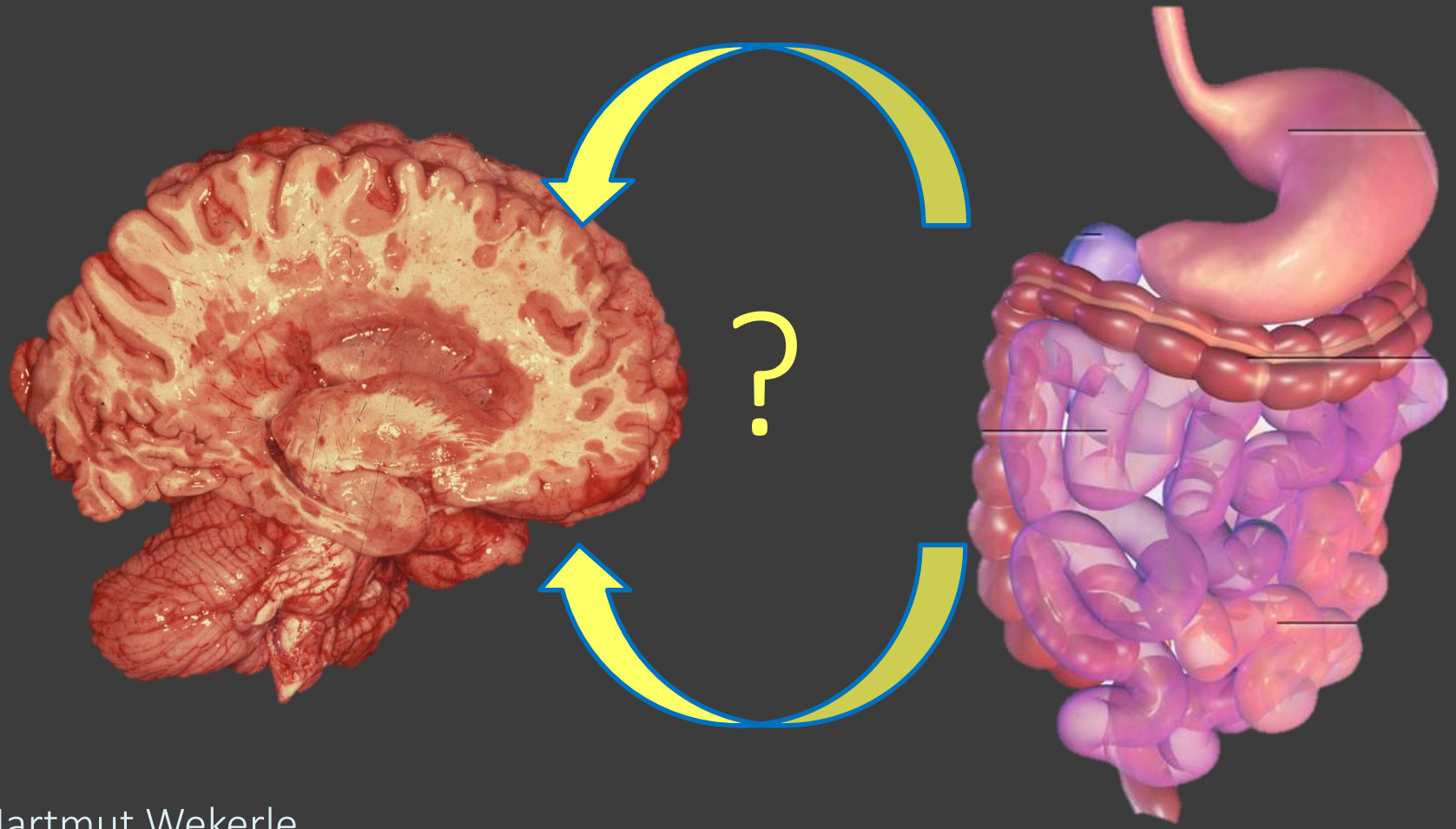
The Microbiome in Multiple Sclerosis



Hartmut Wekerle,
Max-Planck-Institute of Neurobiology,
Martinsried, Germany

Barcelona, 19-06-2019

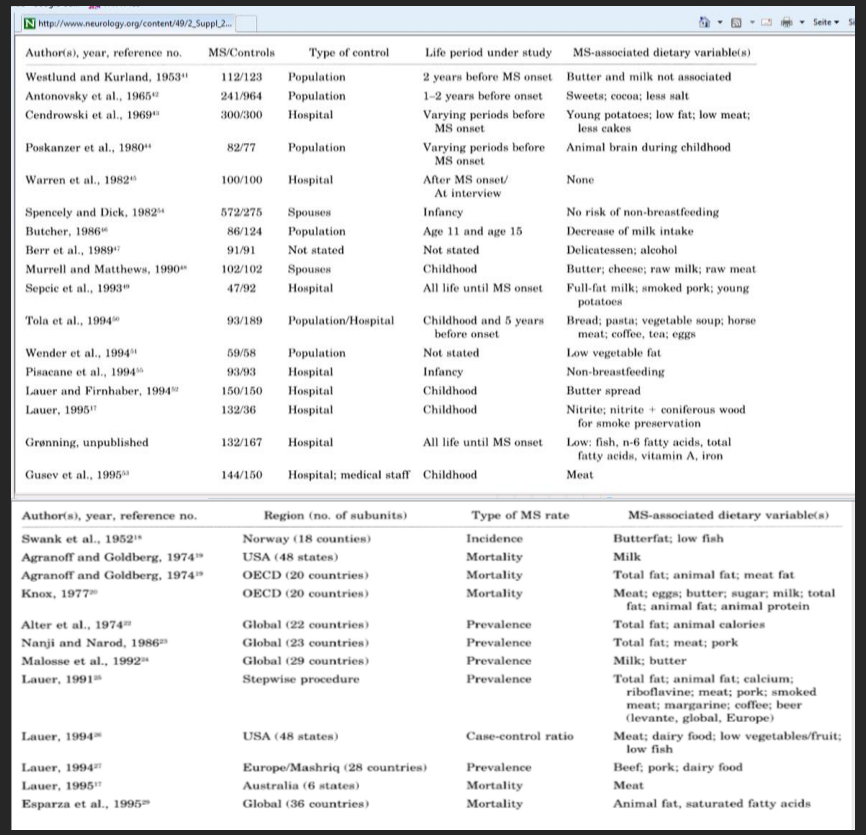
MS and Gut - Traditional

- Functional troubles (obstipation etc.)
- Diets

Multiple Sclerosis in Rural Norway — Its Geographic and Occupational Incidence in Relation to Nutrition

