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Targeted Therapeutics and Nanodevices for Vascular Drug Delivery: Quo Vadis?

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Summary

This issue of the journal is dedicated to targeted delivery of therapeutics in the vasculature, an approach that holds promise to optimize treatment of diverse pathological conditions ranging from ischemia and tumor growth to metabolic and genetic diseases. From the standpoint of drug delivery, circulation system represents the natural route to the targets, whereas its components (blood and vascular cells) represent targets, carriers or barriers for drug delivery. Diverse nanodevices and targeted therapeutic agents that are designed and tested in animal and early clinical studies to achieve optimal and precise spatiotemporal control of the pharmacokinetics, destination, metabolism and effect of pharmacological agents will be discussed in this introductory essay and subsequent critical reviews in this series.

Keywords

liposomes; nanocarriers; endothelium; erythrocytes; cell adhesion molecules

In pharmacological sciences, the term “targeted therapeutics” conventionally refers to the agents that relatively specifically interfere in functions of their molecular targets—enzymes, ion channels, transcription factors, mediators, and other biomolecules involved in the disease process. However, therapeutic effects of all drugs (even those with specific targets for action) will benefit from achieving spatiotemporal control of their action by providing site-selective delivery and initiation and/or termination of their activity in desirable areas of the body: pathological sites, tissues, cells, and subcellular compartments. Furthermore, somewhat paradoxically (but in retrospect not entirely contraintuitively), drugs with highest specificity and potency, such as biotherapeutics (*e.g.*, enzymes and tools for genetic interference including siRNA), in fact require site-selective delivery at nanoscale level to exert their effects. Thus, a relatively young (by standards of established disciplines such as pharmacology) and rapidly growing field has evolved a few decades ago, focused on devising, exploring and employing drug carriers (*e.g.*, liposomes, micelles, polymers, and polymeric nanocarriers), targeting moieties (*e.g.*, antibodies and other affinity ligands), stealth technologies, molecular probes, and other approaches to achieve targeted drug delivery and effect, a Holy Grail of modern medicine.

This field transcends disciplines of medicine, pharmacology, bioengineering, chemistry and biochemistry, biotechnology, immunology, molecular and cellular biology, nanotechnology

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and imaging, among others. In addition to efforts in academia (concentrated primarily in the schools of medicine, pharmaceutical sciences, and engineering), the pharmaceutical and biotech industry invests increasing resources and efforts in this direction. The number of disclosures in this area has grown exponentially since the early 1990s. Protected intellectual property in this sector now represents a significant share of the bio/pharma enterprise. Collectively, these developments are paving the path for the ultimate translation of laboratory findings into the clinical domain.

One way to localize effects of a drug is to administer it locally, directly to the pathological site. In fact, local delivery of drugs and drug carriers including drug-eluting implants and stents represents a tremendously active area of research and clinical application. This approach allows deployment of agents via oral, dermal, airway, ocular, vaginal, and rectal routes, and also using local injections (*e.g.*, intracranial, cardiac, and tumor injections). Furthermore, therapeutic and diagnostic agents and their carriers (*e.g.*, stents) can be deployed in selected vascular areas via catheters. However, when location of the pathological site is unknown, or inaccessible for local delivery means, or pathological process is not local, the systemic drug delivery is needed.

Of course, oral administration is preferable to avoid injections, but at the present time efficacy of delivery of many agents, especially biologicals, via gastrointestinal tract is, mildly put, suboptimal. Denaturing conditions and limited permeability of the digestive system pose especially difficult challenges for oral delivery of labile biomolecules and complex submicron scale drug delivery systems aimed at directing drugs to the site of their desirable action. Packaging drugs into carriers protecting cargo en route and facilitating permeation of mucosal, epithelial, and other biological barriers may help to obviate the need for intravascular injections. Review by Mahmud et al. in this issue provides an example of such an approach, using polymeric filomicelles for drug delivery in the pulmonary vascular compartment via the airways. Nevertheless, at the present time, direct intravascular injection remains the most useful route for administration of drugs and drug carriers in the circulation, offering a natural delivery pathway to reach diverse therapeutic targets.

