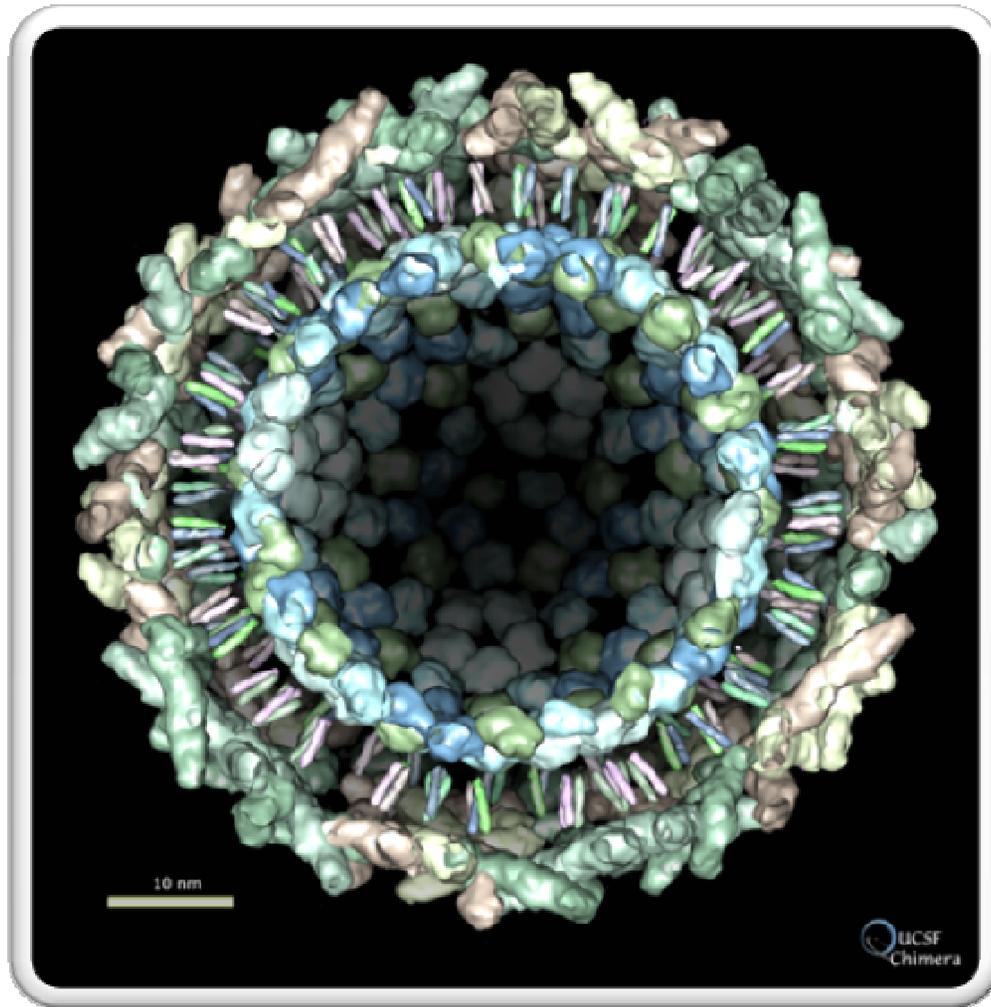


From crystal structure to cancer therapeutic

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02.25.2008

Sindbis virus



- Alphavirus

- Small, positive-stranded enveloped RNA virus

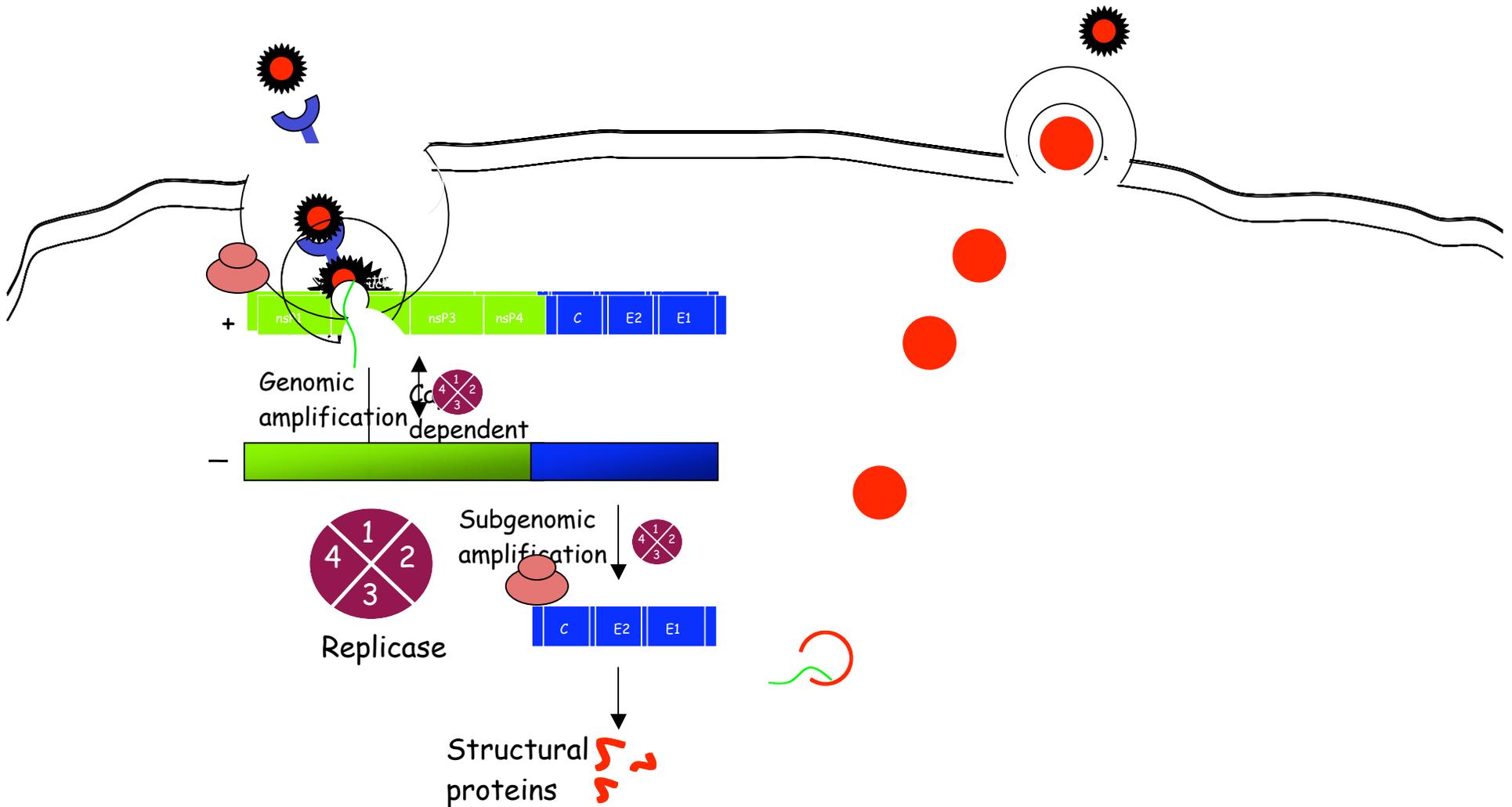
