Looking beyond IGF-1R, some companies also see therapeutic potential in administering forms of the IGF-1 growth hormone itself (Box 1). And although Tepezza may be the only drug on the market deliberately designed to block IGF-1R, it is not the only approved agent that binds the receptor: Novartis's Zykadia (ceritinib) also inhibits IGF-1R, albeit with much lower potency than it has against its primary target, anaplastic lymphoma kinase (ALK).

A [case report](#) published last year suggests that Zykadia may be helpful against IGF-driven brain tumors. But when it comes to Zykadia's approved indication of treating lung tumors with ALK fusions, the drug's activity against IGF-1R is generally seen as off-target, not part of any therapeutic effect. As Tony Mok, an oncologist at the Chinese University of Hong Kong who specializes in targeted therapies for lung cancer, points out: "It is hard to imagine a weak IGF-1R inhibition would induce dramatic tumor

responses, which is what we usually observe clinically with ceritinib."

Meanwhile, several firms are taking advantage of elevated IGF-1 signaling in cancers to deliver therapeutic payloads directly to tumor tissue. For example, IGF Oncology's covalent conjugate drug involves a standard chemotherapeutic, methotrexate, tethered to an engineered form of IGF-1. Pierre Fabre has an antibody–drug conjugate called W0101 that combines a cytotoxic auristatin derivative with IGF-1R targeting. And Fusion Pharmaceuticals has taken an IGF-1R-binding antibody that previously entered clinical testing — ImmunoGen's humanized IgG1 mAb AVE1642 — and attached a potent alpha-particle-emitting medical isotope to create a [radiotherapeutic that localizes to tumors](#).

All three drug programs exploit the fact that IGF-1R, upon binding to its ligand or an antibody, undergoes receptor-mediated endocytosis, resulting in internalization of any bound molecules. Off-target toxicity

is minimized because IGF-1R activity is mostly limited to internal compartments of the cell in vital organs such as the heart, and only a few tissues in the bladder, prostate and endometrium show low to moderate surface expression of IGF-1R, according to a preclinical [study](#) of W0101 from biochemist Jean-François Haeuw and his colleagues at Pierre Fabre's Center of Immunology in Saint-Julien-en-Genevois, France.

Notably, the overarching goal of this new crop of IGF-1R-directed therapies is different than what was tried before with Tepezza and its ilk. "We are not trying to block the target," says Valliant, the Fusion CEO. "We're simply using it as a shuttle to bring [the therapeutic cargo] into the cell." □

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Around the world in a month

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