BM Systems

PREDICTIVE INTEGRATIVE BIOLOGY

GEMMA
Multi-Omics Research in Autism

GEMMA

Genome, Environment Microbiome & Metabolome in Autism
H2020 Program

An integrated multi-omic systems biology approach to identify biomarkers for personalized treatment and primary prevention of Autism Spectrum Disorders

December 2018.

CONFIDENTIAL

3 complementary programs

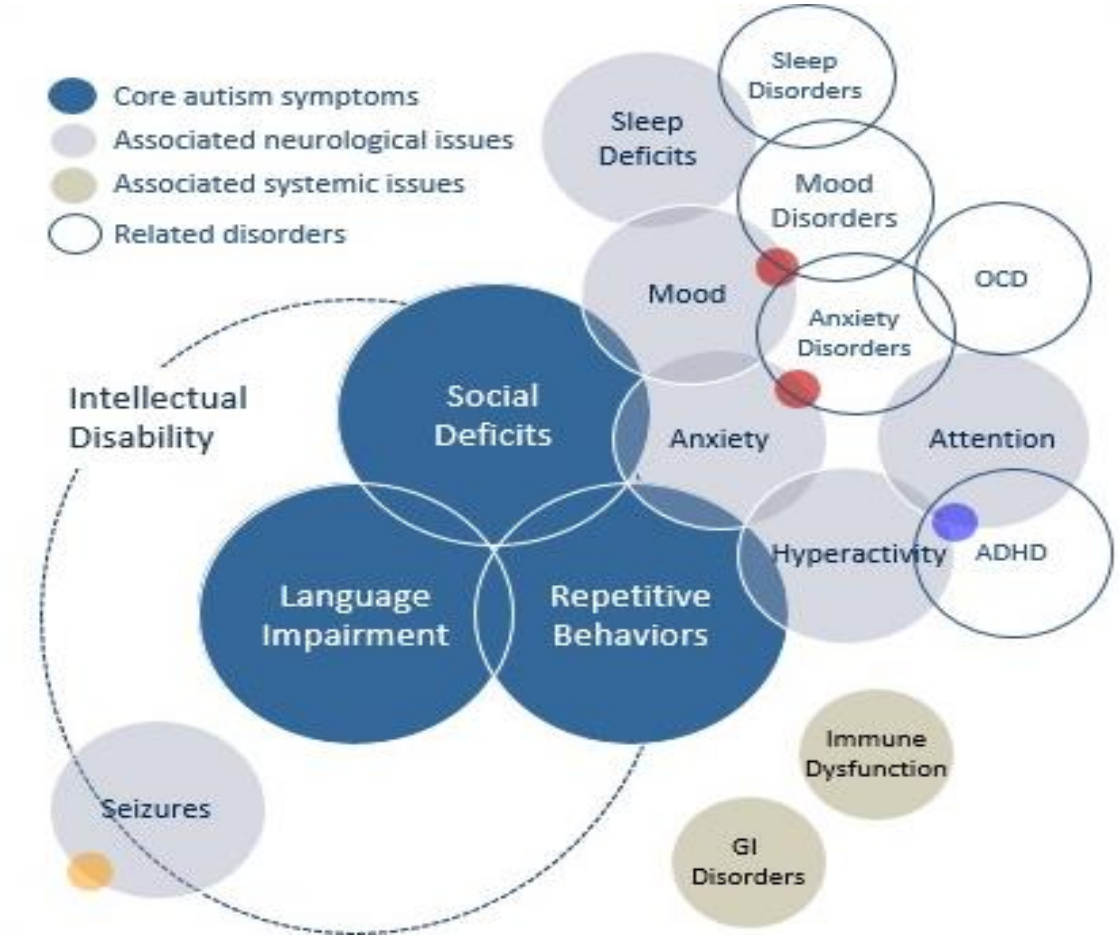
Microbiota & Autism H2020 program selected for 14 M€ funding. GEMMA program (Genome, Environment, Microbiome and Metabolome in Autism) gathers an international consortium of scientists to study the role of the gut microbiome in the development of Autism Spectrum Disorders (ASD).

Etiology & Epigenetic for metabolic disorders program self funded. UMANG program How does maternal nutrient restriction coupled with defective one-carbon metabolism alter the foetal development program, leading to enhanced predisposition to T2D in adolescence? Centre of excellence in Epigenetics IISER Pune India

Diagnostic & Therapeutic evaluation program self funded. The French Chronic Fatigue Syndrome Association decides to clinically evaluate the ME/CFS pathogenesis model produced by Bio-Modeling.

Autistic Spectrum Disorders (ASD)

Autistic Spectrum Disorders (ASD) are a major concern for healthcare systems as they now affect **1 in 68 children** around the world (a 35-fold increase since 1960) and carry **larger societal costs than cancer, heart disease and stroke combined**.



Autism: What is it?

Autism is one of the four pervasive (brain) developmental disorders (PDD) which are characterized by widespread abnormalities in social interactions and communication, severely restricted interests and highly repetitive behaviours, all starting before a child is three years old, and generally following a steady course without remission or relapse.

These are cumulatively called **Autism Spectrum Disorders** (ASD)

Autistic Disorder

- General form of Autism
- Communication and Socializing problems

Asperger's Syndrome

- Normal Intelligence and verbal skills
- Communication issues

Autistic disorder and Asperger's syndrome are grouped, averaging a 4:1 male-to-female ratio.

However, unlike Autistic disorder, Asperger's
- has no substantial delay in language development,
- is often not identified in early childhood, and
- many individuals do not receive diagnosis until after puberty or when adults.

