# Webinar | IMI2 - Call 12

# Discovery and characterization of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases

Elisabetta Vaudano, IMI

IMI webinar • 03.07.2017

# Today's webinar

**Will cover all aspects of the Call topic**

- Introduction to IMI programme
- Proposed project
  - Objectives, need for public-private collaborative research
  - Key deliverables
  - Structure of the project
  - Expected contribution of the applicants
  - Contribution of industry consortium

**Will not cover rules and procedures**

- A webinar on rules and procedures will take place on
  **Monday 17 July, 14:30-16:00**
- Register here

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# IMI – Europe's partnership for health

**IMI mission**

IMI facilitates open collaboration in research to advance the development of, and accelerate patient access to, personalised medicines for the health and wellbeing of all, especially in areas of unmet medical need.

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# IMI – Ecosystem for innovative collaborations

- Allow engagement in a cross-sector, multi-disciplinary consortium at the forefront of cutting-edge research
- Provide the necessary scale by combining funding, expertise, knowledge, skills and resources
- Build a collaboration based on trust, creativity and innovative and critical thinking
- Learn from each other - new knowledge, skills, ways of working
- Take part in transformative research that will make a difference in drug development and ultimately patients' lives

IMI is a **neutral platform** where **all involved** in drug development can engage in **open collaboration** on **shared challenges**.

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# IMI 2 budget (2014 – 2024)

**EU funding goes to:**

Universities

SMEs

Mid-sized companies

Patient groups

etc…

**€1.638 bn**

**€1.425 bn**

**Other €213 m**

**IMI 2 total budget €3.276 billion**

**EFPIA companies**

receive no funding

contribute to projects ‘in kind’

Associated Partners e.g. charities, non-EFPIA companies

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# How a topic is generated

Industrial partners align themselves around a real challenge for industry and agree to work together **and commit resources**

New ideas from public sector, universities, SMEs etc. are needed to address the challenge

Scale is a key to success and is provided through IMI funding

Outcomes should be transformative for the industry as well as having a clear “public” value

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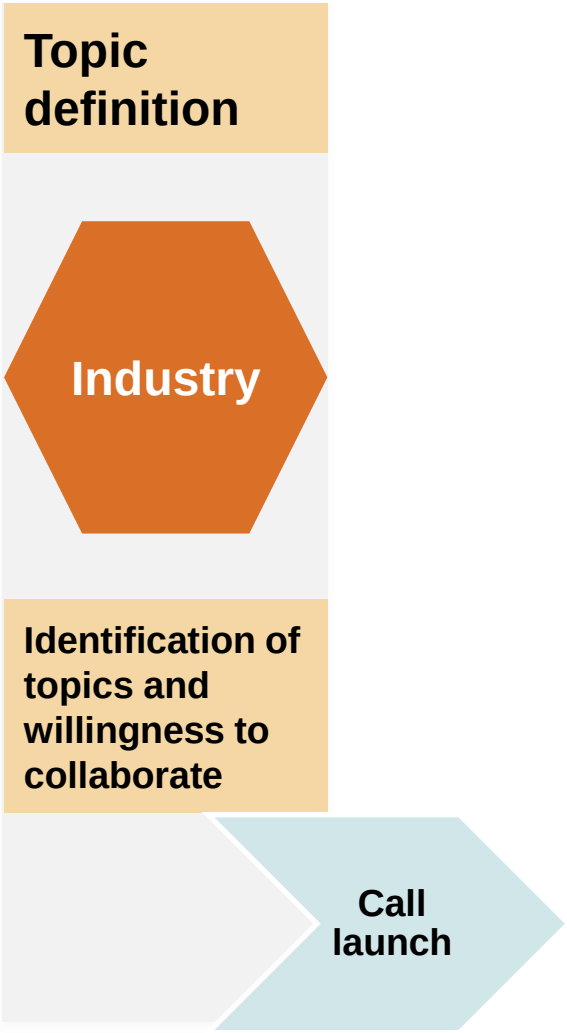
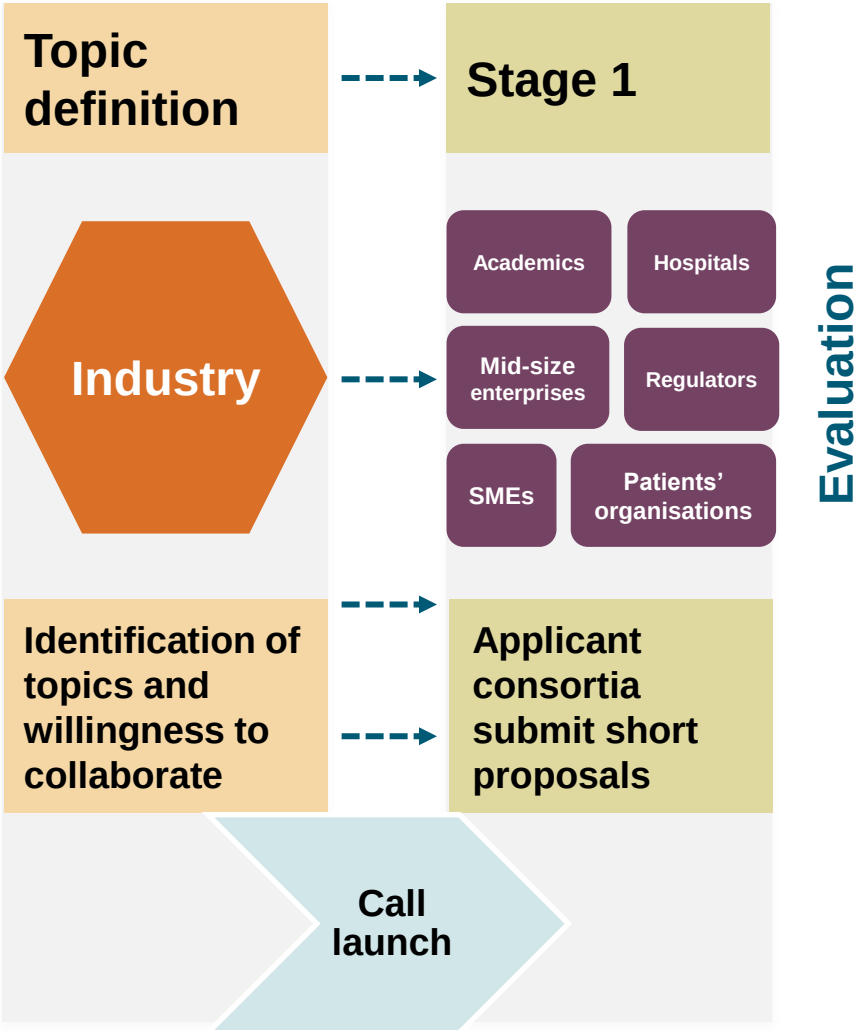
# Typical IMI project life cycle



