**MAKING THE PAPER**

**Sunny Xie**

Four years’ hard labour earned a picture of gene activity in single cells.

Sunny Xie’s identical twin daughters have the same set of genes but different personalities. Why? The question has intrigued their father since the girls’ birth six years ago. Now, a study reported on page 358 of this issue showing how genes are activated in cells may bring him a little closer to an answer.

Up to this point, scientists have studied gene expression in many cells at once. The ability to home in on a protein molecule being manufactured in a single cell would not only offer a more accurate view of the process but could help scientists understand how the same genes produce different phenotypes. This possibility prompted Xie’s lab at Harvard University to embark on a project that took four years to complete.

During a lab meeting, Xie proposed the idea of using β-galactosidase, a bacterial enzyme, to monitor the expression of a single protein in a living cell. The enzyme is routinely used as a reporter in gene-expression studies, because a single molecule of protein generates many fluorescent compounds (fluorophores), creating a detectable signal. Xie’s lab had already started using the enzyme to study gene expression in *vitro*, but lab members were wary of going into living cells. One problem was that the fluorophores quickly ooze out of the cell, making measurements *in vivo* difficult. In addition, no one in Xie’s lab had expertise in molecular-biology techniques. “Most people thought it would not work,” says Xie.

In the end, a first-year graduate student, Long Cai, took the plunge. He was later joined on the project by postdoc Nir Friedman, with whom he shares first authorship of the *Nature* paper.

Xie also recruited a molecular biologist to the team. “I interviewed half a dozen candidates and they all turned me down,” he laughs. “They looked around the lab and got scared.” Finally, Jie Xiao accepted his offer and trained half of Xie’s group on molecular-biology techniques.

The team tried different strategies to measure β-galactosidase expression, but initially nothing panned out. “Every time we thought we got the system to work, it turned out to be an artefact,” says Xie. Two years into the project, Cai and Friedman decided to give microfluidics, tiny devices that hold nanolitres of liquid, a try. They placed individual cells in microfluidic chambers to trap the fluorophores. The signal in each chamber was then measured in real-time using a fluorescence microscope.

Using this system, Xie and his colleagues determined that protein expression occurs in short, randomly timed bursts in each cell. The number of protein molecules made during each burst follows an exponential distribution. In addition to providing footage of gene expression, the technique opens the door to monitoring many genes — one gene and one cell at a time — in response to different stimuli. “I knew this was going to be a significant experiment,” says Xie. “Although, I guess I could not articulate why as well as I can now.”

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**QUANTIFIED PODCASTS**

A numerical perspective on Nature authors.

The *Nature* podcast, a free audio show featuring highlights from the current issue, goes online each week. Chris Smith, a virologist and radio presenter from the University of Cambridge presents the show. It includes discussions on topical issues with *Nature* journalists, and short interviews in which the authors of *Nature* papers explain the significance of their work and talk about what drew their attention to the problem, how experiments were carried out and what they have learned for the future.

This week, four authors discuss their research on the *Nature* podcast, covering a variety of topics from folding DNA (see page 297) to firefly lights (see page 372).

You can download the *Nature* podcast at www.nature.com/nature/podcast.

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