual is scheduled to begin before May 15, with a target of at least 2,000 patients nationwide by Dec. 1. Sites participating in the institute's Cancer and COVID-19 Longitudinal Cohort can count on full reimbursement for each patient enrolled, NCI officials said.

"We have patients, we have institutions that want to participate in learning more about this situation in cancer patients," James Doroshow, deputy director for clinical and translational research at NCI, said April 9 in an emergency virtual meeting of the NCI Board of Scientific Advisors and the National Cancer Advisory Board. "We clearly have the resources to allow full case reimbursement for participation in this longitudinal trial across all the various networks that we have.

"We also very definitely need to enroll, because of the data that we are now starting to see about the ravages of COVID-19 in minority patients who have cancer, we very much need to enlist the help of our minority NCORP sites to try to accrue to this cohort," said Doroshow, who is also director of NCI's Division of Cancer Treatment and Diagnosis and head of the Oxidative Signaling and Molecular Therapeutics Group of NCI's Developmental Therapeutics Branch.

The study's goals are to:

- Accrue cancer patients infected with COVID-19 comprising all age groups for collection of a comprehensive dataset on the cancers, treatments, medications, symptoms, course, and recovery, and co-morbidities with longitudinal follow-up every 1-2 months until return to pre-morbid status,
- Follow subset of patients for over a year to assess impact of COVID-19 on survivorship and quality of life,
- Collect blood samples at study entry and then every two months for a year to estimate antibody re-



sponse, genetic susceptibility, and for biomarker development; collect blood from family members, and

- Create a public database of biospecimens.

"The infrastructure is being built as we speak, with all of the infrastructure that NCI has," Doroshow said. "I have basically refocused the entirety of the NCI's clinical trials research enterprise."

Doroshow's remarks to BSA and NCAB follow:

I appreciate the opportunity to discuss with this group what we've been doing over the past several weeks at the NCI to address some of the clinical trials and clinical research issues that all of us are feeling very acutely.

This is some recent data from hospitals in Wuhan. We know that the cancer patients who get COVID-19 are predominantly male.

The death rate is really pretty extraordinary, associated with the high ICU admission rate. The thing that is also becoming clear is that it's patients with advanced disease, lung cancer and metastatic cancer, that may be at the highest risk of dying from infections.

I just think it's important once again, for all of us to express our appreciation to the enormous numbers of health professionals who are trying to help cancer patients everywhere, both in inpatient and outpatient settings, patients with this virus. It is really an incredible endeavor to try to maintain standard of care for these patients.

Let me give you some data regarding what the coronavirus infection has done to accrual to NCI at clinical trials. This is a table for data up through the end of March. I have data as well for the following week. It's for interventional trials, and for the various NCTN groups.

Decrease in accrual for trials

What you can see is that we were cruising along through February and most of March at a standard 300 patients per week accrual to interventional trials. Then, the cliff hit at the last week of March, down about 45% to 50% in terms of accrual across the board, from organization to organization. That's true as well for the first week of April.

It turns out that of course, it's not just the interventional studies, but screening trials—trials that involve a screening step before the intervention is assigned—have also taken a very similar nosedive.

NCTN Accrual for "Intervention" Step in Trials by Lead Group & Week: 2-3-2020 to 3-29-2020 (CTSU Open Data)

Intervention / Cohort Step Enrollments	2/3-2/9	2/10-2/16	2/17-2/23	2/24-3/1	3/2-3/8	3/9-3/15	3/16-3/22	3/23 to 3/29	% Change Last Week Vs Avg of 7 Prior Weeks
ALLIANCE	93	88	83	93	105	94	67	30	-66%
CCTG	2	5	5	4	6	3	6	4	-10%
COG	43	53	47	45	51	58	41	34	-30%
ECOG-ACRIN	45	56	47	51	45	45	43	35	-26%
NRG	44	57	44	59	45	46	49	24	-51%
SWOG	49	46	43	54	54	46	54	35	-29%
TOTAL	276	305	269	306	306	292	260	162	-44%

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I think that these numbers are not surprising, and furthermore, they not only apply to all of our NCTN groups, but basically the data for all NCI clinical trials networks. The early clinical trials networks, our immunotherapy networks across the board, trial accrual is down about 45% to 50%, and is certainly consistent with the fact that many institutions have shut down accruals in most of their studies, and in particular, in New York, the accrual rates have plummeted, because it's really an all-hands-on-deck situation, where physicians are really needed to take care of this enormous patient load.

I wanted to point, however, that that's not true universally, that there are some institutions that have been able to accrue some patients—that's true at the [NIH] Clinical Center, true at some other organizations.

And, I think where that is reasonable is with respect to the studies that offer patients curative therapy. And so, it would seem to me that patients with acute myelogenous leukemia, or advanced lymphoma, who have curable diseases that really can benefit from treatment on studies where it's possible to do that, as well as patients who really have no other therapeutic options. I think as it's been pointed out by many of the folks on the line, accrual to non-therapeutic studies has taken a much greater hit across all of our networks.

COVID-19 Longitudinal Cohort

Now, I'd like to come to this longitudinal cohort that we've been working on that Doug referred to. This is really something that is, as far as I'm concerned, if we can do this, then we can change the entire NCI-supported clinical trial system. We started about two weeks ago or less, on developing a large cohort.

We don't know what the final cohort size is going to be, because the sample size estimates are ongoing, to develop a way to collect data across all of the NCI sites across the NCTN, across the ETCTN, across NCORP, at cancer centers, to include high, moderate, and currently low-prevalence regions. And, we're going to do this, not only because it's the right thing to do, but also because, as you saw in the numbers, our accrual is down 50%.

We have patients, we have institutions that want to participate in learning more about this situation in cancer patients. It's a special situation, and since all of our sites were re-funded for the full 2020 academic fiscal year just last

NCTN Accrual for "Screening" Step in Trials by Lead Group & Week: 2-3-20 to 3-29-20 (CTSU Open Data)

Screening Step Enrollments	2/3-2/9	2/10-2/16	2/17-2/23	2/24-3/1	3/2-3/8	3/9-3/15	3/16-3/22	3/23 to 3/29	% Change Last Week vs Avg of 7 Prior Weeks
ALLIANCE	24	22	25	28	22	27	13	7	-70%
CCTG	7	10	18	10	6	10	6	11	15%
COG	9	14	14	9	5	9	9	5	-49%
ECOG-ACRIN	17	9	15	14	15	16	13	6	-58%
NRG	13	5	9	6	8	7	13	2	-77%
SWOG	20	28	28	23	30	24	23	21	-16%
TOTAL	90	88	109	90	86	93	77	52	-42%

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month, we clearly have the resources to allow full case reimbursement for participation in this longitudinal trial across all the various networks that we have.

We also very definitely need to enroll, because of the data that we are now starting to see about the ravages of COVID-19 in minority patients who have cancer, we very much need to enlist the help of our minority NCORP sites to try to accrue to this cohort.

The infrastructure is being built as we speak, with all of the infrastructure that NCI has. I have, with Ned's permission, basically refocused the entirety of the NCI's clinical trials research enterprise to be able to put up a trial on the [Clinical Trials Support Unit], to develop blood banking, to enlist the NCI CIRB to develop case report forms with a collaborative extramural NCI leadership team that has basically started a working group about 10 days ago, is meeting daily. It has representation from all of the appropriate specialties, with the goal of developing a cohort of all aged patients, to have a comprehensive data set for treatment, medications, course recovery, comorbidities, with follow-up regularly over the course of about a year.

We want to follow subsets of patients for longer than a year to understand the impact of COVID-19 on cancer survivorship and quality of life. We pointed at the regularly collecting blood samples at entry, and then at regular intervals to estimate antibody response, genetic susceptibility, to develop biomarkers, and to collect blood eventually from family members.

And, all of this data will be up in a public website, and the biospecimens will be available for the research community to share as this moves forward.

“We also very definitely need to enroll, because of the data that we are now starting to see about the ravages of COVID-19 in minority patients who have cancer, we very much need to enlist the help of our minority NCORP sites to try to accrue to this cohort.”

NCI Cancer and COVID-19 Longitudinal Cohort (2)

Critical Study Milestones:

- Initiate patient accrual before May 15, 2020: **from idea to active trial in < 6 weeks**
- Enroll the first 500 patients within 3 months of trial activation
- Complete accrual of 2000 patients nationwide by 12/1/2020
- Complete follow-up and survivorship evaluations by end of 2021
- Begin biomarker studies on blood samples soon after initial 500 patients accrued

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We hope to actually have a trial up and going by the second week of May. We actually have a goal of having a written protocol document next Monday. That'll be two weeks to get a full document up and running, to enroll our first 500 patients within the three months of activation; complete accrual by the end of this calendar year and survivorship evaluation for the end of 2020. And then, rapidly begin biomarker studies on the samples, as soon as the initial 500 patients are accrued.

I don't want to end, because it would be very inappropriate to do so without calling out the more than a dozen NCI-designated cancer centers who've developed their own therapeutic trials for cancer patients.

Now, I only know about a dozen, because there were at least a dozen NCI-designated centers that submitted requests for supplemental funds for clinical trials that are being carried on at their institutions. There may be many, many more. But, there are a wide range of activities that have been sponsored, and are being sponsored locally, which we really might need to be able to support.

I also want to call out the Vanderbilt Comprehensive Cancer Center, who stood up, beginning this past Monday, their COVID-19 and Cancer Consortium, that will use de-identified information, open access to Internet database, that is now endorsed by over 70 cancer centers, hospital systems, and large practices, to rapidly get information that will be useful for clinical practice.

And also, we shouldn't neglect our colleagues in pharma, who have several ongoing phase III trials of IL-6 receptor antibodies, or antivirals, and other activities in the cancer space that will contribute to this entire amount of information that has been stood up in just a remarkably short period of time.

I wanted to thank all of these individuals across the NCI, as well as collaborators at Vanderbilt and several other extramural cancer centers, who have come together to help us put together this large cohort, and also who are involved intimately in the standing up of the kinds of data collection systems, and biosample collections, that we will need to really understand the impact of COVID-19 on cancer patients.

And finally, I think it is not unreasonable to suggest that this whole episode demonstrates that the NCI, working with its grantees, really can be flexible to try to do something that is timely in a major national emergency.

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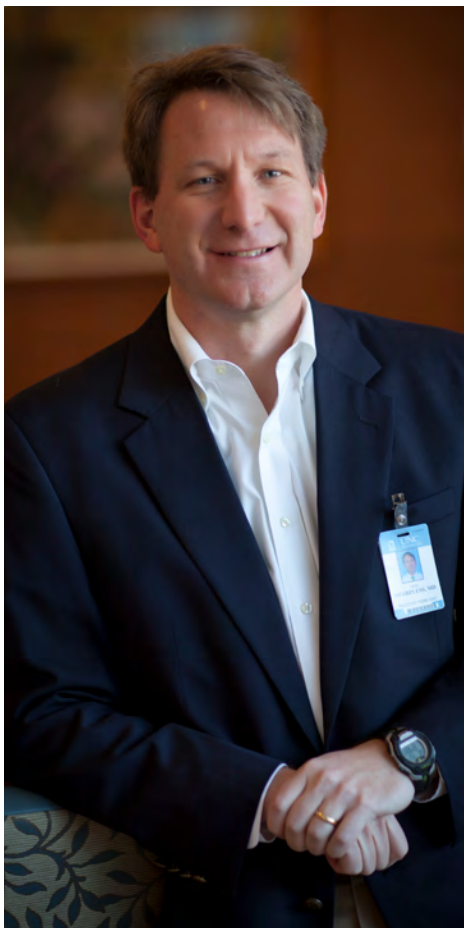
NCI DIRECTOR'S REPORT

Sharpless: NCI is fully operational, we have a moral obligation to help in the COVID-19 pandemic response

By Matthew Bin Han Ong

In spite of disruptions caused by the coronavirus pandemic, NCI continues to review grants, disburse funds, and support extramural research, said NCI Director Ned Sharpless.



"I really won't sugarcoat our present circumstances. This epidemic is bad, and it's going to continue to be bad for a while, especially the next few weeks," Sharpless said April 9 in an emergency virtual meeting of the NCI Board of Scientific Advisors and the National Cancer Advisory Board. "We have suspended lab operations on campus and we have stopped all non-essential activities.

"But I want to reiterate right now, from an extramural funding point of view, we are fully operational. But, no doubt, things have gotten more complicated, and we have received many, many questions from our investigators about grants, lab suspensions, and what this all means for them.

"When we do reach uniform agreement about these funding policies, the NCI is fully committed to disseminating that information as quickly as possible through blogs, our website, Twitter streams, etc."

Thus far, two lessons for U.S. health care and oncology can be derived:

"We've shown that, in a meaningful way, we can take care of patients via telehealth, and I predict cancer patients are going to like this in the future," Sharpless said. "Another area where I've seen a real example of something that, I think, will last after the pandemic, for the good, is the fact that the government can, when it needs to, move really quickly.

"We have been involved in complex multi-agency endeavors, but we've been able to really cut through a lot of the process and the usual steps to launch large, innovative, complex research efforts in a matter of days."

The institute, with its research capabilities, has a moral obligation to be involved in the U.S. national response to the pandemic, Sharpless said.

"NCI has a long and storied history of intramural virology research, from Doug Lowy and John Schiller and Harold Varmus, to Bob Gallo, to Sam Broder—pathbreaking, groundbreaking work on HPV and HIV and RNA tumor viruses—and to not use the virology expertise at the NCI during the current pandemic would seem to be a missed opportunity," Sharpless said.

NCI is finalizing plans to use its clinical trials networks to administer a compassionate use protocol for distribution of tocilizumab, a drug that blocks the inflammatory protein IL-6. Under the institute's protocol, the drug will be made available to cancer patients at institutions that are not participating in Genentech's phase III trial of the drug (*The Cancer Letter*, April 10, 2020).

Other updates at NCI include:

- Enrollment of the first patient in a CD33 CAR T trial, a collaboration between the institute and the Children's Hospital of Philadelphia; and
- Appointment of Dan Gallahan as director of the Division of Cancer Biology.

On March 27, Congress passed a $2 trillion coronavirus relief package, the Coronavirus Aid, Relief and Economic Security (CARES) Act. The bill appropriates pandemic response funds in the following amounts: $4.3 billion for CDC, $945.4 million for NIH, $80 million for FDA, and $200 million for CMS (*The Cancer Letter*, March 27, 2020).

"The Congress has done some stuff for coronavirus," Sharpless said. "Most probably relevant for the NIH is phase 3, the CARES Act, which provided significant new money for the NIH as well as the FDA and CDC, and it also—an issue I'm sure very important to many of the board members—provided significant funding for hospitals, given the massive drop in revenues some hospitals are seeing with the cessation of elective surgeries and that type of issue."

Normalcy will return, Sharpless assured the advisory boards.

"I'm here to tell you we'll get through this," he said. "And this is going to be a tough period for the NCI, for cancer research, but it will come to an end."

Sharpless's remarks to BSA and NCAB follow:

Welcome to our first-ever virtual joint board meeting. This is an emergency meeting that I called to discuss the NCI's response to the coronavirus pandemic. Thank you to all of you for making time. The pandemic has no doubt scrambled your schedules and I really appreciate your being available on short notice. NCI really needs your advice on some complex issues.

We'll have talks by Doug Lowy, Dafna [Bar-Sagi] and Jim [Doroshow], and in a closed session Dinah [Singer] will have some further remarks. As noted, there will be time for discussion after the remarks, this is a vital part of today's meeting. I'm sure we will all be saying many times today, "Could you please all mute?" as with my experience with prior WebExs.

One thing I want to make clear from the outset is that this is an emergency meeting to discuss the NCI response to the pandemic. And, necessarily, we're going to be talking a lot about the coronavirus pandemic, but I want to make very clear right now that the primary focus of the National Cancer Institute is on cancer research and cancer care. That is our primary focus for now and forever. And this meeting will not supplant other scheduled NCAB or BSA meetings where we will continue to talk more about usual NCI business in those meetings.

