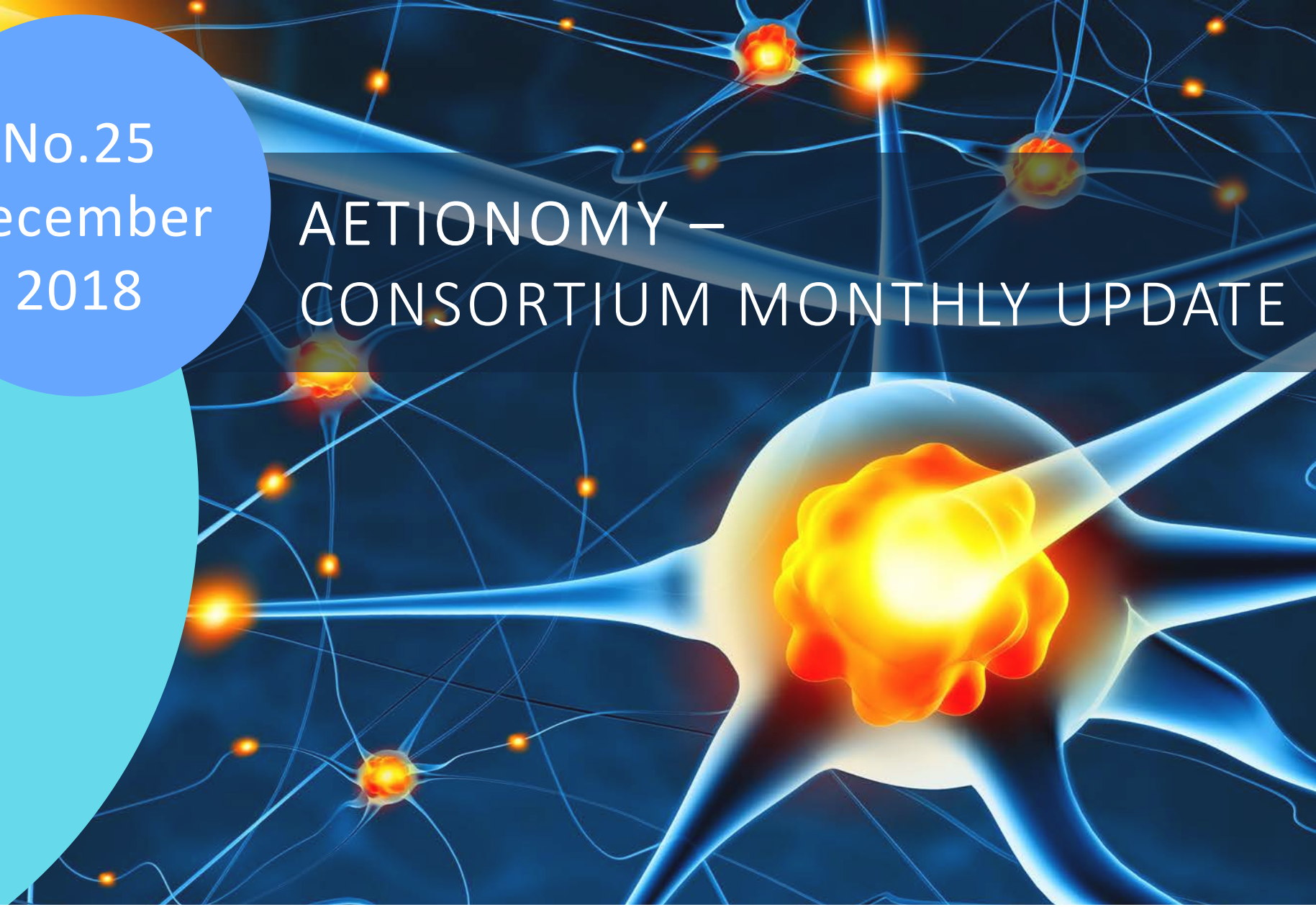
No.25
December
2018

AETIONOMY – CONSORTIUM MONTHLY UPDATE



Inspired by patients. Driven by science.

Fraunhofer SCAI

efpia

imi innovative medicines initiative

AETIONOMY

Message from the Coordinators

Dear AETIONOMY partners,

Reflecting on the project from the perspective of the end of five years (and more for some), it is difficult not to dwell on the challenges and missteps that we faced throughout the project. Nevertheless, despite these setbacks it is clear now that we can look back and be proud of the achievements that have come from participating in this complex alliance between partners.

From the outset, working in a challenging clinical domain and applying a controversial 'data-led' approach meant that the odds were stacked against us.

However, as we explored in the Final Symposium in Bonn, we have good reasons to believe that the taxonomy of complex idiopathic disorders will indeed be modified by approaches like ours. While we are not able to say today that clinical practice has been directly impacted, we have started the ball rolling and hope to see these effects in the not too distant future.

It is important to recognise the fact that our legacy will be felt in many ways, impacting well beyond the confines of the funding period.

From the recognition in the community that reinforce the principles that drove the project from the inception – specifically the need to place a strong emphasis organising the data and knowledge of an entire domain in order to successfully explore it.

To the scientific legacy, both in the investigation of clinical and mechanistic insights in Neurodegenerative disease, but also in the computational method development.

And finally, the project leaves a footprint which will serve our community for years to come. The high quality and well organised data and algorithmic resources, maintained by UL and Fraunhofer, will certainly be the starting point of countless explorations into the complexity of Neurodegeneration in the near future.

All presentations of the Final Symposium including the description of our project outcomes are available on the AETIONOMY Webportal, and, following FAIR principles, the AETIONOMY Knowledge base offers data sets, but also method descriptions, disease models and candidate mechanisms, hypotheses, workflows and web services. Education and training are supported by recorded webinars and tools, providing knowledge discovery, disease modelling and analytics.

From the coordinators and the project office, thank you all for your stimulating debate, your engagement, your scientific, medical and computational insight and your collaboration for the last five years.

We wish you all the very best for the future.

Thanks, your PO

(Phil, Martin, Jacqueline, Stephan and Tobias)

AETIONOMY Partners

Inspired by patients. Driven by science.

Fraunhofer SCAI

Aix*Marseille université Initiative d'excellence

Alzheimer Europe

barcelonaβeta Brain Research Center

Erasmus MC

ICM Institut du Cerveau et de la Moelle épinière

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

Karolinska Institutet Anno 1810

Leibniz Universität Hannover

PHARMACOIDEA

universitätsklinikumbonn

Boehringer Ingelheim

uni.lu Universität Luxemburg

SANOFI

NOVARTIS

UCB

Inspired by **patients.**
Driven by **science.**

UCB as Coordinator has lived and breathed this project since before its inception.

From the proposal generation, to the call stage, to meeting the consortium and the leading partner (Fraunhofer), to the finalization of the Grant Agreement and Project Agreement, through the kick-off meeting in Brussels and the myriad of amendments and agreements, plus teleconferences and face-to-face work-package meetings and general assemblies, and now through to the end of the final report which we will submit next year - we have seen deep commitment from many parts of the organisation.

