Streptavidin-Biotin system in drug delivery

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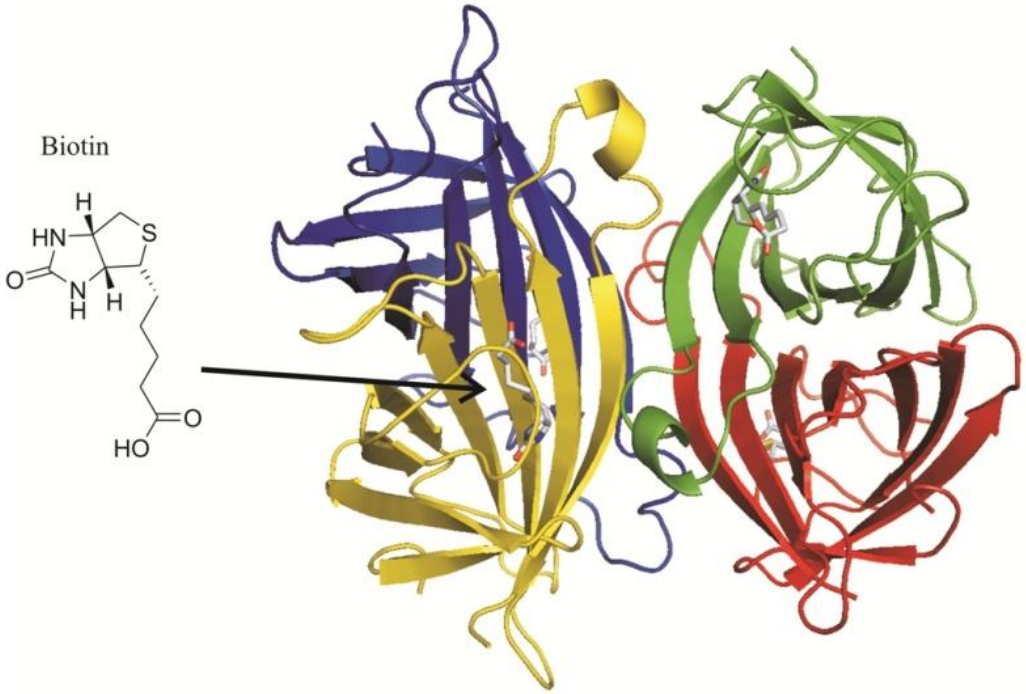
15/10/13

1. Streptavidin/ Avidin



- **A protein purified from the bacterium *Streptomyces avidinii***
- **Extraordinarily high affinity for biotin (dissociation constant 10^{-14} mol/L)**
- **Binding of biotin to streptavidin is one of the strongest non-covalent interactions known in nature**
- **Streptavidin-biotin complex is resistant to harsh conditions such as organic solvents, denaturants, extremes of temperature and pH**
- **Streptavidin is a tetramer and each subunit bind biotin with equal affinity**

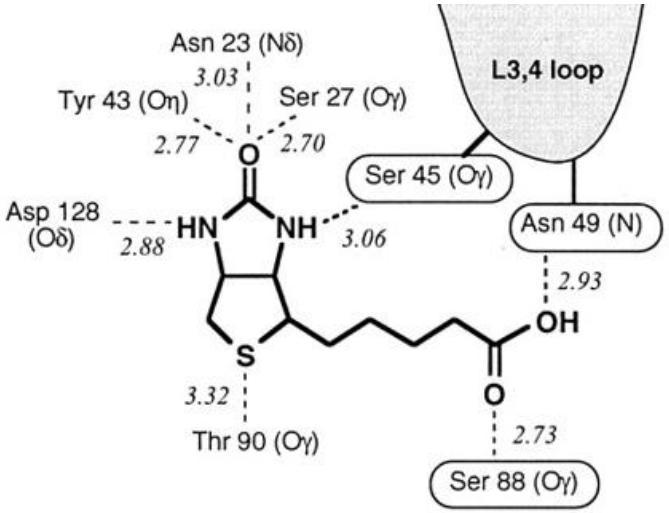
Origins of the high affinity between streptavidin and biotin:

- **High shape complementarity between binding pocket and biotin**

- **Extensive network of hydrogen bonds**
  - **First shell hydrogen bonding: eight hydrogen bonds directly made to residues in the binding site**
  - **Second shell hydrogen bonding: residues that interact with the first shell residues**

- **Van der Waals force mediated contacts and hydrophobic interactions**

- **Stabilization of a flexible loop which closes over the bound biotin**



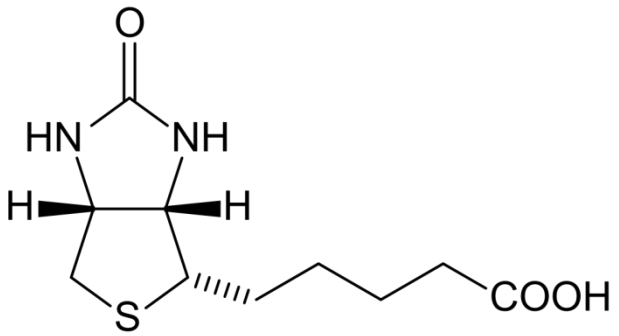
1. Streptavidin/ Avidin

Avidin-30% sequence identity to streptavidin, but almost identical 2nd, 3rd, 4th structure

•Avidin is the other most notable biotin-binding protein, which is originally isolated from egg white.
•Avidin has higher affinity for free, unconjugated biotin, while streptavidin is the better biotin-conjugate binder.

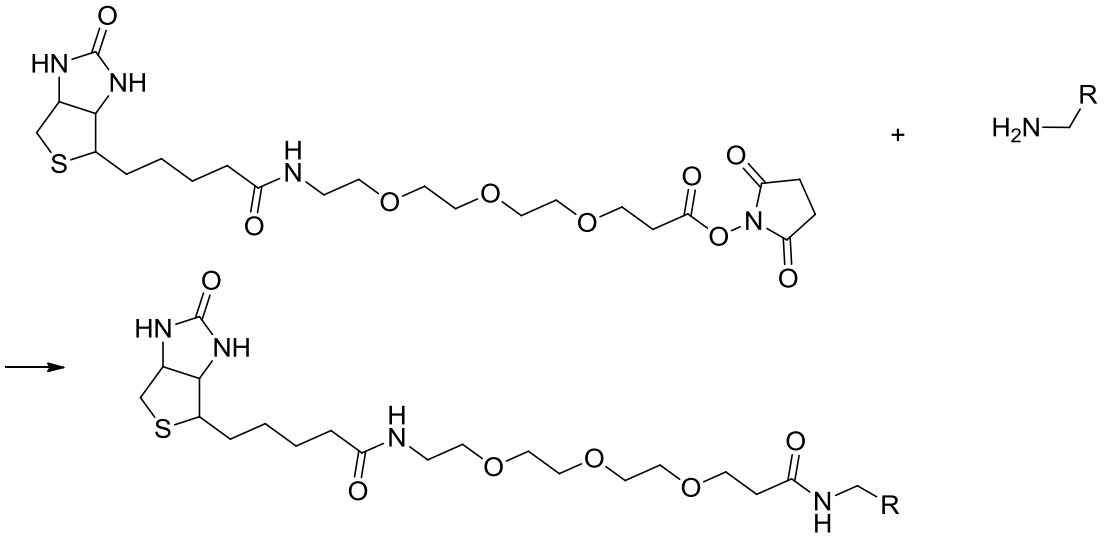
Applications

The valeric acid chain is used to conjugate biotin to other chemical groups, taking advantage of the free terminal carboxylic group

