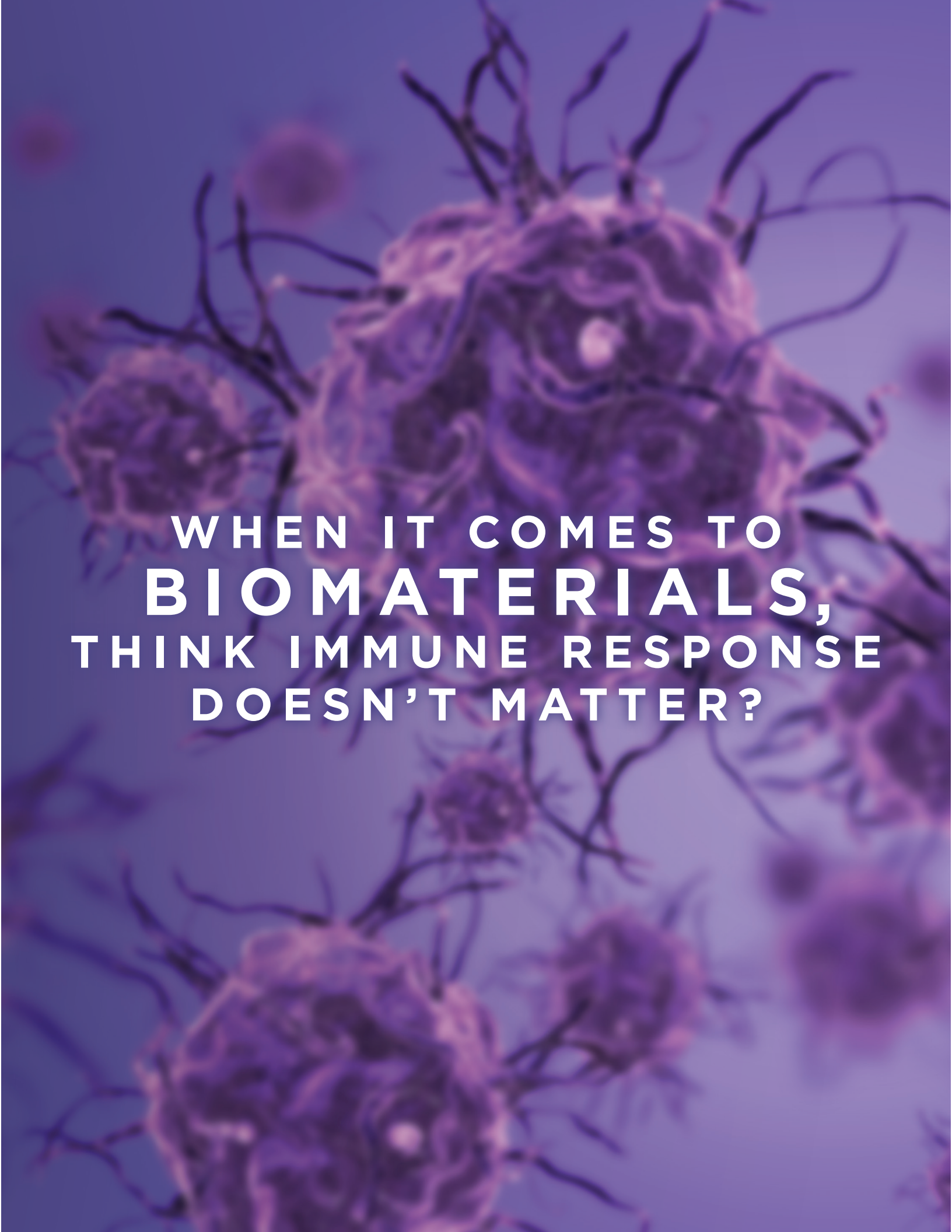
