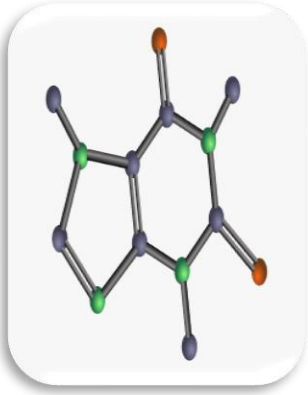
KASTURBA MEDICAL COLLEGE
MANIPAL
(A constituent unit of MAHE, Manipal)

THE DRUG TIMES

Newsletter from Department of Pharmacology, Kasturba Medical College, Manipal
Issue 6, August 2022

The current issue of THE DRUG TIMES provides information about network pharmacology, ecopharmacovigilance, nomenclature of monoclonal antibodies, FDA new drug approvals, newer drug molecules like dostarlimab, dual acting GLP-1 and GIP receptor agonist.

"Network Pharmacology": The Next Model in Drug Discovery

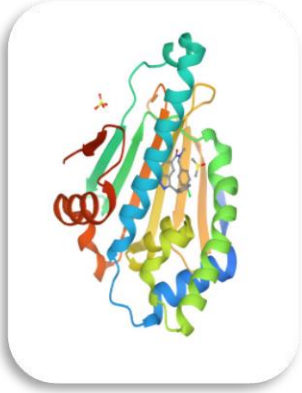


Network Pharmacology is a new discipline which gives an understanding of drug actions and interactions with many targets. It helps to find novel drug leads and targets and also in drug repurposing.

Current one drug-one target -one disease approaches in drug discovery have become increasingly inefficient. Network pharmacology defines disease mechanisms as networks best targeted by multiple, synergistic drugs.

Network ethnopharmacology
Many databases that give botanical information provide a link between traditional medicines and modern molecular biology.

Ayurveda and network pharmacology
As Indian traditional medicine Ayurveda has many formulations, it will serve as a good database for Network pharmacology



Applications of network pharmacology
It is the new model in drug discovery. It is gaining popularity due to its better cost factor and efficient predictability.

a) Traditional medicine
-Substitutes for endangered botanicals.
-Scientific proof for the therapeutic use of ayurvedic medicines
-Predicting the mode of action, safety and efficacy of Ayurvedic medicines.

"Network Pharmacology": The Next Model In Drug Discovery (Continued....)

b) Pharmacology

-Drug repurposing
-To find new leads from natural sources
-Predicting new indications, potential drug interactions, toxicity

c) Drug Research

-Discovering new drug targets
- *Insilico* evaluation resulting in lesser cost and time
-Diagnostic biomarkers
-Studying antibiotic drug resistance
-Understanding signalling pathway of disease types.

Major limitations

-Due to limited free access, target identification can be accessed through few databases.
-*In silico* tools cannot provide complete information about the exact interactions in a living organism

References:- *Chandran U, Mehendale N, Patil S, Chaguturu R, Patwardhan B. Network Pharmacology. Innovative Approaches in Drug Discovery. 2017:127–64.*
*-Hopkins, A. L. Network pharmacology: the next paradigm in drug discovery. Nat. Chem. Biol. **4**(11), 682–690 (2008).*

DUAL-ACTING GLP-1 AND GIP RECEPTOR AGONISTS

Tirzepatide is a novel, dual acting glucagon-like peptide 1(GLP-1) and glucose-dependent insulinotropic polypeptide (also termed as gastric inhibitory polypeptide [GIP]) receptor agonist. It is administered as a subcutaneous injection once weekly. It has showed effectiveness in the treatment of obesity in patients with and without diabetes mellitus

●In an open-label trial including over 1800 patients with diabetes, once-weekly tirzepatide was compared with semaglutide 1 mg . At 40 weeks, reduction in body weight with all doses of tirzepatide was greater compared with semaglutide.

●In a double-blind placebo-controlled randomized trial including over 2500 adults with obesity (but without diabetes), tirzepatide once weekly was compared with placebo. At 72 weeks, reduction in body weight at all tirzepatide doses was greater compared with placebo. In studies, the most frequently reported adverse effects of tirzepatide were nausea, diarrhea, and constipation (at higher doses). Tirzepatide is not approved for the treatment of obesity as yet.

References: 1. *Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery, SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022 Jul 21;387(3):205-216.*
2. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter T et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. JCI Insight. 2020 Sep 3;5(17):e140532.

Dostarlimab: A game changer?

In June 2022, the news report of a drug, dostarlimab showing 100% cure rate against a subtype of rectal cancer in a clinical trial created quite a buzz worldwide. These findings were seen in a phase 2 trial conducted on 12 patients with mismatch repair-deficient stage II or III rectal adenocarcinoma. All the 12 patients had complete clinical cure. So what do we know about this wonder drug?

