



## Antibodies – The “Magic Bullets” for Drug Delivery?

Karel Petrak\*

2121 Mid Lane, Suite 538, Houston, Texas, USA

\*Corresponding author: Karel Petrak, 2121 Mid Lane, Suite 538, Houston, Texas, USA, Tel: 541147747472; E-mail: [klpetrak@gmail.com](mailto:klpetrak@gmail.com)

Received July 22, 2015; Accepted August 18, 2015; Published August 24, 2015

### Abstract

Efforts to develop clinically effective cell-specific drug-delivery technology have not as yet been successful. This prospective review gives and analyzes reasons for the lack of progress in this area, and argues that the use of antibodies as drug carriers offers the best currently available approach. For this approach to work, drugs to be delivered must exhibit the pharmacokinetic properties matching the essential requirements of cell-specific drug delivery. Examples from targeting cancer drugs are used.

**Abbreviations:** Ab/Abs: Antibody/Antibodies; CD19: Cluster of Differentiation antigen associated with B-lymphocyte Antigen; CD4: Cluster of Differentiation glycoprotein on the surface of e.g., helper T cells; DNA: Deoxyribonucleic Acid; EGF/r3: Anti-epidermal growth factor receptor; Fc: “Fragment crystallizable” of the Ab molecule; FcRn: The neonatal Fc receptor; IgG1: Immunoglobulin G1; mAb: Monoclonal Antibody; PBPK: Physiologically Based Pharmacokinetic; PD: Pharmacodynamic; PK: Pharmacokinetic; RNA: Ribonucleic Acid

**Keywords:** Antibodies; Drug; Pharmacokinetics; Pharmacodynamics

The idea of “magic bullet”, of a drug that would seek out the locus of disease and “cure” it remains to this day a fantasy, a science fiction.

In 2014, I published an article on “Targeting Drug-Delivery Systems: Promises, Promises, and More Promises. Let’s Change the Paradigm” [1], pointing out that over 3,000 publications that appeared in previous 10 years (based on a PubMed search for “target” and “drug and delivery and promise) promised new targeting drug-delivery platforms none of which had as yet “delivered” on their promises. I also pointed out that previously tested technologies (particles, liposomes, polymers, etc.) were being used over and over again, uncritically and optimistically, sometime under a new name such as “nano”. A new name might bring new funding but it does not change the outcome.

A search for “drug delivery” on PubMed in June 2015 produced 171,773 “hits”, but there is no effective targeted-drug products used in clinical practice today. Advances in biological and medical knowledge of diseases will no doubt require that effective ways of delivering therapeutic agents to specific cell populations *in vivo* will be needed to turn such knowledge to tools for preventing and curing diseases.

In related publications [2,3] I elucidated the reasons why efforts so far have not been successful, what the essential pharmacokinetic and pharmacodynamic requirements are for targeted, and in particular cell-specific delivery of drugs to work, and also suggested how this could be achieved. My solution, in a sentence is that both new drug-delivery vehicles and mainly new drugs are needed, both selected on the basis of their pharmacokinetics in the body and with respect to the site of disease.

In this current communication I want to “narrow the field” in this “race”, leave out the also-runs and “promising candidates” from my consideration and instead focus on currently most-likely winning approach. To illustrate my argument, examples from targeting anti-cancer drugs are used.

According to Espicom Business Intelligence [4], “By 2018, 19 companies are expected to have new or improved targeted drug delivery products in the market”, and that “By 2018, over 30 new products will be launched resulting in a global market for advanced targeted delivery products worth over US\$8.5 billion”

According to the Nanotechnology in Medical Devices Market by Product, Application - Global Forecast to 2019 for Nanotechnology in Medical Devices Market by Product (Biochip, Implant Materials, Medical Textiles, Wound Dressing, Cardiac Rhythm Management Devices, Hearing Aid), Application (Therapeutic, Diagnostic, Research) [5], the global nanotechnology-based medical devices market is expected to grow at a significant CAGR of around 11-12% during the forecast period (2014-2019). Targeted/cell-specific drug delivery products have not been included in these forecasts.

There are several reasons why efforts in developing drug-targeting delivery have not been successful.