- T=4 icosahedral symmetry

- Structural proteins: E1, E2, E3, capsid

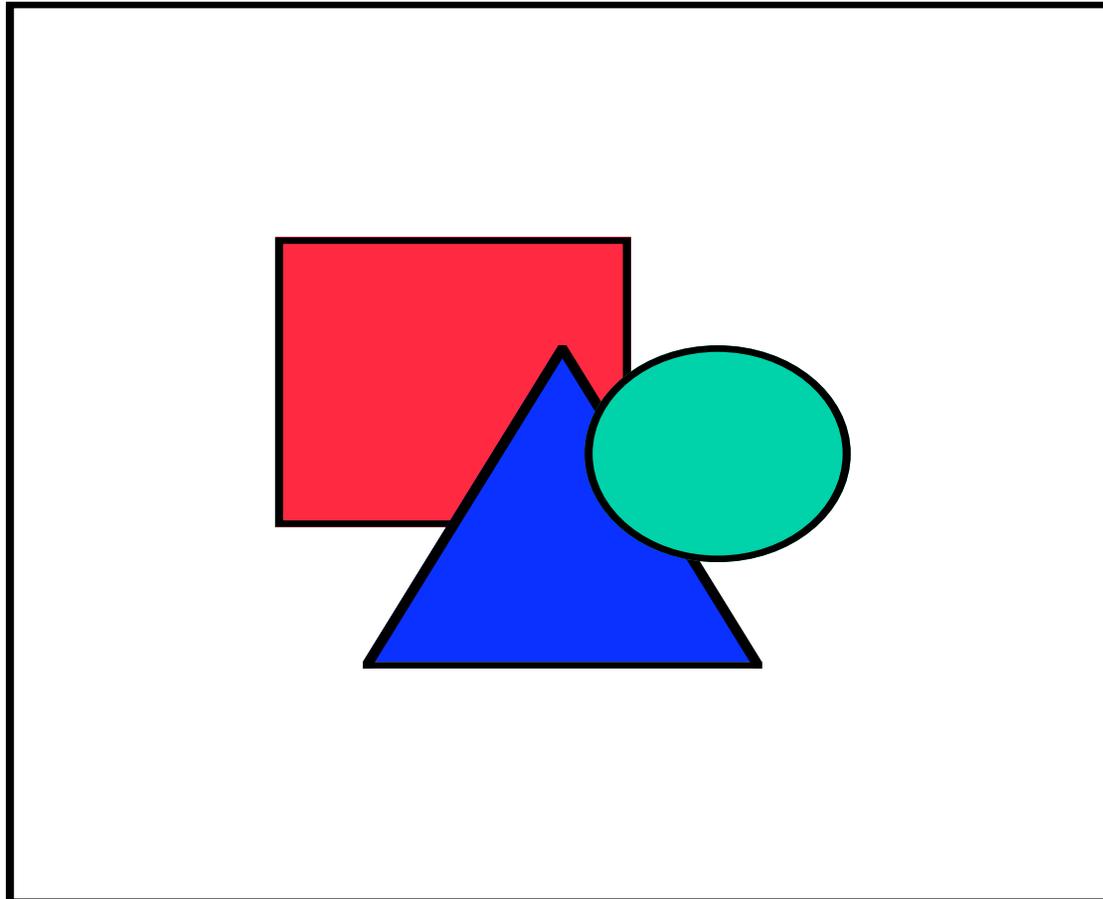
- Nonstructural proteins: nsp1-4

- Two surface glycoproteins (E2 and E1) mediate viral attachment, fusion, and penetration

