

SMI, 2005, Cologne

Intracellular MR Contrast Agents based on *l*-Tat and *d*-Tat: A Comparative Study

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Noninvasive imaging techniques like MRI possess the prospective to observe molecular-genetic and cellular processes. But the exogenously administered molecular imaging agents are often unable to reach their molecular and cellular targets as the lipid bilayer of the cell poses a formidable natural barrier. However, a unique class of peptides known as cell penetrating peptides (CPPs) has the ability to traverse this barrier and convey cargo molecules attached to it across the cell membrane. Amongst a variety of natural and chimeric CPPs, HIV-1 tat protein derived Tat peptide (Tat₄₉₋₅₇) has received much attention mainly because of its high efficiency to deliver a large variety of cargo molecules across the membrane.

Considering the potential of Tat as a molecular transporter, we coupled its derivatives with fluorescence imaging agent FITC as well as with MR agent Gd-DTPA, thus obtaining bimodal cell internalizing agents. We aimed at comparing the effect of chirality on the internalization efficiency and thus synthesized *l*-Tat₄₉₋₅₇ and its retro-inverso isomer *d*-Tat₅₇₋₄₉. The effect of the two isomers on the vitality of cells and induction of metabolic changes was also studied. Fluorescence microscopy and spectroscopy as well as MRI were used on cell cultures for these studies.

Although both the peptides showed concentration and time dependent cellular delivery, the unnatural *d*-Tat coupled agent exhibited better cellular internalization compared to the natural form. This could be attributed to the increased stability of the *d*-form of the peptide to enzymatic cleavage. Also the *d*-form affected the cell vitality at concentrations above 9µM and induced slight changes in metabolic activities.