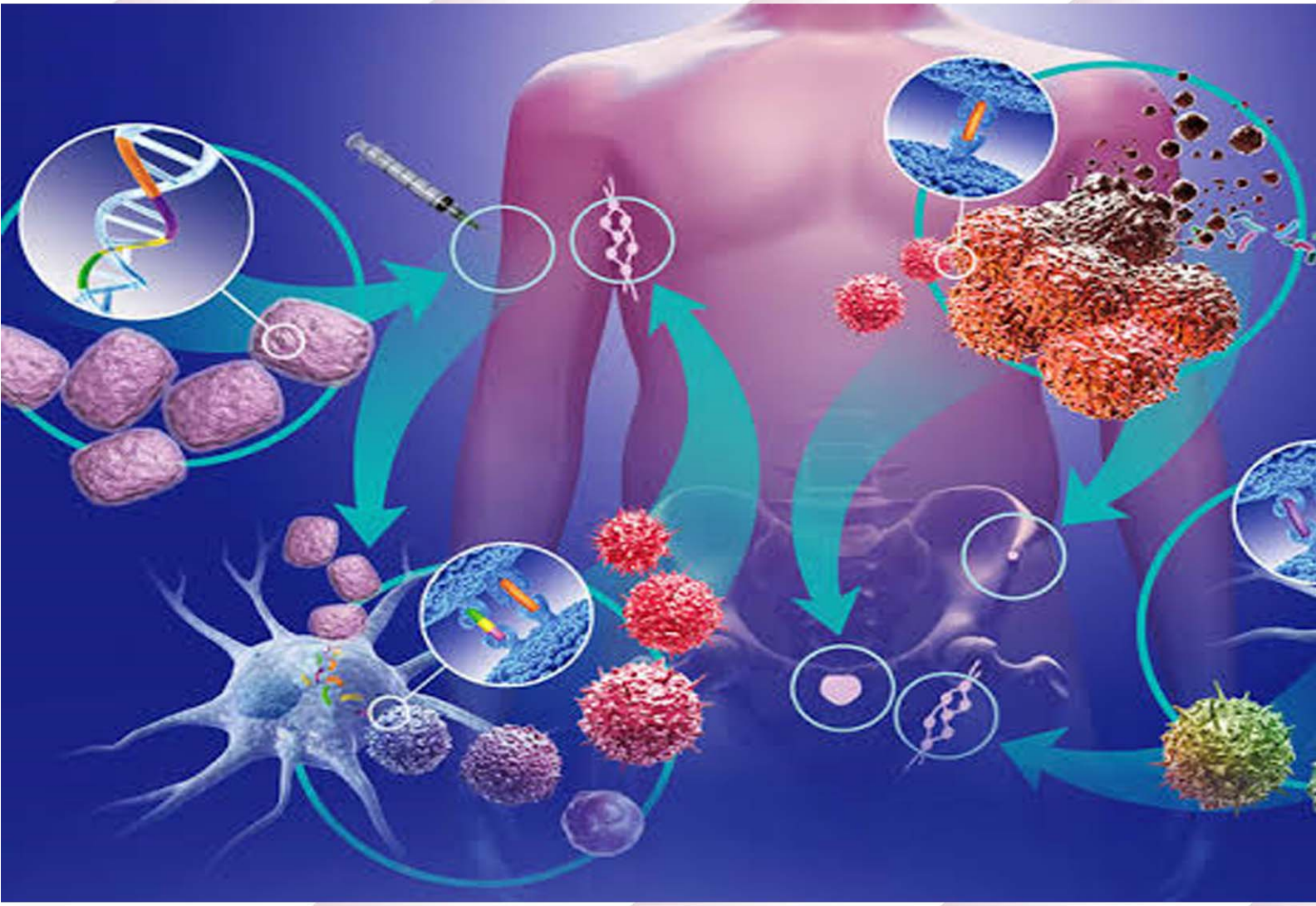
NEMPSule

THE E-BULLETIN OF NEMPS

North Eastern Medical Pharmacological Society



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NEMPS
(NORTH EASTERN MEDICAL PHARMACOLOGICAL SOCIETY)

Design by **Ashish Debnath** on behalf of **Creative Design,** Dibrugarh, Assam

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Obituary...

Late Dr. Dhriti Kumar Brahma, Additional Professor, Department of Pharmacology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong, breathed his last on the 24th of December 2024 at around 4 am in the morning. A man known for his fun-loving and amiable personality, Dr. Dhriti Brahma was born at Tamulpur, Bodoland Territorial Autonomous District (BTAD), Assam, on 28th of July 1968. He completed his Matriculation and his Higher Secondary from Jhargaon High School and Tamulpur H.S. School respectively. He joined Gauhati Medical College and Hospital as a medical student in the year 1989 and also completed his post graduation (MD degree) in Pharmacology from the same institute. His professional career started when he joined Assam Medical College and Hospital, Dibrugarh as a Demonstrator in the year 2001. In the year 2009 , he joined NEIGRIHMS as Assistant Professor in the Department of Pharmacology. Ever since then there was no turning back for Dhritida; as he gradually climbed the ladder to attain the rank of Additional Professor in the Department of Pharmacology of NEIGRIHMS in 2016. An extremely hardworking and diligent person, late Dr. Dhriti Brahma da played a pivotal role in setting up and uplifting the Department of Pharmacology, NEIGRIHMS to it's present prestigious position. He was an apt teacher, researcher and academician and had several research projects and journal publications to his credit. He was also the 1st and founder Organizing Secretary of NEMPSCON 2022, the 1st national conference of NEMPS held in NEIGRIHMS, Shillong. His sudden demise has created an irreplaceable void amongst Pharmacologists both at the National and Regional levels. Dr. Dhriti Brahma da is survived by his wife Dr. Anju R Marak and a daughter and a host of relatives and friends.

As we bid adieu to Dhritida with tearful eyes, our earnest prayers to the Almighty to grant him eternal peace in Paradise.

Dr. Gayatri Sarma
Editor, NEMPSule
On behalf of the entire NEMPS family.
Heartfelt gratitude to
Dr. Reuben, Senior Resident ,
Department of Pharmacology, NEIGRIHMS,
for providing necessary information.

From The Desk of The Editor

"Years's end is neither an end nor a beginning but a going on with all the wisdom that experience can instil in us." – Hal Borland (American writer, journalist and naturalist)

Seasons greetings and warm wishes on New Year! As another year unfurls, liberating new hopes, new aspirations, new opportunities, the North Eastern Medical Pharmacological Society (NEMPS) presents to you the second volume of its official e-bulletin, the NEMPSule.

We are all aware that the NEMPSule is a biannual e-bulletin that attempts to encompass all aspects of Pharmacology and Therapeutics including regulatory updates and recent guidelines , medical education, adverse drug reactions etc. The 1st two issues of the NEMPSule have received warm acceptance and appreciation and we, the members of the Editorial Board, are immensely grateful for the same.

This issue of NEMPSule brings forth an array of interesting articles by several young, dynamic pharmacologists which will surely hold you in awe from the first till the last pages of the e-bulletin. We have an article on the ethical concerns of stem cell therapy which highlights the scope of stem cell therapy and also it's challenges & future directions. There is an article on MDM2 (Murine Double Minute 2) inhibitors for cancer therapy which have the potential to add a totally new dimension to cancer treatment and also an article elaborating the first gene therapy for treatment of aromatic l-amino acid decarboxylase deficiency. Another article throws light on Nafithromycin, India's first indeginous antibiotic for drug-resistant bacterial infections.

An article on Pharmacovigilance suggests the different course modules and practical sessions that need to be introduced in the MD Pharmacology curriculum for enhancing the career prospects of the newly passed out MD Pharmacologists in the field of Pharmacovigilance. Another article stresses on the moral obligations of reporting adverse drug reactions.

We have an article highlighting the importance of Clinical Pharmacologists in hospitals and health care centres. Another article states the importance of standardised evaluation techniques for excipients to prevent the occurrence of adverse events related to excipients. Lastly, we have an interesting and unique article on the techniques of starting an entrepreneurial startup in India.

I take this opportunity to express my deepest gratitude to all the contributors from the bottom of my heart for taking out time off their busy schedule to pen down a few lines for the e-Bulletin . I also thank the President NEMPS, Dr. Babul Bezbaruah Sir and NEMPS General Secretary, Dr. Swapnanil Gohain for their persistant support and advice. I thank all members of the scientific committee Dr. Meghali Chaliha, Dr. Chinmoyee Deori and Dr. Anju L.Saikia, for having offered their valuable time to review the articles.

