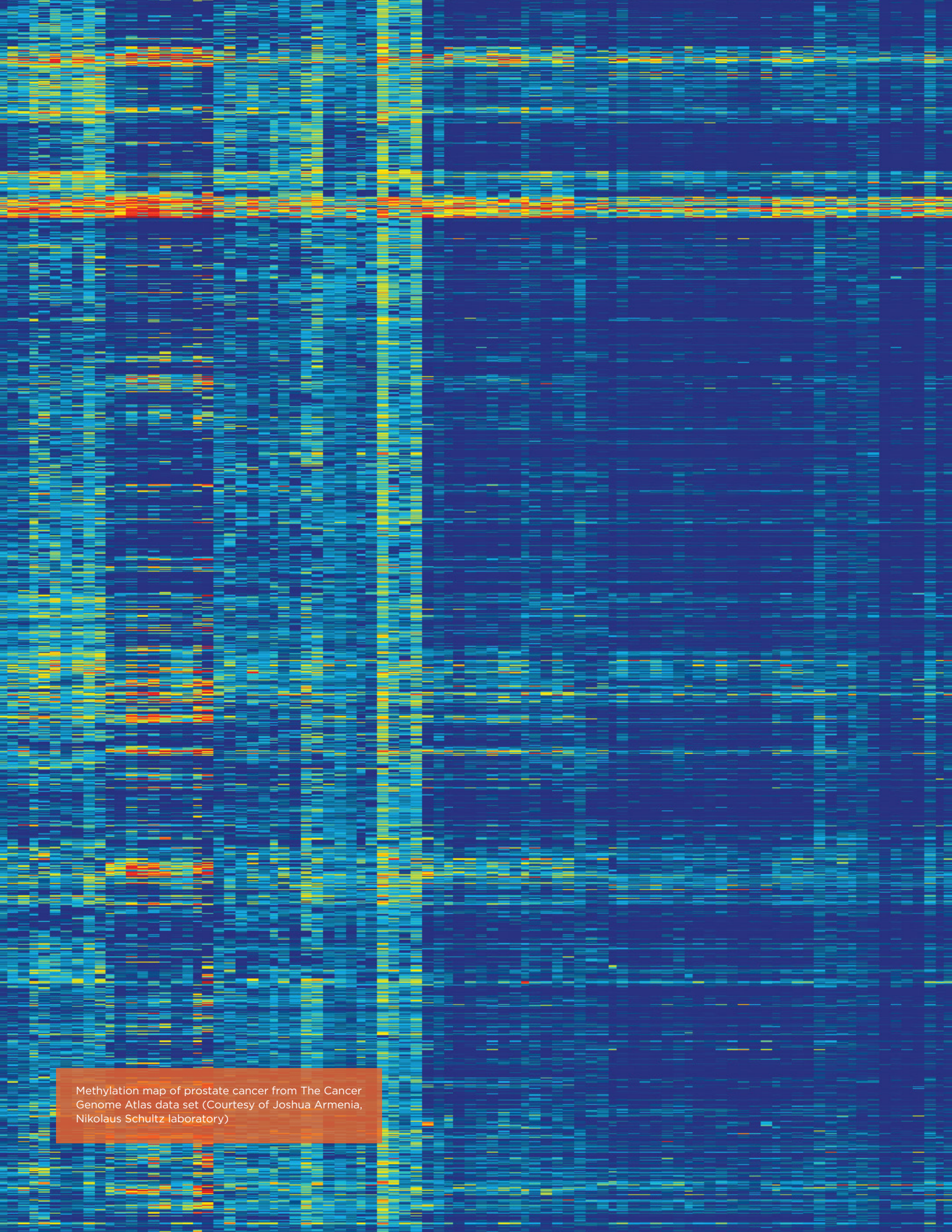
HOPP

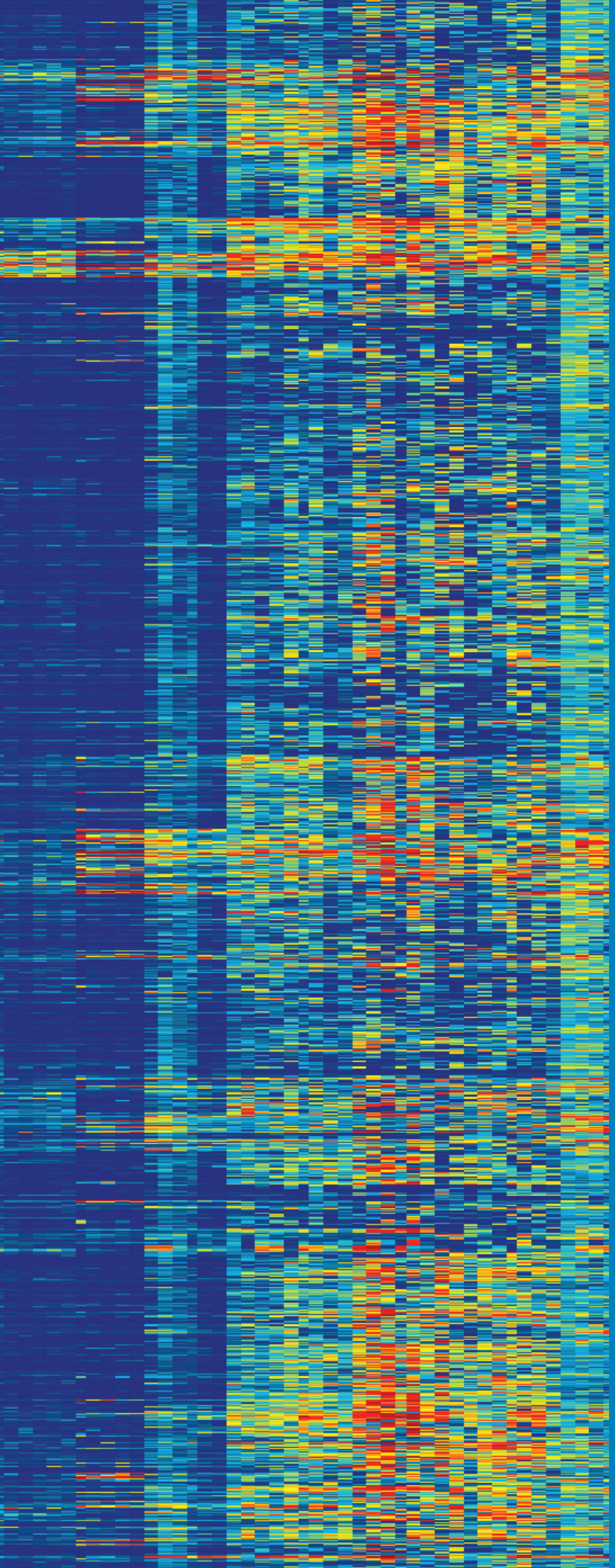
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

A DECADE OF IMPACT, 2007–2017

Memorial Sloan Kettering
Cancer Center



Methylation map of prostate cancer from The Cancer Genome Atlas data set (Courtesy of Joshua Armenia, Nikolaus Schultz laboratory)



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MESSAGE FROM THE CHAIR

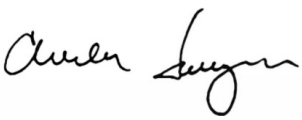
Although it was my hope, I could not have imagined how deeply the Human Oncology and Pathogenesis Program (HOPP) would influence the study of cancer biology today and its translation into meaningfully advanced therapies for patients in just over ten years. In this progress report, we celebrate a decade of impact made by HOPP members at Memorial Sloan Kettering Cancer Center and beyond.

Before joining MSK, I helped develop two exciting new therapies to treat chronic myeloid leukemia, imatinib (Gleevec®) and dasatinib (Sprycel®). What was once a fatal disease became a manageable chronic condition. It was life- and practice-changing for patients and for me. These drugs were effective and precise because they targeted only the specific proteins that were overactive in leukemia cells, sparing patients from undesirable systemic effects. These experiences served as powerful examples of how rational drug design could drive translational medicine, and I wanted to bring this approach to treating other kinds of cancer. I knew that if there were a place where it could be done, it would be MSK.

Investigators at MSK, including then President Harold Varmus, had seen similar success with a targeted agent against epidermal growth factor receptor for non-small cell lung cancer. Through our interactions on the MSK scientific advisory board, we shared an understanding that, despite our success, the research landscape was still deficient in bridging the laboratory and clinic. Dr. Varmus, together with Thomas Kelly, Chair of the Sloan Kettering Institute, and Robert Wittes, Physician-in-Chief, had started to shape opportunities at MSK for these two worlds to come together. Their vision and backing were the seeds of HOPP. They invited me to be its inaugural Chair, with few specific instructions except to recruit and support the kind of talent who could bridge the divide between bench and bedside.

The cultural gap between basic science researchers and clinical scientists was large. It became clear to me that a HOPP investigator wasn't just someone who understood how to work collaboratively. A HOPP investigator also needed to be able to overcome barriers between research cultures. I decided to create a department of physicians and scientists doing the very best translational cancer research. These investigators would have a foot in both worlds, which meant that they could engage with and be trusted by researchers on both sides. With both kinds of insider knowledge, they would be in a special position to frame precise, clinically relevant research questions and would already be situated to bring promising, rationally based therapies directly to the clinic. I was onto something. Here, we collaborate tirelessly and bring innovative thinking to tackling current problems in cancer research. There has been unimaginable synergy at HOPP, and much to be proud of.

A true testament to HOPP's impact is that we continue to attract high-caliber researchers and engage in influential extramural partnerships. Today, our faculty number about 25 members, specializing in diverse cancers, and are a driving force in bringing precision medicine to all aspects of cancer care. HOPP members have developed and direct many of MSK's Collaborative Research Centers. Our members also serve on the editorial boards of prestigious scientific journals, have been invited to lead national steering committees for large projects (such as the National Cancer Institute's Cancer Moonshot), and direct several unique, specialized research grants, including Translation Research in Oncology Training (TROT) fellowships and the Thyroid SPORE detailed in the following pages. We have trained hundreds of graduate students and postdoctoral and clinical fellows, most of whom have moved on to scientific positions at leading academic and industry organizations in the United States and internationally. Cancer genomes were largely uncharted in 2006. We now have the map and the tools to find, develop, and test undiscovered cancer targets, and to cure cancer. I look forward to our next decade of impact.



