A special issue on Pharmaceutical Biology and Pharmacokinetics

FEATURES

Physiologically-based pharmacokinetic (PBPK) modelling in pharmacotherapy
“Drug trafficking” with benefits
Mitochondria in health and diseases
Designing nanotherapeutics, predicting populations
Treatment of Alzheimer’s disease
Table of Contents

OPINION

2 Physiologically-based pharmacokinetic (PBPK) modelling in pharmacotherapy

RESEARCH FEATURE

4 “Drug trafficking” with benefits
6 Mitochondria in health and diseases
8 Designing nanotherapeutics, predicting populations
10 Treatment of Alzheimer’s disease

NEWS ROUNDUP

12 New department to advance the food industry
12 Universal latent anion donors for ultralow work function solution-processable electrodes

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On the cover: Researchers working on the characterisation of molecular signatures to develop novel therapeutic strategies for overcoming liver-based injuries and diseases.

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Physiologically-based pharmacokinetic (PBPK) modelling in pharmacotherapy

The contributions of PBPK modelling to precision medicine in the future

Introduction

The path towards achieving optimal pharmacotherapy (i.e. treatment using pharmaceutical drugs) is like walking on a tightrope. When a patient takes less medication than is needed (underdosing), it leads to poor therapeutic outcomes. Conversely, overdosing results in undesirable effects. For effective treatment, questions on the right drug, its dosage, frequency, and duration (i.e. dosage regimen) need to be addressed. Historically, the dosage regimen is optimised empirically via small dose adjustments. However, this is an unsafe approach that depends more on experience and observation than on the scientific principles underlying an effective dosage regimen.

Dose-exposure-response paradigm

Since 1850s, scientists developed the dose-exposure-response paradigm (Figure 1) to provide a pragmatic framework for delivering personalised medicine tailored to each patient’s condition. The paradigm consists of two components: Pharmacokinetics and Pharmacodynamics. Pharmacokinetics describe the relationship between the dosage regimen and the resulting concentration of drug present in the blood over a period of time (i.e. how the body handles the drug). Pharmacodynamics characterise the relationship between the drug plasma concentration and its desired and adverse effects over time (i.e. how the drug affects the body). A basic understanding of drug absorption (A), distribution (D), metabolism (M) and excretion (E), and the relationship between kinetics and dynamics, are fundamental in pharmacokinetic and pharmacodynamic modelling.

In pharmacokinetics, the compartmental model is widely used in drug development and pharmacotherapy. The one-compartment model of the oral dosage regimen and its concentration-time plot are illustrated in Figure 2(A) and 2(B). It is based on a differential equation (Equation 1) related to drug concentration (C) which is derived from the difference between the rate of drug absorption and the rate of drug elimination (Figure 2(C)). By applying mathematical integration to Equation 1, the concentration versus time profile of a drug that observes this kinetic model can be obtained (Equation 2). Critical pharmacokinetic parameters can then be derived from the model to guide the effective administration of pharmaceutical drugs (Figure 2(B)).

However, the compartments and parameters from the compartmental model do not have physiological relevance. The empirical models describe the data but do not explain the mechanisms underlying the observations. As a result, these models cannot be extended to effectively predict other sets of data beyond those observed in clinical trials. Also, there is an underlying assumption that there is little variability across patient population in response to the given drugs. In practical situations, pharmacokinetic and pharmacodynamic variabilities exist within the population. The causes of variability include the patient’s age, body weight, drug-drug interaction, drug-food interaction, ethnicity, gender, genetics and medical condition. Counterintuitively, dosage regimens have largely been guided by results from clinical trials where only a small fraction of patient characteristics is represented due to the stringent selection criteria for such trials. The problems associated with this one-size-fits-all approach are particularly acute for drugs with a narrow therapeutic window (Figure 2(B)).

