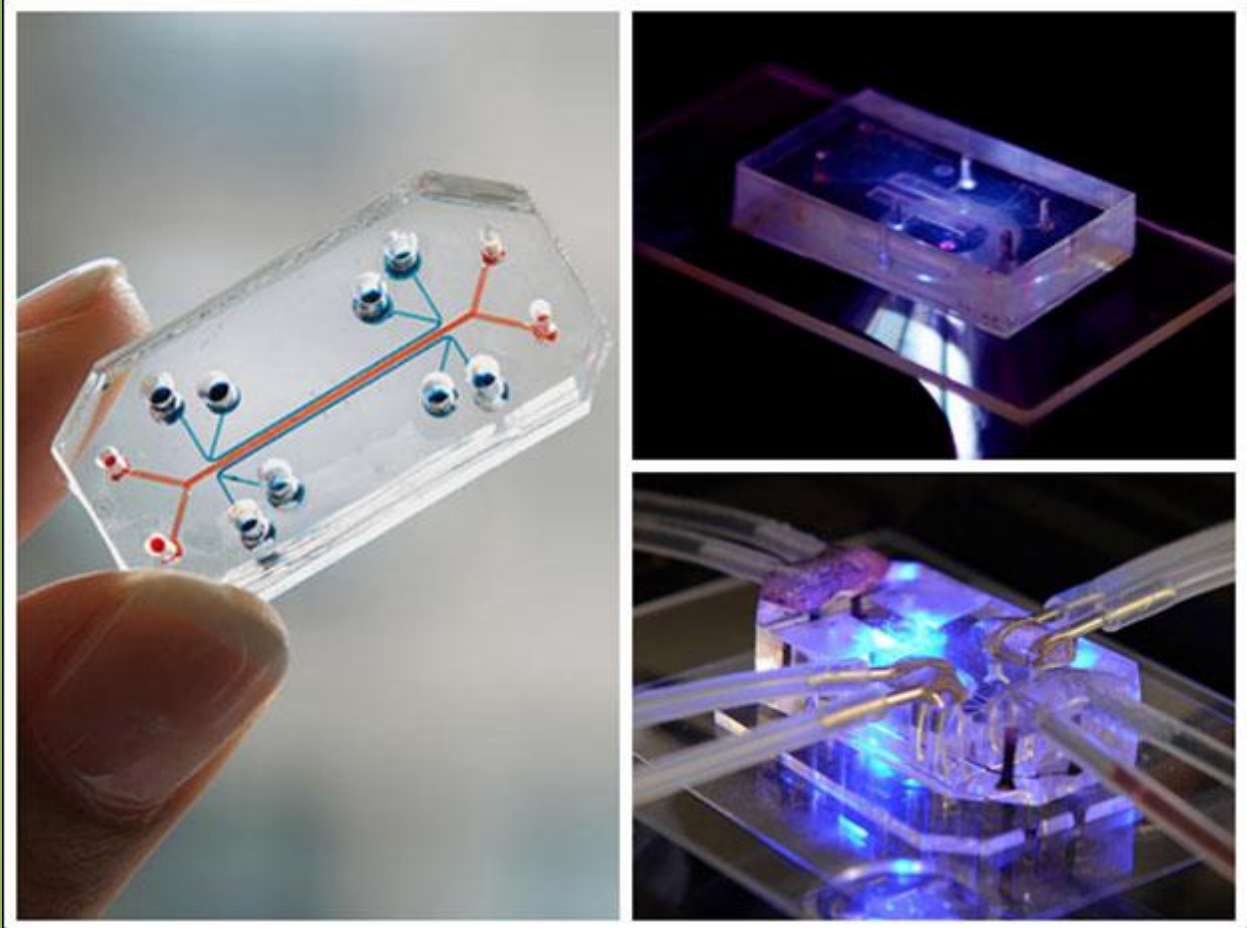




BIOTECHNOLOGY KIOSK

JUNE 2019



Featured Article

Topic: Regenerative Medicine

“Organ-on-a-chip” technology: the promising new face of preclinical testing and drug development

Volume 1, Issue 1

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From the Publisher's Desk



Welcome to Biotechnology Kiosk!

We decided to launch a dedicated magazine in biotechnology with a goal to provide a common platform to academic and industrial professionals that seek latest information in all areas of biotechnology R&D happening around the world. Our motivation to start a new magazine in biotechnology stems from the fact that professionals do need a one-stop-place in biotechnology to read, discuss and advance their understanding in any area of modern biotechnology that has been or being developed. Such a

forum is essential to generate and cater new ideas for future breakthroughs in science and technology. This magazine is designed to fulfil exactly this objective.

This magazine serves a dual purpose of providing a high-value editorial content in various areas of biotechnology and industrial news along with a medium for industry to showcase their technologies and products to the readers. Our goal is to keep a high content of about 70 percent for editorials written by top experts in each issue. This makes this magazine unique to our readers. In the first issue of the magazine, we have tried to cover a number of current 'hot' biotechnology R&D areas that include

regenerative medicine, medical biotechnology, enzyme biotechnology and reliability issues in medical technologies and devices. Each of these areas has tremendous global market potential that runs into billions of dollars impacting modern healthcare. Going forward with every issue of the magazine, it is our desire to cover every topic in biotechnology that can influence our society. We do hope that this magazine will be liked and we will receive kind support from our readers. We would appreciate any feedback or suggestions to improve the magazine.

Please feel free to write to us with any questions or suggestions at megha@biotechkiosk.com (Megha Agrawal, PhD) and shyabiswas@biotechkiosk.com (Shyamasri Biswas, PhD).

Dr. Megha Agrawal and Dr. Shyamasri Biswas

Executive Publishers and Editors

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Topic: Regenerative Medicine

“Organ-on-a-chip” technology: the promising new face of preclinical testing and drug development.

***Shripriya Singh, PhD* - Contributing Editor**



Failure is part of scientific experiment and research, however, sometimes the price one has to pay for a failure might dilute the rewards of success altogether. Researchers in the field of predictive toxicology and drug development face failures as opposed to success most of the time. The past two decades has witnessed a steady rise in the rate of clinical trial failures that has led to increased healthcare costs. It takes nearly 10-12 years to develop a single potent drug with a monetary investment worth 2.5 billion dollars [1]. These numbers are taxing to the drug industry and cannot be ignored. Therefore, the

diagnostic window needs to be shortened so that resources can be spent judiciously on effective treatment. This has led to the idea of “fail early and fail cheaply” within the pharmaceutical industry. Rapid, fast paced, reliable, cost effective and reproducible predictive models of human physiology are the need of the hour.

Predictive toxicology and bio-safety assessment of each and every chemical entity present in the environment is crucial as every chemical substance can be toxic or effective at a particular concentration/dose. The same applies to

drugs, which are intended for therapeutic purposes but can be toxic and life threatening if not profiled stringently for their potential side effects and secondary targets. When the human body is subjected to a toxic insult, the response elicited is not restricted to one organ or one gene. A complex interplay of organ-organ interaction and gene-gene interaction takes place. Profiling these interactions in the conventionally advanced three-dimensional (3D) culture system and organoid culture is not feasible. Stem cell derived organoids have been instrumental in studying the molecular mechanisms and pathophysiology of diseases and find

widespread application in regenerative medicine. However, an isolated organoid is not capable of mimicking the complex physiology that exists within a human body and the absence of vasculature further restricts the profiling of drug metabolism.

“Organ-on-a-chip” technology is the emerging trend in the field of clinical/medical research that has partially brought the long-standing financial feud to an end and has unlocked completely new avenues. “Organ-on-a-chip” is simply the amalgamation of software designing, microfluidics, 3D organotypic system culture and tissue engineering (Figure 1).

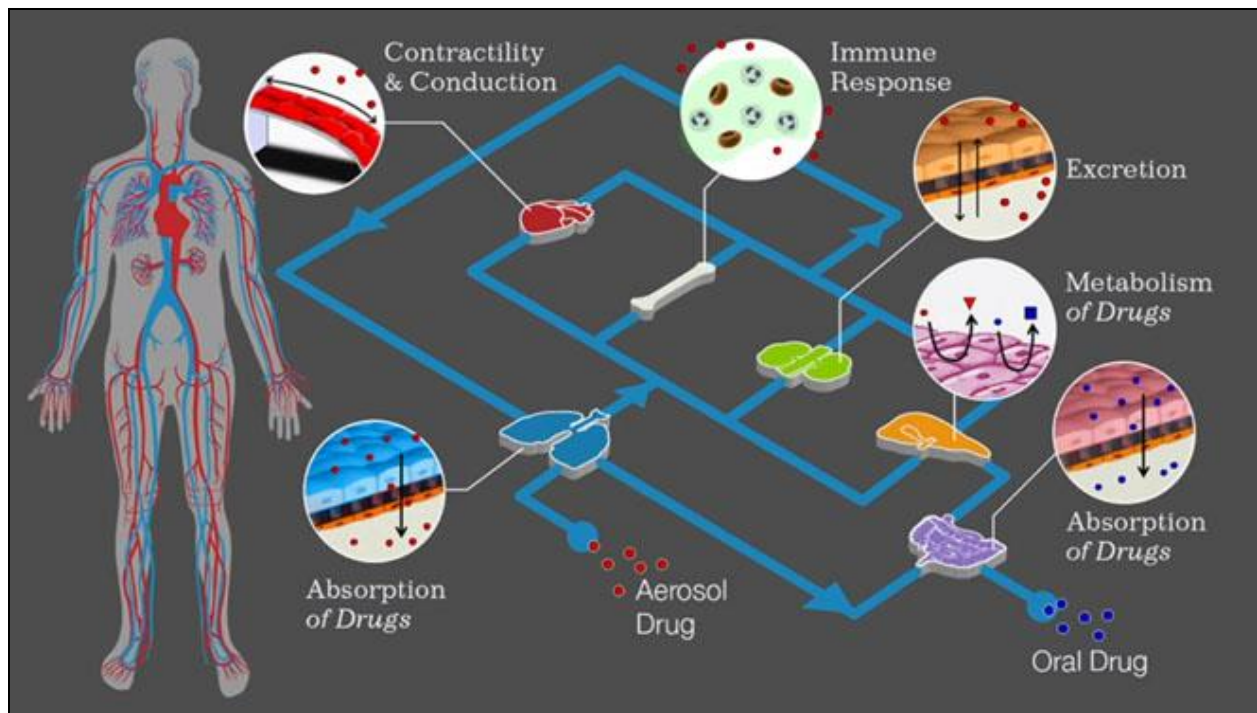


Figure 1: Concept of 'organ- on-chip' devices [Source: Findings from Wyss Institute, DARPA and IBM joint ventures 2015].

