

CURRENT AND FUTURE WAYS TO CLOSED LIFE SUPPORT SYSTEMS

2022
MELISSA
CONFERENCE

8-10
NOVEMBER
TOULOUSE
(FRANCE)



CREATING A CIRCULAR FUTURE

Human-microbes symbiosis in health and disease, on earth and beyond our planetary boundaries

*Joël Doré - INRAE, Université
Paris-Saclay, France*

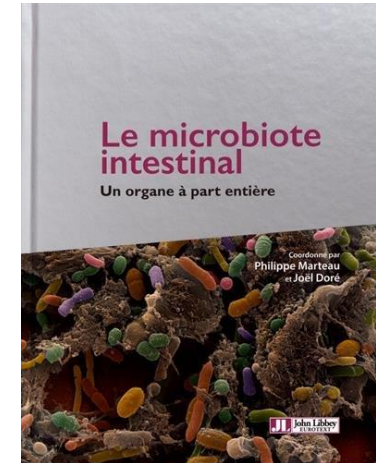


Disclaimer – links of interest :

- *Lectures for BMS, Janssen, Danone, Biocodex, Sanofi, Adisseo, Seventure, MaaT Pharma, ...*
- *Editorial work Biocodex ‘The Intestinal Microbiota’*
- *Research co-funded by Danone, Nestle, Pfizer, Adisseo, Enterome, MaaT Pharma, Ipsen, Roquette, Bridor, ...*
- *Co-founder and Scientific advisor of MaaT Pharma, Novobiome and GMT.*



**The intestinal
microbiota**
A full fledged
organ



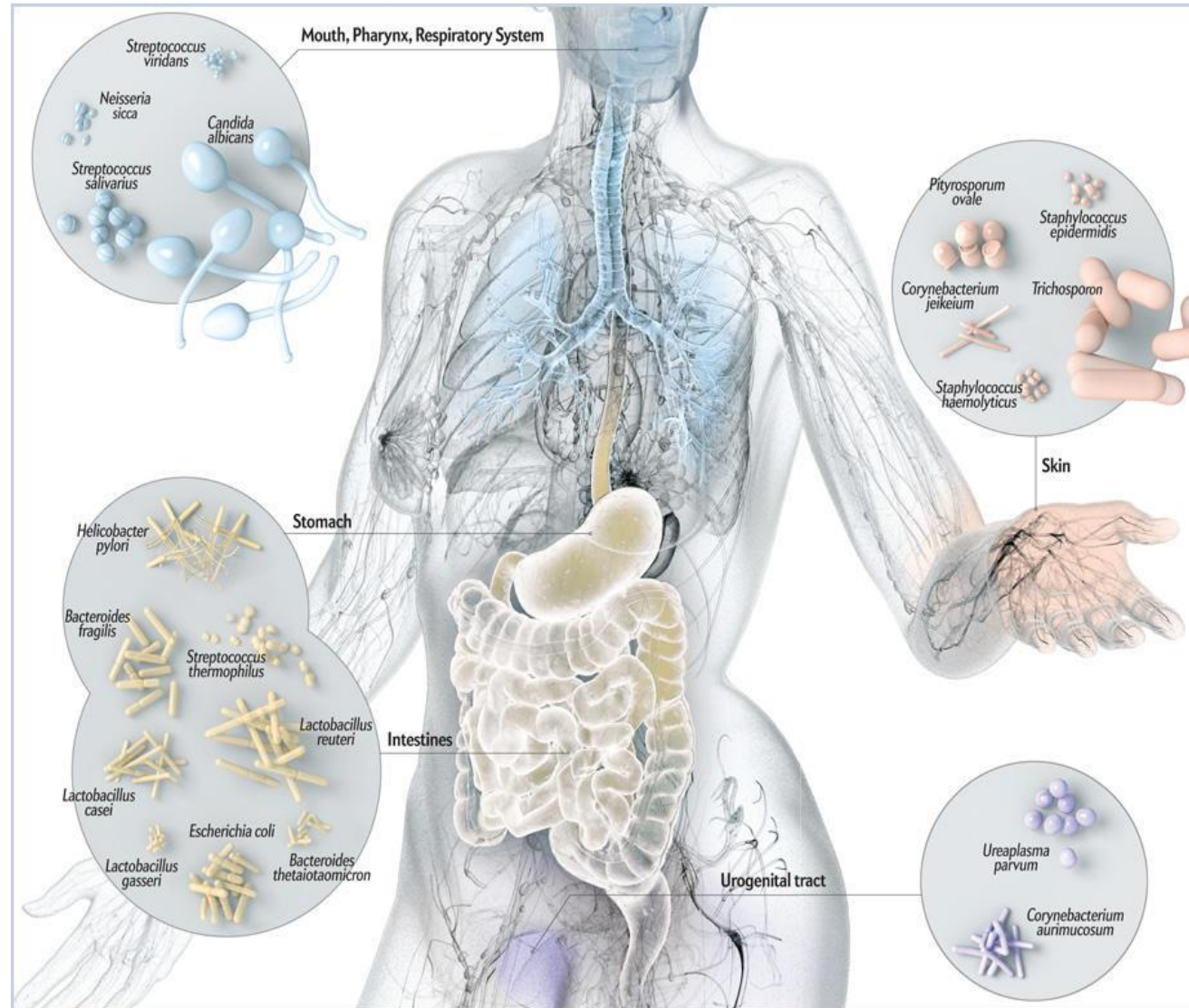
Philippe Marteau,
Sorbonne Universités, UPMC Univ Paris VI, Paris ;
INSERM-ERL 1157, CHU Saint-Antoine 27, Paris ;
UMR 7203, Paris ; services d'hépatologie,
de gastro-entérologie et nutrition, APHP,
Hôpital Saint-Antoine, Paris



Joël Doré, directeur de recherche, directeur
scientifique de l'unité de service MetaGenoPolis,
INRA, Jouy-en Josas

Humans are microbial, ecosystems, symbiosis

50 000 000 000 000 bacteria and many more microbes

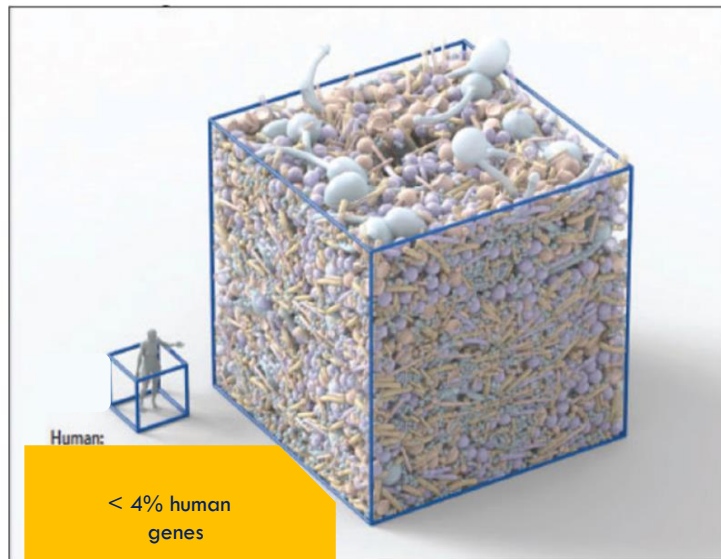


Microbiome-conferred protective functionalities

**23000 human
genes and functions**

Host-microbes symbiotic relationship

**600000 microbial genes
and functions**



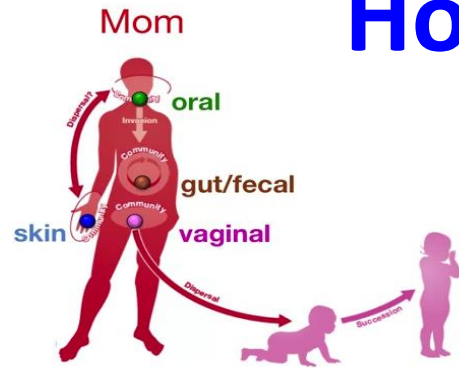
Microbiome acting as:

- **Endocrino-metabolic regulator**
 - Potentiate dietary ingredients (fibers to scfa, micronutrients, vitamins,..)
 - Bioconverts bile acids ; detoxifies
- **Immuno-inflammation regulator**
 - Promotes immune homeostasis
- **Antimicrobial protector**
 - Drives competitive exclusion
- **Neuro-vegetative regulator**
 - Promotes tissue renewal, mucin production
 - Drives systemic signaling

Microbiome Science is changing the landscape

MetaHIT Consortium. Qin et al., Nature 2010
Grice et al, Annu Rev Genomics Hum Genet 2012
HMP Consortium et al., Nature 2012

Host-microbiome symbiosis



adapted from Gonzalez et al. 2011, EMBO reports

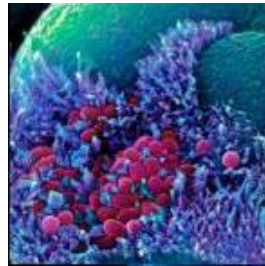
Starting at birth...



