IFPW FOCUS IFPW

Vol. 29, No. 5 International Federation of Pharmaceutical Wholesalers March 3, 2022

Repurposing FDA-approved Drugs to Combat COVID-19

(Source: A Staff Article for World Pharma News)

Several FDA-approved drugs - including those for type 2 diabetes, hepatitis C and HIV - have been shown to significantly reduce the ability of the Delta variant of SARS-CoV-2 to replicate in human cells, according to new research led by scientists at Penn State University. Specifically, the team found that these drugs inhibit certain viral enzymes, called proteases, that are essential for SARS-CoV-2 replication in infected human cells.

"The SARS-CoV-2 vaccines target the spike protein, but this protein is under strong selection pressure and, as we have seen with Omicron, can undergo significant mutations," said Joyce Jose, assistant professor of biochemistry and molecular biology, Penn State. "There remains an urgent need for SARS-CoV-2 therapeutic agents that target parts of the virus other than the spike protein that are not as likely to evolve."

Previous research has demonstrated that two SARS-CoV-2 enzymes - proteases including Mpro and PLpro - are promising targets for antiviral drug development. Pfizer's COVID-19 therapy *Paxlovid*, for example, targets Mpro. According to Jose, these enzymes are relatively stable. Therefore, they are unlikely to develop drug-resistant mutations rapidly.

Katsuhiko Murakami, professor of biochemistry and molecular biology, Penn State, noted that these virus proteases, because of their capabilities to cleave or cut proteins, are essential for SARS-CoV-2 replication in infected cells.

"SARS-CoV-2 produces long proteins, called polyproteins, from its RNA genome that must be cleaved into individual proteins by these proteases in an ordered fashion leading to the formation of functional virus enzymes and proteins to start virus replication once it enters a cell," Murakami explained. "If you inhibit one of these proteases, further spread of SARS-CoV-2 in the infected person could be stopped."

The findings published on February 25, 2022 in the journal *Communications Biology*. The team designed an assay to rapidly identify inhibitors of the Mpro and PLpro proteases in live human cells.

The researchers used their assay to test a library of 64 compounds - including inhibitors of HIV and hepatitis C proteases; cysteine proteases. From the 64 compounds, the team identified eleven that affected Mpro activity and five that affected PLpro activity based on a cut-off of 50% reduction in protease activity with 90% cell viability.

Next, the team evaluated the antiviral activity of the 16 PLpro and Mpro inhibitors against SARS-CoV-2 viruses in live human cells in a BSL-3 facility, the Eva J. Pell ABSL-3 Laboratory for Advanced Biological Research at Penn State, and discovered

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In Brief...

- **Walgreens Boots Alliance (WBA)** released its fiscal *2021 Environmental, Social and Governance 2021 (ESG) Report*, outlining the company's commitment to its four corporate responsibility pillars – Healthy Communities, Healthy Planet, Healthy and Inclusive Workplace and a Sustainable Marketplace. The Report highlights the company's work in health and vaccine equity and the ongoing progress WBA has made on sustainability targets and initiatives. "We have made much progress over the past year, solidifying our ongoing commitment to our four pillars," said *Ornella Barra*, WBA's Chief Operating Officer, International and Chair of the company's Corporate Social Responsibility Committee. "At Walgreens Boots Alliance, we have cemented our role as a corporate leader, led by example with our health equity initiatives and diversity, equity and inclusion policies, and laid the groundwork for our part in creating a sustainable and livable planet for the generations who will come after us."
- **Biocon** has reached a deal with **Viatris** to acquire its biosimilars assets for up to US$3.3 billion (including cash up to US$2.3 billion), accelerating its direct commercialization push across key markets while bringing with it rights to key in-licensed therapies, including the biosimilar *adalimumab*, as well as an option to acquire the US firm's rights for the biosimilar *aflibercept.*
- **GlaxoSmithKline (GSK)** announced that **Haleon** will be the newly independent company following the demerger of the GSK consumer healthcare business. In an update to investors, it was announced that the proposed listing of the new company will be in July of 2022. "Today is an important milestone for GSK as we formally introduce Haleon to investors," *Emma*

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A Turning Point for US Biosimilars is Approaching

(Source: An article by Jessica Merrill for Scrip Intelligence)

2022 will be an important year for manufacturers in the biosimilar sector, as the Humira biosimilars prepare to enter the U.S. market in 2023, and the sector adds new areas, such as ophthalmology and insulin to its portfolio. Some of the most enticing commercial opportunities for biosimilar manufacturers and the biggest potential savings to the US health system will be prominent in the next several years. Drugmakers and other stakeholders are already laying the foundation for that expansion.

The next wave of biosimilars is expected to prove more competitive than the initial wave, posing new challenges for biosimilar manufacturers seeking leadership positions in crowded drug classes. In addition, these launches will take

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Repurposing Drugs (cont.)...

that eight of them had dose-dependent antiviral activities against SARS-CoV-2. Specifically, they found that *Sitagliptin* and *Daclatasvir* inhibit PLpro, and MG-101, *Lycorine HCl* and *Nelfinavir mesylate* inhibit Mpro. Of these, the team found that MG-101 also hindered the virus's ability to infect cells by inhibiting protease processing of the spike protein.