Sindbis Virus Lifecycle

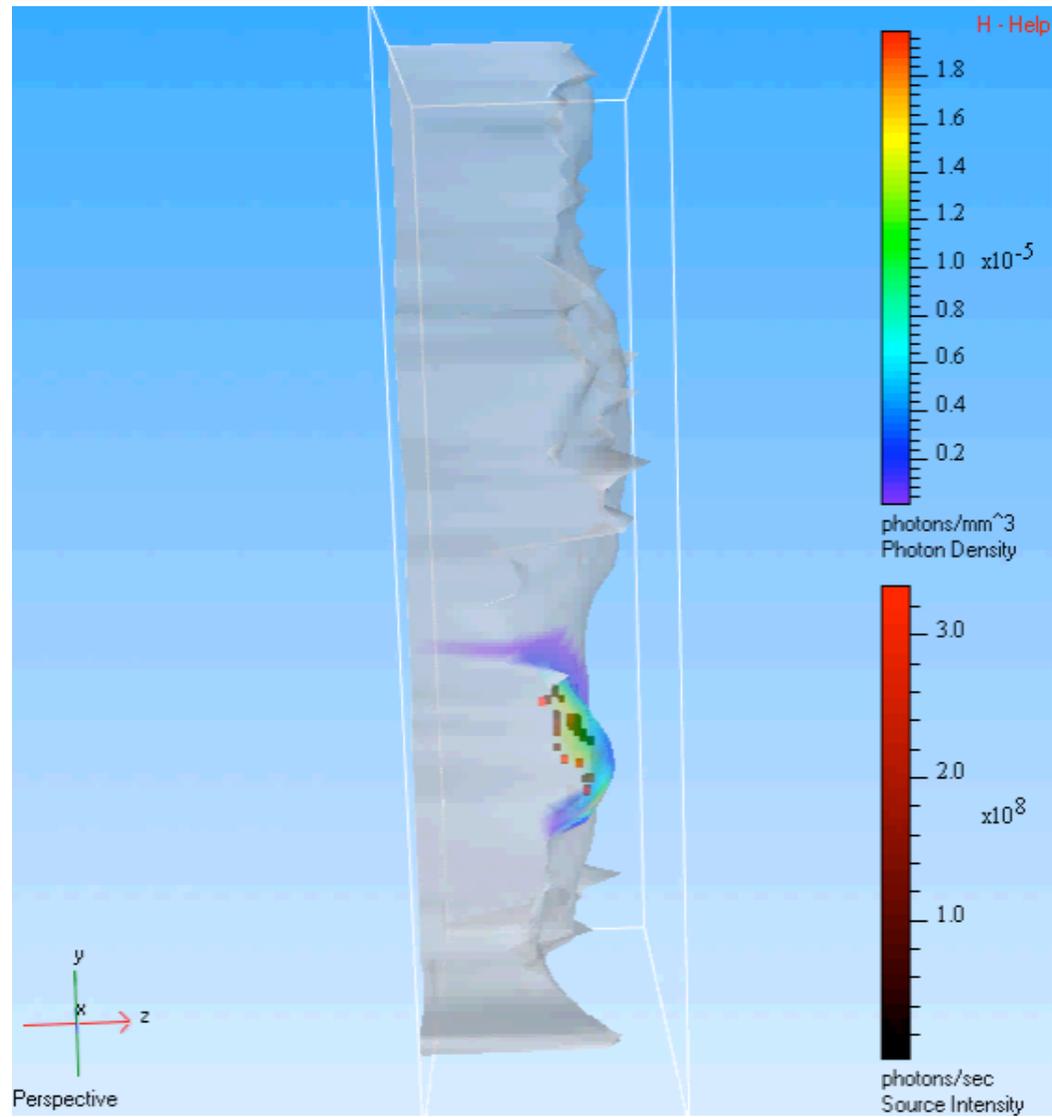


In vivo Sindbis vector targeting

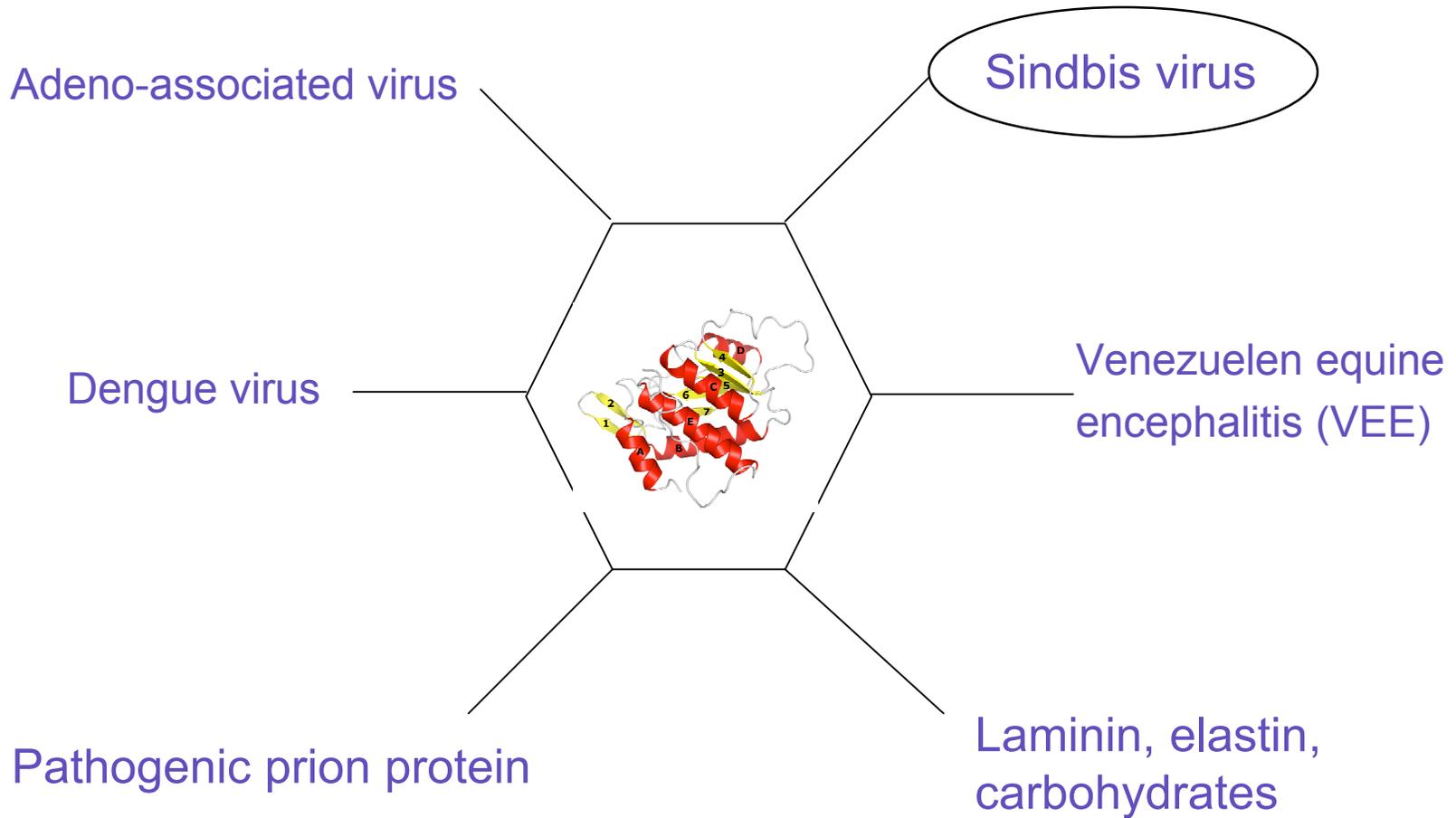


-Addition of Sindbis vector causes shrinkage of tumor mass

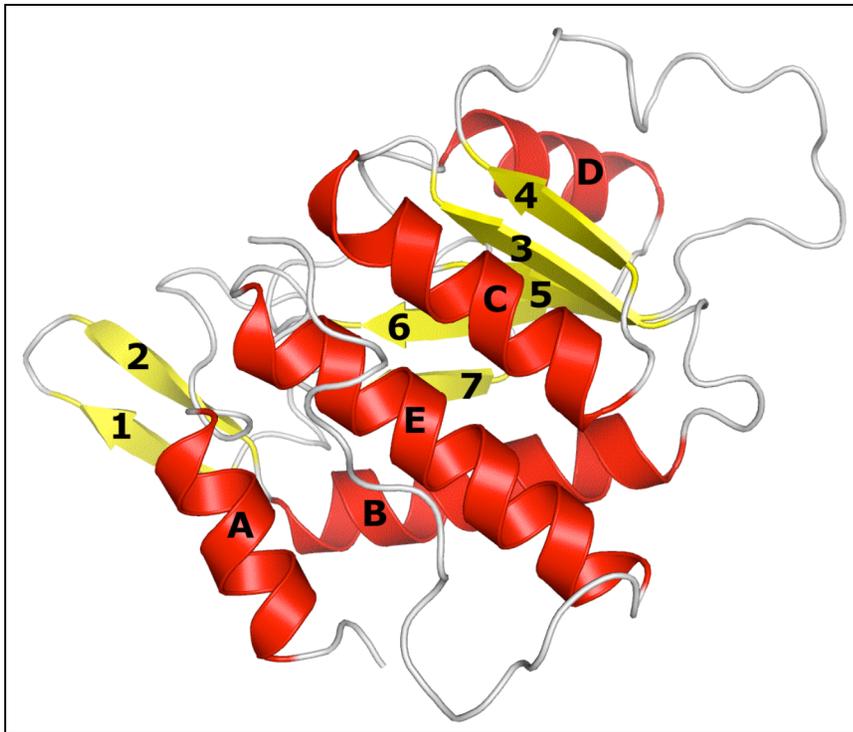
IVIS: 3D imaging



Laminin receptor as a therapeutic target



Laminin Receptor (LamR):



