S-08-004
Translational approaches targeting the Neuregulin-ERBB4 pathway in schizophrenia

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Objective: The Neuregulin1 ligand and its receptor ERBB4 have been shown to be essentially involved in the control of myelination and inhibitory circuit formation of the brain. Moreover, both genes have been associated with schizophrenia based on genetic findings. We have generated several cellular screening tools and mouse models targeting this pathway to validate novel treatment options and to perform translational approaches towards biomarker discovery.
Methods: We applied cell-based screenings with clinically approved compounds and validation of candidates in Neuregulin1 mouse models assessing biochemical, electrophysiological and behavioral readouts. Moreover, proteomic approaches were applied to search for translational biomarkers in serum of schizophrenic patients and Neuregulin1 mouse models.
Results: From the cell-based repurposing screen, we identified the diuretic drug Spironolactone as inhibitor of the Neuregulin-ERBB signaling pathway. Chronic administration of Spironolactone in Neuregulin mouse models can revert biochemical and behavioral alterations caused elevated activation of the Neuregulin-ERBB pathway. Acute application of the drug on prefrontal cortex slices increases amplitudes and frequencies of inhibitory post synaptic currents as assessed by patch-clamp recordings. Based on these pre-clinical results, a clinical study was initiated and the design and intermediate results will be presented. We also subjected serum samples from Neuregulin mouse models as well as schizophrenic patients to a proteomic profiling and first results regarding translational biomarkers will be presented.
Conclusion: Translational research focused on the Neuregulin-ERBB signaling pathway may lead to novel therapy options and biomarkers for schizophrenia.
Policy of full disclosure: MR is co-founder and shareholder of SYSTASY Bioscience GmbH who holds the rights of the split-Sensor technology applied for repurposing screens and is a consultant of Boehringer Ingelheim AG & Co. KG.

S-09 Prevention of schizophrenic and other psychoses—activities for implementation in Europe

S-09-001
The Clinical High Risk state for psychosis (CHR-P): challenges and future implementations

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Objective: To critically review ongoing challenges that are limiting the Clinical High Risk state for Psychosis (CHR-P) and discuss future implementations.
Methods: Critical review of ongoing challenges underlying the CHR-P field.
Results: This lecture will report on different recent studies which have tackled several conceptual challenges underlying the CHR-P paradigm: (i) poor detection ability, (ii) heterogeneity of inclusion criteria, (iii) impact of recruitment strategies, (iv) inconsistency of prognostic performance, (v) negative trials for psychosis prevention. (i) First, we will analyse the proportion of first episode patients pragmatically detected by CHR-P services. We will then introduce a clinically based risk calculator that can be used to improve the detection of at risk cases in secondary mental health care. (ii) Second, we will present new results indicating that there are different levels of risk within the CHR-P group (BLIPS vs APS vs GRD). A revised CHR-P model that is based on clinical staging of these different subgroups will be proposed. (iii) Third, we will review the prognostic performance of the CHR-P instruments presenting up-to-date meta-analytical results. In particular, we will focus on the relationship between pre-test and post-test probability of developing psychosis within CHR-P instruments. (iv) Fourth, we will review the profound impact of the recruitment strategies on the pre-test risk enrichment that is occurring before individuals are assessed with CHR-P instruments. Prognostic models and stratification algorithms developed to optimize recruitment and prognosis of CHR-P individuals will be presented. (v) Fifth, we will discuss the negative impact of these challenges on the recent randomised controlled trials of preventative interventions for CHR-P individuals. Possible solutions for addressing them will be introduced.
Conclusion: This lecture will summarise ongoing challenges for the detection, assessment, treatment of CHR-P individuals and will suggest some possible solutions for overcoming them.
Policy of full disclosure: None.

S-09-002
EPA guidance on the early detection of CHR states

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Objective: The EPA Guidance project aims to improve the quality of mental health care in Europe by disseminating written information based on best evidence and psychiatric practice and to facilitate countries learning from each other in areas where guidelines are lacking. One of these areas is the early detection of a clinical high risk (CHR) for psychosis in patients with mental problems.
Methods: A meta-analysis of studies reporting on conversion rates to psychosis in CHR samples according to ultra-high risk (UHR) and/or basic symptoms criteria was conducted with special attention to potential moderators (different UHR criteria definitions, single UHR criteria).
Results: Conversion rates in the identified 42 independent samples with altogether more than 4000 CHR patients who had mainly been identified by UHR criteria and/or the basic symptom criterion 'cognitive disturbances' (COGDIS) showed considerable heterogeneity. While UHR criteria and COGDIS were related to similar conversion rates until 2-year follow-up, conversion rates of COGDIS were significantly higher thereafter. Differences in onset and frequency requirements of symptomatic UHR criteria or in their different consideration of functional decline, substance use and co-morbidity did not seem to impact on conversion rates. The 'genetic risk and functional decline' UHR criterion was rarely met and only showed an insignificant pooled sample effect.
Conclusion: Although more research into potential sources of heterogeneity in conversion rates is needed to facilitate improvement of CHR criteria, six evidence-based recommendations for an early detection of psychosis were developed and published in European Psychiatry (Vol. 30, Issue 3, March 2015). In brief, these include the recommendations to alternatively employ the two symptomatic UHR and COGDIS criteria irrespective of the level of psychosocial functioning exclusively in help-seeking samples, in that they should be assessed—or at least their assessment be supervised—by specifically trained mental health professionals.
Policy of full disclosure: None.