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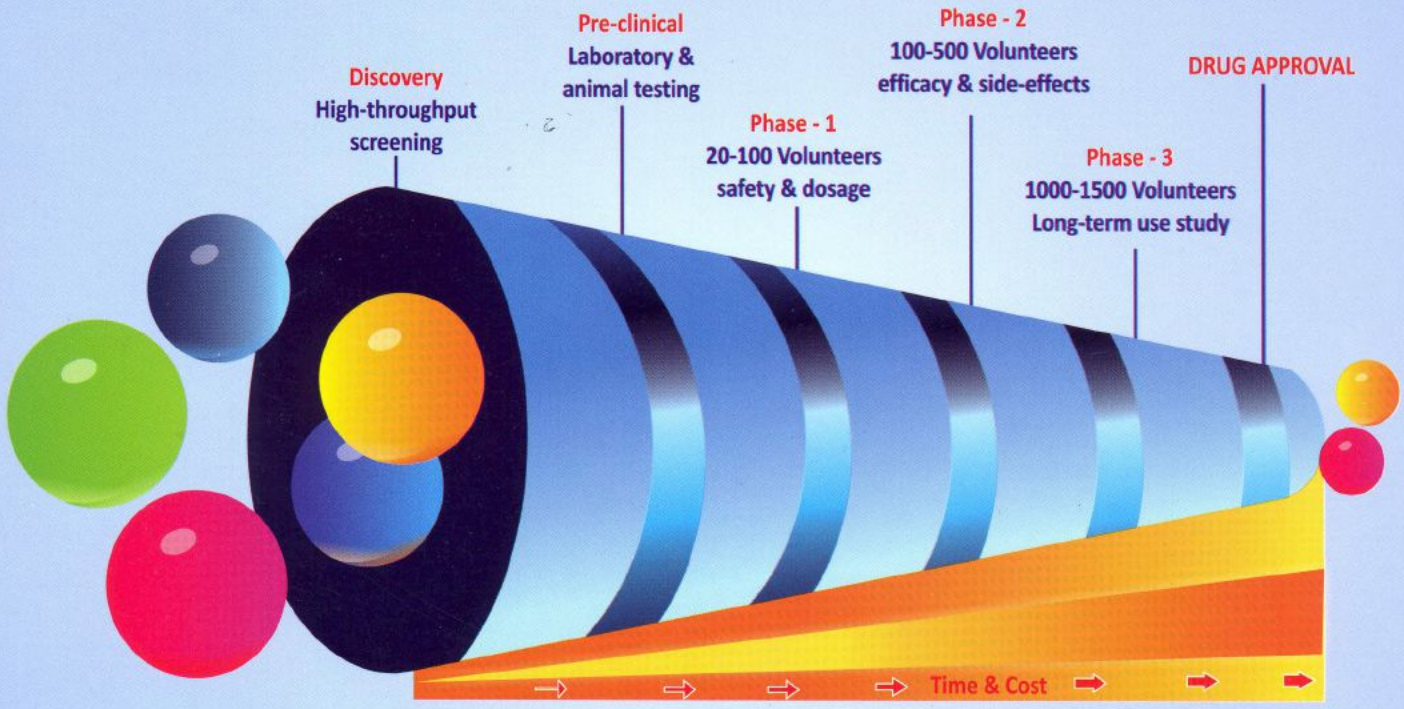

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EDITORIAL

We happily announce the launch of NIPER-Hyderabad in-house journal **"Current Trends in Pharmaceutical Sciences (CTPS)"** with over 2-3 articles in each issue encompassing a broad range of topics in Pharmaceutical research. This journal is an initiative of National Institute of Pharmaceutical Education and Research-Hyderabad and will be a forum for review articles in pharmaceutical research field. We aim to attract articles that will influence the field conceptually, by focused reviews and/or new research findings. We invite articles which are stimulating, novel and build up interesting concepts and will be informative to academia as well as pharmaceutical industries across globe. Articles will be reviewed with careful attention to appropriate interpretation and the high quality of data in the publications will be maintained.

The inaugural issue focuses on drug discovery and development. The articles focus on the hurdles in drug discovery process and suggests few steps that can help to overcome these hurdles. Drug discovery and development process has gained much momentum during the last few decades. However, there are still mammoth type hurdles mainly, timeline schedule, high costs and regulatory requirements and failure, which prevent the availability and affordability. These hurdles can be eliminated by emphasizing on strategies like proper target selection, individualized medicine, predictive toxicology approaches and by using techniques like high throughput screening, allostery and RNA interference. Drug repurposing in drug discovery is a form of serendipitous findings i.e. drug is purposed for indication other than for which they were clinically developed. Few of the drugs like thalidomide repurposed from sedative to leprosy, mefipristone from antiglucocorticoid to antiprogestin, fluoxetine from antidepressant to premenstrual dysphoria are suitable examples of classical repurposing in drug discovery.

The article on NIPER-Hyderabad from scratch to wonders explains how NIPER-Hyderabad has established itself in the within a short span. The alumni of NIPER-Hyderabad are now serving in various capacities in organizations mapping throughout India. NIPER-Hyderabad under the mentor ship of Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad, has deeply rooted itself and now is fully equipped with various competent laboratories doing research in areas of pharmaceutics, pharmacology and toxicology, pharmaceutical analysis, medicinal chemistry along with newly opened divisions like pharma management, process chemistry and regulatory toxicology. A glimpse of the effort of NIPER-Hyderabad and the way this institute has grown from scratches to glory has been penned in this article.

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Challenges in Drug Discovery: Overcoming the Hurdles

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Hurdles, Challenges

ABSTRACT

Research and development stands as a back bone for the pharmaceutical industry, since it directly relates with their success in terms of their business, reputation and growth. Additionally an improved research in the area of drug discovery and development is vital for society to face emerging health hazards. Significant technological advancement has helped the pharmaceutical industries to make tremendous progress during the last few decades, and successfully bring some of the novel biological therapeutics into the market. However the conventional problems associated with drug discovery and its development process still persist. The current review aims at covering the recent advances in drug discovery and development processes and discusses various barriers to this process, measures to curb these hurdles along with detailed overview on collaborations of various organizations which can be useful in the drug discovery and development process. The article also details about some of the recently conceived topics in the area of drug discovery like drug repositioning and orphan drugs.

INTRODUCTION

Drug discovery and development involves a series of phases through which a new molecule has to successfully pass through to enter the pharmaceutical market. This process (Figure 1) is cumbersome takes approximately 10-15 years and a huge amount of expense averaging about $1.2 billion [1]. Although, the risks outweigh the benefits, drug discovery and development is essential for the survival of pharmaceutical companies and to bring better therapeutic alternatives and healthcare to the world population. With the advent of new molecular techniques and novel strategies, the drug discovery process of the present day has been revolutionized. By using techniques like high throughput screening, around 100,000 compounds can be screened in a single day to identify lead compounds [2]. As a result, the number of new molecular entities (NMEs) approved by FDA have been increased considerably during the last few years (Figure 3). However, the process has become extremely complex and is limited by the cost associated with the development of new drugs,. prolonged timeline, intellectual property issues and regulatory requirements [3]. Significant number of drugs have been withdrawn from the market due to unintentional toxicity profiles associated with them, which has been graphically presented in the figure 2. These issues have to be addressed and a rational approach has to be taken so that novel drug molecules are available to the needy at affordable prices.

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HURDLES OR CHALLENGES IN DRUG DISCOVERY

Drug discovery and development is a complicated process, which takes decades to translate a product from lab side to clinic. Commercial challenges and stringent regulatory needs are the major hurdles for drug discovery process along with the cost and failures associated with them.

Cost and time required for development

Development of new drug is an expensive and lengthy process. Recent estimates revealed that full term development of a drug approximately consumes around $1.3 billion [4]. The development of a new drug candidate demands huge investment of capital, human resources, technological expertise and stringent regulatory requirements, which increases the total cost of drug discovery and development. The probability of a drug failure at any stage of drug development further complicate the process and failure at any stage can result in loss of huge investments. Most of the capital incurred for pursuing a NCE is consumed by clinical trials. In 2004 GlaxoSmithKline advertisement concluded a message that "today's medicines finance tomorrow's miracles" [5], implying the importance of potential profits made by approved drugs which are meant to be invested in the development of pipeline of products. Estimation of cost for developing a new drug takes into account several aspects such as type of methods, data sources, samples used and also on type of subjects used for investigation in addition to performing various tiers of health and economic modelling studies. It has been assumed that large companies can develop drugs at lower prices due to their huge economic scale and healthy turnover [6]. The rapid rise in cost of pharmaceutical R&D is mainly because of animal testing, clinical trials and discontinuation of molecules in advanced stages such as clinical