Charles L. Sawyers, MD
CHAIR
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

MESSAGE FROM THE DIRECTOR

It has been a privilege to be an administrator for HOPP since its earliest days. I have watched this department grow quickly, establishing itself as an influential model for translational research at MSK and across the country. Though their primary responsibilities are to lead lab-based research, HOPP investigators are jointly appointed in hospital departments. As part of Disease Management Teams, HOPP investigators can apply their research findings more directly to clinical care. Conversely, patients' disease progression guides the investigators' research in their labs. To support their exploration, HOPP investigators create unique collaborations between clinicians, clinical trial leaders, basic scientists, technology experts, and computational biologists. As you will read, this team-based approach in translational research has led to great advances in understanding and treating cancer.

Since HOPP began, it has maintained a start-up culture of innovation and collaboration. Although a large department, we have fostered a close-knit community of investigators who support one another's research advancement. Through work-in-progress meetings, seminar series, and mentoring programs, investigators share their progress, discuss challenges, and identify new areas of collaboration. This community has grown exponentially in the last decade, and this robust support system extends to all who work in HOPP. One of the aspects that I am most proud to discuss is the strong partnership between the faculty and administration. Together, we have demonstrated that groundbreaking science can take off with the right support, and that having business partners frees up investigators to pursue important research endeavors. Through resources within HOPP and in central offices, we have a team of administrators whose primary responsibilities are to manage the finances, grants, administration, operations, facilities, and training programs. Administrative team members may be found helping fellows submit new grants, organizing the highly competitive high school science program, or managing a portfolio of finances for an investigator. This dynamic partnership between investigators and administration creates an environment where every team member's contributions have an impact on cancer research.

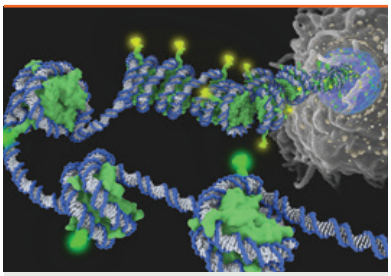
The partnerships within HOPP have had a tremendous influence in building a core foundation for team-based research at MSK. These alliances have led to the creation

of many Collaborative Research Centers (CRCs) and Programs, for which I oversee the business operations. Many HOPP faculty are embedded as program leaders or members of these CRCs, and each CRC is focused on addressing a specific scientific or disease objective. The CRCs are established to bring together faculty, trainees, and staff from across departments and programs. Similar to the HOPP model, the CRCs reach across disciplines to create a synergistic environment that enhances the research of its investigators. By partnering skilled lab-based scientists with experienced clinical trial leaders, the CRCs are poised to tackle some of the most difficult questions in translational cancer research.

HOPP investigators are often at the forefront of cutting-edge research. Each year I see how much the investigators have accomplished and find great pride in knowing that each staff member and trainee of the department has contributed to advancing science. Working with visionary leaders, talented trainees, and dedicated staff members has been more than a rewarding experience. Most importantly, we're working together to make a difference in cancer care.

Ederlinda Paraiso
DIRECTOR OF RESEARCH OPERATIONS
HUMAN ONCOLOGY AND PATHOGENESIS PROGRAM

RECENT HOPP BREAKTHROUGHS



NEW GENE FUNCTION DISCOVERED

Timothy Chan, Ross Levine, **Ingo Mellinghoff**, and Craig Thompson labs
2012, *Nature*

Discovered that mutations in certain metabolic enzymes cause cancer by changing how DNA is organized in the cell.

PROSTATE CANCER TARGET DISCOVERED

Charles Sawyers Lab
2013, *Cell*

Solved how the glucocorticoid receptor acts as a bypass in antiandrogen-resistant tumors.

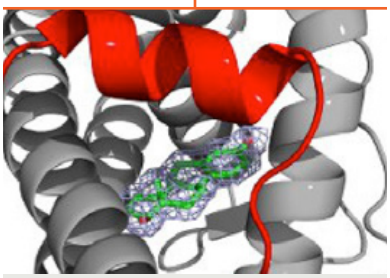
HOPP MEMBERS ARE EXPERTS AT DISCOVERING AND TESTING NEW CLINICALLY RESPONSIVE CANCER TARGETS.

2012 | 2013 | 2014

DEFINED EXCEPTIONAL RESPONDERS

Michael Berger, Timothy Chan, **David Solit**, and Barry Taylor Labs
2012, *Science*

Linked a complete response to the drug everolimus (Afinitor®, Zortress®) to mutations in *TSC1*: launches the National Cancer Institute's Exceptional Responders Initiative.



IDENTIFIED BREAST CANCER DRUG RESISTANCE MUTATIONS

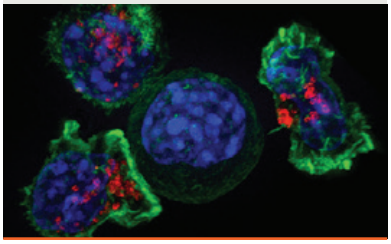
José Baselga, Michael Berger, and **Sarat Chandarlapaty** Labs
2013, *Nature Genetics*

Identified mutations in the ligand-binding domain of the estrogen receptor (*ESR1*).

GENOMICS PREDICTS IMMUNOTHERAPY RESPONSE

Timothy Chan and Jedd Wolchok Labs, with collaborators
2014, *New England Journal of Medicine*
2015, *Science*

Compared and analyzed genetic variations among cancer patients to predict who responds best to anti-CTL4A and anti-PD1 immunotherapy, harnessing the patient's immune system to fight cancer.

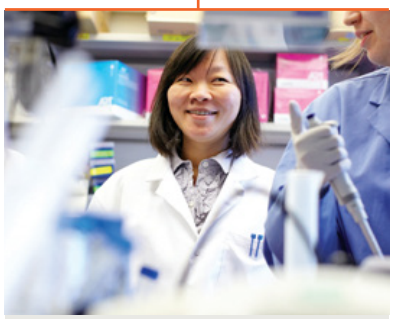


PRECISION MEDICINE FOR BREAST CANCER

José Baselga, Sarat Chandarlapaty, and Maurizio Scaltriti Labs
2015, *Science Translational Medicine*

Demonstrated that PI3K pathway inhibition upregulates estrogen receptor function.

2015



TARGETABLE MUTATION IDENTIFIED

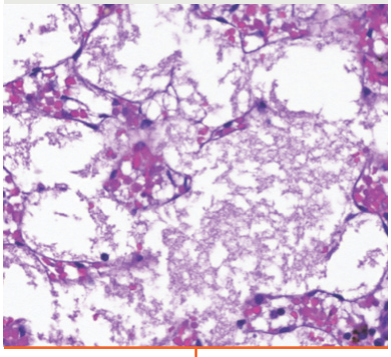
Michael Berger, Timothy Chan, **Ping Chi**, James Fagin, and Marc Ladanyi Labs
2015, *Science*

Discovered a novel oncogenic form of the ALK protein in melanoma and thyroid carcinomas, generated from an alternative transcription start site.

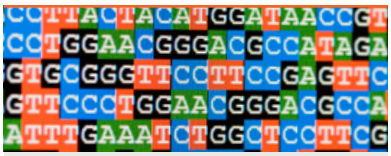
TARGETED THERAPY FOR LEUKEMIA

Omar Abdel-Wahab Lab
2016, *Nature Medicine*

Treated genetically defined myelodysplastic syndrome and acute myeloid leukemia patients by targeting splicesomal proteins.



2016



INTERNATIONAL DATA SHARING LAUNCH

AACR Project GENIE, a multi-institutional, international initiative led by **Charles Sawyers**
2017, *Cancer Discovery*

Phase I release of genomics data from 19,000 cancer patients, linked to clinical outcomes and shared publicly on an open-source platform. More researchers worldwide will have access to powerful cancer data sets.

2017

MSK CLINICAL SEQUENCING ASSAY ESTABLISHED

José Baselga, **Michael Berger**, **Marc Ladanyi**, **Nikolaus Schultz**, **David Solit**, and **Barry Taylor** Labs, with others at MSK
2017, *Nature Medicine*

Assembled 10,000 patients for the MSK-IMPACT™ project, providing publicly accessible data on clinically relevant genomic alterations.

WHO WE ARE

HOPP addresses the challenges of 21st-century cancer research, bringing together investigators from across disciplines to bridge discoveries made in the laboratory with those made in the clinic.

Ping Chi is a physician-scientist who studies molecular mechanisms that drive the growth of solid tumors, such as sarcoma and melanoma. She is translating her laboratory findings into early-stage clinical trials for new anticancer therapies.

A Q&A WITH JAMES FAGIN

An endocrinologist and internist, Dr. Fagin has been a member of HOPP since joining MSK in 2006. His research focuses on finding new treatments for patients with advanced thyroid cancer and aggressive forms of the disease.

How did you come to Memorial Sloan Kettering and HOPP?
I received an offer to join MSK, and while [I was] debating the opportunity, Charles [Sawyers] contacted me saying he was becoming Chair of this brand-new program. It felt like a perfect fit.

So the idea of HOPP figured into your decision to join MSK?
It did. For a long time I'd been interested in trying to understand the genetic basis of thyroid cancer and working to discover what genes are mutated in various stages of the disease. At that point, we'd made a number of observations in my lab that told us we could in all likelihood therapeutically target some of these defects.

However, continuing the research at my previous institution simply wasn't feasible. There was not the right supportive environment. And, of course, Charles had already made a spectacular advance in chronic myelogenous leukemia, which was a paradigm in the field: He'd demonstrated in a very clear way that you could selectively target an oncoprotein and obtain major therapeutic responses. This was precisely what I was aiming to do with the rest of my career — so it was an easy sell!

In addition, Memorial Sloan Kettering had a very good clinical thyroid cancer program. What I thought it lacked — and what I might offer — was a group interested in the overall mechanisms of the disease, a group whose work could stimulate more mechanism-based approaches to thinking about treatments.

> "While we spend a great deal of time in our laboratories, it is fundamental to the HOPP model that we remain embedded in the clinical or Disease Management Team relevant to our work."

