ADVANCED THERAPY MEDICINAL PRODUCTS **(Chairs Giuliana Ferrari, Maria Themeli)**

SUPPORTING YOU FROM DISCOVERY TO THERAPY, MATCHING EXPERTISE, REDUCING RISK.

Advanced Therapy Medicinal Products (ATMP) represent a new category of medicines with a wide therapeutic potential for treating different types of diseases such as cancer, neurodegenerative and cardiovascular diseases. They include Gene Therapy Medicinal Products (GTMP), Cell Therapy Medicinal Products (CTMP), and Tissue Engineered Products (TEP). Clinical application of the two latter types is frequently referred to as 'Regenerative Medicine'.

The EATRIS ATMP platform offers over 35 state of the art European centres covering the entire ATMP production and development pipeline.

The platform provides the most qualified and state of the art technologies for the critical issues in this development area, such as specialised GMP facilities, imaging facilities for in vivo animal studies, availability of dedicated/ tailored animal models, clinical expertise and access to patients for high prevalence and/or rare diseases, as well as to clinical facilities.

The platform includes a network of experts for regulatory affairs specialised in the ATMP field to ensure compliance with the preclinical and clinical development guidelines within Europe.

EATRIS ATMP services facilitate project advancement in the minimum of time and with the most efficient use of resources, while also ensuring high levels of scientific discipline and regulatory expertise.

EXPERTISE

- Key opinion leaders in cell and gene therapy as well as in tissue engineering.
- Interaction between clinicians and specialised scientists, biotechnologists, biostatisticians in close coordination with regulatory affairs experts and national authorities throughout ATMP development.
- Experience in many disease areas ranging from oncology or neurodegenerative disorders to regenerative medicine.

TARGET REVALIDATION AND PRE-CLINICAL DEVELOPMENT

- State of the art genomics, proteomics platforms.
- State of the art vectorology, cell biotechnology.
- Animal facilities up to BSL3 containment with a large range of animal models and species.
- Preclinical imaging (µPET, µCT, µMRI, US, µSPECT, optical imaging as well as hybrid systems) to revalidate the target.
- Assessment of the regulatory requirements for future clinical development.

GMP PRODUCTION OF ATMPS

- GMP pharmaceutical plants authorised by the local competent authorities.

- Production of a great variety of all types of ATMP for human use.

TOXICOLOGY

- Evaluation of general safety and efficacy for the application in clinical studies.
- GLP compliant facilities for toxicology in rodents, rabbits and pigs.

CLINICAL DEVELOPMENT

- Local clinical trial centres to cover phase I and II clinical studies jointly with university medical centres to foster interactions between clinicians and specialised scientists.
- Support of the trial design and execution under GCP.
- Clinical imaging for image acquisition, analysis, integration and interpretation in various patient cohorts.
- Data analysis centres to handle, process, integrate and store multimodality data.

SMALL MOLECULES **(Chairs Alfredo Budillon, Maddalena Fratelli)**

INNOVATIVE TRANSLATIONAL DRUG DISCOVERY & DEVELOPMENT FROM PRE-CLINICAL VALIDATION TO PROOF OF CONCEPT

The EATRIS Small Molecules platform supports the pre-clinical and clinical development of drug candidates, utilising academic expertise around novel targets and molecular scaffolds. The platform offers 25 expert translational medicine institutions and has access to advanced screening facilities with innovative cell-based assays as well as integrated use of the latest biomarker techniques.

Tailored animal models help shorten the time to in vivo proof of concept and study the mode of action of novel drug candidates and targets, supported by experts in pharmacology, medicinal chemistry, analytical chemistry and toxicology. In addition, crossover synergy is provided by the EATRIS Imaging & Tracing and Biomarker platforms to speed up small molecules development programmes to achieve early proof of concept all within one infrastructure.

INFRASTRUCTURE AND EXPERTISE:

- Development of xenograft models for translational in vivo screening
- Advanced screening using 3D cultures and primary cells
- Access to patient-derived primary cells (e.g. tumor cells, and fibroblasts)
- High throughput and (automated) high-content analysis compatible 3D cell cultures
- Modified liquid-overlay culture for spheroid production
- Flow cytometry read-outs to detect cell differentiation
- Transcriptomic analysis of multi-drug resistance
- Cellular screening for novel drug candidates (and drug combinations) including radiochemotherapy using X-rays
- Studying the penetration of DNA de-methylating drugs in reporter cell spheroids
- Application of pH microsensors for screening under extracellular acidosis conditions
- Compliant handling of patient samples (i.e. signed informed consent and ethical approval)

ADME PROFILING:

- Determination of chemical stability (non-enzymatic degradation), stability in biological fluids (plasma, saliva, gastric juice)
- Assessment of passive absorption and permeability in the gastrointestinal tract
- Identification of drug transporter substrates
- Prediction of blood brain barrier permeability
- Microsomal stability and drug plasma protein binding assays
- Advanced mass spectrometry (MALDI) analysis of drugs and metabolites
- Quantitative determination of the distribution in organs and tissues of small rodents by LC-MS
- In silico prediction and PK/PD modeling of human ADME profile

