Lambda Research Newsletter

September 2019

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Research Accelerated

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Clinical Research NEWSletter

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GLOBAL NEWS

1. Gene-targeted cancer drugs: sustain release to overcome resistance

A new method to address failures in a promising anti-cancer drug has been developed by the Biomedical engineers at Duke University. They have developed this tool with the help of fusion from genome engineering, protein engineering and biomaterials science to provide a combination of CRISPR-based targeting called a protein "depot" that allows slow and sustained release of the drug with a high affinity towards the binding system. This tool will improve the efficacy, accuracy and longevity of certain cancer therapies.

The new strategy could overcome three critical problems that limit the efficacy of many cancer drugs:

- Limited potency
- Quick elimination from the body
- Ability of cancer cells to develop resistance to the drug

The findings of their study are published in the journal *Science Advances*.

Using a combination of the three tools, a highly potent protein drug "depot" is developed that allows for sustained release of the drug. The CRISPR/Cas9 based gene editing pinpoint the cause of resistance to the drug. Researchers demonstrated that this strategy could provide a solution.

Source: worldpharmanews.com

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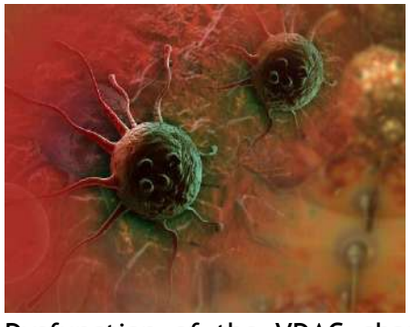
GLOBAL NEWS

2. New drug target against cancer



An international team of researchers from the National Academy of Sciences have identified a potential new drug target in the fight against cancer.

The researchers have described a mechanism of closing of mitochondria through the cancer-linked version of the protein mitoNEET as to how the primary gateways "voltage-dependent anion channels" (VDACs) are closed on the outer surface of the mitochondria that supply chemical energy to the cells.

Dysfunction of the VDAC channel, which is responsible for transport of metabolites between the cytosol and the mitochondria, is involved in many diseases including cancer and fatty liver disease. Targeting the VDAC complex in diseased states can be fine-tuned through MitoNEET, which naturally adheres to the outer surface of the mitochondria. This discovery provides a new platform for investigations into development of methods to induce cancer cells to commit cell suicide, or apoptosis/ferroptosis, in a cancer-specific, regulated process. Development of drugs specifically altering the redox-state of interaction between VDAC and mitoNEET would allow new strategies to battle several cancers.

Source: eurekalert.org

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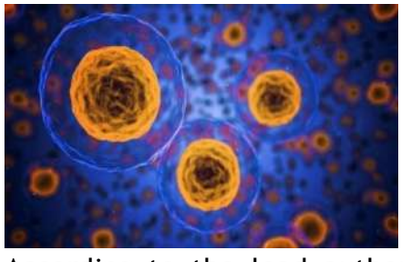
GLOBAL NEWS

3. Nano-sized cells of body may help in fighter cancer



Researchers from the Michigan State University (MSU) and Stanford University have evaluated that nano-sized cells that transfer genetic material to other cells may behave like mini treatment transporters to kill tumor cells.

The findings of the study are published in the journal, *'Molecular Cancer Therapeutics'* focused on breast cancer cells in mice.

According to the lead author of the manuscripts, an assistant professor of pharmacology and toxicology in MSU's Institute for Quantitative Health Science and Engineering, Masamitsu Kanada "What we've done is improve a therapeutic approach to delivering enzyme-producing genes that can convert certain drugs into toxic agents and target tumors."

These drugs, or prodrugs, start out as inactive compounds, but are immediately activated once they metabolize in the body. These prodrugs can get to work on fighting everything from cancer to headaches. Aspirin is an example of a common prodrug. In this case, extracellular vesicles (EVs) were used by the researchers to deliver the enzyme-producing genes that could activate the prodrug combination therapy of ganciclovir and CB1954 in breast cancer cells. They reported a 14-times higher efficacy of minicircle DNA at delivery and even more successful at killing cancerous cells.

A phase-one clinical trial using EVs and a type of therapeutic RNA molecule for the treatment of metastatic pancreatic cancer will start soon in the U.S.

