Richard W Horobin declares the following presentation, entitled

In situ imaging of tumors using smart probes – are they as smart as people think?

In situ imaging of tumors using "smart probes"— are they as smart as people think?

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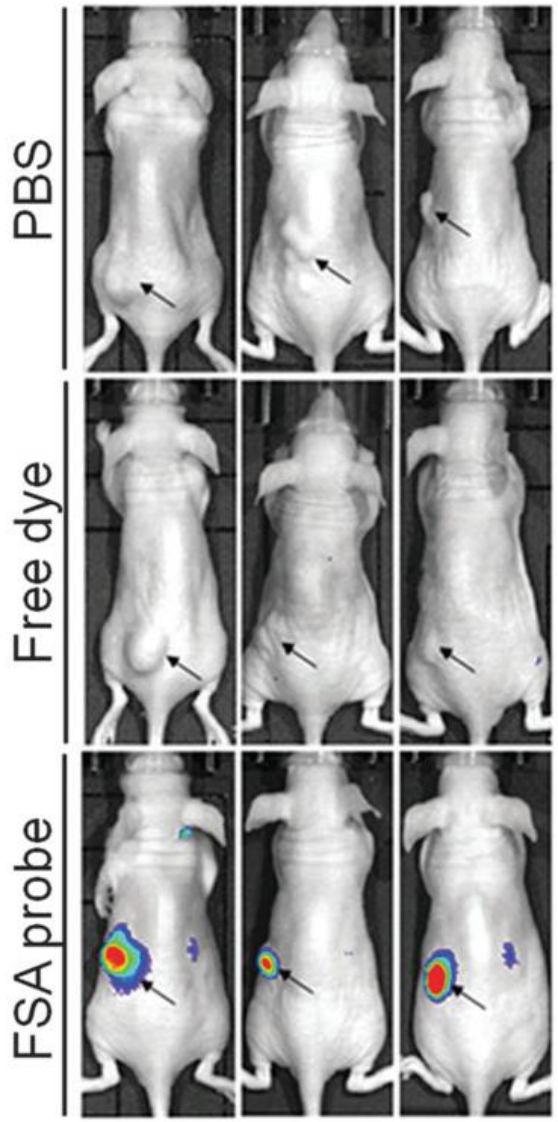
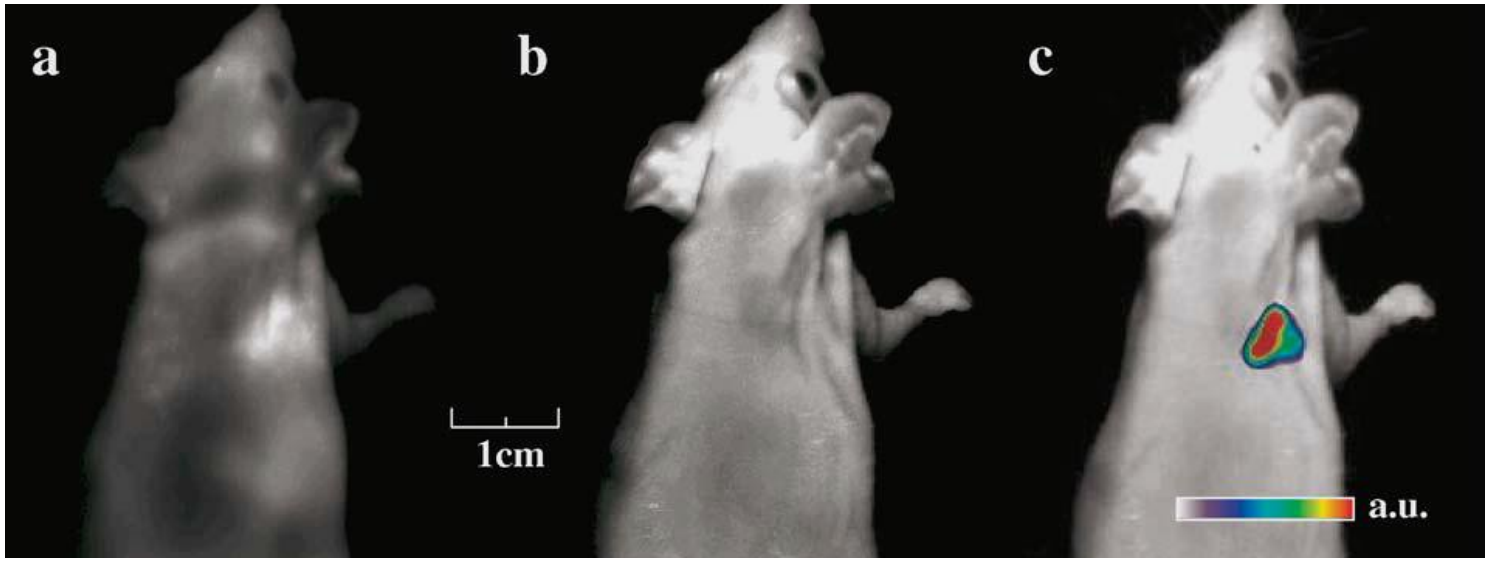
BIOLOGICAL STAIN COMMISSION

“In situ tumor imaging”?
Just what are we talking about here?



Lee et al 2014



Ntziachristos et al 2003

What clinical applications are envisaged for in vivo tumor imaging?

