The CONFIRM Initiative

Objectives, Organization and Proposed Interlaboratory Research Program

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The CONFIRM Initiative

OBJECTIVES

- **CONFIRM** → **CO**llaborative **N**etwork **F**or **I**mmunological safety **R**esearch in **M**inipigs
- **Primary objective** : provide convincing evidence that the minipig is a relevant species for the immunological safety evaluation of drugs (including biologics)

Objectives

The CONFIRM Initiative is intended to:

1. serve as a trigger for immunological safety research in Göttingen Minipigs
2. share and spread state-of-the art knowledge and new findings to the scientific and regulatory toxicology community → **web-hosted database**
3. assist and synergize fundamental, translational and regulatory investigative efforts relevant to immunological safety evaluation in minipigs
   → **interlaboratory research program**

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ORGANIZATION

- **Collaborative network** +++
- **Members** : individual researchers, scientists in academic institutions, employees of private organizations/companies
- **Membership** : exclusively granted after formal acceptance of the Members' Charter and approval of application by ad-hoc sub-committee

  → full access to all CONFIRM webpages <u>including database</u>
  → active participation to General Assembly convened once a year
  → contribution to network activities via focused workgroups

Organization

- **Webpages** hosted by Ellegaard Göttingen Minipigs website (https://minipigs.dk/knowledge-base/the-confirm-initiative)
  - → free-access section including public information on the CONFIRM Initiative and immunological safety evaluation
  - → password-protected section restricted to members, essentially a database compiling available experience about immune reagents and in vitro assays that can (or should not) be used in minipig studies.
- **Confirm Initiative LinkedIn group**

  (https://www.linkedin.com/groups/13544253)

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Proposed Interlaboratory Research Program : a 2-step approach

- **STEP 1**

Interlaboratory validation study to demonstrate the reproducibility and value of results generated by several laboratories using the same methods and study plan, in order to facilitate the regulatory acceptability of immunological safety evaluation in the minipig

- **STEP 2**

Collaborative studies to identify and qualify innovative approaches and read-outs, case by case, with the aim to assess and expand the use of Göttingen Minipigs for the immunological safety evaluation of novel pharmaceuticals and biologicals

Step 1: study design

- **Proposed test item**: Cyclosporine (CSP)
  - *Rationale: widely accepted reference immunosuppressive agent*
  - *No need for DRF study as main data available (Van Mierlo et al., Clin Exp Pharmacol, 2013)*
- **Test System**: 4-5 month-old Göttingen Minipigs
- **Study duration**: 4 weeks + 2-week recovery (standard general toxicity design)
- **Treatment regimen**: daily oral gavage
- **3 groups:** 1 control + 2 CSP-treated groups (2 dose levels) : 3 animals/sex/group
- **Standard toxicological endpoints**: clinical observations, body weight, food consumption, clinical pathology, macroscopic examination, histology examination of lymphoid organs/tissues (thymus, spleen, bone marrow, lymph nodes, GALT, BALT…) + main vital organs (liver, kidneys, heart, lungs), proof of exposure (TK)

Step 1

- **Selected immunological safety endpoints**
  - *Immunophenotyping (whole blood): Total T cells, $CD4^+$ and $CD8^+$ T cells, $\gamma\delta$ T cells, B cells*
  - *Anti-KLH IgM and IgG response measured by ELISA*
- **Biobanking** of organs/serum/plasma for further analysis
- **Any optional add-on welcome, but** strict adherence to agreed minimal design absolutely required
- **Deliverables** = presentations to congresses, article(s), recommended SOPs

Step 2: introduction

- **Proposed objectives**
  - *Development of innovative strategies focused on selected classes of immunotoxicants*
  - *Study and qualification of innovative (including potentially disruptive) read-outs* applicable to immunology safety evaluation in Göttingen Minipigs
  - *Deliverables*: same as STEP 1 (presentations to congresses, article(s), recommended SOPs)
- **Proposed context**
  - *Only collaborative studies*: academia, pharma, agencies (?)
  - *Objectives, study plan, modalities to be discussed* by open interactions between collaborating institutions, case by case
  - *Coordination and logistics* through the CONFIRM Initiative

Step 2

- **FOCUS ON SELECTED CLASSES OF IMMUNOTOXICANTS**
  - Immune checkpoints inhibitors
  - Anticancer and recombinant prophylactic vaccines
  - Therapeutic proteins and recombinant cytokines
  - Small immunostimulatory molecules
  - Cell or gene therapy
  - …

- **FOCUS ON INNOVATIVE READ-OUTS AND APPROACHES**
  - Expanded immunophenotyping
  - Multi-antigen responses
  - Cytokine (T_{H1}/T_{H2}) profiles
  - Genomics/transcriptomics
  - Host resistance assays
  - Anti-drug antibodies (ADA)
  - Cytokine release
  - Complement activation
  - …

Interlaboratory program: conclusion

- **2 STEPS**

  - **STEP 1**: strict interlaboratory validation study using a widely recognized reference agent, and both conventional study plan and measured endpoints
  - **STEP 2**: open set of collaborative studies to contribute to a better immunological safety evaluation, especially in Göttingen Minipigs

Your active contribution to this program is very welcome !