What are “Organ-on-a-chip” devices?

Research and development sectors and multidisciplinary team of collaborators have successfully engineered microfluidic culture devices that can easily mimic the physiology of an organ as well as the cellular micro architecture. Computer microchip manufacturing methods coupled with mechanobiology have been employed to produce these micro devices representing miniature human organs such as kidney, intestine, lung, bone marrow, skin etc. [2]. The basic design of an organ chip comprises a computer memory stick sized clear flexible polymer that contains hollow microfluidic channels. These channels are lined by human organ-specific living cells that are interfaced with human endothelial cell-lined artificial vasculature. In order to mimic the physical microenvironment of living organs such as peristaltic movement in the intestine and breathing motions in lung, artificial mechanical forces are applied. In addition to create artificial blood flow and mimic the

dynamic nutrient distribution externally, controlled microfluidics is applied.

These micro devices represent the three-dimensional cross-sections of major functional units of complete living organs. The most common material used for the microfluidic device fabrication is Polydimethylsiloxane (PDMS) but its applicability is restricted due to its property of absorption of hydrophobic drugs. To overcome this limitation tissue culture grade plastics such as styrene-ethylene/butylene-styrene copolymers, polystyrene and Polymethyl methacrylate (PMMA) have been used as suitable alternatives. These chips are further integrated with noninvasive biosensors that can potentially monitor cell behavior, receive stimuli and can perceive elicited drug response. By interconnecting different organ chips into one micro device, it is possible to simulate and recapitulate the complex multi-organ system functionality that exists within a human body. This advanced technology shall enable the screening and profiling of

drug metabolism and pharmacokinetics
(Figure 2) [3].

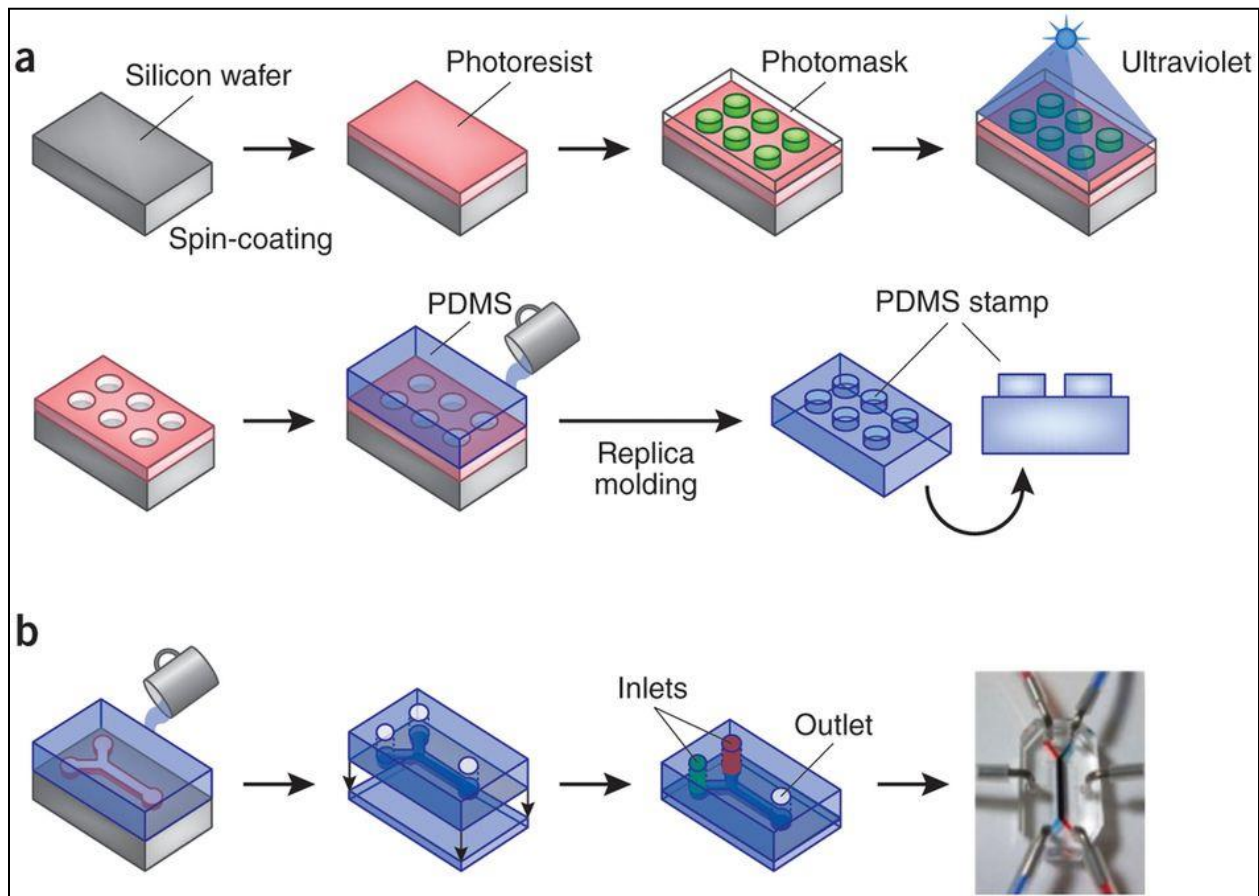


Figure 2: Basic design of an organ chip [Source: Nature biotechnology. 2014 Aug;32(8):760].

What are the applications of “Organ on chip” devices?

Equipped with the ability to integrate the different tissue types that make up human organs, these micro devices offer an ideal system for studying cellular and molecular mechanisms of disease, modeling species-specific disease states and even serve to

identify novel therapeutic targets. Scientists have successfully created therapeutically pertinent interfaces such as the blood brain barrier and the alveolar-capillary interface with the help of these organ chips [1]. These devices are routinely employed to model diseases such as cystic fibrosis, neuropsychiatric disorders, study

microvascular obstructions and compare various organ functions such as those of lung and kidneys. Another potent application is to study the effect of microbial influence on health and disease by culturing living microbiomes in direct contact with living human intestinal cells over an extended period to study intestinal infections or culturing influenza virus particles with lung epithelial cells to model lung infections. Organ chips have also been used to investigate environmental factors such as cigarette smoke's detrimental effect on tissue health and patient physiology. For this purpose human smoking behavior is mimicked by a smoking machine, which directly pumps cigarette smoke into the airspace of a human 'Lung Airway Chip' and the impact on human lung airway functions can be effectively modeled *in-vitro*. One of the pioneers in this field of organ on chip technologies has been the Wyss Institute of Harvard University where a team of researchers have successfully developed an integrated device which couples the functioning of various organs within a single chip and mimics the complexity of a multi organ system vasculature by circulating a fluid

between their common vascular channels. This unique device has combined the physiological and biochemical functioning of ten different organs into one and is an efficient mimic of the whole-body physiology. Equipped with controlled artificial fluid flow and cell viability the device allows for a real-time monitoring of the cultured cells and organ tissues. This holistic approach has led to the formulation of "human Body-on-Chips" devices that can be used as predictive models of pharmacokinetic and pharmacodynamics (PK/PD) responses of drugs *in vitro* [4].

The research endeavors are successfully being commercialized by means of startup companies that have been licensed to develop and market this "Organ-on-a-chip" technology. This technology is being incorporated into routine laboratory research by academic institutions, pharmaceutical companies, cosmetic industry as well as hospitals for the sake of personalized medicine. The technology holds promise to improve the current face of preclinical drug testing by providing an accurate tool for testing the drug efficacy as well as toxicity (Figure 3).

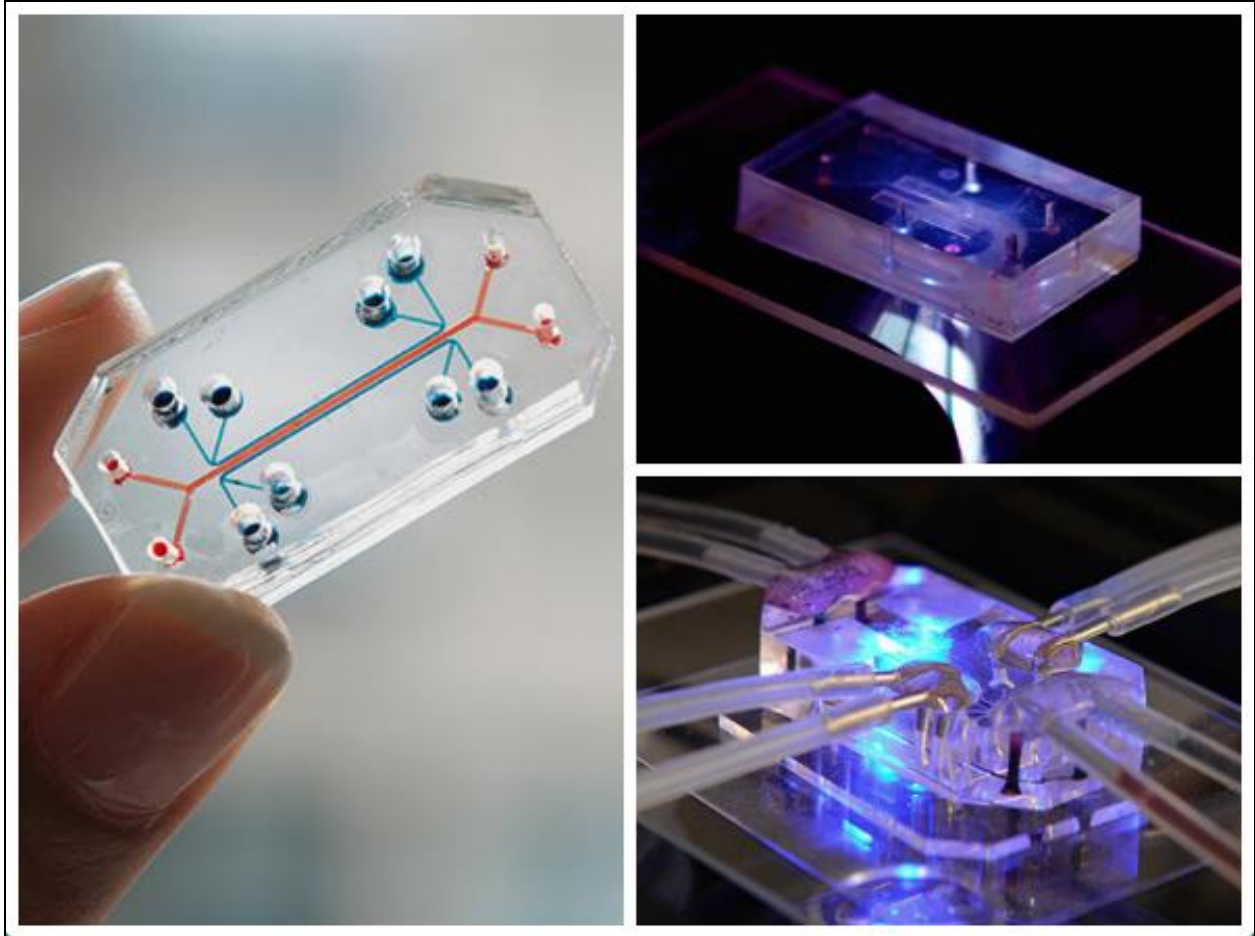


Figure 3: A sample of commercially available organ chip devices [Source: National Center for Advancing Translational Sciences].

