NOVEMBER/DECEMBER 2016 # 08

the Translational Scientist

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In an ocean of data, how do you capture what's relevant – and avoid biting off more than you can chew? We go fishing for answers with three gurus of big data.

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Image of the Month

A pediatric burn patient at Shriners Hospital for Children in Galveston, TX, interacts with SnowWorld – the first virtual reality world for pain distraction. Here, the patient is undergoing painful skin stretching physical therapy exercises to maintain skin elasticity and maximize function after recovery.

Credit: Hunter Hoffman, www.vrpain.com

Submit an Image! Email charlotte.barker@texerepublishing.com

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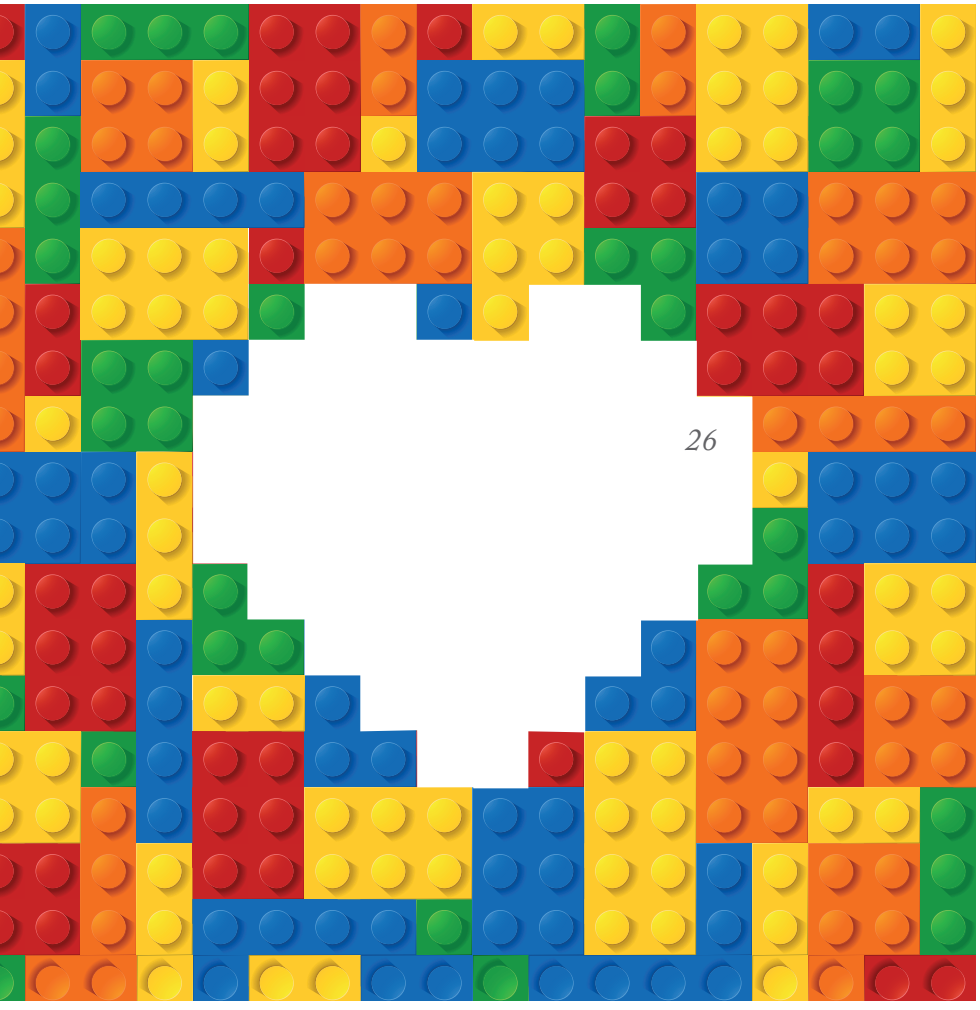

On The Cover

Our three gurus are seen fishing for insight in a big data ocean.

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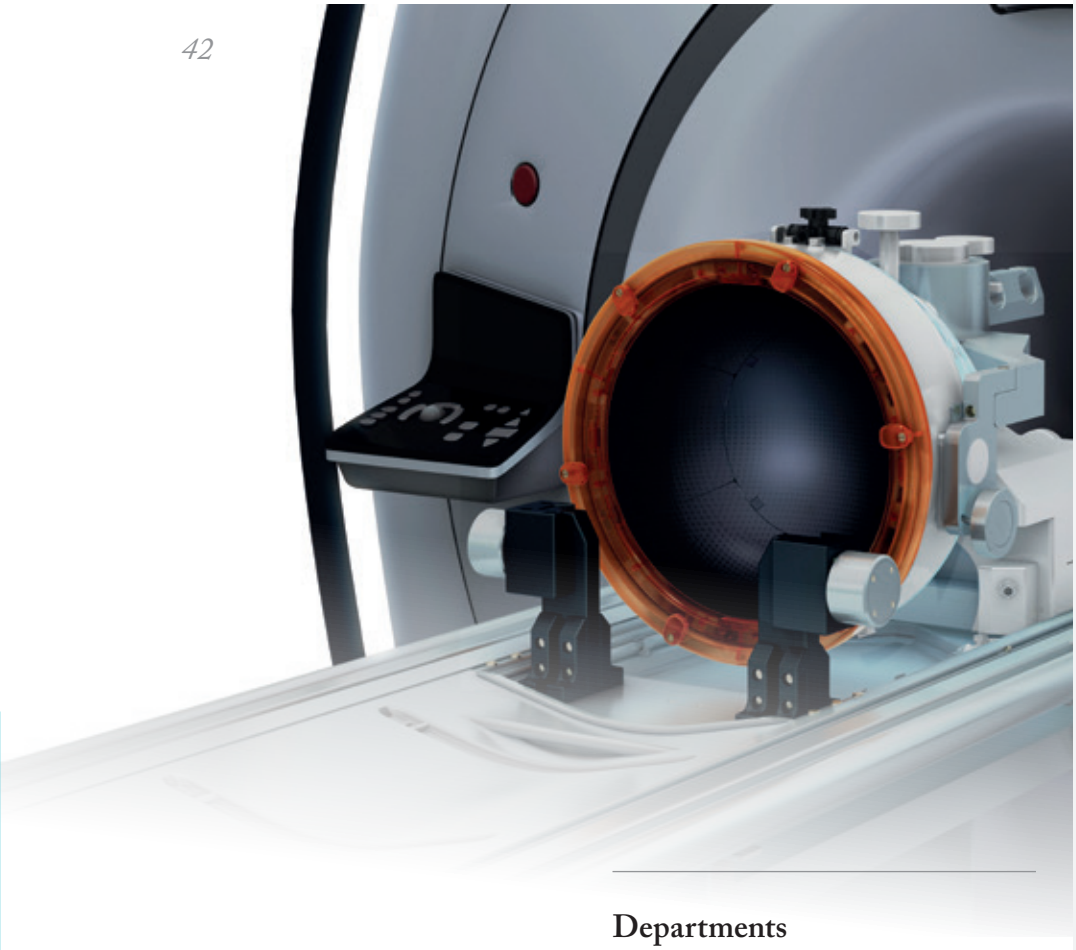

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Hope Springs Eternal

Is cryonics a reflection of humanity's optimism for biomedicine, or a costly distraction?

A recent court case involving a terminally ill teenager has reignited the ethical and scientific debate around cryonics. The 14-year-old wanted to be cryogenically frozen after death in the hope that, one day, she could be "woken up" and cured of cancer – and she won her legal battle to ensure her wishes were followed (1).

A growing number of people are choosing to have their bodies preserved in cryonics facilities, most of them in the US. There are estimated to be more than 250 bodies already cryopreserved in the US and 1500 people who have made arrangements to be frozen on their death (2). Others choose to have only their brain frozen, hoping that future advances will make it possible to download their memories and personality into a computer. Essentially, these people are betting on the progress of science.

Who can really blame them for thinking that medicine may be in a very different place in 100 years? In this issue of The Translational Scientist, we can see just a few of the leaps that have been made in recent decades – the tools now at our disposal for genome editing (page 38), tissue engineering (page 26), and big data (page 18) were entirely unimaginable 100 years ago. And it is almost impossible to predict what will be possible in the next 100...

So why are many scientists deeply sceptical about cryonics? Some advocates of the field blame stigma, saying that researchers who express support risk disapproval from colleagues and could even be thrown out of scientific societies (3). That point out that concepts such as IVF and space travel were initially ridiculed. As Michael West recounts on page 32, science is not immune to fads and fashions, with aging research going from being the preserve of "kooks" to one of the hottest fields in biomedicine.

But there may be a simpler explanation for the lack of enthusiasm for cryopreservation from the scientific community; though the vitrification techniques used in cryonics are routinely applied to freeze and thaw tissue samples and embryos, there is simply no evidence that whole humans or organs can tolerate the same treatment. Even if the body could be reanimated, there remains the not insignificant challenge of reversing the original cause of death.

Ultimately, the case for cryonics hinges on hope. Is any hope – however tenuous – better than none? What are the ethical implications of selling (often at great cost) what may well prove to be false hope?

Whether you believe its proponents are optimists or fools, charlatans or visionaries, cryonics represents the ultimate expression of hope for the future of biomedical science.

Charlotte Barker
Editor

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Upfront

Reporting on research, personalities, policies and partnerships that are shaping translational science.

We welcome information on interesting collaborations or research that has really caught your eye, in a good or bad way. Email: edit@texerepublishing.com

Bionic Neurons

An upgraded electronic chemical array delivers neurotransmitter signals in milliseconds

Electrical stimulation has been used to trigger and stimulate nerve signals in the past, but now Swedish scientists have developed an electronic ion pump that can stimulate nerve cells with neurotransmitters – just as nature intended – and almost as fast (1). "With the electronic release of neurotransmitters, we can achieve much more selective regulation of neuronal signaling, as we are using the natural signal entities of mammalians," says Magnus Berggren, Director of the Strategic Research Center for Organic Bioelectronics at Linköping University, and one of the paper's authors.

The team had previously used a similar device to pump GABA neurotransmitter directly into the spinal cord of rats, and found that it reduced the animals' reactions to pain (2). However, the team's ongoing prime objective is to develop a generic "tool" that is able to address many neurological diseases, according to Berggren – and that requires a faster and more precise system. "One of our projects relates to the suppression of epileptic seizures, which requires the local release of neurotransmitters within just a few tens of milliseconds," he says. The next-generation pump can precisely deliver neurotransmitters at speeds comparable to the body's own synapses, opening many new avenues of therapeutic potential. The team is already running projects that target chronic pain, epilepsy, and loss of hearing via the spinal cord, brain tissue, and cochlea, respectively.

The newest version of the ion pump has yet to be tested in live cells, but the team have big plans, with their sights set firmly on making the device more easily implantable. "We're also developing technology to allow us to electronically deliver more interesting molecules," says Berggren. *WA*

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2. *A Jonsson et al., "Therapy using implanted organic bioelectronics", Sci Adv, 1, e1500039 (2015). PMID: 26601181.*

The Artificial Vision Endgame

Can we skip the retina and the optic nerve – and stimulate the brain directly to restore sight?

Scientists have long dreamed of restoring sight to the blind. But so far, the only approach that has brought the blind some semblance of sight is the implantation of retinal prostheses – arrays of tiny electrodes that fire in response to input from a camera. They're a revelation to those who have received them – but recipients are not going to be driving down to the shops any time soon...

Close your eyes and rub them hard. If you see little spots of light, those are phosphenes – and this is what the electrodes evoke when activated by the camera. It's nothing like normal vision, but it's enough to tell the difference between light and dark, or a wall and doorway, and it helps the blind recover some of their independence. Unfortunately, the implants don't work for everyone – they only replace the function of the light-sensing photoreceptors and rely on the rest of the retina to be sufficiently intact to relay the signal to the optic nerve and on to the brain. If the patient has a retina ravaged by wet age-related macular degeneration or an optic nerve destroyed by glaucoma, no "bionic eye" could ever help. But there is another approach: visual cortex prostheses (VCPs). First envisaged back in the 1920s (1), VCPs bypass the eye completely and stimulate the part of the brain that's ultimately responsible for processing most of your vision: the visual cortex.

Nearly 100 years later, Second Sight recently reported the "first successful implantation and activation of a wireless multichannel visual cortical stimulator in a human subject," providing proof of concept for the company's Orion I visual cortical prosthesis. There are good reasons why it has taken almost a century to get VCPs to this stage; placing the implant requires craniotomy, and once you've removed a portion of the skull to gain access to the brain, you have to deal with a brain anatomy that's both distorted relative to the visual input, and plastic to neural input. In other words, even if you can safely place it, can you "tune" it and keep it tuned over time without requiring repositioning? There are also worries over "kindling" – seizures caused by electrical stimulation. However, for the millions of people worldwide who are legally blind, the impact could be huge.

"We expect patients to find objects, follow lines, conduct orientation and mobility," says Second Sight's Vice President, Gregoire Cosendai, but adds that it is too early to tell if those hopes will be realized.

The company reported that the first patient to receive the Orion I device "was able to perceive and localize individual phosphenes with no significant adverse side effects" – much like a patient with a retinal prosthesis. *MH, CB*

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Stealing Third BACE

Merck & Co's verubecestat enters phase III trials for Alzheimer's disease

Developing drugs for Alzheimer's disease is a fraught undertaking. With a whopping drug failure rate of 96.6 percent – including some high-profile phase III failures – big pharma has seen little reward for their efforts in this arena. So the news that BACE1 inhibitor verubecestat is moving into phase III trials is being greeted with (cautious) optimism.

A popular, though disputed, explanation for what causes Alzheimer's disease is the amyloid cascade hypothesis, which suggests that amyloid β (Aβ) peptides clump together to form insoluble amyloid plaques in the brain – leading to disruption of normal brain function and neuronal death.

There are two types of amyloid-targeting therapies currently being investigated by pharma. Monoclonal antibodies (mAbs) work to clear the amyloid plaques by targeting and binding to Aβ – Biogen's aducanumab has been shown to remove the build-up of amyloid in the brain and slow the decline in memory and thinking skills in people with Alzheimer's disease in a phase I study (1). BACE1 inhibitors, on the other hand, are small molecules that target BACE1 – the enzyme responsible for the initiation of the production of the Aβ peptide in the brain. But both mAbs and BACE1 inhibitors have previously run into safety concerns.

In a recent study, the Merck BACE inhibitor discovery team, at Merck Sharp & Dohme (MSD), successfully took their BACE1 inhibitor – verubecestat – through a phase I clinical trial (1). The drug was well tolerated and there were no study discontinuations due to adverse events.

"While we want to be careful to manage expectations and not draw conclusions beyond what the science currently supports, we are very encouraged by the findings from our Phase I studies," says Matthew Kennedy, Director Merck Neuroscience and the program's lead biologist. "In initial Phase I studies of healthy volunteers and people with Alzheimer's disease, patients taking verubecestat over a one week period showed significant decreases in the levels of Aβ in the cerebral spinal fluid of up to 80 percent."

Following an initial phase II safety analysis, the researchers are now pursuing two phase III studies – one in patients with mild-to-moderate Alzheimer's disease, and another in patients with prodromal stage Alzheimer's (mild cognitive impairment and a positive amyloid PET scan) – they will be completed in 2017 and 2019 respectively.

"We believe that these clinical trials represent an important test of the amyloid cascade hypothesis and that the data produced will potentially have broader implications for the entire field and significantly contribute to our overall understanding of the disease process and etiology," says Kennedy. *JS*

Reference

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Zinc Finger on the Trigger

Gene therapy allows researchers to repress Huntington's disease in pre-clinical models

Imperial College London researchers have used synthetic zinc finger proteins to switch off the Huntington's disease gene in mice for up to six months using a single viral injection (1). We spoke with Mark Isalan, lead researcher, and reader in Gene Network Engineering at Imperial College London, to find out more about the implications of the work.

