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the Translational Scientist

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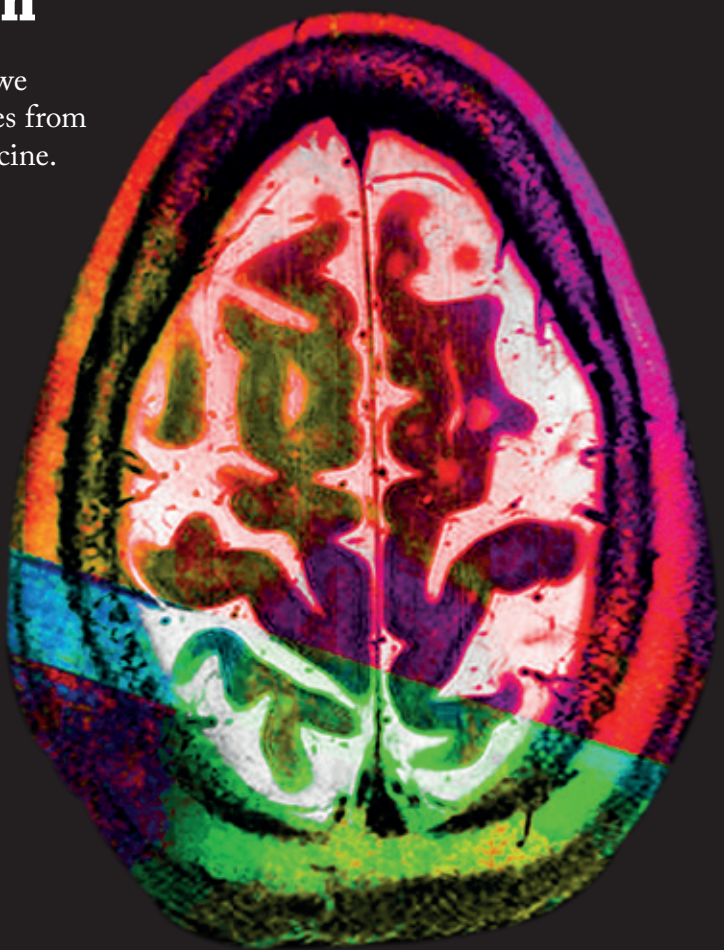

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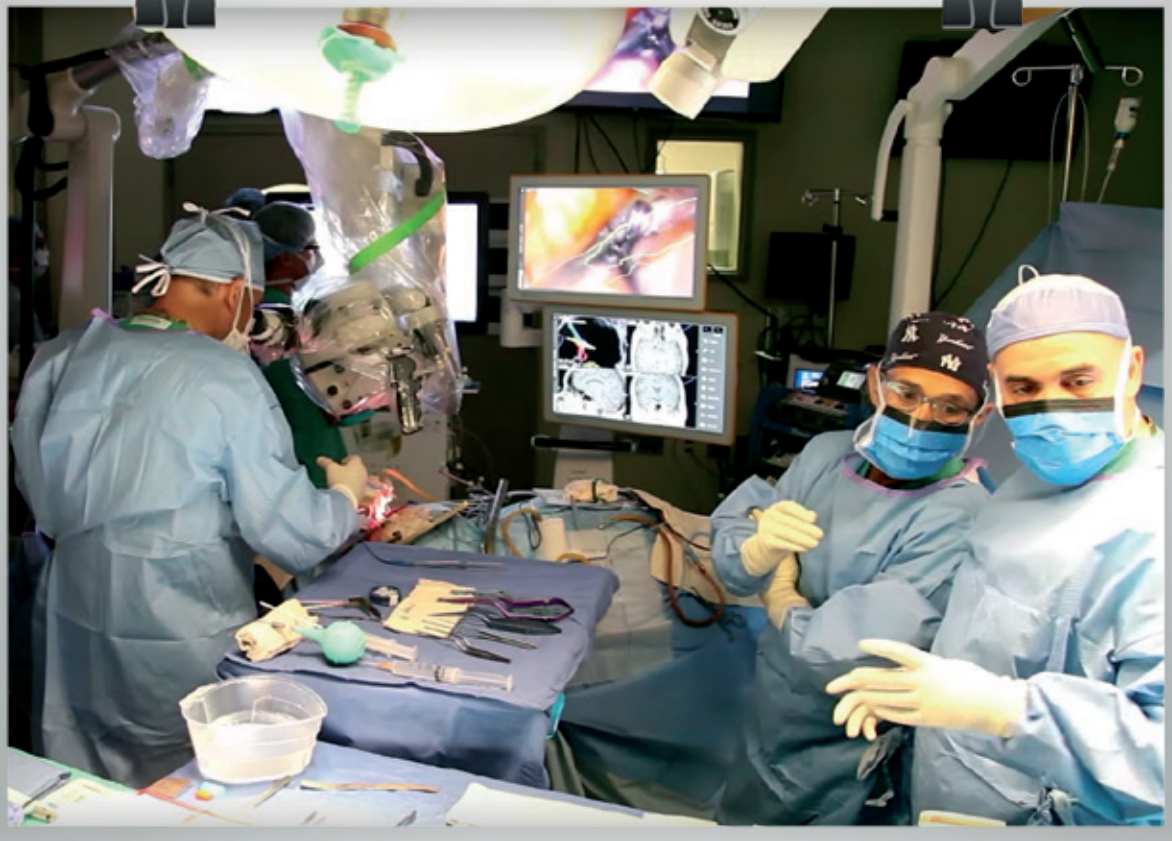
Video of the Month



Joshua Bederson, Professor and System Chair in the Department of Neurosurgery at Mount Sinai Hospital, introduces an imaging system that overlays vital regions of the brain onto the microscope eyepiece during neurosurgery. The augmented reality technology adjusts in real-time as surgery is performed, to display the outline of major arteries and cerebral structures that are in the surgeon's viewfinder, and help make neurosurgery more efficient. Credit: Mount Sinai Health System.

View the video online at http://tts.txp.to/0616-votm.
We'll be adding a new video every month at www.thetranslationalscientist.com.

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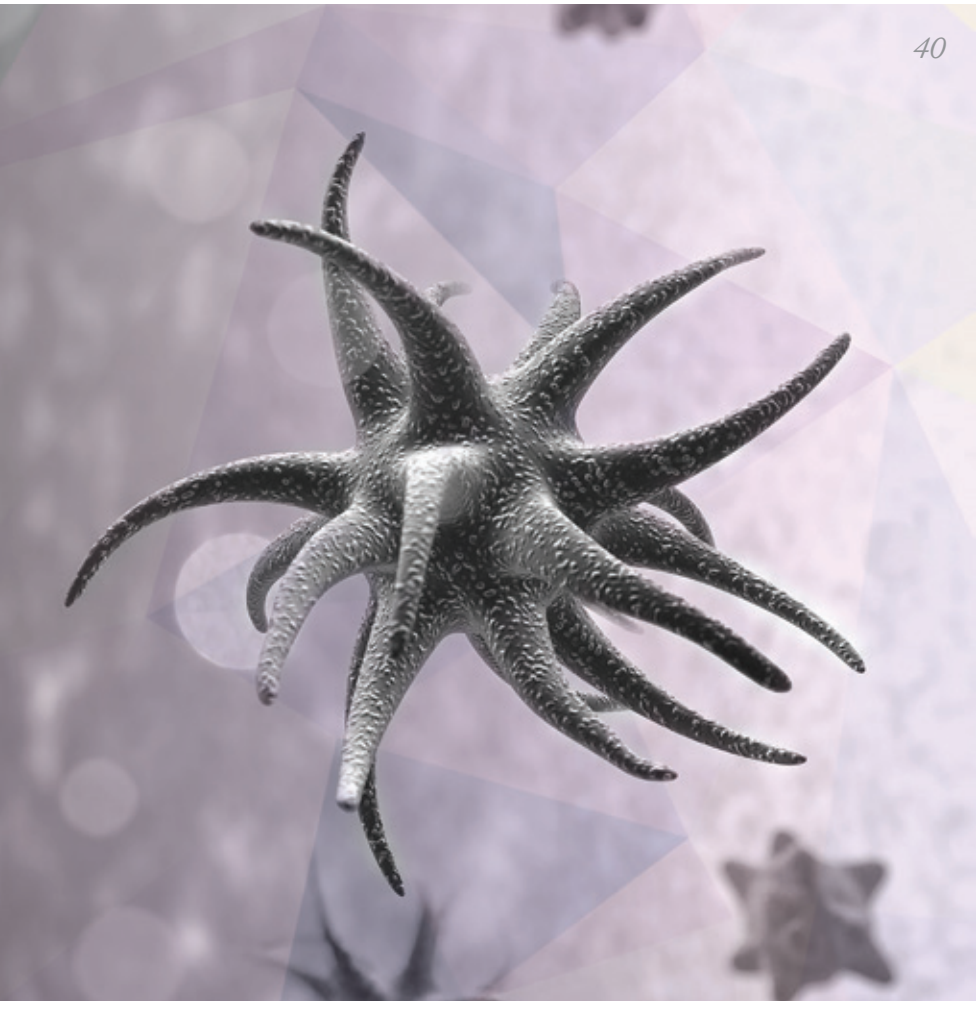

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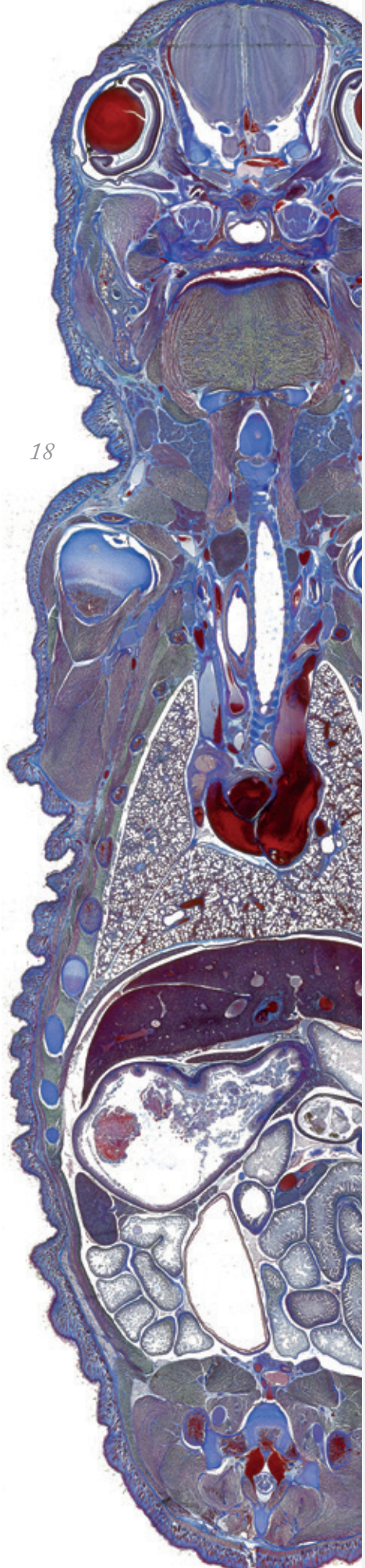
On The Cover

Good Egg – an axial view of the artist's brain, by Elizabeth Jameson. Part of our Art of Translation special issue.



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Change of address:
tracey.nicholls@texerepublishing.com
Tracey Nicholls, The Translational Scientist, Texere Publishing Ltd, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745200
sales@texerepublishing.com

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Smoke and Mirrors – and Red Tape

Knowledge lags behind practice on medical marijuana. Cutting back on excessive bureaucracy for researchers is likely to help us all catch up.

In August 2016, the US Drug Enforcement Agency (DEA) lifted rules that restricted scientists to a single, government-run source of marijuana for medical research. With medical marijuana legalized in 25 US states, the DEA accepts that an expanded supply and greater variety of marijuana for research is needed.

However, cannabis remains a Schedule I substance in the US, and researchers wishing to study the drug have a number of regulatory hoops to jump through. Funders and review boards are wary of research involving marijuana, creating a somewhat contradictory situation – patients can access marijuana in many states, while medical researchers wishing to carry out clinical trials often cannot. The drug remains Schedule I in part because there is a lack of evidence to justify medical use, but the classification makes it an uphill slog for researchers to generate such evidence – classic catch-22.

Despite the hurdles, there is evidence to suggest that cannabis and its active ingredients are effective in a number of therapeutic areas (1). There are two FDA-approved cannabinoid drugs (Marinol and Syndros) containing one of the main psychoactive ingredients of marijuana, tetrahydrocannabinol (THC), which are used to stimulate appetite in AIDS or cancer patients (2, 3). Sativex, approved in Canada, New Zealand, and several European countries to treat multiple sclerosis-related spasticity, mainly contains THC and non-psychoactive cannabidiol (CBD) (4). CBD is also showing promise in some hard-to-treat epilepsies (5).

The most common reason for a medical marijuana prescription is pain relief. It is thought that cannabinoids may help control chronic neuropathic pain, which – as we learnt in our March feature "The Problem with Pain" (6) – often fails to respond to existing therapies. We need more and larger studies if we're to determine whether cannabis is an effective painkiller – but research is being held back by the polarized nature of the debate. Meanwhile, patients prescribed medical marijuana are exposed to the risk of an untested product of variable strength and quality.

Though some of those in favor of legalization like to present the drug as a 100 percent safe "cure all", cannabis – like all drugs – is not without side effects, which makes it all the more important that unbiased, controlled studies are conducted. Only rigorous research can clarify the benefit and harm of medical marijuana – as well as allowing doctors, patients, and governments to make informed decisions.

Charlotte Barker
Editor

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Read more about the challenges of cannabis research in "The Cannabis Scientist", a supplement to The Analytical Scientist. http://tas.txp.to/0916/TCS

Upfront

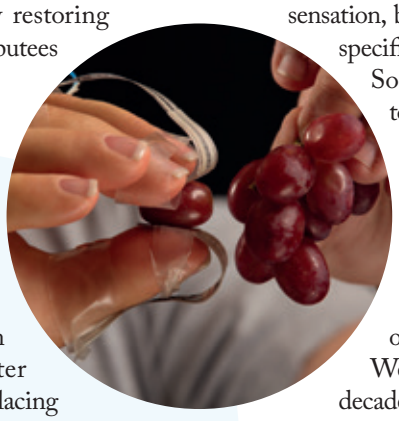
Reporting on research, personalities, policies and partnerships that are shaping translational science.

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

More Than a Feeling

A new prosthetic hand reaches out with the sense of touch

Dustin Tyler, professor in the Functional Neural Interface lab at Case Western Reserve University, is developing a prosthetic hand that allows users to regain the sense of "feeling". We caught up with Tyler to find out how restoring sensation is helping amputees to reconnect.



How did you get into this area?

Throughout my career I've been building devices that connect to the brain's "peripherals". At first, I focused on motor restoration after spinal cord injury – replacing severed neural connections with a device that stimulates the muscles to contract in response to signals from the brain. Over time, I became interested in communication in the opposite direction – passing information from the body to the brain. A lot of progress has been made with cochlear and even visual prosthetics, but there has been very little success in the area of touch.

Sounds like a tough challenge – why take it on?

Tactile sensation is what connects us to the world. When I speak with arm or hand amputees, they say that losing that connection is almost worse than the loss of function. People tend to discuss their prosthetic as a tool attached to their body, and not a part of who they are. I wanted to restore that sense of touch, and help them reconnect to the world. So my lab began applying the same technology we had used in motor restoration to a different problem. We asked: how can we communicate with the brain, and what does it mean when we do?

How confident were you that it was even possible?

We were pretty confident that we'd get sensation, but we weren't sure how specific or useful it would be. Some of my colleagues told me it would feel like a grinder on the hand, or that any sensations would not be localized enough to be useful. There were a lot of unknowns, and really only one way to find out. We knew from nearly a decade of experience that the electrode technology was safe, so we embarked on a feasibility study with two people who had lost a lower arm and hand.

What did participants want to get out of the study?

Naively, we thought that the greatest gains would come from better function. Without sensory feedback, the person has to watch the prosthesis the whole time to know that they haven't dropped or crushed something – restoring touch would make manipulating objects much easier. People do appreciate that, but what they want most of all is that sense of connection – to hold something in their hand and be able to feel it. Mostly, they just wanted to hold hands with their spouse.

In simple terms, how does it work?

When you lose your hand, the sensors that detect touch are gone but the nerves

that connected those sensors to the brain still exists. Our device wraps an electrode around a nerve, and allows us to electrically activate it. In effect, we replace the sensor that was on the hand with one on the prosthesis. When the brain receives a signal along the nerve, it doesn't know that it is artificial – users report experiencing the sensation as if the prosthesis was their hand.

Is the sensation that users get from the prosthetic "normal"?

Not exactly. We can stimulate and they'll feel the hand – but it may not feel quite like they are used to. We can make an analogy with language. When I speak, you can understand because we use a specific pattern of sounds. If I just made random noises, you'd recognize it as sound but it wouldn't be language. It's similar with the sensory input – they are feeling something, but it doesn't necessarily translate into familiar sensations.

One of the biggest breakthroughs in this work is that the way we apply stimulation changes the quality of the sensation the person experiences. It might start off as a tingling or a buzz, but by changing the pattern of stimulation, it can transform into a more natural sensation of pressure, or of something moving across their skin. As we learn more, we don't just apply current, but use it to convey information, so that the person's brain begins to interpret it as natural sensation. We're still doing baby talk right now – we can communicate in a basic way, but we have a lot of language to learn.

What are the next steps for the lab?

The work is still experimental and there is a lot of work to do to validate our early results. Recently, we have been able to allow a participant to go home with the device for a two-week period, which has been fascinating. From the data we record, we can see that he uses the prosthetic differently when the sensation is turned on. Without sensation, he tends to use it for bracing or holding things, but with sensation he becomes a more active user, grasping and manipulating things more often. We've learned a lot from that experience, and we're now looking to make the device suitable for longer-term use. We're adding electrodes that can communicate with the brain, so that the person can simply think about moving their fingers and it happens. Our goal is to get it feeling as much like a real hand as we can.

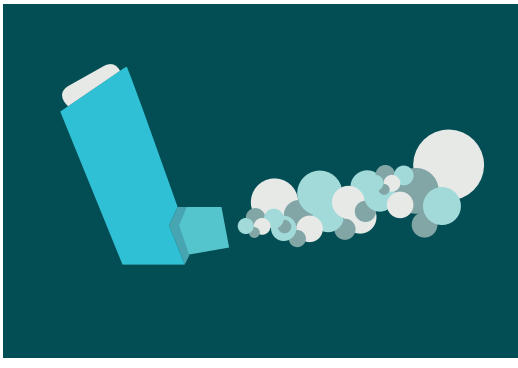
Efficacy vs Effectiveness

Tightly controlled trials are poor predictors of real-world outcomes

Traditional efficacy trials are not enough to guarantee that an intervention will work in the more diverse population seen in the clinic, according to researchers who evaluated the effectiveness of an inhaled drug combination for chronic obstructive pulmonary disease (COPD) in everyday clinical practice (1).

"Efficacy studies are limited in their usefulness to clinicians as they are often restricted in their inclusion criteria, meaning that they show what the drugs can do in a controlled setting but not necessarily what they can do in the real world," says Jørgen Vestbo, first author and professor of respiratory medicine at the University of Manchester. In fact, the authors suggest that fewer than 10 percent of COPD patients would normally be eligible for efficacy trials, since they typically exclude anyone with a coexisting condition. The investigators carried out a randomized study in patients under the care of general practitioners, without the frequency, monitoring or strict eligibility criteria of a controlled trial, to allow for the variation in adherence, dosing frequency, and inhaler technique seen in unsupervised patients.

Rather than efficacy under ideal conditions, the trial assessed the real-world effectiveness of an inhaled combination of fluticasone furoate and vilanterol. The results showed that a broad population of COPD patients benefitted from the inhalant combination, without a significantly greater risk of adverse effects. The authors argue in their paper that incorporating effectiveness trials as a standard component of the translational process would provide much clearer evidence on which to base clinical decisions.



"It's not a question of either/or," says Vestbo, "Efficacy studies are still needed; however, effectiveness studies are also required to ensure that the drugs have the expected effects in the real world." *WA*

Reference

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Making Waves – and Microbubbles

Boosting the efficacy of cancer drugs with sonoporation

The use of ultrasound to increase cell membrane permeability – sonoporation – is a fast-growing avenue of investigation (1, 2). Here, sonoporation expert Spiros Kotopoulis gives us a rapid rundown of this emerging field.

Tell us about your research.

