Universities make investments all the time — in faculty hires, in technological infrastructure and even in football recruits. One place where savvy academic investments have the potential for a big societal payoff is in backing drug discovery projects.

But developing new drugs is notoriously difficult, and many promising leads simply won’t pan out. This is why small seed grants can be vital in helping scientists to determine whether a novel line of inquiry is worth pursuing further.

“The path from a biological insight to a clinical trial is strewn with pitfalls,” says Vincent Groppi, Ph.D., the director of the University of Michigan’s Center for the Discovery of New Medicines — which launched in 2012 as a partnership between the U-M Life Sciences Institute, Medical School, Comprehensive Cancer Center, College of Pharmacy, and Provost’s Office to provide mentorship and early-stage support for drug discovery projects.

“What we’re really looking for is strong science and an unmet medical need, paired with the potential for commercial success,” Groppi continues.

The center, which was initially championed by the LSI, continues to be housed there, along with two of the core labs that support drug discovery efforts across the university: the Center for Chemical Genomics and the Center for Structural Biology.

“In its first five years, the CDNM has really blossomed into a truly collaborative, campus-wide resource and coordinating hub for drug discovery,” says LSI Director Roger D. Cone, Ph.D. “And the LSI is very proud to support those efforts not only administratively, but scientifically with our core technology and expertise in high-throughput screening and X-ray crystallography.”

The center awards investigators up to $50,000 in seed funding,
the vast majority of which must be used for experiments in the two LSI core labs, or within the medicinal chemistry and pharmacokinetics cores at the College of Pharmacy.

An executive committee of senior researchers from bioscience departments across campus reviews the project proposals and selects the most promising prospects to back.

Last year, a project to further develop a promising new approach to treat ovarian cancer received $37,000 in seed funding from the CDNM. With that investment, the researchers were able to generate the proof-of-principle data they needed to secure a three-year, $1.8 million grant from the National Cancer Institute.

“It’s a bit of a Catch-22,” says Scott Larsen, Ph.D., research professor of medicinal chemistry at the College of Pharmacy, director of U-M’s Vahlteich Medicinal Chemistry Core and co-principal investigator on the NCI grant. “You have a great idea, but you need to prove it’s worth funding. To get that data, you might need to do high-throughput screening or medicinal chemistry or pharmacokinetics — and that takes money. So these pilot funds are extremely important.”

About 21,000 women in the United States will be diagnosed with ovarian cancer this year. While surgery and chemotherapy initially will seem to cure most of them, 14,000 will relapse and die of the disease.

“So there’s this huge, huge need. And we really haven’t pushed the needle in ovarian cancer very far in the past 30 years,” says Ronald Buckanovich, M.D., Ph.D., the other U-M investigator on the NCI grant.

The high mortality rate, scientists believe, is due to a small pool of chemo-resistant cells that drive recurrence and metastasis.

“Imagine a field of dandelions,” says Buckanovich, a medical oncologist and researcher, who this fall took a position at the Magee-Womens Research Institute at the University of Pittsburgh.

“You can mow them and the field will look great. But the roots are still there, and a week later you have a field full of dandelions again. We think these cancer stem-like cells are the cancer equivalent of the dandelion root.”

Buckanovich’s lab has been investigating the biology of these cells and looking for ways specifically to target them. An important characteristic they share is increased activity of an enzyme called aldehyde dehydrogenase, or ALDH for short.

“The obvious question is, ‘What is that ALDH doing?’” he says. “It’s known that ALDH can promote chemotherapy resistance, but how it does this is not completely known. In some cases, it can directly metabolize the chemotherapy drugs and make them inactive.”

The hope was that disrupting ALDH’s ability to function would...
Rob the cancer stem-like cells of their ability to survive chemo and thus to start a new wave of cancer growth.

