BIOWORLD™ TODAY

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PANEL NOTES GI SAFETY ISSUES

Merck, Alk-Abello's ragweed tablet, Ragwitek, glides through FDA panel

By Randy Osborne, Staff Writer

Qualms about gastrointestinal safety and lack of data in older age groups did not deter the FDA's Allergenic Products Advisory Committee from giving its nod to recommend approval of Ragwitek, the sublingual ragweed allergy therapy for adults from Merck & Co. Inc. and Alk-Abello A/S.

The committee voted 6-2, with one abstention on the matter of whether the available efficacy data support approval of Ragwitek for patients 18 to 65, but the naysayers told the FDA they would have voted yes if the question had been worded to specify

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Idenix raises $106.7M war chest for clinical trials, patent litigation

By Marie Powers, Staff Writer

Shares of Idenix Pharmaceuticals Inc. (NASDAQ:IDIX) climbed steadily on Tuesday after the company disclosed that it plans to sell 16.4 million shares of common stock at $6.50 apiece to entities managed by the Baupost Group LLC. The hedge fund increased its stake in Idenix from 27 percent to approximately 35

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REGULATORY

Patents critical component to development of innovative drugs

By Mari Serebrov, Washington Editor

If Congress wants a healthy biopharma sector that continues to produce innovative therapies to cure the world's ills, it needs to ensure that those therapies have strong patent protection.

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ASIA

Today in *BioWorld Asia*

Actavis plc drops China to focus on other markets, sells local operations to Chiral

Shenzhen Kangtai Biological Products Co.'s HBV vaccine cleared of links to 17 dead children, back on market

Bayer AG doubles down on Chinese innovation, sets up second R&D center

Feng Shui masters bullish on markets

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NEWCO NEWS

Tunitas fusion proteins take double aim at allergic disease

By Marie Powers, Staff Writer

Although Tunitas Therapeutics Inc. has its namesake in California's Tunitas Creek, which meanders from the Santa Cruz Mountains to the Pacific Ocean, the company's progress has been anything but a long and winding road.

Established early in 2009 by Nolan Sigal, president and CEO, and Andrew Saxon, acting chief scientific officer, the San Francisco-based biotech is developing a family of fusion proteins that interact with two receptors on a number of key allergic cells.

The technology inhibits the release of both mediators, such as histamines and leukotrienes, as well as cytokines produced by those cells. Over a longer period of time, the proteins turn off IgE production, the key trigger for allergic disease.

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OTHER NEWS TO NOTE

Aegerion Pharmaceuticals

Ariad Pharmaceuticals

Emergent Biosolutions

Hapten Sciences

Provectus Biopharmaceuticals

Vaxinnate

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THE BIOWORLD BIOME

LATITUDE-BASED VACCINES?

Cutting off sugars may enable broad-spectrum flu vaccine

By Anette Breindl, Science Editor

Scientists from the Taiwanese Academia Sinica reported that they have developed an influenza vaccine that was broadly protective in mice and ferrets by focusing

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Asia

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for Year of the Horse, not so much for biopharma

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OTHER NEWS TO NOTE

Aegerion Pharmaceuticals Inc., of Cambridge, Mass., is facing class action litigation filed by law firm Lieff Cabraser Heimann & Bernstein on behalf of purchasers of the company's securities between March 15, 2012, and Jan. 9, 2014. The action alleges that the defendants made false and/or misleading statements and failed to disclose material adverse facts about Aegerion's business, operations and its prospects, specifically that the firm marketed its drugs in violation of the Federal Food, Drug and Cosmetic Act and, as a result, faced heightened scrutiny by the FDA and other governmental bodies. According to the law firm, news reports revealed in Nov. 8, 2013, that CEO Marc C. Beer had received an FDA warning letter regarding statements he reportedly made regarding Juxtapid capsules during broadcast interviews on CNBC's "Fast Money," airing June 5, 2013, and Oct. 31, 2013. Subsequently, the company received a subpoena from the U.S. Department of Justice requesting documents regarding the marketing and sale of Juxtapid, sending shares of Aegerion falling nearly 11 percent Jan. 10, 2014. Juxtapid (lomitapide) is approved as part of an adjunct to a low-fat diet and other lipid-lowering treatments in patients with homozygous familial hypercholesterolemia.

Ariad Pharmaceuticals Inc., of Cambridge, Mass., and **Specialised Therapeutics Australia Pty Ltd.** (STA), of Melbourne, Australia, inked a deal, with Ariad granting STA exclusive rights to commercialize Iclusig (ponatinib) in Australia for patients with Philadelphia-positive leukemias. Under the terms, STA will be responsible for obtaining marketing authorization and pricing and reimbursement approval of Iclusig and assisting Ariad in regulatory filings in Australia. The term of the agreement is seven years from the first commercial sale of Iclusig, with an option at the conclusion of that term allowing Ariad to take over commercialization or to extend the agreement with STA. Ariad submitted a marketing authorization application in Australia in the third quarter of 2013. Pending approval, Iclusig could launch in Australia in the fourth quarter of this year.

