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Different points on the research spectrum were under the microscope at the Wharton Health Care Business Conference (http://www.whcbc.org/) last month as two panels of biotech, pharmaceutical and investment leaders discussed the state of R&D among big pharmaceuticals and the progress of stem cell research. Distinct but related themes emerging from the back-to-back sessions could be boiled down to "Big Pharma R&D: Too little hope?" and "Stem cells: Too much hype?"

In the panel titled, "Lagging R&D Productivity: What Should the Pharmaceutical Industry Do to Address This Dilemma?" moderator Charley Beever, vice president of Booz Allen Hamilton, described the problem as "one everyone believes they have a solution to. But if you look at the evidence, it's hard to believe anyone has found the magic bullet." He seemed right: By the time the panel ended, there were plenty of suggestions on the table, but as yet no clear prescription.

First up was J. Anthony Ware, vice president of Lilly Research Laboratories, who said he would give a "two-minute diagnosis of the problem," then joked that, with so little time, "I'm glad my malpractice insurance is still in full force." While affirming Big Pharma's commitment to R&D, Ware ticked off some reasons for the slowdown in new drugs coming to market. First, focusing on "novel targets" that involve a different mode of action than already existing drugs can lead to higher attrition rates. (Sanofi-Aventis's anti-obesity drug rimonabant, or Acomplia, is based on a novel target.) Also, there is more expense and time involved in developing new drugs because clinical trials are getting longer and larger to prove safety and efficacy. With the stakes higher, "this leads to non-technical attrition of drug candidates," Ware said, adding that the regulatory climate has also changed.

He noted that the genome project, which involved mapping the entire human genome, perhaps led to too much hope that new treatments would quickly follow. "It was easy to put on rose-colored glasses." Now the big challenge is to "find out what all the snippets of DNA" mean.

Vlad Hogenhuis, who heads Merck's new product marketing group, agreed with Ware that the "low hanging-fruits" have already been picked, leading to blockbuster classes of drugs such as the cholesterol-lowering statins. "Our technologies have not changed since the 1990s," he said, noting that the basic approach was to identify an enzyme and block it. "We're now on the verge of new technologies," he added, including the emerging field of pharmacogenetics, which could lead to more personalized drugs instead of a one-pill-fits-all approach. A growing use of biomarkers in drug testing and development also "is the wave of the future," he said, noting that "the early pipeline ... is filling up" and predicting that patients will see results of today's R&D in three to five years.

Robert Bagdorf, senior director, licensing and development, for Pfizer, also gave a rather upbeat diagnosis on the state of R&D, saying, "I don't think it's all doom and gloom as everyone makes it sound." He acknowledged that companies such as his are taking a big hit with drugs coming off patent, but said there are many good signs if you "fast forward 10, 12 years from now.... The early pipeline is flush" with promising products.

However, Roland Gerritsen van der Hoop, senior vice president of R&D and regulatory affairs at Endo Pharmaceuticals, a specialty drug company, didn't go along with what the Big Pharma panelists had to say, noting that drug companies' return on investment for their R&D efforts are "abysmal from a Wall Street point of view. The business model is basically broken. You are seeing a struggling business model trying to say that in three to five years things will be different."

Beever, picking up on that contrarian point of view, agreed that it's easy for the industry to say, "stay tuned." "But what's the truth here?" he asked. "Is the business model flawed? What is it that Big Pharma companies have to do differently?"

The panelists indicated there would be a push to develop novel drugs, as distinct from "me-too" products. But Bagdorf stressed that "the blockbuster is not dead .... It's just going to be different." He said tomorrow's drugs are going to be based on society's needs, such as drugs for obesity and Alzheimer's and other age-related diseases.

In terms of business structure, panelists said Big Pharma would rely on more in-licensing arrangements and alliances with biotech companies, although the gamble was in deciding at what stage of development to enter into such deals. According to Bagdorf, about 60% of deals are done in the pre-clinical stage. "As you move earlier and earlier, up-front payments become less ... but it's certainly riskier." In the case of Lilly, Ware added, of nine drugs launched

since 2000, six were discovered in-house and three elsewhere, although one of the six also involved a partnership.

Hogenhuis suggested that drug companies ask themselves, "Do you buy or do you build?" when deciding whether to do something in-house or through a deal with another company. Drug companies also must think in terms of a "portfolio" in plotting R&D strategy, he added. "One bet is just one bet. What is in your pipeline in two or three years that is not hocus-pocus? That is something you can measure."

Paul Spreen, senior vice president at Quintiles Transnational, a company in Research Triangle Park, N.C., that provides a range of services to the pharmaceutical and biotech industries, talked about another trend: the outsourcing of work at various stages of drug development, whether it's managing data or running a clinical trial. "What we are seeing is value in outsourcing," Spreen said, noting that outsourcing allows drug companies to conduct larger clinical trials with more geographic and ethnic diversity and to collect more safety data. Drug studies, once mostly confined to the U.S., are increasingly being done in China, India, South Africa and Eastern Europe -- places that represent potential markets for selling the drugs that pass muster.

Beever did not let the panel sidestep a tricky issue in R&D: when to "kill things," or, in gentler terms, when to shelve a project. "Is the industry getting better at killing earlier?" he asked. "Science can be a cruel mistress," added Ware, who noted that there are once-killed drugs that turned out to be successes. Panelists suggested that doing toxicity and safety studies early on can help companies make better decisions on whether to proceed. Gerritsen van der Hoop questioned the rationale of "modest efficacy," where drug companies hang on and end up with a drug that offers only a small advantage. He called it the "maybe we can make something out of it anyway" approach.

The various trends in R&D mean there will be more blurring in the distinction between the big, traditional companies and the smaller start-ups, panelists noted. As Ware put it: "It's going to become very murky [as to] who is biotech and who is Big Pharma."