Thanks and regards,

Dr. Gayatri Sarma
Associate Professor of Pharmacology,
Assam Medical College and Hospital,Dibrugarh

Dr Dhriti Brahma – A Tribute

Dr Dhriti Kr Brahma is known to many because of his warmth and have always been a great host. We knew him to be charming and happy in every situation. He is one batch junior in MBBS days of Guwahati Medical College but joined MD together. We used to study together and Hostel 4 used to be our rendezvous. Dr Rituparna Phukan Roy was the master of the department. Pharmacology was not our first choice and by default we joined the subject never to regret till now. We joined as demonstrators in the department and in the next promotion Dhriti joined Assam medical College Dibrugarh. NEIGRIHMS Shillong was about to start and he joined the new institute. NEIGRIHMS Shillong was really challenging and Dhriti established the department to it's present status. He single handedly managed many activities of the institute and people all over knew him. His slides were very popular. Pharmacovigilance was his special forte. We organised many conferences together. He was a good manager and organiser. His classes are favourite among the students even in AIIMS Guwahati. He was fond of football and photography. Facebook posts by him were a delight. He used to make reels and share. He was gem of a person and suddenly when he was expected to join us in GMCH for the NEMPSCON 2024, he left us prematurely and leaving us all shocked and sad. He left his wife Dr Anju and their only daughter Piki.

It is great loss to our fraternity and we are going to miss him always.

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Ethical concerns in Stem Cell Therapy

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Stem Cells are undifferentiated cells that have the potential to develop into various specialized cell types.[1] They are the building blocks of all tissues and organs in the human body. Stem cell therapy is a medical approach that utilizes these cells to treat diseases and injuries.[2]

Types of Stem Cells:

- Embryonic stem cells: Derived from embryos, they are pluripotent, meaning they can differentiate into any cell type in the body.
- Adult stem cells: Found in various tissues throughout the body, they are multipotent, meaning they can differentiate into a limited number of cell types.
- Induced pluripotent stem cells (iPSCs): Created by reprogramming adult cells, they have similar properties to embryonic stem cells.[3]

How Stem Cell Therapy Works:

1. **Harvesting:** Stem cells can be obtained from various sources, including embryos, adult tissues (like bone marrow or fat), and induced pluripotent stem cells (iPSCs), which are created by reprogramming specialized cells.
2. **Culturing:** The harvested stem cells are cultivated in a laboratory environment, where they can be multiplied and differentiated into specific cell types.
3. **Injection or Transplantation:** The differentiated cells are then injected or transplanted into the affected area of the body.
4. **Regeneration:** The transplanted cells interact with the surrounding tissues, promoting healing and regeneration.

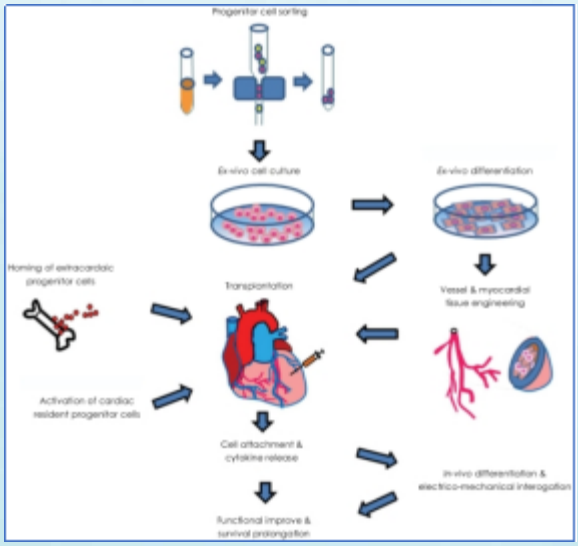

Figure 1: Schematic flow-diagram of stem cell therapy in cardiac disease

Potential Applications of Stem Cell Therapy:

Stem cell therapy is a promising field of medicine that leverages the unique ability of stem

cells to differentiate into various cell types and regenerate damaged tissues. These cells can potentially treat a wide range of diseases and injuries, including:

- **Neurological diseases:** Parkinson's disease, Alzheimer's disease, spinal cord injuries, and stroke.
- **Cardiovascular diseases:** Heart failure, heart attacks, and arrhythmias.
- **Autoimmune diseases:** Type 1 diabetes, multiple sclerosis, and rheumatoid arthritis.
- **Orthopaedic conditions:** Osteoarthritis, cartilage damage, and bone fractures.
- **Burns and wounds:** Severe burns and non-healing wounds.
- **Cancer:** Certain types of cancer, such as leukaemia and lymphoma.

Challenges and Future Directions:

Despite its promising potential, stem cell therapy faces several challenges, including ethical concerns, technical limitations, and the need for further research. However, ongoing advancements in this field offer hope for the development of effective treatments for a wide range of diseases. The future of stem cell therapy is bright, with ongoing research and advancements leading to exciting possibilities. Some key areas of development include:

- **Improved cell culture techniques:** More efficient methods for culturing and differentiating stem cells will make treatments more accessible and affordable.
- **Enhanced targeting:** Researchers are working on ways to precisely target stem cells to specific tissues and organs, reducing the risk of unwanted side effects.
- **Combination therapies:** Stem cell therapy may be combined with other treatments, such as gene therapy or drug therapy, to achieve better results.
- **Ethical considerations:** Addressing ethical concerns related to stem cell research, particularly the use of embryonic stem cells, will be crucial for the field's progress.

Ethical Considerations in Stem Cell Therapy

Stem cell research has been a subject of significant ethical debate,[4,5] primarily due to the use of embryonic stem cells. Here are some of the key ethical considerations:

1. **Embryo Destruction:** The most contentious issue is the destruction of embryos to obtain embryonic stem cells. The Moral Status of the Embryo comes into question.
   - **Personhood Debate:** A central question is when human life begins. Some argue that life begins at conception, making the destruction of an embryo morally equivalent to killing a person. Proponents argue that embryos are not yet persons, while opponents contend that they represent potential human life.
   - **Potential for Human Life:** Others argue that an early-stage embryo, while possessing the potential for human life, is not yet a person with moral rights.

2. **Potential for Misuse:** There are concerns about the potential misuse of stem cell technology, such as creating human embryos for research or therapeutic purposes. This raises ethical questions about the boundaries of scientific research and the implications for human dignity. The Risk of Misuse is a potential threat which can't be ignored.
   - **Cloning and Genetic Engineering:** There are concerns about the potential for misuse of stem cell technology, such as creating human clones or genetically engineered humans.
   - **Unintended Consequences:** Some worry about the long-term consequences of manipulating human biology, including unforeseen side effects and societal implications.

3. **Therapeutic Potential vs. Ethical Concerns:** Balancing the potential therapeutic benefits of stem cell research with the ethical concerns surrounding embryo destruction is a complex challenge. The debate on use of Human Embryos for Research has been going on for several decades, since stem cell therapy concept was envisaged.
    - **Sacrifice for the Greater Good:** Proponents of embryonic stem cell research argue that the potential benefits to humanity, such as cures for debilitating diseases, outweigh the ethical concerns. Others believe that alternative sources of stem cells, such as induced pluripotent stem cells (iPSCs), should be prioritized.
    - **Respect for Human Life:** Opponents contend that using human embryos for research is inherently wrong, regardless of the potential benefits.

4. **Regulation and Oversight:** Ensuring proper regulation and oversight of stem cell research is essential to prevent unethical practices and protect the rights of patients. Establishing clear guidelines and ethical frameworks is crucial for the responsible development and use of this technology.
5. **Informed Consent:** Obtaining informed consent from patients undergoing stem cell treatments is vital. This involves providing clear information about the potential risks, benefits, and uncertainties associated with the procedure.
6. **Equity and Access:** Ensuring equitable access to stem cell therapies is a major challenge, especially in developing countries. Efforts should be made to ensure that these treatments are available to all patients who could benefit, regardless of their socioeconomic status or geographic location. The high cost of developing and administering stem cell treatments may limit their availability to a privileged few.

It's important to note that the ethical landscape of stem cell research is constantly evolving. As scientific knowledge advances, so too do the ethical questions. Ongoing discussions and debates are crucial to ensure that stem cell research is conducted responsibly and ethically.