Can you talk about the early days of HOPP?
We knew from the outset that we had to attract investigators who were doing research of a caliber that would be valued across all constituencies, both on the clinical side and by the more fundamental scientists at the institution.

So the idea was that we needed to fit between both arms of the institution and maintain credibility with both. By and large I believe we've succeeded. HOPP faculty are an integral part of each community. That is what is special about the program — we have a foot in both worlds.

How does HOPP facilitate research?
If there is a leitmotif common to all HOPP faculty, it's that we approach research as both physicians and scientists — many of us are also caring for patients. Some of us focus on one disease or set of diseases, while others may be interested in mechanisms common to several cancer types. While we spend a great deal of time in our laboratories, it is fundamental to the HOPP model that we remain embedded in the clinical or Disease Management Team relevant to our work.

Our connections to the clinic allow us to learn early and firsthand about observations in patients that merit further laboratory investigation. This two-way street — lab to clinic and clinic to lab — is the spirit of HOPP.

Could you say something about your own projects?
I think my lab has become most well known for our studies leading to new treatment approaches for patients with metastatic radioiodine-refractory thyroid cancers.

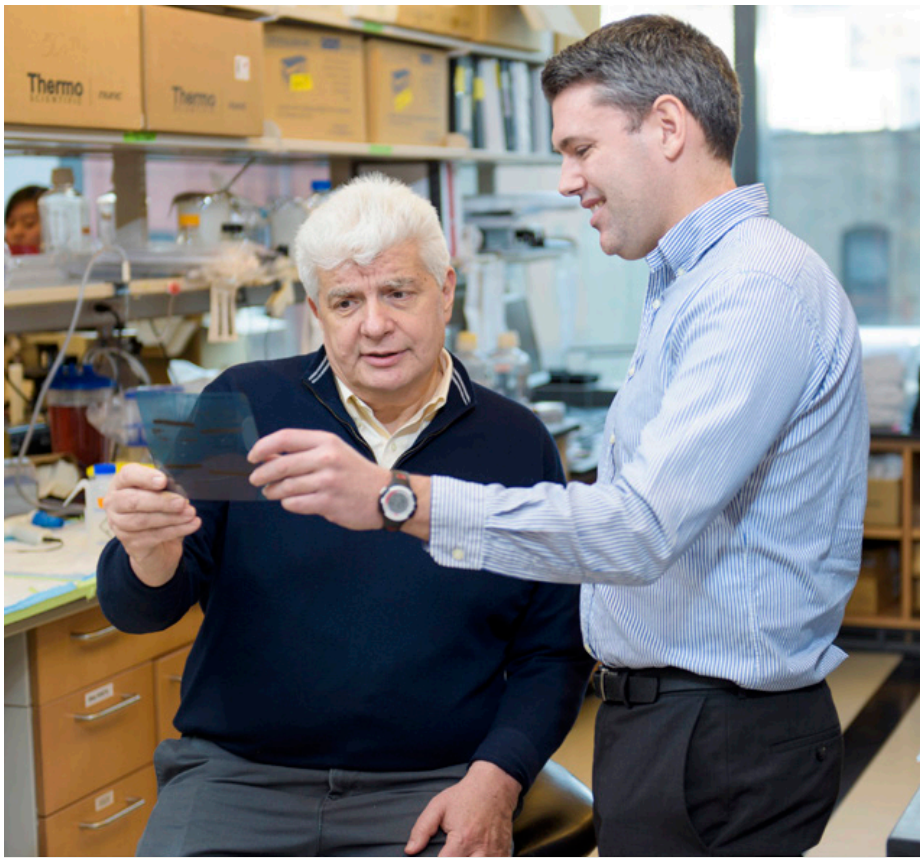
Based on our discoveries — beginning in cell culture and then in mouse models — we've revealed mechanisms that relate to the genes that cause thyroid cancer and how they actually disable the machinery of the cell that is required to trap iodine.

What we've shown, using small molecules that interfere with these cancer-causing pathways, is that the process is reversible and that we can restore radioactive iodine responsiveness. The principle has been proven in mice and in clinical trials. There are several ongoing trials, including phase III trials that may lead to approval of a new drug.

Much of our more recent work is coming out of our studies of the genomics of the most virulent forms of thyroid cancer and new lesions we have now identified.

As we've discovered these, we have modeled them, usually in mice, to try to understand their biology and how to treat these tumors.

Virtually all HOPP research is translational in nature, and MSK is one of only two institutions in the nation to have a SPORE (Specialized Programs of Research Excellence) in thyroid cancer, which is a National Cancer Institute–supported translational research grant. Can you explain the nature of SPORE grants?
That is correct. And I believe HOPP is conceptually the right home for it because SPORE projects are required to have clinical ramifications. SPOREs provide support for multiple research projects as well as core facilities that support their activities. They also pay for smaller projects that are in earlier stages of development and for research performed by promising young scientists.



James Fagin (left) with visiting investigator Anthony Glover

What are some of the projects you and your colleagues are pursuing under the SPORE?
One relates to a phenomenon that has become apparent in recent years in which imaging studies are unmasking a subclinical prevalence of thyroid cancers — what we call papillary microcarcinomas (PMC) — leading to overtreatment of this form of the disease.

We are working to identify genetic predictors of disease progression to distinguish small thyroid cancers destined to remain small from those more likely to progress. We have a prospective observational study of hundreds of patients with PMC who have elected not to have their tumors removed, and we've learned that the great majority [of those tumors] have not progressed.

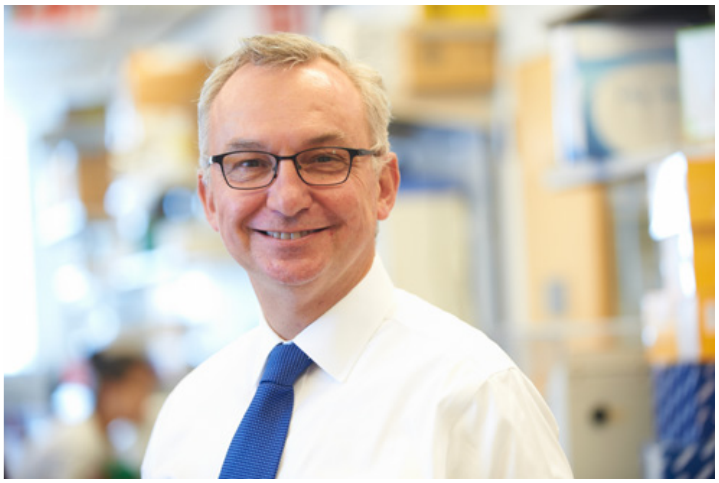
You also have a project related to a rare form of thyroid cancer called Hurthle cell cancer (HCC).
Yes. HCCs account for a disproportionate share of mortality from thyroid cancer because they are almost all refractory to radioiodine therapy and don't respond to available treatments. Tim Chan and his group are currently preparing a paper that will define HCCs as a unique entity with very peculiar mutations that can tell us a lot about pathogenesis in a number of cancer types. I think it will be a hallmark in the field.

Thyroid cancers can develop resistance to therapy. What research are HOPP investigators pursuing under the SPORE to address this problem?
As we've developed targeted therapies against key drivers of the disease, we've also revealed that these cancers adapt rapidly to drugs — and do so in a way that's peculiar to thyroid cancer cells, essentially allowing the cells to bypass the drugs' growth-inhibitory effects.

As an example of the work we're doing in this regard, several of my clinical colleagues designed trials to see if they could interrupt these mechanisms. A study they presented at the 2017 annual meeting of the American Society of Clinical Oncology showed remarkable responses to a combination of inhibitors of two proteins — BRAF (BRAF mutations are the most common mutations in thyroid cancer) and an adaptive mechanism, an activation of HER2 and HER3. It demonstrated that the addition of a HER2/HER3 inhibitor sensitizes the cancer cells to growth suppression by BRAF inhibitors, and that the therapy was safe and well tolerated. So we're not just studying how to target abnormalities in thyroid cancer but implementing strategies to overcome their adaptive resistance mechanisms.

PATIENT-DERIVED XENOGRAFTS

José Baselga, MD, PhD
Member, HOPP
Physician-in-Chief and Chief Medical Officer, Memorial Hospital

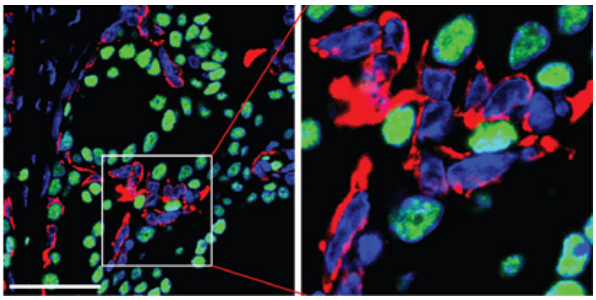


Molecularly targeted therapies have extended patient survival by years, but drug-resistant tumors can develop in some patients. How do researchers identify susceptible patients? How do resistant tumors emerge? Patient-derived xenografts (PDXs), patient tumor samples that are implanted into immunosuppressed mice, are powerful tools that can be used to address these questions in a diseaselike setting. The José Baselga lab has established many breast cancer PDXs with defined genetic lesions and uses these PDXs to study the mechanisms of drug resistance and test the effectiveness of specific therapies. In a classic example, Dr. Baselga's group established a PDX from a breast cancer lung metastasis sample; the patient responded to PI3K inhibitors at first, but the disease progressed after ten months of therapy. Dr. Baselga used a PDX model to identify potential mechanisms of drug resistance and discovered a loss of *PTEN* gene activity. Then using the same PDX model, his group devised a novel approach and demonstrated therapeutic effectiveness using an alternative PI3K-pathway inhibitor. Dr. Baselga has since used PDX models to address how a number of different genes and pathways contribute to breast cancer progression and to create preclinical tests of the efficacy of novel targeted inhibitors or therapeutic combinations.