As a PO we have worked side by side with Tobias, Stephan and Martin bringing leadership and ensuring the project runs to time and deliverables are properly managed – this has been necessarily administrative at times but the final results show how important it was to achieve our collective goals.

As partners in work packages we have brought expertise from bioinformatics and data science, data management and governance, legal and ethical, statistical analysis and design, clinical-study execution and a range of other contributions along the way.

Throughout the project we have had a leading role in that data analysis components of the project, in both early stages in partnership with Karolinska, and particularly in the later stages of the project in close partnership with Fraunhofer and ICM. The latter has lead to the development of novel computational methods to validate the stratification potential of disease mechanisms and to link these mechanisms to disease risk . More specifically, a highly predictive AD risk machine learning model (Khanna et al., Sci Rep 2018) and a joint clustering of AD and PD patients based on convergent genetic features have been developed, hence making a first step towards a molecular disease taxonomy. In addition, partnership with AMU and Fraunhofer has lead to the development of a first computational approach for realistic simulation of longitudinal clinical patient trajectories, realizing the concept of a Virtual Dementia Cohort (manuscript submitted).

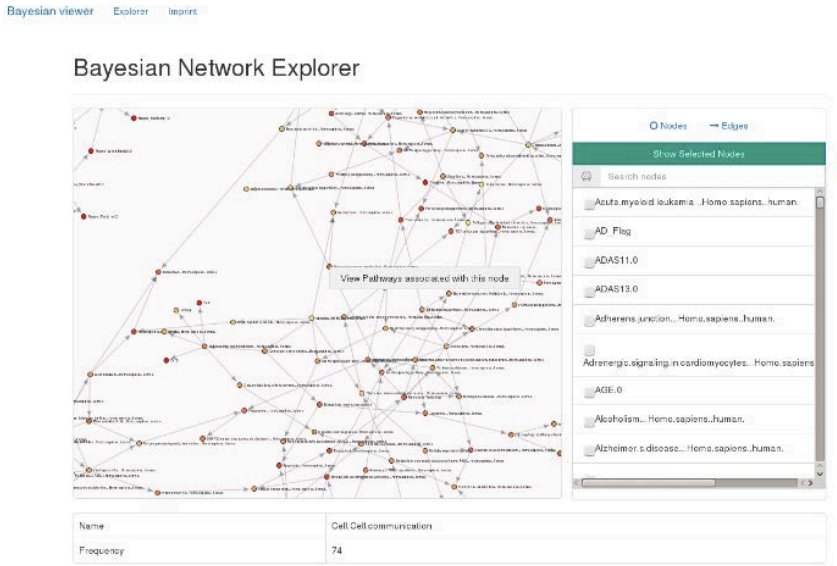
From the monthly bulletins, the Steering Committee Meetings, the General Assemblies, the workshops and the symposiums, it is possible to tell the entire story of the project and it is only reflecting on this which allows us to realize just how far we have come and how the legacy will continue beyond the project end.

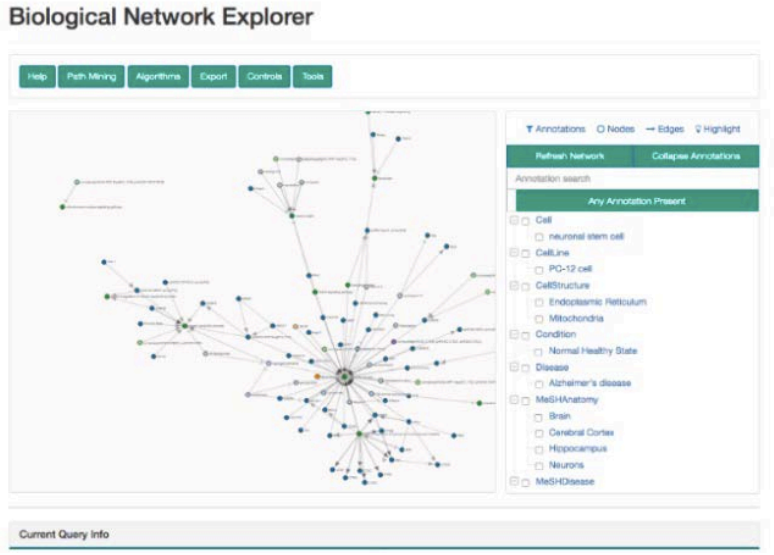
Thank you all for being part of this journey.

Fraunhofer

Fraunhofer has initiated the AETIONOMY project with assembling the academic part of the consortium in 2013. We, and other academic partners, did not start from scratch: we all brought important disease models, data, tools, and analysis strategies to the project. Some of these resources had an impact on the modelling and validation of the taxonomy and have proven their value already. The overall concept of “organising knowledge and data that is out there” rather than starting yet another “biomarker fishing expedition” has been shown to work really well.

Fraunhofer has contributed major elements of the AETIONOMY success story. Amongst the highlights are the generation of the comprehensive inventory of disease mechanisms and its implementation in the mechanism-enrichment server NeuroMMSig. Furthermore, we have developed part of the AETIONOMY knowledge base, curated data and knowledge at an unprecedented scale and turned knowledge about disease mechanisms into computable models that could be used in stratification experiments.



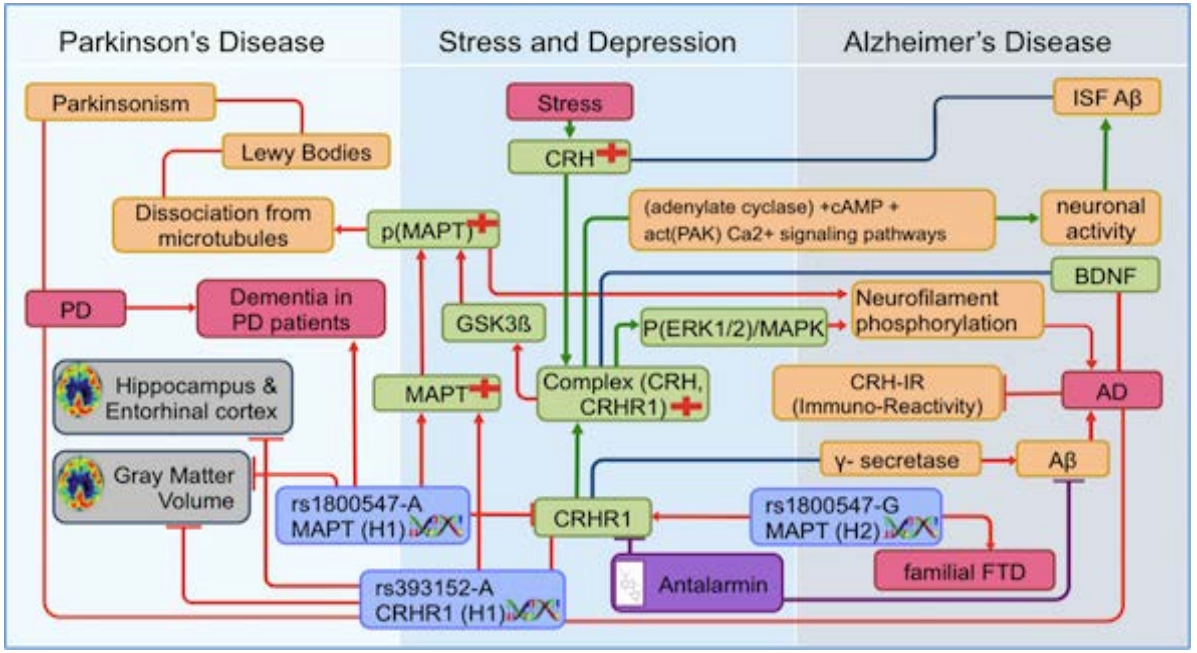


Fraunhofer

Fraunhofer SCAI

Most important: the ”Shared mechanism hypothesis” identified and published by a systematic computational analysis of “Genetics variation shared by AD and PD” has lead to the identification of one strongly discriminating / stratifying mechanism context that does not only link AD and PD, but also reaches out to the world of quantitative neuropsychiatry through the stress sensor HPA axis.

