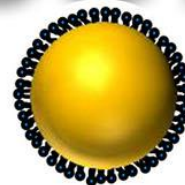


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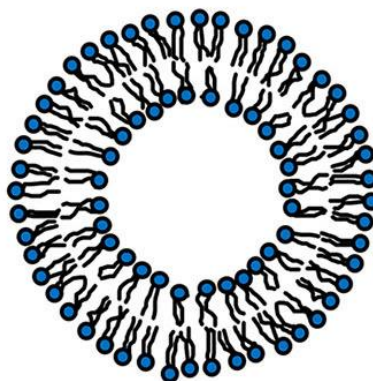
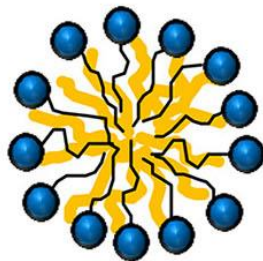
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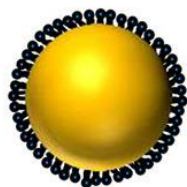
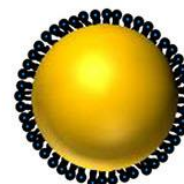
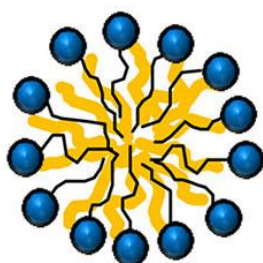
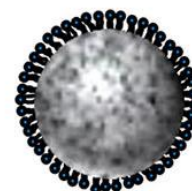
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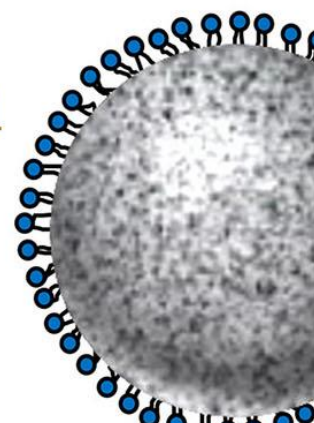
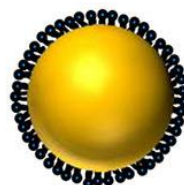
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COLLOIDAL DRUG DELIVERY SYSTEMS



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From the Publisher's Desk



Welcome to Biotechnology Kiosk!

At the outset, we wish our readers a very Happy New Year 2020! The current issue of Biotechnology Kiosk (BK) is ready for our readers with the regular features that include high-end editorials by experts, biotechnology advances around the world and industry news from pharma and biotech sectors.

This issue contains editorials on the therapeutic benefits of polyphenolic compounds that are rich in anti-oxidants, and nano- and micro-particle based drug delivery, and also the latest advances in anti-aging research along with editors' picks in the areas

of pathogens and infectious disease, organoids, cancer biotechnology and many more reporting on research breakthroughs from around the world.

We are happy to announce that we will soon launch special editions in biotechnology in partnership with leading publishers of high tech magazines. We are tirelessly working to make BK better and better with all the required information that our readers may need to update about the latest discoveries and inventions happening around the world. We do hope that you will enjoy reading this

issue of Biotechnology Kiosk. Please do write to us with your comments and feedback. Your suggestions are always appreciated.

Dr. Megha Agrawal and Dr. Shyamasri Biswas

Executive Publishers and Editors





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Cellular & Anti-aging Biology

By Shripriya Singh, PhD

Contributing Editor



Have humans finally discovered path to reverse aging: Synergistic interaction between cellular pathways is the new hope in combating old age

Quest for the pathway to reverse aging

Ever since times immemorial human beings have strived towards achieving immortality. Ancient texts, historical accounts, scriptures, and even fiction tales have often described magical potions that could make humans immortal and ever youthful. The ultimate hunt for 'ambrosia' may seem like a distant folklore but its essence is rooted in the minds of almost every living human being. Scientific and medical progress has allowed us to combat disease and illnesses and thus considerably extend the lifespan of individuals. Although, diseases expedite mortality but even healthy living beings gradually perish and die naturally. This slow yet potent biological phenomenon of gradual deterioration of health and senescence is popularly known as '**Aging**'. It was earlier believed that aging is an irreversible phenomena and once triggered will only progress with time. This concept rendered humans in a state of helplessness and instilled the idea of superficially masking the

signs of aging. This led to a boom in the cosmetic industries which promise to camouflage and even mask traces of aging, although only superficially.

Science has explained that aging like all other natural biological processes has an underlying cellular and molecular mechanism which is complex in nature and is multi-factorial. However, certain medical conditions, diseases, unhealthy lifestyles, dietary habits and environmental factors may trigger premature aging. This topic has become a hotspot for research where researchers are not only trying to understand the mechanism but also find ways of reversing the process of aging. The biggest hurdle in human age related research is the choice of an accurate animal or cell model which can precisely serve as an alternative to human beings.

In this regard *Caenorhabditis elegans*, a free living nematode is widely used for development, genetic and aging studies. A

simple nervous system, genetic homology with mammals, a short life span of three weeks and a fully mapped connectome are some of the unique features that has enabled *C.elegans* to serve as a classical model organism. A recent study published in the journal 'Cell Reports' by scientists of the MDI Biological Laboratory, in collaboration with scientists from the Buck Institute for Research on Aging in Novato, Calif., and Nanjing University in China, has shed new light on the mechanism of aging. The team of scientists has identified cellular pathways that work in a synergistic manner for longevity in *C. elegans* and that amplify its lifespan fivefold than usual (1). Figure 1 summarizes the different regulatory pathways and their effects on the lifespan of *C. elegans*.

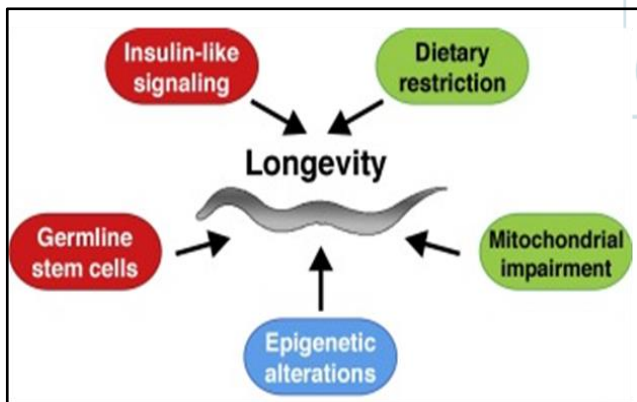


Figure 1: Graphical depiction of lifespan regulatory pathways in *C. elegans*. Green-pathways that promote longevity; Red-pathways that limit lifespan; Blue-pathways with variable effects on longevity. [Source: Drug Discovery Today: Disease Models, 2018.]

