Regulatory changes may be coming as Novartis faces legal trouble in South Korea

By Haky Moon, Staff Writer

HONG KONG – Swiss multinational Novartis AG’s South Korean unit is facing further scrutiny after being charged with illegal rebates in February. South Korean prosecutors indicted a former chief executive of Novartis South Korea, Moon Hak-Sun, along with five other former and current company managers over allegations that they illegally paid doctors KRW2.6 billion (US$2.3 million) in return for prescribing the company’s drugs to patients over the span of five years, from 2011 to January this year. The Seoul Western District Prosecutors’ Office said it has indicted 28 other...

See Novartis, page 3

NEWCO NEWS

Kleo looks to new I-O tack with ARMs and SyAMs

By Marie Powers, News Editor

Yale University spinout Kleo Pharmaceuticals Inc. raised a series A to fund development of its antibody recruiting molecules, or ARMs, and synthetic antibody mimics, or SyAMs, developed in the lab of Yale researcher...

See Kleo, page 4

REGULATORY

OIG report accuses patent examiners of abuse

By Mark McCarty, Regulatory Editor

The Office of Inspector General (OIG) at the Department of Commerce has issued a report alleging that patent examiners at the U.S. Patent and Trademark Office (PTO) have abused their time-off privileges to such a degree that it has...

See Regulatory, page 5

IN THIS ISSUE

Financings, p. 2
Other news to note, p. 2, 7
In the clinic, p. 5

GUT FEELINGS

SSRI effects are too much of a good thing for bones

By Anette Breindl, Senior Science Editor

The long-term use of selective serotonin reuptake inhibitors (SSRIs) raises serotonin levels in the brain enough to deactivate signaling pathways that...

See SSRIs, page 6

BENCH PRESS

BioWorld Senior Science Editor Anette Breindl takes a closer look at translational medicine

Read this week’s edition

Left on the garbage heap of the 114th Congress?

By Mari Serebrov, Regulatory Editor

Add this to the list of things the 114th U.S. Congress likely won’t get done before it fades into history on Jan. 3: providing relief from the inter partes review (IPR) intimidation racket. It’s not for want of trying. But the only attempts were specifically aimed at keeping drug companies from being pushed around by the government-sanctioned playground bullies who use the threat and filing of IPR patent challenges to demand a lot more than lunch money.

The trouble is a lot of lawmakers didn’t want to stand up for drug companies, who aren’t the most popular kids on the block right now because of public outrage over their prices. As a result, the reform language was no more than a placeholder in the Senate PATENT Act, which hasn’t made it out of the Senate.

See Perspectives, page 7
FINANCINGS

Cocrystal Pharma Inc., of Tucker, Ga., closed on proceeds of about $4 million in a private placement offering of about 9.7 million shares at 41 cents each. The purchasers included three members of the company’s board.

OTHER NEWS TO NOTE

Amgen Inc., of Thousand Oaks, Calif., won FDA accelerated approval for a supplemental biologics license application for Blincyto (blinatumomab) that adds new data supporting the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The approval is based on results of an open-label, multicenter, single-arm phase I/II trial, which evaluated the efficacy and safety of Blincyto in pediatric patients with relapsed or refractory B-cell precursor ALL. Blincyto first gained FDA approval in December 2014. (See BioWorld Today, Dec. 4, 2014.)

Arena Pharmaceuticals Inc., of San Diego, formed Beacon Discovery Inc., an independent, privately held drug discovery incubator, in a move to transition from an early stage research company to a late stage clinical development organization. Beacon will focus on identifying and advancing molecules targeting G protein-coupled receptors, or GPCRs, from concept to clinic, engaging global pharmaceutical partners to facilitate discovery and early stage development. Arena will retain certain rights to compounds developed by Beacon and will collaborate with Beacon to support Arena’s pipeline programs and the company’s collaboration with Boehringer Ingelheim International GmbH, of Ingelheim, Germany, initially focused on drugs to treat schizophrenia. Arena also said it will be entitled to certain rights to potential cash flow generated by Beacon. Additional terms were not disclosed. In conjunction with Beacon’s formation, Dominic Behan, Arena’s co-founder, will relinquish his position as Arena’s chief scientific officer to become Beacon’s CEO and chairman of Arena’s scientific advisory board. (See BioWorld Today, Jan. 14, 2016.)

