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WHEN YOUR HARMONICA PLAYER WINS THE NOBEL PRIZE

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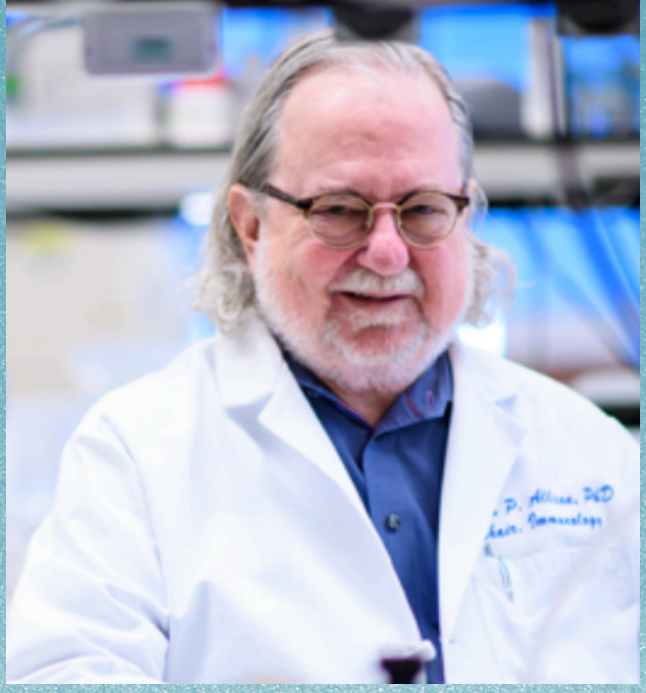

ACT *for* NIH congratulates our Advisory Committee member Jim Allison 2018 Nobel Prize winner

ACT *for* NIH

ADVANCING CURES TODAY

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GUEST EDITORIAL

WHEN YOUR HARMONICA PLAYER WINS THE NOBEL PRIZE

THE CHECKPOINTS were born in 2007 on an escalator in Chicago. Here's the story...

By Rachel Humphrey
Senior vice president and chief medical officer, CytomX Therapeutics
Lead singer of THE CHECKPOINTS

Back then, in an oncology era that we'll fondly call "The Dark Ages," no one, except a small gaggle of Don Quixotes, believed that the immune system could cure cancer. Immunotherapy stalwarts (like my friends and I) were such outcasts that our presentations at the American Society of Clinical Oncology annual meeting were scheduled for the last day of the conference (when just about everyone had already gone home) and assigned to a lecture hall that was too remote for anything but sensible shoes.

In fact, the trip was so laborious that we never bothered to walk it more than once per day. Instead, we just planted ourselves there early in the morning and didn't leave until lunchtime.

Access to the ASCO immuno-oncology diaspora required travel on an enormous lumbering escalator, with enough transit time between landings to eat a full tuna sandwich. It was on this very escalator, at the end of a satisfying, if ill-attended, series of lectures, that Tom Gajewski and Patrick Hwu wistfully wondered about starting a blues band.

They still needed a singer and a bass player, and couldn't find anyone to sign up. "I can sing," I laughed, "and how hard can it be to learn how to play the bass?"

By the time we got to the bottom of the escalator (really, I'm not kidding) we had a plan. Patrick Hwu would play

keys, Tom would play lead guitar, and I would be the singer.

Jim Allison was recruited a few hours later. He would play blues harmonica, and although none of us lived in the same US state, we didn't worry. We knew it would work. Oh, and by the way, since we didn't have a bass player, I went right out, bought a bass, and started lessons. Anything was possible in those days!

But, aside from my delusional ambition to be a bass player, we were all serious musicians.

Tom and Patrick had already played in multiple bands with professional-quality skill (read: "wow! Who knew he could do that?!"), Jim had played harmonica with Willie Nelson (read: "say what?!"), and I had produced, directed and had lead roles in musicals for over a decade with a popular community theater company in Connecticut. All of us played multiple instruments, some better than others, and the formation of a band wasn't too much of a stretch.

That first year, we gathered for rehearsals a half-dozen times at various IO conferences around the United States. With the best of intentions we attended some of the lectures, but mostly we were there to play music in poorly lit hotel basements until the wee hours of the morning. It was loads of fun.

The only snag, at least for me, was that it took a while before our setlist included songs for girls. You see, the guys preferred to play the tunes they'd practiced in their basements during puberty. I mean, really, how many times did I have to sing "Pretty Woman" before I couldn't take it anymore? Even now, adjusting pronouns in the lyrics doesn't always work ("Brown Eyed *Boy*"? Meh).

Eventually, we filled the setlist with great blues and covers that fit my voice neatly. I love the Cranberries and Susan Tedeschi! Aretha is now on the list, and

Allison, Nobel laureate, on the harmonica

Sweet Home Chicago, our oldest favorite, is gender neutral (hurray!) and perfect in every way.

By the fall of 2007, as we sat in an empty bar at 3 a.m., we declared ourselves "not terrible" and ready to pick a name for the band. "THE CHECKPOINTS" was Jim's idea. It made sense since we were all working on the first checkpoint inhibitor, ipilimumab: Jim was the Nobel-worthy scientist who had made the seminal observation at the bench that led to ipilimumab, Tom and Patrick were the brilliant clinician-scientists who treated patients with the drug and were, themselves, making great strides in IO, and I was the senior supervisor of all of the ipilimumab global development program at Bristol-Myers Squibb.

Actually, now that I think about it, we'd already been THE CHECKPOINTS long before we'd ever thought to play music together.

Over the subsequent years, both THE CHECKPOINTS and IO matured in parallel. Our setlist has now grown from the original six songs, which we played over and over (and over) at our first SITC gig, to six hours of tunes! As for IO, CTLA-4 and PD-1/PD-L1 inhibitors have transformed cancer therapy and IO lectures routinely fill the Plenary halls at ASCO. Not shabby.

Oh, and Jim, our high priest of the Church of the Holy T cell and the magician on the blues harps, has just won a Nobel Prize. (read: "how great is THAT?").

If you're wondering, we routinely practice on multiple late nights in Chicago during ASCO-week before we play on that Sunday, and put in more late nights later in the year at the Society of Immunotherapy for the Treatment of Cancer annual meeting before we play the president's dinner that Saturday.

Large mushroom pizzas and red wine is all it takes to keep us going. We compete to see who can bring the best bottles.

The band has now grown to 10 musicians from the first humble four. Dirk Spitzer, our fabulous drummer, has been a CHECKPOINT since just about the beginning, and we've now got a gifted (real) bass player named Brad Reinfeld. (I'm a terrible bass player,

THE CHECKPOINTS, performing live at SITC's fundraiser at the House of Blues in Chicago, 2017.

> By the fall of 2007, as we sat in an empty bar at 3 a.m., we declared ourselves 'not terrible' and ready to pick a name for the band. 'THE CHECKPOINTS' was Jim's idea. It made sense since we were all working on the first checkpoint inhibitor, ipilimumab.

let's just leave it at that.) John Timmerman is our talented second guitar player, and our new brass section includes some awesome folks: Ferran Prat on sax, Jason Luke on trumpet, and Russell Pachynski on trombone.

We also have two permanent guest artists: Lisa Butterfield sings back-up sometimes and graces us with her own terrific cameos. Per Thor Straten goofs it up and brings down the house at SITC with an original IO-focused rewrite of a different famous song every year. Pam Sharma, Jim's wife, and world-renowned IO scientist herself, is the original groupie, the vanguard of all CHICKPOINTS and CHUCKPOINTS that followed.

All of us work in IO. It's the ticket in. After all, we wouldn't be THE CHECKPOINTS without a solid download of our recent data in the Green Room before a gig. You'd be amazed what you can learn over pickled artichoke hearts and a Stella.

We've also begun to write original material. Our first fresh song, an homage to the power of immunotherapy, and written by John Timmerman and Patrick Hwu, is called "You Don't Belong Here."

When we introduced the song at SITC last year, everyone, all hundreds in the packed audience, bounced up and down and called out, with arms raised, "YOU DON'T BELONG HERE!!" to cancer! We bounced too. The energy was infectious. Excerpts from the lyrics are below. Recordings of this and other songs are in the works, so stay tuned.

These days, The CHECKPOINTS band is the SITC "House Band." We play cool places every year like the House of Blues

and Buddy Guys in Chicago. Once, we even had an "all-expenses-paid" trip to Frankfurt, Germany, where we slept on flea-infested mattresses, stayed in bed until 11 am, went to bars with groupies until 3 a.m., and lived like rock stars.

Then we came home (with real rashes) and became scientists again.

In any event, we all send Jim Allison warm congratulations for his well-deserved recognition by the Nobel committee. His life's work has brought new life and hope to patients with cancer. We couldn't be prouder or feel more honored that he is our friend. (And he most certainly ain't a bad harmonica player either!)

You Don't Belong Here

(A song written from the perspective of a circulating T-cell)

I was cruising around, just surveying the town,
circulating and free, with no place to be
I don't mind, bein' young and naïve,
I ain't got no engagements, and no memory

But while making my rounds, find myself face-to-face
With a big ugly mutant, taking over the place
He's proliferating, necrosis and blight
I know he's a cancer, and I'M IN FOR A FIGHT!.....

CHORUS 1:
You're mutated, but I'm educated
You're done proliferating, 'cause I'm infiltrating
I got no inhibitions, I got no fear
You're gonna be lysed 'cause...
YOU DON'T BELONG HERE!!

Published with permission from John Timmerman and Patrick Hwu.

Check out this YouTube video from SITC, 2017.

You can see and learn more about the band, including YouTube videos and photographs here.

All proceeds from the sale of T-shirts and other fun stuff go to SITC.

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GUEST EDITORIAL

Thank you, Jim Allison

By Ronald A. DePinho
Professor & past president,
Harry Graves Burkhart III Distinguished University Chair,
Department of Cancer Biology, MD Anderson Cancer Center

The year was 1998, location, Italian Alps. Jim and I were attending an intimate Pezcoller meeting organized by David Livingston. At that meeting, Jim presented something I had never seen in the entirety of my career—the eradication of cancer in mice following treatment with an antibody designed to inhibit a T cell checkpoint mechanism.

Afterwards, we talked about his provocative science and the potential of a new class of cancer drugs. As a physician scientist, I can vividly recall how deeply impressed I was with Jim's intense passion to convert his science into a new medicine that could help cancer patients.

