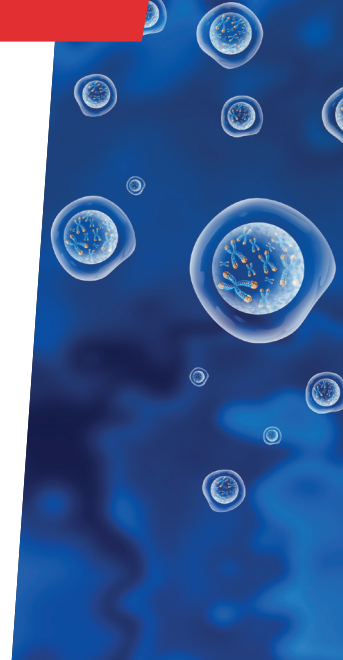


# Telomeres: the chromosome tips that stave off ageing

The ends of our chromosomes are capped with structures called telomeres, which protect our DNA when cells divide. Over time, chromosomes get shorter, and scientists think this erosion plays a role in the ageing process. **Professor Julie Cooper** and her team at the **University of Colorado Anschutz Medical Campus** in the US are investigating the wide range of enigmatic functions of telomeres, which has implications for our understanding of cancer, reproduction and how we grow older.



**Professor Julie Cooper**

Chair of the Department of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus, USA

## Field of research

Molecular genetics

## Research project

Investigating the roles of telomeres in living organisms

## Funders

US National Institutes of Health (NIH), National Institute of General Medical Sciences (NIGMS), University of Colorado

In every cell in your body, your DNA is contained in long molecules called chromosomes. When cells divide to allow the body to grow or repair (through a process called mitosis), these chromosomes are duplicated so that each of the two new cells has a full set. However, this duplication process is imperfect, and the ends of each strand of genetic material are especially vulnerable. “The ends of chromosomes can be degraded, potentially losing crucial genetic information, or fused together with other chromosome ends, which leads to a damaging ‘tug of war’ when each duplicate is pulled to opposite ends of the cell before cell division,” says Professor Julie Cooper. “Thankfully, telomeres help fend off this risk.”

Talk like a ...

## molecular biologist

**Chromosome** — a thread-like molecule containing DNA supported by proteins

**Epigenetic** — related to changes in characteristics caused by changes in gene expression (but not by changes in the DNA sequence) that can be inherited by offspring

**Meiosis** — cell division that results in cells with half the chromosomes of the parent cell (used to produce egg and sperm cells)

**Mitosis** — cell division that results in cells with the same genetic information as the parent cell (used for growth and repair of tissue)