My work at the University Hospital of Bergen in Norway primarily focuses on the therapeutic use of ultrasound and microbubbles to deliver chemotherapy drugs. We started with simply simulating bubble behavior in different situations, and moved on to studying the relationship between microbubbles, ultrasound, and drug uptake. Using high-speed microscopy, we can visualize the interaction at frame rates of up to several million frames per second. We put bubbles and cells in a culture chamber under a microscope, and apply the ultrasound, to force the microbubbles into the cells. The culmination of that work so far was a clinical trial showing that chemotherapy in conjunction with sonoporation nearly doubled the median survival time in pancreatic cancer patients, with no added side effects, compared with chemotherapy alone (1).

Is the technique restricted to cancer applications?

From disrupting the blood–brain barrier (so drugs can cross it) to increasing the rate at which bone fractures heal, there are numerous potential medical applications. The benefit of sonoporation is that you can get more of a drug into a specific location.

Ultrasound scanners are a common and easily-accessible tool – why hasn't there been more focus on sonoporation?

I think the answer is simply that there haven't been many large-scale human trials of sonoporation in action. If larger international clinical trials confirm the results from smaller trials like ours, I think it will quickly become much more widespread. Study into sonoporation is relatively recent, so research has been pretty limited. But there does seem to be an exponential increase every year, with more and more people entering the field and bigger conferences dedicated to therapeutic ultrasound.

A fantastic place to witness the growth and diversity of therapeutic ultrasound is the biannual Acoustical Society of America meeting. There are many labs working on an array of applications at the meeting, but the main bulk of the research can be split into two broad categories; high-energy ultrasound, where you burn or heat tissue, and low-energy ultrasound (sonoporation), where you make membranes more permeable to molecules. To me, both sides are very interesting and show a lot of promise, so I'm hopeful that they will develop in parallel.

What makes this an exciting field to work in?

Sonoporation is a multidisciplinary, divergent field. My background is that of an engineering physicist, and in my lab there are biologists, chemists, pharmacists, and more – all working to reach a common goal. Sonoporation may have started as physicists playing with cells, or biologists playing with ultrasound, but the increasing emphasis on translational research in science today has helped to bring us together into a distinct field.

I believe the future of sonoporation is bright. I'm optimistic that its growth will continue, and ultimately improve patients' quality of life and survival.

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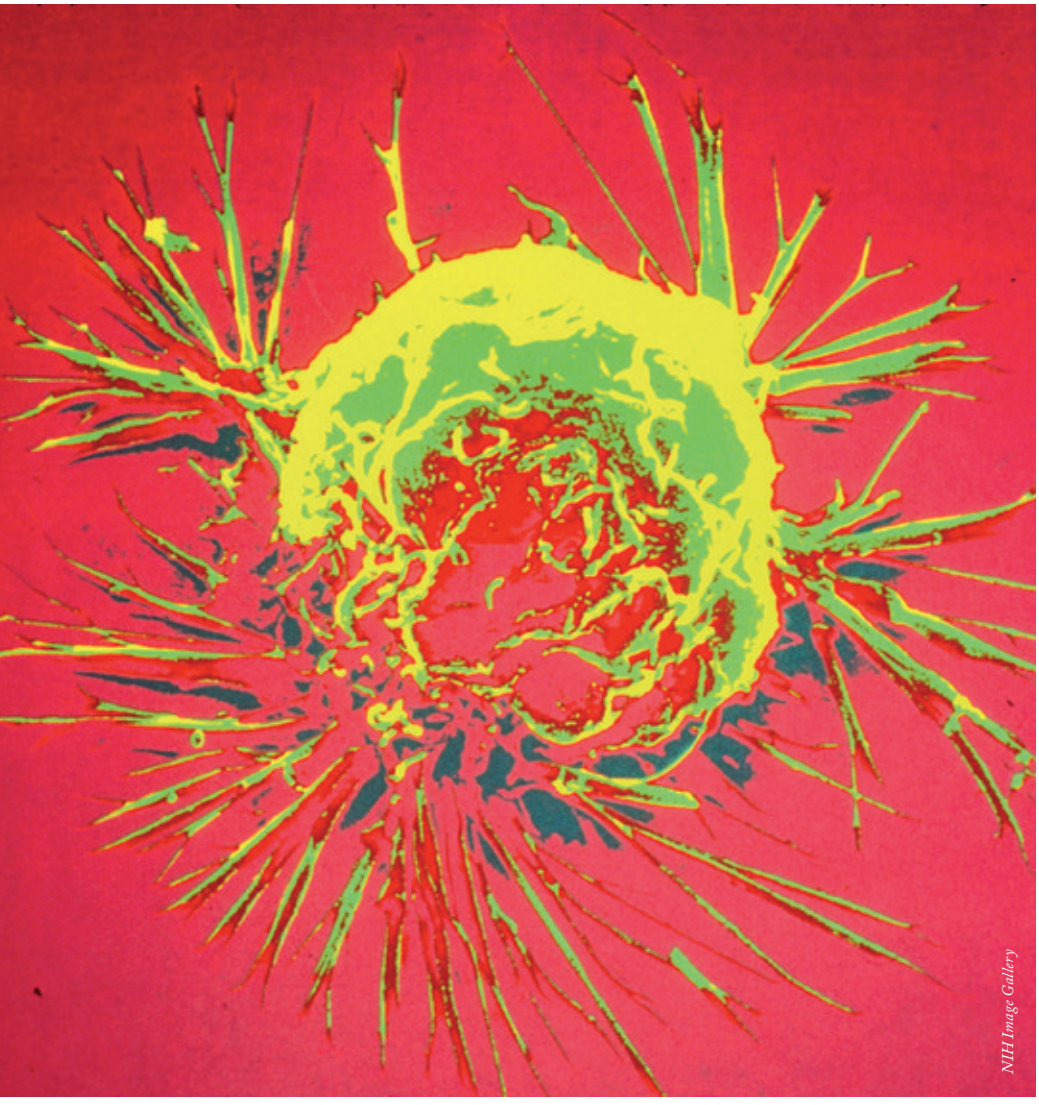

NIH Image Gallery

Rac Attack

Could a protein that "cleans house" in breast tissue be harnessed to clear cancer cells?

Researchers have discovered an important role for the Rac1 protein in remodeling breast tissue (1) – and hope that the finding could prove valuable for cancer research.

When a woman becomes pregnant, dormant cells in the breast begin a process of growth and differentiation to provide milk. After a woman has stopped breastfeeding, the milk-producing machinery in the breast must be dismantled. The new study suggests that Rac1 plays an integral role not only in preparing the breasts for lactation, but in safely clearing away redundant tissue afterwards, by inducing breast epithelial cells to become phagocytic and engulf dying cells and surplus milk.

Without this housekeeping function, the apoptotic cells would be cleared via inflammatory processes, which could lead to tissue scarring and issues in producing milk during subsequent pregnancies. It's this anti-inflammatory function that the researchers believe could be important in cancer.

"There's compelling evidence that inflammation is linked to cancer, and tumor cells become necrotic, invoking inflammatory phagocytes. If healthy breast epithelia could be stimulated to remove the dying tumor cells it would keep the inflammatory phagocytes at bay; however, considerably more research is required first" says Nasreen Akhtar, first author, and Head of the Cell Polarity and Cancer Group at The University of Sheffield.

Aside from the potential for cancer therapy, there is much more to discover about mammary epithelia, as Akhtar explains, "The mammary gland is fascinating – it is one of the very few organs that develops postnatally, so by launching a pregnancy cycle you can uncover a goldmine of information about how cells grow, organize, differentiate, die, and are removed. And what we discover in the mammary gland is likely to teach us about the way other epithelial organs function."

Akhtar and her team plan to continue investigating Rac1, as well as studying larger systems, "We are discovering the mechanisms by which our organs are shaped, using the mammary gland as a model system. Discovering how cells organize themselves within organs and how tissues are shaped is hugely important both for understanding cancer development and for organ replacement therapy, where one day we hope to grow our own organs in a tissue culture dish." *WA*

Reference

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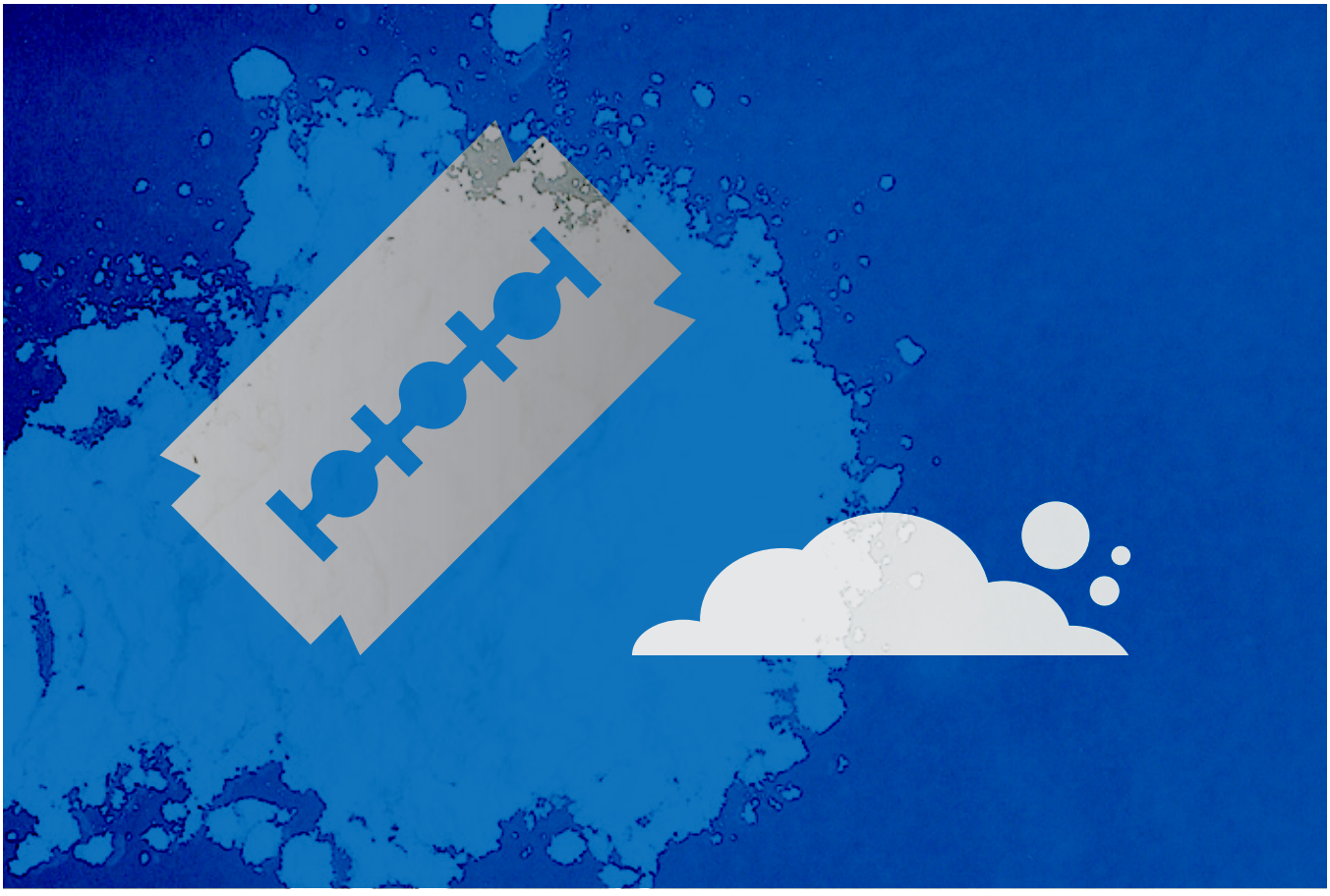

Breaking the Habit

Can a cancer drug be repurposed to cure cocaine addiction?

Illegal drug use is on the rise and there is a need for new treatments that can break addiction, particularly cocaine use, for which there is no approved medication in the US. But perhaps drugs already in development could provide a helping hand.

The key to the transition from recreational to compulsive drug user lies in the creation of long lasting memories and cues that become associated with the intense pleasure felt when taking the drug. This is especially true of cocaine, which produces its addictive effects partially by acting on the brain's limbic system. For a number of years, researchers at Cardiff University in the UK have been studying the Ras-ERK signaling pathway – a neuronal cascade involved in learning and memory, and behavior plasticity – and its role in addiction. Previous animal studies from the researchers have shown that manipulating this signaling cascade can correspondingly change behavioral responses to both cocaine and morphine (1–3).

From there, the research team began to examine whether drugs already in clinical trials could potentially inhibit Ras-ERK signaling (4). "We tested a number of MEK and RAF inhibitors already in clinical trials for cancer therapy, but only one – the MEK inhibitor PD325901 from Pfizer – effectively and completely blocked Ras-ERK signaling in the nanomolar range," says Riccardo Brambilla, lead author of the study and Professor of Neuroscience at Cardiff University.

Brambilla and his collaborators are not just relying on drugs being developed by others; they have also devised cell-penetrating peptides that hold "interesting promises" for CNS drug development. Two of the molecules – RB1 and RB3 – could also block Ras-ERK signaling.

"A single administration of both RB1/RB3 and PD325901 completely blocked expression of cocaine mediated conditioned place preference (CPP) in mice," explains Brambilla. CPP occurs when a subject prefers a location that has previously been paired with something rewarding – in this instance, cocaine. Brambilla adds, "The memory associated with cocaine is likely to be entirely erased, since it cannot be recovered after three weeks from testing."

Next, the researchers are hoping to reach a deal with Pfizer to take PD325901 to clinical testing for cocaine addiction. "We also plan to evaluate the effectiveness of PD325901 and RB1/RB3 in blocking other drugs of abuse, especially legal drugs like nicotine and alcohol," says Brambilla. *JS*

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Chiral Quest

A new synthetic route to 'one-handed' drugs

Your left and right hands are chiral objects – they are mirror images but cannot be directly superimposed over each other. Many chemical reactions create both chiral forms (enantiomers) of a molecule, something that has proved problematic when synthesizing new drugs, as the two forms may have quite different properties. In the case of thalidomide, one enantiomer acts as a sedative and anti-emetic, while its mirror image causes nerve damage and severe birth defects.

As a result, most modern drugs contain only a single enantiomer, but with few chemical reactions available that guarantee success, it is no easy task. Now, a team from The Scripps Research Institute (TSRI) have engineered a more effective way of producing a single chiral form of a molecule (1).

"Drug discovery has seen a shift of interest towards three dimensional chiral molecules due to the potential to explore new chemical space in molecular recognition in biological systems," says Jin-Quan Yu, lead researcher, and Frank and Bertha Hupp Professor of Chemistry at The Scripps Research Institute.

Yu's lab engineer asymmetry into a potential drug molecule by directing a palladium catalyst to selectively break carbon–hydrogen bonds, and replace the hydrogen molecule with a variety of aryl groups, commonly used in drug development. Previously, this has been achieved by the process of conjugate addition, which requires an additional step of creating a double bond at the carbon. The new technique is easier, more precise, and reliably produced only the desired chiral form.

"This reaction constructs a beta-chiral center, which is a cornerstone in the synthesis of chiral molecules," says Yu. The team have successfully tested the reaction with aliphatic amides and free carboxylic acids – common starting compounds for drug synthesis – and hope to expand the technique further. TSRI partner Bristol Myers-Squibb is already applying the new reaction to make a chiral amino acid needed to produce a candidate drug. *WA*

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

When is a Negative a Positive?

Therapeutic successes of cancer drugs in mice are common, and yet failure is the norm in clinical trials. Improving mouse cancer therapy models will require a change in attitude about the value of publishing "negative" results.

By Robert S. Kerbel, Sunnybrook Research Institute, University of Toronto, Canada.

If one browses through the preclinical cancer research literature, past and present, it becomes apparent that thousands of papers have been published reporting highly encouraging therapeutic outcomes of new drugs in mice. In striking contrast, the majority of randomized phase III oncology clinical trials (over 60 percent) are negative (1). Such clinical failures add to the enormous cost of the cancer drugs that do make it to market. Not to mention that they also highlight how huge numbers of patients enrolled in trials end up being treated with ineffective therapies. What is the source of this discrepancy? How can mouse cancer therapy models be improved to minimize it? Moreover, what are the implications for publication when using such improved models?

There are numerous proposed reasons for the failure of mouse studies to more faithfully predict clinical outcomes. Only three will be mentioned here, not only because they are rarely considered, but also because of the financial and publication problems they pose. First, there is the issue of sample size and statistical power. Typically, groups of 6–10 mice (or fewer) are used in most studies, resulting in a high risk of false positives. Second, there is the problem of age. The vast majority of mouse therapy studies involve treatment of mice that are around 2–4 months old – the clinical equivalent of pediatric oncology patients. The way much older adult cancer patients metabolize and handle drugs can be vastly different to their pediatric counterparts. Yet using mice that are over one year of age is rare – and prohibitively expensive. Third, most mouse therapy studies involve treatment of localized primary tumors. In contrast, the therapeutic target in phase I, II, and most phase III trials is distant, difficult-to-treat metastatic disease in sites such as the brain, liver, lungs, and bone. Replicating treatment of late-stage disease in mice is much more complex, cumbersome, and expensive. Researchers don't like to do it.

"We must not let significantly increased preclinical costs deter enthusiasm for a rigorous approach."

So let's suppose that we consider dealing with all three of these problems in an experimental design. For example, we might start with a large number of older mice (12–15 per group) and direct treatment towards established visceral metastatic disease, using clinically relevant endpoints, such as progression-free or overall survival. Three serious problems would emerge. First, the financial cost would be daunting – what funding agency would support such studies? Second, the therapy outcomes, in most cases, would likely be negative or somewhat disappointing. If so, how do we ask graduate students or postdoctoral fellows to undertake such studies? The second point also drives the third problem: how do you get "negative" results, no matter how rigorous they are, to be published in respected journals?

Considering the cost of a single failed randomized phase III oncology trial (usually over $100 million) we must not let significantly increased preclinical costs deter enthusiasm for such a rigorous approach. Regarding the second and third problems, a change in attitude by editors and reviewers about publishing "negative" results based on excellent preclinical studies, would be a good start.

We all need to accept that the high rates of failure in oncology drug development are the norm and ought to be reflected in more realistic preclinical studies, which will make the "positive" exceptions all the more promising.

Reference

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Diversity, Equity, and Problem-solving

Organizational psychology tells us that if we want to solve the type of complex problems often thrown up by biomedical science, we need diverse teams.

Kimberly Tanner, Professor and Director, SEPAL, SFSU Department of Biology, University of California San Francisco, USA.

As director of the Science Education Partnership and Assessment Laboratory (SEPAL) research group, I help oversee the lab's three main aims:

1. We study difficulties in biology learning.
2. We work on discovery learning.
3. We promote diversity and equity.

It's important to understand that diversity and equity aren't just about being nice – they're also about solving complex problems. Studies have shown that divergent points of view are how we access new ways of thinking (1), which can lead to improved avenues of research. To facilitate that, we need to encourage diversity in the scientists of tomorrow. Unfortunately, there is evidence to suggest that there isn't always a welcoming atmosphere for students who aren't from the dominant culture here in the US. And it's driving away young scientists who may otherwise have significantly contributed to the field.

Much of problem stems from a bias known as stereotype threat, which includes marginalizing a subset of students. For example, if you take a group of students who all score above the 85th percentile for math and tell them that women aren't as good at math as men before they take a related test, the scores of the women in the group plummet by around 50 percent (2).

Faculty tend to elaborately plan the scientific content of their teaching, but the unplanned, non-scientific part of their interaction with students can have huge psychological and sociological influences, so that's where SEPAL steps in. We're interested in retaining more students in the sciences – biology in particular – and trying to make sure that the perspectives retained in the discipline are diverse. That diversity could relate to cultural background, gender, socioeconomic status, and much more.

Traditional methods of teaching generally involve the faculty telling the students what the current state of knowledge in their discipline is, but we're encouraging a much more active learning process. A major part of what we do at SEPAL involves professional development. In the US, we all-too-often train scientists to be outstanding researchers, then dropkick them into teaching college classes all over the country without much training in how to teach other people. SEPAL wants to support those talented, dedicated

"It's important to understand that diversity and equity aren't just about being nice – they're also about solving complex problems."

researchers in doing the best job possible in the classroom, which includes encouraging their lessons to involve more real-world scientific problems to promote problem-solving skills. We also collect data from students about their learning experience and engagement in the classroom, which we then give to the faculty to help them learn what their students' aspirations and misconceptions are.

I've been at SFSU for 12 years and I definitely came here with the intention to make the experience of students more positive, but you don't accomplish that as one person. You need an engaged community too; 85 percent of our faculty here have spent at least 100 hours on professional development, which is unheard of. I'm incredibly proud that we've stepped up to the plate, and I think faculties across the country will soon do the same. We're making real progress at SFSU, but like everyone else, we still have quite a way to go.