Dostarlimab is a humanized IgG4 monoclonal antibody. It binds to the PD-1 receptor on T-cells. This leads to inhibition of programmed cell death-1 (PD-1) activity. It is an immune checkpoint inhibitor.PD-1 receptor signalling mediates negative immune regulation which is inhibited by blocking of the PD-1 pathway. This drug is presently approved for the treatment of mismatch repair deficient (dMMR), recurrent or advanced endometrial cancer /solid tumors in adults. It is administered through IV infusion.

The results of the study in rectal carcinoma patients appear promising. However, it is premature to consider that this is a wonder drug that could cure all cancers. The above study was conducted in a small group of patients and in those with the particular subset of rectal cancers. Currently, the drug is priced at Rs 8.5 lakh/dose which makes it unaffordable for majority of the patients. Nevertheless, this trial proves that, in cancer therapy, there is immense success in the path of personalized medicine (tailoring the treatment according to the individual patient's genetic/biomarker information).

Dostarlimab is a programmed death receptor-1 (PD-1)–blocking antibody. On binding to the PD-1 receptor on T cells, the PD-1 ligand inhibits proliferation of T-cells and production of cytokines. In certain tumours, there is upregulation of these ligands thereby causing inhibition of T-cell function. Dostarlimab binds to the PD-1 receptor which prevents the PD-1 ligand interaction with the receptor. This leads to the overcoming of PD-1 pathway-mediated immune response inhibition.

***Reference**: Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022 Jun 23;386(25):2363-76.*

FDA New Drug Approvals

(March- August 2022)

	Drug	Indication
1.	Lutetium (177Lu) vipivotide tetraxetan	Prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer following other therapies
2.	Oteseconazole	To reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are not of reproductive potential
3.	Mavacamten	Obstructive hypertrophic cardiomyopathy
4.	Vonoprazan, Amoxicillin, and Clarithromycin	*Helicobacter pylori* infection
5.	Tirzepatide	To improve blood sugar control in diabetes, in addition to diet and exercise
6.	Tapinarof	Plaque psoriasis
7.	Vutrisiran	Polyneuropathy of hereditary transthyretin-mediated amyloidosis

Accessed from : https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022

ECOPHARMACOVIGILANCE

Pharmaceutically active compounds (PhACs) are a category of emerging contaminant (EC) which has become a potential threat to human health and the environment. PhACs mainly consist of organic compounds including pharmaceuticals, personal care products, disinfectants, hormones, food additives, pesticides, plasticizers, flame retardants, laundry detergents, surfactants, wood preservatives, hospital wastes, plant wastes, agricultural operations and wastewater treatment plants (WWTPs) and various organic compounds produced by human and industrial activities. PhACs include drugs such as antibiotics, analgesics, anti-inflammatory medication, steroid hormones antidepressants and antihypertensive drugs which have come under the radar of the scientific community. As they are water soluble, aquatic organisms amass them primarily from water.

Ecopharmacovigilance (EPV) involves “applying pharmacovigilance in environmental science to reduce the risk posed by PhACs, and thereby, curtail adverse reactions occurring in humans”. It is defined as “the knowledge and activities associated with detection, assessment, understanding and prevention of pharmaceutical related adverse effects in our environment”.

Various approaches promoted under EPV help to diminish environmental footprint of pharmaceuticals. The list includes enhanced prescribing methods, dispensing practices, drug take-back, supervision and disposal of unutilized medicines, green drug design and minimization of manufacturing and hospital emissions.

Standardization and regulation of activities needs to be done such as prescribing, consuming, disposal behavior of the general public, health professionals and drug manufacturers. The public needs to be encouraged for safe drug use and rational medicine disposal. Avoid discarding unused or expired drugs by flushing down the sewer system. Special package inserts with directions for proper disposal will improve compliance of the consumer. Pharmaceutical levels in various aquatic beings can be employed as indicators for the purpose of detecting water pollution. Upgradation of drinking water treatment plants needs to be undertaken in order to remove pharmaceutical residues. The composition analysis of raw sewage for pharmaceutical residues leads to tracing the possible route of drug entry. Reduction of the concentration of pharmaceuticals in the environment due to human excretion relies on an efficient sewage treatment. “Targeted EPV”, a boosted EPV management strategy can also be employed in which EPV measures are realized through centering on individual pharmaceuticals on a prioritized basis.

References: Holm G, Snape JR, Murray-Smith R, Talbot J, Taylor D, Sörme P. Implementing ecopharmacovigilance in practice: challenges and potential opportunities. Drug Saf. 2013 Jul;36(7):533-46.

NOMENCLATURE OF MONOCLONAL ANTIBODIES: CHANGING PARADIGM

The nomenclature of monoclonal antibodies is a naming strategy for providing generic or nonproprietary, names to McAbs. The categorization for McAb names is described in INN publications from 2014, 2017, and 2021. Each McAb would be identified and named by a prefix-infix-suffix.

This new INN McAb nomenclature system is used for any drugs that contain an immunoglobulin variable domain containing pharmacologically active components. A bold decision was also taken to scrap the suffix/stem "-mab" henceforth, which has been traditionally used to identify most of the drugs of this group, and facilitate with new suffixes/stems that are distinct from each other into four groups as shown in the table.

