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Innovation in Medicine: New Ideas for Translation

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Abstract: ***Innovation in medical science singularly relies on the concept of critical thinking, and theoretical modelling. Application of basic finding to diagnosis, prevention or treatment of disease using cell, animal or human models are the main components of Translational Research. Translational medicine (TM) is the progression of research from bench side to bedside. In the last 10 years or so TM researchers have developed a more telescopic vision, slowly and steadily translational research is becoming a central theme in many educational and central government strategies with the primary objective to construct integration of research from trivial disciplines and conjoining academic and clinical centres into a consortium and make a collaborative expertise. Translational research is understood as the systematic inquiry directed toward the creation of knowledge, and Translational Innovations should be carried out through the mere act of thinking, acting, cooperating and building.***

Keywords: Translational research, translational medicine, translational innovations

1. Introduction

Over the years translational medicine (TM) has been developed as a result of practice rather than the need of the academic dominion. Since long clinicians, researchers or academician, no one was ready to address the big elephant sitting in the room, as there is an old saying that when your only option is a hammer then everything looks like a nail and this was exactly the scenario in medical research fraternity. Earlier we were not even sure about the definition of translational medicine.

Translational medicine can be defined as an application of basic finding to diagnosis, prevention or treatment of disease using cell, animal or human models or any research having a direct impact on the health of human or animals. More so it validates the concept of knowledge synthesis, from scientific discovery to the systematic review of what we know and what we do not know and how we know it. In terms of applicability, TM is a progression of research from bench side to bedside. In the last 10 years or so TM researchers have developed a more telescopic vision, slowly and steadily translational research is becoming a central theme in many educational and central government strategies with the primary objective to construct integration of research from trivial disciplines and conjoining academic and clinical centres into a consortium and make a collaborative expertise.

Now with new advancements in translational medicine robust changes with diverse implications have started taking shape. The gap between the target and solution is slowly narrowing and the results are looking promising. This has opened a whole new world of clinical empiricism, as many organizations have restructured their working module and collaborated not just with their peers but with different diverse sectors ranging from bioinformatics to biophysics & advanced translational mathematics with the common objective to bring out an umbrella organization. In the past few decades, we have seen many breakthroughs in the fundamental knowledge necessary to understand, prevent, diagnose and treat many diseases. Sequencing human genome, novel ways for targeting cancer cells, stem cells therapy are some examples.

2. Present and Future

Let's look into the present and future of the TM and kind of research and new innovation happening with intersectoral development & coordination. Needless to say, that Nanoscience seems apprehensive beyond contemplation**. But what if we can hybridize the Nanoscience further, something like Nano - Translation? Imagine a Nano - relay signal chip designed with homunculus genes which can search, target and modify the cancer cells rather than directly killing them.**

The other object of the wide practical application is 3 - D printing. With the integration of geometrical, mathematical & biological axioms we can design organs, HLA typing and graft rejections can also be fixed with neutral biological tissues. Transplant, post - burn and vascular graft surgeries can use organs and graft can be made viable with translational printing.

Drug delivery with Nanoparticle technology is already in advance stage of development but what about the next generation of personalized medicine! With TM in near future, we can study the genomics and gut microbiota, can fix the vectors for the preselected target, and they can design a customized drug for an individual patient.

Prosthesis devices, be it heart valves, stents, orthopaedic implants, cochlear implants, in this sector we already have attained some milestones but here also still we have scope for better innovative solutions. Like heart valves & knee prosthesis, many other smart autologous implants can be bioengineered with next generation of anti - inflammatory substrates and antioxidants.

Genome editing techniques like CRISPR has already revolutionized the precision and speed with which we can generate new animal models for different diseases. Developments in the field of bioengineering are spawning new in vitro systems for studying disease biology and the effects of novel drugs on the human cells.

Right from the days of Sushruta and Aristotle, we always tried to look for the cause of a disease, factors which are primarily triggering and responsible for the vicious cycle. There is something called the French Paradox, which

explains that why French people are relatively less prone to have cardiovascular & metabolic syndrome type of diseases, despite the fact that they are predisposed to many risk factors such as smoking, alcohol consumption, high saturated fatty acid intake. The paradox says that they have some genetic mutation which gives relative protection from metabolic syndrome and diabetes also. Researchers have reservations against French Paradox, but it has arisen a potential question which needs to be answered. The question is ‘’Are there lucky mutations which can give relative protection to some individual against a particular disease’’? The concept of Reverse Translation can be used to answer this question, bed - side to bench - side. In fact, Edward Jenner’s 1796 discovery of the first Small Pox vaccine was based on the observation that milkmaids who had previously caught Cow Pox developed resistance to Small Pox. Genome - Wide Association studies (GWAS) and Next Generation Sequencing (NGS) have identified hundreds of novel genes and gene variants associated with risk of or protection against human diseases. One recent example is, we are looking for protective Single Nucleotide Polymorphisms (SNP) in Southern Indian population in smokers which protects them from developing Chronic Obstructive Pulmonary Diseases.

Data generated through GWAS, NGS and SNP analysis can be used to create new genetically engineered Induced Pluripotent Stem Cell Models and maybe animal models of diseases also. Here reverse translational research data can be used for screening many rare genetic diseases and also for new - born screening.