Biogen Inc., of Cambridge, Mass., said the FDA granted fast track designation to aducanumab (BII8037). The move came days after investigators reported complete removal of amyloid plaque in one patient at 54 weeks and suggested a slowing in cognitive decline among patients with prodromal Alzheimer’s disease or mild cognitive impairment who had a positive amyloid PET scan. (See BioWorld Today, Sept. 1, 2016.)

The nonprofit Biopontis Alliance for Rare Diseases, of Raleigh, N.C., and, and VIB, a life science research institute in Brussels, formed a strategic partnership in rare diseases, with the first program aimed at developing a treatment for one form of Charcot-Marie-Tooth disease, a rare, progressive neuropathy with no approved therapies.

Catalyst Pharmaceuticals Inc., of Coral Gables, Fla., said the FDA granted the company orphan drug designation for Firdapse (amifampridine phosphate) for the treatment of myasthenia gravis.

Merck & Co. Inc., of Kenilworth, N.J., is discontinuing the development of odanacatib, an investigational cathepsin K inhibitor for osteoporosis, and will not seek regulatory approval for its use. The company previously reported a numeric imbalance in adjudicated stroke events in the pivotal phase III fracture outcomes study in postmenopausal women. It decided to discontinue development of the candidate after an independent adjudication and analysis of major adverse cardiovascular events confirmed an increased risk of stroke. Data from the analysis will be presented at the American Society for Bone Mineral Research annual meeting in Atlanta, to be held Sept. 16-19.

**HOLIDAY NOTICE**

BioWorld’s offices were closed Monday, Sept. 5, in observance of the Labor Day holiday in the U.S. No issues were published that day.
Novartis
Continued from page 1

people, including 15 doctors and six publishers of medical journals, amounting to a total of 34 people. The first of what may wind up being several trials is scheduled to start Sept. 22. “We will take proper punitive measures against the company and people responsible, according to our regulations, after further investigations in the case,” the South Korean Ministry of Food and Drug Safety said in a statement.

Illegal kickbacks were extended through seminars and academic events organized by medical journal publishers. The kickbacks were disguised as ‘attendance’ fees. This is not the first time the Novartis South Korean unit has been in legal hot water associated with drug rebates. In 2011, the company was fined KRW2.3 billion for offering KRW7.1 billion of illegal rebates from 2006 to 2009. But this time around, the consequences Novartis is facing could be much more serious.

South Korean prosecutors are asking for the suspension of Novartis’ South Korean operation. Medical regulations in South Korea stipulate that companies offering illegal rebates to doctors could face a ban of up to six months on the sale of the drugs.

“We’re trying to boost the transparency in South Korea’s pharmaceutical market. We are currently at the stage where the government is imposing harsher punishments [instead of drafting new laws] while the health care industry is devising methods to come up with an autonomous filtering system,” Jang Woo-Soon, head of the insurance policy department of the Korean pharmaceutical manufacturers association, told BioWorld Today. In other words, the regulators want companies to police themselves.

Policies aiming at eradicating illegal drug rebates were introduced in 2010 and 2014. In November 2010, a dual punishment system (DPS) was introduced to stop increases in drug prices.

Under this policy, both doctors and companies are liable for punishment if indicted. Prior to the DPS, only pharmaceutical companies were punished for illegal drug rebates.

TWO-OUT POLICY

Despite harsh measures implemented by the South Korean government to crack down on illegal drug rebates, the practice remained rampant. This pushed the government to introduce its “two-out policy” in July 2014. Under the two-out system, if a company is charged with an illegal drug rebate offence more than twice, the drug would be eliminated from the health insurance remuneration list.

Taking it out of the list could drive up the price of the drug in question, eventually ousting it from the market. Despite harsh rules in place, illegal drug rebates are still pervasive in the South Korean pharmaceutical industry.

Regulators worry that pharmaceutical companies have been searching for other ways to reward doctors that prescribe their drugs.

“I doubt the case of Novartis would make regulations more stringent than now. Novartis is just one of many drug rebate cases in South Korea,” said Jang.

For instance, Yooyoung Pharmaceutical Co. Ltd. was indicted for extending rebates that amounted to KRW4.5 billion (US$4.03 million) last June. The company gave out cash, cash coupons and golf clubs. The sales team of the company went even further and helped the children of doctors to commute to school or bought snacks for the children.

Small- to medium-sized drug companies are, more often than not, much more aggressive in drug rebates, because South Korean prescribers generally prefer original drugs to generic drugs.

Generic drugs are the bread and butter of smaller pharmaceutical companies and the competition is fierce.

