Webinar | IMI2 – Call 13
Mitochondrial dysfunction in neurodegeneration

4 December 2017 • 10:30 CET
Agenda

- How to use GoToWebinar – Catherine Brett, IMI
- Introduction – Elisabetta Vaudano, IMI
- The Call topic – Ian Reynolds & Neta Zach, Teva
- Involvement of SMEs & regulators – Elisabetta Vaudano, IMI
- Questions & answers
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Before we start…

- This webinar is being recorded and will be published on the IMI website and/or IMI YouTube channel
- Presentation slides will be published on the webinar web page
- A participant list will be circulated
- IMI2 – Call 13 has been launched and all Call documents & details of how to apply can be found on the IMI website
Webinar | IMI2 - Call 13
Mitochondrial Dysfunction in Neurodegeneration

Elisabetta Vaudano
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 Thursday 7 December, 15:00-16:30
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.
**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**.
EU funding goes to: Universities, SMEs, Mid-sized companies, Patient groups etc…

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
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.
Typical IMI project life cycle

- **Topic definition**
- **Identification of topics and willingness to collaborate**
- **Industry**
- **Call launch**
Typical IMI project life cycle

**Stage 1**
- Identification of topics and willingness to collaborate
- Applicant consortia submit short proposals
- Evaluation

- Academics
- Hospitals
- Mid-size enterprises
- Regulators
- SMEs
- Patients’ organisations

**Call launch**

**Industry**

**Topic definition**
Typical IMI project life cycle

**Stage 1**
- **Identification of topics and willingness to collaborate**
  - Applicants (consortia)
  - Call launch

**Stage 2**
- **Full consortium submits full proposal**
  - Applicant consortium
  - Merger: applicants & industry

**Evaluation**
- Academics
- Hospitals
- Mid-size enterprises
- Regulators
- SMEs
- Patients’ organisations

**Topic definition**
- Industry

**Identification of topics and willingness to collaborate**
- Industry

**Applicant consortia submit short proposals**
- Applicant consortium

**Full consortium submits full proposal**
- Industry
Typical IMI project life cycle

**Stage 1**
- Identification of topics and willingness to collaborate
- Applicant consortia submit short proposals

**Stage 2**
- Full consortium submits full proposal

**Evaluation**
- Full Proposal Consortium

**Call launch**
- Merger: applicants & industry

**Groups involved:**
- Academics
- Hospitals
- Mid-size enterprises
- Regulators
- SMEs
- Patients’ organisations
- Industry
- Mid-size enterprises
- SMEs
- Patients’ organisations
- Industry

**Typical IMI project life cycle**

**Topic definition**

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**Industry**

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**Identification of topics and willingness to collaborate**

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** Applicant consortia submit short proposals**

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**Full consortium submits full proposal**

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**Evaluation**

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**Merger: applicants & industry**

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**Call launch**

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Typical IMI project life cycle

**Topic definition**

- **Industry**
- **Identification of topics and willingness to collaborate**

**Stage 1**

- **Applicant consortia submit short proposals**
- **Academics**
- **Hospitals**
- **Mid-size enterprises**
- **Regulators**
- **SMEs**
- **Patients’ organisations**

**Stage 2**

- **Full consortium submits full proposal**
- **Full Proposal Consortium**

**Grant Preparation**

- **Consortium Agreement**
- **Grant Agreement**

**Evaluation**

**Call launch**

**Merger: applicants & industry**

**Grant Preparation**

**Project launch!**
Submitting a proposal

# 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**

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<td>Expected impacts</td>
<td>4.1</td>
<td>Participants (applicants)</td>
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</table>
Evaluation Criteria (1/2)

- **Excellence (threshold 3.0)**
  - 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 (threshold 3.0)**
  - 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](http://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](mailto:infodesk@imi.europa.eu)
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.
Find project partners

- Network with **your contacts**
- **Network** with fellow webinar participants
- Use **Partner Search Tools:**
  - German NCP partner search tool: [www.imi-partnering.eu](http://www.imi-partnering.eu)
- Get in touch with your **local IMI contact point:** [www.imi.europa.eu/about-imi/governance/states-representatives-group](http://www.imi.europa.eu/about-imi/governance/states-representatives-group)
- Talk to your **Health National Contact Point** (NCP)
- Network on **social media** (e.g. IMI LinkedIn group)
Participation of SMEs, patient groups, regulators

