Monocyte-mediated drug carriers targeting cancer spheroids in a 3D microfluidic cell culture that reconstitute tumour microenvironment

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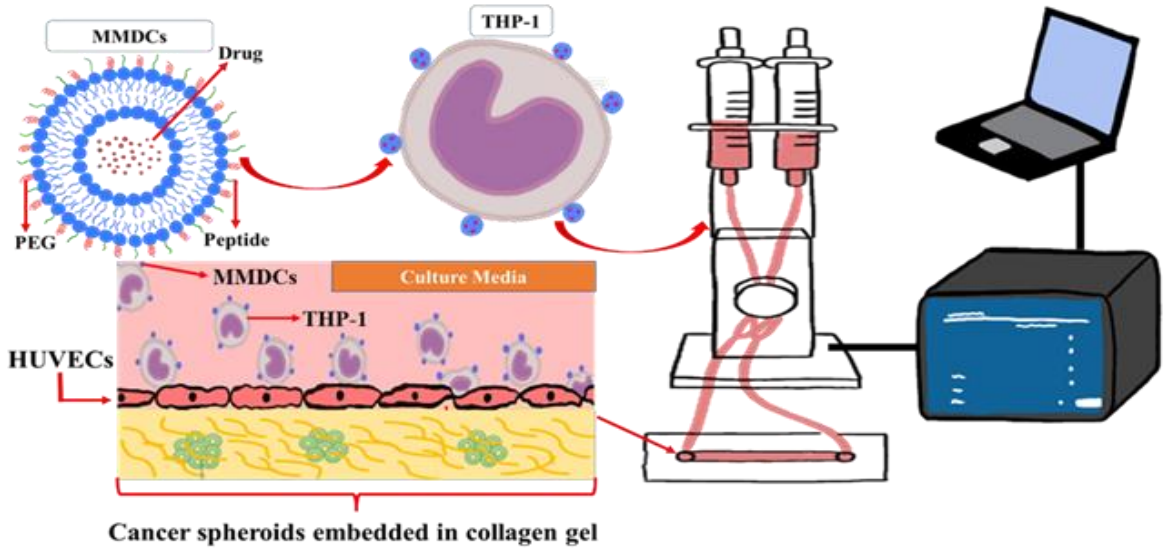
In patients with cancer, the EPR effect only **provides less than 2-fold increases** in delivery to tumour tissue compared to normal organs. Therefore, there is a need to develop a novel nanoparticle-based targeted therapy that can facilitate drug delivery in an EPR-effect-independent manner. We have developed **monocyte-mediated drug carriers (MMDCs)** that could deliver therapeutics to the targeted sites **without depending on the EPR effect.** Using a commercially available microfluidic system, the MMDCs were demonstrated to successfully hitchhike onto circulating monocytes (THP-1) under physiological flow rates, as opposed to the classical formulation of PEGylated liposomes. The targeting specificity of MMDCs was further demonstrated in a **3D microfluidic cell culture** that reconstituted some of the critical features of the tumour microenvironment. The 3D culture consisted of human breast cancer **(MDA-MB-231)** spheroids embedded in a collagen matrix, with human endothelium (**HUVECs**) established on top. MMDCs were shown to undergo trans-endothelial migration **through monocyte hitchhiking**. In contrast, MMDCs **could not** undergo trans-endothelial migration without monocytes. Furthermore, **either circulating THP-1 or MMDCs could not** undergo trans-endothelial migration when the collagen matrix was embedded with HEK293, **not MDA-MB-231**. This indicated in our 3D microfluidic cell culture that circulating monocytes could only undergo trans-endothelial migration in the presence of cancer spheroids. Moreover, the MMDCs **could only** target cancer spheroids and not non-cancer cells.



The monocyte-mediated drug carriers (MMDCs) showed specific recognition of the tumour microenvironment. Cancer spheroids consisted of human breast cancer cells, MDA-MB-231 were embedded in a collagen-filled chamber slide. A layer of the endothelium (HUVECs) was established on top of the spheroids-embedded gel. The chamber slide was perfused using a computer-controlled microfluidic system. Human monocytes (THP-1) were allowed to circulate in the chamber slide for 2 hrs, followed by injecting the MMDCs. The MMDCs could hitchhike onto the circulating monocytes and undergo trans-endothelial migration through monocyte hitchhiking.