View Point

Need for the Development of Clinical and Translational Science Institutes in India

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There is considerable interest among researchers, clinicians and policy makers, for developing early biomarkers, both for genetic and molecular diagnosis and using them for clinical studies. According to National Cancer Institute (NCI) of the National Institutes of Health (NIH), USA, one of the most widely recognized roadblock to progress in cancer research is the lack of standardized, high-quality biospecimens. If a State-of-the-art bio-repository were established in India, with international protocols, and NCI best practices procedures in place, it would provide a wealth of standardized clinical samples for all kinds of studies. The genetic diversity as well as cancer diversity in India is huge. We see a lot of collaborative projects spawning from such a platform. Kidwai Memorial Cancer Institute of Oncology (a national platform for oncology), Bengaluru, has already established such multicenter collaborations with Indian Institute of Sciences, National Center for Biological Sciences, St John's Medical Academy, Bangalore and prestigious John's Hopkins University, USA and generated useful information on genomics and proteomics of squamous cell carcinoma. We at the Rajiv Gandhi University of Health Sciences (RGUHS), Bengaluru, are also contemplating establishing a common research and development platform for following areas of interest; biomarker development, biomedical device development, drug discovery and therapeutics, nanotechnology for drug delivery and therapeutics, preclinical and clinical validation of innovations, bench to clinic development of drugs and devices, tissue engineering and regenerative medicine and stem cell biology. Furthermore, efforts are underway at RGUHS, to help develop centers of excellence in allied sciences, encourage collaborative research between various research institutions, in the State of Karnataka and build a common translational science platform, to promote the development of science from bench to clinic. An expert committee has been formed to coordinate these efforts. In this overview, we will present strengths and weakness of the programs in India and present a strong case for national and international collaboration, to develop much needed biorepositories and translational science centers in India, similar to the Clinical and Translational Sciences Institutes (CTSIs) of National Institutes of Health (NIH), USA. In this overview we have used RGUHS as an example, however, the ideas that we have articulated in this article could be used, for developing regional as well as national CTSIs in India.

If we look at the contribution of Indian research and development platforms, the National Laboratories established in pre-independence days, in India, stand out. The Council of Scientific & Industrial Research (CSIR) - the premier industrial Research and Development Organization in India, was constituted in 1942 by a resolution of the then Central Legislative Assembly. It is an autonomous body and aims to provide industrial competitiveness, social welfare, and strong Sciences (S) and Technology (T) base for strategic sectors for advancement of fundamental knowledge. The new Science and Technology Policy 2003 of Government of India, emphasizes realities such as facing open global competition; need for examining social, economic and environmental consequences of S&T; and, aggressive international benchmarking and innovation. It advocates strong support for basic

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research. It emphasizes manpower buildup and retention as important challenges. It advocates dynamism in S&T governance, through the participation of scientists and technologies. According to a recent write up on the web pages of CSIR (www.csir.res.in), these institutions offer a unique mix of multi-disciplinary expertise, sound technical knowledge and talent for innovation that characterizes CSIR and these platforms cover sectors as diverse as Aerospace, Biotechnology, Chemicals, Drugs & Pharmaceuticals, Energy, Food & Food Processing, Information Dissemination, Leather and Metal, Minerals & Manufacturing to name a few. In the field of developing Intellectual Property Rights, CSIR's track record seems to be enviable given its rather recent entry into the area. Of the 229 US patents granted in 2004-05 to Indian inventors (excluding foreign assignees), CSIR has 140 (61.1%). According to their claim, if one considers Indian inventors including foreign assignees, CSIR's share is still 28.3%, which is significant. However, if we look at this achievement from the Global Perspective in terms of number of patents filed from each country or according to the money spent on R&D or on the basis of patents filed with respect to their respective GDP, a different picture emerges. In a recent issue of MIT Technology Reviews (www.technologyreview.com, March/April 2011), Brian Bergstein has published a composite data on which countries generate an outsize number of ideas (patents), relative to their economic might or R & D resources. India, Estonia and Belgium rank at the bottom and South Korea, Japan, Moldova, China, Russia and USA top the list in that order.

