Cooperative Research Project

REALiGN-HD: Revisited Ethical and Legal Concepts for Precise Genome Engineering Approaches of Hereditary Diseases

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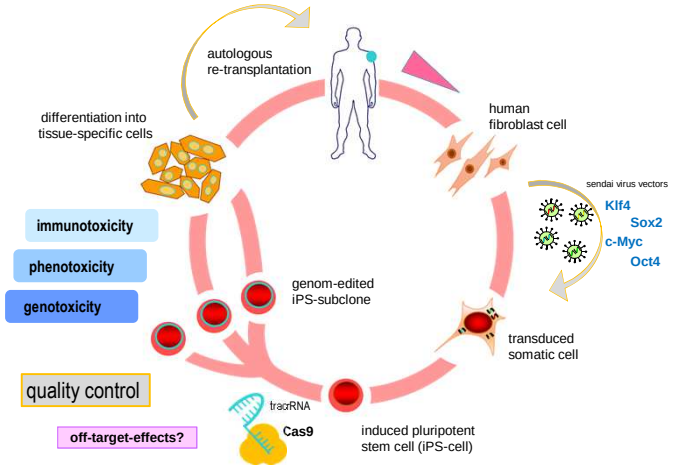
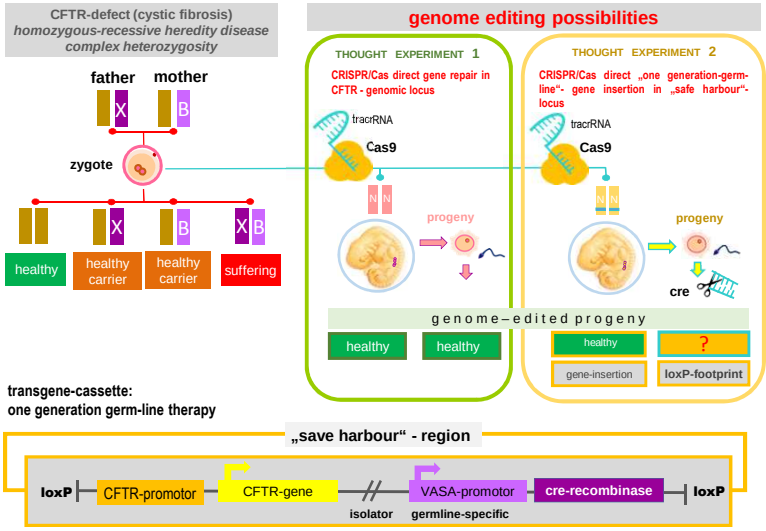
Since the discovery of the CRISPR/Cas-mechnism in bacteria new models for gene-therapy for the prevention of hereditary diseases have been evolved and applied to basic research. Within our interdisciplinary research collaboration we want to design and analyze two scenarios of gene therapy to develop an ethically reflected legal framework providing an appropriate basis for policy-making in the field of human gene therapy.
The scenarios are: (A) human iPS cells to be differentiated into somatic cells for autologous re-transplantation as well as (B) human single-cell embryos in the pronuclear stage or the stage of the zygote. Scenario (B) will be exemplified in two thought experiments: 1) “100% efficient genome editing” in any case, regardless of affected or not and 2): “one generation germ-line therapy” mediated through a germline specific self-removing transgene-cassette.

BIOMEDICINE

SCENARIO A:



SCENARIO B:



LAW

Genome editing in iPSC-derived cell transplants

Genome editing in human embryos at the pronuclear or the zygote-stage

Regulatory framework?

Directive 2001/83/EC Regulation (EC) No. 1394/2007 MPA EPA GEA GDA TA …

Regulatory gaps?

Adjustments of the regulatory framework

Constitutional implications

- Status of embryos, in particlular pronuclear embryos
- Human dignity, dignity of humankind, idea of man
- „Naturalness“, „sacrosanctity“, „contingency“ of human life
- …

Right to bio-informational self-determination

Conflict with regulatory requirements for therapy with genetically modified iPSC-derived cell transplants

Patient: Data protection

Biodata

Public authority: disclosure

- Assessments of safety, quality and efficacy by public authority
- Patient‘s right to endanger himself/herself
- Dealing with coincidental findings
- Reconsideration of the prior informed consent (PIC) principle
- …

ETHICS

Medical Indication

- Does a medical indication exist for therapeutic genome editing in the embryo? (presumed genetic alteration in the embryo’s genome cannot be verified since precise genetic diagnosis is not possible without destroying the embryo)
- By which arguments is therapeutic genome editing in embryos to be justified? (reference to disease is not possible; does possible (!) disease prevention provide a sufficient reason?)
- Is genome editing an instance of gene therapy or rather of intentions beyond the therapeutic context? By which criteria is the distinction between therapy and enhancement to be defined in the context of genome editing?

Safety

- What degree of efficiency, precision, and risk defines (sufficient) safety?
- How can/should possible side-effects be examined on a case-by-case basis (by PGD or postnatal)? How are such examinations to be judged in ethical terms? How are possible side-effects and other non-intended effects of genome editing to be judged in ethical terms?
- Are the terms of ‚natural risk‘ and ‚safety‘ equal in extension?

Responsibility for Future Generations

- The potential benefits of genome editing, e.g. in CTFR, are limited to the respective embryo; if the corrected CTFR gene is self-removing in germ cells, descendants of the embryo are again exposed to the risk of developing CTFR. Is this approach justifiable in ethical terms?
- Is hereditability of gene editing in individuals of future generations to be considered problematic by principle in ethical terms?
- Is the genetic modification itself (=remaining loxP-Sites) in individuals of future generations relevant in ethical terms?

Initial Application

Which ethical criteria will be relevant for the decision-making with regard to a first-time application of genome editing in human embryos?

Naturalness and Intentionality

- What is the relationship between naturalness and moral value?
- Does the loxP-footprint as an intentional element in the embryo’s genome alter it’s state of naturalness/ its moral status?
- Moral reference to the modification‘s function (intention) vs. reference to the modification itself (naturalness)

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