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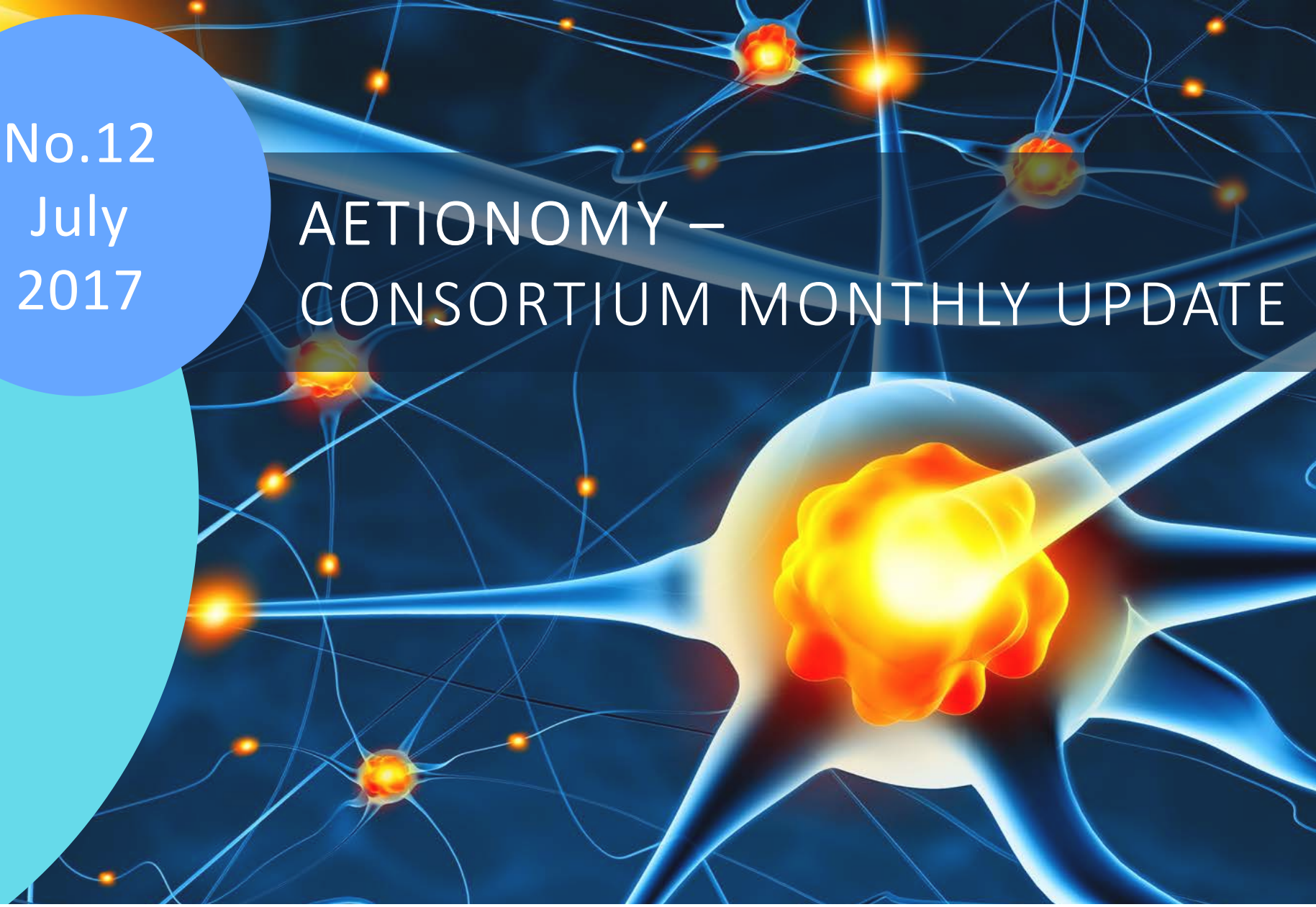
AETIONOMY – CONSORTIUM MONTHLY UPDATE



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Message from the Coordinators

Dear AETIONOMY partners,

As you will be aware, this month we finalized the departure of two partners – UCL and NEURORAD - from the consortium, we thank them both for the partnership and contributions and wish them all the best in their future endeavors. This is indeed a loss for us, but as you will read in the next pages to address our goals, further collaborations have been initiated or are being planned. There is still a lot of work to do and some considerable steps to overcome but we believe in the fortitude of the members and their on-going commitment to the goals of the project.