The details and relevance of the study

Human based research is practically difficult because it is not possible to carry out experiments directly on human subjects and

only few animal species can serve as representative animal models. Thus research based on age related aspects is further crucial owing to the long lifespan of humans and the complexities associated with the same. *C. elegans* has been considered a classical model organism and several aging studies and age associated disorder studies have been carried out on this simple nematode worm. The present research delves at the mechanistic aspect of two cellular pathways that majorly govern aging in *C. elegans* and how their interaction leads to increased longevity in the worm. Since the nematode worm has a short lifespan of only three to four weeks it is easier to assess and analyze the effects of environmental and genetic interventions to extend healthy lifespan in the organism. These are "conserved" pathways which have been passed down to humans through evolution and thus are being considered attractive targets for research.

These two pathways are the insulin-like signaling (IIS) and target of rapamycin (TOR) pathways and it is documented that perturbation of this pathways can help in the genetic modulation of aging (3). Further aging is associated with disrupted energy homeostasis and mitochondrial dysfunction (4). To carry out mechanistic studies on the nematodes researchers use mutant strains, these are genetically modified organisms in which only one gene or sometimes one pathway is altered precisely. Similarly a double mutant strain will carry alterations in two different genes/pathways. In this study scientists used a *daf-2 rsk-1* double mutant strain of *C.elegans*. DAF-2 is the *C.elegans* ortholog of the insulin growth factor 1 (IGF-1)

receptor and its inhibition doubles the lifespan of the adult worm. RSKS-1 is the *C. elegans* ortholog of ribosomal S6 kinase (S6K) which plays a major role in TOR pathway and its alteration can alter the lifespan of the organism. Genes act at transcriptional and translational levels and have pivotal roles in several cellular pathways (5). It is further reported that reduction in mRNA translation can reduce aging but the underlying mechanism is not

clear. In this study it was reported that an alteration in the IIS pathway increases the lifespan of the worm by 100 percent. An alteration in the TOR pathway increases the lifespan of the worm by 30 percent. So it was assumed that the double mutant should increase the lifespan by 130 percent. However, contrary to the assumption the lifespan in double mutants was amplified by 500 percent.

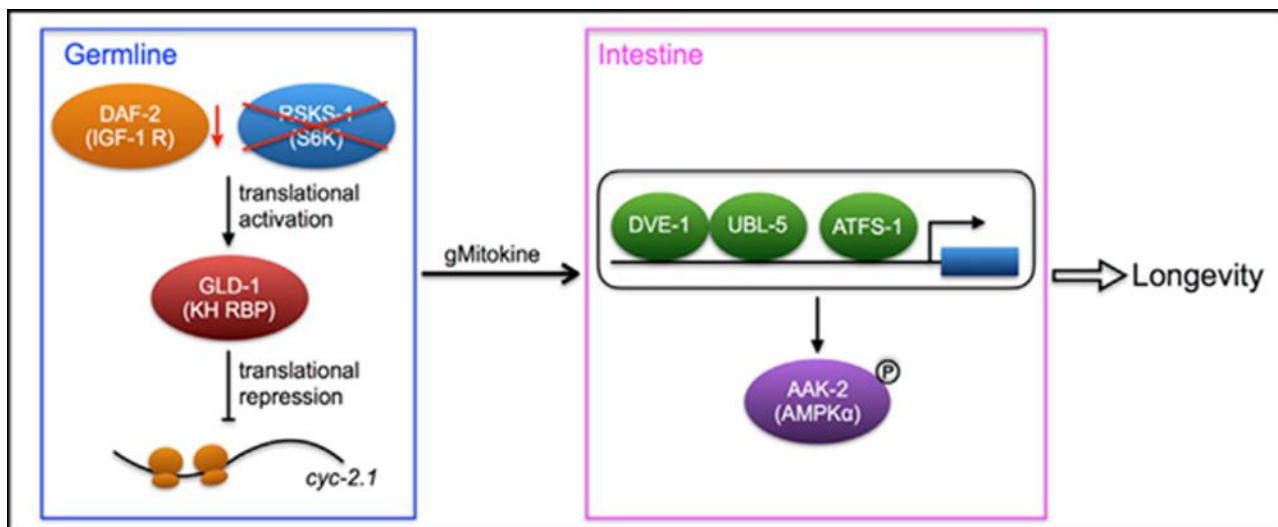


Figure 2: Graphical depiction of the synergistic interaction between cellular pathways. [Source: Cell reports, 2019]

This clearly shows that these two pathways have a synergistic effect on longevity and the research has elucidated the underlying mechanism and given us a clear picture of how the two different pathways interact via translational machinery to bring about the effect. To briefly summarize, polysomal profiling was performed to understand the role of translational regulation and cytochrome c (CYC-2.1) and ribosomal genes were identified as the key mediators of longevity. The knockdown of *cyc-2.1* extends

lifespan significantly by activating the intestinal mitochondrial unfolded protein response (UPRmt), AMP-activated kinase (AMPK) and mitochondrial fission. Further *cyc-2.1*'s translational repression is mediated by RNA binding protein GLD-1 which is important for the non-autonomous activation of UPRmt and synergistic longevity of the *daf-2 rsk-1* mutant. These results show translationally regulated nonautonomous mitochondrial stress response mechanism in the modulation of lifespan by insulin-like

signaling and S6K (1). The results have clearly shown that in order to study longevity and aging scientists have to investigate the roles of cellular networks and cross talk between different pathways instead of focusing on single individual pathways. The results showed that the effect of genetically altering pathways was not one plus one equals to two, instead one plus one equals to five. If the results are extrapolated in human beings the increase in lifespan would be equivalent to 400 to 500 years. Figure 2 summarizes the crux of the research graphically.

Future prospects and applications of the study

This study has unlocked new possibilities and revamped the concept of aging and longevity. It has given us a potent cue that if aging has to be targeted we will have to look into the complex cellular and genetic networks even if they are completely different from each other. Nature works in synergy with different elements to bring about order or chaos similarly synergistic interaction is responsible for the lifespan and aging of living beings. This study has also explained why scientists have not yet been able to identify a single gene or pinpoint a single pathway which is responsible for the potential of some humans to live to extraordinary old ages devoid of any major age-related diseases until shortly before their deaths. The study has further paved way for the experiment of combination therapies and molecular targets for drug development. This research is going to be

pivotal in the development of drugs that would extend the healthy lifespan of individuals and help in combating the ill effects of old age. The research holds potential of bringing a revolution in the field of anti-aging therapies and medical treatments. Sustaining and extending the healthy lifespan of our fast aging population is the need of the hour and will help us build a pool of long living healthy humans instead of crippled aged individuals. The study has proven that combating old age is after all no longer a work of fiction but an act of research and medicine.

