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Neurodegenerative conditions like multiple sclerosis (MS) continue to impact millions of people worldwide, despite a growing treatment landscape. In the United States alone, the total cost associated with MS is $28 billion annually (1). Yet despite standard of care, over 2.3 million people globally struggle in their fight to manage this chronic condition (2). Existing MS therapies focus on shortening the duration of relapses, reducing the frequency of those relapses, and delaying disability progression, thus enabling continued physical functioning. But what about “hidden symptoms” that impact daily life?

Future treatments can do more to address the entire range of MS symptomology, targeting both the cardinal and hidden symptoms of MS to forge a much-needed path forward for patients. From a neurological perspective, the priority is rooted in managing the clinical outcomes of the disease. Current treatments focus on blocking immunologically reactive lymphocytes from getting through the blood-brain barrier, thus preventing the lymphocytes from damaging the myelin nerve sheath in the central nervous system. Positively affecting the lymphocyte-myelin sheath interaction and slowing the inflammatory phenomenon that causes lesions is a strong and necessary starting point for MS treatments (3). Most people with MS also experience relapses and remission of their neurological symptoms; as a result, relapsing forms of MS make up roughly 85% of all cases (4).

MS symptoms include but are not limited to fatigue, impaired mobility, mood swings, cognitive changes, pain, visual disturbances, slurred speech, sensory problems, and sexual dysfunction (5). Many of these symptoms are not visible from the outside, yet they impact a person’s movements, senses, or activities and therefore can be classified as invisible. Additionally, because these symptoms are not always visible, they can often lead to misunderstandings, false perceptions, and judgement (6). This challenge is further complicated by the fact that those around the patient may not easily understand or acknowledge the difficulties of their MS symptoms. As a result, MS patients can experience limitations in their social life as well as emotional challenges tracing back to the disease (7).

Understanding and responding to fatigue

At Janssen, we take a patient-centric approach to treating neurodegenerative conditions. In the case of MS, this means understanding that from the patient’s perspective, the disease’s cardinal symptoms are not the only ones that impact their daily life.

Janssen recently conducted a global patient survey to
better understand the impact of a common invisible symptom of MS: fatigue (8). Findings indicated that most participants experience fatigue daily, and often find it difficult to explain to others just how much it impacts them. Additionally, while 95% of respondents had taken steps to address the issue, including discussing their concerns with their doctor, most stated that their fatigue had worsened since their diagnosis and reported feeling lonely as a direct result (9). Additionally, Janssen conducted a real-world evidence study that enrolled 200 U.S. patients with relapsing MS (RMS) and measured MS-related fatigue and its impact on daily life using the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS), a novel disease-specific scale. The study found that the majority of patients experienced MS fatigue daily, and that fatigue was the most impactful MS-related symptom affecting daily functioning, followed by walking difficulties (8).

It’s important for people living with MS to understand that they are not alone in this fight. As doctors, patient advocates, loved ones, and friends of those affected by MS, we need to make it clear that although we may not be able to see all the symptoms they are experiencing, we recognize their effects. More to MS (https://moretoms.com) is an educational resource currently available to help patients and their caregivers manage MS symptoms. The site provides firsthand accounts, resources, and guidance for discussing these issues with doctors, family, and friends.

When pursuing new treatments for MS, the medical community cannot lose sight of the significant impact hidden symptoms have in reducing health-related quality of life. A study from the Journal of Neuroscience Nursing comparing the life impact of visible versus hidden symptoms of MS found that throughout at least the first 11 years of the disease, hidden symptoms were significantly more likely to cause health distress than their visible counterparts (10).

This finding in no way diminishes the severity of the cardinal symptoms of MS or the need for future treatments to continue targeting those symptoms. But it does mean that if treatments are to provide the maximum benefit to the patient, they should target the entire spectrum of MS. As we move forward in treating MS, our ultimate goal should be to improve the holistic well-being of the patients we treat—which means striving to create safe and efficacious treatments that address both the hard and hidden symptoms of this debilitating disease, while helping those affected to live fulfilled and meaningful lives.

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A scientific approach to solving global problems

When COVID-19 began to spread across the world in January 2020, academics from the Hong Kong Institute for Advanced Study (HKIAS) at the City University of Hong Kong (CityU) were quick to act.

