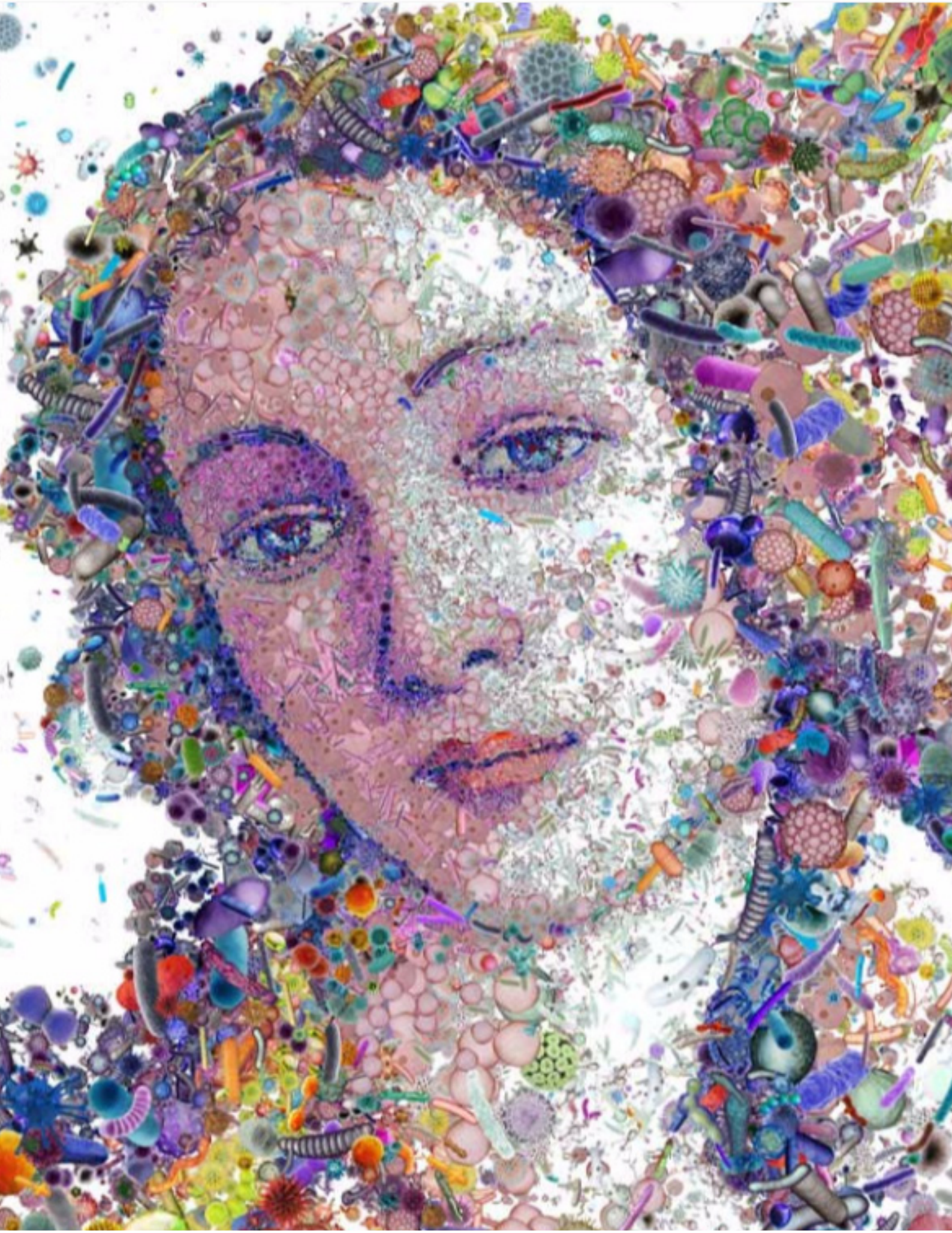

The problem starts in your gut

MICROBIOME Evidence that what we eat and how we live affects our health is becoming greater. The bacteria, who have been colonising our skin and gut since our very beginning, seem to play an important role as sensors for environmental triggers of chronic diseases of civilisation. Since it became clear that restoring the balance of the microbiome cures 90% of people with Clostridium difficile infections, food and pharma companies and researchers have started to dive into further indications. Multiple sclerosis is the latest addition.

