Editorial:

Translational Research in Paediatrics

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Louis Pasteur once said, "To him who devotes his life to science, nothing can give more happiness than increasing number of discoveries, but his cup of joy is full when the results of his studies soon find practical applications." That means, our goal must be to turn knowledge into applications so that these benefit people at large. Such application research is called translational research. It is defined as, "Research that applies discoveries generated in the laboratory to studies in humans (From bench to bed-side) or that speeds adoption of best practices into community settings (From bedside to practice)". In fact, it is an integrated process of 'Knowledge transition'. Therefore, the priority of funding agencies is to "Facilitate translation of basic and clinical research into clinical practice, through evidence based decision making, thereby improving people's health".

Phases:

- T1–"Bench to Bedside," moves a basic discovery into a clinical application
- T2 –"Bedside to Practice" provides evidence or value of taking the basic discovery for application in clinical setting
- T3– Research that moves evidence-based guidelines developed in phase 2 into health practice
- T4 –Research to evaluate "Real world" health outcomes of the original (T1).

Translational research is an onward and feedback mechanism, operating from stage 1 through 6 and in a feed–back mechanism directly from 3, 4 and 5 back to 1 for necessary modification, if any in a continuous manner. Once a new concept is found and tested, it is developed for application on ground. This very process is translational research.

When the product is further developed and delivered to user system for wider use at grass-root level in primary care, public health level or speciality care practice, the process is called 'Research translation'. The basic science findings are translated into clinical applications, and / or clinical observations to generate new research topics. The process is better explained with examples as under:

Basic Discovery:

Identifying a new epidemiologic concept or any promising molecule or gene target or a candidate vaccine strain or a protein biomarker. (e.g. - Discovery of a human-bovine re-assortant rotavirus 116Estrain from neonates at AIIMS, considered promising as candidate vaccine not causing any significant disease.)

Early translation: Constitutes partnerships collaboration with academia, government, industry intervention development and Phase I/II trials. e.g. - Developing 116E Rotavirus strain further as an attenuated strain by serial passage through green

Discovery - Delivery Continuum:

1.Basic Discovery	2.Mechanistic studies	3.Human testing	4.Proof of efficacy	5.Proof of effectiveness	6. Dissemination to healthcare
Early translation		***Late translation***			***Dissemination, Adoption***

monkey in-vivo in collaboration with the department of biotechnology, Government of India and FDA, USA and conducting phase-I/II trials, roping in industry - Bharat Biotech, Hyderabad.

Late Translation:

Multicentric III trials, regulatory approval (DCGI, GOI), partnerships, production, commercialization, Phase-IV trials (BB) –approval from Govt. of India for additional uses. Payment mechanism(s) established to support the adoption (Marketing, MoU with Government to include 'Rotavac' in national immunization program).

Diffusion:

It is a passive process by which a growing body of information about an intervention, product or technology is initially absorbed and acted upon by a small body of highly motivated recipients. It can be compared to phase-III study.

Dissemination:

It is an active process through which the information needs the pull of target groups working in specific contexts, assessed, information is "tailored" to increase awareness, acceptance and using lessons learnt from science. It involves information dissemination to scientists, practitioners and medical institutions (On vaccine efficacy, seroprotection vis-à-vis other vaccines in market, cost, safety and adverse effects), besides conducting data collection, support outcome research, intervention refinement at health services and research establishments.

Adoption:

Adoption of the vaccine, its price and safety by health providers, hospitals, paediatricians, patients, parents, public, industry and the media in all aspects.

Translation:

"The transfer of evidenced-based knowledge to routine or representative practice."

Integrating Research with Practice:

It requires a common understanding developed about meaning of knowledge translation, knowledge integration and nature of evidence. New and extended ways to disseminate and implement research evidence needs first to review existing models, develop new conceptual frameworks to integrate science with service, practice and policy. Research and partnership are critical to future intervention, diffusion, dissemination and implementation of results in practice.

Evidence:

It can be objective and subjective. The various forms of evidence can be received are: (1) Surveillance data, (2) Systematic review of several research, (3) Expert opinion / reviews, (4) Single research, (5) Program/policy evaluation, (6) Word of mouth/media, (7) Marketing/lobbying (8) Personal experience.

Evidence-based Practice:

It is the integration of 'Best Research Evidence' with 'Clinical expertise'.

Translational Research Centres:

Several centres of excellence in medical research and hospitals have established such TRCs with following goals: Therapeutic innovation constitutes impactful, practical and real world application. It is team centric and integrated learning system, with non-linear thinking, interactive and collaborative approach. Future challenges and opportunities are visualized and plan of action strategized. The centre forms the home for clinical and translational researchers, coordinating their activities, supporting training of faculty and staff, provide centralized support for efficient research, and track research efficiency to remove barriers.