Kimberly Tanner was interviewed by William Aryitey

References

1. *KW Phillips, "How diversity makes us smarter", Scientific American, 1 October (2014). Available at: http://bit.ly/1qLZR2E. Accessed August 8, 2016.*
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Beyond the Moon

The launch of a new data sharing initiative in cancer genomics has been welcomed by doctors and data scientists alike. To make the most of this unique opportunity, we can't lose sight of the practicalities.

By Jens Hoefkens, Director of Research, Strategic Marketing, Informatics, PerkinElmer, Inc., Waltham, Massachusetts, USA.

Over the past few months, the scientific community has responded eagerly to the creation of the National Cancer Institute's Genomic Data Commons (GDC) – a first-of-its kind, open-access cancer database that will ultimately help advance Vice President Joe Biden's Cancer Moonshot Initiative.

The GDC is a step in the right direction and has the potential to help the scientific community advance their understanding of complex diseases, such as cancer. Public data sets, including The Cancer Genome Atlas (TCGA) and the 1000 Genomes Project, have already contributed to our evolving understanding of, and approach to, disease research. For example, according to the National Cancer Institute and National Human Genome Research Institute, the publicly available TCGA dataset includes 2.5 petabytes of data from over 11,000 patients, and has already contributed to more than a thousand cancer studies for 33 types of cancer. And though most agree that greater data sharing will benefit cancer researchers, the details of how best to support such a monumental database are less clear and present a number of interesting challenges. Through my experience working with customers and their multitude of research partners, I know that developing the necessary infrastructure to support the integration of data from varying sources – and different types – will be the cornerstone of success for this unique database.

As we've seen in other examples of translational research and pharmaceutical R&D, increasingly large datasets from diverse high-content methodologies, such as genomics, are typically stored in silos, which makes access and searching more difficult (or impossible). Here are some of the most common challenges we've seen researchers and scientists encounter

when trying to integrate disparate data sources and varieties:

1. Availability of data. The willingness and ability of researchers to share their data varies; some organizations may not want to share proprietary information about their genomic trials.
2. Consent and legal issues. Publication of data may not be a part of patient consent procedures.
3. Scope. Although genomics is an important piece of translational medicine, there are many other profiling technologies not supported by the GDC. A good example comes from PerkinElmer's Quantitative Pathology team. While PD-L1 expression (genomics in nature) is an important biomarker for cancer immunotherapies, studies have shown that spatial distribution of immune system cells around the tumor can also be a predictor of response to treatment. The digital pathology data required for this kind of analysis are not currently in scope for the GDC.
4. Access control. The GDC is designed to be an open platform and has little focus on restrictions. Though an open-access strategy makes sense for sharing public data, access controls are an important and complex part of a commercial solution dealing with clinical data.

Researchers need – and want – to be able to easily aggregate internal and external data, while maintaining their focus on the science. Complementary systems offered by experienced and specialized companies can help mitigate the challenges and advance collaborative efforts. Ultimately, the data that need to be integrated fall into three categories: public data, in-house data that could be public, and in-house data that cannot be public. The GDC gives companies the tools to make the second kind of data public. However, it's the integration tools that will allow companies to merge their proprietary data (e.g., data from ongoing clinical trials or patient data from patients who have not consented for their data to be publicly available). These integration solutions can contribute to greater insights and faster conclusions about potential treatments. With self-service access to a wide variety of data, researchers can more efficiently identify and manage biomarkers, which could help to streamline the development of drugs tailored to unique health needs.

"Researchers need – and want – to be able to easily aggregate internal and external data, while maintaining their focus on the science."

Data sharing in itself is not enough to accelerate cures – researchers also need the appropriate tools to interpret, visualize, and analyze data. Ultimately, ensuring the success of the GDC may not only lead us closer to a cure for cancer, but also transform the way we approach translational research for a wide range of additional diseases.

THE ART OF TRANSLATION

Join us on a journey through the wonderful and diverse world of translational science. From art inspired by science, to microscopy images reminiscent of abstract paintings – beauty abounds.

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Art Meets Science
These artists have taken their inspiration from the body – in sickness and health.

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Fantastic Voyage
Exploring the building blocks of the body – beautiful images of life at a cellular level.

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Amazing Animals
Animal models are a vital component of the translational pathway – and a source of incredible images.

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New tools and techniques are giving us a close-up view of cells and organs.

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New therapeutics or diagnostics in preclinical development.

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Into the Patient
Translation in action, as science and engineering turns to medicine.

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Guess What?
Can you identify our mystery images? Answers at the bottom of the page.

Art Meets Science

These artists have taken their inspiration from the body – in sickness and health.

Brains and Beauty

Elizabeth Jameson uses MRI scans as a starting point for images that capture the mystery and beauty of the brain. She says, “Reclaiming my MRIs through printmaking, color, and the elements of design disrupts the unsightliness of these digital images and allows a view of the brain that combines beauty and complexity."

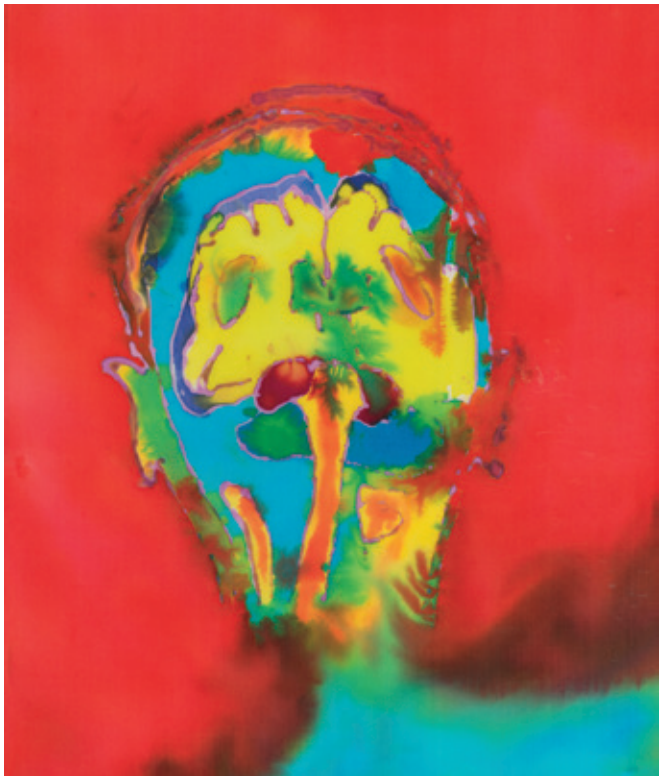
Shown here is "Valentine", a coronal view of the Artist’s brain stem, cerebellum, and lateral ventricles.

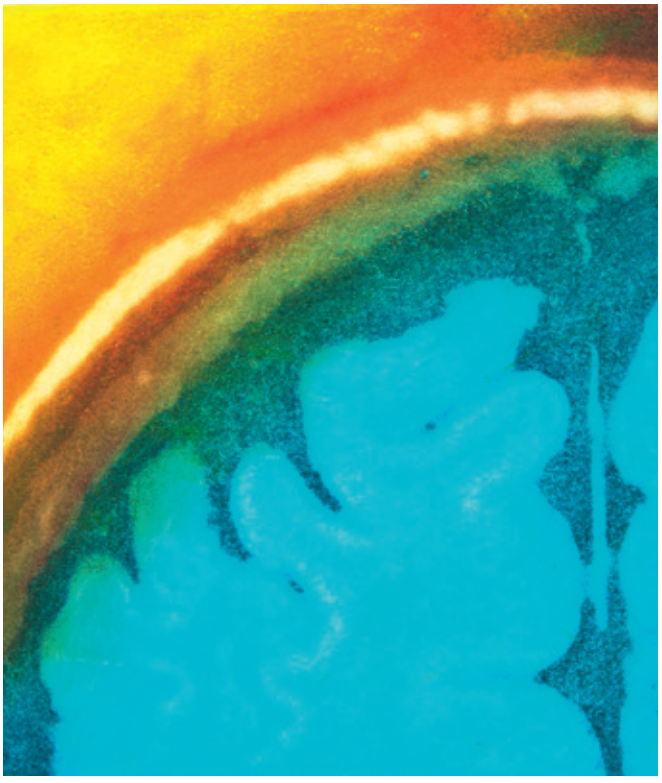
Credit: Elizabeth Jameson, www.jamesonfineart.com

A Tiny World of Green and Gold

Artist Sara Parent-Ramos has been inspired by the microbiome. She says “In my work I explore the wonderful and terrifyingly elusive world thriving inside and outside us, blurring the boundaries between the microscopic and macroscopic in an effort to raise questions about the extent of human agency.” This sculpture is entitled "Symbiont Commensal Parasite 1".

Credit: Sara Parent-Ramos





Self Portrait of the Artist's Brain 2

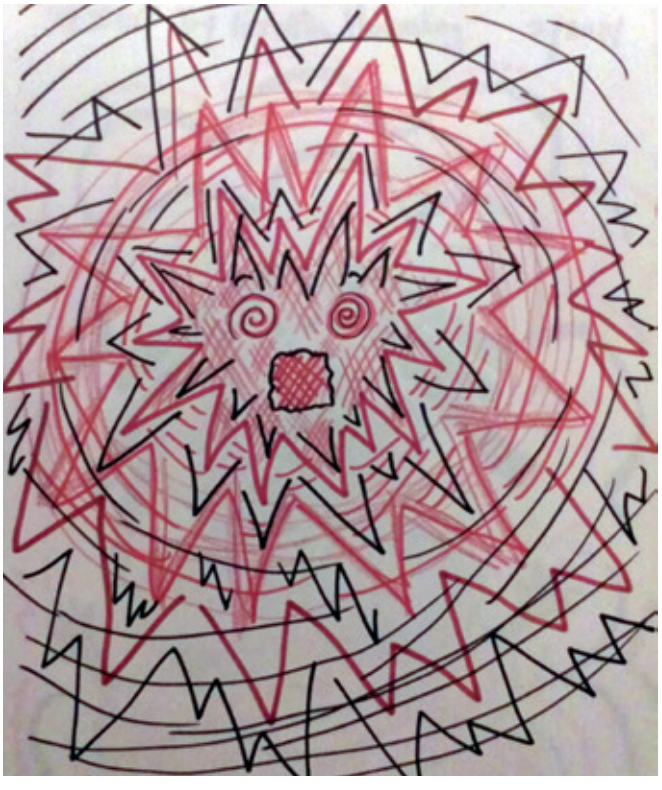
Sagittal MRI view of the artist's brain. A silk painting of an abstract view of the artist's brain. It contains all the emotion and chaos that a black and white brain scan cannot convey.

Credit: Elizabeth Jameson, www.jamesonfineart.com

Emerging

Coronal view of the neo-cortex. "Emerging" shows both the interior and the exterior of the brain. The bright white line of the skull in between acts as the divide between mankind and the universe beyond.

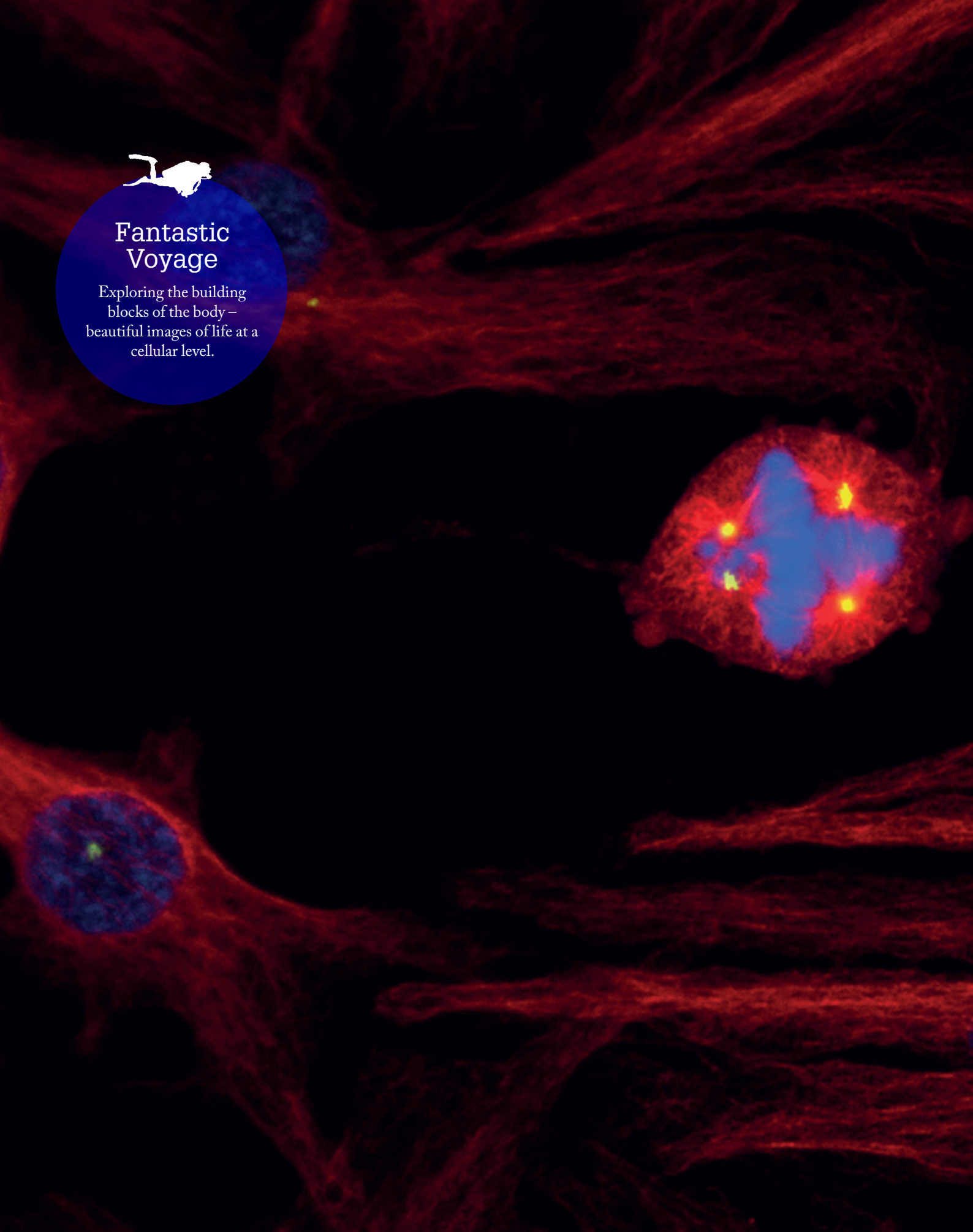
Credit: Elizabeth Jameson, www.jamesonfineart.com



Attack of Overwhelm

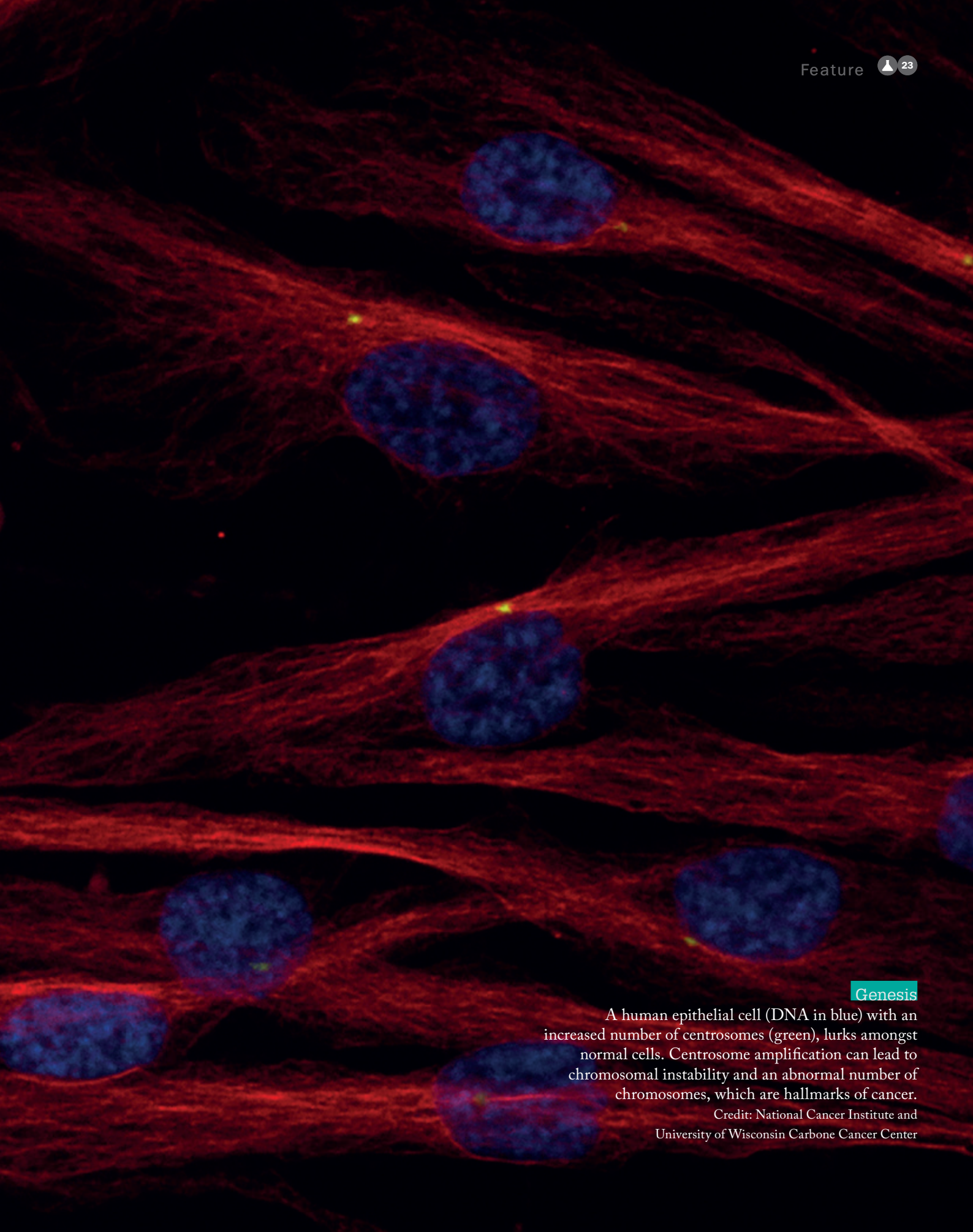
The PAIN Exhibit is an online educational visual arts exhibit, showcasing work from artists with chronic pain. www.painexhibit.org

Credit: Gretta Hansing



Fantastic Voyage

Exploring the building blocks of the body – beautiful images of life at a cellular level.



Genesis

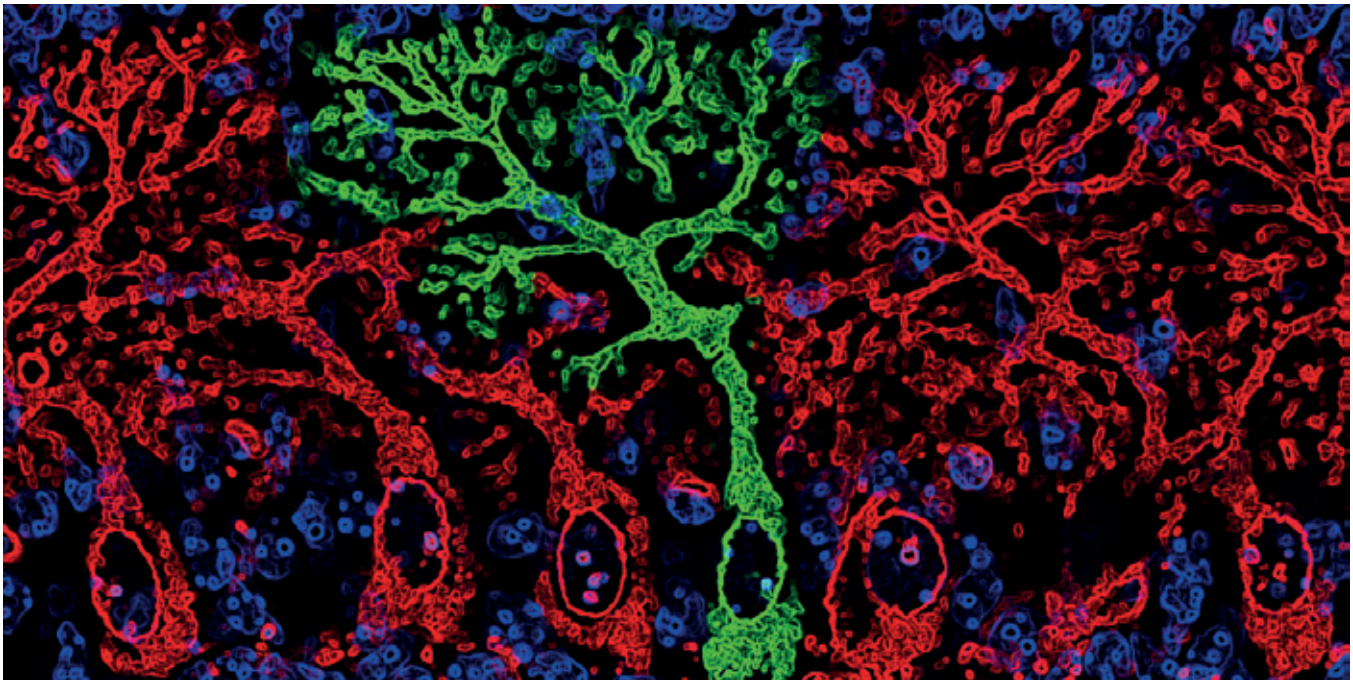
A human epithelial cell (DNA in blue) with an increased number of centrosomes (green), lurks amongst normal cells. Centrosome amplification can lead to chromosomal instability and an abnormal number of chromosomes, which are hallmarks of cancer.

