# BioWorld

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Actionable Intelligence • Incisive Analysis

Clarivate Analytics

June 19, 2017
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BIO 2016 to BIO 2017

## Taking stock: Investors remain upbeat on biotech's future

*By Peter Winter, BioWorld Insight Editor*

SAN DIEGO – The Biotechnology Innovation Organization's (BIO) International Convention, which runs June 19-22, returns to the thriving southern California biotechnology hub of San Diego just three years since it last hosted the giant event in 2014. The meeting allows a chance for industry leaders to take stock of progress that has been made to date. Overall, it appears that the report card is good. The

See Investors, page 3

## After U.K. election, industry hopes to preserve interests post-Brexit

*By Nuala Moran, Staff Writer*

LONDON – The equivocal result in the snap U.K. general election has amplified uncertainty but left the life sciences sector more hopeful of a Brexit that preserves its interests in trade, regulation and access to skills.

"There has been a change in the Brexit weather," said Steve Bates, chief executive of the

See Brexit, page 5

## European leaders to finalize rules on EMA relocation contest this week

*By Cormac Sheridan, Staff Writer*

DUBLIN – The heads of the European Union's member states are due to agree on the ground rules for the contest to decide on a new location for the London-based EMA during a European Council meeting in Brussels this coming Thursday. The beauty pageant involving more than a dozen European cities will then begin in earnest,

See EMA, page 6

## Checkmate lines up chess pieces, eyes pivotal program with $27M series B

*By Marie Powers, News Editor*

Checkmate Pharmaceuticals Inc. might be the only immuno-oncology (I-O) company that's not attending the BIO International Convention in San Diego. Instead, the Cambridge, Mass.-based firm will spend the week plotting the next moves to

See Checkmate, page 7

## CFDA challenged by huge patent surge amid policy changes

*By Carmen Ho, Staff Writer*

HONG KONG – China has seen a huge spike in patent applications, many of which are for pharmaceutical products. However, regulatory agencies such as the CFDA have yet to adapt to the changing patent landscape and to cope with the rapid surge.

The number has spiked so much that in one week

See CFDA, page 9

### Newco News

## Korea's Orum Therapeutics raises $8M in series A financing

*By Haky Moon, Staff Writer*

HONG KONG – South Korean startup Orum Therapeutics Inc. has a shot at effectively blocking RAS gene function with an innovative technology co-developed with Ajou University in South Korea and last week raised $8 million in a series A round

See Orum, page 11

### The BioWorld Biome

A(lzheimer's) to Z(ika virus)

## Development to dementia, stem cells help understand the brain

*By Anette Breindl, Senior Science Editor*

BOSTON – The human brain, Jürgen Knoblich told the audience at the 2017 annual meeting of the International Society for Stem Cell Research (ISSCR), consists of "86 billion neurons that have

See Stem cells, page 8

## Australia's Senate passes TGA reform bill for drugs, devices

*By Tamra Sami, Staff Writer*

PERTH, Australia – Industry stakeholders in Australia welcomed the Senate passage of the drug and device reforms contained in the Therapeutic Goods Amendment (2016 Measures No. 1) Bill 2016 last week.

Approved by Australia's House of Representatives on March 27, the bill will now go to the Attorney General to be signed off as law. The bill is the first of three expected to make it through Parliament that will overhaul the nation's drug and device regulations.

See Australia, page 10

### Bench Press

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

Read this week's edition

## Regulatory front

The **FDA** said its voluntary pilot project that introduced industry to an automated form for field alert report (FAR) submissions has been successful, and the agency is making a new version of the automated form – FDA 3331a – publicly available on its website. The new version incorporates feedback from pilot project participants. The FDA said it encourages all of industry to use this new automated form to submit FARs for both the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research-regulated drug products approved under an NDA or an abbreviated NDA.

## Financings

**Argos Therapeutics Inc.**, of Durham, N.C., entered a note purchase agreement for the sale of a secured convertible promissory note in the principal amount of $6 million to **Pharmstandard International SA**, of Moscow, in a private placement. The sale of the note is expected to close on June 21.

**Celsion Corp.**, of Lawrenceville, N.J., said in an SEC filing that it would withdraw its proposed stock offering of about 2.45 million shares and warrants. The company's stock price (NASDAQ:CLSN) closed Friday at $3.20, up $1.15, or 56 percent.

**Mersana Therapeutics Inc.**, of Cambridge, Mass., set terms for its IPO, aiming to raise $75 million through the sale of 5 million shares at a price range between $14 and $16. J.P. Morgan, Cowen & Co. and Leerink Partners are the joint bookrunners on the deal.

**Prometic Life Sciences Inc.**, of Laval, Quebec, entered an agreement with Cantor Fitzgerald Canada Corp. as a lead underwriter and sole bookrunner, on its own behalf and on behalf of a syndicate of underwriters, under which the underwriters have agreed to buy, on a bought-deal basis, about 31.2 million shares in the capital of the company at a price of C$1.70 (US$1.29) per share for gross proceeds of about C$53.1 million. Underwriters have an option to purchase about an additional 4.6 million shares at the same price.

**Recce Ltd.**, of Sydney, entered an agreement for a flexible funding commitment of up to about A$6 million (US$4.5 million) with the Australian Special Opportunity Fund LP, providing capital to support Recce's synthetic antibiotic through its IND application with the FDA and phase I trials with RECCE-327, a sepsis candidate.

## Other news to note

**Bavarian Nordic A/S**, of Copenhagen, said the Biomedical Advanced Research and Development Authority intends to award a sole source contract to the company for the procurement of lyophilized Imvamune, a smallpox vaccine.

**Bristol-Myers Squibb Co.**, of New York, said it is selling its small-molecule active pharmaceutical ingredient manufacturing facility in Swords, Ireland, to **SK Biotek Co. Ltd.**, of Daejeon, South Korea, a wholly owned subsidiary of SK Holdings. The deal is planned to be completed by the fourth quarter, at which time SK Biotek will continue to manufacture the current portfolio of small-molecule pharmaceutical products at the site. Financial details on the transaction were not released.



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# Investors

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biopharmaceutical sector, despite some major challenges in the intervening years, is continuing to generate support from investors, and that is reflected by the 10 percent growth in the BioWorld Biopharmaceutical Index in that period, and the almost $140 billion collectively raised by public and private companies to fuel their product development activities.

However, it has been a bumpy ride for the sector. The famous Dickens quotation, "It was the best of times, it was the worst of times," aptly sums up its performance since BIO 2014 was held.

The BioWorld Biopharmaceutical Index hit a record high, up more than 36 percent, a month after BIO 2015 convened in Philadelphia and the collective market caps of public companies hovered around $1 trillion. Gilead Sciences Inc., for example, reached a market cap of $175 billion and Amgen Inc.'s market cap stood at $120 billion.

Unfortunately, that high point for the industry was quickly forgotten in the months that followed BIO 2015, as the sector ran into some major turbulence when the cost of innovative drugs become a key item on the political agenda. (See *BioWorld Insight*, Oct. 5, 2015.)

By the time BIO 2016 rolled around in San Francisco, all those gains had been erased and the mood heading into last year's meeting was decidedly pensive, with a number of issues top of mind, including drug pricing, the mounting costs of R&D and decreasing innovation in terms of new drugs being approved. The industry's collective market cap had also slipped to $725 million and Gilead had ceded its number one spot in terms of market capitalization to Amgen. (See BioWorld Biopharmaceutical Index BIO14-BIO17, below.)

Drug developers have also seen their valuations whipsaw dramatically since the end of June 2014. The BioWorld Drug Developers Index has followed a similar trajectory to their blue chip colleagues oscillating between a 40 percent rise in value to a 30 percent reversal in fortunes, with emerging

## Biopharma fund raising ($M)

| | BIO14-BIO15 | BIO15-BIO16 | BIO16-BIO17 |
|---|---|---|---|
| **Public Offerings** | 20,373 | 34,238 | 26,530 |
| **Public/Other** | 9,435 | 7,057 | 11,796 |
| **Private** | 7,350 | 9,751 | 12,213 |
| **Total** | 37,157 | 51,046 | 50,539 |

R&D-focused companies taking the brunt of the ongoing drug pricing debate. However, after touching that low point, the index has seen a remarkable recovery regaining its losses and climbing back into positive territory. (See BioWorld Drug Developers Index BIO14-BIO17, p. 4.)

### On an upswing

The 16,000-plus delegates attending BIO 2017 this week will certainly be in a more positive mood as the sector appears to have got its groove back once again. In the 12 months since BIO 2016, the Biopharmaceutical index has climbed in value almost 10 percent and the Drug Developers index an even more dramatic 38 percent. (See BioWorld Biopharmaceutical Index BIO15-BIO16, p. 4, and BioWorld Drug Developers Index BIO15-BIO16, p. 12.)

The upswing has been driven by investors being attracted back into the space thanks to companies posting solid first-quarter 2017 financial returns and projecting a bullish period for their drug sales for the rest of the year.

Also helping the sector has been the strong performances of the general markets over the past year, with the Nasdaq Composite hitting record highs and gaining 28 percent and the Dow Jones Industrial Average up about 18 percent in the same period.

