*Meeting Report*

# KAIMRC'S Second Therapeutics Discovery Conference

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**Abstract:** Following the success of our first therapeutic discovery conference in 2017 and the selection of King Abdullah International Medical Research Centre (KAIMRC) as the first Phase 1 clinical site in the Kingdom of Saudi Arabia, we organized our second conference in partnership with leading institutions in academic drug discovery, which included the Structural Genomic Constorium (Oxford, UK), Fraunhofer (Germany) and Institute Material Medica (China); the participation of members of the American Drug Discovery Consterium; European Biotech companies; and local pharma companies, SIPMACO and SudairPharma. In addition, we had European and Northern American venture capital experts attending and presenting at the conference. The purpose of the conference was to bridge the gap between biotech, pharma and academia regarding drug discovery and development. Its aim primarily was to: (a) bring together world experts on academic drug discovery to discuss and propose new approaches to discover and develop new therapies; (b) establish a permanent platform for scientific exchange between academia and the biotech and pharmaceutical industries; (c) entice national and international investors to consider funding drugs discovered in academia; (d) educate the population about the causes of diseases, approaches to prevent them from happening and their cure; (e) attract talent to

consider the drug discovery track for their studies and career. During the conference, we discussed the unique academic drug discovery disrupting business models, which can make their discoveries easily accessible in an open source mode. This unique model accelerates the dissemination of knowledge to all world scientists to guide them in their research. This model is aimed at bringing effective and affordable medicine to all mankind in a very short time. Moreover, the program discussed rare disease targets, orphan drug discovery, immunotherapy discovery and process, the role of bioinformatics in drug discovery, anti-infective drug discovery in the era of bad bugs, natural products as a source of novel drugs and innovative drug formulation and delivery. Additionally, as the conference was organized during the surge of the epidemic, we dedicated the first day (25 February) to coronavirus science, detection and therapy. The day was co-organized with the King Saud bin Abdulaziz University for Health Sciences, Kingdom of Saudi Arabia(KSA) Ministry of Education to announce the grant winner for infectious diseases. Simultaneously, intensive courses were delivered to junior scientists on the principle of drug discovery, immunology and clinical trials, as well as rare diseases. The second therapeutics discovery forum provided a platform for interactive knowledge sharing and the convergence of researchers, governments, pharmaceuticals, biopharmaceuticals, hospitals and non-profit organizations on the topic of academic drug discovery. The event presented showcases on global drug discovery initiatives and demonstrated how collaborations are leading to successful new therapies. In line with the KSA 2030 vision on becoming world leaders with an innovative economy and healthy population, therapeutic discovery is becoming an area of interest to science leaders in the kingdom, and our conference gave us the opportunity to identity key areas of interest as well as potential future collaborations.

## 1. First Day (25 February 2020): Opening Ceremony and Workshop Program

Coinciding with our second therapeutic discovery conference, COVID-19 established itself as a worldwide pandemic. Our program already included a full session on infectious diseases, with a particular focus on coronavirus. The first day was jointly co-organized with the KSA Ministry of Education to award the scientists whose grants focused on the infectious diseases with funding by the ministry. The program was led by Dr. Mai Alajaji, Vice-Dean of the Pharmacy College, female campus, who was among the awardees on a proposal for the culture-independent discovery of new antibiotics from soil metagenomes. The project is to be carried out in collaboration with Prof. Sean Brady from Rockefeller University, who is a pioneer in the field. Other programs awarded were also in collaboration with international researchers in Europe and USA. These included the following projects: (a) an integrated approach with in vivo molecular imaging and machine learning to characterize tissue microenvironments for the accurate diagnosis and prognosis of infection, inflammation and cancer; (b) the usage of modern technologies to predict the emergence of infectious diseases and to detect outbreaks of pandemics; (c) the elicitation of protective immunity against multi-drug resistance to *Acinetobacter baumannii* by removing inhibitory natural anti-glycan antibodies; (d) the development of rapid and efficient diagnostic platforms for the detection of emerging viruses in KSA; (e) the preclinical evaluation of the immunogenicity, efficacy and safety of a novel Rad vector-based trimeric S1 vaccine against MERS-CoV; (f) the design and development of cost-effective rapid diagnostic tests for infectious diseases. The morning opening ceremony ended with the signing of two Memorandom of Understanding

MOUs between KAIMRC and the local pharma industry, SPIMACO and SudairPharma to collaborate on drug discovery and development. The afternoon program included intensive courses starting with "Foundation Workshop: Introduction to Drug Discovery", delivered by Dr. Sheraz

Gul, Fraunhofer, Germany, and KAIMRC medicinal chemist Dr. Imadul Islam. After that, there were three workshop tracks: (a) "Comparative effectiveness of therapeutics—Differentiating alternative phenotype-guided therapies", led by Mr. Saeed Noibi, GlaxoSmithKline (GSK); (b) "ImmunoAssay for Drug Discovery", delivered by Dr. Tlili Barhoumi, KAIMRC; (c) "Process to Target Validation: Rare Diseases", led by Prof. Wyatt Hue, Structural Genomics Consortium (SGC), Oxford, UK. The total number of attendees of the courses was 150, including junior researchers, medical doctors, pharmacists and universities faculty members. The attendees were also given the chance to have a one on one meeting with the respective speakers. They also later had the opportunity to visit KAIMRC's research facility and, in the late afternoon, they were escorted for a social tour of Riyadh's historical sites.

