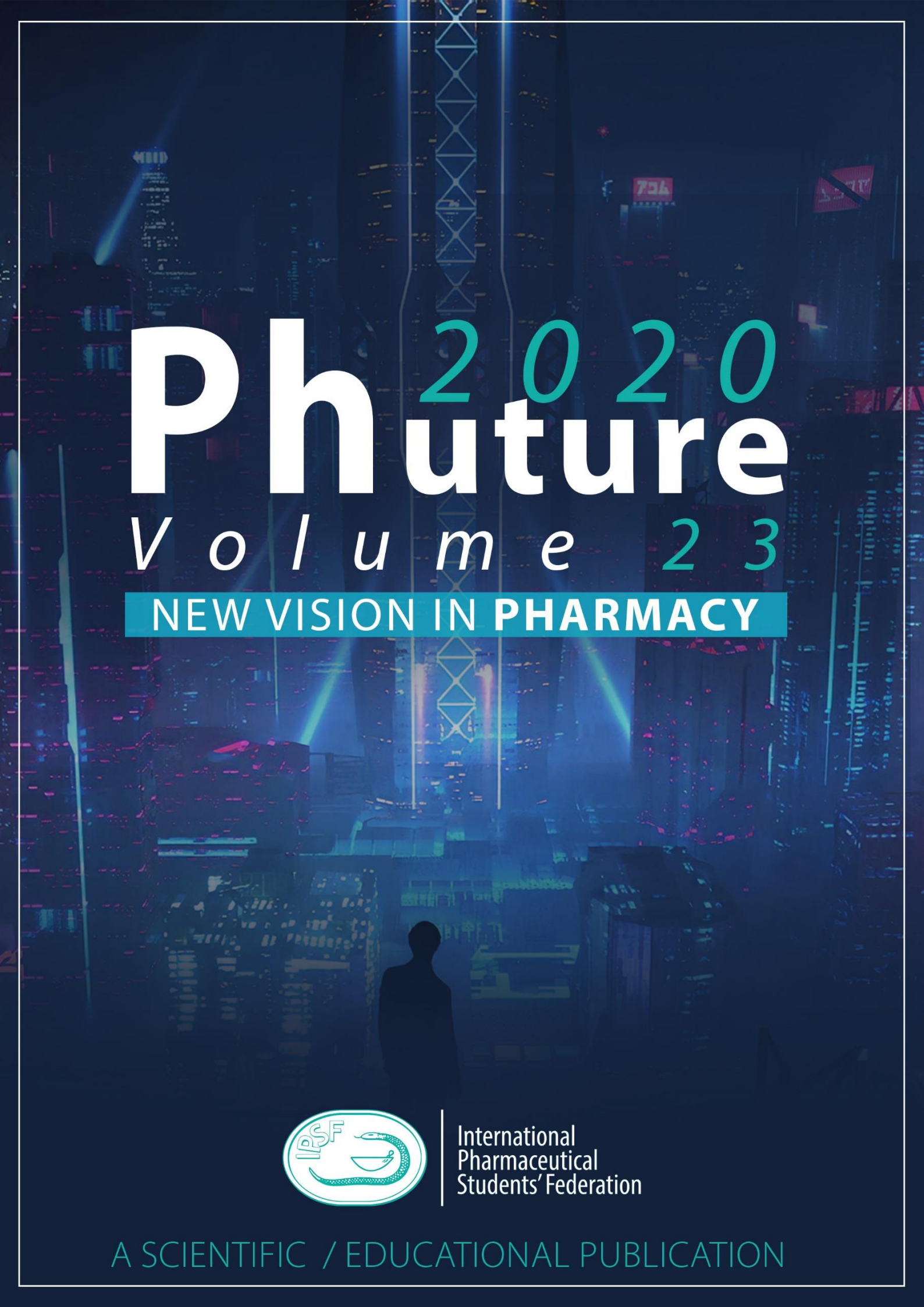

Phuture 2020

Volume 23

NEW VISION IN **PHARMACY**

International Pharmaceutical Students' Federation

A SCIENTIFIC / EDUCATIONAL PUBLICATION

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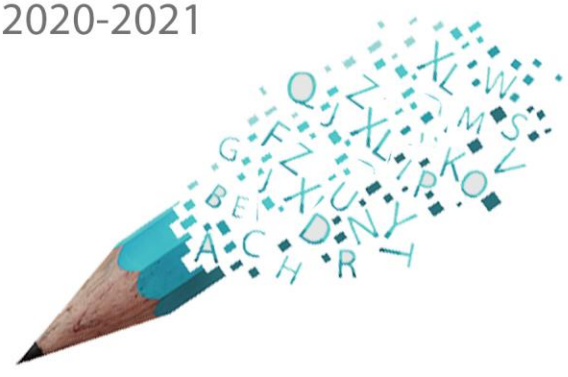

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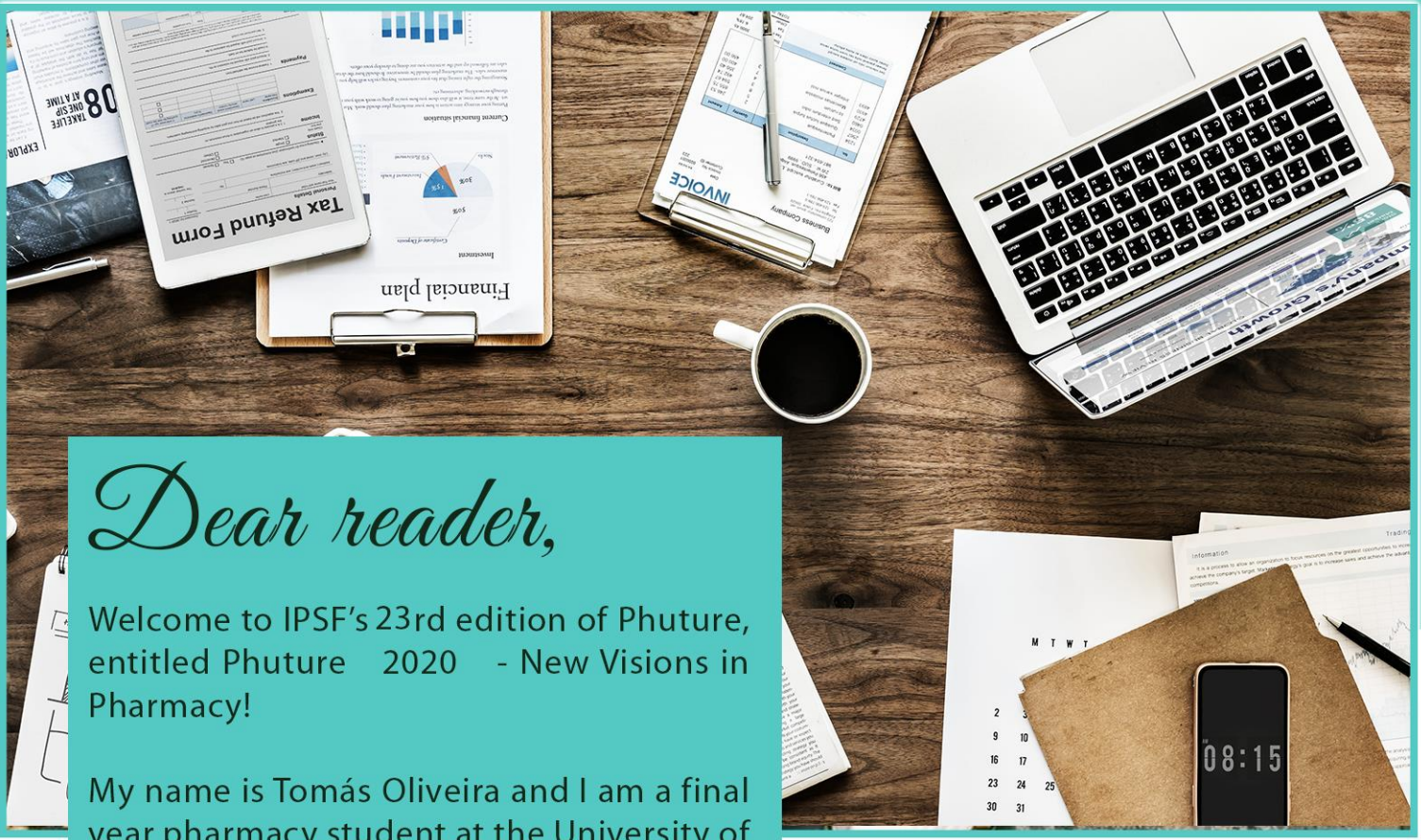

Dear reader,

Welcome to IPSF's 23rd edition of Phuture, entitled Phuture 2020 - New Visions in Pharmacy!

My name is Tomás Oliveira and I am a final year pharmacy student at the University of Porto, Portugal. I started my mandate in October 2020 and it is with great pride and sense of responsibility that I conclude this project which started since the previous mandate.

If this is your first time reading a Phuture publication, I would briefly describe it as a scientific publication of the International Pharmaceutical Students' Federation (IPSF), which is published annually. You can find articles (submitted by students or recent graduates) in which particular sets of issues related to pharmaceutical sciences and practices are tackled; always with an eye on the future and the possible role that pharmacists can play in it.

In this edition, Phuture delves into four topics: **Pain Management, Novel Drug Delivery Systems and Pharmaceutical Technology, Pharmacogenomics, and Digital Health and Telemedicine**.

I am hoping that while going through the pages of this publication, you will notice that the articles selected are capable of showing you why these topics are relevant, which innovative research strategies are being explored, what are the questions left to be answered, and the challenges left to be solved. The final goal of this is to ensure that patients' quality of life is optimized

Lastly, allow me to thank all the people involved in the process of making this publication come to fruition; from proofreading, to designing, to supervision. A special thanks also goes to all those who submitted their articles for publication thereby enabling IPSF to produce an interesting content such as this. Viva la pharmacie!

Tomás Oliveira

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Are *Opioids* Effective for the Management of Chronic Non-Cancer Pain?

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Are Opioids Effective for the Management of Chronic Non-Cancer Pain?

Hossam Moustafa Moawad[1]
Fayoum University, Egypt

A brief summary on Pain management and controlling

Basically, Chronic Non-cancer Pain (CNCP) is usually defined as pain persistent beyond 3 months, deemed the duration of tissue healing[1]. Many examples include diabetic neuropathy, low back pain, chronic pancreatitis, and fibromyalgia. CNCP results from combined biologic, psychologic, and social factors, and most often requires a multifactorial approach to management. In addition to nonpharmacologic therapies, many patients require medications to manage pain. Based on statistics, in 2016, an estimated 50 million adults in the United States were living with CNCP, many of whom were prescribed opioid medications. Consequently, opioid prescriptions increased by 7.3 percent from 2007 to 2012[2]. However, the effects of opioids on CNCP are uncertain, whereas the harms found to be associated with prescription opioids include diversion, addiction, overdose, and death[3]. This topic will discuss the use of opioids in the management of chronic non-cancer pain.

Mechanism of action

Opioids have been classified by strength, duration of action, or source (natural, semi-synthetic, or synthetic). They exert their effects via binding to specific proteins, called opioid receptors [TABLE 1][1]. By acting on central and peripheral μ-, kappa-, and delta-opioid receptors, opioids inhibit the transmission of nociceptive signals and the perception of pain[2].

Mu	
Mu1	
	Supraspinal analgesia
	Bradycardia
	Sedation
Mu2	
	Respiratory depression
	Euphoria
	Physical dependence
Delta	
	Spinal analgesia
	Respiratory depression
Kappa	
	Spinal analgesia
	Respiratory depression
	Sedation

TABLE 1: Properties of opioid receptors

Indications and uses

Opioids are used to treat moderate to severe pain that does not respond to nonopioids alone. They are often combined with nonopioids because this permits the use of

lower doses of the opioid (i.e., dose-sparing effect). Nearly all types of pain respond to opioids; however, nociceptive pain is generally more responsive to opioids than neuropathic pain, which may require higher doses of opioids. Opioids play a major role in the treatment of acute pain (e.g., trauma, postoperative pain), breakthrough pain, cancer pain, and some types of chronic noncancer pain (CNCP). Because responsiveness to opioids varies greatly among individuals, a patient who has failed to respond to an adequate trial of one opioid should try another. Although opioids vary in potency, more potent agents are not necessarily superior. Opioids are also categorized as weak opioids and strong opioids[6] [TABLE 2].

