Job Dekker: 2018 Edward Novitski Prize

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The Genetics Society of America's (GSA) Edward Novitski Prize is awarded to researchers who have solved challenging problems in genetics through experiments that demonstrate exceptional creativity and ingenuity. Job Dekker of the University of Massachusetts Medical School has been selected for the 2018 award in recognition of his innovative approach to understanding chromosome interactions and nuclear organization. Among Dekker's contributions are the development of the now-ubiquitous approach of chromosome conformation capture and the discovery of topologically associating domains.

When Job Dekker began his postdoctoral research at Harvard University in 1998, he did not set out to engineer an experimental approach that would transform his field; he was simply focused on how homologous chromosomes recognize each other so they can properly pair during meiosis. This fundamental question in genetics had remained unanswered, he realized, because it could not be addressed using existing methods, so he came up with his own.

Dekker's idea was risky, but his postdoctoral advisor, Nancy Kleckner, was supportive. "I told him, 'If this really works, it's huge. I think you should try it.'," she says. His plan was to identify the DNA sequences at the locations where homologous chromosomes touch, information he hoped would reveal how their ability to recognize each other is encoded. To find these physically interacting regions, he devised an approach in which stretches of nearby DNA are chemically cross-linked to each other, then digested into fragments. The cross-linked segments are then ligated, the cross-links reversed, and the newly joined sequences analyzed by PCR. Dekker called the method chromosome conformation capture, or 3C, a name now recognized far beyond the field of homologous pairing.

It was not long before Dekker realized that if he could make 3C work, he could learn about more than just pairing. He had the key idea that if he could generate a matrix of all pairwise interactions between segments of genomes, he would be able to determine the three-dimensional structures of chromosomes. Such data would provide previously unattainable insight into critical topics such as how genes are regulated, and how chromosomes are folded during meiosis and mitosis.

Still, the project was far from a guaranteed success, and since his time as a postdoctoral researcher would be limited, Dekker gave himself 1 year to produce some evidence that 3C could work. After 11 months, the first hint that he was on the right track appeared in the form of a single band on a gel. "Had it been one more month, I might have given up," Dekker says.

Dekker gives a great deal of credit to Kleckner for his eventual success. "I could not have developed 3C anywhere else, because you need to have an environment where wild ideas are supported, and she was critical for that," he says.

Once he had a working protocol, Dekker knew that he would need to use polymer models to quantitatively interpret the contact frequency data, and he had no experience with polymer physics. Dekker sent emails to several people whose papers on the subject he was trying to understand, and only Karsten Rippe, who had just started his own research group at the University of Heidelberg, responded. "I still think that was so generous of him, because he didn't know me," Dekker says of Rippe, who ended up being one of the four authors of the original paper describing 3C (Dekker *et al.* 2002). "But he took all that time to help me and to teach me these things."

Dekker says that kind of generosity is something he tries to emulate to this day. And there has been no shortage of people asking Dekker about 3C; as soon as the first paper was published, it immediately generated enthusiasm from researchers eager to try it themselves. "Job has spent an enormous amount of his time helping people to do things correctly, writing papers about how to do things correctly, and providing that computational infrastructure so that people can do these kinds of experiments," Kleckner says.

Dekker's attitude toward sharing and cooperation has led to his participation in numerous—often interdisciplinary—collaborations. One such collaboration yielded Hi-C: a method

based on 3C that uses next-generation sequencing to probe the conformations of entire genomes (Lieberman-Aiden *et al.* 2009). The method proved useful for such genome-wide studies, but it has also become commonly used for an unanticipated purpose. Unexpectedly, Hi-C has become a core method used for a problem that is not related to chromosome structure at all: genome assembly.

Assembling a genome requires thousands of fragments to be pieced together correctly and it can be difficult to see how they fit, especially when there are many repetitive sequences. Hi-C methods revealed how to go from a one-dimensional sequence to a three-dimensional structure, and using those rules in reverse has made it possible to use three-dimensional contact data from Hi-C to help generate a linear genome sequence. Using Hi-C for genome assembly has proven particularly useful for plant genomes, which can be challenging to assemble because they are often large and polyploid.

In 2012, another of Dekker's collaborations led to a highly influential finding in chromosome biology: topologically associating domains (TADs). Dekker had connected with Edith Heard, whose laboratory at the Curie Institute was studying the mouse X-inactivation center, a large locus required for silencing one entire X chromosome in every XX cell. Using a 3C-based technique, Dekker, Heard, and their groups found that the locus was divided into a series of smaller domains and that genes within a given domain were related through patterns of gene expression. Around the same time, Bing Ren's group at the University of California, San Diego also discovered TADs during a Hi-C study; the two teams published their results side-by-side in the same issue of *Nature* (Dixon *et al.* 2012; Nora *et al.* 2012). It is now known that TADs influence gene expression in many eukaryotes, including humans, and their disruption has been linked to specific diseases. "We weren't looking for these kinds of things," he says. "We just saw them in the data; the structure revealed them."

Just this year, Dekker and several collaborators used Hi-C along with biophysical modeling, microscopy, and genetics to determine the structure of a mitotic chromosome, something that has been his long-term goal since starting his laboratory in 2003 (Gibcus *et al.* 2018). "I never thought I would get there before my retirement," he says.

In Dekker's eyes, the future of the field will involve digging deeper into chromosomes' structures, including the biophysical processes and molecular mechanisms driving their formation, how they influence gene expression, their dynamics, and how they vary from cell to cell. The field's evolution will undoubtedly require him to continue adapting and seeking knowledge outside his current areas of expertise, a challenge that he finds more exciting than daunting. "That's the one aspect I really enjoy most," Dekker says. "I have no idea what I'm going to do in 5 years. It's probably going to be totally different."

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