When Dr. Terry Wahls was diagnosed with remitting-relapsing multiple sclerosis (MS) in 2000, she did what a professor for internal medicine at University Iowa usually does. She took one of the ABC medicines (Avonex/Betaseron/Copaxone, see table p. xx) her doctor prescribed to suppress the autoimmune reaction in her Central Nervous System (CNS) that targets the myelin insulation of her neurons – and hoped the best. But after she had developed the untreatable secondary progressive MS form three years later and ended up in a no-gravity wheelchair in October 2007, she decided to use her medical knowledge to find a way out. "Strictly science-driven" the expert for clinical trails began to research the scientific literature for alternatives to the mainstream immuno-suppressive drugs (tee table, p. xx), that can slow but not cure the neurodegenerative disorder. She ended up in conducting self-experiments.

One year later, after having invented a combination of electrostimulation and a self-designed "paleo-like" diet preventing gluten-rich and enriching non-processed foods in her meal, the stood up and recovered from heat intolerance and fatigue, a top cause of MS disability. Inspired form the miracle, she set up a foundation with 90.000 followers and wrote a book to bring her message to the 2.5 million MS patients globally. In it she says, "medication can't take away your auto-immune disease, but your body can heal itsself."

"Probiotic therapy is the golden goal"

Wahls' proposition to cure the neurodegenerative autoimmune disease by what she calls "the Wahls Protocoll" hasn't inevitably to be obscure. It's not only 70% of European consumers who believe that healthy food positively impacts on health. A huge number of scientific publications have linked the composition of our gut bacteria or "microbiome" to the susceptibility to chronic diseases as different as diabetes, autism, chronic bacterial infections, cancer and autoimmune disorders such as Crohn's disease, psoriasis, arthritis – and multiple sclerosis. Since it has been shown, that fecal microbial transplants (FMT) cure recurrent infections with antibiotic-resistant *Clostridium difficile* bacteria by an average of 91%, researchers and companies are in a true goldrush to find the nuggets: understand which factors in the microbiome interact with our body to trigger diseases, which share a chronic low-threshold inflammation as common feature.

As imbalances of our microbiome, scientifically dubbed dysbiosis, are clearly dependent on what we eat it's not just pharma but also food companies that have entered the space. While AstraZeneca and Merck, Sharp and Dohme have installed large microbiome research centres in Europe, other big players aim to cherrypick the best approaches from the growing number of microbiome SMEs (see table p xx): In December 2015, Swiss pharma major Novartis and global food gaint Nestlé acquired inter-

SERGIO BARANZINI **Director at UC San Francisco and initiator of the International Multiple Sclerosis Microbiome Study (IMSMS)**

? How about industry interest for your new approach vs MS?

! *Industry is interested, but in my view they would like to see more evidence before they jump into his with full force.*

Pictures: http://www.multiplems.eu (right), Naked Biome Inc (left)

ests in the only VC fund so far, exclusively dedicated to investments into microbiome-related companies: Seventure's €160m Health for Capital Life fund. "The next five years will see the first microbiome products coming out of clinical studies and into the markets", Seventure partner Eric de la Fortelle told European Biotechnology at the BIO-Europe in Berlin (see interview). "We have already some products in Phase IIb and III. These will become medical or nutritional products, and the range of indications will keep expanding," he said. Analysts predict the microbiome market could become as big as biotech in the next 20 years, projecting a market value for microbiome-derived medicines of US$658m by 2030.

No microbiome = no MS

"There is a huge hype around microbiome research. In the past two years, huge amounts of money have been channeled into the field," says Christiane Lang, CEO of Novozymes subsidiary Organobalance, a specialist for lactobacterial interventions. "Last year, about US$700m have been invested in the US, and around €600m in Europe. I am convinced that we currently just see the tip of the iceberg. However, understanding of the microbiome is early stage and the next step is to investigate, what happens in the gut, mechanistically. Nobody currently knows whether microbial products or an accumulation of certain bacterial species triggers disease," she adds.

Taconic, to date the only provider of model mice without microbiome or with customised microbiomes globally, reports growing interest from academic groups: "Demand has expanded exponentially in the last two years," says Randi Randi Lundberg, Field Applications Scientist Microbiome Products and Services at Taconic Biosciences in Denmark.