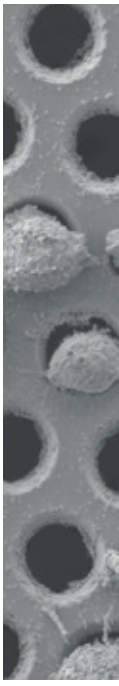
Credit: National Cancer Institute and University of Wisconsin Carbone Cancer Center

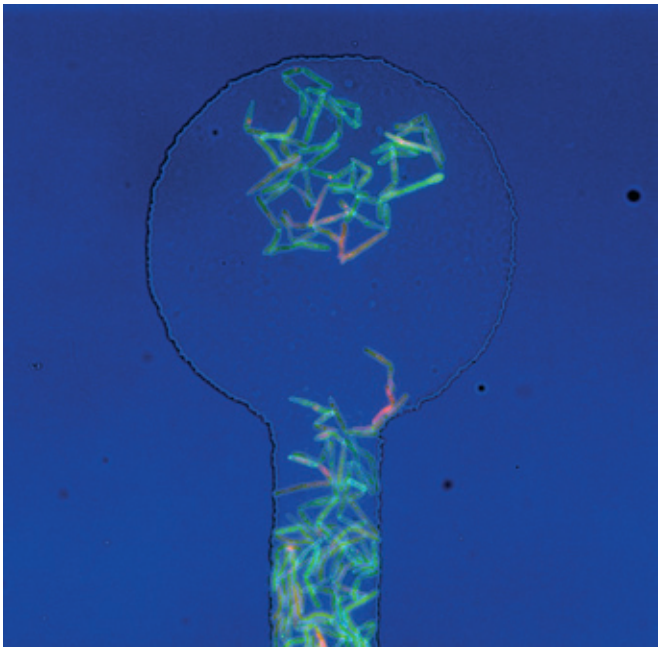
Tree of Life

Mouse cerebellum stained to reveal a Purkinje neuron (green), by researchers studying the expression of ALS-associated genes in the brain.

Credit: Andrew L. Bashford and Vasanta Subramanian, University of Bath



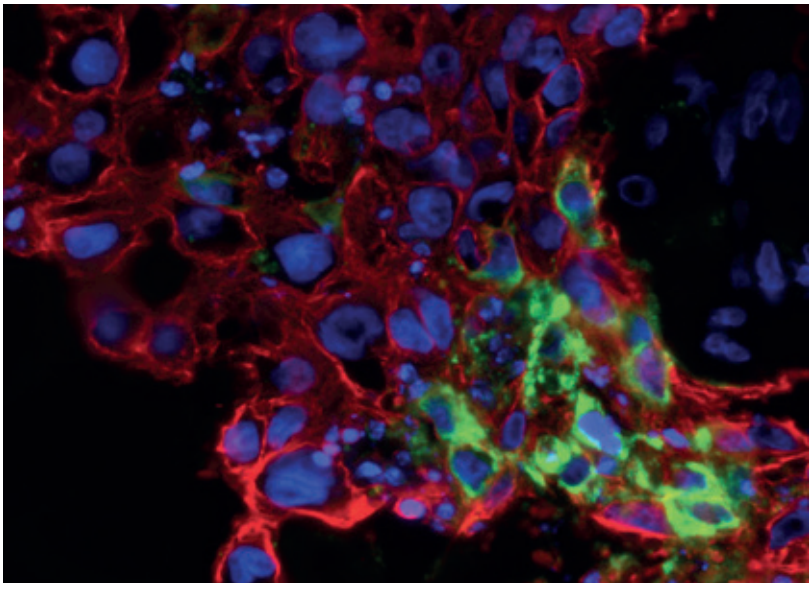




Microbes and Microfluidics

Mycobacteria growing in a microfluidic chamber. Individual mycobacteria respond differently to the antibiotic rifampicin, even if they are genetically identical.

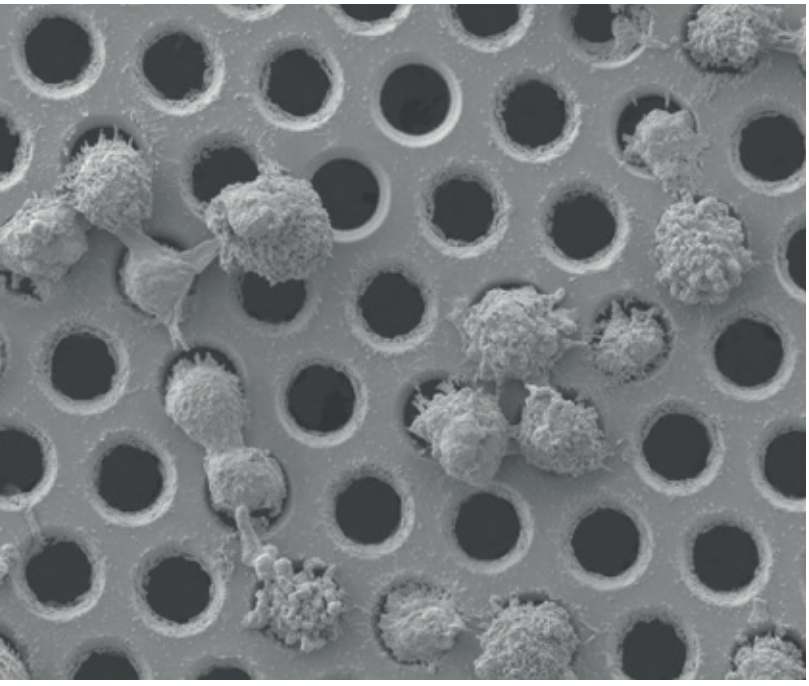
Credit: Bree Aldridge, Tufts University

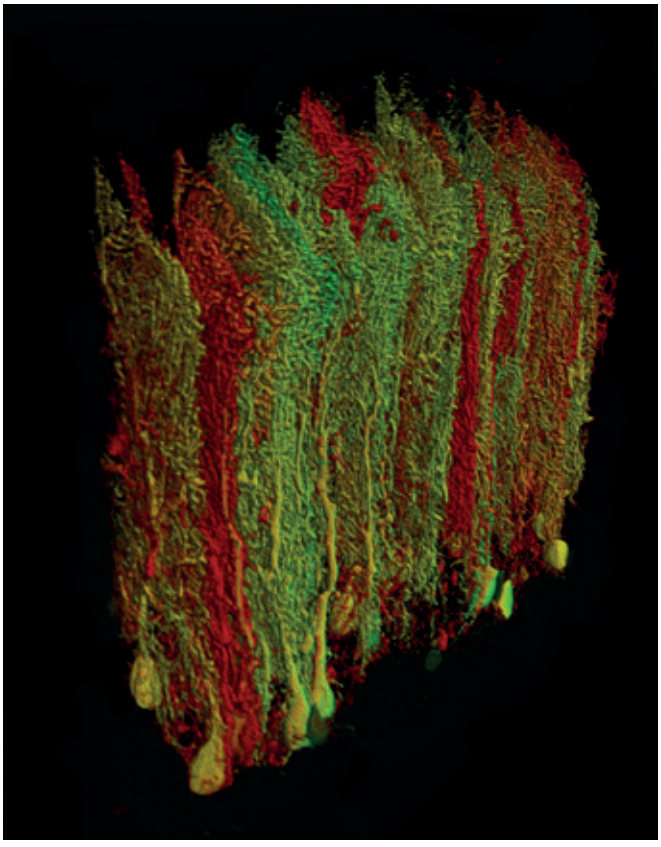


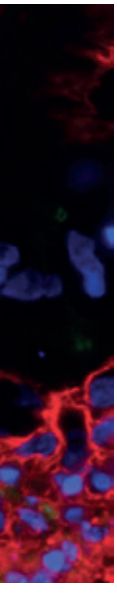
Mapping Zika's Routes to the Fetus

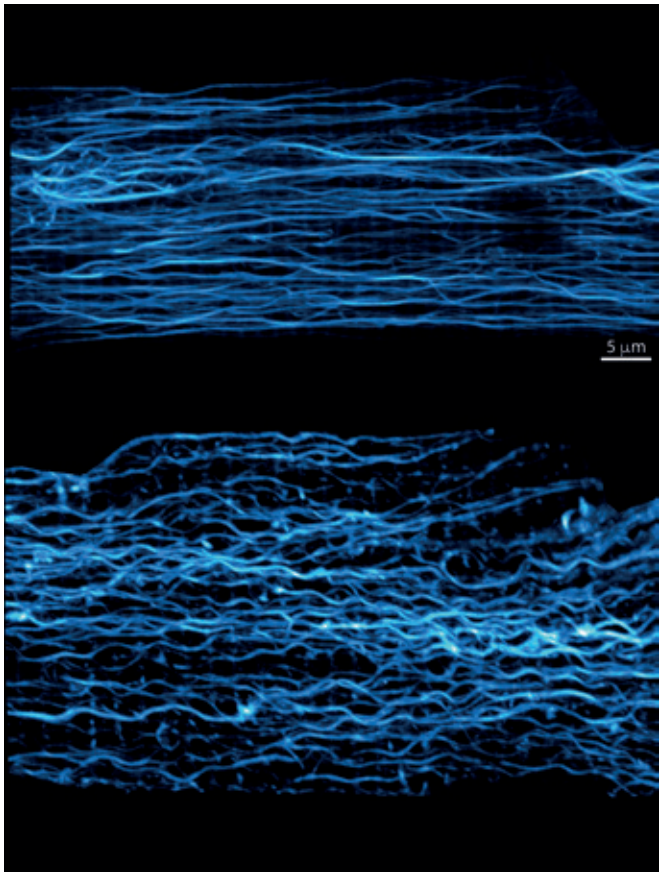
Cytotrophoblasts (red) in the chorionic villi are stained green with antibodies to a non-structural Zika virus protein, indicating active replication of the virus. Blue highlights the cell nucleus. The researchers were able to identify two routes from mother to fetus (amniotic and placental) and found that the antibiotic duramycin blocked infection of cells involved in both.

Credit: Takako Tabata









Cancer Clusters

Clusters of human endothelial cells captured using a custom-designed micro-device. By analyzing the captured cells, researchers at A*STAR have cast doubt on the 50-year-old theory that the clusters cause metastasis.

Credit: Min-Han Tan et al. / Institute of Bioengineering and Nanotechnology

Dimensions

This 3D rendering from fluorescent images shows neuronal Purkinje cells, in part of a study exploring how they transmit data during sensorimotor coordination.

Credit: OIST

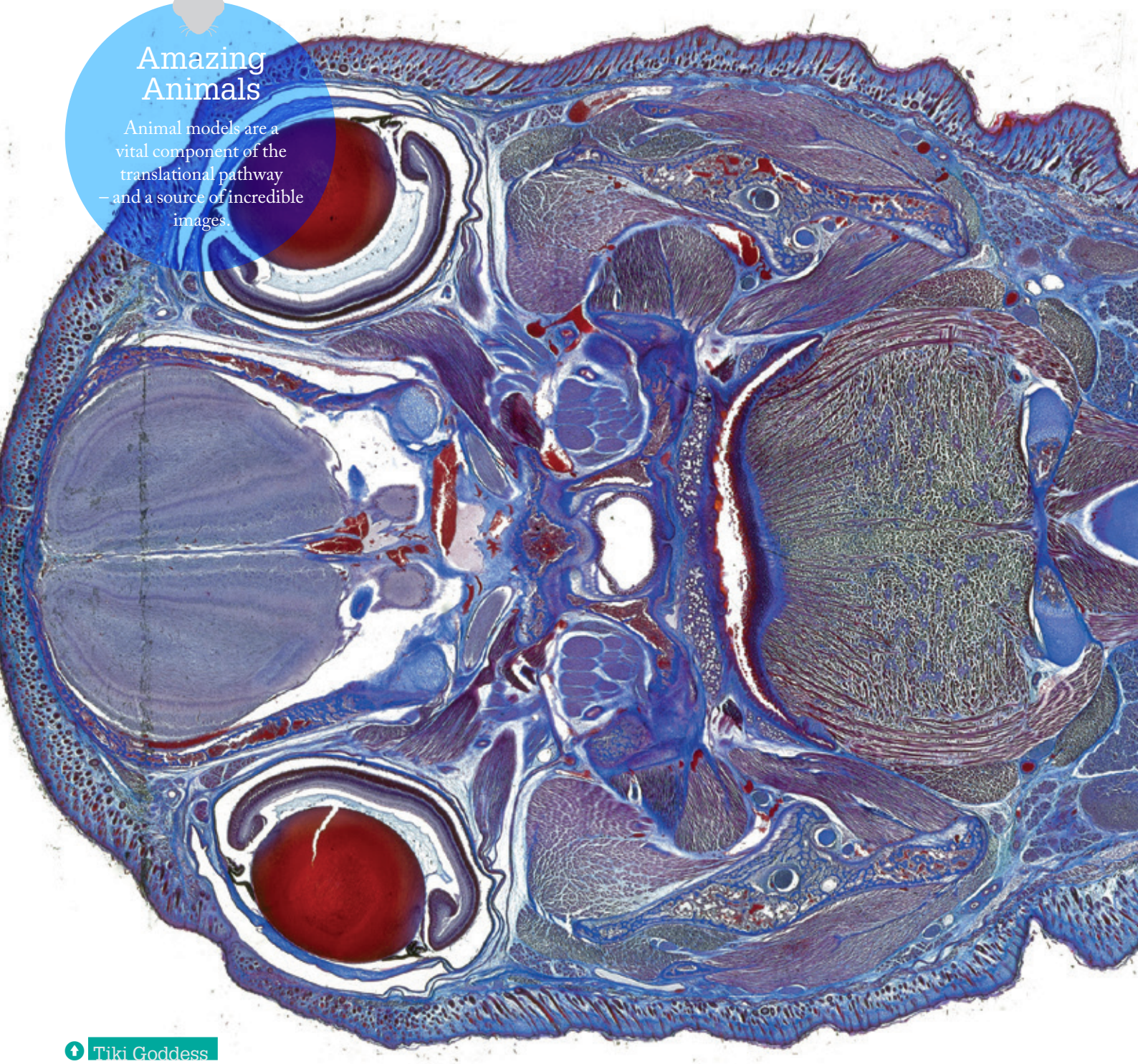
Be Still My Beating Heart

Microtubules in a cardiomyocyte at rest (top) and when compressed (bottom). The Prosser lab is gaining new insights into the mechanics of the process.

Credit: Ben Prosser lab, Perelman School of Medicine, University of Pennsylvania

Amazing Animals

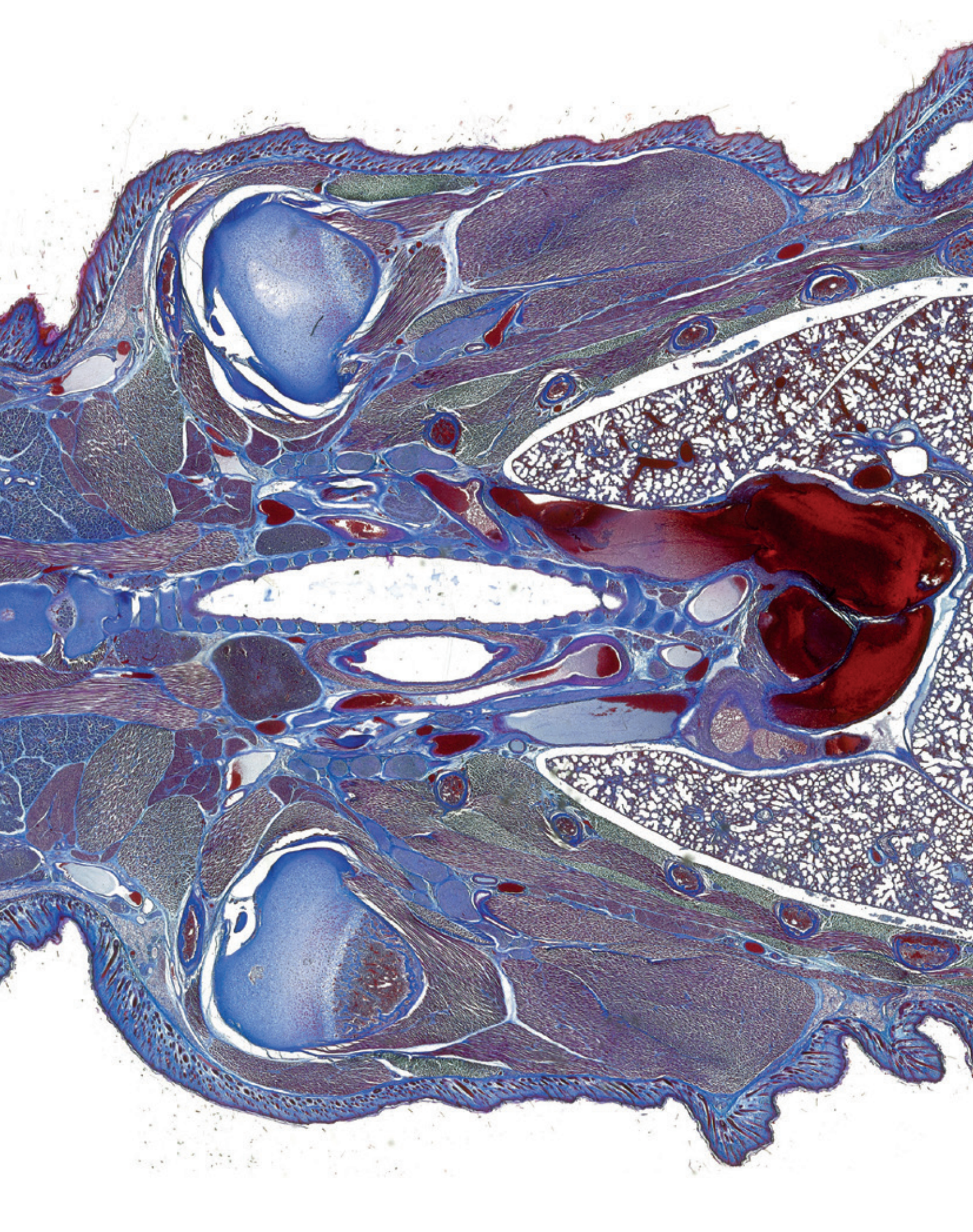
Animal models are a vital component of the translational pathway – and a source of incredible images.



