Contents

3 Welcome Message from Kevin Hanlon and Bob Hanlon
3 Goals of the Exon 20 Group
4 Kevin Hanlon’s Generosity: The Group’s First Major Gift
6 Poziotinib Report from World Conference on Lung Cancer
8 Preclinical Data Summary of TAK-788
9 Call to Action: Who We Want to Recruit
10 Spotlight on Heidi Greulich, PhD
11 Ask the Experts: Two Exon 20 Insertions?
13 Robert T. Hanlon, PhD: What are the US and Global Exon 20 Populations?
14 Volunteering for the Exon 20 Group
15 Marshall Spiegel: Understanding Clinical Trials and Study Teams
16 Who’s Who at the Exon 20 Group
19 Please Donate to the Exon 20 Group
20 Scott M. Kahn, PhD: Oncogene Addiction and Exon 20
25 Jacqulyne Ponville Robichaux, PhD: Abstracts Tour: Hanmi Data
25 Case Studies: Call for Submissions
26 Eric J. Thompson, PhD: Data Standardization
27 Carey Gold: Effectively Addressing Anxiety
28 Sherry Weinstein: Closing Comments
When informed “you have lung cancer,” my first order of business was simply recovering from the spin…the nearly vertigo-inducing spin…followed quickly by searching for knowledgeable people to help guide, advise, and advocate for me. Our family quickly realized that this battle would not be won by standing alone on an island. The pace at which we were required to absorb, understand, translate, and act upon information was overwhelming. As we began finding similarly situated patients and advocates willing to help, we soon realized we’d be better able to fight alongside these allies…and they felt the same way. Some even had great ideas about how to form and operate an organized working group…they just needed a seed around which to crystallize these ideas. We feel blessed that the Exon 20 Group is that seed.

The Exon 20 Group’s goal is to transform EGFR and HER2 exon 20 insertions into manageable, chronic diseases. To do this we must first find all exon 20 insertion patients in the world and then, working with expert clinicians, provide each with guidance on optimal treatment strategies. Success will require the active participation of both patients and lung cancer experts (oncologists, researchers, pharmaceutical companies, regulatory, pathology, lab testing, etc.). We’ve designed our multi-stakeholder group accordingly. The overarching requirement driving all of this is communication, which brings us to the immediacy of this newsletter. In the belief that knowledge is power, and shared knowledge is even more powerful, we intend to use this newsletter to share valuable content across the many stakeholders in the Exon 20 Group. Thank you for sharing the newsletter with others and for spreading the word to friends and colleagues about joining the group.

Welcome to the Exon 20 Group!

Kevin Hanlon (in hat) and his brother Bob Hanlon

Kevin M. Hanlon  
Founder and Exon 20 Patient

Robert T. Hanlon, PhD  
Co-Founder

---

Goals of the Exon 20 Group

1. Encourage global awareness of profiling NSCLC EGFR and HER2 exon 20 insertions
2. Curate and catalogue response heterogeneity of exon 20 insertion genotypes, post-treatment genetic alterations, and patient outcome data through Remission Coach, our Biobanking, Patient Registry, and Clinical Trials Matching service
3. Expand and accelerate the exon 20 drug pipeline
Kevin Hanlon’s Generosity Supports the Exon 20 Group’s First Major Gift

Scott M. Kahn, PhD
Chairman, ICAN Biomarkers Council

As an exon 20 insertion patient himself, Exon 20 Group Founder Kevin M. Hanlon understood precisely what is needed to conquer EGFR and HER2 exon 20 insertions—a worldwide effort to go after these exceedingly rare lung cancer mutations. Robert T. Hanlon, PhD, Kevin’s brother and co-founder with Kevin of the Exon 20 Group, explained:

Kevin has never shied away from a challenge. Whether as an individual, a family member, an athletic teammate, or a citizen, Kevin has continually led the charge to take on whatever challenge was in the way, helping out others in the process. Exon 20 is the next challenge. He’s had great success in building his own company in upstate New York. Now he’s looking to achieve the same great success in helping to build the Exon 20 Group.

Fueled by the critical need for such a multi-stakeholder coalition, Marcia Horn, President and CEO of ICAN, International Cancer Advocacy Network, and Director of the Exon 20 Group, enthusiastically adds: “Thanks to Kevin’s unswerving generosity, tremendous business sense, and strategic savvy, I have no doubt that all of this is going to happen. Kevin and Bob Hanlon have a compelling vision and plan, and we are going to get there because lives depend upon it.”

Sherry Weinstein, Chair of the ICAN Board of Trustees, remarked: “We know the ambitious goals we all have for the Exon 20 Group are achievable. I am thrilled at the progress we’ve made thus far. We’re delighted that Kevin and Bob Hanlon have launched this effort and are also co-chairing our International Corporate Council as well as the Exon 20 Group Grant Committee.”

By funding the Exon 20 Group’s first major grant of $100,000 to the John V. Heymach, MD, PhD Laboratory at MD Anderson, Kevin is paving the way for the Exon 20 Group at ICAN to become a major philanthropic force. Reflecting on his gift, Kevin was laser-focused:

We want the Exon 20 Group to be a force to be reckoned with. As a patient myself, I’ve come to know several patients on our Patients and Families Council. We all have amazing families we don’t want to leave behind. We have a compelling list of urgent research projects that top physician-scientists who are working with their own world-class labs are tackling for the benefit of patients diagnosed with EGFR or HER2 exon 20 insertions. The only way we are going to tame this rare lung cancer and truly turn it into a maintenance disease versus a lethal diagnosis is to make sure that patients have a drug pipeline that offers them a succession of viable options and not wasted time. What immediately interested me about John Heymach’s laboratory is that he and his tremendous group of clinicians and scientists are zeroing in on the mechanisms of resistance and how and why patients might resist exon 20-specific drugs. By anticipating and outwitting drug resistance from every conceivable angle, the Heymach Laboratory is poised to stay many moves ahead of it and make exon 20-specific agents work longer and better. They’ll be able to figure out what needs to happen if a patient does not respond to an exon 20-specific agent.

John V. Heymach, MD, PhD, Chair of the Department of Thoracic/Head and Neck Medical Oncology, who also holds the David Bruton, Jr. Chair in Cancer Research, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center, expressed optimism about the work his lab is doing and the role the Exon 20 Group is playing in their research:
The Exon 20 Group has already played a critical role in helping connect patients with our poziotinib study [at MD Anderson Cancer Center, NCT03066206], enabling it to enroll patients far ahead of schedule. In fact, we have had to recently expand the study because it was originally projected to enroll 30 patients over two years but, thanks to the Exon 20 Group and ICAN, we enrolled more than 10 patients in the last month alone.

What we are trying to do now is to look ahead and anticipate how these exon 20 mutant tumors might develop resistance to poziotinib, and then develop new drugs or combinations to treat these resistant tumors or, even better, prevent them from emerging in the first place. For our group, the funding is like the jet fuel we need to launch these efforts. Traditional grant funding from the National Cancer Institute (NCI) or other government sources has about a 10% chance of getting funded, and would take a year or more from the time of submission before funding begins. This funding from the Exon 20 Group is particularly important to us because it lets us get to work immediately on the problem that we are addressing in the lab, so that we can then hopefully directly translate our results into benefit for our patients.

Bob Hanlon, who has been involved daily with Kevin and ICAN in the new exon 20 insertion world since March, underscored: “Kevin is passionate about the game plan for the Exon 20 Group. This is not a hobby for him. This is a calling on behalf of patients affected worldwide.”

And Kevin is not about to back down, emphasizing:

*I keep hearing that cancer likes to play multi-dimensional chess, but the brain trust that we’ve assembled at the Exon 20 Group is hopefully going to finally put that cliché to rest, because now exon 20 insertions will have to compete with the likes of John Heymach, Kwok-Kin Wong, and Jacquelyne Robichaux, plus Pasi Jänne, Bob Doebele, Daniel Costa, Michael Eck, Matthew Meyerson, and Heidi Greulich, among many other top minds in the field. It’s a whole new era that we in the Exon 20 Group look forward to embracing with optimism.*

For additional information about supporting the Exon 20 Group, or learning more about the Exon 20 Group’s grant process, please email marcia@exon20group.org.
Drug Yields High Response Rates for Lung Cancer Patients with Harsh Mutation

Scott Merville, University of Texas MD Anderson Cancer Center

MD Anderson Moon Shots Program finds poziotinib strikes EGFR exon 20 insertion

HOUSTON – A targeted therapy resurrected by the Moon Shots Program™ at The University of Texas MD Anderson Cancer Center has produced unprecedented response rates among patients with metastatic non-small cell lung cancer that carries a highly treatment-resistant mutation.