Weak opioid	Strong opioid
Codeine	Morphine
Hydrocodone	Hydromorphone
Dihydrocodeine	Fentanyl
Tramadol (depends on the dose and has been classified as strong in BNF*)	Diamorphine
	Buprenorphine
	Methadone
	Oxycodone

*BNF=British national formulary

TABLE 2: Classification of opioids in regard to their potency

Routes of administration, formulations, and dosing

Opioids are administered via multiple routes (e.g., oral, sublingual, rectal, parenteral, transdermal, intrathecal, epidural). Oral or transdermal administration is generally preferred for chronic treatment. Intramuscular (IM) administration, especially repeated, should not be used due to its multiple disadvantages (e.g., pain, unreliable absorption, tissue fibrosis).

Opioids should only be initiated for the treatment of CNCP when:

- Alternative lower risk therapies have not provided sufficient pain relief or cannot be used;
- Pain is adversely affecting a patient's function and/or quality of life;
- When the potential benefits of opioid therapy outweigh potential harms;
- After discussion with the patient of all risks, benefits, and alternatives to opioid therapy[2].

Indeed, opioids should only be continued when there is a well-documented benefit after a trial of opioid therapy. When possible, opioids should be combined with nonopioid pharmacotherapy and non-pharmacologic therapies as appropriate to achieve therapeutic goals with the lowest effective doses of all medications[2].

On the other hand, opioids have adverse effects that many patients cannot tolerate (e.g., nausea, sedation, constipation). Other

disadvantages include the risk of addiction or addiction relapse, opioid-induced hyperalgesia (OIH), and many potential drug interactions[4].

Finally, patients of chronic opioid therapy should be monitored periodically and as warranted by changing circumstances. Monitoring includes drug screening, frequent visits, single pharmacy, pill counting, and urinal screening for abuse detection[5].

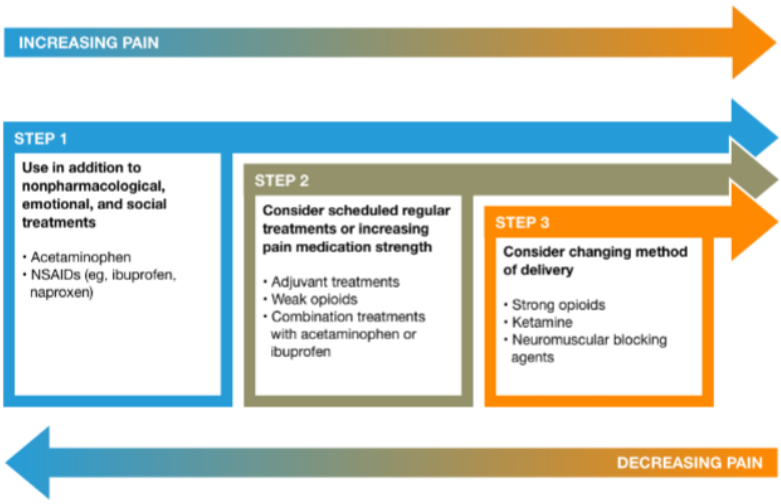

FIGURE 1: Modified three-step pain management ladder - illustrates the three steps on controlling pain in sequence.

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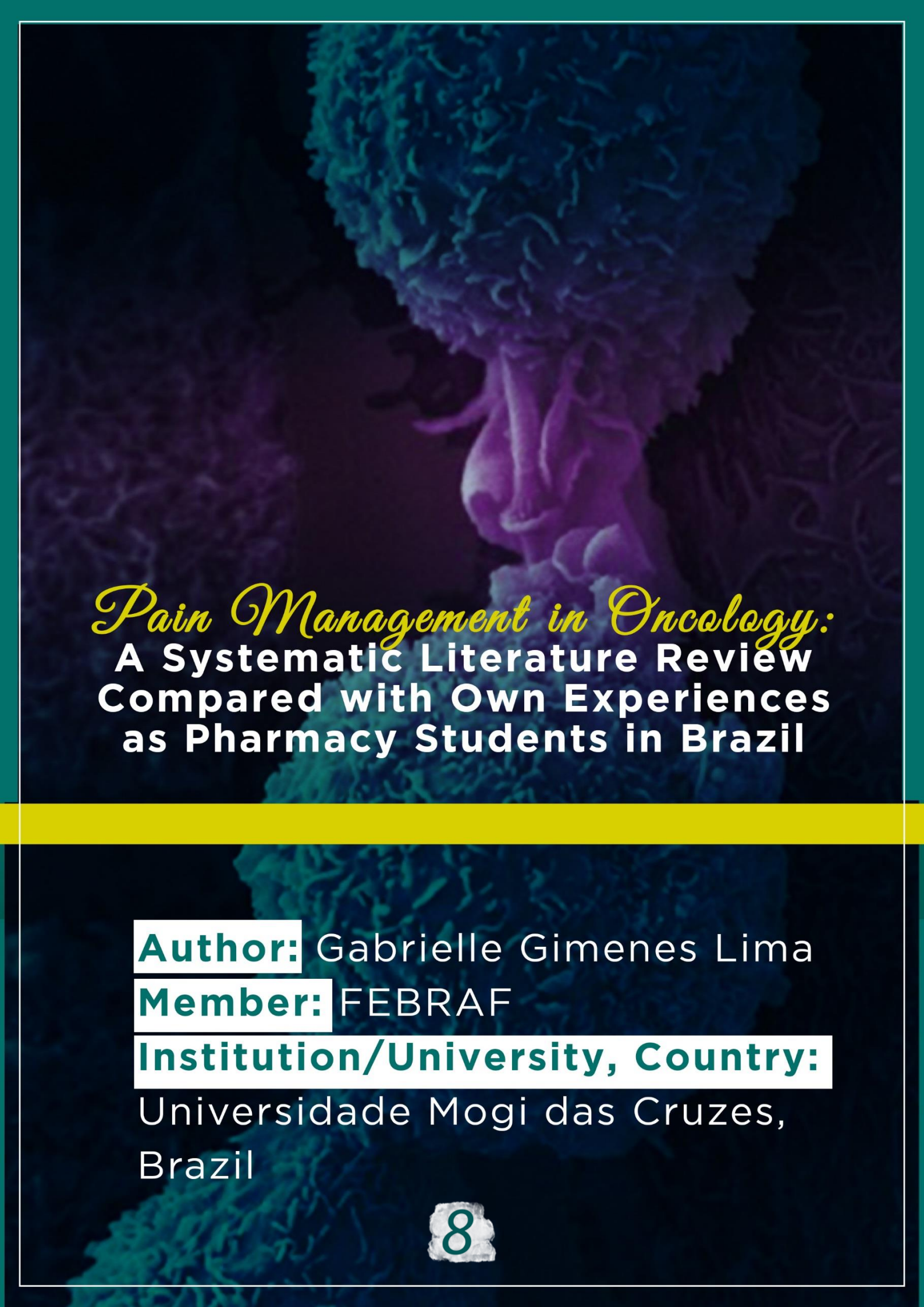

Pain Management in Oncology: A Systematic Literature Review Compared with Own Experiences as Pharmacy Students in Brazil

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Pain Management in Oncology: A Systematic Literature Review Compared with Own Experiences as Pharmacy Students in Brazil

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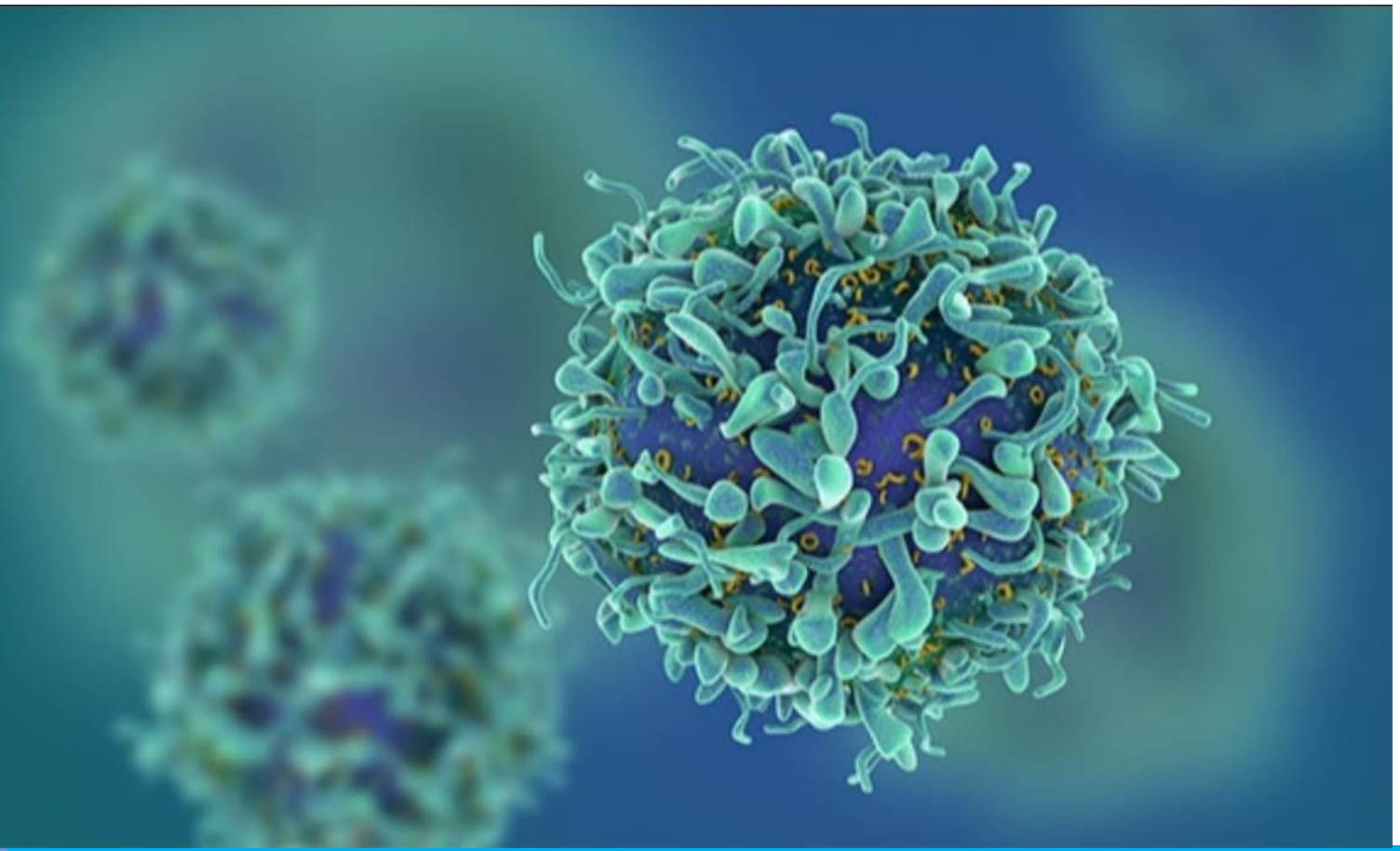
Introduction/Background

Advanced cancer often causes pain, defined as an unpleasant sensory and emotional experience associated with potential tissue damage, according to the International Association for the Study of Pain (IASP)[1]. Every year, it afflicts approximately 17 million people worldwide[2]. In a recently published systematic review, pain prevalence rates were 39.3% after curative treatment, 55.0% during anticancer treatment, and 66.4% in advanced, metastatic or terminal disease[3].

Cancer pain is prevalent at all stages of the disease and often can be the first symptom. The end of a complex process that can involve emotional, spiritual, cognitive, and sensory components[7]. Cancer pain control can be performed using drugs such as anti-inflammatories, opioids, antidepressants, anticonvulsants, benzodiazepines, corticoids, beta-blockers, vasoconstrictors, among others[5].