**Nucleotides** — the basic building blocks of DNA

**Primer** — a short nucleotide sequence that provides a starting point for DNA replication

**Senescence** — the process by which cells stop dividing

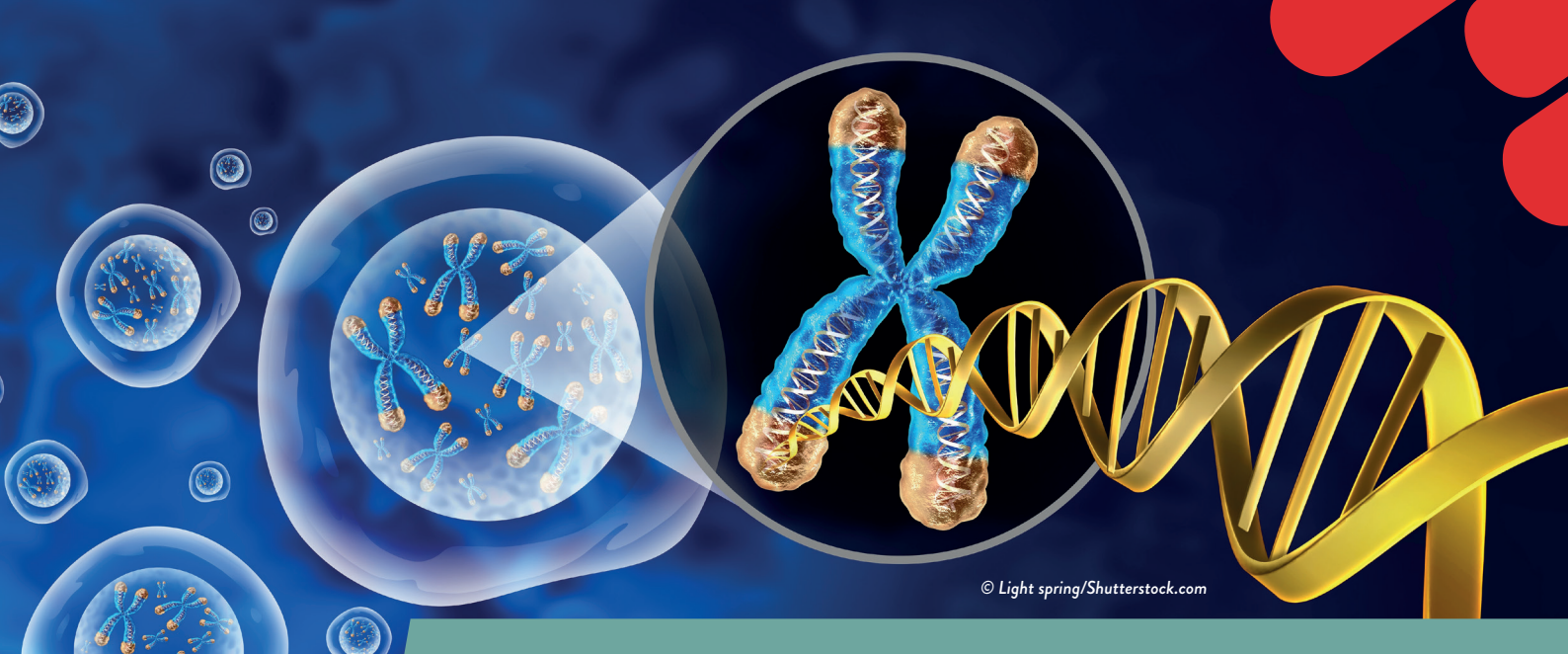
**Telomerase** — the enzyme that adds telomere DNA sequences to the ends of chromosomes

**Telomere** — the structure made from repeated DNA sequences (in vertebrates, always TTAGGG) and proteins found at the ends of chromosomes, to protect them from degradation and fusion

## The end replication problem

DNA is made of two complementary chains of paired molecules called nucleotides. During cell duplication, these chains are ‘unzipped’, breaking up these pairs to prepare for new pairs to form. However, the enzymes

that help form these new pairs cannot work without a small part of existing chain to work from. RNA primers are molecules that bind to specific sequences on the unzipped DNA, providing a base from which the enzymes create a new complementary DNA strand.



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As DNA replication only ever happens in one direction, the nucleotides to which the primer binds, plus any nucleotides 'upstream' of the primer in the replication process, will not form new pairs and so this part of the DNA sequence will not be present on the new strand. The 'end replication problem' also exists at the other end of the chromosome, because the paired nucleotides do not perfectly match up, resulting in a short overhang of a single strand of DNA. The lack of double-stranded DNA at the 'downstream' end of the chromosome means there is no template for the RNA primer to copy.

### The role of telomeres

Telomeres are made of simple repeated DNA sequences and proteins and are found on the ends of chromosomes to protect them. As DNA replication machinery is unable to accurately replicate the extreme ends of chromosomes, DNA degradation occurs each time a cell duplicates, as genetic material is lost. "Telomeres provide a 'buffer' at the ends of chromosomes because they are degraded during duplication instead, preventing the degradation of important genetic material," explains Julie. However, the buffering effect cannot last forever. Once telomeres shorten below a threshold length, they lose the ability to protect chromosome ends from rampant degradation and fusion.

Another key function of telomeres is to prevent chromosome ends from fusing together. If a chromosome breaks, enzymes will repair it by fusing the broken ends back together. However, a natural chromosome end would look the same as a damage-induced broken end if it was not protected by a telomere.

### Telomerase: the secret ingredient

Because bits of telomere are lost in every round of DNA replication, telomeres become shorter every time cells divide. "This limits the 'replicative lifespan' of our cells," explains Julie. "When telomeres become too short to function properly, the cell stops dividing – a process called senescence." The accumulation of senescent cells in the body begins to limit its ability to grow and repair. This increases the risk of developing a wide range of diseases, which is a key indication of ageing.