Current and future prospects of the technology

Organ on chip technology has amalgamated wet laboratory biological research with novel computational dry laboratory approaches to facilitate fast paced and cost effective preclinical drug testing. The approach is currently being employed to identify novel clinical biomarkers, therapeutics, development of vaccines and drug delivery portals.

Human stem cells are being incorporated within these chips to further differentiate and develop into specialized cell types and thus pave way for patient specific disease modeling and personalized medicine. A recent development of a 3D-printed 'Heart Chip' with soft strain sensors integrated within shows that the technology is gradually progressing towards increased complexity and shall

eventually resolve the clinical trial failure

dilemma at large and forever.

Author's Biography

Dr Shripriya Singh

Dr. Singh holds a doctorate degree in life sciences from the Indian Institute of Toxicology Research, a premier research center managed by the Council of Scientific and Industrial Research in India. She has research experience of more than five years in the field of Developmental Neurobiology and Neurotoxicology. She is a prolific researcher and writer. She has published a number of peer reviewed research papers in world's best scientific journals. Dr. Singh has given several talks at national and international

meetings in stem cell biology, neuroscience and biotechnology and received first prize for the best oral presentation award at the IBRO/APRC Associate School of Neuroscience: 'Dawn of the aging world-nipping neurodegeneration in the bud', held at Selangor, Malaysia from August 8th-14th, 2016. She is an invited reviewer of a number of international research journals and member of many prestigious scientific societies across the globe. Dr. Singh can be reached at shripriyasingh@gmail.com

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Topic: Medical Biotechnology

Biotechnology Enabled Nerve Regeneration: Hope for the Elusive Cure for Neurodegenerative Disease



Megha Agrawal, PhD - Executive Editor

Neurodegenerative disease and spinal cord injury are serious medical conditions that result in irreversible nerve damage and subsequent damage to the central nervous system. Our nervous system is made of neurons. The principal role of nerves is to carry messages from one part of the body to another in the form of tiny electrical signals (Figure 1). These messages carried by nerves are referred as nerve impulses. The consequences of nerve damage from neurodegeneration are huge that can trigger catastrophic health events leading to severe functional deficits, paralysis and eventual cell deaths.

Advances in medical biotechnology have made it possible for the researchers to synthesize rare enzymes that promote regeneration and growth of injured nerve cells. To this end, researchers are pursuing Neurotrophins (NTs) as a possible avenue for nerve regeneration. NTs are proteins that involve a sequence of small molecular chains that possesses potent neurotrophic properties, which promote the development of neurons. NTs correspond to a family of neurotrophic growth factors and found to be the key for the development and functional maintenance of the central nervous system (CNS). They participate in neurogenesis, neuronal survival, axonal growth, synaptogenesis and activity-dependent forms of synaptic plasticity [1].



Figure 1: Messages are carried by the nerve cells from one part of the body to another [Source: www.planet-science.com/].

NT Treatments Enhance Neuronal Survival and Repair after Spinal Cord Injury (SCI) and Traumatic Brain Injury (TBI)

As we discussed above, NTs play important roles in many aspects of nerve regeneration after traumatic CNS injury that leads to spinal cord injury (SCI) and traumatic brain injury (TBI). NT treatments have been reported to enhance neuronal survival, axonal regrowth, remyelination and synaptic plasticity (Figure 2) [1].

Trauma to the spinal cord causes devastating health damages. These include severing axons and disrupting microvasculature that eventually kills

neurons and glia, and induces the formation of a dense glial-fibroblastic scar, which results in a permanent impairment or loss of sensory and motor functions. Researchers studied severed neurons that showed ongoing and progressive apoptosis. They found that surviving neurons make only a limited spontaneous attempt to regrow. However, the regenerating axons fail to enter or traverse the lesion area (Figure 2). The applications of NTs have shown that some functional recovery can be achieved by systematic treatments of NTs. In the injured spinal cord, neurotrophin delivery takes place by various methods, which supports the growth of discrete neuronal populations. For example, it has been observed that nerve growth factor (NGF) supports the sprouting and regeneration of cholinergic local motor axons, primary nociceptive axons, and cerulospinal axons [1].

Traumatic brain injury (TBI) is a complex medical condition that is summarized into four categories including primary injury, secondary injury, inflammatory response and repair-regeneration. The hallmark features of TBI are ongoing and progressive cell death and diffuse axonal injury. NT treatments have received broad attention in the therapy of TBI. NT-based treatment methods include restorative and regenerative strategies that have focused on enhancing the survival of injured neurons and replacing dysfunctional and dead cells. The research data demonstrates that combined neuronal

replacement and neurotrophin therapy may selectively improve cognitive function following TBI [1].

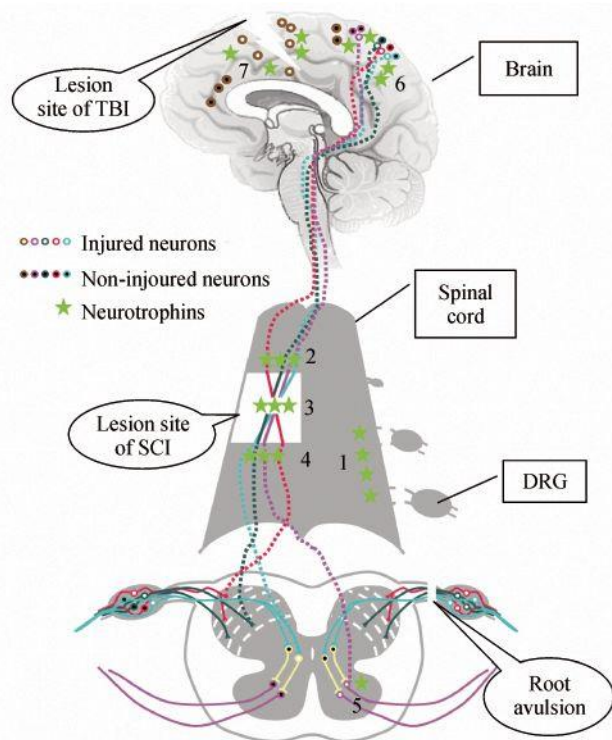


Figure 2: Schematic illustrations of the treatments with Neurotrophin on nerve regeneration after neurotrauma. Traumatic injury in CNS, such as root avulsion, spinal cord injury (SCI), and traumatic brain injury (TBI), results in

death of injured neurons and failure of severed axonal regeneration. Neurotrophin treatments are shown to induce sensory axons to regenerate through the dorsal root entry zone (DREZ) after (1) root avulsion (2) severed axons to re-grow (3) across the lesion site (4) into distal host tissues that enhance neuronal survival after SCI and TBI [Source: Front Biol (Beijing). 2013 Oct 1; 8(5): 486–495].

Concluding Remarks

Medical biotechnology advances in synthesizing clinically important enzymes and proteins such as Neurotrophins have shown promise in a critical area in neuromedicine – nerve regeneration. To be able to restore the nerves and the functions of central nervous system and fatal injuries to spinal cord and brain is a huge step forward to discover new medical pathways to battle neurodegeneration. The future of medical biotechnology enabled drug industry looks bright.

Author’s Biography

Dr. Megha Agrawal

Dr. Megha Agrawal is executive publisher of Biotechnology Kiosk. She has held senior academic positions at top-tier US institutions including

University of Florida at Gainesville, Children’s National Medical Center in Washington DC and the University of Illinois at Chicago, where she was a research faculty and principal investigator. Currently, she directs R&D programs in biotechnology at USA Prime Biotech. She received her Ph.D. in Biotechnology from the Indian

Institute of Technology at Roorkee, which is one of the premier institutions in India with an outstanding reputation across the globe. She won a highly competitive research award given by the Council of Scientific and Industrial Research in India to carry out her PhD work. Dr. Agrawal's research on resveratrol has provided novel pathways to develop new therapeutics to combat neurodegenerative disorders. Dr. Agrawal has made significant contributions to develop a rapid, cost effective and more sensitive mechanism based in-vitro model of ischemic stroke as first tier of screening of neuroprotective drugs for their anti-stroke potential. Her research has impacted significantly to initiate new areas in neurodegeneration, neuroprotection and novel approaches to treat cerebral stroke related injuries and prevention.

Dr. Agrawal has published in internationally prestigious scientific journals in the field of biotechnology,

neuroscience, stroke and molecular biology and biochemistry. She has been invited to give several talks at national and international meetings. Dr. Agrawal also serves as an Associate Editor for the international journal 'Frontiers in Molecular Bioscience (Molecular Diagnostics and Therapeutics)', a Nature-Frontier publication. In addition, she is on the editorial board of Drug and Metabolism Reviews and a contributing editor in Vacuum Advances in Biotechnology for Vacuum Technology and Coating Magazine and writes a monthly column in biotechnology. Dr. Agrawal can be reached at meghaagra@gmail.com

Reference for further reading:

1. Kelamangalath L & Smith G M (2013) Neurotrophin treatment to promote regeneration after traumatic CNS injury. *Front Biol (Beijing)* 8(5): 486-495.