Fraunhofer is proud to have contributed not only to the administration of the project (and at this point again a big THANK YOU to Stephan Springstubbe, Tobias Rechmann, Meike Knieps on the Fraunhofer side and Jacqueline Marovac, Phil Scordis on the UCB side), but also actively stirred the project by strategic decision making. To pick an example: The inclusion of the lab of Prof. Viktor Jirsa (Univ. Aix Marseille) into AETIONOMY has helped, to build a bridge from our IMI project to the Human Brain Project.

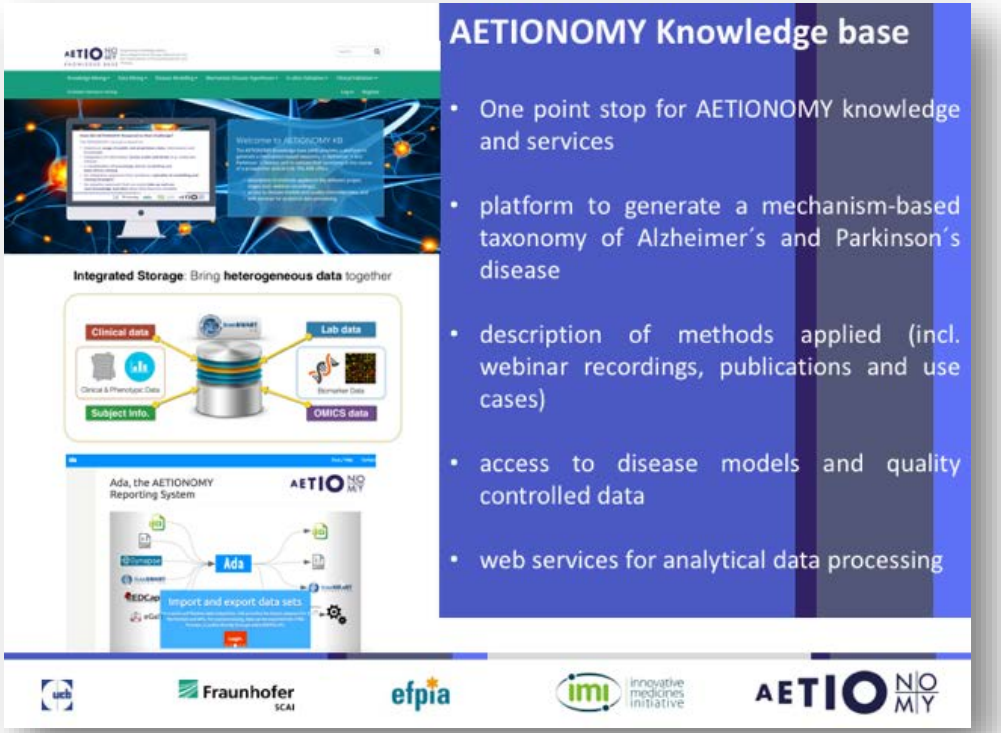


University of Luxembourg

During the span of the AETIONOMY project we have systematically collecting publicly available and proprietary data contributed by academic and pharmaceutical industry partners. All of the available data has been brought together into a single repository and can be mined to identify new molecularly defined subgroups of patients with Alzheimer disease and Parkinson disease. All curated data, the entire semantic framework and all disease models are being made 'publicly' (sometimes in compliance with restrictions defined by the data owners) available to the scientific community via the AETIONOMY Knowledge base (AKB).

You can access the AKB at: https://data.aetionomy.scai.fraunhofer.de/

The AKB includes a tranSMART and an Ada component that holds clinical data and data from neuroimaging studies. We have designed the AKB to target specific user groups with linked information relevant to them. Potential information identified to be beneficial to different target group are organised into section where they will be redirected to relevant and specific information.



University of Luxembourg

For awareness, training and quick access (direct links) to data sets, information and especially services for beginners or new users and to help users, we have consolidated webinars, tutorials a nd use cases for each service or tool.

Check out our webinar for an overview of the AKB and the services we offer:
https://www.aetionomy.eu/en/media/webinars.html

After the duration of the AETIONOMY project in Dec 2018, the AETIONOMY Knowledge Base will continue to be maintained for another 5 years.
All clinical and public datasets will be available for access through a Data Access Committee.
The disease models and services will continue to be developed and updated regularly.

BBRC

barcelonaβeta
Brain Research Center

BBRC has performed several analysis related to AETIONOMY. In the first place, we have shown that age-corrected YKL-40 levels were increased in prodromal AD versus preclinical and dementia due to AD and showed an inverse u-shaped association with p-tau values. A similar nonlinear relationship was found between gray matter volume and YKL-40 in inferior and lateral temporal regions in MCI and AD. These observations reveal that CSF YKL-40, a biomarker of glial activation, is associated with a cerebral structural signature distinct from that related to p-tau neurodegeneration at the earliest stages of cognitive decline due to Alzheimer Disease (AD). Secondly , BBRC has performed a mechanism-focused analysis of brain imaging features from YKL40 and AD markers (abeta 42, tau) using data from two samples with distinct pathologies (AD and Parkinson Disease (PD)). We analysed parameters from diffusion-weighted images and looked for possible common associations between diffusion metrics and CSF markers across the two subject groups, as a potential reflection of shared neurobiological mechanisms independent from the pathology.

Finally, we have also performed probabilistic tractography on two independent samples that include control and preclinical AD individuals, patients diagnosed with mild cognitive impairment (MCI) due to AD and AD patients and were able to identify white matter changes between subsequent disease stages and, notably, also in preclinical AD.

