TRUE DETECTIVES

The importance of seeking fundamental knowledge in an outcomes-obsessed world
Lois Weisman has studied yeast for nearly three decades. She’s spent much of that time trying to understand how precisely an organelle known as the vacuole is transferred from mother to bud when the single-celled fungi reproduce.

The vacuole performs a variety of important housekeeping functions for the cell, and Weisman discovered that the inherited portion is moved from parent to offspring by means of a molecular motor that moves along filaments in the cell.
The motor also moves several other organelles. Weisman’s lab has been delving into the mechanisms that tell the motor which cargo to pick up, where to take it and when to drop it off. They’re also investigating how and why the vacuole membrane changes its shape.

Why would anyone dedicate a significant portion of their career to the mysteries of the yeast vacuole?

“Yes, the research is about the yeast, but what’s fascinating is that we’re learning about fundamental cellular processes that apply to all organisms, including people,” says Weisman, a faculty member of the University of Michigan Life Sciences Institute, where her lab is located, and a professor of cell and developmental biology at the U-M Medical School. “These processes have a bearing on human health — in cancer, neurological diseases, aging.”

She offers up the examples of Leland Hartwell and Randy Schekman, scientists who each shared Nobel Prizes, in 2001 and 2013 respectively, for insights gleaned from yeast — insights that have opened new avenues of research for a variety of human illnesses.

“My research career has been motivated by a desire to understand cancer,” Hartwell said in his Nobel lecture. “Each time I have identified an intriguing aspect of the cancer problem, I have found that it could be approached more effectively in the simpler eukaryotic cell, Saccharomyces cerevisiae, than the human cell.”

The highly orchestrated movement of the yeast vacuole inspired Weisman.

“The right piece gets moved to the right place at the right time in the cell cycle,” she says. “Every cell in the human body, from a neuron to a skin cell, is similarly organized in space and time — and I realized that I could study larger underlying questions using this very simple system.”

It is this type of basic scientific investigation by which researchers at the LSI and across the globe are quietly widening the sphere of biomedical knowledge, usually to little fanfare. While the latest new drugs and medical innovations grab headlines, this “applied” research is almost universally built upon years of dogged, detective-like questioning by basic researchers: What? How? Why?

“Everything that happens in the cell happens for a reason, everything is regulated,” says Weisman. “Nothing is just floating around or randomly changing shape.”

“It’s not, she adds, that Hartwell and Schekman (a member of the LSI’s Scientific Advisory Board) set out to become Nobel laureates. “They started with really good, really important biological questions. How does the cell cycle work? How do cells transport and secrete proteins?”

The aim of basic scientific research is to deepen our understanding of nature and the laws that govern it, noted Vannevar Bush, who served as scientific advisor to President Franklin Roosevelt and who helped to create the National Science Foundation.

“Basic research leads to new knowledge,” he wrote. “It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn.”

Because such research is investigatory by nature, without a clear and immediate payoff, it is primarily supported by the federal government, rather than private corporations or philanthropy.

“University research is an investment in the future,” says S. Jack Hu, Ph.D., interim vice president for research at U-M. “Even if the new ideas and insights that emerge don’t make it to the marketplace in the short term, the research we conduct on campus is an essential part of how we prepare our students to be the next generation of innovators in industry and aca-
Basic research accounts for less than 20 percent of total research and development spending, the National Science Board reported in 2008.

And even this level of support is increasingly uncertain. Nondefense research spending fell from a peak of nearly 6 percent of the federal budget in the late 1960s to less than 2 percent today, according to the American Association for the Advancement of Science. And National Institutes of Health funding has been on a slow but steady decline since the mid-2000s.

In 2014, the Chronicle of Higher Education surveyed 67,000 researchers holding NIH or NSF grants to find out how the current funding climate was affecting them.