Emergent Biosolutions Inc., of Rockville, Md., said the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 has expired in connection with the firm's proposed acquisition of **Cangene Corp.**, of Winnipeg, Manitoba. The deal, disclosed last month, is an all-cash transaction valuing Cangene at about $3.24 per share, for an aggregate purchase price of $222 million. (See *BioWorld Today*, Dec. 13, 2013.)

Hapten Sciences Inc., of Memphis, Tenn., has partnered with Particle Sciences Inc., a drug delivery contract development and manufacturing organization, to progress its lead product, a vaccine developed to lessen or eliminate contact dermatitis from poison ivy, oak and sumac exposure, into the clinic. Particle Sciences will manufacture Phase I/II materials for the first human studies, set to start later this year.

STOCK MOVERS 1/28/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$60.77	+2.44%
Alimera Sciences Inc.	+$0.86	+13.96%
Enanta Pharmaceuticals	+$3.34	+11.16%
Idenix Pharmaceuticals Inc.	+$1.17	+17.03%
Onconova Therapeutics Inc.	+$1.56	+13.03%
Regulus Therapeutics Inc.	+$1.03	+13.10%

Biotechs showing significant stock changes Tuesday

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FDA

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"18 to 50 years old" instead.

On the question of whether the safety data suggest the drug should be approved for the 18-to-65 age group, the vote was 8 yes and 1 abstain.

Panelist John Kelso, a physician with the Scripps Clinic's division of allergy, asthma and immunology in San Diego, wanted to know about the effects of higher doses of Ragwitek than Merck, of Whitehouse Station, N.J., and Horsholm, Denmark-based Alk-Abello are seeking in the label.

"We were told that in some of the initial dose-ranging studies, there was a 24-unit dose and a 50-unit dose and that those were abandoned because of high rates of adverse events," Kelso said. "Once these [tablets] are out there, I guarantee you, people are going to be taking two or three of them."

Hendrik Nolte, a consultant and professor at the University of Copenhagen, said that "overall, the safety escalation study was a small number of patients," and described such effects as chest and throat tightness. "None of these are of a serious nature," he said.

"I still have a concern, and I don't know how we incorporate that into the whole approval or recommendation for approval process," Kelso replied. "We don't have a lot of data. We need to have something incorporated in the prescribing that strongly discourages" taking more than the recommended dose.

"Not for this product but for the grass tablets, there must be loads of aftermarket experience" in patients with GI trouble such as eosinophilic esophagitis (EOE), "thought to somehow be a consequence of having been on sublingual immunotherapy" such as the Grastek (approved in Europe as Grazax) provides.

Jennifer Maloney, Merck's director of respiratory clinical development, noted that the grass allergy tablet has been on the market since 2006, and "within the spontaneous reports that have come in, there were two" reports of EOE, out of 175,000 patient treatment years. "There doesn't appear to be a signal," she said.

Kelso conceded that "most patients who develop [EOE] have coexisting genetically atopic disease, such as allergic rhinitis." While it's important to investigate EOE as a possible side effect, he said, the FDA should "at least acknowledge that it's entirely possible" the patients who turned up with EOE came down with it "coincidentally," and not as a result of treatment.

Several panelists wanted post-licensure trials in patients with EOE and other co-morbidities, as well as non-white people. Jane Peterson, professor emeritus of nursing and anthropologist at Seattle University College of Nursing, brought up the subject "just so that they have a real sense of the safety and efficacy of this drug for them."

She was "also interested in adherence and in what happens with interruptions – every day, living it out, not in clinical trials, but what happens to people and how they proceed with the medication."

Andrea Apter, professor of medicine in the pulmonary, allergy and critical care division of the Perelman School of Medicine at the University of Pennsylvania raised the question of long-term tolerability.

"If somebody is allergic to grass and ragweed, they will be on sublingual immunotherapy virtually all year with their mouths itching, perhaps, and it might be something that is very hard to comply with," she said. "It's something to be sorted out."

The same FDA committee last month agreed unanimously that available data supported the efficacy of Grastek for treatment of Timothy grass pollen-induced allergic rhinitis in patients 5 to 65. (See *BioWorld Today*, Dec. 13, 2013.) //

Idenix

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percent of outstanding shares.

Meanwhile, Idenix shares never lost steam, adding $1.17, or 17 percent, to close Tuesday at $8.04.

The registered direct offering, priced at a 5.4 percent discount to Monday's close of $6.87, will net Idenix approximately $106.7 million. The Cambridge, Mass.-based company plans to use the proceeds for clinical trials of its hepatitis C virus (HCV) drugs and for ongoing patent litigation against Gilead Sciences Inc.