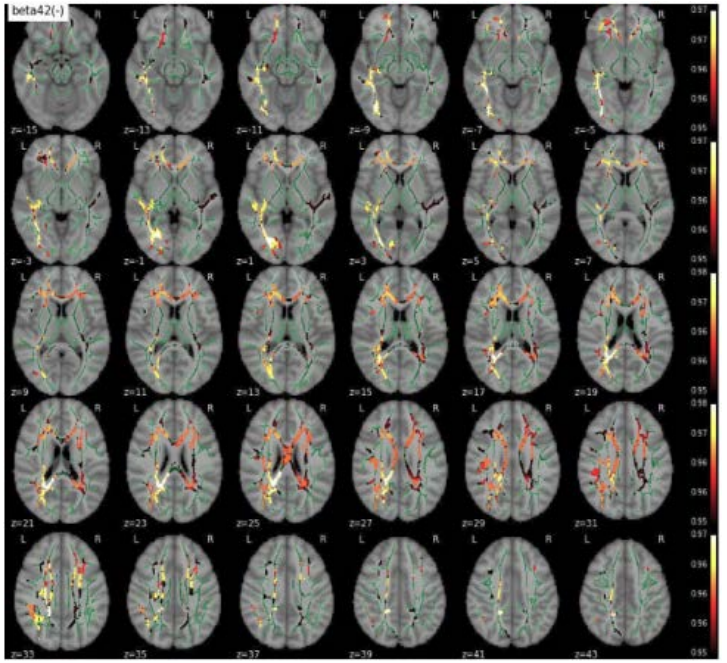
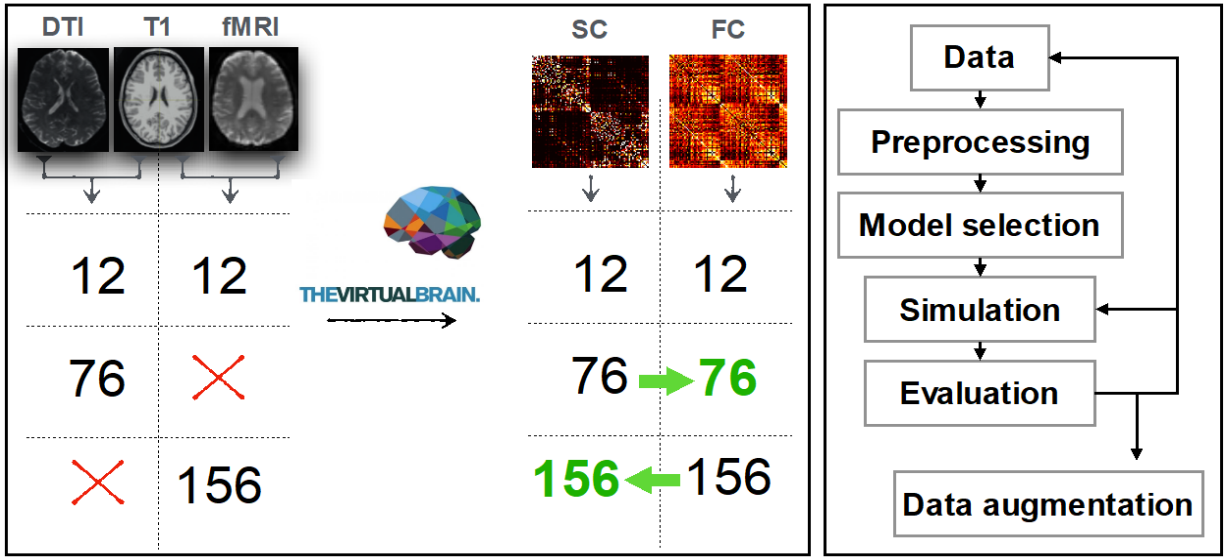


Figure: Negative association between levels of Aβ42 and mean diffusivity in a group of subjects with two distinct pathologies (AD and PD)

AMU

The AMU partner in AETIONOMY has provided proof of concept of generatively modelling a Virtual Brain Cohort. They demonstrated the viability of generating personalized virtual Structural and Functional Connectivity (SC and FC) derived from DTI and fMRI respectively, in order to complete incomplete data in the ADNI database. In this project, after pre-processing the structural and functional connectomic data for a total number of 244 subjects, AMU used mean-field whole brain models from The Virtual Brain (TVB) neuroinformatics platform, to fill the gaps in ADNI, as shown in the figure below.

After optimizing the parameters in neural-mass models, the simulated results were validated against 12 subjects, for which their SC and FC were simultaneously available. Establishing a systematic workflow, they generated surrogate data of a large number of virtual subjects based on the statistics of the original 12 real subjects (data augmentation).



UKB - AD

At the UKB laboratory of Michael Heneka, work focused on neuroinflammation as a pathological hallmark of neurodegenerative disorders and on methods of inflammatory biomarker detection. While evidence for involvement of the immune system in neurodegeneration grows year by year, until today it is difficult to trace these processes by specific biomarkers. Work at the lab included screening for new promising markers with advanced techniques (https://www.sciencedirect.com/science/article/pii/S016502701730287X?via%3Dihub) as well as optimization of techniques for quantitation of already well-known immune mediators. By this approach, biomarker candidates were continuously updated and added to already existing panels

Starting 2016, the lab analyzed 399 cerebrospinal fluid (CSF) samples from its local UKB biobank, a study that was published in spring 2018 (https://alzres.biomedcentral.com/articles/10.1186/s13195-018-0353-3). This study showed that previously contradictory results found in the literature might be caused by limitations of assay techniques, whereas detectable inflammatory biomarkers were associated with tau pathology rather than diagnosis. Discriminative power of immune biomarkers appeared to be limited, though.

Finally, in 2018, the lab received 217 CSF samples from non-demented (ND), MCI, AD and IPD patients from the collective cohorts of AETIONOMY, ICEBERG and IDIBAPS. At the same time, CSF samples from the previously published UKB cohort were shared with the AETIONOMY WP5 partner labs.

In the AETIONOMY/ICEBERG/IDIBAPS samples, a panel of 21 immunity biomarkers was measured (data for YKL-40 were kindly shared by Raquel Sanchez-Valle from IDIBAPS). Data were analyzed comparing clinical groups and other clinical features and associations with pathology-biomarkers amyloid and tau. Furthermore, results were compared to literature and the data of the UKB dataset.

In brief, this comparison showed effects for nearly all of the markers selected for the panel. Multiple previous findings were validated. Predominantly, immune biomarker changes were associated to pathology hallmark markers such as amyloid or tau rather than clinical diagnosis.

UKB - AD

In particular, multiple markers showed age-dependent trajectories that changed between individuals with presumable neurodegeneration (as measured by tau isoforms) independent of their clinical diagnosis.

This effect was reproducible in both the AETIONOMY/ICEBERG/IDIBAPS as well as the UKB cohorts. Furthermore, biological covariates such as APOE genotype and sex, but also technical factors such as the pre-analytical protocol used for sample preparation were found to be highly influential for immune biomarker levels. In conclusion, immune biomarker levels are associated with pathological amyloid levels and neurodegeneration independent of the clinical diagnosis, reflecting brain pathology rather than symptoms.

However, immune marker levels require stratification for covariates, in particular aging, sex and pre-analytics, to reveal their full potential.

These findings highlight promising directions for further research and support the stratification potential of immune / inflammatory markers for neurodegenerative disorders.

A publication including detailed results and analysis of this data is in preparation. All data from these datasets are available in the AETIONOMY knowledgebase.

