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IMMUNOTHERAPY ROLLS ON

Aduro's $55M series C to fund pancreatic, other cancer trials; adds to J&J agreement

By Randy Osborne, Staff Writer

Fresh from a prostate cancer deal with Johnson & Johnson unit Janssen Biotech Inc. and in the midst of ushering an immunotherapy bid against pancreatic cancer through phase IIb trials, Aduro Biotech Inc. nailed down $55 million in a series C round that should see the privately held company into 2016.

The arrangement with Janssen brought the potential for $365 million, if all milestones are reached. "Of course, a lot of that is downstream, but there was a very significant up-front payment," said Stephen Isaacs, CEO of Berkeley, Calif.-based

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Another 'weight' for Contrave; Orexigen falls on FDA delay

By Jennifer Boggs, Managing Editor

Already trailing approvals of obesity drugs Belviq (lorcaserin) and Qsymia (phentermine/topiramate) by two years, Orexigen Therapeutics Inc.'s Contrave (naltrexone/bupropion) is facing another delay at the hands of the FDA, which pushed back the PDUFA date by three months to Sept. 11.

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THE BIOWORLD BIOME

PUTTING IN THE MIDDLEMAN

Studies show exercise-induced immune control of metabolism

By Anette Breindl, Science Editor

In two separate studies, researchers have identified new links between immunity and metabolism, showing that exercise activates immune cells that can turn

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DEALS AND M&A

Ruiyi, Ihuman GPCR partnership exploits 'classic Chinese scale'

By Marie Powers, Staff Writer

Ruiyi Inc. and the Ihuman Institute forged a research collaboration allowing the upstart educational institution, housed at China's Shanghaitech University, to apply the company's

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REGULATORY

Sovaldi's price haunts search for innovation incentives

By Mari Serebrov, Washington Editor

The specter of more drugs that cost upward of $84,000 hovered over a House subcommittee hearing Wednesday on whether current incentives are adequate to spur development of therapies for unmet medical needs such as Alzheimer's disease.

Since patients with diseases like Alzheimer's need long-term therapy, the FDA generally requires longer trials to assess the safety and efficacy over time for investigational drugs and devices targeting chronic diseases and conditions. With each Alzheimer's trial taking three to five years, developing treatments for the space is a slow process that can eat up much of a product's patent life before it gets to market, Sam Gandy, Mount Sinai professor of Alzheimer's disease research, told the House Energy & Commerce

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CHINA

Wuxi looks to bridge trust gap, get innovative drugs to market faster

By Shannon Ellis, Staff Writer

SHANGHAI – While Wuxi Apptec may be best known for its biologic manufacturing capabilities, it could be overlooked that the firm has ratcheted up its capabilities in clinical drug

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FINANCINGS

Alzprotect, of Lille, France, said it completed a €2 million (US$2.7 million) series A financing round and has been matched by an additional €1 million support from Bpifrance in the form of subsidies and refundable advance payments. The funding will allow the company to accelerate the development of its drug candidate AZP2006 that has demonstrated several preclinical proofs of concept in the treatment of frontotemporal dementia and Alzheimer's disease.

OTHER NEWS TO NOTE

Amarin Corp. plc, of Dublin, published results of a retrospective analysis of patient cases that examined the drug's effect on lipids in hyperlipidemic patients who were switched from Lovaza (omega-3-acid ethyl esters, Glaxosmithkline plc) capsules, to Vascepa (icosapent ethyl) capsules. After the switch, 12 patients experienced a decrease in triglyceride and low-density lipoprotein cholesterol levels and 13 patients experienced a decrease in triglyceride and non-high-density lipoprotein cholesterol levels. Changes in high-density lipoprotein cholesterol levels were also assessed, but the results were mixed, with no change in one patient, decreases in nine patients, and increases in four patients. (See *BioWorld Today*, Jan. 22, 2014.)

Cortexyme Inc., of San Francisco received as much as $350,000 from Breakout Labs, a program of the Thiel Foundation, to develop a diagnostic, treatment-monitoring method, and small-molecule candidates targeting Alzheimer's disease. **G-Tech Inc.**, a Palo Alto, Calif. company developing "a wireless, wearable EKG for the gut" and the New York-based bone reconstruction company **Epibone**, also received awards from Breakout.

Foamix Inc., of Rehovot, Israel, said it established a U.S. subsidiary, Foamix Pharmaceuticals Inc., located in Bridgewater, N.J., to conduct clinical development operations, including planned trials of minocycline foam, that can be used for the treatment of acne, skin infections and rosacea, and to manage regulatory affairs and to build commercial infrastructure.

Nordic Nanovector AS, of Oslo, Norway, gained EMA orphan status for its lead product candidate Betalutin for treatment of follicular lymphoma. The radiotherapeutic is currently undergoing a phase I/II dose-escalation trial in patients with relapsed CD37 positive non-Hodgkin lymphoma. On June 6, the company said it planned to raise up to NOK150 million (US$25.6 million) in a private placement to support further development of Betalutin.

Regeneron Pharmaceuticals Inc.'s development partner **Bayer HealthCare Pharmaceuticals Inc.**, of Whippany, N.J., submitted an application to the EMA to gain EU marketing authorization for Eylea (aflibercept) for the treatment of macular edema following branch retinal vein occlusion. Regeneron, of Tarrytown, N.Y. has exclusive rights to the drug in the U.S., where its seeking approval for the same indication.

Seattle Children's Research Institute and Seattle-based **Kineta Inc.** launched a pediatric research and funding collaboration designed to speed development of new medications for children and teens with lupus nephritis (LN) and other autoimmune diseases like multiple sclerosis, type 1 diabetes and rheumatoid arthritis. The new Alliance for Children's Therapeutics has already begun conducting preclinical tests to advance Kineta's lead compound, ShK-186, as a potential treatment for LN.

STOCK MOVERS 6/11/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	-$2.33	-0.09%
Celladon Corp.	+$1.48	+16.17%
Conatus Pharmaceuticals	+$3.43	+56.69%
Galmed Pharmaceuticals	+$1.35	+15.62%
Orexigen Therapeutics Inc.	-$1.00	-14.68%

Biotechs showing significant stock changes Wednesday

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Aduro

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Aduro. The prostate program is preclinical.