Along the way, the exciting developments in immuno-

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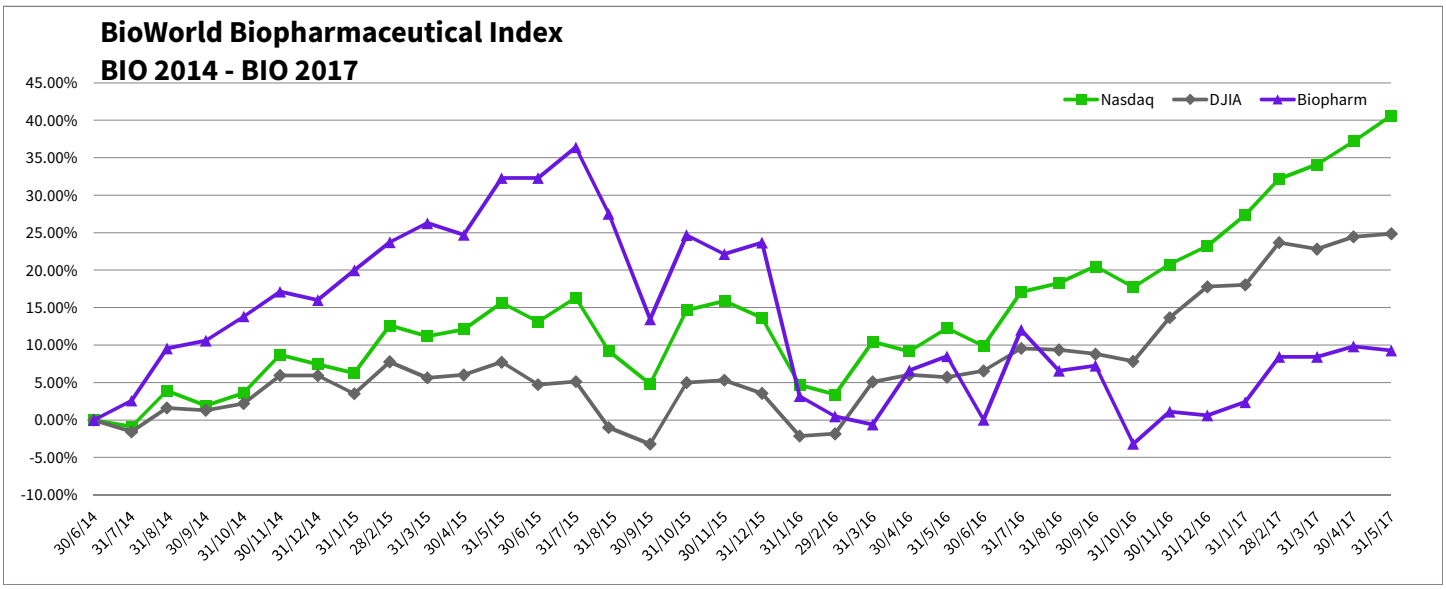

## Investors

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oncology, gene editing and gene therapy, which are paving the way for new approved medicines, continue to keep investors engaged.

The sector's investments to discover new technologies looks as though it is also back on track to make up for its poor return when only 22 new molecular entities (NMEs) received the FDA's green light in 2016, the fewest number for five years. However, in the first quarter of this year, 12 NMEs were approved, outperforming comparable periods since 2013.

At that pace, the industry could be on target to beat the record total of 45 new medicines that were approved in 2015. (See *BioWorld Insight*, Dec. 27, 2016.)

> *"Despite the uncertainties on the capital markets during the past three years, public and private biopharma companies have had no difficulty raising capital – almost $139 billion, in fact.*

Breaking down the data between the BIO conventions, in the 12 month period since BIO 2016, 29 NMEs have been approved by the FDA, compared to 45 between BIO 2015 and BIO 2016, and 38 new medicines between BIO 2014 and BIO 2015.

While the total approval of 112 new medicines in three years

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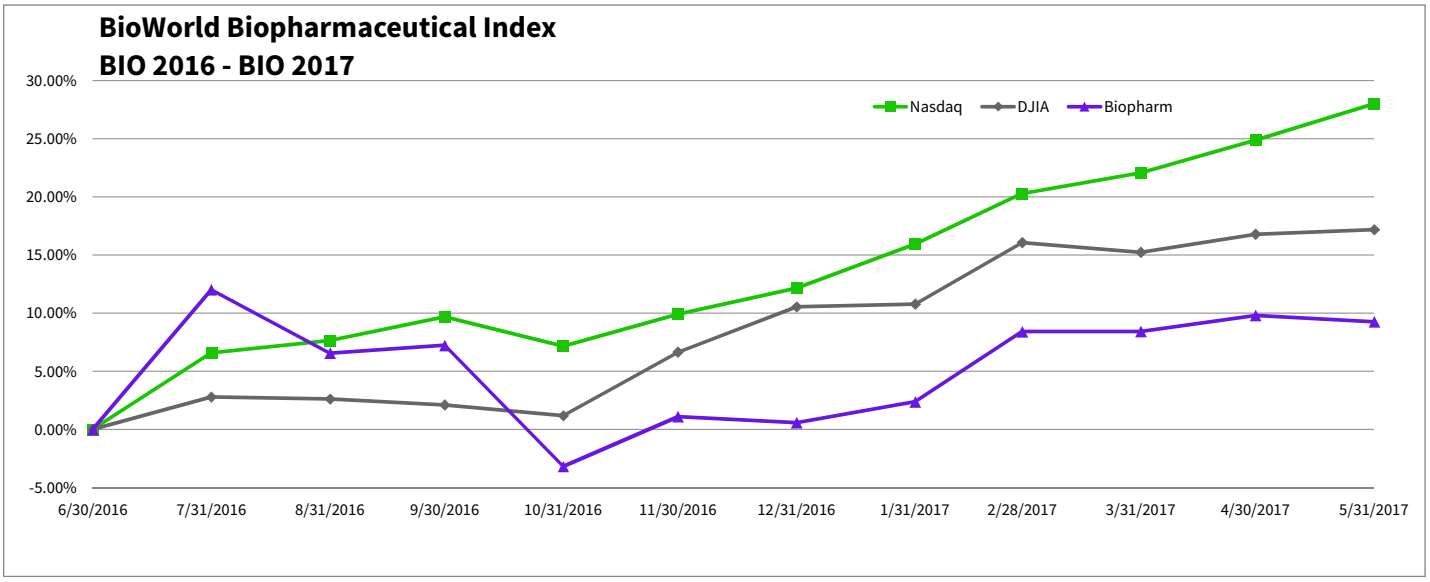


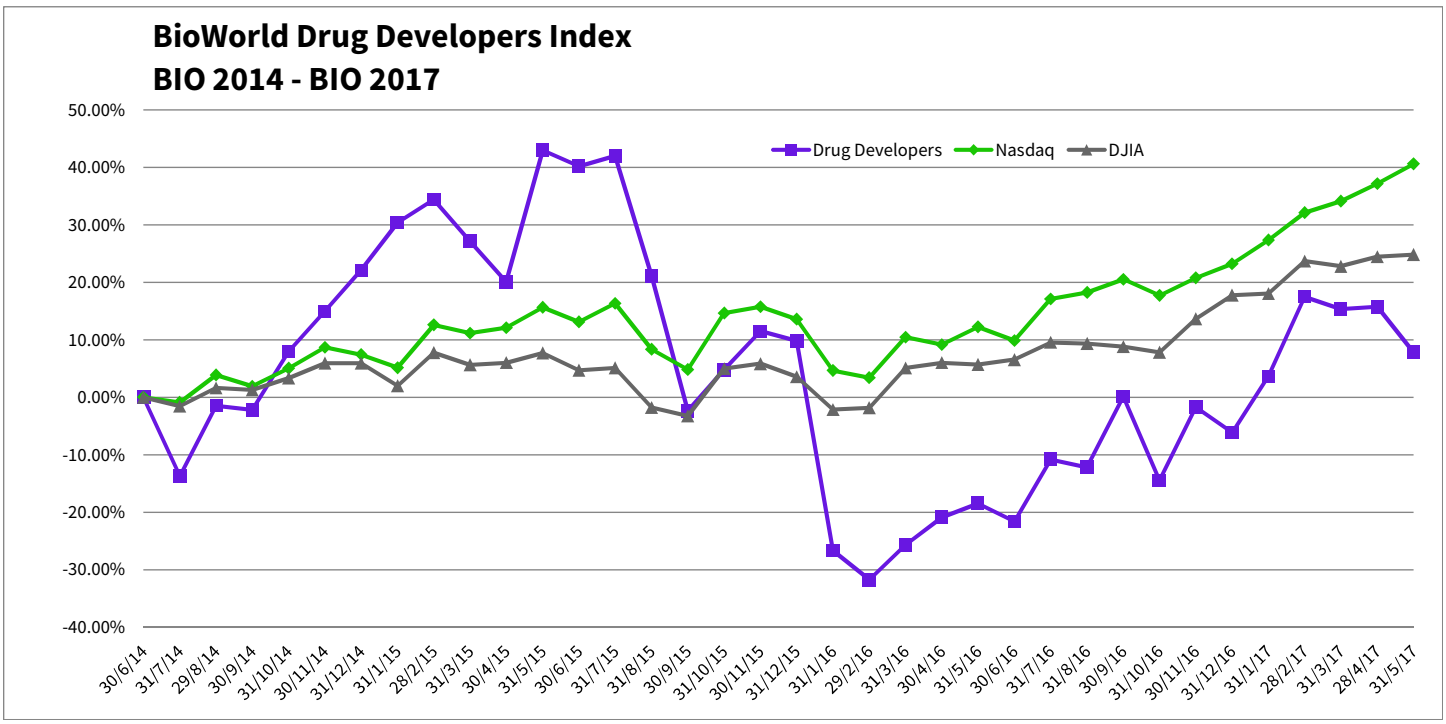

# Brexit

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Bioindustry Association.

Prime Minister Theresa May called the election in a bid to secure a firmer mandate for a hard, cliff edge Brexit, in which all ties with the EU are cut at the point of withdrawal in March 2019.

But having lost seats and ending up with no overall majority, the government is exposed to public opinion and its backbench members of Parliament (MPs). "It feels like there is not the desire or so much vocalness to push through such a hard Brexit," said Bates, in the monthly Brexit webinar he has been staging to keep BIA members up to date on the state of play.

Formal negotiations on the U.K.'s withdrawal begin in Brussels Monday. These are fraught with difficulty for a minority government, especially given that one of the first items on the EU's agenda is the size of the U.K.'s "divorce bill." As Bates observed, "The EU is ready to go, the U.K. is weak and wobbly – the government is still sorting itself out."

May has signaled she is sticking to the plan for Brexit she set out in January, in which the U.K. would be outside the customs union, the single market and regulatory agencies, including the EMA.

BIA and the Association of the British Pharmaceutical Industry have been working behind the scenes to protect the interests of the sector, which the two trade bodies framed around four requirements following consultation in September 2016. The industry wants to retain a common system of regulation, the ability to trade goods and capital across borders, long-term predictable public funding for research and access to Europe's talent pool.