I'd like to reiterate the points on the slide here that cancer research and cancer care remain job number one at NCI, even though our operations have been somewhat disrupted by the pandemic. And even during these difficult times, I think we are still making progress toward our mission of reducing cancer suffering.

"A moral obligation"

But today is an emergency meeting to talk about a crisis that has gripped our nation and disrupted our work. And I'm sure many of you would agree the National Cancer Institute has to be involved in the pandemic response. NCI has unique research capabilities and capacities, so, to help in this complex situation, we believe, is a moral obligation.

First off, the NCI has a long and storied history of intramural virology research, from Doug Lowy and John Schiller and Harold Varmus, to Bob Gallo to Sam Broder—pathbreaking, groundbreaking work on HPV and HIV and RNA tumor viruses—and to not use the virology expertise at the NCI during the current pandemic would seem to be a missed opportunity.

Also, the Frederick National Lab, which the NCI administers in collaboration with [the National Institute of Allergy and Infectious Diseases], has unique capabilities and resources that are really tailor-made for an emergency situation like this. The facilities at the Frederick Lab are quite exceptional, like the cryo-EM facility and the serology lab that can be useful and deployed in the current pandemic.

Frederick National Lab has unique contracting authorities that allow it to move very quickly to set up new research as needed. And it has the

NCI & COVID-19

Intramural Research Program

Leaders in virology research

- *Lowy, Schiller, Varmus, Gallo, Broder*

Frederick National Laboratory for Cancer Research

- *Facilities: CryoEM, Serology, more*
- *Unique contracting authorities*
- *Robust collaborative relationships*

Grantee Institutions and Networks

diverse skills and powerful technology

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ability to form robust collaborative relationships, both with extramural scientists as well as industry. And so for these reasons it's really well suited to take on the coronavirus pandemic. And Doug Lowy will be talking about many of the ways we've been using Frederick National Lab in conjunction with NIAID during the present crisis.

And then, lastly, the NCI supports the world's best scientists bar none, and through our extramural funding programs, and that's through our networks and our individual investigator-initiated grants, and these individuals have tremendous research capabilities and skills that can be very useful in a pandemic. So, not to involve the extramural fundees would seem, also, a missed opportunity. And we have heard a lot from you on this question.

I've had many conversations and emails with cancer center directors and scientists, with clinicians, with trainees at the various cancer centers about what you can do to work on the coronavirus pandemic and how the NCI can support those efforts. And thank you for giving us that feedback, and thank you for volunteering your expertise. In short, because of these reasons and others, we believe the NCI has important contributions to make during the coronavirus pandemic.

Operational updates

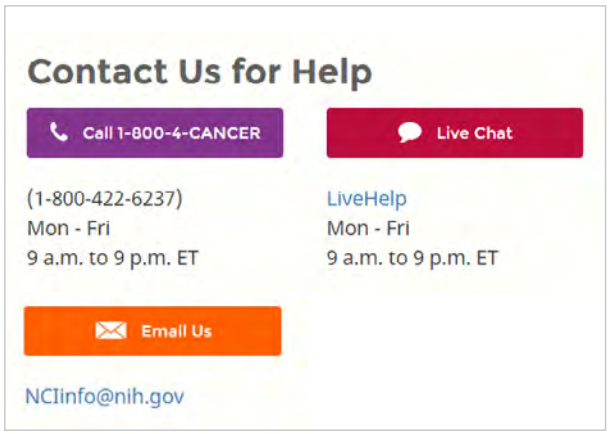
Just as the pandemic, no doubt, has changed operations at your institution, it has radically changed how the NIH and the NCI operate. We're still able to keep research going while complying with physical distancing. One of our awesome WebExs is to do a senior weekly leadership meeting by this format and how well that works. We have suspended lab operations on campus and we have stopped all non-essential activities.

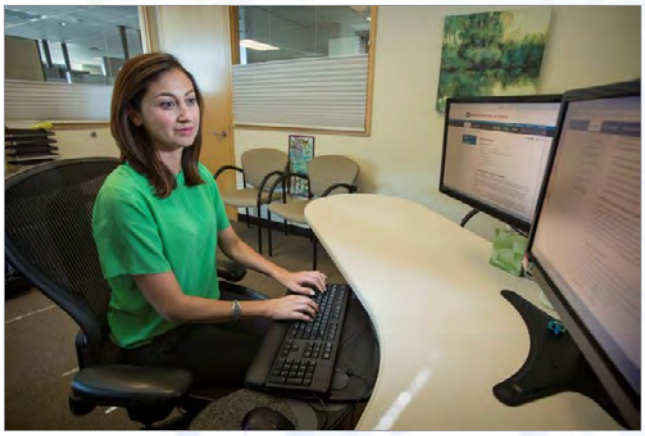
But the clinical center is still operational—treating patients, including cancer patients, with lifesaving therapies. It has reduced elective procedures and has taken in some COVID-19 patients, but it still continues to work, and NCI staff work there under, as you can imagine, difficult circumstances.

In order to reconfigure a 3,000-personnel organization with thousands of contractors in such a rapid capacity is really a challenge, but I've been thrilled and impressed by how much we've been able to do, even virtually. I'm also very excited to see how cross-government collaborations have sprung up in a very rapid and direct manner, both across the NIH and the rest of federal government.

In the last few weeks, the NCI has started very important mutual re-

Cancer Information Service | 1-800-4-CANCER





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search efforts with NIAID, with [the National Institute of Biomedical Imaging and Bioengineering], with [the National Heart, Lung, and Blood Institute], and with the Aging Institute. We are also working very intimately with other federal agencies, including the FDA, the CDC, BARDA, and other parts of the HHS.

One other point I'll make is that although the pandemic has disrupted operations, I believe we will take some very valuable and meaningful things from this experience. Some of the changes that are being inflicted upon us may actually lead to some good overall.

Two important examples: the first, I believe telehealth is here to stay. We've shown that, in a meaningful way, we can take care of patients via telehealth, and I predict cancer patients are going to like this in the future. They're going to like the ability to see their doctor sometimes virtually, rather than in person.

And by the way, I will mention now that this is a tremendous pop-sci research opportunity. If you're studying implementation science, your moment has arrived, because a thing like this where we've gone from nobody using telehealth to a large part of the country using telehealth—in, really, a couple of days—is a tremendous change in our practice, and really will lead to some great research, I believe.

Another area where I've seen a real example of something that, I think, will last after the pandemic, for the good, is the fact that the government can, when it needs to, move really quickly. We have been involved in complex multi-agency endeavors, but we've been able to really cut through a lot of the process and the usual steps to launch large, innovative, complex research efforts in a matter of days.

Jim Doroshow will talk about some of the clinical trials the NCI has recently stood up. I think these are some of the fastest trials that we've ever gotten started at the NCI in our history, and Doug Lowy will talk about many of the efforts at Frederick National Lab, including a serology effort they're working with the FDA, it just has to be seen to be believed what they've started in just a few weeks (*The Cancer Letter*, April 10, 2020).

We also won't cover everything the NCI is doing. It is just too much. We really have too many activities in this space, so I won't really talk about our work with BARDA or what we're doing in the SBIR program with small companies that work on coronavirus, or a very interesting set of collaborations with the NIBIB on a novel data plat-

form that is aimed to help people get back to work.

But we will focus on a few of the more visible efforts in later talks. I hope that as life gets back to normal, we in the federal government can take these lessons we're learning from the pandemic about how to do business differently and that will help cancer research in the future.

Resources for caregivers, patients

I'm pleased to report that the NCI's Cancer Information Service, 1800-4-CANCER is fully operational and has been up continuously throughout the pandemic, even though it's gone remote. We've already received hundreds of inquiries related to the coronavirus, as of yesterday. Most of the questions from cancer patients for their loved ones involve questions about risk and whether they are considered immunocompromised, whether their cancer puts them in increased risk.

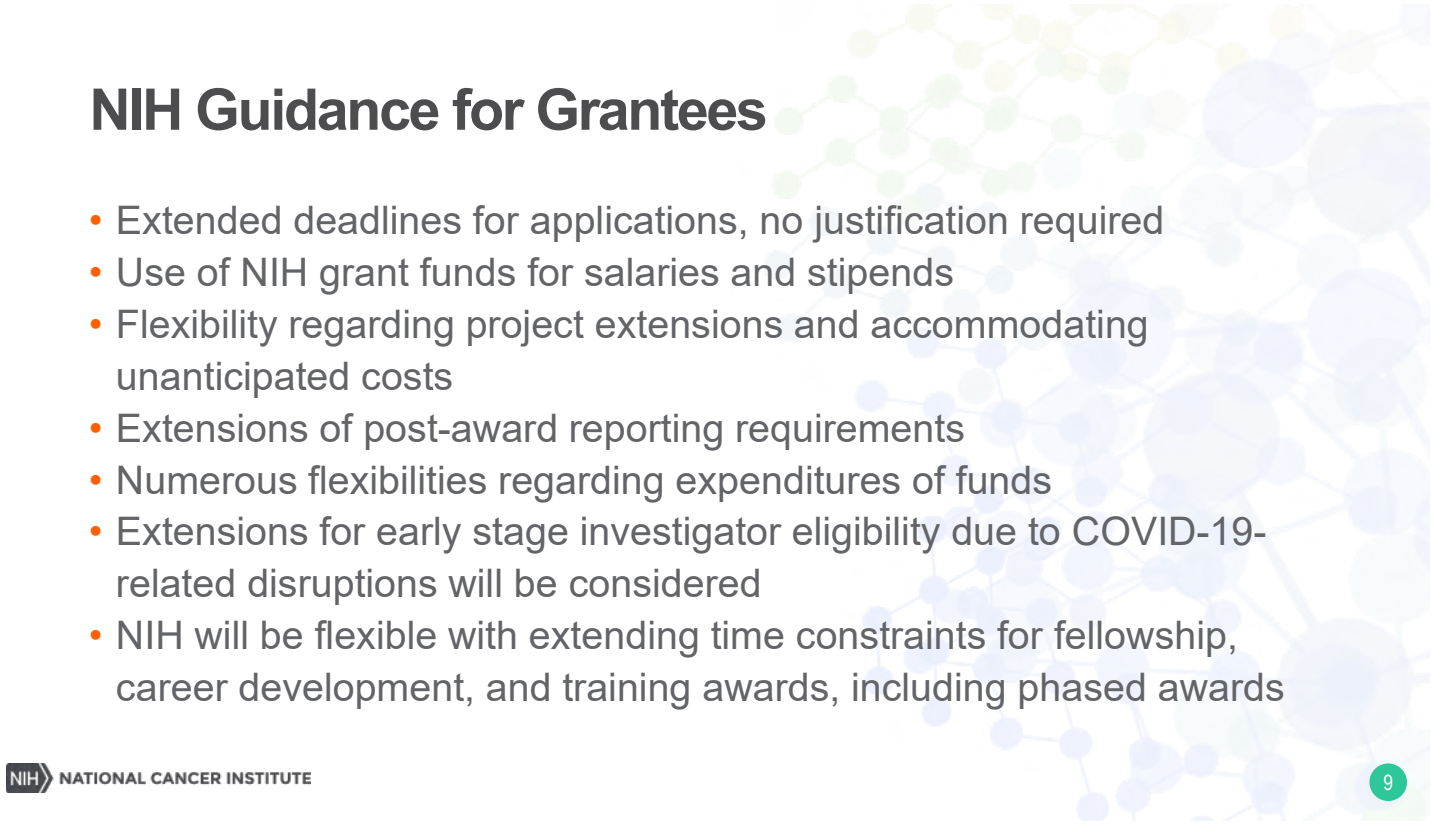
As you can imagine, the nature of calls to 1800-4-CANCER really has changed during the pandemic. We get questions now like, "Should I go to my doctor? Can I get my scheduled chemotherapy? Can I get a blood transfusion?" I'm sure your institutions are dealing with these same questions. The Cancer Information Service is a highly visible service of the NCI that we provide for patients and it is moving along rapidly and working fully in a full capacity, even during the pandemic.

We've also produced some new key resources for patients and caregivers. A few examples are shown here. So, we stood up a coronavirus page with information for people with cancer as of March 13, that website has already received more than 60,000 visits. It's the fourth most-visited page on our website. In addition, we have also stood up a coronavirus page targeted to researchers as of March 25, and that website has received 1,400 visits and we'll provide these links in the material for the meeting and they can also be easily accessed from cancer.gov.

Extramural funding

In addition, we're trying to maintain really strong communications to our research community. There's been lots of internal communications. I did a virtual town hall meeting using the similar format to this that had 4,000 live attendees.

Here, I'm highlighting some of our external communications efforts: we've done cancer.gov websites, as I men-



tioned, we've had several blogs, we've done social media through many of our Twitter accounts, including the highly popular NCI Director account.

We really want people to understand what's going on with grants and other funding matters. I had an NCI Bottom Line blog post on NCI funding during the coronavirus pandemic that's received 5,500 visits since its publication on March 23, and it has some useful information for extramural fundees, and I commend it to all of you.

Also, Oliver Bogler has written a Bottom Line blog post about training grant issues, K awards, and F awards, and T awards and their deadlines and their reporting requirements, and how the NCI is going to handle those issues. That's up now, and I commend it to all of you. In summary, we're trying to maintain communications to all our stakeholders, NCI employees, researchers, caregivers, and most importantly, patients throughout the time of the pandemic.

The coronavirus has really affected how we do business at the NCI and, no doubt, how you do business at your institutions. But I want to reiterate right now, from an extramural funding point of view, we are fully operational. We are up and running, we can review grants, we can disburse funds, we can do what we normally need to do to support the extramural research community. But, no doubt, things have gotten more complicated, and we have received many, many questions from our investigators about grants, lab suspensions, and what this all means for them.

Cancer center directors, trainees, postdocs, integrated research programs, individual scientists have all been asking us lots of questions and I've listed some of the key issues here, like deadlines for applications and the use of funds and flexibility around reporting requirements and extensions for training periods. And let me say, I provided some material in advance from the Office of Extramural Research, Mike Lauer's office at the NIH, that has a lot of really great information in that document, recently updated and is current, and I commend it to all of you, because it talks about a lot of these issues in detail.

Certainly, we can talk about any one of these more in a Q&A, if there's interest. But I will say, as a general principle, the NCI is trying to provide maximal flexibility to investigators so they can get their important work done during this crisis. We really want to avoid work stoppages, we want to avoid layoffs, we want to avoid a loss of the research capacity for cancer research in the United States.

Although, it has to be acknowledged that the policies we adopt at the NCI

Leadership Update

Daniel Gallahan, Ph.D.

Director, Division of Cancer Biology

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have to fit within policies of the greater federal government, we cannot really go it alone on extramural grant policies, as what we do has to agree with what the NIH and other grant making organizations within the federal government do.

But when we do reach uniform agreement about these funding policies, the NCI is fully committed to disseminating that information as quickly as possible through blogs, our website, Twitter streams, etc.

It's also important to note that we have a number of funding opportunities both not related to coronavirus, and I think those are out and probably familiar to many of you, and we also expect to have some coronavirus-related funding opportunities appearing soon, so please stay tuned for that.

We have some good news from a leadership point of view here at the NCI. Dan Gallahan, after being acting director of the Division of Cancer Biology for a while, has now become the director of the Division of Cancer Biology. We have really benefited from Dan's leadership, and NCI is very lucky to have Dan in this role, which is tremendously important for the NCI. I would like to give a round of virtual applause for Dan Gallahan. Hey, alright, that worked!

I would also like to thank Dinah Singer, who held this position prior to Dan. She has now moved to become the deputy director of the NCI, and as I mentioned, we'll be hearing from Dinah later on some important topics related to the NCI's extramural programs.

