SEEKING A PhD CANDIDATE
IN PHARMACOLGY AND IMMUNOLOGY

SUPERVISOR :

PhD Director : Nathalie Heuzé-Vourc'h ; co-supervisor: Thomas Sécher ;
Inserm UMR1100 Research Center for Respiratory Diseases
Team « Pharmacology of inhaled Pharmaceuticals »
Faculty of Medicine
2 boulevard Tonnellé
37032 Tours cedex, France

Email : nathalie.vourch@univ-tours.fr; thomas.secher@inserm.fr

TITLE: Comprehensive analysis of immune responses to mRNA-based vaccines

KEYWORDS : mRNA vaccine, synthetic formulations, inhalation, mucosal delivery, infectious diseases, cancers

PROJECT DESCRIPTION:

Recent achievements of messenger RNA (mRNA)-based vaccines against SARS-Cov2 have confirmed the therapeutic potential of mRNA and lipid nanoparticle-based formulations (1). However, these vaccines have limitations proven by the short duration of the induced immune response requiring frequent boosters and their ineffectiveness to prevent infections in vaccinated subjects (2-5). The RNAVAC consortium gathers 11 french academic laboratories to accelerate the production of innovative vaccines for future viral outbreaks and for mucosal cancers with unmet medical needs. It focusses on developing mucosal mRNA vaccines along with mucosal routes of administration as musical routes increase the duration, polyclonality and match location of the immune response with the site of infection or cancer (6-8). In particular, RNAVAC aims at developing mucosal mRNA vaccine administrated by inhalation (intranasal or intrapulmonary route) as these routes are suitable to fight both head and neck, lung cancers and respiratory pathogens.

Objectives: To document and compare the innate, adaptive and potential inflammatory responses induced by mRNA vaccines, produced within the RNAVAC consortium, after administration through different routes, to guide pre-selection of lead candidates.

The project is divided in 3 main tasks:

1. Analysis of *in vitro* innate immune responses induced by the various mRNA formulations. Determination the impact of mRNA on innate immune, in particular looking at immune training of immune cells.
2. Comparison of innate and adaptive immunity responses induced by mRNA vaccine models, *in vivo*, after administration by nasal, pulmonary, as compared to the intramuscular route in naïve wild-type mice. At early (48h) and later time-points (10 days), assessment of innate signals (chemokine, cytokines…) and measurement of the variations in blood and mucosal tissues of innate immune cells (ILCs, NK cells,

neutrophils, macrophages), adaptive immune cells and humoral immune responses (secretory IgA, IgG) and tissue-resident memory T/B cells which participate to protection against infection/cancer, in the respiratory tract (lung, nose).
The antigen models will be ovalbumin and E7 as many tools to assess specific immune response are available (recombinant protein, pools of peptides, Elispot, tetramer, cytometry panels,..)

3. Analyze immune responses of the various mRNA formulations after nasal or pulmonary immunization. Depending on results got from the first task, the most promising mRNA vaccines will be evaluated in naive murine animals (wild-type or relevant gene-inactivated animals) with a defined route of immunization. The choice of antigens will be based on results of other groups optimizing mRNA vaccine formulations. The innate and adaptative immune responses will be evaluated, as described before.

Expected results:

- Characterize the innate and adaptive immune responses associated to mRNA vaccines depending on the route of administration, *in vitro* and *in vivo* to determine the most promising mucosal route to be used for preclinical evaluation of lead candidates in murine models of tumors and infections.
- RNAVAC program aims to create a unique network on mRNA-based vaccines that masters state of the art techniques in mRNA design, production and formulation, with ad hoc tools for screening and evaluation. This PhD project is one of the pillar of this network.

REFERENCES

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ENVIRONMENT:

The Research Center for Respiratory Diseases (french acronym: “CEPR”) was established on 1st January 2012 and managed ever since by Dr. Mustapha Si-Tahar (DR2 Inserm). It is affiliated to Inserm and University of Tours.
The research of CEPR is aimed at developing innovative translational research that can both increase our knowledge of the mechanisms of specific infectious and inflammatory lung diseases as well as facilitate the emergence of more efficient aerosol therapies and devices.
The CEPR is organized in 4 teams. Team 3 “Pharmacology of inhaled Pharmaceuticals” is a technology-oriented group composed of scientists, engineer and clinicians- conducting a multidisciplinary and translational research focused on the delivery, deposition and pharmacology of therapeutics by the inhalation route, to treat respiratory diseases. Its singularity relies on long-term and fruitful interactions with the socioeconomic environment, which is mandatory to obtain the tools – devices or biotherapeutics, coming from industrial partners- for testing scientific hypotheses and transfer its results to the clinic. The group has established an international reputation in inhalation medicine by (1) developing new experimental models/methods to help bridge the gap between preclinical studies and clinical

trials and accelerate the development of inhaled pharmaceuticals and devices for inhalation, (2) addressing the physical, chemical and biological barriers to achieve efficient drug deposition in the respiratory tract to reach the molecular target, (3) offering unique expertise in inhalation delivery of protein therapeutics and antibodies, and (4) demonstrating the clinical relevance in appropriate populations to substantiate practical application, determine configurations allowing optimal targeting and, ultimately, put forward recommendations for clinical use.

The PhD project is included in a broader program "RNAVAC" (https://pepr-biotherapies.fr/en/2023/12/08/rnavac-en/) gathering 11 academic laboratories with complementary expertises to work together on a goal-oriented project of high priority consisting in conceiving 2nd generation of mRNA vaccine candidates possessing mucosal immune response ability. It is founded as part of France 2030 plan and PEPR "Biotherapies and Bioproduction of innovative therapies".

The RNAVAC project is confidential and the host team is classified as "restricted", thus applications will be submitted to the security defense officer for approval, prior to recruitment.

SKILLS AND EXPERIENCE

- Higher education diploma in fields pertinent to the profile (Life science, Phamacology, Immunology) with a minimum of 5 years training after High school diploma
- Training for animal experiments is preferred
- Experience in immunology is preferred

- proficiency in standard office/scientific software
- fluency in written and spoken English
- Initiative, autonomy and reactivity
- Accuracy, organizational skills and ability to prioritize
- Ability to analyze and synthesize
- Ability to relate to others and work as part of a team
- Aptitude for multi-tasking and teamwork
- Excellent writing and communication skills