In a phase 2 clinical trial, the drug poziotinib has shrunk tumors by at least 30 percent in eight of 11 (73 percent) non-small cell lung cancer patients whose cancer includes an epidermal growth factor receptor (EGFR) mutation called an exon 20 insertion. Shrinkage ranged from 30 percent to 50 percent among the eight patients reaching partial response. One patient has progressed on the clinical trial, which began in March. All patients experienced some tumor shrinkage.

“We’ve had no effective drugs for these patients, who historically have progression free survival of about two months, and a response rate of less than 20 percent for other therapies,” said clinical trial leader John Heymach, M.D., Ph.D., chair of Thoracic/Head and Neck Medical Oncology at MD Anderson and holder of the David Bruton Junior Chair in Cancer Research. “These early results are highly encouraging, and our research shows that poziotinib’s structure makes it a great potential fit for attacking this mutation,” Heymach said. Preliminary results were presented at the International Association for the Study of Lung Cancer 18th World Conference on Lung Cancer in Yokohama, Japan, by Yasir Elamin, M.D., assistant professor of Thoracic/Head and Neck Medical Oncology.

The investigator-initiated clinical trial marks the latest progress in the identification and development of poziotinib for this group of patients conducted by MD Anderson’s Lung Cancer Moon Shot™, which is co-led by Heymach as part of the institution’s Moon Shots Program™. The program was launched in 2012 to accelerate the development of new approaches to cancer based on scientific discoveries.

About 2 percent of non-small cell lung cancer patients (about 3,500 annually in the United States) have an EGFR exon 20 insertion. The trial has enrolled 27 patients and is expected to enroll up to 50. Other tyrosine kinase inhibitors against EGFR have been approved by the U.S. Food and Drug Administration, but none have proved effective against the exon 20 insertion.

Six of 11 patients have had their dose reduced due to side effects, mainly due to rash but also diarrhea, mucositis and paronychia – inflammation of the tissue around finger nails and toenails.

Preclinical research points to poziotinib vs. exon 20

Poziotinib had been tried and abandoned as a general EGFR inhibitor against lung cancer when Heymach’s team turned up evidence of its potential against exon 20 through a drug screening program that’s part of the moon shot.

Postdoctoral fellow Jacqulyne Robichaux, Ph.D.,
tapped the Genomic Marker-Guided Therapy Initiative (GEMINI), which includes tumor samples and detailed clinical information on more than 4,000 lung cancer patients treated at MD Anderson since 2012.

Robichaux developed EGFR exon 20 NSCLC cell lines as well as patient-derived xenograft models, and tested a variety of EGFR inhibitors against them under the Lung Moon Shot’s drug repurposing program.

“Poziotinib is the only drug we’ve ever found that was dramatically better for exon 20 than it was for the classical EGFR mutation, T790M, that everyone tests,” Heymach said.

Working with Shuxing Zhang, PHARMD, Ph.D., associate professor of Experimental Therapeutics, the multidisciplinary team identified structural aspects of the drug that explain that divergent impact.

Heymach and colleagues then contacted Spectrum Pharmaceuticals, a Nevada-based biotechnology company that initially developed poziotinib. Subsequent collaboration included compassionate use of poziotinib for some patients with advanced disease and rapid development of the phase 2 clinical trial.

Based on the MD Anderson team’s discoveries, the institution is developing intellectual property related to the use of poziotinib for the treatment of these mutant cancers.

The Lung Moon Shot has funded the effort from the beginning, from preclinical identification and confirmation through the clinical trial. A scientific paper describing the group’s preclinical research is pending with a major journal. Spectrum has provided poziotinib and also partially funds the trial.

Co-authors with Heymach, Elamin, Robichaux and Zhang are Vincent Lam, M.D., Anne Tsao, M.D., Charles Lu, M.D., George Blumenschein, M.D., Jonathan Kurie, M.D., and Monique Nilsson, Ph.D., of Thoracic/Head and Neck Medical Oncology; Zhi Tan of Experimental Therapeutics; Julie Brahmer, M.D., of the Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore; Anna Truini, Ph.D., and Katerina Politi, Ph.D., Yale School of Medicine; Adriana Estrada-Bernal and Robert Doebele, M.D., Ph.D., University of Colorado School of Medicine; Shengwu Liu, Ph.D., Ting Chen, Ph.D., Shuai Li, M.D., and Kwok-Kin Wong, M.D., Ph.D., of Perlmutter Cancer Center at New York University Langone Medical School, and Zane Yang, M.D., of Spectrum Pharmaceuticals, Henderson, Nev. Zhi Tan also is a graduate student in the MD Anderson UTHealth Graduate School of Biomedical Sciences.

About MD Anderson

The University of Texas MD Anderson Cancer Center in Houston ranks as one of the world’s most respected centers focused on cancer patient care, research, education and prevention. The institution’s sole mission is to end cancer for patients and their families around the world. MD Anderson is one of only 47 comprehensive cancer centers designated by the National Cancer Institute (NCI). MD Anderson is ranked No.1 for cancer care in U.S. News & World Report’s “Best Hospitals” survey. It has ranked as one of the nation’s top two hospitals for cancer care since the survey began in 1990, and has ranked first 13 times in the last 16 years. MD Anderson receives a cancer center support grant from the NCI of the National Institutes of Health (P30 CA016672).

Reprinted with the kind permission of MD Anderson Cancer Center.

Araldo Caster and Bobbi Johnson, Members of the Exon 20 Group’s Patients and Families Council, met at the University of Texas MD Anderson Cancer Center in October.
Preclinical Data Summary of TAK-788 (formerly known as AP32788) an Exon 20 drug candidate

- Potent inhibitor of:
  - EGFR exon 20 insertions, and also uncommon mutants
  - HER2 exon 20 insertions
- Binds EGFR irreversibly (via Cys797)
- Selective over WT EGFR
- Phase1/2 ongoing (NCT02716116)
- Favorable pre-clinical PK and Tox profile
- AP32788 was acquired by Takeda Pharmaceuticals in early 2017

Reprinted with permission: François Gonzalvez, ARIAD Pharmaceutical, Inc., AP32788, a potent, selective inhibitor of EGFR and HER2 oncogenic mutants, including exon 20 insertions, in preclinical models. April, 2016

AACR Abstract: http://cancerres.aacrjournals.org/content/76/14_Supplement/2644

TAK-788 (AP32788): A potent, selective inhibitor of EGFR and HER2 oncogenic mutants, including exon 20 insertions, in preclinical models


In non-small cell lung cancer (NSCLC), multiple classes of activating mutations have been identified in EGFR and HER2 that vary widely in their sensitivity to available tyrosine kinase inhibitors (TKIs). Erlotinib, gefitinib, and afatinib are approved for use in patients with the most common forms of EGFR activating mutations (ie, exon 19 deletions or L858R substitutions). However, no TKIs are approved for patients with EGFR activated by any other mutation, including exon 20 insertions or other uncommon substitutions, or for patients with any class of HER2 activating mutation (including exon 20 insertions). As inhibition of wild-type (WT) EGFR is associated with dose-limiting toxicities, a TKI that inhibits oncogenic EGFR and HER2 variants more potently than WT EGFR is more likely to be able to be dosed to efficacious levels. AP32788 is a potent inhibitor of all oncogenic forms of EGFR and HER2, including exon 20 insertions, with selectivity over WT EGFR.

