



ORIGINAL RESEARCH PAPER

Emergency Medicine

ACCELERATING DISCOVERIES IN MEDICINE AND ADVANCING CLINICAL BREAKTHROUGHS

KEY WORDS: mRNA technology, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), Neurotechnology, Artificial Intelligence, 3D printers,

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ABSTRACT

Technology and medicine have gone hand and hand for many years. Consistent advances in pharmaceuticals and the medical field have saved millions of lives and improved many others. Medical advances of great importance in improving diagnosis, treatment or prevention of disease are often called 'breakthroughs'. A medical breakthrough significantly enhances diagnosis, treatment or prevention of human disease. Examples are vaccines (preventive medicine), X-rays and imaging in general (diagnosis), antibiotics (treatment), anaesthetics (surgery), dialysis and heart-lung machines (organ support) and insulin (hormone replacement). Clinical advancements are increasingly turning what was once impossible into what is achievable. mRNA technology has been put under the spotlight recently as the new vaccines for Covid-19 use this science. With their high effectiveness, capacity for rapid development, and potential for low production costs, mRNA vaccines offer an alternative to the traditional vaccine approach. Neurotechnology helps to understand the brain, call to mind its procedure and control, repair its functions. These components can be computers, electrodes, or any other devices that can be set up to intercept electric pulses that run through the body. Artificial Intelligence is one of the most exciting technologies changing healthcare. 3D printers have become one of the hottest technologies on the market. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is the most advanced gene-editing technology. Telehealth and telemedicine have become increasingly in demand since the Covid-19 pandemic began in 2020.

INTRODUCTION

Respiratory syncytial virus vaccine is indicated for active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus in people 60 years of age and older (1)

Knowledge of **DNA sequences** has become indispensable for basic biological research, DNA Genographic Projects and in numerous applied fields such as medical diagnosis, biotechnology, forensic biology, virology and biological systematics. (2) Comparing healthy and mutated DNA sequences can diagnose different diseases including various cancers, characterize antibody repertoire, and can be used to guide patient treatment (3)

Despite increasing pharmaceutical R&D efforts, times, costs, and spending, these efforts are not being reflected in the

numbers of new drugs being brought to the market (4)

It is as a matter of fact, widely reported that there has been a decline in the rate of development of new drugs over past several decades (5)

Self-replicating RNA vaccines have displayed increased immunogenicity and effectiveness after formulating the RNA in a cationic nanoemulsion based on the licensed MF59 (Novartis) adjuvant (6)

Another effective adjuvant strategy is TriMix, a combination of mRNAs encoding three immune activator proteins: CD70, CD40 ligand (CD40L) and constitutively active TLR4. (7)

Tirzepatide is a novel diabetes medication that has been approved by the Food and Drug Administration (8)

It is the first of its kind to act as a dual-acting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist (9,10)

Inclisiran (Leqvio) is a synthetic, chemically modified, double-stranded siRNA. The sense strand is conjugated with a triantennary *N*-acetylgalactosamine (GalNAc) ligand to enable targeting of hepatocytes via the asialoglycoprotein receptor (ASGPR) (11)

The nasal mucosa is the first anatomical and immunological barrier the SARS-CoV-2 virus must overcome to induce infection (12)

Current intramuscular COVID-19 vaccines are designed to elicit robust systemic immunity but induce limited mucosal immunity, which may be critical to block SARS-CoV-2 infection and transmission that allow breakthrough infections in fully vaccinated individuals (13,14)

By producing both mucosal protective immunity at the site of infection and systemic immunity, an intranasal vaccine may offer the advantage of being efficacious against the disease and infection, while also decreasing transmission (15)

Bharat Biotech International Limited (BBIL), India, has developed BBV154, a chimpanzee adenoviral-vectored SARS-CoV-2 intranasal vaccine encoding a prefusion-stabilized spike protein with two proline substitutions in the S2 subunit (GenBank: QJQ84760.1) (16)

In preclinical studies conducted in mice, rats, hamsters, and rabbits, BBV154 elicited robust mucosal and systemic humoral and cell-mediated responses (17)

Tissue damage and degeneration is a rather common phenomenon among humans; however, the regenerating capabilities of the human body are rather insufficient to deal with this trauma. (18)

Additive manufacturing is one of the most advanced techniques that has been utilized in this area of tissue engineering. It encompasses the principles of material science with biology for the fabrication of organ and tissue framework (19)