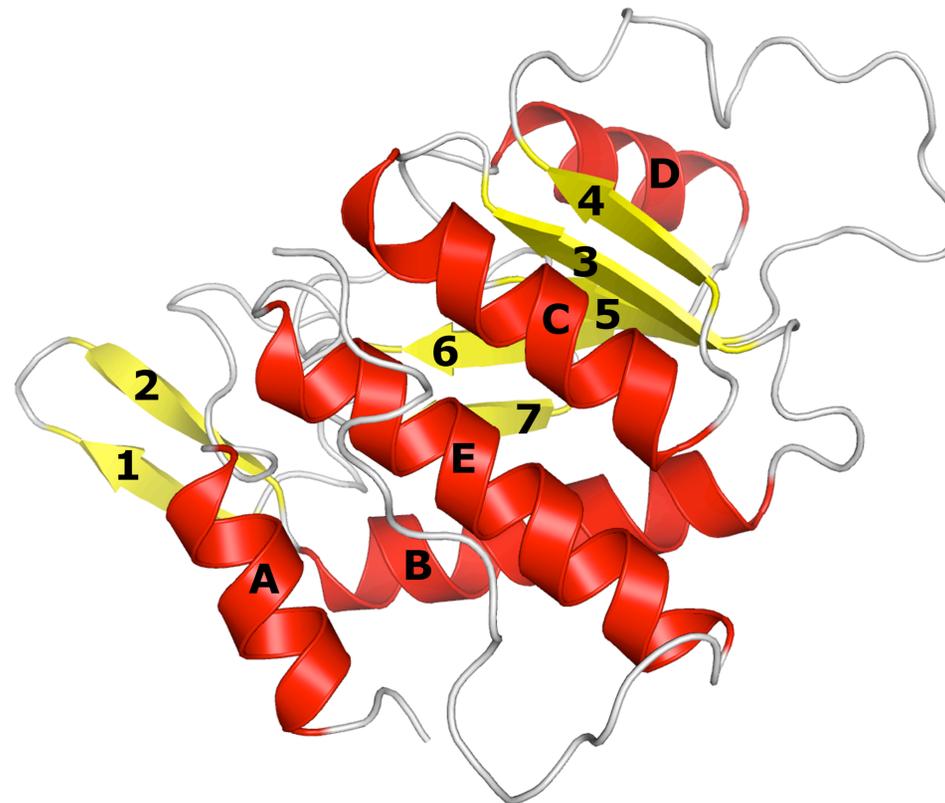
Jamieson et al., 2007

- LRP/p40 gene encodes 295 amino acid long protein
- Exists as both a monomer (37 kDa) and a dimer (67 kDa) at the cell surface
- Intracellular LamR/p40 associates with 40S ribosome
- The entire length of 37LRP is conserved among vertebrates
- **Highly** overexpressed on tumor cells

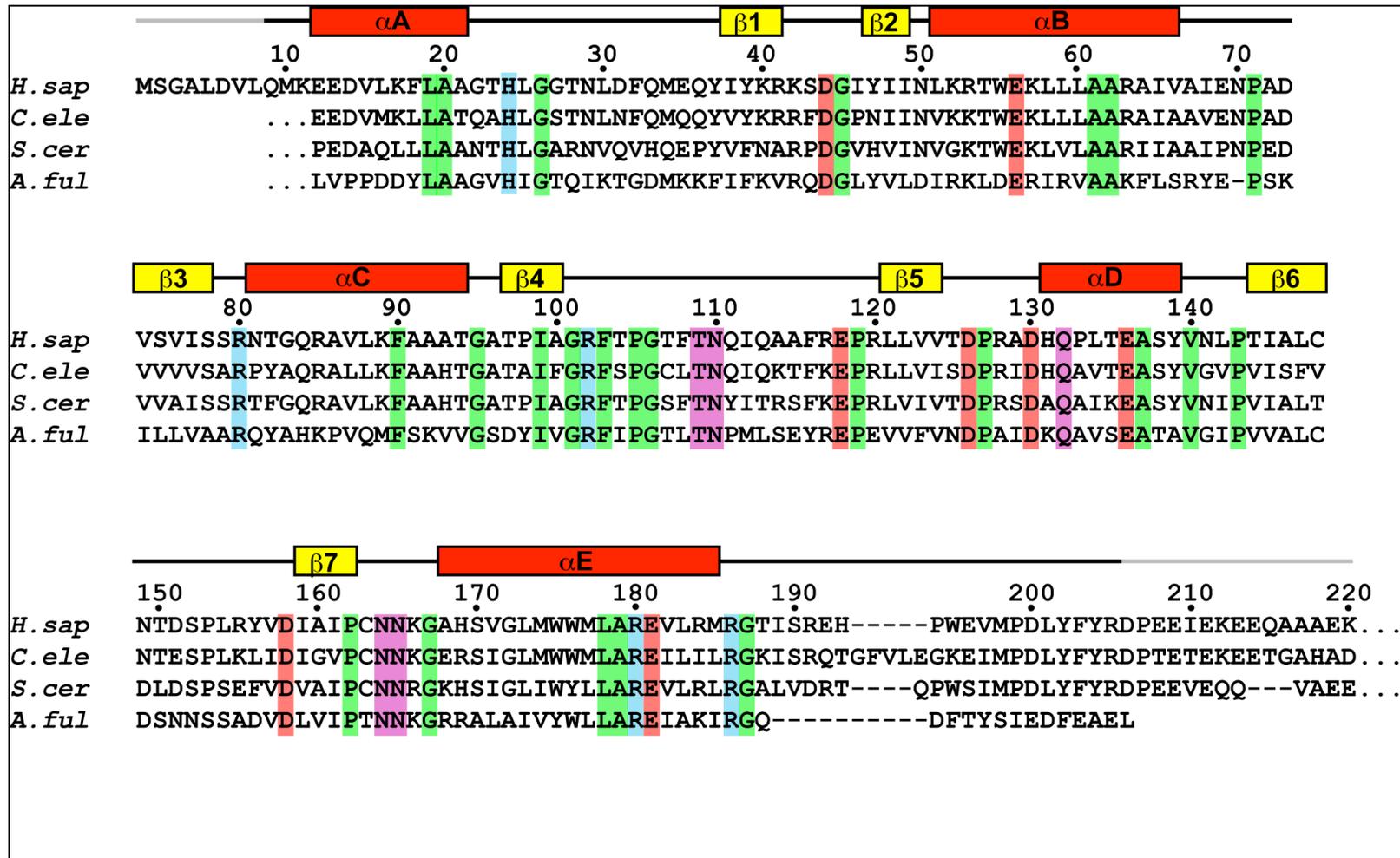
Laminin Receptor crystal structure at 2.15 Å