## 2. Second Day (26 February 2020): Focusing on Academic Drug Discovery

Learning from our first therapeutic discovery conference in 2017 [1], the program of 25 February 2020 was divided into three sessions followed by a round table discussion. We aimed to introduce academic drug discovery as a research theme of high priority. In addition, we discussed infectious diseases, an area that is currently affecting the world, and rare diseases, which are a prominent issue for the local population.

### 2.1. Session 1: Academic Drug Discovery Platforms

The academic drug discovery platform session started with an outstanding presentation by Dr. Sheraz Gul from Fraunhofer Institute, Hamburg, Germany. At the outset, Dr. Sheraz emphasized the need for collaboration and coordination between academia and the pharmaceutical industry. He laid the groundwork for the benefits, attributes and achievements of academic drug discovery. With the high cost of drug discovery and development, Dr. Sheraz discussed the paradigm shift in bioscience drug discovery. To contain the cost of drug discovery to a reasonable amount, investing in academic drug discovery makes good scientific and financial sense. He mentioned that approximately half of the drugs launched by pharmaceutical companies have an academic or small biotech signature. Dr. Sheraz also mentioned that the process of drug discovery is more open and collaborative, and that academic institutions will play a crucial role in providing a research foundation which will lead to improvements in the discovery of novel medicines. He gave two case studies, one working actively with a partner using well-defined Clustered Regularly Interspaced Short Palindromic Repeats-associated Cas 9 protein (CRISPR-Cas9) variables which resulted in a patent and publication. He also talked about how working remotely on a project is a reality, given you have good collaborator.

The second presenter in the first session was Dr. Yasser Al Obaida, CEO and founder of SudairPharma, KSA. Dr. Yasser talked about the pharma sector in the Kingdom of Saudi Arabia. Saudi Arabia has the largest population out of the Gulf Cooperation Council (GCC) countries and has the largest market for pharmaceuticals. The pharmaceutical sales in the kingdom are approximately $9 billion and are increasing at the rate of 3% per year. Only 20% of generics are manufactured in the kingdom. He mentioned that more revenue comes from the oil sector but that the healthcare and pharma industries can become economy drivers. Dr. Yasser talked about the "Vision 2030" aims to transform the Saudi economy away from being oil based. Dr. Yasser mentioned that the pharmaceuticals industry will play a significant role in transforming the Saudi economy. He referred to salient features from Vision 2030, such as the national transition plan 2020, the national industrial strategy, the formation of industrial clusters and keeping the pharma industry as a key performer. He argues that the kingdom has resolved to increase its generic market share by 40% from 20% by 2030 and also to invest in biologics, biosimilars, sterile dosages, active pharmaceutical ingredients (API), vaccine production, plasma production and bioequivalence testing centers. Dr. Yasser concluded his presentation by informing the crowd that the pharma industry is in alignment with Vision 2030 and will be one of the most important industries in carrying the economy forward. Also, the kingdom is encouraging foreign investment in the pharma

industry to set up manufacturing plants to manufacture pharmaceuticals in partnership with Saudi individuals.

The last presenter was Dr. Julen Oyarzabal, who is a partner and Chief Scientific Officer of Columbus Venture Capital, a Spanish independent venture capital that invests in outstanding and high growth opportunities in life sciences. Since Dr. Julen was in academia, government and industry and is now partner in a venture capital entity, he gave the perspective of a venture capital firm on drug discovery in academia. Dr. Julen talked about the cost of developing a drug and how to control the cost to bring a medicine from "lab bench to clinic bedside". He put forth the argument that innovations not only come from the pharmaceutical industry, novel and disruptive science but that ideas similarly come from academic centers. Financial support from venture capital, reimbursement help from the government and fast track approval benefits and vouchers from regulatory agencies help to reduce the cost of approval and increase the benefits of getting medicine to patients. Then, he gave the example of Vivet Therapeutics, a gene therapy company that emerged out of research done at the University of Navvara. Researchers at the university focused on monogenic liver disease and adeno-associated virus as a gene delivery vehicle. Vivet was later acquired by Pfizer. Dr. Julen emphasized the collaboration between academic labs, pharma companies and venture funds to support new areas of research for the benefit of patients.