While stem cell therapy holds great promise, it is important to note that it is still a relatively new field, and more research is needed to fully understand its potential and limitations. However, with continued advancements, stem cell therapy could revolutionize medicine and provide hope for patients with previously incurable diseases.

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New Perspectives: MDM2 Inhibitors for Cancer Therapy

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Introduction & Background

Since the report of the first MDM2 (murine double minute 2) inhibitor more than 30 years ago, various approaches to inhibit MDM2 have been attempted, with hundreds of small-molecule inhibitors evaluated in pre-clinical studies and numerous molecules tested in clinical trials. Although many MDM2 inhibitors and degraders have been evaluated in clinical trials, there is currently no Food and Drug Administration (FDA)-approved MDM2 inhibitor on the market. Nevertheless, there are several current clinical trials of promising agents that may overcome the past failures, including agents granted FDA orphan drug or fast-track status.

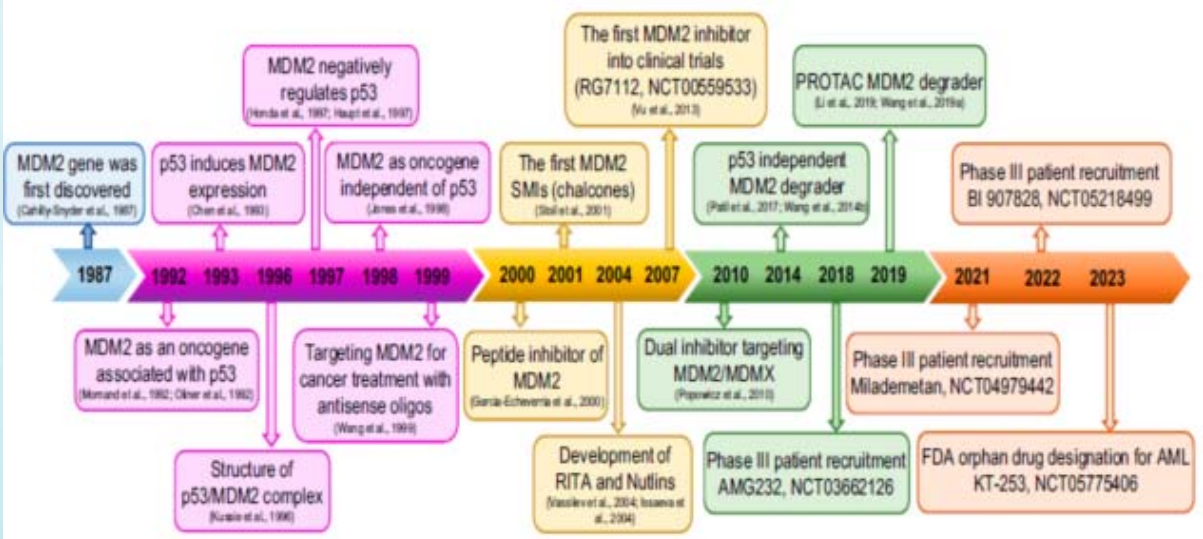

Fig. 1. Simplified timeline of the milestone discoveries of MDM2 and its inhibitors.

The mouse double minute 2 (MDM2) oncogene was first identified by researchers investigating the DNA sequences that were associated with double minutes (DM). *Mdm2* was first identified from the murine tumorigenic cell line 3T3-DM. This cell line shows an amplified genomic region in the form of double minute chromosomes, and *Mdm2* (murine double minute 2) was found

to be the transforming gene contained within this amplicon. Double minute chromosomes (DMs) are small, circular fragments of DNA that are found in extrachromosomal space in human tumors. They lack centromeres and telomeres, replicate autonomously, and contain amplified oncogenes and drug resistance genes. They are highly lethal due to the combination of oncogenes and amplification and are found in many human tumors, including breast, lung, ovary, colon, and neuroblastoma. Mechanistically, MDM2 contributes to cellular transformation through interaction with p53 and inhibition of its transcriptional activity via its E3 ligase activity that directly ubiquitinates and targets the p53 protein for proteosomal degradation. Dysregulated MDM2 functions as an oncogenic protein that regulates proliferation and apoptosis by altering p53-mediated death and survival signaling. Besides, MDM2 functionally regulates metastasis and the epithelial- mesenchymal transition (EMT) and is associated with genomic instability, a hallmark of carcinogenesis. MDM2 is now known to exert a wide variety of effects, many via p53- independent mechanisms, and contributes to other human diseases, such as chronic inflammation, neurologic conditions, and autoimmune disorders, via alterations in inflammation or cell signaling. Clinical studies have also provided evidence that there is overexpression and amplification of MDM2 in different cancer types, and overexpression of MDM2 is associated with a poor prognosis for all of these cancers. These observations suggest that targeting MDM2 represents a potentially effective approach for preventing or treating various pathologic conditions but with particular utility for cancer.

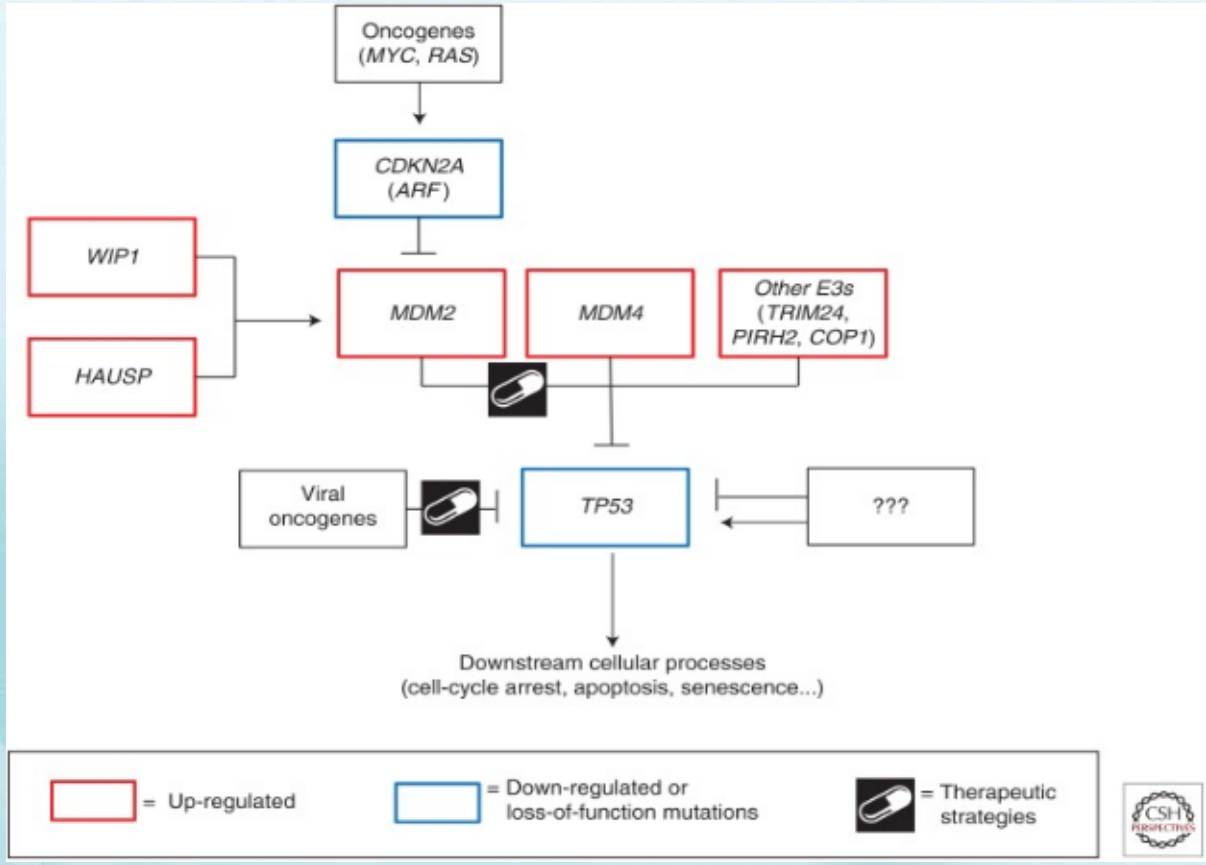

Fig. 2. **The p53 pathway**

A few years after its discovery targeting MDM2 was proposed as a new approach to cancer therapy. Those initial studies demonstrated that inhibiting MDM2 not only led to anticancer activity in vitro and in vivo but also sensitized cancer cells to DNA-damaging agents. During the next 20-plus years, various strategies were validated to target MDM2. Most of these were intended to block the interaction between MDM2 and p53 to reactivate p53 in tumors harboring wild-type p53 (p53WT). However, following the discovery that MDM2 has p53-independent functions, small-molecule inhibitors, protein destabilizers/degradation enhancers, and proteolysis-targeting chimeras (PROTACs) have been explored to directly target MDM2, with promising data obtained for several different molecules. Unfortunately, phase I trials with most of the small-molecule MDM2 inhibitors have demonstrated limited effectiveness and notable thrombocytopenia as a dose-limiting toxicity associated with persistent MDM2 inhibition. Nevertheless, several small-molecule MDM2 inhibitors are currently undergoing phase II/III clinical trials for the treatment of p53WT tumors.