# Typical IMI project life cycle

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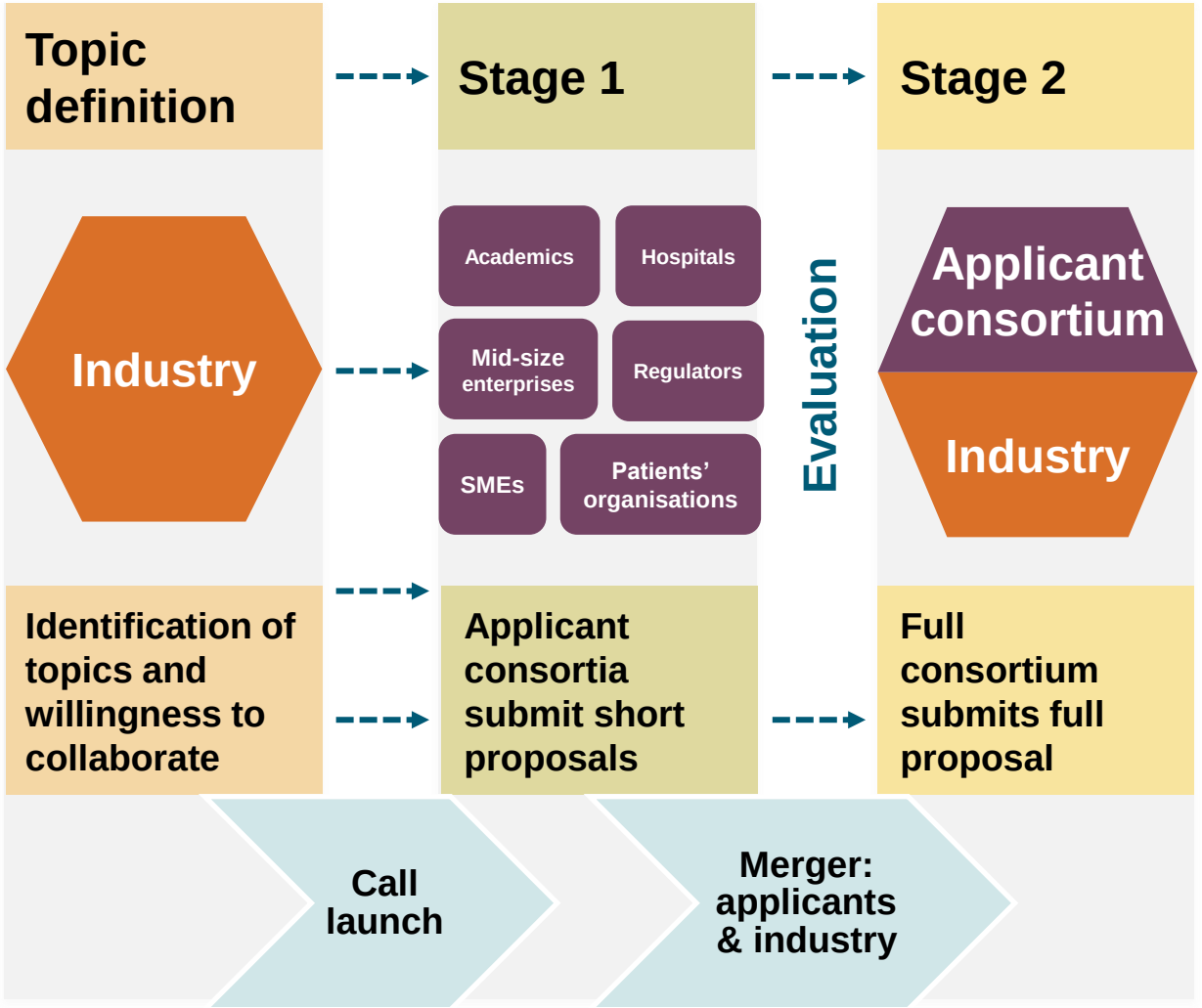
# Typical IMI project life cycle

