Development and usefulness of transgenic rabbit models of inborn arrhythmogenic diseases

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Addendum to the thesis by Michael Brunner, which will be defended on dec 9th, 2024:

Propositions:

1.) For arrhythmia research, rabbits are a markedly more useful model than mice. [this thesis]

2.) Hormonal influences on the arrhythmogenic substrate can be demonstrated in transgenic rabbits leading to potential new approaches to treatment. [this thesis]

3.) Pharmacological models of inborn arrhythmias are sometimes useful, but in many aspects not equivalent to genetic models. [this thesis]

4.) Overexpression (e.g., of a dominant negative) gene is a good model, but direct gene-editing would be closer to a perfect model. Until now, no Crispr/Cas or similar rabbit-model of arrhythmias has been created, but for CPVT or Brugada syndrome this might be the best (or only!) way to do it. [partially this thesis]

5.) Artificial intelligence will markedly change the way we diagnose diseases in the ECG, with applications way beyond cardiac diseases, and this will happen very, very rapidly.

6.) The phenotype of the same mutation in LQTS is variable and its characteristics depend on yet unknown factors, which are likely compensatory alterations of ion currents. Analyzing these factors might show options to alleviate symptomatic LQTS.

7.) Conduction system pacing should become the standard of care in most patients in need of ventricular stimulation by a pacemaker.

8.) The transgenic rabbit models (LQTS and SQTS) presented in this thesis already impacted science (and society), not to the least by enabling an in vivo study of gene therapy (suppression and replacement) which might – in some form or another be useful in humans one day. The ethical considerations of the first-in-man study to use a genetic therapy in patients with other treatment options will be at least as hard to solve as the technical problems of homogenous gene delivery. [this thesis]