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Big Data & Drug Discovery

By Peeyush Prasad, MSc

Contributing Editor



High-Throughput Strategy for Drug Discovery

How Integration of Data Leads to Drug Discovery

To understand any scientific phenomenon one has to apply careful strategy of designing and proving hypothesis. In many areas of science including biology we want not only to understand any phenomenon but our main aim is to use that understanding for human use. Exploring the disease at cellular level requires the information about all the cellular components. Drug discovery is a complex process from finding lead compound against a particular molecular target to developing safe drug for use. To find the drug target at molecular level one can either use the existing knowledge to test the hypothesis or one can generate the data at global level for finding all the alteration or aberration. Diseases are usually caused by change in the molecular dynamics which can be genetic or epigenetic. Major components of these changes are genes, transcripts, proteins and metabolites.

Approximately, 25000-30000 genes are present in a human cell. These genes express differentially in different types of cells

which lead to specific function or phenotype. A slight change in these genes may have detrimental effect on the cell. Many diseases are complex in nature and it is difficult to pin point a specific cause. To overcome these challenges, high-throughput based approaches are employed. Approaches such as genomics, transcriptomics, proteomics and metabolomics are employed to understand disease or to find a drug particular target. These approaches use the high-end technology which requires highly trained man power but they take less time and give definitive answer in a particular context. Integration of artificial intelligence and high-throughput data has made the process more refined and accurate. Further single cell omics analysis and system biology approach has been developed for better understanding the data. Figure 1 depicts the integration of different data for drug discovery.

Different High-Throughput Approaches for Drug Discovery

Genomics seek to understand gene and its regulatory element. Genomics profile gives

the information regarding mutations, single nucleotide polymorphism (SNPs) and information regarding regulatory elements. Diseases such as cancer are complex disease and there are several types of mutations present in a tumor. Mutation in the genes leads to change in several signaling

and metabolic pathways. These changes may cause the survival and progression of cancer cells. Similar is the case with other disease such as diabetes. Therefore, finding the dysregulated molecules at gene level may help in finding the factors responsible for disease and its progression.

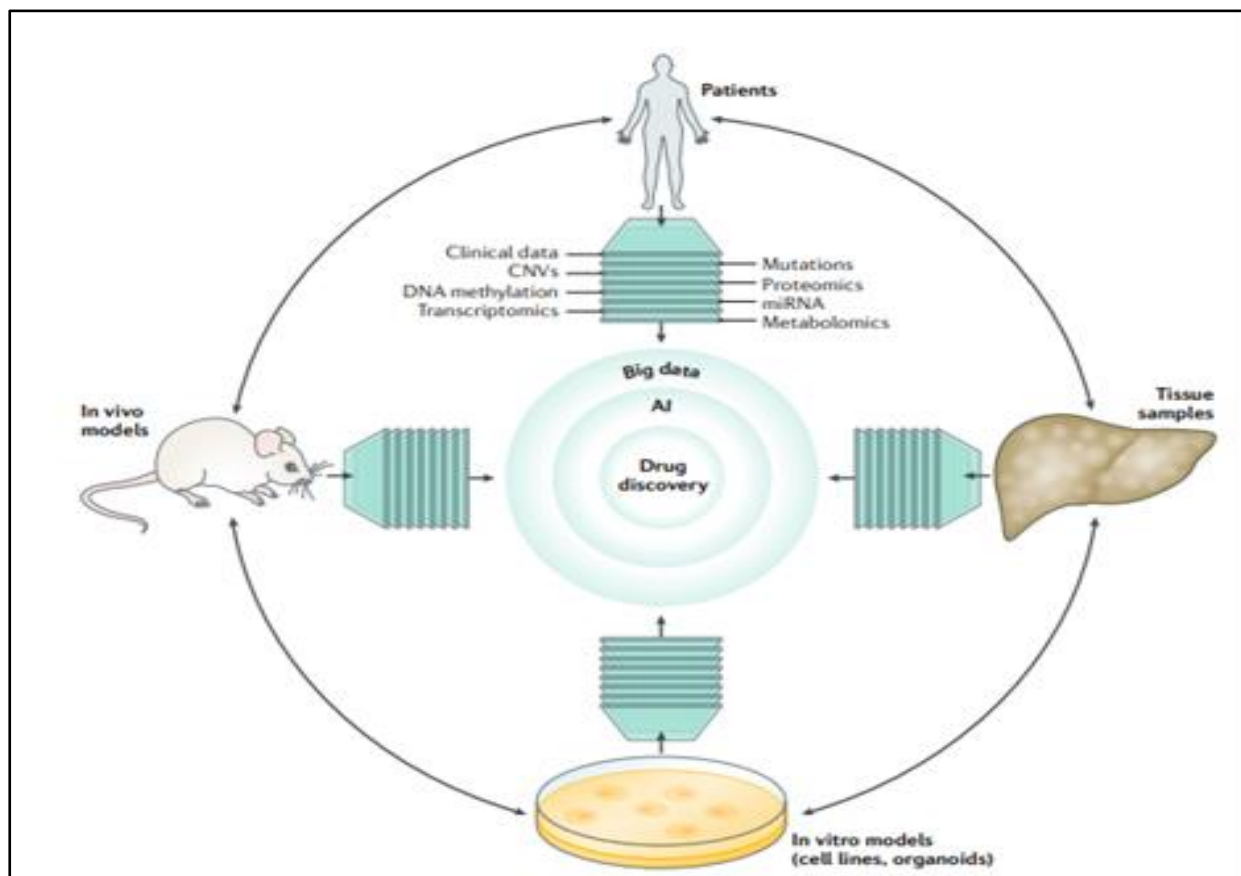


Figure 1. Translational research and big data. Translational research comprises four main components: patients, tissues, in vitro models (cell lines and organoids) and in vivo models. Each component can be characterized by different molecular modalities (such as genomics, epigenomics and functional genomics). Artificial intelligence (AI) can be used to improve the insights from big data by delineating differences and similarities and further facilitating efficient therapeutic discovery. CNV, copy number variation; miRNA, microRNA [Source: Nature Reviews, Chen B et. al., 2020].

Further mutational analysis also helps in identifying the mechanism of drug resistance. Mutational landscape of cancer cells vary from patient to patient [2]. Therefore, genomic profile of a patient can help in designing the personalized medicine. Transcriptome profiling of a disease gives the

idea about the expressed genes. Only limitation of RNA based analysis is not all the mRNAs get translated into the proteins and hence do not contribute to the phenotype. One of the advantages of transcriptome based analysis is it gives the idea about the regulatory RNA such as miRNA and lncRNA.

