Translational Science: Turning Discovery into Health

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Abstract

Success requires someone who understands the idea intimately, and who can build a multidisciplinary team to guide it along the translational path. Intellectual and cultural barriers must be disregarded. Translational researcher must be fluent in many disciplines and thrive on collaboration. Only in this way we can increase the health span and ultimately quality of life will be improved.

Keywords: Multidisiplinary approach; Disease targeted therapy; Personalized medicine; Team work

Introduction

Development of new treatments, tests for the ongoing medical problems is not an easy task. Transforming ideas into actions i.e., lab bench to patient's bedside is hard task accomplished by efforts of the several scientists.

Research is a broad term that complements three basic kinds of medical research i.e., basic, clinical, translational. Basic research deals with queries related to nature while translational research applies the work of basic research into development of solutions to medical problems. Finally these solutions are tried in clinical trials completing the entire loop of research.

Basic research or curiosity driven research is the first brick of the foundation of research, an essential initiating point of advanced applications. First of all core building blocks of life like DNA, Protein, secondary metabolites etc. are taken under investigation to know about their architecture and later their functional studies are performed.

Clinical research studies are conducted to evaluate the effectiveness of the results of the basic research. It confirms that whether new medication or remedy or technique is producing the desired results or not in patients under controlled clinical trials. Successful clinical researchers must have good command not only on medical training but also on statistics and regulatory affairs.

Translational research bridges the gap between basic research and clinical research in order to further refine and advance the discovery. We cannot transform directly study to patients. In translational research identified candidate is tested on models in laboratory then work is done on the pharmaceutical aspects (dosage form, dose, safety etc.) and finally undergo the clinical trials.

So we can say that translational research is an interdisciplinary complex science of many sciences. It is a continuous cycle of research and comprise of three basic pillars like bench side, bedside and community.

Translational Science

The pivotal objective of translational medicine is to amalgamate resources (disciplines, expertise, and techniques) in order to improve existing as well as building novel effective healthcare system accepted globally [1].

It is an evidenced based research that helps to improve the health of population. This disease-targeted research coordinates the current observations in clinical practice and incorporates these questions into scientific hypothesis in laboratories. In this way new therapeutic strategy established through basic research which later is clinically evaluated. Then feedback provided by various bedside-to-bench factors will help to improve new therapeutic approaches.

Physicians consider it as a need to enhance integration of research benefits into clinical medicine However, researchers find it as analyzing the novel concepts which later referred by industrialists as a process intend to accelerate the development and commercialization of therapies. So, a common goal is achieved through different priorities so are not reciprocally exclusive. Translational medicine augments the biomedical discovery rather than attempting to amend present practices and is a unified concept in fragmented fields of biomedical research.

Implication of Translational Research

In recent era enormous breakthrough is observed in the field of medical science but still there is a arduous list of medical conditions need to be addressed besides this many new discoveries still need to be transformed in their final shape. Multiple factors are effecting out of them funds and technical expertise are the major contributors.

It takes years of work to turn scientific discovery into a new medical solution, out of thousands such discoveries few make it to market. Highest percentage of drug development projects before undergoing clinical trials. Very few undergoes clinical trials and hardly one passes through regulatory department.

## Translational Science – A Cost Effective Solution to Health Care Delivery

The question is in everyone's mind that why we need translational medicine?

Firstly, it shortens the duration of clinical trials by accelerating the inclusion of novel endpoints in to clinical evaluations.

Secondly, it helps us to deal with innovative diagnostic and therapeutic tools of modern technology which will undergo clinical trials before they are converted into medicine.

Thirdly, figure of testable agents is significantly higher as compared to number of subjects. Even the higher cost of clinical testing and limited predictive accuracy of models aggravate the current situation of not allowing reliable preclinical screening of candidate products.

However, translational medicine aids in shortening the route of testable agents to clinic to rapid validation of novel products ultimately reducing preclinical testing cost (Figure 1).

