ERA-NET Neuron

NEWSLETTER 30

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News From NEURON Cofund

14 projects were chosen for funding under the fourth Joint Transnational Call (JTC) of ERA-NET NEURON Cofund on "Mental Disorders", 2018.

The Mid-Term Symposium of JTC 2016: "External Insults to the Nervous System", will take place in Bonn, January 2019, followed by the meeting of NEURON's Network Steering Committee.

From the desk of the coordinator | December 2018

Marlies Dorlöchter

The ERA-NET NEURON organizes annual foresight symposia to explore scientific cutting-edge fields. In the past two decades conceptual frameworks to understand the roles of biomarkers and clinical markers themselves were specifically developed in cancer. In view of the significance of brain disorders, NEURON thus set out to explore 'Biomarkers in Neurology and Psychiatry' with a scientific symposium organized by INSERM and CNRS in May 2018 in Nice, France.

The term "biomarker" or "biological marker", refers to a broad subcategory of medical signs or biological measurements – that are objective indications of medical state observed from outside the patient. The biomarkers include clinical signs measured using specific

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More information can be found on our website
http://www.neuron-eranet.eu/index.php
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rating scales, measurements on biological tissues, and even imaging or physiologic measurements. They are particularly useful for an accurate diagnosis, the follow-up of the disease progression, to test the efficacy of the treatments and even to monitor their side effects. With the new developments in the field of human imaging and the new genetics, molecular and biochemical technics called "omics", the field of biomarkers for human disease is in a crucial period of evolution.

Thus, it was timely to learn about the progress of 'biomarkers' in the area of brain disorders, their specific conditions, advantages and challenges. The symposium joined highly reputed researchers from different scientific disciplines and we are indeed glad to present to our distinguished readers on the following pages the essence of their lectures.

Marlies Dorlöchter.

Speakers of the Symposium 'Biomarkers in Neurology and Psychiatry', Nice, France. From left to right: Toni Andreu, Etienne Hirsch, Frauke Zipp, Heleen Riper, Marlies Dorlöchter, Bernard Poulain, Giovanni Frisoni, Kaj Blennow, Alexandra Durr, Chris Turck, Andrea Wutte, Luc Mallet

Symposium on 'Biomarkers in Neurology and Psychiatry'

Kaj Blennow

Cerebrospinal fluid biomarkers for diagnostics of neurodegenerative and inflammatory disorders

Kaj Blennow
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A biomarker is an objective measure of a biological or pathogenic process that can be used to evaluate disease risk or prognosis, guide clinical diagnosis and monitor therapeutic interventions. For Alzheimer's disease (AD), cerebrospinal fluid (CSF) biomarkers have been developed to monitor the main pathological hallmarks of the disease. These include CSF total tau (T-tau) reflecting the intensity of neuronal degeneration, phosphorylated tau (P-tau) reflecting brain tau pathology, and ß-amyloid protein (Aß42 or Aß42/40 ratio) reflecting cortical Aß deposition into plaques.

These core CSF biomarkers have very consistently been found to have high diagnostic accuracy for AD, early in the very early stages of disease. Low CSF Aß42 also show high concordance with another biomarker, amyloid PET, that measures amount of brain amyloidosis. Further, high CSF T-tau adds to predict progression of symptoms, while high CSF P-tau adds specificity to differentiate from other brain disorders. Last, the novel synaptic biomarker neurogranin is seemingly specific for AD.

The AD CSF biomarkers are key in research diagnostic criteria for AD, and in the recent National Institute of Aging – Alzheimer's Association (NIA-AA) biological definition of AD, and are increasingly used for clinical diagnosis in the assessment of patients with suspected AD.

New technical and analytical developments based on ultra-sensitive techniques also allow for precise quantification of these biomarkers in blood samples, and recent publications suggest that it may be possible to use blood tests as screening tools for neurodegeneration and brain amyloidosis.

Biomarkers for Psychiatric Disorders

Chris W. Truck

Chris W. Turck
Max Planck Institute of Psychiatry, Munich, Germany

Major Depressive Disorder, Bipolar Disorder, Anxiety Disorders, Schizophrenia are psychiatric disorders with complex multidimensional phenotypes that overlap. As a consequence, the diagnosis of psychiatric disorders presents a great challenge and often suffers from imprecise disease classification. Recent efforts to develop new antidepressant drugs have by and large been unsuccessful in part due to the uniquely human symptoms of psychiatric disorders that make translation from preclinical models to clinical endpoints difficult.