FINDING A SIMPLER WAY TO STUDY PROSTATE TUMORS

Yu Chen, MD, PhD
Assistant Member, HOPP
Assistant Member and Assistant Attending, Department of Medicine
Assistant Program Director, Medical Oncology Fellowship Program

An ongoing challenge for cancer researchers is to keep pace with the discovery of new molecular targets and leverage these findings therapeutically. Advances in prostate cancer research, for instance, could be accelerated dramatically if there were an easily maintained, clinically responsive culture model. In 2014, Yu Chen and others successfully developed a new culture system to maintain organoids of prostate stem cells taken from humans and mice. Unlike a mouse model, which can be costly and time-consuming, organoids develop in suspension relatively quickly and can be readily adapted to study prostate cancer at different stages and over time. Two features of this system are particularly notable: Organoids faithfully give rise to all the major tissue types found in the normal or cancerous prostate, and organoids can be manipulated genetically. Dr. Chen has established a bank of about 20 patient-derived prostate organoids. This resource will allow Dr. Chen and others to ask important questions about how prostate cancers originate at a cellular level, how the cancer evolves, and how cancers with defined mutations will respond to certain drugs as the cancer progresses. Dr. Chen was formally a postdoctoral fellow in the Charles Sawyers lab and started his own laboratory in HOPP in 2011.

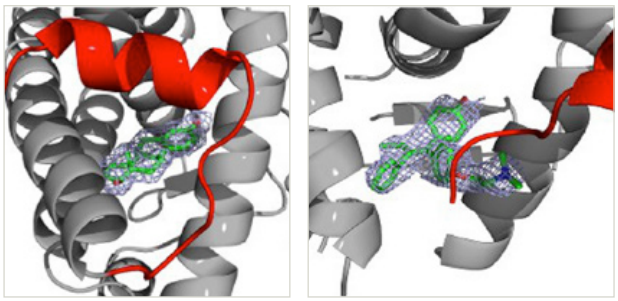


Antibody staining of human prostate organoid sections against Ck5 (red) and ERG (green) and DAPI staining (blue) of cell nuclei

HOW DO BREAST CANCERS BECOME DRUG-RESISTANT?

Sarat Chandarlapaty, MD, PhD
Assistant Member, HOPP
Assistant Attending, Department of Medicine

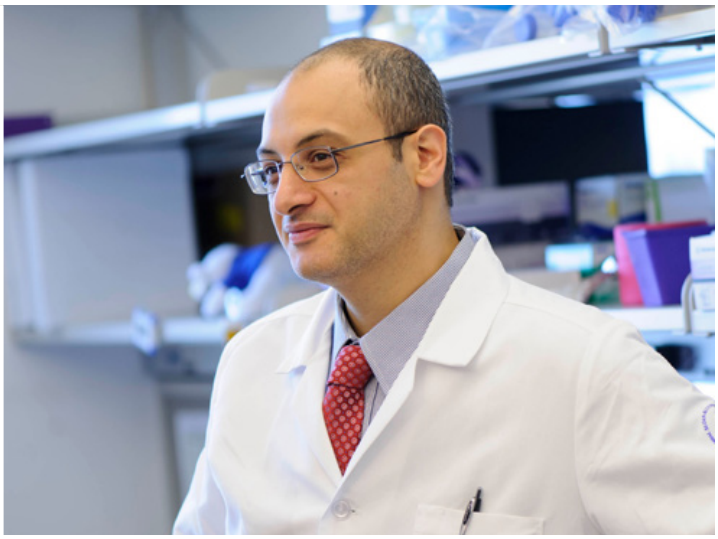
Estrogens stimulate the growth of nearly 70 percent of all breast cancers. Unfortunately, patients with advanced or metastatic breast cancer often develop resistance to aromatase inhibitors, drugs that block estrogen signaling and are a mainstay in breast cancer therapy. Sarat Chandarlapaty's lab sought the molecular basis of aromatase inhibitor resistance in breast cancer and identified activating mutations in the gene for the estrogen receptor, *ESR1*. With collaborators, Dr. Chandarlapaty showed that the mutant estrogen receptor structure was in an activated conformation (an active shape), even without the hormone estrogen present. Dr. Chandarlapaty's lab also demonstrated that these mutations occur in about 10 percent of patients with metastatic breast cancer and are likely to be responsible for the resistance to aromatase inhibitors. Applying these findings, they created an easy blood test to screen patients for *ESR1* mutations, thus enabling the selection of the appropriate targeted therapy. Now their focus is on identifying drugs to treat these mutations, some of which are in clinical trials at MSK. Dr. Chandarlapaty was formerly a postdoctoral fellow in the Neal Rosen lab at MSK and now leads his own independent research program.



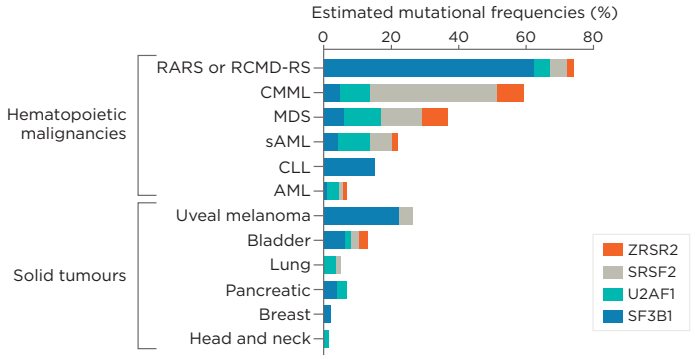
Crystal structures of the mutant estrogen receptor protein reveal that different estrogen inhibitor drugs (green) cause the protein to adopt a more active (left, red and gray helices) or less active (right) shape. (Source: Fanning, *eLife* 2016)

TARGETING SPLICING FACTORS TO TREAT LEUKEMIA

Omar Abdel-Wahab, MD
Associate Member, HOPP
Associate Attending, Department of Medicine



Several cancers demonstrate mutations in splicing factors, part of the cellular machinery that edits gene expression. In their standout *Nature Medicine* paper from 2016, Omar Abdel-Wahab's group cleverly engineered mouse genetic models to have mutations in only one copy of the splicing factor Sfsr2 — just like those commonly found in human patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (*SRSF2*P95H) — and showed that these mice were more likely to develop leukemia. Just as significant, his group also showed that it was possible to pharmacologically block the progression to leukemia by administering a splicesome inhibitor. This finding represents a very promising therapeutic strategy for MDS and AML patients with these types of mutations. Dr. Abdel-Wahab was formerly a postdoctoral fellow in the Ross Levine lab.



Mutations in splicing factors occur frequently in hematopoietic cancers and certain solid tumors.

FROM BEDSIDE TO BENCH — AND BACK

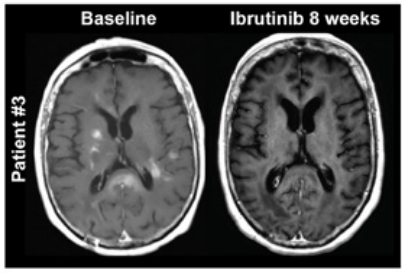
Adrienne Boire, MD, PhD
Assistant Member, HOPP
Assistant Attending, Department of Neurology

As cancer treatments improve, patients are living longer. In turn, advanced complications, such as leptomeningeal metastasis (LM), in which cancer cells spread into the cerebrospinal fluid, have also increased. LM can lead to disability, pain, and seizures, among other symptoms — and there are few treatment options to halt its progress. As a neuro-oncologist, Adrienne Boire specializes in caring for patients with metastasis to the nervous system. She was inspired by her patients to focus her laboratory's investigations on LM. In the laboratory, Dr. Boire discovered that LM cancer cells secrete a factor that encourages the cell barrier encasing the cerebral spinal fluid to open

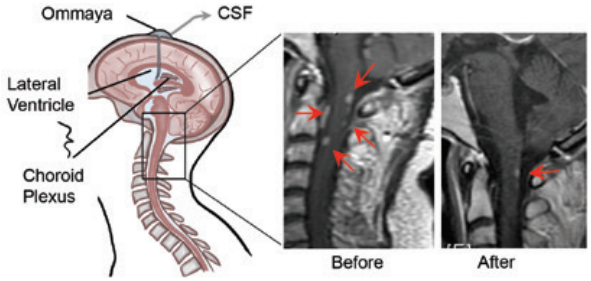
DISCOVERING NEW THERAPIES FOR BRAIN CANCER

Ingo K. Mellinghoff, MD
Member, HOPP
Vice Chair for Research, Department of Neurology
Attending, Department of Neurology

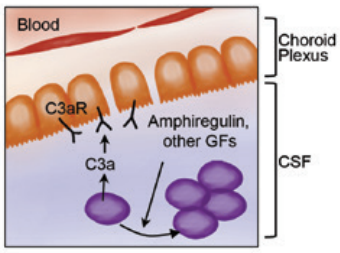
Malignancies of the central nervous system (CNS) are among the most difficult cancers to treat. Recent advances in genomics research have allowed researchers to see how genes are expressed, packaged, and mutated and have made it possible to understand CNS cancers from a new perspective. Ingo Mellinghoff is leveraging these insights to develop molecularly targeted treatments for brain tumors, including glioblastoma, lower grade glioma, and CNS lymphoma. In 2012, he and others described the function of *IDH1* mutations in glioma, and revealed that mutations in *IDH1* resulted in changes to histone- and DNA-methylation, the biochemical markings that affect how DNA is packaged and read by normal versus cancerous cells. His team is now completing early clinical trials of *IDH1* inhibitors in glioma patients and is developing new approaches to monitor the presence and activity of the mutant enzyme through liquid biopsies of cerebrospinal fluid and non-invasive imaging. More recently, through a combination of genomic and functional studies in newly derived experimental models, Dr. Mellinghoff and his colleagues discovered that CNS lymphomas are extraordinarily dependent on the activity of Bruton's tyrosine kinase which plays an important role in several other human B-cell malignancies. Mellinghoff's group designed a clinical trial to follow up on this observation and indeed observed frequent tumor responses to ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase, in patients with recurrent or treatment-refractory CNS lymphoma. This discovery now offers a new treatment option for patients facing this rare type of cancer and demonstrates how HOPP investigators are positioned to make exciting intellectual leaps between the clinic and laboratory and vice versa.



slightly, which permits nutrients in to feed cancer cells. Dr. Boire's decision to act, and her fundamental discoveries about the biology of LM, have made it possible to design and test more-precise therapeutic strategies to get at the root of this devastating yet increasingly common complication of advanced cancer. As a new HOPP investigator, she is poised to bring innovative solutions to treating LM from her lab into the clinic in the near future.



