IN FOCUS

SPRING/SUMMER 2021

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A Eureka Moment for Paul Yang Boosts Advancement of Vision-Saving RP Drug

Paul Yang, MD, PhD

Early in his clinical research career, Paul Yang, MD, PhD, received a Foundation Fighting Blindness clinical research fellowship award to evaluate a drug called mycophenolate that showed the potential to save vision for many people with retinitis pigmentosa (RP), regardless of the gene mutations causing their vision loss. He'd previously used the drug, already FDA-approved for other conditions, for uveitis (an inflammatory eye condition), and felt optimistic he'd had a good treatment candidate for RP.

Vision loss for many people with RP and other inherited retinal degenerations is caused by the accumulation of a molecule called cyclic guanosine monophosphate (cGMP). While cGMP is an important messenger molecule for converting light into electrical signals in the retina, too much of it is toxic. Mycophenolate can help regulate cGMP, thereby reducing the toxic accumulation.

"Mycophenolate is one of several medications we use a lot when trying to control inflammatory disease in the eye, but it is the only one that inhibits the pathways that are also specific to cGMP accumulation," says Yang. "We've used it off label for treating uveitis for decades. We have a good idea of how to use it for eye conditions."

But his pilot experiments with mycophenolate weren't working. "I was a week away from the end of my fellowship and was prepared to put my project aside and move on," he recalls. "I decided to give it one more try." In his initial experiments, he reared the mice in darkness. Doing so, Yang hypothesized, would slow degeneration

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COVER STORY
CONTINUED FROM FRONT COVER

and give the drug more time to work. But working in the dark had been tedious, so he decided to try one more experiment with the mice reared in normal light, even though, from a scientific standpoint, it didn't make sense to him. With that lighting change, the treatment worked.

"It was one of those Eureka! moments in science that make all the other failures worthwhile," says Yang. "Just because it doesn't make sense doesn't mean it is not worth investigating further. Sometimes we just don't understand the science very well, and we learn more when unexpected things are observed."

Yang used the data from that study to get a subsequent Foundation Fighting Blindness career development award, which supported additional experiments to confirm the original results. Recently, Yang received a $900,000 Foundation translational research acceleration program (TRAP) grant to move the therapeutic approach toward a clinical trial. The TRAP grant is enabling him to select a lead treatment candidate and test it in additional mouse models. Given that mycophenolate and the other drugs being evaluated are already clinically approved, the time needed for safety and toxicology studies in preparation for a clinical trial in inherited retinal degenerations is likely reduced.

Yang came to Casey Eye Institute, Oregon Health & Science University (OHSU), for an ophthalmic genetics fellowship in 2012 after completing his ocular immunology fellowship at Massachusetts Eye Research & Surgery Institution (MERSI), and internship and residency at Moran Eye Center, University of Utah. He subsequently stayed on at OHSU as faculty.

Yang's timing for joining Casey was exquisite with the advent of gene therapy clinical trials for many inherited retinal diseases. Today, he is the lead investigator on eight clinical trials, including Applied Genetic Technologies Corporation's (AGTC) X-linked RP gene therapy study, 4D Molecular Therapeutics' X-linked RP gene therapy study, ProQR's CEP290 and USH2A RNA therapy studies, and Stargazer's study of its drug for Stargardt disease. He is also a co-investigator on 13 other human studies and sees patients in the clinic.

Yang was inspired to get into science and ophthalmology by his father, an electrical engineer, as well as his biology studies in school. He says, "During my education, I realized that the retina is the most complex, highly organized system in the body. It is essentially a 3D circuit that turns light into electrochemical signals. It is actually a part of the brain — the only part of the brain which the doctor can see with the naked eye in the clinic, and by doing so, can diagnose and treat conditions."

Yang shares his passion for ophthalmology with his wife, who is a pediatric ophthalmologist at Casey. They met when they were both in training at Moran. "We share information and refer patients to each other over dinner," he says. "A patient can only hope their two specialists are married."

Yang is grateful to his many mentors — including Richard Weleber, MD, Mark Pennesi, MD, PhD, Catherine Morgans, PhD, and Robert Duvoisins, PhD, from Casey, C. Stephen Foster, MD, from MERSI, and Paul Bernstein, MD, PhD, and Albert Vitale, MD, from Moran — all of whom helped him get grants and advance his career.