Bates said the industry's preferred position has not changed following the election. He said he believes there has been progress in agreeing that while the EMA will relocate its London headquarters, the U.K. regulator, the Medicines and Health products Regulatory Agency (MHRA), will remain a member of the EMA club.

"I expect the government position on this in the next few weeks. We have ensured this is at the top of ministers' in-trays," said Bates.

BIA is holding its annual joint meeting with MHRA on July 14 and Bates is hoping to hear more then.

### Wriggle room

There was consternation in April, as the EMA opened discussions with national regulators on how the workload currently carried out by MHRA should be reallocated, to see the working assumption that the U.K. will no longer participate in the work of the EMA and the European medicines regulatory system. (See *BioWorld Today*, May 2, 2017.)

That concern was heightened last month when the EMA and the European Commission published a notice for all marketing authorization holders advising them to make legal preparations for the eventuality the U.K. is outside the system.

Bates said the EMA was providing the advice "in case we end up with a hard Brexit." However, there is more than one potential outcome and the EMA has "left wriggle room" for a future deal in which MHRA stays in the club.

> *"Our position remains the same. Whatever the location of EMA, the U.K. should be part of it.*
>
> Steve Bates
> CEO, Bioindustry Association

"Our position remains the same. Whatever the location of EMA, the U.K. should be part of it," said Bates.

The European Council is due to endorse the procedural arrangements for the relocation of EMA at its next meeting this week. The council will then decide where EMA's new home will be in October. (See story in this issue.)

The pressure for the enfeebled U.K. government to adopt a more nuanced approach to Brexit applies particularly to trade in the single market and customs union.

Prominent members of May's Conservative party, including former prime minister David Cameron – who is due to make a keynote address at the BIO International Convention in San Diego this week – former prime minister John Major and former leader of the Conservative party William Hague, have each questioned whether May has a mandate for a hard Brexit, and called for a softer approach.

May's poor showing in the election left her without the authority to shuffle ministers and her cabinet consists of 15 remainers (she herself was in the remain camp in the referendum) and seven who campaigned to leave the EU.

What politicians as a whole take away from the general election is "unclear and open to interpretation," Bates said. "The government is split; Parliament is split; the country is split."

An arrangement under which the government is to be propped up by 10 MPs from the Democratic Unionist party of Northern Ireland only gives an overall majority of six, and there are many elements of Brexit-related legislation on which May cannot necessarily rely on the support of all her own party.

As Bates noted, minority governments are rare in the U.K. and traditionally they do not last long. "There will be little opportunity to get contentious legislation through, the government will be unable to make big decisions and ministers will have all their time taken up by [getting legislation through] Parliament," he said. "There is a reasonable chance of another election this year." ♦

# EMA

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with a winner expected to be named in October.

The EU's top two officials, European Council President Donald Tusk and European Commission (EC) President Jean-Claude Juncker, have already circulated a draft proposal on how to proceed. They suggested six criteria according to which competing bids would be assessed: accessibility, educational facilities for the children of EMA staff, labor market access for the spouses of staff, business continuity, and whether the new location would meet the EU's twin policy objectives of ensuring a geographical spread of its agencies and of locating new agencies in eastern European states.

The heads of the EU's member states will have the final call on defining the key parameters, however. Tusk and Juncker have also set out an indicative timetable for the decision-making process. "They are proposing that member states submit their bids at the end of July, with the aim of taking a decision in the autumn," an EU official told *BioWorld*. "The final decision is to be voted on by the member states."

This week also marks the start of formal Brexit negotiations, in which the precise terms according to which the U.K. will leave the EU will be hammered out between the U.K. government and an EU negotiating team. That is a parallel process, however, with no direct bearing on the EMA relocation initiative.

The U.K. is due to finalize its exit from the EU at the end of March 2019. The EC wants to have the EMA up and running in its new home by then as well, which gives the drug regulator about 18 months to plan and execute its move. It's a tight timetable but one that may not be strictly necessary to adhere to, given that the EMA has a lease on its present building in London that runs through 2039. Nevertheless, several cities have incorporated that deadline into their plans, by nominating existing buildings as the EMA's possible future home.

Barcelona is proposing Torre Glóries, a 38-story building with 320,000 square feet of office space located about a dozen blocks from the Mediterranean. Milan is offering space in its iconic Pirelli building. Copenhagen had initially intended to offer a purpose-built office building, but has since shelved that plan in favor of an existing building near the city's airport, Lars Rebien Sorensen, special envoy on the Copenhagen bid, told *BioWorld*, because of the emphasis on ensuring business continuity.

Dublin is sticking with its original plan of developing a new building from scratch if it wins the bid. It has identified two possible locations, in the city's rapidly developing north docklands area or in a new office park which is being built adjacent to the city's airport. Either option would offer fast access to the airport. Also in the running are Stockholm, Amsterdam and Lille, a city in northern France which is easily reached from Paris and Brussels.

Sorenson, who last year completed a highly successful 10-year stint as CEO of Denmark's flagship biopharma firm, Novo Nordisk A/S, adds real heft to the Copenhagen bid. He also brings a typical Scandinavian candor to the contest. "It's a coin toss between the leading candidates," he said. "I think the EMA could function in at least five to seven locations in Europe."

> *"It could easily be felt very quickly if we end up in a dysfunctional situation.*
>
> Lars Rebien Sorensen
> Special envoy on the Copenhagen bid for the EMA

Those with strong research institutions and academic medical centers are the best places, he said. "The most important thing is we get EMA located in a place where EMA can function."

Its successful operation in London means that many European citizens may not be aware of its importance. "It could easily be felt very quickly if we end up in a dysfunctional situation," he said.

### Location, location, location

Copenhagen is one of Europe's strongest biopharma hubs. It also offers, Sorenson said, a good quality of life, a green environment and is a secure place to live. Its northerly location, however, is not ideal. "The location of Copenhagen is one of those things you cannot change," he said.

Amsterdam, in contrast, offers a central location as well as one of Europe's best connected aviation hubs. Although Sweden's Medical Products Agency punches well above its weight within the EMA network, Stockholm is even less ideally located than Copenhagen.

Dublin is also on Europe's periphery, even if it is just a short hop from London. Of all the remaining 27 EU member states, Ireland is most exposed to economic risks from Brexit, although Dublin itself stands to benefit from a wave of financial services firms transferring certain functions currently from London to an EU base.

The Dublin bid will not be helped by a recent report from Ireland's National Competitiveness Council on the Cost of Doing Business in Ireland, which identified the current housing shortage in Ireland as "an impediment both to attracting mobile inward investment and the expansion of operations by enterprises." Housing in Dublin has reached crisis proportions, with spiraling rents and a shortage of homes to buy. The shortage does not affect well-paid professionals, Tommy Fanning, head of biopharmaceuticals at IDA Ireland, the country's inward investment agency, told *BioWorld*. "We have a housing issue for people on low incomes."

Supplying up to 400 hotel rooms per night could also prove a stretch – the city currently suffers from under-capacity, although that will be ironed out in the coming years. Other contenders, such as Amsterdam and Copenhagen, also suffer from "growing pains," Fanning said. "We're no different."

Dublin is setting out its stall on the strength of its biopharma manufacturing base, its English language environment, and the prominence of its drug regulator, the Health Products

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# Checkmate

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advance its only asset, CMP-001, after completing a $27 million series B preferred financing led by new investor F-Prime Capital Partners.

"We're not in partnering mode," founder and CEO Art Krieg told *BioWorld*.

Existing investors Sofinnova Ventures and Venbio Partners participated in the round, intended to advance the development of CMP-001 into, though not through, a pivotal program in melanoma that will serve as the company's next major inflection point. Checkmate is enrolling patients in a phase Ib trial examining the CpG-A oligonucleotide, which activates the innate immune system via Toll-like receptor 9 (TLR9), in combination with Keytruda (pembrolizumab, Merck & Co. Inc.) in primary refractory melanoma patients who progressed on or failed anti-PD-1 therapy.

The company is working with the FDA to assess the regulatory pathway for CMP-001 and to seek guidance on the structure of pivotal studies – notably, whether the agency will require a randomized, controlled, two-arm design with a comparator or allow single-arm trials.

"We can't say, for sure, how long the financing round is going to take us in melanoma until we have those discussions," Krieg said.

The company is eyeing additional tumor indications for CMP-001 and expects to move the combination approach into one or two more studies around the first quarter of 2018.

The round came together quickly and fairly easily, even considering that "it's not that hard raising money in I-O," Krieg admitted.

Checkmate completed a $20 million series A in 2015 – drawing down half the amount in its first tranche and the other half in 2016, according to SEC filings – and added a $5 million extension earlier this year.

"We had some early positive clinical data with the first $20 million but not as much as we really wanted to establish the efficacy of the drug," Krieg explained.

With the series A extension sufficient to see the company into the fourth quarter, "we were casually having conversations" with potential investors about initiating a series B later in the year, "but we weren't pursuing anyone," he said. With noticeable interest in the asset, Ben Auspitz, an F-Prime partner, came forward with a term sheet.

"We liked the terms and we like Ben, so we decided to move forward," existing investors in hand, Krieg said.

### 'We can show this is working in the clinic'

An immunologist who discovered immune stimulatory CpG DNA in 1994, Krieg previously co-founded Coley Pharmaceutical Group to develop the technology. That company hit the skids in 2007 when its lead candidate, a TLR9 agent targeting hepatitis C, showed limited efficacy in phase I and II trials and ran into competitive challenges in the indication. (See *BioWorld Today*, Jan. 24, 2007.)

> *"We're not in partnering mode.*
>
> Art Krieg, founder and CEO
> Checkmate Pharmaceuticals Inc.

Pfizer Inc. acquired Coley in 2008, and Krieg was named chief scientific officer of the New York-based company's oligonucleotide therapeutics unit until the pharma exited the field in 2011. At that point, Krieg co-founded Rana Therapeutics Inc., also of Cambridge, Mass., serving as its CEO through 2013, when he was named chief scientific officer at Sarepta Therapeutics Inc., of Cambridge, a post he held for a year. (See *BioWorld Today*, Nov. 19, 2007, and Jan. 19, 2012.)