Of particular focus, during the last months we have all worked hard to pull together information on candidate mechanisms for both AD and PD and to prepare the analysis of patient data information for validation, excellent collaboration between Work packages 3 and 5 is fundamental for these activities.

In the following pages you will find updates on the progress of all our work packages and news on planned events.

We wish you all the best for the upcoming vacation period and will be in contact again with you very soon.

Kindest regards,

The Project Office

General Information

Recruitment Update				
Site	**PD**	**AD**	**Controls**	**Total**
ICM	95	3	38	136
KI	64	0	16	80
UKB	54	0	12	66
CHU	1	0	0	**1**
Total:	**214**	**3**	**66**	**283**
EPAD	x	x	82 BBRC	289 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.

Remember to follow the **IMI mandatory** communication guidelines with regards to funding statements and logos.

Upcoming Meetings

- Fraunhofer&KI Candidate mechanisms validations at Karolinska in 28th August – 1st September 2017
- WP3 & 5 Workshop at Karolinska in October 2017 (see doodle sent)
- General Assembly IV at Novartis, in Basel on 30th Nov & 1st Dec 2017
- EAN & AETIONOMY Symposium June 2018, Lisbon

Deliverables due to IMI in 2017 (late)

- D2.4.2. User documentation for querying interface (**M37-Jan)**
- D3.3.4 Webinar and report to review the pathophysiology graphs and potential hypotheses to be tested (**M38-Feb)**
- D3.8 Data analysis work plan for the WP5 clinical study (**M40-Apr)**
- D5.1.3.8 To confirm choice of biomarkers for final protocol **(M40-Apr)**
- D2.5.2 Report describing the complete inventory of trajectories and distributions **(M41-May)**
- D2.2.3. Examination of data together with users for inconsistences (**M41-May**)
- D3.3.5 Webinar and report to review the pathophysiology graphs and potential hypotheses to be tested (**M42-Jun)**

WP1 – Governance & Coordination

- The **III Annual Report (AR)** for IMI on both scientific and financials has been approved by IMI. Payments should be released shortly
- We are still planning on using the **EAN congress in June 2018 in Lisbon** as our final congress presenting all AETIONOMY results. . AE has been very helpful and has drafted a general info poster. Please block the dates to be there to support us
- We are still working on obtaining access to the Tuebingen samples for use in validating our hypotheses. Legal agreements are currently being drafted.
- The PO is also planning a new format for the IV General Assembly to be held at Novartis on 30 Nov & 1st Dec. Please plan to join us.
- The 4th amendment to the DoW has been submitted to IMI removing UCL and NeuroRAd. We are still waiting approval from IMI on this so until further notice we are working on the DoW vs 4.1_21 Nov 2016.

WP2 – Knowledge & Data Management

- On the 6th/7th July 2017 we executed a **WP2 Virtual Dementia Cohort workshop** in Marseille at the University campus, INS institute. Main focus of the meeting was on the next steps towards generating the Virtual Dementia Cohort (VDC). A broad spectrum of methods, metrics and time scales were discussed. We are planning to visualize the longitudinal progress of the diseases, representing biomarker measurements which are related to disease specific mechanisms. During the workshop AMU presented the "functional dynamics" and "functional connectivity dynamics" (FC, FCD) methods, which enables us to complete missing imaging data from the ADNI cohort for our patient model. This will increase the set of currently 15 virtual patients (with full imaging data) to a cohort of 916, which will be the basis for the further generation of a huge cohort. In the next steps Fraunhofer and AMU will generate an ADNI merge file incl. the main features and their related brain regions.
- Furthermore, Martin Hofmann-Apitius gave a talk at the INS institute about the „*Systematic Identification and Validation of Mechanisms underlying Neurodegenerative Diseases: a computational approach*".

WP3 – Knowledge Integration & Mining

After the sucessful completion of many WP3 tasks, the partners are focussing now on the four on-going tasks:

- As a substitute for the largely delayed deliverable in **Task 3.3**, originally defined as *„Identifying and sourcing Omics indices and their mapping to the Pathophysiology Graph“* we executed a *„Webinar on Bayesian Modelling of clinical Data (ADNI)“* and demonstrated, how this approach can contribute to the analysis of candidate mechanisms. A full report **D3.3.3** and more information are available on the BSCW server under the URL: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/67158*

- The next webinar as part of deliverable **D3.3.4** is in preparation; that deliverable will provide an overview on the results of the work on analysing candidate mechanisms.