Pain has a severe impact on patients' life quality and is associated with numerous psychosocial responses[4]. Patients report that it increases the difficulty of concentrating, thinking, and performing normal daily activities. More than a third describe cancer-related pain as distressing or even an intolerable aspect of cancer[6]. When it persists or worsens, it can serve as a sign of the disease progression creating a feeling of hopelessness. Patients fear that it is not worth continuing like this and start thinking that his life has no



meaning if living in pain[8].

Evidence suggests that adequate pain management results in clinically relevant improvements in patient health. In spite of several advances in the understanding of pathobiology and pain management, even with the use of drugs and complementary therapies, pain suppression is not always successful which remains a major international health problem requiring further study on the treatment of cancer pain[9].

Therefore, this article brings a literary review on how pain management is performed in cancer patients compared with our experience as pharmacy students. It can be concluded that it is necessary to take several precautions in the treatment, since the adequate support by professionals trained for pharmacological and non-pharmacological interventions is of main importance, leading to an improvement in the patient's life quality by reducing pain and summarizing expenses.

Methods of Research

A systematic search of the literature published between 2010 and 2016 was performed using the databases PubMed, Medline, Embase, CINAHL, and Cochrane. Search terms comprised "cancer pain" and "prevalence" or "pain management" and "chemotherapy supportive care" in combination with "pain measurement", in the title, abstract, or key words. 28 articles were found and 19 were excluded due to lack of depth in the discussions on the topic in study.

Major Findings and Discussion

In the articles investigated, it was found that the patients studied were mostly female, white, and only completed elementary school. Regarding the type of cancer, it was analyzed that, in women, there is a predominance of breast, bowel, and ovarian cancer; in men, lung and prostate cancer predominate. In cases between 12 and 18 years of age, tumors of the central nervous system, bone tumors, soft tissue sarcoma, lymphoma, and leukemia predominate.

In addition to cancer, many patients, especially those in the adult age group, usually have other diseases such as systemic arterial hypertension, dyslipidemia, diabetes, lung, kidney, and liver diseases. These are usually diagnosed before cancer, however, they can also appear as a consequence of this, either because of the effects of the disease or treatment on the body, or because of a drop in the personal care of the patient who, when receiving the diagnosis of cancer, faces symptoms of depressive and anxiety disorders such as discouragement, low self-esteem, loss of appetite, among others[11].

Among the most common treatment modalities for cancer, we can mention: surgery, chemotherapy, radiation, immunotherapy, and hormone therapy. In Brazil, some of the most used drugs are: Cyproterone Acetate and Gosserrelin for prostate cancer; Capecitabine, Methotrexate, and Goserelin for breast cancer; Cisplatin, Carboplatin, Methotrexate, and Vinblastine for lung cancer; Capecitabine and Fluorouracil for colon and rectal cancer; and Temozolomide for brain cancer. All of these types of treatment can cause an immense number of effects and other medical problems, such as hair loss, nausea and vomiting, fatigue, weight loss or gain, intestinal irritation, peripheral neuropathy, sexual and fertility problems, anemia, urinary and renal problems, metabolic imbalances, nutritional depletion, anorexia, decline in the patient's performance and mental behavior, thrombocytopenia, and neoplasms. In addition, cancer costs are high for both the patient and the healthcare system.

For example, SUS (Brazilian Unified Health System) offers care to cancer patients (according to Ordinance 874/2013 that establishes the National Policy for the Prevention and Control of Cancer) in specialized health establishments (which

currently total 317 in all the national territory) and the financing of cancer drugs does not happen through the Pharmaceutical Assistance Components of the system, neither the Ministry of Health nor the Municipal and State Health Departments directly make these medicines available to patients. The SUS procedure table does not refer to cancer drugs, but specific tumor situations described regardless of which therapeutic regimen is adopted. To have access to pharmacotherapeutic treatment, the patient is subjected to a bureaucracy in which he/she must look for hospitals accredited by SUS and qualified in Oncology that make the request for the existing drugs within a SUS subsystem called APAC-SIA (Authorization of Procedure for High Complexity of the Ambulatory Information System), purchase and are reimbursed by the Ministry of Health according to the procedure code registered with APAC.

In this context, the pain of cancer is not only a physical feeling arising from the side effects of the treatment or even the disease, but also a psychological and emotional problem that comes, initially, from all the taboo that society nourishes either by its lethal history, either due to the difficulty of accessing information, preventive methods, diagnosis, and treatment. What we noticed in our experience is that the patient, upon receiving the diagnosis, soon considers it as bad news, a sign that his life is at an end, although they also understand that there is treatment for it and most of the time it is efficient, given the progress in the improvement of the current ones and the discovery of new treatments offering greater efficacy and safety. In the second point, along with the good and bad news, there is more information for the patient, that he/she will have to follow the treatment for his whole life, which returns that feeling of "it is the end". And then we started to analyze the side effects mentioned above, as raised by the articles studied, focusing on the pain of cancer.

Although reports vary widely, the range of reported pain prevalence is highest for the following tumors: head and neck (67-91%), prostate (56-94%), uterine (30-90%), genitourinary (58-90%), breast (40-89%) and pancreatic (72-85%); the location being dominant in the upper and lower limbs and chest and the intensity characterized as moderate pain. The articles mention the combination of pharmacological and non-pharmacological methods as treatment and management of these pains. Most patients only request some type of medication when the level of pain is extremely intense using analgesics and anti-inflammatory drugs. Some make joint use of unconventional alternatives such as the use of medicinal plants as mastruz and aloe vera. As a non-pharmacological measure, we can mention: behavioral interventions, psychotherapy, relaxation techniques, and acupuncture.

At this point, pharmacotherapy remains a pillar in the management of cancer pain in patients at all stages of the disease. The recommendations found indicate that severe pain should be treated with rapid titration of short-acting opioids because they have the advantage of a rapid onset of analgesic effect; moderate pain should be treated similarly to severe pain, starting with a slower titration of short-acting opioids; and mild pain should be treated with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or a very slow titration of short-acting opioids. In Brazil, in the population of children and adolescents, paracetamol and dipyrone are most frequently used to treat mild to moderate pain; codeine and tramadol for moderate to severe pain; morphine, fentanyl and methadone to relieve moderate and severe chronic pain. There are also adjuvant drugs, such as dexamethasone and amitriptyline, for example, used to reduce anxiety levels, minimize side effects or even potentiate analgesia. In the table below, we can see the list of cancer pains and their response to management:

Potentially curable	Highly responsive (Response rates >50%)	Moderately responsive (Response rates >30%)	Less responsive (Response rates <30%)
• Acute myeloid leukemia • Acute lymphocytic leukemia (childhood) • Chronic myelogenous leukemia • Hodgkin's disease • Non-Hodgkin's lymphoma (some subsets) • Hairy cell leukemia • Germ cell tumors • Gastrointestinal stromal tumors	• Breast carcinoma • Ovarian carcinoma • Androgen-dependent prostate cancer (hormonal therapy) • Small cell lung carcinoma • Osteogenic sarcoma • Multiple myeloma	• Non-small cell lung cancer • Colorectal cancer • Transitional cell carcinoma of the urothelial tract (e.g. bladder cancer) • Sarcoma (some subsets) • Endometrial carcinoma (hormonal therapy)	• Gastric carcinoma Esophageal carcinoma • Head and neck carcinoma • Pancreatic carcinoma Hepatocellular carcinoma • Renal cell carcinoma • Malignant melanoma • Mesothelioma • Anaplastic thyroid cancer • Islet cell and carcinoid tumors

[TABLE 1]: Causes and prevalence of cancer pain[10]

The reflex to pain includes a set of neurophysiological factors, considerations, convictions, emotions and memories, so, even though there are so many other effects of cancer treatments, the main complaint of patients is pain, a sum of everything they are feeling physically and emotionally. While the administration of analgesic medication interferes with the sensory dimension of pain, non-pharmacological measures act on other components, such as mood, behavior and emotional response to the painful situation. It is essential to highlight the importance of pain management, which, if left untreated, can cause anxiety, fear, tension in the patient, greater awareness of pain, which may result in reducing the response to drug treatment and refusing to perform the necessary procedures.

Future Directions

The main problem noted in this review and also in our experiences related to pain management is the fact that patients' pain is not correctly measured resulting in undertreatment. Persistent pain not treated effectively and attentively affects the quality of life, in general, of patients, causing physiological changes, limitations in carrying out daily activities, losses in the quality of sleep and in the learning process, impairing cognitive functions, generating anxiety and depressive symptoms, in addition to significantly decreasing the ability to interact with family and friends.

The correct thing is to make an evaluation of all the adverse effects and complications of the cancer treatments periodically, in short-term intervals. Specifically for pain, there are several ways of measuring from numbering (where 0 means no pain and 10 means the worst pain ever felt) to more complex forms considering the pain behavior in the individual. The difficulty lies in finding a standard or a system that best applies to cancer patients and that can be carried out on a regular basis to observe the effectiveness of the treatment and the patients' life quality, guaranteeing their compliance. In addition, psychosocial support and educational materials should be offered to the patient.

In fact, several characteristics of cancer and its treatment can affect mental and physical balance and many patients also end up experiencing status changes in their employment, social relationships, and their role within the family. Therefore, starting from the concept of Pharmaceutical Care, it is also our responsibility to provide personalized, individualized and humanized care, assessing the family and social context in which the

patient is, his/her history, seeking to understand what are his/her complaints, inconveniences, and doubts, what is a problem for him/her and what is not and, together with the multi-professional health team, look for the best way to manage his pains, whether they come from cancer or not.

Conclusion

Cancer patients are often treated with multiple lines of therapy to keep the disease under control and prolong survival. At some point in time, tumors acquire mutations and begin to become resistant to therapies or side effects to replace their benefits. Patients should be monitored closely so that the decision to stop systemic cancer-targeted therapies and make a transition to palliative care is made at the right time.

Therefore, pain management in these patients is of main importance. Adequate supportive care can help improve clinical outcomes, reduce medical costs and help cancer patients live longer, happier, healthier lives.

Pharmacists, in this context, can (and should) monitor adverse effects; provide instructions and detailed information on how to manage complicated medication regimens, such as oral chemotherapy, antiemetics and pain medications; help assess the adequacy of chemotherapy and supportive care regimens; guide the multidisciplinary health team and provide recommendations for adjustments in treatment; in addition to actively participating in the scientific research of new treatments.

Regardless of the practice, pharmacists play a vital role in the supportive treatment of cancer patients, especially when it comes to pain management. They can significantly help to reduce the adverse effects related to treatment and cancer and also find solutions to reconcile treatment efficacy and safety with the specific needs of each patient. For these reasons, it is important that pharmacists have a solid understanding of how to prevent, treat and improve pain management.