Source: health.economictimes.indiatimes.com

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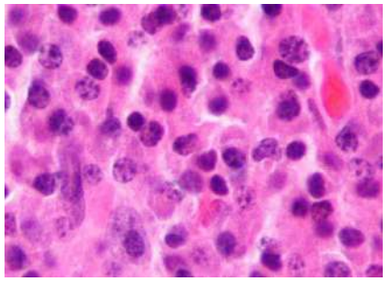
GLOBAL NEWS

4. Major biological processes in myeloma development revealed: ICR



The researchers from the Institute of Cancer Research (ICR) have uncovered the major biological processes involved in the development of myeloma. The Myeloma UK-funded research increases the known knowledge on the process of development and evolvement of myeloma. Also, it suggests a key role of the mutational signatures in helping identify high risk myeloma patients and predicting patient outcomes. These developments will facilitate improved diagnosis and assessment of prognosis and more personalized treatments for myeloma patients.

In their study, the researchers reported identification of 80% of the mutations found in myeloma: ageing, errors in DNA repair, dysfunction of the RNA/DNA editing activation-induced deaminases and dysfunction of apolipoprotein B editing complexes.

“Understanding of the genetics of myeloma plays a key role in identifying why myeloma is such a complex and individual cancer” according to Professor Richard Houlston, Institute of Cancer Research, London. The researchers are further performing state of the art molecular analyses to understand the process of genetic mutations effects on gene function. The information was collated from analysis of the whole-genome sequencing and whole-exome sequencing data from CoMMpass trial including >800 myeloma patients.

Source: pharmatimes.com

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PHARMA INDIA

1. India joins global antimicrobial resistance research and development hub

The Global Antimicrobial Resistance (AMR) Research and Development (R&D) Hub was launched in May 2018 at 71st Session of the World Health Assembly. Now, India has joined the AMR R&D Hub as a new member.

This association will expand the global partnership working to address challenges and improve coordination and collaboration in global AMR R&D to 16 countries, the European Commission, two philanthropic foundations and four international organizations (as observers).

The Global AMR R&D Hub identifies the gaps, overlaps and potential for cross-sectoral collaboration and leveraging in AMR R&D and thus, supports global priority setting and evidence-based decision-making on the allocation of resources. A Secretariat in Berlin financed through German Federal Ministry of Education and Research (BMBF) and the Federal Ministry of Health (BMG) grants supports the operation of the Global AMR R&D Hub.

India will be a member of Board of Members of Global AMR R&D Hub from this year onwards and looks forward to working with all partners to leverage their existing capabilities, resources and collectively focus on new R&D intervention to address drug resistant infections.

Source: www.pharmabiz.com

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PHARMA INDIA

2. Gujarat FDCA plus US FDA: capacity building of drug inspectors

The Gujarat Food and Drug Control Administration (FDCA) has partnered with the US FDA for capacity building of its state drug inspectors through knowledge sharing and training.

A quarterly review meeting of Gujarat FDCA with the US FDA officials concluded recently which chalked out plans to equip drug inspectors on the latest global regulatory demands for effective compliance through knowledge sharing.

"As part of the global harmonization programme to enhance regulatory output and compliance, US FDA and Gujarat FDCA officials deliberated on four components of capacity building like training, networking, knowledge sharing and compliance," mentioned informed Gujarat FDCA Commissioner Dr H G Koshia.

The maximum numbers of US FDA approved drug manufacturing units in India are located in Gujarat. The visit is an important milestone as Indian pharmaceutical industry is expected to address risk based inspections and embrace global standards. Training has already been provided to the Gujarat FDCA inspectors on current good manufacturing practices (cGMP) and good laboratory practices (GLP) in collaboration with foreign regulatory agencies.

Source: pharmabiz.com

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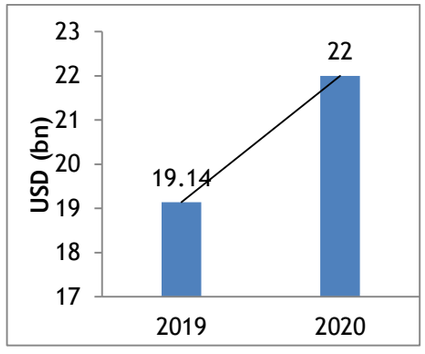
PHARMA INDIA

3. Indian pharma exports: up to $22 bn in FY '20

Indian pharma exports may touch USD 22 billion during the current financial year against USD 19.14 billion in FY '19.



Mr. Uday Bhasker, director-general of Pharmexcil, a body under the Ministry of Commerce and Industry, opined that the policy decisions being taken by the Chinese government may align favorably to Indian pharma exporters.

Indian exports recorded 21.7% growth to 1.72 billion in July 2019 (April to July exports: USD 6.17 billion).

- Cumulative growth of Indian exports was 13% for April-July
- Domestic generic pharmaceutical exports have grown 2.7-2.8 times faster than global generic market
- The prices (in USA market) are now stabilized

India currently imports APIs (Active Pharmaceutical Ingredient) and other chemicals worth USD 2.5 billion from China while drug exports to the country at USD 230 million.