The Medical Council of India, currently (2011) fully recognizes a total of 345 medical colleges, able to train 40,525 medical students. There are probably equal number of undergraduate training programs in the " Indian Traditional Medicine" disciplines and trains an equal number of Indian Medicine Graduates (Vaidyas) in various disciplines, such as Ayurveda, Yoga, Unani, Siddha and Homeopathy (AYUSH). In spite of producing over 100,000 medical graduates per year, the opportunities for basic and clinical research in health sciences are severely lacking. India has made a spectacular progress in its economy, yet, the funding for health care is less than 1% of the Gross National Product (GDP). Many of the developing Nations with much less GDP, spend more for healthcare than India. In the USA, there are currently 131 Medical Colleges and health care spending is close to 18% of the GDP and is reaching over 2.7 trillion per year. National Institutes of Health (NIH), the premier platform for research and development in health sciences, has a budget of over 30 billion USD and is the biggest platform for research in biomedical sciences in the World. It has set aside over 200 million USD, to speed scientific discoveries and innovations that directly improves the quality of healthcare. The National Center for Research Resources of NIH has established Clinical and Translational Science Awards (CTSA), to promote clinical and translational research at the Academia and the Industry. There are over 60 centers of excellence in this area of research, distributed in 30 States (http://www.ncats.nih.gov). These research and development platforms called, Clinical and Translational Science Institutes (CTSIs), have been functioning as multidisciplinary platforms since 2005, in most of the major health science universities in the USA. Translational research programs bring together physicians, bench scientists, bioengineers, epidemiologists, patent experts, and much more to this platform. The goal is learning to communicate across disciplines, to achieve advances in health care. A translational scientist should be able to move an idea, all the way from basic research to a clinical application.

If we look at the mission statement of one of the premier healthcare organizations in the World, Mayo Clinic of Rochester, Minnesota, USA, it becomes evident the purpose of establishing such centers in major academic institutions. The goal of the Mayo Clinic CTSI program is, to present Mayo Clinic's vision for the integration and expansion of its innovative clinical and translational research activities, so that a highly functional academic home for clinical and translational research is developed at the Mayo Clinic. The Center for Translational Science Activities is founded on the Mayo Clinic's long-standing excellence in and commitment to clinical and translational research, which includes the support of key infrastructure and a commitment to career development. To achieve this goal, Mayo Clinic will take a comprehensive approach to the key elements of the CTSA Request for Applications and focus on enhancing: 1) clinical research core resources that provide innovative tools to investigators; 2) career development and education programs that prepare the next generation of investigators; 3) compliance and regulatory affairs support that ensures patient safety and privacy, and customer service-oriented approaches to support investigative teams; 4) community affairs support to enhance participation, diversity and community support for clinical and translational research; 5) collaboration with industry and clinical practices to translate research discoveries into routine clinical

practice; and 6) continued and expanded institutional support that includes an academic home for clinical and translational research.

The CTSA programs in the USA provide infrastructure support, to facilitate translational research, to promote the training and career development of translational researchers, and to develop innovative methods and technologies to strengthen translational research. These platforms form a national consortium, which shares a common vision of improving human health by transforming the research and training environments for clinical and translational science. At the University of Minnesota (UMN) CTSI facility (www.ctsi.umn.edu), following services are available for researchers and clinicians: Project Management, Regulatory Support, Biostatistical Design and Analysis Center, Clinical Research Ethics Consultation Service, Informatics Consulting Service, Clinical Research Support Staff, Nutrition Research Center, Clinical Research Facilities, Translational Research Resources, Assistance for Junior Investigators, Support for Community-Engaged Research. Research Project Managers are certified clinical research professionals, who provide assistance with investigator-initiated and industry-sponsored studies. The Biostatistical Design and Analysis Center (BDAC) team includes professional biostatisticians and a database programmer to provide collaboration and assistance. The Clinical Research Ethics Consultation Service (CRECS) provides those involved in human subjects research, with a structured approach for identifying, analyzing and resolving ethical issues. The Informatics Consulting Service (ICS) enables clinical-translational researchers, to improve their effectiveness, efficiency and impact by providing them with access to informatics tools, resources and expertise. The CTSI Nutrition Research Center provides nutrition research expertise and support for clinical protocols. The Office of Discovery and Translation (ODAT) is a UMN-wide integrator, facilitator, and catalyst of bench-to-bedside translation. In addition, UMN has a NIH funded Clinical Research Center (CRC), which can be used by investigator-funded clinicians and scientists. Some of the translational science on going programs include; Cell-based therapies, Novel imaging, Genomics and proteomics, Drug discovery, Clinical pharmacology, Translational medicine, Medical device development, Comparative medicine.