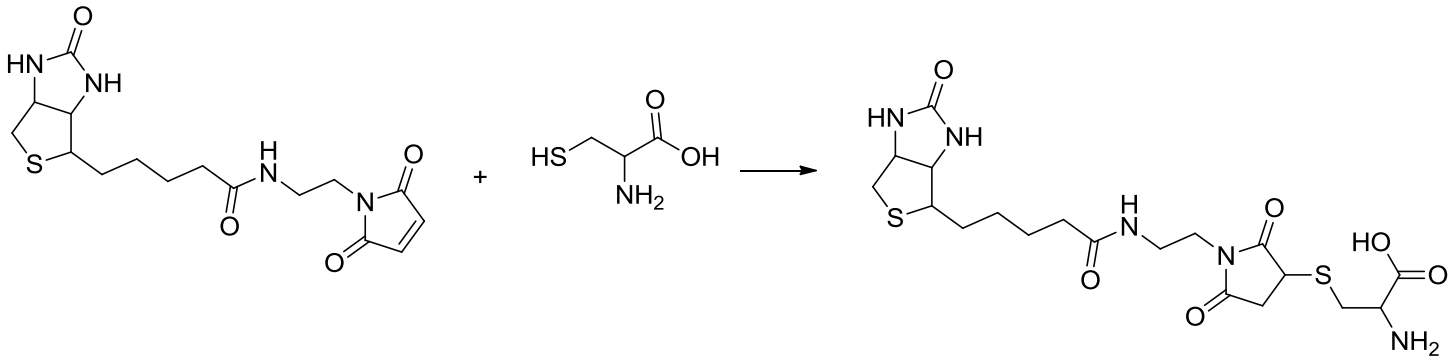


2. Biotinylation methods

- **N-dydroxysuccinimide (NHS) esters: target at primary amine groups**

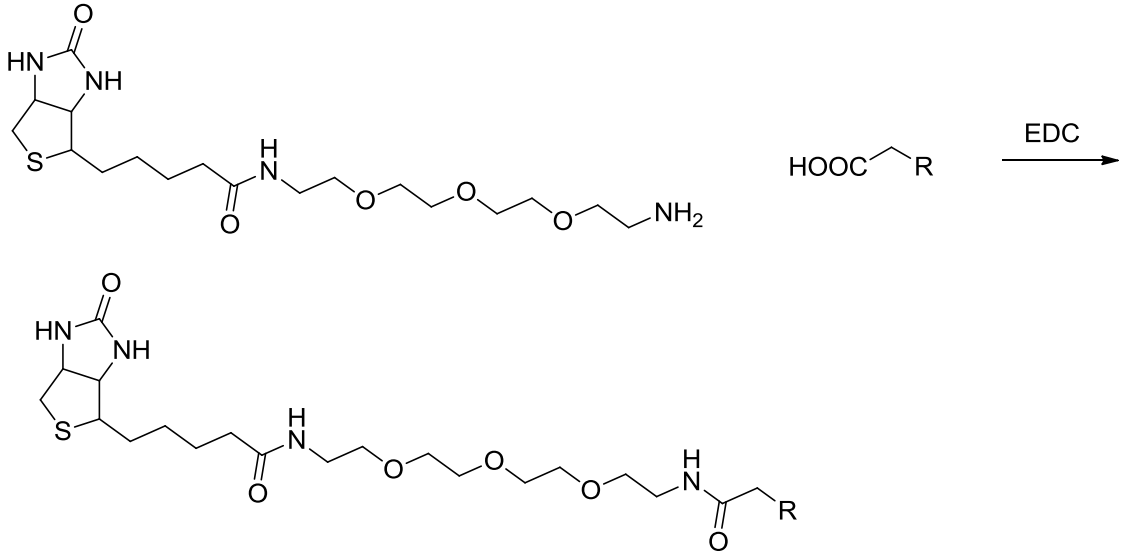


- **Maleimides: target at sulfhydryl groups**

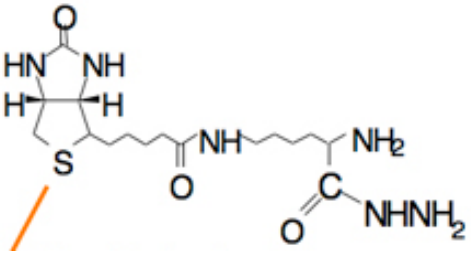