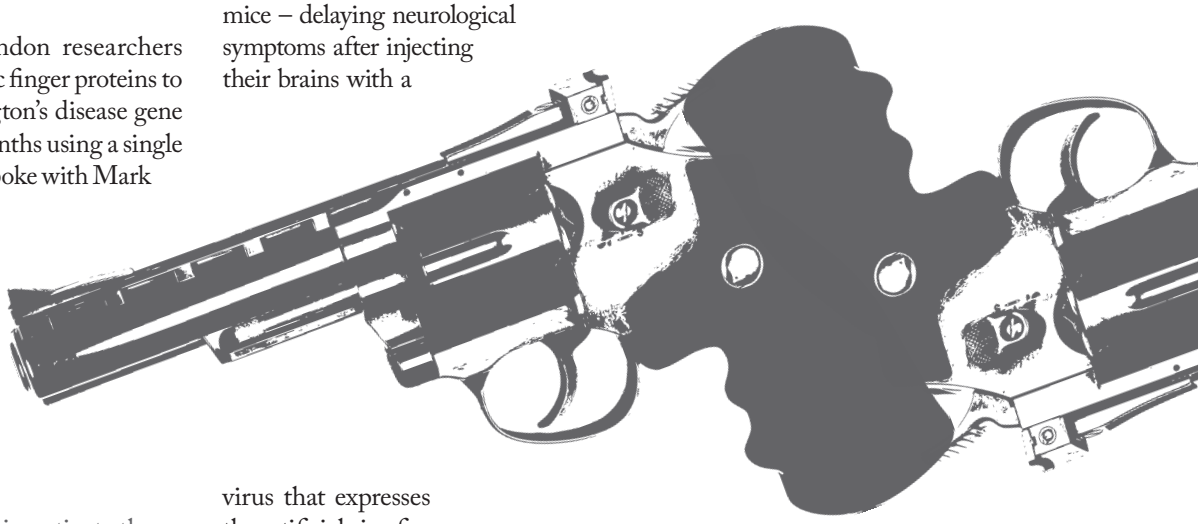
Why did you decide to investigate the huntingtin gene?

First of all, Huntington's is a terrible disease and a cure is desperately needed. Second, the huntingtin disease mutation contains expanded poly-glutamine (CAG codon) DNA sequences, which are ideal for zinc fingers to stick to.

Back in 2001 I had the embryonic idea. I had already been working on zinc fingers for a long time and I was well aware that they could easily be re-engineered to bind guanine–cytosine-rich sequences, but I made the leap to Huntington's after I had been working near Max Perutz in the MRC Laboratory of Molecular Biology. In the last few years of his life, he developed a great interest in poly-glutamine diseases, and Huntington's is the most prevalent of these. He kept mentioning poly-glutamines and the idea got stuck in my head.

How do the zinc fingers work?

Our zinc fingers are designed, DNA-binding proteins that recognize and bind to poly-glutamine in the mutant huntingtin gene. They are gene switches, and by attaching another protein called a repression domain, they can shut down a gene in a long-term, stable manner. Back in 2012, we were the first to show that we could use zinc fingers to shut down the "bad" mutant huntingtin gene for a couple of weeks in mice – delaying neurological symptoms after injecting their brains with a virus that expresses the artificial zinc fingers.



We've had to work quite hard to make the effects last longer, which is the breakthrough reported in this latest paper. By making the zinc finger protein generally more invisible to the immune system, and by producing it with a different promoter gene expression system, we were able to shut down the mutant gene very effectively for several months. In fact, the effect lasted up to six months at levels that we previously showed to alleviate symptoms in mice.

How close are you to creating clinically applicable zinc fingers?

We still have some work to do before moving into humans, although I believe we are getting closer. We need to answer important questions around the safety of the intervention, whether repeat treatments are effective, whether there might be longer-term side effects, and whether we can extend and increase the benefits beyond six months. We also need an industrial partner to take this very exciting result towards the clinic and we are actively seeking one out, while trying to secure follow-on funding. Securing funding has been surprisingly difficult all the way through this project.

What's next?

We think that higher doses and repeat doses are likely to give even longer-term effects, so we're planning to try this out in mice. We are also doing more safety and specificity testing to confirm promising early results which indicate that we are targeting the mutant gene specifically without affecting other related genes in the cells.

Reference

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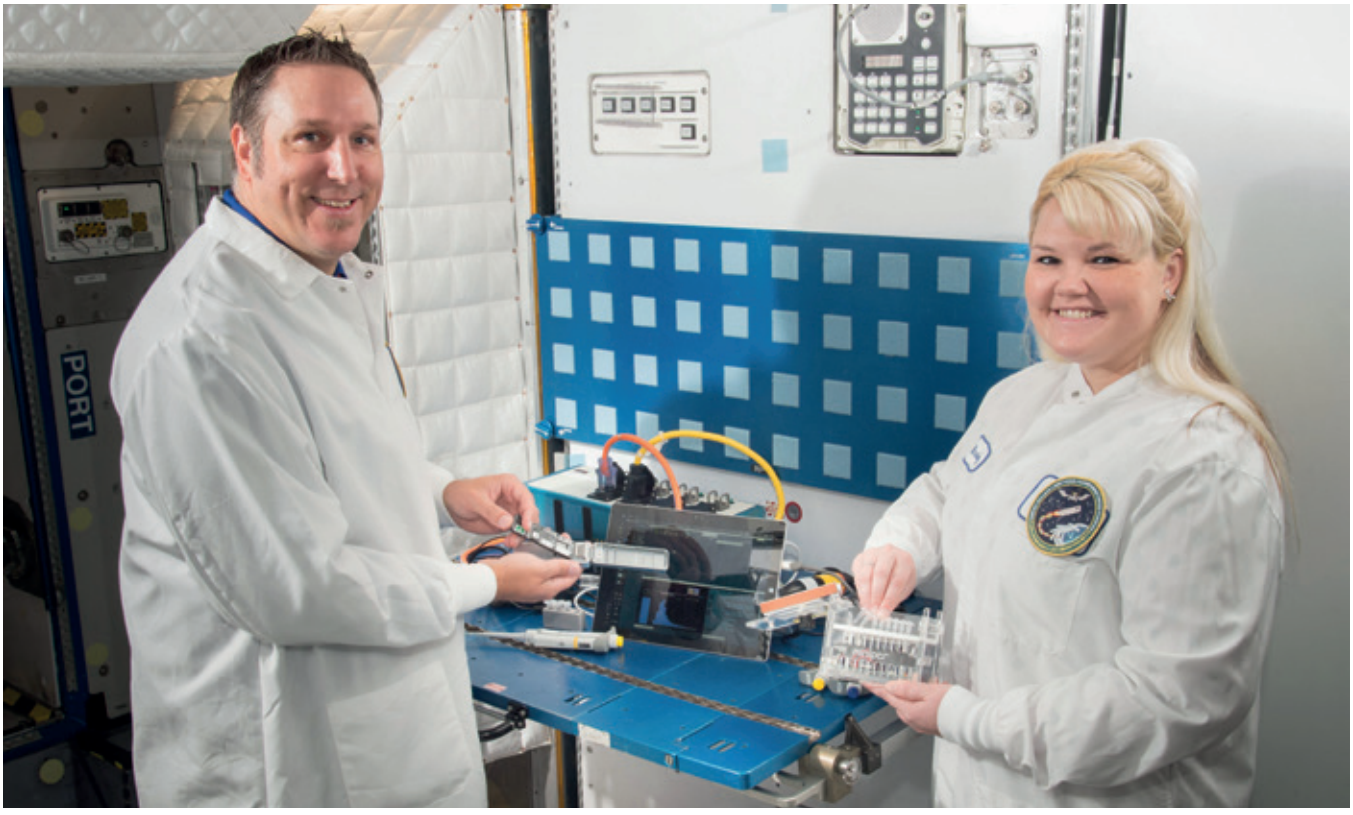

Aaron Burton and Sarah Wallace with the MinION in the International Space Station mock-up at the Johnson Space Center.

One Small Sequence, One Giant Leap

Gene sequencing blasts into orbit

NASA runs a full program of biomedical research, with this year seeing space studies on the effect of stem cell-derived cardiomyocytes and drug pill properties, amongst others. Now, the agency has completed the first DNA sequences in space (1), rapidly sequencing one billion base pairs aboard the International Space Station (ISS).

Why sequence in space? Sarah Wallace, project manager of the investigation at the NASA Johnson Space Center, explains, "Right now, we don't have any abilities to diagnose infectious disease or identify any microbial contaminants that are on the ISS. The crew do take samples, but we have to wait until we get them back to our lab on Earth before we can tell the astronauts what was in the air they've been breathing, the water they've been drinking, or on surfaces they've been touching..."

Most conventional sequencing devices are large, power-intensive, and vibration-sensitive – not optimal for transport or operation aboard the ISS. It was the availability of a palm-sized sequencer, the MinION, that made the project feasible, says Aaron Burton, principal investigator of the project at the NASA Johnson Space Center, "A DNA sequencer like the MinION is really versatile, especially for a task like microgravity sequencing, and no doubt there are people out there who can think of even more creative ways to use it."

As well as the team at the NASA Johnson Space Center, the NASA Ames Research Center, Goddard Space Flight Center, Cornell University, and the University of California San Francisco were all involved with the collaborative project.

"We really hope that this is a capability that transforms space flight research. We will be making the data accessible in the not too distant future, so look out for that..." concludes Wallace. *WA*

Reference

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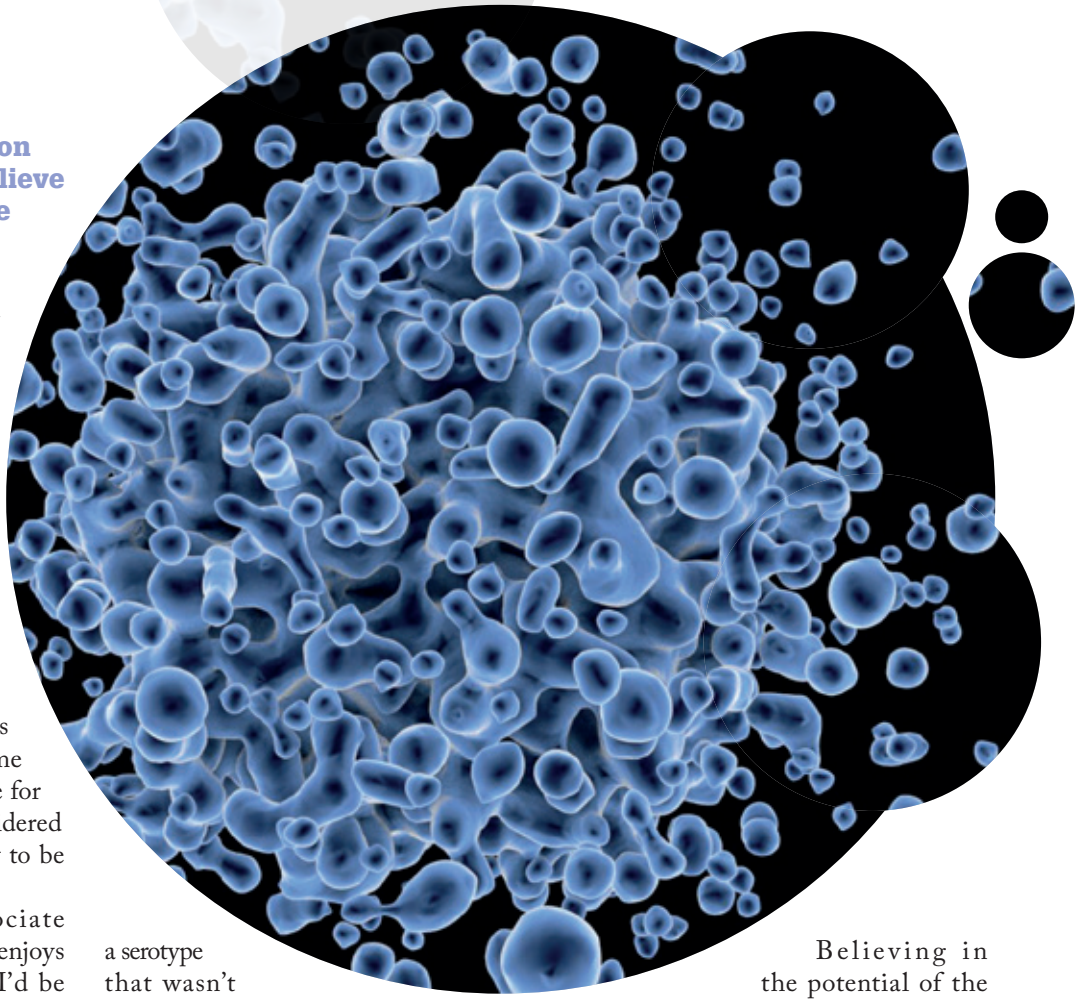
The Cold War

Is a vaccine for the common cold impossible? Many believe so, but some scientists are up for the challenge



The common cold is more than just a nuisance: it is one of the leading causes of community-acquired pneumonia requiring hospitalization in children, and can cause serious problems for people with asthma and chronic obstructive pulmonary disease. The majority of common colds are caused by rhinoviruses, but so far scientists haven't been able to develop a vaccine. Why? There are 170 serotypes (or strains) of rhinovirus, whereas poliovirus (which is in the same family) only has three. A vaccine for the common cold has been considered by many in the pharma industry to be an insurmountable problem.

But Martin Moore, Associate Professor at Emory University, enjoys a challenge. "I didn't know if I'd be able to tackle it, but that's what makes it fun!" says Moore. "We delved into old literature from the 1970s – and found that teams from the University of Virginia, the US National Institutes of Health, and the UK Medical Research Council's Common Cold Research Unit had shown that a monovalent-killed rhinovirus vaccine could induce protective antibodies and prevent colds when volunteers were challenged with the homologous strain."

The vaccines were safe and worked fairly well in the clinic, but the number of serotypes was a problem – the original researchers managed to pick out 10 different serotypes and combine them into one shot, but it wasn't enough. When they challenged someone with a serotype that wasn't in the vaccine, they'd catch the cold.

In Moore's study, the team managed to combine 50 different serotypes into one vaccine (1). "Others have looked for conserved proteins and protein regions among the rhinovirus serotypes. But we want to utilize natural immunogens, and we wanted to base our vaccine on a clinically successful approach – killed virus. So we just mixed them together – a solution that in retrospect seems simple but was not obvious. Thanks to modern technology, we were able to include a higher quantity of each strain in our vaccine compared to the old studies, and that made the difference," says Moore. The vaccine proved to be broadly and potently immunogenic in rhesus monkeys.

Believing in the potential of the vaccine, Moore has co-founded a startup company to take the project further: Meissa Vaccines. The key question his team now faces is how to manufacture and scale up the vaccine. "The process would be similar to inactivated poliovirus vaccine," says Moore. "We are looking into specific patient populations, the molecular epidemiology of the virus, and manufacturing processes – which are our major challenges." The company also has support from the US National Institute of Health to develop a manufacturing plan. *JS*

Reference

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In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of translational science. They should be under 600 words in length and written in the first person.

Contact the editors at edit@texerepublishing.com

Taking Cues from the City of Notions

The US is leading the field in drug discovery, but the UK could soon be hot on their heels.

By Chas Bountra, Professor of Translational Medicine, Nuffield Department of Medicine, University of Oxford, UK.

Over the last few decades, I've worked in both academia and industry, and with colleagues on both sides of the Atlantic, developing new targets and trying to facilitate their translation into the clinic. The US culture and environment is very different to that in the UK.

Take Boston – a buzzing drug development hub, full of brilliant universities, fantastic hospitals, several pharma companies, a plethora of biotech companies, and crucially, lots of investment. Biotech venture capitalist funding in the UK averages £8 per head, in California it's £50 per head, but in Massachusetts it's £250 per head.

There are many elements that make the region so successful, but an important one is the culture. For example, I hear about students coming out of US universities who are already writing their second or third business plans before their first has even been funded. That spirit of parallel entrepreneurship, more risk-friendly investors, and a multitude of avenues for investment make Boston a haven for the drug discovery industry.

But that's not to say that the UK doesn't have its advantages. We also have an exciting and unique drug discovery ecosystem. We have phenomenal universities in the field – the medical school in Oxford has been number one in the world for the past six years. I believe we are producing some of the world's great innovators, entrepreneurs, and leaders. Our leaders have had the vision to fund great infrastructure resources: The Francis Crick Institute, the Catapults, the Sanger Institute, the Dementia Discovery Fund, and many more. We excel in innovation. But I believe where the UK really shines is in its most unique elements – the NHS, and our culture of open innovation.

The NHS is a phenomenal resource for accessing real-world data, for carrying out clinical studies much faster, and ensuring quicker adoption of innovation. I work with many clinicians in the NHS, and they are passionate about trying to discover new drugs, biomarkers, diagnostics, and devices – and we need to make use of that.

Europe as a whole is strong when it comes to open innovation, and the UK leads the charge. When I say open innovation, I don't just mean sharing data with the people who are funding you, I'm talking about sharing all of it with the whole world, immediately.