Source: health.economictimes.indiatimes.com

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PHARMA INDIA

4. Manufacturing of new drugs: DCGI approves multiple facilities

According to the Drugs Controller General of India (DCGI), manufacturers can now manufacture new drugs in their additional manufacturing facility if they establish the similarity by way of technology transfer with respect to the manufacturing process.

In addition to the technology transfer, equipments, process parameters, process capability and bridging validation for technology transfer wherever required between the proposed additional manufacturing sites and the approved manufacturing site are also considered.

A pharmaceutical manufacturer generates chemistry, manufacturing, and control (CMC) data in one of its manufacturing facility that is required for the approval or permission for manufacturing the new drug.

It was recommended to ensure stability of all drugs before grant of license so that patients get quality medicines as per Rule 71, 71b and 76 of Drugs and Cosmetics Act (D&C Act).

The stability data needs to be submitted by the companies seeking manufacturing license. A detailed six month observation report of a drug for which manufacturing license application is made needs to be submitted.

Source: pharmabiz.com

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REGULATORY ROUND-UP

1. First MDR certificate issued for class III device

Germany based TÜV SÜD is part of a first group of Notified Bodies that has signed the voluntary Code of Conduct for Medical Device Notified Bodies. TÜV SÜD has announced the issuance of first Medical Devices Regulation (MDR) certificate for one of Germany-based Biotronik's Class III (highest-risk category) medical devices, in addition to its quality management system.

Biotronik's Renamic programmer software, the newly certified device, enables physicians to program and test implanted cardiac devices such as pacemakers, implantable cardioverter-defibrillators and cardiac resynchronization therapy systems.

From previous 2.5 years, Biotronik has been working to develop a strategy related to transition of its devices and quality management system into the new EU legal framework for devices. The new EU legal framework will be fully implemented in May 2020. Germany-based TÜV SÜD became the second notified body to be designated under MDR in May 2019.

To provide the services under the new legislative framework, TÜV SÜD has started working on shifting and preparing related resources. After the announcement of the certification of Biotronik's quality management system and class III device, BSI's UK notified body has announced that the Novartis Concept1 inhaler is the first device to be certified under MDR.

Source: www.raps.org

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REGULATORY ROUND-UP

2. New tool to simulate immune response to biologic drugs

A new computational tool has been developed by the US Food and Drug Administration (FDA) that will assist in predicting whether the body will mount an immune response that blocks the activity of biological drugs.

The newly developed tool 'dubbed TCPro' simulates the process of body's CD4+ T cells response to bio therapeutics, thus, predicts the formation of auto-anti-drug antibodies. The use of TCPro facilitates the evaluation of potential for antibody formation even before the routinely performed laboratory testing.

The challenges associated with the traditional immunogenicity testing such as collection of samples for diverse human genome makes it expensive and time consuming. Major histocompatibility (MHC) class II molecules present on the surface of antigen presenting cells (APCs) are the most diverse in the human genome:

- challenging to collect cell samples that accurately reflect the presence of all possible MHC-II proteins in a patient population.

The test was validated by comparing its predictions for 15 protein therapies against reported clinical data for those same products.

Source: www.raps.org

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REGULATORY ROUND-UP

3. Project Orbis: FDA, TGA and Health Canada project

Project Orbis provides a framework for concurrent submission and review of oncology drugs. This project is an initiative by the FDA Oncology Center of Excellence (OCE). The FDA, the Australian Therapeutic Goods Administration (TGA) and Health Canada collaboratively have reviewed the applications for two oncology drugs and allowed for simultaneous decisions in all three countries.

The collaboration among international regulators will provide easier and early access to the drugs in countries where there were significant delays in regulatory submissions, regardless of whether the product has received FDA approval. The partial reason for this delay is the different standards of care around the world that also have an impact on the increasingly international conduct of cancer clinical trials. Ultimately, the developments of anticancer products are slowed down.

Project Orbis facilitates a collaborative review to identify any regulatory divergence across review teams with a framework for concurrent submission and review of oncology drugs. The 'Real-Time Oncology Review' (RTOR) pilot program, which can streamline the submission of data prior to the completion and submission of the entire clinical application, was used for the two drugs reviewed under this project.

Source: worldpharmanews.com

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REGULATORY ROUND-UP

4. CDRH to operationalize new safety and performance based pathway

The US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) has issued four draft guidance documents that will identify the performance criteria and testing methodologies for certain devices within four class II device types. These guidance documents were issued to implement the optional Safety and Performance Based Pathway for medical devices. The final guidance explaining the new pathway has also been released. Three types of 510(k) submissions are allowed: Traditional, Special and Abbreviated.

