Board of examiners

Prof. Dr. Ron Kooijman
Department of Pharmacology and Pharmacokinetics
Vrije Universiteit Brussel

Prof. Dr. Lilianne Tenenbaum
Clinical Neuroscience Department
University of Lausanne, Switzerland

Prof. Dr. Joris Vermeesch
Department of Human Genetics
KU Leuven

Prof. Dr. Jacques De Keyser, Chair
Department of Neurology
Universitair Ziekenhuis Brussel, Belgium

Prof. Dr. Marinee Chuah, Promotor
Department of Gene Therapy and Regenerative Medicine
Vrije Universiteit Brussel

Prof. Dr. Thierry VandenDriessche, Promotor
Department of Gene Therapy and Regenerative Medicine
Vrije Universiteit Brussel

VRIJE UNIVERSITEIT BRUSSEL

PhD in Medical Sciences
2016-2017

INVITATION to the Public defence of

Shilpita SARCAR

To obtain the academic degree of **'DOCTOR IN MEDICAL SCIENCES'**

Development and validation of novel computationally designed cis-regulatory modules for muscle-directed gene therapy: implications for Duchenne muscular dystrophy.

Monday 10 July 2017
Auditorium **Piet Brouwer**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:
http://www.vub.ac.be/english/infoabout/campuses

Summary of the dissertation

Gene therapy is emerging as a promising therapeutic modality for the treatment of neuromuscular disease, such as Duchenne muscular dystrophy (DMD). Nevertheless, there is still a need to generate the next-generation vectors for gene therapy in order to express higher levels of the therapeutic transgene in the affected muscles at lower vector doses. This should minimize the risk of immune responses and toxicity. To increase the potency of gene therapy for muscle disorders, we explored the use of novel genome-wide computational strategies to boost vector performance. This resulted in the identification of hyperactive skeletal muscle-derived transcriptional cis-regulatory modules (designated as Sk-CRMs) associated with a robust increase in skeletal muscle gene expression following AAV9-mediated transduction in mice. All of the identified Sk-CRMs showed increased reporter gene expression as compared to the control AAV vector devoid of Sk-CRMs. The best Sk-CRM (Sk-CRM4) also led to a 30 to 40-fold increase in cardiac expression. We also evaluate the performance of the most robust muscle-derived Sk-CRM4 in a therapeutically relevant setting. In particular, we used Sk-CRM4 to boost expression of human micro-dystrophin (μDYS) and follistatin (FST), as an effective combination gene therapy to treat muscular dystrophy in SCID/mdx mice. Subsequently stable and widespread expression of the therapeutic μDYS and FST proteins in skeletal muscle and heart, was confirmed by immunohistochemistry and ELISA, respectively. Most importantly, the high expression levels of μDYS and FST led to a robust functional correction of the dystrophic phenotype of the treated SCID/mdx mice by assessing physical fitness and endurance using a treadmill assay.

Curriculum Vitae

Shilpita Sarcar was born on December 27th, 1985 in India. During her graduation in India, she obtained a Bachelor degree in Biotechnology followed by a Master degree in Biotechnology in 2009 with highest distinction. She then acquired industrial experience at a stem cell research based company in India, before starting her PhD research in May, 2011 at the Department of Gene Therapy & Regenerative Medicine, Vrije Universiteit Brussel, under the supervision of Prof. Dr. Marinee K.L. Chuah and Prof. Dr. Thierry VandenDriessche. Her research focused on the development and validation of novel computationally designed cis-regulatory modules for muscle-directed gene therapy: implications for Duchenne muscular dystrophy. She was also engaged in several other projects beyond her immediate PhD thesis subject, the research outcomes from which have been validated in several publications. The scientific output from her research includes 6 publications in international peer-reviewed journals. In addition, 1 of her first author papers from Molecular therapy (IF = 6.93) was selected for a commentary. She is currently employed as Research Associate in the Department of Cell and Developmental Biology, University College London.