Krieg saw an opportunity in I-O with the asset then known as CYT-003, held by struggling Cytos Biotechnology AG (now Kuros Biosciences AG), of Schlieren, Switzerland, which had failed a phase IIb attempt in allergic asthma in dramatic fashion. A one-time board member of Cytos, Krieg formed Checkmate and scooped up the asset and its underlying phage Qbeta-based virus-like particle (VLP) technology in a deal worth $90 million in milestones and double-digit royalties on related product sales. (See *BioWorld Today*, April 15, 2014, and Aug. 13, 2015.)

The emergence of checkpoint inhibition provided a scientific rationale for the failure of TLR-based therapies as originally envisioned, Krieg reasoned, and the incomplete success of checkpoint inhibitors provided TLR-targeting therapies with a significant opportunity.

"What's missing in the checkpoint inhibitor approach is you still need to have the immune system activated in order for this to work," Krieg said at the time.

By packaging a CpG-A oligonucleotide with a VLP – the only candidate of its kind in clinical development to do so, he said – CMP-100 is designed to activate the innate immune system via TLR9 and mediate tumor control by the subsequent induction of innate and adaptive antitumor immune responses.

"What differentiates our drug in terms of mechanism of action is that we act more specifically than any other therapeutic that I am aware of to activate the particular type of immune cell that we think is an underappreciated keystone cell in regulating tumor immunity," Krieg pointed out.

That body of cells, known as plasmacytoid dendritic cells, or PDCs, is unfamiliar even to many "self-proclaimed immuno-oncologists," he contended. "We think these cells control the tumor microenvironment and regulate whether a tumor is going to be cold or hot."

PDCs represent the body's largest producer of type 1 interferons, Krieg said, "and we know the best criteria to distinguish hot tumors from cold tumors is interferon."

Last year, the company reported data at the American Association for Cancer Research (AACR) annual meeting in New Orleans showing that, in mice challenged bilaterally with B16F0 melanoma, CMP-001 VLPs locally, but not distally, decreased

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## Stem cells

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to be born at the right time, move to the right positions and wire up in the right way."

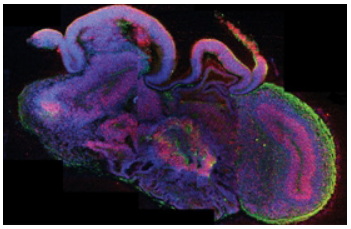
Knoblich is the deputy scientific director of the Institute of Molecular Biotechnology of the Austrian Academy of Sciences, and researchers in his laboratory were among the first to develop brain organoids, or cell cultures that can recapitulate the 3-D organization of various areas of the developing brain. (See *BioWorld Today*, Aug. 29, 2013.)

At the ISSCR meeting, Knoblich chaired a session on organoids during which he gave an overview of how his team has continued to develop the technique.

While the first brain organoids consisted of multiple types of brain cells, and multiple brain regions, the spatial relationships of those organs to each other did not necessarily mirror those of the developing brain. The biggest current limitation of brain organoids, Knoblich said, are that they are "extremely variable" in their anatomical organization.

His team, however, is developing several ways to reduce such variability.

One possibility is to provide the organoids with engineered scaffolding during their development. Madeline Lancaster, who was the first author of the papers originally describing brain organoids and is now a principal investigator at the British Medical Research Council Laboratory of Molecular Biology, has shown that growing the brain organoids in the presence of rod-like fibers will induce them to take on a rod-like shape themselves.



*Brain organoid (photo: Madeline Lancaster)*

The utility of scaffolds were discovered in a way that echoes Alexander Fleming's discovery of penicillin – through contamination, when "some fibers from Madeline's shirt fell into culture." The team is now working on coupling the fibers with growth factor gradients, in an attempt to recreate the anterior posterior axis of the developing brain.

Another avenue Knoblich's team is exploring is to start with more specific brain regions, and then co-culture them to allow them to establish connections. Through such multistep culturing, the team has engineered organoids whose dorsal and ventral regions have the correct spatial relationship to each other. That, in turn, has enabled them to study the migration of interneurons, which migrate from the ventral to the dorsal part of the organoid, as they do in a developing brain.

In the developing brain, such migration also takes place along blood vessels, and integrating blood vessels into the organoids is another goal for brain organoid developers. That particular advancement, though, is still waiting for a stroke of luck akin to dropped fibers. "We've tried the simple things, and they don't work so well," Knoblich said.

The organoids developed by Lancaster are at the developmental stage of a 9-week old brain, and at the

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# CFDA

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last month, the number of patents registered for the week doubled from around 50,000 on average.

"With the rapid development of local innovations in the health care industry, the patent applications have shown a sustained rising trend in the recent three years, which results in the heavy workload of the CFDA," Neil Wang, global partner at market research company Frost & Sullivan, told *BioWorld*.

According to the latest figures from the World Intellectual Property Organization (WIPO), in 2015 there were more than 1 million patent applications in China, a sharp increase from 10 years before. In 2005, there were only 97,948 applications. In 2014, there were 837,817 applications, and in 2013 there were 734,096. WIPO statistics show a consistent increase since 2001.

Pharmaceuticals account for 5.37 percent of the total patent applications from 2001 to 2015.

To put that into perspective, the U.S. saw 529,632 patent applications in 2015, a slight increase from 509,521 in 2014. In contrast with China's consistent increase, U.S. patent trends have seen dips and small upturns. However, the share of pharmaceuticals in its patent game is higher, at 6.21 percent of all applications from 2001 to 2015.

Pressured by the World Trade Organization to comply with intellectual property (IP) regulations, China is seeing more and more patented drugs enter the market. However, patented drugs still amount to only 22 percent of total drug sales, according to the 2016 ITA Pharmaceuticals Top Markets Report on China.

Over the past decade, patented drug sales have enjoyed double-digit growth rates, but in the last few years, government policy changes regarding reimbursement, tendering, hospital financing and sales promotion have hurt revenues significantly.

And despite impressive growth in the pharmaceutical sector in China, the industry still relies heavily on generic drug production since most domestic drugmakers cannot compete with multinational pharmaceutical giants.

"The increase in the number of patent applications indicates the emerging transition from generic-based to local innovative-based in [the] domestic health care market. Coping with the surging demand of patent applications, the effectiveness of examination and approval in CFDA should also be improved accordingly by speeding up its reporting frequency and optimizing its approval process," said Wang.

"At this point, the health care industry in China is facing great challenges from both government supervision and enterprise competition during the transition period," he added.

Recently, there has been some serious discussion in China regarding the use of IP laws to encourage more innovative drugs. One major step forward was the March amendments to China's Patent Examination Guidelines. The Decision on the Revision of the Patent Examination Guide (2017) (No. 74), which came into effect on April 1, permits post-filing supplementation of data in certain circumstances.

In addition to that reform, there have been discussions on issues involving data exclusivity, lack of patent term extension and patent linkage.

"We want to study the policy of encouraging drug innovation, improve patent linkage and the data protection system, and to achieve domestic and international clinical data mutual recognition, reducing the cost of R&D," said CFDA Commissioner Bi Jingquan during a press conference at the time of the National People's Congress (NPC) Meeting on Feb. 27.

In October 2016, Bi made a similar remark, stating that "efforts should be made in research clinical trial management, data protection, patent linkage and other policies closely related to innovation, to promote regulatory innovation and the transformation and upgrading of the pharmaceutical industry."

### Enforcement, compliance issues

However, although the law states that IP rights are protected, the reality still shows rampant problems involving patent-violating drugs. Weak enforcement of the law often allows manufacturers to go unpunished for patent violations.

"China lacks patent linkage rules to resolve disputes before infringing products are launched on the market. Chinese law requires that a product must actually be sold in the market before a patent holder can even bring an infringement action," said the International Trade Administration (ITA) in its 2016 ITA Pharmaceuticals Top Markets Report on China.

"Further, although China's laws theoretically allow for injunctive relief, in practice injunctions are rarely, if ever, granted in pharmaceutical cases due to procedural and practical barriers. Moreover, monetary damages awarded by Chinese courts have proven far insufficient to cover lost revenue or discourage infringement."

The report further mentions the "serious problem" of the lack of patent term adjustment or restoration provisions to compensate for regulatory review and patent office delays, given the huge patent application review backlog at the State Intellectual Property Office and the CFDA.

All things taken together, China is moving rapidly in the direction of more reliable IP protection, but effective enforcement by government authorities and full compliance by pharmaceutical firms is yet to come. ♦

### Other news to note

**Cantargia AB**, of Lund, Sweden, and **Panorama Research Inc**., of Sunnyvale, Calif., said they entered a collaboration agreement to jointly accelerate Cantargia's second program directed toward autoimmune and inflammatory diseases. Cantargia's antibodies, against the molecular target IL1RAP, will be affinity-matured and humanized using Panorama's technology. In addition, Panorama will generate cell lines optimized for high level GMP production. Cantargia said it will be responsible for subsequent downstream development. In exchange for a fraction of future incomes from third parties or future sales, Panorama will share the risk in the project.

# Australia

Continued from page 1

The government has committed to implementing the reforms in a staged approach over the next two years, with a second bill covering further reforms expected to be introduced later this year.

Overall, the reforms stress a systems-based approach that focuses on long-term sustainable goals to both increase access to therapies and remove unnecessary regulatory burdens for industry. Among the reforms are new pathways that allow for earlier access to drugs and devices. (See *BioWorld Today*, Sept. 20, 2016.)

Bringing products more quickly onto the Australian market will be achieved, in part, by greater use of approvals by comparable overseas regulators like the U.S. FDA and the EMA. Under the current regulatory structure, Australian patients have to wait up to 15 months longer than the U.S. and Europe to access breakthrough medicines.

The move also brings Australia in line with other international regulators.

Regulatory reforms were especially needed since plans to form a joint "Australia New Zealand Therapeutic Products Agency" fell apart almost a decade ago. When those negotiations were put on hold, the Australian government agreed to introduce reforms to the TGA.

