ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

JULY - AUGUST 2022, ISSUE 17

FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 17th issue of ESSENCE.

The idea to treat a disease through transferring genetic material into cells of the patients to correct the genetic anomaly has been quite fascinating and appealing. In the recent times, gene therapy has become a reality and many FDA approved therapies are available to treat various diseases ranging from monogenic disorders to haemoglobinopathies to cancer. The current issue of ESSENCE highlights the advances in this new promising approach including the types of gene therapy, FDA approved gene therapy products. We also have an article on Epigenetics, which is the study of modifications to DNA that change the way genes are expressed. This is of special interest as epigenetic medications are already used to treat various malignancies and neurological conditions.

Sunscreens are preparations used to protect skin against the harmful effects of ultraviolet radiation (UVR). They are widely used and hence it is important to understand the various aspects of the pharmacology of these preparations. The present issue has a guest article which provides an expert view of these aspects.

Further, as always, we have recent updates from the world of medicines, new drug approvals, Drug safety alerts, and cross word puzzle quiz on 'Drugs causing Hyperglycemia'.

Link to access quiz is given below: Winners will be declared in the next issue

https://docs.google.com/forms/d/e/1FAIpQLSd3EKhI7NJr8JGr-SnKnXhwDU00-MfCajXWiRz-n4i_4IEv7Q/viewform?vc=0&c=0&w=1&flr=0

Happy Reading,

Jai Hind

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

The idea of 'Gene Therapy' took birth around 45 yrs ago when Theodore Friedman proposed that a gene can be delivered into specific cell types and its expression can lead to therapeutic benefit, dramatically improving the patients' quality of life. Gene therapy is the treatment of a disease through transferring genetic material into cells of the patients. In the case of gene therapy, the drug is a gene, is packaged within a vector used to facilitate its entrance into the patients' cells. In the beginning, the idea of gene addition was particularly applicable in monogenic diseases based on the notion of "adding the missing gene or the normal allele to compensate for the expression of the mutated allele." However, as per current thought process, gene therapy does not correspond to an addition of a gene, otherwise missing in the patient's cells, but with a gene that could provide therapeutic benefit to the affected individual.

There are basically three types of gene therapy: *ex vivo*, *in vivo*, and *in situ*.

***Ex vivo* gene therapy:** In this, the target cells are removed from the patient's body, and then engineered either by the addition of the therapeutic gene or by other genetic manipulations that allow correction of the phenotype of the disease. The "corrected" cells are subsequently re-infused to the patient. This type of intervention is particularly applicable to blood diseases; In the case of leukemias, the target cell may be T or NK cells, and the therapeutic gene being the chimeric antigen receptor (CAR). In the case of monogenic diseases, the target cell is the hemopoietic stem cell (HSC) and the transgene varies analogous to the disease. The viral vectors utilized in both cases are mostly retroviral vectors, belonging either in the lentiviral or the oncoretroviral families.

In vivo gene therapy: if the target organ is the brain, the spinal canal, or the liver, another type of therapy is employed, called '*in vivo*' gene therapy. In this setting, the therapeutic vector is administered systemically in the blood circulation or the cerebrospinal fluid of the patient, and depending on the disease, different types of viral vectors are utilized, such as adenoviral vectors (AVs) or adeno-associated viral vectors (AAVs).

In situ gene therapy: In this type of gene therapy, the viral vector is administered *in situ*, i.e., to a specific organ or area in the body of the patient either through direct injection, e.g., into the tumor (in the case of melanoma) or into suitable brain areas (in the case of neuropathies) or by an insertion of a catheter in the case of heart.

The selection of the procedure depends entirely on the type of indication, the affected tissue, and the cell type that requires correction. In contrast to HSCs (CD34+ cells) that can be easily isolated from the patients, nerve stem cells are difficult to obtain for ex *vivo* manipulation. In addition, stem cells are only partially characterized in the liver. Hence, gene therapy for specific organs or indications is dependent on systemic or *in situ* administration of the therapeutic vector.

