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Five Prime to Gross $64.5M

Five Prime Goes Public in Upsized Offering, Aerie Joins IPO Parade

By Jennifer Boggs
Managing Editor

This year's flurry of initial public offering (IPO) activity continued Wednesday, as protein and antibody drug developer Five Prime Therapeutics Inc. priced an upsized offering to gross $64.5 million and ophthalmology firm Aerie Pharmaceuticals Inc. added its name to biotech's IPO queue.

And more news is expected.

"The big picture is that there is a very exciting story unfolding this week," said Michael Brinkman, managing director at Jefferies, which acted as joint book-running manager for Five Prime's IPO, alongside BMO Capital Markets and Wells Fargo LLC and co-manager Guggenheim Securities LLC.

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JOBS Act Succeeds in Jumpstarting Bio IPOs

By Mari Serebrov
Washington Editor

In the wake of the Jumpstart Our Business Startups (JOBS) Act, more than 230 initial public offerings (IPO) are expected this year, with small biotechs and other emerging growth companies (EGCs) accounting for much of the resurgence in IPO interest.

"We've got the most robust IPO market" since 2007, Joel Trotter, a partner at Latham & Watkins LLP, told *BioWorld Today*. He credits most of the

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FINANCINGS

Sangamo Biosciences Prices its $65M Public Offering

By Catherine Shaffer
Staff Writer

Sangamo Biosciences Inc. will collect about $65 million in gross proceeds from a public offering of 6.1 million shares of common stock in an underwritten public offering. The company will funnel the money into

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IN THE CLINIC

Prima Biomed Backpedals After Inconclusive PFS

By Marie Powers
Staff Writer

Shares of Australia's Prima Biomed Ltd. were jolted Wednesday after top-line data from the company's Phase II study of cancer vaccine candidate Cvac showed no observed difference in estimated median progression-free

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U.S.

Biopharm America

Dress for Success: Panel Mulls Best Early Stage Deal Chances

By Randy Osborne
Staff Writer

BOSTON – Even with a solid strategic fit, quality assets on the table and the likelihood of reimbursement by payers, intellectual property (IP) glitches can hurt a deal, warned Sanjeev Munshi, director of worldwide licensing and acquisition for Merck & Co. Inc.

Munshi's remarks came during a panel talk called "How to Position Your Early Stage Company for Success" at Biopharm America, a three-day event focused on partnering. He cited Whitehouse Station, N.J.-based Merck's July 2012 deal with Chimerix Inc.

The arrangement gave Merck exclusive worldwide rights to CMX157, a Phase I-stage lipid acyclic nucleoside phosphonate for HIV infection.

Chimerix, of Research Triangle Park, N.C., got $17.5 million up front and up to $151 million in potential

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EUROPE

EpimiRNA Consortium Gets $15M to Study Role Of miRNA in Epilepsy

By Cormac Sheridan
Staff Writer

A consortium led by the Royal College of Surgeons in Ireland (RCSI) has secured €11.5 million (US$15.4 million) in funding from the European Commission (EC) to build a comprehensive picture of microRNA

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THE BIOWORLD BIOME

Taking Off the Brakes

Stem Cell Advance Transforms the 1% into the 99%

By Anette Breindl
Science Editor

Researchers have identified a protein that is critical for keeping adult cells from turning back into induced pluripotent stem (iPS) cells. In cells that lack this protein, the transcription

See Stem Cells, Page 9

Other News To Note

• **Chemocentryx Inc.**, of Mountain View, Calif., said **Glaxosmithkline plc** (GSK), of London, returned rights to CCRP antagonist vercirnon (Traficet-EN, or CCX282) for all indications. GSK also will transfer the full dataset from clinical trials, including studies that were not completed. Chemocentryx plans to review the data to determine whether the drug maintains remission in Crohn's disease, as indicated in the maintenance phase of a previously conducted trial. Last month, vercirnon missed its endpoint in the first of four Phase III studies in moderate to severe Crohn's. Two other development programs – CCRI inhibitor CCX354 in rheumatoid arthritis and C5a complement inhibitor CCX168 in anti-neutrophil cytoplasmic antibody vasculitis – are continuing under the 2006 alliance between the companies. On Wednesday, shares of Chemocentryx (NASDAQ:CCXI) fell 34 cents, to close at $6.08. (See *BioWorld Today*, Aug. 25, 2006, and Aug. 26, 2013.)

• **ITM Isotope Technologies Munich AG**, of Garching, Germany, said it entered an agreement with **Progenics Pharmaceuticals Inc.**, of Tarrytown, N.Y., for pharmaceutical development and commercialization of radiolabeled DOTA-conjugated somatostatin analogue DOTA-[Tyr3]-octreotide (edotreotide) for human oncology therapeutic use. Further terms of the agreement were not disclosed.

• **Ocera Therapeutics Inc.**, of San Diego, said it plans to close its research center in Sherbrooke, Quebec, effective Nov. 11, following its merger with Tranzyme Inc., which previously operated the facility. Ocera will retain full rights to the chemistry technology platform, MATCH (Macrocyclic Template Chemistry), pursued at the center. The restructuring plan will allow Ocera to focus resources on advancing lead candidate, OCR-002 (ornithine phenylacetate), in hepatic encephalopathy associated with acute and chronic liver disease. The company plans to initiate Phase IIb trials of OCR-002 during the fourth quarter.

