Make Way for the Neuro-Immune Revolution

By the time the pharmaceutical industry began exploring B cell depletion as a treatment for relapsing-remitting multiple sclerosis (MS), Amit Bar-Or, MD, FRCPC, was already well on the way with his own B cell research.

“Our lab and a few others had been interested in B cells’ role in MS for some time, so we were very happy to get involved in these studies,” explains Dr. Bar-Or, Chief of the MS Division at the University of Pennsylvania’s Department of Neurology and Director of Penn’s Center for Neuroinflammation and Experimental Therapeutics (CNET).

The ensuing work led researchers to a crucial revelation that has propelled both MS research and treatment. “Contrary to what many believed, we discovered that the B cells themselves, and not the antibodies they produced, were responsible for triggering relapses in these patients,” Dr. Bar-Or shares.

A little over 10 years later, Ocrevus, an anti-CD20 therapy and the first FDA-approved treatment for both relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) came to market. And while Ocrevus isn’t the only drug available for people with RRMS, Dr. Bar-Or shares that it is one of the best to match the profile of a desirable MS treatment: easy to take, generally safe, well-tolerated and highly effective. The fact that it has some capacity to also limit the progression of PPMS is an important added benefit, though he cautions that it can’t fix what’s already broken.

“While we used to think that T cells of the immune system were the main triggers of MS relapses, we now understand that relapses involve important interactions between B cells and T cells that take place outside the central nervous system (CNS),” Dr. Bar-Or explains. “These interactions result in waves of activated immune cells tracking into the CNS and causing inflammation and damage. Remissions between these attacks can be partial or complete and the inflammation may leave residual damage, even after symptoms disappear.”
Programmatic Strengths

Anchoring Penn Neurology are five core strengths where research and clinical assets combine:

- **Neurodegenerative disorders:** A historic strength at Penn, this field encompasses our well-respected programs in movement disorders, Alzheimer’s disease, multiple sclerosis and epilepsy. Our Center for Neurodegenerative Disease Research is an international leader in determining the causes and mechanisms of age-related brain diseases and degeneration. It remains the only NIH-funded Alzheimer’s Disease Core Center in the Delaware Valley. And our newly launched Molecular Integration in Neurological Diagnosis (MIND) initiative is helping usher in the “molecular era” in which patients with neurological diseases will be characterized at the DNA and biomarker levels in order to improve clinical care and accelerate therapeutic development.

- **Neuroimmunology:** Our Center for Autoimmune Neurology is dedicated to helping patients with autoimmune and paraneoplastic disorders affecting the nervous system. In recent years, a large and growing family of autoimmune causes of encephalitis and other related disorders has been discovered, many of them by our group here at Penn. Today, we have unique immunological panels that can pinpoint the exact cause of some of the most refractory neuroimmunological conditions, such as limbic encephalitis, and create precision therapies. We are also offering advanced immunosuppressive therapy for multiple sclerosis, based on recent discoveries of new target mechanisms.

- **Network neuroscience:** This growing field of study provides computational methods to uncover structure in brain imaging data. In turn, knowledge about this structure allows us to better understand how signals travel naturally across the brain’s highways and how stimulation can alter that travel in a way that supports better cognitive function. At Penn, we are using fMRI to literally map brain networks in disease and then using guided treatments such as ablating pathways that are responsible for refractory epilepsy or targeting focused ultrasound to networks causing essential tremor and Parkinson’s disease.

- **Neurogenetics:** Genomic analysis is reshaping the neurology field in all areas. Penn Neurology has a neurogenetic service, including a dedicated neurogenetics counselor, to evaluate the genetic basis of disease across many subspecialty areas of neurology, including those syndromes that have been previously undiagnosed. In addition, we are now able to provide gene modifier therapy for neurological conditions such as blindness and neuromuscular conditions, and are working on a number of new directions including upcoming trials for Huntington’s disease.

- **Sleep:** Within our Center for Sleep and Circadian Neurobiology, research ranges from basic science to original clinical trials to translational research. Of particular focus is our work looking at how sleep is deregulated in neurological disease and how it may be contributing to the disease process.

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A Message from the Chair

Recognizing that not all neurological care needs to be provided by neurologists, we have also partnered more closely with PCPs on screening services and lower-complexity cases.

