“Targeted adenoviruses for the cell-specific delivery of cancer therapies”

Our group has developed an adenoviral delivery system that allows for specific targeting of adenovirus serotype 5 (Ad5) to discrete cell populations through the use of interchangeable designed bispecific designed ankyrin repeat protein (DARPin) adapters. In contrast to other strategies utilizing Ad5 for its oncolytic properties, we have engineered Ad5 into a non-oncolytic, ‘shielded’ delivery vehicle for therapeutic genes due to its large packaging capacity (up to 36 Kb) and the feature that the viral DNA remains episomal rather than randomly integrating into host chromosomes, providing an additional safety margin for clinical applications. The generation of this generic delivery system has enabled its use as a therapeutic platform. The primary approach aims as at targeting adenoviral particles to selectively transduce tumor cells or tumor stromal cells with the genes encoding cocktails of secreted monoclonal antibodies (mAb)- and/or other protein-based therapeutics (e.g. cytokines). The transduced subpopulation of cells then serves as a ‘biofactory,’ secreting therapeutic combinations that act in a paracrine fashion within the tumor microenvironment to collectively target multiple oncogenic pathways, increase anti-tumor immunity, and/or enhance tumor perfusion with additive or synergistic effects to reduce the risk of tumor escape and the development of drug resistance. We argue that in situ therapeutic production could provide an attractive alternative to treatment with repeated high bolus injections of drug combinations, as secretion by the tumor itself could provide high local concentrations that act in a paracrine fashion over an extended duration with limited toxicity to peripheral tissues. In a secondary immunotherapy application, bispecific adaptors have been generated for mediating viral delivery to the surface of discrete T cell populations (e.g. CD4+, CD8+) as potential in vivo delivery vehicles for cell-mediated immunotherapies. We propose that this approach could provide a less cumbersome alternative to ex vivo modification of T cells with tumor-specific T cell receptors (TCRs) or chimeric antigen receptors (CARs) for autologous transfer.