DRUG DISCOVERY PROCESS-CHALLENGES

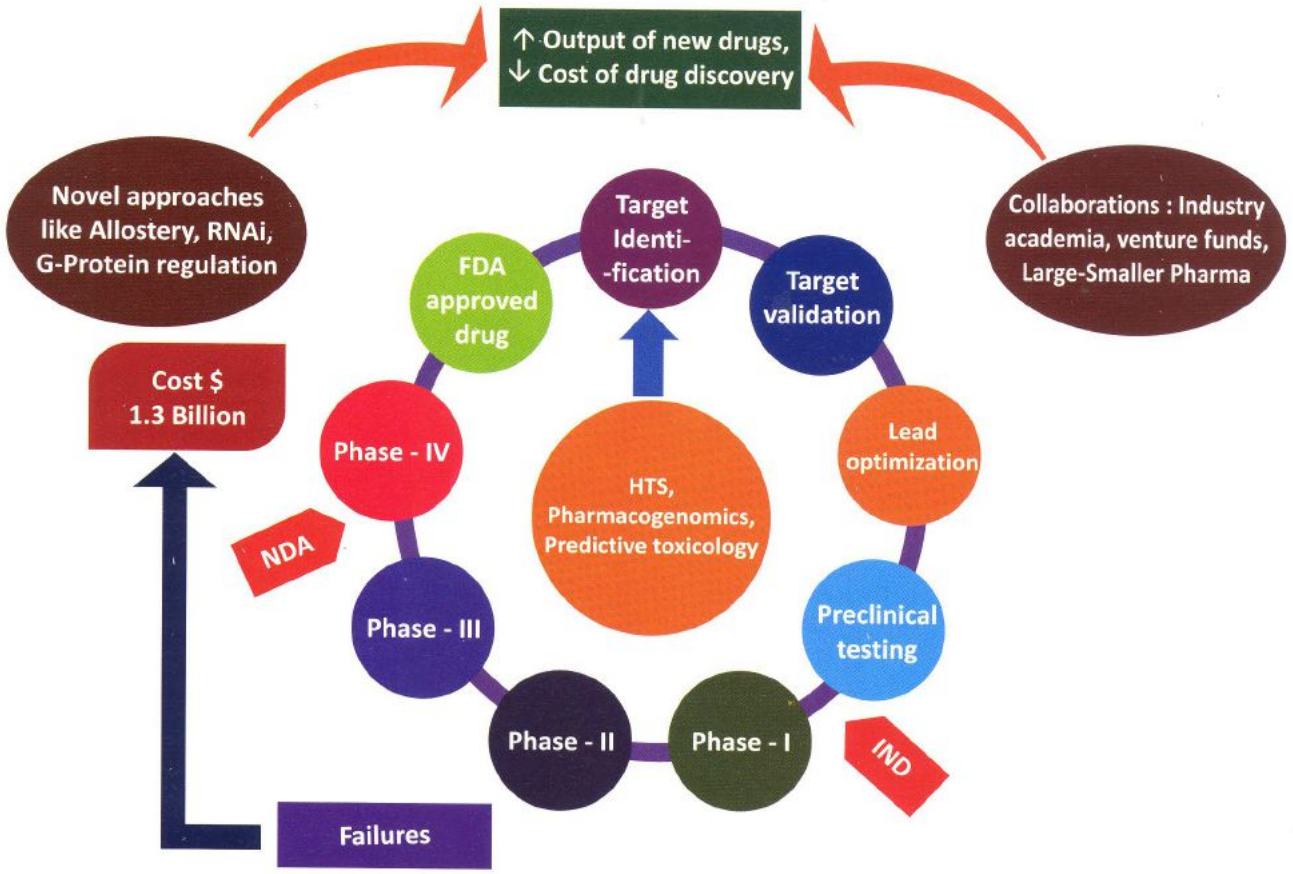


Figure: 1 Schematic overview of drug discovery process: This process consumes approximately $ 1.3 billion and involves various steps like target identification, target validation, lead optimization, preclinical testing and clinical trials.

Phase II and Phase III which leads to massive financial losses and contribute in intensifying burden on the budget [7; 8].

Risks in drug discovery

Risk is an unavoidable feature associated with drug discovery and its development. In order to mitigate risks, its assessment and management involves multifactorial and multidisciplinary approach. The major risks involved in drug discovery are broadly categorized into three types which include: investment risk, risk to the patient, and risk for therapeutic failure [9]. The risk regarding investment towards development by pharmaceutical company or venture capitalists/angel investors/high net worth individuals is determined by the potential for success or failure of the developmental product. This type of risk depends not only on available financial resources but also on the expertise needed for drug development, regulatory filing and approval and time lines for the development. Risk to the patient is an important aspect to the stakeholders who are advocates for patient safety in drug development and includes pharmaceutical companies, investigators, the institutional review boards and government regulators. Patient safety is the prime focus of Food & Drug Administration (FDA) regulations; drug approval depends ultimately on the arguments of risk versus benefit or safety [10]. Risk for therapeutic failure will focus on the effectiveness of product in patients and whether it is better and safer compared to existing products. The appropriate tools and informatics can be used to facilitate detailed information so that regulatory decisions can be made to develop effective therapeutic medications. Quality risk assessment throughout the process of drug development will help to mitigate risks at much

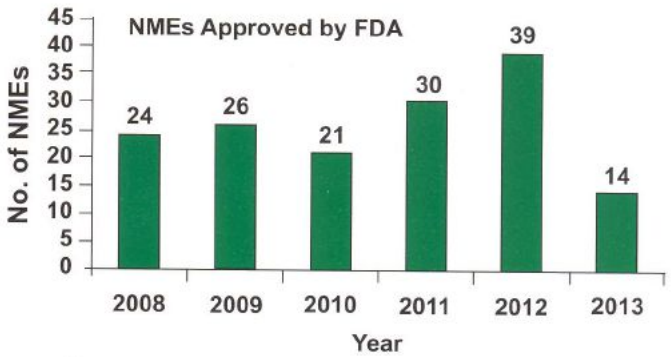


Figure: 2 Drugs approved by US FDA during 2008-2013.

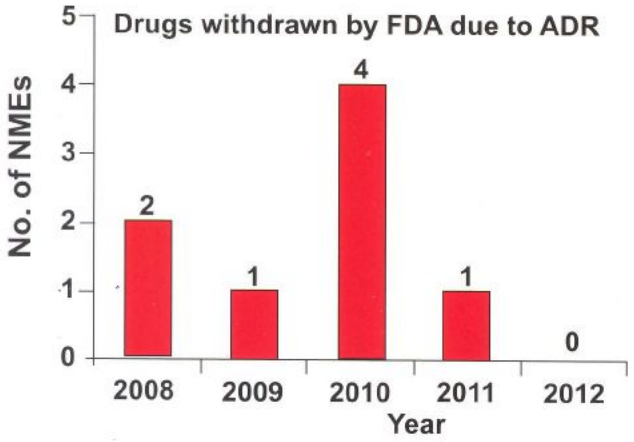
earlier stages compared to encountering failure at later stage of drug development. Drug-drug interaction (DDI) risk assessment will prevent potential drug interactions at earlier stages before drug reaches market. Significant risk in pharmaceutical industry still remain even at during late stages of drug development due to the scientific, regulatory and economic uncertainty [11].

Regulatory requirements

Regulatory risks can affect the cost of drug development because investors demand premiums to compensate for uncertainty. Regulatory affairs play a major role in early stages of drug discovery process; regulatory activity is concerned with registration and maintenance of drug products. Centre for drug evaluation and research (CDER) is the largest of five FDA's centers, which concerns with the safety and efficacy of drugs marketed in the country. In early stages of drug discovery, after getting information from laboratory studies, industry has to file investigational new drug application (IND) to CDER before initiating clinical studies. Once the IND is accepted for review by the CDER the response to the sponsor is given within 30 days. If the response is an approval letter from CDER the sponsor can start clinical studies. On the other hand if FDA finds any problem in the IND application, it can call for clarification or can reject the application. During the clinical studies FDA can put a clinical hold and stop the trial. Once all the three clinical studies are completed then at the end of Phase III the company has to submit new drug application (NDA) to FDA which must contain information about all the studies that have been conducted in a format that has been determined by the FDA. Abbreviated new drug application (ANDA) is used generally for drug products registered previously under NDA [12].

Failures and reasons for failures

Failures in drug discovery are very common and occurs due to multiple factors such as manufacturing problems, toxicity, efficacy, market size, competition and development of serious adverse events during clinical trials [13]. Sometimes drugs that have already been commercialized have produced serious adverse events and had to be withdrawn from the market. Inefficient use of early combinatorial chemistry and high throughput screening results in faulty drug selection which can be potential reasons of failure in drug development. Current socio-economic status and high failures in drug discovery pose new challenges to the pharmaceutical companies. A report by "Centre for Medical Research" analyzed that drug failures in clinical trials occurs mainly in Phase II and Phase III [8].



2008 – Lumiracoxib (Osteoarthritis), Rimonabant (Anti obesity drug)
2009 – Efalizumab (Psoriasis)
2010 – Sibutramine (Oral anorexiant), Gemtuzumab ozogamicin (Acute myelogenous leukemia), Propoxyphene (Opioid analgesic), Rosiglitazone (Anti diabetic)
2011 – Drotrecogin alfa (Anti thrombotic)

Figure: 3 Drugs withdrawn by US FDA during 2008-2012 due to adverse drug reactions.

OVERCOMING HURDLES

Over the past century, the pharmaceutical industry had witnessed several constraints, which have brought it to lower priority when compared with other sectors. The task of bringing the drug discovery to lime light requires intense efforts. This may occur if operations in this sector improve on all fronts and lead to efficient and quicker discovery of drugs and establish continuous successful launch of novel molecules to the market.

Target selection

It is the first and very crucial step in drug discovery process. Target may be cellular or molecular (protein or gene) that exists naturally in pathology of interest and has specific binding site to which the molecule of interest potentially interacts to alleviate the pathological process. The selection of most suitable drug target for a particular disease is a complex process, because it is purely based on molecular understanding of the disease process. The molecular processes are complex and most of the time multiple processes are involved in a disease; this complicates the process of proper selection of a target for most of the diseases. The target selection has become an innovative strategy by the introduction of In-silico, Molecular Docking, Scoring techniques in drug discovery which are probably thought to be superior approaches for overcoming unmet clinical needs. It holds a great promise to fulfil the essential criteria of targets such as potency, improved efficacy, less frequent dosing for better compliance and therapeutic utility, as well as to abolish poor targets as early as possible [14]. The quality of target selection is considered as the most significant factor in improving the productivity of pharmaceutical industries which often identifies the targets on the basis of studies at molecular level.

High Throughput Screening

It is a rapid and reliable scientific technique which involves identification of one or more lead molecules from a pool of possible candidates based on a specific criteria. The ultimate goal of this technique is to speed up the drug discovery process. In order to accomplish the high throughput screening (HTS) the target selection, reagent preparation, compound management, assay procedures, high throughput library screening should be performed with accuracy. The outcomes of HTS can serve not only as suitable start for drug discovery but also in optimizing the activity of drug moieties in development. This will also enable us to understand possible interaction of drug moiety with a particular biochemical process [15]. Hits are the small molecules with desired molecular size generated from HTS and further transformed into more extensive form by optimization giving rise to promising lead compounds. Various novel technologies like DNA microarray, fluorescence, surface plasma resonance, chromatography, NMR are used for screening more than hundred thousand samples per day and are able to provide information about affinity of the screened compound and its possibility of becoming a drug candidate. Application of screening principles in life sciences with the advances in bioinformatics, better instrumentation and auto imaging has expanded the role of HTS into an era of cell based HTS often termed as high content screening, a multi-parametric approach which serves as a valuable tool in drug discovery and biological research for identifying structural and molecular components of cell.

