

Pakistan Journal of Biochemistry and Molecular Biology

Preface

Fourteenth Biennial Conference of Pakistan Society for Biochemistry and Molecular Biology (PSBMB) was held during December 9-12, 2018 at Dr. A.Q. Khan Institute of Biotechnology & Genetic Engineering (KIBGE), University of Karachi, Karachi, Pakistan. Theme of the conference was “MOLECULAR BIOSCIENCES: RESEARCH AND INNOVATIONS”. Hundreds of scientists, post-doctoral fellows and graduate students from all over Pakistan and other countries attended this conference.

Here we present abstracts of **keynote lectures** delivered during the conference. Editorial board is grateful to the organizing committee of PSBMB 2018 for providing abstracts of keynote lectures for publication in PJBMB.

Editorial board

Pakistan Journal of Biochemistry and Molecular Biology

Keynote Lectures of 14th Biennial Conference of PSBMB (December 2018)

THE STRATEGIC USE OF RESEARCH RESOURCES IN DEVELOPING COUNTRIES

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Available data and reports from the various international agencies suggest that research progress in developing countries including Pakistan is slowly and gradually picking up, when number of research projects, publications and PhDs produced through indigenous programs are considered as indicators. Over the last 20 yrs or so government based programs in Pakistan have provided reasonable funds and facilitated the research and higher education to a significant extent. However, in biomedical sciences many of the quality research publications have resulted due to “parachute science” phenomenon, where researchers from developed countries grab opportunities to collect samples and insist on carrying out most of the sophisticated analytical work under a consortium at their home countries without even allowing a chance to develop capacity and technology transfer to the collaborating institute in the developing world. This all is happening in despite the emphasis to minimize the 10/90 Gap by the Global Forum for Health Research.

Last two decades have seen in Pakistan a vast increase in the number of research institutes, the real focus to address

issues in health sciences is inadequately planned to deal with emerging threats of communicable and non-communicable diseases. Recent WHO and World Bank reports have shown a gradual change in the pattern of life-threatening illnesses over the last twenty years.

Undoubtedly searching for solutions to health issues require research with concerted efforts and successful outcome can only be achieved, by applying real hard work, strategic planning and judicious utilization of resources. Although Pakistan may be regarded as a resource poor country, mainly due to economic constrains and underdeveloped infrastructure, yet there have been success stories exemplified by many researchers.

A well plan approach with specific aim to use available resources prudently, rapid and significant research goals can be achieved. While such a plan could include enhancement of scientific careers, institutional support and collaboration within the local scientific community. By encouraging resource sharing, making training opportunities available to deserving younger generation of scientists and creating repositories of high-quality biological samples, registries of diseases and databanks, huge wealth of material needed for health research can be made available to achieve desirable results. However, some of the most intractable challenges would come up due to certain political issues, exacerbated by the unjust controls over distribution of resources. In spite of this, the most encouraging fact is the notable commitment and enthusiasm of younger generation of scientists, promises a great potential that is about to produce high quality research to successfully confront the growing threats of health problems.

ROLES OF EUPATORIN AND HYMECROMONE AS POTENT INSULIN SECRETAGOGUES AND THEIR MECHANISMS

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Insulin secretory defect is a key feature in the pathophysiology of non-obese type 2 diabetes, mostly found in Asia. Classical insulin secreting agents, such as sulfonylureas, stimulate insulin secretion irrespective of glucose concentrations which is the main cause for hypoglycemia. Therefore, there is an urgent need for developing new insulin secretagogue(s) which could avoid uncontrolled insulin secretion and minimize the risk of hypoglycemia. Taking advantages of pure compounds available at H.E.J. Research Institute of Chemistry, University of Karachi, we have tested more than 400 compounds to identify novel insulin secretagogue(s).

Eupatorin (purified from *Saliva mirzayanii*) and Hymecromone (purified from *Hippophae rhamnoides*), the two best molecules, were identified and explored their insulin secretory mechanism(s) focusing on K_{ATP} channel-dependent and K_{ATP} channel-independent pathways. Freshly isolated mice islets were co-incubated with Hymecromone or Eupotarin for 60 min at 37°C in KRB buffer along with different pharmacological agonists/antagonists at 3 mM and 16.7 mM glucose concentrations and secreted insulin was measured. Hymecromone stimulated insulin secretion only at high glucose, whereas Eupotarin stimulated insulin secretion both at low and high glucose concentrations. Both Hymecromone and Eupotarin exerted additive effect in tolbutamide-induced insulin suggest that the insulin secretory mechanism(s) of Hymecromone and Eupotarin is different from sulfonylurea and act distal to the K_{ATP} channel. Interestingly, we observed partial inhibition in Hymecromone- and Eupotarin-induced insulin secretion by diazoxide, a K_{ATP} channel opener; whereas; complete inhibition by verapamil, an L-type Ca^{2+} channels blocker which indicates the crucial role of Ca^{2+} in their insulin exocytosis. Furthermore, depolarizing the islets using KCl (25 mM), and excluding the role of K_{ATP} channel using diazoxide, the insulin secretory ability of Hymecromone and Eupotarin were further enhanced at 16.7 mM glucose, suggests their mimicking effect in addition to the blockage of K_{ATP} channel channels. Subsequently, Hymecromone and Eupotarin showed no effect in IBMX- (a phosphodiesterase inhibitor) and forskolin (adenylate cyclase activator)-mediated insulin secretion, suggest that these molecules neither activate adenylate cyclase nor

