



NIGHT science

Like to take risks and tackle intractable problems?
As construction motors on at Janelia Farm, the call is out
for venturesome scientists with big research ideas.

By MARY BETH GARDINER

Day science calls into play arguments that mesh like gears, results that have the force of certainty... Conscious of its progress, proud of its past, sure of its future, day science advances in light and glory. By contrast, night science wanders blind. It hesitates, stumbles, recoils, sweats, wakes with a start. Doubting everything, it is forever trying to find itself, question itself, pull itself back together. Night science is a sort of workshop of the possible where what will become the building material of science is worked out.

—FRANÇOIS JACOB
Of Flies, Mice, and Men

BESPECTACLED AND BEARDED, clad today in shirt and tie instead of his trademark black turtleneck and trousers, Gerald M. Rubin doesn't look much like a biblical figure. But in his role as director of Janelia Farm Research Campus, Rubin has been called a modern day Noah, readying his "ark" and rounding up the best and brightest scientists—of every stripe—to fill it.

"Gerry is not trying to populate Janelia Farm with all the world's best chemists," says HHMI investigator Stuart L. Schreiber, a chemical biologist at Harvard University and a core faculty member of the interdisciplinary Broad Institute recently founded by Harvard University, MIT, and the Whitehead Institute for Biomedical Research. "He'd like to have a couple of them, though. It's like Noah's ark—he wants a healthy mix of very different kinds of scientists."

As girders and rebar give shape to Janelia's physical aspects, and as the process for recruiting scientists unfolds, Rubin and colleagues continue to sculpt the conceptual underpinnings of the science that will take place there.

SAFE HAVEN

Located in Loudoun County, Virginia, HHMI's Janelia Farm

PAUL FETTERS



Research Campus will house a multidisciplinary, collaborative community of scientists. But how does one build such an environment? “Suppose someone said you could build a new research institute and there were no rules—you could do anything you want,” Rubin ventures. “How would you decide what to do?” It’s a challenge he accepted with relish. “Janelia is going to be unique, not because we pick problems that are seen as outside the mainstream, but because of the way we approach those problems.”

The plan for Janelia Farm grew out of an acknowledgment by HHMI leaders that while most biomedical problems are handled well in a university setting, there are some that might be better addressed in a place where small groups of researchers with different skills can work together without the barriers typically encountered at a university. Development of new tools to facilitate biological discovery, for example, can require diverse expertise, such as that of engineers, physicists, and computer scientists. But at universities, scientists from different fields are often compartmentalized, and demands placed on researchers by home departments may restrict collaboration outside those walls. “A physicist who wants to work

Where now one sees girders, rebar, and cranes, one will soon find a community of scientists: the Janelia Farm Research Campus.

on a biological problem would likely not get tenure in a university physics department,” says Rubin.

In developing the concept for Janelia, Rubin, HHMI President Thomas R. Cech, Vice President and Chief Scientific Officer David A. Clayton, and their advisers aimed high: They sought to create an environment where researchers from a variety of disciplines will work together with the freedom to apply their collective talents to tough biological questions, the kinds of questions that can’t be answered in the three to five years that most federally funded grants cover. The Janelia campus, Rubin says, will provide a “safe haven for a unique subset of researchers.” Freed from most of the administrative, grant writing, and teaching duties that consume time at a university, Janelia’s scientists will be “functioning scientists” who will be able to spend the bulk of their days working at the bench or engaging in collaborative discussions.

The campus and its scientific program will closely complement HHMI’s longstanding investigator program. That program currently consists of more than 300 researchers at 66 uni-

versities, medical schools, and research institutes throughout the United States who have the freedom and flexibility to push the bounds of knowledge in some of the most important areas of biomedical research.

FOLLOW YOUR NOSE

The concept for Janelia, Rubin points out, evolved out of tried-and-true best practices. “You make a list of the most successful research institutions,” he says, “and look for common principles.”

A handful of places stood out. Eventually, Rubin focused on two of the world’s most highly regarded institutions, the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England, and AT&T’s Bell Laboratories in Murray Hill, New Jersey. Funded by the British government, the MRC hosted no more than 300 scientists at any given time during its heyday, yet it spawned a string of notable discoveries, including the structure of DNA, protein crystallography, DNA sequencing, monoclonal antibodies, and the *Caenorhabditis elegans* model system for genetic studies. Bell Labs, with a staff of about 3,000, was similarly productive in the fields of solid-state physics and electronics—for example, it was there that the transistor and the laser were developed.

