ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 19th issue of ESSENCE.

Human drug development is a complex, expensive and long drawn process. It involves in-vitro, animal (preclinical) and then finally clinical trials (Phase 1-4). It takes around 12-15 yrs for a new drug to be developed with estimated costs touching close to 1 billion dollars. Further, out of 100 drug candidates only 1-2 candidates reach the approval stage. To salvage this situation, a novel experimental strategy known as Phase Zero (0) clinical trials has been created. The current issue highlights the role of Phase 0 in new drug development.

The primary sites for cellular respiration and energy production are mitochondria are the primary sites for cellular respiration and energy production. Mitophagy can remove unhealthy or malfunctioning mitochondria and has also been known to reduce the production of ROS and reduce their ability to trigger tumours. The current issue looks in detail at the role of Mitophagy in cancer therapeutics.

Allergic Rhinitis is one of the very common conditions seen in clinical practice and we have a Guest column featuring the Pharmacotherapy of this important condition.

Further, as always, we also have the recent news & updates, drug safety alerts, new drug approvals, cross -word puzzle and drug cartoon.

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

Human drug development is complex, expensive and long drawn process. It involves in-vitro, animal (preclinical) and then finally clinical trials (Phase 1-4). It takes around 12-15 yrs for a new drug to be developed with estimated costs touching close to 1 billion dollars. Out of 100 drug candidates only 1-2 candidates reach the approval stage. Why is the failure rate so high? This is because despite detailed preclinical studies in animals, the extrapolation is less than desirable. A vast majority of the compounds that pass animal tests fail in Phase I clinical trials. Similarly, the attrition rate in phase II and Phase III is also very high. The pharmacokinetic profile of a medicine is a crucial component and suboptimal pharmacokinetics is stated to be one of the primary reasons for failures during drug development. Failures in efficacy can result from too low drug concentrations in the target organ for shorter periods of time, and on the other hand toxicity can result from high concentrations reaching the wrong targets for longer periods of time.

What is Phase Zero (0) clinical trial?

The FDA released the document "critical path" to highlight the issues with drug development and to encourage novel approaches into the present drug development to salvage the situation and improve the approval rate of new drugs. In order to address problems with drug metabolism and pharmacokinetics, a novel experimental strategy known as Phase 0 or microdosing research was created. A phase 0 stage is positioned midpoint between the preclinical and phase I stages, hence the name. In microdosing, extremely low, non-pharmacologically active doses of a drug are used to define the agent's pharmacokinetic profile in humans. Thus, by definition, microdosing means use of 'less than $1/100^{th}$ of the dose calculated to yield a pharmacological effect of the test substance to a maximum dose of < 100 micrograms and a maximum microdose of < 30 nanomoles for protein products.

Advantages of Phase Zero trials in drug development

Microdosing has the potential to assist in reducing or replacing the extensive kinetic testing of substances on animals, which may subsequently be disproven in human research. Microdose studies therefore use very small amounts of the drug and are not meant to have any pharmacologic effects when given to humans; as a result, they may not have any negative side effects as well, but they may produce useful pharmacokinetic data and aid in the further development of the compound. To measure drug and metabolite concentrations in the low picogram to fentogram range, analytical techniques that are ultrasensitive and precise are needed. Accelerator mass spectrometry (AMS) and liquid chromatography coupled with tandem mass spectrometry (LC-MS-MS) are the most used of these (AMS). In contrast to LC-MS-MS, the latter approach is incredibly sensitive. Compounds must, however, be isotopically labelled, typically with C^{14}. Although using AMS may have this drawback, the dose of radiolabelled substance used in

nanocuries. Furthermore, while phase 1 studies are conducted in healthy volunteers, phase 0 enables these properties — which are critical to informed drug development decision-making — to be immediately studied in patients, that is, the target population. Compared to traditional phase I research, phase 0 studies are typically smaller, quicker, and less expensive. Usually, a single cohort study with 4–12 participants can be finished in a month or less, and the entire phase 0 study can be completed in under 6–8 months. The studies are usually conducted at a single site, with the costs being just a fraction (US$350,000) as compared to a of those for a phase I trial which can be upwards of US$1.5 million).