"We feel now that we are very well funded and we can be selective about what we do," Isaacs told *BioWorld Today*. "We don't feel pressure, which is nice for a change, to do any particular deal that we don't like or do a financing that we don't like the terms of."

By the time 2016 arrives, "we see other opportunities for financing the company through traditional and nontraditional channels, and we believe we're going to be able to make the right deal" rather than bow to necessity, Isaacs said. Meanwhile, the pancreatic cancer effort is "our most expensive program" and will "consume a big chunk" of resources, he added.

Proceeds from the series C also will fund clinical development in mesothelioma and glioblastoma, as well as expansion into more indications and advancement of Aduro's small-molecule program targeting the immunomodulatory STING (stimulator of interferon genes) receptor.

Aduro disclosed at the J.P. Morgan Healthcare Conference in January that the phase IIa trial of CRS-207 and Gvax Pancreas in combination against metastatic pancreatic cancer was halted early on the recommendation of the data safety monitoring board and approval by the FDA after the study met the primary efficacy endpoint at a pre-planned interim analysis. (See *BioWorld Today*, Jan. 15, 2014.)

Details of the immunotherapies' success in the 93-patient study rolled out at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium conference earlier this year. The combo garnered a statistically significant survival benefit vs Gvax Pancreas vaccine alone. The median overall survival of the patients receiving the combination turned out to be 6.1 months compared to 3.9 months for those receiving Gvax monotherapy (HR = 0.59, one-sided p = 0.0172). The results formed the basis for the ongoing, randomized 240-patient phase IIb trial called Eclipse in metastatic pancreatic cancer patients who have progressed after at least one line of therapy.

In February of last year, Aduro acquired all the Gvax assets from Biosante Pharmaceuticals Inc., of Lincolnshire, Ill., including intellectual property and cell lines. The set of vaccines is based on human cancer cell lines that are genetically modified to secrete granulocyte macrophage colony-stimulating factor, and initially were developed by Cell Genesys Inc., which was acquired by Biosante in 2009 following disappointing GVAX data in phase III studies. (See *BioWorld Today*, July 1, 2009.)

Aduro previously had licensed rights to two Gvax members – directed at pancreas and prostate cancers – for use in combo with its Listeria-based vaccines. Aduro paid Biosante $1 million up front for the full roster and committed to additional milestone and royalty payments.

CHECKPOINT INHIBITORS? CHECK

The company's platform of live-attenuated double-deleted (LADD) Listeria monocytogenes strains, which drew Janssen to the table, have been engineered to induce a potent innate immune response and to express tumor-associated antigens to induce tumor-specific T cell-mediated immunity.

CRS-207 is one of a family of candidates that grew out of the LADD platform. Aduro engineered it to express the tumor-associated antigen mesothelin, overexpressed in many cancers including mesothelioma and pancreatic, non-small-cell lung, ovarian and gastric cancers.

At this month's ASCO meeting, the company presented data from a phase Ib trial of CRS-207 with standard chemotherapy in treatment-naïve patients with unresectable malignant pleural mesothelioma. Of 16 evaluable patients, 69 percent (11/16) had confirmed partial responses and 25 percent (4/16) had stable disease after CRS-207 and chemo, resulting in an overall disease control rate of more than 94 percent.

In glioblastoma, the company has ADU-623, also from the LADD platform. "There we use two antigens that are overexpressed in that indication," Isaacs said, with a dose-escalation study underway. A program in non-small-cell lung cancer (NSCLC) is in the works, too.

Aduro's combos will be tried in pancreatic cancer with checkpoint inhibitors, too, specifically with an anti-PD1 agent, at Johns Hopkins. "There are disease states where they work very well, such as melanoma, renal cell carcinoma and NSCLC, but there are other diseases such as pancreatic cancer where they don't work very well," Isaacs said. "The thought is that there's not really a T-cell population in the first place to 'take the brakes off of,' in the vernacular. So the major pharmaceutical companies – Bristol-Myers Squibb Co. [BMS], Roche, Merck, Astrazeneca, and so on – are looking for companies that can stimulate that T-cell response, put the army in place, and the checkpoint inhibitors can make sure they continue to have bullets to fight the battle."

The interest in Aduro's combo approach "all flows from the fact that we got efficacy in metastatic pancreatic cancer, which is basically the hardest nut to crack," Isaacs said. "People believe if you can get something there, it's going to be much better in early stage disease. And 94 percent disease control in mesothelioma is beginning to show that the hypothesis has legs."

In pancreatic cancer, the phase IIb trial is "not designed as a registration per se" and the company is making no claims in that regard, "but stranger things have happened," Isaacs said. "We're in the metastatic setting, not in the surgical setting, and about 85 percent of patients who are diagnosed metastatic disease. We almost doubled survival relative to our control vaccine, which was Gvax. If the results hold up, we would hope that would be looked at in the aggregate. We do believe we'll have to do a phase III, but if the data are very good, I'm sure the agency will take note."

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Orexigen

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While frustrating for investors who expected approval on the June 11 PDUFA date and sending shares (NASDAQ:OREX) falling $1, or 14.7 percent, to close Wednesday at $5.81, the news is unlikely to affect the chances for approval. San Diego-based Orexigen said the FDA indicated the extension is intended to provide extra time to reach agreement on the postmarketing obligation related to ongoing cardiovascular outcomes (CVOT) trial.

"This issue came up late in the review, as postmarketing requirement discussions typically do," Preston Klassen, senior vice president and head of global development, explained on a conference call, assuring investors that the postmarketing CVOT obligation was "the issue" on which the FDA was focusing to complete the review of Contrave, which the company now refers to by generic name NB-32.

"I'm confident we'll get the job done," President and CEO Michael Narachi added.

Orexigen execs declined to offer specifics at this time, except to say that the outstanding issue relates to data transparency with the unblinded interim analysis of the CVOT, the safety trial conducted with the agreement of the FDA to satisfy cardiovascular (CV) concerns raised in the 2011 complete response letter (CRL). Since the CVOT is ongoing, the disclosure of those interim data could have an impact on the study. (See *BioWorld Today*, Sept. 22, 2011, and Jan. 9, 2013.)

