Laudation for Dr. Irma Querques

Assistant Professor & Group Leader
Max Perutz Labs, University of Vienna
Austria

Finalist of the Eppendorf Award for Young European Investigators 2024

by Dr. Madeline Lancaster, MRC Laboratory of Molecular Biology,
Cambridge, United Kingdom
Member of the independent Eppendorf Award Jury

The genome is the blueprint of life. It encodes the beautiful, complex dance of proteins and enzymes inside each of our cells. It makes us who we are and is therefore shared and identical from cell to cell within our bodies. Or is it? The genome is often thought to be rather static, only undergoing minor changes from generation to generation, but now we know that more substantial changes can arise even within cells of the same individual.

This genomic plasticity comes about because of a constant battle being waged within our DNA. Small mobile elements called transposons encode proteins that process and insert those same bits of DNA elsewhere in the genome seeking to replicate and proliferate, while at the same time host proteins called repressors work to keep those transposons silent. Too much transposition and you get rampant mutation, but too little and you don't leave much room for evolution.

Transposable elements are not simply annoying selfish genes. In fact, they can be useful both to organisms and as tools in biotechnology and medicine. The CRISPR-Cas bacterial defence system is related to these mobile DNA elements, and involves genomic insertions that provide a mechanism akin to vaccination to foreign viral DNA. But there are also modified versions of CRISPR-Cas that enable RNA-guided transposition, thus providing site-directed insertion into specific loci of the genome.

How these work has been unclear and so using them to engineer specific insertions for biotechnology or clinical applications has been difficult. But Dr. Irma Querques, a Finalist for this year's Eppendorf Young Investigator Award, has set out to do exactly that.

Irma Querques grew up in a small town in the south of Italy called Lucera, a city known for its medieval and ancient Roman historical significance. She initially wanted to be a writer, but soon discovered the joy of scientific investigation and the stories it can tell. Like a detective novel, she found joy in the mysteries of science, and that curiosity took her to the University of Bologna, where she completed a Bachelor's and then a Master's in Biotechnology. From there, Querques came here, to the EMBL in Heidelberg, where she completed a PhD with Dr. Orsolya Barabas.

The focus of her PhD was on a special transposon called Sleeping Beauty. Sleeping Beauty is a powerful transposon system used by scientists to introduce many copies of a gene of interest into a host genome. It's a wonderful way to get stable expression in a cell line, for example. However, it is unpredictable and not a viable option for medically relevant applications. So Querques sought to engineer a Sleeping Beauty system that could be tightly controlled to avoid runaway transposition. By first working out the crystal structure of the Sleeping Beauty transposase enzyme, she was able to engineer a more soluble form that could be introduced directly into target cells, bypassing the need to express the protein from exogenous DNA that could itself become integrated in the genome. This new tool was shown to work well when introduced into CAR-T cells, a game-changing new therapy for cancer.

After a highly successful PhD, Querques joined the lab of Dr. Martin Jinek at the University of Zurich as a postdoctoral fellow, where she set her sights on special CRISPR-Cas systems that perform RNA-directed transposition. The mechanism of such site-directed transposition was unknown. By again taking a structural approach to elucidate through cryo-electron microscopy the structure of the Cas complex, she was able to uncover how the complex selects and primes the target DNA for insertion. With this information in hand, it is now possible to engineer a programmable Cas-transposon system for site-specific gene insertion.

Irma Querques has an insatiable thirst for knowledge, and a creative and inquisitive mind. Her PhD advisor praised her independence even at such an early stage of her career, and her ability to bring together the tools and expertise to complete a challenging project, all the while with a level of excitement and positivity that made her the "sunshine of the lab". It is this enthusiasm that has enabled her to already make several breakthroughs.