Figure 1: Expediting drug progress.
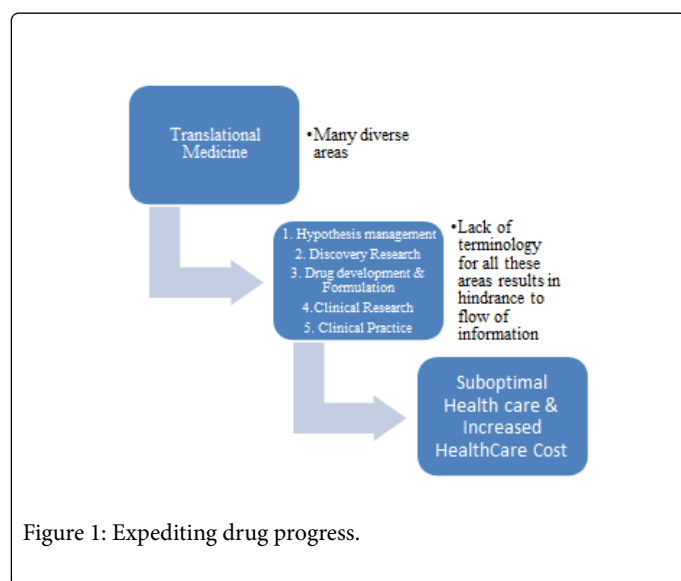
The prime challenge among many currently translational medicine is experiencing the cost in transferring biomedical research into clinical benefit i.e., if failure to generate projected revenue. So, it must be identified along with insufficient funding issues of both basic science research and large scale clinical investigation must be resolved.

Funding for the Development Pipeline is as follows:

- Basic Research: By public
- Translational Research: By Governments and private
- Clinical Development and FDA Review and Approval : Industry and For profit organizations.

More than billion dollars are required to bring one new therapy from laboratory to market. So to translate science into cures joint efforts of many funders from lowest level to the highest that is academic researchers, academic institutions, nonprofit foundations and the pharmaceutical and biotechnology industries etc. are required.

Obstacles along the Path of Translational Research

Translational research transformation whether it is a new treatment, a drug, device, diagnostic or behavioral intervention is concerned it is a slow, expensive and not a easy task few issues are need to be resolved, these are the following:

Bridging the gap is facing obstacles like,

- Lack of complete knowledge of translational science

- Limited number of multi and inter disciplinary investigative team
- Inefficient organizational structures and lack of incentives
- Inflexible and inefficient clinical trials
- Regulatory science issues.

Team work is highly needed for the translational journey it involves scientists, clinicians, traditionally separate scientific disciplines and organizations [2].

Nodes of translational research

There are four nodes of translational result [3], they are as follows:

T1, Translational research – Laboratory to humans : A mechanism-oriented clinical research involves laboratory based research to define disease mechanism, developing drugs, devices to improve health. In this discoveries turn into initial clinical testing.

T2, Translational research – Evidence to practice research: Focused on the propagation and application of best practices in prevention and treatment in the community. It involves in identification of public, patient, physician and administrative issues serving as barriers or facilitators of translational research.

T3, Translational research – Practice to community: It moves out of the controlled environment to the real world. It involves comparison of the effectiveness of approaches and interventions on small as well as large scale (Phase IV Clinical trials). In phase IV clinical trials drug is tested on some population. i.e., primary care practices, ambulatory care centers, community clinics.

T4, Community to public health: In this evaluation of the implementation and efficacy of policies, medical practices is done. It is based on cost-benefit analysis, policy analysis, surveillance studies etc (Figure 2).

Figure 2: Translational research structure development: Scientometric approach.
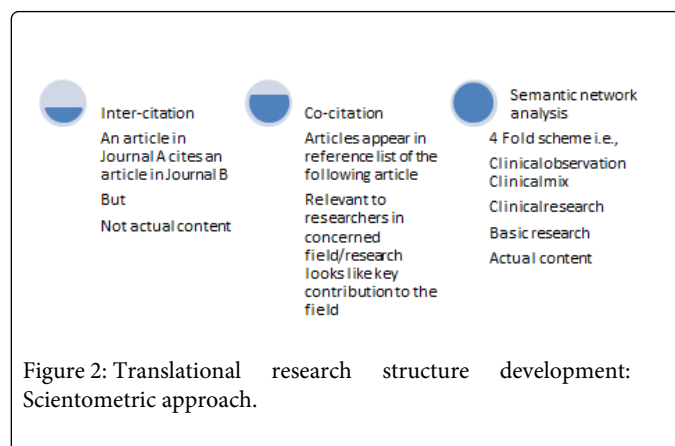
Inter-Institutional Collaboration

The existing administrative model of fragmentation into different disciplines (surgery, radiology, nursing, pathology) also act as an endemic to the path of clinical research. A goal-oriented, adaptive "adhocracy" model is highly desired i.e., departments around a goal than a discipline. So, we can say inter-institutional collaborations must be promoted in order to overcome the existing barriers in the path of translational research. A balanced approach will encourage associations and help in establishment of positive feedback loop of research to development of new products.

