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Newsletter Issue 4

**AETIONOMY – Organising Knowledge about
Neurodegenerative Disease Mechanisms for the
Improvement of Drug Development and Therapy**

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Professor Martin Hofmann-Apitius**

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EDITORIAL

Towards a mechanism-based taxonomy of Alzheimer's and Parkinson's Disease

The AETIONOMY project will generate a refined taxonomy and testable mechanisms underlying the derived stratification of patients.

The main objective of the AETIONOMY clinical study is to test in real clinical samples the validity of the hypothesized underlying pathogenic mechanisms of Alzheimer's (AD) and Parkinson's disease (PD). Although not fully understood, the pathophysiology of neurodegenerative diseases results from the complex interplay between several biological pathways. It is thus likely that the maps generated by the AETIONOMY project will comprise several distinct biological hypotheses and subgroups of patients defined by 1 or more of these hypotheses. The AETIONOMY clinical study will assemble a state of the art standardized clinical, brain imaging, and biological dataset from AD patients, PD patients and healthy controls to validate the model(s) proposed by the AETIONOMY project. The Consortium will identify potential pathogenic pathways (established and novel) involved in AD and PD and will deliver surrogate markers which serve as readouts of the involved pathways. The model will be considered validated if the selected makers allow subject stratification in the AETIONOMY clinical study according to what has been postulated in the model.

AETIONOMY has assembled a consortium of expert clinicians and scientists to build upon (i) considerable public domain resources generated by large international communities (e.g. the Neuroscience Information Framework [1]), and (ii) results from ongoing IMI projects (e.g. DDMoRe [2], OpenPHACTS [3], eTRIKS [4], EMIF [5]), providing a unique combination of tools and expertise to discover the core criteria that make for a good drug target and, in so doing, classify patients according to these criteria.

The AETIONOMY protocol has been submitted to French Regulatory Authorities and national Ethical Committees. Final approvals have been obtained in France (22&29 April 2015), in Germany (21 December 2015) and in Sweden (25 November 2015). The first subject was included in September 2015.

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GENERAL APPROACHES

Identification of underlying pathogenic Mechanisms

Presently, neither in AD nor in PD do we have a clear understanding of the molecular and cellular mechanisms underlying the aetiology of the disease even in the familial forms where the phenotypes can vary despite a common mutational starting point. As a consequence, AETIONOMY aims at modeling disease in a way that allows for the generation of testable hypotheses on possible mechanisms underlying AD and PD.

The identification of these hypotheses requires mining strategies that follow different routes, as there is most likely not "one golden path" (one algorithmic approach) that bears all the problem-solving potential. **We have therefore decided to follow several mining approaches that make use of all available data and that may take a priori knowledge into account:**

- An **unbiased approach** that starts with clustering of clinical data and aims at identifying measurable outcomes that together form a mechanistic context that can be tested. This approach is completely unbiased and is not imposing any restriction to the type of measurable variable that is used – as long as it can be interpreted in an (anatomical and) functional context
- A **model-driven mining approach** that makes extensive use of a priori knowledge (including even scientific speculation and hypotheses) and that combines a knowledge-driven with data-driven approaches.