Tiki Goddess

A trichrome-stained frontal baby mouse tissue section. http://bit.ly/2cHqi7U

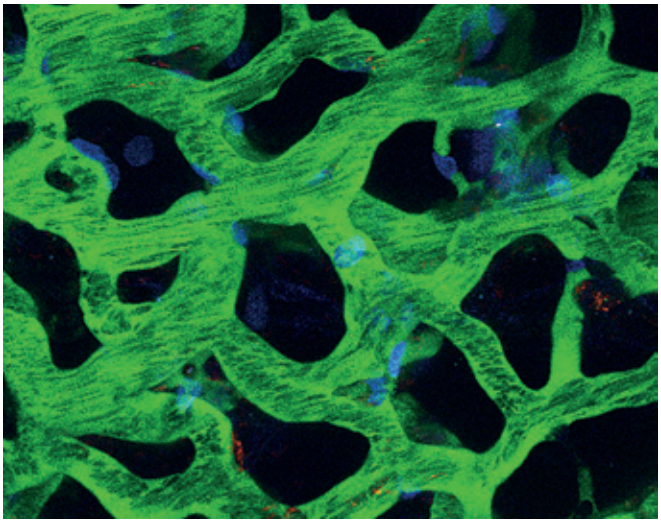
Credit: George McNamara

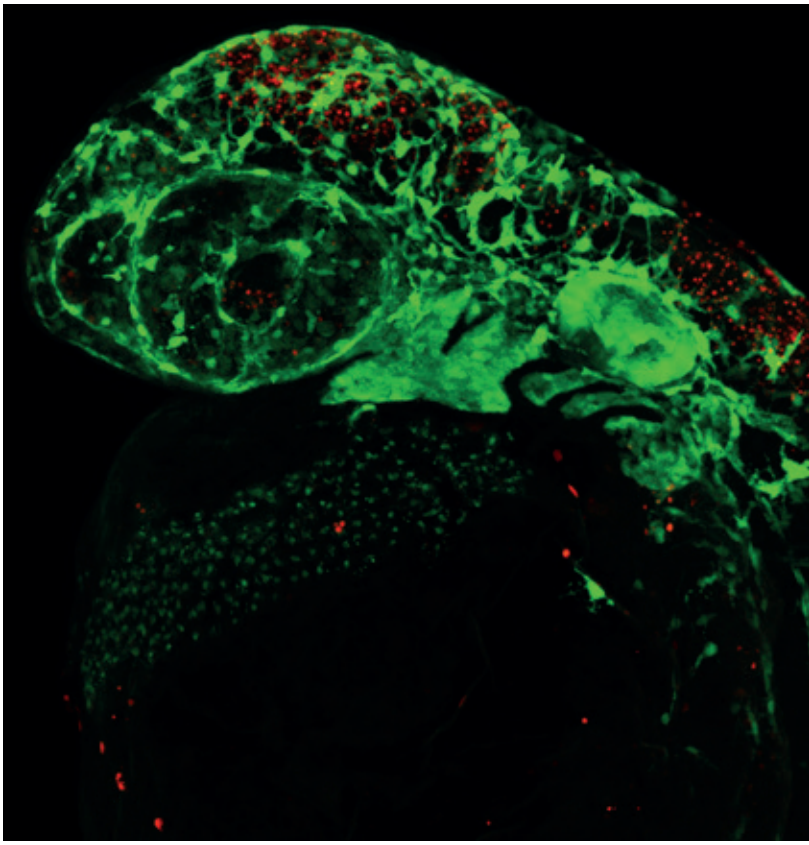


Living Lungs

Three-dimensional reconstruction of FITC-labeled pulmonary microvasculature (green) surrounding normal alveolar airspaces (dark regions), imaged with intravital two-photon microscopy in real time in a living (fully anesthetized) rat. Nuclei are stained blue and neutrophils orange. Red blood cells flowing through the microvessels appear as black streaks.

Credit: Mary Beth Brown, Robert G. Presson Jr, Amanda J. Fisher, Ruben M. Sandoval, Kenneth W. Dunn, and Irina Petrache





A Fragile Web

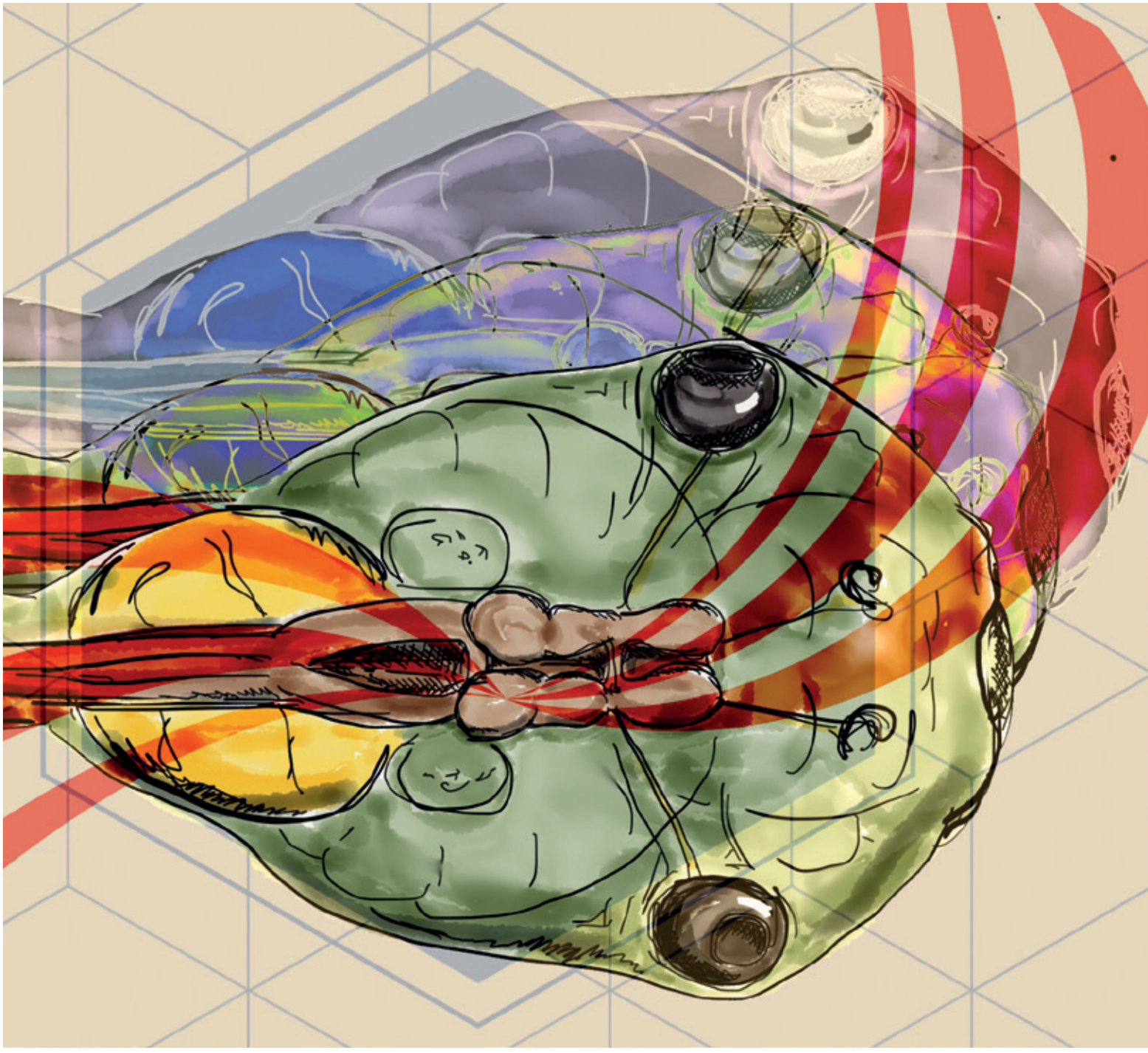
Visualization of the coronary vasculature patterning of an adult mouse heart. By studying expression of ErbB2, Penn researchers have shed light on the cardiovascular risks of breast cancer drug trastuzumab.

Credit: Young Kuk Cho and Haig Aghajanian, Perelman School of Medicine at the University of Pennsylvania

Forming a Face

Cell death (red) within the neural crest cell progenitor population results in fewer neural crest cells (green) in a *polr1d* mutant zebrafish embryo, showing how the mutation causes Treacher-Collins syndrome in humans.

Credit: Kristin Watt and Paul Trainor, Sowers Institute for Medical Research



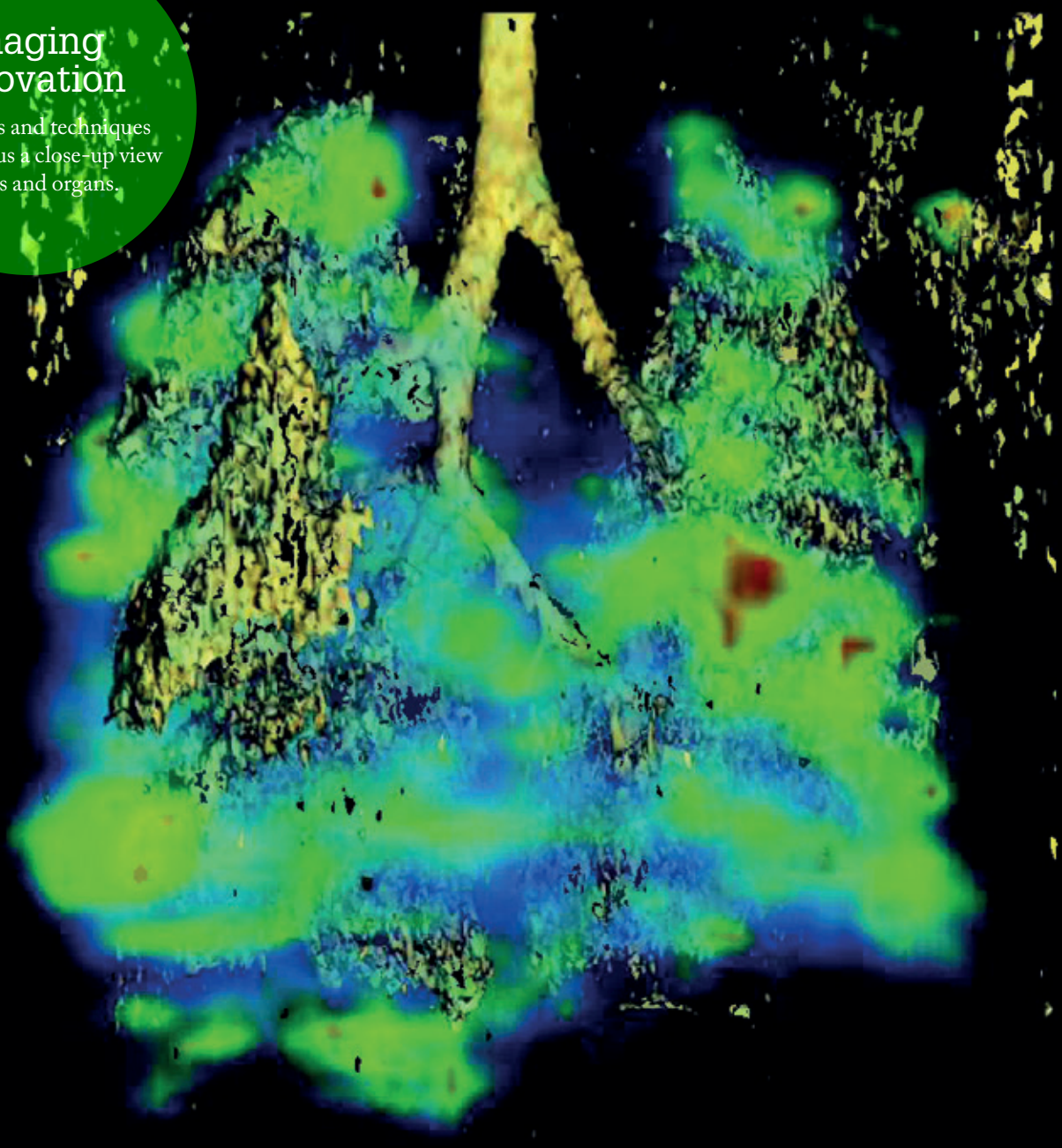
Sensory Overlap

A less common animal model, the tadpole, was used to reveal how the brain develops the ability to sense when different sensory inputs are simultaneous.

Credit: Carlos Aizenman

Imaging Innovation

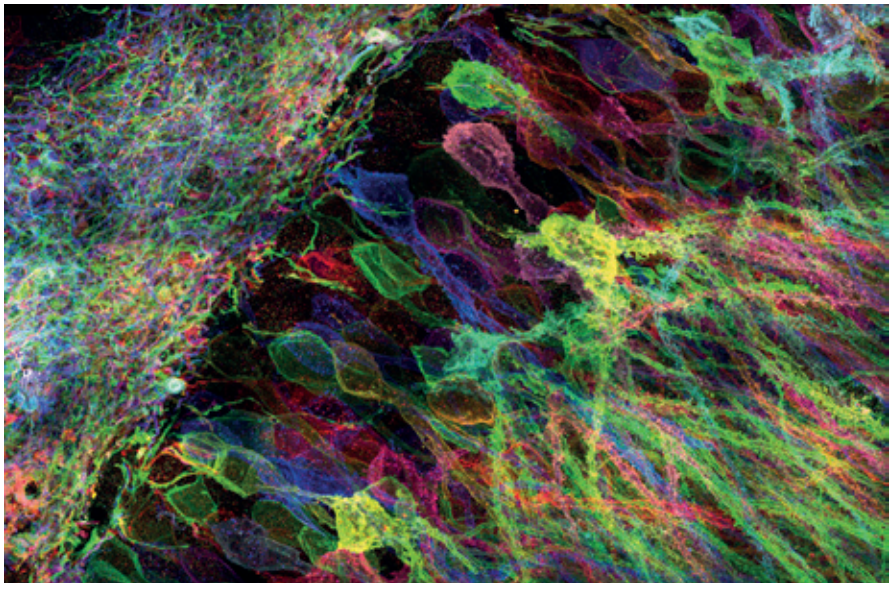
New tools and techniques are giving us a close-up view of cells and organs.



Multimodality Imaging

In a metastatic model of melanoma, a lung CAT scan (in solid yellow) is fused with a SPECT image highlighting metastatic lesions (blue-to-red to indicate lesion density).

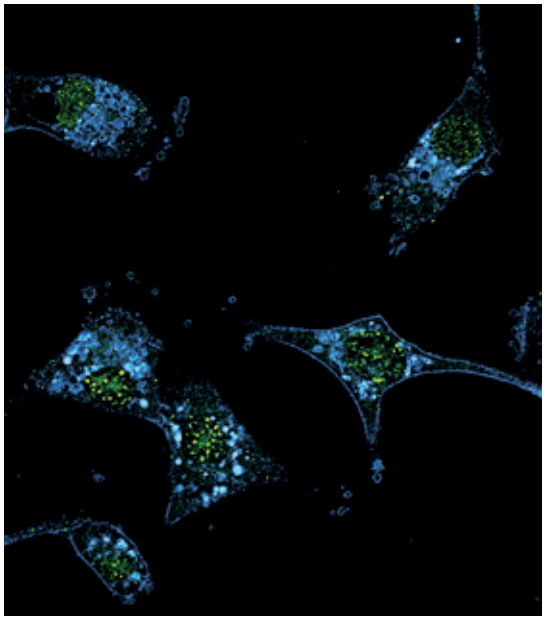
Credit: National Cancer Institute



RNA at the Nanoscale

MIT researchers have developed a new way to image proteins and RNA inside neurons of intact brain tissue, using expansion microscopy.

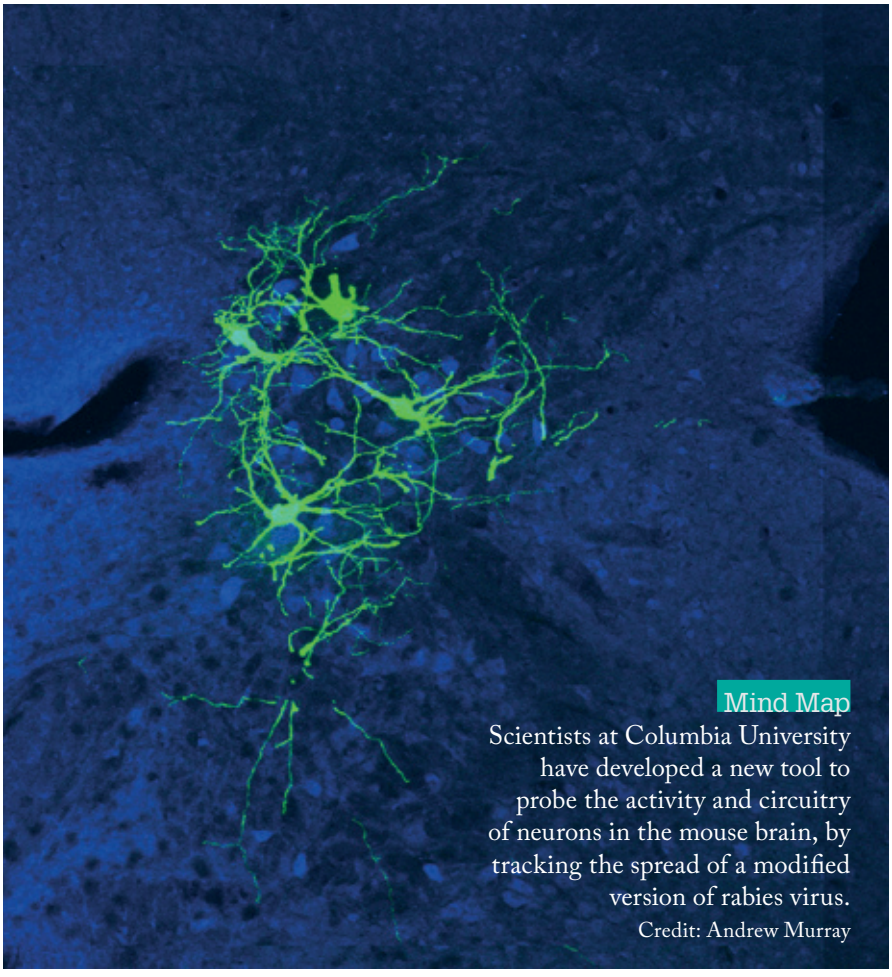
Credit: Yosuke Bando, Fei Chen, Dawen Cai, Ed Boyden, and Young Gyu



Smart Probes

SmartFlare Detection Probes, developed at Northwestern University, isolate Nodal-positive melanoma cells from a heterogeneous population. The Nodal-positive cells (blue) are also positive for CD-133 (green), another biomarker associated with cancer stem cells and drug resistance.

Credit: National Cancer Institute



Mind Map

Scientists at Columbia University have developed a new tool to probe the activity and circuitry of neurons in the mouse brain, by tracking the spread of a modified version of rabies virus.

Credit: Andrew Murray

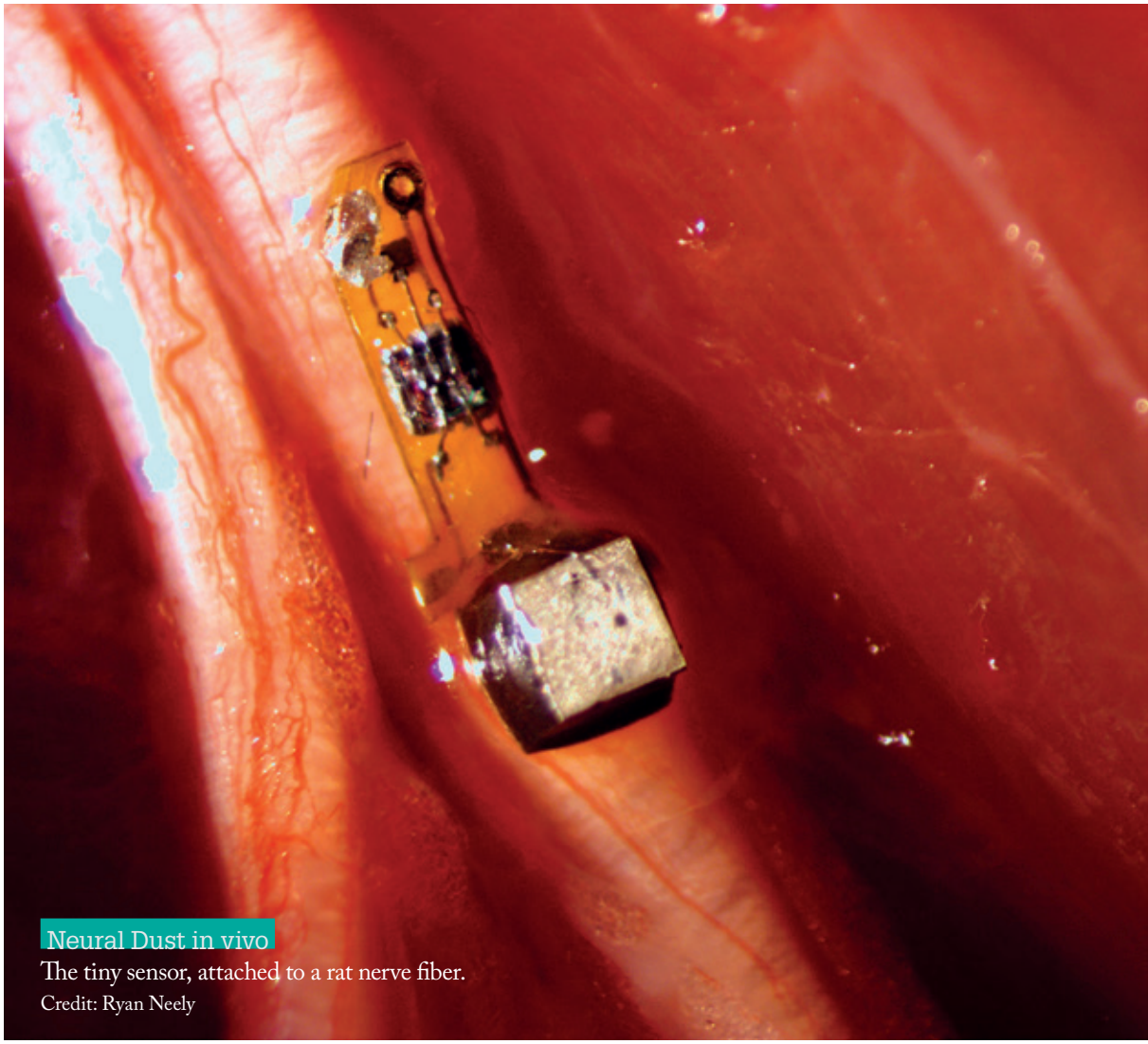
Breaking Through

New therapeutics or diagnostics, in preclinical development.