### Is the research focused on the relevant issues?

Cell-specific drug delivery aims to achieve pharmacological levels of drug in the relevant cells at a chosen anatomical site, typically at the site of disease. In an earlier publication [6] we provided a mathematical definition of the conditions required for it to occur. The following general rules can be derived from this and expressed verbally as follows.

- It is essential that the drug-carrier conjugate is not removed too rapidly from circulation. If it is eliminated from systemic circulation more rapidly than it is delivered to the target site, the amount of conjugate at the target site might never be enough to provide the required concentration of free (unbound) drug. For optimal targeting, systemic elimination of the complete drug-carrier conjugate should be minimal; typically, the liver is mainly responsible for the removal of drug conjugates from the circulation.
- The release of drug away from the target site could nullify any benefits that might potentially come from delivering the drug to the target site.
- If the drug conjugate reaches the target site too slowly, the supply of free drug (as governed by its rate of release at the site from its conjugate) might never be sufficient to generate the concentration required to elicit the desired therapeutic effect at the site of action.
- The capacity of the system selected for the release of free drug from the conjugate needs to process the entirety of the drug-

carrier conjugate arriving at the target site, and doing so at a rate that ensures drug accumulation at this site.

- Only drugs that are retained at the site of delivery and action benefit from targeting. Most existing drugs would have a tendency to diffuse away from the site when converted into their free, non-conjugated form.
- The rate of elimination of free drug from the systemic circulation should be rapid relative to its escape from the target site, to ensure that the drug-delivery system will at least achieve a decrease in the drug-associated toxicity (in cases when the site of toxicity is different from the site of therapeutic effect).

### Other than research issues?

It can be argued that non-research; “organizational pressures” negatively influence progress in this field.

- In academia, researchers have a need to generate publications. It is often not desirable to give definitive and especially negative answers, and consequently change the direction of research work. It is often preferred to “spin” the projects so that more publications can be produced.
- In industry, a commercial product is the desired outcome of research and development. Drug development is a “relay” of projects being passed from one discipline/department to another; it is therefore not easy to “spot” the weak link. Further, drug delivery is often used to extend the life of successful drugs. However, drugs developed using the conventional drug-development process are very unlikely to
- Benefit from site-specific delivery (for pharmacokinetic reasons as described below). Suggesting that new drugs need to be developed specifically to suit drug-delivery requirements has not been accepted by the industry as an attractive strategy.
- Consequently, the scientific “truth” loses out to other interests. Thousands of publications that “promised” new and effective drug-delivery systems could not have all failed for different reasons; most likely the same reasons are common to all. Apart from biological “complications” such as the avoidance of recognition and removal, and molecular targets being located at sites other than the site of intended delivery (i.e., disease target), one feature nearly that all such failed promises have in common is

### The Choice of Drug – Pharmacokinetics

It should be noted that site-targeting of conventional drugs that typically reach their targets of action via absorption across biological membranes is unlikely to be effective. The reason is that these drugs can equally well diffuse away after their release at the site. Instead, efforts should focus on target delivery of macromolecular therapeutic entities such as DNA and RNA since these “drugs” cannot reach their intracellular targets by simple diffusion, and equally are less likely to diffuse away from the target site after their release from the delivery vehicle.

It is of paramount importance to pay attention to the above considerations at the start of developing any drug-carrier targeting-system.

### In vivo Testing

Fundamental information that should be generated by *in vivo* testing is data on the distribution of the drug throughout the body and

mainly a demonstration that the drug is indeed preferentially delivered to, and released at the required site, and that it stays there. It should be demonstrated that the pharmacologically required drug concentration is indeed reached and maintained at the site over time. Far too often, the “efficacy” of new delivery systems is tested *in vivo* by monitoring a disease parameter (e.g., mortality, duration of survival, etc.) and compare this to the efficacy of free drug. Even if such comparison shows that the “targeted delivery” exhibits higher efficacy or lower toxicity it provides no information on whether drug targeting to the intended site actually occurred.