Company	Function	Link
Agilent Technologies	Working in the field of biopharm cancer research and cell analysis along with diagnostics, food and energy.	https://www.agilent.com/
Danaher	Genomic company working in the field of healthcare, diagnostics and life sciences.	https://www.danaher.com/
23andme	Genetic testing and analysis	https://mediacenter.23andme.com/
Verge Genomics	Uses machine learning and human genomics for drug discovery.	https://www.vergegenomics.com/
Cytomyx	Company works on comparative proteomic analysis of different samples for drug discovery.	https://cytomx.com/
Evotec	Provide advanced technology platform for protein expression analysis and modifications.	https://www.evotec.com/en

Table 1: Top companies working in the field of high-throughput technology.

Proteins and metabolites are major factors responsible for cell behavior and phenotype. Proteomics based analysis helps in identifying the drug target. Mutations at gene level are often reflected in protein structure which may cause its activity to increase or diminish. Further, change in protein level is

often observed in diseases. Proteome based analysis reveal expression level of proteins and bioinformatics based analysis of the data can help in identifying the drug target. Several diseases are the product of error in metabolism and metabolomic profile can give us idea about the indicators of cellular state

such as bio-energetic pathways, toxicity level, anabolic pathways and pathways associated with drug metabolism. Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) tests are usually performed to predict the effectiveness and safety measures associated with the drug [3]. Metabolic profile of a disease patient can help us in designing drug which is not only effective but safe also. Table 1 mentions some of the top companies working in the field of high-throughput technology.

Concluding Remarks and Future Perspective

High-Throughput study is the future for drug discovery science. More and more companies are now employing these technologies for finding better drug. Several high-throughput studies have identified the overlapping molecular mechanism between two different diseases [4]. This disease-disease relationship can help in repurposing the drugs where one drug can be used for more than one disease. On the other hand multi-omic analysis will help in identifying the exact drug target and its effectiveness. Some of the technological challenges still we need to overcome such as development of platform with high sensitivity and specificity. For example, false identification in high-throughput study is one of the major

problems. Easy to use pipeline needs to be developed for analysis of large data sets. Integration of AI, high-throughput data and chip based technology can further enhance and accelerate the drug screening process.

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Medical Biotechnology

By Megha Agrawal, PhD

Executive Editor



Therapeutic, Health-Aiding and Tumor Suppressing Roles of Polyphenols

Polyphenols Offering New Therapeutic Avenues to Battle Complex Diseases

Polyphenols belong to a structural class of naturally occurring or synthetic/semisynthetic organic materials. They are versatile antioxidant compounds and offer medically and clinically important functional properties. The unique physical and chemical characteristics of polyphenols are due to their high molecular weights (500–4000) and phenolic substructures that consist of proteins and amino-based organics [1]. Previous studies have also shown that the formation of particular metal complexes, such as intense blue-black iron(III) complexes contribute to unique physical and chemical properties of polyphenols [1]. Resveratrol and flavanols, notably (-)-epicatechin are widely researched polyphenolic compounds [1, 2].

The ongoing research has revealed the potentials of polyphenols as extremely efficient drug agents that can be leveraged for new therapeutic designs for combating stroke related injuries, cancer and renal failures [1-3]. To this end, researchers have

shown that polyphenols could be ideal alternatives especially when co-administered with other drugs that are recommended for better efficacy and safety [3]. Lately, the naturally derived polyphenols that are plant and fruit derived secondary metabolites consisting of chemically contained benzene rings with OH moieties have emerged very promising for therapeutics [3, 4].

As new therapeutic applications are emerging, the family of polyphenols are getting extended from simple flavonoids and phenolic acids to structurally more complicated polyphenolic compounds including colored anthocyanins [5]. Such compounds are known to play important roles in the defense and protective mechanisms of plants [3]. Extensive research have been carried out on this chemical group of compounds covering both the extracts as well as the isolated compounds [3, 6]. Recent research conducted in these areas have indicated enormous potentials of these compounds exhibiting dynamic therapeutic and health aiding properties [3]. For example, natural resources of polyphenols including

green tea, almond, and berries have demonstrated beneficial and pharmacological activities in prevention of neurodegeneration, aging, tumorigenesis, and metabolic disorders and also diabetes. In

addition, the application of polyphenol has also shown beneficial activity in the treatment of pathogen infection, hypertension, and cardiovascular diseases (Figure 1) [3].