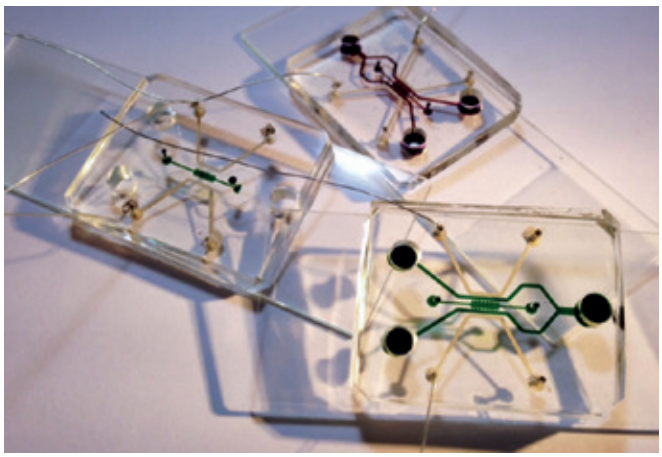
Neural Dust

University of California, Berkeley engineers have built a tiny, wireless sensor - dubbed neural dust - that can be implanted in the body. Once implanted, the battery-less sensor is powered (and the data read out) by ultrasound.

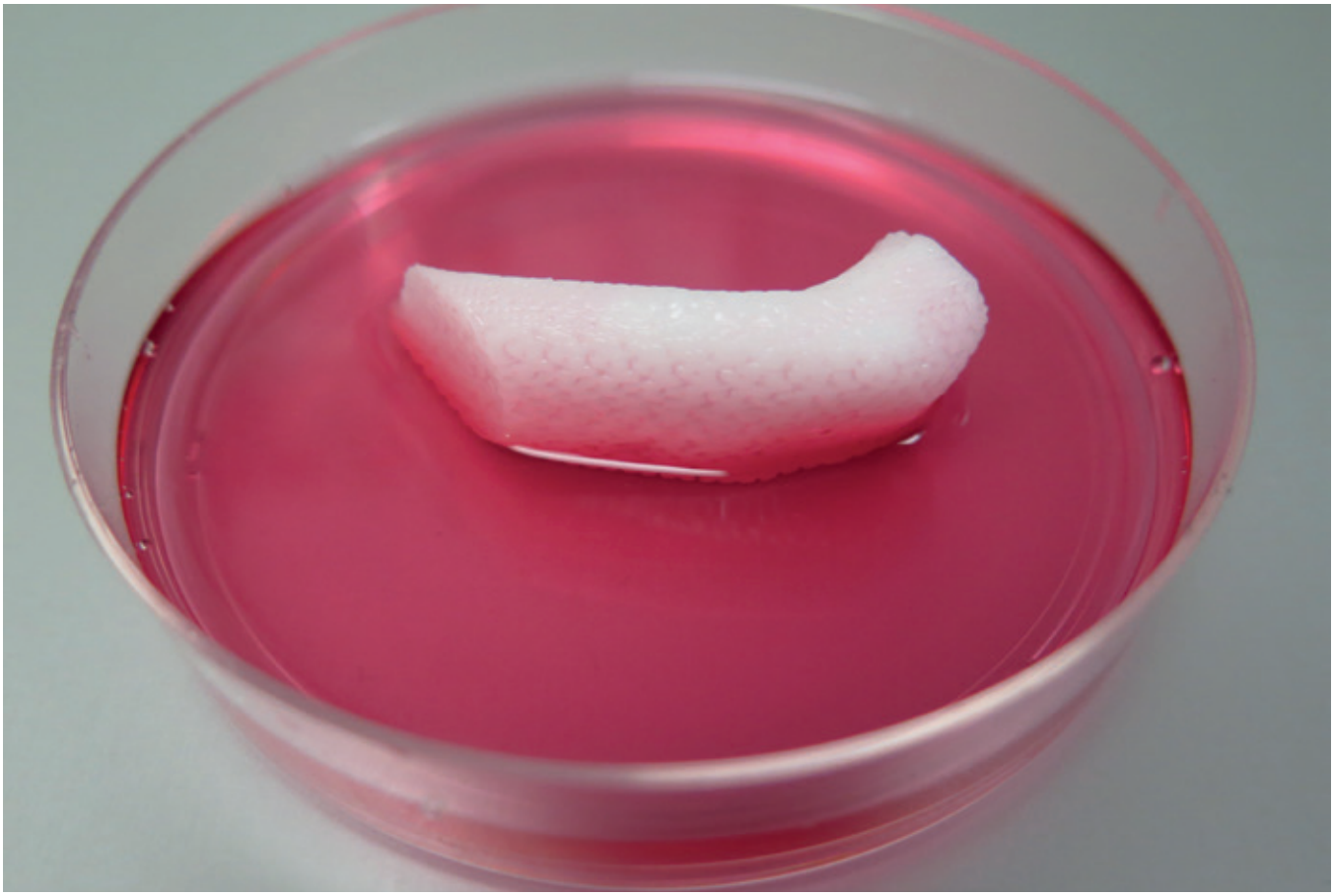
Credit: Ryan Neely

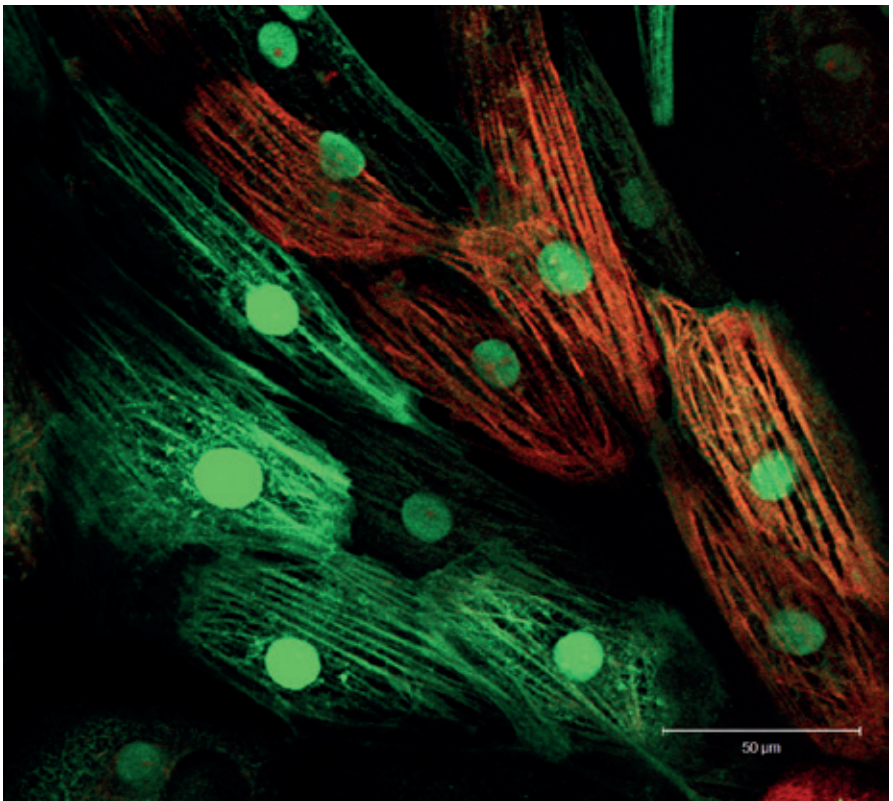


Neural Dust in vivo
The tiny sensor, attached to a rat nerve fiber.
Credit: Ryan Neely



Cancer Force Field
The Singapore–MIT Alliance for Research and Technology (SMART) has designed microfluidic devices to help scientists identify safe ranges of electric fields that might be used to noninvasively treat cancer.
Credit: SMART





Printing Bone

Wake Forest Institute for Regenerative Medicine caused a stir earlier this year by unveiling a 3D printer capable of printing living tissues – in this case a segment of jaw bone.

Credit: Wake Forest Institute for Regenerative Medicine

Taking Stem Cells to Heart

Cardiomyocytes differentiated from iPSCs – derived from human amniotic fluid cells using Sendai Virus encoding for OSKM. The cardiomyocytes were stained at differentiation day 38 with MLC2v (green), A4.95 antibody (red), and Dapi (blue).

Credit: Guihua Jiang, Todd J. Herron, Shaun M. Kunisaki, Department of Surgery, University of Michigan

Nanoscale Medicine

Researchers at the Northwestern University Center of Cancer Nanotechnology Excellence (NU-CCNE) are developing gold and silver nanostructures for use in various biomedical applications. This stack of gold nanocubes with concave surfaces could be used for cancer detection.

Credit: National Cancer Institute

Into the Patient

Translation in action, as science and engineering turns to medicine.

Lungs to Go

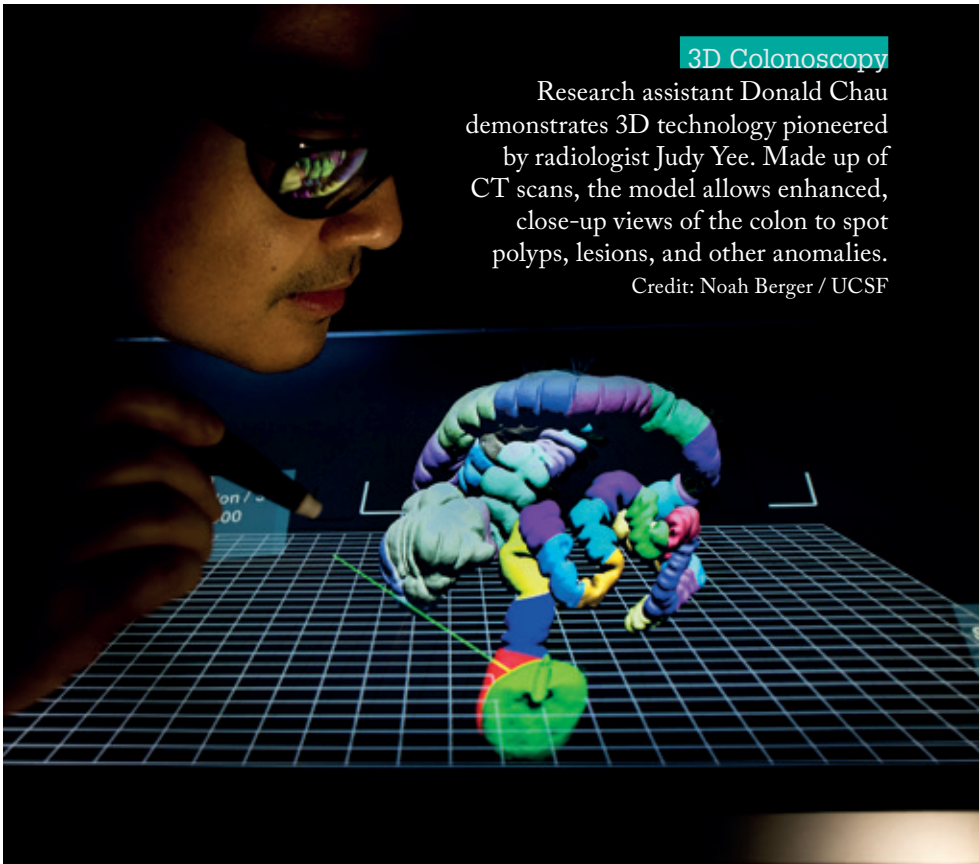
The XVIVO Perfusion XPS machine is being used to keep the donor lung active and circulate solution through the blood vessels to increase its viability for donation.

Credit: Hôpital Foch, Paris

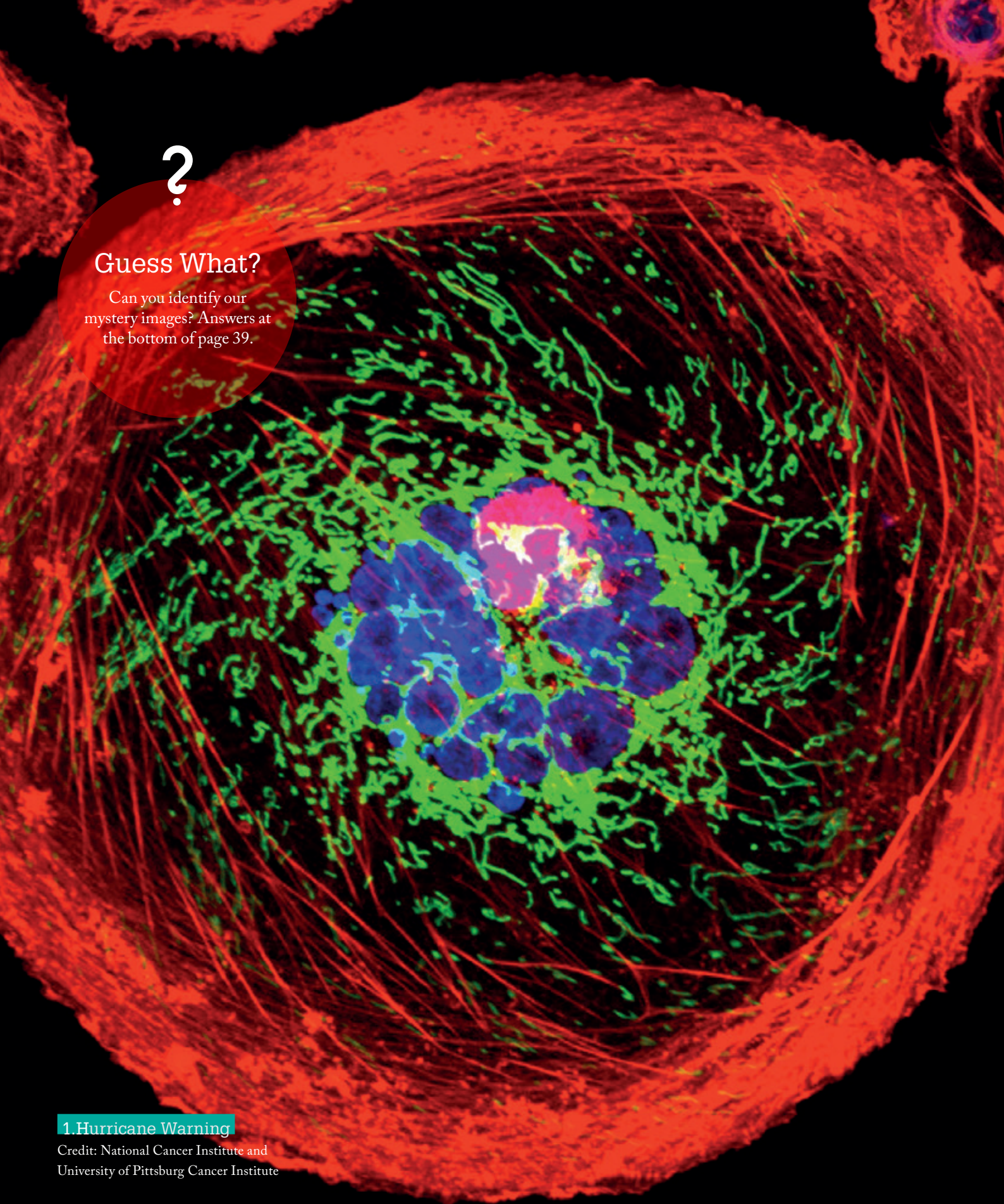
Destination: Immunization
The world's first public dengue immunization program, in the Philippines.
Credit: Sanofi Pasteur / Norbert Domy

Open Wide
Every child counts in the ongoing fight to eradicate polio.
Credit: d'Arcy Lunn

Freedom of Movement
A pioneering surgical technique allows an amputee to attach a Modular Prosthetic Limb, designed by Johns Hopkins Applied Physics Laboratory (JHUAPL), directly to his residual limb, enabling a greater range of motion and comfort.
Credit: JHUAPL



3D Colonoscopy
Research assistant Donald Chau demonstrates 3D technology pioneered by radiologist Judy Yee. Made up of CT scans, the model allows enhanced, close-up views of the colon to spot polyps, lesions, and other anomalies.
Credit: Noah Berger / UCSF



Guess What?

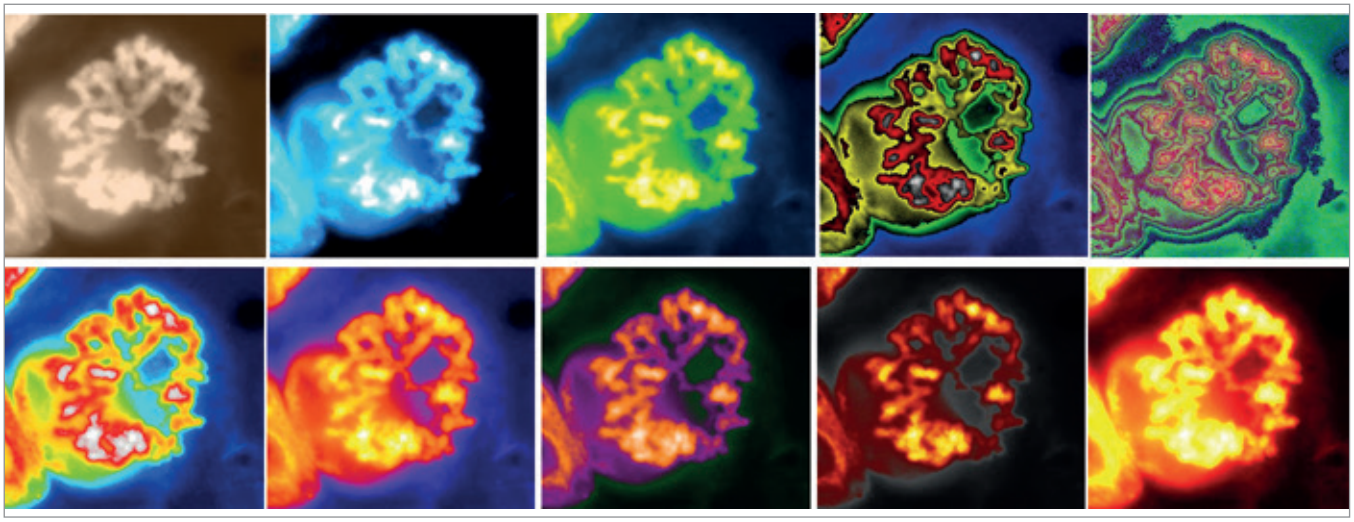
Can you identify our mystery images? Answers at the bottom of page 39.

