Publishable Summary 1st periodic report MOODSTRATIFICATION (July 2019)

1. Context and objectives

MOODSTRATIFICATION brings together 11 partners (psychiatrists, immunologists, epidemiologists, industry) from 7 countries stratifying patients with a major depressive episode on the basis of immune profiles.

The hypothesis of our project is that a large proportion of severe mood disorders are the result of deviant immune reactions, caused by (Inborn and acquired) monocyte/macrophage and T cell defects which result in

1. mal development and malfunctioning of the brain, and
2. flares of chronic inflammation, further impacting brain functioning.

We test and refine this novel concept by further exploring the earlier collected large datasets of previous EU funded research MOODINFLAME (2008–2012) and PSYCH-AID (2013-2017).

The aim of MOODSTRATIFICATION is not only to refine the hypotheses above, but also to develop simple blood tests to measure the above mentioned immune defects in clinical practice (WP1).

Another aim is to carry out proof-of-principle clinical studies with T cell enforcing therapies (thymus hormone and low dose IL-2) to correct the defects (WP2), and to develop in later phases of the project – on the basis of the outcomes of our refinement studies (see WP1) – new immune correcting therapies in immune-stratified patients using the developed simple blood tests. Immune stratification is meant to select patients with a high likely hood to react to these novel immune therapies (WP3). In WP4 we estimate the economic costs and benefits of these new interventions.

2. Work performed

WP1. Further refinement studies into the immune defects of mood disorder patients

a) We carried out more extensive monocyte gene expression studies with gene panels including inflammatory, apoptosis and growth genes, and cholesterol pathway genes on combined patient panels of MOODINFLAME and PSYCHAID (> 200 MDD patients, >200 BD patients and >200 healthy controls). We compared outcomes to a large set of clinical variables (age, gender, severity of disease, childhood trauma, suicide risk, BMI, medication use) of the patients.

b) We carried out more extensive FACS determinations for lymphocyte (and in particular T cell) apportioning in these larger data sets of patients and controls and compared outcomes to the clinical variables.

c) We developed simple and reliable ELISAs for hsCRP, IL-6, sCD25, IL-7, BDNF and SCF and tested with these ELISAs the larger data sets of patients and controls.

d) We developed a simple whole blood gene expression assay, based on venepuncture and collection of blood in PAXGENE tubes. These genes measured in whole blood had to correlate with the previously found monocyte gene expression and T cell FACS abnormalities. We presently investigate the possibilities for further simplification to a finger prick collection.

WP2. T cell enforcement studies in mood disorder and immune deficient patients

Partners (EMC, AP-HP, KU-Leuven and OSR) worked hard to prepare all documents for ethical and administrative approval for use of thymus hormone and/or low dose L-2 therapy of mood disorder patients at their institutions. This turned out to be a lengthy and cumbersome procedure. This was not envisaged. For this reason we adapted out time schedule and made an amendment in the original time schedule and plan.

EMC has evaluated the psychologic and psychiatric state of their primary immune deficient patients. In addition EMC is in detail clinically evaluating their CVID patients and collecting blood for immune phenotyping in a manner similar to what we do for mood disorder patients.

WP3. Collection of historical controls and planning of further Interventions on the basis of outcomes in WP1

UMCG has taken the lead to organize face-to-face and tele-meetings to organize the collection of historical controls (treatment as usual) by the clinical partners.

EMC and LMU have undertaken a study on the effect of add-on anti-inflammatory agents in depressed patients stratified for high and low signs of inflammation on treatment outcome. We have used literature data and data from MOODINFLAME for this. A paper has been published.

WP4. Estimate the socio-economic benefits from the novel immune diagnostic and immune therapeutic approaches.

AU is studying in the first years the costs of severe Major Depressive Disorder using the Danish register data.

3. Results

WP1. Further refinement studies into the immune defects of mood disorder patients

In the coordinator's opinion break-through progress has been made on the immune pathogenesis of severe mood disorders on the basis of the outcomes of the new assays and by studying the entire cohort of MOODINFLAME and PSYCHAID.

A. In essence all found immune aberrancies in monocytes/macrophages, lymphocytes and cytokines/growth factors in mood disorders can be categorized under the concept of Premature Immuno-Senescence (PIS). The found components of PIS are:

1. Enhanced mitochondrial apoptosis of monocytes/macrophages leading to enhanced ROS production and enhanced TNF production
2. T cell defects leading to higher levels of T memory cells with poorer function
3. Abnormalities in T effector/T regulator ratio's with poorer suppressor function
4. Proneness to inflammation (so-called "inflammaging"): High activities of the "inflammasome" with high production of CRP, IL-6 and IL-1β
5. Low levels of IL-7, IL-7 plays a prominent role in immuno-senescence.

