

## THE AUTHOR FILE

## Jason W. Chin

How to combine biology, chemistry and synthetic biology to add synthetic amino acids to a protein, and why creativity matters.

Jason Chin trained first as a chemist and then as a biologist but says these classifications have never particu-



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larly interested him. He enjoys the company of people with many perspectives. “I think one of the ways we become better scientists is by exposing ourselves to new ideas and unlearning the biases that come from our particular education,” says Chin, who is a group leader at the Medical Research Council Laboratory

of Molecular Biology (MRC LMB) in Cambridge. He founded the LMB’s Centre for Chemical and Synthetic Biology, and he also has an appointment in the University of Cambridge’s chemistry department.

“Proteins are fascinating molecules in their own right,” says Chin. Assessing the specifics of how proteins get things done in cells and organisms is hard, especially when trying to link molecular changes to macroscopic phenomena. He and his team have combined chemistry, molecular biology and synthetic biology techniques to modify one component of cellular chromatin in mouse embryonic stem cells and measure the changes’ impact.

Understanding the outcomes of specific chromatin modifications can help biologists and engineers. “If we can engineer chromatin modifications that are heritable and control the properties of a daughter cell, then we would have synthetically controlled the epigenetic state of a cell and realized synthetic epigenetics,” says Chin.

Chin and his team made stable cell lines that incorporate unnatural amino acids at efficient and consistent levels into histone proteins. The researchers genetically encoded a specific kind of acetylated lysine at multiple positions in histone H3: *N*- $\epsilon$ -acetyl-lysine replaces lysine. The scientists could then perturb the cells and compare responses between cell populations that incorporated the unnatural amino acid and wild-type populations.

The work involves creating a kind of parallel universe with respect to the cell’s intrinsic system: a pyrrolysyl-tRNA synthetase/tRNA<sub>CUA</sub> pair, which is an enzyme plus tRNA, the vehicle that delivers the amino acid corresponding to the three-letter nucleotide sequence on the mRNA. The new synthetase and tRNA work with

each other and without cross-reacting with any of the synthetases or tRNAs in the cell, says Chin. The artificial amino acid is attached to a growing amino acid chain in the place of a stop codon that has been engineered into the cell’s genetic code. Instead of stopping translation, this amino acid is built into the polymer.

Manipulating just the enzyme that modifies chromatin could change the amino acids in chromatin, but it would also modify many other proteins. “This means that we cannot assign any effects we see to the modification at a particular site in chromatin,” says Chin. Modifying chromatin via this parallel but independent route modifies solely the target amino acid in chromatin, which makes it possible to understand the effects of that one modification.

Chin’s colleague Shankar Balasubramanian, a chemist at the University of Cambridge, calls Chin “an imaginative, mild-mannered fellow who elegantly addresses challenges that are complex and important.” Chin obtained his PhD in chemical biology at Yale University, followed by a postdoctoral fellowship at Scripps Research Institute and then his position at MRC LMB.

In the lab, Chin cultivates creativity. Discussion helps the lab team to see beyond any training biases “and allows us to arrive at a collective vision of what we want to create,” he says.

Chin fuels his creativity through literature. He has read almost everything by Haruki Murakami and David Mitchell and is currently re-reading Alan Hollinghurst’s *The Line of Beauty*, a decade after it left its first impressions on him. The novel focuses on the experience of gay characters who were unlike anyone Chin knew when he first read the book. Later, he says, he met people like them.

“Hollinghurst’s book is beautifully written and is worth reading just for that,” says Chin. It is set in several time periods, including Thatcher’s Britain, which Chin remembers from his childhood and teens. Re-reading the book now reminds Chin of his teenage activities, which included demonstrating against Clause 28 in the UK, and, he says, “I’m proud of my teenage self for that.” The legislative amendment Clause 28, which has been viewed by many as homophobic, was introduced in 1988 and repealed in 2003.

Chin says he enjoys when concepts he imagined can be transformed into tangible realities in the lab, and, he adds, “of course each success opens so many new possibilities for the imagination to explore that you never really spend time thinking about what you have accomplished.”

#### Vivien Marx

Elsässer, S.J., Ernst, R.J., Walker, O.S. & Chin, J.W. Genetic code expansion in stable cell lines enables encoded chromatin modification. *Nat. Methods* **13**, 158–164 (2016).

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