Disciplines of translational science

Translational natural science-bioactive compounds: Phytochemicals are optimized as drug like molecules since the history of medicine and it's unique chemical diversity still cannot be compared with synthetic libraries. Novel discoveries in the world of science are still influenced by phytochemicals [4].

Phytochemicals are the primary source for the synthesis of novel therapeutic and preventive drugs. Bioactive components of natural products in practice around the globe are already under the process of screening for their effective and safe use. Besides this investigations of mechanism of action (MOA) of bioactive components of natural origin will play a dynamic role in location of validated novel molecular targets of innumerable diseases.

All this search of finding novel molecules is not as simple task as it seems because of the highly complex biopharmaceutical characteristics associated with natural products. Previous concept of scientific community that is bioactive components discovered will provide ultimate cure of diseases is not yet accomplished. It has raised a question mark on the efficiency of healthcare system.

High throughput screening (HTS) and combinatorial synthesis shifted trend towards synthetic libraries and abandoned many natural product programs initiated by pharmaceutical companies which ultimately resulted in significant decline in discovery of new drug leads [5].

However, some discoveries like microbial avermectins and artemisinin [6] are again compelling the scientists to reconsider the value of natural medicinal materials [7]. Even species on the verge of extinction can be produced due to innovation in the fields like microbial cultivation [8,9]. Nature's biosynthetic machinery can be modified and production of natural medicinal materials can be increased. This pace of discovery of life saving therapies has been increased due to some new revolutionary technologies (Strain prioritization) [10,11] (Figure 3).

Figure 3: Disciplines of science evaluating structure activity relationship (SAR).
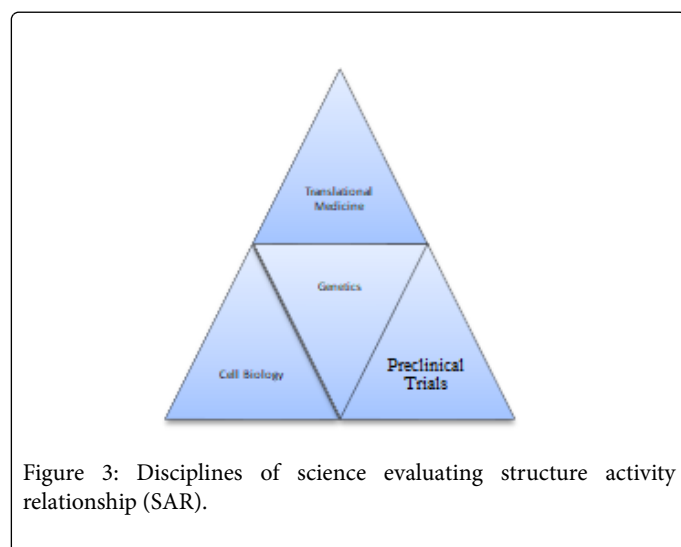
Of bioactive components along biopharmaceutical evaluation

So, it is highly recommended to consider advances in translational pharmacology, target validation, mechanism of action as well as study of structure activity relationship as a group.

Translational chemical science-investigating bioactive compounds: Once biological compound is isolated chemist will work on finding it's mechanism of action. This will later help chemist in synthesizing more therapeutically active compounds (Figure 4).

Figure 4: Translational chemical science.
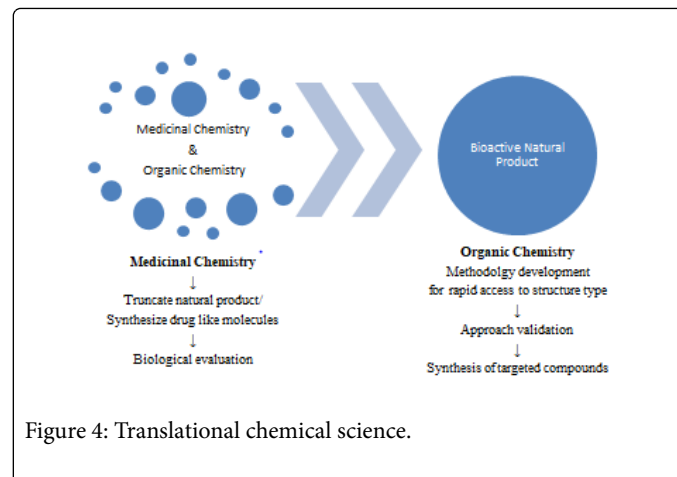
Most therapeutically active compound will be selected and tested known as lead compound. However, further refinement is done to reduce adverse effects and increase in specificity of the lead compound. This iterative process will help in study of structure activity relationships. Even by probing the cellular processes using these newly synthesized lead compound disease processes can be identified.