Strategies for Targeting MDM2

Over the past several decades, many strategies have been developed to target MDM2, including the use of peptides, antisense oligonucleotides, and a number of small molecules with different core structures.

A. Blocking the MDM2-p53 Interaction

Strategies intended to block the binding between p53 and MDM2 were the first attempts at MDM2 inhibition (Fig. 1). These early inhibitors had limited efficacy and also often had serious side effects in clinical trials.

1. **Peptide-Based MDM2 Inhibitors**: p53-derived peptides were used to block the interaction between MDM2 and p53. These peptides were modified to mimic the a-helix of p53, resulting in more potent peptide inhibitors, such as the retroinverso p53 peptide and b-hairpin peptide. However, the binding of these peptides to MDM2 was low due to the conformational differences between the peptides and the whole protein. Cyclic-helical peptides have emerged as a potential alternative to stabilize targets based on hydrocarbon interactions. Examples are the a-helix cyclic peptide ATSP-7041 and its modified version ALRN-6924, both of which are selective dual inhibitor of MDM2 and murine double minute X (MDMX; also named MDM4, another inhibitory protein that leads to the degradation of p53) that effectively activated the p53 pathway in tumors in vitro and in vivo.
2. **Small-Molecule Inhibitors Blocking the MDM2-p53 Interaction**:

Single-ring core derivatives: The **Nutlins** (Nutlin-1, -2, and -3) were the first potent and selective nonpeptidic small-molecule MDM2 inhibitors. Nutlins stabilize p53 and activate the p53 pathway in human cancer cells with p53WT but not in cells with mutant p53, activating p53 target genes, cell-cycle arrest, and apoptosis. Nutlin-3a is a Nutlin-3 enantiomer and is the most biologically active among the Nutlin analogs that have been reported to date. Nutlin-3a was optimized to yield the 2,4,5-triaryl imidazoline analog **RG7112** (RO5045337, Roche). This derivative has seen extensive application in both preclinical and clinical studies. Others include MDM2 inhibitors with spiro-oxindole core structures like **MI-77301** (SAR405838) and **APG-115** (AA-115, alrizomadlin). APG-115 has already been granted fast-track designation by the US FDA for the reatment of relapsed or refractory (R/R) unresectable or metastatic melanoma and orphan drug designations for gastric cancer, acute myeloid leukemia, soft tissue sarcoma, and retinoblastoma as well as stage IIB–IV melanoma and neuroblastoma. It is currently being investigated alone or in combination in ongoing phase I and II

studies. **Milademetan** (DS-3032, DS-3032b, Rain-32) is another potent spiro-oxindole–based inhibitor of the MDM2-p53 interaction licensed by Rain Therapeutics from Daiichi Sankyo. It showed antitumor efficacy and has been tested in clinical trials.

Bicyclic and multicyclic core derivatives: Novartis designed and developed CGM097 (NVP-CGM097) and then subsequently developed DM201 (NVP- HDM201, siremadlin) to inhibit the interaction between MDM2 and p53, representing a new class of pyrrolido-noimidazole-based MDM2 inhibitors. Boehringer Ingelheim developed BI 0252 and BI 907828 (brigimadlin), a new class of spirooxindole MDM2 inhibitor. Subsequently, Merck identified MK-4688, a more drug-like and low molecular weight novel purine carboxylic acid–derived MDM2 inhibitor. Imidazo-indoles are another class of potent inhibitors with a multicyclic core that blocks the interaction between MDM2 and p53. Several compounds, including WK23 and WK298, were developed based on the optimization of these imidazo-indoles. The first isoindolinone-based inhibitor (NU8231) was developed using computational methods.

Other core structures: A National Cancer Institute anticancer drug screen identified the small molecule 2,5-bis(5-hydroxymethyl-2-thienyl) furan, later named RITA, which was originally reported to act via a p53 dependent mechanism. Subsequent research suggests that it has biologic activity even in the absence of p53. Further research is essential to understand RITA's full range of interactions and to determine its optimal use in treating cancers. Chalcone derivatives, that were initially designed to inhibit tumor growth, have potential to re-activate p53 and has been evaluated based on their putative function as a small molecule targeting MDM2.

B. Small Molecules Directly Targeting MDM2

Direct negative regulation of MDM2 could be an alternative way to not only activate p53 but also to inhibit other functions of MDM2 by decreasing its expression, inhibiting its enzymatic activity, and/or inducing the degradation of the MDM2 protein. Makaluvamine analogs were initially designed to inhibit topoisomerase II. MA242, a recently developed makaluvamine analog, has shown highly selective and potent inhibition of MDM2 by inducing its autodegradation. SP141 is a pyrido[3,4-b] indole-class (b-carbolines) inhibitor, which not only blocks the interaction between MDM2 and p53 but also directly induces the degradation of MDM2. A b-carboline–based chalcone, CPI-7c, has been demonstrated to induce the degradation of MDM2 . This observation supported the possibility that b-carboline–based chalcones can be used as degradation inducers for MDM2, similar to SP141. In line with the findings for other potent MDM2 degraders, the anticancer drug SQ0814061 has been shown to downregulate MDM2. Together, these studies suggest that inducing the degradation of MDM2 may represent an effective strategy and may be more beneficial than just blocking the interaction between p53 and MDM2.

C. Proteolysis-Targeting Chimeras (PROTACs)

PROTACs were developed using chimeric small molecules that guide proteins for ubiquitination-mediated degradation. More than 20 years after their initial development, PROTACs have been widely applied preclinically to downregulate differenttargets for cancer treatment. Some PROTACs are currently being evaluated in clinical trials.

The Wang laboratory at the University of Michigan designed and developed the first PROTAC MDM2 degraders, MD-222 and MD-224. MD-222 and MD-224 induced complete degradation of the

MDM2 protein, accumulation of p53 protein, and induced apoptosis in p53WT human leukemia cells. The research group further optimized MD-224, resulting in the development of AA-265 which is more potent. Currently, it is undergoing advanced preclinical evaluation in preparation for progression to clinical trials. They further modified MD-222 resulting in the identification of MG-277 which only moderately degrades MDM2 and does not activate p53 in cancer cells. However, it effectively inhibits the growth of cancer cells regardless of their p53 status.

The Tang group at the University of Wisconsin-Madison made significant advancements in the field of PROTAC MDM2 degraders with the discovery of WB156 and WB214.

KT-253 is also a heterobifunctional MDM2 degrader developed by Kymera Therapeutics that has shown remarkable efficacy, with greater than 200-fold improvements in in vitro cell growth inhibition compared with small-molecule MDM2 inhibitors. KT-253 has received the FDA orphan drug designation for the treatment of AML and is currently being investigated in patients with R/R high-grade myeloid malignancies, ALL, R/R lymphoma, and R/R solid tumors in a phase I trial.

Others include the development of a PROTAC von Hippel-Lindau (VHL)-recruiting MDM2 degrader, MS3227, for p53WT leukemia, and YX-02–030- another MDM2-targeted PROTAC that degrades MDM2. Currently, most MDM2-targeting PROTACs, with KT-253 as an exception, are in preclinical testing. It is anticipated that more PROTACs targeting MDM2 will advance to clinical trials.

D. Dual Inhibitors

These agents target both MDM2 and MDMX (or MDM4)- both downregulators of p53- and more effectively activate p53. These include MEL23 and MEL24 (small-molecule MDM2-MDMX E3 ligase activity inhibitors), DIMP53-1 (a small molecule inhibitor), Indolyl hydantoins (RO-2443 and RO5963), and the ˜-helical peptide inhibitors (ATSP-7041 and ALRN-6924).

