Invite to Innovate

AMBER
Advancing Materials for Impact

nibrt
National Institute for Bioprocessing Research and Training

A World Leading SFI Research Centre

Science Foundation Ireland SFI For what's next

Non-viral Gene Delivery

(for Gene Therapy and Biomanufacturing)

AMBER are investing up to **€2m** in the development of **Non-Viral gene delivery platforms.**

Additional opportunity to work with **AMBER** and **NIBRT** on development of stable and scalable nanotechnologies for nucleic acid delivery.

We are seeking industry partner(s) willing to collaborate on these exciting initiatives with **Matched** funding.

HOST INSTITUTION
Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

PARTNER INSTITUTIONS
CRANN · RCSI · UCC · Tyndall · DCU · NUI Galway OÉ Gaillimh · University of Limerick · TUS · University College Dublin An Coláiste Ollscoile, Baile Átha Cliath

Introduction

The utilisation of the mRNA-based COVID-19 vaccines represents the culmination of many years of non-viral nucleic acid delivery, but more importantly, they signify a massive clinical scientific success.

The increasing level of knowledge re the genetic basis of disease has opened up the potential to **modulate gene expression to enable gene based therapeutic purposes**.
A range of nucleic acids including antisense oligonucleotides, siRNA, MiRNA, pDNA, mRNA and CRISPR have the capacity to achieve **gene replacement, gene silencing, gene editing and vaccination**. The main challenge to translating these concepts into the clinic is the design and manufacture of effective and **safe delivery systems** (nonviral vectors).

According to market research, the global gene therapy market is expected to be valued at over US$15 billion by 2030. This expected growth has generated a huge pressure on biomanufacturing companies to develop new technologies to be able to satisfy the high demand of gene therapy products / technologies.

With recent regulatory approvals, the rapid growth in demand for viral and non-viral based products highlights the need for proven, scalable manufacturing solutions that can fully meet the demand.

Biomanufacturing

Non-viral vectors have several advantages in the development of gene therapies in comparison to viral vectors, such as their relatively low cytotoxicity and immunogenicity. However, commercial manufacturing of non-viral vector-based gene therapies remain a significant hurdle. **Process optimisation** for vector production, purification, and formulation are key challenges.

A robust analytical testing strategy is required for manufacturers to determine the identity, purity, potency, and safety of the final product. In addition, investigations into product development perspectives related to a vector's physical and chemical stability during formulation preparation and product storage are required as these factors can have a significant impact on the overall efficiency of the vector and hence the therapy itself. Enhancing our understanding of the requirements for process development has the potential to accelerate the delivery of new gene therapies to patients.

Two Challenges

Challenge A:
Successful translation of gene medicine from bench to bedside requires deep knowledge of the targeted disease, well designed pre-clinical/clinical investigation including immune response, toxicity studies, efficacy and access to suitable scale-up manufacturing that complies with good manufacturing process (GMP).

Non-viral vectors are simple in theory but complex in practice.
Despite the **immense possibilities** presented by nucleic acid- based therapeutics, they all face significant challenges in terms of clinical and commercial translation including the **need for effective and safe delivery vehicles**. As therapeutics, nucleic acids are large, negatively charged molecules and are rapidly cleared by circulating nucleases in the body. New materials are needed to meet the delivery challenges of these macro molecules. The safety of both the delivery mechanism and the gene based therapy itself is the **key for successful translation**. Apart from intra cellular and extracellular barriers, **several other challenges also needs to be overcome** to increase the effectiveness of non-viral gene transfer.

Challenge B.
Rigorous quality control throughout the manufacturing process is essential to ensuring the safety and efficacy of any biotherapeutic. It is important to define the appropriate critical quality attributes and critical process parameters not only to assure product quality but also to accelerate product development.
Due to the inherent variability and complexity of some non-viral vectors, the assessment of factors such as contaminants and batch-to-batch consistency is a considerable, but fundamental, challenge to address.
The development of advanced analytical approaches to enhance the understanding of the biophysical and biological attributes of non-viral vector quality attributes are required. Significant challenges in chemistry manufacturing and analytical strategies to allow for comprehensive characterisation of the biotherapeutic are still to be overcome to bring non-viral nucleic acid-based therapies to their full potential.

Approaches by AMBER and NIBRT

Challenge A Approach (AMBER lead):

Development and commercialisation of gene based therapeutics involving new and emerging technologies present the market with challenges in creating customised solutions

At AMBER, we rise to this challenge by applying our **breadth and depth of experience** in the **synthesis of novel polymeric and lipid like gene delivery nano systems** with strong capabilities in nanomaterial modification, characterisation, 3D modelling of tissue & disease and pre-clinical evaluation. AMBER Centre has **World renowned expertise** in the study and generation of non-viral gene delivery nanomaterials that could offer critical platforms for **new gene-based therapies** and **combination product development**.
As examples, a number of projects funded by highly prestigious European Research Council grants (including two recently awarded ERC Advanced Grants) are focused on the **development of nanomedicines** in the form of **gene therapeutics complexed with nanoparticles**.