Biomarkers, defined as objectively measured characteristics that reflect physiological, pharmacological and disease processes, are critical to improve diagnosis and drug development efforts in psychiatry. For diagnostics, biomarkers would be beneficial to pre-symptomatically detect disease and follow its path. In the area of drug development, biomarkers are indispensable for patient group stratification and monitoring clinical treatment response. Biomarkers can also add valuable information to genetic studies and for an improved understanding of psychiatric disorder pathobiology by delineating affected molecular pathways. Whereas genetic biomarkers can indicate individual differences for disease susceptibility, protein and metabolite biomarkers are dynamic molecular entities that allow monitoring therapy response. The delineation and clinical laboratory implementation of molecular biomarkers in blood, the preferred specimen for routine analysis, is the ultimate goal. More than 100 FDA-approved protein-based plasma or serum analytes are presently measured in clinical laboratories, most of them with immunoassays. Examples are cardiac troponin for myocardial infarction, C-reactive protein for inflammation and cardiovascular risk and PSA for prostate cancer. Unfortunately, no such biomarkers are available for psychiatric disorders.

Our laboratory is using mouse models that represent defined aspects characteristic for psychiatric disorders for biomarker discovery efforts. Inbred mouse strains kept under controlled environmental conditions exhibit homogeneous phenotypes. Although mouse models can never mimic the complexity of psychiatric disorders they are able to represent selected endophenotypes. Mice also share cellular and molecular processes with humans and are frequently used to test the efficacy of new drug candidates.

A particular focus of our studies is the antidepressant treatment response that is presently unpredictable for patients suffering from Major Depressive Disorder. Our goal is to delineate molecular pathway activities that correlate with drug response and non-response and ultimately use this information for patient stratification in the clinical laboratory using blood or cerebrospinal fluid as peripheral specimens.

European Consorted Research on Internet-based Prevention & Treatment of Depression

Heleen Riper

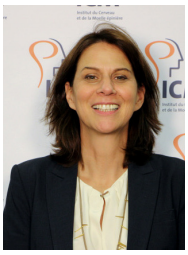
Heleen Riper

Faculty of Behavioural and Movement Sciences, Dept. of Clinical, Neuro and Developmental Psychology, VU University/VUmc, Amsterdam, the Netherlands

In this presentation Riper discussed recent developments in e-mental-health research illustrated with the results of a number of European projects. She showed that the digitalisation of prevention and treatment of common mental disorders such as depression and anxiety has gained momentum over the last two decades. Ample scientific studies have shown that the digital treatment of depression, for example by means of cognitive behavioural therapy, is as effective as face-to-face treatment and it is even effective without therapeutic guidance. Little is known yet, however, for whom it works and how it works as is true for traditional psychotherapies as well. In addition to traditional clinical diagnostics, the developments within the domains of neuro-imaging, (epi)genetics and 'omics' such as proteomics have contributed to improved insights into the heterogenous expression of depression and the variety of treatment responses of individuals suffering from it.

However, a biological model of depression doesn't tell the full story. Smartphones and wearable sensors hold promise to become an additional vehicle for improving the understanding of the various parameters constituting depression including behaviour and emotion (e.g. affect, geographical mobility), cognition, environmental (social proximity) and physiological (e.g. skin conductance) data. Given their ubiquitous nature these devices are able to collect enormous amounts of active and passive data ('digitomics') of individuals in real time and in their own ecological environments over extended periods of time and with little or no hazards against low costs. By making smart use of innovative machine learning methods this may lead in the near future to the identification of distinct digital phenotypes which in combination with biological markers and clinical profiling may constitute personalised treatment strategies. Riper illustrated the potential of digital phenotyping by some of her team's work including a passive evaluation of individual smartphone use to tap the dynamics of mood.

The challenges of genetic biomarkers for neurodegenerative disorders



Alexandra Durr

Alexandra Durr

Genetic department of the Pitié-Salpêtrière's hospital, Institut du Cerveau et de la Moelle, Paris, France

In inherited neurological progressive disorders, such as familial forms of Parkinson disease and Alzheimer's dementia, even more in monogenic diseases such as Huntington disease, patients go through different phases of the disease.