Its primary objective is the restoration of damaged tissues or organs, with its fundamental goal being to emulate the native complexity of biological tissue (cellular niche) that will aid in the cell differentiation and tissue regeneration. (20)

Bringing game changing health care technology Treatment to reduce LDL cholesterol

A new drug called Leqvio, was approved by the Food and drug Administration (FDA) to be used to help lower cholesterol levels. The RNA therapy is said to block translation of the PCSK9 gene. Leqvio is a medicine used to reduce cholesterol in the blood. It is used in adults with primary hypercholesterolemia or mixed dyslipidemia (conditions that cause high levels of fats, including cholesterol, in the blood). It should be used with a low-fat diet.

Next-gene mRNA Vaccinology

The mRNA Vaccine technology is one of the greatest breakthroughs in medical history.

Recent improvements in mRNA vaccines act to increase protein translation, modulate innate and adaptive immunogenicity and improve delivery.

mRNA vaccines have elicited potent immunity against infectious disease targets in animal models of influenza virus, Zika virus, rabies virus and others, especially in recent years, using lipid-encapsulated or naked forms of sequence-

optimized mRNA

New Type-2 diabetes drug

A new diabetic drug called Tirzepatide is a once weekly injectable dual glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide receptor agonist (GLP-1) that aim to control blood sugar.

CRISPR Gene editing technology

Clustered regularly interspaced short palindromic repeats (CRISPR) is said to be the biggest breakthrough of the decade. It is said to alter human DNA so as to correct any defective genetic coding.

Postpartum depression treatment

Researchers at Reddy, have discovered a new treatment based on neurosteroids that helps to treat postpartum depression.

Covid nasal vaccine

China rolled out the first needle free Covid-19 vaccine, developed by biotechnology firm CanSino biologists. The inhalable Covid vaccine target the virus present in the mucus membrane

3-D Printing organs

3-D printing organs are also called bioprinting, helps to recreate artificial organs that are not rejected by the body's immune system.

Breakthrough device for severe paralysis

A new technology uses implanted electrodes to collect movement signals from the brain, which help restore voluntary motor impulses in patients with severe paralysis.

Hypertrophic cardiomyopathy medication

Mavacampten is a very new drug that is used to treat obstructive hypertrophic cardiomyopathy (HCM) HCM is heart disease in which the heart muscle thickens.

New finding may improve type-2 diabetes treatment in India:

Scientists have found genetic similarities and differences between various forms of type 2 diabetes in India and Europe, an advance that they say can be used to improve the treatment of the disease in the country.

Sperm Damage Test Offers Hope for Improved Fertility

A recent study in *Scientific Reports* introduces the rapid Sperm Deoxyribonucleic Acid (DNA) Fragmentation Releasing Assay (SDFR) as a diagnostic method for double-strand breaks (DSBs). The study, conducted at Lee Womens Hospital in Taiwan between May 2020 and December 2021, involved 640 infertile males aged 20 to 60 seeking assisted reproductive therapy. The SDFR assay, R11, investigated the connection between DSBs and reproductive outcomes. Researchers assessed sperm concentration, progressive motility, total motility, and the total DNA fragmentation index (DFI) using Sperm Chromatin Dispersion experiments. SDFR exhibited high sensitivity and specificity in response to dose/time-dependent simulated DSBs. It employed a modified polyacrylamide network to trap DSBs, generating a distinct halo on immunological slides. The R11 DFI increased with elevated treatment duration and dosages, specifically with Alu I and DNase I treatment, while remaining stable after H2O2 treatment. (21)

Proudest achievements

1. Katalin Karikó and Drew Weissman ---“ Discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19”.
5. William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza----“ Discoveries of how cells sense and

- adapt to oxygen availability”**
6. James P. Allison and Tasuku Honjo-- “Discovery of cancer therapy by inhibition of negative immune regulation”
 17. Robert G. Edwards--- “Development of in vitro fertilization”
 19. **Harald zur Hausen-----“Discovery of human papilloma viruses causing cervical cancer”**
 20. Françoise Barré-Sinoussi and Luc Montagnier “Discovery of human immunodeficiency virus”
 21. Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies-- “ Discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells”
 23. **Barry J. Marshall and J. Robin Warren---- “Discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease”**
 26. **Sydney Brenner, H. Robert Horvitz and John E. Sulston-- “ Discoveries concerning genetic regulation of organ development and programmed cell death”**
 27. Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse--- “ Discoveries of key regulators of the cell cycle”
 28. Arvid Carlsson, Paul Greengard and Eric R. Kandel--- “ Discoveries concerning signal transduction in the nervous system”

