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Ethnic Population Specific Drug Design

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Chemotherapy is a treatment of disease conditions with chemical compounds that was an obvious end point of most of the biological research until a separate branch launched as 'gene therapy' where genetic information could be manipulated for treatment of diseases. However, much promising 'gene therapy' field has achieved little success due to various reasons [1,2]. But the traditional chemotherapy field continues to grow and, until now the most prominent approach for new drug development. The modern chemotherapy started with the production of recombinant molecules by genetic engineering to use as drugs was pioneered by Boyer (1971) for insulin [3]. After that several hundreds of recombinant molecules such as interleukin, interferon etc were successfully produced and being used as drugs. In the next approach, disease specific genetic and genomic information were used to develop gene specific drugs. Although not many, but the first and most successful rational drug design is Gleevac, developed by Novartis for some leukemia patients against tyrosine kinase using the information of BCR-ABL translocation specific hyperactivation. In the post genomic era vast explosion of disease specific genetic and genomic information lead to emergence of numerous companies and involvement of academia for developing drugs using patient specific genetic signatures. These also led to the formulation of many directions of the field as pharmacogenomics, pharmacogenetics etc.

But the basic problems of chemotherapies remain elusive. Why a particular drug does not respond to everybody or why different individuals respond differently for a same treatment or why apparently similar individuals experience different complications for a same treatment? Most intriguing problem is that after initial response, some individuals get resistance to the drug and the symptoms relapse. The recent evidences suggest that individual genetic signature might play important role for some of these problems. Identification of genetic variation and its association with drug metabolism could indicate the outcome of drug treatment. When lung cancer patients with EGFR mutation were treated with Gifatinib with an EGFR mutation directed drug, some of the patients were resistant. Subsequent genetic analysis showed that these resistant patients tumor have a second mutation in the same EGFR gene that confers resistant to Gifatinib [4]. Similarly, genetic association studies reveal that HLA-DRB genotype is a major determinants for flucloxacillin induced liver injury [5]. Thus, genetic association studies could be incorporated for treatment of drug to treat the particular genotype carrying patients. But the most challenging part is to implement the genetic informations in drug design and chemotherapy. High density SNP microchip genotyping or whole genome sequencing data would complement the chemotherapeutic response for a specific drug to understand why the same drug behaves differently in patients with similar symptoms or a specific group of patients develop other complications.

Again, in many cases genetic signatures are mostly ethnic population specific. i.e a particular polymorphism (SNP) that is associated with a specific phenotypes vary from one population to another. In one population SNP could be monomorphic means only one form exists but could be polymorphic to other population. Thus a drug developed against the product of the risk allele carrying genes only would work in that population where this risk allele existed. This drug could be useless to other population where risk allele did not present. It is evident that carbamazepin increases hypersensitivity to only european patients due to interaction with particular genotype carrying patients that is present only in european population [6]. Thus, ethnic population specific genetic informations from all parts of the world are important prerequisite for next generation drug design and efficcacy.

Drug resistance seems to be more towards alteration of the physiology of the cell like changes in MDR (multiple drug resistance) activation or ROS (reactive oxygen species) generation in the cell. However, genetic component for ROS management or MDR are also emerging as a influencial factor for chemotherapeutic drug resistance [7]. FDA approved approximately 200 drug metabolism and transporter genes are already in considerations for many studies involving drug resistance. However, large scale association studies with these genes and drug metabolisms seem to be extremely important for specifying drug induced resistance or development of other complications and could be initiated for successful chemotherapy.

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