IMI's experience in the 3Rs and relevance to COVID-19 R&D

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Intergroup on the welfare and conservation of animals:
The role of non-animal approaches in COVID-19 related research
May 20th 2020 - Brussels

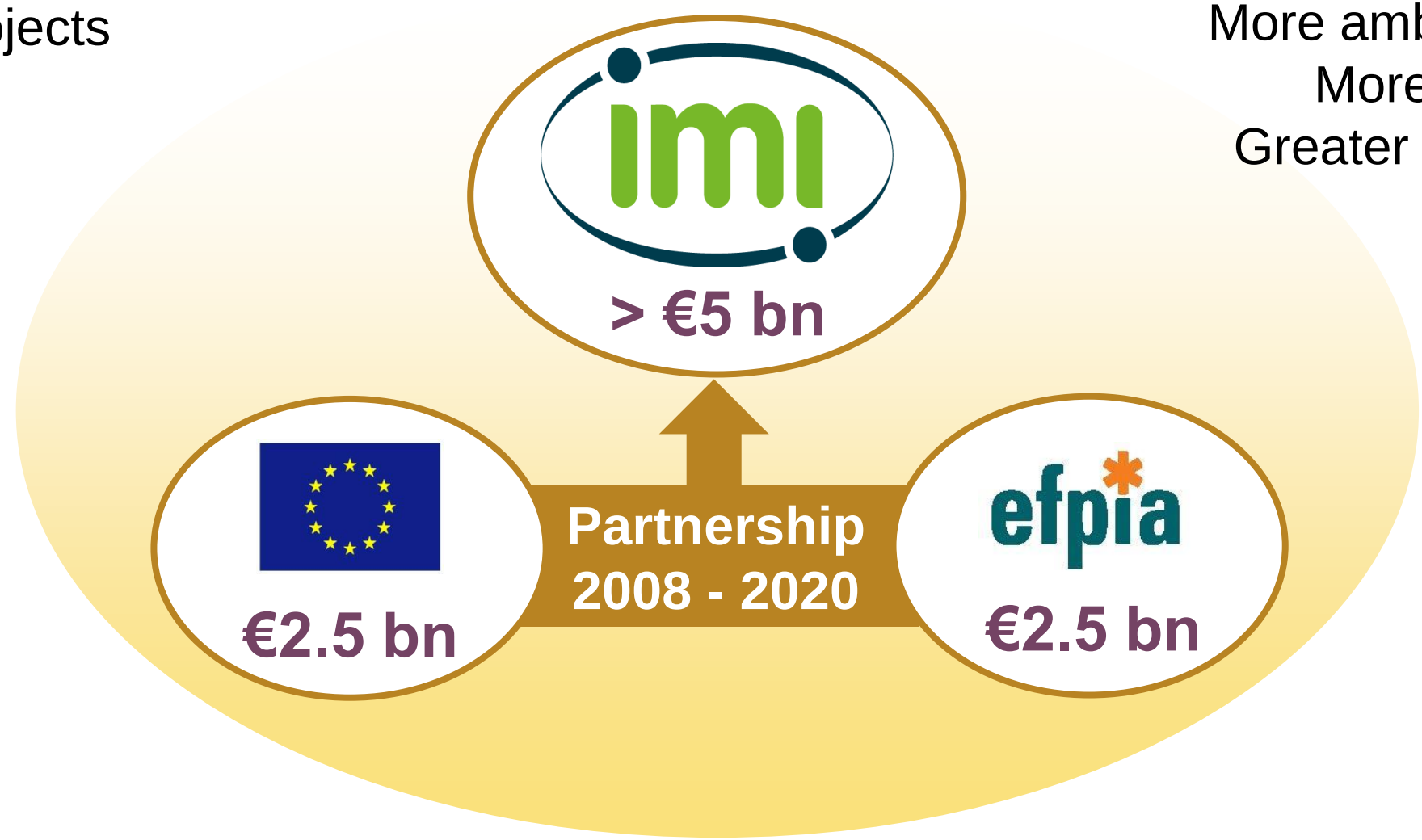
IMI – Europe's partnership for health

IMI1: 2008-2013

€2 bn budget
59 projects

IMI2: 2014-2020

€3.3 bn budget
More ambitious
More open
Greater scope



10 YEARS OF BREAKTHROUGHS
A HEALTHIER FUTURE