### 2.2. Session 2: Anti-Infective Drug Discovery in the Era of Bad Bugs

The last decades witnessed the emergence of new resistant bacteria and new viruses that negatively affect human health. These include antibiotic-resistant bacteria, Ebola, SARS-COV-1, MERS-COV and COVID-19. It has become necessary for biohealth researchers to focus on this important area of research by understanding their biology with the aim of discovering new therapies and diagnosis tools to manage the diseases. The session covered a wide range of topics, starting with a presentation by Dr. Lim Theam Soon from Universiti Sains Malaysia titled "Antibody Phage Display for Infectious Diseases". The presentation began with a brief walk down memory lane about the phage display technique development and the different types of antibody libraries—the naïve library, immunized library and synthetic libraries. Then, Dr. Theam talked about a case study of his own, which was the production of antibodies against the hemolysin toxin *S. typhi* using the phage display technique. He started his work by studying the immunogenic features of the HIyE toxin and the nature of the toxin. He concluded that the toxin was functional in its native form and denatured form. After that, he developed his approach, which was summarized in four steps: immunogenic, epitopes, in silico and monoclonal antibodies (Mabs) isolation. Finally, in the Mabs step, the Mabs were isolated and identified against the identified epitopes. Furthermore, he analyzed the structural conformational epitope of HIyE to check the interaction between the Mabs and the epitopes. For more confirmation, he conducted a site-directed mutagenesis analysis to highlight the most influential residues. Finally, the speaker concluded his presentation by summarizing the advantages of phage display.

Next, Dr. Naif Alharbi, research scientist at KAIMRC, gave an overview of the MERS-COV vaccine from the bench to clinical trial development. He detailed the methodology pursued to produce the vaccine in collaboration with Oxford University and how it was tested successfully in the camel prior to launching the phase one clinical trial. This latter is being conducted at the KAIMRC clinical trial unit in the Ministry of National Guard-Health Affairs (MNGHA) hospital. Next, two KAIMRC scientists, Dr. Sabeena Mustafa and Dr. Nimer Mehyer, presented the center efforts in discovering new therapies for MERS-COV. Using structural-based modeling studies, Dr. Mustafa identified 20 peptides that have the potential to bind to the MERS-COV spike protein and prevent its interaction with its cellular receptor, DDP4. Dr. Miyer developed an in vitro assay to screen MERS-COV helicase inhibitors. Through his efforts, he identified a number of compounds that inhibit the enzyme in vitro at high potencies; a few of them are being tested in vitro to inhibit the live virus in cells.

Next, Dr. Raha Orfali, from the Collage of Pharmacy, King Saud University, talked about bioactive constituents of extremophilic fungi and new leads in battling multi-resistant microbes and

cancer cells. Dr. Raha stated that only 7% of the estimated 1.5 million fungi species have been described and only a small number have been explored for the production of pharmacologically active metabolites [2]. "Extremophilic fungi" are fungi which grow in environments different than those that would have traditionally been considered life supporting. It was found that, for such organisms, the extreme stress might activate silent genes and induce unique biosynthetic pathways to produce bioactive metabolites [3]. In this study, a series of extremophilic fungi (halophilic and thermophilic) were isolated from different extreme ecological regions in Egypt and Saudi Arabia and subjected to chemical and in vitro pharmacological investigation in order to isolate and identify antimicrobial and anticancer metabolites. The results presented here suggest that extreme-tolerant fungi are a rich source of anticancer and antimicrobial metabolites, which could have implications for pharmaceutical preparations in the future.

The last talk of the session was delivered by Prof. Asaad Khalid from Jazan University and titled "Discovery of natural anti-mycobacterial and anti-plasmodial bioactive compounds". Just like searching for the legendary lost city of gold, El Dorado, the road to the discovery of bioactive compounds and drug hits in medicinal plants could be full of challenges and adventures. The unique, unorthodox and often unanticipated chemical structures available in natural products are what offer novel leads for clinically useful drugs. The hit rate of natural products is on average 3%–10%, compared with ~0.03% of that of compounds from a synthetic origin [4,5]. Therefore, most of Food and Drug Administration(FDA)-approved drugs are either natural products or natural product-derived compounds.

Focusing on the diverse medicinal plants available in Saudi Arabia, for which we have recently established the first extract bank of Saudi medicinal plants, this lecture gave an overview of the research on discovering natural bioactive hits that target neglected diseases. In particular, some successful stories of our cell- and target-based research on TB and malaria were highlighted. This research has led to the identification of interesting anti-plasmodial and anti-mycobacterial natural products that kill M.tb intracellularly.

*2.3. Session 3: Rare Disease Targets and Orphan Drugs Discovery*

Rare diseases (RDs) are generally considered to be diseases that affect fewer people (~1 in 2000 people) and are a complex mix of heterogeneous diseases, currently numbering 5000 to 7000 in total [6]. However, the local population is known to have a high rate of rare diseases due to consanguinity, and many inborn errors in Saudi Arabia are very high compared to world statistics, affecting 1.5 in 1000 newborns.