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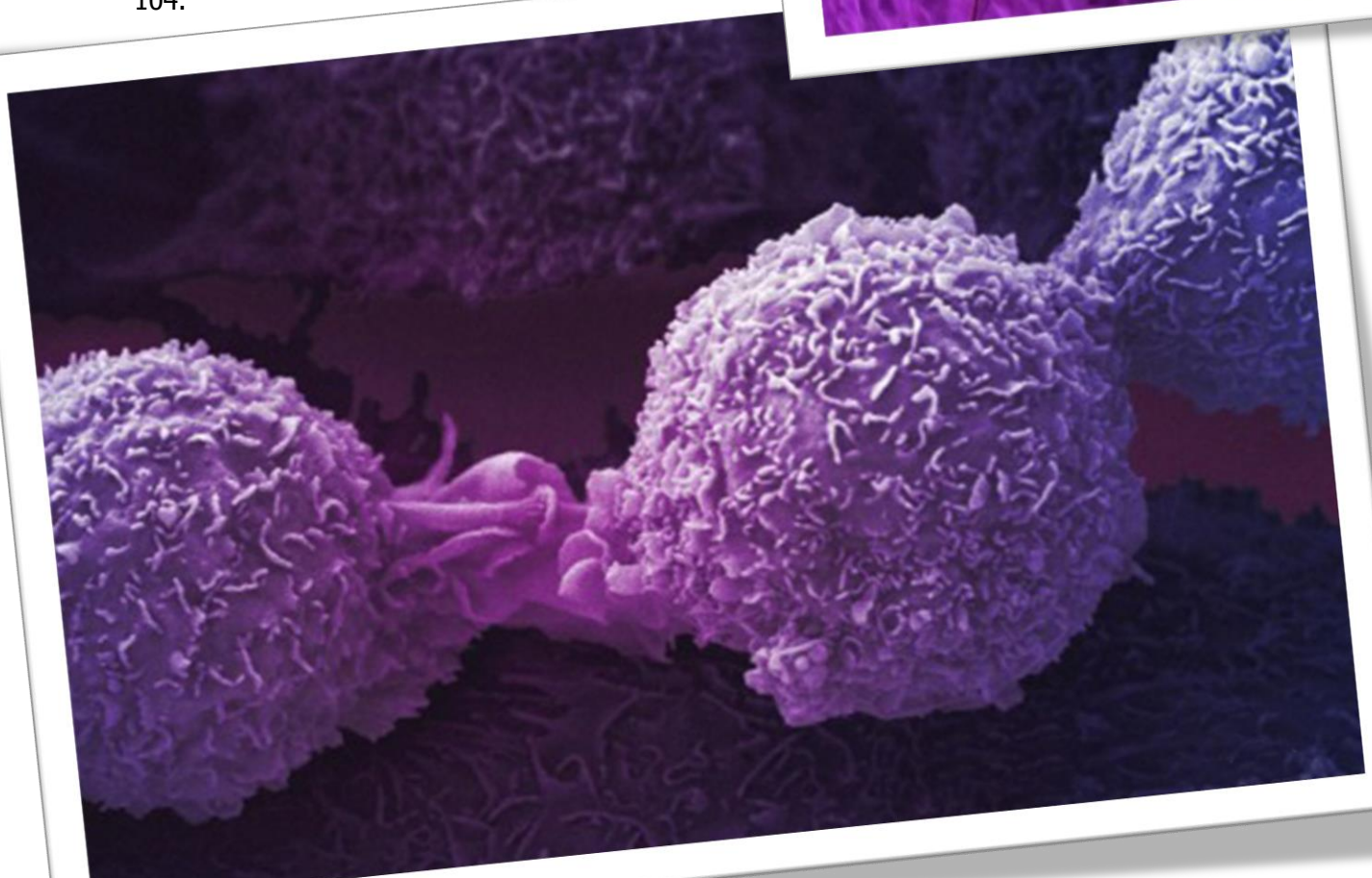

A New Era for the Medications

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A New Era for the Medications

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Introduction

Novel Drug Delivery Systems (NDDS) are carriers that retain the concentration of drugs in therapeutic range for longer periods and deliver the material to the site of action, if necessary. These systems have a lot of advantages over conventional drug delivery[1]:

- The optimum concentration of therapeutic drugs in the blood or tissue can be maintained for an extended time;
- Pre-determined release levels can be reached over an extended period;
- The duration may be increased for short half-life drugs;
- By targeting the site of action, it may eliminate the side effects;
- Regular dosing and wasting of the drug can be minimized or omitted;
- Good patient adherence can be assured.

History

In the last six decades controlled drug delivery technology has progressed. It began with the launch of the first sustained formulation in 1952. The 1st generation of drug delivery (1950-1980) concentrated on improving oral and transdermal sustained release systems and defining the regulated mechanisms for drug release. The 2nd generation focus (1980-2010) was devoted to the development of zero-order release systems, self-regulated drug delivery systems, long-term depot formulations, and delivery systems based on nanotechnologies. The latter part of the 2nd century was used primarily to research formulations of nanoparticles[2].

Effect of transporters on drug transport and DDI

Both influx and efflux transporters are contained in various tissues in the human body, so we may face the following problems when we use drugs[3]:

1. The drug's plasma concentration may be reduced due to a rise in drug efflux.
2. Two or more drugs are used simultaneously; the crossing of the transporter substrate may cause drug interactions, which may affect the drug's efficacy, and may increase the drug's cytotoxicity.

Development of new drug delivery systems

1. Microspheres

Microsphere refers to a microparticle structure that is prepared by encapsulating a product into a polymer substrate and has a particle diameter between 1 and 250 μm. Microsphere skeleton material mainly comprises gelatin, alginate, chitosan, and polylactic acid-co-glycolic acid (PLGA)[3].

2. Nanoparticles

Nanoparticles are stable colloids of 1-100 nm particle size. Nanomaterials have been widely used by many anticancer medicines to formulate corresponding Nano-formulations, including paclitaxel, doxorubicin (DOX), dexamethasone, and 5-fluorouracil (5-FU)[3].

3. Liposomes

Its unique bilayer phospholipid structure (similar to the physiological membrane) has made it more compatible with BBB's lipoid layer and helps the drug enter the brain[3].

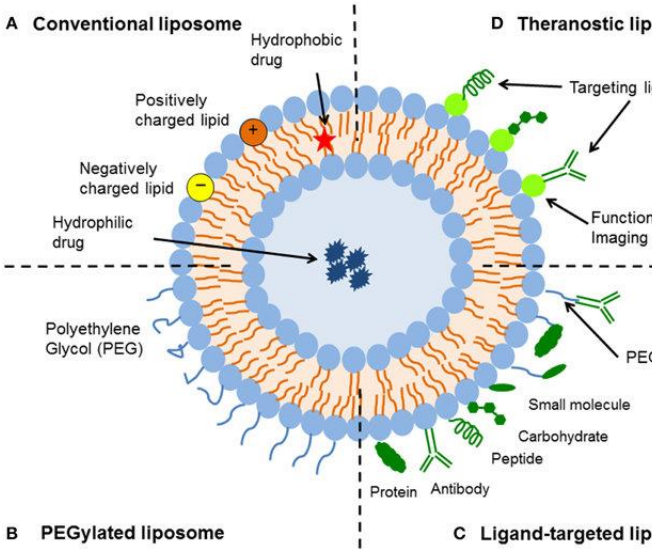

FIGURE 1: Schematic representation of the different types of liposomal drug delivery systems

4. Dendrimers

Dendrimers are three-dimensional spherical polymers which are strongly branched, monodisperse. Different synthetic processes regulate their structure including the characteristics of form, scale, charge, and solubility[3].

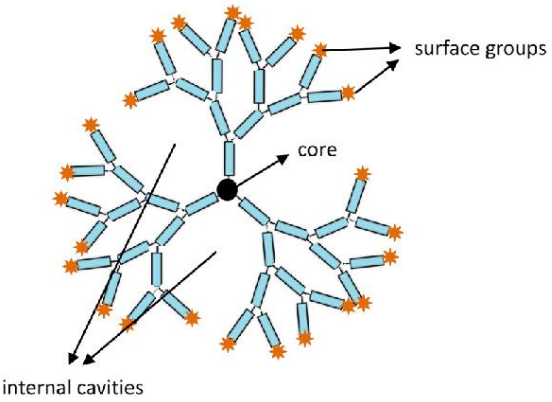

FIGURE 2: Dendrimer structure

5. Polymer micelles

Polymer micelles are colloidal particles that are self-assembled in aqueous media by amphiphilic block copolymers which have a narrow distribution of size. The micelles have excellent stability characteristics, good drug-charge properties, and long cycle time. They can dissolve anticancer drugs that are water-insoluble and realize sustained release[3].

6. Stimuli-responsive strategy

Many stimulus-responsive systems that contain sensitive segments can be used to deliver drugs to a target tissue and to achieve a drug release on demand. Also, the surface properties and nanostructures of stimulus-responsive nanoparticles can be modulated by intrinsic or extrinsic stimuli to improve cellular uptake and penetration ability[2].

7. Co-delivery strategy and theranostics

It is common in clinical practice. Potential application in cancer therapy is to overcome drug resistance and metastasis[2].

8. Ligand-modified target drug delivery strategy

It provides improvements in various characteristics including permeation across physiological barriers, penetration into target sites, target cell internalization, and specific subcellular locations[2].

Medical Applications

1. Transporter-based Nano-formulation against MDR

MDR is a significant problem that hampers the effectiveness of cancer pharmacotherapy as a key factor in the production of resistance to chemotherapeutic agents. One common mechanism is the overexpression of cancer cells of certain transporters. P-GP-mediated MDR is the most significant of the major transporters and has become a major obstacle in the clinical treatment of diseases. The drug can be modified by using nanotechnology to improve its fat solubility so that the drug can be quickly absorbed and efflux based on P-GP is reduced[3].

2. Transporter-based nucleic acid Nano-preparation against cancer

The development of efflux transporter-based tumor resistance is also associated with the up-regulation of individual genes. The goal is to achieve a tumor resistance reversal by down-regulating the gene. One approach is to use siRNA to knockdown gene expression, which can prevent tumor proliferation, reducing the cancer cells' chemical resistance[3].

3. Transporter-based Nano-formulation to improve cellular uptake

The presence of transporters in the body mostly regulates the processes of drug absorption, distribution, and excretion. It also decides whether the drug will function at the target site. Changing the drug with the nano-preparation will enhance the drug's physicochemical properties and increase the drug's exudation at the target site[3].

Advanced techniques for drug delivery

1. 3D printing-based drug delivery technology

It is a layer-by-layer process technology able to create formulations for the delivery of 3D drugs from digital designs. It has advantages in manufacturing complex, customized, and on-demand products that improve the safety, efficacy, and accessibility of medicines[2]. Examples of 3D printed tablets: Ibuprofen (NSAID); Captopril: (Hypertension)[6]

2. Microneedle-based transdermal drug delivery technology

It has greatly accelerated the development of the transdermal drug delivery system. The microneedle can penetrate the transdermal delivery systems' stratum corneum barrier without reaching the nerve fibers and blood vessels[2].

3. Nanocrystals

It is stabilized by surfactants and their particles are composed of pharmaceutical active ingredients without any carriers leading to increased dissolution rate[2].

4. Prodrug Nanomedicines

It is a bio-reversible derivative of the generally inactive drug molecules that can be transformed into their active forms[2].

Conclusion

Important progress has been made in the last three years in the delivery mechanisms, and alternative materials to improve product bioavailability, biocompatibility, and therapeutic index. Developing innovative drug delivery systems and new formulations will be possible and effective solutions to improve such therapeutic indices and rising side effects. However, balancing draggability and practical design should not be overlooked, as the final emphasis of this research should be the clinical application[2].

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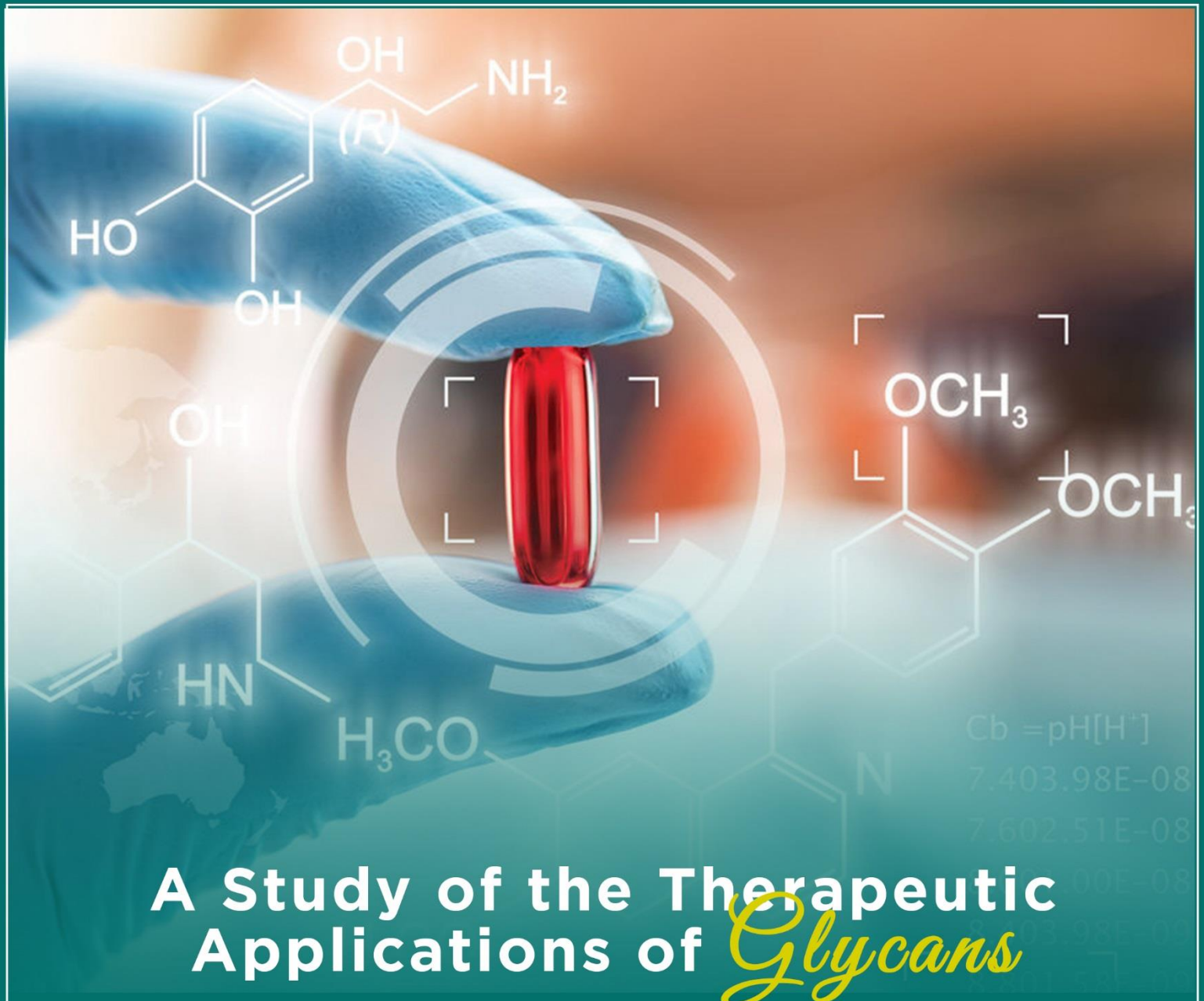

