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Disease-Target Drug Delivery - Science or Fiction?

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Abstract

For limiting the action of drugs to cells that carry the disease, unique molecular targets associated with the disease must be available. In the pursuit of targeted drugs, researches need to take full account of the essential conditions that need to be met for such effective human therapies to be possible. Instead, too often approaches already shown to be ineffective are being pursued. Without unique disease targets and new paradigms, cell-specific drug delivery continues to remain a science fiction.

It has been argued [1] that the term "targeted drugs" is being used too broadly to describe drugs' specificity of action. When such targeted drugs act on general pathways that are associated with both the disease and also healthy cells, their action results in a large number of often very serious undesirable side effects.

New knowledge continues to be generated about mechanisms that operate in human cells with a view that these could be exploited for developing targeted, precision drugs. For example, Zhang et al. [2] recently reported the development of a "targeted delivery method that permits specific expression of homologous Ras-family small GTPases (i.e., Ras, Rap2, and Rap1) in different subcellular microdomains, including the endoplasmic reticulum, lipid rafts, bulk membrane, lysosomes, and Golgi complex, in rodent hippocampal CA1 neurons." Their results indicate that," under physiologic conditions, homologous Ras and Rap proteins use distinct subcellular microdomains to create multiple specific signaling responses to regulate different forms of synaptic plasticity". It is not clear, however, whether any of this mechanism could be used to develop therapies that would offer an increased precision of disease-target action. Let us hope that authors' optimism [3] that this is "A Way to Make Drugs without Side Effects" leads to generating effective targeted drug delivery outcome especially in the diseases such as cancers and neurological conditions such as autism and Alzheimer's highlighted by the authors. The necessary next step for progress in this direction is to determine what molecular structures that could be targeted are uniquely associated with disease origination, progression, regression or termination.

Unfortunately, not all current research in drug targeting is ground breaking. Although it may appear intriguing, development reported by University of Mainz researchers [4-5] on "using miniature drug-filled nanocarriers to target headaches and tumors" sounds more like a science fiction. They describe their "miniature drug-filled nanocarriers to dock on to immune cells" as "miniature submarines". The suggestion that this "may lead to targeted treatment that can largely eliminate damage to healthy tissue" is no more that repeating hundreds of similar promises made in other scientific publications [6]. As it happens, Prof. Helmut Ringsdorf, an eminent researcher at the same academic institution hypothesized some two decades ago that the same could be done by attaching a drug and an antibody to a polymer [7], but gave up the idea after few years. The area of polymeric conjugates for drug delivery have been reviewed by Larson et al. [8], and by many since 1975; PubMed lists 94 reviews with "polymer drug delivery" in the title since 1975 to date.

The above less-than-critical approach to promoting science is far from unique. Science Magazine [9] reported that "nanomachines drill holes into cancer cells". It is hard to see a merit of science reporting as follows:" A stationary stator holds the machine in place while a moving rotor spins and drills across the cell membrane. The paddle like rotor, a series of three rings of carbon atoms, begins rotating 2 million to 3 million times per second when hit by ultraviolet light. On either side of the stator are arms of carbon, nitrogen, and oxygen that stretch out and grip the surface of the cell.", in particular since disrupting cell membranes, or "making holes", is a cell mechanism well recognized and studied [10], i.e., the Endosomal Sorting Complex Required for Transport (ESCRT) machinery which is an evolutionarily-conserved, multi-subunit membrane remodeling complex. Alas this is not the only time that this far-fetched parallel / analogy between electric motor and drug delivery has been used [5]. In this case, the researches aimed and hoped to "develop the rocket so it can be used in any environment, for example to deliver drugs to a target area of the body".

There are at least two key requirements that need to be put in place for targeted drug delivery to produce precision drugs i.e., effective drugs with no or minimal side effects:

1. Unique molecular structures associated with the given disease need to be identified to which drugs could be targeted, and
2. The drug to be delivered needs to have pharmacokinetic properties that would enable the drug to remaining at the target site after its delivery.

These critical conditions for success of targeting are being ignored by material scientists and others in developing targeted, precision drugs.

Antibodies have been of much interest recently both as drugs (therapeutic antibodies) and as careers of drugs. The interest has been stimulated by the ability of antibodies (immunoglobulins) to recognize and bind to unique molecule structures through a paratope (a "lock") that is specific for one particular epitope (a "key") on another biological molecules (such as pathogen, cells, proteins, etc.), allowing the two structures to bind with precision and strength. Therapeutic antibodies bind to structures that are linked to disease and modify their functionality. More than 50 therapeutic-antibody drugs have been approved by the FDA that has been labeled as being "targeted" [11]. However, in this case, most of these drugs act on the *pathways* that may play a role in the disease but not on actual disease targets, i.e., on molecular structures *uniquely associated with the disease*. Cellular pathways are generally ubiquitous and as such are functioning in both the disease and healthy cells. Consequently, altering pathways in disease cells may lead to a degree of efficacy in treating diseases but it is equally likely to

generate many, and often severe side effects. Specific recognition in this case does not result in disease target-specific drug delivery.

Similarly, antibodies have been considered as vehicles for delivering drugs. Here again, antibodies that are used do not bind to unique disease targets; and even if that would be achieved, most drugs that have been attempted to be targeted do not have pharmacokinetic properties to benefit from such delivery. So again, despite promises, claims and "targeted" label, using antibodies as drug careers does not result in an effective delivery of drugs to disease target [12-14].

Conclusion

Although "targeted drugs" and "precision drugs" are envisaged as being the future of much improved human therapy, very little consideration is being given to essential principles that need to be pursued in order to develop such effective human therapies. Technology for drugs acting, or being delivered to act specifically on molecular targets of disease is yet to be developed.

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