To make that happen, the government commissioned an independent review panel in October 2014 to examine Australia's drug and device regulatory framework to identify areas that were duplicative or ineffective, and to look for opportunities to position Australia to be more globally competitive.

Numerous industry consultations were held over the last two years, and the government signed off on the majority of the 58 recommendations made by the review panel.

Health Minister Greg Hunt told the Senate Standing Committee on Community Affairs that the bill would support the implementation of eight key recommendations of the Expert Review of Medicines and Medical Devices Regulation.

"These recommendations aim in particular to enable faster access to important new medicines and medical devices for Australian patients, as well as to streamline administration and reduce regulatory burden in several areas," Hunt said.

Some of those streamlined processes would replace the need for pre-approval with notifications for some variations to products that do not affect product safety and would lower costs to industry and, potentially, consumers through decreased TGA fees, he said.

AusBiotech said in its comments to the Senate committee that the reforms are expected to provide industry with annual savings of around A$75 million (US$57 million) by reducing unnecessary red tape and regulation on the drug and device industries. The association that represents biotechnology companies in Australia said it has been pushing for those reforms for more than a decade.

> *"These recommendations aim in particular to enable faster access to important new medicines and medical devices for Australian patients, as well as to streamline administration and reduce regulatory burden in several areas.*
>
> Greg Hunt
> Health Minister, Australia

"Priority review of medicines that offer substantial benefits over existing therapies or which address high unmet clinical needs for Australian patients will reduce registration working days by almost half," the association said in its submission. It also stressed that more efficient Special Access Schemes for patients would also mean a "life-saving difference."

The bill also enhances patient safety by collecting more postmarketing safety and efficacy data from sponsors to provide more information about new medicines approved under an expedited pathway.

### Wide support

AusBiotech CEO Glenn Cross told *BioWorld* that the association is "strongly supportive of the Therapeutic Goods Amendment (2016 Measures No. 1) Bill 2016, which will help reduce costs and administrative burden for industry, while ensuring safety and quality for patients."

Medical Technology Association of Australia (MTTA) CEO Ian Burgess said the association welcomed the passage of the new bill, particularly "the decision for greater use of overseas assessment to fast-track access to innovative and life-saving products, without compromising the integrity and safety of medical devices in Australia."

MTTA member companies are mostly small-to-medium sized companies that "complain about the avoidable red-tape, [and] this bill will go to streamlining the regulatory burden," he added.

The Australian Dental Association (ADIA) also praised the bill and the anticipated reduction in bureaucratic red tape. "ADIA has been a strong proponent for these reforms that will reduce the costs associated with conformity assessment," said ADIA CEO Troy Williams.

"This is a significant reform that's long overdue and we congratulate the commitment of the Australian Government to making the changes necessary to reduce the complexity of obtaining market approval for new and innovative patient diagnostic and treatment options," Williams said.

### Seeking comment on expedited pathways

The TGA is working on the next rollout of reforms that outline two separate expedited pathways.

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## Orum

Continued from page 1

to advance work in oncology indications.

The venture round included investments from Intervest Co. Ltd, KB Investment Co. Ltd, Solidus Investment Co. Ltd. and LB Investment.

"The financing will support our first program in oncology targeting activated RAS protein, a highly validated cancer drug target involved in aggressive cancers," Sung Joo Lee, co-founder and CEO of Orum, told *BioWorld*.

About 30 percent of all human cancers, including a high percentage of pancreatic, lung and colorectal cancers, are driven by mutations in RAS genes. And developing ways to block RAS gene function has been ineffective for almost about three decades, according to the National Cancer Institute.

The main members of the RAS gene family – KRAS, HRAS and NRAS – encode proteins that have a pivotal cytoplasmic role in cell signaling. When RAS genes are mutated, cells grow uncontrollably and evade death signals.

"Discovered nearly 35 years ago, the mutant RAS protein has been considered a highly validated cancer drug target, but also has a reputation as being undruggable," said Yong Sung Kim, principle investigator on the paper, co-founder of Orum and professor in the department of molecular science and technology at Ajou University.

Not only do RAS genes play a part in tumor formation, tumors with activating RAS mutations often do not respond to current treatment options, such as the EGFR-targeting drug Erbitux (cetuximab, Eli Lilly and Co.).

Along with scientists at Ajou University in South Korea, Orum developed a novel monoclonal antibody called RT11-i, which is internalized by the cell and directly targets the activated form of RAS.

"This cell-penetrating platform is significant. People have been trying this, but nobody really succeeded. Our recent publication supported the further development of our cell-penetrating antibodies as an anticancer agent. This shows that we have a real chance," added Lee.

Scientists at Ajou University published a study in *Nature Communications* showing that RT11-i binding is specific to activated RAS, binds those proteins inside the cell and blocks interactions with effector proteins. The result is an inhibition of downstream oncogenic signaling.

When given to tumor-bearing mice, RT11-i inhibited tumor growth in several xenograft models and was shown to be well-tolerated.

"This data shows that with our cell-penetrating antibody technology, we now have the ability to selectively inhibit activated RAS to achieve antitumor activity with a systemically administered monoclonal antibody," Kim explained.

In contrast to other approaches, Orum Therapeutics' antibody platform can target specific cell types, is easily adaptable to target different cell types and different intracellular proteins, and does not require chemical modification. This provides new opportunities to treat severe genetic diseases and cancer.

"We believe our technology has the capacity to create the first-in-class RAS-targeted therapeutic antibody for pancreatic, colon and non-small-cell lung cancers with RAS mutations," said Lee.

In connection with the financing round, Yeo Jung Moon, investment division director at Intervest, will join Orum's board.

"We were impressed with Orum's cell-penetrating antibody platform, which can transform antibodies to effectively target undruggable cytosolic targets, without chemical conjugation and with target cell specificity," Moon said. "We look forward to providing our expertise and guidance as the company creates new treatments for cancer and rare diseases."

Investing in biotech has been long-perceived as too-risky among conservative South Korean investors, which is a large majority, but the startup will need more than $8 million to bring the technology to patients.

"Our goal is to enter [a] phase I clinical trial by 2019. That's our first goal," Lee said. "It's probably going to cost more than $8 million. With $8 million, you can hardly finish phase I."

Plus, he noted, RAS is not the only target Orum has in its sights. "We need to try different targets." ♦

## Australia

Continued from page 10

The provisional approval pathway would allow sponsors to seek a time-limited provisional registration of certain medicines that don't meet full clinical data requirements, where the potential benefit of earlier availability outweighs the risk that additional data are still required.

The priority review pathway would involve faster assessment of certain prescription medicines that meet the TGA's full data requirements, with a target time frame of 150 working days for an approval decision. The provisional approval pathway, meanwhile, would be supported by broader reforms to develop more comprehensive postmarket monitoring for drugs and devices.

"The objective of the provisional approval pathway is to allow certain promising new medicines to reach patients with unmet clinical needs earlier than might otherwise be the case, while ensuring appropriate measures are in place to manage the risks inherent in the fact that additional data are still required," the draft guidance says. The pathway could allow medicines to reach Australian patients up to two years earlier than under the current framework.

The provisional approval pathway would involve four separate phases: A designation process where sponsors would apply for the expedited pathway; a premarket registration process whereby sponsors would submit a registration application and supporting dossier; a postmarket requirement in the provisional registration period; and a lapsing or transition to full registration. The TGA said it might allow rolling submissions that would be decided on a case-by-case basis. (See *BioWorld Today*, May 3, 2017.) ♦

## Investors

Continued from page 4

is not a bad haul, it is a number that can be improved upon. There are several sessions at this week's meeting devoted to improving on research and development, clinical trial design and regulatory oversight – measures that can speed more novel medicines to patients.

### By the numbers

Despite the uncertainties on the capital markets during the past three years, public and private biopharma companies have had no difficulty raising capital – almost $139 billion, in fact. (See Biopharma Fund Raising, p. 3.)

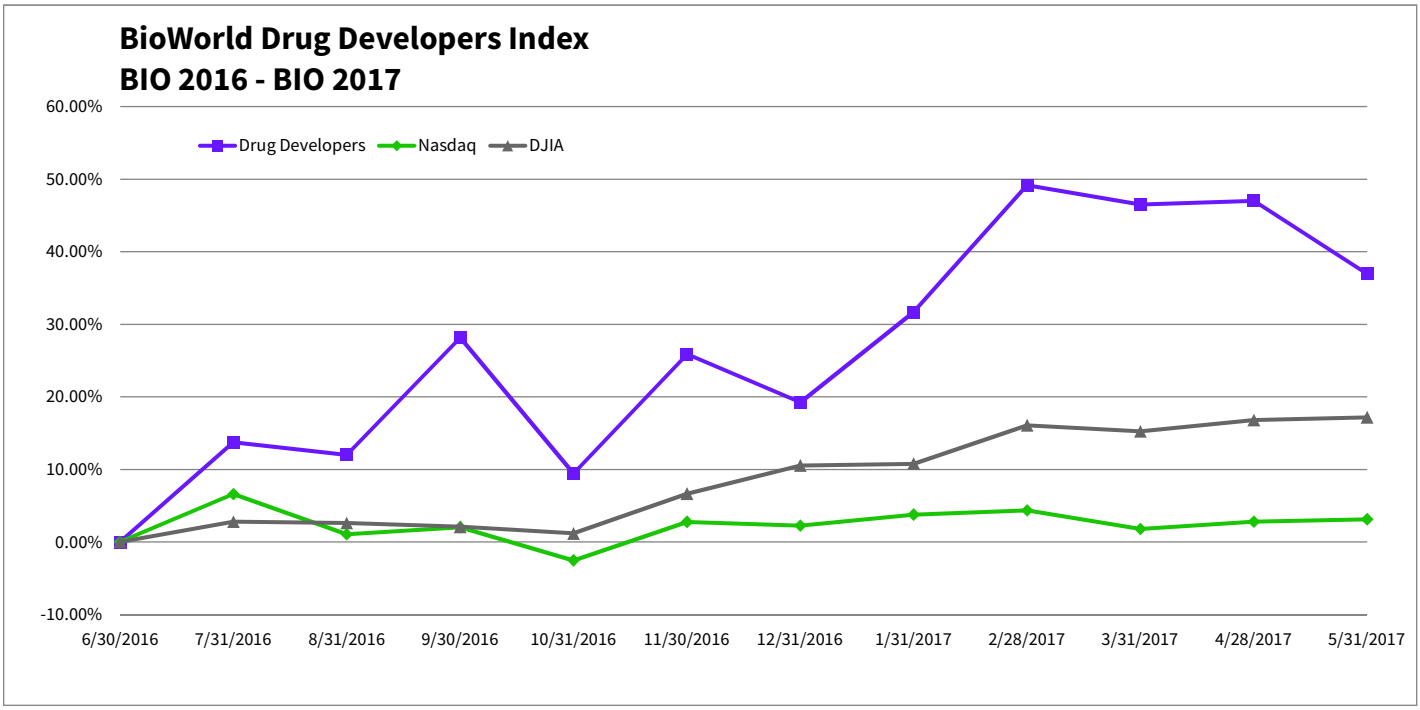
Of that total, approximately 60 percent was generated by public offerings, including follow-on financings and IPOs.