Most of my academic colleagues (be they basic or clinical scientists) are keen to work together – we just need to catalyze that discussion and make it happen. We all complain that there is never enough money, but personally I'm more concerned about identifying the scientific problem, and bringing together the right people. If we get that right, the funding will flow freely...

Biomedical research funding is currently split between academics, biotechs, and pharma companies –

everyone wants more funding but the amount in the pot is finite. If we want to make the most of our resources, we need to be more efficient in drug development, and a simple way to do that is to reduce the amount of duplication and wastage in biomedical research. For example, we in the Structural Genomics Consortium only work on novel or impossible targets, and not those for which there are already several hundred publications.

I think that the UK is well on its way to becoming a large, booming drug development ecosystem, but we need to keep pushing forward and taking advantage of our assets to continue growing. I love working in Oxford – for me it is the "Boston of Europe".

Speed Versus Safety for Cell Therapy

Faster translation into the clinic is a worthy goal, but not at the cost of patient safety and public trust.

By Karen Nichols, Chief Regulatory Officer, ISCT, and Jacques Galipeau, Chair, Mesenchymal Stem Cell Committee, ISCT.

The Reliable and Effective Growth for Regenerative Health Options that Improve Wellness (REGROW) Act, proposed by US Senators Mark Kirk, Joe Manchin, and Susan Collins, seeks to speed up access to experimental cell therapies. The International Society for Cell Therapy (ISCT) welcomes efforts to accelerate clinical translation of promising cell therapies, but has grave concerns over the REGROW Act in its current form.

Cell therapies in the US fall under either section 351 or section 361 of the Public Health Service Act. Section 361 applies to cellular and tissue products that are minimally manipulated and often autologous – typically well-established procedures such as fat grafts. These products have less intensive regulatory requirements and would be unaffected by the proposed legislation. Section 351 covers cell products that are meaningfully manipulated; in other words, cells grown in culture, cells that have undergone genetic or physiological modification, or any cell product that involves a manufacturing step. Section 351 products are more highly regulated by the FDA – you need to get an Investigational New Drug license (IND), present rigorous evidence of safety and efficacy, and receive market authorization. The REGROW Act seeks to introduce a conditional approval pathway for these 351-designated products that would allow them to be administered to patients based on preliminary safety data and a "reasonable expectation of effectiveness" – in practice, meaning that critical Phase III clinical trials could be bypassed. Unlike other accelerated approval pathways, REGROW would not require the product to address an unmet medical need or life-threatening illness.

ISCT supports conditional approval, but only if it remains under FDA oversight and there is a clear path towards final approval, predicated on the unambiguous demonstration that the cell therapy is effective. Our concern is that REGROW would allow manufacture and marketing of very expensive therapies, for which there is no demonstrable proof of efficacy.

If this legislation is enacted, patients could legally pay for conditionally approved therapies that have no clear efficacy data. Insurers may refuse copayment on the grounds that the therapies have no proven efficacy, so the therapies are likely to be limited to the one percent of the population who can afford to pay privately for them.

Unfortunately, there is a perception that cell therapies are a magic bullet for a wide array of ailments, from baldness to autism, which obviously isn't the case. In the Internet era, desperate patients are already just a few clicks away from clinics offering unproven therapies at astronomical costs – the REGROW Act could be seen as endorsement for these therapies from the FDA.

Despite excoriating the agency publicly, there is an implicit trust amongst the public and scientists alike that the FDA's mandate is to protect the public. When talking to people around the world about a new product, one of the first things they ask is: do you have FDA approval or an IND? An unintended side effect of the legislation would be decreasing the moral and intellectual authority of the FDA, which not only affects the public's trust in existing therapies and efficacious cell therapies going forward, but also in other products that the FDA approves, such as food and drinks.

For an emerging field like cell therapy, public trust is critical. Without trust, there is no funding, and without funding there is no research. We believe that REGROW could damage that trust and delay legitimate medical research in the field.

A Universal Shot

Development of a universal flu vaccine is not impossible for the industry – we just need bioinformatics to show us the way forward.

By Derek Gatherer, Lecturer at Lancaster University, UK.

I've recently been involved in a project to design a potential universal flu vaccine using bioinformatics (1). There will be a lot of people who after reading our paper will say (and indeed have said): been there, done that, didn't work – give up! But we can't really afford that attitude when it comes to influenza. Currently, our situation regarding the flu is like living in a region prone to storms; we have a fairly reliable drill for dealing with storms, but very occasionally there will be a hurricane – and the standard storm drill will be fairly useless when that happens. Standard vaccination regimes are unlikely to cut it during a pandemic. We can simply wait for the big one, shrug our shoulders and see what fate brings, thinking about ways to deal with it in the meantime – or we could try to prevent it. In other words, we shouldn't give up on the development of a universal flu vaccine just because it's a tough challenge to solve.

Past R&D experience with universal flu vaccines has not been very encouraging. The general principle is obvious – if the HA and NA surface proteins on the flu particle evolve so fast, then why not use something slower moving as a therapeutic target? And the answer is obvious too – it's the fact that the immune system mostly reacts to the surface proteins, which is why they are under such evolutionary pressure. You can choose to immunize with parts of the HA that are further from the surface – the "stalk" approach – or you can choose one or more of the other proteins, but the immune system won't react as strongly. The optimal method so far has been to use real viruses – inactivated, of course – as the immunogen. You get the strongest response that way, at the cost of having to refurbish and redistribute the vaccine on an annual basis. Response to a synthetic vaccine may be longer-lasting, but if it's many times weaker, what's the point? Our current flu vaccination methods, although relatively safe and effective, can't possibly be the best approach. It's a massive undertaking to identify the dominant strains and to manufacture the vaccines – all credit to those who organize it.

I believe there is reason for renewed optimism that the industry can develop a one-shot vaccine. The field of biology continues to advance and we now know a lot more about flu genomes and the human immune system than we did 20 years ago – or even just 10 years ago. When researching a universal flu vaccine, the first step is to try to define the conserved regions of the viral genome. There are thousands of complete sequences of viral genomes, and at least one complete from almost every one of the 144 possible subtypes, so you can reliably identify the conserved regions. This has been done many times in the past, but new data are being added all of the time. Previous universal vaccines relied, to a large extent, on predicted immunogenicity, but now we can bring in evidence. In our work, we have combined available experimental data with informatics-based immunological predictions to help design vaccines that are potentially able to induce cross-protective T-cells against multiple influenza subtypes.

There are a few technical difficulties when it comes to bioinformatics, but the main problem is simply that the field and its potential are not always fully appreciated. In physics, the theoretical physicist is regarded as the equal of the experimental physicist. Unfortunately, this is not quite the case in biology. Theoretical biologists, whether they describe themselves as computational biologists, bioinformaticists, or choose to identify more with one of the specialities (such as phylogenetics or genome analysis) can still find themselves cast into a service role – or not regarded as "the real thing" (look at #dataparasites on Twitter, if you want an example).

"Current flu vaccination methods, although safe and effective, can't possibly be the best approach."

Bionformatics is essential for everything in biology now – and more attention is being directed at this field and how it can benefit drug development. But for those of us who have been in the business for more than 30 years, it feels like very slow progress. With bioinformatics, I believe that we can solve many drug development challenges – including the design of a universal flu vaccine. Viruses, in particular, are excellent subjects for bioinformatics. You just need to have a little faith.

Reference

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Three Gurus of Big Data

Big data. Everyone's talking about it, but what exactly is it? How can it be harnessed to advance translational science? And what perils lie within the oceans of data that now surround us? Three experts from different backgrounds go fishing for answers.

Gone are the days of trekking to a library to thumb through research papers or handing out paper questionnaires to collect patient data. Now, we can gather terabytes of data at the click of a button. But are we making the best use of the data we're collecting? Here, data experts Dipak Kalra, Iain Buchan, and Norman Paton join the debate.

Dipak Kalra

Dipak is President of the European Institute for Health Records (EuroRec), and Professor of Health Informatics at University College London, in the UK. As a physician working in London in the early 1990s, he found that the computer systems of the time couldn't give him the insight he needed into his patients' data. He joined a European research project on health records and soon realized that creating truly useful electronic health records was a massive and exciting challenge. Twenty-five years on, Dipak is still working to improve health informatics. He also leads a non-profit institute that aims to promote best practice regarding health data in research and communicate with the public about how their health data is used.

Iain Buchan

Iain is Director at the Farr Institute of Health Informatics Research, and Professor in Public Health Informatics at the University of Manchester in the UK. As a medical student, Iain Buchan saw the rise of the PC revolution. It was obvious to him that there was a need to fuse pathophysiological and biological reasoning with a statistician's view of analysis and inference. Buchan created a statistical software package (www.statsdirect.com) that quickly attracted tens of thousands of users. Over the years, he became increasingly interested in the interplay between medicine, statistics, and public health data. Buchan's team (www.herc.ac.uk) is addressing what they see as a fundamental flaw in observational medical research – currently, research orbits around data sources, but it should orbit around questions and problems, pulling in data from various sources as necessary.

Norman Paton

Norman is Professor in the School of Computer Science at the University of Manchester in the UK, where he co-leads the Information Management Group. He is a computer scientist by training, with a PhD in object-oriented database systems. His work focuses on data integration, which involves bringing together data from multiple sources in a manner that allows for easy interpretation. Previously, the process has been quite slow and small scale. With the rise of big data, the process needs to be streamlined and made more effective. Paton is currently working in data wrangling – collecting and cleaning up data so that it can be analyzed in an integrated form. Data wrangling is an expensive and time-consuming process, so Paton is working to automate as much of the process as possible.

What is big data?

Dipak Kalra: This is an interesting question, and one that the healthcare community as a whole has yet to conclusively answer. For me, the characteristics of greatest importance are: a large number (millions) of patients, combining multiple data sources (with various interoperability and linkage challenges), and data recorded over time to allow trajectories to be determined. I'm interested to see what answers my colleagues will give.

Norman Paton: I think of big data as more of an era than a specific size or type of data. More and more data is being accumulated from different places, and that creates an opportunity for people to use and exploit it. "Big data" has been used as a blanket term to cover numerous cases in different contexts, so it's difficult to find a single definition. However, I believe that it reflects a combination of an increasing number of data sources, an increasing number of domains that have a surplus of data, and the variety that exists within those.

Iain Buchan: There are many possible definitions based around the 'four Vs' – volume, velocity, variety and veracity – but ultimately, I define big data as big enough to address the challenge at hand – with sufficient accuracy and timeliness to inform better actions.

What impact is big data having on biomedical research?

DK: Big data allows us to finally have fine-grain, routinely collected clinical data. Soon we will be able to look at large numbers of patients retrospectively and at a much lower cost, which will explode our understanding of diseases, treatments, biomarkers, health service care, pathway patterns, and how to optimize patient outcomes. I cannot imagine a more exciting time than this.

NP: Big data allows more diversity in research opportunities. For example, we might want to better understand the efficacy of a certain cancer treatment; every hospital has records, but pooling together the relevant data from all of them would be an unmanageable task. Computer systems need to be developed that make the process of identifying, integrating, and interpreting diverse data sets more cost-effective. In medical sciences, opportunities are everywhere because information is constantly being produced in hospitals, drug trials, labs, and so on. I don't expect to see one mega project using all the information, but many relatively small-scale, focused projects.

IB: Big data, properly harnessed, gives us bigger science. It allows us to network teams and universities across the world, to collaborate rather than compete. And that collaboration becomes more powerful as the ensemble of data, analytics and experts gets bigger. There are two levels of big data: one is the scale of data and algorithms working machine-to-machine autonomously across locations, and the other is allowing humans to work in a much bigger team. You might think of this as "assisted reasoning for team science".

How can you ensure the quality of your data?

NP: It's extremely difficult to gain a clear understanding of your data set. It's not just a case of "good" or "bad" quality, but knowing whether the data is fit for purpose; what is fit for one purpose may be completely unusable for another. There are many metrics used to measure quality – completeness, accuracy, freshness, and so on, but fitness for purpose may be quite domain-specific.

DK: One has to be careful. When organizations collect data for any purpose (management, tracking, administration, and so on), they select the fields of interest relevant to them and disregard the rest, which is good practice. Then they filter and select the data to fine tune it further. The problem starts when somebody else wants to use that data for a different purpose, without being aware of all the previous filtering. It creates a risk of misinterpretation.

IB: I think one of the best ways to improve data quality is to "play back" what you have done to the people closest to the data. As soon as you talk to someone familiar with that data supply chain, they are likely to point out problems that might go undiscovered if you just suck up data. This turns tacit knowledge into explicit metadata – increasing the discovery power per unit of data.

What are the greatest challenges when dealing with big data?

DK: I can see four main issues. The first is in establishing trustworthy practices. This era of big data brings a very different set of governance challenges, which require new codes of practice, as well as winning the trust of society and healthcare providers.

The second is interoperability. I think the adoption of standards is too limited, with many data sets and electronic health records applying different internal data architectures and terminology. There needs to be a range of widely adopted standards so organizations and individuals are able to interface with each other and compare data.

The third is data quality, which we've already discussed.

The fourth is that, as a field, we have been slow to promote the value we get from health data. When we do make great discoveries from health data, we don't always make it clear to society or to funders that it was the result of significant investment in IT, as well as helping patients to be more comfortable with how their data are being used.

"This era of big data brings a very different set of governance challenges, which require new codes of practice, as well as winning the trust of society and healthcare providers."

IB: I would add that a common mistake is naïve translation of tools from one environment to another. I've seen cases where dashboards designed for business intelligence have been directly translated into healthcare, which means clinicians are faced with a blizzard of dashboards they don't have time to digest. When designing user interfaces, we need to take note of basic learning from avionics, where it is long-established that a pilot cannot focus on more than seven or so dials in his or her field of view.

Another common mistake is to apply machine learning to data as if it were an unbiased sample of human health. In medicine, there is so much "missingness" and measurement error in the data, and so many things that can't be measured directly, that data-structure is meaningless without overlaying prior information about the structure that would be in the data if you could observe it. The mistake is looking for patterns in "buckets" of data when we should be starting with the patterns we know and building more patterns around that. Machine learning requires a very careful approach when dealing with biology and health data.

#datasaveslives

The #datasaveslives social media campaign promotes the positive impact that data is having on health. Projects recently highlighted by the campaign include:

- Sea Hero Quest: a video game that collects data on memory decline and dementia. In the online game, players have to find their way through a virtual world to save an old sailor's lost memories. In the process, the game records information about navigational ability – disorientation is a key feature in early Alzheimer's disease. The researchers behind the project estimate that the data collected from the first 2.4 million people playing the game would have taken 9400 years to generate in the lab. Read more at www.seaheroquest.com.

- AliveCor Kardia: a heart monitoring device that works with smartphones and watches. The device takes an ECG of the heart with a simple finger sensor and records the resulting data on your mobile or Apple Watch to detect atrial fibrillation, a condition associated with 130,000 deaths per year in the US alone. AliveCor hope that data being collated from millions of ECGs recorded by Kardia devices can be used to accelerate research into heart rhythm.

- Healtex: the UK healthcare text analytics network. A lot of health data is stored in the form of free text – clinical notes, letters, social media posts, literature, and so on. Healtex is a multidisciplinary research network that develops tools to analyze this unstructured data, and so make better use of it. Read more at www.healtex.org.

How important is the public perception of big data?

IB: It's vital. My group has a rule when speaking with those outside the field that we don't talk about data, databases, or information systems in the first part of the conversation. Instead, we talk about problems that the data can be harnessed to address. We need the public on board to help unravel the vast gaps in our knowledge – for example, how best to treat patients with more than one condition. Take a look at twitter.com/hashtag/datasaveslives to see this in action.

DK: Trust and engagement from the public is mission-critical in the growth of big data and its use in research and healthcare. The public have to be confident that the use of their data is in their interest, and in the long-term interest of society. It's also important that the patients feel a sense of personal autonomy about health and wellness. To help foster that, I think we should all be able to access and use our own data, to help us make better decisions about our health.

NP: It's important for the public to have a wider understanding of the opportunities big data presents and how their data is involved with that, but it's difficult when organizations remain relatively opaque in relation to the use they are making of personal data.

DK: I see a lot of news stories focusing on security breaches or data leaks – a missing CD, a stolen laptop, a USB stick found in a waste bin. It leads to a natural distrust about how organizations look after our data. In reality, most data are

very well protected – increasingly so, as we implement state-of-the-art security measures. But we need to increase public confidence.

