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REVIEW ARTICLE

Building Indian Biomedical Leadership to Bridge the Gap Between Science, Primary Health Care and Public Health

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Abstract | The Indian biomedical landscape has been characterized by the existence of somewhat polarized institutional structures and professional growth. While some scientific and public health challenges have been met with existing structures, there is still a large unmet scientific and public health need. Broadly, the physical separation of science, engineering, medical campuses and industry has led to silos of excellence and accomplishment with huge gaps in innovation and implementation. The lack of inter-disciplinary educational options has further reinforced the cultural underpinning of "guilds" that have found it difficult to collaborate. Strikingly, with almost a comparable number of institutions that train doctors in the allopathic or traditional disciplines such as Ayurveda, Unani etc., an "integrative medicine" framework has not emerged, apart from an over reliance on specialization at the expense of primary care. This paper is written by two physician-scientists, the first is located in a basic life science research center. The second, a practicing family physician, from the institutional anchor of a life sciences research institution. In this, we trace our experiences, primarily from a principal investigator's perspective, describing the scientific projects and try to explore the lessons learnt along the way. We will first describe the research in the lab's core area of human cervical cancer progression and our more recent effort with Dengue genomics and vaccine design. We then describe the lab's engagement with medical campuses and other agencies as well as review our various meetings and interactions so far with our colleagues from Africa to grasp what might be the "generalizable lessons" for the future. The Indian council of medical research initiated a program with Africa in health sciences. Building upon those interactions, we have taken some incremental steps in that direction and described our efforts.

1 Introduction

Recent surveys measuring the health-related sustainable development goals in 188 countries: (a baseline analysis from the global burden of disease study 2015) position India at 143 out of 188 countries. This suggests that the entire approach to innovation and health care needs a fresh thinking as the country heads into this century.

In this paper, written from the institutional anchor of a life sciences research institution, we trace the journey and define the challenges and lessons learnt. We show a transition from a focus on basic biomedical research to an integrative,

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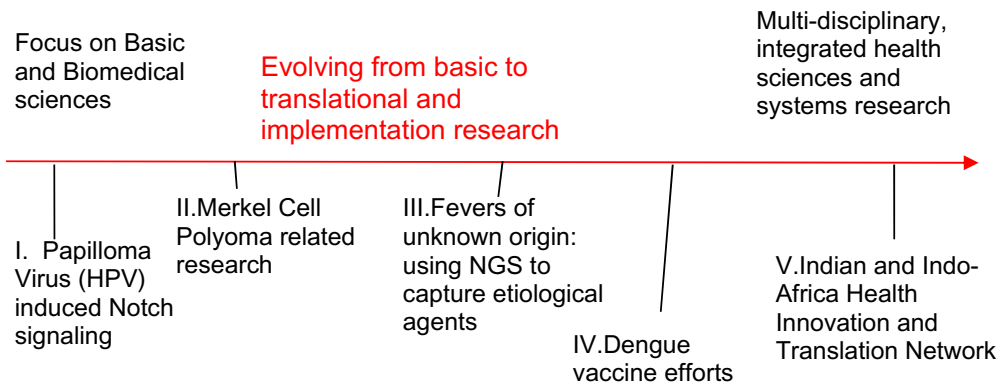

Figure 1: The evolving transition from Basic science/Biomedical Research focus to a multidisciplinary translational network.

multi-disciplinary, network with clinicians, public health and policy experts and researchers (Fig. 1), informed by attempts to bridge the gap between Science, Primary Health Care and Public Health. We hope that our gleanings constructively add to the ongoing dialogue on bridging the gap between scientific research, primary care, and public health. We further layout our plans and commitments for the coming years.

1.1 Human Cervical Cancer Progression (Funded Primarily by NCBS, TIFR and DBT)

Cervical cancers are a major cause of cancer-associated mortality among females in the developing world, are caused by high-risk human papilloma viruses (HPV). Implementation of screening strategies for HPV has yet to take off on any level of scale. Vaccine trials have also run into trouble. Given the continued presence of the burden of this disease for several decades to come, we have focused on a better understanding of the mechanisms of progression in order to lay the foundation for drug development and synergistic therapies.