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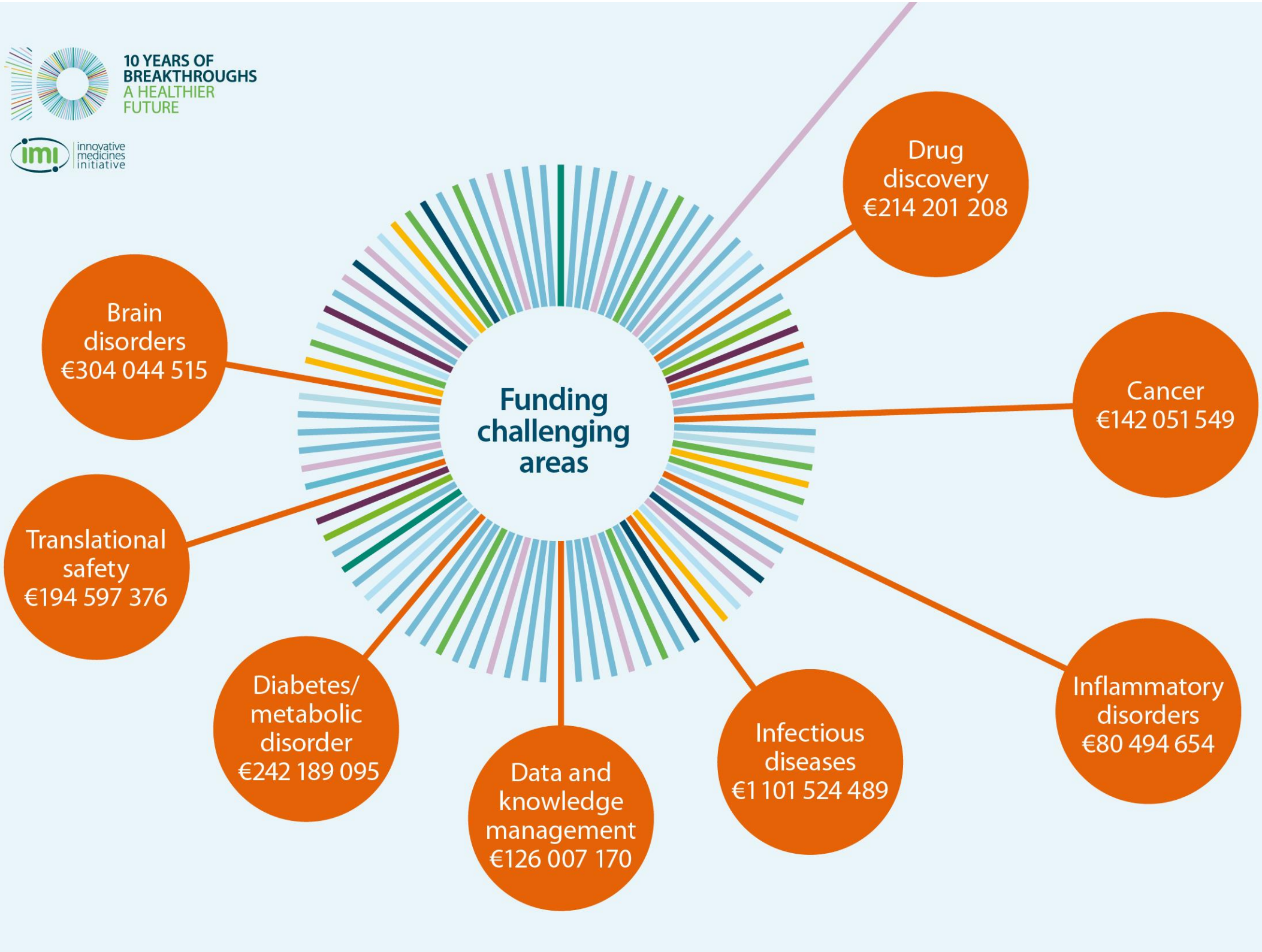

Through advances in science and technology, the use of animals in research has been revolutionised

- Using new *in vitro* models
  - Developing human cell based assays
  - The use of induced pluripotent stem cells (iPSC)
- Using new *in silico* models
  - Predictive toxicology
  - Use of AI
- Using only highly relevant animal models
  - Standardisation of *in vivo* models
  - Increasing the relevance to human situation
  - Moving to lower phylogenetic levels