Activity of AP32788 and other TKIs was assessed by measuring viability of Ba/F3 cell lines engineered to express 20 mutant variants of EGFR (n = 14) or HER2 (n = 6): 4 EGFR variants containing a common activating mutation with or without a T790M resistance mutation, 8 EGFR/HER2 variants containing an exon 20 activating insertion (eg, EGFR ASV, HER2 YVMA), and 8 EGFR/HER2 variants containing other uncommon activating mutations (eg, EGFR G719A, HER2 G776V). Inhibition of WT EGFR was assessed by measuring effects on EGFR phosphorylation in cells (A431) that over-express WT EGFR. Consistent with their clinical activity, erlotinib and gefitinib generally only inhibited the 2 EGFR variants with common activating mutations more potently than WT EGFR (IC50s 71 and 56 nM, respectively), and afatinib generally only inhibited EGFR with common activating mutations or uncommon substitutions more potently than WT EGFR (IC50 4 nM). In contrast, AP32788 inhibited all 14 mutant variants of EGFR (IC50s 2.4-22 nM), and all 6 mutant variants of HER2 (IC50s 2.4-26 nM), more potently than it inhibited WT EGFR (IC50 35 nM), including all 8 variants with exon 20 activating insertions. In mice implanted with a patient-derived tumor containing an EGFR exon 20 activating insertion, or with engineered Ba/F3 cells containing a HER2 exon 20 activating insertion, once daily oral dosing of AP32788 induced regression of tumors at doses that were well tolerated (30-100 mg/kg). In vivo efficacy was associated with inhibition of EGFR signaling in the tumor.

AP32788 potently inhibited all activated forms of EGFR and HER2 tested, including exon 20 insertions, more potently than WT EGFR, suggesting it may have the selectivity necessary to achieve efficacious levels of exposure in patients. A phase 1/2 clinical trial of AP32788 in NSCLC patients was initiated in early 2016.

Reprinted with the kind permission of Takeda Oncology.
Call to Action

The Exon 20 Group is recruiting:

- Exon 20 Insertion Patients
- Thoracic and Medical Oncologists
- Exon 20 Scientists
- Physician-Scientists
- Molecular Pathologists
- Molecular Profiling Laboratory Scientists
- Pharma Scientists and Executives
- Biotech Scientists and Executives
- Patient Advocates
- Regulatory Affairs Experts
- Payers

We would love to include YOU in the Exon 20 Group!
Information: 602-618-0183 exon20@exon20group.org
Spotlight on Heidi Greulich, PhD

Introducing Heidi Greulich, PhD, Senior Group Leader at The Broad Institute, for the first in our Exon 20 Group Spotlight series of interviews with leading molecular biologists and other scientists in the exon 20 insertion field.

Indelible News: You began your work on EGFR exon 20 insertions many years ago in collaboration with Dr. Matthew Meyerson, who runs one of the top cancer genomics labs, with a major effort on EGFR. Tell us a little about your background and what prompted you to focus on this rare mutation area.

Heidi Greulich: Dr. Meyerson and I and several other colleagues had an interest in a class of proteins, termed tyrosine kinases, and specifically whether recurring mutations in this enzyme class could be identified by systematic sequencing of the genes coding for these kinases in DNA from human tumor samples. Back when we started, sequencing was so expensive that we only had the funding to sequence two short regions of the proteins known to be involved in regulation of activity. Luckily, this was enough to identify mutations of the Epidermal Growth Factor Receptor, or EGFR, in lung cancer samples, and then we could commit to sequencing the full-length EGFR gene in lung cancers. Through our work and the work of colleagues at MGH and MSKCC, it was determined that these mutant forms of EGFR promoted cancer, but also conferred sensitivity to the first-generation EGFR inhibitors, erlotinib and gefitinib.

Soon after we made these discoveries, we came across a new type of mutation in exon 20 of EGFR that promoted cancer but did not confer sensitivity to the first-generation EGFR inhibitors in the laboratory. Second-generation inhibitors, such as afatinib, showed some activity in cell and animal models but, due to toxic effects on normal EGFR in noncancerous cells, could not be dosed high enough in patients to elicit a therapeutic response. Because there are no FDA-approved targeted therapies for patients harboring these exon 20 insertions, we’ve had an ongoing interest in what can be done to combat activity of this mutation class.

Is there any way to describe in simple terms what an exon 20 insertion is?

On one level, exon 20 insertions are exactly what they sound like: insertion of extra DNA into the EGFR gene. Going back to high school biology class, DNA codes for RNA, which codes for protein. However, the protein-coding sequences, or exons, for a particular gene are interrupted by unused sequences, called introns. These introns are coded by the DNA but spliced out of the RNA before the RNA is used as a template to make a protein. Exon 20 is the twentieth of these interrupted coding sequences in the EGFR gene, slightly more than halfway along the length of the gene.

An amino acid in a protein is coded for by three nucleotides (base pairs) of DNA and RNA. Now, you can imagine that adding anything except a multiple of three nucleotides would completely mess up the protein sequence, since parts of the three nucleotides of the resulting RNA coding for one amino acid would all of a sudden be used to code part of the next one. Such out-of-frame insertions and deletions also frequently cause premature termination of an amino acid sequence, resulting in shortening or even complete degradation of the encoded protein. However, the cancer-causing exon 20 insertions are always “in-frame,” or found in multiples of three nucleotides, meaning they preserve the original amino acid sequence coded for by the normal EGFR gene following the insertion.
Are there any theories of why exon 20 insertions are highly heterogeneous? How many total exon 20 insertions are there, at last count?

It’s currently not clear why there are so many different insertions in EGFR exon 20. Interestingly, there seem to be a more limited selection occurring in the related cancer gene, ERBB2 (HER2). I have to admit, I don’t actually know the total number of different EGFR exon 20 insertions that have been found in patients so far, but it is likely on the order of 40-ish, or even more. That being said, there are some that occur at higher frequencies, such as the V769-D770insASV or the D770_N771insSVD. In this shorthand nomenclature, the capital letters refer to amino acids and the numbers refer to the position in the protein. These two higher frequency insertions are therefore: insertion of alanine-serine-valine between valine 769 and aspartate 770 of EGFR, or insertion of serine-valine-aspartate between aspartate 770 and asparagine 771 of EGFR. In each of these two examples, nine nucleotides of DNA were inserted into the EGFR gene to code for the three new amino acids in the mutant EGFR protein.

As a senior group leader at the Broad Institute with your impressive background at Dana-Farber Cancer Institute, are you continuing your work with DFCI and are you collaborating with other medical teams and other exon 20 labs in the US or abroad?

We are currently focused on development of new drugs that specifically target the EGFR exon 20 insertions, a task made more complicated by the wide variety of insertion sites and inserted amino acids. If we are successful in this endeavor, we will want to collaborate with as many other medical teams as possible!

We’ve discussed Sloan Kettering’s Maria Arcila and her pivotal study on the variety of exon 20 insertions. What the Exon 20 Group will be doing via our Remission Coach Patient Registry/Clinical Trials Search Engine is cataloging every exon 20 insertion, whether EGFR or ERBB2 (HER2) based on Exon 20 Group patients worldwide who join our Registry. In addition to collecting patient outcome data plus additional genetic alterations as seen from post-treatment tissue and liquid biopsies, what other data points in addition to amino acid position and amino acid mutation should we be collecting from our laboratory medicine and clinician members regarding the exon 20 insertion sequences they are dealing with?

You’ve done a pretty good job of defining the important data already. Age and smoking status would also be helpful from a research point of view, although the majority of exon 20 insertions appear to occur in patients who do not smoke. Also, following on the elevated frequency of drug-sensitive EGFR mutations found in females and East Asians, gender and ethnicity would be helpful to understand the etiology of these cancers. We don’t necessarily expect mutations in other genes to play a role in cancer development in exon 20 insertion patients, but there will come a day when we understand more about how mutations in different genes interact to cause or even mitigate cancer, and these data will be helpful too.

The Broad Institute is, of course, associated with leading-edge technological advances in the molecular oncology space. What advances do we need to see in sequencing or other technology to fully understand exon 20 insertions?

Same lab, same patient, two different exon 20 insertions reported. What’s going on?

Here is what his lung tumor showed:
EGFR Exon 20 c.2307_2308 Insertion GACAAC  D770_N771dup

Here is what his brain metastasis showed (same lab 17 months later):
EGFR Exon 20 n.1249_1254dupGTTGTC  p.V769_D770insVV

Calling all experts—molecular pathologists, exon 20 scientists, and thoracic oncologists: What does this seem like to you? Aren’t the chances for two separate exon 20 insertions next to none?