Innovation

The way towards optimal pharmacotherapeutic outcomes necessitates a shift from the conventional one-size-fits-all method to a tailored, more personalised approach. This evolving paradigm shift is contributed by innovations in several disciplines, including artificial...
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References


In our laboratory, we are particularly intrigued by the potential of PBPK modelling in predicting complex drug-drug-disease interactions. Rivaroxaban is a widely used oral anticoagulant for stroke prevention in patients with atrial fibrillation (a heart rhythm disease). It is eliminated from the body system through liver metabolism and kidney excretion. It is also susceptible to both intrinsic (pathophysiological) and extrinsic (concomitant drugs) variabilities that can potentially cause serious bleeding risks. Based on the build–validate–learn–refine cycle, our group discovered for the first time the mechanistic role of a previously arcane kidney transporter that plays an important role in the renal elimination of rivaroxaban[1]. Our model is also applied to guide dosage regimens to ensure the safe use of rivaroxaban for the management of atrial fibrillation in patients with renal impairment [2].

Future perspectives
We envision a future landscape where healthcare and in silico modelling technology will converge and synergise to direct and inform precision medicine, not just for subsets of patients based on genetic factors, but also for each individual patient based on physiological, pathological and external environmental factors.
"Drug trafficking" with benefits

The use of nanoparticles for the treatment of liver diseases

Collectively, the spectrum of chronic liver diseases presents a significant healthcare burden in this part of the world. Amongst which, chronic viral hepatitis (especially in the form of chronic Hepatitis B infection) remains prevalent within the local population. Another alarming observation is the rising trend of fatty liver disease due to the build-up of fats in liver tissues. It is estimated that about one-third of the population has some degree of fatty liver-related conditions. While many of these conditions do not present symptoms of the disease in the early stages, a few of them do and often progress to more severe diseased states of inflammation, fibrosis, liver failure and even liver cancer. This becomes irreversible when it progresses to an advanced stage. The use of available medications is often limited due to impaired liver function, which can complicate the way medications "traffic" (move) and are metabolised in the body. A successful liver transplant, which is currently the only curative solution, is often hampered by the availability of organs from suitable donors. Consequently, preventive measures such as vaccination (e.g. against Hepatitis B) and lifestyle modifications (reduction of total calories intake) provide the most workable solutions to date, even though they have limited effectiveness.

Exploiting a double-edged sword

Amongst various chronic liver diseases, liver fibrosis is a key process that is common in most causes of liver disease. Fibrosis is a process where liver cells, in response to different injuries, deposit scar tissues (e.g. collagen) as part of wound healing. However, this is a double-edged sword. If the cellular signals that drive the deposition of collagen do not stop when the healing is complete, then fibrosis can develop into a separate problem. The excessive collagen that
is deposited will reorganise itself into a firm layer that causes the liver to harden. This impedes the flow of blood into the organ. It will affect the ability of the liver to process nutrients and detoxify substances which the body is exposed to. Over time, liver functionality gradually declines and the obstruction of blood flow can lead to secondary problems such as hypertension and internal bleeding. The progressive damage can also result in the alteration of cellular behaviour that promotes cancer formation.

Within the last few years, we have discovered a potential countermeasure to this critical problem by exploiting the use of nanomedicines, which include the delivery of active molecules (drugs) at the diseased area through the use of miniaturised nanocarriers/nanoparticles. However, nanomedicines are also double-edged swords! How so? While nanoparticles have been touted as useful tools that support the delivery of medication to specific tissues, there are concerns that prolonged exposure can lead to accumulation and toxicity effects. Interestingly, the liver is the most common site in the body where nanoparticles tend to accumulate. Therefore, we questioned ourselves if this accumulation effect can be utilised to solve a liver-related problem.

We started by using titanium dioxide (TiO$_2$) nanoparticles as a prototype, and found a surprising and significant effect. These nanoparticles are able to block the activity of hepatic stellate cells (the key cellular machinery that makes and deposit collagen within the liver) (Figure 1). This blocking effect is dependent on both the particle size and the type of material used. We found that only nanoparticles in the low nanometre size range are able to assert a significant biological effect as they can be easily absorbed by the cell. For different types of inorganic nanoparticles, the biological effect varied. This discovery opens up new possibilities whereby nanoparticles may not simply be a carrier of medicines, but may even possess intrinsic therapeutic activity - “drug trafficking” with benefits.

