Nanotek & Expo 2014

Biodegradable nanobrushes for drug delivery

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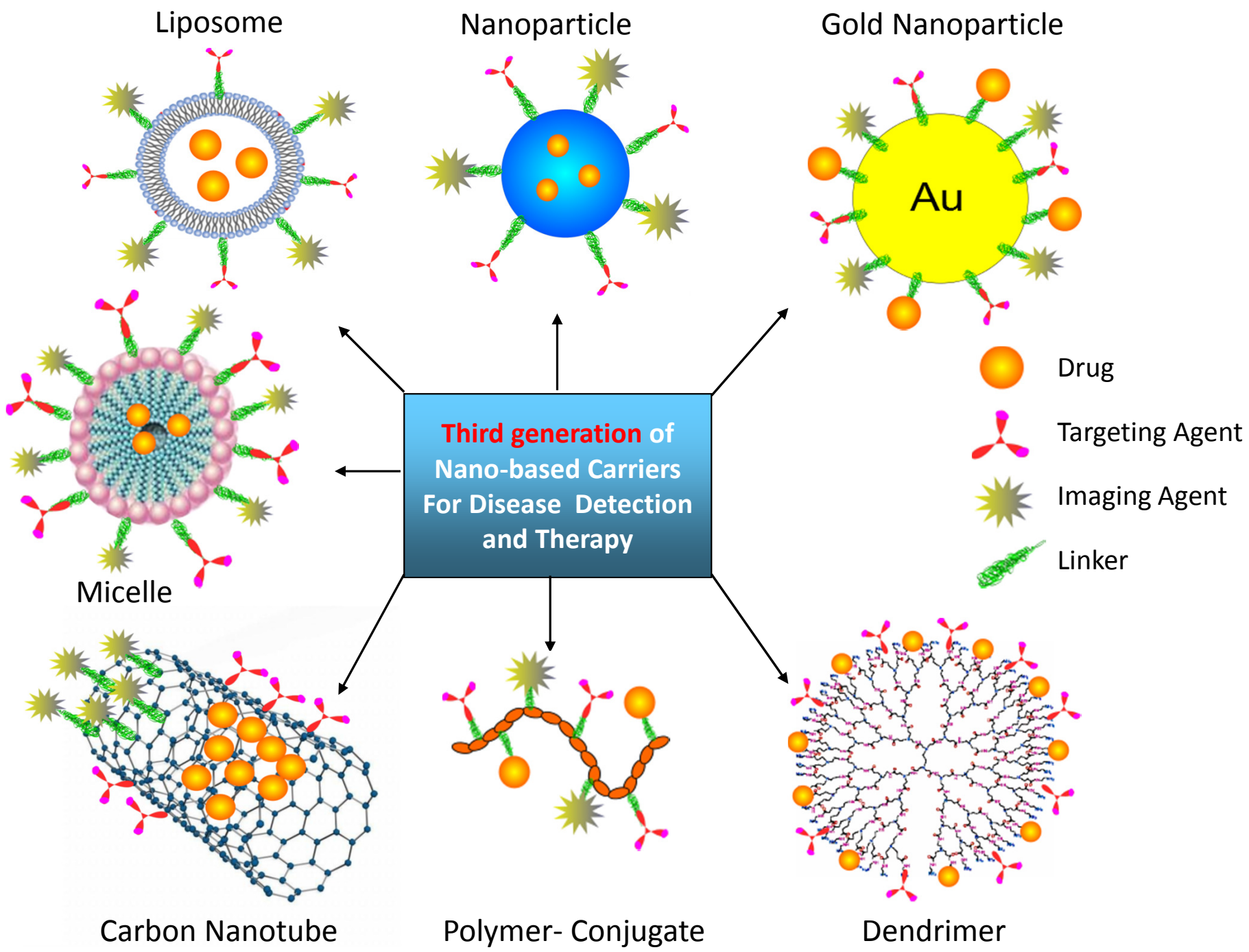
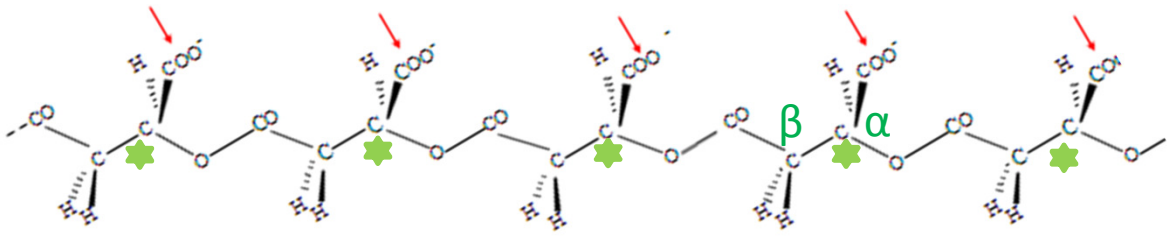