Pharmacogenomics

Human body response to a drug is a complex trait, involving many genes. Understanding the variations in pharmacokinetics and pharmacodynamics is difficult without the prior knowledge about the genes involved. The study of these inherited genetic differences in drug response and metabolism is termed as pharmacogenetics. The new knowledge base created by the human genome project reflected the term pharmacogenomics; broadly meaning the study of variations of DNA and RNA characteristics which relate to drug response. Conventional studies from candidate gene approaches only explain variability in diseases but do not provide the basis for variable drug response. Hence research in pharmacogenomics provides an insight for developing personalized medicine which means development of drugs to the respective genotype. It maximizes the therapeutic efficacy and minimizes the risk of drug toxicity [16]. The personalized medicine is not that simple as it appears to be, because there are issues like individual variation and response to drugs which may be due to single nucleotide polymorphisms (SNPs) or mutations. Therefore, studies on these issues is the corner stone in evaluating the genetic profile of an individual, this could be achieved by the rapidly advancing genetic techniques. This also provide the opportunity for biologists, geneticists, pharmacologists to bridge the gap between gene sequence and face the challenges in research determining which genes can be essentially made into the novel potential drug targets. This newer approach found to be applicative in current multiple aspects of drug discovery right from target identification to clinically useful drug molecule. It involves identification and characterization of gene encoding the drug target, and can possibly help in selecting dose range and modification in the dose, and also aid us in the interpretation of test results. Based on pharmacogenetic test results, we can sub categorize responders and non responders identifying the susceptible population for high risk of adverse effects [17].

It can be extremely beneficial for pharmaceutical companies as the research in pharmacogenomics will create an opportunity to reconsider the drugs which have been withdrawn from market already, and to avoid investments on unfavourable products by abolishing them at early stages of drug discovery. Pharmacogenomics promises a better management strategy for diseases by providing a drug therapy based on the individual genetic profile. With this underlying concept clinical trials based on genetically defined populations would give rise to a better, effective and safer therapeutic output which however may take some time [18].

Predictive toxicology

Toxicity and safety are the major reasons for the drug candidate failure during drug development. The objective of predictive toxicology is to avoid risk and potential liabilities during drug discovery and help in reducing the attrition of drug candidates[19]. Provisions have been made to attain integrative toxicological access early in drug discovery. In this aspect the role of predictive toxicology is a major strategy as it includes the early safety assessments of drug discovery and developmental process. Since each chemical acts through a particular mechanism and induces a unique toxicity profile under a given set of conditions. Therefore, it is important to consider novel drug targets and selection of chemical series with inherent safety by eliminating risk factors and toxicological profiling of potential drug candidates. Predictive toxicology assists in prediction methods to hasten the rate at which compounds could be evaluated for toxicity in initial stages of drug discovery and also reduces the length of toxicological studies as well as costs associated with them. Conventional toxicology has emerged as a valuable tool in updating the data assessments related to histopathology and organ toxicities. With the help of modern computational procedures like QSARs, correlation can be done in a better way that aid in the understanding of the mechanisms involved in toxic exposure [20].

Novel Approaches to overcome hurdles in drug discovery process

Along with the aforementioned approaches, the following novel strategies were also identified to overcome the challenges of drug discovery process.

Allostery

Allostery is the regulation of a protein from a distant site other than orthosteric site or principal ligand binding site. On a receptor level, it can be defined as change in conformation of ancillary site which can cause change in conformation of active site [21]. Allosteric regulation of proteins and enzymes can lead to better targeting of small therapeutics with reduced side effects. The conventional binding site or orthosteric ligand site of protein is highly conserved among the associated proteins and hence gives a broad specificity to the ligand thus associated with drug induced adverse effects. However, the ancillary site is less conserved among protein subfamilies and hence pharmacological modulation of allosteric site is associated with minimal toxicity profile. Further, the regulation of druggable targets using allostery could lead to the better therapeutic outcome, which cannot be achieved by conventional on/off receptor modulators. Thermodynamically, an allosteric effect can induces an allosteric wave at the allosteric site, which travels to the active site via population shift. Population shift is the perturbation of atoms moving along the allosteric wave in a protein [22].

Allostery can regulate the physiological functioning through modulation of cellular signalling machinery. Allosteric modification of proteins and enzymes confers a constraint to the ligand binding and hence adapts to a series of regulated reactions, which leads to a particular physiological response [23]. Particularly this allosteric plasticity is known to be observed in the case of kinases, which because of their inherent complexity result in wide array of cellular effects. Allostery is also found to be observed to be the cause of certain diseases. An allosteric mutation can cause change in the conformational state of the allosteric site and hence modifies the active site conformation or by changing the dynamic redistribution of the propagation pathways in the protein structure [21]. Allosteric modifications can also cause disease states by changing post translational modifications [24]. Allosteric drugs act by binding to the ancillary site of the protein can modify the conformation and functional pathway of protein. Allosteric drugs can be classified into two types, non-covalent and covalent drugs. Non covalent drugs bind loosely with allosteric site and most of the currently used allosteric drugs belong to this category. Examples include benzodiazepines which can bind to the allosteric site of GABA receptors and cinacalcet which binds to the Ca^{+2} binding receptors on the parathyroid gland [25]. Covalent allosteric drugs act by forming covalent linkage with allosteric site and are generally associated with complex patterns of heterogeneity; example includes caspase inhibitors [26].

Allostery concept evolved as a novel concept in the drug discovery process leading to the identification of novel small molecule allosteric receptor modulators. The peptide based drugs have several disadvantages with respect to their large conformation and binding to the receptor, route of administration, patient compatability and cost of drugs. These disadvantages can be overcome by development of small allosteric non peptide, orally active drugs. Allosteric modulators with fewer side effects can be useful tool for both monotherapy and for combination strategy. Allosteric drugs can work not only by direct

binding to the protein but also by modifying the allosteric signalling among a group of proteins [27]. It has been recently identified that allostery is also possible not only among proteins but also in case of molecules such as cholesterol.

Regulation of G-Proteins

Guanosine nucleotide triphosphate proteins are a group of signalling proteins involved in the transmission of signal from extracellular space to intracellular environment. Their activity is regulated by those proteins which can have the ability to hydrolyze GTP. Generally G-proteins are coupled to the G-protein coupled receptors (GPCR) and aid in neurotransmission, hormonal transmission and other endogenous ligand signalling pathways. Through these receptors, G-proteins regulate metabolic enzymes, ion channels and other cellular machinery like transcription, translation, motility, contractility and secretion aspects of a cell [28]. It has been observed that most of the receptors found in the physiological system are of GPCR type. Hence, G-proteins play a crucial role in the physiological and pathological regulation. Modification of these G-proteins can result in diverse phenotypes [29].

Allosteric regulation of G-proteins results in fine tuning of the cellular responses in various disease states. With the advent of mammalian conditional expression vector systems along with RNA interference technology, identification of drug molecules can be made easy in a disease which involves mutation of genes, especially those of G-proteins. Since G-proteins are found to play key role in pathological states of many diseases, their regulation will result in the development of novel drugs [30].

RNA interference

RNA interference is a novel biological phenomenon found to be observed in the cell, in which RNA molecules inhibit the translation by binding to the mRNA molecule. It is also called as post transcriptional gene silencing [31]. This technique is widely used in drug screening programmes to selectively silence desired genes and to identify the novel drug molecules. It is used mainly in genome scale high throughput screening to identify the loss of mutation and relation to the corresponding biological phenotype [32]. RNA interference play a key role in the drug discovery process, mainly it is being used for target identification and target validation [33]. In target identification, this technology allows to identify whether a specific gene/protein is deregulated or functional in a particular disease phenotype. Once the involvement of a particular gene is identified, then the next step is to identify whether the modulation of protein is useful to alleviate the disease condition, if so a series of synthesized library of compounds can be screened for their binding efficacy to the particular target protein. RNA interference is also found to play an important role in assay development and biomarker identification [33]. In assay development, standard small interfering RNA are used as positive control and hence can be used to test the inhibitory capacity of a test drugs on a specific protein. Treatment with specific small interfering RNA in a disease state, and then identification for change in a particular protein and disease condition would allow us to discover the biomarkers for the disease. The functional significance of RNA interference has been recently identified and was forecasted to play a key role in the drug discovery process. RNA interference application in other areas of drug discovery is being realized by scientists and application of this technique to other steps will surely hasten the drug discovery and development [34].

COLLABORATIONS

The pharmaceutical industry is facing challenges for developing new drugs due to various reasons which includes increasing costs, decreasing productivity and attrition of projects. In order to face and overcome these challenges companies need to respond with extensive re-organisation, restructuring and re-focusing which necessitates mixed models for drug discovery [35]. Collaboration in pharmaceutical sector helps to protect small scale industries which face challenges in self sustainability to see through many potential projects. Many partnering models are helpful in promoting drug discovery like industry academia, collaborating small and large pharma industries and venture funding. These collaborations are aimed at achieving goals like identification and validation of new targets, development of new methods, tools and assays for hit generation, identification of new therapeutic approaches, new biomarkers for prediction of safety and efficacy of a drug and its validation. These kinds of collaborations are supported by public and private sources like pharmaceutical industries, academic institutes, government sectors and some charitable institutions. In this kind of partnerships both the partners have the access to the data and technology[8].

Industry academia

Academic research is traditionally being considered as the destination of pure basic research and universities are powerhouses for innovative drug target-based discovery. Initially the industries ignored the potential of academic research, but later the academic and the industry drug discovery research is linked to exploit the potentials of both sectors, fully and efficiently. The development of the new partnership is to bridge the transitional gap and to give more scope for early stages of drug development. The purpose of academic research is to pursue innovation and the industry is to pursue these innovative ideas into therapeutics that can possibly address unmet clinical needs [35]. For example, Sanofi Aventis collaborated with elite research institute of France (Sanofi Aventis – AVIEASAN) attempting new treatment options in the areas like inflammatory diseases, infectious diseases, aging and regenerative medicine. 'Center for Therapeutic Innovation (CTI)' was established by PFIZER as an open innovation partnering models with universities and hospitals, to identify novel biologic therapeutics for unmet needs [8]. In order to have successful partnerships, the academia scientists need to maintain the standards like applying industrial project management techniques, development of robust assay systems, using standard operating guidelines for assuring the high standards of data reporting & quality control. Many academic centres have established specialty wings with modern technologies to help small biotech companies with constrained capabilities. It is also important to develop collaboration models that reward all the participants.