Genetic polymorphisms and chronic viral infections (CMV) are important determinants in early aging of the immune system, leading to the defects as described above.

B. In major depressive disorder the monocyte apoptosis and monocyte inflammation were found to be the most outspoken abnormalities within the PIS syndrome.
   IN case of childhood adversity, this strongly enhances the inflammatory state of monocytes/macrophages via reduction of mevalonate kinase (an important cholesterol pathway enzyme; inborn deficiencies give fever syndromes). These "high inflammatory" patients are also at higher risk for suicide. Such suicidal MDD patients are further more characterized by higher Th17 cell levels in the circulation.
   For an adjustment of the original MDD model see the added Figure.

C. In bipolar disorder (not fully evaluated at present) T cell defects and abnormalities in the T effector/T regulator ratio seem to be the most outspoken abnormalities within the PIS syndrome.

D. We have developed gene correlates in whole blood for the monocyte inflammatory state (high inflammasome IL-1 activity) and the abnormalities in the T effector/T regulator state. They are respectively TGFBR3, NFATC2, CAMP, MRC1, ABCG1, HMOX-1, FOXP3, TBX21 and ROR-γ. This discovery enables a simple test for these correlates in PAXGENE material.

E. We have performed a literature study (systematic review) showing that T cells have a clear impact on brain development and function, in particular on nuclei involved in the stress response.

F. We also evaluated all data on the relationship of monocyte inflammatory state and the activity of the tryptophan break down pathways in the Muenster and Munich MOODINFLAME MDD cohorts. We found that the specific pro-inflammatory monocyte state of MDD patients (involving inflammasome components) led to a de-activation of the kynurenin pathway (KP), in particular of the potentially neurotoxic metabolites, such as 3(OH)-Kynurenin. IFN-induced inflammation, which is different from the inflammasome related pathway and not activated in MDD, does lead to activation of the KP route.

WP2. T cell enforcement studies in mood disorder and immune deficient patients

The situation with regard to the T cell enforcement studies in WP2 in July 2019 is as follows:

1. AP-HP has got approval. The low dose IL-2 clinical study will start in the fall of 2019. AP-HP will use IL-2 from our partner ILTOO.
2. OSR has got approval from their ethical committee, but needs some last approvals from a central drug registration office in Rome (minor questions). They also foresee to start in the fall of 2019. OSR will use IL-2 from Novartis and has bought enough stock to also supply KU-Leuven
3. EMC has delivered the paper work to their ethical committee, after having prepared all documents with a clinical trial office in discussion with the ethical committee. They will be allowed to use thymus hormone initially in a pilot trial of 5 CVID patients. This is also planned for the fall of 2019. Thereafter we will evaluate if it is worth to expand the thymus hormone studies
4. KU-Leuven will not use thymus hormone for treatment of 22Q11DS patients (in fact there is no optimal administrative cooperation of the Chinese firm), but will switch to the Novartis low dose IL-2. They have to clear some laboratory issues regarding blood collection and will then deliver to documents to the ethical committee

With regard to the psychological/psychiatric state of Primary Immune deficiency patients EMC found a significantly higher burden of distress, depression, anxiety and somatization in the patient population than in general population controls (a paper is in preparation). The partner has also collected detailed clinical information and frozen leukocytes/serum of 40 well-typed CVID patients and 26 age/gender matched controls. The control series will be expanded to 40 in the coming months and then tests will be carried out and evaluated.

WP3. Collection of historical controls and planning of further Interventions on the basis of outcomes in WP1

UMCG has got permission to collect data and blood from mood disorder patients treated as usual. They will act as sponsor for this endeavour for the other partners involved in this collection.

The literature and original study on add-on anti-inflammatory agents delivered the following: Only in situations of a high inflammatory state (e.g. high CRP) an add-on anti-inflammatory therapy is effective, it is even contra-productive in situations of low inflammatory activity (low CRP). This outcome will help us device new studies in WP3.

WP4. Estimate the socio-economic benefits from the novel immune diagnostic and immune therapeutic approaches.

AU found that

• Individuals with treatment resistant depression have a significant excess mortality compared to individuals who respond to treatment, mainly due to suicide.

• Men and women with treatment resistant depression lose on average 1.21.and 1.36 excess life years, respectively, from all-cause mortality.