Thus, microdosing enables not only the selection of drug candidates with a higher chance of being successfully developed but also the calculation of the initial dose for the ensuing Phase I clinical trial. Additionally, fewer animal investigations are needed prior to Phase I clinical trials if human screening of compounds is done sooner in the drug development process. As a result, using drugs with inappropriate pharmacokinetic characteristics won't require any additional animal research. Even a 10% improvement in identifying failing candidates before classic clinical trials could also save US$100 million in development costs per drug

Limitations of Microdosing:

There are many questions which need to be answered regarding the predictive accuracy of microdosing as it is unclear whether the body's reaction to a particular compound is similar, when used as microdose as compared to its pharmacological dose. Another concern is whether microdosing predicts pharmacokinetic parameters accurately for drugs showing nonlinear kinetics Thus, caution should be exercised when microdosing is employed to drugs with complex pharmacokinetics, especially during early drug development of new chemical entities.

Conclusion:

In conclusion, microdosing may benefit patients and the pharmaceutical industry by making new test medications available sooner and reducing compound attrition at later stages of drug development. In addition to allowing for the selection of drug candidates with a higher chance of being developed successfully, microdosing also aids in establishing the first dose for following Phase I clinical investigations.

References:

1. FDA. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. http://www.fda.gov/oc/initiatives/ criticalpath/whitepaper.

2. Boyd RA, Lalonde RL. Nontraditional approaches to first-in-human studies to increase efficiency of drug development: Will microdose studies make a significant impact? Clin Pharmacol Ther. 2007;81:24–5.

3. Langley G, Sebastien Farnaud S. Microdosing: safer clinical trials and fewer animal tests. Bioanlysis. 2010;2(3):393-5

Recent new/Update from the world of medicines ….

First Nasal Spray to Treat COVID Patients in India Launched

Glenmark in partnership with a Canadian pharmaceutical, SaNOtize launched a nasal spray named FabiSpray in India. After the Phase 3 trials, reduction of viral load, up to 99 per cent in 48 hours have been shared in some reports. The company received a green signal from India's drug regulator, Drugs Controller General of India (DCGI) for Nitric Oxide Nasal Spray to be successfully manufactured and marketed.

The nasal spray is meant for topical use only. It is a manual pump spray, convenient to use, ideally, it must be sprayed, over nasal mucosa a maximum of 3 times per day. It acts as a barrier against the virus, both physically and chemically. FabiSpray claims to be an effective aid for adult patients suffering from COVID-19. It can control the multiplication of the COVID-19 virus in the upper respiratory tract itself.

New spray can have a dual impact in the fight against antibiotic resistance

A group of researchers at Chalmers University of Technology in Sweden are now presenting a new spray that can kill even antibiotic-resistant bacteria, and that can be used for wound care and directly on implants and other medical devices. A new antibacterial material that consists of small hydrogel particles equipped with a type of peptide that effectively kills and binds bacteria and become an effective tool to fight antibiotic resistance.

The researchers have shown that 99.99 per cent of bacteria are killed by the material and that the bactericidal capacity is active for approximately 48 hours, enabling its use in a wide range of clinical applications. Since the materials are non-toxic, they can be used directly on or in the body, preventing or curing an infection without adversely affecting the natural healing process.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Metronidazole	Prolonged QT and ventricular tachycardia
2.	Nirmatrelvir/Ritonavir	Anaphylaxis
3.	Pregabalin	Major congenital malformations in children exposed in-utero
4.	Teicoplanin	Acute generalised exanthematous pustulosis (AGEP)
5.	Topiramate	Risk of neurodevelopmental disorders in children exposed in-utero
6.	Molnupiravir	Hypersensitivity

The primary sites for cellular respiration and energy production are mitochondria, which are organelles covered by the bilayer membranes mitochondrial inner membrane (IMM) and mitochondrial outer membrane. Utilizing glucose and preserving mitochondrial function are necessary for this massive energy expenditure. Therefore, maintaining the integrity and activity of the mitochondrial network is necessary. The mechanisms of mitochondrial fusion, fission, biogenesis, and mitophagy—known as "mitochondrial dynamics"—that regulate the morphology, quality, and abundance of mitochondria—have lately been linked to various disease.

In the development of cancer and carcinogenesis, mitophagy performs a variety of roles. The status and subtypes of cancer cells have a significant impact on whether it acts as a tumour promoter or suppressor. To keep the balance between the number and quality of mitochondria, mitophagy can remove unhealthy or malfunctioning mitochondria. After mitophagy, functioning mitochondria produce fewer ROS and reduce their ability to trigger tumours. On the other hand, mitophagy can work as a cytoprotective strategy to direct tumour progression against chemotherapy-induced apoptosis once the tumours have already begun. Functional mitophagy suppresses the build-up of damaged mitochondria and halts the development of cancer. The PINK/Parkin pathway has the ability to activate mitophagy in liver cells, eliminate damaged mitochondria, and lessen ROS production. Mitophagy suppression can be caused by the deletion or mutation of genes such PARK2 and BNIP3, which can promote carcinogenesis and the spread of cancer.

