Nanocarriers for targeted drug delivery

Benefits and challenges of nanotechnology for medicine

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Nanocarriers

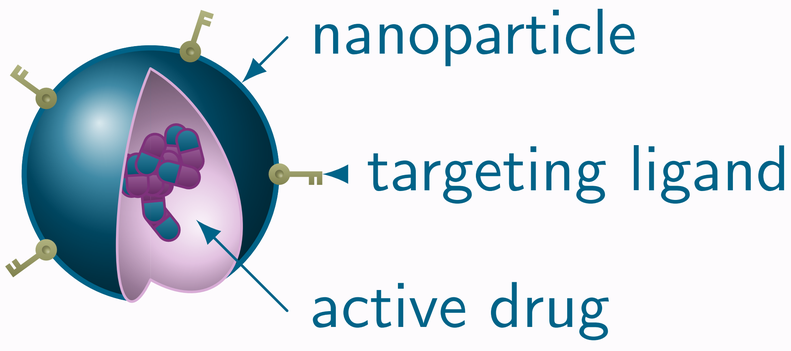

Figure 1: *General structure of a nanocarrier, including the optional active targeting ligands.*

A nanocarrier is a biocompatible nanoparticle encapsulating a drug, with size of the order 1 nm to 100 nm. The general structure of a nanocarrier can be seen in Figure 1.

Nanocarriers provide a range of improvements over free drugs, including reduced toxicity and immunogenic response; longer circulation time; and improved solubility.

This is achieved using encapsulants with a hydrophilic surface; typically phospholipids or polymers which form stable single layer micelles and bilayer liposomes suspended in water and blood. Some encapsulating nanoparticles are illustrated in Figure 2. Drug conjugates are distinct in that the active drug is covalently bonded to a protein, polymer or antibody.

Polyethylene glycol (*PEG*) is a hydrophilic polymer which has been shown to mask immunogens such as the phospholipids used to build liposomes [1], resulting in a new class of nanoparticles—immunoliposomes.

However employing nanocarriers for drug delivery raises additional challenges: new toxic side-effects; biodegradability; the cost and complexity of formulation.

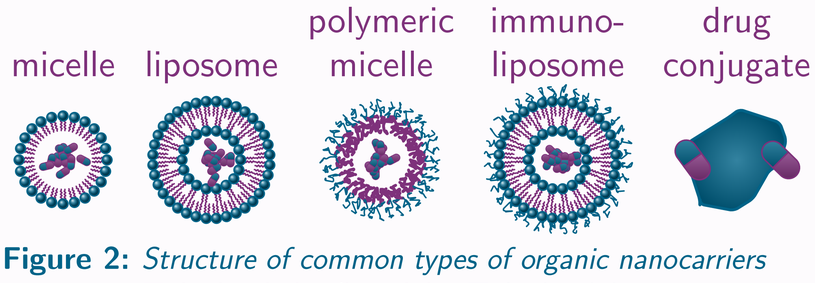

Figure 2: *Structure of common types of organic nanocarriers* ■ *hydrophobic/lipophilic,* ■ *hydrophilic*

Targeted drug delivery

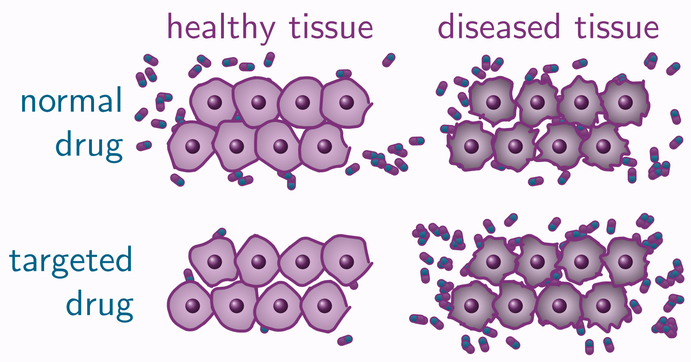

Figure 3: *Effect of drug distribution in healthy and diseased tissue when using drugs targeted to a specific diseased tissue*

The goal of targeted drug delivery is to maximise therapeutic benefit and minimise side-effects by increasing the concentration ratio of the active drug in the diseased tissue compared to healthy tissue.

The textbook example of targeted drug delivery is chemotherapy for tumour treatment.

Targeted drug delivery can be divided into three categories: first generation passive targeting, next generation stimuli-responsive targeting and active targeting.