Recent advances in cell and gene therapies have enabled the treatment of a wide range of conditions, from congenital disorders to solid cancers. Some of the FDA approve gene therapies are given as under:

Gene therapy products approved by FDA

1. Zolgensma (Onasemnogene Abeparvovec)

Disease: Spinal Muscular Atrophy

Indication: For the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.

Methods: Utilizes NAV AAV9 to deliver functional copies of the SMN1 gene to neurons.

2. Yescarta (Axicabtagene Ciloleucel)

Disease: Large B-cell Lymphoma

Indication: Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

Methods: The patient sits for leukapheresis, and the product is sent to a lab. There, the T cells are genetically enhanced to attack cancerous cells and expanded.

3. Luxturna (Voretigene neparvovec-rzyl)

Disease: Retinal Dystrophy

Indication: Adeno-associated virus vector-based gene therapy indicated for the treatment of patients with biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).

Methods: A functional copy of RPE65 is introduced to patients via a subretinal injection of Adeno-associated viral vector solution.

4. Kymriah (Tisagenlecleucel)

Disease: Large B-cell lymphoma

Indication: Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Methods: Patient's T cells are modified to recognize CD19 on B cells, expanded, and reintroduced to the patient to combat Large B-cell Lymphoma.

5. Zynteglo (Betibeglogene autotemcel)

Disease: Beta-Thalassemia

Indication: Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Methods: Hematopoietic Stem Cells (HSCs) are collected from the patient, then treated with a lentiviral vector to introduce functional genes for beta-globulin. HSCs are then re-introduced to the patient.

6. Strimvelis (Autologous CD34+)

Disease: Adenosine Deaminase Deficiency (ADA-SCID)

Indication: Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Methods: A sample of the patient's bone marrow is taken, and the CD34+ cells are transduced with a retroviral vector in order to restore gene function before being reintroduced to the patient.

7. Tecartus (brexucabtagene autoleucel)

Disease: Mantle Cell Lymphoma

Indication: For the treatment of adult patients with relapsed/refractory mantle cell lymphoma (r/r MCL).

Methods: Patient undergoes leukapheresis. Lymphocytes are expanded and transduced with genes that strengthen the immune response to CD19+ cells. Autologous anti-CD 19 CAR T cells are reintroduced to the patient intravenously.

References:

Papanikolaou E, Bosio A. The Promise and the Hope of Gene Therapy. Front. Genome Ed. 2021:3;618346

Recent new/Update from the world of medicines ….

CRISPR gene editing for curing high cholesterol enters human trials

A new gene therapy using CRISPR is designed to permanently deactivate a gene in the liver that controls the production of PCSK9. In monkey trials, the treatment reduced LDL cholesterol by 70% in just two weeks. The trial will use a base editor to convert an adenine base (A) to a guanine one (G) in the DNA encoding for PCSK9, a key regulator of blood cholesterol levels. The approach, developed by Verve Therapeutics in Cambridge, Massachusetts, aims to reduce the amount of functional PCSK9 in people with a condition called heterozygous familial hypercholesterolemia, which causes high cholesterol and can lead to heart disease. Disabling PCSK9 has been shown to reduce cholesterol levels and cut the risk of heart disease, and several therapies already on the market reduce PCSK9 activity.

New $2.8-million gene therapy becomes most expensive medicine in history

The Food and Drug Administration (FDA) on Wednesday approved the first gene therapy treatment that could offer a permanent cure for patients of Beta-Thalassemia. The therapy has been developed by bluebird bio company under the brand name *Zynteglo* at a whopping cost of $ 2.8 million (Rs 22 crores) making it the most expensive treatments of all time. The single dose treatment could be a game changer and works by genetically modifying the patient's bone marrow stem cells, making it so they are able to produce functional hemoglobin and avoiding the mandatory regular red blood cell transfusions every two to five weeks.