The Imperial drug discovery model is true partnership in the drug discovery process, in which the skills and capabilities of each partner are utilised, rather than reproducing unique or expensive capabilities and facilities. It is a two-way interaction model in which the facilities not available in the university system are provided by the industry [35]. GSK-Imperial College has been established in 2003 as an initiative for alternate drug discovery and new therapeutics for pain. Astra – Imperial College was developed for cancer targets[8].

Virtual company model is gaining importance from last five years. In this model, a core team directs the organization to validate and advance projects to reach the aimed targets. It has some advantages like quick decision making, easy accessibility to global technologies, research flexibility and cost-effectiveness. Chrous has been established by Eli Lily as an independent virtual company for establishing rapid, cost-effective clinical proof-of-concept for internal and licensed molecules[8].

Venture funds

Venture fund provide financial capital to early-stage, high risk, high reward projects usually with growth oriented start up companies. The venture capital fund is usually invested to get equity in the companies. These are risk shared deals in which innovation is the driver for making a deal and the early collaborations between the preferred partners, these kind of initiatives have been intensified during the past few years [36]. Based on the developmental stage different kinds of funds are available. Investment funds at the idea generation phase include, Imperial Innovations and Biogeneration Ventures. The groups venture funding the industries at the advance early stage assets through proof-of relevance are Lilly-Mirror Fund (Lilly offers 20% capital for disease and technical expertise with rights to purchase back the successful molecules), Forbion, Aretus (Virtual), Velocity Pharma Development (VPD), Astra-Medimmune (invests the funds in early biotech companies with buy back rights), Atlas Venture, and Sofinova Ventures (late phase molecules through approval). Large pharmaceutical companies are participating in venture funds with a goal to expand their product pipeline[8; 37].

Large Pharma- Smaller Pharma

The big pharma companies are seriously involved in the late stages of drug development than the early stages, as an effort to reduce costs of research and development to produce a new drug. Small pharmaceutical/biotech firms simply have limited financial or technical resources for either getting marketing approval from the regulatory bodies or marketing their own products. So, smaller biotech's and research institutions focus more on the innovative side of drug development. For this purpose big pharma companies collaborate with small companies. The partnership with smaller companies helps in the innovation of the new concepts and technologies. The partnership especially with the small companies providing a valuable step in the drug discovery chain minimizes the extreme costs of the industry. By this way both the partners get benefited: the big pharmaceutical company can contract for the research with low cost and the small companies can market their innovations through the most efficient and the profitable channels[38; 39].

DRUG REPOSITIONING, ORPHAN DRUGS AND LIFE EXTENSION OF DRUGS

The problems associated with biopharmaceutical industry have forced many drug developers to think about alternative use of existing medications. This usage of existing, approved drugs for other clinical indications is popularly known as drug repositioning [40]. It can also be called as redirecting, repurposing or reprofiling. At the starting of 21st century, two blockbuster repositioning strategies have stimulated many companies to focus their shift in this field. These strategies include use of Viagra which was actually discovered for treating angina and use of thalidomide for multiple myeloma, which was designed for use in morning sickness [41]. Similarly, duloxetine and dapoxetine which are selective serotonin reuptake inhibitors and are basically developed to treat depressive illness have been successfully repositioned to treat stress urinary incontinence and premature ejaculation respectively[42].

Drug repositioning is a recent industrial practice, gained much importance in the last decade, where the existing marketed drugs or withdrawn drugs are being tested for other rare diseases for their therapeutic utility. Pharmaceutical giants like Sanofi Aventis invested extensively in drug repositioning rather than in generic drug discovery[8]. Matching mechanism of existing drug off targets to the targets of rare diseases can lead to the development of potential new therapeutics.

Currently there are around 23,000 diseases and more than 1,000,000 drug molecules and hence drug repositioning can be useful to derive better therapeutic alternatives for these conditions. Drug repositioning is associated with certain advantages. It lessens the time scale for drug development, increases safety and reduces development costs[42].

Several public agencies realized the importance of drug repositioning and started carrying it in a large scale using high throughput screening programmes to identify the therapeutic utility of drug molecules in rare, orphan, neglected diseases. Patent extension for orphan drugs is provided by drug regulatory agencies, to encourage the private sector companies to undertake the research in these rare areas. US Orphan drugs act (ODA) provides 7 years exclusivity to the orphan drug manufacturers and tax exemption for certain development costs[41].

Translational failure:

Another constraint for the drug discovery involves the clinical failure of the drugs which were proved to have pre clinical efficacy. Many novel categories of drugs like PARP inhibitors [43], TRH analogues [44], peroxynitrite decomposition catalysts [45], GSK3β inhibitors [46], mTOR inhibitors [47] have been proved to have pharmacological efficacy in many experimental animal models and in vitro models were failed at the clinical stage due to inefficient translational approaches used in drug discovery process [48]. Careful consideration of experimental design and time course exposure to drug during pre clinical stage will pave the way for better therapeutic drugs to come into the market. Correlation between biomarkers used in both pre clinical and clinical studies, translatability scoring system will also aid in better therapeutic output [49; 50].

SUMMARY

Drug discovery and development process has gained much momentum during the last few years. However, it still suffers from severe drawbacks such as long timeline schedule, high costs and regulatory requirements, which prevent the availability of the drugs to the needy at right time and at right cost. These hurdles can be eliminated by careful execution of the certain measures like target selection, individualized medicine, predictive toxicology approaches and by using techniques like high throughput screening, allostery and RNA interference. It has also been realized that collaborations between industry and academia, is essential to bridge the gap between discovery and development. The banned drugs and the drugs withdrawn from the market should be repositioned to test their efficacy against rare diseases so as to reduce the cost and failure rate associated with drug development process. The drug regulatory requirements need to be streamlined without compromising the quality outcome of pharmaceuticals and novel strategies need to be applied in every aspect of the discovery process to make available the best therapeutic option at a lesser cost.

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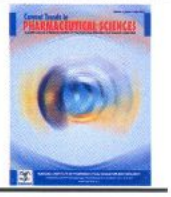

Drug Repurposing: A New Era in Drug Discovery

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Drug Discovery,
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ABSTRACT

Drug repurposing in drug discovery is finding of one thing while looking for other i.e. drug is purposed for conditions other than for which they were clinically developed. Classic examples for this are thalidomide repurposed from sedative to leprosy, mefipristone from antiglucoronoid to antiprogestin, fluoxetine from antidepressant to premenstrual dysphoria etc. The field of repurposing drugs is an evolving example for advancements and improvements in drug discovery process. This article gives an overview of examples for such discoveries in various disease categories and also a brief on the current research and the present market potential of repurposing drugs.

INTRODUCTION

The process of drug discovery involves many stages but can be categorized into three stages namely: lead identification followed by preclinical testing in animals and then clinical trials in humans. Despite of getting approval from FDA after the clinical trials are declared safe, the long term safety of drug molecules in humans cannot be guaranteed. A classic example in this case is thalidomide that entered the market as sedative but was withdrawn once its teratogenicity in pregnant women was discovered. The cases wherein development of serious adverse events takes place and decreased efficacy in human beings during clinical trials are two common reasons for a compound failing to reach the market [1].

In order to avoid such long term process of conventional drug discovery reverse engineering process is gaining importance. Another alternative in drug development strategy is exploration of drugs that have already been approved for treatment of other diseases and/or whose targets have already been discovered. Drug repositioning is the application of existing drug to new indication by targeting diseases other than those for which it was originally intended or discovered. It is also known as- drug repurposing, drug re-profiling, therapeutic switching, drug re-tasking [2]. Today, pharmaceutical industry faces number of challenges from rising drug development cost to high rate of drug attrition during clinical trials. Heightened concern for drug safety and expiring patents with generic competition makes these challenges a hefty task. These problems along with ever increasing regulatory hurdles have forced drug developers to explore new uses for existing drugs [3]. Thus, drug repositioning is not just identifying new target but also several aspects are taken into consideration such as relevance to disease, side effect tolerability at new dose and intellectual property rights.

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Apart from creating value to drug, drug repositioning has a number of advantages such as reduction in R&D timeline, reduced developmental cost and an improved chance for the success of the molecule [3]. Patents are the normal means of gaining market exclusivity by protecting structure or formulation. On the other hand, the failure rate of molecules is estimated to be 150-200 compounds per year [4]. Market exclusivity and R&D incentives is provided by the Orphan Drug Act in the USA for drugs, including repositioned drugs, with an approved orphan drug status. Thus, drug repositioning has now transformed from opportunistic approach to scientifically robust and logical approach to find new uses for the existing drugs (Figure 1)

Figure 1 Drug repurposed for various disease categories

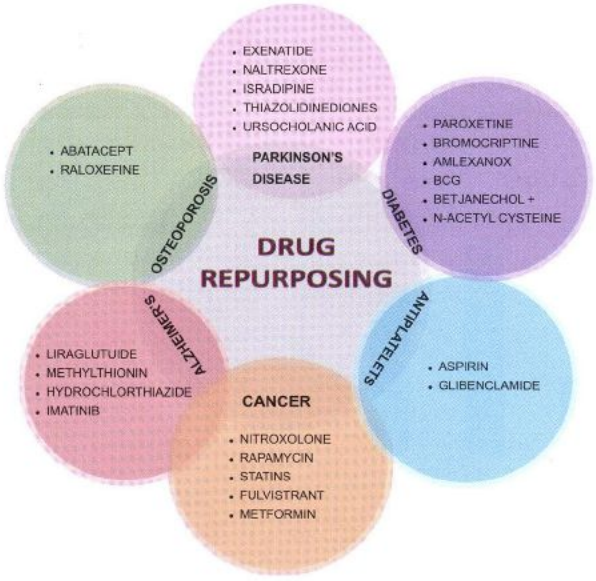

Table 1.Various drugs that are being repurposed or have been already repurposed for various disease categories