Conclusion & Perspectives

Although the previous and current inhibitors targeting MDM2 have shown promising results in preclinical and some clinical trials, there are currently no approved MDM2 inhibitors marketed for any indication. It should be noted that most of the MDM2 inhibitors investigated in clinical trials were designed to block the interaction between MDM2 and p53, which may actually increase the level of MDM2 and even increase its oncogenic activity. This may at least partially explain the failure of such MDM2 inhibitors in clinical trials. In contrast, directly inhibiting MDM2 using agents such as MDM2 degradation inducers or PROTACs would lead to more effective treatment with a better safety profile. More detailed analyses of patient gene and protein expression profiles are needed to individualize treatments, allowing the patients to achieve a more robust and durable response.

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■■■

FDA Approves First Gene Therapy for Treatment of Aromatic L-amino Acid Decarboxylase Deficiency

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The U.S. Food and Drug Administration (FDA) has approved Kebilidi (Eladocagene exuparvovec-tneq), a gene therapy for aromatic L-amino acid decarboxylase (AADC) deficiency in adults and children. This one-time, adeno-associated virus vector-based treatment targets the ultra-rare and fatal genetic disorder, which causes severe physical, mental, and behavioural disabilities from infancy. This treatment, approved for both adult and paediatric patients, marks the first FDA-approved gene therapy for the condition and the first ever gene therapy administered directly into the brain. It has been already approved in Europe under the brand name Upstaza in 2022 for patients 18 months and older. It has also been approved in Israel, Brazil, and Taiwan. The FDA delayed approval due to additional data requests but accepted drug application in May.

Kebilidi, the first FDA-approved brain-delivered gene therapy for AADC deficiency, offers hope for patients with this rare disorder.

The global prevalence of AADC deficiency is estimated at 1 in 30,000 to 90,000 newborns. It is more common in East and South Asia, especially in Taiwan. Aromatic L-amino acid decarboxylase deficiency (AADCD) is a rare, autosomal recessive, neurometabolic disorder characterized by impaired synthesis of the catecholamines (dopamine, epinephrine, and norepinephrine) and serotonin. AADCD typically presents in infancy with hypotonia, oculogyric crises, and developmental delay. Mood and sleep disturbance, autonomic dysfunction, and intellectual disability are additional disease features [1,2].

Most patients with AADCD experienced limited benefit from the available medical therapies [3]. Gene therapy was under investigation using two different stereotactic neurosurgical approaches to deliver gene vector either to the putamen or the midbrain (ClinicalTrials.gov Identifier: NCT02852213). New methods were already implemented for diagnosis in some newborn screening programs and these prospective novel therapeutic opportunities, an improved knowledge of the natural history of the disease, modified by available medical treatments, is critical [4].

Due to the rarity of AADCD, there is inadequate international clinical expertise for evidence-based management. Treatment response is often disappointing and treatment strategies vary between single expert centres [5]. Some patients are treated with a variety of different drugs, while others only receive one or two different drug classes [6]. A small subset of patients shows a good response to L-Dopa [7] or dopamine agonists [8], but often patients show no or poor response [6]. For most patients, treatment response cannot be predicted. To improve care for patients with neurotransmitter related disorders, including AADCD, the International Working Group on Neurotransmitter Related Disorders (iNTD) was founded in 2013 [9]. Today, iNTD is a growing worldwide network of 38 neurometabolic centres from 24 countries. In addition to keep patient registry [10], one of its goals is to develop consensus care guidelines for neurotransmitter related disorders by pooling all published evidence and experience of leading expert centres. This guideline on diagnosis and treatment of AADCD is the first guideline developed by iNTD.

Kebilidi: Replacing the Mutated Dopa Decarboxylase (DDC) Gene with a Functional Version via Gene Therapy

A mutated DDC gene is the primary cause of AADCDwhere mutations in the DDC gene lead to decreased activity of the AADC enzyme, resulting in impaired production of important neurotransmitters like dopamine and serotonin.

Kebilidi is a gene replacement therapy that replaces the mutated DDC gene with a functional version, delivered via an adeno-associated virus. Administered in a single surgical session, the therapy involves four infusions into the putamen, a brain region involved in motor control and learning. The gene vector is injected using magnetic resonance-guided convection-enhanced delivery (CED), ensuring stable and effective gene transfer. The therapy restores the deficient enzyme, increasing dopamine production in the brain.

The FDA approved Kebilidi based on an open-label study of 13 AADC patients aged 16 months to 10 years. All the patients had no gross motor function. These patients were compared to untreated AADC patients. Results showed Kebilidi improved gross motor function in eight of the 12 treated patients at 48 weeks. Three patients achieved full head control, and two were able to sit with or without assistance. Earlier treatment led to better outcomes. Two patients treated before age 2 could walk backward by week 48. Four patients aged 2.8 to 10.8 years did not achieve new motor milestones.

The most common adverse reactions of Kebilidi are dyskinesia (involuntary muscle

movements), fever, low blood pressure, anaemia (low red blood cell count), increased saliva production, insomnia, low levels of potassium, phosphate, and/or magnesium, and procedural complications such as respiratory and cardiac arrest. It is also contraindicated in patients who have not achieved skull maturity assessed by neuroimaging.

Kebilidi was approved using the Accelerated Approval pathway. Accelerated approval allows the FDA to approve certain products for serious or life-threatening conditions based on evidence of a product's effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. In the FDA's evaluation of Kebilidi for accelerated approval, evidence of effectiveness is based on early improvements in gross motor function measured at 48 weeks after treatment. Continued approval for this indication may be contingent upon verification and description of clinical benefit of the product, such as the durability of the improvements, in a confirmatory clinical trial. A confirmatory trial is ongoing to verify Kebilidi's clinical benefit.

The application received Priority Review and Orphan Drug designation, and was granted a rare paediatric disease priority review voucher by the FDA. The FDA also authorized the SmartFlow Neuro Cannula, an infusion tube inserted into a target in the brain (parenchymal tissue), to deliver Kebilidi. The SmartFlow Neuro Cannula is currently the only FDA authorized device indicated for use to administer Kebilidi.

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Pharmacovigilance : A Career Guided Overview for Post Graduate Doctors in Pharmacology

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WHO defines Pharmacovigilance as " the science and activities relating to the detection, assessment, understanding and prevention of adverse effect or any other medicine related problem". (WHO 2004)

As most of the cases go undetected, it is quite impossible to estimate the actual scale of the huge effect of poor product quality, adverse drug reactions and medication errors on health care. Thus the demand for professionals in this field is on the high with the increasing focus on patient safety and efficient drug monitoring being the need of the hour. Pharmacovigilance or drug safety undoubtebly has multiple career opportunities with a well designed journey. Also increasing awareness on Pharmacovigilance all over the world can help prevent the occurrence of serious and costly drug related problems. The need for Pharmacovigilance professionals also continues to grow with the rise in demand of drugs and safety regulations in the healthcare industry.

Based on the professional demand, Pharmacovigilance career prospects can work in different forms such as the drug safety department, clinical research department in various kinds of organizations, regulatory affairs, contractual research organizations etc.

There are different online courses and training programs specifically in India to pursue Pharmacovigilance as a career option. Also in the post graduate MD pharmacology, different courses and modules can be included to create awareness as well as to motivate them to opt Pharmacovigilance as a career option.

Different courses and modules can be included in MD Pharmacology courses are:

Theory:

1. Principles of Pharmacovigilance
2. Adverse event reporting and management
3. Signal detection and risk management
4. Regulatory requirements (ICH, FDA, EMA)
5. Pharmacovigilance databases and software

Practical:

1. Hands on training on Adverse event reporting software (Argus, Rave EDC)
2. Signal detection exercises using Oracle Empirica Signal or IBM Watson Health
3. Database management using Veena Vault or Documentation
4. Regulatory submission training using RIMS or Global Submit
5. Data analytics and visualization using Tableau or Power BI

Course Curriculum:

Module 1: Introduction to Pharmacovigilance

- Overview of Pharmacovigilance
- Regulations and guidelines
- Pharmacovigilance software overview

Module 2: Adverse Event Reporting and Management

- Adverse event reporting principles
- Argus safety and Rave EDC training
- Case studies

Module 3: Signal detection and Risk management

- Signal detection methods
- Oracle Empirica Signal and IBM
- Watson Health training
- Risk management strategies

Module 4: Pharmacovigilance database management

- Database principles
- Veena Vault and documentation training
- Data management best practices

Module 5: Regulatory Compliance and submission

- Regulatory requirements
- RIMS and GlobalSubmit training
- Ectd submission guidelines

Module 6: Data Analytics and Visualization

- Data analytics principles
- Tableau and Power BI training
- Data visualization best practices

Module 7: Medical Writing and Document Management

- Medical writing principles
- DocuSign and Adobe Acrobat training
- Document management best practices

Faculty :

- Pharmacovigilance experts
- Software trainers
- Regulatory affairs specialists
- Medical writers

Duration:

- 1-2 weeks(theory)
- 2-4 weeks (practical training)

Assessment:

- Written exams
- Practical assignments
- Case studies
- Software proficiency tests

By incorporating these software tools and modules into the MD Pharmacology course, students will gain hands on experience and practical knowledge in Pharmacovigilance, enhancing their career prospects in the industry.

