Nanocarriers for targeted drug delivery

Benefits and challenges of nanotechnology for medicine

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ENGI4131 Advanced Semiconductor Devices

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Nanocarrier delivery systems

Structure, types and features

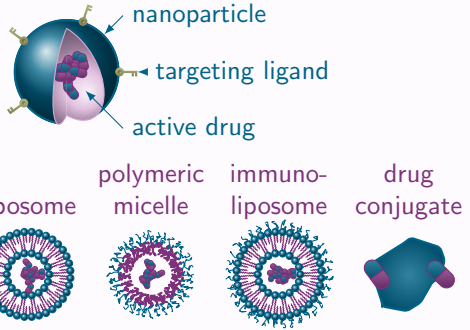

Figure: *Structure of common types of nanocarriers* ■ *hydrophobic/lipophilic,* ■ *hydrophilic*

Definition: nanocarrier

- Biocompatible nanoparticle encapsulating a drug

Characteristics

- Nanometer scale
- Biodegradable
- Non-immunogenic
- Long half-life
- Low toxicity
- Hydrophilic
- Soluble

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Targeted drug delivery

How is targeted drug delivery effective?

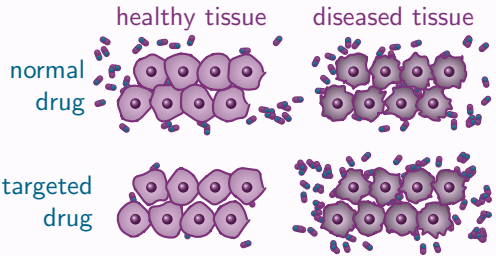

Figure: *Goal is to increase drug concentration ratio for diseased tissue*

Targets diseased tissue

- Maximise therapeutic effects
- Minimise effective drug dose
- Common targets are solid tumours, inflamed and infected tissue

Avoids healthy tissue

- Minimise toxic side-effects

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Enhanced permeability and retention effect

Basis for **first generation** nanomedicines [1]

Illustration of the EPR effect

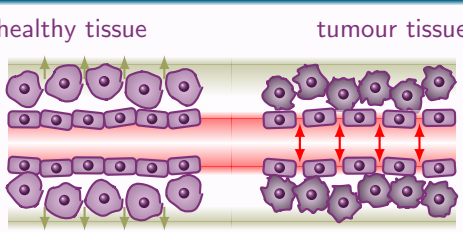

Figure: *Lymphatic system drainage and blood vessel permeability in solid tumours*

Definition: EPR effect

- Tendency for nanoparticles to accumulate in solid tumours [2]

Accumulation procedure

1. Molecules leak from blood into tissue due to enhanced vascular permeability
2. Blocked lymphatic system due to dense rapidly growing tumour cells [3]
3. Large particles become trapped

[1] A. Wicki *et al.*, *Journal of controlled release* **200**, 138–157 (2015).
[2] H. Maeda *et al.*, *Journal of controlled release* **65**, 271–284 (2000).
[3] T. P. Padera *et al.*, *Nature* **427**, 695 (2004).

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Internal stimuli-responsive nanocarriers

Example

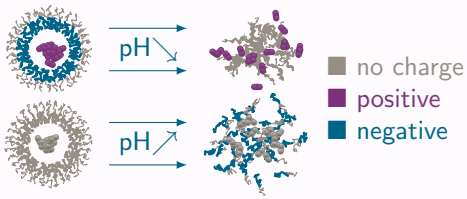

Figure: *Polymeric micelles with pH-responsive polymers for electrostatic release [4]*

Bioindicators used to trigger release

- pH level
- Redox potential
- Enzymes
- Temperature

Target sites for pH-responsive nanocarriers

- Tumours have been observed with lower pH than healthy tissue [5, 6]
- Individual organelles within the cell maintain their own unique pH [1]

[1] A. Wicki *et al.*, *Journal of controlled release* **200**, 138–157 (2015).

[4] T. Sun *et al.*, *Angewandte Chemie International Edition* **53**, 12320–12364 (2014).

[5] I. F. Tannock, D. Rotin, *Cancer research* **49**, 4373–4384 (1989).

[6] L. E. Gerweck, K. Seetharaman, *Cancer research* **56**, 1194–1198 (1996).

