Innovative Medicines Initiative (IMI)

IMI2 Call 17: indicative future topics

Topic 1: Optimising Future Obesity Treatment

The scope of the topic is **to identify pathophysiologically and clinically meaningful subgroups of obesity that will allow for optimisation of prevention and treatment of obesity and its complications**. Establishing (or revisiting) a robust sub-classification may include the current use of body mass index as the best anthropometric measure, or alternatively waist circumference or waist to hip ratio; it may include a direct or indirect measure for the duration of disease (e.g. acknowledging the difference between paediatric onset obesity and decades of metabolic insult); genetics and epigenetics, to name a few.

More specifically the objectives of the topic are to:

- Establish a federated database by pooling of the baseline data from pre-existing cohorts from observational or interventional studies to achieve as broad and detailed information on patients with obesity as possible, including sufficient clinical phenotyping and multi-omics data.

- Perform data driven analysis of the federated database to identify and characterise patient subgroups and potential biomarkers for diagnosis, prediction of the development of complications, and potentially inform on appropriate type of and response to treatment.

- Fill the gaps of information regarding selected biomarkers by reanalysing pre-existing biobank samples. Such biomarkers should be affordable and operational in the context of real world clinical practise and clinical development of innovative medicines and other treatments.

- Address specifically type 1 diabetes (T1D) as an example of a co-morbid condition in which both clinical phenotype and treatment is influenced by obesity in an intricate manner, including public education about obesity in T1D. As part of this, datasets from the T1D Exchange programme will be available.

- Collect and integrate patient perspectives in relation to diagnosis and treatment of obesity to understand the need, perceived barriers and value of determining medical treatment for patients with obesity.

- Conduct a shared value analysis among key stakeholders reflecting values and challenges within the obesity landscape for optimising treatment and prevention. Engagement of external stakeholders is encouraged to generate educational material to support a common understanding of obesity. The content could include determinants and consequences of obesity including weight management.

- Establish a Patient Advisory Board including representatives from patient organisations in order to ensure that patient-driven research and insights relevant for the project are identified and considered within and across the different work packages.

Topic 2: Open Access Chemogenomics Library and Chemical Probes for the Druggable Genome

Currently, the druggable human genome is estimated to consist of at least 3,000 genes. This topic aims to generate potent, well-characterized functional small molecule modulators for a significant number of these and, at the same time, lay the foundation for identifying a set of openly accessible (i.e. unencumbered from restriction on use) tool compounds for the entire druggable human genome. With this set of chemical tools available, scientists will be poised to interrogate the latest findings emerging from big data approaches and human genetic studies, thus compressing time from gene discovery to target prioritisation, and ultimately to patient benefits. Importantly, although we imagine the consortium can make great progress by assembling and characterizing pre-existing compounds into an initial chemogenomics set, this is not enough. It is imperative to fill the significant gaps by discovering and developing novel chemical tools/probes against under-studied proteins (or protein families) that may be involved in the initiation and progression of disease.

The overall aim of this topic will be as follows:

- Establish a framework to assemble an open access chemogenomics library for the druggable genome – namely a physical library supported by compound meta-data.
- Further enrich the open access library by inventing new, deeply-characterized chemical probes to selected specific protein families.
- Develop open access assays from well characterized human disease tissue with a special emphasis on immunology, oncology (including immune-oncology) and neuroscience to profile the chemical tools and chemical probes.
- Establish sustainable infrastructure, with high priority on accessible platforms and appropriate governance, for prolonged discovery and dissemination of tool compounds, assays, and associated data, beyond the lifetime of this project.
- Develop a communication plan to facilitate the dissemination of the compound sets and to ensure their appropriate use.

Topic 3: Intelligent prediction and identification of environmental risks posed by human medicinal products

The overall objective of this project is to **ensure the environmental safety of human medicinal products through patient use** by providing innovative and predictive tools to:

(i) identify environmental hazards and risks associated with candidates in drug development;

(ii) to screen and prioritise established, 'legacy' pharmaceuticals for a tailored environmental assessment;

(iii) make environmental data for human medicinal products more transparent to all stakeholders through the development of a publicly available database.

This project aims to **validate approaches to prioritise the risks of human medicinal products**. It is important that the predictive in silico, in vitro and in vivo tools and models:

(i) are extended to include other targets and endpoints in a wider range of taxa and environmental compartments;

(ii) have their predictive capability maximised at a systems level through the application of innovative machine learning approaches and artificial intelligence innovation;

(iii) are validated to understand their predictive capability and applicability domain;

(iv) are assessed for their feasibility to be integrated earlier into drug development to flag environmental concerns sooner than within the current industry model; and

(v) are applied to established active pharmaceutical ingredients (APIs) that lack comprehensive datasets to address and prioritise concerns about the environmental risks associated with legacy medicinal products.

Thus, the focus of this project will be on **developing methods and guidance for targeting predictions and screening assays on the various types of compound classes represented in the area of human pharmaceuticals.** To deliver these objectives the following issues or themes fall within the scope of the project:

- To work across a broad group of stakeholders including the pharmaceutical industry to define what constitutes a greener API;
- To weigh the feasibility of designing greener APIs with the priorities of patient efficacy and safety;
- Drive innovative approaches to assess environmental risks. Such innovative approaches should include: (i) improving the predictability and applicability of the fish plasma model, (ii) providing three-dimensional in vitro cell culture approaches to assess API uptake, metabolism, elimination and toxicity in fish as a key priority for the pharmaceutical industry given the high level of drug target conservation in fish, and (iii) applying Artificial Intelligence and Machine Learning approaches to improve comparative toxicological predictions between preclinical and environmental safety assessments. The tools being developed must have the potential to be applied much earlier within drug development than existing environmental assessment and possibly be aligned with ongoing preclinical drug, safety and metabolism assessments;

- To consider environmental impacts in other environmental taxa and for other environmental compartments beyond surface waters, e.g. groundwater, secondary poisoning etc.
- To address concerns with off-target effects and the environmental relevance of these effects;
- To assess and determine the validity of the tools and models for underrepresented mechanisms-of-action (MOA) classes of APIs and define the applicability domain for the each of the tools and models according to Organisation for Economic Co-operation and Development standards;
- To apply and validate the tools, models and methodologies developed with an ambition to assess at least 25 legacy APIs, including key metabolites, selected in agreement with key external stakeholders. It is expected that any ERA data for priority APIs identified, generated and validated in this project will be made publicly available outside the iPiE-25 programme;
- To maximise the knowledge generation potential of the a pharmaceutical ecotoxicology/environmental database including the integration of predictive capabilities and maximisation of data accessibility and transparency to all stakeholders;
- Enabling the pharmaceutical ecotoxicology/environmental database to capture spatially refined exposure assessments and measured environmental concentrations for prioritised compounds and the integration of tools and models to provide probabilistic or semi-probabilistic approaches to ERA;
- To develop a database as a central resource for the collation of environmental risk assessment (ERA) supporting data with the support of the EMA and National Competent Authorities, in order to minimise duplicate testing and remove any requirement for inefficient monograph type approaches.

As APIs that are potential sex steroid receptor agonists and antagonists have a categorical inclusion, and require a tailored ERA, fall outside the remit of this topic call. Also given that antibiotics have a mode of action largely restricted to prokaryotic organisms and only require limited testing to conclude on environmental risk they don't require further consideration within this topic call. Finally, due to complexity of investigating environmentally relevant mixtures of APIs and other chemicals models should be developed and validated based on exposure to single compound exposures. However, it should be recognised that many of the tools and models being developed and validated in this project could be applied to mixture assessments.