For diagnosis

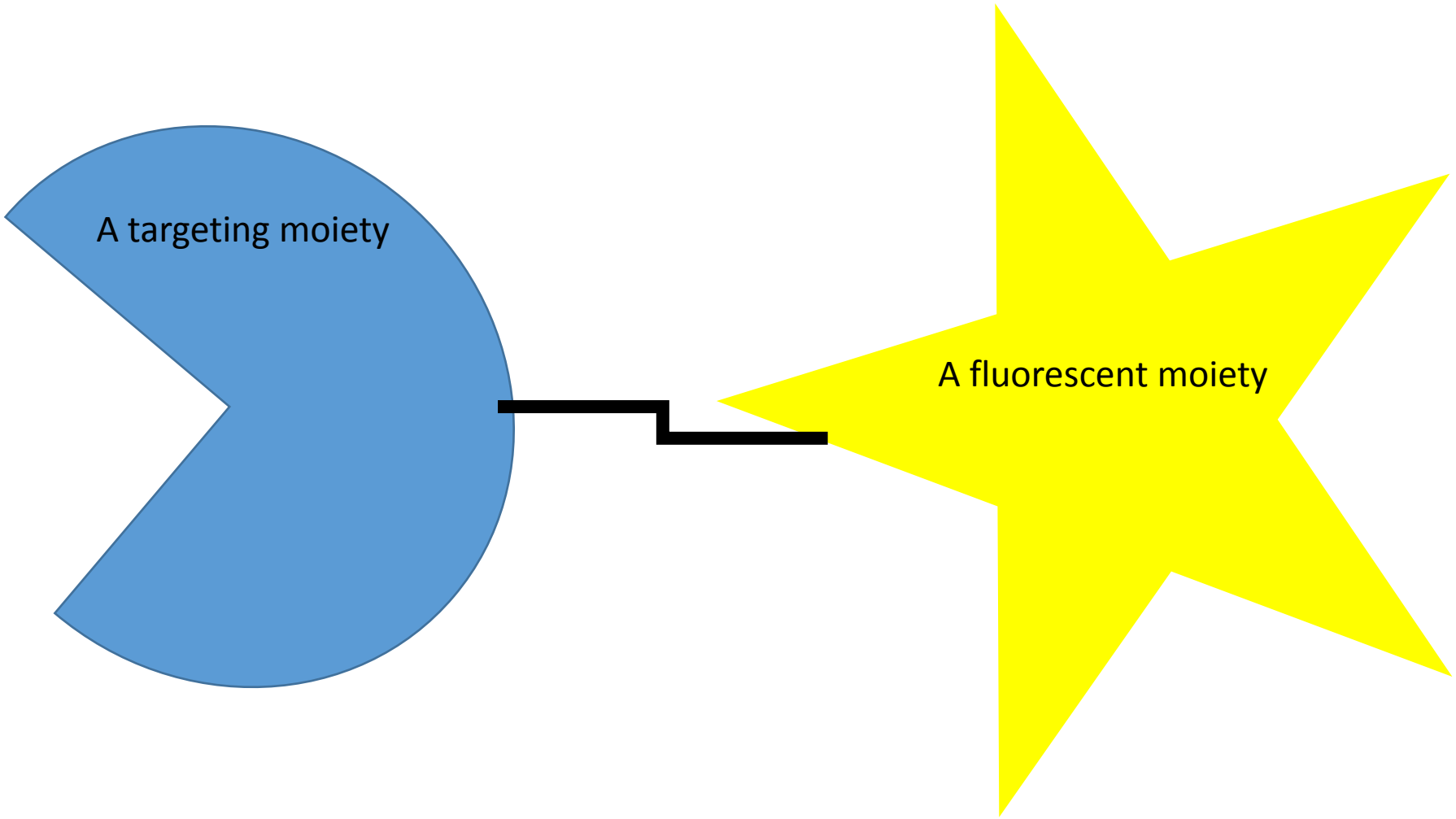
For guiding surgery

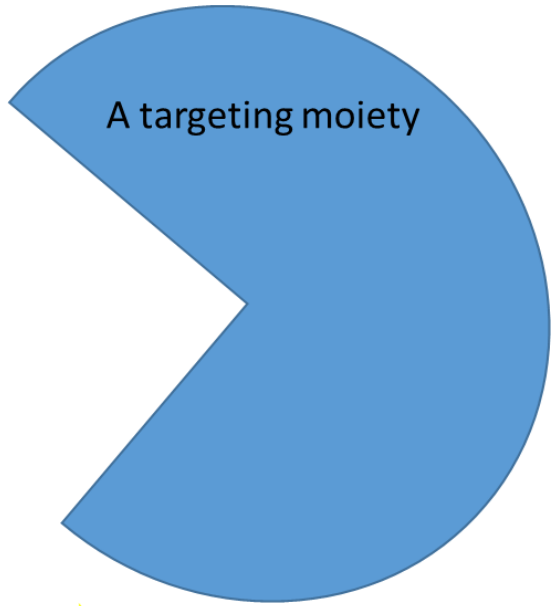
For monitoring chemotherapy

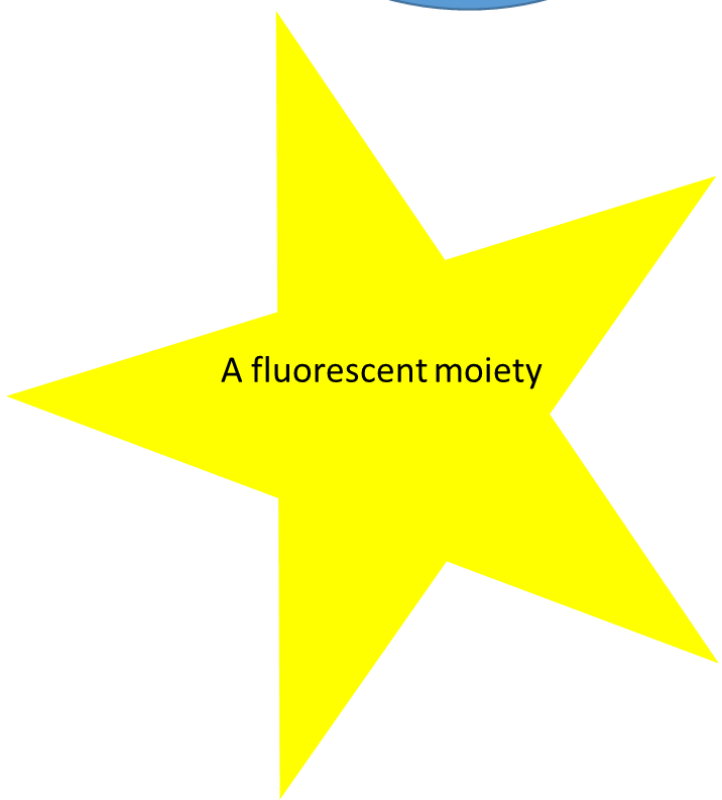
What are “smart probes”?

And, more particularly, what kinds of smart probes are we concerned with today?

Small-molecule fluorescent compounds with the ability to target biochemically or metabolically anomalous tumor cells in a live animal.


