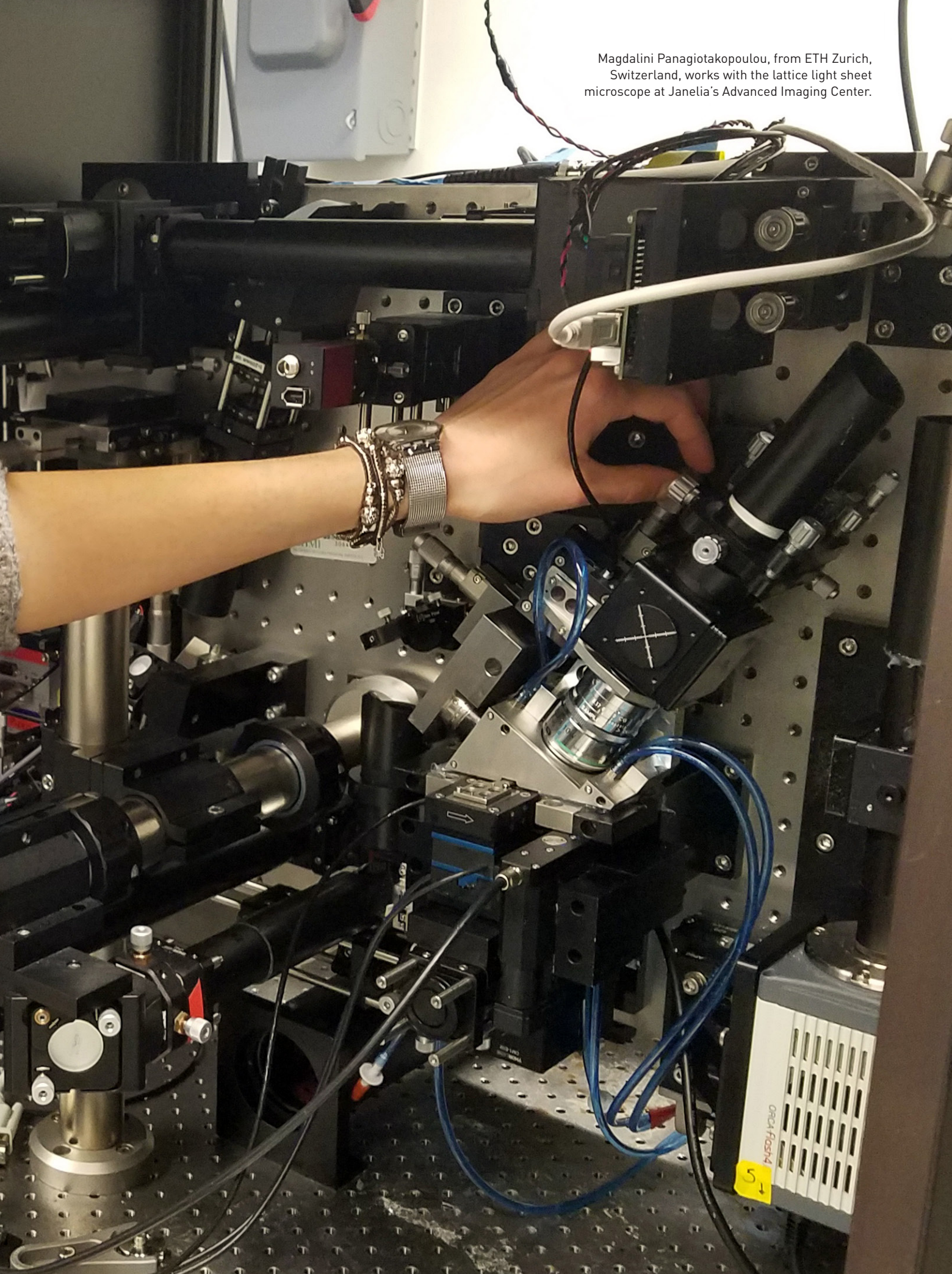
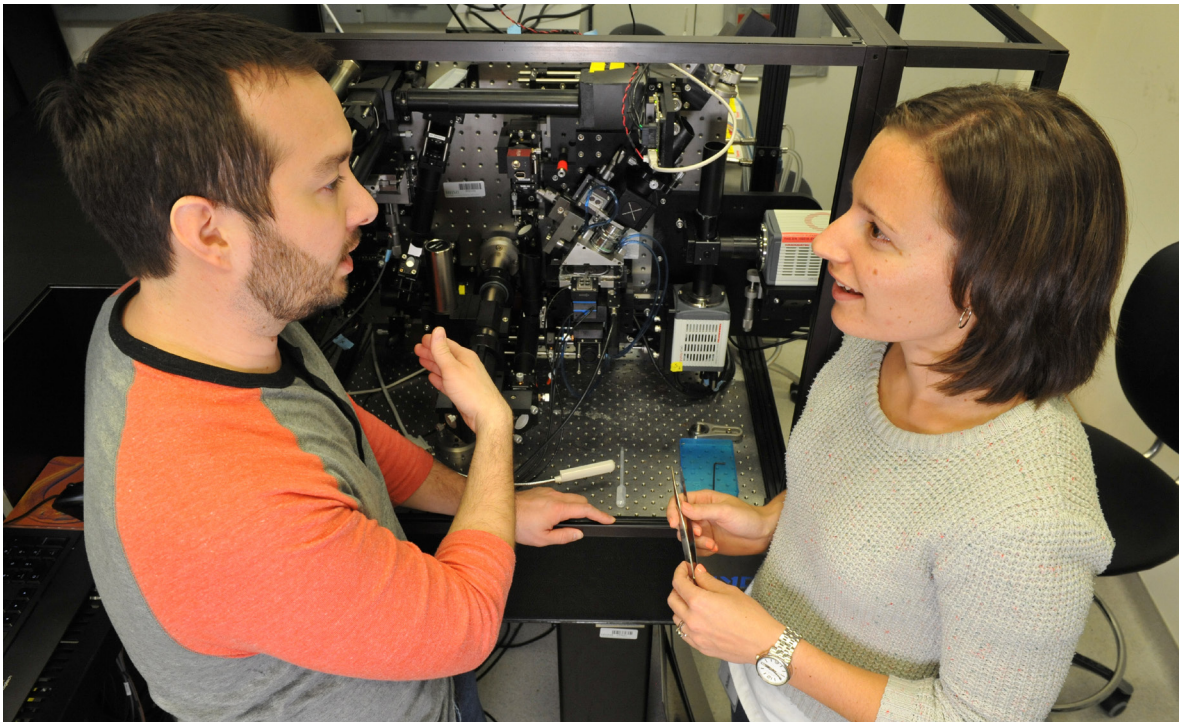
Teng-Leong Chew, Reed George, Alex Soell and Eric Betzig

