Cell transfer restores sperm production in infertile mice

By Stephen Bradt

Scientists at the School have successfully transplanted specialized cells that are critical to sperm development in mice, restoring sperm production in once-infertile animals.

The research may give scientists a better understanding of how Sertoli cells—which surround spermatogenic stem cells—nourish sperm production and the survival of stem cells.

"Spermatogenesis is a highly organized process, requiring just the right environment, or 'niche,' around the germ line stem cells," said **Ralph L. Brinster, V'60**, professor of reproductive physiology at the School. "The Sertoli cells are essential to this environment, and it appears that by replacing them, we can essentially reconstruct the niche in which sperm development takes place."

Much of the volume of a mammalian testis consists of tightly coiled seminiferous tubules that hold mature sperm. Sperm development also occurs within these tubules, which are home to spermatogenic stem cells, the seeds from which spermatogenesis arises. Seminiferous tubules are lined with Sertoli cells, which are thought to nurture sperm cells as they develop and facilitate their eventual passage out of the testis.

Brinster and colleagues worked with Steel mutant mice, which are congenitally infertile due to a Sertoli cell defect. Before inserting healthy Sertoli cells, the researchers treated the mice's testes with busulfan and cadmium to remove any defective germ cells and Sertoli cells. The seminiferous tubules remained, likely providing the structural support needed to completely reconstitute spermatogenesis from donor cells.

The Brinster group's technique for transplanting Sertoli cells will likely allow scientists to study stem cells' specialized environment in a way that has not been possible before. Currently, the best-studied stem cells are those that generate blood cells, even though these cells, which reside in bone marrow, are relatively inaccessible to researchers.

"I believe Dr. Brinster's new results have catapulted the spermatogenic stem cell system into a position of maximum experimental flexibility among all other stem cell systems in the body," said John R. McCarrey, professor of cell and molecular biology at the University of Texas at San Antonio, who was not involved in this work. "This may lead to significant new insight into the manner in which the spermatogenic stem cell works in particular as well as to additional information about how all stem cells work in general."

Brinster's work could eventually prove useful in the treatment of certain types of infertility in men, although complete spermatogenesis was established in only 1.5 to 3 percent of seminiferous tubules in this experiment.

"Male infertility can be caused either by defective germ cells or by a testicular environment that fails to promote proper spermatogenesis," Brinster said. "While several assisted reproductive technologies, such as in vitro fertilization or intracytoplasmic sperm injection, are now available for patients with low sperm counts, infertile patients with Sertoli cell defects have limited options."

The technique developed by Brinster and his colleagues may provide a new way of replacing defective Sertoli cells with healthy ones, which may initiate normal spermatogenesis in some infertile patients.

Brinster was joined in the research by Takashi Shinohara, now at Kyoto University, and **Kyle E. Orwig** and **Mary R. Avarbock** in Penn's School of Veterinary Medicine. The work was funded by the Japan Society for Promotion of Science, the National Institute of Child Health and Human Development, the Commonwealth and General Assembly of Pennsylvania and the Robert J. Kleberg Jr. and Helen C. Kleberg Foundation.