CONVERGENCE IN BOSTON

HOW MULTIDISCIPLINARY R&D IS DRIVING BENCH-TO-BEDSIDE BREAKTHROUGHS

BY NICK PAUL TAYLOR

Biotech Week Boston

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The area in and around Boston, Massachusetts is as dense with world-renowned scientific experts as anywhere on earth. Here, in an area a little larger than one square mile, researchers from Harvard University, Massachusetts Institute of Technology (MIT), and a multitude of biotechs and Big Pharmas are driving the evolution of the technology and business of science. In doing so, research teams are increasingly looking to share data, research, and ideas.

Collaboration has always been key to science, but, as researchers have taken on ever-more complex projects, the need to work with people from different disciplines, backgrounds, and organizations has increased. Such collaborations run counter to the secretive, ego-driven, or financially-motivated sides of science, but have nonetheless taken root, even in for-profit fields, as organizations have realized the value of expanding the breadth of their internal expertise while looking outside of their walls for collaborators.

In this feature, we look at three people who have embraced the collaborative, multidisciplinary ethos and, in doing so, have influenced science, business, and the lives of patients to a far-greater degree than would have been possible through an isolationist approach. Their goals are diverse. One is working to improve drug availability in low and middle-income countries through the advance of biomanufacturing. Another is looking to nature for answers to biomedical problems that blight the lives of patients. Our third is coordinating a global campaign to unlock the secrets of the genome.

What links the three researchers is not the type of science they do, but the way they do it. Each is an example of what scientists, particularly in hotspots such as Boston, can achieve when they are open to the sharing of data, research, and ideas.

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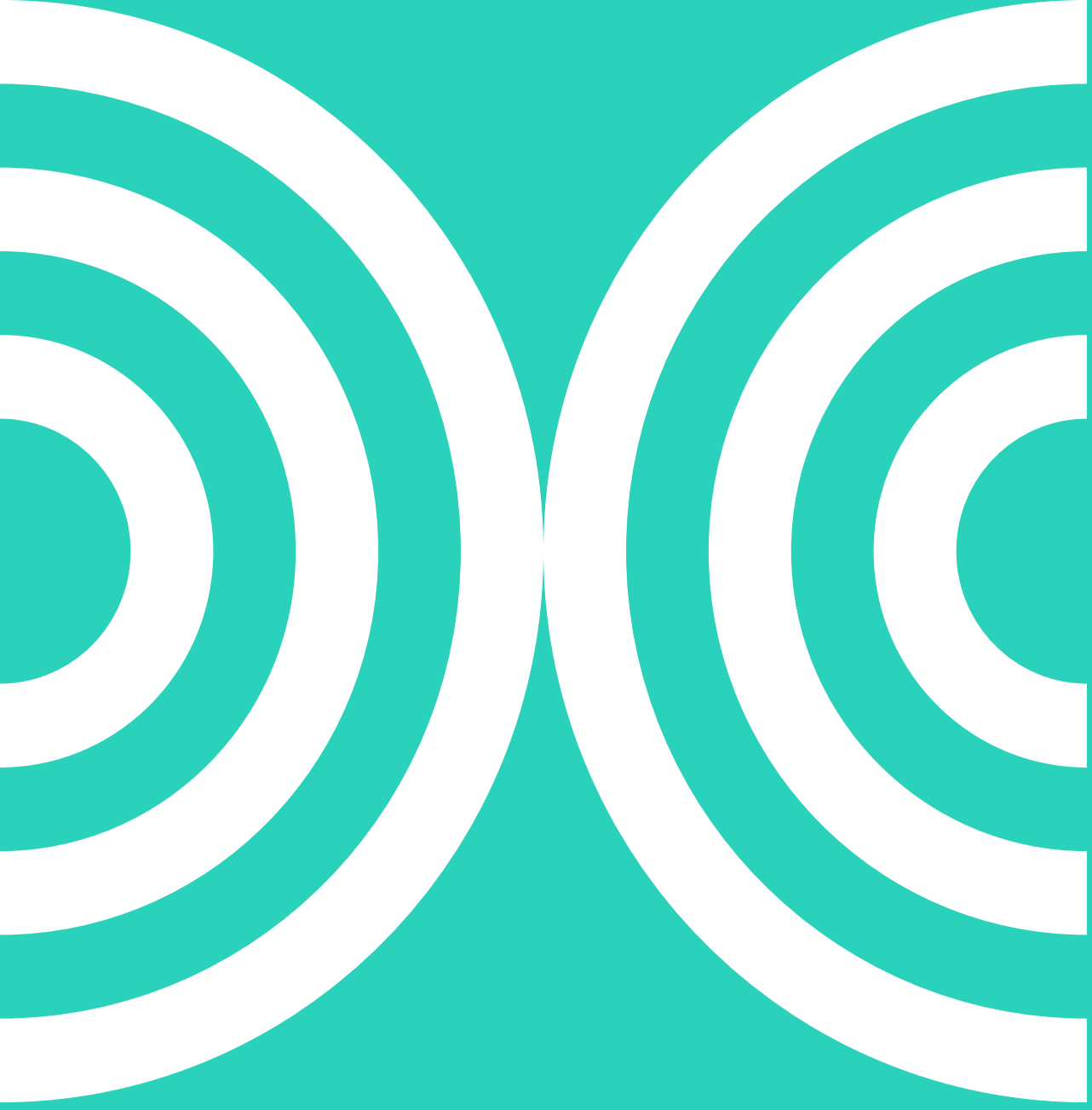