PDD-NOS

- Impaired Social Interaction
- Verbal skills are better than General Autism

Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS), is a 'sub threshold' condition in which some, but not all features of Autism or another explicitly identified PDD are identified.

Rett's Syndrome

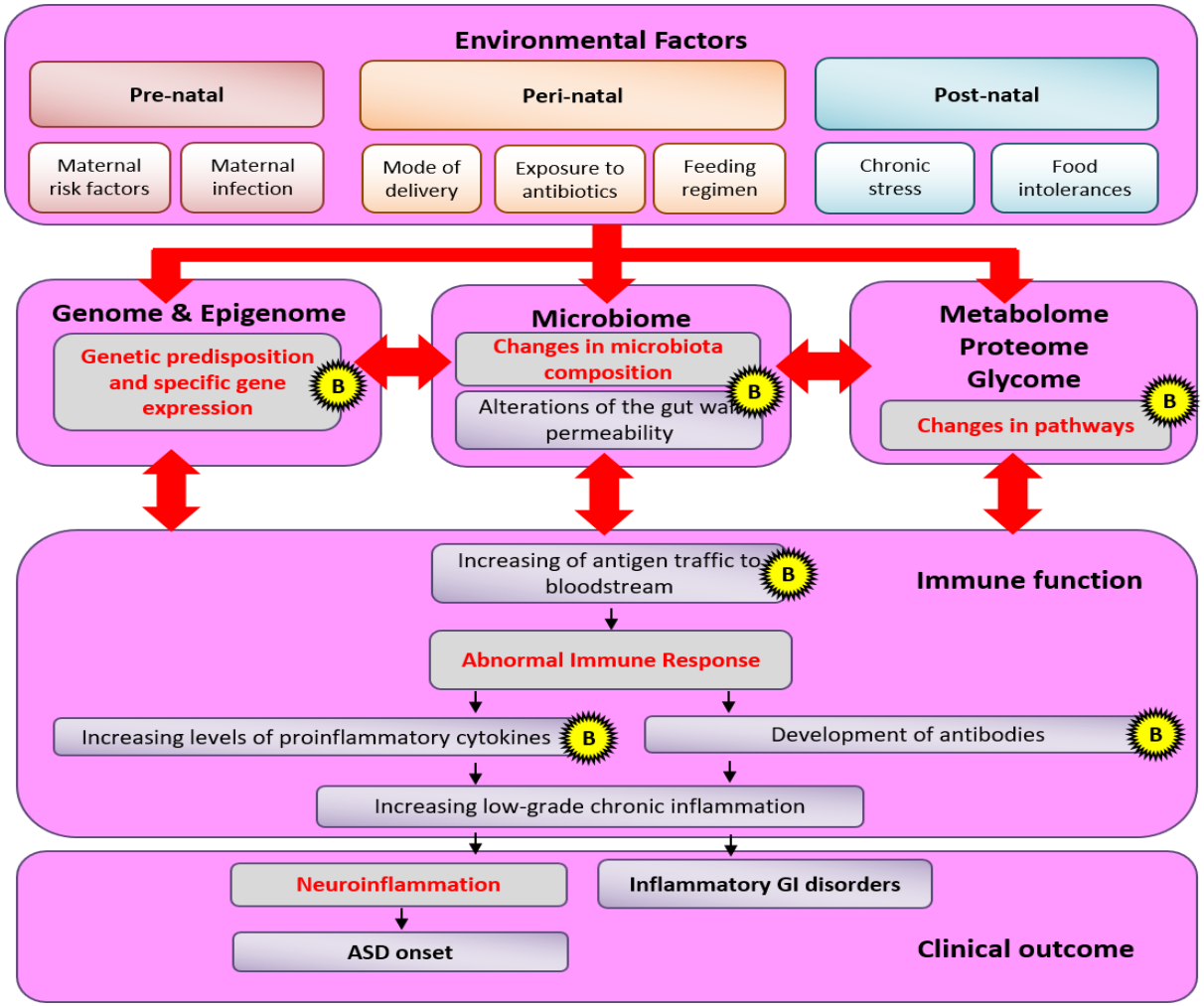
- Common in Girls **(MECP2 mutations, X-linked)**
- Lost ability to speak and process speech

Rett's syndrome, is a progressive neurological disorder and one of the less common ASDs.
The symptoms are easily confused with those of cerebral palsy. Affected girls are very prone to seizures and gastrointestinal disorders, typically have no verbal skills, and about 50% are ambulatory.

The GEMMA project will explore:

- The hypothesis that gut bacterial dysbiosis leads to epigenetic modifications, changes in metabolite profiles, increased gut permeability, increased antigen trafficking and, ultimately, to altered immune responses to promote disease in a subset of individuals at-risk of ASD.
- The hypothesis that the genome/metagenome interplay is responsible for the switch from immune tolerance to immune response to environmental stimuli (antigens) including dietary and microbial factors leading to neuroinflammation responsible of behavioural changes that characterize ASD and gut inflammation causing its GI co-morbidities.
- ***If proven correct***, these hypotheses support the possibility that early identification of vulnerable patients through the identification and validation of biomarkers mechanistically associated with disease pathogenesis could translate in targeted interventions to prevent the onset (or attenuate the severity) of ASD and their GI comorbidities.