"Expanding range of indications"

MICROBIOME GOLDRUSH European Biotechnology met Seventure Partner Eric de la Fortelle at BIO-Europe in Berlin to talk about his vision of the future of microbiome-inspired treatments and food products.

EuroBiotech_Why did Seventure step into the microbiome field so early?
De la Fortelle_*Our Health for Life Capital fund, which closed in December 2015 with €160m, is the first and only fund dedicated to microbiome-related pharma and nutrition companies. We have Novartis and Nestle as limited partners, which have a strategic interest in the field. Our CEO, Isabelle de Cremoux, invented the concept between 2008 and 2010 because she realised that the range of indications in which research into the microbiome can help consumers or patients will keep expanding. It's a real high motivator for us that applications range from immuno-oncology, dermatology and neurology to metabolic and auto-immune diseases.*

EuroBiotech_Food and pharma products in one portfolio – could that really work?
De la Fortelle_*Microbiome-related products will not simply address a single market, but rather many ones. It's a lot of new thinking around the role of the microbiome since it is becoming clearer and clearer that what we eat has a significant impact on our health. Food and pharma companies have complementary kknowledge; combining it, it could be very useful. In the future, your doctor might prescribe you a drug or tell you to change your diet or unhealthy lifestyle. Accordingly, Seventure has a highly diversified portfolio of investments.*

EuroBiotech_Could you characterise it?
De la Fortelle_*Typically, we invest €3m to €10m per transaction but also smaller amounts into seed companies. Our first company, back in 2011, was Paris-based Enterome, currently in Phase II with a small molecule targeting proinflammatory gut bacteria to prevent Morbus Crohn. Additionally, they are active in the immuno-oncology space. Today, we have 12 investments, including cancer companies such as Anaeropharma or MaaT Pharma; personalised nutrition companies such as DayTwo, Polaris or the neurology player TargEDys, and companies that develop novel antibacterial products such as Eligo and Vedanta.*

EuroBiotech_Given the diversity and complexity of these approaches, what is the biggest challenge for Big Pharma?
De la Fortelle_*The pharmaceutical industry has been very focussed on finding and targeting the bad guys. In the future, it will be also important to redress an disturbed equilibrum.* ■

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ERIC DE LA FORTELLE Since 2014, Eric has been Venture Partner with Seventure Partners. The structural biologist has more than 20 years of experience in the bio-pharma sector and has been working for Roche and Delenex. He is is a Board member of Mint Solutions BV, Maat Pharma SA, TargEDys SA.

Pictures: EMD Serono/Merck

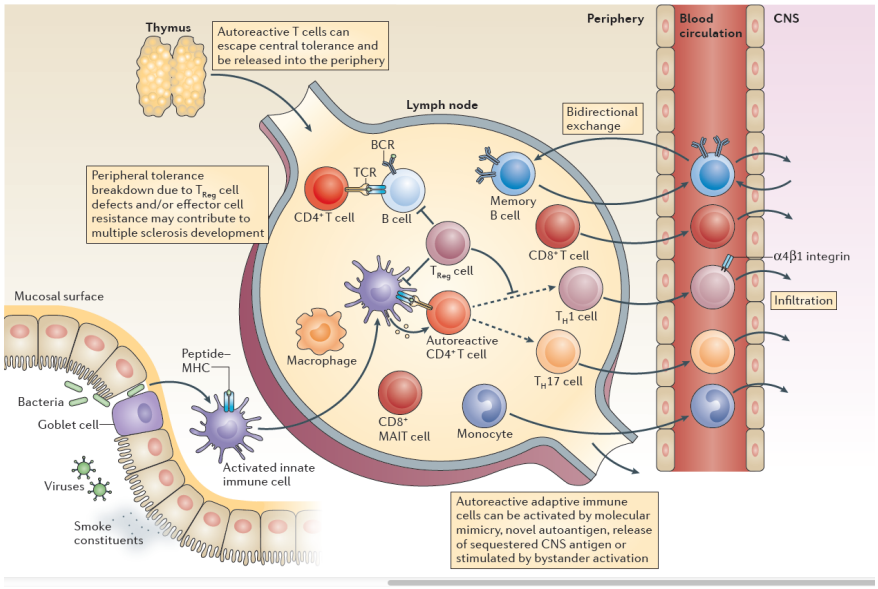
Back in 2011, it was a mouse model, which proved that multiple sclerosis genesis is indevisibly linked to the microbiome. "We know more than 200 genes that make people susceptible to MS," says Hartmut Wekerle, a top-MS researcher from Munich-based Max-Planck-Institute of Neurobiology. "For onset, however, it needs a trigger". Since the intestine is actually the most intimate connection between the outside world and the immune systeme, his team investigated if the microbiome is the missing link between the environment and the immune system. But to do so, they had to solve another problem, first. "Current models of experimental autoimmune encephalitis (EAE) didn't work for that purpose, because they externally supply the mice with the human myelin protein to induce the brain inflammation. So, we designed a model that mimicked many aspects of spontaneously developing MS. Our mice express a transgenic T cell receptor, which detects the myelin autoantigen and make them develop EAE spontanously after 6-8 weeks." Using this model, Wekerle's team prooved that MS cannot develop in the absence of the microbiome. "When we reared such mice in an germ-free environment, they didn't develop EAE. When we transplanted them with a microbiome, they did. "This was the ultimate proof that a factor linked to the microbiome triggered MS in animals," Wekerle explains. "We hypothesise that the gut microbiome pushes the intial activation of autoreactive T-cells, which might initiate MS." (see p. xx). If this holds true in humans, microbiome-derived pre- or probiotics, defined fecal microbial transplants or therapies that correct dysbiosis could transform the current US$22bn MS market in the future.

