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Microscopic marvels

Microscopes are changing the face of biology. Researchers should innovate and collaborate if they want to be part of the new vision.

Watching molecular-scale events unfold in a living cell can be an inspiring experience. The inner workings of the nucleus, the shuttling of cellular cargo, the passage of messages through a membrane — seeing this tumultuous activity up close can fire the scientific imagination in a way that abstract data from genetic sequences or chemical analyses can never quite equal.

This helps to explain why microscopes are such essential tools in science, and why scientists' desire to see more is driving rapid innovation in the field. Five microscopes representative of these innovations are featured in this issue, starting on page 629. They range from 'super-resolution' devices that use light to reveal details once visible only with electron microscopes, to an electron microscope that can peer into thick samples once accessible only to optical ones.

Few of these new imaging technologies come cheaply, however. One new-generation light microscope can easily cost US$500,000 or more, not counting the staff and training required to use it. There is no room for error on an instrument so sensitive that the slightest vibration or misstep in the experimental set-up creates artefacts.

As a result, biologists may have to get used to sharing their instruments. Research groups often prefer to buy their own microscopes so that lab members can use them whenever they want. But to stay at the forefront of image-led science, they will increasingly have to work with their departments, universities and funding agencies to create shared microscopy facilities staffed by specialists.

Getting engineers into the mix will be a good idea, and computational biologists will be a must. Automation, computer processing and image reconstruction are now central to microscopy and imaging. This means that there is increasing separation between the sample placed in the microscope and what scientists actually see, and that there are numerous points at which inaccuracies can inadvertently be introduced. The only way to interpret the images the system spits out is to understand (and explain alongside the final results) precisely what went into their creation. Not that this problem is new: scientists have struggled with how to interpret microscope images since the instrument's earliest days (see page 642).

As well as sharing microscopes, cell and molecular biologists will need to share the instruments' output. A good way to do that would be through a central repository or framework for biological images modelled on existing data repositories such as GenBank. Such a resource would not only help to make the images universally available — using widely accepted data standards — but could be a driver for the development of analysis techniques that extract deeper meaning from existing images. A database launched last year by *The Journal of Cell Biology* (http://jcb-dataviewer.rupress.org) is already a start towards this goal. Such experiments deserve the community's support and participation.

"The era of systems microscopy could soon be here."

Meanwhile, some labs are exploring an alternative to the fat-price-tag rule: instead of buying one machine for $500,000, buy 50,000 microscopes for $10 apiece. By creating microscopes that are small, cheap and even disposable, these researchers hope to accelerate the development of microscopy into a high-throughput, automated procedure that can quickly collect data on living cells as systematic changes are made to one gene, protein or receptor at time. The era of systems microscopy could soon be here.

The wonderful thing about thinking visually is that it is so easy to think big. And that's exactly what researchers should do as they move ahead. By thinking about what they really want to see, they will help to devise microscopes — as well as computation, labelling and sample-preparation techniques — that make that vision possible. Thinking big might lead to microscopy that allows individual molecules to be tracked across thousands of cells in real time in living tissue; that can watch a single cell over the months or years that lapse from birth to death; or that can map the intricate form of every neuron in the brain across multiple species. The deeper biologists look, the more they will find there is to see. ■

Stem-cell clarity

The draft NIH guidelines on stem-cell research are a good first step, but some revision is needed.

The proposed guidelines on federal funding for stem-cell research issued in April by the US National Institutes of Health (NIH) are a welcome effort to assert ethical and regulatory leadership over this field — especially given the vacuum in oversight left by the previous US administration. Yet concerns aired by the scientific community during the public comment period that closed last week have underscored the need for the NIH to revise the guidelines to allow the responsible progress of research.

For example, the NIH has acted admirably in setting forth nine strict informed-consent provisions regarding the source material for stem-cell lines that are eligible for federal funding. As currently written, however, the provisions would probably exclude funding for most embryonic stem cells now in use, because the cells were derived from leftover embryos at fertility clinics under rules less stringent than the ones now called for. In particular, one provision requires that embryo donors affirm that they are donating "without any restriction or direction" regarding the patients who may benefit from the research. Few of the consent forms currently in use by fertility clinics ask for that affirmation. Also absent from many forms is the stipulation that the donors "would not receive financial or any other

benefits" from commercial development of the research.

It is doubtful that the guidelines are intended to bar future NIH funding from stem-cell lines that are currently eligible — or, indeed, from the hundreds of lines that are now in use but are not among the score of US-approved lines. That would contradict US President Barack Obama's intention, stated on 9 March, to "expand NIH support for the exploration of human stem cell research". The NIH should explicitly state that the informed-consent provisions apply only to newly created lines. All previously eligible lines should continue to be eligible, and existing non-eligible lines should become so — provided that the latter were created in accordance with guidelines issued by the US National Academies or the International Society for Stem Cell Research.