- For Task 3.6, originally named “Identification of Disease Subgroups from Analysis over Clinical and Omics Indices”, Partner Fraunhofer generated the report **D3.6** *„Generation of specific Hypotheses about disease sub-groups“*, which is mainly focussing on the NeuroMMSig approach to identify in- silico candidate mechanisms and their related patient subgroups. It is noteworthy at this point, that – in a close collaboration between UCB Biopharma (Prof. Holger Froehlich) and the team at Fraunhofer – it was possible now to demonstrate that the mechanism-based stratification of patient subgroups using NeuroMMSig Server and Bayesian representations of ADNI data actually works. A paper describing the analysis strategy is currently in preparation.

- In **Task 3.8** “*Contributions to the design of Clinical Study*”, we are currently focussing on the longitudinal modelling of disease progression based on ADNI and PPMI data. A first analysis of ADNI data showed substantial differences between the “reference biomarker trajectory model” published by Clifford Jack in 2010 (and its updated version in 2013) and ADNI data projected into the same, comparable metrics system.

- The work presented here is an example for the fruitful crosstalk between AETIONOMY and EPAD; the "study viewer" developed for EPAD contains now both reconstructed Clifford Jack models and the ADNI biomarker trajectories extracted from ADNI data. For details please visit: *http://epad.scai.fraunhofer.de/app/alzheimer-model.*

  Results of this analysis will be described in the report D3.8 "*Data analysis work plan for the WP5 clinical study*".

- Our main work is currently of course Task 3.9 „*Validation of selected Candidate Mechanisms*", in which we compare our candidate mechanisms against patient data. Here we have 3 subtasks:
  - Subtask 3.9.1 IN-SILICO VALIDATION OF SELECTED CANDIDATE MECHANISMS (lead: Fraunhofer).
  - Subtask 3.9.2 TARGETING HEPARAN SULFATE PROTEOGLYCANS AS KEY PLAYERS BEHIND NEURODEGENERATION (lead: PHI).
  - SUBTASK 3.9.3 VALIDATION OF THE CHROMOSOME 17 LOCUS MECHANISM (lead: EMC).

- Preparatory steps are made for all three validation activities, for example BEL modeling of the candidate mechanisms incl. further evidences on the causal chains, and contacts to owners of (independent) patient data.
- As a recent update on the "access to patient-level data" frontier, we can now announce that the colleagues at C-PATH institute have agreed to make their clinical data collection accessible to partner FRAUNHOFER; we expect a small team of Fraunhofer scientists to fly to Tucson, AZ, very soon.

WP4 – Ethical & Legal Governance

- WP4 continues to assist in the drafting and circulation of two new data-sharing agreements to cover the secure sharing via UL tranSMART of clinical data with AETIONOMY's new partners, AMU and BBRC; these have now been finalised for signature. As regards a key task foreseen for AMU, namely generation using existing data of new 'virtual dementia cohorts', LUH is presently analysing the ethical and data protection implications. It plans to include this analysis in a joint dissemination article with WP2.

WP5 – Clinical Validation

- The 2nd amendment for the AETIONOMY protocol (only for France) has been approved by the EC on June 6th:
  - 3 new clinical sites (Besançon, Bordeaux & Toulouse) have recently been initiated and are ready to recruit PD patients and Healthy Controls (~80 subjects total); first recruited patient this month in Toulouse!
  - 2 new groups of subjects: PD patients or first degree relative of a PD index case with SNCA gene mutations (25+25 subjects);
  - End of recruitment period delayed to December 2017.
- A first AD patient has been enrolled on June 6th at ICM and 4 more AD patients should be screened by the end of July.
- The amendment in Sweden has been approved by EC, locally increasing the estimate number of PD group inclusion up to 105 subjects.
- A list of mandatory REDCap variables required for analyses has been edited to plan an upcoming data management review (e.g. year of birth, gene mutated or MDS-UPDRS data).
- We are starting to organize the routing of DNA samples from KI (on progress) and UKB (on September) to ICM, for NeuroChips assessments to be performed by the end of the year / beginning of next year.

Clinical Study Recruitment