Companies hope for rare win with cancer stem cell therapies

The pharmaceutical start-up Verastem garnered attention among drug industry pundits when it raised $55 million this year in its initial public offering—a surprisingly high outlay for a one-year-old company with only a preclinical pipeline. The robust valuation demonstrates an enthusiasm for the Cambridge, Massachusetts–based company's approach to tackling tumors by going after cancer stem cells (CSCs), the rare, hardy population of cells that are thought to reseed cancers after chemotherapy and drive metastasis.

"Unless we knock out the cells with stem cell–like characteristics, we likely can't cure the patient," says Daniel Hayes, clinical director of the breast oncology program at the University of Michigan Comprehensive Cancer Center (UMCCC) in Ann Arbor.

Several up-and-coming drugmakers are now exploring ways of curtailing CSCs, either through direct inhibition or by forcing the cells to differentiate into run-of-the-mill bulk tumor cells that are susceptible to standard treatments. Verastem, for example, has used a proprietary screening technique developed by company cofounder Robert Weinberg to build up a robust pipeline of experimental agents that selectively inhibit CSCs. "I'm enthusiastic that, for the first time in my career, my research has the prospect of direct therapeutic utility," says Weinberg, who helped launch the Cambridge, Massachusetts–based Whitehead Institute for Biomedical Research in 1982.

Meanwhile, ImmunoCellular Therapeutics, a Los Angeles–based clinical-stage company founded in 2004, has developed a therapeutic dendritic cell–based vaccine called ICT-107 that is designed to specifically target the antigens highly expressed on brain tumor CSCs. The therapy is currently being tested in up to 200 people at 23 sites across the US following a phase 1 trial that demonstrated safety and promising early signs of efficacy in a trial of 16 people with newly diagnosed glioblastoma. Looking ahead, the company also hopes to begin phase 1 trials for another vaccine, ICT-140, which targets the antigens on ovarian bulk and cancer stem cells, before the end of the year.

Signaling change

Also founded in 2004, California-based OncoMed Pharmaceuticals is developing antibodies that target a signaling molecule particularly active in cancer stem cells. Three years ago, company scientists first showed that blocking a protein called delta-like ligand 4 (DLL4), which is involved in the formation of blood vessels that feed tumors, not only inhibited tumor growth but also reduced the frequency of CSCs (*Cell Stem Cell* **5**, 168–177, 2009). Then, last year they showed the same was true for mutated colorectal tumors that are often impervious to other therapies (*Cancer Res.* **71**, 1520–1525, 2011). Buoyed by these findings, OncoMed now has an DLL4-targeting antibody in phase 1 trials for people with a range of solid tumor types, and the company is also advancing antibodies directed to the related Notch and Wnt signaling pathways in early clinical testing.

Other pharmaceutical companies are also interested in targeting DLL4, but more as a strategy to block angiogenesis broadly than to hit rare CSCs specifically. "As we learn more about tissue stem cells, we are going to find that there is overlap with cancer cell signaling mechanisms there," says Courtney Williams, a scientist in the oncology and angiogenesis group at Regeneron Pharmaceuticals in Tarrytown, New York. "But the rationale behind targeting those things was not the cancer stem cell hypothesis." Regeneron, together with France's Sanofi, is developing a DLL4-targeting antibody, currently in a 46-person phase 1 trial.

Some experts caution, though, that CSC populations paradoxically increase when blood vessel growth is curbed. This was the finding from an experiment published in January from Max Wicha's lab at UMCCC that examined two US Food and Drug Administration–approved angiogenesis treatments—Pfizer's Sutent (sunitinib) and Roche's Avastin (bevacizumab)—in human breast cancer xenograft models (*Proc. Natl. Acad. Sci. USA* **109**, 2784–2789, 2012). As such, Wicha, a cofounder of OncoMed and a principal investigator on some of the company's trials, believes that combining antiangiogenic agents such as Avastin with CSC-blocking drugs such as the ones in early clinical testing could have the potential to improve patient outcomes in the long run. "We want to now move into the clinic with a cancer stem cell therapy plus an antiangiogenic agent, which can debulk a tumor," he says.

Anna Azvolinsky

Battle looms over regulatory classification of complex drugs

NEW YORK — Therapeutic agents have traditionally fallen into two basic categories: small-molecule drugs that can be synthesized in the laboratory and larger 'biologic' drugs that must be extracted or produced from cell cultures or other living systems. But biology is not always so straightforward, and in recent years a third class of drugs has emerged that straddles the traditional drug divide.

These so-called 'nonbiologic complex drugs'(NBCDs), which include nanomedicines, synthetic peptides and prescription mineral supplements, are manufactured chemically yet have the molecular complexity of biologics such as antibodies. In the past, drug agencies in the US and Europe have treated NBCDs primarily as small molecule agents. But with NBCDs starting to come off patent, experts are calling on regulatory bodies to evaluate NBCDs with a greater degree of scrutiny.

"[NBCDs] are much more like biologics than they are like small molecules," says Christopher Holloway, group director of regulatory affairs for the ERA Consulting Group, a biopharma-focused consultancy headquartered in Walsrode, Germany. "Their mechanisms of action are too vaguely understood to be characterized in the same way as other synthetic compounds."

At a conference here on 9 March at the New York Academy of Sciences, scientists, analysts, pharmaceutical company officials and regulators came together to discuss how authorities on both sides of the Atlantic should define and appraise NBCDs. Currently, such drugs are regulated by the Center for Drug Evaluation and Research at the US Food and Drug Administration (FDA) as opposed to the agency arm that deals with biologics. The European Medicines Agency (EMA) follows a similar process.

But critics—and experts who were at last month's meeting remain divided. "The important measure for complex drugs, whether they are biological or not, is clinical efficacy," says Huub Schellekens, a biostatistician at Utrecht University in the Netherlands. But Beatriz Silva-Lima, a pharmacologist at Lisbon University in Portugal, thinks that poor laboratory-based assays are the major roadblock to demonstrating bioequivalency for NBCDs. "What we need are new ways—better ways—to test the pharmacokinetic interactions of complex drugs with their targets," she says.

Whereas generic versions of small