It's not completely new territory for the FDA, which has reviewed three diabetes drugs based on interim CVOT data since 2008, when CV safety studies prior to approval first were suggested in the wake of negative headlines with Avandia (rosiglitazone, Glaxosmithkline plc) – though the agency has done some backtracking since. (See *BioWorld Today*, July 3, 2008, and Nov. 27, 2013.)

"One of the complexities is how to address data transparency and compliance" when dealing with interim analyses from unblended studies, Klassen said.

He and Narachi referred to three prior diabetes drugs, but declined to identify them by name. Wells Fargo analyst Michael J. Andrews, however, said his firm's research suggest they include Johnson & Johnson's SGLT2 inhibitor Invokana (canaglifozin) and Nesina (alogliptin), a DPP-4 inhibitor from Orexigen's Contrave partner Takeda Pharmaceutical Co. Ltd.

Nesina gained approval on interim data from the EXAMINE CVOT in January 2013 and later went on to complete the EXAMINE trial, with positive results, in September 2013. Invokana was approved after an advisory committee discussed data from its ongoing CVOT study, CANVAS, though J&J opted to start a second CVOT to address postmarketing requirements.

The bottom line, Andrews wrote in a research note, is that "regulatory precedent appears to exist to approve Contrave under either scenario." He added, "Importantly, the delay does not appear related to concern about Contrave's CV profile based on LIGHT data, a positive, in our view."

Contrave is the only obesity drug so far for which a CVOT was required prior to approval. Both Arena Pharmaceuticals Inc.'s Belviq and Vivus Inc.'s Qsymia both have CVOT requirements as part of their postmarketing obligations.

In fact, before the FDA's CRL in 2011, Contrave had looked like the best contender in the obesity space. Belviq and Qsymia had both gotten negative advisory committee (adcom) votes followed by FDA rejections, but Orexigen's adcom went favorably, with panelists voting that the drug's benefit to weight loss outweighed the risks, including heart attacks. (See *BioWorld Today*, Dec. 8, 2010, and Feb. 2, 2011.)

Despite initial reservations, Orexigen launched the onerous and expensive CVOT study, dubbed LIGHT. The FDA later amended its position to allow Orexigen to refile with interim analysis from LIGHT, and data from that analysis last year succeeded in meeting the pre-specified criteria in 8,900 patients who were randomized to Contrave or placebo and monitored for major adverse cardiovascular events (MACE). (See *BioWorld Today*, Jan. 9, 2013, and Nov. 26, 2013.)

In the meantime, Contrave's two competitors got an early jump on the market. Qsymia was launched in September 2012, while Belviq, though technically the first to win FDA approval, got hung up in a protracted Drug Enforcement Agency scheduling process and wasn't launched until a year ago. Neither has gotten off to a good start, however, leaving analysts wondering whether Contrave could suffer the same fate.

NOT A ZERO SUM GAME?

Ironically, Contrave's data from the CVOT may help make the difference commercially. Piper Jaffray analyst Charles Duncan noted in a research report last month that the two main factors impeding market update or obesity drugs are "cost and physicians' and patients' views on risk benefit."

"Accumulating evidence has highlighted the benefits of reducing weight, even by 5 percent, and safety as demonstrated by the LIGHT CVOT should reduce concerns around risk, we believe," he wrote.

In addition to satisfying the FDA, the CVOT data also are expected to position Orexigen for potential approval in Europe, where both Qsymia and Belviq have stumbled. Arena, last year, yanked its marketing authorization application for Belviq amid review by the EMA's Committee for Medicinal Products for Human Use. (See *BioWorld Today*, May 6, 2013.)

Approval in Europe also is expected to help Orexigen land an ex-U.S. partnering deal.

Orexigen has pointed to LIGHT data demonstrating Contrave's safety in roughly 7,600 patients with type 2 diabetes. A Contrave label with a type 2 diabetes claim "and superiority on MACE outcomes has the potential to meaningfully improve reimbursement coverage compared to other obesity drugs," wrote Wells Fargo's Andrews in a May 9 note.

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Metabolism

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energy-storing white fat into one type of energy-burning brown fat.

It's no secret that exercise has beneficial effects on metabolism, and the current studies followed up on earlier work dissecting more direct links between the two. In those studies, researchers had identified irisin as a hormone that is produced by muscle cells during exercise, and stimulated switching of white fat to so-called beige fat cells, which are one type of brown fat. (See *BioWorld Today*, July 30, 2009, and Jan. 12, 2012.)

Irisin's production is stimulated by the transcription factor PGC1-alpha, and an alternative splicing variant of PGC1-alpha induced another hormone, meteorin-like.

"Meteorin-like is elevated with exercise that includes an element of resistance training," especially in muscle cells, Bruce Spiegelman told *BioWorld Today*. Cold exposure, on the other hand, stimulated production of the hormone in white fat cells. Transgenic animals that produced high levels of the hormone also had larger numbers of beige fat cells than wild-type controls.

But when Spiegelman, who is at Harvard Medical School and his team applied meteorin-like to white fat cells in culture, "we did not see browning at all," implying that there must be a middleman of some sort that was mediating the hormone's effects.

The team looked at the effects of transgenic meteorin-like expression in vivo in more details. They found that an increase of meteorin-like also led to an increase in interleukin-10, which is produced by an immune cell type known as M2 macrophages.

Further study, both by Spiegelman's group and by an independent team led by the University of California at San Francisco's Ajay Chawla, identified a "thermogenic circuit" comprised of macrophages, another immune system cell type called neutrophils, interleukin-4, and, at the end, new beige fat.

The two papers exploring those relationships appeared back to back in the June 5, 2014, issue of *Cell*.

The findings shed new light on how the body stimulates the production of beige fat. Classical brown fat – the type possessed by hibernators and newborn babies – is situated in parts of the body that are heavily innervated, and signals from neurons control its activity.

Chawla's group, in fact, approached the thermogenic circuit via the question of how beige fat – which is basically white fat running a brown fat gene expression program – is induced, since white fat tissue is poorly innervated.

Spiegelman said his group's current first order of business is to identify the receptor that meteorin-like signals through.