One of the most successful innovations in translational research from "bench to clinic" was the discovery and development of monoclonal antibody based anti-platelet therapy for the prevention of acute vascular events, which began in SUNY, Stony Brook, New York, in the early 1980s. When platelets adhere to and aggregate on blood vessels narrowed by atherosclerosis, they can close off the blood vessel and cause a myocardial infarction (heart attack) or stroke. By studying the receptors responsible for platelet aggregation and patients who genetically lack the receptors, Dr. Barry Coller and his associates at Stony Brook University School of Medicine (1976-93) and Mount Sinai School of Medicine (1993-2001), New York, established the platelet αIIbβ3 (GPIIb/IIIa) receptor, as an important target for antithrombotic therapy (1,2). This led them to develop monoclonal antibodies to the αIIbβ3 receptor that inhibit platelet aggregation. Working with scientists at Centocor, Dr. Coller and associates developed, a derivative of one of these antibodies into the drug abciximab, which was approved for clinical use by US FDA in 1994, to prevent ischemic complications of percutaneous coronary interventions, such as stent placement in patients with myocardial infarction and related conditions. Abciximab/ReoPro, is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin ($\alpha_v\beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells. The chimeric 7E3 antibody is produced by continuous perfusion in mammalian cell culture. The 47,615 dalton Fab fragment is purified from cell culture supernatant by a series of steps involving specific viral inactivation and removal procedures, digestion with papain and column chromatography. More than four million patients worldwide have been treated with abciximab (2-10). Professor Barry Coller, the innovator of this novel technology, joined the prestigious Rockefeller University in New York in 2001, as David Rockefeller Professor and Head of the Blood and Vascular Biology Division. He also serves as physician-in-chief of the Rockefeller University Hospital and (http://www.rockefeller.edu/research/faculty/labheads/BarryColler), vice president for medical affairs. Dr. Coller also serves as principal investigator of the university's Clinical and Translational Science Award, director of The Rockefeller University Center for Clinical and Translational Science, and director of the Center for Basic and Translational Research.

Anti-platelet agents such as Integrelin (GSK), ReoPro (Eli Lilly) and Aggrastat (Merck) form a critical component in the treatment of unstable angina and non-ST-elevation

myocardial infarction. In 2012 sales in the USA, France, Germany, Italy, Spain, UK and Japan reached 129 million for Integrelin, 95 million for ReoPro and 30 million for Aggrastat. The market for therapeutic monoclonal antibodies (mAbs) is one of the most dynamic sectors within the drug discovery and development platform. Next generation antibodies for oncology, arthritis, immune-inflammatory diseases and for the management of cardiometabolic disorders are forecast to continue to lead the market, towards USD 30 billion mark. Here is a window of opportunity for the Indian Biotechnology Clusters, to focus on the development of biomarkers and a variety of antibody based applications for early detection, management and prevention of clinical complications associated with cardiometabolic diseases and other non-communicable diseases.

The experimental studies that lead to the perfection of angioplasty as a routine preventive procedure, also could be considered as an equally important "bench to clinic" development of a successful interventional therapy. Forssmann's (Nobel Laureate) landmark placement of catheters in his own heart, achieved very little practical use, until World War II, when Cournand and others developed catheter-based techniques, to measure cardiac output during shock states and for targeted delivery of drugs (11). Guentzig could not have developed angioplasty techniques, but for the pioneers who developed the use of catheters for various cardiovascular interventional procedures (11). Andreas Gruentzig presented his idea of percutaneous dilation of an artery at the American Heart Association meeting in Miami in 1975. The first American cases to use these procedures were performed simultaneously in March of 1978, by Myler at San Francisco and Stertzer in New York. It is now well established that angioplasty can be performed in suitably selected, multivessel-disease patients, in over 5000 patients; however, the recurrence rate still drives an excess of angioplasty patients toward repeat procedures. Technical advances have improved the ability to perform angioplasty with low-profile balloons, long balloons, high-pressure balloon material, perfusion and monorail devices, and improved guide wires and guide catheters. It remains to be proved, as to what degree, these new technologies can improve the treatment of multivessel disease and reduce clinical complications associated with this interventional procedure.

In terms of "bench to clinic" development for CVD applications, Prof. Barry Coller's work on ReoPro, stands out as outstanding. Can we expand these innovative ideas to develop novel therapies for instance for cancer management? It is well established that tumor metastasis causes 90% of cancer related deaths. Researchers at MIT (Trafton A: MIT. Tech. Rev 116, 2013) lead by Prof. Sangeeta Bhatia and associates, exposed tumor cells to about 800 different pairs of cell matrix components. They found that majority of them stuck to galectin-3 and fibronectin. They have discovered that the cell matrix component that promotes this behavior of cellular spreading is fibronectin. Using this knowledge, just like the studies conducted by Dr. Coller and associates, one can target these molecules with appropriate antibodies and use them for the prevention of metastasis of tumor cells. This knowledge of utilizing cell matrix components for the development of various clinical applications, can be used for tissue engineering as well. For example, if we are developing a biomaterial scaffold, to be used for cardiovascular applications, we need a variety of cell matrix components to achieve our goal. Fibrin could be used as the starting material, since one can use it to develop bio-gel in various shapes and sizes from autologous plasma. Plasma can be made into a gel by treating with sterile calcium or human thrombin. This method could be used for developing fibrin-based surgical sutures. One can seed the type of cell needed for tissue repair or engineering on such fibrin strands. Researchers at (Worcester Polytechnic Institute) for example, have developed a polymer-based surgical suture infused with stem cells (12).

