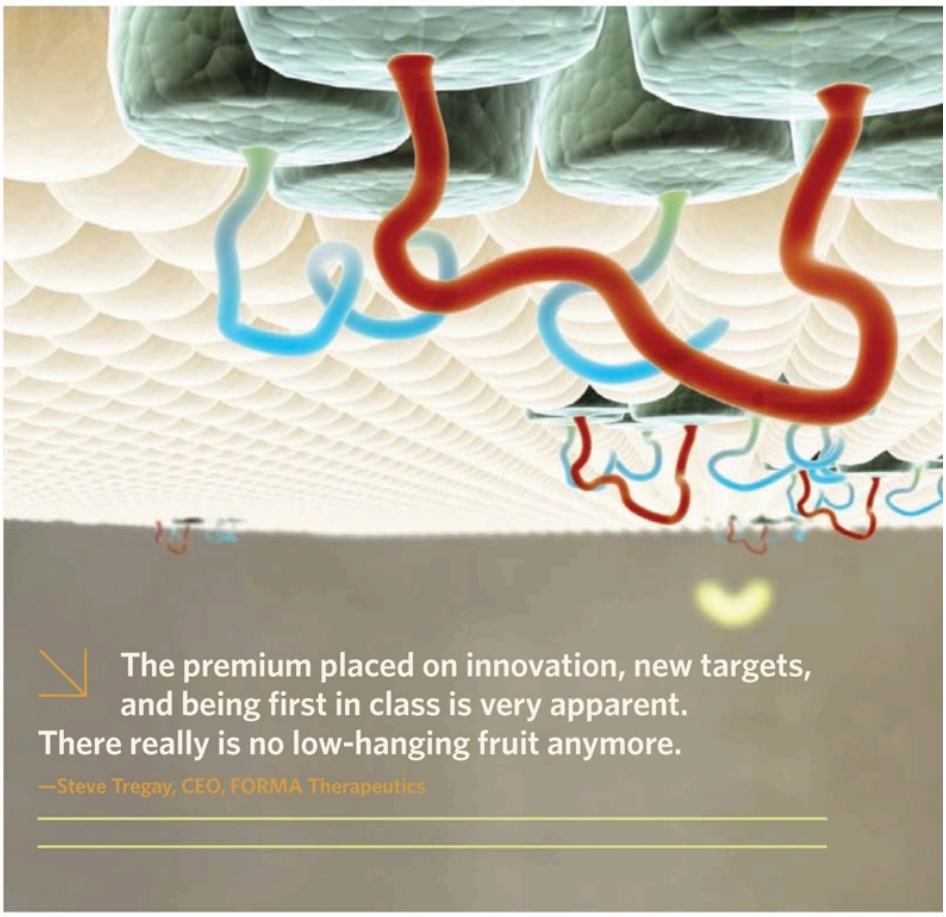
At least, it used to. Today, companies like NeurAxon are capitalizing on the decades of research on these slippery targets and demonstrating some the first successes in reaching them. NeurAxon already has two nNOS inhibitors in clinical trials, one for neuropathic pain in Phase I and a second for acute migraines already in Phase II. But even with strong data, such previously undruggable targets are never an easy sell, say biotech executives. Even if the new approach targets a well-known molecule and could be worth billions if it works, investors still worry: When pharmaceutical companies have given up on it, maybe it's not possible.

"[Going after undruggable targets] is a risk we take," says Rick Jones, CEO of Anchor Therapeutics, a biotech in Cambridge, Massachusetts. "People have been banging on it for so long that they have gotten tired of it or just assume it can't be done."

But the risks have their rewards. More and more, large pharmaceutical companies are putting their money into innovative, even seemingly crazy, efforts to hit elusive targets. Anchor, for example, is working on drugging a class of supposedly undruggable membrane receptors for Novartis and Ortho-McNeil-Janssen Pharmaceuticals who have paid fees and milestone payments in excess of $200 million and $400 million, respectively. And this past August, Roche committed $25 million up front and another $1.1 billion in milestone payments to Aileron Therapeutics to go after protein–protein interactions, some of the most intractable drug targets in the business. "It's one of the largest preclinical deals ever done," says Juan Enriquez, managing director of Excel Venture Management, an investor in Aileron. "You don't make bets on this scale unless you think there's something absolutely fundamental and transformative here."

The days of Lipitor—the fifth drug of its type to the market—are over, says Steve Tregay, CEO of FORMA Therapeutics in Cambridge, Massachusetts. Incremental advances against previously drugged targets are simply no longer going to be rewarded in the marketplace. "The premium placed on innovation, new targets, and being first in class is very apparent," says Tregay. "There really is no low-hanging fruit anymore."



The premium placed on innovation, new targets, and being first in class is very apparent. There really is no low-hanging fruit anymore.

—Steve Tregay, CEO, FORMA Therapeutics

COURTESY OF ANCHOR THERAPEUTICS AND ARKITEK STUDIOS

Turning pharma heads

At potential investor meetings, Tregay often witnesses what he calls "sit-up-in-their-seats" moments. He points to a list of high-value targets in oncology, FORMA's specialty. Perusing the list, investors and pharmaceutical executives lean back in their chairs, remarking on how great it would be to drug any one of those. "Then I say, 'Let me tell you about where we are on all of them,'" chuckles Tregay. "It really captures their attention."

Founded only 2 years ago, the 85-person company already has a partnership with the Leukemia & Lymphoma Society to develop compounds targeting Bcl-6, a transcription repressor that downregulates genes in non-Hodgkin's lymphoma. Bcl-6 is a member of one of the largest class of undruggable targets—those that exert a function through protein–protein interactions. The proteins c-Myc and K-Ras, for example, are each activated in nearly half of all human cancers, but neither has been successfully targeted with an approved therapy because they function through associations with other proteins, which to date have proven too chemically complicated to affect.

But FORMA relishes the challenge. To go after Bcl-6, among other targets, the company employs a unique assay to screen full-length proteins within living cells, then uses computational mapping tools to visualize protein interactions and probe them for novel druggable hotspots.

To reduce the risk of going after a single high-value target, FORMA tackles many at the same time. "We'll run close to 15 different highly validated 'holy grail' oncology targets this year alone," says Tregay. "Yes, these are incredibly hard targets, and, no, we won't succeed against all of them. But that's why we've built an infrastructure to dwarf a traditional biotech's productivity."

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