GEMMA Global Program

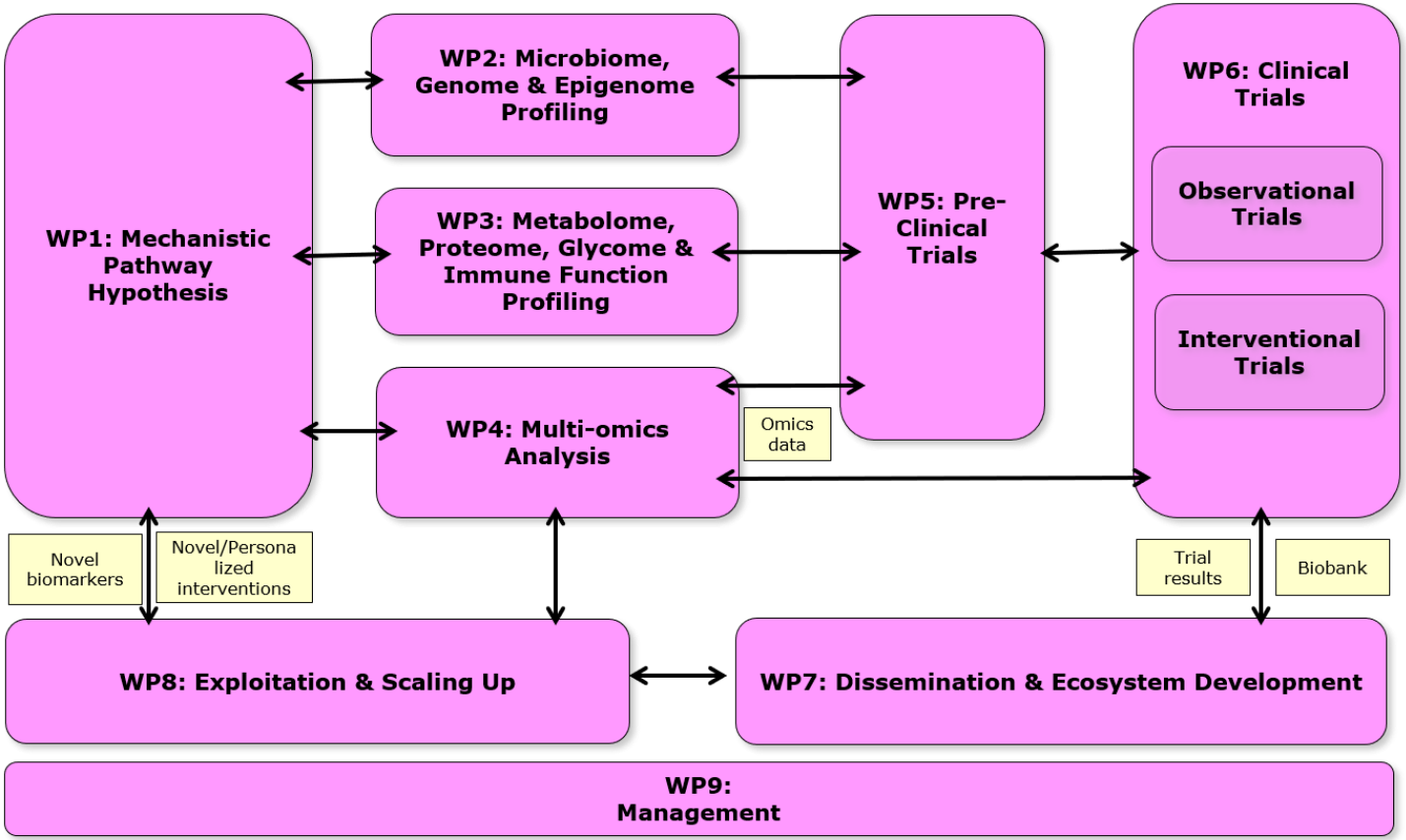


Interplay between environment, genome, epigenome, microbiome, metabolome, proteome, glycome and immune function

B

Biomarkers targeted by the pre-clinical and clinical studies

GEMMA Overall work plan structure



- Foundation (WP1 EBRIS and BMSystems co-leaders)
- Omic and Multi-omic Analysis (WP2 (INRA) , WP3, WP4 (BMSystems))
- Pre-Clinical Trials and Clinical Trials (WP5, WP6)
- Dissemination, Exploitation and Overall Management (WP7, WP8, WP9)