> "I think of big data as more of an era than a specific size or type of data. More and more data is being accumulated from different places, and that creates an opportunity for people to use and exploit it."

What are the most common misconceptions about big data?

IB: I think the biggest misconception is that big data is the answer to everything, and that bigger data will always lead to a better answer, which is a myth. Indeed, there are some cases where more raw data can reduce discovery power, when the heterogeneity of the data sources increases but there is no metadata to make that heterogeneity useful in analyses. So, it isn't a case of getting as much data as possible, but rather finding the most powerful analytics possible with the data. It's about bigger science, not just bigger data.

NP: I agree that there is too much focus on size. Although big data is often spoken about in terms of the four Vs, it's easier to get a handle on volume than the others so there is the tendency to associate big data mostly with size.

What are the most important applications for big data?

DK: If I could pick a headline issue for big data to rally behind, it would be that we're an aging society and the number of patients who have multiple long-term conditions is rising. Our historic scientific knowledge of diseases and treatments have usually been based on the study of single diseases, so our knowledge of how multiple diseases interact is fairly limited. Big data will give us the ability to study populations so that if you have a patient with diseases A, B, and C, and you want to find out the effect of treating them with drug X, you'll have a sufficient sample size to get a useful answer.

IB: Multi-morbidity is definitely a key priority. As Dipak says, we're an increasingly aging population with a prevalence of multiple concurrent conditions, and to address that we need actionable analytics – statistical surveillance of primary care and prescription data, with feedback to physicians so they can determine the patient's best care pathway.

Another area of importance to me is infrequent clinical observation giving way to consumer health technologies that can tap into the rhythms of a patient's life via wearables or mobile technologies. If I had arthritis, my patterns of movement might reflect a temporal pattern of symptoms currently invisible to the

clinic. That takes me to the third area, which is information behavior. If you're able to use technologies in ways that slot into the rhythms of daily life and don't annoy people, then they will be used more often and so give a less biased sample. The next step is to help influence health behaviors; for example, getting people to exercise more or to persist with preventative medicines that we might otherwise give up on because of a lack of feedback about the benefits we can't easily see. Our bodies are our own laboratories in which we run n=1 experiments, which big data and big analytics may bring to life in new ways.

NP: I think big data is going to be important for almost every application. That doesn't mean it's going to affect every aspect of everything, but big data is going to crop up everywhere so I personally feel like it's difficult to narrow down a few specific important applications.

> "I think the biggest misconception is that big data is the answer to everything, and that bigger data will always lead to a better answer."

Where do you think the future of big data lies in five years – or 50 years?

DK: There are many exciting prospects for big data over the next five years. Biomarker discovery, using genetic information, metabolomics and proteomics, will become more efficient. Big data could also make assisted technologies more useful for people with functional difficulties. Then, there are sensors and wearables, which are appearing now but will become much more integrated and useful in the future. In the far future, I think the relationship between healthcare professionals and patients will become more symbiotic. Computer applications will be seen less as tools and more as collaborative agents able to provide insight from large volumes of data – almost like a digital colleague or companion.

NP: In the next five years, I think big data processing is going to become more predictable – we will better understand what we can and can't do with it, and be able to build more mature tools and technologies to support data management and analytics. In 50 years, I believe automation will free up data scientists to focus on how to use data more efficiently, and drive the field forward at a more rapid pace. I don't think we're very far from automated software that, for example, can read through scientific papers and extract key information about a particular protein, pathway, or topic you're interested in. These kinds of applications will make a big difference to a lot of daily life tasks.

IB: Increasingly, we live our lives connected to each other's behaviors through social digital technologies. In 50 years, I think we'll be talking a lot more about how we influence health behavior, as individuals and as societies. Therein lies a "big connectedness" of information – the fusion of biology, behavior, and environmental data, and new understanding of how those three principal components interact – that will push healthcare, consumer health, and public health forward as greater than the sum of their parts.

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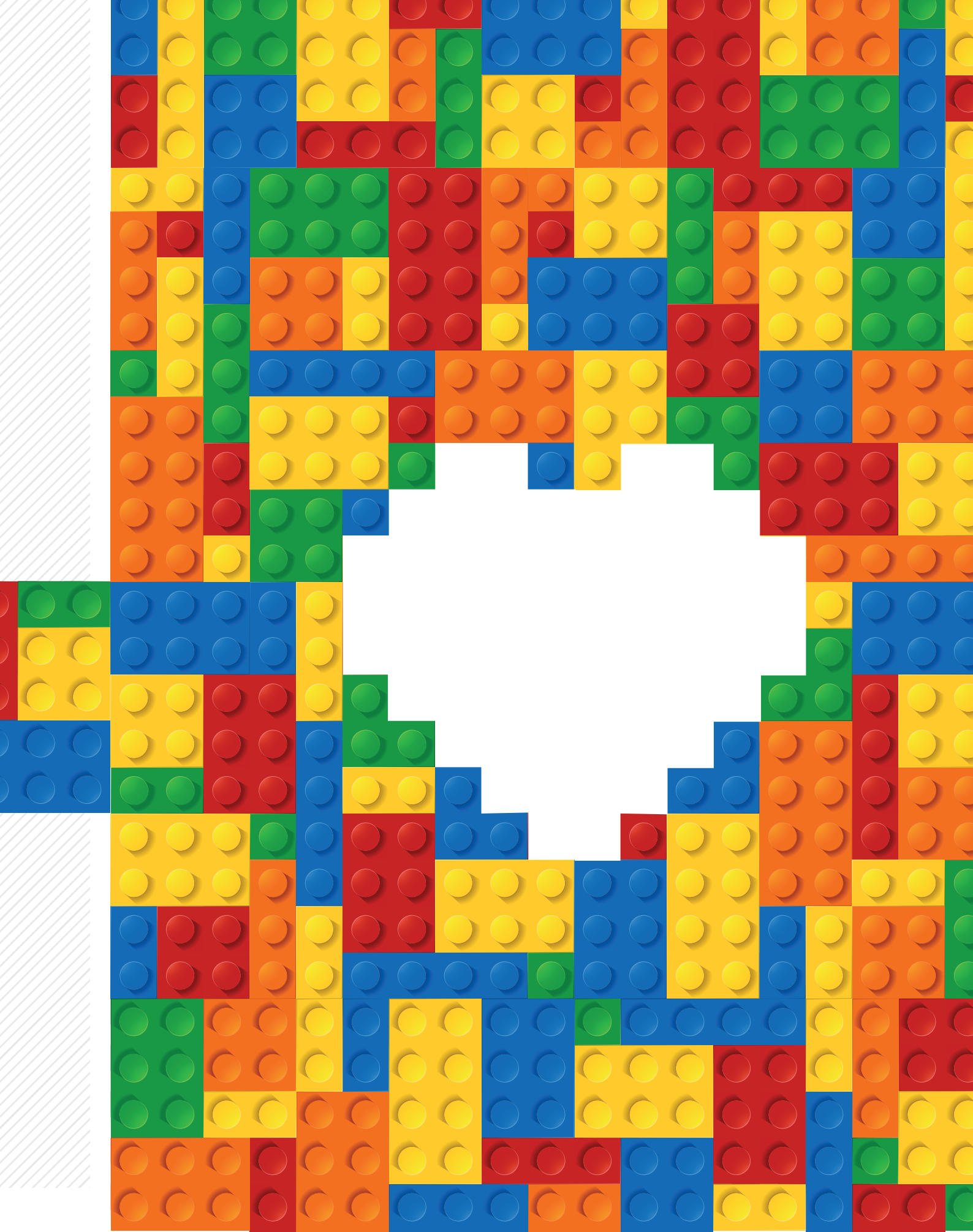
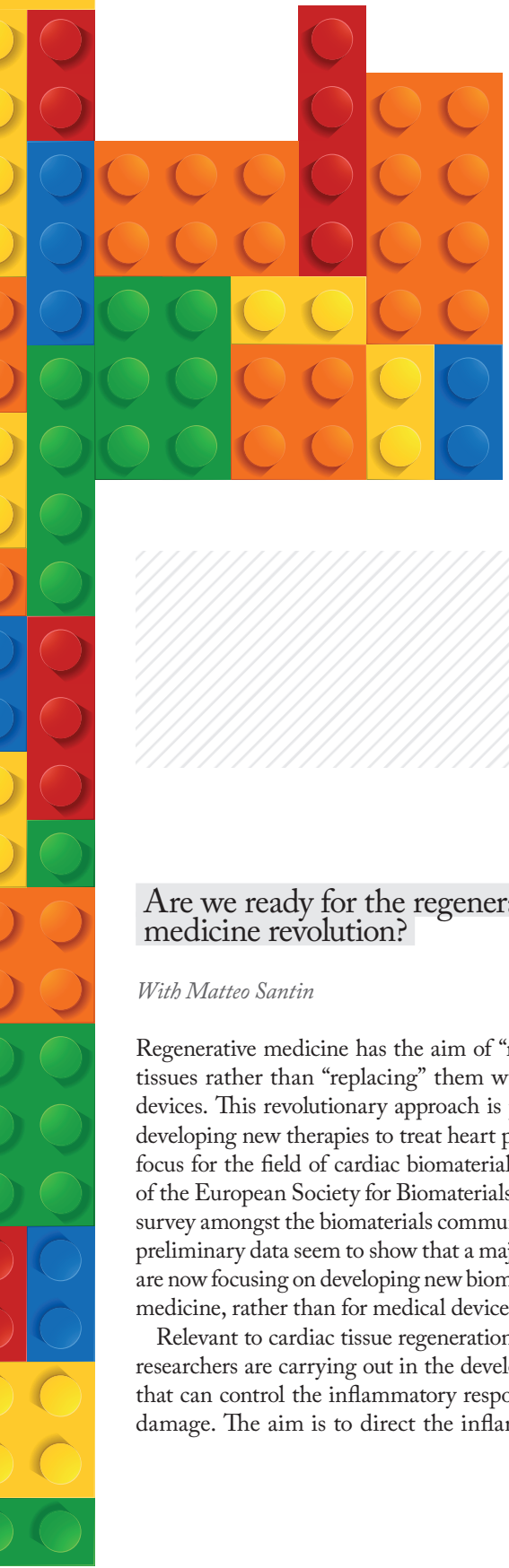




Biomaterials at the Heart of Regeneration

Ingenious scaffolds, gels, and matrices are giving cardiac regenerative medicine a boost. Here, three pioneering researchers share how they are taking inspiration from nature, improving delivery, and speeding translation of novel engineered materials – from injection-molded heart valves to cell-delivery patches – for cardiac care.

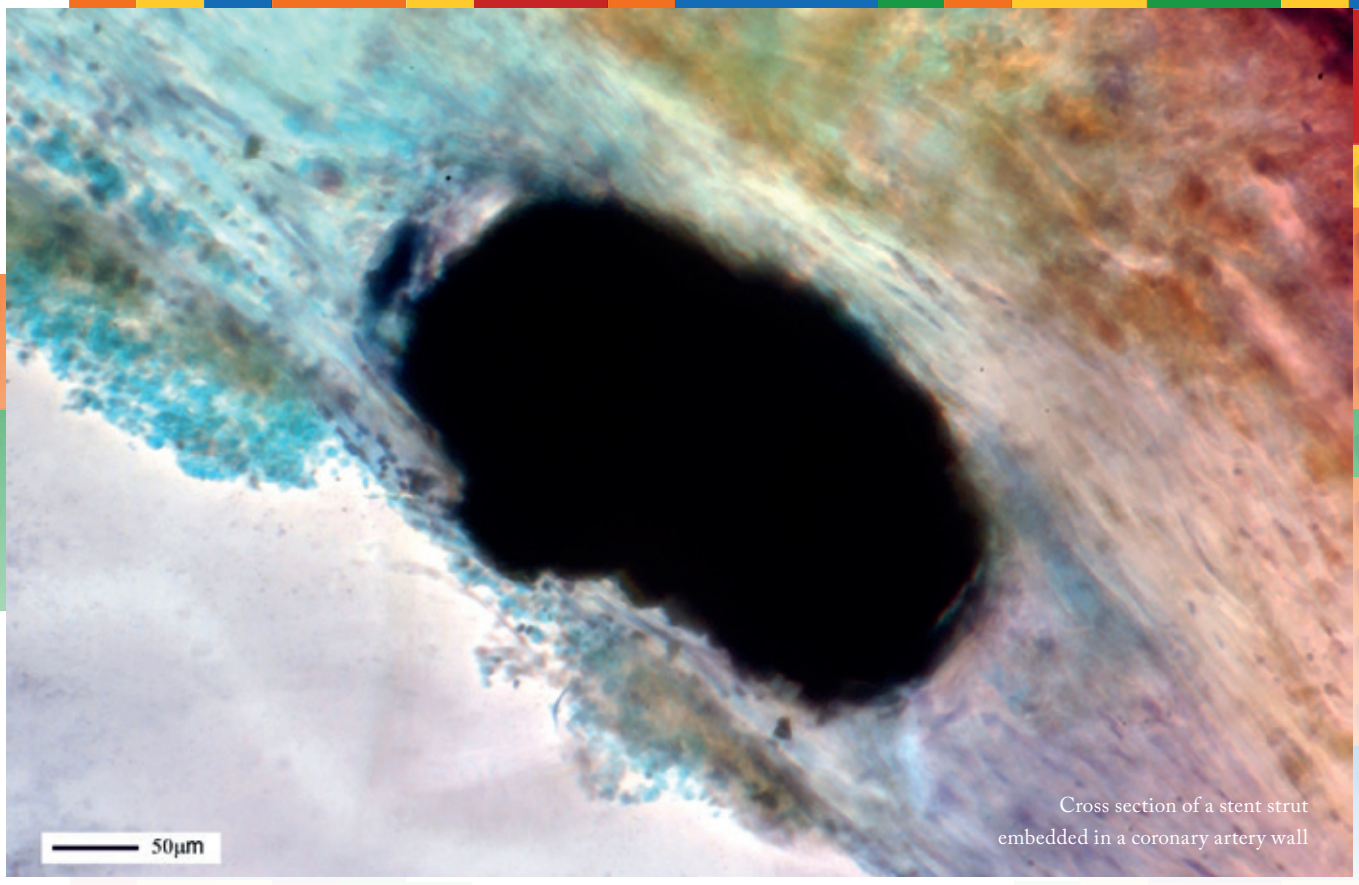
Are we ready for the regenerative medicine revolution?

With Matteo Santin

Regenerative medicine has the aim of "regenerating" damaged tissues rather than "replacing" them with implanted medical devices. This revolutionary approach is particularly relevant in developing new therapies to treat heart pathologies, and is a big focus for the field of cardiac biomaterials. Indeed, as President of the European Society for Biomaterials (ESB), I've launched a survey amongst the biomaterials community in Europe, and the preliminary data seem to show that a majority of our researchers are now focusing on developing new biomaterials for regenerative medicine, rather than for medical devices.

Relevant to cardiac tissue regeneration is the work that many researchers are carrying out in the development of biomaterials that can control the inflammatory response triggered by tissue damage. The aim is to direct the inflammatory cells towards the production of growth factors that favor the regeneration of tissue without the occurrence of scarring; this will restore the full physiological function of infarcted myocardial areas. Likewise, biomaterials have been designed that can promote tissue regeneration by controlling the activity of host or transplanted stem cells. These cells can be either recruited or transplanted at the site of infarction to deposit new tissue and stimulate the formation of new blood vessels necessary to ensure the long-term survival of the damaged tissue.

