1. PUBLISHABLE SUMMARY

Summary of the context and overall objectives of the project (For the final period, include the conclusions of the action)

The hypothesis of MOODSTRATIFICATION is that a large proportion of severe mood disorders, i.e. of major depressive disorder (MDD) and bipolar disorder (BD), are in part caused by deviant immune reactions, which result from (inborn and acquired) monocyte/macrophage and T cell defects. Since these immune cells are essential for a proper development and function of the brain, in particular of the emotional brain, this consequences for the
1. development and function of the brain, in particular the limbic system, and also result in
2. flares of chronic inflammation, further impacting brain function.
Since severe mood disorders are prevalent (5% of the population) and very disabling for patients and relatives, improved diagnoses and new cures are required.
MOODSTRATIFICATION addresses the development of such improved diagnoses and new avenues for treatment using the immune theory for mood disorders.

Objectives
Workpackage 1 (WP1): The first objective of MOODSTRATIFICATION is to test and refine this novel immune concept for mood disorders by further exploring monocyte, T cell and cytokine abnormalities in the earlier collected large datasets of previous EU funded research MOODINFLAME (2008–2012) and PSYCH-AID (2013-2017).
The second objective (also addressed in WP1) is to develop simple blood tests to measure the above mentioned immune abnormalities in clinical practice .
WP2:The third objective is to carry out proof-of-principle clinical studies with T cell enforcing therapies (low dose IL-2and thymus hormone) to correct the immune defects,
WP3: The fourth objective is to develop in later phases of the project – on the basis of the outcomes of our refinement studies (see WP1) and the literature on successful interventions - new immune correcting therapies in immune-stratified patients using the developed simple blood tests.
In WP4 we want to study the socio-economic benefits of such new intervention.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far (For the final period please include an overview of the results and their exploitation and dissemination)

With regard to objective 1 we have found that the immune defects in MDD and BD differ.
1. MDD is characterized by premature senescence of the T helper and monocyte/macrophage compartment leading to mild low grade inflammation, which under circumstances of childhood trauma and obesity will lead to more signs of inflammation (clear monocyte inflammatory activation, higher serum levels of pro-inflammatory cytokines).
2. BD is characterized by a defect in the generation of T effector memory cells and a reduced level of IL-7 (a T cell differentiation factor), particularly after childhood trauma. T central memory cells, including Th17 cells are increased. During depressive or manic episodes stronger signs of low grade inflammation are evident (monocyte activation, increase in inflammatory cytokines)

With regard to objective 2 we have developed simplified and reliable blood tests. APD (commercial partner, Belgium) has developed a set of reliable and sensitive ELISAs for IL-7, IL-6, hsCRP, BDNF and sCD25, while PRONTO (Israel) has developed a finger prick assay to test for the immune blood cell defects using limited gene expression profiles.

With regard to objective 3 we have started:
A) Two double blind placebo-controlled DEPIL trials using low dose IL-2 in Paris (AP-HP) and Milano (OSR). Since recruitment was slow (corona pandemic) we are delayed, but trials were designed in such a way that pooling is possible. At present (October 2022) 22 bipolar and 17 MDD patients have been included. We will continue till December 2022 (the required patients per group have already been reached) to analyze data in the first half of 2023, focusing on improvement of T regulatory cell function (primary aim). Secondary aims are changes in other immune parameters and signs of clinical benefit.
B) The open label TIDAM study in 2022 in Rotterdam (EMC) to treat depressed immune deficient (i.e. CIVD) patients with thymus hormone (Thymalfasin). After long discussion with the ethical review board (in which we had to proof the abnormal immune MDD-like profile in CIVD patients, which we did), we are allowed to treat up to 20 patients to monitor a putative improvement of the T cell defects (primary aim restoration of naïve CD4/CD8 T cell balance).There are 4 patients in the study and we will continue to the end of the study (July 2023) with a first analysis in April 2023, also including clinical improvement.

With regard to objective 4 we have amended the GA (on the basis of internal discussion and the literature on succesful immune restoring interventions) and started the MOODSTRATA trials, in which we treat depressed patients with physical training schemes with proven efficacy. Controls are treated as usual. The primary aim is to find an immune senescence parameter which predicts favorable outcome (it is known that physical activity combats immune senescence). Secondary aims involve clinical improvement of the intervention and predictive capability and change of other immune parameters. The trials started in 2021 and run in Muenster (WWU), Leuven (KU-Leuven), Ulm (UULM) and Groningen (UMCG). Trials are designed to be pooled. We have included in October 2022 in total 45 physically trained and 48 control patients. We have thus reached half of the patients to be able to perform a statistically meaningful evaluation (calculated as 90-10 patients in each group). We expect to reach 90 patients per group in the first months of 2023. In April 2023 we plan a first analysis.
In WP4 we estimate the economic costs and benefits of physical endurance therapy, particularly in patients with recurrent and drug-resistant depression. These patients were shown by AU (Aarhus) in earlier phases of MOODSTRATIFICATION to have the strongest adverse socio-economic consequences of their disease.

