OUR OWN MEDICINE

What makes U-M one of the premier academic cancer drug development programs in the country?

BY IAN DEMSKY

WHEREVER SHE GOES, KELLY SEXTON'S MESSAGE IS THE SAME — WHETHER SHE'S MEETING WITH PHARMACEUTICAL EXECUTIVES IN THE BAY AREA, VENTURE CAPITALISTS IN NEW YORK OR OTHER POTENTIAL PARTNERS IN TURNING SCIENTIFIC ADVANCES FROM THE UNIVERSITY OF MICHIGAN INTO NEW MEDICINES FOR CANCER AND OTHER DISEASES.

Kelly Sexton, Ph.D.

Eric Fearon, M.D., Ph.D.

"When we meet with investors and executives, they're surprised to learn that we have the largest annual research volume of any public university in the country — over $1.6 billion — and that we're No. 2 in the country for research funding from the National Institutes of Health," says Sexton, Ph.D., who heads the university's office of technology transfer, which is responsible for the commercialization of research discoveries.

She also likes to point out that when it comes to drug discovery, an analysis by researchers at Yale and Washington University found U-M has discovered more novel molecular entities that have eventually led to compounds approved by the Food and Drug Administration than any other university or research institution in the world.

"At U-M, we bring the great breadth and depth of our expertise to bear on the fundamental genetic, molecular and cellular mechanisms underlying human pathology," Sexton says. "And when you have a university as big as Michigan, additional layers of connection and support are critical — which is why we have programs to provide funding, mentorship and commercialization assistance."

That level of support has made a striking impression on ovarian cancer researcher Analisa DiFeo, Ph.D., who recently received an internal drug discovery grant to work with the U-M Center for Chemical Genomics to find inhibitors of a micro-RNA that is amplified in recurrent tumors.

"Having recently come from another institution, I can say the support for drug discovery at U-M is phenomenal," says DiFeo, associate professor of pathology and of obstetrics and gynecology at Michigan Medicine. "It's not like they just give you the money and say good luck. We just had the kick-off meeting for my project, and you could tell that everyone in the room was invested in its success."

The goals of the Rogel Cancer Center mirror those of the larger university, says Eric Fearon, M.D., Ph.D., Emanuel N. Maisel Professor of Oncology and director of the Rogel Cancer Center.

"The top goal is always to generate knowledge for the public good," says Fearon. "And while building knowledge about human health is tremendously valuable in itself, scholarly work also needs to have a tangible effect on people's lives."

A formidable foe

Developing new drugs is notoriously difficult and expensive — just 14% make it from early-stage clinical trials to approval by the FDA, according to an MIT study from 2018, the largest of its kind. And many thousands of efforts wash out before ever making it to an initial trial.

The success rate for oncology drugs in particular is even lower, the study found.

There are many reasons, including the nature of cancer itself — its stubborn intractability and the havoc wreaked in the body by the poisons used to curb it.

"Because of the sheer number of cells that you're trying to treat in a patient with advanced cancer and the high mutation rate, there's a strong likelihood there will be drug-resistant populations, even if you have a particularly good, targeted therapy approach," Fearon says.

This necessitates looking not only for new and better ways to shut down cancer's runaway growth and ability to spread, but also at multi-drug cocktails that aim to cut off every avenue by which cancer might retreat and retrench.

The Michigan difference

Despite the inherent challenges, U-M has developed one of the preeminent academic cancer drug development programs in the country, Fearon says.

"That's in terms of the quality and scope of the science, the number of targets that are being evaluated, the number of potentially interesting compounds that are being developed," he says. "In recent years, we've had nine compounds make it into initial human trials. That's a pretty enviable record for any academic institution."

At present, U-M Tech Transfer is tracking about 50 active anti-cancer drug-development projects that are closing in on a lead compound to advance to clinical trials, says Sexton.

"If we look at earlier-stage projects, it's in the hundreds," she says.

Cancer therapeutic technologies account for nearly 10% of Tech Transfer's entire portfolio. And out of these efforts, two to three new startups are formed annually to bring oncology discoveries to the clinic.