Mitophagy and drug resistance

Some chemotherapy medications cause mitochondrial malfunction, release harmful by-products such ROS, and alter normal metabolic processes. Mitophagy is a cytoprotective process that aids in the body's response to chemotherapy. As a result, focusing on mitochondria is thought to be a promising anticancer treatment.

A platinum-based drug with extensive use, cisplatin exhibits anticancer efficacy against a number of malignancies. Cancer cells eventually develop cisplatin resistance. As a result, getting around medication resistance is difficult. The non-small cell lung cancer cell line A549 is resistant to cisplatin in part due to caveolin-1 (Cav-1)/Parkin-mediated mitophagy. Due to the downregulated Rho-associated coiled-coil-containing protein kinase 1 (ROCK1), which in turn reduces Parkin-mediated mitophagy, the cav-1-knockdown A549 cells seem more susceptible to cisplatin. Apurinic endonuclease 1 (APE1), which is overexpressed in A549 cells and triggers Parkin-mediated mitophagy, is crucial for the cisplatin resistance of these cells. The inhibition of APE1 enhances cell death and restores cisplatin sensitivity. Additionally, in the of Parkin, the E3 ubiquitin ligase ARIH1 is necessary for starting PINK1-dependent mitophagy. A549 cell death brought on by cisplatin is prevented by ARIH-induced mitophagy. The same dose of cisplatin has a

dominating effect on cell proliferation in ARIH1 knockout cells. By inducing mitochondrial apoptosis, the novel betulinic acid (BA) derivative, B5G1 displays powerful anticancer action against cancer cells that are resistant to many drugs. However, by the activation of PINK1 and subsequent recruitment of Parkin, B5G1 can trigger mitophagy. Drug-resistant cancer cells become susceptible to B5G1 when mitophagy is inhibited by mitochondrial division inhibitor 1 (mdivi-1) or bafilomycin.

Doxorubicin, a DNA-damaging substance, has a significant impact on cell survival because it causes cell death and mitochondrial malfunction. However, to lessen oxidative stress and promote cell survival in colorectal cancer, damaged mitochondria are eliminated through BNIP3L-mediated mitophagy. Its susceptibility to doxorubicin is considerably increased by the suppression of mitophagy caused by BNIP3L deletion.

Mitophagy as a target for anticancer therapeutics

Although mitophagy helps cells survive stress by adapting, it can also kill cells if it clears too many mitochondria. Therefore, both mitophagy inducers and inhibitors may be equally useful in the therapy of cancer.

A key factor in reducing cancer cells' drug resistance is the prevention of mitophagy. Chemotherapy for cervical cancer is less effective due to cisplatin drug resistance. A well-known endogenous indoleamine and antioxidant, melatonin (N-acetyl-5-methoxytryptamine) lessens hypoxia-ischemia damage and enhances sleep. Additionally, it can stop the growth of tumours and stop mitophagy. Melatonin inhibits mitophagy via inhibiting c-Jun N-terminal kinase (JNK), which in turn inhibits Parkin, and thereby worsens cervical cancer cell apoptosis.

Due to innate mitophagy and autophagy, chemotherapy medicines like cisplatin do not effectively eradicate cancer cells in hepatic carcinoma. To improve mitophagy, cisplatin stimulates the dynamin-related protein 1 (DRP1). Instead of immediately inducing apoptosis, mdivi-1 or bafilomycin, inhibitors of lysosome function, improve the sensitivity of liver cancer cells to cisplatin. Liensinine, a mitophagy inhibitor, can significantly boost breast cancer cells' sensitivity to cisplatin. By preventing excessive autophagosome accumulation, autophagosome-lysosome fusion, and the development of numerous critical lysosomal hydrolases, liensinine suppresses mitophagy.

Additionally, improved mitophagy may offer a potential plan for therapeutic intervention in various malignancies. An oral antifungal drug called ketoconazole stimulates PINK1/Parkin-mediated mitophagy by suppressing the production of COX-2, which encourages hepatic cancer cells to undergo apoptosis.

Additionally, sorafenib promotes mitophagy, which is regulated by PINK1/Parkin, which leads to the death of liver cancer cells. In order to start mitophagy, it stabilises PINK1 on the mitochondrial outer membrane and attracts Parkin to damaged mitochondria.