The COVID-19 global pandemic is an example of how systems engineering theories can be used to manage a crisis,” said systems engineer Way Kuo, HKIAS senior fellow, distinguished professor, and CityU president, in a lecture on September 30, 2020, which formed the first virtual event in the four-part HKIAS Distinguished Lecture series hosted by the institute this semester and drawing hundreds of viewers. In his lecture, titled “Data-Driven Global Pandemic Management,” Kuo proudly shared that CityU was very quick to ensure its students had full online access to their academic courses, a move that reflects Kuo’s ambition to apply scientific solutions to everyday challenges.

Managing crises

Kuo was the first foreign expert invited to Japan to assess the aftermath of the Fukushima Daiichi nuclear power plant accident in 2011 and said that he sees parallels between the management of that event and the COVID-19 crisis, where a robust system is needed to rapidly deploy government resources and ensure public safety.

“Decision-makers need to identify the critical elements that determine how a system works,” explained Kuo. “In the case of Fukushima, there was a need to identify operational faults. During the spread of COVID-19, early identification and communication of the critical elements that impacted the rate of the infection were crucial,” he added.

During the early spread of COVID-19, in locations across the world there were times when the information transmitted from the situation on the ground to decision-makers was either delayed or ignored, said Kuo. “The need for robust data gathering and communication systems could not have been clearer at such moments.” In his presentation, Kuo noted that in the case of COVID-19, high numbers of health care professionals were infected with the virus, a situation that could have been avoided if leaders had moved more quickly to allocate appropriate levels of personal protective equipment.

“Effective data gathering is at the heart of any response to an emergency,” concluded Kuo—as he has demonstrated with his own systems research.

Printing in four dimensions

During the second lecture in the series, HKIAS senior fellow and materials scientist Jian Lu demonstrated that recent advances in manufacturing will enable researchers to make stronger, more ductile materials that will improve the efficiency of technologies ranging from aircraft to smartphones.

In his lecture of October 6, 2020, titled “Progress in Additive Manufacturing: From 2D Printing to 4D Printing of Structural Materials and Functional Devices,” Lu explained how the research field of additive manufacturing, or 3D/4D printing—a process during which a computer deposits materials to create three-dimensional objects—has expanded exponentially in recent years.

Lu’s work bridges the divide between fundamental research into additive printing techniques and its real-world application. For example, his team is currently focused on developing strong yet biodegradable hip implants that do not cause damage as the material gradually wears away inside the body.

These implants are currently being tested on large animals, and Lu hopes they will soon be available for use in human patients.

“Advances in 4D printing research will enable scientists to make bespoke materials that are highly adaptable,” said Lu. “An object that is printed using 4D technology can change shape over time, unlike traditional 3D printed structures.” Lu sees tremendous possibilities for advanced technology sectors such as the aerospace and biomedical industries, as scientists design materials that are tailor-made to adapt to their environments. For example, a building could theoretically adapt its structure to better withstand changes in the climate.

The lecture series at HKIAS, supported in part by the Kwang Hua Educational Foundation, provides the opportunity to witness how scientists at CityU are laser-focused on finding solutions to society’s challenges, whether via developing better management systems or by changing the material structure of the world through cutting-edge research.

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Life science today is a victim of its own success. Over the last two decades, the ability of life scientists to record genomics, proteomics, single-cell, imaging, and other data has leaped by orders of magnitude. Technological innovations in genomics boosted sequencing speed while dropping costs, to the point that what initially took 10 years is now done in a day. This same revolution is happening in other fields such as single-cell transcriptomics, where researchers can reveal the entire transcriptome for individual cells.

As such, life science is experiencing a pivotal change. Traditionally, researchers relied heavily on their own hypotheses to design specific wet-lab experiments, collect the data, analyze it, and publish their findings. Their data may have ended up in a publication or in a public repository, but more likely was filed away in laboratory notebooks. Today, many researchers still work that way. But the tides are shifting. The mountains of systematic, comprehensive, and deep data now available in the public domain allow scientists to mine it for unexpected, unpredictable relationships and new knowledge. And at the same time, computing power, machine learning, artificial intelligence (AI), and other technologies available to crunch that data have dramatically improved.

These changes mean that data—and not only the technologies used to gather them—have become key drivers of life science research. This shift is the basis for an upcoming national program on data-driven life science launched by SciLifeLab (Science for Life Laboratory) in collaboration with the Knut and Alice Wallenberg Foundation and enabled by their support. The program is intended to train the next generation of life scientists and to change the way life science is carried out.