Immune maturation

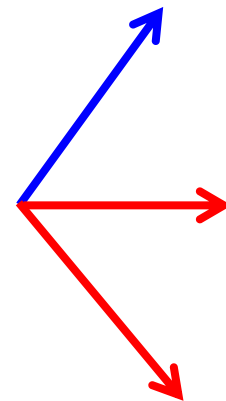


&



Development of microbiomes

Symbiosis :
gut microbiome
recognized
as a component
of 'self'



Symbiosis =
health and well-being

Ecological imbalance =
Loss of antimicrobial barrier
&
Risk of infection

Loss of immune tolerance =
Loss of homeostasis
&
Risk of immune-mediated condition

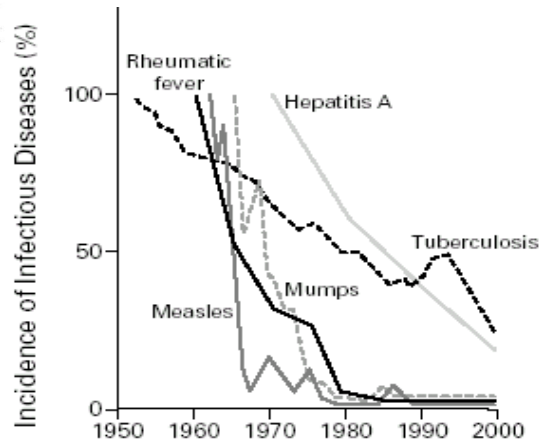
50,000,000,000 bacteria per gut microbiome
600,000 genes &
300 species on average
...and diminishing...

in spite of major progress in medicine ; an urgent need for innovation in prevention and therapy

The incidence of chronic conditions and their comorbidities
have been rising, uncontrolled, since the 1950's...

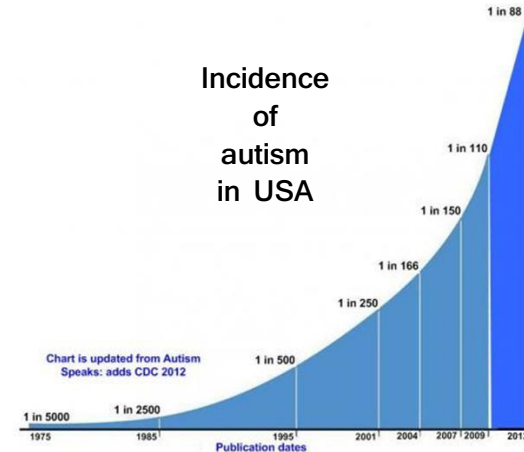


Infectious conditions



Bach JF, N Eng J Med 2002

Immune conditions



1 human in 4
by 2025 (WHO)

Recent
transitions...

- ✓ Birth mode & environment
- ✓ Life and dietary habits
- ✓ Exposure to xenobiotics

...life expectancy already impacted in the USA

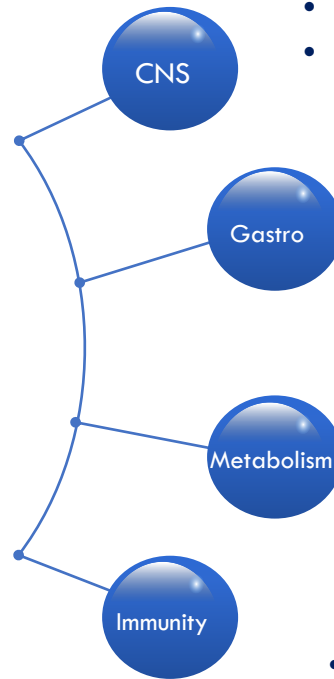
The common thread in chronic conditions

Dysbiosis : A disruption of host-microbes symbiosis

Altered microbiota
+
'leaky gut' syndrome
+
inflammatory state (mostly low-grade)
+
oxydative stress



With no current preventive
nor curative solutions



- Autism Spectrum Disorders
- Major Depressive Disorders
- Multiple sclerosis

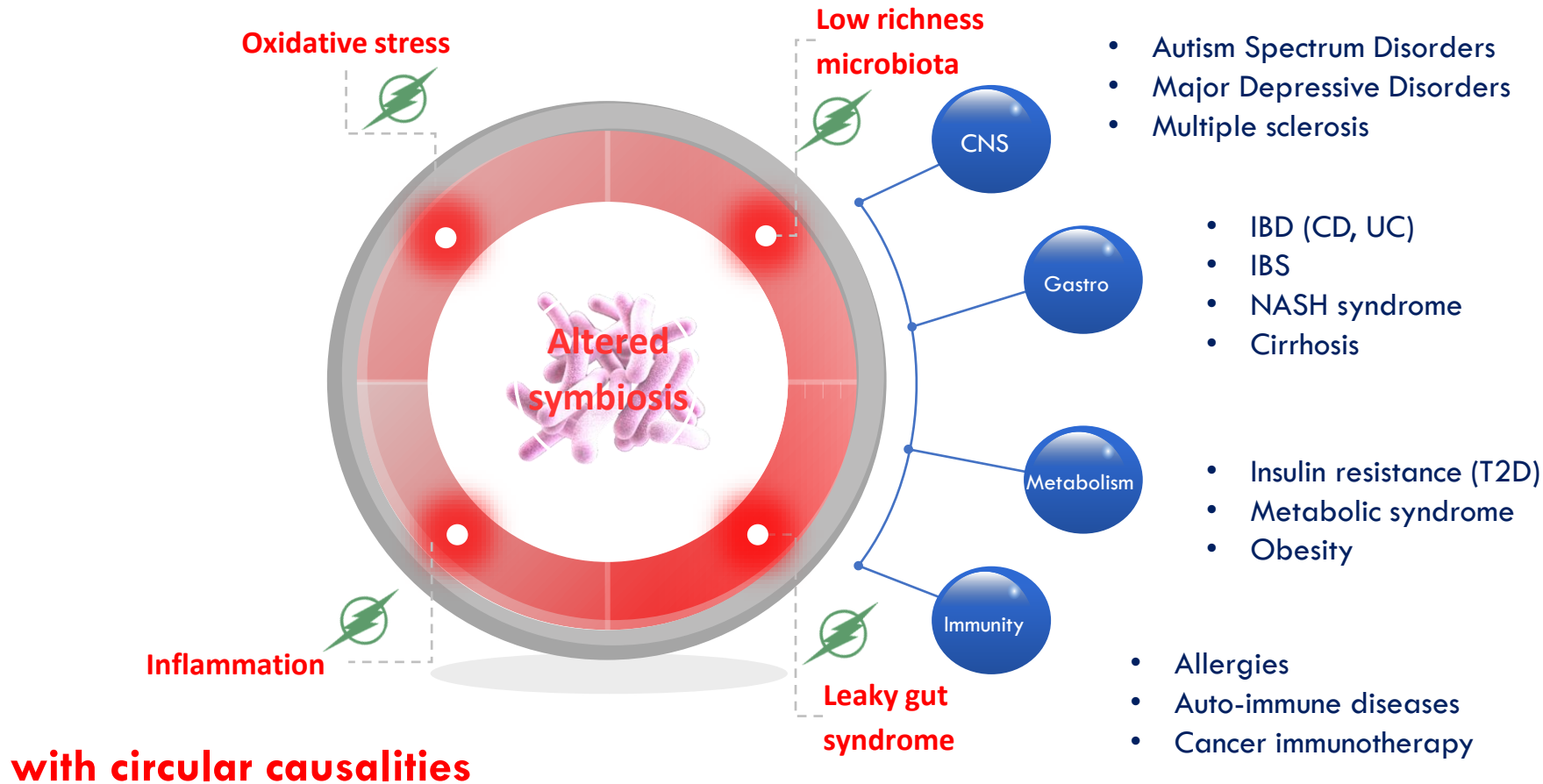
- IBD (CD, UC)
- IBS
- NASH syndrome
- Cirrhosis

- Insulin resistance (T2D)
- Metabolic syndrome
- Obesity

- Allergies
- Auto-immune diseases
- Cancer immunotherapy

The common thread in chronic conditions

Dysbiosis : A disruption of host-microbes symbiosis



Van de Guchte, Blottiere & Doré.
Microbiome. 2018

Van de Guchte, et al.
Microbiome. 2020

Van de Guchte, Mondot,
Doré. Gastroenterology 2021

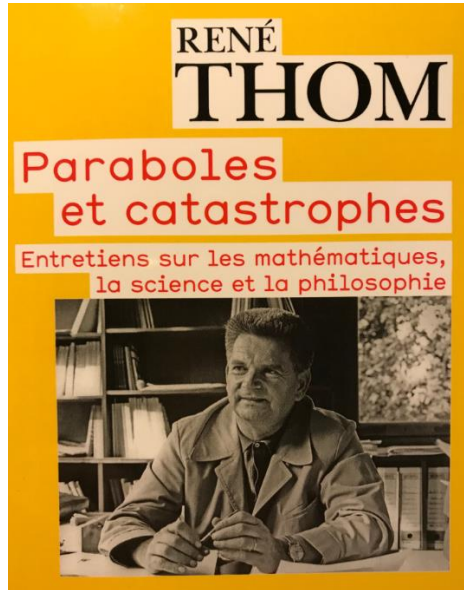


Four actionable triggers
for diagnosis, prediction,
prevention and therapy

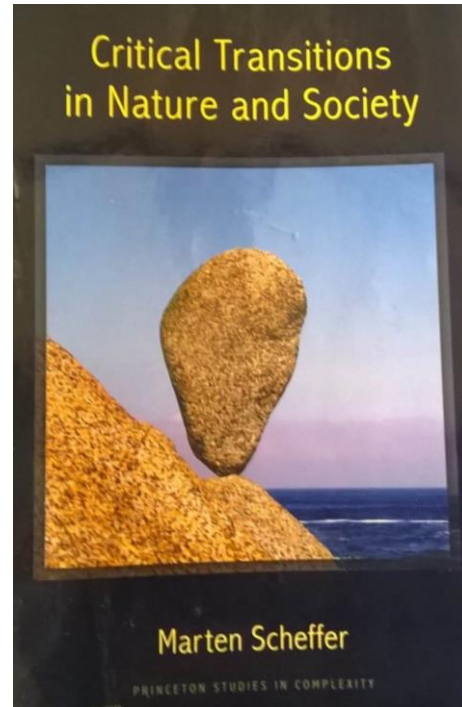
Doré et al. Therapy. 2017.