For many rare diseases the exact cause remains unknown, but for a significant portion, the problem can be traced to changes, or mutations, in a single gene. Moreover, rare disease treatments are costly. The session was dedicated to reviewing the current understanding of the diseases, their possible diagnoses and therapy breakthroughs. The speakers were among the world's leading researchers. The first presentation was given by Dr. Majid Alfadhel, KAIMRC's Deputy Executive Director and head of the Genetics Division, Department of Pediatrics, at MNGHA. Dr. Alfadhel's presentation was titled "Inborn Errors of Metabolism Drug Discovery: An Update". The past two decades have given rise to significant progress in the treatment of inborn errors of metabolism (IEM). Dr. Alfadhel gave a summary of the latest therapeutic approaches, which include dietary reduction; examples of this treatment are aminoacidopathies and organic aciduria for toxic metabolites disposal. This treatment has been given to patients with urea cycle disorders with supplementary cofactors, as in molybedenum cofactor deficiency and cobalamine defects. Enzyme-replacement therapies, like mucopolysaccharidosis treatments, substrate-reduction therapies and supportive treatments have been given for all of them. The presentation also detailed the current available therapeutic options and those that are being evaluated in preclinical studies. On the horizon are gene therapies, chaperon therapies, proteostasis regulators, clustered regularly interspaced short palindromic repeats (CRISPER)-based genome editing, mRNA medications and inhibitors like inhibitor of NLRP3-inflammasome pathway (CHRID3) in primary hyperoxaluria. None of these options are applicable to all IEM patients and most of the approaches have important

limitations related to the bioavailability of therapeutic agents, toxicity, immune response, and their impact on patient quality of life. The possibilities of combining different approaches in order to obtain the highest therapeutic efficacy and personalizing treatment protocols for each disorder and each individual patient must be explored.

The second lecture was presented by Prof. Wyatt Yue, SGC, Oxford, UK, and was titled "Structure-guided drug discovery for rare metabolic disorders". Inborn errors of metabolism (IEM) represents a group of ~500 rare disorders, each associated with inherited defects in a metabolic enzyme, regulatory protein, or protein complex. Despite the well-established genetic linkage and clinical manifestations of IEMs, there remains a lack of transformative therapy. This, in large, relates to the conceptual challenge of the majority of IEMs being loss-of-function disorders, rendering pharmacologic rescue difficult. Prof. Wyatt's research addresses this gap, using structural biology approaches to enable drug discovery for IEMs. It focuses on proof-of-concept studies to rationalize therapeutic approaches for substrate reduction and pharmacological chaperoning and perform crystallography-based fragment screening to identify chemical starting points and druggable pockets for small molecule drug development. The third lecture was given by another prominent researcher on rare disease, Prof. Fowzan S Alkuraya, King Faisal Specialized Hospital, KSA, and was titled "The Druggable Genome: Opportunities for Saudi Arabia". The skyrocketing expenditure on drug development has not been met with a corresponding boost in productivity, a crisis that is widely acknowledged in the pharmaceutical community. To increase the chances of discovering and developing novel drugs with lower failure rates, Prof. Alkuraya proposes using human genetics as a guiding principle to not only discover novel drug targets but also predict their safety profile. Human genetics-inspired/supported molecules are twice as likely to succeed, and many pharmaceutical companies are now investing heavily in the "druggable genome". Prof. Alkuraya made the case for the value in investing in human genomics in the Saudi population to boost the yield of the druggable genome.

Pro. Mo Li, from King Abdullah University of Science and Technology (KAUST), Kingdom of Saudi Arabia, spoke about how "Long-read Individual-molecule Sequencing Reveals CRISPR-induced Genetic Heterogeneity in Human ESCs". Accurately quantifying the genetic heterogeneity of a cell population is essential to our understanding of biological systems. He developed a universal method to label individual DNA molecules for analyzing diverse types of rare genetic variants with frequencies as low as $4 \times 10^{-5}$ using short- or long-read sequencing. It enabled the base-resolution haplotype-resolved quantitative characterization of rare variants. It provided the first quantitative evidence of persistent nonrandom large deletions and insertions following the DNA repair of double-strand breaks induced by CRISPR-Cas9 in human pluripotent stem cells.

Dr. Shahida Aziz Khan, from King Fahd Medical Research Center, Jeddah, presented her preliminary results, which suggest that a comprehensive nutritional strategy incorporating omega-3 fatty acids could be introduced in future therapeutic use to help children with sickle cell disease lead better lives. The session was closed with a presentation titled "Development and validation of LC-MS/MS method for quantization of N-acetylated amino acids in aminoacylase I deficiency patients" by Dr. Bandar Alghanem, a scientist at KAIMRC. Aminoacylase 1 (ACY1) deficiency is a rare inborn error of metabolism (OMIM Entry #609924) and is characterized by the excretion of N-acetylated amino acids in urine. Dr. Ghanem reported a rapid extraction method without a derivatization step followed by a stable-isotope dilution liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) method for accurate quantification. The developed method was comprehensively validated for a panel of N-acetylated amino acid biomarkers, including valine, serine, glutamic acid, methionine, leucine and alanine. Furthermore, the validated method was then utilized to analyze these biomarkers in eleven patients' urine samples. The results revealed a significant difference between patients and healthy individuals for all the amino acids with a $p$ value < 0.01. In conclusion, Dr. Ghanem showed a highly sensitive and cost-effective quantitative method that relies only on one isotope internal standard for all the six amino acids.

