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From Development to Regeneration: The Power of Bioelectricity

Bioelectrical gradients guide embryonic development by creating an electrical scaffold for tissue and organ growth. Researchers harness the power of bioelectricity to devise strategies for regenerating various tissues, including promoting brain recovery after stroke.

Welcome to *The Scientist* Speaks, a podcast produced by *The Scientist'*s Creative Services Team. Our podcast is by scientists and for scientists. Once a month, we bring you the stories behind news-worthy molecular biology research.

In this episode, Iris Kulbatski from *The Scientist* spoke with Paul George, a physician scientist in the Department of Neurology at Stanford University to learn more about his team's research on bioelectricity for stroke recovery.

Bioengineering a Younger Brain Environment

Narrator: With a background in bioengineering and stroke neurology, Paul George occupies a unique niche as a physician and researcher. George is motivated to improve clinical therapies available to patients with neurological injuries, with an emphasis on promoting post-traumatic nerve regeneration following stroke. Because the adult brain does not recover well following injury, George focuses on developing strategies that help nudge brain cells towards more youthful regenerative behaviours. While pursuing his PhD, George explored how biomaterials interact with the body, leading him to study how they can modulate electrical signals to promote nervous system recovery after injury. For example, his team develops electrically conductive hydrogels, biocompatible, water retentive, and malleable materials often used by bioengineers to replicate the cellular microenvironment. George and his team pack hydrogels with electrically conductive fillers to help replicate the conditions of the developing nervous system and guide differentiation of transplanted stem cells to support brain repair.

Paul George

On the research side, having the frequent contact with patients and their families and caregivers really helps focus the things that we put our efforts into, trying to find therapies or devices that can improve recovery. Nothing focuses that more than seeing someone who's not able to walk or speak like they used to before a stroke. Lab work helps me be a better clinician because you can experience those frustrations with the patient, that there's no treatments available to them, but you can start to tackle that problem, with research. The research component really helps keep me motivated to tackle those problems that you see on the clinic side that don't have answers yet.

Narrator: The exploration of bioelectricity for treating various diseases and disorders is hardly new. Despite this, scientists still do not know exactly how electrical signals influence the human body. Because the nervous system relies on electrical gradients and signals for communication, it is especially responsive to electrical modulation. Scientists seek a deeper understanding of these processes to improve treatments and therapies for traumatic brain injuries such as stroke. While electrical stimulation following stroke has shown some protective benefit, more information about developmental processes may help scientists tip the balance towards better regenerative strategies.

Paul George

The electrical signals that are there close to the beginning of when our bodies are forming play key roles. When you think about cells dividing and then specializing into certain organs, they're largely guided by physical, chemical and electrical cues, especially the brain, spinal cord and peripheral nervous system have electrical signals that guide their formation and functions. People have been using the fact that the body reacts to electrical stimulation for a long time. Understanding that is important to help decipher how the body works. I think it's amazing. We've used, it in many ways, for treatments of depression, other clinical applications, but still, the fundamental understanding of exactly how it works is still a little bit of a mystery.

Narrator: George and his team focus on creating cell and tissue environments that mimic the brain's natural plasticity to improve recovery. They tap into bioelectrical pathways to influence tissue regeneration and address the complex problem of regenerating the adult nervous system following trauma. Their approach is to bioengineer a more youthful environment for nerve cells using biomaterials, to recapitulate some of this early neuroplasticity and coax regeneration.

Paul George

At various times in life, the brain is really adaptive and plastic. It can be rewired so people who suffer stroke, even before they're born, can, in their adulthoods be almost normal, just because the brain can adapt at those early stages. People have used omics looking at genetic changes across different diseases. There seem to be weird windows where the brain and the nervous system just naturally revert back to those windows where things are a little more plastic. We've really tried to use our interventions to expand that and hopefully improve recovery by creating that environment where neurons regenerate or reprogram, to take on function that was lost.

Implantable Conductive Polymers Support Stem Cell Therapy

Narrator: George and his team modeled this younger environment by developing an implantable conductive polymer system that serves a dual function as a stem cell delivery system that can also electrically stimulate the brain after stroke. Polymers such as hydrogels are good implantable devices for delivering stem cells to the brain because they are soft, flexible, and can conform to the shape of biological tissues. George and his team loaded electrically conductive polymers with stem cells and imbedded them into the brains of stroke injured rodents. After transplantation, they applied gentle electrical stimulation through a conductive platform to the transplanted cells and tracked neural recovery.