The sale is expected to close on or about Jan. 31.

Idenix also granted Baupost board observer rights provided the fund continues to hold at least 25 percent of the company's outstanding common stock. In its prospectus supplement, filed Tuesday with the SEC, Idenix reported 134.3 million common shares outstanding as of Jan. 24.

The offering, combined with cash and equivalents on hand, will see the company into at least the second half of next year. At the 32nd Annual J.P. Morgan Healthcare Conference in San Francisco earlier this month, Idenix CEO Ron Renaud said the company ended 2013 with cash and equivalents of $122 million.

Renaud declined to discuss how the deal came together but described Baupost as "a good long-term investor that shares our vision of how to move the company forward, both on the pipeline side and on the litigation side."

According to Renaud, the top priority for Idenix is its effort to combine lead nucleotide prodrug program, IDX21437, currently in a proof-of-concept study that will report data in the first half of the year, with its NS5A inhibitor, samatasvir (formerly IDX719), which has fast-track designation from the FDA.

"We're really focused on trying to develop a regimen that can be pan-genotypic, once a day, to treat patients with HCV," Renaud told *BioWorld Today*. "Right now there's one company that's focused on a similar regimen, and that's Gilead."

Renaud conceded that Gilead has "a significant lead in the marketplace," requiring Idenix to conduct "much bigger studies than we've seen in the HCV industry" in order to gain ground.

Other studies are moving forward. A year ago, Idenix inked a nonexclusive collaboration with Janssen Pharmaceuticals Inc., a unit of Johnson & Johnson, of New Brunswick, N.J., to develop an all-oral, direct-acting antiviral HCV combination therapy. The partners are evaluating combinations that include samatasvir, once-daily protease inhibitor simeprevir (TMC435, Medivir AB/Janssen Pharmaceuticals Inc.) and TMC647055 – a once-daily non-nucleoside inhibitor in development by Janssen. Idenix currently is enrolling patients in HELIX-2, a 12-week, randomized, open-label safety and efficacy study of the regimen in patients with genotype 1 HCV.

"We're optimistic on that study but we won't have data until the second half of this year," Renaud said.

The company also is weighing whether to combine other drugs in its nucleotide prodrug program with its NS5A "or even, potentially, a nuc-nuc strategy, like we've seen in the HIV setting, which may be more convenient and equally effective" as a pan-genotypic drug, he added.

Idenix is making every effort to slow Gilead on the litigation front, as well. The company continues to pursue two HCV patent interference disputes at the U.S. Patent and Trademark Office (PTO). In March 2013, a PTO appeals board reversed an earlier decision, concluding that Foster City, Calif.-based Gilead was first to file for the once-daily oral nucleotide analogue sofosbuvir, which the FDA approved in December 2013 under the brand name Sovaldi. (See *BioWorld Today*, March 26, 2013, and Dec. 9, 2013.)

That skirmish centers on Gilead's issued U.S. Patent No. 7,429,572, covering the metabolites of sofosbuvir as well as RG7128 (partnered with Roche AG), and Idenix' overlapping patent application No. 12/131,868. The PTO still must rule on which firm can claim rights to first invention, but as the junior party in the dispute, Idenix now faces a high burden of proof. (See *BioWorld Today*, March 5, 2013.)

In fact, patent interference is just the tip of the iceberg, as Renaud ticked off a list of actions by Idenix against Gilead, including infringement cases filed in Massachusetts and Delaware, an interference case in Delaware and ongoing invalidity actions in Canada, Norway and Australia.

"There are a lot of battles being fought on many fronts here, and these legal expenses can mount pretty quickly," he said, suggesting the cases will play out over several years.

In an industry update issued last week, Leerink Partners LLC analyst Howard Liang noted that, "by our count there are a total of 19 interferon-free regimens" that have demonstrated sustained virological response. Renaud acknowledged the size of the HCV space but said Idenix is focused on treating patients, regardless of genotype, with a single, daily pill while most competitors – Gilead aside – are focused on genotype 1.

Over the past 12 to 18 months, the company also began to mine its compound library "to see what can be leveraged to go beyond virology," he added, suggesting potential applications in other areas of infectious disease as well as oncology, where the company's targeting approach may reduce systemic exposure and related toxicity.

"But we are committed to getting HCV right first," Renaud emphasized. "These explorations into non-HCV therapeutic areas are still very early days."

In other financings news:

Aastrom Biosciences Inc., of Ann Arbor, Mich., said it entered a stock purchase agreement with Lincoln Park Capital Fund LLC for the right to sell up to $15 million in common stock over a 30-month period, subject to certain limitations. The agreement enables the company to sell shares from time to time on market-based terms. Aastrom will control the timing

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Patents

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That's one of the takeaways from a new Congressional Research Service (CRS) analysis of the U.S. biopharma patent scene in the wake of last year's Supreme Court ruling in *The Association for Molecular Pathology v. Myriad Genetics Inc.*

In striking down the patent eligibility of isolated DNA, the court's unanimous decision threatened to erode the underpinnings of numerous diagnostic and biologic patent claims and created a lot of uncertainty about other gene-based claims. (See *BioWorld Today*, June 14, 2013.)