The lifetime cost of medical care for a patient with transfusion-dependent beta-thalassemia can reach up to $6.4 million in the U.S., the company said. Patients also usually have a shorter lifespan. In that sense the $ 2.8 million single dose gene therapy is being touted as a cost-effective option.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Amoxicillin	Potential risk of aseptic meningitis
2.	Ceftriaxone	Potential risk of hepatitis and encephalopathy
3.	Clindamycin	Potential risk of acute kidney injury
4.	COVID-19 vaccine AstraZeneca (ChAdOx1-S)	Potential risk of transverse myelitis (TM)
5.	Donepezil	Risk of cardiac conduction disorders
6.	Dexmedetomidine	Risk of mortality in patients aged 65 years and less

Epigenetics is the study of modifications to DNA that change the way genes are expressed. It does not alter the underlying genetic code of an individual. Epigenetic modifications affect when genes are turned on and off. Epigenetic changes such as DNA methylation, chromatin packaging (histones) and histone deacetylases alter gene expression at the level of transcription by upregulating, downregulating, or silencing genes completely. Pathological dysregulation of epigenetic processes can result in the development of cancer, neurological disorders, metabolic diseases, and cardiovascular diseases. Therefore, it is of great clinical interest to find medications that block these epigenetic changes. In fact, epigenetic medications are already used to treat various malignancies and neurological conditions.

Epigenetics can be helpful for drug discovery in at least two ways. First, it is possible to target the enzymes that modify the epigenetic coding. Alternately, aberrant epigenetic alterations may be used to identify specific genes that cause disease. The improperly regulated gene may be the target of drug research efforts.

Identifying Drug Targets in Cancer using Epigenetics

Most diseases in people include a loss or alteration of cell identity. Alzheimer's disease is an example of a degeneration. Neurodevelopmental diseases are examples of an immature condition. Drug development is therefore attracted to proteins that are involved in adding, removing, or writing these epigenetic marks. For clinical usage in subtypes of leukemia and lymphomas, DNA demethylating drugs and histone deacetylase inhibitors have been approved in the field of oncology. Three families of epigenetic proteins—writers, readers, and erasers—control the intricate interplay between epigenetic phenomena. Readers identify and interpret the numerous chemical modifications that writers make to DNA and histones, while erasers delete the alterations. In actuality, epigenetic medications are able to target each of these epigenetic regulators.

Today, a number of epigenetic medications have been approved for the treatment of cancer, and numerous others are undergoing clinical trials. 5-azacytidine and 5-aza-20-deoxycytidine are the drugs inhibiting the DNA methyltransferases DNMT1 and DNMT3B, which are regarded as writers, are being utilized as first-line treatments for myelodysplastic syndrome. Histone deacetylases (HDACs) functioning as erasers, are targeted by romidepsin and vorinostat. Drugs that target epigenetic readers are known as bromodomain (BET) inhibitors.

Cancer Epigenetic Drugs:

DNA methyltransferase inhibitors: In order to understand the role of DNA methylation in various processes (such as X-chromosome inactivation and DNA imprinting) and as an anti-cancer therapy, DNA methyltransferase inhibitors (DNMTi) are frequently utilized as pharmacological tools for hypomethylating

the genome. The most effective epigenetic medications to date are still the DNA methyltransferase (DNMT) inhibitors **azacytidine** and **decitabine**, even if their usage for oncological disorders is constrained by their relative toxicity and low chemical stability. The two drugs are currently first-line therapy for myelodysplastic syndrome (MDS) when stem cell therapy is not suitable and are additionally used to treat chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML).

Histone deacetylase inhibitors: Histone deacetylase (HDAC) inhibitors are a relatively recent family of anti-cancer drugs that are crucial in the regulation of epigenetic or non-epigenetic processes. The growth of tumor cells in culture and in vivo is inhibited by HDAC inhibitors by increasing the expression of cell cycle genes and repressing transcription by preventing elongation. This results in cell cycle arrest, differentiation, and/or apoptosis. Four HDAC inhibitors have so far received US Food and Drug Administration approval: Vorinostat, Romidepsin, Panobinostat, and Belinostat. These HDAC inhibitors are primarily utilized in clinics for hematologic tumors with less side effects.

