petitive on the market. If successful, cheaper methanesulfonic acid could replace mineral acids in more and more special applications, although the costs most probably will never fall to the level of sulfuric acid.

So, is it likely that this process allows the use of substantial amounts of stranded natural gas, which is currently flared? The amount flared is estimated at about 140 billion cubic meters annually (*10*), corresponding to around 100 million MT of methane, from which about 600 million MT of methanesulfonic acid could be produced. Thus, even if the methanesulfonic acid production would increase dramatically, its methane consumption is still dwarfed by the amounts flared. Only transportation fuels are demanded at a level corresponding to the currently flared natural gas. However, chemicals with their much higher added value compared with fuels could be attractive first options for the use of surplus gas. The initial industrial plants would probably rather be located at highly developed industrial sites instead of in remote locations. Nevertheless, independent of where such plants would be located, the work of Díaz-Urrutia and Ott foreshadows a new chemical process for the synthesis of an interesting chemical, and such a reaction cycle, including an activated methane species, may also be useful for the production of other chemicals. ■

In a typical methane flare, gas associated with oil production is burned.

PHOTO: LEONID IKAN/SHUTTERSTOCK

REFERENCES AND NOTES

1. C. Díaz-Urrutia, T. Ott, *Science* **363**, 1326 (2019).
2. K. L. Ding *et al.*, *ACS Catal.* **2**, 479 (2012).
3. R. A. Periana *et al.*, *Science* **280**, 560 (1998).
4. T. Zimmermann, M. Soorholtz, M. Bilke, F. Schüth, *J. Am. Chem. Soc.* **138**, 12395 (2016).
5. N. Basickes, T. E. Hogan, A. Sen, *J. Am. Chem. Soc.* **118**, 13111 (1996).
6. L. J. Lobree, A. T. Bell, *Ind. Eng. Chem. Res.* **40**, 736 (2001).
7. S. Mukhodphadyay, A. T. Bell, *Angew. Chem. Int. Ed.* **42**, 1019 (2003).
8. A. K. Richards, Patent WO 2005069751 A2 (21 June 2003).
9. F. Fabian, "BASF to expand capacity for methane sulfonic acid at its Ludwigshafen site," 19 December 2018; www.basf.com/global/en/media/news-releases/2018/12/p-18-409.html [accessed 9 February 2019].
10. C. D. Elvidge *et al.*, *Energy Strategy Rev.* **20**, 156 (2018).

10.1126/science.aaw7738

REPRODUCTION

Stem cell–based options to preserve male fertility

Grafting of immature monkey testis tissue enables generation of sperm and offspring

By **Nina Neuhaus** *and* **Stefan Schlatt**

An increasing number of adult men face subfertility or even permanent infertility due to a loss of spermatogonial stem cells as a side effect of pediatric gonadotoxic treatments, including cancer therapies as well as treatments for benign sickle cell disease or thalassemia (*1*, *2*). Adult men can cryopreserve sperm as a fertility reserve, but prepubertal patients do not have this option. Removal and cryobanking of testicular tissue containing spermatogonia could offer a strategy to preserve the prepubertal individual's germline (*1*). Although cryobanking has started, there are currently no protocols available to derive sperm from the banked tissue. Advances in this research field are imperative. The primary treatment of severe male infertility is intracytoplasmic sperm injection (ICSI) into an oocyte. Although after its first description in 1992 the implications and risks associated with ICSI have been intensely debated, the technique has developed into a globally accepted therapy and has meanwhile led to the birth of hundreds of thousands of children (*3*). A major difference of ICSI to natural fertilization is that only a few spermatozoa are required to achieve successful fertilization. Therefore, even inefficient strategies to generate limited numbers of sperm allow treatment of male infertility. On page 1314 of this issue, Fayomi *et al.* (*4*) show that sperm isolated from grafted macaque testicular tissue fragments have the full potential to produce a healthy baby by using ICSI. Therefore, autografting of immature testicular tissue may become an option for human male fertility preservation.

Because spermatogenesis is a stem cell–driven process, stem cell–based regenerative cell therapies can be envisioned to generate sperm from spermatogonia, the male germline stem cells. These cells derive from primordial germ cells (PGCs) during embryonic development. During sex differentiation, they respond to the testicular somatic microenvironment and become spermatogonia through a number of intermediate stages. In the fetal and prepubertal testis, spermatogonia expand slowly and colonize the basement membrane of the seminiferous tubules. The generation of differentiating progeny begins at puberty when the stem cell niche is activated, and spermatogonia expand clonally to generate differentiating precursors while a small proportion of undifferentiated cells remain as reserve (see the figure). Functionally, the least differentiated adult male germ cells (A-spermatogonia) in the human testis can be separated into an occasionally cycling reserve stem cell population and a regularly dividing and self-renewing progenitor population (*5*). The modes of mitotic expansion and maintenance of the stem cell pool are species-specific and appear to balance the need for lifelong sperm production against a small population of stem cells undergoing a sustainable rate of mitotic divisions (*5*). Although the traditional models of spermatogonial differentiation assume a hierarchical differentiation cascade, alternative models and single-cell gene expression data reveal the presence of additional spermatogonial subtypes and a high level of spermatogonial plasticity (*6*).