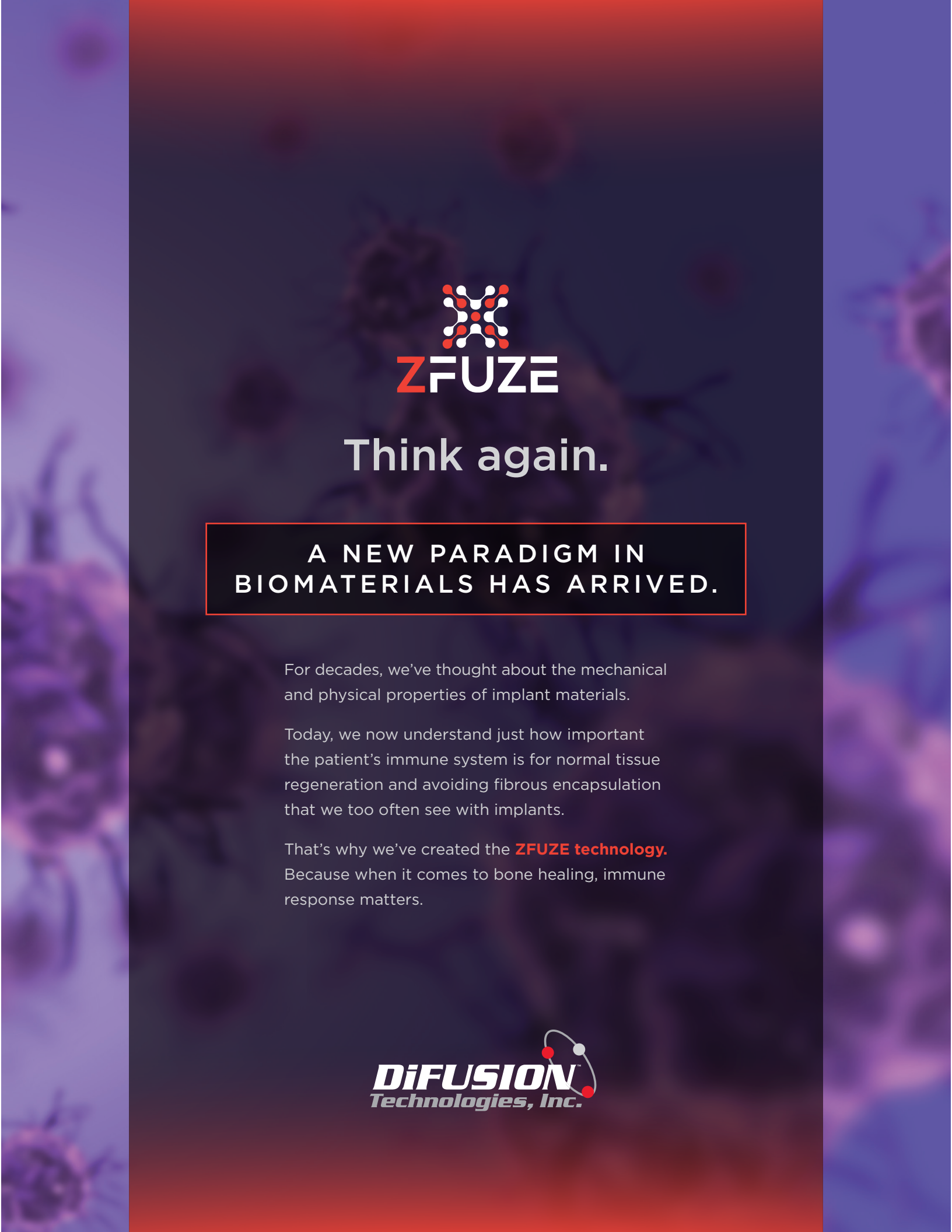

