IMBI:

FRAMEWORK FOR INNOVATIVE MULTI-TRACER MOLECULAR BRAIN IMAGING

Report of a JPND Working Group on Harmonisation and Alignment in Brain Imaging Methods

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Framework for Innovative Multi-tracer molecular Brain Imaging (IMBI) - final report -

Brief summary of proposed work

Positron emission tomography (PET) is a highly sensitive method to detect disease specific molecular alterations *in vivo*. In neurodegenerative diseases (ND) PET may detect (i) protein deposition (amyloid, tau), (ii) chronic neuroinflammation (NI), and (iii) changes of neurotransmission and -metabolism. The working hypothesis of the Framework of Innovative Multi-tracer molecular Brain Imaging (IMBI) working group (WG) around key experts from the field of PET imaging in ND is that by employing innovative PET molecular markers and improving the use of established PET ligands, it will be possible to image the hallmarks of ND at various disease stages, which will provide novel information on the ND course. This will enable both early disease detection and personalised implementation of ND modifying therapies.

The **objective** of the IMBI WG is to address

(i) how PET imaging can help to discriminate different types of ND;
(ii) which innovative molecular targets should be placed in focus for the development of new PET radiopharmaceuticals (e.g. alpha-synuclein tracers, purinergic receptors to differentiate microglia phenotype);
(iii) in what way PET data acquisition and quantification protocols have to be harmonised to allow pooled data analysis from various centres;
(iv) harmonisation of PET acquisition protocols and PET(/CT/MRI) system performance, especially for the following radiotracers/applications:
- **AV1451**, **THK-5317**, **THK-5351**, and **PBB3** to detect paired helical tau (AD, other tauopathies)
- **PIB**, **florbetapir**, **florbetaben** and **flutametamol** for amyloid-ß (AD) and other amyloidopathies
- **new radiotracers** to detect alpha-synuclein (PD, DLB, MSA)
- **DPA-714**, **PBR28**, **GE180** and **VC701** to detect microglial TSPO (various ND)
- **SMW139** and **JNJ54173717** to detect microglial $P2X_7R$ (various ND)
- **ABP688** and **FPEB** for mGluR5; **GE179** for NMDA (various ND)

(v) how to standardize quantification methods for amyloid, tau, micro- and astroglia PET imaging tracers, and recommending appropriate simple methods for clinical use;
(vi) how to further establish multi-centre databases (e.g. for PK11195; DPA-714);
(vii) possible trial design for ND stage- and treatment-specific multi-tracer PET studies including neurotransmitter PET with harmonised PET data acquisition and quantification protocols (timing and spatial relationship of the different molecular measures in subpopulations of ND); the various disease stages to be discussed include: presymptomatic, early clinical phase, during disease progression, and under disease-modifying intervention.

The **goal** is to give a repository and consensus framework of innovative PET methods and radiotracers together with harmonised, validated and simplified data analysis procedures, which shall be used in

(i) research on the *in vivo* pathophysiology of ND
(ii) design of multi-centre ND trials at a European and even international level (e.g. patient selection, monitoring disease progression and effects of intervention)
(iii) clinical settings (diagnostic flow-charts)
(iv) cohort studies of natural history of disease

The **work plan** consists of face-to-face (F2F) meetings and WebEx conferences to allow sufficient discussion to provide a structured framework for innovative multi-tracer molecular PET-based brain imaging in ND.

For **exploitation,** a consensus report will be delivered to the EC and the scientific community on a methodological framework on which established and innovative PET radiotracers should be used in what way and in which context of ND.

Work performed

Although a first notice that the IMBI project had been selected for funding arrived the project coordinator, Prof. A.H. Jacobs, already in June 2016, the IMBI project officially started only on February 1st 2017. This was due to a delayed communication of the final grant approval and funding procedure between the actual project sponsor, the Italian Ministry of Health (IT-MOH), and the project coordinator and co-coordinator, Prof. D. Perani.

In order to get started with the project and prepare for the first WG F2F meeting, a first preparative conference call (CC) for all project partners was organised already on November 4th 2016, thus before the official start of the project. Following this CC, dedicated working subgroups for (i) radiopharmaceuticals, (ii) methodology, (iii) standardisation and (iv) clinical trials each with an own working subgroup chair were established. Furthermore the project coordinators got in contact with the coordinators of the other funded JPND initiatives involving PET imaging (PET-METPAT, ASAP-SynTau, SRA-NED and ND-PETMRI) and suggested to start collaboration and information exchange between the different projects to avoid work overlap. The coordinators of the former three projects agreed on exchange of knowledge and expertise.

