You're as old as your stem cells

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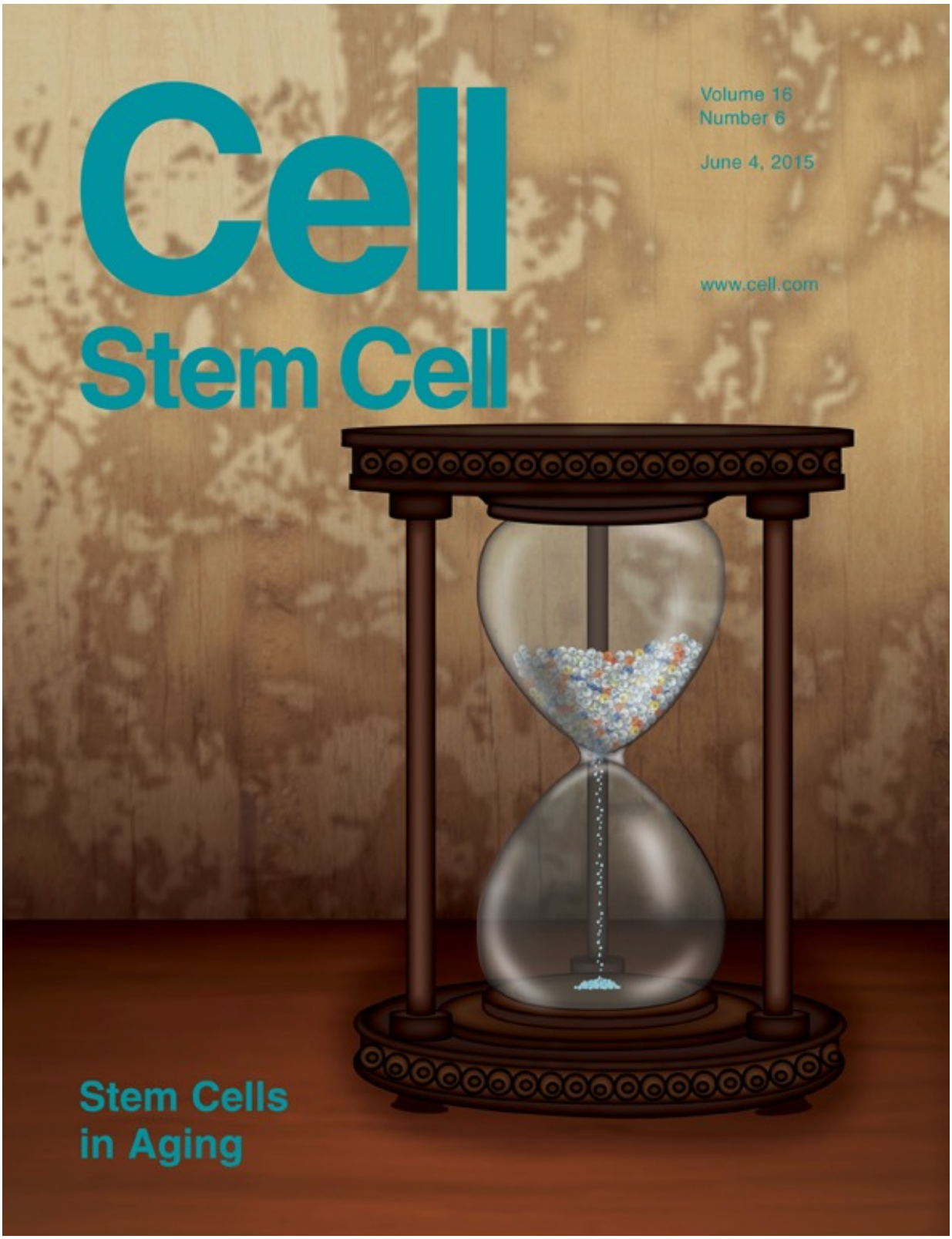

Cover of the *Cell Stem Cell*. Credit: Yvonne Blanco/*Cell Stem Cell* 2015

A special issue of *Cell Stem Cell* published on June 4 includes a collection of reviews and perspectives on the biology of aging.

Highlights include:

The secret to a longer life? Be a female.