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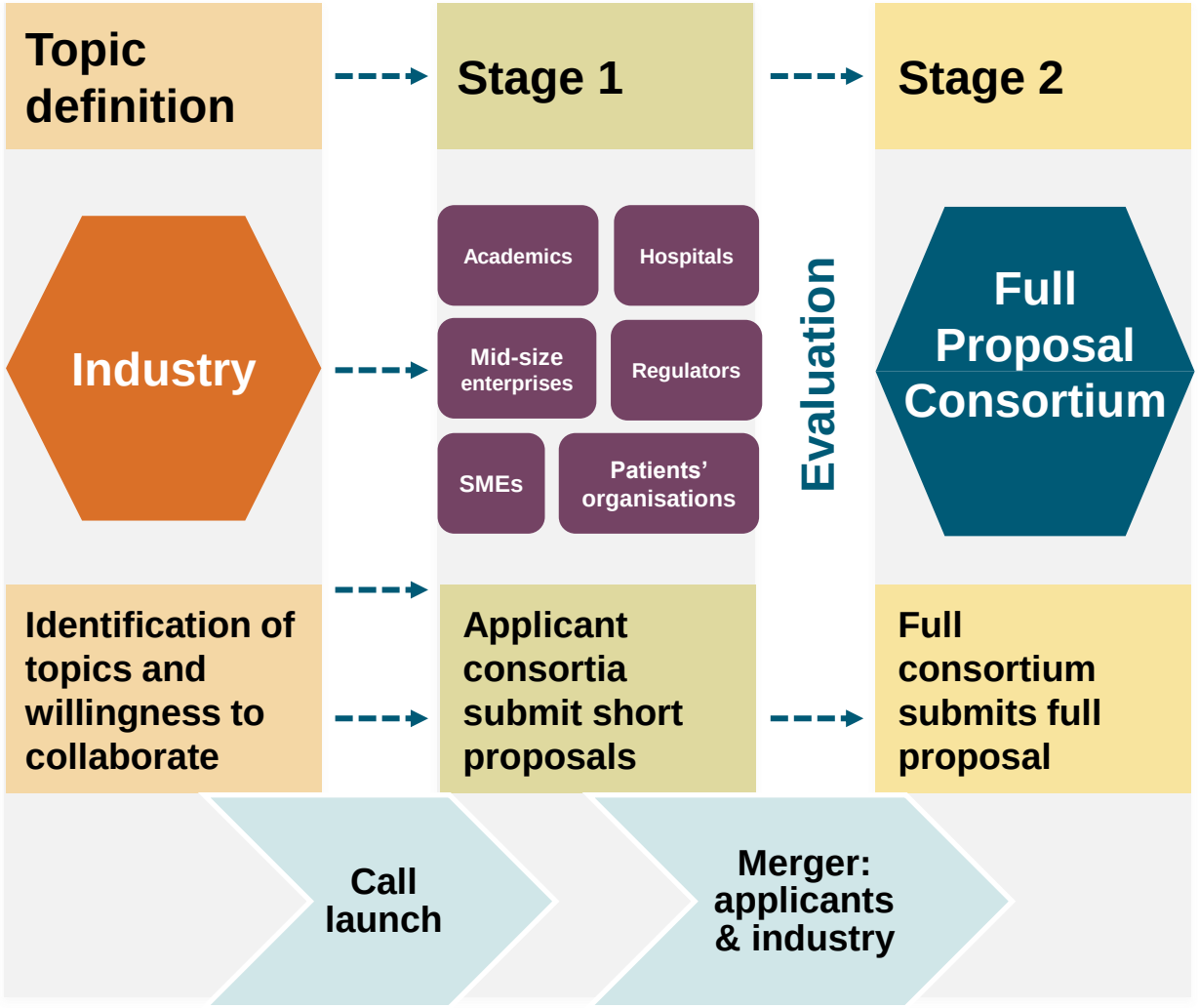