A Study of the Therapeutic Applications of *Glycans*

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A Study of the Therapeutic Applications of Glycans

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An overview of glycans

Glycans are a universal component of cells and are represented either by a polysaccharide complex (when they are a part of the mucus) or by polysaccharides conjugated with lipids or proteins. In addition, they can be connected by a matrix of stereochemical bonds, leading to a wide variety of structures. Furthermore, by changing the functional groups of the molecules, several types of glycans can be created, such as glycans connected to the nitrogen atom, which contain mannose, fucose, galactose, sialic acid, and N-acetylglucosamine in various proportions[1].

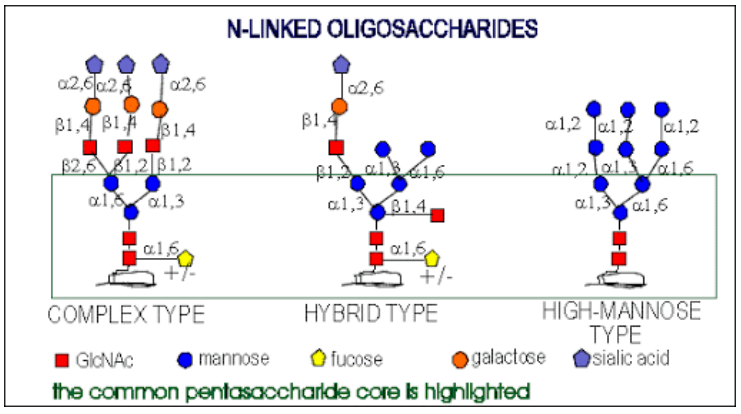

FIGURE 1: The structure of N-linked glycans

Glycans play a key role in cell adhesion, migration and development, disease progression, and modulation of the immune response. In spite of this, they are not directly encoded by the genome; their biosynthesis and assembly being entirely dictated by the metabolism and the cell status. Because of this, the formulation of glycane-based drugs has been a difficult process, hampered by a lack of necessary medical technology, until the early 21st century when a limited number of such drugs appeared on the market[2].

21st century drugs

The first group of glycans that are used as drugs is small molecule glycans. They inhibit some enzymes whose activities are directly involved in pathological mechanisms of certain diseases such as diabetes or Gaucher disease.

Acarbose inhibits intestinal glucosidases and amylases, thus reducing the quantity of carbohydrates absorbed in the gut. In this role, it is used to treat type II diabetes mellitus.

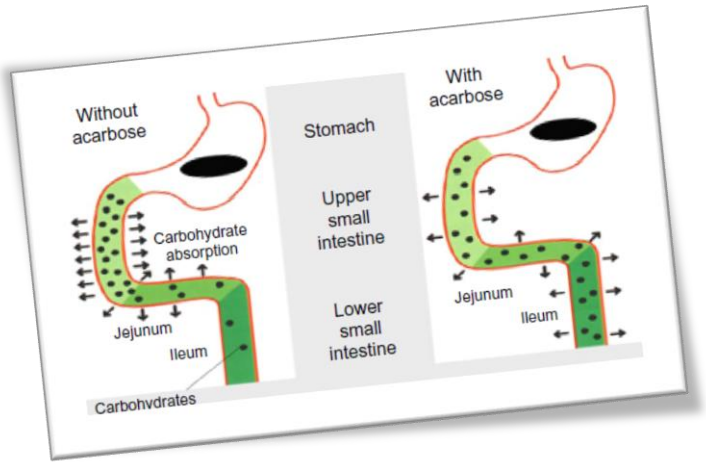

FIGURE 2: The mechanism of action of Acarbose

Miglustat (Miglitol) inhibits glycosyltransferases involved in sphingolipid biosynthesis. It is used to treat type I Gaucher disease[3].

Another example of small molecule glycans are glycosaminoglycans (GAGs). These are a class of linear polysaccharides secreted by and

linked to the cell surface. The main representatives are hyaluronic acid, dermatan sulfate, keratan sulfate, and heparin [FIGURE 3], the latter being a successfully used anticoagulant (Fondaparinux)[4]. [FIGURE 4]

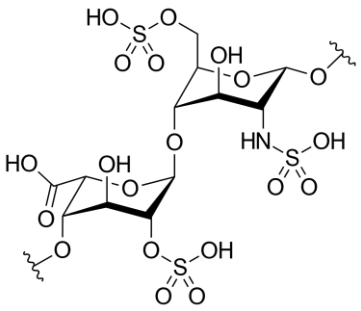

FIGURE 3: Heparin

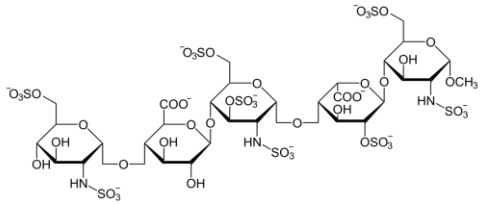

FIGURE 4: Fondaparinux

The second group of glycans used as drugs is represented by glycodendrimers. These are macromolecules made up of monomers that are spatially arranged in a tree form around a multifunctional central nucleus. The three-dimensional structure gives them a high degree of functionality and versatility, the dendrimers often being called "the polymers of the 21 st century"[5]. [FIGURE 5]

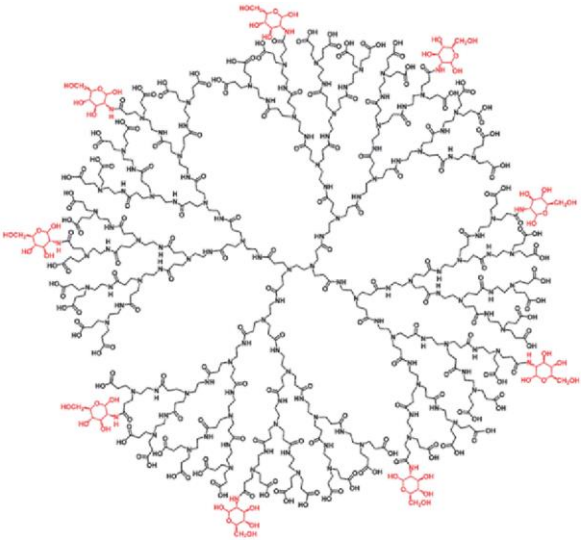

FIGURE 5: The structure of a glycodendrimer

In the pharmaceutical field, the most prescribed glycodendrimers are STARFISH and recombined DC-SIGN[6]. Starfish has in vitro inhibitory activity against the Shiga toxin which causes gastrointestinal disorders[7]. [FIGURE 6]

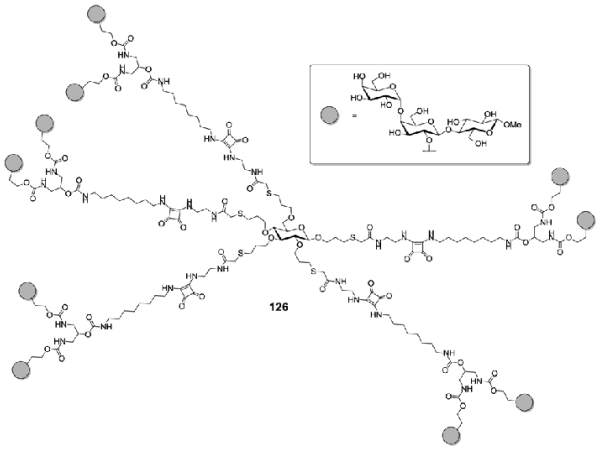

FIGURE 6: The STARFISH molecule

DC-SIGN is used to prevent HIV infection. It has a structural region to which various viruses bind through the mannose-rich fraction on their protein coat[8]. GAGs work in a similar way; the main difference being the structure of the GAG binding site viruses. Thus, certain changes in the structure of DC-SIGN or GAG can prevent the entry of viruses into the host cell. [FIGURE 7]

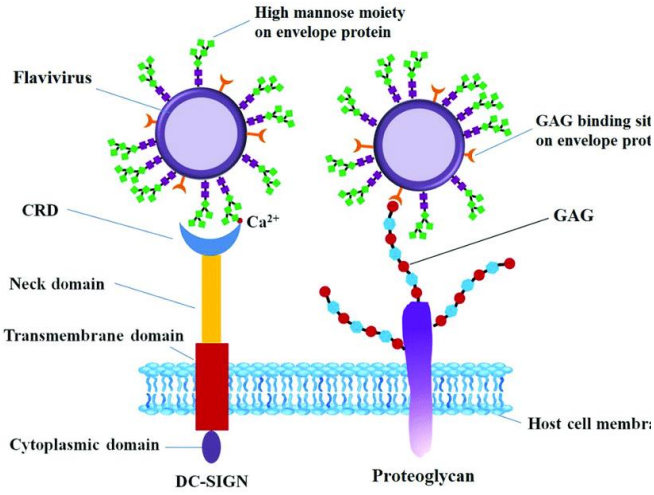

FIGURE 7: The structures of recombined DC-SIGN and GAGs

The third group of glycans used as drugs is represented by carbohydrate-based vaccines. These can be of two types: natural and synthetic.

Among the natural ones are the vaccines against Neisseria meningitidis (MENACTRA [FIGURE 8]), Streptococcus pneumonia (PREVNAR), Haemophilus influenzae type b (HIB, HIBERIX, COMVAX), and Salmonella typhi (TYPHIM Vi).

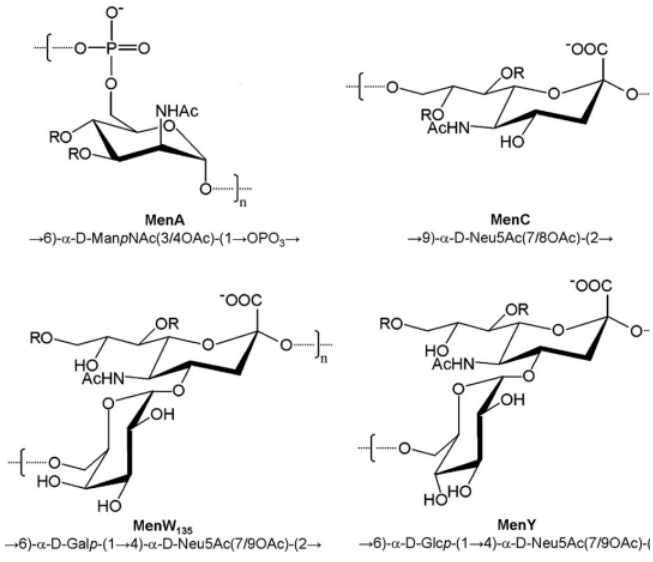

FIGURE 8: Menactra

However, these constructs use non-specific methods of conjugation to carrier proteins. Because of this, many recent advances have been made in the use of glycogenated synthetic vaccines to create better-defined therapies that generate carbohydrate vaccines selectively attached to protein carriers[4].

