Brain Quest

Charting Complex Terrain Within Neurons

Promising insights into how brain cells are formed, how brain development goes awry and mechanisms in degenerative brain disease are emerging from a lab on the fifth floor of Skirkanich Hall.

"As we generate maps of how the genetic sequence, the DNA, folds and coils into complex 3-D structures inside the nucleus of brain cells, we're exploring an aspect of genetics that has not yet been examined," says Jennifer Phillips-Cremins, assistant professor in Bioengineering, who joined Penn's faculty in early 2014.

As her lab develops the first-ever maps of 3-D genome folding patterns inside neurons, Cremins advances her hypothesis that "how genetic material folds is intricately associated with how genes are expressed and how the brain 'wires up' during early development." Her ultimate goals are to uncover new mechanisms for how the brain works, use that knowledge to better understand the onset and progression of disease, and then someday find ways to reverse-engineer that knowledge to control precisely how genes are expressed so they don't get dysregulated in disease.

Amid a buzz of excitement about yet-to-be-published discoveries, Cremins describes the key finding in her most-cited paper in *Cell*: "We uncovered evidence that 3-D genome folding patterns change in dramatic ways as stem cells from the early embryo turn into brain cells during early development. Now we're focused on understanding what these three-dimensional patterns mean for brain function and disease."

CURIOSITY AND COMPASSION

Cremins recently received the 2015 NIH New Innovator Award for her novel research techniques and aims. In early 2015, she also received an Alfred P. Sloan Research Fellowship as an emerging scientific leader, following her designation in 2014 by the New York Stem Cell Foundation as a Robertson Investigator, an honor bestowed on the world's preeminent stem cell scientists.

Curiosity and compassion drive Cremins' experimental focus on neurodegenerative diseases like Alzheimer's, and neurodevelopmental diseases such as Fragile X. "I recently became interested in underlying mechanisms regulating brain development during the earliest years of life and how that development goes awry, ultimately leading to debilitating neurological diseases," she notes.

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Her interest in brain dysfunction began during her first job as a caretaker for an individual with Alzheimer's, which was also her grandfather's diagnosis years later. "Then, near the time when I started my lab at Penn, I also introduced my own son into the world," she recalls. "I have watched in wonder and awe as my son grows and acquires advanced cognitive processes and abilities. I strategically picked Fragile X because I wanted to help children with devastating brain disease and intellectual disabilities in particular. There are 20 or more diseases with the same trinucleotide expansion mutation problem as Fragile X, including Huntington's disease and many of the ataxias. We hope the mechanisms we study will matter across many neurodevelopmental diseases."

Cremins hopes to someday develop techniques that go beyond screening for genetic errors to also block the recurrence of key mutations. "My goal is to gain new knowledge that can be used to develop new strategies to prevent neurodevelopmental diseases altogether instead of treating symptoms." For neurodegenerative diseases, she likewise hopes to find ways to block early steps in the cascade of errors within the genome so the full onset of the disease is blocked from progressing.

