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Pre-Clinical Drug Research: Is it becoming a Misguided Missile?!

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Editorial

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Editorial

Therapeutics has undergone a sea change in the last millennium, with some revolutionary treatment modalities becoming available for needy patients, for instance the advent of monoclonal antibodies in cancer chemotherapy and a targeted approach to prevent left ventricular hypertrophy in heart failure. Most of these novel approaches to treatment are the result of extensive and intensive drug research at the molecular level, subsequent to the identification of targets of drug action. This is in sharp contrast to the previous techniques to identify potentially active molecules, where serendipity played a crucial role and the process was painfully tedious. High throughput screening and reverse pharmacology followed suit, with astonishing and very welcome results. It started appearing as if we had reached the zenith of optimal pharmacophore identification in pathophysiological processes, and that permanent cure of almost every disease was just at an arm's length.

The drift towards irrationality was very subtle and barely noticeable. In our zeal to find immediate solutions to disease processes, we began to target the symptoms in order to come up with revolutionary symptomatic treatment modalities! A burning example is the management of Type 2 Diabetes Mellitus (T2DM). It is known to all that T2DM is basically an outcome of a reduced response to insulin, even if the insulin levels in the body are physiologically normal. It is a perceived insulin deficiency where insulin resistance due to receptor dysfunction is the major reason for hyperglycemia, in contrast to Type-1 DM where there is an actual deficiency of insulin from the beta cells of the Islets of Langerhans. If we closely examine the time tested drugs for the treatment of T2DM, the Sulfonylureas and the Biguanides, we will see that it is only the biguanides like *metformin* which actually target the basic pathology of the disease. Sulfonylureas, being insulin secretagogues, just keep on straining the already over-functional pancreas, with an additional threat of repeated hypoglycemia if the patient is not careful of his/her meal timings. However, even now, newer sulfonylureas like *gliclazide, glipizide* and *glimepiride* are still the mainstay of treatment of T2DM. Even if this kind of therapy amounts to flogging a dying horse, we have never even thought of challenging it in this age of rational drug therapy. The thiazolidinediones like *pioglitazone* was another honorable attempt at re-sensitizing insulin receptors, but these drugs were only partially successful and further research was abandoned once the toxicity of *rosiglitazone* was established.

We began going overboard with the advent of SGLT-2 inhibitors in T2DM. Sodium-Glucose Cotransporter-2 (SGLT-2) is a protein on the epithelial cells of the proximal convoluted tubule (PCT) of the kidney, which is responsible for the simultaneous reabsorption of glucose and sodium into the blood from the glomerular filtrate. By virtue of binding to and blocking this protein, SGLT-2 inhibitor drugs like *dapagliflozin, canagliflozin* and *ertugliflozin* prevent the reabsorption of glucose back into the blood and thus cause iatrogenic glycosuria! This is ironical since the very description of diabetes had glycosuria as one of its signature signs. In short, the philosophy of achieving a reduction in blood glucose

levels "*by hook or by crook*" seems to underline the basis of the development of these drugs. In this process, the basic pathology of insulin resistance was conveniently forgotten. SGLT-2 inhibitors are now the most recognized and widely appreciated drugs for T2DM these days. Whither rationality? We are patting our backs while we continue to augment the symptomatology of this disease in the name of management, ignore the basic pathological processes of the same, and frequently end up with Urinary Tract Infections! Is this what we had bargained for? Don't we need a rethink?

What is even more painful is the way we justify the use of these drugs by incessantly coming up with reported therapeutic advantages of SGLT-2 inhibitors, which, in fact, are a result of a lowered blood sugar and have no direct attributability to these drugs, in sharp contrast to the tall claims of the manufacturing and marketing establishments. The same advantages would have been seen had we targeted the re-sensitization of insulin receptors and reversed the disease process, rather than forcing iatrogenic glycosuria as well as a false sense of victory over the disease! Such blind adherence to symptomatic therapeutics may well open a Pandora's box of irrational treatment modalities which may inflict irreversible damage to medical practice in the coming days.

Similarly, our approach towards the treatment of most chronic diseases like Bronchial asthma, hypertension, so also malignant disorders, has been merely of palliation rather than addressing the root cause of the disorder. Most of the anti-asthmatic drugs just cause transient bronchodilation, and have to be repeated almost lifelong for survival. Frequent fluctuations in the response to these drugs (especially beta-2 agonists like *salbutamol*) add to the misery of asthmatic patients. We did not even begin thinking about targeting the pathophysiology of asthma till very recently when leukotriene receptor blockers like *montelukast* and lipoxygenase pathway inhibitors like *zileuton* were identified. Unfortunately, drugs like *zileuton* fizzled out prematurely due to their toxicity. It is indeed inexplicable as to why our drug researchers have not even begun targeting the triggering mechanisms which lead to bronchoconstriction in asthma, while the medical community seems contented in bringing about transient bronchodilation and palliation for such patients. Immunotherapeutic approaches towards the management of cancer have taken a beating, especially with the advent of monoclonals. Thus, with a dogged consistency, we have failed to address the disease process and have continued to address the eventual outcome of the process. This is probably with the objective of "*pleasing*" the patient rather than "*treat*" the patient!

Renin inhibitors like *remikiren, enalkiren* and *aliskiren* instilled some hope amongst hypertensive patients, where, even if partially, the pathology of hypertension was attempted to be targeted. However, these drugs were not successful due to extremely poor bioavailability. Most of the other anti-hypertensive agents just bring about palliation in the form of blocking certain receptors like the alpha and beta adrenergic receptors, angiotensin converting enzyme, angiotensin receptors, or calcium channels. Another palliative approach is the use of diuretics. The primary question of why sodium and water are being retained in primary hypertensives has not succeeded in inspiring any interesting research question in the minds of our drug researchers! Why haven't we ever thought of identifying and reversing the basic disease process?

Gene therapy did sound like a final redemption but it got stuck in a quagmire of technical complications. Indeed, it would be pertinent to keep on attempting novel targets of drug action and not always resorting to palliation in the name of advances in medicine. Financial interests of pharmaceutical companies may also contribute towards the acceptance of irrational drugs, since short term financial gains often prompt drug manufacturers to push not so useful drugs as revolutionary discoveries. Marketing skills overwhelm rationality, and the medical community wholeheartedly welcomes such new molecules! Ironically, we call it evidence based medicine!

Thus, it is high time that we thoroughly reconsider the direction of drug research, get driven by rationality rather than commerce, by attempting to cure rather than suppress and to adopt evidence based medicine in letter in spirit, for the eventual benefit of the sick and infirmed.