Stock Movers

09/18/13

Company	Stock Change	
Nasdaq Biotechnology	+$24.26	+1.11%
ANI Pharmaceuticals Inc.	+$0.87	+10.74%
Geron Corp.	+$0.37	+16.02%
Medgenics Inc.	+$0.55	+11.34%
Oxigene Inc.	+$0.35	+15.77%

(Biotechs showing significant stock changes Wednesday)

• **Stemcells Inc.**, of Newark, Calif., said preclinical data published in *Investigative Ophthalmology and Visual Science* confirmed that the firm's HuCNS-SC cells (purified human neural stem cells) preserved photoreceptor cells and visual function in a rat model of retinal degeneration. Data also showed not only that HuCNS-SC cells preserved the number of photoreceptors that would otherwise be lost, but also that the surviving photoreceptors appeared healthy and normal and were able to maintain their synaptic connection to other cells necessary for visual function. Stemcells said the results are relevant to disorders of vision loss such as age-related macular degeneration (AMD). A Phase I/II study in the dry form of AMD is under way.

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IPOs

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Brinkman was referring to the other biotech IPOs expected to price this week, including Acceleron Pharma Inc. and Fate Therapeutics Inc.

"We'll see what prices and what doesn't and how well those newly priced stocks fare on Nasdaq," he said.

For its part, South San Francisco-based Five Prime got off to a fairly good start. The firm increased the number of shares by 8 million, selling a total of 4.8 million shares at $13 apiece, the midpoint of its proposed range, to raise $64.5 million in gross proceeds. Another $9.4 million could come if underwriters exercise their full overallotment option of 720,000 shares.

The company's shares (NASDAQ:FPRX) had an impressive opening on Wall Street Wednesday, jumping 23 percent on debut, though shares lost most of their buoyancy throughout the day to close at $13.08, up 8 cents. About 4.4 million shares changed hands.

Most biotech IPOs this year have had similar stories, pricing at or even above their proposed ranges and making solid trading debuts. One of the biggest success stories is Epizyme Inc., which saw its shares jump a whopping 53 percent on the first day of trading. The stock has jumped another 58 percent since then. (See *BioWorld Today*, June 3, 2013.)

"If it trades above, that means a stock is trading on its own," Brinkman noted. "It takes a lot for a stock to hold up above its IPO price."

Biotechs going public now are attracting "a lot of interest from short-term investors. They're the ones you see buying into the IPO and flipping," Brinkman said. But the core investors – the same roughly 75 biotech investors every company sees on their road shows – are the ones who matter, and they remain as discriminating as ever.

Their participation is "more correlated with long-term success," he told *BioWorld Today*."The larger percentage of investors in that group that get behind an IPO, the more successful that IPO is likely to be."

And the best way to attract those investors is with data. And "it doesn't matter what stage," Brinkman added. Investors want encouraging data that the drug works.

The current IPO window also has been good for platform companies. "People are enthusiastic" about those firms again, "even though they're early stage, and that's different from the last decade when nobody cared about platform companies," he said.

That trend is evident by the successful IPOs of firms with platform technologies, including Epizyme, Agios Pharmaceuticals Inc., Oncomed Pharmaceuticals Inc. and now Five Prime.

Moving to the Clinic

In fact, to date much of Five Prime's funding – more than $220 million – has been from collaborations involving its platform tech. The company boasts a library of more than 5,600 human extracellular proteins, which has led to a series of collaborations with Glaxosmithkline plc, of London, including a product collaboration, initially inked with GSK acquisition Human Genome Sciences Inc., for FP-1039/GSK3052230, a protein therapeutic designed to trap and neutralize cancer-promoting fibroblast growth factors (FGF). Under the terms, Five Prime retains a co-promotion option in the U.S.

Data from a Phase Ib study testing FP-1039 in patients with abnormally high levels of FGFR1 are expected in the second half of next year.

GSK also is using Five Prime's drug discovery platforms and protein libraries for programs aimed at muscle diseases, respiratory diseases and cancer. (See *BioWorld Today*, April 18, 2012.)

Other collaborations have involved Pfizer Inc., Johnson & Johnson unit Centocor Research & Develoment and UCB SA.

Much of Five Prime's own pipeline, however, remains in early stage development. The company has FPA008, an antibody designed to inhibit colony-stimulating Factor-1 receptor to treat inflammatory diseases such as rheumatoid arthritis. A Phase I study is slated to start this year, with preliminary data available by the end of 2014.

FPA144, an antibody to inhibit FGFR2b for treating gastric cancer and possibly other solid tumors, is set to move into the clinic in the second half of next year.

Proceeds from the IPO will be used largely for those studies. Funds will add to the $28.2 million in the bank as of June 30. (See *BioWorld Today*, July 30, 2013.)

Five Prime, which is headed by founder Lewis "Rusty" Williams, has an eclectic investor list, including partners Pfizer and GSK, Advanced Technology Ventures, Domain Associates, HealthCap and affiliates, Johnson & Johnson Development Corp., Kleiner Perkins Caufield & Byers, Texas Pacific Group and Versant Ventures.

