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THE HUB

HHMI's Biggest Experiment

Janelia scientists walk and talk through one of the sinusoidal halls of the Ashburn, Va., campus. Credit: Jeff Goldberg/Esto.

Ivan Amato, *C&EN*

Nine years after opening its doors, how is the Janelia Research Campus living up to its founders' visions?

Gerald Rubin glows with satisfaction when he retells the story of Janelia Farm. On a crisp, early January morning, he sits in his capacious office in the sinusoidal, 900-foot-long research building at the end of Helix Drive, in Ashburn, Va., and explains how it all seemed to fall in place.

He and his colleagues at the Howard Hughes Medical Institute had invested $500 million to build a research campus with the intention of creating a great engine of biological discovery. They lured top-notch talent, some young and some already established, to partake in what amounted to a magnificent sociological experiment in the way science is done. They took a deep breath and set it all in motion. And then one of their first hires at the institution earned a Nobel Prize—less than a decade after they had opened their doors.

Of course, Nobel prizes are just one indicator of success for an institution—hundreds of institutions have a Nobel Prize to brag about. In their heydays last century, both of the primary institutional inspirations for Janelia—the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) and Bell Laboratories—collected Nobel Prizes on eight separate occasions. So Rubin, Janelia's first and so far only director, and Eric Betzig, the early hire that brought in the Nobel, realize that Janelia is an ongoing experiment whose success or failure will not be assessable for another decade. Still, nine years in, they're starting to examine what is working and what isn't.

The first glimmers of the Janelia experiment appeared in 1996 when David Clayton, a developmental biologist at Stanford University, joined HHMI as its senior scientific officer. He soon began to imagine an in-house research organization that could leverage HHMI's vast financial resources into a culture that would renovate biomedical research, not just add some momentum to the existing model. At the time, HHMI's primary model of research support, which remains in place, was to select and generously fund hundreds of top-tier academic researchers, known as HHMI investigators, around the world.

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In 1999, Thomas Cech, a biochemist at the University of Colorado, Boulder and Nobel Prize winner, became HHMI

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president, and latched onto Clayton's idea, setting into motion the course that would lead to the opening of what HHMI now refers to as the less agricultural-sounding Janelia Research Campus. Rubin joined the cause in 2000 when he took on the job as HHMI's vice president for biomedical research and then, three years later, the directorship of Janelia.

Some researchers outside HHMI were skeptical of the Janelia idea. "I was opposed to it at first, because I thought it would be better to invest in more Hughes Investigators", says Eric Kandel, a neurobiologist at Columbia University, another Nobel Prize winner, and an advisor who had been in early discussions about the idea.

But Clayton, Cech, Rubin, and the HHMI board thought spending more money the old way would lead to diminishing returns and wouldn't make much difference in furthering research progress. The reason was that, at the time, the National Institutes of Health was flush with cash. "Good people were getting money, so we did not have to save the [government funding] system", Rubin says. And if HHMI simply continued on its own course, it would become a mini-NIH with a budget utterly dwarfed by the federal agency.

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Instead they wanted to bring back what had gone all but missing in the scientific landscape: the Bell Laboratories and MRC-LMBs of the world where science trumps administration, management, and just about everything else. When the HHMI visionaries examined these institutions and other storied research cultures at places such as Cold Spring Harbor Laboratories, they discerned a common core of traits that they wanted to emulate as they grew their own research culture.

Key among these traits are small research groups with scientists who want to do science and do not want to manage the large-scale, often company-like operations that have become common in academic settings; generous internal funding that buys precious freedom from the need to chase grants; and a promise of patient and renewable support without the potentially creativity- and passion-killing institution of tenure.

Rubin says that Janelia's approach carries risks. Among them is its isolated location in suburban Virginia—a problem it solves with a vibrant visiting scientist program. Also a risk is the adoption of a research agenda that is, Rubin says, far narrower than that of a typical university biology department, albeit far more diverse in the multidisciplinary tools and strategies it applies to those problems. The campus focuses on how the nervous system works at the level of cells and circuits, and the challenge of developing new biological imaging and image-analysis tools.

After nine years, is the experiment working?

Kandel thinks so, though he would say Janelia has so far hit a triple, not a home run. He notes that Janelia is training a ton of people, and generously sharing their genetic, molecular, and imaging methodologies.

Betzig is on the fence. "The culture has lived up to my expectations, but in some ways it hasn't", he acknowledged, observing that Janelia's present formula for instigating collaboration falls short of what he experienced in the 1990s when he was at Bell Laboratories. "At Bell, they didn't have defined directions, and the groups were incredibly small", even smaller than the half-dozen or so members characteristic of most of Janelia's 60 research groups. A Bell group consisted of a principal investigator and two other scientists and/or engineers, which Betzig says led to more individual groups and, as a result, more diversity of expertise and points of view. "Most everything got done [at Bell] because of stochastic interactions", Betzig says, by which he means chance interactions of the mindsets and skillsets that distinguished each Bell group.