Yang also says that support from the Foundation has defined his clinical and research careers. "Without the Foundation, none of this would exist. I would be somewhere else doing something else."

MY RETINA TRACKER REGISTRY

Are You on the Clinical Trial Radar Screen?

The Foundation Fighting Blindness launched its free, global patient registry — available at **MyRetinaTracker.org** — to connect people with inherited retinal diseases (IRDs) with researchers and companies developing therapies. More than 16,000 people are now in the registry and the Foundation is working hard to boost that number.

"It is important to remember that IRDs are rare, affecting about 200,000 people in the US, and it is often challenging for investigators to identify patients for their clinical trials," says Todd Durham, PhD, vice president of clinical development at the Foundation. "For companies who partner with the Foundation, the My Retina Tracker Registry serves as a hub for clinical trial recruitment. Even if a therapy developer isn't planning to launch a trial immediately, they often want to know that patients for their study will be available down the road."

FOUNDATION FIGHTING BLINDNESS

My Retina Tracker® Registry

My Retina Tracker Registry was recently upgraded to be more user-friendly, including for those with vision loss. Much of the data entered

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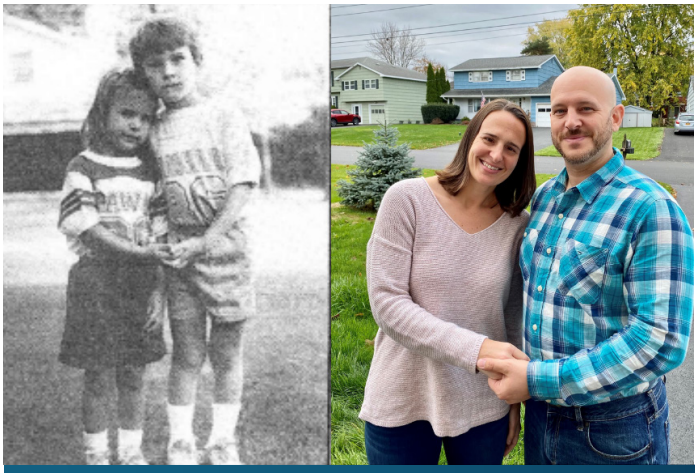
BEACON STORY

Erin's Unwavering Determination, Then and Now



Left: Erin and her brother Matt are holding hands for a feature in a Foundation fundraising campaign in the 1990s. Right: Erin and Matt now.

Erin Czadzeck (previously Scala) was diagnosed with retinitis pigmentosa (RP) at the age of four, after her parents, John and Barbara, noticed that she was tripping around the house and grabbing onto them when it was dark. John recalls the ophthalmologist immediately recognizing that Erin had RP, but there wasn't any genetic testing readily available then to confirm the diagnosis.

From there, Erin's parents started to research resources and found the Foundation Fighting Blindness (then known as the National Retinitis Pigmentosa Foundation) in 1990. Over the years, the Scala family attended many VISIONS conferences, ran an annual local golf tournament, and started a Syracuse (NY) chapter, in which John was the president. All their efforts were to raise funds for research to find Erin and others with RP, treatments and cures.

As a child, Erin was tenacious and known for her spunk. She loved to play soccer and ride her bike, never letting her visual impairments stop her from keeping up with her friends and siblings. Because of her drive at such a young age, the Foundation featured Erin in several fundraising campaigns throughout the 1990s. Erin was featured with her older brother, Matt, as well.

Today, Erin is resilient as ever. She's now 34 years old, married, and has a one-year-old son. Erin earned her bachelor's degree in public justice and currently works as an employment specialist at a residential facility for youth with sexual, emotional, or behavioral challenges. Erin works with these youth to teach them job-related and life skills, often using assistive technology like JAWS on her laptop or voice over on her iPad and iPhone. Erin also uses a white cane for independent mobility.

"I'm constantly teaching myself and learning about new technology because I hate asking for help," says Erin. "I know there's always a way I can accomplish a task, and the result will always be the same; I just may go about it differently."

Erin's vision loss has continued to progress over the years, as now she can only see light and dark and cannot decipher faces or color. But this progressive vision loss over time has taught Erin to appreciate what she has and to continue to persevere regardless.