Aerie Files for IPO

With Five Prime's pricing, a total of 29 biotechs have gone public in 2013, according to BioWorld Snapshots. Its offering brings the total IPO proceeds this year to about $1.96 billion, with an average IPO haul of $67.5 million.

As to how long the hunger for biotech IPOs will last, "We'll be able to tell more in a week," Brinkman said. "But we feel the market is healthy and sustainable."

Most of the companies that have priced in the current IPO window are high-quality companies that are pricing appropriately and then trading above their offering prices. "When a good IPO for a good company trades down, that's when we have a problem," he said.

Meanwhile, companies continue to add their names to the IPO wish list. As of Wednesday, nine biotech IPOs are

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JOBS

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activity to the Title I provisions of the Jobs Act, which was signed into law in April 2012. (See *BioWorld Today*, April 16, 2012.)

For the most part, these are not bargain-basement deals. Most IPOs for EGCs over the past 17 months priced within or above the expected range. While 25 percent came in below the range, 55 percent were within the range and 19 percent were above it, according to a Latham & Watkins report, which was presented Tuesday to the SEC Advisory Committee on Small and Emerging Companies.

Eighty-five percent of all IPOs undertaken since the JOBS Act became law have been by EGCs, and more than 90 percent of the EGCs going public have used at least one provision of the act to ease their way, the report indicated.

While the EGCs using the JOBS Act represent a variety of sectors, a healthy number have been biotechs. Jeffrey Solomon, CEO of Cowen and Co., told the advisory committee that 31 biotechs have used some of the JOBS provisions to raise a total of $2.5 billion. That's about 15.5 percent of the $16.1 billion raised by EGCs in IPOs across all sectors since the JOBS Act was passed.

The most popular provisions of the legislation to date for biotechs include the confidential review, the ability to test the waters through active discussions with institutional investors and the five-year IPO "on-ramp" that reduces the regulatory burden, and cost, of going public, Trotter said.

In years past, small start-ups were held to the same regulations as large successful companies that had been public for years, he explained, but the JOBS Act offers a regulatory scheme scaled to the size of the company.

As a result, EGCs are taking advantage of such Title I provisions as the extended phase-in of the internal controls audit and the streamlined executive compensation disclosure. For instance, Latham & Watkins found that:

• About 40 percent of the EGCs with a recent IPO provied two years of audited financial statements;

• About half of the EGCs with annual revenue of less than $100 million provided two years of audited financial statements;

• About a third of the EGCs with three years of audited financial statements had fewer than five years of selected financial data;

• At the time of their IPO pricing, about 15 percent of the EGCs had an operating history of less than five years.

Two decades ago, exit strategies for investors in small companies were evenly split between IPOs and mergers and acquisitions (M&As), Trotter said. But in the past decade, 90 percent of exit strategies were M&As, which was bad news for the economy since an M&A doesn't produce the jobs that an IPO can. The aim of the JOBS Act was to re-create a robust IPO market that would once again make IPOs an attractive option for small companies – before they become household names.

It appears to be working. More than 80 percent of the EGCs going public since April 2012 had annual revenue of less than $250 million, with nearly 66 percent having annual revenue of less than $100 million, according to the Latham & Watkins report.

In the biotech sector, Solomon said, that trend could lead to exponential growth for companies developing cancer therapies and orphan drugs and provide a complementary source of financing to National Institutes of Health grants.

Since the SEC hasn't fully implemented the JOBS Act – it has yet to raise the Regulation A cap or draft rules for crowd-funding – it could take years before the full impact of the act is realized, Trotter said. (See *BioWorld Today*, May 2, 2013.)

Meanwhile, experts are already considering next steps. At Tuesday's meeting, Solomon pointed out the need to help small companies that went public before the JOBS Act was passed. He also called for fostering more liquidity and analyst research for small-cap stocks.

The lack of research sponsorship and the difficult market structure remain the "biggest impediments to fundamental trading liquidity," he said. ■

Other News To Note

• **Xbiotech Inc.**, of Austin, Texas, said it is collaborating with US Oncology Research to conduct a pivotal Phase III trial for colorectal cancer. Leveraging its national network of affiliated oncology centers, US Oncology Research will treat patients with the company's Xilonix anti-cancer therapy and report clinical outcomes. The compound, a first-in-class True Human antibody blocks inflammation involved in tumor growth and metastasis. Sterile inflammation caused by malignant tumors is known to stimulate angiogenesis and tissue matrix remodeling, key steps in ongoing tumor growth and spread. Patients receiving Xilonix in an earlier study have shown improved overall survival and recovery of lean body tissue.

• **Xenikos BV**, of Nijmegen, the Netherlands, said its T-Guard, a combination of two toxin-loaded anti-T-cell antibodies to help reset the body's immune system, has been granted FDA orphan drug designation for the treatment of graft-vs.-host disease.

Sangamo

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continued research and development of its engineered zinc finger DNA-binding proteins (ZFP).

It also has product candidates in development in HIV/AIDS, hemophilia, Huntington's disease and other disease indications.