Despite the fact, that the causal genetic variations are present since conception, patients develop symptoms and signs of the disease 40 to 60 years later in life. This premanifest phase of the disease, free of symptoms, constitutes a window on pathological mechanisms and preventive treatment opportunities. The challenge will be to evaluate the benefit of such treatments without the possibility of clinical evaluation.

Other markers, biological or genetic markers, are needed to be identified for follow up. Cerebral imaging in Huntington disease has been shown to be sensitive to assess changes different from aging in carriers of the genetic variations but without symptoms. Precision of individual trajectories will be key on identifying individual biomarker combinations to evaluate preventive attempts in neurological progressive conditions.

Biobanking - BBMRI-ERIC quality management services

Andrea Wutte

Andrea Wutte

Quality Manager, BBMRI-ERIC, Graz, Austria

BBMRI-ERIC is the Biobanking and BioMolecular resources Research Infrastructure – European Research Infrastructure Consortium. It provides expertise and services in order to facilitate the use of European sample collections and data for the benefit of human health. The members of this consortium are: Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Latvia, Malta, Netherlands, Norway, Poland, Sweden, the United Kingdom and Bulgaria, Observer countries are Switzerland, Cyprus, Turkey and the International Agency for Research on Cancer.

BBMRI-ERIC serves researchers, biobankers, patients, clinicians, politicians, partners and the industry. It offers: 1) support with ethical, legal and societal issues; 2) IT tools and expertise; and 3) quality management services.

To this end, BBMRI-ERIC has established Quality Expert Working Groups involving more than 110 experts, including researchers from 20 member and observer states and the WHO / IARC. Together, solutions have been developed to better meet sample quality requirements, the main tool being the development of the BBMRI-ERIC Self-Assessment Surveys (BBMRI-ERIC SAS) based on the preliminary testing procedures established by CEN / Technical Specifications (CEN / TS from cen.eu). The BBMRI-ERIC SAS offers biobankers this free SAS tool to: 1) implement quality requirements and 2) evaluate their performance. When biobanks meet the criteria of the BBMRI-ERIC SAS, they receive recognition by being marked in the BBMRI-ERIC directory. Therefore, BBMRI-ERIC promotes those biobanks that are able and willing to provide access to high-quality samples / data.

Future needs for translational research

Toni Andreu
Scientific Director, EATRIS, The Netherlands


Toni Andreu

The process of translating novel biological insights into effective interventions is a highly complex undertaking, requiring significant dedicated expertise and infrastructure. The hope generated by the revolution in biology stemming from the unravelling of the human genome and subsequent explosion of a variety of 'omics fields was not met with an increase in effective medical interventions.

Development failure rates remain stubbornly high, while concomitant to this reality is the continuing trend that industry is reducing its investments in the early phases of discovery and translational research and development. This is particularly significant in the field of drug development for neurological diseases where the high rates of irreproducibility at the preclinical level combined with a particular market strategy of the pharma industry may result in a shortage of novel molecules for the treatment of neurological conditions,

The field of translational science is a highly multi-disciplinary enterprise, tasked with gaining a fuller mechanistic understanding of both disease process and the mode of action that a would-be therapeutic would utilise to modulate its effects. This is a move away from more empirical methods of development, and is in part a response to increasing scrutiny from regulators, who are more and more requiring that developers show (a) understanding of the mechanisms behind their investigational drugs, and (b) increasing onus on the ability to stratify potential responders from non-responders ex ante on the basis of companion diagnostic tests.

Due to these developments in the field, the development pipeline finds itself in a transitional stage, where developers are trying to validate tools that can support in discriminating early in the R&D process which drug candidates have high potential versus those that will fail, as well as significant resources deployed to identify and validate potential biomarkers for patient stratification and prognostication. It is in this biology-driven, technology-rich area that academia is proving to be a significant driver of productivity, both in terms of novel tools for development, as well as in the very interventions that ultimately will transition along the pipeline towards the patient.

EATRIS ERIC was created to defragment the substantial European efforts in this field, with the mission to improve productivity of the translational R&D pipeline, by providing high quality research services to public and private research entities.