According to the South Korean Ministry of Food and Drug Safety, in 2014 a total of 851 pharmaceutical-related companies were registered in the country. After adding multinational pharmaceutical companies and wholesale distributors, the number increased to 2,500.

There are now approximately 26,000 drugs on the market. Despite drug rebate scandals, observers are skeptical of whether more stringent regulation would be developed in the near future to tackle the problem.

The industry has been pegged to become the next economic powerhouse in South Korea; introducing limitations may dampen the enthusiasm of new entrants in the pharmaceutical sector.

“Even the South Korean judicial authorities said that they wouldn’t put further regulation on the pharmaceutical sector, and they expressed this to the media as well,” said Jang. Instead, the South Korean government introduced another system four years ago that could incentivize drug companies to focus on R&D rather than on selling generic drugs.

The policy is translated as an “innovative pharmaceutical company verification system” and companies with histories of illegal drug rebates are automatically disqualified to receive the subsidies given through the system. “In this regard, I believe we are showing improvements,” said Jang.

However, industry observers say the efficacy of the policy remains unclear, as government subsidies for these types of policies are rarely seen as being enough. //
Kleo
Continued from page 1

David Spiegel, who founded the New Haven, Conn.-based company last year, Kleo principals were murk on the amount of the round, but the sole investor was Biohaven Pharmaceutical Holding Co. Ltd., also of New Haven, which holds other intellectual property (IP) from Yale and was said to take a “substantial” equity stake in the newco.

Spiegel, a professor of chemistry and pharmacology, has devoted much of his research career to the development of immunotherapeutic approaches that use small molecules rather than biologics – which heretofore served as the “gold standard” in immunotherapy, he said – to prompt the immune system to target and kill specific disease cells. ARMs and SyAMs, he maintained, offer the opportunity to raise the bar in attacking cancer and infectious disease.

“We were very excited about the technology and published a fair amount in this area,” Spiegel told BioWorld Today, leading to conversations with Yale’s Office of Cooperative Research about securing a license to develop the molecules. Kleo gained global rights to the IP and lead molecules for all aspects of the ARM and SyAM platform with the exception of a single target – prostate-specific membrane antigen – that was licensed by Yale last year to the Allied-Bristol Life Sciences partnership formed by Bristol-Myers Squibb Co. (BMS) and technology development and commercialization specialist Allied Minds. (See BioWorld Insight, Sept. 8, 2014, and BioWorld Today, April 27, 2016.)

As Kleo’s chief operating officer and chief financial officer, co-founder Roy Prieb – a long-time acquaintance of Spiegel and former technology consultant with expertise in business formation and capital raising – took on the role of shepherding the tech transfer process, seeking investors and overseeing prioritization of the company’s assets and development plans. ARMs are bifunctional or “two-headed” chemical structures; one head interacts with disease-relevant molecular targets while the other interacts directly with the antibodies in a person’s bloodstream. SyAMs are synthetic molecules that possess both the targeting and effector cell activating functions of antibodies.

The technology offers multiple layers of differentiation in I-O, according to Spiegel, citing the stability and rational design of ARMs and SyAMs, their oral availability and non-immunogenicity and the ability to mass produce them at low cost.

“Then, there’s tissue penetration, which is a big limitation for biologics, especially in solid tumors,” he said. “We think this is going to be a disruptive, paradigm-shifting technology.”

‘SO BIG THAT WE COULDN’T DO IT ALONE’

Kleo plans to move into the clinic “as soon as possible,” targeting indications that exploit the technology’s advantages, Spiegel added, though he hesitated to define a development timetable.

“We’ll have to see what the data tell us,” he said.

In addition to the financing, Kleo and Biohaven inked a clinical development master services agreement designed to leverage Kleo’s proficiency in chemistry discovery and Biohaven’s expertise in drug development. Biohaven’s management team includes Vlad Coric, a former associate clinical professor of psychiatry at the Yale School of Medicine who also served as I-O lead for neuro-oncology and glioblastoma at BMS, and Robert Berman, chief medical officer, who also had tenure at Yale and BMS. Declan Doogan, Biohaven’s chairman, spent 25 years at Pfizer Inc., capping his career there as senior vice president and head of global drug development, while Greg Bailey, director and senior vice president of business development, is a serial entrepreneur who took an early stake in Medivation Inc., which last month went to Pfizer Inc. for $14 billion. (See BioWorld Today, Aug. 23, 2016.)