We encourage the participation of a wide range of health research and drug development stakeholders in our projects

- SMEs and mid-sized companies
  – check the list of interested SMEs on the Call 13 web page
- Companies / organisations from related fields (e.g. diagnostics, animal health, IT, imaging etc…)
Mitochondrial Dysfunction in Neurodegeneration

Ian Reynolds, Neta Zach
Teva Pharmaceuticals

04.12.2017 • IMI webinar
Introduction

Mitochondrial dysfunction (such as respiratory function, biogenesis, trafficking, fission, fusion and mitophagy) is a common mechanism implicated in all neurodegenerative diseases. Yet, little is known about the precise role of mitochondrial dysfunction in disease etiology and severity. We are still lacking the tools and models to elucidate this question.

→ Our Goal: To develop the understanding and tools to assess the evolution of mitochondrial dysfunction, preferably in human-derived cellular models and animal models of neurodegeneration, and to identify key molecular drivers of such processes.
Objectives of the full project

- Exploring mitochondrial dynamics and dysfunction in models of neurodegenerative disease
- Connection between mitochondrial morphology and function
- Connection to protein misfolding
- Incorporating elements of mitochondrial ageing

Exemplary Indications: Parkinson’s disease
Need for public-private collaboration

**Pharmaceuticals companies**
- Established models
- Access to human tissue for validation
- Drug discovery expertise

**SMEs**
- Novel research tools
- Drug discovery

**Academic partners**
- Established PD models,
- Novel tools and assays
- Innovation

**Charity**
- Research tools and technologies
- Communication
- Project management
Expected impact

**Better tools** to understand mitochondrial dysfunction and its impact on neurodegenerative diseases

**Identification of key molecular drivers and potential targets** for treatments for PD, expandable to other neurodegenerative diseases

Biotech **SMEs** will be able to ‘stress-test’ their technologies in a non-competitive open innovation environment
**Scope of the project**

**In vitro**
- Understand the impact of mitochondrial dysfunction on disease severity in established *in vitro* models of PD
- Demonstration of mitochondrial dysfunction induced by α-synuclein in a humanised model system such as inducible Pluripotent Stem cell (iPSC)-derived neurons
- Evaluate the impact of ageing on mitochondrial dysfunction using *in vitro* models

**In vivo**
- Assess the contribution of mitochondrial dysfunction on disease severity, in a well characterised *in vivo* models of PD
- Focus on aged animals – transgenic or injected with fibrillary forms of disease associated proteins to trigger neurodegeneration
- Quantify the relative contribution of abnormal respiratory function, biogenesis, dynamics and mitophagy to mitochondrial dysfunction.
We would like to highlight that there are topics in the proposal that are of lower priorities and are not mandated part of the submission. These include:

- *In vitro* trauma and brain injury

- *In silico*: Reconstruct a mechanistic computational model of mitochondrial function to account for the gene products of each gene associated with mitochondria and closely associated organelles.
## Suggested architecture of the project

### WP1: Cellular models of AD and PD preferably based on human cells

- Establish impact of mitochondrial dysfunction (respiratory function, biogenesis, trafficking, mitophagy) on the development/severity of disease phenotype
- Identify points of invention
- Correlate function to morphology
- Develop markers for mitochondrial dynamics
- Include tools to modify mitochondrial function
- Develop cellular model into a robust model for target finding and validation of therapeutics targeting mitochondrial function.

### WP2: In vivo models of PD - Integrate ageing as a factor

- Validation of in vitro results - understand changed mitochondrial dynamics on neuronal and synaptic health
- Substantiate evidence for point of invention
- Include state of the art or new technological methods e.g. super-resolution microscopy
- Complementary animal model to support validation of therapeutics targeting mitochondrial function.