From technology-driven to data-driven life science

During the last decade, SciLifeLab has risen to meet data-wrangling challenges by evolving into a trusted technology hub for Swedish life science research. By coordinating some of the country’s top university research resources and facilities, SciLifeLab has created a national multidisciplinary research and infrastructure collaboration that spans a dozen research campuses and 40 infrastructure facilities. Its infrastructure is funded directly by the Swedish government, by the Knut and Alice Wallenberg Foundation, and by governmental strategic research funding through its founding universities KTH Royal Institute of Technology, Karolinska Institutet, Stockholm University, and Uppsala University.

Publications generated by researchers at SciLifeLab or resulting from research performed at SciLifeLab’s facilities are published across the entire spectrum of life sciences, from basic biology, ocean microbiomes, and agricultural crop genomics to new diagnostics, new therapies, and molecular precision medicine.

“International evaluations of SciLifeLab have called it a model for how national research infrastructures in Europe can be optimally organized,” says Olli Kallioniemi, director of SciLifeLab and professor of precision medicine at Karolinska Institutet in Stockholm.
Keeping data at the core of research is a primary goal at SciLifeLab. In 2017, it set up the SciLifeLab Data Centre to support its technology facilities and get ahead of the data curve in areas such as sequencing and imaging. The Data Centre supports data science and data-driven research by ensuring that SciLifeLab facilities have the IT support they need as well as the correct tools for data management, storage, analysis, and dissemination.

“We want to make SciLifeLab an organization where data is really at the heart,” says Johan Rung, head of the SciLifeLab Data Centre and a researcher at Uppsala University. To do that, his team constantly surveys the requirements of the SciLifeLab researchers using the services. “This ensures that the data we produce doesn’t just sit on some server without becoming an integral part of the science.”

The challenge is to ensure a seamless connection between data generation at SciLifeLab facilities, data storage and sharing on platforms or repositories, and the research groups analyzing the data. It is of critical importance to both the Data Centre and the data-driven life science program that SciLifeLab is positioned to maximize research value while also enhancing data reproducibility, quality, and transparency in accordance with the FAIR principles of open science and open data, which strive to make data Findable, Accessible, Interoperable, and Reusable.

“Holding data close is not how you produce the biggest impact,” Rung says. “More long-term results come from published datasets where other researchers can provide new research angles or meta-analyses, or generate whole new projects by combining datasets.”

### Streamlining COVID-19 research through national coordination

Openly shared data can increase the pace of research, as has been exemplified by international collaborations on coronavirus research. “The COVID-19 pandemic has brought to light how inefficient traditionally structured academic research often is,” says Kallioniemi.

That research structure relies on mostly isolated groups, led by principal investigators (PIs) who compete with other PIs for funding. They may all have similar ideas, but they are working in siloed departments, in siloed institutions.
If all departments are trying to build their research capabilities and technologies independently, says Kallioniemi, it’s much less efficient than coordinating between universities to ensure that researchers nationwide have access to the very best materials and technological facilities, and are able to share data.

In many ways, COVID-19 research has served as an eye-opening test case to show that SciLifeLab can move beyond infrastructure to integrate and coordinate national research efforts. For instance, SciLifeLab moved quickly to streamline work on COVID-19 by having its infrastructure facilities prioritize coronavirus research. And together with the Swedish Research Council, SciLifeLab deployed a national COVID-19 data portal that is coordinated with the European Open Science Cloud. The portal serves Swedish researchers who want to collaborate, connect, and share their data widely.

SciLifeLab and the Knut and Alice Wallenberg Foundation have also teamed up on several efforts during the pandemic—setting up large-scale, national COVID-19 diagnostic and antibody testing and launching a national COVID-19 research program.

When reviewing the program’s applications, the team was struck by the patterns that emerged: “Everyone was submitting proposals with the same good ideas: find new drugs, reposition old drugs, search for therapeutic antibodies, create a vaccine, and identify diagnostic biomarkers,” says Kallioniemi. “But each proposal often had only a part of the solution.”

SciLifeLab selected the best 67 proposals for funding, but then did something slightly radical. They sorted the winning grants into nine research areas and funded them to work together as a group, not in isolation. Kallioniemi was pleasantly surprised that almost all of the researchers who might normally be competitors were interested in collaborating.

All of the program’s components—from funding and research groups to infrastructure and data portals—are connected. “This is a case study demonstrating that the SciLifeLab model could change the whole concept of how life science gets done,” says Kallioniemi. 

