

Genome editing in the germline

Controversial cuts

In the hands of molecular biologists, genome editing is a powerful tool for the precise engineering of genetic material, something that scientists have long desired. But the revolutionary technology currently taking biomedical laboratories by storm is throwing up ethical and legal questions about the responsible limits of its use. 2015 was the year in which scientific academies worldwide launched an intensive debate on setting guidelines for the use of genome editing. Central to the discussion is the engineering of egg cells, sperm cells and newly created embryos in what are known as germline experiments. German stem cell researchers have stated their position in the debate.

Genome editing is now an established part of basic biomedical research. The designer nuclease system CRISPR/Cas9 took just three years to conquer biomedical laboratories (see GSCN Annual Magazine 14/15). This technology can be used to edit the genetic material in every conceivable type of cell – not just somatic cells but also germline cells, which include egg cells, sperm cells and embryos in the early stage of development. If their genome is edited, this produces a heritable modification that can be passed on to progeny. As exciting as the possibilities of genome editing may seem, the technique is not free from possible errors and risks. Last year saw the unfolding of a scientific debate on the medical applications of genome editing. While the debate was initiated primarily by researchers in the U.S., it was quickly taken up in Germany too.

Call for a moratorium

The debate was triggered by thought-provoking appeals from top researchers in the journals *Science* and *Nature* in March 2015. Leading molecular biologists and bioethicists called for a worldwide moratorium on human germline engineering in reproductive medicine. The International Society of Stem Cell Research (ISSCR) and the German Stem Cell Network (GSCN) also spoke out in favor of a moratorium on clinical germline experiments. The German academies of science likewise turned their attention to the issue. In July, the interdisciplinary Gene Technology Report research group at the Berlin-Brandenburg Academy of Sciences (BBAW) produced a highly regarded analysis of human genome engineering that elucidated the ethical and legal aspects of the new technology and interventions in the germline. The paper states that germline therapies and artificial modification of the genome in germline cells are in principle prohibited in Germany under the Embryo Protection Act – but there are a number of loopholes and exceptions. For example, purely in vitro experiments on human germ cells are permitted. There is also no ban on producing germ cells from iPS cells as the law does not cover this relatively new technology.

The authors of the BBAW paper support the call for an international moratorium on germline experiments. They hope that during the self-imposed suspension scientists

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Research at the Max Planck Institute for Molecular Genetics (MPIMG) concentrates on genome analysis of man and other organisms to contribute to a global understanding of many biological processes in the organism, and to elucidate the mechanism behind many human diseases.

It is the overall goal of all MPIMG's groups to gain new insights into the development of diseases on a molecular level, thus contributing to the development of cause-related new medical treatments. In this context, stem cell research is

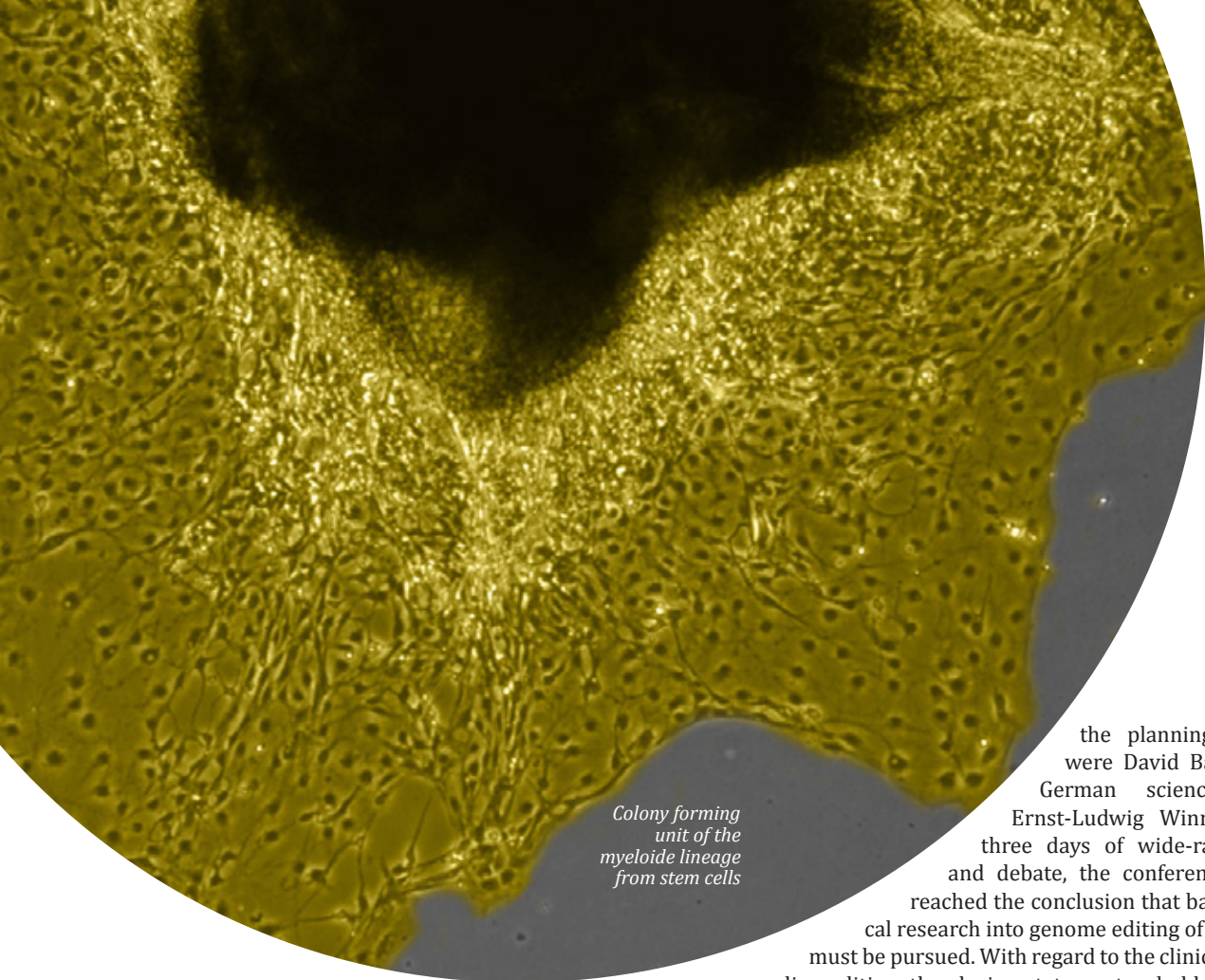
gaining increasing importance. In particular, MPIMG researchers are working on a better understanding of gene regulation networks for tissue formation and homeostasis, as their dysfunction may result in numerous diseases

