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Review Article

Precision Medicine and Site-Specific Drug Delivery: Consensus, Ambiguity and Challenges

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ABSTRACT

The whole idea of Precision medicine is to prevent and treat diseases that can be segregated in terms of people's individual gene variations, environment and lifestyles. Diagnosis of diseases like cancer can be done accurately with precision medicine, but an improved therapy won't be provided. The goal of drug targeting is to produce pharmacologically effective drug combo concentration at the site of a disease and keeping a minimal concentration of that same drug in other parts of the body. "Precision drugs" are coined from targeted drugs needed to draw in precision medicine into clinical practice. Putting the area of cancer research in perspective, this generalized review studies the essential requirements which are mandatory for cell/tumor-targeted drug delivery systems to work. It studies the up-to-date progression rate and concludes an optimal paradigm for drug delivery systems in the future. Precision medicine is an emerging area integrating scientific research and current clinical practice to develop a platform which can precisely guide tailor-made medical practice and can improve patient care. This will result in targeted therapy according to the needs of individual patients fitting to their genetic, biomarker characteristics and bioinformatics determining better clinical outcome. The potential of inputting the concept of precision medicine has been favored and improved by the new development of large-scale biological databases (such as the human genome sequence), proteomics, metabolomics, genomics, drug designing, protein modeling, even with mobile health technology.

INTRODUCTION:

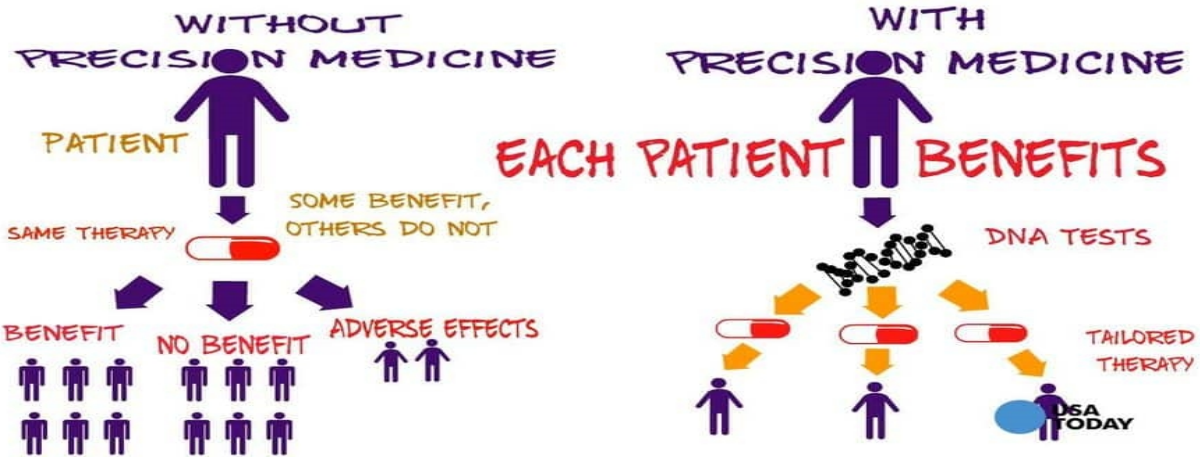
Recently the medical research area of Precision Medicine attracted headline attention when President Obama announced a $US215 million initiative to amass genetic data on about 1 million Americans, with the goal of "discovering genetic causes of disease and finding new drugs that will target dangerous mutations".Therefore one of the biggest bottlenecks for precision medicine is computational. The only way towards progress in personalized medicine is long term investment in basic sciences such as mathematics, physics and chemistry which would help us to build better technologies for better computers, materials and imaging equipment. It is high time we alerted the Federal and State governments and the corporates about the importance of investing in research projects with ultra-long term goals. The major foundation of precision medicine is the potential to develop target specific health care decisions on individual's risk basis. This establishment has been made possible by assessing genetic variability determining the susceptibility to develop a disease and likely response of medicines[1]. Another approach is moving big data which offers a possibly powerful complement to genome-based precision medicine . The big data in the form of administrative claim datasets and large clinical trial data sets have generated a precise huge amount of clinical subtypes which can help in clinical decision making.

While precision medicine initiative is slowly maturing towards its applications mainly in cancer and few other diseases, fitness and sport associated precision medicine is yet to start its journey. This is probably due to lack of interest of majority of people in their fitness or not giving the importance to the subject. However, if one of the aims of precision medicine is early prediction and prevention, physical fitness must be considered as a key component of precision medicine. Physically fit people are more resistant to disease and various fitness associated traits are known to be genetically governed. However, only few genetic markers associated with physical fitness are well established. Therefore, fitness genomics needs to be considered as an integral part of precision medicine approach and the field needs to be explored for identifying highly specific markers for various fitness associated traits towards using those markers in precision medicine[2]. Although the initiative of precision medicine may yield its greatest benefits years down the road, there should be some pronounced nearest future successes. In conjunction with the cancer study results earlier described, large research cohort studies exposed to many kinds of therapies may provide early insights into pharmacogenomics; enabling patients to be provided with the right drugs and right dose. If humans with rare loss of function mutations that protect against common diseases can be identified, it may be directed towards drug targets to a wider population. Also, observations of beneficence of using mobile health technologies may upgrade methods for preventing and managing chronic diseases[3]. The whole idea of Precision medicine is to prevent and treat diseases that can be segregated in terms of people's individual gene variations, environment and lifestyles. The current precision-medicine initiative of the US Government accordingly, is to "generate the scientific evidence needed to move the concept of precision medicine into clinical practice".