“Our expertise at Kleo is in early stage, cutting-edge scientific development,” Spiegel said. “Biohaven has clinical development leaders from industry. We felt there would be a tremendous synergy in being able to bridge the gap between early stage discovery and the clinic.”

Biohaven has another drug development connection. The company is majority owned by Portage Biotech Inc. (PBI), of Toronto, formed in 2012 to assemble a series of subsidiaries to conduct drug discovery and development on in-licensed assets – a strategy thought to de-risk its product portfolio. Doogan serves as PBI’s CEO, with Bailey as chairman.

PBI’s first subsidiary was Portage Pharmaceuticals Ltd., which is developing Cellporter, a cell penetrating peptide that can be used to deliver large molecules into cells, across the blood-brain barrier and throughout the body. The most compelling feature of the technology is its ability to carry the payloads without disrupting the cell membrane. (See BioWorld Today, Jan. 3, 2014.)

The combination of talents and technologies could be especially useful in attracting strategic partnerships to advance Kleo’s assets, especially in I-O combination efforts, Spiegel suggested.

“The versatility of the immune system allows us to go after any number of targets, he said.

“We very much recognized when we started out that the opportunities related to this platform were so big that we couldn’t do it alone,” Prieb added. “We’re looking to establish the science in our lead programs, but we’re going to need as many strategic partners as possible to really develop this field.”

For Kleo, which took its name by combining elements from the first names of Spiegel’s wife and young son, the next step is to build out the company’s team and infrastructure while looking for those early partners. Spiegel predicted that Kleo will “grow pretty rapidly” and hinted at “some exciting hires” by year-end. Long term, the collaboration with Biohaven positions Kleo “to have soup to nuts expertise,” he said, taking assets through the clinic and, potentially, to market. “This is part of what’s so exciting to us about having gifted clinical partners.”
Regulatory
Continued from page 1

affected the backlog of patents. One of the more troubling aspects of the OIG report, however, is that the purported abuse could account for twice as many hours of clock time as described in the report.

The OIG investigation was sparked by allegations that an unnamed examiner, dubbed Examiner A, had falsely claimed to have worked at least 730 hours during the course of fiscal year 2014, and the investigation into the hours worked by roughly 8,000 of the 10,000 patent examiners at PTO disclosed that 137,000 hours logged over a nine-month period could not be supported by documentation. A separate analysis of records spanning 15 months disclosed 288,000 unsupported hours, but the report stated that OIG had “adopted a conservative approach in considering the evidence.”

“It is important to recognize and understand that the OIG report did not focus on individual employees; instead, it was based on a comparative analysis of large computer record datasets,” according to a statement from the PTO.

An analysis of a subset of examiners’ records suggested that the allegation of abuse could have covered twice the number of reported hours, and the conservative estimate for the nine-month analysis would equal nearly $8.8 million in salaries and other compensation.

The OIG said a quarter of the unsupported hours from the nine-month analysis were for overtime hours, and that 226 examiners were associated with more than 42,000 unsupported hours. Those 226 employees also “received above-average annual performance ratings,” and of this group, 36 examiners had claimed hours that would account for three working days for every 80 hours of computer-related work time.

The report stated that the OIG had relied on a minute-by-minute review of data for both the nine-month and 15-month datasets, although the OIG noted that there were instances in which employees appeared to have worked more hours than claimed, which could be at least partly explained by the PTO electronic badge policy. The OIG said it had corroborated its methodology for assessing unsupported hours with an analysis of the data from Examiner A.

The OIG concluded that the PTO system of internal controls for time and attendance tracking need to be upgraded, and that the volume of unsupported hours calls into question the efficacy of the PTO performance goal metrics.

“The OIG concluded that there was a lack of a digital footprint in approximately 2 percent of the total hours claimed by the patent examiners during the 15 month period – a percentage that continued to shrink following the introduction of new USPTO controls, and during the course of the IG review,” according to the PTO response. “The USPTO recognizes that there may be many reasons for the lack of a digital footprint and is committed to analyzing the recommendations offered by the OIG, continuing to conduct our own review, and, if needed, improving the extensive measures already implemented.” //

IN THE CLINIC

Chemocentryx Inc., of Mountain View, Calif., disclosed the initial 12-week overall response rate (ORR) results from an ongoing open-label, single arm phase lb trial with CCX872 in patients with advanced pancreatic cancer. CCX872 is a selective inhibitor of the chemokine receptor known as CCR2. The ongoing study aims to evaluate the safety and effects of orally administered CCX872 when added to standard-of-care FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) in patients with advanced non-resectable pancreatic cancer. Under the study protocol, patients may continue to receive CCX872 for an indefinite treatment period as long as there is no evidence of disease progression. The company expects to report progression-free survival by the end of 2016. The ORR was 37 percent, or 15 of 41 patients, in the pre-specified evaluable patient population.