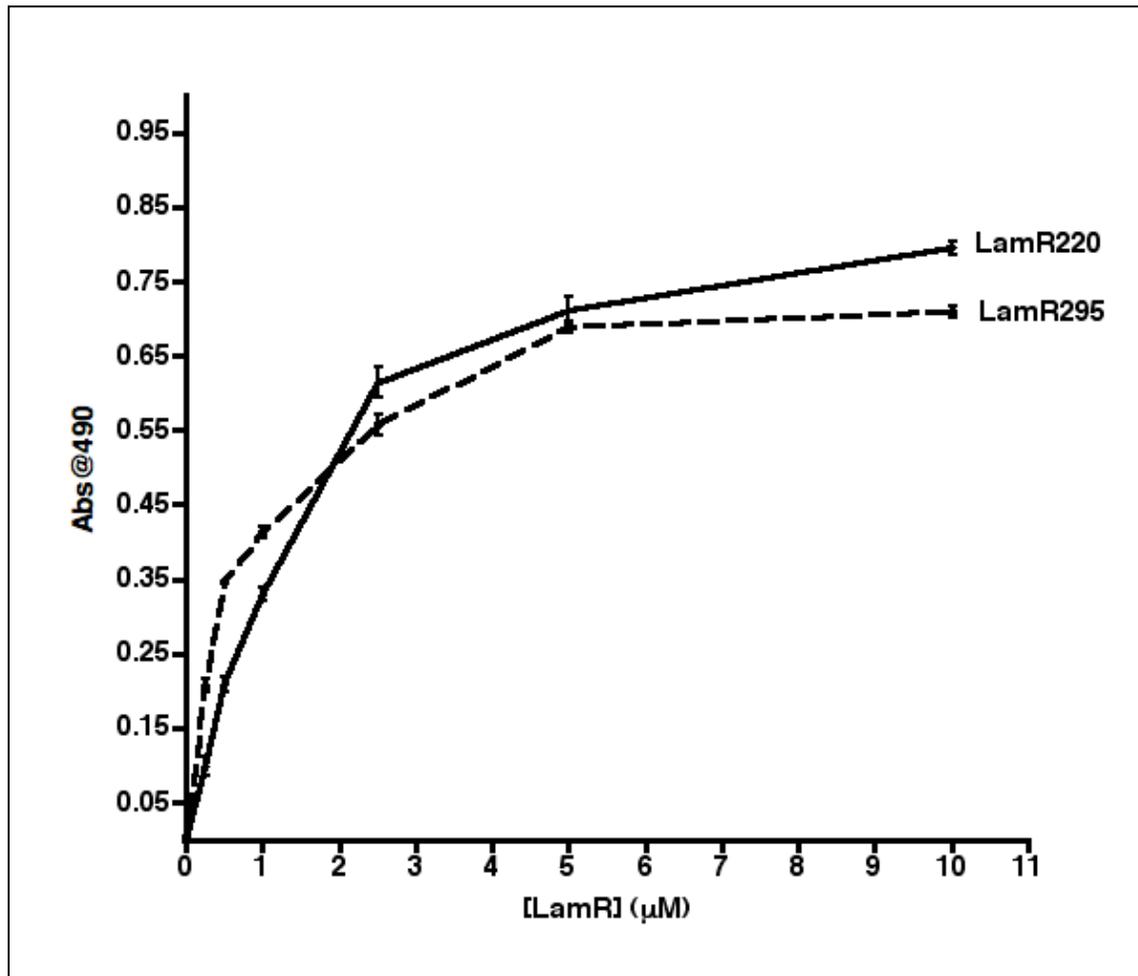
Sindbis vector targeting via LamR



LamR sequence conservation

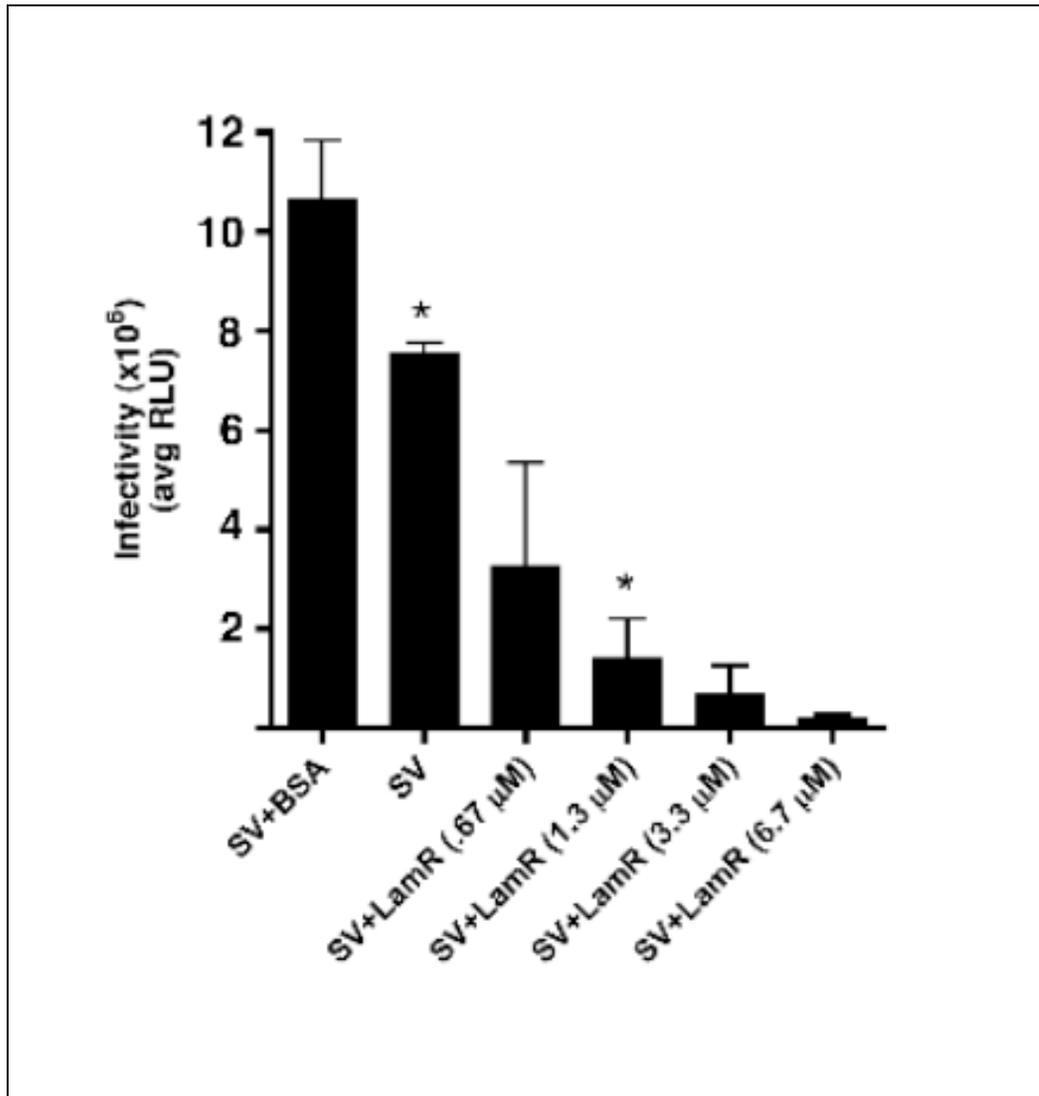