Ask the Experts:

Please write us if you have comments at exon20@exon20group.org
Please let us know if we can quote you by name in the next issue!
I think the sequencing technology that we need is all in place. The next scientific frontier in EGFR exon 20 insertion sequencing will include single cell sequencing before and after treatment to better understand heterogeneity in the tumor, both upon diagnosis and in response to traditional chemotherapy and targeted therapies currently in clinical trials.

That being said, I think it’s important that every exon 20 insertion patient and their oncologist know the exact nature of their insertion, in terms of position in EGFR exon 20 and amino acids inserted. This is currently most important for patients with an A763_Y764insFQEA mutation, as Dr. Daniel Costa and colleagues have shown that patients with this particular mutation can respond to erlotinib. We also have preliminary data that indicate that response to inhibitors may depend on the exact location of the insertion within exon 20. This information may someday, hopefully soon, influence choice of targeted therapy. So the point I’m trying to make is that the relevant sequencing technology needs to be available in a diagnostic setting to all lung adenocarcinoma patients, and this is not yet the case.

In addition to the exon 20-specific agents that the Exon 20 Group is following — and we have Exon 20 Group patients in all relevant clinical trials — you are a firm believer that the space needs a new class of agents altogether. Would you give us an idea of what is involved in the discovery and development of new drugs with novel mechanisms of action that could target exon 20 insertions and what exon 20 insertion researchers worldwide need to prioritize in order to meet the research challenges that your lab has identified?

I’d like to start by saying that I would be thrilled for exon 20 insertion lung cancer patients if any of the agents currently in clinical trials proved to be effective. My only concern is that not all of them were developed to minimize activity against the normal EGFR in noncancerous cells compared to EGFR exon 20 insertions, so it is unclear if they can be dosed at high enough levels to combat the exon 20 EGFR without significant toxicity. But the clinical trials will provide the answer. Our other concern is that different agents may need to be developed for patients with different exon 20 insertions. Again, clinical trials will answer this question. In the meantime, the search for new and effective small molecules should continue, focusing on specificity for exon 20 insertions and selecting against activity toward the normal EGFR in noncancerous cells.

In terms of genetic mutations that co-exist with exon 20 insertions as seen on post-treatment tissue or liquid biopsies, do you see any candidates for targeted agents that could be accelerated into combination clinical trials with either EGFR-TKIs — to give them new life and resonance with the exon 20 insertion patient subgroup or perhaps that could be added to the various immunotherapies that are currently available?

The major cancer-causing mutations in lung cancer tend to be mutually exclusive, so there aren’t any obvious candidates for combination therapy. Combination with immunotherapy is an intriguing approach though.
What is a typical day in your lab?

I currently have teams working on EGFR exon 20 insertions, as well as a novel small molecule with anti-cancer properties, DNMDP. I spend a significant part of each day meeting with my colleagues. Keeping all this research on track is a full-time job, although I do try to sneak experiments in when I can.

You were the advocate for your dad when he was battling lung cancer. Do you have any advice, based on your experience, for families who are immersed in this ever-challenging journey?

I was surprised by how powerless I was to help my father, even though I’ve studied lung cancer for over 10 years. Even to this day, it is not clear to me that his EGFR was ever sequenced. His oncologist said it was and the results were negative, but I was not able to track down a copy of the results. I can’t emphasize enough how important it is that a patient be able to obtain test results, such as EGFR sequencing, that could influence treatment. And then, at a certain point, supporting my father in a way that he could make the most of what time he had left became more important.

If you weren’t working on exon 20 insertions, what would be the top priorities of your group in addition to your ongoing work on DNMDP?

We have an ongoing interest in sifting through tumor sequencing data to find recurring mutations in cancer genes that might be suitable targets for therapy. We have several publications in this area, but would like to continue making an impact by finding new targets to help cancer patients for whom no targeted therapy is currently available.

Thank you so much, Dr. Greulich. We wish you the very best in your ongoing work.

My pleasure. My colleagues and I at the Broad Institute will continue to follow the Exon 20 Group’s activities and initiatives with interest.

Dr. Greulich will be the Keynote Speaker at the Lung Cancer Research Foundation’s Twelfth Annual Lung Cancer Awareness Luncheon on Wednesday, November 1, 2017 at The Pierre, in New York City, Noon to 2:00 PM. For information, please contact Mollie Wein at LCRF at 212-588-1580.

What are the US and Global Populations of Exon 20 Insertion Patients?

Robert T. Hanlon, PhD, Co-Founder, Exon 20 Group

The best estimate of the number of Exon 20 patients diagnosed each year in the United States is about 3,500.

- 225,500 new lung cancer cases are diagnosed each year in the US.
- Non small cell lung cancer (NSCLC) cases are 80% to 85% of all lung cancer cases.
- Exon 20 Insertion Patients = 2% of the NSCLC patients, or approximately 3,500.

Given the lack of testing/profiling for Exon 20 insertions, it could be higher in the U.S. and around the world. Do you have a different calculation for U.S. patients?

And, we ask our international readers, or those with international experience, to weigh in with estimates of Exon 20 patients around the world. Do you have a number for anticipated global cases and/or cases by country or region of the world? Please write us at exon20@exon20group.org, and we will publish the feedback that we receive in the next issue of Indelible News.
Exon 20 Group Volunteer Opportunities

Spread the Word!

Please consider volunteering or recruiting your clinical staff, your study teams, colleagues, family, and friends for one or more of the following activities:

1) **Fundraising** — help to create an Exon 20 Group Grant Committee that funds major exon 20 research projects to speed the drug pipeline. We are launching a multi-million dollar campaign to increase our clout and to become a major grantor for drug discovery and drug development projects. Please reach out to your circles of influence who might be able to help us solicit major gifts. The Exon 20 Group needs to be able to fund gaps in exon 20 insertion research as well as speed the clinical trials pipeline.

2) **In-kind Donations** — seek out and recruit in-kind donors (for example, printing services for our global awareness and outreach campaigns).

3) **Social Media Team** — suggest articles from the Literature team/NewsWire E-Blast team to post on our Facebook page; suggest tweets for @Exon20Group; help with Constant Contact e-blasts. We also need a team who will help us monitor social media sites — Inspire.com and other sites — to send, if appropriate, invitations to new members of the Exon 20 Group.

4) **Journal and Abstract Review** — proofread, select, and organize medical and scientific journal articles and abstracts collated by other volunteers for upload to our exon20group.org website (under construction). We also need help with finding relevant articles through pubmed.gov and other medical/scientific journal websites.

5) **Key Word Searches** — find articles on key words that we are following via Google Alerts (and academic journal alert systems). Your searches would greatly contribute to our news/articles digests. We need as many volunteers as possible to cover many topics.

6) **Buddy System** — serve as a buddy for a current patient or patient family member. We are also creating an optional mentor-mentee system for newly diagnosed exon 20 patients who lack a support system in their lives.

7) **Raise Awareness** — send an email to oncologists, molecular profiling laboratory executives, and/or scientists we want to recruit to the Exon 20 Group. We will provide the email text to you. Go one step further by joining the Membership Committee of the Exon 20 Group and meet with oncologists in your city to invite them and their patients to join the Exon 20 Group. If you can’t meet directly with oncologists, then please deliver handouts and invitations to their chief nurses or practice managers to set in motion their oncologists receiving our invitations.

8) **Speakers’ Bureau** — join the Exon 20 Group Speakers’ Bureau, especially if you have public speaking experience.

9) **Welcome Wagon** — send a Welcome Letter by email to new members of the Exon 20 Group. We will provide the Welcome Letter to you.

10) **Administrative Assistants** — help us finalize letters in Microsoft Word/Adobe PDF; join our database entry team; provide Excel spreadsheet or PPT design support, as needed.

11) **Expert Bank** — obtain, organize, and update bios and photos of oncologists, scientists, and other experts on the Exon 20 Group for presentation on the website and in other materials.

12) **Ambassador** — become one of our ambassadors in your country and handle some “PR” and outreach assignments for the Exon 20 Group.

We welcome your suggestions for other volunteering opportunities. Please send an email to Marcia Horn at marcia@exon20group.org or Carole Klein at crklein16@gmail.com to volunteer for any of these activities or to give us your ideas for other volunteering activities!

