Jan van Deursen: From knockout pioneer to antiaging innovator

van Deursen's career visits both sides of the cancer–senescence coin.

Now that he's run his own laboratory for 19 years, Jan van Deursen looks back at his doctoral student days with wry amusement. His advisor, Bé Wieringa at the University of Nijmegen in the Netherlands, put him on a project to make one of the first genetic knockout mice. "What was he thinking?" van Deursen now wonders.

The mouse, lacking the muscle creatine kinase gene, had totally normal muscles but could not sprint to save its life (1). That pioneering work allowed van Deursen to essentially skip postdocing and establish his own group at St. Jude Children's Research Hospital in Memphis, Tennessee, in 1996. In 1999, he moved to the Mayo Clinic in Rochester, Minnesota, where he used his experience with genetically engineered mice to probe how aneuploidy relates to cancer (2, 3) and investigate the cell biology of senescence (4, 5). Another powerful genetic manipulation—using apoptosis through targeted activation of caspase (ATTAC) to remove senescent cells—allowed his laboratory to make their biggest splash yet by delaying aging in a progeroid mouse model (6).

Now, the cancer biologist is chair of biochemistry and molecular biology at Mayo. He recently chatted with *JCB* about his obsession with decades-old hypotheses and why he's not seeking the fountain of youth.

COUNTING CHROMOSOMES

Did mastering transgenic technology early on launch your career?

From the beginning, I was fascinated by the potential of the technology. When I was done with my PhD, there were very few people in the world who had the skills to go through the whole procedure. I got many job offers simply because a lot of institutes wanted to set up a facility.

My PhD advisor said, "That's fine for you to help others knock out their most interesting genes, but you also need to develop your own research program." That was really good advice at the time.

When I started my own program, I became very interested in Nup98, a component of the nucleocytoplasmic transport machinery that was implicated in cancer. I wanted to figure out what the normal roles of Nup98 and its binding partner Rae1 were. Eventually, we showed that the Rae1–Nup98 complex is a mitotic regulator that prevents aneuploidy.

Which comes first, aneuploidy or cancer?

That question really drew me to this field. Aneuploidy was thought to drive cancer—that hypothesis was 100 years old at the time—but there was really no good in vivo evidence.

When we independently knocked out Rae1 or Bub3, a structurally related protein, we found that both had mitotic phenotypes—cells cannot accurately segregate their chromosomes. But surprisingly few cancers developed in these mice. The thinking at that time was that if a cell becomes aneuploid, it's really on the highway to cancer. That didn't seem to be the case.

> "There is a lot of evidence that cancer can be an outcome of aneuploidy, but it's not an obligatory outcome."

Was that disappointing?

My sense is that a lot of people in the field were disappointed and moved on to something else. We stuck with it because I wanted to better understand how aneuploidy might contribute to cancer.

We challenged these animals with carcinogens or hits to critical tumor suppressor genes, and we found that mutations in mitotic checkpoint proteins could accelerate tumorigenesis in some cases.

Today, I think there is a lot of evidence that cancer can be an outcome of aneuploidy, but it's not an obligatory outcome. There are maybe 500–600 genes in humans, that, when you alter them, cause chromosome number instability. Now we are finally starting to make progress on which of these genes, when mutated, actually predispose you to tumorigenesis, and why.

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Jan van Deursen

AN ODDBALL MODEL

Much of the work in your lab relies on mice with various levels of gene expression, using heterozygous or hypomorphic strains. Why this approach?

Hypomorphic mutations initially arose from aberrant gene-targeting events that reduced normal messenger RNA by 90% or so. That was a way to get protein at a much lower level than you would have from a heterozygote.

When I had these embryonic lethal phenotypes for the checkpoint proteins, using hypomorphic mice became very valuable. You could get much lower than just the 50% of normal protein of a heterozygote.

Hypomorphs were basically artifacts from my PhD, but it was a great influence on how my research developed. And it led to the most interesting animal model that I've ever made: the BubR1 hypomorphic mouse.

What made it so interesting?

We were trying to create a cancer model for aneuploidy. But instead of developing cancer, those mice aged at a highly accelerated rate.