Research priorities relevant to Care of Children in Indian Scenario:

We must focus on biology of high burden diseases such as - prematurity, neonatal, immunity, infections, drug discovery systems, microbiota and designing affordable vaccines through innovations.

To grapple all these and any other, we need multicentric collaborative efforts with effective coordination. The ongoing indigenous Rotavirus vaccine development; studies on common infections and their prophylaxis, therapy and prevention through novel molecules and newer vaccine development initiatives such as – Rotavirus, Hepatitis-A, Dengue, Japanese encephalitis, Malaria, Tuberculosis, HIV at the Vaccine and Infectious Disease Research Centre (VIDRC) in collaboration with THSTI, AIDS Vaccine initiative (IAVI), Society for Applied Studies (SAS), Population Science Partnership Centre (PSPC), School of tropical Medicine Kolkata, National Institute of Tuberculosis, Agra; goat surfactant project of CDSA,AIIMS and Cadila laboratories; AS, PSPC of THSTI collaboration in elucidating role of gut and systemic inflammation and gut microbiota in limiting efficacy of clinical rehabilitation of malnourished children; THSTI initiative in establishing a clinical facility at Ballavgarh district hospital to support its inter-institutional program on genomic epidemiology and biomarker discovery related to premature birth, renal biology and neonatal immunology by AIIMS and National Institute of Immunology (NII); Studies on CRISPRi system used for targeted gene regulation in E. coli to manipulate Mycobacterium genome successfully repressing gene expression by VIDRC scientists; reversal of drug resistance studies in infections and malaria; correlating FUT2 gene secretor status with enterovirus infections e.g. – Rotavirus and Norovirus diarrhoea, field trials in spot breath test for detection of pulmonary TB and the ongoing efforts to identify novel genes, enzymes, proteins or pathways that could predict developing active disease in latent tuberculosis or as potential drug targets or vaccine candidates at MGM Institute of Health Sciences Mumbai are few humble but promising initiatives. It is thought that a 'Carbon switch system' is critical for My. TB to slow down replication and metabolism for switching to latent forms for survival in host. At VIDRC, scientists are generating an interactive map of the regulatory pathways of cholesterol utilization in My TB, based on the transcriptome data. At least 40 genes essential for cholesterol utilization have been identified which could possibly be critical for carbon specific regulation of My TB physiology and metabolism. They have generated deletion knockout strains specific to 15 of these genes whose molecular and functional characterization are in progress. The goal is to identify critical cholesterol catabolic pathway genes as novel target for developing live-attenuated vaccine against tuberculosis. My. TB secretes various molecules for its pathogenesis and physiological functions for survival. These are lipids, proteins, sugars and other smaller molecules, several not yet characterized. The VIDRC scientists are developing tools to identify such protein effectors that access macrophages. Besides My. TB membrane vesicles (MVs) packed with proteins that may be pathogenic or have important physiological functions have been reported. These MVs could be utilized as vehicles to carry the desired proteins with antigenic properties for delivering as vaccine antigens. There are efforts also to produce recombinant MVs from My. smegmatis, anon-pathogenic mycobacterium. Sky is the limit for taking up such issues for translational research, so relevant to our country scenario.

Steps for making a project for translational research:

First identify a translational opportunity; may be involving clinical problem(s), specimens. Better to identify a clinical colleague with whom to work; on-site or off-site. On-site is better if planning to seek grants, as that would be easier to co-ordinate and integrate in a bidirectional manner. It is better if basic research plays a role in selecting patient samples and or clinical specimens. There is a need to visualize how the specimens are to be analyzed in order to rule them in or out of the study and how the research feedback is or are likely to be relevant to clinical application and the understanding of a disease further.

MAKING A RESEARCH PROPOSAL:

Aims ad objective:

Maximum in one page, should be self explanatory, not just bare specific aims 3-5 specific aims are sufficient. Straight forwards aims with best prelim data go first, risky aims at the end if at all. Aims should talk to and build on one another. Must contain enough information to make specific aims clearly understandable

Back-ground and significance:

It should be in 2-3 pages at the most and must end with a specific note on its significance. It should mention what is known, what is not known, why it is important to study what is not known and how the aims will address this. Justify each specific aim.

Preliminary results:

May be in 5 to 10 pages. It is important to convince reviewers that the proposal is worth doing. Preliminary results should be convincing that the work is actually doable. Refer to specific aims, noting how the preliminary findings make it possible to achieve goals. Identify key technologies, reagents and collaborators.