S.No.	Drug	Original Indication	New Indication	Indicated Mechanism of Action	Reference
A.	**Drugs repurposed for cancer therapy**				
1	Aspirin	Analgesic, antipyretic	Colorectal cancer	Aspirin inhibits cyclooxygenase-2 (COX-2), over expressed in colorectal cancers that promotes inflammation and cell proliferation.	[15]
2	Statins	Hypertension	Prostate cancer, leukemia	Reduced activation of the small GTPases Ras and Rho involved in regulation of the cell cycle and apoptosis is one proposed mechanism for growth inhibition	[16]
3	Imipramine & Promethazine	Antideprassant	Small cell lung cancer	Cause cell death by engaging with G-Protein Coupled Receptors (GPCR's) and downstream signalling mechanisms.	[17]
4	Metformin	Diabetes type II	Breast cancer	Activation of AMP kinase via an Liver kinase B1- dependent mechanism that acts as a tumor suppressor gene in epithelial tissues	[18]
5	Celecoxib	Osteoarthritis and adult rheumatoid arthritis Breast cancer	Colon cancer Breast cancer	Induces Apoptosis by Inhibiting 3-Phosphoinositide-dependent Protein Kinase-1 Activity May involve COX-2 mediated HER-2/neu-induced mammary tumor formation	[19] [20]
B	**Drugs repurposed for diabetes therapy**				
1	Paroxetine	Antidepressant	Type I and type II	Acts as an antioxidant and inhibits diabetic endothelium dysfunction	[21]
2	Bromocriptine	Parkinsons	Type II	Reverses metabolic alterations associated with insulin resistance and obesity by resetting central hypothalamic circadian organs of monoaminergic neuronal activities.	[22]
3	Amlexanox	Asthma and mouth ulcers	Type I diabetes	Inhibition of IKK-ε and TANK binding kinase 1 (TBK 1)	[23]
C	**Drugs repurposed for neurodegenerative disorders**				
1	Omega-3 Fatty Acids	Dietery supplements	Schizophrenia	Unclear	[24]
2	Folate	Vitamin supplement	Schizophrenia and bipolar disorder	Reduces the level of homocysteine, an amino acid thought to exacerbate some psychiatric symptoms and also involved in the synthesis of neurotransmitters and in many other metabolic pathways	[24]
3	Imatinib	Chronic myelogenous leukemia, gastrointestinal stromal tumor	Alzeimers disease	Uncertain but may interacts with Y- secretase activating protein (GSAP) reducing GSAP expression significantly decreasing amyloid-β levels	[25]
4	Carvedilol	Hypertension	Alzeimers disease	Posesses strong anti- Aβ fibrillation/oligomerization activity, interferes directly (or indirectly) with fibrillary and oligomeric Aβ formation and prevents its neurotoxic interactions at the dendritic spine and synapse level	[26]
5	Gallantamine	Polio, paralysis, anaesthesia	Alzeimers disease	Acetylcholine esterase inhibitor	[27]

D	Drug repurposed for orphan diseases				
1	Tretinoin	Vitamin A supplement	Acute Promyelocytic Leukemia (APL)	Associated with leukemic cell differentiation and expression of an aberrant Retinoic acid receptor-α (RAR-α) nuclear receptor	[28]
2	Sildinafil	Erectile dysfunction	Pulmonary Arterial Hypertension (PAH)	Inhibits phosphodiesterase type 5, thereby enhancing the cyclic guanosine monophos phate– mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lung.	[29]
3	Eflornithine	Hair loss	Sleeping sickness	Selective irreversible inhibitor of ornithine decarboxylase (ODC), deplete polyamines in trypanosomes, which bring them into a static state that renders them vulnerable to the host's immune attack	[30]
4	Ceftriaxone	β lactam antibiotic	Neuroprotective amyotrophic lateral sclerosis (ALS),	Brain expression of glutamate transporter GLT1 and its biochemical and functional activity	[30]
5	Thalidomide	Sedative	Erythema Nodosum Leprosum (ENL)	Anti-inflammatory effects, particularly an inhibition of neutrophil chemotaxis, immunosuppressive effects	[31]
6	Sulindac	Cyclo- oxegenase inhibitor	Cancer	Apoptosis inducer	[32]
7	Losartan	Blood pressure medication	Marfan syndrome	Activation of AT1 by angiotensin II resulting in the production of thrombospondin (TSP)-1, a key regulator of Tissue Growth Factor-β (TGF-β) activation.	[33]
E	Drugs repurposed for other disease categories				
1	Tofisopam	Anxiety related conditions	Irritable bowel syndrome	Unclear	[3]
2	Minoxidil	Hypertension	Male pattern baldness Erectile dysfunction	May cause prolongation of anagen and increases hair follicle size Phosphodiesterase type5 (PDE5) inhibition	[34] [35]
3	Paclitaxel	Cancer	Restenosis	Therapeutic concentrations was found to arrest the process responsible for neointimal hyperplasia after angioplasty and stenting by cytostatic inhibition of smooth muscle cells	[36]
4	Zidovudine	Cancer	HIV/AIDS	Reverse transcriptase inhibition	[3]
5	Phentolamine	Hypertension	Impaired night vision	α-adrenoreceptor antagonism (intraocular delivery causes inhibition of pupil dilation)	[3]
6	Topiramate	Epilepsy	Obesity	state-dependent Na^+ channel blockade GABA stimulation kainate / AMPA antagonism	[3]
7	Cicloprox	Antifungal	Antibiotic	Alters galactose metabolism and Lipopolysaccharide (LPS) biosynthesis, two pathways important for bacterial growth and virulence	[37]
8	Cicloprox	Antifungal	Cancer	Inhibition of lymphangiogenesis by downregulation of vascular endothelial growth factor receptor 3 (VEGFR-3) expression, extracellular signal-related kinase 1/2 (ERK1/2) pathways	[38]

2. DRUG REPURPOSING

Drug repurposing can be done either by the analysis of the pathway of action, disease pathway and proteins. The various approaches for the repositioning of drugs are:

1) *Based on drug character:* Structural features of a molecule when compared to originally developed molecule for different indication, gives a QSAR model for the new indication of a molecule. Such drug character based repositioning is less but are gaining importance in modern research[5, 6].

2) *Target or disease characters:* Based on the pathway of disease or the mechanism by which a disease or disorder progresses makes the drug to be evaluated in such condition. Biomarkers of diseases are also target for the drugs. Knowledge of these pathways help investigator to investigate new indication for drug and provides scope for drug repositioning [5, 6].

3) *Serendipitous:* This includes the serendipitous discovery of new indication for the existing drugs. It mostly occurs during the clinical trials and also during the post marketing surveliance. Drug repositioning through this approach is most common.

Accidental discoveries have always been a part of drug discovery and repositioning. Many examples are available in market for drugs which have been developed for one indication and then used and approved for a new indication. This list continues to grow as time progresses and these add up to the new indication of existing molecule.

The case of **Mefipristone** is an evolving example of drug repurposing that revolutionized the field of medical abortions. First synthesized by Roussel-Oclaf as a glucocorticoid receptor antagonist but the preclinical trials revealed its anti progestin activity resulting in pregnancy termination. Hence, this was repurposed for another cause long before it gained approval for medical usage. This anti progestin got US-FDA approval in September 2000 as an abortion pill. It took almost 12 years for it to achieve approval for the indication for which it was synthesized. In February 2012, FDA approved mefipristone to control hyperglyceaemia in adults with endogenous Cushings syndrome and not eligible for surgery [7].

One other similar molecule is **Bimatoprost,** whose ophthalmic solution is available for the treatment of glaucoma under the brand name of Lumigan. The clinical trials of Lumigan indicated warning of eyelash growing longer, thicker and darker. This lead the investigator to evaluate the efficacy of Bimatoprost in patients with insufficient eyelashes. In early 2009, Bimatoprost was approved and is being marketed for patients with thin or not enough eyelashes [8].

Aspirin, a chemical first prepared by research chemist Felix Hoffman in 1897 became one of the most globally popular drugs of all time. Initially developed as an analgesic and antipyretic it journeyed as an analgesic to an antiplatelet in cardiovascular diseases and now seems to be promising in colorectal cancer. Its mechanism in cancer is still unknown with one hypothesis pointing its activity at targeting intestinal stem cells and the other on host cells or gut microbiota [9].

Bupropion being evaluated as an antidepressant, saw participants of clinical trials quit smoking without trying. Many volunteers stopped smoking remedies like lozenges or patches containing nicotine. This tendency hinted investigator about the potential of Bupropion as smoking remedies. After specific testing it was seen that the smoking desire of patients disappeared. This was attributed to its action of altering chemical signals in brain, diminishing effect of nicotine withdrawal. In 1997, Bupropion was approved as stop smoking aid.

Sildenafil is a well known example of drug repositioning. It was first tested by the researchers in Pfizer as new cure for angina. It was supposed to work by expanding the blood vessel but also lowered blood pressure. Expanding blood vessel in erectile dysfunction worked as in positive favor for participants of clinical trial. In 1998, it was approved as an oral remedy for erectile dysfunction [10].

Amantadine was initially screened as an antiviral prophylactic agent against Avaian influenza and treatment of Influenza A virus and was approved in October 1966. In 1969, it was accidentally discovered to reduce symptoms of Parkinsonism; drug induced extrapyramidal syndromes and akinesia. This led to widespread investigation of amantadine as a potential therapeutic agent against parkinsonism [11].

Paramomycin .an aminoglycoside antibiotic is yet another example for drug repurposing. It is a protein synthesis inhibitor found to be effective against gram positive and gram negative bacterial but now is no longer used as an antibiotic. However it was successfully repurposed for visceral leishmaniasis and licensed for the same in 2007 in India after a phase III trial was conducted in Bihar in between June 3003 and November 2004 [12].

Simply drug repurposing can be divided into two types: the former is known compound new target that involves identification of secondary indications for a known compound. An example of this is **Thalidomide** that was developed as a sedative ,withdrawn from the market because of its teratogenic potential leading to childbirth defects but was reinvestigated after its leprosy abating effects were observed by an Israeli doctor. This led Celegene to get FDA approval in 1998 to market thalidomide under the brand name Thalomid. It has also been found to be effective against multiple myeloma and approved for the same in 2006. Further it was found to be effective in angiogenesis by inhibition of Tumor necrosis factor- α (TNF-α). The latter is known mechanism –new indication quoting **finasteride** as an example. Initially approved for prostate enlargement cases under the name Proscal but in 1997 got approval for treatment of male pattern baldness under the name Propecia. It works on both by inhibiting conversion of testosterone to dihydrotestosterone [13, 14]. Various drugs that are being repurposed or have been already repurposed for various disease categories are listed out in table 1.

