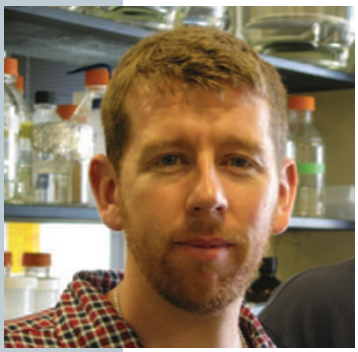
THE AUTHOR FILE

Tom Muir

From the netherworld between biology and chemistry comes a new method that leverages both fields and delivers acceleration to chromatin biochemistry.



Princeton University

Tom Muir

During the FIFA World Cup, everyone in his lab pulled for their national teams, making it a fun workplace, says Tom Muir, whose lab is in Princeton University's chemistry department. Muir's group includes students and postdoctoral fellows from all over the world, and he feels lucky to enjoy the international atmosphere and their talents.

Fun in the lab is also part of studying how nature deploys chemistry. "How could the journey that is being a research scientist not be fun?" Muir asks. He makes sure his lab celebrates achievements, adding, "being of Scottish background, I have always needed little stimulus for a good celebration."

The latest celebration revolves around a way to do chromatin biochemistry in a much quicker and more sensitive way than was previously possible. Muir praises his team, and particularly postdoctoral fellow Uyen Nguyen, for their determination. The lab had no previous experience with DNA sequencing and data analysis and the researchers deserve "amazing credit for pulling this off and for developing a very robust technology."

DNA is wrapped around proteins called histones, eight of which make up a nucleosome. Histones are not inert spools but are chemically modified in many ways. Muir thinks of these modifications as a "very complicated, dynamic signaling hub." Distinct patterns of histone modification accompany certain genomic states, which creates an epigenetic signaling puzzle that has many missing pieces. Correlative genome-wide studies will help find them, and Muir hopes his "biochemistry causality" can also contribute.

Previous methods to analyze nucleosomes required one-by-one analysis. This restricted the number of nucleosome variants that could be studied and hindered a systems-level view of epigenetics.

Muir's team created DNA-barcoded libraries of modified nucleosomes, separated them with chromatin immunoprecipitation and used second-generation sequencing to sort nucleosomes by the histone modifications they carry.

Not being a "DNA guy," Muir originally doubted that the method could be as sensitive and as quantitative as needed. "Fortunately, I was wrong," he says. Integrating second-generation sequencing sped up the method by a "shocking degree" and made it orders of magnitude more sensitive.

Over the years, Muir's lab has developed a number of technologies in various areas. Some have been widely adopted and others have not, "including some of my favorites," he says. It is "quite mysterious" why some methods stick and others do not.

As Muir turns some of his attention to chromatin biology, "our field is profiting from his puzzle-solving talents," says C. David Allis, who directs the laboratory of chromatin biology and epigenetics at the Rockefeller University, where Muir was a professor before joining Princeton's faculty in 2011. Muir also talks about 'designer chromatin', for which chemistry is used to synthesize chromatin from pieces, which Allis calls "masterful."

Allis did not know Muir before his time at Rockefeller, but he guesses that Muir was "extremely good at putting puzzles together or building Lego toys" long before he received any formal training in chemistry. No matter how many pieces to the puzzle, says Allis, Muir could take on the most challenging ones, "even if blindfolded."

Muir is at home in chemistry and biology, where he is caught, he says, "in some kind of netherworld between the two, stuck in permanent twilight and forced to hide from the bright light that is pure chemistry or pure biology." Biological questions drive his work, and he is not concerned with whether he should, for example, only use chemistry to study these questions. "We use whatever is best, and often this means a bit of everything," he says. "In my humble view, this is the only way forward for tackling many complex biochemical problems."

> "How could the journey that is being a research scientist not be fun?"

Muir did his PhD in chemistry at the University of Edinburgh and was a postdoctoral fellow at the Scripps Research Institute before landing a professorship at Rockefeller. He has received 15 honors and awards. For the scientists he mentors, his path seems a difficult one to follow, and, he says, "I seriously had no plan and indeed remain resolute in this approach to life."

Muir calls himself "the most naive person imaginable" and says he aligned himself with friends and mentors such that doors opened. "I could not recommend such a foolhardy approach to things to others," he says. "Fortunately, most students and postdocs are way more savvy than I was."

Vivien Marx

Nguyen, U.T.T. *et al.* Accelerated chromatin biochemistry using DNA-barcoded nucleosome libraries. *Nat. Methods* **11**, 834–840 (2014).