**Coordinating services at the cutting edge**

It’s clear that the SciLifeLab model has both the agility and horsepower to keep up with the shifting demands of modern research. Take for example the relatively new SciLifeLab Cryo-Electron Microscopy (Cryo-EM) facility, funded by the Knut and Alice Wallenberg Foundation and located at SciLifeLab’s Campus Solna in Stockholm. It’s the first of its kind in the Nordic region, capable of imaging subcellular structures and molecules at super-high resolution. SciLifeLab installed another major facility at Umeå University, and smaller Cryo-EM machines have been placed at other universities, where SciLifeLab helps with setup, training, and best practices. Scientists can then validate their sample preparations first on the smaller instruments before booking time on the larger systems.

This represents another success for the SciLifeLab model. By coordinating the installation and management of infrastructure facilities, SciLifeLab provides early access to new technologies for all researchers, regardless of their university affiliation. This democratizes access and short-circuits unnecessary competition.

The power of the SciLifeLab model lies in its people—the expert scientists who operate the facilities—says Emma Lundberg, professor at KTH Royal Institute of Technology, director of SciLifeLab’s Cell Profiling facility, and one of the very first SciLifeLab group leaders. “They have so much expertise at their fingertips,” says Lundberg. “They can help researchers figure out how to answer their research questions with available technologies so that they design the best experiments to deliver results.”

Like all SciLifeLab facilities, the Cell Profiling facility is evaluated every 4 years to keep its technologies state-of-the-art. It has now evolved to include immunostaining of tissues and cells as well as access to CODEX (Co-Detection by InDiEXing) technology for highly multiplexed cell imaging. “For the future, we will be expanding the scope of highly multiplexed imaging such as this, as well as in situ sequencing, to give researchers detailed data on the spatial orientation and distribution of both proteins and RNAs within cells,” says Lundberg.
Looking forward to the next 10 years, SciLifeLab will use its national infrastructure as a foundation to build a research community connecting scientists performing technology-focused or data-driven life science research across Sweden and Europe.

Putting data in the driver’s seat

Having refined its 40 national facilities, SciLifeLab can now marry that infrastructure with data capabilities, enabling research that can be performed more efficiently and under open science principles.

Data scientists and computational biologists will become much more active players as they shepherd in this new era of data-driven life sciences. “The Data Centre should perhaps be a research group’s first stop, to determine what kind of data they plan to generate and to come up with a data management plan to coordinate it across facilities,” says Rung. Data scientists along with AI experts will guide how data can be analyzed in new ways using machine-learning or deep-learning algorithms. Those models will offer new insights into the data, which can then feed back to inform further experiments.

The evolution of the scientific community will also be key, requiring much closer collaboration between wet-lab biologists, computational scientists, and hybrid scientists who can work as easily on a benchtop as a laptop.

SciLifeLab Fellow and computational biophysicist Lucie Delemotte’s group operates in this hybrid fashion already. Her team at SciLifeLab’s Campus Solna studies the physical properties of cellular membrane proteins that allow cells to communicate with their neighbors and environment. “We essentially build a movie of how a protein moves over time by taking information from static snapshots, such as a cryo-EM image or crystal structure, and simulating what might be happening in between those snapshots,” she says.

The work is both computing- and data-intensive, and Delemotte, an associate professor of biophysics at the KTH Royal Institute of Technology, appreciates being embedded in SciLifeLab to connect with other biologists doing similar molecular simulation work. She has also made meaningful connections and collaborations through the SciLifeLab Fellows program, which provides generous startup funding and leadership training for promising early-career researchers from all over the world.

“For me, data is the beginning of the game. I like having data and digging for information there,” says Delemotte. “I see data-driven life science as a hybrid between traditional, hypothesis-driven research and the leveraging of data tools to both design experiments more efficiently and make data analysis more robust.” For example, in a study of membrane receptors, Delemotte’s group is running simulations using machine learning to predict how these receptors twist and change shape in response to several slightly different binding partners. The simulations allow the researchers to choose the wet-lab experiments that will most likely yield productive results.

When cell biologist Lundberg moved her research group from KTH to SciLifeLab’s Campus Solna in 2010, the organization occupied just one floor of one building. But she was convinced that this was the place to carry out her work as codirector of the Human Protein Atlas project, and was confident that SciLifeLab would grow into a strong research environment. “I truly believe that collaborative research is the future of science. And being surrounded by other people working on similar, interdisciplinary areas in large-scale systems biology really appealed to me.”