SECTION 1

BUILDING A TEAM TO MIMIC EVOLUTION

The need for multidisciplinary teams is most intense when facing complex projects, particularly those that are nearing the point at which they will start to make a difference to the lives of patients. This description is a good fit for **The Karp Lab**, a Cambridge, MA-based translational research center that has made its name through bioinspiration projects. Bioinspiration, also known as biomimicry, is the practice of looking to nature for solutions to problems.

While the development of Velcro, the best known example of bioinspiration, was driven largely by one person, the challenge of copying natural innovations that took billions of years to evolve typically requires a multidisciplinary team. At Karp Lab, mechanical, electrical, and chemical engineers work alongside biologists, immunologists, material scientists, and surgeons. This breadth has enabled Karp Lab to use everything from porcupine quills to jellyfish tentacles as the basis for a breakthrough.

Jeff Karp, who oversees the eponymous lab, picks out the development of a tissue glue as a good example of the process. Faced with the need to develop a glue that remains adhesive when exposed to blood so it can patch a hole in a beating heart, Karp's team looked to the viscous secretions of slugs, snails, and sandcastle worms for inspiration. To turn this idea into an experimental glue, Karp worked with heart surgeons, mechanical engineers, polymer chemists, and a fiber optics expert.

Bringing all of these people together is just the first step. Karp also creates an environment designed to make the most of everyone's capabilities, specifically by minimizing overlap in expertise.

"[That way,] when people get together to brainstorm, everybody can bring something unique," Karp said. "Everybody feels validated, everybody's motivated because they're the only ones who can bring that particular perspective or expertise."For Karp, the breadth of perspectives is as important as the range of expertise. This way of thinking has led Karp to populate his lab with people from around the world.

"We've had people from over thirty different countries," he said. "I think this has been important because people

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in different places, they have different ways of thinking, different ways of solving problems."

The idea that teams with diverse backgrounds and life experiences are better at problem solving is backed up by decades of research. People who grew up in the same parts of a country and went to similar schools often have comparable approaches to solving problems. As such, homogeneous groups of these individuals tend to get stuck on problems at the same point. Diverse teams, in contrast, come at problems from lots of different angles, enabling them to find creative solutions.

Karp has leveraged the abilities of his diverse, multidisciplinary teams to accelerate the advance of products with the potential to make a meaningful difference to patients. The aforementioned tissue glue is joined by needles that stop when they reach a particular part of the body, porcupine-inspired medical staples that cause minimal tissue damage, and jellyfish-like tentacles of DNA that capture circulating tumor cells on the list of Karp Lab's most promising projects.

Translating such research projects into real-world products is a key part of Karp's work. Cellular medicine company Mesoblast is among the businesses to license technology from the lab, while Karp has also cofounded companies to develop and commercialize his research.

Karp is working with Gecko Biomedical to develop the aforementioned tissue glue and Skintifique to advance skincare technology. Setting up a business allows Karp to stay involved in the advance of a technology, something he sees as having some advantages.

"I'm very interested in getting technologies out into the clinic to help patients," Karp said. "The nice thing about starting a company is that then I can remain very close to the technology and I can push really hard to make sure that it gets to patients."

This ethos is evident at Frequency Therapeutics, a Cambridge-based biotech Karp cofounded with a fellow serial entrepreneur, MIT's Robert Langer. Karp set up the business to develop an approach that uses small molecules to activate stem cells. Once activated, the cells proliferate and differentiate to form tissues. Karp sees applications for the approach in the intestine and inner ear.

Frequency is going after the inner ear opportunity, but, in its short life to date, has kept a very low profile and revealed little about its technology or R&D strategy. That is about to change.