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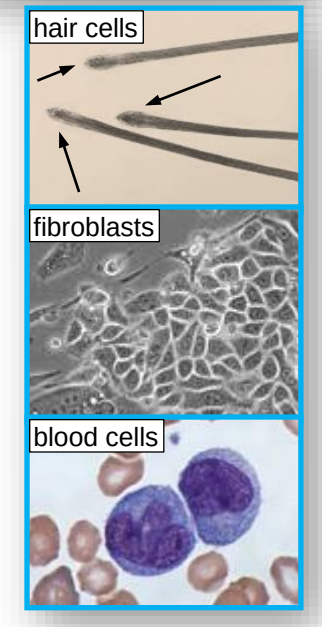
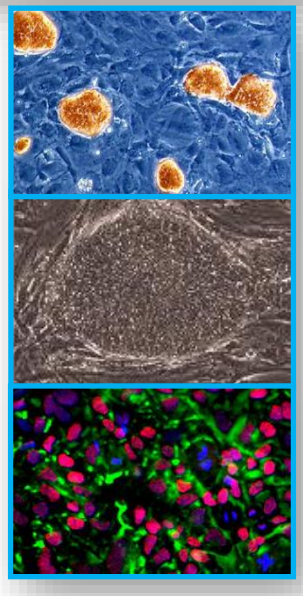
Patient derived iPSCells as disease models

EU-AIMS
Autism Research in Europe

Harvest cells from patients



Reprogramming into pluripotent stem cells

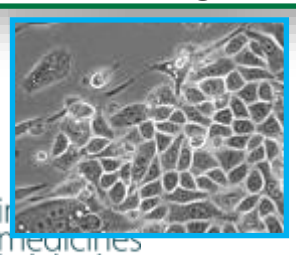


Differentiating neurons

Phenotyping neurons

- Morphology
- Synaptogenesis
- Protein expression
- Biochemistry
- Receptor pharmacology
- Synaptic physiology

Genome editing



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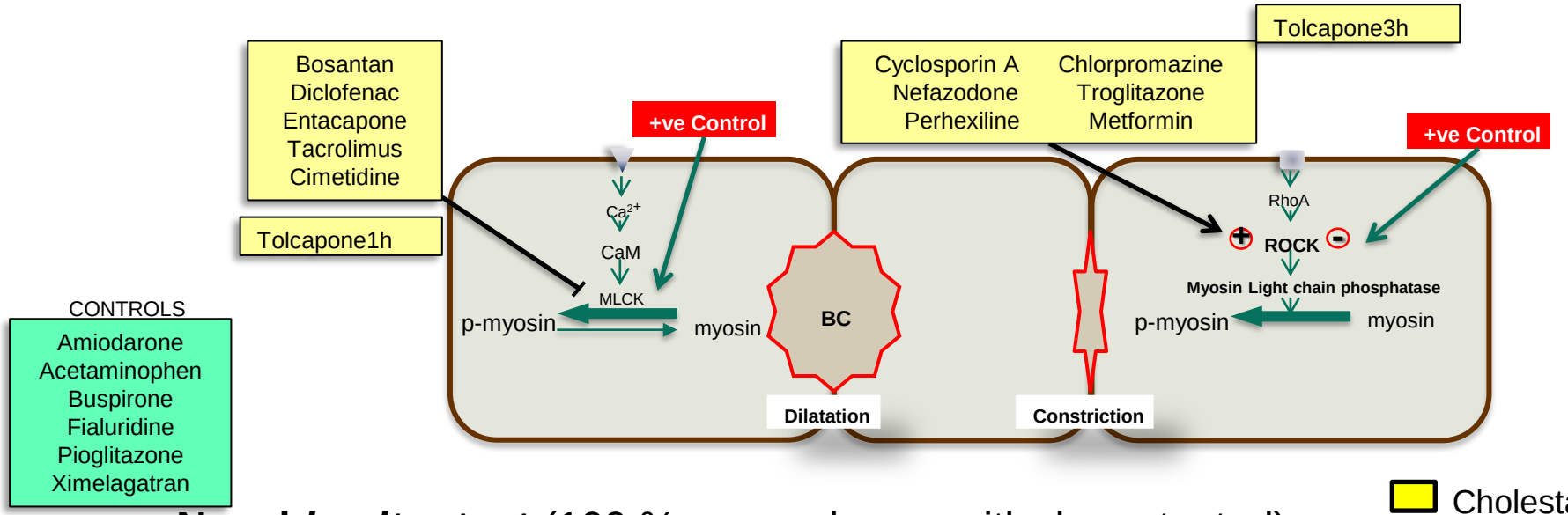
Better prediction of Drug Induced Liver Toxicity (DILI) by in vitro models