Recombinant LamR binds laminin-1 in vitro



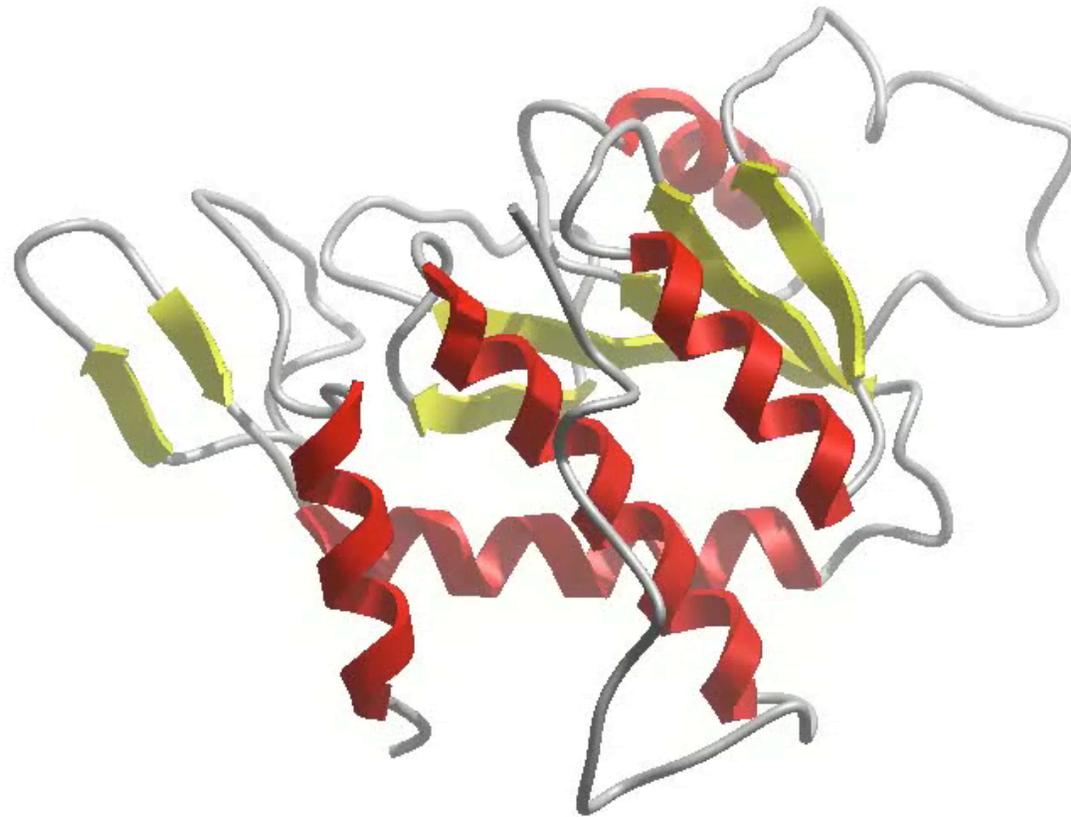
Jamieson et al., 2007

Recombinant LamR inhibits Sindbis vector infection