"It's a really exciting time for biomedical research and drug discovery at U-M," says Sexton, noting that $500 million in new funds are supercharging investments in faculty recruitment, cutting-edge technologies and research programs. These include President Mark Schlissel's $150 million Biosciences Initiative, a transformative $150 million gift to the cancer center from Richard and Susan Rogel, $38 million for the university's Precision Health research initiative, $30 million to create the Chad Carr Pediatric Brain Tumor Center and a $17.5 million gift to establish the Forbes Institute for Cancer Discovery within the cancer center.

Philanthropy is also helping to accelerate the development of new therapies. Tom McConnell, who sits on the Rogel Cancer Center's National Advisory Board, and his wife, Trish Turner McConnell, recently established a fund for early stage drug development efforts.

"The Rogel Cancer Center has the opportunity to fund deeply knowledgeable U-M cancer experts in early stage drug discovery," McConnell says. "These research scientists understand the etiology of the cancer disease process and have the expertise to develop novel compounds based on this understanding. Academic scientists at U-M may have more leeway to pursue innovative compounds targeting novel cancer disease pathways than traditional pharmaceutical developers who are constrained strictly by a profit motive."

Another factor in U-M's success, Sexton says, is Michigan Drug Discovery, an umbrella group that helps find, fund and mentor drug discovery projects across the breadth of campus. The Rogel Cancer Center is a major sponsor of the effort and is well-represented on its executive board.

The group awards pilot grants for use within the university's core laboratories for high-throughput screening, structural biology, pharmacokinetics and medicinal chemistry. To date, the effort has invested about $2.3 million into more than 70 therapeutic projects — helping to secure more than $17 million in additional support while advancing them from the bench toward the bedside.

Follow the science

Basic science researchers at the Rogel Cancer Center are divided into four programs, one of which is focused specifically on drug discovery. This developmental therapeutics program is co-led by Jolanta Grembecka, Ph.D., associate professor of pathology at Michigan Medicine, and Judith Sebolt-Leopold, Ph.D., research professor of radiology and pharmacology at Michigan Medicine. Both sit on the Michigan Drug Discovery executive committee.

Sebolt-Leopold spent two decades developing oncology drugs for Parke-Davis and Pfizer in the same scientific complex where her U-M lab now resides. Before she left the pharmaceutical industry, she headed up a department of more than 100 scientists involved in early stage drug discovery across many therapeutic areas.

"Greater than 80% of the members of the Rogel Cancer Center's developmental therapeutics

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program have filed patents or have intellectual property disclosures that have contributed to our portfolio," Sebolt-Leopold says. "To me, that's a great measure of how successful and active our program has been."

Sebolt-Leopold can count herself among that number. In addition to her research program at U-M, she co-founded Mekanistic Therapeutics, a startup company dedicated to the rational design and development of kinase inhibitors that selectively inhibit multiple oncogenic pathways.