Modern drug delivery systems have multifaceted functions including protection of the body from the drug and vice versa, optimization of time window for the effect, site-specific delivery to desired area in the body, and, if necessary, to a proper cellular compartment—plasmalemma, cytosol, vesicular organelles, mitochondria, or nucleus. Approaches and techniques pursued in the design and studies of targeted therapeutics include “classical” phospholipid liposomes and a plethora of newer types of nanocarriers, PEG-based stealth technology, affinity ligands and their conjugates, and recombinant proteins and their fusions. Research efforts in this area have also focused on the identification of cell-specific target determinants, understanding and exploiting mechanisms of intracellular delivery, pharmacokinetics and dynamic interactions of targeted therapeutics, carriers and probes with biological barriers, and normal and pathological components of the organism and cells—both intended targets and unintended bystanders or cleaners.

Vascular drug delivery is one of the key rubrics of targeted therapeutics and nanodevices. First, the cardiovascular system itself is a common and important target for medical interventions in ischemia, inflammation, thrombosis, myocardial infarction, bleeding disorders, vascular and pulmonary maladies, stroke, and other conditions primarily involving its key components: heart, blood, and vessels. Second, many (if not all) disease conditions localized outside the vascular compartment involve cardiovascular system, secondarily: diabetes, tumors, pneumonia, asthma, and neurological and gastrointestinal diseases. Finally, vasculature is a natural route of drug delivery to all targets—tumors, neural system, and glands. Therefore, advances in vascular targeted therapeutics and

nanodevices support progress in treatment of all diseases, because of both the utility of common principles and modalities (*e.g.*, biocompatible nanocarriers) and importance of the vascular system for delivery to diverse therapeutic targets.

Starting from the pioneering work of Paul Erlich, who proposed to create “Magic Bullets” by conjugating toxic drugs with antibodies a century ago, the field of targeted therapeutics evolved in the last century mostly in the realms of oncology. The need to localize dangerous effects of toxic antitumor agents is obvious and compelling, especially for drugs delivered via the vascular route. However, in the last few decades, increasing efforts are dedicated to targeting imaging and therapeutic agents for management of nononcological conditions: inflammation, ischemia, thrombosis, bleeding and stroke, among others. Targeted therapeutics for treatment of these conditions have both commonalities and differences with their oncologic counterparts. Many aspects of targeting (therapeutic goals, adverse effects, target molecular determinants, delivery routes, etc.) and the pathophysiological context for interventions (pathological mechanisms, organ systems, drugs, etc.) differ in oncologic *versus* heart, lung, and blood domain. For example, concerns of targeting selectivity are paramount in treatment of cancer, because drugs are toxic and off-target side effects are dangerous. On the other hand, damaging side effects inflicted to the target cells (*e.g.*, via activation of immune system) represent a bonus in the oncologic realms. In opposite, many nononcologic drugs are not especially toxic (*e.g.*, anti-ischemic, antioxidants, enzyme replacement therapies, and modulators of angiogenesis) and may actually exert beneficial systemic effects. Here, the selectivity of targeting is of a secondary importance, whereas harmful side effects toward the target cells (*e.g.*, vascular endothelium and blood cells) must be thoroughly avoided.

The present collection of reviews provided by leading experts in their fields introduces some ideas, modalities, and approaches for vascular drug delivery. They include such basic, yet novel aspects of nanodevice design as control of their geometry parameters—size, shape, and plasticity, which dramatically modulate behavior of the carriers in the circulation, cellular uptake, and intracellular trafficking (1). For decades, spherical carriers (in particular, liposomes) dominated the majority of studies. However, new methods for carrier formulation have provided carriers of diverse geometries, with some displaying advantages over their spherical counterparts. For example, recent animal studies revealed that asymmetrical elongated nanodevices exert prolonged circulation time and enhanced specificity of interaction with the target cells (2). Reviews from Discher and DeSimone labs illustrate this novel aspect of nanotechnology, promising to change our way of drug delivery via vascular, pulmonary and, perhaps, other routes.