On Capitol Hill

It is clear that Congress is extremely interested in our activities during the coronavirus pandemic. This is a hearing that was held on March 4—that was like a month ago—Labor-HHS subcommittee for the House Appropriations Committee, where there were a lot of questions about how the United States is responding. Doesn't this really seem like a lifetime ago? I mean, here we all were, packed in a room, close together, not wearing masks, talking to each other. I had hair back then, that was a while ago.

Sitting beside me, by the way, is America's most famous scientist, Tony Fauci [director of NIAID]. I think Tony and I have had a very close working relationship my entire time at the NCI, but it has really gotten a lot closer, because of the joint NIAID-NCI activities during the pandemic, and I think the nation as a whole is so lucky to have Tony's leadership during this time. He is a remarkable American institution.

House Appropriations Labor-HHS Subcommittee Hearing
FY 2021 NIH Budget Request - March 4, 2020

- Participated alongside Dr. Collins, and IC Directors from NIAID, NHLBI, NIDA, and NICHD
- 8 questions including from the Chair and Ranking Member
- Topics included NCI's increase in applications, CCDI update, clinical trials, and kidney cancer
- Senate budget hearing postponed indefinitely as Congress determines next steps in Appropriations process during COVID-19

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At this hearing, as you can imagine, there was a tremendous amount of questions about the coronavirus and the pandemic, but also this is the subcommittee, I remind you, chaired by Rosa DeLauro (D-CT) and Tom Cole (R-OK).

There was a lot of interest in cancer research. That group is very committed to cancer science and we had some great discussions about cancer research, paylines, pediatric cancer, clinical trials and many other topics. So, while Congress is very interested in coronavirus for the moment, they are consistently also very interested in supporting cancer research as they have done generously for a while.

I would say this congressional interest since this March 4 hearing has significantly even further intensified. Over the last week alone, I have spoken with, I think, maybe three or four senators and representatives about NCI activities related to the pandemic, and also with various staff for the House and the Senate, and these conversations really continue.

The Congress has done some stuff for coronavirus. Shown here are three fairly large supplemental spending packages that have moved rapidly through Congress to support a number of things regarding science and patient care, and the American economy. Most probably relevant for the NIH is phase 3, the CARES Act, which provided significant new money for the NIH as well as the FDA and CDC, and it also—an issue I'm sure very important to many of the board members—provided significant funding for hospitals, given the massive drop in revenues some hospitals are seeing with the cessation of elective surgeries and that type of issue.

Another thing we just learned recently is the FDA position regarding the CARES Act, which has a provision that all Americans can get testing for the coronavirus. And as I said, the FDA interprets that to mean both RT-PCR testing for the coronavirus as well as serologic IgG, IgM antibody testing for the coronavirus. This has very significant implications for the Frederick National Lab serology effort that Doug Lowy will be talking about later. There's also talk, I'm sure many of you heard, about the possibility of a fourth supplemental spending bill. Should that happen, there is a good chance, I think, that there will be funding in that for the NIH and for the clinical center.

Progress in cancer research

I really couldn't resist, as I said, even though you know it's a lot of coronavirus going on around here right now, cancer really does continue at a brisk

Legislative Updates: Three Aid Packages to Address COVID-19

Phase 1 (March 3rd)

- $8.3B in funding for health agencies – vaccine development and testing, plus small business loan subsidies ($2.2B to CDC, $836M to NIAID & NIEHS)

Phase 2 (March 18th)

- $100B in tax credits for employers offering paid sick leave, increases to unemployment benefits, and food assistance

Phase 3: CARES Act (March 27th)

- Largest stimulus in U.S. history - $2 trillion in loans and support for industry and small business
- $130B in aid for hospitals, doctors, nurses, and health centers
- $4.3B to CDC, $945.5M to NIH (NIAID, NHLBI, NIBIB, NCATS, NLM, NIH OD), $80M to FDA
- Telehealth flexibilities, coverage of diagnostics and preventive services for COVID-19
- Direct payments to individuals, unemployment benefits, student loan deferral, election adjustments

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pace despite all the measures being taken to mitigate the pandemic, and I just wanted to highlight a few of those examples. These are things that have just happened in the last few weeks to give everyone a sense of how things are still moving along in the cancer research enterprise.

So, one about which I'm very excited is we enrolled our first patient on our CD33 CAR T trial. This is a trial for young adults and children with acute leukemia that has relapsed or refractory. And this is a first-in-man trial of a new CAR antigen and that reflects the work of Nirali Shah and collaborators at CHOP.

And that's all important, but what is particularly remarkable at this trial in my mind is that the cells were made at our new Frederick National Lab facilities. So, that cellular therapies facility is open for business now.

We have a vision of doing several types of highly personalized cancer therapy for patients at Frederick National Lab, and I think the cellular program is just the beginning of that. So, I'd really like to congratulate Jim Doroshow and the Frederick National Lab team for getting this facility up and running so quickly.

The facility can make the CAR T cells there, and then ship them to a participating clinical trial site, in this case CHOP. And this technical advance is great news for kids and adults with leukemia, but I think we'll see it spread to other CAR T trials soon.

This is a paper that came out from the intramural program from [Division of Cancer Epidemiology and Genetics] about a week or two ago, also with collaborators at NIA and CDC, and this shows a very strong association of steps per day with all-cause mortality.

So, people who get 12,000 steps per day have a lower all-cause mortality than people who get 8,000 steps per day, who have a lower all-cause mortality than people who get 4,000 steps per day.

When I'm sheltering in place during a pandemic, this issue is really key. I've been trying to get out of the house to get my steps in, not just for my all-cause mortality, but for my mental health, and this great study was led by Chuck Matthews and others in DCEG.

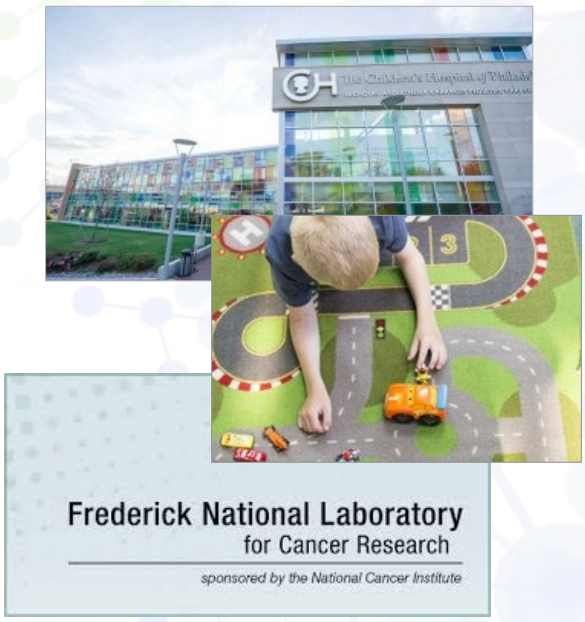
This is a wonderful story 30 years in the making, 30 years of intramural research at the NIH about the use of selumetinib in NF1. It started with a fresh faced young geneticist named Francis Collins, who, while faculty at the University of Michigan, along with others, first discovered the gene NF1 that is mutated in this congenital pediatric cancer predisposition syndrome. And then people like Doug Lowy and oth-

CD33 CAR T Trial

Study of Anti-CD33 Chimeric Antigen Receptor-Expressing T Cells (CD33CART) in Children and Young Adults With Relapsed/Refractory Acute Myeloid Leukemia

ClinicalTrials.gov Identifier: NCT03971799

Principal Investigators:
- Nirali Shah, MD, MHSc, NCI
- Richard Aplenc, MD, PhD, Children's Hospital of Philadelphia



Steps per day and all-cause mortality

NCI Press Release

Higher daily step count linked with lower all-cause mortality

Posted: March 24, 2020

Contact: NCI Press Office
240-760-6600

In a new study, higher dail
associated with lower mor
causes. The research team
investigators from the Nat
(NCI) and the National Ins
both parts of the National
well as from the Centers f
Prevention (CDC), also fou
steps a person takes each
intensity of stepping, had
with mortality.

The findings were published March 24, 2020, in the *Journal of the American Medical Association*.

JAMA | Original Investigation

Association of Daily Step Count and Step Intensity With Mortality Among US Adults

Pedro F. Saint-Maurice, PhD; Richard P. Troiano, PhD; David R. Bassett Jr, PhD; Barry I. Graubard, PhD; Susan A. Carlson, PhD; Eric J. Shiroma, ScD; Janet E. Fulton, PhD; Charles E. Matthews, PhD

Selumetinib & NF1

ers figured out what NF1 does from a biochemical standpoint and its role in Ras/MEK signaling.

And then a lot of studies, a number, over a decade of studies in the intramural program to try and address NF1 in patients. And those were largely led by Brigitte Widemann pictured here. And finally, after a lot of things that didn't work, recently the NCI and Brigitte have developed this therapy that is really a notable success. It's published recently in the New England Journal. This is not a cure for neurofibromatosis, but it's incredibly meaningful for patients and vastly improves their quality of life. I really want to take my hat off to the people in the pediatric oncology grants who have developed this over so many years.

There's just too much great science in the extramural community to mention it all and it's so rapid and staggering in its output. I thought I would show one slide that I particularly liked, which is a story from my old friend Sean Morrison's lab showing this interesting relationship between metastasis and melanoma spread.

Metastasis is one of the great unsolved riddles of cancer research, and I think science like this that helps us understand the cellular basis of that process is really, really key, and is a good example of why basic research is what really moves the needle, in my opinion, for cancer patients over the long term.

And this is why I've been such a fierce defender of the RPG pool my entire time, because it produces great basic science like this, and I believe someday we're going to be able to prevent metastasis because of studies in this vein.

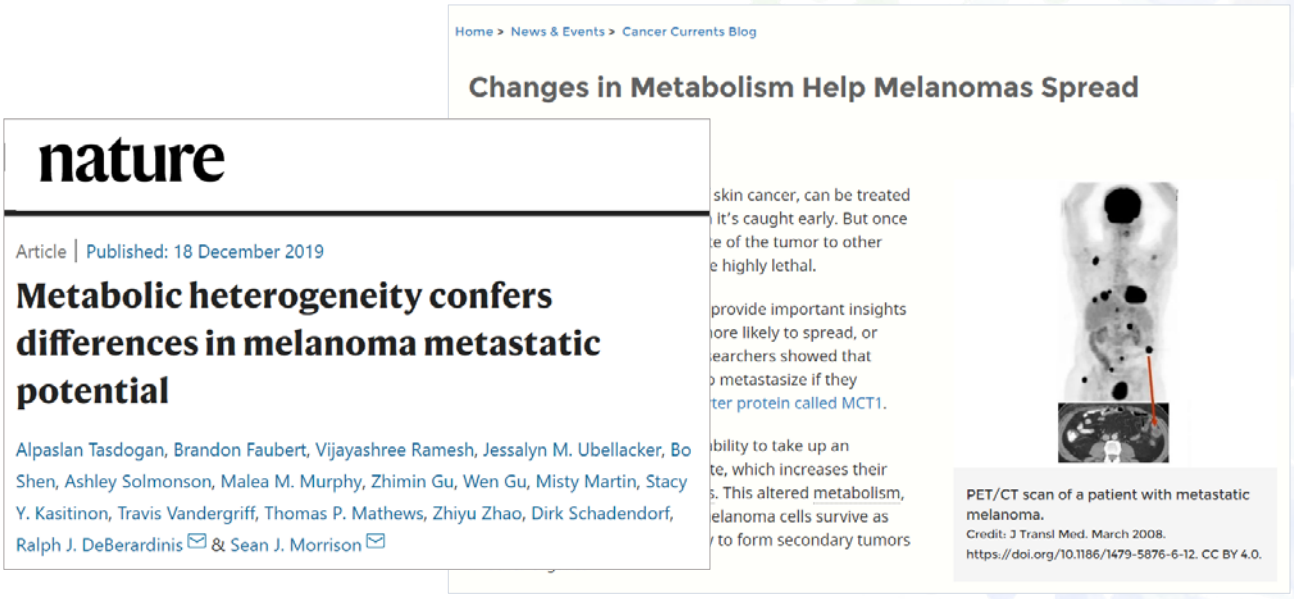
"Battalions of sorrows"

So, let me close now. I really won't sugarcoat our present circumstances. This epidemic is bad, and it's going to continue to be bad for a while, especially the next few weeks. This period of waiting for some normalcy to return has made me think a lot about what it was like when I was a leukemia doctor.

In leukemia, in acute leukemia, you give patients a big bolus of chemotherapy, and then you wait four to six weeks for them to recover their bone marrow and go home. And induction chemotherapy, as many of you know, involves a lot of waiting and a lot of anxiety, hoping for a return to a more normal time.

And this period now reminds me a lot of waiting for bone marrow to return and the inpatient service while we're waiting for this pandemic to abate.

Metabolism & metastasis



And in particular, I've been thinking about a former patient from that time. He was an English professor who taught undergrads English literature, and he'd gotten his induction chemotherapy, and was waiting in that hospital for his bone marrow to recover, so he could go home.

Now, a little-known fact is that I was an English major for about a month, as an undergraduate, before I realized how much writing an English major entails, and then I switched to become a math major. But I've always loved literature, and I've always taken the chance to learn from my patients. So, when I would come in every morning with my huge team of residents, medical students and pharmacists to round on this patient, we would always ask him for some great thought from English literature to summarize his day.

This guy had an amazing memory, and he never disappointed in producing these sonnets and couplets on the spur of the moment, always with something that fit the mood of the day. And it kind of became a fifth vital sign. We'd have his blood pressure and his heart rate, and his thought for the day from classical literature, and we could tell when he was doing better or worse based on what he said that day.

And one morning, on a bad day at the nadir of his chemotherapy, right after he'd received several pieces of bad news, he gave us a little known quote from Hamlet: "When sorrows come, they come not single spies, but in battalions."

And I've been thinking about that a lot lately. I see these stories about ICUs full of patients in New York, and I imagine what it's like to work in that situation, and I just can think of nothing but battalions of sorrows.

But I'm here to tell you we'll get through this, just like my team and I got that guy through his induction chemotherapy—he went home in remission, back to a more normal life. And this is going to be a tough period for the NCI, for cancer research, but it will come to an end.

And I want to thank everyone again for their time and for what each of you are doing at your own institutions to address this pandemic, in the tragedy of the current set of circumstances, but also to continue to make progress against cancer, an ancient and terrible disease that causes immense human suffering in its own right.

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As treatments get cancelled because of COVID-19, patients worry about adequacy of care

By Alexandria Carolan

To prevent the spread of COVID-19, oncologists are either limiting or canceling adjuvant care, in effect staging a population-level experiment.

"How people are treated in the adjuvant setting is supposedly based on high-level clinical trials, results of those trials, results of high-level evidence. That's what we're told," Fran Visco, president of the National Breast Cancer Coalition, said to *The Cancer Letter*. "And so, people are willing to take the risks of treatment—the economic hit from treatment, all of that—because we're told this is the best we can do for you right now.

"So, if we're going to change that, those changes better be based on the same level of evidence, or—why would we trust any recommendation for treatment in the future if we can just change it?"

Patients are left with the gnawing thought that perhaps, as a result, they're not getting the best treatment.

"Everyone, everywhere has a great deal of anxiety, given the pandemic, but it's certainly particularly exacerbated in people with a life-threatening disease who are facing the possibility of changes in their treatment protocols and delays in their treatment," Visco said.

In a survey conducted by NBCC, 19% of respondents indicated that they had experienced challenges accessing care, mostly related to cancellations, postponed follow-ups, blood tests, imaging, treatments, infusions, and surgeries. NBCC is conducting a follow-up survey with results that will be published in the upcoming weeks.

"Losing their medical insurance because they've lost their jobs—there are so many issues out there that, on top of the issues all of us have to face now day to day—that people undergoing cancer treatment have to face," Visco said.

Among 564 respondents to the survey, 94.3% described themselves as breast cancer patients or survivors, and 5% of these individuals said they have metastatic breast cancer. Two percent of respondents listed themselves as caregivers, and 23% described themselves as "other," which includes advocates, health care professionals and researchers.

