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Lymphatic drug delivery: therapy, imaging and nanotechnology☆

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The lymphatic system represents a relatively untapped biological highway to deliver targeted drug molecules, nanoparticle drug-conjugates, imaging agents, vaccines and gene therapies. The applications of this delivery route are ideal not only for cancer therapeutics, but also in circumstances where pharmacokinetics of the circulatory system lack the dynamics to deliver a sustained-release drug or imaging agent. In the past, lymphatic drug delivery has been hampered by both physical constraints and inadequate drug-design technology. With recent advances in targeted-drug discovery, nanotechnology, and nanoscopic polymer conjugation techniques, drugs can be tailored for preferential delivery through the lymphatics. This issue of ADDR provides a cutting-edge overview of how the lymphatics can be harnessed for multiple drug-delivery applications. The articles compiled in this issue highlight the major areas of lymphatic drug delivery starting with an understanding of the physiology of the lymphatic system, to its biology and pathophysiology related to the changes that occur with infection, injury and cancer. As malignancy is a seasoned traveler of the lymphatic highway, the applications of delivering chemotherapeutics to tumor-bearing tissues and lymph nodes represent a novel strategy to boost drug levels to cancer cells and allow an enhanced interaction between the drug and tumor that surpass what many systemic or targeted therapies can achieve.

The first article reviews the role of the lymphatics in cancer metastasis and chemotherapy. The discovery of specific markers for lymphatic endothelium and growth factors that stimulate and promote lymphatic growth has led to a significant renewal of research into the lymphatic system. The lymphatic system, previously thought to play a passive role in cancer metastasis, is now known to play an integral role in the metastatic spread of disease. Knowledge of the growth factors and endothelial markers of lymphangiogenesis and lymphatic cancer spread has allowed for elucidation of the mechanisms mediating lymphatic cancer metastasis and thus provides novel therapeutic targets in malignant disease.

Current lymphatic imaging modalities with visible dyes and radionucleotide tracers offer limited sensitivity and poor resolution; however, newer tools using nanocarriers, quantum dots, and magnetic resonance imaging promise to vastly improve the staging of lymphatic spread without needless biopsies. Concurrent with the improvement of lymphatic imaging

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agents, has been the development of drug carriers that can localize chemotherapy to the lymphatic system, thus improving the treatment of localized disease while minimizing the exposure of healthy organs to cytotoxic drugs. Dr. Nune and colleagues review in their article the use of various nanoparticulate and polymeric systems that have been developed for imaging and drug delivery to the lymph system, how these new devices improve upon current technologies, and where further improvement is needed.

Dr. Bouvet and colleagues review recent efforts in imaging the interaction of cancer cells and the lymphatic system. Fluorescence imaging has allowed for visualization of lymphatic delivery and trafficking of cancer cells and therapeutic agents. Antibody-fluorophore conjugates and fluorescent-protein-labeled cancer cells play an important role in understanding the interaction of cancer cells and the lymphatic system. MECA-79-antibody-fluorophore conjugates can identify lymph nodes, trastuzumab-fluorophore conjugates can localize specifically to HER2-expressing cancer cells, VEGFR-2 and VEGFR-3 antibodies can inhibit lymphatic hyperplasia and cancer cell seeding into the lymphatic system, and anti-LYVE-1-fluorophore conjugates can clearly delineate the lymphatic system and allow in vivo visualization of RFP-expressing cancer cell trafficking. The use of dual-photon imaging and red-shifted fluorophores can increase the depth capabilities of fluorescence imaging allowing more non-invasive imaging of the interaction of cancer cells and the lymphatic system. The combination of these technologies with target-specific antibodies provides an evergrowing understanding of the critical interplay between cancer cells and the lymphatic system.

In a review by Drs. Porter and Kaminskas, the lymphatic system can be targeted using dendritic polymers called dendrimers. Dendrimers are unique biomaterials that are constructed by the stepwise addition of layers (generations) of polymer around a central core. Dendrimers are macromolecular polymers that can be constructed with a range of molecular weights with low polydispersity and with a polyfunctional surface that facilitates the attachment of drugs, contrast agents and functional moieties such as PEG or targeting agents. Dendrimers have many properties that make them ideal candidates as lymph targeted delivery systems. Specificity for lymphatic access is dictated by differences in the endothelial architecture of lymph and blood vessels. Dendrimers provide an attractive opportunity to promote lymphatic targeting, since they can by synthesized to provide sufficiently high molecular weight to promote lymphatic transport and can also be surface modified or tailored to manipulate targeting and pharmacokinetic properties. In particular, appropriate modification may promote both drainage from the injection site and uptake into the lymph, abstraction into the lymph nodes, transport into the systemic circulation and ultimately ongoing circulation between the systemic circulation and the lymphatics.