Some of the above given drugs have already passed the FDA approval process either because of safety trials or else they were already proven to be safe for the original indication. The market of drug repurposing is growing and making huge commercial potential with many drugs under clinical trials as given in table 2.

3. CURRENT UPDATE

Discovering New Therapeutic Uses for Existing Molecules, a program launched by Naitonal Institute Of Health's (NIH) 19 months old National Center for Advancing Translational Sciences (NCATS) in May 2012, is keenly focused on revitalization of the research strategy to find out innovative new uses for compounds that have undergone significant research and development by industry, including safety testing in humans.

AbbVie (formerly Abbott), AstraZeneca; Bristol-Myers Squibb Company; Eli Lilly and Company; GlaxoSmithKline; Janssen Research & Development, LLC; Pfizer; and Sanofi provided 58 compounds for the pilot program. Subsequently in June 2013, NIH awarded $12.7 million to fund nine projects through this NCATS-led pilot program. These

Table 2. Clinical trials updates for drug repurposing				
S.No.	Clinical Trial Title	NCT No.	Phase	Status
1	Type II Diabetes Mellitus in Patients Exposed to Pravastatin and Paroxetine	NCT01602913	-	Ongoing, but not recruiting participants.
2	Amlexanox for Type 2 Diabetes and Obesity	NCT01842282	2	Currently recruiting
3	Exendin-4 as a Treatment for Parkinson's Disease - Pilot Study	NCT01174810	2	Ongoing, but not recruiting participants.
4	The Effects of Bethanechol on Glucose Homeostasis	NCT01434901	1	Ongoing, but not recruiting participants
5	QR-Bromocriptine as an Adjunct to Insulin and Metformin in the Treatment of Type 2 Diabetes	NCT01474018	4	Completed
6	Safety and Tolerability Study of Cycloset in Treatment of Type 2 Diabetes	NCT00377676	3	Completed
7	Minocycline for the Treatment of Early-Phase Schizophrenia	NCT00733057	3	Completed
8	Adjunctive Minocycline in Clozapine Treated Schizophrenia Patients	NCT01433055	-	Currently recruiting
9	Efficacy of Pregnenolone in Patients With Schizophrenia	NCT00615511	2	Ongoing, but not recruiting participants
10	Study of a Neurocognition Enhancing Agent in Patients With Schizophrenia	NCT00894842	2 & 3	Completed
11	Pioglitazone in Alzheimer Disease	NCT00982202	2	Completed
12	Efficacy of Pulsatile IV Insulin on Cognition and Amyloid Burden in Patients With Alzheimer's Disease	NCT01636596	-	Not yet open for recruitment
13	Mechanisms of Insulin Facilitation of Memory	NCT01145482	-	Recruiting participants.
14	SNIFF 120: Study of Nasal Insulin to Fight Forgetfulness (120 Days)	NCT00438568	2	Completed
15	Randomized Phase II Trail of Ritumaximab With Either Pentostatin or Bendamustine for Multiple Relapsed Or Refractory Hairy Cell Leukemia	NCT01059786	2	Recruiting participants.

milestone-driven, cooperative agreement awards will be valid for two or three years and pair academic research groups with a selection of pharmaceutical industry compounds exploring new treatments for patients in eight disease areas, including Alzheimer's, Duchenne muscular dystrophy and schizophrenia. The NIH Common Fund provides funding for the pilot phase of these awards.

One of the projects is saracatnaib by Astra Zeneca as an anti cancer inhibiting Src family kinases (SFK) after it was found to be marginally effective. Since the drug was proved ot be safe in clinical trials the drug is intended to be tested in early stage alzeimers patients. Another compound is Sanofi's for Duchanne muscular dystrophy, Saracatanib again, for lymphangioleiomyomatosis and an endothelin antagonist for peripheral artery disease. Another unnamed Sanofi compound is being studied for calcific aortic valve stenosis. Two Schizophrenia Projects namely Eli Lilly's selective estrogen receptor beta agonist LY500307 and Pfizer GlyT1 inhibitor [39].

4. CONCLUSIONS

The field of repurposing drugs is not new to drug discovery process. Increasing cost and time required for a drug to complete the process of drug discovery, high attrition rates and also its safety is questionable even after clinical trials. On the other hand the concept of repurposing an existing drug molecule is far safer because of its decreased cost and time in development. Moreover already available pharmacokinetic and pharmacodynamic data from clinical trials make it a better option. Many drugs have already been repurposed and some are still under studies and clinical trials. Many new phases and discoveries are yet to come in this approach. This concept of repurposing drugs that have failed in human trials or else withdrawn from the market though is old but still has the potential to commercialize the field of drug discovery.

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HYDERABAD

Current Trends in Pharmaceutical Sciences

Journal homepage : www.niperhyd.ac.in/ctps

NIPER-HYDERABAD: FROM SCRATCH TO GLORY

National Institute of Pharmaceutical Education and Research (NIPER-Mohali) is the first national level institute with a proclaimed objective of becoming a centre of excellence for advanced studies and research in pharmaceutical sciences. The Government of India has declared NIPER as an 'Institute of National Importance'. It is an autonomous body set up under the aegis of Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India. After grand success of NIPER, Government of India expanded NIPERs legacy in the form of 6 new NIPERs spanning across Indian subcontinent and NIPER Hyderabad (NIPER-H) is one of them. The new NIPERs borrowed the curricula, teaching techniques, class room and lab designs, of NIPER-Mohali. But the efforts of NIPER-H and IICT, Uppal Road Tarnaka (mentor to NIPER Hyderabad) have helped to create a distinctive educational environment.

Under the mentorship of Indian Institute of Chemical Technology (IICT), NIPER-H has been able to establish itself from that of scratch to glory. In pursuance of the decision of the Government of India, NIPER – H started functioning as one of the six new NIPERs in September 2007, in the premises of IDPL R & D centre, Balanagar, Hyderabad. In terms of the MOU between the DOP and CSIR (Council for Scientific and Industrial Research), Indian Institute of Chemical Technology, Hyderabad, a reputed R & D institute under CSIR, was bestowed with the responsibility of Mentorship of NIPER-H. The institute has been functioning with the mission of developing human resource with excellence through conducting 2 year post graduate course M.S (Pharm) for the students enrolled based on the Joint Entrance Examination for all the NIPERs every year. NIPER-H is conducting the courses in various disciplines i.e. Medicinal Chemistry, Pharmaceutical Analysis, Pharmacology & Toxicology, Pharmaceutics, Regulatory Toxicology and Process technology & Process chemistry based on semester system. The students have to undertake the course work during 1st & 2nd semesters and to carry out dissertation work in reputed industry/R&D institutes like IICT, NIN, ILS and various pharma industries during 3rd & 4th semesters to get exposure to the best R&D practices. Some of the dissertation works have been published as peer reviewed papers and a good number of students have been placed through campus placement. Ph.D programme has also been initiated in pharmaceutical Sciences ie. Medicinal Chemistry, Pharmacology & Toxicology and Pharmaceutics in the year 2011 and Pharmaceutical Analysis in the year 2012. NIPER-H has also started a two-year full-time MBA program in Pharmaceutical Management from 2012 onwards. As the program has set high standards of management education in the pharmaceutical management sector, it has attained the status of a premier program in the country. Our students go for training and placement to a large number of pharmaceutical organizations. Amongst new NIPERs, NIPER-Hyderabad has taken centre stage which is further reflected in the infrastructure, research and development and research outcomes.

The story of NIPER-H in the year 2007 provides a distinct contrast to more conventional accounts of the development of Indian pharmaceutical professions in the long-established pharmaceutical centres of the India. This is especially true in light of its early development in Hyderabad, which in five years developed from scratch to a glorious institute hosting 7 post graduate and 4 PhD specializations.

Rapid development in technological and theoretical aspects has helped to transform pharmaceutical education. In pharmaceutical education this took the form of replacing traditional didactic lectures with hands on experience and research experience gained during dissertation work. In the field of pharmaceuticals, the practice of manually preparing dosage forms (tinctures, extracts, pills, powder papers etc.) has been replaced by patented medicines and industrially-produced drugs. This led eventually to increasingly sophisticate pharmaceutical chemistry and the development of the disciplines of pharmacognosy and pharmacology, revolutionizing the relationship between pharmacists and physicians.

At present all the departments of NIPER-H are equipped with most recent technologies and infrastructure and are performing research in various thrust areas like diabetes, cancer, inflammation and gene therapy. All the faculty members of NIPER-H are excel in their research activities with more than 80 peer reviewed international / national publications and presented more than 60 posters at different national & international conference / Symposia. Some of the faculty members Dr N Sateesh kumar (Department of Pharmaceutical Analysis) and Dr Ashutosh kumar, Dr VGM Naidu (Department of Pharmacology & Toxicology) were awarded with research funding from organisations such as DBT, DST, and CSIR. Some of the faculty members were also honoured with prestigious awards such as OPPI Young Scientist (Dr N Shankaraiah, Dr Nagendra Babu) and IDMA Young Pharmaceutical Analyst Awards (Dr Narendra Kumar) for their research contribution.

(Editorial Team)

NIPER HYDERABAD EVENTS

Training Programme on Instructional Design & Delivery System NITTR Chennai (March 18-22)

A training programme on Instructional Design & Delivery System was organized by NITTR at NIPER Hyderabad from 18-22 March 2013 for all the faculty members with an objective to enhance progress of the system by stating the principles of learning, preparing plans for teaching, using different effective methods of instruction, applying appropriate strategies for motivating students, to evaluate students' performance effectively and to appreciate the usefulness of micro-teaching for enriching teaching skills. This program includes training on identification of demotivated students and there by motivating, guiding and counseling them. The entire faculty were participated enthusiastically and the programme was lead by Prof. Dr. S. Mohan (Director), Dr. R. Ravichandran (Resource Centre: Course Coordinator), Dr. T. Jagathrakshakan (Associate Professor of Civil Engg: Course Coordinator). Teaching – Learning Process and Adolescent Characteristics, Instructional Objectives, Classroom Communication, Instructional Methods and Media, Basics of Evaluation Techniques, Student Motivation, Design of Test Paper, Micro Teaching Practice were included in the course curriculum.