# Opening a Path to Commercialization

To smooth the academic-to-industry transition, one institution is experimenting with offering biomedical researchers pre-commercial open access to new optical imaging systems still under development. The approach, the authors of this case study suggest, can be a win on both sides.



Magdalini Panagiotakopoulou, from ETH Zurich, Switzerland, works with the lattice light sheet microscope at Janelia's Advanced Imaging Center.



AIC application scientist John Heddleston discusses the application with Kate Butler, a visiting scientist from Walter and Eliza Hall Institute, Australia.

Commercializing a novel technology incubated in academia—always an arduous process—faces particular challenges when the technology has an interdisciplinary audience. For technologies such as a new advanced microscope, for example, collaboration between optical physicists, engineers and biomedical end users is essential for success. But arranging that collaboration can pose significant challenges, owing not just to logistics but also to the inherent compartmentalization of these separate disciplines. And the effort carries big risks for the commercializing company as well, which must grapple with establishing meaningful proof-of-principle cases and protocols, with avoiding hype, and with determining the market potential of a technology not yet widely proven or known.

One way to address these issues is to meet them head-on, by creating a mechanism to facilitate access to the evolving instrument by its potential end users, and interactions of those users with the instrument's inventors and manufacturer—along the lines of the beta-testing model common in software development. For the past several years, the Janelia Research Campus of the Howard Hughes Medical Institute (HHMI) has developed such a pre-commercial open-access platform, the Advanced Imaging Center (AIC; http://janelia.org/aic), to address these early challenges. In this article, we provide a look at the center, its approaches and some of its outcomes, in the context of one case study: the lattice light sheet microscope (LLSM) developed at Janelia and subsequently licensed and commercialized by Carl Zeiss Microscopy GmbH.

## Technology transfer's "teething pains"

Developing and commercializing an advanced microscope isn't solely a problem of optical engineering. To reach full maturity, the instrument must be vetted by its actual end users: biologists. And that collaboration can raise significant challenges for the instrument's inventors.

***Time.*** However invaluable the interaction for improving and advancing the invention, the collaboration creates a tremendous time-sink for the inventor, and requires the considerable effort of bringing together scientists from disparate fields—for example, pairing optical physics and engineering with biology.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***Disciplinary silos.*** Most nascent technologies encounter a steep, prolonged discovery phase that might be played out in specialized publications and conferences. Biologists rarely have time or reason to comb through the specialized literature in optics. Such academic compartmentalization creates huge hurdles in getting the word out on a novel instrument. And even if an end user becomes aware of a promising new technology, he or she may lack the cross-disciplinary professional connections required to gain access to the technology and test it out in a research setting.

***Risk.*** Likewise, a manufacturer seeking to commercialize a potentially disruptive new technology faces a road fraught with challenges: identifying appropriate applications; devising experimental protocols; establishing successful proof-of-principle cases; minimizing unreasonable expectations and hype; persuading funding agencies to accept paradigm-shifting, yet-to-be-widely-proven technologies. A rigorous decision requires hard answers to a raft of questions on the instrument's marketability, potential advantages, and feasibility. It adds up to a time-consuming process that, again, requires close collaboration with end users. Yet the very challenges imposed by uphill battle of discovery and disciplinary silos can stretch out this timeline, raising the risk that the technology will be outdated by the time it reaches the market.

How can these "teething pains" for an emerging, potentially commercial instrument be overcome? One potential approach is to confront the challenges directly. Such an approach would involve creating a dedicated technical-liaison team to bridge the knowledge gulf between engineering and physics and life sciences, an adequately supported physical facility for access to instruments while still under development, and an access mechanism to manage the process.

Starting in 2014, HHMI's Janelia campus has experimented with just such an approach at its Advanced Imaging Center. And the center's early efforts suggest that such a pre-commercial open-access platform can carry benefits for the instrument developer, the instrument manufacturer, and the end user alike.

## Creating the AIC

In 2012, representatives from HHMI and the Gordon and Betty Moore Foundation—two organizations with a shared interest in supporting scientific research, and in the development of advanced microscopy tools and techniques in particular—met at HHMI's Janelia campus. In the course of those meetings, the organizations devised a conceptual framework to address the dilemmas of commercializing advanced technology: a pre-commercial, open-access platform that houses emerging imaging technologies, making them accessible to end users that can benefit from the technologies.

As envisioned in these meetings, this imaging center would have three main objectives: to ease collaboration between microscope developers and a wide range of users, and thereby allow the developers to evaluate and improve their inventions; to provide an avenue for accessing these microscopes well before they become commercially available; and to open access to researchers in fields that are conventionally not well served by advanced microscopy. And the result of those initial discussions, the AIC, works to achieve those goals through three mechanisms.

***Broad access.*** Research at HHMI's Janelia campus focuses on neurobiology. To maximize input and instrument potential, however, the AIC provides open access to pre-commercial equipment to *all* nonprofit researchers, irrespective of discipline, research focus, or institutional affiliation.

***Expert support.*** The pre-commercial instruments in the imaging center, such as the prototype LLSM discussed in this case study, don't have instruction manuals, service agreements or polished user interfaces. They are research tools, usually still being refined, and require high levels of technical expertise to align, maintain and operate. That means that end users, typically limited to visits of only two to three weeks, must be hosted by a team of highly capable imaging scientists who can get the visitors quickly up to speed on the equipment and enable them to do meaningful research.