Janet Belltaylor, Fundraising
Paula Hockster, Chair, Social Media
Bobbi Johnson, Social Media and Speakers’ Bureau
Susan Johnson, Chair, Patient Rendezvous
Carole R. Klein, JD, Chair, Abstract Review
Araldo Caster, Xing Luo, and Hilary Shaw, Ambassadors
Understanding Clinical Trials and the Work of Clinical Trials Study Teams

Carole R. Klein, JD and Kendall Palmer

Marshall Spiegel, formerly Clinical Research Coordinator in the Thoracic Oncology section of UCLA's Jonsson Comprehensive Cancer Center, recently spoke to the Exon 20 Group Patients and Families Council about clinical trials and the drug development process. Here are highlights from Marshall’s presentation:

- Drug development is a long and expensive process. The majority of drugs fail in the preclinical phase, often after significant investments of time and money. The few drugs which survive the preclinical phase move on to testing in humans through clinical trials.

- Patients and families seek out clinical trials for life-saving cures, but, because clinical trials are a form of human experimentation, there are organizations and mechanisms in place, including the Food and Drug Administration (FDA), agencies, Institutional Review Boards (IRBs), and federal and state laws to ensure that human participants are protected and that the trials further scientific discovery. Clinical trials must balance the protection of trial participants and the scientific inquiry and protection of people. It would be unethical to test drugs in a way that endangers patients and fails to provide knowledge on the safety and effectiveness of the drugs for future patients.

- The screening process for participation in clinical trials is often very frustrating for patients. There may be a sense of “hurry up and wait” as the patient may have to quickly complete screening requirements, but then may have to wait for approval from the doctor or study coordinator to enter the trial.

- The inclusion and exclusion criteria for clinical trials are often complicated, and a patient may not qualify or experts may disagree on whether a patient qualifies. Larger trials may require confirmation from multiple experts in multiple time zones or countries.

- A patient should ask assertively, but politely, about his or her qualification for a trial, how long it will take to get an answer, and whom to call with questions the patient or family may have.
Who’s Who at the Exon 20 Group*

**Honorary Chairs**

Kenneth J. Bloom, MD  
*Human Longevity, Inc.*

John V. Heymach, MD, PhD  
*MD Anderson Cancer Center*

Bruce E. Johnson, MD  
*Dana-Farber Cancer Institute/President, ASCO*

Razelle Kurzrock, MD  
*UCSD Moores Cancer Center*

Tony Mok, MD  
*Chinese University of Hong Kong/Prince of Wales Hospital*

**Founding Co-Chairs**

Kevin M. Hanlon

Robert T. Hanlon, PhD

**Physician-Scientists**

Daniel B. Costa, MD, PhD, MMSc

Pasi A. Jänne, MD, PhD

Robert C. Doebele, MD, PhD

Kwok-Kin Wong, MD, PhD

**Medical Oncologists/Thoracic Oncologists**

Mehmet Altan, MD

Geoffrey R. Oxnard, MD

Christina S. Baik, MD

Vassiliki A. Papadimitrakopoulou, MD

Pavel Bezecny, MD

Sandip Patel, MD

Collin Blakely, MD, PhD

Zofia Piotrowska, MD, MHS

Young Kwang Chae, MD, MPH, MBA

Gregory J. Riely, MD, PhD

David Chu, MD

Jonathan Riess, MD, MS

Jeffrey Melson Clarke, MD

Michael Roberts, MD

Edward B. Garon, MD

Anthony J. Scalzo, MD

Sarah B. Goldberg, MD, MPH

Mark A. Socinski, MD

Fred R. Hirsch, MD, PhD

Benjamin Solomon, MBBS, PhD

Thomas John, MBBS, PhD

Alexander I. Spira, MD, PhD, FACP

Timothy Kasunic, MD

Daniel SW Tan, BSc, MBBS, MRCP

Edward S. Kim, MD

Nishan Tchekmedyian, MD

Sylvia M. Lee, MD

Christina To, MD

J. Paul Marcoux II, MD

Victor E. Velculescu, MD, PhD

Mark V. McNamara, MD

Heather A. Wakelee, MD

Barb Melosky, MD, FRCPc

H. Jack West, MD

Paul Mitchell, BHB, MBChB, FRACP, MD

Rudolph Willis, MD

Robert Nagourney, MD

James Chih-Hsin Yang, MD, PhD

**Anatomic Pathologists and Molecular Pathologists**

Dara L. Aisner, MD, PhD

Anthony Magliocco, MD

Suzanne Kamel-Reid, PhD, FACMG

Katerina Politi, PhD

Roger Klein, MD, JD

Qingmei Xie, MD

*We regret if we have inadvertently omitted your name or if you have joined the group after our printing deadline. We would love to have your involvement. Please email marcia@exon20group.org to join the Exon 20 Group.*
Exon 20 Scientists
Michael J. Eck, MD, PhD
Heidi Greulich, PhD
Matthew L. Meyerson, MD, PhD
Jacquelyne Ponville Robichaux, PhD

Pharmaceutical and Biotech Companies
AstraZeneca
Genentech
Pfizer
Roche
Takeda Oncology
Spectrum Pharmaceuticals

Laboratory Medicine
Biocept
Cancer Genetics, Inc.
Caris Life Sciences
Foundation Medicine
Geneseeq
Guardant Health
Human Longevity, Inc.
The Jackson Laboratory
Nagourney Cancer Institute
Paradigm Diagnostics
Personal Genome Diagnostics
Phosphorus
Tempus

Interventional Radiologists
Charles Nutting, DO

Radiologists
Mitchell Achee, MD
Gregory Goldstein, MD

Clinical Research Coordinators
Marshall Spiegel, Chairman
Karen J Núñez, MS
Dahlia G. Mack

Patients and Families Council
Shelly and Steve Allen
Janet Belltaylor, Fundraising
Araldo Caster, Exon 20 Group Liaison to the Netherlands
Laurel Davis
Spencer Davis-VanNess
Nica Digmon
Mindy and Chad Erickson
Elena Gershanov, Abstracts Committee
Paula Hockster and Phil Lindquist, Chairs, Social Media
Dawn and Greg Horner
Bobbi Johnson, Social Media and Speakers’ Bureau
Rita Ryan Johnson and Richard D. Johnson
Susan and Sherman Johnson, Outreach
Robbi and Jeremy Killen
Carole R. Klein, Chairman, Abstracts
Xing Luo, Liaison to China
Liba Mikula
Katerina Mikula
Pavla Mikula, Web Research Committee
Bhavya Nag
Kendall Palmer, Advisor
Ross and Mark Richardson, Fundraising
Cynthia Romero
Sylvia Romero
Adriana Saucedo
Hilary Shaw, Liaison to the UK
Rita and Roy Staring
Fran Phillips Taft and Stephen M. Taft, Abstracts Committee
Zuxiang Tan
Lynn and Tom Theobald, Advisors
Rachel Frey Zanardi
**SPECIAL ADVISORS**

Janet Freeman-Daily
Carey Gold
Kim Norris

Steven Young
Winnie Yu
Colleen Zogby, RN

**ATTORNEYS’ COUNCIL**

Mark H. Kolman, JD, Chairman
Kirk T. Hartley, JD, Co-Chair
Ann Theobald Hollenbeck, JD

Carole R. Klein, JD
Mark L. Richardson, JD
Fran Phillips Taft, JD

**EXON 20 GROUP GRANT COMMITTEE**

Kevin M. Hanlon and Robert T. Hanlon, PhD, Co-Chairmen

**ICAN EXECUTIVE LEADERSHIP AND DIRECTOR, EXON 20 GROUP**

Marcia K. Horn, JD
President and CEO
ICAN, International Cancer Advocacy Network

www.exon20group.org 602-618-0183 (direct)
exon20@exon20group.org 602-926-8109 (fax)

Twitter: @Exon20Group

**ICAN BOARDS AND COUNCILS**

Sidney M. Rosen, Esq.
*Founding Chairman*

Sherry Weinstein
*Chairman, Board of Trustees*

Cheryl J. Hintzen-Gaines
*Honorary Chairman, Board of Trustees*

Robert H. Tamis, MD
*Chairman, Physicians Council and Lead Inventor, Remission Coach*

