CAREERS

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TECHNOLOGIES

The right tool

Research-tool developers must be creative, innovative and willing to collaborate with people from a variety of fields.

BY KELLY RAE CHI

Gregory Buckner once dreamed of being a surgeon. But his father, a civil engineer, convinced him to try engineering. Now, as a mechanical engineer at North Carolina State University in Raleigh, Buckner combines the two interests. He creates, builds and develops biomedical tools such as robotic catheters for use in minimally invasive cardiothoracic surgery. Buckner does not work directly with chest pain or lacerations. Instead, he deals with batteries and circuit boards and plastic tubing.

Tools from lab instruments to software can refine research and open new fields of enquiry. And the people who make them are a varied bunch — they might be full-time university researchers, or they might be hired by larger teams in academia or industry. The boundaries are fluid. Buckner, for example, has worked as a consultant, licensed his inventions to industry and even launched his own company.

Industry jobs involve specific goals with fast turnarounds. They are often at companies that sell scientific instrumentation, medical devices or software, such as Life Technologies, based in Carlsbad, California; Oxford Instruments in Abingdon, UK; and Medtronic in Minneapolis, Minnesota. Options are many for those keen on focusing their skills and scientific know-how on tools rather than lab research.

"There's certainly a diversity of ways to impact science through tool building," says Eric Betzig, a group leader at the Howard Hughes Medical Institute's Janelia Farm Research Campus in Ashburn, Virginia, who at Janelia and elsewhere has led the development of microscopes that can image features smaller than half the wavelength of the light used to illuminate them. Often overlooked in the past, designing and building biomedical tools has been receiving growing respect as a career track. There are now grants and publications dedicated to the craft, and toolmakers are increasingly integrated into research teams to help not only with the development of tools, but also with their application. Although they may not be responsible for the actual findings, toolmakers can help to overcome research obstacles in the lab or the clinic.

ALL WALKS OF LIFE

Successful tool builders typically have expertise in fields such as engineering, computer science, bioinformatics, maths or physics — and occasionally biology. They also tend to have a willingness to learn, a knack for picking up mechanical and research skills and enthusiasm for collaboration. Members of Janelia Farm's instrument design and fabrication group, for example, have worked in the defence and automotive industries. They learn neuroscience on the job at Janelia, says Chris Werner, the group's shared-resource director. Tool builders shadow scientists in the laboratory until they understand the problem at hand, and they may even be named as co-authors on publications. "Besides technical skills, what's really important and makes the difference is their soft skills — communication, giving credit, taking credit — the ability to play nice," says Werner.

Toolmakers need to be good listeners, ▶

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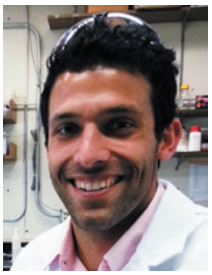
alert to the challenges of bench research — whether those are imaging a live cell or analysing a huge number of data. Developing tools to solve such problems involves making multiple test runs and repeatedly conferring with users or customers to make sure that the instrument or algorithm is doing what it needs to. This can be a big challenge — often researchers are unsure of exactly what they need. And success can mean being anchored to a project for a long time; tool builders frequently get roped into collaborations and companies centred on their technologies.

Armon Sharei, a PhD student in chemical engineering at the Massachusetts Institute of Technology in Cambridge, saw at first hand the healthy dose of trial and error that can be involved in tool development. Sharei embarked on the path to an invention by chance, when he was trying to shoot cells with a jet of liquid to deliver proteins, DNA, nanoparticles and other large molecules into the cells for research and clinical applications. The delivery worked, but not for the reasons that he expected. Instead of directly injecting the membrane with fluid, the jet seemed to be squashing the cells — squeezing them so much that it caused their membranes to open temporarily and allow the fluid to diffuse in. But delivery efficiency was poor. "The prospects didn't look good but what kept us going is that, in principle, this method was so simple it could make a big difference if we could improve it," says Sharei.