***Robust review.*** A final pillar of the AIC is a proposal and review process that, while not overly formal or complex, is robust enough to ensure that the pre-commercial, open access to new technology enables the very best science and the best use of available resources. Twice a year, the center puts out open calls for proposals; in those proposals, applicants submit a description of the proposed use of these instruments, a detailed justification of their need, and a variety of other information to allow an assessment of the project's scientific merit and potential.

The proposals then undergo a technical review to determine their feasibility and safety. Projects that pass technical review proceed to the second phase, scientific review. In this phase, experts in both the scientific subject area and in the instrument and its applications evaluate the research strategy and potential impact of the proposed experiments under a variety of criteria, assign priority scores to the proposals under consideration, and decide on a cutoff for acceptance. The result is a prioritized list of successful proposals to schedule for use of the microscopes—and a slate of diverse, interesting work with a high probability of both scientific impact for the end users and technical insight for the instrument developers and manufacturers.

## Measures of success

The AIC has now operated for three full proposal years. How successful has it been? One indication comes from the scientific users themselves, who have reported that the ability to use the advanced LLSM technology at the center, coupled with the AIC's fully integrated support ecosystem, has allowed them to realize an experimental success rate of 85 percent.

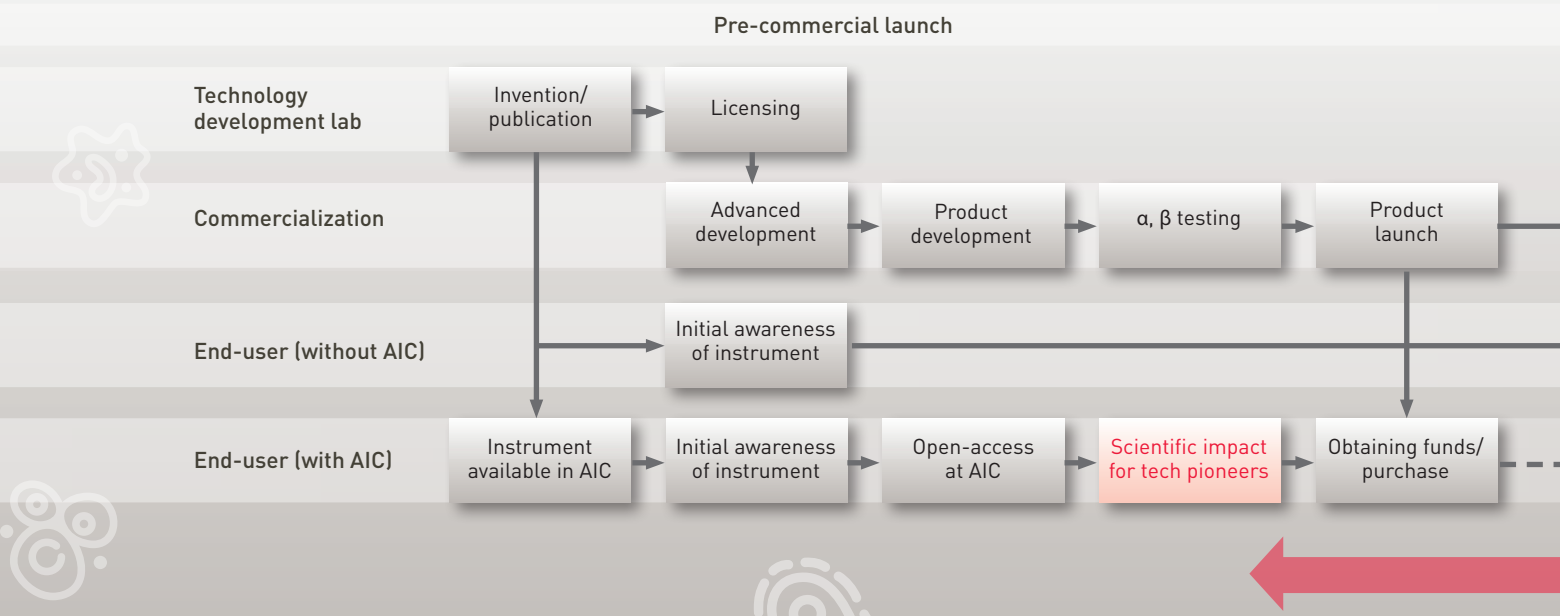
Even more compelling are some of the individual research stories underlying that number, a few of which are highlighted on p. 44. AIC has created impact not only in successful publications, but also has led to subsequent spin-off start-up and also replication of LLSM at visitors' home institutions.