Passive targeting

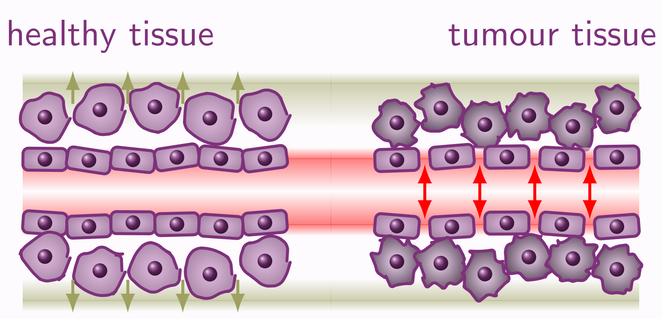

Figure 4: *Lymphatic system drainage and blood vessel permeability in solid tumours*

Passive targeting is dominated by the enhanced permeability and retention effect (EPR effect) whereby nanoscale particles can accumulate preferentially in solid tumours, first noticed by Maeda *et al.* [2].

Figure 4 highlights the differences between healthy and tumour tissue. Permeable blood vessels in solid tumours let nutrients and nanoscale particles easily cross the endothelium. Padera *et al.* discovered rapidly proliferating cancer cells compress lymph vessels [3], retaining nanopaticles by preventing the tumour from easily draining.

The EPR effect forms the basis for the first generation of approved nanomedicines [4], but it has its limits.

Solid tumours are heterogeneous: nanocarriers cannot uniformly penetrate deep into solid tumours—Jain and Stylianopoulos describe methods for overcoming this barrier [5].

Smaller tumours may not develop the abnormal vascular systems necessary for the EPR effect to dominate. Next generation stimuli-responsive and active targeting drugs can address this.

Stimuli-responsive targeting

Passively, nanocarriers are allowed to break down at the target site releasing the drug, but efficacy can be improved using stimuli triggered release.

Internal stimuli are bioindicators of disease and locality, including pH, temperature, redox potential and enzymes.

For example, solid tumours have been observed with a lower pH than healthy tissue [6, 7]. pH-responsive nanocarriers are detailed in Figure 5.

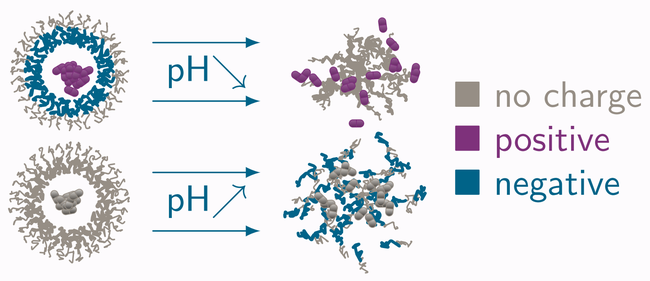

Figure 5: *Polymeric micelles with pH-responsive polymers that readily protonate as pH falls, or deprotonate as pH increases, resulting in destructive charge imbalances [8]*

External stimuli can be applied electric or magnetic fields, ultrasound, heat and light.

Hyperthermia can be induced by applying direct heat until the tumour reaches 40 °C to 45 °C [9, 10]. Alternatively iron-oxide containing nanoparticles can be used to convert oscillating magnetic fields into heat [11]. Temperature-responsive liposomes are illustrated in Figure 6.

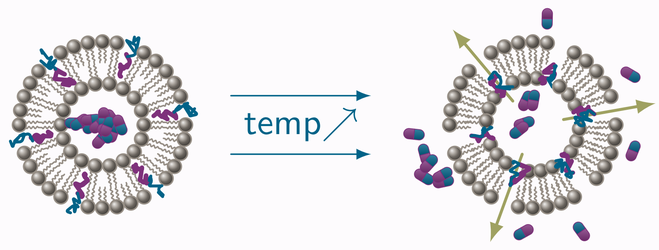

Figure 6: *Liposomes modified with thermosensitive polymers which deform at hyperthermic temperatures, disrupting the liposome barrier [12, 13]*

Active targeting

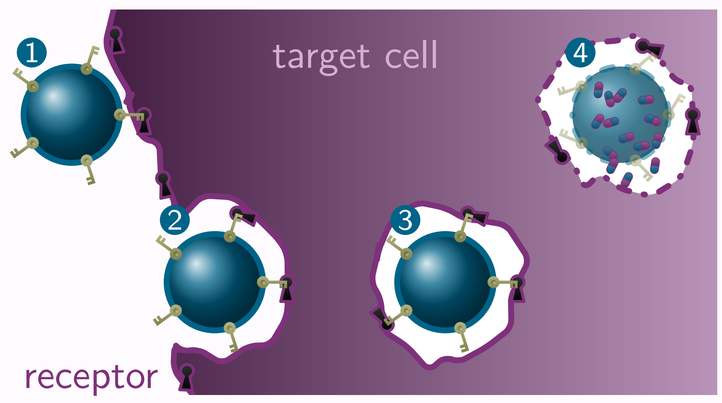

Figure 7: *Receptor-mediator endocytosis. In order: nanocarrier binding ❶, endocytosis ❷, endosome transport ❸, and drug release ❹*

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