The Special and Abbreviated 510(k) programs facilitate the review process for certain types of submissions subject to 510(k) requirements. The FDA split this "New 510(k) Paradigm" in 2019 into separate guidance documents: The Special 510(k) Program and the Abbreviated 510(k) Program. The Safety and Performance Based Pathway is an expansion of the concept of the abbreviated pathway for certain, well understood device types.

All four of the short draft guidance documents offer information on what specific devices are subject to each guidance, as well as the testing and performance criteria. Spinal plating systems, conventional Foley catheters cutaneous electrodes for recording purposes, and orthopedic non-spinal metallic bone screws and washers are covered under this guidance.

Source: raps.org

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MERGERS /ACQUISITIONS /COLLABORATIONS

1. AstraZeneca amends collaboration with Ironwood for IBS-C drug

The IBS-C (irritable bowel syndrome with constipation), characterized by abdominal pain and constipation, is a chronic functional gastrointestinal disorder. There are currently few treatment options available for this condition. Linzess (linaclotide) is a first-in-class new treatment for patients with IBS-C. AstraZeneca has amended its collaboration agreement with Ironwood Pharmaceuticals, Inc. (Ironwood) in China mainland, China Hong Kong and China Macau for 'linzess'.

According to the mended agreement, AstraZeneca gets the sole responsibility for developing, manufacturing and commercializing the 'linzess' in all three Chinese continents. Ironwood will transfer manufacturing responsibility of Linzess to AstraZeneca and will no longer be involved in the research and development or the commercialization.

Between the two companies, the collaboration to co-develop and co-commercialize Linzess was signed in 2012, under which AstraZeneca and Ironwood were jointly responsible for strategic oversight of the development and commercialization of Linzess in China. AstraZeneca had primary responsibility for local operational execution. The National Medical Products Administration has approved Linzess for adults with IBS-C in January 2019 in China, where it is expected to be launched in 2019.

Source: worldpharmanews.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

2. Oncoheroes and Boehringer signs licensing deal for volasertib

Oncoheroes Biosciences, a US-based biotech company, has signed an agreement with Boehringer Ingelheim for the intellectual property volasertib, an investigational cancer drug. Oncoheroes will get the exclusive global rights to research, develop, sell and sublicense the drug. Boehringer discovered and developed volasertib – a drug that inhibits the Polo-like-kinase 1 (PLK1) enzyme, which is associated with cancer progression in multiple diseases.

The target for development of this drug was to treat a type of leukemia, but the clinical development was suspended after a Phase III clinical trial in adult patients did not meet primary goals.

However, the data supported the development of volasertib for rhabdomyosarcoma and other pediatric cancers. Oncoheroes plans to develop and commercialize volasertib for cancer indications in children.

This is probably the first example of an investigational compound being specifically repurposed to investigate it as a treatment for a form of childhood cancer.

Source: pharmaceutical-technology.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

3. Happify and Sanofi to advance digital therapeutics for multiple sclerosis

Sanofi and Happify Health have announced the signing of an agreement to advance the application of digital therapeutics to address key co-morbidities for individuals living with multiple sclerosis (MS).

Happify will develop a version of its digital platform specifically for people with multiple sclerosis. The company also plans to submit the digital therapy to the US Food and Drug Administration (FDA) for clearance as a medical device.

Nearly 25% reduction in symptoms of anxiety and >25% reduction in symptoms of depression were reported for those using Happify at the recommended level according to a study published in the *International Journal of Wellbeing*.

"These capabilities, along with Sanofi's demonstrated commitment to digital transformation, made for an ideal collaboration rooted in exploring innovative, safe and effective therapies aiming to improve the lives of individuals with MS," said Ofer Leidner, co-founder and president of Happify Health.

Source: pharmatimes.com

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MERGERS /ACQUISITIONS /COLLABORATIONS

4. Medtronic and Novo Nordisk: Digital diabetes solutions deal

Medtronic and Novo Nordisk have entered an agreement to provide "integrated digital solutions" for people with diabetes. Dosing data from Novo Nordisk smart insulin pens will be shared with Medtronic Continuous Glucose Monitoring devices to provide the solutions.

People with diabetes and their healthcare professionals and caregivers will be able to automatically track glucose monitoring and insulin dosing in a single place, by integrating glucose monitoring and insulin dosing data. This will give people living with diabetes one less thing to think about in the daily management of their condition.

Further, a more productive conversation between patients and their doctors is expected with the availability of both the parameters that will enable more informed decisions on the management of glucose levels.