Our experience suggests that a key ingredient to successes such as these is putting the experimental design in sync with the instrument's capabilities and limitations, and communicating those capabilities and limitations to the users. The feedback and guidance of an expert support team thus forms a critical link in developing the right combination of biological application and instrument—without which, needless experimental failures might dampen enthusiasm for a novel, promising instrument, and hold back an otherwise potentially transformative technology.

An open-access platform such as the AIC also allows underserved research disciplines—areas that

## A technology transfer timeline

By facilitating pre-commercial interaction among multiple stakeholders, including end users, the AIC can materially speed both an instrument's commercialization and its scientific impact.



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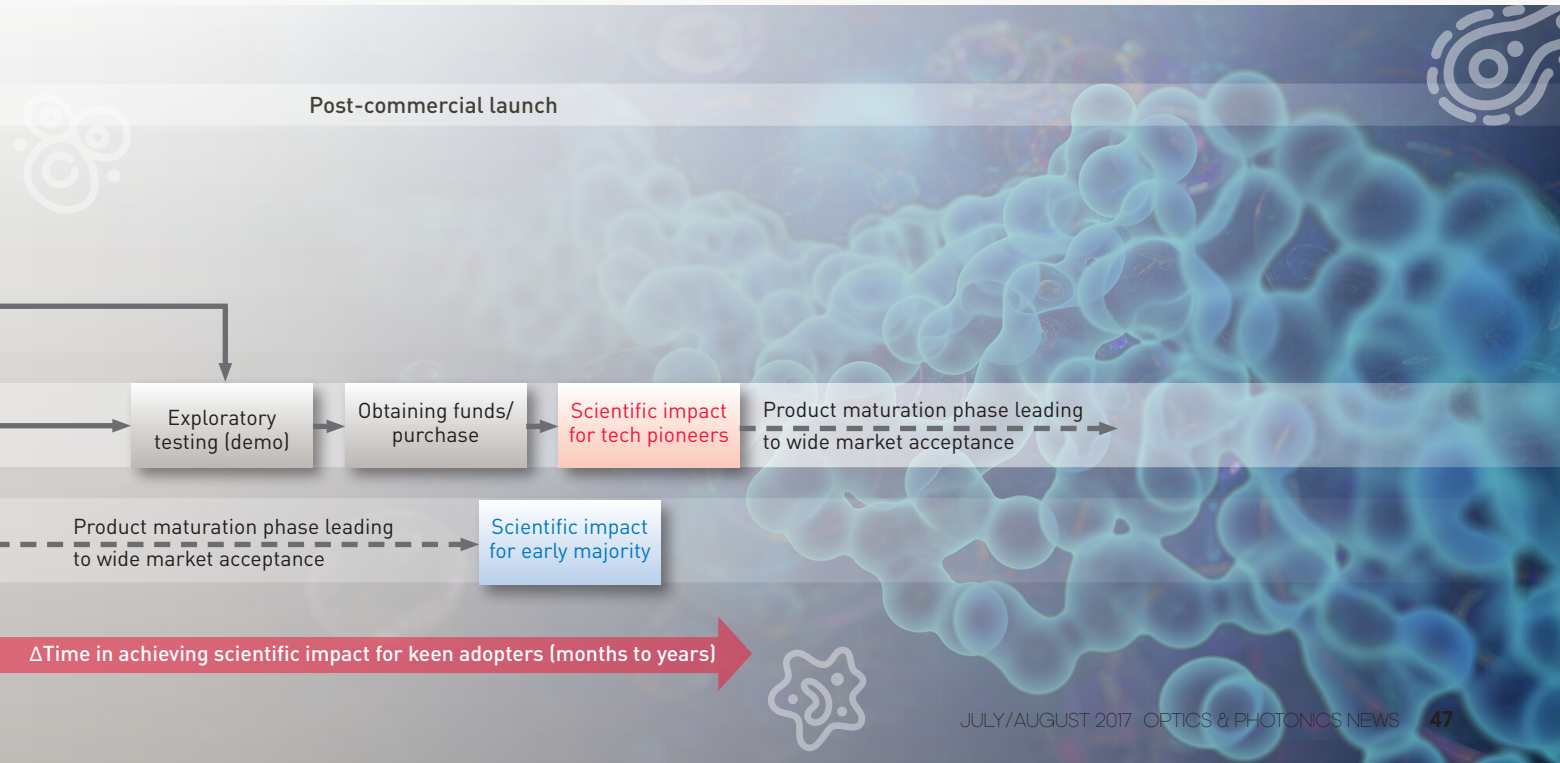
conventionally may not have leveraged the power of advanced microscopy—to get access to cutting-edge instruments, with full technical and data analysis support. We think that provides a strong incentive for scientists to fully explore how imaging can advance their science, relatively unencumbered by the burden of grant writing and potential failure, in ways that can stimulate bold ideas and experimental approaches.