Roy L. Swank, M.D.†, Ola Lerstad, M.D.‡, Axel Strøm§, and Julie Backer, Ph.D.¶

Swank et al. NEJM **1952**

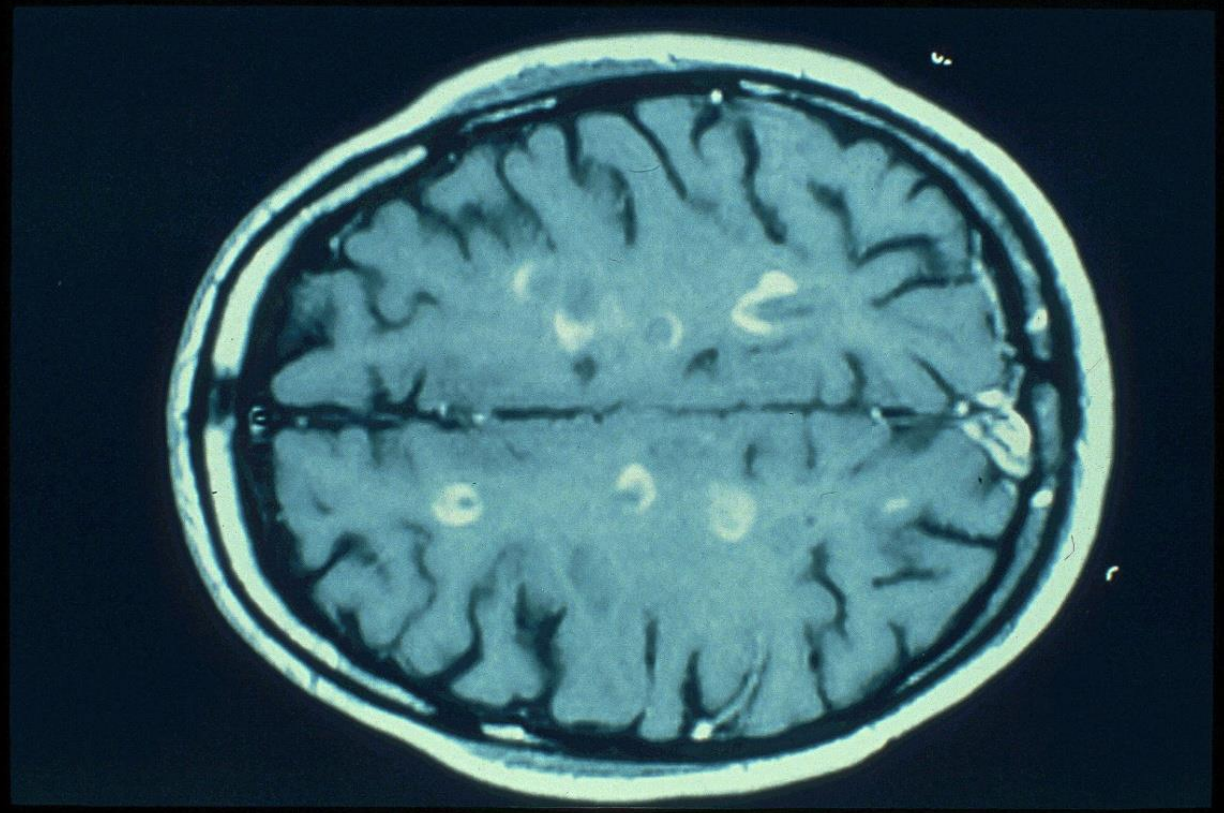


Author(s), year, reference no.	MS/Controls	Type of control	Life period under study	MS-associated dietary variable(s)
Westlund and Kurland, 1953[41]	112/123	Population	2 years before MS onset	Butter and milk not associated
Antonovsky et al., 1965[42]	241/964	Population	1–2 years before onset	Sweets; cocoa; less salt
Cendrowski et al., 1969[43]	300/300	Hospital	Varying periods before MS onset	Young potatoes; low fat; low meat; less cakes
Poskanzer et al., 1980[44]	82/77	Population	Varying periods before MS onset	Animal brain during childhood
Warren et al., 1982[45]	100/100	Hospital	After MS onset/ At interview	None
Spencely and Dick, 1982[54]	572/275	Spouses	Infancy	No risk of non-breastfeeding
Butcher, 1986[46]	86/124	Population	Age 11 and age 15	Decrease of milk intake
Berr et al., 1989[47]	91/91	Not stated	Not stated	Delicatessen; alcohol
Murrell and Matthews, 1990[48]	102/102	Spouses	Childhood	Butter; cheese; raw milk; raw meat
Sepcic et al., 1993[49]	47/92	Hospital	All life until MS onset	Full-fat milk; smoked pork; young potatoes
Tola et al., 1994[50]	93/189	Population/Hospital	Childhood and 5 years before onset	Bread; pasta; vegetable soup; horse meat; coffee, tea; eggs
Wender et al., 1994[51]	59/58	Population	Not stated	Low vegetable fat
Pisacane et al., 1994[55]	93/93	Hospital	Infancy	Non-breastfeeding
Lauer and Firnhaber, 1994[52]	150/150	Hospital	Childhood	Butter spread
Lauer, 1995[17]	132/36	Hospital	Childhood	Nitrite; nitrite + coniferous wood for smoke preservation
Grønning, unpublished	132/167	Hospital	All life until MS onset	Low: fish, n-6 fatty acids, total fatty acids, vitamin A, iron
Gusev et al., 1995[53]	144/150	Hospital; medical staff	Childhood	Meat

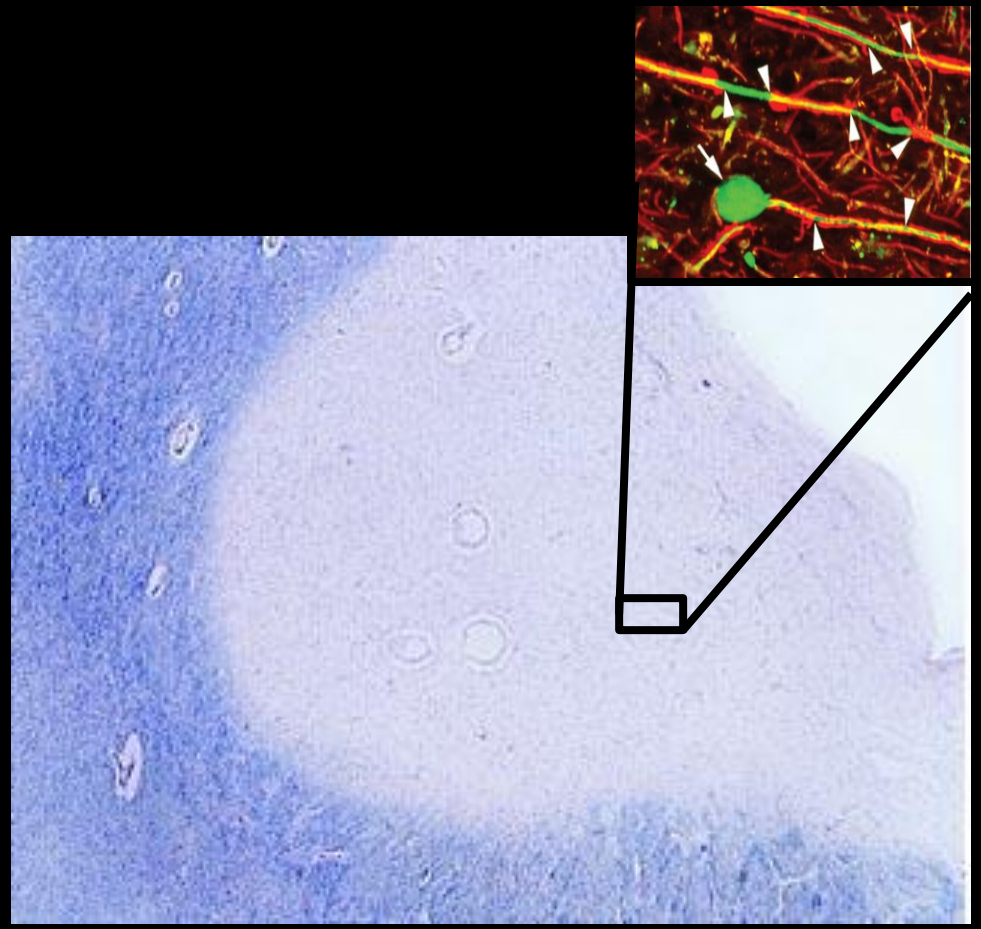
Author(s), year, reference no.	Region (no. of subunits)	Type of MS rate	MS-associated dietary variable(s)
Swank et al., 1952[18]	Norway (18 counties)	Incidence	Butterfat; low fish
Agranoff and Goldberg, 1974[19]	USA (48 states)	Mortality	Milk
Agranoff and Goldberg, 1974[19]	OECD (20 countries)	Mortality	Total fat; animal fat; meat fat
Knox, 1977[20]	OECD (20 countries)	Mortality	Meat; eggs; butter; sugar; milk; total fat; animal fat; animal protein
Alter et al., 1974[22]	Global (22 countries)	Prevalence	Total fat; animal calories
Nanji and Narod, 1986[23]	Global (23 countries)	Prevalence	Total fat; meat; pork
Malosse et al., 1992[24]	Global (29 countries)	Prevalence	Milk; butter
Lauer, 1991[25]	Stepwise procedure	Prevalence	Total fat; animal fat; calcium; riboflavine; meat; pork; smoked meat; margarine; coffee; beer (levante, global, Europe)
Lauer, 1994[26]	USA (48 states)	Case-control ratio	Meat; dairy food; low vegetables/fruit; low fish
Lauer, 1994[27]	Europe/Mashriq (28 countries)	Prevalence	Beef; pork; dairy food
Lauer, 1995[17]	Australia (6 states)	Mortality	Meat
Esparza et al., 1995[29]	Global (36 countries)	Mortality	Animal fat, saturated fatty acids