Although the decision explicitly upheld the patent eligibility of complementary DNA, the Supreme Court provided no guidance to lower courts on how to apply the ruling to other biologic products, such as antisense DNA, microRNA, nucleic acids, proteins and stem cells, CRS noted. The lack of guidance undoubtedly will lead to more litigation.

While many claims were endangered by the ruling, the overall impact hasn't been as disastrous for biopharma as some had predicted, Lawrence Sung, a partner at Wiley Rein LLP, told *BioWorld Today*.

"The industry had been preparing for that decision for quite some time," he said. As a result, companies were able to develop workarounds and rely on other claims to protect their products. For instance, in the seven months since the decision came down, Myriad has sued several companies for infringing other claims related to the BRCA1 and BRCA2 genes, which are used in breast and ovarian cancer diagnostics.

That's not to say the ruling hasn't had consequences. One of the more direct impacts is at the Patent and Trademark Office (PTO), Sung said, where examiners are more emboldened to reject claims as they try to apply the court's ruling beyond the scope of *Myriad*. That is causing delays and increased costs as biotechs are forced to challenge PTO decisions and rework their claims.

The decision also has dampened the promise of personalized medicine by making it more difficult for bioinformatics companies to patent information about biomarkers and their correlation to specific conditions.

Since *Myriad*, Sung said, there has been somewhat of a withdrawal of investments from biotechs that rely solely on biomarker discovery. However, many of those companies are being acquired by big pharma, which understand the value of that information. As a result, biomarker information, which once would have been disclosed in a patent, is now being closely protected as a trade secret.

The same sense of secrecy may now shroud early stage academic research. Since discovery of a promising DNA sequence can no longer be patented, researchers are more apt to keep their work quiet until it advances to a level that produces patent-eligible claims, Sung said.

Anything that makes it harder to patent a claim provokes trade secret mentality, which means the public loses since other researchers are denied knowledge of that discovery early on, he added.

RELIANCE ON PATENTS

Moreso than any other industry, biopharma relies on patents to attract the investment needed to fund costly R&D, CRS found. It noted that for every dollar spent on early academic research or discovery, upward of $10,000 may be needed in private funding to develop the early stage work and bring it to market.

The report cited several studies that indicated 65 percent of biopharma inventions wouldn't have made it to market without patent protection, whereas about 8 percent of innovations in other industries would have been derailed without patent protection.

Although new drugs are costly to develop, they can be relatively cheap to copy, according to the report. That's why patents are needed to protect the innovator's R&D investment and level the playing field a bit. Drug patents can raise the cost of developing a copy 40 percent by forcing developers of me-too drugs to license the intellectual property or invent around the claims.

In comparison, patents contribute about 30 percent to the cost of imitating major new chemical products and 25 percent for other chemicals. For electronics, patents add about 7 percent to 15 percent to the cost of developing a copy.

"To date, the U.S. system of research, development and commercialization has had a clear impact on the pharmaceutical and biotechnology industries. . . . Now with the decision in *Myriad*, it remains to be seen what the effect may be on research and development in this area and on innovation in the health care arena," CRS concluded. //

OTHER NEWS TO NOTE

Provectus Biopharmaceuticals Inc., of Knoxville, Tenn., and Xenotech, a preclinical contract research organization, said an article published in *Xenobiotica* indicated that the risk of PV-10 causing clinically relevant drug-drug interactions is likely minimal. PV-10, a 10 percent solution of rose Bengal, is designed to target and destroy cancer cells without harming surrounding healthy tissue. The preclinical work was undertaken prior to initiating of the now-ongoing Phase I study testing the intralesionally administered drug in combination with Nexavar (sorafenib, Amgen Inc. and Bayer AG) in hepatocellular carcinoma patients.

Vaxinnate Corp., of Cranbury, N.J., said it received $2.1 million in nondilutive financing through New Jersey's Technology Business Tax Certificate Transfer Program. This is the fifth year that the company has been selected to participate in the program, a state initiative designed to spur innovation and job creation by assisting promising early stage biotech, life sciences and technology firms. Vaxinnate said it will use the funds to continue its research and development of vaccines to prevent infectious diseases, including seasonal and pandemic flu, *Clostridium difficile* and dengue.

Tunitas

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Epsi-gam, the company's lead candidate, is composed of the Fc portions of human IgE and IgG1, linking the receptors for IgE on basophils, mast cells and B cells with the FcgRIIb receptor on those cells to inhibit their function. Advanced to investigational new drug-enabling studies, the technology directly inhibits basophil and mast cell function – the primary cellular mediators of allergic disease – by turning off their signaling through the IgE receptor and then suppressing IgE production.