Platelet-rich fibrin gel can be used for a variety of applications, including wound healing, bone regeneration and for targeted drug delivery. This novel technology could be used for local delivery of anti-inflammatory drugs, antibiotics, or chemotherapeutic agents. Such studies are in the planning stages at the JSS Medical College, Mysore. ICMR funded studies on evaluating the effect of PRP-Fibrin-gel for wound healing and bone regeneration in patients that undergo tooth extractions, is in progress at RV Dental College, Bangalore (Rao GS et al: J. Maxillofac. Oral Surg.12:11-16, 2013). Fibrin gels can be used for developing a variety of scaffolds for tissue engineering. Embedded cells in the fibrin-gel will survive well and keep their shape and integrity. However, if we want them to spread and establish as a monolayer or in any particular orientation, then we need to develop a bioreactor, which provides the optimum growth conditions. We also need appropriate cell matrix components or polymer compounds to develop the needed composition of such a scaffold. Fibrin-gel can be used for developing natural surgical sutures, as well

as biological glue, patches to cover the areas of exposure during the surgery instead of meshes, for developing cellular patches for tissue engineering and repair of the damaged organs, such as heart, kidney, liver etc.

Pioneering work of Professor Doris Taylor and associates, at the University of Minnesota demonstrated, as to how one can develop the world's first "beating heart", using tissue-engineering technologies (13). The research team took a whole heart, removed the cells and used the resulting cell-free native biological scaffold and repopulated it, with new cardiac cells. What this pioneering work demonstrates is, that this kind of technologies can be used to grow and develop liver, kidney, lungs and pancreas, indeed virtually any organ with a blood supply. Basically one can begin with human or pig cells, use human, pig or bioartificial tissue engineered scaffold to create the needed organ, in a customized, large bioreactor. Decellularized (cell free) scaffolds of biological organs could be developed, by using appropriate detergents like, 3-{(3-cholamidopropyl) dimethylammonio}-1propanesulfonate, or sodium dodecyl sulfate (SDS). The technology of developing bio-artificial organs is too expensive but doable. Using similar tissue engineering approaches, bioartificial liver has been developed by a Minnesota company, Excorp Medical Inc. The US FDA has approved the bioartificial liver as an orphan devise and currently it is being developed at Hyderabad, India (Synthochirals Excorp Biologicals India, Ltd), as a joint bilateral venture between USA and India. Preliminary work on similar lines, to develop a tissue engineered bioartificial kidney is in progress in Bangalore, by a group of entrepreneurs. Studies from University of Minnesota researchers in early 80s demonstrated in a drug induced (type-2 diabetes) animal model, that pancreatic islet cell transplantation can indeed reverse the pathology and patho-physiology of the animal (14). Halberstadt et al in 2013 demonstrated, that the transplantation of allogeneic pancreatic islets into the liver via portal vein, coupled with low dose immunosuppression, could lead to insulin independence and tight control of blood sugar (15). Based on the success of earlier studies, it has been clinically demonstrated that islets cells isolated from cadaveric pancreases and transplanted into the portal vein of immunosuppressed patients, can maintain a state of insulin independence for up to 5 years. Such novel approaches are of great importance for India, as we have the highest number of diabetics in the world.

When we think of developing tissue-engineering applications, we should pay attention to the use of appropriate components, to develop the desired end point. If we want a permanent scaffold, then we need to use non-degradable polymers, whereas, if we need a degradable scaffold (vascular grafts for small diameter arteries), then we need to use biodegradable polymers. In addition, using synthetic polymers, one can develop a variety of targeted drug delivery applications. Dr. Rao and associates have worked extensively on the use of microspheres and nanospheres for targeted delivery of drugs, cell encapsulation, tissue engineering, as well as for management of tissue repair (16-27). In one of such novel studies, MIT researchers have developed capability to inject oxygen to the blood using this technology (MIT Rev. 115, 89, 2012: Ref: 28). They have shown that oxygen saturated microspheres or liposomes can be used for delivery of oxygen to the blood by infusion of these oxygen-rich vehicles. These ideas can be further expanded to develop platelet substitutes for emergency life-saving applications. One can take outdated platelets and break them by freeze thawing or mild sonication, to produce microparticles of these cells. These particles, which become micro-vesicles retain their receptors such as αIIbβ3, which facilitate fibrinogen binding. These platelet vesicles will bind fibrinogen and aggregate. Moreover, it is well known that circulating platelet microparticles express tissue factor and are pro-coagulant. Well-characterized platelet particles (vesicles), therefore, could be used as substitutes for fresh platelets, to arrest bleeding under a variety of clinical conditions.