"There's nothing I can do about my vision right now, so I try just to stay positive and think about all the good things that I do have," says Erin. "I can still read a Braille book to my son in the dark or change his diaper at night, so I always try to remember that I can still do what I need to."

A way Erin continues to thrive is by keeping active outdoors. Erin loves to snowboard, rollerblade, hike, and compete in triathlons and Tough Mudders with a guide, using a tether rope for swimming and running, and a tandem bike.

"Some people say I'm crazy, but it's so fun for me, and I'm just living life and enjoying it," says

Erin. “I can still swim, bike, and run; I just need someone with me. And it’s way more fun to do it with someone else than by yourself anyway.”

With Erin’s busy schedule, she continues to stay up to date with RP research updates from the Foundation, social media support groups, and podcasts.

“Research is exploding now,” says Erin. “Every little bit of research leads to more, so I’m very hopeful. And the awareness about retinal diseases has grown over the years and is reaching more than ever before.”

She recently had genetic testing to find her mutated genes before having her first child.

“The research has gone from mice to men over the years,” says Erin’s dad, John. “Way back when we first started getting involved with the Foundation, all you heard about was research on mice, but now they’re actually working on humans. We’ve even met people that have participated in clinical trials, and that’s so encouraging.”

As independent as Erin is now, she’s happy to have her family and friends to rely on, if needed. Her older brother, Matt, who is now 36, is always there for Erin when she needs help with anything.

“Erin’s diagnosis has made me realize, on more than one occasion, that I shouldn’t take anything for granted,” says Matt. “It’s interesting to think about how Erin manages to conquer each day without her sight. It’s an understatement to say she’s inspirational to me.”

Erin strives to inspire many more and to help raise awareness that blindness doesn’t affect everyone in the same way.

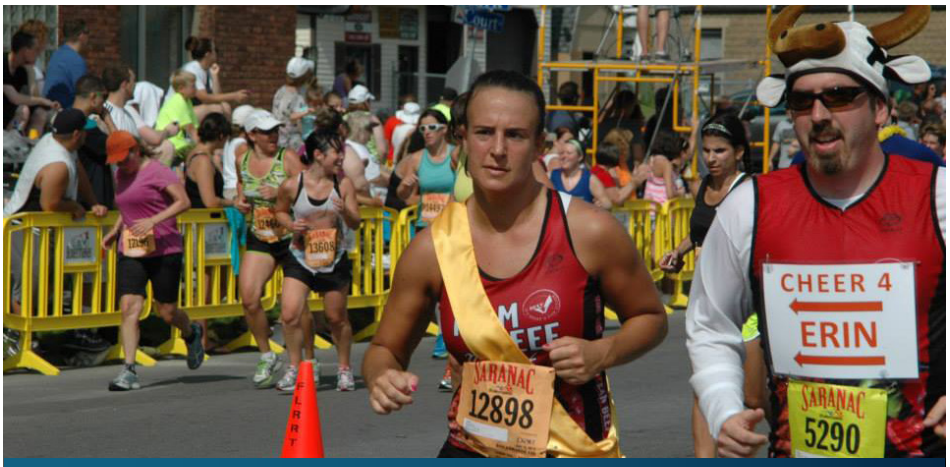
“You can still live a positive, uplifting, and enlightening life with vision loss,” says Erin. “Life would be boring for me if I didn’t have RP, honestly. My vision loss is just another obstacle to overcome, and it’s just a different way to live.”

Erin’s family has learned a lot about blindness over the years, which they want to share with other families of those newly diagnosed with a retinal disease at a young age.

“As a parent, it’s important not to shelter them,” says Erin’s dad, John. “You don’t want your child to grow up thinking they’re different. They can still do anything they put their mind to.”

Erin’s brother Matt lives by the “golden rule” to treat others the way you want to be treated.

“That would be the advice I would give anybody growing up with a sibling with RP,” says Matt. “Go above and beyond to make your loved ones, especially if they are living with a disability, feel like they are wanted and do everything you can to help.”



Erin participating in the Boilermaker Road Race with her guide running to the right of her.

Erin participating in an Iron Girl Triathlon with a guide riding a tandem bike with her.