Papillomaviruses belong to the family of small DNA tumor viruses, and the study of these agents has been extraordinarily influential in driving key concepts in cancer biology. With very few activated Ras mutations in human cervical cancers, we have been interested in the pathways that may phenocopy Ras. Our laboratory for over two decades has been analyzing the signals that complement the function of papillomavirus oncogenes (for review see[1]), and our focus has been on the role of Notch signaling. Our cumulative data over decades has led us to suggest that ligand dependent Notch pathway activation acts as a "second signal" in human cervical cancer progression (reviewed in[1]). Extensive analysis of the reported literature on cytogenetic events in human cervical cancers shows a striking gain and loss of function, respectively of genes that amplify and inhibit Notch signaling respectively, consistent with a major role for this pathway in driving these malignancies.

Our work on notch signaling led us to identify a distinctive tumorigenic sub-set of cells that are positive for cell surface marker CD66+, and which are dependent on this pathway in human cervical cancers.[2] Following our initial characterization of these cells in cancers, we have extended this observation to define a role for CD66+cells in cervical precancers in collaboration with Laimonis Laimins laboratory at Feinberg School of Medicine, Northwestern University, USA. A particularly intriguing observation has been the relationship of CD66+ cells and the papillomavirus life cycle.[3]

An important challenge was to examine the role of CD66+ cells in the process of metastasis, by looking at outcomes in a reasonable sized retrospective study in collaboration with the Adyar Cancer Centre. We found an association of CD66+ and CD49f+ cells with metastasis and local recurrence, respectively. In parallel, there are very distinctive associations of CD66 and CD49f cells in the various layers of cohesive cell migration.[4] In the absence of effective implementation of cervical cancer prevention in India for some time to come, CD66+ cells will be potential major targets for novel therapeutic and diagnostic approaches. With the emergence of migration

of human cervical cancer cells as a major theme in the group, Calvin Rodrigues and Leanna Rose Joy from the SK lab are examining various aspects of epigenetic regulation[5] and the dependence on the CD66+ protein on migration, respectively in human cervical cancers.

1.2 The Case of Merkel Cell Polyomavirus: MCV (Funded Primarily by DBT-Wellcome India Alliance and NCBS, TIFR)

An important aspect of our ecosystem is to have independent post-doctoral fellows working on related but distinct projects: Reety Arora, a post-doctoral fellow at the SK lab leads an independent project on Merkel Cell Polyomavirus, another oncogenic DNA tumor virus. In a landmark recent publication "MCV truncated large T antigen interacts with BRD4 in tumors" Reety discovered and described a key interaction between the viral protein MCV LT and the host chromatin-binding factor BRD4, which may play a role in the viral replication cycle.[6]

1.3 Setting Up an Off-Campus Biology-Medicine Interphase Program (Funded Primarily by DBT and NCBS, TIFR)

This describes in brief about our experience in navigating the existing barriers between a basic science and a medical institution:

In 2005, in order to focus energy on translational research, numerous discussions between basic scientists at NCBS and colleagues from St. John's medical college campus were conducted in order to understand the perspectives of medical professional around teaching, immediate service and diagnostic innovation needs, affordable therapeutics in contrast to the longer-term perspectives of basic research organizations. Through these insights, several joint courses with clinicians and scientists with a focus on hematological malignancies were conducted in collaboration with St. John's Medical College over 3 years (2008–2011).

With strengthening bio-medical collaborations, between 2011 and 2016 a parallel lab infrastructure at St. John's medical college was set up with the support of NCBS and DBT through the Glue grant program.

Molecular biology labs, confocal, flow cytometry and tissue culture were set up. With this facility in place, from 2011, the research focus has been hematology centric and platform oriented, in particular, exploiting gene editing and HLA platforms towards enabling national registries until 2016. One of the most successful projects has been led by one of SK's graduate students, Chitra Pattabiraman around using next generation sequencing to determine causative agents of fevers of unknown origins.[7–9]

1.4 From Sequencing for Dengue to the Vaccine Development Initiative (Funded Primarily by N.R. Narayana Murthy, Co-founder Infosys)

With the beginning of the above mentioned cross-talk and collaborations, a critical component of our effort was a continuous set of workshops that enabled clinicians and scientists to develop a common language and share challenges. Through one such interaction (as mentioned in the previous section), a focus evolved around fevers of unknown origin.