"The implication is you're told this is the best protocol for you, and now that's changed," Visco said. "And there isn't a great deal of evidence—scientific evidence—behind those changes. That certainly adds to the stress that people in treatment are dealing with right now."

Changing standards of care?

Guidelines from The American Society of Clinical Oncology recommend that practices postpone routine follow-up visits of patients not on active can-

cer treatment, which can exclude adjuvant care.

For patients receiving adjuvant care that has lapsed as a result of COVID-19, there may be heightened anxiety, said Shelley Fuld Nasso, chief executive officer of the National Coalition for Cancer Survivorship.

"We always hear the survivors talk about that fear of recurrence. And I worry about the heightened fear of recurrence, knowing that they did not have access to something that otherwise they would have," Nasso said to *The Cancer Letter*. "I think that's going to have an effect on a lot of people that end up not having it. But if the data shows that they do just as well, then maybe it will result in changes in standards of care."

Recently, NCCS held a webinar on the impact of coronavirus on cancer. Adjuvant treatment may be postponed in the COVID-19 setting because it can put patients at risk, Otis Brawley, the Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University, said during the webinar with Nasso. A full transcript of the webinar is posted here.

"Many hospitals are not doing adjuvant chemotherapy for breast, colon, and lung cancer right now—because we have done a weighing of what's the odds that this chemotherapy is going to prevent the person from relapsing in the future, versus the odds that it's going to increase their chances of getting coronavirus and having a bad outcome today," Brawley said during the webinar. "If we lower their white count and they get coronavirus, that is a ticket to not doing well with the disease. So many hospitals are only giving or clinics are only giving chemotherapy to people who truly need chemotherapy right now."

Cancer patients are at higher risk of complications from COVID-19, and have a high mortality rate, according to data from Istituto Superiore di Sanità, the Italian National Institute of Health. In Italy, cancer patients account for 16.5% of deaths stemming from the novel coronavirus (*The Cancer Letter*, April 3).

Adjuvant treatment can increase that risk.

In the NBCC study, 9% of respondents (51) reported fear of being immunocompromised and high risk, and 8% (47) reported feeling anxiety or emotional distress because of COVID-19. Four percent of respondents have reported being denied access to COVID-19 testing after reporting symptoms (*The Cancer Letter*, March 20).

"I am personally very concerned about people who got adjuvant chemotherapy for breast cancer or colon cancer a year or two ago and have finished that," Brawley said. "We know that their immune systems are still damaged, if not totally recovered, from that adjuvant chemotherapy."

In some patients, adjuvant chemotherapy is going to reduce risk of relapse by 10%, Brawley said.

"And maybe your risk of getting COVID-19 is high, and the risk of not doing well is high, and so a 10% reduction is not worth it. There are other people where adjuvant therapies is going to reduce their risk of relapse by 40 or 50%," Brawley said. "There are certain patients who should get the adjuvant chemotherapy right now and we are giving them the adjuvant chemotherapy, but there's a bunch of patients who can forego it."

Could this change how cancer patients receive treatment in a post-pandemic setting?

"Pandemic has taken priority over cancer and cancer treatments. It's the priority now. And so, people are having a hard time accessing the care they were told that they should have," Visco said.

"Of course, we understand why that's happening—but we're concerned about—are the changes really thought through enough? Are they—the people who are making these recommendations—really looking at the evidence we have of what these changes mean for cancer patients?

"And then, equally importantly, we're very concerned about, are we accumulating data in the right way, that will answer all of these questions, so that the next time we have a more evidence-based approach to how we deal with cancer patients in this type of a situation?"

> "Are they—the people who are making these recommendations—really looking at the evidence we have of what these changes mean for cancer patients?"
>
> *– Fran Visco*

American Cancer Society announces a wave of furloughs and layoffs as COVID-19 constricts fundraising

By Alexandria Carolan

The American Cancer Society earlier this week announced immediate furloughs and layoffs of its staff citing "a significant financial hardship" triggered by the novel coronavirus.

"The American Cancer Society has never faced a threat to our mission like the coronavirus," the charity said in a statement. "The COVID-19 pandemic has severely impeded the American Cancer Society's annual fundraising activity. Regrettably, this has created a significant financial hardship and is forcing several cost saving measures.

"While we are pulling back in every area, there is no way to close the gap between current revenue and expenses without immediate furloughs and a reduction in workforce over the next several weeks. It is an aggressive timeline with painful outcomes, but it is the only path forward for ACS to conserve the most resources to fund our life-saving mission."

It's not publicly known how many staff members will be furloughed, downgraded to part-time work or laid off. ACS currently has about 4,000 employees.

Concurrently with announcing broader staff cuts, the society has terminated the position of Chief Cancer Control Officer Richard C. Wender, a family physician whose role at ACS became unclear after the hiring of William G. Cance to the job of chief medical and scientific officer (*The Cancer Letter*, Sept. 6, 2019).

At the time of his hiring, Cance was given a role that included oversight of cancer control.

Wender's role was previously carved out of the portfolio of Otis W. Brawley, the previous chief medical and scientific officer. Brawley left ACS a year earlier (*The Cancer Letter*, Nov. 9, 2018).

Wender announced his departure in an email to ACS and ACS Cancer Action Network staff April 13.

"I'm writing to share the news that I'll be leaving the American Cancer Society at the end of the month," Wender wrote. "The position of chief cancer control officer has been eliminated as part of the reorganization of our integrated global headquarters mission work that Dr. Cance is leading.

"I am humbled and proud to have had the opportunity to serve as this organization's chief cancer control officer. I took this job to see if, working together, we could accelerate incidence and mortality reductions and reduce suffering from cancer, here and around the world.

"Thanks to the work of a great many people, I can point with satisfaction to measurable and concrete evidence of progress: increases in colorectal cancer screening rates and HPV vaccination rates, new patient navigation collaborations and innovations, risk-stratified survivorship care, low colorectal cancer screening age based on new evolving data, new resources for caregivers, patient programs more focused on improving access to care, new momentum in lung cancer, striving for equity in breast cancer, lowered smoking rates, and so much more."

The layoffs announced this week follow a reorganization that occurred in February, when ACS brought on Kris Kim, executive vice president for the Northeast Region. As an acting chief operating officer, Kim took over the society's day-to-day operations, a responsibility relinquished by Chief Executive Officer Gary Reedy (*The Cancer Letter*, Feb. 20).

"I recognize the need for me to focus my efforts externally, which requires different leadership to oversee day-to-day operations," Reedy said in an email dated Feb. 5 and addressed to the ACS staff. "To that end, we are embarking on the process of recruiting a chief operating officer."

Over recent weeks, three senior officials have left the charity. They are: Sharon Byers, chief development and marketing officer; Phil Monaghan, senior vice president, talent strategy; and Bob Crutchfield, the recently recruited managing director of what was described as the charity's $100 million venture capital fund.

> "While we are pulling back in every area, there is no way to close the gap between current revenue and expenses without immediate furloughs and a reduction in workforce over the next several weeks."
>
> *– American Cancer Society*

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GUEST EDITORIAL

Amid COVID-19 pandemic, cancer community responds to fill data gap

Richard L. Schilsky, MD, FACP, FSCT, FASCO
Executive vice president, chief medical officer, American Society of Clinical Oncology

As clinicians in a medical specialty that relies on evidence to guide treatment plans for individuals with cancer, we face an unfortunate dearth of data to help steer us during the coronavirus pandemic.

Questions abound:

- What is the COVID-19 susceptibility among patients with cancer?
- What is the severity of infection in cancer patients?
- How do we effectively treat our patients during a pandemic, while minimizing the risk of infection in patients and the cancer care workforce?
- And, what are the outcomes of individuals with cancer who have COVID-19?

We need answers to these questions—and quickly—to help navigate uncharted waters during the current public health crisis and beyond.

For our part, the American Society of Clinical Oncology has launched the ASCO Survey on COVID-19 in Oncology Registry to help the entire cancer community learn about how the pandemic is impacting the delivery of cancer care as well as the treatment and outcomes of our patients.

The ASCO Registry will help inform cancer care and decision-making now and during future disease outbreaks by collecting data on the pattern of symptoms and severity of COVID-19 among patients with cancer, modification of cancer treatment plans in patients with confirmed COVID-19, and the outcomes of both the viral infection and the cancer in patients followed prospectively.

To make sure we capture more than just a snapshot in time, the ASCO Registry will collect both baseline and longitudinal data on how the virus impacts care and outcomes into 2021. This will allow us to learn about the short-and the long-term effects of COVID-19 and its impact on cancer care and if the virus resulted in specific complications for patients, delayed patients' ability to get a specific type of cancer treatment, or if certain approaches resulted in better outcomes for patients.

We'll be able to learn if delays or alterations to treatment plans—disruptions in the standard of care that practices across the United States have had to implement—are having a deleterious impact on our patients. We might also learn that certain methodologies, previously thought undesirable, might actually allow us to deliver care more efficiently or safely without jeopardizing patient outcomes.

When sufficient patient data have been collected and analyzed, ASCO will deliver periodic reports and develop peer-reviewed manuscripts to share key learnings with the cancer community and the broader public. Data on the implementation of telemedicine in the cancer treatment setting and characteristics of de-identified patients with cancer most impacted by COVID-19 will be among these new insights.

Regular reports will provide the oncology community with current information to help inform treatment approaches for patients with cancer who have a confirmed COVID-19 diagnosis. In addition to issuing reports from analysis of the registry data, ASCO's real-world data platform, CancerLinQ, will periodically report on the characteristics, treatment and outcomes of cancer patients at CancerLinQ subscribing practices who develop COVID-19. These complementary data sources will enable ASCO to provide a comprehensive assessment of the impact of the pandemic on cancer care.

To support the registry, ASCO will be drawing on its extensive network of providers who are caring for patients with cancer and COVID-19 infection. The web-based registry will collect data from patients with all types of cancer who are undergoing all types of cancer treatment and is open to all U.S. oncology practices, including physician-owned, academic, and hospital/health system-owned practices. Consideration will be given to opening patient enrollment to international centers in the future.

Participating practices will complete a baseline data capture form on each patient with cancer who has a confirmed diagnosis of COVID-19, and subsequent follow-up information on status, treatment, and outcomes. Limited patient identifying data, including zip code, date of birth, gender, race, ethnicity, type of cancer, and comorbidities, will be collected in a secure way to make longitudinal analysis possible.

Data from practices participating in the registry will be collected and securely stored on the CancerLinQ platform. The registry has been reviewed by an institutional review board (IRB) and determined to be exempt from IRB oversight as it does not meet the definition of human subjects research.

All participating practices will receive nominal financial support to cover research data-entry costs. The funding is supported by Conquer Cancer, The ASCO Foundation.

Data collection is of the utmost importance during this rapidly evolving global pandemic, so I am very pleased that others in our community are working to address this urgent need to collect and analyze data on the impact of COVID-19.

The COVID-19 and Cancer Consortium is collecting information from cancer centers across the United States and the American Society of Hematology Research Collaborative COVID-19 Registry for Hematologic Malignancy will focus on patients with hematologic malignancies and COVID-19.

I understand that other multi-site registries are in development and many single institution registries have already been launched. All of these efforts are vital to document and learn from the experience of cancer patients with COVID-19.

We applaud all organizations that have developed patient registries and will look for opportunities to collaborate as the cancer community comes together to address this unprecedented crisis.

We encourage all oncology practices to participate in one or more registries based on their specific needs and to reflect the patients they serve. Each of these registries has a different focus and timeline, so participating in multiple registries will not compromise our efforts or prevent all organizations from working together.

Such a collaboration will allow us to learn from every patient, in every practice and practice setting, in every state across the country.

As noted in my previous guest editorial for *The Cancer Letter*, the ASCO Registry is part of ASCO's ongoing efforts to provide the most current information and resources on COVID-19 to its members and the larger oncology community to help ensure that individuals with cancer receive high-quality care.

ASCO has compiled a wide range of COVID-19 resources to support clinicians, the cancer care delivery team, and patients with cancer. This information is frequently updated, so check back often.

Learn more about the ASCO Registry.

GUEST EDITORIAL

Cancer care continues during COVID-19 pandemic—with new tools and old challenges

By Ted Okon
Executive director,
Community Oncology Alliance

While the news these days is rightly focused on hospitals and the government fighting public enemy number one, aka COVID-19 (the novel coronavirus), independent community oncology practices continue to treat and comfort patients who are at war with that insidious disease we call cancer.

Cancer doesn't stop for even a global pandemic, and neither does the need of cancer patients to get treated. Community oncology practices have had to quickly shift gears and adapt to a new, challenging COVID-19 world, replete with the same issues the rest of the health care community is facing, including safety, staffing, and supply shortages.

Oncology practices quickly embraced telehealth to keep the normalcy of patient care on schedule while protecting all involved from the COVID-19 virus. At the same time, practices remain frustrated and angry that cruel indignities like prior authorization are still around—but now worse. And cancer professionals are baffled that the dangerous idea of home infusion of chemotherapy by a third party, such as a home health agency, is being put forth during this crisis.

A huge ray of hope came from Washington a few weeks ago when Administrator Seema Verma and her team at the Centers for Medicare & Medicaid Services (CMS) quickly unveiled new tele-

> And while telehealth is indeed a godsend, it doesn't enable an oncologist to reach through the screen if a patient reacts badly to an infused drug.

health rules that gave oncologists the flexibility to seamlessly continue treatment with cancer patients on a computer or telephone without exposing them to COVID-19. The new CMS rules furnish 80 more services via telehealth and allow practices to bill for telehealth visits at the same rate as in-person visits. These are a godsend to struggling practices and scared patients.

One oncologist told us she did 31 Zoom check-ins just a week ago with patients who didn't need to be seen in person. A seriously overworked oncologist, Sibel Blau at Northwest Medical Specialties in Washington state—an early epicenter of the pandemic in this country—said telehealth saved her 90 minutes of commuting time and enabled her to get something in short supply for providers during the pandemic: sleep.

> "We know that as the COVID-19 pandemic slowly recedes, the curve flattens, and the new "normal" eventually comes into focus for most Americans, community oncology clinics will still be there, treating patients with cancer who need them."

Even without COVID-19, Salem, OR, cancer patient Tom Bailey, a retired urologist, is extremely happy with his new telehealth appointments. "I would prefer to do it this way. It saves a trip over there. It's convenient. I don't have to drive and park. It would be different if I didn't have an established relationship."

While telehealth is a huge benefit for patients with cancer who need to be seen by their physicians, the pandemic has not stopped bad and even inhumane practices. In fact, it has made them worse.

Take prior authorizations (PAs), the bane of oncologists whose well-considered treatment prescriptions are subjected to second-guessing by penny-pinching insurance and pharmacy benefit manager (PBM) bureaucrats with less education, real-world experience, or even knowledge of the individual patient's needs.

Troy Ebberson, the insurance authorization specialist for Salish Cancer Center in Fife, WA, reports a significant uptick in the amount of time needed to obtain PAs due to staffing shortages at insurance companies, which creates procedural challenges.

"The most significant impact felt has been the additional time needed when contacting insurance companies to verify authorizations due to the delays," Ebberson lamented. "Any delay in obtaining an authorization can cause a delay in patient care which can have a significant impact on their health."

Since a PA is required for services ranging from radiology reports to biopsy results, COA took the unusual step of writing to President Trump urging him to, "request that all health insurance companies immediately waive prior authorization requirements for cancer treatments during this COVID-19 crisis."

"If PA is lifted at this point, and we had the flexibility to choose a less toxic regimen or to bring a patient to clinic less often, it would be so much better and safer for our patients," Blau said.

While extending the oncology office to the patient's home with telehealth is a good idea, and prior authorizations wrapping a doctor's informed medical decision in red tape makes a bad idea worse, the mere notion of even considering home infusions of chemotherapy drugs is just plain baffling, and remarkably dangerous.