Now that we have discussed the importance of translational science in bringing innovations from "bench to clinic", in the USA with few successful examples, let us examine the scenario in India. Majority of Medical Colleges, as well as other Colleges offering degrees in health sciences, lack infrastructure for conducting research at their facilities. They also lack trained personnel, to conduct and guide research. Let us consider the state of affairs in the State of Karnataka for example and discuss the strengths and weaknesses in this area. The premier administrative body for the health sciences in the State of Karnataka, Rajiv Gandhi University for Health Sciences (RGUHS), was established in 1996 in Bangalore. The University promotes and imparts higher education in health sciences in the State of Karnataka. The university has been approved by University Grant Commission (UGC) but not funded by the UGC. It is a self-contained, State University. Around 625 colleges in the State of Karnataka, conducting health science related courses are affiliated to Rajiv Gandhi University, in order to achieve uniform standards in

academics and administration. RGUHS is a member of the Association of Indian Universities (AIU). This is a unique kind of set up in the sense, it has no real infrastructure for teaching and conducting research, as you would visualize in Medical Universities across the Globe. It is just an administrative unit for the health science colleges, for the entire State of Karnataka. The Governments in other States in India also have set up similar administrative health science universities. In the absence of research facilities at the four-year colleges as well as at the RGUHS, the progress of basic science and clinical research is limited. There are number of Deemed Universities in the State, but by and large, they also lack research infrastructure, financial resources and trained personnel to conduct and guide research.

Need of the hour therefore, is to initiate projects and proposals that address these issues in an unbiased manner, prioritize the research, basic as well as clinical and quick start the deployment of these ideas. Let us consider some possible action plans based on how we can bridge this gap in the knowledge. One way to achieve these objectives is, to procure funds from the RGUHS and develop an independent Clinical and Translational Science Platform similar to the CTSIs of US, which we have discussed previously. The advantage of this approach is that the funds are available, the space is available, trained personnel are available in the RGUHS affiliated colleges. In that case, what is preventing us from developing such a platform? We need a committed leadership to develop such one of a kind platform in India. It needs determination, passion and elaborate planning. The platform though funded initially from the RGUHS resources, should become self sufficient in five years. It should have needed infrastructure including state-of-the-art research laboratory, project managers, experts in regulatory issues, informatics consulting service, clinical research facility and supporting staff, basic science research facility and support staff, translational research supporting staff, support for grant writing, project performance and guidance to junior investigators and finally staff for servicing contract research. The advantages of developing such a platform under the aegis of RGUHS will be, that it can serve a large section of health science colleges in the state, it can also help centers of excellence in various fields, develop a bilateral national and international collaborations and serve as a working model for the other states. Similar models can be developed for the other State Health Science Universities also.

Another possibility is to work with the "centers of excellence in various disciplines" in the State, develop memorandum of understanding and working arrangements with them, so that these institutions could be developed as clinical and translational science facilities. Rajiv Gandhi University of Health Sciences has established an expert committee to identify, assess the strengths and weaknesses of these centers of excellence, in the State of Karnataka. Dr. Rao as one of the senior members of this committee has identified several institutions in the State as "centers of excellence" and the work is in progress to establish bilateral collaboration with these institutions. The advantages of such an approach is that we need not have to establish a separate platform, but use the existing infrastructure and manpower and build on it. Association of these institutions with RGUHS will give them credibility and accreditation for establishing educational programs. On the other hand RGUHS will get a multidisciplinary research platform that could be used by the staff of affiliated colleges of RGUHS, for advanced clinical and basic research. Even then, we need to procure funding to strengthen these facilities, so that they can serve as state-of-the–art research and development facilities. We also will have to set up a project management team, which will coordinate with various centers of excellence. Some of the laboratories and institutions identified in a preliminary survey include (not limited); St. John's Medical Academy, Bangalore Medical College, M. S. Ramaiah Medical College, Sri Jayadeva Institute of Cardiology, Karnataka Diabetes Institute, Narayana Hrudayalaya, Narayana Nethralaya, Sri Research Centre for Tissue Engineering and Regenerative Medicine, National Design Research Forum (NDRF) of Institute of Engineers, Kidwai Memorial Institute of Oncology and Health Care Global (HCG) Platform for Oncology. This is just a preliminary list generated for evaluating feasibility studies and develop bilateral collaborative working arrangements. Not included in this list, but of great importance for developing such a network are institutions like, prestigious Indian Institute of Sciences (Tata Institute), National Centre for Biological Sciences (NCBS), Jawaharlal Nehru Centre for Advancement of Sciences (JNCAS), National Institute for Mental Health and Neurosciences (NIMHANS), National Tuberculosis Institute (NTI) and to be established Public Health Institute and Centre for Disease Control (RGUHS).

