

# PhD position available (4 years)

## Preclinical assessment of the immunogenicity of protein drugs

### Project background:

Antibodies induced by therapeutic proteins are associated with severe side effects and loss of efficacy. In the case of therapeutic proteins of non-human origin, these antibodies are induced by the classical immunological pathway in which B-cells produce antibodies in a T-cell dependent manner. However, also human proteins induce antibodies, sometimes even with a high incidence. How these products break B-cell tolerance is still incompletely understood. Aggregates are thought to play an important role, probably because they may present epitopes in a repeated array from which may initiate the activation of B cells. However, the potential involvement of T-helper cells and the necessity of additional stimuli are less well understood. This lack of understanding hampers the prediction of immunogenicity.

### Goal of the project

The goal of the project is improvement and expansion of pre-clinical tools for the assessment of immunogenicity of therapeutic proteins using transgenic mice which are tolerant for human proteins.

### Experimental approach

Several validated mouse models will be used; transgenic mice expressing human interferon alpha 2 or human interferon beta (eventually also transgenic mice expressing human Ig). In these mice, the physico-chemical characteristics of protein drugs (aggregates) and the impact of mode of administration on the potential to break B cell tolerance will be explored. In collaboration with Roche, the involvement of T-helper cells will be determined.

### Profile

A highly motivated candidate with an interest (or expertise) in immunology and animal experiments. A background in biomedical or pharmaceutical sciences (or similar) is required. Other qualities are good communication skills and knowledge of the English language (spoken and written).

### Place (project leaders)

Utrecht Institute for Pharmaceutical Sciences (UIPS), dept of Pharmaceutics, Utrecht University, The Netherlands.

Prof. H. Schellekens (Utrecht University), Prof. W. Jiskoot (Leiden University)

### Contact

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