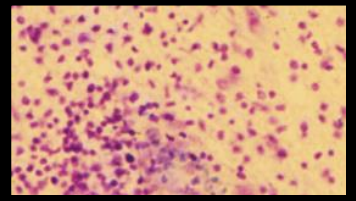
Lauer, 1997

Multiple Sclerosis: Clinical Signs, Lesions



The MS Plaque



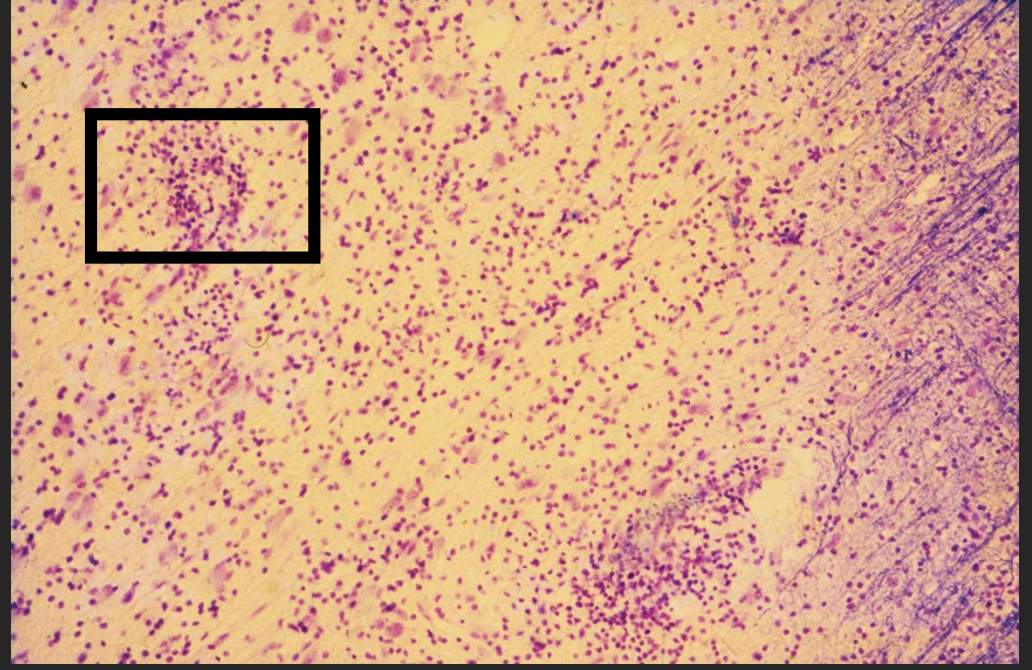


Noseworthy et al. NEJM 2000t

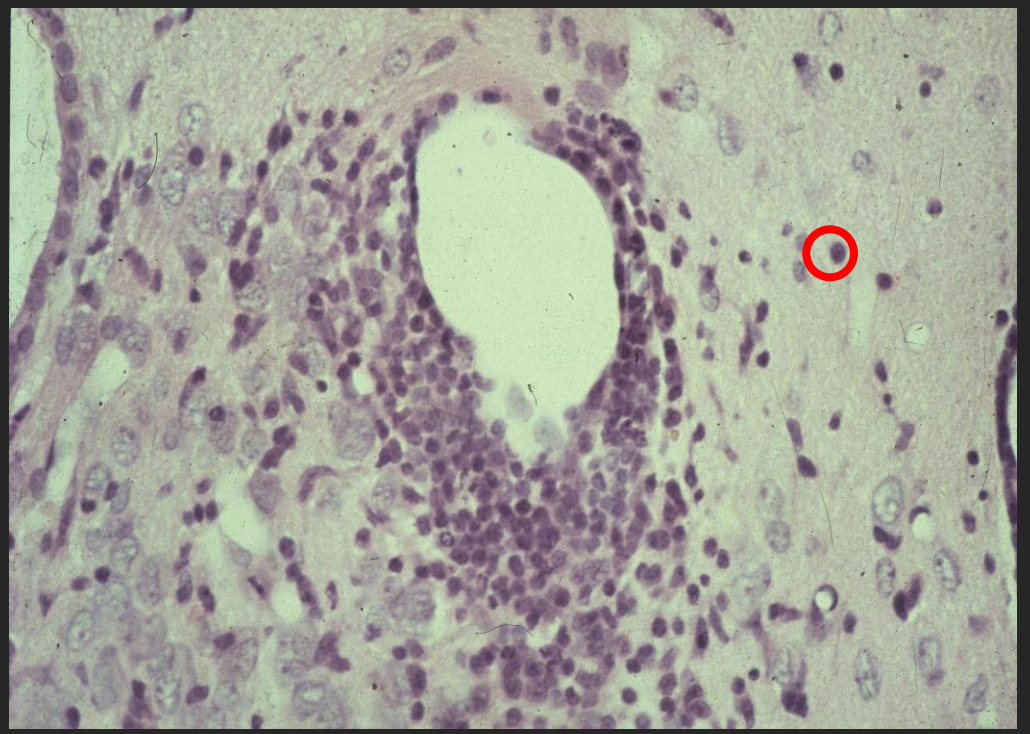
Lesions?

- Infection?
- Neurodegeneration?
- Tumor?
- „Allergic“ ???