Over long periods, solely we will need to evaluate the most promising methods in much larger numbers of people over longer periods. In this perspective, we envision gathering over time a longitudinal cohort of a million or more American volunteers towards this research. These volunteers will be asked to give consent for extensive distinction of biologic specimens (cell populations, proteins, metabolites, RNA and DNA; adding whole-genome sequencing if cost friendly) and behavioral data, all connected to electronic health records. With appropriate confidential patient protection, qualified researchers from many organizations will have access to the cohort's data, so that the world most knowledgeable and experienced clinical minds can contribute insights and analysis. This information collected will also empower observational studies of drugs and medical devices and potentially fasten more rigorous interventional studies that address specific questions. The ongoing use of antibiotics provides an easy illustration of application of precision medicine. Diverging the methods physicians provide antibiotics against bacterial infections, precision medicine approach would promptly determine the sort of bacterium involved and the prescribe the most appropriate antibiotic. In the first approximation, precision medicine may provide a more accurate diagnosis of the disease such as cancer in the first approach but may not have the cause to offer an improved therapy. "Precision drugs"/ Precision medications" that are yet to be developed will be needed in targeting cells in which a precisely diagnosed mechanism drive (Fig:1). Paul Ehrlich in 1906 predicted the concept of precision drugs, stating that "soon chemists would be able to produce

substances that would target only specific disease-causing agents". The term he used was "Magic Bullets".

Figure:1 Precision Medicine Target Multiple tumors



Bioengineering and Imaging Bottleneck

Precision medicine is not only about drugs and genes as many believe. It extends to advanced biomaterials, imaging techniques, nanotechnology, etc. This is important because many diseases cannot be solved by precise drug molecules alone. Precise delivery is also important. In many cases a precise cure can be achieved only by precise removal or transplantation of a cell or its organelles. This is especially true for neurodegenerative diseases as well as 'natural' ageing[4]. Precise identification and removal of damaged neurons or repair of neuronal connections require imaging technologies with high resolution and precision. The physical removal might require precision drug delivery system or 'nano surgery'. In order to achieve all these, we require more robust technology and this in turn require several quantum jumps in fundamental sciences namely mathematics, statistics, physics and chemistry.

Drug-attachment/carrying element

So many papers have been published about drug carriers. In august 2015, a PubMed search for "drug AND carrier*" was which produced 44,070 hits. Rationale for using carriers for drugs adopts the idea that bio-distribution and pharmacokinetics of drugs can be altered by attachment to a macromolecular carrier and that the drug will inferentially follow the bio-distribution and the kinetics of the carrier. However, this is possible specifically only when the drug is released, as it must arrive, from the carrier. After this the freed drug then follow its own distribution and pharmacokinetics. Generally, such drug carriers do not have any ability specifically to interact with disease targets. What they do is reach disease targets by passive distribution and hence only a very small fraction of the administered dose arrives at the desired anatomical location. Notwithstanding many of the carriers, like the water-soluble polymers, can remain in circulation for a longer period. Such macromolecules are better attached with a meaningful amount of drugs, which alters their behaviors and make them remain in circulation.

Targeting structure

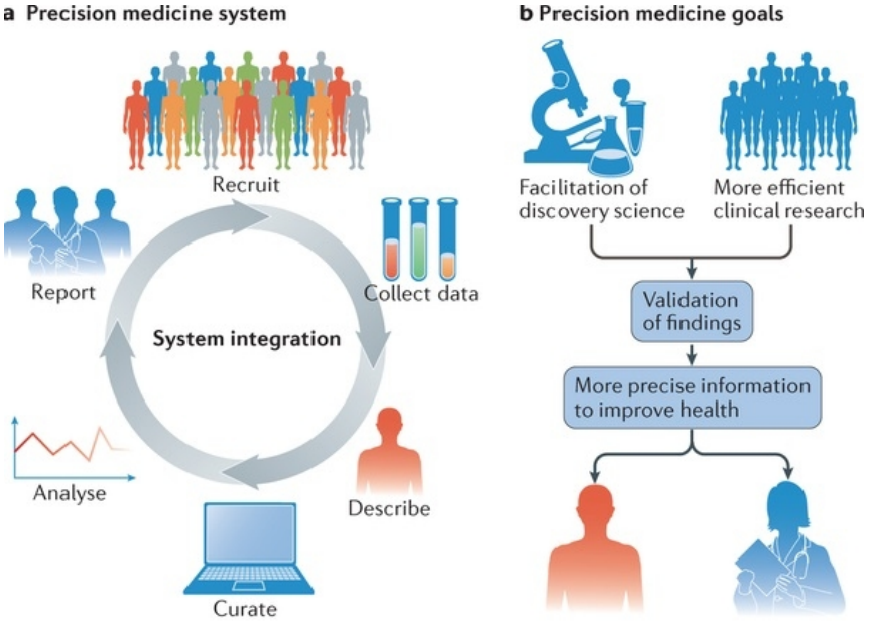
An essential prerequisite to site-specific targeting of drugs is the existence of unique molecular features, a "unique address" if you like, associated with the target of disease. Many of such drug targets are potentially available. The therapeutic target should be abundantly expressed by most diseased cells or tissues and absent from healthy tissues. Opportunities exist for utilizing unique molecular structures for targeting to various organs and tissues, including cancer molecules and tissues. Notably, antibodies (Abs) have been raised to such unique molecular structures and used as therapeutic agents. More than 20 monoclonal antibodies have been approved to date as therapeutic drugs by the US Food and Drug Administration (for example, Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab, Palivizumab, Panitumumab, Rituximab). The use of antibodies as carriers of other drugs to specific targets has been explored since antibodies exhibit many relevant properties - good solubility and stability, avoidance of removal from circulation by the liver, high selectivity and specificity, and bioconversion to non-toxic metabolites.