Now, 10 years later, SciLifeLab has matured into just such a research environment, with Lundberg directing its world-class Cell Profiling facility. Lundberg is “100 percent convinced” that the SciLifeLab principles of open science and open data accelerate research. When the data can be reanalyzed by others and used to ask new questions in new ways, it’s a win-win, she says.

Lundberg notes that classic cell-biology methods of microscopy imaging and spatial-sequencing technologies have shifted into big-data pursuits. “And big data can drive research in different directions—toward hypothesis-based discovery and unbiased inquiry. It can lead you to things you haven’t even thought of.”

That kind of data-driven discovery is the vision for the next decade at SciLifeLab, says Kallioniemi. “We want to be driving this change, and we have a structure that lets us do it on a national scale.”

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Can patients’ gut microbes help fight cancer?

A healthy gut microbiome seems to be required for immuno-oncology therapies designed to turn up the body’s immune response to attack tumors. Researchers have many “black boxes” to fill in on how gut microbes directly or indirectly influence the T cells unleashed by immune checkpoint inhibitor therapies. But several groups are betting that microbiome-based therapies can help more patients respond to immunotherapies and become one of the biggest breakthroughs in cancer treatment in decades. By Kendall Powell

At first glance, it might seem odd that our gut microbiome plays an influential role in our immune system response. It’s not so strange, though, considering that the vast majority of our immune cells, up to 70%-80% of them, hang out in the intestine regularly. There, in the great “transit hub” of the body, they are directly exposed to the outside world and to the incredible genetic diversity of our gut microbes. Made up of trillions of mostly bacterial cells, the microbiome pumps out metabolites as it goes about its daily business of aiding digestion and helping synthesize vitamins and other nutrients. Roving immune cells ensure that “good” microbes and the body’s cells are tolerated while invaders get rooted out.

Although the molecular details are far from being completely understood, it’s become clear that having a healthy gut microbiome ensures that T cells are broadly primed against antigens and activated into cytotoxic CD8+ T cells that infiltrate and attack tumor cells. Advances in immune checkpoint inhibitor (CPI) therapies have shown that sometimes, when the checkpoints, or brakes, are taken off the cytotoxic T-cell responses, even metastatic tumors can be shrunk and controlled. However, oncologists have been frustrated to find that only a minority of patients—typically less than 30%-40%—respond to CPI therapies.

Now, research is showing that when combined with CPI therapies, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 immunotherapies, a healthy, diverse gut microbiome results in better patient responses. Figuring out which microbes—or which metabolites or products—are shaping these immune responses has become a competition among researchers in the field. But these “microbe managers” are hopeful they can find ways to nudge, sway, or push patient microbiomes to energize their tumor-fighting T cells and convert more patients into CPI responders.

“There’s an emerging body of literature appreciating the role of the intestinal microbiota in calibrating systemic immune responses,” says Alexander Khoruts, director of the Microbiota Therapeutics Program at the University of Minnesota in Minneapolis. He was among a pioneering group of gastroenterologists that first used fecal microbiota transplants (FMTs) to treat patients with recurrent Clostridioides difficile infections.

Uncovering the gut-cancer connection

In 2013, Laurence Zitvogel and her group at the Gustave Roussy Cancer Campus in Villejuif, France, concluded that mice with missing or depleted gut microbiomes had a weaker immune response to chemotherapy than mice with intact microbiomes did (1).

It was such a novel idea that it immediately drew skepticism. Bernat Olle, CEO of Vedanta Biosciences in Cambridge, Massachusetts, recalls thinking at the time, “Hm, I don’t know if I believe that.” Cancer has been thought of as a disease of the genome and accumulating mutations, he says. “But, we now know that cancer is also a disease involving an ineffective immune response.”

Work by Zitvogel’s group in 2015 convinced Olle and kicked off this field. When they treated sarcomas in mice with ipilimumab, they found that the CPI could control the tumors in pathogen-free mice, which have normal gut microbiomes, but not in germ-free mice, which have no gut microbiome (2).

The clincher was that transferring beneficial species of bacteria back into these mice restored the anticancer activity of the CPI.

Vedanta’s scientific cofounder, Kenya Honda, a team leader at RIKEN Center for Integrative Medical Sciences in Saitama, Japan, discovered that the induction of CD8+ cytotoxic T cells happens in the intestine and depends on the microbiome’s presence (3).