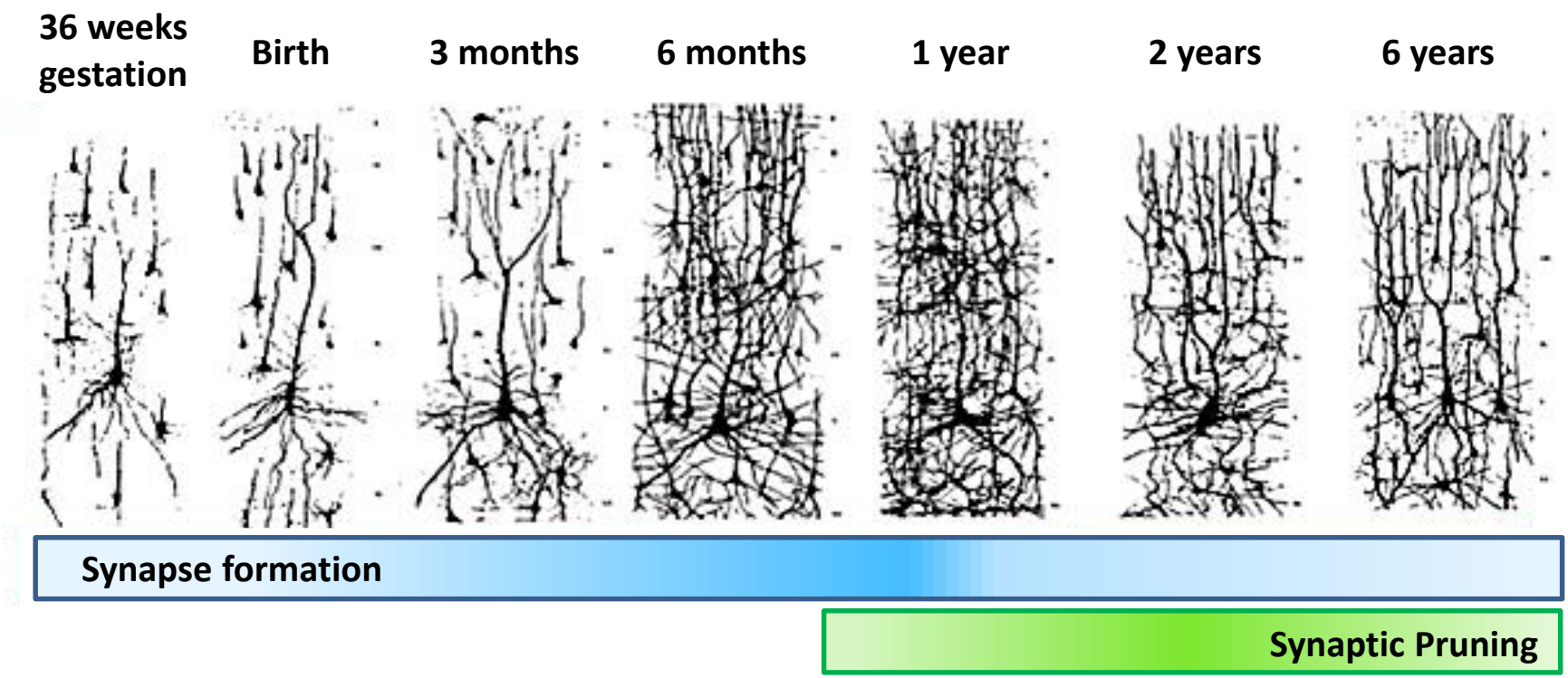
The 2 Adebiotech's members roles

- Bio-Modeling Systems, with its operational CADI™ Discovery platform, is the Integrative Biology partner of GEMMA this ground-breaking autism research project to explore the interaction between microbiome, metabolome, epigenome and immune function to provide possible diagnostic and preventive approaches.

- The GEMMA consortium invited INRA-MetaGenoPolis and INRA-MICALIS to join the project. Both units are involved in several microbiome-related projects and are founding members of IHMC. INRA will be our interface between the GEMMA project and IHMC.

The anatomical characteristics of brain

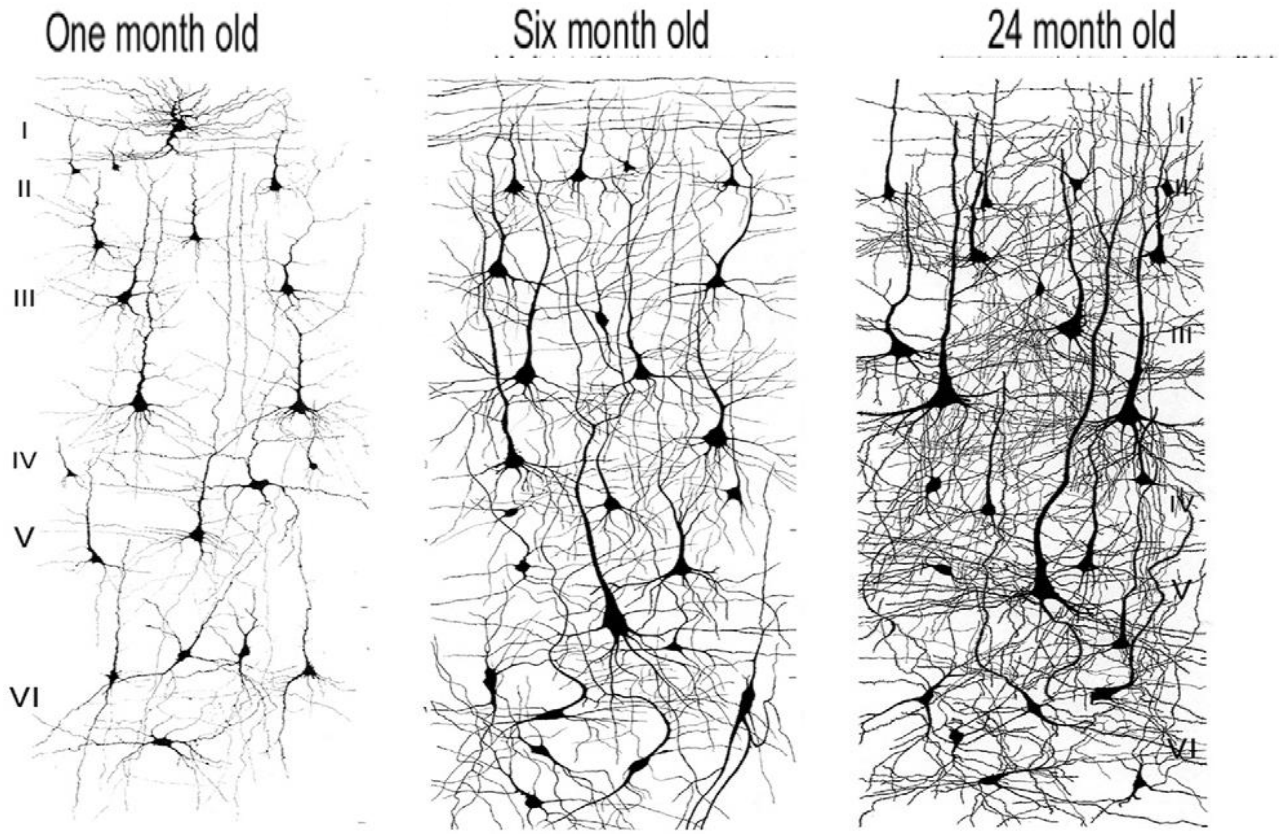
Normal development of the brain in many mammals including humans is governed by a synaptic overgrowth, followed by selective synaptic pruning.



