ATMP workshop
Project ideas for discussion

Magda Papdaki (ABPI)
Luc Kupers (Genzyme)
Wilfried Dalemans (Tigenix)

Precision Genome Editing (PGE)

Problem statement

Novel technologies, with a number of bottlenecks yet to be addressed:

- Safety and efficacy:
  - Lack of tools to quantify and minimize off-target effects.
  - Lack of reliable paradigms for basic biology and preclinical testing.
- Broader gene therapy optimization: PGE vector design, delivery and targeting, immuno/onco-genicity, transgene expression control.
- Need for flexible policy and ethical frameworks.

Scope

- Address gaps in our understanding of precision genome editing (PGE) biology, function and applicability.
- Increase confidence in the accuracy, safety and efficacy of the technologies for both research and therapeutic applications.

Gene Editing– examples of deliverables

- Novel characterization assays and tools for the **quantification of on-target/ off-target effects,** ie. New DNA analytic technologies or advanced ‘next generation sequencing’ (NGS) platforms.
- Optimization of existing PGE platforms - ie. **Bioinformatic tools** and design guidelines to increase target selectivity.
- Development of new **pre-clinical cell/animal testing** paradigms, ie:
  - Humanized models and their inflammatory or oncogenic profile.
  - Germline modification assays, genotoxicity and carcinogenicity studies.
  - Bio-distribution and tissue accumulation assays.
  - Development of bespoke iPSC or organoid systems for patient-level SNP screening to determine cell differentiation and off-targets.
- Develop and provide access to qualified **reagents, platforms and data**.
- **Define the boundaries between the competitive and precompetitive space,** through continued dialogue between researchers, manufacturers and platform development, throughout the programme.

Clinical Development

Problem statement

Multiple sources of data needed to substantiate impact on long term disease management and cure, however landscape and utility extremely complicated:

- Vast number of registries currently used by different groups.
- Variability in data collection standards and quality.
- Opaque environment of methodologies, standards and regulations.

Scope

- Devise an efficient framework for the data-enabled optimization of clinical trials for different types of ATMPs.
- Investigate the necessary infrastructure and methodologies for the efficient utilization of existing and new registries and other data repositories.
- Enhance interoperability between databases and integration of data across Europe for long-term patient follow up and product supply monitoring.
- Update policies, processes and qualification pathways to assess clinical utility of existing data and new evidence requirements.

imi innovative medicines initiative

Clinical Development – examples of deliverables

- Develop the **technical capabilities** around data source standards and interoperability.
- Enhance the **quality standards**, accuracy and regularity of data entry, reporting and analytics.
- Increase **stakeholder collaboration** on governance, access and oversight.
- Develop new **data network architectures and** links, as well as dataset query protocol designs, to avoid fragmentation.
- Increase built in **flexibility** to accommodate emerging knowledge and changing requirements.
- Address challenges in **database maintenance**, sustained collection and funding resources.
- Clarify status of **patient level data** protection, access controls and surveillance.
- Clinical trial registries could also expand to provide evidence in further **support of HTA evaluations**, focused on patient outcomes.

Patient Access

Problem statement

Numerous ATMP-specific challenges for market access, as science, policy, skills, and services co-evolve with the technology in real-time:

- Evidence and confidence on the long-term effects at the point of approval and pricing are limited.
- Increasing need for real-time monitoring and use of patient outcomes, ie through registries.
- Investment requires increased clarity on the journey to market, and the views of regulators and payers.

Scope

- Capture the challenges across the pathway from the bench to the bedside, and across the different types of ATMPs.
- Clarify evidence requirements for a comprehensive assessment and commercialization framework.
- Allow sufficient flexibility to accommodate the pace of scientific progress.
- Secure the appropriate use of hospital exemption and leverage existing schemes, ie. Orphan/rare disease funds.

imi innovative medicines initiative

Patient Access – examples of deliverables

- Perform a detailed **record of ATMP developers** in Europe and internationally.
- Analyze pipeline **projects** and commercial **products**, investment decisions and transactions.
- Identify **success/failure drivers** and key go/no-go decision factors across the product journey from R&D to the health systems (case studies).
- Devise analytical frameworks and performance **indicators to compare EU** countries, with US and other global competitors.
- Model/propose **novel reimbursement** and payment schemes.
- Tabulate the key **HTA considerations** and contrast with evidence for regulatory approvals and surveillance.
- Analyze case examples on **hospital exemption** across Member States.
- Identify and evaluate existing and propose new **modelling methods and data tools** (ie. Registries) through specific projects and work streams.
- Establish links with **existing projects** (IMI and others) that seek to balance investment with health budget sustainability.
- Enable the **stakeholder interactions needed** to balance access to ATMPs with stakeholder management of current uncertainty.

Manufacturing

Problem statement

Major obstacle on the path to industrial transposition of ATMPs

- lack of appropriate manufacturing means and protocols, which leads to challenging scalability and costs of production
- considerable regulatory effort
- Quality/consistency concerns

Scope

- Technological innovation in cell therapy and gene therapy production, with specific attention to closed systems, automation and monitoring technologies
- Particular emphasis on therapeutic scale production and GMP standards at reasonable cost, achieving regulatory compliance.

imi innovative medicines initiative

Manufacturing – examples of deliverables

- **Two main types of automation processes** should be developed in order to address both conditions of optimal cell growth, namely for adherent cells in flasks and for cells in suspension or semi-suspension in bioreactors.
- **Robotised technologies and controlled methodologies for cGMP banking of cell therapy products**. Large-scale banking of clinical-grade cell therapy end-products requires increasing appropriately all safety measures and designing fully controlled procedures both for freezing and thawing.
- Addressing the question of a **huge diversity of cell and gene therapy products**.
- **Quality controls and standards** using the procedures of Quality by Design and Quality Risk Management (ICH paradigm used for chemical compounds production)
- **Rules for continued engagement** between scientists/manufacturers and regulators based on risk assessment along the programme

Immunogenicity

Problem statement

Allogeneic cell therapy products offer major advantages in terms of large scale manufacturing, product consistency, cost of goods and bedside use. However, they are prone to immune responses of the host with possible impact on safety and efficacy. Current knowledge of the impact of anti-cell immune responses is limited, hampering prediction of possible clinical consequences of such immune responses, in particular upon repeated use of the product(s).

Scope

- Immunogenicity of different types of allogeneic cell sources.
- Impact of the disease on the immune responses.
- Impact of the route and schedule of cell administration.
- Clinical investigation of immune responses and their impact on safety and efficacy of the ATMP.

imi innovative medicines initiative

Immunogenicity– expected deliverables

- Understanding the innate and adaptive immune responses against different allogeneic cell types.
- Insight in the intensity, specificity, kinetics, and persistence of such immune responses.
- Dynamics of memory responses upon repeated administration.
- Understanding the influence of given pathologies on the anti-cell immune responses.
- Clinical assessment of the associated safety aspects.
- Clinical assessment of the impact of immune responses on ATMP efficacy.
- Knowledge of the impact of HLA matching and mismatching on safety/efficacy.