Because Epsi-gam is not allergen-specific, the platform offers the potential advantage of treating multiple food and/or inhalant allergies with a single therapeutic, according to Sigal, who said Phase I studies seeking initial proof of principle could begin late this year. The company, which also has earlier-stage programs in cat and peanut allergen vaccines, previously demonstrated both mechanisms in nonhuman primates.

Saxon, a professor and former chief of clinical immunology and allergy at the University of California Los Angeles (UCLA) School of Medicine, developed the fusion protein platforms in the early 2000s but was frustrated by foot-dragging at the institution's technology transfer office. Sigal, a colleague who began his career as the University of Toronto studying pediatric immunodeficiency and bone marrow transplantation, had since moved to industry. For a decade, he served as head of immunology research at Merck & Co. Inc. before co-founding Pharmacopeia Inc., which was taken public in 1996. In 2000, Sigal joined Cytokinetics Inc., where he spent several years as head of R&D, before taking the helm of Trellis Bioscience Inc.

Around 2007, Saxon contacted Sigal, looking to jumpstart the fusion protein technology.

"I'm sure I wasn't the only person he contacted," Sigal admitted. "I'm sure he went through his entire Rolodex. But we reconnected."

The reacquaintance was providential. After meeting nearly weekly for several months, Sigal recognized in Saxon's technology the potential to leapfrog allergy compounds in development at the time. Taking a license to the technology from UCLA, Tunitas was born.

With experience in raising capital from venture financings and initial public offerings (IPO), Sigal thought the next step would be the easy part.

"From my track record of building two successful companies, I had assumed – maybe a little naively – that I would call my friends in the venture community and in a couple of months I'd have $10 million in the bank," he said.

Needless to say, that didn't happen. In addition to the crisis in the capital markets, Tunitas confronted a wall of uncertainty about the allergy space, with prospective investors snubbing an indication "that wasn't rheumatoid arthritis, wasn't cancer and wasn't Alzheimer's disease," Sigal recalled. "Their view was that the medical need wasn't clear."

The trained academics turned to a funding source they knew intimately. "We rolled up our sleeves and started writing grants," he said.

Tunitas since has attracted $10 million in grant funding, mostly from the National Institutes of Health, and eschewed venture capital altogether. The company has spent only half of that war chest advancing its lead protein into preclinical development, with the remainder providing a potential runway of two to three years.

"We still have a lot of research money to take other products in our platform and move them to the point where we will nominate molecules for formal preclinical development," Sigal said. "Having been born and bred at Merck, I think of this in a little bit more formal way than a lot of biotech companies. It's a very rigorous nomination process."

In the meantime, the allergy space has witnessed "a sea change" in the potential commercial opportunities associated with unmet medical need, while pharmas and investors have grown curious about the company's technology in light of its eight-figure grant funding, he added.

Tunitas has plenty of company in allergy development. A search on Cortellis Clinical Trials Intelligence shows that nearly 150 allergy compounds are in development, most at biotechs and pharmas rather than academic centers. Of those, only 15 are reported to have progressed to Phase IIb or beyond. Circassia Ltd., ALK-Abello A/S, Cytos Biotechnology Ltd., Circassia Ltd. and Stallergenes SA are among the biggest names in allergy development, but promising newcomers include DBV Technologies SA, Immunomic Therapeutics Inc., Sitari Pharmaceuticals Inc. and Immusant Inc. (See *BioWorld Today*, Dec. 14, 2011, March 8, 2013, Oct. 21, 2013, and Nov. 22, 2013.)

Because the Epsi-gam platform, targeting allergic asthma, will require large trials, "we know we will partner that out," Sigal said, "but we'd like to keep it as long as possible to increase its value."

With that goal in mind, Sigal is considering venture funding as the next step in the financing plan. Although he's "fairly agnostic" about fundraising options, Sigal suggested an ideal scenario would be a $5 million to $6 million venture round – "with the right syndicate of investors who would add value to the company" – to provide initial clinical data that would attract a more advantageous pharma or venture deal to fund Phase II studies.

Either way, "the most important thing right now is to get our initial drug into trials and see whether it works," he added. "We have enormous confidence that it's going to work, but you never know until it actually does."

The company has a timetable for the Phase I study, but execution is "dependent on financing," Sigal said. The initial trial, in Australia, could begin as early as the fourth quarter, with top-line data reporting in early 2015.

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Vaccine

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not on the amino acid sequence of the vaccine antigen, but on how many sugars were attached to those amino acids.

The addition of sugars, also called glycosylation, is one form of post-translational modification, and serves a variety of functions, from stabilizing proteins to helping them fold correctly.

And by luck or design, one function of glycosylation of flu virus proteins is to hide conserved sequences from the immune system.

