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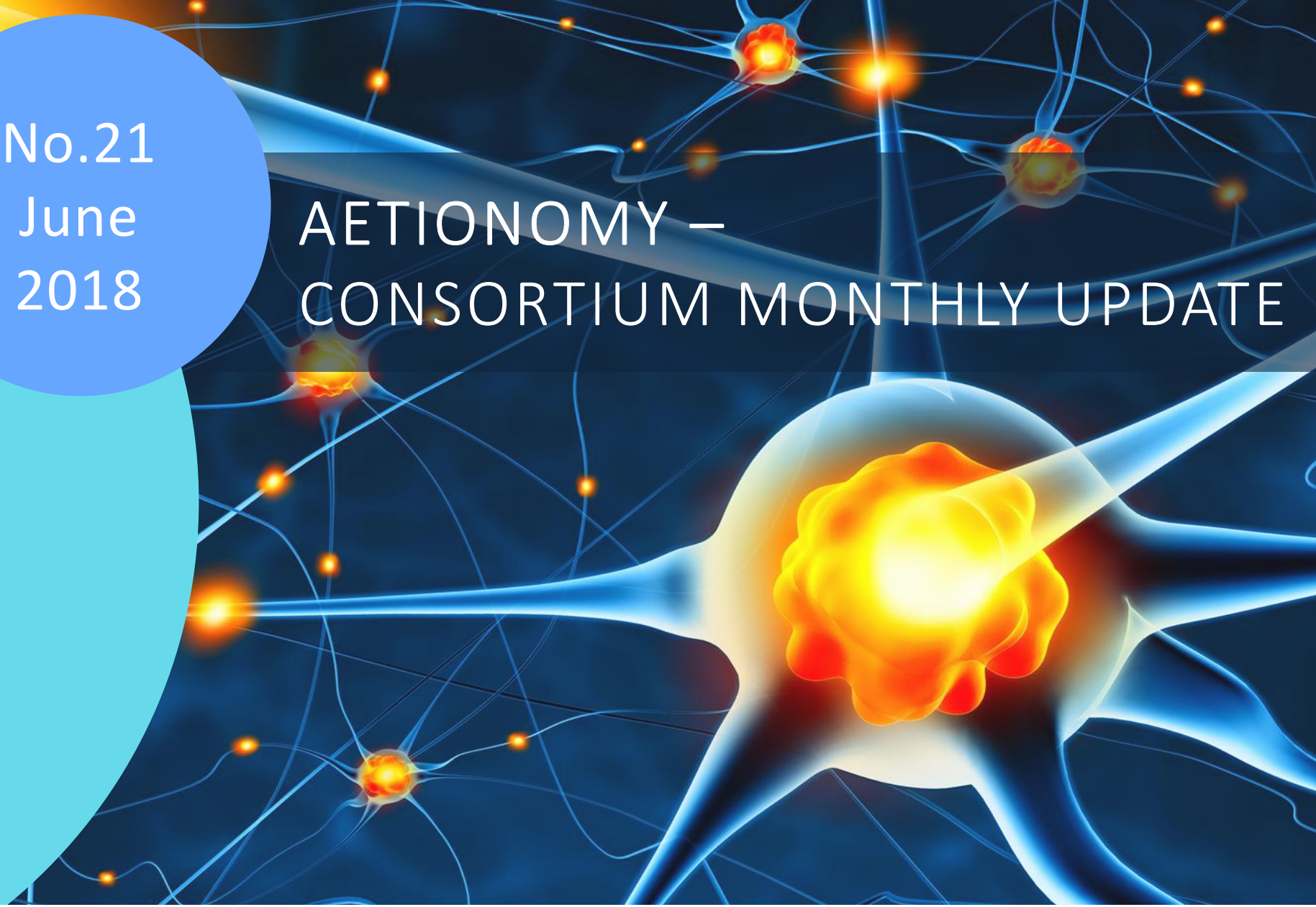
AETIONOMY – CONSORTIUM MONTHLY UPDATE



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AETIONOMY

Message from the Coordinators

Dear AETIONOMY partners,

The summer period is almost upon us, and as this marks the start of our final six months this is an important time to take stock and understand where we are in the life of the project.

Once again the generation of data from our clinical samples is a key delivery, and according to the tables on slide 8 there has been some significant progress but there are still some major deliveries outstanding and some delays. We understand that everyone is working hard on bringing these data to the forefront, but it is clear that the richness of our taxonomy is highly dependent on the analysis and interpretation of these data and further delays jeopardies the quality of these analyses.

The PO will be meeting in early July to explore the outstanding challenges in the project and to understand what we will need to do in order to ensure our joint delivery by the end of the year.

One key element of the consortium delivery that we are clearly lagging on is the quantity of joint publications – we shared a list of potential titles/topics one month ago (see slide 11) but there has been little follow up – please let us re-emphasize the importance not only of our individual publications but also of those joint activities.