Mito-CP and Mito-Metformin, two mitochondria-targeted medications, liberate ULK1 from mTOR-mediated regulation, lower mitochondrial membrane potential, and suppress the growth of colorectal cancer cells by mitophagy.

Reference: Chao J, et al. (2017) Role of Kallistatin Treatment in Aging and Cancer by Modulating miR-34a and miR-21 Expression. Oxid Med Cell Longev 2017, 5025610.

New Drug Approvals…

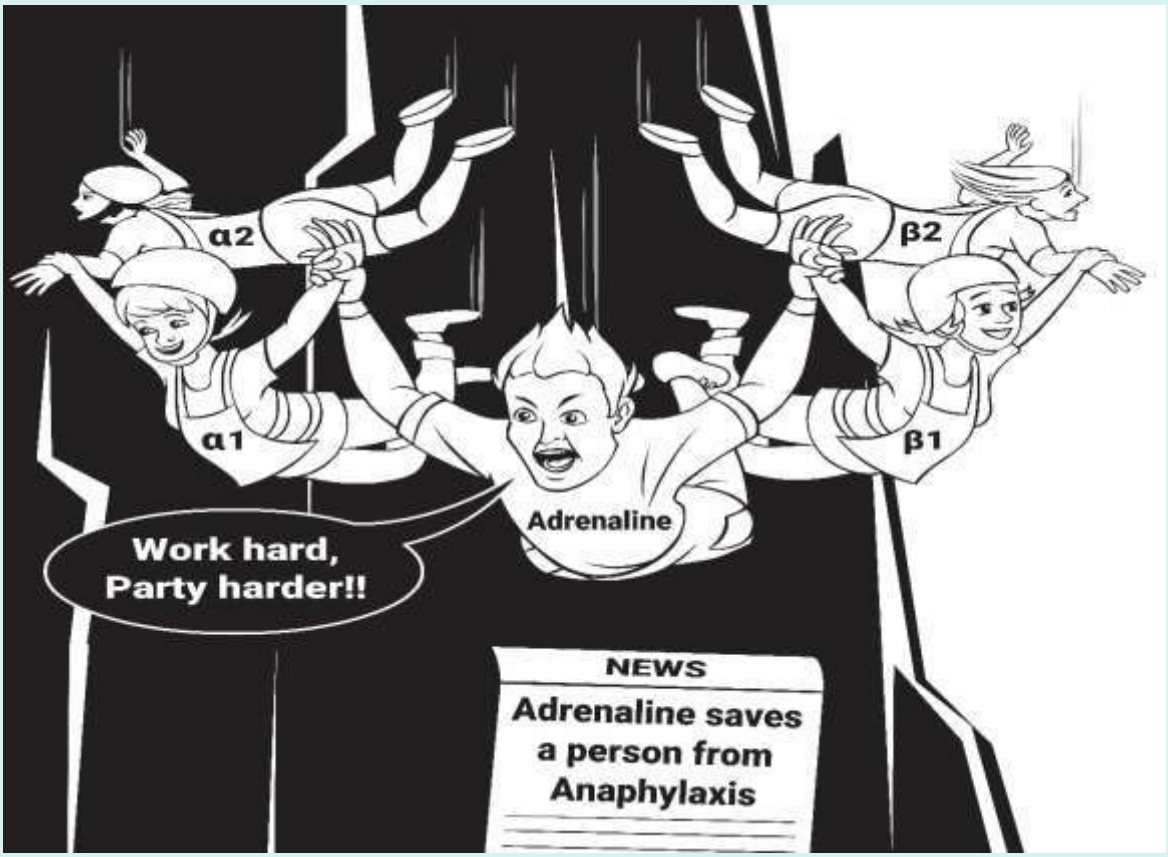
Teplizumab is a CD3-directed antibody indicated to delay the onset of Stage 3 type 1 diabetes (T1D). The recommended dose is 65 mcg/m^2 – 1030 mcg/m^2 intravenous infusion daily for 14 days.

Lenacapavir is a long-acting HIV-1 capsid inhibitor approved for the treatment of multi-drug resistant (MDR) HIV-1 infection in combination with other anti-retroviral drugs. The recommended dose is 927 mg SC injection along with 600 mg oral dose on day one and 600 mg orally on day 2 followed by maintenance dose every 6 month.

Olutasidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor approved for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation. The recommended dose is 150 mg orally twice a day.