"That lucky first observation or experiment comes to everyone. It's just a matter of recognizing it and developing its potential."
Armon Sharei

His research advisers took a risk and the group overhauled the design. The team eliminated the jet and created different versions of a microfluidic chip that worked by essentially squeezing the cells. The team patented the technology and in March launched SQZ Biotech in Boston, Massachusetts, to commercialize the device. Applications might include delivering reprogramming proteins to convert fully developed cells into induced pluripotent stem cells. "I think that lucky first observation or experiment comes to everyone once in a while. It's just a matter of recognizing what it is and developing its potential," says Sharei.

Serendipity aside, tool ideas often come from a deep understanding of customers' needs, which provides insight into ways to make improvements. Ideas for most of Buckner's developments — which include a finely controlled robotic catheter and a chest retractor that measures force during open-heart surgery — come from watching surgeons, cardiologists and radiation oncologists. "They are true experts in the field and know what the technical hurdles of their current practices are," says Buckner, who has patents on multiple inventions.

Tool development itself often spawns further ideas; one project may proliferate into many. Through a clinical collaboration in 2007–08, Buckner's group was working to automate the tying of knots in sutures during surgery on the mitral valve of the heart. The researchers had to test their prototypes on live pigs, which proved both costly (at US$2,500 per pig) and time consuming. So they developed a 'dynamic heart system' that pumped fluid through a dead pig heart so that it functioned realistically. The device allowed the team to test its technologies for less than $25 a go.

SILVER LINING

Toolmakers must be ready for some disappointment — and if the end product fails to live up to the original idea, they should be nimble enough to tweak it, find other applications or move on. Betzig experienced difficulties with near-field microscopy, a high-resolution imaging method. The technique turned out to have some physical limitations that made it less than ideal for its intended use in imaging biological samples. In the end, he moved on to different projects, although others have continued to pursue near-field microscopy. "The thing about tools is that they're kind of like your children," says Betzig. "When they're born, you say, 'Oh, he could be president! Or an astronaut! Cure cancer!'." But toolmakers often come to the realization that their work might not have quite the impact that they anticipated. Betzig says that his tools have failed in various ways — and that by focusing on the flaws, he can find opportunities to develop better versions.

Once a tool builder based in academia believes that he or she has something ready for the marketplace, another set of challenges awaits. In the United States, for example, the developer must often file an invention disclosure with his or her university's technology-transfer office, allowing the office to evaluate the potential for commercializing the tool. If it looks promising, the office then usually files a provisional patent application. If certain conditions specified by the US Patent and Trademark Office are met within 12 months, the application can be made non-provisional.

After a patent is issued, there are numerous possibilities. The inventor might seek funds from industry or the government to refine the prototype. The technology-transfer office might work with the inventor to find companies that are willing to license it. Any tools geared for clinical use will need to be submitted for regulatory approval. And the inventor could launch a company with the help of partners or

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NCSU/BECKY KIRKLAND

Mechanical engineer Gregory Buckner (right) works with a graduate student.

advisers who have business and legal expertise. After tools are sold, new applications might come to light, and the company can develop these or create spin-offs to do so.

BUILDING SKILLS

Just like researchers, toolmakers can learn through an apprenticeship of sorts. "As a more-junior graduate student, one can learn these skills very deeply by working with more-senior graduate students, postdocs and principal investigators," says Samuel Hess, a physicist at the University of Maine in Orono who has invented high-resolution imaging methods. Degrees in fields such as biomedical engineering or computational biology can help people to build skills at the intersection of toolmaking and medicine or biology. Even after obtaining their PhDs, toolmakers can learn or refine their skills by working with more-experienced researchers during a postdoctoral fellowship, on sabbatical or in industry. Whenever it happens, learning to build is a hands-on process — with a lot of mistakes made along the way, says Betzig.