Some of the treatment options we can now offer our patients were almost unthinkable as recently as 10 years ago. These include new pharmaceutical and biological treatments, medical devices, and new biomarkers for diseases. Penn has been at the forefront of these advancements, most prominently multiple sclerosis and other autoimmune diseases such as limbic encephalitis; neuromuscular disorders and their gene therapies; movement disorders including Parkinson’s disease and Huntington’s disease; epilepsy; neurodegenerative conditions such as amyotrophic lateral sclerosis; and multiple forms of dementia.

In the research realm, we have been among the top 10 neurology departments with respect to NIH funding over the last decade. The vast resources found at Penn—from our School of Engineering to our School of Arts and Design—help us spark innovation and hasten care delivery. It’s very common for our neurology faculty members to partner with colleagues from across the university. These can include the work we do through Penn Healthtech with the School of Engineering, biomedical discovery with other centers such as Genetics and Immunology and Inflammation, as well as those that reach more broadly outside of science and technology. For an example of this cross-discipline collaboration, see the story on page four about the new Penn Center for Neuroaesthetics.

Our emphasis on collaboration and innovation allows us to “de-silo” disease sets and examine underlying common mechanisms, which in turn accelerate discovery and implementation. Our department, like the field of clinical neuroscience in general, is undergoing an unprecedented and dynamic change, and Penn Neurology is helping lead the charge.

Thank you for your past and future support of our department and staff. I invite you to contact me anytime, come in for a visit and connect with us.

Best regards,

Frances E. Jensen, MD, FACP
Professor and Chair, Department of Neurology
Penn Medicine
“Ocrevus targets and eliminates many B cells that have the CD20 molecule on their surface,” he continues. “By eliminating them, the B cells are less likely to overly activate the T cells thereby limiting new relapses and CNS damage in individuals with MS.” To date, 700 people have been treated with this therapy at Penn Medicine. Two-thirds of these are individuals with RRMS and the balance have PPMS.

With RRMS now targeted quite effectively, Dr. Bar-Or and his colleagues at Penn’s CNET have turned much of their attention to gaining a better understanding for primary and secondary progressive MS.

“Some people historically considered RRMS to be driven by the immune system in contrast to progressive MS being driven by degeneration,” says Dr. Bar-Or. “We’ve learned that progressive MS also most certainly involves important components of inflammation, but in these patients, we think the inflammation becomes compartmentalized within the CNS, ‘setting up shop’ there and contributing to progressive injury even when immune cell attacks from the periphery are no longer taking place.”

Dr. Bar-Or shares that there are currently 12 MS clinical trials taking place at the center, most of which are cutting-edge, early-phase, higher-impact clinical trials. Through these, exciting new insights continue to be gained into how cells of the immune system interact with CNS cells to contribute to ongoing injury. These insights are starting to translate into new treatment approaches that will hopefully limit or stop these cellular interactions contributing to progressive injury. It’s an area where Penn is emerging as a global leader.

“Neuroinflammation is an area that is really transforming, and our center’s translational approach to understanding neuroinflammation across the age-span—as it relates to MS as well as a range of other conditions—is positioning us as one of the top programs,” says Dr. Bar-Or. “By developing and incorporating novel immune assays into well-designed clinical trials for MS, we’ve been able to gain at times surprising insights into disease mechanisms and develop biomarkers of response to therapy, while also evaluating the safety and efficacy of novel MS therapies.”

Recently, the center’s focus has shifted to the variances of MS at the biological level. “Subsequent studies have shown that people with MS are biologically different, in that the relative contribution of the immune cells (B and T) varies from patient to patient,” explains Dr. Bar-Or. “So, while many people are diagnosed with the same condition, important biological differences call for a more tailored treatment approach. What we are doing now is following people over time, collecting samples and measuring the state of their immune systems as part of a comprehensive biological approach to define what cellular combinations lead to each person’s MS activity and how to more precisely recommend the most appropriate immune therapy.

“Essentially, we’re unlocking the black box of MS...and that’s precision medicine,” he says.

Enhancing Patient Care, One Process at a Time

Kristin McCabe, MSN, RN, CNRN never fails to be impressed by her patients with multiple sclerosis (MS). In an effort to maintain a normal day-to-day routine, her patients stay up-to-date on their research and understand their bodies well.

