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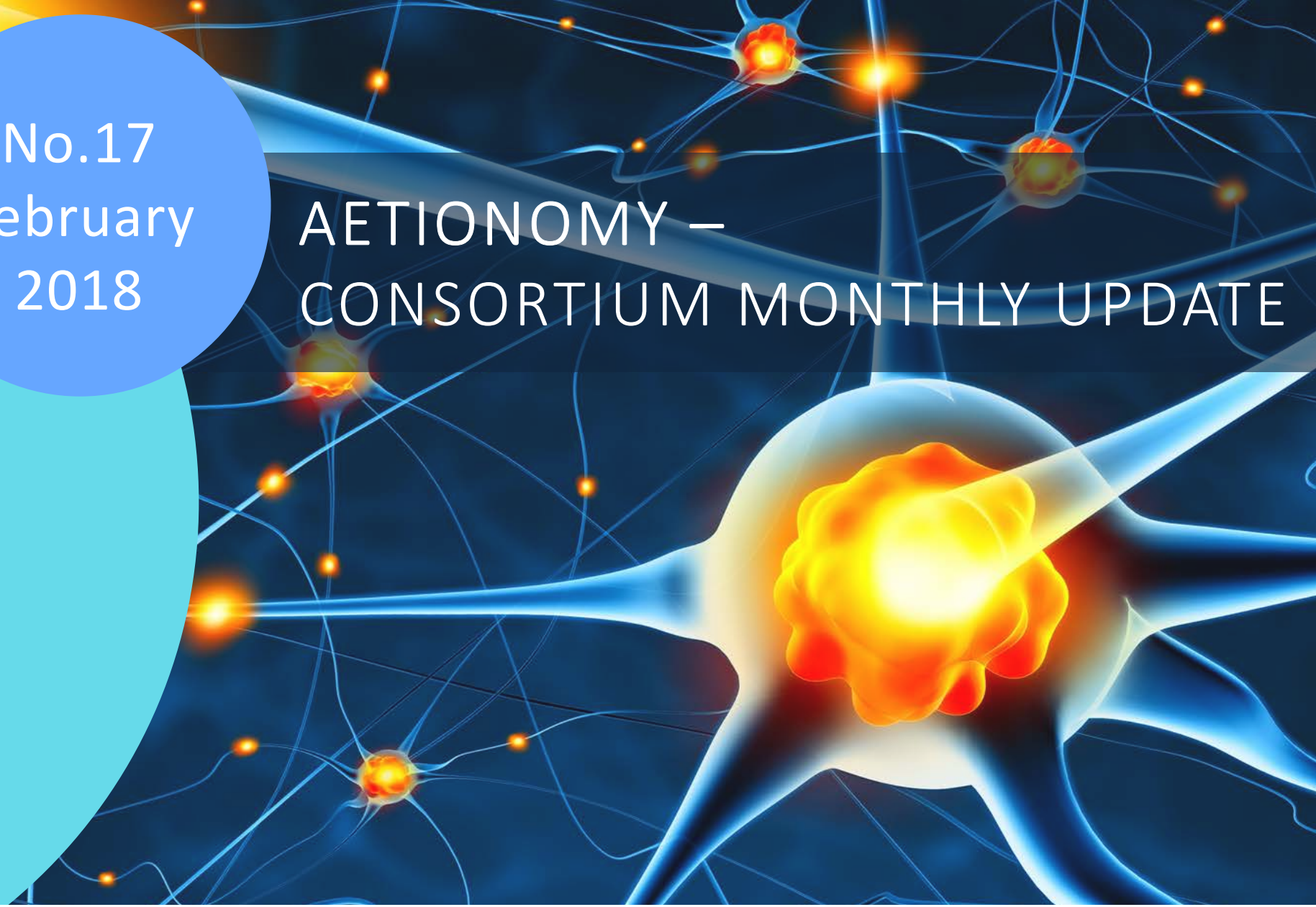
AETIONOMY – CONSORTIUM MONTHLY UPDATE



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AETIONOMY

Message from the Coordinators

Dear AETIONOMY partners,

With the 2017 Annual review rapidly moving towards completion as coordinators of a complex multi-partner consortium it is hard not to reflect on the challenges of communication and the many interacting agendas that we have to delicately weave into the final delivery in a few months time – a daunting task indeed.

The recent message from the coordinators to WP3 and 5 is an example of the aim for focus and simplicity and the complexity of the interpretation of this message. We hope that you can all recall the original perspective that we had entering this project and help guide us towards the end as smoothly and collaboratively as possible.