Though the two labs were different in many ways, they did have several things in common. Both institutions kept research groups small, and principal investigators worked at the lab bench. All funding was provided by the single sponsor—applying for outside grants was not allowed—and good support services and infrastructure were in place. Notably, says Rubin, both institutions evaluated their own people rather than rely on expert opinions from outsiders. That was important, he says, because the scientists needed an environment “where they could tackle difficult problems without making the kind of progress that would be visible to someone 3,000 miles away looking at their CV.”

Similarly, Rubin sees Janelia Farm as a place that will appeal to self-directed scientists just starting their careers who are looking for independence, and also to established scientists who want to explore new scientific questions. Charles V. Shank, a member of Janelia’s advisory board, supports that notion.



As director of Janelia Farm, Gerald Rubin has his sights set on research questions that are on science’s horizon. Below, Janelia takes shape.

Shank signed on at Bell Labs just out of graduate school and ended up staying 20 years. Currently director of the Lawrence Berkeley National Laboratory and a professor of physics and chemistry at the University of California, Berkeley, Shank says his time at Bell Labs had a “huge impact on my career. I had an opportunity to pursue science in a way that didn’t fit into the narrow box one would see in a university.” Shank’s degree was in electrical engineering, but at Bell, his interest shifted to chemistry and physics. “In science, people reinvent themselves on a regular basis,” he says. “Over that 20 years, I was given the opportunity to go where my nose led me.”

The nature of such pursuits implies that few of the scientists who come to Janelia Farm will spend their entire career there, says Rubin. “Unlike a lot of institutions that want to hold on to their people, we want turnover in order to ensure a fresh flow of ideas. If you’re worried about tenure, you’re probably too risk-averse to function well in a Janelia-like environment.”

“There’s another advantage of scientists spending 5 to 10 years at Janelia and then moving on,” adds Tom Cech. “When they move back to academia, they’ll be ambassadors for the frontier technology developed at Janelia. We want to spread the instruments and computational tools created at Janelia around the world, and these alumni of the Farm will provide one mechanism for dissemination.”

Nancy M. Bonini is an HHMI investigator at the University of Pennsylvania School of Medicine. Asked if she might have forgone her traditional postdoctoral training path if a stint at Janelia Farm had been an option, Bonini’s response was immediate: “Why wouldn’t I have applied to a place like that? I want a vibrant, interactive, intense environment where it will be fun to do science and that will give me the freedom to do the kind of science I want to do.”

ACCIDENTAL LANDINGS

Creating such a collaborative atmosphere where exploration and risk taking are encouraged will be key to Janelia Farm’s success, Rubin says. “If you’re wandering around in the unknown, you’ll



often land at the cutting edge—not intentionally, but because you’ve made some accidental observation,” he says. “That’s the way a lot of important discoveries happen.”

Something that Rubin and his advisers felt would promote collaboration and collegiality at Janelia Farm was to level the playing field. In lieu of the typical university hierarchy of assistant, associate, and full professor, the more egalitarian designation of “group leader” will be given to scientists regardless of career stage, from those just finishing postdoctoral training to senior researchers. One other researcher category, “fellow,” could be an individual just out of graduate school looking for an alternative to traditional postdoctoral training, or he or she could be a more advanced researcher who wants to change fields or move, say, from industry to academia. As with the group leaders, fellows will be independent—“essentially free agents,” says Rubin—able to control their own resources and ally with collaborators of their choosing.

To promote interaction, group size at Janelia Farm will be small—between two to six lab members for each group leader and one to two per fellow. With scientists spending less time at their desks and more time in the lab, opportunities for discussion and mentoring within and between lab groups will arise more frequently.

Postdoctoral trainees and graduate students will also be a part of the culture at Janelia, though integrating predoctoral students into the mix will be more complex, since they require affiliation with a degree-granting institution. Rubin is exploring the idea of tapping into HHMI’s network of international research scholars to recruit students from abroad, where graduate programs typically include little coursework. “I want to ensure that Janelia Farm has an international flavor, and I think this will work,” he says. “They would be close to Washington, a very international city. And this will appeal to people who have an adventurous spirit, which is what we’re looking for.”

One of the most innovative elements of the plan for Janelia Farm is to make it a place where researchers can come as visiting scientists to work on short-term individual or group projects. Building into the program this “research hotel” concept is unique to Janelia, says Stuart Schreiber, and an idea whose time is due.