Liposome
Nanoparticle
Gold Nanoparticle
Au
Drug
Targeting Agent
Imaging Agent
Linker
Third generation of Nano-based Carriers For Disease Detection and Therapy
Micelle
Carbon Nanotube
Polymer- Conjugate
Dendrimer

Synthesis and degradation

Poly(β-L-malic acid)



Physarum: **HOOC** ~~~~ **OH**

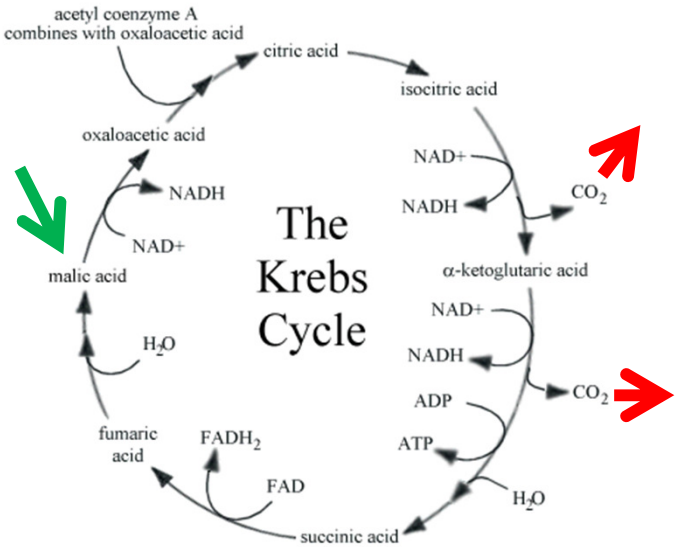
n = 500 to 3000