Innovative Brain Implant Translates Thoughts to Speech: Study

Researchers developed a prosthetic device that can decode signals from the brains speech center and predict a person intended speech. This groundbreaking technology, featured in *Nature Communications*, offers hope to individuals unable to communicate due to neurological disorders, potentially restoring their ability to convey thoughts through a brain-computer interface. The device is a small, flexible, medical-grade plastic component, no larger than a postage stamp, equipped with 256 microscopic brain sensors. It was temporarily implanted in four patients who were undergoing brain surgery to address conditions such as Parkinsons disease or tumor removal. During this period, it captured activity within each patients speech-motor cortex, orchestrating the movements of nearly 100 muscles.(22)

Recent advances in clinical biochemistry:

Clinical Biochemistry plays a critical role in patient care by providing valuable information for diagnosing, monitoring, and treating diseases. The latest technologies in instrumentation have made clinical chemistry more reliable and accessible, allowing for faster and more accurate diagnosis. Clinical biochemistry is further emerging as an important field in the healthcare system, striving to provide quality of life and help to get better outcomes, by newer innovations in introducing sophisticated techniques to retrieve reliable results, and newer methods with newer technologies. Thus, recent technological advances have revolutionized the modern laboratory of medicine by adding significant value and visibility to its role in healthcare and contributing towards quality in clinical decision-making (23).

One such practice towards quality in terms of specificity, sensitivity, and reliability with minimized turnaround time (TAT) has enabled the use of artificial intelligence (AI) in clinical diagnosis and laboratory purposes. Artificial intelligence (AI) has come into view as a promising and transformative tool in the field of clinical chemistry, offering substantial potential for advancement in disease diagnosis and the development of a predictive model for monitoring medical treatment response. AI tools have also been applied to interpret test results and establish personalized reference ranges—a development with profound implications for disease diagnosis and interpretation in clinical chemistry. Additionally, Machine learning (ML) techniques have proven valuable for result validation, quality control, and laboratory information systems. Thereby, enabling automation in test result verification, improving laboratory operations, and

supporting clinical operations and research demands (24)

Various researchers have been working in the above-mentioned fields and have developed impressive algorithms and models to power clinical decision-supporting tools, which, in turn, can facilitate in optimizing utilization of laboratory tests. The study by Azarkhish et al. successfully worked on developing a neural network model, which is capable of speculating the serum levels of iron and helping in the identification of its deficiency i.e, iron deficiency anemia this is achieved by using information extracted from a complete blood picture (25).

Yet another study by Lee et al. developed a deep learning-based neural network model that predicts low-density lipoprotein cholesterol (LDL-C) based on lipid profile parameters. It was learned that the model outperformed the traditional methods like Martin's method and Friedewald equation, which is an established method in practice for the estimation of LDL-C(26)

Similar studies were taken up which involved the potential prediction of the test results derived from clinical data and other laboratory parameters by Luo et al (27)

Several smartphone-based analytical devices have been developed in the present era like biosensors, microfabrication, mathematical algorithms, microfluidics, and 3-D printing used as point-of-care testing tools which are delivering satisfactory results with zero pain and minimal sample volume. For instance, smartphone-based diagnostic applications include endocrinology (like hormones), molecular-based analysis like quantification of nucleic acids by using paper-based sensors digital droplet assay, and microfluid chips, (Fig:-1)etc., usually used for viral detection (28).

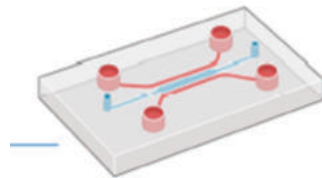


Fig1: Microfluidic and lab-on-a-chip Technology

These emerging technologies have given rise to the eHealth movement using digital networking systems like Wi-Fi, Bluetooth leading to the development of wearable microfluidic devices, that enable real-time data transfer from the device to the centralized location facilitating continuous monitoring at the point of care (POC) (29).