Source: pharmatimes.com

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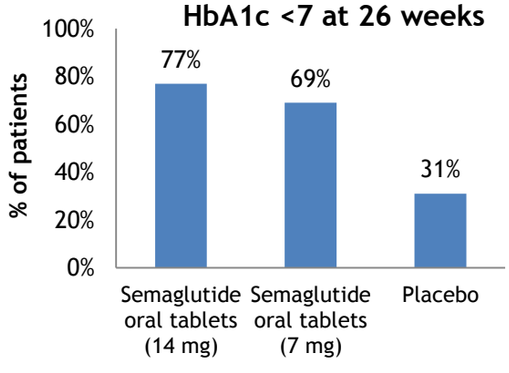
DRUGS: APPROVALS AND LAUNCHES

1. Semaglutide: first oral GLP-1 treatment approved by USFDA

The US Food and Drug Administration (US FDA) has approved the semaglutide oral tablets (Rybelsus, Novo Nordisk) 7 mg or 14 mg for the treatment of type 2 diabetes. Semaglutide is the first oral glucagon-like peptide (GLP-1) receptor protein treatment to receive the regulator's approval. Semaglutide oral tablets are indicated to improve control of blood sugar in adult patients in adjunction with diet and exercise. GLP-1 drugs are noninsulin treatments for patients with type 2 diabetes

"GLP-1 receptor agonists are effective medications for people with type 2 diabetes but have been underutilized in part because they have, until now, only been available as an injectable treatment," said Vanita R. Aroda, MD, director of Diabetes Clinical Research, Brigham and Women's Hospital, Boston, MA, and a clinical trial investigator. The efficacy and safety of semaglutide in reducing blood sugar were studied in 10 PIONEER clinical trials, 2 of which were placebo-controlled and several of which were compared to other GLP-1 injection treatments. The drug was evaluated as a stand-alone therapy or in combination with other therapies, including metformin, sulfonylureas, sodium-glucose co-transporter-2 inhibitors, insulins, and thiazolidinediones in 9543 enrolled participants.

As a stand-alone therapy, semaglutide oral tablets resulted in a significant reduction in blood sugar compared with placebo and the results are shown in the Figure.



Semaglutide oral tablets will be available in the United States in the 4th quarter of 2019, according to Novo Nordisk.

Source: pharmacytimes.com

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DRUGS: APPROVALS AND LAUNCHES

2. FDA approves Nucala (mepolizumab) for asthma in children

The US Food and Drug Administration (FDA) has approved Nucala (mepolizumab) for use in children as young as six years old who are living with severe eosinophilic asthma.

Developed by GlaxoSmithKline, mepolizumab is the only targeted biologic that is approved for treating eosinophilic asthma in the six to 11-year age group in the US. Mepolizumab is a first-in-class monoclonal antibody that targets IL-5. This approval (40mg dose subcutaneous injection) extends the current indication in the US for Nucala to patients aged six to 11 years.

The decision was supported by an open-label pharmacokinetics, pharmacodynamics and long-term safety study conducted in children aged six to 11 years suffering from severe eosinophilic asthma. Mepolizumab (100mg fixed dose subcutaneous injection) is licensed as an add-on maintenance treatment for patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Nucala (3 x 100mg subcutaneous injection) is licensed for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). Nucala is not approved for the relief of acute bronchospasm or status asthmaticus.

Source: pharmatimes.com

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DRUGS: APPROVALS AND LAUNCHES

3. Boehringer to launch first reusable soft mist inhaler

Boehringer Ingelheim has announced the launch of 'Respimat' as a reusable inhaler that can be used with up to six cartridges. This will create a 71% reduction in the product's carbon footprint, compared with using six of the previous Respimat (disposable) inhalers with one cartridge each.

Due to the release of its new reusable, soft mist inhaler - Respimat reusable - 1.2 million fewer inhalers may be disposed of each year in the UK.

The new reusable method delivers the chronic obstructive pulmonary disease (COPD) and asthma medications including

- Spiolto (tiotropium/olodaterol)
- Striverdi (olodaterol)
- Spiriva (tiotropium)
- Spiriva (tiotropium)

The reusable inhaler was devised following patient and healthcare professional feedback, as part of the National Health Services (NHS) Long Term Plan, which outlines its targets to reduce carbon emissions and single-use plastics.

Source: pharmatimes.com

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DRUGS: APPROVALS AND LAUNCHES

4. Roche's Gazyva gets FDA breakthrough therapy designation

The US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation (BTD) to Roche's Gazyva (obinutuzumab) for adults with lupus nephritis. There are currently no US FDA approved therapies for lupus nephritis.

The designation was provided based on the Phase II NOBILITY study, in which obinutuzumab in combination with standard of care (mycophenolate mofetil or mycophenolic acid and corticosteroids), showed enhanced efficacy compared to placebo and standard of care alone in achieving complete renal response at one year.