G. Robert Pettit, PhD
*Chairman, Scientific Advisory Council*

Scott M. Kahn, PhD
*Chairman, Biomarkers Council*

Linda Jenckes
*Chairman, Federal Affairs and Strategic Alliances*

Carey Gregory
*Chairman, Board Governance*

Cathy Dalzell
*Chairman, Advisory Council*

Kevin M. Hanlon and Robert T. Hanlon, PhD
*Honorary Co-Chairmen, International Corporate Advisory Council*

Mark Mondavi
*Honorary Chairman, International Board of Advisors*

Jeff Veness
*Chairman, California Board of Advisors*

Chuck Clayton
*Chairman, Texas Board of Advisors*

Mitchell Achee, MD and Gregory Goldstein, MD
*Co-Chairs, Radiology Council*

Charles Nutting, DO
*Chairman, Interventional Radiology Council*

Anthony Magliocco, MD
*Chairman, Molecular Pathology Council*

Steve Horn, PhD
*Director, Governmental Relations*

**ICAN VOLUNTEERS: PATIENT SERVICES AND RESEARCH SERVICES**

Regina Marie Klopfef, Director, Research Services and Strategic Planning
Andrew Young, III, Director, Global Volunteer Network
Ashraf Said Abdel-Ghany, Research Team Leader
Shelley Blam, PhD, Research Team Leader
Christian Brian, Research Team Leader
Arpan Dahal, Research Team Leader
Neha Ramjuttun, MBBS, Research Team Leader

Shom Teoh, Research Team Leader
Sushma Sangita Thiruvoipati, MBBS, Research Team Leader
Jeff Wiese, Research Team Leader
Nouran Amin, Web Research Intern
Avani Karvat, PhD, Executive Assistant, Research Services
Karishma Borse, MBA, Executive Assistant, Research Services
Please Consider a Gift to the Exon 20 Group!

Please consider naming “the Exon 20 Group at ICAN, International Cancer Advocacy Network (EIN 86-0818253)” as recipient of a charitable gift. All donations to the Exon 20 Group are fully deductible, as ICAN is a 501(c)(3) charitable organization, EIN 86-0818253. [http://www.askican.org](http://www.askican.org)

**Charitable Giving Options**

1. **IRA Charitable Rollover** — if you are at least age 70½, then:
   a. You may make a tax-free gift from your IRA
   b. Up to $100,000 per person in a calendar year
   c. Gift will count toward required minimum distribution
   d. Plan administrator must transfer funds directly to charity

2. **Gifts from your Estate** — A bequest from your estate costs nothing now and allows you to retain the control and use of the assets during your lifetime. Depending on the size of your estate, a charitable request can reduce estate taxes. Options include:
   a. Will or a Living Trust
   b. Pension, or another retirement account such as a 401(k) or a 403(b) plan
   c. Beneficiary under a Life Insurance Policy

3. **Current Gifts** — A current gift generally results in an immediate charitable income tax deduction that will reduce your current income tax liability. Options include:
   a. Cash
   b. Appreciated Securities
   c. Real Estate
   d. Art
   e. Complex Assets
   f. Transfers from Donor Advised Funds

4. **Gifts that also pay you an Income Stream** (along with a charitable income tax deduction)
   a. Charitable Remainder Trust – this trust can also be used to avoid capital gains tax on the sale of appreciated assets
   b. Charitable Gift Annuities

5. **Other vehicles to support the Exon 20 Group at ICAN**
   a. Charitable Lead Trust – trust is generally used to allow current payments to the charity with remainder of assets to family
   b. An earmarked tax-deductible donation to the Exon 20 Group at ICAN

For additional information regarding how to make a fully tax-deductible gift to ICAN, strictly earmarked for the Exon 20 Group, please call ICAN’s Planned Giving Council at 602-861-3777 or email plannedgiving@askican.org.
Oncogene Addiction and Exon 20-Specific Agents

Scott M. Kahn, PhD

As the Exon 20 Group spearheads and facilitates efforts to expedite the development of novel targeted therapies against EGFR and HER2 exon 20 mutations, I wanted to take this opportunity to reflect upon the recent presentation by Dr. John Heymach and his terrific group, and how their research puts into practice our early vision for the use of targeted therapies when we developed the theory of “Oncogene Addiction” in the 1990s.

The epidermal growth factor (EGFR) gene on human chromosome 7p11.2 is a common mutational target in lung cancer, as well as in other tumor types (Figure 1). Transforming mutations that affect the ATP binding site domain result in a constitutively activated, oncogenic protein that promotes cell growth. The more common EGFR mutations detected in tumors became an early focus for biopharma, and clinically effective targeted drugs were developed that bind to its ATP pocket and inhibit EGFR activation. However, as the Exon 20 Group is well aware, these targeted drugs are ineffective for the minor, but consequential subgroup of patients with EGFR exon 20 insertion mutations in the EGFR (Figure 2), and who present in the thousands every year.

During Dr. Heymach’s inspirational presentation to the Exon 20 Group Patients and Families Council this September, he provided structural evidence for why currently approved EGFR inhibitors do not work in these patients. Simply put, exon 20 insertions induce positional changes within the ATP binding site that affect the conformation of the binding pocket and preclude earlier drugs from fitting in. He has screened a panel of molecules to identify those that possess the correct stereochemistry to fit snugly into the pocket of EGFR exon 20 insertion mutants. One such molecule, poziotinib, fits the bill. Not only does it bind to and inhibit exon 20 insertion mutants used in initial screening assays, it inhibits all known EGFR exon 20 insertion mutants. And at therapeutically relevant concentrations. Perhaps most promising, Dr. Heymach stated that all known exon 20 EGFR insertions tested to date appear to be oncogenic drivers of cancer. Thus, according to Dr. Heymach, poziotinib could be an effective therapy for lung (and perhaps other) cancer patients whose tumors exhibit EGFR exon 20 insertions, as these cancers exhibit “Oncogene Addiction.”

Please allow me to diverge a bit here, and share with you personal anecdotes from earlier in my research career. In this, and succeeding articles, I thought it might be interesting for the Exon 20 Group to offer a glimpse into the evolution of personalized medicine from my research group’s perspective, acknowledging that this is one of many. Many researchers at the time shared a vision for personalized medicine. Following the discovery of cellular oncogenes and activating mutations in tumors in the 1960s through 1980s, it was a common idea that future cancer therapies would focus on genetic changes in tumors. Such visions were in place years ahead of available technologies. The “–omics” era has fostered technological advancements that have ushered in the early stages of personalized medicine, and more and more companies and researchers are now developing targeted therapies.

The work that Dr. Heymach, his colleagues, and other researchers are performing in the area of exon 20 mutations is remarkable. As a member of the Exon 20 Group, it is humbling that in some small way, our work at Columbia University on the theory of “Oncogene

Indelible News
Addiction," may have offered a theoretical nugget of support for such work.

The late 1980s were an exciting time in cancer research. Oncogenes were being discovered, their functions were being elucidated, technologies were evolving, and the field was deconstructing the cellular signaling pathways that drive cancer cells. The first biotechnology companies were being established to develop protein-based drugs. And, applications of the polymerase chain reaction were revolutionizing all aspects of cancer research.

One of the foremost cancer research scientists of that time was I. Bernard (Bernie) Weinstein, who was Director of Columbia’s Comprehensive Cancer Center, now known as the Herbert Irving Comprehensive Cancer Center, and President of AACR. A true mensch and a thought leader’s thought leader, Bernie had a formidable mind, able to tackle and distill the most complex questions in cancer biology. The road to his office, overlooking the Hudson River on 168th Street in New York, was worn with the footprints of the world’s top cancer scientists. Among Bernie’s many contributions, his model of multistage carcinogenesis—initiation, promotion, and progression, provided a fundamental framework that guided cancer research throughout the 1980s and 1990s. Bernie was also one of the great mentors, having trained many renowned students. Among these were Mike Wigler, who discovered the cellular H-ras gene and has gone on to a remarkable career at Cold Spring Harbor Laboratory as one of the leading geneticists of our time, and Richard Axel who was awarded the Nobel Prize in Physiology or Medicine in 2004, in recognition of his pioneering research on the molecular biology of smell. Mike and Richard co-developed and patented gene transfer methodologies for mammalian cells while working with Bernie, providing a lucrative royalty stream for Columbia from some of the first biotechnology companies to generate therapeutic proteins in mammalian cells.

