

Scientists

Following a Hunch

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Sunney Xie's development of innovative technologies for single-molecule analyses caught our attention. Curious to know more, *BioTechniques* contacted him to find out about the ambition, character, and motivation that led to his success.

What experience most defined your research focus?

When I started my independent career, I embarked on single-molecule studies, which were very compelling to me. I certainly didn't see what this field would become through the crystal ball; my decision was just a hunch. But probably the pivotal event that shaped our applications of the technology came when I arrived at Harvard and audited a molecular biology course taught by Richard Losick.

During the class, Losick showed cartoons demonstrating how polymerases and ribosomes worked. While watching those, I thought it might be possible to make real-time movies of those processes in live cells one day. That idea motivated us to develop the technologies required to see and study live single-cell gene expression.

What do you consider to be your most important scientific contribution?

After working out many technical details, I was among the first to do single molecule fluorescence imaging and spectroscopy at room temperature. In a first of its kind experiment, we applied this technology to follow the enzyme cholesterol oxidase, which was fluorescent in the oxidized form, but not when reduced. During enzymatic cycling, the fluorescence turned on and off, so we could read the emissions from immobilized enzyme molecules and follow this cycle in real-time. Our experiments resolved some key issues about how enzymes work. We discovered a phenomenon that was otherwise hidden in previous experiments—enzymes work hard for a while and then slow down, but the Michaelis-Menten equation holds even at the single-molecule level.

In terms of new technologies, we pioneered Coherence Anti-Stokes Raman Spectroscopy (CARS) and also Stimulated Raman Scattering (SRS) microscopy. Molecules have characteristic vibrational frequencies corresponding to different chemical bonds, which can be probed by Raman spectroscopy. The signal is rather weak, so it's not appropriate for imaging. SRS and CARS are label-free methods that allow us to image DNA, protein, small molecule metabolites, or drug molecules in living tissues with significantly more sensitivity than previous methods.

Since then, we have gone on to study gene expression in single cells at the single-molecule level and imaged protein and mRNA production, one molecule at a time. In doing so, we were able to describe these processes in a live cell at a quantitative level. It's fair to say that due to the contributions of many research groups, the single-molecule approach has changed the way many biological questions are addressed.

What are you working on now?

Our latest direction is single-cell genomics. Individual DNA molecules in living cells change with time by acquiring copy

number variations and SNPs. Activity in different cells cannot be synchronized, so we must study heterogeneity on a single-cell basis. To do this, we developed a bias-free whole genome amplification method called MALBAC for single cells.

After development, we used MALBAC to create a new procedure for IVF, which is now in clinical trial in China. We sequence polar bodies, the two small cells spit out by the fertilized egg that are dispensable. From that sequence, we can deduce if the fertilized egg is viable since precise counting allows us to avoid chromosomal segregation errors. The trial is ongoing, but so far, it's clear that this approach improves IVF birth rates and increases the average age of IVF patients. This approach also avoids point mutations associated with Mendelian diseases from either parent by selecting a fertilized oocyte that does not have the mutated allele.

We are also studying de novo mutations, particularly those that lead to cancer. MALBAC is good for detecting these mutations, but it is not the endgame. We are now developing better methods to uncover new mutations. With this kind of technology, we will be able to answer scientific questions, but could also use it immediately for medical diagnosis.

What has been the highlight of your career so far?

The most exciting part has been helping the patients in the clinical trial. One patient came to me because he had a point mutation inherited from his father that caused him to develop bone cancer at age 10. He didn't want his child to have the same outcome. I worked with them and the clinicians, and was actually waiting outside the room when they had their first ultrasound. You can imagine how excited they were to confirm the pregnancy, and to believe that the baby will be free of disease.

Interviewed by Kristie Nybo, Ph.D.
Image courtesy of Harvard University.

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