The quest for more advanced carriers will never cease and likely yield more sophisticated and exotic objects, such as carbon nanotubes and multilayered stealth nanoparticles. Future studies will define their utility and limitations for practical medical applications. However, even the current arsenal of nanodevices is already quite extensive. It includes liposomes, polymeric and nonpolymeric carriers, micelles, dendrimers, magnetic particles, and natural components of blood. Some of these carriers (*e.g.*, liposomes and red blood cells) are being tested or already used in the clinical practice. Historically, in the early 1970s, RBC drug delivery was proposed and explored for enzyme replacement therapy well prior to the use of liposomes (3). However, technical and regulatory issues and safety concerns related to blood-born pathogens decelerated this area of research in the beginning of the HIV era in the 1980s. Nevertheless, novel approaches of drug delivery using RBC—vascular carriers designed by the Mother Nature and ideally suited for intravascular route-produce very encouraging results in animal and clinical studies (4, 5). Reviews by Biagiotti et al. and Carnemolla et al. introduce this approach.

In addition, endothelial cells lining the vascular lumen represent arguably one of the most important targets and barriers in drug delivery (6). In many cardiovascular, pulmonary, and neurological conditions (*e.g.*, ischemia, inflammation, thrombosis, angiogenesis, oxidative stress, and stroke), therapeutic and diagnostic agents should be targeted to endothelium. Identification of specific determinants and epitopes on quiescent and pathologically altered endothelium for prophylactic and therapeutic interventions in a plethora of diseases including inflammation and tumor growth is a hot area of research, employing modern high-throughput approaches of phage display and proteomics (7–9). A review by Kowalski et al. illustrates some modern concepts of targeting anti-inflammatory drugs and biotherapeutics to inflamed endothelium. In a closely related article, Swaminathan et al. offers the analysis of the dynamic parameters of anchoring carriers coated with affinity ligands to target endothelial cells helping to understand how flow, surface density of the anchoring molecule, and design of the carrier govern vascular targeting.

Reviews by Carnemolla et al. and Chorny et al. further extend the horizons of vascular drug delivery in the realms of targeted agents for management of thrombosis and arterial poststent stenosis, respectively. The first article introduces a new series of recombinant fusion proteins anchoring thrombolytic agents on endothelial surface, for short-term thromboprophylaxis in the vascular areas predisposed for inflammation, blood stagnation, and thrombosis. The newest iterations of this class of targeted antithrombotic agents include mutant recombinant prodrugs that are activated locally by thrombin, which provides almost ideal spatiotemporal control of the antithrombotic effect (10). The second approach involves delivery of antiproliferative and protective agents to the sites of angioplasty using magnetic nanoparticles that accumulate in the stented vessel.

Finally, discovery and exploitation of natural and induced cellular pathways for intraendothelial and transendothelial drug delivery provided by caveolar and other mechanisms holds promise to revolutionize drug delivery to variety of vascular and extravascular therapeutic sites (11, 12). This topic is illustrated by reviews from Molema and Malik Labs, focused on cytosolic delivery of siRNA into endothelium and using caveolar endocytosis for drug delivery into and across vascular endothelium. The latter aspect, targeted drug delivery to extravascular compartments in given areas in the vasculature, is of global importance for the optimization of treatment of cancer and many other dangerous maladies. Taken in the context of other ideas and approaches presented in this issue, it epitomizes the significance and promise of vascular drug delivery. Answering the question posed in the title of this introductory note, enthusiasts of the field may dare to say: "*Per aspera—ad astra*." Translating figuratively, this means that vascular targeting will optimize drug delivery to therapeutic sites of diverse locations and size, despite biological and technical barriers. In all, the potential biomedical benefits of this approach are difficult to overestimate.

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