

The peptide increased adenoviral uptake when applied in solution and when conjugated to PEG attached to the viral capsid (Drapkin et al., 2000). Peptide-based targeting employed in non-viral gene delivery is discussed in more detail in Section 1.5.3.

Having discussed the need for improved therapy and the methods employed to target therapies, the uPA receptor and its use as a novel target are now examined.

#### **1.4 Rationale for the Choice of uPAR as a Target**

A cancer cell receptor of increasing interest for targeting is uPAR. Though currently less well understood than many of the other targets being investigated, this receptor may show advantages for targeting either for novel therapeutics or delivery systems. In this section the role, presence and targeting potential of uPAR are described.

##### **1.4.1 Physiological Role and Functions of uPAR**

uPAR, also designated CD87, it is a glycosylphosphatidyl inositol (GPI)-linked receptor of approximately 55 kDa. This GPI linkage means that the protein is attached to the cell membrane at the C-terminal aa only (Fig. 1.6). It is composed of three similar disulphide bonded domains (Fig. 1.7; (Blasi & Carmeliet, 2002)). The crystal structure of the soluble (cleaved at the GPI link) receptor was recently solved with a non-natural peptide ligand antagonist bound (AE147) (Llinas et al., 2005). There is a central cavity 19 Å deep formed between the three domains where the antagonist peptide binds (Llinas et al., 2005). It has been proposed that uPA also binds in this cavity (Llinas et al., 2005). The primary function of uPAR is to bind uPA, which catalyses plasminogen activation to plasmin (Ramage et al., 2003). Plasmin is a serine protease that hydrolyses peptide bonds in fibrin clots and thus prevents thrombosis (Fig. 1.8; (Stryer, 1995)).

By binding uPA at the surface of the cell, uPAR focalises the activity of uPA. It is suggested that this enables cell migration through the digestion of extracellular molecules (Blasi & Carmeliet, 2002). The binding of uPA to uPAR is a high affinity interaction with a  $K_d$  in the low nM range 0.1 - 17 nM (Picone et al., 1989). This makes it particularly attractive in the concept of receptor targeting. The affinity of uPA for uPAR expressed in a (uPAR) transfected cell line (LB6, murine fibroblast) was reported as 1-10 nM (Roldan et al., 1990).