“The project office (PO) appreciates the effort to generate the agreed (& mechanism-related) biomarker data from the clinical cohorts (either partner biomaterial banks or the prospective AETIONOMY PD cohort) and looks forward to obtaining the majority of those data by the end of April 2018.The necessity of imposing this deadline is driven by our overarching goal (namely the identification of patient-subgroups that are characterized by identifiable pathophysiology mechanisms), as it is WP3 who will be tasked with the wider integration of polyomic data there is a need to gain access early enough to facilitate the data pre-processing and data analysis tasks (incl. mechanism-association of patterns found) before our ultimate deadline.

WP3 remains committed to establishing the relationship between our internally derived (WP5) biomarker measurements and those external clinical / biomarker data sets (i.e. ADNI, EMIF-1000, AddNeuroMed, AIBL for AD; PPMI, MAP2PD – as an aside each of these named datasets should be considered as data only, as none of the studies are likely to provide sufficient samples to be integrated into our biomarker workflows).

The PO asks WP5 partners to redouble efforts to provide a "data generation plan", which consists of the complete picture of resource planning (incl. timelines) for the generation of their respective centres’ biomarker data, and the logistics of any sample transfers. This is important both for the planning for subsequent data transfer activities but is also critical for us to get the financial status of the project in line and ensure that budget is appropriately distributed. This description should make explicit whether any further characterization of biomarkers is planned in patient samples outside of the AETIONOMY cohort.

In parallel WP3 is likewise challenged to update the various analysis plans so that the requisite effort can be likewise costed, and naturally the flow of data around the consortium and into the central AKB needs to be managed by UL and Fraunhofer and therefore WP2 needs to appreciate the effort required.

Please note that both, the "data generation plan" and the "data analysis plan" will become part of the DoW in its final version for the last months of AETIONOMY.”

Thanks

Your PO (Phil, Martin, Jaqueline, Stephan and Tobias)

General Information

Upcoming Meetings

- WP3-5 Workshop & Datathon – UCB, UK April 27 2018
- EAN Conference 16-19 June 2018, Lisbon
- ISMB Conference 6-10 July 2018, Chicago
- PO/SC Meeting, Luxembourg 5/6 July 2018
- Final WP3-5 Workshop & Datathon – BBRC, 21 Sept
- Final General Assembly and NDD Symposium on 29th & 30th Nov 2018 – Bonn, Germany

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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.

Did you know that **AETIONOMY** should always be capital letters?

Deliverables due to IMI in 2017 (DoW v5.1, Aug 2017)

- D1.2.8 Annual Report due 28 February
- D3.3.5 due M47 (planned M50)
- D5.1.7, D5.3.2 & D5.3.5 due M48
- D1.4.2 due M49
- D2.5.3.3. & D2.5.3.4 due M50
- D3.9.2.1 due M50

Important Timelines to Project End

M49	M50	M51	M52	M52	M53	M54	M55	M56	M57	M58	M59	M60	
31-Jan-18	**15-Feb-18**	**Mar-18**	**26 or 27 Apr**	**30-Apr-18**	**may**	**june**	**Jul-18**	**August**	**20-21 Sep**	**3-5 Oct 18**	**29 & 30 Nov**	**31-Dec**	**28-Feb-19**
all known samples documented in excel planner	planned shipment date of samples to analysis labs	Data analysis on data sets already available EMIF 1000	final Workshop WP3/5 & datathon? UK	results available	biomarker data analysis	biomarker data analysis	SC mtg / results interpretation UL	Holiday	final Workshop WP3/5 & datathon? BBRC, Barcelona	Granada Genomics Conference / Joint Taxonomy Mtg?	NDD Conference & Final GA	Project ends	Final report due to IMI
	clean	cohort data											
	Draft Agenda for NDD ready												
	Project Plan for analysis due from WP3	Newsletter Identification of new mechanisms for NDD	Determine if amendment is needed / budget shifts			Newsletter - the Virtual Dementia Cohort	02-05/2018 5th July Luxembourg (JC)				Newsletter - The new Taxonomies		

Did you know that all the project deliverables submitted to IMI are available on our BSCW Server?

Check them out at: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/42644*

WP1 – Governance & Coordination

- The annual report is due to IMI on the **28th February** for all partners to report their scientific and financial contributions to the project. We have had a few rounds of comments and appreciate your input.
- Due to some changes in strategy and budget shifts needed to ensure the delivery of the new taxonomy, we are making the final amendment to the Description of Work. This is the last chance to update tasks, milestones and deliverables. All feedback due to the PO by **2nd March 2018**.
- The Final Symposium and last General Assembly date will now be held on the **29th & 30th November 2018**. This will take place in Bonn, Hotel Hilton. We will communicate further info in the next bulletin. We expect all partners to present at this final conference on neurodegeneration.
- The PO again would like to ask all WPs to please try to submit the deliverables on time as we are being measured on this!

