Future fertility: Giving hope to men who received childhood cancer treatment

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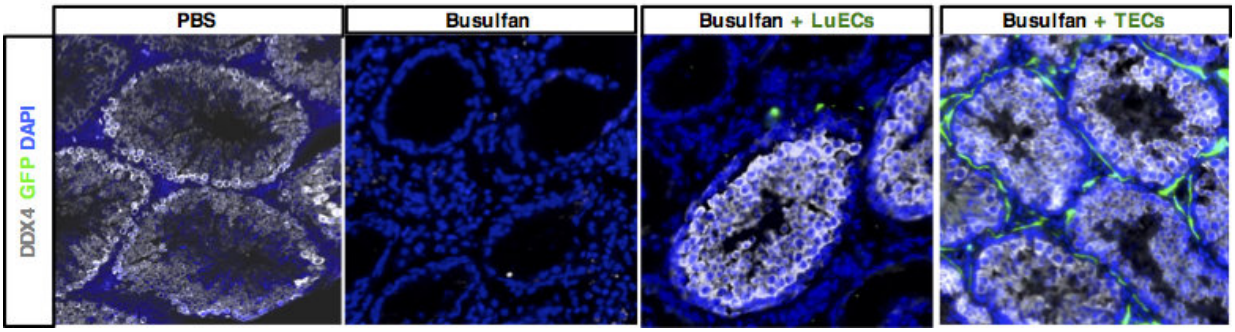

Transplanting testicular endothelial cells (but not lung endothelial cells) into the testes of mice after destruction of sperm due to treatment with the chemotherapy drug busulfan restores developing sperm. Credit: Dong-Ha Bhang, Penn Medicine: *Nature Communications*

Researchers have discovered a way to grow human stem cells destined to become mature sperm in an effort to provide fertility options later in life to males who are diagnosed with cancer and undergo chemotherapy and radiation as children. The findings are published today in *Nature Communications* from a team led by Sandra Ryeom, Ph.D., an associate professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania and co-leader of the Tumor Biology Program at the Abramson Cancer Center.

"For years researchers have been trying to find ways to grow and expand

these cells from testicular biopsies donated by young patients prior to their cancer treatment, but until now, there has not been a consistently successful approach," said Ryeom.

According to the American Cancer Society, about 1 in 530 young adults between the ages of 20 and 39 years is a survivor of childhood cancer. Cancer treatments leave a majority of boys infertile, as chemotherapy and radiation often kill sperm-producing stem cells (SSCs). While there are ways to preserve fertility for boys diagnosed with cancer after puberty, no such options exist for prepubescent boys.

"We have never had any fertility preservation options for prepubescent boys," said study co-author Jill Ginsberg, MD, a pediatric oncologist and director of the Cancer Survivorship Program at Children's Hospital of Philadelphia. "The findings in this work are a great first step forward for our youngest patients."

Researchers have known that the production of sperm could be restored in mice that were sterilized after treatment with the chemotherapeutic agent busulfan by injecting immature sperm cells from a donor into their seminiferous tubules—located in the testes. From this, oncologists suggested that SSCs might be harvested from boys before the start of chemotherapy and reintroduced into their testes when treatment was complete. However, the testes of prepubescent boys contain such a small number of SSCs that, in order for this approach to be successful, the cells would need to be grown and multiplied in the lab prior to subsequent reinjection.

Given these challenges, the team identified testicular endothelial cells as a critical niche population for the maintenance and expansion of human SSCs in the lab. More importantly, they also identified five growth factors produced by testicular endothelial cells that are necessary for keeping human and mouse SSC cultures alive over the long term.

Eventually patient samples could be expanded then frozen until needed.

Mouse cells in long-term culture restored the ability of mice after chemotherapy-induced infertility to produce sperm. Ultimately the SSCs were functional as demonstrated by the birth of live pups after being fathered by mice with the transplanted SSCs and growth factors.

"Our next step is to determine whether we can re-inject or engraft the expanded SSCs into patients after they are cancer free," Ryeom said.

Provided by Perelman School of Medicine at the University of Pennsylvania