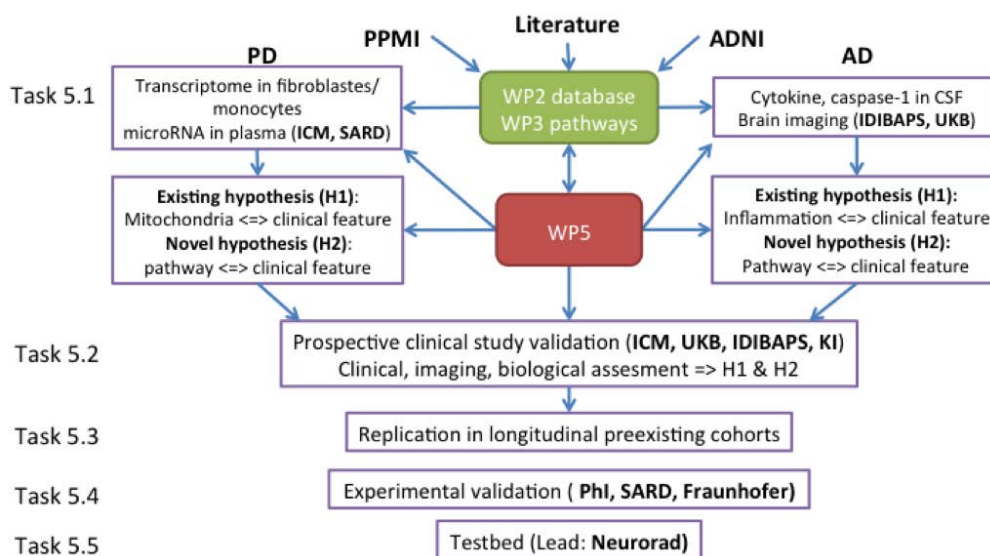


Figure: WP5 approaches for hypothesis generation

AETIONOMY PROSPECTIVE STUDY

Collecting standardized clinical, biological dataset, and brain imaging

The AETIONOMY clinical study is one of the main tasks of WP5 which is lead by Prof Jean-Christophe Corvol (ICM) and Dr Ana Graf (NOVARTIS).

CROSS-SECTIONAL STUDY

- Recruitment period: 2 years
- Assessment period: max. 90 days
- 4 countries: France, Germany, Spain and Sweden

POPULATION TO BE RECRUITED (total n=655)

PD groups (n=325):

- Idiopathic PD (n=240)
- Genetic PD with mutation in Parkin, LRRK2 or GBA (n=40)
- Subject at risk of PD: first degree relatives or iRBD (n=45)

AD groups (n=150):

- MCI/Prodromal AD (n=90)
- Preclinical AD (n=60)

Healthy controls (n=180):

- 90 matching PD
- 90 matching AD

ASSESSMENTS

- Clinical history and motor examination (PD)
- Environmental questionnaires
- Neuropsychological assessments
- Brain imaging (AD only)
- Standardized biosampling: blood, CSF, fibroblasts

Recruitment has started in September 2015 and up to now 62 subjects (50 PD, 12 Controls) have been recruited. AD patients will be recruited through the AETIONOMY collaboration partner EPAD as described on page 11.

PARTNER PROFILES

Joint Expertise for clinical Research

The sponsor of the AETIONOMY clinical study is INSERM, a French public organisation for Health Research. INSERM is assisted by the European Clinical Research Infrastructures Network (ECRIN) for the protocol submission, the ICFs translation and adaptation to country specific requirements in Germany and Sweden. WP4 partners from LUH and Alzheimer Europe have reviewed the protocol and the Informed Consent Forms to assess legal and ethical issues. An eCRF through REDCap services is used to collect data stored at University of Luxembourg (WP2). Data management and statistical analysis are in charge of UCB.

ICM

INSTITUT DU CERVEAU ET DE LA MOELLE ÉPINIÈRE



The Institut du Cerveau et de la Moelle épinière – ICM (Brain & Spine Institute) – is an international brain and spinal cord research center whose innovative concept and structure make it the only institute of its kind in the world. The ICM brings patients, doctors and researchers together with the aim of rapidly develop treatments for disorders of the nervous system and enable patients to benefit from them as quickly as possible.

The best scientists from all backgrounds and countries come together at the Institute to perform leading-edge research in this area. To help researchers advance in their work and give patients tangible reasons for hope, we must all play a role: government agencies, corporate actors and individuals. No one can afford to idly stand by, because this fight is vital to every one of us.



Prof. Jean-Christophe Corvol (Paris, France)

Professor of Neurology at the Pitié-Salpêtrière Hospital (Assistance Publique Hôpitaux de Paris). Prof. Corvol is the head of the Clinical Research Center for Neurosciences Parkinson's disease, and co-chair of the French clinical network for Parkinson's disease and movement disorders (NS-PARK network/FCRIN, INSERM). His fields of research are the molecular basis, genetics and pharmacology of Parkinson's disease. Prof. Corvol leads the clinical work-package (WP5) for AETIONOMY and is the Principal Investigator of this multi center study and has recruited 35 patients to date.

