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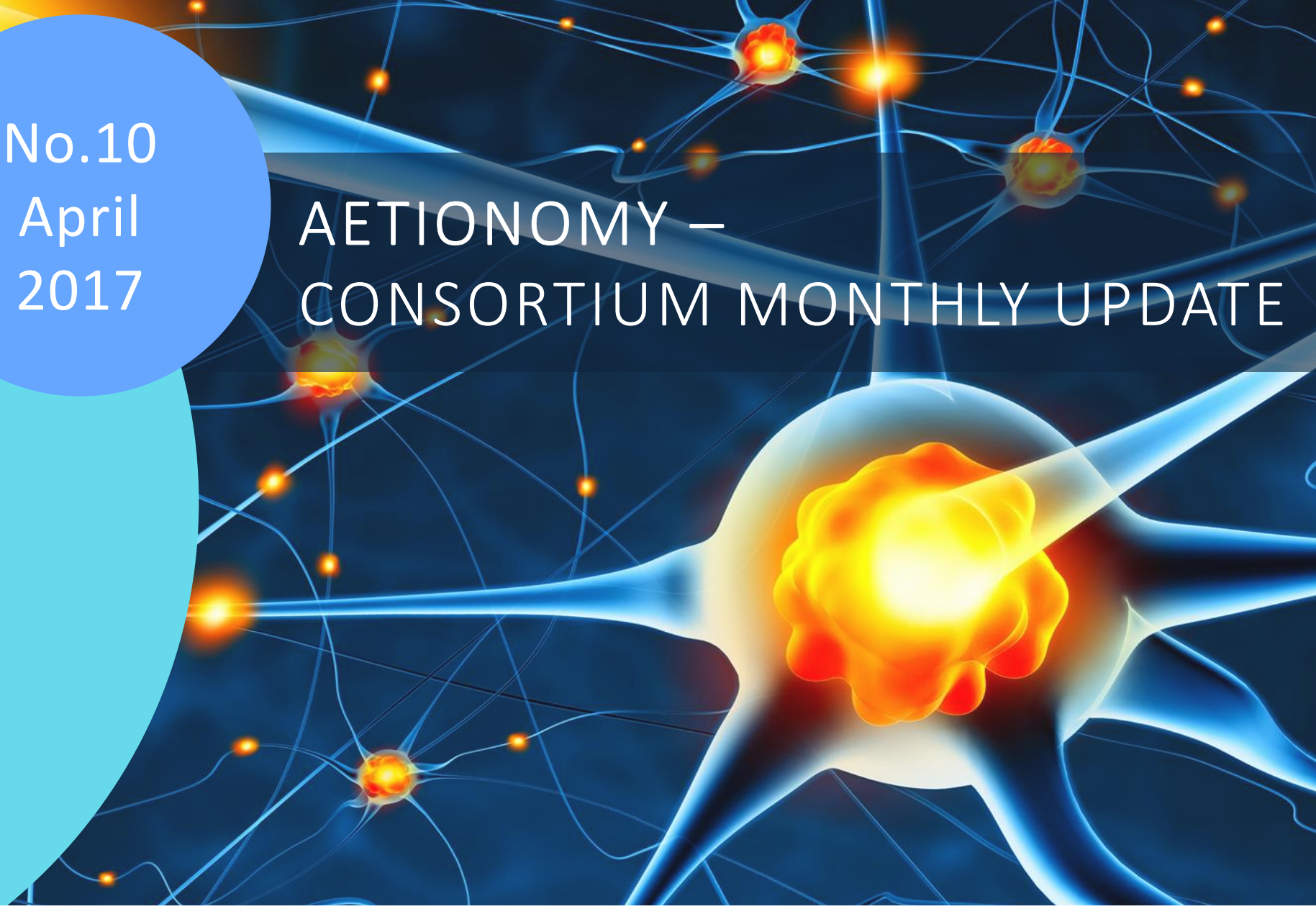
AETIONOMY – CONSORTIUM MONTHLY UPDATE



ucb Fraunhofer SCAI efpia imi innovative medicines initiative AETIONOMY

Message from the Coordinators on the Interim Review 2

As you know we had our second and final interim review by IMI on the 21st March 2017 in Brussels. We wanted to provide you with the feedback on our work from the reviewers.

First of all we want to thank everyone for all their hard work both in preparing the interim review and more importantly in the project so far. The reviewers were very complementary about the large amount of progress that has been made since the last review. They continue to be impressed by the very innovative and creative solutions that have been developed. They agreed that we had mostly addressed the comments from the earlier review and that we can and should carry on with the program.