It was at Bell where Betzig began the work that led to his 2014 Nobel Prize in Chemistry for the development of super-resolved fluorescence microscopy. He shared that prize with Stefan W. Hell of the Max Planck Institute for Biophysical Chemistry and William E. Moerner of Stanford University.

Despite Betzig's chemistry award, chemists are noticeably underrepresented at Janelia. Sit down with Luke Lavis in his third-story office suite overlooking a bucolic tree-bordered pond about a half-mile from the Potomac River and he will explain his present role at Janelia as this: "I am *the* chemist."

Lavis and his group have been synthesizing a rainbow's worth of fluorescent probes for use both by in-house research groups and by many laboratories around the world to render specific biomolecules inside of cells visible and trackable. The chemist moved to Janelia in 2008 when he

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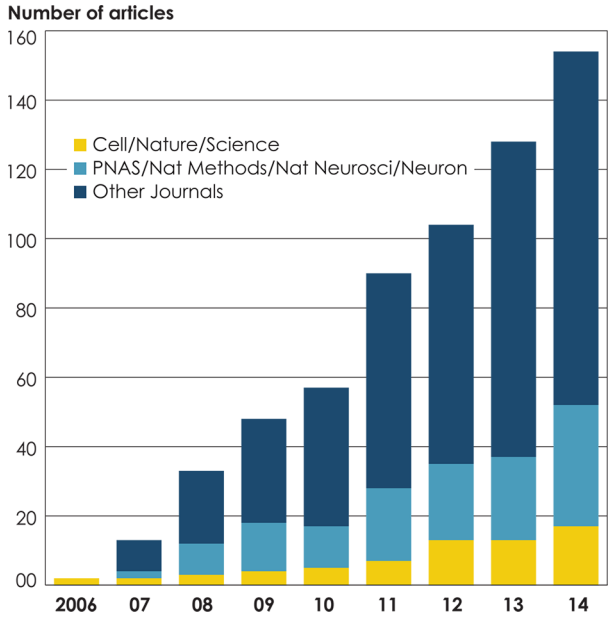
finished his Ph.D. at the University of Wisconsin, Madison, and last year had his first appointment renewed. "Janelia is what every first year graduate student dreams academe will be", he says with a wry, bespectacled smile.

> "I am *the* chemist."—Luke Lavis

A perk for being a chemist at Janelia, he notes, is that it is cheaper to run a high-end chemistry operation than a high-end biology one. "We have more equipment than some [chemistry] departments", he notes. "We are people limited, not equipment limited."

His group collaborates with many others at Janelia, sometimes stemming from the spur-of-the-moment interactions that Rubin and Janelia's elders envisioned. One of those chance encounters in the hall led to a quick project to whip up a synthetic pheromone designed to interact with a genetically engineered receptor in fruit fly larvae. "I just did it; it took me a day", Lavis says, enjoying the opportunity to recount the episode. "When you are the only chemist, you have to try to be a good colleague", which means that part of his work is of the job-shop variety. He says his several-year stint in industry instilled in him that it takes more than just a beautiful journal-worthy synthesis to make useful molecules.

Although it was made clear to him that publishing papers in quantity would not be a highly weighted metric by which he would be assessed, Lavis noticed that some colleagues took this freedom to an extreme. Without papers, he says, "no one will know who you are outside of this bubble." And because Janelia has no tenure, leaving the bubble, sooner or later, is part of Janelia's model. Lavis wholeheartedly embraces his freedom from seeking external research money, which he points out is a requirement even at other leading research venues such as the Broad Institute, a joint venture of the Massachusetts Institute of Technology and Harvard University. "It's very freeing", Lavis says. And that has left him with the time to be the bench chemist that he trained to be and wants to remain.



Over its nine-year existence, publications from Janelia researchers have steadily increased. Source: Janelia Research Campus.

Rubin estimates that of the 150 full-time scientists at Janelia, 10 are chemists and only one of those is a group leader. But he says he wants to see that change. "We designed this building before we hired anyone, and we put 24 eight-foot hoods in for chemistry in six of the rooms", Rubin says. In practice so far, Rubin says, there has been a cultural disconnect that has been hard to circumvent. Many top-tier chemists elsewhere in the world sit in an office and have 20 graduate students working away. "The small-lab mentality was a stretch for biologists, but poses an enormous gulf for chemists", Rubin argues.

Besides hiring more chemists, Rubin has more big-picture goals for Janelia. At the 20-year mark for Janelia, which will be in 2026, he says he would hope to pass his own metrics of success: "Did Janelia make a difference in 20 years compared to the option of just adding more HHMI investigators?" Vague as that sounds, it gets right at the point of Janelia. "The basic argument is that you need diversity in the way you do science", Rubin says. "There is science that doesn't happen at universities."

> "The basic argument is that you need diversity in the way you do science. There is science that doesn't happen at universities."—Gerald Rubin

Another way Rubin ponders the success or failure of Janelia as a sociological experiment is by way of a deletion test: If Janelia had never come to be, would the science and tool building that has come out it have popped up elsewhere?

Ivan Amato is a freelance writer for C&EN, the weekly newsmagazine of the American Chemical Society.

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