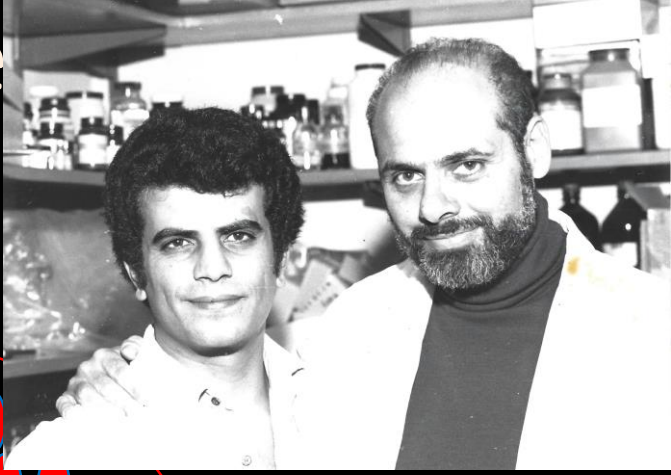
MS Lesion

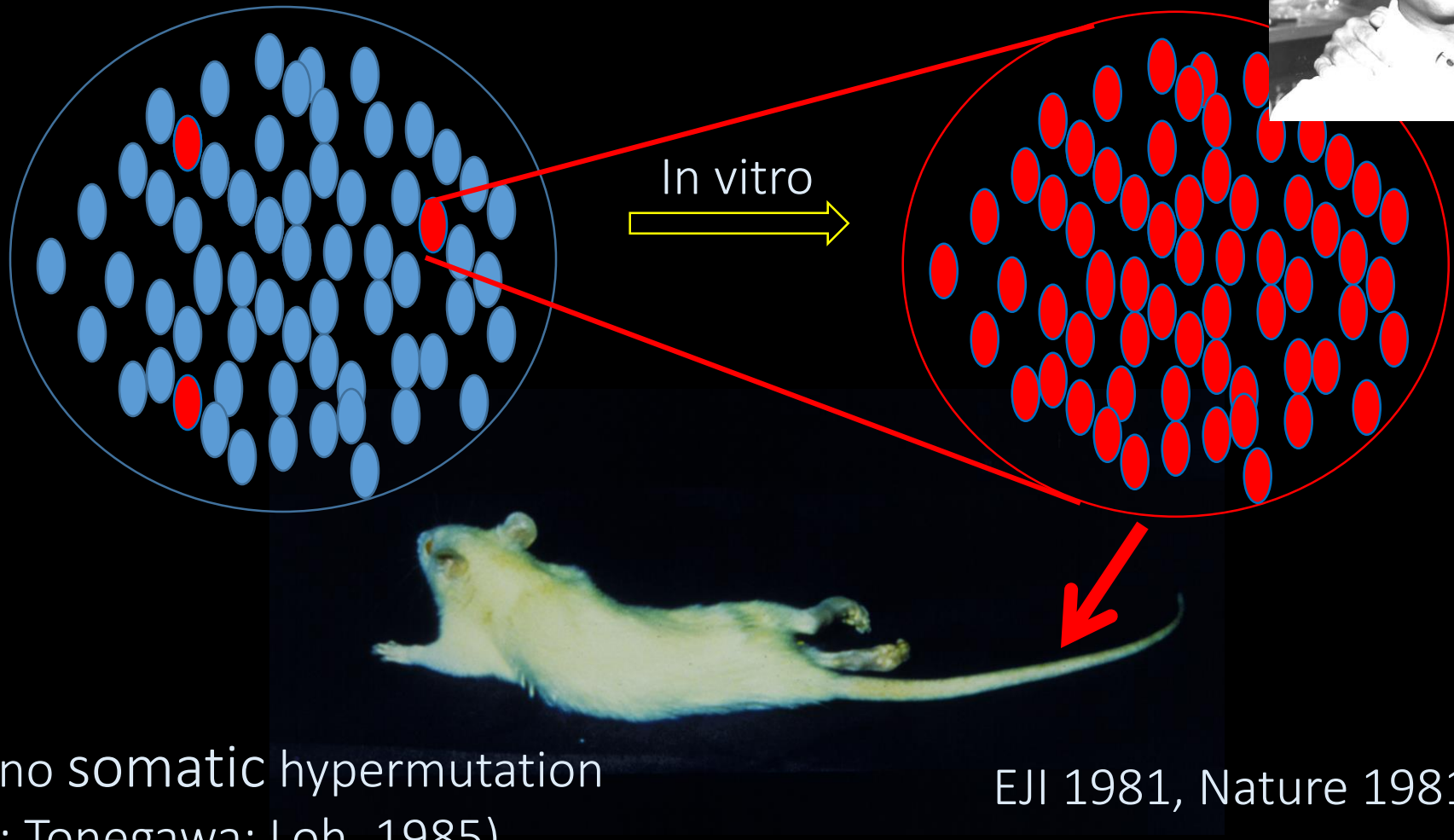


EAE Lesion
(autoimmune!)



1981 - Self-Reactive T-Cell Clone
the HEALTHY Immune Repertoi





TCR – no somatic hypermutation
(Hood; Tonegawa; Loh, 1985)

EJI 1981, Nature 1981

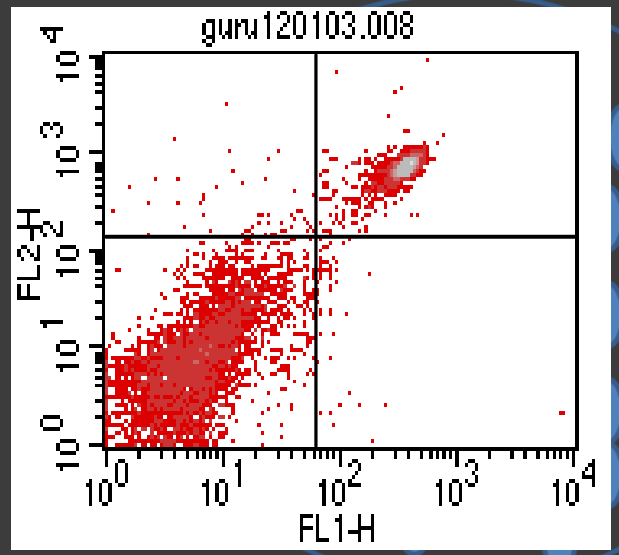
Basic Rules of (Brain) Autoimmunity:

- Self-*reactive* CD4 T cell clones are contained within the healthy immune repertoire
- Only upon *activation* these T cells become auto-*aggressive* Th1/Th17 effectors
- Could they be beneficial?

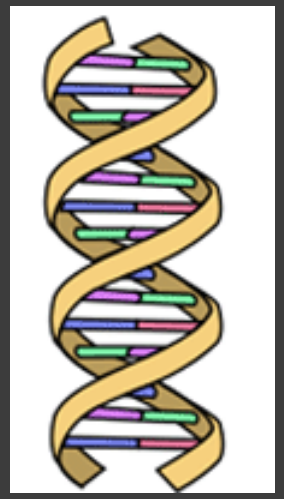
Etiological Rodent Models for MS?

- Actively induced EAE?
- Passively transferred EAE?
- Spontaneous EAE?