Different online courses for a career in Pharmacovigilance are:

Basic courses:

1. Pharmacovigilance Fundamentals (Coursera, University of Delhi)
2. Introduction to Pharmacovigilance (edX, University of California, Berkeley)
3. Pharmacovigilance and Risk Management (Udemy)
4. Basic Pharmacovigilance Training (Linkedin Learning)

Advanced Courses:

1. Pharmacovigilance and Drug Safety (University of Strathclyde, FutureLearn)
2. Advanced Pharmacovigilance Training (Oracle University)
3. Pharmacovigilance and Regulatory Compliance (ComplianceOnline)
4. Signal Detection and Risk Management (Bioclinica)

Specialized Courses:

1. Pharmacovigilance in Clinical Trials (ICH-GCP, Coursera)
2. Medical writing for Pharmacovigilance (American Medical Writers Association)
3. Pharmacovigilance Auditing and Inspection (Pharmaceutical Training Institute)
4. Pharmacovigilance Data Management (Veena Systems)

Certification Programs:

1. Certified Pharmacovigilance Professional (CPP, ISPE)
2. Certified Safety Professional (CSP, ISPE)
3. Diplomate in Pharmacovigilance (DPV, American Board of Pharmacovigilance)
4. Certified Pharmacovigilance Associate (CPVA, Pharmaceutical Education & Research Institute)

Training Providers:

1. Oracle University
2. Bioclinica
3. Pharmaceutical Training Institute
4. Compliance Online
5. ISPE (International Society for Pharmaceutical Engineering)
6. DIA (Drug Information Association)
7. PIPA (Pharmaceutical Information and Pharmacovigilance Association)

Course Duration:

1. Basic courses : 2-6 weeks
2. Advanced courses: 6-12 weeks
3. Specialized courses : 1-3 months
4. Certification programs: 3-6 months

Key Skills:

1. Pharmacovigilance regulations (ICH, FDA, EMA)
2. Adverse event reporting and management
3. Signal detection and risk management
4. Data analysis and interpretation
5. Medical writing and communication

Career Paths:

1. Pharmacovigilance Officer
2. Drug Safety Specialist
3. Risk Management Specialist
4. Medical Writer
5. Clinical Research Associate

There are also various professional software used in the Pharmacovigilance industry along with potential inclusion in MD Pharmacology courses.

The software used in Pharmacovigilance are:

1. Adverse Event (AE) reporting and management :

- Argus Safety (Oracle)
- Rave EDC(Medidate)
- Safety Tracker (Bioclinica)

2. Signal Detection and Risk Management:

- Oracle Empirica Signal
- IBM Watson Health
- PRISM (Pfizer)

3. Pharmacovigilance Database Management:

- Veena Vault
- Documentation (Dell)
- SharePoint(Microsoft)

4. Regulatory Compliance and Submission:

- RIMS (Regulatory Information Management System)
- Electronic Common Technical Document (eCTD)

5. Data Analytics and Visualization:

- Tableau
- Power BI (Microsoft)
- qlikView

6. Medical Writing and Document Mnagement:

- DocuSign
- Adobe Acrobat
- Microsoft Word

Also Pharmacovigilance professionals can identify and analyze safety signals through artificial intelligence, data analysis and statistics.

Pharmacovigilance professionals should not only be knowledgeable but also must have good communication and collaboration skills to work efficiently. Those candidates who want to grow their career in Pharmacovigilance should consider acquiring the necessary skills and education in heathcare industry. By staying up to date with the latest trends and development in drug safety, regulations and norms , one can get a better career prospect in this field.

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A Drowning Child and Moral Obligation of Reporting Adverse Drug Reactions

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Adverse drug reactions (ADRs) are a major health sector problem. It is estimated that 10% of hospitalized patients face ADRs, and 3.5% of all hospital admissions are due to ADRs in Europe[1]. ADRs also came to focus during Covid vaccine rollout and vaccine hesitancy due to fear of ADRs. It underlined the need to bridge the trust deficit between the general population and health care.

Various pharmacovigilance programs across the globe are involved in the detection, assessment, understanding, and prevention of ADRs as defined by the World Health Organisation [2]. Pharmacovigilance programs rely on the spontaneous reporting of ADRs. These programs can be effective only with adequate reporting of ADRs by health care professionals(HCPs). However, all such programs are plagued by underreporting across the world.

A study was conducted in Germany to find the subjective reasons for the nonreporting of ADRs by health care professionals[3]. It found that 44 percent of HCP either do not have time or it takes too much of their time to report. 27% found the process to be too complicated. PV awareness campaigns emphasize the importance of spontaneous reporting of ADRs by HCPs. However, it may be construed to be an extra responsibility and burden of work on HCPs in addition to the already existing roles and responsibilities. It may be argued that the primary duty of HCPs lies with the patient, and reporting ADR is not an inherent part of that duty, as reporting is not going to benefit the patient. We argue that ethical justification for ADR reporting may be found in Peter Singer's Drowning child analogy[4].

Peter singer's Drowning Child thought experiment.

In his essay 'Famine Affluence, and Morality,' Peter Singer gave a thought experiment of a drowning child. In his words- "if I am walking past a shallow pond and see a child drowning in it, I ought to wade in and pull the child out. This will mean getting my clothes muddy, but this is insignificant, while the child' would presumably be a very bad thing."

We can ask ourselves a series of questions. Will it matter if we have new clothes or shoes? Or if we had money in our pockets? Or would we get late for dinner? Will we then save the child? We would agree that it would have a minor loss or inconvenience, but we would save a much more valuable life in return.

Will it matter if there were other people around, but they are not doing anything to help? We all will agree that whether others are helping is immaterial. If we can save that child, we will save the child irrespective of what others are doing. We

feel morally obligated to save the child even if others don't feel such an obligation. Others not doing their part does not absolve us from our duty.

Finally, we can ask ourselves, does it really matter whether the child is drowning in front of us or whether it is halfway around the world? **If we cannot see the child, do we still save the child**? Peter Singer argues, "It makes no moral difference whether the person I can help is a neighbour's child ten yards from me or a Bengali whose name I shall never know, ten thousand miles away." In his essay, Peter Singer referred to the people dying in East Bengal (now Bangladesh) in 1971 when a civil war was ongoing.

Pharmacovigilance saves lives,just not in front of our eyes. As the drowning child thought experiment has shown, most causes of non-reporting do not pass the test of ethical behaviour. Medical professionals are involved in saving lives and alleviating human suffering. Questioning ourselves in the case of a drowning child has shown that lack of time or being busy or inconvenienced does not free us of our moral obligation to act. It has also revealed that non-reporting by peers is also not a valid reason for not reporting ourselves. And just because the impact on someone's life is not in front of us, it should make no difference in our actions. We are morally obligated to report ADRs. As Singer puts it, "If we accept any principle of impartiality, universalizability, equality, or whatever, we cannot discriminate against someone merely because he is far away from us (or we are far away from him).

It can therefore be argued that medical professionals are morally obligated to report ADRs. Reporting ADRs is not something beyond the call of duty, 'charity,' or an extraneous part of being a medical professional. ADR reporting is not something that, if done, will be good and not wrong if not done. On the contrary, it is ethically wrong not to report an ADR.

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Clinical Pharmacology Consultation: A Strategy For Better Patient Outcomes.