Tremelimumab is a human IgG2 monoclonal antibody directed against the T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4) approved for the treatment of unresectable hepatocellular carcinoma. The recommended dose is 300 mg IV single dose along with durvalumab.

Cartoon Corner…



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

Allergic rhinitis (AR) is an IgE-mediated chronic inflammation of the nasal mucosa triggered by exposure to airborne allergens and affects approximately one-sixth of the world's population. Genetics, environment, and family susceptibility all play a role in the aetiology. It can be seasonal or perennial, and the typical symptoms include nasal itching and sneezing, rhinorrhoea, nasal congestion, and eyelid edema. The disease reduces the quality of life by affecting sleep, attention, study, work, and leisure activities and may be associated with allergic conjunctivitis and asthma. The pharmacotherapy of AR includes

Oral antihistamines (AH)

For decades, A.H.s has been the most utilized class of medications for treating AR. AH target H1 receptors (H1 antihistamines) at binding sites that differ from histamine. There are two generations of oral antihistamines (first and newer-generation AHs), with newer-generation AHs being an improvement of their predecessor. First-generation AHs, such as diphenhydramine, are associated with adverse central nervous system side effects, like sedation and mental impairment in addition they also have anticholinergic side effects, such as dry mouth and dry mouth eyes, urinary retention, and constipation. Newer generation H1-antihistamines like cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, ebastine, and the latest bilastine have shown to be safer than first-generation agents and are recommended as the first-line for the treatment of allergic rhinitis.

Intranasal antihistamines (INAH)

Intranasal antihistamines (INAHs) deliver the directly to the nasal mucosa, thereby enhancing the local anti-allergic and anti-inflammatory effects and minimize the systemic exposure to therapy. Examples of INAH are olopatadine, azelastine, and levocabastine out of which azelastine is the most well-studied and used INAH. They improve all the symptoms like sneezing, rhinorrhoea, nasal congestion, and nasal itching with faster onset and similar efficacy to intranasal steroids.

Intranasal corticosteroids (INC)

INCs are superior to AHs in improving total nasal symptoms score and in relieving symptoms like nasal obstruction, rhinorrhoea, itching, sneezing, and improving the quality of life. The allergic rhinitis and its impact on asthma (ARIA) guidelines recommend INCS as the best option for both mild and moderate to severe AR in both children and adults. INCS inhibit the early and late-phase allergic in A.R. by preventing the recruitment of immune cells and the release of inflammatory mediators from cells involved in the pathophysiology of AR. Examples of INCs are beclomethasone, Fluticasone, Mometasone, Budesonide, etc. All of them are efficient in controlling symptoms of AR, such as nasal congestion and itching, rhinorrhoea, and sneezing but vary in their efficacy and side effects.

The systemic side effects like growth suppression, and ocular effects, are minimal as compared to oral steroids due to reduced dose and lower bioavailability. Local side effects are epistaxis, nasal drying, burning, and

stinging sensations. Commonly used INCS are Fluticasone propionate, Fluticasone furoate, and Mometasone furoate. In addition, combination of azelastine with fluticasone is also available and is useful in patients with higher ocular symptoms of allergic rhinitis, those not responding to INCS alone, and those with severe allergic rhinitis symptoms.

Leukotriene receptor antagonists (LTRA)

Leukotrienes especially LTC4 and LTD4 are responsible for majority of AR symptoms like nasal congestion, mucus production and inflammatory cell recruitment. LTRAs block the activity of cysteinyl leukotrienes (CysLTs), thereby blocking the production of these leukotrienes. Examples include montelukast, zafirlukast, etc.

Compared with a placebo, montelukast improves patients' disease-specific quality of life with persistent AR. A caution in their use has been the neuropsychiatric side effects with montelukast especially suicidal thoughts and therefore it is discouraged its use as first-line therapy for mild AR. They are not recommended for acute exacerbations but are recommended for prophylaxis and chronic treatment.

Probiotics

The World Health Organization (WHO) defines probiotics as live microorganisms that, when administered appropriately, can benefit the host's health. The best probiotics are human-derived, safe, and free from carriers that can create antibiotic resistance and pathogenic or virulent factors. At the same time, probiotics significantly benefit the body by fighting pathogens and stimulating the immune system.

