Editorial

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Molecular Biology, A Revolutionary Science at Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad

Sheikh Riazuddin

Professor Emeritus, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad

Address of Correspondent
Prof. Sheikh Riazuddin
Professor Emeritus, Shaheed Zulfiqar Ali Bhutto Medical University Islamabad
Email: riazuddin@aimrc.org

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Ever since the creation of living beings on this planet, Man has struggled to understand Life. However, the phenomenon of Life has remained shrouded in mystery. Philosophers in the times of Aristotle and Omar Khayyam discussed Life in abstract terms. During the second half of the last century and the first two decades of the present century, breakthrough researches {in the structure and function of DNA (1953), isolation of DNA polymerase (1958), reverse transcriptase (1969), restriction enzymes (1970) and use of restriction enzymes in gene mapping & gene cloning (1971-72), sequencing of DNA (1977) cracking the genetic code and use of plasmids as vectors for cell transformation (1983), gene amplification (polymerase chain reaction), sequencing of the human genome (2000), the discovery of the functions of RNA, micro RNA and non-coding DNA (1993), and more recently applications of tools of bioinformatics and artificial intelligence to solve complex biological problems} have enabled biologists to penetrate deep into the intricate web of life. As a consequence, a scientific concept of life has emerged that biological activity is the expression of information stored in DNA and its translation into RNA and proteins. The study of biologically active “molecules” is called "Molecular Biology”.

The largest of all biologically active molecules, "DNA", determines the characteristics of a living being. The DNA of all living beings — be that a tiny bacterium, a giant elephant or a mammoth banyan tree — is made up of four nitrogenous bases, adenine, guanine, thymine and cytosine. It is the order in which these four organic molecules are arranged on a strand of DNA (nucleotide sequence) that distinguishes one living being from another. In 1970’s it became possible to generate new DNA molecules (recombinant DNA) by polymerizing individual nucleotides or joining together pieces of existing DNAs from different species, thus producing the molecular equivalent of a chimera, the legendary animal {part lion, part goat, and part snake} of Greek mythology. Such capabilities have helped biologists not only to learn more about how a living cell does what it does but also in harnessing living organisms to do more useful work for mankind. This has made molecular biology the most exciting of all sciences as well as a new endeavor called "Biotechnology."

Biology has been harnessed since antiquity to fulfill humanity's most fundamental needs — from increasing food supplies to improving health care. The availability of new and novel methodologies has greatly expanded the scope of applications of biology, limited only to the imagination of people using it. For the first time in the history of mankind, it seems within reach of human endeavors to custom make nutritionally improved foods, new pharmaceuticals, and novel vaccines. Identification of human pharmaceutical protein genes and their expression in bacteria and yeast has enabled the production of wonder drugs to fight against cancer, hepatitis, leprosy, AIDS, cardiovascular, viral and parasitic diseases. It is no more a dream but a reality to diagnose and treat (via gene therapy) human genetic disorders even before the birth of the affected child.

As coincidence would have it, another breakthrough was made in the 1980’s and 1990’s when it was discovered

that certain kinds of somatic cells possess inherent capability (or can even be induced) to develop into different lineages such as skin cells, brain cells, lung cells and so on. This revolutionary discovery has given birth to a new era of medicine called regenerative medicine, opening doors to new clinical applications. The promise of regenerative medicine to revolutionize medical care for a wide variety of diseases is beyond imagination. The vast panorama of applications of molecular biology and stem cell technology is already unfolding for the benefit of mankind

The challenge of applying innovative laboratory research to solve unique and specific problems of health and medicine requires the talents of soundly trained manpower which can define problems and devise strategies that will work in the local setting. To develop a researcher having "hands-on" experience of various molecular biology and stem cell techniques, training of manpower needs to be carried out in local hospital situations to see how many things can go wrong and how to get around those hurdles and solve problems. The quality of human training will depend on the condition of training laboratories. Traditionally, our medical university laboratories that are the breeding grounds for future medical practitioners of new and revolutionary technologies, have been even more deficient than the laboratories of general universities and research institutes in the country. As a consequence, medical university training in Pakistan has suffered from laboratory experience that is so vitally important for building the intellectual maturity of future medical practitioners. It is exceedingly important, therefore, to improve the local laboratory infrastructure to promote therapeutic applications of new and revolutionary medical technologies in our tertiary care hospitals as well as improve the quality of training of our medical graduates.