Years later, I learned that his intense drive for clinical impact was fueled by the loss of his mother when he was only 10 years old.

It took another 10 years for Jim's dream to be realized. His drug for melanoma was approved, and early stage clinical trials showed signals of activity in other tumor types.

Fast forward another 7 years: Jim and his wife, Pam Sharma, a brilliant cancer immunology physician in her own right, were awakened at 5:30 a.m. by a call from his son proclaiming "Dad, you did it!"—Jim has won the 2018 Nobel Prize for Medicine or Physiology, along with Tasuku Honjo for their pioneering work in the use of immune checkpoint blockade inhibitors to treat cancer.

It was the first Nobel ever awarded for the treatment of cancer.

The morning of the announcement was a thrilling one. I had a front row seat to many of his congratulatory calls—including one from Vice President Joe Biden—as well as a major press conference where Jim talked about his science, his gratitude for the patients, and the need for more cancer research. Jim repeatedly expressed sincere gratitude for the good work of his students and support of his colleagues at UC Berkeley, Memorial Sloan Kettering Cancer Center, and the University of Texas MD Anderson Cancer Center. He was both humble and inspirational.

Like many of us in cancer research, Jim's science profoundly influenced the direction of my science and my career. When I became president of MD Anderson in 2011, Jim was my number one recruitment priority, not only because his science was propelling a transformation in cancer therapy, but also because his passion for clinical impact made him the ideal leader of a cancer immunotherapy platform in the MD Anderson Cancer Moonshot, a program designed to accelerate clinical research and amplifying impact of immunotherapy.

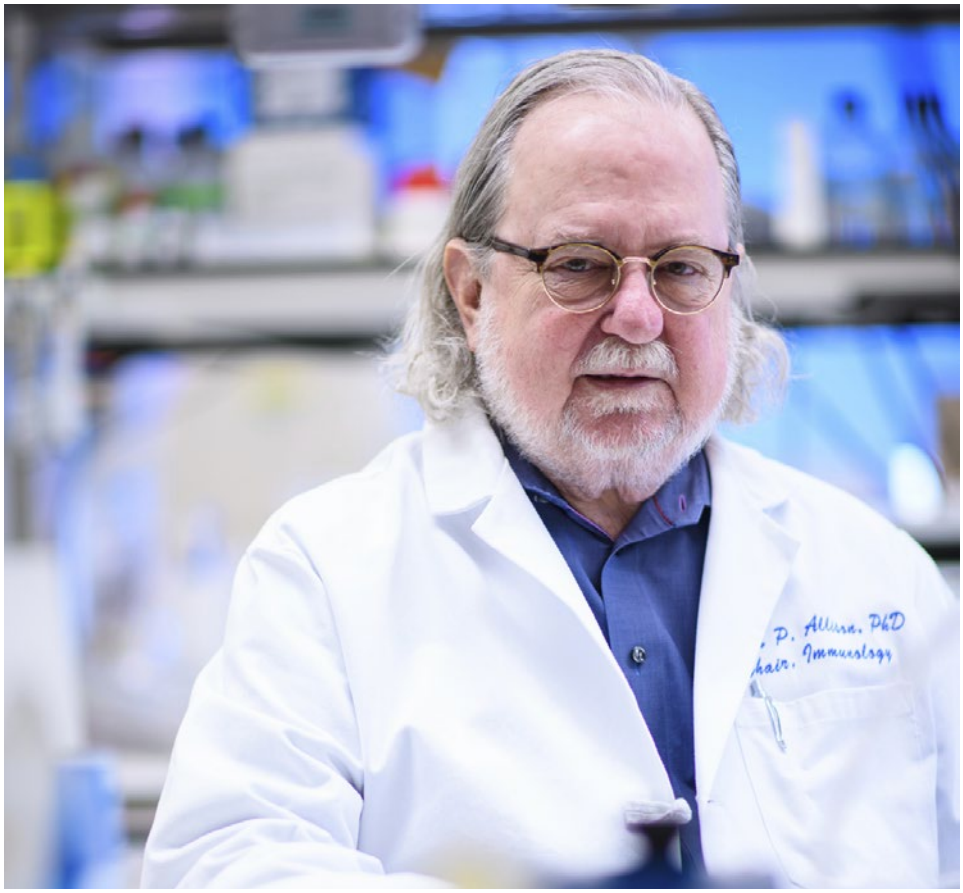
Indeed, under his (and Dr. Sharma's) leadership, the immunotherapy platform has been a shining example of the power of collaboration, fueling hundreds of innovative clinical trials across all disease centers that has already produced numerous practice changing advances for our patients.

Thanks to Jim, immune checkpoint therapy has transformed not only our institution but the entire cancer field, providing a revolutionary new treatment strategy and real hope for countless cancer patients. In addition, Jim's story stands as one of the best examples of the importance of sustained investment in basic biomedical research.

Jim didn't set out to cure cancer. Instead, his quest was to elucidate the mechanisms governing T cell function. Once he made his discovery after years of investigation, it was only then that he asked whether such insights might have clinical relevance. Jim's basic research, coupled with his desire to translate his discoveries, is now saving lives.

While Jim's most celebrated discovery is the immune checkpoint blockade, he has made key contributions to our understanding of T cell biology on several levels.

Jim was the first to identify the protein structure of the T cell receptor, which initiates T cell activation. He also realized that engagement of the T cell receptor by itself is insufficient to drive T cell activation, which then led to his discovery that CD28 is the critical co-stimulator for T cell activation.



Then, when a homolog of CD28, CTLA-4, was identified as a third T cell molecule, Jim fought the top scientists who proposed that CTLA-4 was another co-stimulatory molecule, demonstrating that CTLA-4 is an inhibitory molecule and acts to restrict T cell responses.

He refined the framework to reflect our new understanding that T cell responses are regulated by positive and negative signals; T cell receptor and CD28 costimulation are required to activate T cells, and a critical third signal, CTLA-4, provides homeostasis by restricting T cell responses. Again, it is truly remarkable that Jim contributed to three major discoveries in the T cell field.

The Nobel was awarded for the novel concept that anti-tumor responses could be elicited by blocking inhibitory signals generated by CTLA-4. This was a true paradigm shift in cancer therapy in two ways: first, it focused on targeting the immune system rather than the cancer cell, and thus should be effective against a variety of tumor types, and second it was directed at unleashing the immune system by blocking regulatory circuits that would turn off responses rather than trying to initiate responses to tumor antigens.

And, if such a discovery was not enough, he went on to test his hypothesis by developing an anti-CTLA-4 antibody and treating tumor-bearing mice. This work clearly demonstrated that anti-CTLA-4, both as monotherapy and combined with other strategies (such as antigenic vaccines, chemotherapy, and radiation therapy) could lead to dramatic anti-tumor immune responses and tumor rejection in a variety of tumor types.

Jim led a charge to test his idea of CTLA-4 blockade in the clinic. Since the field of oncology had tried many different immunotherapeutic strategies with limited success in the clinic, he found it difficult to convince companies to pursue an immunotherapy program based on blocking a single molecule.

However, driven by cancer's impact on his family, he persisted and worked with a biotech company, Medarex, to develop a clinical grade fully human anti-CTLA-4 antibody, ipilimumab. Several phase I and II clinical trials conducted with ipilimumab in patients with metastatic melanoma, prostate cancer, ovarian cancer, renal cell carcinoma, and other tumor types showed clinical responses and even complete regression of all tumors in a subset of treated patients.

Based on these data, two phase III registration trials in patients with metastatic melanoma were completed. These trials showed an increase of about four months in median survival benefit, with about 22 percent of patients surviving for over four years.

This led to FDA-approval of anti-CTLA-4 (Ipilimumab, Bristol-Myers Squibb) in 2011. A follow-up study in 2014 of about 5,000 patients showed that 20 percent of metastatic melanoma patients were still living 10 years after treatment, indicating that these patients were essentially cured. Today, many thousands more have received immunotherapy.

In this era of precision medicine, anti-CTLA-4 and related therapies represent a rationally-designed mechanistic immunotherapy agent that is now a standard-of-care in the clinic. Since anti-CTLA-4 targets a molecule on T cells, as opposed to a tumor-specific molecule, it is being tested worldwide across multiple other tumor types, alone or in combination.

The new field of "immune checkpoint therapy," has catalyzed nearly all pharmaceutical companies to launch thousands of trials targeting T cell inhibitory pathways, including PD-1 and PD-L1. Anti-PD-1 antibodies from two companies, nivolumab from Bristol-Myers Squibb and pembrolizumab from Merck, and anti-PD-L1 antibody from Roche have all gained FDA approval for the treatment of cancer patients, including patients with melanoma, lung cancer, kidney cancer, head & neck cancer, Hodgkin's lymphoma, and bladder cancer.

Since anti-CTLA-4 and anti-PD-1 target two distinct T cell inhibitory pathways, these agents have been tested in combination as a treatment strategy for cancer. Initial studies reported improved anti-tumor immune responses and tumor rejection in mice with anti-CTLA-4 plus anti-PD-1 combination therapy.

Then, a phase I and a subsequent phase III clinical trial showed that concurrent treatment with a combination of ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) showed objective responses in approximately 50 percent of patients with metastatic melanoma—it is notable that 10 years ago, metastatic melanoma was uniformly lethal within one year.

In 2015, the FDA approved this combination therapy as treatment for patients with metastatic melanoma. This combination treatment has also been approved for RCC, and is now being tested for multiple other tumor types, including bladder cancer and lung cancer.

As a result of Jim's and Dr. Honjo's pioneering work and concepts, for the first time the field of oncology has mechanistically-designed rational immunotherapy agents that elicit clinical benefit in a significant subset of patients, with tens of thousands of patients having benefited already and the future looking even brighter as novel immune checkpoint agents and combination therapies are developed with curative intent.

For all his contributions and achievements, Jim has been recognized by many honors and awards including the Lasker. However, as an accomplished harmonica player, Jim often conveys that one of his highest honors was the privilege of playing with Willie Nelson in concert—you see … he is really is a rock star. Levity aside, above all, what Jim values most is helping patients and saving lives. One story that Jim often shares is that of "Sharon".