Despite the encouraging results achieved by many projects worldwide, clinical translation of innovation in the field of regenerative medicine is difficult for two main reasons: limited private investment, and a restrictive regulatory framework. These two points are linked because the regulatory framework of regenerative medicine products – which the European Commission classifies as "advanced therapy medicinal products" – presents gray areas that make the process of approval uncertain, cumbersome, and therefore not attractive for investors. There are not many specialized venture capital firms in the field of

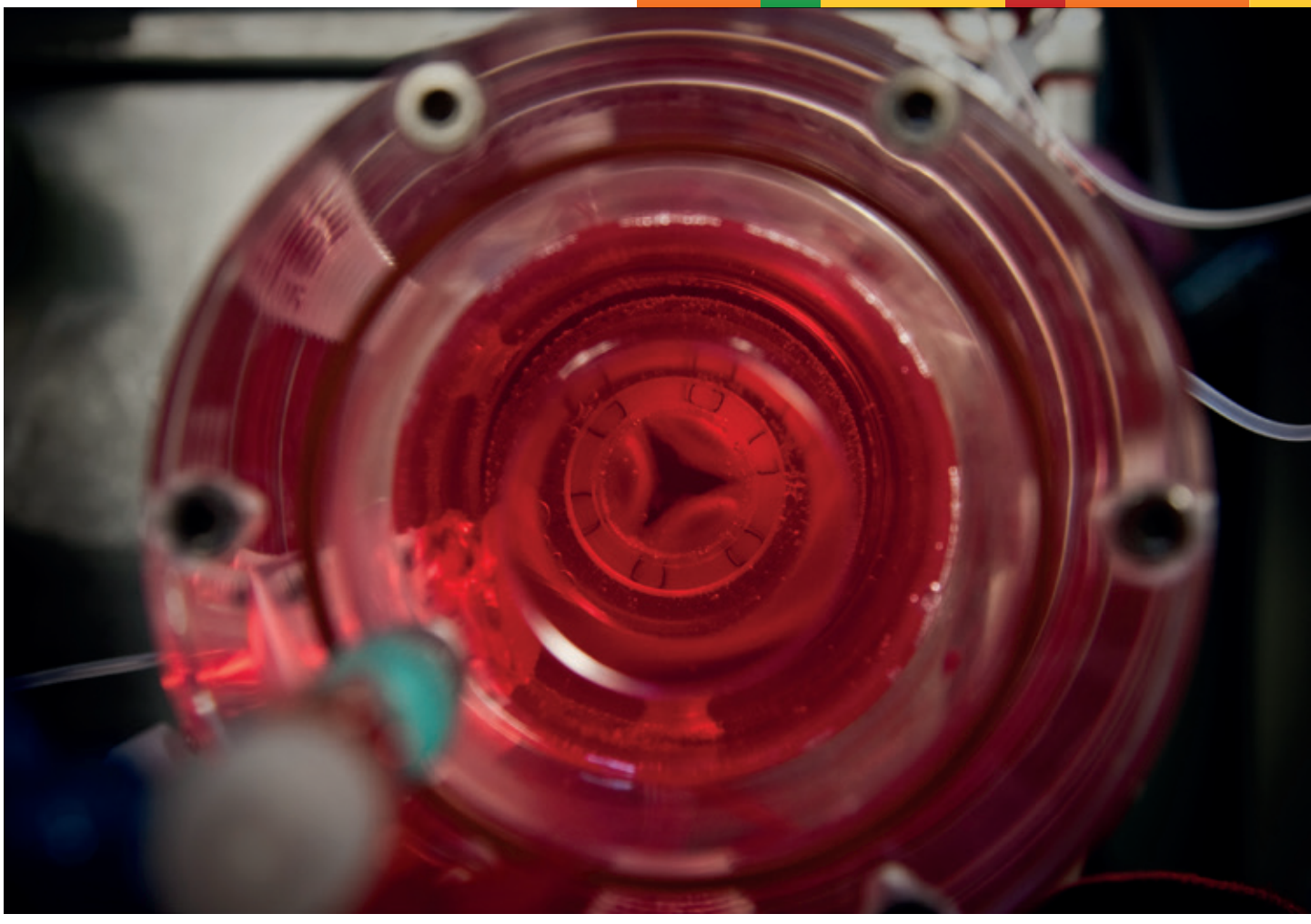


Cross section of a stent strut embedded in a coronary artery wall

regenerative medicine; most perceive this type of innovation as too risky for their business. We are very supportive of any regulatory framework that protects our patients, and we don't want research that isn't thorough or that could put patients' lives at risk. On the other hand, if regulation is risk adverse and vague in its prescriptions, it makes translation more expensive and product development will appear riskier than it actually is.

From a scientific and regulatory point of view, a major problem is variability. For example, we have seen some fantastic proof-of-concept work involving decellularizing cardiac tissue and recellularizing it with cells from the recipient (1). But there is a question mark over whether these scaffolds of biological origin could ever have the batch-to-batch reproducibility necessary to secure a consistent clinical outcome in all patients. That is why the European Commission is pushing for more focus on research into extracellular matrix analogues of synthetic origin, which are highly reproducible in their manufacturing process. Their availability will reduce the risk of failures of biomaterial scaffolds, such as those used in the manufacture of cardiac patches. We believe this is the way forward.

Matteo Santin is President of the European Society for Biomaterials, and Lead Professor of the Brighton Centre for Regenerative Medicine, University of Brighton, UK.



How can bio-inspired textile scaffolds be used to engineer stronger heart valves?

With Stefan Jockenhövel

My background is that of a cardio-thoracic surgeon, but I was rather abruptly pulled into the field of tissue engineering by a former professor of mine. He returned from a conference for heart surgeons in 1999 proclaiming that tissue engineering was the future, and promptly put me in charge of this new research. I knew nothing about the field, so I spent some time at the University Hospital of Zurich to learn more. There, I collaborated with material scientist Jeff Hubbell, who had done a lot of work with fibrin hydrogels; his lab was just across the road from mine. Purely biological implants often lack the reproducibility we need, whereas purely material implants can't always provide high biocompatibility – it made sense to me that the ideal structure is a combination of the two.

Back home in Aachen, I developed an injection molding technique to make complex hydrogel structures – scaffolds for tissue engineered heart valves and vascular grafts. However, I could see that the hydrogel alone could not withstand the high pressures of the heart. I had to step back and think about the challenge from a different angle. Eventually, I found inspiration from the textile industry. To make tough, lightweight materials – for example, in the aerospace industry – textiles are used to form a carbon fiber composite structure. We began researching textiles with different compositions to find the best fit for our hydrogel and the high-pressure heart valve environment. With European funding, a few years ago we fabricated the first textile-reinforced tissue engineered vascular graft, followed by a tissue engineered mitral-valve,

by integrating a textile mesh inside the heart valve (2).

As I always tell my students, humans are textile products. Fibers define the mechanical properties of our bodies. So our next goal is creating bio-inspired textile scaffolds, which mimic the patterns of fibers in the human body.

The individual variety that inevitably comes with the biological component of biohybrid implants is still a challenge. We have a pre-conditioning protocol that each implant goes through, which consists of the same process of increasing the load (pressure and flow) on the construct in a defined time schedule. But one person's cells may take five days, and another person's might take two weeks. We'd like to eventually automate the pre-conditioning procedure to make it faster and more efficient, but the individualization of cells makes this a difficult task.

Even without working with living cells, clinical translation of cardiac devices is always hard because regulation is – understandably – so strict. If a bone graft fails, it's a shame. If a cardiac device fails, a patient may die. Add to that the variability and the potential for inflammation, even with a patient's own cells, and there are a lot of hurdles to overcome. But I believe we'll get there in the next few years.

As for the future of the field overall, I hope that there will be more preclinical and clinical studies of implants, which we're beginning to see from brave surgeons in the US. In the long term, I think we'll see cardiac medicine move towards an even more personalized therapy approach where not only the cells, but also the materials used, are tailored to each patient.

Stefan Jockenhövel is Director of the Department of Biohybrid & Medical Textiles, RWTH Aachen University, Germany, and Director of the Aachan-Maastricht Institute for Biobased Materials, Maastricht University, the Netherlands.

How can we accelerate clinical translation of regenerative therapies for heart attack?

With Garry Duffy

I've always been interested in the translational aspects of stem cell therapy, and over a decade of research into stem cell delivery in cardiac repair has given me an appreciation of the size of the challenge – and of the opportunity.

One of the biggest hurdles is cell retention. Right now, around 75 percent of cells are lost after implantation. The problem with getting cell therapies into the heart (and getting them to stay there) is the fact that you're dealing with a beating organ. Any cells you inject into the heart are simply going to be squirted back out. So to improve retention we have to find ways to avoid leakage of the cells away from the injection site, and promote cell survival.

At the Royal College of Surgeons in Ireland, we've been working as part of a research consortium called Advanced Materials for Cardiac Regeneration (AMCARE) to tackle these problems head on. To combat cell site leakage, we have developed biomaterial gels to keep the cells at the site of injury. And our AMCARE colleagues at Celyad have created a specially-designed injection catheter to help anchor the hydrogel to the heart wall and increase cell retention. The catheter enters an artery in the thigh and is fed up to the heart.

Keeping the cells alive during what we call "the integration phase" was a bigger issue to overcome because, after a heart attack, the environment within the heart is quite hostile for cells. To help the cells gain a foothold, we functionalized our gel to contain peptide sequences for the cells to latch on to, which helps them withstand the pressure.

"One of the biggest hurdles is cell retention. Right now, around 75 percent of cells are lost after implantation."

As well as acute cardiac injuries requiring the delivery of cells to the heart wall, we also want to treat patients with larger cardiac infarcts, which are likely to need delivery over a larger area and for a longer time. For these larger infarcts, we would carry out a mini-thoracotomy (create a small space in the chest wall) and deliver a cardiac biomaterial patch to the heart's surface. The patch essentially contains the same number of cells and materials as the injection; it's just using a different delivery method to get the most efficient clinical results.

I believe that cell therapy and tissue engineering approaches both have an important role to play, at different stages of disease. For a more acute cardiac setting like a heart attack, I think that regenerative medicine may be the better choice, but for chronic conditions, where you've got a wider area to treat or remodeling is needed, grafts can fulfill that need.

To allow clinical translation, we will need to lower costs. In part, that comes back to the issue of cell retention – it's not sustainable to lose 75 percent of your product. But as we improve retention and adapt the dosing regime, costs should come down. We can also speed up translation by giving clinicians tools that are intuitive and aligned with current treatment regimes. The catheters and medical devices we work with are similar to existing products that cardiac surgeons are already comfortable with. The goal of the AMCARE project is to provide the tools to help clinicians deliver these therapies. I think if we can overcome the delivery issues, it will encourage more widespread clinical adoption.

Garry Duffy is a researcher at the Royal College of Surgeons in Ireland.

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LESSONS I'VE LEARNED,

With Michael West

Visionary gerontologist and stem cell scientist Michael West has been a leading figure in the field of regenerative medicine since its inception. In the early 1990s, he founded Geron Corporation, where he oversaw several crucial breakthroughs in aging research, and set up the collaboration that led to the first isolation of human embryonic stem cells. He is now CEO of BioTime, a Californian company that aims to lead the regenerative medicine revolution. We caught up with West to find out what he's learnt from his years in science and business.

It wasn't the school system that shaped my career choices

For me, it was the movies that first made me want to be a scientist. I was born in 1953 and grew up watching films that portrayed science as a powerful force – a force that could unlock the mysteries of nature. It was the era of the nuclear race and Sputnik, and I was surrounded by images of atomic explosions and rockets taking off. By nine years old, I had a laboratory in my garage and knew I was destined to be a scientist. In college, I gravitated towards medicine, as the field of science that could most profoundly affect the human condition.

The process of aging is one of the great unsolved problems

Aging is a universal process – it happens to everyone – and yet when I started my research career, we had very little understanding of how or why. While working on my Master's degree, I saw a TV show featuring children with progeria, the premature aging syndrome. The children suffer from a young age with many of the classic diseases of aging – heart disease, osteoporosis, cataracts, and so on. At that time the exact cause was unknown but it was clear that it was a genetic disorder. That brought it home to me that the aging process was

About Michael West

1953:
Born in Niles, Michigan

1989:
PhD from Baylor College of Medicine, concentrating on the biology of cellular aging.

1990:
Founded Geron, Inc, with VC funding from Kleiner Perkins Caufield and Byers, and Venrock.

1992–1998:
Director and Vice President of Geron, running programs in telomerase diagnostics, oligonucleotide-based telomerase inhibition as anti-tumor therapy, and telomerase-mediated therapy.

1995–1998:
Managed the research collaboration between Geron, James Thomson, and John Gearhart that led to the first isolation of human embryonic stem cells.

1998–2007:
President and Chief Scientific Officer at Advanced Cell Technology, Inc, overseeing programs in nuclear transfer, retinal differentiation, and derivation of clonal human embryonic progenitor cell lines.

2007:
Appointed CEO of BioTime, Inc.

2009:
BioTime received $4.72 million in grant funding from the California Institute for Regenerative Medicine.

2013:
BioTime acquired stem cell assets from Geron.

controlled by molecular mechanisms. And if there were mechanisms, I reasoned that they could theoretically be targeted.

In those days, if you said you were trying to understand aging to intervene in age-related diseases, people immediately labeled you as a kook. If you wanted to be taken seriously, you had to say you were studying cellular aging. I thought it was absurd – after all, what hurts people more than aging? Luckily, I'm a contrarian; I love it when people say, "it's crazy". I was determined that someday viewpoints would shift, and I'm happy to say that we're now in the midst of a long-overdue upswing in aging research. Research goes in cycles – back at the turn of the millennium, suddenly everyone wanted to study pluripotent stem cells, despite little previous interest. Now everyone is interested in the biology of aging, and of course the congruence of stem cells and aging.

Immortality is a misunderstood term

Part of the distrust of this type of research is a misunderstanding about terminology that goes all the way back to the 1800s. August Weismann, the German naturalist, built on Charles Darwin's theory of evolution by proposing that if the reproductive cells transmit hereditable traits from generation to generation, then those cells must proliferate as a lineage of cells indefinitely. However, the non-reproductive (somatic) cells in the body lose that ability and have a finite lifespan. He called the reproductive cells "immortal". The term was not popular with some scientists of the time, who disliked its connotations of eternal life, and argued vehemently against it. But the term stuck and now we refer to cells that replicate without limits (stem cells, reproductive cells, and malignant cancer cells) as immortal, while those with a finite lifespan (all human somatic cell types) are termed mortal.

When pluripotent stem cells were isolated in the 1990s, we talked about these cells being immortal, and therefore an infinitely renewable source of cell types of all kinds. But people often make a leap and assume that we are talking about making human beings immortal.

Our understanding of human aging has been transformed over the past 30 years

At Geron, the company I founded in 1990, our first goal was to clone the gene for the active component of telomerase, to confirm our theory that the enzyme plays a key role in cell aging. It took several years and upwards of 40 million dollars but, finally, we got there. On the day of the first crucial test, I handed the team a panel of RNAs – some from mortal cells, some from immortal cancer cell lines, and one

from the testes. We gathered around the screen and watched as the imaging results slowly appeared. It was a magic moment – the pattern was exactly as we had predicted, with no band in the mortal cells, a band in all the cancer cells, and the strongest signal in the testes.

Another big breakthrough came when we were able to immortalize a human cell by transfecting it with the telomerase gene. Renowned gerontologist Leonard Hayflick visited the company and donated a piece of skin from his leg for the experiment. Hayflick was dogmatic about the fact that we would never be able to intervene in human aging, but his cells ended up being the first to be immortalized.

Scientists can be blinkered

It's amazing to me that most people didn't immediately see the therapeutic potential of stem cells. When I first heard of the mouse embryonic stem cell, I immediately thought they were magical – the idea that cells could be cultured in a dish and turned into mice. Human embryonic stem cells, if they could be isolated, were predicted to be an infinitely renewable source of all the body's cell types. And because they can be expanded indefinitely, you can genetically modify a single cell precisely and expand it into a whole new population of cells. I saw this as a very powerful platform technology. Now, there are tens of thousands of papers on PubMed using the search term "pluripotent stem cells", but back then most scientists either simply hadn't considered the therapeutic implications – or were focused on one narrow area.

"In those days, if you said you were trying to understand aging to intervene in age-related diseases, people immediately labeled you as a kook."

I was collaborating with Roger Pedersen, who was then at the University of California, San Francisco. One day, I mentioned the idea of isolating human embryonic stem cells, and he just stared at me. I thought maybe I had offended him. A few years later, Bill Clinton had signed legislation that banned federal funding for research that destroyed human embryos, and Pedersen called me and said, "Do you remember some time ago you mentioned this idea of making human embryonic stem cells – would you be willing to fund it?" As it turned out, Roger was staring at me in silence that day, not because he was offended by the idea of human embryonic stem cells as a source of cells for transplantation, but because he shared my vision. He understood exactly how important this could be for medicine.