Topic: Enzyme Biotechnology

Mutant Enzyme Breaks Down Plastic: A Potential Solution to Global Plastic Pollution Crisis

Shyamasri Biswas, PhD - Executive Editor



Plastics have become an integral part in our society and in our daily lives. Their everyday use is driven by their incredible versatility combined with their low production costs. While plastics have found indispensable place in our daily lives, their incredibly high resistance to biodegradation is a serious problem that results in ultra-long life times of these materials. In addition, recyclability of plastics is another major challenge. This implies that they can likely last centuries in the environment causing catastrophic global pollution threats.

The heavy dependence on plastics in our modern society can result in the continuation of massive build-up of plastics unless solutions are found to

this global pollution threat, especially in marine ecosystems. According to an estimate, about 1 million plastic bottles mostly made of Poly(ethylene terephthalate) (PET) are sold each minute around the globe and, with just 14% recycled, many end up in the oceans, where they are believed to pollute even the remotest parts, thereby harming marine life and potentially also people who eat seafood. PET is one of the most abundantly produced synthetic polymers. However, the high resistance of PET to biodegradation results in its accumulation in the environment at a staggering rate as discarded bottle packaging and also textiles and pose environmental concerns [1].

Secreted Mutant Enzyme PETase (PET-Digesting Enzyme)

Enzyme Technology is one the most promising disciplines in modern biotechnology and offers hope to mitigate global plastic pollution crisis and associated environmental concerns. Enzymes have a wide range of applications because they are non-toxic, biodegradable and can be produced in

large amounts by microorganisms. Recently, biotechnologists discovered a bacterium, *Ideonella sakaiensis* 201-F6 that was shown to exhibit the rare ability to grow on PET as a major carbon and energy source [2]. This plastic eating bacteria *Idonella sakaiensis* is unique and different from other plastic attacking micro-organisms as it can be grown easily and can adhere to PET effectively to facilitate degradation. Researchers have found that this bacteria when left in a jar with warm water and some nutrients can grow fast and easy. The PET biodegradation was shown to be triggered by a secreted mutant enzyme PETase (PET-digesting enzyme)

(Figure 1) [1]. As illustrated in Figure 1, researchers demonstrated that an *I. sakaiensis* enzyme dubbed PETase (PET-digesting enzyme) converts PET to mono(2-hydroxyethyl) terephthalic acid (MHET), with trace amounts of terephthalic acid (TPA) and bis(2-hydroxyethyl)-TPA as secondary products. Subsequently, a second enzyme, MHETase (MHET-digesting enzyme), further converts MHET into the two monomers, TPA and ethylene glycol (EG). Both enzymes are believed to be secreted by *I. sakaiensis* and likely act synergistically to depolymerize PET [1, 2].

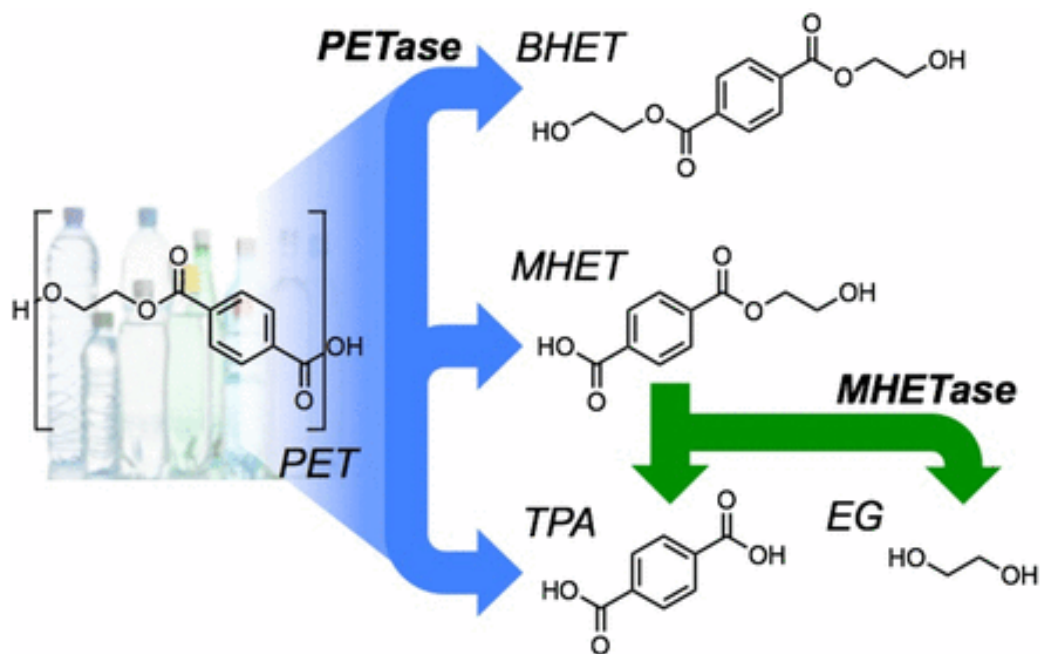


Figure 1: Schematic illustration of mechanism of how PETase catalyzes the depolymerization of PET to bis(2-hydroxyethyl)-TPA (BHET), MHET, and TPA. MHETase is shown to convert MHET to TPA and EG [Source: PNAS 115, 2018].

Researchers characterized the 3D structure of this newly discovered enzyme that can digest highly crystalline PET, which is the primary material that is used in the manufacture of single-use plastic beverage bottles, in textiles for clothing, and also in carpets. They engineered this enzyme for improved PET degradation capacity and further demonstrated its capability to further degrade an important PET replacement, polyethylene-2,5-furandicarboxylate.

The structure as revealed by crystallography of the enzyme was observed to be very similar to one evolved by many bacteria to break down cutin, a natural polymer that is used as a protective coating by plants. However, when the researchers manipulated the enzyme to explore this connection, they observed that its ability to eat PET was significantly improved. This provides new opportunities for bio based plastics recycling [1]. The structure/function relationships investigated by the researchers could be used to guide further protein engineering to more effectively depolymerize PET and other synthetic polymers. This innovative biotechnological strategy can help mitigate the environmental pollution of plastic accumulation in nature [1].

Concluding Remarks

The advances in enzyme biotechnology have enabled to open new R&D avenues to find biodegradable mechanisms of synthetic plastics. To

this end, the discovery of a bacterium that uses PET as a major carbon and energy source offers hope to provide enzymatic mechanism functions that enable effective breaking of highly resistant polymeric substrate that appears to survive for centuries in the environment. Future research needs to be directed towards additional protein engineering to increase PETase performance and extend the knowledge of structure-property correlation for biodegradation to other synthetic polymers that are used in commercial packaging.

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Dr Shyamasri (Shya) Biswas is executive publisher of Biotechnology Kiosk. She received her PhD in biotechnology from Banaras Hindu University, Varanasi, India. During her PhD, she received the prestigious

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Dr. Biswas is a contributing editor in Vacuum Advances in Biotechnology for Vacuum Technology & Coating Magazine and writes a monthly column in biotechnology. In addition, she is a reviewer for many biochemistry and biotechnology journals. She gave several invited talks at national and international meetings in Biotechnology. Dr Biswas is the owner of USA prime Biotech LLC, a startup company registered in the state of Florida. She can be reached at shyabiswas@gmail.com

Topic: Reliability of Biomedical Devices and Technologies

Medical Electron Device Reliability is Critical, and Therefore Ability to Quantify it is Paramount

Dr. Ephraim Suhir- Contributing Editor



Introduction

Some questions asked in connection with the today's state-of-the-art and practices in the area of reliability evaluations and assurances of microelectronics and photonics materials and devices, including medical devices, are formulated, and some references to the related published work are indicated. The emphasis is on the author's publications during his long career in the field of electronics materials and devices reliability. The substance of the recently suggested probabilistic design for reliability (PDfR) concept, the attributes of the failure-oriented-accelerated-testing (FOAT) and Boltzmann-Arrhenius-Zhurkov (BAZ) constitutive equation (model) are briefly discussed and numerical examples are provided. It is concluded that the application of the PDfR concept and its experimental basis FOAT, geared to the flexible and physically meaningful BAZ model, put the art of creating reliable electronic products on a "reliable" applied science foundation and, owing to that, enables making a viable electron device, and particularly, medical device, into a reliable product.

Today's practices and some questions asked

- Electron devices that underwent highly accelerated life testing (HALT) [1, 2], passed the existing qualification tests (QT) and survived burn-in testing (BIT) [3, 4] often exhibit nonetheless premature field failures. Are these methodologies and practices, and particularly the HALT procedures, adequate [5]?
- Do electronic industries need new approaches to qualify their products, and if they do, what should be done differently [6]?
- Could the existing practices be improved to an extent that if the product passed the reliability tests, there is a way to assure that it will satisfactorily perform in the field [7]?
- In many applications, such as, e.g., aerospace, military, long-haul communications, and, certainly medical, high reliability of electronics materials and products is particularly critical. Failures are a catastrophe and are not acceptable. Could the operational (field) reliability of an electronic product be assured, if it is

not predicted, i.e., not quantified in advance, at the design and product development stage [8-10]? It is well known that when NASA receives such products from big companies, NASA has to re-qualify these products and established their “remaining useful lives (RUL)” to make sure that these products are good enough to be installed in a, say, space shuttle. But it is too late in such a situation to change the materials, or the designs, i.e., too late to create a “genetically healthy” product. Such a practice triggered therefore the s.c. prognostics-and-health monitoring (PHM) practice. Such a practice might be good in addition to an effort of creating a “genetically healthy” product, but not instead of it. Agree?

- And if such a quantification is found to be necessary, could that be done on the deterministic, i.e., on a non-probabilistic basis, or, since nothing is perfect, and because the difference between a highly reliable product and an insufficiently reliable one is “merely” in the difference between their never-zero probabilities of failure, the probabilistic approach should be applied [11-19]?
- Should electronic product manufacturers keep shooting for an unpredictable and, perhaps, unachievable and unnecessary very long, such as, e.g., twenty years or so, product lifetime or, considering that every five years a new generation of devices appear on the market, the industries and particularly medical device manufacturers should settle for a shorter, but well substantiated, predictable and assured lifetime, with a high probability of non-failure?
- And what should be the role of predictive modeling, both computer-aided simulations, like, say, finite-element-analysis (FEA) and the “old-fashioned” analytical modeling [20-24]?