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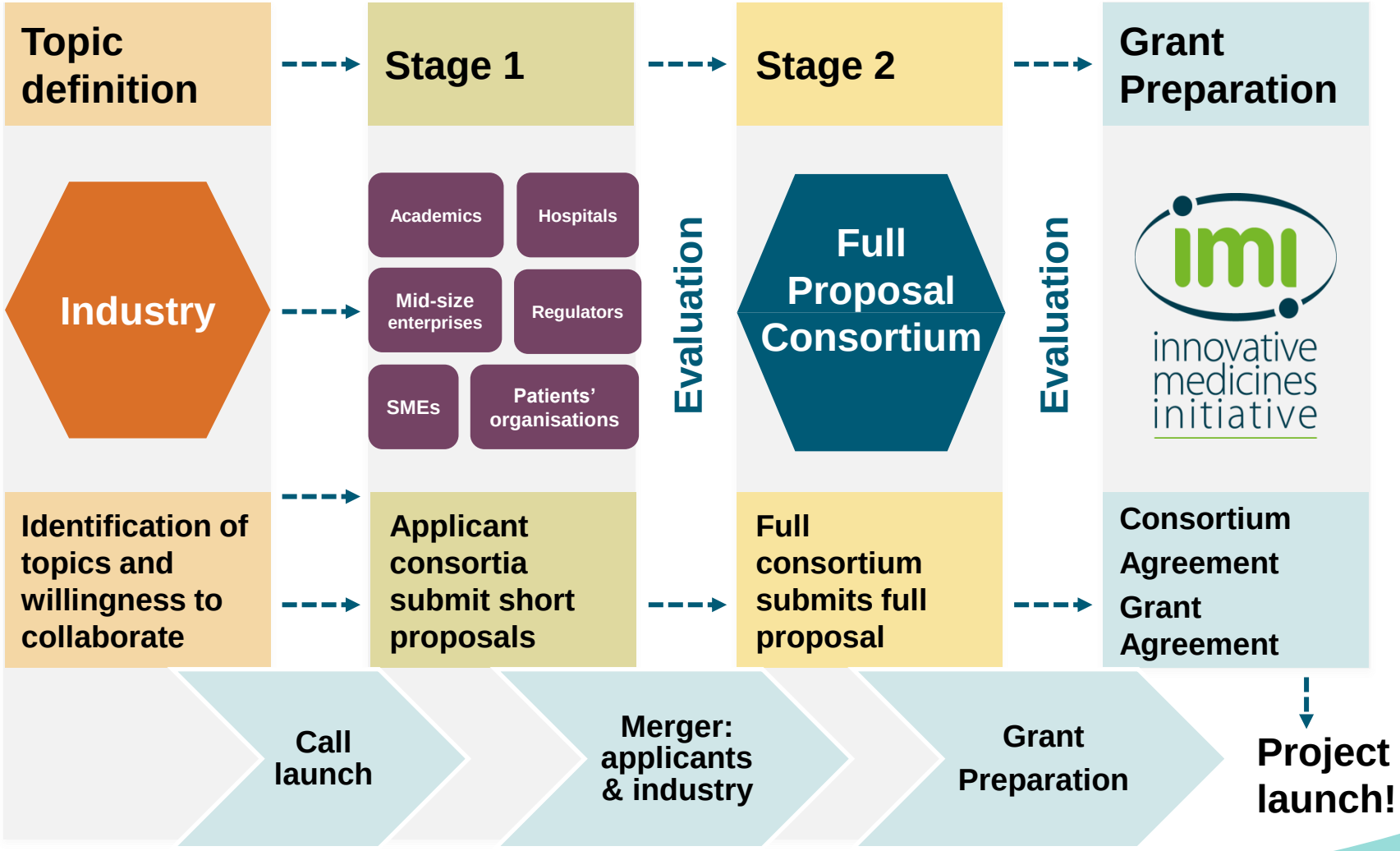


