DRUG DELIVERY TO LYMPHOID CELLS OF IMMUNE NETWORK

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- Tissues relating to the lymphatic system.
- A thin, yellowish fluid, called lymph fluid, travels throughout the body. The lymphatic system helps control fluids in the body.
- **Lymphocytes** are white (leukocytes blood cells) that provide an immune response that attacks specific kinds of nonself cells and foreign substances (antigens).

TWO MAJOR CLASSES OF LYMPHOCYTES

- **T cells** originate in the bone marrow, mature in the thymus gland. T cells attack self cells that have been invaded by pathogens, abnormal self cells (such as cancerous cells), or nonself cells (such as those that might be introduced in an organ transplant).

- **B cells** originate and mature in the bone marrow. When B cells encounter an antigen (a toxin, virus, or bacterium), they produce plasma cells and memory cells.

- **Plasma cells** release antibodies that bind to the antigen and inactivate it.

- **Memory cells** circulate in the lymph and blood with the capacity to produce additional antigens for future encounters with the same antigen.

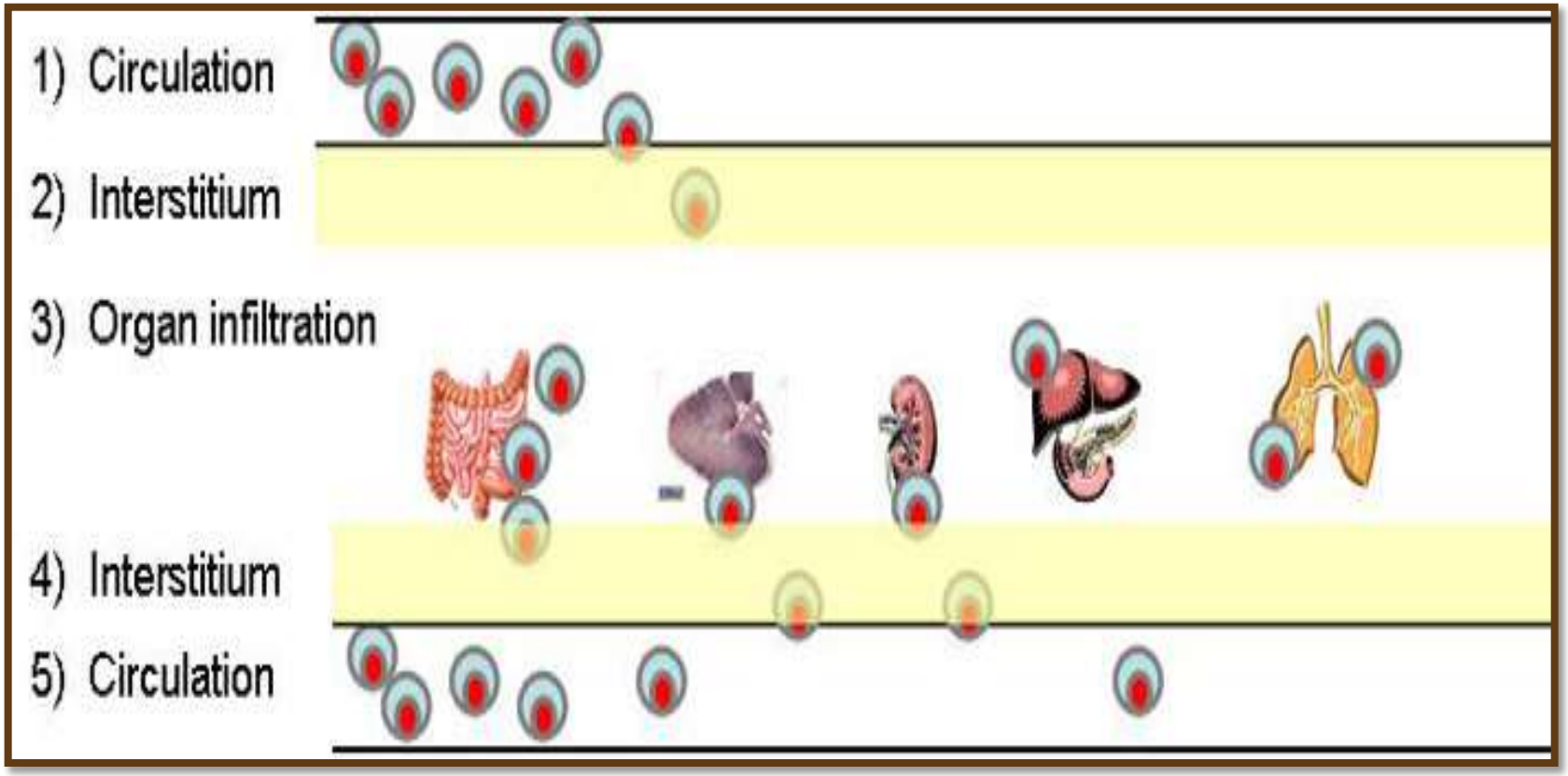
NANOSYSTEMS FOR IMAGING AND DRUG DELIVERY TO T CELLS

T-cell response defines the pathogenesis of many common chronic disease including diabetes, rheumatoid arthritis, and transplant rejection.