WP2 – Knowledge & Data Management

- 7 datasets from BI and 14 from UCB were received by WP2 for data curation and incorporation to the AETIONOMY Knowledge base;
- UL is testing the portable version of the Ada server for installation on the dedicated AETIONOMY Server. This will provide further workflows.
- On the **15th/16th February 2018** the third Workshop on the Virtula Dementia Cohort (VDC) modelling and implementation strategy was held at partner site AMU in Marseille. Starting point was the information on the related research activities in HBP and TVB, and of course the status of our VDC activity. Furthermore:
  - AMU informed about the current status of their mechanistically driven virtual brain simulations (based on ADNI imaging data) as well as measures of brain functional connectivity (dynamics).
  - Fraunhofer described their current work on trajectories and longitudinal aspects for both AD and PD based on ADNI and PPMI.
  - Fraunhofer described their work on OpenBEL encoded disease mechanisms.
  - UCB presented the longitudinal Bayesian Network modelling approach to enable the generation of virtual patients based on ADNI and PPMI data.

  All three partners discussed how these different approaches should be integrated to generate the first VDC prototype (ADNI Avatar).

WP3 – Knowledge Integration & Mining

Currently we are focusing in WP3 mainly on task T3.9: '*Validation of selected candidate mechanisms'.*

Regarding the in-silico validation of candidate mechanisms, we follow the agreed strategy to analyse candidate mechanisms against real patient data, e.g. AddNeuroMed data and the Oxford PD cohort. So we are explicitly looking into ADNI- and PPMI-independent data to look mainly for genetic overlaps to our candidate mechanisms.

Additionally, we proceed to map data-derived information (pathway level summaries of SNPs) to literature-derived knowledge (NeuroMMSig). This was just shown to be highly successful in the context of our newly developed AD risk model (Khanna et al., Scientific Reports, revised) and is now explored in greater extend for a mixed AD/PD cohort from ADNI and PPMI. The resulting patient stratification will be related BEL disease models (NeuroMMSig).

With one of the candidate mechanisms, we are investigating, evaluating and validating the chromosome 17 locus mechanism. The genes involved are KANSL1, KIBRA, and MAPT, and the imaging readout mentioned is hippocampal atrophy. MAPT is a well known gene related to AD. The KANSL1 gene is a relatively new biomarker and the hypothesis is that related genetic mutations play an important role in AD. EMC is analyzing this candidate mechanism with a large scale evaluation on population and clinical data.

After HASE experiments on 1.175 ADNI subjects using a set of about 300.000 SNPs (phenotype-genotype associations), EMC continued with this regression analyses experiments using a new set of about 2.3 million SNPs, in this case from 802 subjects. Significant results were coming up connected to APOE-related SNPs, especially with volumes of the hippocampus subparts (FS6.0). Chromosome17-SNPs showed interesting trends. At the moment, a publication is in preparation on these findings, in combination with related research from the Fraunhofer team. Furthermore, a set of 260 imaging FS6.0-biomarkers from 1.715 ADNI baseline scans were computed at EMC to be used for the next Bayesian Modeling approaches coordinated by UCB. Finally, EMC is currently exploring new event-based modeling techniques (EBM) on the ADNI database, where longitudinal and APOE-epsilon4-related info will be taken into account.

A webinar on in-depth validation of imaging-related candidate mechanisms using advanced strategies, like regression analysis on genetic and imaging biomarkers (HASE), Voxel-Based Morphometry (VBM), and Event-Based Modeling (EBM) will be announced soon.

On the 13th Feb 2018 Fraunhofer held another Webinar to review the pathophysiology graphs & potential hypotheses. The main hypotheses were described as graph representations (NeuroMMSig) and additionally it was shown, how a machine learning approach (BN) was able to identify a major subset of the well-known AD mechanisms to predict time of AD diagnosis.
12 links that were reconstructed using NeuroMMSig and how they relate to the main short-listed hypotheses proposed by AETIONOMY. We uploaded all information of the webinar to the BSCW AETIONOMY workspace incl. the web recording, slides and the report D3.3.5 under the URL: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/74377*

WP4 – Ethical & Legal Governance

Following the circulation of the draft data protection supplemental agreement to update the project data protection framework in line with the new EU General Data Protection Regulation, LUH has begun discussions with partner legal departments and Data Protection Officers, with a view to adopting the agreement in good time prior to the new rules taking effect this May. Dr Marc Stauch, LUH, has also been invited to address the March GA of AETIONOMY's sister-project, PRECISESADS, on compliance issues stemming from the GDPR."