The most successful case was the production of the Cuban Hib vaccine. This is the first fully synthetic, clinically approved carbohydrate vaccine based on the structure of the capsular polysaccharide antigen from Hib[4].

The malaria vaccine made by the automatic synthesis of glycosylphosphatidylinositol (GPI) from Plasmodium falciparum has been shown to be effective against many symptoms that are normally found during this parasite infection, including cerebral acidosis and pulmonary edema[4].

Moreover, the first synthetic vaccine created against cancer cells was GLOBO H [4]. [FIGURE 9]

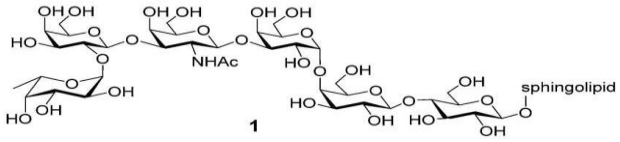

FIGURE 9: GLOBO H

The fourth group of glycans used as drugs is represented by proteins obtained by glycoengineering. The majority of them are produced as a mixture of glycoforms, each with its own biological efficacies and properties that must be adjusted for therapeutic application[9]. For example, the physical properties of glycosylation may protect proteins against proteolysis or increase the stability and solubility of the respective compounds. In addition, each glycoform may have a distinct biological response, with differences in pharmacodynamics and effector functions. Protein-based therapies must be constantly monitored, even blockbuster drugs showing changes in glycosylation status over time[9].

Oligosaccharides linked to variable antigen domains can slow or enhance antigen binding, prevent the interaction between 2 proteins by creating a steric barrier, extend the half-life of the antibody, and interfere with the aggregation and formation of immune complexes[9] [FIGURE 10].

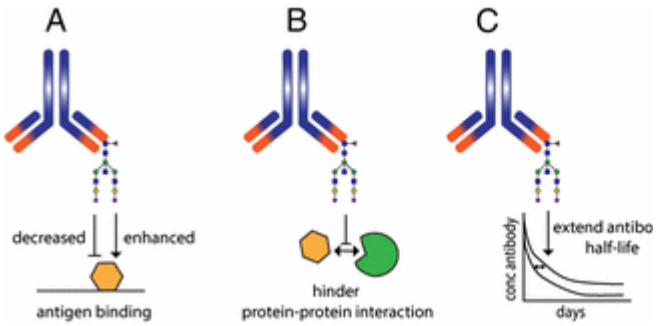

FIGURE 10: Influence of Fab glycosylation on IgG function

Glycosylation can also affect the efficacy of many other therapeutic proteins. For example, recombinant EPO (epogen) is widely used to treat anemia[10] [FIGURE 11].

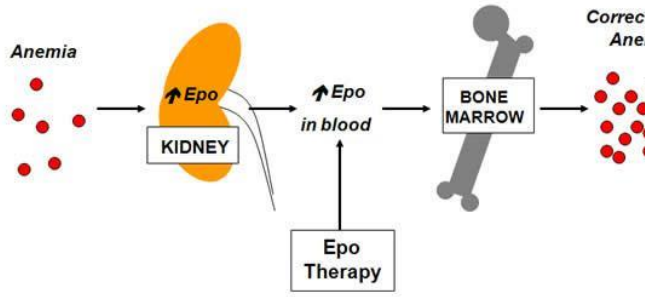

FIGURE 11: Epo Therapy

Another method of creating new glycoforms is cell interface glycine engineering. This means introducing ketone, azide, thiol, and alkynyl functional groups into glycans. The ketone group added to sialic acid plays a role in targeted anticancer therapy. Activated endothelial cells secrete selectin which helps cancer cells roll over the endothelium and migrate to other areas of the body[11] [FIGURE 12].

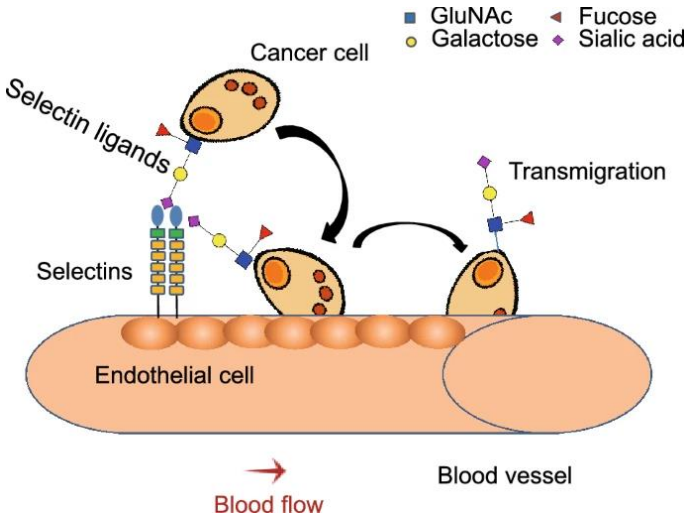

FIGURE 12: The role of selectin-binding ligand in tumor metastasis

There is also the possibility of removing glycan epitopes from the surface of various molecules, a technique used to create different blood types[4] [FIGURE 13].

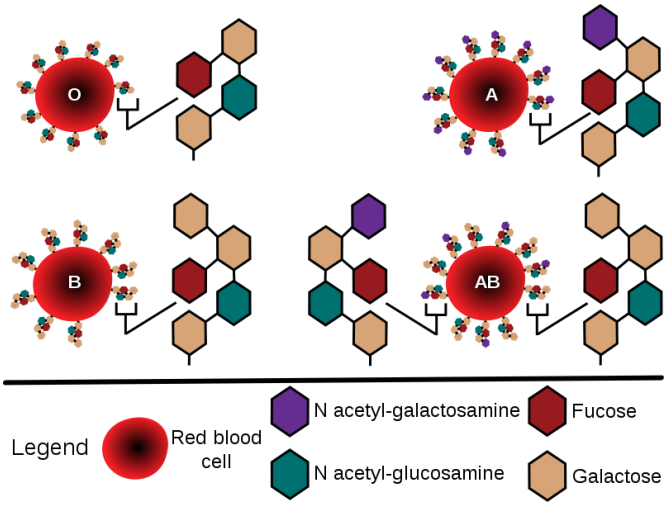

FIGURE 13: Diagram showing the carbohydrate chains that determine the ABO blood group

Perspectives

Glycans promise great advances in areas as diverse as pharmacy, medicine, and bioengineering. By being involved in a multitude of physiological processes, they could be used as new drugs for treating a variety of conditions from cancer and various infectious diseases to skin aging.

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3D Cell Cultures

Two Models for Testing New Drug Delivery Systems

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3D Cell cultures – Two models for testing new drug delivery systems

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Introduction

The development of novel drug delivery systems represents one of the most studied fields in pharmaceutical technology research. Delivery systems, able to mediate cell-specific targeting, offer great potential to treat diseases more effectively while reducing drug side effects. 3D cell cultures provide a model that better reflects the complexity and spatial organization of the human body in comparison to conventional 2D models. 3D cultures have been applied in many research fields such as tumour biology, cell adhesion, cell migration and epithelial morphogenesis. Moreover, 3D cultures can help to reduce animal testing[1]. The aim of our research was to integrate T cells in 3D co-cultures. T cells play a key role in several diseases and are being investigated extensively as targets for immunotherapy. Here, we specifically focused on two diseases, asthma and pancreatic cancer, for which T cell targeted treatment is promising. The aim of this study was to determine if it was possible to co-culture T cells with other cell types in 3D cell cultures and what impact it has on the culture environment. First, we developed an Air-Liquid Interface (ALI) co-culture model formed by bronchial epithelial cells and T-cells. Second, we cultured a subset of T cells, T regulatory cells, with pancreatic cancer cells in a spheroid model.

Air-Liquid Interface

Air-Liquid Interface (ALI) is a special cell culture technique used to mimic the lungs more closely by culturing epithelial cells exposed to the air. For ALI cultures, we used so-called transwells that are formed by an apical and a basolateral chamber. The basolateral chamber contains cell culture medium, while cells are grown on the apical one [FIGURE 1]. The two compartments are separated by a thin polyester membrane, in which cells grow to form the epithelium, fed by the media on the one side and in contact with the air on the other. Establishing an intact epithelium on the upper chamber required several steps. On the first day, medium was poured in both chambers and epithelial cells were seeded on the apical side of a 0.4 µm polyester membrane in 11 wells. In this study Calu-3 cells, a bronchial epithelial adenocarcinoma cell line, were chosen due to their ability to develop tight junctions, as they express high levels of occluding and e-cadherin[2(p11)]. Tight junctions are an essential element to form a solid epithelium. In the first days of submerged culture, cells attach to the membrane until confluent, forming a monolayer. After three days, the airlift is performed. This step consists of the removal of the medium from the apical chamber and the replacement of the medium in the basolateral chamber with an ALI-specific medium. Afterwards, Calu-3 cells can differentiate into an epithelium which highly resembles in vivo epithelium due to air exposure[3(p3)]. The development of the epithelium is measured as transepithelial electrical resistance (TEER). TEER is the difference in electric potential across the epithelium, i.e. in the two chambers. An epithelium in an advanced stage of development shows higher TEER values, which

are proportional to the number of tight junctions, and correlates with increased barrier functionality. The final TEER value is calculated by subtracting the electrical resistance of the filter insert in the absence of epithelial cells (blank) from the value measured with cells, and then multiplying the result by the surface area of the insert. Hence, the result of TEER is given in Ω per cm^2 [2(p7)]. With this tool we were able to monitor the development of the epithelium. On Day 7, high values of TEER were reached and we added Jurkat cells in the basolateral chamber. Jurkat cells are human leukemia T-cells that produce high amounts of interleukin-2 (IL-2). IL-2 is a T-cell growth factor that helps to culture them, through stimulating proliferation. Jurkat cells are the most popular cell line used for T-cell experiments[4]. The idea behind this 3D model was to create a system able to mimic the lung environment of asthmatic patients. This was in turn used to test the ability of an siRNA-based therapy to cross the airway epithelium and reach activated T cells. Once the siRNA polyplexes reach T cells, they can reduce the production of cytokines by downregulating a key mediator of the inflammatory response. This therapy could help in treating patients affected by severe asthma and help in preventing acute episodes[5(p2)]. We saw that culturing these cells together in the Air-Liquid Interface had no negative effects on the 3D culture. Both cells were able to grow in culture and tight junctions were not affected by the presence of Jurkat cells. The TEER values were still rising on the day after adding the T cells. This means that IL-2 secreted from Jurkat cells does not affect barrier intactness and this 3D model is potentially applicable for testing inhaled drug delivery systems.

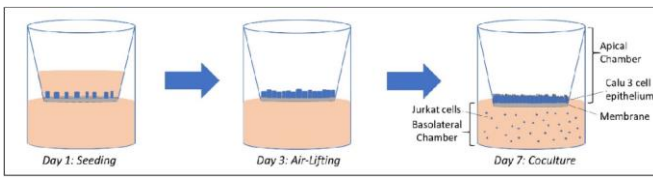


FIGURE 1: Development of the Air-Liquid interface model.