The findings suggest that the immune system may be a pharmaceutical target for weight control. With a third of Americans now obese, diseases related to obesity being a more serious concern than those related to malnutrition for a majority of the world's population, and incoming ASCO president Clifford Hudis calling obesity "the new tobacco" at the society's recent annual meeting, such new ideas would be welcome additions to the physician's arsenal. Spiegelman is the co-founder of Watertown, Mass.-based Ember Therapeutics Inc., which has licensed his team's findings.

While the exact mechanism is not clear for either of the two currently approved weight loss drugs, Qsymia (phentermine/topiramate) and Belviq (lorcaserin hydrochloride), both target the brain. So does Orexigen Therapeutics Inc.'s Contrave (naltrexone/bupropion), whose PDUFA date was pushed back from June 10 to Sept. 11 by the FDA this week. (See the article in this edition.)

Researchers are also putting their hope in brown and beige fat stimulation as a possible treatment for diabetes. The upcoming annual meeting of the American Diabetes Association, for example, includes a symposium on "Brown Fat, White Fat, Cold Fat, Warm Fat." //

Aduro

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A decade or so ago, "you couldn't get anybody to talk to you" about immunotherapy, Isaacs said. "It's like you were untouchable, but now it's completely flipped, and it's in the sunlight. All these companies like BMS that made deals with companies like Medarex, and people thought, 'Oh how you could possibly pay $2.4 billion for that?' Now it's probably worth 10 times that to them. The point is, look what it's doing for patients. This is what we've all been waiting for." New York-based BMS bought Medarex Inc., of Princeton, N.J., in 2009. (See *BioWorld Today*, Aug. 6, 2009.)

New investor Johnson & Johnson Development Corp. joined the Morningside group and other new and existing investors in Aduro's latest round. Privately held Aduro has raised a total of $84 million from equity financings so far. //

OTHER NEWS TO NOTE

X-Chem Inc., of Waltham, Mass., agreed to use its drug discovery engine for a multi-target collaboration with New York-based **Pfizer Inc.** The collaboration is focused on the potential development of several programs for the treatment of inflammatory and orphan diseases. Pfizer has an exclusive option to license any compounds generated in the course of the collaboration. Financial terms of the agreement were not disclosed.

Ruiyi

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intermembranous conformation antigen presenting system, or iCAPS, technology for the creation of monoclonal antibodies (MAb) that specifically bind to G protein-coupled receptors (GPCR). The goal of the program is to investigate the biological function and structure of GPCRs.

Ruiyi – based in La Jolla, Calif., but with R&D in Shanghai – will benefit from scale, acceleration, data and rights to MAbs emerging from the partnership, according to Paul Grayson, the company's president and CEO. The deal was facilitated, in part, because Ruiyi's scientific founder Ray Stevens also is the founding director of Ihuman. (See *BioWorld Insight*, May 19, 2014.)

"We've been working very closely with Ray and building out our team and our technology to enable the discovery of antibodies to GPCRs," Grayson told *BioWorld Today*. "We hope to create a lot of interesting therapeutics."

Using its iCAPS platform, Ruiyi can isolate and present functional GPCRs in their correct confirmation to identify selective MAb inhibitors or activators with specificity, enabling the development of therapeutics with improved efficacy and safety. The company's lead candidate, RYI-008, is an anti-IL-6 MAb targeting autoimmune diseases and cancer. Ruiyi plans to file an investigational new drug (IND) application for RYI-008 and initiate clinical trials in multiple countries next year.

Ruiyi has a collaboration with Genor Biopharma Co. Ltd., of Shanghai, to develop the antibody in China. (See *BioWorld Today*, May 17, 2013.)

From iCAPS, Ruiyi also identified a second candidate, RYI-018, as its first internally developed MAb. RYI-018 is specific and selective to cannabinoid receptor 1, or CB-1, a commercially validated GPCR target. Ruiyi is advancing RYI-018 through protein engineering and IND-enabling studies, targeting fibrotic and metabolic disease.

RYI-018 "continues to progress and, knock on wood, get better every day," Grayson said. Ruiyi recently completed the antibody's humanization process, which resulted in a fivefold increase in potency rather than the usual loss of affinity and functionality, accelerating "our whole development timeline for the antibody," he pointed out.

Ruiyi's team completed the process from post-target selection to validation in nine months. Using that discovery template, the company has tripled its efforts and now is using iCAPS to generate proteins against three "equally creative and challenging" targets, Grayson said.

But these endeavors represent "the very tip of the iceberg" in terms of the total opportunity in GPCRs, he maintained. Partnering with Ihuman enables Ruiyi to tap into the vastly larger pool of Chinese capital supporting Shanghai Tech, a research university modeled after the Massachusetts Institute of Technology and developed from the ground up by the Shanghai Municipal Government and Chinese Academy of Sciences.

"It is classic Chinese scale," Grayson acknowledged, noting that access to nondilutive funding is "elusive" for small companies in China and even harder for firms without Chinese roots.

Although specific terms were not disclosed, Ruiyi and Ihuman expect to share both risk and potential reward from the partnership. The company granted the institute full intellectual property rights to the platform, which Ihuman will use for co-crystal structure analysis, the discovery of chemical probes and the development of tools to study the signal transduction of GPCR antibodies. Ihuman is focused on the basic and applied science of human cell signaling.

In turn, Ruiyi will have the opportunity to scale from its small team to several hundred Ihuman researchers, with the goal of accelerating its internal iCAPS discovery process from three to 20 targets over the next year. The company also will have access to data generated from the partnership, which will facilitate target selection and antibody discovery. Most important, Ruiyi will have rights to antibodies that emerge from the collaboration for a variety of diagnostic, therapeutic and other uses.

Ihuman's risk is mostly financial, since the institute will foot most of the bill for the research partnership.

"While the platform has shown early success, we don't know if it will be useful for all of the various targets they're going to explore," Grayson said.

For Ruiyi, the greatest risk is "letting the technology out the door and having to worry about where it might end up," he admitted. "But, in this particular case, we firmly believe the rewards are far superior to the risks."