TOXICITY PROFILING:

- Good Laboratory Practice (GLP) compliant toxicity studies in mice, rats or rabbits
- Extended single dose (microdose) toxicity studies with hematology, clinical
- Chemistry, necropsy, and histopathology data
- Neurotoxicity, cardiotoxicity (ECG, BP) and respiratory toxicity
- 28-days or 90-days repeated toxicity studies with non-compartmental toxicokinetics

- Design of preclinical safety studies for authorization

PRECLINICAL VALIDATION OF NANO MEDICINES:

- Nanoparticle formulation design and development
- Nanocarrier characterisation (size, shape, distribution profile)
- Enhanced drug delivery using peptides, conjugates and liposomal formulations

EARLY CLINICAL DEVELOPMENT:

- Experience in many disease areas, with particular strength in oncology, neurodegenerative disorders, cardiovascular disease and rare diseases
- Support for clinical trial design, execution and analysis in clinical centres, including biostatistics and legal and ethical approval
- Access to patient materials and cohorts
- Close interaction with regulatory affairs and clinical experts (IMPD, clinical dossier, orphan drug designation, clinical expert opinions)

VACCINES, INFLAMMATION AND IMMUNE MONITORING **(Chairs Jan Langermans, Lucia Gabriele)**

INFRASTRUCTURE AND EXPERTISE BRIDGING THE TRANSLATIONAL GAP AND FOSTERING INNOVATION AND COLLABORATION BETWEEN ACADEMIA AND INDUSTRY

The EATRIS *Vaccines, Inflammation and Immune Monitoring* (VIIM) platform covers the entire vaccine development and production pipeline ranging from late-phase pre-clinical development to clinical trials. Partnering with 15 of Europe's most advanced development centres, the *Vaccines, Inflammation and Immune Monitoring* platform offers proven state-of-the-art resources for all critical issues related to vaccine development.
They include specialised GMP provision with accompanying formulation and adjuvantation; disease specific animal models with facilities up to BSL3 containment; immunomonitoring, and access to clinical facilities with relevant patient groups up to phase IIa trials.
The EATRIS Vaccines platform also provides a network of experts on regulatory affairs specialised in vaccines, to ensure compliance with all pre-clinical and clinical development guidelines within Europe.
This allows us to bring projects forward in the minimum of time and with the most efficient use of resources, while ensuring high levels of scientific discipline and regulatory compliance.

EXPERTISE

- Experts including vaccinologists, immunologists, biochemists, toxicologists, pharmacists, physicians, veterinarians, and epidemiologists.
- Experts on regulatory and legal issues, manufacturing, quality management, technology transfer, and liaison with various authorities (e.g. FDA/EMA for the authorisation of first in man studies).
- Experience with vaccines for infectious diseases and non-infectious diseases.

ANTIGEN CHARACTERISATION

- Laboratories, animal houses and core facilities available to characterise in vitro and in vivo the status of a target and the standardisation of validation protocols.
- Verification of regulatory requirements and patent status.

VACCINE FORMULATION

- Optimisation of vaccine formulation in preparation for scale-up under GMP conditions.
- Appropriate strategy for a delivery system and adjuventation.

PRE-CLINICAL VALIDATION

- Development of in vitro and in vivo validated assays for pre-clinical studies.
- Development of validated measures for the evaluation of humoral and cellular immune responses at systemic, mucosal and in situ levels.
- Development of adequate potency tests.
- Pre-clinical in vivo validation in disease-specific animal models including primates

- up to BSL3 containment.
- Pre-clinical evaluation of vaccine immunogenicity, efficacy and toxicology.

PROCESS DEVELOPMENT

- Exploration of upstream processing; evaluation of expression system.
- Exploration of downstream processing (incl. possible inactivation).
- Confirmation of a feasible small-scale process (scalability, reproducibility).
- Scalability, reproducibility and initial process validation as required for phase I.

GMP VACCINE PRODUCTION

- GMP pharmaceutical production centres with vaccine authorisations. Preparation of GMP batches of vaccines for toxicology and clinical studies.

CLINICAL DEVELOPMENT

- Clinical trial centres for phase I and II studies in conjunction with a university medical centre to foster interaction between clinicians and specialist scientists.
- Support for trial design and GCP execution.
- Clinical imaging for analysis, integration and interpretation in various patient cohorts.
- Data analysis centres manage the processing and integration of multi-modality data.

BIOMARKERS **(Chairs Alain van Gool, Maria Laura García Bermejo, Andreas Scherer)**

SUPPORTING DRUG DEVELOPMENT TO DIAGNOSTICS DEVELOPMENT

In the era of personalised medicine, biomarkers play a crucial role in diagnostic and treatment decisions. Biomarkers also represent a key strategy for innovative clinical trials (e.g. patient stratification) that will facilitate cost-effective and speedy assessment of new drugs for efficacy and marketing approval.