The stock will be offered at $10.58 per share. Sangamo stock (NASDAQ:SGMO) gained 51 cents, to close at $11.09 on Wednesday.

"We've had a fairly modest burn rate, and we are expanding our pipeline. We felt it was prudent to do a financing to make sure the company continues to have a strong balance sheet," Sangamo CFO Ward Wolff told *BioWorld Today*.

Wolff noted that the offering price for the stock was the same price at which the stock closed Tuesday, with no discount. "Because of demand and a strong group of biotech investors, we were able to do the offering at the same price we traded at the end of the day yesterday," he said.

A robust financing environment for the life sciences over the past 12 to 18 months contributed to the company's decision to pursue a public offering.

"We're pleased based on the performance today as well as the interest in the transaction," Wolff said.

Sangamo's lead ZFP therapeutic, SB-728-T, for HIV/AIDS, is being studied in two clinical trials. It recently reported data from a Phase II trial of that product showing functional control of the virus at or below the limit of detection in CCR5 delta 32 heterozygote HIV-infected subjects treated with SB-728-T. It also has data from another study showing depletion of the HIV viral reservoir in subjects treated with SB-728-T.

Sangamo is partnered with Shire AG for development of several products. In an agreement signed with the Dublin-based pharma in 2012, Sangamo granted exclusive worldwide rights to Shire for the use of technology targeting four genes for blood-clotting Factors VII, VIII, IX and X in exchange for $13 million up front, plus research funding, milestones and royalties on product sales. Sangamo took responsibility for all activities through submission of an investigational new drug application and European clinical trial applications. Shire is responsible for clinical development and commercialization.

Sangamo's program in Huntington's disease also is partnered with Shire. Data from that program was presented at the annual meeting for the Society for Neuroscience in New Orleans in 2012, showing that a ZFP therapeutic can selectively repress the expression of the mutant disease-causing form of the huntingtin gene while leaving expression levels of the normal gene unchanged in cells derived from HD patients.

Sangamo also has license agreements with Sigma-Aldrich Corp. and Dow Agrosciences LLC. Its agreement with Sigma provides exclusive rights to develop and market laboratory research agents based on ZFP technology and ZFP-modified cell lines for commercial production.

Sangamo's license with Dow Agrosciences, a subsidiary of Dow Chemical Corp., gives Dow access to ZFP technology and rights to use it to modify genomes or alter protein expression of plant cells, plants or plant cell cultures.

Sangamo added adeno-associated virus gene therapy technology to its capabilities with its acquisition of Ceregene Inc. in August. The assets it gained include CERE-110, a delivery system for Alzheimer's disease currently in Phase II trials. (See *BioWorld Today*, Aug. 28, 2013.)

Ceregene's large AAV intellectual property estate – more than 120 patents – will contribute to Sangamo's development of ZFP therapeutics. Sangamo is using AAV for delivery of all of its in vivo ZFP therapeutic programs.

Wolff said that with the current financing, Sangamo will continue to invest in its technology for gene editing and gene regulation. "That's what we're known for, a robust preclinical pipeline," Wolff said. "We will now focus on potentially expanding that pipeline. We do that with the notion that we're pretty good custodians of investor dollars."

Sangamo's public offering includes a 30-day option to underwriters to purchase up to an additional 915,000 shares of common stock to cover overallotments, if any. The offering will close Sept. 23. Lazard Capital Markets LLC, JMP Securities LLC and Piper Jaffray and Co. are joint book-running managers and Cowen and Co. LLC are co-lead managers for the offering.

Sangamo had 53,974,452 shares of common stock outstanding on June 30, 2013.

In other financings news:

• **Agenus Inc.**, of Lexington, Mass., said it entered a definitive $6.5 million purchase agreement with institutional investors to sell an aggregate of 2,166,667 shares of its common stock and warrants to purchase up to approximately 650,000 additional shares of its common stock. Each unit, consisting of one share of common stock and a warrant to purchase 0.3 of a share of common stock, will be sold for a purchase price of $3. The warrants to purchase additional shares will be exercisable at $3.75 per share beginning six months following issuance and will expire five years from the date on which the warrants are initially exercisable.

• **Galena Biopharma Inc.**, of Portland, Ore., said it closed an underwritten public offering of 17.5 million shares of common stock, and warrants to purchase an aggregate of 6.125 million shares of common stock at an exercise price of $2.50 per share. The underwriters also exercised their overallotment option to purchase warrants

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Prima

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survival (PFS) compared to control in epithelial ovarian cancer patients in first or second remission. On the Nasdaq Global Market – the first of the company's public markets to react to the news – shares (NASDAQ:PBMD) fell 74 cents, or 31.3 percent, to close at $1.61.

Separate estimates of median PFS by stage of remission were inconclusive, favoring the control arm compared to Cvac for patients in first remission and Cvac for patients in second remission. Neither trend was statistically significant.

On the plus side, the autologous dendritic cell-based product was well tolerated, with no serious adverse events considered related to protocol therapy. Most nonserious adverse events were mild and transient in nature.