A much less clear-cut issue is whether federal funding should support work on lines created from sources other than leftover embryos. The NIH's draft guidelines currently exclude support for research on lines created through somatic-cell nuclear transfer (SCNT), also known as therapeutic cloning. And they prohibit funding for lines created through the generation of an embryo from an unfertilized egg cell.

Some investigators have protested this provision of the guidelines, arguing that the NIH should not cut off any avenues of research. Their contention is somewhat hypothetical, however, because no one has yet shown conclusive evidence that SCNT can successfully create a human embryo. Regardless of this, the ethical issues involved are extremely sensitive. Polls consistently show that a majority of the American public is willing to pay for research on stem cells derived from embryos that would be discarded otherwise. But it is not clear that a majority would support the use of taxpayers' money to study stem cells from embryos created and destroyed for research purposes alone. So unless the scientists arguing for federal funding of research on SCNT-derived stem cells can make a much stronger case, by spelling out the specific situations in which the research might be warranted and explaining how they will ensure proper oversight of the work, the NIH's proposed exclusion should stand.

At the same time, however, the NIH should affirm that it will revisit its draft guidelines as the science progresses. The past decade shows us that basing research policy on arbitrary cut-off dates does not serve science or the public interest well. ■

Power vacuum

The US president's delay in naming an NIH director is symptomatic of a widespread problem.

As *Nature* went to press, US president Barack Obama had still not nominated a director for the National Institutes of Health (NIH), the $30.3-billion agency that is the world's largest funder of biomedical research. Regardless of when a director is named, the delay is already too long: Obama took office 136 days ago. In the interim, the NIH has been forced to navigate multiple sensitive issues under temporary leadership, including decisions about how to spend a massive $10 billion in economic stimulus money; the drafting of guidelines for expanded federal funding of human embryonic stem-cell research (see above); and the launch of a proposal to tighten conflict-of-interest reporting requirements for its extramural investigators.

Moreover, the problem goes well beyond the NIH. The installation of senior agency leaders, most of whom have to be nominated by the president and confirmed by a majority vote of the US Senate, seems to go ever more slowly with each passing administration.

Granted, the Obama White House has been trying. As of Monday the Senate had confirmed 145 people for a total of 373 jobs that need filling, which is not too different from the pace set by the incoming Bush administration in 2001. But that still leaves only 4 of 21 Senate-confirmable posts filled at the Department of Health and Human Services (HHS). Among those HHS posts still waiting for a permanent occupant — in addition to the NIH directorship — are the assistant secretary for health, the top public health adviser to the new HHS secretary, Kathleen Sebelius; the assistant secretary for planning and evaluation, her top policy adviser; and the assistant secretary for preparedness and response, her top adviser on bioterrorism and other public-health emergencies.

Even appointments that don't require Senate confirmation have been slow to materialize. Richard Besser, the acting director at the Centers for Disease Control and Prevention, was left to deal with the emergence of swine flu — Thomas Frieden, Obama's permanent appointee for the job, won't begin work until 8 June.

Other science agencies are in similar straits. At the National Oceanic and Atmospheric Administration, Jane Lubchenco was confirmed as administrator in mid-March, but she still lacks a chief scientist and two assistant administrators, one for atmosphere and one for oceans. No nominees are in sight. At NASA, the two top posts went unfilled until 23 May, when Obama finally nominated former space-shuttle astronaut Charles Bolden as administrator and Lori Garver as his deputy. But no Senate hearings have yet been scheduled for them. And at the National Science Foundation, there is still no nomination for a deputy director — a key strategic post that encompasses the duties of chief operating officer.

This dilatory pace is partly a result of Obama's promise to run a squeaky-clean administration staffed by officials not beholden to lobbyists or other moneyed interests. But it is mostly the result of the Senate confirmation process, which in recent decades has become increasingly obsessed with savaging nominees over even the most minor slip-ups on taxes or nannies. To minimize the chances of embarrassment, the administration now requires Senate-confirmable nominees to fill out lengthy vetting questionnaires. These are so onerous that many feel compelled to spend their own money hiring accountants and lawyers to help fill them in. Other qualified people simply refuse to go through such an ordeal, and take themselves out of contention.

The administration and the Senate together must find a way to restore common sense to this process. Given the challenges faced by the United States, ranging from nuclear proliferation to climate change and potential pandemics, its government needs to recruit the best minds it can find — without subjecting them to a protracted, politically motivated vetting process that does nothing to solve real problems. ■