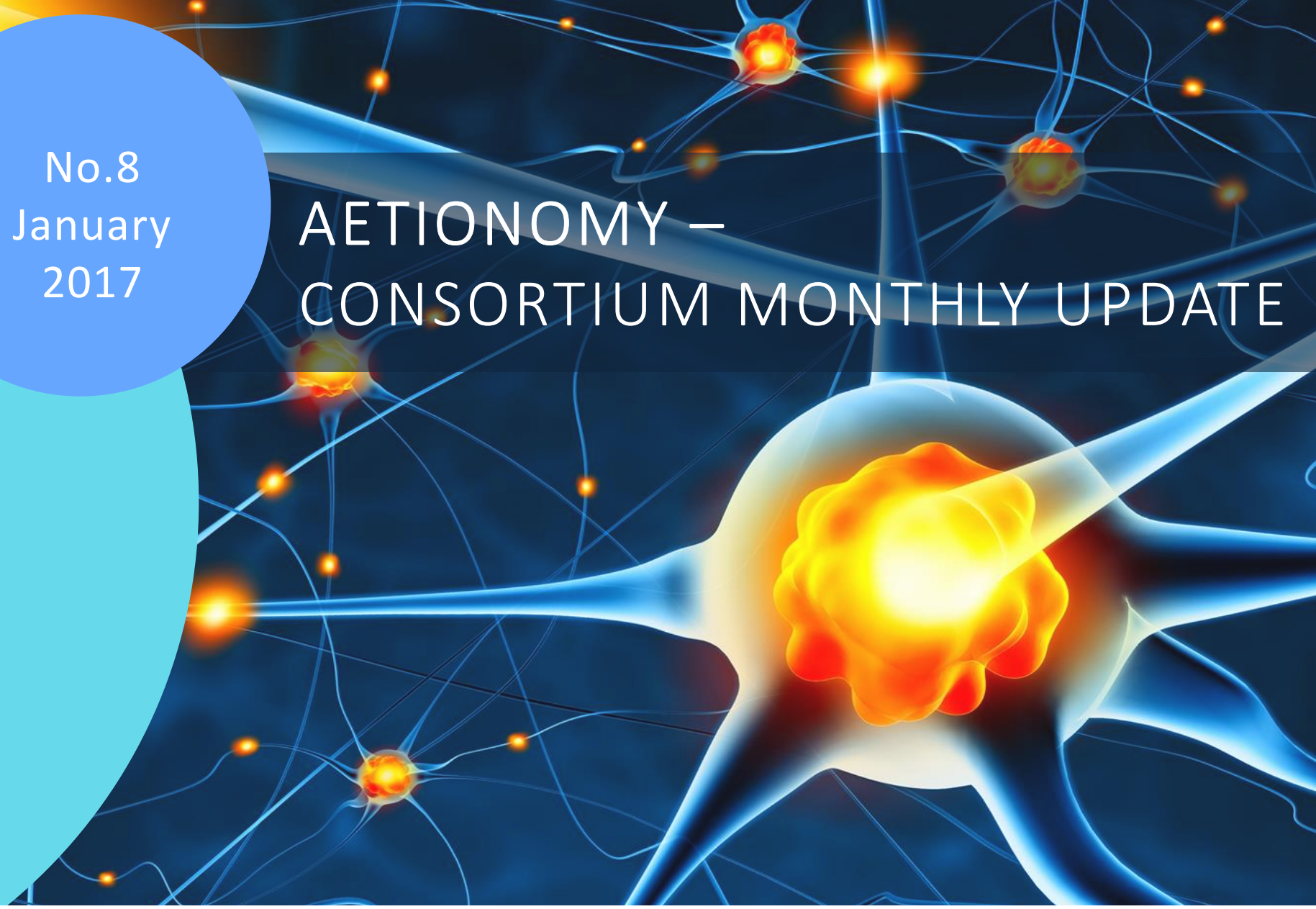
No.8
January
2017

AETIONOMY – CONSORTIUM MONTHLY UPDATE



ucb Fraunhofer SCAI efpia imi innovative medicines initiative AETIONOMY

Message from Duncan

Welcome back to everyone and I hope you all managed to have a break over Christmas.

We are now starting a really critical phase of the project. We have spent the first 3 years setting up the Knowledgebase, populating it with data, identifying mechanisms and starting he clinical trial. We now have to deliver the most innovative and creative parts of the project. The whole project hinges on us being able to extract more knowledge from all of the public literature and available data than we would have done, if we had just run a prospective observational trial. We have now assembled the datasets and whilst we will continue to add more data as it becomes available, we now need to extract the knowledge in terms of mechanisms, and use this mechanistic knowledge to build a revised taxonomy. This is the time to answer the original challenge that was set.