- What role could play the recently suggested Failure-Oriented-Accelerated-Testing (FOAT) and Boltzmann-Arrhenius-Zhurkov (BAZ) analytical model in predicting, on the probabilistic basis, the device’s probability of failure and its useful lifetime [25-28]?
- It is clear that higher specified probabilities of non-failure result in shorter expected lifetimes. Then how such lifetimes should be related to the acceptable (specified) probability of non-failure for particular products and applications?
- Considering that the principle of superposition does not work in reliability engineering, how to establish the adequate physically meaningful stressors, their combinations and levels for the appropriate accelerated tests?
- The best engineering product is the best compromise between the requirements for its reliability, cost effectiveness and time-to-market; it goes without saying that, in order to make the desired optimization possible, the reliability of such product should also be quantified, but how to do that[29]?
- Bathtub curve, the experimental “reliability passport” of a mass-produced device reflects the inputs of two critical irreversible processes – the statistics-of-failure process that results in a reduced failure rate with time (this is particularly evident from the infant mortality portion of the curve) and physics-of-failure (aging, degradation) process that leads to an increased failure rate with time (this trend is explicitly exhibited by the wear out portion of the bathtub diagram). Could these two critical processes be separated? The need for that is due to the obvious incentive to minimize the role and the rate of aging, and this incentive is especially significant for products like lasers, solder joint interconnections and

others, which are characterized by long wear out portions and when it is economically infeasible to restrict the product's lifetime to the steady-state situation, when the two irreversible processes in question compensate each other [30].

- A related question has to do with the fact that real time degradation is a very slow process. Could physically meaningful and cost-effective methodologies for measuring and predicting the degradation (aging) rates and consequences be developed [30]?
- Yet another related question has to do with the BIT of electron devices. It is unclear even whether such testing is always necessary, and if it is decided upon that it is, how long should it last and at what level, so that the infant mortality portion of the bathtub curve is eliminated [31-33]?

In the references to the published work below many questions asked above the outline that follow (including references) some of these questions are answered on the basis of the recently suggested PDfR concept. The next sections summarize some main features of this concept, address the attributes of the FOAT vs traditional HALT, and show some simple examples of the application of the PDfR concept, including BAZ model.

PDfR and its “ten commandments”

The PDfR concept is an effective means for improving the state-of-the-art in the electronics and photonics reliability field by quantifying, on the probabilistic basis, the operational reliability of a material or a product by predicting the probability of its likely failure under the given loading conditions and after the given service time, and to use this probability as a suitable and

physically meaningful criterion of the expected product's performance. The following ten major (governing) principles (“commandments”) reflect the rationale behind the PDfR concept:

- 1) When reliability of a product is imperative, ability to predict it is a must; reliability cannot be assured, if it is not quantified;
- 2) Nothing is perfect; the difference between a highly reliable and an insufficiently reliable product is “merely” in the level of their never-zero probability of failure, and therefore such a quantification should be done on the probabilistic basis;
- 3) Reliability evaluations cannot be delayed until the product is made and should start at the design stage; it should be taken care of, however, at all the significant stages of the product's life: at the design stage, when reliability is conceived; at the accelerated testing stage, using electrical, optical, environmental and mechanical instrumentation; at the production/manufacturing stage, when reliability is implemented; and, if necessary and appropriate, reliability should be maintained in the field during the product's operation; then there will be a reason to believe that a “genetically healthy” product is created and its “health” could be maintained by using various popular today prognostics-and-health monitoring/”management” (PHM) methods, as well as redundancy, troubleshooting and other more or less important means that could be considered to maintain adequate reliability level, especially if the “genetic health” of the product is not as high as it could and should be;
- 4) Product's reliability cannot be low, of course, but need not be higher than necessary either: it has to be adequate

for the given product and application, considering its lifetime, environmental conditions and consequences of failure;

- 5) The best product is the best compromise between the requirements for its reliability, cost effectiveness and time-to-market; it goes without saying that such a compromise cannot be achieved if reliability is not quantified;
- 6) One cannot design a product with quantified, optimized and assured reliability by limiting the effort to the widely used today “black box” - highly accelerated life testing (HALT); understanding the underlying physics of failure is crucial, and therefore highly cost-effective and highly focused failure-oriented-accelerated-testing (FOAT) should be considered and conducted as a possible and natural extension of HALT;
- 7) FOAT, unlike HALT, is a “white/transparent box” aimed at understanding the physics of failure and should be geared to a limited number of pre-determined simple, easy-to-use and physically meaningful predictive reliability models and is viewed as the experimental basis and important constituent part of the probabilistic design for reliability (PDfR) effort;
- 8) Physically meaningful, easy-to-use and flexible multi-parametric Boltzmann-Arrhenius-Zhurkov (BAZ) model can be used as a suitable one for the assessment of the remaining “useful” life (RUL) of an electronic product,
- 9) Predictive modeling, not limited to FOAT models, is a powerful means to carry out, if necessary, sensitivity analyses (SA) with an objective to quantify and practically nearly eliminate failures by making the probability of failure sufficiently low; this principle could be referred to as the “principle of practical confidence”.

- 10) Consideration of the role of the human factor is highly desirable in the PDfR effort: not only “nothing”, but also “nobody” is perfect, and the human role in assessing the likelihood of the adequate performance of a product,

FOAT (“transparent box”) vs HALT (“black box”)

A highly focused and highly cost effective FOAT is the experimental foundation and the “heart” of the PDfR concept. FOAT should be conducted in addition to and, in some cases, even instead of HALT, especially for new products, whose operational reliability is unclear and for which no experience is accumulated and no best practices nor HALT methodologies are not yet developed. Predictions, based on the FOAT and subsequent probabilistic predictive modeling, might not be perfect, at least at the beginning, but it is still better to pursue this effort rather than to turn a blind eye on the fact that there is always a non-zero probability of the product’s failure. Understanding the underlying reliability physics for the product performance is critical. If one sets out to understand the physics of failure in an attempt to create a failure-free product (in accordance with the “principle of practical confidence”) conducting a FOAT type of an experiment is imperative. FOAT’s objective is to confirm the usage of a particular more or less well established predictive model, to confirm (say, after HALT is conducted) the physics of failure, and establish the numerical characteristics (activation energy, time constant, sensitivity factors, etc.) of the particular FOAT modal of interest.

FOAT could be viewed as an extension of HALT. While HALT is a “black box”, i.e., a methodology which can be perceived in terms of its inputs and outputs without a

clear knowledge of the underlying physics and the likelihood of failure., FOAT, on the other hand, is a “transparent box”, whose main objective is to confirm the use of a particular reliability model that reflects a specific anticipated failure mode. The major assumption is, of course, that this model should be valid in both AT and in actual operation conditions. HALT does not measure (does not quantify) reliability. FOAT does. HALT can be used for “rough tuning” of product’s reliability, and FOAT could and should be employed when “fine tuning” is needed, i.e., when there is a need to quantify, assure and even specify the operational reliability of a product. HALT tries to “kill many unknown birds with one (also not very well known) stone”. HALT has demonstrated, however, over the years its ability to improve robustness through a “test-fail-fix” process, in which the applied stresses (stimuli) are somewhat above the specified operating limits. This “somewhat above” is based, however, on an intuition, rather than on a calculation. There is a general perception that HALT might be able to quickly precipitate and identify failures of different origins. FOAT and HALT could be carried out separately, or might be partially combined in a particular AT effort. Since the principle of superposition does not work in reliability engineering, both HALT and FOAT use, when appropriate, combined stressing under various stimuli (stressors).

New products present natural reliability concerns, as well as significant challenges at all the stages of their design, manufacture and use. An appropriate combination of HALT and FOAT efforts could be especially useful for ruggedizing and quantifying reliability of such products. It is always necessary to correctly identify the expected failure modes and mechanisms, and to establish the appropriate stress limits of HALTs and FOATs with an objective to

prevent “shifts” in the dominant failure mechanisms. There are many ways of how this could be done (see, e.g., [8]). The FOAT based approach could be viewed as a quantified and reliability physics oriented HALT. The FOAT approach should be geared to a particular technology and application, with consideration of the most likely stressors.

Some simple PDfR examples

Adequate heat sink

Consider a device whose steady-state operation is determined by the Arrhenius equation (1). The probability of non-failure can be found using the exponential law of

reliability as
$$P = \exp\left[-\frac{t}{\tau_0} \exp\left(-\frac{U}{kT}\right)\right].$$

Solving this equation for the absolute temperature T , we have:
$$T = -\frac{U/k}{\ln\left(-\frac{\tau_0}{t} \ln P\right)}.$$

Addressing, e.g., surface charge accumulation failure, for which the ratio of the activation energy to the Boltzmann’s constant is $\frac{U}{k} = 11600^{\circ}K$, assuming that the

FOAT- predicted time factor τ_0 is $\tau_0 = 2 \times 10^{-5}$ hours, that the customer requires that the probability of failure at the end of the device’s service time of $t = 40,000$ hours is only $Q = 10^{-5}$, the above formula yields: $T = 352.3^{\circ}K = 79.3^{\circ}C$. Thus, the heat sink should be designed accordingly, and the vendor should be able to deliver such a heat sink. The situation changes to the worse, if the temperature of the device changes, especially in a random fashion, but this situation can also be predicted by a simple probabilistic analysis, which is, however, beyond the scope of this article.

Reliable seal glass

The maximum interfacial shearing stress in the thin solder glass layer can be computed by the formula: $\tau_{\max} = kh_g \sigma_{\max}$.