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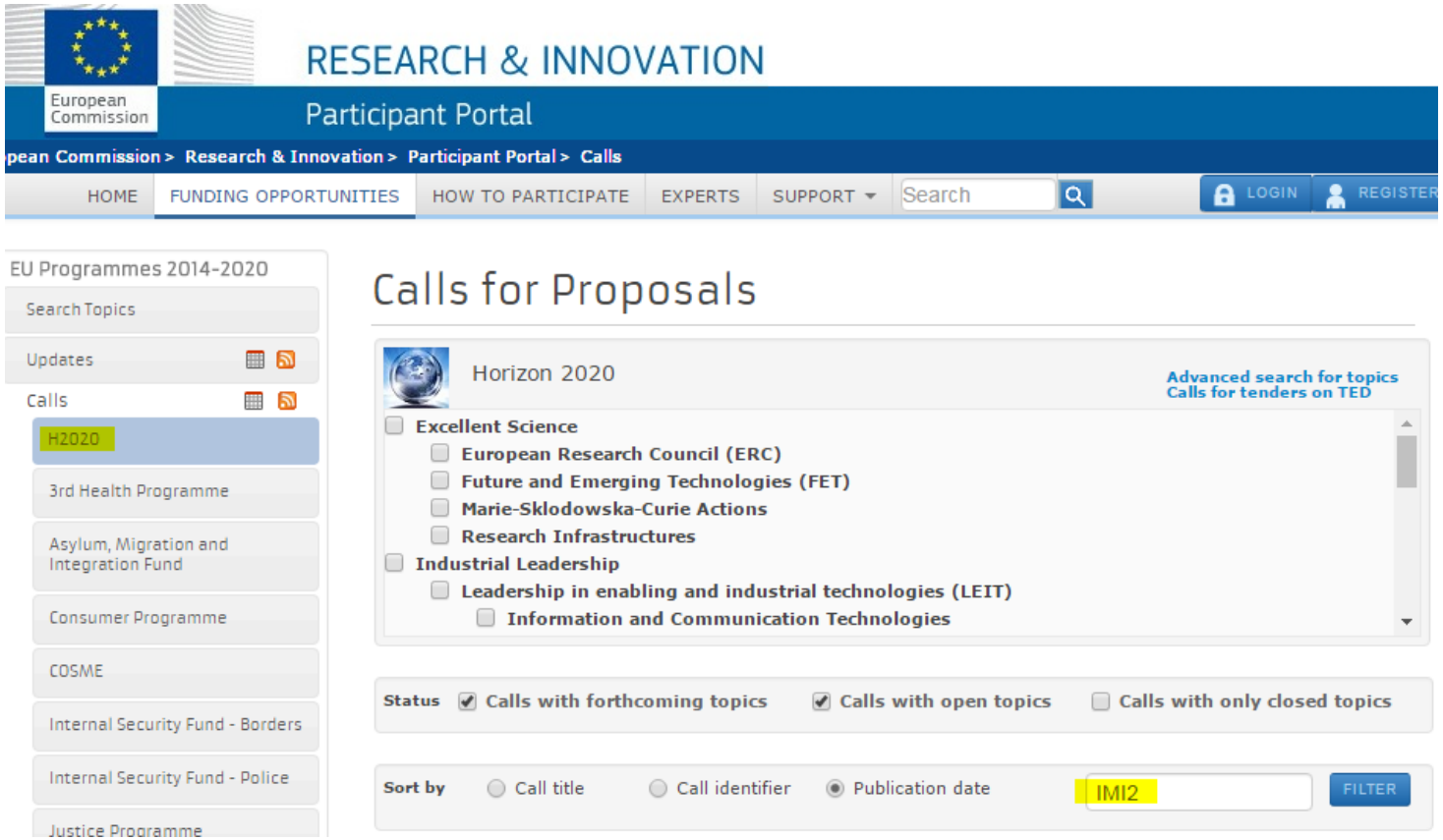
# Submitting a proposal

- https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/index.html

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# Proposal Template

- Available on IMI website & H2020 submission tool
- For first stage proposals, the page limit is **30 pages**.

**Title of Proposal**

**List of participants**

**Table of Contents**



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# Evaluation Criteria (1/2)

- **Excellence**
  - Clarity and pertinence of the proposal to meet all key objectives of the topic;
  - Credibility of the proposed approach;
  - Soundness of the concept, including trans-disciplinary considerations, where relevant;
  - Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;
  - Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.
- **Impact**
  - The expected impacts of the proposed approach as mentioned in the Call for proposals;
  - Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;
  - Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;
  - Improving European citizens' health and wellbeing and contribute to the IMI2 objectives.

# Evaluation Criteria (2/2)

- **Quality and efficiency of the implementation**
  - Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks,  resources, timelines and approximate budget;
  - Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal;
  - Appropriateness of the proposed management structures and procedures, including manageability of the consortium.

# Tips for writing a successful proposal

- Read **all the call-relevant material:**
  www.imi.europa.eu
- Begin forming your consortium **early**
  Partner search tools & networking events
- Provide **reviewers** with all the information requested to allow them to evaluate your proposal
- **Finalise and submit your proposal early**
- Contact the **IMI Office** (**NOT** industry topic writers):
  infodesk@imi.europa.eu

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# Common mistakes

- Admissibility/Eligibility criteria not met**:**
  - submission **deadline** missed
  - minimum of **3 legal entities** from **3 member states & H2020 associated countries** not met
- The proposal does **not address all the objectives** of the topic
- A proposal is **scientifically excellent** but will have **limited impact**
- **Complementarity** with Industry consortium not well described.

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# Find project partners

- Network with **your contacts**
- **Network** with fellow webinar participants
- Use **Partner Search Tools:**
  - IMI http://www.imi.europa.eu/content/partner-search
  - German NCP version: http://www.imi-partnering.eu
  - Fit for health: http://www.fitforhealth.eu/
- Get in touch with your **local IMI contact point**: www.imi.europa.eu/content/states-representatives-groups
- Talk to your **Health National Contact Point** (NCP)
- Network on **social media** (e.g. IMI LinkedIn group)

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# Understanding the blood-brain barrier in health and disease and identification of brain delivery systems