## 3. Third Day (27 February 2020): Therapeutic Discovery Tools

*3.1. Session 1: Role of Bioinformatics in Drug Discovery*

The recent advancement in the fields of biology, computer and information sciences has merged into the single discipline of bioinformatics, which generally aims to first organize data in a way that allows scientists to access existing information and submit new entries as they are produced; second, develop tools and resources that help in the analysis of data; and third, apply these tools to analyze the data and interpret the results in a biologically meaningful manner [7]. This session aimed to provide examples of different applications of bioinformatics in the field of drug discovery, from target identification through the identification of a novel mutation, to then applying machine learning methods to predict the impact of that mutation, to utilizing computational tools to design novel molecules. The speakers in this session were Prof. Saleet Jafri (Professor at the School of Systems Biology and the Director of the Interdisciplinary Program in Neuroscience at George Mason University, USA), Dr. Shahul H. Nilar (Global Blood Therapeutics Director, Computational Chemistry, San Francisco, USA), Dr. Mamoon Rashid (Associate Research Scientist, KAIMRC, KSA), Dr. Omer Aldibasi (Postdoctoral Researcher, KAIMRC, KSA) and Dr. Lamya Alomair (Postdoctoral Researcher, KAIMRC, KSA).

The session started with Prof. Jafri, who talked about predicting drug resistance by applying machine-learning (ML) methods to classify disease-causing mutations and drug specificity and the resistance of mutation in cancer. He presented leverage simulation methods to determine the functional consequences of mutation by applying ML to identify and quantify the features of all-atom molecular simulations to predict the specific functional effect and disruptive severity of genetic variants. The talk started by introducing the molecular dynamic (MD) simulation, which is a computer method for studying the movement of atoms and molecules by providing the time-dependent behavior of atoms and molecules in a system. Prof. Jafri then described the necessary steps to integrate the technologies of ML and MD in calculating the amount of deviation characterizing the mutation correlates with the amount of deviation from the normal function, which then can provide information on the severity of the phenotype that the mutation can cause. The presented method was able to distinguish between changes in the conformational population of variant structures by increasing the number and source of descriptive features and using more advanced classification methods. It makes the prediction of the functional severity of genomic variants possible in silico with the ability to differentiate between different phenotypes. Dr. Shahul H. Nilar then presented his work on "Fragment Based Approaches as a Computational Chemistry tool in the Design of Novel Molecules in Drug Discovery".

Dr Shahul Nilar discussed the fragment-based approach as a computational chemistry tool in the design of novel molecules in drug discovery. The success of fragment-based drug design in small molecule drug discovery has been extensively discussed in literature. In his talk, Dr. Nilar reviewed these successes from a theoretical approach based on the concepts of molecular complexity. The importance of complementary biophysical techniques in making a prudent selection of viable fragments was emphasized. A case study on the application of Pharma Fragment-Based Drug Discovery (FBDD) techniques in the design and synthesis of inhibitors against the Dengue Virus NS5 polymerase was then presented, in which an X-ray-based fragment screen of Novartis' fragment collection resulted in the identification of a biphenyl acetic acid fragment 3, which bound in the palm subdomain of RdRp. The subsequent optimization of the fragment hit 3, relying on a structure-based design, resulted in a >1000-fold improvement in its potency in vitro and caused it to acquire anti-dengue activity against all four serotypes with a low micromolar EC50 in cell-based assays. The lead candidate, 27, interacts with a novel binding pocket in the palm subdomain of the RdRp and exerts a promising activity against all clinically-relevant dengue serotypes [8].

Dr. Rashid Mamoon talked about his work on the identification of somatic mutations in cancer using bioinformatics methods and their functional relevance. The somatic mutations play a crucial role in cancer development and progression. Therefore, the identification of somatic mutations is one of the most challenging tasks in cancer genomics. This can be achieved in two different

ways—(i) with data from tumors and matched normal samples, (ii) with tumor data only. In the first case, he assumes that normal samples contribute to germline mutations and hence could be used as a background for tumor samples to identify somatic mutations in the tumor sample. The second approach is de novo methods, utilizing the properties of genetic alterations such as allele frequencies and read depth.

Moreover, the de novo approach has its limitations. In his talk, Dr. Mamoon presented a study that used the whole-exome sequencing of a breast tumor cell line and matched normal samples to identify a set of somatic mutations in breast tumors. Then, a series of public databases of genetic variants (like dbSNP, COSMIC, 1000 g, ExAC, gnomAD) were used to filter the novel somatic mutations. Only non-synonymous mutations in the exonic region of the coding part of the genome were kept. Furthermore, a pathway enrichment analysis was used to select the mutations or underlying genes contributing to the important biological pathway. A careful and detailed analysis of the top-ranked pathways with the guidance of the phenotype of the breast cancer cell line led to the discovery of a few novel functional mutations exclusively present in his sample. This approach has identified one of the mutations in a cytokine receptor, which was predicted to be a transforming mutation and thus could explain the ligand-independent nature of the breast cell line. Therefore, the proposed method in this study could be used as a general framework by the scientific community to identify or discover novel somatic mutations, explaining the phenotypes of the samples in the study.