Here $k = \sqrt{\frac{\lambda}{\kappa}}$ is the parameter of the

interfacial shearing stress, $\lambda = \frac{1-\nu_c}{E_c h_c} + \frac{1-\nu_g}{E_g h_g}$

is the axial compliance of the assembly,

$\kappa = \frac{h_c}{3G_c} + \frac{h_g}{3G_g}$ is its interfacial compliance,

$G_c = \frac{E_c}{2(1+\nu_c)}$, $G_g = \frac{E_g}{2(1+\nu_g)}$ are the shear

moduli of the ceramics and glass materials,

$\sigma_{\max} = \frac{\Delta\alpha\Delta t}{\lambda h_g}$ is the maximum normal stress

in the midportion of the glass layer, Δt is the change in temperature from the soldering temperature to the low (room or testing) temperature, $\Delta\alpha = \bar{\alpha}_c - \bar{\alpha}_g$ is the difference in the effective coefficients of thermal expansion (CTEs) of the ceramics and the

glass, $\bar{\alpha}_{c,g} = \frac{1}{\Delta t} \int_t^{t_0} \alpha_{c,g}(t) dt$ are these

coefficients for the given temperature t , t_0 is the annealing (zero stress, setup) temperature, and $\alpha_{c,g}(t)$ are the time dependent CTEs for the materials in question. In an approximate analysis one could assume that the axial compliance λ of the assembly is due to the glass only, so that

$\lambda \approx \frac{1-\nu_g}{E_g h_g}$ and therefore the maximum

normal stress in the solder glass can be evaluated as $\sigma_{\max} = \frac{E_g}{1-\nu_g} \Delta\alpha\Delta t$. While the

geometric characteristics of the assembly, the change in temperature and the elastic

constants of the materials can be determined with high accuracy, this is not the case for the difference in the CTEs of the brittle materials of the glass and the ceramics. In addition, because of the obvious incentive to minimize this difference, such a mismatch is characterized by a small difference of close and appreciable numbers. This contributes to the uncertainty of the problem in question justifies the application of the probabilistic approach. Treating the CTEs of the two materials as normally distributed random variables, we evaluate the probability P that the thermal interfacial shearing stress is compressive (negative) and, in addition, does not exceed a certain allowable level [9]. This stress is proportional to the normal stress in the glass layer, which is, in its turn, proportional to the difference $\Psi = \alpha_c - \alpha_g$ of the CTE of the ceramics and the glass materials, one wants to make sure that the requirement

$0 \leq \Psi \leq \Psi_* = \frac{\sigma_a}{E_g} \frac{1-\nu_g}{\Delta t}$ takes place with a

very high probability.. For normally distributed random variables α_c and α_g the variable Ψ is also distributed in accordance with the normal law with the mean value and standard deviation as $\langle \Psi \rangle = \langle \alpha_c \rangle - \langle \alpha_g \rangle$

and $\sqrt{D_\Psi} = \sqrt{D_c + D_g}$, where $\langle \alpha_c \rangle$ and $\langle \alpha_g \rangle$ are the mean values of the materials' CTEs, and D_c and D_g are their variances.

The probability that the above condition takes place is

$P = \int_0^{\Psi_*} f_\Psi(\psi) d\psi = \Phi_1(\gamma^* - \gamma) - [1 - \Phi_1(\gamma)]$, where

$\Phi_1(t) = \text{erft} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-t^2/2} dt$ is the error

function, $\gamma = \frac{\langle \Psi \rangle}{\sqrt{D_\Psi}}$ is the SF for the CTE

difference and $\gamma^* = \frac{\psi^*}{\sqrt{D_\psi}}$ is the SF for the

acceptable level of the allowable stress. If, sealing (fabrication) temperature is $485^\circ C$, the lowest (testing) temperature is $-65^\circ C$ (so that $\Delta t = 550^\circ C$), the computed effective CTE's at this temperature are $\bar{\alpha}_g = 6.75 \times 10^{-6} 1/^\circ C$ and $\bar{\alpha}_c = 7.20 \times 10^{-6} 1/^\circ C$, the standard deviations of these STEs are $\sqrt{D_c} = \sqrt{D_g} = 0.25 \times 10^{-6} 1/^\circ C$ and the (experimentally obtained) ultimate compressive strength for the glass material is $\sigma_u = 5500 \text{ kg/cm}^2$. With the acceptable SF of, say, 4, we have $\sigma^* = \sigma_u / 4 = 1375 \text{ kg/cm}^2$. The allowable level of the parameter ψ is therefore

$$\psi_* = \frac{\sigma_a}{E_g} \frac{1 - \nu_g}{\Delta t} = \frac{1375}{0.66 \times 10^6} \frac{0.73}{550} = 2.765 \times 10^{-6} 1/^\circ C.$$

The mean value $\langle \psi \rangle$ and variance D_ψ of the parameter ψ are $\langle \psi \rangle = \langle \alpha_c \rangle - \langle \alpha_g \rangle = 0.450 \times 10^{-6} 1/^\circ C$ and $D_\psi = D_c + D_g = 0.25 \times 10^{-12} (1/^\circ C)^2$, respectively. Then the predicted SFs are $\gamma = 1.2726$ and $\gamma^* = 7.8201$, and the corresponding probability of non-failure of the seal glass material is $P = \Phi_1(\gamma^* - \gamma) - [1 - \Phi_1(\gamma)] = 0.898$. Note that if the standard deviations of the materials CTEs were only $\sqrt{D_c} = \sqrt{D_g} = 0.1 \times 10^{-6} 1/^\circ C$, then the SFs would be much higher: $\gamma = 3.1825$ and $\gamma^* = 19.5559$, and the probability of non-failure would be as high as $P = 0.999$.

Extreme response in temperature cycling

Let an electronic device be operated in temperature cycling conditions, and the random amplitude of the induced stress, when a single cycle is applied is distributed

e.g., the elastic constants of the solder glass are $E_g = 0.66 \times 10^6 \text{ kg/cm}^2$ and $\nu_g = 0.27$, the

in accordance with the Rayleigh law, so that the probability density function of this amplitude is $f(r) = \frac{r}{D_x} \exp\left(-\frac{r^2}{2D_x}\right)$. Our

objective is to assess the most likely extreme value of the stress amplitude for a large number n of cycles. The probability distribution density function and the probability distribution function for the extreme value Y_n of the stress amplitude can be found as $g(y_n) = n\{f(x)[F(x)]^{n-1}\}_{x=y_n}$ and $G(y_n) = \{[F(x)]^n\}_{x=y_n}$, respectively. Then the following expression for the probability density distribution function $g(y_n)$ can be

obtained: $g(y_n) = n\zeta_n^2 \exp\left(-\frac{\zeta_n^2}{2}\right) \left[1 - \exp\left(-\frac{\zeta_n^2}{2}\right)\right]^{n-1}$,

where $\zeta_n = \frac{y_n}{\sqrt{D_x}}$ is the sought

dimensionless amplitude. Its maximum value could be determined from the equation $g'(y_n) = 0$, which yields:

$$\zeta_n^2 \left[n \exp\left(-\frac{\zeta_n^2}{2}\right) - 1 \right] - \left[\exp\left(-\frac{\zeta_n^2}{2}\right) - 1 \right] = 0.$$

If the number n is large, the second term in this expression is small and can be omitted, so

that $n \exp\left(-\frac{\zeta_n^2}{2}\right) - 1 = 0$, and

$y_n = \zeta_n \sqrt{D_x} = \sqrt{2D_x \ln n}$. As evident from this result, the ratio of the extreme response y_n , after n cycles are applied, to the maximum response $\sqrt{D_x}$, when a single cycle is applied, is $\sqrt{2 \ln n}$. This ratio is 3.2552 for 200 cycles, 3.7169 for 1000 cycles, and 4.1273 for 5000 cycles.

Quantifying reliability using BAZ model

BAZ model $\tau = \tau_0 \exp\left(\frac{U_0 - \gamma\sigma}{kT}\right)$ can be used

when the material or the device experience combined action of elevated temperature T and external loading σ (not necessarily mechanical). Although in Zhurkov's tests the loading σ was a constant mechanical tensile stress, it has been recently suggested that any other stimulus of importance (voltage, current, thermal stress, humidity, radiation, etc.) can be used as such a stress. The effective activation energy

$$U = kT \ln \frac{\tau}{\tau_0} = U_0 - \gamma\sigma$$

plays in the BAZ model the role of the stress-free energy U_0 in the Arrhenius model ($\sigma = 0$). The BAZ model and the Arrhenius equation can be obtained as the steady-state solution to the Fokker-Planck equation in the theory of Markovian processes. This solution represents the worst case scenario, so that the reliability predictions based on the BAZ model are conservative and advisable in engineering practice [12]. Let the lifetime τ in the BAZ model is viewed as the MTTF. Such an assumption suggests that if the exponential law of probability $P = \exp(-\lambda t)$ of non-failure is used, the MTTF corresponds to the moment of time when the entropy of this law reaches its maximum value. Indeed, from the formula $H(P) = -P \ln P$ we obtain that the maximum value of the entropy $H(P)$ is equal to e^{-1} and takes place for $P = e^{-1} = 0.3679$. With this probability of non-failure, the BAZ model yields: $t = \tau_0 \exp\left(\frac{U}{kT}\right)$. Comparing this result with the original Arrhenius equation we conclude that the MTTF expressed by this equation corresponds to the moment of time when the entropy of the time-depending process $P = P(t)$ is the largest.

Multi-parametric BAZ model

Let us elaborate on the substance of the multi-parametric BAZ model [27] using as an example a situation when the product of interest is subjected to the combined action of the elevated relative humidity H and elevated voltage V . Let us assume that the failure rate of a product is determined by the level of the leakage current: $\lambda = \gamma_I I$. Then one can seek the probability of the product's non-failure as

$$P = \exp\left[-\gamma_I I t \exp\left(-\frac{U_0 - \gamma_H H - \gamma_V V}{kT}\right)\right].$$

Here the γ factors reflect the sensitivities of the device to the change in the corresponding stressors. Although only two stressors are selected – the relative humidity H and the elevated voltage V - the model can be easily made multi-parametric, i.e., generalized for as many stimuli as necessary. The sensitivity factors γ should be determined from the FOAT when the combined action of all the stimuli (stressors) of importance is considered. Because of that the structure of the multi-parametric BAZ should not be interpreted as a superposition of the effects of different stressors (as is known, superposition principle does not work in reliability engineering), but rather as a convenient and physically meaningful representation of the FOAT data. The physical meaning of the above distribution could be seen from the formulas

$$\frac{\partial P}{\partial I} = -\frac{H(P)}{I}, \quad \frac{\partial P}{\partial t} = -\frac{H(P)}{t}, \quad \frac{\partial P}{\partial U_0} = \frac{H(P)}{kT},$$

$$\frac{\partial P}{\partial H} = -\frac{H(P)}{kT} \gamma_H = -\gamma_H \frac{\partial P}{\partial U_0},$$

$$\frac{\partial P}{\partial V} = -\frac{H(P)}{kT} \gamma_V = -\gamma_V \frac{\partial P}{\partial U_0},$$

where $H(P) = -P \ln P$ is the entropy of the probability $P = P(t)$ of non-failure. The

following conclusions can be made based on these formulas:

1) The change in the probability of non-failure always increases with an increase in the entropy (uncertainty) of the distribution. This probability decreases with an increase in the leakage current and with time, which certainly makes physical sense.