Some of the most important causes of fever across Asia are mosquito-borne viruses such as dengue virus. In addition, novel agents associated with acute febrile illness continue to be discovered. Current molecular diagnostic techniques, such as polymerase chain reaction, are pathogen-specific and therefore pose limitations, as they may fail to detect co-infections and novel agents not commonly associated with the disease syndrome. Unbiased metagenomic sequencing of clinical material from patients with acute fever could overcome these limitations and thus Chitra Pattabiraman developed a metagenomics effort, using funding from NCBS and the Department of Biotechnology.

This work resulted in complete genome sequences of Influenza A (H1N1) virus from the 2015 Influenza outbreak in India.[8]

Similar analogous efforts were made to sequence dengue genomes across India. This resulted in a collaboration among six Indian institutions: Translation Health Sciences and Technology Institute (THSTI), All India Institute of Medical Sciences (AIIMS), International Center for Genetic Engineering and Biotechnology (ICGEB) from Delhi and the National Center for Biological Sciences (NCBS), the Indian Institute of Science (IISc) and the National Institute for Mental Health and Neuroscience (NIMHANS) from Bengaluru working in a collaborative cluster.[7,9]

This paper also characterized the replication kinetics of isolates from patients with mild or severe infection, which were found not to be significantly different. However, the viral titers between the isolates varied by two orders of magnitude, suggesting differences in replication fitness among the circulating isolates. Some of the non-synonymous mutations in B-cell and T-cell epitopes suggested a positive selection force driving viral evolution. We obtained 103 full genomes (DENV I-31, DENV II-48, DENV III-9, DENV IV-6 and Multiple infections-9) and 72 near complete genomes of dengue viruses. Genome analysis mapped the circulating DENV I strain to the genotype V, DENV II and DENV III strains to cosmopolitan and genotype III, respectively. We have identified non-synonymous mutations in the exposed surface of the envelop protein of DENV and speculate that they might contribute to viral evolution in the presence of neutralizing antibodies. In particular, highly prevalent DENV variant (E62, E392 and E395) that likely arose as an immune escape variant in response to pressures exerted by fusion loop antibodies. Mutations in the non-structural proteins mainly in NS1 and NS3 possibly affect the viral replicative fitness. These mutations are yet to be validated by in vitro experiments to find their biological relevance. Thus, an improved understanding of the molecular determinants that regulate conformational dynamics on dengue viruses has the potential to inform both the design of novel vaccines and identification of antiviral compounds (Sankaradoss and Roy et al., in preparation).

The complexity of the current Dengue vaccines is best exemplified by the halt of the Sanofi vaccine trials by the Philippines regulatory authorities.[10]

While there are several candidates worldwide and one licensed by the WHO, the Indian effort has largely centered around the work of Navin Khanna of the ICGEB group, who use a Dengue envelope-based 'four-in-one' virus-like particles to induce tetravalent neutralizing antibodies in mice[11,12].

Knowing the recent issues with the dengue vaccines, it is important to understand the evolution of dengue virus strains in India to better prepare for vaccine constructs and trials. In a nutshell, the challenges around the vaccines have revolved around the multiple serotypes, the differential immune responses on subsequent infections (which can lead to adverse outcomes), the differential immune response in previously infected versus uninfected individuals, age group issues, importance of local strains and variants and so on. Hence our approach has been to conduct serology, serotype and then assess clinical and biochemical parameters prior to sequencing.