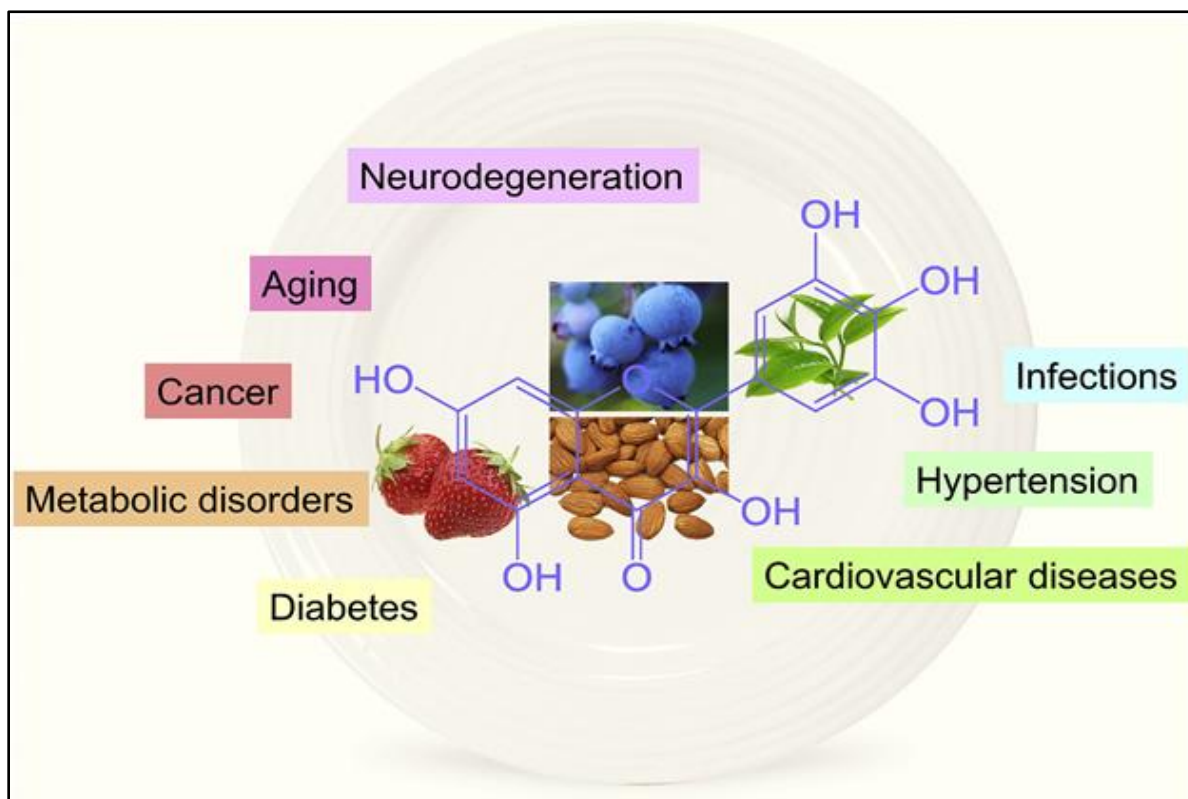


Figure 1: Versatile applications of polyphenols that exhibit high therapeutic potential in various complex diseases and medical conditions [Source: Biotechnology Advances (2020)].

The Potential Anti-Cancer Activity of Polyphenols

Researchers have shown numerous signaling pathways including the death receptor (extrinsic) pathway, the mitochondrial (intrinsic) pathway and the perforin-granzyme apoptotic pathway through which polyphenols are believed to carry out potential anticancer activity [3, 7]. Especially, investigations on the p53 signaling pathway have suggested its significant contributions in cell cycle

regulation, metabolism, aging and development, reproduction, and suppression of tumor expression [3]. Polyphenols were shown to use p53 signaling pathway to produce anticancer activity through apoptosis in variety of cancers [3]. However, it is also of concern that several genomic studies have revealed that p53 frequently encounter mutation in different cancer cell lines, which can compromise its functional role [3].

The Possibility of Polyphenols Modulating p53 Signaling Pathways

The p53 protein that is encoded in humans by the tumor suppressor 53 (TP53) gene is known to be located on the short arm of chromosome 17 [3]. The important role of P53 is defined by its activity as a sequence-specific nuclear transcription factor that binds to defined sites within the DNA. Subsequently, it negatively regulates transcription of genes that controls cell cycle progression DNA repair, metabolism, senescence, cell death, and angiogenesis [8].

Various studies have demonstrated multiple mechanisms such as induction of

apoptosis, regulation of various signaling pathways, regulation of cell cycle, and activation of receptors at the level of plasma membrane as the important factors of anti-carcinogenic effects of polyphenols [3]. In this regard, research studies have indicated the anticancer effects of polyphenols due to their ability to modulate glucose uptake and metabolism in various cancer cells [3]. It has been shown that the overexpression of p53 protein can be induced by a number of polyphenolic compounds such as resveratrol, curcumin and epigallocatechin-3-gallate [1, 3].

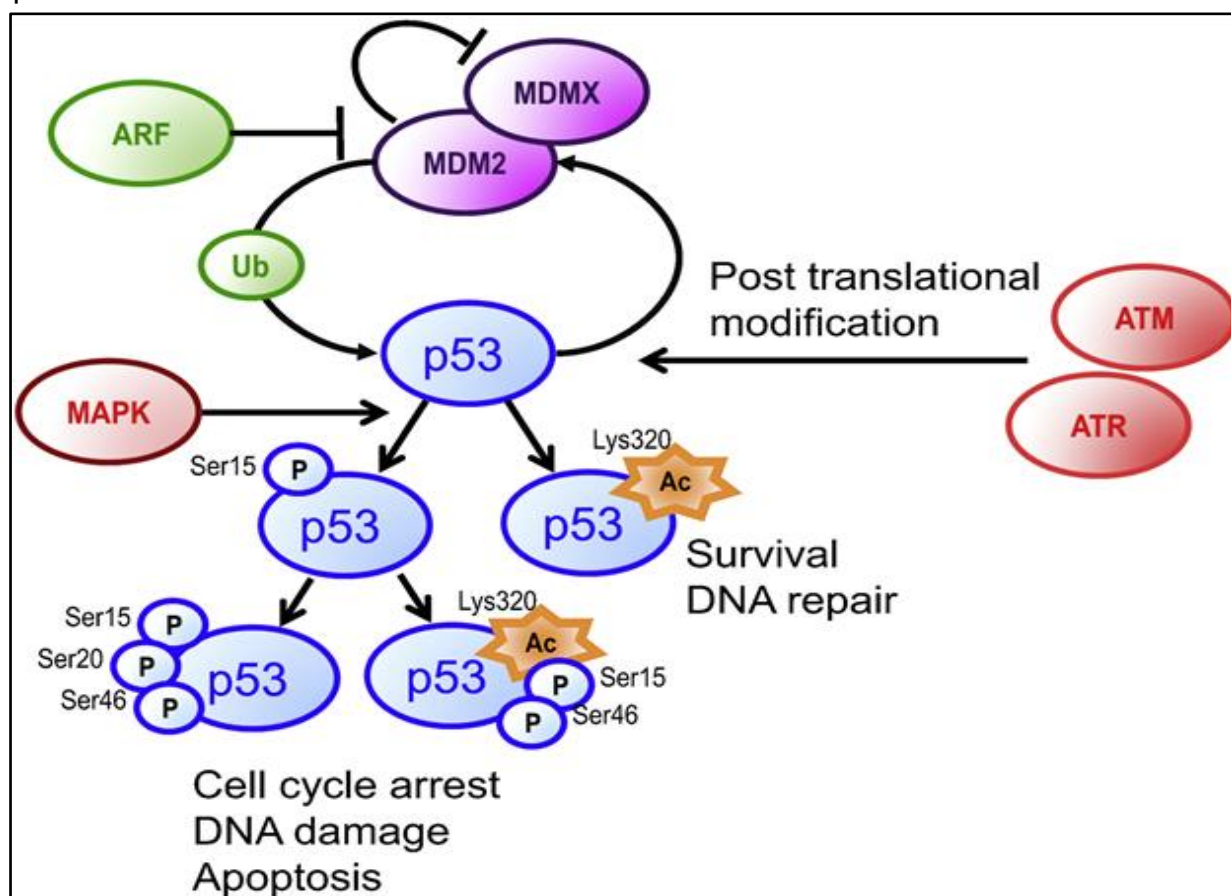


Figure 2: Polyphenols can induce various post-translational modifications of p53 that eventually control the function of p53. Ac, acetylation; P, phosphorylation; Ub, ubiquitination [Source: Biotechnology Advances (2020)].