UKB – PD

universitäts klinikum bonn

Epigenetics of Parkinson's disease

DNA-methylation was chosen among the mechanisms to be tested in order to create a mechanism-based taxonomy of neurodegenerative diseases as several lines of evidence pointed to the involvement of epigenetic mechanisms in neurodegenerative disorders (1). In the initial investigations in existing cohorts, we first identified differential methylation of the alpha – synuclein (SNCA) gene (2) and second also differential methylation of other genes (3) in Parkinson's disease (PD) patients, ie phosphodiesterase (PDE) 4 and Meteorin, Glial Cell Differentiation Regulator-Like (METRNL). SNCA is prominently involved in PD, as the expressed protein is the main component of intraneuronal protein aggregates (Lewy bodies) and was initially identified as the non-amyloid component (NAC) of plaques in Alzheimer's disease (4). PDEs have 3',5'-cyclic-AMP phosphodiesterase activity and degrade cAMP, which acts as a signal transduction molecule. PDE regulates the cellular levels, localization and duration of action of these second messengers (cAMP).

Metrnl is expressed in undifferentiated neural progenitors and in the astrocyte lineage, including radial glia and plays important roles in both glial cell differentiation and axonal network formation during neurogenesis. Upon completion of the AETIONOMY prospective study that had recruited 421 subjects, the changes of DNA methylation in these genes, i.e. SNCA, PDE4D and METRNL have been investigated in greater detail with regard to available meta data, in particular tobacco smoking and coffee consumption. Apparently, the additional information of exposure and gender improved the accuracy of the observed changes which might suffice as a biomarker for a subgroup of PD patients. While a meta-classifier of the investigated genes alone achieved a specificity of ~ 0.65 for men with a sensitivity of ~ 0.55; with the additional information the specificity rose to ~ 0.9 and a sensitivity of ~ 0.9 for current smokers among the male PD patients. We will continue to develop this potential biomarker further in the future.

UKB – PD

universitäts klinikum bonn

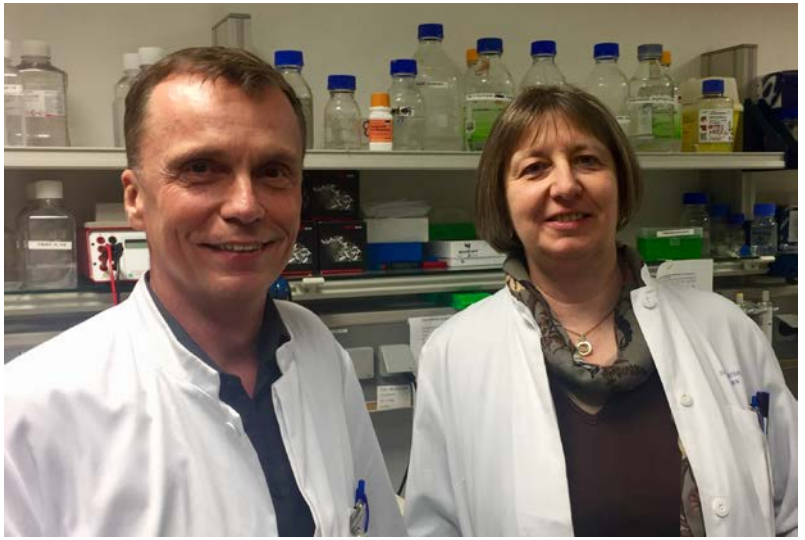
Literature

1) Luca Lovrečić, Aleš Maver, Maja Zadel and Borut Peterlin. The Role of Epigenetics in Neurodegenerative Diseases. 2013 InTech http://dx.doi.org/10.5772/54744

2) Schmitt I, Kaut O, Khazneh H, deBoni L, Ahmad A, Berg D, Klein C, Fröhlich H, Wüllner U. L-dopa increases α-synuclein DNA methylation in Parkinson's disease patients in vivo and in vitro. Mov Disord. 2015 ;30(13):1794-801. doi: 10.1002/mds.26319. Epub 2015 Jul 14.

3) Epigenome-wide DNA methylation analysis in siblings and monozygotic twins discordant for sporadic Parkinson's disease revealed different epigenetic patterns in peripheral blood mononuclear cells.Kaut O, Schmitt I, Tost J, Busato F, Liu Y, Hofmann P, Witt SH, Rietschel M, Fröhlich H, Wüllner U. Neurogenetics. 2017;18(1):7-22. doi: 10.1007/s10048-016-0497-x. Epub 2016 Oct 6.

4) Culvenor JG, McLean CA,Cutt S, Campbell BCV, Maher F, Jäkälä P, Hartmann T, Beyreuther K, Masters CL and Li Q-X. Non-Aβ Component of Alzheimer's Disease Amyloid (NAC) Revisited NAC and α-Synuclein Are Not Associated with Aβ Amyloid Am J Pathol. 1999 Oct; 155(4): 1173–1181.



LUH

Leibniz Universität Hannover

WP4 developed an innovative data protection framework for regulating the flow of sensitive health data in the Project between data providers, UL's tranSMART data management system, and partners using the data to carry out research.
This placed binding reciprocal obligations on the parties to ensure their use of the data was legally and ethically compliant, including by respecting the wishes of participant data subjects and ensuring highest standards of data security.
The framework was customized to diverse Project data-flows, and proved adaptable and scalable, being extended to new data flows, and new partners as the Project evolved.
Subsequently it was updated in the later stages of the Project to maintain compliance with the new EU data protection regime, following the entry into force of the new General Data Protection Regulation (GDPR) 2016/629.
In addition the Work package engaged in a detailed legal and ethical analysis of the implications of the prospective clinical study in WP5 with its aim of stratifying patients into distinct AD and PD patient subgroups, as well as wider societal implications of such studies and the trend to personalized medicine. This also included assessment of other options, such as creating and using virtual patient cohorts, as well as considering issues arising from collection and analysis of genetic materials, such as information feedback and ongoing data/sample stewardship obligations.

Regulation (EU) 2016/679

European Union regulation	
Title	Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (Data Protection Directive)
Made by	European Parliament and Council of the European Union
Journal reference	L119, 4 May 2016, p. 1–88
History	
Date made	14 April 2016
Implementation date	25 May 2018
Preparative texts	
Commission proposal	COM/2012/010 final – 2012/0010 (COD)
Other legislation	
Replaces	Data Protection Directive
Current legislation	

BI

Boehringer Ingelheim

The team at Boehringer Ingelheim believe that the knowledge base and methods developed throughout the AETIONOMY project will act as a roadmap and a rich resource of information for investigators in the field of neurodegenerative research.

Although Boehringer Ingelheim is no longer strategically invested in undertaking neurodegenerative disease research, our team believe the biological insight gained during AETIONOMY will greatly add to ongoing research efforts. As such the team are currently embarking on re-purposing efforts to utilise both the modelling approaches and data mining techniques developed in this project.

It is our opinion that methods including the longitudinal disease progression modelling, ComPath and resources such as NeuroMMSig will provide valuable insight in future research.

For further extending the AETIONOMY concept and in close collaboration with SCAI, a literature data-based approach with a new concept of target identification for neuropsychiatric disorders has been developed. A matrix has been generated, allowing the identification of novel interacting neuronal circuits in their functional context and environment.