In addition to dendrimers, liposomes and engineered solid lipid nanoparticles are important carriers for lymphatic drug delivery. Dr. Cai and colleagues review the role of lymphatic chemotherapy for patients with metastatic cancers. Recurrence is frequent in many cancers, especially those diagnosed at advanced stages. The failure to address these cases is due in part to occult disease residing in the deep tissues and distant lymph nodes and dose-limiting toxicities of existing protocols that prevent patients from receiving full recommended regimens. Lymphatic therapy using drug-encapsulated liposomes and solid lipid

nanoparticles emerges as a new technology to provide better penetration into the lymphatics where residual disease exists. It can be used in the clinic either as a neoadjuvant to achieve early disease control, or be administered post treatment to serve as a cleanup therapy to eradicate micro- and nano-metastases, preventing cancer recurrence. In addition, these nanoparticle formulations provide a number of advantages for delivery of poorly water-soluble, unstable, and cytotoxic drugs, to the lymphatic system. By optimizing the preparation procedure and choosing the proper administration route, significant enhancements in bioavailability and lymphatic uptake can be achieved.

Drs. Pal and Ramsey review the role of the lymphatic system in the immune response with respect to vaccine trafficking. Vaccines are designed to generate strong immune responses to a particular antigen delivered to the body thereby imparting immunity against a dangerous infectious agent. They discuss the role of the lymphatic system in vaccine-activated immunity and some of the recent advances made at improving vaccines. Emerging technologies will continue to provide a more complete picture of vaccine trafficking processes, and improvements in biomaterials and drug delivery systems will bring to fruition new strategies for designing safer, more effective vaccines. It remains clear that continued research in the area of vaccine trafficking by leukocytes and the factors that regulate them is necessary as the field strives to develop the next generation of vaccines against diseases such as cancer, AIDS, malaria, and tuberculosis.

While the lymphatics are located throughout the body, intestinal lymphatics play an important role, particularly in drug absorption and delivery from oral agents. Intestinal lymphatic transport, as reviewed by Dr. Yanez and group, has been shown to be an absorptive pathway following oral administration of lipids and an increasing number of lipophilic drugs, which once absorbed, diffuse across the intestinal enterocyte and while in transit associate with secretable enterocyte lipoproteins. The increasing development of highly lipophilic drugs coupled with the increasing interest in understanding the mechanisms by which drugs access the lymph is cause for a newly found interest in intestinal lymphatic drug transport. It has been recognized as a suitable alternative to enhance bioavailability and systemic exposure of high liver first-pass metabolized drugs as it initially gains access to the systemic circulation without passing through the liver. Multiple formulation approaches are being developed to enhance the lymphatic transport of drugs, but also to have a better understanding at the cellular level of the digestion, uptake, intracellular metabolism, and packaging of food-derived lipids and drugs into chylomicrons, their intestinal lymphatic drug transport process and enterocyte metabolism, and how they are impacted by the co-administration of various formulation-derived lipids and excipients.

Lavasanifar and colleagues review cancer vaccine formulations for targeting dendritic cells with PLGA. Currently only two prophylactic cancer vaccines and one therapeutic cancer vaccine are approved by the FDA for human use. Their review describes the rationale behind the choice of dendritic cells as the target for delivering vaccine components. Different mechanisms by which the dendritic cells can uptake, process and present vaccine antigens are described. Toll-like receptor (TLR) ligands play a crucial role as potent immunostimulatory adjuvants in cancer vaccine formulations. Monophosphoryl lipid A (MPLA) is one of the most promising candidates of TLR ligand's family. The rational and

expected outcomes of simultaneous delivery of antigen and adjuvant to dendritic cells using particulate vaccine delivery systems such as PLGA nanoparticles is described including an overview on the application of lipid and polymer based nanoparticulate delivery systems for the development of therapeutic vaccines.

The last article explores the role of the lymphatics in translational research applications for cancer imaging. First the modalities available for lymphatic imaging are examined ranging from early modalities, such as ultrasound to more modern techniques such as positron emission tomography (PET). The remainder of the article is dedicated to describing newer cutting-edge modalities currently in development and their potential uses for translational cancer imaging including photoacoustic imaging, quantum dots, and nanocarrier MRI contrast agents.

Significant progress has been made in the last decade with regard to development of promising technologies to harness the lymphatic system for both imaging and transport of drug compounds. As nanotechnology is advanced, prior barriers to drug delivery are overcome allowing improved targeting and delivery options for improved cancer therapy and enhanced imaging of metastatic disease. Dendrimers, nanocarrier vaccines, and quantum dots have provided clinicians and researchers with novel tools to fight disease and cancer. The future of lymphatic drug delivery holds great promise as a field and ongoing research continues to push the envelope of cancer therapy and our ability to limit drug toxicity and improve human health worldwide. We hope you will enjoy this issue of ADDR and that it stimulates further interest in this exciting field.