QnAs with Gerald M. Rubin

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On a rolling meadow along the Potomac, in a suburb of Washington, DC, stands the sprawling embodiment of a bold idea born more than a decade ago. Designed by the Uruguay-born architect Rafael Viñoly, the serpentine structure—glass walls, macadam-gray facade, and gleaming floors terraced into a grassy landscape—was built to serve as the home of the Howard Hughes Medical Institute's (HHMI) stand-alone research lab. At the Janelia Research Campus, biologists, physicists, and engineers work together to address elemental questions in neuroscience and develop new imaging methods unhindered by administrative and teaching responsibilities. The lab was born out of a conviction that steeping talented researchers in a collaborative culture with generous resources for pursuits with uncertain payoffs would yield revolutionary results. In the short span of a decade, the lab has positioned itself as a powerhouse in neuroscience, developing tools that have transformed researchers' ability to peer into cells at increasingly unprecedented levels of detail and to trace neural circuits with stunning precision. Less than a decade after the lab was launched, the development of photoactivated localization microscopy for high-resolution imaging of molecules within living cells earned one Janelia researcher a share of the Nobel Prize in chemistry. Likewise, researchers at the lab optimized a now-ubiquitous tool for tracing the flow of calcium ions in neurons, vastly speeding efforts to map neural circuits. On the occasion of the lab's 10th anniversary, PNAS asked geneticist Gerald M. Rubin, Executive Director of the Janelia Research Campus and a member of the National Academy of Sciences, to chart the progress of the grand experiment in research administration that the lab represents.

PNAS: When Janelia was conceptualized, biological imaging was chosen as one of its leitmotifs. Why did you pick imaging as a focal point around which to build an entire institute?

Rubin: HHMI has a long history of supporting scientists working in fields that HHMI thought were important, but which were underfunded by others. For example, in the mid-1980s, the institute identified structural biology as such an area and actively sought to support X-ray crystallographers at academic centers across the United States, jumpstarting structural biology in this country. And in 2000, the institute took the same approach with computational biology.

Gerald Rubin. Image courtesy of Matt Staley (Janelia Research Campus, Ashburn, VA).

When HHMI decided to launch Janelia as a free-standing research campus, we had a couple of criteria for picking the areas we wanted to focus on. The first was, of course, to pick what we considered important science. We felt that just as molecular biology had revolutionized biology in the latter half of the last century, imaging was poised to have a similar impact. Second, we wanted to pick a research area that was not already well-funded by other organizations and that might be difficult to pursue in a university setting because it required close interaction and collaboration among scientists in different departments. During our planning workshops, we asked ourselves what kind of research would need a dedicated institute where researchers from different disciplines could work as a close-knit group under one roof in a way that would not be possible in traditional academic settings. That's how we settled on biological imaging, in which optical physicists, protein engineers, chemists, and computational biologists of the highest sophistication work together with experimental biologists in real time to develop new methods that remove roadblocks limiting biological discovery. The combination of proximity and shared objectives provides a rapid feedback loop between tool user and tool developer; these researchers don't have to wait to build on each other's findings until after they are published in journals months later.

PNAS: Janelia's other major focus is the study of neural circuits. Why neurocircuitry?

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Janelia Campus. Image courtesy of Anthony Leonardo (Janelia Research Campus, Ashburn, VA).

Rubin: With advances in our ability to manipulate and measure the activity of individual cell types in animals, like fruit flies and mice, we felt that there was a real opportunity to study the function of neural circuits at the level of individual, identified cells. This was also an underfunded area; the main priorities of the National Institutes of Health in this area were disease-oriented and translational, and less on long-term basic research that would shed light on the functioning of healthy brains of experimentally tractable organisms. We felt that such studies might reveal evolutionarily conserved mechanisms underlying the function of biological computational devices. So we decided to embrace the opportunity and fill a need. In fact, during our initial planning, we used former NIH director Elias Zerhouni's five-year plan for the NIH as a guide. We decided that if it was in the NIH plan, we would not consider doing it.

PNAS: The lab was modeled after famous forerunners, particularly the Laboratory of Molecular Biology [LMB] in Cambridge, England and Bell Labs in New Jersey, United States, and the research environment at Janelia has long been billed as a sort of sociological experiment in interdisciplinary basic research outside academia. Was it easy to convince top-notch researchers to take part in the experiment?

Rubin: For a small subset of adventuresome individuals, yes. We always felt that if most scientists wanted to work at Janelia, that would be a sure sign that we've become too conventional. This place is best suited for a certain kind of independent investigator who wants to continue doing science with their own hands, and can collaborate and complement their colleagues' cutting-edge work. Also, many of the people we set out to hire at Janelia would not typically thrive in university environments. Several of our early recruits had trained in places, such as the LMB and Bell Labs, and understood what we were trying to create. And we are not afraid to take a chance on unusually talented and passionate people, even if they lacked experience. Many of our hires had just finished their graduate work when we recruited them as independent lab heads.

PNAS: Speaking of rookies, the singular advance for which the lab is perhaps best known is the suite of tools to image calcium ions in neurons as a way to detect neuronal firing. Although the sensors themselves were developed in the early 2000s, it wasn't until a young scientist at Janelia honed them that they were widely adopted. Can you recount the story of the development of the genetically encoded calcium-sensing protein GCaMP?