One day seminar on Export Business Opportunities for Pharma products in Africa (Focus To Ghana) (6th May 2013)

A seminar on "Export Business Opportunities for Pharma products in Africa" was held on 6th May 2013 at NIPER Hyderabad in association with pharmexcil and Ghana High Commission. The guest of honour was Dr. P.V.Appaji, Director General- pharmexcil. He addressed on the topic Indian export to African countries. The chief guest was Mr.Iddrisu Tahiru, Counsellor in charge of political and economic relations, 'Ghana High Commission', gave a brief gist about the pharma business opportunity in Ghana. The other speaker Dr.E.Murali Darshan, professor, consultant and placement officer of NIPER Hyderabad gave a brief insight about the pharma "Why Africa? Growth and sustainability" and regarding its trade and business. Mr.Braj kumar Karna, director, Packaging Clinic and Research Institute(PCRI), Hyderabad spoke about the importance of packaging in food and pharma industry. At the end Mr.Pramodh Reddy, International lawyer, quoted the significance about the legal aspects in Africa. Bilateral talks have been carried to establish an Memorandum Of Understanding(MOU) for student exchange and faculty exchange programme between India and Ghana.

Seminar by Prof.Andrew D Miller, Institute of pharmaceutical sciences, King's college, London. (9thMay 2013)

Prof.Andrew D Miller, CEO & CSO of Global Acron Ltd delivered a presentation on **Lipid based Nanoparticles: The Foundation for Advanced Therapeutics and Diagnostics on 9thMay 2013**. Dr Miller addressed regarding optimization of the liposomes and their targeting. He explained the basics about liposomes and various lipids used for the preparation. Stress was given on the synthesis of the lipid derivatives to optimize the properties of liposomes. Also the use of such derivatives in targeting and increasing the liposomal stability was explained. For improving the liposomal circulation in blood, ABCD approach was described wherein role of stealth liposomes that surpass the reticuloendothelial system were highlightened.

1st INTER NIPER SPORTS MEET – 2013:

The inter NIPER sports meet for the first time was hosted and organized with special efforts of NIPER Hyderabad, held from 18th to 22nd Feb 2013 to explore and highlight the significance of sports along with studies. It was a unique event which promoted the interaction and communication among all the NIPER's. It was inaugurated on 18th Feb by Dr.Ramanachari, Dr.Ahmed Kamal, Dr.N.Satya Narayana and Dr.Nalini Sasthri, followed by a parade and cultural programmes. Sports like cricket, volley ball, badminton, table tennis, throw ball, caroms and chess were conducted. All the NIPER'S participated very actively and in a committed manner. NIPER HYD won the champion ship in maximum number of the events. The valedictory function was held at end of the event on 22nd Feb 2013 by Dr.Ahmed Kamal.

FUNDING/GRANTS RECEIVED

1. Experimental bioassay and pharmacokinetic evaluation of anti-cholinesterase pharmaceuticals from natural origin for the treatment of Alzheimers Disease

PI: Dr N Sateesh Kumar

Funding agency: Council of Scientific and Industrial Research (CSIR), Govt of India

2. Targeting adipocyte differentiation as a pathway for the treatment of obesity: implication in the development of obesity associated insulin resistance

PI: Dr N Sateesh Kumar

Funding agency: Department of Science and Technology (DST) under DST fast track young scientist scheme, Govt of India

LIST OF PUBLICATIONS (2011-2013)

MEDICINAL CHEMISTRY

- Copper Oxide Nanoparticles Supported on Graphene Oxide-Catalyzed S-Arylation: An Efficient and Ligand-Free Synthesis of Aryl Sulfides; Kamal, A.; Srinivasulu, V.; Murty, J. N. S. R. C.; Shankaraiah, N.; Nagesh, N.; Reddy, T. S.; Rao. A. V. S. Adv. Syn. Cat. 2013, 355, 2297–2307.
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PHARMACEUTICAL ANALYSIS

- M.V.N. Kumar Talluri, Naveen Reddy. Kandimalla, Ramesh, Raju, R. Srinivas, Development of a Validated Selective Stability-Indicating RP-HPLC Method: Identification and Characterization of major Stressed Degradation Products of Zotepine using LC-ESI-MS/Q-TOF,

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PHARMACOLOGY AND TOXICOLOGY

- Durga Prasad laveti, Manoj kumar, R Hemalatha, Ramakrishna Sistla, V.G.M. Naidu, Venu Talla, Vinod verma, Navrinder Kaul and Ravinder Nagpal. Anti-inflammatory treatments for chronic diseases: A Review. Inflammation & Allergy-Drug Targets, 2013.
- Naidu V.G.M, Atmakur Hymavathi, Bhavana devabakthuni, Anudeep Kota, Chenna Keshava Reddy S, Madhusudhana K, MVPS.Vishnu Vardhan, Prasad Kulkarni, Katragadda Suresh Babu, Janaswamy Madhusudana Rao, Ramakrishna Sistla. Antioxidant, Hepatoprotective and Cytotoxic effects of icetexanes isolated from stem-bark of Premna tomentosa. Phytomedicine. 2013 (Manuscript accepted)
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- Eameema Muntimadugu, Lakshmi SailajaDuvvuri, Wahid Khan, and Abraham J. Domb, Chapter-11, Polyanhydrides (Edited By. Sangamesh Kumbar, Cato Laurencin and Meng Deng), In Book Natural and Synthetic Biomedical Polymers (2013), Elsevier (In press).

SCIENCE DIGEST

Fish oil: a natural remedy for treatment of chronic pain:

Duke university study revealed that derivative of DHA (Docosahexanoic acid), a main ingredient of over the counter fish oil supplements, can sooth and prevent neuropathic pain caused by injuries to the sensory system. The research identified a compound called neuroprotectin D1=protectin D1, is present in human white blood cells which was named after its ability to resolve abdominal and brain inflammation. This compound not only useful in alleviating neuropathic pain but also helps to reduce swelling of nerves by inhibiting cytokine and chemokine production. It has also been identified that NPD1=PD1 can relieve pain at very low doses without any physical dependence or enhanced tolerance towards the lipid compound. (Jul 2013, Medical news today)

Gilotrif: FDA approved drug for treatment of lung cancer:

Non small cell lung cancer (NSCLC) is common and major (85%) type of lung cancers. Gilotrif (Afatinib) is recently (July 12th) approved by FDA for the treatment of non small cell lung cancer. It belongs to the family of tyrosine kinase inhibitors, and was found to inhibit mutations in the epidermal growth factor receptors (EGFR). These EGFR mutations accounts for almost 10% cases of NSCLC. Gilotrif was marketed by Boehringer Ingelheim Pharmaceuticals Inc of Ridgefield Conn. (July 2013, WebMD News from Health Day)

Middle East Respiratory Syndrome Coronavirus: MERS-CoV Treatment Effective in Monkeys

MERS Corona virus has been emerged first at Middle East region in early 2012 and spreading throughout the world by mass gatherings. The potential risk of spreading the disease is through the visit of so many Muslims to the pilgrimages in Saudi Arabia like umrah and hajj. Scientists at national institute of health (NIH) have found the pharmacological efficacy of a combinational anti viral regimen against a monkey model of MERS-CoV. They found that combination of ribavarin and interferon-α 2b, was effective against MERS-CoV infection. (September 2013, Science daily)

Blindness can be cured by using stem cell therapy:

Photoreceptors are the retinal cells that convert the light into electrical signals and send's to brain. These cells may die or damage due to some harmful reasons and may cause blindness. **Scientists at Moorfields Eye Hospital and University College London** showed the possibility of replacement of the Photoreceptors to reverse the blindness. They collect thousands of stem cells which transform into photoreceptors and injected them into the eyes of blind mice. These cells hook up with already existing cells and begin to function. But out of 200000 transplanted cells only 1000 cells start functioning. The advantages of this technique are, immune system is weak in the eye and tens in thousands of transplanted cells can improve the vision. Prof Chris Mason, from University College London told that this is a significant beak through for the cure of blindness through stem cell technology. (July 2013, BBC news health)

"Ret kinase" Target for Breast Cancer Drugs

Researchers at Friedrich Miescher Institute for Biomedical Research and the University of Basel, found that elevated levels of receptor protein was observed on the surface of human breast cancer cells which might serve as new drug target for treatment of breast cancer. Experimental studies on mice carried out by four different kinds of cell lines revealed that specific inhibitor of Ret kinase blocks the progression and metastasis of cancer. Hence targeting it with antibodies or small molecular inhibitors could serve as clinically promising approach in cancer therapy for selected group of population. (July 2013, Science daily)

A welcome addition "Tecfidera" to treat multiple sclerosis

Multiple sclerosis (MS) is an auto immune disease of the central nervous system that disrupts communication between the brain and other parts of the body. No drug provides cure for multiple sclerosis. Based on the results obtained from clinical trials a new drug "Tecfidera" with impressive efficacy and safety profile has been approved to treat adults with relapsing forms of MS. FDA revealed that even though Tecfidera may lower the white blood cells, there is no significant increase in infections. Nausea, vomiting, flushing and diarrhea were the most common side effects associated with Tecfidera. (March 2013, Web MD - Health day news)

Treatment-Related Mortality in Patients with Advanced-Stage Hodgkin Lymphoma: An Analysis of the German Hodgkin Study Group

Hodgkin lymphoma (HL) has become one of the most curable cancers in adults because of improved irradiation techniques and development of multiagent chemotherapy such as MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).The introduction of BEACOPP escalated (escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has significantly improved tumor control and overall survival in patients with advanced-stage Hodgkin lymphoma. However, this regimen has also been associated with higher treatment-related mortality (TRM). Thus, the present clinical trials are analyzing the clinical course and risk factors associated with TRM during treatment with BEACOPP escalated. With the introduction of this BEACOPP escalated therapy, the outcomes for the patients has been further improved resulting in overall survival of 86% when treated with eight cycles of escalated version, even though this escalated therapy is associated with more acute hematologic toxicity and possibly more infertility compared with ABVD. So further research and trials are required inorder to eradicate treatment related mortality and related side effects. (August 2013, J Clin Oncol;2013; 31:2819-2824.)