A targeting moiety
A fluorescent moiety





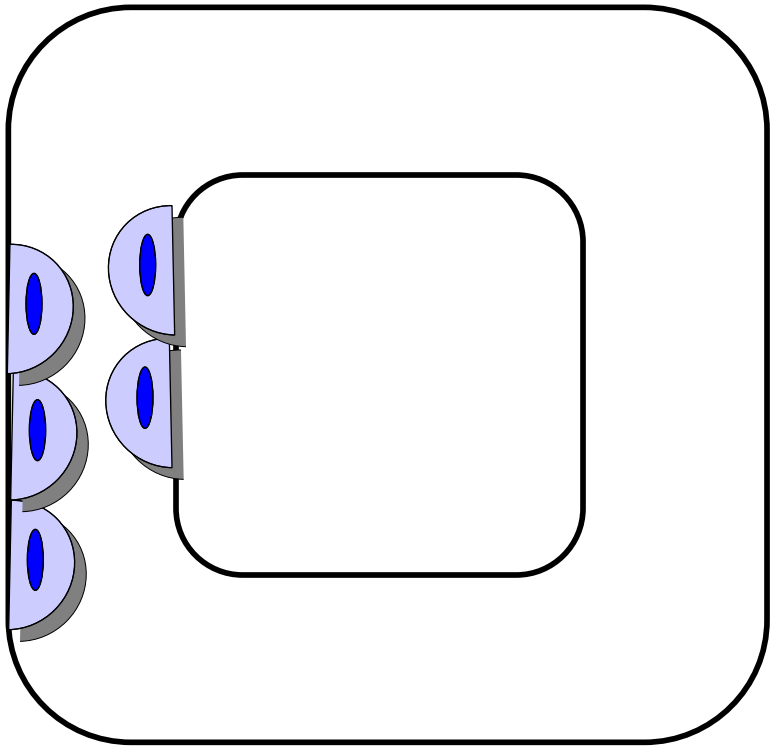
Lee et al 2014

Typical development protocol for a novel "smart probe"

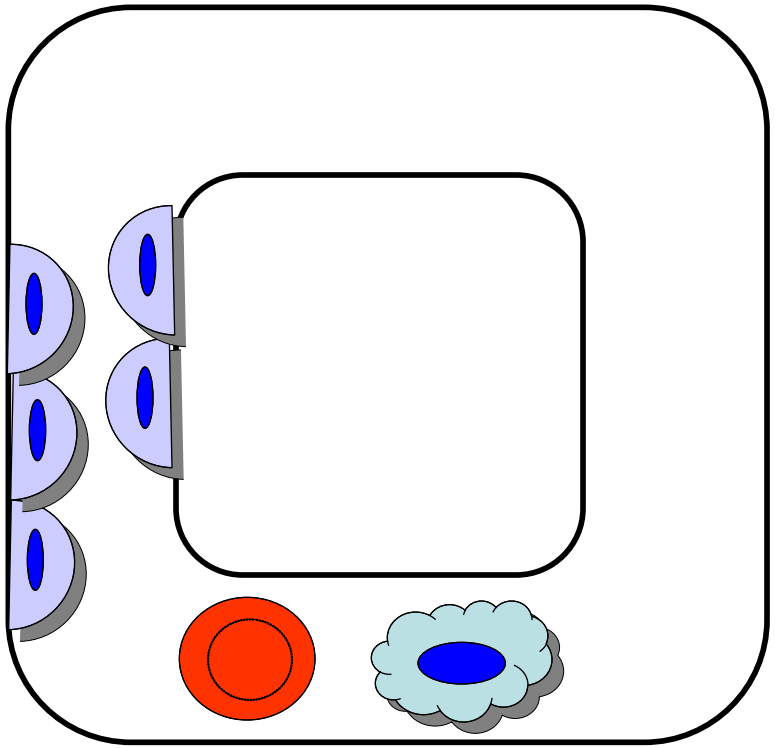
1. Have an idea, synthesize a novel probe.
2. In cell culture, check if the probe binds with cancer cells & does not bind to non-transformed cells. If probe ***is*** selective for cancer cells …
3. Check if the probe binds to experimental tumors in a lab rodent.
4. If yes … publish.

Blood vessels of the circulatory system

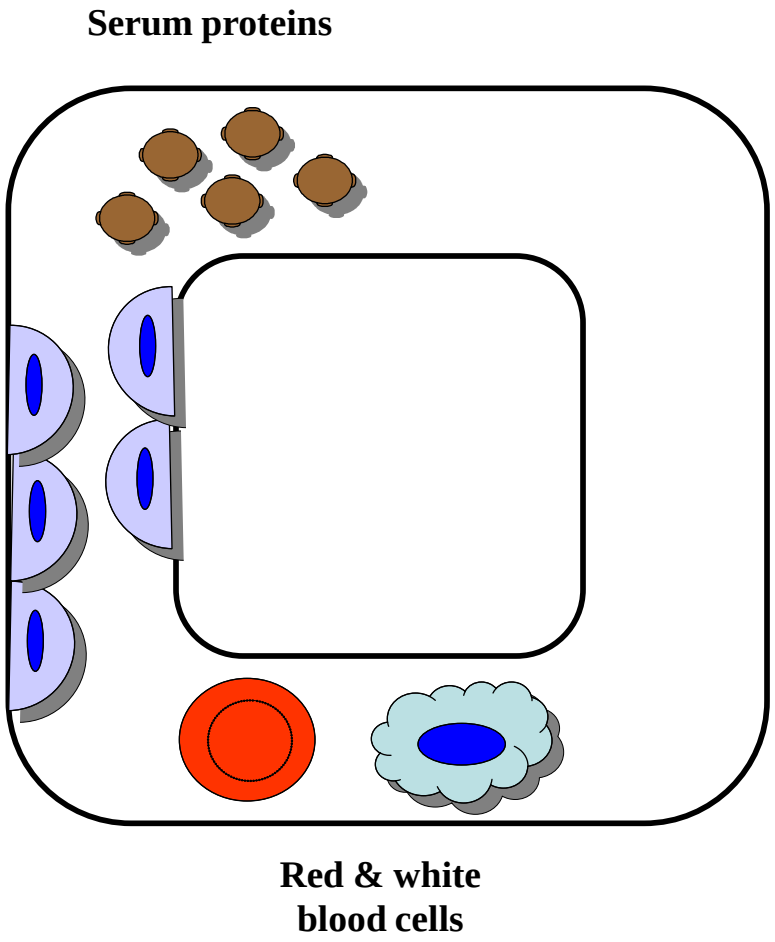
Endothelial cells lining the blood vessels