2 Dengue Vaccine Construct Strategy

There are broadly three strategies we intend to pursue to generate vaccine constructs:

1. Use the information based on our preliminary model of changes (non-synonymous) in the envelope protein of Dengue II (unpublished observations), a key vaccine candidate to generate appropriate changes in the envelope protein.
2. We have designed a vaccine construct based broadly on the following design principles:
3. can we predict homology region across the four serotypes to essentially create one molecule which works across them?
4. can we eliminate potentially cross-reactive pathogenic responses using a combination of bioinformatics and structure predictions based on the literature and then test these constructs in appropriate assays?
5. we are embarking on optimizing T cell peptides that can work across the MHC spectrum and hopefully contribute to the one of the biggest vaccine challenges i.e. improving T cell activation and memory.

Our working strategy over the next year is to engage other organizations in academia and industry with interests in the Dengue vaccine space, to build partnerships for a longer term sustainable roadmap in terms of capacity, vaccine products and inter-disciplinary skill development and clinical trials in India and Africa.

2.1 Next Steps Forward: Indo-Africa Health Innovation & Translation Network (Funded Primarily by N. R. Narayana Murthy, Co-founder Infosys Under the Dengue Vaccine Initiative)

For any vaccine or other innovation to reach or penetrate the community, the engagement of stakeholders at the primary care level is crucial. A major challenge with academic research including vaccine development efforts is that nearly all the data emerges from academic medical centers/hospitals located in metropolitan cities which

typically capture highly skewed patterns of illness. These data are not generalizable to communities at large. Hence, it is proposed to form a network of primary care practitioners and other researchers at government and private centers as well as clinicians at hospitals with research groups. This network will help conduct high-quality epidemiological and molecular genetic studies. Furthermore, this will advance the understanding of the gaps and interactions between the community and various other factors that influence health seeking behavior and management of acute febrile illness (such as dengue) at the primary care level across a network of PHCs (primary health centers) in India, South Africa, and Kenya.

One of critical missing links towards dengue vaccine development and roll out planning is the absence of seroprevalence, serotyping, and viral sequencing data at the community level in India and Africa.

For instance, among the only maps of seroprevalence to dengue comes from a study in Chennai by Rodríguez-Barraquer et al.[13] where they mapped the burden and the comparative seroprevalence of Dengue versus Chikungunya across the metropolis of Chennai in South India.

These are the kinds of community level data that would be essential for vaccine design and uptake success.

To ensure this, we are currently working on four objectives:

a) **Creation of a vaccine resource database**
b) Create a searchable database linking sample details and storage with anonymized clinical data
c) Publish data summaries and analyses, systematic reviews, policy briefs, and SOPs pertaining to the dengue vaccine
d) Establish a primary care practice based research network (PBRN) that includes researchers along with the network of PHCs in India, South Africa, and Kenya.

b) To develop a primary health care innovation and translation network

Over the next 12 months, it is proposed to form a network of primary care practitioners and other researchers at government and private centers as well as clinicians at hospitals with research groups. This network will help conduct high-quality epidemiological and molecular genetic studies in the community level in India, South Africa, and Kenya.

Determine the knowledge, attitude and practices of management of dengue and the need for dengue vaccination among various stakeholders, including the government, global health leaders, health care professionals, pharma companies, basic scientists, industry, and the community.

iii) To nucleate a Data Science & Health Intelligence Hub**:** There is a strong and urgent need for hyper-local insights at the community/primary care level. Primary care due to its closeness with the community has the opportunity to generate insights that are relevant at a micro/local level. Many global or national screening programs and treatment guidelines have to be adapted using local insights to be effective.
iv) To establish a product development cell

See Fig. 2.

3 Our Efforts in Africa

With the award of the Dengue grant in December 2017, we held a meeting at the NCBS campus in Jan 2018.

A team from NCBS held two workshops at the KAVI center in Nairobi in March 2018 on nanopore sequencing of pathogens and flow cytometry. A three-member team from our group also attended the annual collaborative meeting of the KAVI center in Jan 2019. A joint grant by KAVI and NCBS on the rapid detection of carbapenem resistance using next generation sequencing was submitted to the Chan Zuckerberg-Bill and Melinda Gates (CZBM) foundation grant; results are awaited.