### WP3: Management and communication

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**Project duration: 36 months**
Suggested architecture of the project

<table>
<thead>
<tr>
<th>Work package 1- <em>In vitro</em></th>
<th>Work package 2- <em>In vivo</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of specific mitochondrial dysfunctions in established PD models (<em>implementation of tools modulating mitochondrial functions</em>)</td>
<td>Identification of specific mitochondria dysfunctions in established PD models (<em>longitudinal assessment</em>)</td>
</tr>
<tr>
<td>Establishment of quantitative detection of mitochondrial dysfunction</td>
<td>Establishment of quantitative detection of mitochondrial dysfunction (<em>and genetic or pharmacological modification</em>)</td>
</tr>
<tr>
<td>Understanding the role of identified mitochondrial dysfunction on disease phenotype (<em>adding ageing model</em>)</td>
<td>Understanding the role of identified mitochondrial dysfunction on disease phenotype.</td>
</tr>
<tr>
<td>Identification and quantification of the relative contribution of key molecular drivers</td>
<td>Identification and quantification of the relative contribution of key molecular drivers</td>
</tr>
<tr>
<td>As necessary, development of new robust tools and assays</td>
<td>As necessary, development of new robust tools and assays. (<em>for example imaging</em>)</td>
</tr>
</tbody>
</table>

Work package 3- Project management and communication
Expected contributions of the applicants

**Models**

- Expertise in using *in vivo* and *in vitro* models of PD, experience with seeding models an advantage
- **Access to in vitro models** which exhibit a robust and well characterised disease phenotype, i.e. protein aggregation in models such as primary cultures or iPSCs.

**Tools**

- Expertise in **evaluation of key elements of mitochondrial function in vitro**, including bioenergetics, ROS production, biogenesis, fission, fusion and mitophagy;
- Tool for **in vitro/in vivo imaging of mitochondrial morphology and trafficking**. For example, expression of mitochondrial-targeted fluorescent proteins in relevant cell populations;
- Knowhow and tools for **manipulation of mitochondrial function**. For example morphology changes through expression of DRP1, mitofusin 2, OPA1 or Miro.
- Development of **novel tools and assays to quantitatively assess mitochondrial dysfunction** in models of PD;
- Expertise in **approaches to model mitochondrial ageing in in vitro models**

The budget is 4.5Mil
Expected (in kind) contributions of industry consortium

- Well established in vivo transgenic and seeding models in rodents (SNCA-OVX Tg mice, F28 mice. Pre formed fibrils (PFF) mouse and rat model, α-synuclein rat model as well as assay protocols, seed material, and α-synuclein pathology endpoint analysis.
- Access to iPSC lines, iPSC neuronal progenitors and protocols for differentiation into neurons and glia. Protocols and tools for viral transduction and siRNA knockdown of proteins in iPSC neurons.
- Access to human tissue samples for validation studies (~1000 PD cases and 200 controls)
- Evaluation of consistency and robustness of mitochondrial dysfunction key molecular endpoints to ensure future application for target identification/validation.
- Support communication and project management.

The indicative in-kind contribution is 3.27Mil Euro
Key deliverables of the full project

- Development, validation and application of robust tools and assays to study and quantitatively address mitochondrial dysfunction in well characterised *in vitro* and *in vivo* models of neurodegenerative diseases with emphasis on PD;
- Understanding the impact mitochondrial dysfunction on disease progression/severity;
- Introduce *ageing* component to *in vitro* models;
- Understanding of the role of *misfolded proteins*;
- Identification of *key molecular drivers* of mitochondrial dysfunction promoting neurodegenerative diseases.
What’s in it for you?

New insights and novel drug targets are our best way to

- Develop drugs
- Innovative tools
- Cutting edge research

Bring hope to patients with Parkinson’s disease and many more of the most disabling diseases of our times!
Thank you
Involvement of SMEs & regulators

Elisabetta Vaudano
SME participation

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

- SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

- For these reasons, applicants should consider engaging SMEs throughout the proposal. Thus participation of SMEs with relevant knowhow and standardised technologies and assays is strongly supported.
Interactions with regulators

- Consider having a **plan for interaction with relevant milestones, resources allocated**
- You may need to go through a **formal regulatory process** to ensure regulatory acceptance of project results (e.g. qualification procedure for biomarkers)
- Get familiar with **services offered for dialogue** (e.g. at EMA through qualification advice, Innovation Task Force, briefing meetings)
- If regulators are not project participants, consider including them in an **advisory board**
- Consider also a plan for dialogue with **HTA bodies / payers** if relevant

To maximise impact of science generated by projects

Engage in dialogue with regulatory authorities

More info: ‘Raising awareness of regulatory requirements: A guidance tool for researchers’

Questions
Questions?

Raise your hand if you want to ask a question orally

Send a question in writing

After the webinar, send any questions to the IMI Programme Office
infodesk@imi.europa.eu