Novartis Pharma AG



Novartis Pharma AG is a multinational pharmaceutical company based in Basel, Switzerland with approximately 100,000 associates in 140 countries worldwide. Novartis focuses on discovering, developing and successfully marketing innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life. Our products are concentrated in the major therapeutic areas Cardiovascular and Metabolism, Oncology and Hematology, Neuroscience and Ophthalmics, Respiratory, and Immunology and Infectious Diseases. The Novartis Neuroscience portfolio includes products covering Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and Schizophrenia.

Novartis is committed to innovative research and development of new tools for drug development, and participates in collaborative research projects with other industrial and academic participants. For example Novartis actively participates in a number of consortia and public private partnerships under the Critical Path Initiative, in the European InnoMed PredTox program for non-clinical safety assessment as well as in 31 of the already running and planned Innovative Medicines Initiative projects.

In Aetionomy, Novartis is EFPIA-lead for WP5.



Ana Graf, MD (Basel, Switzerland)

Global Program Head, Neuroscience at Novartis

Neuroscience drug development, in particular Alzheimers disease over 20+ years in all areas of clinical development, from first-in-man to post-submission activities. Involved in regulatory submissions, consultations with HAs (including CHMP, FDA, Japan).

IDIBAPS



The Hospital Clinic is a university hospital founded in 1906, which serves as a community hospital, and is the main public provider within its district in Barcelona. It also serves as a high-complexity tertiary hospital, and is recognized as an institution of reference, both domestically and internationally. A significant part of the hospital's research activities are coordinated by the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). The Alzheimer's disease and other Cognitive Disorders Unit (ADCDU) is a clinician-based unit focused in the diagnosis, treatment and research in neurodegenerative disorders that present with cognitive decline. The ADCDU is a leading centre, nationally and internationally, in the study of preclinical and prodromal Alzheimer's disease. It also focuses on early onset cognitive impairment and genetically determined dementias, with a dedicated genetic counselling program for monogenic dementias (PICOGEN).

The research activity of the ADCDU is carried out at the facilities of the Neurological department of the Hospital Clinic (Outpatient clinic and Day Care unit) and at the research laboratory on neurodegenerative diseases (IDIBAPS).



Prof. José Luis Molinuevo, MD, PhD, (Barcelona, Spain)

He is a clinical researcher at the IDIBAPS and also directing the early detection program of the Pasqual Maragall Foundation. He is also a member of the European Alzheimer's Disease Consortium (for therapeutic and intervention studies), he also is part of the Alzheimer's Biomarker Standardization Initiative (ABSI), the Spanish Coordinator of the BIOMARKAPD of the Joint Programming on Neurodegenerative Diseases, member of the dementia panel for the European Federation of the Neurological Societies and part of the International Working Group for developing new research criteria. He is principal investigator or co-investigator of multiple clinical trials and research studies on AD and will contribute patients to the AD portion of the AETIONOMY study via EPAD.

Karolinska University Hospital and Institutet



Karolinska University Hospital is one of Scandinavia's premier health facilities. Together with the world-respected Karolinska Institutet, it contributes to the improvement of human health by conducting research and education. Since 1901 the Nobel Assembly at Karolinska Institutet has selected the Nobel laureates in Physiology or Medicine.

The Movement Disorder Unit at Karolinska University Hospital follows patients with different diagnoses among which Parkinson's disease is the most common. We follow around 1200 Parkinson's disease patients and have established a cross-sectional cohort of patients with Parkinson's disease at different stages. Investigations involves biomarker sampling and careful clinical examinations. Clinical data are registered in the national Parkinson's disease register.



Prof. Per Svenningsson (Stockholm, Sweden)

Professor of Neurology at the Departments of Neurology and Clinical Neuroscience at the Center for Molecular Medicine (www.cmm.ki.se) at Karolinska Institutet and Karolinska University Hospital. He heads a research group with medical background working at the clinic or with clinical samples and with animal and cellular models of Parkinson's disease or depression. The team is focused on improving neuro-psycho-pharmacological treatment in Parkinson's disease with an emphasis of non-motor symptoms. He is also Principal Investigator in the AETIONOMY study with his team and has recruited 21 patients to date.

