

## **Project Summary**

### **John Hansen Research Grant 2021**

#### **Inducible CAR-T-cells derived from a donor-derived peptide-stimulated oligoclonal T-cell population with on/off-switches for targeted immunotherapy post-hematopoietic stem cell transplantation**

Ignazio Caruana, PhD

Although the majority of children with leukaemia are cured with conventional chemotherapy, certain subgroups still bear a high-risk of relapse even after an allogeneic haematopoietic stem cell transplantation (aHSCT), the most powerful weapon we have today to fight these malignancies. Strategies to intensify therapy before aHSCT are problematic due to increased toxicity. Chimeric Antigen Receptor (CAR) T cell treatment is a novel and promising form of immunotherapy, where the patient's own T cells are collected from their blood and gene-modified to express a molecule capable to recognize and attack tumour cells. Based on the success of this treatment approach, CAR-T cell therapy has been recently approved for the treatment of certain leukaemia and lymphoma types. However, CAR T-cell technology so far has been implemented mostly as either a bridge or alternative to stem cell transplantation. In this project, we aim to provide a new approach to implement CAR-T-cell technology early after stem cell transplantation by using donor-derived T cells which, unlike those of the patient, never came into contact with chemotherapeutic agents. In consequence, this approach requires higher safety measures, which consist of three layers: 1) gene-modified cells will be equipped with a inducible suicide switch, allowing immediate termination of treatment in case of severe adverse reactions; 2) the CAR itself is designed as an inducible option, which means that it will only be expressed when it is needed, e.g. for molecular relapse; and 3) to reduce the allogeneic, and potentially dangerous, activity of the donor cells, an oligo-clonally expanded virus-specific T-cell population will be selected for gene modification. The later not only reduces the risk for Graft-versus-Host disease, but also allows boosting of the T-cells via their endogenous T-cell receptor using commercially available vaccines.

Thus, rather than being a bridge-to-transplant, we envision our post-transplant strategy as a bridge-to-Graft-versus-leukaemia effect, which is needed to reach a long-term cure from high-risk leukaemia.