Self-Reactive T-Cell Receptors in Transgenic RR Mouse

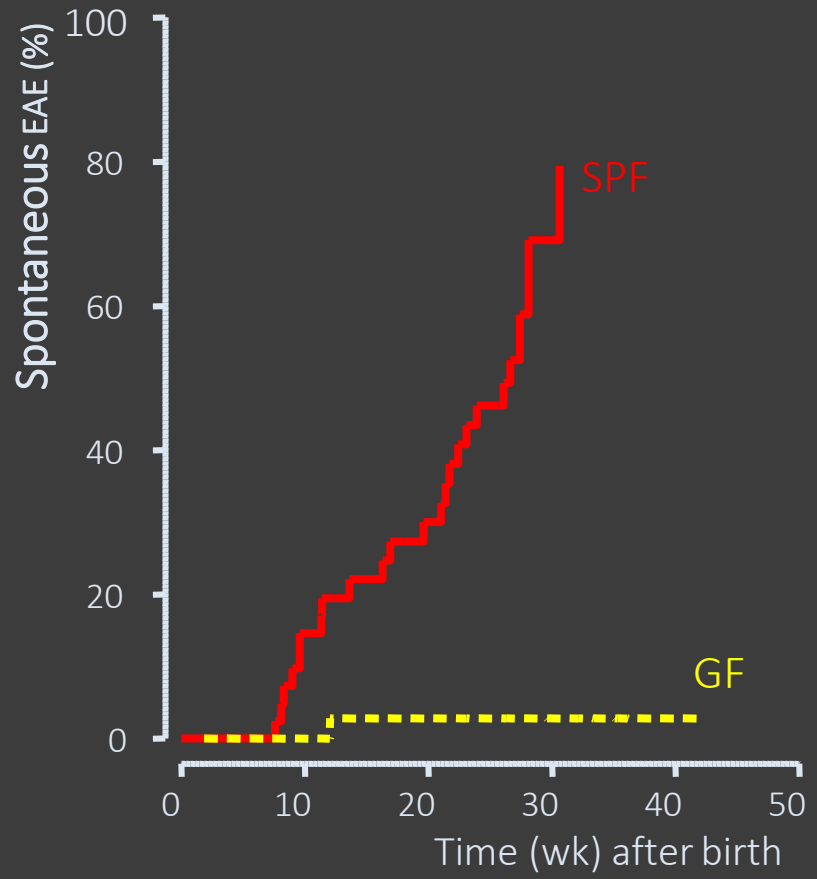


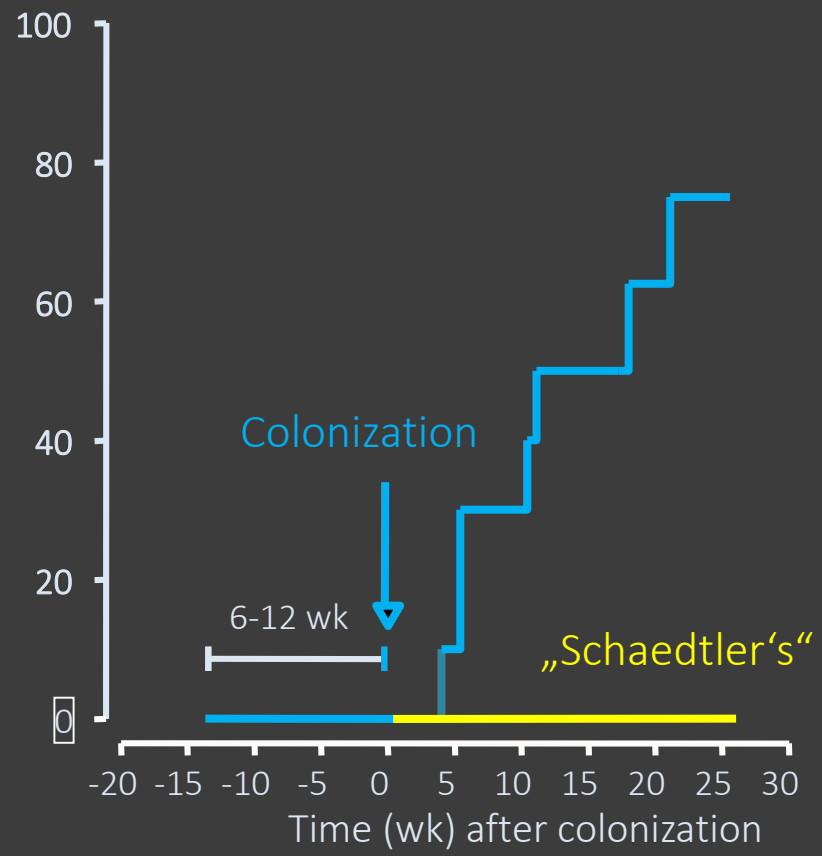
TcR Genes



I-A^s/MOG 92-106

Microbiota and Spontaneous RR EAE





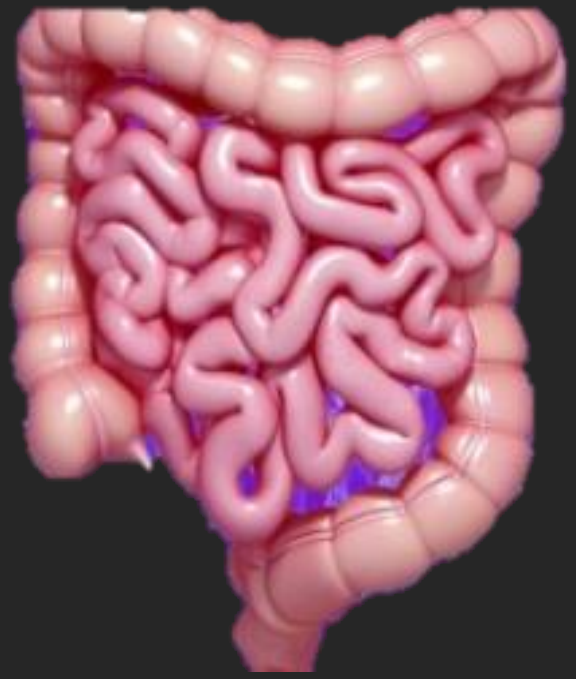
Berer et al., NATURE 2011

Gut and CNS Autoimmunity

(Auto-) Antigen Presentation

Microbial & Dietary Products

Immune Cells



Bacterial structures (LPS)
Gut metabolites (SFA)
Hormones (serotonin)
Neurotransmitters (GABA)
Innervation (N. vagus)

Pattern forming ligands
Antigenic mimicry

MS and Gut: Now Microbiota!

Gut and CNS

- Microglia
- Astrocytes
- Neurons

Gut and Immune System

- Innate immune reactivity
- Adaptive immune reactivity
  - Maturation
  - TCR recognition (mimicry …)

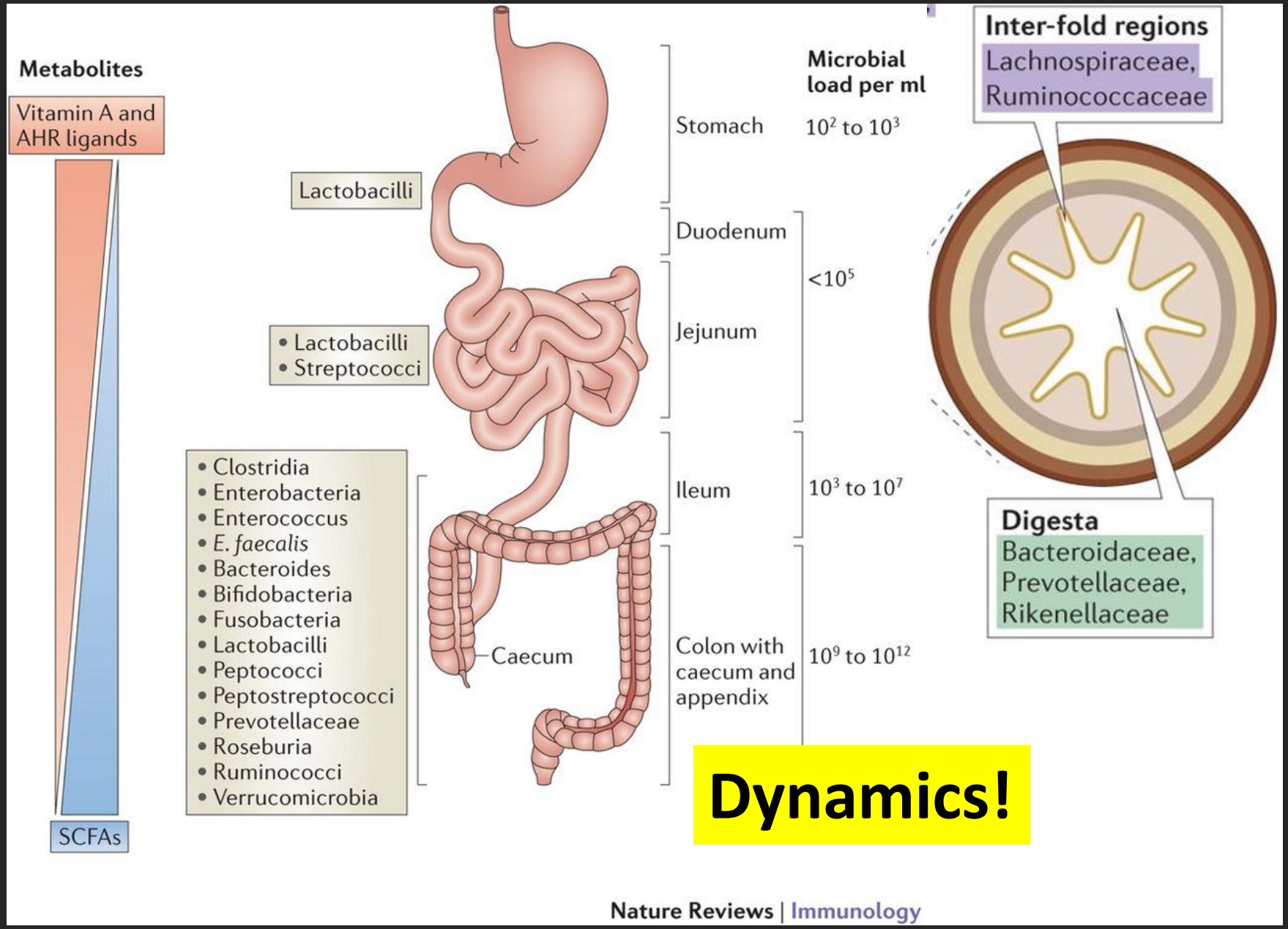
Gut Microbiota and CNS?