The tool allows to visualize the interrelation between multiple neuronal circuits comprising psychiatry-related information. The expectation is that this matrix tool will reveal contexts for target identification, which have yet escaped notice.

Pharmacoidea

PHARMACOIDEA

Heparan sulfate proteoglycans (HSPGs) are emerging as novel targets in neurodegenerative disorders. HSPGs have been implicated in several pathogenic features of Alzheimer's disease (AD), including its colocalization with amyloid plaques. A number of HSPGs, including two members of the syndecan family of HSPGs – a conserved family of transmembrane proteoglycans – are significantly increased in human AD brains and through modulating Aβ aggregation and clearance they promote amyloid pathology. Syndecans were also found to be associated with the majority of senile plaques in AD brains.

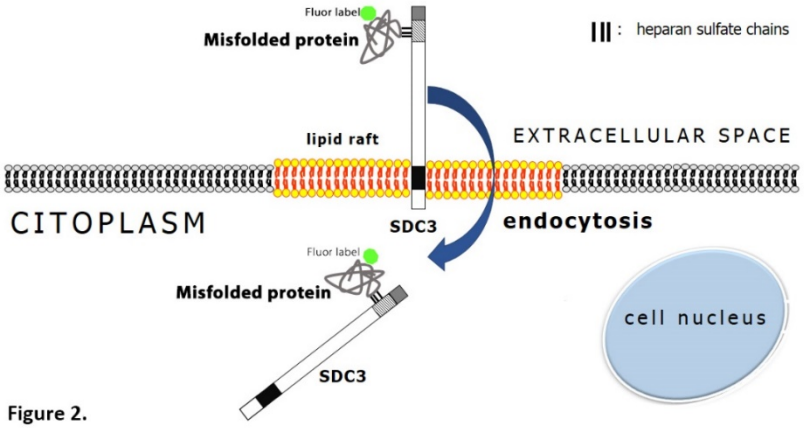


Figure 2.

Considering the growing evidence on the involvement of syndecans in neurodegeneration, Pharmacoidea (PHI) has been analyzing the contribution of syndecans (SDCs) to key pathophysiological steps of neurodegeneration, including aggregation and cellular internalization of the amyloid beta peptide (Aβ). Utilizing SDC specific cellular assays, PHI demonstrated that SDCs overexpression trigger the aggregation and subsequent cellular internalization of Aβ (Fig. 1). PHI's data highlight SDCs, especially the neuron-specific syndecan-3 isoform, as important players in amyloid pathology and show that SDCs, regardless of cell type, facilitate key molecular events in neurodegeneration.

Figure: SDC overexpression trigger the aggregation and subsequent cellular internalization of misfolded proteins involved in neurodegeneration.

ICM

The prospective, observational, cross-sectional, multicenter, European AETIONOMY Clinical Study (AETIONOMY-CS) was designed in 2014 by WP5 clinicians and received a regulatory approval in 2015, under the INSERM sponsorship and the ICM coordination. After 2 years of subjects' recruitment (Dec 2015 to Dec 2017), the ICM and all the WP5 partners involved in the AETIONOMY-CS have achieved the aim of collecting clinical data, biological samples (blood, DNA, CSF and skin biopsies) and brain imaging data from PD patients (idiopathic or genetic), subjects at risk for PD and matched healthy controls, in order to validate the patient stratification biomarker hypotheses generated by WP3 and WP5.

An overall population of 405 evaluable PD subjects and controls was recruited. In addition, all partners contributed by providing clinical data and biological samples from their own cohort leading to a large number of samples and data to be analyzed by the Consortium, in both PD and AD groups. After centralization at the ICM, all the results and associated clinical datasets were shared into the AETIONOMY Knowledge Base, allowing the partners to get access to all the needed datasets and covariates, for combined and/or further analysis.

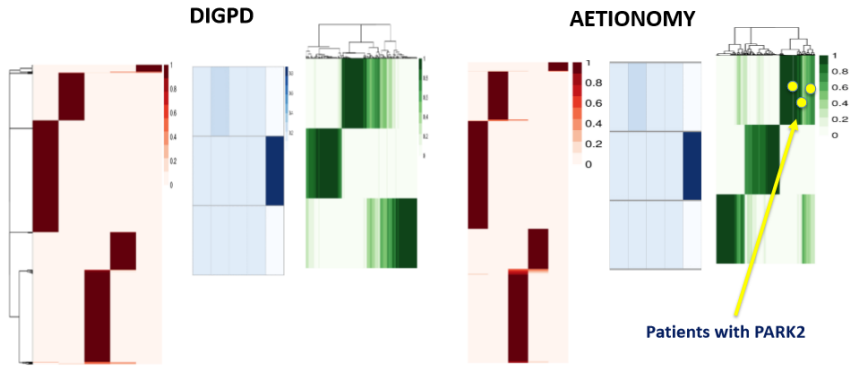
Clinical				
IDIBAPS	IDIBAPS AD CSF	AD	137	Demographic Clinical Neuropsychological Biospecimen Genetic Proteomics Analysis (KI) Inflammatory Analysis (IDIBAPS) Inflammatory Panel (UKB)
	IDIBAPS AD Screening	AD	17	Demographic Clinical Neuropsychological MRNA/miRNA Expression
	IDIBAPS AD Validation	AD	35	Demographic Clinical Neuropsychological MRNA/miRNA Expression
	IDIBAPS AD Dementia	AD	164	Demographic Clinical Neuropsychological
ICM	INSIGHT	AD	23	Demographic Clinical Neuropsychological Environment Proteomics Analysis (KI) Inflammatory Analysis (IDIBAPS)
	DIGPD	PD	409	Demographic Clinical Neuropsychological Biospecimen Medication Environment
	GenePark	PD	360	Demographic Clinical Neuropsychological
	NGC/ PD Repository	PD	5011	Demographic Clinical Neuropsychological
	PD Transcriptomic data	PD	36	Demographic mRNA/miRNA Expression
	ICEBERG	PD	93	Demographic Clinical Neuropsychological Biospecimen Medication Environment Proteomics Analysis (KI) DNA Methylation analysis (SNCA, METRNL, PDE4D) Inflammatory Analysis (IDIBAPS) Inflammatory Panel (UKB)
AETIONOMY Consortium Subject data: ICM, Karolinksa, IDIBAPS, UKB (AD & PD) Analysis: Proteomics : Karolinska Astroglial Inflammation: IDIBAPS Inflammation: UKB AD(Heneka) PD Methylation: UKB PD (Wuellner)	AETIONOMY PD	PD	405	Demographic Clinical Neuropsychological Biospecimen Medication Environment Proteomics Analysis (KI) Inflammatory Analysis (IDIBAPS) Inflammatory Panel (UKB)
	AETIONOMY AD	AD	8	Demographic
UKB AD (Heneka)	UKB AD Inflammation 2	AD	220	Demographic Clinical Neuropsychological Biospecimen Proteomics Analysis (KI) Inflammatory Analysis (IDIBAPS)
	UKB AD Inflammation	AD	399	Demographic Clinical Neuropsychological
	UKB AD Cytokine	AD	95	Demographic Clinical Neuropsychological
UKB PD (Wuellner)	UKB Methylation PD	PD	1057	Demographic Clinical Methylation Analysis
EMC	Imaging ADNI	AD	57	BIGR Connectome Freesurfer
Public Resources				
ARRAY EXPRESS/GEO (Fraunhofer/ UL(eTRIKS))	AD Public Studies	AD	43 Studies	Demographic
	PD Public Studies	PD	16 Studies	Demographic Clinical mRNA/miRNA Expression