"When we compare the amino acid sequence of hemagglutinins among different strains, the sequences near glycosylation sites are more conserved," Che Alex Ma told *BioWorld Today*. Ma is at the Academia Sinica and a corresponding author of the paper detailing the vaccination strategy, which appeared in the Jan. 27, 2014, advance online issue of the *Proceedings of the National Academy of Sciences*.

Hemagglutinin is one of the two major viral proteins used to classify influenza viruses, and one of the antigen components of flu vaccines.

Such vaccines currently need to be developed annually, because many parts of the flu virus change very rapidly. But the need for a broad-spectrum flu vaccine is clear and only becoming more urgent. Even for seasonal flu strains, annual vaccination presents a range of problems.

Predicting which flu strains will actually cause the biggest clinical issues in a given season – as much art as science – is followed by possible challenges in making a vaccine to those strains, and then the scramble to get that vaccine distributed and convince people to get their shots. If the distribution part worked out and their doctor has vaccine, that is.

Even when the system works as it is supposed to, it may not lead to particularly effective vaccine. Effectiveness is dependent on how well researchers have been able to predict the most dangerous flu strains at the beginning of the annual process. And some scientists now suggest that for large countries like China, circulating strains are so geographically diverse the optimal strategy would be to develop different vaccines for different latitudes.

The biggest public health threat, though, is the specter of a highly pathogenic flu strain causing a pandemic. Which strain has been most worrisome to public health officials over the years has varied. Recently, top honors have gone to avian influenza strain H7N9, which, according to World Health Organization updates, is now causing new infections in China on a daily basis.

H7N9's fatality rate is about 25 percent. Like the even more lethal H5N1 strain that is also a pandemic candidate, it does not spread easily from human to human, or even particularly easily from birds to humans. But while H5N1 is as deadly to chickens as it is to humans, H7N9 is mostly harmless to birds – and that means this particular strain can spread undetected in poultry markets whose offerings are a staple of dietary protein for many Chinese individuals.

Earlier in January, the United Nations' Food and Agriculture Organization (FAO) warned of the need to be vigilant with respect to possible cases of H7N9 infection during the upcoming Chinese New Year celebrations, as "millions of people and poultry are expected to be on the move and many households will slaughter poultry at home to celebrate the New Year."

The realization that manipulating the glycosylation patterns may enable the development of a broad-spectrum vaccine, Ma said, was "an accidental discovery when we studied the roles of glycans in influenza virus infection."

He added, "We did not anticipate reduction of glycans would lead to better protection." But when the team removed sugar groups that did not affect protein folding from recombinant hemagglutinins, the proteins induced better cross-protection to different strains of the flu in both mice and ferrets.

The Academia Sinica is in a licensing deal with Opko Health Inc., which hopes to develop a broad-spectrum flu vaccine based on the approach.

And the relevance of the findings may not be limited to the flu. Ma pointed out that "viruses such as HIV and HCV are highly glycosylated and currently without good vaccines." //

Tunitas

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A member of the University of California San Francisco's California Institute for Quantitative Biosciences, or QB3, network, Tunitas keeps a low burn rate by accessing shared lab space and other research facilities. The company employs eight scientists and uses collaborators for other development and manufacturing work. In December 2013, Tunitas inked an agreement with DSM Pharmaceutical Products, of Parsippany, N.J., the manufacturing and technology business of Royal DSM, to begin process development for its lead Fc fusion protein.

Long term, Tunitas will consider a variety of options, including partnering other assets in the pipeline or taking the company public through an IPO.

"As a young company, you can't rule out any avenue," Sigal said. //

CLINIC ROUNDUP

Cancer Research UK, of London, said its Drug Development Office launched a new clinical trial to treat lymphoma patients using the body's own immune system to attack cancerous B cells growing out of control. Specifically, the study will test antibody DI-B4, which is designed to target a molecular marker specific to B cells and cells destined to become B cells. About 40 patients will be enrolled, and the study will last four and a half years, with an 18-month follow-up.

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and amount of any common stock sale to Lincoln Park, which is obligated to the purchases, with no limitations on the price per share, use of proceeds or other restrictions. Aastrom said it plans to use the facility to advance its Phase IIb Ixcell-DCM trial in patients with advanced heart failure due to ischemic dilated cardiomyopathy and for other corporate purposes. On Tuesday, the company's shares (NASDAQ:ASTM) gained 19 cents to close at $3.61. (See *BioWorld Today*, March 28, 2013.)

Alimera Sciences Inc., of Atlanta, said it obtained commitments from institutional investors to purchase 6.25 million shares of its common stock at $6 apiece for proceeds of $37.5 million. The private placement is designed to provide working capital to support continued commercialization of Iluvien (fluocinolone acetonide intravitreal insert) in Europe and to continue to pursue FDA approval of the drug. The transaction is expected to close the week of Jan. 27. Cowen and Co. LLC served as sole placement agent. On Tuesday, the company's shares (NASDAQ:ALIM) gained 86 cents to close at $7.02.

