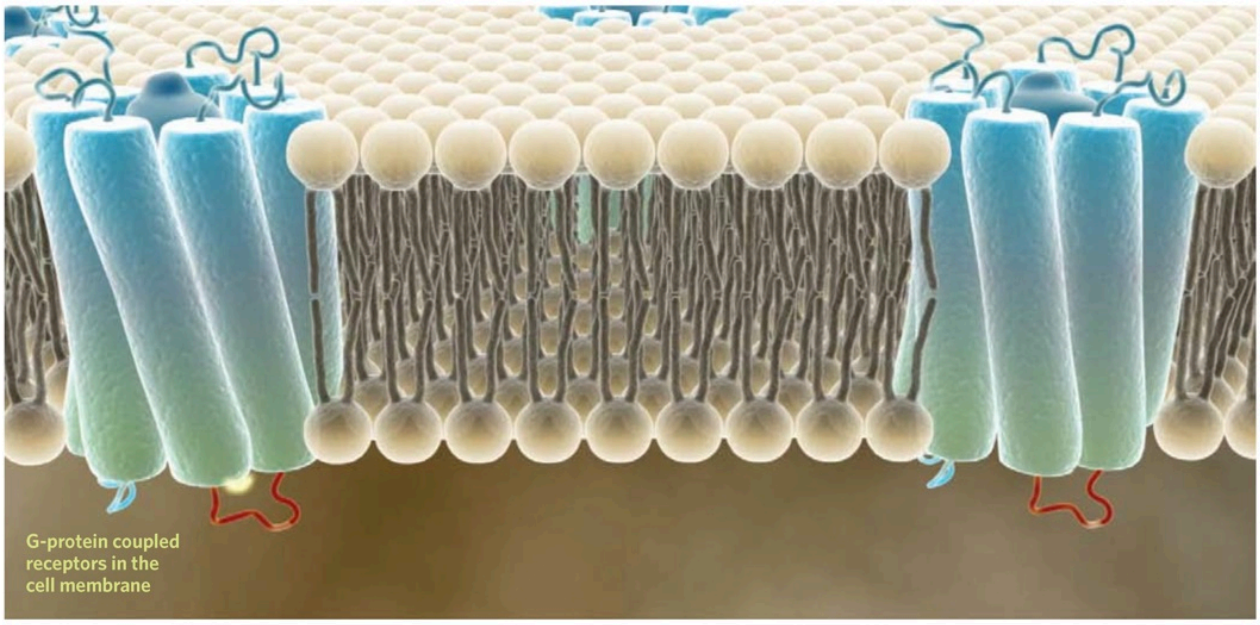
By Megan Scudellari

BIOBUSINESS

The Undruggables

Can young biotechs chasing elusive drug targets succeed where so many have failed? They think so.



G-protein coupled receptors in the cell membrane

COURTESY OF ANCHOR THERAPEUTICS AND ARKITEK STUDIOS

John Andrews finished his presentation and turned to the roomful of pharmaceutical employees. Chief scientific officer for NeurAxon, a small Canadian biotech developing pain therapeutics, Andrews braced himself for the onslaught. The comments came rapid-fire: *Can it be produced efficiently?* Yes, in just a few steps. *It is really soluble?* It has been from day one. *Is it truly selective?* Yes.

In the back of the room, a senior chemist stood up. He, like many of the scientists present, had been working unsuccessfully for years to develop a similar drug. "Well," he said, "You're either geniuses, extremely lucky, or frauds." Andrews smiled.

NeurAxon, founded in 2004, had done what numerous pharmaceutical giants have tried and failed to do for more than 20 years—develop a drug that targets neuronal nitric oxide synthase (nNOS), an enzyme implicated in nerve injury, neuropathic pain, and migraines. In the past, scientists have been unable to selectively inhibit nNOS without also shutting down endothelial NOS (eNOS), causing a rise in blood pressure. After years of unsuccessful attempts, nNOS became known as one of the "undruggables"—molecular targets, typically proteins, which scientists have tried but failed to "drug."

In a 1997 review in *Clinical Cancer Research*, two Harvard biochemists revealed a disheartening fact: 70 to 80 percent of all human proteins are beyond the reach of the two established classes of drugs. Biologics—a range of drug products including therapeutic proteins, vaccines, and blood components—are restricted to extracellular targets, which make up less than 10 percent of human proteins, because of their size. Small-molecule drugs, on the other hand, can cross cell membranes to target proteins inside cells, but only about 12 percent of those proteins have hydrophobic pockets suitable for tight binding of this class of drugs. That leaves around three-fourths of potential protein targets unapproachable by current drugging methods, the authors concluded.[1]

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There are many undruggable targets with enormous therapeutic and economic potential that have rankled even the best-funded laboratories over the years. Their names—Bcl-2, Ras, beta-catenin, p53, Mcl-1—are enough to induce a glassy-eyed look from scientists and a skeptical grunt from pharma executives and investors.

"The word 'undruggable' is a profoundly important one because it has a powerful psychological effect," said Stuart Schreiber, director of the Chemical Biology Program at the Broad Institute in Cambridge, Massachusetts, in a 2009 news article on the Institute's Web site.[2] "It limits what people think can be done," added Schreiber, a member of *The Scientist*'s editorial advisory board.

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