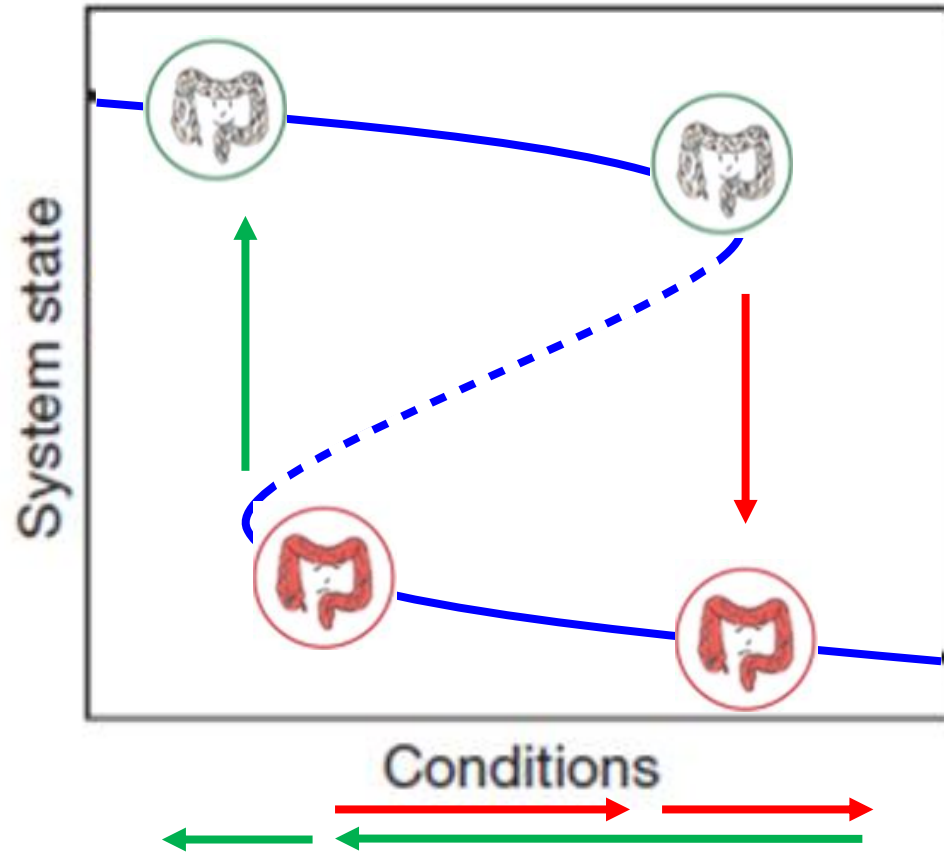
« Catastrophic shift » or critical transition ; leading to alternative stable states and hysteresis



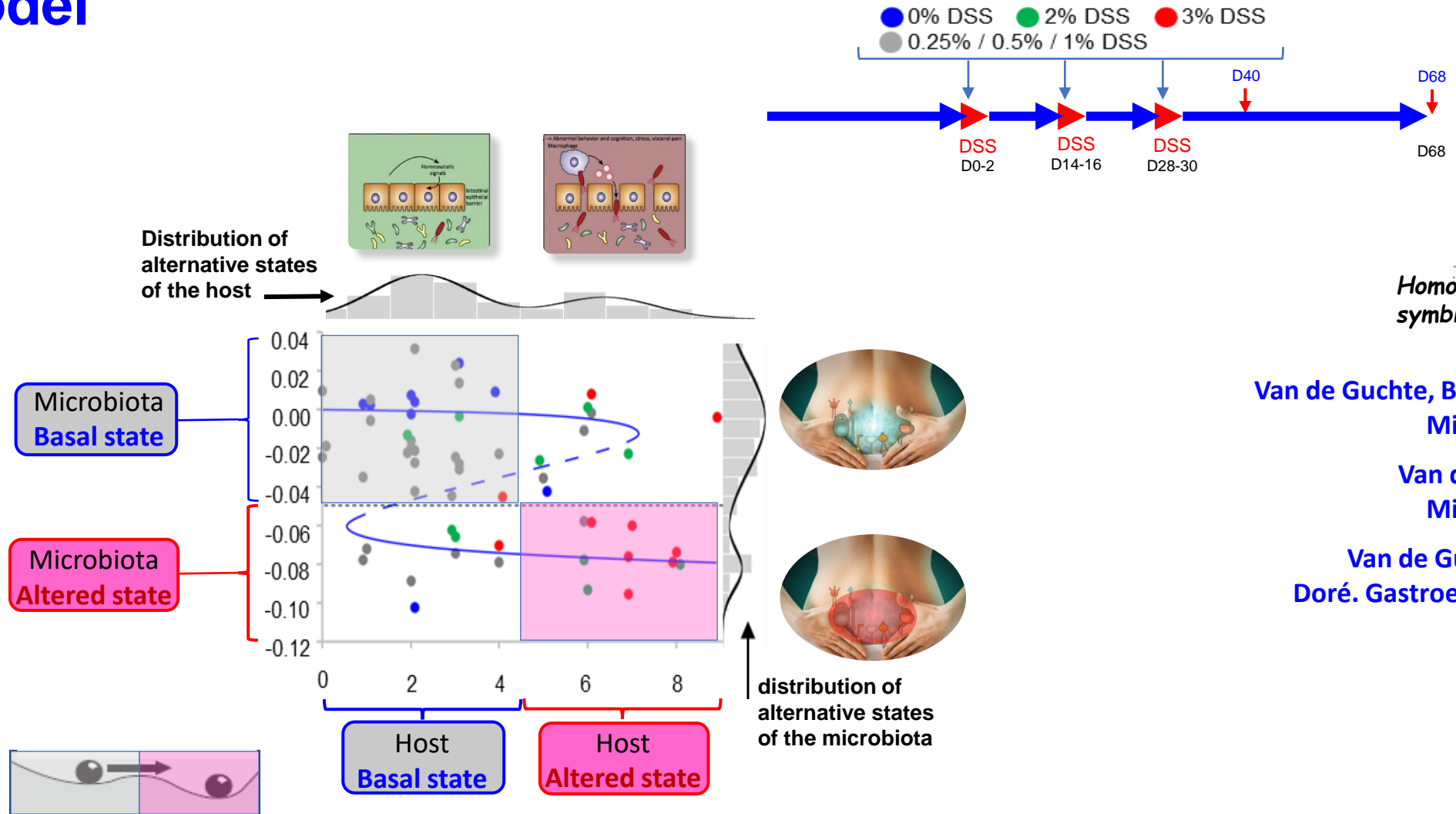
René Thom, 1983



Marten Scheffer, 2009



Inflammation alone can induce durably altered symbiosis – a rat model



Van de Guchte, Blottiere & Doré. *Microbiome*. 2018

Van de Guchte, et al. *Microbiome*. 2020

Van de Guchte, Mondot, Doré. *Gastroenterology* 2021

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Space-flight associated stress
to host-microbes symbiosis:

- microgravity
- radiation
- lack of 'symbiosis-friendly' dietary stimuli

Can we mitigate these
and promote the maintenance
of a balanced, functional
host-microbes symbiosis



Many options will not be available

“The invisible extinction” :