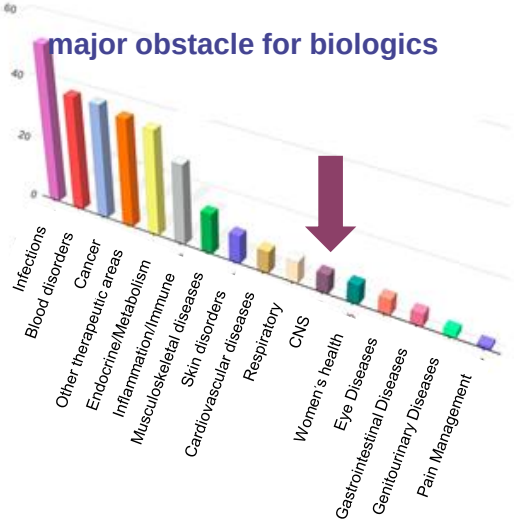
**Dominique Lesuisse**, Philippe Rocolle, Arjo de Boer, Peter Van Asten,Doug Burdette, Georg Terstappen, Wandong Zhang, Marc Mercken, Robert Joe Mather, Natasha Kablaoui, Robert Bell, Stephen Buckley

With the help of Elisabetta Vaudano, Salome Juliette Koussoroplis, Catherine Brett

03-07-2017 • IMI webinar

# Introduction

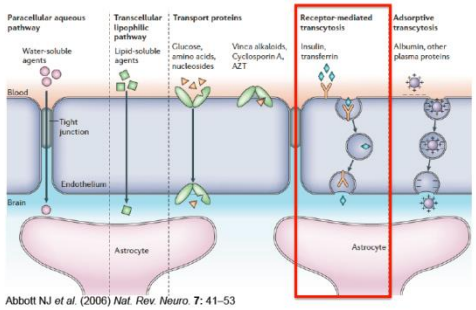
**The blood brain barrier (BBB) remains a major obstacle for biologics**




PhRMA, March 25, 2014

**Transport receptors have been exploited to ferry drugs across the BBB**

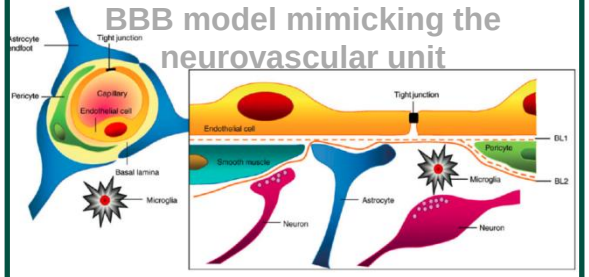
Mostly receptor-mediated transcytosis (Transferrin Receptor )




Abbott NJ *et al.* (2006) *Nat. Rev. Neuro.* **7**: 41–53

**BBB models predictive of in vivo exposure of biologics have yet to be identified**

No fully reconstituted hIPSC-derived BBB model mimicking the neurovascular unit




From Wolff et al., J.Pharm. Sci. 104:2727–2746, 2015.

**Compromised BBB has been reported for several neurological diseases but remains in many cases a matter of debate**

See for instance Neuwelt et all Nature Rev Neuroscience 2011

**The vascular hypotheses of some neurological diseases involve BBB dysfunction in their pathogenesis**

See for instance B.V.Zlokovic, BBA 1862, 887-900 (2016)

- **Build a precompetitive consortium to further the understanding of the BBB in health and disease and for identification of innovative brain delivery systems**
- **Synergize and capitalize on findings from other relevant IMI initiatives**

# Objectives*

- Discovery and development of innovative and efficacious brain delivery systems
- Establishment and characterisation of  BBB models with good predictability
- Identification of translational readouts closer to the pathogenesis of neurodegeneration and mimicking altered BBB under disease conditions
- In-depth understanding of the biology of the BBB and characterization of various transport mechanisms across the BBB

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*see full topic call for extensive details

# Need for public-private collaboration & expectations

*Bringing expertise together*

**Biotech & SMEs**

- Know-How in iPSC- or progenitor-derived cells and/or defined extracellular matrix hydrogels and/or human BBB models
- Innovative technologies
- New tools

**Academic Groups**

- Know how on BBB & disease models
- Characterization of mechanisms of brain transport or virus-mediated transport
- Expertise in establishing iPSC-based endothelial cultures/models
- Develop a full BBB neurovascular unit

**Leading Pharma**

- Understanding of pre-clinical and clinical consequences of disease-modified BBB
- Chemical/analytical resources with state-of-the-art equipment
- Powerful and connected bio-informatics
- Direct link into the clinic

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# Proposal (1)

**WP1 Identification of genes or pathways candidates associated with neurodegenerative diseases and expressed in brain endothelial cells**

- Genetic analyses of existing data (GWAS, others)
- Transcriptomic, proteomic on patient primary cells or tissues
- Transcriptomic, proteomic on preclinical disease models primary cells
- Glycomics of BBB cells and/or cerebral vasculature of diseased brains

**Deliverables**: Candidates disease-associated or differentially expressed genes or pathways in brain endothelial cells of potential importance for brain delivery.