- Which bugs?
- The site of activation?

Which Bugs?

- Not ALL bacteria (not SFBs)
- Heat resistant (but which ones?)

Microbiota in Human GI Tract Segments



MS Research:
From Bedside to Bench and Back

Reinhard Hohlfeld

Berer et al., PNAS Sept. 2017

MS Associated Bacteria?

Proebstel et al., 2018

Table 1 Overview of the current literature on the microbiome as determined by 16S rRNA gene analysis in multiple sclerosis

Reference	No. of patients (disease course)	Treatment	Controls (household?)	Ethnicity	OTUs or genera increased in MS
[52]*	7 (RRMS)	5 treated (GA), 2 untreated	8 (no)	White	*Akkermansia* *Faecalibacterium* *Coprococcus*
[51]	20 (RRMS)	13 treated (IFN-β and/or PSL), 7 untreated	40+10 (no)	Asian	*Eggerthella lenta* *Streptococcus thermophiles/salivarius* Clostridia cluster XIVa and IV (including *Faecalibacterium prausnitzi*, *Coprococcus comes*) *Anaerostipes hadrus* *Eubacterium rectale*
[50]	31 (RRMS)	20 treated (IFN-β, NTZ, GA), 11 untreated	36 (no)		*Pseudomonas*, *Pedobacter* *Mycoplana* *Blautia*
[48]	60 (RRMS)	28 untreated	43 (no)	White, black ($n = 2$)	*Akkermansia* *Methanobrevibacter* *Butyricimonas* *Paraprevotella* *Haemophilus* *Slackia*
Tremlett et al. [44]	18 (RRMS)	9 untreated, 9 treated (IFN-β, NTZ, GA)	17 (no)	White (50%), nonwhite (50%)	*Bilophila* *Bifidobacterium* *Desulfovibrio* *Christensenellaceae*
[44, 49]	71 (RRMS)	71 untreated	71 (yes)	White	*Acinetobacter calcoaceticus* *Akkermansia muciniphila* *Eggerthella lenta*
[49, 53]	34 (22 RRMS, 7 SPMS, 3 CIS, 2 PPMS)	15 untreated, 19 treated (13 IFN-β, 4 NTZ, 1 GA, 1 AZT)	34 (monozygotic twins)	White	*Akkermansia muciniphila*

Clinical Trial

(Prof. Reinhard Hohlfeld et al.*)

- Monozygotic twin pairs, discordant for MS (>50!)
- Genomic profiles
- Metagenomic profiles (gut flora)
- Fecal transplants to germfree RR mice