By Sarah Schenck

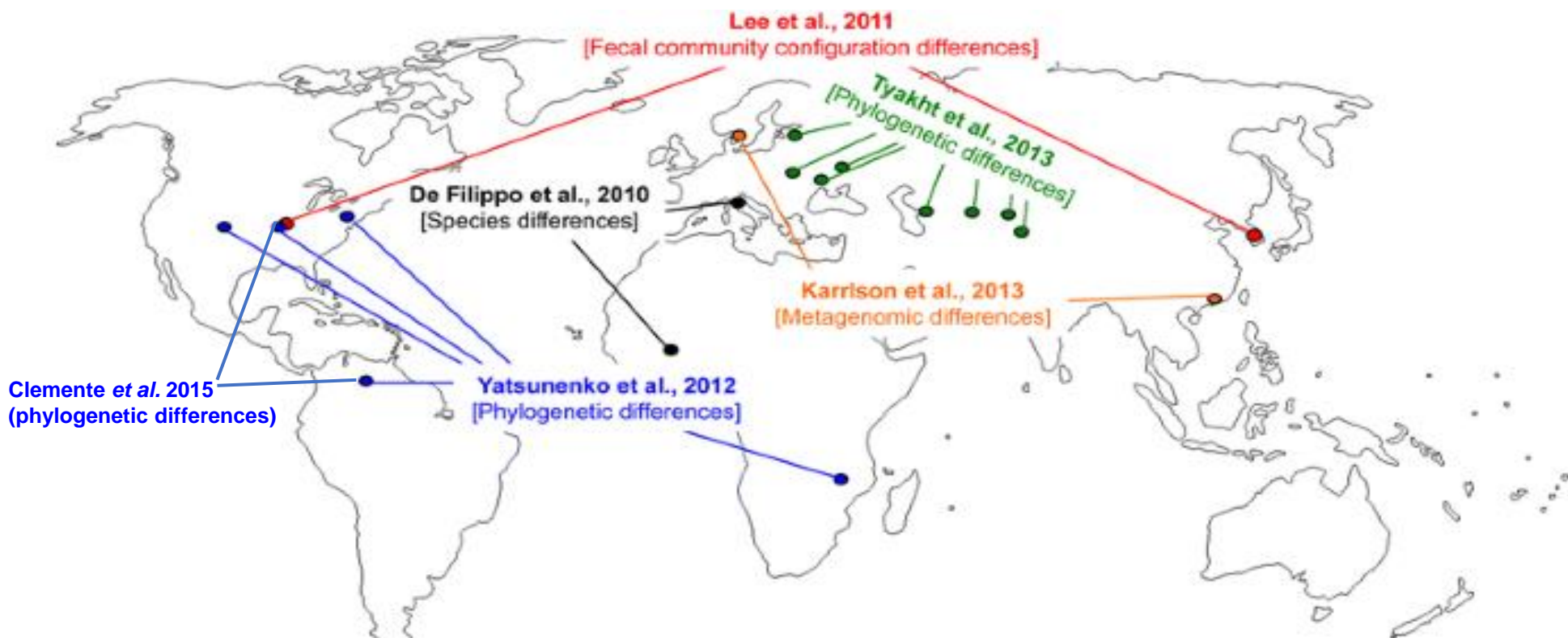
...

Loss of microbiomes richness

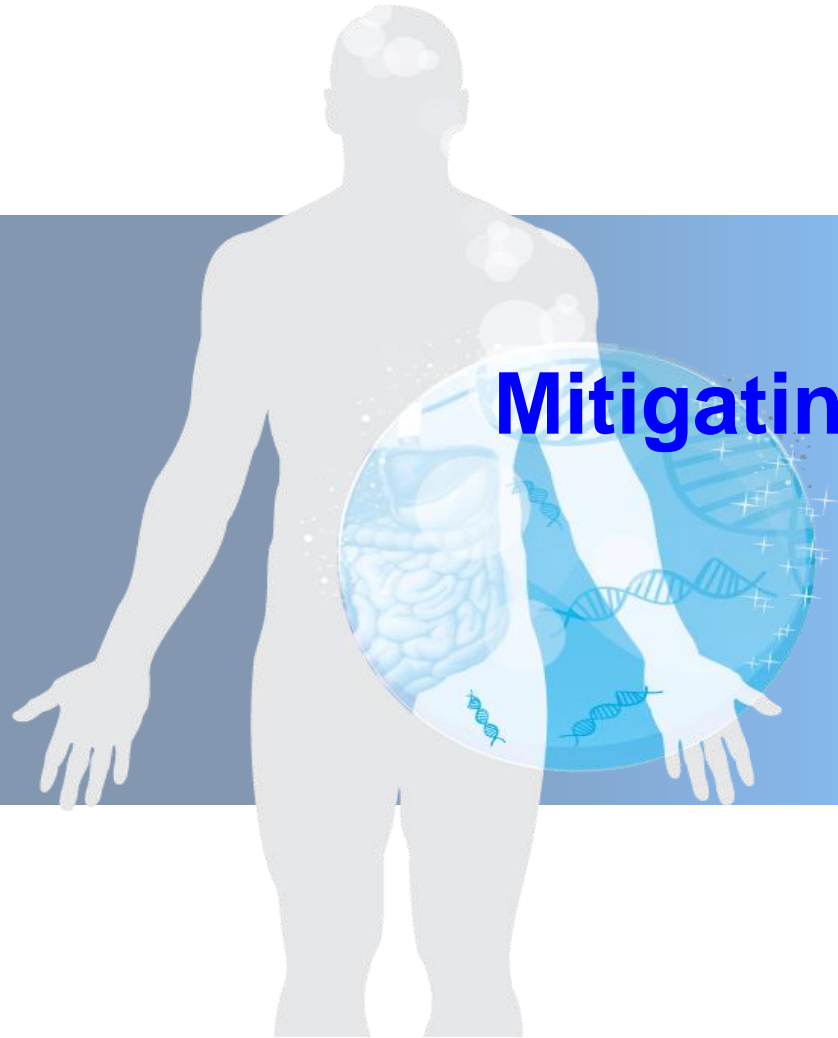


Transculturation

50% loss of
microbiome
richness



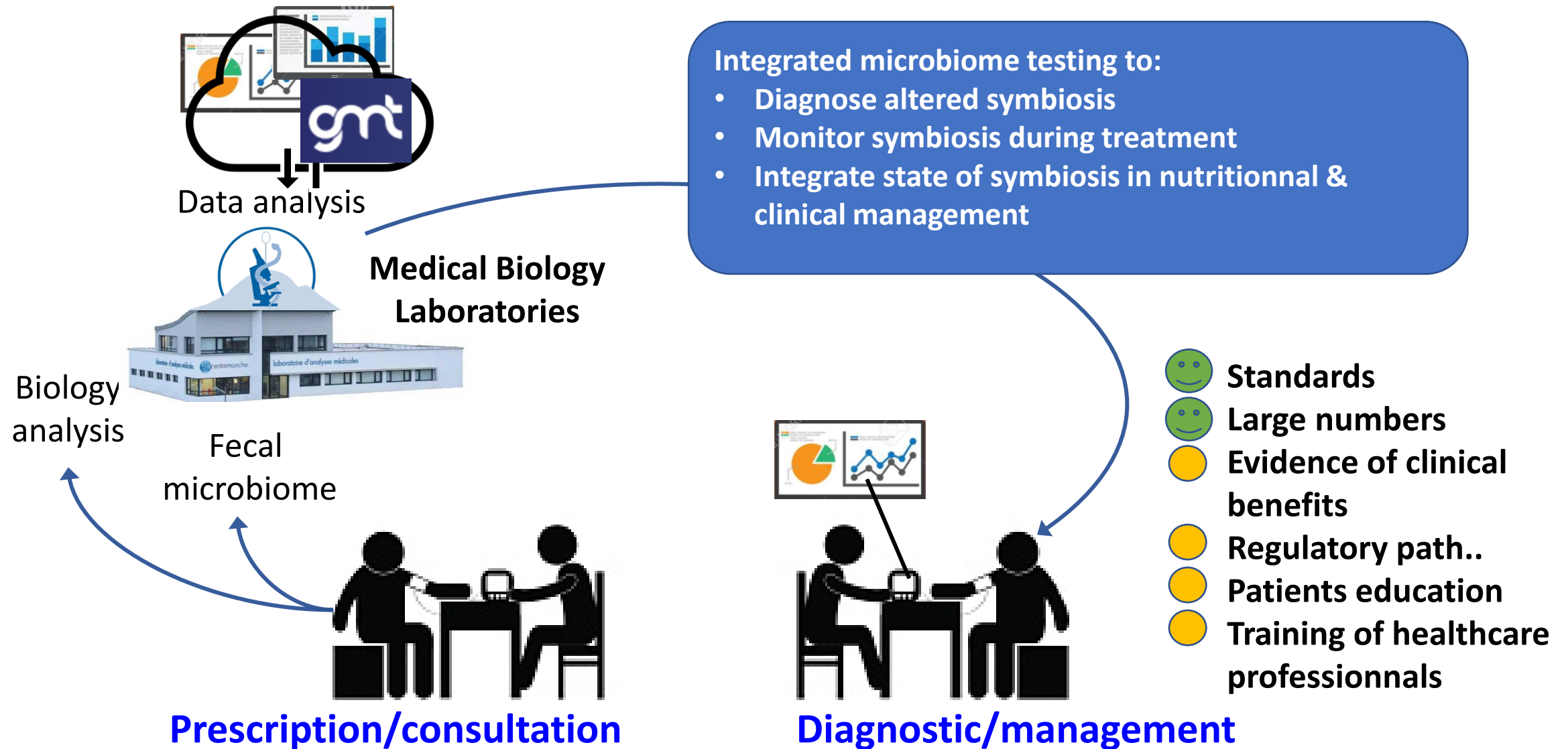
Martin Blaser (Rutgers University).. In “Missing Microbes”