Translational chemical biology: Chemical biology stands between chemistry and biology. It's application aids in crafting a bonafide chemical probe i.e., adopting a route to its applied domain however, successful outcome rely on many facts. Critical issues in the path of drug development must be eliminated for their perfect clinical effectiveness because we need to increase the quantity with quality and effectiveness [12].

Clinical perspective of discovered chemical probes is highly desired to convert a therapeutic target hit leap form being only an *in vitro* compound to a candidate of clinical potential which currently is still at its embryonic stage. Chemical biologist's potential role need attention for implementation of a useful translational chemical systems biology approach.

In recent years combinatorial chemistry (CombiChem)/high throughput synthesis and screening restricted to only making of libraries of flat, planar molecules with remarkable lack of chirality and scaffold diversity. However, highly stereospecific naturally derived molecules were neglected because of some complications in their large scale production. But failure of synthetic drug molecules in market leads to significant shift to traditional knowledge.

Professor Robert Burns famously stated: "The art and science of chemistry is one that is more easily exemplified and epitomized than it is articulated and summarized [12].

Translational chemical-systems biology to drug discovery: The systems biology with analytical and bioinformatics tools and technologies helps in evaluation of complex disease mechanisms which will later form the basis for onset, progression and effective treatment.

- Network biology discovery – Multi-omics analysis at the gene, protein and metabolite level.
- (DNA methylation, miRNA and mRNA transcriptomic data).

- Identification of potential targets – The network biology analysis should provide a prioritized list of target genes.
- Functional validation – Utilization of RNAi screens to either overexpress or knock down each of the selected genes in neurons for efficient, high throughput approach to generating the data required for the analysis of transcriptional networks.
- RNA profiles derived from each experimental condition will allow the empirical reconstruction of the molecular networks in the target, human cell types to confirm the pathways identified in our initial integrative analyses. This component of the pipeline has several purposes:
- Refine the networks and confirm the genes of expected effects expected when disrupted on an individual basis.
- Identify other genes of the network having similar functional consequences
- Identify transcriptional programmes or 'gene sets' used as outcome measures in future drug screening.
- Identify nodal points in each network, 'hubs' for a given pathway i.e., effective targets for the disruption of a given cellular pathway.
- Drug candidate screen

For complete understanding of translational chemical biology we should know meaning of following terms, "Accuracy is the proximity of measurement results to the true value; precision is the repeatability, or reproducibility of the measurement".

Valley of death the process involving progression from (discovery to regulatory approval), clinical trial data versus clinical data, Drug safety (dosing, toxicology), Comparative Effectiveness (CER), Biomarkers, Co-morbidities, Compliance, Adherence, Diagnosis, Disease state versus disease trajectory, Unmet clinical need/unstated unmet clinical need.

Translational molecular science

Diseases-disease pathway-bioactive compound: Disease is an abnormal state of condition developed in the body due to multiple factors which need consideration in order to cure it properly. Environmental factors and unhealthy lifestyle of major population are the primary factors contributing towards the development of disease. Every disease adopts a specific path and dysregulate certain signaling pathways (nuclear factor kappa-B (NF-κB), signal transducer and activator of transcription 3 [13].

Synthetic drugs available to correct or repair these pathways are expensive and have associated adverse reactions so it has created an urgent need of highly efficacious agents. Natural products are still the best source of new lead compounds in line of defense against many chronic diseases.

Extensive study of molecular modulators i.e., transcription factors (NF-κB, STAT3), specific enzymes (e.g, cyclooxygenase-2 (COX-2), matrix metalloproteinase-9 (MMP-9), cytokines (e.g., tumor necrosis factor alpha (TNF-α), interleukins (IL-1,-6,-8), chemokines, free radicals, UV-light, X-rays, Gamma rays, promoter region, regulating genes encoding cytokines, cytokines receptors, cell adhesion molecules is required to establish a disease targeted treatment [14].