So Buckanovich partnered with Larsen at the U-M College of Pharmacy’s medicinal chemistry core to identify ALDH inhibitors to test in cell lines and mouse models. Based on a lead aldehyde-based inhibitor from the literature, they selected a dozen commercially available analogs, one of which — 673A — yielded particularly promising results.

“We took this lead compound, and we showed that it made chemotherapy more effective,” Buckanovich says. “We showed that we could take mouse models in which the cancer is never curable and we could cure 60 percent of the mice by adding this drug. So we were seeing really, really exciting results.”

However, he adds, federal funding agencies and pharmaceutical companies weren’t interested in developing 673A further because other aldehydes are known for being too toxic for patients. So the U-M team partnered with investigator Thomas Hurley, Ph.D., at the Indiana University Medical School, whose work on ALDH had turned up a different class of inhibitors.

Buckanovich applied to the CDNM for the seed funding to conduct additional medicinal chemistry and pharmacokinetics work in the core labs at the College of Pharmacy to identify and refine analogs of the compounds from Indiana that would be at least as effective as 673A.

“We tested their compounds and again they depleted the stem cell pool,” Buckanovich says. “So that’s a good indication that ALDH really is the target. We now have two different chemical structures — completely different drugs — that do the same thing and lead to the same result.”

The additional information the researchers were able to glean was instrumental in securing the federal grant to further optimize and test the new series of ALDH inhibitors.

And, in this case, it was an even larger win, because the money for the seed grant originated with a philanthropic gift from a Michigan family to support this very type of early-stage drug discovery.

“It makes us feel really good that our contribution enabled this continued search for a new treatment for ovarian cancer,” says donor Jamie Stuart. “We couldn’t have hoped for a better return on our investment.”

Even if the ALDH inhibitor research continues to show success, a human clinical trial would still be at least five years away, the researchers say.

“This will be a major pillar of what we will do for the next 10 years, and my plan is not to retire
until we’ve got something we can take into the clinic where we can make a real difference for patients,” Buckanovich says. “People often ask if it’s difficult to be a doctor who primarily sees patients with advanced cancer. I always say, ‘That’s when you need a good doctor the most, right?’ As a clinician, I get to know my patients. When things are not going well, when the end is coming, they know me and I can help them make a good transition. While that is a challenge, it is also a positive. And as a researcher, I know I’m doing everything possible to find new treatments.”

Meanwhile, ALDH inhibitors aren’t the only U-M research to have found success after receiving seed funding from the Center for the Discovery of New Medicines. Researchers Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D., of the U-M Department of Pathology and Comprehensive Cancer Center, for example, used seed funds to help design a series of menin-MLL inhibitors that were the first small-molecule compounds to target the protein interaction responsible for an acute form of leukemia. In 2015, the project — which started with screening in the Center for Chemical Genomics at the LSI — was licensed by Kura Oncology, where it is in preclinical development.

Another seed-funded project, which also began with a screen in the CCG, this year led to a collaboration between U-M and a major pharmaceutical company to develop a drug to treat chronic kidney disease.

“This is an excellent example of the type of collaboration that can happen at a place like U-M,” says Groppi, the director of the drug discovery center. “The drug targets were developed by studying patients with the disease. The project utilized our high-throughput screening, structural biology and medicinal chemistry cores. It paired biochemistry and nephrology expertise from different Medical School departments, and it is being further advanced with additional streams of internal and external funding.”

The U-M Office of Technology Transfer was also instrumental in developing the partnership agreement.

“Taking the lead from President Mark Schlissel’s biosciences initiative, all of the campus units involved with drug discovery are focused more than ever before on identifying new opportunities for collaboration and synergy,” says James Dalton, Ph.D., dean of the College of Pharmacy and chair of the drug discovery executive committee. “We’re looking very closely at how the university is supporting drug discovery from early stages up through clinical trials — because we know that even small investments, when made correctly, can have big payoffs for advancing research and ultimately for society.”

Small drug discovery seed grants can blossom into big benefits for researchers and for society.