In addition, the researchers found that treating cells with a combination of Mpro and PLpro inhibitors had an additive antiviral effect, providing even greater inhibition of SARS-CoV-2 replication.

The team is in the process of designing new compounds based on the structures they determined by X-ray crystallography. They also plan to test the combination drugs that they already demonstrated to be effective in vitro in mice.

Although the scientists studied the Delta variant of SARS-CoV-2, they said the drugs will likely be effective against Omicron and future variants because they target parts of the virus that are unlikely to mutate significantly.

Turning Point (cont.)...

place in therapeutic areas with less biosimilar experience, such as diabetes, ophthalmology, and immunology. Success will require continued education of physicians and pharmacists and navigating pharmacy benefit reimbursement, where biosimilars have faced some headwinds.

"With this inflection point and the entrance into new therapeutic areas, new reimbursement models, new sites of care, you essentially have this whole new stakeholder group that hasn't really been tapped into yet to focus education efforts on," Cardinal Health, Inc. VP-biosimilars Sonia Oskouei said in an interview.

"There is a significant need to do that and have proactive efforts with, for example, retina specialists, with ophthalmologists, endocrinologists, even primary care physicians that prescribe insulin, and very notably, retail pharmacists and those that work in retail or specialty pharmacies that will now be in a position to drive adoption of biosimilars through interchangeability designations that we have started to see," she said.

Cardinal Health, a wholesaler and drug distributor, released its first report on biosimilars this year. According to Oskouei, the biosimilars market's expansion and Cardinal Health's goal of becoming a resource to stakeholders in the field drove the work.

The report reveals that, despite strong growth estimates for biosimilars in the US through 2025, there remains a substantial educational challenge in the market among pharmacists and certain health care providers, as well as reimbursement concerns.

Biosimilars will deliver over US$133 billion in aggregate savings to the US health care system by 2025 and estimates that total savings to patient out-of-pocket costs, based on just the current approved list of biosimilars, will reach up to US$238 million, according to the report.

The biggest opportunity approaching is the closely-tracked launch of the first biosimilar versions of AbbVie's Humira *(adalimumab)* for certain auto-immune conditions. The first Humira biosimilar is Amgen's candidate, which is expected to hit the market first, followed by six other brands.

In addition, six other big brands face similar biosimilar competition for the first time in 2024. They include Roche's *Lucentis (ranibizumab)* and *Actemra (tocilizumab)*, Amgen's *Neulasta Onpro (filigrastim)*, J&J's *Stelara (ustekinumab)* and *Simponi (golimumab)*, and Regeneron's *Eylea (aflibercept)*.

The new generation of biosimilars will be more substantial than previous ones, given the size of Humira's market.

Manufacturer	Brand Name	Ant. Entry Date
Amgen	*Amgevita*	Jan-23
Organon	*Hadima*	Jun-23
Boehringer-Ingelheim	*Cyltezo*	Jul-23
Coherus	*Yusimry*	Jul-23
Viatris	*Hulio*	Jul-23
Sandoz	*Hyrimoz*	Sep-23
Pfizer	*Abrilada*	Nov-23

(Source: Cardinal Health: 2022 Biosimilars Report, Feb. 2022)

In Brief (cont.)...

Walmsley, GSK's CEO said. "It comes ahead of what promises to be the most significant corporate change for GSK in the last 20 years, to create two new growth companies that will positively impact the health of billions of people."

- **Moderna** has signed a distribution deal in Latin America for COVID-19 vaccines with **Adium Pharma**, a private Latin American pharmaceutical company, to support the commercialization of the Moderna COVID-19 vaccine. The agreement covers 16 countries, including Brazil, Mexico, Colombia and Argentina. Moderna has commercial presence in 11 countries worldwide, including Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, Switzerland, the U.K. and the U.S.
- **Biohaven Pharmaceuticals** is taking over **Bristol Myers Squibb's** treatment for Duchenne muscular dystrophy through a worldwide licensing agreement, with plans to develop *taldefgrobep alfa* in spinal muscular atrophy. The agreement covers licensing rights in exchange for an undisclosed amount of money, contingent on regulatory and sales-based milestones.
- The Saudi Arabian pharmaceutical market is expected to expand at a CAGR of 9% over the forecast period of 2016-2026. The significant rise in lifestyle-related diseases and developments in healthcare infrastructure are expected to influence demand for pharmaceuticals, with a significant upsurge in prescription-type branded products. Generic drugs are also expected to see robust growth as healthcare insurance providers promote the use of generics.
- **Chugai Pharmaceuticals** was named the leader in the Japanese pharmaceutical industry for the first time in 2021 on a "promotional company" basis, a gauge of the true ability of drug makers. IQVIA defines a promotion company as "a company that carries out promotion activities by way of sales reps." Chugai realized sales of ¥516.8 billion (US$4.5 billion), surpassing prior leader **Takeda** by ¥23.2 billion (US$201.9 million). The figure does not include sales of of its COVID-19 antibody cocktail *Ronapreve* purchased by the Japanese government. Growth is primarily attributed to its oncology franchise.

(Sources: Company Press Releases, Drug Store News, Fierce Pharma, Pharma Japan, RSS Newsletter, Scrip Intelligence, and World Pharma News)