CLINICAL-TRIAL PIPELINE

Retinal-Disease Therapy

Inherited Retinal Diseases and Dry AMD: 43 Trials (Select) | Updated March 2021

GENE THERAPIES	Progress
Achromatopsia (CNGB3) – AGTC	Phase 1/2
Achromatopsia (CNGB3) – MeiraGTx/Janssen	Phase 1/2
Achromatopsia (CNGA3) – AGTC	Phase 1/2
Achromatopsia (CNGA3) – Tubingen Hosp	Phase 1/2
AMD (Dry) – Gyroscope	Phase 2
Choroideremia (REP1) – 4DMT	Phase 1/2
Choroideremia (REP1) – Biogen (Nightstar)	Phase 3
Choroideremia (REP1) – Spark	Phase 1/2
Choroideremia (REP1) – Tubingen Hosp	Phase 2
LCA (GUCY2D) – Atsena	Phase 1/2
LCA and RP (RPE65) – MeiraGTx/Janssen	Phase 1/2
LCA and RP (RPE65) – Spark	FDA Approved
RP (PDE6B) – Horama	Phase 1/2
RP, Usher, others (optogenetic) – Allergan	Phase 1/2
RP, Usher, others (optogenetic) – Bionic Sight	Phase 1/2
RP, Usher, others (optogenetic) – GenSight	Phase 1/2
RP (RLBP1) – Novartis	Phase 1/2
RP (PDE6A) – Tubingen Hosp	Phase 1/2
Retinoschisis (RS1) – NEI	Phase 1/2
X-linked RP (RPGR) – AGTC	Phase 1/2
X-linked RP (RPGR) – MeiraGTx/Janssen	Phase 1/2
X-linked RP (RPGR) – 4DMT	Phase 1/2
X-linked RP (RPGR) – Biogen (Nightstar)	Phase 2/3

CELL-BASED THERAPIES	Progress
AMD-dry (RPE) – Astellas	Phase 1/2
AMD-dry (RPE) – Cell Cure	Phase 1/2
AMD-dry (RPE from iPSC) – NEI	Phase 1/2
AMD-dry (RPE on scaffold) – Regen Patch	Phase 1/2
RP, Usher (retinal progenitors) – jCyte	Phase 2b
RP, Usher (retinal progenitors) – ReNeuron	Phase 2
Stargardt (RPE) – Astellas	Phase 1/2

MOLECULES, PROTEINS, AONS	Progress
AMD-dry (C3 inhibitor) – Apellis	Phase 3
AMD-dry (CB inhibitor) – Ionis	Phase 2
AMD-dry (C5 inhibitor) – Iveric bio	Phase 2
LCA (CEP290, AON) – ProQR	Phase 2/3
LCA (CEP290, CRISPR) – Editas	Phase 1/2
RP (RHO, AON) ProQR	Phase 1/2
Stargardt disease (emixustat) – Acucela	Phase 3
Stargardt disease (deuterated vit A) – Alkeus	Phase 2
Stargardt disease (C5 inhibitor) – Iveric bio	Phase 2
Stargardt disease (anti–RBP4) – Belite Bio	Phase 1
Stargardt disease (anti-RBP4) – Stargazer	Phase 2
Usher syndrome (NACA-anti-oxidant) – Nacuity	Phase 1/2
Usher syndrome 2A (AON) – ProQR	Phase 1/2

Visit **ClinicalTrials.gov** for more details and trial contact information. This document is for informational purposes only. Information is subject to change, and its accuracy cannot be guaranteed.

VISIONWALK SPOTLIGHT

Denise Compton: Getting Creative for the Virtual VisionWalk

Denise (right) and her mother, Betty, (left) wearing and holding their homemade face masks.

Nine members of Denise's VisionWalk team, Eyes With Vision, with their homemade 2020 VisionWalk sign.

When the COVID-19 pandemic hit, Denise quickly realized there was a vast need for face masks. So, she decided to put her prior quilting skills to use and sell homemade face masks to benefit the Foundation Fighting Blindness.

Denise has had a hearing impairment since preschool and was diagnosed with Usher syndrome (type 2A) at 29 years old. Denise continued in her career in accounting until 2016. Now 56 years old and residing in New Braunfels, Texas, Denise's family means the world to her, crediting her husband as her "biggest supporter."