In fact, biotech IPOs have heated up of late. To date, 14 biopharma companies have successfully closed their IPOs on U.S. markets this year, generating $1.1 billion, according to *BioWorld.*

Since BIO 2014, no fewer than 132 companies have closed their IPOs on U.S. markets and a further 40 firms have completed IPOs elsewhere, bringing the total amount raised in that period to more than $17.4 billion, or an average deal size of $101 million.

In the 12 months since BIO 2016, the sector has raised a massive $50.5 billion comparable to $51 billion raised in the 12 months leading up to BIO 2015.

Those data demonstrate that delegates to this year's meeting have every reason to smile – investors appear to be onside, capital is flowing to support research and development and new medicines are reaching the market. However, there are still challenges to be faced, including the thorny issue of drug pricing, which continues to create headwinds for the sector. ♦




## EMA

Continued from page 6

Regulatory Authority, within the EMA organization. "Ireland has had a huge influence on the EMA, although it's a small agency," he said.

Filling the gap left by the possible departure of the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) from the EMA structure is, of course, a different issue.

The EMA reiterated on Friday that it "is working on the assumption that the U.K. will become a third country as of 30 March 2019," while noting that: "This is without prejudice to the outcome of the withdrawal negotiations." The agency is also carrying out impact assessments to help it to prepare for the move and to help it retain as many staff as possible once the move happens. The EMA board has also "endorsed principles and a working methodology" for undertaking a redistribution of its workload, in the event that the MHRA will no longer participate in its activities.

The EMA also said on Friday that its board decided to delay the introduction of a new EU clinical regulation, because of technical delays in setting up a clinical trial portal and database, which is intended to streamline the authorization and oversight of clinical trials across Europe. Originally intended to go live in 2018, this will not happen until 2019 at the earliest – the EMA will set out the timetable after the next meeting of its management board in October. Although the delay is not directly linked to the looming upheaval brought on by Brexit, it is not surprising to see key projects fall behind their implementation schedules. The EMA is having to rebuild itself physically and virtually over the next 18 months, while also discharging an already onerous set of responsibilities. ♦

## Stem cells

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meeting, Guo-Li Ming, a professor of medicine at the University of Pennsylvania, described generating organoids whose molecular signatures were "compatible with human prenatal development up to the second trimester," she told the audience.

How such model systems can be used to study both normal and aberrant development is intuitively obvious, and multiple presentations at the meeting reported on using stem cells to better understand neurodevelopmental disorders such as the microcephaly that can result from prenatal infection with Zika virus.

But scientists have also managed to use stem cells to gain new insights into neuronal diseases of aging.

At the meeting, Lawrence Goldstein, who is the director of the Sanford Stem Cell Clinical Center at the University of California at San Diego School of Medicine, described his team's work with iPSCs to understand the molecular mechanisms of Alzheimer's disease (AD).

By creating iPSCs from individuals with either familial or sporadic AD, and comparing them to iPSCs from individuals without dementia, Goldstein and his colleagues have been able to see differences that have led Goldstein to develop a two-hit theory of Alzheimer's disease, where deficiencies in axonal transport interact with the processing of amyloid precursor protein (APP) into Abeta in a way that ultimately causes neurodegeneration.

Goldstein and his colleagues compared iPSCs from AD patients to those from control individuals. Jerome Mertens, a postdoctoral research associate at the Salk Institute for Biological Studies, described an alternate approach. His team has developed a direct reprogramming method that can convert stem cells directly into neurons. And because the intermediate step of generating an iPSC from a skin cell is what strips the cell of its age, the directly reprogrammed cells, called induced neurons, or iNs, act like old cells rather than young ones. (See *BioWorld Today*, Dec. 2, 2015.) ♦

## Checkmate

Continued from page 7

tumor growth and modestly increased survival time. In an A20 B-cell lymphoma mice model, CMP-001 VLPs decreased local as well as distal tumor growth and improved survival time.

In December 2016, preclinical data presented at the American Society of Hematology meeting in San Diego showed that, in mice with A20 B lymphoma, the combination of CMP-001 and programmed cell death protein-1 induced systemic and durable antitumor responses. And preclinical data presented this year at the AACR annual meeting in Washington showed complete responses in both treated and untreated CT26 tumors in approximately 40 percent of the mice, using the triple combination of CMP-001, programmed death-ligand 1 antagonist and OX40 agonist. In addition, increased median survival time was seen with the triple combination compared with vehicle alone, single agents or double combinations of immune modulators.

In addition, "we can show this is working in the clinic," Krieg maintained. The open-label phase Ib study, expected to enroll approximately 60 participants with stage IV melanoma, is expected to report top-line data in mid-2018, according to Cortellis Clinical Trials Intelligence.

CMP-001 likely would qualify for orphan drug status from the FDA, according to Krieg, and the company is considering an application for breakthrough therapy designation.

"In talking with some of the [key opinion leaders] in the field, we have a data package that should support that," he said. "That's very appealing to us because it simplifies the pathway of discussing what an accelerated approval could look like."

Checkmate is considering ex-U.S. investigator-sponsored trials and agreed to provide its product for a number of investigator-initiated combination studies outside the U.S. – moves that Krieg said would help to position CMP-001 for filings with other regulatory bodies.

To that end, the company last week named Karen Brennan as chief operating officer. A 30-year biopharma veteran, Brennan most recently served as vice president of clinical and development operations at Forum Pharmaceuticals Inc., of Watertown, Mass., and previously held similar roles at Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, and its Takeda Oncology unit. Brennan's appointment completed Checkmate's senior management roster, bringing the company's head count to about 18 people. Although half of those are part-time consultants, the company expects to add six to 12 positions over the next 12 to 18 months, likely converting most of its consultants to full-time employees.

With M&A the long-term strategic goal, Checkmate is "in communication with pretty much everybody out there that has a PD-1 or PD-L1 in the body," Krieg said. "But we're definitely not in active discussions for partnerships. We are in active discussions for clinical collaborations, and we're eager to get those underway as quickly as possible." ♦

### Other news to note

**Conatus Pharmaceuticals Inc.**, of San Diego, is presenting a poster addressing preclinical results with lead pancaspase inhibitor emricasan at the Symposium on Cells of the Hepatic Sinusoid in Galway, Ireland. Human cirrhotic hepatocytes cultured in an advanced fluidic device that mimics the liver sinusoid, and treated in vitro with emricasan for 24 hours, exhibited higher albumin (+60 percent) and urea (+17 percent) production than vehicle-treated control hepatocytes, suggesting improved synthetic capacity. Similarly, hepatocytes isolated from cirrhotic rats after treatment with emricasan for seven days showed increased production of urea (+160 percent) and albumin (+156 percent), and higher cytochrome P450 3A4 (a liver enzyme) activity (+101 percent) compared with hepatocytes isolated from vehicle-treated control cirrhotic rats, suggesting improved synthetic and detoxification capacity.

## In the clinic

**Aurinia Pharmaceuticals Inc.**, of Victoria, British Columbia, presented duration of remission data from its phase IIb AURA-LV study in lupus nephritis during the European Congress of Rheumatology meeting in Madrid, Spain, showing that, over the course of the 48-week trial, patients on voclosporin stayed in remission approximately twice the amount of time as those in the control group. Those differences were statistically significant vs. the control arm. As previously reported, treatment with low-dose voclosporin showed statistically improved efficacy over the control arm at both 24 and 48 weeks, with a doubling of remission rates at 48 weeks vs. the control arm (49 percent vs. 24 percent). Of the low-dose voclosporin patients that achieved complete remission (CR) at 24 weeks, 100 percent remained in CR at 48 weeks. (See *BioWorld Today*, Oct. 3, 2016.)

**Bavarian Nordic A/S**, of Copenhagen, updated the expected timing of final results from its phase III PROSPECT study testing Prostvac (rilimogene galvacirepvec/rilimogene glafolivec) in men with metastatic castration-resistant prostate cancer. The company now expects data from the 1,297-patient trial, which measures overall survival as the primary endpoint, in the fourth quarter of the year, narrowed from an expectation of the second half of the year. In September, the independent data monitoring committee will meet to conduct the third interim analysis of the data to see if the trial should continue as planned, or potentially be stopped early for efficacy or futility.

**Beigene Ltd.**, of Beijing, reported data from a phase I trial testing its Bruton's tyrosine kinase inhibitor, BGB-3111, combined with the anti-CD20 antibody Gazyva (obinutuzumab, Roche Holding AG) in patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) and follicular lymphoma (FL) at the International Conference on Malignant Lymphoma in Lugano, Switzerland. The combination was well-tolerated with an overall response rate (ORR) of 89 percent, including 22 percent complete responses (CRs), in 18 patients with CLL and SLL who were previously untreated, and an ORR of 92 percent, including 16 percent CRs, in 25 CLL/SLL patients who were relapsed/refractory (R/R) to other treatments. Additionally the combination produced an ORR of 73 percent, including 33 percent CRs, in 15 R/R FL patients. Beigene plans to run a phase II pivotal trial of BGB-3111 in combination with Gazyva compared to Gazyva alone in patients with R/R FL. The company also plans to start a phase III trial comparing BGB-3111 with Treanda (bendamustine, Teva Pharmaceutical Industries Ltd.) plus Rituxan (rituximab, Roche/Biogen Inc.) in patients with treatment-naive CLL, based on data with BGB-3111 monotherapy presented earlier at the meeting.

