Geron's quixotic fate

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Why did Geron—corporate standard bearer for regenerative medicine—fail, whereas technology pioneers in other areas persist?

The discovery of human embryonic stem cells (hESCs) in 1998 was hailed as the biggest scientific advance of the past millennium. Buried in the fine print at the end of his heralded *Science* paper that detailed the breakthrough, the University of Wisconsin's James Thomson acknowledged financial support from his university and from a little-known cancer biotech company, Geron (Thomson, J.A. *et al. Science* **282**,1145–1147, 1998).

Fueled by both the promise of the cells and the controversy around their source—two-day-old human embryos—the paper signaled the beginning of what would be a complicated and sometimes contentious relationship between Geron (Menlo Park, CA, USA), researchers and government officials. This all abruptly came to an end last November 14, when publicly traded Geron announced it was halting the first clinical trial using oligodendrocytes derived from one of the original Thomson lines, and it dropped the second shoe by saying it would no longer pursue hESC work at all. Geron, which had been founded in 1990 and symbolized the edgy frontier of a subfield of cell-based therapies, was out of the game.

Though it will continue with its telomerase and oncology R&D, the company downsized, laying off 66 workers, ~38% of its workforce. It said unwinding that phase 1 trial and reducing headcount would cost about $8 million, and it refunded a nearly $6.5-million loan (including interest) it had obtained from the California Institute for Regenerative Medicine.

How did Geron's R&D program meet such a demise? After all, the company raised more than $583 million through 23 financings, including two venture rounds, and plowed more than half a billion dollars into R&D (about half of that into hESC work) through 2010.

There are problems with being at the forefront of unknown territory. Of Geron's development efforts, the hESC trial was the most prominent, and fraught. Therapies based on hESCs were new territory for the US Food and Drug Administration (FDA), and it eyed Geron warily. The investigational new drug application (IND), filed in 2008, was twice put on clinical hold while more animal data were collected among fears that nonmalignant tumors would result from stray hESCs that escaped the purification process. Geron says it spent $45 million on the application, and at 22,000 pages, it was reportedly the largest the agency had ever received.

Geron hoped to reap the benefits of a robust patent estate. From the University of Wisconsin's nonprofit technology arm, WiCell, it negotiated exclusive licenses for neural, cardiac and pancreatic derivatives from the Thomson lines, and launched active R&D projects for each. Geron (along with WiCell) became known for bargaining hard with universities looking to use its technologies for research, and it aggressively defended its intellectual property (IP) in the European Union, where hESC patents have come under fire. At investor meetings, company executives talked about the firm's growing stem cell patent estate.

Yet financial health did not follow. The company received just $69 million through collaborations, license fees and royalties from 1992 through 2010. It had little support from big pharma, which has been profoundly uninterested in pursuing hESC applications as therapies. As it ramped up its trials, Geron's losses skyrocketed. Its $37 million net operating loss in 2007 nearly doubled in 2009, and then jumped to $111 million in 2010; incoming revenue averaged <$4 million annually over that same period.

Compare Geron to Isis (Carlsbad, CA, USA), a company also formed with an unproven and clinically risky technology. Isis was founded in 1990 to exploit oligonucleotide-based antisense and subsequently set about cornering the lion's share of IP surrounding the technology. The FDA now has experience reviewing antisense INDs; 1988 marked the landmark approval of Vitravene (fomivirsen) against cytomegalovirus retinitis. After the introduction of more efficacious, later-generation oligo chemistries, trials followed for AIDS (2004), hemorrhagic fever and cancer (2006), and, in 2010, high cholesterol. All of this has been accompanied by growing interest from investors, who financed a spate of startups, including Silence Therapeutics (London), Tekmira Pharmaceuticals (Burnaby, BC, Canada), Calando Pharmaceuticals (Pasadena, CA, USA), Marina Biotech (Bothell, WA, USA) and Traversa Therapeutics (San Diego).

Antisense also drew attention from pharma. Isis had little troubling cashing in, forming a collaboration with Novartis and then Boehringer Ingelheim in 1995, which bought $28.5 million in equity at closing. It added AstraZeneca, Abbott, Elan and Aventis as partners, all before entering a collaboration in 2001 with Eli Lilly that included a $75-million purchase of Isis common stock. Over 1994–2010, Isis pulled in $864 million through collaborative agreements, joint ventures, or license fees and/or royalties, and had a cash position of $343 million at the end of 2011.

Another comparator is Alnylam (Cambridge, MA, USA), a pioneer in the RNA interference (RNAi) field. The company was formed in 2002 and like Isis built a strong RNAi IP estate that attracted pharma. Alnylam formed alliances with Roche, Novartis, Merck and Isis. Though Alnylam has recently faced tough times—Novartis ended a five-year collaboration, Roche moved out of the RNAi space entirely, and in January Alnylam reduced its headcount by 33% to focus on its lead products—the company has far outpaced Geron in revenue generation. It brought in $384 million from inception through 2010 from research collaborations.

Geron's former CEO, Thomas Okarma, pushed for the high-risk, high-reward promise of regenerative medicine. Although the venture capital markets seemed ready for the bet early on, the company faced four headwinds: scientific, regulatory and investment uncertainties first pushed Geron back; politics finally knocked it down. Having seen this, Geron CEO John Scarlett's actions in November were pragmatic. Thus, a word to Advanced Cell Therapeutics, the remaining company developing hESC therapies: your technology may be revolutionary, your team may be dedicated and you may believe. But it does not matter if no one else will stand at your side.

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