Mitigating alteration of host-microbes symbiosis

- **Monitoring** microbiome & symbiosis
- **Restoring** microbiome & symbiosis
- **Resetting** microbiome & symbiosis

Monitoring the state of symbiosis as a new tool for health care professionals






Elisabeth Hohmann (Harvard Med School).. “we need microbiome clinics and we need microbiome clinicians”

Standards ...

nature
biotechnology



Towards standards for human fecal sample processing in metagenomic studies

Paul I Costea¹ , Georg Zeller¹, Shinichi Sunagawa^{1,2} , Eric Pelletier³⁻⁵, Adriana Alberti³ , Florence Levenez⁶,
...
Liping Zhao²⁶, Erwin G Zoetendal¹², S Dusko Ehrlich^{6,27}, Joel Dore⁶ & Peer Bork^{1,28-30}

Costea et al Nat Biotec 2017

<http://www.microbiome-standards.org>

>>

<http://www.mgps.eu>




... and large numbers :

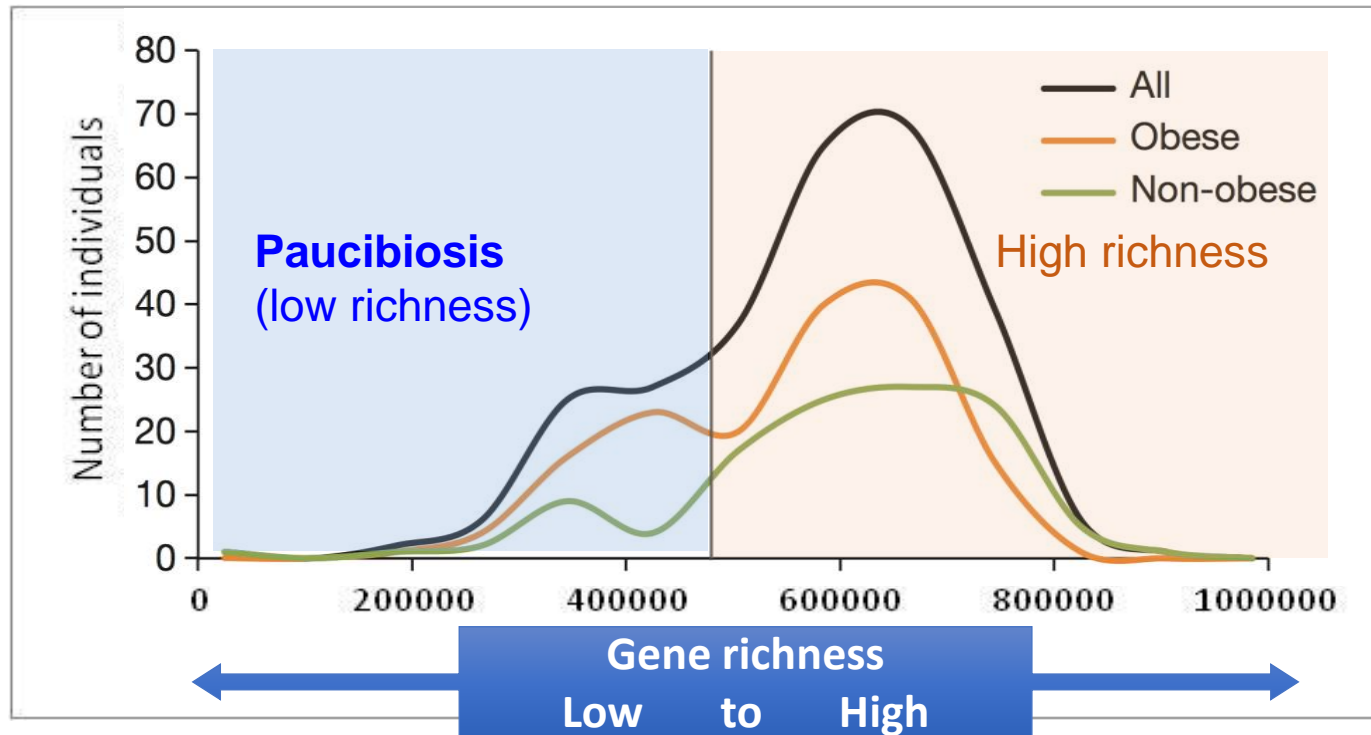
Million Microbiomes of Humans Project MMHP

Officially launched the October 26th, 2019 at the 14th International Conference on Genomics (ICG-14)

International microbiome research program

including... **Le microbiote français -**  **Le French Gut**
100,000 microbiomes of French citizens
- Inrae promoter ; AP-HP investigator -

Evidence of clinical benefits : gene richness as a health biomarker



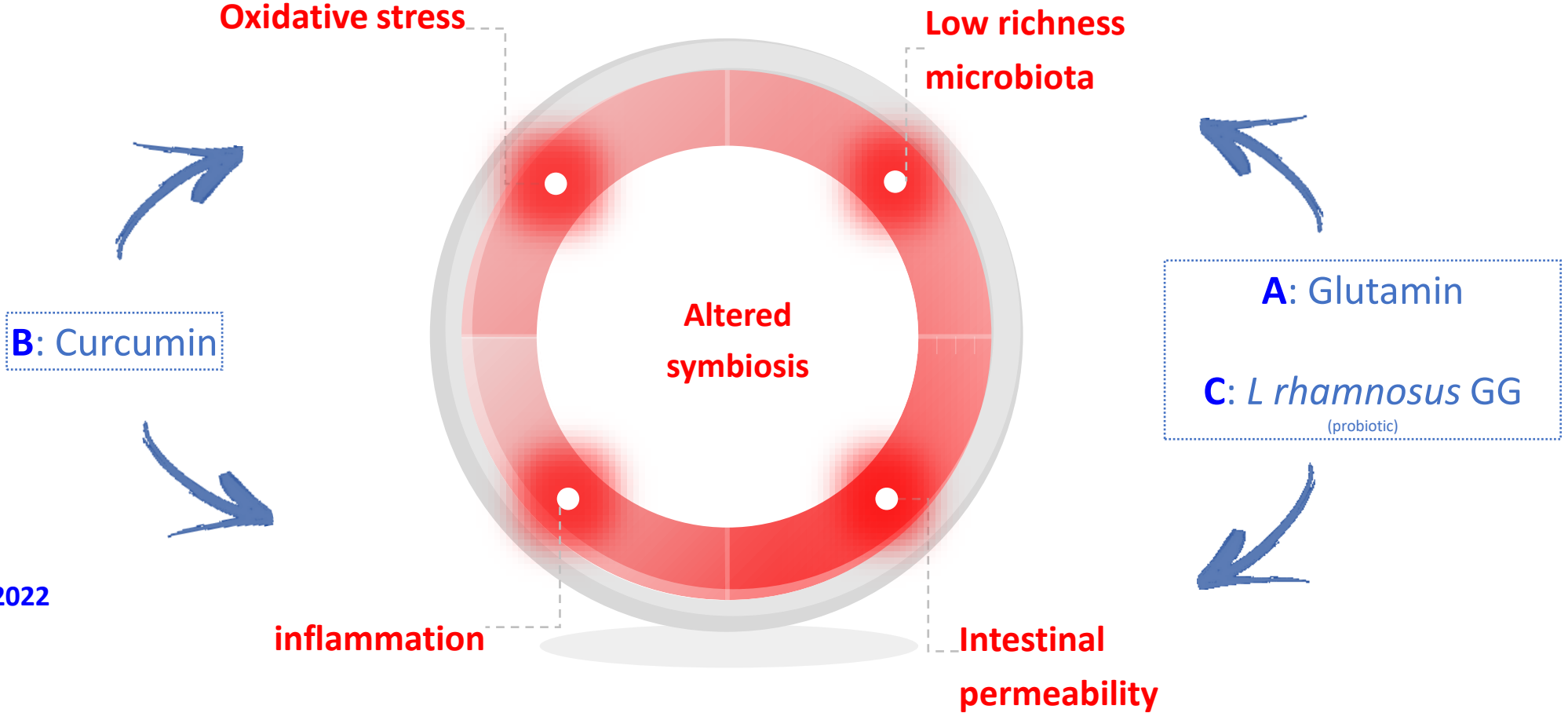
Le Chatelier et al,
Nature 2013

Paucibiosis (low gene richness) is associated with :

- Altered metabolic & inflammatory traits in overweight and obesity (**LeChatelier *Nature* 2013**)
- Non-response to a caloric restriction in obesity (**Cotillard *Nature* 2013**)
- Higher severity/faster progression in severe liver conditions (**Qin *Nature* 2014, Solé Gy. 2021**)
- Reduced progression-free survival post immunotherapy in melanoma (**Gopalakrishnan *Science* 2018**) or lung cancer (**Routy *Science* 2018**)
- Reduced survival after Stem Cell Transplantation (HSCT) in blood cancer (**Taur *Blood* 2014, Peled *NEJM* 2020**)
- higher risk of GvHD post HSCT in blood cancer (**Pamer *Blood* 2014, Jenq *Biol Blood Marrow Transpl* 2015**)