MIP-DILI

Cholestasis is a major sub-form of DILI (20-40% incidence rate in human). Its study requires chronic toxicity studies, particularly in larger species

BUT Unknown translatability of pre-clinical findings to human



- **Novel *in vitro* test** (100 % concordance, with drugs tested)
- Direct **translational relevance** to *in vivo* **human pathophysiology**
- In many cases, transporter inhibition appears secondary
- Composition of the Bile acid profile changes in cholestasis
- Currently developing a robust diagnostic test for industrial application

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Burbank *et al.* Drug Metab Dispos 44:1–14 2016 Sharanek *et al* Drug Metab Dispos Sept 2017

An holistic approach that has concrete impact on the 3Rs

- Extensive use of optimal design and pharmacometric methods
- Miniaturisation of bioanalysis and non-destructive PK sampling
- Focussing of in vivo experiments using information from in vitro systems
- Clarification of role of individual models e.g. GP and NHP

"The work of the PreDICT TB project has done much to develop and apply the 3Rs to research as it has developed tools to improve TB detection which will decrease and refine animal use, such as the molecular bacterial load assay (MBLA) and flow cytometry techniques to provide information not only about inhibition of mycobacteria but about the whole population, whether alive, dormant or dead. The study design has been improved to decrease the number of animals used, to decrease the amount of time they spend on study and by moving to the use of zebra fish, a lower phylogenetic species is being utilised."

-Ethics Advisory Board Report 2017

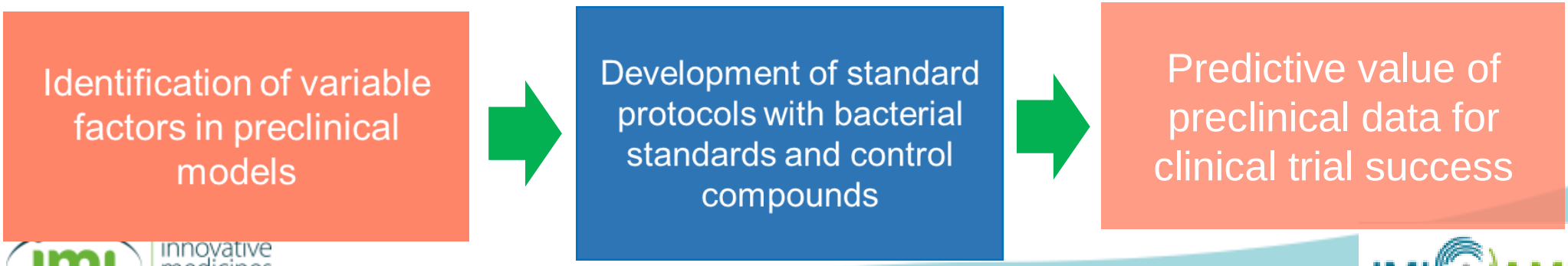
EAB Chair
Sarah Wolfensohn

Promoting standardisation and translation of in vivo infection models

- COMBINE will develop standardised protocols for rodent models, establish a reference strain data bank, and provide a framework to make use of the results to improve translation to the clinic via mathematical modelling approaches.

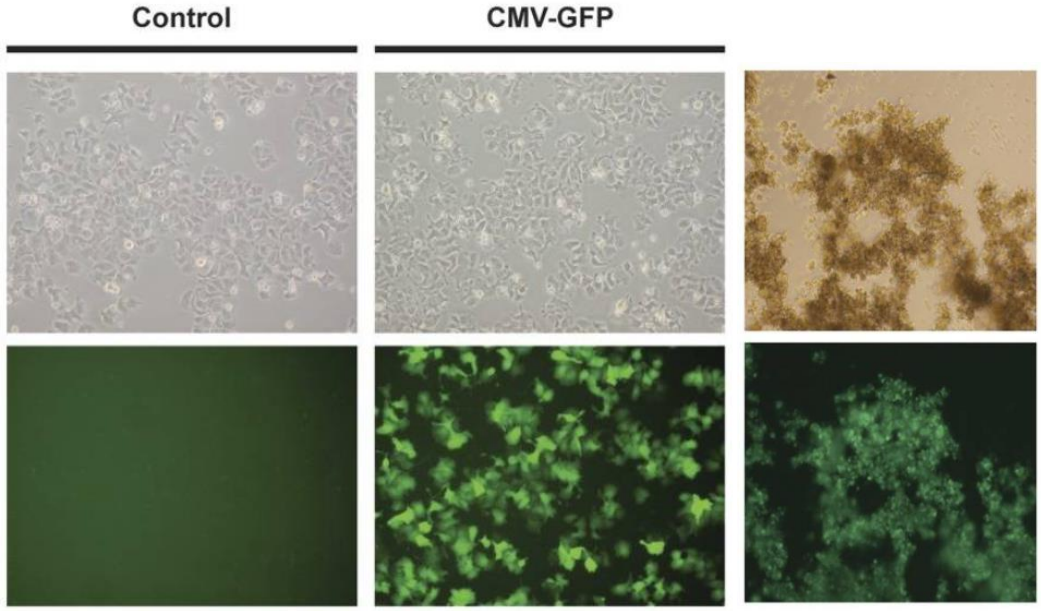
- All animal models will use clinically relevant, well-defined reference Gram-negative strains.