**WP2 Phenotypic validation of these genes or pathways in endothelial cells**

- Generation of endothelial cells from iPSC or Progenitors
- Generation of iPSC cells from primary cells from patients
- Induce mutations of genes/pathways involving BBB permeability and transport by genome editing (such as CRISPR cas9 technology)
- Produce evidence for phenotypic or transport differences in monocultures or 3D/co-cultures

**Deliverables**: Validated disease-specific or differentially expressed genes or pathways of potential relevance to brain transport

# Proposal (2)

**WP3 Develop best state-of-the-art (e.g. hiPSC- or progenitor-derived) BBB models**

- Differentiation into brain endothelial cells and barrier formation characterization
- Mono- or co-cultures, 3D-settings, microfluidics or other settings
- Mathematical/in silico modelling of receptor-/carrier-mediated transcytosis across the BBB and PK of biopharmaceutics in the brain

**Deliverables**: At least one in vitro BBB-model and an in silico model reproducing/predicting disease features and BBB permeability in vivo in healthy and disease state. Characterize apical/basolateral receptor activity, validate model by comparing to in vivo BBB properties, validate candidates in vitro

**WP4 Characterisation of neurotropic virus-based BBB and brain penetration mechanisms**

- Genetic and proteomics analyses of the viral genes, proteins and protein fragments for their interactions with human cells and proteins
- Cellular, molecular and biochemical characterization of viral interactions with cellular proteins and/or receptors and virus-mediated penetration of BBB or peripheral nerve/neuronal cells;
- Preparation and testing of viral particles (empty viral vesicles) for interactions and penetration across the BBB in vitro or in vivo animal models;

**Deliverables**: new targets/mechanisms and/or delivery systems for selective BBB delivery

# Proposal (3)

**WP5 Follow-up on identification and characterisation of new potential targets from WP2**

- new mechanisms of brain delivery; including synergy with potential new mechanisms identified in COMPACT.
- new potential targets involved in the vascular hypotheses of neurodegeneration.

**Deliverables**: Tools for validation of the new mechanisms (Ab's, ligands, cell lines). Validated new brain-delivery targets (by demonstration of increased in vivo brain exposure of Ab or ligand of the target). Validated new neurovascular target with potential in a neurodegenerative disease in disease model.

**WP6 Management, communication, dissemination**

- Overall coordination of the scientific work packages, budgets, delivery and dissemination of findings and sustainability planning.

**Deliverables**: Tools for data exchange, reports, publications

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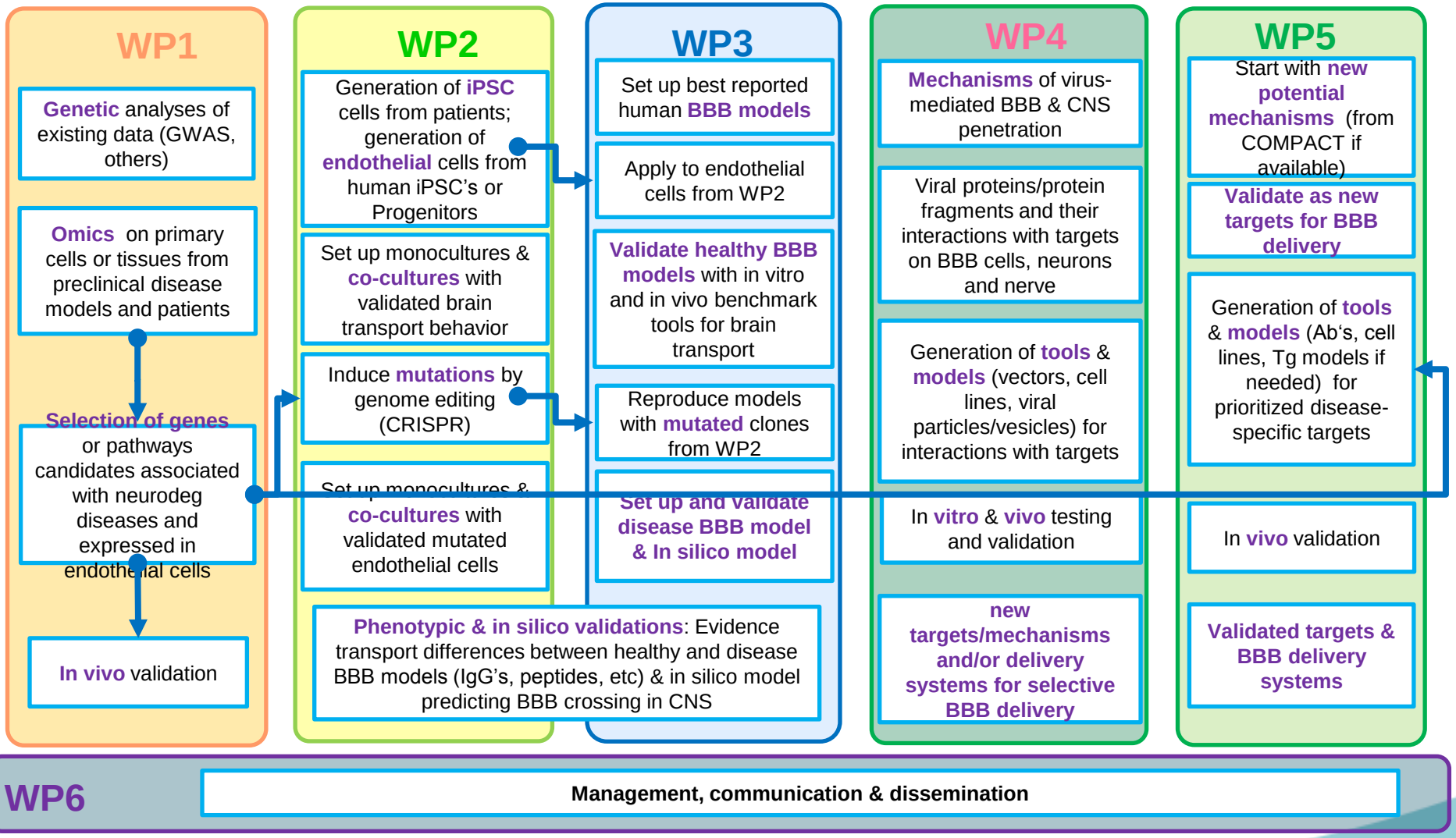
# Proposed architecture