In the fall of 1988, I joined Bernie’s research group. The passion and excitement shared amongst his group members was pervasive, and the group approached its research with a combination of optimism and conviction. On my very first day in Bernie’s group in 1988, I invented what rapidly became a state of the art PCR-based biomarker assay to detect ras gene mutations in tumors. Thus, we were able to test tumor samples and obtain results within hours, whereas prior methodologies usually incorporated radioactivity, and required days to complete. This creativity seemingly impressed Bernie, and he released me from being assigned to specific grant funded projects. In early 1989, we became interested in the genetics of esophageal cancer, as a colleague from China had access to precious samples from an area of high incidence. We noted that a specific region on chromosome 11q, band 11q13, was often amplified in esophageal tumors. The human genome project was still a long way off, and relatively few genes had been assigned to their chromosomal locations. The 11q13 region was the focus of intense research. A number of groups around the world were investigating two genes in particular, Int2 and Hst1, which were located on this amplicon and implicated in other cancer types. However, neither was expressed in esophageal tumors, so we did not believe these two genes to be causative. While perusing through heavy journal binders well...
before Pubmed became available to relieve our biceps, we had our “aha moment.” We had come across a recently published report of the human cyclin D1 gene, a major positive regulator of the cell cycle, as being located on chromosome 11q13 (Figure 3). We quickly demonstrated that cyclin D1 was both amplified and overexpressed in esophageal tumors. When normal cells are stimulated by growth factors to undergo replication and cell division, a signaling cascade causes cyclin D1 to form an active complex with a cell cycle kinase (cdk4 or cdk6). This active complex enables cells to enter the cell cycle (the G0 to G1 transition), and prepare for subsequent DNA replication and mitosis. We demonstrated that overexpression of cyclin D1 hastens this G0 to G1 transition, and that it malignantly transforms cells.

We also noticed that when cyclin D1 was amplified in cancer cells, the expression of certain other cell cycle regulatory genes that normally inhibit the function of the cyclin D1-CDK complex became elevated as well. These changes were seemingly an attempt by cells to reprogram themselves to reestablish an equilibrium between cell cycle activation and cell cycle inhibition. Over the course of many discussions in Bernie’s office, we concluded that in order for cancer cells with amplified cyclin D1 to survive, there must be an exquisite balance of expression established to produce

an equilibrium between levels of cyclin D1, the cell cycle activator, and its inhibitors. Cancer cells actively, and perhaps irreversibly, reprogram their cellular signaling and feedback networks to enable survival and proliferation.

Thus, to overcome elevated levels of inhibitory factors, esophageal cancer cells with amplified cyclin D1 would require ongoing overexpression of cyclin D1 to maintain their survival. They were “addicted” to elevated cyclin D1 levels. If cyclin D1 expression could be inhibited, these cells would succumb due to their continued elevated levels of cell cycle inhibitors. In fact, such experiments by colleagues in our group clearly showed this indeed to be the case.

Bernie then expanded this idea to cells that had been malignantly transformed by the overexpression of protein kinase C, a modulator of certain receptor-mediated growth signaling pathways. Malignant cells that were ‘addicted’ to elevated levels of protein kinase C expression were demonstrably killed by inhibiting its activity.

So, from our basic interrogation of esophageal cancer evolved the theory of “Oncogene Addiction” (Figure 4). Oncogenes can direct the reprogramming of cellular signaling networks. In certain cases they exert a yin/yang effect on cells, by altering the expression of both positive as well as negative growth signals. For malignantly transformed cells to survive, they would require the sustained activity of oncogenic drivers.

We immediately recognized the fundamental implications that “Oncogene Addiction” has for the treatment of cancer patients. In tumors that display “Oncogene Addiction,” the inhibition of oncogenic ‘drivers’ would kill cancer cells. Thus, the development of targeted therapies could be an invaluable therapeutic tool for cancer patients. Bernie referred to this as the Achilles ‘heal’ of cancer. Indeed, the successes of drugs like Herceptin and Gleevec appear to support this contention.

Fast forward to today, and we are still in the dawn of the Personalized Medicine era. Biopharma and academic labs have developed a number of effective targeted drugs for patients with specific cancer types. Unfortunately, we remain confounded by many cancer types that are not responsive to, or evade targeted therapy-based strategies. The reasons appear to be many, and I believe that we need to understand them with urgency. Cells may re-reprogram themselves to escape the effects of targeted therapies, cells may progress through stages of development where different tumor drivers control growth, cancer cells may acquire secondary mutations in driver genes that render them insensitive to selected targeted therapies, secondary mutations may have already occurred in minor cell populations enabling subpopulations to survive and grow. And, for certain tumor types, “Oncogene Addiction” may simply not be a proper and appropriate model.

However, we remain hopeful that the future is promising. We continue to acquire data on the efficacy of combination targeted therapies and other strategic regimens. Ultimately, computer-based systems biology approaches should enable scientists to reproduce

Figure 3. Cyclin D role in the cell cycle. Mitogenic signals from growth factor receptors, including EGFR cause cells to transition from a resting state (G0), into the cell cycle. Early in the G1 phase, Cyclin D associates with a cyclin dependent kinase (CDK), either CDK4 or CDK6, to form an active complex. This complex phosphorylates target proteins, enabling cells to progress further through the cell cycle. Later stages are mediated by other cyclin-CDK complexes. The activities of cyclin-CDK complexes are negatively regulated by cell cycle kinase inhibitory proteins (Cdkis). Aguilar and Coll, EMBO Mol Med 2010;2(9):338-48
a patient’s cancer cell signaling networks, identify therapeutically responsive signaling nodes, and better predict how a patient will respond to existing therapies. And, where early detection is fundamental to effective treatment, improved diagnostic testing will enable more sensitive screening, if we can bring reimbursement entities onboard.

If ongoing clinical trials with poziotinib, and other exon 20-specific agents in development, and in clinical trials, confirm that tumors with EGFR exon 20 mutations are beholden to “Oncogene Addiction,” we will have a precious addition to our targeted therapy arsenal.

As for Her2, this appears to be a more complex story. According to Dr. Heymach, not all Her2 exon 20 mutations detected in tumors may be oncogenic drivers. Thus, targeted drug development will require a focus on specific activating mutations that confer “Oncogene Addiction.”

The Exon 20 Group is a model for how patients and all relevant stakeholders can drive new drug development. By funding promising initiatives, helping to enroll eligible patients in clinical trials, incorporating a state of the art clinical data management system represented by ICAN’s Remission Coach (in development, not yet launched), and taking other proactive measures, the Exon 20 Group is well on its way to finding needed solutions for cancer patients. I am confident that the Group’s passion, dedication, and focus on urgency will undoubtedly influence future cancer drug development initiatives.

Scott M. Kahn, PhD, has been chairman of ICAN’s Biomarkers Council since 2011 and is continuing to convene molecular tumor boards for ICAN patient cases while working with pharmaceutical and biotech members of the Exon 20 Group.

---

**Figure 4. Model of Oncogene Addiction.** In normal cells, numerous prosurvival signals (thin green arrows) predominate and keep the various pro-apoptotic (cell death) stimuli (thin red arrows) in check. In cancer cells, the activation of an oncogene results in an oncogene-addicted cancer cell (indicated by the black shaded box). The oncogene causes a reprogramming of signaling networks, that in addition to bypassing normal growth and inhibitory signaling pathways (dotted lines), can include the concomitant upregulation of certain death signals. In oncogene addicted cancer cells, the reprogrammed positive growth signals predominate over negative death signals, thus enabling their survival.

Upon treatment of cancer cells with targeted therapies that inhibit oncogene activity, there is a diminishing of positive growth signals, and the negative death signals predominate. This provides a time window during which cells irrevocably activate death signaling pathways. *Sharma, and Settleman, Genes Dev. 2007;21:3214-3231*
Abstracts Tour: Hanmi Clinical Data for HM781-36B/poziotinib

Hanmi Pharmaceutical, headquartered in Seoul, South Korea, licensed the drug poziotinib to Spectrum Pharmaceuticals. The Exon 20 Group is grateful to Jacqulyne Ponville Robichaux, PhD, of the John V. Heymach, MD, PhD Laboratory at MD Anderson, for providing these links.