RGUHS has funds and resources available for expansion of their activity. If the expert committee of the RGUHS can articulate these ideas well with the University Senate, Academic council of RGUHS and the administrators, it

is possible to develop a robust Clinical and Translational Science Facility that can serve the needs of the State. University of Minnesota has a CTSA funded Clinical Translational Science Institute (www.ctsi.umn.edu). This is one of the 60 such facilities funded by the National Institutes of Health USA, to promote clinical and translational science. The operational budget exceeds 50 million dollars and has over 150 clinical studies in progress. We have initiated dialogue with the Director and other senior staff members of this institute. They have expressed their interest in developing a bilateral collaborative program with the RGUHS. Indian Council of Medical Research and University of Minnesota have established a MoU for funding bilateral research programs. RGUHS can take advantage of this existing working relationship and develop tri-sector collaboration with UoM, ICMR and develop a CTSI in Karnataka. Since Prof N. K. Ganguly the former Director General of Indian Council of Medical Research heads a platform dedicated, to the development of Infrastructure for Translational Research and Clinical Trials (NCR Health Biotech Cluster) in India, It is possible to articulate these views with his group and expand these ideas to cover the entire country.

A country like ours has very challenging health problems. We have the highest incidence of hypertension, central abdominal obesity, metabolic syndrome, type-2 diabetes, coronary artery disease and stroke (29-31). According to some guesstimates, by 2030, 50% of the world's diabetics will be South Asians. Medical education programs in India at the undergraduate level although introduces the students to the diagnosis, clinical complications, and management of these chronic diseases, do not expose them to research methodologies. As such the majority of doctors are not well trained to do research and compete for funds to establish research programs. In addition to this, many of the RGUHS affiliated colleges lack infrastructure and manpower, to get approval for doing research at their campuses from major funding agencies like ICMR, DST, DBT, DRDO and UGC. In order to address these problems, expert committee of the RGUHS met and decided, to develop common research platforms. Whether these initiatives materialize or not, we feel that the time has come for us to keep these options open and articulate these views at national and international levels. With an idea to develop bilateral programs in this area, Professor Gundu Rao presented his views at the BRN Symposium organized by the NCI/NIH at Bethesda, Maryland, USA in 2012 and discussed these ideas with the staff members of CTSI at the University of Minnesota and NCI of NIH, USA **(*development* of bio-repositiories and translational science facilities ...*biospecimens.cancer.gov/.../Poster%2066_Rao_RGUHS%20N).***

As we have mentioned early on in this overview, there is a great need for the development of translational science research platforms in all the major areas of science and technology, yet in view of our interest as well as the epidemic nature of chronic cardio-metabolic diseases, we will discuss some examples as they relate to cardiometabolic disorders. For instance, currently we have in India over 60 million diabetics and an equal number of pre-diabetics. These subjects numbering over 100 million have to get their blood checked for glucose levels often. Monitoring of blood glucose involves finger pricking, to obtain a drop of blood and the use of test strips, to determine the concentration of glucose. Although one can get a glucose meter for a nominal price repeated use of diagnostic strips is considerably expensive. If one comes up with a technology, which eliminates finger pricking and use of expensive diagnostic strips, then this process becomes simple, accessible, acceptable and affordable. We (Indus BioMedical Devices: IBMD, Mysore) are in the process of developing a non-invasive blood glucose monitor using near infrared spectrometer with funding from the Indian Council of Medical Research at National Design Research Forum of Institute of Engineers, Bangalore. This type of research becomes what we define as prioritized translational research, based on the needs of the country.