As the global landscape for health and medicine is changing, new strategies are being developed that involve combining basic laboratory research and clinical practices. The question arises are we preparing ourselves to meet the challenges posed by new and revolutionary molecular and cellular technologies? The short answer is big “NO.” The main reason is that we have neither recognized the impact of changing International scenario nor have we allowed our scientists to take bold initiatives. In 2006, Centre of Excellence in Molecular Biology (CEMB), University of the Punjab, Lahore took the first initiative to set up a cGMP compliance protein purification facility, which is an essential requirement for the indigenous production of human pharmaceuticals proteins from genetically engineered microbes. The project was approved in pre CDWP but withdrawn “hours” before it was to be discussed for approval in the CDWP meeting. Consequently, the project died even before its birth and all relevant facilities and infrastructure at CEMB went down the drain. Regrettably, as of to-date, there is no USFDA or EMEA approved cGMP compliance protein purification and/or stem cell production facility in Pakistan, neither in the public sector nor in the private sector. Countries that are now leading in the world (including India and China) are the ones that established cGMP compliance facilities during 2000-2010. In 2008, Indian President Dr. Abdul Kalam inaugurated India’s largest cGMP compliance biopharmaceutical laboratories complex at Wockhardt Biotech Park, Aurangabad, India. This state-of-the-art complex comprises several dedicated facilities built following US FDA and EMEA standards. Since then the establishment of such cGMP compliance laboratories have proliferated from coast to coast forming a sound base for the production of clinical-grade materials in India whereas there is none in Pakistan.

Recognizing future needs in the health sector in a background of the above international scenario and to place Pakistan on a firm footing concerning uses and applications of new and revolutionary medical technologies, the federal government has established Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), as a premier medical teaching and research university. Besides teaching undergraduate and postgraduate courses in Health Sciences and Allied Subjects, the university, with the approval of the Higher Education Commission, has initiated a regular M.Phil. and Ph.D. program in Molecular Biology with a strong backup of basic medical research. A consortium, comprising the University of Punjab thru its centre of excellence in molecular biology, Lahore, university of health sciences, Lahore, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad and Jinnah Burn and reconstructive surgery center, Jinnah hospital, Lahore have joined hands to pool efforts in overcoming the inherent constraints of a shortage of specifically trained manpower and laboratory infrastructure. To this end, an autonomous laboratory unit is established on the fourth floor of Jinnah burn and reconstructive surgery centre, Jinnah hospital, AIMC, university of Health Sciences, Lahore, jointly managed by the partnering institutions. The said consortium laboratory unit is headed by Dr S.

Riazuddin, professor Emeritus, SZABMU, Islamabad. In addition to M.Phil/Ph.D. teaching, Dr. Riazuddin's research team has initiated a program of high-quality research in two areas.

Firstly; to elucidate the molecular and genetic basis of hereditary hearing & vision impairment and intellectual disabilities, in collaboration with Johns Hopkins University, Baltimore, and the University of Maryland, Baltimore, USA. As a consequence of input into these studies during the last five years, the group has published 36 research papers in well-reputed journals such as Am J Hum Genet, J Clin Invest and Mol Psychiatry with a cumulative impact factor of 178.16. [1-36]

Secondly; to investigate the therapeutic potential of adult stem cells in the repair of burnt skin, impaired vision and damaged cartilage, in collaboration with the University of Miami, Florida, USA. As part of these collaborative studies, researchers have been working on a variety of stem cells, including adult stem cells found in umbilical cord blood and /or in adipose tissues. As part of clinical studies, skin tissues or adipose tissues are collected from a patient and reprogrammed to give them desired characteristics and delivered back into the patient to treat his or her disease. Consequently, early clinical trials are emerging in this lab, individually and in collaboration with scientists at Johns Hopkins University, University of Maryland and University of Miami, USA.