Ruiyi also disclosed a $4 million venture loan from Silicon Valley Bank. Earlier this year, the company closed a $15 million series B round from its existing investors, which include 5AM Ventures, Versant Ventures, Apposite Capital, SR One, Merck Serono Ventures and Aravis SA. (See *BioWorld Asia*, April 2, 2014.)

Ruiyi turned to a debt financing rather than pulling down a tranche from its series B with an eye to extending its financial runway into the second half of 2016.

"The key to financing is finding that right blend of equity vs. debt," Grayson explained. "Debt typically is more expensive, but at the same time you want to make sure you have cash in the bank to get through key inflection points on the value creation curve. Establishing a really close relationship with your bank – especially during times when you have a full account – helps out during those times when you need additional capital to get through those inflection points." //

Congress

Continued from page 1

Subcommittee on Health.

Because of the lengthy development, it's difficult to attract early investment in therapies for chronic diseases, Third Rock Ventures' Alexis Borisy testified at the third hearing on the 21st Century Cures Initiative. (See *BioWorld Today*, May 8, 2014, and May 21, 2014.)

Mike Carusi, speaking on behalf of the National Venture Capital Association, agreed. His firm isn't funding Alzheimer's drugs because the "math doesn't work. We need enough incentive to make the math work," he said.

One possible answer is a proposed 15-year exclusivity for some therapies. Three years longer than the exclusivity granted to novel biologics, the 15-year period would be awarded to "dormant therapies" intended for unmet medical needs under the Modern Cures Act.

While the longer exclusivity could help attract the early investment needed to develop treatments for diseases largely ignored by industry, some lawmakers and experts worried that the end result could be drugs for chronic diseases being priced like Gilead Sciences Inc.'s Sovaldi (sofosbuvir). The small-molecule hepatitis C drug is priced at $1,000 per pill – or $84,000 for the full course of treatment.

If every American eligible for treatment with Sovaldi were given the drug, the cost would equal the country's total annual drug spend, said Steven Miller, senior vice president and chief medical officer for Express Scripts Holding Co.

The economic impact would be even greater if the same pricing structure were used for a drug intended to be used over years by tens of millions of Americans with Alzheimer's or diabetes. "It's no good having drugs people can't afford," Miller said, adding that access must be considered as part of the conversation on exclusivity.

A longer exclusivity would maintain higher prices while discouraging innovation, Rep. Henry Waxman (D-Calif.) said. Too much exclusivity is as damaging as too little, he added, as excessive periods of exclusivity allow innovators to sit back and relax rather than invest in more R&D.

If a longer exclusivity is offered as an incentive, it should be narrowly targeted, Scott Hemphill, a professor at Columbia Law School, said.

IT'S ABOUT THE SCIENCE

Such a lengthy exclusivity also defies science. Fred Ledley, a professor at Bentley University, pointed out that 15 years would be out of proportion given the pace of scientific discovery. Instead, he pushed for incentives that would boost 21st century cures that are based on 21st century science. Under the current system, new therapies, including monoclonal antibodies, are based on 40-year-old scientific discoveries, he said.

One way Congress could help is to better fund basic science through the National Institutes of Health, Miller said. If funding for basic science is choked off, the rest of the development process won't work. The second most important factor to ensuring new cures is improving regulatory certainty, he added.

Currently, 95 percent of drugs in development never make it to market, and 95 percent of patients have no effective therapy, Rep. Fred Upton said.

A lack of regulatory predictability adds to those failures and increases the time and cost of development. When the FDA moves the bar during the development of a product, "millions of dollars are flushed down the drain," Carusi said.

The FDA isn't the only government agency creating uncertainty. Medicare is requiring more and more data to justify device reimbursement, Rep. Jim Matheson (D-Utah) said. The resulting uncertainty is a cost that devicemakers have to cover.

It's difficult to continue funding devices to get the additional data Medicare wants, Carusi agreed.

While investors understand the importance of data, the bar can't be continuously moving. Because of these regulatory problems, Carusi said more venture firms are shifting their investment overseas where the regulatory path, especially for devices, is faster and more predictable.

Regardless of predictability and the incentives the government offers, the best way to attract investment to a space is success. Gandy said once a promising new Alzheimer's therapy is approved, investment will flow into that therapeutic area. //

IN THE CLINIC

Capstone Therapeutics Inc., of Tempe, Ariz. and its joint venture affiliate, Lipimetix Development LLC reported the initiation of dosing for the AEM-28 (Apo E mimetic peptide) phase Ib/IIa trial in refractory hypercholesterolemic subjects who are already on optimal cholesterol lowering therapy but are unable to reach target cholesterol levels. The study is the multiple ascending dose component of a blended phase I/II randomized, placebo-controlled, double-blinded, single center dose-escalation study. The single ascending dose component of the study, in healthy volunteers with elevated cholesterol, began in April, and has progressed through the first five out of six cohorts.

Celator Pharmaceuticals Inc., of Ewing, N.J., said the independent data and safety monitoring board (DSMB) for their phase III study of CPX-351 (cytarabine:daunorubicin) liposome injection vs. the conventional cytarabine and daunorubicin treatment regimen (commonly referred to as 7+3) as first-line therapy in older patients with high-risk (secondary) acute myeloid leukemia (AML) has completed a planned safety review and recommended that the study should continue without any modifications. The assessment was based on a pre-planned safety analysis on the first 150 randomized patients included in the study with a minimum of 60 days of follow-up. The DSMB will conduct additional periodic reviews after 225 patients and 300 patients become evaluable for safety review. The company recently announced that the 300-patient study had achieved 75 percent enrollment.

Wuxi

Continued from page 1

development as well.

This was signaled by the recent hire of Hua Mu as senior vice president of operations and global head of the newly minted Product Development Service and Partnership business unit. Mu gave an exclusive interview to *BioWorld Today* and a glimpse into how the ambitions of Wuxi are driving its expansion from a contract resource organization (CRO) – to a first-of-its-kind fully integrated service platform for companies to discover and develop innovative drugs.

Wuxi has long been a leader in China, being the go-to services provider for many international companies looking to reduce costs while maintaining quality. According to Mu, Wuxi has the largest talent pool for chemists in the world, a reflection of their successful beginnings in the chemical services.

