Editorial

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http://www.imedpub.com

Archives in Cancer Research
ISSN 2254-6081

2016
Vol. 4 No. 1:47

On Cell-Specific Drug-Delivery Development

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Received: January 29, 2016; **Accepted:** January 31, 2016; **Published:** February 02, 2016

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Citation: Petrak K. On Cell-Specific Drug-Delivery Development. Arch Cancer Res. 2016, 4:1.

The current efforts of Precision Medicine with the aim of "discovering genetic causes of disease and finding new drugs that will target dangerous mutations" [1] may prepare the ground for the "magic bullets" of Paul Ehrlich - compounds that would seek-out specific disease-causing agents [2] - to become a therapeutic reality. Precision Medicine's approach is to prevent and treat diseases that take into account people's individual variations in genes, environment, and lifestyle. Making use of Precision Medicine-generated new knowledge will require development of Precision Drugs [3].

Efforts to develop such effective technology started in early 1950s [4] but has so far met only with a very limited success. Searching PubMed for [promising drug and delivery] over the last 10 years returned 9,596 hits (2,437 of these being reviews). The fact is that existing publications offer little in a way of fundamentally new concepts. Old approaches are being re-examined often under a new name. Many promises are being made that are hardly ever followed up by further experimental data and validation in clinical studies.

There are several fundamental reasons for this perpetual failure of research efforts. Many of the existing "delivery systems" are perceived by the body as being "foreign" and are rapidly removed by the liver. Further, many of the systems are inherently non-specific with respect to the intended targets. Consequently, most of the drug to be delivered is deposited at sites other than the intended target. It is true that such delivery may alter the overall drug kinetics and may provide a therapeutic advantage (e.g., by diverting the drug from the organ of its toxicity), however, any such is not due to "cell-specific targeting".

A three-compartment pharmacokinetic (PK) model analysis of targeting efficiency by Boddy et al. [5], aiming to define conditions for developing an optimal drug-carrier complex and the choice of drug, concluded that the pharmacokinetic properties of the drug-carrier complex, rate of free-drug release, and rate of elimination determine the outcome of drug-targeting. The analysis further indicated that targeting advantages may be lost if release of free drug is not confined to the response compartment. This analysis and conclusions are relevant to cases when drug targets are located outside the central compartment, e.g., as in targeting to solid tumours. Consequently, selecting the right drug to target is fundamental for the success of drug targeting. In the vast majority of cases, existing drugs are being used in new delivery systems. In order to exert their pharmacological effect, drugs need to act on specific receptors. Most receptors are distributed broadly throughout the body, and typically both on the disease and on the healthy cells. Further, effective conventional drugs reach most of the body compartments and their action is not restricted to a specific cell type. Delivering such drugs to a specific site in the body will likely be followed by a rapid redistribution of the drug from the site. Again, some advantages may be accrued in this way due to a "controlled release" effect on the overall drug pharmacokinetics. However, for a cell-specific targeting requires the use of drugs that meet different PK requirements.

The overall outcome of drug targeting does depend on the PK requirements being met also in the systemic (central) and toxicity compartments. However, it is clear that in the target/response compartment, the overall rate drug elimination (by "escape"/transport away from the target and by degradation) must be several orders of magnitude lower than the rate of free-drug release and its binding to the intended target.

Recently, Panowksi et al. [6] stated that antibody-drug conjugates can be used successfully to deliver potent cytotoxic drugs, with the success depending on four factors - target antigen, antibody, linker, and payload. Panowksi et al. focused on improving the methods of production of conjugates. I want to add two further critical considerations. First, the form in which the free drug is released from the antibody-drug conjugate must meet the above-stated PK characteristics. Second, it is fairly standard to evaluate drug-carrier conjugates by testing their efficacy *in vivo*. However, determining efficacy (such as e.g., tumour growth, mortality) provides no information needed to improve or optimize the delivery system. Quantitative pharmacokinetic information is needed about the fate of drug in the response compartment.

Weber et al. [7] recognized in 2008 that imaging of molecular targets is crucial to the development of targeted drugs. Similarly, Neubert et al. [8] argued that quantitative information on target binding and associated PK/PD (pharmacodynamics) needs to be generated. Methodology available for quantitative analysis of

biomarkers, drugs and toxins in biological samples [9] and for autoradiography of drug distribution [10] have been reviewed recently. It is high time that these techniques are fully utilized in the process of developing Precision Drugs!

Acknowledgement

We would like to thank NIH for the support of grant (1R41HD046305).

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