Dr. Omer Aldibasi's talk focused on the role of microbiome analysis in drug discovery towards a probiotic treatment of bacterial vaginosis (BV), which is the most common vaginal infection in women of reproductive age. It is an imbalance of the normal vaginal microbiome and can be characterized as a decrease in the lactobacilli genus and the overgrowth of other types of bacteria. Probiotics have the potential of being an alternative therapeutic tool for treating and preventing the recurrence of BV. To fully characterize the etiology of BV, he analyzed 176 vaginal specimens from 14 participants who developed incident BV during the study. Using SParse InversE Covariance Estimation for Ecological ASsociation Inference (SPIEC-EASI), he assessed microbial networks arising in the 14 days leading up to the incident BV. A robust network of three bacteria was identified, consisting of *Gardnerella vaginalis, Atopobium vaginae*, and *Aerococcus*, which increased in abundance in the five days prior to the incident BV.

Dr. Lamya Alomair presented her work on an MD simulation for early target identification for the treatment of dengue fever, which is an infectious disease that is transmitted to humans via mosquitos. Currently, there are no vaccines or antivirals that can prevent this infection, and that is why researchers are diligently working to find a cure. The Dengue virus genome codes for multiple nonstructural proteins, one of which is the nonstructural protein 3 (NS3) enzyme that participates in different steps of the viral life cycle, including viral replication, viral RNA genome synthesis and host immune mechanism. In this work, Dr. Alomair presented her in silico study to provide a powerful approach to gain a better understanding of the biological systems at the gene level, showing that NS3 has the potential to be phosphorylated by any of the ~500 human kinases. The analysis predicted potential kinases that might phosphorylate NS3 and calculated a Dena ranking score using neural networks and other machines' learning-based web server programs. These scores identified the top kinases that phosphorylate Dengue virus (DENV) NS3. Thus, preventing the phosphorylation of NS3 may interrupt the viral replication and participate in antiviral evasion. Multiple sequence alignment bioinformatics tools were then utilized to verify the results of the highly conserved residues and the residues around active sites, whose phosphorylation may have a potential effect on viral replication. This work proposed that the host-mediated phosphorylation of NS3 would affect its capability to interact with NS5 and that knocking out one of the interacting proteins may inhibit viral replication, which could open new doors for further investigation. Future work is expected to help identify the key inhibition mechanisms.

*3.2. Session 2: Source of Novel Drugs: Natural Products and Combination Chemistry*

Natural products (NPs), also known as secondary metabolites, are molecules of great medical relevance. They usually originate from bacteria, fungi and plants. The screening of NP extracts has

traditionally been the most effective method for identifying new compounds with unique cellular targets, which are potentially useful as lead structures in the development of new therapeutics. Although used in nearly all therapeutic areas, NPs have had their largest impact as antimicrobial agents [9]. Over 60% of FDA-approved anti-infective agents originated from NPs. NPs have served as powerful therapeutics against pathogens since the golden age of 1960–1970. After this period, the rate of discovery of new products dramatically decreased, and the increasing frequency of antibiotic-resistant infections demonstrated that new antibiotics are extremely needed. The rediscovery of NP product structures poses a big challenge for pharmaceutical-lead compound discovery, due to traditional methods that mainly rely on complex bioactivity assays, product isolation and purification processes [10]. NPs have evolved under the pressure of natural selection to evade resistance mechanisms, solve the problem of bioavailability and interact with specific targets. There is growing evidence for revisiting NPs for drug discovery by implementing state-of-art modern technologies, including omics approaches and computational and engineering tools for NP-based screening [11,12]. To better understand the value of integrating NP libraries into the modern biotechnology arena, insights on new research advancements and ongoing development in this field were discussed by well-respected experts from both academic and industry settings.

The contributors to this session were Dr. Didem Torumkuney (Scientific Director of Infectious Diseases, GSK, USA), Prof. Dr. Stuart Maudsley (Adjunct Director of VIB Center of Molecular Neurology (CMN) and Vice-Chair of the Department of Biomedical Sciences, University of Antwerp, Belgium), Dr. Adel Nefzi (Director of the Department of Chemistry at Torrey Pines Institute for Molecular Studies, Port St. Lucie, Florida, USA) and Dr. Nessar Ahmed (Department of Life Sciences, Manchester Metropolitan University, UK).

Dr. Didem Torumkuney's presentation was titled "Importance of antibiotic surveillance studies and survey of antibiotic resistance (SOAR): Their contribution to new drug discovery". Dr. Torumkuney introduced the problematic global health threat of antibiotic resistance, particularly in low and middle-income countries where antibiotic resistance showed a disproportionate impact. She shared her experience and expertise in the infectious diseases field, including the latest findings from SOAR studies that were conducted in 17 countries and 43 centers in the Middle East, Africa, Latin America, Asia and Europe. Dr. Torumkuney also shed light on a study on antibiotic susceptibility in Turkey, where antibiotic susceptibility in *H. influenza* remained very stable in 2002–2009 and levels of β-lactamase were low compared with many other parts of Europe. In addition, Dr. Torumkuney showed that there were significant differences in resistance trends between countries. However, Turkey had lower penicillin and macrolide susceptibility levels than other countries. Dr. Torumkuney addressed the need for the implementation of strong surveillance programs that are essential to effectively identify, understand and predict shifting antibiotic resistance patterns. Furthermore, she emphasized that continued country-specific surveillance is required to fully understand the dynamics of antimicrobial resistance.