In individuals with autism this synaptic pruning process happens to a far lesser degree, a lot of “redundant” connections remaining intact.
By late childhood, spine density of neurons drops to about half in the neurotypical brain, whereas it drops only about 16% in autistic brains.

The extent of synaptic pruning defects in ASD

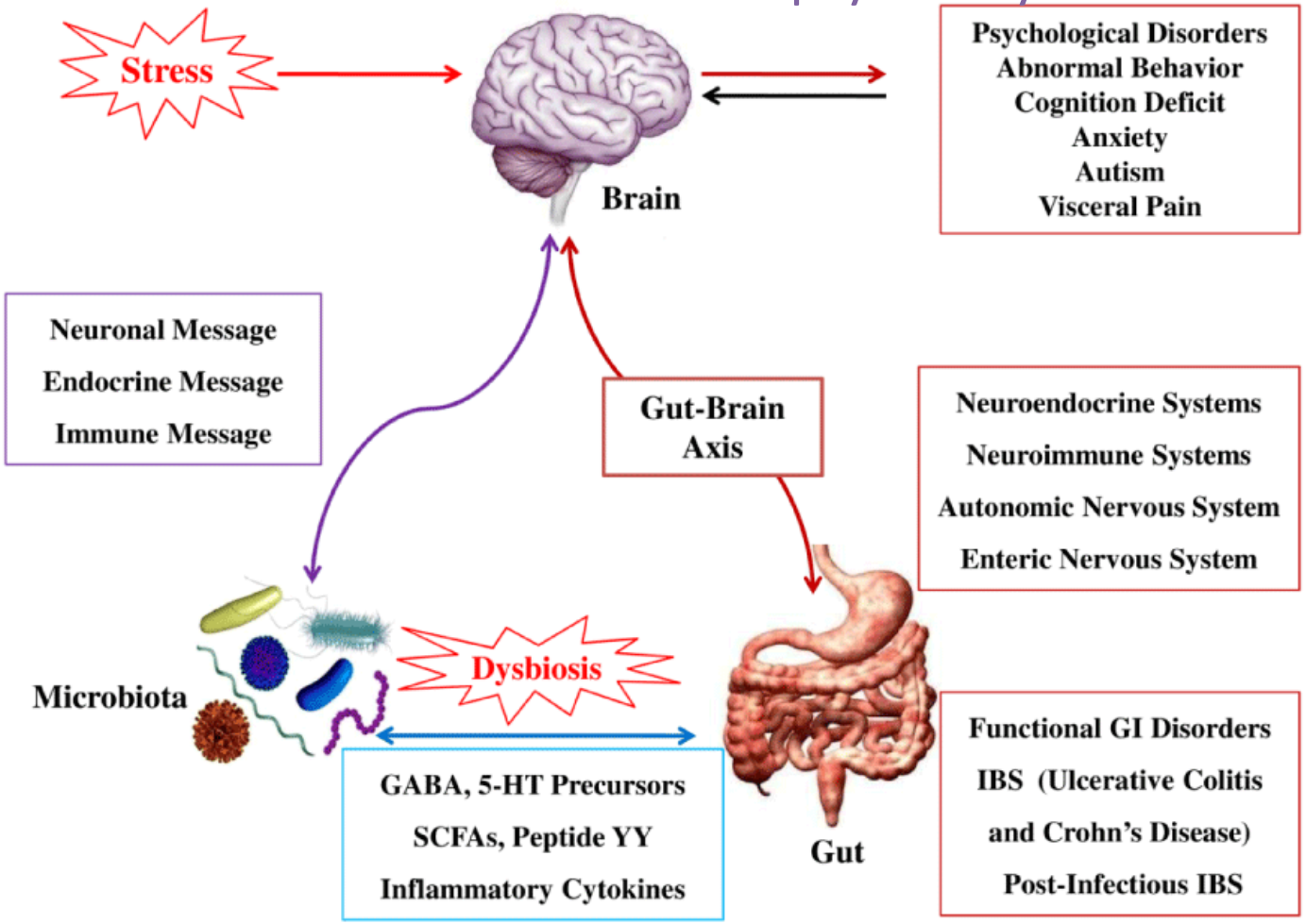
The extent of dendritic growth in the BA9 cortical area of ASD brains at 1, 6 and 24 months of age.



Within the first year of life, there is a dramatic increase in dendritic growth.
By 2 years of age, the minicolumns are spaced farther apart with a lower cell density in a given region of cortex. Dendritic bundles and axonal fasicles that extend throughout several layers of the cortex occupy the space between minicolumns.

The BA9 area is involved in short term memory, overriding automatic responses, verbal fluency, error detection, auditory verbal attention, inferring the intention of others, inferring deduction from spatial imagery, inductive reasoning, attributing intention, sustained attention involved in counting a series of auditory stimuli, etc.