On February 3rd 2017 each working group had a dedicated CC session to discuss in more detail their working plan and the steps required to get prepared for the first IMBI F2F meeting. This F2F meeting took place on March 24th 2017 at the San Raffaele Congress Centre in Milan, Italy. Upfront of the meeting an inventory was compiled with all ND animal models and tracers (including details on radiochemistry and preclinical/clinical application) available in the IMBI consortium. During the F2F meeting each tracer category was discussed in detail with respect to current knowledge on their validity in clinical trials and action points still needed from a radiopharmaceutical point of view. The tracer categories discussed included: (i) amyloid tracers; (ii) TSPO and other microglia tracers; (iii) MAO-B; (iv) Tau and Alpha-synuclein tracers; as well as (v) tracers for the dopaminergic, serotonergic and cholinergic systems. From a clinical perspective IMBI planned to specify for these tracers definitions for the best tracer for a specific ND disease entity, their potentials and limitations and how these tracers should be applied in clinical studies. FDG was considered as a well-established tracer that is also being analysed within the JPND PET-METPAT WG and, therefore, the IMBI consortium decided not to include this tracer in their recommendations. For these tracer categories action points from the radiochemical and –pharmaceutical point of view should focus on recommendations for proper target identification and characterisation, tracer binding and specificity, tracer validation as well as efficient and broad scaled tracer production. From the methodological perspective the importance of kinetic modelling for clinical studies was stressed and it was decided to define in the following months guidelines for minimal requirements for tracer kinetic models/input functions to reach reliable quantitative outcome measures. In line, the standardisation group pointed to the importance of standardised instrumentation and instrumentation performances, harmonisation of imaging procedures, acquisitions and analysis methods and intended to work out guidelines for these themes.

During the second F2F meeting (July 9th 2017, Stresa, Italy) the discussion primarily focused on neurodegenerative disease spectrums (instead of tracer categories). This fits well with increasing evidence on how the same neuropathology can trigger very diverse clinical phenotypes or, from another angle, how similar phenotypes can be associated with different underlying neuropathology, prompting the consideration of a pathology-based spectrum of diseases, rather than on a single nosographic disease distinction, as of the most appropriate approach to study neurodegenerative conditions using molecular neuroimaging. From all the above stems how advanced multi-tracer PET molecular imaging with existing or novel PET tracers should be used in the future (next 5 to 10 years) to evaluate the neuropathological substrates and receptor/transport systems involved with special respect to their

evidence-based clinical utility, their strengths, limitations and perspectives in research and clinical applications. It was felt that these issues (current status, unmet needs, recommendations) together with their radiopharmaceutical, methodological and standardisation implications should be compiled into an IMBI consensus paper also taking into account the outcome of the discussions of the first meeting. The neurodegenerative disease spectrums included: amyloidopathies, tauopathies, alpha-synucleinopathies, TDP-43 pathology, prion protein pathology and neuroinflammation. The coordinators of the JPND projects PET-METPAT, ASAP-SynTau and SRA-NED also attended the second F2F meeting and presented the work and results achieved within their projects.

Currently the guidelines for the research topics and questions that need to be tackled within the next 5-10 years are still being worked out. A first draft of the IMBI position paper containing this framework has been written but needs further shaping before a clear statement can be given and submission to a peer-reviewed journal will be possible.

Outcome / Deliverable

Report on methodological framework for PET in ND employing innovative radiotracers and established PET ligands: Consensus paper with working title 'A new perspective for advanced PET molecular imaging in neurodegenerative diseases' still in preparation.

This paper will be published in a peer-reviewed scientific journal and posted on the JPND website. The WG members will also present the framework to the scientific community at upcoming national and international meetings. For all kinds of dissemination activities project partners will make sure that JPND funding will be acknowledged.

Furthermore, the IMBI consortium expects that the results can set the basis for funding agencies (at national and European levels) and also for industry to design future multi-centre clinical trials for the assessment of ND at early diagnosis, during disease progression and under novel disease-modifying agents by innovative and multi-tracer PET imaging.