We do have the next (and last) interim review in March, and this will provide us with an independent view on both the quality and direction of work that we doing, and should be doing in the future. Once we are through this, then we need to focus on validating the mechanisms, building the taxonomy and publishing the science. We want this to be the year when we really see an increase in cross work package publications. If we are to be successful in significantly refining the current taxonomy of AD and PD, then we need to publish the work.

I wish everyone the greatest luck in what should be a great year for AETIONOMY.

Message from Martin

Building the New Taxonomy

The new year – our fourth year – starts with some changes in the organisation of the project.

WP2 has implemented the AETIONOMY knowledge base within year 1 to year 3; this work package will therefore reduce its activities to maintenance and updating of the current implementation. The new activity in WP2 that will keep us busy during the next 2 years is the Virtual Dementia Cohort (VDC). The VDC is an attempt at using generative models to “fabricate” entire virtual patient cohorts. These cohorts will mimic major studies such as ADNI and PPMI, effectively leading to “ADNI avatars” and “PPMI avatars”. Later in the course of this activity, we intend to generate large numbers of diverse virtual patients that can be used for in silico experimentation.

WP3 is now focusing entirely on validation of the candidate mechanisms identified and characterized in the first three years of the project. The validation efforts in WP3 will be jointly coordinated by Martin Hofmann-Apitius and Luc Canard. The inventory of candidate mechanisms, the NeuroMMSigDB server, holds now 126 candidate mechanisms for AD and 75 candidate mechanisms for PD. Some of the mechanisms show overlap and some are in fact “shared” between AD and PD. The WP3 team has started discussions to re-focus activities on validation and various strategies for in silico validation of candidate mechanisms – in particular those, that have been chosen for validation in the course of the prospective clinical study – are being developed.

WP5 will also see an organisational change: partner Pharmacoidea will change its WP assignment from WP5 to WP3. A close collaboration between in silico modelling and mining and wet-lab validation activities is already planned and first promising results have been generated. A tighter integration between computational and experimental biology approaches looks indeed very promising in the context of the syndecan – mediated uptake and spreading of “misfolded” peptides, the main focus of partner Pharmacoidea.

General Information

Recruitment Update				
Site	**PD**	**AD**	**Controls**	**Total**
ICM	64	0	21	85
KI	41	0	12	53
UKB	31	0	10	41
Total:	**136**	**0**	**43**	**179**
Neurorad	0	7	34	**53**
Oxford	0	0	0	Not started
EPAD	x	x	38 BBRC	100 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

- Interim Review Rehearsal at UL on 1st & 2nd March
- IR rehearsal at UCB HQ on 20 March
- IR at IMI-JU on 21st March 2017
- AD/PD Conference 2017 – Vienna (A), 29 March – 2 April 2017
- AAIC Conference July 16-20, 2017, London
- General Assembly IV at Novartis, Basel on 30 Nov & 1st Dec 2017

Deliverables due to IMI in 2016 (late)

- D3.3.2 Webinar and report to review the pathophysiology graphs and potential hypotheses to be tested (M30)
- D3.7.2 Report of the generation of specific pathophysiological mechanisms that induce class separation for NDD sub-groups (M32)
- D3.1.3.6 Report of the generation of specific pathophysiological mechanisms that induce class separation for NDD sub-groups (M32)
- D3.3.3. Webinar and report to review the pathophysiology graphs and potential hypotheses to be tested (M32)

WP1 – Governance & Coordination

- The III General Assembly Meeting took place in Paris in December at Sanofi. We thank our Advisory Board members & IMI who attended and provided excellent feedback.
- The collaboration with Prof. Simon Lovestone's group and Frauhhofer is still under negotiation but we hope that work with the post docs will start soon.
- The 2nd Interim Review is scheduled on the 21st March at IMI-JU. All work package leaders will be present to present the project's advances since the 18 month review. Rehearsals are planned in UL & UCB.
- The Annual Report (AR) for IMI on both scientific and financials, is due to IMI by 27th February. Please make sure your work package leaders receive all partner's input on time.
- IMI officially approved the Description of Work (DoW) vs 4.1 of 21 November 2016 on 15th December. All other versions are now obsolete and the AR should be aligned to vs 4.1.