In this connection, it has been observed that polyphenols like genistein, luteolin, quercetin, and wogonin that are abundantly in grapes, black and green tea or berry-derived products can account for its upregulation expression of p53 protein [3]. To this end, researchers have shown the ability of MDM2 and MDMX protein to regulate the stability of p53 through ubiquitination. Further, studies have indicated that phosphorylation of p53 at different serine residues can lead to cell cycle arrest, DNA damage, and apoptotic cell death. This occurs together with acetylation at lysine residue that tune the function of p53 in cell survival and DNA repair (Figure 2) [3].

Researchers employed assays for the activities of resveratrol and black tea polyphenols separately and also their combined forms in a mouse model of skin tumors. They showed that treatments significantly reduced the tumor incidence and volume. The mechanism of action was thought to be the raise in phosphorylated p53, the inhibition of MAPKs signaling and the induction of apoptosis [3].

Pre-Clinical Trials of Polyphenols for Cancer Prevention

In view of the promising results for cancer prevention, current R&D has focused on clinical trials of polyphenols including curcumin, genistein and Broccoli Sprout that contain sulforaphane and polyphenols containing sulforaphane and polyphenols [3]. Lately, the application of new technologies such as bionanotechnology have shown for different therapeutic modifications that have been employed improve the solubility, biocompatibility and bioavailability of polyphenols [9]. In this regard, researches

included new design of dynamic drug carrier systems for specific targeting and encapsulation techniques [3]. In a significant study, naringenin was shown to be a promising candidate for treatment of hepatocarcinogenesis. This study reported naringenin inhibiting cell proliferation that induced apoptosis cell death in human hepatocellular carcinoma [10]. In another pre-clinical study, quercetin was shown to arrest S phase in human breast cancer cells by increasing p53 and p57 proteins [3].

Concluding Remarks

The ongoing research on the natural polyphenols has shown tremendous promise for polyphenols to be an alternative therapeutic agent that is more effective and less toxic. Researchers have shown the anticancer effects of polyphenols that are attributed to several signaling pathways including the tumor suppressor gene tumor p53 protein. Several polyphenolic compounds can be derived from a wide variety of dietary sources including curcumin, resveratrol, genistein, luteolin, quercetin, wogonin and epigallocatechin-3-gallate. Studies have strongly suggested that these compounds can potentially upregulate p53 expression in several cancer cell lines through distinct mechanisms of action. Further, it has been shown that polyphenols can stabilize p53 protein through p53 phosphorylation, p53 acetylation and reduction of oxidative stress. We anticipate more in-vitro and in-vivo studies of polyphenols for their promising anticancer effects would be undertaken in the future that would involve modulation of p53 signaling pathways.

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Plant Based Products & Drug Delivery

**By Shyamasri Biswas, PhD
Executive Editor**



Nanoparticle and Microparticle based Drug Delivery Systems for Bioactive Phytochemicals

What are Bioactive Phytochemicals?

Bioactive components that are isolated from plant sources are known as phytochemicals. Lately, there has been a lot of research interests in phytochemicals for their potential use in functional foods, supplements, and pharmaceuticals. However, the applications of these bioactive components in foods, supplements, and pharmaceuticals are often limited due to their poor solubility, stability, and bioavailability [1, 2]. Researchers have shown that many of these bioactive phytochemicals could potentially promote human health and wellbeing by preventing or treating certain diseases, or by improving physical or mental performance [1, 2]. Phytochemicals based drugs are different than traditional drugs in terms of the dosage administration. For example, unlike conventional drug administration that happens in a specific dose at a particular time under well-controlled conditions, bioactive phytochemicals are usually taken at low and variable levels. This is usually done as part of

a complex diet at irregular intervals over extended periods of time [3].

A considerable amount of research has focused on to ascertain whether any change in health status can be associated with consumption of a particular phytochemical [2]. Additionally, research has also been conducted on phytochemicals to understand any chemical or physical alteration during processing, storage, and ingestion. The reason is such alterations can affect their bioavailability and bioactivity [2]. Further, it has also been shown that the quantity, composition, and structure of the foods consumed can seriously affect the efficacy of a phytochemical that is employed with the specific food [2, 4].

Types of Phytochemicals that can be incorporated into Foods

Researchers have shown many different bioactive phytochemicals for their incorporation into foods, supplements, and pharmaceuticals along with their potential health benefits, including carotenoids,

flavonoids, essential fatty acids, peptides, and glucosinolates [5]. However, these phytochemicals are known to vary in their molecular weights, functional groups, charges, and polarities. This leads to differences in their solubilities, partitioning, physical states, and chemical stabilities [2]. In

view of these differences, the knowledge of the specific molecular and physicochemical characteristics of the phytochemical to be encapsulated is critically important. This enables suitable design of a viable phytochemical oral delivery systems (PODS) [6].