Celladon Corp., of San Diego, lowered the proposed deal size for its initial public offering (IPO), disclosing in an S-1/A filed Tuesday that it will seek to raise $40 million by offering 5 million shares at $8 apiece. The company granted underwriters a 30-day option to purchase up to an additional 750,000 shares to fill overallotments and said existing stockholders, officers and directors indicated interest in purchasing up to approximately $11.6 million in shares at the offering price. In its initial filing in October 2013, the company indicated it would seek to raise up to $86.25 million. Celladon postponed its IPO a month later, citing poor market conditions. Filing as an emerging growth company under the Jumpstart Our Business Startups Act of 2012, Celladon plans to list on Nasdaq under the ticker "CLDN." Barclays is the sole bookrunner on the deal. (See *BioWorld Today*, Oct. 14, 2013.)

Eagle Pharmaceuticals Inc., of Woodcliff Lake, N.J., set terms for its initial public offering. In an S-1/A filed with the SEC, the company said it will seek to raise $52.8 million by offering 3.3 million shares in a range of $14 to $16. The company granted underwriters a 30-day option to purchase up to 500,000 additional shares to fill overallotments and said principal stockholders and their affiliates indicated interest in purchasing up to approximately $10 million in shares at the offering price. In its filing, the company reported 10.6 million shares of common stock outstanding as of Dec. 31, 2013. Eagle, which filed as an emerging growth company under the Jumpstart Our Business Startups Act of 2012, plans to list on Nasdaq under the ticker "EGRX." Piper Jaffray and William Blair are joint bookrunners on the deal.

Epizyme Inc., of Cambridge, Mass., filed an S-1 with the SEC seeking to raise up to $140 million in an underwritten public offering. The company did not disclose the number of shares or offering price. Citigroup Global Markets Inc., Cowen and Co. LLC and Leerink Swann LLC are acting as joint book-running managers, which will also include common stock offered by other shareholders. Epizyme said it will use proceeds it receives to fund a portion of its share of the global development costs for DOT1L histone methyltransferase inhibitor EPZ-5676, partnered with **Celgene Corp.**, of Summit, N.J., including costs of the expansion stage of the ongoing Phase I trial in adult acute leukemia patients with mixed lineage leukemia-rearranged (MLL-r) gene and adult acute leukemia patients with MLL-partial tandem duplication and of its planned Phase Ib trial in MLL-r pediatric patients. Epizyme also plans to fund

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a portion of its share of U.S. development costs for EPZ-6438, including costs of its planned Phase II trial of EPZ-6438 in non-Hodgkin lymphoma patients with EZH2 point mutations and its planned Phase II trial of EPZ-6438 in synovial sarcoma. In addition, Epizyme will seek to fund additional R&D efforts to build its product platform and advance its preclinical pipeline. The company reported 28.5 million shares outstanding as of Dec. 31, 2013. On Tuesday, the company's shares (NASDAQ:EPZM) lost $1.84 to close at $31.20. (See *BioWorld Today*, April 26, 2012, and Jan. 8, 2014.)

Igenica Inc., of Burlingame, Calif., said it raised $14 million in a Series C extension, bringing the total round to $47 million. The company's major investors participated in the round, including the Column Group, 5AM Ventures, Orbimed and Third Rock Ventures. Igenica said the funds will be used to advance lead compound IGN523 through early clinical trials aimed at safety and clinical activity assessments in acute myelogeneous leukemia. (See *BioWorld Today*, June 13, 2012.) //

CLINIC ROUNDUP

Cell Therapeutics Inc., of Seattle, said the Gynecologic Oncology Group told the firm it completed patient enrollment in the GOG-0212 Phase III trial testing Opaxio (paclitaxel poliglumex) as a maintenance therapy in ovarian cancer. The study is testing monthly Opaxio or paclitaxel for up to 12 consecutive months, compared to surveillance among women with advanced ovarian cancer who have no evidence of disease following first-line platinum-taxane-based therapy. The primary endpoint is overall survival, while secondary endpoints include progression-free survival, safety and quality of life.

Cytodyn Inc., of Vancouver, Wash., said it plans to expand its clinical program for PRO 140 and inked a deal with Amarex Clinical Research LLC to prepare two Phase IIb trial protocols to explore additional therapeutic indications. One of those protocols is expected to be completed in first quarter of 2014 and the second is expected in the second quarter. PRO 140, designed as a viral entry inhibitor, is a humanized monoclonal antibody directed against CCR5.