WHEN IT COMES TO
BIOMATERIALS,
THINK IMMUNE RESPONSE
DOESN'T MATTER?


ZFUZE
Think again.
A NEW PARADIGM IN BIOMATERIALS HAS ARRIVED.
For decades, we've thought about the mechanical and physical properties of implant materials.
Today, we now understand just how important the patient's immune system is for normal tissue regeneration and avoiding fibrous encapsulation that we too often see with implants.
That's why we've created the ZFUZE technology. Because when it comes to bone healing, immune response matters.
DiFUSION Technologies, Inc.

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The End of an Era? – New ZFUZE Biomaterial Bridges the Gap Between PEEK and Titanium

Throughout a spine surgeon's career, he or she will encounter a myriad of implants each derived from different materials. Because implants can be manufactured in countless ways – ranging from 3D printing to injection molding – there's no shortage of options in the spinal surgery industry.

While various implant materials have come and gone, PEEK and titanium remain the most common. When Paul Kraemer MD, of the Indiana Spine Group in Carmel, launched his practice, PEEK was establishing itself as the go-to substance for implants. Dr. Kraemer understood PEEK's appeal but also saw challenges related to its use, particularly its inability to fully osseointegrate due to its bioinert hydrophobic properties. In recent years the industry shifted back to titanium, and while Dr. Kraemer noticed improvements to osseointegration with 3D titanium, he still saw complications. Specifically, problems with revision surgery, modulus and visualization.

"The next generation of implants is not going to be plain PEEK," Dr. Kraemer said. "Instead, it's going to be a PEEK 2.0. Whether that's titanium coated or surface coated or altered PEEK, it's the same pendulum that goes back and forth. It gets better every time, and each time a little more refined."

Despite the quality of implants continuing to improve, the spinal interbody market has never had a load-bearing biomaterial specifically engineered for bone growth and the immune response. To fill this need, DiFusion has developed ZFUZE, the first load-bearing biomaterial specifically engineered for spinal fusion. ZFUZE is a combination of PEEK with additive compounding of a negatively-charged-super-hydrophilic ZEOLITE. The negatively charged zeolite changes the surface chemistry from inert-plain-hydrophobic PEEK to a super hydrophilic and negatively charged ZFUZE surface, resulting in more bone and less inflammation.

By changing the surface chemistry of PEEK, from an inert, hydrophobic surface to a negatively-charged super hydrophilic surface for ZFUZE, the immune system does not illicit a foreign body response. This lack of long term inflammation contributes to higher bone mineralization density and osseointegration.

Not only does the ZFUZE negative, super-hydrophilic charge allow for early cellular adhesion and proliferation, it promotes an early switch from proinflammatory M1 Macrophages to the M2 Macrophage which is a key marker for the start of the pro-healing phase of the immune response. A prolonged M1 response leads to the formation of granularized tissue and fibrous encapsulation currently associated with plain PEEK implants.

In 2013, PEEK commanded 73% of the $1.4 billion spinal interbody submarket. Surgeons and OEM's began to realize that they were seeing implants with fibrous encapsulation in PEEK revision surgeries. This has pushed the pendulum back to titanium as surgeons have foregone the visualization and modulus benefits of PEEK for the better osseointegration properties of 3D printed titanium. OEM's have rushed to commoditize the 3D titanium market as almost every company now has a 3D printed titanium implant with little to no differentiation.

The swinging pendulum of titanium and PEEK

When surgeons began using implants, titanium quickly emerged as the preferred material because of its sturdy consistency and the ability to customize it. Nevertheless, titanium is still not the perfect implant material. The body will sometimes reject titanium due to its rigidity. "The biomechanics of the titanium [implants] were such that they could sometimes impair normal healing by being too rigid and too stiff," said spine surgeon Nitin Bhatia, MD, of UC Irvine.

The inelasticity in titanium implants spurred researchers and spine surgeons to explore alternate material options. Around 15 years ago, PEEK was introduced to the spine implant industry. PEEK has an advantage over titanium because its biomechanics are more consistent with bone.

"The theory was that if the biomechanics were more consistent with bone there wouldn't be as many issues of subsidence, which is when the [implant] breaks into the bone being fused together," Dr. Bhatia said.

