the intersection of Parkinson's disease and addiction

Dr. Waszczak's work is a powerful example of why BRF's non-specific disease approach is so effective. Often breakthroughs come from unexpected places.

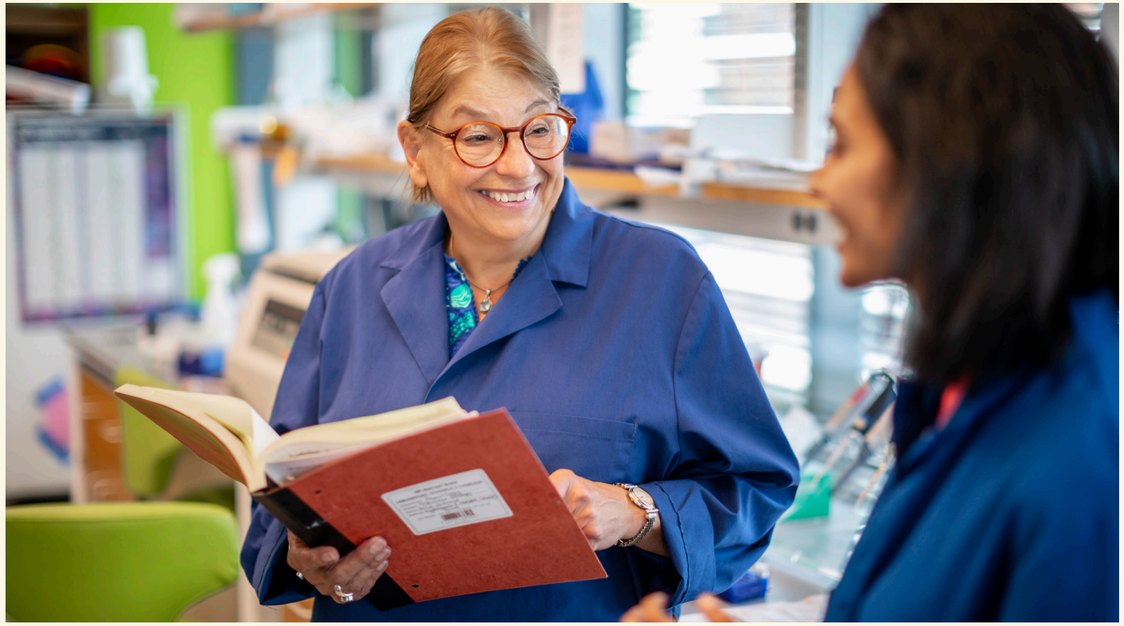
A detour in Parkinson's disease research led Barbara Waszczak, Ph.D., professor in the Department of Pharmaceutical Sciences at Northeastern University in Boston, in an unexpected direction–opioid abuse relapse research.

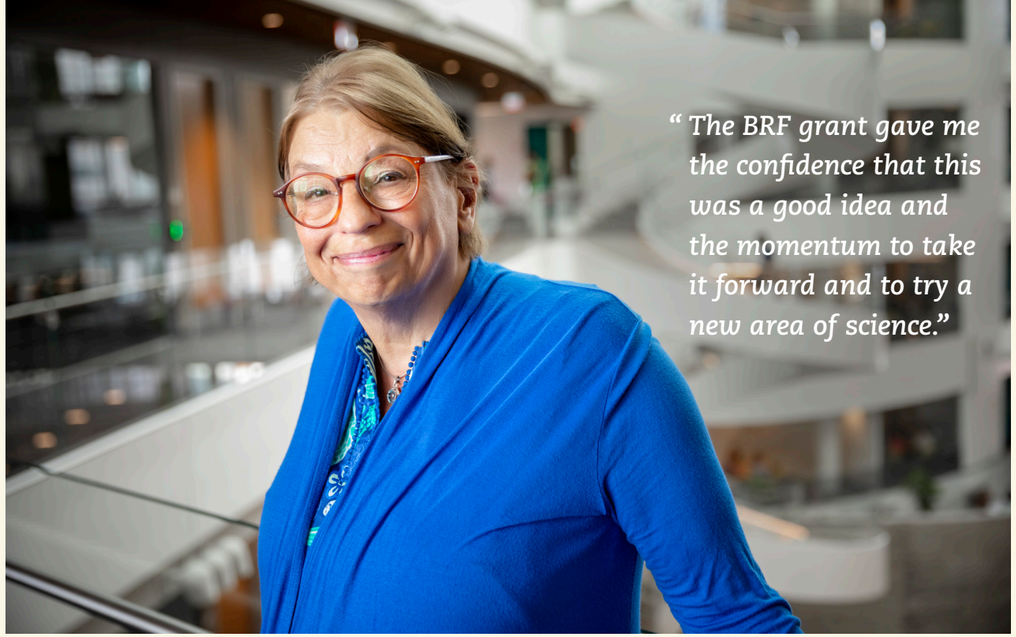
Dr. Waszczak had been studying glial cell-derived neurotrophic factor (GDNF) as a potential treatment for Parkinson's disease for about a decade. Parkinson's disease kills brain cells that produce the neurotransmitter dopamine, which is released during pleasurable activities. Though it is normal for dopamine-producing brain cells to die off across the course of the human lifespan, the process is accelerated in Parkinson's disease. Evidence shows that GDNF increases the survival, size, and dopamine-production of these cells.