But step-by-step, Wuxi has been putting the pieces together to be much more. According to Mu the "mission is to provide a solution, not just be a simple service provider but more importantly provide a full solution based on client needs."

As a successful drug developer, Mu is keen to bring his skills in the clinic to the service of other companies and share the lessons he has learned. But he goes on to add a point that he has made repeatedly since he joined four months ago: "Wuxi is still a service company and will remain a service company; what I will be doing is not in conflict."

Wuxi's and Mu's prominence has led some to question whether Wuxi has gotten the itch to get into the business of drug development itself.

In his last position at Hutchinson Medipharma Ltd., Mu was chief medical officer and part of a team that obtained five investigational new drug application approvals and one phase II/III CTA approval from the CFDA in four years. A returnee, Mu also spent time at Roche AG, Abraxis Bioscience Inc. (acquired by Celgene Corp.), Biogen Idec Inc. and Genentech, now a part of Roche.

It is these experiences in both small and large molecules that he brings to Wuxi in service to others. "The nature of our work is we are like a biotech company, we are targeting to develop the drug and win regulatory approval. That is our ultimate goal," Mu explained. "The major difference between us and other biotech companies, is conventional biotechs only develop their own drugs, we are helping others to develop their drugs."

While it is well known that the Chinese government is keen to promote homegrown innovation, there is disjuncture in the system as it undergoes reforms to meet the country's substantial unmet medical needs. Wuxi executives said that its integrated platform can bridge the gaps in the Chinese context.

TWO PATHS, BUT WHICH IS FASTEST?

The approval system has two pathways that companies can take. One that requires an imported drug license (IDL) for drugs manufactured outside of the country, and the other is specifically for domestic drugs.

Most large pharmas, for regulatory or business reasons, have had little choice but go down the IDL path and suffer the painful time lags: Drugs in China reach patients on average four or five years and sometimes eight years after they are available in other markets.

Mu is keen to promote the domestic pathway, which he said in theory should be much quicker, but nonetheless has its own challenges.

This is where his new unit comes in, tasked to leverage the full resources of Wuxi's capabilities.

"Big pharma can't use or enjoy the local pathway, while local pharma don't know how to utilize it," Mu noted.

YOU HAVE TO TRUST YOUR PARTNER

One significant hurdle for small biotechs and large pharmas alike is the requirement that the license go with the manufacturer of the drug and not necessarily the patent holder.

"Many Chinese companies are in a awkward situation, they don't have the resources to invest in a manufacturing site and some of them don't want to take a risk or gamble on who will be holding the manufacturing license," Mu said. "You need a trusted partner."

Mu pointed to the several deals at Hutchinson that he experienced firsthand with the likes of Nestle Health Sciences as well as Wuxi's deal with Medimmune (the biologics division of London-based Astrazeneca plc), where the asset to be developed was put into a Chinese joint venture. The local partners, Wuxi and Hutchinson, are responsible for the manufacturing as well.

But the trust issue can loom large, and extends to issues beyond the quality of the clinical development. Mu mentions things as prosaic as different accounting standards in China that can make foreign companies balk at having full co-development agreements that are more prevalent stateside.

"There is huge potential for certain companies. I think China ultimately will revise the policy, but before that, whoever can build the trust of customers will win the game," Mu explained.

Meanwhile local companies have the added challenge of putting together a quality clinical program that will win the regulators' favor – either in China or elsewhere without much experience of doing so. While regulators also lack exposure to approving truly innovative drugs. It's a shaky mix that leads Chinese regulators to be conservative in their approach.

For Mu, developing a quality "clinical plan is both a science and an art." The eight-person team that Mu heads up will be working closely with the 400-person Wuxipra Clinical Research Co. Ltd., a joint venture with a leading international CRO that came online last year.

"CMC, preclinical, biology, MOA, pharmacology efficacy,

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Orexigen

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Also in its favor is the fact that Contrave would not be a scheduled controlled substance, which means it could be given out on a sample basis.

But possibly the biggest advantage is the fact that Orexigen's U.S. partner, Takeda, has committed to an aggressive launch plan. Osaka, Japan-based Takeda, which already boasts a large sales force for its type 2 diabetes drugs, said earlier this year it would have 900 sales reps pitching Contrave to primary care physicians.

That effort positively dwarfs the 150-member sales team at Vivus, the only three of the obesity firms lacking big pharma might, a fact that has led to shareholder discontent at the Mountain View, Calif.-based firm. (See *BioWorld Today*, July 10, 2013.)

Arena's partner Eisai Inc., meanwhile, has been steadily increasing its commercial team. It assembled 200 reps to roll out Belviq last year and later added 200 more. Last month, the Woodcliff Lake, N.J.-based firm announced plans for another 200, bringing the total to 600 reps.

News of Contrave's delay did little to either stock. Vivus' shares (NASDAQ:VVUS) closed flat Wednesday at $5.21, while shares of San Diego-based Arena (NASDAQ:ARNA) gained 22 cents to close at $6.18.

But the "substantial resources" and efforts backed by Takeda could be collaterally beneficial for the entire obesity space, according to Leerink analyst Marko Kozul in a recent note. It could "inject necessary momentum to more appropriately build the obesity market and unlock the large existing revenue potential."

Orexigen's U.S. partnership already has proved lucrative. Takeda paid $50 million up front in 2010 for rights to Contrave in the U.S., and the deal includes up to $1 billion in milestones. The company is expecting about $100 million between approval through first commercial sale, payments that will be delayed due to the PDUFA extension, though Orexigen execs said the firm, with about $155 million in cash, equivalents and marketable securities as of March 31, was in solid financial shape. //

Wuxi

Continued from page 8

pharmacokinetic, safety in animals, clinical plan and protocols – these all have to be put together in a detailed, well-thought out program so CFDA or any regulatory agency will look," he said.

The art may come from some of Mu's experience speeding things along.

At Hutchinson, he devised a strategy of getting a quick start in Australia for the first-in-human phase I trials for their c-Met inhibitor, using that data to jumpstart the a China phase I that has now passed the Australian trial.

With the global data in hand they made up time with by being able to start at a higher dose and China's quick patient enrollment.