ICM

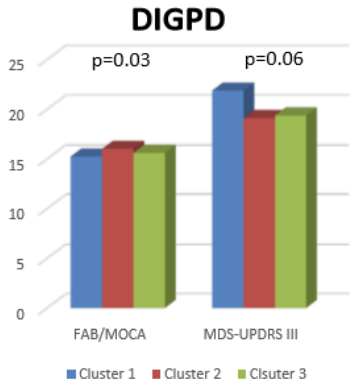
At the ICM, we did a genomic based stratification and we found 3 clusters of PD patients with different profiles. These results obtained in the DIGPD cohort were replicated in the AETIONOMY-CS cohort.

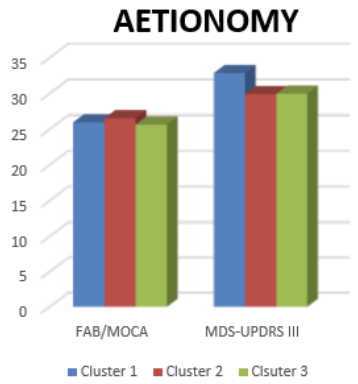
The correlation with the biological markers, generated by all the partners, particularly the proteomic analysis, will successfully mark the official end of the AETIONOMY project, with our final report on the "*Final validation of the initial taxonomy draft*".

Replication in the AETIONOMY cohort



Similar variant map profile
Similar number of patients in clusters
Similar relationship with mechanisms





EMC

The final contributions/results from EMC to AETIONOMY were based on a combination of genotype-phenotype (HASE) associations and discriminative event-based modeling (DEBM), both developed at EMC. Patient staging in DEBM can be used for diagnosis, prognosis, and disease prediction. Also stratification of subjects may be possible with this disease staging mechanism.

One of the interesting results was that sub-cohorts from the ADNI-database (controls and AD patients), created by splitting on the base of the APOE epsilon4 alleles (0, 1, or 2), showed a different timing in biomarkers becoming abnormal. In the sub-cohort with APOE=2, there seem to be more 'normals' with already slightly abnormal (imaging) biomarkers.

A second important result from the work at EMC in the last period was to see which part of the hippocampus is showing atrophy earlier if ADNI-subjects are positioned further on the disease staging pipeline. FreeSurfer 6.0, a well-known image segmentation tool, is able to split the hippocampus in MR data into subparts (Figure 1). In the outcome of DEBM-staging (Figure 2), it can be seen that the tail of the hippocampus is shrinking early, as is known from the international literature.

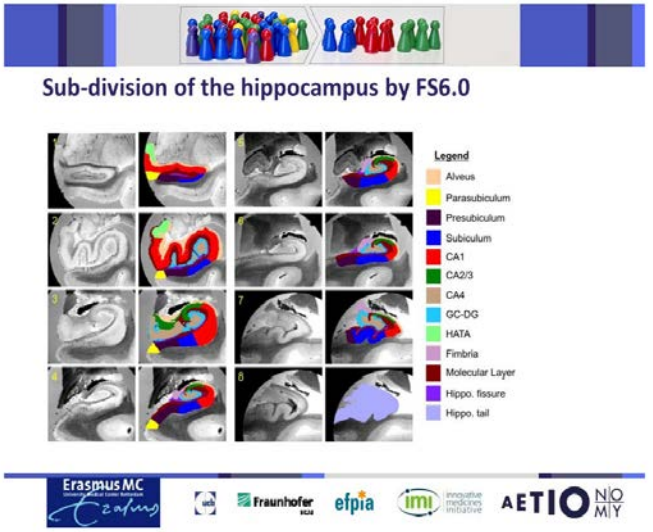


Figure 1: A nice feature of FreeSurfer V6.0 is that it has an advanced model to segment twelve subparts of the hippocampus, an important structure regulating the short-term memory.

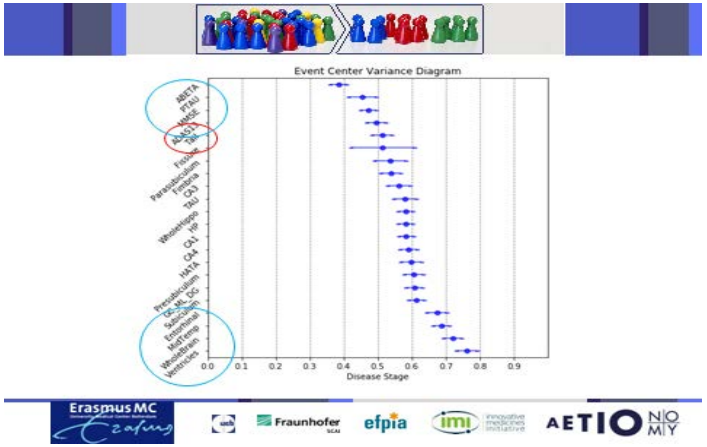


Figure 2: Results from Discriminative Event-Based modeling (DEBM) after including hippocampus subparts and other imaging and non-imaging measurements as biomarkers. Experiments were carried out on the ADNI-database.

Alzheimer Europe

Over the course of the project, in collaboration with the University of Hanover, Alzheimer Europe has contributed towards important ethical debates linked to various issues which arose and which were relevant to the lives and wellbeing of people with Alzheimer's and Parkinson's disease. Examples of this contribution include reports on the major ethical issues linked to the projects (such as data governance, consent issues, the management of incidental findings, promoting the wellbeing of participants etc.) and more recently involvement in discussions surrounding the concept of a virtual brain cohort and the retention and possible sharing of data beyond the end of the project in the context of the GDPR (e.g. linked to balancing protection of data with participants' own interest in the maximum use of their data, as well as issues related to the possible need for further consent for the re-use of data).

Alzheimer Europe has also been an active member of the Legal and Ethical Advisory Board.

Sanofi

A team at Sanofi was dedicated to progress AETIONOMY project .The concept of redefining diseases taxonomies on a mechanism based rational is of value to provide better and right treatment to the Patient.

The AETIONOMY Sanofi sub-team has contributed with wet-lab biomarker analysis in WP5 in collaboration and alignment with industrial and academic partners - some results will be communicated for one part this week (and later added to the AETIONOMY Knowledge Base) and the other part before the end of the year. Sanofi has also contributed by putting lots of efforts in the WP3 (Data Mining and Patient Stratification) which enabled cross fertilization of the team (knowledge, processes) at the contact with our colleagues from the public research.