The decision to discontinue research often has nothing to do with science

I left Geron in 1998, but in 2013 I led efforts to acquire Geron's stem cell assets in my current role as CEO of BioTime, Inc. When Geron stopped work on their OPC1 therapy for spinal cord injury, a lot of people assumed that there must be a safety issue or that something wasn't working. It certainly had a tough road to clinical trials; it was the first clinical trial of a human embryonic stem cell-derived therapy so they had to work with the FDA to set the ground rules on safety, and trials were put on hold a couple of times. But I knew there were no skeletons in the closet, so we were thrilled to acquire those assets. As well as the clinical trial data from OPC1, Geron had pre-clinical data on numerous other applications, from diabetes to heart failure to cancer vaccines – plus, probably the largest set of intellectual property assets of any company in the sector. Today, that work continues in our subsidiary Asterias Biotherapeutics. Geron never got past safety studies, and were using tiny doses of OPC1 – Asterias is now carrying out dose-escalation studies and administering therapeutic doses to patients.

In business, expect to face criticism for any and every decision

Some people have said that it's crazy for BioTime to have so many subsidiaries, but our reasons are twofold. Firstly, many subsidiaries are a reflection of acquisitions; secondly, there are so many disparate applications. A company using stem cells for drug screening, for example, is a very different kind of business to one that aims to treat patients. Could we do all of these things within the parent company, BioTime? Yes, but we made a decision that we believe creates the most value for our shareholders and accelerates progress, and that means having several companies running in parallel.

"I think the impact of induced tissue regeneration on medicine will be even be more powerful than the stem cell approach."

Great things lie ahead

We don't talk much about it, but we're working on something now that I think will be massive – I call it "induced tissue regeneration." Just as you can induce pluripotency by adding specific gene products to a cell, I believe you can induce an adult cell or tissue to regenerate. Everyone knows that some animals, like salamanders, can regenerate whole limbs. It seems obvious that the mechanisms of regeneration in these animals are the same mechanisms that form the tissue in the first place – they just never turn it off. Human embryos also have the ability to regenerate to some extent – for example, prior to eight weeks of gestation, human skin has scar-less wound repair. Once embryogenesis is complete, these pathways get turned off and scar tissue is formed whenever certain tissues and organs are damaged. We believe that the genes that control tissue regeneration can be identified and used therapeutically to reintroduce the regenerative potential that exists during development. To that end, we announced a collaboration with Insilico Medicine to use artificial intelligence to analyze large amounts of transcriptomics data to compare early embryonic development with adult cells and tissues. I think the impact of induced tissue regeneration on medicine will be even be more powerful than the stem cell approach, because it exploits an intrinsic ability of the body.

My experiences have made me more certain than ever that science can uncover mysteries of nature that we couldn't have imagined – and unlock their power. And we're not finished yet – I believe there are still a lot of surprises to come.

Publication Picks

1994

NW Kim et al., "Specific association of human telomerase activity with immortal cells and cancer", Science, 266, 2011–2014.

Showed, for the first time, that telomerase activity strongly correlates with malignancy in a large number of diverse cancer cell lines, and in malignant tumors.

1995

J Feng et al., "The RNA component of human telomerase", Science, 269, 1236–1241.

This was the first paper reporting the cloning of a component of human telomerase, which led to studies of the effects of its knockout in mice and other applications.

2000

RP Lanza et al., "Extension of cell life-span and telomere length in animals cloned from senescent somatic cells", Science, 288, 665–669.

Demonstrated that somatic cell nuclear transfer could reset the telomere length of aged cells back to that of early embryonic cells and thereby restore the replicative lifespan to aged cells.

2002

JB Cibelli et al., "Parthenogenetic stem cells in nonhuman primates", Science, 295, 819.

Reported the first isolation of pluripotent stem cells from primate parthenogenetic embryos.

2004

I Klimanskaya et al., "Derivation and comparative assessment of retinal pigment epithelium from human embryonic stem cells using transcriptomics", Cloning Stem Cells, 6, 217–245.

The first report on the isolation of human retinal pigment epithelial cells from human embryonic stem cells.

2008

MD West et al., "The ACTCellerate Initiative: large-scale combinatorial cloning of novel human embryonic stem cell derivatives", Regen Med, 3, 287–308.

The first report on the large-scale isolation of clonal embryonic progenitor cell lineages from human embryonic stem cells.

2010

H Vaziri et al., "Spontaneous reversal of the developmental aging of normal human cells following transcriptional reprogramming", Regen Med, 5, 345–363.

Reported the resetting of telomere length in somatic cells following transcriptional reprogramming.

Toolbox

Key tools
New technology
Emerging techniques

DNA on the Cutting Room Floor

CRISPR technology has revolutionized genomic editing – but is there still a place for first-generation tools?

By Charlotte Barker

There's no doubt CRISPR (clustered regularly interspaced short palindromic repeats) technology has been a game changer for genome editing. Cheap, easy, and efficient, it has resulted in an explosion of research in the field, with translational scientists using the new tool for everything from studying the origins of cancer to developing gene therapies that replace "faulty" genes. However, it is by no means the first or only technology to allow genome alteration. And though CRISPR may be the "latest and greatest", it isn't necessarily the best option for every application.

There are three main categories of engineered nucleases on the market: zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR. All are targeted "genomic scissors" that combine an engineered DNA-binding protein with a DNA-cleaving enzyme to make a double-strand break at a specified location in the organism's DNA. After the relevant sequence has been snipped out, the breaks are sewn neatly back together by the cell's own repair machinery.

"It is a very exciting time for people like me who are interested in genome editing and now have access to this great toolkit," says Jon Chesnut, Senior Director of Synthetic Biology and R&D at Thermo Fisher Scientific.

DNA scissor debut

ZFNs were the first onto the market and opened up a whole new world, recalls Supriya Shivakumar, Head of Strategy and Portfolio Development, Gene Editing and Novel Modalities at MilliporeSigma, which licenses the technology for research use.

"We already had the ability to downregulate genes using RNA, but we were missing a piece of the puzzle – the ability to knock out a gene entirely," says Shivakumar.

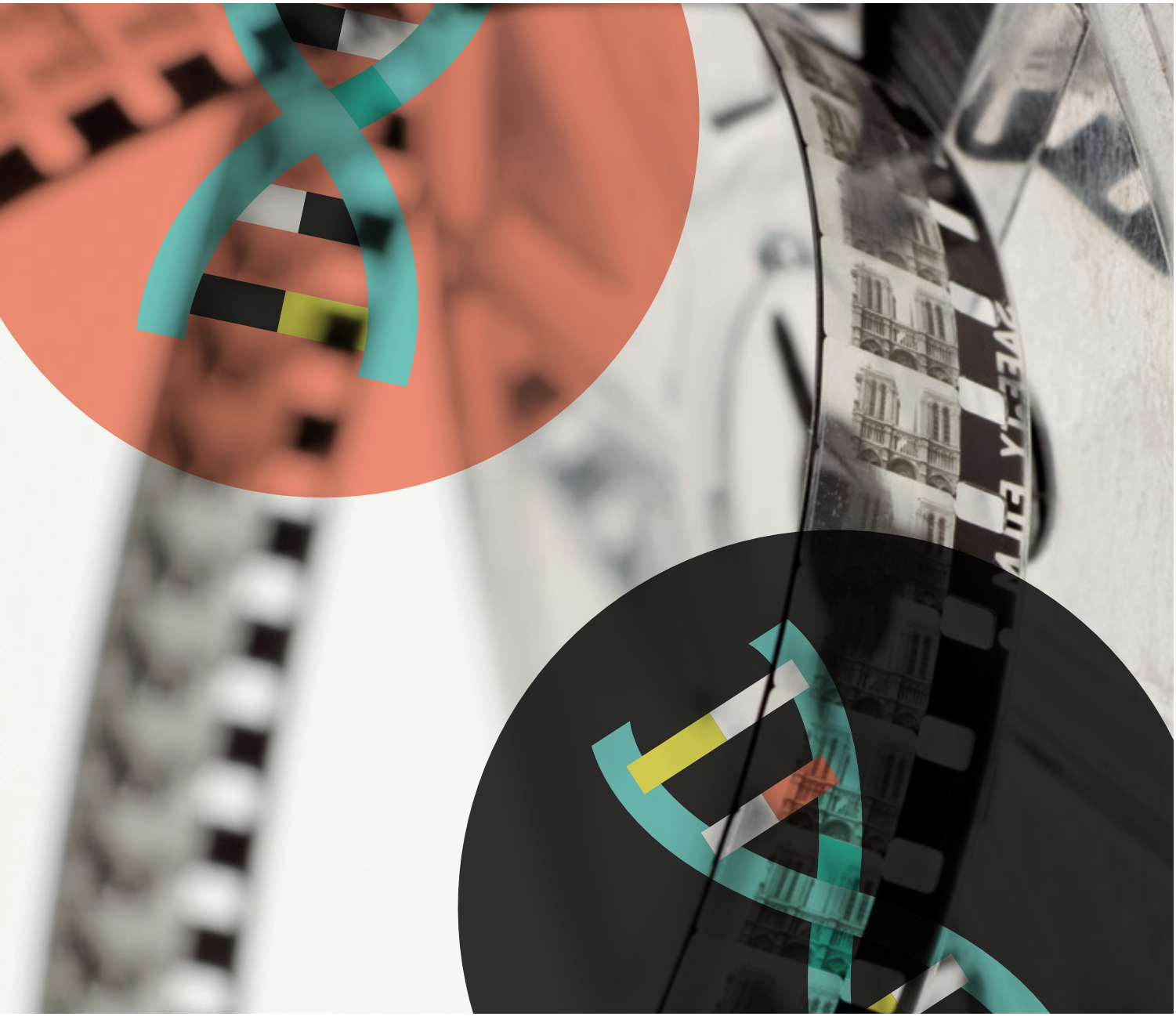
Each zinc finger recognizes three or four bases, and by combining these modules in different configurations, almost any sequence can be targeted. ZFNs are heterodimers, with the zinc fingers joined to a FokI endonuclease domain that cleaves the DNA. FokI will only produce the desired double-strand break when dimerized, which increases specificity by ensuring that cleavage only occurs when two DNA-binding events occur together.

ZFNs cannot really be described as "do-it-yourself" technology – they are time consuming and expensive to make, so most users turn to vendors for custom-made solutions. "ZFNs are hard to get completely right. We have an archive of experimentally-derived information, and without it there is a real chance that longer nucleotide recognition sequences won't work," says Shivakumar.

"It is a very exciting time for people like me who are interested in genome editing and now have access to this great toolkit."

An alternative to ZFNs became available in the late 2000s – TALENs. They harness plant pathogen proteins (TAL effectors) for DNA binding, again linked to a nuclease that snips the DNA.

TALENs are built from arrays of 33–35 amino acids – each array targets a single base pair. Constructing DNA-



binding domains with TALENs is less complex than with ZFNs, meaning that labs can save money by creating their own. However, they are large molecules, which can make them difficult to deliver efficiently, and still require a level of skill to engineer.

CRISPR fever

"TALENS and ZFNs are expensive and time-consuming, and so are typically used when you want to create a specific cell line. What was missing was the 'what if?' – the ability to play and explore," says Shivakumar. Enter CRISPR/Cas.

CRISPR/Cas originated as a form of adaptive immunity in bacteria. When a bacterial cell is infected, short sequences of the viral genome (CRISPRs) are incorporated into the bacterial genome. CRISPR-associated (Cas) proteins process these sequences

Precarious Patents

The well-publicized patent dispute over CRISPR/Cas looks set to run and run

Although the sequences were first described by Osaka University researchers in the late 1980s, the term CRISPR wasn't coined until the early 2000s. The potential of CRISPR/Cas in genome editing became clear when University of California, Berkeley (UCB) researcher Jennifer Doudna and collaborators published work in 2012 showing that they had reprogrammed the system to target specific sites in bacterial DNA. In early 2013, several groups, including one led by the Broad Institute's Feng Zhang, reported that the system also worked in eukaryotic cells, including human cells. Both UCB and Broad Institute have filed patents covering the fundamentals of genome editing by CRISPR/Cas, and licensed them to a number of companies. Now they are locked in a fierce dispute through the US Patent and Trademark Office (USPTO) and European Patent Office.

It's thought the proceedings may drag on for years as the authorities try to determine whether the use of CRISPR/Cas in eukaryotic cells was an obvious follow-on from Doudna's original work, or a separate (and patentable) breakthrough. The battle has become less diplomatic in recent months, with harsh words and accusations of impropriety being exchanged by the opposing institutions. Given the huge potential earnings for the institutions and their licensees, it seems likely that the fight will be a long and drawn-out one.

The mudslinging and high profile of the scientists involved has ensured that most of the attention has been focused on the foundational patents described above. However, a number of smaller groups have also filed important patents relating to CRISPR/Cas, including MilliporeSigma. "It's interesting that the whole focus has been on the dispute between these two major scientific institutes. I think there are some dark horses in this race," says MilliporeSigma's Supriya Shivakumar

"The IP situation surrounding the newer technology could also prove a major headache for those looking to bring a CRISPR/Cas-based gene therapy to market."

and attack the virus by cutting matching DNA sequences in the viral genome. By engineering plasmids encoding both CRISPRs and Cas, a hugely efficient genomic editing tool is created.

"The biggest benefit to CRISPR/Cas is ease of design," says Chesnut. "You can change the specificity of the nuclease just by changing the sequence of a small piece of RNA, which has really opened up genome editing."

Most labs are very comfortable with the technology; as Shivakumar puts it, "You can make CRISPRs in your garage." High speed, low cost, and impressive efficacy make CRISPR suitable for screening studies. For example, researchers can knock out thousands of different genes in cancer cell cultures to find out which are responsible for drug resistance. "That puts it in a different category to ZFNs and TALENs – you can not only study known targets, but find entirely new targets," says Shivakumar.

Many companies now provide off-the-shelf or custom-designed libraries for screening studies, says Chesnut. "We just launched our Lenti-based arrayed CRISPR libraries, and we hope to cover the entire human genome by early 2017."

Shivakumar also notes the rise of library platforms: "We don't want to convince someone to buy CRISPRs from us if it is quicker and cheaper to do it themselves, so we haven't focused on making individual CRISPRs, but rather making whole-genome libraries with the Sanger–Wellcome Trust and the Broad Institute."

Ultimately, what makes CRISPR so exciting is the freedom it offers. "The 'sandbox' environment that CRISPR enables is where great leaps in science originate," says Shivakumar. "It has opened the door to a number of new technologies that we never predicted."

Cut to the chase

If CRISPR is the fastest, cheapest, and most efficient technology, why would you consider using ZFNs or TALENs? Well, there are some situations in

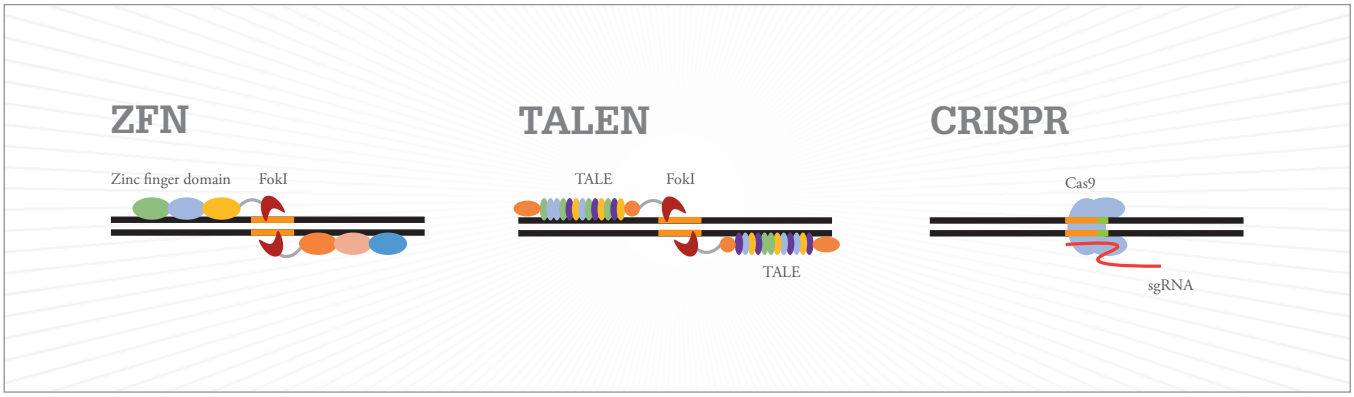


Figure 1. Mechanisms of ZFN, TALEN and CRISPR/Cas9 genome editing.

which the older technologies actually work better, says Chesnut. "We know of applications where TALENs are technically more effective than CRISPR. In transcriptional modification, TAL effectors appear to be at least as efficient as CRISPRs in delivering transcriptional activators and repressors."