Orexo AB, of Uppsala, Sweden, said the REZOLV retrospective study with its Zubsov (buprenorphine and naloxone) for opioid dependence has been completed as planned in August. With 1,080 patients, the study is the largest retrospective study completed in the U.S. aimed at optimizing the treatment of opioid dependence. Overall, the study was a success, with 978 of the 1,080 patients in total confirmed as being evaluable for treatment efficacy. From the patients evaluable for treatment, 77.6 percent (n=759) were determined to have been a treatment success, defined as a patient who completed 28 days of treatment and tested negative for opiates on the last follow-up drug screen, the company said.

Taiwan Liposome Co. Ltd., of Taipei, Taiwan, disclosed preliminary results from the bioequivalence and safety study of doxorubicin hydrochloride liposome injection (project code name: TLC177) in patients with advanced carcinoma of the ovary. In this open-label, two-period, two-way, crossover study each subject received two doses: one dose of TLC177 and one dose of the reference drug Caelyx (liposomal doxorubicin, known as Doxil in the U.S., Johnson & Johnson). Subjects were randomly assigned to two treatment groups. According to the crossover design, one group received an initial dose of TLC177 and then received a dose of Caelyx, while the other group received an initial dose of Caelyx and then received a dose of TLC177. Each dose was followed by a 28-day observation period. The study results demonstrated bioequivalence between TLC177 and Caelyx in total form, doxorubicinol (the main metabolite) and liposome-encapsulated doxorubicin, with free doxorubicin exhibited greater variation, which requires further verification, the company said.
SSRIs
Continued from page 1

increase bone formation, providing the solution to a long-term riddle – why SSRIs, which increase the availability of serotonin in the brain, increase fracture risk even though brain serotonin signaling increases bone formation.

The risk of fracture for the elderly has decreased with the advent of osteoporosis drugs. But the lifetime risk of a bone fracture in individuals older than 50 is still one in three. And while a bone break in a healthy young athlete amounts to a cast and a war story, fractures in the elderly can initiate a downward slide toward immobility that can double the risk of death within a year of a fracture.

Because menopause accelerates bone loss, women have a higher risk of fractures than men. And that fracture risk is further exacerbated by their higher use of antidepressants.

According to a 2011 report by the National Center for Health Statistics, 10 percent of Americans overall, and about 20 percent of women older than 60 years, take antidepressants. SSRIs are the most commonly prescribed class of antidepressants.

Roughly a decade ago, “physicians started to notice that patients who took SSRIs for a long time had an increased risk of fracture,” Patricia Ducy told BioWorld Today.

Such an increased risk could in theory be due to the SSRIs, or the underlying depression, and so “there were several large-scale retrospective studies that evaluated whether this was just a fluke or whether it was reality.” Those studies, as well as animal studies, mostly confirmed that SSRI use rather than depression itself increased fracture risk.

SSRIs have also been approved for treating hot flashes in postmenopausal women.

“And what characterizes most postmenopausal women,” Ducy said, “is that they lose bone.”

As a result, “there was a tendency to give this particular drug to women that were already at risk.”

Ducy, who is an assistant professor at Columbia University, and her laboratory have been interested “in serotonin for a long time, and been working on serotonin’s role in the gut, but also in the brain, and its relationship to bone mass,” she said.

The epidemiological data showing an increased risk of fractures puzzled her and her team.

With SSRI use, “we should have a gain of bone, because we knew from previous studies that brain serotonin is good for your bones,” she said. “So we could not understand why increasing the availability of serotonin in the brain would be bad for your bone.”

There are two separate serotonin systems in the brain and in the gut, which have largely separate roles. Both, however, have an effect on bone formation, which is a constant process of bone destruction and remodeling. (See BioWorld Today, Feb. 9, 2010.)

To add to the confusion, while most studies did indeed show an increased risk of fractures, a few showed a decreased risk.

The first clue came from the fact that studies showing a decreased risk of fractures were in women who had used SSRIs for a short time.

Normally, SSRIs are used for at least six months to decrease the risk of relapse. Treatment duration of one to two years is not unusual, and about 15 percent of individuals who take antidepressants do so for a decade or more.