Challenge B Approach (NIBRT lead):

AMBER and **NIBRT** would like to further interrogate and understand the nucleic acid complexes to better characterise the gene-loaded nanoparticles using advanced characterisation, refine the transfection procedure using current GMP ready materials and/or assess the potential for new gene delivery materials as alternatives. We seek to harness AMBER's and NIBRT's infrastructure and expertise across sites to address these challenges.

Roles of each collaborator:

AMBER: Pharmaceutical formulation development and characterisation and material synthesis work will be conducted in AMBER labs

NIBRT: Provision of unique bioprocessing facilities and testbed capabilities as well as in depth engineering, analytics and characterisation expertise.

Industry Partner(s): Working collaboratively with one or both centres

Lead Investigators

AMBER
Advancing Materials for Impact

Prof. Sally Ann Cryan

Prof. Andreas Heise

Prof. Caitriona O'Driscoll

Dr Piotr Kowalski

Dr. Caroline Curtain

Prof. Fergal O'Brien

Details of the wider AMBER PI team available at AMBER PEOPLE

nibrt
National Institute for Bioprocessing Research and Training

Prof.Niall Barron

Dr. Jonathan Bones

Dr. Colin Clarke

Details of the wider NIBRT PI team available at: NIBRT TEAM

AMBER's Expertise & Capabilities

AMBER, The SFI Centre for Advanced Materials and BioEngineering Research, brings a multi-disciplinary team together across all the Universities in Ireland to deliver world class material science research.

We have **state of the art material manufacturing and characterisation capabilities**, **pre-clinical models** and **access to patient derived cell lines** to develop clinically relevant non-viral vectors for use to combat elusive diseases.

AMBER's expertise in materials modification, characterisation and 3D modelling include:

- **Non viral gene therapy** (SiRNA/MiRNA/mRNA/pDNA)
- **Synthesis** of novel polymeric and lipid-like gene delivery nanosystems - polymers, cyclodextrins and lipids.
- **Biomaterial development** for broad tissue engineering applications and functionalised scaffold based therapeutics for biomolecule delivery.
- **Design and formulation** of targeted RNA & DNA nanocarriers and conjugates.
- **Evaluation of RNA therapeutics** in disease relevant animal models.
- **Regulatory approval pathways** e.g. Biosimilars & ATMPs
- **Regulatory Science** –new tools, standards and approaches to assess the safety, efficacy, quality of CGTs.
- **In-vitro physiologically based 3D models -** organoids, collagen-based scaffolds.
- **Immunology -** for characterising immune response to nanomedicine
- **Chemistry Expertise** – for design, synthesis & modification of gene based therapeutics.

Processing & Characterisation Capabilities include:

- **Design and pharmacological evaluation** of non-viral delivery systems for gene therapy
- **Physicochemical characterization** of nano- sized delivery systems
- **Microfluidic-based formulation** of nanoparticles
- **Bio-predictive in-vitro and in-vivo testing** of siRNA/mRNA formulations.
- **Design, synthesis, purification, and characterization** of biomaterials and API (mRNA)
- **Freeze-drying/Lyophilisation 3D Printing**
- **Nanomaterials characterisation** (Advanced Microscopy Lab, AMBER)

NIBRT's Expertise & Capabilities

Inspired by the manufacturing challenges facing the industry, the NIBRT Research team makes transformative discoveries across multidisciplinary areas such as analytical science, cell and genetic engineering, informatics, and bioprocess engineering.

These discoveries are utilised to advance the state of the art in their fields and revolutionise the manufacture of recombinant proteins, vaccines and cell and gene therapies.

Characterisation and Comparability Lab

- **Utilisation of liquid phase separations** hyphenated to state-of-the-art mass spectrometry instrumentation to enable in depth characertisation of:
- **Small Molecules:** including extractables and leachables, impurities, media and metabolite profiling, lipid nanoparticles, microplastics/nanoplastics.
- **Biotherapeutics:** including Adeno-associated virus (AAV), monoclonal antibodies, fusion proteins, antibody-drug conjugates, biosimilars, host cell proteins, mRNA.
- **Process Analytics:** including process parameters, cell culture parameters, Critical Quality Attributes, determination of process gases, spectroscopic techniques.

Cell Engineering Group

- **Improving viral gene therapy manufacturing platforms** through engineering or selecting better host cell lines for the production of AAV and LV. Modifying the component plasmid vectors used to generate viral particles (in both HEK293 and S9f cells).
- **Engineering CHO cells** for biopharmaceutical production (profiling of miRNA, mRNA and protein expression analysis to identify engineering targets for improved CHO cell phenotypes)
- **Developing advanced recombinant DNA engineering strategies** for improved phenotypic stability and selection of producer lines.
- **Epitranscriptomic engineering.**

Systems Biology and Data Analytics Laboratory

- **Next generation sequencing** and integration of multi-dimensional data
- **Utilising of single cell analysis** for biopharmaceutical process development
- **Harnessing big data technologies** specifically for biopharmaceutical production improvement

To hear more or submit an **Expression of Interest** please contact denise.carthy@tcd.ie

or go to

This Form

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