It is by using strategies like this that Mu's five-year plan seems doable: to have at least two if not five drugs on the market in oncology and autoimmune disease. He is responsible for the development of MEDI5117, a monoclonal antibody for autoimmune and inflammatory diseases in China in cooperation with the Medimmune JV.

Deals such as the one with Medimmune could be a trend – which again begs the question: Is Wuxi closer to a drug development role?

But Mu clarifies this is not the case – clients can take the position of retaining full control of their asset and using Wuxi as a service platform for every stage of drug development. Or, if the need arises, there is the possibility that Wuxi can be an investor to help finance the deal along.

"We are just extending our service to be a real solution to people. What is their final purpose – it is to get the drug on the market." //

IN THE CLINIC

Celgene Corp., of Summit, N.J., reported results of additional analyses from the phase III trials of Otezla (apremilast), its oral, selective inhibitor of phosphodiesterase 4, including long-term, 52-week analyses from the PALACE 1, 2 and 3 studies, at the European League Against Rheumatism meeting in Paris. Those data demonstrated that treatment with Otezla improved measures of psoriatic arthritis disease activity, including tender and swollen joints, compared to placebo at 16 weeks, with all measurement of disease activity showing sustained improvements through week 52 for patients continuously treated with Otezla. Long-term safety results from an analysis of pooled data from the PALACE studies identified no new safety findings for up to 52 weeks of treatment. Celgene also presented data from a work productivity analysis from the PALACE 1 study showing that treatment with Otezla increased work productivity and improved work limitations compared to placebo at 16 weeks. The drug gained approval in psoriatic arthritis earlier this year. (See *BioWorld Today*, March 25, 2014.)

Navidea Biopharmaceuticals Inc., of Dublin, Ohio, reported results from combined analyses of phase III trials testing Lymphoseek in lymphatic mapping for identifying pathology-positive lymph nodes across multiple tumor types, with data indicating that the agent's sensitivity for sentinel lymph node mapping was consistent across the tumor type studies, regardless of whether surgery was conducted on the same day as, or on the day after injection of Lymphoseek. For patients with head and neck cancer, Lymphoseek demonstrated a low false negative rate of 2.6 percent.

PHARMA: OTHER NEWS TO NOTE

Abbvie Inc., of North Chicago, disclosed results from its multi-country ALIGN study showing that, across six chronic immune-mediated inflammatory diseases, treatment compliance generally was higher among patients on TNF inhibitors compared to those treated with conventional therapy. In addition, patients who were "accepting" toward their medication were compliant more often than those who were "ambivalent" toward their medication. The ALIGN study was designed to explore the beliefs, concerns, attitudes and adherence of patients (n = 7,197) toward TNF inhibitors and selected conventional therapies, used alone or in combination to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis or psoriasis. Patients completed validated questionnaires, including the Beliefs about Medicines Questionnaire (BMQ) and the short Morisky Medication Adherence Scale. According to BMQ sub-score results, patients treated with TNF inhibitors, with or without conventional therapy, had an increased perception of "necessity" for treatment compared to those treated with conventional therapy. Ratings of "concern" about current treatment were similar between those treated with TNF inhibitors and conventional therapy. The findings were presented at the annual meeting of the European League Against Rheumatism in Paris.

PHARMA: IN THE CLINIC

Bristol-Myers Squibb Co., of Princeton, N.J., released new data from its phase IIIb AVERT (Assessing Very Early Rheumatoid arthritis Treatment) trial showing that the T-cell co-stimulation modulator, Orencia (abatacept), in combination with methotrexate (MTX) achieved higher rates of DAS-defined (DAS28 CRP < 2.6) remission at 12 months than treatment with standard of care MTX (60.9 percent vs. 45.2 percent, respectively), in biologic and MTX-naïve patients with early active rheumatoid arthritis (RA). The active-controlled trial enrolled 351 adults with symptoms of RA for less than two years, positive for anti-CCP antibodies, with DAS28 CRP > 3.2. Patients were randomly assigned to 12 months of weekly treatment with Orencia 125 mg subcutaneous plus MTX, Orencia 125 mg subcutaneous alone or MTX alone. A co-primary endpoint assessed maintenance of remission following the withdrawal of RA drug therapy, including Orencia, MTX and steroids. A small but statistically significantly higher number of patients treated for 12 months with Orencia plus MTX, vs. MTX alone, maintained remission six months after RA treatment was withdrawn. Orencia was well tolerated, with serious adverse events (AE), serious infection events and discontinuation due to serious AEs comparable to patients treated with MTX alone. The data were presented at the annual meeting of the European League Against Rheumatism in Paris.

Eli Lilly and Co., of Indianapolis, said the phase III REACH trial of Cyramza (ramucirumab) in patients with hepatocellular carcinoma did not meet its primary endpoint; overall survival favored the drug arm but was not statistically significant. Encouraging single-agent Cyramza activity was observed, with meaningful improvements in key secondary endpoints of progression-free survival, overall response rate and time to progression. The drug was approved by the FDA in April to treat patients with advanced stomach cancer or gastroesophageal junction adenocarcinoma, a form of cancer located in the region where the esophagus joins the stomach.

Otsuka Pharmaceutical Co. Ltd., of Tokyo, said enrollment has begun for a new phase IIIb study of tolvaptan for adult patients with autosomal dominant polycystic kidney disease (ADPKD). The company reached an agreement with the FDA on a special protocol assessment for the design and planned analysis of this multicenter, placebo-controlled, double-blind, parallel-group trial designed to compare the efficacy and safety of tolvaptan (45 to 120 mg per day split-dose) in subjects with chronic kidney disease between late stage 2 and early stage 4 due to ADPKD.

IN THE CLINIC

Northwest Biotherapeutics Inc., of Bethesda, Md., said in an ongoing phase I/II trial of Dcvax-Direct for all types of inoperable solid tumors, all nine patients who have received four of the six planned injections are showing tumor cell death, tumor shrinkage, substantial immune cell accumulation in their tumors and/or stabilization of their advanced cancers. In addition, three of those nine patients had biopsies showing no live tumor cells in the injected tumors. Shares of Northwest (NASDAQ:NWBO) gained 68 cents, or 12 percent, to close Wednesday at $6.41.