However, it is important that cells stop dividing once telomeres stop functioning. "If the cell keeps growing and dividing without a proper telomere, the end of the chromosome will be degraded and/or recognised as damaged DNA and subjected to fusion," explains Julie. "This leads to 'genome instability', where the arrangement of information in our chromosomes becomes scrambled, causing malfunctioning genes." This instability can cause cancerous tumours, which are made of uncontrollably dividing cells.

Telomere degradation does not happen in all cells. "The enzyme telomerase copies RNA into DNA – a process that acts in reverse of the 'central dogma' of biology, which states that DNA is copied into RNA, which is translated into proteins," explains Julie. "Telomerase uses an RNA template that matches the repeating sequence of DNA found in telomeres, which it adds to the ends of chromosomes to reverse degradation." In humans, telomerase is only active in germline cells, which produce sperm and eggs, and stem cells. This ensures that, if sperm or egg

cells go on to create a new human, or if stem cells are transformed into whatever specialised cell is needed in the body, they start out with a full set of telomeres.

### Surprising discoveries in the lab

Julie's team is using a wide range of laboratory methods to study the functions of telomeres. "We use genetic techniques to introduce mutations into yeast or human cells to study the functions of the proteins we are mutating," says Julie. "We use microscopy to study chromosomes in live cells, and we analyse chromosome size and shape using various gels."

Through these processes, the team has uncovered some intriguing discoveries. "We found that cells lacking telomerase can switch to a 'survival mode' that uses other repeated sequences of DNA to protect the ends of their chromosomes," says Julie. "These sequences acquire end protection ability epigenetically, meaning that they become associated with specialised proteins, forming a protective DNA-protein structure that can then be inherited by offspring." The team has also discovered unexpected behaviours during meiosis, the process that forms egg and sperm cells. "During meiosis, telomeres gather at the edge of the nucleus and coordinate the movements of the chromosomes along with the breakdown of the nuclear membrane," explains Julie. Building understanding of telomeres' intricate functions could help combat the effects of ageing, the development of cancers, and infertility.

# Meet the team



## Meet Lakshmi

**Dr Lakshmi Sreekumar**  
Postdoctoral researcher,  
From Kerala, India

**I was introduced to bacterial genetics in high school.** Some of the earlier molecular biology experiments from the 1950s (by biologists such as the Lederbergs, Benzer, Meselson and Stahl) made a mark on me and inspired me to pursue research. In my opinion, no amount of high-throughput data compares to the brilliance and elegance of these classical papers!

**One of our goals is to understand how cells survive in the absence of telomerase.** Cancer cells, for instance, can use alternative means to maintain stable chromosome ends to remain immortal. I study one such survival pathway using fission yeast cells that lack telomerase and instead use DNA repeats found in internal regions of the chromosome to stabilise their ends. A typical day involves lots of cell cultures and performing genetic crosses to make mutant cells. I occasionally use the microscope to image cells containing fluorescent proteins.

**As a biologist, I get to explore detailed aspects of cellular pathways.** Pursuing research has taught me to navigate failures – both in and outside the lab. In

fact, troubleshooting failed experiments has taught me more than the successes.

**This is a great time to get excited about scientific research.** The COVID-19 pandemic is an example of why we can all greatly benefit from a scientific mindset. Even with the wealth of information being generated, there are many areas of biology that are poorly understood and need scientific exploration. Research continues to be a thrilling experience for me.

### Lakshmi's top tip

Be curious and keep the big picture in mind.



## Meet Rishi

**Dr Rishi Kumar Nageshan**  
Postdoctoral researcher,  
From Mysore, India

**Curiosity drove me to become a biologist.** As a child, I remember we had plants with different-coloured flowers growing next to each other in the garden. Later, when I grew new saplings from seeds of these plants, the colours were different. I thought a lot about it, and asked my parents, but we couldn't think why. Years later, we studied Mendelian genetics

(which looks at biological inheritance) at school. That was my first epiphany that science is real, and it works!

**In college, I majored in biochemistry, microbiology and biotechnology.** Some professors were very influential in how I think about science, especially Ms Parvati, who taught me about evolution and the basics of microscopy and encouraged me to think about topics that were not in the curriculum.