Particularly relevant to the translational field is the fact that CRISPR/Cas is still very much the new kid on the block. "With CRISPR, you can play. But once you have a target that works, there are a couple of reasons to switch to a more established tool, such as ZFNs or TALENs," says Shivakumar. "ZFNs were one of the first technologies on the market and there has been a lot of work to show that there are no off-target effects or toxicity. It was one of the first to be used clinically, so there is a proven pathway."

The IP situation surrounding the newer technology could also prove a major headache for those looking to bring a CRISPR/Cas-based gene therapy to market. The ongoing patent dispute (outlined in "Precarious Patents") could be a source of unwelcome uncertainty for years to come. "We are watching the patent dispute around CRISPR closely, both in terms of how it may affect our customers, and as a fascinating view into how an emerging technology can stir up so much discussion. Scientists aren't usually so emotionally invested in the subject – at least in public," says Shivakumar.

"There's a significant amount of confusion about who's going to end up owning the IP rights for CRISPR, in contrast to the clear IP landscape for TALENs and ZFNs," says Chesnut. "It comes down to what your end goals are. If you want to create SNP-edited or knockout cell lines, certainly CRISPR seems to be the go-to. But if you are thinking further ahead and want to commercialize, then you have to consider IP."

Gene editing: the sequel

Will CRISPRs be all-conquering, or will they themselves be replaced by the next big breakthrough technology? What great advances in science and medicine will result? The field is moving so fast that it's hard to tell what the future holds. "Whatever happens – it's going to be surprising," says Shivakumar.

Gene therapy – a dirty word just a decade ago – is once again a major research focus, bolstered by the success of CAR-T cell therapy for cancer. "In our lifetime, I think we will see gene and cell therapy in regular use," says Shivakumar.

Genome editing is also finding applications in the pharmaceutical industry, creating in vitro models for drug safety and toxicity testing, and replacing RNAi screens for discovery. "We devote a lot of effort to working with pharma customers to use genome editing to create better cell screening models for drug discovery – both specifically edited cell lines and screening library approaches," says Chesnut.

Shivakumar believes that using CRISPR in detection technologies could have a big impact on day-to-day life. For example, farmers could grow plants that would change color to indicate nitrogen levels in the soil. In medicine, this could take the form of sophisticated sensors for disease detection and monitoring. "Perhaps one day we'll all have the equivalent of a Star Trek tricorder," she suggests.

However, lest we get swept away by the brave new world of CRISPR/Cas, Shivakumar also strikes a note of caution. "With the explosion of papers coming out, there has been a sense that if you tie your work to CRISPR, it will get a wider audience. So my advice to researchers new to the field would be to regard reported advances with a critical eye, and make sure you are using the right assay for your needs. No matter what you are doing – the better your assay, the better the process."

Translated

Celebrating success
Translation in action
Bench-to-bedside

Sonic Scalpel

In July 2016, INSIGHTEC received FDA approval for the first MR-guided focused ultrasound device to treat essential tremor. But could the noninvasive tool find wider utility as a safer alternative in other brain surgery procedures – or surgery in general? Eyal Zadicario shares the story and the science behind Exablate Neuro.

How did you get involved in the field of therapeutic ultrasound?

I have been with INSIGHTEC since it was founded in 1999. The company brought together a group of engineers and scientists who shared a vision of a breakthrough surgical tool that was not only noninvasive but also allowed the physician to monitor and optimize treatment in real time.

Ultrasound is essentially a wave of pressure that travels through tissue. Under certain parameters, this pressure wave is absorbed in the tissue and transformed into heat – when the temperature exceeds a critical point, the proteins in the tissue are denatured and the tissue dies, a process known as thermal ablation.

We knew that focused ultrasound had the ability to penetrate deep into the body, while having a very sharp focal effect, operating with sub-millimeter sharpness and millimeter accuracy. In fact, work had been going on for decades into therapeutic application of ultrasound, with some success. But targeting was not always as accurate, and effects not as reproducible, as required for a surgical tool.

How did you tackle the problem of precision?

To turn it into a repeatable, durable, and sustainable procedure, we needed to provide a means to guide this "virtual scalpel" to the target and get feedback on how the tissue responds during treatment. The solution we came up with was to link high-energy focused ultrasound technology to the most advanced imaging method available – MRI – to create MR-guided focused ultrasound (MRgFUS).

After several years spent developing the technology, we gained approval for the device to be used to treat uterine fibroids and painful bone lesions in metastatic cancer. But we always felt that the Holy Grail was operating noninvasively in the brain. The common understanding at the time was that ultrasound would not penetrate the bony structure of the skull. We have devoted almost two decades to developing the hardware and software needed to achieve that goal, and have conducted a series of clinical trials.

Why target the brain?

There is a major clinical need for a noninvasive alternative to surgery in this area. It's not a coincidence that "brain surgery" is used as shorthand for a difficult, detailed task – it requires extreme accuracy, delicacy, and precision. You don't want to expose the brain to any collateral effects, however small. There are also the risks that come with any invasive surgery – infection, side effects from general anesthetic, pain around the wound site, and so on.

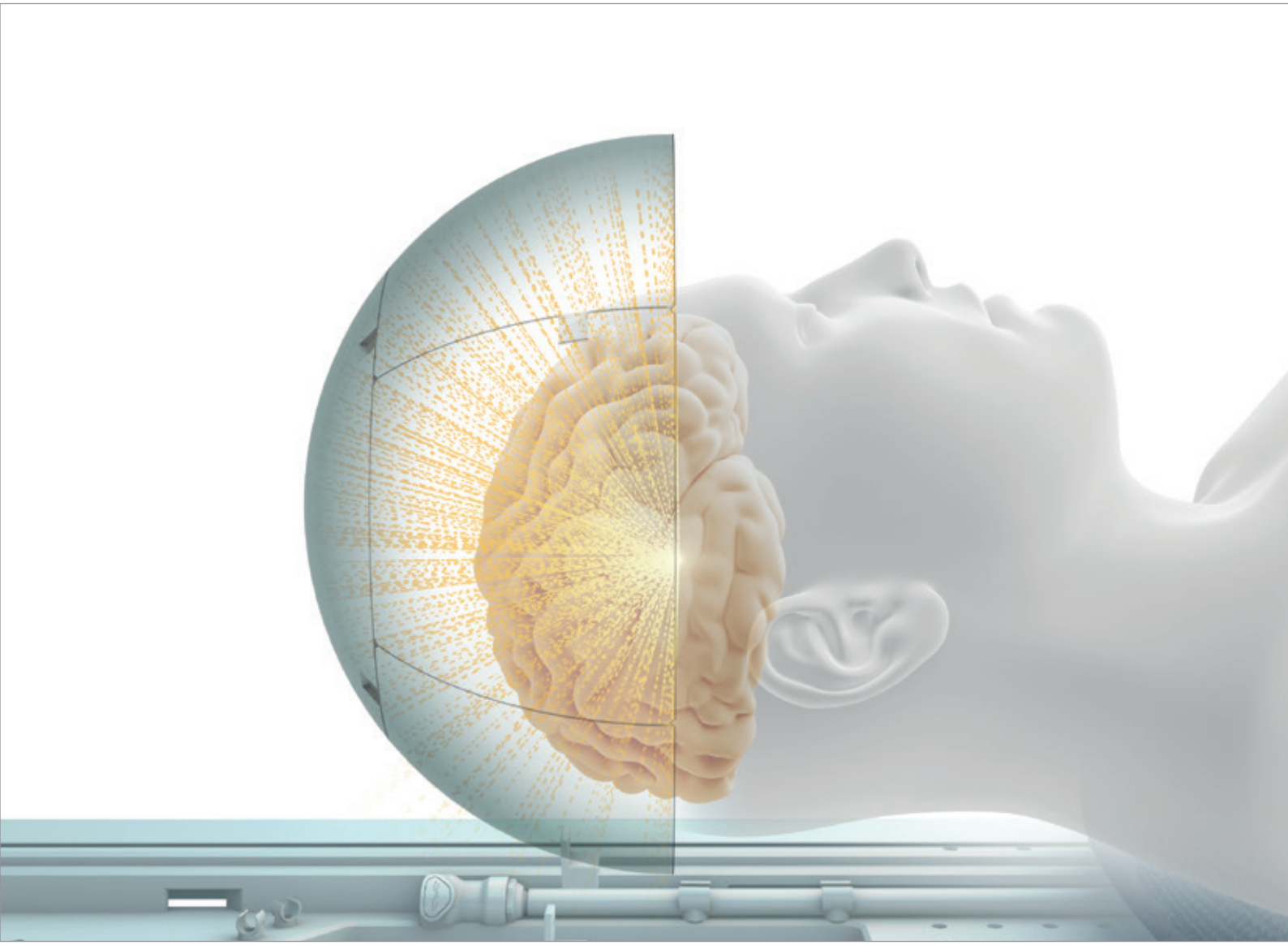
Radiation therapy offers a noninvasive option for certain conditions, but it takes weeks or months for the tissue to be destroyed. The beauty of thermal ablation is that the tissue is destroyed as soon as it reaches a specific temperature. That means that the physician and patient can see right there and then whether it has been effective – and there is little risk of delayed side effects.

What were the challenges of working in the brain?

We realized early on that predictability was the crucial hurdle to overcome. Experiments with focused ultrasound in the brain had been going on for some time but there were several missing elements to make it a viable medical device. For a start, variability between patients meant there was no way to accurately predict what ultrasound parameters would generate the right level of heat in the right location. With the real-time monitoring that MRI provides, we were able to resolve that problem.

The other major challenge was getting the ultrasound waves into the brain in the first place. Many types of ultrasound are completely blocked by the dense tissue of the skull. Plus, the thickness of the skull is highly variable, making it hard to focus the ultrasound to the target. We developed hardware that can produce ultrasound powerful enough to penetrate the skull, and sophisticated software that can correct for skull shape and thickness.

The first clinical trials targeting the brain started in 2005. After several feasibility cases to prove the safety of the device, the FDA approved the pivotal study for treating essential tremor. There



is a lack of good therapies for these patients and the FDA was very supportive, but it was a long, thorough process.

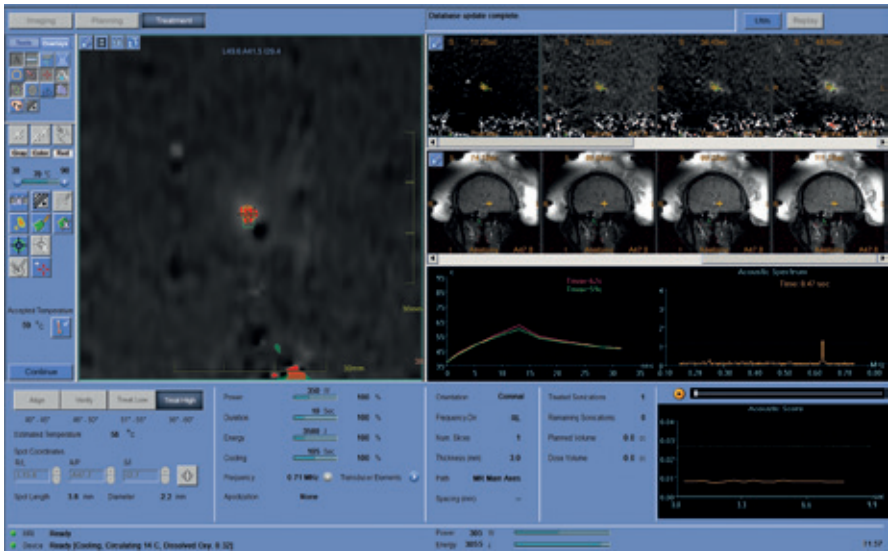
And 10 years on, you now have FDA approval…

The device, Exablate Neuro, has now been approved in Europe and the US for the treatment of essential tremor. It's a common condition that causes uncontrollable shaking, most commonly in the hands. Medication often comes with serious side effects and isn't always effective.

It has been known for decades that tremor can be controlled by disrupting the Vim nucleus of the thalamus. The problem is that it's a tiny focal point (3-4 mm diameter), located deep in the brain, and surrounded by several vitally important neural networks. Currently, the most common approach to reach this

At a Glance

Device: Exablate Neuro
Technology: MR-guided focused ultrasound
Developed and marketed by: INSIGHTEC
FDA approval: 2016 – for essential tremor



Exablate monitor showing thermal dose at target during treatment.

target is deep brain stimulation, which involves implanting an electrode into the thalamus, powered by a controller placed under the skin on the chest. It can effectively suppress tremor, but carries the same risks as any brain surgery and requires regular follow-up and battery replacements. Not surprisingly, many essential tremor patients choose not have this invasive surgery, instead deciding to live with their symptoms. Now, focused ultrasound treatment offers them an alternative.

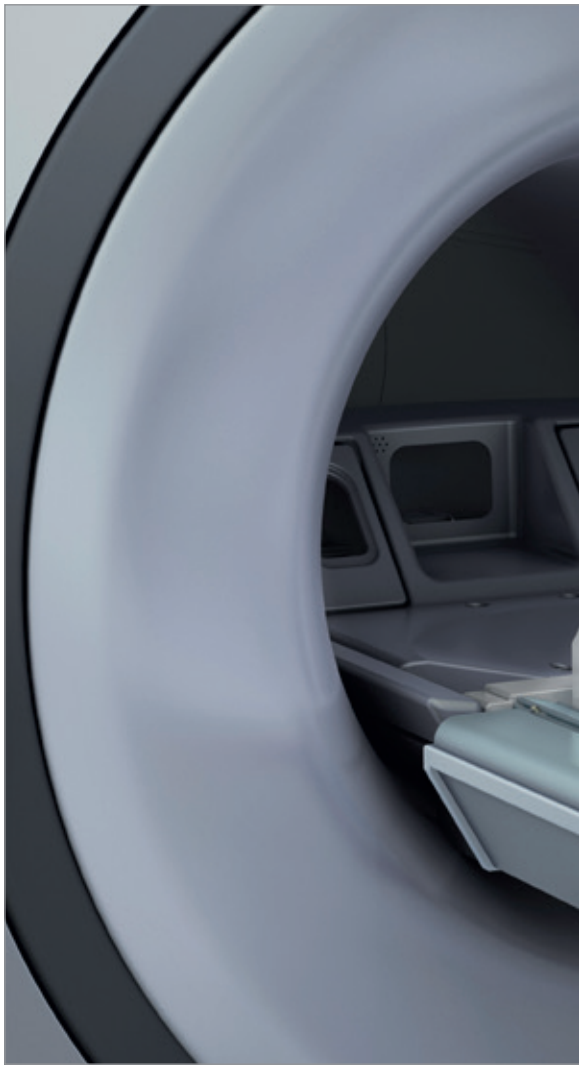
How does essential tremor affect patients' lives?

The patients who are treated with our device have typically suffered for most of their life with essential tremor in their hands. Over time, their condition worsens, until they may have difficulty with everyday tasks. They can't hold a glass of water. They can't eat unaided. They can't write. They can't drive. They can't do anything that involves delicate motor action. At rest, the tremor may be invisible, but as soon as they try to move their hands, it escalates, and the more delicate the movement they try to make, the more pronounced the tremor. Many are forced to stop working, and may be embarrassed to go out in public or eat with their family – it is very limiting.

What does treatment with Exablate Neuro look like?

This is a single-session treatment and we treat the tremor in the dominant hand. The patient – fully conscious – enters the MRI scanner, which is equipped with the focused ultrasound device. The physician views images from the MRI, marks the target on screen, and the focused ultrasound is directed to that target. The patient is completely awake during the procedure, and can be evaluated as the tremor improves and for any side effects. The physician will increase the temperature gradually, while monitoring the patient – if the patient starts to show signs of off-target effects, the treatment is adjusted before reaching a therapeutic temperature.

The patient spends around three hours in the MRI machine, and most walk away with their tremor significantly improved. Often, patients get very emotional – they may not have been able to eat or drink normally for many years, and then suddenly the tremor is gone in a few hours. It is very rewarding to see the impact on patients' lives. It has been a very long, challenging technical development process, and seeing patients benefit from what is now 17 years of work is what keeps us all inspired.



There are now over 30 centers using the Exablate Neuro for both research and clinical use, with over 600 patients treated worldwide. We see this as the first test of taking the technology into the brain.

What's next?

At the moment, we treat the dominant

Exablate Neuro treatment bed inside the MRI.

hand only, and patients with tremor in both hands are already asking why they cannot have the other hand treated too, so our immediate priority is to evaluate the possibility of bilateral treatment. We are also looking at other neurological causes of tremor, such as Parkinson's disease. After that, we plan to turn our attention to other brain disorders that are currently treated with conventional surgery, such as tumors or epilepsy.