In addition, immune monitoring data indicated Cvac induced a T-cell response that may prove beneficial in treating ovarian cancer, and the data showed no evidence of antibody response after Cvac administration.

The data, though early, showed once again the challenges biopharmas face in designing trials that demonstrate the therapeutic value of cancer vaccines. Just two weeks ago, London-based Glaxosmithkline plc reported cancer immunotherapy candidate MAGE-A3 failed to significantly extend disease-free survival in melanoma patients compared to placebo in the Phase III DERMA trial. (See *BioWorld Today*, Sept. 6, 2013.)

Prima, based in Sydney, sought to put a positive spin on the CAN-003 findings, emphasizing the trial was not adequately powered to detect statistical significance in PFS. In addition to MAGE-A3, other cancer immunotherapeutics have reported inconclusive PFS data during clinical studies, including marketed products Provenge (sipuleucel-T, Dendreon Corp.) and Yervoy (ipilimumab, Bristol-Myers Squibb Co.), said company CEO Matthew Lehman.

"What we're seeing is not unlike most other cancer immunotherapies, where endpoints like response rate or progression-free survival or disease-free survival just simply don't seem to give us very much information," Lehman told *BioWorld Today*. "We do see a product that is very well tolerated. It is immunologically active, so we're very comfortable that this product is helping patients and we're getting the right kind of immunological or biological response."

Lehman conceded, however, that the company must wait longer to see how that activity translates clinically and affects overall survival (OS), where data are still immature. OS generally has been favored by the FDA as an endpoint in cancer therapies and served as the basis for marketing approvals for Provenge and Yervoy.

"We've actually been a little surprised by the low number of deaths, thus far, on the study," Lehman said, estimating mature OS data could be a year away.

In the meantime, the company said additional information from CAN-003 will be presented at the European Cancer Congress in Amsterdam on Oct. 1, followed by a management conference call to discuss the Phase II results in greater detail.

Still, jitters were understandable considering the impact of potential delays to the lead program, in which the company has invested the lion's share of resources. The biggest immediate effect was the suspension of enrollment in the pivotal Phase III CANVAS trial of Cvac, already under way in multiple countries, which was designed with PFS as the primary endpoint.

"We don't see any reason to withdraw patients," Lehman said. "We don't see any safety concerns. But, clearly, having PFS as the endpoint is something we have to change."

The company will meet with regulators to discuss an amended clinical development plan for CANVAS that includes a new primary endpoint and, potentially, a different enrollment target to generate an appropriate clinical signal.

"The product is having the right kind of activity in the patient," Lehman said. "It's really a question of finding the right endpoint to evaluate clinical benefit."

Prima did not identify any specific genetic marker or baseline patient criteria to suggest Cvac should be targeted to a particular subset of epithelial ovarian cancer, Lehman said, noting that the company will continue to examine individual patient profiles in more detail.

"The key message here is that the [CAN-003] data are not negative," he added. Although inconclusive data may hamper the company's ability to use PFS as a potential surrogate endpoint, "it doesn't really affect the overall clinical development plan and the potential to benefit patients and extend survival."

In addition to Cvac, a half-dozen immunotherapy candidates targeting ovarian cancer are in Phase II or registration studies, according to Thomson Reuters Cortellis Competitive Intelligence. They include candidates from Galena Biopharma Inc., Gradallis Inc., Mabvax Therapeutics Inc., Immunovaccine Inc., Avax Technologies Inc. and Quest Pharmatech Inc.

Lehman said Prima has sufficient resources to see Cvac to the end zone, including approximately A$30 million (US$28.6 million) in the bank and two nondilutive research grants.

"There's no immediate pressure on our financial situation," he said. "We do have appropriate space to make the adjustments and move forward." ■

Biopharm

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milestones payments, plus royalties on future sales.

"It was a good deal," Munshi said, but Merck spent six months ironing out a problem with Chimerix's licensing of the technology from the University of California. "Something was not paid attention to," he said.

IP problems can turn out significantly worse, said panel moderator Sandra Kuzmich, partner with Frommer, Lawrence & Haug LLP. Arthur Hiller, CEO of Scifluor Life Sciences Inc., of Cambridge, Mass., said he "made a decision early on" to hire only the best IP counsel. "There are a lot of ways of getting cost-effective – I'll use that term nicely, diplomatically – IP counsel," he said, but it's a bad idea, especially when an eventual deal is planned.

"You can rest assured that the buyer will have high caliber, gold standard IP counsel, and unless you have an individual across the table who can have an intelligent conversation and gain the respect of the buyer's IP counsel, then you have probably added a layer of complexity and problem into your discussions that you didn't need to add," Hiller said. And this will most likely mean more cost.

He said he "went to bat" against an investor who wanted "cost-effective" lawyers, instead of the firm chosen by Hiller, whose firm uses fluorine to modify the chemical structure of a drug, with the motive of improving potency, selectivity, tissue penetration, half-life and metabolic stability. (See *BioWorld Today*, Oct. 26, 2012.)

"I'm sure I could have saved 20 percent, 30 percent, whatever, by going with less expensive IP counsel, but in the long run I think it would have come back to haunt us," he said. "That's my philosophy, and it's held true up to this point. I don't think there will be any surprises going forward."