Sharon was one of the first patients to be enrolled in a study with Jim's drug. Sharon was a young mother of two who suffered from lethal metastatic melanoma. She knew the grim statistics and that her options were limited, but when her oncologist informed her about a new clinical trial for a new class of cancer-fighting drugs, it didn't take long for Sharon to decide.

Sharon wanted to live long enough to see her son graduate from high school, so she took the chance. Fifteen years later, Sharon is still alive. Jim's drug worked, and within six months of treatment, her tumors were completely gone. Now, years into her complete remission, Sharon had the chance to meet Jim, an exchange flooded with tears and hugs.

That's what drives Jim. That's his true Nobel. It is difficult to overestimate the impact of his work on cancer treatment and the lives of cancer patients around the world, today and in future generations. There's no doubt in my mind that Jim Allison will go down in history as the 'Jonas Salk' of our time. Thank you Dr. Jim Allison for placing us all on a path to make cancer history. #endcancer

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Craig Thompson resigns from two corporate boards as MSK crisis shifts to board roles

By Paul Goldberg

Craig Thompson, president and CEO of Memorial Sloan Kettering Cancer Center, resigned from two corporate boards of directors—the pharmaceutical company Merck & Co., and Charles River Laboratories International Inc., a company focused on early-stage drug development and manufacturing of novel compounds.

Thompson announced his resignation from the corporate boards in an email to the MSK faculty and staff Oct. 2.

"I've heard from a number of you that you'd like me to be even more present at MSK," Thompson wrote. "I take that feedback seriously and intend to lead by example. To that end, I am resigning from my positions as a member of the Board of Directors of Merck and Charles River, effective immediately. I believe this is the right decision for Memorial Sloan Kettering and will allow me to redouble my focus on MSK priorities: quality patient care, faculty, scientists, and staff."

The scandal began on Sept. 8, when The New York Times and ProPublica published a story stating that José Baselga, MSK's chief medical officer and physician-in-chief at the time, had systematically failed to disclose conflicts of interest. On Sept. 16, the Times published an editorial about conflicts of interest at the cancer center.

On Sept. 20, another Times-ProPublica story questioned MSK's role in establishing Paige.AI, an artificial intelligence start-up that aims to use the hospital's pathology archive—consisting of data from 25 million patients—to develop machine learning algorithms and create a decision support system for pathologists.

Thompson's decision to resign from the two boards comes after The New York Times and ProPublica on Sept. 29 reported that an MSK technology transfer official, Gregory Raskin, received a $1.4 million stake in Y-mAbs Therapeutics, a biotech company when it went public last week.

Y-mAbs has licensed MSK's antibodies for the treatment of advanced neuroblastoma. Raskin immediately turned over his stake in the company to MSK, and the cancer center changed its conflicts policy, limiting the center's board members and employees' roles in for-profit companies.

"Effective immediately, we have implemented a moratorium on appointments of MSK board members to serve on the boards of MSK start-ups or to make any direct investments in them," MSK officials said as they announced the new policies on Sept. 29, the day the Times and ProPublica story was published. "Additionally, we intend to codify, as standard policy, that any potential equity that could be attained by employees appointed as MSK-designees to outside boards will be returned to the institution and dedicated to research."

In an apparent effort to make the point that MSK's underlying work in neuroblastoma isn't being questioned, the cancer center created a hub to feature this work.

Contentious "town hall" meeting

Thompson's resignation from the boards of Merck and Charles River follows a "town hall" meeting with the faculty, where Thompson and Douglas Warner, the chairman of the MSK board of managers and overseers, placed much of the blame for the ethics problems on Baselga, who resigned in the first days of the scandal.

A transcript of the town hall meeting, which was held on Oct. 1, appears to have been sent to the Times and ProPublica reporters, apparently by mistake.

On Oct. 2, Thompson announced his board resignations in the following email:

Dear MSK Colleagues,

After yesterday's discussions with medical faculty and much thought around the feedback I received, I wanted to alert you to additional actions that I am taking to build on the reforms we announced last week.

I've heard from a number of you that you'd like me to be even more present at MSK. I take that feedback seriously and intend to lead by example. To that end, I am resigning from my positions as a member of the Board of Directors of Merck and Charles River, effective immediately. I believe this is the right decision for Memorial Sloan Kettering and will allow me to redouble my focus on MSK priorities: quality patient care, faculty, scientists, and staff.

Additionally, I wanted to announce a series of steps designed to further our institutional mission and ensure we learn from recent events.

To start, as requested by faculty, we will be conducting a root cause analysis (RCA) of the issues that have come to the fore in recent weeks so that we ensure our path forward is expertly guided by what we learn. Medical professionals know that you don't simply treat and remedy a condition, you work to understand how it developed. The RCA will do that.

We will be taking several actions to ensure the perspective and voice of our clinicians is more deeply reflected in institutional decision-making. To that end, we are appointing an elected medical staff representative to the search committee to identify a new physician-in-chief. The experience and concerns of our clinical staff, who are on the front line of patient care, are vital to ensuring we identify the best candidate.

The MSK Board has also asked the elected president of the medical staff to play a formal role on the

Boards of Overseers and Managers, representing the interests of faculty at all regularly scheduled board meetings. This will better inform policy that impacts our faculty and patient care.

Lastly, we are developing a formalized council of department chairs to serve as an advisory committee to the physician-in-chief and provide critical insight into issues that staff face every day.

As I made clear last week, we are taking actions to enhance communication, transparency, disclosure, and oversight of outside activities, and are undertaking a full and deliberative review of our policies and procedures related to conflicts of interest.

I deeply appreciate the continued feedback and constructive engagement we are receiving in this process. It's been invaluable as we move forward. But most importantly, I appreciate your deep faith in Memorial Sloan Kettering and unwavering commitment to delivering exceptional care and developing the therapies of tomorrow.

I look forward to continuing our dialogue.

All the best,
Craig Thompson, MD

Baselga's scientific work isn't being questioned, but his failure to disclose competing interests may affect hundreds of papers and lectures (The Cancer Letter, Sept. 14).

On Oct. 1, The New England Journal of Medicine became the first journal to publish a correction related to two papers:

- Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations (Original Article, N Engl J Med 2015;373:726-736),
- Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer (Original Article, N Engl J Med 2017;377:122-131).

The NEJM correction reads:

Disclosure information for Dr. Jose Baselga was inaccurate in two articles. In the 2017 article, the disclosure footnote (p. 131) should have included the following statement:

"Dr. Baselga reports receiving personal and other fees from Northern Biologics, Infinity Pharmaceuticals, ApoGen Biotechnologies, PMV Pharma, Juno Therapeutics, Roche/Genentech, Novartis, Eli Lilly, Verastem, Chugai Pharmaceuticals, AstraZeneca, Sanofi-Aventis, Aragon Pharmaceuticals, Bayer Pharmaceuticals, and Seragon."

The article is correct at NEJM.org. With both the 2015 article and the 2017 article, updated disclosure forms for Dr. Baselga have been posted.

Editor's note: Dr. Baselga failed to disclose in these articles his multiple, substantial financial associations, which are now apparent in the updated disclosure forms. When we learned of this breach of trust, we conveyed our concern to Dr. Baselga's institution, Memorial Sloan Kettering Cancer Center.

Dingell questions MSK's role in AI spinoff

Rep. Debbie Dingell (D-MI) requested information about MSK's handling of patient data in an Oct. 1 letter to Thompson.

"While there are many potential advancements artificial intelligence applications will bring for patients and doctors alike, there are also many open questions about the impacts this technology will have on privacy and the use of deeply intimate patient data," Dingell wrote.

Dingell's questions to MSK follow:

- Does Sloan Kettering get consent from all patients to have their medical information used by a third party when they are admitted to your facilities? How is that consent obtained? Is there a standard form for patient consent for all third-party sharing, or do you seek consent each time patient information is shared? Do you identify for the patient the third party with whom the data will be shared? Please provide a copy of all notices and consent forms provided.
- Did Sloan Kettering get consent from all patients whose medical information was shared with Paige.AI to share their tissue slides with Paige.AI?
- Were the tissue slides shared with Paige.AI images of slides, or the physical tissue sample slides themselves?
- Are patients able to opt-out of third-party use of this information? How?
- If patients were given the ability to opt-out of this type of disclosure, were those patients excluded from the 25 million tissue slides shared with Paige.AI?
- What level of anonymization was used when providing tissue slides to Paige.AI? How were patients able to give consent that their personal medical information can be used by a technology that did not yet exist?
- What custodial obligations does Paige.AI have to protect patient information under this data sharing agreement? And do those obligations extend if Paige.AI declare for bankruptcy?
- Has Sloan Kettering entered into agreements like the Paige.AI partnership with other companies?

Q & A

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

CONVERSATION WITH THE CANCER LETTER

Roy Jensen: "In general, I think cancer center directors still enjoy a certain amount of respect"

Roy A. Jensen
President of the Association of American Cancer Institutes
Director, The University of Kansas Cancer Center

"It's a group that has remarkable access to senators, House members, governors and state legislators. And so, we're listened to, whether we go to the Hill or to our state capitol."

As the new president of the Association of American Cancer Institutes, Roy Jensen will focus on public policy at the state and local level as his presidential priority.

"What we'd really like to do is empower cancer centers to promote good public policy at the state and local level," said Jensen, director of The University of Kansas Cancer Center, whose two-year term as AACI president began earlier this week. "The mechanism we have come up with is to leverage AACI's existing government relations forum to develop model legislation on issues such as clean indoor air, tobacco taxes, radon, oral chemotherapy--things that have a real impact on cancer incidence and mortality."

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

To put this in perspective, you are on a train, traveling from the AACI meeting in Chicago to Kansas City. Where are you right now?

Roy Jensen: I'm in Missouri.

Could we talk about your AACI presidential initiative?

RJ: Sure. What we'd really like to do is empower cancer centers to promote good public policy at the state and local level. The mechanism we have come up with is to leverage AACI's existing government relations forum to develop model legislation on issues such as clean indoor air, tobacco taxes, radon, oral chemotherapy—things that have a real impact on cancer incidence and mortality.

Essentially, we want to utilize AACI as a clearinghouse for model pieces of legislation and rely on the government relations forum for their to refine that legislation and develop best practices of public policy that cancer centers can then take up and adapt to their local situation.

What about national politics?

RJ: There may be some opportunities to do some things there. But, frankly, it's so difficult to mount a national campaign, and it takes so much in the way of resources that I'm not optimistic that that we'll be able to get much done there. But there is great potential at the state and local levels.