We also found that such nanoparticles can alter the leakiness of the capillaries that carry blood to the liver. While this phenomenon may be detrimental in other blood vessels, the effect is beneficial in a fibrotic liver where reduced blood flow due to occlusion by scar tissues (formed upon collagen deposition) is an inherent problem that needs to be overcome. In this case, the TiO$_2$ nanoparticles mediate the opening of gaps at the vessel wall without triggering significant toxicity in the process. These gaps facilitate the passage of other small molecules, such as medications, to cross from the blood circulation system into the liver at higher concentration than in the absence of nanoparticles (Figure 2).

**What is the next step for this work?**

These research outcomes provide important proof-of-concept that increases the use of various nanoparticles for potential liver disease applications. It offers a different perspective of nanoparticles that are traditionally seen as being detrimental to the liver due to their accumulation and possible toxicity effects. These nanoparticles are also amenable to modifications by linking them with other molecules containing medications to provide a more robust arsenal to address liver diseases.

Figure 2: Illustration showing nanoparticles promoting the leakiness of the blood vessels within the liver cells. This increases blood flow and the passage of other drug substances into the liver.

**References**


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Mitochondria in health and diseases

Development of cell-based screens to search for drug-like molecules targeting MOAP-1 and Bax-beta at mitochondria

Introduction

“Mitochondria” are rapidly being recognised as key organelles in cells that control a variety of physiological processes (e.g. cell death, inflammation and metabolism) which are intimately linked to health and diseases. A wide range of human diseases impacting the ageing population has been linked to some aspects of abnormality in the mitochondrial function in cells. Hence, identifying and studying critical proteins that play important roles in regulating physiological functions in mitochondria could yield valuable insights to better understand diseases, and possibly to develop drugs for various major diseases.

Apoptosis, a cell suicide program which exists in every one of our cells, is a physiological process where unwanted, damaged or infected cells are eliminated from multicellular organisms. Many cancer chemotherapeutic drugs achieve their therapeutic effects through selective induction of apoptosis of cancer cells. Unfortunately, cancer cells also have reduced efficiency in sensing, or responding to apoptosis signals. Therefore, it is difficult for many cancer drugs to realise their full therapeutic potential, given the resistance inherent in, or acquired by cancer cells.

Mitochondria are major organelles where apoptotic signals are processed before the cells are killed by apoptosis (Figure 1). It is envisioned that drug-like compounds that can target the command centre of apoptosis signalling in mitochondria would have the potential to be developed as pharmaceutical drugs which are more effective at a lower dosage.
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References


Figure 3: Strategy for designing cell-based high-throughput screens to identify compounds that can stabilise or destabilise MOAP-1 or Bax-beta. (A) Schematic showing the potential targeting points by which small molecule compounds may interfere with the signalling events associated with the UPS regulation of MOAP-1 or Bax-beta. E1, E2, E3 represent the ubiquitin-ligating enzymes and DUB represents the de-ubiquitinating enzyme. (B) An example of a validation assay performed on the genetically engineered cell lines expressing fusion protein consisting of MOAP-1 and nano-luciferase (Nluc) reporter or the control Nluc alone. The plot shows that the MOAP-1 level (higher level of orange bar) is much more active in the sample containing the MG132 proteasome inhibitor, compared to the control group (DMSO).

