Anchor Therapeutics, a Tufts Medical Center spin-off that opened its laboratory doors in 2008, has its sights set on a different, yet tempting, family of undruggables—G-protein coupled receptors (GPCRs). Despite the facts that these membrane receptors are involved in almost all signaling pathways in the human body and that nearly one-third of commercialized drugs target GPCRs, only about 10 percent have been drugged.[3]

Anchor's approach to GPCRs is literally inside out: They have demonstrated an ability to activate or inhibit GPCRs from inside cells by using pepducins, peptides with short lipid tails that anchor in a cell membrane. Once the pepducin is latched on to the membrane, it flips into the intracellular space to hit the interior portion of a GPCR, altering the receptor's shape to increase or inhibit activity. "We can go after any kind of GPCR," says Jones, CEO of the company, including orphan GPCRs with no known natural ligand. "Other people, in the absence of a natural ligand, can't even begin to work with those receptors."

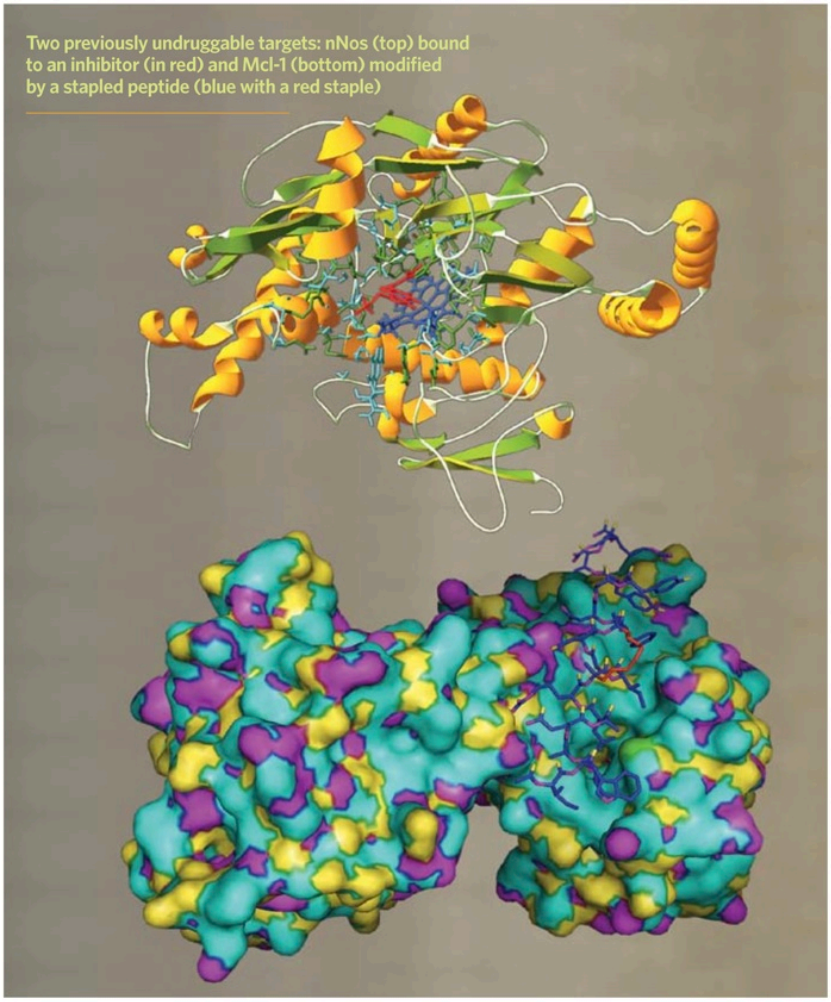
Anchor's drug candidates include an agonist pepducin for CXCR4, a GPCR found on progenitor cells of the immune system that directs them to areas of injury. Many companies have designed antagonists of CXCR4, including Genzyme's Mozobil, which prevents blood stem cells from localizing in the bone marrow so that they are released into the circulation instead, where they can be harvested for stem cell transplants. But an agonist for CXCR4 has proven more difficult to manufacture. Anchor's candidate would be the first to market.

In contrast to CXCR4 antagonists, the new drug increases the cells' ability to hone in on areas of injury, such as a bone fracture or heart tissue damaged by a heart attack. The company is also pursuing GPR39, an orphan receptor for the treatment of Type 2 diabetes, and C5A, a protein fragment that binds a GPCR implicated in inflammatory conditions. "We've chosen to concentrate on targets that we believe have been difficult for other people to hit," says Jones, "so it will likely result in a first-in-class molecule."

One of the most talked-about biotechs going after undruggables is Aileron Therapeutics of Cambridge, Massachusetts. Last year, the company secured $40 million from a quartet of big pharma companies—Novartis, Roche, Eli Lilly, and GlaxoSmithKline—to develop their stapled peptide platform, a technology that stabilizes synthetic peptides with a chemical "staple" so they don't lose their shape, like a slinky held together with a twist-tie. While most peptides are digested by enzymes in the bloodstream within minutes of injection, stapled peptides, which can target protein–protein interactions, hold their shape for up to several days.

"When you get four pharmas into the same deal, and there aren't guaranteed targets, that's telling you that they're not looking at this for a blockbuster compound, but as a new industry," says investor Enriquez, who co-led the $40 million round of financing for the company. And with the additional billion-dollar commitment from Roche last August, Aileron plans to start clinical trials next year.

Someday soon, "undruggables" could be nothing but a misnomer if these biotechs fulfill their lofty goals. But above all, the pharmaceutical industry should not give up on difficult drug targets, says Andrews. "Our job is not to produce the same old stuff," he says. "Our job is to make things [that] improve people's lives...and these high-hanging fruit are some of the best ways to do that." ■



Two previously undruggable targets: nNos (top) bound to an inhibitor (in red) and Mcl-1 (bottom) modified by a stapled peptide (blue with a red staple)

TOP: COURTESY OF NEURAXON BOTTOM: COURTESY OF AILERON

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