GAZYVA® obinutuzumab injection

The trial also met its secondary endpoints, showing improved overall renal responses (complete and partial renal response) and serologic markers of disease activity as compared to placebo.

Gazyva is an engineered monoclonal antibody designed to attach to CD20, a protein found only on certain types of B-cells. It is thought to work by attacking targeted cells both directly and together with the body's immune system.

Source: pharmatimes.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

1. Ocrelizumab for multiple sclerosis

The longer-term data from the Phase III open-label extension studies of OPERA I, OPERA II and ORATORIO demonstrated a reduced risk of disability progression in relapsing MS (RMS) and primary progressive MS (PPMS) in patients receiving ocrelizumab for ≥6 six years. These results suggest earlier treatment with ocrelizumab reduced the risk of disability progression and this effect was sustained over time.

New safety data representing 4,611 patients with RMS and PPMS, and 14,329 patient years of exposure to ocrelizumab, across all clinical trials, remained consistent with the medicine's favorable benefit-risk profile.

The ocrelizumab data highlight that the benefit of delaying, and possibly preventing, disability progression is greater when the treatment is used earlier in the disease course for both relapsing and primary progressive forms of MS.

- Ocrelizumab is the first and only therapy approved for both RMS (including relapsing-remitting MS (RRMS) and active, or relapsing, secondary progressive MS, in addition to clinically isolated syndrome in the U.S.) and PPMS.
- OCREVUS is dosed every six months
- OCREVUS is now approved in 89 countries across North America, South America, the Middle East, and Eastern Europe, as well as in Australia, Switzerland and the European Union.

Source: worldpharmanews.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

2. Novartis' MS drug trumps Sanofi's Aubagio

According to the data presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Novartis showed that its multiple sclerosis (MS) drug, ofatumumab, was able to reduce annualized MS relapse rates (ARR) by 50.5% and 58.5% in the ASCLEPIOS I and II trials respectively, compared to Sanofi's Aubagio (teriflunomide).

Both studies met their primary endpoints where ofatumumab showed a highly significant and clinically meaningful reduction in the number of confirmed relapses. The treatment also showed highly significant suppression of both Gd+ T1 lesions and new or enlarging T2 lesions compared to Aubagio.

Further, ofatumumab showed a relative risk reduction of 34.4% in three-month confirmed disability progression (CDP) and 32.5 in six-month CDP versus the Sanofi drug.

Ofatumumab:

- Fully human anti-CD20 monoclonal antibody
- Works by binding to the CD20 molecule on the B-cell surface and induces potent B-cell lysis and depletion.
- Self-administered by a once-monthly subcutaneous injection
- Indicated for multiple sclerosis

Source: pharmatimes.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

3. Santen's Ikervis effective for dry eye

The data presented at the European Society of Cataract and Refractive Surgeons (ESCRS) congress, showed that Ikervis (ciclosporin) has achieved effectiveness, tolerability and safety targets in the PERSPECTIVE trial.

Santen has announced that its dry eye therapy Ikervis showed that the eye drop emulsion provided significant improvements in corneal fluorescein staining (CFS) grade at Week 24 (77.4%). Statistically significant improvements were observed at Week 24, from baseline, concerning tear break-up time (TBUT) as well as objective and subjective measures.

Most physicians regarded Ikervis to be more effective than previous treatments in the real-world setting. Also, the tolerability was rated high as per both physicians and patients.

Source: pharmatimes.com

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DRUGS: DEVELOPMENT & CLINICAL TRIALS

4. Spravato reduces depressive symptoms in 24 hours

Janssen has announced data from two pivotal Phase III clinical studies on its anti-depressant drug esketamine. The data has shown a reduction in the depressive symptoms at 24 hours after the first dose of esketamine. The depressive symptoms were measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).

The trials evaluated the efficacy and safety of esketamine in addition to comprehensive standard of care (SOC) in adult patients with major depressive disorder who have active suicidal ideation with intent. The 456 patients who participated in the trials had moderate-to-severe major depressive disorder. More than 85 percent were rated by clinicians to be moderately to extremely suicidal. The study results demonstrated a clinically meaningful and statistically significant superiority for esketamine over placebo in rapidly reducing symptoms of major depressive disorder. The safety profile was also consistent across the two studies.

Janssen has submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for the Spravato treatment-resistant depression indication in Europe in October 2018.