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CASE 1

A particular Mr Dulal, was suffering from persistent myalgia in both calf and thigh muscles since the last one month. He had visited an orthopedician who had conducted a myriad of tests on him. All the tests, Xray, USG leg came out to be normal. A detailed history of the patient revealed that he had a past history of Transient Ischemic Attack and has been diagnosed with Coronary Artery Disease as well. These are the prescriptions of medicines which the patient is following currently:

1. Prescription of Medicine consultant:

	Medications	Dose	Frequency	Duration	Remarks
1	STORVAS CV75/20 *Clopidogrel 75+ Atorvaststion 20*	1 tablet	0 – 0 – 1 After dinner	Till next visit	
2	Pantop 40mg *Pantoprazole 40mg*	1 tablet	1 – 0 – 0	10 days	Take 1 tablet before breakfast
3	Bevon susp *Multivitamin*	10ml	10 – 0 – 10ml	30 days	Take 2tsf twice daily after meals

2. Prescription of neurologist:

℞

Medicine	Dosage	Timing-Freq-Duration
1. Telista 40 tablet *Composition : Telmisartan 40mg*	1- 0 – 0	After breakfast- daily- till next visit
2. Clopitab CV Gold 20 *Composition : Clopidogrel 75mg+ Aspirin 75mg+Atorvastatin 20mg*	0 - 0 – 1	After dinner- daily –till next visit

Advice:
Salt restriction.

3. Prescription of cardiologist.

1. Ecospirin 75

Sig- 1 tablet at bed time to continue.

2. Tonact 80.

Sig- 1 tablet at bed time to continue.

3. Concor Cor 2.5

Sig- 1 tablet after breakfast.

4. Nitrolong 2.6

Sig- 1 tab below if required.

A detailed evaluation of the prescriptions revealed that the patient was taking Atorvastatin, total of 120 mg. It is a well known fact that the most common side effect of statins is myalgia. The patient was deprescribed the multiple statin therapies and put on a single Atorvastatin 40mg and Aspirin 75mg. The patient got relieved of the myalgia within 4 days.

CASE 2

Ms Jyoti had underlying depression for which she visited a psychiatrist. She was prescribed with paroxetine 12.5mg. She also complained of recurrent unilateral headaches for which she was referred to a neurologist. She was diagnosed with migraine for which she was prescribed with ibuprofen S.O.S for acute attacks and with amitriptyline for prophylaxis. After 2 weeks she presented to the emergency department with symptoms of restlessness, sweating, tremors, abdominal cramps, twitching of facial muscles. She was again referred to the psychiatrist following which the dose of paroxetine was in-

creased to 50 mg. The symptoms increased without any relief. By chance the patient was encountered by a pharmacologist. She was diagnosed as having serotonin syndrome because of taking paroxetine and amitriptyline together. She was prescribed with propranolol for migraine prophylaxis after which all her symptoms subsided.

Why did these particular scenarios arise? Ideally all the physicians should have taken the drug history of the patient and taken into account of all possible drug interactions before prescribing anything. However this is rarely the case in most of the occasions due to a multitude of factors. (Patient load, paucity of time, ego, lack of pharmacological knowledge). This calls for the need of clinical pharmacological care/consultation for better patient care. Clinical pharmacology is basically the science of what drug does to the body and what the body does to the drug. It encompasses drug interactions, polypharmacy, side effects, adverse effects, dose optimization, drug prescription and deprescribing wherever necessary. An audit performed in a private clinical pharmacology clinic in Kolkata, West Bengal revealed that Patient Satisfaction Survey (PSS) was significantly enhanced. [1]

A non official survey done in many private hospitals across Assam revealed that none of the hospitals employed a clinical pharmacologist. Certain NABH accredited hospitals also do not have a certified clinical pharmacologist although NABH 's accredition requires hospitals to have a clinical pharmacologist. Some of the hospitals have appointed pharmacy background individuals as clinical pharmacologists. But the NMC clearly mandates that a clinical pharmacologist should have knowledge and skills related to drug use, efficacy, side effects and prescribing competency which are possessed only by a doctor having a DM in Clinical Pharmacology or at least a MD Pharmacology. [2]

Clinical pharmacologists are also underutilized even in government medical colleges and hospitals. Their skills and knowledge related to a multitude of aspects regarding patient care are left in the cold. There is a huge gap in patient care in matters of polypharmacy, drug interactions, pharmacokinetic considerations which can only be bridged by a trained pharmacologist. Moreover the NMC and accreditation bodies like NABH should also be more rigid in such matters which will go a long way in enhancing the quality of healthcare system.

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Excipients

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An excipient is a constituent of a medicinal product other than the active substance (active pharmaceutical ingredients), that are not intended to exert therapeutic effects, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance). In general, excipients are considered to be inert. It is desirable that excipients should have little or no pharmacological action of their own. However, not all excipients are inert substances; some do have certain recognized adverse events.

In 1937, Massengill Company, a pharmaceutical manufacturer, created an oral preparation of sulfanilamide using diethylene glycol (DEG) as the solvent or excipient, and called the preparation “Elixir Sulfanilamide”. The company started selling and distributing the medication in September 1937. By October there were reports of several death caused by the medication. Following the 1937 elixir of sulfanilamide catastrophe, in which numerous children died from ingesting the medicine due to an untested excipient, the Drug and Cosmetic Act of the US-FDA (1938) was brought into force. It requires manufacturers to perform safety testing of pharmaceuticals before marketing. Similar regulations are in place as per local requirements of the region. Regulatory agencies like FDA, EMA and WHO evaluate excipients based on standard guidelines.

Majority of medicinal products require excipients for their production. One or more excipients are needed in the formulations of tablets, capsules, suspensions, and other products. It can also be used to improve medication penetration through the skin or in preparations for prolonged release. It includes fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, absorption enhancers, sustained release matrices, and coloring agents.

All excipients should be appropriately evaluated for pharmacological activity using a battery of standard tests. Acute toxicology studies should be performed in both a rodent species and a mammalian nonrodent species by the route of administration intended for clinical use. It is recommended that the absorption, distribution, metabolism, and excretion of the excipient be studied following administration by the clinically relevant routes to the same species that are used in the nonclinical safety studies.

The information concerning the used excipients in the medicinal product must appear on the outer packaging of the productor, where there is no outer packaging, on the immediate packaging if the medicinal product is an injectable or a topical or eye preparation.The list of excipients that have a known action or effect, must appear on the labelling of all medicines as per the local regulatory requirements along with the standard warning text.It is accepted that excipients may only show an effect above a certain amount called the 'threshold' of that excipient.

Few commonly used excipients along with the adverse events:

Excipient Name	Adverse event
Aspartame	Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
Tartrazine (Colouring agent)	Allergic reactions.
Benzoic acid	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
Glycerol	Headache, stomach upset and diarrhea.
Maltitol	Mild laxative effect.
Polysorbates	Polysorbates can have an effect on your heart and blood circulation (e.g., irregular or abnormal heartbeat, or low blood pressure).
Sulphur dioxide	Severe hypersensitivity reactions and bronchospasm.
Sorbitol	Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need.
Stearyl alcohol	Contact dermatitis
Xylitol	Laxative effect
Cyclodextrins	Digestive problems/Diarrhoea

It is also to be worried that some of these excipients which include coloring agents or emulsifiers are used in food products like coconut milk and various other preparations. If gone unchecked these could have serious health implications.

While generally safe, certain populations may experience adverse effects, requiring careful considerations from medical professionals. For sensitive patients hypoallergic or preservative free options should be provided whenever available. By understanding the functions and safety profile of excipients, clinicians can make informed decisions to optimize patient care.

Further readings:

i) ICH guidelines for industry S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies and S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies (http://www.fda.gov/cder/guidance/index.htm)

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Nafithromycin: A breakthrough in combating antimicrobial resistance

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Nafithromycin, India's first indigenous antibiotic, marks a significant milestone in addressing the global challenge of antimicrobial resistance (AMR). Developed under the aegis of the Biotechnology Industry Research Assistance Council (BIRAC), part of India's Department of Biotechnology, this novel antibiotic is positioned as a potent solution for treating drug-resistant infections, particularly Community-Acquired Bacterial Pneumonia (CABP).

Nafithromycin, a lactone ketolide antibiotic, emerged from 14 years of rigorous clinical trials conducted across the United States, Europe, and India. The research effort, costing approximately ?500 crores, was a testament to effective public-private collaboration, with Wockhardt Pharmaceuticals playing a pivotal role. Branded as Miqnaf, this antibiotic has shown remarkable efficacy, being 10 times more effective than azithromycin and achieving therapeutic results with just a three-day regimen?.