Stem Cell Therapy: Unrealized Potential?

To launch the panel titled, "Stem Cells and Regenerative Medicine: Entrepreneurial Opportunities and Challenges," moderator Robert J. Easton peppered the panelists with such questions as: "How big can this actually be?" "Is this an area where there is more heat than light these days?" Is the field of stem cells and regenerative medicine merely "a collection of neat technology?" Or, "does it have the potential" for making money?

Easton, chairman and co-founder of Easton Associates, a New York-based health-care consulting company, brought some skepticism to his opening remarks because stem cell therapy is far from proven, and significant confusion exists in the public's mind over what the technology may someday offer. The belief that stem cell therapy will be the next great frontier of medicine has been fueled by thoughts of paralyzed people being able to walk again and failing minds becoming clear. Stem cells have been promoted as possible cures for a long list of ills, including Parkinson's disease, Alzheimer's, diabetes and spinal cord injuries as scientists attempt to grow tissue and organs in the laboratory to replace defective or worn-out body parts.

So far, however, the potential of stem cell therapy has been demonstrated mostly in the lab and in animals, not in people, and the controversy surrounding the use of embryonic stem cells creates a less-than-ideal research and funding environment.

Nevertheless, conference panelists offered glimpses of how the future is taking shape, noting that stem cell therapies could be particularly appealing for age-related diseases and rare conditions for which good treatments don't exist. Overlying the optimism, however, were questions of whether investors would buy into the uncertain science and whether the healthcare system could afford the new technologies.

Robert F. Willenbucher, who leads Johnson & Johnson's newly-formed stem cell internal venture effort, started with a tutorial, underscoring how the term "stem cell" can mean different things. A lot of attention is on embryonic stem cells -- primitive cells taken from embryos that have the potential to become various specialized cells. President Bush in 2001 banned federal funding for almost all human embryonic stem-cell research, except for work on existing cell lines.

But there are also non-embryonic, or adult, stem cells, which typically give rise to the type of cells in the tissue in which they are found. Non-embryonic stem cells can come from the patient himself or from a donor, Willenbucher said, adding that the business of regenerative medicine involves many facets, from harvesting the cells, to creating good laboratory cultures and "scaffolding" to grow cells and tissues, to devising delivery techniques to get the final product back into the patient. "Once you pick your product, it has important implications for the business," he said.

Steven Nichtberger, president and CEO of Tengion, a regenerative medicine company in King of Prussia, Pa., talked about his company's quest to grow replacement bladders using a patient's own cells. The technology, which could replace surgery currently done, would be aimed initially at children with spina bifida or people with spinal cord injuries who lose bladder function. The technique involves doing a biopsy of the patient's bladder to collect "progenitor cells," which are capable of regeneration. The cells are placed on a biodegradable scaffold in the shape of a bladder and given time to grow and mature. The neo-bladder is then implanted in the patient and becomes functional.

"Manufacturing is an absolutely essential expertise," Nichtberger said of the process. Tengion is establishing a central manufacturing facility in Pennsylvania to make the neo-bladders and hopes to begin clinical trials in the second half of this year.

Martin McGlynn, president, CEO and director of StemCells, a biotech company in Palo Alto, Calif., said his company is targeting human neural stem cells derived from adult brain tissue. The company has FDA approval to begin transplanting the cells into children with Batten disease, a fatal, inherited neurodegenerative disorder. "That will be the number-one agenda item for our company in 2006," he said.

His company does no research using human embryonic stem cells. Instead, it focuses on uncovering new types of adult stem cells and has found some interesting candidates in the liver and pancreas. "We mine human organ systems ... fishing out very rare cell populations, then look at the properties of the cells in the laboratory," McGlynn said.

Stephen W. Webster, president, CEO and director of Neuronyx, a biopharmaceutical company in Malvern, Pa., said his researchers are working with stem cells from adult human bone marrow to devise treatments for heart disease and other disorders. A small sample of cells from a donor can be turned into a big batch of cells that can be frozen and then thawed and administered as needed. He likened the therapy to "little factories that secrete a potent cocktail" of pro-regenerative cells. In animal models, the cells promote repair of damaged heart tissue. Neuronyx has applied to the FDA to next begin testing the therapy in heart attack patients.

Webster pointed out that while the technique may be on the cutting edge, it is cost-effective. A sample of cells from a single donor can be turned into six billion doses of therapy, he said, adding that "It's going to keep the cost of these regenerative therapies reasonable down the road."

William M. Caldwell IV, CEO of Advanced Cell Technology, offered a different vantage point than the other panelists: His biotech company is not staying away from the political minefield. "Our company is totally dedicated to embryonic stem cell development ... and potential cures," he said. When Bush placed a virtual ban on federal funds for human embryonic stem cell research, he noted, "most embryonic stem cell companies either had to find another basis to get funding or go out of business."

His company has its new headquarters and research facility in Alameda, Calif., a state where voters in 2004 approved an initiative to provide $3 billion in state funding for embryonic stem cell research over 10 years. "We are one of the benefactors of that," Caldwell said. On the research agenda: developing therapies for macular degeneration, heart disease and skin problems, such as burns.

Reni J. Benjamin, senior biotechnology analyst for Rodman and Renshaw, followed the science updates with the money side of the equation, noting that he was "one of the few on Wall Street to take a stab" at the stem cell field. While regenerative medicine can take healthcare in a whole new direction, venture capital companies are cautious, he noted. "We have heard about the potential of stem cells for a long time." But investors want a clearer indication of the "amount of time it would take to get these therapies to market."

Companies must do a better job explaining the status of their research, added Willenbucher. "It's important to not only talk about the promises" but also "about the near-term realities and what is going to happen incrementally."

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