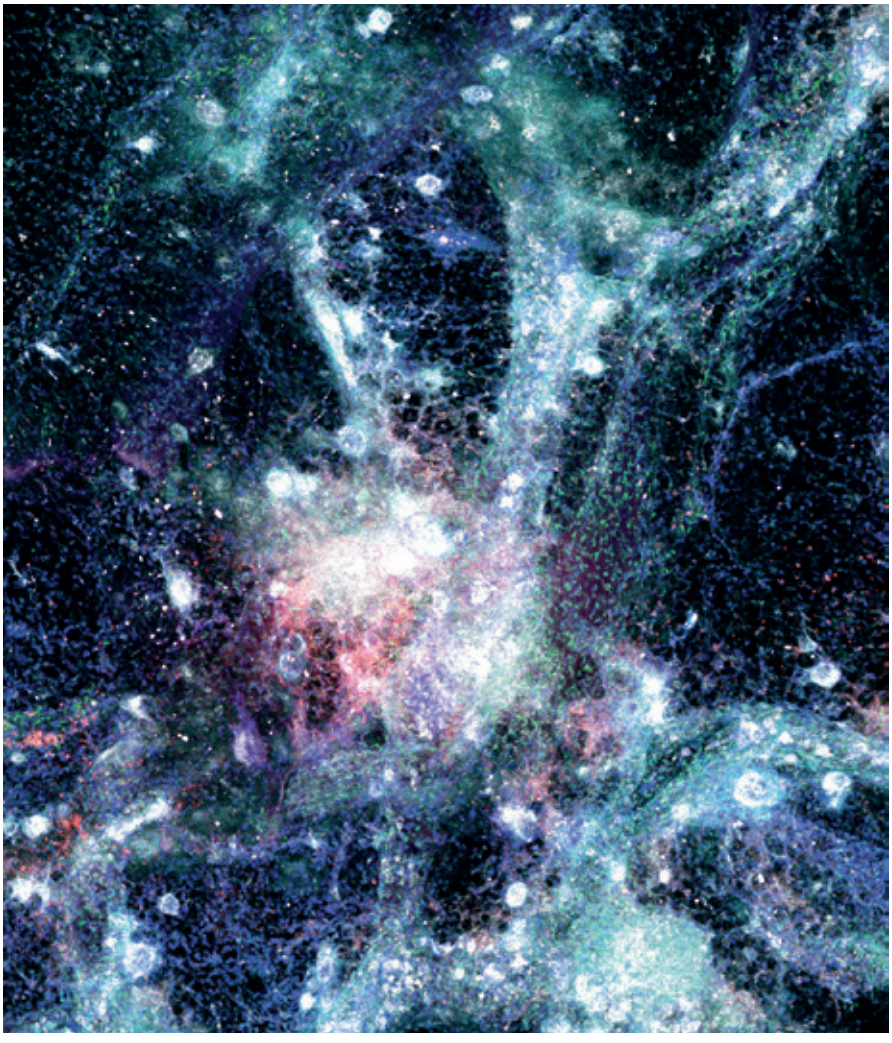
1.Hurricane Warning

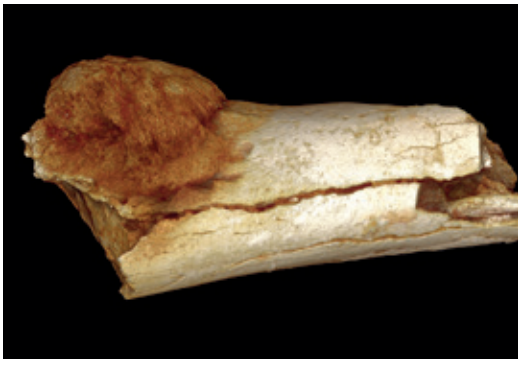
Credit: National Cancer Institute and University of Pittsburg Cancer Institute

2. Flower Power

Credit: May C. Morris







3. Animal, Vegetable, or Mineral?

Credit: Patrick Randolph-Quinney (UCLAN)

4. The Final Frontier

Credit: NIAID

1. A polyploid giant cancer cell from triple-negative breast cancer.
2. Hoechst staining of DNA in a HeLa cell during cell division, captured by epifluorescence imaging with a Leica microscope. Images acquired using Metamorph and colored using ImageJ.
3. A foot bone dated to approximately 1.7 million years ago, with definitive evidence of malignant cancer.
4. Not a distant galaxy, but a confocal image of myeloid hematopoietic cells in mesenteric adipose tissue.

Toolbox

Key tools
New technology
Emerging techniques

Taking the Guesswork out of Bacteriotherapy

Forewarned is forearmed. A new software tool – MDSINE – predicts how a simplified mouse microbiome reacts to probiotic intervention. Next? The human microbiome.

By William Aryitey

An imbalance in the microbiome – the micro-organisms living on and in the body – can have serious health implications. Reintroducing "healthy" bacteria (probiotics) to bring the microbiome back onto an even keel has great potential, but it can be hard to predict how a patient's individual microbiota will react. Now, researchers at Brigham and Women's Hospital at Harvard Medical School and the University of Massachusetts have created a new tool to help develop better bacteriotherapies. The Microbial Dynamical Systems INference Engine (MDSINE – pronounced M-Design) is a suite of computer algorithms that can forecast microbial behavior in complex ecosystems like the mammalian gut (1).

Gut reaction

The open-source software uses time-series data (a series of data points collected over time) to predict how different interventions will affect the microbial community in the gut – and could help with the development of better probiotics, says Georg Gerber, lead researcher and Assistant Professor of Pathology at Harvard Medical School. "We created MDSINE as a tool to aid research into therapeutic avenues for diseases relating to the gut microbiota, such as inflammatory bowel disease and *Clostridium difficile* infection."

MDSINE can predict how the microbial community will grow and interact, the stable states it will form, and the species most critical to maintaining stability or most vulnerable to perturbations in the system. The basic concept of MDSINE – looking at a system over time and predicting future patterns – is not new. But when dealing with a system as complex as the gut microbiome, the data pose unique problems. "In trying to describe the interactions that happen within these ecosystems, we found that even the simplest models need to be fairly complicated to capture even the key factors," says Gerber. "We also ran into the problem of too much noise in the datasets, or data that weren't regularly sampled." Consequently, the team spent a lot of time developing models that could adjust for the inherent features of microbiome data.

In a recent paper in Genome Biology (1), the group explain how they validated the software with extensive computer simulations, and two real-life studies with mice. In the mouse experiments, they used MDSINE to identify the combinations of microbiota that most effectively inhibit *C. difficile* infection, and analyzed the impact of diet on a probiotic cocktail intended to treat inflammatory bowel disease (IBD). Both studies gave intriguing results. A combination of three bacteria was predicted to be sufficient to inhibit *C. difficile* – one inhibits the pathogen directly, while the other two play a supporting role. The second study tested whether the thirteen bacteria in a probiotic cocktail for IBD were affected by changes in the diet of the recipient – an important factor for human IBD patients, who often try dietary interventions alongside medication. The data confirmed that diet does affect the probiotic bacteria, suggesting a new avenue for research.

Forward thinking

Gerber has worn many hats over the course of his career, studying pure mathematics, computer science, computational biology, microbiology, and pathology. He even spent a few years in the digital entertainment industry, before gaining his PhD and MD, and training as a clinical pathologist. Microbiomics was a perfect opportunity to bring his interests together, recounts Gerber; "I saw new technologies like high-throughput sequencing emerging and vastly expanding our ability to understand the microbiome, and I was

hooked." Gerber is now Co-director of the Massachusetts Host–Microbiome Center at Brigham and Women's Hospital, as well as an assistant professor of pathology at Harvard Medical School.

Gerber and his colleagues made the choice to release MDSINE as open source software for two key reasons, he says. "Firstly, scientific integrity – I think it's crucial for people in the scientific community to know exactly how we built our algorithms. If your peers can't look at the source code, they can't critically evaluate the algorithms. Secondly, we created the software to help make more and better probiotics. I strongly believe that tools meant for academic research shouldn't be locked up as proprietary code, but should be openly available for the scientific community to use."

MDSINE is now freely available to researchers, both as source code (zenodo.org/record/50624#.V8BL6q0p6Uk) and as an executable open source package (bitbucket.org/MDSINE/mdsine/), but the team's work isn't over. "We're going in two different directions with it at the moment; applying the existing algorithms to more scenarios and data sets, and extending the algorithm," says Gerber. "We named the tool MDSINE for a reason; our focus is on designing probiotics in a rational way. We're looking at a range of different systems and different questions relevant to that goal."

The aim is to be able to move on to human microbiome data, though that will require some further work to extend the algorithms. Their published paper used data from mice whose microbiomes consisted entirely of known organisms. These "gnotobiotic" mice provided a controlled system; "Using gnotobiotic mice was great for our proof of principle, but scaling the algorithm for human datasets is definitely a challenge," says Gerber.

Another challenge is finding human datasets to work with, as Gerber explains, "A lot of time-series studies looking at dynamics of the microbiome are very limited for human data, with only two or three time points per person recorded. For an algorithm like MDSINE we need a minimum of about ten time points. Ideally, the subjects in the study have to undergo some type of experimental perturbation of their microbiome, like a change of diet or a course of antibiotics." These studies are hard to find, but more are being published every year, and Gerber hopes to be able to apply MDSINE to human data in the near future.

Therapy by MDSINE

Gerber's lab is also starting to consider applications for MDSINE outside of the gut. "Knowledge of the skin microbiome is increasing, so that is of interest to us. We would expect the skin microbiome to have a much stronger link with the external environment than the gut, which is a more contained ecosystem. So we have been thinking about how we could incorporate these environmental factors," he says.

Further afield, the researchers are working on a DARPA-funded project, which involves engineering consortia of interacting microbes. Gerber says the project has allowed them to go from simply studying microbial interactions to directly influencing them: "We're using MDSINE to learn what the wild-type interactions are, and asking if there are leverage points that we can apply to the genetic circuitry to change those interactions, or even to change the large-scale properties of the ecosystem, like stability. Ultimately, if we can engineer an ecosystem of microbes to adhere to certain behaviors, this really opens up exciting possibilities for therapeutics."

A possible application for these engineered communities is suggested by the emerging field of fecal transplantation. "As a researcher, I'm very excited about the potential of fecal transplants, but as a physician I believe we need to be cautious," explains Gerber. "The analogy that comes to mind is blood transfusion. It's saved many lives, but we've also had transmission

of infectious agents like HIV and hepatitis. It worries me that there aren't really any uniform standards for fecal microbiota transplants. I'm hopeful that MDSINE can help us rationally design precisely defined cocktails of microbes for these transplants. MDSINE could also be used to predict who the best donor would be, or even modulate the patient's pre-existing microbiota to make them more responsive to therapy."

As well as the ongoing work in his own lab, Gerber is looking forward to seeing how other researchers will apply the software, and is excited to see what datasets researchers will come up with, now they have a robust tool for analyzing their data.

Reference

1. *V Bucci et al., "MDSINE: microbial dynamical systems inference engine for microbiome time-series analyses", Genome Biol, 17, 121 (2016). PMID: 27259475.*

Translated

Celebrating success
Translation in action
Bench-to-bedside

Science in the Time of Cholera

The recent FDA approval of Vaxchora could fill an important niche in cholera prevention. We speak with Myron M. Levine, a professor at the University of Maryland School of Medicine, who played an integral role in the development of the vaccine.

Why focus your work on vaccine research?
Since my student days, I've been interested in what we now call "global health". My first involvement with research was as a senior medical student in the 1960s, when I worked for three months on a project studying diarrheal diseases at the Jinnah Children's Hospital in Karachi. My appetite for research in tropical pediatrics whetted, on my way home from Pakistan I stopped off in what is now Bangladesh (then East Pakistan) and spent some time at the Cholera Research Laboratory in Dhaka, now known as the International Center for Diarrheal Disease Research, Bangladesh.

My post-graduate training in infectious diseases was mentored by John Robbins, one of the developers of the *Haemophilus influenzae* type b (Hib) vaccine, and I did my military service obligation in the Commissioned Corps of the U.S. Public Health Service as an Epidemic Intelligence Service Officer at the Centers for Disease Control. I spent the following almost half century in vaccine development, though I love clinical work and still enjoy making clinical rounds at some of our overseas sites on occasion. It's important to keep in touch with the patients and families we are trying to help.

I set up the Center for Vaccine development (CVD) in 1974 and directed it for 40 years, stepping down in 2014 to become Associate Dean for Global Health, Vaccinology and Infectious Diseases, which essentially gives me a license to pursue all the research interests that are on my "bucket list".

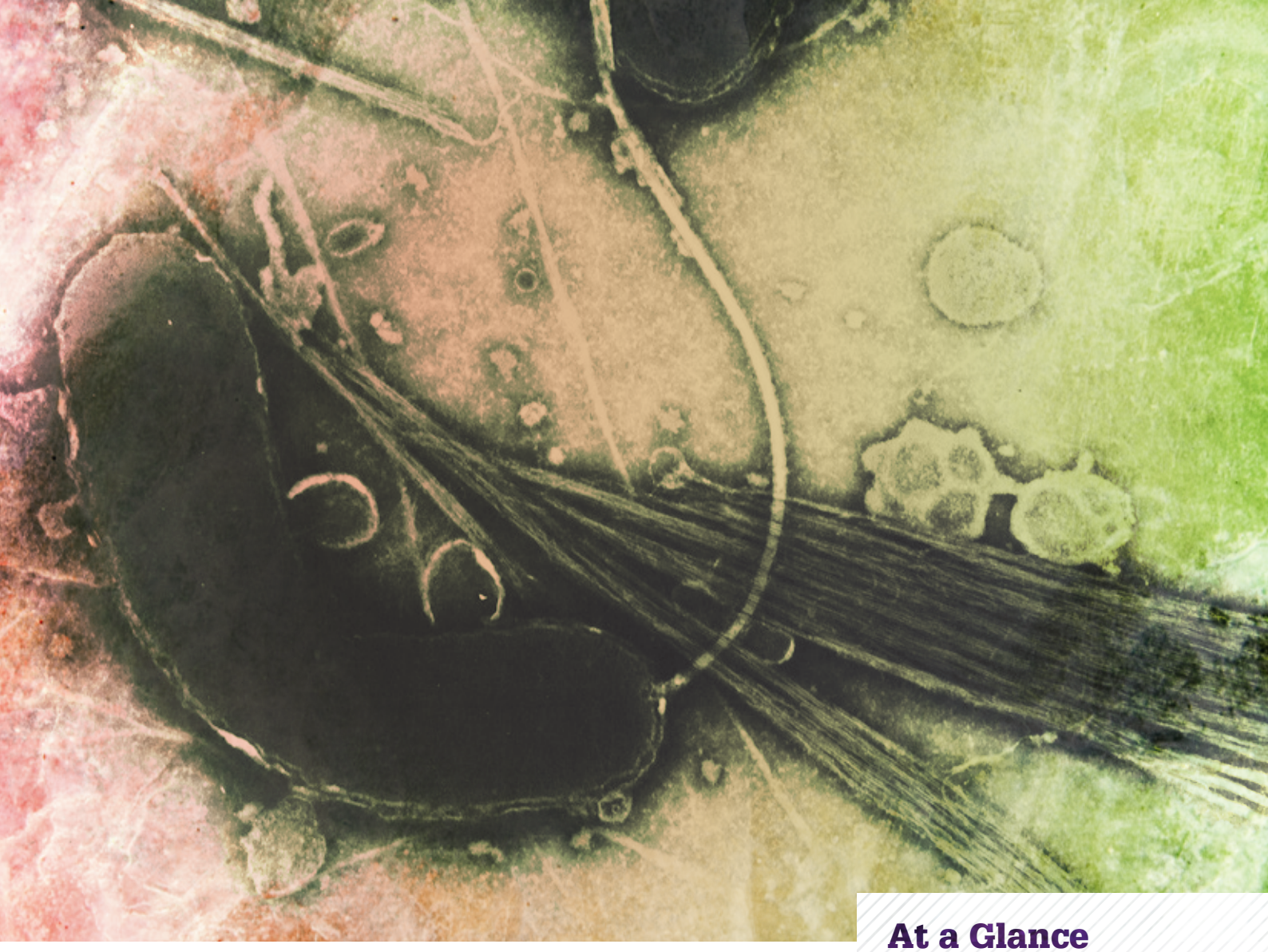
What is the ethos of the Center for Vaccine Development?
Our mission from the start has been to address infectious diseases that afflict impoverished populations in developing countries but are rare in industrialized nations, and therefore get little funding or attention. We tried to fill a niche as a public sector research entity that tries to do everything a small vaccine company would do, other than manufacture and market the product. That includes clinical and laboratory research, epidemiology, biostatistics, regulatory affairs, and so on – everything that is needed to create candidate vaccines, move them through clinical trials, and find industry partners to commercialize them at an affordable cost. From the beginning, we limited ourselves to one major disease area – bacterial enteric infections, such as cholera, shigellosis (bacillary dysentery), typhoid, and various types of diarrhea-causing *Escherichia coli*.

The Center came into existence at an exciting time for vaccine research. Just one year after its inception saw the advent of recombinant DNA technology, which came to be a very important tool for us. At the same time, advances were being made in clinical research, such as formalized institutionalized review boards (ethical committees) and innovative clinical trial designs.

Is cholera on the rise?
It fluctuates. Cholera is one of the very few true pandemic bacterial diseases. We are currently in the seventh cholera pandemic in recorded history, which began in the early 1960s. During the pandemic, the disease has periodically lain quiescent for a few years, before exploding again, typically in new geographic areas.

What has become clear in recent years, as diagnostic capabilities have improved, is that cholera is a much bigger problem than previously appreciated. In 2013, the CVD reported results from a large Bill and Melinda Gates Foundation-funded project looking at the etiology and burden of moderate-to-severe diarrheal diseases in children in sub-Saharan Africa and Asia – the Global Enteric Multicenter Study (GEMS). We enrolled 22,568 children under five years of age and looked for over 40 pathogens. In all South-Asian sites we were somewhat surprised by the relative importance of *Vibrio cholerae* as a pathogen responsible for moderate-to-severe pediatric diarrhea.

What led to the discovery of the vaccine?
In the 1980s, we were asked by the NIH to set up a model of cholera challenge in order to test a vaccine intended to stimulate antitoxin antibodies to neutralize cholera



toxin. A field trial had given disappointing preliminary results and the NIH wanted us to test the vaccine in naïve individuals as well as study the immune response in depth.

We found that the toxoid vaccine against cholera toxin had conferred only a very modest protective effect, and most of our student volunteers developed cholera diarrhea. This led me to wonder what level of protection Mother Nature herself provided. We asked our earlier volunteers to return and re-challenged them with cholera – there was complete protection and we could not grow *V. cholerae* in direct stool cultures of the re-challenged subjects, suggesting that anti-bacterial immunity was playing the key role in protection rather than anti-toxin immunity. We continued this research, including re-testing some challenged volunteers up to three years after their first cholera diarrhea and showed that the protection persisted. We concluded that the best approach to prevent cholera would be a live, attenuated vaccine. This was the early days of recombinant DNA technology and there were methods available to delete genes, thereby creating precise attenuations. By the mid-1980s we had developed a strain of *V. cholerae* O1 that looked very promising, with a deletion in the A (enzymatically active) subunit of the cholera toxin (CVD 103-HgR) and insertion of a mercury resistance gene marker in the gene encoding Hemolysin A.

What happened next?

The live, attenuated vaccine was shown to be well tolerated and effective in clinical trials

At a Glance

International non-proprietary name (INN): Cholera Vaccine, Live, Oral
Brand name: Vaxchora
Previously marketed as: Orochol, Mutacol, Orochol E
Developed by: Center for Vaccine Development, University of Maryland
Marketed by: PaxVax (previously manufactured by the Swiss Serum and Vaccine Institute [SSVI])
Drug class: Live-attenuated vaccine
Approval status: Approved by FDA for US adults traveling to cholera-affected regions in June 2016. (Note - The SSVI formulations were previously approved in Switzerland, Canada, Argentina, Australia and New Zealand).

On Virgin Soil

Six years on, Haiti's cholera epidemic isn't over yet – and neither is the political fall-out.

Ten months after the 2010 earthquake that saw hundreds of thousands displaced into temporary camps, Haiti was struck by a devastating cholera outbreak. Cholera has since infected an estimated 800,000 (seven percent of the population) and killed around 10,000.

Cholera can kill within hours if left untreated, and death rates were particularly high in the early stages of the outbreak (1). Death from cholera is a result of dehydration and shock, caused by severe diarrhea – most deaths could be prevented with inexpensive oral rehydration salts (2). Cholera had never before been reported in Haiti, so people were unaware of the danger and the need for prompt rehydration treatment – with tragic results. The incubation period for the disease can be as short as two hours, and aid agencies were left playing catch-up as it spread like wildfire.

In 2016, Haitians are still suffering with cholera. However, dedicated cholera treatment centers and access to rehydration therapy have cut the death toll, while education and sanitation efforts have curbed transmission. A vaccination program administering Shanchol to 100,000 people has also shown good efficacy – around 65 percent (3) – demonstrating an important role for reactive vaccination programs in controlling cholera outbreaks.

The impact of the outbreak has not just been medical; the fact that cholera is an "imported" disease has provoked anger. Within a week of the onset of the outbreak, locals pointed the finger at a United Nations base near the Artibonite River, used as a source of drinking water by most of the first victims. Although the UN persistently denied the reports, resentment towards the agency persisted, and distrust slowed the implementation of control measures.

Only in August 2016, after a slew of evidence that peacekeeping troops were the most likely source of the outbreak, did the UN acknowledge their own role in the outbreak. The agency faces legal action from victims who claim that the UN failed to screen soldiers or ensure adequate sanitation at the camp.