We received written feedback on the 8th of April and now are required to provide some responses back to them. The key points from the reviewers was the need to develop and publish our methodologies for mechanism validation, as well as testing the 7 initial key mechanisms we have selected so far. In addition they want to see a more detailed proposal for the virtual patient cohort so they can truly understand how it will positively impact the program.

So as we address this feedback, we did want to congratulate everyone on a very successful 2nd review, but of course now the challenge turns to the need to focus on delivering the science on the next 20 months.

Please note there are currently some outstanding requests for information regarding the annual report for last year (due to 3rd May 2017) and the responses to the feedback of the interim review (due to 7th June). The Program Office has started on the responses for both documents but we are anticipating your contributions, we will keep everyone updated on the responses as they are generated.

Kindest regards,
The Project Office

URL Annual Report: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/d66633/115568_AETIONOMY_Periodic%20Report_P3_2017_Feb28_vf.pdf*

URL IR2 Report: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/65785*

General Information

Recruitment Update				
Site	**PD**	**AD**	**Controls**	**Total**
ICM	76	0	26	102
KI	49	0	13	62
UKB	41	0	12	53
Total:	**156**	**0**	**46**	**217**
Neurorad	0	7	34	**53**
Oxford	0	0	0	Not started
EPAD	x	x	71 BBRC	187 Global

Reminder that all publications need to be submitted to the Project Office **before** submission. Same for Congress abstracts, etc. Please review the Project Agreement for more details and follow the IMI mandatory communication guidelines.

Upcoming Meetings

- eTRIKS mtg 15-16 May in Barcelona
- The Virtual Brain (TVB) Node 5 training at AMU on 15-16 May 2017 in Marseille
- WP3/WP5 Mtg 22 June at ICM, in Paris
- AAIC Conference 16-20 July 2017 in London
- General Assembly IV at Novartis, in Basel on 30th Nov & 1st Dec 2017

Deliverables due to IMI in 2016 (late)

- D3.3.3. Webinar and report to review the pathophysiology graphs and potential hypotheses to be tested (M34 & M38)
- D2.2.3. Examination of data together with users for inconsistences (M36)
- D3.6. Generation of specific hypotheses about disease sub-groups (M36)
- D5.1.6.1. To confirm choice of principal biomarkers (M36)
- D2.4.2. User documentation for querying interface (M37)

WP1 – Governance & Coordination

- The **Annual Report (AR)** for IMI on both scientific and financials has been reviewed by IMI and we need to respond to questions on both the scientific & financial part. It has been sent to all partners and responses are due to the PO by 20 April 2017. Thank you for abiding by this deadline. Payments are stopped until IMI is satisfied with our responses.
- We have also received feedback on the **Interim Review** and a formal response together with the final DoW amendment is due to IMI by June. We will be sending out the template for the WPs to respond to the report and the DoW has already been sent to all partners for their updates. NOTE: this is the last time we will amend this as the project ends in 20 months.
- The **collaboration with Oxford** (Prof. Simon Lovestone's group) **and Fraunhofer** has started and a legal agreement is currently being signed to allow us to test our proposed mechanisms on the databases that Oxford have. Exciting adventures.
- We are planning on using the **EAN congress in June 2018 in Lisbon** as our final congress presenting all AETIONOMY results. We are currently trying to obtain information on costs and methods. AE has been very helpful in collaborating on this.

WP2 – Knowledge & Data Management

- WP2 welcomes AMU! The **AMU** is responsible for the virtualization of patients, e.g. to be taken from the ADNI database. To enable a large capacity of the virtualization pipeline, including reconstruction of anatomy and connectivity from structural and diffusion MRI, the group is currently adapting the pipeline. First patient connectomes have been generated.
- The migration of the UL infrastructure is now complete with the **new release of tranSMART**. The Clinical datasets from DIGPD, NGC and GenePark cohorts (ICM) have been curated and loaded in the AKB and is now available provided the agreements are in place. Please visit the ticketing system to request access.
  IDIBAPS AD Dementia dataset is under curation and will also be loaded as soon curation is complete.
- Save the date: 15-16 May 2017 at Barcelona. The **BioTransR 2017** (https://www.etriks.org/bioinformatics-meeting-2017/) , is being organised by IMI funded project eTRIKS, which over the course of 4 years has helped 41 translational research projects to get more value out of their data. The 2 main themes of the meeting are: understanding the landscape of Bioinformatics infrastructure and how to reduce fragmentation, and giving Translational Researchers the knowledge and the tools they need to collaborate on making sense of Translational Research data faster.