In principle, three spermatogonia-based approaches can be explored to produce sperm for fertility preservation: One approach is in vitro spermatogenesis by means of either cell or organ culture, which may serve as a pathway to generate sperm for ICSI (*7*). A second approach is germ cell transplantation by using the individual's own cells (autologous transplantation), which can be considered if in vitro propagation of spermatogonia can be established on a larger scale. Recolonization of the germ cell–depleted testes could thereby cure male infertility (*5*). Currently, none of these cell-based strategies have reached a stage of efficiency and safety to be considered for clinical use. The third approach relies on the developmental potential of immature testicular tissue. Small fragments of fresh or cryopreserved tissue can be placed ectopically under the skin of host organisms (testicular grafting). This strategy was first described in 2002 to induce complete spermatogenesis and enabled the extraction of sperm (*8*). The approach has quickly been ap-

Centre of Reproductive Medicine and Andrology, Albert-Schweitzer Campus 1, 48149 Münster, Germany. Email: stefan.schlatt@ukmuenster.de

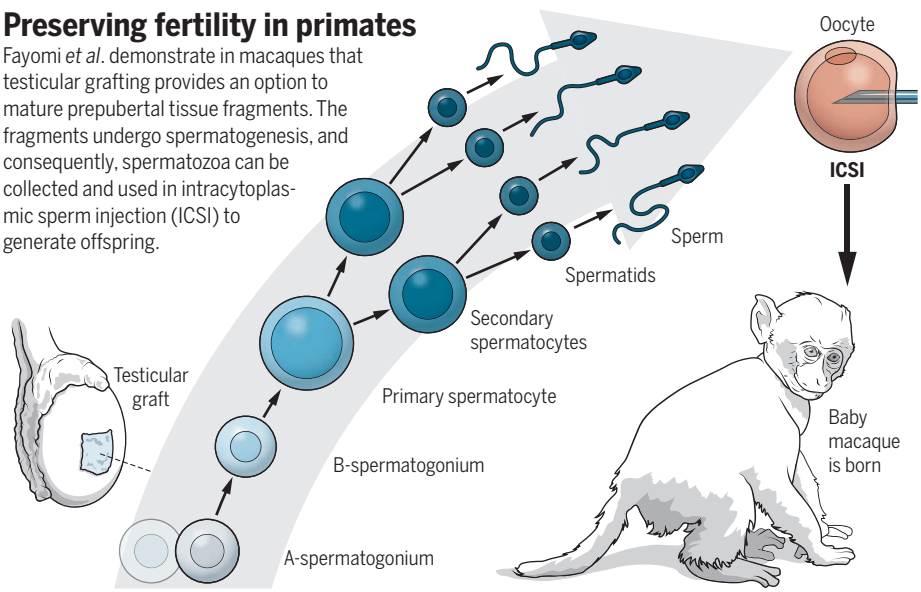
plied in many species (*9*). Using nonhuman primate testes, sperm were retrieved from fresh or cryopreserved immature testicular tissue grafts (*10*–*13*). However, the efficiency of overall sperm retrieval was low, and no offspring were generated after autologous grafting. In these studies, the grafting site played an important role for full spermatogenic induction, with the scrotum being the most efficient grafting site.

Although tissue grafts have led to the birth of healthy offspring in a number of mammalian species (*9*), autologous grafting can only be considered safe for humans when such success can be repeated in primates and after healthy offspring are obtained. Strikingly, Fayomi *et al.* report two major breakthroughs in regard to efficiency and success of the procedure. First, they describe an improved autologous grafting technique, with graft retrieval rates of 100%. Such high success may be related to surgically implemented connections of testicular tissues to the subcutaneous layer of the skin, which improves vascularization of the grafts. The authors also used larger tissue fragments, which reaggregated. They consider this beneficial for paracrine communication. It is also noteworthy that 82% of the grafts contained sperm, without an impact of grafting site or an adverse effect of cryopreservation. Second, they demonstrated functionality by using sperm from a scrotal graft in ICSI. After transfer of 11 blastocyst stage embryos into six recipient females, one pregnancy resulted, and a healthy female "graft-derived baby" (Grady) was born.