“One of our inspirations was what happened in the yeast field, when two geneticists and a molecular biologist went on sabbatical at Cold Spring Harbor Laboratory in the mid-1970s to work together in a shared lab,” says Rubin. “What they accomplished greatly accelerated the development of the yeast molecular genetics field. Few places today, however, have the physical or financial resources to accommodate independent visitors.”

At Janelia Farm, external scientists will be able to put in a group application for funding and space, including housing. “This will be for novel, collaborative projects,” says Rubin, “some of which may involve other researchers at Janelia, but not necessarily.” A more conventional use will be sabbatical visits. “A number of our investigators would never consider moving to Janelia, but they might want to come for a year—we’d be able to offer housing for them and their families,” he says. “We hope to have two or three investigators at Janelia at any given time.”

Even shorter-term visits will be possible—for example, a scientist might send a postdoc to use special instrumentation unavailable back home. As Cech points out, the setup is ideal. “With Washington Dulles International Airport just a few miles away and short-term housing available on the campus, a visiting scientist will be able to fly in and get right to work.”

VOLUNTARY ASSEMBLIES

With so many of the organizational decisions already made, and construction well under way, Rubin’s attention is now focused on two other critical

PARTNERING WITH LOUDOUN COUNTY

Local school kids will rub shoulders with scientists at Janelia Farm.

With the sun barely clearing the pines that rim the construction site, a group of Loudoun County Public Schools (LCPS) teachers and administrators as well as community and business leaders joined HHMI officers and staff at Janelia Farm this past March for breakfast and an announcement that had the guests “hovering just a little above the floor,” according to LCPS Superintendent Edgar B. Hatrick.

The group had gathered for the formal announcement of an HHMI commitment to invest at least \$1 million per year in support of science education in the LCPS system. Though the Institute has funded science education since the inception of its grants program in 1988—more than \$1.4 billion have been invested thus far in a range of activities for students of all ages—this partnership marks the first time that HHMI will work directly with recipient schools.

College scholarships, each worth \$7,000 per year, have been established for two outstanding seniors at every Loudoun County high school. In addition, HHMI will bolster two programs already in the county budget: the start-up of a district-wide science academy at the recently built Dominion High School and the development of a new middle school science curriculum.

Space for a public academy was built into the plan for Dominion, says Hatrick, though the nature of the academy had been undefined. “Through our work with the Institute, what was a somewhat cloudy vision at first is becoming much clearer,” he says. Developing a science academy with a cross-pollination of activities at both Dominion and Janelia Farm will “create opportunities for science education that will be unbeatable anywhere in America.”

Modernizing the middle school curriculum will involve the creation of hands-on activities to pique interest at this “prime time” in a student’s development, says Peter J. Bruns, HHMI’s vice

president for grants and special programs. HHMI will hold a summer workshop to familiarize teachers with the new tools as well as a two-day booster class just before school begins. To further ensure success, a group of long-time HHMI grantees from Pennsylvania—who developed the nationally renowned “LabLion” program for elementary schools—will provide support throughout the school year.

It is the national and international network of HHMI grantees and scientists, and not just dollars, that makes the value of the partnership so immense, says HHMI President Thomas R. Cech. The well of experience of the more than 200 grantees at research universities across the United States should prove a major resource for innovative ideas for Loudoun County teachers. And, says Hatrick, the value to students of the proximity of the Janelia Farm campus cannot be underestimated. “For them to have the chance to rub elbows with researchers who are opening the world of science to things we can’t imagine right now, the potential is boundless.”

—MARY BETH GARDINER



Guests from Loudoun County survey a model of the Janelia Farm Research Campus.

MOORE TAPPED AS JANELIA COO

In March, HHMI named Cheryl A. Moore as associate director and chief operating officer of the Janelia Farm Research Campus. Helping to develop an administrative and management structure for the research facility, Moore will oversee all fiscal and administrative services at the 281-acre campus.

Moore comes to HHMI from the Burnham Institute, a private, nonprofit life-sciences research center in La Jolla, California, where she has been senior vice president, chief operating officer, and chief administrative officer. A graduate of the University of San Diego and a member of the American Institute of Certified Public Accountants,



she has held top-level management positions with an international financial services firm and two managed healthcare companies.