Portola Pharmaceuticals Inc., of South San Francisco, said its phase II proof-of-concept study in healthy volunteers demonstrated that andexanet alfa, a factor Xa inhibitor antidote, immediately reversed the anticoagulation activity of enoxaparin, a low molecular weight heparin and standard of care in venous thromboembolism prevention. Andexanet alfa was well tolerated, with no serious adverse events reported. The trial enrolled 27 healthy subjects who were administered enoxaparin 40 mg subcutaneously once daily for six days and then randomized in a 2-to-1 ratio to andexanet alfa, given as an intravenous bolus, or placebo. Portola is developing the drug, which has FDA-designated breakthrough therapy status, to reverse the anticoagulation activity of factor Xa inhibitor-treated patients who are experiencing a major bleeding episode or who require emergency surgery.

APPOINTMENTS AND ADVANCEMENTS

Abbvie Inc., of North Chicago, named Michael Severino executive vice president, research and development, and chief scientific officer.

IN THE CLINIC

Theravance Inc., of South San Francisco, and **Glaxosmithkline plc**, of London, reported results from two phase III studies, showing that patients with chronic obstructive pulmonary disease (COPD) who received anticholinergic Incruse Ellipta (umeclidinium 62.5 mcg) or umeclidinium (UMEC) 125 mcg (an unlicensed dose) in addition to Relvar/Breo Ellipta (fluticasone furoate/vilanterol, FF/VI), an inhaled corticosteroid/long-acting beta2 agonist combination, achieved an additional improvement in lung function, compared to patients receiving FF/VI plus placebo. Studies showed that for the primary endpoint of trough FEV1 at day 85, the addition of UMEC 62.5 mcg or UMEC 152 mcg resulted in a statistically significant improvement in lung function compared to FF/VI plus placebo in COPD patients.

Xenetic Biosciences Inc., of Lexington, Mass., said partner the Serum Institute of India dosed the first patient in the second cohort of a phase IIa trial, testing sequential single-dose administration of intravenous Erepoxen for the treatment of anemia in chronic kidney disease patients on dialysis. Patients in the second cohort will start with a single Erepoxen dose of 1.5 mcg/kg and will be monitored for pharmacodynamics, pharmacokinetic and immunogenic parameters for the next 28 days. Dose levels in escalating forms will then be administered. Erepoxen is a polysialyated form of erythropoietin.

APPOINTMENTS AND ADVANCEMENTS

Actavis plc, of Dublin, announced several changes following the acquisition of New York-based **Forest Laboratories Inc.**, anticipated for midyear: Paul Bisaro will become executive chairman, Brent Saunders CEO and president, and a member of the board, and Robert Stewart will become chief operating officer.

Agios Pharmaceuticals Inc., of Cambridge, Mass., named Chris Bowden chief medical officer.

Array Biopharma Inc., of Boulder, Colo., named Nicholas A. Saccomano chief scientific officer and Robert E. Winkler vice president of clinical research and development.

Avalanche Biotechnologies Inc., of Menlo Park, Calif., named Linda C. Bain chief financial officer.

Avedro Inc., of Waltham, Mass., added Robert J. Palmisano to its board.

Clarus Therapeutics Inc., of Northbrook, Ill., named Patrick Shea chief commercial officer.

Discovery Laboratories Inc., of Warrington, Pa., appointed Steve Simonson vice president, clinical development, and Lawrence Weinstein vice president, medical device development.

Egenix Inc., of Millbrook, N.Y., appointed Hans-Guido Wendel to its scientific advisory committee.

Emmaus Life Sciences Inc., of Torrance, Calif., appointed Duane Kurisu, Moni Miyashita, Phillip Satow and Mayu Sris to its board.

Finox Biotech AG, of Burgdorf, Switzerland, appointed Luigi Marro chief financial officer; Ken Shields executive vice president, head of European commercial operations; and Nicole Stigemar executive vice president, head of marketing and business development.

G1 Therapeutics Inc., of Research Triangle Park, N.C., named Mark Velleca chief executive officer.

Intrexon Corp., of Germantown, Md., appointed Christopher Basta vice president of investor relations.

Jazz Pharmaceuticals plc, of Dublin, appointed Russell J. Cox chief operating officer.

Karolinska Development AB, of Stockholm, added Robert Holland, Henrijette Richter and Carl Johan Sundberg to its board.

Madison Vaccines Inc., of Madison, Wis., added Michael Richman to its board.

Meditope Biosciences Inc., of Los Angeles, named Dan Dumitru vice president of translational research.

Moderna Therapeutics Inc., of Cambridge, Mass., appointed Noubar Afeyan, John Aunins, Scott Canute, Fred Regnier, James Swartz, Jack Szostak and Richard Willson to its new technology board.

Nektar Therapeutics Inc., of San Francisco, named Ivan Gergel senior vice president, drug development, and chief medical officer.

Neos Therapeutics Inc., of Grand Prairie, Texas, named Richard I. Eisenstadt chief financial officer.

Nuevolution A/S, of Copenhagen, Denmark, added Brian Zambrowicz to its board and appointed him senior scientific advisor.

Oxigene Inc., of South San Francisco, named David (Dai) Chaplin president and CEO.

Pharmacyclics, of Sunnyvale, Calif., appointed Gregory R. Wade executive vice president of business development.

Prana Biotechnology Ltd., of Melbourne, Australia, added Ira Shoulson to its board.

Provectus Pharmaceuticals Inc., of Knoxville, Tenn., appointed Jacob M. Plotsker to its strategic advisory board.

Purdue Pharma LP, of Stamford, Conn., named Saeed Motahari senior vice president and chief commercial officer.

Regado Biosciences Inc., of Basking Ridge, N.J., named Nicholas Pelliccione senior vice president of regulatory affairs and quality assurance.

Tesaro Inc., of Waltham, Mass., added Earl M. (Duke) Collier Jr. to its board.

Trevena Inc., of King of Prussia, Pa., appointed John M. Limongelli senior vice president, general counsel and corporate secretary.

Vaxart Inc., of San Francisco, named John Harland chief financial officer.

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