WP2 – Knowledge & Data Management

- WP2 has started its new activity, the work focusing on the Virtual Dementia Cohort (VDC). Our new AETIONOMY partner AMU (University Aix Marseille) brings advanced modelling and simulation capabilities to the project; which will be combined with the knowledge-driven modelling used for the inventory of candidate mechanisms, NeuroMMSigDB.
- The pyBEL framework for the management of BEL-based models has been released in the end of 2016 (at the tranSMART user conference in San Diego) and there is growing interest in this open source framework in the OpenBEL community.
- Partner UL has added impressive analysis and visualisation tools to the tranSMART portion of the AETIONOMY KB. At the general assembly in Paris we could get a glimpse of what is now possible by analysing and visualising data from various clinical studies in the tranSMART portion of the AETIONOMY KB.
- WP2 is in talks with WP5 for the Deliverable D2.2.3 **Examination of data together with users for inconsistencies**, the clinical partners examine the uploaded datasets for consistencies and approval.The DIG-PD, GenePark and NGC data, is under examination for curation needs and to estimate the curation effort, after which it will be uploaded to the AKB.
- Migration to the new tranSMART version and server is in progress and will be completed soon. The new tranSMART is enhanced with the new smartR plugin for highly dynamic and interactive visualisation and analysis.

WP3 – Knowledge Integration & Mining

- NEuroMMSigDB, the inventory of candidate mechanisms in AETIONOMY, is now accessible online under http://neurommsig.scai.fraunhofer.de/
- The system was presented to the AETIONOMY consortium at the general assembly in Paris; the main developer of NeuroMMSigDB (Daniel Domingo-Fernandez) implemented this key functionality of AETIONOMY in the course of his Master Thesis at the University of Bonn.
- A complete overview of modelling and mining approaches in AETIONOMY has been generated; this overview will provide the basis of an internal deliverable and will also be used as the starting point for another joint publication on in silico validation strategies for candidate mechanisms in dementia research.