Seeking the gold nugget

Since Wekerle's groundbreaking study, myriads of teams have begun classifying disease-relevance of gut bacteria according to its abundance in MS patients – with moderate success. A brand-new study carried out by Wekerle's US part-

Companies active in the microbiome field and some of its proprietary products. CDI: Clostridium difficile infections, UC: ulcerative colitis, FMT: fecal microbial transplant

Company	Business	Stage
› Anaeropharma Science (Tokyo)	Cancer-targeted intestinal bacteria producing cytotoxic compounds, APS001F, or antibodies	clinical (Phase I)
› Artizan Biosciences (Durham)	small molecules targeting IBD microbiota	preclinical
› Axial Biotherapeutics (Boston)	gut-selective CNS disorders (Autism, parkinson	n.a.
› biomX (Ness Ziona, Israel)	bacteriophages targeting Acne (BX001), IBD (BX002), GI cancer, immuno-oncology	preclinical
› Caelus Health (Amsterdam)	Metabolic syndrome (CP01)/Diabetes (CP02)	clinical (Phase I)
› C3J Therapeutics (Los Angeles)	dental caries, i.e. C16G2 (antimicrobial)	clinical (Phase II)
› Caelus Health (Amsterdam)	FMT reversing metabolic syndrome (CP01)/ insulin resistance (CP02)	clinical (Phase I)
› DayTwo (Ayer, US)	Low glyc nutrition app based on microbiome	commercial
› Eligo Bioscience (Paris)	microbiome editing for pharma, cosmetics, and functional nutrition	research
› Enterome (Paris)	gut-selective drugs to treat Crohns disease (EB88018), IBD (licensed), innuno-oncology (licensed) and glioma (EO2315)	clinical (Phase I)
› Epibiome (San Francisco)	antiinfective phage therapy	n.a.
› Evelo Biosciences (Boston)	microbial drugs in oncology and inflammatory diseases announced to go Phase I in 2018.	preclinical
› LNC Therapeutics (Bordeaux)	gut microbiome targeted nutrition vs obesity	n.a.
› MaaT Pharma (Lyon)	Autologous FMT Maat001.3 to treat AML	clinical (Phase I)
› Metabogen (Mölndal. S)	Microbiome CRo for pharma and probiotics	n.a
› Microbiotica (Cambridge, UK)	CDI FCM, IBD, immunooncology	n.a
› Microbiome Therapeutics (New Orleans)	Prebiotics vs IBD and metabolic diseases,i.E. NM504	pilot studies
› Naked Biome (San Francisco)	skin-derived probiotic therapy, Acne	clinical (Phase I)
› Rebiotix (Roseville)	FMT vs CDI (RBX2660, RBX7455), UC, UTI, etc	clinical (Phase III)
› Seres Therapeutics (Boston)	oral microbiome therapeutics vs CDI (SER-109, Ser 262) and Colitis ulcerose (Ser278)	clinical (Phase II)
› Second Genome (San Francisco)	small microbiome-targeted inhibitor vs IBD (SGM-1019), metabolic diseases	clinical (Phase I)
› Synlogic (Boston)	microbiome-targeted inhibitors (Synb1020) vs urea cycle disorder + hepatic encephalopathy	clinical (Phase I)
› TargeDys (Longjumeau, F)	appetite regulatiing probiotics targeting ClpB	preclinical
› Ubiome (US)	metagenomics, microbiome sequencing	n.a.
› Vedanta Biosciences (US)	defined microbials vs CDi, UC (CE02, VE03)	preclinical