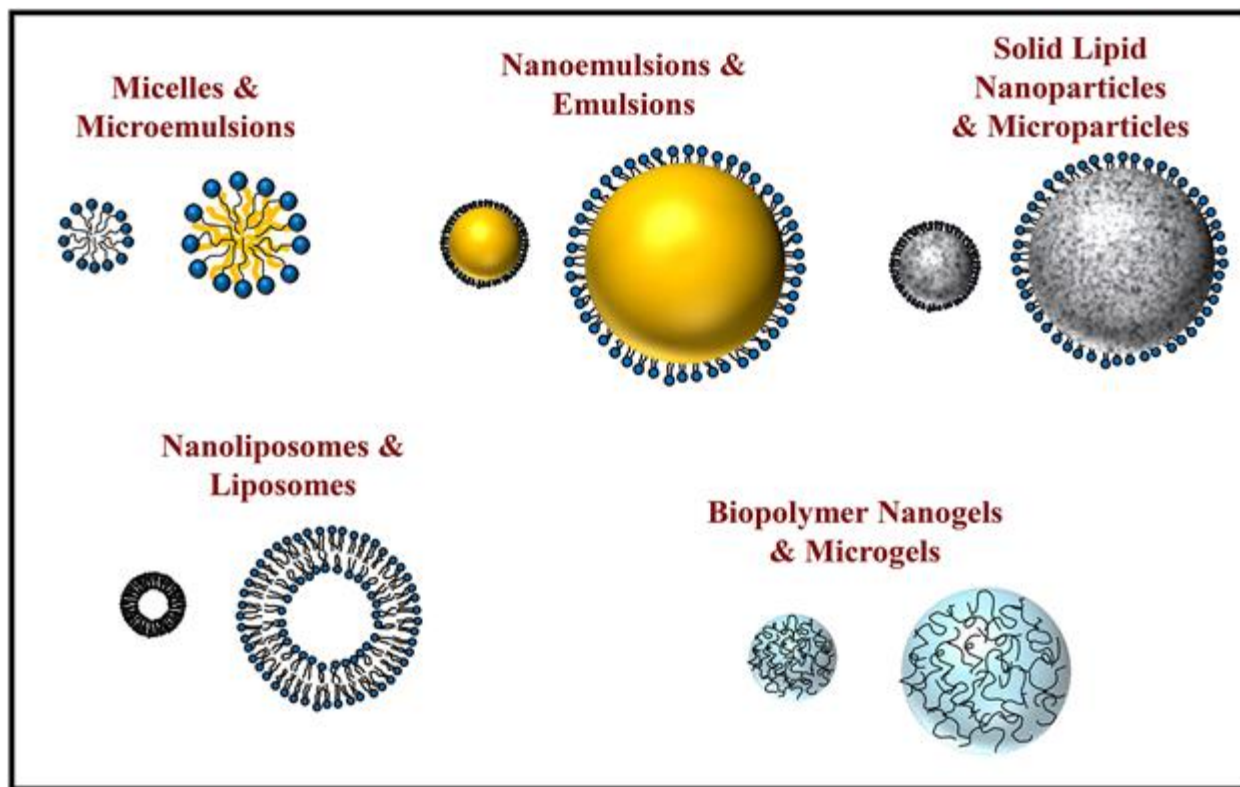


Figure 1: Typical examples of colloidal delivery systems based on nano and microparticles that can be used to encapsulate phytochemicals [Source: Biotechnology Advances (2020)].

Phytochemical Oral Delivery Systems based on Micro and Nanoparticle Encapsulations

Phytochemical oral delivery systems (PODS) consist of phytochemical-loaded nanoparticles or microparticles that can overcome the challenges of efficient delivery phytochemicals. Researchers have demonstrated production of PODS in liquid, gel, paste, or solid forms [2]. However, it is usually recommended that these PODS must

be carefully formulated in order to be compatible with the product matrix, economical, robust, and also to maintain phytochemical bioactivity [2].

Many different kinds of colloidal delivery systems have been developed to encapsulate phytochemicals for use as PODS) including micelles, emulsions, solid lipid nanoparticles, liposomes, and biopolymer microgels (Figure 1) [2]. These delivery systems have been shown to vary in

terms of the composition, structure, and dimensions of the particles they contain [2]. In these systems, nano and microparticles that are used typically have diameters that lie within the range of about 1 and 100 nm and 100 nm and 1000 μm , respectively [7]. In general, it has been shown that many colloidal delivery systems exhibit relatively broad particle size distributions and may therefore contain both types of particles (nano and micro) [2].

Current research has focused on optimizing the composition, size, charge, and loading characteristics of the colloidal particles. This is aimed for their optimal selection to make it sure that they are compatible with the final product matrix, such as pH, ionic strength, ingredient interactions, mechanical stresses, and thermal stability [2]. Research focus has also been to study the appearance, rheology, flavor profile, and shelf-life of the final product to identify suitable PODS that are compatible with the food matrix [2].

Concluding Remarks

Bioactive phytochemicals that are derived from plants offer attractive possibilities for drugs and new therapeutics to solve many health challenges and issues. We anticipate future studies to be focused on producing PODS that are commercially feasible. This implies cost-effective large scale production of such PODS for delivery of phytochemicals. It is also required that the process employs generally recognized safe food ingredients and commonly utilized processing operations in order to be commercially viable.

References for further reading

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Biotechnology Advances around the World

Editor's Picks

Every issue of Biotechnology Kiosk presents select latest research news picked by the executive editors on significant research breakthroughs in different areas of biotechnology around the world. The aim is to promote further R&D in all of these cutting edge areas of biotechnology. The editors have compiled and included the following innovations and breakthroughs to highlight the recent biotechnology advances.



Dr. Megha Agrawal
Executive Editor



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Cancer Biotechnology

Revealing the anti-cancer potential of non-oncological drugs

In a recent discovery, researchers in the United States created a public resource containing the growth-inhibitory activity of 4,518 drugs that were tested across 578 human cancer cell lines. In a recent paper published in the journal Nature Cancer (Discovering the anticancer potential of non-oncology drugs by systematic viability profiling, Nature Cancer, 2020; DOI: 10.1038/s43018-019-0018-6), researchers have developed PRISM (profiling relative inhibition simultaneously in mixtures), which is a molecular barcoding method that is employed to screen drugs against cell lines in pools. Researchers envision that the PRISM drug repurposing resource is a starting point to develop new oncology therapeutics, and also for potential direct clinical translation in the distant future.

In their study, researchers demonstrated an unusually large number of

non-oncology drugs that selectively inhibited subsets of cancer cell lines in a manner that was predicted in the literature from the molecular features of the cell lines. Their findings included compounds that killed cancer cells by inducing phosphodiesterase 3A-Schlafen 12 complex formation, vanadium-containing compounds. It was observed that the killing of cancer cells depended on the sulfate transporter SLC26A2 and the alcohol dependence drug disulfiram. This killed cells with low expression of metallothioneins, and the anti-inflammatory drug tepoxalin, which killed cells via the multidrug resistance protein ATP-binding cassette subfamily B member 1 (ABCB1).

These breakthrough findings that also reveal novel drug mechanisms and potential targets pave way to open up new avenues and therapeutic pathways for the development of new cancer drugs or repurpose existing drugs to treat cancer.

Pathogens and Infectious Disease

Engineered mosquitoes to neutralize dengue virus

The World Health Organization has projected dengue virus as a source of major infectious disease that threatens millions of people in tropical and sub-tropical climates. It is believed that dengue is a leading cause of serious illness and death especially among children in many Asian and Latin American countries. Further, according to a recent report by the Pan American Health Organization, the data shows that the

Americas have the highest number of dengue cases ever recorded. Dengue virus infects patients that triggered compromised immune systems, which result in flu-like symptoms such as severe fevers and rashes. It can also include serious medical conditions such as life-threatening bleeding. Unfortunately, there is currently no specific treatment that exists that can effectively battle dengue virus infection. Therefore, it is widely believed that prevention and control are the only ways to stop the spread of the virus.

An international collaborative team of scientists from the United States, Taiwan and Australia recently demonstrated synthetically engineered mosquitoes that can halt the transmission of the dengue virus. They published their breakthrough research in PLOS Pathogens (Broad dengue neutralization in mosquitoes expressing an engineered antibody, PLOS Pathogens, 2020; 16 (1): e1008103 DOI: 10.1371/journal.ppat.1008103). In this study, researchers developed a human antibody for dengue suppression in *Aedes aegypti* mosquitoes, the insects that spread dengue.