There have been a large number of clinical studies on probiotics in the treatment of AR, these studies have found improved symptoms, lower eosinophil counts in both nasal as well as peripheral blood and improved quality of life in patients. Some probiotics that have been found to be useful are a mixture of bifidobacteria (B. longum BB536, B. banfanits M-63, B. breve M-16V), probiotic mixture (B. longum IM55, and Lactobacillus plantarum IM76) mixture containing two Bifidobacterium strains (Lactobacillus BB12 DSM 15954 and Enterococcus faecium L3 LMG P-27496), a mixture of (Lactobacillus paracasei GM-080TM, Lactobacillus acidophilus, Lactobacillus fermentum GM-090TM, Lactobacillus paracasei GMNL-133), Clostridium butyric, etc

The mechanism of probiotic treatment of allergic rhinitis is by reducing serum pro-inflammatory factors, increasing the number of immune cells, regulating Th1 and Th2 balance, increasing t regulatory cells, and inhibiting Th17. In addition, probiotics increase the level of beneficial bacteria to regulate the stability of the gut microbiota, restoring the intestinal mucosal barrier. The pharmacotherapy of patients suffering from allergic rhinitis needs to be individualized and tailored according to the symptoms, tolerance and associated side effects of the medications

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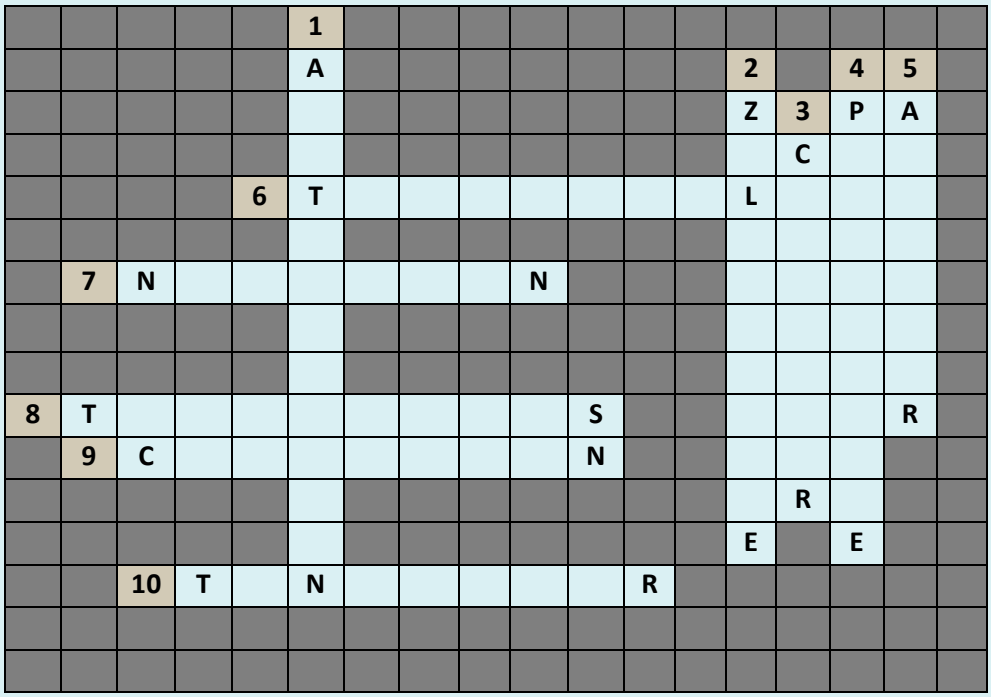

Downward	Across
1. NSAID with good antipyretic but with poor anti-inflammatory actions (*13*) 2. Third generation Bisphosphonate with high potency (*11*) 3. Antiviral drug effective against CMV infection (*9*) 4. Antimicrobial agent effective against *Pneumocystis jiroveci* pneumonia (*11*) 5. Antiviral drug used for the treatment of HBV infection (*8*)	6. Broad spectrum antimicrobial agent (*12*) 7. Aminoglycoside used as topical preparation (*8)* 8. Immunosuppressant which is a Calcineurin inhibitor *(10)* 9. Anticancerous platinum compound *(9)* 10. Antiviral drug effective against HIV infection *(9)*

Click on the link below to access the quiz:
https://docs.google.com/forms/d/e/1FAIpQLSehdy2N6p1R7KodFwoXM2ARTsSWGsBCPD371bG3qJQsHUozzQ/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 [18th Issue]
Dr. Vishal and Dr. Pranav

Answer to the previous Crossword Puzzle (18th Issue) is given in the link below:
https://docs.google.com/forms/d/e/1FAIpQLSeSQrjBLCxFJ0t7gpJzT5EHcDCgUXrjP_fYq3Ag4oNnYhbQ7Q/viewform?vc=0&c=0&w=1&flr=0