**Challenge**

The use of biological drugs, such as hormones, antibodies or enzymes, is increasingly used in the treatment of many diseases. In many cases, this can replace the action of our own cells, which also produces biomolecules in response to different conditions.

**Pros and cons of biological drugs**

- **Higher molecular specificity:** Small molecule drugs react with almost any receptor, while biological drugs react with a specific receptor.
- **Positive effects:** biological drugs.
- **Negative effects:** may cause adverse reactions.

**What are the features of an ideal therapy?**

- **Delivery:** where they are needed
- **Combination:** different drugs in the correct temporal order
- **Complete safety**
- **Affordability:**

**Solution**

We aimed to develop an implantable cellular device for local, regulated and safe delivery of therapeutic proteins.

**Our solution:**

- Use engineered mammalian cells to produce and deliver therapeutic proteins into the affected tissue.
- Semi-permeable microshells could be implanted into the affected tissue to ensure an immune privileged environment.

**Multiple genetic switches need to be developed for introduction into engineered cells, allowing for temporal and spatial control over therapeutic delivery.**

**Safety and efficacy:**

- **Efficacy:** delivery of the right therapeutic agent to the right place.
- **Safety:** minimal adverse effects.

**Feasibility:**

- Key features of this IP is therapy for hepatic C.

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**Design**

An engineered switch is a genetic circuit designed to memorize its state and maintain expression of a gene of choice even after the inducer has been removed. Envisioning a network of multiple toggle switches, we sought to design such a system as a novel therapeutic biomolecular domain. The use of orthogonal TAL-based regulators seems perfectly fit this task due to their modularity, which allows a broad choice of DNA binding sites with high specificity and balanced properties.

**The switch**

**Bistable switch with a positive feedback loop**

The switch enhances the classical toggle switch by a pair of positive feedback loops with activators activating themselves and repressors of the opposite state, with activators and repressors competing for the same operators (designed TAL binding sites A and B).

**Safety mechanisms**

We are aware that social aspects of synthetic biology are important for the success of a new technology. The formation of a Society is required in order to keep up with the ethical and regulatory environment.

**ESCAPE**

Surface expression of NKG2C-tagged effector cells for efficient destruction of host natural killer cells.

**Implementation**

Hepatitis C virus primarily infects the liver. 200 ml of blood are infected worldwide. HCV represents an important part of the therapy of hepatitis C infection. Side effects of treatment are very common due to systemic application.

- **Engaged:** mammalian cells containing the therapeutic protein with a positive feedback loop will activate for use in hepatic therapy and infected into the liver for systemic administration.
- **Non-engaged:** production of therapeutic proteins.

**Pharmacokinetic model**

A mouse model for the mouse gammaherpesvirus thymus-expressed T-cell virus gene (Mp80) used for delivery of therapeutic proteins.

**Conclusions**

- **Hepatitis C virus infection:**
- **Ischaemic heart disease:**
- **ESCAPE:**
- **Implementation:**
- **Conclusions:**

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