**Biophytis SA**, of Paris, said it contracted with SGS Life Science Services to conduct the MACA-PK study of Macuneos in age-related macular degeneration (AMD). The phase I/IIa study is designed to evaluate safety, pharmacokinetics and pharmacodynamics in healthy volunteers this year, and then in patients with dry AMD in 2018, according to an optimized protocol. An oral treatment, Macuneos (BIO-201) is based on the activation of PPAR receptors to limit accumulation of A2E and slow down retinal degeneration.

**Bristol-Myers Squibb Co.**, of New York, reported extended follow-up data from the phase II CheckMate -205 study testing Opdivo (nivolumab) in adult patients with relapsed or progressed classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) at the International Conference on Malignant Lymphoma in Lugano, Switzerland. In 63 patients who hadn't received Adcetris (brentuximab vedotin, Seattle Genetics Inc.) previously, Opdivo produced an objective response rate (ORR) of 65 percent, with a complete response (CR) in 29 percent of patients. In those patients, the median duration of response (DOR) was 20 months and the median progression-free survival (PFS) was 18.3 months. In 80 patients who received Adcetris after ASCT, the ORR was 68 percent, with CR in 13 percent of patients. The median DOR was 16 months and the median PFS was 14.7 months in those patients. In a third cohort of 100 patients who received Adcetris before, after, or both before and after ASCT, the ORR was 73 percent, with CR in 12 percent of patients. And the median DOR was 15 months and the median PFS was 11.9 months. Opdivo was approved in the U.S. and EU for relapsed or refractory cHL following ASCT and Adcetris in 2016.

**Cerveau Technologies Inc.**, of Boston, said the FDA cleared its IND for its tau imaging agent, [18F]MK-6240. The company plans to work with its pharma partners to use MK-6240 in positron emission tomography scans to assess the status and progression of neurofibrillary tangles in the brain of patients with neurodegenerative diseases, including Alzheimer's disease. Cerveau licensed MK-6240 on a worldwide basis from **Merck & Co. Inc.**, of Kenilworth, N.J.

**Delmar Pharmaceuticals Inc.**, of Vancouver, British Columbia, presented a poster at the Society for Neuro-Oncology's 4th Pediatric Neuro-Oncology Basic and Translational Research Conference in New York, supporting the use of its interstrand DNA crosslinking drug, dianhydrogalactitol (VAL-083), in pediatric high-grade gliomas. Treatment of the brain cancer is limited, as the only approved therapy, alkylating agent temozolomide, is ineffective because pediatric brain tumors have high expression of the temozolomide-inactivating enzyme 06-methylguanine-DNA methyltransferase (MGMT) and low activation of the mismatch repair (MMR) pathway that temozolomide works through. VAL-083, on the other hand, is designed to maintain functionality regardless of the MGMT or MMR status and is also not affected by the p53 status of the tumor cells. VAL-083 has been shown to cause a robust and irreversible cell cycle arrest of cancer cells in vitro, potentially leading to programmed cell death.

## In the clinic

**Eli Lilly and Co.**, of Indianapolis, reported results from the extension period of the phase III SPIRIT-P1 trial testing Taltz (ixekizumab) in patients with active psoriatic arthritis (PsA) at the European Congress of Rheumatology in Madrid, Spain. Patients treated with Taltz at either 80 mg every two weeks or every four weeks following a 160-mg starting dose experienced either no progression or minimal radiographic progression of structural joint damage as measured by the change from baseline in the van der Heijde modified Total Sharp Score for PsA at 52 weeks. The most common treatment-emergent adverse events observed in patients treated with Taltz were nasopharyngitis and injection site reaction, consistent with what was seen in the phase III studies of Taltz for the treatment of moderate to severe plaque psoriasis. Taltz is currently under review by the FDA as a treatment of adult patients with active PsA. The drug is already approved for treatment of PsA in Japan, and submissions to other regulatory agencies around the world are expected later this year.

**Galera Therapeutics Inc.**, of Malvern, Pa., said it completed enrollment in its phase IIb study testing GC-4419, a dismutase mimetic, in reducing the incidence and duration of oral mucositis (OM) in head and neck cancer patients receiving chemoradiation therapy. The double-blind, randomized, controlled trial involves 223 head and neck cancer patients treated with either 30 mg or 90 mg of GC-4419 or placebo infusion on the days they receive their radiation treatment. The primary outcome measure is the duration of severe OM (defined as World Health Organization grade 3 or 4) experienced by patients receiving seven weeks of radiation therapy plus cisplatin. Secondary endpoints include incidence of severe OM.

**Genmab A/S**, of Copenhagen, reported preliminary data from the ongoing phase I/II study of tisotumab vedotin in solid tumors, with 11 of 34 evaluable patients in the cervical cancer cohort in part two of the study achieving a response. With a median time of treatment of 4.9 months, seven responders are still ongoing or in follow-up for progression. The safety profile of tisotumab vedotin was consistent with known MMAE-based antibody-drug conjugates, including peripheral neuropathy and neutropenia. Additionally, conjunctivitis was identified as a tisotumab vedotin-specific toxicity, which led to introducing of prophylactic management. Genmab has a license and collaboration agreement for tisotumab vedotin with **Seattle Genetics Inc.**, of Bothell, Wash., under which Seattle Genetics has the right to exercise a co-development option at the end of phase I development. (See *BioWorld Today*, Sept. 11, 2014.)

**Incyte Corp.**, of Wilmington, Del., and **Eli Lilly and Co.**, of Indianapolis, reported analysis of data pooled from eight Olumiant (baricitinib) clinical trials, showing that patients with moderate to severe rheumatoid arthritis (RA) treated with Olumiant had 3.8 serious infections per 100 patient-years during the first 24 weeks of treatment, similar to the 4.2 serious infections per 100 patient-years seen in the placebo group. The results were presented at the European Congress of Rheumatology in Madrid, Spain, where the companies also reported new data from the long-term extension of phase III trials in RA patients showing that two years of Olumiant treatment significantly lowered the rate of joint damage progression, measured by change in the van der Heijde modified total sharp score, and maintained an overall low disease activity, measured by the Simplified Disease Activity Index, throughout the two-year extension period. Olumiant was approved in February for the treatment of adults with moderate to severe RA in the EU and received a complete response letter from the FDA in April. (See *BioWorld Today*, April 17, 2017.)

**Pfizer Inc.**, of New York, reported results at the European Congress of Rheumatology in Madrid, Spain, and published in *The Lancet*, from the ORAL Strategy phase IIIb/IV, head-to-head noninferiority study testing JAK inhibitor Xeljanz (tofacitinib) 5 mg twice daily as a monotherapy or in combination with methotrexate (MTX) compared to anti-TNF-alpha drug Humira (adalimumab, Abbvie Inc.) plus MTX in moderate to severe rheumatoid arthritis. On the primary endpoint, the percentage of patients achieving an ACR50 response at month six, 46 percent of patients in the Xeljanz plus MTX group, 38.3 percent in the Xeljanz monotherapy group and 43.8 percent in the Humira/MTX group achieved ACR50. Adverse event (AE) rates were comparable between treatment arms, and rates of serious AEs and discontinuations due to AEs were generally similar between treatment arms.

**TG Therapeutics Inc.**, of New York, reported data from its phase III GENUINE trial at the International Conference on Malignant Lymphoma in Lugano, Switzerland, showing that adding TG-1101 (ublituximab), its glycoengineered anti-CD20 monoclonal antibody, to BTK inhibitor Imbruvica (ibrutinib, Abbvie Inc. and Johnson & Johnson) improved overall response rate (ORR), complete response rate and minimal residual disease in high-risk patients with chronic lymphocytic leukemia (CLL). The trial met its primary endpoint, demonstrating a statistically significant improvement in ORR, as assessed by blinded independent central radiology and hematology review by iwCLL (Hallek 2008) criteria, compared to ibrutinib alone in both the intent-to-treat population ($p=0.001$) and treated population ($p<0.001$).

**Xencor Inc.**, of Monrovia, Calif., presented interim data at the European Congress of Rheumatology meeting in Madrid, Spain, from an ongoing, open-label, pilot phase II study of Xmab-5871 in patients with active IgG4-related disease, showing that 93 percent of patients achieved a response to therapy, 12 of them within two weeks of their first dose. Every-other-week intravenous administration of Xmab-5871 has been well-tolerated. Xmab-5871 is a monoclonal antibody that targets CD19 with its variable domain and uses Xencor's Xmab immune inhibitor Fc domain to target FcγRIIb, a receptor that inhibits B-cell function.

## Other news to note

**Genmab A/S**, of Copenhagen, said the FDA approved the use of Darzalex (daratumumab), a CD38-targeting monoclonal antibody, in combination with Pomalyst (pomalidomide, Celgene Corp.) and dexamethasone for treating multiple myeloma patients who have received at least two prior therapies, including Revlimid (lenalidomide, Celgene Corp.) and a proteasome inhibitor. Darzalex is partnered with Janssen Biotech Inc., a unit of New Brunswick, N.J.-based **Johnson & Johnson**. Genmab will receive milestone payments totaling $25 million from Janssen in connection with the approval and first commercial sale of Darzalex under the newly expanded label.

**Ipsen SA**, of Paris, said the FDA expanded the approved use of Dysport (abobotulinumtoxinA) for injection for the treatment of spasticity in adults, based on its supplemental BLA in lower limb spasticity.

**Johnson & Johnson**, of New Brunswick, N.J., said it completed the acquisition of Allschwil, Switzerland-based **Actelion Ltd.** for a total purchase price of approximately $30 billion in cash. The deal was completed through an all-cash public tender offer by the company's Swiss subsidiary, Janssen Holding GmbH, to acquire all publicly held shares of Actelion for $280 each. Actelion will now become part of the Janssen Pharmaceutical Companies of Johnson & Johnson. (See *BioWorld Today*, Jan. 27, 2017.)