WP3 – Knowledge Integration & Mining

- We reached two important milestones:

  (i) The provision of a **Pathophysiology graph**, based on NeuroMMSigDB and ApiNATOMY, and

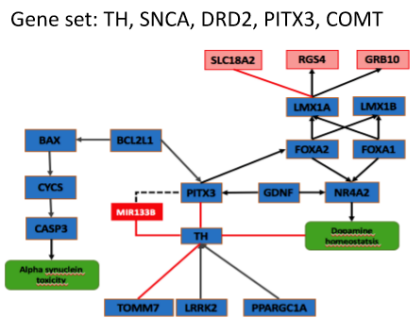
  (ii) **a repository of** more than 200 in-silico **candidate mechanisms for AD/PD** based on different data mining approaches.

  We are now looking forward to the validation against patient data. The WP3 members agreed on a **validation strategy** which will be realized during the next months. Main sources for the validation against patient data are the contributions from our clinical and EFPIA partners. Besides these data ADNI and PPMI are currently intensively inspected. Additionally we plan to benefit from several collaborations and contacts to get further access to patient data, e.g. EPAD, Univ. of Oxford, Univ. of Tuebingen, and C-PATH.

- URL of the Validation Strategy Concept: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/66713*

- WP3 provided all candidate mechanisms incl. available evidences in their **Biomarker Lounge** under the URL: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/45602*

Example of a schematic representation of a NeuroMMSig's subgraph



WP4 – Ethical & Legal Governance

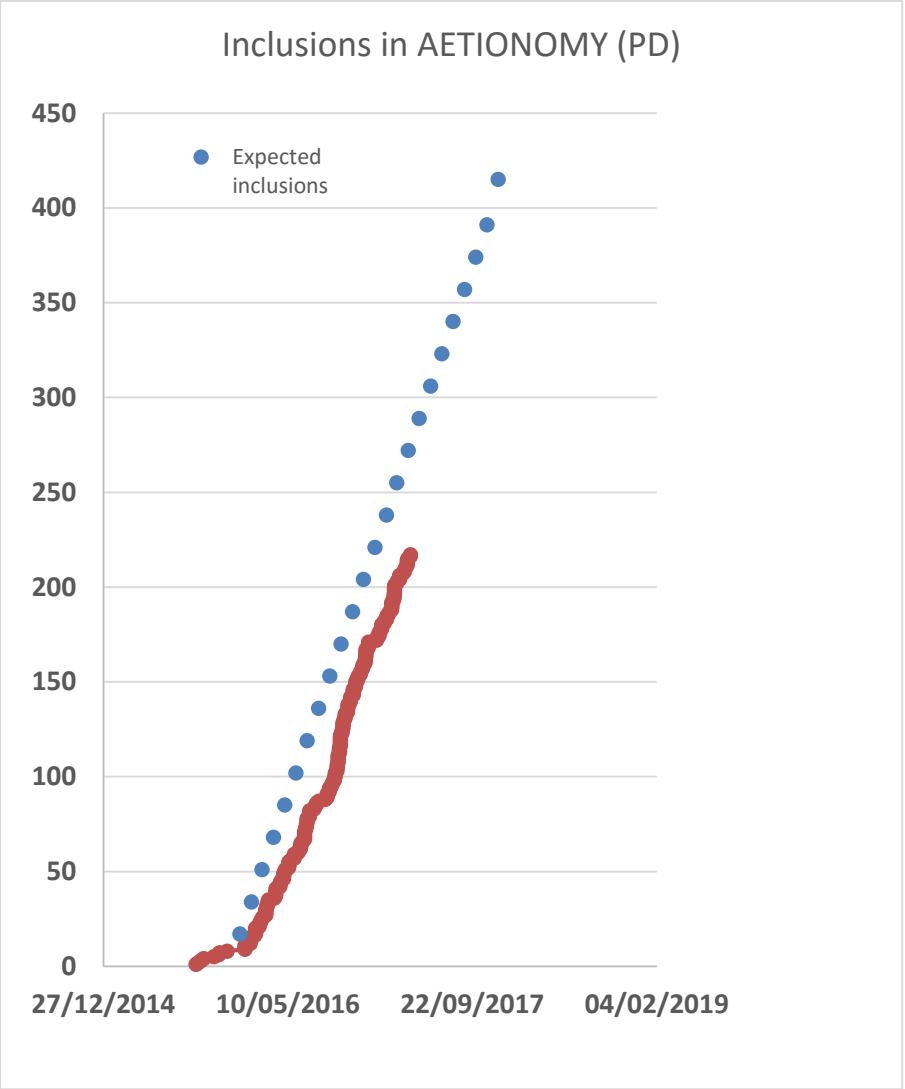
- In Task 4.3, WP4 is preparing for the **second joint legal and ethics workshop** between **AETIONOMY** and its IMI sister-project, **PRECISESADS**.
- This event, which is kindly being hosted by Bayer AG, will take place in Berlin on 25 April, and inter alia addresses the impact of the new EU General Data Protection Regulation on health data processing.
- Within Task D4.1, LUH has prepared **data sharing agreements** to cover data use by AETIONOMY's two new partners, AMU and BBRC.