What about something like 340B, for example? That's a national issue.

RJ: The public policy initiatives that we are going to focus on are not related to reimbursement issues. In fact, we're going to try and stay away from reimbursement-focused issues. However, AACI will be looking at reimbursement issues related to CAR T-cell therapy and the board has agreed to develop an initiative around this topic.

We have a committee of individuals who are working to try to find a workable solution for how this therapeutic approach can be paid for. Obviously, that's going to require a national effort, but that's separate and distinct from my presidential initiative.

Just being at the meeting, I'm realizing how powerful a group this can be, because here is the entire academic oncology all in one place, people who are very focused, and who don't need any more education than they already have to see what the issues are. There is no need for lengthy discussion before they can agree.

RJ: You are absolutely correct, Paul. It's a group that has remarkable access to senators, House members, governors and state legislators. In general, I think cancer center directors still enjoy a certain amount of respect and cache among those type of folks. And so, we're listened to, whether we go to the Hill or to our state capitol.

KU Cancer Center has had great success with moving ae number of pieces of legislation forward that over time will a tremendous impact on cancer incidence and mortality in our region.

Plus you can turn on a dime.

RJ: Yes, in large part due to our strong partnerships with other like-minded groups like American Cancer Society Cancer Action Network, American Lung Association, American Heart Association and the Leukemia and Lymphoma Society.

There are many groups out there that see public policy as a way to do a lot of good.

Just thinking about the presidential initiative. You'll be president for two years. Then it's something that Karen Knudsen [AACI president-elect, director of Thomas Jefferson University Sidney Kimmel Cancer Center] would have to continue after your term is over. It's not something you just start and go away from.

RJ: Right. Karen and I have talked my initiative, and she is very enthusiastic about it. We see this initiative as something that can grow in value over time. We're not going to try to boil the ocean right away. I think we are going to focus on two to three issues that will be decided upon by the government relations forum in terms of what pieces of model legislation we want to develop.

As sample legislation is developed and added to our library, so to speak, we will progress to additional key issues and continue building that portfolio. Over time, our small library will grow to be a broad portfolio of public policy initiatives.

One of the issues that we have is there is huge variability across the country in terms of statutes that are enacted and the level of protection or coverage that people have. For instance, coverage for routine care for patients enrolled in clinical trials.

If that's not in place, that can be a huge barrier to people having access to good clinical trials. We want to make sure that things like that are in place.

What are you doing in Kansas? Is there anything about Kansas that people should know about?

RJ: Statewide adoption of Tobacco 21 will be a major topic of discussion during the upcoming legislative session. A number of states have already enacted Tobacco 21. The data says is that by increasing the age to 21 at which people can buy tobacco products, you can decrease the number of adult tobacco users by about 10 percent.

And that's a pretty good number. So, anything that we can do to drive down the number of adult smokers is going to be beneficial in a whole host of ways.

And you're spearheading this?

RJ: We are working closely with ACS CAN and the Greater Kansas City Chamber of Commerce. It's had a major push in this regard, and a lot of the momentum has come from the fact that in the greater Kansas City metropolitan area, there are about 1.5 million people who now live in the city with Tobacco 21 ordinances on the books.

And so, we're very excited about that. Of course, we've been involved with that effort from the very beginning, and I think it's about time that we try to move this on to the state level.

What about best practices for the cancer community for the cancer centers? Does AACI potentially have a role to play on establishing model policies on, say, conflicts of interest?

RJ: Obviously this is a hot topic in the news right now. At the board meeting, we discussed this issue, and are putting together next year's program committee. I anticipate next year's meeting will include a session on conflict of interest. One of the agenda items for our upcoming board meeting in the latter part of November is to try to put a framework in place for developing a policy around that issue.

“We're not going to try to boil the ocean right away. I think we are going to focus on two to three issues that will be decided upon by the government relations forum in terms of what pieces of model legislation we want to develop.”

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AN APPRECIATION

Philip DiSaia, former head of Gynecologic Oncology Group, dies at 81

By Krishnansu Tewari

The grandson of Italian immigrants, Philip John DiSaia was born on Aug. 14, 1937 in Providence, Rhode Island. He earned his Bachelor's in Science at Brown University and his MD at Tufts University.

Upon the advice of his mentor in medical school, DiSaia obtained two years of general surgery training, followed by residency in obstetrics & gynecology at Yale University where he met Edward Quilligan, creator of the fetal heart rate monitor.

During residency, DiSaia published the paper that first brought to light the teratogenic effects of warfarin on the human fetus.

He next fulfilled his commitment to serve in the U.S. Navy and then successfully competed for a grant through the American Cancer Society, which funded his fellowship in gynecologic oncology under the tutelage of Felix Noah Rutledge at MD Anderson Hospital and Tumor Institute in Houston.

During this period, he would form long-lasting bonds with his co-fellow, William Creasman. In 1976, DiSaia was recruited following a national search for a chair for the Department of Obstetrics & Gynecology at the University of California, Irvine.

Accompanied by Quilligan, DiSaia sought to establish a traditional academic department at UC Irvine and would ultimately distinguish the Department of Ob/Gyn as one of the preeminent institutions dedicated to women's health.

In addition to a nationally recognized residency program and robust volunteer clinical faculty comprised of community ob/gyns, the department flourished under his leadership with the establishment of four clinically directed and research-driven Divisions in Gynecologic Oncology, Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, and Urogynecology.

Embedded in each division was a highly sought after fellowship training program.

DiSaia established the first four-year program in Gyn Oncology, created a direct corridor for translational research collaboration with the basic scientists in UCI's School of Biological Sciences, and was the first to obtain NIH funding through a T32 grant to fund the two research years of the fellowship.

DiSaia has served as president of the Society of Gynecologic Oncology and president of the American Board of Obstetrics & Gynecology.

During his four consecutive terms as group presiding chair of the NCI's Gynecologic Oncology Group, DiSaia spearheaded the practice-changing clinical trials that established the role for adjuvant radiotherapy for early stage high-risk endometrial cancer, chemotherapy for advanced/recurrent endometrial cancer, anti-angiogenesis therapy and intraperitoneal chemotherapy for newly diagnosed advanced ovarian cancer, chemoradiation for locally advanced cervical cancer, anti-angiogenesis therapy for recurrent/metastatic cervical cancer, and sentinel lymphatic mapping for early stage vulvar cancer.

At UC Irvine, his research endeavors have had as their focus the immunology of tumor biology, the safety of estrogen replacement therapy among breast and endometrial cancer survivors, and the development of less disfiguring surgical approaches for vulvar cancer.

DiSaia's and Creasman's, Clinical Gynecologic Oncology, is the most widely read textbook in the subspecialty and is currently in its 9th edition and has been translated into several languages.

DiSaia is the recipient of the University of California Gold Medal and a Certificate of Commemoration from the United States Senate.

At the turn of the millennium, DiSaia was granted an audience with Pope John Paul II, and shortly thereafter was granted an Honorary Degree from the University of Brescia in the region of Lombardy in northern Italy.

DiSaia's legacy lives in the hearts of the numerous residents and fellows he has trained over the past 42 years at UC Irvine.

During this period, he treated thousands of women who struggled with gynecologic malignancies.

He loved old medical tomes, the New England Patriots, and Italian wines. DiSaia passed away peacefully at his home on Thursday, Sept. 27, 2018. He is survived by his loving wife, Patti DiSaia, four sons and their wives, and numerous grandchildren.

The author is the director of the Division of Gynecologic Oncology at the University of California, Irvine

IN BRIEF

Ruth O'Regan named chief scientific officer of Big Ten Cancer Research Consortium

Ruth O'Regan was named chief scientific officer of the Big Ten Cancer Research Consortium.

O'Regan is the division head of hematology, medical oncology and palliative care in the Department of Medicine at the University of Wisconsin School of Medicine and Public Health and associate director for clinical research at the UW Carbone Cancer Center.

An active member of the Big Ten CRC's Breast Clinical Trial Working Group, O'Regan is the sponsor-investigator of the consortium's BTCRC-BRE15-024 , a new approach to triple-negative breast cancer.

The trial is also open at the cancer centers at the University of Illinois, Michigan State, Penn State, and Rutgers.

O'Regan will serve a renewable three-year term as CSO. In this role, she will guide the research and scientific mission of the consortium, the most promising clinical trials to be conducted through the consortium.

O'Regan will serve as the primary spokesperson for the research and scientific activities of the consortium, and she will support the Steering Committee and Clinical Trial Working Groups in their interactions with the biotech and pharmaceutical industry.

Before she joined the UW Carbone Cancer Center in 2015, O'Regan was professor of hematology and medical oncology at Emory University School of Medicine, where she also served as chief of hematology and medical oncology at the Georgia Cancer Center for Excellence at Grady Memorial Hospital, medical director of Winship Cancer Institute's Glenn Family Breast Center, vice chair for educational affairs for the Department of Hematology and Medical Oncology, and director of the hematology oncology fellowship.

Peter Wiklund named director of the Bladder Cancer Program at Mount Sinai

Peter Wiklund, a surgeon who pioneered robot-assisted cystectomy, has been appointed director of the Bladder Cancer Program at the Mount Sinai Health System and professor of urology in the Department of Urology at the Icahn School of Medicine at Mount Sinai.

Prior to joining Mount Sinai, Wiklund was chair of urology, molecular medicine, and surgery, and professor of urology at the Karolinska Institutet in Stockholm, where he built a leading cystectomy program.

He has performed more than 3,000 robotic operations and has extensive experience in advanced oncological surgery in patients whose tumor is growing on several pelvic organs (multi-organ tumor, bladder, prostate, colorectal, ovarian, and uterine).

Wiklundis chair of the scientific working group of the European Urology Robotic Section of the European Association of Urology and is an international member of the American Urological Association.

2018 NIH Director's awards for high-risk, high-reward research program announced

NIH has awarded 89 grants that will provide funding to scientists proposing innovative research to address major challenges in biomedical science.

The grants are part of the NIH High-Risk, High-Reward Research Program, which supports ideas with potential for great impact in biomedical research from across the broad scope of the NIH.

The awards, which are managed by the NIH Common Fund, total approximately $282 million expected over five years, pending available funds.

Program applicants are encouraged to think outside-the-box and to pursue creative, trailblazing ideas in any area of research relevant to the NIH mission.