This breakthrough is quite significant as it shows the first engineered approach in mosquitoes that successfully targets the four known types of dengue. This approach improves upon previous designs that addressed only single strains. Researchers envisioned that the engineered mosquitoes could easily be paired with a dissemination system, such as a gene drive based on CRISPR/CAS-9 technology. This enables the capability of spreading the antibody throughout wild disease-transmitting mosquito populations.

Food & Health Science

The consumption of yogurt may lead to lesser risk of breast cancer

Previous studies indicated inflammation triggered by harmful bacteria as one of the causes of breast cancer. It is believed that there are approximately 10 billion bacterial cells in the human body. Out of these bacterial cells, most are considered harmless. However, some bacteria cells can create toxins, which can trigger inflammation in the body.

It has been shown that while chronic inflammation can destroy the harmful germs, it can also simultaneously damage the body. Gum disease or periodontitis is considered as one of the most common inflammatory conditions, which has already been connected to oral, oesophageal, colonic, pancreatic, and prostatic and breast cancer.

Now, in a paper published in Medical Hypotheses (Hypothesis: Bacterial induced inflammation disrupts the orderly progression of the stem cell hierarchy and has a role in the pathogenesis of breast cancer, Medical Hypotheses, 2020; 136: 109530 DOI: 10.1016/j.mehy.2019.109530), scientists in UK presented hypotheses and advised consuming natural yogurt to minimize the risk of breast cancer. Researchers showed that the beneficial bacteria that was found to dampen inflammation was similar to the bacteria found in breastfeeding mothers. Their hypotheses is that the bacteria can be protective because breast feeding can reduce the risk of breast cancer. So, the conclusion of the researchers is that the consumption of yogurt is associated with a reduction in the risk of breast cancer.

Organoid Science & Technology

Use of snake stem cells to create organoids that produce snake venom

Organoids can be defined as self-organizing 3D biological structures that are grown from stem cells and that recapitulate essential features of the tissue under study. Within the arena of organoid science and technology, the feasibility of growing mammalian salivary gland organoids is of immense research interests. However, very little is known about the biology of adult stem cells in reptiles such as snakes.

Now, researchers have used it in a surprising and unexpected way for the production of snake venom for use as anti-venom to treat deadly snake bites. In the journal *Cell*, researchers in the Netherlands reported (Snake Venom Gland Organoids, *Cell*, 2020; 180 (2): 233 DOI:

10.1016/j.cell.2019.11.038) the innovative creation of organoids of the venom glands of the Cape coral snake (*Aspidelaps lubricus cowlesi*) and that these glands were demonstrated for their capability of producing venom.

In this study, researchers established and showed long-term culture conditions for functional snake venom gland epithelium using R-spondin-based organoid technology. The researchers were then able to identify at least four distinct types of cells within the venom gland organoids. They confirmed that the venom peptides produced were biologically active and resembled the components of venom from live snakes. This research opens up further avenues to develop anti-venom serums.

Compiled and Edited by Dr. Megha Agrawal and Dr. Shyamasri Biswas.



Biotech and Pharma Industry Roundup

Epizyme wins FDA approval for epithelioid sarcoma Drug

The U.S. Food and Drug Administration (FDA) granted accelerated approval to Epizyme's tazemetostat, which is an oral potent, first-in-class EZH2 inhibitor for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. The approval of the drug, now dubbed Tazverik, was based on the overall response rate and duration of response in a Phase II clinical trial [Source: <https://www.biospace.com/>].

AstraZeneca commits for zero carbon emission

AstraZeneca's recently announced their "Ambition Zero Carbon" strategy that will accelerate the company's already-existing sustainability plans. The company's plan includes a doubling of energy productivity and using renewable energy for both power and heat. The goal is to switching to a 100% electric vehicle fleet that will be completed by 2025 and the total cost for this switch is expected to be about \$1 billion [Source: <https://www.biospace.com/>].

SMA drug produced by Roche gets a boost with new study data

Roche recently announced that its experimental drug risdiplam helped babies

with the severest form of the rare disorder spinal muscular atrophy sit unassisted one year after beginning treatment. This finding should help Roche's case for approval now before the FDA. It is expected that if this drug is finally approved by the FDA, risdiplam will enter a highly competitive field already served by two injectable drugs, Biogen's Spinraza and Novartis' gene therapy Zolgensma [Source: <https://www.biopharmadive.com/>].

Sanofi plans to stop diabetes, heart research and \$2.2B in cost cutting going forward

Sanofi's new CEO, Paul Hudson plans to shake up the French pharma giant in a recent announcement. As a future plan, Sanofi will stop all research in the disease areas involving diabetes and cardiovascular programs, and reduce costs by 2 billion euros, or about \$2.2 billion, by 2022. These savings are expected to come from spending less on expenses such as travel, consultants and training costs, and reduced investments in deprioritized businesses including diabetes and cardiovascular, and manufacturing improvements [Source: <https://www.biopharmadive.com/>].

Blue Cross Blue Shield partners with Civica on generic drug mission

In a recent announcement, the Blue Cross

Blue Shield Association said that together with 18 affiliate BCBS companies, it will invest \$55 million to create a new subsidiary of Civica Rx. This generic drug company was created by hospital systems in 2018. [Source: <https://www.biopharmadive.com/>].

Merck diversifies its cancer drug pipeline through a \$2.7 billion acquisition of biotech firm ArQule

Merck & Co. recently announced its plans to diversify its cancer drug pipeline through a \$2.7 billion acquisition of ArQule. [Source: <https://www.biopharmadive.com/>].

Lilly Seeking out more deals in 2020

By following the previous example of its recent \$1.1 billion takeover of dermatology specialist Dermira, Eli Lilly expects to sign one deal worth between \$1 billion and \$5 billion per quarter in 2020.

Madrid-based RNA specialist Bioncotech Therapeutics enters

into a Phase II clinical trial collaboration with a MSD subsidiary

The clinical collaboration between Bioncotech Therapeutics and Merck Sharpe & Dohme's aims at providing clinical Phase II evidence that RNA-based cancer lead BO-112 can improve the efficacy of PD1 checkpoint inhibitor pembrolizumab in patients with advanced-stage solid tumors with liver metastases [Source: <https://european-biotechnology.com/>].

Agriculture ministers in Europe commit to global trade rules

In a recent meeting in Berlin, Germany, ministers from 72 countries came together at the Agriculture Ministers' conference to discuss and adopt a joint communiqué on global trade. In this deal, the ministers agreed to strengthen rule-based free trade. This deal strengthens local, regional and global value chains and promotion of agricultural trade; equitable distribution of welfare gains across all countries and social strata [Source: <https://european-biotechnology.com/>].



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