Hiller also pointed to hazards when licensing IP, which often, "especially out of universities and tech-transfer offices and that sort of thing, has lots of warts on it. I'm not talking in terms of the way it's drafted. I'm talking in terms of the way you can actually execute – whether it be a product, a platform, or whatever – against that IP."

Expect "speed bumps," Hiller said. "What comes out of a university is much different from what the needs are commercially. Even if you get sign-off from a great IP attorney [who] says everything is in order, the i's have been dotted and the t's have been crossed, that doesn't mean that IP is ready for commercial application."

Best in Class, First in Class?

Even IP, of course, isn't everything, or even the main thing, for sellers to consider, though it's "way up there," allowed Merck's Munshi.

"No matter how good the asset is, if it's not fitting into the strategy we have – if it doesn't serve a certain need that I'm looking for – then obviously I'm not the right partner to be talking to," he said. "That, to me, is priority number one," followed closely by the proven – insofar as possible – merit of the candidate itself. "More often than you'd like to see, some key, killer experiments have not been done," he said.

Once all, or most, of the elements are in place, it's still not easy to value a deal or predict its chances. "If you think about some transactions over the last couple of years, some of them are kind of hard to put in perspective," said Scifluor's Hiller. "We could start with Gilead and Pharmasset, and try to figure out how a company justifies paying $11 billion for an asset that just has a handful of [data from] patients around it."

In late 2011, Foster City, Calif.-based Gilead Sciences Inc. forked over $137 per share in cash for Pharmasset Inc., of Princeton, N.J. The move was based on "a dream that you could treat hepatitis C virus without interferon," Hiller said – a dream that could be on its way to realization. (See *BioWorld Today*, Nov. 22, 2011.)

"Or, if you look at some of the recent [initial public offerings (IPOs)] that have been tremendously successful, in many cases oversubscribed – again, handfuls of patients, in companies like Epizyme, for instance," Hiller said. "I have tremendous respect for [CEO] Robert Gould at Epizyme, and I think highly of the company, but they have something like eight patients' worth of data, and their market cap is $1 billion."

Cambridge, Mass.-based Epizyme Inc.'s IPO this summer hit the top end of the pricing range and added more than a million more shares than expected, with a next-day aftermarket performance that seemed to prove how thrilled investors remain with epigenetics. The firm had completed Phase I work with EPZ-5676 in mixed lineage leukemia, a particularly virulent subtype of the most common forms of leukemia. (See *BioWorld Today*, June 3, 2013.)

Often, Hiller said, companies in the mood for buying "don't want best in class, they want first in class," and sellers need to know where their asset stands. "Unless you do that homework, you're going to be wasting a lot of resources as a small company," he said. "John Wayne used to say, 'We're burning daylight.' Well, as a small company, every day that goes by, when you're paying the resources to support a staff and other overhead and such, and not getting a partnership deal, is a shorter day in your runway to life, essentially. Because the company's going to run out of cash."

Value is Sometimes a Riddle

The picture grew even more complex when Thomas Hanke, director of biopharmaceuticals innovation sourcing for Novo Nordisk A/S, of Bagsvaerd, Denmark, pointed out that first in class vs. best in class may be a "somewhat

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Epilepsy

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(miRNA) biology in patients with epilepsy.

The group hopes to identify new miRNA drug targets that could form the basis of future therapies and to develop miRNA-based diagnostic methods for identifying molecular signatures of the condition and for monitoring patient responses to therapy.

The EpimiRNA consortium, which is funded under the EC's 7th Framework Program (FP7), involves 11 academic institutes across eight countries, including the U.S. and Brazil, plus another six European biotechnology firms.

The partners will build on early observations indicating that miRNA species may have a causal role in the development of epilepsy, with a particular focus on temporal lobe epilepsy. "It's designed to be a fresh, almost unbiased look," project coordinator David Henshall, of the Dublin-based RCSI, told *BioWorld Today*.

The group will sequence the miRNA genome – encoding some 1,500 individual miRNA species, plus associated proteins – of about 1,000 patients to determine whether they exhibit any unique features. The consortium will also study tissue samples taken from severely drug-resistant patients undergoing surgery, in order to identify all functional miRNA species, using a method called high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation (HITS-CLIP).

Many studies at present involve a global view of all miRNA molecules present within a given cell or tissue sample. The HITS-CLIP technique will enable the research consortium to identify only those species that are bound to argonaut proteins, which are required to mediate miRNA-based gene silencing.

The consortium also will conduct clinical studies with patients in order to identify possible blood-based miRNA signatures of the disease. "MicroRNAs seem to circulate in the bloodstream in a stable form," said Henshall. Any such molecular correlates of the disease could be a useful guide to monitoring responses to therapy. "There's a lot of trial and error with finding the right drug for an epileptic patient," he said. Moreover, many patients are not well served by present anti-convulsant therapies. "There's a significant drug-resistance problem in epilepsy," Henshall said.

As well as screening for new molecules implicated in epilepsy, the partners will also study early leads in parallel. For example, Henshall has obtained preliminary evidence which suggests that miRNA-134 may contribute to the pathogenesis of the condition. Blocking it with an antagomir elicited a pronounced effect in experimental mice. "It really reduced seizures in our animal models," he said.