Nanosystems can be used for simultaneous tracking and drug delivery to those cells. Because of their versatility, these systems combine specific receptor targeting with an imaging agent and drug delivery.

MIGRATION OF T CELLS

- In healthy individuals, these cells traffic from circulation to tissue, then to lymphatics and back to circulation.



- Nanosystems that bind to these targets in a specific manner may offer a powerful approach to imaging the T cells' movement and delivering a therapeutic drug dose.

- The ideal nanosystems, therefore, must possess certain properties (eg, small size for internalization, multivalent attachment for enhanced avidity of interaction with cells, visibility by invasive and noninvasive modalities, high drug dose–carrying capacity, control over drug release, safety) to allow for translational applications in humans.

TRACKING T-CELL TRAFFICKING AND MIGRATION

- A variety of cellular imaging techniques have been developed to track the distribution and locomotion of T cells in vivo .

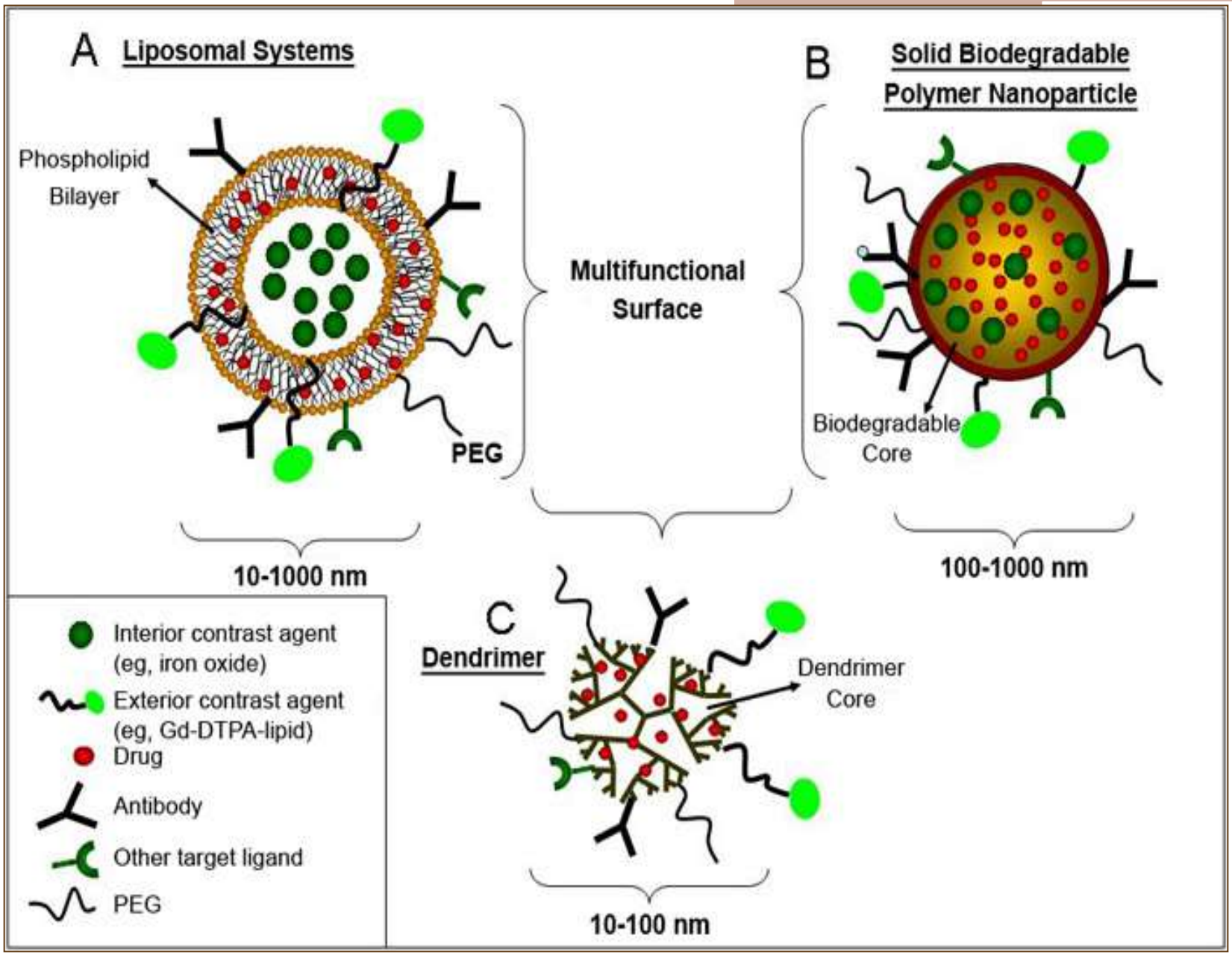
- Different imaging systems available, magnetic resonance (MR) imaging offer the best potential for noninvasive imaging deep into tissue, high sensitivity, and spatiotemporal resolution through the use of appropriate contrast agents.

