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Genzyme To Pay \$1B In Cash, Stock For Renigel Partner GelTex

By Kim Coghill
Washington Editor

Industry analysts say the \$1 billion merger of Genzyme General and GelTex Pharmaceuticals Inc. is a good strategic fit for both companies, given their past joint-venture success selling the dialysis drug Renigel.

Cambridge, Mass.-based Genzyme Monday announced plans to acquire GelTex, a Waltham, Mass.-based company that develops and markets non-absorbed polymer drugs that bind and eliminate targeted substances within the gastrointestinal tract. The transaction is expected to close in the fourth quarter, pending regulatory and GelTex shareholder approval.

Genzyme stock (NASDAQ:GENZ) closed Monday at \$57.69, down \$7.62. GelTex stock (NASDAQ:GELX) closed at \$43.25, up \$5.87.

The deal values GelTex at approximately \$1 billion. The
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HGS Gains Principia's Albumin Fusion Platform For \$120 M In Stock

By Matthew Willett
Staff Writer

Making therapeutics just got easier for protein and peptide leader Human Genome Sciences Inc., thanks to the fusion protein technology the Rockville, Md.-based company gets through its acquisition of Principia Pharmaceuticals.

HGS said Monday it acquired the Norristown, Pa., company in a stock swap worth \$120 million, a price based on a 20-day average of HGS' share price. Principia thus became a wholly owned subsidiary of the aspiring big-pharma company that just last week filed a universal shelf registration with the SEC worth as much as \$1 billion.

That registration's stated purpose was acquisition, and CEO and Chairman William Haseltine said the grab for a "mature technology" isn't likely to be the last from HGS.

"The acquisition helps us and is clearly in the area of
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Cracking Common Drug's Uncommon Secrets

Heparin's Oddest-Ball Molecular Sequence Yields To MIT Biotech Group's Analytical Tool Formula

By David N. Leff
Science Editor

There's a multi-billion-dollar drug – that's been on the market since 1935 – whose composition and mode of action leave the FDA largely in the dark, along with the pharmaceutical industry and the surgeons who inject it every day.

This deep-cover compound is heparin – the across-the-board anticlotting agent of choice. "It's extensively used when you have people undergoing coronary bypass surgery," observed self-styled biotechnologist and heparin researcher Ram Sasisekharan, at the Massachusetts Institute of Technology, "and putting them in extracorporeal devices such as heart-lung and kidney dialysis machines, where you don't want the blood to clot. And heparin is used

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Vertex Plans \$200M Offering, \$175M Note Redemption

By Randall Osborne
West Coast Editor

With seven potential products in Phase II trials, Vertex Pharmaceuticals Inc. said it plans to fuel their development by offering \$200 million in convertible subordinated notes to institutional buyers – and will call for redemption next month of \$175 million worth of convertible subordinated notes issued earlier.

Cash is a "strategic asset" for the company, as it explores multiple ways at once to "exploit the opportunity of the human genome," said Michael Partridge, spokesman for Cambridge, Mass.-based Vertex. The company had \$378 million as of June 30.

The new notes, due (like the earlier ones) in 2007, would be convertible into common stock at the holder's option. Vertex said it will file a registration statement for resale of the notes, and the shares of stock issuable on con-

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post-surgically as well, to prevent thrombus formation – obstruction of blood vessels.”

Heparin – more correctly heparan sulfate – occurs in every tissue throughout the bodies of all mammals. It's expressed on the surface of cells, and in the extracellular matrix between them. It's produced most abundantly in liver, lungs and the intestinal mucosa. The pharmaceutical industry extracts it from this porcine source.

But what it extracts is like no other FDA-approved compound.

“For instance,” explained Ram [as Sasisekharan is known], “if you had a protein drug like EPO [erythropoietin], the first thing the FDA asks for is the precise molecular composition of what's in a vial of EPO. Imagine that all one could do was extract it from serum and say, ‘Contained in that vial is EPO with such-and-such a biological activity – but there are a lot of other things in it besides.’ So with heparin, you're talking only in terms of fractions in the range of function instead of precise, controlled amounts of material content that correlates with its anti-clotting activity.