JENNIFER PHILLIPS-CREMINS
Assistant Professor in Bioengineering

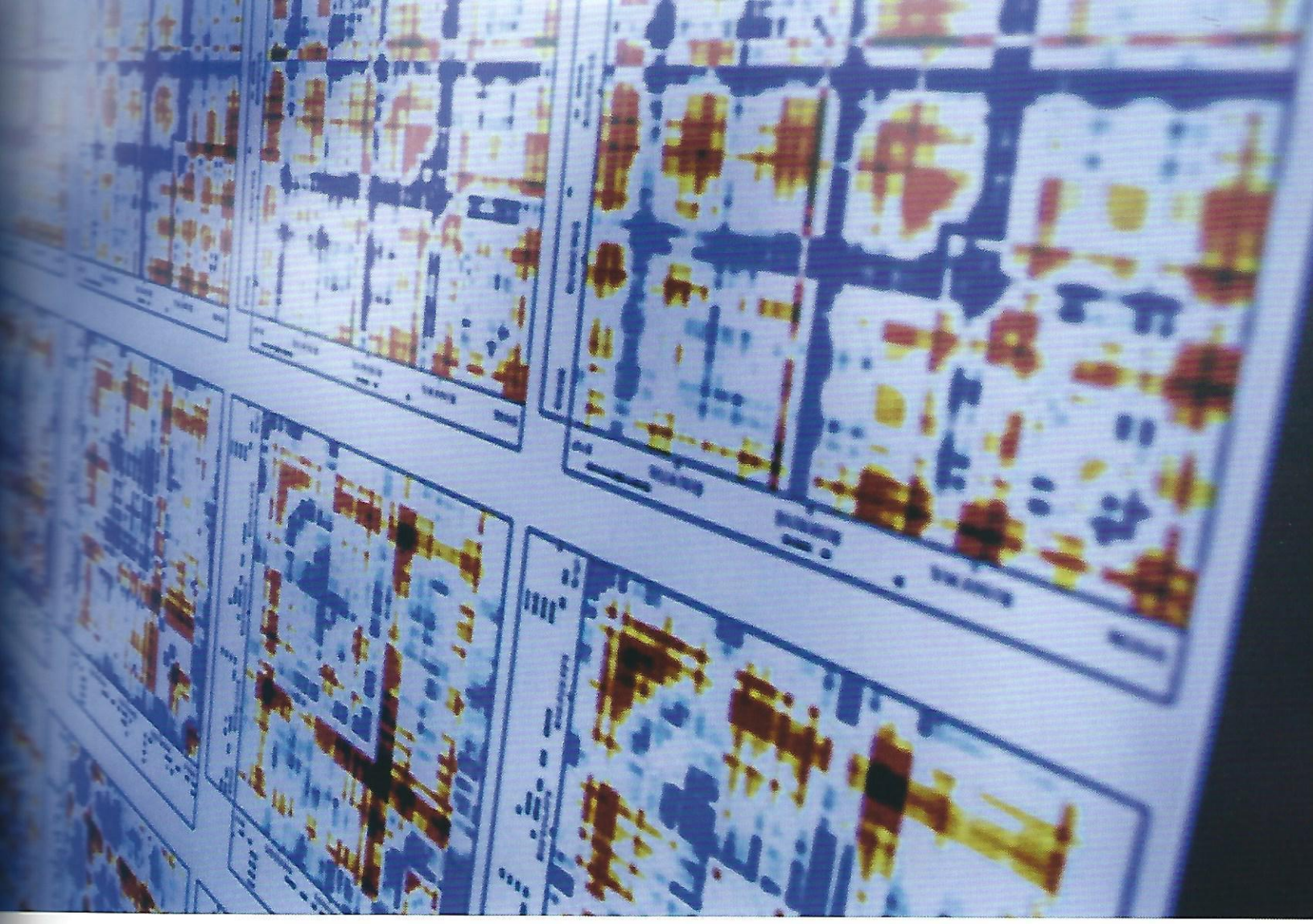
Jennifer Phillips-Cremins (foreground) studies genome architecture heatmaps with doctoral students Heidi Norton and Jonathan Beagan. These maps give researchers a snapshot of how genes and other important segments of DNA interact with each other in 3-D space.

She's forthright that her high-risk research goals may or may not come to fruition during her career. Such caution mixed with optimism reflects the legacy of the mapping of the human genome in 2001, when early hopes were deflated by gene therapy failures. The next wave of related discovery focused on epigenetic switches that regulate gene expression, trigger cell differentiation throughout the body from conception to end of life, and respond to environmental cues such as nutrition, exercise and stress—an elegant synthesis of nature-nurture.

CHROMATIN CARTOGRAPHER

In early 2015, the human epigenome was mapped for the first time in linear form, not as it exists within actual cells. Cremins' lab focuses on that next frontier: creating 3-D maps showing how the genetic sequence (roughly two meters in length when stretched out end-to-end) fits inside the nucleus, which is about the size of the head of a pin. Discoveries occur when patterns of spatial proximity between distant sections of chromatin (a complex of DNA, RNA and histones) are linked to regulation of gene expression for a particular type of neural cell. Form informs function, says Cremins, offering two metaphors: how an airline flight map shows key hubs of activity where lines join cities connected by frequent travel, and how a particular knot pattern is tied for a specific use and purpose.

Her lab's biggest discovery since coming to Penn occurred in early 2015. Doctoral student Jonathan Beagan observed that when a somatic (mature) cell is reverse-programmed to a pluripotent cell (capable of becoming several different cell types), it retains traces of the 3-D genomic folding configuration of its mother cell. This result may yield clues to new ways to prevent or reduce side effects of therapeutics and to engineer cells for desired characteristics.



"When I observed 3-D genome folding memory for the first time," remembers Beagan, "that moment of discovery was thrilling."

REMEMBER THIS MOMENT

Heidi Norton, also a doctoral student in the Cremins lab, likewise describes a not-yet-disclosed breakthrough. "I showed the data to Dr. Cremins and she said, 'This is huge! You should remember this moment because they come along rarely in science.'"

Discoveries like these may soon occur with greater frequency in the Cremins lab, which currently has $4.1 million in funding, including recent funding through the NIH 4D Nucleome Common Fund initiative. Cremins and her team of ten graduate and undergraduate students, computational scientists and research technicians, in collaboration with Arjun Raj, assistant professor in Bioengineering, and Gerd Blobel, professor in Pediatrics at the Children's Hospital of Philadelphia, all work to cross-train one another. They aim to combine "wet lab" and "dry lab" skills in molecular and cellular experimentation plus coding, computation and data analysis.

"Beyond the biology, there's a complex data science component to our work: how to analyze a massive amount of data and how to appropriately use statistical principles to find patterns in big data and interpret the biological significance of the patterns correctly," says Cremins. "Watching my students grow into talented and purposeful multidisciplinary researchers who collaborate to make discoveries is inspiring. They're equipped to make a big impact on the future with the depth and breadth of skills needed to integrate and drive biological discovery."

By Jessica Stein Diamond