Conclusion and impact

The main conclusion we can draw after the 1st 18 months of study in MOODSTRATIFICATION is that we are gradually changing the conventional DSM psychiatric diagnosis “Severe Mood Disorder” (based on meticulous description of subjective

symptoms) to a diagnosis of “Premature Immune-Senescence (PIS)” (based on objective immune parameters) and comprising various other internal conditions (proneness to auto-immunity, infection and atherosclerosis). The inflammatory aspects of PIS can be aggravated by (early) life stress, acting via changes in the immune-metabolism (MVK in the cholesterol pathway). Clinically applicable relatively simple test systems have been developed and are operative to diagnose PIS and its relevant inflammatory and other aspects.
Many components of PIS have impact on brain development and function (see Figure)
The impact of the concept change (psychiatric diagnosis to immune diagnosis) is that we will design treatments targeting the abnormalities of PIS, such as low dose IL-2 therapy (already planned), IL-7 therapy, intensive exercise, and treatments targeting the inflammatory aspects of PIS. This is foreseen in the later phases of MOODSTRATIFICATION.

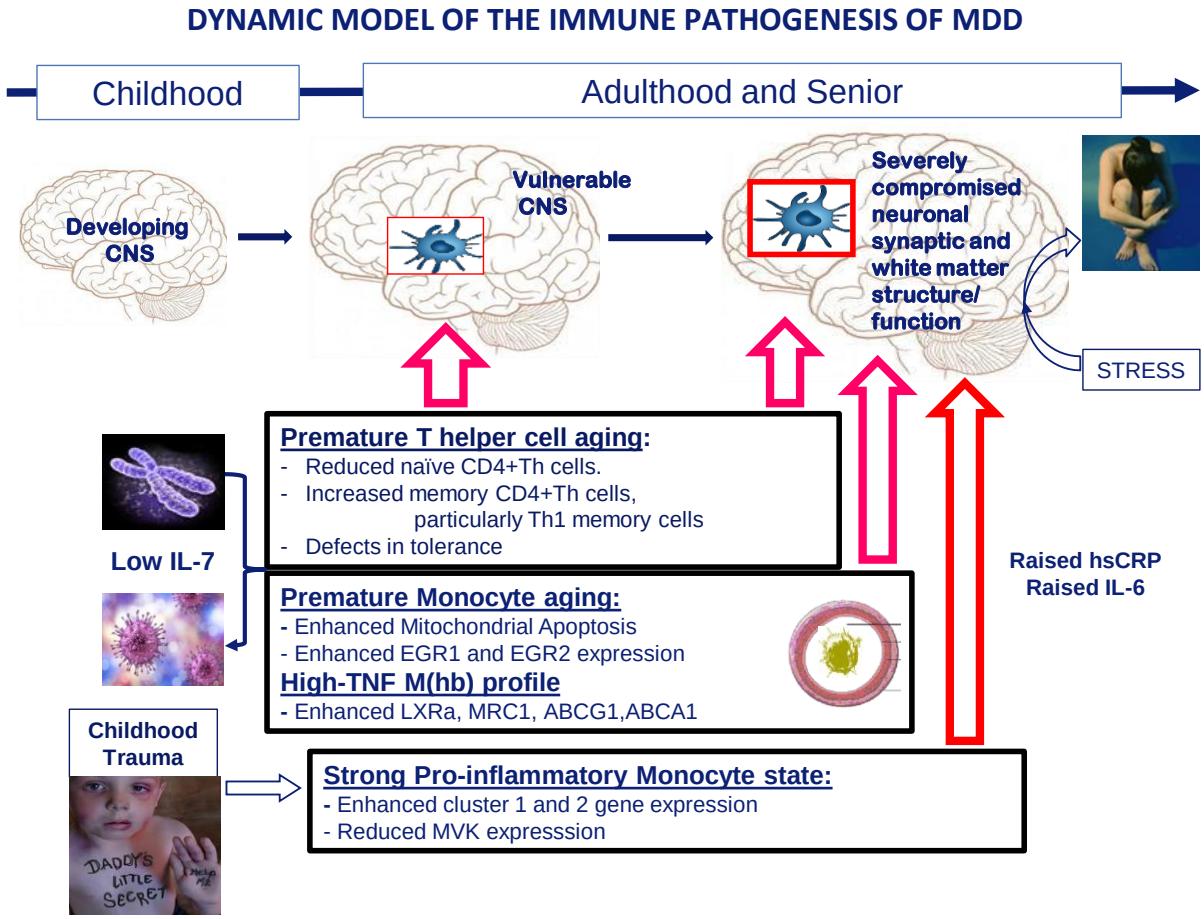

Figure1. The model of the immune pathogenesis of major depressive disorder (MDD) in the presence of a history of childhood adversity (around 50% of severe major depression). In the absence of a history of childhood trauma a milder state of inflammation is reached due to the underlying premature senescence of T cells and the monocyte/macrophage system.

Public website

www.moodstratification.eu

See this website for list of publications, contributions to meetings and patient meetings