Many established toolmakers are essentially self-taught and self-motivated. "I hire lots of programmers and engineers. The best programmers are always former biologists who pick up the programming bug," says Chris Beecher, an analytical chemist and co-founder of IROA Technologies in Ann Arbor, Michigan, who has invented platforms that quantify the small molecules produced by metabolism in cells or tissues.

At Waters Corporation, an analytical science instrumentation company based in Milford, Massachusetts, some of the product developers are not engineers, but scientists who have previous experience using analytical chemistry instruments as part of their research, so they know what customers need, says Steven Cohen, life-sciences director in research and development at the company. Such developers work with a manufacturing workshop to design instruments and build prototypes.

In academia and the non-profit sector, tool development is often funded through a larger research project. But researchers can also apply for grants specific to tool building. Genome Canada in Ottawa, for example, supports the development of genomic technologies through funding competitions. Naveed Aziz, the organization's director of technology programmes, says that he receives funding applications led by bioinformaticians as often as by researchers. And the US National Science Foundation (NSF) runs an Instrument Development for Biological Research grant to support development of tools that enable new research capabilities, markedly improve current technology or transform a prototype into something more broadly usable.

Several US federal agencies — the NSF, the National Institutes of Health and the Department of Defense — also offer Small Business Innovation Research and Small Business Technology Transfer grants, which aim to spur technological innovation and lower the barriers to commercialization. The Wellcome Trust in London, one of the world's biggest biomedical research charities, uses its Translation Fund and Health Innovation Challenge Fund to speed the commercialization of biomedical technologies.

"One can learn these skills by working with more-senior graduate students, postdocs and principal investigators."
Samuel Hess

Grants like these can help toolmakers make a lasting difference to a given field. It is always nice to go "beyond the narrow scope" of the original project, notes Charles Schmitt, director of informatics at the Renaissance Computing Institute, based in Chapel Hill, North Carolina. But although it is gratifying when a tool is adopted widely, it sometimes means that toolmakers must train others to use their inventions, and must surrender control to groups with their own skill sets and agendas. Toolmakers can take pride in their impact, but lose command of their brainchild. Moving on, says Schmitt, "is always a big challenge". ■

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CHEMISTRY

Improving lab safety

A US National Research Council committee met on 15–16 May in Washington DC to start developing safety recommendations for chemical researchers in academic and national laboratories. The project was spurred in part by three high-profile accidents at US academic laboratories between 2008 and 2011. Behavioural scientists, chemists and safety experts will identify problems at research institutions and learn from effective safety systems in industry to develop the recommendations, which will be released next spring. Chemists and behavioural scientists "can learn from each other," says committee chairman Holden Thorp, chancellor of the University of North Carolina at Chapel Hill.

BRAIN DRAIN

Workers flee corruption

A growing number of highly skilled workers including researchers are leaving corrupt nations where government officials demand bribes and control access to the labour market, finds a study published on 17 May (A. Ariu and M. P. Squicciarini *EMBO Rep.* http://doi.org/mkh; 2013). Nations with relatively low corruption benefit from an influx of scientists who write influential papers and patents and create businesses, says the study, which examined movement patterns in 123 nations against an international corruption index. "It is not a positive thing for a researcher to be in a country that is highly corrupt," says study co-author Mara Squicciarini, an economist at the Catholic University of Leuven in Belgium.

IMMIGRATION

Postdocs hit by scam

Confidence tricksters are targeting international postdocs and students in the United States, according to complaints passed on to the National Postdoctoral Association (NPA) in Washington DC. Telephone callers claiming to be from US Citizenship and Immigration Services (USCIS) tell trainees that they have improperly completed a form, and that they face a fine or deportation. This is not agency procedure, says the NPA. Callers know the target's name, date of birth, address, phone number and case number. People who suspect that they have been targeted should report the scam at go.nature.com/poexjx. The USCIS did not respond to requests for comment.

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