It is observed that exact management of chronic diseases is only possible when we will have in depth scientific investigation i.e., natural derived bioactive compounds, structure elucidation, understanding molecular pathways of disease etc [15].

Advanced approaches and technologies: Bioactive compound to market place

To lead a bioactive to marketplace new approaches and technologies play a vital role and these are as follows:

Reverse pharmacology: Utilizing primordial concepts of medicine with recent scientifically-validated and technologically-standardized natural bioactive compounds forms the basis of reverse pharmacology as well as systems biology.

On the basis of existing previous knowledge it is compulsory to continue process of pharmaceutical development along with pharmacodynamic studies with controlled clinical studies i.e clinics to laboratories (reverse pharmacology).

Revitalization of natural bioactive compounds: Naturally occurring bioactive compounds are not the simple compounds but are the rich source of valuable molecules since time immemorial. Architectural complexity of natural bioactive compounds is a source of inspiration for scientists. Therapeutic potential of natural bioactive compounds is 'pre-validated by nature' (interaction with biological macromolecules).

Bioactive natural products contain chiral functional groups that are potential sites for protein binding. However, it is not necessary the natural product containing chemical entities are always therapeutically active but by some modification these can be modified as drug like. Efforts by scientists can help to reconfigure simple chemical compounds to chemical hybrids which will later evaluated against targets.

Scientists should consider more important aspects like further exploration of known activities focusing specific biological targets and biosynthesis of valuable intermediates. Expanding the role of chemist will help to obtain remarkable compounds besides difficult synthesis. This doesn't stop here but require help of medicinal chemistry for commercialization.

Synthesis of hybrid molecules: Hybrid molecules are chemical entities with two or more structural domains having different biological functions and dual activity" they are able to act as two distinct pharmacophores (artemisinin and chloroquine with Vitamin K3 in oncology).

These unique molecules has been utilized to improve the effectiveness in both natural and synthetic products they are formed even in the same structure.

Flow chemistry: Microchemistry or continuous flow chemistry involves pumping of reactive components at one point and then they are flowed down under controlled temperature condition and the entire process takes place in a pipe/tube for the rapid optimization and refinement of organic process of compound of interest. Bound reagents further help in flow by converting batch reactions (oxidants, reductants, bases, acids, encapsulated catalyst etc.)

Variants of flow chemistry:

- Micro flow
- Meso flow
- Tethered reagent flow

Due to multiple reasons it is preferred over conventional batch chemistry i.e:

- Pressure (Allow reactions at higher boiling points)
- Continuous sequence in case of multi-step reactions

- Incorporation of gaseous reagents
- Rapid automation
- Impurity profiles
- Rapid assembly of building blocks
- Optimizing intra and intermolecular transformations (bioconjugations, PEGylations, glycosylation).

Chemoinformatics: Cheminformatics (also known as chemoinformatics, chemioinformatics and chemical informatics) involves, "the use of computer and informational techniques applied to a range of problems in the field of chemistry" in silico techniques used by pharmaceutical companies.

Methodological strengths of computational chemistry with translational science play a critical helping role in therapeutic optimization. Initially we are idea rich but with poor data hence lack a predictive value. However, extensive computer generated data of key issues of medical interest is difficult to assess.

Biomolecular structural insight e.g., NMR with Comparative Binding Energy (COMBINE) models specific ligand –receptor interactions can be seen in SAR [16] however if there is no receptor structure information computational tool can still help in contrasting features of specific hits against various evaluating parameters like curative efficacy and toxicity [17].

Molecular modeling with chemical informatics can help in selecting a candidate ligand of interest of good deliverability and great efficacy by overcoming barriers like volume of distribution, blood brain barrier, pharmacokinetic and pharmacodynamics issues [18,19] and help in designing of excipients as well 16. It is helping in assessment of trace component toxicity either present in initial phase or emerge as a result metabolic conversions 18.

Chemical informatics with bioinformatics pronounces the translational aspects of pharmaceutical practice in precision medicine i.e., personalized genome profiling with chemical biological data on patient level (toxicity, efficacy).

Concept to commercialization: Process chemistry takes drug from concept to commercialization. Concepts of 'Process Chemistry-Driven Drug Discovery' with drug discovery methodologies led to the path of new chemical entities of clinical significance.