An interim final rule released by CMS on March 30 would allow for infused or injected Medicare Part B drugs to be administered at home by a home health agency so long as a provider is present, via telehealth. As COA noted in an official position statement on the issue, this might be reasonable for certain diseases and drugs. However, for cancer, this is not appropriate and can be extremely dangerous.

While it's true that traveling to one's oncologist during the pandemic is at times impractical and potentially risky

for an immunocompromised cancer patient, home health agency administration of cancer treatment is problematic, even when considering the possibility that patients could miss a chemotherapy treatment cycle due to the COVID-19 outbreak.

Cancer drugs can produce serious side effects or adverse reactions that the average home health nurse, spouse, or family caregiver is ill-equipped to manage. These can be sudden, severe, even deadly. And while telehealth is indeed a godsend, it doesn't enable an oncologist to reach through the screen if a patient reacts badly to an infused drug.

Avoiding side effects and adverse reactions from chemotherapy, or reacting to them, is the job of a trained oncology nurse under the oncologist's on-site supervision. Once home infusion treatment begins, the individual administering the treatments does not have access to the team of providers, additional drugs, tools, or equipment to deal with a potential adverse reaction. These can be potentially life-threatening.

Oregon Oncology Specialists' Bud Pierce, a 43-year veteran oncologist, puts it more succinctly.

"We don't need to compound this crisis with the unsafe administration of complex cancer drugs. If we don't do it right, it will hurt or kill somebody. Let's not go off the deep end with unsafe practices," Pierce said.

The expansion of telehealth services has allowed practices to focus on making in-office infusions as safe as they can be for patients. With less patients visiting in-person and stringent sanitation protocols in place, the likelihood of disease transmission is significantly lowered.

As hospitals have stepped up and committed their resources to stopping the deadly spread of COVID-19, community oncology clinics are doing their part to continue to provide quality care for those who carry the burden of cancer. Each member of the health care field plays a vital role in this emergency, and community oncology providers are standing fast for their patients.

We know that as the COVID-19 pandemic slowly recedes, the curve flattens, and the new "normal" eventually comes into focus for most Americans, community oncology clinics will still be there, treating patients with cancer who need them.

But it will not be the same as before the crisis.

Community oncology clinics will continue embracing telehealth into treatment plans. Community oncology clinics will continue to fight with insurers over prior authorizations. Community oncology clinics will never allow ill-conceived ideas like home health agency infusion to become a reality. And, perhaps most importantly, community oncology clinics will continue being the local, affordable, and accessible site of care for patients.

And we will never forget the men and women who fight in the trenches every day against pandemics like COVID-19 or devastating diseases like cancer, and, most importantly, who they are fighting for.

As Winston Churchill said so memorably when the chips were down in the midst of World War II: "Never was so much owed by so many to so few."

Ted Okon is the executive director of the Community Oncology Alliance (COA), a national association of independent, community cancer providers.

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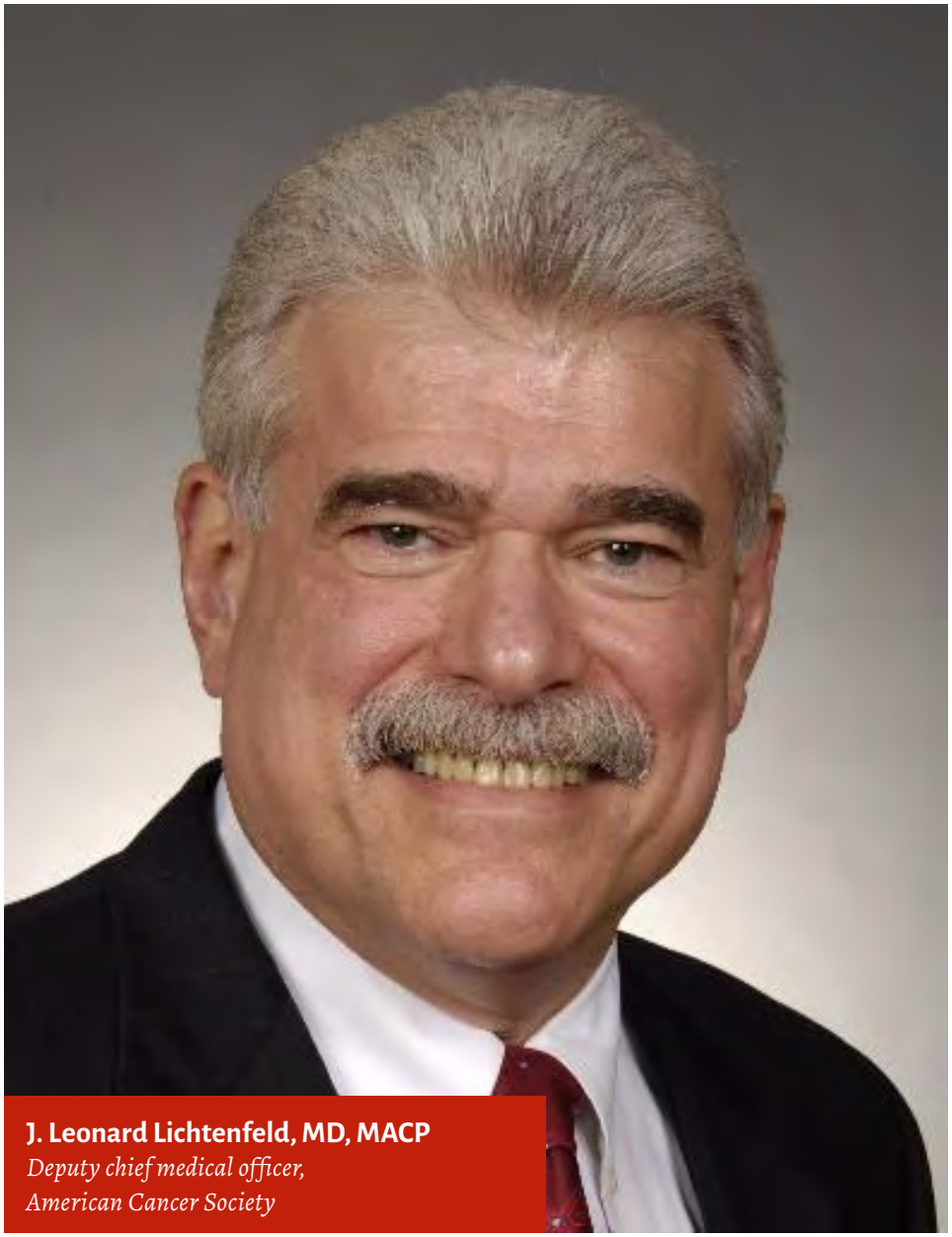
Q & A

Lichtenfeld spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Lichtenfeld: COVID-19 exposed weaknesses in the U.S. health care system



J. Leonard Lichtenfeld, MD, MACP
Deputy chief medical officer, American Cancer Society

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How has the COVID-19 pandemic affected oncology?

What will the long-term impact be?

"The virus will expose the weaknesses of our system at many, many levels. And research is one. And health care is another. And outcomes are going to be another still," said J. Leonard Lichtenfeld, deputy chief medical officer of the American Cancer Society.

"If there's anything that's good, it's a fact that we didn't have the number of deaths that we anticipated. Or at least it appears that we will not have a number of deaths we anticipated. Possibly, we could have had even less. But that's a discussion for another day.

"We're doing better than many of us thought, but there are so many areas where we have significant problems that none of us would have wanted to face."

The Cancer Letter asked Lichtenfeld to focus on issues including:

- The pandemic's impact on cancer care, including telemedicine,
- Long-term issues of cancer screening,
- Problems of health disparities at a time of rising unemployment,
- Potential pent-up demand for cancer care after the pandemic subsides,
- Economic impact on private practices and cancer hospitals, including community hospitals and NCI-designated cancer centers,
- Long-term impact on clinical and basic research.

"I think health care will come back, and there'll be more than enough demand for health care. The problem in health care, aside from the prioritization, may be how are people going to pay for it?," Lichtenfeld said. "Approximately 10% of our workforce, as of today, is out of work. And it may go even higher."

Lichtenfeld spoke with Paul Goldberg, editor and publisher of *The Cancer Letter.*

Paul Goldberg: Here's the reason I'm calling: I don't know many other people who have more breadth of knowledge in this field, everything from community oncology all the way to funding of research.

You have a model in your head, and I hope you will let *The Cancer Letter* take it for a spin as we try to figure out what the impact of this crisis has been and what the new normal would look like when it's over.

My first question is: What has the COVID-19 crisis shown us about our medical system, how it operates? What do we see in oncology as a result of this?

Leonard Lichtenfeld: I think what we're seeing in oncology mirrors what we've seen systemically, that is, we were faced with a pandemic that others had talked about, but nobody had really implemented plans for.

As we moved into the COVID pandemic worldwide, oncology teams here in the United States responded by creating programs and plans and contingencies to move forward during a very acute and unusual moment in time. I have to say that from what I have seen from a larger picture, I think they've responded as best they can.

I currently see teams coming together, and by that I mean organizations coming together to provide more firm guidance. And I'm hopeful that as we move through the pandemic and try to get to a point of relative normalcy, we will consider what has to be done to care for our patients under those circumstances.

Oncology has an infrastructure for getting quick answers to hairy medical questions. Has it been put to good use?

LL: I think we have a good infrastructure.

I'm not sure it was ever designed to respond to something as serious and as intensive as COVID-19, something that has completely disrupted our systems. I think we have a process where we can evaluate, where we can respond, but no one was prepared for something of this magnitude.

The clinical trials system in oncology is like no other in any other country or in any other therapeutic area.

LL: Our clinical trials system is outstanding when it's done right, and we owe that system a tremendous amount of gratitude for what they have done to advance cancer care and cancer research over the course of decades. However, even the clinical trials system is being faced with issues they never anticipated.

Some trials have had to be suspended. Some trials that were supposed to start could not get started, and even those that have been ongoing have had to change their metrics to respond to

COVID-19. We won't know the full impact of COVID-19 and the coronavirus on the clinical trial outcomes for some time.

We are still in that learning phase. We're still trying to gather information. We're still trying to make sense of what's going on.

How would you use the COVID-19 crisis as a foundation for research questions?

LL: From my perspective, we're going to be looking at this pandemic for months and years to come. There are a number of topics.

First and foremost, what did cancer centers do in this moment of crisis? And many of the academic centers responded by going to virtual visits, by eliminating unnecessary visits, by trying to make sure that patients who needed care got the care—period. They set up triage systems to make sure that those most in need and having the most acute problems were able to get in to see the teams. And they created outreach mechanisms.

By the same token, they decided what did not have to be done. Furthermore, they responded by altering treatment courses.

They may have taken some patients, such as women with very early, non-aggressive DCIS, and initiated alternative treatments rather than going directly to surgery. At the same time, they tried to make sure the patients with the most acute demands, such as those with acute leukemia, advancing lymphoma, those receiving CAR T were able to get care.

But at the same time, we're going to have a substantial backlog of care that's going to have to be addressed.

I, for one, find it interesting to see how we're going to incorporate what we have learned. In other words, we have things we want to do for our patients: treatments, scans, whatever, but now we're learning what we have to do for patients.

Will that alter the care we offer for months to come? Those will all be the topic of research questions, to take a look at what the acute response was and what the outcomes are.

More importantly, we're clearly going to examine long-term outcomes. In other words, were there patients who could have been treated more effectively that didn't receive that treatment? Did it impact their outcome? Did we see increasing mortality as a result of the inability of patients to get the treatment that they needed? Epidemiologists are going to be busy for a while.

We, at the American Cancer Society, have looked at the impact of disasters in the past. We recently published a paper—in July of last year—where we looked at the impact of hurricane disasters on outcomes in early-stage lung cancer treated with radiation therapy.

Even in that circumstance, we found that the outcomes were worse for patients in disaster areas versus those who were not in disaster areas, or areas where disasters were declared. With a hurricane, you can send patients elsewhere, the disaster is fairly time limited. With this pandemic, you don't know how long it will last, and you have no place to send your patients, because it's nationwide.

What can we see on the issue of disparities?

LL: Disparities are coming front and center on a national level.

As has been true with so many things in the pandemic, we're examining major questions at a very high population level. We're talking about disparities in how they impact the pandemic and the number of deaths from COVID-19 among different populations.

However, have no doubt that the same issues facing various populations—whether they be African American, Latino, or any other minority population—have no doubt that those disparities are going to magnify the outcomes for cancer patients as well.

We as a profession have to be certain that we pay attention to that problem and that we do everything in our power to make sure the care is given appropriately and given equally.

So, you're saying that first we are going to see the impact of COVID in terms of disparities, but then we are going to see it again in terms of cancer care and disparities.

LL: Yes.

So, it's really a double-whammy.

LL: Yeah, it's going to be a double-whammy, because, as we come out of the pandemic, and we try to get back to a "normal environment," and it won't be normal, and those who have the least voice are at risk of being put to the back of the line. We cannot let that happen.

What about impact on early detection? There's good early detection and there is bad early detection; there's over-treatment. Is this pandemic and interruption in care going to be making it possible to study over-treatment?

LL: I think we're going to be seeing over-treatment a bit of a different way. We won't call it over-treatment and we won't call it over-detection.

What we will do is prioritize those who are a greatest need. So, for example, you're already hearing conversations among competent and reputable oncologists and radiologists about who needs to have a mammogram the quickest. So, we have, obviously, concerns about breast cancer and early detection.

We have some women who are obviously at higher risk—for example, women with BRCA mutations and other mutations who need to be screened more regularly. They should probably go to the front of the line.

On the other hand, we know about the conflict in mammography guidelines, with some organizations saying you have to have a mammogram every year. Other organizations say you can start at age 50, every other year.

The American Cancer Society has its own set of recommendations, and you're starting to hear some folks say, "Well, if we delay a mammogram in a woman at average risk for 18 months, that's really not a bad thing." So whether that ever gets incorporated into routine practice, I don't know.

But as part of the prioritization process, I believe we will see those in greatest need, where we know we have to get the women screened on a very regular basis, even every six months, they should be screened first, and women who are at much lower risk and those who may be older, for example, may see a greater delay in terms of getting a mammogram.

You're also seeing researchers say, "Maybe this is a good opportunity to start bringing risk-based screening into play," that is, those where we know or where we believe there's evidence that we can assess risk, maybe we should start applying that information to a screening procedure to try to help prioritize those who should move to the front of the line.

Do you think real-world evidence is being generated in sufficient depth to answer some of these questions?

LL: I think real-world evidence is being generated. The secret will be whether we can move the real-world evidence into genuine evidence. There are some systems in place, which will be mined for all the information they can provide, because they offer it in a reasonably standard format.

The sad reality is that many of our systems don't provide data in a fashion that can be analyzed easily. There are a lot of researchers trying to make that happen, but that research is in progress. It hasn't gotten to the final point where we can routinely say, "We can take information from multiple systems and bring it together."

That's one of the difficulties that will become more apparent. We don't have a rapid data system in place that helps us understand what's happening today. When you talk to epidemiologists about how we can understand the impact of coronavirus and the pandemic, they're telling us that it will take months and years to get accurate datasets, because it takes that long for data to move through the system.

Perhaps, and as a result of this pandemic, one of the beneficial consequences that may come out of it, is that we'll find other means of getting data together, so we can understand at an earlier moment. We may not have data that's perfect, but we should not let the perfect be the enemy of the good. We need rapid data. We need to know what's happening.

We need to be able to implement those plans, because this may not be the only go-around we have with coronavirus. We may see a second round, possibly even a third round, because of what I believe is going to happen as we come out of this phase of the pandemic.

You're talking about SEER, but what about data from the billing systems and electronic medical records and so forth?

LL: There's SEER data, there's mortality data, and we know how long it takes for the validated data to become available. We will have it, and whether it's whatever EHR one may favor, there's no question there's a tremendous amount of data in there. But researchers have not yet gotten to the point where they have faith in that data.

There's a lot of information contained in medical records that is not standardized, and not accessible. Billing data still takes time to go through any system before it can be collated and analyzed. So we don't have a good rapid response system.