Ducy and her team treated mice with fluoxetine, an SSRI inhibitor and the active ingredient in Prozac (Eli Lilly and Co.), for either three weeks or six weeks to understand the relationship between serotonin and bone density.

Given the short life span of mice, she said, those treatment durations are “quite representative,” of the clinical situation, though “of course, in humans the time frames are longer.”

The team found that SSRIs affected both the brain and gut serotonin signaling in both the brain and the periphery.

The peripheral effects, Ducy said, appeared “very quickly. . . . Fluoxetine goes straight to osteoclasts” – which destroy bone, while osteoblasts lay down new bone – “and inhibits their function.”

As a result, “now the osteoclasts are somewhat on strike,” leading to less bone resorption and higher bone density overall.

“When you treated mice for a longer time, this effect was still there. But unfortunately, the effects of fluoxetine in the brain started to appear,” she said.

Those effects were to increase the availability of serotonin to the bone-signaling pathway “so much that you totally desensitize the pathway,” she said. “This is how the mice started to lose bone. Instead of having the pathway sensitized, they had it downregulated.”

When it is active, the brain serotonin pathway increases bone formation by inhibiting adrenergic signaling in the bone, and so Ducy and her team inhibited peripheral adrenergic signaling in SSRI-treated mice by adding a beta-blocker to their regimen. That combination did indeed reverse the effects of SSRIs on bone density.

Ducy and her team published their findings in the Sept. 9, 2016, online issue of Nature Medicine.

In collaboration with Columbia University’s department of psychiatry, “we have started to look – again, retrospectively – with very large cohorts of patients that were treated with both SSRIs and beta-blockers to see whether combination treatment appeared to reduce fracture risk.”

The team is also looking at the underlying molecular mechanisms of the relationship between brain serotonin and bone formation, to see whether there are other points where pharmacological intervention could decrease the fracture risk of SSRI treatment. //
Because Congress has refused to step in, drug companies are no longer the only target of IPR threats. Now the bullies and would-be stock manipulators are picking on one of the popular kids – high-tech Silicon Valley companies, like Power Integrations Inc. In its attempted shakedown of Power Integrations, Silver Star Capital LLC made no bones about the fact that its threats were all about a payoff, in one form or another.

It all began earlier this year when Kevin Barnes, principal of Silver Star, threatened Power Integrations with an IPR challenge to one of its critical patents, but said he was “open to a collaborative discussion . . . [to] consider alternatives.” He later called the company with his settlement offer – Power Integrations could pay $600,000 up front plus 10 percent of the gross of any damages it collected for infringement of the ‘079 patent going forward or pay $1.8 million up front plus 3 percent gross of any damages collected. In exchange, Silver Star wouldn’t file the IPR petition.

(A bit of irony here. Silver Star wants a share of future infringement damages for a patent it claims is obviously invalid?)

When Power Integrations, through its attorney, rejected the offer, Barnes took offense at the company’s characterization of his tactics as an improper scheme to game the patent system. In a letter to the company, Barnes said (wait for it, another wielding of the iron) he would “not be intimidated by Power Integrations’ legal posturing and attempts to mischaracterize the facts.”

As a side note, Barnes also founded Ferrum Ferro Capital LLC, which tried a similar tactic on Allergan plc last year. Like Power Integrations, Allergan refused to pay up. In that case, the Patent and Trademark Appeal Board (PTAB) rejected Ferrum’s IPR petition challenging a patent covering Allergan’s glaucoma drug Combigan (brimonidine and timolol).

Silver Star and Ferrum are not the only short-sellers looking to make a quick buck or two off the IPR process. In opening IPR petitions to all comers – not just those wanting to actually compete in the market – Congress created a new money-making scheme for short-sellers and others willing to shrug off public disdain about their tactics.

IT’S ALL ABOUT THE MONEY

As long as the bullies picked on drug companies that surround their long-term investment in pricy drugs with a high patent fence, many in Congress saw no need to confront them. And the high drug prices gave hedge fund managers and the like an altruistic excuse for their bullying. Yes, they stood to profit, but they also were “looking out for the public interest” because their patent challenges could open the market to competition and lower drug prices.

But in tackling companies like Power Integrations, the bullies are no longer bothering to cite a social good. It’s all about the money. For instance, Barnes was up front about Silver Star holding “various long/short positions in the securities of an assortment of global semiconductor technology enterprises,” adding that the company was just “supporting its investment interests” with its IPR threat.