Cerebrospinal fluid of patients with leptomeningeal metastasis (LM) was sampled and analyzed for C3, amphiregulin, and other blood or cerebrospinal fluid components via an Ommaya reservoir. LM patients were treated with trastuzumab (an inhibitor of amphiregulin), which was also delivered to the lateral ventricles by the reservoir (left). Comparison of an MRI from a patient just prior to treatment (before) and later (after), demonstrates a clinical response. Deposits of LM appear as white plaques over the cervical spine and are indicated by red arrows.



In this model of leptomeningeal metastasis (right), cancer cells (purple) within the cerebrospinal fluid produce C3, initiating a chain of events that compromises the barrier function of the choroid plexus. Select plasma components, including the growth factor amphiregulin, gain entry to the cerebrospinal fluid, where they support cancer cell growth.

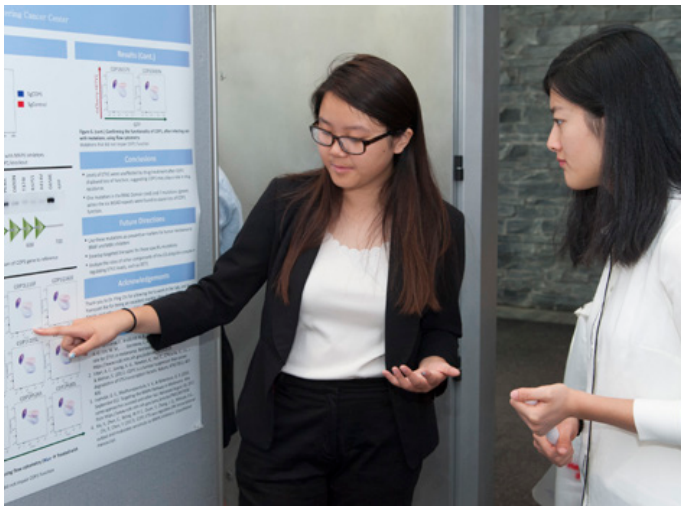
OUR IMPACT

Since its establishment, HOPP has fostered innovative programs and collaborations spanning laboratory research, preclinical discovery, clinical investigations, and training the next generation of translational investigators.

Marie-Josée and Henry R. Kravis Center for Molecular Oncology Director **David Solit** (right) and Associate Director **Michael Berger**

IMPACT ON TRAINING

HOPP emphasizes a culture of collaboration and innovation among its investigators. We share this with younger scientists through a number of unique training initiatives, such as the HOPP Summer Student Program, our new Science Enrichment Program, and the Translational Research Oncology Training Program.



HOPP Summer Student Program (SSP)

Each year HOPP hosts 20 to 28 students in a popular eight-week lab-intensive summer internship. In addition to conducting their own research projects, students participate in a number of other activities. They are given a tour of an OR, are taught by a postdoctoral fellow about how to read and interpret a scientific journal article, attend multiple special seminars, and are invited to weekly luncheons hosted by principal investigators. The goals of the SSP are to expose high school students to a breadth of cancer research in the basic and clinical sciences, promote the students' knowledge about translational and clinical research, and enhance their critical thinking skills, with the aim of encouraging them to further their interest in science and cancer research.

"HOPP was by far the most intellectually stimulating and engaging program I've ever attended. Being immersed in the lab setting fueled my curiosity for translational research and opened my eyes to the physician-scientist career."

—SSP attendee in 2017

Science Enrichment Program (SEP)

HOPP was awarded a grant in 2016 to pilot an enrichment program for ten students per year through the supplement mechanism of the P30 Center Core Grant.

The goal of the SEP is to supplement the scientific education of selected high school students from under-resourced schools or underprivileged backgrounds. The program provides a broad introduction to the laboratory and clinical research environments, as well as fields of study in oncology, while utilizing the cohort-learning model for support and encouragement. In the first year, the SEP exposes students to cancer biology and genetics. Students have the opportunity to learn basic lab skills at biweekly workshops. At the end of the first year, students are invited to participate in apprenticeships, mentored laboratory or clinical research experiences that begin in the second year. Finally, the program aims to significantly impact the career trajectory of its participants by providing them with opportunities to build a professional network that they can rely on for future support and exposure.

Translational Research Oncology Training (TROT) Program

HOPP specializes in translational cancer research, sometimes referred to as bench-to-bedside (and vice versa) research. The TROT program, directed by Charles Sawyers, is a two-year grant that supports the ongoing training of two PhD fellows who are interested in applying basic science research findings to clinical practice. The program is designed to provide a structured learning environment in which fellows work under the mentorship of a successful scientific investigator and an appointed clinical adviser while also attending a course of lectures, and seminars throughout the fellowship years.

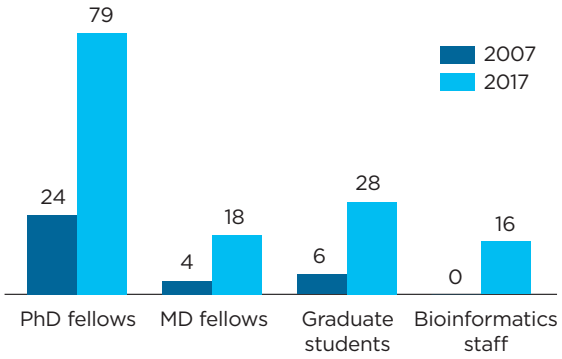
> **"A great opportunity to become involved in the research world and make new friends and connections before entering college."**
>
> **— SSP attendee in 2014**

In 2015, HOPP administration applied for a competitive renewal of the program. We are happy to announce that we have been funded through 2021.

Also, the generosity of the Junming Le Foundation and First Eagle Investment Management has allowed us to extend program funding to two additional TROT fellows. These partnerships have allowed us to recruit and train talented postdoctoral fellows who may not be eligible for National Institutes of Health fellowship funding.

We look forward to continuing these and new partnerships in our efforts to train the next generation of translational cancer researchers.

HOPP Trainees



Clinical and postdoctoral research fellows are at the final stages of training before becoming independent investigators. Finding a position is competitive. Our research fellows are making an impact around the world, in academia, industry, and other areas.

Where do our research fellows go next?

Academic Institutions

32

Industry or Commercial Ventures

8

Hospitals or Nonprofits

3

Government Research Centers

3

Canada	Sherbrooke
China	Nanjing
	Shanghai
	Xi'an
Finland	Helsinki
France	Bron
	Paris
Germany	Munich
Ireland	Dublin
Israel	Beersheba
Italy	Catanzaro
Japan	Fukuoka
	Kanazawa
	Tokyo
The Netherlands	Groningen
South Korea	Ulsan
Spain	Madrid
Sweden	Gothenburg
	Lund
Turkey	Malatya
United Kingdom	Brentford
	London
United States	Boston
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	Detroit
	Fayetteville, Arkansas
	Gainesville, Florida
	Montvale, New Jersey
	Nashville
	New York
	San Francisco
	St. Louis, Missouri
	Stony Brook, New York
	Thousand Oaks, California
	Washington, D.C.

HOPP Numbers

2007

61
HOPP faculty and staff

2017

300+
HOPP faculty and staff

2016

HOPP members authored
169 unique publications

Over half of HOPP faculty have an **H-index of**
40 or higher*
*40 papers cited at least 40 times each

HOPP members received
87 new grants,
with an overall funding success rate of 63% (from federal, nonfederal external, industrial, and internal peer-reviewed sources)

NIH 2016 FISCAL YEAR

19% of total applications for large federal grants (R-01 or equivalent) were successful.
HOPP investigators had a **success rate of 40%**

2007–2017

To date, HOPP faculty members have led
178 clinical research protocols
at MSK (as either a principal investigator or co-principal investigator)

- **75** Biospecimen
- **54** Therapeutic
- **27** Retrospective Reviews
- **11** Diagnostic
- **7** Specimen Banking
- **2** Clinical Genetic
- **2** Quality of Life

IMPACT THROUGH LEADERSHIP

Project GENIE

Led by HOPP Chair, Charles Sawyers, Project Genomics Evidence Neoplasia Information Exchange (GENIE) is an international consortium of eight cancer institutions that share genomic and clinical outcome data from patients in an open-source fashion for widespread use in the cancer community. This offers researchers access to larger, and therefore more powerful, data sets to understand rare cancers, clinical progression, and patient outcomes, and to advance precision medicine practice.

In the pilot phase, Project GENIE has:

- developed a blueprint for multi-institutional collaboration that balances efficient data sharing with protecting patient privacy
- established uniform standards for clinical genomic data collection
- publicly released the first baseline and genomic data from approximately 19,000 patients
- published the first assessment of potential clinical actionability (i.e., treatment available based on a patient's mutational profile) in *Cancer Discovery* in August 2017 — estimated to be greater than 30 percent across cancer types

These accomplishments have been widely recognized. Additional member institutions will be added in 2018, and samples are expected to grow to more than 100,000 in five years. Other MSK leaders supporting GENIE are David Solit (HOPP Member); Nikolaus Schultz (HOPP Affiliate Member) and Stuart Gardos, bioinformatics and data infrastructure consultants; and Lillian Smyth and David Hyman who are co-leading a GENIE-enabled project on patients with a rare subtype of breast cancer.

A data set of more than

32,000

genomic records

released in 2017 predicts

clinical actionability

>30%

The Cancer Moonshot

HOPP Chair Charles Sawyers (left) and MSK Physician-in-Chief José Baselga (right) with Joe Biden at the 2016 World Economic Forum in Davos, Switzerland.

HOPP leaders have played a critical strategic role in shaping the Cancer Moonshot, an initiative announced in President Obama's 2016 State of the Union address and led by Vice President Joe Biden. The goal of the Cancer Moonshot is to double the rate of advance in cancer diagnosis, prevention, and cures. Charles Sawyers (HOPP Chair) and José Baselga (HOPP Member and MSK Physician-in-Chief), both past presidents of the American Association for Cancer Research, were early consultants and panelists of the "Cancer Moonshot: A Call to Action" discussion, which convened in January 2016 at the World Economic Forum in Davos, Switzerland. Dr. Sawyers was also a member the Blue Ribbon Panel, an expert advisory panel guiding the scientific approach and implementation of the Cancer Moonshot Initiative.