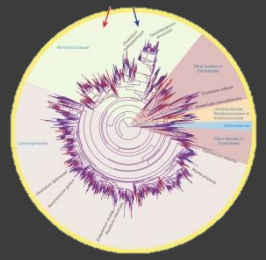
*Cooperation with BGI

MS Twin Study: Fecal Transfer

MS twin

Germ free RR mice

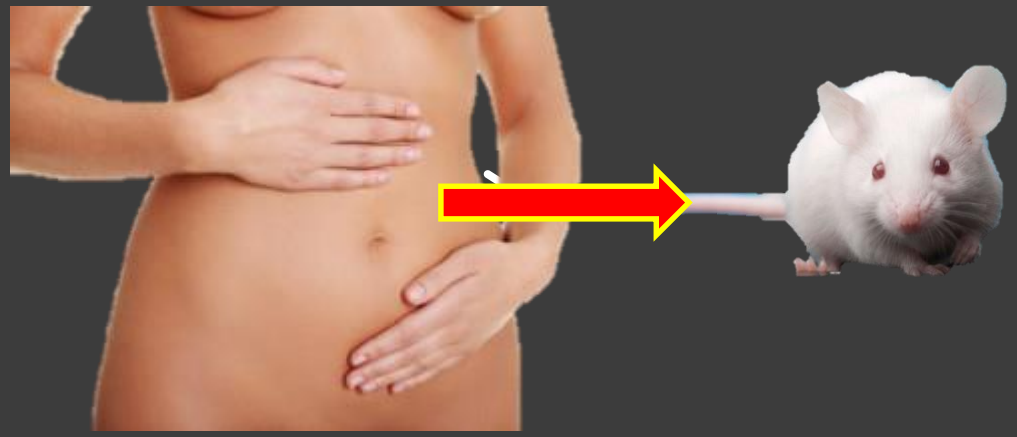
Humanized gnotobiotic RR

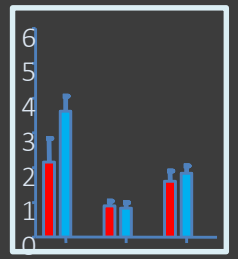


Microbiota

Spontaneous EAE

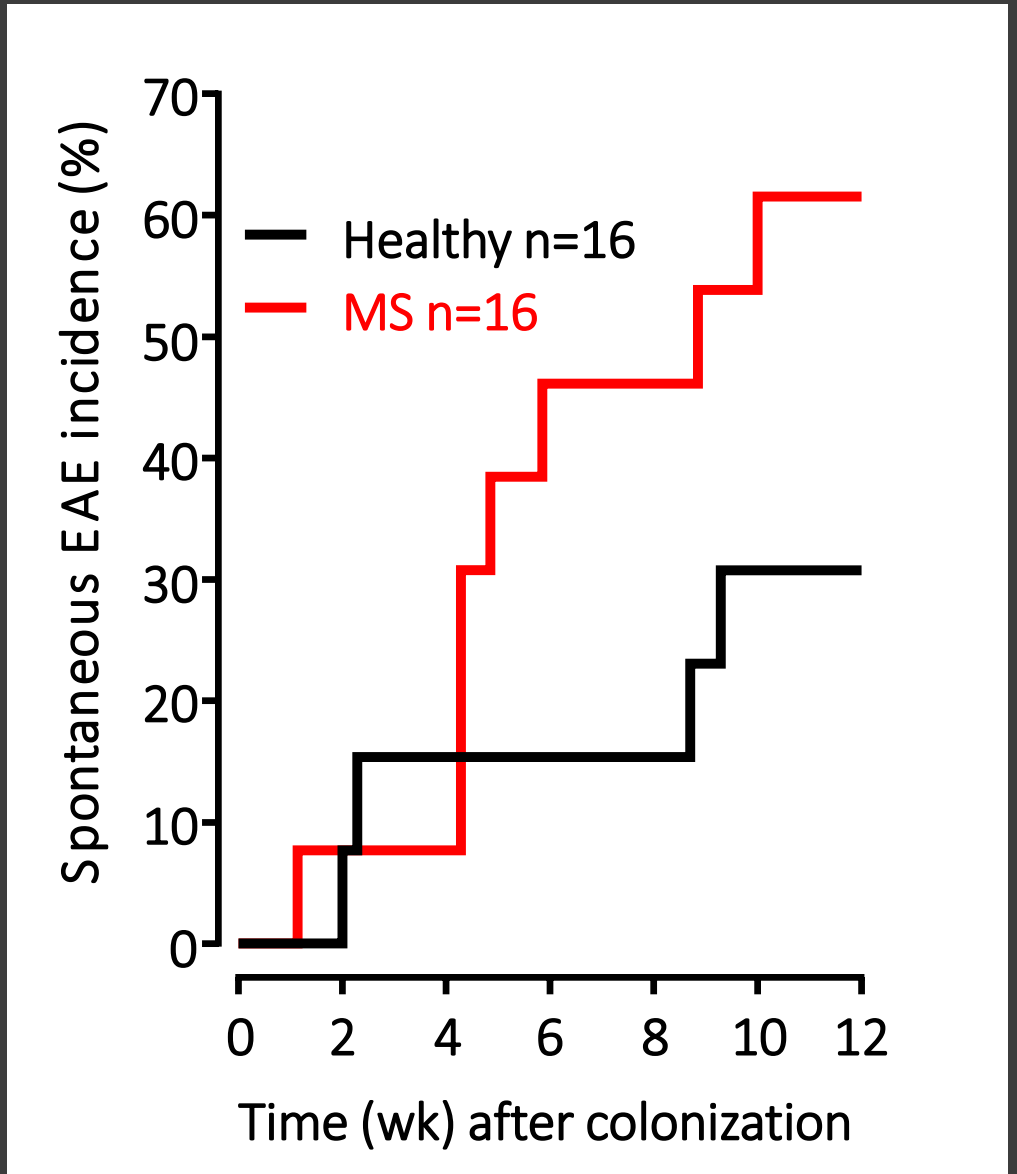
Healthy twin





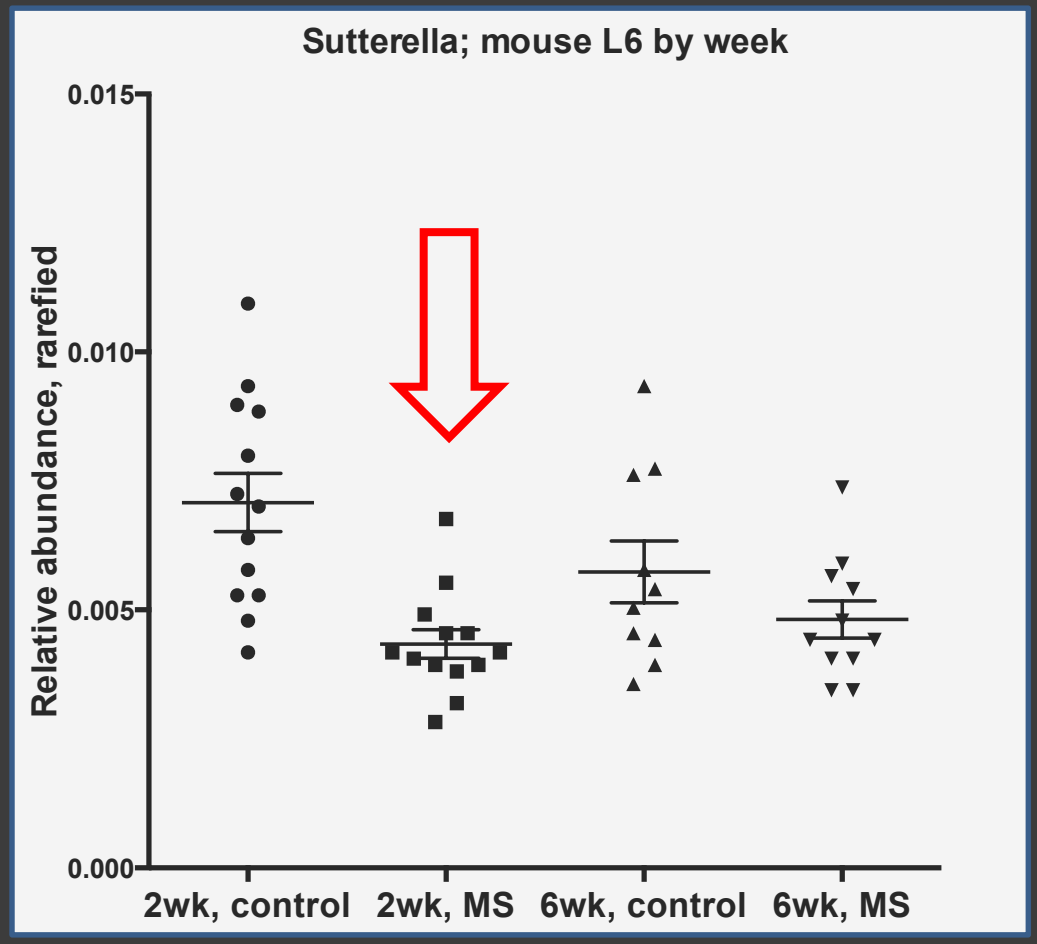
Immune functions

“Humanized” Gnotobiotic RR Mice
(5 Twin Pairs)



