

THE DEVELOPMENT OF BIOHYBRID PLATELET-BASED DRUG DELIVERY VEHICLES FOR POTENTIAL TREATMENT OF ISCHAEMIC STROKE

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RESEARCH ABSTRACT

Ischaemic strokes are caused when areas of the brain are deprived of oxygen, due to an interruption of blood flow that may be caused by a blood clot. The current ischaemic stroke treatment methods have many associated limitations that impede their use. Nonspecificity of the treatment and damage to the blood-brain barrier (BBB) are two examples of major limitations. In an attempt to overcome these limitations and develop a system that may improve the likelihood of positive treatment outcomes, scientists have suggested that a targeted thrombolytic approach be adopted. Therefore, this study investigated the possibility of using natural platelets as drug delivery vehicles for the thrombolytic agent tissue plasminogen activator (tPA). Platelets may be modified in a number of ways to give rise to different therapeutic modalities that are aimed at targeted treatment. Due to the structure and multiple functions of platelets within the body, these different platelet-inspired therapeutic modalities have been investigated for their use in an array of conditions. However, no known research has been undertaken on the use of platelets to cross the BBB for the targeted treatment of neurological conditions that illicit a platelet response. In this study platelets were explored as carriers for tPA, for the potential penetration of the BBB. This approach potentially has two ways in which platelets may be loaded with tPA. The first way involves the direct loading of tPA into the platelets. The second way involves the loading of a tPA-encapsulated nanoparticle into the platelets, and the system that is formed is known as a biohybrid delivery system as it is composed of a natural element (platelets) as well as the synthetic nanoparticle (biopolymer-based). An investigation was conducted on the suitability of five nanomaterials that may potentially be used to encapsulate tPA, in the design of a biohybrid platelet-based system. The nanomaterials that were investigated included silica nanoparticles, carbon nanotubes, cerium (IV) oxide nanoparticles, nanoliposomes, and poly methyl methacrylate (PMMA) particles. The investigation analysed the effects of the nanomaterials on

erythrocyte morphology and aggregation behaviour, in an attempt to investigate the erythrocyte compatibility of the particles. From the nanomaterials tested, the nanoliposomes exhibited the greatest erythrocyte compatibility, therefore, it was recommended that further research be conducted on their use in the design of a biohybrid platelet-based system. Experiments were then conducted on the ability of natural platelets having undergone direct tPA loading, to induce clot lysis. The experiments conducted showed that the platelets were able to encapsulate tPA with an average encapsulation efficiency of 63%, and that the platelets were effective in releasing 15.2% of the encapsulated tPA upon activation by thrombin. It was also observed that loading the platelets with tPA did not result in any morphological changes to the platelets, nor did it alter the integrity and ability of the platelets to respond to vascular injury. The tPA-loaded platelets on average were able to cause 72% clot lysis when tested using an *in vitro* whole blood clot model. Additionally, the tPA-loaded platelets were not seen to alter the colloidal suspension stability of blood as well as the degree of erythrocyte aggregation, thereby promoting their erythrocyte compatibility profile. The results from this research provided *in vitro* evidence to support the use of tPA-loaded platelets in the potential treatment of ischaemic stroke.