The High-Risk, High-Reward Research program manages the following four awards, including two awards aimed specifically to support researchers in the early stages of their careers:

- The NIH Director's Pioneer Award, established in 2004, challenges investigators at all career levels to pursue new research directions and develop groundbreaking, high-impact approaches to a broad area of biomedical or behavioral science.
- The NIH Director's New Innovator Award, established in 2007, supports unusually innovative research from early career investigators who are within 10 years of their final degree or clinical residency and have not yet received a research project grant or equivalent NIH grant.
- The NIH Director's Transformative Research Award, established in 2009, promotes cross-cutting, interdisciplinary approaches and is open to individuals and teams of investigators who propose research that could potentially create or challenge existing paradigms.
- The NIH Director's Early Independence Award, established in 2011, provides an opportunity to support exceptional junior scientists who have recently received their doctoral degree or completed their medical residency to skip traditional post-doctoral training and move immediately into independent research positions.

The Pioneer awards were received by:

Janelle Ayres
The Salk Institute for Biological Studies
Project Title: Host-Microbe Interactions: Harnessing Co-Evolution to Treat Disease
Grant ID: DP1-AI144249

Daniel Colón-Ramos
Yale University School of Medicine
Project Title: Powering the Brain: The Cell Biology of Neuroenergetics
Grant ID: DP1-NS111778

Christina Curtis
Stanford University School of Medicine
Project Title: Forecasting Tumor Evolution: Can the Past Reveal the Future?
Grant ID: DP1-CA238296

Viviana Gradinaru
Caltech
Project Title: Circuit-Specific Delivery of Large Cargo Across the Nervous Systems of Adult Mammals and Embryos Via Novel Engineered Systemic Vectors
Grant ID: DP1-NS111369

Jonathan Kipnis
University of Virginia, School of Medicine
Project Title: Neural Code of the Immune Responses
Grant ID: DP1-AT010416

Hyungbae Kwon
Max Planck Florida Institute for Neuroscience
Project Title: Cracking the Neuromodulation Code at Single Cell Resolution
Grant ID: DP1-MH119428

Michelle Monje
Stanford University
Project Title: Glioma Circuitry: Bridging Systems Neuroscience and Cancer
Grant ID: DP1-NS111132

Gabriel Victora
Rockefeller University
Project Title: Quantifying Cell-Cell Interactions in the Immune System by Trans-Synaptic Labeling
Grant ID: DP1-AI144248

Amy J. Wagers
Harvard University, Harvard Medical School and Joslin Diabetes Center
Project Title: Uncovering Molecular Effectors of Mammalian Aging
Grant ID: DP1-AG063419

Peng Yin
Harvard University
Project Title: High-Throughput Single-Molecule Protein Identification Via Super-Resolution Imaging
Grant ID: DP1-GM133052

Queen's University Belfast and the University of Leeds researchers win the 2018 European Health Award

Researchers from Queen's University Belfast and the University of Leeds, as part of a pan-European partnership called the European Cancer Concord, have won the 2018 European Health Award.

The award-winning project, entitled: 'The European Cancer Patient's Bill of Rights: A Catalyst for Change and an empowerment tool for cancer patients across Europe' involves an equal partnership between cancer patients, healthcare professionals and cancer researchers.

Mark Lawler, chair in Translational Cancer Research at Queen's University Belfast and vice president of ECC, received the award on behalf of the partnership during the opening ceremony of the European Health Forum Gastein, the premier European Health Policy Conference and an official event of the Austrian European Council Presidency.

One of the key outputs from the research has been the development of a 70:35 Vision, 70 percent long term survival for all cancer patients across Europe by 2035.

"Our 70:35 Vision is built upon the pillars of cross border and interdisciplinary cooperation, sharing best practice and ensuring that research and innovation gets translated for the benefit of patients," explained Peter Selby, professor of Cancer Medicine at the University of Leeds and President of ECC. "This is a superb example of how cooperative European activities that involve sharing best practice between countries can result in top class prize-winning initiatives."

This award honors initiatives that help tackle some of Europe's most pressing health challenges.

Shirley Mertz elected chair and Christine Benjamin vice chair of Metastatic Breast Cancer Alliance

Shirley Mertz was elected chair of the MBC Alliance and Christine Benjamin was elected vice chair beginning Nov. 1.

The MBC Alliance is a coalition formed in 2013 by a dozen nonprofit patient advocacy and research organizations.

Shirley Mertz

Christine Benjamin

Both Mertz and Benjamin are founding members and have been active members of the MBC Alliance. Mertz has co-chaired the Alliance's research task force the last four years, while Benjamin has co-chaired the information task force. Both serve on the MBC Alliance executive group.

Mertz is the president of the MBC Network, a founding member of the MBC Alliance. She received a diagnosis of metastatic breast cancer in 2003, twelve years after being treated for DCIS. She is a former consumer reviewer for Susan G. Komen and the DOD Breast Cancer Research Program.

Moving Breast Cancer Treatments Forward

October 17, 2018
Bethesda, MD
8:00am-4:30pm

Register at
www.jktgfoundation.org

Register today for this free conference featuring more than a dozen leading breast cancer researchers. Helen Piwnica-Worms, Ph.D., MD Anderson Cancer Center, will give the 3rd Annual Jayne Koskinas Memorial Lecture and the day's panel topics include:

- New leads from the clinic and other new developments
- What does Immuno-Oncology hold for breast cancer patients: can the limiting of toxicity issues be overcome?
- Converging common biology and treatment paradigms in breast and ovarian cancer
- Issues, problems and potentials in breast cancer brain metastasis
- Interdisciplinary collaborations: identifying solutions efficiently

Sponsored by

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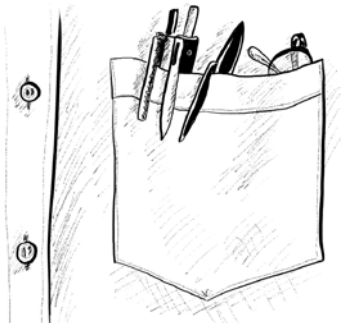
THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

How tumor-specific modulation frequencies were discovered

By Boris Pasche
Charles L. Spurr Professor of Medicine,
Chairman, Department of Cancer Biology,
Director, Comprehensive Cancer Center of Wake Forest University

In the spring of 2001, I visited a longtime friend and collaborator, Alexandre Barbault, to share with him my vision of using low levels radiofrequency electromagnetic fields for the treatment of cancer.

We had worked together for the previous 15 years, developing a medical device emitting low levels 27 MHz radiofrequency electromagnetic fields with the goal to treat insomnia. This work had been fruitful, as we had identified specific modulation frequencies with a sleep-restoring effect in humans(*1-3*).

Despite clinical evidence of efficacy from a multicenter randomized study conducted in the US that included 106 patients with chronic insomnia(*4*), there were lingering concerns about the long-term toxicity of radiofrequency electromagnetic fields because of the emerging cell phone controversy in the 1990s, which suggested that long-term use of cell phones was associated with increased cancer risk, especially with respect to brain tumors.

Symtonic, the company built around this technology, was not able to find partners to bring this device to the market as most pharmaceutical companies were concerned about the long-term liability of a novel technology making use of radiofrequency electromagnetic fields.

Following completion of my clinical training in Hematology/Oncology at Memorial Sloan Kettering Cancer Center and a postdoctoral fellowship in the laboratory of Joan Massagué at Sloan Kettering Institute, I had garnered peer reviewed funding from the National Cancer Institute and moved to Northwestern to develop my own laboratory research focusing on TGF-ß and cancer susceptibility.

Reflecting on the work conducted with Alexandre Barbault, I postulated that specific modulation frequencies could target tumor growth. This hypothesis was based on our own previous work identifying specific modulation frequencies with a sleep-inducing effect in patients with a diagnosis chronic insomnia, but not in patients without sleep problems.(*5*)

This hypothesis was further supported by the pioneering work of Drs. Ross Adey and Carl Blackman, who had identified and validated in mammalian models the so-called "window effect," which resulted in calcium efflux in mammalian models exposed to low levels radiofrequency electromagnetic fields when amplitude modulated at specific frequencies. This effect did not occur with unmodulated radiofrequency electromagnetic fields or when the radiofrequency electromagnetic fields were amplitude modulated outside these windows.(*6-8*)

These findings were consistent with the existing scientific literature at the beginning of the 21st century indicating that mammalian cells were insensitive to athermal radiofrequency electromagnetic fields, i.e. radiofrequency electromagnetic fields that did not result in any measurable heating of a biological system. However, Adey and Blackman discoveries strongly suggested that low levels of radiofrequency electromagnetic fields could affect calcium flux in brain cells, but only when the fields were amplitude modulated at specific frequencies.

As a freshly trained oncologist, I had become aware that most chemotherapy drugs had serious toxicity, which was considered acceptable given their potential to control disease progression and extend life. I also realized that the toxicity profile of chemotherapy was far more concerning than the hypothetical long-term risk of exposure to low levels of radiofrequency electromagnetic fields. I concluded that assessing the potential antitumor effects of low levels radiofrequency electromagnetic fields would be a clinically attractive and acceptable option, especially for patients with limited treatment options.

I asked Alexandre Barbault whether he would be willing to test this hypothesis with me and embark on a new adventure assessing the potential of this approach for the treatment of cancer. He agreed, and we decided to give ourselves three years to determine whether this postulate was worth pursuing or not. We also agreed that we would fund these studies ourselves.

In December 2001, Barbault and I met in Switzerland and started examining patients with a diagnosis of cancer by exposing them to low levels radiofrequency electromagnetic fields, which were amplitude modulated from 0.1 Hz to more than 1 kHz.(*5*) A proprietary methodology was used to identify cancer specific frequencies, employing the evaluation of the patient's pulse pressure, the difference between the systolic and diastolic blood pressure, during exposure to amplitude modulated radiofrequency electromagnetic fields.(*9*)

Correlations between hemodynamic parameters and radiofrequencies defined specific frequencies. We discovered that changes in pulse pressure in patients with a diagnosis of cancer were predominantly identified at modulation frequencies above 1000 Hz. These findings prompted the design and development of novel emitting devices with a signal synthesizer of high precision as our initial emitting devices lacked precision at higher frequencies. These new devices were equipped with a Direct Digital Synthesis (DDS) based synthesizer with a frequency precision of 10^{-7} and were developed in collaboration with Niels Kuster at the Swiss Federal Institute of Technology in Zurich, Switzerland.(*9*)

Using this new equipment, we found that patients with the same tumor type, i.e. breast cancer or hepatocellular carcinoma, exhibited reproducible hemodynamic changes in pulse pressure when exposed to the same frequency modulations. Specifically, 78 percent of the 1024 frequencies discovered were tumor-specific, i.e. hemodynamic changes were only detected in patients with the same tumor type, irrespective of their age, gender, and ethnic status. The remainder of the frequencies were not tumor-specific, i.e. changes were detected in patients with different primary tumors. These findings suggested the existence of a tumor frequency profile, like the gene expression profile identified in many tumor types.