To justify his demands, Barnes quoted a ruling last year in Coalition for Affordable Drugs VI, LLC v. Celgene Corp. in which PTAB refused to sanction the coalition, run by hedge fund manager Kyle Bass, for alleged abuse of the IPR process.

“Profit is at the heart of nearly every patent and nearly every inter partes review. As such, an economic motive for challenging a patent claim does not itself raise abuse of process issues,” PTAB said. “We take no position on the merits of short-selling as an investment strategy other than it is legal, and regulated.”

Ironically, the IPR process was high-tech’s solution to shutting down an earlier playground bully – patent trolls, aka patent-assertion entities. The idea was that an IPR would allow companies playing in the marketplace to challenge a troll’s flimsy patents before the Patent and Trademark Office rather than resorting to expensive, lengthy litigation.

But the way Congress conceived it, the IPR process isn’t limited to troll hunting. Anyone can use it to try to invalidate any patent, based on prior art. Thus, the law gave birth to the so-called “reverse patent trolls” who try to exploit the IPR process to short-sell the stocks of targeted companies.

While the 114th Congress isn’t likely to take down this new breed of bullies in the time it has remaining, perhaps the new in-your-face shakedowns of high-tech companies will finally be enough to force the next Congress to slam the door on the extortion practices it legitimized when it revised the U.S. patent system a few years ago. //

OTHER NEWS TO NOTE

Myriad Genetics Inc., of Salt Lake City, completed its acquisition of Mason, Ohio-based Assurex Health, a specialist in genetic testing for psychotropic medicine selection. Myriad paid $225 million up front for the company with the potential for $185 million in additional performance-based milestones to be paid in the future. At the announcement of the deal, Myriad President and CEO Mark Capone said that the deal would help position Myriad for long-term growth. To fund the transaction, Myriad entered a credit agreement with JP Morgan Chase Bank for an aggregate principal amount of $200 million.

Respirerx Pharmaceuticals Inc., of Glen Rock, N.J., moved ahead with a 1-for-325 reverse stock split following stockholder approval of the move at special meeting held on Aug. 26. The action will consolidate the number of outstanding shares (OTCQB:RSPI) of the company’s common stock from about 656.2 million to about 2 million.
Caloric restriction tans fat . . .

Caloric restriction led to the browning of white fat via immune-mediated signaling, and that may be a common feature of conditions of negative energy balance, where energy expenditure is greater than energy uptake. Caloric restriction by roughly 40 percent is the simplest, though not the easiest, way to extend life span in a variety of species. In their work, the authors from the Swiss University of Geneva investigated whether caloric restriction had an effect on converting energy-storing white fat to energy-using beige or brown fat. Such fat browning occurs in different conditions that lead to weight loss including endurance exercise, microbiome depletion, and gastric bypass surgery. They found that caloric restriction increased immune infiltration of white fat and led to its browning. Their work appeared in the Aug. 25, 2016, online issue of *Cell Metabolism*.

. . . But cachexia may not

Cancer-associated cachexia, a wasting syndrome that affects about 30 percent of late-stage cancer patients and hastens death, was characterized by an energy-wasting cycle in white fat cells that was molecularly distinct from the conversion to brown or beige fat. Previous studies have described browning-like processes in fat cells during cachexia, but in their experiments, the authors from the German Helmholtz Center Munich showed that in mice with cachexia, white fat cells began dissipating rather than storing energy in a process that was independent of UCP-1, the key protein in the activity of beige and brown fat cells. Instead, the cells downregulated the Amp kinase, and upregulated its interacting protein Cidea. By stabilizing Amp kinase with a peptide, the team was able to ameliorate wasting both in cell culture and in animal experiments. The study was published in the Aug. 29, 2016, online issue of *Nature Medicine*.

Tumor suppressor hot and cold spots

Even in the absence of functioning tumor suppressor genes, epithelial tissues have microenvironment hotspots where tumors form that are characterized by two separate prerequisites. When tumor suppressors were inactivated in drosophila, in some locations, growing cells separated from the cell layer they were in and migrated toward the upper or apical side of the tissue layer, where they took advantage of JAK/Stat signaling to continue growing. In “cold spots,” cells delaminated to leave on the basal side of their cell layer, did not activate JAK/Stat signaling, and underwent apoptosis. The authors from Florida State University and the Japanese National Institute of Genetics concluded that “two independent processes, apical delamination and JAK/STAT activation, are concurrently required for the initiation of . . . tumorigenesis.” Their work appeared in the Sept. 1, 2016, issue of *PLoS Genetics*.