“For better or worse, the nation’s scientists have embarked on an unequivocal downsizing of their capability to perform basic investigative research,” the Chronicle reported. “Nearly half have already abandoned an area of investigation they considered central to their lab’s mission. And more than three-quarters have reduced their recruitment of graduate students and research fellows because of economic pressures.”

Moreover, the survey found great concern that the funding environment encouraged support of “safe,” incremental advances over more uncertain, but potentially revolutionary, exploration.

“I wish the public better understood how important it is to fund a mixture of better applications for what we already know, and pioneering leaps to see if we can discover something brand new,” says Weisman.

SI faculty member Anna Mapp, Ph.D., emphasizes basic research’s importance in developing a deep understanding of a biological system if you want to find a solution to a problem involving that system.

“I think most people intuitively understand that,” says Mapp, a professor of chemistry in the College of Literature, Science, and the Arts at U-M, and director of the Program in Chemical Biology.

When Mapp started investigating a motif in a protein known as p300 the better part of a decade ago, she didn’t have a clear picture of where the work might lead.

“It’s an important protein and I had a gut feeling we were going to find something of note eventually, but there was no straight line,” she says. “In the last couple of years it’s emerged as a key player in two types of cancer, adenoid cystic carcinoma and acute myeloid leukemia. And not only have we developed some small, drug-like molecules that can be tested as potential therapeutics, but we now have good knowledge about how to go about finding even better compounds.”

Mapp’s research focuses on transcription — the process by which genetic instructions in our DNA are read and acted upon.

“Unlike a car or a computer, which gets built once, the machine that reads the DNA in every cell is actually assembled each time the reading needs to happen,” she says. “There’s a lot that we know about this process — what the components are, how that composition of the machine changes, the identity of the activator protein in any given gene. But what we don’t understand well is the actual assembly step.”

Errors in this assembly process have been linked to human diseases from cancer to diabetes.

“Everything we do is aimed at developing tools so that we can better understand how the activator protein is assembling that machine to transcribe the DNA, and then we use a variety of techniques to identify molecules that can block problematic interactions,” she says.

Traditional genetic and biochemistry techniques have been able to produce only a limited picture of the assembly process, Mapp says.

In a new process that also relies on a yeast model, Mapp’s lab has been able to hijack the cell’s own machinery to add a designer amino acid into the activator protein. It remains fully
functional until mild ultraviolet light is shined on it — a tanning bed setup is squirreled away in the lab for just this purpose — at which point it locks onto the protein it’s interacting with, freezing the action mid-assembly.

“It took a lot of work, and an incredibly dedicated graduate student, to get the system up and working, but we’ve been able to use that now to map individual interactions between proteins,” she says.

Mapp is one of a growing number of scientists who see targeting these protein-protein interactions as a promising and exciting direction for drug discovery.

“Traditionally, when people have thought about drugging a key protein complex, they might think about targeting the enzyme that’s driving the biochemical action,” she says. “But if you block the enzyme, you block everything that complex does. If you hit the protein-protein interactions, then you can be more selective about the context inside of the cell.”

In basic research, new avenues of investigation can open up unexpectedly.

A postdoctoral researcher in the lab of Yukiko Yamashita, Ph.D., was the first to notice microscopic threads of connection between germ line stem cells in male fruit flies and the central hub where they reside.

Yamashita, a developmental biologist at the LSI, checked her collection of older images. Sure enough, they were there, too.

“I had seen them, but I wasn’t seeing them,” Yamashita says. “They were like a little piece of dust on an otherwise normal picture. After we presented our findings at meetings, other scientists who work with the same cells would say, ‘We see them now, too.’ ”

As she and her colleagues outlined in *Nature* in June, these nanotubular structures explain how a directive can be communicated directly to the stem cell without it being broadcast to other nearby cells. More importantly, perhaps, it serves as a reminder that there’s still a lot we don’t know about how cells communicate the right signals to just the right recipients at the right time.