We do not mean not to emphasize the progress that is described in the WP updates across the remainder of this newsletter, in particular we should emphases the planning of the Final Symposium which is almost complete, but you must forgive us as a PO for keeping the pressure on despite the holiday season.

We hope you enjoy the break and come back refreshed and enthused to drive the project to its ultimate conclusion for the remainder of the year.

Thanks

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

General Information

Upcoming Meetings

- PO/SC Meeting, Luxembourg, 4/5 July 2018
- ISMB Conference, Chicago, 6-10 July 2018,
- Joint Taxonomy Workshop, Barcelona, 20 Sept 2018
- Final WP3-5 Workshop & Datathon, Barcelona (BBRC), 20 & 21 Sept 2018
- PRECISESADS Conference on Genomics, Granada, 4/5 Oct 2018
- Neuroinflammation School 2018, , Conil de la Frontera, 15-20 Oct 2018
- Final General Assembly and NDD Symposium, Bonn, 29-30 Nov 2018

Reminder that all publications need to be submitted to the Project Office **before** submission, ame 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 2018 (DoW v5.1, Aug 2017)

- D2.5.3.4 (AMU) was due M50
- D3.9.3.1 was due M50
- D3.9.1.4 was due due M52
- D1.4.2 due M55'

In 2018 we need to generate 34 deliverables accordingly the DoW!

WP1 – Governance & Coordination

- The **Annual report for 2017** has been approved by IMI and the Project Office is busy getting the payments ready. Please notify Tobias if your bank account information has changed.
- The **Final Amendment** to the Description of Work, v6.1 was submitted to IMI who came back with minor comments. Approval is imminent and expected very soon.
- The **NDD Final Symposium and last General Assembly** will take place on **29th & 30th November 2018** in Bonn, Hotel Hilton. We expect a representative from each partner to be present at this final conference on neurodegeneration. Please register under the URL: *https://www.aetionomy.eu/en/events/aetionomy-final-symposium.html*
- We would like to point out that there are **34 deliverables due to the end of the year**! The PO again would like to ask all WPs please try to submit the deliverables on time and plan accordingly as we are being measured on this!

WP2 – Knowledge & Data Management

The WP2 team is still incorporating data to the AETIONOMY Knowledge base (AKB) and preparing all the next deliverables which are due in June and July:

- D2.4.2.1 '*Documentation of usability improvement*' will mainly adress restructuring the content of AKB and to simplify the graphical user interface. Users should get quiet an easy overview on the approaches, models, data, and services of the AKB and of course a direct access, if not restricted.
- D2.4.3.2 '*Updated user documentation for pipelines*'. For the integration of pipelines into the AKB we are still incorporating datasets into the ADA server to enable further data analyses and exploration.
- D2.4.3.3 '*Feedback on Public Webinar about the knowledge management Platform*'. In this webinar we will present features, services and data of the enriched and updated AKB.

- We are finalizing **D2.5.3.4**, a '*Manuscript describing the VDC modeling and implementation strategy ready for submission*'. This will be a joint publication of the contributing partners AMU, Fraunhofer, LUH and UCB. A first draft is under discussion.

WP3 – Knowledge Integration & Mining

Also WP3 is working intensively on their deliverables incl. the execution of three webinars:

- **D3.9.1.1** '*Paper on strategies for in silico validation of candidate mechanisms*'. The partners have agreed on an in-silico validation concept. Additionally under the leadership of UCB an analysis plan was generated, which will be the main basis for this deliverable.

- **D3.9.1.3** '*Webinar: Demonstration of high-throughput in silico validation using NeuroMMSig-Server*'.
  This webinar was held on 14th June 2018. Fraunhofer introducing the following topics:
  - NeuroMMSig, the repository of candidate mechanisms stored as computable networks;
  - the **Candidate Mechanism Perturbation Amplitude** algorithm for the scoring of the biological networks and supporting **cause-and-effect modelling of disease mechanisms;**
  - applying this approach for PD (mitochondrial dysfunction) and AD (neuroinflammation).

  First mapping from a data-derived graph to a knowledgebase. The CMPA algorithm enables to identify mechanisms regulated with different intensities in different stages of a disease and regions of brain. Further implementation includes running the CMPA on available NeuroMMSig signatures to get insights of highly perturbed mechanisms specific to the disease stages. The current implementation takes into account only the expression profiles. The algorithm should extended such that influence of genetics, epi-genetics, protein modifications is considered for perturbed mechanisms.
  Further info e.g. slides, report and the recorded webinar can be found on our server: https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/76902

- D3.9.1.4 '*Webinar: Mining on Bayesian representations of major cohort studies (incl. ADNI and PPMI)*'. This webinar was held on 25th June 2018 and informed about this analysis approach and the longitudinal modelling of Parkinson's Disease using Bayesian Networks. Realized by a collaboration between Fraunhofer and UCB the following topics were addressed:
  - completion of data by imputations;
  - aggregation of features into groups for dimensionality reduction;
  - identification of progression biomarkers;
  - Modelling of temporal processes analyzing causal relationships from multi-modal data;
  - estimated success of PD modifying therapeutic trials;
  - analysis of what-if-cases and virtual patient simulation for AD and PD.