"If GDNF could stop whatever is killing these neurons, you could arrest disease progression and maybe even promote some recovery of the cells that haven't yet died," she said. "It could stop the disease in its tracks."

The challenge has been finding a way to get GDNF into the brain. Some other research labs have injected GDNF directly into the brain, but clinical trials of that approach failed to show a benefit. "It wasn't clear whether they were succeeding in getting GDNF into the brain appropriately," Dr. Waszczak explained. But she and her colleagues had an alternate delivery method.

"Our unique approach was to use intranasal delivery of GDNF," she said. "It doesn't require a surgical procedure. It relies upon the fact that things can travel from the nose into the brain by getting through small





spaces between olfactory neurons that enter the nasal cavity and project into the brain."

Her team published studies in the early 2000s showing that intranasal delivery of GDNF in rats with a Parkinson-like condition protected the dopamine-producing cells. Dr. Waszczak later refined her GDNF delivery approach by partnering with company called Copernicus that makes nanoparticles of the DNA that encodes GDNF.

"We thought a better approach might be to use intranasal delivery to get the gene into the brain so that it could produce levels of GDNF that might be neuroprotective for a longer period of time than a single intranasal dose of the protein," Dr. Waszczak said. They even showed this new delivery method helped rats with a Parkinson-like disorder. But she struggled to find funders to support her work on GDNF as a treatment because of the earlier failed clinical trials.

It seemed like an insurmountable roadblock. But then she discovered evidence that GDNF might be useful for treating a range of other brain diseases, including addiction. Dr. Waszczak was awarded a 2018 Opioid Initiative grant from BRF to test whether nasal delivery of the DNA that encodes GDNF reduces relapse-like behavior in rats administered opioids. Her work is almost complete, and the data so far suggest it works.

She's begun applying for grants to conduct the studies necessary to confirm her findings in rats, which would pave the way to test this therapy in people with opioid addiction. She is also collaborating with another scientist to test a theory about why it works: "Overuse has caused the dopamine-producing neurons to become deficient," she proposed. "That's why people who've been using drugs for a while can't stop taking them. They need to take them in order to feel any kind of positive rewarding feelings. If GDNF could restore the dopamine levels in the brains of these people, they might stop craving and be able to recover."

Dr. Waszczak's project is almost complete and the data indicate that her innovative hypothesis may lead to a novel treatment for addiction.

Dr. Waszczak's work is a powerful example of why BRF's approach is so effective. Often breakthroughs come from unexpected places, in this case at the intersection of Parkinson's disease research and addiction research.

"Without the BRF grant I would not have pursued this," she said. "It would've been something I considered outside my domain. The BRF grant gave me the confidence that this was a good idea and the momentum to take it forward and to try a new area of science."

Funding for this research was generously provided by BCBSA

BRF's opioid initiative leverages research intersections to tackle a crisis

$78.5 billion/year is the total economic burden of prescription opioid misuse in the US, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.

up to **90%** of opioid users who seek treatment experience relapse

Every day, **130 people** die from opioid-overdoses in the United States

Nationally, **2.1 million people** currently have an opioid use disorder

It's estimated that **80%** of people who use heroin first misused prescription opioids

The midwest region saw a **70% increase** in opioid overdoses from July 2016 through September 2017

The ongoing opioid epidemic is one of the most devastating public health crises the United States has ever faced. It's estimated that more than 130 people die from opioid-overdoses each day in the US, and 2.1 million people currently have an opioid use disorder[1]

To help combat the crisis, in 2017 the BRF formed the Opioid Advisory Committee (OAC) made up of leading scientific experts on opioid dependency and addiction. **The committee recommended that BRF focus on funding research aimed at reducing relapse.** Nearly a staggering 90% of those who seek treatment for opioid use disorders experience a relapse, and there is an urgent need to develop new relapse prevention therapeutics.

"BRF's OAC has shined a light on the possibility that an opportunity may exist today that will help people on the path to recovery from opioid addiction from sliding back into the grasp of chemical addiction," said Dr. Terre Constantine, Executive Director and CEO of BRF. "The scope of this crisis is such that even a modest, positive effect on relapse would be of monumental benefit."

With generous funding from the Blue Cross Blue Shield Association, BRF awarded its first two opioid initiative grants in 2018 to two researchers who are working to develop and repurpose drugs that could prevent the opioid cravings that lead to relapse. Like many of the scientists BRF funds, these scientists are looking for insights at the intersection of research on different brain diseases to accelerate progress.

Their work is essential to bringing an end to the opioid crisis and relief to those in recovery, their loved ones, and their communities.

Members of Brain Research Foundation's OAC were chosen for their experience and expertise in the area of opioid addiction.

The OAC identified the focus on reducing relapse and reviewed and recommended the proposed projects to receive funding.

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[1]US Department of Health and Human Services. About the Opioid Epidemic. https://www hhs.gov/opioids/about-the-epidemic/index.html.