Neuromed / Neurorad Imagistic Center



Neurorad is a diagnostic imaging center founded in 2002 in Timisoara, Romania. It is associated with the Neuromed Diagnostic Imaging Center established in 1999 as a private healthcare company. The main field of business of the center is represented by the high performance magnetic resonance (MRI) and computed tomography (CT) investigations, used in all the medical fields nowadays, in the absence of which the high quality medicine is no longer conceived.

Within Neuromed center the modern equipment is used by experienced physicians and operators. The images obtained are of the highest quality, a more precise diagnostic being enabled. The personnel structure of the center consists of 160 employees. Neuromed currently owns equipment like Siemens magnetic resonance scanners (MRI), computed tomography scanners and radiology devices.

During the 17 years of operation, Neuromed became a reference medical diagnostic center very well known in the country, both by the physicians and by the patients. The accuracy and the precision of the radiology images and the diagnostics are the elements that recommend us and that have a major utility within the clinical medicine.



Dr. Stanca Ples (Timisoara, Romania)
Vice-President of Neuromed and
Senior Neurosurgeon at "Pius Brinzeu"
Emergency County Hospital of Timisoara, Romania.

Neurorad participates in the AETIONOMY study by scanning 400 Alzheimer's disease patients for the generation of the neuro-image gold standard. To date 24 patients have been scanned.

UNIVERSITAETSKLINIKUM BONN (UKB)



University Hospital Bonn (Universitaetsklinikum Bonn) is the Center of Medical Research and Education of the University of Bonn. The University Hospital Bonn is a legal person on its own. Two groups from the Department of Neurology are participating in AETIONOMY: the research team of Prof. Heneka (for AD) and the research group of Prof. Wuellner (for PD). Both researchers are also affiliated with the German National Centre for Dementia Research (DZNE).



Prof. Michael T. Heneka (*Bonn, Germany*)

Professor (W3) for Clinical Neurosciences at the Rheinische Friedrich-Wilhelms-Universität Bonn. Since 2010 Prof. Heneka has been the Neurological Director of the joint Memory Clinic of the Departments of Psychiatry and Neurology (Clinical Treatment and Research Center, KBFZ), University Hospital Bonn. He will contribute by recruiting AD patients into the AETIONOMY study.



Prof. Ullrich Wuellner (*Bonn, Germany*)

Research fellow in Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Associate Professor at the Dept. of Neurology, Univ. of Bonn, Head of movement disorder clinics and the gene bank project of the "Kompetenznetz Parkinson", group leader at the German Centre for Neurodegenerative Diseases (DZNE).

He will contribute by recruiting PD patients into the AETIONOMY study and has recruited 5 patients to date.

EPAD COLLABORATION

Creating an Alzheimer's Disease Platform

In March 2015, the Innovative Medicines Initiative (IMI) and its AETIONOMY, EMIF and EPAD projects announced the creation of the IMI Alzheimer's Disease Research Platform. The platform will facilitate collaboration between the three projects, helping them to deliver results faster.

The announcements came during a symposium held at the 12th International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD 2015), and in the wake of a major World Health Organization (WHO) conference on dementia.

Dementia already affects over 35 million people globally, and as populations age, this figure is set to rise to over 115 million by 2050. The disease places a huge and growing burden on health and social care systems and on the families and carers of those affected. Yet despite decades of research, there is still neither treatment nor cure for the disease.

- The challenge of developing new, effective treatments for dementia is simply too great for any organisation to tackle alone, and so IMI has launched a number of projects that bring together leading experts from the pharmaceutical industry, universities, small biotechs, and patient organisations from across Europe and beyond. The three projects in the new IMI Alzheimer's Disease Research Platform have a combined budget of €138 million and address complementary areas of Alzheimer's disease research.
- AETIONOMY is paving the way towards a new approach to the classification of neurodegenerative diseases, particularly Alzheimer's and Parkinson's diseases, thereby improving drug development and increasing patients' chances of receiving a treatment that works for them.
- EMIF is developing a common information framework of patient-level data that will link up and facilitate access to diverse medical and research data sources, opening up new avenues of research, particularly in the fields of Alzheimer's disease and obesity.