Having gathered experimental evidence that patients with a given tumor type exhibit hemodynamic changes in pulse pressure when exposed to specific modulation frequencies, we tested the hypothesis that administration of these frequencies could be used as a novel cancer treatment. We designed a feasibility study in which 28 patients with advanced cancer and limited therapeutic options were offered compassionate treatment with an experimental device emitting 27 MHz radiofrequency electromagnetic fields, which were amplitude modulated at the same specific frequencies identified in patients with the same primary tumor type, i.e. frequencies previously discovered in patients with breast cancer were used to treat patients with a diagnosis of breast cancer.(*9*)

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All patients had discontinued any other anticancer therapy for at least 4 weeks prior to treatment with radiofrequency electromagnetic fields. The output of the device was adjusted to 100 mW into a 50 Ohm load using a sinusoidal modulated test signal. Treatment consisted of 27 MHz radiofrequency electromagnetic fields, which were sinusoidally amplitude modulated for 3 seconds at each of the tumor-specific frequencies previously discovered in patients with the same tumor type.

A spoon-shaped antenna was connected to the battery-powered device and the spoon was placed on the anterior part of the patient's tongue for treatment (Fig. 1). Treatment was administered for 60 minutes 3 times a day until progression of disease. Sixteen of the 28 patients enrolled in the study could be evaluated for response according to the RECIST criteria(*10*) and all imaging studies were independently reviewed by Drs. Brad Bottger and Reggie Munden, two U.S. board certified radiologists.

The results were encouraging. One patient with hormone refractory stage IV breast cancer metastatic to bone and the adrenal gland had a complete response lasting 11 months. Another patient with hormone refractory stage IV breast cancer metastatic to the liver and bone had a partial response lasting 13.5 months. Five additional patients had stable disease for at least 4 months. One of them with thyroid cancer metastatic to the lungs had stable disease for 7 years. This patient is still alive and receiving daily treatments with the device as of October 2018, more than twelve years after enrolling into the study.(*9, 11*)

Importantly, treatment was well tolerated with grade 1 fatigue and grade 1 mucositis being the only side effects reported, even after years of treatment. These results demonstrated that low levels of amplitude modulated radiofrequency electromagnetic fields administered by means of a spoon-shaped antenna placed in the patient's mouth had a systemic effect in patients with advanced cancer, were well tolerated, and could be easily administered by the patients themselves in the comfort of their home.

Figure 1: Patient receiving treatment with the TheraBionic P1 device

These exciting results led Frederico Costa, a former Sloan-Kettering colleague of mine, to propose a trial testing the safety and effectiveness of the therapy in patients with a diagnosis of advanced hepatocellular carcinoma, a group of patients with limited therapeutic options. Using Barbault and Pasche's newly developed medical devices and hepatocellular carcinoma specific frequencies discovered by Barbault and Pasche, Pasche and Costa designed and Costa conducted a phase I/II study in patients with advanced hepatocellular carcinoma and limited therapeutic options.(*12*)

The study was conducted at the University of São Paulo, Brazil, which was a major site for the recruitment of patients in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) registration study,(*13*) which led to the approval of sorafenib for the treatment of advanced hepatocellular carcinoma. The TheraBionic phase I/II study was run in parallel with the SHARP study and

“The results were encouraging. One patient with hormone refractory stage IV breast cancer metastatic to bone and the adrenal gland had a complete response lasting 11 months.”

enrolled patients with Child Pugh A or B advanced hepatocellular carcinoma and limited therapeutic options. Prior systemic treatment with chemotherapy or sorafenib was allowed.

The results of this study were also compelling. Similar to the findings of the feasibility study,(9) treatment with amplitude modulated radiofrequency electromagnetic fields was well tolerated, even after several years of continuous treatment, and there were no NCI grade 2, 3 or 4 toxicities. The study met its primary efficacy end point, which was progression free survival equal or greater than 6 months in 20 percent of patients.

Indeed, 14 (34.1%) of the 41 patients enrolled in the study had stable disease for more than 6 months. Median progression free survival was 4.4 months and median overall survival was 6.7 months. One patient previously enrolled in the SHARP study(13) and with evidence of disease progression at the time of enrollment, remained on therapy with a near complete response for 5 years and two months prior to expiring to causes unrelated to her malignancy.(11, 12)

There were four partial responses resulting in a 9.8 percent response rate, which were independently reviewed by Desiree Morgan, a U.S. board certified radiologist. Drs. Al Benson from Northwestern and Leonard Saltz from Sloan-Kettering reviewed the data and were impressed by the single agent activity of amplitude modulated radiofrequency electromagnetic fields in these patients. We compared these results with those by Abou-Alfa et al.(14) who conducted a large phase II study assessing the effects of sorafenib in patients with HCC and Child–Pugh A and B who had not received previous systemic treatment.

Abou-Alfa et al. observed partial responses using the WHO criteria in 2.2 percent of patients. This compares to 9.8 percent with the TheraBionic device, which is an over fourfold higher percentage. Investigator-assessed median time to progression in the sorafenib study was 4.2 months, and median OS was 9.2 months. Of note, all 137 patients from that study had evidence of disease progression after 14.8 months. At the same time point, four (9.8%) of the patients enrolled in the TheraBionic study did not have evidence of disease progression.

These findings suggest that treatment with the TheraBionic device may increase the time to radiological progression in advanced HCC. Importantly, the ratio of Child-Pugh A patients vs. Child-Pugh B patients was higher in the Abou-Alfa (2006) study than in the Costa et al. (2011) study. Thus, better outcome in the Costa et al. (2011) study cannot be attributed to better general physical condition.

In 2007, Barbault and I filed a patent application entitled "Electronic system for influencing cellular functions in a warm-blooded mammalian subject", which described the novel device we had developed as well as the tumor-specific frequencies we had identified. The same year, we established TheraBionic LLC to further develop our novel technology.

In 2008, I moved from Northwestern to the University of Alabama at Birmingham to become chief of the Division of Hematology/Oncology and associate director for translational research at the UAB comprehensive Cancer Center. In 2009, the results from our feasibility study were published and attracted the attention of Jackie Zimmerman, a UAB MD/PhD student who was interested in undertaking her graduate work in my laboratory.

Despite my suggestion to focus on projects related to TGF-ß, which were funded by two separate R01 awards from the National Cancer Institute, Zimmerman insisted on studying the biological effects of amplitude-modulated radiofrequency electromagnetic fields in cancer. I explained to her that we had not yet uncovered any evidence of in vitro activity on tumor cells. Based on the mode of discovery of tumor specific frequencies, my hypothesis was that systemic administration of these frequencies was a prerequisite for antitumor effect and that we might not observe any direct antitumor effects on cancer cells.

We both agreed that the only way to test this hypothesis was to create an in vitro exposure model replicating the in vivo conditions. Working closely with Ivan Brezovich, director of the Medical Physics Division in the UAB Department of Radiation Oncology, we developed a system for in vitro exposure replicating human exposure.(15)

Within a few months, Zimmerman generated experimental evidence that breast cancer modulation frequencies inhibited the proliferation of the MCF-7 breast cancer cell line. This "reverse translational work" testing the antitumor effects of modulation frequencies identified in patients with a diagnosis of cancer was expanded to other cancer cell lines using both corresponding and non-corresponding tumor-specific frequencies as well as randomly chosen frequencies.

Zimmerman and collaborators demonstrated that the proliferation of breast cancer cells was inhibited by breast cancer specific modulation frequencies. Similarly, proliferation of hepatocellular carcinoma cells was inhibited by hepatocellular carcinoma specific frequencies. Breast cancer specific modulation frequencies, however, did not affect the proliferation of hepatocellular carcinoma cells and vice versa. Additionally, randomly chosen modulation frequencies did not affect the proliferation of either breast cancer cells or hepatocellular carcinoma cells. Furthermore, tumor-specific modulation frequencies did not affect the growth of noncancerous cells.

Michael Pennison, another graduate student in my laboratory, asked the question whether amplitude modulated radiofrequency electromagnetic fields would disrupt the mitotic spindle of tumor cells, similarly to the mechanism of action of the tumor treating fields technology developed by Yoram Palti and collaborators.(*16, 17*) He found that there was pronounced disruption of the mitotic spindle of hepatocellular carcinoma cells after exposure to amplitude modulated radiofrequency electromagnetic fields.(*15*)

The work of Zimmerman and Pennison has been significantly expanded by Hugo Jimenez, whose work has dissected the mechanism of action of amplitude modulated radiofrequency electromagnetic fields both in vitro and in vivo using a custom-designed small animal model exposure system, which replicates in mice the same levels of exposure as when patients use the TheraBionic device.(*18*)

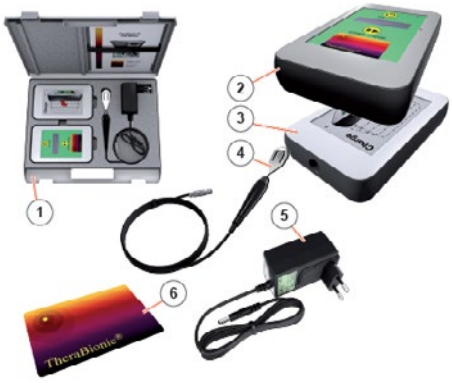
In 2013, Barbault and I founded TheraBionic GmbH in Ettlingen, Germany with the goal to develop and produce a medical device suitable for commercial use in Europe. Following the development of the OncoBionic P1 device, which was used in two clinical studies(*9, 12*), Barbault and I, with the assistance of Hans-Peter Völpel, the engineer who designed the current TheraBionic P1, conducted a critical analysis of our then existing OncoBionic P1 device. As a result of this analysis, the current TheraBionic P1 device was developed. Among the improvements incorporated into the TheraBionic P1 device (Fig. 2) are:

1. Avoidance of missed treatment time when the ohmic contact between the spoon-shaped antenna and the patient's oral mucosa is lost. The new TheraBionic P1 device constantly monitors the impedance of the coaxial cable ending with the spoon-shaped antenna placed on the anterior part of the patient's tongue. The device interrupts treatment and starts beeping whenever it detects a significant change in the impedance of coaxial cable ending with the spoon-shaped antenna. Treatment resumes as soon as the patient places the spoon-shaped antenna back on the tongue. This improvement addresses the need for continuous monitoring of treatment delivery ensuring that physicians will know the exact treatment time delivered between each visit. It also informs the patient if treatment is not being delivered appropriately and that the spoon-shaped antenna needs to be replaced on the patient's tongue.