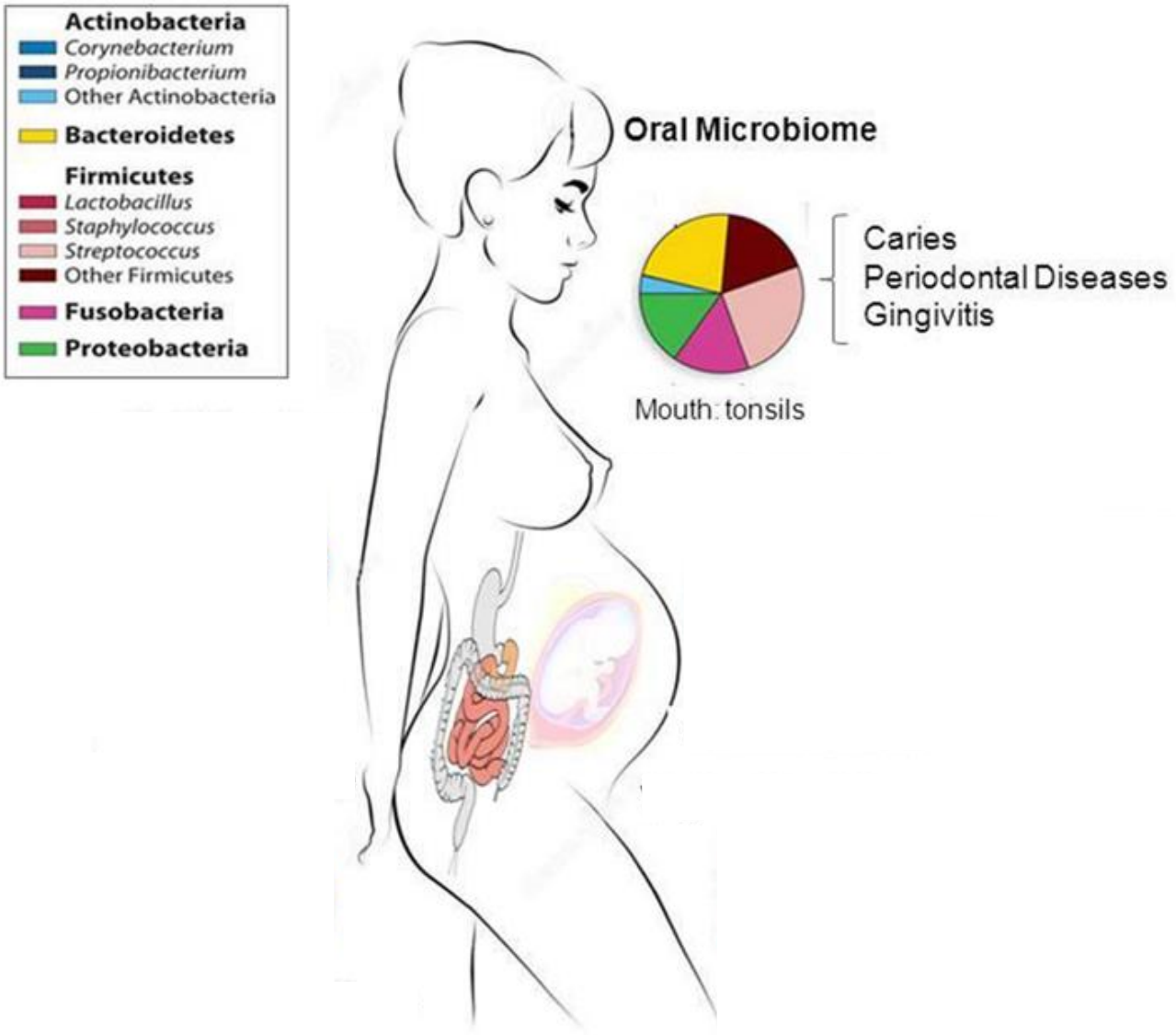
There are well established links between microbiota and psychiatry



Microbiota dysbiosis is a primary source of low grade systemic inflammation.