The procedures reported in the study of Fayomi *et al.* brings this experimental approach close to clinical application. This opens possibilities for all patients undergoing gonadotoxic exposures because of disease. Caution may be warranted for prepubertal individuals undergoing treatment for hematological cancers because their tissue grafts may contain malignant cell contaminations. Cancer patients who do not have any risk of relapse will benefit from the autologous grafting approach. Clinical trials testing this strategy on patient material should now be performed. Because ICSI is a routine procedure for humans but highly experimental and often inefficient in nonhuman primates, it is expected that the limited outcome of one offspring from 11 transferred blastocysts into six foster mothers reported by Fayomi *et al.* will be more efficient with human material. However, careful analysis of the dissected human tissue (*2*) and of male gametes obtained from autologous grafts should be performed because it must be confirmed that epigenetic and genetic changes are not introduced in male germ cells of grafted testes. ■

Preserving fertility in primates

Fayomi *et al.* demonstrate in macaques that testicular grafting provides an option to mature prepubertal tissue fragments. The fragments undergo spermatogenesis, and consequently, spermatozoa can be collected and used in intracytoplasmic sperm injection (ICSI) to generate offspring.



REFERENCES AND NOTES

1. H. M. Picton *et al.*; ESHRE Task Force On Fertility Preservation In Severe Diseases, *Hum. Reprod.* **30**, 2463 (2015).
2. L. Heckmann *et al.*, *Hum. Reprod.* **33**, 636 (2018).
3. P. Rubino *et al.*, *Hum. Reprod. Update* **22**, 194 (2016).
4. A. Fayomi *et al.*, *Science* **363**, 1314 (2019).
5. S. Sharma *et al.*, *Hum. Reprod. Update* (2019). 10.1093/humupd/dmz006
6. J. Guo *et al.*, *Cell Res.* **28**, 1141 (2018).
7. M. Komeya, T. Sato, T. Ogawa, *Reprod. Med. Biol.* **17**, 407 (2018).
8. A. Honaramooz *et al.*, *Nature* **418**, 778 (2002).
9. L. Arregui, I. Dobrinski, *Reproduction* **148**, R71 (2014).
10. C. M. Luetjens *et al.*, *Endocrinology* **149**, 1736 (2008).
11. K. Jahnukainen *et al.*, *Cancer Res.* **72**, 5174 (2012).
12. E. Ntemou *et al.*, *Hum. Reprod.* **34**, 403 (2019).
13. Z. Liu *et al.*, *Cell Res.* **26**, 139 (2016).

ACKNOWLEDGMENTS

The authors are grateful to T. Pock for help preparing the figure.

10.1126/science.aaw6927

PALEONTOLOGY

A treasure trove of Cambrian fossils

The Qingjiang biota reveals previously unknown taxa from the dawn of animal life

By **Allison C. Daley**

One of the most important discoveries in paleontological history was the Burgess Shale in the Canadian Rocky Mountains, discovered in 1909 by Charles Walcott. At this 508 million–year-old fossil locality, soft-bodied fossils are exquisitely preserved, showing skin, eyes, and internal organs such as guts and brains. The Burgess Shale and similar localities found since—including the equally diverse and important Chengjiang biota of China (*1*), numerous other sites in China (*2*), and the Emu Bay Shale in Australia (*3*)—record the sudden appearance of a huge diversity of animals in a geologically short period of time, an event called the Cambrian Explosion (*4*). On page 1338 of this issue, Fu *et al.* (*5*) reveal a stunning new locality, the Qingjiang biota, which is slightly older (518 million years) than the Burgess Shale. The fossils from the site fill gaps in our knowledge and raise questions about the earliest animal ecosystems.

Fossil localities such as the Burgess Shale reveal the soft tissues and entirely soft-bodied organisms that typically do not make it into the fossil record, and provide a detailed window into what animal life looked like during the earliest stages of its evolution (*4*). Many of these animals have anatomies that do not directly resemble anything alive today, leading to lively debates on how they may be related to living animals. Other than the Burgess Shale (508 million years old) and the Chengjiang biota (518 million years old), numerous localities around the world were reported in the 20th century, including from Canada, China, the United States, Poland, Spain, and Australia (*6*). Burgess Shale–type fossils have even been found in the early Ordovician Fezouata biota (~485

Institute of Earth Sciences, University of Lausanne, Geopolis, CH-1015 Lausanne, Switzerland. E-mail: allison.daley@unil.ch

GRAPHIC: V. ALTOUNIAN/*SCIENCE*

Stem cell–based options to preserve male fertility

Nina Neuhaus and Stefan Schlatt

Science **363** (6433), 1283-1284.
DOI: 10.1126/science.aaw6927