   Link: https://link.springer.com/article/10.1007%2Fs00280-014-2621-7

   Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5266390/

   Link: https://www.researchgate.net/publication/273468001_Antitumor_Activity_of_HM781-36B_alone_or_in_Combination_with_Chemotherapeutic_Agents_in_Colorectal_Cancer_Cells


   Link: https://www.ncbi.nlm.nih.gov/pubmed/23422737

   Link: https://www.ncbi.nlm.nih.gov/labs/articles/21306821
The newly-formed Exon 20 Group is an exciting opportunity to advance patient care. We have the opportunity to understand the impact of molecular events in EGFR and Her2 on the susceptibility to various small molecule and/or antibody drugs. Understanding drug susceptibility is crucial to effective clinical utilization of drugs in cancer care.

However, there are a number of hurdles that stand in the way of success of the Exon 20 Group. One of the most crucial issues facing any type of consortium or large group effort is that of data standardization. This endeavor will face many such issues, and we should start planning immediately to resolve these issues to ensure success.

One of the most important issues is that of the data pipeline. There are a variety of software packages used to make indel [an insertion or deletion of bases in the genome] calls from raw Next-Generation Sequencing (NGS) read data today. There are at least three major ways in which such software works (for an evaluation see Hasan, M. S., Wu, X., & Zhang, L. (2015). Performance evaluation of indel calling tools using real short-read data. Human Genomics, 9(1), 20.), and they don’t all reach the same conclusions with the same data inputs. This will make it critical for those experts involved in the Exon 20 Group to determine which indel calling software we should use. Once such a determination is made, we will need to determine whether historic data should be reinterpreted using the agreed upon analysis pipeline if raw data is available. Such redetermination will of course require appropriate resourcing, which will have to be a part of the conversations. We will also have to determine if we have the resources to store the raw data over the long term to re-analyze it should better algorithms become available.

Along with harmonizing the data on interpretation of sequencing data, we will need to harmonize our clinical data inputs. There are a lot of variables to consider, and where a best practice exists we should strongly consider adopting it. In the case of clinical data, CDISC (Clinical Data Interchange Standards Consortium) has many standards that are in use. However, we will likely have to harmonize existing data with their standards should we adopt them. Standards used for description of drug dosing, drug response, pathology terms, toxicity/adverse events and a host of other clinical issues will need to be agreed upon.

Harmonization of the laboratory data will be equally important. We must determine the ontology that will be used in the database(s) and design the databases so that only data that follows the correct ontology can be accepted. Small issues, such as entering the database as Her2 versus Her-2 versus Her2/Neu versus ERBB2 must be addressed. This example may be trivial given the general acceptance of HUGO names for genes, but the necessity for the work is not. Cleaning data after entry is much more difficult than doing so up front. This becomes of particular importance if we are to incorporate retrospective data into the database. Diligent effort at the planning stage will prevent a lot of the data clean up that is often needed prior to data analysis. Failure to normalize data up front will result in a resource drain at the analysis step that can prevent success of the Group.

Data normalization is crucial to the success of this endeavor. Without it, attempts to combine data from multiple sources become mired in data cleaning and disagreements about who needs to do the work. These details matter, and getting them right will allow us to focus on answering important clinical questions for patients whose tumors harbor indels in exon 20 of EGFR and ERBB2 (or is it Her2?).

Eric J. Thompson, PhD has been a member of ICAN’s Biomarkers Council since 2010 and is Vice President, Biomarker Research, Paradigm Diagnostics, Inc. in Phoenix, Arizona. He will be working with key laboratory members of the Exon 20 Group.
Effectively Addressing Anxiety

Carey Gold

For most lung cancer patients, anxiety is an unwelcome companion. When many people complain of anxiety, they describe tension often accompanied by intrusive (and unhelpful) thoughts. Often these thoughts are repetitive in nature, and they become more fearsome by their familiarity. The most effective method of dealing with this type of anxiety is to 1) identify it and 2) interrupt it. By achieving those two goals, we gain a sense of control, which helps us feel less vulnerable, while offering a sense of safety and protection.

COUNTING TENS

The simplest and most immediate intervention is a method I came up with two decades ago, called Counting Tens. I was seeking a quick, easy and effective method of defusing anxiety that could be done anywhere, using no tools. And while it is easily done and always accessible, the description sounds a bit simpler than the actual process. What most people find is that it is almost impossible to feel anxious while performing this exercise.

While seated in a comfortable chair (preferably a desk chair with arms that support an upright posture), close the eyes and count s-l-o-w-l-y from 1 to 10, while at the same time visually picturing each numeral clearly before proceeding on to the next. This can (and should) be repeated several times throughout the day. Most people find that simply having this exercise available—knowing they can interrupt anxiety at any time—reduces the anxiety level and decreases the power it holds. It seems to interrupt the neural circuits that support anxiety.

FLOATING DOWN

A second effective method of releasing anxiety involves another imaginative exercise, and one that seems to be particularly effective when anxiety interrupts sleep, causing insomnia. This exercise is best performed lying down in a darkened room, in a comfortably relaxed position—preferably, with the arms softly outstretched. With the eyes closed, imagine that it is a mild, balmy evening, and you are gently floating downward—in slow motion—from the top of a tall building, counting the windows on each story of the building “aloud” in your mind, as you slowly float down toward your bed, which is waiting below. This exercise is also very effective for anxiety related to MRI exams.

RHYTHMIC BREATHING

Here is an exercise that can be done during a five minute break from work, or whenever anxiety intrudes. It is best performed in a relatively quiet, but not necessarily silent, room. Close the eyes, and begin to inhale on a slow count of five, hearing yourself say the numbers in your mind. Allow about one second per number, and try to maintain an even rhythm: 1-2-3-4-5...1-2-3-4-5... The more even the rhythm the better. This can effectively lower blood pressure that is elevated by anxiety.

FINDING A CALM, QUIET PLACE

Anxiety can be an unsettling intruder, interrupting calm, rational thought. In a number of well-conducted studies in both animals and humans, anxiety has been shown to disturb endocrine function, interfering with medical treatment and causing profound biochemical alterations. Identifying anxiety allows us an opportunity to relieve it, restoring a sense of control and discouraging anxiety’s return. And it takes just a few seconds.

Carey Gold, Special Advisor to the Exon 20 Group, is the founder and president of The Health Advisory, based in New York.
Closing Comments

Sherry Weinstein, Chairman, ICAN Board of Trustees

Thanks to the visionary, determined leadership of Kevin and Bob Hanlon, along with our ICAN team led by Marcia Horn, Bob Tamis, Scott Kahn, and Eric Thompson, we are gratified by the groundswell of support for the Exon 20 Group.

Although recruiting for the Exon 20 Group is well ahead of schedule, we encourage you and your colleagues to reach out to others who might have an interest in joining us.

Our ambitious goals are viable — as long as we can count on your help. Please be sure that patients you meet in social media venues as well as patients you are treating in the clinic (or whose lab results you are reporting) are all aware of the benefits of joining the Exon 20 Group. Chief among these are: the relief of obtaining world-class patient navigation (always free to the patient), plus ICAN’s Tumor Board approach, knowledge of clinical trials, and arranging pre-approval access or “compassionate use” of drugs where needed. We will be launching a global sequencing campaign which will help identify not only exon 20 insertion patients, but also other NSCLC subgroups—who otherwise might not be profiled at all.

Collectively, each professional and patient involved in our Exon 20 Group will be integral to making a positive impact on this tough little corner of cancer. But stay tuned … we’re just getting started!

Members of the Exon 20 Group's Patients and Families Council met at the University of Texas MD Anderson Cancer Center in October. They discussed their various experiences battling Exon 20 insertions and their hopes for the Group. From left to right: Mike Johnson, Susan Johnson, Janet Belltaylor, Araldo Caster, Joyce Sleebos, Hilary Shaw, Bob Hanlon (Co-Founder), Mindy Erickson, Chad Erickson, Kevin Hanlon (Founder), and Sherman Johnson.