Prof. Stuart Maudsley talked about developing future multidimensional therapeutic models to stop the aging process by regulating aging-induced oxidative damage in cells. He demonstrated how G protein-coupled receptor (GPCR) systems can be used to control the complex molecular signaling architecture of aging-related diseases such as cancer, cardiovascular disease and diabetes. Dr. Maudsley further discussed the role of GPCR-targeted therapies in controlling hyper-complex biological events through a specific control of the so called 'Keystone' proteins. Dr. Maudsley concluded that such an approach will help improve therapeutic designs to slow down age-associated damage and reduce the development of age-related diseases.

Dr. Adel Nefzi highlighted recent advances in the application of mixture-based synthetic combinatorial libraries, which offer a tremendous enhancement in the rate of drug discovery. His talk focused on experimental methodologies that have been developed to speed up drug discovery processes, including high-throughput screening and combinatorial chemistry. Dr. Nefzi emphasized the importance of complex combinatorial libraries (experimental or virtual) as a notable source of chemically related compounds. Dr. Nefzi concluded his talk by thanking the organizers for their generosity and hospitality and pronouncing his willingness to collaborate with KAIMRC.

Dr. Nessar Ahmed concluded the session with a talk about the potential use of NPs as anti-glycation agents for diabetic complications. He first introduced an overview of diabetes and its complications and highlighted the implication of advanced glycation end products (AGEs) in disease development. Natural compounds with antioxidant properties can inhibit AGE formation. Dr. Ahmed presented a series of newly identified lead molecules with anti-glycation activities. He proposed the inhibition of the glycation of proteins as a good strategy to avoid late diabetic complications. In this regard, compounds such as green tea and garlic have been shown to prevent AGE formation both in vitro and in vivo. Thus, the anti-glycation activity of plant extracts could be attributed to their antioxidant properties. Dr. Ahmed showed that aged garlic extract inhibits the formation of AGEs more effectively than fresh garlic extract, suggesting that the daily consumption of aged garlic extract might be beneficial for the prevention of lifestyle-related diseases. Dr. Ahmed summarized his talk by stating that dietary supplementation with antioxidants may be a safe and simple way of complementing traditional therapies aimed at targeting and preventing diabetic complications.

*3.3. Session 3: Immuno-Therapy Discovery and Process*

Dr. Julen Oyarzabal from the discovery and biopharmaceutical industry was introduced to present computation strategies to design anti-tumor immune responses. He spoke in detail about how the DNA methyltransferase (DNMT) inhibitor was identified. The key was in using a new approach focusing on novel data mining linked with multiple libraries. The results were validated with a biological activity analysis with high throughput screening run by European lead factories. DNMT inhibitor was just an example of a successful novel system to identify effective compounds against cancer. More information about DNMT has been published by the speaker [13].

Next, Dr. Andrei Popov (CEO and Co-founder of ECRINS Therapeutics) presented a first-in-class inhibitor of protein phosphatase I (PP1) ET-D5. This inhibitor was determined through phenotypical screening which showed promising activity against different cancers. The inhibitor inhibits vascularization in malignant tumors and reduces metastasis. On the other hand, it has a non-significant effect on normal endothelial cells. The range of the ET-D5 treatment doses starts as low as 2 nM for some cancers and goes up to 3 uM for others. One interesting point is that ET-D5 starts to affect normal endothelial cells at 6 uM, which is two times higher than its high dose used for therapeutic effects.

The Director of the Biological Product Evaluation sector for the SFDA (Saudi Food and Drug Administration), Dr. Abdulaziz Alsayyari, presented the steps to get approval for therapeutic antibodies in Saudi Arabia. In addition, he talked about life cycle-related products and the best route for SFDA approval. He stressed that preclinical and clinical studies are strong contributors to SFDA approvals. Nonetheless, SFDA approvals involve but are not limited to the assessment of GMP (good manufacturing practice), GLP (good laboratory practice) and CMC (chemistry manufacturing and control). He concluded that any industrial entity could submit their approval submission as an inquiry to get comments and help to avoid delays in actual submissions. Dr. Alsayyari responded to questions and inquiries, refuting a previous report [14].

Later, the team leader of drug and aptamer screening, Dr. Atef Nehdi, presented the use of drug repurposing for biological activities. This approach could save time and money by documenting a new use for an existing drug. In his approach, he screened a compound library containing 800 Food and Drug Administration-approved drugs as anti-leukemic treatments. He identified the ability of an isoprenaline-induced intracellular ATP depletion compound to sensitize primary leukemic cells to fludarabine-based treatment. Functional assays have shown synergism against Chronic Lymphocytic Leukemia (CLL) with a suggestion to push for clinical validation and trials.

The last speaker of the Immuno-Therapy session was Dr. Abdullah Alshuhri, chief clinical investigator at SFDA for medical devices. He presented the methods of SFDA that allow approval for medical devices, especially if those devices were subject to implantation inside the body. The guideline is mostly compatible with international guidelines validated by committee no. SFDA.MDS.TC194, which is closely tied with the WHO's similar committee, ISO/TC 194 [14].