This advancement had turned smartphones into read-out platforms in diagnostic testing converting the expensive and complex tests into simple and less expensive shifting them from the immobile central clinical laboratories to the pocket-friendly, portable tests done at POC (30).

The advantage of this technology is time-saving, and less expensive, with no labor enabling to dispatch of uncompromised and competent results similar to the expensive and sophisticated giant equipment. To establish total laboratory automation (TLA) merge the robotic track system with AI linking all the stages of analytical processes by Marzinke (31).

To Provide quality diagnostic test results in modern clinical Chemistry labs, different companies have developed different types of commercially available TLA systems, such as CobasR (Roche Diagnostics), Accelerator (Abbott), the Power Express Clinical Automation system (Beckman), TCAutomation™ (Thermo Fisher), AptoR Automation

(Siemens Healthineers), and VITROSR Automation Solutions (Ortho Biomedical).

An accelerator, developed by Abbott Diagnostics to achieve the preanalytical tasks can be connected to a multi-instrument core laboratory system by integrating into a third-party system and can improve the consolidation of testing across the clinical chemistry laboratories.

Another advancement in using technology in cancer diagnosis introduced the concept of liquid biopsy enabling to achievement of promising results with precision oncology facilitating prediction of therapy response, monitoring response and treatment resistance, and helping in the early detection of cancer, replacing the traditional method of diagnostic process (32).

Health ATM (Automated Teller Machine) is a one-stop digital touch-point integrated machine that has been designed in the healthcare system to diagnose all chronic disease conditions, aimed to deliver primary care and diagnostics. Health ATMs consist of touch-screen kiosk hardware, designed to manage health-related information through any internet-connected web browser. Smart Health Kiosk monitors vital signs for the following- Blood glucose, Blood pressure, Lipid Profile, Fat % and blood Oxygen Saturation(33).



Your choice today can safeguard countless lives tomorrow

Recent advances in the approach to Pulmonary Hypertension

Pulmonary hypertension (PH) is a heterogeneous disease with high morbidity and mortality. The original definition of PH used mean pulmonary artery pressure (mPAP)

≥ 25 mmHg and required pulmonary vascular resistance (PVR) ≥ 3.0 Wood units (WU) for patients. This was derived from expert consensus opinion originally reported some 45 years ago in the absence of sufficiently powered data (34)

Subsequent studies suggested a significant increase in mortality and hospitalization risk emerges with mPAP >20 mmHg and PVR >2.0 WU. These are associated with impaired exercise tolerance or other measures of PH disease burden. In patients with mPAP >20 mmHg and PVR >2.0 WU, pathogenic changes are also observed to the pulmonary vasculature (35)

Newer recommendations also clarify treatment strategies as well as the indications and timing for expert center referral. It is important to understand these changes as a 2-year delay in PH diagnosis is reported if the earlier definition is followed (36)

There are broadly 5 clinical categories of PH that focus on the underlying cause of elevated pulmonary artery pressures: pulmonary arterial hypertension (PAH); left heart disease; lung diseases and/or hypoxia; pulmonary artery obstructions (particularly thromboembolic syndromes); and undifferentiated or multifactorial causes, including sickle cell disease and sarcoidosis. Among these, PH attributable to left heart and lung diseases are the most prevalent sub-types,

with an estimated prevalence of 50% to 70% and 30% to 50%, respectively (37)

Patients with idiopathic PAH (but not other PH subtypes) are considered for Vaso-reactivity testing with inhaled nitric oxide (NO). A decrease in mPAP ≥ 10 mmHg from baseline to ≤ 40 mmHg without a decrease in cardiac output generally warrants initiation of oral calcium channel antagonist therapy, such as nifedipine or amlodipine. Although vasoreactivity is uncommon ($\approx 12\%$), this is an important subgroup because $>50\%$ will achieve dramatic (ie, near curative) long-term clinical response to treatment (38)

If patients with PAH do not demonstrate vasoreactivity but are at high risk for adverse outcome (eg, WHO-FC III/IV symptoms, syncope, chest pain, other parameters, cardiac index <2.0 L/min per m^2 , or PVR ≥ 12 WU), parenteral or subcutaneous prostacyclin therapy, followed closely by initiation of dual endothelin receptor antagonist + phosphodiesterase type-5 inhibitor oral therapy, is recommended (39)