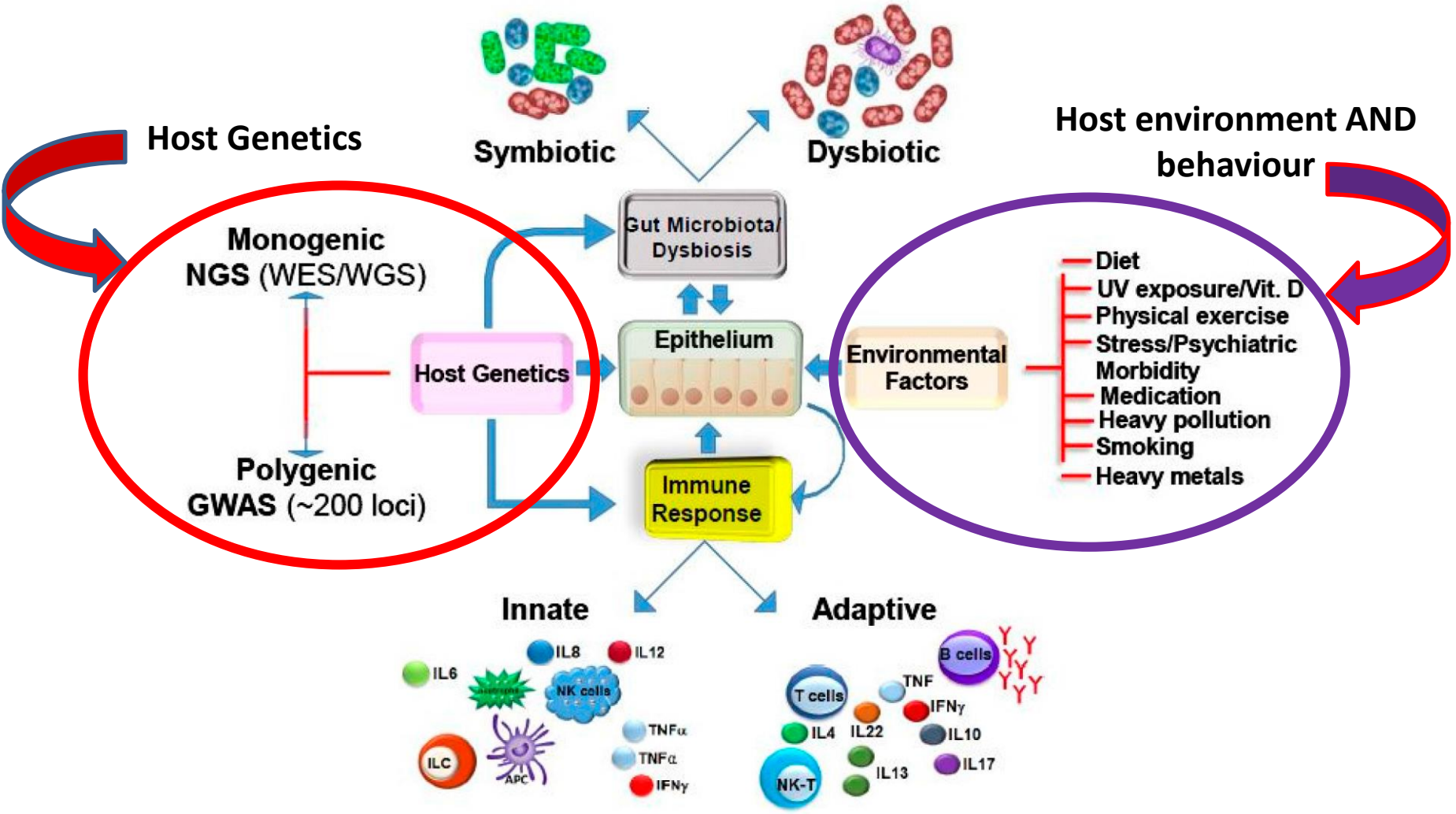
But, what constitutes a medically relevant dysbiosis?

We are walking zoos and the zoo inmates affect us



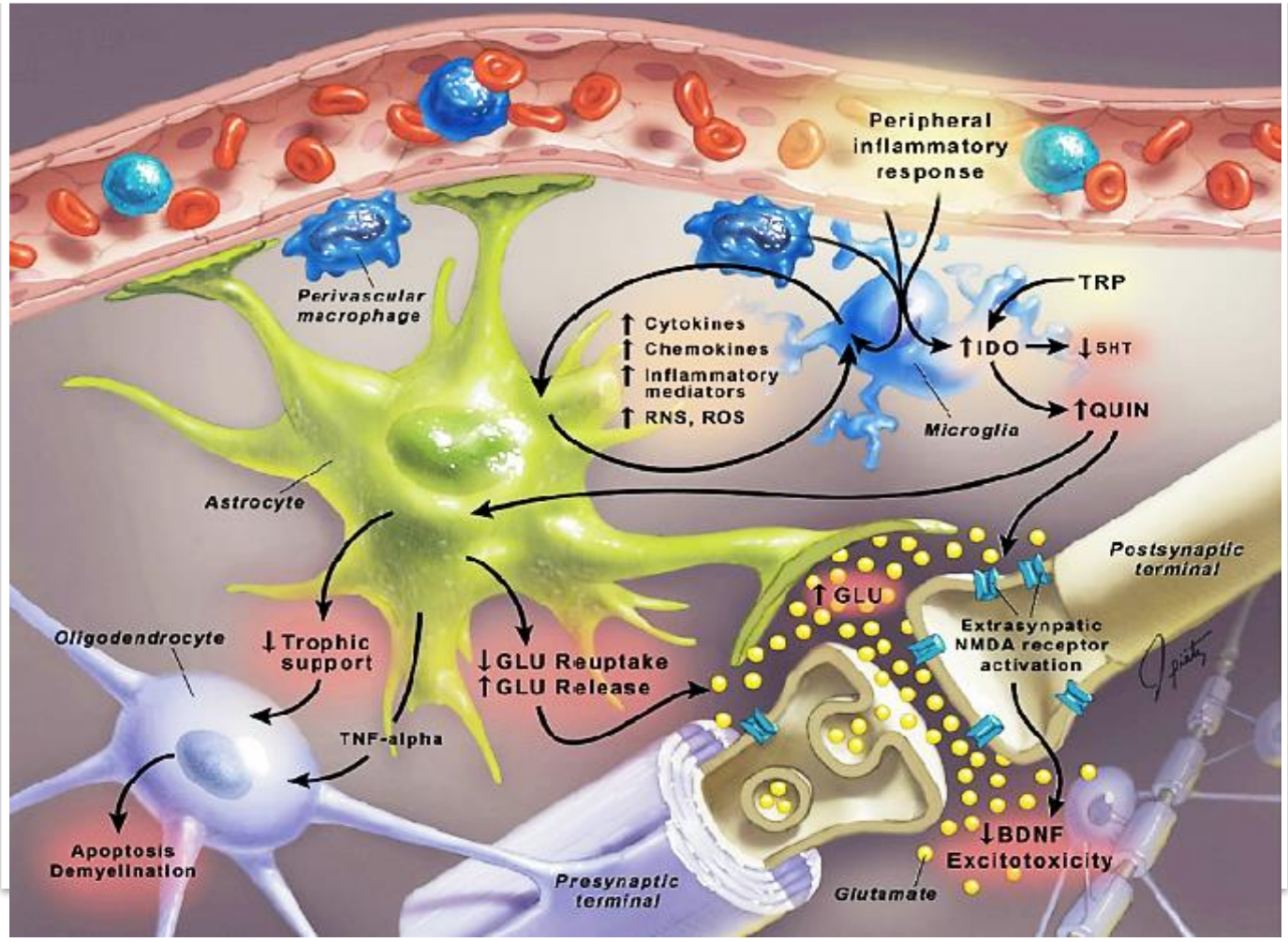
But we also affect the components of the zoo