“Obviously, my first reaction to Zitvogel’s initial discovery was wrong,” says Olle. Just 10 years ago, he recalls, we used to think that the immune system’s function was to tell the difference between self and nonself. But Olle believes that its role should now be considered as broader—it performs triage, making quick decisions on who to attack and who to tolerate. “Maybe the immune system is more like a gardener in the human body,” he says.
deciding which weeds must be pulled and thrown out and which can stay in the lawn."

Since the Zitvogel group’s initial discovery, many studies have shown that patients who receive a broad range of antibiotics known to diminish gut mucosal populations do not respond well to CPIs (4, 5) and have worse adaptive immune responses to vaccines (6).

One of the microbiome’s potential mechanisms for influencing T cells, and therefore cancer immunotherapy, is through the vast number of gut metabolites that can act as immune-modulating signals. "T cells can get their education from the bacteria in the intestine, and then are circulated out to the rest of the body multiple times per day," says Olle. "What happens in the intestine affects the entire immune system."

Black boxes between microbes and T cells

How exactly these interactions unfold between microbes, their metabolites, T cells, and other immune cells remains largely a mystery.

"Having certain bacteria present influences the balance of activated, cytotoxic CD8+ T cells," says Sarah Highlander, microbial genomic scientist at the Translational Genomics Research Institute in Flagstaff, Arizona.

But researchers still need to identify which beneficial bacteria must be present, and how they molecularly switch on T cells. Highlander and her collaborator, Sumanta Pal, a medical oncologist at City of Hope cancer center in Duarte, California, have longitudinally tracked the microbiomes of patients undergoing anti-PD-1 CPI therapies.

They found that metastatic renal-cell carcinoma patients who responded to CPIs had more diverse microbial diversity and an increasing abundance of Akkermansia muciniphila in particular (7), as compared to nonresponders.

In Pal’s mind, gut epithelial response to certain neighboring microbes by secreting inflammatory cytokines, which then influence the activation of T cells. This is how Olle envisions the process, too. Vedanta has shown that its commensal bacteria mix must be alive—and therefore producing metabolites and signals—to be effective.

But there are many steps along this pathway where the mechanism is unknown: Are microbes directly or indirectly signaling to T cells? What other types of T cells (helper T cells? T regulatory cells?) does the microbiome influence? Once T cells are fully activated in the gut, how do they find their way to and infiltrate tumors?

One reason there are several black boxes between what the microbes are producing and what exact population of T cells become activated, is that extracting those T cell populations from human patients and studying them is extremely difficult, Khoruts explains.

Another camp of researchers takes that theory one step further, arguing that among the flood of microbial products found in the gut, some might mimic tumor antigens and more directly create a tumor-directed population of T cells.

“We believe the intestine is a reservoir for T cells that can recognize bacterial antigens that mimic tumor antigens,” says Christophe Bonny, chief scientific officer at Enterome in Paris, France.

Microbiome-based drugs

Now, the race is on to develop and test microbiome-based approaches designed to convert a cancer patient into a CPI responder.

"That’s the holy grail," says Highlander. "Adding a mix of bugs, in a pill form, to transform a patient into a good CPI responder." She predicts there may be many successful products that fulfill this goal. "We know from the Human Microbiome Project that people can have very different microbiome community compositions, but they are functionally the same."

She is involved in testing a combination therapy of CBM588, a crystallized form of Clostridium butyricum, alongside CPI treatment. This bacterium produces butyrate, a short-chain fatty acid thought to enhance the growth of certain Bifidobacteria, one of the groups found in responders’ microbiomes.

Vedanta Biosciences has developed VE800, a purified, freeze-dried mix of 11 bacterial strains based on Honda’s work that can activate interferon-gamma-producing cytotoxic CD8+ T cells (3). It is being tested in combination with the CPI nivolumab in patients with advanced colorectal cancer, gastric cancer, and melanoma. During the trial, Vedanta plans to sequence patient stool samples to see whether and to what degree the VE800 strains colonize the gut.

Seres Therapeutics in Cambridge, Massachusetts, is testing another bacterial consortia drug candidate, SER-401, in metastatic melanoma patients in combination with nivolumab. SER-401, which contains strains fractionated and purified from healthy human donor stool, will be given daily over 8 weeks, starting before the CPI course and continuing alongside it. The design of the drug is based on a collaboration with Jennifer Wargo at MD Anderson Cancer Center in Houston, Texas, which revealed key signatures of strains associated with CPI response, including bacteria from the Ruminococcaceae family (8), says Matthew Henn, executive vice president and CSO at Seres.