It took us a couple of years to figure out the phenotype, because the model was really odd. After four to five months, the mice started to look like they were very, very sick. They looked like they would keel over at

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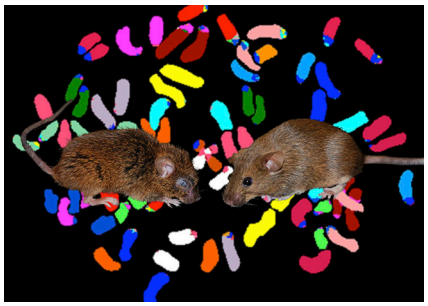

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A 5-month-old BubR1 hypomorphic progeroid mouse (left) sits next to its littermate control (right). The background shows an example of premature sister chromatid separation visualized by spectral karyotyping.

any moment, but they could look like that for several months. Finally, I saw a picture of a trichothiodystrophy (TTD) mutant mouse, which is predisposed to DNA damage. It started to click that we had a model of a progeroid syndrome.

Two months after our paper came out in *Nature Genetics*, another paper showed there are people with mutations in BubR1 who have a similar accelerated aging syndrome.

Does BubR1 play a role in normal aging?

In older, normal mice, the levels of BubR1 drop to the same level as in our hypomorphic mice with this progeroid syndrome. But the key finding was that the tissues subjected to this accelerated aging accumulated a lot of cells that were senescent. We started to think that maybe either the formation or presence of these cells has something to do with the age-related decline in tissue function.

Maybe I'm not that original, because everyone thought we already knew this. When Leonard Hayflick and Paul Moorhead coined the term "senescence" in 1961, they proposed that, when cells run out of proliferative potential, it should affect tissue renewal and therefore tissue function.

But then there's 50 years where nobody was really able to provide in vivo evidence for a connection between the accumulation of senescent cells and the development of age-related decline or pathologies. My lab was basically handed that trophy.

How did you show that connection?

We had a very simple approach. If we could prevent cells from going into senescence, maybe we could delay the onset of age-related pathologies such as muscle wasting, fat dysfunction, and cataracts.

So we looked at the pathways that were thought to drive cells into senescence: the p16 and p53 pathways. We knocked out the p16 pathway in our BubR1 hypomorphic mice, and you couldn't find any senescent cells. And the mice looked healthier—they didn't age as fast.

To confirm this, we tried to remove senescent cells after they had formed to see if we could get the same antiaging effect. We designed a transgenic mouse, in which we could use a drug to induce p16-positive cells to undergo apoptosis. When we crossed this into the BubR1 hypomorphic background, we removed senescent cells after they accumulated, and, again, the mice didn't age as fast.

SLOWING DOWN AGING

Why does removing senescent cells have such a dramatic effect?

Senescent cells might only represent 1–5% of the cells in a tissue. But they are so aggressive—their secretome consists of proteases, growth factors, and inflammatory cytokines that have a very profound effect on the neighboring cells and the tissue as a whole.

That's actually perfect if you think about it as a therapeutic approach: get rid of a few cells and make a big impact on the organ, but still keep the tissue structure and cellularity largely intact.

Were there skeptics about this "fountain-of-youth" mechanism?

Many in the field don't believe that progeroid models reflect natural aging. So we've started investigating what happens when you get rid of senescent cells in normal mice.

Interestingly, the 2011 *Nature* paper where we forced these cells into apoptosis mimicked what you could maybe achieve with a drug that targets senescent cells.

Was there a media frenzy?

It was a little bit uncontrolled. *The New York Times* wanted to do an interview, and then called back the next day to say they wanted to put the story on the front page and they needed a picture of the mice. I remember spending a couple of hours in the mouse room, because it's not so easy to take side-by-side pictures of mice. They don't sit still.

Then it was crazy for a while. I realized that researchers have to deal with laypeople who have their own expectations or see our work from their own perspectives. It made me realize that one has to be careful when translating laboratory findings about aging because people seem to be paying attention.

> "The New York Times... wanted to put the story on the front page."

Will we soon have a pill to slow aging?

If I was a naïve scientist, I would be extremely optimistic. But since I have attended many meetings with people who have expertise in developing drugs, this makes me approach it more like a marathon, rather than a sprint.

I'm 52 and I like to run marathons, but I've had to face my decline. I have three teenagers who remind me daily that I'm old! But I'm not the type of person who wants to know, "Can I slow down my aging?"

I think everyone wants to have a long and healthy life. But the emphasis is on healthy. You hardly ever meet people who want to live longer and suffer.

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van Deursen and Mayo colleague Rick Bram wait to start the 2013 Boston Marathon.