Breakthroughs in pancreatic islets biology

Autoimmune destruction of insulin-producing pancreatic β cells, resulting in persistent hyperglycemia, underlies the pathogenesis of type 1 diabetes. Preserving and restoring functional β -cell mass is therefore a fundamental objective of diabetes therapy. However, adult human β cells have limited regeneration potential, therefore the possibility of reprogramming other cell types into glucose-responsive, insulin-secreting β -like cells is being actively pursued. Pancreatic α cells represent a potential source of β -like cells due to their developmental similarities and their location in the pancreatic islet. Moreover, a marked decrease in α cells in mice does not affect normal glucose metabolism. Pedro L. Herrera and colleagues interrogated mechanisms regulating islet cell plasticity (40)

They determined the cellular mechanisms regulating the expression of insulin in glucagon+ α cells with a focus on the “brake” signals. They found that paracrine repressive signals originating from β and δ cells maintain the α -cell identity, with a constant repressive influence of somatostatin and insulin. Local signals drive the conversion of α -cells, such that inhibition of proximal β and δ cells leads to a substantial increase in insulin+ α -cell numbers. Finally, they report that α -cell conversion is only partially improved by dual inhibition of insulin and somatostatin signals, which suggests that α -cell conversion is synergistically influenced by multiple signals.(41)

Battle for breath:--

New spray technique developed by scientists could usher in new era of transdermal medication

Advanced biological or “bioactive” materials – such as drugs and vaccines – can be costly to produce, especially if any of the material is wasted, which can greatly limit whether a patient can receive a given treatment. Scientists at Rutgers University have devised a highly accurate method for creating coatings of biologically active materials for a variety of medical products. Such a technique could pave the way for a new era of transdermal medication, including shot-free vaccinations, researchers said. Writing in *Nature Communications*, researchers described a new approach to electrospray deposition, an industrial spray-coating process. Essentially, Rutgers scientists developed a way to better control the target region within a **spray zone** as well as the electrical properties of microscopic particles that are being deposited. The greater command of those two properties means that more of the spray is likely to hit its microscopic target

The next big advance in cancer treatment could be a vaccine

For a vaccine to work, it needs to teach the immune system's T cells to recognize cancer as dangerous, said Dr. Nora Disis of UW Medicine's Cancer Vaccine Institute in Seattle. The next big advance in cancer treatment could be a vaccine.

After decades of limited success, scientists say research has reached a turning point, with many predicting more vaccines will be out in five years. These aren't traditional vaccines that prevent disease, but shots to shrink tumors and stop cancer from coming back.

Targets for these experimental treatments include breast and lung cancer, with gains reported this year for deadly skin cancer melanoma, and pancreatic cancer. "We're getting something to work. Now we need to get it to work better," said Dr. James Gulley, who helps lead a center at the National Cancer Institute that develops immune therapies, including cancer treatment vaccines.

CONCLUSION

Immunologists and virologists at The Rockefeller University with the Support from Griffin Catalyst advanced the development of effective convalescent plasma therapies in just five months. The plasma therapy has saved the lives of more than one hundred thousand COVID-19 patients. mRNA technology has been put under the spotlight recently as the new vaccines for Covid-19 use this science. Scientists discovered ZOLGENSMA world's costliest drug ever \$2,125,000 (Indian Rs.18 Crores/dose) of Novartis is a gene therapy for Spinal Muscular Atrophy (SMA) a very rare inherited genetic disorder caused by survival motor neuron-1 gene that is missing or not working properly in the affected person where the patient suffers inability in using his/her arms, legs throat and many other areas in the body. Artificial intelligence (AI) has come into view as a promising and transformative tool in the field of clinical chemistry, offering substantial potential for advancement in disease diagnosis. Machine learning (ML) techniques have proven valuable for result validation, quality control, and laboratory information systems. Bio engineers discovered smartphone-based analytical biosensors, micro fabrication, mathematical algorithms, microfluidics, and 3-D printing used as point-of-care testing tools which are delivering satisfactory results with zero pain and minimal sample volume. For instance, smartphone-based diagnostic applications include endocrinology molecular-based analysis like quantification of nucleic acids by using paper-based sensors digital droplet assay, and microfluid chips, usually used for viral detection. Health ATM (Automated Teller Machine) is a one-stop digital touch-point integrated machine that has been designed in the healthcare system to diagnose all chronic disease conditions, aimed to deliver primary care and diagnostics.

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