On a more practical level, challenges for a nascent technology can continue even after it has been commercially licensed (LLSM, for example, was licensed by Carl Zeiss). Even the most promising technology must mature to a certain level before it can achieve wide market acceptance, and a key factor in such maturity is an extensive, well-tested portfolio of protocols for sample preparation and for data handling and analysis. A multidisciplinary center such as the AIC is uniquely positioned to encounter a wide-range of specimens and applications; indeed, the center has developed and documented extensive sample preparation and mounting protocols compatible with optimal imaging conditions on the LLSM—a potentially significant value add that can help lessen the challenges of an otherwise steep learning curve for a new technology.

## Managing a flood of data

Finally, the AIC has helped clarify and address the "big data" challenges of modern microscopy. An instrument such as the LLSM can generate terabytes of heterogeneous, multi-dimensional data in a single experiment—a data flood that demands customized analysis strategies. The bioinformatics requirements of this flood can put significant constraints on scientists' ability to convert that data into knowledge. The combination of gentle illumination and high spatio-temporal resolution in all three dimensions afforded by the LLSM has enabled imaging of rapid and subtle, dynamic biological processes, some of which cannot be analyzed by existing algorithms.

The AIC has attempted to ameliorate these bottlenecks by providing customized image-processing



# AIC: Some research snapshots

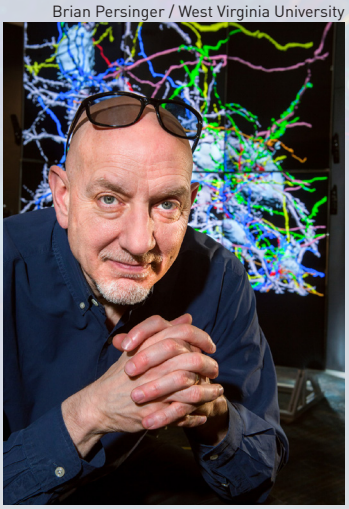
Here are a few examples of research results that have come out of the AIC program.

## *Neuronal dance*

Neuroscientist George Spirou and his research team at West Virginia University use the developing auditory system in mice to study the competition through which cells a one-to-one connection at the neuronal synapse. Because brain development happens so fast, though, a commercially available two-photon microscope isn't useful. Access to the LLSM solved that problem, allowing the team to visualize neurons in a fresh brain slice competing to form a synapse with another neuron.

After just two visits to the AIC, "we were able to observe [neurons] dancing together," says Spirou. "It is unprecedented to see the early development of synapse formation at such high spatial and temporal resolution." These experiments, performed in the AIC, not only advanced the group's science, but also helped fuel the development of a startup company that uses virtual-reality technology to visualize and analyze large 4-D data sets.