Aureobasidium: HOOC ~~~~ OH

n = 40 to 80

Depolymerisation:
Spontaneous
& Enzymatic

Malate



Purification

Plastic bags

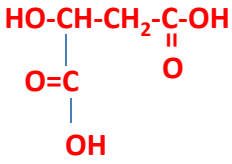
Medical support

Drug delivery
Malignancy
Infection

Contrast agents
Imaging

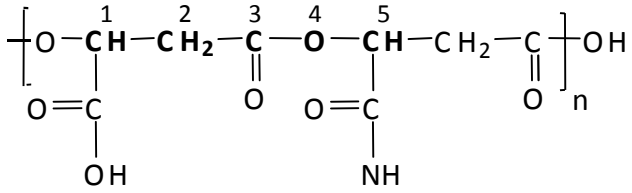
Nano scale

Polycefin – Functional Core



L-Malic acid

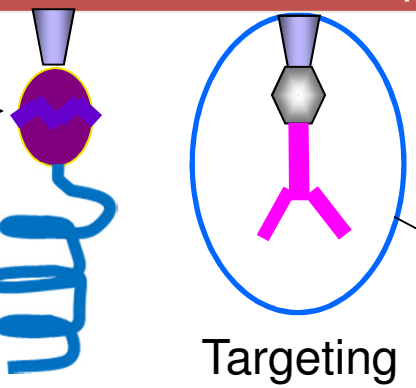
Polymalic acid-trileucine copolymer



Leu-Leu-LeuCOOH

Polymalic acid-trileucine copolymer

Disulfide, cleaved by Glutathion in the Cytoplasm

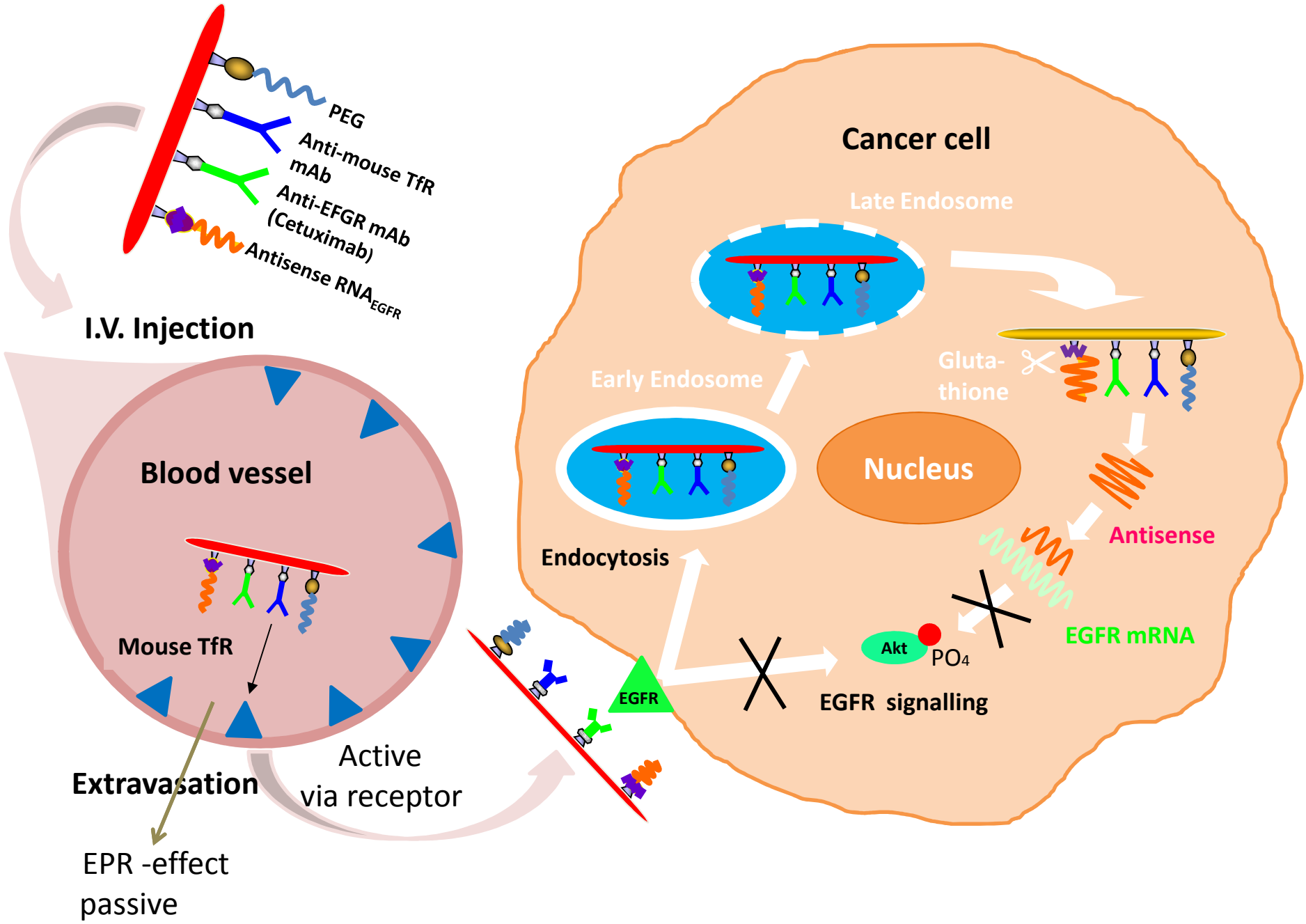


Targeting

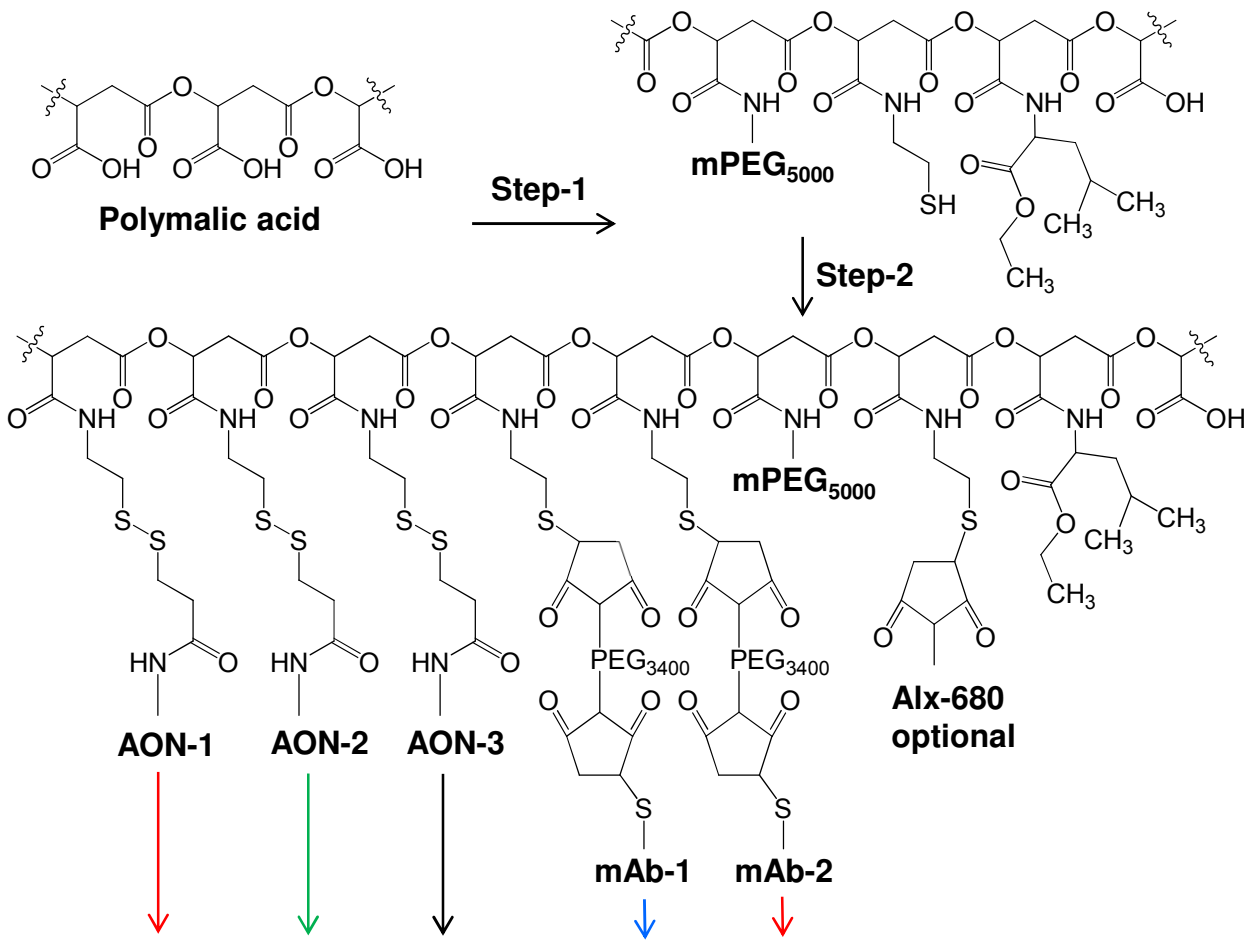
Prodrug

Antisense Oligonucleotide

Monoclonal Antibody (mAb)


