THE AUTHOR FILE

Ulrich Elling

Improving single-cell data in CRISPR screens, with inspiration from open-air theater performances.

Our love of hypothesis-driven ideas can mean that people prefer to verify rather than falsify them, says Ulrich Elling, who works at the interface of genomics, developmental and stem cell biology and has been a group leader at the Institute of Molecular Biotechnology of the Austrian Academy of Science (IMBA) since 2014. "We do validation experiments, not failed falsification experiments," he says. "That is why I love unbiased screens." A screen can offer answers but also deliver unexpected, humbling experiences: a defined, specific question can turn out to be neither.

Greifvogelwarte Riegersburg

Ulrich Elling

Elling and his team now present CRISPR-UMI, an approach to CRISPR-based screens that complements single-cell RNA sequencing. The new method uses unique molecular identifiers (UMIs) to label individual cells before they are clonally expanded. Labs can distinguish these labeled cells and capture the heterogeneity of a population at the single-cell level. In a typical screen, labs might be looking at one mutagenesis event without knowing it, says Elling. Some cells dominate the observed population-level behavior; some single guide RNA (sgRNA)–barcode combinations enrich massively in sequenced reads, for unknown reasons. Adding a molecular fingerprint resolves such issues, he says.

CRISPR-UMI also lets labs analyze how reproducible positive selection events are—whether, for example, only one clone is enriched in a resistance screen or whether it is seen reproducibly in many cells carrying the same sgRNA. "There really is a world out there we were blind to in screening so far," says Elling. "We can ask how much the cells deplete that show depletion. Do they grow slower or die?" 'Freak' clones can be ignored, and a lab can observe single-cell-derived clones in thousands of biological replicates. He hopes the method can serve labs performing *in vivo* screens in which experimenters watch clones in a complex environment. It might let researchers analyze several guide RNAs per cell in parallel. He would like to use CRISPR-UMI for his continued work on stem cell reprogramming and transdifferentiation.

Elling grew into a fan of screening as he worked toward his PhD at the University of Regensburg and the European Molecular Biology Laboratory (EMBL) in the stem cell biology lab of Mathias Treier, and then during his postdoctoral fellowship in Josef Penninger's lab at the IMBA. Elling found that "one-by-one genetic studies are a tough business," in that they too rarely deliver the anticipated phenotype and seldom confirm a hypothesis. CRISPR screens can solve this problem, but a gene linked to a phenotype has to be inferred by counting a few sgRNAs in populations. He missed capturing the biological complexity and having the thousands of mutations per gene "that I got to love so dearly from haploid genetics," he says. Using this many replicates made it possible to study gene function in thousands of biologically independent mutations generated by random mutagenesis.

At IMBA, Elling likes the culture of tossing ideas around among faculty, postdoctoral fellows and students. Its community spirit is reminiscent of his enjoyable EMBL experience where, he says, it was beneficial to have hundreds of scientists "trapped on a mountain."

When he finds the time, he, his partner and their two sons go hiking and biking, both mountain and road. Before they had small children, they traveled widely: to Vietnam and Cambodia, hiking in the Himalayas, and to the Andaman Islands in the Bay of Bengal. With the children, they travel to Greece, where they combine snorkeling with visits to historic sites.

> "That is why I love unbiased screens."

Elling's friend Alex Stark, now also at IMBA, did his PhD work at EMBL alongside Elling. "Uli is a super social guy, who loves to organize trips or barbecues to bring people together," says Stark. "Scientifically, he's a method wizard: very creative in problem solving and inventing new methods, while at the same time very sharp, with an intuitive understanding what might work and what not—constantly performing sanity checks, questioning things that others might take for granted."

Perhaps because of that sociable streak, Elling likes being a science communicator and sees the big effect that technologies such as CRISPR will have on society. "We cannot solve the ethical, political and sociological aspects amongst scientists in the Ivory Tower," he says; it will take discussions with all of society. He also has stage experience: he began acting in theater companies during his PhD studies. He loved the acting and the new challenges of each piece, and the experience made him more self-aware in front of an audience. "I also acted in front of kids in the Heidelberg Castle open-air theater," he says. "Most honest audience you can have, obviously."

Vivien Marx

Michlits, G. *et al.* CRISPR-UMI: single-cell lineage tracing of pooled CRISPR–Cas9 screens. *Nat. Methods* **14**, 1191–1197 (2017).