DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Fourth, Oct– Dec 2021

Dear Readers,
The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights recent drug approvals, pharmacometabolomics, antimicrobial resistance and few interesting potential preclinical research. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

Pharmacometabolomics

Pharmacometabolomics or pharmacometabonomics is the study of how differences in metabolites in an individual or subset of the population can be used to predict their varied responses to a drug or medical intervention. The concept behind pharmacometabolomics is the that an individual's metabolic profile is related to their health-to-disease status, which has been referred to as their "metabotype". Genetics, gender, gut microflora, nutrition, age, health status, or other environmental factors may impact the metabolic profile of an individual and influence the individual response to pharmaceutical compounds. As such, metabolomics profiles obtained prior, during or after a drug or medical intervention can provide predictive, prognostic, and pharmacodynamic response biomarkers to a drug or medical intervention. The pharmacometabolomics data may aid understanding of varied drug responses (i.e. responders vs non-responders), be used to in precision medicine to determine drug dose levels or specific drugs to prescribe for an individual, provide biomarkers related to drug efficacy or toxicity effects and, often simultaneously, provide pharmacokinetics information making pharmacometabolomics valuable for precision medicine.

Individual drug-response prediction – It involves creating a population -based drug-response curve against a particular disease using samples collected before and after the drug treatment. The metabolic profiling is performed on samples selected from the ends of the curve (high responders or low responders) or across the curve (general responders). Both targeted and non-targeted metabolomics tools are used to define the metabolic 'signature' of drug treatment indicating the drug-induced changes in metabolites and metabolic pathways (cellular phenotype) that are associated with the drug-response.

Evaluation of drug-response variability – The interplay between pharmacogenomics and pharmacometabolomics is a significant factor in deciding the drug-response phenotype of a particular medical condition. The identification of metabolic pathways affected by a specific drug treatment through pharmacometabolomics and subsequent analysis of genetic variations within these metabolic pathway components through pharmacogenomics could pave the way for personalized medicine.

New Drugs Corner

Avacopan
MOA: Complement 5a receptor (C5aR) antagonist
Indication: Adjunctive treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis.

Pilocarpine hydrochloride ophthalmic solution
MOA: Cholinergic muscarinic receptor agonist
Indication: Treatment of presbyopia (age-related blurry near vision).

Asciminib
MOA: Tyrosine kinase inhibitor
Indication: Treatment of patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML).

Ropeginterferon alfa-2b-njft
MOA: Interferon alfa-2b
Indication: Treatment of adults with polycythemia vera.

Vosoritide
MOA: C type natriuretic peptide (CNP) analogue
Indication: To increase linear growth in pediatric patients with achondroplasia.

Maribavir
MOA: Cytomegalovirus (CMV) pUL97 kinase inhibitor
Indication: Treatment of post-transplant CMV infection/disease

Reference: USFDA

The Pill Box Quiz: 04

Instructions:
Scan the QR code to get the questions and correct answers.

SCAN ME

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Antimicrobial resistance: Potential news

About 700,000 people are estimated to die every year because of antibiotic resistant bacteria, and that number is expected to rise to millions. Without effective antibiotics, life expectancy is predicted to drop by 20 years. Few potential research in the field are mentioned below:-

Antibiotic resistance outwitted by supercomputers

A multi-pronged computer-guided strategy used to make a new antibiotic from an existing one which bacteria have developed resistance. The strategy is to simulate many aspects of a redesigned antibiotic at the same time, including how soluble it is, how effective it is at entering into the bacteria, and how efficient it is at blocking their protein production. Using a computational approach makes the development of new antibiotic derivatives faster and cheaper, and predicting whether a chemical compound is going to be active before it is synthesized also reduces chances of failure.

Reference: Gerhard König, Pandian Sokkar, Niclas Pryk, et al. Rational prioritization strategy allows the design of macrolide derivatives that overcome antibiotic resistance. *Proceedings of the National Academy of Sciences*, 2021; 118 (46).

Potential test determines antibiotic resistance in less than 90 minutes

A technique that measures the metabolic activity of bacteria with an electric probe can identify antibiotic resistance in less than 90 minutes. This technique can provide quickly which antibiotics will or won't work for a patient's life-threatening infection. The bacteria that are still metabolizing and "breathing" after antibiotic treatment are considered resistant. Previous attempts to measure the electrochemical activity of bacteria had been limited because most bacterial species are not capable of transferring electrons directly to an electrode. The researchers added a chemical mediator to their assay, which acted as a shuttle, taking the electrons from the surface proteins of the bacteria and moving them to the researchers' electrode, where the electric signal can be measured.

