Innovation Partnership
year one progress report
2009-10
From Discoveries to Cures
The successful movement of a new medicine through the pipeline—from the initial observation by a scientist to clinical deployment to patients—requires funding, collaboration, and the expertise of many people along the way.

Lack of leadership, ownership, and funding at the critical point where government research support ends causes research discoveries to stagnate and potential drugs and treatments to go undeveloped, never reaching the patients who need them.

The Innovation Partnership at the U-M Life Sciences Institute (LSI) takes on this problem by infusing the projects of LSI scientists with funding and expertise from leaders in the top ranks of business, venture capital, and the biomedical industry.

The First Year: Science and Business Converge
The Innovation Partnership awarded $635,000 in gift funds from individuals and businesses to support four projects in 2009, thus creating an effective new model for shepherding early stage scientific discoveries through to the next phase of development.

Of the four funded projects, one became a spin off company, which will focus on diabetes and its associated problems, and the other three made phenomenal progress in the areas of neurodegenerative disease, bacterial infection, and cancer.

As a scientist who received funding in the Innovation Partnership’s first year, Jason Gestwicki, PhD, describes its impact, “Getting an experienced mentor group in place who can see the entire trajectory of your project and place it in context, and know what people and resources are needed to get your discovery from the bench to the bedside is so valuable. Either directly or indirectly, they can put the pieces in place to get the process moving in the right direction.”

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Neurodegenerative disease: Targeting the protein quality control pathway yields results in treating Alzheimer’s and other diseases

5.3 million people have Alzheimer’s disease, which is caused by abnormal protein misfolding and accumulation that leads to the formation of a neurotoxic tangled structure in the brain that kills neurons for good.

The lab of LSI faculty member Jason Gestwicki, PhD was interested in answering the question: What prevents this from happening in everyone? Is there a “protein quality control” process in the brain that prevents the accumulation of these toxic proteins? How does it work?

The team searched for small molecules that stimulate the activity of a protein called Hsp70, which prevents the protein misfolding in brain cells that causes progressive neurological diseases like Alzheimer’s. After screening tens of thousands of potential compounds in the LSI’s Center for Chemical Genomics (CCG), the Gestwicki team identified two particularly interesting chemicals and figured out how they bind to and regulate Hsp70.

They next turned their attention to a mouse model of Alzheimer’s disease. Preliminary experiments revealed that giving the compounds to the mice produced an improvement in learning and memory that correlated well with their activity on Hsp70, without any untoward side effects. These important findings validate this novel approach to Alzheimer’s disease and set the stage for a full-blown drug discovery project.

Gestwicki and team along with medicinal chemists at U-M are tweaking these compounds to improve both their activity and drug properties, with the goal of moving towards clinical trials in humans. They have already overcome one important hurdle with finding that their compound is able to cross the blood brain barrier and assess sites in the brain where the protein tangles arise.

Dr. Gestwicki says, “Pharmacologically targeting the protein quality control pathway so that it degrades a toxic substrate rather than rescues and misfolds it is how neurodegenerative disease will be prevented—helping the brain to get rid of the bad stuff before it does its damage.”

Targeting the protein quality control pathway may also lead to treatments for similar neurodegenerative diseases, such as Parkinson’s, ALS, and others.

Gestwicki says his Innovation Partnership mentor group was key in helping to decide which of his molecule finalists to pursue for further work as well as offering advice on crucial development decisions regarding safety and efficacy. Likening the drug discovery process to a relay race, Gestwicki says, “They know what questions need to be asked so the next person in the relay is willing to take it to the next phase, otherwise, it’s just seen as good science.”
Diabetes: Developing a new drug to treat Type 2 diabetes

Tens of millions of Americans have been diagnosed with Type 2 diabetes and millions more remain undiagnosed. The observation that most patients with type 2 diabetes are obese led LSI Director Alan Saltiel, PhD and his lab to explore this link. They have honed in on an interesting new hypothesis: this link is an inflammatory one—obesity gives rise to a state of inflammation and it is the inflammation that causes Type 2 diabetes.

After investigating many inflammation pathways, one stood out as particularly interesting—IKKE—an enzyme that they found to be elevated in obese mice compared to non-obese mice. When they deleted the IKKE gene, Saltiel says, “It was fabulous and surprising that not only did the knockout mice not become diabetic after a high-fat diet, they were also less obese than the corresponding mice who had IKKE.” They are currently investigating the biochemistry and cell biology that underlies this effect of deleting the IKKE gene.