SECTION 2

WHY GENETICISTS NEED ETHICISTS

The desire to translate research into medicine is also at the core of the recent work of our second scientist, **Kristin Ardlie**. In her capacity as director, biological samples platform at The Broad Institute of MIT and Harvard, Ardlie plays a central role in the Genotype-Tissue Expression (GTEx) program.

GTEx was set up in response to a boom in genome-wide association studies (GWAS) and subsequent sharp increase in knowledge of the links between genetic variants and human diseases. On one level, knowledge of these variants marked a major advance in our understanding of the root causes of disease and, by extension, our ability to treat or prevent them. However, with most of the GWAS variants not coding for proteins, the molecular mechanisms through which they lead to the development of diseases were poorly understood. This is where GTEx came in.

"We wanted to assess what affect the genome is having on gene expression. We do that by correlating gene expression and genetic variation," Ardlie said. "We wanted to do that across the human body, across multiple tissues because we know that different genes are expressed in different organs and tissues."

The need to analyze different tissues could have scuttled GTEx before it got started. While people are willing to donate blood, perhaps a little subcutaneous adipose tissue, and whatever samples can be taken during surgery, these sources were insufficient for the breadth and scale of the sequencing program envisaged for GTEx. In response, the GTEx team looked into sourcing samples from people who had died recently, an approach that would alleviate its tissue supply bottleneck but create a new set of ethical and legal questions.

A separate wing of GTEx was established to research what motivates a family to donate the tissue of a loved one to research following their death. Branching out in this way has made GTEx an unusually broad, multidisciplinary initiative that, through an ethical, legal, and, social issue substudy, has driven advances in fields far beyond genetics. Notably, the substudy has supported the development of best practices and training resources for people who have to ask grieving families to donate tissues.

This work has given GTEx, and other initiatives, a platform from which to gather the tissues that are essential to their work. It has also created a dialogue between biospecimen specialists, ethicists, geneticists, and the families of donors.

"The project as a whole has reached out to the next of kin who made the donations and told them what we're doing," Ardlie said. "It turns out that people are very interested in genetic studies."

These conversations have linked the three pillars of GTEx, namely the donors and their families, the ethical and legal experts, and the team that is processing and analyzing the samples. Ardlie is part of this third component of the program.

Working as part of a consortium that includes researchers at medical centers, academic institutes, and government agencies in ten American states, plus three European countries, Ardlie has helped to fill some of the gaps in knowledge that have stopped drug developers from translating GWAS variants into experimental therapeutics.

Specifically, Ardlie and the rest of the team at Broad are involved in the processing, sequencing, and analysis of tissue samples collected by other members of the consortium. The last step in the process is very much a team effort.

> “There are several groups that would like to continue and expand the project and the sampling,” Ardlie said.

“There are multiple labs across the world, including Geneva and Barcelona as well as California and various east coast and Chicago labs, who are engaged with us in methods and analysis development,” Ardlie said. “We have a very large analysis working group that’s been developing methods of analysis to deal with all these tissue samples and perform new analyses.”

GTEx has then gone one step further by opening up the data to scientists outside of the consortium and holding outreach meetings with the wider community. These meetings give GTEx a chance to learn how people are using the data and address any questions they may have.

Now, with the tissue collection phase of GTEx over and the sequencing stage due to wrap up in a year or so, the range of analyses being run, both by consortium and external teams, is expanding. Searches for epigenetic marks and projects to understand methylation patterns are underway.

Through these and as-yet-unstarted analyses, the data derived from years of work and sacrifice by the families of donors, ethicists, legal experts, biospecimen specialists, geneticists, and others will continue to yield scientific discoveries. And, while GTEx in its current form is nearing the end, there are pilot projects linking it to single cell analyses and other mooted extensions that are just getting started.

“There are several groups that would like to continue and expand the project and the sampling,” Ardlie said. “Our particular project won’t be continuing, but there’s a lot of interest in pushing a continued project forward, maybe internationally. We’ve had one meeting already.”

SECTION 3

USING MANUFACTURING TO IMPROVE GLOBAL HEALTH

Our third researcher, Stacy Springs, is also looking internationally for her next project. As director of the Biomanufacturing Program (BioMAN) and executive director of the Consortium on Adventitious Agent Contamination in Biomanufacturing. (CAACB) at the MIT Center for Biomedical Innovation (CBI), Springs works on multiple initiatives involving industry, regulators, and academia. The latest project might be the most ambitious yet.

"We have a new global health initiative that hasn't really been publicized yet," Springs said. "It is very much focused on the different ways we need to think about ... making biologic medicines available and accessible to middle and low-income patients around the world."