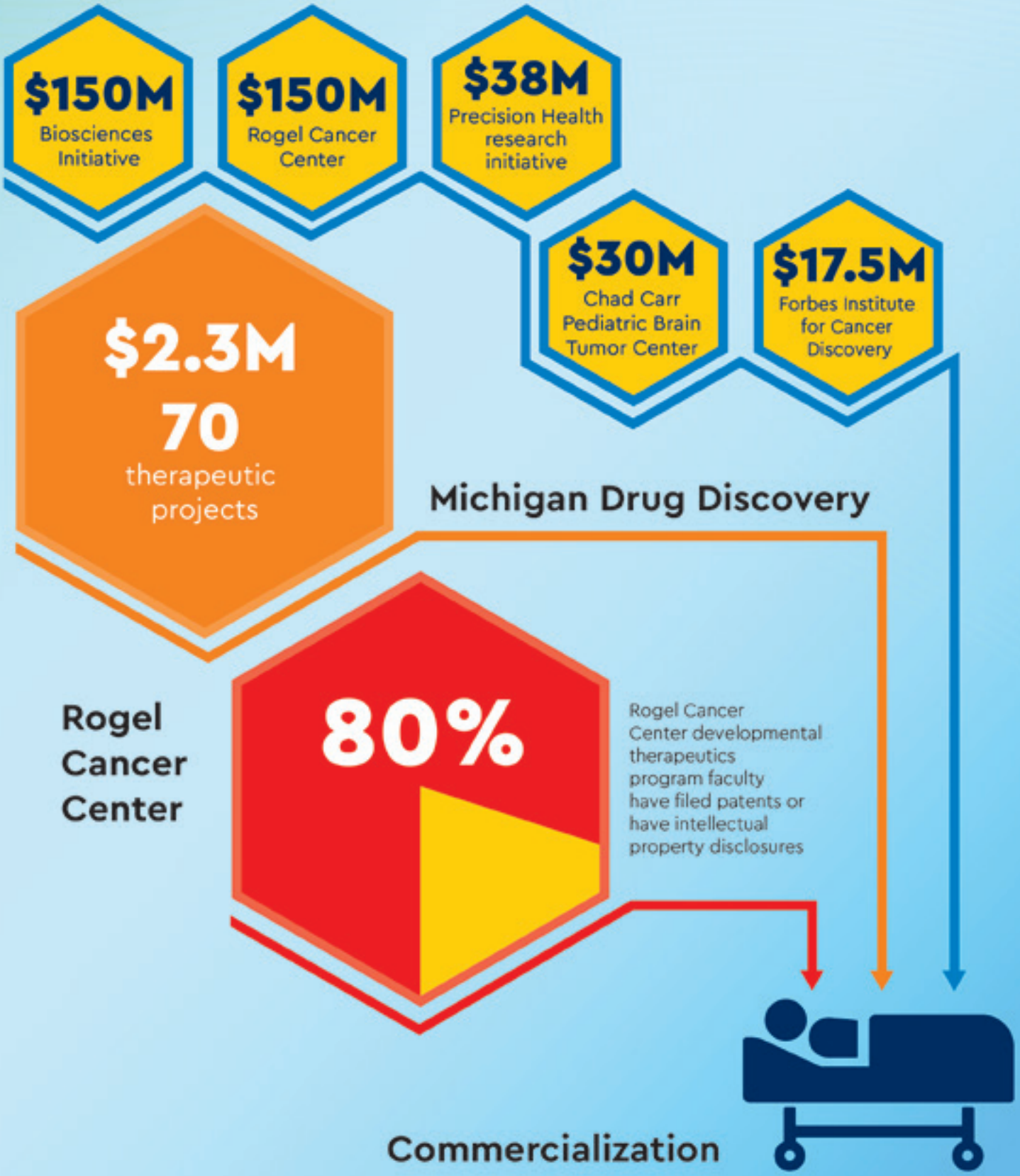
Together with Christopher Whitehead, Ph.D., also a former member of Pfizer's MEK inhibitor research team, Sebolt-Leopold developed a lead compound — MTX-211 — which represents a first-in-class molecule that selectively and potently inhibits EGFR and PI3K, two critical oncogenic kinases known to drive progression in a number of tumor types, including squamous carcinomas and colorectal cancer.

"It's effectively a combination approach in a single molecule," she says, adding that the company expects to file its application with the FDA to launch clinical trials in 2020.

Meanwhile, she stresses how proud she is of the therapeutics program as a whole.

"We have a nice balance of projects at every stage of the drug discovery continuum," Sebolt-Leopold says. "And we have great diversity in the approaches our faculty are taking. There is no one right way. You have to follow the science with the ultimate goal of matching the right drug to the right patient."

Funding the Future of Discovery across U-M



DRUG DISCOVERY SPOTLIGHT

With dozens of U-M projects across every stage of the drug discovery pipeline, here's a look at how several Rogel Cancer Center researchers aim to turn insights made at the lab bench into tomorrow's treatments.

Lasting tumor regression in leukemia and lymphoma mouse models

For decades, a transcription factor known as STAT3 has been a major therapeutic target in cancer. But STAT3 has largely been considered undruggable due to the difficulty of developing compounds to effectively inhibit its activity.

Researchers at the Rogel Cancer Center have taken a promising new approach to targeting STAT3 — developing a small-molecule compound that harnesses the power of a natural cellular "cleanup" system to get rid of it entirely, rather than traditional methods that have tried to block its action.

Shaomeng Wang, Ph.D.

The U-M compound was able to achieve a long-lasting and nearly complete elimination of tumors in mouse models of leukemia and lymphoma, the authors reported in *Cancer Cell*.