Source: pharmatimes.com

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Volume 9 / September 2019

Clinical Research NEWS letter
www.lambda-cro.com

PATENTS: NEW APPROVALS /LITIGATIONS /SETTLEMENTS

1. NDMA in ranitidine: discovery prompts lawsuit

The discovery of N-nitrosodimethylamine (NDMA) contamination of ranitidine was made by Valisure, a mostly web-based pharmacy. Now, both the Food and Drug Administration (FDA) and European Medicine Agency (EMA) have announced NDMA contamination of ranitidine medicines and a lawsuit was immediately filed against manufacturers for 'concealing' the carcinogen.

The lawsuit filed states that Sanofi and Boehringer Ingelheim are the two companies that stand accused of *"knowingly manufacturing and selling over-the-counter Zantac containing a concealed carcinogen to millions of people in the US"*. The lawsuit suggests that Sanofi, which is the current US rights owner of Zantac since 2017, and Boehringer, the previous US rights owner (from 2007 to 2017) *"knew or had reason to know that Zantac exposes users to unsafe levels of the carcinogen NDMA."*

The sales of the branded drug, Zantac, reached $128.9m (€117m) during 2018, despite being off-patent.

Source: www.in-pharmatechnologist.com

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2. Obstacles to Bayer settling roundup lawsuits

More than 18,400 American lawsuits have been filed against Bayer AG claiming that that the company's Roundup weed killer causes a type of cancer called non-Hodgkin's lymphoma. The company has lost three American jury trials in the Roundup litigation till date. Now, the company is in mediation to potentially settle these lawsuits. However, the cases raise questions that may prevent an easy settlement according to some legal experts. The company is appealing the decisions, saying Roundup and its active ingredient glyphosate are not carcinogenic and are safe for human use.

Roundup, first sold in 1974 by Bayer unit Monsanto remains widely available. Bayer has repeatedly said Roundup is safe and important to farmers who use the herbicide in combination with the company's genetically modified seeds.

The plaintiffs have claimed association of Roundup with non-Hodgkin's lymphoma; however, the disease is largely considered to have no known cause despite the discovery of several risk factors leading to non-Hodgkin's lymphoma.

Source: producer.com

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3. Novel approach for treating headaches via ear pressure modulation

Nocira LLC is a pre-market medical device company aimed at developing safe and rapidly effective, drug-free treatments for migraine headaches and other neurological disorders. Nocira has announced the issuance of its fourth and fifth US patents (US 10,251,790 and 10,278,868) by the US Patent and Trademark Office. These patents are related to its novel approach for treating headaches via ear pressure modulation.

The use of ear pressure modulation for the treatment of migraines was first done by Nocira. The company has continued to develop and evaluate the patented approach in a clinical development program since over half a decade. Nocira has come up with its investigational "Automated Variable Pressure Insufflation" (AVPI) approach, in which a small pocketable air pressure device is connected via thin tubes to comfortable earpieces. The pressure is controlled via Bluetooth in a mobile phone app and provides a user interface and digital health platform.

Source: pharmabiz.com

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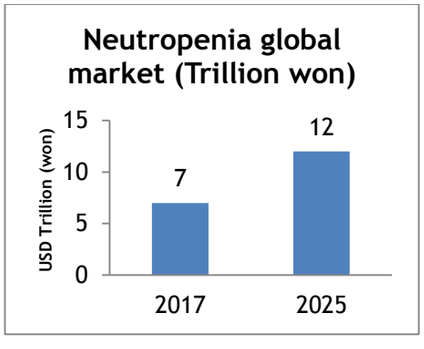
4. Hwail and SupexBNP win patent for neutropenia treatment in US

Hwail Pharmaceutical and SupexBNP have registered a patent in the United States for G-CSF (Granulocyte Colony Stimulating Factor) bio-better, a new G-CSF candidate substance that has a faster drug expression and superior pharmacokinetics (PK) over the first and second generation G-CSF agents.

G-CSF is a drug used for the treatment of neutropenia that occurs during chemotherapy. It is an essential medicine adjunct to chemotherapy. The two companies' treatment is a bio-improved new drug that replaces amino acids in the nucleus using protein engineering technology.

The faster drug expression and PK profile provides an excellent therapeutic effect and low side effects. The neutropenia treatment global market is expected to grow to 7 trillion won ($5.8 billion) in 2017 to 12 trillion won by 2025. Post approval, the two companies expect to receive a high price premium from this product.



"By registering EU patent in the first half of this year and U.S. patent recently, the bio-business of the two companies is progressing smoothly," a company official said.

Source: koreabiomed.com

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TECHNOLOGY /NDDS

1. New minimally invasive injectable embolic hydrogel

An embolic hydrogel (called a gel embolic material: GEM) has been developed by Obsidio, a Columbain medical device company (South Carolina). The GEM has been developed to be delivered through a clinical catheter for blood vessel occlusion. For transcatheter embolization, the gold standard treatment remains delivering multiple metal coils into a blood vessel that promotes coagulation so that the clot around the coil stops the flow of blood.