While there are multiple barriers to global medicine availability, at least some of them relate directly to manufacturing and logistics. Springs and MIT CBI's history of working at the forefront of innovation in biomanufacturing means they are well placed to try to address these issues. The project is still being fleshed out — students are currently looking at what changes would make the biggest impact — but Springs already has ideas about ways to improve availability.

Possible areas of focus include the development of innovations that lower the cost of goods sold or flexible manufacturing platforms that make it possible to produce drugs in hard-to-reach parts of the world. Such platforms could mitigate the lack of a cold chain in a region by allowing drugs to be produced closer to where they are needed. Springs also thinks there might be value in adapting the formulation, stability, and packaging of medicines for use in low and middle-income countries.

As biomanufacturing cannot address all the barriers to drug availability — and organizations are already working to get medicines to patients around the world — Springs is talking to other teams about what is happening today and where MIT CBI can contribute.

"We certainly have been engaged in discussions with the Bill & Melinda Gates Foundation, with PATH, and others about our goals," Springs said. The Gates

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Foundation is among the organizations already working to drive down the cost of manufacturing, but its focus is limited to drugs against its target diseases. Springs' nascent initiative is broader in scope. It may, for example, look at ways to improve the availability of insulin around the world.

The intention to engage with nonprofits, drug manufacturers, and other types of organizations for the global health initiative is in keeping with the way Springs has worked throughout her years at MIT. In her capacity as director of BioMAN, Springs works with a consortium that brings together thought leaders from industry, the government/FDA, and academia to address a range of topics some of which, such as flexible platforms and global delivery, overlap with the new health program.

Springs' other consortium, CAACB, is even larger. CAACB brings together more than 20 leading drug product and equipment companies, such as Amgen, Biogen, Genentech, and Sanofi Pasteur, to gather confidential information on viral contamination. Such contaminations are too rare for any individual company to have enough data to develop best practices, but, by pooling resources at the neutral forum of MIT CBI, companies can learn from their collective experience.

Many drugmakers have traditionally been reticent to cooperate with their competitors, but attitudes have changed over the past decade as executives have come to accept that some challenges are too big for any single company to address. Having been involved in the consortia, as well as a more direct collaboration with Sanofi, Springs is clear about what defines successful relationships.

"It's truth, transparency, and trust. Setting the ground rules and understanding how you want to work together is definitely very helpful," Springs said. "There are always going to be issues arising in any collaboration. You just need to make sure that you can quickly resolve them."

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WHY CONVERGENCE FAVORS BOSTON

The ability to facilitate and participate in collaborations with people who have different backgrounds and, in some cases, different objectives will prove critical to addressing the big challenges science will face in the coming decades.

In 2000, many pundits tipped the coming one hundred years to be the "century of biology," a prediction underpinned by excitement about Human Genome Project. The work of Ardlie, Karp, and Springs shows the vision of biology driving advances in human health around the world is alive and well, but it equally reveals the "century of biology" line to be an oversimplification. In 2016, no one discipline can claim dominion over science.

Rather, the researchers who are best equipped to build a bridge from bench to bedside are those who welcome talents from outside their field and organization. Karp, a chemical engineer by training, would never have developed the tissue glue without the contributions of heart surgeons, fiber optics experts, and others. A similar breadth of expertise is the bedrock of the work of Ardlie and Springs.

This trend toward the convergence of scientific disciplines puts Boston at an advantage. In a scientific era in which the path from the lab to the clinic to real-world use is built on the work of experts in life sciences, engineering, physics, computer science, chemistry, and, mathematics, there is value in having the concentration of expertise found in the Boston-Cambridge area.

About the Author:

Nick Paul Taylor is a journalist who has been published in *Nature*, *FierceBiotech*, *Regulatory Focus*, *Life Science Leader*, *Outsourcing-Pharma*, and *in-PharmaTechnologist*. He has particular interests in drug development, biotech IT, pharma outsourcing, and regulatory trends. Nick can be found on Twitter.

Biotech Week Boston

We're proud to have all three innovators featured in this report: **Jeffrey Karp** of the Karp Lab, **Kristin Ardlie** of the Broad Institute's GTEx program and **Stacy Springs** of MIT CBI BioMANufacturing Program at **Biotech Week Boston** this **October 4-7, 2016** at the **Boston Convention and Exhibition Center.**

Biotech Week Boston is the destination where passionate scientists and innovators converge to partner and share groundbreaking data, research and ideas. Biotech Week Boston will also feature other top healthcare and technology innovators including: **Steve Wozniak**, founder of Apple Computers Inc., **Toni Hoover**, Director Strategy Planning and Management for Global Health, Bill & Melinda Gates Foundation, and **Rick Berke** the Executive Editor of STAT News.

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