With such data, PK parameters of drugs may be scaled across species, via the principles of allometry, with reasonable precision. Work relevant to this discussion is the work of Mordenti et al. [7]. In their work, the authors applied power models to five therapeutic proteins, including a fusion protein composed of CD4 and the Fc portion of an IgG1 molecule, and showed that the clearance and volume data from preclinical species could be reasonably well used to predict clinical parameters. In the absence of relevant PK data, most of reports “promising” new drug-delivery systems on the basis of animal studies are not supported by relevant scaling of the preclinical data to human applications.

### Is there a Way Forward?

In my view the currently most appropriate combination of a vehicle and a drug combines two classes of compounds – antibodies + gene fragments (RNA/DNA). The successful use of antibodies to deliver cancer drugs is not new. Rowland et al. [8] results published in 1980s “...clearly demonstrate that the administration of Ida-anti-CD19 conjugates can result in complete tumour regression in an experimental model” (sic). However, translation of this technology to humans has proven to be difficult.

I am happy to say that I am not alone in thinking that this approach is worth pursuing [9]. However, as the slow progress on this to date illustrates, this approach is not without issues that need to be addressed and resolved.

### Advantages and Limitations of Antibodies

Antibodies as such can often function as therapeutic entities. In here we consider antibodies only for carrying other drugs to their intended target.

Antibodies offer several “ready-made advantages as potential drug carriers:

- Relative “inertness” since they are recognized as “self” by the body, hence antibodies can remain in circulation for an extended period of time;
- Antibodies “home” on specific molecular structures and can thus be engineered to recognize specific, unique features including those identified as being associated with diseases of interest.

Therapeutic antibodies have been found to have several additional characteristic properties [10] that are also essential for using antibodies for delivering drugs. They have good solubility in biological aqueous media, good stability, and their biodegradation presents a low risk of producing toxic metabolites. It is an advantage when Abs is considered for drug delivery that the rate of antibody elimination from tissues is primarily determined by the convective elimination clearance and by the rates of antibody catabolism within tissue. Consequently, provided that an Ab-drug construct reaches the target cells they are likely to remain there long enough for the next stages of drug delivery to take place.

Some of their drawbacks include very poor oral bioavailability, only a partial absorption after intramuscular or subcutaneous administration, and uneven biological distribution and elimination.

Extravasation of antibodies after systemic administration is slow as would be expected for molecules of Abs size. The rate of distribution in tissues is correspondingly also slow, further slowed down in tissues that possess corresponding Ab epitopes. Mathematical models suggest that antigen-antibody binding in tumors can retard antibody percolation and that increasing antibody dose leads to better percolation and more uniform distribution [11,12].

Any exogenous protein administered systemically to humans may be expected to elicit an immune responses leading to the generation of endogenous antibodies against the protein. Even if a completely human Ab is used for delivering a drug, the attachment of the drug to the Ab may lead to the construct to be seen as a foreign protein. Limits placed by this on the amount of drug any antibody can effectively carry needs to be determined and used in appropriate scaling to humans to determine whether any given approach (i.e., an antibody and drug combination, the portion of dose reaching the therapeutic site, the amount of free drug released and its retention at the site) indeed support the assertion as “being promising”. Consequently, the type and strength of an immune response to Ab-drug constructs must be always taken into consideration.

An essential property that will determine the efficacy of antibody-drug complexes is the antibody’s drug-loading capacity. Ideally, very potent drugs so that only few molecules per antibody would need to be carried will become available. As mentioned above, selecting the right drugs will be critical for the therapeutic success of antibody-drug conjugates.

Although reports may suggest [7] that allometric power relationships may be used to predict clinical antibody pharmacokinetics, one must proceed with caution when macromolecules are involved. Assumptions underlying allometric scaling include the absence of nonlinear pharmacokinetics and species-specific clearance, which may not hold true for most antibodies. For example, in an unsuccessful attempt, allometric scaling failed to predict clearance of a murine antiEGF/r3 mAb in cancer patients [13]. This is likely because of both the low affinity of murine antibodies for human FcRn and the increased target-mediated clearance in cancer patients. Another approach for predicting drug pharmacokinetics in humans based on preclinical data is to employ physiologically based PK (PBPK) modeling [14,15]. PBPK models represent the body as several interconnected compartments, each representing an organ. The size of each compartment is based on the physical size of distribution spaces within the organ of interest, and the intercompartmental transfer functions relate to physiological processes (e.g., blood perfusion and lymph flow).