Combinatorial approach to restore symbiosis in depression - a pilot preclinical study

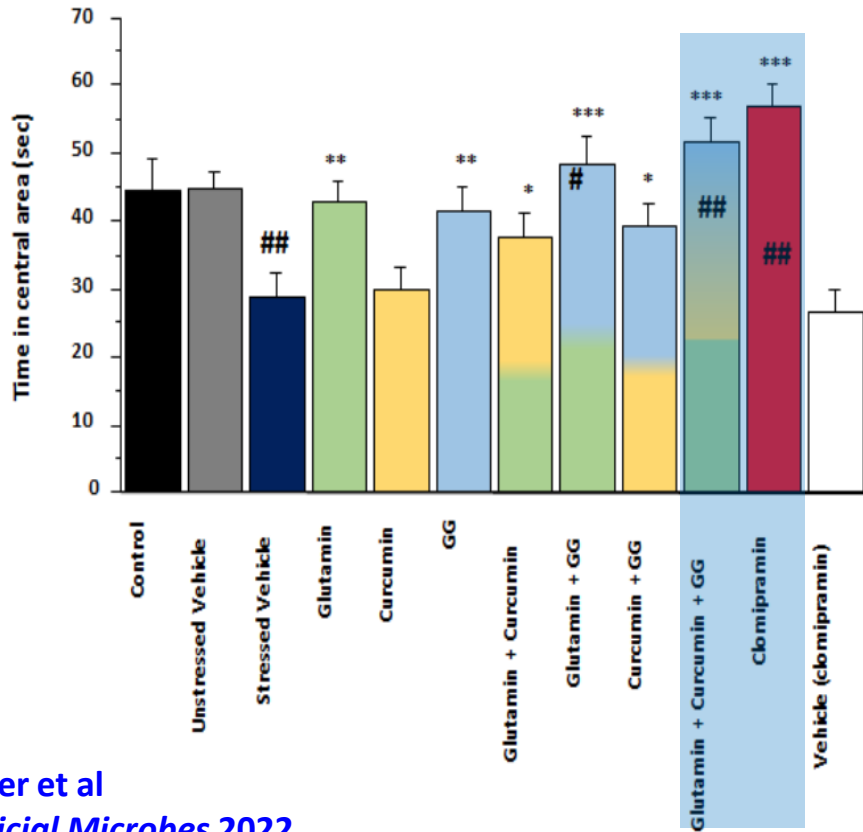
Combining bioactives (aa, micronutrient and probiotic) to alleviate symptoms in a mouse model of depression



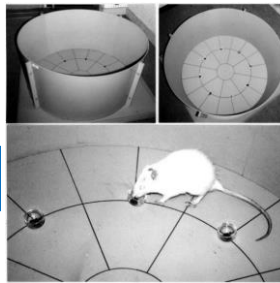
Faucher et al
Beneficial Microbes 2022

Preclinical results

Anxiety-like behaviour



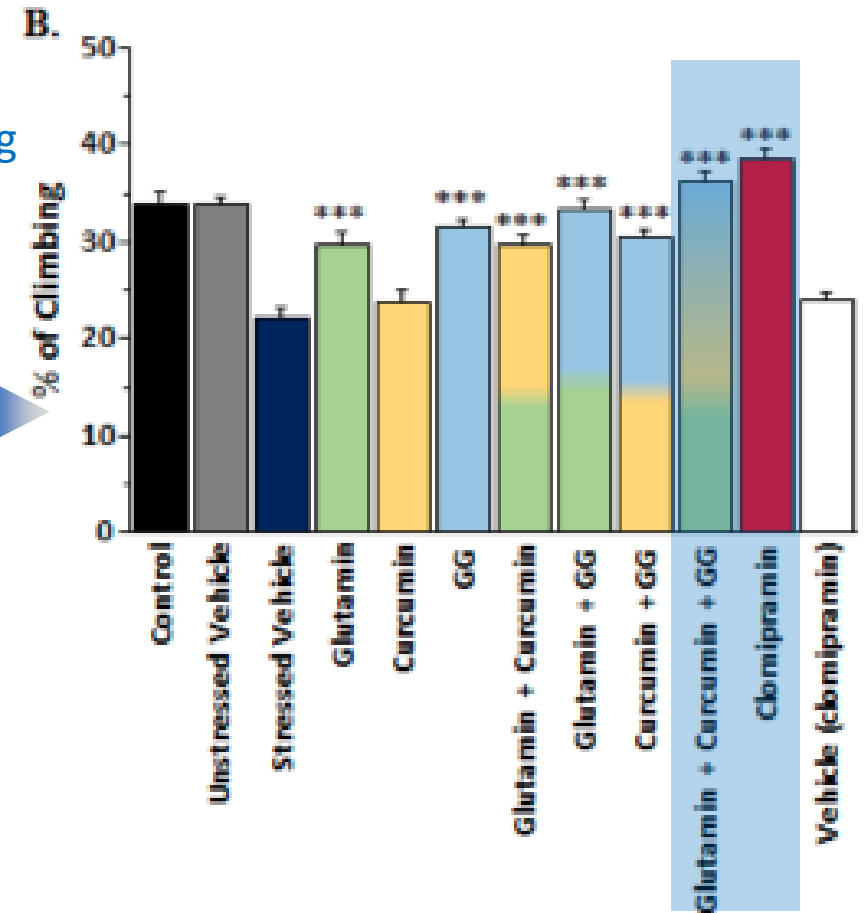
Open-field performance



Climbing test



Depressive-like behaviour



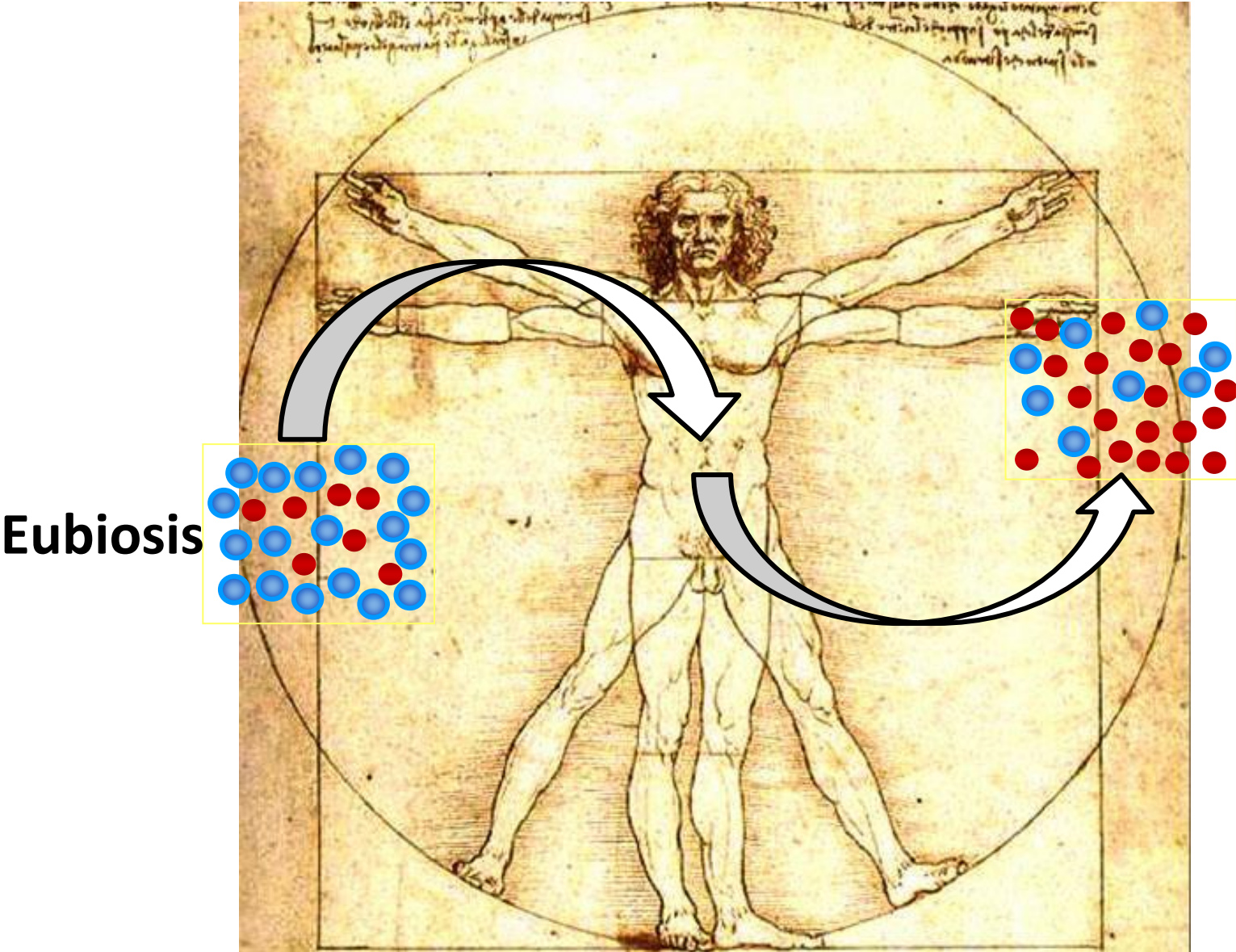
*** p < .001 vs stressed + placebo

p < .01 vs unstressed + placebo

Faucher et al
Beneficial Microbes 2022

A combotherapy with 3 food-grade bioactives shows a synergistic efficacy comparable to tricyclic parenteral antidepressant Clomipramin

