Validating new biomarkers for unmet needs in the management and treatment of depression

The Experimental Medicine Network are discussing the potential formation of academic-industry alliances that will address two important challenges in the treatment and management of depression:

(i) Optimising the treatment pathway for rapid-acting antidepressant (RAAD).
(ii) Developing biomarkers sensitive to the therapeutic effects of non-reuptake blocking antidepressants

We propose an academic-industry partnership to jointly develop and validate new biomarkers, tasks, or other methods for providing solutions to these challenges. An initial meeting to discuss the path forward was held on **Tuesday 7** and **Wednesday 8 February 2023** (see below for program details and directions). This meeting was hosted by **Prof. Andreas Reif** at the **University Hospital Frankfurt** and financially supported by the ECNP Experimental Medicine Network.

(i) **Optimising the treatment pathway for rapid-acting antidepressant (RAAD).**

It is estimated that 10-30% of patients diagnosed with low mood meet the criteria for treatment resistant depression (TRD) [1]. Fortunately, treatments for TRD with various mechanisms of action (MOA) that provide near immediate reduction in symptoms are emerging rapidly. These rapid-acting antidepressant (RAAD) generally produce rapid improvements, but relapse rates can vary markedly between patients [2], which is an emerging issue in treatment management.

Even for currently marketed treatments, such as SPRAVATO® (esketamine), the optimal treatment algorithm is determined on a patient-by-patient basis [3]. Ideally, a precision medicine approach, in which the next dose is given prior to relapse, would be developed for each patient. However, this approach requires sensitive biomarkers that are predictive of relapse before, or just as, symptoms emerge. Moreover, such biomarkers should be unobtrusive, discretely administered at home or work, or passively monitored by wearables or phone apps.

(ii) **Developing biomarkers sensitive to the therapeutic effects of non-reuptake blocking antidepressants**

There is increasing awareness that selective serotonin reuptake inhibitors (SSRIs) do not successfully alleviate the hallmark features of major depressive disorder (e.g., anhedonia, fatigue, and avolition) in a significant group of affected individuals. As a result, there has been growing interest in pharmacological agents that exert their beneficial effects via other MoAs. Recent work has shown promising results for agents that act primarily on opioidergic [4], glutamatergic [5] and/or complementary (non-reuptake blockade) serotonergic mechanisms [6].

Importantly, however, the neural and psychological mechanisms by which these “new” candidate antidepressants exert their beneficial effects are not fully known. Biomarkers that are sensitive to the effects of these agents and that can identify likely responders and non-responders are therefore urgently needed.

Aims and Objectives of the meeting

We aim to explore the possibility to form academic-industry partnerships to evaluate and validate biomarkers for RAAD and to assess the therapeutic effects of non-reuptake blocking antidepressants.

For RADD such biomarkers should not only be deployable discreetly in real world settings but also in clinical trials evaluating new treatments as qualified biomarkers. Thus, it is likely that these requirements will favour a digital approach, but other methodologies such as EEG suitable for home may also have a relevant and valuable role.

The development of robust endpoints for novel antidepressants will require understanding of their unique psychological and neural effects, which can be achieved via advanced task- and neuroimaging-based methods. However, some novel antidepressants are of key interest because they exert effects on biological stress systems (e.g., HPA axis, inflammatory activation) [4], and thus have the potential to modify putatively causal symptom mechanisms that are not directly targeted by SSRIs [7]. Examining such effects may necessitate assessments of stress-sensitivity (e.g., responsivity to acute stress challenges, neural responses to acute stress, markers of inflammation, ambulatory measurements of real-life stress), in depressed individuals with, and without, high cumulative stress. Ultimately, these activities have the potential to result in the identification of endpoints that will identify subgroups of individuals that are likely to optimally benefit from this novel wave of antidepressants.

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