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Colony forming unit of the myeloide lineage from stem cells

and academics will engage in open, transparent and critical discussion of the experimental, ethical and legal aspects of germline therapy, elaborate the opportunities and risks of the technology for humans and nature, and draw up recommendations on future regulation. In September, the German National Academy of Sciences Leopoldina and the German Research Foundation (DFG) expressed similar views.

Genome engineering summit in Washington

The scientific debate reached an interim climax at the International Summit on Human Gene Editing held in Washington in early December. The conference was organized by the national science academies of the United States, the United Kingdom and China; among the members of

the planning committee were David Baltimore and German science manager Ernst-Ludwig Winnacker. After three days of wide-ranging input and debate, the conference delegates reached the conclusion that basic and clinical research into genome editing of somatic cells must be pursued. With regard to the clinical use of germline editing, the closing statement upholds the existing reservations, stating that because of unresolved safety issues it would be irresponsible to proceed, especially given the lack of a broad societal consensus. However, the dialogue is set to continue, and some national academies have started to draw up guidelines on genome editing.

Stem cell researcher Albrecht Müller of the University of Würzburg has closely followed the recent debate on genome editing and has attended many related events, including the summit in Washington. Müller doubts that genome editing will ever be used to correct an unwanted mutation. "That will probably be done by means of pre-implantation diagnostics (PID)," he says. PID involves taking one cell from each of several embryos produced by in vitro fertilization and examining their genetic material. This enables embryos that are free from genetic defects to be iden-

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Leibniz Institute for Zoo & Wildlife Research (IZW) in the Forschungsverbund Berlin e.V.

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with stakeholders and the public. The Department of Reproduction Management, headed by Prof Dr Thomas B Hildebrandt, develops cellular techniques for conservation. This new approach is an essential, promising option for highly endangered wildlife. For this purpose, the IZW builds up international networks on „cellular techniques“, including international expert meetings of the world's leading scientists in the field of „cellular techniques“, and develops new methods of securing and preserving wildlife tissue samples.



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tified. "Genome editing for monogenic disorders makes little sense, and for polygenic ones it makes no sense at all," comments Müller. He reports that a possible application that was discussed in Washington is human enhancement, which involves modifying traits such as skin color. According to Müller, the conference participants were clear that such techniques are ethically highly controversial.

Further discussion needed

With regard to germline experiments in Germany, Müller believes that there must be a very clear boundary: no genetically modified embryo should be implanted in a womb. (Implantation is in any case banned under the Embryo Protection Act.) "But researchers should be able to use embryos left over from PID in their genome editing work," says Müller. He is of the view that the present discussion must be pursued by scientists and society at large. He maintains that "the solutions must come from science itself; the law shouldn't act prematurely, as happened with the Stem Cell Act. We are just at the beginning of the road here."

Hans Schöler, Director of the Max Planck Institute for Molecular Biomedicine in Münster, is highly critical of genome editing in the germline. He currently rejects intervention in human embryos, even for research purposes. "It doesn't seem to me at the moment that off-target effects can be controlled sufficiently for errors to be excluded," says Schöler. He points out that his own experiments on mouse cells have shown that even with recent versions of the CRISPR/Cas system a large number of faulty cuts in the genome still occur. In a germline experiment, an embryo is doubly stressed since its genes must be both checked and corrected. "In my view it would make more sense to test several embryos and transfer one that has no genetic defects." However, if the technique of genome editing were perfected and there was a valid reason for using it – instead of PID – Schöler says he might be able to accept it. However, he points out that this is nowhere near being the case at present. Nevertheless, he believes that now is the right time for public discussion of the ethically controversial matter of intervention in the human genome.

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