inhibit phosphodiesterase for amplification of insulin exocytosis. H-89, a protein kinase A (PKA) inhibitor, showed moderate inhibitory effect on Hymecromone- and Eupotarin-induced insulin secretion at 16.7 mM glucose, suggest that the effect of insulin secretion *per se* PKA-dependent. Molecular docking studies also revealed that there are good interactions with Hymecromone and Eupotarin with PKA catalytic site. All the data suggest that Hymecromone and Eupotarin exert insulin secretion through the PKA-dependent amplifying pathway. Further insulin secretory kinetic studies are underway to derive the conclusive mechanism of Hymecromone- and Eupotarin-induced insulin secretion.

SCIENCE AT THE INTERFACE OF CHEMISTRY, BIOLOGY AND MEDICINE

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As developing world face food security issues, it also confronts with the drug insecurity challenges. Nation states must prioritize the agenda for developing safe and effective drugs against local diseases. The current drug development paradigm is cost, time and labor intensive, which developing countries cannot afford to invest. There is, therefore, a need of appropriate, efficient and cost-effective strategies for drug development, which must be based on indigenous knowledge resource base, S&T capacity, and people-friendly approval process. In last two decades, we

identified a large number of new and novel chemical substances, and their synthetic analogues with potent activities against various disease-related targets.

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2014 (second most common cancer overall). This represents about 12% of all new cancer cases and 25% of all cancers in women. Incidence rates vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In most of the developing regions the incidence rates are below 40 per 100,000. It has been reported in 2015 as the most prevalent cancer in women. Approximately one-third of all breast cancer patients and two-thirds of postmenopausal breast cancer patients have hormone-dependent (estrogen-dependent) breast cancers, which express estrogen receptors and require estrogen for tumor growth. Aromatase inhibitors are currently being tested as primary prevention therapy in large randomized trials. While only a few chemotherapies such as exemestane and tamoxifen are in clinical practices for the inhibition of aromatase functions. Therefore, there is a need to identify new structural analogues of available drugs and evaluate their anticancer potential. In this study, we will synthesize the new derivatives of existing aromatase inhibiting drugs through biotransformation and conventional synthesis and evaluate their potential against aromatase enzyme. During this research we have synthesized a number of new structural analogues of aromatase inhibitors and other steroidal drugs including exemestane, formestane, testolactone, mibolerone, boldenone, indomethacin, levonorgestrel, through biotransformation. This has provided an efficient method

for the synthesis of new analogues of existing aromatase inhibitors. The new analogues of the mentioned drugs were found to be moderate to potent inhibitors of aromatase enzyme as compared to standard drugs letrozole, and exemestane.

Glycation is a nucleophilic reaction which leads to post-translational modifications of biomolecules (e.g., proteins, lipids, nucleic acids, etc.) and results in the long-term complications in diabetes. Several natural compounds of natural origin were evaluated for their antiglycating ability such as polyphenols, cyclopeptide alkaloids, steroids, coumarins, flavonoids, and etc.

During this presentation, underlying philosophy and approach of our research on cost-effective discovery of lead molecules by using ethnobotany, natural product chemistry, and drug repositioning strategies will be discussed.

MODERN CLUSTER ANALYSIS TOOLS FOR DATA FROM GENOME-WIDE ASSOCIATION STUDIES

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Genome-wide association study (GWAS) is an observational study, widely used for investigating the underlying genetic architecture of complex human diseases. The primary aim of a GWAS is to understand how

and to what extent diseases and traits are related at the genome level. However, GWAS can equally be applied to any other genetic variants in humans or any other organisms. Cluster analyses are widely used hierarchical methods to group similar objects within data sets. The techniques have been extensively used in genetics and genomics to generate hypotheses of organism's evolution. Cluster analysis has also been applied to explorative analysis of the relationships between disease-associated genome-wide data. Here we present different methods for cluster analysis of disease-associated genomic tracks. We also introduce a new approach in cluster analysis and discuss its efficacy for exploring the extent to which diseases share genetic components.