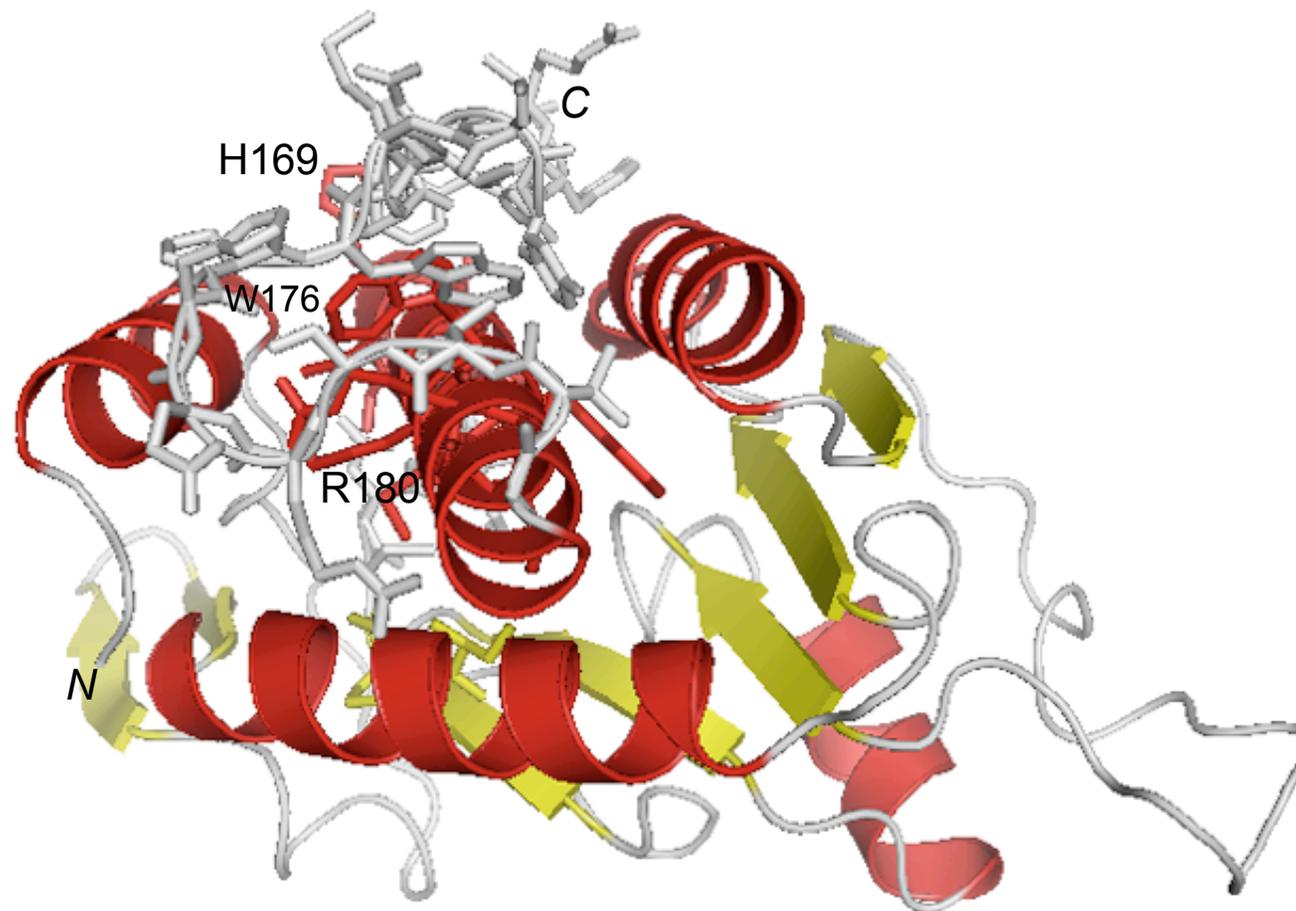


SV = Sindbis vector
LamR = recombinant
LamR 1-220

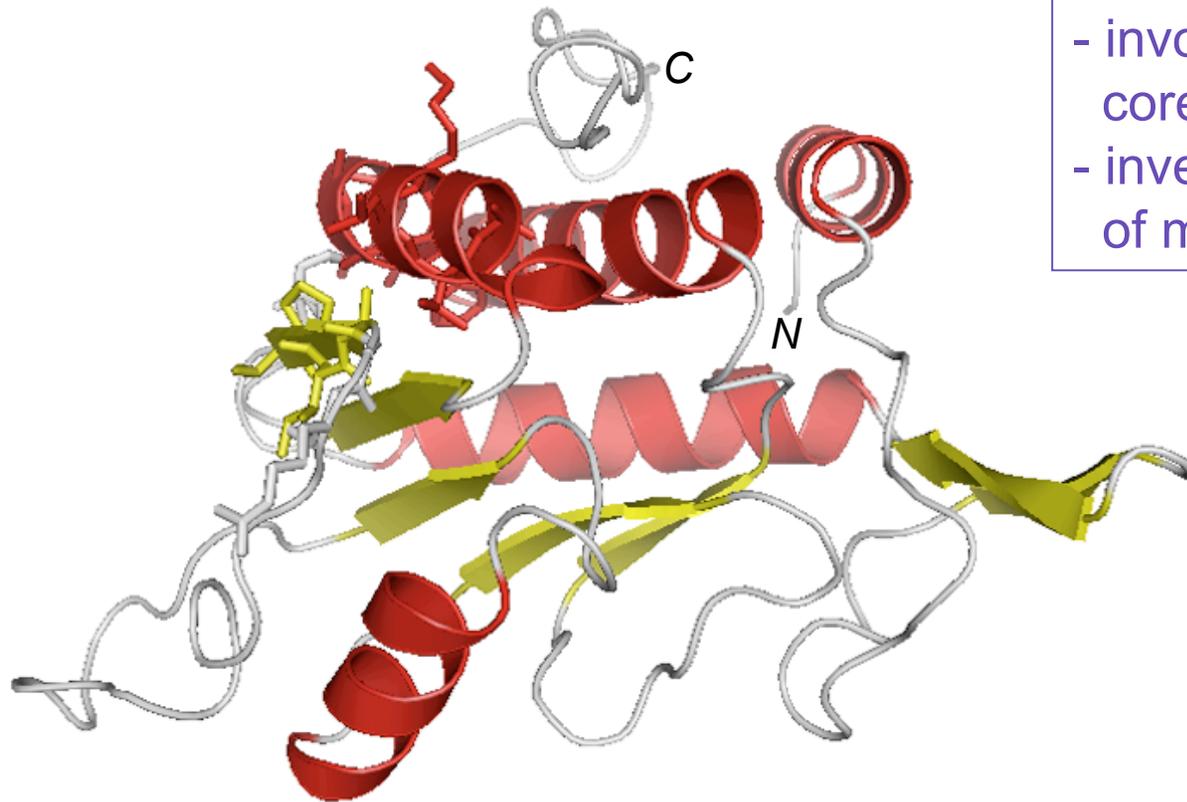
Laminin Receptor crystal structure at 2.15 Å