Association Between Red and Processed Meat Intake and Mortality Among Colorectal Cancer Survivors

At present there are more than 1.1 million colorectal cancer (CRC) survivors in the United States. Understanding the potential role of diet in this group of patients has strong clinical and population health relevance.. Recent advances revealed that Red and processed meat

intake is convincingly associated with colorectal cancer (CRC) incidence. A research team lead by Marjorie L. McCullough *et.al* examined associations of red and processed meat consumption, self-reported before and after cancer diagnosis, with all-cause and cause-specific mortality among men and women with invasive, nonmetastatic CRC. There is evidence that diet rich in red and processed meat are associated with increased incidence of CRC. It is reported that Red and processed meat consumption may contribute to higher mortality risk among CRC survivors, through promotion of micrometastases, *N*-nitrosation, oxidative damage, and effects on circulating markers of inflammation and endothelial dysfunction. So, dietary restrictions play an cardinal role in CRC survivors. (August 2013, J Clin Oncol; 2013; 31: 2773-2782.)

Explaining the Unexplainable: EGFR Antibodies in Colorectal Cancer:

Scientists reported that Cetuximab and panitumumab, monoclonal antibodies (mAbs) against the epidermal growth factor receptor (EGFR), have efficacy in the treatment of advanced colorectal cancer as single agents and in combination with conventional chemotherapy. EGFR mAbs have reported activity in various therapeutic settings and have been successfully used in combination with different chemotherapeutics in randomized trials, including irinotecan- and oxaliplatin-based regimens. Recent evidences have shown that EGFR mAbs as single agents or in combination with chemotherapy showed activity only in *KRAS* wild-type colorectal cancer. It is said that observed improvement of progression-free survival (PFS) was independent of the line of therapy in which the EGFR mAb was used and the increased response rate with EGFR mAbs in patients with *KRAS* wild-type tumors was observed even in trials that did not meet their time-related end points of PFS or overall survival (OS); and cetuximab and panitumumab had interchangeable activity. Further it is reported that addition of panitumumab to infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) to *KRAS* wild-type cancers, an EGFR mAb can indeed add efficacy to a FOLFOX backbone .Finally introduction of targeted agents in the treatment of advanced colorectal cancer was welcomed which produce improved efficacy of medical therapy that clearly could not be met. It is hoped that development of better preclinical models will produce fruitful results. (August 2013, J Clin Oncol; 2013; 30: 1735-1737)

E6 protein in blood increases risk of throat cancers:

Scientists at cancer research UK say that E6 protein, a strain of the HPV virus in blood increases risk of throat cancers by attacking the p53 protein, which protects cells against cancer. HPV enhances the risk of developing cervical, vulval, anal and penile cancers. The offered vaccination includes HPV16 and HPV18 but it is not yet known whether this vaccination could protect against oral HPV infections or oral cancers. Researchers at University of Oxford performed a comparative study and found that greater than one third of the study cases who had oropharyngeal cancers, carried antibodies to E6, a key cancer-causing proteins detected in patients' blood even when samples were collected earlier for more than 10 years before the disease was diagnosed. It has shown that less than 1% of people without cancer also carried the antibodies. It has been estimated that the patients with oropharyngeal cancers when related to those having the HPV infection had higher survival rate than people whose cancers were not linked to the infection. The HPV virus, an extremely common virus may have the chance to infect 8 out of 10 people during their life period. It spreads through oral or genital contact. Besides it was known that HPV vaccine also protects against oral HPV infections and proved to have a broader potential protective effect. Indeed much better research is required to understand more about HPV infections in the mouth so as to reduce the further consequences of HPV infection in future. (August 2013, Daily Me news)

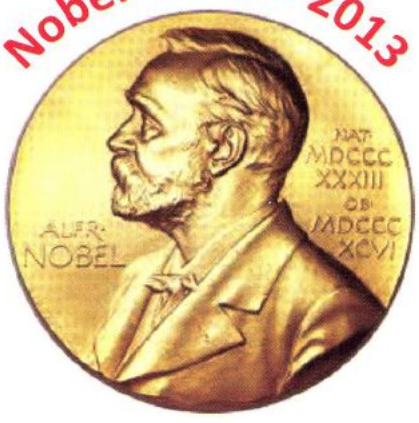
Researchers target breast cancer's energy supply:

Scientists suggest a novel approach for the treatment of breast cancer by blocking the energy supply of tumours. Molecules called cyclic peptide inhibitors were found to be having the activity of diminishing this energy supply worked out at the university of Southampton. This is estimated as an effective treatment against cancer that has become resistant to the existing current chemotherapies. It has been found that the energy generation and utilization of the glucose by cancer cells is different from those of normal healthy cells. The proteins called ctBPs were involved in breast cancer multiplication process via sticking together their by forming the pairs and aids in proliferation. These ctBPs possess a potential advantage in the selectivity aspect as they are mostly active towards cancer cells therefore considered as exhibiting low toxicity in normal cells and reduced side effects compared to present treatments. So researchers began to develop a series of compounds having the property of inhibiting formation of ctBP pairs. Among these compounds, they identified CP61 as the most effective and it is developing into a small drug like molecule which in future may indicate to treat breast cancer. Despite its usefulness it can't be formulated as a conventional tablet and is difficult to administer. So more interesting and useful research has to be done in order to get the benefits of it. (August 2013, Cancer research UK – cancer news)

UK'S super mouse yielding major discoveries in cancer research:

The super mouse (cancer resistant mice developed by using Par-4 gene) created by researchers at the University of Kentucky Markey Cancer Center, revealed a new avenue to research for preventing and/ or treating many types of cancer. A gene identified as Par-4 was discovered which selectively kills cancer cells without killing normal cells. Reports on Par-4 gene proved for its capability in creating a healthy and tumor free environment, and its down regulation affects breast cancer recurrence. The lower levels of Par-4 allow cancerous cells to survive and multiply even after the treatment. Tumor cells with high levels of Par-4 are eliminated by apoptosis. The prominence of Par-4 lies in its selectivity towards killing of cancer cells rather than normal cells. In order to make human cancerous cells vulnerable to therapy, restore the expression of Par-4 by developing safe and effective remedy is essential. Research on Par-4 further would help in understanding the complexities of cancer, especially of those that have spread from their origin to distant tissues. (July 2013, university of Kentuky news)

Nobel Prizes - 2013



The Nobel prize is a set of annual international awards given by a group of Swedish and norwegian committees for excellence in scientific and cultural contributions. Initiated in the year 1901, several prizes have been awarded worldwide to top level scientists working in the fields of physiology & medicine, physics and chemistry in addition to people working in economic sciences, peace and literature work. The Nobel prizes for the year 2013 have been announced recently. The Nobel Prize for this year in physiology & medicine was awarded to three US scientists named James E. Rothman, Randy W. Schekman and Thomas C. Südhof for their discovery of mechanism regulating cellular vesicle trafficking. The 2013 Nobel Prize for physiology and medicine has been jointly given to three scientists who have solved the mystery of cell transport system. Various products like insulin are manufactured by one type of cells and released into the blood. Another example of such substances includes neurotransmitters which are sent from one nerve cell to another. The three Nobel Laureates have discovered the molecular principles that govern how this cargo is delivered to the right place at the right time in the cell.

Noble prize in chemical sciences was offered jointly to Martin Karplus, Michael Levitt and Arieh Warshel for the development of multiscale models for complex chemical systems. This year's Nobel Laureates in chemistry took the best from both worlds and devised methods that use both classical and quantum physics. In the 1970s, Martin Karplus, Michael Levitt and Arieh Warshel laid the foundation for the powerful programs that are used to understand and predict chemical processes. Computer models mirroring real life have become crucial for most advances made in chemistry today.

The Nobel Prize in Physics 2013 was awarded jointly to François Englert and Peter W. Higgs for the theoretical discovery of a mechanism that contributes to our understanding of the origin of mass of subatomic particles, and which recently was confirmed through the discovery of the predicted fundamental particle, by the ATLAS and CMS experiments at CERN's Large Hadron Collider.

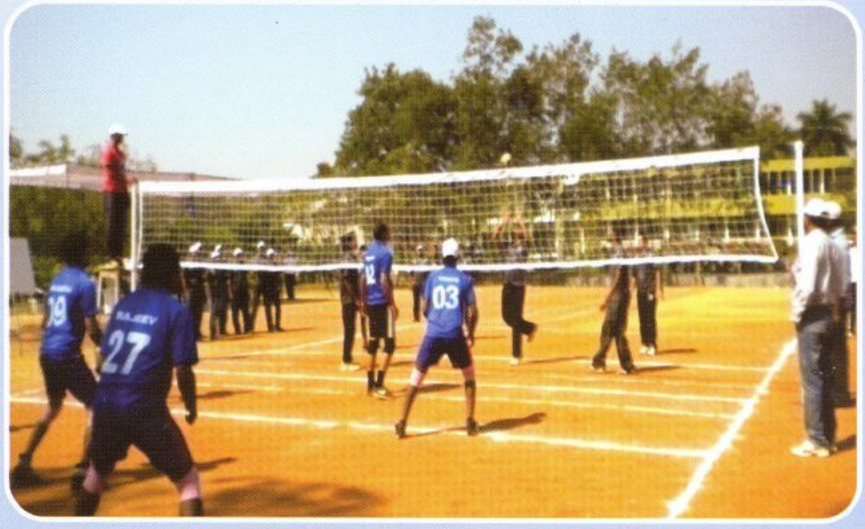
(www.nobelprize.org)

Discipline	Scientist name	Affiliation at the time of award
Physiology & medicine	James E. Rothman	Yale University, New Haven, CT, USA
	Randy W. Schekman	University of California, Berkeley, CA, USA, Howard Hughes Medical Institute
	Thomas C. Südhof	Stanford University, Stanford, CA, USA, Howard Hughes Medical Institute
Chemistry	Martin Karplus	Université de Strasbourg, Strasbourg, France, Harvard University, Cambridge, MA, USA
	Michael Levitt	Stanford University School of Medicine, Stanford, CA, USA
	Arieh Warshel	University of Southern California, Los Angeles, CA, USA
Physics	François Englert	Université Libre de Bruxelles, Brussels, Belgium
	Peter W. Higgs	University of Edinburgh, Edinburgh, United Kingdom

Inauguration of 1st Inter NIPER Sports meet at NIPER Hyderabad by Dr Ramanachari, Dr Ahmed Kamal, Dr N. Satyanarayana & Dr Nalini Sastry

Participants from all NIPER'S doing Parade after the inauguration Cermenoy of 1st Inter NIPER Sports meet at NIPER Hyderabad

Teams participating in Volley ball match at Inter NIPER Sport event



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