AETIONOMY had the ambitious goal of tackling this problem in the field of neurodegenerative diseases (Parkinson's and Alzheimer's diseases) and the consortium reached some interesting goals which we are determined to translate as much as possible in actions to enable the discovery of new drugs for Alzheimer's and Parkinson's patients.

Beyond neurodegenerative diseases, we believe that the model developed during the AETIONOMY consortium is a role model and will surely have an impact on the development of sister models for other diseases. One example is the fruitful interaction that we had the opportunity to develop with the PRECISESADS colleagues who are working on the difficult topic of unravelling the complexity of autoimmune diseases.

Finally, the Sanofi-AETIONOMY team is thanking all members of all organizations that have contributed to the AETIONOMY consortium and made it being a success.

We wish you all, a nice end of the year 2018 and many successes for Year 2019!

Novartis

Novartis contribution was primarily as co-lead of Work package 5, with input to clinical trial protocol design and implementation. We had best intentions to provide samples but this has turned out to be an impossible endeavour with privacy hurdles that only increased over time - a big lesson learned to think further ahead.

Not to be forgotten are the two General assemblies hosted by Novartis: first one in Barcelona remembered by a small bar in Bario Gotico saving us with a glass of Cava from heavy rain, and the second in Basel by the ships passing by on the Rhine (but both of course also with intense scientific exchanges).

IDIBAPS

Institut D'Investigacions Biomèdiques August Pi i Sunyer

In the last period of this fruitful collaborative project, IDIBAPS analysed YKL40 and AD markers (abeta42, tau, ptau) of the whole samples (controls , PD and AD patients), including samples received from the different centres plus subject from IDIBAPS new cohort. The results were delivered to WP5 leaders in an excel file format.

Publications: Multi-biomarker analysis paper (IDIBAPS);
In preparation: **Synaptic, axonal damage and inflammatory CSF biomarkers in neurodegenerative dementias**
Anna Antonell, Adrià Tort-Merino, José Ríos, Mircea Balasa, Sergi Borrego, Josep M. Auge, Cristina Muñoz-García, Beatriz Bosch, Neus Falgàs, Lorena Rami, Oscar Ramos-Campoy, Kaj Blennow, Henrik Zetterberg, José Luis Molinuevo, Albert Lladó*, Raquel Sánchez-Valle*.

Karolinska Institute

Protein Array experiment at SciLife/KTH/Karolinska Institutet

Quality check has been performed from the data of the protein array which covered 824 CSF and plasma samples from patients with Parkinson´s disease, Alzheimer´s disease and controls. Data from 216 proteins, which were covered by 307 antibodies, is being analyzed with different statistical pproaches and stratified with clinical outcomes. As shown in the figure 1, the overall signal is similar for the different cohorts.

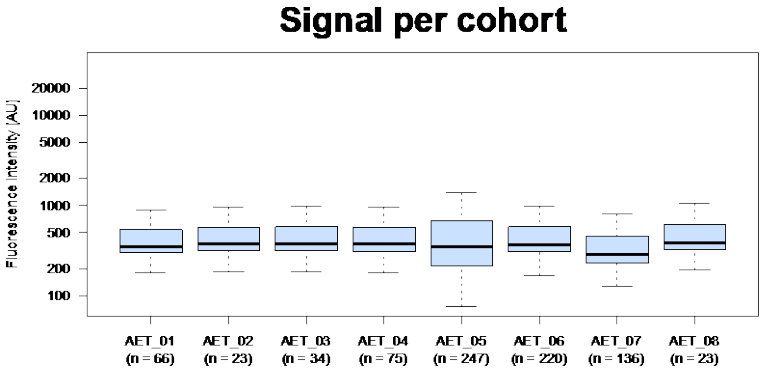


Figure 1. Total signal for all antibodeis from each of the studied cohorts.

For the analysis, a particular emphasis is being put on proteins regulated in a disease-specific manner in the different cohorts (Figure 2).

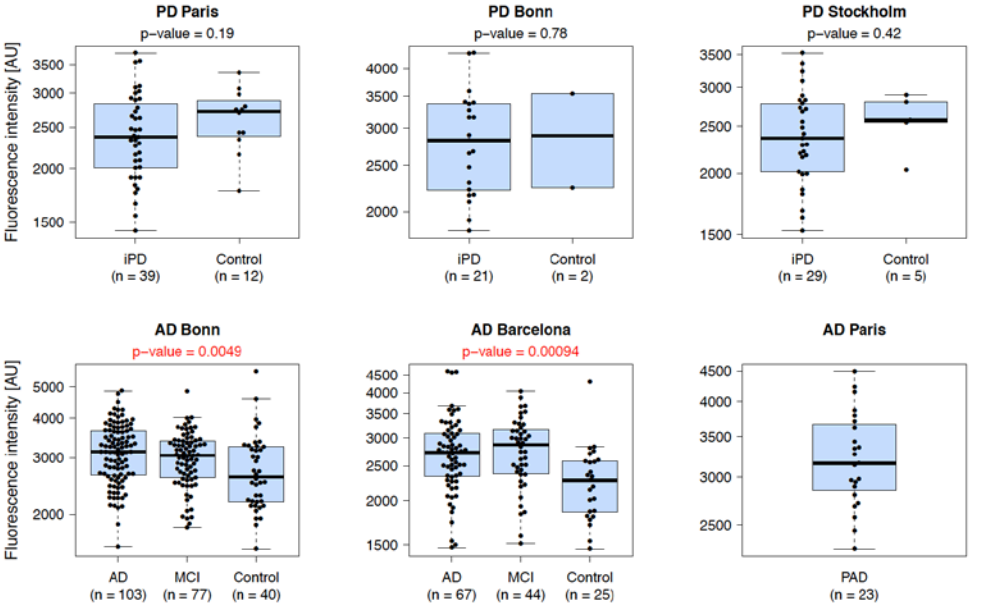


Figure 2. Regulation of Aquaporin 4 in CSF samples from the different cohorts. Note the significant difference in the Alzheimer cohorts.

In particular, the 39 proteins, covered by 70 antibodies, that specifically covered AETIONOMY-based mechanisms are being investigated. A manuscript is currently being written up based on the initial analysis.

General Information

Important Dates

- Project ends officially, 31 December 2018
- Final report draft to PO: 25 January 2019
- Finances & CFS to PO: 15 February 2019
- Final report due to IMI, 28 February 2019

Deliverables due to IMI

D5.3.2.9

- Neuroexosomes levels in plasma and CSF: results available through AETIONOMY knowledge base

D5.3.3.2

- Report on the validation of the taxonomy through biomarkers of mechanisms: one or two pathways validated for PD and AD

Reminder that all publications need to be submitted to the Project Office before submission, same for Congress abstracts, etc.! **Open Access** is encouraged for all publications.

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 written in capital letters?

AETIONOMY

2018 | 2019

ORGANISING KNOWLEDGE ABOUT NDD MECHANISMS FOR THE IMPROVEMENT OF DRUG DEVELOPMENT AND THERAPY

Thank you all for 5 years of collaboration and for helping us to realise our vision.

We wish you a Merry Christmas and a happy and successful 2019.

Phil, Martin, Jacqueline, Stephan and Tobias