"My goal is to work with Gerry Rubin to create a uniquely creative research environment free of bureaucratic hassles, in an atmosphere of openness, support, and freedom," Moore says. "My goal in managing the business of research is to remove as many impediments to the advancement of science as I can, to help our researchers move more quickly toward scientific discovery. I will know

that Janelia Farm is successful when people comment on how much fun it is to work there because of the sense of teamwork and intellectual stimulation."

dimensions: pinpointing the kinds of biological problems that Janelia's scientists will tackle and recruiting the right people to work on them. "Those two tasks are completely linked," he says, "because whatever we decide to do, we only want to do it if we can attract some subset of the best people in the world for that problem."

Rubin knows very well that Janelia offers an extraordinary opportunity to extend scientific knowledge. Accordingly, the questions he's considering for Janelia's core work are on science's horizon—the kinds of problems, he says, that are too premature to warrant funding from the National Institutes of Health or similar sources.

For guidance about specific areas, Ruben has organized a series of workshops (see sidebar below) that engage many of today's leading scientists in wide-ranging discussions about scientific problems and opportunities. To help attendees think beyond typical short-term project timelines, Ruben challenges them with what he calls the "thousand-person-year problem." He instructs them to "imagine you were given the resources to assemble a group of 100 people and to support that group for 10 years. The rules are that the problem has to be really important, but you must make a convincing case that you have at least a 20 percent chance of solving it."

Outcomes from the workshops are "exceeding expectations," says Ruben. "There have been lively and open exchanges, and eventually there was some loose consensus on what people thought were the main issues." David J. Bishop, a 26-year veteran of Bell Labs who is now its vice president of nanotechnology research, participated in the workshop on the biochemistry of the single cell. "There are certain classes of problems, such as this one, where a principal investigator and three postdocs and graduate students just can't make headway," he says. "You have to have multidisciplinary teams going after them." They are the kinds of problems, Bishop says, that have won Bell

Labs scientists eleven Nobel Prizes and nine U.S. National Medals of Science over the years.

When fully staffed, the research campus will host 20 to 30 group leaders. Though two-thirds of them will likely focus on two central projects, that doesn't translate into a loss of independence for the researchers. Ruben anticipates that those who come to Janelia will be drawn by the diversity and the opportunity to work on a problem larger than any single lab can tackle. "We hope that the project teams will self-identify—creating 'voluntary assemblies,' if you will—as we recruit," he says.

"The question is, do you simply hire the brightest people, irrespective of research field, hoping that the mix will create synergy?" he continues. "Or, because you need computational biologists, instrument builders, and cell biologists for a particular problem, do you specifically hire from those fields to work on it together? We're trying to strike that balance."

Building flexibility into Janelia's approach is key, says Ruben. "Undoubtedly, there will be a lot of details that we don't get right. We look at this not as a set of rules that define how Janelia is to be run forever, but as a working hypothesis," he says. "We will evolve as we go." **H**

FIELDS OF INTEREST

Janelia Farm's research agenda will be not proscribed, but evolutionary. There will be a strong focus on developing new tools—experimental methods, computer software, and scientific instruments—needed to advance research capabilities. The aim is to identify important biomedical problems for which future progress requires technological innovation and then nurture the development of integrated teams of venturesome biologists and tool builders.

To narrow the focus to three to five ideas for initial research, Gerald Ruben and colleagues are organizing a series of workshops with leaders in several fields of interest. While not pinpointing future Janelia research, the topics here hint at broad directions for Janelia's science:

- *Perception and behavior*, organized by HHMI investigators Cornelia I. Bargmann and Richard Axel. Neuroscience, imaging, and computation.
- *Biochemistry of single cells*, organized by HHMI investiga-

tors Robert Tjian and Gerald R. Crabtree. Methods required to study biochemical reactions and processes in single cells.

- *Membranes, membrane proteins, and membrane-associated molecular machines*, organized by HHMI investigators Rodrick MacKinnon, Eric Gouaux, and Tom A. Rapoport. Overcoming the unique challenges limiting experimental study of cellular processes that occur at or within membranes.

- *Functional imaging in living systems*, organized by HHMI investigators Roger Y. Tsien and Eric R. Kandel and Max Planck Institute directors Winfried Denk and Nikos K. Logothetis. Emerging methods for monitoring gene activity, protein modification and subcellular localization, ion fluxes, and other metabolic activities in living cells.

- *Imaging cellular structures*, organized by HHMI investigators David A. Agard and Eva Nogales and Max Planck Institute directors Wolfgang Baumeister and Stefan W. Hell. Emerging methods in light and electron microscopy for determining the structure of cellular components.