2. Biotinylation methods

•**Free amine on the biotinylation reagents: target at carboxyl groups**

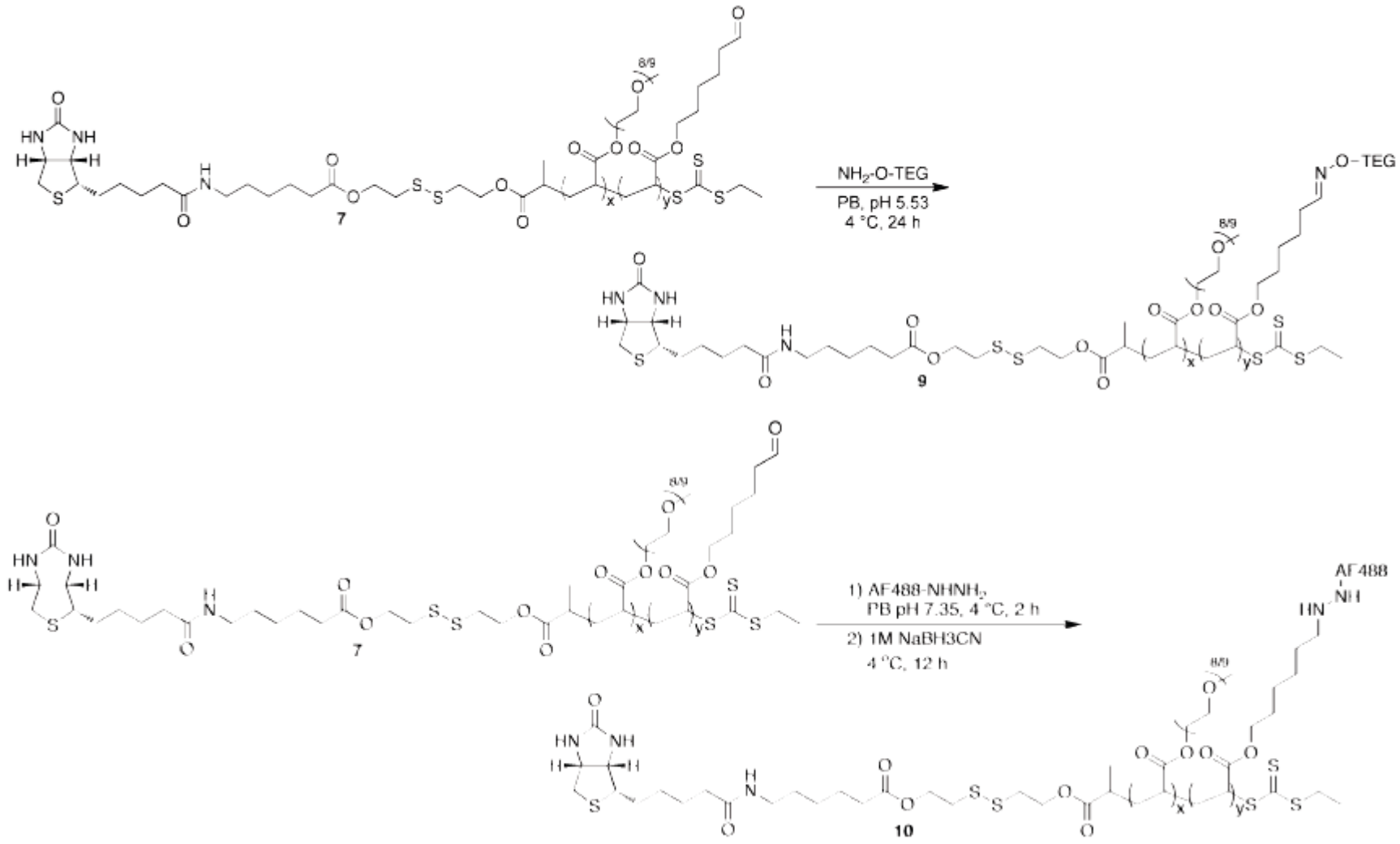


•**Hydrazine based biotinylation reagents: target at sugars (oxidized to aldehydes with sodium periodate, then condensation with biotinylation reagents)**