“The simple way to picture it,” Ram continued, “is just imagine putting heparin into a food blender and getting smaller fragments of polysaccharides – sugar molecules. You'd end up with a mixture of one-sugar oligosaccharides, dual dodeca, quadruple tetradeca levels. But still each is a fragment of the larger fraction.”

Until a decade or so ago, normal commercial heparin weighed in at 12,000 to 20,000 Daltons molecular weight. Then, in recent years, low-molecular-weight versions emerged, tending to fall in the category of around 6,000 D. “That's where we are with low-molecular-weight heparin [LMWH],” Ram pointed out. “Still dealing with it in an analogous fashion in terms of extract purity and consistency.”

Ram is senior author of two back-to-back papers in today's *Proceedings of the National Academy of Sciences (PNAS)*, released Sept. 12, 2000. Their respective titles: “Sequencing of 3-O sulfate containing heparin decasaccharides with a partial antithrombin III binding site,” and “Cleavage of the antithrombin III binding site in heparin by heparinases and its implication in the generation of low molecular weight heparin.”

Clot-Busting Depends On Thrombin-Blocking

A deficiency of antithrombin-III (AT-III) prevents inhibiting the clotting factor, thrombin, causing recurrent thromboses. When heparin binds to AT-III, its action increases several fold. Ram's first *PNAS* paper revealed that analysis of heparin fragments generated in a fashion similar to the first American LMWH, Dupont-Merck's Tinzaparin, released last July, points to the fact that AT-III is cleaved off. It does not contain the intact AT-III binding decasaccharide (10-sugar unit). “These serious quality-control issues,” Ram

said, “arise because there has been no way to put a finger on the exact composition-activity relationship of either the high or low MW heparins.”

He and his co-authors have activated that analytical finger. Their novel tool is based on the fact,” he observed, “that the heparin field has lagged far behind the mainstream work on DNA and proteins. That's because the complex sugars have many more building blocks than their better-known cousins. DNA relies on four nucleotides – adenine, cytosine, guanine and thymidine (A-C-G-T). Proteins depend on the 20 essential amino acids. Heparin's sugars consist of 32 building blocks.

“Our MIT analytical tool,” Ram went on, “is a quick, easy way to determine the structure, or order of building blocks, in these sugars. Once you have their sequence for a given polysaccharide,” he added, “you can start cracking its function in the body.

“So we developed,” he recounted, “what we called a binary or alphanumeric code, which is the sort of language the computer uses. One particular code would contain additional characteristic information – as for instance the building blocks that make heparin are sulfated in different positions. So the tool we fashioned was a way to translate that data in a single code so the computer could very easily handle that information. Essentially packaging as much information as possible in a code, rather than just one alphabetical character, as a way to visualize a heparin building block.”

Heparin's Rap Sheet Foretells Its Down Side

Given its highly variable and unpredictable content, clinical heparin is not without its side effects, mainly hemorrhage and bleeding.

“Also,” Ram observed, “there's a very specific autoimmune indication known as heparin-induced thrombocytopenia. In this whole mixture of heparin, only between 20 and 30 percent – depending on how you prepare it and who prepares it – has an active anticoagulant ingredient. The rest of the mix has nothing to do with its clot-curbing function.

“But we're now beginning to understand that heparin also plays a role in modulating numerous growth factors and cytokines found in blood. One such molecule is platelet factor 4 – one of the original products that Repligen has brought to market. Heparin forms a complex in the blood with PF4, to which the body raises autoantibodies – the makings of an autoimmune disease.