Nutritional anemia is one of India's major public health problems. The prevalence of anemia ranges from 33% to 89% among pregnant women and is more than 60% among adolescent girls. This chronic public health problem is preventable. Even to this day, in India 30% of all the children born are of low birth weight. These underweight babies develop metabolic disease in greater proportion than the normal weight babies. One of the ways to address this issue is to develop, a simple non-invasive method to determine blood levels of hemoglobin and then develop administering multiple micronutrients to improve the blood levels of hemoglobin. Preliminary work from our group has already demonstrated that the same technology that we have used for detecting blood glucose, with minor modifications can be used for developing a non-invasive hemoglobin meter. As a complementary measure we can also develop simple cocktail of micronutrients that can be used as daily supplement for improving general

nutrition status as well as blood hemoglobin. We are in the process of developing such a program with the Public Health Department of RGUHS. Using similar non-invasive method by using near infrared as well as red light, one can monitor the level of blood oxygen saturation also. Masimo a US based company, has developed an iPhone Oxygen Scanner (US$ 249.00) and smart phone applications for general use (MIT Tech Rev 116:20, 2013). If we combine these three methodologies, then we will have a multifunctional diagnostic device. Ultimate goal of IBMD is to develop a mobile diagnostic platform, that can do the blood chemistry and associated diagnostic techniques on a "tablet" so that the tests can be performed anywhere in the country. With appropriate built in communication packages the diagnostic data can be made available to any clinic in the country.

Coronary artery disease (CAD) is a major health burden in India. Major interventional modalities to prevent coronary occlusion and death in recent years have been balloon angioplasty and bypass surgery. With the advent of vascular stents there is considerable improvement in the treatment of CAD. Improvements in the recent years have increased the demand for drug eluting stents (DES) to prevent complications associated with balloon angioplasty. It is estimated that the current market for this device exceeds 5 billion dollars. In spite of the initial success of this technology, there is concern about inflammation, clot formation, re-occlusion, and sudden deaths. Based on available information, it is reasonably clear that techniques and methods are available for developing safer effective tissue engineered bioartificial small diameter grafts, capable of integrating with the surrounding tissue and responding to the stimulus in a normal fashion. University of Pittsburgh (USA) recently demonstrated a novel innovation, a cell-free biodegradable artery, which regenerates itself in vivo and in 90 days, degrades leaving behind no trace of synthetic graft materials in the body. We are in process of developing a network of stakeholders in tissue engineering and regenerative medicine in Bangalore, with the specific aims to develop a novel, intelligent, acellular, biological scaffold, which upon implantation, will prove to be infection resistant, non-immunogenic, thrombo- resistant, biocompatible and supports the growth of vascular cells.

How do we prioritize our research in basic sciences and clinical areas? One-way of addressing these questions is to examine the health care burden of the country. If we look at the number of children born with low birth weight (30%), it becomes clear that the maternal and neonatal nutrition is of primary importance. Similarly, if we examine the trends in the incidence of anemia in general population, especially in pregnant women and adolescent girls, then we realize the importance of this area as of great public health importance. We have already discussed about the high incidence of cardio-metabolic diseases such as hypertension, visceral fat accumulation, type-2 diabetes, CAD and stroke. If we talk of non-communicable diseases in general, then cancer also becomes an important part of this group of diseases. Now that we have listed a few examples for prioritizing the disorders of public health importance, we need to develop "novel" indigenous methods to combat these chronic diseases. Starting from early detection of risk factors to the better management of these diseases, everything can be tackled under the CTSI agenda.

For instance, development of simple non-invasive methods for the detection of blood hemoglobin, oxygen and glucose will help improve the accessibility, acceptability and affordability of these methods for mass screening and surveillance studies. Similarly early detection methodologies for detecting vascular dysfunction could be developed indigenously, by using appropriate pressure transducers and algorithms, to monitor the blood flow velocity in small diameter vessels. Studies done by Dr. Ravi Kasliwal and associates at Medanta Heart Institute, New Delhi, has demonstrated the usefulness of this method to manage hypertensive patients. One can develop ability to monitor the compliance of regional blood flow and thereby keep an eye on any changes in the function of these vessels. Using the IT infrastructure that exists and combining the emerging technologies in computing, a variety of mobile applications can be developed for early detection, remote monitoring, better management of the risks, for following progression or regression of the risks and prevention. As we have articulated earlier we can develop mobile stand-alone diagnostic platforms, develop the capability to communicate with clinics and service providers via web or cloud, initiate web-based consultations with the clinicians, provide electronic prescriptions and facilitate low cost drug delivery at the community level.