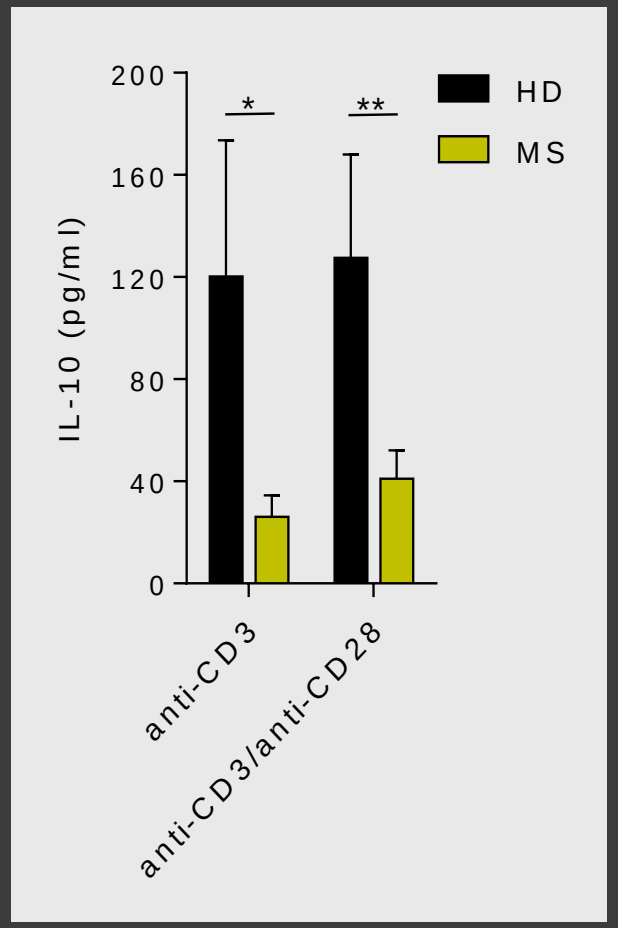
Berer, Gerdes et al., 2017, in revision

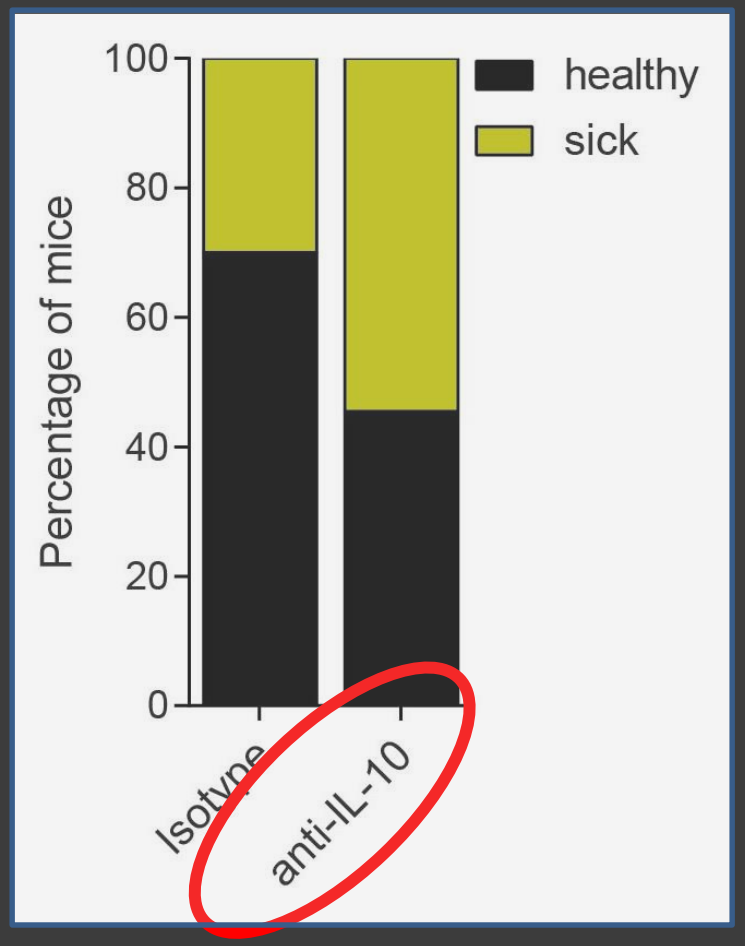
MS Twin Study: Sutterella* in „Humanized“ Gnotobiotic Mouse Microbiota



*Gram-, anaerobic ß-proteobacterium (autism?)

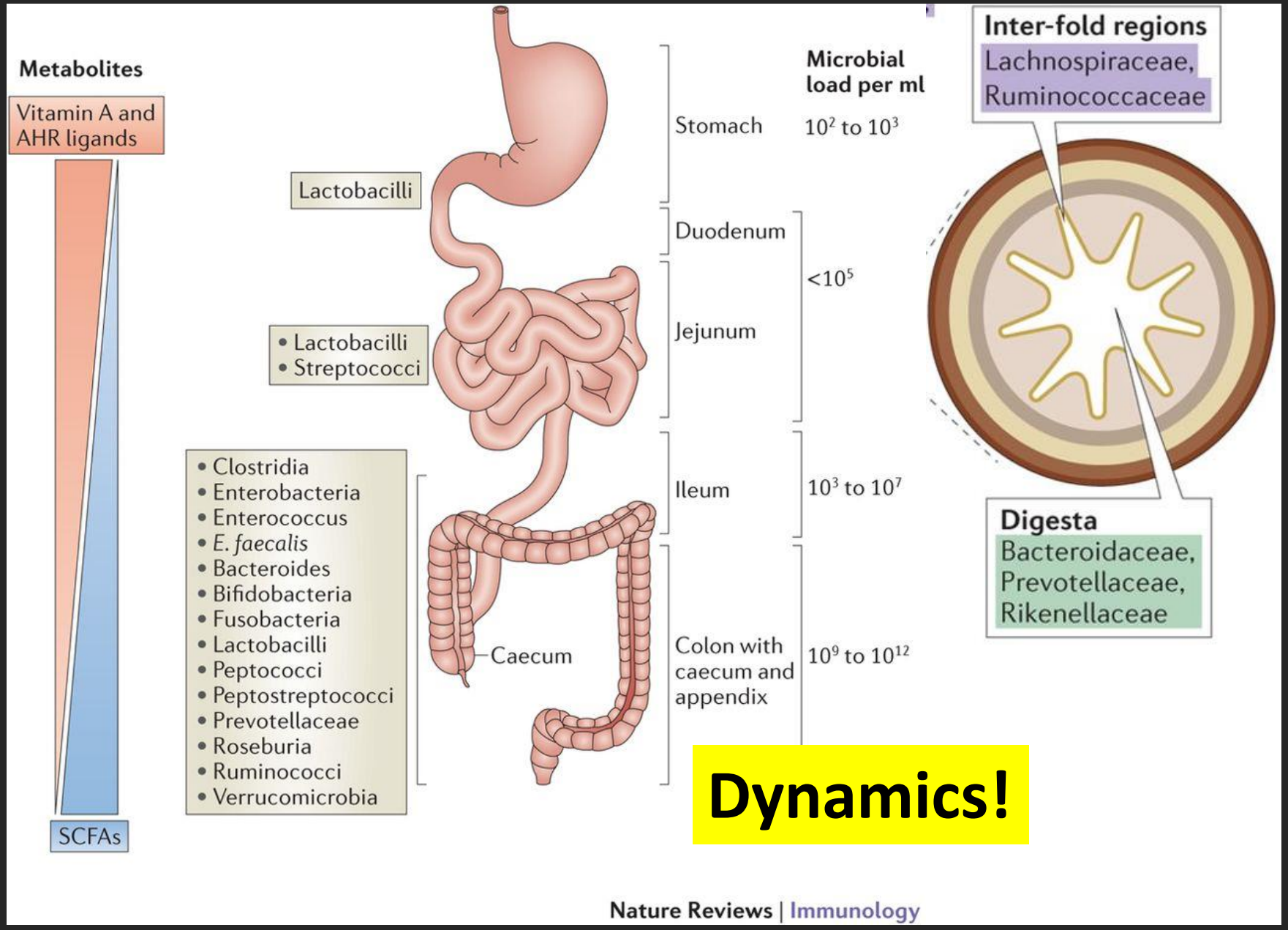
Neutralization of IL-10: spEAE (OSE)





Berer, Gerdes et al., 2017, in revision

Trigger of MS Pathogenesis ??



Manipulation of the Gut Flora?

- Antibiotics?
- Phage
- Probiotics?
- Bariatric surgery?
- Fecal transplantation?
- Diet?

Conclusions

- Inflammation, neurodegeneration and microbiota are inseparable
- Microbiota act on CNS autoimmunity:
  - On CNS tissue via microglia (plus?)
  - On peripheral (auto-) immune response
- Is inflammation “good” or “bad” for the brain?
  - neurodegeneration?
  - Infection?
  - Tumor?

Thanks:

- HERTIE Foundation (Senior Pr
- DFG (Koselleck Award, Transr
- Max-Planck Society
- KKNMS, SynErgy

& Co (Now ERC group)