2) The last two of the above formulas show the physical meaning of the sensitivity factors γ : they can be found as the ratios of the change in the probability of non-failure with respect to the corresponding stimuli to the change of this probability with the change in the stress-free activation energy.

The equation for the probability of non-failure contains four empirical parameters: the stress-free activation energy U_0 and three sensitivity factors γ : leakage current factor, relative humidity factor and elevated voltage factor. Here is how these factors could be obtained from the highly focused and highly cost effective FOAT data. *First* one should run the FOAT for two different temperatures T_1 and T_2 , keeping the levels, low or high, of the relative humidity H and elevated voltage V the same in both tests; recording the percentages (values) P_1 and P_2 of non-failed samples (or values $Q_1 = 1 - P_1$ and $Q_2 = 1 - P_2$ of the failed samples); assuming a certain criterion of failure (say, when the level of the measured leakage current exceeds a certain level I_*), we obtain:

$$P_{1,2} = \exp \left[-\gamma_I I_* t_{1,2} \exp \left(-\frac{U_0 - \gamma_H H - \gamma_V V}{kT_{1,2}} \right) \right].$$

Since the numerators in these relationships are kept the same, the following equation must be fulfilled for the sought sensitivity factor γ_I of the leakage current:

$$f(\gamma_I) = \ln \left(-\frac{\ln P_1}{I_* t_1 \gamma_I} \right) - \frac{T_2}{T_1} \ln \left(-\frac{\ln P_2}{I_* t_2 \gamma_I} \right) = 0. \text{ Here } t_1 \text{ and } t_2 \text{ are the times, at which the failures}$$

were detected. It is expected that more than just two series of FOAT tests and at more than two temperature levels are conducted, so that the sensitivity parameter γ_I could be predicted with a high enough degree of accuracy (certainty). *At the second step*, FOAT tests at two relative humidity levels H_1 and H_2 should be conducted for the same temperature and voltage. This leads to the relationship:

$$\gamma_H = \frac{kT}{H_1 - H_2} \left[\ln \left(-\frac{\ln P_1}{I_* t_1 \gamma_I} \right) - \ln \left(-\frac{\ln P_2}{I_* t_2 \gamma_I} \right) \right]. \text{ Similarly, at}$$

the *next step* of FOAT tests, by changing the voltages V_1 and V_2 , the following expression for the sensitivity factor γ_V can be obtained:

$$\gamma_V = \frac{kT}{V_1 - V_2} \left[\ln \left(-\frac{\ln P_1}{I_* t_1 \gamma_I} \right) - \ln \left(-\frac{\ln P_2}{I_* t_2 \gamma_I} \right) \right]. \text{ Finally, the}$$

stress-free activation energy can be computed as $U_0 = \gamma_H H + \gamma_V V - kT \ln \left(-\frac{\ln P}{I_* t \gamma_I} \right)$

for any consistent humidity, voltage, temperature and time. The above relationships could be obtained particularly also for the case of zero voltage, i.e., without a high-voltage bias. This will provide additional information of the materials and device reliability characteristics. Let, e.g., the following input information is available: 1) After $t_1 = 35h$ of testing at the temperature $T_1 = 60^\circ C = 333^\circ K$, the voltage $V=600V$ and the relative humidity $H=0.85$, 10% of the tested modules exceeded the allowable (critical) level of the leakage current of $I_* = 3.5\mu A$ and, hence, failed, so that the probability of non-failure is $P_1 = 0.9$; 2) After $t_2 = 70h$ of testing at the temperature $T_2 = 85^\circ C = 358^\circ K$ at the same voltage and the same relative humidity, 20% of the tested samples reached or exceeded the critical level of the leakage current and, hence, failed, so that the probability of non-failure is $P_2 = 0.8$. Then the equation (12)

results in the following transcendental equation for the leakage current sensitivity factor γ_I :

$$f(\gamma_I) = \ln\left(\frac{0.10536}{\gamma_I}\right) - 1.075075 \ln\left(-\frac{.022314}{\gamma_I}\right) = 0. \quad \text{This}$$

equation yields: $\gamma_I = 4926 h^{-1} (\mu A)^{-1}$. Thus, $\gamma_I I_* = 17241 h^{-1}$. This concludes the *first step of testing*. At the *second step*, tests at two relative humidity levels H_1 and H_2 , were conducted for the same temperature and voltage levels. This led to the relationship:

$$\gamma_H = \frac{kT}{H_1 - H_2} \left[\ln\left(-0.5800 \times 10^{-4} \frac{\ln P_1}{t_1}\right) - \ln\left(-0.5800 \times 10^{-4} \frac{\ln P_2}{t_2}\right) \right]$$

. Let, e.g., after $t_1 = 40h$ of testing at the relative humidity of $H_1 = 0.5$ at the given voltage (say, $V=600V$) and temperature (say, $T = 60^\circ C = 333^\circ K$), 5% of the tested modules failed, so that $P_1 = 0.95$, and after $t_2 = 55h$ of testing at the same temperature and at the relative humidity of $H_2 = 0.85$, 10% of the tested modules failed, so that $P_2 = 0.9$. Then the above equation for the γ_H value, with the Boltzmann constant $k = 8.61733 \times 10^{-5} eV/K$, yields:

$\gamma_H = 0.03292 eV$. At the *third step*, FOAT at two different voltage levels $V_1 = 600V$ and $V_2 = 1000V$ have been carried out for the same temperature-radiation bias, say, $T = 85^\circ C = 358^\circ K$ and $H = 0.85$, and it has been determined that 10% of the tested devices failed after $t_1 = 40h$ of testing ($P_1 = 0.9$) and 20% of devices failed after $t_2 = 80h$ of testing ($P_2 = 0.8$). The voltage sensitivity factor can be found then as follows:

$$\gamma_V = \frac{0.02870}{400} \left[\ln\left(-0.5800 \times 10^{-4} \frac{\ln P_2}{t_2}\right) - \ln\left(-0.5800 \times 10^{-4} \frac{\ln P_1}{t_1}\right) \right] = 4.1107 \times 10^{-6} eV/V$$

After the sensitivity factors of the leakage current, the humidity and the voltage are found, the stress free activation energy can

be determined for the given temperature and for any combination of loadings (stimuli). The third term in the equation for the stress-free activation energy plays the dominant role, so that, in approximate evaluations, only this term could be considered. Calculations indicate that the loading free activation energy in the above numerical example (even with the rather tentative, but still realistic, input data) is about $U_0 = 0.4770 eV$.

This result is consistent with the existing experimental data. Indeed, for semiconductor device failure mechanisms the activation energy ranges from 0.3 to 0.6eV, for metallization defects and electromigration in Al it is about 0.5eV, for charge loss it is on the order of 0.6 eV, for Si junction defects it is 0.8 eV.

Possible next generation QT

The next generation QT could be viewed as a “quasi-FOAT,” “mini-FOAT”, a sort-of an “initial stage of FOAT” that more or less adequately replicates the initial non-destructive, yet full-scale, stage of FOAT. The duration and conditions of such a “mini-FOAT” QT could and should be established based on the observed and recorded results of the actual FOAT, and should be limited to the stage when no failures, or a predetermined and acceptable small number of failures in the actual full-scale FOAT, were observed. PHM technologies (“canaries”) could be concurrently tested to make sure that the safe limit is established correctly and is not exceeded. Such an approach to qualify electronic devices into products will enable the industry to specify, and the manufacturers - to assure, a predicted and adequate PoF for an electronic product that passed the QT and is expected to be operated in the field under the given conditions for the given time. FOAT should be thoroughly designed, implemented, and

analyzed, so that the QT is based on the trustworthy FOAT data.

Conclusion

The application of FOAT, the PDfR concept and particularly the multi-parametric BAZ model enables one to improve dramatically the state of the art in the field of the electronic products reliability prediction and assurance. Since FOAT cannot do without simple, easy-to-use and physically meaningful predictive modeling, the role of such modeling, both computer-aided and analytical (mathematical), in making the suggested new approach to QT practical and successful. It is imperative that the reliability physics that underlies the mechanisms and modes of failure is well understood. Such an understanding can be achieved only provided that flexible, powerful and effective PDfR efforts are implemented.

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Ephraim has authored 400+ publications (patents, technical papers, book chapters, books), presented numerous keynote and invited talks worldwide, and received many professional awards,

Dr. Ephraim Suhir is on the faculty of the Portland State University, Portland, OR, USA, and Technical University, Vienna, Austria. He is also CEO of the Small Business Innovative Research (SBIR) ERS Co. in Los Altos, CA, USA. Ephraim is Foreign Full Member including 1996 Bell Laboratories Distinguished Member of Technical Staff (DMTS) Award (for developing effective methods for predicting the reliability of complex structures used in AT&T and Lucent Technologies products), and 2004 ASME Worcester Read Warner Medal for outstanding contributions to the permanent literature of engineering and laying the foundation of a new discipline “Structural Analysis of Electronic Systems”. Ephraim is the third “Russian American”, after S. Timoshenko and I. Sikorsky, who received this prestigious award. This year Ephraim received the 2019 IEEE Electronic Packaging Society (EPS) Field award for seminal contributions to mechanical reliability engineering and modeling of electronic and photonic packages and systems.



Editor's Selections: Biotechnology Advances around the World

Microbial and Synthetic Biotechnology

Researchers employing bacteria therapy in a dish: Engineering bacteria to intelligently sense and respond to disease states

A current promising R&D area in biotechnology is to engineer bacteria that can intelligently sense and respond to serious medical conditions including infections to cancer. To this end, advances in genetic engineering can be leveraged to program cells to perform various sophisticated tasks. Previous research on employing genetic engineering tools has shown that a network of genes can be wired together to form a genetic circuit. In such circuits, it is possible to engineer cells that can be used to sense the environment including modulating their behavior. It can also be stimulated to produce molecules in response.

