The age-old problem of telomere maintenance

Kelly Nguyen, having just won the 2022 Eppendorf Award for Young European Investigators, is interviewed by Adam Levy.

Kelly Nguyen is the 2022 Eppendorf Young European Investigator. She is a Group Leader at the MRC-Laboratory of Molecular Biology in Cambridge, UK. She spoke to Adam Levy about her pioneering work on the structure and function of telomerase, and its vital role in everyday cell function and disease. Nguyen describes how revelations about its structure also kept her going through lockdown.

This Q&A is an edited version of the podcast which can be found at: go.nature.com/eppendorf2022

What is telomerase?

DNA provides information that tells each cell what to do. In order to pack all the DNA into cells, it needs to be condensed into structures that we call chromosomes. Telomeres are located at the ends of the chromosomes, and because chromosomes cannot be fully copied every time the DNA replicates, the telomeres get shorter over time — which results in ageing and eventual death of the cell. Telomerase is an enzyme that can compensate for this shortening by maintaining telomeres at a stable length, helping to protect chromosomes against degradation and fusion.

How is telomerase implicated in disease?

Mutations that compromise telomerase's function can lead to a number of premature ageing diseases, such as aplastic anaemia and pulmonary fibrosis. On the flip side, cancers can also activate telomerase in order to make themselves immortal.

Why is it hard to analyse telomerase structure?

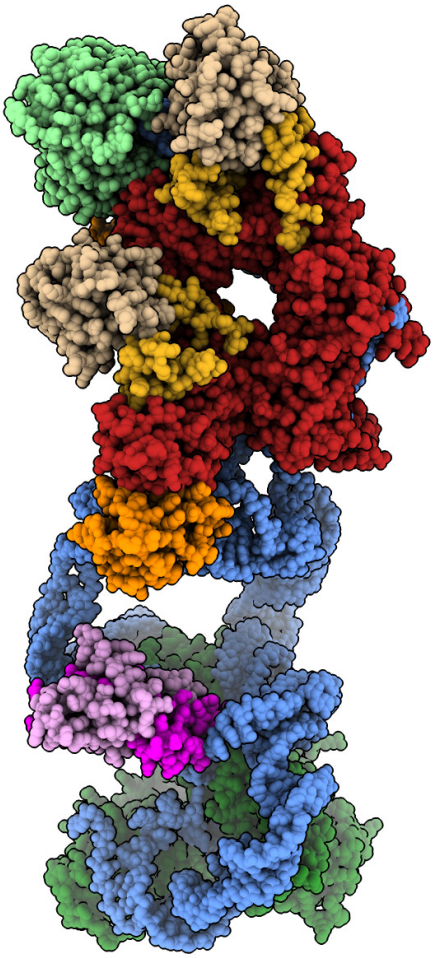
Telomerase is one of the rarest enzymes in the cell – being able to make sufficient amounts to image it is one of the biggest bottlenecks that my group encountered. Conventional techniques, such as X-ray crystallography and nuclear magnetic resonance, require at least 1,000-fold more enzymes than we can produce. The technique we eventually used, cryogenic electron microscopy, was not ready for it until recently, so analysing telomerase wasn't really possible for a long time.

What approach did you develop to investigate telomerase?

We start by 'hijacking' the cells. We identify the limiting factors and boost their levels, then force the cells to assemble the telomerase enzyme. This allows us to make the enzyme in sufficient quantity for imaging.

We then image the telomerase with cryogenic electron microscopy, which uses a beam of electrons to examine the structures of molecules and materials at the atomic scale. It gives us high-resolution images of the specimen, essentially magnifying the molecules. And we do this by putting the molecule under cryo conditions: they are frozen in a layer of glassy ice.

One of the main problems with studying structures like telomerase is their flexibility: it's very difficult to get the snapshot. Freezing helps to keep them in place while imaging. We take hundreds of thousands of images, and we're able to sort out any heterogeneity within our sample in order to get the final structure.



The newly revealed, high-resolution structure of telomerase may give insights into cancer and diseases of ageing.

How much detail can you get for telomerase?

In 2018, as a postdoctoral fellow, I was able to image it at about 0.8 nanometres resolution. In the last couple of years, my group pushed it further down to around 0.3–0.4 nanometres. That is at the level where one can start to build models with atomic details. In 2021, we published the first atomic model of telomerase constructed by cryo-EM (Ghanim, GE *et al. Nature* **593** [2021]).

We discovered entirely new components that have never been predicted before, which is really exciting. We can also address the underlying cause of disease mutations. It is possible to map where they are and why they cause telomerase deficiency.

How does it feel to see telomerase in such detail?

For a structural biologist, it's a privilege. We collected the data before the pandemic in 2020, and the image emerged when we were in lockdown. It really kept me going through the difficult times, and we could not wait to get back to the lab to continue the work.

Will these high-resolution images of telomerase have clinical implications?

We're not at true atomic levels. But a lot of the time, in order to understand how it works, you don't need to get to that point. A lot of our research can hopefully be used for rational drug design. There's big therapeutic potential here.

I am speaking to a number of scientists who are interested in this. For example, if a chemist is able to make a new drug that can bind to telomerase, inhibiting it, then we are able to visualize and observe how it interacts with telomerase. So we don't do the actual drug design, but we are talking to other scientists who do.

You've also used cryogenic electron microscopy to image a molecule called the spliceosome. Is this similar to telomerase?

Technically they are very similar in multiple ways, even though they are involved in very different biological processes. The spliceosome, like telomerase, is a very large machine that contains RNA and proteins. They're both flexible and they're both very difficult to obtain.

What motivates your work: scientific understanding or the medical implications?

A combination of the two. I'm always excited about experiments, even if they're small. But in the big picture, I always think of the end point — what we will learn when we get the structure, and from there, what else we will be able to learn from what we found.

Understanding structure and function is of foremost importance before we can think about developing therapeutic targets. However, it's simply exciting just to finally see and understand how something works. After all, curiosity is a big part of human nature. So that's something that really motivates me.

eppendorf

ABOUT THE AWARD (EST. 1995)

Presented in partnership with *Nature*, the Eppendorf Award for Young European Investigators recognizes outstanding work in biomedical science. Besides a prize money of €20,000, it provides the opportunity for European researchers to showcase their work and communicate their research to a scientific audience. The winner is selected by an independent jury of scientists: Sadaf Farooqi, Wellcome MRC Institute of Metabolic Science, Cambridge, UK; Madeline Lancaster, MRC Laboratory of Molecular Biology, Cambridge, UK; Ben Lehner, Center for Genomic Regulation PRBB, Barcelona, Spain; Laura Machesky, Beatson Institute for Cancer Research, Glasgow, UK; under the chairmanship of Reinhard Jahn, Director Emeritus at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. Eppendorf and *Nature* do not influence the selection.

APPLY FOR THE 2023 EPPENDORF AWARD FOR YOUNG EUROPEAN INVESTIGATORS.

We invite biological and biomedical researchers with an advanced degree, not older than 35 years who work in Europe, to apply for the 2023 Eppendorf Award. Applications will be accepted from 1st October 2022 and the deadline for entries is 15th January 2023. The prize ceremony will take place at the EMBL Advanced Training Centre (ATC) in Heidelberg, Germany, on 22nd June 2023.

For more information see: www.eppendorf.com/award

EPPENDORF AWARD FOR YOUNG EUROPEAN INVESTIGATORS