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# Definitions of Diseases

- Disease/pathology considered in the Call:
  - Neurodegenerative diseases :
    - Alzheimer Disease (AD)
    - Parkinson Disease (PD)
    - Amyotrophic Lateral Sclerosis (ALS)
    - Multiple Sclerosis (MS)
  - Metabolic diseases with CNS impact :
    - Diabetes
    - Obesity

# Potential synergies with other consortia

COMPACT
COLLABORATION ON THE OPTIMISATION OF MACROMOLECULAR PHARMACEUTICAL ACCESS TO CELLULAR TARGETS

Brain targets

neurobid

New drug delivery strategies for large molecules

stem BANCC
Stem Cells for Drug Discovery

iPSC

EBiSC
European Bank for induced pluripotent Stem Cells

euripides

Molecular imaging tool

FP7 Projects on BBB

JUST BRAIN

Structure and function of the BBB

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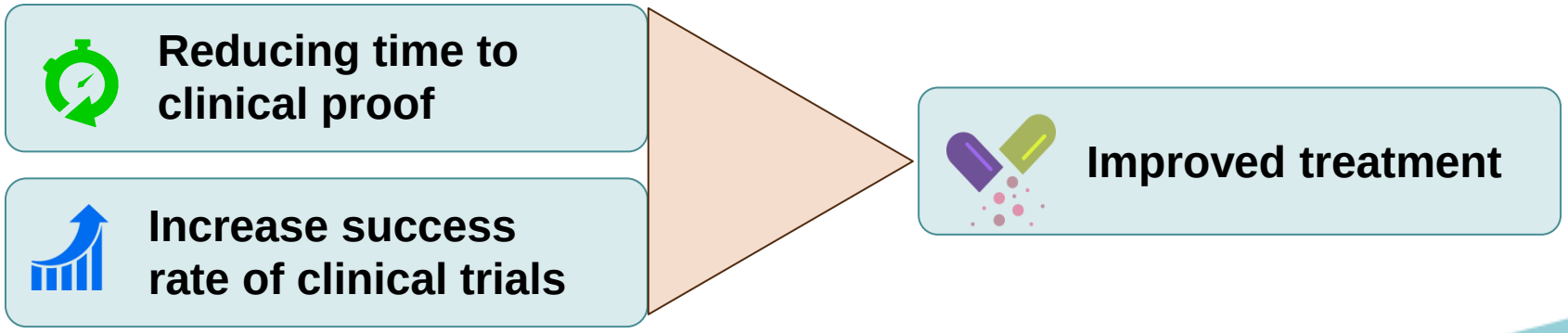
# Expected impact

- On R&D
  - Better translational tools and models to assess efficacy
  - Biomarkers for diseases clearly linked to clinical relevance
  - Better models (including in silico models) for predicting BBB permeability and PK
- On diseases :
  - Development of new delivery systems and/or therapies for diseases of this topic text



# Thank you

Contact the IMI Programme Office
infodesk@imi.europa.eu • www.imi.europa.eu

**All questions** should go through the **IMI Executive Office**

www.imi.europa.eu
@IMI_JU

# SME participation

Elisabetta Vaudano, IMI
IMI webinar • 03.07.2017

# SME Participation

IMI encourages the participation of SMEs in applicant consortia as they can offer a complementary perspective to other organisations.

For example, being closer to the market, SMEs can drive the tangible outputs of the project, and help ensure these outputs are sustained beyond the project lifetime and therefore help lead to faster impact on healthcare.

Therefore, where possible, include SMEs in your Short Proposal

# SME Participation

In particular, in this topic, SMEs can participate in:

- contributing with innovative technologies and tools and know-how in iPSC- or progenitor-derived cells and/or defined extracellular matrix hydrogels and/or human BBB models.
- Biotech/SME companies will be able to stress-test their technologies in a non-competitive open innovation environment which will help them to bridge the “valley of death” for turning these into products ready for market.