**I study how chromosomes are equally divided between two daughter cells during mitosis.** Specifically, I research the events that help the cell ensure equal segregation of chromosomes when the chromosomes are not completely duplicated but still undergo mitosis.

**Our lab is a very collaborative environment:** we discuss a lot of science, bounce ideas around, and think about each other's experiments. Interactions with my fellow researchers and students are some of the best parts of my job.

**We have barely scratched the surface in understanding the complexity of biological systems.** With the advent of new technologies, the excitement has just begun! There is so much to understand that could help our society.

### Rishi's top tip

Ask questions, then listen to and think deeply about the answers you receive.



## Meet Rahul

**Dr Rahul Thadani**  
Postdoctoral researcher,  
From Mumbai, India

**I have always been fascinated by how things work.** As a child, my parents encouraged my curiosity by providing increasingly elaborate encyclopaedias and science kits, and I was lucky to have several inspiring biology teachers at school. I remember being particularly fascinated by the first draft of the human genome, which was published in the run-

up to my college applications and was a particularly exciting time in biology.

**My own path to becoming a biologist was quite meandering.** I studied computing, chemistry, bioinformatics, and, finally, cell and molecular biology! But the skills I picked up along the way have been tremendously useful.

**I am examining the structure of telomeres.** All our DNA wraps around proteins, but the way this happens in telomeres is highly unusual. Understanding this structure will tell us something fundamental about telomere biology. A typical week has a mix of days with long experiments, while others are

spent analysing and organising data.

**I enjoy the hands-on aspects of our experiments.** They almost never work as expected the first time and typically require extensive troubleshooting. Science is more collaborative than people think; we get to work with scientists from all over the world.

## Rahul's top tip

Stay curious and study whatever interests you. There are many paths to becoming a biologist, and an indirect route (like mine) will allow you to develop many skills that will be useful in a range of contexts.



## Meet Ana

**Ana Lopez Morales**  
Research assistant,  
From Guerrero, Mexico

**I am a first-generation high school and college graduate** and have the privilege of being the first scientist in my family. As a high school student, I had a love for biology, but a pivotal part of my journey was an internship at the Metropolitan State University of Denver in Dr Liu's

genetics lab. Dr Liu's mentorship and passion for genetics was so inspiring that it allowed me to fully appreciate the vast interconnectedness of biology.

**The plethora of unknowns within the field** drove me to pursue a career in biology. My internship was transformative, as it allowed me to apply knowledge from the classroom to practical experiments, which cemented my love for biology. I found science despite no one in my family having a science background, so know that you can explore and foster a career in science too.

**I focus on centromeres, chromosomal landmarks crucial for cell division.** Although Julie's lab primarily focuses on telomere biology, an exciting thing

about biology is how seemingly unrelated components may often interact. We discovered a unique moment during meiosis where telomeres are required for centromere assembly, and my research aims to understand how telomeres facilitate this process.

**A typical day involves conducting experiments in the laboratory** and reading the literature to stay updated on current knowledge. Science is about performing experiments and generating new knowledge but also involves thinking about existing information to build a better understanding of your research topic. In addition to this, discussing our experiments is a vital part of research and often one of the most exciting parts of the day!

## Classic molecular biology experiments

**Lederberg experiment, 1952:** Esther and Joshua Lederberg duplicated plates of bacteria and then applied the antibiotic penicillin to all plates. The same colonies on different plates survived, leading them to conclude the bacteria strains had penicillin resistance before, not as a result of, exposure. This led them to conclude that genetic mutations can be random.

**Benzer experiment, 1953:** Seymour Benzer found that crossing two different bacteriophage virus mutants without a certain gene could lead to a hybrid with the gene present. He theorised that the parent mutants both had an incomplete part of the gene, which were combined in the hybrid. This led to his theory that genes are divisible stretches of nucleotides, rather than single indivisible points on a chromosome.

**Meselson-Stahl experiment, 1958:** Matthew Meselson and Franklin Stahl were investigating whether DNA underwent semiconservative replication (in which each new DNA molecule contains one strand of the original and one new strand). They generated parent DNA with a heavier isotope of nitrogen and, after duplication, found this isotope ended up in both new DNA molecules in equal quantities, supporting the theory.