WP5 – Clinical Validation (1/2)

- All the subjects (except 1 at Pellegrin hospital) have completed their visits, if subsequent visits were needed to perform all the protocol activities.
- Clinical centers participating in AETIONOMY-CS have collected ~530 samples (blood sampling + CSF) and all partners offered to share samples from existing cohorts for AETIONOMY analysis plan (~1200 DNA/CSF samples).
- We have established an exhaustive shipping/receipt plan of DNA samples and biofluids collected during AETIONOMY-CS, as well as for samples provided by all WP5 partners (UKB, ICM/IM2A, IDIBAPS/BBRC, KI).
- All details about samples to be sent to labs that will perform analyses are fully listed in a shared spreadsheet between partners. These shipments are summarized below, with an actual update on their status.
- Data collected during AETIONOMY protocol are being completely entered into the REDCap eCRF. Data management plan is set as follow:
    - All data entered by **2 March**
    - Queries sent by **8 March**
    - Queries answered by **21 March**
    - Database lock by **29 March**

WP5 – Clinical Validation (2/2)

From	Samples	To	Status	Actual/estimated date
KI (Prof. Svenningsson)	105 DNA	ICM	Partially	
	150 DNA add. cohort	ICM		12 MAR 18
	32 CSF	UKB (MH)	Planned	
	32 CSF	IDIBAPS		To update
UKB (Prof. Wuellner)	94 DNA	ICM	OK	26 FEB 18
	22 CSF	KI		To update
	22 CSF	IDIBAPS	Planned	
	22 CSF	UKB (MH)		NA (on site)
UKB (Prof. Heneka)	240 DNA add.cohort	ICM	Planned	To update
	220 CSF add. cohort	KI	OK	20 FEB 18
	220 CSF add. cohort	IDIBAPS		26 FEB 18
ICM (Prof. Corvol)	43 CSF + 15 add. cohort	KI		
	43 CSF + 15 add. cohort	UKB (MH)	Planned	7 MAR 18
	43 CSF + 15 add. cohort	IDIBAPS		
	213 DNA + 492 add. cohort	UKB (UW)		As soon as all received
IM2A (Prof. Dubois)	7 DNA + 682 add. cohort	ICM		NA (on site)
	7 CSF + 96 add. cohort	KI	Planned	
	7 CSF + 96 add. cohort	IDIBAPS		To update
	7 CSF + 96 add. cohort	UKB (MH)		
IDIBAPS (Prof. Sanchez-Valle)	80 CSF (add. cohort)	UKB (MH)	Planned	7 MAR 18

Table: AETIONOMY samples and shipping status

Publications Corner

- Carles Falcon, Alan Tucholka, Gemma C. Monté-Rubio, Raffaele Cacciaglia, Grégory Operto, Lorena Rami, Juan Domingo Gispert, José Luis Molinuevo, for the Alzheimer's Disease Neuroimaging Initiative: ***Longitudinal Structural Cerebral Changes Related to Core CSF Biomarkers in Preclinical Alzheimer's disease: a Study of Two Independent Datasets***, under review in Neuroimage: Clinical.

  In this article we compare longitudinal rates of gray matter atrophy in cognitively healthy individuals with positive and negative amyloid cerebrospinal biomarkers from two independent cohorts: a subset of ADNI and a local cohort with identical inclusion criteria. Our results show important discrepancies in gray matter atrophy rates and topological patterns between the two cohorts which may lead to important differences in samples size required to detect changes in gray matter atrophy in AD prevention trials. We conclude that continuous biomarker indexes are more sensitive and comparable to detect gray matter changes than dichotomized categories.

- Gemma C. Monté-Rubio, Carles Falcon, Marc Suárez-Calvet, Oriol Grau-Rivera, Grégory Operto, Raffaele Cacciaglia, Raquel Sánchez-Valle, Lorena Rami, Christian Haass, Juan Domingo Gispert, José Luis Molinuevo: ***Longitudinal cerebral volumetric changes associated to CSF YKL-40 and STREM2 levels in preclinical Alzheimer's disease***, prepared for submission to Journal of Alzheimer's disease.

  In this article we describe longitudinal gray matter (GM) volume changes associated to two cerebrospinal fluid (CSF) neuroinflammation biomarkers (sTREM2 and YKL-40) in cognitively healthy individuals with amyloid accumulation, i.e. at the preclinical stages of Alzheimer 's disease (pre-AD). We found both increments and decrements of GM volume between the pre-AD and control groups and that individuals with higher CSF sTREM2 levels tended to maintain more stable GM volumes than those with lower ones, whereas the opposite was found for YKL-40. Our findings are compatible with sTREM2 exerting a protective effect against neuroinflammatory events secondary to amyloid accumulation. To our knowledge, this is the first report of longitudinal GM changes associated to CSF glial biomarkers.

- Skouras, Stavros; Falcon, Carles; Tucholka, Alan; Gispert, Juan-Domingo; Rami, Lorena; Sanchez-Valle, Raquel ; Lladó, Albert ; Molinuevo, José Luis: ***Neural reserve and functional compensation patterns delineated by eigenvector centrality mapping of the biological continuum from normal cognition to Alzheimer's dementia***. Under review in the journal Human Brain Mapping.