The entire program of collaborative research in the consortium lab unit is financed by grants from HEC, Pakistan Science Foundation, National Institute of Health and Bethesda, Maryland (USA). As such, there is no financial liability on the part of partnering Institutions except salaries of two Assistant Professors by SZABMU and laboratory infrastructure by Jinnah Burn and Reconstructive Surgery Centre, Allama Iqbal Medical College and University of Health Sciences, Lahore. Execution of the research program, as well as management of the laboratory unit, exhibits an excellent model of management and research output, evidenced by an impressive number of high impact factor/International publications as well as clinical applications in both areas of research. There is no non-academic services expenditure. It is envisioned that this consortium unit, located in Lahore will serve as a nucleus for the National Institute of Advanced Research to be established by SZABMU in Islamabad as part of its vision 2025.

Publication from SZAB Medical University

1. Iqbal Z, Tawamie H, Ba W, Reis A, Al Halak B, Sticht H, Uebe S, et al. Loss of function of SVBP leads to autosomal recessive intellectual disability, microcephaly, ataxia, and hypotonia. Genetics in Medicine. 2019;21(8):1790-1796.
2. Richard, E. M, Santos-Cortez, Faridi R. Global genetic insight contributed by consanguineous Pakistani families segregating hearing loss. Hum Mutat.2019; 40(1): 53-72.
3. Ansar M, Riazuddin S, Sarwar MT, Makrythanasis P, Paracha SA, Iqbal Z, Khan J, et al.. Biallelic variants in LINGO1 are associated with autosomal recessive intellectual disability, microcephaly, speech and motor delay. Genetics in Medicine. 2018;20(7):778-784.
4. Biswas P, Naeem MA, Ali MH, Assir MZ, Khan SN, Riazuddin S, Hejtmancik JF, et al. Whole-Exome Sequencing Identifies Novel Variants that Co-segregates with Autosomal Recessive Retinal Degeneration in a Pakistani Pedigree. InRetinal Degenerative Diseases.Adv Exp Med Biol.2018;1074: 219-228.
5. Branham K, Guru AA, Kozak I, Biswas P, Othman M, Kishaba K, Mansoor H, et al. Identification of Novel Deletions as the Underlying Cause of Retinal Degeneration in Two Pedigrees. InRetinal Degenerative Diseases. Adv Exp Med Biol. 2018;1074:229-236. doi: 10.1007/978-3-319-75402-4_28.
6. Chen Y, Huang L, Jiao X, Riazuddin S, Riazuddin SA, Hetmancik JF. A novel LRAT mutation affecting splicing in a family with early onset retinitis pigmentosa. Human genomics. 2018;12(1):35.
7. De Brouwer AP, Jamra RA, Körtel N, Soyris C, Polla DL, Safra M, Zisso A, et al. Variants in PUS7 Cause Intellectual Disability with Speech Delay, Microcephaly, Short Stature, and Aggressive Behavior. Am J Hum Genet.2018; 103(6): 1045-1052.
8. Imtiaz A, Belyantseva IA, Beirl AJ, Fenollar-Ferrer C, Bashir R, Bukhari I, Bouzid A. et al. CDC14A phosphatase is essential for hearing and male fertility in mouse and human. Hum Mol Genet 27(5): 780-798.
9. Li L, Jiao X, D'Atri I, Ono F, Nelson R, Chan CC, Nakaya N, et al. Mutation in the intracellular chloride channel CLCC1 associated with autosomal recessive retinitis pigmentosa. PLoS genetics. 2018;14(8):e1007504.
10. Yousaf R, Ahmed ZM, Giese AP, Morell RJ, Lagziel A, Dabdoub A, Wilcox ER, et al. Modifier variant of METTL13 suppresses human GAB1-associated profound deafness. J Clin Invest.2018; 128(4): 1509-1522.
11. Yousaf, R., Gu, C., Ahmed, Z. M., Khan, S. N., Friedman, T. B., Riazuddin, S. and Shears, S. B. (2018b). Mutations in Diphosphoinositol-Pentakisphosphate Kinase PPIP5K2 are associated with hearing loss in human and mouse. PLoS Genet 14(3): e1007297.
12. Anjum MS, Mehmood A, Ali M, Butt H, Khan SN, Riazuddin S. Transplantation of stromal-derived factor 1alpha and basic fibroblast growth factor primed insulin-producing cells reverses hyperglycaemia in diabetic rats. Growth Factors.2017; 35(2-3): 88-99.
13. Baig MT, Ali G, Awan SJ, Shehzad U, Mehmood A, Mohsin S, Khan SN. Serum from CCl4-induced acute rat injury model induces differentiation of ADSCs towards hepatic