The cross-talks between microbiota, host and environment



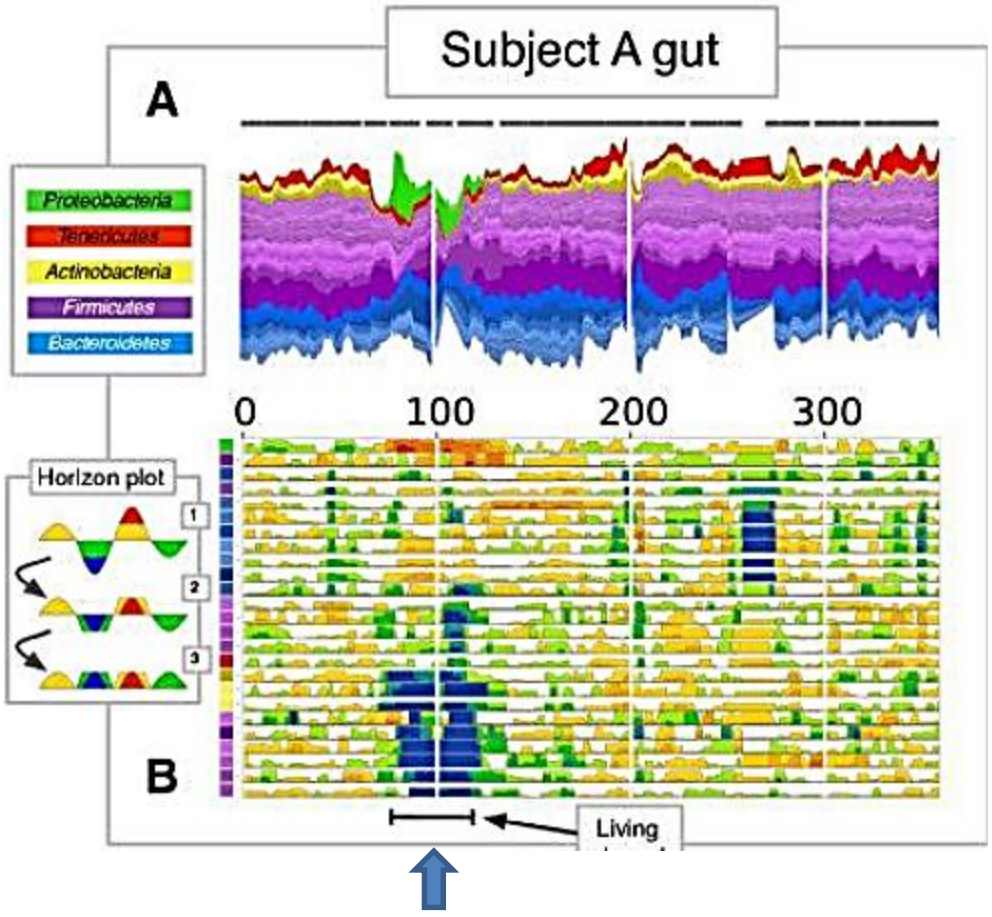
NGS: next-generation sequencing;
WES/WGS: whole-exome (mRNA)/whole-genome sequencing;
GWAS: genome-wide association study

Systemic sub-threshold pro-inflammatory conditions dysregulate CNS functions.



Neuroglial cross-talk dysregulations are typically associated with psychiatric disorders such as schizophrenia, major depression, bipolar disorder, etc..

Although over a year human-associated microbial communities appear relatively stable, they can be quickly and profoundly altered by common human actions and experiences.



Travel episode

Furthermore, microbial communities composition and populations dynamics differ significantly not only between subjects but also seasonally within a same subject.

The problems in terms of integrative biology.

Because of well installed CNS functional alterations, successful treatment of psychiatric disorders is particularly difficult to achieve by the time they become clinically evident.

Prevention is thus highly desirable.

- Given the impact of alterations in microbiota metabolic and populations dynamics upon the development of subthreshold systemic inflammation,
- The impact of subthreshold systemic inflammation upon CNS function and architecture, particularly during early pregnancy,
- The significant seasonal differences in microbial communities composition and populations dynamics observed not only between different subjects but also within a same individual, together with
- The different seasonal incidence characteristics that distinguish different psychiatric disorders,

Solid data addressing the forms of microbial dysbiosis and the conditions under which they could provoke significantly increased risks of clinically relevant psychiatric alterations becomes an inescapable prerequisite to the construction of any integrated model capable of suggesting valid preventive actions.

Hence, so long as we remain ignorant of which forms of alterations in microbial populations AND metabolic dynamics could constitute clinically relevant “dysbiosis”, designing preventive measures against psychiatric disorders pathogenesis must be addressed.
Bio-Modeling Systems launched in 2018 a CADI program to understand and manage dysbiosis.