When Denise was first diagnosed, she learned about the Foundation and participated in the first local VisionWalk in 2008. But with being a busy working mom and not feeling quite ready to accept her visual impairment, she didn't feel like her vision was a top priority yet. But in just the last couple of years, Denise's vision loss has started to progress more rapidly, so she began to get involved with the Foundation again by participating in chapter seminars and the local Austin-San Antonio VisionWalk.

"I'm just so thankful for all the ongoing research that the Foundation is funding," says Denise. "I just hope the funds we raise now will mean that there will be a cure for the next generation."

So, when Denise found out that the VisionWalk would be virtual, she decided to use her face mask making as a fundraiser for her Austin-San Antonio VisionWalk team, Eyes With Vision.

To make the masks, Denise would use her fingers to feel through cutting and pinning, and her mother would assist her with the sewing. After making face masks for family and a few close friends, word started to get around as the mask demand increased.

In addition to word of mouth, Denise posted on her neighborhood and personal Facebook pages for anyone to place an order. In the end, Denise and her mother made over 400 masks, raising over $2,200.

"Everyone was very supportive and excited for their money to go toward the Foundation," says Denise. "We worked hard and diligently, and the timing was just right for us. I'm hoping to keep our fundraising momentum going into next year's VisionWalk as well."

If you weren't able join us virtually in 2020, you can participate in our **Spring National Virtual VisionWalk** on **Saturday, June 12, 2021**. Register to participate by visiting: **VisionWalk.org**

CHAPTER SPOTLIGHT

Introducing: Lulie's Next Chapter for Light & Vision

LULIE'S NEXT CHAPTER *for*
LIGHT & VISION

From the beginning, Lulie Gund was there. She was a voice of inspiration in the early days of Gordon Gund's fight against retinitis pigmentosa and always present as a guiding hand, helping him realize his vision… for the Foundation Fighting Blindness. As the Foundation Fighting Blindness enters its 50th year, we begin **Lulie's Next Chapter for Light & Vision**.

The chapter program, originally conceived by Lulie herself, is the backbone of the Foundation's mission. It provides resources, education, and revenue in the fight against the entire spectrum of blinding retinal diseases. Moving forward, it is important that Lulie's memory remains at the core of the work of the chapter program.

Lulie's Next Chapter will include transformational initiatives such as Lulie's Leadership Training, which will bring together the best of chapter leadership to participate in leadership training and team development seminars – and Lulie's Light Award, which will annually recognize the work and impact of leadership from the Foundation's chapter network around the nation. This initiative will ensure that all of our chapters, like Lulie, will always be there.

FOUNDATION UPDATE
CONTINUED FROM PAGE 3

by the patient is done through pull-down menus.

When researchers work with the Foundation to recruit for studies, Foundation staff send contact letters to potentially eligible participants based on information recorded in their Registry profile. It is then up to the patient to contact the researcher if interested in the study. Researchers never have access to personal information — only de-identified disease information may be provided to them.

While a patient's genetic information is good to include in their record, the patient doesn't have to know their IRD gene to be in the registry. But the more information and data that can be included, the better.

"We strongly encourage registrants to include as much information in their records as possible and provide any updates as their vision or medical history changes," says Dr. Durham. "The more complete the record, the more likely a patient will come up in a researcher's search."

Visit **MyRetinaTracker.org** to register.

SCIENCE HIGHLIGHT

A Family Full of Hope

Greg and Paula Dubecky of Avon, Ohio, may have an amazing opportunity for their 18-year-old son to be enrolled in a gene therapy clinical trial for X-linked retinitis pigmentosa (XLRP). It is amazing because there are potentially four clinical trials for them to choose from, which would have been unheard of 15 years ago when their son, Marty, was first diagnosed at the age of three.

When he was a toddler, his parents noticed Marty had trouble seeing books that they read to him. Paula and her brother, Wally Anders, both have XLRP, so the family was no stranger to the disease and its symptoms. Since the diagnosis, the Dubeckys hit the ground running, doing everything in their power to stay informed and connected through the Foundation Fighting Blindness. They are leaders in the local Cleveland chapter and do extensive fundraising every year for VisionWalk, which they look forward to every spring; they said it feels like a second Christmas for their family.