Reference: Gretchen Tibbits, Abdelrhman Mohamed, Douglas R. Call, et al. Rapid differentiation of antibiotic-susceptible and -resistant bacteria through mediated extracellular electron transfer. *Biosensors and Bioelectronics*, 2021; 113754.

Gold to reduce antibiotic resistance

According to a recently published study, gold nanoclusters (each made up of about 25 atoms of gold) can target and disrupt bacterial cells, making them more susceptible to standard antibiotic treatments. In the study, researchers tested three antibiotics from different class against methicillin resistant *Staphylococcus epidermidis* (MRSE) with and without the gold nanoclusters). There was an improved antimicrobial effect in cases where the antibiotic was used in combination with the gold nanoclusters, with 128-fold decrease in the amount of antibiotic needed to inhibit growth of MRSE.

Reference: Zeyang Pang, Qizhen Li, Yuexiao Jia, et al. Controlling the pyridinium–zwitterionic ligand ratio on atomically precise gold nanoclusters allowing for eradicating Gram-positive drug-resistant bacteria and retaining biocompatibility. *Chemical Science*, 2021.

Telaprevir increases antibiotic potency, limits antibiotic resistance

Telaprevir, approved by the FDA to treat hepatitis C, has shown to inhibit chaperone function in bacteria. Due to their critical role in folding proteins and protein misfold leading to toxicity in the cell, chaperones are the targets of ongoing drug discovery research. In recent study, the researchers demonstrated that telaprevir binds to mycobacterial chaperones and blocks their ability to fold proteins. This made the mycobacteria more sensitive to antibiotics, including streptomycin, a commonly prescribed tuberculosis drug. Chaperones can also stabilize the proteins in the cell that cause antibiotic resistance, so using telaprevir to block chaperone function lowered mycobacteria's resistance against the first-line tuberculosis drug rifampicin.

Reference: Jordan Hosfelt, Aweon Richards, Meng Zheng, et al. An allosteric inhibitor of bacterial Hsp70 chaperone potentiates antibiotics and mitigates resistance. *Cell Chemical Biology*, 2021.

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Antimicrobial agents: A glimpse

Organism	Preferred drug
Gram + cocci	
Streptococcus *-S. pneumonia* *-Hemolytic groups A, B, C, G* *-S. viridans*	 -Penicillin G -Penicillin G -Penicillin G
Staphylococcus *-Non penicillinase producing* *-Penicillinase producing* *-Methicillin resistant (MRSA)* *-Coagulase negative*	 -Penicillin G -Penicillinase resistant penicillin (cloxa, oxa, naf or dicloxacillin) -Vancomycin -Vancomycin
Enterococcus *-Faecalis* *-Faecium*	 -Ampicillin -Vancomycin
Gram + bacilli	
Actinomyces	Penicillin G
Bacillus including *anthrax*	Penicillin G
Clostridium	Penicillin G
Cornybacterium	Erythromycin (For C. jeikium, vancomycin is DOC)
Listeria	Ampicillin
Spirochetes	
Treponema (pallidum, pertenue)	Penicillin G
Leptospira	Penicillin G
Borrelia (burgdorferi, recurrentis)	Doxycycline
Chlamydiae	
-C. psittaci *-C. trachomatis* *-C. pneumonia*	-Doxycycline -Doxycycline or Azithro -Doxycycline
Rickettsiae	Doxycycline
Mycoplasma	Azithromycin

Organism	Preferred drug
Gram - cocci	
Neisseria *-Meningitidis* *-Gonorrhae*	 -Penicillin G -Ceftriaxone+ Azithromycin/ Doxycycline
Moraxella	Cefuroxime
Gram - bacilli	
Campylobacter, Legionella, Bordetella	Macrolides
Brucella	Doxycycline + Rifampicin
Acinetobacter	Carbapenems
Hemophilus -Serious infections like meningitis -Respiratory infections, otitis *-Ducreyi* (chancroid)	 -Ceftriaxone -Ampicillin-sulbactam -Azithromycin
Prevotella	Clindamycin
Burkholderia *-Mallei (glanders)* *-Pseudomallei (melioidosis)* *-Cepacia*	 -Streptomycin+Tetracycline -Ceftazidime -Cotrimoxazole
Vibrio (*cholera, sepsis*)	Tetracyclines
Enterobacteriaceae *-Salmonella* *-E. coli UTI* *-E. coli sepsis* *-Klebsiella* *-Proteus vulgaris* *-Proteus mirabilis* *-Enterobacter* *-Serratia* *-Shigella* *-Yersinia (plague)*	 -Ceftriaxone -Nitrofurantoin/ Fosfomycin -Ceftriaxone -Ceftriaxone -Ceftriaxone -Ampicillin -Carbapenems -Carbapenems -Fluoroquinolones -Streptomycin ± Tetracyclines
Nocardia	Cotrimoxazole

Drugs effective against anaerobic organisms: Clindamycin, Cefotetan, Cefmetazole, Cefoxitin, Chloramphenicol, Metronidazole, Moxifloxacin, Vancomycin.

