

Leaders of the field

What does the future hold for single molecule technology?

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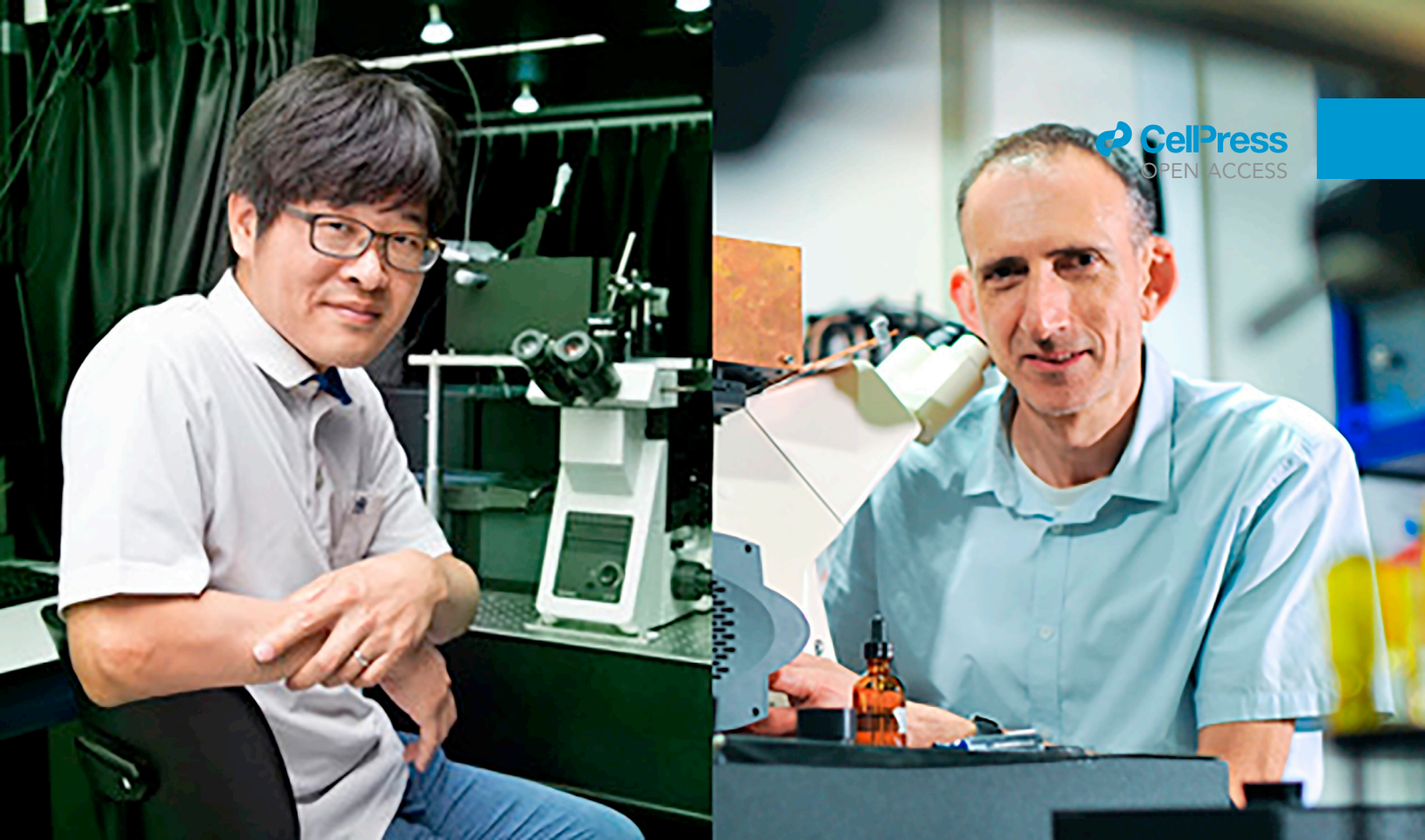
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Backstory

Leaders of the field: What does the future hold for single molecule technology?

Chirlmin Joo¹ and Amit Meller²

In recent years, single molecule technology has experienced a rapid growth, with exciting developments in fundamental research and real-world applications. Detecting and studying biological phenomena on the single molecule level requires a unique synergy between researchers working on instrumentation, physics, and the life sciences. In the *iScience* special issue “Single Molecule Technology – From Biotechnology to Biomedical Applications”, guest edited by Amit Meller and Chirlmin Joo (Figure 1), we are highlighting a variety of research on nanopore technology, single molecule fluorescence, and a selection of other ultra-sensitive detection methods. More content in the special issue can be found here: <https://www.sciencedirect.com/journal/iscience/special-issue/10PGSBV55N0>. The guest editors in this backstory share their thoughts on what is currently exciting in the field, and the advances they think will make an impact in the near future.

MOTIVATION

What originally interested you in the field of single molecule detection? Did you train in this area or are your research interests naturally aligned with the developing field?

Joo: I got to know about molecular biology only near the end of my undergraduate study, but I was extremely intrigued by the molecular mechanism of biological systems. So, after entering University of Illinois at Urbana-Champaign for a graduate program, I decided to do my PhD study under the supervision of Taekjip Ha, a pioneer of the single-molecule fluorescence technique. Ever since, I have been enjoying looking at the molecular processes under a single-molecule microscope.

Figure 1. Guest editors Chirlmin Joo (left) and Amit Meller (right) of the *iScience* special issue “Single Molecule Technology – From Biotechnology to Biomedical Applications”.