Progress beyond the state of the art, expected results until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far)

Despite considerable delays, due to the lock downs of the corona pandemic and (administrative) struggles with our ethical review boards, we envisage that after the 5 and a half years of study we will reach virtually all of our aims and will deliver important new data:
a) We are changing conventional DSM psychiatric diagnoses as MDD and BD to - at least in part - clinical immunological diagnoses based on objective immune parameters. These new nosological immunologically defined disorders not only lead to mood disturbances but also to proneness to auto-immunity, infection and vasculopathy depending on other endogenous and exogenous factors. Clinically applicable simple test systems have been developed for the diagnosis of these immunologically defined disorders.
b) The immune diagnoses of MDD and BD differ and differences in immune profiles between these two disorders exist. This facilitates an early differential diagnosis between the disorders

c) The impact of the paradigm shift (psychiatric diagnosis to immune diagnosis) is that we are able to test novel treatments targeting the immune abnormalities (low dose IL-2, thymus hormone physical endurance training) and the possibilities to predict outcome on the basis of the immune signatures:
1. We are evaluating pharmaceutical interventions (low dose IL-2 and Thymalfasin) to restore the abnormal T cell and inflammatory immune profiles of MDD and BD, with hopefully also hints towards clinical beneficial effects.
2. We are testing an immune profile in MDD and BD patients (using our developed relatively simple methods), which is in particular sensitive to react in a clinical beneficial way to physical training schemes to enable
personalized treatment.

Address (URL) of the project's public website

www.moodstratification.eu

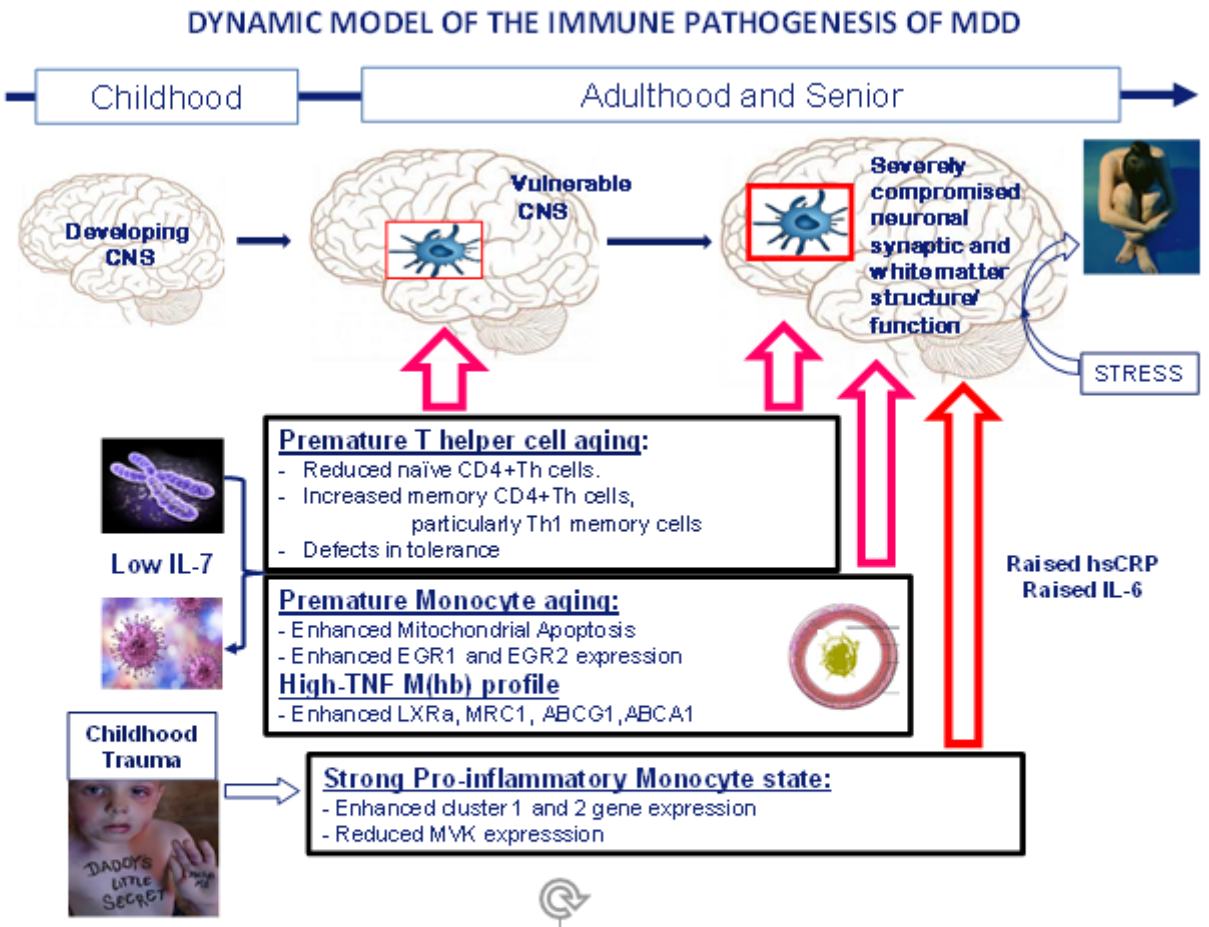

Figure1. The model of the immune pathogenesis of major depressive disorder (MDD) in the presence of a history of childhood adversity (around 50% of severe major depression). In the absence of a history of childhood trauma a milder state of inflammation is reached due to the underlying premature senescence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