Pancreatic Cancer Spheroids

Spheroids are 3D cellular conglomerates in which cells are allowed to assemble unconstrained without scaffolding material. In our case, cells spontaneously formed spheroids in a static suspension[6]. Sutherland et al. showed that multicellular spheroids could be exploited to discover the interactions happening in the tumor microenvironment[7]. Based on these results, we developed a co-culture model to imitate the tumor conditions. The co-culture was composed of three cell lines: first, the PANC-1 cell line, which are pancreatic cancer cells. Second, the Human Pancreatic Stellate Cells (HPaSteC), the fibroblastic cells of the pancreas responsible for the extracellular matrix, and third T regulatory cells (Treg). The pancreatic cancer microenvironment is characterized by a heterogeneous cellular population, with stellate cells and T regulatory cells amongst others[8(p7),9]. To obtain a higher resemblance to the tumor in the spheroid model, we incorporated the three different cellular types mentioned above. We gathered primary T regulatory cells from blood samples. First, cells were separated from plasma through density centrifugation. Then the Tregs were separated from the other cells via magnetic-activated cell sorting (MACS). Here an antibody connected to a magnetic particle binds to a specific target, in our case the CD4 and CD25 receptors on the cell surface[10(p12)]. CD4 and CD25 are specific, amongst others, for T regulatory cells[11(p487)]. After a short incubation time, the tube containing the cells is placed in a magnet. The cells presenting the surface markers are held at the tube walls due to the binding of the magnetic particles, while all other cells are easily removed by discarding the supernatant. Several washing steps are required to collect the final cells. The purity of this sorting was then confirmed by flow cytometry with appropriate antibodies and was about 96%. The Treg cells were held in suspension for two days for activation with phytohaemagglutinin

and IL-2. On day 3, the spheroids were seeded in the following ratio: PANC-1: HPaSteC: Treg 1200: 600: 600 cells per well in a volume of 100 µl. We used a 96 well plate with ultra-low-attachment, one plate with Treg and one without as control. We took images of the spheroids, six different per plate, to study the morphology [FIGURE 2]. Augustine et al. found differences in morphologies when incorporating Tregs in 3D cell cultures[12(p11)]. We also observed a distinct change in spheroid morphology with the addition of Tregs [FIGURE 2]. Spheroids with Tregs were not as compact as the control group and less spherical and intact. The spheroid size was 540-660 µm for the control group and about 690 µm for the spheroids with T regulatory cells. This difference in morphology underlines the important role played by T regulatory cells in the tumor microenvironment. Durymanov et al. showed that spheroids of pancreatic cancer can be used to test nanoparticle delivery to the tumor in an in vitro setting[13(p188)]. In fact, this co-culture composed of three different cell lines gives a better representation of the tumor and could also be used to study specific treatments especially in immunotherapy. One idea is to specifically target and deplete Treg with novel drug delivery systems.

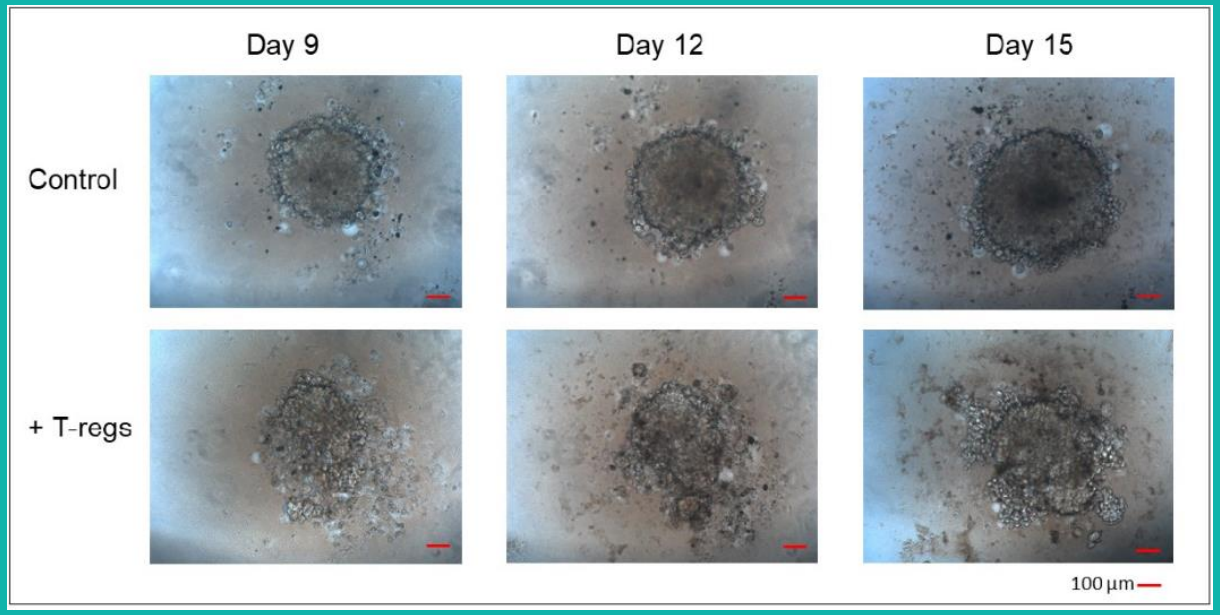
FIGURE 2: Different morphology in the spheroid's development.

Conclusion

With these 3D co-culture models, we were able to study the effect of T cells on these cultures. We obtained a better understanding of their interactions with other cell types and the models we developed could represent a promising strategy to test new drug delivery systems.

Acknowledgment

I want to thank DAAD for the opportunity and financial support for a research project in the lab of Prof. Reineke. In addition, thank you to Prof. Merkel, Prof. Reineke, Domizia Baldassi and Ailin Guo for all their support during these projects.



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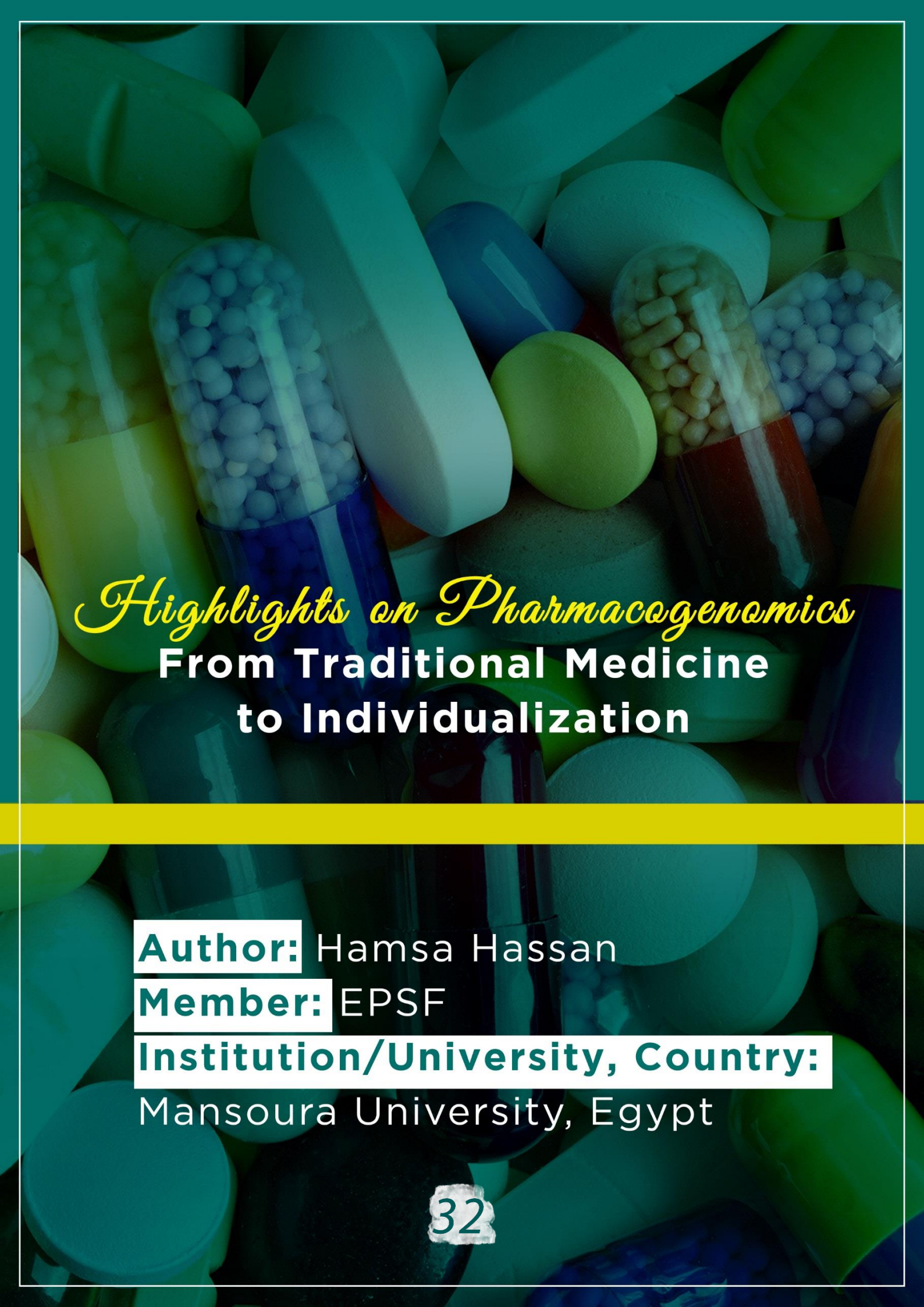

Highlights on Pharmacogenomics

From Traditional Medicine to Individualization

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Highlights on Pharmacogenomics:

From Traditional Medicine to Individualization

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Introduction

Taking medicines is an important action that is present in a lot of people's daily routine who's life may be dependent on these drugs, but it also exposes us to one of its unwanted features, adverse drug reactions (ADRs). According to a study that was established in the USA, in 1998, it revealed that ADRs account for more than 100.000 deaths each year, which makes them the fourth cause of death following heart diseases, cancer, and stroke[1].

ADRs are classified according to the degree of danger. Scientists consider some of them are safe, but 6.7% of them are fatal with a 0.32% death rate among patients admitted to the hospitals because of ADRs, and those having ADRs while being in hospitals[12].

Researchers have oriented their efforts to obtain the reason why some drugs can be safe and effective with patients, but ineffective with others, despite the same dose. They found that genes are the only variable controlling these unwanted events. This article is going to discuss the main aspects of pharmacogenomics, barriers against its implementation, and the role of pharmacists in this field.

History

When a drug is administered to the body, it may be affected by some factors including: age, sex, diet, concomitant medications, persistent medical conditions, and body weight. The term "pharmacogenetics" was firstly introduced in 1959 to describe the association between genes and drugs. The variety of genes encode metabolizing enzymes will affect body response to the same drug with a similar dose. This may require drug alteration or dose modification to avoid ADRs or ineffectiveness[3] [FIGURE 1][4]. Pharmacogenomic testing helps identify possible adverse drug reactions, toxicity, or absence of efficacy. There are several drugs reported as being affected by genes, and it is necessary to carry out the test before prescribing them to decide whether to adjust the dose or shift to an alternative drug[3].

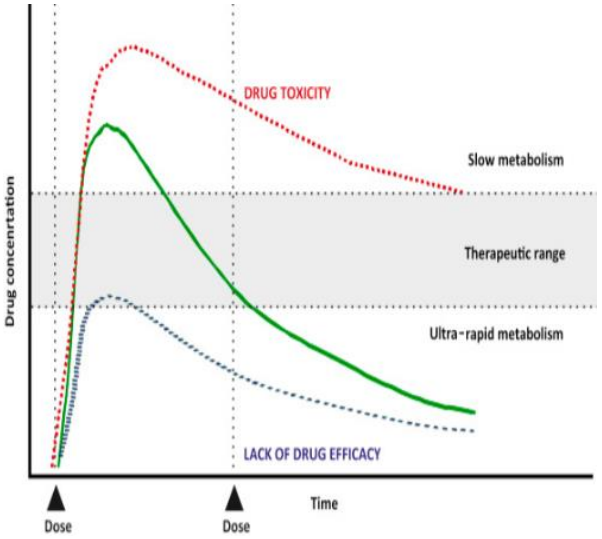

FIGURE 1: Variable drug responses the rate of metabolism

Examples of drugs affected by genes

a) Isoniazid

It is used in combination therapy for the treatment of tuberculosis. N-acetyltransferase

2 (NAT 2) gene participates in metabolizing isoniazid to be excreted from the body. Patients with low or no NAT 2 are considered as slow acetylators, and hence the drug will remain longer in their bodies making them vulnerable to toxicity. A randomized clinical trial has revealed that dose reduction may decrease the incidence of hepatotoxicity, and other serious side effects in slow acetylators[3].

b) Clopidogrel

This is a prodrug, used in antiplatelet therapy. P450 CYP2C19 gene is essential for the expression of the enzyme that contributes to the activation of clopidogrel into the active form; to reduce platelet aggregation rate. The FDA stated that CYP2C19 poor metabolizers may not benefit from it. Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends the use of another antiplatelet drug such as ticagrelor in poor metabolizers[3].