cells and reduces liver fibrosis. Growth Factors.2017; 35(4-5): 144-160.
14. Biswas P, Duncan JL, Ali M, Matsui H, Naeem MA, Raghavendra PB, Frazer KA, et al. Mutation in IFT43 causes non-syndromic recessive retinal degeneration. Hum Mol Genet.2017; 26(23): 4741-4751.
15. Butt H, Mehmood A, Ali M, Tasneem S, Anjum MS, Tarar MN, Khan SN, et al. Protective role of vitamin E preconditioning of human dermal fibroblasts against thermal stress in vitro. Life Sci.2017; 184: 1-9.
16. Chen J, Wang Q, Cabrera PE, Zhong Z, Sun W, Jiao X, Chen Y, et al. Molecular Genetic Analysis of Pakistani Families With Autosomal Recessive Congenital Cataracts by Homozygosity Screening. Invest Ophthalmol Vis Sci.2017 58(4): 2207-2217.
17. Faridi R, Rehman AU, Morell RJ, Friedman PL, Demain L, Zahra S, Khan AA, et al. Mutations of SGO2 and CLDN14 collectively cause coincidental Perrault syndrome. Clin Genet.2017; 91(2): 328-332.
18. Ivanova, EL., Mau-Them, F. T., Riazuddin, S. Homozygous Truncating Variants in TBC1D23 Cause Pontocerebellar Hypoplasia and Alter Cortical Development. Am J Hum Genet.2017; 101(3): 428-440.
19. Li L, Chen Y, Jiao X, Jin C, Jiang D, Tanwar M, Ma Z, et al. Homozygosity Mapping and Genetic Analysis of Autosomal Recessive Retinal Dystrophies in 144 Consanguineous Pakistani Families. Invest Ophthalmol Vis Sci.2017 58(4): 2218-2238.
20. Riazuddin S, Hussain M, Razzaq A, Iqbal Z, Shahzad M, Polla DL, Song Y, et al. Exome sequencing of Pakistani consanguineous families identifies 30 novel candidate genes for recessive intellectual disability. Mol Psychiatry. 2017; 22(11): 1604-1614.
21. Biswas P, Chavali VR, Agnello G, Stone E, Chakarova C, Duncan JL, Kannabiran C,et al. A missense mutation in ASRGL1 is involved in causing autosomal recessive retinal degeneration. Hum Mol Genet.2016; 25(12): 2483-2497.
22. Irum B, Khan SY, Ali M, Daud M, Kabir F, Rauf B, Fatima F,et al. Deletion at the GCNT2 Locus Causes Autosomal Recessive Congenital Cataracts. PLoS One.2016; 11(12): e0167562.
23. Irum B, Khan SY, Ali M, Kaul H, Kabir F, Rauf B, Fatima F,et al. Mutation in LIM2 Is Responsible for Autosomal Recessive Congenital Cataracts. PLoS One.2016; 11(11): e0162620.
24. Jiao X, Kabir F, Irum B, Khan AO, Wang Q, Li D, Khan AA, et al. A Common Ancestral Mutation in CRYBB3 Identified in Multiple Consanguineous Families with Congenital Cataracts. PLoS One.2016; 11(6): e0157005.