*3.4. Session 4: Innovative Drug Formulation and Delivery*

The last session of the conference was focused on innovative drug formulation and delivery. In particular, it focused on the application of nanotechnology in drug delivery systems in producing a new innovative generation of drugs. Nanoparticles are employed to conquer some challenges encountered with many active ingredients. Novel developments in nano-drug formulations can improve their physicochemical properties, site specific delivery, dosage forms and dosing intervals, and can also enhance their therapeutic efficacy. In addition, the nano-encapsulation of water-insoluble active ingredients can dramatically improve their solubility and bioavailability.

During this session, expert speakers gave actual examples of innovative drug formulations based on nanotechnology as tools to deliver active ingredients. The first speaker of the session was Dr. Amokrane Reghal, the chief executive officer of Atlangram company, France. Dr. Amokrane's talk was about the use of nanomedicine in fighting antibacterial resistance. During his talk, he presented the role of Lipid Nano-Capsules (LNCs) in delivering daptomycin. Daptomycin is currently available as an IV formula; Dr. Amokrane and his team have developed an LNC-daptomycin (LNC-DAP) formulated in a gel with other antistaphylococcal drugs. The LNC-DAP formula was tested on rabbits and compared with conventional daptomycin and other antistaphylococcal drugs. The LNC-DAP showed significant in vivo activity and a therapeutic efficacy that can be maintained for up to 14 days after one application. In conclusion, LNCs proved to be a promising tool to optimize the delivery of antibacterial agents.

In addition, Dr. Alaa Eldeen Yassin (professor of pharmaceutics at College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences) presented his work on a novel nano-formulation of 5-Flourouracil (5-FU). The 5-FU was incorporated within biodegradable nanoparticles to reduce the dose of 5-FU and enhance its therapeutic efficacy. Two polymers were used to create the nanoparticles—polycaprolactone (PCL) and polylactic-co-glycolic acid (PLGA), with or without polyethylene glycol 6000 (PEG 6000). The (5-FU)-loaded polymeric nanoparticles (NPs) were characterized by Fourier Transform Infrared Spectroscopy and X-ray diffraction spectra. The in vitro release assay of 5-FU NPs showed a rapid release of 5-FU in the first 8 hours, followed by a period of slow release for up to 72 hours. Furthermore, the cell death and apoptosis induction in response to 5-FU NP exposure were measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) and Annexin–V/7-amino-actinomycin D (7-AAD) assays respectively in Daoy, HepG2 and HT-29 cancer cell lines. The cells exposed to NPs exhibited a significant cell death when correlated with the ratio of PEG in the formulations in the Doay and HepG2 cells but not in the HT-29 cells. In summary, Dr. Yassin showed that the physical PEGylation significantly enhanced the entrapment and loading efficiencies of 5-FU in NPs formulated with PLGA and PCL. Hence, these formulations show great promise in cancer treatment.

The last talk of the session, titled "New mechanistic insights into a potential allergic response of silver nanomaterials", was presented by Dr. Naser Alsaleh, assistant professor at King Saud University. Dr. Alsaleh's talk focused on the wide use of silver nanoparticles (AgNPs) in consumer products. He stated that AgNPs are generally considered inert with a minimal toxicity, however, previous studies reported that AgNPs might have potential immunomodulatory properties. Dr. Alsaleh presented his experiments on bone marrow-derived mast cells isolated from C57Bl/6 mice. The mast cells were exposed to AgNPs; it was found that AgNP-induced mast cell degranulation is calcium dependent and is mediated through the activation of cell signal transduction pathways involved in regulating calcium—including PI3K, PLC and PKC—and the influx of calcium through calcium release-activated channels. The data showed that pre-exposure to AgNPs resulted in an exacerbated allergic response, potentially through an alteration of cell signalling homeostasis. Additionally, it was observed that exposure to AgNPs for an extended time at relatively high concentrations was not associated with cellular toxicity. Dr. Alsaleh's findings suggest the immunomodulatory properties of AgNPs, which underscores the critical importance of understanding ENM-immune cell interaction at the molecular level for the safe implementation of nanomaterials.

## 4. Recommendations

The feedback received from all speakers, attendees and organizers was that the program was comprehensive and covered most aspects of therapeutic discovery and development. All of us learnt something new and made new connections for future collaborations and partnerships.

The top recommendations are:

- With the increase in infectious diseases, which includes the coronavirus type of diseases and genetic diseases, we call for more open science and shared therapeutic discovery platforms between all the sectors working in this area.
- It is necessary to advocate for more interaction, collaboration and partnership between the pharma industry, biotech sector and academia to develop competitive and transformational drug discovery programs.
- With the KSA2030 vision to be leading economic power outside the oil industry, it is necessary for the KSA to invest adequately in academic drug discovery and development in order to be able to produce its own medications.
- To increase the number of talented individuals considering careers in drug discovery and development, we advocate for opening postgraduate programs in this field.
- Natural products should be considered as sources for chemistry, and regulatory bodies should loosen their processes for approving these types of drugs, taking into consideration that most antibiotics and chemotherapy drugs are natural products.

In summary, we found the conference very useful and all recommended that we organize our third therapeutic discovery conference in 2022.

**Conflicts of Interest:** Authors declare no conflict of interest.

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