Experimental design, if relevant:

Different reviewers look for different things. In case of an young investigator, better to emphasize on how will do things, propose sections in possible outcomes and pitfalls. Do not build the entire project on conjectural basis or dependent on a reagent(s) not existing / available at the moment. Adequately refer back to preliminary results.

Surviving and thriving in research:

Need hands (Students, Post-Docs, technicians) and resources (Start-ups, grants) to produce Science (Publications, patents, collaborations and affinity groups).

Attracting students:

Attracting students is an important aspect in developing the laboratory for translational research. The initial difficulty is, the PI may be new and relatively unknown. There may not be enough students in the lab yet, with higher faculty to student ratio. The advantages could be that students often get attracted to young faculty, viewed as dynamic, more accessible, besides more hands on lab facility. Teaching gives PI the opportunity to access students.–Seminars and workshops are more effective than lectures. It spreads the work all around, makes the classes vibrant and interesting. Opportunities must be availed to take classes and guest lectures in other centres. Working with students, papers with them, talking to them frequently are good investments. Better get involved in the recruiting process and look for grants (e.g. T32 grant under NIH, USA)

Technicians:

Technicians are real strength of any clinical or experimental research laboratory. Must look for pool of technicians at neighbouring colleges and universities. Many students might wish to work for 1-3 years before going for M.Sc. or medical colleges. It is beneficial to train own junior technicians. Give them feedback - both positive and negative, paying due attention to probationary period. Time to time widing out the ill motivated is also important to maintain standards.

Finding an affinity group:

It is possible to find collaborators by holding joint laboratory meetings. Visualize availability of collateral resources, core facilities and other faculties who can collaborate. Communications received from outside be assigned priority to respond. It is important to stay in touch with people.

Seeking Grant:

The Principal investigator (PI) and a Co-PI – involved in case of a joint project are decided. Both need to benefit and play an active role. The DCGI guideline spells out specific information that must be included like patient enrolment, specimen, sample collection process and so on. Better to seek advice from seniors. Prepare grant sufficiently in advance so that it can be shown it to colleagues, supervisors and experts for discussion.

Grant Programs for Career Development:

Young Investigator Grant (e.g. - Under K21 of NIH):

A series of grant programs, designed to help young or mid-career investigators, appropriate for translational research are available under this, not known to many. Specific requirements, guidelines vary from institute to institute, available on web. Competition for these is not as intense as it is for R01 and R21 grants.

Post-Doc Grant (e.g. - K22):

The primary objective is to help awardee develop a strong, independent career. Accomplished by supporting outstanding post-doc scientists as they move to 1st academic position (AP level). The award is likely to ease the transition so that the recipient can concentrate on establishing a viable research laboratory prior to applying for research support, generally for 2 years as post-doc scholarship. If awarded, the scholar has a year before an academic position as the grant begins.

Mentored Patient Oriented Research (e.g.- K23):

The purpose of this award is to support the career development of investigators who have made a commitment to focus their research endeavours on patient-oriented research. This provides support for 3-5 years of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research. Clinically trained professionals or those with a clinical degree and interest in further career development in biomedical research not involving patients are to seek the 'Mentored Clinical Scientist Career Development (K08) Award'.

Mid-career Investigator Award in Patient-Oriented Research (e.g. - K24):

This is to support clinicians for longer period to devote patient-oriented research and to act as mentors for fresher clinical investigators. They should be outstanding clinical scientists, actively engaged in patient-oriented research, generally within 15 years of their specialty training. Must be able to demonstrate the need for a period of intensive research as a means of enhancing clinical research careers, committed to mentoring the next generation researchers.

Mentored Quantitative Research (e.g.- K25):

Such grant is meant to support investigators whose quantitative research has thus far not been focused primarily on questions of health and disease e.g.- Mathematics, statistics, economics, computer science, imaging, informatics, physics, chemistry and engineering. Supports career development in basic or clinical biomedicine, bioengineering, bio-imaging or behavioural research for a period of supervised study from post-doc to senior faculty level.

Publication:

On completion of the project work and analysis of result, maximum number of papers must be carved out as quickly as possible without waiting to write a 'Perfect paper'. The PI usually is the senior author. Joint publications are helpful, but only if already have sufficient number of senior author papers. It is better to avoid publishing with own previous mentors. Too many joint publications with well-known senior scientist are better avoided, unless one has sufficient number of papers not involving the said scientist. However, an effective collaboration greatly accelerates research and makes it easier to move into new areas, giving both scientific and funding diversity. Timely publication of the research findings in reputed scientific journals and their application in human health for ultimate benefit of the community is always considered gratifying for any scientist. It immensely enhances the investigator's image in the scientific world, further attracting more students from far and near, besides more grants for cutting edge research in a cyclic manner.