EPAD [6] is pioneering a new, more flexible approach to clinical trials of innovative Alzheimer's disease treatments designed for people who have the disease but have not yet developed dementia.

In order not to duplicate efforts in terms of subjects recruitment, AETIONOMY intends to access data and samples from EPAD in lieu of recruiting own subjects for the cross-sectional study. Subjects will not be signing an informed consent for both EPAD and Aetionomy.

DISSEMINATION

Publications and References

We do emphasize the role and importance of joint publications, reflecting the close collaboration between industrial and academic partners in AETIONOMY, which will soon be intensified.

PUBLICATIONS

Gautier C.A., Erpapazoglou Z., Mouton-Liger F., Muriel M.P., Cormier F., Bigou S., Duffaure S., Girard M., Foret B., Iannielli A., Broccoli V., Dalle C., Bohl D., Michel P.P., Corvol J.C., Brice A., Corti O.:

The endoplasmic reticulum-mitochondria interface is perturbed in PARK2 knockout mice and patients with PARK2 mutations.

Accepted by human molecular genetics in May 2016.

Wüllner U., Kaut O., deBoni L., Piston D., Schmitt I.:

DNA methylation in Parkinson's disease

Accepted in April 2016 for publication in Journal of Neurochemistry.

Suárez-Calvet M., Kleinberger G., Araque Caballero M.Á., Brendel M., Rominger A., Alcolea D., Fortea J., Lleó A., Blesa R., Gispert J.D., Sánchez-Valle R., Antonell A., Rami L., Molinuevo J.M., Brosseron F., Träschütz A., Heneka M.T., truyfs H., Engelborghs S., Sleegers K., Van Broeckhoven C., Zetterberg H., Nellgård B., Blennow K., Crispin A., Ewers M., Haass C.:

STREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers

Published by EMBO Molecular Medicine, Volume 8, Pages 466–476, 2016

Sánchez-Valle R., Monté G.C., Sala-Llonch R., Bosch B., Fortea J., Lladó A., Antonell A., Balasa M., Bargalló N., Molinuevo J.L.:

White Matter Abnormalities Track Disease Progression in PSEN1 Autosomal Dominant Alzheimer's Disease.

Published in Journal of Alzheimer's Disease, Volume 51, No. 3, Pages 827–835, 2016

Schmitt I., Kaut O., Khazneh H., deBoni L., Ahmad A., Berg D., Klein C., Holger Fröhlich H., Wüllner U.:

L-dopa increases α -synuclein DNA methylation in Parkinson's disease patients in vivo and in vitro.

Published in Movement Disorders, Volume 30, Issue 13, Pages 1794–1801, November 2015

Gispert J.D., Rami L., Sánchez-Benavides G., Falcon C., Tucholka A., Rojas S., Molinuevo J.L.:

Nonlinear cerebral atrophy patterns across the Alzheimer's disease continuum: impact of APOE4 genotype.

Published in *Neurobiology of Aging*, Volume 36, Issue 10, Pages 2687–2701, October 2015

Valech N., Mollica M.A., Olives J., Tort A., Fortea J., Lleo A., Belén S.-S., Molinuevo J.L., Rami L.:

Informants' Perception of Subjective Cognitive Decline Helps to Discriminate Preclinical Alzheimer's Disease from Normal Aging

Published in *Journal of Alzheimer's Disease*, Volume 48, No. s1, Pages 87–98, September 2015.

REFERENCES

- [1] <http://www.neuinfo.org>
- [2] <http://www.ddmore.eu>
- [3] <http://www.openphacts.org>
- [4] <http://www.etriks.org>
- [5] <http://www.emif.eu>
- [6] <http://www.ep-ad.org>

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More information:

www.aetionomy.org

www.ep-ad.org

www.imi.europa.eu