Importance

Pharmacogenomic testing is crucial to improving therapeutic outcomes, minimizing adverse drug reactions and toxicity, and avoiding drugs that will not give any therapeutic response, despite their cost. It will help design the right drug and dosage regimen for each unique patient[3]. From all of the above, precision medicine or an individualized medicine approach has been proposed. This refers to tailoring the medication according to the patient's medical record, and especially, his genes[6].

Oncology

Cancer is considered one of the most interesting topic areas in precision medicine. Genetic tests predict the risk of developing a certain medical disorder, in addition to the determination of the drug of choice. Some genetic mutations involved in different types of cancer have been established (e.g. BRCA 1 and 2 in breast cancer). Pharmacogenomic testing helps identify the best medication (e.g. Herceptin is used in the treatment of female breast cancer with HER-2 expression [FIGURE 2][7])[8].

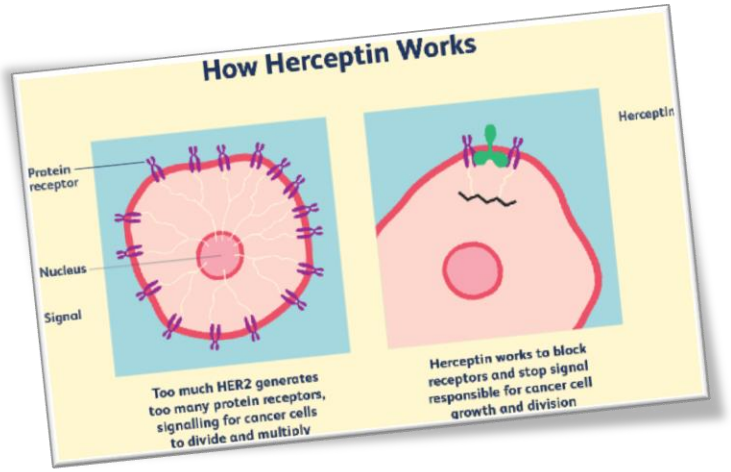

FIGURE 2: Herceptin therapy for breast cancer

Challenges

1. The diversity of pharmacogenomic testing guidelines between different professional organizations and lack of recommendations to support clinicians.
2. Next-Generation Sequencing (NGS) allows to test many individuals at once, that is why it is cost-effective. It has some challenges:
    a. No appropriate infrastructure (database or server);
    b. No skilled personnel to deal with the results;
    c. It is not able to activate the validation process (sensitivity, specificity, positive, and negative predictive value) when there is more than one analyte.
3. Most of the drugs are affected by the CYP2D6 gene, which has a very complex structure with over 100 variants. It is confusing while analyzing and interpreting the results.

4. The drugs are not administered in isolation (more than one gene affects the response of the drug), leading to collecting the results from multiple genes.
5. Non-white populations are not included in databases heavily.
6. Ethical issues related to privacy and financial obstacles[9].

Solutions proposed to overcome these challenges

1. Clinicians should be provided with education and resources that keep them in touch with the updated pharmacogenomics guidelines. PharmGKB will help the clinicians to determine the necessity of carrying out the test.
2. Precise documentation of the NGS process used to generate the results.
3. Adoption of quality assurance testing.
4. Compliance with all relevant policies.
5. Involvement of highly skilled personnel[9].

Pharmacist's role in pharmacogenomics implementation

Pharmacists must have a basic understanding of pharmacogenomics to provide appropriate patient care recommendations since they are responsible for patients and other health-care providers' education. Besides, it is important for pharmacists to participate in research to accelerate the implementation of pharmacogenomics into clinical practice. Pharmacists are responsible for designing a patient's specific drug and dosage regimen, based on the medical records, and especially the patient's pharmacogenomic profile[5].

Relevant education

Pharmacy schools have adopted some educational courses related to pharmacogenomics. Pharmaceutical students may be prepared for a Master's degree in clinical pharmacogenomics, and other related diplomas, after their graduation to fit this career pathway[10].

Conclusion

Pharmacogenomic testing is improving every day with new techniques. Newly discovered genes help us identify and predict possible adverse drug reactions. Although the cost is still debatable, we predict it will fall soon and the personalized medicine approach will be available for everyone.

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Digital Health
Together Against Coronavirus

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Digital Health - Together Against Coronavirus

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Introduction

Imagine that you or anyone of your family are sick and you are in a bad need to see a doctor, but you can't because we are in quarantine due to COVID-19: what will you do? One could advise you to use technology: digital health and telemedicine can provide you with clinical health care and medication counseling without the need to leave your house.

So, what is Telehealth (Digital health)?

Generally, telehealth is the utilization of telecommunications technologies and electronic information to support and promote long-distance clinical health care, patient and professional health education, health administration, and public health[1].

Categories of digital health:

1) Mobile health:

Digital health sector providing healthcare support, delivery, and intervention via mobile technologies[2].

2) Health information technology:

HIT is the area of healthcare that oversees the technology systems healthcare providers use to manage patient data. HIT includes technology like digital health records (DHRs) and e-prescriptions.

3) Medical Wearable Device:

Electronic devices that consumers can wear, like smartwatches, which are designed to collect the data of users, personal health, and exercise[3].

4) Personalized Medicine:

Tailor therapy with the best response and highest safety margin to ensure better patient care by enabling each patient to receive earlier diagnoses, risk assessments, and optimal treatments[4].

5) Telehealth - "healing from a distance":

The use of telecommunications and information technologies to provide remote clinical services[5]. Unlike telemedicine, telehealth also covers non-clinical events like continuing medical education (CME), administrative meetings, and physician training. Telehealth is not a specific service, but a collection of methods to improve patient care and education delivery[1].

Generally, one can think of digital health as all-encompassing, as telemedicine and telecare fall under its umbrella.

Source: IQVIA

History of Telemedicine:

Telemedicine has been used since the 1960s in the sectors of the military and space. Over the past several decades, the use of wireless broadband technology has become more advanced. Telemedicine protects both the physician and patient; preventing possible spread of COVID-19 while allowing for an effective patient care system. Much advancement has been made to modify smart devices to be used as smart stethoscopes, otoscopes, and taking high definition photographs for physician assessment[6].

Examples of telemedicine applications:

1) Teleradiology (gap service coverage): obtaining specialist opinion by the transmission of digital X-ray images to a radiologist elsewhere. Teleradiology is an example of an important acute care telemedicine service to rural hospitals in the rapid diagnosis of strokes and traumatic injuries.
2) Telestroke (urgent service): model urgent telemedicine services used during the "golden" 1 to 3 hours when intravenous thrombolysis tissue plasminogen activator can be administered to eligible patients with acute ischemic stroke.
3) The electronic intensive care unit program: a commercialized version of a computerized decision support system originally developed by intensivists which combines clinical expertise, vital sign monitoring, trending, alerting, and electronic expert systems[7].

   Ex1: Application of telemedicine during the COVID-19 pandemic in India: Telemedicine provides us with a useful opportunity to help diabetic patients and other endocrine diseases. Encouraging management points include dose adjustment of anti-hyperglycemic agents, demonstration of the correct way to inject insulin, diagnosis of skin lesions (e.g. chickenpox), foot infections, and gangrene[8].

   Ex2: Digital therapeutics (DTx): Software that delivers a clinical mechanism of action, either alone or in combination with other standard-of-care treatments, to improve outcomes. DTx products have different potential functions including modifying patient behavior independent of the use of a pharmaceutical product, modifying the

use of medications, and treating a medical condition or affecting the underlying physiological response of the patient to provide data to health care providers[9].

How pharmacists use Digital therapeutics (DTx)?

DTx products require a prescription and will have their distribution to patients managed by providers, including pharmacists and patient-service centers; others are available on a nonprescription basis and can be obtained through a wide range of platforms. Pharmacists also have skills and expertise focused on optimizing medication treatment regimens that can be applied to support the use of DTx. Managed care pharmacists supporting formulary drug systems are skilled in appraising, evaluating, and selecting drugs for the formulary; they also have experience utilizing both subjective and objective patient information to direct medication use and adapt these skills to assessments of DTx data. Community pharmacists can recommend DTx, help monitor patients' therapy, receive results, and counsel patients on the use of prescription drug use related software so that patients use the product correctly and understand the software component. They can also educate patients about the availability of these products and their use in conjunction with traditional prescription drugs, and direct patients to the appropriate coverage options (e.g., over the counter or medical coverage)[9].

Telemedicine is experiencing a bubble which will burst post-COVID-19 virus:

Normally, regulations and pricing issues might stifle its growth, as it has been the case so far, though another public health crisis is likely to happen; in less than a decade, we've seen Ebola, Zika, and COVID-19 viruses. Health systems have developed automated logic flows that refer moderate to high-risk patients to nurse triage lines but are also permitting patients to schedule video visits with established providers, to avoid travel to in-person care sites[7].

Obstacles of telemedicine:

1) Poor internet connection leads to poor audio/video quality.
2) Improper handling of smartphones.
3) Poor understanding/poor hearing ability.
4) Patients sometimes still need to be physically present for the collection of samples for imaging and laboratory testing[8].

Source: Jabil

Conclusion:

Digital health is a positive contribution to healthcare and telemedicine could promote patient disease management, and facilitate in-between health care visit monitoring as hospitals are learning to adapt to telehealth during pandemics. However, more research is needed to determine optimal methods to integrate telemedicine into routine clinical care.

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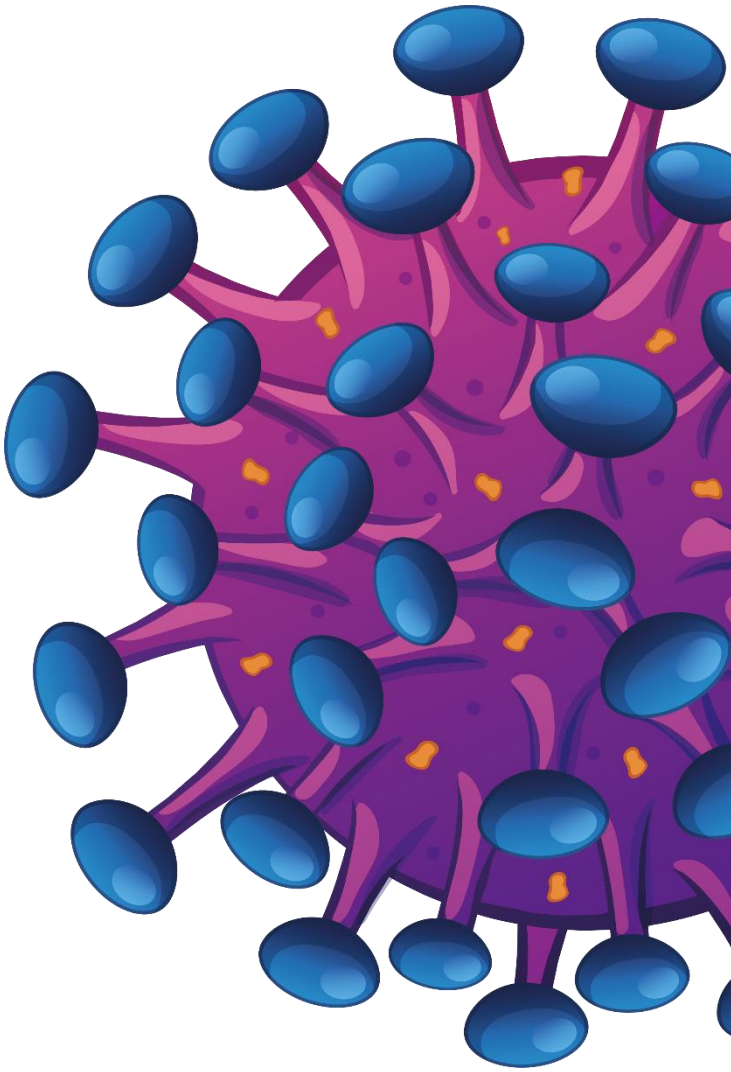

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