Consortium member Gerhard Schratt, of Philipps University Marburg, in Germany, recently published a paper indicating that miRNA-134, under the control of a DEAH-box helicase enzyme called DHX36, localizes to the dendrites of hippocampal neurons, where it influences the size of dendritic spines, the dynamic, bulbous projections that play a key role in synaptic plasticity. The study, titled "The DEAH-box helicase DHX36 mediates dendritic localization of the neuronal precursor-microRNA-134," appeared in the May 1, 2013, issue of *Genes & Development*.

Henshall and colleagues have also previously reported that tissue samples from drug-resistant patients with hippocampal sclerosis, a common feature of temporal lobe epilepsy, have major reductions in levels of mature miRNAs compared with tissue samples from autopsy controls. They proposed that this effect is due to loss of Dicer, the RNAse III enzyme involved in miRNA processing. The findings are reported in a paper, titled "Reduced Mature MicroRNA Levels in Association with Dicer Loss in Human Temporal Lobe Epilepsy with Hippocampal Sclerosis," which was published online in *PLOS One* on May 15, 2012.

Felix Rosenow, also of Philipps University Marburg, another early European leader in studying the role of miRNA in epilepsy, is co-coordinator of the consortium. The influential population geneticist David Goldstein, of Duke University, in Durham, N.C., also is involved. ■

Sangamo

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to purchase an aggregate of 918,750 shares of common stock. The net proceeds are expected to be approximately $32.6 million.

• **Oxygen Biotherapeutics Inc.**, of Morrisville, N.C., said it converted $4.6 million in outstanding principal of a convertible promissory note that was scheduled to mature July 1, 2014, and carried an annual interest rate of 15 percent. The move reduced the company's debt from $4.9 million to $300,000. The debt was retired Aug. 24 in conjunction with a private placement of $4.6 million in shares of the company's Series D 8 percent convertible preferred stock.

• **Protalix Biotherapeutics Inc.**, of Carmiel, Israel, said it closed its offering of $69 million principal amount of its 4.5 percent convertible notes due 2018 through a private offering, including $9 million aggregate principal amount of notes related to the initial purchaser's overallotment option, which was exercised in full. ■

Stem Cells

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factor cocktail that is used to turn cells into iPS cells worked basically without fail; the efficiency of generating such cells skyrocketed from 1 percent of cells to more than 90 percent.

Pluripotency is a double-edged sword. It is necessary for getting a whole organism out of a single cell. But in order to actually get anywhere with the work of making an organism, cells quickly need to give up their potential and settle down into one role. And stick with it.

As a result, during development, Jacob Hanna told *BioWorld Today*, "the stem cell state is not retained – it is very transient."

Pluripotency lasts for only a few days, and by the time the embryo implants into the uterine wall, the party's over. "This brake comes on, and it stays on, in every cell in our body" – including the adult cells that are reprogrammed in the generation of iPS cells. Given this state of affairs, the fact that induced pluripotent stem cells (iPSCs) exist at all – that it is possible to reprogram an adult cell into an embryonic stem cell-like state by the addition of a mere four transcription factors – is astonishing.

And the reason why most cells do not turn into iPS cells even when reprogramming factors are added becomes obvious. Such transduction in the presence of inhibitory factors is essentially an attempt to push them into pluripotency without removing the obstacles in their way.

Hanna, who is at the Israeli Weizmann Institute, likened reprogramming under the influence of the repressor to "driving a car by pressing on the gas and the brake at the same time."

In their experiments, which were published in the Sept 18, 2013, advance online edition of *Nature*, Hanna and his colleagues first identified Mbd3 as a possible master of repressing stem cell-like behavior through screening experiments. They found that when they depleted cells of Mbd3 before adding the usual cocktail of reprogramming factors, the efficiency of reprogramming skyrocketed to nearly 100 percent. Moreover, the cells reprogrammed more or less in lockstep, rather than at random times after the addition of the reprogramming factors.

Last week, Spanish researchers reported that they have managed to make iPS cells directly in vivo, rather than in cell culture. (See *BioWorld Today*, Sept. 12, 2013.)

Hanna said that blocking Mbd3 could also be done in vivo, so that the two methods could potentially be combined – although he was skeptical of the Spanish team's assertions that the in vivo cells are closer to totipotency than those produced in culture, calling those assertions "unproven claims."

Hanna said that the work could improve the chances for using iPS cells clinically directly. Even though such transplantation does not need numbers of cells that are out of reach with the current efficiencies. But Hanna noted that to make such cells true contenders for the clinic "we need methods that do not modify the genome." The efficiency of such methods is currently far below the 1 percent that can be achieved by inserting the genes for transcription factors, and so increases makes it much more realistic to use such methods for generating iPS.

But the work may ultimately be more influential by allowing scientists to better understand iPS cells than by its effects on their ability to make the cells in the first place.

Hanna pointed out that because each adult cell transforms into an iPS cell according to its own timetable, and only 1 percent of them transform at all, it is currently a tall order to study such cells prospectively. Basically, the only way to do so is to follow 99 cells that don't transform for every cell that does and yields data – a daunting enterprise no matter how much high-speed computing and high-throughput measurements are applied to it.