  Further info e.g. slides, report and the recorded webinar can be found on our server: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/76902*

- D3.9.3.1 '*Webinar: 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).*'

  This webinar was held also on 25th June 2018 and informed about EMC's analyses of imaging-related candidate mechanisms following three approaches:
  - Genotype-phenotype studies on the Rotterdam Scan Study
  - Genotype-phenotype associations on the ADNI database
  - Event-based modelling approaches on the ADNI data
  - Combining genetics and event-based modelling

  Interesting results, showing insights and trends in the effects of specific genes on gray matter volumes. In our opinion, the outcome of HASE on RSS gives useful data and information for further validation experiments, including non-imaging. Bonferroni is an issue (exploration versus validation).

Decreasing number of pheno- and geno-types can be fruitful; KANSL1 Proxy-SNPs seem to be related with the local shrinking. EBM is a strategy that can provide insight into disease progression mechanisms. Patient staging in DEBM can be used for diagnosis, prognosis, and disease prediction. Stratification of subjects may be possible with this disease staging mechanism. Using SNP-information in DEBM shows interesting results.
Further info e.g. slides, report and the recorded webinar can be found on our server: *https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/77110*

- D3.9.3.2 ‚*Paper manuscript 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)*‘.

  Based on the research presented in the webinar a paper manuscript of the above described experiences and results will be generated and submitted soon.

WP4 – Ethical & Legal Governance

- The AETIONOMY Data Protection Supplemental Agreement has now been signed by all partners continuing to process personal data for the project. The aim of this revised framework is to ensure that data processing in the Project remains compliant with the new EU rules on data protections applicable since the General Data Protection Regulation's entry into operation on 25 May 2018. In this regard, a key function of the Agreement is to encourage transparency, and serve as a practical roadmap for the relevant partners in the remaining phase of the Project, by highlighting and interpreting the most significant measures required to achieve compliance. Here it operates – similarly to the initial AETIONOMY data protection framework that referenced the earlier EU Data Protection Directive – to clarify the duties imposed upon Project partners under the law. Moreover, in reciprocally entering the Agreement, the partners acknowledge their mutual commitment to undertake their important scientific research mindful of the interests and rights of the data subjects, and for the specific and limited purposes of the project.

WP5 – Clinical Validation (1/2)

- **AETIONOMY Sample Plan:** The sample plan has been achieved this month (Table 1).

From	Samples	To	Status	Actual/Estimated date
KI (Prof. Svenningsson)	105 DNA	ICM	OK	26 MARCH 18
	34 CSF	UKB (MH)	OK	4 APR 18
	34 CSF	IDIBAPS	OK	9 APR 18
	23 CSF INSIGHT cohort	IDIBAPS	OK	JUN 18
UKB (Prof. Wuellner)	94 DNA	ICM	OK	26 FEB 18
	40 DNA	ICM	OK	24 APR 18
	23 CSF	KI	OK	28 MARCH 18
	23 CSF	IDIBAPS	OK	5 MARCH 18
	19 CSF	UKB (MH)	NA	Internal transfer
UKB (Prof. Heneka)	240 DNA add. Cohort	ICM	Cancelled	Data transfer
	220 CSF add. Cohort	KI	OK	20 FEB 18
	220 CSF add. Cohort	IDIBAPS	OK	26 FEB 18
ICM (Prof. Corvol)	41 CSF + 14 add. Cohort	KI	OK	7 MARCH 18
	37 CSF + 9 add. Cohort	UKB (MH)	OK	7 MARCH 18
	41 CSF + 14 add. Cohort	IDIBAPS	OK	7 MARCH 18
	318 DNA + 642 add. Cohort	UKB (UW)	OK	11-12 APR 18
	25 CSF (PD/AD/HC)	SARD	OK	5 JUN 18
IM2A (Prof. Dubois)	7 DNA + 364 add. Cohort	ICM	NA	Internal transfer
	23 CSF add. Cohort	KI	OK	9 MAY 18
	23 CSF add. Cohort	IDIBAPS	OK	11 JUN 18
IDIBAPS (Prof. Sanchez-Valle)	137 CSF add. Cohort	UKB (MH)	OK	6 MARCH 18
	118 DNA add. Cohort	ICM	OK	28 MAY 18
	137 CSF add. Cohort	KI	OK	16 APR 18

Table 1: *Final AETIONOMY samples shipment status*

- All the **AETIONOMY Clinical Study** samples and external samples made available by the Consortium have been shared and are being analysed by all the WP5 partners (Table 2).