Under these state-of the-art centers (CTSI or NCR Health Biotech Clusters), standardized clinical studies could be developed, to evaluate the effectiveness or otherwise of various indigenous medicines (phytochemicals and their combinations) and newly

discovered drugs of therapeutic importance. Although India contributes significantly in the area of manufacture of generic drugs for the Global Market, it does very little in the development of newer synthetic drugs or novel drugs from phytochemicals. There is a great window of opportunity for the development of low cost drugs for local consumption as well as for the Global Market. Successful examples of importance in this area are the randomized clinical studies on Siddha medicine for type-2 diabetes management done at Sri Ramachandra Medical College at Chennai, by Professor Thanikachalam and his associates and the NIH funded study on the benefits of Ayurvedic medicine on arthritis at the AVP facility in Coimbatore by Dr. Manohar and associates (www.avpayurveda.com). Using this kind of approach studies are in progress in Mysore, to develop a "polypill" for the management of type-2 diabetes.

We already have discussed some of the applications related to the development of antibody-based assays, tissue engineering and regenerative medicine approaches (development of biological scaffolds, bio-artificial arteries, valves and organs) that are in progress. If we have functional CTSI facilities, we can develop a variety of technologies in the area of drug discovery, device development, biomarker applications, as well as cellular and molecular therapy. With such multidisciplinary platforms, it is possible to develop a robust epidemiology, disease surveillance, risk assessment, risk management, and risk prevention strategies. Newer areas of genomic, proteomic sciences can be put into effective use for the assessment and development of population based studies. For instance the question of why South Asians have higher incidence of cardio-metabolic disorders could be addressed from genomic, proteomic, metabolomic and gene expression perspective. Why do Indians have a genetic predisposition for developing central abdominal obesity? We can develop scientific evidence and appropriate interpretation and use for the classical "Dosha System" of Ayurvedic medicine. Such fundamental questions can be studied using the multidisciplinary approach. When we think of translational science applications, the sky's the limit. It is just an extension of the studies done at the laboratories to the next logical step, clinical and therapeutic applications.

What are some of the aims and goals of the Clinical and Translational Science Platforms in India? Newly established Health Science Universities have done a good job of bringing under one-platform, the education and training aspect of health sciences disciplines. Similarly, if we can develop "one stop centers" for prioritizing, training and guiding in basic science and clinical research, the purpose of establishing these national platforms will be well served. Why did we select this model (RGUHS)? This is one way of utilizing the infrastructure that already exists. There are more than seventy Medical Universities in the country and over a dozen Health Science Universities. In addition to these dedicated medical and health science universities, there are number of national and international research institutes such as, National institute of Immunology (NII), International Center for Genetic Engineering and Biology (ICGEB), Institute of Genetics and Integrative Biology (IGIB), Indian Agricultural Research Institute (IARI), Jawaharlal Nehru University (JNU), National Plant Genome Research Institute (NPGR), National Research Center for DNA Fingerprinting (NRCDF), which provide a great atmosphere for research in various areas of science and technology. Another example that comes close to our thinking is, the Regional Center for Biotechnology (RCB: www.rcb.res.in), a newly created institution in the National Capital Region (NCR) with the help of UNESCO, which is supposed to provide world-class research, training and education in biotech sciences. Health Biotech Clusters, seem to be the nucleus of research activities in this emerging field of applied biotechnology. Department of Biotechnology, Government of India, describes the growth of biotechnology sector as follows: "The Indian biotechnology sector has, over the past two decades taken shape through a number of scattered and sporadic academic and industrial initiatives". Policy makers in the area of science and technology should not leave the growth in these cutting edge areas to chance, but prioritize, thoroughly plan and develop them on a need basis. They also should consider the points articulated in this essay for developing clinical and translational sciences in the healthcare sector.

We started this essay with the basic question of how to provide a translational science platform, to the hundreds of health science colleges in the country. We have developed a model, that revolves around existing Medical and Health Science Universities. These Health Science Universities have several hundred affiliated colleges. But these affiliated colleges lack the research infrastructure and trained personnel. It is difficult and costly to equip all of the affiliated institutions with the needed infrastructure and research staff. If we develop a CTSI under each Health Science University or at each Biotechnology Cluster, then these platforms can provide the needed infrastructure, resources, training

and guidance in both basic science research as well as clinical research. All affiliated colleges, public and private research institutions can utilize such a common platform, to develop their research programs or use the facility to do contract research on a fee for service basis. Even before India attained its Independence, the elite policy makers were smart enough, to think of establishing National Laboratories for developing a knowledge base, for Scientific and Industrial Research. It is high time, that we develop similar clinical and translational science facilities, at regional levels as well as at the national level, to achieve a level playing field for competing Globally in the Biomedical Sciences, Healthcare and put India on the translational science ”map” of the world.

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