And even researchers who try to rely on Medicare billing data, or private billing data, and there are some systems that do bring that data together, still have concerns about accuracy and validity. That does hinder our ability to have a quick analysis that helps us see where the problems may be. It's not just a matter of a pandemic.

But it also has to do with our everyday research as well.

One point I think is important: We need to remember that a lot of people are getting care through telehealth, but the telehealth regulations have been substantially altered as a result of the pandemic. CMS has stepped up to the plate, changed its rules, allowed different means of communication with patients, and much of that is not captured in any way close to the routine way we do business.

So, you can use telephones, you can use facetime, but the records may not be as accurate as they were. So, we're, we're in the midst of, as we say, uncharted territory.

But when it comes to understanding the research issues that we face when it comes to trying to answer the research questions that are important we will still have a number of barriers to making sure that data is in a format that's useful for the research we would like to do.

I started struggling with this really the first time I heard about telemedicine being used more often and in more settings: What does this do to the concept of catchment area for cancer centers, for example?

LL: Well, actually that's an excellent question. That's actually two questions.

I'm going to put something first that you didn't ask. We assume when we talk telehealth that everybody has access to online visits, and that people are comfortable doing that. I happen to be located, as we have this conversation, in a rural community. My ability to use broadband effectively is extremely limited. That's number one.

Number Two: There are a lot of people in various communities who are not comfortable doing telehealth. They don't have a computer, they don't have internet, and they're not comfortable talking to a clinician over the telephone.

So, those already are barriers that we don't think about.

We're really talking about digital divide, which is also urban-rural. Actually, that is fascinating and truly something that needs to be studied. But first, let's dispense with my question about the impact of telehealth on catchment areas for cancer centers.

LL: They are dealing with an issue that has some of the centers concerned, and that is, how do you do telehealth across state lines when you're not licensed in the other state?

And I can share that I have had conversations with colleagues where that has become a real issue. So, you have the legal departments saying you can't do a telehealth consultation from state A to state B, because you're not licensed in state B.

And it turns out the doctor at the cancer center happens to be a national expert in a very specific area of cancer care that's not widely available, and he or she has to make a decision whether they're going to do that consult, and possibly be in violation of the state licensing law.

My hope is that under these circumstances ,where cancer centers have to deal with patients around the country, if not around the world, that all of us will understand that these are very special circumstances and not make a major issue about licensure in a telehealth consultation—at least during the course of this pandemic.

We could deal with the issue in normal times at a later date. But for now, we have seriously ill patients with particular diseases who are located in other states, and we should allow the experts, particularly those from the cancer centers, to interact.

I have heard one solution, and this was in the past where the center said you can do a virtual consultation in another state if that patient has already been seen and cared for in our center. The real question comes up: What happens if someone is in another state and they'd never been seen at your center and they want a consultation?

I do think that consultations between health professionals, between clinicians and doctors and other clinicians in one state to a cancer center, are probably going to be less problematic.

But the concern becomes whether another doctor in another state who hears about a doctor from the first state calling their patient in another state may not appreciate that. Could a complaint be filed? And, of course, as we all know, the answer is, yes, anybody can file a complaint about anything.

I hope that we have enough compassion and enough understanding with regard to what's going on today, that we don't get caught in those legal and technical dilemmas.

Now, let's go through the list of areas of oncology and talk about how they qre going to be impacted. So the list is going to include the private practices, the hospitals, the cancer centers—and research funders. Let's start with the oncology practices.

LL: I think the impact on oncology practices is uncertain at this time. Information I've had from major centers—and I admit it's not a random sample—reveals the incredible diligence and attention that most of these centers gave to the questions and the problems very early on. We know that a number of cancer centers immediately went to virtual visits.

They immediately excluded people who didn't have to come into the center. They screened people coming in. They did everything they could to minimize the risk and exposure of the cancer patients coming in to get treatment. I also know that they paid attention to how treatment could be altered safely as a result of this pandemic.

On the other hand, we did get phone calls from cancer patients around the country. Again, far from a scientific sample, expressing concern about what was going on in the centers they were attending, the community centers and practices that they were attending.

I have no reason not to believe that most smaller programs also did what they could do to limit patient care to only what is absolutely necessary. However, I'm also aware that some centers did not, and this was a source of concern to patients.

Part of the problem, of course, is financial, and cancer practices are no different than any other medical practices. And what you see going on in the larger scene, a larger picture of medical practices, is a lot of doctors are having a great deal of difficulty, particularly those in small private practices.

But now you're hearing reports in the news, and not necessarily about cancer practices, but other specialties, such as dermatology where in the case of private practices where there's a heavy private equity investment, that they're being held open, and patients were being told to come in as though nothing was wrong. And that has me extremely concerned.

I hope it's not widespread. But I'm seeing enough reports, and actually had a personal experience to suggest that some practices were staying open in an environment where that presented increased risk to the patients they serve.

Will they ever be made whole at the end of this? I mean, how do they survive—or is this going to be a massacre?

LL: My concern is that we're going to lose some practices. There may be physicians who are near retirement age who may just say, "I quit." Some may determine they don't have the wherewithal or the time to make up the loss.

My understanding is that the American Medical Association and other organizations are working to keep practices whole and make sure that they have a source of funding to tide them through. But you can't look at the private practices around this country and not be concerned.

We are at a place now where less than half of the practices are actually owned by the physicians. Less than half the practices are in the traditional model of physician ownership.

The other concern is whether the practices that are owned by private equity are going to have enough investment available to stay open. And although I hope this is not the case, are additional pressures going to be put on those practices to engage in behaviors that would be less than desirable?

I hope that's not the case. But experience suggests to me that that may be a concern.

What about hospitals?

LL: I think hospitals are going to have difficulty also. Again, the larger institutions stepped up to the plate early by putting a number of programs in place that had and will continue to have incredible cost to the institution.

There are larger medical schools and universities and hospitals, affiliated hospitals, that canceled their routine clinics, that told a good portion of their workforce to remain at home, or set up alternative arrangements, such as virtual visits, and only having the most necessary visits continue. But that costs money. Now, maybe they have deeper pockets, but even there they have fundamental fixed expenses that have to be met, and one has to have concern.

But I looked at a number of industries that have been impacted, and although I don't believe that restaurants and medical practices are of the same intensity of service, the reality is they're

in the same boat. That is, their source of funding has been cut considerably.

And many medical practices are very much on a cash-in/cash-out basis, so any interruption may hurt. They may be able to survive for one or two months, but whether they can last three, four, or five months—is unknown. And, particularly, can they last if a second or third wave comes along.

Talking about the hospitals: There are a lot of hospitals in rural parts of this country that are already in serious financial danger. Before the pandemic hit here in Georgia, we've had a number of hospitals close down. And we're not unique.

All through the country, rural hospitals are in trouble. One can only imagine what's going to happen if in some rural communities they get overwhelmed with COVID-19, as has already occurred at southwest Georgia.

These are not hospitals that have, for the most part, large endowments. They serve communities, where a lot of their care is Medicaid,no-pay, and Medicare, and they don't have large private insurance bases. They don't have large private companies in many of these small towns. I'm extremely worried that we're going to see substantial closures once this pandemic clears.

What about cancer centers?

LL: Cancer centers will hopefully survive, if we're talking about the cancer centers that enjoy excellent reputations and are NCI-level centers. My sense is that they will get through this. Now, in that scenario, what concerns me are the research programs.

We haven't talked about research, but research can't be ignored as having consequences and impact from COVID-19. We've done a non-scientific survey, where we reached out to our grantees around the country, and we received a substantial response, about 60% of the people we reached out to responded.

Half of them cannot go into their research labs at all. Almost the other half, not all, but almost the other half, are severely restricted from going into their labs.

And on the clinical side, some of the researchers who were doing the clinical or lab research have now been re-directed to working with COVID-19 patients. So the toll on research programs is highly uncertain at this point.

And how the funders, including the American Cancer Society, are going to be able to intervene and sustain those researchers is a story that is currently being written. Our hope is that we'll be able to fund our researchers and keep them whole.

But it's not just American Cancer Society, it's clinical trials, it's, obviously, NCI funding, it's a large segment of young researchers, postdocs, for example. All of those folks are being impacted.

Once again, our major national focus is at a very, very high level. We're looking at the highest level of population impact, and we're concerned about many levels below that, such as the unfortunately substantial number of people who are being unemployed.

But as we have talked about, the impacts are going to go even further. They are going to go into medical practices, they're going to go into hospitals, and they're clearly going to go into the research enterprise—both in the clinical and the basic sciences.

What about issues like the uninsured?

LL: Well, the uninsured, along with the disparities, are issues that have faced this country for a long period of time. And now we have a pandemic that is going to expose some of the most serious and worst weaknesses of our system of care.

Those who have not had access or have been denied access, and how are they going to get care today?

Today, hospitals are saying, and I have no reason to doubt them, that people who need to be in that hospital are getting care.

The virus will expose the weaknesses of our system at many, many levels. And research is one. And health care is another. And outcomes are going to be another still.

If there's anything that's good, it's a fact that we didn't have the number of deaths that we anticipated. Or at least it appears that we will not have a number of deaths we anticipated. Possibly, we could have had even less. But that's a discussion for another day.

We're doing better than many of us thought, but there are so many areas where we have significant problems that none of us would have wanted to face.

Do you have any thoughts on how one would restart the economy?

LL: Well, I don't know that I'm an expert in the economy.

> The virus will expose the weaknesses of our system at many, many levels. And research is one. And health care is another. And outcomes are going to be another still.

You are, in one aspect of it—health care.

LL: I think reopening the economy is going to be a bit more difficult than some people think. Some are starting to say, "Let's get past this, and we can put everything in place, and we'll be fine in our business."

I focus on health care, and I think the health care economy will restart. I think it will be overwhelmed by pent-up demand. And that pent-up demand is going to be put on top of a demand that was already being stretched in many areas.

So, going back to my comments previously about prioritization, and thinking about how to get the right people in the door the earliest is so important. I think health care will come back, and there'll be more than enough demand for health care.

The problem in health care, aside from the prioritization, may be how are people going to pay for it? Approximately 10% of our workforce, as of today, is out of work. And it may go even higher.

And if we open up too early. If we don't do what needs to be done as we come out of this from a medical standpoint, we will quickly be back in it. Meaning, if we don't wait until the number of cases has diminished substantially. If we don't practice effective contact tracing, if we don't really understand that this is not the end of this pandemic, if we don't take all of those things to heart, we'll be right back in the soup.

Health care as an industry has been expanding demand to fill the available opportunities. But the question is going to be who can pay for it?

Because you have so many people who had health insurance who don't have it now. And health care has gotten so expensive that the idea of going to get care and being able to pay for it is beyond the reach of, if not every American, certainly a vast majority of Americans.

Some couldn't pay for it before, but now people who had jobs and now don't have jobs, how are they going to pay for it? And I don't think we've come to grips with that.

One of the suggestions was to open up the ACA, at least give people an option to purchase a plan with subsidies. But best I can tell, that is not going anywhere in the near future.

So, yes, health care will be there. But the question is, how will we be able to pay for the health care people need?

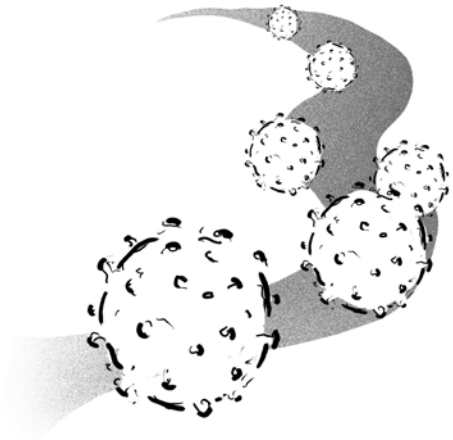
Since we are talking, ACS has just announced austerity measures. Are you the right person to talk to about that?

LL: We will share our official statement. However I will say that just like many non-profits, we are facing some very serious fundraising issues and we will have to make difficult choices as we move forward.

Is there anything I've missed?

LL: We've covered a lot here. I think you probably have enough for a book!

COVID-19 UPDATES



AstraZeneca trial to test Calquence in COVID-19 patients

AstraZeneca said it will initiate a randomized, global clinical trial to assess the potential of Calquence (acalabrutinib) in the treatment of the exaggerated immune response (cytokine storm) associated with COVID-19 infection in severely ill patients.

The trial design is based on scientific evidence supporting the role of the Bruton's tyrosine kinase (BTK) pathway in the production of inflammatory cytokines and on encouraging early clinical data. Calquence is a next-generation, highly selective BTK inhibitor currently used to treat certain types of blood cancers.

The trial, called CALAVI, is based on early clinical data with Calquence demonstrating that a decrease in inflammation caused by BTK inhibition appears to reduce the severity of COVID-19-induced respiratory distress. The goal of the trial is to evaluate the efficacy and safety of adding Calquence to best supportive care (BSC) to reduce mortality and the need for assisted ventilation in patients with life-threatening COVID-19 symptoms.

"We can confirm that NCI is involved with administration of off-label use of acalabrutinib in a small number of selected patients with severe COVID-19," NCI said in a statement. "While some clinical benefit has been observed in select patients with advanced lung disease caused by COVID-19, it is premature to conclude that it will provide benefit across patients with advanced lung disease due to the very early and limited use of this agent in COVID-19 at this time.

"Thus, it will be necessary to gather data from randomized, controlled clinical trials in order to understand the best and safest treatment options for patients. NCI's chief concern is the safety and well-being of patients, caregivers, and researchers, and staff."

This large, multicenter, global, randomized trial uses a two-part patient-centric design developed in record time to accelerate data capture and analysis. Part One evaluates the addition of Calquence to BSC versus BSC alone in patients hospitalised with COVID-19 who are not in the intensive care unit. Part Two evaluates the addition of Calquence to BSC in a cohort of patients in the ICU.

"With this trial, we are responding to the novel insights of the scientific community and hope to demonstrate that adding Calquence to best supportive care reduces the need to place patients on ventilators and improves their chances of survival," José Baselga, executive vice president and head of Oncology R&D at Astrazeneca, said in a statement. "This is the fastest launch of any clinical trial in the history of AstraZeneca."

The CALAVI trial is expected to open for enrollment in the coming days in the U.S. and several countries in Europe. Wyndham H. Wilson, of NCI, will serve as the principal investigator of the trial.

"Given the well documented role of the protein BTK in regulating inflammation, it is possible that inhibiting BTK with acalabrutinib could provide clinical benefit in patients with advanced COVID-19 lung disease," Louis M. Staudt, chief of NCI's Lymphoid Malignancies Branch and senior investigator of the CALAVI trial, said in a statement. "As with all new treatments, it will be necessary to gather data from clinical trials in order to understand the best and safest treatment options for patients."

Clinical trial accruals at OneOncology increase in the face of COVID-19

Enrolling patients in clinical trials at OneOncology partner practices has slightly increased in March and April, as the COVID-19 pandemic hit its communities hardest.

OneOncology, a national partnership of independent, community oncology practices, includes five large community oncology practices representing over 400 physicians practicing at more than 160 sites of care in the United States.

"Elective medical procedures have stopped, but caring for cancer patients isn't elective," Jeff Patton, OneOncology's acting CEO and president of Physician Services, said in a statement. "Not only do community oncology centers remain open, providing patients life-saving treatments, we also continue to provide clinical trials at a steady to increased rate. Our centers are continuing to fulfill our collective mission."

When the Centers for Medicare and Medicaid temporarily loosened its regulations to allow providers to be reimbursed for telehealth visits, the agency allowed researchers to keep some clinical trials open by evaluating and enrolling out-of-state patients.

"By loosening the regulations at both the federal and state levels, we were able to evaluate patients for eligibility in

clinical trials that we otherwise couldn't because of state licensing requirements," Natalie Dickson, chief medical officer at Tennessee Oncology and chair of OneCouncil, the partnership's all-physician committee, said in a statement.