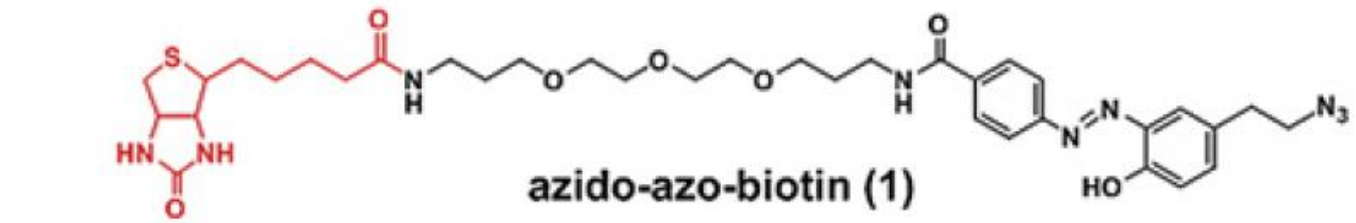


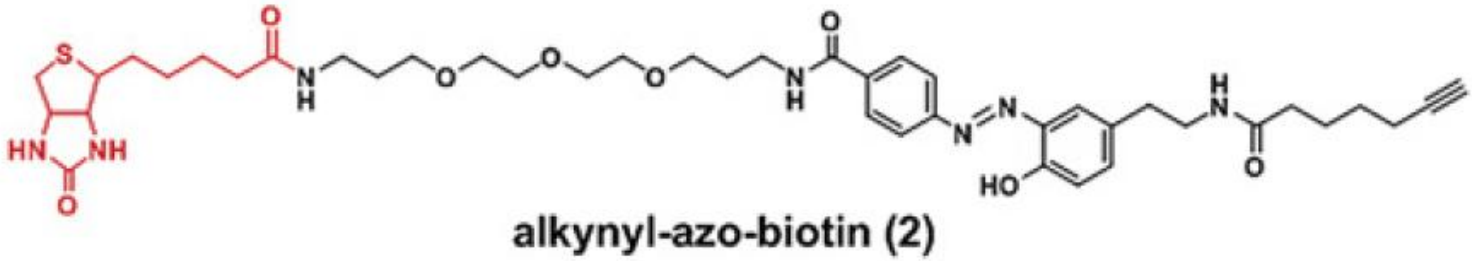
2. Biotinylation methods

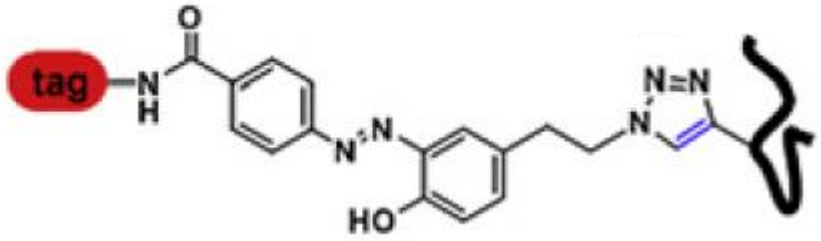
- **Biotinylated aldehyde: target at hydroxyamines, and hydrazines**