Meller: My undergraduate training is in Physics and I was focusing on soft condensed matter physics during my PhD work. Around 1995, David Bensimon (Ecole Normale Superior, Paris) arrived for a sabbatical in the lab I worked at the Weizmann Institute and asked me to construct an experimental system to apply force on a single Beta-Galactosidase enzyme while monitoring its enzymatic activity, using a combination of an optical trap and fluorescence. I was immediately captured by the incredible and unique information that could be accessed using *in singulo* biomolecular assays. I started reading on the various single-molecule techniques such as optical/magnetic tweezers, patch-clamping, and sm-fluorescence and drifted toward *nanopore sensing* which has just started these recent years. A couple of years later when I joined the Rowland Institute (Cambridge, MA) I had a chance to work with Dan Branton (Harvard) and meet and interact with other pioneers in the field including Howard Berg, Steve Block, and a few years later, Evan Evans. These events shaped my research interests for the future.

“I was immediately captured by the incredible and unique information that could be accessed using *in singulo* biomolecular assays”

What kind of scientific background do you have, and is this typical for other researchers in the field to have?

Joo: I have very interdisciplinary backgrounds which are necessary for single-molecule biophysics research. My backgrounds are mixed with physics (undergraduate), biophysics (PhD), and biochemistry (post-doctoral training). By working with diverse collaborators, I am expanding my expertise to chemistry, proteomics, bioinformatics, computational simulations, nanotechnology, and cell biology.

Meller: I must say that even today after more than 20 years in a “Bioengineering” faculty I consider myself a physicist more than anything else. I have been teaching in this area for some time now and always find myself talking about the underlying physics for all biological and bio-technological topics covered.

INTERDISCIPLINARITY

What role does interdisciplinarity play in your research?

Joo: Biophysics is intrinsically interdisciplinary, requiring a wide spectrum of expertise in fundamental and applied sciences. Developing single-molecule protein sequencers requires even wider expertise including protein chemistry, machine learning and engineering, among other related skills.

What suggestions would you give to a young scientist interested in the single molecule field?

Joo: There are huge opportunities for the use of single-molecule biophysics for real-world applications. For example, a single-molecule protein sequencing tool will revolutionize the fields of biology and medicine when its commercial form is achieved (Figure 2). Manufactured as a table-top machine, it will be routinely operated by clinicians in hospitals, bringing about personalized diagnostics. To develop this technique beyond proof-of-concept, the community is looking for young talents who are willing to take a risk.

Meller: Don’t spare any moment dwelling into the fine details of any single-molecule technique that you are interested in. It is critical to be familiar with the basic physical and chemical and engineering rules before you use it to study a complex system.

What are the other disciplines that should look to this field with interest?

Joo: The new technology will create the opportunity for single-cell proteomics and real-time screening for on-site medical diagnostics.

Meller: Single-molecule technique is producing incredible amounts of data and information. This trend will accelerate in the years to come and would invite researchers from information analyses fields, including artificial intelligence (AI) to use for the benefit of science and technology.

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Figure 2. Single molecule protein sequencing will decode the proteome of the cell.

FUTURE

What are the most important, exciting, and interesting questions in the field currently, and why do they matter?

Joo: There is the need for a platform for highly sensitive protein analysis tool. By analyzing proteins molecule by molecule, this will provide a wide dynamic range of detection. Unlike conventional sequencing, this sequencing will be less error-prone for its direct measurement. Single-molecule detection is sensitive enough for this approach to require only a small amount of sample. This novel sequencing approach will change the paradigm of sequencing techniques.

Meller: I cannot agree more with my colleague Chirlmin Joo on this point.

What do you think are the biggest challenges that the field is facing?

Meller: When systems are out of thermal equilibrium, which is often the case in biological system studied *in-vitro* or *in-vivo*, we lose a big portion of the basic intuition and are challenged with interpreting our observations. Of course, we can resort to computer simulations, but they involve certain assumptions about the basic interactions and such. I wish we had much deeper comprehension of biomolecular dynamics outside of thermal equilibrium.

Joo: Since 1990 when the first single-molecule fluorescence detection was demonstrated, single-molecule studies have revolutionized the field of molecular biology and cell biology. I think that single-molecule techniques will continue to make breakthroughs when the methods are further developed to study intrinsically complex biological phenomena and for applications such as molecular diagnostics. To achieve this, we need talented people from all different disciplines.

“We need talented people from all different disciplines ... the community is looking for young talents who are willing to take a risk”

What breakthroughs do you imagine or hope to see in upcoming years?

Meller: I hope to see more and more single-molecule techniques affecting the field of precision and personalized medicine. I predict that we will see more and more “portable” and highly sophisticated technological solutions for biomedical sensing involving SM methods.

Joo: What is happening in the field of RNA therapeutics and genome editing is inspiring. Decades of RNA studies have been translated to small RNA therapeutics and mRNA vaccines. A recent discovery from CRISPR biology is being translated to genome editing by numerous start-up companies, and we hear success stories almost every week. As the interface between academia and industry is becoming blurry, I hope to see that single-molecule detection, particularly single-molecule protein sequencing, is achieved through active collaboration between academia and industry soon. The recent launch of several start-up companies for single-molecule protein sequencing is very encouraging.

FINAL THOUGHTS

Single molecule biotechnology is undergoing a transformation, which is due in no small part to recent technological advances, including the development of new tools to sequence and study proteins. Advances in the field are being driven by increased accessibility of new technologies to applied researchers, and innovators who are crossing the boundaries between academia and industry. A new generation of interdisciplinary researchers bringing together biophysics, molecular biology, clinical science, and artificial intelligence will lead this field to a bright future.