2. Minimizing the risk of electrocution at all times. The new TheraBionic P1 device is made of two separate units, one docking station connected to the mains, which charges wirelessly the treatment unit. Hence, the risk of electrocution has been markedly reduced as the treatment unit is powered by a 5 V battery, which cannot cause any significant harm to the human body.

3. Optimization of the spoon-shaped antenna: The spoon-shaped antenna of the new TheraBionic P1 is permanently connected to the coaxial cable, which ensures optimal connection between the coaxial cable and the spoon-shaped antenna. The entire spoon-shaped antenna is a barcoded disposable unit, which can only be used by one single patient.

4. Minimizing the risk of uncontrolled treatment and providing accurate monitoring of treatments received. The TheraBionic P1 device is delivered to patients with 20 treatment hours so that treatment can be initiated as soon as prescribed by the physician. Additional treatments can only be received following reloading with an activation chip card, which adds 93 one-hour sessions. This provides a well-defined system to control the number of treatments, which can be traced with chip cards. Indeed, the physician will know exactly how many hours and minutes of treatment have been administered at each return visit. The number of hours and minutes of treatment administered is equal to the number of treatment hours loaded in the device (20 hours at the time of delivery, 113 hours after activation of 93 additional one hour treatment sessions, 206 hours after activation of 186 additional one hour treatment sessions, etc.) minus the number of hours and minutes left, which is displayed on the TheraBionic device whenever it is turned on.



1 **Device carrying case**

2 **Therapeutic device**

3 **Docking station**, for wireless charging of the therapeutic device

4 **Patient spoon**, of stainless steel with connecting cable to the therapeutic device

5 **Power supply**, to power the docking station

6 **Activation card**, for insertion into the docking station, allows activation time upload into the therapeutic device, void after data transfer

Figure 2: Components of the TheraBionic P1 medical device

Following the successful development of the novel TheraBionic P1 device, TheraBionic GmbH began the European registration procedure with Regina Müller overseeing the quality management systems. In July 2018, TheraBionic GmbH received European certification for the TheraBionic P1 device as a class II a (low risk) medical device for unmet medical needs according to the European MDD 93/42/EEC guidelines and ISO 13485:2016 quality managements systems regulatory requirements for medical devices. Production of the certified devices has begun and the first devices will become available for commercial use in Europe in October 2018.

The European regulatory approval is the first step towards the further development and expansion of this novel technology for the diagnosis and treatment of various tumor types using TheraBionic discoveries. Upcoming clinical trials will include randomized studies of the TheraBionic P1 device in the first-line and second-line treatments of advanced hepatocellular carcinoma in combination with current standard of care therapies. Additional studies will be launched to assess the safety and effectiveness of TheraBionic treatment in women with stage IV refractory breast cancer with or without brain metastases. Preliminary data generated by Sambad Sharma in the laboratory of Kounosuke Watabe at Wake Forest Baptist Comprehensive Cancer Center suggest activity in breast cancer brain metastases.

European regulatory approval is only the beginning of the large-scale clinical use of amplitude modulated radiofrequency electromagnetic fields, which may well usher a new era in oncology.

Disclosures: Boris Pasche is the cofounder of TheraBionic LLC, TheraBionic Inc., and TheraBionic GmbH. He holds stocks in TheraBionic Inc. and TheraBionic GmbH.

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CLINICAL ROUNDUP

Aspirin lowers risk of ovarian and hepatocellular cancer

Regular use of aspirin can reduce the risk of developing ovarian cancer and hepatocellular carcinoma, according to two studies published Oct. 4 in JAMA Oncology.

The studies were conducted by Moffitt Cancer Center and Massachusetts General Hospital.

The Moffitt study found that women who reported taking a low-dose aspirin every day had a 23 percent lower risk of ovarian cancer compared to nonaspirin users. For this study, Shelley Tworoger, associate center director for Population Science at Moffitt, worked with researchers at Huntsman Cancer Institute and the Harvard T.H. Chan School of Public Health to analyze data from more than 200,000 women who took part in the Nurses' Health Studies based at Brigham and Women's Hospital in Boston.

Ovarian cancer is the most fatal gynecological cancer, largely due to lack of early detection strategies. It is believed that inflammation that occurs during ovulation plays a role in the development of this cancer. But anti-inflammatory medications, such as aspirin, have been shown to lower the risk of certain types of cancers.

Of the participants, 1,054 developed ovarian cancer. Researchers looked at the participants' use of aspirin (325 milligrams), low-dose aspirin (100 milligrams or less), non-aspirin NSAIDs and acetaminophen. Their analysis found that low-dose aspirin use was associated with a lower risk of ovarian cancer while standard-dose aspirin use was not.

Conversely, the data showed that women who took non-aspirin NSAIDs often, defined by at least 10 tablets per week for many years, had an increased risk of developing the disease. The findings help confirm research published earlier this year by Tworoger in the Journal of the National Cancer Institute.

The study, which used data pooled from 13 studies in the Ovarian Cancer Cohort Consortium, included more than 750,000 women, of which 3,500 were diagnosed with ovarian cancer. It found that daily use of aspirin reduced ovarian cancer risk by 10 percent.

"We're not quite at the stage where we could make the recommendation that daily aspirin use lowers ovarian cancer risk. We need to do more research. But it is definitely something women should discuss with their physician," said Tworoger.

The Mass. General report, which analyzed data from two long-term epidemiologic studies appears in JAMA Oncology, found that regular aspirin use—taking two or more 325 mg tablets a week for five years or more—led to a significantly reduced risk of developing HCC, which is the second leading cause of cancer death worldwide.

"Regular use of aspirin led to significantly lower risk of developing HCC, compared to infrequent or no aspirin use, and we also found that the risk declined progressively with increasing aspirin dose and duration of use," says Tracey Simon, a research fellow in the MGH Division of Gastroenterology, and lead author of the report. "Since regular aspirin use carries the risk of increased bleeding, the next step should be to study its impact in populations with established liver disease, since that group is already at risk for primary liver cancer."

Aspirin is known to block the production of inflammatory lipids that can lead to liver injury, and while some previous studies have suggested that regular use could help prevent HCC, information on the optimal dosage and required duration of treatment has not been available.

The research team examined more than three decades of data collected as part of the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), which have compiled comprehensive health data on more than 170,000 participants since the 1980s. As part of the biennial questionnaires, participants were asked whether they took aspirin on a regular basis, how many standard-dose (325 mg) tablets they took a week and for how long. Information on HCC diagnosis was also compiled from the questionnaires and from the National Death Index of the National Center for Health Statistics.

Among the more than 133,300 participants whose data was analyzed—more than 45,800 women and 87,500 men—regular aspirin use, defined as two or more standard-dose tablets a week, led to a 49 percent reduction in the relative risk of developing HCC. Among those taking aspirin for five years or more, the relative risk was reduced by 59 percent.

Just as the risk reduction increased with longer duration of aspirin use, it also decreased if aspirin was discontinued, disappearing by eight years after aspirin use was halted. Regular use of acetaminophen or nonsteroidal anti-inflammatory drugs like ibuprofen had no impact on HCC risk.

"The long duration of aspirin use could be necessary because primary liver cancer takes many years to grow. Aspirin may act at the earliest stages of cancer development, or even at precancerous stages, by delaying or preventing inflammation or liver fibrosis," says Simon. "While it's still too early know whether starting aspirin therapy might be an effective strategy to prevent HCC, efforts to understand the mechanisms behind these beneficial effects could help identify urgently-needed prevention strategies or biomarkers for a cancer that is a growing public health problem."

Senior author Andrew Chan, chief of the MGH Clinical and Translational Epidemiology Unit in the Department of Medicine and the Division of Gastroenterology, adds, "Aspirin use is already recommended for prevention of heart disease and colorectal cancer in certain U.S. adults. These data also add to a growing list of cancers for which aspirin appears to have anti-cancer activity, which could be a rationale for more patients to discuss an aspirin regimen with their physicians." Chan is a professor of Medicine at Harvard Medical School.

Genentech's Entrectinib showed durable response of more than two years NSCLC

Genentech announced the results for its investigational medicine entrectinib, from an integrated analysis of the pivotal phase II STARTRK-2, phase I STARTRK-1, and phase I ALKA trials, which showed that entrectinib shrank tumors (objective response rate) in 77.4 percent of people with locally advanced or metastatic ROS1-positive non-small cell lung cancer.

Genentech is a member of the Roche Group.

In addition, entrectinib demonstrated a durable response of more than two years (duration of response was 24.6 months). Entrectinib was shown to shrink tumors in more than half of people with cancer in the central nervous system (intracranial ORR: 55 percent).

The safety profile of entrectinib was consistent with that seen in previous analyses, and no new safety signals were identified. Based on the integrated analysis of these studies, Genentech plans to submit these data to global health authorities.

ROS1 gene fusions have been identified in 1-2 percent of people with NSCLC. NSCLC is the most common type of lung cancer and accounts for 85 percent of all lung cancer diagnoses. Approximately 30-40 percent of people with ROS1-positive NSCLC have brain metastases at time of diagnosis.

The integrated analysis included data from 53 people with ROS1-activating gene fusions from the phase II STARTRK-2, phase I STARTRK-1 and phase I ALKA trials. The studies enrolled people across 15 countries and more than 150 clinical trial sites.