•**Click chemistry: alkyne or azide**







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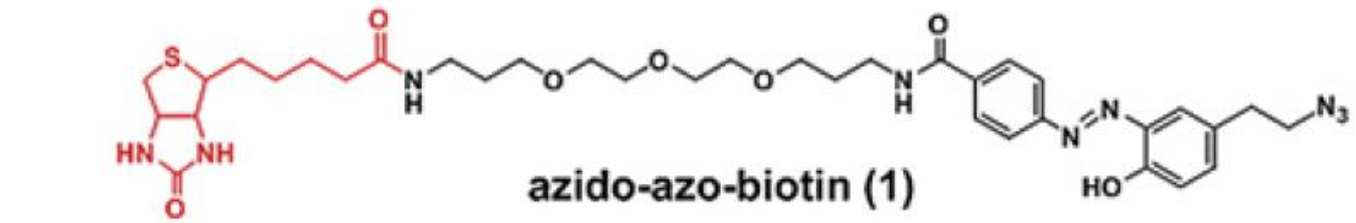
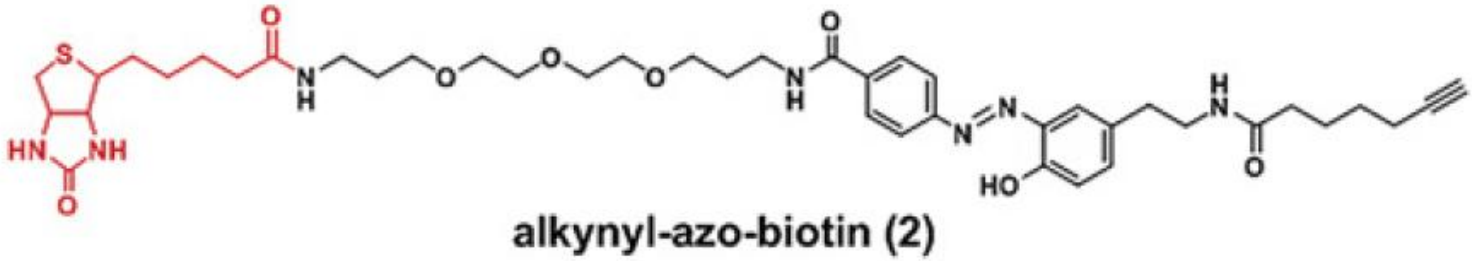
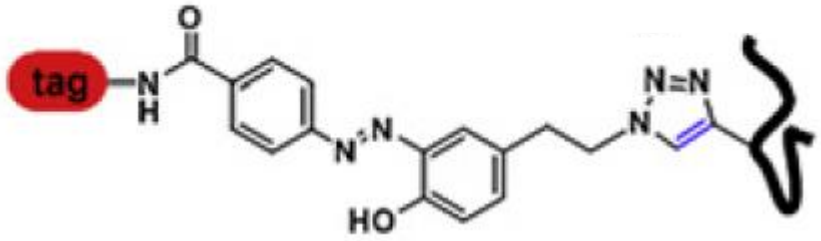






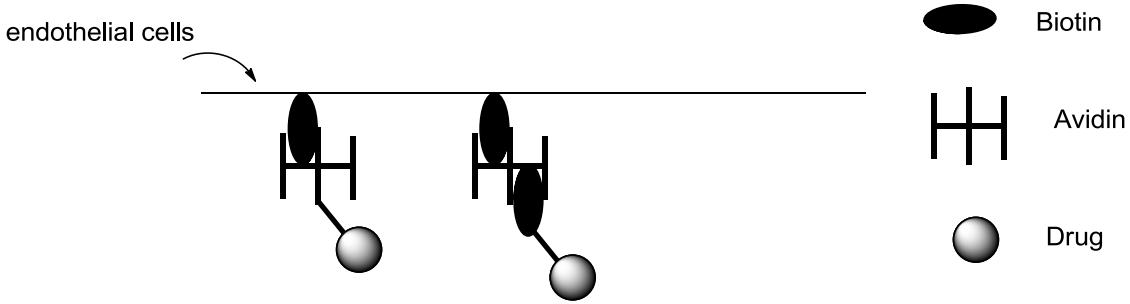
3. Applications in drug delivery

Example I: A novel intravascular drug delivery method using endothelial biotinylation and avidin-biotin binding

The use of a vascular catheter has allow the delivery of drugs to a limited region selectively. However, the blood flow usually flushes away drugs as soon as they are injected.

Solutions:

- **endothelial cells were first biotinylated directly by biotin-LC-NHS**
- **Bound by an avidinated drug or, using avidin as a linker, a biotinylated drug**



Results:

The drugs that were fixed to the cells resist being flushed away with blood flow, allowing continuous drug delivery in certain target organs

Example II: Electrically controlled drug delivery from biotin-doped conductive polypyrrole

Conducting polymers (e.g., polypyrrole) offer the possibility of controllavle drug administration through electrical stimulation.

- **Attach molecules to the surface of PPy through biotin-streptavidin coupling**
- **After attachment of the desired molecule to the biotin dopant, drug release is triggered through electrical stimulation (3 V was applied, or an external field being applied)**