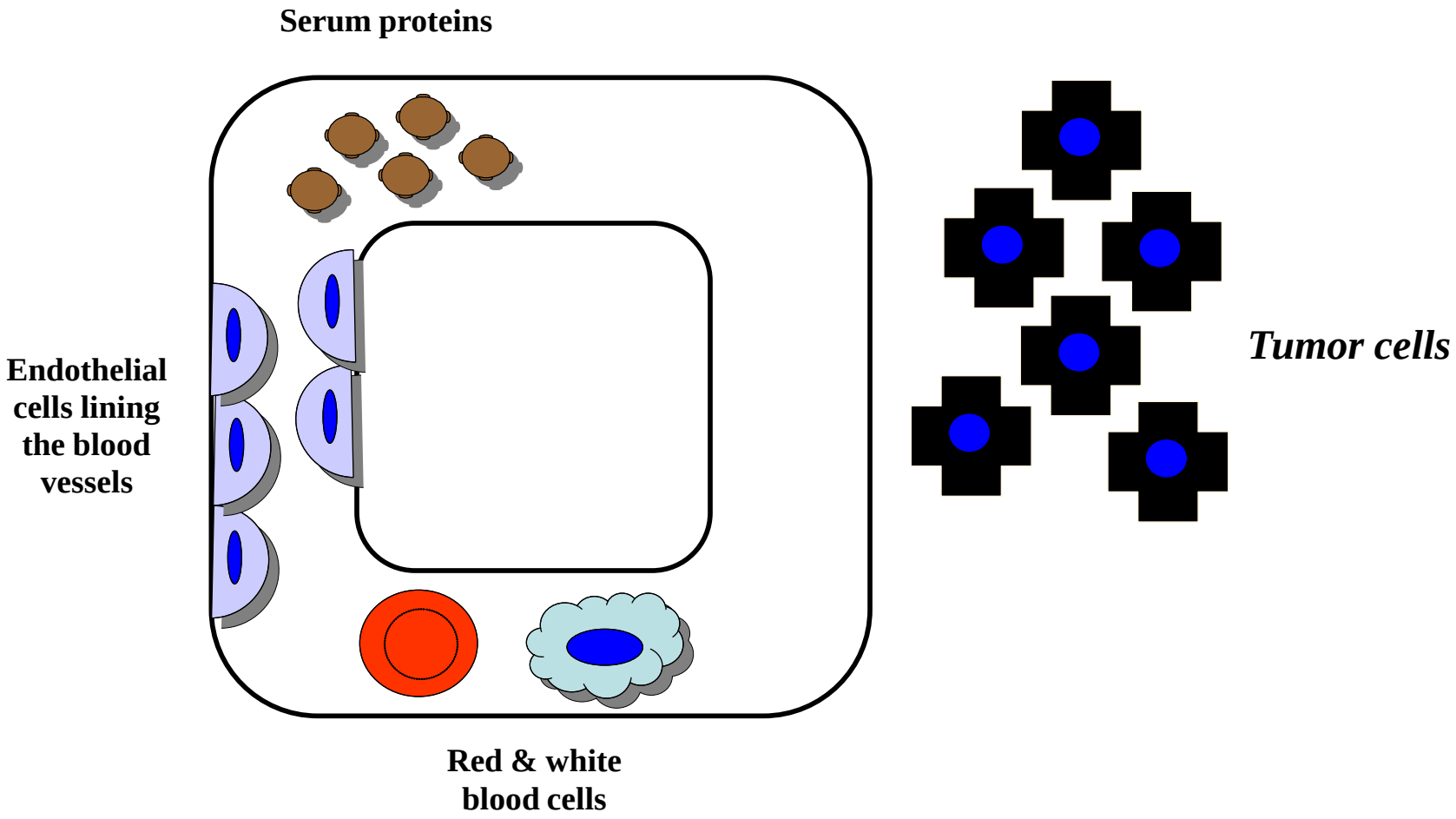
Blood vessels of the circulatory system



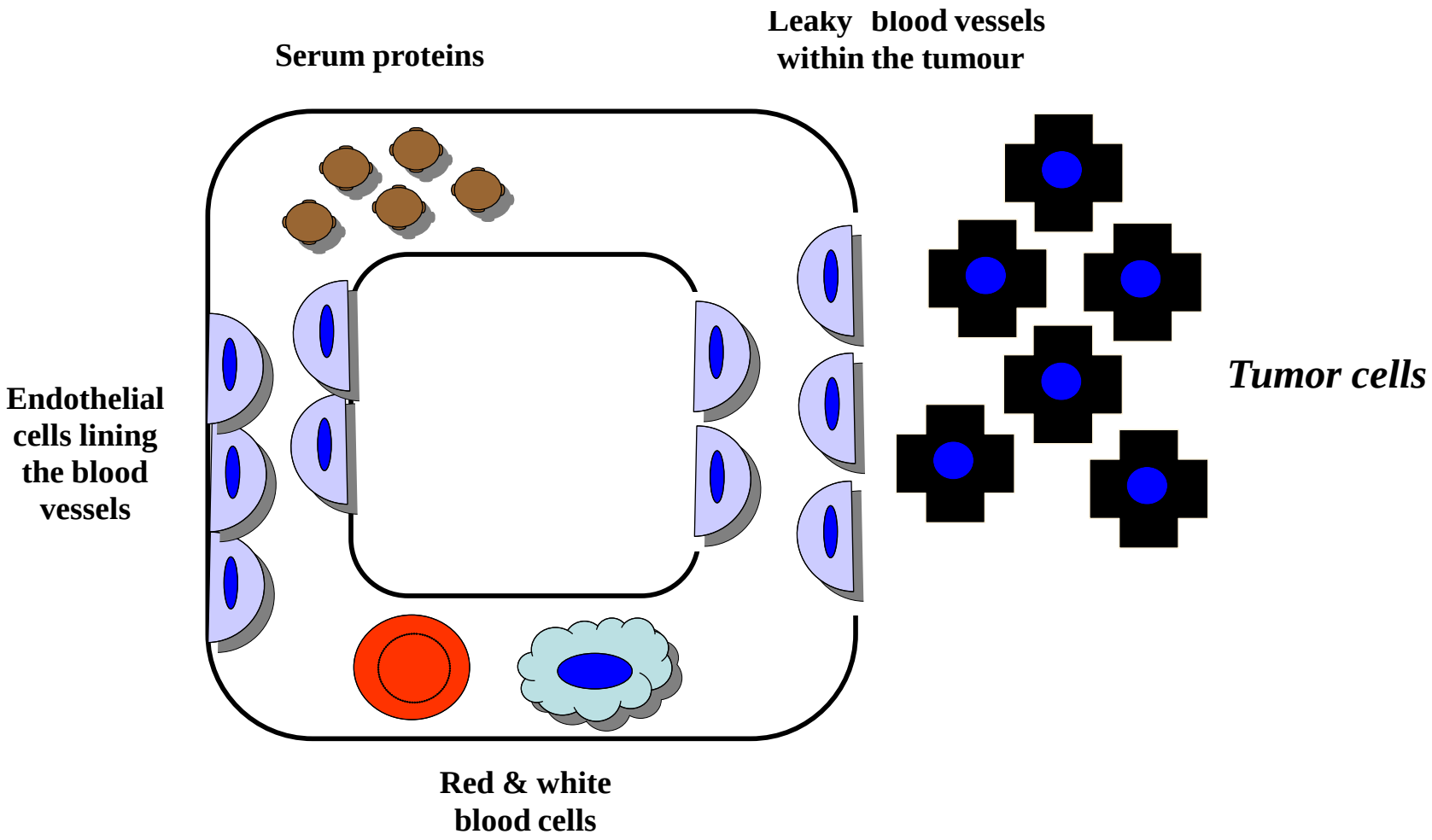
Blood vessels of the circulatory system



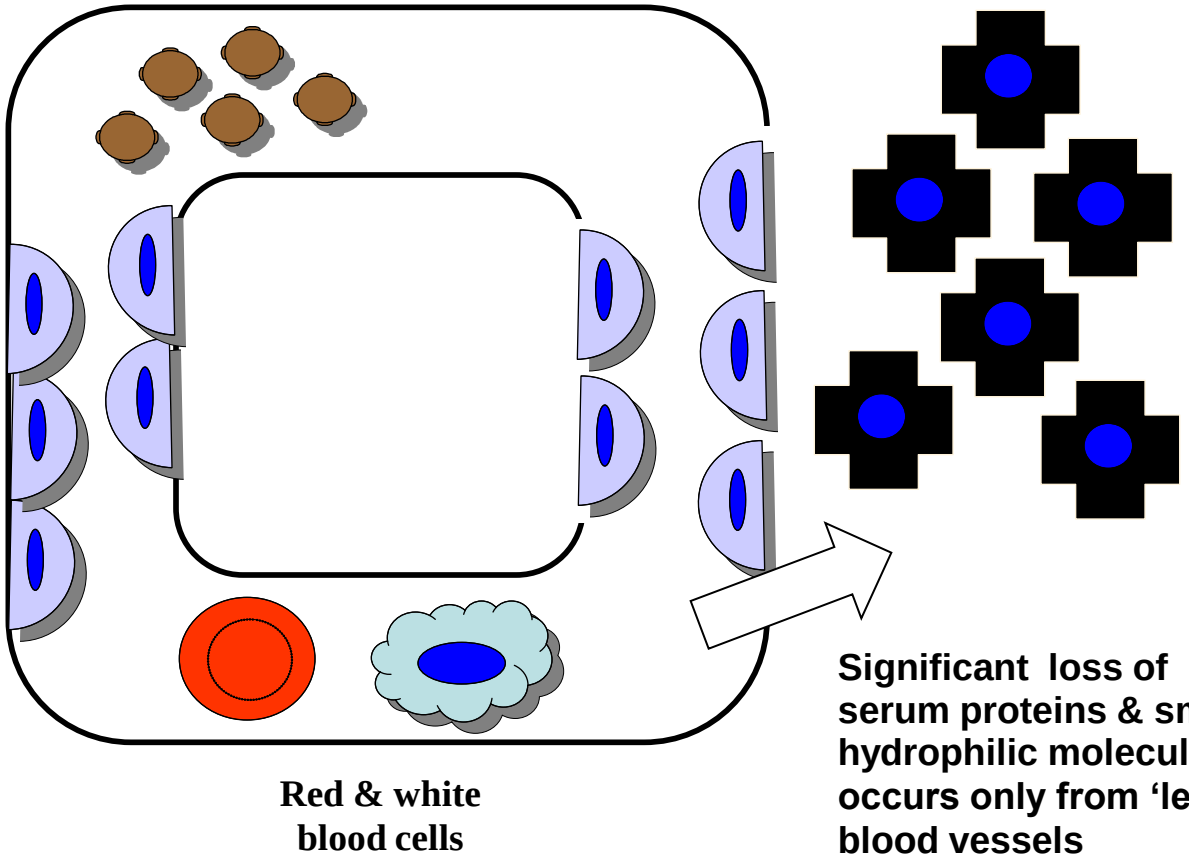
Blood vessels of the circulatory system



Blood vessels of the circulatory system



Blood vessels of the circulatory system



Consequently, slow diffusing probes will accumulate due to this "enhanced permeability and retention effect"

Probe accumulation in a tumor is favoured by enhanced permeability and retention

This effect is additional to any "smart targeting".

How do probe properties influence enhanced *permeability*?

High water solubility ✓

Strong binding to proteins ✓

Strong binding to cells ✗

How do probe properties influence enhanced *retention*?

Slow diffusion in free solution ✓

Strong binding to proteins ✓

Strong binding to cells ✓

Distinguishing effective from ineffective probes — building & testing a simplistic model