The drug to be delivered

Note that targeting the sites of conventional drugs that typically reach their targets of action via absorption

across biological membranes possibly cannot be effective. This is because, these drugs can diffuse away equally after they have been released at the site[5]. So drugs chosen for targeting should a) have an elevated potency (i.e. a very low pharmacodynamic concentration) and b) should also have a diminished tendency of removal (either by degradation/metabolism, diffusion or binding) from the target site after their release and in free form. Therapeutic targets should be acted on solely by new drugs with minimal effects on other biomolecules. New drugs should act on the intended therapeutic target, with minimal effects on other biomolecules. Its advisable to consider some properties of antibodies generally; poor oral bioavailability, only a partial absorption after intramuscular or subcutaneous administration, and an uneven biological pharmacokinetics. Extravasation of antibodies following systemic administration is slow as would be expected of molecules of antibody sizes. Therapeutic monoclonal antibodies i.e mAbs present high affinity and extraordinarily specific towards their targets. Nonetheless, mAbs can only approach targets on the cell surface or in the extracellular space, while most disease-specific targets disperse inside of target cells. Mechanism of action of antibody-based drug delivery will need to inculcate cellular uptake (e.g, through endocytosis). Different mathematical models suggest that binding of antigen and antibody in tumors can delay antibody percolation (Fig:2). Also, increasing antibody dose leads to better percolation and more uniform distribution. In addition, antibodies attached to drugs may be expected to evoke an immune responses leading to the generation of endogenous antibodies against the protein. Even if a completely human Abs is used for delivering a drug, the attachment of the drug to the Abs may result to the construct to be seen as a foreign protein[6]. This result to a decrease of drug-delivery effectiveness. As a result, the type and strength of an immune response to Ab-drug products must be always, taken into consideration.

Fig:2 Essential features and goals of a precision medicine system



Computational Bottleneck

However, in order to make further progress we need to know a lot more.

1) Association of genes with diseases. A great deal about the mutations, SNPs, polymorphisms.

2) Interactions between genes and gene products-the intricacies of cell signaling pathways and their cross talks.

3) Precise three dimensional modelling, structure and interaction prediction of peptides and proteins

Newer ways to design and synthesis proteins and small molecules in large scale. We are still taking baby steps in these areas. One of the great challenges faced by humanity is the huge conformational possibilities of peptides and proteins under different physical and chemical conditions. This is by and large a computational challenge. Therefore, one of the major bottle necks is our computational limitation. We need to invest heavily on the fundamental advancement of computational technologies such as quantum computing and neuromorphic chips. It may be noted that the analysis, interpretation and storage of 'big data' is only one small edge of this polygon[7].

Conclusions

Advancement of the nation's regulatory frameworks is required in achieving the goals of precision medicine. The NIH is working in hand with the Department of Health and Human services to bring the common rule; decades-old rule, originially designed to offer protection for research participants and mostly those that wishes to be active volunteers in modern science. This will help unleash the power of people to take part in innovative research methods. The FDA is working with the science community to maintain that views of genomic technology supports innovations, and also ensuring safety of efficacy of these technology, to help speed up the translation of precision medicine discoveries. Initiatives of Precision medicine possibly can offer more precise diagnosis of disease. However, "precise drugs" will need to be constructed for the diagnosis to be alternated by equally precise therapy. It is deduced from the current status of site-specific drug delivery systems that this field research need to adopt a recent paradigm that focuses on "self-targeting carriers", e.g combination of antibodies with high potent drugs specifically designed *de novo* that completely meet the specific pharmacokinetic needs of targeted drug delivery. Drug delivery mechanisms using carrier-antibodies will need not just recognition but also a cellular uptake of the designed antibody-drug.

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