“I respect the amount of self-teaching they do,” McCabe says. “They’re willing to do the research to stay on top of what they know is a lifelong disease.”

It’s one of the reasons she’s proud to serve as the MS Nurse Manager for Penn’s Department of Neurology’s Multiple Sclerosis Center, a relatively new position that allows McCabe to help improve the quality of patients’ care.

McCabe has a deep history with Penn. She spent 11 years as a clinical nurse in the inpatient neurology unit at the Hospital of the University of Pennsylvania before joining the center in 2018. She earned her MSN from the University of Pennsylvania in 2013 with double minors in patient safety processes/quality improvement and organizational dynamics—skillsets that she uses regularly to manage day-to-day operations for the center.

“MS is growing rapidly, so my role is to look at the big picture and supervise our everyday workflows to accommodate this growth,” McCabe says. “We strive to be as efficient as possible, so our patients get superb care in a timely manner.”

In her first year in this position, one primary focus has been streamlining the center’s ability to offer Ocrevus infusions for patients with relapsing-remitting and primary-progressive MS.

“At this point, we’re making small adjustments to these processes while continuing to develop close relationships with area infusion centers,” she says.

Projects like this are by no means solo ventures. McCabe is motivated by her team’s ability to turn new challenges into opportunities for patients.

“The clinicians and staff at the center give 110% every single day, in every single thing we do,” she says. “This team mentality translates into wonderful outcomes for our patients.”
Unraveling the Science of Beauty and Art
New Penn Center for Neuroaesthetics studying how and why aesthetics affect decision making

When two people look at the Mona Lisa or a Jackson Pollock painting, they often form completely different conclusions. What makes them like or dislike the art comes down to neuroaesthetics—the biological study that aims to understand how humans process beauty and art.

It’s a field that received a significant boost in 2018 when Penn Medicine launched the Penn Center for Neuroaesthetics, the nation’s first research center dedicated to uncovering the biological basis of aesthetics. The center will advance the understanding of human nature and preferences with consumer choices, the principles of design, and the appreciation and production of art. In short, things that give people meaning in their lives.

Leading the center is Anjan Chatterjee, MD, currently Chair of Neurology at Pennsylvania Hospital and the Elliott Professor of Neurology in the Perelman School of Medicine at the University of Pennsylvania, who is assembling an interdisciplinary team of experts in neuroscience, psychology, business, architecture and the arts.

"Even though aesthetics affect countless decisions—from what you wear in the morning to who you date—little of the psychological and neural underpinnings of aesthetics are known," says Dr. Chatterjee. “People’s aesthetic choices make them feel better and affect how others treat them.

“This center allows us to bring together, build upon, and advance knowledge of the mysterious world of aesthetic experience,” he continues. “Our goal is to evolve basic and translational research, educate the next generation of scholars, and serve as a hub for creative experts interested in the nature and neural basis of beauty, art and architecture.”

The center focuses on three programmatic elements: basic science, translational science, and communication. Experts from across Penn will investigate the neural system that underlies aesthetic experiences and choices, answering provocative questions dealing with how the pleasure of beauty differs from primary pleasures like food, whether beauty affects values such as morality, and how context and education affects aesthetic experiences.

30 Seconds with Dr. Chatterjee

Why did you decide to get involved in the field of neuroaesthetics? “I always have been interested in art and the idea of beauty. Beauty tends to have intrinsic value, which is not applicable to anything else. People spend money on artwork. For example, someone might spend more than $50 million on a Jeff Koons piece. But the piece is not something you can eat, nor does the face of it have any practical value, and yet we spend a lot of time thinking and spending resources on such objects. So, there is an inherent paradox in beauty and aesthetic experiences. For me, that makes it an interesting topic to study. Neuroaesthetics, especially experimental neuroaesthetics, is a very young field and generates a lot of interest. There are many questions to answer right now, and that makes it an exciting time to be working in this field.”
For instance, is there a common neural currency to beauty?” Dr. Chatterjee says. “Neuroscience offers possible answers to questions that philosophy poses about why we gravitate toward beauty, enjoy it and try to reproduce it. Art doesn’t feed us, clothe us or shelter us. So why do we care about it?”