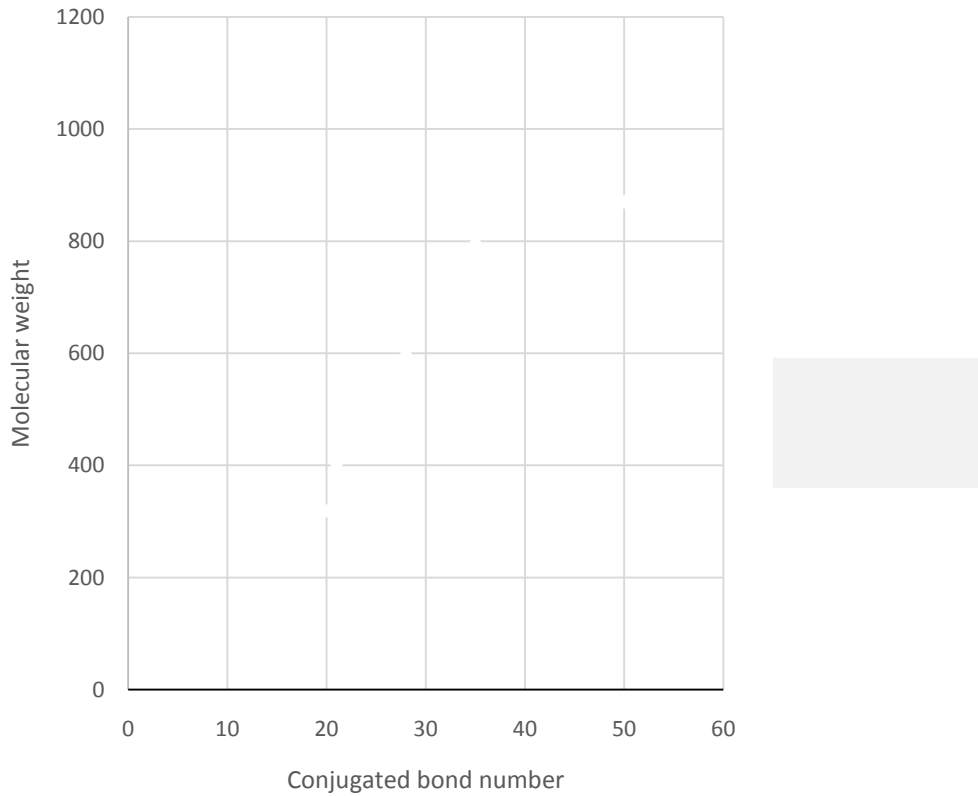
Assuming enhanced permeability & retention

1. Assume diffusion and protein binding of probes are both important factors.
2. Assume rate depends on overall molecular size; and protein binding depends on aromatic system size.
3. Model overall & aromatic system sizes by molecular weight and conjugated bond number respectively.

Distinguishing effective from ineffective probes — building & testing a simplistic model