**Pharmamar SA**, of Madrid, Spain, said PM-1183 (lurbinectedin), its third molecule of marine origin and analogue of Yondelis, will receive the trade name of Zepsyre. The product is currently undergoing development for the treatment of solid tumors. After recently reporting positive results in BRCA2-associated metastatic breast cancer and endometrial cancer, respectively, the company plans to initiate pivotal phase III studies in each indication.

**Recordati SpA**, of Milan, Italy, said it signed an exclusive license agreement with **Mimetech**, an Italian development-stage company founded by scientists from the University in Florence, for the development and subsequent commercialization on a global basis of a low-molecular-weight peptidomimetic of human nerve growth factor for the treatment of neurotrophic keratitis. The drug previously received an orphan drug designation in the EU. Recordati will make an up-front payment and further milestone payments will be linked to the development process and commercial performance.

**Resq Pharma Inc.**, of Chicago, said the FDA has granted orphan drug designation for Lipidrescue therapy for the indication of local anesthetic systemic toxicity. In addition, the company received an advice letter from the FDA guiding it to prepare a new drug application for the therapy based on the existing literature, case reports and new manufacturing specifics via the 505(b)2 pathway. The company said it is on track to file the application in the first half of next year.

# Bench Press

## BioWorld looks at translational medicine

*By Anette Breindl, Senior Science Editor*

### Artisanal pharmaceuticals

As medicines have become more potent and patient groups have become more targeted, the need has arisen for cGMP (current good manufacturing practices) processes that are suitable for producing drugs at volumes of kilograms, which is far less than is produced in one manufacturing run by classical batch manufacturing systems. Researchers from Eli Lilly and Co. have developed a novel manufacturing process for producing prexasertib monolactate monohydrate (LY-2606368), a checkpoint kinase 1 inhibitor that is in phase Ib and II trials as a cancer treatment. The team showed that its continuous processing manufacturing method, which was used to produce 24 kg of material over eight days, had advantages, including "improved safety for a hazardous reaction, better yield and impurity rejection via countercurrent multistage extraction, improved containment of a highly potent material," and others. Team members predicted that "this mode of pharmaceutical manufacturing will become common within the industry within the next decade." They published their method in the June 16, 2017, issue of *Science*.

### Finding MLL drivers and co-pilots

Mixed-lineage leukemias (MLL), a subset of acute myeloid leukemias (AMLs) that occur most often in infants and collectively have a poor prognosis, occur when the MLL1 gene, also known as KMT2A, fuses with any one of more than 70 possible partners. Affected cells have one copy of the fused gene, but retain one functioning copy of MLL. Some previous work had suggested that the functioning copy and the fused copy might collaborate to drive leukemia. Researchers from the University of Colorado at Denver have shown that deleting the functional copy of MLL1 did not prevent the fusion copy from driving aberrant growth. However, deletion of its nearest relative, MLL2, did stop growth, and when both MLL1 and MLL2 were deleted, the deletion of MLL1 had an additive effect. The team concluded that "these findings highlight the relevance of MLL2 as a drug target in MLL-rearranged leukemia and suggest its broader significance in AML." They published their findings in the June 12, 2017, issue of *Cancer Cell*.

### 3,2,1, pandemic flu?

The avian influenza strain H7N9 emerged in China in 2013, leading to a pandemic in chickens and widespread closure of poultry markets. H7N9 can also infect humans, and the World Health Organization has tallied more than 1,400 infections, and the CDC estimates the fatality rate to be 40 percent. However, for now, most infections result from exposure to infected chickens. There are few case reports of likely human-to-human transmission, and no reports indicating that the virus has acquired the ability to spread easily from one person to another, which is a prerequisite for a pandemic. A team from the Scripps Research Institute conducted mutation analyses to see how many mutations it would take for the virus to go from targeting chicken hemagglutinin (HA) receptors to binding most efficiently to human HA receptors, and found that such a switch could be the result of three mutations. The authors noted that "ideally, it would be important to assess the impact of the switch in receptor specificity in the ferret model that . . . is used to assess the propensity for air droplet transmission of human viruses. However, the introduction of the mutations that switch receptor specificity into an actual H7N9 virus background would represent gain-of-function (GoF) experiments that are currently prohibited." Nevertheless, they suggested, "this knowledge will aid in surveillance. If these amino acid mutations are observed to arise during natural selection in humans, timely actions could be taken." Their work appeared in the June 15, 2017, online issue of *PLoS Pathogens*.

### Fatty liver: Turning up the heat . . .

When it progresses to nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) is now the leading cause of liver failure. But understanding that progression and how to prevent it has been difficult due to a lack of good animal models that progress to NASH. Researchers from the Cincinnati Children's Hospital Research Foundation and the University of Cincinnati College of Medicine have discovered that mice housed at 30 to 32 degrees Celsius rather than the standard housing temperature of 20 to 23 degrees led to profound metabolic changes in the animals, including "augmented intestinal permeability, an altered microbiome and activation of inflammatory pathways." Both female mice, which are resistant to developing NAFLD at standard housing conditions, and male mice developed NAFLD when they were fed a high-fat diet. Thus, the authors concluded, "thermoneutral housing provides a sex-independent model of exacerbated NAFLD in mice and represents a novel approach for interrogation of the cellular and molecular mechanisms underlying disease pathogenesis." Their work appeared in the June 12, 2017, online issue of *Nature Medicine*.

### . . . and keeping the liver young

Another study has demonstrated that clearing senescent liver cells reduced fatty liver. The incidence of NAFLD increases with age, and researchers at the British Newcastle University

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# Bench Press

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investigated whether that increase was related to an increase in the number of senescent cells. Senescent cells, which are no longer dividing, secrete a number of factors that promote disease. The team targeted senescent cells either genetically, by inducing apoptosis in cells expressing the senescence marker p16Ink4a, or through pharmacological treatment. Both treatments reduced fatty liver, while inducing senescence promoted fat accumulation in the liver. The authors concluded that "cellular senescence drives hepatic steatosis and elimination of senescent cells may be a novel therapeutic strategy to reduce steatosis." They published their results in the June 13, 2017, issue of *Nature Communications*.

### KRACing KRAS

KRAS is an oncogene that is frequently mutated and often targeted, albeit so far not in the clinic. Researchers from Astrazeneca plc and Ionis Pharmaceuticals Inc. have published another preclinical attempt, demonstrating that the KRAS mRNA-targeting antisense oligonucleotide (ASO) AZD-4785 "potently and selectively depleted cellular KRAS mRNA and protein, resulting in inhibition of downstream effector pathways and antiproliferative effects selectively in KRAS mutant cells." The authors cautioned that "we have yet to explore the impact of a therapeutic KRAS ASO on KRAS mutant tumors in situ or in the presence of an intact immune microenvironment," but nevertheless concluded that "our data demonstrate that AZD-4785 is a potent and well-tolerated KRAS . . . ASO with robust antitumor activity at doses relevant to the clinical setting and suggest that AZD-4785 has potential as a therapeutic to help address the high unmet clinical need represented by mutant KRAS-driven human cancers." Their work appeared in the June 14, 2017, issue of *Science Translational Medicine*.

### Heading RET off at the pass

RET fusion genes are a driver in 1 percent to 2 percent of lung adenocarcinomas. Other fusion genes, beginning with Bcr-Abl and continuing through ALK rearrangements, have been successfully targeted, but inhibitors of RET fusion genes have had disappointing results: median progression-free survival of less than six months and response rates of less than 20 percent. Now, researchers from the German University of Cologne have shown that success in RET targeting may come from going after the inactive form of the drug. The team screened a group of drugs with known anti-RET activity, and found that ponatinib and AD-80 were by far the strongest inhibitors of cell growth. Both drugs target the catalytically inactive form of RET, preventing it from turning active, rather than inhibiting the active form. The authors concluded that "our data provide mechanistic insight into the druggability of RET kinase fusions that may be of help for the development of effective therapies targeting such tumors." They published their results in the June 14, 2017, issue of *Science Translational Medicine*.

### Childhood stress, adult depression

Adverse experiences in childhood can increase the likelihood of stress-related depression in adulthood. Researchers from the Mount Sinai School of Medicine have identified a protein that is affected by childhood stress. The team showed that levels of the developmentally active transcription factor Otx2 were temporarily reduced in response to stressful experiences in 3-week-old mice that primed the ventral tegmental area, one of the reward areas of the brain, to enter a depression-like state after additional stressful experiences in adulthood. Transient knockdown of Otx2 in juvenile rats also increased stress susceptibility, while knockdown in adulthood had no effect. Overexpressing Otx2 protected animals from vulnerability to stress-induced depression. "Understanding how Otx2 programs lasting stress susceptibility will provide insight into ways of reducing the deleterious effects of early life adversity," the authors wrote. Their work appeared in the June 16, 2017, issue of *Science*.

### Biofilm buster?

Antibodies to alphatoxin and clumping factor A could prevent the formation of bacterial biofilms on medical implants in preclinical models. Medical implants such as pacemakers and artificial joints can serve as a surface for bacteria to cluster. The resulting bacterial biofilms are resistant to many antibiotics. Scientists from Johns Hopkins University School of Medicine and Medimmune LLC developed a preclinical model to understand the processes underlying biofilm formation after bloodstream infection with *Staphylococcus aureus*. Through repeated imaging, they showed that alphatoxin and clumping factor A were key secreted factors that led to biofilm formation. They also demonstrated that monoclonal antibodies to alphatoxin and clumping factor A were able to inhibit biofilm formation, with additive effects if both were given. The team concluded that alphatoxin and clumping factor A could be targeted to prevent the formation of biofilms on medical implants. Their work appeared in the June 12, 2017, online issue of the *Proceedings of the National Academy of Sciences*.

## Let us know what you think

We welcome your feedback. Contact Anette Breindl at anette.breindl@clarivate.com, or (770) 810-3134.