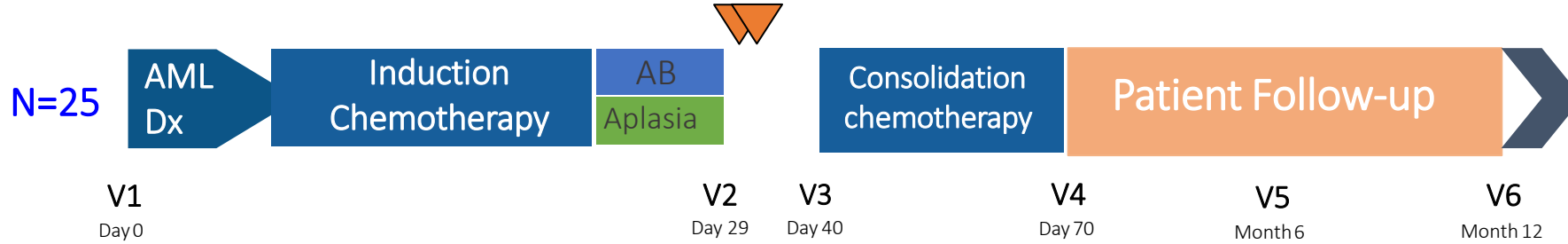
Fecal Microbiota Transfer : whole ecosystem microbiotherapy



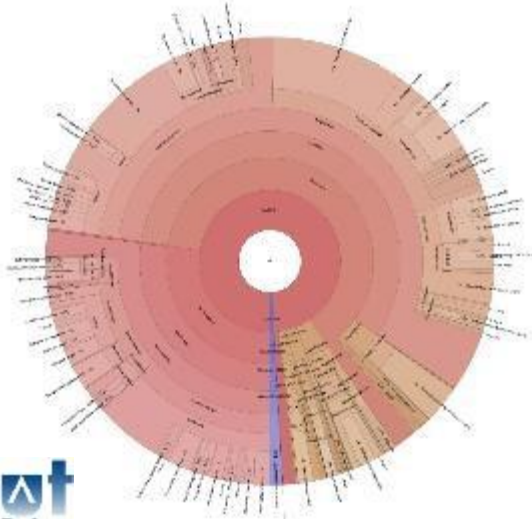
Dysbiosis

An approach aiming to reset a functional host-microbes symbiosis

PoC reset of symbiosis post chemotherapy in acute myeloid leukemia by autologous fecal microbiota transfer

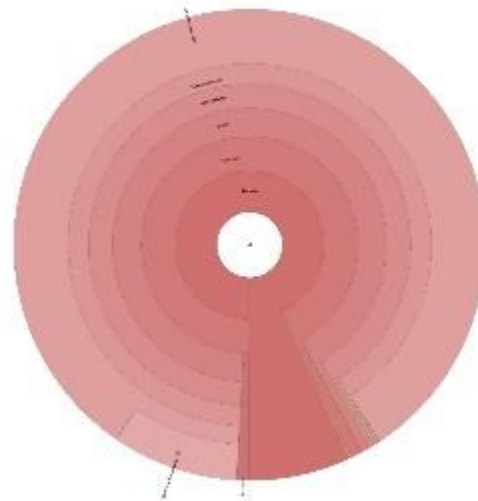


V1: AML Diagnosis



Simpson Index: 0.91

V2 (D29): Dysbiosis



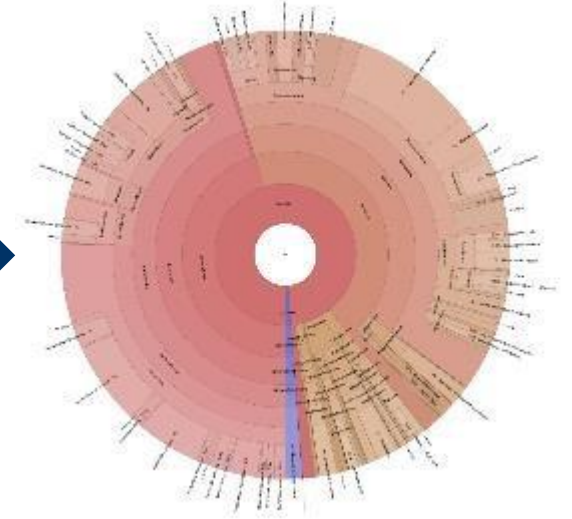
Simpson Index: 0.05

Enterococcus domination (90%)



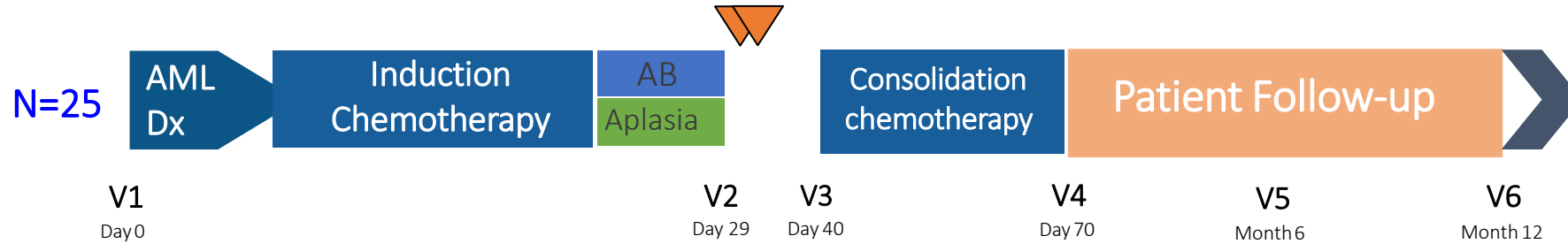
Autologous Enema

V3 (D40): Restoration



Simpson Index: 0.95

PoC reset of symbiosis post chemotherapy in acute myeloid leukemia by autologous fecal microbiota transfer