The center will also investigate the applications of neuroaesthetics to medicine and culture, uncovering how aesthetic experiences can be used therapeutically. For example, can architectural design be used to help well-being in patients such as those with memory problems? Would exposure to art enhance medical student training?

Additionally, the center has a goal to expand its hub of specialists to host scholars from around the world and artists in residence. Dr. Chatterjee also wants to partner with institutions like the Barnes Foundation to complement the center’s agenda.

“We expect to have an artist who is interested in the nature of memory spending time in the lab with us, creating a true collaboration between art and science,” Dr. Chatterjee says. “Collaboration could take place with a psychologist who studies decision-making and reward systems; a Wharton professor interested in how purchasing decisions are made; or a faculty member who studies a remote tribe with little exposure to the Western world and our media-saturated culture.”

The “real world” applications of the center’s work are far reaching. Consider just one area: the hiring process.

“Attractive people are often perceived as being smarter, friendlier, more energetic and more qualified for a job,” Dr. Chatterjee says. “On the flip side, people with things like small scars, facial abnormalities or who aren’t perceived as attractive have all kinds of implicit bias against them. These triggers have deep roots in our biology, but we have a huge frontal lobe that can counteract them.”

The Penn Center for Neuroaesthetics is just the latest example of how Penn Neurology is breaking new ground.

“Penn has extraordinary strengths that make it the right place for such an innovative center,” says Frances E. Jensen, MD, FACP, Chair of Neurology at Penn. “Beyond the rich research environment, our strengths in cognitive neuroscience and academics set us apart. These are early days in the discipline of neuroaesthetics and this new center will shape the field for years to come.”

Dr. Chatterjee echoes that sentiment, noting that most people working in the field of neuroaesthetics are largely doing so in isolation.

“We want to change that. It’s our hope that our center will become a home for researchers from around the world,” he says.

continued from page 3

Make Way for the Neuro-Immune Revolution

A Center that Spans the Specialties

Like so many conditions that affect the CNS, the cumulative effects of MS relapses and progression cause symptoms to worsen over time. This makes early diagnosis and intervention crucial. It’s a fact that led Dr. Bar-Or and long-standing collaborator and friend Brenda Banwell, MD, Chief of the Division of Neurology at Children’s Hospital of Philadelphia (CHOP), to launch the CHOP-Penn Age-Span Program in MS and related disorders. This program aims to ensure a seamless transition of care from pediatric to adult care for individuals with MS and related disorders.

“Through our age-span program we can follow individuals from day one with clinical, imaging and biological assessments to gain a better understanding of that individual’s biology and course,” explains Dr. Bar-Or. “This allows us to better educate and advocate for the best treatment on behalf of each person we see.”

While MS research and the Age-Span Program in MS and related disorders are at the heart of Penn’s CNET, they represent just a portion of its extensive and evolving work in the broader arena of neuroinflammation. “This field cuts across multiple disciplines at both Penn and CHOP and brings together people with different clinical and research interests and expertise,” Dr. Bar-Or says.

As proof, the center’s research interactions extend well beyond MS to include a range of other neurological conditions, psychiatric disorders, autoimmune conditions and cancer.

“There are a lot of people already engaged in top-notch neuroinflammation research and many others who have joined as part of the NeuroInflammation Research Forum (NIRF), as the amazing potential across Penn’s diverse community is galvanized,” he shares. NIRF, which represents another outcropping of the center, now has over 100 members among Penn Medicine researchers and physicians and brings them together several times a year to hear from, and meet with, global leaders in the area of neuroinflammation.

“A major attraction for NIRF members is to learn what one neuroinflammatory condition can teach them about another,” explains Dr. Bar-Or. “This has spurred us to think about the science of neuroinflammation collaboratively and emphasize the clinical and therapeutic opportunities that could be explored across specialty areas. It’s really incredibly exciting to think about the possibilities that lie before us as part of the ‘neuro-immune revolution!”

©
Realizing the Future of Neurodegenerative Disease Care...Today

Lauren Elman, MD, remembers learning about polio in medical school. “There were pictures of people in iron lungs in our textbooks and I was fascinated but so grateful to live in a world where this was largely a historical phenomenon,” she says. “It makes me wonder what disease medical students will have a similar reaction to 50 years from now.”