Surgeons also gravitated toward PEEK's radiolucent characteristics. On an X-ray, the PEEK implants are hidden to the eye. This removes chunks of metal that often cloud X-rays when patients receive titanium implants. The radiolucent implants also allow surgeons to better evaluate whether the bone is healthy around the implant and if fusion was achieved.

However, PEEK makes for an imperfect implant too. The predominant issue surgeons encounter with PEEK is bioinertness. The implants did not always heal to the bone, making it just a piece of plastic in the body, according to Dr. Bhatia. "PEEK is very bioinert, meaning nothing happens to it," he said. "In fact, if anything, the body creates a layer between the cage and the bone that the bone won't heal to."

As a result, titanium implants reemerged. But researchers discovered a new issue with the substance. Multiple studies found titanium implants may release metal ions upon impaction that have adverse effects on bone cells, which could lead to implant failure and infection. One 2013 study published in the *Clinical Cases in Mineral and Bone Metabolism* provided an overview of the adverse effects of metal particles on bone cells and peri-implant bone

Importance of the immune response

It's long been known that the immune system plays a vital role in tissue healing. But only recently have experts come to understand the importance of the immune system in tissue remodeling and regeneration. In fact, researchers are now starting to better understand the different types of inflammatory responses that occur and the adaptability of immune cells.

Stephen Badylak, DVM, MD, PhD, is Deputy Director of the McGowan Institute for Regenerative Medicine and is among the foremost experts in immune response and biomaterials. "What's become incontrovertible now is that the immune system plays an absolutely critical part in any biomaterial that's put in the body with respect to transplant outcome," Dr. Badylak said.

Macrophages are our primary host defense, and their activation and response are based on the environment they are exposed to. In the initial stages of the immune response, macrophages will express an M1-like phenotype. The major function of M1 macrophages is to kill microbes through phagocytosis. The M1 cells produce proinflammatory cytokines and present antigens to T-cells in order to protect against foreign bodies, bacteria and viruses.

"If one suffers a knife wound we would see a M1 pro-inflammatory phenotype in the surrounding tissue almost immediately. At day 4 or 5 we then see the expression of M2 pro-healing phenotypes. If a piece of the knife blade were to break off in the wound, we would see an extended M1 response which ultimately signals the body to wall-off the foreign body with fibrous granularized tissue".

What researchers are now better understanding is that for healing to occur, "whether the affliction is a knife blade, a spinal implant or a cardiac stent, the proinflammatory M1 macrophage needs to convert or transition into the opposite M2 phenotype. The M2 macrophage cells are anti-inflammatory and promote healing" said Dr. Badylak.

"Imagine having two materials and being able to make identical devices in terms of the mechanical properties, such as pore size, but one material promotes an inflammatory response (PEEK) and the other material (ZFUZE) promotes a remodeling response," Dr. Badylak explains. "With the inflammatory response, surgeons are going to get encapsulation or chronic inflammation around the implant whereas the remodeling response provides for the development of bone and that material incorporates the device into the bone that is being remodeled.

These new biomaterials are not rapidly available in the market. "I think the only reason that you don't see these biomaterials is because it's such new information. We have tested over 300 different biomaterials with the M1/M2 Assay and have never seen immunomodulation like we have for ZFUZE in anything other than a natural molecule." ■

ZFUZE STUDIES

- In Vitro Osteoblast Proliferation Assays – 700% increase
- Rabbit Critical Defect Model – Increased Bone Mineralization Index
- Ovine Cervical Fusion Model – Statistically Significant Reduction in Interleukin 1-beta
- In Vitro Immunomodulation Studies – Positive M2 Immunomodulation

DiFUSION Technologies, Inc.

DiFusion, Inc. is an advanced biomaterials manufacturer located in Austin Texas and has engineered multiple patented SMART Surgical Polymers. DiFusion was founded by Matthew Geck, MD of Austin Texas and Gary Ghiselli, MD of Denver Colorado. ZFUZE is currently pending FDA 510(k) clearance.