Putative laminin-1 binding site is not surface exposed

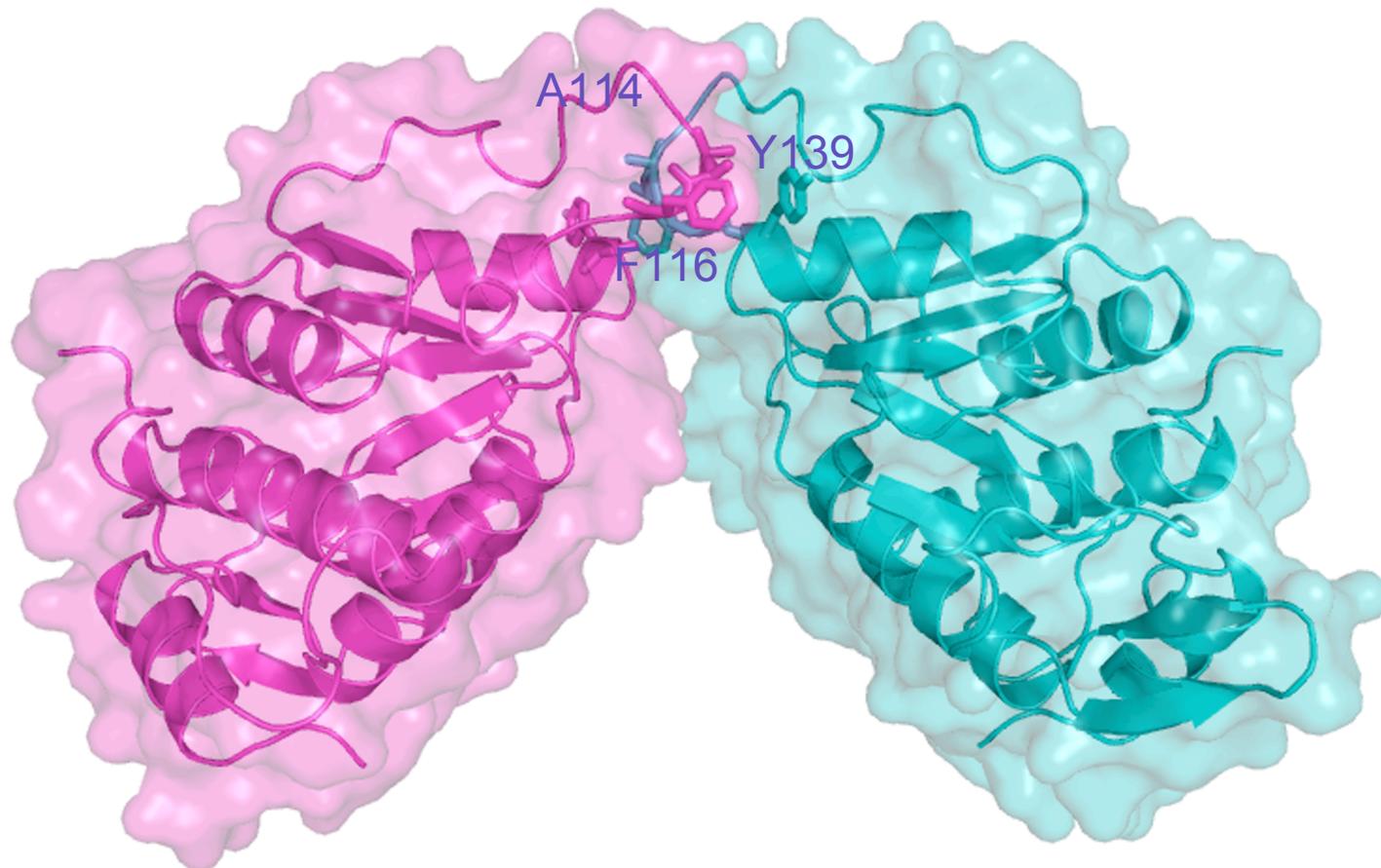


LamR cell-membrane anchorage transmembrane domain independent

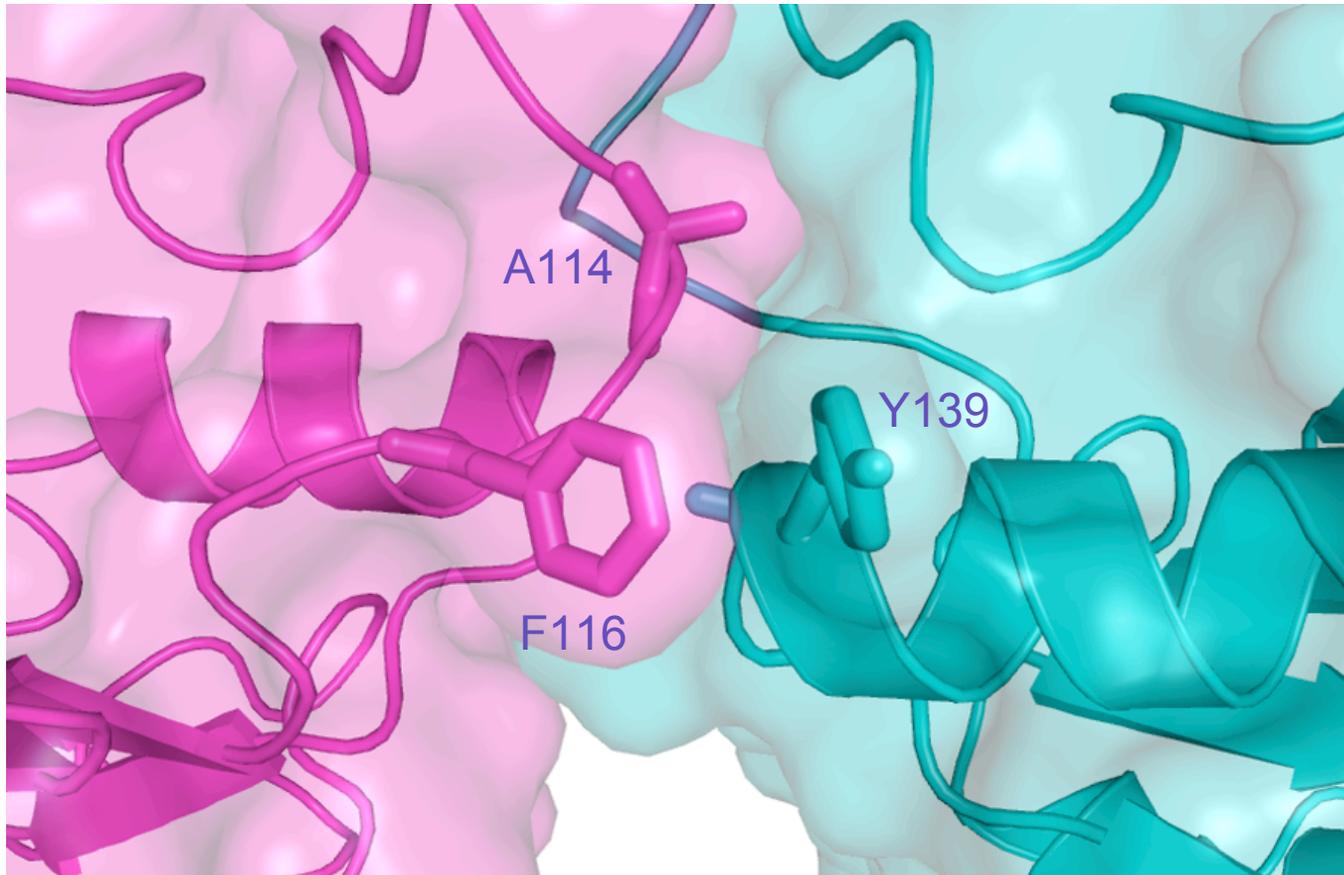


- putative transmembrane domain (residues A86-R102)
- involved in tight packing of core of LamR
- investigation of other means of membrane anchorage

LamR crystallographic dimer



LamR crystallographic dimer



LamR effective target for anti-cancer therapy



- Sindbis vector effectively targets tumors and reduces tumor mass via LamR
- (-)-epigallocatechin-3-gallate (EGCG) elicits anti-cancer effects in vivo (Tachibana et al., 2008; Munshi et al., 2006)
- LamR is the receptor for EGCG (Yamada et al., 2004)
- Future prospects: development of small molecules that, like EGCG and SV, effectively target and eradicate cancer

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