Khoruts and the Microbiota Therapeutics Program are testing an "FMT in a pill" formulation called MTP101, in combination with the CPI... cont.>
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durvalumab, to treat non-small cell lung cancer. In contrast to the Vedanta and Seres candidates, MTP101 is a whole microbiome purified and freeze-dried from healthy donor fecal material.

Khoruts concedes that trials like his, using an FMT-like whole-microbiome pill, should happen in parallel with the other approaches that have narrowed down to a handful of strains. “We can all learn from each other [and] from the data,” Khoruts says.

Whether encapsulated bacterial mixtures will actually colonize a cancer patient’s gut is an open question, says Ryan Weight, medical oncologist at the University of Colorado Anschutz Medical Campus in Aurora. This is also true for other types of patients—no “FMT in a pill” products have yet to be proven to colonize human guts, and it is still up for debate exactly how FMTs in C. difficile infection patients shift their gut microbiota over time.

“All of these belong to a class of therapeutics that physicians haven’t used yet,” says Khoruts, adding that it’s an entirely new area of pharmacology to assess these drugs’ formulation, dosing, fate in the body, and pharmacodynamics.

Khoruts points out that these approaches are very also different from using FMTs to treat C. difficile because those patients’ native microbiomes have been nearly wiped out by heavy-duty antibiotics. That’s akin to having a field decimated by herbicides and fertilizers and expecting it to grow a healthy crop. Cancer patients typically still have their own indigenous, intact microbiome, which is more like an established prairie that an oncologist is trying to oversee with some beneficial species.

It could also be true that different tumor types might need different bacterial species in the gut to activate T cells against those specific tumors, says Weight. “By 2040, we might be in a place where we have probiotic cocktails directed against colon cancer.”

Mining the microbiome for antigens

Enterome is taking an altogether different approach, based on the idea of tumor antigen mimics. Recently, the company and its collaborators published 20 million genes from sequencing more than 8,000 people’s gut microbiomes, representing more than 4,600 species of microbes (9).

“The beauty of the microbiome is that digging into this pool of 20 million gene products is like going into the Amazonian jungle to look for drugs among all the biodiversity there,” says Bonny.

To winnow down which of the 20 million bacterial products might be responsible for the immune responses in CPI responder patients, Enterome ran several bioinformatics filters on the dataset to get to a “short list” of 20,000 proteins. These were small, secreted molecules resembling cytokines, chemokines, or hormones that were likely to interact with human cell receptors.

Next, Enterome fished among those bacterial peptides to look for molecules that resembled specific tumor antigens, such as IL-13Ra2, which is uniquely expressed by glioblastoma tumors. Enterome identified three bacterial antigens to put into its vaccine product EO2401, in hopes of awakening T cells that recognize these antigens.

In testing, glioblastoma patients receive a vaccination shot every 3 weeks during the first couple of months of their CPI course of treatment. “If we are correct, we are targeting memory T-cell populations that have already seen these microbial antigens,” says Bonny. “So we expect it to be fast.”

Promise amidst potential pitfalls

Work in this field in the last five years has shown that oncologists “need to pay attention to how this complex interplay comes into effect in treating our patients,” says Weight. In his practice, that means advising patients against taking antibiotics if possible in the 6–8 weeks before starting CPI therapies, and surprisingly, also advising them against taking over-the-counter probiotics at this stage. According to Weight, there’s no evidence of probiotics increasing the efficacy of CPI therapies, and in fact, these highly selected strains could pose a risk of disrupting a patient’s natural microbiome which can be protective, he says.

Pal also cautions that researchers need to better understand how the microbiome is influencing immunotherapy. “Before we give a product fortifying Akkermansia in patients, we need to know that it’s really Akkermansia that is a key player,” he says.

Researchers have many questions left to answer in this incredibly complex space.

“Immuno-oncology has been a huge breakthrough in cancer research,” says Khoruts, noting that former President Jimmy Carter is alive because of CPI therapy. He notes that the microbiome-oncology field is at very early stages, with many different ideas to pursue and candidates to put through testing. “Even in the best cases, only 40% of patients respond to CPIs,” he says. “There is a lot of room for us as a field to make that percentage better.”

References

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