As a result, transformation has remained a black box of sorts – until now. The team's discovery of Mbd3 means, Hanna said, "that we can finally study the mechanisms of transformation, because we are not dealing with only 1 percent of cells." ■

Clinic Roundup

• **Creabilis SA**, of Luxembourg, said it treated the first patients in its Phase IIb study of lead product CT327, a TrkA kinase inhibitor, in patients with atopic dermatitis. The study is enrolling 210 adult and adolescent patients with mild to moderate atopic dermatitis and at least moderate pruritis, with the primary endpoint designed to assess pruritis using a visual analogue scale and control of disease determined by Investigator Global Assessment. Quality of life measures also will be analyzed. Results are anticipated in the second quarter of 2014.

• **GW Pharmaceuticals plc**, of London, said it started a Phase I trial of GWP42006, a nonpsychoactive cannabinoid, for the treatment of epilepsy. According to clinicaltrials.gov, the study will enroll healthy volunteers, with a primary objective of evaluating safety and tolerability of single-ascending and multiple doses of GWP42006 vs. placebo.

• **Medivir AB**, of Huddinge, Sweden, signed a license agreement with **Grupo Ferrer International SA**, of Barcelona, Spain, for commercialization of Adasuve (Staccato loxapine) in the Nordic region. Adasuve is approved in Europe for mild to moderate agitation of patients with schizophrenia or bipolar disease. Under the agreement, Ferrer will give Medivir rights to promote, market, sell and distribute Adasuve in countries including Denmark, Finland, Norway, Iceland and Sweden. Medivir will be the exclusive supplier of the drug in those regions. In return, it will pay make an up-front payment to Ferrer, plus milestone payments on cumulative sales performance.

Biopharm

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artificial" distinction, since buyers mainly want superiority over standard of care.

"While, for first in class, this may surface early on, for best in class it may surface later, because the differentiator may be something more subtle," he said.

"Are we speaking game changer or are we speaking incremental improvement? Is my platform technology product-specific?" The latter, he said, is "not necessarily a bad thing, but you want to be aware of it" before making a pitch.

Gilead came up again. An audience member puzzled over how the company could pay $510 million for YM Biosciences Inc., of Mississauga, Ontario, just three years after YM gained the lead drug candidate, CYT387, in its buyout of the Australian firm Cytopia Ltd., for just $10 million. (See *BioWorld Today*, Oct. 7, 2009, and Dec. 13, 2012.)

How could the myelofibrosis therapy CYT387 gain so much perceived value in such a short period of time?

An oral Janus kinase (JAK)/JAK2 inhibitor formulated for once-daily dosing, CYT387 proved impressive in a Phase I/II with 166 patients who have the progressive, chronic bone marrow disorder, showing not only improvement in spleen enlargement and constitutional symptoms of the disease but also a strong, unexpected effect on anemia. (See *BioWorld Today*, Dec. 14, 2011.)

"There are components of the continuum in product development that have more and less luster around them," Hiller said, adding that a "novel, hot target" brings the chance of a surprising deal. He used the example of PCSK9, which he allowed was "probably a little dated." But then, maybe JAK inhibitors are, too, and the Gilead takeover of YM – laid alongside YM's of Cytopia – would stay a mystery.

"There's always a dance with the potential buyer around whether you can get them to bite before you get to the next level of data," Hiller said, adding that a "really challenging balancing act" is complicated further by reimbursement concerns.

Those, according to Merck's Munshi, figure strongly. "It's not [about] the science anymore," he said. "It's the payer's perspective. If you have doubt in that equation, all bets are off."

The Biopharm America conference, sponsored by the EBD Group, ends today. ■

IPOs

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pending, including the latest filing by ophthalmology firm Aerie. The Bedminster, N.J.-based firm has not disclosed the number of shares or share price but said in its S-1 that it aims to raise $58 million and to gain a listing on Nasdaq under the ticker "AERI."

Proceeds would be used to support Aerie's ophthalmology pipeline, including AR-13324, a dual-action candidate designed to inhibit both Rho kinase and norepinephrine transporter for treating glaucoma and ocular hypertension, that has completed Phase IIb testing and is slated to move into registrational trials in the middle of next year.

Aerie also has a triple-action drug, PG324, comprising a fixed-dose combination of AR-13324 and prostaglandin analogue latanoprost, a commonly prescribed drug for glaucoma. That program is expected to start Phase IIb testing in early 2014.

As of June 30, Aerie had about $2.4 million in cash and equivalents. ■

Clinic Roundup

• **Viralytics Ltd.**, of Sydney, said that its Phase II trial of Cavatak (coxsackievirus A21) for late-stage melanoma met its primary endpoint of immune-related progression free survival (irPFS) at six months after the first dose. The study aims to enroll 54 patients with late stage (IIIc and IV) malignant melanoma. The goal was to observe 10 patients out of 54 reporting irPFS at six months, and that was achieved after evaluating only 30 patients, with an irPFS rate of 33 percent. There are now 44 patients enrolled, with full enrollment expected by the end of 2013.