The EATRIS Biomarkers Platform facilitates the validation and development of biomarkers for the prevention, diagnosis and prognostic assessment of disease as well as for the prediction of therapy response.

EATRIS institutions in the Biomarkers Platform utilise cutting edge infrastructures as well as a range of scientific, technological, clinical and regulatory expertise to operate professional and high-quality standardized services in the development of biomarkers.

The EATRIS Biomarkers Platform independently validates biomarkers in distinct clinical groups by providing access to clinical samples, develop standardised assays or gather experts to assess the clinical and commercial relevance of the biomarkers.

The Biomarkers Platform has a variety of technological expertise, such as tissue-based biomarkers, multiplex assay and imaging expertise, as well as disease expertise, including cancer, neurological disease, infection or inflammation.

EATRIS PROVIDES SUPPORT IN A WIDE VARIETY OF TECHNOLOGIES RELATED TO BIOMARKERS:

- Genomics, next-gen DNA/RNA sequencing, and bioinformatics
- Molecular pathology with qualified pathologists
- Antibody libraries, antibody engineering and immunoassay development
- Multiplexed immunoassays and immunostaining of cells/tissues/TMAs
- Automated images analysis and web microscopy
- Lipids and lipoproteins
- Cytokines
- Microvesicles characterization
- Targeted mass spectrometry
- Multiparametric flow cytometry

BIOMARKERS PLATFORM SERVICES:

- Access to biobank samples (e.g. tissues, cells, DNA, serum, plasma) for validation of drug targets and biomarkers.
- Identification and validation of biomarkers for drug response.
- Access to medical data & clinical experts.
- Assay development & validation.
- Testing and comparison of biomarker assays.
- Patient-derived models for drug testing and biomarker research.

Supporting drug development to diagnostics development

EATRIS PROVIDES EXPERTISE ACROSS A WIDE VARIETY OF DISEASES, SUCH AS:

- Oncology including solid tumors and
- Hematological neoplasia
- Rare diseases
- Cardiovascular disease
- Neurology
- Infections and inflammation

IMAGING & TRACING **(Chair Albert D. Windhorst)**

HIGH-END INFRASTRUCTURE FOR ADVANCED TRANSLATIONAL MOLECULAR IMAGING TO SUPPORT DRUG DEVELOPMENT

The EATRIS Imaging and Tracing Platform provides a single point of entry to high-end expertise and cutting edge translational imaging facilities, defragmenting the scattered nature of technical know-how and making optimal use of resources to improve R&D output.

With over 35 institutions, the Imaging and Tracing platform covers the entire scope of tracer development and molecular imaging and offers multi-centre clinical trials capabilities with validated imaging-based biomarkers.

Disease-specific tracers, contrast agents and radiolabeled drugs (manufactured to GMP guidelines in certified labs) can be tested pre-clinically and clinically in combination with a full range of high-end multi-modal imaging techniques (PET/MRI, PET/CT, SPECT, ultra-high field MRI, MRS, ultrasound or optical) and advanced image analysis.

BENEFITS OF IMAGING FOR DRUG DEVELOPMENT:

- Visualisation and quantification of disease targets and therapy responses help to understand disease mechanisms and enhance the prediction of therapeutic efficacy of new drug compounds.
- Dose finding studies can be completed faster and with fewer volunteers in phase I, allowing early elimination of dead-end compounds and reducing development times.
- Projects are derisked at a much earlier stage with decision making in drug development supported by dedicated imaging data analysis centres, allowing quantitative PK/PD modelling, confirmation of the current status of promising drug targets and drugs.

INFRASTRUCTURE AND EXPERTISE:

- High-end radionuclide production and imaging facilities
- Access to over 75 tracers for preclinical and clinical PET imaging
- GMP-compliant production and clinical development of novel tracers
- Ultra-high field clinical imaging for visualisation and quantification of tissues, drugs and therapy responses with various imaging modalities (PET/
- MRI, PET/CT, US and optical)
- Key opinion leaders in nuclear medicine, radiology, medical physics, radiopharmaceutical chemistry, in vivo pharmacology and kinetic modelling
- Radionuclide and tracer production facilities offering the full range of clinical grade isotopes
- Dedicated hot cells and automated manufacturing processes for GMP compliant radiolabeling of biologicals and small molecular drugs for human application
- GMP compliant manufacture of optical imaging probes
- Proof of concept studies in animal models using multimodal and ultra high field imaging techniques
- Development of novel tracers for in vivo imaging of disease specific markers in drug and diagnostics development
- Visualisation and quantification of tissues, diseases, drugs and therapy responses using an array of imaging technologies

- Image acquisition, analysis and integration as well as image interpretation with tracers or imaging based biomarkers in various patient cohorts
- Support of your clinical trial design and execution in our clinical imaging centres which have years of experience in phase I-III trials
- Ultra-high field MRI to develop imaging biomarkers for high precision medicine