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External stimuli-responsive nanocarriers

Example

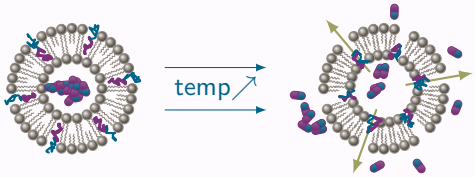

Figure: *Liposomes modified with thermosensitive polymers for controlled release [7, 8]*

Mechanisms used to externally trigger release

- Electromagnetic fields
- Heat
- Ultrasound
- Light

Induced local hyperthermia

- Target temperature is 40–45 °C [9, 10]
- Direct heat can be applied to target
- Magnetic fields can be used to heat iron oxide nanoparticles at target [11]

[7] T. Ta, T. M. Porter, *Journal of controlled release* **169**, 112–125 (2013).
[8] K. Kono, *Advanced drug delivery reviews* **53**, 307–319 (2001).
[9] A. Jhaveri *et al.*, *Journal of controlled release* **190**, 352–370 (2014).
[10] S. Ganta *et al.*, *Journal of controlled release* **126**, 187–204 (2008).
[11] F. Scherer *et al.*, *Gene therapy* **9**, 102 (2002).

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Nanocarriers with surface ligands

Receptor-mediated endocytosis of nanocarriers

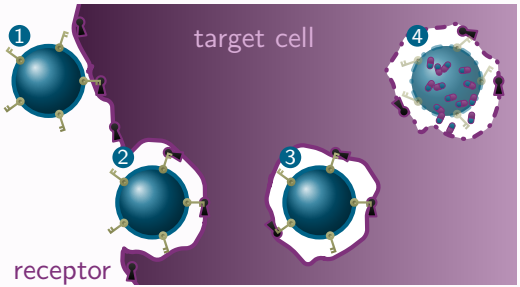

Figure: *Nanocarrier binding* ❶, *endocytosis* ❷, *endosome transport* ❸, *and drug release* ❹

Definition: active targeting

- Targeted drug delivery to specific cell types by encouraging cell uptake

Cell uptake procedure

1. Passive targeting delivers nanocarrier to solid tumour, *eg.* via EPR effect [2]
2. Surface ligands on nanocarrier bind to surface receptors on target cell
3. Cell absorbs nanocarrier via receptor-mediated endocytosis [4]

[2] H. Maeda *et al.*, *Journal of controlled release* **65**, 271–284 (2000).

[4] T. Sun *et al.*, *Angewandte Chemie International Edition* **53**, 12320–12364 (2014).

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Nanocarrier chemotherapy drugs on the market

Doxil®/Caelyx® [12]

- *Peg*ylated liposomal *doxorubicin*
- Immunoliposome using *polyethylene glycol* (*PEG*) stealth coating
- Passively targeted *doxorubicin*
- Reduced cardiac side effects [1]
- Clinical trials are exploring actively targeted variations [13]

Abraxane® [14]

- Nanoparticle *albumin*-bound *paclitaxel*
- Protein-drug conjugate—*albumin* is a common transport protein in blood
- Passively targeted *paclitaxel*
- Improved solubility [1]
- Unavailable on NHS from 2015–2017, partly due to cost [15]

[1] A. Wicki *et al.*, *Journal of controlled release* **200**, 138–157 (2015).
[12] M. Harrison *et al.*, *Journal of clinical oncology* **13**, 914–920 (1995).
[13] C. Mamot *et al.*, *The lancet oncology* **13**, 1234–1241 (2012).
[14] N. Desai *et al.*, *Clinical cancer research* **12**, 1317–1324 (2006).
[15] National Institute for Health and Care Excellence, [Accessed: 2018-11-30] (https://www.nice.org.uk/guidance/ta362).

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Thank you, any questions?

1. A. Wicki *et al.*, *Journal of controlled release* **200**, 138–157 (2015).
2. H. Maeda *et al.*, *Journal of controlled release* **65**, 271–284 (2000).
3. T. P. Padera *et al.*, *Nature* **427**, 695 (2004).
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15. National Institute for Health and Care Excellence, [Accessed: 2018-11-30] (`https://www.nice.org.uk/guidance/ta362`).

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