

**P018** Proteoglycans as internalizing receptors – elucidating their physiological role and exploiting the route for drug delivery  
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Heparan sulphate proteoglycans (PGs) emerge as an important route of entry of a diverse set of ligands, e.g. cell penetrating peptides (CPPs) and CPP-nucleic acid complexes, as previously demonstrated by our group and others. More recently, we have identified endogenous proteins released to the cell culture media with some characteristics of synthetic or virus-derived CPPs. We show that naked DNA forms complexes with endogenous cell medium proteins, which is a pre-requisite for subsequent rapid DNA internalization through PGs. While the exact internalization pathway remains to be characterized in more detail, our data suggest that the main entry pathway of these complexes shares many similarities with macropinocytosis. Complex uptake is insensitive to disruption of clathrin-mediated endocytosis by dominant-negative dynamin or Eps15; internalized complexes show poor co-localization with exogenous transferrin and caveolin-1, while showing strong co-localization with dextran. Furthermore, complex internalization is sensitive to macropinocytosis disruptive drugs. Taken together our results reinforce the importance and pervasiveness of PG-dependent endocytosis in the field of CPPs and macromolecular drug delivery. Present investigations aim at a detailed understanding of the intracellular trafficking mechanisms involved in PG-dependent transport, using phage display derived antibodies recognizing specific HS sulfation patterns.