## Conclusions

Because of their size, antibodies need to be administered by injection into circulation. Their access to extra-vascular sites is principally by convective transport and is further limited by binding to tissue sites, and by rates of catabolism within cells that take up antibodies. Antibodies typically exhibit target-mediated disposition, where antibody-antigen binding influences the rate and extent of antibody distribution and elimination. Overall, most antibodies show nonlinear, dose-dependent pharmacokinetics. Consequently, accurate pharmacokinetic PK/PD models for predicting antibody safety and efficacy in humans are yet to be developed effectively to guide cell-specific drug delivery.

As gene therapy is now being successfully applied to treat human diseases [16] “gene medicines” will be an important treatment option, with antibody-drug constructs offering the best option for further development. The researchers in this field need do adopt a new paradigm that centers of “self-targeting carriers” such as antibodies and on using drugs specifically selected or developed *de novo* that fully meet the specific pharmacokinetic requirements of targeted drug delivery.

## References

- Petrak K (2013): “Targeting Drug-Delivery Systems: Promises, Promises, and More Promises. Let’s Change the Paradigm”, in *Recent Advances in Drug Delivery Research* (Editor Valerio Voliani), pp. 167-180.
- Petrak K (2012) Targeted Drug Delivery – Quo Vadis? *Drug Dev Res* 73: 59-65.
- Petrak K (2005) Essential properties of drug-targeting delivery systems. *Drug Discov Today* 10: 1667-1673.
- [http://www.espicom.com/Prodcat2.nsf/Product\\_ID\\_Lookup/00002130?OpenDocument](http://www.espicom.com/Prodcat2.nsf/Product_ID_Lookup/00002130?OpenDocument)
- Nanotechnology in Medical Devices Market by Product, Application - Global Forecast to 2019 for Nanotechnology in Medical Devices Market by Product.
- Boddy A, Aarons L, Petrak K (1989) Efficiency of drug targeting: steady-state considerations using a three-compartment model. *Pharm Res* 6: 367-372.
- Mordenti J, Chen SA, Moore JA, Ferraiolo BL, Green JD (1991) Interspecies scaling of clearance and volume of distribution data for five therapeutic proteins. *Pharm Res* 8: 1351-1359.
- Rowland AJ, Pietersz GA, McKenzie IF (1993) Preclinical investigation of the antitumour effects of anti-CD19-idarubicin immunoconjugates. *Cancer Immunol Immunother* 37: 195-202.
- Wang J, Shen WC, Zaro J (2015) (eds.) *Antibody-Drug Conjugates: The 21st Century Magic Bullets for Cancer*, Volume 17 of the *Pharmaceutical Sciences Series*, Springer.
- Wang W, Wang EQ, Balthasar JP (2008) Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 84: 548-558.
- Eger RR, Covell DG, Carrasquillo JA, Abrams PG, Foon KA, et al. (1987) Kinetic model for the biodistribution of an 111In-labeled monoclonal antibody in humans. *Cancer Res* 47: 3328-3336.
- Fujimori K, Covell DG, Fletcher JE, Weinstein JN (1990) A modeling analysis of monoclonal antibody percolation through tumors: a binding-site barrier. *J Nucl Med* 31: 1191-1198.
- Duconge J, Fernandez-Sanchez E, Alvarez D (2004) Interspecies scaling of the monoclonal anti-EGF receptor for EGF/r3 antibody disposition using allometric paradigm: is it really suitable? *Biopharm Drug Dispos* 25: 177-186.
- Wang J, Iyer S, Fielder PJ, et al. (2015) Projecting human pharmacokinetics of monoclonal antibodies from nonclinical data: comparative evaluation of prediction approaches in early drug development. *Biopharm Drug Dispos*.
- Chetty M, Li L, Rose R, Machavaram K, Jamei M, et al. (2014) Prediction of the Pharmacokinetics, Pharmacodynamics, and Efficacy of a Monoclonal Antibody, Using a Physiologically Based Pharmacokinetic FcRn Model. *Front Immunol* 5: 670.
- MacLaren RE, Groppe M, Barnard AR, Cotttriall CL, Tolmachova T, et al. (2014) Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. *Lancet* 383: 1129-1137.