Human supercentenarians share at least one thing in common—over 95 percent are women. Scientists have long observed differences between the sexes when it comes to aging, but there is no clear explanation for why females live longer. In a discussion of what we know about stem cell behavior and sex, Stanford University researchers Ben Dulken and Anne Brunet argue that it's time to look at differences in regenerative decline between men and women. This line of research could open up new explanations for how the sex hormones estrogen and testosterone, or other factors, modify lifespan.

It's known that estrogen has direct effects on stem cell populations in female mice, from increasing the number of blood stem cells (which is very helpful during pregnancy) to enhancing the regenerative capacity of brain stem cells at the height of estrus. Whether these changes have a direct impact on lifespan is what's yet to be explored. Recent studies have already found that estrogen supplements increase the lifespan of male mice, and that human eunuchs live about 14 years longer than non-castrated males.

More work is also needed to understand how genetics impacts stem cell aging between the sexes. Scientists have seen that knocking out different genes in mice can add longevity benefits to one sex but not the other, and that males in twin studies have shorter telomeres—a sign of shorter cellular lifespan—compared to females.

"It is likely that sex plays a role in defining both lifespan and healthspan, and the effects of sex may not be identical for these two variables," the authors write. "As the search continues for ways to ameliorate the aging process and maintain the regenerative capacity of stem cells, let us not forget one of the most effective aging modifiers: sex."

Cell Stem Cell, Dulken and Brunet: "Stem Cell Aging and Sex: Are We Missing Something?" http://dx.doi.org/10.1016/j.stem.2015.05.006

Modeling aging in a dish

One of the problems with modeling genetic diseases in a dish using stem cells is that those cells are not the same age as patients who experience the diseases that are being studied. You could take skin cells from a 65-year-old patient with ALS, reprogram them into induced pluripotent stem cells (iPSCs), and then differentiate the iPSCs into neurons, but those neurons will be just a few weeks old. Such reprogrammed stem cells have been shown to have rejuvenated metabolism, a decrease in DNA damage, and longer telomeres than the mature cells they originated from. If that's the case, then what's in the dish may not be an accurate representation of what's happening in the patient.

Memorial Sloan Kettering Cancer Center scientists Lorenz Studer, Elsa Vera, and Daniela Cornacchia review strategies that advance the clock in stem cells for the purpose of modeling late-onset conditions. For example, research groups have used small molecular screens that speed up human embryonic stem cell differentiation; however, these methods do not push cell maturation. For iPSCs, one method used by labs is to stress cells out by exposing them to toxins. Another strategy is to express genes known to cause diseases of premature aging.

"The ability to direct both cell fate and age in iPSC-derived lineages will allow modeling of human disorders at unprecedented precision," the

authors write. "Such studies could yield more relevant disease phenotypes and define novel classes of therapeutic compounds targeting age-related cell behaviors. The ability to program and reprogram cellular age on demand will present an important step forward on the road to decoding the mystery of aging."

Cell Stem Cell, Studer et al.: "Programming and Reprogramming Cellular Age in the Era of Induced Pluripotency"
http://dx.doi.org/10.1016/j.stem.2015.05.004

Selecting for immortality: A theory for why germ cells don't seem to age

A difference in metabolism between the cells that make up our bodies compared to the cells we use for reproduction (germ cells; i.e., those that become sperm and eggs) could help explain why the former are subject to aging and the latter are seemingly "immortal." Stem cells make energy by breaking down sugar, which is less efficient and leads to more mutations than obtaining energy though mitochondrial respiration, which is what germ cells do.

In his opinion piece on stem cell maintenance and aging, Columbia University's Hans-Willem Snoeck makes a case that from an evolutionary perspective, stem cells don't need to last forever; they only need to get an organism to reproductive age. They accumulate DNA damage over time and repair themselves but continue to function at a lower and lower capacity. Germ cells, on the other hand, are strongly selected so that only the fittest will be used for reproduction. Snoeck argues that the very different ways of generating energy may underlie the difference between maintenance in stem cells and selection in germ cells. How cells use nutrients has been connected with longevity before; it's widely reported that caloric restriction in mammals, worms, and

other animals can boost lifespan.

Cell Stem Cell, Snoeck: "Can Metabolic Mechanisms of Stem Cell Maintenance Explain Aging and the Immortal Germline?" http://dx.doi.org/10.1016/j.stem.2015.04.021

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