What drives mice to drink

The effects of alcohol on neural transmission in the cerebellum may be a reason why some mice (and by extension, some humans) drink more than others. Alcohol abuse clearly has genetic underpinnings, but the molecular mechanisms that underlie risk genes remain largely unknown. Researchers from Washington State University have focused on neural transmission in the cerebellum as a possible mediator of abuse susceptibility, and shown in earlier work that GABAA transmission was affected differently by alcohol in mice bred to be susceptible to binge drinking than in those that were naturally moderate drinkers. In their current studies, the researchers treated binge mice with a GABA-A receptor agonist, modulating their neural transmission in the cerebellum to be like that of moderate drinkers. The tipplers did not quite turn into teetotalers with such treatment, but their alcohol consumption did decrease to levels akin to those of the mouse strain that was not susceptible to excessive drinking. The authors concluded that “genetic differences in cerebellar response to alcohol contributes to alcohol consumption phenotype, and targeting the cerebellar GABAA receptor system may be a clinically viable therapeutic strategy for reducing excessive alcohol consumption.” They published their findings in the Aug. 31, 2016, issue of the *Journal of Neuroscience*.

Zika screening bears fruit

Researchers have identified compounds that could protect cells from either Zika virus (ZIKV) infection, or prevent cell damage in infected neuronal cells and progenitors. The team from Florida State University, Johns Hopkins University and the National Institutes of Health screened a library of 6,000 compounds, which included some FDA-approved drugs as well as experimental drugs and pharmacologically active compounds. The researchers identified a number of compounds including the FDA-approved antiparasitic drug Niclosamide (niclosamide) and the caspase inhibitor emricasan (Conatus Pharmaceuticals Inc.) that either prevented ZIKV from replicating, or prevented the activation of Caspase 3, which is responsible for the damage to infected neuronal progenitors. Also, the team found that “combination treatments using one compound from each category (neuroprotective and antiviral) further increased

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Inhibiting the bcr-abl kinase, a fusion kinase that is also called the Philadelphia chromosome, in acute lymphoblastic leukemia (Ph+ ALL) patients was the first triumph of targeted therapies, but resistance to bcr-abl inhibitors develops over time. Resistant tumor cells do not induce apoptosis, and so the authors added Venclexta, which targets an anti-apoptotic protein, to tyrosine kinase inhibitors. They found that such a combination was synergistic in cell culture experiments as well as in xenografted tumors. “These data suggest that the combination of dasatinib and venetoclax has the potential to improve the treatment of Ph+ ALL and should be further evaluated for patient care,” the team from Ohio State University reported. They published their results in the Aug. 31, 2016, issue of Science Translational Medicine.

Kidney cells galore

Nephron precursor cells (NPCs) could be maintained in a pluripotent state long-term by culturing them in a 3-D system, rather than in the layers that are the mainstay of older culturing systems. Nephrons are functional subunits of kidneys, responsible for filtering blood and producing urine. During embryonic development they exist only briefly, and getting them to stick around for longer periods of time in culture systems has been a challenge, as the cells soon differentiate into mature cell types when cultured by traditional mechanisms. A team from the Salk Institute developed culture conditions that allowed them to culture mouse NPCs, human NPCs, and NPCs derived from induced pluripotent stem cells that remained in a progenitor state long-term, and could form nephrons that connected to the vascular system and filtered blood when transplanted into animals. They concluded that “these findings provide a technological platform for studying human nephrogenesis, modeling and diagnosing renal diseases, and drug discovery.” Their work appeared in the Aug. 25, 2016, online issue of Cell Stem Cell.

Group B Strep and preterm birth

Group B Streptococcus (GBS) bacteria produced membrane vesicles that destabilized the amniotic sac both mechanically and through setting off inflammation, ultimately leading to preterm birth in animal models. Preterm birth is the leading cause of mortality in newborn babies, and mothers who are infected with GBS in their genitourinary tract have a higher risk of preterm birth. Scientists from the Indian Institute of Technology looked for such membrane vesicles because other types of bacteria produce them and they can damage membranes. They showed that GBS do produce such vesicles, and injecting just the vesicles into the amniotic sacs of pregnant mice could cause preterm birth and fetal death. They reported their findings in the Sept. 1, 2016, issue of PLoS Pathogens.
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