"STAT3 plays a major role in almost every aspect of human cancer," says study senior author Shaomeng Wang, Ph.D., Warner-Lambert / Parke-Davis Professor of Medicine at the U-M Medical School and professor of medicinal chemistry at the College of Pharmacy. "It also has been implicated in autoimmune and inflammatory diseases. So, there's a lot of therapeutic potential if one can target STAT3 successfully."

Working with Oncopia Therapeutics, a U-M start-up company co-founded by Wang, the research team is completing studies required for filing an investigational new drug application with the FDA, which is required to initiate human clinical trials.

U-M-developed STAT3 degrader achieves long-lasting elimination of tumors in mouse models

U-M-developed drug for acute leukemia enters clinical trials

Protein-protein interactions, such as those that occur between menin and MLL fusion proteins in a rare type of acute leukemia, had long been considered undruggable. And current treatments are not very effective, with just over a third of patients surviving five years.

Rogel Cancer Center researchers Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D., developed the first small molecule inhibitors of the interaction between menin and MLL.

"The MLL-menin interaction is a good drug target because it's the primary driver of this type of leukemia," says Grembecka, associate professor of pathology at Michigan Medicine. "By blocking this interaction, it's very likely to stop the cancer."

The interaction is found in about 10% of adult acute leukemia cases and 70% of infant cases.

To advance their research findings into clinical trials, the university partnered with Kura Oncology. Joint efforts led to the development of a clinical candidate compound, KO-539, which received approval from the FDA in March 2019 for a phase 1 trial. The trial, in patients with relapsed acute myeloid leukemia, launched in September.

Meanwhile, Grembecka and Cierpicki, associate professor of pathology at Michigan Medicine, have been collaborating with other U-M researchers to assess the activity of their menin-MLL inhibitors in prostate cancer, Ewing sarcoma and melanoma, which feature the same interaction.

Tomasz Cierpicki, Ph.D. and Jolanta Grembecka, Ph.D.

KO-539

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Machine learning: A United Nations approach to drug discovery

On one side of the equation, there are some 100,000 human proteins or protein-protein interactions that are potentially druggable, says medicinal chemist Nouri Neamati, Ph.D., John G. Searle Professor of Medicinal Chemistry at the College of Pharmacy.

On the other side, the number of chemicals that could potentially serve as drugs: a one followed by dozens of zeroes.

"You'd want to mathematically match the right chemical with the right target, right?" he says. "But, no — it's impossible, because for any given target you have billions and billions of possibilities."

Neamati's approach is to let smart computer algorithms do the heavy lifting — drawing on the same machine learning techniques used by services like Netflix and YouTube to personalize recommendations based on what other users with similar tastes have watched.

"Machine learning is used in practically every area of life, but in terms of drug discovery it's fairly new," says Neamati.

Neamati has developed a database containing 10 million compounds, which he's grouped together into different clusters. He keeps 40,000 reference samples in 11 freezers in his lab.

"We call them the United Nations of compounds because of the way the United Nations works: you have one person representing an entire country," he says. "So we have one compound from each cluster of compounds — sulfonamides, benzamides — representing all the rest."

When a promising result is found, a cluster can be explored more deeply. In a recent interview, Neamati pointed to two ongoing projects that have emerged using the technique.

While antioxidants may be popular dietary supplements, recent research in lung cancer patients has shown they may actually make things worse. Neamati's group has found promise in an opposite approach.

"Normal cells can cope with adding pro-oxidants, but a cancer cell is already so stressed, when you add the pro-oxidants the cells just crash and burn," he says, expressing optimism about preclinical studies underway in a pancreatic cancer model.

Another of his lab's projects targets a protein that is responsible for correctly folding thousands of other proteins so they can function correctly. As cancer cells replicate, this protein is essential to maintaining a semblance of order inside the rapidly dividing cells, especially in brain cancer.

"Imagine you go into a clothing store and instead of being neat and orderly on the shelf, the clothing is just piling up everywhere in a big mess," Neamati says. "If we inhibit this key protein, the cancer cells die because they can't cope with so much unfolded protein everywhere."

Nouri Neamati, Ph.D.