- The 2 most widely used contrast agents for cellular tracking are **gadolinium-based agents**, which are T_1 contrast agents that cause positive contrast enhancement and provide brighter images on accumulation in the target site.

- **Superparamagnetic iron oxide particles**, which are T_2 contrast agents that give negative contrast enhancement and thus darker images in areas of accumulation.

Nanosystems have been developed that can potentially achieve this drug delivery

- Liposomal-based systems
- Macromolecular systems such as dendrimers
- Solid nanoparticles, such as those fabricated from biocompatible polymers


A Liposomal Systems
Phospholipid Bilayer
PEG
10-1000 nm
Multifunctional Surface
B Solid Biodegradable Polymer Nanoparticle
Biodegradable Core
100-1000 nm
C Dendrimer
Dendrimer Core
10-100 nm
Interior contrast agent (eg, iron oxide)
Exterior contrast agent (eg, Gd-DTPA-lipid)
Drug
Antibody
Other target ligand
PEG

NANOSYSTEMS & LIPOSOMAL SYSTEMS

- Liposomes are composed of amphiphilic phospholipids and cholesterol into bilayers encapsulating an aqueous interior.
- These can be formulated into small structures (between 80 and 100 nm) that encapsulate either hydrophilic drugs in the aqueous interior or hydrophobic drugs within the bilayer.
- Encapsulation is achieved using a variety of loading methods, the pH gradient method (used for loading vincristine) or the ammonium sulfate method (used for loading doxorubicin).
- liposome surface can be engineered to improve its properties. Thus, the most surface modification is the incorporation of the hydrophilic polymer polyethylene glycol (PEG), which serves as a barrier preventing interactions with plasma proteins, thus retarding recognition by the reticuloendothelial system and enhancing the liposome circulation lifetime.

MACROMOLECULAR SYSTEMS: DENDRIMERS

- Dendrimers are monodisperse polymers distinguished by their repeated branching structure emanating from a central core. This branching of dendrimers, leads to a geometric growth of the polymer that can nearly approximate a sphere with increased branchings or higher generations (generation 6 or above).

- The branching suited for entrapment of a variety of small molecules such as drugs. dendrimers have been used for a large number of applications, including drug delivery and contrast enhancement in MR applications.

- Polyamidoamine (PAMAM) dendrimers, synthesized by the repetitive addition of branching units to an amine core such as an ammonia or ethylene diamine, are widely used for drug delivery and imaging applications.

- Dendrimers have been exploited for targeting and visualization of a variety of tissue and cell types: by conjugation to folic acid for targeting tumors, prostate-antigen-specific antibodies for targeting the prostate, and peptides for targeting vascular endothelium and intestinal epithelium.

SOLID BIODEGRADABLE NANOPARTICLES

- Solid biodegradable nanoparticulates fabricated from natural constituents such as proteins or lipids or synthetic polymers have been widely studied for targeted drug delivery to different types of cells.

- Emerging applications are now beginning to use some of these systems for imaging purposes.

- These systems are based on either natural systems such as proteins conjugated to MR contrast agents or artificial polymers incorporating paramagnetic agents.

- The most widely used types of synthetic polymers, are aliphatic polyesters
  - **hydrophobic poly(lactic acid) (PLA),**
  - **the more hydrophilic poly(glycolic acid) (PGA),**
  - **copolymer, poly(lactide-co-glycolide) (PLGA).**

- The drug can be encapsulated by hydrophobic entrapment to conjugation to the polymer, providing further versatility in dosing.

- The physiologic compatibility of PLGA and its homopolymers PGA and PLA have been established for safe use in humans.

- These materials have been used for more than 30 years in various human clinical applications, including drug delivery systems.