Nymox Pharmaceutical Corp., of Hasbrouck Heights, N.J., said its two pivotal studies – NX02-0017 and NX02-0018 – have completed enrollment. The trials are testing NX-1207 in benign prostatic hyperplasia. Unblinding and data analyses of the studies will commence in the second quarter of this year. In Europe, patient recruitment is ongoing in a Phase III blinded comparator-controlled trial under the sponsorship of European licensing partner **Recordati SpA**, of Milan, Italy. Nymox also is testing the drug in a Phase II study for localized prostate cancer, with results from that trial expected near the end of this quarter or early next quarter.

Therapeuticsmd Inc., of Boca Raton, Fla., reported final pharmacokinetic results from two studies of TX 12-004-HR, a rapidly acting vaginal preparation capsule, vs. Vagifem (estradiol vaginal tablet, Novo Nordisk A/S), showing substantially lower systemic estradiol exposure of TX 12-004-HR compared to Vagifem. The maximal concentration of TX 12-004-HR estradiol was about half that observed with Vagifem and the overall exposure to estradiol was approximately one-third that observed with Vagifem. The company said it will use those results to submit to the FDA a clinical plan for TX 12-004-HR for the treatment of vulvar vaginal atrophy in postmenopausal women.

Vaxil Biotherapeutics Ltd., of Ness Ziona, Israel, said it recruited the first patient for a study, VAXIL-010, testing therapeutic vaccine Immucin in patients with metastatic breast cancer. The trial will include up to 20 patients with metastatic breast cancer displaying cancer marker MUC1, who will receive 12 injections of Immucin in combination with hormone therapy.

PHARMA: OTHER NEWS TO NOTE

Les Laboratoires Servier, of Paris, and Curie-Cancer, the body which leads the Institut Curie's industry partner research activity, said they renewed their partnership with the aim of identifying therapeutic targets for treating triple-negative breast cancers. The partnership will continue for a further three years. Financial terms were not disclosed.

U.S. PATENT DISCLOSURES

Adocia SAS, of Lyon, France, was issued a U.S. Patent for its BioChaperone polymer, which covers the company's research on chronic wound healing, and in particular, diabetic foot ulcers.

Alitair Pharmaceuticals Inc., of Morristown, N.J., was issued U.S. Patent No. 8,617,602 for its ion exchange resin drug delivery technology, REA.

Alkermes plc, of Dublin, received a notice of allowance for U.S. Patent application 14/032,736, "Prodrugs of fumarates and their use in treating various diseases." The patent covers ALKS 8700, a small-molecule prodrug of monomethyl fumarate for the treatment of multiple sclerosis.

U.S. PATENT DISCLOSURES

Brainstorm Cell Therapeutics Inc., of New York, was issued a notice of allowance for its U.S. Patent application 11/727,583, "Isolated Cells and Populations Comprising Same for the Treatment of CNS Diseases," related to its NurOwn stem cell therapy.

Galectin Therapeutics Inc., of Norcross, Ga., was issued a notice of allowance for U.S. Patent application No. 13/550,962, "Galactose-Pronged Polysaccharides in a Formulation for Anti-fibrotic Therapies." The patent covers composition claims and uses for GR-MD-02, a carbohydrate-based galectin inhibitor compound to treat patients with liver fibrosis in combination with other potential therapeutic agents.

Immunomedics Inc., of Morris Plains, N.J., was issued U.S. Patent No. 8,617,558 for additional claims regarding "Camptothecin-binding moiety conjugates," and No. 8,617,518 with additional claims for "Methods and compositions for improved F-18 labeling of proteins, peptides and other molecules."

Lpath Inc., of San Diego, was issued U.S. patent, No. 8,614,103, "Compositions and Methods for Treating Ocular Conditions." The patent covers its iSONEP program, used in treating ocular conditions including wet age-related macular degeneration.

Neostem Inc., of New York, was issued a U.S. Patent notice of allowance to expand the intellectual property protection for AMR-001, a chemotactic stem cell product enriched for CD34+ cells that treats injury from vascular insufficiency.

Rxi Pharmaceuticals Corp., of Westborough, Mass., received a notice of allowance for its U.S. Patent application covering sd-rxRNAs, the company's self-delivering RNAi compounds, including RXI-109, used in treating fibrosis.

Supernus Pharmaceuticals Inc., of Rockville, Md., received U.S. Patent No. 8,617,600 for Oxtellar XR, a once-daily extended-release oxcarbazepine product.

Therapeuticsmd Inc., of Boca Raton, Fla., was issued U.S. Patent No. 8,633,178, "Natural Combination Hormone Replacement Formulations and Therapies." The patent covers the company's platform technology and TX 12-001-HR, an oral bioidentical 17β-estradiol and progesterone combination drug candidate.

Veloxis Pharmaceuticals A/S, of Horsholm, Denmark, was issued a notice of allowance for U.S. Patent application No. 13/167,420, covering the diurnal-independent administration of Envarsus. The product uses the company's MeltDose technology in evening dosing for kidney transplant patients.