American Cancer Society opens COVID-19 tracking study

The American Cancer Society is inviting participants to join its ongoing Cancer Prevention Study 3 (CPS-3) to use a new app to help investigators track the COVID-19 epidemic and inform future research efforts.

The app, the COVID Symptom Tracker, was created by doctors and scientists at the Harvard T.H. Chan School of Public Health, Massachusetts General Hospital, King's College London, and Stanford University School of Medicine, working in partnership with the health science company ZOE. It is available to anyone in the United States or United Kingdom.

Participants of the study are asked to download the app and track whether they feel any symptoms each day.

The goal of the app is to:

- Better understand symptoms of COVID-19,
- Evaluate how fast the virus is spreading in different areas,
- Identify high-risk areas in the country,
- Identify who is most at risk by better understanding symptoms linked to health conditions; and
- Identify the exposure of healthcare workers to COVID-19.

"By inviting CPS-3 participants to use this app, we hope to be able to help address the immediate and long-term needs of cancer patients and survivors," Alpa Patel, senior scientific director, epidemiology research and lead investigator for CPS-3, said in a statement. "In the short term, data gathered from the app will help characterize the progression of symptoms and trajectories related to coronavirus. Over time, the data can be combined with CPS-3 data to study the longer-term health effects related to infection, including in vulnerable populations like cancer survivors."

The Cancer Prevention Study includes more than 300,000 participants from 35 states and Puerto Rico who completed a comprehensive baseline survey that included extensive medical, lifestyle, and other information. Participants are contributing to a better understanding of the roles of lifestyle, genetic, and other factors in cancer.

COVID-19 Tracker can be used with other major studies, including the Nurses' Health Study, one of the largest and longest-running scientific studies in the world with 280,000 participants, many of whom are active health care workers treating people with COVID.

Research!America urges Congress to modify budget caps, increase FY21 funding for health agencies

Research!America is urging Congress to modify the budget caps and increase funding for health agencies for FY21 in light of the COVID-19 pandemic.

The letter from President and CEO Mary Woolley follows:

"Dear Chairman Shelby, Chair Lowey, Vice Chairman Leahy, and Ranking Member Granger:

"On behalf of the Research!America alliance, please know how sincerely grateful we are for your bipartisan efforts to mitigate the devastating effects of the COVID-19 pandemic. Your determination to advance the Fiscal Year 2021 appropriations process is an important facet of those efforts, and we deeply appreciate your leadership and commitment.

"In that context, we fully support the strategy of modifying the FY21 budget caps in a manner that enables our nation to end the COVID-19 threat and dramatically build out our public health threat preparedness and response capabilities. COVID-19 is a warning our nation must heed, knowing that the next threat could follow directly on the heels of COVID-19.

"Further, we firmly believe that FY21 funding should respond to what we as a nation are witnessing in real time: research-driven medical and public health progress conveys value to society that profoundly exceeds our investment in it.

"It is not only imperative to ramp up COVID-19 related funding for NIH, CDC, FDA, AHRQ, NSF, BARDA and our nation's other research and public health agencies; it is imperative to assign a higher funding priority to the day-in-and-day-out efforts of these agencies to combat deadly and debilitating health threats and to ensuring our nation's research ecosystem can emerge from COVID-19 stronger than ever.

"By modifying the budget caps and prioritizing funding for the Labor, Health and Human Services, Education, and Related Agencies Subcommittee, Congress can begin to empower a future in which emerging health threats like COVID-19 cannot blindside our nation, and longstanding health threats like Alzheimer's

and cancer cannot rob Americans and populations across the globe of hope, independence and time.

"Thank you again for your considered leadership, and please thank your respective staff members for their hard work in support of your efforts."

NAS, NAE, and NAM presidents: U.S. funding for WHO should not be interrupted during COVID-19 pandemic

The presidents of the National Academy of Sciences, National Academy of Engineering, and National Academy of Medicine are urging the U.S. government to continue funding for the World Health Organization during the COVID-19 pandemic. NAS President Marcia McNutt, NAE President John L. Anderson, and NAM President Victor J. Dzau wrote the following:

"It is critical for the U.S. to continue its funding for the World Health Organization in the midst of the COVID-19 pandemic, given the WHO's lead role in coordinating an international response, especially in developing countries. The WHO's leadership in helping to curb the pandemic in other countries undoubtedly benefits the United States as well, as we cannot begin to fully recover here until the threat of the pandemic subsides in other nations. Even a temporary halt in U.S. funding would have a potentially damaging impact on the WHO's essential activities and global health security.

"Continued funding to the WHO is critical to ensure global access to primary care and essential medicines; train the health workforce; improve monitoring and prepare for future public health emergencies; prevent noncommunicable diseases; and promote mental health, among countless other important services. Any threat to WHO's funding could cut off a lifeline for low- and middle-income countries and place hundreds of millions of people at risk.

"The U.S. has long been a leader in global health, and we must not reverse course now. For more than 20 years, the National Academies have conducted periodic assessments of U.S. strategic priorities in global health to inform federal policymakers. Our 2017 report *Global Health and the Future Role of the United States* concluded that 'the U.S. government should maintain its leadership position in global health as a matter of urgent national interest and as a global public benefit that enhances America's international standing.' The National Academies stand ready to evaluate U.S. investment in global health, but the nation's commitment to funding the WHO should not waver during this pandemic."

White House expands coverage for essential diagnostic services

Centers for Medicare & Medicaid Services and the Departments of Labor and the Treasury issued guidance to enable Americans with private health insurance to get coverage of COVID-19 diagnostic testing and other related services, including antibody testing, at no cost.

Issued on April 11, the guidance implements the recently enacted Families First Coronavirus Response Act and Coronavirus Aid, Relief, and Economic Security Act, which require that private health issuers and employer group health plans cover COVID-19 testing and certain related items and services furnished during the COVID-19 pandemic, with no out-of-pocket expenses.

The guidance requires group health plans and group and individual health insurance to cover diagnostic testing and certain related items and services provided during a medical visit with no cost sharing. This includes urgent care visits, emergency room visits, and in-person or telehealth visits to the doctor's office that result in an order for or administration of a COVID-19 test.

Covered COVID-19 tests include all FDA-authorized COVID-19 diagnostic tests, COVID-19 diagnostic tests that developers request authorization for on an emergency basis, and COVID-19 diagnostic tests developed in and authorized by states.

Bipartisan bill proposes telehealth expansion

House Health Subcommittee Chair Anna G. Eshoo (D-CA) and Rep. Don Young (R-AK) introduced H.R. 6474, the Healthcare Broadband Expansion During COVID-19 Act, which would provide $2 billion to expand telehealth and high-quality internet connectivity at public and nonprofit healthcare facilities, including mobile clinics and temporary health facilities deployed to respond to the coronavirus pandemic.

Nebraska Medical Center develops infectious aerosol capture mask to protect health care workers

Health care workers at Nebraska Medical Center began using Infectious Aerosol Capture Masks to capture exhaled aerosolized particles at their source from patients.

Approved by the Nebraska Medicine Innovation Committee, the hospital plans to initially deploy the IACM in the operating room for use with patients who aren't showing symptoms of COVID-19, but may or may not have the disease.

Steven Lisco, chair of the UNMC Department of Anesthesiology, developed the mask, which was put to use April 15

The device is intended for use on patients undergoing monitored anesthesia care, and will be used during and after emergence from general endotracheal anesthesia, as well as in the post-anesthesia care unit. If successful in this environment, the IACM could also be used for patients confirmed to have COVID-19 and are receiving care in the ICU or emergency department.

Patients with COVID-19 produce microscopic aerosol particles, which fill the patient's environment and increase the risk of disease transmission. A small percentage of patients also may produce aerosols when not showing symptoms or before showing symptoms.

These patients are a challenge for providers, as they may unknowingly produce infectious aerosols when coughing, wearing supplemental oxygen or undergoing aerosol-generating procedures like intubation and extubation—all common occurrences in operating rooms and in post-anesthesia care units.

The IACM device uses a face tent positioned upside down with a viral filter attached, connected to wall suction. The apparatus attaches to the vacuum source via standard suction tubing adapted to the device via a plastic piece created with a 3D printer by Nicholas Markin, director of perioperative imaging.

"The IACM performed very well in laboratory testing in conjunction with a nasal device used to deliver supplemental oxygen, catching more than 90% of airborne particles expelled in the mask, ultimately preventing the aerosol from entering the patient environment," Lisco said in a statement. "Even when the vacuum wasn't turned on, the mask was still 85% effective as a barrier."

In these areas, patients are often given nasal cannula oxygen, which has been shown to increase the rate and density of aerosolized particles, Lisco said.

"We think it is far superior to put this device on patients in the PACU or ICU versus a surgical mask over a nasal oxygen delivery device," Lisco said.

FDA authorizes blood purification device to treat COVID-19

FDA issued an emergency use authorization for a blood purification system to treat patients, ages 18 and over, with confirmed COVID-19 admitted to the intensive care units with confirmed or imminent respiratory failure.

The authorized product reduces the amount of cytokines and other inflammatory mediators, i.e., small active proteins in the bloodstream that control a cell's immune response by filtering the blood and returning the filtered blood to the patient. The proteins that are removed are typically elevated during infections and can be associated with a cytokine storm that occurs in some COVID-19 patients, leading to severe inflammation, rapidly progressive shock, respiratory failure, organ failure and death.

FDA issued this emergency use authorization to Terumo BCT Inc. and Marker Therapeutics AG for their Spectra Optia Apheresis System and Depuro D2000 Adsorption Cartridge devices.

Adolescent, young adult cancer non-profits provide guidance on COVID-19

Six non-profit adolescent and young adult cancer advocacy organizations have launched CovidAYACancer.org, a resource for young people with cancer and the health professionals who treat them.

Teen Cancer America, Stupid Cancer, The Leukemia and Lymphoma Society, Cancer and Careers, Lacuna Loft and CureSearch have formed an alliance with oncology specialists, including Craig Nichols, Archie Bleyer and Stu Seigel, to develop the website.

CovidAYACancer.org aims to be a repository for critical information specifically benefittng AYA cancer patients, patient advocates and medical professionals working with this unique population.

Oncologists in the AYA cancer field treat immunocompromised patients who are at elevated levels of risk as a result of COVID-19.

CovidAYACancer.org provides AYA cancer patients and survivors with financial resources, virtual events, employment and psychosocial support. It plans to provide access to online supportive programs and guidance to patients and their families.

The site also provides guidelines for doctors and frontline health teams. Nichols, Bleyer and Siegel have been consulting with colleagues about best practices during COVID-19, as normal protocols for oncological treatment have changed significantly.

The CovidAYACancer alliance is supported by international pharmaceutical company Servier, which is providing coordination and technical support.

FAQs and Guidances

Federal government:

- NCI source book and resources: clinical and laboratory operations
- NCI Emergency Resources: What people with cancer should know about the coronavirus
- NCI guidance: Interim guidance for patients on clinical trials supported by the NCI Cancer Therapy Evaluation Program (CTEP) and the NCI Community Oncology Research Program (NCORP).
- CTEP coronavirus guidance
- COVID-19 scientific interest group
- FDA guidance: Conduct of clinical trials of medical products during COVID-19 pandemic
  - FDA Medical Countermeasures Initiative on COVID-19
  - FDA guidance update: Blood donations
  - FDA continues to facilitate access to crucial medical products, Including ventilators
  - FDA provides update on patient access to certain REMS drugs during COVID-19 public health emergency
  - A message to patients with cancer and Health Care Providers About COVID-19
  - Update: Diagnostic testing for COVID-19
  - Resources for patients and caregivers
  - FDA enforcement policy for extracorporeal membrane oxygenation and cardiopulmonary bypass devices
- Centers for Medicare & Medicaid Services FAQ: Interim final rule

Professional societies:

- American Society of Clinical Oncology FAQ: Emerging issues and challenges in caring for patients with cancer during the coronavirus pandemic
  - ASCO recommendations for the oncology community
  - ASCO COVID-19 in oncology registry
  - ASCO/National Coalition for Cancer Survivorship FAQ
- American Association for Cancer Research FAQ: Information on virtual annual meetings
- American Cancer Society FAQ: Common questions about the new coronavirus outbreak
  - ACS clinical guidance: COVID-19 elective case triage guidelines for surgical care
  - Create a surgical review committee for COVID-19-related surgical triage decision making
  - COVID-19 and 2020 ACS Grants
- National Coalition for Cancer Survivorship webinar with Otis Brawley
  - NCCS resources for survivors
- Society for Immunotherapy of Cancer Resources: Patient management and basic and translational research
- Community Oncology Alliance resources: Coronavirus (COVID-19) practice resources and protocols
- Leukemia & Lymphoma Society FAQ: Resources and what you should know about the coronavirus
- American Society for Radiation Oncology FAQ: COVID-19 recommendations and information
- Joint recommendations for treatment of patients with breast cancer
- American College of Surgeons resources: For the surgical community
- Society for Immunotherapy of Cancer resources: Implications for patients, translational research
- GO2 Foundation for Lung Cancer resources
- Adolescent and young adult resources
- American Society for Transplantation and Cellular Therapy resources
- European Blood and Marrow Transplantation Society recommendations
- World Marrow Donor Association resources
- National Institute for Health Care Management Foundation resources

Research centers:

- St. Jude Children's Research Hospital FAQ: COVID-19 and children with cancer

Journals:

- Journal of the National Comprehensive Cancer Network: How to manage cancer care during COVID-19 pandemic
  - NCCN best practices
  - Special Feature: How to keep cancer patients and healthcare workers safe

Companies:

- Advarra: Coronavirus guidance
- Asbestos.com: Coronavirus guidance

IN BRIEF

J. Alan Diehl named deputy director and chief operating officer of Case CCC

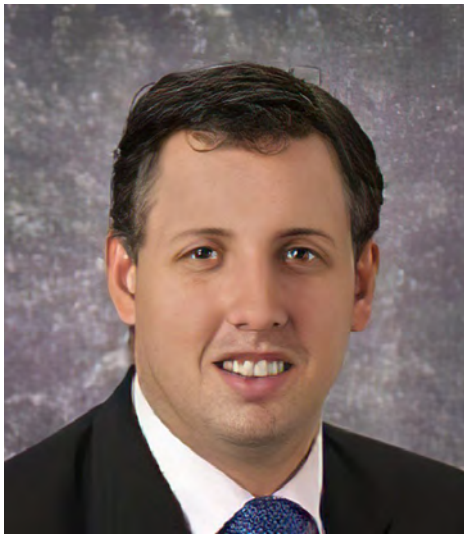
J. Alan Diehl was named deputy director and chief operating officer of the Case Comprehensive Cancer Center.

Diehl will work closely with Stan Gerson, director of Case Comprehensive Cancer Center, to coordinate activities based on the recently updated strategic plan, priorities identified by the executive committee Diehl has been a member of, and to lead multi-investigator initiatives and grant applications.

Diehl joined Case Western Reserve University in 2019 as chair of the Department of Biochemistry in the School of Medicine. Diehl was director of the Cancer Cell Biology Program at the Abramson Family Cancer Research Institute at the University of Pennsylvania, and most recently served as associate director of basic science at Hollings Cancer Center at the Medical University of South Carolina.

Diehl's research focuses on the discovery of molecular mechanisms that contribute to uncontrolled cell proliferation and decreased cell death. He is an expert in Program Project Grants and has already advised Case CCC member groups gearing toward submissions. Diehl also serves on multiple External Advisory Boards for NCI-designated cancer centers.

Andres F. Correa joins Fox Chase Cancer Center



Andres F. Correa will join Fox Chase Cancer Center as an assistant professor in the Department of Surgery in the Urologic Oncology Division starting May 4.

Correa, who was a Society of Urologic Oncology Fellow at Fox Chase, is returning to the center after serving as attending surgeon and assistant professor in the division of urology in the department of surgery at MD Anderson Cancer Center at Cooper University Hospital.