Rubin: An HHMI investigator at Duke brought protein engineer, Loren Looger, to our attention. At the time, Loren had completed his PhD at Duke and was a postdoc in a plant biology department. During his job interview at Janelia, he got up in front of the panel and said he was a protein engineer who knew almost nothing about neurobiology but was confident he could build tools to sense things in neurons and was happy to rely on his colleagues to tell him what sensors were needed.

Here was someone who was incredibly creative and fearless but unfocused and unproven; not your typical hire at places like Harvard, MIT, or Caltech. But he was perfect for us. He understood the importance of calcium sensors and was willing to improve on the early proof-of-principle efforts of others to make sensors good enough to detect changes in calcium levels in neurons of live animals as a readout for neuronal activity. The first calcium sensors, such as the early GCaMP versions, were not useful in practice due to low signal-to-noise ratios and toxicity. And there was not a lot of incentive for academic scientists to optimize the sensor; that kind of work does not lead to publications in high-profile journals and is simply unsuitable for graduate students and postdocs at traditional academic settings, given the current incentive structure. Loren's lab made a series of incremental improvements to GCaMP to turn it into a useful neurobiological tool, GCaMP3; then we spent close to $2 million per year for five more years to support a larger collaborative team that generated the current version, GCaMP6. But that painstaking effort and substantial investment have paid off. Today, there are hundreds of labs worldwide using these improved calcium sensors. A majority of optical brain imaging experiments

you read about today use the sensors developed at Janelia.

PNAS: The lab is also involved in an array of projects aimed at mapping the complete projections of neurons across fly and mouse brains, a goal integral to the connectome projects currently underway. Are Janelia scientists involved in the BRAIN [Brain Research through Advancing Innovative Neurotechnologies] initiative?

Rubin: I like to think that one way to mark the success of Janelia is through the influence of our work on the BRAIN initiative. If you look at how we defined our neurobiology program in 2005, you will find that it's strikingly similar to the proposals in the BRAIN initiative, written less than two years ago. The report of the BRAIN initiative's advisory committee cites Janelia as a model for the kind of interdisciplinary research that it proposes. We collaborate closely with a number of scientists involved in the BRAIN initiative, such as researchers at the Allen Brain Institute. Because we don't receive federal government funding, we are precluded from any grants from the BRAIN initiative. So we are active participants in the initiative but with our own funds.

PNAS: Although your original remit was to pursue imaging and neural circuits, you also intended to branch out into new directions. Have you broadened your research focus since you launched a decade ago?

Rubin: No one has tenure at Janelia, and once we have made substantial inroads into a topic or when a research problem ceases to be cutting-edge, we want to be able to switch focus. Our plan has always been for the research areas to gradually evolve, and that's already happening. We are de-emphasizing certain areas of neurobiology in favor of neuronal cell biology, for example. Part of this move is a response to the BRAIN initiative, which does not include the cell biology of neurons as one of its primary goals. We think it's an important area that requires sophisticated imaging and complements circuit-level neurobiology.

PNAS: Tell us more about the neuronal cell biology program. How, for example, did you convince Jennifer Lippincott-Schwartz [a cell biologist whose decades-long work in imaging the movement of proteins within cells has earned her wide recognition in the field] to leave the NIH for Janelia?

Rubin: In 2011, at our five-year mark, shortly after Bob Tjian became HHMI president, we hosted a series of scientific workshops to decide what new areas Janelia might move into. One of those areas was neuronal cell biology, largely because we realized the importance of understanding what is happening in individual neurons, such as receptor trafficking and biochemical mechanisms underlying plasticity. So we set about finding a key hire for that area, and that person was Jennifer. While she was at the NIH, she had published several papers in collaboration with Eric Betzig and Harald Hess, so she had strong ties to Janelia. It took 3 years to convince Jennifer to move here from the NIH, and it was an important hire for us because she is not only a great scientist but also prominent in the cell biology field. That was a way to signal our interest in the field. James Liu, whom we recruited when he finished his graduate work with Tjian, is also on the cell biology program. Erin O' Shea, the new HHMI president, is moving her laboratory here from Harvard, and David Clapham, HHMI's Chief Scientific Officer, who will move his laboratory from Harvard Medical School next summer, will also become part of the program.

PNAS: Taking the long view and a translational perspective, which findings from the lab have enhanced our understanding of human mental disorders?

Rubin: It's too soon to tell; we are focused on the basic science needed for such advances, but it may take a decade or more for this work to deliver insights that can be translated.

PNAS: You have said that the ultimate success of Janelia as an experiment can be gauged with a knockout test: at the 10-year milestone, would the world be any different without the lab?

Rubin: I would say yes. The new microscopes we have built, beyond the one that won Eric [Betzig] the Nobel Prize, the calcium sensors, new fluorescent dyes, and a variety of genetic tools for cell-type–specific manipulations in flies have all been game-changing. They are unlikely to have been developed as quickly, if at all, if Janelia did not exist as an independent lab. We have proven that an alternative model of research, one that complements research in academic settings, can have real impact in today's environment, just as our role models Bell Labs and the LMB did in an earlier era. Our hope and challenge is to maintain our venturesome spirit and move into new areas. There was a lot of skepticism when Janelia started, but I don't think you would find many people today who think it was a bad idea.