As Director of Clinical Research for Penn Medicine’s Comprehensive ALS Center and Director of Penn’s Muscular Dystrophy Association (MDA) Clinic, she has a few ideas. “One thing that is on the way for spinal muscular atrophy (SMA) and potentially other neuromuscular diseases is gene therapy,” Dr. Elman says. “This could transform the way these diseases are treated and lead future generations of clinicians to look back on them much as I looked back on polio.”

That future is approaching more rapidly than some might think. Penn Neurology is actively involved in a number of pre-clinical projects in this area, including a significant amount of biomarker work.

“Researchers are working aggressively on SMA, Kennedy’s disease and ALS quantitative imaging biomarkers,” she says. “Because gene therapy trials typically enroll very small numbers of patients—sometimes 6 to 10 people with no placebo group—you need very sensitive quantitative biomarkers to meet outcomes and determine efficacy.

At Penn, we’re exploring novel biomarker outcomes to move that forward and help with clinical trial design.”

Much of this work falls under the banners of the Penn Comprehensive ALS Center, which was created in 1999 to care for people with this life-altering disease, and Penn’s MDA Center, which has been serving the community since the early 1970s. The centers, with a caseload of hundreds of patients, bring together specialists from a wide variety of fields, including neurology, genetics, nursing, pulmonology, cardiology, endocrinology, physical and occupational therapy, speech and language pathology, and nutrition.

Research plays a prominent role with regular partnerships on projects with Penn specialists in the areas of neuroradiology, neuropathology and neurogenetics. There are currently five active clinical trials for adults with ALS and other neuromuscular diseases, and other opportunities to participate in research as well.

“Some of the things we’re able to offer patients today were science fiction when I was in training,” says Dr. Elman. “For example, most adult patients with SMA didn’t bother to see a neurologist in the past because we had nothing to offer them. Today, we have Spinraza, a relatively new drug that can significantly slow disease progression and, in some cases, improve strength among patients. This is a huge victory.

...”
because there has never actually been a truly meaningful
treatment for neuromuscular degenerative disease until now.”

Penn has one of the largest adult Spinraza programs in the
nation, with the capacity to infuse the drug in patients with
complicated anatomy.

“Since the drug is given by lumbar puncture and many patients
have had complex orthopedic surgery or rods put in for
scoliosis, infusion of this drug can be challenging.”
Dr. Elman explains. “At Penn, we formed a team with specialists
from neurology, interventional radiology and pharmacy to
accomplish this. Four loading doses are given over a 10-week
period and then every four months after that. We were one
of the first adult-only centers to administer the drug.”

Where Spinraza is having the most profound affect is in the
pediatric population, according to Dr. Elman.

“In children, the drug is reinventing the natural history of
this disease,” she says. “Children with SMA1 used to die
in childhood, but now they’re not and that means we’re in
uncharted territory. At Penn, we are collecting clinical data
on adults being treated with the drug, since no adults were
involved in the initial clinical trials.”

Another cutting-edge therapy offered at Penn for
neuromuscular disease is Exondys51, which is an exon-skipping
therapy for patients with Duchenne muscular dystrophy.
Approximately 13% of patients with Duchenne are amenable
to this drug, as it is mutation-specific. It is still early days in
determining the clinical benefit of this drug in adults, but so
far, it is well-tolerated and many patients are eager to try it.
Exondys51 is the first in class and drugs of similar mechanism
that will target other mutations are currently in late-stage trials.

“Because of the new and projected availability of mutation-
specific treatments, we’re aggressive to make sure that all
of our patients know their mutations, so they know if they are
amenable to drugs or not,” Dr. Elman says. “Additionally, gene
therapy for Duchenne is an active and exciting area
of research.”

Thanks to an established relationship with the Children’s
Hospital of Philadelphia (CHOP), Penn often assumes care
of patients with childhood-onset muscle and nerve diseases
once they reach adulthood. The Penn clinicians share a joint
conference with the neuromuscular specialists at CHOP and
frequently confer about diagnostic and care issues, making the
transition to adult care as seamless as possible. Additionally,
the Penn team is lucky to have a dedicated social worker and
nurse for the MDA clinic to facilitate these transitions from
pediatric to adult care.