CONTROLLING HUMAN RISK FACTORS ASSOCIATED WITH LIFE SCIENCE RESEARCH

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The mitigation of human risk factor in biological laboratories are of biggest concern all around the world. The strategy of life science research focuses on human risk factors which is based on reduced incidents and accidents and decreases in overall near misses. The understanding and controlling of human risk factor is the blending

approach of psychology, engineering, statistics of epidemiology of disease, research design, operation of research and anthropometry. The risk is always changing and never static depending upon the varying situation. The seven human risk factors are categorized which effect on human beings. These risk factors are identified as environmental conditions, agent-human interference, limitations of research, capabilities of researchers with respect to their emotional, mental and physical states. These factors are continuously depending upon one another. A single risk factor or more than one might not possess any serious cultural risk to the environment. In contrast, a multiple combination of these factors might increase in the level of risk and threat to the safety culture in the research laboratories. All humans have basic need, which when challenged will produced behaviors. Therefore, the importance of safety culture with human beings and all of these human risk factors should be considered because researchers always deal with the human behaviors about safety and the risk in laboratory environments of life science. The key message of controlling human risk factor with life sciences research is to promote and share the knowledge globally with the concept of doing safety together.

SCAFFOLD CONCEPT IN DRUG DISCOVERY AND DESIGN: ROLE OF MOLECULARLY IMPRINTED POLYMER

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The old lock and key concept has been an inspiration for many drug design theories and pharmaceutical purification and analysis tools. One of the off-shoots of such concept is MIP or Molecularly Imprinted Polymer. MIP is basically a cavity containing polymer that has been created in the presence of a drug template using the molecular imprinting technique. This process would finally produce a polymer matrix with an affinity for the original drug template molecule and to similar extent to that drug family. In terms of size, the MIPs can be nano-size themselves or be produced to contain cavities of nano-scale or less. The first option is offered during the polymerization step or by pulverization after the polymer has been synthesized. The second option is mainly depending on the template and would have a limited range.

Selectivity of MIPs is appreciated in comparison to many other biomolecules or catalysts. In biological systems, the action of most drugs relies on the pharmacophore sites based on molecular recognition. Binding of minimum three functional groups serve as binding spots arranged in space at any particular molecule-receptor interaction would lead to high selectivity. The same rule can apply to MIPs and has been reflected in their manufacture and applications.

Other applications of MIPs include drug/toxin extraction, drug delivery and biosensor formation. In this lecture,

methods of production and pharma specific applications of MIPs with focus on drug discovery potential is discussed.

GOVERNANCE OF RESEARCH: THE RESEARCH COMMUNITY SAFEGUARDS AND SCIENTIFIC INTEGRITY

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Recent development in Science and Technology and especially life sciences have raised several questions of governance issues in the universities and research institutions. Major issues include, mapping the current landscape of dual use governance activities across the full life cycle of research, including formal legal and policy measures, self-governance measures undertaken by the scientific community, and education and outreach. International community is engaged to develop ways and means to ensure conduct of responsible science. Hence, we must analyze outcomes of these efforts as to what has worked and not worked and lessons learned, and analyzing gaps and opportunities. Based on these analyses, we can recommend future goals for improving governance of dual use research, and discussing specific actions for the short-, medium-, and longer term to achieve them. We can also promote sustained global dialogue and increased common understandings of the essential elements of governance. Science does not stand apart from society and scientists have a responsibility to ensure that scientific debates are informed by solid scientific evidence, logical argument, reasoning and sound advice.

One of the major issues is the dramatic demographic shift. It is estimated that there are 1.8 billion under 25-year olds in the world and over a billion of these are in the 15 – 24 age group. Emerging markets (Including Pakistan) have by far the largest percentages. This is referred to as a “youth bulge” because it should decrease over time with improved education and health care. Not unexpectedly, youth unemployment and underemployment have now reached a critical level globally with the ‘crisis’ of unemployment now so pronounced that the current cohort of youth has been referred to as “generation jobless” (The Economist, 2013). One hardly needs to emphasise the results of an inability to harness that energy – social upheaval, political crises, instability and violence. Young researchers aspire to explain the world and fix its problems but they are increasingly finding their ambitions thwarted. Major players in all these activities are the universities. Universities are no longer viewed predominantly as places driven by curiosity and a thirst for knowledge. Instead, they are drivers of economic development.

Success is defined by graduate employment. Research is problem-oriented. Scientists are budding entrepreneurs.

We should also realise that the science we do is not entirely our property. Whether the taxpayer helps fund our scientific education or not, most of our training and research is paid for by the public – in grants from the research councils or charities. Hence, public and civil society have a stake in our activities that we do. Therefore, it is our responsibility to communicate our work as effectively as possible, because ultimately it is done on behalf of society and because its adverse consequences may affect members of the society in which we all live.

Finally, there are various pressures on the academia too. Beside publish or perish, there is a continuous demand from the policy makers about innovation and commercialization of research. However, universities have their own problems, e.g., (1) commercialization of R&D has not been traditionally a high priority of universities; (2) the policy of promotions and appointments based on impact factor etc forced the academia to publish or perish; (3) during the last decade these efforts have been restructured in leading universities; and (4) increased emphasis has been put on connecting R&D capabilities to the commercial strengths and responsibilities of the university; (5) Pressure on scientists to publish has led to a situation where any paper, however bad, can now be printed in a journal that claims to be peer-reviewed; (6) Ensuring conduct of responsible Science is the need of hour in global community.