

***In vivo* Delivery of Gene Therapy to Tumours**

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Cancer-specific viruses are able to replicate tumour cells and destroy them [1]. Early clinical trials show encouraging anti-cancer activity with regression of single tumour nodules. The technique is limited to isolated tumours because the virus is unable to spread between the disseminated tumour masses. Unfortunately, most common cancer types present with multiple metastatic tumors, which are delivered via the blood stream of the host. Virus particles are generally not compatible with intravenous administration because they are rapidly cleared by the liver and the bodies defence mechanisms.

The group led by Dr Len Seymour in the Department of Clinical Pharmacology at Oxford, has devised a novel way of treating virus particles with polymers in order to ensure the particles are less susceptible to attack by the host immune system [2]. These polymer coated vectors are able to circulate in the blood stream for sufficient time to reach distant tumours [3].

The leaky vasculature typical of tumours lends itself to accumulation of virus particles delivered via the blood stream. Unlike the continuous endothelium of most normal tissues, the endothelium of tumour capillaries is discontinuous with gaps between cells [4]. Fluid and particles can leave the blood stream through these gaps and enter the tumour stroma (area between capillary and tumour cells). Small molecules such as water percolate through the tumour structure and leave through draining blood capillaries. Large particles are trapped in the tumour stroma by a network of extracellular proteins effectively filtering and concentrating virus particles [5].

Although this effect has been reported qualitatively, little quantitative information can be found in the literature. In principle, the relationship between number of virus particles in the blood stream and rate of movement through the endothelial 'gaps' can be calculated. However there are a number of important parameters that have to be considered such as the viscosity and pressure of the blood, size and frequency of the gaps, interaction of virus particles with blood components.

Questions

The Study Group participants are asked to focus on providing answers to the following questions.

1. Due to the laminar flow properties of fluid moving through a capillary, particles have a tendency to concentrate in the central region of flow. What is the most likely distribution of virus particles (100 nm) across the diameter of the capillary (5000 nm) and how is this affected by flow rates?
2. The gaps in the endothelial walls of tumour capillaries can vary in number and size. How does gap size (50-1000 nm) and frequency of gaps affect the rate of particle (100 nm) escape from the capillary lumen?
3. How does the presence of blood cells (~ 50 % of blood volume) affect the calculations?

References

1. Thorne, S.H. and D.H. Kirn, *Future directions for the field of oncolytic virotherapy: a perspective on the use of vaccinia virus*. *Expert Opin Biol Ther*, 2004. **4**(8): p. 1307-21.
2. Fisher, K.D., et al., *Polymer-coated adenovirus permits efficient retargeting and evades neutralising antibodies*. *Gene Ther*, 2001. **8**(5): p. 341-8.
3. Green, N.K., et al., *Extended plasma circulation time and decreased toxicity of polymer-coated adenovirus*. *Gene Ther*, 2004. **11**(16): p. 1256-63.
4. Feng, D., et al., *Pathways of macromolecular extravasation across microvascular endothelium in response to VPF/VEGF and other vasoactive mediators*. *Microcirculation*, 1999. **6**(1): p. 23-44.
5. Seymour, L.W., *Passive tumor targeting of soluble macromolecules and drug conjugates*. *Crit Rev Ther Drug Carrier Syst*, 1992. **9**(2): p. 135-87.