P-450 Polypharmacy: P-450 Polypharmacy is commonly observed in the aging, chronic conditions cause various adverse drug reactions and drug-drug interactions (DDI) or irreversible changes. Cytochrome P-450 mono-oxygenase enzymes catalysis biological oxidations and heme proteins are activated by hydrogen peroxide (catalases, peroxidases, lignases) via two electron oxidation of ferric to oxoferryl porphyrin cation radical.

Toxicological and pharmacological studies on the metabolites form a crucial segment in the identification of a clinical candidate [20-22].

Complications in using biological systems in studying drug metabolism:

- Small quantities of the product produced *in vitro*. Due to hydrophilic nature of primary metabolites isolation is difficult whereas reactive and unstable intermediates have interaction with biological neutrophils
- Animal studies are expensive
- Lack of knowledge of pharmacologist about the structure of the metabolites.

In vivo metabolic processes are mimic by metallopophyrins. It will be useful to study metalloporphyrins as mimics of the *in vivo* metabolic processes. Efficient, sterically-protected and electronically activated organic biomimetic catalysts have now been developed.

Automated oxidation chemistry: Development and implementation of automated oxidation chemistry to obtain diversified analogues, both as new chemical entities in their own right, and also as substrates for further synthetic conversions, hold significant promise.

This approach affords an efficient method for the systematic preparation and identification of the entire spectrum of metabolites from a chosen drug. Relatively low cost as the starting library is already made, and this would provide new compounds which are more polar, water-soluble and contain handles for further derivatisation.

Significance of P-medicine: Precision medicine (PM) is a medical model that proposes the customization of healthcare, with medical decisions, treatments, practices, or products being tailored to the individual patient. The pharmaceutical industry considers once developed and marketed drug to be safe and effective for the maximum number of patients which is not found true according to recent observations. Biological systems complexity and individuality is to be considered in order to understand the behavior of unresponsive patients. So modern medicine's call of 'P-Medicine' i.e., Personalised and Precision Medicine, is of significant value for the effective drug therapy in translational chemical biology [23].

Precision Medicine is related to medical treatment to the patient individual characteristics whereas 'personalized medicine' involves unique treatment designed for every individual. Precision medicine encompasses personalized and modern conventional medicine [24].

Although modern biotechnological tools are helping scientists to polish therapeutic as well as clinical procedures but it has shown to complicate the evaluations due to cellular substances, cells/tissues modifications and alteration of physiological functions another obstacle translational medicine is facing.

With the completion of human genome project it has become possible to accelerate the testing of multiple variables at once associated with human physiopathology, along with these bioinformatics techniques with its immense computational capacity able to handle large data. We can promote the concept of personalized medicine using technological advances like nutrigenomics (effects of food on gene expression), the human microbiome (commensal flora and the human organism interaction analysis). Complex multifactorial phenomena of interaction of human disease and response to treatment are highly under the influence of individuals genetically determined characteristics. If this issue of interaction of individuals genetics, diseases and reaction of treatment is resolved it will lead to cost-efficient approaches to therapeutic interventions ultimately will help in implementing "personalized medicine"[25,26].

An Unanswered Question: Investment in Clinical Trials or Disease Specific Things is Beneficial or Not?

Herold Varmus answered the question by throwing light on a very important issue of just investing in clinical trials/disease specific things helpful or not by directing our attention on advances in various disease research which are based on biotechnological science (recombinant DNA technology, genomics and protein chemistry) [27].

So, only mutual liaison between basic and applied research must be communicated by scientific community to show people how science actually works which will later stabilize the nation's scientific enterprise. True purpose of recognizing these issues is to know the current position of basic research and translational research. Day by day it is determined that data obtained from animal models is not practically always applied to humans so it is essential to properly conduct translational research in humans [28].