Histone methyltransferase inhibitors: They are in development for the treatment of both solid and hematologic malignancies. Targeted therapy is included for inhibiting the histone methyltransferase enhancer of zeste homologue 2 (EZH2), which attacks Lys27 of histone H3. EZH2 normally causes functional mutations in lymphomas which may be treated with EZH2 inhibitors. The most recent approval of the methyltransferase inhibitor is tazemetostat. Tazemetostat, an EZH2 inhibitor, was approved by the FDA in January 2020 for the treatment of adults and paediatric patients aged 16 years and older with metastatic epithelioid sarcoma. Pinometostat, an inhibitor of histone methyltransferase DOT1L activity, is another potential drug that has undergone significant clinical testing but is not yet FDA-approved.

Numerous epigenetic medications are now used to treat cancer on a global scale. The tissues of interest can be reached rather easily by conventional epigenetic medications, which have been shown to be successful in treating leukemia and myelodysplastic syndromes. However, the success of using epigenetic medications to treat solid tumours was lower. The biggest obstacles facing conventional epigenetic medications are overcoming the growing resistance and expanding the therapeutic profile beyond hematological malignancies. Finally, we must stress how incredibly promising CRISPR/dCas9 technology is as a tool for precise epigenetic therapy. It can be predicted that the field of epigenetic editing will start to flourish with the development of CRISPR/dCas9-based technologies.

References:

1. Heerboth et al. Use of Epigenetic Drugs in Disease: An Overview. Genetics and Epigenetics 2014:6;9–19.
2. Majchrzak-Celinska A, Warych A, Szoszkiewicz M. Novel Approaches to Epigenetic Therapies: From Drug Combinations to Epigenetic Editing. Genes 2021:12;208.

New Drug Approvals…

Vutrisiran is a double-stranded small interfering RNA (siRNA) approved for the treatment of polyneuropathy associated with hereditary transthyretin-mediated amyloidosis. The recommended dose is 25 mg SC every 3 months.

Zonisamide oral suspension: Zonisamide is a voltage-dependent sodium channel inactivator. The Liquid formulation is approved for the treatment of partial-onset seizures in adults and paediatric patients aged 16 years and older with epilepsy. The recommended initial dose is 100 mg daily.

Tapinarof is an aryl hydrocarbon receptor agonist approved for the topical treatment of plaque psoriasis in adults. It is available as 1% cream.

Betibeglogene autotemcel is a genetically modified autologous CD34+ cells that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the β A-T87Q-globin gene. It is approved for the treatment of adult and paediatric patients with beta-thalassemia who require regular red blood cell (RBC) transfusions. The recommended dose is 5.0 × 106 CD34+ cells/kg by intravenous infusion single administration.

Cartoon Corner…

Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

GUEST COLUMN: Shedding light on Sunscreens

Sunscreens are topical agents used to protect skin against the harmful effects of ultraviolet radiation (UVR).

Ultraviolet radiation (UVR)

UVR lies between X-rays and visible light in the electromagnetic spectrum. UVR is made of three types of UV rays:

- UVA (320-400nm) rays have longer wavelengths and reach the epidermis and dermis. UVA can pass through window glass.
- UVB (290-320nm) rays have shorter wavelengths and reach the epidermis. UVB helps in the cutaneous production of vitamin D. It is blocked by window glass.
- UVC (200-290nm) rays are blocked by the ozone layer.

Sunlight is the most common form of UVR. It has several beneficial effects. Phototherapy involves the therapeutic use of carefully monitored doses of specific wavelengths of UVR. It is used in the management of several diseases such as psoriasis, eczema, and vitiligo. However, excessive exposure to ultraviolet radiation (UVR) can lead to reactive oxygen species (ROS) production, DNA damage, immune suppression, and carcinogenesis. UV**A** causes premature **A**ging. UV**B** causes sun**B**urns. Chronic exposure to UVR can also damage almost all of the ocular structures.