“There’s so much more to understand about everything,” adds Yamashita, a Howard Hughes Medical Institute investigator, MacArthur Fellow and associate professor at the U-M Medical School.

There’s no doubt we are living at a time of unprecedented growth in knowledge. By one estimate, scientific output is doubling every nine years.

Recall, when the LSI opened its doors in 2003, it had been just months since the project to map the human genome was declared complete. Scientists have spent the years since developing increasingly sophisticated techniques to interrogate what our genes do and figure out how they work together. This past April, for example, LSI faculty member Ivan Maillard, Ph.D., published findings that identified a gene critical to controlling the body’s ability to create new blood and immune cells — opening new lines of inquiry into its role in cancers involving other members of the same gene family.

Scientific jurisdictions have also expanded as collaboration has become the watchword of academic research. (Search PubMed for “collaboration” and you’ll see the number of articles returned jump by more than 140 percent between 2004 and 2014.)

“Sometimes it’s a little scary to be a scientist,” says Weisman. “You always feel like you don’t know enough. We’ve advanced so much, people might get the sense that we know at least the outlines of everything, that the rest is just coloring them in — and every time you think that, you are so wrong. You are so wrong.”

She adds, “I still feel like a grad student — I honestly do — because I have to study as hard as the grad students to keep up. That is what I love so much. You have to stay young to do it, but it also keeps you young.”
In this age of instant gratification, the period between an initial insight and a practical application can feel glacial.

In 2002, a postdoctoral researcher at U-M named Ken Inoki was the lead author of a study in *Nature Cell Biology* that suggested an antibiotic known as rapamycin might be a potential treatment for a relatively common genetic disorder known as TSC, which causes benign tumors to grow in organs including the brain, heart and lungs.

The meat of the paper — which laid out its case in more than 5,000 words, seven illustrations and citations of 50 previous research studies — pried into the molecular mechanisms by which mutations associated with the disease trigger this damaging overgrowth of cells.

Inoki and his colleagues found that what gives rise to tuberous sclerosis complex, or TSC, is the removal of natural checks on an important signaling pathway that regulates cell growth and proliferation.

“What we were doing was pure biochemistry,” says Inoki, who today leads his own lab at the LSI. “You identify the proteins and test what happens if you delete this protein or that protein. How does it actually work? How much effect is there?”

In May, he learned that his long-ago observation had contributed to a big payoff. The FDA had approved a new use for rapamycin: treating a debilitating lung disease that affects some patients with TSC.

“We proposed this more than 10 years ago, and now I get the news that this drug was approved. It’s very nice, and I read about patients who were so thankful to all the researchers,” says Inoki, who holds an M.D. and Ph.D. from Japan, where he practiced medicine and treated patients with chronic diabetes before dedicating himself to research.

In recent years, Inoki’s work has focused on better understanding the role of the same pathway — mTOR, which stands for mammalian target of rapamycin — in the progression of diabetes and cancer.

“Basic research leads to new knowledge.”

“In diabetes, the problem is cell size; in cancer, it’s how many cells. Both are regulated by the same pathway,” says Inoki, who is also an associate professor of molecular and integrative physiology, and of internal medicine, at the U-M Medical School. “Because this pathway is so essential to life, you can’t block its activity completely, but the idea is that maybe you can find a way to limit it.”

Inoki says it’s the complexity of basic research, along with timelines that can span decades, that can make it difficult to convey its importance to non-scientists.

“I would consider it a nice achievement to make one more contribution like this during the rest of my career,” he says.

Each of the LSI researchers also notes that one of the keys to their success has been the institute’s organization and culture.

“There are so many advantages to being at the LSI,” Mapp says. “There are the obvious things like the fact that the core facilities are fantastic. But having 20-some colleagues who are not only top scientists in a variety of specialties, but who also are intensely curious about science, bringing their perspective, their questions, their insight to your work — there’s nothing like it.”

Ken Inoki, M.D., Ph.D.