Assuming enhanced permeability & retention

4. Identify a set of **non**smart probes which accumulates in tumors, and another set which does not.
5. Plot these sets on a MW-CBN diagram.
6. If the model is valid, the two sets should fall in different parts of the diagram.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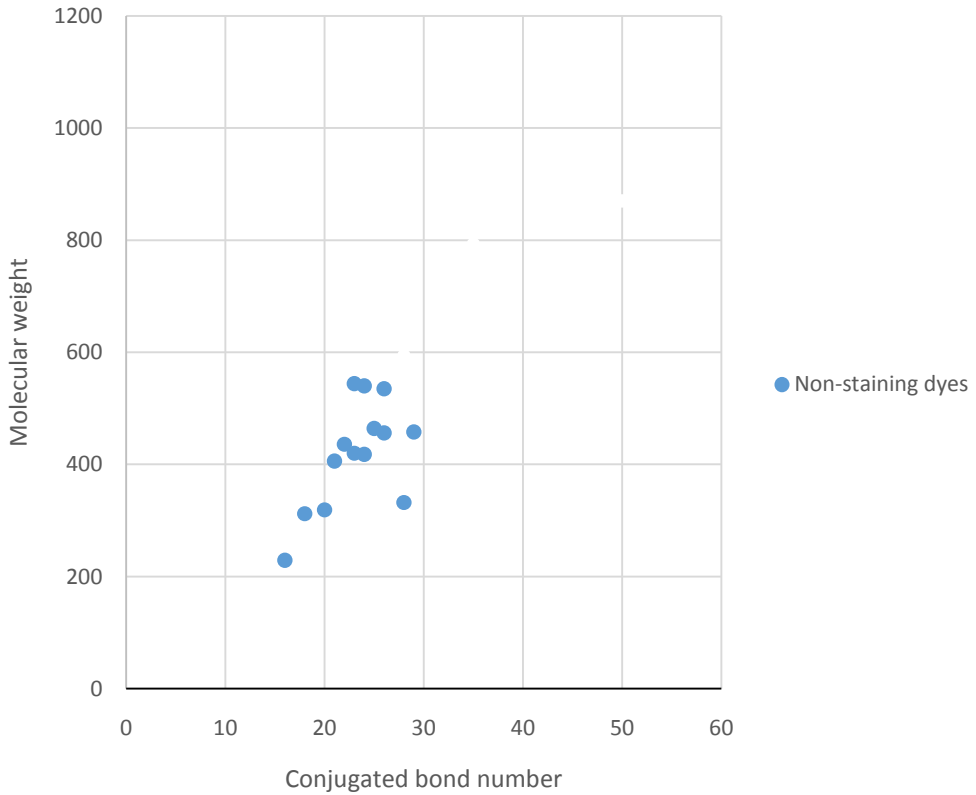
Conjugated bond number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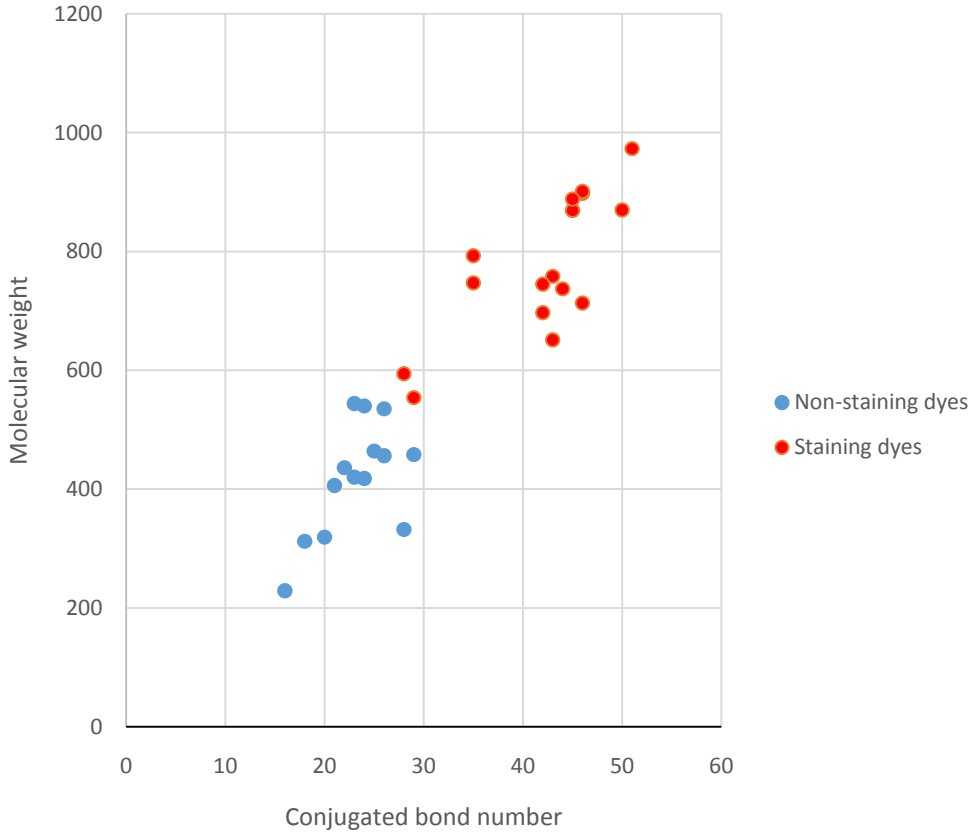
Non-staining dyes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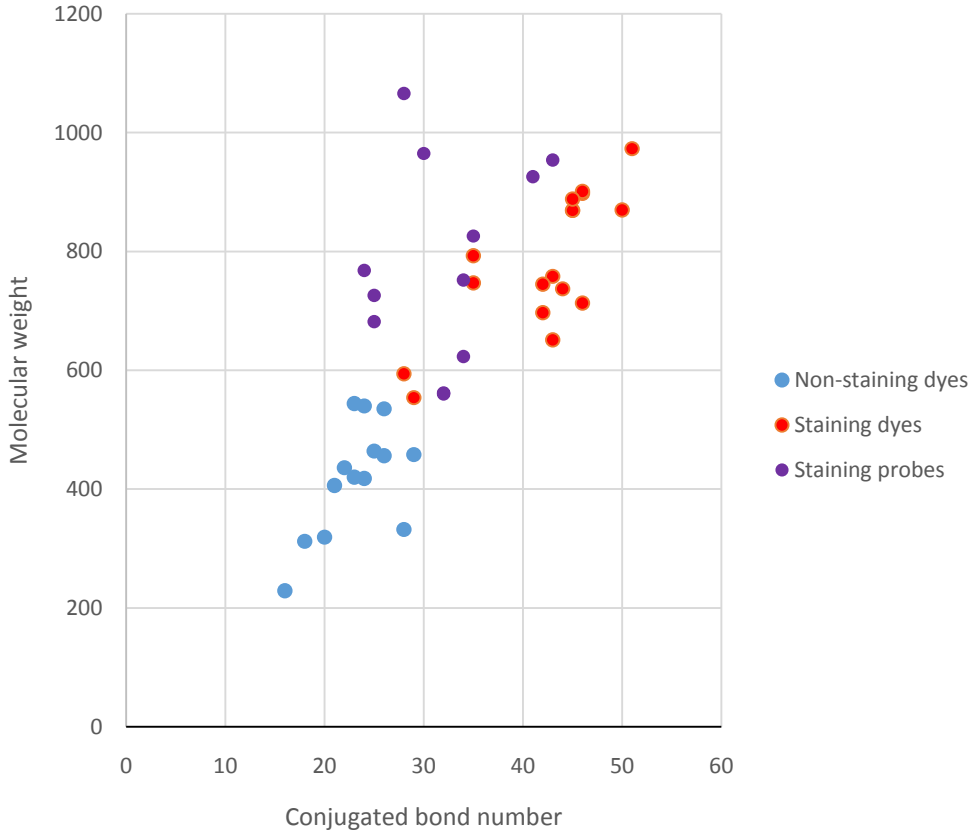
Non-staining dyes
Staining dyes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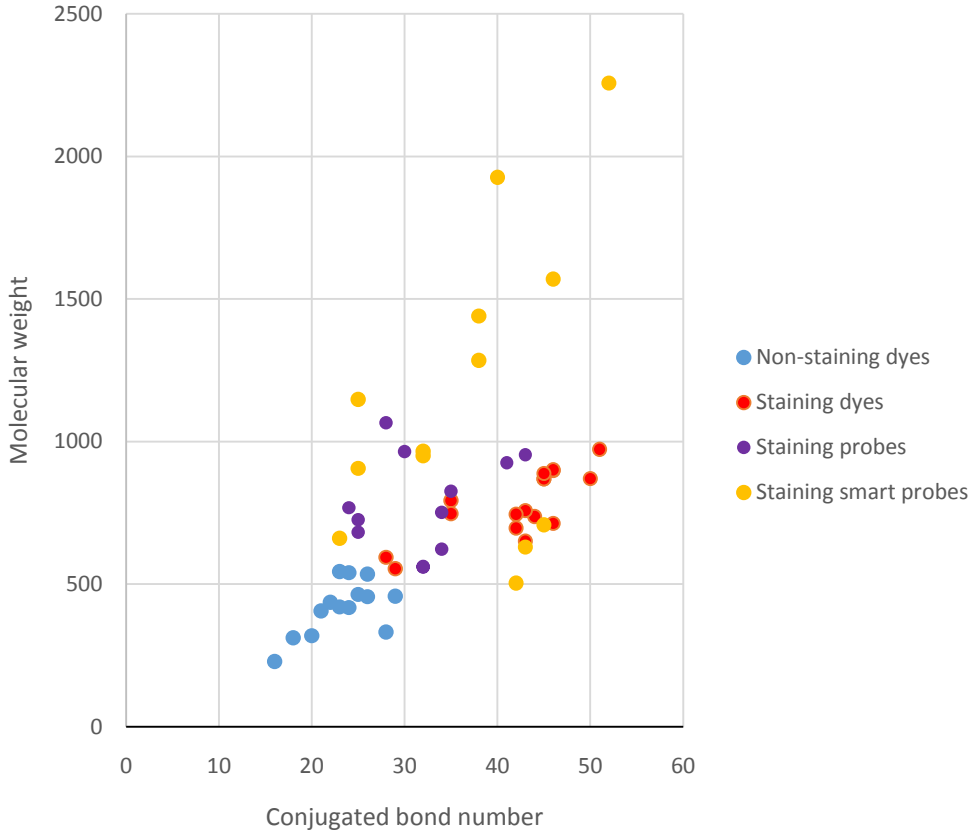
Non-staining dyes
Staining dyes
Staining probes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Conjugated bond number
Non-staining dyes
Staining dyes
Staining probes
Staining smart probes