The IKKE gene encodes for an enzyme that Saltiel thought might be amenable to chemical inhibitors, suggesting a new drug discovery program. “The Innovation Partnership is allowing us to investigate this part of the story.” Saltiel says, “This is what’s great about the Innovation Partnership—it can take forward projects such as this, that could result in the discovery of a drug to combat obesity, diabetes, fatty liver, and other associated problems.”

The team is currently working to profile IKKE and discover new chemical inhibitors by screening in the CCG library. With the funding provided by the Innovation Partnership, they have already identified small molecules that they hope to improve by studying their structures, properties, and potency, ultimately planning to test these compounds in obese animal models.

So confident and excited by the promise of the Saltiel lab’s work, his Innovation Partnership mentor group provided business advice and support to help form a new company around the project. The company, Vega Therapeutics, is focused on the area of inflammation and diabetes, and is the Innovation Partnership’s first spinoff—a major milestone for year one.
Bacterial infection: Focusing on a key pathway that controls the virulence of Strep and other infections

There are several million cases of strep throat and more than 10,000 cases of invasive group A Strep (GAS) diseases in the U.S. each year, which in some cases lead to death. Interested in the relationship between the blood-clotting system and how we protect ourselves from bacterial infections, LSI faculty member David Ginsburg, MD and his lab discovered that the human body uses blood clots to surround the Strep A bacterial infection as a natural defense.

However, a protein made by Strep A bugs—streptokinase—activates human plasminogen, which dissolves the blood clots, allowing the infection to spread rapidly throughout the body. This observation led the Ginsburg team to wonder whether they could render the bacteria innocuous by blocking production of streptokinase and in the process also reducing the threat of antibiotic resistance?

The lab, along with collaborators at the U-M Vahlteich Medicinal Chemistry Core and at the University of Missouri, searched for small molecules that turn off the production of the protein in live bacteria, with the hope that they could interfere with the mechanism used by the bacteria to spread the infection.

After screening tens of thousands of chemicals in the LSI’s CCG, the team identified ten promising lead compounds. Ginsburg says, “This is the classic ‘valley of death’ scenario. We could publish papers on the biology of our findings and the science community would be interested in reading it, but it’s not quite the platform for fundable research. We wouldn’t have pursued the project to the stage that we’re at now without the funding and advice provided by the Innovation Partnership.”

Another potential by-product of this project is the effect their compounds may also have on staph infections, which are highly resistant to existing antibiotics. Ginsburg plans to explore the possibility using their compound against this disease mechanism as well. “We’ve come upon a key pathway used by a lot of bacteria for turning on and off their virulence for causing infection.”

The team now plans to complete more chemistry to choose the right compound, test their potency, and start studying these compounds in animal models of infection.
Cancer: Creating novel anti-metastatic drugs for treating cancer

The incidence of cancer continues to increase. In 2010, 207,000 new cases of breast cancer are expected, along with 43,000 cases of pancreatic cancer, 21,000 cases of ovarian cancer, and 22,000 of glioblastoma (brain tumor). Many of these diseases are particularly hard to treat and for this reason are of special interest to LSI faculty member Stephen J. Weiss, MD.

The Weiss lab, under the direction of Dr. Weiss and LSI associate research scientist Dr. David Dudley, has been interested in understanding why cancer cells metastasize. They have developed procedures to grow cancer stem cells along with endothelial cells in a three-dimensional culture that mimics the growth of both metastatic cancer cells and the new blood vessels that feed their growth in the human body.

They are using cells grown in this more flexible model to generate panels of monoclonal antibodies that are then screened for their ability to block tumor cell spreading or neovessel formation in the three-dimensional model.

This experimental platform translates into an integrated program for accelerating the discovery of new therapeutic monoclonal antibodies that can prevent cancer cell growth and metastasis, which is what leads to untimely death.

This work has already yielded several promising antibodies that block the ability of breast cancer cells or glioblastomas to grow and invade tissues. Next steps involve expanding the panels to include ovarian and pancreatic tumors, creating more clones for screening, and examining antibody activity in animal models.

“This is a perfect example of an approach that would not be suitable for traditional funding—it’s a great idea but just needed the experimental traction that could only be obtained through innovative funding. For this project, the Innovation Partnership was utterly essential,” says Dr. Dudley.

The team is now at the point of narrowing down the number of molecules and proteins on which to focus. Dudley believes that the next stage will benefit greatly from the Innovation Partnership mentor group’s advice and guidance. While the project will generate papers, and add to the knowledge on cancer cell growth and migration in the human body, there is another force that moves this project forward, Dudley says, “Cancer treatments are the goal.”

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—Dr. David Dudley

Dudley and a lab member in the Weiss lab design experiments related to understanding why and how cancer cells metastasize.
The Innovation Partnership

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