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2. *WHO Factsheet on Cholera, http://bit.ly/1p2wvsD*
3. *LC Ivers et al., "Effectiveness of reactive oral cholera vaccination in rural Haiti: a case–control study and bias-indicator analysis", Lancet Glob Health 3, 2162–e168 (2015). http://bit.ly/2bLQYpr*

and was licensed to the Swiss Serum and Vaccine Institute, a company based in Berne, Switzerland. Unfortunately, the 1990s were a tough time for vaccine companies and, to cut a long story short, production of the vaccine was halted for financial reasons in 2004. A decade passed before the engineered vaccine strain was picked up again by PaxVax, Inc, whose philosophy is not dissimilar to the CVD. They develop vaccines that fulfill a global health need, achieving commercial viability by first targeting the traveler's market. The vaccine, Vaxchora™, was approved by the FDA in June 2016 and recommended by the Advisory Committee on Immunization Practices for adults traveling to cholera-affected regions. And CVD and PaxVax have already started to look at applications in the developing world using an appropriate formulation for that purpose (slightly higher dose).

How did you feel when you found out that the vaccine would be withdrawn?

The experience taught me to think downstream and take into account business factors from the start. For the first two decades of my career, I was very naïve about the business and financial aspects of bringing a vaccine with very low profit margins to market and making it sustainable. Most big pharmaceutical companies will only consider vaccines that will return their investment within a year or two, which rules out vaccines against many of the infections found in the developing world. That wasn't widely appreciated by researchers during the 1990s – we thought "if we build it, they will come". In reality, high development costs and regulatory hurdles meant that many vaccine companies in the developed world were struggling, while very few manufacturers in the developing world were able to produce high-quality vaccines. The advent of Gavi (the Global Alliance for Vaccine and Immunization), launched in 2000, dramatically changed the market landscape; we are now in a much improved situation with respect to the global supply of vaccines and in

Vaccine Type	*Monovalent inactivated*	*Bivalent inactivated*	*Live attenuated*
Products	Dukoral®	mORC-Vax™ (Vietnam), Shanchol™ (India) and Euvichol® (Korea)	Vaxchora™
Manufacturer	Crucell (the Netherlands)	Vabiotech (Vietnam); Shantha Biotechnics Ltd (India); Eubiologics (Korea)	PaxVax
Recommended age for vaccination	2+ years	1+ years	Adults
Schedule	Oral, two doses ≥1 week apart	Oral, two doses ≥2 weeks apart	Oral, single dose
Licensure	International (1991)	Vietnam (1997/2009), India (2009)	USA (2016)
Storage	Refrigerated	Refrigerated	Frozen

Table 1. Cholera vaccines compared.

providing immunization for the world's most disadvantaged populations.

How hard is it to recruit volunteers to be infected with cholera?

Perhaps surprisingly, not hard at all. Even in our early studies back in the 1980s, when there was no real precedent for human challenge trials, we were able to recruit volunteers. When we ask our volunteers about their motivation, we find that they are driven by two things. First, the thrill of doing something that is unusual, and that makes them feel good about themselves. Second, since they were modestly compensated (at the same daily rate as someone on jury service in Montgomery County, MD, where NIH is located), they made plans for use of their compensation. Volunteers often told me that they intended to use the money on activities like mountain climbing, skate boarding, white water rafting – things that I would consider much more dangerous than taking part in our studies. Young people exude an air of invincibility!

It probably helps that most of our volunteers don't feel seriously unwell – cholera mainly manifests in copious watery diarrhea, and with adequate rehydration therapy there is little malaise, nausea, or pain. I often give the example of one volunteer who developed quite severe diarrhea and required intravenous fluids. Despite this, he felt well enough to spend most of his time on the Research Isolation Ward playing ping pong, while still hooked up to his IV drip. Every so often, he would disappear to the bathroom, proceed to the nurses' cubby to provide his specimen and then go right back to his ping pong game.

Did your human experimental challenge model lead to regulatory challenges?

There is a lot of discussion at the moment about how more frequent use of human challenge models could diminish the costs of bringing vaccines to licensure. As the first FDA approval based on data from challenge trials, the precedent set by our model could help others follow the same path, and we were aware of being "under a microscope". However, the FDA was very supportive and realistic throughout the process. Previously, there was no FDA-approved cholera vaccine, and with the Haiti epidemic still ongoing not far from the Florida coast, many US citizens visiting affected regions, and our armed forces frequently deployed on missions in the developing world, there was a clear demand.

How is Vaxchora different to existing cholera vaccines?

Our aim is in no way to replace the currently available oral killed vaccines. Existing vaccines are effective for populations who are immunologically primed, preventing seasonal outbreaks of cholera in known hotspots. But for children, or others who have yet to be exposed to the bacteria, they offer much lower protection, and require two full doses to be effective. Live vaccines like Vaxchora achieve correlates of protection much faster than killed ones – and with a single dose. That makes Vaxchora suitable for its current indication as a traveler's vaccine, and we believe it could also help to limit so-called "virgin soil" epidemics, like the one in Haiti in 2010.

These epidemics occur in populations who have not previously experienced cholera, but where the conditions favor fast transmission. As was seen in Haiti, the first few weeks or months of such an outbreak often see high mortality and morbidity, with healthcare systems struggling to respond to the new threat. In these circumstances, an easily administered single-dose vaccine is required and we hope that Vaxchora can fill that need.

In 2000, when the vaccine was still being manufactured by the Swiss Serum and Vaccine Institute, there was an outbreak of cholera on the Micronesian island of Pohnpei. The logistics made a two-dose vaccination schedule unfeasible, so the WHO asked the company to provide 40,000 doses of the live attenuated vaccine for a reactive immunization program. The vaccine was very successful, with an estimated efficacy of 79 percent. To see Vaxchora being used to limit future outbreaks around the world would definitely be a career highlight.

In Perspective

The big picture
Global health
Populations

A Personnel Story

On the long road to improving cancer care in Africa, training dedicated cancer specialists is the first step.

By Rasha Kelej

Did you know that the number of practicing oncologists barely hits double digits in most African nations? In fact, there are only 13 oncologists in Kenya (all based in Nairobi) for a population of 47 million – that's one oncologist per 3.6 million people. It's even worse in Ethiopia, where a population of more than 100 million is served by just four oncologists in Addis Ababa (you don't need me to do the math). For perspective, consider that there is one oncologist for every 75,000 or so people in the UK.

We learnt all this after extensive research into the challenges of access to cancer care in sub-Saharan Africa and it made us realize that the first priority in most sub-Saharan African countries should be to increase the number of oncologists, before discussing investment in infrastructure or drug donations.

To that end, Merck KGaA has joined forces with the University of Nairobi to launch a medical oncology fellowship program that provides specialist cancer training to doctors in sub-Saharan Africa. It's part of the Merck Cancer Access Program, which launched in Kenya, Uganda, and Tanzania at the beginning of 2015, and will fund nine doctors with an advanced degree in internal medicine to take part in a two-year fellowship program at the University of Nairobi. Merck is also sponsoring another five doctors from sub-Saharan Africa to train at Tata Memorial Hospital, Mumbai, India, in pediatric and adult medical oncology.

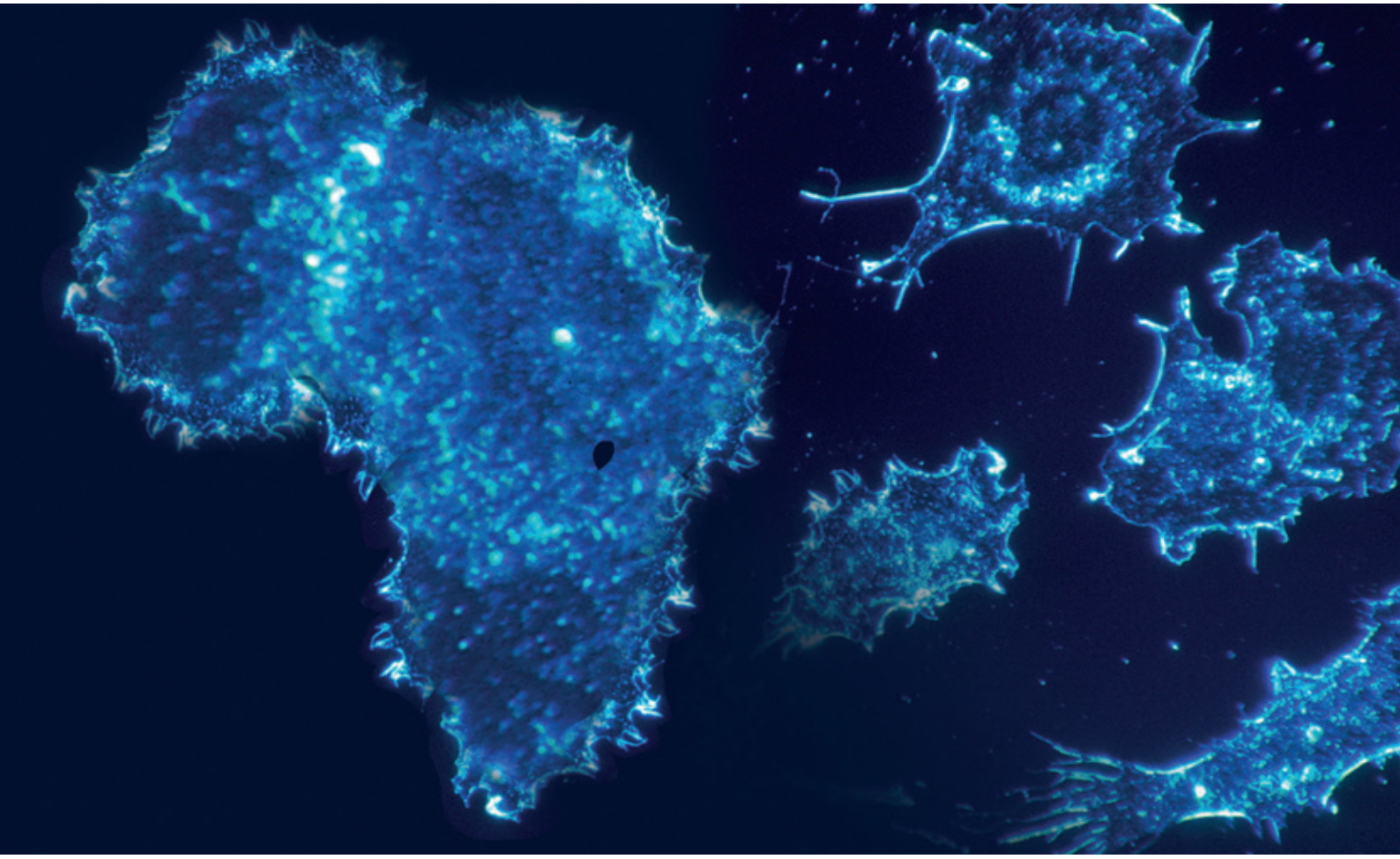
In Africa, the lack of financial resources is never the only challenge. It is sobering to consider that many countries in sub-Saharan Africa have no radiotherapy facilities, especially given that as many as 50 percent of patients with cancer would be expected to benefit from radiotherapy as part of their treatment. But the real bottleneck is the scarcity of trained healthcare personnel capable of tackling prevention, early diagnosis, and management of cancer. For example, when we started our work with the University of Addis Ababa, we soon found that the University needed to expand its oncology set-up – it was the only cancer center in the country, after all. Ethiopia's Ministry of Health has offered them expansion into a new four-story building for patient chemotherapy – a great opportunity, but with so few trained specialists, it is difficult for the center to take full advantage.

A growing problem

Cancer is set to be a huge economic and social burden on Africa. By 2020, the World Health Organization (WHO) predicts there will be 16 million new cases of cancer every year, 70 percent of which will be in developing countries, where governments are least prepared to address growing cancer rates and where survival rates are often less than half those of more developed countries. The numbers represent a massive challenge for African nations, whose healthcare systems are largely built to tackle a very different mix of diseases.

"By 2020, the World Health Organisation predicts there will be 16 million new cases of cancer every year, 70 percent of which will be in developing countries."

Building professional capacity takes a long time but the long-term impact is significant, so I firmly believe that "now"



is the right time to start this movement for change. I prefer to use the term "movement" rather than program or initiative because, if applied successfully, it will change the cancer care landscape all over Africa. We have now overcome logistical hurdles to find eligible candidates and develop the program in two locations – University of Nairobi and Tata Memorial Hospital. The two programs target African doctors from all over Sub-Saharan Africa, and we have ensured that after graduation every candidate will be able to practice in his or her own country and in the public sector, so that we can achieve our goal to improve access to cancer care for underserved patients.

We have received applications for the fellowship from many African countries, including Uganda, Kenya, Tanzania, Ethiopia, and South Africa. The scientific committee has selected eligible candidates holding a Master's degree in internal medicine for the University of Nairobi program, and pediatricians for the medical oncology fellowship in India. According to WHO, 30 percent of cancer cases can be prevented, and another 30 percent will respond to basic treatment if detected early, so having trained experts will provide great support.

A fight on many fronts

Africa is an important region for Merck and we have a number of other initiatives ongoing to help cancer patients in the continent. We will shortly launch our "Merck More than a Patient" campaign, which aims to empower female cancer survivors in Africa; it helps them to establish small businesses so that they can generate a good monthly income to support themselves and take a full role in society. The new campaign follows on from our "Merck More than a Mother" campaign, which we hope will help infertile African women, who often face stigma and social isolation.

Clearly, cancer is not the only problem facing African healthcare systems. But by running campaigns that target the

Top: Students from African universities at a Merck Cancer Control Program.
Bottom: Rasha Kelej (right) and Ugandan Minister of Health Sarah Opendi (center) with patients at a Merck combined cancer and diabetes campaign.

"The size and complexity of the task is so great that no single organization or institution can manage on its own, so integration of efforts is vital to achieve the health gains that our citizens deserve."

common risk factors behind several non-communicable diseases, such as tobacco use, alcohol abuse, unhealthy diets and physical inactivity, we can cost-effectively target cancer alongside other diseases on the rise in the region, such as diabetes and cardiovascular disease.

In reality, even with more oncologists and better treatment, cancer isn't always curable, so there is a need to make palliative medicines available at affordable prices. Without access to palliation, most cancer patients in Africa would die in severe pain – an important humanitarian element for cancer care on the continent.

All hands on deck

I firmly believe that the only way to effectively prevent, detect, and treat the rising number of cancer cases in Africa is through public–private partnership models that involve health ministries, NGOs, academia, patient associations, and industry.

The size and complexity of the task is so great that no single organization or institution can manage on its own, so integration of efforts is vital to achieve the health gains that our citizens deserve. I believe that prevention is better than cure, so awareness-raising and education will play a big part in any campaign to reduce death rates, but we also need to improve access to basic cancer treatment and palliative care.

By partnering with ministries of health and universities in Africa to implement our Cancer Access Program, we hope to rapidly achieve our objective of advancing cancer healthcare capacities and reducing the socioeconomic burden of the disease. Now is the time to take action, and we hope other companies will join us in supporting healthcare systems in Africa as they face this emerging challenge.

Rasha Kelej is Chief Social Officer for Merck Healthcare.

The Human Element

We spoke with Isaac O. Kibwage, Professor and Principal of the College of Health Sciences, University of Nairobi, to get his view on the partnership with Merck and the future of cancer care in Kenya.

How did you become involved with the fellowship program?

Rasha and I were speaking about emerging diseases that are increasingly impacting Kenya. One of the diseases that our government is already taking urgent steps to address is cancer, with investment into better facilities and access to care. We discussed our plans for training oncology specialists and Rasha raised the possibility of Merck joining us in the venture. Now, we have formalized the partnership, with Merck providing funding for students from Kenya and other African nations to take part in an oncology fellowship program here at the university.

How did you decide where to focus your efforts?

You have to start with the human element. Even if you have adequate equipment and drugs, if there are no specialists to diagnose people or oversee their treatment, you won't get far. The lack of oncologists in Kenya has led to two key problems; first, the quality of diagnosis is very low, and second, patients cannot access specialist care, especially outside of the main cities. If we can train enough oncologists to provide high-quality cancer care around the country, we will be able to help our own citizens, and even welcome medical tourists from elsewhere in the region.

To take part in the fellowship at University of Nairobi, candidates must already be internal medicine specialists, as the need is urgent and these students will be the fastest to train.

Why are cancer rates going up in Africa?

Cancer cases are increasing all the time. We speculate that this relates to changes in lifestyle – we are more sedentary, eat more refined food, and have more environmental pollution than our ancestors. Also, more cases are identified as better diagnosis becomes available.

Why are there so few oncologists in Africa?

Historically, cancer has been less common, so there was limited demand. In addition, some doctors have told me that the high mortality and morbidity rates made it a less appealing area, as even specialists could do little to help patients. Now that we have the means to treat and even cure some cancers, there are more doctors gravitating towards the field, but training opportunities have been scarce.

The Synthesizer

Sitting Down With... Jef Boeke, Founding Director, Institute for Systems Genetics, Professor, Department of Biochemistry and Molecular Pharmacology at New York University School of Medicine, USA.

How did you get your start in genetics?
I didn't really start considering genetics until my late college years. Before then, I was thinking more along the lines of being a naturalist. During my last year of college, I worked with a geneticist who opened my eyes to the power of experimental laboratory science. From there, my PhD advisors Norton Zinder and Peter Model, and my post-doc advisor Gerald Fink – all geneticists through and through – inspired me to continue in that direction.

What made you hone in on transposons?
As a graduate student, I started out as a bacteriologist, but wanted to move up to eukaryotes. That's when I joined Fink's lab – which was focused on yeast – and planned to undertake a project on transcriptional regulation. When I arrived at his lab, I was annoyed to find that someone else was working on that project, and Fink had assigned me to work on a project with transposons. I rather grudgingly accepted it, but soon realized it was actually a better project! I certainly didn't set out to work on transposons, but it ended up being a wonderful project.

What's the current focus of your lab?
About a third of the team is still working directly on transposon-related research, which began in yeast but has morphed into the study of mammalian retrotransposons, which is what the majority of my NIH-funded work is focused on right now. The rest of the researchers in my lab are working on projects related to the synthetic yeast genome project – Sc2.0 – that we started 10 years ago.

How did Sc2.0 begin?
The idea germinated from our frustration at not being able to express proteins from retrotransposons. One of my PhD students, Jeffrey Han, identified the source of the problem at the RNA level, rather than the level of translation. In desperation, he decided to re-code the entire transposon open reading frame, leading to high levels of protein expression. That got me thinking about the interesting possibility of redesigning a small genome.

Soon after, I was talking with Srinivasan Chandrasegaran – a Professor at Johns Hopkins – about another synthesis project. I suggested synthesizing a yeast chromosome and he got really excited, so we started planning out what we would remove and alter in the genome.

It took over a year to synthesize the first 90kb chromosome arm in conjunction with a biotech company, and it became obvious we needed a different approach. We hit on the idea of crowdsourcing – we developed a course called "Build a Genome" and got undergraduates to make DNA pieces for us. Today, Sc2.0 has spiraled into a project that involves labs and companies across four continents.

Can you describe your experience with Sc2.0?
It's been pure fun, and we've learned a lot about both *Saccharomyces cerevisiae* – the yeast we used – and about synthetic biology. Editing and deleting certain genomic elements has allowed us to build yeast more efficiently and stop problems before they start. For example, the tRNA genes are prone to causing chromosomal breaks, but they're essential to the yeast. So we've removed them and built their function into what we're calling a specialized "neochromosome."

As I mentioned, it's been a decade since we started, and we're more than halfway done. That may not sound like much, but almost all the synthesis is finished, so now we just need to put the chromosomes together and complete the assembly.

How did your involvement with Human Genome Project (HGP)-write come about?

"We developed a course called 'Build a Genome' and got undergraduates to make DNA pieces for us."

Andrew Hessel from Autodesk Research wrote a paper in 2012 proposing that the synthesis of the human genome should be the next big thing. Then at last year's Sc2.0 conference he mentioned it again. I was initially skeptical, but Nancy Kelly – who helped me organize the conference – and George Church (renowned geneticist) were excited about the prospect. The four of us started brainstorming, and I became more and more enthusiastic. HGP-write will be a bigger undertaking than Sc2.0 but it's not a quantum leap. It's going to be more expensive and less efficient than working with yeast, but if we focus on improving our technologies in tandem then we'll be able to deal with those challenges.

Will knowledge gained in Sc2.0 help with HGP-write?
Definitely. We believe that it would be possible to do the same sort of iterative design process I've been using with the yeast project in HGP-write, but it's certainly not the only option. If we're going to scale up, we need to figure out a way to parallelize multiple teams as we did with yeast. But it's still early days, and what we can do or how fast we can do it obviously depends on funding. I think we would have the highest chance of success if we can get strong buy-in from government and public funding. But I'm happy to talk to anyone who's interested in funding the initiative.

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