Correa is skilled at surgical modalities including robotics, laparoscopy, and traditional open surgery, and has expertise in prostate, kidney, bladder, testicular, and other genitourinary cancers.

Esther Welkowsky named VP, clinical operations, at Elicio Therapeutics

Esther Welkowsky was named vice president of Clinical Operations at Elicio Therapeutics, a next generation immuno-oncology company. Welkowsky has managed clinical operations teams for oncology clinical trials and was most recently executive director of Clinical Operations at Allogene.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Elicio Therapeutics and NCI study ELI-002 mutant KRAS targeting mechanism

Elicio Therapeutics and NCI are working together to characterize T cell responses to ELI-002 in animals.

The collaboration will be led by James Yang, senior investigator in the Surgery Branch of the Center for Cancer Research at NCI.

Elicio has demonstrated in multiple tumor models that improving the targeting of immunogens and cell-therapy activators to lymph nodes, where resident immune cells potently orchestrate immunity, can substantially amplify their ability to induce effective tumor-killing immune responses. ELI-002 is an "AMP KRAS-vaccine" containing seven amphiphile mKRAS peptides and a proprietary amphiphile adjuvant, administered subcutaneously.

KRAS mutations are present in 90% of pancreatic cancers, 40% of colorectal cancers, 30% of non-small cell lung, 30% of bile duct, 14% of endometrial, and 14% of ovarian cancers. ELI-002 has completed preclinical validation, IND-enabling GLP toxicology studies, and a pre-IND meeting with the FDA. P1/2 trials will be multi-site, starting with an open label dose escalation, progression to expansion cohorts in KRAS mutated solid tumors, and seamlessly progressing into a randomized, controlled cohort.

"This research investigates the mechanism of action of ELI-002 in mice that have key human HLA genes important for immune response," Christopher Haqq, Elicio's executive vice president, head of Research and Development, and chief medical officer, said in a statement. "Dr. Yang is a pioneer of T cell therapy for solid tumors, and we are excited to collaborate in the study, which may help monitor patient responses in the planned clinical study of ELI-002, and would set the stage for clinical trials combining ELI-002 with KRAS targeting T cells."

The Elicio Amphiphile platform enables precise targeting and delivery of immunogens and cell-therapy activators directly to the lymphatic system, the "brain center" of the immune response, to significantly amplify and enhance the body's own system of defenses, defeat solid and hematologic cancers, and prevent their recurrence. Elicio's ELI-002 targets seven position 12 and 13 KRAS mutations, present in approximately 25% of all human solid tumors. ELI-002 has the potential to become a multi-targeted mKRAS therapy with the ability to treat and prevent disease recurrence for hundreds of thousands of patients with mKRAS-driven cancers, including pancreatic, colorectal, lung, bile duct, endometrial, and ovarian.

ACS study: JUUL sales bounced back within weeks of self-imposed flavor ban

Juul sales recovered within weeks following a dip after the company withdrew some flavored products from stores, eventually surpassing sales from before the change, according to a study by American Cancer Society researchers in the *American Journal of Public Health*.

In November 2018, under pressure from FDA to curb rising youth vaping rates, Juul removed most of their flavored products, excluding tobacco, menthol, and mint flavors, from retail stores. Using Scantrack data on e-cigarette sales in the United States from January 2015 to October 2019 provided by The Nielsen Company, investigators led by Alex Liber, senior scientist, with the Economic & Health Policy Research program at the American Cancer Society, looked at sales trends to characterize the effects of Juul removing mango, crème brûlée, fruit medley, and cucumber flavors from store shelves.

From 2017 through 2018, Juul sales grew, with a concurrent increase in the share of fruit-flavored e-cigarettes sold in Nielsen-tracked retail channels. Fruit-flavors rose from 12.9% of sales ($10,161,000 per month) in January 2017 to 33.3% of sales ($96,486,000) in October 2018. Fruit briefly exceeded menthol/mint as the flavor category with the largest proportion of sales in October 2018. At the same time, tobacco-flavored e-cigarettes' share dropped from 39.7% of sales to 16.6% of sales.

Juul's voluntary decision to remove fruit flavors in November 2018 led to a decline in sales of fruit-flavored products across Nielsen-tracked retailers to 9.1% ($30,494,000) by April 2019. During this period, the share of menthol/mint flavor spiked from 33.0% to 62.5% ($95,592,000 to $209,567,000), and the share of tobacco flavor rose from 16.6% to 22.3% ($48,038,000 to $74,789,000).

Fully 91% of the growth in tobacco and all of the growth in menthol/mint was captured by Juul. Juul sales surpassed their previous maximum within 12 weeks, as Juul consumption shifted marginally toward the tobacco and heavily toward the menthol/mint flavors that remained on shelves. Fruit-flavor sales began to increase again to 15.8% ($60,594,000) by September 2019, driven by sales of the NJOY brand.

Notably, e-cigarette sales in the Nielsen data peaked in August 2019 at $441 million per month (including hardware). The authors say while it is too soon to determine why sales slowed after that peak, plausible explanations include consumers' reactions to media reports detailing the outbreak of vaping-related illnesses and announced government actions including forthcoming bans on the sales of all or some e-cigarettes by the governors of several states and the president of the United States.

"Companies' attempts to self-impose their own restrictions are unlikely to improve public health. Juul's withdrawal of fruit-flavored products was quickly offset by a combination of increased fruit-flavored sales by Juul's competitors and increased sales of other flavors—notably, mint/menthol—by Juul," Liber said in a statement. "It is highly unlikely that overall youth use declined given the short-lived impact on sales trends for Juul cartridges and the rapid recovery of flavored cartridge sales within the very retail channels that should have seen the largest declines from Juul's actions."

"Our study shows when exceptions to regulatory policies are made, the market will fill the void. The growth of fruit-flavored sales experienced by NJOY once Juul stopped selling mango-flavored e-cigarettes is a striking indication of that happening. If governments exempt some e-cigarettes from a flavor regulation and not others –for example if governments exempt disposable or "open system" e-cigarettes from prohibitions on selling flavored products—we might expect consumer demand for flavored products to migrate to those types of products."

Chronic stress can impact response to radiation therapy

New preclinical research from a team at Roswell Park Comprehensive Cancer Center suggests a strategy for significantly increasing both the local and distant, or "abscopal," effects of radiation, according to a study.

Results of the study, led by Elizabeth Repasky of Roswell Park Comprehensive Cancer Center, were published in *Nature Communications*.

"Our work suggests that the benefits of radiation therapy, both on the target site and in tumors located elsewhere in the body, are directly related to the degree of stress an individual may be experiencing," Repasky, Cell Stress Program co-leader and William Huebsch Professor of Immunology at Roswell Park, said in a statement.

"In our laboratory studies, irradiated tumors went away faster when stress was reduced, and even distant tumors that did not receive radiation also shrunk or disappeared. Repasky said. "We have demonstrated that even mild stress that occurs over a longer period of time — not just singular moments, but chronic stress—can significantly influence the efficacy of radiation therapy."

"People often say, 'Stress is a part of life.' And while that's true, because there is frequently more stress that occurs in cancer patients because of their cancer diagnosis, we need to work to mitigate those enduring, longer-term stressors, because our work shows that it can inhibit the ongoing immune responses to cancer and an individual's response to therapy," first author Minhui Chen,, a senior postdoctoral researcher in Repasky's lab, said in a statement.

The effects the team observed in their preclinical study hinge upon the body's fight or flight response to stresses through the network of nerves and organs known as the adrenergic nervous system.

The team reports that when adrenergic stress was lessened, triggering lower levels of the neurotransmitters adrenaline and norepinephrine, tumor control in both irradiated and non-irradiated sites improved. This enhancement of the effects of radiation therapy also occurred when signaling through the β2-adrenergic receptor was reduced, suggesting that blockade of β2 adrenergic signaling could be a safe and feasible option for patients receiving radiation. Based on earlier preclinical research, Repasky and colleagues are investigating in clinical studies whether the efficacy of chemotherapy and immunotherapy can be improved by giving patients beta blockers, such propranolol — a common blood pressure medication.

"Researchers have suspected a relationship between stress and cancer treatment outcomes for some time, but many questions remain," co-author Anurag Singh, director of radiation research and professor of oncology in the Department of Radiation Medicine at Roswell Park, said in a statement. "This research has uncovered a major molecular and immunological pathway that appears to underlie the association between how

much stress an individual is experiencing and how they respond to cancer therapy. Our results suggest that by blocking the β2 adrenergic receptor, you may not only make radiation and chemotherapy work better, you give a boost to the immune system — and may even be able to reduce metastasis, or spread of a tumor to a different part of the body."

DRUGS & TARGETS

FDA approves Koselugo for neurofibromatosis type 1

FDA has approved Koselugo (selumetinib) for the treatment of pediatric patients, two years and older, with neurofibromatosis type 1, a genetic disorder of the nervous system causing tumors to grow on nerves.

AstraZeneca and Merck sponsor the drug.

Koselugo is the first drug approved by FDA to treat this debilitating, progressive and often disfiguring rare disease that typically begins early in life.

"Everyone's daily lives have been disrupted during the COVID-19 pandemic, and in this critical time we want patients to know that the FDA remains committed to making patients with rare tumors and life threatening diseases, and their unique needs, a top priority. We continue to expedite product development for these patients," Richard Pazdur, director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research, said in a statement.

Koselugo is approved specifically for patients who have symptomatic, inoperable plexiform neurofibromas, which are tumors involving the nerve sheaths (coating around nerve fibers) and can grow anywhere in the body, including the face, extremities, areas around the spine and deep in the body where they may affect organs. Koselugo is a kinase inhibitor, meaning it functions by blocking a key enzyme, which results in helping to stop the tumor cells from growing.

NF1 is a rare, progressive condition caused by a mutation or flaw in a particular gene. NF1 is usually diagnosed in early childhood and appears in an estimated one out of every 3,000 infants. It is characterized by changes in skin coloring, neurologic and skeletal impairments and risk for development of benign and malignant tumors throughout life. Between 30% and 50% of patients born with NF1 develop one or more PNs.

"We are committed to regulatory flexibility and providing extensive guidance to industry in an effort to bring drugs forward that fulfill unmet medical needs. Koselugo represents this commitment," Pazdur said. "For the first time, pediatric patients now have an FDA-approved drug to treat plexiform neurofibroma, a rare tumor associated with NF1."

FDA approved Koselugo based on a clinical trial conducted by NCI of pediatric patients who had NF1 and inoperable PN (defined as a PN that could not be completely removed without risk for substantial morbidity to the patient).

The efficacy results were from 50 of the patients who received the recommended dose and had routine evaluations of changes in tumor size and tumor-related morbidities during the trial. Patients received Koselugo 25 mg/m2 orally twice a day until disease progression or until they experienced unacceptable adverse reactions.

The clinical trial measured the overall response rate , defined as the percentage of patients with a complete response and those who experienced more than a 20% reduction in PN volume on MRI that was confirmed on a subsequent MRI within 3-6 months. The ORR was 66% and all patients had a partial response, meaning that no patients had complete disappearance of the tumor. Of these patients, 82% had a response lasting 12 months or longer.

Other clinical outcomes for patients during Koselugo treatment including changes in PN-related disfigurement, symptoms and functional impairments. Although the sample sizes of patients assessed for each PN-related morbidity (such as disfigurement, pain, strength and mobility problems, airway compression, visual impairment and bladder or bowel dysfunction) were small, there appeared to be a trend of improvement in PN-related symptoms or functional deficits during treatment.

FDA granted this application Priority Review and Breakthrough Therapy designation. Koselugo also received Orphan Drug designation and Rare Pediatric Disease Designation for the treatment of pediatric NF1. The application is awarded a Rare Pediatric Disease Priority Review Voucher.

FDA approves mitomycin for low-grade upper tract urothelial cancer

FDA has approved mitomycin (Jelmyto) for adult patients with low-grade upper tract urothelial cancer.

UroGen Pharma sponsors the drug.

"Although our nation's emphasis is on the need to combat COVID-19, patients with cancer and their unique needs continue to be a top priority for the FDA," Richard Pazdur, director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research, said in a statement. "We continue to expedite oncology product development in this critical time. Our staff is continuing to meet virtually with drug developers, academic investigators and patient advocates to push forward the coordinated review of drugs, biologics and devices for cancer."

Efficacy determination was based on OLYMPUS (NCT02793128), an ongoing, single-arm, multicenter trial enrolling 71 patients with treatment-naïve or recurrent low-grade non-invasive UTUC with at least one measurable papillary tumor located above the ureteropelvic junction. Patients who had larger tumors could have had prior tumor debulking. Patients received weekly Jelmyto 4 mg per mL instillations via ureteral catheter or nephrostomy tube for 6 weeks. For patients with a complete response at 3 months, instillations were to be administered monthly for a maximum of 11 additional instillations.

While the majority of urothelial cancers occur in the bladder, UTUC corresponds to a subset of urothelial cancers that arise in the lining of the kidney or the ureter. UTUC can block the ureter or kidney, causing swelling, infections and impairment of kidney function in some patients. UTUCs can develop as low-grade or high-grade tumors. In general, low-grade tumors are not invasive and very rarely spread from the kidney or ureter.

However, they often recur and management involves treating visible tumors and trying to preserve the urinary tract, as these tumors are more likely to recur in the urinary system than they are to spread. Low-grade UTUC is rare, but affects 6,000-8,000 new patients in the United States every year.

"This is the first approval specifically for patients with low-grade UTUC and provides an option for some patients who may otherwise require a nephroureterectomy," said Pazdur. "Due to substantial treatment challenges associated with the complex anatomy of the upper urinary tract, many patients need to be treated with radical surgery – usually complete removal of the affected kidney, ureter and bladder cuff. Jelmyto gives patients, for the first time, an alternative treatment option for low-grade UTUC."

The major efficacy outcome measures were CR and CR durability. CR was defined as complete absence of tumor lesions 3 months after Jelmyto initiation and was assessed by urine cytology and ureteroscopy. If warranted, a biopsy was performed. Forty-one patients (58%) achieved a CR three months following treatment initiation and were continued in follow-up; 29 patients received at least one dose of maintenance therapy.

Durability of response in those with CRs was evaluated at 3, 6, 9 and 12 months, following the CR determination.Seven patients had documented recurrences and nineteen patients remained in CR at 12-months following CR determination. The median response duration had not been reached (range: 0, 18.8+ months).

Ontruzant, biosimilar of Herceptin, introduced in the U.S.

Merck April 15 introduced Ontruzant(trastuzumab-dttb), a biosimilar of the reference biologic medicine Herceptin, to the U.S. Ontruzant is available in both 150 mg single-dose vials and 420 mg multiple-dose vials.

Ontruzant will be introduced in the U.S. at a list price (wholesaler acquisition cost) of approximately $1,325 for the 150 mg single-dose vial and $3,709 for the 420 mg multiple-dose vial (prices are rounded), representing a 15% discount to the current list price of Herceptin.

Wholesaler acquisition costs do not include discounts to payers, providers, distributors and other purchasing organizations.

Ontruzant is indicated for adjuvant treatment of HER2 overexpressing nod- positive or node-negative (ER/PR negative or with one high risk feature) breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; as part of a treatment regimen with docetaxel and carboplatin; as a single agent following multi-modality anthracycline based therapy.

Patients are selected for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Merck launched Ontruzant in the U.S. as part of a development and commercialization agreement with Samsung Bioepis. Under the agreement between the companies, Samsung Bioepis is responsible for preclinical and clinical development, process development and manufacturing, clinical trials and regulatory registration. Merck will be responsible for all commercialization activities for products approved in its partnered territories, including the U.S.

FDA approved Ontruzant in January 2019 based on the review of Samsung Bioepis' comprehensive data package, which included extensive structural and functional analytical data, nonclinical and clinical pharmacokinetic data, and a comparative clinical study demonstrating that Ontruzant is highly similar to its reference product, Herceptin, in terms of the safety, purity and potency of the product.