Vice President Joe Biden visited with Lindsay Saunders, research fellow, and **Ross Levine** (right) before hosting a roundtable discussion with members of the New York City cancer community to brainstorm ideas for the Cancer Moonshot initiative.

OUR EVOLUTION

HOPP investigators continue to reveal new insights into cancer genetics, make seminal contributions to the development of transformative targeted therapies, and implement leading-edge clinical trials.

Expansion of the Collaborative Research Centers

MSK has 22 Collaborative Research Centers, strategic groupings of laboratory investigators and clinicians who focus on a theme in cancer biology, led by an MSK faculty member. HOPP has taken a particularly active role in growth of the following:

Center for Hematologic Malignancies
DIRECTOR: Ross Levine

David M. Rubenstein Center for Pancreatic Research
DIRECTOR: Steven Leach

Geoffrey Beene Cancer Research Center
CO-DIRECTOR: Charles Sawyers

Immunogenomics and Precision Oncology Platform
DIRECTOR: Timothy Chan

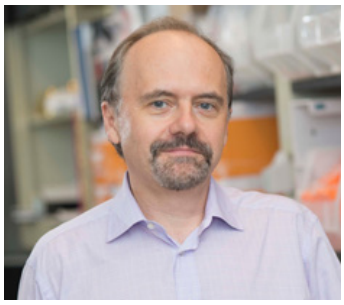
Marie-Josée and Henry R. Kravis Center for Molecular Oncology
DIRECTOR: David Solit

Neuro-Oncology Research Translation in Humans Program
DIRECTOR: Ingo Mellinghoff

THE ORIGINS OF THE MARIE-JOSÉE AND HENRY R. KRAVIS CENTER FOR MOLECULAR ONCOLOGY

In the last decade, there has been a surge in clinical sequencing data from projects such as The Cancer Genome Atlas. By sequencing the genomes of thousands of cancer patients and relating that data to patient outcomes and treatment responses, researchers have a road map to understanding cancer biology and drug development. In 2007, Charles Sawyers, Harold Varmus, and other MSK leaders founded a centralized tumor sequencing effort known as the Beene Core, with support from the new Geoffrey Beene Cancer Research Center. The Beene Core quickly became an important resource for many clinical and laboratory investigators, demonstrating the potential for MSK to become a powerhouse in cancer genomics research. When José Baselga (a HOPP Member) joined MSK as Physician-in-Chief, he too recognized that this wealth of data would be at the heart of personalized cancer medicine, and that MSK was poised to be at the forefront of change. MSK was already in the truly unique position of having unparalleled access to patient genomic samples through its cancer tissue banks. MSK researchers were not only experts in disease biology but also had access to professionally staffed core facilities that allowed them to test and find new molecular drivers of cancer quickly, using the latest in gene and protein expression technologies.

Left to right: Physician-in-Chief José Baselga, Marie-Josée and Henry R. Kravis Center for Molecular Oncology Associate Directors Agnès Viale and Michael Berger, and the center's Director David Solit.



Marc Ladanyi, Chief, Molecular Diagnostics Service

Maria E. Arcila, Director, Diagnostic Molecular Pathology Laboratory

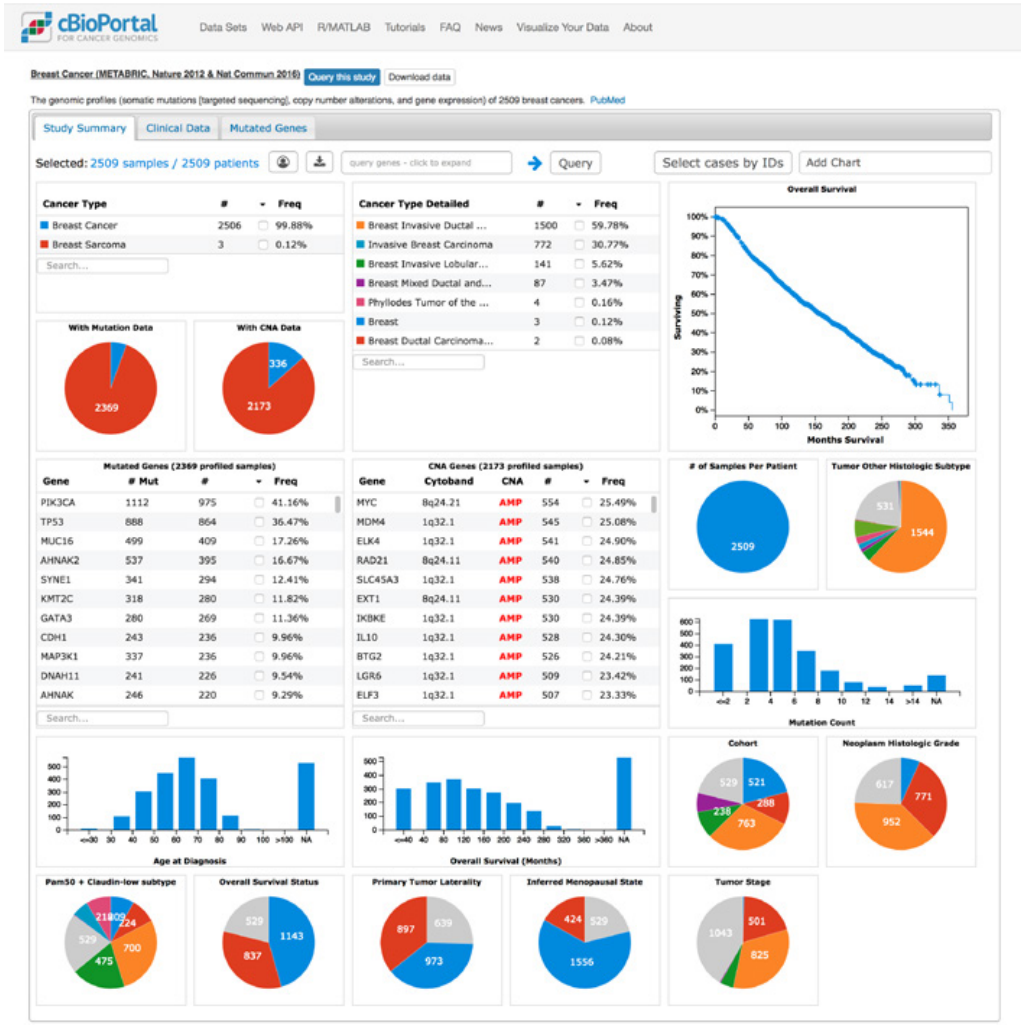
To achieve the kind of genomic medicine that MSK leadership envisioned would require multidisciplinary collaboration along with formalized mechanisms and expertise to take genomic findings into clinical practice. Dr. Baselga prioritized the formation of a group that would bring this all together: the Center for Molecular Oncology (CMO). By design, CMO is closely allied with investigators in HOPP, Cancer Biology & Genetics, Pathology, and the Clinical Trials Unit. Along with senior leadership, Dr. Baselga instituted a plan to enhance and modernize MSK's tissue banking and database infrastructure, and he searched for the right talent to build and run the CMO, starting with the appointment of David Solit as its inaugural Director and Marc Ladanyi and Maria Arcila to establish the molecular diagnostics workflow. Marie-Josée and Henry Kravis appreciated this vision, and with their financial backing, the Marie-Josée and Henry R. Kravis Center for Molecular Oncology became a reality in 2014. In a short time, the CMO has selected exceptional experts, such as Michael Berger, to design and implement the MSK-IMPACT™ clinical test now offered by the Molecular Diagnostics Service, and Nikolaus Schultz, who led the creation of cBioPortal, an open-access, open-source computational interface. Computational biologist and HOPP Assistant Member, Barry Taylor, now Associate Director of the CMO, was recruited to lead investigators in navigating and mining this rich data source. The CMO has already delivered remarkable clinical outcomes for patients in its basket studies, clinical trials that allow patients with metastatic cancer to receive a targeted agent as defined by their mutational profile. Precision oncology — basing treatment on the tumor mutation, rather than its location — is a paradigm-shifting approach to cancer care and an advance that will impact cancer cure and prevention profoundly.

Focus of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology

HOPP began as an experimental model for clinical-science-based translational cancer research, and it has been a success. Our collaborative framework of shared ideas, expertise, and resources has paved the way for a number of other translational initiatives at MSK, including the Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO), launched in 2014. The CMO is led by inaugural Director and HOPP Member David Solit, MD, an expert on defining the molecular drivers of bladder cancer and understanding how a patient's genetic information predicts disease outcomes and response to treatment. The CMO's mission is to pull together a diverse pool of investigators, many of whom are HOPP faculty, to translate novel molecular insights into clinical practice, with the aim of matching individualized therapies to each patient's cancer.

CMO investigators focus on:

- defining the natural history of tumors at a molecular level
- identifying genetic signatures that promote oncogenesis and represent potential therapeutic targets
- identifying patients who are predisposed to treatment resistance
- leading cross-disciplinary, collaborative team science efforts based on MSK discoveries
- designing assays for new targets and facilitating entry into target-based clinical trials



cBioPortal, a computational biology platform developed at MSK, is a popular resource for cancer researchers.

Barry Taylor, Associate Director, Center for Molecular Oncology

Nikolaus Schultz, Head of Knowledge Systems, Center for Molecular Oncology

A Q&A WITH TIMOTHY A. CHAN

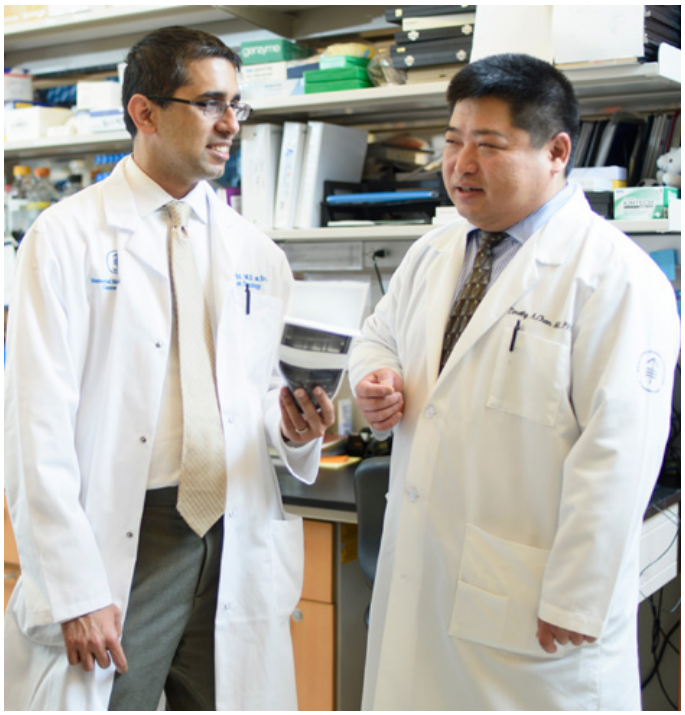
Physician-scientist and cancer geneticist Timothy Chan joined HOPP in 2007. Dr. Chan is Vice Chair of the Department of Radiation Oncology and Director of the Translational Oncology Division. In addition, he heads the recently established Immunogenomics and Precision Oncology Platform (IPOP), a program that grew out of HOPP.

