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# Visions but Not False Promises Should Be Funded

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**Abstract**

Efforts to develop cell-specific drug-delivery systems have been under way for decades but have not as yet generated effective and reliable therapeutic products. The effect of repeatedly unfulfilled promises is starting to cause a decrease in funding support for research and development in this area. In this commentary, principle flaws in the current approaches are listed and discussed. Further, the manner in which approaches and paradigms for further development should change is suggested.

## Introduction

It has been argued repeatedly [1] that the approaches employed over decades for developing technology for delivering drugs specifically or at least preferentially in clinical significant amounts to the cellular targets of disease are fundamentally flawed. Very briefly, frequently missing essential components include

- A lack of disease- specific cellular and molecular targets (e.g., antigen, receptors).
- Corresponding target-specific ligands having the required binding strength.
- Drug that has adequate potency and pharmacokinetic properties.
- Drug-carrier linkage enabling timely release of the drug in its required form.
- Drug-carrier constructs having minimal non-specific interactions *in vivo.*
- Drug-carrier construct having sufficient stability away from the target site (i.e., no or minimal release of the drug away from the target to minimize toxicity and side effects).
- Drug-carrier constructs carrying enough drugs to generate the required pharmacological concentration of the drug at the intra-cellular target site.
- Adequate access to the disease-target cells.

Over the years, researchers have reported on thousands of "promising" drug-delivery systems [2] that however never came to pass. It is perhaps understandable but not sustainable that as long as funding in response to promises is being made available there has not been a pressing need to change.

The scientific argument for an urgent need to change is clear, but it is likely that this will not happen until a "hitting where it hurts" event occurs. There may be a sign that this has indeed started to happen.

As reported recently [3], BIND Therapeutics, a drug-delivery company that hoped to use nanoparticles to deliver drugs to tumors declared bankruptcy early this May.

Let us look what it is that BIND Therapeutics "promised". Their website [4] says that "At BIND, we seek to significantly improve patients' lives and treat disease by developing ACCURINS®, our novel targeted and programmable therapeutics."

What are Accurins? BIND company says that these are "targeted and programmable therapeutics that are designed with specified physical and chemical characteristics to target specific cells or tissues and concentrate a therapeutic payload at the site of disease to enhance efficacy while minimizing adverse effects on healthy tissues" [4].

"Encouragement" to the use of particles for drug delivery was given when the FDA approved in 1995 Doxil [5] that combines doxorubicin with lipid nanoparticles. Doxil uses so called "Stealth" liposomes that avoid the innate immune system defence– principally the liver. The size of these liposomes is on the upper limit (100 nm) of what is classified as a nanoparticle (i.e., the range from 10 to 100 nm), hence these particles are too large to cross the normal blood-vessel endothelium, and consequently they stay in circulation for a prolonged time. However, the notion that these liposomes can "seep out" of the leaky blood vessels often found in tumors is without experimental proof [6]. It is now important that drug-delivery developers learn from the accumulated experience generated by the clinical use of Doxil [7].

The FDA approves drugs on the basis of safety and improved benefit/risk ratio; no quantitation of "drug targeting" is required for product market approval. The mode of action of Doxil formulation can better be described as "controlled drug release" rather than "wished for" tumor targeting. However, the clinical use of Doxil product is by no means free of serious side effects [8].

BIND Therapeutics claim that their Accurins® "nanoparticles were designed to target tumors more precisely than liposome particles can. The company's lead product, BIND-014, uses a polymer particle coated with a molecule that steers the particle to a protein found in many tumors. The particle releases the chemotherapy drug it carries, called docetaxel, inside the tumor." [9].

Given that Accurins® are made up of hydrophobic polylactide-polyethylene glycol (PLA-PEG) co-polymers it is rationalized that the polymer and an active hydrophobic drug form a particle core while the hydrophilic PEG part of the polymer is anticipated to be positioned at the particles' surface and evade innate immune system by the same manner as Stealth liposomes. Since the size of Accurins® particles is typically 100 nm [10] their ability to enter tumors in therapeutically meaningful numbers and release the pharmacologically effective amount of the drug is very much in question. Accurins® nanoparticles are fundamentally not different from Doxil liposome particles (apart

from being given a currently popular "nano" label). It is fair to argue that if drug-delivery developers repeat the same thing they should not expect a different result.

Reported early tests in animals and small clinical trials suggested that the BIND-014 delivery system was safer than docetaxel alone and generated a US$70.5 million initial public-offering funding, only to be followed later by disappointing clinical trials.

Such outcome is by no means unusual in drug research and development. Results in animal models may predict likely toxicity of new investigational drugs in humans but not so well their efficacy, even for relatively "simple" low molecular-weight compounds. The unreliability of animal models is amplified when drug-delivery systems that are typically composed of multiplicity of components are evaluated.

The manner in which BIND Therapeutics has been promoting its technology [4] has become endemic to the drug-delivery field. Instead of providing information about the characteristics, properties and capabilities of the technology supported by strong and relevant data, it offers a list of "wished for" outcomes yet to be achieved – for example "targeted and programmable therapeutics", "designed with specified physical and chemical characteristics to target specific cells or tissues", and "concentrate a therapeutic payload at the site of disease", etc.

National Cancer Institute, on its website [11], lists a large number of "targeted therapies" that have been approved by the FDA and are currently available to treat cancer. It defines the term "targeted therapies" as drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer". In this context the term "targeted drug" should not be understood to mean that drugs are actually delivered to the intended target of disease. More often than not, a biological mechanism is "targeted", i.e., the drug developer intents to influence a mechanism that is either known or assumed to play a role in the initiation or progression of a given disease and to derive a therapeutic benefit this way. In this case, the drug is likely to act on the given mechanism anywhere in the body and not solely at the site of disease (i.e., both at the normal and cancerous tissues). In fact, for a vast majority or perhaps all of the drugs listed on the website there are no data in the drug-approval packages confirming that cell-specific drug delivery has been achieved. Further, so called "targeted cancer therapies" can have substantial side effects [11].

The field of cell-specific drug delivery would much benefit from adopting a new, "disruptive" rule–namely, NOT to initiate human clinical studies until data have been gathered in animal models demonstrating that significant cell-specific drug delivery has been achieved. The actual value of "significant" would depend on the overall bio-distribution of the drug and the consequent benefit/risk ratio–the higher the ratio of the amount of drug at the site of disease to the amount of drug at sites of toxicity the better. But above all, new approaches to developing cell-specific drug-targeting systems need to be found and implemented.

Visions deserve support and should be funded but not false promises based on faulty rationales.

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