STARTRK-2 is a phase II, global, multicenter open-label basket study in people with solid tumors that harbor an NTRK1/2/3 or ROS1 gene fusion. The primary endpoint is ORR. Secondary outcome measures include DoR, time to response, clinical benefit rate, intracranial tumor response, progression-free survival, CNS, PFS and overall survival.

STARTRK-1 is a phase I, multicenter, open-label dose escalation study of a daily continuous dosing schedule in people with solid tumors with NTRK1/2/3 or ROS1 gene fusions in the U.S. and South Korea. The trial assessed the safety and tolerability of entrectinib via a standard dose escalation scheme and determined the recommended phase II dose.

ALKA is a phase I, multicenter, open-label dose escalation study of an intermittent and continuous entrectinib dosing schedule in people with advanced or metastatic solid tumors with ROS1 gene fusions in Italy.

Entrectinib (RXDX-101) is an investigational, oral medicine in development for the treatment of locally advanced or metastatic solid tumors that harbor NTRK1/2/3 or ROS1 gene fusions. It is a selective tyrosine kinase inhibitor designed to inhibit the kinase activity of the TRKA/B/C and ROS1 proteins, whose activating fusions drive proliferation in certain types of cancer.

Entrectinib can block ROS1 and NTRK kinase activity and may result in the death of cancer cells with ROS1 or NTRK gene fusions. Entrectinib is being investigated across a range of solid tumor types, including non-small cell lung cancer, pancreatic cancer, sarcomas, thyroid cancer, salivary cancer, gastrointestinal stromal tumors, and cancers of unknown primary.

DRUGS & TARGETS

FDA releases draft guidance on master protocol studies

FDA has published a draft guidance titled "Master Protocols--Efficient Clinical Trial Design Strategies to Expedite Development of Cancer Drugs and Biologics."

Because of the growing interest in master protocol trial designs, which are complex due to concurrent evaluation of multiple drugs and/or disease populations within a single trial, as well as their potential regulatory impact, it is important that the trials are well-designed and well-conducted to ensure patient safety and to obtain quality data that may support drug approval.

This guidance provides advice to pharmaceutical sponsors, the academic community, institutional review boards, and the public on aspects of master protocol designs and trial conduct that pose additional regulatory consideration, such as biomarker development and statistical analysis considerations, and provides advice on the information that sponsors should submit to FDA and how sponsors can interact with FDA to facilitate efficient review.

Sponsors who anticipate developing drugs under a master protocol are strongly encouraged to communicate with FDA early in the development program to obtain feedback on the design of the protocol before submitting an investigational new drug.

Please refer to the guidance for more details.

FDA approves Kyprolis with dexamethasone for relapsed or refractory multiple myeloma

FDA has approved the supplemental New Drug Application to expand the prescribing information for Kyprolis (carfilzomib) to include a once-weekly dosing option in combination with dexamethasone (once-weekly Kd70) for patients with relapsed or refractory multiple myeloma.

The drug is sponsored by Amgen Inc.

The approval is based on data from the phase III A.R.R.O.W. trial, which demonstrated that Kyprolis administered once-weekly at 70 mg/m2 with dexamethasone achieved superior progression-free survival and overall response rates, with a comparable safety profile, versus twice-weekly Kyprolis administered at a dose of 27 mg/m2 in combination with dexamethasone (twice-weekly Kd27). Kyprolis is not approved for twice-weekly 27 mg/m2 administration in combination with dexamethasone alone.

FDA reviewed the application under its Oncology Center of Excellence Real-Time Oncology Review and Assessment Aid pilot programs, which aim to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible. The FDA approved the application in just over one month after the final component of the application was submitted.

A.R.R.O.W. included 478 patients with relapsed and refractory multiple myeloma who received at least two or three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent.

Patients in the trial treated with once-weekly Kd70 achieved a statistically significant 3.7 month improvement in PFS compared to the Kd27 twice-weekly regimen (median PFS 11.2 months for once-weekly Kd70 versus 7.6 months for twice-weekly Kd27; HR=0.69; 95 percent CI: 0.54-0.88; one-sided p=0.0014).

The ORR in patients treated with once-weekly Kd70 was 62.9 percent vs. 40.8 percent for those treated with twice-weekly Kd27 (p<0.0001). In addition, 7.1 percent had complete responses or better in the once-weekly arm versus 1.7 percent in the twice-weekly arm in this refractory patient population.

The overall safety profiles of the two arms in A.R.R.O.W. were comparable, with no new safety risks identified in the once-weekly arm. Discontinuation rates due to adverse events were similar in the two arms. The most frequently reported treatment-emergent adverse events (greater than or equal to 20 percent) in either treatment arm were anemia, diarrhea, fatigue, hypertension, insomnia and pyrexia.

The interim data were presented during an oral session at the 54th Annual Meeting of the American Society of Clinical Oncology and simultaneously published in The Lancet Oncology.
About A.R.R.O.W.

The A.R.R.O.W. (RAndomized, Open-label, Phase 3 Study in Subjects with Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination with Dexamethasone, Compar-

ing Once-Weekly versus Twice-weekly Carfilzomib Dosing) trial evaluated 478 patients with relapsed and refractory multiple myeloma who have received at least two but no more than three prior therapies, including bortezomib and an immunomodulatory drug.

Those included in the study were randomized to receive a 30-minute infusion of once-weekly KYPROLIS (20 mg/m2 on day 1 of cycle 1; 70 mg/m2 on days 8 and 15 of cycle 1; and 70 mg/m2 on days 1, 8 and 15 of subsequent cycles) with dexamethasone (40 mg) versus a 10-minute infusion of twice-weekly KYPROLIS (20 mg/m2 on days 1 and 2 of cycle 1; 27 mg/m2 on days 8, 9, 15 and 16 of cycle 1; and 27 mg/m2 on days 1, 2, 8, 9, 15 and 16 of subsequent cycles) with dexamethasone (40 mg).

The primary endpoint of the trial was PFS, defined as the time from randomization to disease progression or death. Secondary endpoints included ORR, overall survival, and safety and tolerability.

FDA authorizes first next-gen sequencing-based test in patients with ALL, MM

FDA has permitted marketing of ClonoSEQ assay, a next generation sequencing-based test for minimal residual disease in patients with acute lymphoblastic leukemia or multiple myeloma.

The marketing authorization was granted to Adaptive Biotechnologies.

MRD is a measure of the amount of cancer cells remaining in a person's bone marrow.

MRD is a general measure of the amount of cancer in the body, specifically the number of cancer cells that remain in a person's bone marrow, either during or after treatment. Measuring MRD provides a tool to detect very low levels of tumor burden. MRD is useful to evaluate in patients who have responded to therapy when their tumor burden is below what can be detected with standard methods.

The detection of MRD is associated with recurrence of the disease in those patients. Currently, providers test for MRD using diagnostics called flow cytometry assays or polymerase chain reaction-based assays. Those methods are usually capable of measuring MRD down to 1 in 10,000 or 1 in 100,000 cells.

The ClonoSEQ assay is an in vitro diagnostic that uses multiplex PCR and NGS to identify and quantify certain gene sequences in DNA extracted from bone marrow from patients with ALL or multiple myeloma.

The ClonoSEQ assay measures the amount of MRD and is capable of detecting MRD at levels below 1 in 1 million cells. This is a single site assay collected by the patient's provider and sent to Adaptive Biotechnologies Corporation for evaluation.

FDA evaluated data to demonstrate clinical validity from a retrospective analysis of samples obtained from three previously conducted clinical studies including 273 patients with ALL, an ongoing study of 323 patients with multiple myeloma, and a study of 706 patients with multiple myeloma.

For patients with ALL, the ClonoSEQ assay was used to assess MRD at various disease burden thresholds to show that the MRD level correlated with event-free survival—the length of time, after treatment, that the patient remains free of certain complications or events.

Patients whose ClonoSEQ assay result was MRD negative have longer event-free survival, while patients with higher MRD assay results had lower event-free survival rates. For patients with multiple myeloma, the ClonoSEQ assay demonstrated similar associations with progression-free survival—the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse—and disease-free survival—the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer.

FDA reviewed the ClonoSEQ assay through the de novo premarket review pathway, a regulatory pathway for novel, low-to-moderate-risk devices of a new type. Along with this authorization, the FDA is establishing criteria, called special controls, which clarify the agency's expectations in assuring the accuracy, reliability and effectiveness of tests intended to be used as an aid to measure MRD to assess the change in burden of disease during and after treatment.

These special controls, when met along with general controls, provide a reasonable assurance of safety and effectiveness for these tests. This action also creates a new regulatory classification, which means that subsequent devices of the same type with the same intended use may go through the FDA's 510(k) process, whereby devices can obtain marketing authorization by demonstrating substantial equivalence to a predicate device.

FDA approves Libtayo as first and only treatment for advanced CSCC

FDA has approved Libtayo (cemiplimab-rwlc) for the treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

The approval was announced by Regeneron Pharmaceuticals Inc. and Sanofi.

Libtayo is a fully-human monoclonal antibody targeting the immune checkpoint receptor PD-1 and is the first and only treatment specifically approved and available for advanced CSCC in the U.S.

Michael Migden is a lead investigator in the pivotal CSCC clinical program and professor in the Departments of Dermatology and Head and Neck Surgery at MD Anderson Cancer Center.

Libtayo was evaluated by the FDA under Priority Review, and was granted Breakthrough Therapy Designation status for advanced CSCC.

The recommended dosage of Libtayo is 350 mg administered as an intravenous infusion over 30 minutes every three weeks, until disease progression or unacceptable toxicity. Libtayo is available as a single-dose 350 mg vial.

Libtayo is expected to provide significant value for patients with advanced CSCC and those who care for them. The U.S. list price, or wholesale acquisition cost, is $9,100 per three-week treatment cycle.

FDA approval of Libtayo was based on a combined analysis of data from an open-label, multi-center, non-randomized phase II trial known as EMPOWER-CSCC-1 (Study 1540) and two advanced CSCC expansion cohorts from a multi-center, open-label, non-randomized phase I trial (Study 1423). Together, the trials represent the largest prospective data set in advanced CSCC.

The major efficacy outcome measures for the integrated analysis of EMPOWER-CSCC-1 and the two CSCC expansion cohorts were confirmed objective response rate, as assessed by independent central review (ICR), and ICR-assessed duration of response. The efficacy analysis was conducted when all patients had the opportunity for at least six months of follow-up.