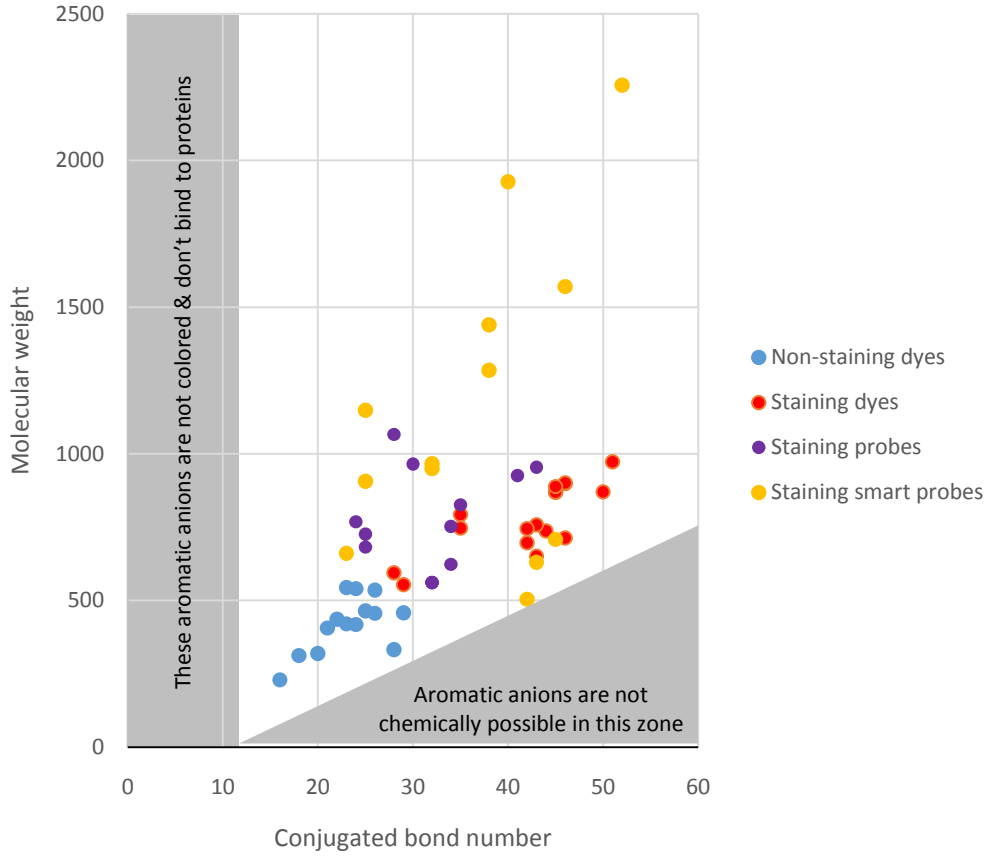
Now we have seen that “smart” probes fall into the same region of the plot as **not**-smart tumor-localizing dyes and probes.

This implies that localization of smart probes is due to both their “smartness” *and* to the enhanced permeability and retention effect.

So does this mean that smart probes are in fact not “smart”?

No, since “smartness” ensures that probes are located on or inside tumor cells, not merely within the tumor.

So maybe we should say that “smart probes” are actually *smarter* than was thought? Or, at least smarter than the chemists who made them had thought?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Molecular weight
These aromatic anions are not colored & don't bind to proteins
Aromatic anions are not chemically possible in this zone
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50
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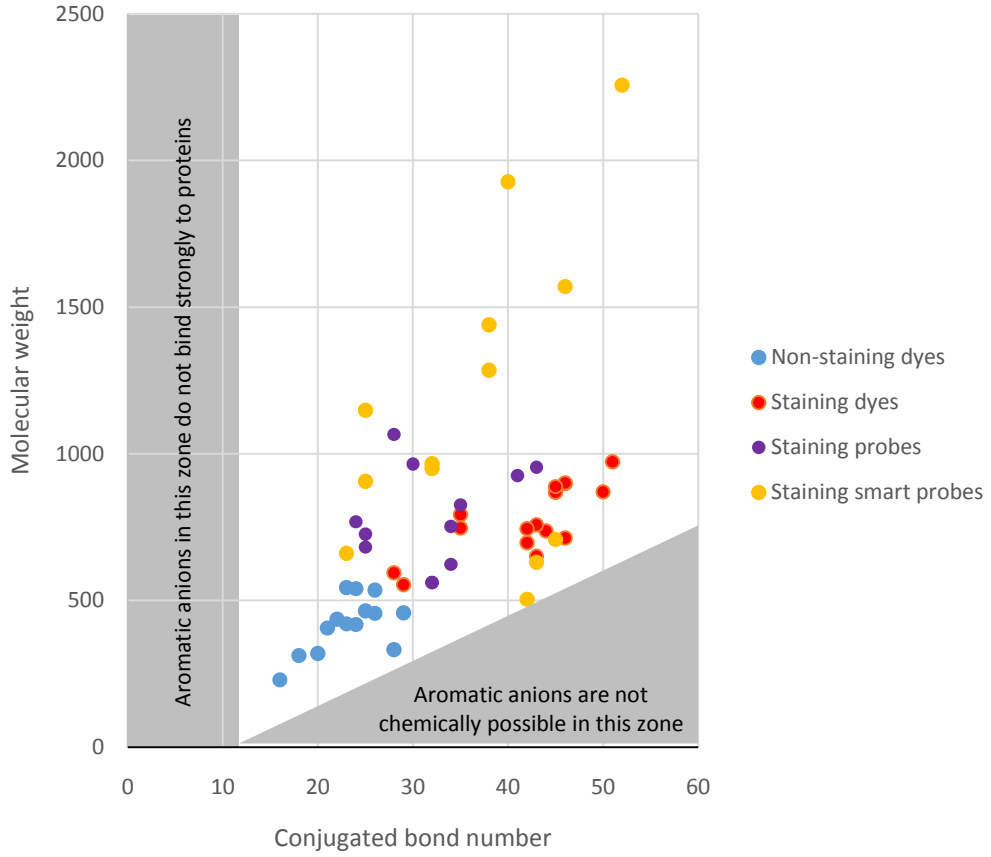
Conjugated bond number
Non-staining dyes
Staining dyes
Staining probes
Staining smart probes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Molecular weight
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Conjugated bond number
Aromatic anions in this zone do not bind strongly to proteins
Aromatic anions are not chemically possible in this zone
Non-staining dyes
Staining dyes
Staining probes
Staining smart probes

Blood vessels of the circulatory system