Paul George

We found that the electrical stimulation changes what those stem cells are secreting and the animals that received electrical stimulation and stem cells almost had a doubling of stroke recovery. We think it's a combination of those chemical signals and the electrical stimulation effects on the stem cells and the brain that improve recovery. We're excited about the next steps in this project looking at how we use the remnant circuits of the brain that survive after injury to trigger electrical stimulation, and then having the right environment with stem cells, chemical cues, as well as electrical stimulation triggered by function could enhance that circuit reformation after injuries like stroke. To keep our research relevant to patients we've gone to older animal models because stroke happens in an older population, generally. We've seen similar responses to some of the brain's own mechanisms of recovery in the animal studies we've done so far.

Narrator: George's team also develops advanced cell culture models using neurons and glia derived from induced human pluripotent and bone marrow derived mesenchymal stem cells. Glia, the non-neuronal cells of the nervous system, play important supportive roles, including maintaining homeostasis and producing myelin, the fatty sheath that insulates nerves and improves electrical conduction. The advantage of using human stem cells is that they allow researchers to study human neural progenitors and differentiated human neurons and glia in vitro, improving the relevance of the model with a simpler experimental format compared to the rodent models. George and his team interrogate the cellular and molecular mechanisms that affect neurons and glia following stroke-like conditions, including reduced oxygen and glucose, and in response to electrically conductive biomaterials. His in vitro studies provide an important proof-of-principle that modifying electrical fields can influence how stem cells behave, including their differentiation patterns.

Paul George

Induced pluripotent stem cells could be taken from an adult, even their skin cells, and then reprogrammed to have a stem cell state, which means that they can differentiate into any cell type. We've looked at various polymer effects. One interesting study looked at a polymer where we created different strengths of electrical fields that the cells experienced and how that affected the stem cells differentiating into various cell types. Those with stronger electrical fields tended more towards a neuronal fate compared to those which had a glia type phenotype. In these settings where maybe some of the brain's own stem cells are coming to help with repair, those electrical fields can have a large effect on those functions, and even the type of cell that maybe those cells change into as they try to improve recovery.

Electrifying the Future of Bench to Bedside Research

Narrator: Spatial control is an important consideration when applying electrical stimulation in the context of tissue regeneration. During embryonic development, variations in bioelectrical gradients coordinate the response of stem cells by nudging them towards specific lineages, migratory paths, and tissue growth. Stem cells respond to the location and intensity of these electrical cues, which act as an electrical template that forms the basis of tissue anatomy. By using gradient electric fields rather than static ones, George's in vitro conductive polymer model may help mimic the non-uniform electrical gradients that stem cells experience during development. As George thinks forward towards the translational potential of his research, implantable conductive devices loaded with stem cells are just one part of his overall approach to improving recovery by augmenting the brain's electrical environment and taking advantage of the regenerative potential of stem cells.

Paul George

There are various thoughts on stem cells and how viable they are for large-scale treatment, but I think what can't be argued is that across hundreds of experiments now and various labs across various countries, stem cells do improve recovery after neurologic injury. Since if we stimulate the stem cells, we see improvement in their ability to help with recovery, we've looked at what factors stem cells are producing to see if there's a therapeutic candidate there. We found, through transcriptomics and other large-scale methods to see what the cells are secreting, a few exciting candidates, one of which we're moving forward. If we just give that protein on its own, it actually has quite an effect on improving recovery and so, it would be developing a more traditional treatment that could make its way to clinic

Narrator: While the road from bench to bedside is a long one, advances in the basic understanding of how cells respond to electrical stimulation provide an important foundation for answering clinically relevant questions. George is excited about the potential for his in vitro and animal models, as well as other novel techniques to examine basic cellular and molecular mechanisms in response to electrical fields and believes that the future for this work is bright.

Paul George

There's a lot of applications of electrical stimulation for cells in the body, but the basic understanding is still at an early stage. People have seen that cells will grow neurites in the direction of fields, different channels get expressed on one side of the cell that are in in an electric field, but even questions like how the mitochondria or different cell parts are affected by electric stimulation are not fully understood. I think that's an exciting area. We have better tools and new techniques that can really study cellular and sub cellular activity. I think over the coming years, we'll have a better understanding. Is it just that cells are inherently charged in some manner so they respond to fields of electrical stimulation, or are there various components that are more responsible for these changes that we see?

Outro: Thank you for listening to *The Scientist* Speaks! This episode was produced by the Creative Services Team for *The Scientist* and narrated by Iris Kulbatski. Please join us again in April, as we learn how researchers explore the neuroscience of gut touch and its role in gastrointestinal health and disease. To keep up to date with this podcast, follow *The Scientist* on Facebook and Twitter, and subscribe wherever you get your podcasts.