“Another big problem associated with heparin [is that] its fragments not involved in anticoagulation, precipitate osteoporosis in patients,” said Ram. “Moreover, it's been demonstrated in the last year or two that in the brain, proteins get deposited on the surface of neurons, and form a big complex with these heparin-like sugars. That leads to the amorphous amyloid texture of amylo-

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Vertex

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version, within 90 days of the offering's closing, which is expected later this month.

Proceeds will fund clinical trials, preclinical studies and research and development, as well as working capital, general corporate purposes and investments in technologies to further an approach called "chemogenics," which uses structural similarity of targets in the same family, such as kinases.

"It's parallel drug design, on multiple targets simultaneously," Partridge said.

Kinase research is the focus of a potential \$800 million chemogenics deal signed earlier this year with Novartis Pharma AG, of Basel, Switzerland. Vertex has another agreement, expanded last year, with Aventis SA, formerly Hoechst Marion Roussel AG, of Frankfurt, Germany, to develop HMR 3480/VX-740, an orally active inhibitor of Interleukin-1 beta converting enzyme, for three different indications, one of which is rheumatoid arthritis. (See *BioWorld Today*, Sept. 2, 1999, p. 1, and May 10, 2000, p. 1.)

Regarding the earlier notes, Vertex said it expects to mail on or before Sept. 15 a notice to call for redemption in October. The company had planned to offer \$200 million worth in the spring, Partridge said. (See *BioWorld Today*, March 6, 2000, p. 1.)

"We raised \$175 million, the most we've ever raised in one offering," Partridge said. "This was the second week in March, right when the biotech market was just turning [down]. After that, there weren't any offerings done."

Until redemption time, holders may instead convert their notes into common stock. Vertex noted that, given the current price of the shares (NASDAQ:VRTX), which closed Monday at \$74.11, down \$12.08, conversion is more likely than redemption.

Holders opting to redeem will get \$1,000 per \$1,000 of the principal amount of the notes, plus interest and a "make-whole" payment of \$82.14 per \$1,000, or \$14.4 million in total.

Those who convert, on the other hand, can get shares at a price of \$40.32 per share, or about 24.8 shares per \$1,000, after adjustment for the 2-for-1 stock split paid in the form of a dividend in August.

Converting all the notes would mean Vertex will issue

about 4.3 million shares of common stock, which would give the company about 58.3 million shares outstanding. In the much less probable event that no shares are converted, Vertex will pay redemptions of \$175 million, plus interest, in addition to the \$14.4 million make-good amount.

"We intend to redeem following the first interest payment, which is on Sept. 14," Partridge said. "That allows us to reduce the make-whole payment." Vertex posted revenues of \$61.65 million last year, with a net loss of about \$41 million, or \$1.61 per share. The company's first approved product is Agenerase (amprenavir), an HIV protease inhibitor, co-promoted by London-based Glaxo Wellcome plc.

Among the drugs in Phase II trials, "probably the drug closest to entering Phase III is VX-175, a pro-drug of Agenerase," Partridge told *BioWorld Today*. "It's more compact dosing. There may be some other clinical benefits we can establish as well, but that's the most obvious feature."

VX-175 is expected to enter Phase III studies by the end of the year, Partridge said. Close behind it in the pipeline is VX-497, for hepatitis C, being tested with interferon-alfa. "It's an inhibitor of an enzyme that regulates guanine nucleotides, which cells use for proliferation and infecting cells use for replication," Partridge said. ■

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dosis - which leads to the beta-amyloid plaques of Alzheimer's disease.

"The new analytical tool will enable us now to tackle the composition and sequences of these sugars associated with amyloid formation. Once we know what they are, we can start designing drugs to target those sequences.

"We're focussing right now in the area of angiogenesis and cancer biology," Ram said. "What you see in amyloid formation also appears in tumor cells. They rapidly change the sugar composition so that they become extremely metastatic. So we're now trying to identify composition and sequences of how normal cells become transformed cells in sugar-associated transformation. Then we can hopefully come up with newer ways to develop anticancer and antimetastatic drugs." ■

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