Brian Persinger / West Virginia University



George Spirou

Courtesy of NYU School of Medicine

Jeremy Nance

## *Imaging cell cannibalism*

New York University School of Medicine lab head Jeremy Nance leads a team that studies embryos of the worm *C. elegans* to understand how cell interaction and migration shape the body during development. For one project, the team wanted to understand how primordial germ cells (PGCs) associate with endodermal cells, and whether the two-way communication between these cell populations determine their long-term fates.

Access to the LLSM, along with Janelia's technical support, led to the group's discovery that the endodermal cells actively digest portions of the PGC cells to reshape the cell population—a form of developmentally programmed cell remodeling involving "cell cannibalism" that was previously unknown outside of few neuronal remodeling events. The Nance team's work in the AIC led to publication of these novel results in *Nature Cell Biology*.

## *Illuminating cell death*

Approximately 100 billion cells in a human body disappear daily through programmed cell death, or apoptosis. How this works in immune cells has intrigued Benjamin Kile, of Australia's Walter and Eliza Hall Institute of Medical Research (WEHI). During apoptosis, the mitochondria—the cell's power plants—release their DNA into the cell body, triggering an immune response, as if the cell were infected with a virus.

Kile and his team wanted to better understand this mitochondrial DNA release during the events of apoptosis. The only way to visualize this delicate process, however, was to circumvent the harsh illumination of conventional microscopes using the LLSM at the AIC. The success turned Kile into "a shameless advocate" for imaging, he says. More important, the success has led WEHI to build its own LLSM through Janelia's program of sharing the LLSM construction plan.

Australia's Prime Minister's Prizes for Science

Benjamin Kile

The Janelia AIC's creation marks only one step toward a larger ecosystem of open-access microscopy platforms.

and analysis, on a case-by-case basis. We think this experience provides an important lesson for similar core imaging facilities elsewhere: Before getting started, make sure that the facility's data-handling capabilities are in sync with an era of big data in microscopy.

This kind of data management effort, indeed, exemplifies how a pre-commercial, open-access platform such as the AIC can inform the instrument manufacturer of implementation challenges—in this case, the emerging problem of big data—before the actual commercial launch. Without such advance knowledge, and a consequent program of consumer education and software development to meet the challenge, a marketing debacle could result, as word-of-mouth from early adopters would lead quickly to a disillusioned user base for an otherwise transformative technology.

## The road ahead

Our experience with AIC thus far suggests that it has marked out a potentially compelling example: an independently staffed, pre-commercial, open-access platform to provide a bridge from invention to commercialization, via intensive, fully supported end-user input. It can allow researchers to get their hands on technology that might otherwise be unavailable to them, and put it to work toward meaningful scientific results—without relying on the limited support bandwidth of the inventors themselves. And it reduces the risk of early commercialization, allowing use cases, protocols and user feedback to be incorporated while the product is still being developed. It also can create a cycle of positive feedback, in which good results from the early users catch the attention of other scientists, helping to ensure faster technology adoption once a commercial product is launched.

In our view, Janelia AIC's creation marks only one step toward a larger ecosystem of open-access microscopy platforms. There are other approaches. EuroBioimaging is a multinational consortium offering open and hourly access to imaging centers across Europe mainly with commercial instruments. The Advanced Imaging & Microscopy Resource at the NIH offers a portfolio of pre-commercial instruments restricted predominantly to intramural access. While other consortia and institutions find other combinations of services more suitable, the AIC thus offers an unusual combination—a portfolio consisting of 100 percent pre-commercial instruments; sharing of Janelia-developed imaging probes and model organisms; dedicated technical support, on-campus lodging, experimental cost coverage, and image analysis, as well as pre-arrival sample preparation.

Looking ahead, the AIC is working closely with efforts such as Euro-BioImaging, and particularly its Global BioImaging project (www.eurobioimaging.eu/global-bioimaging); with the Open Microscopy Environment (www.openmicroscopy.org); and with other regional groups to help pave the way for similar open-access platforms on multiple continents and using multiple technologies. The result, we think, could be a new paradigm for rapidly disseminating cutting-edge microscopes to the end-user community and commercial market. OPN

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