Drugs effective against pseudomonas: Carbenicillin, Ticarcillin, Piperacillin, Azlocillin, Mezlocillin, Imipenem, Doripenem, Meropenem, Aztreonam, Ceftazidime, Cefoperazone, Moxalactam, Cefepime, Cefpirome, Ciprofloxacin, Levofloxacin, Colistin, Polymixin B, Aminoglycosides

Drugs effective against MRSA: Vancomycin, Oritavancin, Dalbavancin, Linezolide, Cotrimoxazole, Teicoplanin, Telavancin, Streptogramins, Daptomycin, Rifampicin, 5th generation cephalosporins.

"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." Alexander Fleming (1945)

Potential molecules

Potential new treatment for Alzheimer's disease

-Recent studies shown that the interplay between amyloid and tau is a greater contributor to Alzheimer's than either by itself. Sildenafil increased brain cell growth and decreased hyperphosphorylation of tau proteins (a hallmark which leads to neurofibrillary tangles), offering biological insights into how sildenafil may influence disease-related brain changes. Researchers determined that sildenafil is associated with 69% reduced incidence of Alzheimer's

Reference: Jiansong Fang, Pengyue Zhang, Yadi Zhou, et al. Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease. *Nature Aging*, 2021.

-The protein α-endosulfine (ENSA) is involved in the development of Alzheimer's disease. Studies in mice showed that eliminating this protein entirely or using drugs to block its function reduced physical changes in the brain associated with the disease and improved memory. Somatostatin normally keeps ENSA in check, which in turn keeps neprilsyin levels high, allowing Aβ to be destroyed before it accumulates.

Reference: Naoto Watamura, Naomasa Kakiya, Per Nilsson, et al. Somatostatin-evoked Aβ catabolism in the brain: Mechanistic involvement of α-endosulfine-KATP channel pathway. *Molecular Psychiatry*, 2021.

Compound 194 provides innovative pain relief

Nerve cells, or neurons, use electrical currents to send signals to the brain and throughout the body, and sodium ion channels are vital to a cell's ability to generate those electrical currents. When a neuron is stimulated, the NaV1.7 channel opens and allows positively charged sodium ions to cross the cell membrane and enter the previously negatively charged cell. The change in charge across the cell membrane generates an electrical current, which increases the excitability of the neuron and sets in motion a cascade of events that leads to pain.

Collapsin response mediator protein 2 (CRMP2), and an enzyme, Ubc9, that both play a role in NaV1.7 activation. CRMP2 is a protein that binds to NaV1.7 and transports it to the cell membrane, where sodium ions are then transferred into the cell. Ubc9 is an enzyme that tags CRMP2 with another protein -- a small ubiquitin-like modifier protein -- to specifically direct control of NaV1.7. The compound 194 directly regulate the activity of NaV1.7 by blocking Ubc9 from interacting with CRMP2.

Reference: Song Cai, Aubin Moutal, Jie Yu, et al. Selective targeting of NaV1.7 via inhibition of the CRMP2-Ubc9 interaction reduces pain in rodents. Science Translational Medicine, 2021; 13 (619).

Retrospective study finds that dasatinib lowers blood glucose

Dasatinib is a tyrosine kinase inhibitor used to treat tumors and malignant tissue, as well as chronic myelogenous leukemia. may have antidiabetic effects comparable to medications used to treat diabetes, and with more research may become a novel therapy for diabetic patients. Dasatinib is a senolytic drug, a type of agent first identified at Mayo Clinic that in animal studies targets senescent cells. These cells accumulate in many tissues with aging and at sites of pathology in chronic diseases, and in animal studies senolytic drugs appear to delay, prevent or alleviate age-related changes, chronic diseases and geriatric syndromes. The findings show that dasatinib lowers serum glucose in patients with pre-existing type 2 diabetes to a greater degree than imatinib and comparable to first-line diabetic medications such as metformin and sulfonylureas.

Reference: Omid Salaami, Chia-Ling Kuo, Matthew T. Drake, et al. Antidiabetic Effects of the Senolytic Agent Dasatinib. *Mayo Clinic Proceedings*, 2021.

"Medicine is a science of uncertainty and an art of probability" : William Osler