MOAP-1 and Bax-beta proteins

In the past decade, my laboratory cloned two proteins, MOAP-1 and Bax-beta, that serve important roles in processing the apoptotic signals found in mitochondria. Both MOAP-1 and Bax-beta are localised at the outer membranes of mitochondria and they appear to be very low abundance proteins in cells because they are the direct substrates of the ubiquitin-proteasome system (UPS) [1,2]. Genetic mouse models obtained by removing the MOAP-1 gene in the mouse genome have been shown to affect the execution of the apoptosis function in the liver [3]. This finding could have important implications for liver diseases, such as liver cancer as well as conditions associated with acute liver failure. Surprisingly, recent work in my laboratory revealed that mice with the MOAP-1 gene deleted in their genomes showed abnormalities not just in their liver; other organs including the brain were also affected. This raises an important question on whether MOAP-1 would have other physiological functions beyond regulating apoptosis in the liver.

Cell-based high-throughput screens have been developed in my laboratory for identifying small chemical molecules that can elevate or suppress the levels of MOAP-1 and Bax-beta proteins. By using a pair of genetically engineered isogenic cell lines - one line with and the other without the presence of MOAP-1 or Bax-beta that is fused to a nano-luciferase (Nluc) reporter (a reporter protein that is used to measure the level of activity) - the system can be validated for responsiveness (Figure 2). The levels of MOAP-1 or Bax-beta Nluc fusion protein can be reliably determined by measuring the intensity of the luminescence light emitted by the Nluc reporter.

Small chemical molecules identified by the cell-based screens described above (Figure 3) will be subjected to a series of additional tests to help in identifying the molecules that affect protein stability of the target protein (i.e. MOAP-1/Bax-beta) via the most desirable mechanism. These selected compounds would become valuable reagents to help us gain further insights into understanding the diverse roles of MOAP-1 in regulating mitochondrial function in health and diseases.
Designing nanotherapeutics, predicting populations

Using *in vitro-in vivo* correlations to improve the performance of nanomedicine

**Introduction**

Throughout history, global trends in science and technology have led to rapid shifts and disruptions in existing activities, bringing positive change and improving treatment outcomes for patients. When the field of “nanomedicine” was born, it opened up new possibilities to deliver medication more effectively. It also brought about the idea of a “magic bullet” for medical therapy. Nanomedicine is envisioned to be able to unleash potent drugs at a predetermined location in the human body, targeting and removing the single diseased cell. However, some 30 years later, there have been setbacks along the way, and this has affected confidence in the technology.

The first automobile was built by Nicolas-Joseph Cugnot in 1769. However, mass adoption by the general population happened only after Henry Ford and Carl Benz brought cars into mass production. Their work created a great impact on the lives of billions of people. Likewise, when developing “nanomedicine” technology, we have to consider what is necessary to make “nanomedicine” feasible? And sometimes even more importantly, making it affordable?

Jörg Kreuter, a prominent researcher in nanomedicine, once said, “We discovered that it works and then, the next 20 years, we tried to find out why.” This statement underscores the importance of understanding why certain drug formulations are more effective than others. With this knowledge, we can improve the efficacy of nanomedicines and make them available to a larger number of patients.

My research area in pharmaceutical science combines knowledge across different disciplines (e.g. chemistry and biology) and the use of novel technologies to develop and advance medical therapeutics. When I started my research career, nanotechnology was still a relatively new area with many unknowns. I was fascinated by the idea of being able to create an item with a high degree of sophistication at the smallest possible dimensions. Also, I envision that the drug delivery systems of tomorrow will consist of tiny multi-tools that change their shape at different temperatures and respond to magnetic fields. They will also have the capability to seek out, and bind to the one single diseased cell within the human body that will soon develop into a tumour.

**Dispersion releaser technology**

The drug release rate is an important characteristic associated with medical therapeutics and it influences the rate and extent of the availability of the active pharmaceutical ingredient to the body. In the 1970s, a research discovery was shaking up the pharmaceutical community. Patients who were regularly treated with the same type of drug responded differently to the treatment depending on the type of tablet they received. At times, they suffered from severe side effects while occasionally, the drug seemed to have no benefit at all. It was discovered that this phenomenon stemmed from the difference in the drug release rate for different types of tablets given to patients. The rate at which a drug is released from a medicinal tablet depends on every single component used during its manufacturing process and it directly affects the effectiveness. At that time, this fundamental...
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Please visit https://nanomedicines.de/ for more information about his research work.
Treatment of Alzheimer’s disease