25. Kabir F, Ullah I, Ali S, Gottsch AD, Naeem MA, Assir MZ, Khan SN, Akram J, Riazuddin S, et al. Loss of function mutations in RP1 are responsible for retinitis pigmentosa in consanguineous familial cases. Mol Vis.2016; 22: 610-625.
26. Khan SY, Vasanth S, Kabir F, Gottsch JD, Khan AO, Chaerkady R, Lee MC, et al. FOXE3 contributes to Peters anomaly through transcriptional regulation of an autophagy-associated protein termed DNAJB1. Nat Commun.2016; 7: 10953.
27. Latief, N., Raza, F. A., Bhatti, F. U. Adipose stem cells differentiated chondrocytes regenerate damaged cartilage in rat model of osteoarthritis. Cell Biol Int.2016; 40(5): 579-88.
28. Rauf B, Irum B, Kabir F, Firasat S, Naeem MA, Khan SN, Husnain T, et al A spectrum of CYP1B1 mutations associated with primary congenital glaucoma in families of Pakistani descent. Hum Genome Var.2016; 3: 16021.
29. Ullah I, Kabir F, Iqbal M, Gottsch CB, Naeem MA, Assir MZ, Khan SN, et al. Autosomal-Recessive Hearing Impairment Due to Rare Missense Variants within S1PR2. Am J Hum Genet.2016; 98(2): 331-338.
30. Ullah, I., Kabir, F., Gottsch, CB, Naeem MS, Guru AA, Ayyagari R, Khan SN, et al. Mutations in phosphodiesterase 6 identified in familial cases of retinitis pigmentosa. Hum Genome Var.2016; 3: 16036.
31. Ullah I, Kabir F, Iqbal M, Gottsch CB, Naeem MA, Assir MZ, Khan SN, et al. Pathogenic mutations in TULP1 responsible for retinitis pigmentosa identified in consanguineous familial cases. Mol Vis.2016; 22: 797-815.
32. Jiaox X, Khan SY, Irum B, Khan AO, Wang Q, Kabir F, Khan AA, et al. Missense Mutations in CRYAB Are Liable for Recessive Congenital Cataracts. PLoS One.2015; 10(9): e0137973.
33. Khan SY, Ali S, Naeem MA, Khan SN, Husnain T, Butt NH, Qazi ZA, Akram J, Riazuddin S, et al. Splice-site mutations identified in PDE6A responsible for retinitis pigmentosa in consanguineous Pakistani families. Mol Vis .2015;21: 871-882.
34. Maranhao B, Biswas P, Gottsch AD, Navani M, Naeem MA, Suk J, Chu J, et al. Investigating the Molecular Basis of Retinal Degeneration in a Familial Cohort of Pakistani Decent by Exome Sequencing. PLoS One.2015; 10(9): e0136561.
35. Naeem, M. A., Gottsch, A. D., Ullah. Mutations in GRM6 identified in consanguineous Pakistani families with congenital stationary night blindness. Mol Vis.2015; 21: 1261-1271.
36. Simon M, Richard EM, Wang X, Shahzad M, Huang VH, Qaiser TA, Potluri P, et al. Mutations of human NARS2, encoding the mitochondrial asparaginyl-tRNA synthetase, cause nonsyndromic deafness and Leigh syndrome. PLoS Genet.2015 11(3): e1005097.