Group 1 "-tug" for unmodified immunoglobulins *Monospecific full length and Fc unmodified immunoglobulins of any class. Molecules which might occur as such in the immune system.*
Group 2 "-bart" for antibody artificial *Monospecific full length immunoglobulins with engineered constant domains (CH1/2/3).*
Group 3 "-mig" for multi-immunoglobulin *Bi- and multi-specific immunoglobulins regardless of the format, type or shape (full length, full length plus, fragments)*
Group 4 -ment for fragment *All monospecific domains, fragments of any kind, derived from an immunoglobulin variable domain (all monospecific constructs that do not contain an Fc domain)*

To produce a distinct name, prefix chosen must adhere to the USAN Program's name-coining requirements and avoiding potential conflicts with names of other McAbs. The suffix is preceded by an infix/substem indicating the target class of the McAb, designated in accordance with the proposed known mechanism of action. The majority of target-related infixes in the new scheme remain intact; however, certain infixes have been tweaked. McAbs targeting cytokines/interleukins and cytokine/interleukin receptors would have -ki- infix, -ler- for allergens, -sto- for immunostimulatory (includes checkpoint inhibitors), and -pru- for immunosuppressive McAbs (-li- for immunomodulatory has been discontinued). The second substem, which defined the antibody's source ("u" for human or "o" for mouse) and whether it is humanized (-zu-) or chimeric (-xi-), was removed since the 2017 guidelines, and remained in effect.

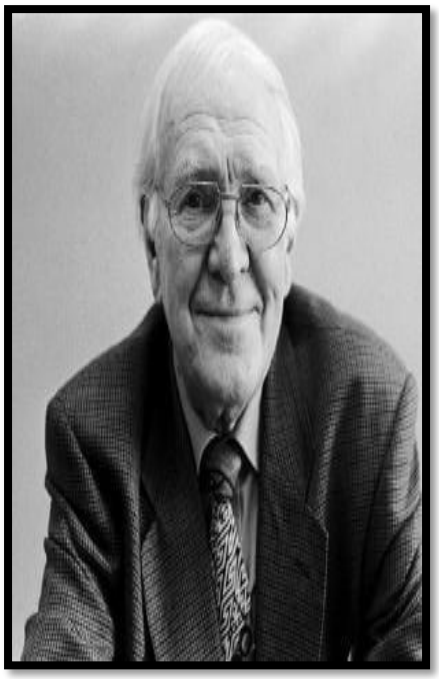
- *Antibody-drug conjugates (ADC) will also use the same naming system as McAbs, with no additional suffixes appended.*
- *A McAb's name may occasionally need to be further defined.*
- *If a radiolabel or toxin is conjugated to a McAb, the conjugation is labelled with a distinct, second word or another suitable chemical identifier.*
- *If a toxin is conjugated, the word "-tox" must be added in the toxin's name (e.g., zolimomab aritox). In some circumstances the payload may be identified by a stem or a chemical name (e.g., brentuximab vedotin).*
- *The word order for a radiolabelled product would include the name of the radioisotope, the symbol of the element with the isotope number, followed by the name of McAb (e.g., Technetium (Tc 99m) biciromab).*
- *Immunoglobulin fusions are only considered in the McAb naming system if both domains include immunoglobulin derived variable domain.*
- *McAb with a cytokine is classified as "-fusp".*
- *In case of pegylated McAbs, a prefix "peg-" can be supplemented provided that it does not lead to an overtly long name. A two-worded schema maybe employed wherein the McAb would be denoted by the first word and "pegol" as the second word (e.g., alacizumab pegol).*
- *A "-pab" suffix can be used for polyclonal pools of recombinant monoclonal antibodies.*

References:

(1) WHO. New INN monoclonal antibody (mAb) nomenclature scheme. Nov 1, 2021. https:// cdn.who.int/media/docs/default-source/ international-nonproprietary-names-(inn)/ new_mab_-nomenclature-_2021.pdf (accessed July 1, 2022).

(2) Balocco R, De Sousa Guimaraes Koch S, Thorpe R, Weisser K, Malan S. New INN nomenclature for monoclonal antibodies. The Lancet. 2022 Jan; 399 (10319):24. Monoclonal Antibodies. American Medical Association. Available from: https://www.ama-assn.org/about/united-states-adopted-names/monoclonal-antibodi

Sir James Whyte Black



- *A Scottish pharmacologist*
- *Won Nobel Prize in the year 1988.*
- *Well known for his break-through discoveries in the field of heart disease and stomach ulcers.*
- *Discovered **Propranolol**, a β blocker and **Cimetidine** a H_2 receptor antagonist.*
- *One of the first researcher to follow the rational drug design approach in drug discovery.*

Image Courtesy:
https://www.thefamouspeople.com/profiles/sir-james-w-black-7474.php

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less." —Marie Curie

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