The search for a cure for Alzheimer’s disease, the most common form of dementia

Introduction

Alzheimer’s disease (AD), the most common form of dementia, is recognised by the World Health Organization (WHO) as a major global public health priority. It is considered a fatal disease that cannot be prevented, cured or even slowed. According to WHO estimates, there are 50 million people living with dementia (including those with AD) globally. As the population ages, this figure has been projected to triple to 152 million by 2050 if remedies are not available. Being a slow progressive disease, patients with AD gradually lose their ability to live independently. Unfortunately, current research findings and clinical trial results in the search for an effective treatment for AD are not promising; and the cause of AD remains largely elusive.

AD is a progressive, irreversible neurodegenerative disorder which affects large areas of the cerebral cortex and hippocampus. The disease is characterised by two key protein abnormalities, namely cerebral plaques laden with insoluble amyloid-β (Aβ) peptides and intraneuronal neurofibrillary tangles made of hyperphosphorylated tau proteins. Presently, most researchers support the amyloid cascade hypothesis, which suggests the accumulation of Aβ peptides as the main cause of AD.

Anti-Aβ therapeutics

As Aβ peptides appear to play a crucial role in the disease, many pharmaceutical companies have focused on developing anti-Aβ peptide therapeutics as potential treatments for AD. These anti-Aβ therapeutics include active (use an antigen to stimulate the production of antibodies against the Aβ peptides) and passive (administer antibodies (e.g. monoclonal antibodies) to target the Aβ peptides) immunotherapy, inhibitors of enzymes involved in the formation of Aβ peptides, and anti-Aβ peptide aggregation agents. Despite a number of clinical trials, these Aβ-lowering therapies had not been successful due to either no obvious clinical efficacy and/or unacceptable side effects.
Our research on the metabolic dysfunction of the brain

Recently, there has been another school of thought that recognises AD as a metabolic disorder. The brain relies on glucose for fuel and the availability of glucose directly affects the cerebral function. In the brain, energy required for most cellular reactions is derived from the phosphorylation of adenosine triphosphate (ATP), and most of this is produced in the mitochondria by the aerobic oxidation of glucose. A decrease in brain glucose consumption is one of the most prominent features of mitochondrial and metabolic abnormalities in AD patients.

In 2015, our Ph.D. student, Mr CHANG Kai Lun applied an in vitro cellular model for AD and demonstrated metabolic disorders as early as 24 hours after incubation. These disorders occurred much earlier than the surge in $\text{A}B_{12}$ peptide that only happened in 48 hours after incubation [1]. The metabolic changes in the AD cellular model from metabolomics analysis are shown in Figure 1. In the study, we also investigated the therapeutic potential of pioglitazone, an anti-diabetic drug for the treatment of AD. Pioglitazone was found able to reduce the $\text{A}B_{12}$ peptide levels and restore the metabolic dysfunction of the mitochondria in the cellular model.

Pioglitazone was subsequently tested in vivo using an AD transgenic mouse model. We observed extensive metabolic alterations in the cortex and cerebellum of the mice [2]. The major pathways affected in the cortex and cerebellum of the AD mice were closely related to the impaired energy metabolism and changes in amino acid metabolism in these mice. The discriminant metabolites in the cortex and cerebellum tissues of normal mice (wild type) and transgenic mice before and after pioglitazone treatment are shown in Figure 2. Treatment with pioglitazone successfully restored the energy metabolism, lowered amyloid-β levels and provided the AD mice with better anti-oxidative capacity in their cortex.

Our follow-up study indicated that in actual conditions, less than 10% of the pioglitazone could actually reach the brain tissues (Figure 3) [3]. Although we discovered a pioglitazone isomer which can penetrate more effectively into brain tissues compared to the racemic mixture, it is technically challenging to synthesise this isomer or isolate it from the racemic mixture.