- The standard protocols will ease harmonisation of non-clinical data and facilitate the establishment of standardized high-quality infection models.



Tackling T1D with a novel in vitro model

A PRIVATE PUBLIC PARTNERSHIP
AGAINST TYPE 1 DIABETES



Bioluminescent reporter assay for monitoring ER stress in human beta cells

www.nature.com/scientificreports

INNODIA developed a novel in vitro model, Gaussia luciferase-based reporter system, which allows tracing endoplasmic reticulum stress in isolated human beta cells.

The model may aid the identification of novel therapeutics aiming at prevention of beta cell stress in human pancreatic islets.

https://www.ncbi.nlm.nih.gov/pubmed/30532033

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Other examples

ADAPTED	Developed a novel method for generating monocytes derived from hiPSCs, and differentiating them into macrophages with a pro- or anti-inflammatory phenotype. The method was implemented by the project to determine the effect of the APOE genotype on inflammation in in vitro models of Alzheimer's disease.
BEAt-DKD	Developed insulin sensitive animal models and insulin-resistant and -sensitive renal cell lines (podocytes, glomerular endothelial cells, mesangial cells, proximal tubular cells) of human and murine origin. Also generated insulin resistant and insulin sensitive human microvascular endothelial cells of non-renal origin and human blood-outgrowth-endothelial-cells- (BOECs) as potential carriers of accessible information about the patient's DKD status.
TransQST	An in vitro/in silico system to predict drug-induced liver injury (DILI) in relation to oral doses and blood concentrations has been established and published (Albrecht et al., 2019, Arch Toxicol).
NEURODERISK	Developed a prototype for the NeuroDeRisk toxicity profiling with 3D-pharmacophore models that will allow virtual screening of compounds against a set of predictive models. The software environment (KNIME- www.knime.org) used for deployment/development of the prototype tools is freely available to the public. Within this environment, several developers can make available dedicated nodes under the so-called KNIME Hub (https://hub.knime.com).
	The project developed 3D-pharmacophore models of γ-aminobutyric acid (GABA-A) receptor agonist and antagonist and picrotoxin channel blocker sites.
ITCC-P4	Two genetically engineered mouse models (GEMMs) models established; drug testing initiated on paediatric organoids generated from paediatric neuroblastoma patients (from primary and relapse) with matched PDX/organoid drug testing for comparison.
	3 paediatric PDX models were established in humanised mice and displayed fast tumour growth kinetics. This is important to explore the potential for the established PDX platform to be used as starting materials for 'humanised' xenografts, aiming for the reinstatement of the human immune counterpart that is typically missed within immune-deficient host mice and to allow for preclinical testing of cancer-immunity molecules.

More recent developments

- Digital pathology- how machine learning and artificial intelligence can enhance interpretation of pathology images
- Engineering of human tissue using CRISPR technology
- Organoids mimicking human organs and shifting from animal based models
- Advanced imaging for brain related research

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Relevance for COVID-19

- Need new screening technologies for innovative drug development
- Trend to speed up entry into clinical assessment of novel treatments and vaccines (human as test target)
- Care needs to be taken not to circumvent important safety testing
- Human cell lines needed to research
  - New viral receptor blocking agents
  - New agents that can block viral replication

IMI Call on COVID-19

- 8 projects have been provisionally selected for funding (from 144 submitted) for a total funding of €117 million
  - (€72m from EC+ €45m from Industry and other contributing partners)
- 5 focus on Diagnostics
- 3 on new therapeutics
- High degree of technology convergence and multidisciplinary teams
- Projects include some repurposing of molecules already used in the clinic
- Others are focused on more innovative longer term approaches specific for Coronaviruses

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Thank you

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