1. Dr Arun Sankardoss: Research and Scientific lead in the Indo-Africa Program

As a Research and Scientific lead, he had the opportunity to conduct workshops on nanopore sequencing in KAVI-ICR. Interacting with the colleagues in Africa, building relationships and writing for collaborative grants with them has been an invaluable experience.

2. Dr Swathi SB, MBBS, FHM: Clinical research Fellow in the Dengue program

Being a primary care physician who is interested in public health and health equity, she has the opportunity to learn through experiences and interactions, the importance of a multidisciplinary approach in dealing with health and disease.

In conclusion, the shift in our efforts from a single, solely basic laboratory research model to a

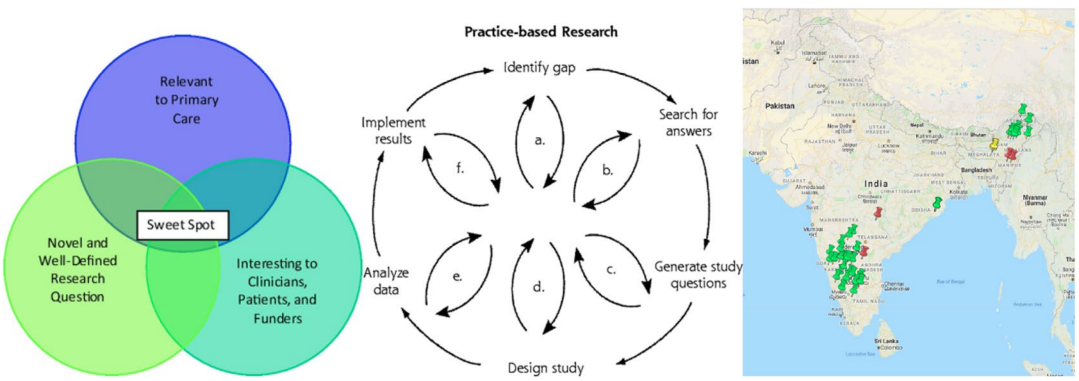

Figure 2: *Left* The Sweet Spot[14] engages multiple diverse stakeholders without losing focus and with an eye to impact. *Middle* Model for Practice Based Research[15]. *Right* PHC networks such as those of Karuna Trust will be harnessed[16].

multi-institutional, cross-disciplinary, integrated approach to virus control has been described above.

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Sudhir Krishna is a distinguished visiting professor at the Indian Institute of Technology, Goa, and former professor at the National Center for Biological Sciences, Bangalore. After his MBBS (St. Johns Medical College), he obtained a PhD (Cambridge University). He had been a principal investigator at NCBS, TIFR, Bengaluru, for the last 30 years. The core interest of his group has been cervical cancer progression. Over the last decade or so, the group has been actively involved in supporting human resources development and creation of platforms in the biology medicine–public health interface. He was instrumental in setting up a state-of-the-art research facility at St. Johns Medical College. He is currently at the Indian Institute of Technology, Goa.

Ramakrishna Prasad is board-certified in Family Medicine (ABFM, USA) with expertise in infectious diseases. In addition to residency in Family Medicine, he holds a Master's in Public Health (Infectious Diseases & Microbiology) and fellowships in HIV/AIDS, viral hepatitis, and faculty development in Family Medicine from the University of Pittsburgh. Besides significant faculty and leadership level experience in the USA and India, he has worked in the Grenada (West Indies), Honduras (Central America), and Mozambique (Southern Africa). Currently, he heads PCMH Restore Health, a patient-centred medical home and incubation center for innovation, people building, and collaborative problem-solving. He also serves as the President of AFPI Karnataka and the AFPI Chair for Primary Care Research & Policy. He is associated with several networks focused on Leadership in Public Health. As a family physician, integrative medicine/care, home-based primary care, and transdisciplinary learning are areas of deep interest in practice. Innovative and impactful ways to interlink family practice, preventive care, health promotion, and restoration of health for those living with chronic diseases including mental health issues by healthy living in harmony with nature that also helps restore natural ecosystems by learning, practicing, and leading at the interface of health, industry, and the environment are an emerging focus of his work.