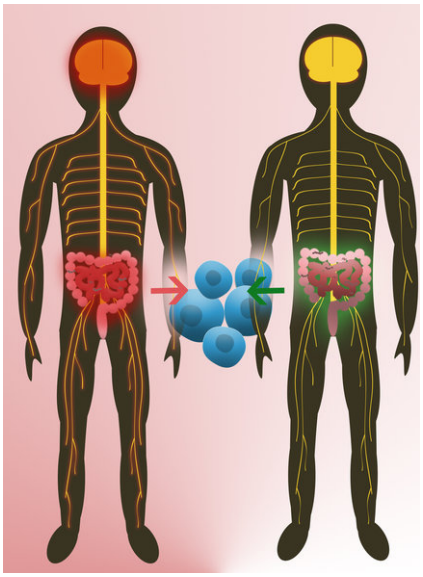


To date, researchers don't know if MS is triggered primarily by a CNS-intrinsic or a CNS-extrinsic event. While nobody knows exactly what factors lead to the increase of CNS-intrinsic microglia and astrocytes in early to late disease stages, researchers have found some putative triggers affecting the peripheral immune response. Based on findings that infections with the Eppstein Barr and Cytomegalie virus, smoking or vitamin D deficiency increase disease susceptibility, they current model is that MS starts with factors (1A) that trigger the activation of autoreactive helper T-cells (CD4+) or which (1B) lead to a breakdown of Treg-mediated pheripheral immune tolerance. According to this model, microbial proteins mimicking i.e. the human myelin basic protein or myelin oligodendrocyte glycoprotein, or altered T-cell-receptor sensivity ends in activation of previously sleeping autoreactive CD4-cells, which in turn activate B- and memory B cells as well as monocytes, T_H1, T_H17, and killer T cells (CD8+) against the autoantigen. They enter the blood and lymphatic system and infiltrate the CNS.

ner group of Sergio Baranzini at UC San Francisco, however, dor the first time adds functional relevance to the data flood. Investigating the microbiomes of 71 MS patients and 71 healthy volunteers, the US team found, that two species enriched in the MS group vs controls – Akkermansia muciniphila and Acinetobacter calcoaceticus - triggered immune cells in vitro to become pro-inflammatory, while those, which were reduced in MS patients – Parabaxteroides distasonis – boosted immune-dampening resonses. When transplanted into germ-free mice without microbiome, first-author Egle Cekanaviciute found the same effect. To investigate how the differences in gut bacteria modulate the immune system's attack on myelin, the researchers performed fecal transplants on mice with induced EAE. Analyses revealed that mice carrying the microbiome of MS patients caused them to lose regulatory T-cells, to prodce less of the immune-regulatory messenger interleukin-10 and to develop more serious neurodegeneration. "It looks like these microorganisms could be making the disease progression worse or better," says Cekanaviciute. "If proven safe and effective, a fecal microbial transplant could be a first-line option for many patients", says Baranzini. "We are working to get IND approval from the FDA and expect to start a Phase I trial early next year." In collaboration with the International Microbiome Study (IMSMS), a consortium of leading US, German, Spanish, UK and Argentian MS research teams, its founder Baranzini at the same time will recruit 2,000 patients with all forms of MS/MS treatments and 2,000 healthy controls to systematically compare differences in the microbiota or its physiology that could be linked to MS. Also in October, Wekerle and his clinical partner, Reinhard Hohlfeld, Director at the Institute for Clinical Neuroimmunology in Munich, have examined whether their findings in mice also apply to humans.