Molecular profiling of patient tissue samples can be used to identify patterns of RNA and protein expression that correlate with disease resistance and responsiveness to therapeutics. In the field of cancer, gene and protein expression profiling of tumors have begun to define molecular signatures associated with better responses to immunotherapy and higher patient survival rates, these signatures can also suggest new targets for drug development. Molecular profiling can also be used to screen and optimize cell - based therapeutics.

One other important application of translation and reverse translational research is in the analysis of results of the failed clinical trials. Taking an illustrative example, the anti - IL - 12B p40 antibody, which showed good results for therapy in Multiple Sclerosis (MS) based on results in mice and marmoset experimental models of autoimmune encephalomyelitis (EAE), failed in human trials. Further analysis of the disease progression in the mouse and marmoset EAE models versus human MS showed that the initiation and progression phases of the disease are driven by different mechanisms in primates and the drug blocks only the initiation mechanism.

3. New Developments

TM is quite instrumental in establishing a therapeutic cohort by targeting environment - gene interactions, the microbiome, and metabolome. The human microbiome contains around 1, 000 species of bacteria, whose exact numbers and proportions vary from person to person. Even the composition of an individual’s microbiome can also change over time in response to environmental factors, including diet and hormones. Controlled or any type of alterations in the gut microbiome have been linked to a growing cascade of diseases such as obesity, diabetes, irritable bowel syndrome, cardiovascular disease, cancer, and autism. Gut microbiome also helps to determine drug efficacy and side effects. Transfer of gut microbiota from one animal to another allows direct testing of suspected roles of the microbiome in disease, and may also enable the creation of new animal models of disease. Meticulous profiling of the microbiome and metabolome, made possible by recent advances in TM namely genome sequencing and chemical analytical technologies such as automated quantitative NMR and liquid or gas chromatography coupled with mass spectrometry can identify new disease signature and translatable biomarkers, and generate hypothesis for translational and reverse translational medicine. And results are astonishing, these approaches have been used to discover the first pre - clinically successful microbiome - targeting drugs in the areas of cancer and cardiovascular disease.

Like one eye - opener happened due to TM research, in the field of gastroenterology, an untargeted metabolomics screen in human patients suggested that a microbe - derived metabolite trimethylamine N - oxide (TMAO) was associated with greater risk for atherosclerosis, experimentally proven in subsequent animal studies. TM studies also identified a small molecule inhibitor of the microbial TMAO pathway that attenuates disease progression in mouse models.

One can ask that what so special and what is the need of emphasizing so much on gut microbiome! The answer lies in the simple arithmetic. The human genome provided 20, 000 gene targets, whereas human microbiome offers several million. So, microbiome and the metabolome each plates mammoth of untapped sources of potential drug targets.

Right from undergraduate & postgraduate days, every student who is from molecular and regenerative medicine background knows the challenges & limitations while working on cell culture. TM research provides the new age concept of Disease - in - a - dish model. We know that cell culture systems are advantageous for preclinical studies because they offer simplified biological models in which environmental factors can be tightly controlled. Nowadays 2D cell culture is kind of regular bread n butter of molecular laboratories. But contemporary 2D cell culture models are inherently non - physiological because they lack the 3D architecture under which cells normally function and communicate with one another and the other mostly they employ non - human cells and or immortalized cell lines that have been selected based on their ability to grow under non - physiological conditions. More so most of the 2D culture systems use only one cell type or line. However, we know that many human diseases involve dysfunctional interactions between two or more cell types. Solution to this cell culture trouble shoots lies within vivo 3D cellular systems.3D cellular systems have a further wider application with Bioprinting, where cells can be grown into many layers of multiple variables and dimensions.

The integrated module of TM research gives us extra hand to amalgamate different techniques and carry forward one concept to the other novel one. Like Organ - on - a - chip, Patient - on - a - chip concept, where bio - printed tissues can be combined with microfluidic, Lab - on - a - chip platforms that provide tissue perfusion, delivery of compounds, and continuous measurements of tissue responses. This approach has now been used to create in vitro models of several diseases and non - alcoholic steatohepatitis (NASH). The latest generation of this parent technology called body - on - a - chip or patient - on - a - chip, up to five different organ types has been functionally coupled on a single hardware platform, allowing the study of disease and drug effects on complex organ system interactions.

4. Conclusion

Above explored examples are just a few of the presently ongoing and some out of the box novel predictions in the challenging and promising arena of Translational Medicine.

Besides portraying varied technical dimensions of TM research, it is paramount to essay out some other aspects also. One common related concern for academicians as well as researchers is that, “Is it possible to judge a particular paper according to a Translational Index”? Answering this question is not easy because one irony of research is there. Why is the complex process of Translational Medical research in academia often led by a person with a deep expertise in only one of or at best a few of the disciplines required to create viable solutions to important unmet medical needs? The government has a critical role to play, as even with best of the intentions our certifying agencies have imposed numerous hurdles on the preparation for and conduct of TM research.

Translational Medicine & its new innovations have three architectural pillars, Practice embedded in the academy, Academy embedded in the practice and Collaboration.

I would like to conclude with the superlative statement, **“If research is understood as the systematic inquiry directed toward the creation of knowledge, then historically Translational Innovations should be carried out through the mere act of thinking, acting, cooperating and building’’.**