The antibiotic targets both typical and atypical bacterial pathogens, offering a broader and faster-acting solution to CABP, a condition linked to over 2 million annual deaths worldwide. Its minimal side effects, lack of significant drug interactions, and food-independent administration enhance patient compliance?.

The rise in resistance to macrolides like azithromycin has diminished the effectiveness of traditional monotherapy for CABP, often necessitating combinations with ß-lactams. Such combinations, however, bring challenges related to patient compliance and the risk of fostering dual-resistant bacterial strains. Nafithromycin, with its potent monotherapeutic profile, addresses these issues, offering a compliance-friendly solution while minimizing the emergence of resistant clones.

India, with a significant burden of pneumococcal infections, stands to benefit greatly from this innovation. The drug's Phase 3 development in India is particularly focused on establishing baseline susceptibility rates in Streptococcus pneumoniae and monitoring potential shifts in resistance patterns.

Nafithromycin's pharmacological strength lies in its sustained high lung concentrations, coupled with anti-inflammatory and immunomodulatory effects. These characteristics enhance its utility in managing respiratory infections, making it a promising candidate for the global fight against AMR?.

By reducing the reliance on hospital resources and lowering treatment costs, Nafithromycin provides a cost-effective solution for low-resource settings. The successful collaboration between government bodies and Wockhardt Pharmaceuticals demonstrates the potential of public-private partnerships in addressing critical healthcare challenges?.

Conclusion

Nafithromycin symbolizes a breakthrough in antimicrobial pharmacology, offering a robust response to drug-resistant CABP. Its development highlights the importance of innovation in combating AMR, positioning India as a significant player in global antibiotic research and development.

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How to Start a Startup in India

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India is emerging as one of the world's most dynamic and promising markets for startups. India offers the ground for entrepreneurial endeavours, with the Department for Promotion of Industry and Internal Trade (DPIIT) recognizing 1,17,254 startups as of December 31, 2023. Starting a startup in India can be both exciting and challenging, so here I will try to pen down the necessary requirements in creating a successful startup.

Identify a Viable Business Idea

Every startup begins with an idea, typically identifying a problem in the market and finding an innovative solution to it. The solution should be one that not only reflects the innovation but also addresses how it can make a business successful, scalable and generate revenue and employment in the process. To create an idea for a startup, remember: "The startup idea should be like a good cup of coffee—strong enough to wake up the market, yet unique enough to leave a lasting taste"

Choose a Suitable Business Structure

The next step is to decide on the legal structure of your business. In India, there are several legal structures for startups:

- **Sole Proprietorship:** A business owned and operated by a single individual. It's the simplest structure but offers no liability protection.
- **Partnership:** A business owned by two or more people. It requires a partnership deed and comes with shared liability.
- **Limited Liability Partnership (LLP):** A hybrid structure that combines the benefits of a partnership and a corporation. The partners' liabilities are limited to their contributions.
- **Private Limited Company:** A separate legal entity, most startups in India choose this structure as it limits liability and makes it easier to raise funds. It requires a minimum of two directors and shareholders.

Business Registration:

Once you've chosen the business structure, the next step is to register your business. The process of registration depends on the structure you've chosen:

- Private Limited Company: Register through the Ministry of Corporate Affairs (MCA) via the online portal. A Digital Signature Certificate (DSC), Director Identification Number (DIN), and a unique company name is necessary for this process.
- Limited Liability Partnership (LLP): Registration is also done through the

MCA, and you'll need to apply for DSC and DIN.

- Sole Proprietorship: This is more straightforward and typically does not require official registration but obtaining a GST number or a Shop and Establishment License may be necessary.

After registering your business, other important licenses need to be applied for, such as Goods and Services Tax (GST) Registration, Drug License, Trade License etc

Set Up Your Business Infrastructure

This includes creating a Office Space with the appropriate Technology and Tools. A professional website is essential for building brand awareness and reaching customers and as the business starts scaling, there may be a need to hire employees.

Marketing and Customer Acquisition:

Marketing strategies play an important role in launching the business. These strategies include Digital Marketing, Content Marketing, Networking are some of the strategies often used for marketing.

The Startup India Initiative

Launched by Prime Minister Narendra Modi on January 16, 2016, Startup India aims to create a conducive environment for startups. The initiative is designed to facilitate the growth of new businesses and support the creation of job opportunities in India.

Eligibility Criteria for Startup India Scheme

Before availing of the benefits offered under Startup India, the business must qualify as a "startup" under the initiative. According to the government's guidelines, the following conditions apply to businesses seeking recognition under Startup India:

1. Incorporation/Registration: The company must be registered as a Private Limited Company, Limited Liability Partnership (LLP), or a Partnership firm under Indian laws.
2. Age of the Startup: The company should be in its early stage, less than 10 years from the date of its incorporation.
3. Annual Turnover: Less than 100 crores in any of the previous financial years.
4. Innovative and Scalable Business Model: The business should be involved in the development or improvement of a product or service with a scalable business model.

Register as a Startup: Registration has to be done with the official Startup India portal.

- Visit the official Startup India website and create a user account with basic details like company name, registration number, and contact information.
- The portal provides an online application form for businesses to apply for recognition. It will ask for details about the nature of the business, innovation, and growth plans. Required documents will also have to be provided which include a copy of the Certificate of Incorporation (for Private Limited Companies/LLPs), a brief description of the business, along with details of its innovative product or service, a statement affirming that your startup is not listed on the stock exchange and has not exceeded 10 years in operation.
- The startup India initiative takes into account two aspects of a company or business: the scalability or the innovation of the product or both.
  - Scalability refers to the expansion of the business and market with an idea which is already available. The higher the scalability of the product, the higher the chance for recognition. To prove that a business or product is scalable, a video providing details enlisting how the product will upscale the market and how it will work differently from previous products of the same kind or the novelty of the idea have to be uploaded.
  - For the purpose of innovation and novelty of a concept, the idea must be new and should meet an existing demand or have

an aspect which has not been previously explored. And in order to show this innovation, the best way is to upload a patent for the same. Or a video showing proof of concept.

- Once the application is submitted, the government will review the details give a certificate of recognition to the startups that meet the eligibility criteria.

Conclusion

Starting a startup in India is now easier, thanks to the Startup India initiative. The government offers a range of incentives and support, including tax benefits, funding opportunities, and a simplified regulatory framework.

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ACCOLADES

Prof. Dr. Babul Kumar Bezbaruah Sir

Professor of Pharmacology
Principal Nalbari Medical College and Hospital, Nalbari
President, AIIMS Guwahati

Has been elected the President of the Indian Pharmacological Society (IPS) for the term from 2025 to 2027 in the International Pharmacology Conference and 54th Annual Conference of Indian Pharmacological Society (IPS) held at AIIMS , New Delhi from 28th to 30th November 2024.

Prof. Dr. Mangala Lahkar Madam

Retd. Professor & HOD,
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Ex- Chief Academic Coordinator, NIPER, Guwahati.
Retd. Officer On Special Duty,
Srimanta Sankaradeva University of Health Sciences,Narakasur Hilltop, Guwahati
National Co-ordinator of PharmacoVigilance from 2010 till 2021

Has been awarded PHARMACOLOGY TEACHERS OF EXCELLENCE AWARD for the year 2024 under the category Indian Pharmacological Society Life Time Achievement Awards in the International Pharmacology Conference and 54th Annual Conference of Indian Pharmacological Society (IPS) held at AIIMS , New Delhi from 28th to 30th November 2024.

Congratulations!

Prof. Dr. Meghali Chaliha Madam

Professor and Head ,
Department of Pharmacology, Assam Medical College and Hospital, Dibrugarh

Has been awarded the “NATIONAL SPOTLIGHT AWARD 2024” in the 3rd National Conference of the National Association of Pharmacology and Therapeutics (NAPT), NAPTICON 2024 held at AIIMS, Nagpur on 22nd and 23rd November 2024. The National Spotlight Award is awarded to the Life Members of NAPT whose significant contributions have advanced the field of Pharmacology and Therapeutics.

Dr. Revathi Radhakrishnan

Final-year Post Graduate student in Pharmacology at Tezpur Medical College, Assam, under the guidance of Dr. Pinaki Chakravarty, won second prize in the Systematic Review/Meta-Analysis category at NAPTICON 2024 for her work titled "RNA-based therapies: Expanding pharmacological horizons and clinical breakthroughs."

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