“There has been a sea of change in this entire field, and I feel
very fortunate to be involved with it,” she says. “We’re starting
to see treatments we only ever dreamed of.”

Lisa Velez-Batista remembers tiring easily as a child and
not being able to keep up with her friends. She always
questioned what was wrong, but she met all her growth
milestones, so her concerns were never addressed.

Things continued to worsen until, at age 20, she fell
in the street in front of a bus and couldn’t get up. That
incident finally led to a devastating diagnosis: spinal
muscular atrophy (SMA).

“I was told there was no treatment, that it was
progressive, and I would be wheelchair-bound in 10
years,” says Velez-Batista, who is now 56. “I had just
completed my associate’s degree but decided to put
my bachelor’s on hold. Soon after I had two children.
I wanted to live life while I could.”

Velez-Batista had SMA-3 and was fortunate that her
disease progressed slowly. She eventually returned
to college and then worked full-time as a speech
pathologist before retiring early due to a knee injury.
But you can’t outrun SMA.

“I’ve become much weaker over the years, and I now
have to use a scooter if I need to walk any distance,”
she says. “I had resigned myself to a slow deterioration.”

Things changed on Christmas Eve 2016 when her cell
phone began blowing up with phone calls and text
messages. “Did you hear?” friends and relatives asked.
The FDA had just approved Spinraza, a drug that can
slow progression of SMA and, in some cases, improve
strength in patients.

“I had heard of this drug being tested in children, but
I didn’t think adults would get it,” she says. “I had the first
of my four loading doses at Penn in October 2017 and
am now on my third maintenance dose.”

Velez-Batista says she almost immediately felt “lighter”
after the first dose. That feeling was backed up by
measurable improvements.

“I started physical therapy and soon I could do small
things I couldn’t do before, like bending my knees
back when I lay on my stomach or ripping a piece of
folded up paper,” she says. At a recent appointment,
Penn neurologist Lauren Elman, MD, even detected a
reflex in Velez-Batista’s right arm, something that hadn’t
happened in years.

“The most important thing is that the disease is not
progressing,” says Velez-Batista. “It’s not a cure, but
I feel stronger and if I’m not getting worse that’s a
great thing.”
Celebrating the Future of Neurology

During their time with our program, residents work with world-class clinicians and researchers in every field of neurology. These robust experiences position our residents for excellence in Fellowship training and their subsequent career. Two-thirds of our residents remain at Penn for their Fellowship, with the balance heading to top institutions across the country.

Congratulations to the Class of 2019

- Whitley Aamodt, MD, MPH
- Stephen Aradi, MD
- Danielle Barber, MD, PhD (Child Neurology)
- Neena Cherayil, MD
- Erin Conrad, MD
- Taneeta (Mindy) Ganguly, MD
- Melissa L. Hutchinson, MD (Child Neurology)
- Sara Manning, MD

- Susan E. Matesanz, MD (Child Neurology)
- Joanna Mattis, MD, PhD
- Susanna O’Kula, MD
- Carlyn A. Patterson Gentile, MD, PhD (Child Neurology)
- Jon Rosenberg, MD
- Etsegenet Tizazu, MD, MS
- Jeremy Wong, MD (Child Neurology)
- Xin (Linda) Zhou, MD

Welcome to the Class of 2023

- Natali V. Baner, MD (Child Neurology)
- Samuel Carrell, MD, PhD
- Ryan Devenyi, MD, PhD
- Alice Ford, MD, PhD
- Stephanie Gandelman, MD
- Michael Guo, MD, PhD
- Peter Hadar, MD, MSTR
- Alexis R. Karlin, MD (Child Neurology)
- Catherine Kulick, MD
- Emily Liu, MD

- Maksym S. Marek, MD
- Salvatore C. Rametta, MD (Child Neurology)
- Sahily Reyes-Esteves, MD, PhD
- Jessica A. Saunders, MD (Child Neurology)
- Christina Swan, MD, PhD
- Joseph Vithayathil, MD, PhD (Child Neurology)
- Denise Xu, MD
- Lauren Zoghlin, MD

Members of Penn Neurology's class of 2019 take a break for some selfie fun.