In the longer term, this technology has much more potential. There are two things we're focusing on: one is thermal ablation for prostate, liver, and pancreatic cancer. The other is to enhance drug delivery to the brain. Drug delivery is quite a different challenge to ablation. Here, we use much lower power and a different frequency of ultrasound, so that the pressure wave is not absorbed and causes no heat, but simply vibrates the tissue structures and membranes. Preclinical trials have demonstrated that if you inject microbubbles into the bloodstream and apply the ultrasound field to certain areas of the brain, the vibrations increase the permeability of the blood–brain barrier and allow the microbubbles to enter. That is the concept, and we're now looking at how to get that into a well-designed clinical trial. There are many therapies that could have potential to treat neurological conditions, but are currently unusable, since they are unable to cross the blood–brain barrier.

There is a lot of excitement about the potential of therapeutic ultrasound at the moment. We hope that the first approval for a neurosurgical indication will push the whole field forwards.

Eyal Zadicario is General Manager at INSIGHTEC.

In Perspective

The big picture
Global health
Populations

Hotline to Predictive Healthcare

What started as a phone line for people worried about dengue has grown into a sophisticated early warning system for outbreaks.

By William Aryitey

Epidemics are tracked in many different ways around the world. The CDC in the US uses interconnected hospital information systems to compare and integrate signals. Google Flu Trends tracks search queries for certain symptoms across time periods and locations. But in many regions high-tech methods like these aren't possible – the right infrastructure isn't in place, and it would be too difficult and expensive to implement. In Punjab, Pakistan, not all hospitals have a shared database of records, and the vast majority of the population doesn't have Internet access. In these circumstances, how can we get the data we need?

Phoning it in

In 2011, there was an outbreak of dengue fever in Punjab that quickly escalated into the largest epidemic the region had ever seen. Dengue causes flu-like symptoms, rash and fever, and its severe form can be fatal, particularly for young children. "There was a sense of public panic, and authorities were unprepared for the scale of the outbreak, leading to massive queues at hospitals," says Lakshminarayanan Subramanian, a Professor in the computer science department at NYU.

To calm the chaos, the government asked the pioneering Punjab IT Board (PITB) to launch a telephone hotline. The hotline was initially built for people to get a quick assessment of their symptoms, determine whether they needed to see a doctor urgently, and prevent hospitals from becoming overloaded. However, it also allowed the PITB to collect data about the number of suspected dengue cases in different areas, as well as keeping track of confirmed dengue cases from the referred hospitals.

Subramanian is a longstanding friend and collaborator of PITB Chairman Umar Saif, and the two decided to launch a research collaboration to explore the hotline's potential for surveillance and forecasting. On analyzing the data, there was a clear trend between calling patterns and later outbreaks of dengue, with the hotline able to predict outbreaks two or three weeks before local hospitals could confirm (1).

The dengue forecast

"The call volume was substantial enough to create good forecasts – but the hotline itself was only the beginning," says Subramanian. The team has now

"On analyzing the data, there was a clear trend between calling patterns and later outbreaks of dengue."

built up a whole ecosystem around the hotline, to track and predict dengue outbreaks. The system comprises more than 25 departments spanning 36 districts of Punjab, a plethora of standard containment practices, dashboards to share information with hospitals, and even public health teams who are sent out to perform containment activities, such as mosquito control.

"Tracking unconfirmed and confirmed cases of dengue by locality gave us very strong signals," explains Subramanian. "Naturally, no single data source can be 100 percent relied on, and the hotline data can be skewed by people calling in about other diseases, reluctance to seek treatment after referral, and hundreds of other factors. To limit noise in the data we collect, we cross-reference it with data from other sources, such as hospital records."

The hotline now also serves functions beyond its initial remit of advice on symptoms and hospital referrals. People can report environmental conditions that encourage mosquitoes (such as stagnant water), request mosquito fumigation of their neighborhood, and make complaints. "This adds value to the hotline and incentivizes its use," says Subramanian.

About PITB

The Punjab Information Technology Board (PITB) was created in 1999 by the government of Punjab to help the region harness rapid advances in the field of IT, and build an internationally competitive IT industry. Today, PITB is working on over 60 projects and services ranging from utility billing, to e-stamping, to creating livestock databases. Since 2011, the Board has been led by computer scientist and entrepreneur Umar Saif, who is widely credited as a driving force behind the Pakistani government's use of technology.

Punjab's Dengue Activity Tracking System

As well as telephone and hospital reporting, the scheme makes use of smartphones to collect real-time data on cases, mosquito breeding grounds and prevention efforts.

- More than 25 departments across 36 districts of Punjab
- 1900 GPS-enabled smartphones used to log dengue cases and mosquito breeding areas
- 39,688 hotspots in four major districts (Lahore, Rawalpindi, Sheikhupura and Faisalabad) under weekly surveillance
- 145 hospitals with dengue data entry systems
- Over 6 million anti-dengue surveillance activities via android mobiles since launch

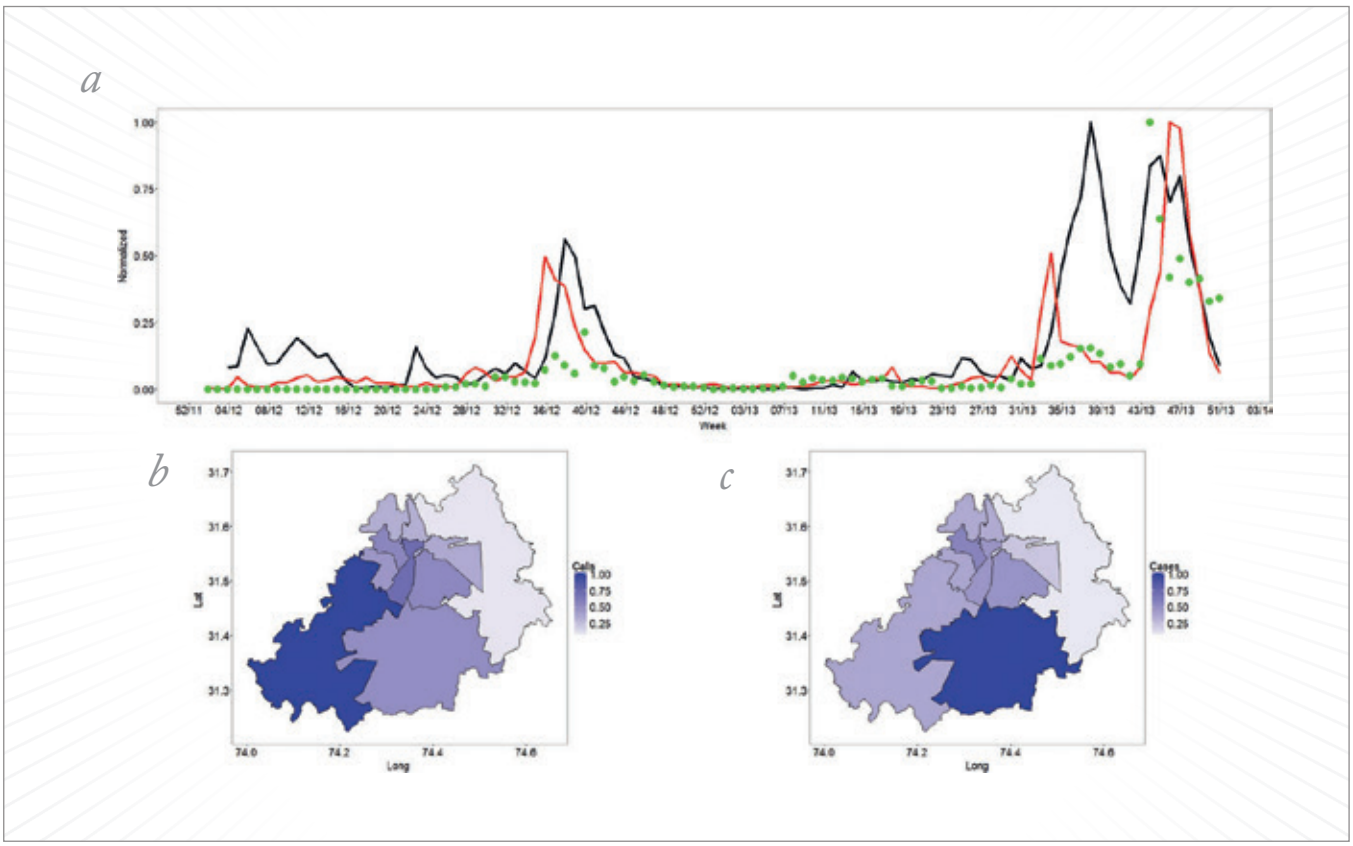


Figure 1. Trends in call volume and suspected dengue cases measured during 2012 and 2013. A) Time series of calls (red), suspected dengue cases (black), and awareness campaigns (green points). Scale normalized by dividing by individual maximum values. (B) Density map of calls across towns in Lahore. (C) Density map of cases across towns in Lahore. The legend is normalized by the maximum value. Lat, latitude; long, longitude. Reproduced from (1).

"There was a sense of public panic, and authorities were unprepared for the scale of the outbreak, leading to massive queues at hospitals."

Subramanian affirms that while the ecosystem they developed started as an afterthought to the original hotline, a lot of follow-up work has gone into subsequent planning and validation, involving multiple collaborations with colleagues at NYU and in the UK. "Working with leading epidemiologists, we carried out detailed studies to maximize our effectiveness and ensure we are moving in the right direction," he says.

The result is an early-warning system that is truly useful, despite its simplicity and low cost. "I think we have found a particular sweet spot of systems coming together to make our forecasting model work," says Subramanian.

Spreading the word

Subramanian believes there are opportunities for similar hotline systems in other regions that lack widespread Internet access or linked hospital networks to take advantage of other forecasting tools; for example, Zika in Brazil, Ebola in West Africa, and even swine flu in certain areas.

The initial outlay is relatively modest, with most of the funds going on setting up and staffing the hotline and running public information campaigns. "The crucial first step is reaching a minimum call volume, because if you receive too few calls you won't be able to build an accurate model," says Subramanian. "Once you have the call volume, you

need to get a good geographical spread and regularity of calls. If you can achieve sufficient scale and spread, you can begin to build on that initial momentum and create an effective forecasting tool."

The strategy could also be applied in developed countries, where Subramanian envisages the hotline taking the form of an Internet-based hub that people can interact with – perhaps even with direct access to health professionals. There are many untapped opportunities within existing systems, too, says Subramanian. "Take the UK for example. The NHS already provides data with scale, spread, and regularity. Alone, this data might be too noisy to be useful, but if you start putting it together with health data that other organizations collect, you could have a very powerful predictive tool. And there are so many more examples like this around the world."

Subramanian is convinced that there are massive opportunities to improve personal and societal healthcare using these data sources. "We just need to implement and utilize tools more effectively to improve disease prevention at very little cost."

References

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More Ways to Predict an Outbreak

From Mice to Men

New research shows that analyzing environmental change can help predict the risk of a zoonotic outbreak – when a disease leaps from animal to human. One such infection is Lassa fever, an acute viral hemorrhagic disease that usually infects West African rodents, but can spillover into human populations. A team at University College London looked at hundreds of past outbreaks of Lassa fever – taking into account location, land use, crop yields, weather conditions, and human population growth. The data from previous epidemics were combined with forecasts of climate change and population density to predict future prevalence (3). The team hope the model can be applied to other zoonotic diseases to help communities prepare for the future.

Mobiles and Mobility

Researchers at Harvard University are using mobile phone data to predict the spread of dengue (4). By looking at (anonymized) call records, the investigators were able to track the movement of people in Pakistan during a major dengue outbreak. Using the information gleaned from call records, alongside climate data, the researchers developed a novel transmission model, which can accurately forecast where and when the disease will strike next. This was the largest set of cell phone records ever analyzed to estimate mobility, spanning over 40 million users.

Catching Up to Ebola

The international community was slow to react to West Africa's devastating 2014/15 Ebola epidemic. To help authorities act faster in future, epidemiologists at Columbia University conducted an analysis of data from the Sierra Leone Ministry of Health in the aftermath of the outbreak (5). They used a novel statistical model to give a detailed picture of the spread of Ebola through the country, and believe that real-time use of the model during future outbreaks could identify opportunities to curb transmission. In the midst of an outbreak, contact tracing can be too slow and cumbersome – the new model provides a faster way to track the spread of the disease, with minimal data required.

Accessing Big Pharma's Conscience

Sitting Down With... Jayasree K. Iyer, Executive Director, Access to Medicine Foundation, Haarlem, the Netherlands.

Credit: Patricia Wolf

How did you get involved with the Access to Medicine Foundation?

I used to be a molecular biologist, developing malaria vaccines. The translation of research into improved global healthcare is very dear to my heart. Later, I became a negotiator between pharmaceutical companies and other public and private partners, focusing on funding solutions for neglected tropical diseases.

I joined the foundation because I was struck by their idea of using good quality data from companies to encourage them and others to do more to promote access to medicine. I believe that the vast majority of people in the medicine industry want to help others – at times, they need a little guidance on what they can do. I was Head of Research for two and a half years, before taking over as Executive Director of the foundation.

What is the goal of the Access to Medicine Index?

The index is an independent examination of what the Top 20 pharma companies are doing for the world's poor. It provides a series of staple expectations for the pharmaceutical industry and shows them how they can up their game. Even companies who are not included in the index use our criteria to help them formulate their access to medicines strategy and measure their progress. The index is also a place where practices can be shared between companies – as competitors, they don't always get that opportunity.

How are companies assessed?

We focus our attention on the 51 most burdensome diseases in 107 low-and middle-income countries. We ask: are companies developing drugs for these markets? And are they making them available and affordable to those who need them?

New to the index this year is an analysis of how well each company's priorities match up to priorities identified by external organizations – we want to know how responsive the industry is to international initiatives. For example, this year we looked beyond whether companies have affordable pricing schemes, to analyze whether the products and countries covered by the schemes match up to global priorities.

How did companies fare in this year's index?

It is a very competitive ranking, with companies jostling for position and often leapfrogging each other. GlaxoSmithKline (GSK) tops the index for fifth time in a row, with Novartis, Johnson & Johnson, and Merck KGaA close behind. Novo Nordisk, Roche, and Gilead dropped this year, while new initiatives helped AstraZeneca and Takeda rise up the ranks.

Overall, companies are doing more. There were new initiatives, important new drugs reaching the market, and new approaches to doing business in developing countries. However, it is an uneven picture, with no progress in affordable pricing, and misconduct still a major issue.

Were there any surprises?

One thing that really stands out is how diverse the industry is – there are very few areas where the companies move as a pack. This diversity illustrates the different ways that access can be approached, and helps us to assess what works and what doesn't.

What are the common factors amongst high-scoring companies?

A key element is leadership. A company that truly believes in improving access and makes it a core part of their commercial strategy is going to do better in the index than a company that limits efforts to a few corporate projects. Companies that do well tend to be those that discuss access to medicines at the very highest levels. Any change in leadership can have a big impact, so it will be interesting to see whether GSK maintain their position at the top of the index after the departure of CEO Andrew Witty next year.

What areas need improvement?

One obvious area is affordability. True needs-based pricing is still rare, with only five percent of drugs meeting our toughest criteria for affordability.

Instances of corruption, bribery, anti-competitive behavior, and unethical marketing practices are still occurring. Companies need to take this very seriously – it's no good bringing access plans to the table if you aren't operating ethically in these countries.

Is improving access to medicines all down to pharma?

Absolutely not. There is a wider ecosystem of governments, regulators, investors, patient organizations, and NGOs – whose support we need to reach our goals. Treating the pharma industry as the "bad guy" is not the solution – working with the industry to come up with the right solutions and address the challenges is a much better bet. It's easy to say we want an endless supply of cheap medicines, but we have to look at how that can be made sustainable. For example, regulatory incentives and disincentives are crucial, and a lot of investors are now starting to look at access to medicine as part of their decision-making, which plays a huge role in motivating companies. In addition, governments need to carefully consider their policy on issues like generic drugs.

Tell us about the foundation's latest project – the Access to Vaccines Index…

It is the first ever tool that measures efforts to make vaccines accessible and affordable. The first index will be released in 2017 and is intended to act as a baseline measure of current performance, but also a guide to how the vaccine landscape needs to evolve if we are to solve some of the unique issues around vaccines, such as high production costs.

You can download the 2016 report at accesstomedicineindex.org.

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