	N Biospecimen	N processed (to date)	Available results
Genome wide genotyping (ICM) D5.3.2.2	~ 1500 DNA	95% 118 samples to be processed	By 15 July (whole panel)
Methylome of SNCA gene (UKB, UW) D5.3.2.3	~ 1000 DNA	100%	June 2018 completed
Cholesterol panel analysis (UKB, UW) D5.3.2.4	~ 250 Plasma	50 ongoing 200 samples to be processed	July 2018 (whole panel)
Neuroinflammatory markers generation in CSF (UKB, MH) D5.3.2.5	~ 240 CSF	100%	June 2018 completed
YKL40 and AD markers (IDIBAPS) D5.3.2.6	~ 500 CSF	95% 23 samples to be processed	By 15 July (whole panel)
Brain imaging features from YKL40, sTREM and AD markers (BBRC) D5.3.2.7	~ 550 MRI	Waiting for data - Data sharing agreements ongoing - ADNI images processed	July 2018 (if received June)
Proteomic analysis in CSF (KI) D5.3.2.8	~ 700 CSF	95%	August 2018 (whole panel)
+ in plasma	~ 250 Plasma	100%	June 2018 completed
IRS and Autophagy markers in CSF (SARD) D5.3.2.9	~ 330 CSF	25 samples Ongoing	September 2018 (1st batch 25 samples)

Table 2: *Status of AETIONOMY WP5 analyses*

WP5 – Clinical Validation (2/2)

- **AETIONOMY Data Flow Plan:** When results are available, the data are processed as followed:
  - Centralization at ICM
    Result files are transferred
  - Unified identification
    A new AETIONOMY ID is attributed to each line of analysis => 1 sample analysed in different labs will have the same unique ID (the same process is done in regards with each sample associated data, e.g. clinical data)
  - Upload into AKB (tranSMART)
    Re-identified results are accessible to all the WP5 partners

- **AETIONOMY Clinical Study Database:**
  - In total, 1.538 queries have been issued and resolved in regards with the whole data entered in the REDCap eCRF.
  - The access to the eCRF is now closed for all the users and the database is being locked.
  - After a final review, the AETIONOMY Clinical Study database will be analyzed in regards to the study objectives and also uploaded into AKB (planned in July 2018): the clinical data associated to the whole batch of samples collected during the protocol and shared between the WP5 partners will then be available for the analysis of the biomarkers assessed in each lab.
  - The global flow chart on the AETIONOMY Clinical Study population has been established:

    421 subjects recruited (412 PD, 9 AD), i.e. 421 informed consents signed

    9 premature ends of study, i.e. informed consents signed but study not completed because:
    - » 3 SF
    - » 3 withdrawals upon investigator decision
    - » 2 withdrawals upon subject decision (of which 1 agreed for the use of the samples and data collected before withdrawal)
    - » 1 withdrawal because of a SAE (no data collected)

    In total, 413 evaluable subjects:
    405 PD subjects and 8 AD subjects

Important Timelines to Project End

M51	M52	M52	M53	M54	M55	M56	M57	M58	M59	M60	
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**
Data analysis on data sets already available EMIF 1000	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
Oxford PD cohort data being analyzed							Taxonomy 20 Sept Barcelona?				
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		

Publications Corner

Abstract accepted at 11th edition of Clinical Trials on Alzheimer's Disease (CtaD2018): ***Non-core biomarkers (neurofilament light, neurogranin, 14-3-3 and YKL-40) in the Alzheimer's disease continuum, frontotemporal dementia and prion diseases diagnosis.*** To be held in Barcelona, Spain on October 24-27, 2018.

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

SUGGESTED JOINED PUBLICATIONS

Please be reminded that our reviewers requested - as a proof of a successful collaboration – **joined publications** from AETIONOMY partners. A list of proposed publication topics and affiliations is being circulated amongst the consortium members:

https://bscw-biosc.scai.fraunhofer.de/bscw/bscw.cgi/76419

SUGGESTED AETIONOMY JOINT PUBLICATION TOPICS
(more information in Phil's email sent on 1st May 2018)

- AETIONOMY the conclusion
- Mechanism based stratification – Genomics clustering and biomarker validation
- The knowledge base and data catalogue
- PD/AD stratification
- AD risk analysis
- Virtual cohort
- EFPIA data analyses
- Methylation and the AET Cohort
- Neuro inflammation – AET Cohort validation
- BBRC Joint Analysis Imaging and Genomic Features
- Proteomics of the AET Cohort
- Joint PRECISESADS and AETIONOMY publications
  - The analytical approaches – multimodal, multi-omics analyses
  - The different journeys towards a molecular taxonomy