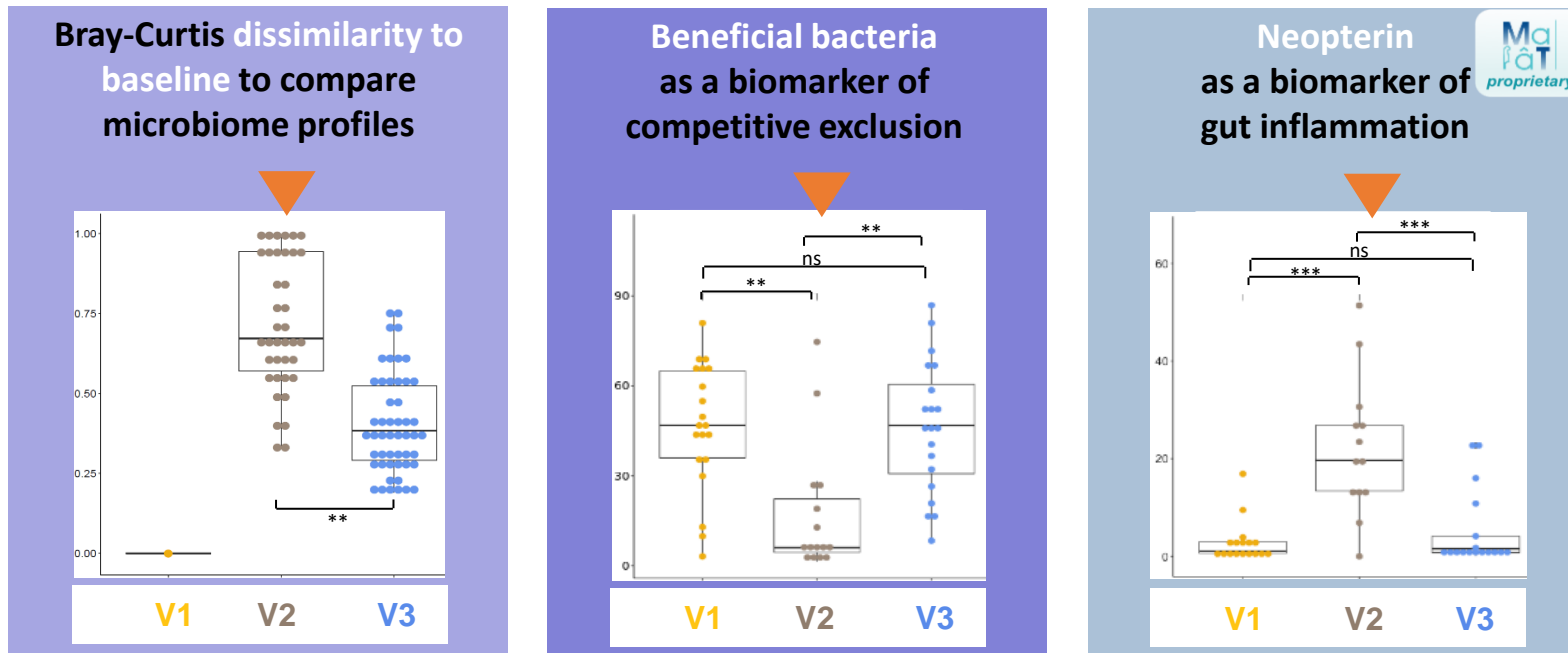
Dubuisson et al.
J Pharm Clin 2018

Burz et al.
Sci Reports 2019

Berland et al.
Sci Reports 2020

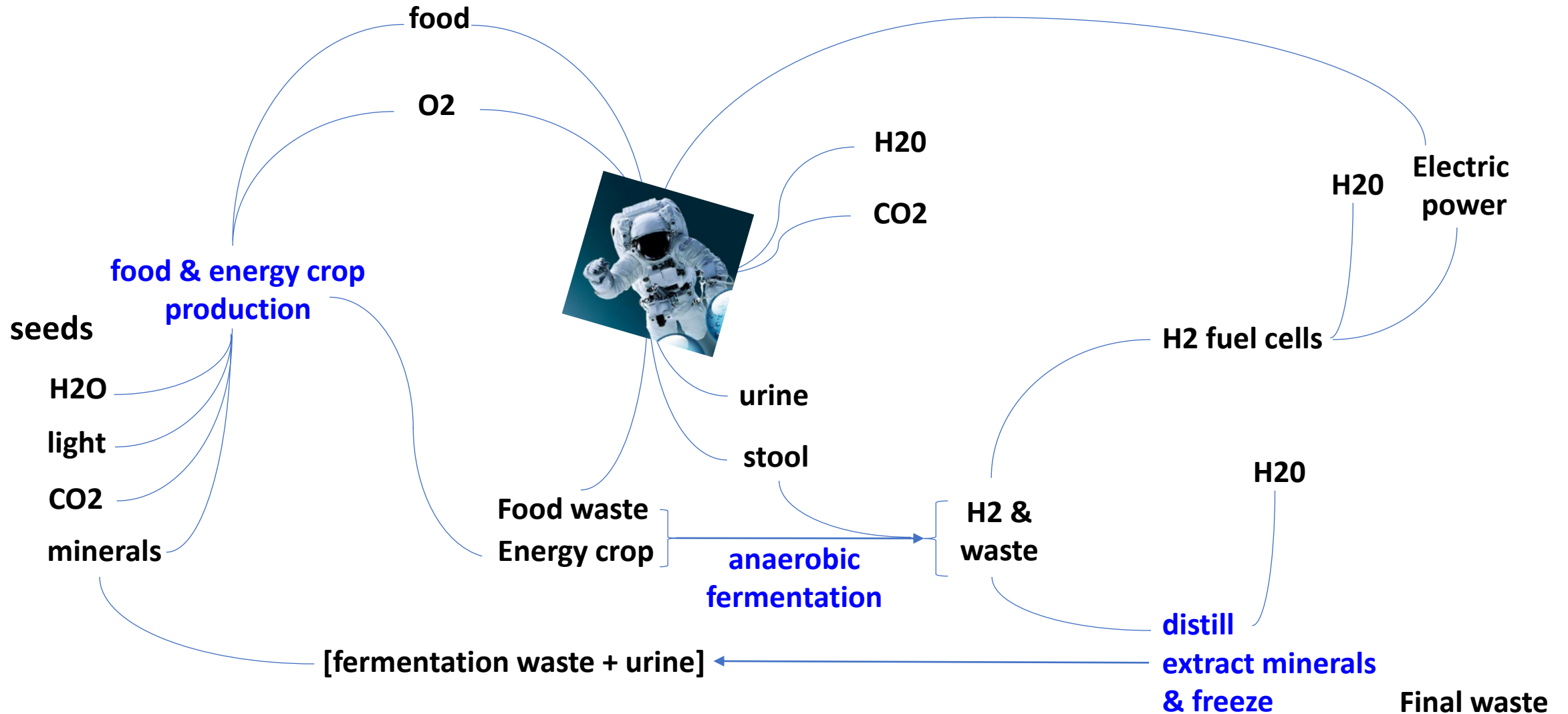
Mallard et al.
Mucosal Immunol 2021

Mallard et al.
Nature Com. 2021

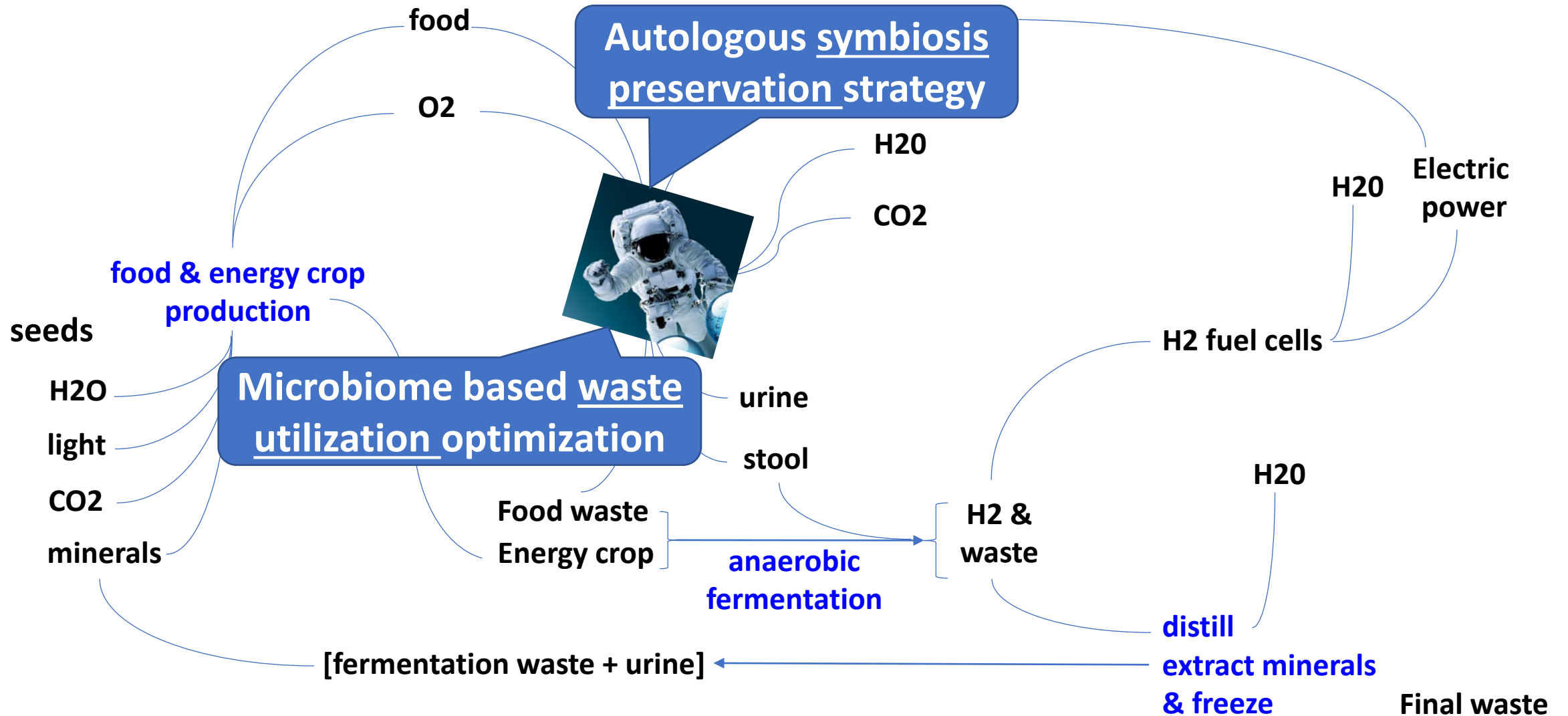


- **90%** Microbiota recovery (Simpson diversity index – Species level)
- Excellent safety profile with **84%** survival after one year (versus **70%** historical control)

Human-microbes symbiosis : needs and wastes in a closed system - health management & waste quality prediction -



Human-microbes symbiosis : needs and wastes in a closed system - health management & waste quality prediction -



Take home messages

...

- altered host-microbes symbiosis will lead to loss of protective functions.
- circular causalities & critical transition applies to host-microbes symbiosis.
- **Monitoring** : integrating microbiome and host parameters to rationalize mitigation strategies in response to specific needs.
- **Prevention or cure** :
 - **Restoring**, targeting several triggers of a vicious circle in altered host-microbes symbiosis, with a crucial place for diverse bioactives.
 - **Resetting**, using full ecosystem microbiotherapy, in autologous format, with oral formulations, or in allogenic format in patients with life threatening conditions.



Merci de votre attention
Take care of your symbiosis



joel.dore@inrae.fr

*Micalis & MetaGenoPolis, INRAE Jouy-en-Josas-Antony,
University Paris Saclay, France*



<http://www.humanmicrobiomeaction.eu>

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