Using this concept of cell programming, biomedical engineers recently demonstrated a unique biotechnological

system of 'bacteria-therapy-in-a-dish', in which they studied 10s to 100s of programmed bacteria within mini-tissues in a dish. The main advantage of this system is the fact that it yields a much faster throughput and the study time can be shortened from several months to days. This research was recently reported in PNAS by a Columbia University Engineering group in the United States (PNAS, 2019 DOI: [10.1073/pnas.1820824116](https://doi.org/10.1073/pnas.1820824116)) in which the researchers showed a developed system capable to study tens to hundreds of programmed bacteria within mini-tissues in a dish. They examined programmed antitumor bacteria using mini-tumors and showed the potential of the developed technology to accelerate future clinical applications of these new bacterial therapies for synthetic biotechnology in clinics around the world.

Biofuel Biotechnology

Developing papaya sugarcane: The production of second-generation ethanol and sucrose extraction

Researchers affiliated with Brazil's National Institute of Science and Technology of Bioethanol used the knowledge of ripening process of papaya to study sugarcane root cell separation for sucrose extraction and large scale production of bioethanol. During papaya ripening process, its cell walls separate that makes the tissue softer and more digestible. This is due to cell contents that become accessible and makes the extraction of sucrose in the fruit relatively easy. Leveraging this concept, researchers studied the genes involved in sugarcane root cell separation to develop transgenic varieties of sugarcane. Their study especially focused on utilizing stem, an important part of the plant, where a

large accumulation of biomass and sucrose occur.

The name "papaya sugarcane" originates from the cell walls that are as soft as in a papaya. To demonstrate their approach, the Brazilian scientists described the first gene sequences involved in sugarcane root cell separation. This research elucidated the functions in this process that showed the promise of the process in the paper that they published in the *Journal of Experimental Botany* (*Journal of Experimental Botany*, 2019; 70 (2): 497 DOI: 10.1093/jxb/ery362) and discussed the potential to produce second-generation bioethanol (obtained from biomass) on a large scale.

Agriculture Biotechnology

Increasing natural oil production in seeds by genetic modification

Our daily diet regularly involves plant seed oil, which is an essential component in our food. Currently, agriculture and plant biotechnologists are focusing on developing ways and strategies to maximize plant seed's yield while reducing environmental effects of crop cultivation. This strategy enables optimized land use that benefits the

agriculture industry. In a significant research, scientists at Nanyang Technological University in Singapore reported a sustainable way to demonstrate a new genetic modification that can increase the yield of natural oil in seeds by up to 15 per cent. In this research, scientists modified a key protein genetically in plants, which

regulates the amount of oil that plants produce.

While the results were obtained in laboratory conditions, the promising approach to increase natural oil production has the potential for industrial scale applications. The approach that shows appreciable increase in the production of seed oil in a sustainable and cost-effective way opens up new doors in global agriculture research. Researchers showed versatility of the new method for its application to crops such as canola, soybean and sunflower. Natural oil from canola, soybean and sunflower represents a multi-billion global industry that continues to see increasing demand in the consumer market.

Cancer Biotechnology

Employing blood, saliva and urine test for cancer detection: A potentially 'Holy Grail' and new route for cancer diagnostics

The approach involving testing for cancer in blood, urine or saliva is considered the "holy grail" for diagnosing cancer in its early stages. Cancer is the second leading cause of death in the world. The latest focus of biotechnology researchers involves whether a cancer test can evolve only by collecting and analyzing a sample of blood, saliva or urine that would enable to detect cancer in its early stage of progression.

In a research that employed saliva test, biomedical researchers in China analyzed saliva samples from lung cancer patients to detect cancer based

The economic aspect of R&D advances in increasing natural oil yield in a sustainable manner is obvious as it is expected to result in higher economic gain. For example, researches done in the past indicated a net gain of US\$ 1.26 billion in the United States market with a small 1.5 per cent increase in oil yield (by dry weight) in soybean seeds. Increase in natural oil yield in seeds can also impact the growing biofuel industry that can benefit from clean fuel produced from organic sources, such as vegetable oils.

This research was published in the scientific journal *Plant Signaling & Behavior* (*Plant Signaling & Behavior*, 2018; 1 DOI: 10.1080/15592324.2018.1482176)

on Surface-enhanced Raman spectroscopy (SERS) technique. SERS is a powerful surface-sensitive molecular detection technique that enhances Raman scattering by molecules adsorbed on surface structures. SERS offers high detection sensibility and fast analysis. It is currently considered a potential promising tool for sensing metabolic cancer molecules in trace amounts. The researchers affiliated with thoracic surgery department in China overserved significant difference between the saliva of patients with lung cancer and healthy controls using the Raman spectrum.

They reported their work in the journal Thoracic Cancer ([Thoracic Cancer](#). 2018 Nov; 9(11): doi: [10.1111/1759-7714.12837](#)). A significant growth of

R&D in this area is anticipated in the near future that could pave the way for a major breakthrough in cancer detection in early stage of the disease.

Cardiovascular and Neuro Biotechnology

Researchers restoring circular and cellular functions to brain

Past researches have shown the high degree of vulnerability of the brains of humans and other mammals to interruptions in blood flow and decreases in oxygen levels. It's a huge medical challenge to restore some brain activity hours after death and the cessation of blood circulation. In a recent breakthrough research conducted in this area described the restoration and maintenance of microcirculation and molecular and cellular functions of the intact pig brain under *ex-vivo* normothermic conditions up to four hours post-mortem.

Scientists at Yale University in the United States demonstrated restoration of some of the brains' molecular and cellular functions. These include spontaneous electrical activity in neurons and important metabolic functions such as consuming oxygen

and glucose. To demonstrate their process, they attached the brains to a specially constructed device and subsequently supplied artificial blood through them to restore the brain functions. Researchers published their work in Nature ([Nature](#). 2019 doi: [10.1038/s41586-019-1099-1](#)). Their findings point out the possibility that under specific medically suitable conditions, the underappreciated capacity of an isolated, intact large mammalian brain could be activated for the restoration of microcirculation and molecular and cellular activity after a prolonged post-mortem interval. This research is expected to lead to further R&D to explore the possibility of restoration of overall brain function. That would be a game changer in neuro and cardiovascular biotechnology.



Pharma and Biotechnology Industry Roundup

Pfizer takes top spot in the global top five pharma companies

In an analysis report produced by GlobalData for pharma companies for the year 2018, Pfizer got the top spot with a market cap of \$253.2 billion. Pfizer replaced Swiss-based pharma giant Roche, which came in at number 2 on the GlobalData list. The report showed a market cap of \$212.5 billion for Roche. It also showed that the only two pharmaceutical companies to cross the \$200 billion market cap threshold in the world were Roche and Pfizer. Although, the GlobalData's survey report gave Pfizer the top spot with the largest market cap, it also showed that Roche actually generated more revenue

of \$58.1 billion compared to Pfizer's \$53.6 billion during the year 2018.

In the same report, Merck & Company took the third spot with a market cap of \$198.7 billion, while Novartis got the fourth place with a market cap of \$198.4 billion right behind Merck. The fifth spot was taken by Illinois-based AbbVie with a market cap of \$139.6 billion that was nearly \$60 billion lower than Novartis. Several companies performed well with double-digit market cap growth. Companies such as CSL, Eli Lilly, Merck and Abbott reported market cap growth of 32 percent, 29 percent, 28 percent and 24 percent, respectively.

Biogen building depth in neuromuscular diseases

In a promising performance, the first-quarter financial results of Biogen showed an 11% increase in revenues that hit \$3.5 billion. The company is focusing on building depth in neuromuscular diseases and movement disorders, and their proposed acquisition of Nightstar Therapeutics is anticipated to provide them with two

potentially clinical assets in specialty ophthalmology. It is expected that by the end of 2020, the clinical programs in MS, progressive supra nuclear palsy, ALS, Parkinson's disease, pain, cognitive impairment associated with schizophrenia, epilepsy, stroke, and lupus will enter in the readouts phase.

BIO implementing diversity program as a key to success in Biopharma

In an important announcement made on April 16, 2019, the Biotechnology Innovation Organization (BIO) presented a strategy that it was implementing a program to improve gender, racial, ethnic and LGBTQ diversity on the boards of directors, executive suites and functional leadership positions in the biopharma industry. The program is

designed to show that inclusion of diversity is a key to achieving success in biopharma business. The diversity program introduced by BIO is a part of “Right Mix Matters” campaign, which includes the Diversity and Inclusion (D&I) Toolkit, BIO Boardlist and several other initiatives.

Several Biotech companies announce initial public offerings

Recently, four biotech companies filed their plans for initial public offerings (IPO) with the U.S. Securities and Exchange Commission. They are Bicycle Therapeutics, Peloton Therapeutics, IDEAYA Biosciences and Karuna Pharmaceuticals.

Among these four companies, Bicycle Therapeutics is based in Cambridge, UK and Boston, Massachusetts, USA. Bicycle Therapeutics filed on April 26 for an IPO to raise \$86 million. Bicycle is the name of the company’s proprietary product platform that deals with bicyclic peptides.

Peloton Therapeutics is headquartered in Dallas, Texas and San Francisco. The company filed IPO for a \$115

million prospectus. The lead product candidate of the company is PT2977 that is prescribed for renal cell carcinoma (RCC). The expansion plans of the company include starting enrollment in a Phase III clinical trial in the second half of this year. IDEAYA which is located in South San Francisco and focuses on precision oncology has filed for a \$70 million IPO. The fourth company Karuna Pharmaceuticals is based in Boston that has filed for an IPO with no financial details released. The company’s fund raise programs have been promising. This is evidenced by the facts that the company has raised \$122 million in two venture rounds so far with the most recent one for \$80 million fund raise.

Biotech acquisitions and mergers

In order to achieve critical mass both in R&D and sales and marketing portfolios, it is a regular practice for drug/biotech companies to merge with or acquire competitors in mega business deals. Mergers and acquisitions of scientific companies promote innovation, share pipeline development costs, eliminate competition and bolster product

portfolios. Recent market trends and analyses have indicated the inclination of larger counterparts paying attention to smaller biotech research firms that investigate new therapy based solutions to complex biomedical conditions. They are interesting pipeline candidates for potential mergers with larger biotech entities. It is anticipated that the drug/biotech industry will probably see

more merger and acquisition activity in 2019.

Key acquisitions that have taken place this year include Novartis acquisition of AveXis and Roche's purchase of

Foundation Medicine. The list also includes Bayer's \$63 billion buyout of Monsanto, a multi-billion dollar buyouts of Ablynx by Sanofi, purchase of Juno Therapeutics by Celgene



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