What are immunogenomics and immunotherapy?
Immunogenomics is the use of large-scale genomics technologies to understand the immune system's response to cancer. This knowledge is critical for us to design therapies that encourage a patient's own immune system to fight cancer (immunotherapy).

Immunotherapy works well in some cancers and some patients but not in others. Broadly speaking, what are the questions you and your IPOP colleagues are trying to answer in this regard?
As the field of immuno-oncology has exploded in the past several years, the whole paradigm for how immunotherapy is used has shifted, and it's become evident that we need to focus on the mechanisms that allow a patient's immune system to recognize and eliminate tumor cells. This is a prime goal in oncology as we try to improve the efficacy of immunotherapy strategies.

As such, we're trying to learn more about how immunotherapy changes the immune cell repertoire and the selective pressure directed against tumor cells. Some of the questions we're asking are how does the tumor cell population evolve as this pressure changes, what underlies resistance and response to immunotherapy, and can we identify which patients and what cancer types are likely to respond to any given immunotherapy? The ultimate goal, of course, is to personalize immunotherapies so that every patient can derive benefit.

What is IPOP designed to accomplish?
IPOP has several goals. We're here to provide MSK with dedicated immunogenomics capabilities, molecular data from immunotherapy-treated patients, and a platform for our investigators to work with the pharmaceutical companies running immunotherapy trials to incorporate correlative work into the trials. We're also working with MSK clinicians and industry partners to design better trials.



Timothy Chan (right), Director of the Immunogenomics and Precision Oncology Platform, with Nadeem Riaz, its Associate Director of Genomics Operations

We are working to use a data-driven approach to develop more-effective immunotherapies.

Can you talk about some of the research at IPOP?
In the area of response and resistance, we're concentrating on a number of cancer types. We have large efforts examining kidney cancer, head and neck cancer, and melanoma. We also have several collaborative projects throughout MSK and major agreements with industry partners.

In terms of treatment response, one of the things we've discovered is that the more mutations a patient's tumor has — what's known as mutational load or mutational burden — the better that patient will respond to immunotherapy. This has not only become a globally used marker of response but also allows us to better understand what mutations the immune system is recognizing (neoantigens). If more mutations mean a better response, then some of these many mutations are what the T cells recognize and can attack. Tests utilizing these concepts are being actively evaluated by the FDA for approval. Our work has been a main factor in the current explosion in research on how the cancer genome influences immunotherapy efficacy. Our studies have also been a prime driving force for the current excitement about neoantigen-based cancer vaccines.

My IPOP colleagues and I are working to build better capabilities at MSK to find neoantigens and novel immunotherapy targets, which we anticipate will form the next generation of cancer-vaccine-based therapies as well as new targets for engineered T cell therapies.

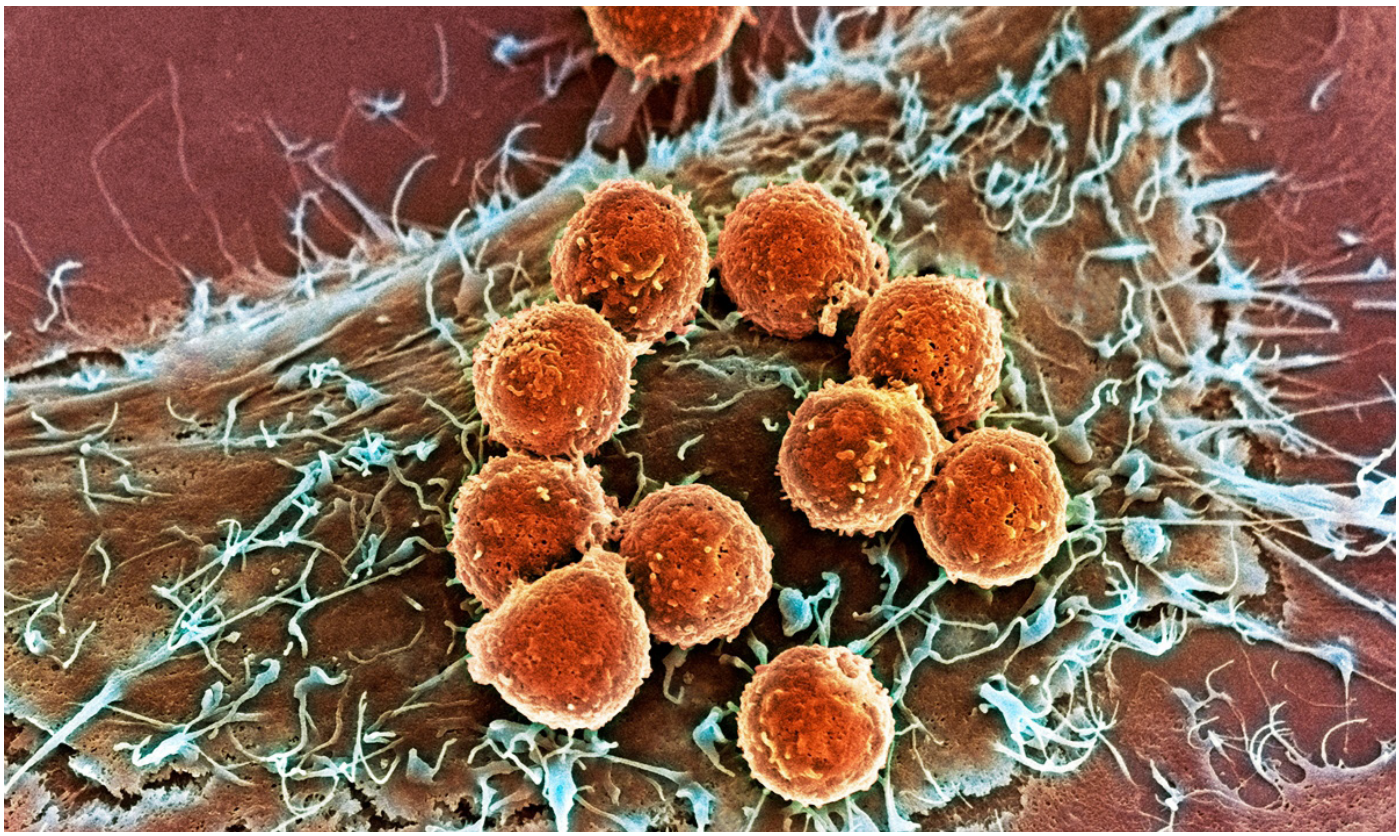
Can you talk about some of the work from your own lab?
The first product that IPOP developed came out of my group. We designed the first genetic test for immunotherapeutic response based on mutation burden. These tests are now used in the clinic as companion diagnostics, and there are a number of trials — in lung cancer, bladder cancer, and small cell lung cancer — that have all shown the value of using high mutational burden as a predictor of which patients will respond to immunotherapy.

We also have a large project in which we are trying to figure out how a person's genetic makeup — the different flavors of normal genes that we all carry — affect immunotherapy response. We recently completed a study of more than 1,500 people showing that a person's genetic makeup can actually influence survival after immunotherapy. We believe these are exciting findings that will open up the next new frontier of investigation in this field.

What collaborative relationships does IPOP have?
Among our most important relationships are those with pharmaceutical companies. We designed IPOP to be a nexus for easy collaborations with these companies and currently have agreements with Bristol-Myers Squibb, Astra Zeneca, and Merck. Our main function is to look at who is responding in their large trials of immunotherapeutic drugs and, based on that data, help design the next generation of trials.

How does HOPP facilitate the work of you and your colleagues?
HOPP is dedicated to using concepts in precision oncology to understand cancers and develop better treatments. The HOPP model is perfect for this type of work. There are lots of innovative ways to apply genomics and precision oncology to this new family of anticancer therapies but the rules remain to be defined. The HOPP faculty provides the deep expertise and open collaborative spirit needed to do this work; and the infrastructure at MSK, the institutional protocols — such as the ability to collect tumors and to sequence tumors quickly — has been vital to advancing our research, with the aim of achieving even better results for more patients.

HOPP has been an absolute gem. I can't see how this work would have been done more quickly in any other institution.



T lymphocyte cells (orange) attached to a cancer cell

OUR PARTNERS

HOPP's progress has been made possible through the generosity of a multitude of supporters. Their commitment allows us to capitalize on the extraordinary discoveries being made in both our labs and our clinics and to generate the preliminary data that leads to vital additional grant funding.

Team HOPP joins **Cycle for Survival** to raise funds for rare cancer research at Memorial Sloan Kettering. Here, HOPP member **Ross Levine** (in black) is joined by researchers (left to right) Stanley Lee, Young Rock Chung, and Santosha Vardhana.

OUR PARTNERS

Cycle for Survival

Cycle for Survival is the movement to beat rare cancers. Since 2007, Cycle for Survival has raised more than $105 million through its signature indoor team cycling events, staged by Equinox fitness centers in cities across the United States. One hundred percent of every donation funds pioneering rare cancer research led by Memorial Sloan Kettering Cancer Center.

Since 2011, Team HOPP has raised $500,000 and grown exponentially to include colleagues, friends, and family. The team now rides at multiple Equinox locations in several cities annually.

