

Targeting ligand selection for nanocarriers

A practical comparison of antibody fragments, affibodies, aptamers and peptides

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Summary

Adding a targeting ligand can move a nanocarrier away from the liver and towards a chosen cell type, but each ligand class brings trade-offs in size, stability, immunogenicity, manufacturability and cost. This paper compares the main classes and describes how our LigandMap™ screen chooses between them.

1. Ligand classes compared

Class	Size	Strengths	Watch-outs
Antibody fragments (Fab, scFv)	25–50 kDa	High affinity; mature discovery tools	Orientation on surface; cost; Fc-free formats preferred
Affibodies	~6.5 kDa	Small, stable, easy to conjugate site-specifically	Fewer validated binders per target
Aptamers	8–25 kDa	Chemically synthesised; low batch variability	Nuclease stability needs chemical modification
Peptides	1–3 kDa	Cheap; high surface density possible	Lower affinity; protease sensitivity
Small molecules (e.g. GalNAc, folate)	< 1 kDa	Simple chemistry; well characterised	Limited to receptors with known small-molecule ligands

2. What matters on a particle

- Density: too few ligands give weak avidity; too many can increase clearance and aggregation.
- Presentation: ligands on PEG spacers must extend beyond the PEG brush to reach receptors.
- Protein corona: serum proteins can mask ligands; test binding in serum, not buffer only.
- Receptor biology: choose receptors that internalise and are expressed more on target than off-target cells.

3. The LigandMap™ workflow

- Receptor shortlist from expression data
- Ligand conjugation at three surface densities
- Binding and uptake in target versus control cells, in 50% serum
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Organ-on-chip and biodistribution confirmation of the best two candidates