Table 1 Companies still standing in IGR-1 targeting

Company, drug	Mechanism	Trial indication and regimen	Status
Bristol-Myers Squibb, BMS-754807	Growth factor 1 receptor/insulin receptor family–targeted small molecule kinase inhibitor	Breast cancer in combination with Femara (letrozole)	Phase 2
		Colorectal cancer	Phase 1
		Head and neck cancer in combination with Erbitux	Phase 2
Boehringer Ingelheim Pharmaceuticals, BI 836845	A fully humanized mAb neutralizing IGF-1 and IGF-2	Neoplasms	Phase 1
MedImmune, MEDI-573	A humanized mAb to IGF-1 and IGF-2	HER-2 negative breast cancer in combination with an aromatase inhibitor	Phase 1
		Unresectable or metastatic hepatocellular carcinoma in combination with Nexavar (sorafenib)	Phase 1

Source: ThomsonPharma Partnering. http://www.ncbi.nlm.nih.gov/pubmed/19023648.

been carried out," writes Renato Baserga, from the department of Cancer Biology, Thomas Jefferson University in Philadelphia. (*J. Cell. Physiol.*, doi:10.1002/jcp.24217). A pioneer in IGF-1 research, Baserga goes on to list some avenues that may still be promising, such as targeting the receptor to prevent metastases in colorectal cancer patients. But in the end, he surmises: "These excuses are poor excuses, [they are] an attempt to reinvigorate a procedure that has failed." Saltz agrees. "This may be the end of the story," he says. "At one point, there were more than ten companies developing these drugs; now this may be the last one that gets put on the shelf."

Scientists uniformly explain IGF-1's problems as being related to biological complexity. "We draw these preclinical rationales out in two dimensions on a piece of paper," says Saltz. "But when you look at the feedback from disrupting those signaling pathways, it's much more complicated." Nadia Rosenthal, acting head and senior scientist at the European Molecular Biology Laboratory in Rome, says that based on recent data, "targeting the receptor may be necessary but not sufficient."

Although receptor-targeting mAbs are probably dead to pharma, there is still potential for two other approaches: inhibiting receptor kinases or mopping up the IGF-1 and IGF-2 ligands (**Fig. 1**). Paul Haluska of the Rochester, Minnesota–based Mayo Clinic says that when the receptor itself is targeted, "there are a lot of adaptive responses, such as upregulation of the insulin receptor and others." Alternate approaches, such as targeting tyrosine kinases or the receptor's ligands directly, may avoid the adaptive responses that arise when the receptor is targeted directly.

Haluska is watching compounds, such as Gaithersburg, Maryland–based MedImmune's MEDI-573, a dual-targeting fully human mAb that neutralizes IGF-1 and IGF-2 ligands. Other companies, he says, may be developing similar compounds. New York–based Bristol-Myers Squibb, meanwhile, has an IGF-1R/insulin receptor kinase small molecule inhibitor, BMS-754807 under investigation in several cancers (**Table 1**).

Pollak agrees that it may be time to better explore these alternate mechanisms. But he also emphasizes the need for biomarker data. "We have to find the subsets where these drugs work best," he says. Biomarkers were, however, incorporated into most of the high-profile IGF-1R trial failures.

Researchers are also still wondering about a single Ewing's sarcoma patient in an early AMG-479 trial, who showed a dramatic response to the drug. Ewing's sarcoma is an extremely rare disease, affecting only several hundred people in America alone each year. A trial of another fully human anti–IGF-1R mAb (Roche and Genmab's R1507) was promising in Ewing's sarcoma patients but was halted by the company when it became clear that the drug lacked efficacy in more common cancers. The sarcoma community is left wondering what would have happened if the study had been taken to completion. Only six such patients have been accrued by the time development of R1507 was discontinued.

AMG-479's failure will likely be a death knell for the field of IGF-1 targeting. But Baserga counters that IGF-1R inhibition has a place in combinations; it's time to accept that the future for targeted cancer drugs will involve administering multiple drugs from the start, he says. IGF-1R inhibitors might then end up in that mix. "The possibility that tumors consist usually of subpopulations of cells with different sensitivities to different agents has to be considered," he writes in his August *Journal of Cellular Physiology* review. For the meantime, though, it looks like industry will be looking at mechanisms other than IGF-1R inhibition in cancer drug development.

Malorye Allison

IN brief

Merck Serono spinouts

After the shutdown of its Geneva headquarters (*Nat. Biotechnol.* **30**, 569, 2012), Merck Serono has found homes for some of its programs in the form of spinouts. Merck Serono, a division of Merck KGaA of Darmstadt, Germany, recently announced two new Geneva-based startups. Both will tap into a €30 million ($37.5 million) seed fund, the Entrepreneur Partnership Program, created by the German pharma in April 2012 to support spinoff and startup companies that continue R&D activities originally started at Merck Serono. One is Prextron Therapeutics, set up to continue work on two metabotropic glutamate receptor programs for Parkinson's disease. The other is Quartz Bio, a services organization that offers biomarker data management and exploratory biomarker analysis. "It's good corporate citizenship for them to do something for their employees and for the region," said Chandra Leo, a partner at HBM Partners of Zurich. As part of the spinoff process, employee teams propose a business plan to develop the assets. When seed money runs out, spinouts will acquire funding through the usual venture capital channels, potentially including Merck Serono Ventures. François Conquet, founder and CEO of Prexton, said his new company "is working to form a new syndicate of [venture capitalists] for the next funding round." Starting with a developed asset and an experienced team should increase the startups' likelihood of success. "By and large, pharma spinoffs tend to be more successful," Leo said, pointing at Roche spinoff Actelion, of Allschwil, Switzerland, as a prime example.

Brian Orelli

IN their words

"We are living in an awkward interval where our ability to capture the information often exceeds our ability to know what to do with it." Francis Collins, speaking of the quandary physicians find themselves in with the availability of complete genome sequences. (*The New York Times*, 25 August 2012)

"America is like a vacuum cleaner, absorbing innovations, part of which were made by our compatriots who emigrated to the US." Andrei Fursenko, a scientific adviser to Vladimir Putin. *(Bloomberg Businessweek,* 23 August 2012*)*

"I would hate to see NIH take money away from basic research because NIH is not good at applied and translational research. That is the role of industry or industry academic partnerships." Douglas Williams, Biogen Idec. (*BioCentury*, 3 September 2012)