WP5 – Clinical Validation

- An amendment to **AETIONOMY protocol** will be submitted next week in France to add 3 more clinical centres for PD group recruitment.
- **WP3/WP5 F2F meeting** will be organized at ICM on the 22nd of June to finalize the analysis plan and to select additional mechanistic hypotheses that could be tested in AETIONOMY clinical study.

A very Happy Easter to all

Clinical Study Recruitment



Publications Corner

Manuscripts under consideration:

- Stavros Skouras, Carles Falcon, Alan Tucholka, Lorena Rami, Raquel Sanchez-Valle, Albert Lladó, Juan D. Gispert, José Luís Molinuevo. Functional connectome signatures from health to Alzheimer's dementia: a characterization of disease-stage-specific mechanisms for network-based functional compensation.
- A presubmission enquiry of this manuscript has been recently submitted and the editorial board has considered it to fit the scope of the special issue of the journal NeuroImage 'Mapping Diseased Brains' and thus be eligible for peer review. Deadline for submission is 1st June 2017.

Manuscripts under preparation:

- CSF sTREM2 is associated earlier than YKL-40 with morphological brain changes in preclinical Alzheimer's disease: A longitudinal study.
- Longitudinal structural changes in preclinical AD: a comparison of a local sample with a sample from ADNI dataset

Analyses undergoing for manuscript preparation:

- Longitudinal changes in functional connectivity in preclinical AD in comparison to normal aging

Publications Corner

Submitted/accepted publications:

- Daniel Domingo-Fernández, Alpha Tom Kodamullil, Anandhi Iyappan, Mufassra Naz, Mohammad Asif Emon, Tamara Raschka, Reagon Karki, Stephan Springstubbe, Christian Ebeling, Martin Hofmann-Apitius: *Multimodal Mechanistic Signatures for Neurodegenerative Diseases (NeuroMMSig): a web server for mechanism enrichment.* Bioinformatics.

- Mufassra Naz, et al.: *Reasoning over genetic variance information in cause-and-effect models of neurodegenerative diseases.* Briefings in bioinformatics 17.3: 505-516.

- Kodamullil, A.T., et al.: *Computable cause-and-effect models of healthy and Alzheimer's disease states and their mechanistic differential analysis.* Alzheimer's & Dementia 11.11: 1329-1339.

- Iyappan, A. et al.: *Towards a Pathway Inventory of the Human Brain for Modeling Disease Mechanisms Underlying Neurodegeneration*. Journal of Alzheimer's Disease 52.4: 1343-1360.

- Alpha Tom Kodamullil, Firas Zekri, Meemansa Sood, Bastian Hengerer, Luc Canard, Duncan McHale, Martin Hofmann-Apitius: *Tracing the money for development of AD drugs: mapping investment to opportunities and possible drug target mechanisms*

- Alpha Tom Kodamullil, Erfan Younesi, Anandhi Iyappan, Reagon Karki, Sumit Madan, Martin Hofmann-Apitius: *Of mice and men: comparative analysis of neuro-inflammatory mechanisms in human and mouse using cause-and-effect models*

- Reagon Karki, Alpha Tom Kodamullil, Mufassra Naz, Martin Hofmann-Apitius: *Comorbidity analysis between Alzheimer's disease and Type 2 Diabetes Mellitus based on disease network models and the role of T2DM drugs*

- Emon MA, Kodamullil AT, Karki R, Younesi E, Hofmann-Apitius M: *Using Drugs as Molecular Probes: A Computational Chemical Biology Approach in Neurodegenerative Diseases*.