Prognosis

Although amyloid-targeting therapeutics are not effective for AD treatment, other therapeutics which target the metabolic dysfunction have shown potential. One of them, pioglitazone, could help to rectify or slow down the metabolic dysfunction in brain tissues. There was a recent clinical trial (phase three) planned across a five year period to study the efficacy of low-dose pioglitazone in delaying the onset of mild cognitive impairment due to AD in elderly participants. However, this trial was discontinued prematurely in early 2018 due to inadequate treatment effects. A relatively low dosage (0.8 mg) was administered in the trial due to a perceived increase in bladder cancer risk. We think that the lack of clinical benefit could be partly due to the low dosage administered, as pioglitazone has limited brain penetration.

Our laboratory is currently developing novel drug delivery systems for delivering pioglitazone and other potential AD drug candidates to brain tissues. Such drug delivery systems have demonstrated their potential for the treatment of AD in vitro and in vivo experiments.

References


[3] Chang KL; Pee HN; Yang S; Ho PC*, “Influence of drug transporters and stereoselectivity on the brain penetration of pioglitazone as a potential medicine against Alzheimer’s disease” SCIENTIFIC REPORTS Volume: 5 Article Number: 9000 DOI: 10.1038/srep09000 Published: 2015.
New department to advance the food industry

The NUS Food Science and Technology Programme (FST) celebrated its 20th anniversary with a new milestone, its elevation to an academic Department under the Faculty of Science, NUS. This was announced by NUS President Professor TAN Eng Chye at the NUS FST 20th Anniversary Gala Dinner at the Kent Ridge Guild House on 8 August 2019.

NUS FST’s two decades of development has seen a doubling of its undergraduate intake, growth of its postgraduate student numbers, and the accreditation of its bachelor’s and honours degrees by the International Union of Food Science and Technology making it, the only certified FST degree in Singapore.

Universal latent anion donors for ultralow work function solution-processable electrodes

NUS scientists reported in Nature (26 September) the discovery of latent universal electron donors from common anions, like oxalate, which can potently transfer electrons to organic semiconductors, realising the dream to achieve electron injection layers with ultralow work functions that can yet be processed from solution in the ambient. This is expected to open many new possibilities, not only for organic electronics, but also other advanced semiconductors, including quantum dots, nanowires, two-dimensional (2D) materials, and perovskites.

The work function of a material is the minimum amount of energy required to remove the least tightly-bound electron to vacuum. This determines the ability of that material to inject electrons into a semiconductor. Electron injection layers require a sufficiently low work function, preferably much smaller than 4 electron-volts, to efficiently inject into (and collect) electrons from many novel semiconductors. However, this typically requires evaporating thin films of reactive metals in vacuum conditions, which limits device architecture, processability, and manufacturability.

Ultralow work function materials become degraded by exposure to air.

Now, the Chemistry team led by Prof Lay-Lay CHUA, and Physics teams led by Dr Rui-Qi PNG and Prof Peter HO, from the Organic Nano Device Laboratory, NUS have demonstrated that multivalent anions, such as oxalate, carbonate and sulfite, can act as powerful latent electron donors, when they are dispersed as small ion clusters in a polymer matrix of suitable conjugate polyelectrolytes. Conjugated polyelectrolytes are polymers with ionic side groups and delocalised electrons in the backbone. Crucially, the mixture can be processed from solution in air, and the anion spontaneously transfers electrons to the polymer host only after drying, thereby serendipitously protecting the material from atmospheric degradation. With the appropriate polyelectrolyte host, work functions as low as 2.4 electron-volts have been attained, overcoming the long-standing conundrum to marry ultralow work function materials with solution processing. The research team has demonstrated the versatility of this discovery by making a variety of high-performance white-light-emitting diodes and organic solar cells using solution-processed electron-injection layers.

The research was performed in collaboration with Cambridge Display Technology Ltd (CDT), a subsidiary of Sumitomo Chemical Co., Ltd (SCC).

More details is available at: http://tiny.cc/ultralow_work_function