Sunscreen ingredients

Sunscreens have been traditionally classified into chemical and physical blockers. Chemical sunscreens are usually aromatic compounds that absorb high-intensity UVR. Examples of chemical blockers include oxybenzone, avobenzone, octisalate, octocrylene, homosalate, and octinoxate. Physical sunscreens mainly act by reflecting or scattering sunlight. These include zinc oxide and titanium dioxide. Sunscreens may also be classified based on the spectrum of UVR blocked. Sunscreens may be used in the form of lotions, creams, sticks, gels, and sprays based on the area of application and patient preferences. The sunscreen vehicle plays an important role in efficacy, aesthetics, durability, and water resistance.

Sunscreen indications:

1. Photosensitivity diseases and photo aggravated dermatoses. e.g., Xeroderma pigmentosum and lupus erythematosus (UVR can flare disease activity in patients with lupus).
2. Sunburn
3. Sun damage, freckling, skin discolouration
4. Prevention of skin aging and skin cancer
5. Phototoxic and photoallergic drug reactions

Contraindications:

Hypersensitivity to any of the active ingredients or vehicles. Sunscreens are not recommended in infants less than six months of age.

SPF (Sun protection factor): The sun protection factor (SPF) is a measure of protection against UVB-induced erythema. SPF ratings range from 2 to 50+ with 50+ sunscreens having the maximum UVB protection.

$$\text{SPF} = \frac{\text{Minimal erythema dose of photo protected skin}}{\text{Minimal erythema dose of unprotected skin}}$$

SPF	Percent reduction in UVB penetration
15	93.3
30	96.7
50	98

Sunscreens should have a minimum SPF of 15, be 'broad-spectrum' to protect against both UVB and UVA, and be water-resistant. Water-resistant sunscreens maintain their SPF after 40 or 80 minutes of water immersion. Some sunscreens (tinted sunscreens) also protect against visible light(400-700nm). Visible light can increase pigmentation in dark-skinned individuals.

Adverse reactions: Adverse reactions to sunscreens include subjective irritation, contact urticaria, allergic and irritant dermatitis, photodermatitis, folliculitis, comedogenesis, and flare of pre-existing acne.

Contraindications: Hypersensitivity to any of the ingredients or the vehicle. Sunscreens are not recommended in infants less than 6 months of age.

Sunscreen and vitamin D: There is little evidence that real-life sunscreen use reduces 25(OH)D levels. However, patients with light-sensitive conditions who regularly avoid sunlight may require testing and vitamin supplementation.

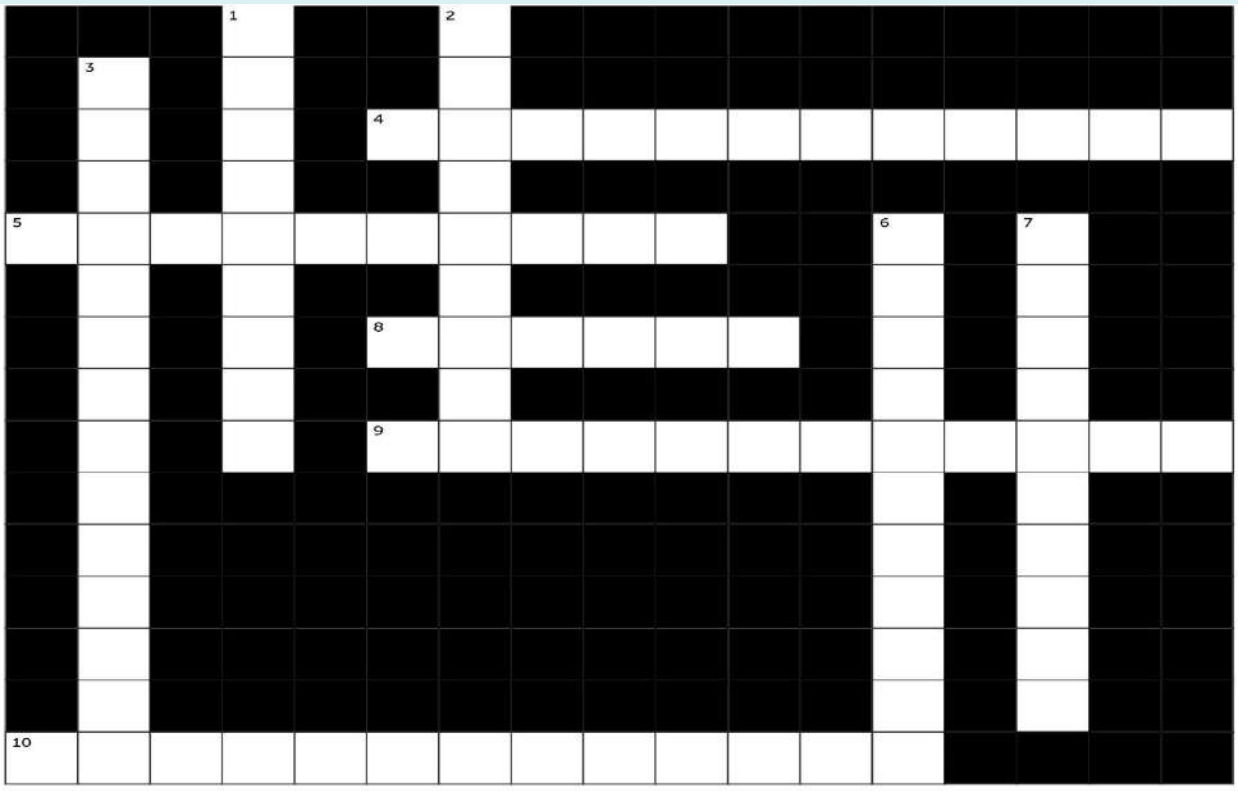
Sunscreen ≠ Sunsafe:

No sunscreen provides 100 % sun protection. Sunscreens are mostly applied inadequately or irregularly. Sunscreens need to be applied adequately($2mg/cm^2$), 15-30 min before sun exposure, re-applied every two hours, and after swimming or sweating. Water, snow, and sand reflect sun rays and increase the chances of sunburn. Photoprotection should include avoiding mid-day sun, sun-protective clothing, sunglasses, wide-brimmed hats, and seeking shade. Thus, sunscreens are just an adjunct to sun safety measures.

References:

1. Mori S, Wang SQ. Sunscreens. In: Wolverton S, Wu J, ed. *Comprehensive Dermatologic Drug Therapy*. 4th edition. Philadelphia, USA: Elsevier, 2020.pp 565-575.
2. Taylor SC, Alexis AF, Armstrong AW, Chiesa Fuxench ZC, Lim HW. Misconceptions of photoprotection in skin of color. J Am Acad Dermatol. 2022 Mar;86(3S):S9-S17

Contributed by:
Dr. Hima Gopinath
Associate Professor,
Department of Skin and VD, AIIMS Mangalagiri.



ACROSS

4 Fluoroquinolone (12)

5 Recombinant growth hormone (10)

8 Vitamin which is also used as hypolipidemic agent (6)

9 Thiazide diuretic (12)

10 Long-acting glucocorticoid (13)

DOWN

1 Atypical antipsychotic agent (9)

2 Arteriolar vasodilator (9)

3 Thiazide like diuretic (14)

6 Antimicrobial agent used against Pneumocystis jirovecii (11)

7 Anti-retroviral drug (10)

Quiz on Crossword Puzzle: *Drugs Causing Hyperglycemia*

Click on the link below to access the quiz: https://docs.google.com/forms/d/e/1FAIpQLSd3EKhI7NJr8JGr-SnKnXhwDU00-MfCajXWiRz-n4i_4IEv7Q/viewform?vc=0&c=0&w=1&flr=0

(Results and Winners of the Quiz will be announced in the next issue)

Winners of Previous Crossword PUZZLE [16th Issue]

1. **Dr. EESHWAR M V, AIIMS Mangalagiri**
2. **Dr. ANAND BODADE, AIIMS Mangalagiri**

Answer to the previous Crossword Puzzle (16th Issue) is given in the link below: https://docs.google.com/forms/d/e/1FAIpQLSfVPlAHeeRnP8beLPuB5pAdMWD9zWIq9OP9RDfid7F3CQKleg/viewform?vc=0&c=0&w=1&flr=0