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Bacteriophage: From applications in infectious diseases to targeted delivery systems for brain tumours through the blood-brain barrier

Current treatments for brain tumours have faced major challenges including lack of tumour selectivity and the blood-brain barrier (BBB). Development of a selective delivery system for brain tumours would play a major advance in the treatment of these tumours. For instance, successful exploitation of numerous therapeutic agents depends, essentially on the development of non-invasive nucleic acid delivery platforms. Indeed, gene therapy is promising in this disease and brain tumours were the first to be treated by clinical gene therapy but success has been limited by the inefficiency of vectors and by the BBB. We have used bacteriophage (phage), bacteria virus, to develop tumour targeted systemic vectors. Phages have a historic safety profile as they have been administered to human over many years to treat infectious diseases. Importantly, the filamentous M13 phage is able to traverse the BBB. However, phage has no strategies to deliver genes to human cells. We reported a bacteriophage vector, as hybrid genome between two single-stranded DNA of human adeno-associated virus (AAV) and filamentous M13 phage, termed AAV phage or AAVP, in which gene expression is under the control of AAV genome. We and independent groups reported efficacy of selective intravenous cancer gene therapy, with the RGD4C-AAVP displaying RGD4C ligand to target the tumour specific $\alpha_v\beta_3$ integrin receptor. To validate our systemic delivery platform for brain tumours, we showed the ability of the phage vector administered intravenously to home selectively to human glioblastoma (GBM), in preclinical models, through the BBB by binding the $\alpha_v\beta_3$ integrin, subsequently delivering a recombinant rAAV genome that delivers a suicide gene therapy in tumour cells, angiogenic endothelial cells and GBM-derived stem cells. Combination with a low dose of temozolomide (TMZ) enhanced gene delivery/therapy by using a tumour specific promoter from an endogenous gene associated with GBM resistance to TMZ chemotherapy. These findings provide evidence that bacteriophage is a promising delivery platform for use in targeted treatment in neuro-oncology.

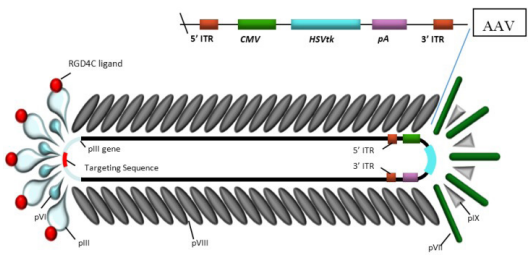

Figure: Structure of the hybrid vector AAV/phage (AAVP) developed by Hajitou et al. (1). The particle contains a chimeric genome of a mammalian transgene cassette flanked by inverted terminal repeats, 3' ITR and 5' ITR, of AAV-2 and the genome of M13 filamentous bacteriophage. The outer capsid belongs to the M13 phage and hence lacks tropism for mammalian cells. The capsid contains a major coat protein pVIII and four minor coat proteins pIII, pVI on one side and pVII pIX on the other. The av-integrin binding ligand, RGD4C, is expressed on the pIII minor coat protein of AAVP in order to allow ligand-directed targeting of the tumor vasculature and tumor cells.

Recent Publications

1. Asavarut P and Hajitou A (2014) The phage revolution against antibiotic resistance. The Lancet Infectious Diseases 14(8):657-778.
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3. Hajitou A, Trepel M, Lilley C E, Soghomonyan S, Alauddin M M, Marini F C, 3rd, Restel B H, Ozawa M G, Moya C A, Rangel R, Sun Y, Zaoui K, Schmidt M, von Kalle C, Weitzman MD, Gelovani J G, Pasqualini R and Arap W (2006) A hybrid vector for ligand-directed tumor targeting and molecular imaging. Cell 125(2):385-98.
4. Frenkel D and Solomon B (2002) Filamentous phage as vector-mediated antibody delivery to the brain. Proceedings of the National Academy of Sciences of the United States of America 99(8):5675-9.
5. Dubos R J, Straus J H and Pierce C (1943) the multiplication of bacteriophage in vivo and its protective effect against an experimental infection with Shigella Dysnteriae. The Journal of Experimental Medicine 78(3):161-168

Biography

Amin Hajitou completed his PhD at the University of Liege, Belgium, where he acquired extensive experience in delivery technologies for therapeutic nucleic acids. Then he did his Postdoctoral training in the world leading MD-Anderson Cancer Center in Texas-USA, where he gained expertise in bacteriophage (phage)-guided gene delivery and phage display technologies *in vitro* and *in vivo*. Importantly, he designed a novel hybrid phage vector for targeted nucleic acid transfer to cancer. The hybrid phage, published in Cell 2006, showed first success of systemic gene targeting to cancer *in vivo*. His team and independent groups reported efficacy of intravenous cancer gene therapy in rodents and pet dogs with naturally occurring cancers. In 2008, he established his research team, as a Lecturer, at Imperial College, then became Senior Lecturer in 2013 and Reader in 2016. His research team has become a leading authority in phage-guided delivery systems to cancer including brain tumours. His leadership in the field has resulted in various awards for his research and a Royal Decoration by his Majesty the King of Morocco, in 2015.

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