Paula and her brother have served as an inspiration to Marty to not let his low vision keep him down. Wally lives a full life as an adventurer, a successful financial planner, and Paula says her brother is the most fearless person she has ever met. Paula herself is a force to be reckoned with, a devoted caregiver to Marty and his two sisters, organizing their day-to-day lives and helping them keep up with all their activities. She only recently stopped driving, which has been a challenge for her. However, they have a newly licensed teenager in the house who is more than happy to step in and help with that.

"I was very fortunate that my vision loss progressed much slower than my brother's. My own diagnosis never hit me hard until Marty's, and mostly because he was so young." Paula said. Not many women have vision loss from XLRP; they are usually unaffected carriers. However, thanks to advances in clinical care and genetic testing, more females are now being diagnosed with XLRP than 10–15 years ago.

Marty is a senior in high school, graduating this May, and is excited about his future. He is currently narrowing down his college choices to two universities in Ohio. He has a close-knit circle of friends from running cross country and track, which he competes in for his high school. "I did play a little bit of rugby in seventh and eighth grade, but it was a little tough because I had to keep track of a ball," Marty said of his high school sports. "But for cross country and track, I just run. My vision doesn't really pose a problem unless I let it." Marty is modest about his success in running track and cross country.

The Dubecky family and their dog, Mullen, wearing their VisionWalk team t-shirts.

X-LINKED RP QUICK FACTS

- Primarily affects males. Women are usually carriers, but are sometimes affected, as well.
- Affects approximately 15,000 people in the US.
- Most people with XLRP have mutations in the gene RPGR.
- XLRP can also be caused by mutations in RP2 and OFD1.
- Four XLRP-RPGR gene therapy trials are underway: AGTC, Biogen, MeiraGTx/ Janssen, and 4DMT.

The Dubecky family: (left to right) Paula, Clare, Annie, Marty, and Greg.

Marty running during a cross country meet.

Greg has kept a close watch on the scientific news and breakthroughs over the years and is well versed in the clinical trial pipeline. Currently, there are four gene therapy clinical trials for XLRP (RPGR mutations underway. Three of the trials – those sponsored by Applied Genetics Technologies Corporation (AGTC), Biogen, and MeiraGTx/Janssen – have reported vision improvements and are in, or advancing toward, Phase 3. 4D Molecular Therapeutics recently launched a Phase 1/2 trial for its XLRP gene therapy.

Greg said one reason that he is anxious to get Marty into a trial is because of the timeline, "The longer Marty has to wait, the less vision he's going to have, and the less opportunity for efficacy." Paula agreed with her husband and added, "I feel good about putting him in a later phase trial, especially because he's 18 and can better understand all of it. I'm not sure if he were very young how I would feel. I'm glad he can be part of the decision."

Marty's feelings about participating in a trial are profoundly selfless for a young person. "It'd be great to fix my vision, obviously, but it's not about me," He said. "I don't think one person is meant to put too much hope for themselves when entering a trial. I just want to be a part of the science that could possibly help other people and other kids like me who have RP. Of course, I'll take the opportunity to be a part of that solution for them."

We asked Marty what he would say to kids his age, or even younger, who are also on a similar journey as him, and he said, "I would have to tell them not to let it stop them. The choices are to either wallow in denial or look at what it has given you. My journey has made me humble and compassionate to other people. I've learned to have empathy for people that I meet because I don't know what they could be going through."

Marty and his family are continuing to stay positive as they weigh their options for a clinical trial. They are proof that the work we are doing at the Foundation is working, and one day we will have cures for blinding retinal diseases like XLRP. When that day comes, Marty can proudly say he was a part of making it happen.

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Leave a Lasting Impression

Many people who don't have the resources to make a significant gift during their lifetime choose to leave a meaningful gift in their will. By leaving a gift to the Foundation, you will provide vital support for the research that will soon find an end to blinding retinal diseases. For more information on how you can leave a lasting legacy, visit: **FightingBlindness.org/Legacy-Giving**.

IN FOCUS

This and previous issues of **In Focus** are available online, where you can get the latest retinal-research information, as well as updates on the Foundation's activities, on your PC and mobile devices.

For an online and accessible version of **In Focus**, visit **FightingBlindness.org/In-Focus-Newsletter**.

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