Different scientists have described basic science and applied science differently some discriminated as a job of academicians or that of industry/government, som gave concpt of enduring dichotomy of both sciences whereas some described it as "revolutionary" and "evolutionary," respectively. However, in a nutshell true purpose of basic research source of discoveries whereas applied research convert them in valuable products [29, 30]. Now there is time to humanize the the work. Although the path from basic discovery to scientific and technological applications isn't smooth and scientific work is not always the same form it's point of discovery to its actual use [31,32] (Figure 5).
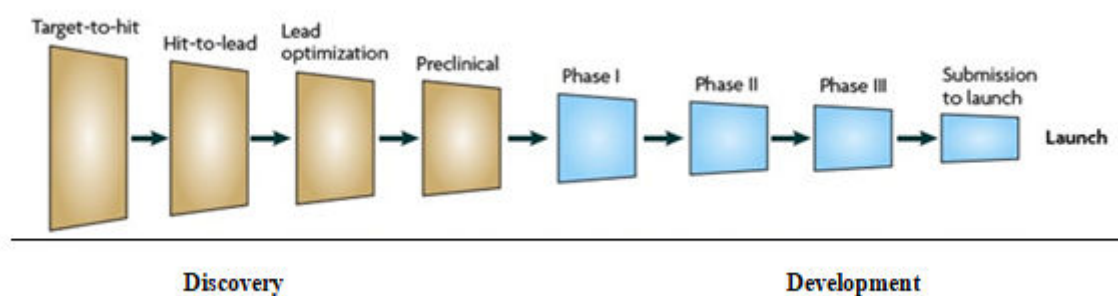

Figure 5: Road to discovery and development: Long and costly.

Practical applications of translational research

The concept of translational research is not a theoretical concept it has already been applied in many medical conditions few are discussed as follows:

Vaccines: Effective implementation of T3 and T4 translational research in the development of vaccine, influenza reduction and drug development for the treatment of leukemia has been succefully performed [3].

Cancer therapy: Far-reaching collaboration of basic researchers, clinicians as well as pharmaceutical industries lead to production of numerous highly efficacious disease targeted anticancer agents. Besides this it has applications in prediction of patient response towards treatment along with development of resistance as well as sensitivity. Treatment using ionizing radiation therapy (lethal DNA damage) kills cancer cells, chemotherapy (systemic drugs to effect cell growth) and molecular targeted therapy are the examples of translation of basic research.

Development of new ways for the prevention, diagnosis, treatment of cancer and scientists are putting efforts to design cancer specific molecules. In this way we can even develop personalized medicine. Practical applications of omics technology in cancer treatment is another milestone of translational research in which advanced biotechnological techniques are involved.

Discovery of new biomarkers o predict cancer and grouped into three categories i.e., diagnostic (CA-125 in ovarian cancer, PSA in prostate cancer), prognostic (hormone receptors, proliferation markers) and predictive (design course of treatment). These examples clearly indicate the impact of translational research.

Nanotechnology using radionuclides specifically target cancer cells, quantum dots (QDs) inorganic fluorophores shows a significant value over traditional fluoresecent markers. Application of such bioconjugates (study of genes, proteins, drug targets) was not a simple work of basic research. Telomerase activity detection technique and new immunotherapies for the treatment of cancer are the result of improved understanding of science. These collaborative efforts are necessary to develop individualized therapy [33].

Behavioral science: A comprehensive model of translational research for behavioral science also exist, though it still needs some refinement. Basic behavioral science is translated to applied science in T1 phase later in T2 progress to patients further tanslated to T3 phase of practice. Phase of clinical trial of behavior differs from that of pharmaceutical trial phase. This established model of translational research provides a coherent, conceptual basis of effects of behavioral science in on health. It is proved through behavioral treatment for regimen adherence in cystic fibrosis (CF). This disease requires a complete medical regimen consisting of dietary changes, medication and enzyme use with daily cleaning of air ways [34], so collaboration rom multiple discipline is required.

Pharmacogenomics: Translational research translate human genomics i.e., complex gene –gene interaction and gene-environment interactions. Genome wide applications offers for common complex disorders that later are translated to health applications. Pharmacogenomics involving new genetic application in health for example, cytochrome P450 microarray test aids in selection and dosage of drugs for the cure of clinical conditions of depression similarly, Herceptin for breast cancer. Human genome Epidemiology network is initiating collaborative work [35].

It takes base pairs to bedside innovative approach to improve health. Following are the domains for its application, Knowing,

- Structural and biological features of genome
- Pathophysiology of disease

- Application of science of medicine
- Refining the health care effectiveness.

A multidisciplinary agenda of "Pull" is highly needed involving clinical and population sciences (epidemeologists, behavioral, social, communication scientists, health service researchers, public health practitioners for the welfare of humanity [36].

Conclusion

Establishment of effective healthcare system is not a one man show but collaborative efforts of multiple disciplines so team work should be promoted for the services of community. New standards of care must be adopted like all the advancements of this centuries. It is an inspiration for all the creative minds (physicians, bench scientists, bioengineers, epidemeolists, patent experts and many more). This communication across the disciplines will renovate the current structure of healthcare system.

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