The applications for GEM include:

- Blood flow control in vascular injuries and aneurysms
- Reduction in tumor blood supply
- Prevention of abnormal blood flow between arteries and veins, such as arteriovenous malformations.

The hydrogel material developed by Obsidio can occlude a target vessel and does not rely on a patient's own coagulation ability. GEM has shear thinning properties, hence, becomes semisolid when subjected to shear stress. The delivery of GEM can be done via a catheter, and it forms a soft solid once in the blood vessel, allowing for minimally invasive embolization.

Source: medgadget.com

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TECHNOLOGY /NDDS

2. STAMP: Minimally invasive biopsies provide maximum pathology data

Researchers at the National University of Singapore have developed a new technology called STAMP (Sequence-Topology Assembly for Multiplexed Profiling), which uses only a small sample taken from fine needle aspiration biopsy and provides the results with near 95% diagnostic accuracy and an extensive pathology data that are currently available through extensive tissue only.

Current pathology techniques require large samples and lack in their ability to detect cancer in small samples. The data gathered from minuscule samples can be rapidly studied for the distribution of protein expression within cells and can be an important tool for early diagnosis and monitoring of cancer. In STAMP technique, only a small sample is taken through fine needle aspiration biopsy. The STAMP is implemented on a small microfluidic device, and the cost for each test is ~$50. Hence, STAMP technology has the potential to find space inside every hospital lab.

STAMP uses 3D DNA barcodes folded as compact nanostructures and has a high labeling efficiency and is devoid of biological degradation. These 3D barcodes are unfolded through heating and a pool of linear DNA is released, which can be studied by Polymerase Chain Reaction (PCR) or DNA sequencing. The study findings are published in the journal *Nature Biomedical Engineering* citing that the researchers could measure and localize billions of protein markers within just a couple of hours by using programmable DNA barcodes.

Source: medgadget.com

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TECHNOLOGY /NDDS

3. Internal bleeding detector 'Early bird'

The US Food and Drug Administration (US FDA) has provided *de novo* approval to a novel bleeding monitoring system called 'Early Bird'. Developed by Saranas, a Houston, Texas firm. The novel Early Bird bleeding monitoring system will be released in the United States.

This device is intended for use during minimally invasive vascular procedures, and it helps identifying the dangerous events such as ruptured or dissected vessels.

In the minimally invasive procedures, there is a risk of such events through the use of large tools i.e., such as those used during transcatheter aortic valve replacements. Also, these events are often undetected for a long period, which may cause extensive internal bleeding or blood extravasation. Early Bird, the only currently available device, uses a vascular access sheath with embedded bioimpedance sensors to detect bleeding and raises an alarm.

"Our first-in-human study demonstrated that clinical concordance with Early Bird detection and CT scans (primary endpoint) was near perfect, and the early discovery of bleed onset and progression during the procedure occurred in 31 percent of cases with 69 percent occurring post procedure," company sources said.

Source: medgadget.com

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TECHNOLOGY /NDDS

4. Alzheimer's: head device reduces memory loss in 7 out of 8 people

A new wearable head device that emits electromagnetic impulses was able to significantly improve memory loss in 7 of 8 patients with Alzheimer's disease within 2 months according to an open label clinical study.

NeuroEM Therapeutics is a medical device company (Phoenix, AZ). The researchers at the company have developed a wearable head device in the shape of a cap that can significantly reduce memory loss in Alzheimer's by disaggregating toxic protein formed in the brain.

Electromagnetic waves are emitted from the device at a frequency that can help reverse memory loss as evidenced in preclinical studies in mice. The groundbreaking results of the open-label clinical study in 8 patients are published in the *Journal of Alzheimer's Disease*.

"Despite significant efforts for nearly 20 years, stopping or reversing memory impairment in people with Alzheimer's disease has eluded researchers," notes the lead researcher.

Source: medicalnewstoday.com

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WHAT'S NEW AT LAMBDA

1. Successful completion of two Phase I First-in-Man studies

Lambda is a pioneer in conducting Phase I studies, particularly First-in-Man studies with New Chemical Entities (NCEs). We recently conducted two Phase I studies - one with an anti-retroviral and the other with a cholecystokinin (CCK) inhibitor. The studies included healthy subjects in various cohorts with single ascending dose of the drugs, in our highly sophisticated Phase I unit in Ahmedabad, as per regulatory guidelines. Both the studies were successfully completed within the stipulated time period under the supervision of our specially trained and dedicated team for Phase I trials.

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