These are the 15 companies that emerged from the best of the best, and we're proud to call them the industry's fiercest biotechs for 2023. (Fierce Biotech)
It's been a tough year for biotech, so how about a little good news? In between all the layoffs, restructurings and last-ditch strategic option hunting, we wanted to take a moment to shine a spotlight on 15 innovative and truly fierce biotechs.

Everyone we talk to in the Fierce Biotech universe tells us that science doesn't stop for the markets. Financing might be a little tough right now, but innovation, breakthroughs and discoveries are all still being made.

The latest crop of Fierce 15 honorees consists of companies pushing the envelope not only in the lab, in the clinic or on the conference circuit—they are also defining what it means to be a modern biotech company, with modalities ranging from radiopharmaceuticals to cell therapy. Indications as diverse as oncology, neurodegenerative disorders, Pompe disease and even pregnancy complications made the list this year.

We have also turned a greater focus toward celebrating diverse teams. We asked for you to nominate companies pushing boundaries not only in the clinic but in the C-suite and beyond. We wanted to see the best of the best, the biotechs fiercely redefining expectations culturally, ethically and in their pipelines.

And here they are. We examined hundreds of nominations for the Fierce 15 this year. When we say we look at them all, we really truly do. These are the 15 companies that really stood out for us this year and we're proud to call them the industry's fiercest biotechs for 2023.

— *Senior Editor Annalee Armstrong*

Palleon Pharmaceuticals, born out of the research by Nobel laureate Carolyn Bertozzi, Ph.D., is pioneering glyco-immunology drug development. (Palleon)

Palleon Pharmaceuticals

By Angus Liu

Targeting sugar molecules on cell surfaces to treat cancer and inflammatory disease

CEO: Jim Broderick, M.D.
Founded: 2015
Based: Waltham, Massachusetts
Clinical focus: Palleon Pharmaceuticals is leveraging the role that cell-surface glycans play in regulating the immune response to treat diseases.

Jim Broderick, M.D. (Palleon)

What makes Palleon Fierce: The 2022 Nobel Prize in Chemistry awarded to Carolyn Bertozzi, Ph.D., brought a couple biotech companies that she co-founded to the spotlight. One of them is Palleon, which plays at the intersection of glycans and immunology.

Bertozzi earned the Nobel for her work in bioorthogonal chemistry, which allows chemical reactions to proceed in living cells without interfering with existing biochemical processes. This technique enabled scientists to study glycans in live biological systems. These sugar molecules coat all cell surfaces and are involved in key aspects of cell biology, but they are not detected by genomic tools, Palleon's CEO and co-founder Jim Broderick, M.D., explained.

Bertozzi established the causal relationship between an abnormal glycan pattern on tumor cells marked by the upregulation of sialoglycans—sialic acid-carrying glycans—and immune evasion in cancer, Palleon's chief scientific officer, Li Peng, Ph.D., said.

But sialoglycans can't be targeted by conventional small-molecule or antibody drugs. The sialoglycans on tumor cells can be recognized by a family of receptors called Siglecs expressed by immune cells. This interaction typically suppresses the immune response in a way similar to that between PD-1 and PD-L1. But unlike the one-to-one binding relationship between PD-1 and PD-L1, 14 functional Siglecs are known to

exist in humans, including nine that appear to play an inhibitory role. And there's an abundance of different sialoglycans.

Bertozzi's third contribution to Palleon's work, Peng said, is the brilliant idea of using a "nature's solution," an enzyme called sialidase, to basically cut off sialic acid in a targeted degradation manner to remove sialoglycans and hence the immune suppression.

"There are thousands of sialoglycans, but it doesn't matter what their structures are; if you remove the sialic acid, the binding doesn't happen anymore," Broderick said.

In fact, Broderick gathered the first funding for Palleon to work on Siglecs blockade. But that idea simply didn't work, so the company pivoted to the enzyme approach about a year and half into its existence.

Having recognized the Siglecs redundancy problem, Peng designed Palleon's lead candidate, E-602, an engineered human enzyme that degrades sialoglycans on tumors and immune cells.

In a phase 1 trial coded GLIMMER-01 conducted in patients with various tumor types, investigators found that E-602 can be dosed up to 30 mg/kg with no dose-limiting toxicities. CD8+ T cells in peripheral blood showed sustained desialylation, corresponding to various signs of increase in immune activation in circulation.

The trial didn't measure tumor response rate like many phase 1 cancer trials would do. To enroll faster, Palleon picked patients that were unlikely to response because of their disease and immune status, including individuals with immune cold tumors, Peng said. The goal of the study was to establish safety and the drug's ability to remove sialic acid and trigger immune response, she said.

Broderick is confident that the immune biomarker in the peripheral blood could translate into anti-tumor activity in the right patient population based on preclinical findings.

"We're creating a whole new field of immune modulation … It required new tools to measure it and required new therapeutic modalities and

new clinical strategies," Broderick said. "We had to have the innovation every step of the way."

Palleon has recently launched a second part of GLIMMER-01 to combine E-602 with Regeneron's PD-1 inhibitor Libtayo. The company is now prioritizing the combo study over monotherapy.

Broderick argued that combination is the way to go because if E-602 can activate the immune system, PD-1 is going to be upregulated. If the combo shows it can benefit patients who no longer respond to PD-1 inhibition, then E-602's contribution can be established, he said.

Moving forward, Peng is working on second-generation molecules that will, like the trending antibody-drug conjugates, have a target arm to help the enzyme—the payload—better localize to cancer cells, which may have relatively low sialoglycans. This multiarm strategy has attracted a lot of business development discussions with other companies "because they have good targets, and they want to overlay this new dimension of glyco-immunology modulation to their targets," Peng said. Since its founding in 2015, Palleon has raised $147 million.

"There are some Big Pharmas that have recognized the importance of this [immune mechanism], and they are interested in partnering potentially quite broadly," Broderick said.

Because of glycosylation's role in immune dysfunction, Palleon is also developing glycan-editing and Siglec-targeting programs for inflammatory diseases.

Investors: Matrix Capital Management, SR One, Pfizer Venture Investments, Vertex Ventures, Takeda Ventures, AbbVie Ventures, Surveyor