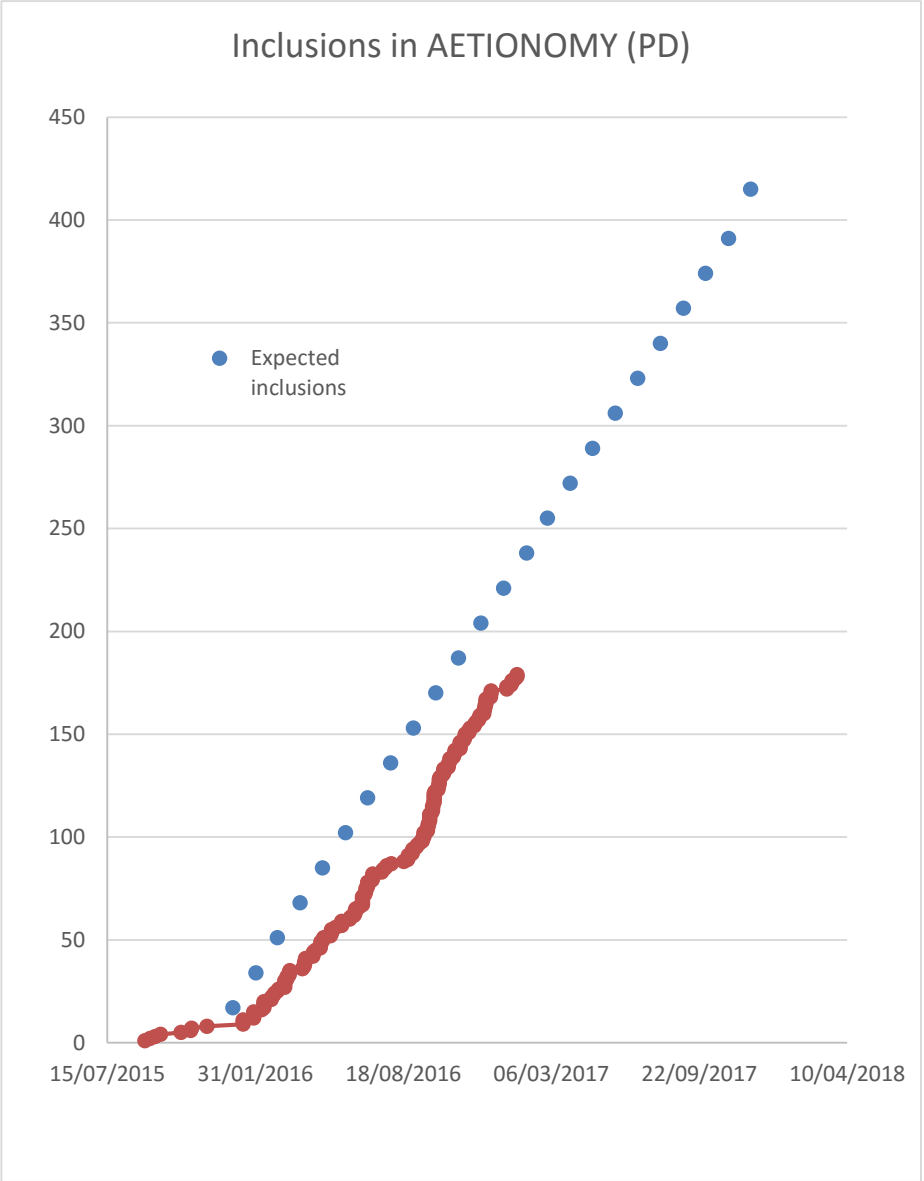
WP4 – Ethical & Legal Governance

- LUH and Alzheimer Europe completed the second part of the legal and ethical guidelines on patient stratification in non-curable diseases, which focus on the AD prospective study; this was submitted to IMI in the form of a deliverable at the end of 2016.
- LUH has started organising and sending out invitations for the second joint legal and ethical workshop with AETIONOMY's sister-project, PRECISESADS, which will be held in Hannover in April. The workshop will focus inter alia on the ongoing initiatives for data and bio-sample sharing in multi-centre projects, including the likely impact of the EU General Data Protection Regulation, which replaces the Data Protection Directive in May 2018.

WP5 – Clinical Validation

- Pharmacoidea has identified a family of cellular receptors responsible for the cellular internalization/spreading of misfolded proteins such as Aβ, a-syn and tau. Studies are underway to cellular effect of blocking this pathway along with the exploration of cellular signalling triggered by syndecan-aggregate interaction. As this pathway is responsible for the interplay of diabetes related enzymes and neurodegeneration, studies are on-going to explore the activation of key cellular players of diabetes/neurodegeneration.
- A draft of data and samples sharing agreement between EPAD and AETIONOMY consortia have been shared with EPAD for discussion.
- Recruitment in the PD group is at 42%. Efforts need to be maintain to achieve recruitment by the end of 2017.
- Recruitment in the EPAD protocol at BBRC and in 3 other EPAD LCS clinical centres is progressing well with around 100 subjects recruited (i.e. 41% of the initial expected inclusion in the AETIONOMY AD prospective cohort).

Clinical Study Recruitment



WP5 – Clinical Validation

The Barcelona beta Research Center (BBRC) is fully dedicated to research on **Alzheimer's disease (AD) prevention** from a clinical, cognitive, genetic, and biomarker, including wet and neuroimaging, perspective.

The setup of preventive studies requires the identification of participants with an increased risk of developing AD in the near future that are suitable to be recruited as asymptomatic individuals in clinical trials. To increase our knowledge of the pathophysiology and pathogenic factors emerging at early preclinical AD stages, we established the ALFA (for ALzheimer and FAmilies) cohort for the prospective follow-up of a cohort of cognitively normal participants, most of them first-degree descendent of AD patients. The ALFA parent cohort is composed of 2743 cognitively healthy participants (45-75 years old) representing the whole spectrum of risk of developing AD that will leverage with different projects. The clinical, cognitive, lifestyle habits, and *APOE* genotype characterization of ALFA cohort members allows us to invite them to specific projects at the BBRC. Currently ongoing ones include the ALFAlife, the ALFAgenetics and the ALFA+ projects. Briefly, the ALFAlife primary prevention study, is a programme of control and intervention on the modifiable AD risk factors. The ALFAgenetics study, aims at the identification of the genetic and cognitive determinants of brain structures and functions of ALFA participants. Finally, the longitudinal ALFA+ project entails, on top of a similar characterization as in the ALFA parent cohort, the acquisition of both wet (CSF, blood) and imaging (magnetic resonance imaging [MRI] and PET) biomarkers. The ALFA+ cohort study will serve, through deep phenotyping, to untangle the natural history of the disease and to model its earliest stages to develop successful trials. Our most ambitious aim is to follow ALFA study participants throughout their lives.

In addition to the projects sponsored by the BBRC, the thorough characterization of ALFA cohort participants enables our involvement in large European-wide cohorts such as the envisioned by the EPAD consortium. The BBRC included its first EPAD cohort participant on the 30th June 2016 and, at the moment of writing this, we have contributed with the inclusion of 41 participants.