Cycle for Survival funding is allocated to HOPP annually to support our department's bold and groundbreaking studies and clinical trials. HOPP and Cycle for Survival are intrinsically linked in the fight against rare cancers, dedicated to finding new and better treatment options for patients everywhere.

MSK President and CEO Craig Thompson receives Cycle for Survival funding.

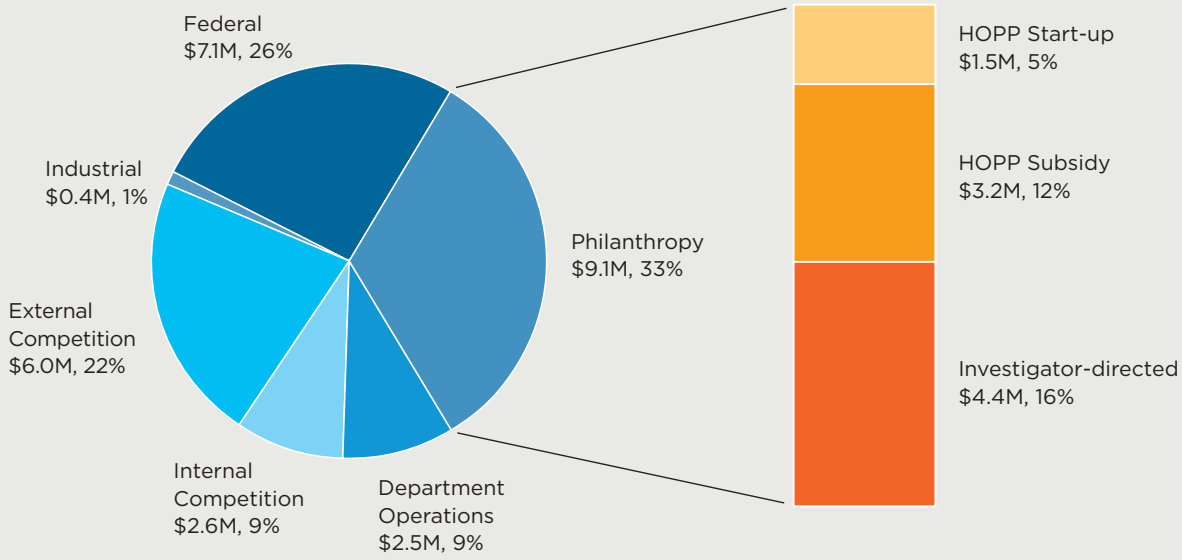
Left to right: MSK Physician-in-Chief José Baselga, MSK President and CEO Craig Thompson, oncologist and breast cancer expert Clifford Hudis, and HOPP Chair Charles Sawyers.

Left to right: Mara Hutton, Executive Vice President, Geoffrey Beene Foundation; Kellan Lutz, Actor and Activist for the Geoffrey Beene Foundation Frame This...Revelations campaign; Christine Iacobuzio-Donahue, Pathology Attending and HOPP Affiliate Member.

Geoffrey Beene Cancer Research Center

The Geoffrey Beene Cancer Research Center at MSK has been dedicated to funding innovative and cutting-edge translational research since it was established in 2006. Throughout the last decade, the center has supported many HOPP faculty members by providing pilot funding for research projects that have then led to competitive awards and federal grants. The center has also presented endowed chairs to young investigators to provide additional support during the lab start-up phase.

HOPP FINANCIALS



For the year 2016, HOPP research expenses totaled nearly $27.8 million. HOPP research expenses are supported in large part by federal and external peer-reviewed grants, internal competitive awards (e.g. Starr Cancer Consortium, the Beene Center), and philanthropic gifts that go directly toward research in laboratories of individual principle investigators.

The department also maintains relationships with philanthropic funding partners, such as Cycle for Survival and others, to support programs that are unique to HOPP. The HOPP Start-up fund provides three years of guaranteed laboratory research funding for new faculty, while the HOPP Subsidy is a grant-matching resource that supports the development of new research projects.

The HOPP Start-up, HOPP Subsidy, and other philanthropic seed funding support the early stages of discovery required to bring truly innovative therapies to patients, making HOPP researchers competitive for large federal and external peer-reviewed grants.

HOPP FACULTY (2007–2017)

	CURRENT	PAST
CHAIR	Charles Sawyers, MD	
MEMBER	José Baselga, MD, PhD Timothy Chan, MD, PhD Emily Cheng, MD, PhD James Fagin, MD Marc Ladanyi, MD Ross Levine, MD Ingo Mellinghoff, MD David Solit, MD	Scott Armstrong, MD, PhD Boris Bastian, MD, PhD William Gerald, MD, PhD Steven Leach, MD
LABORATORY MEMBER		Adriana Heguy, PhD
ASSOCIATE MEMBER	Omar Abdel-Wahab, MD	James Hsieh, MD, PhD
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AFFILIATE MEMBER	Michael Berger, PhD Christine Iacobuzio-Donahue, MD, PhD Jorge Reis-Filho, MD, PhD Michael Roehrl, MD, PhD Maurizio Scaltriti, PhD Nikolaus Schultz, PhD David Tuveson, MD, PhD	

EXTERNAL ADVISORY BOARD MEMBERS

HOPP relies on the advice and expertise of world-renowned cancer experts who form our External Advisory Board (EAB). The EAB meets annually to evaluate research progress and new directions, assist with strategic planning, and help identify new faculty recruits.

ACTIVE

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St. Jude Children's Research Hospital

Todd Golub, MD
Broad Institute, Harvard Medical School

William Kaelin, MD
Dana-Farber Cancer Institute

Kevin Shannon, MD
University of California, San Francisco

Sanford Markowitz, MD
Case Western Reserve University

Kathleen Cho, MD
University of Michigan

EMERITUS

Stanley Riddell, MD
University of Washington,
Fred Hutchinson Cancer Research Center

Steven Leach, MD
Johns Hopkins University

Lynda Chin, MD
MD Anderson Cancer Center

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$10,000,000 – $15,000,000

Cycle for Survival
Arnold Goldstein
Julian H. Robertson
Tow Foundation
DeWitt Wallace Foundation

$1,000,000 – $5,000,000

Geoffrey Beene Foundation
Jamie and Jeffrey Harris
Estate of Donald G. McKeon
Trust of Henry H. Shepard

$500,000 – $999,999

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The Society of Memorial Sloan Kettering Cancer Center

$75,000 – $299,999

Mr. and Mrs. Robert D. Allen
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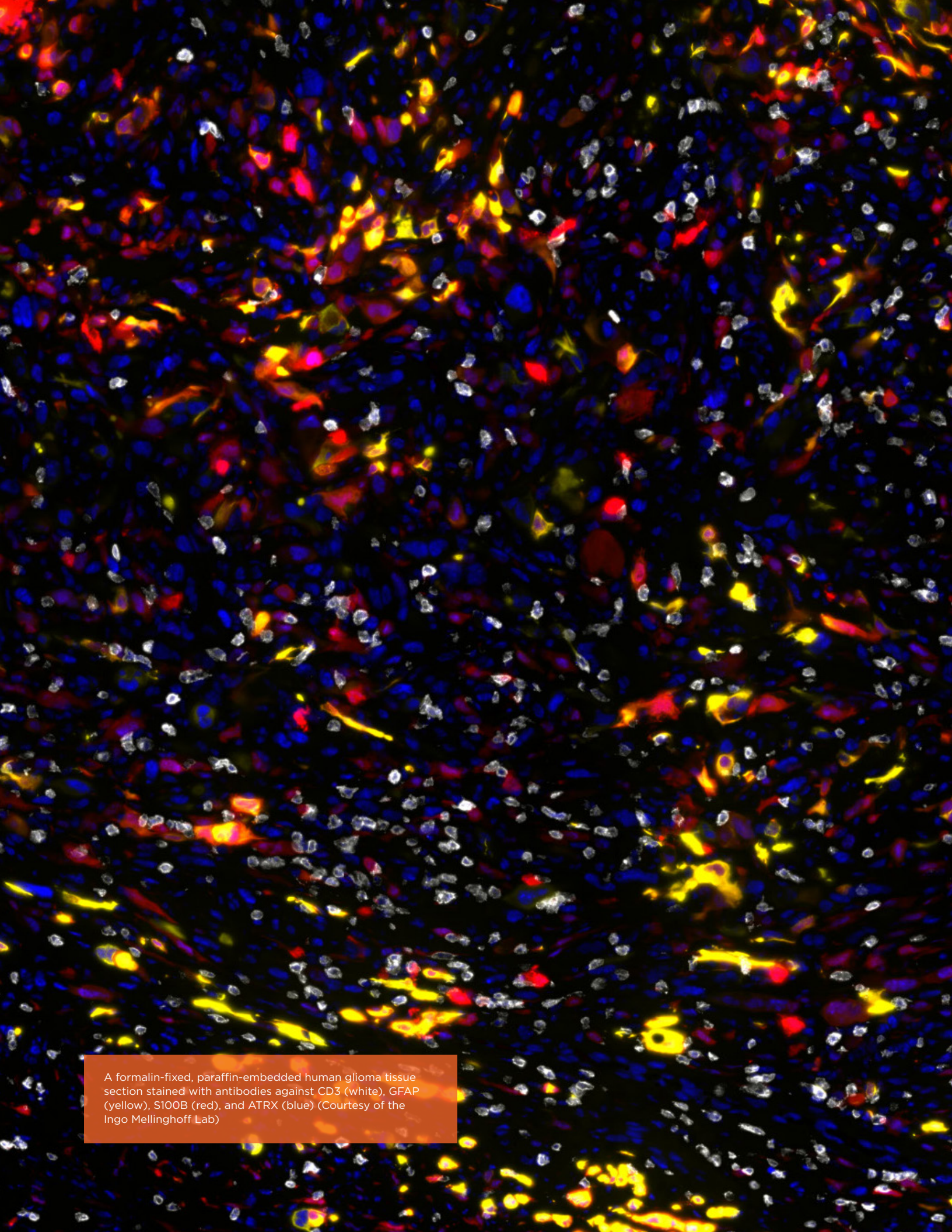

A formalin-fixed, paraffin-embedded human glioma tissue section stained with antibodies against CD3 (white), GFAP (yellow), S100B (red), and ATRX (blue) (Courtesy of the Ingo Mellinghoff Lab)

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