Diet vs fecal transplants

To this end, the Munich researchers recruited 34 identical twins, each with one diseased and non-affected sibling, and transplanted their intestinal microbiome into their germ-free mice, which mimick the spontaneous development of MS. "When the stool of MS-affected twins was transplanted, we observed the spontaneous development of the disease significantly more often and more pronounced", says Hohlfeld. The next step of the German researchers is to find out whether the activation of the autoimmune reaction against the myelin protein in MS patients is triggered by bacteria of the small intestine, which most often trigger pro-inflammatory responses, or occurs in the large intestine, where immune-regulatory processes are dominant. First results, which have yet to be confirmed in further studies, seem to confirm findings of Baranzini's team that reduced immunoregulatory activity in MS patients might trigger the activation of autoreactive T cells that marks the onset of MS (for mechanistic



A Phase I assessment of fecal microbial transplantation in MS patients within the IMSMS is expected to start in H1/2018.

Pictures: MPI for Neurobiology

models see fig. p. xx).
Wekerle hopes his work to encourage not only probiotic therapies but also non-interventional approaches to the effects of nutrition on multiple sclerosis. "While the golden goal of probiotic or dietetic therapy is still a long way to go," he adds, "FMT is also difficult. Nobody currently knows, what makes a healthy fecal transplant. Additionally, there is a lot of obscure providers offering wild transplants. It's essential for the safety of patients to distiguish serious researchers from that groups", he warns.

But there is not only hype around the new field but also setbacks. Published 12-months-results of a open-label clinical pilot study enroling 20 MS patients to proove efficacy of the Wahls Protocol reported only partial success. While patients with moderate motoric defects benefittet, those with severe disability did not respond to the intervention (Degen Neurol Neuromuscular Disease, doi: 10.2147/DNND.S128872). At the end of October, however, a team of Scotch, US and French researchers added further insight into the potentially critical immune regulatory pathway that is defective in patients with MS. The team lead by Siobhan Ni Choileain from the University of Edinburgh reported that an altered glycosylation pattern of the CD46 protein blocked TH1 cells from properly developing into IL-10–secreting type 1 regulatory T (Tr1) cells, which tamp down inflammation and prevent autoimmunity (Science Signal., doi: 10.1126/scisignal.aah6163). Researchers will be now capable to investigate the impact of the microbiome on the newly identified disease trigger. ■

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Approved therapies for multiple sclerosis. BBB: blood-brain barrier

Drug/INN (Company)	Approved	Drug class	MoA
› Betaferon/interferon β1b (Bayer) › Extavia/same (Novartis)	11/1995 05/2008	immunesuppressive cytokine	reduction of neuro-inflammation and BBB leakage
› Avonex/interferon β1a (Biogen) › Rebif/same (Merck Serono)	03/1997 05/1998	immunesuppressive cytokine	reduction of neuro-inflammation and BBB leakage
› Imurek/azathioprine (Wellcome Laboratories); today generics	09/2000 Germany	immunosupp. cytostatic (ic)	blocks T/B cell proliferation by DNA/RNA synthesis halt
› Copaxone/Glatirameracetat (Teva) › Clift/same (Mylan dura)	11/2000 (UK) 09/2001 (D) 05/2016	immunosuppressant	not known
› Ralenova/Mitoxantron (Wyeth)	02/2003	immunosuppressant	DNA intercalator and RNA topoisomerase II blocker
› Tysabri/natalizumab (Biogen)	06/2006	lymphocyte invasion blocker	Integrin α4 blocker, stops migration to inflamed tissue
› Gilenya/fingolimod (Novartis)	03/2011	immunosuppressant	spingosine 1 phophate analogon prevents lymphcytes from leaving lymph nodes
› Aubagio/teriflunomid (Sanofi)	08/2013	immunosuppressant	DHODH blocks T/B cell proliferation
› Lemtrada/alemtuzumab (Genzyme)	09/2013	immunosuppressant	kills $CD52^+$ lymphocytes
› Tecfidera/dimethyl fumarate (Biogen)	02/2014	immunosuppressant	activation of the immunomodulatory Nrf2-pathway
› Ocrevus/ocrelizumab (Roche/Biogen)	12/2017	immunosuppressant	kills $CD20^+$ B lymphocytes RRMS + PPMS

Pictures: xxx