PEG
Anti-mouse TfR mAb
Anti-EFGR mAb (Cetuximab)
Antisense RNA$_{EGFR}$
I.V. Injection
Blood vessel
Mouse TfR
Extravasation
EPR -effect passive
Active via receptor
EGFR
Cancer cell
Late Endosome
Early Endosome
Endocytosis
Gluta-thione
Nucleus
Antisense
EGFR mRNA
Akt
PO4
EGFR signalling

Preparation of nanodrugs for brain tumor treatment

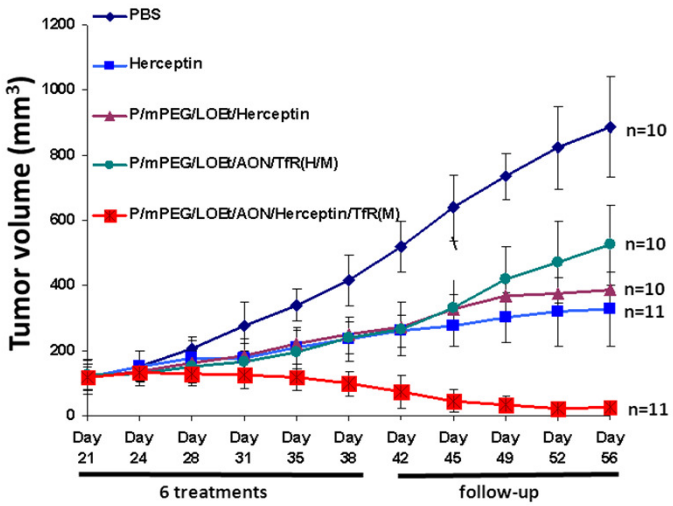


GBM:	Chain-α4	Chain-β1	(-)	anti-MsTfRmAb	anti-HuTfRmAb
HER2-positive breast:	HER2	(-)	(-)	(anti-MsTfRmAb)	Herceptin
Triple-negative breast:	EGFR	(-)	(-)	(anti-Ms-TfRmAb)	Cetuximab

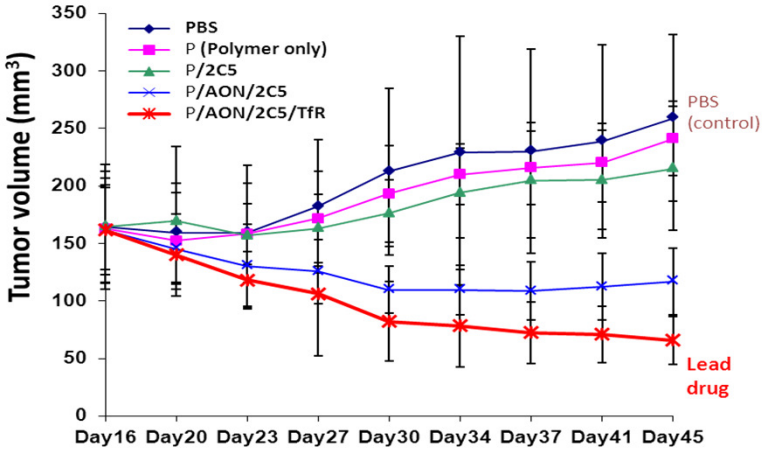
Examples for drug delivery by Polycefin variants

Primary breast cancer

Primary **HER2-Positive Breast Cancer**



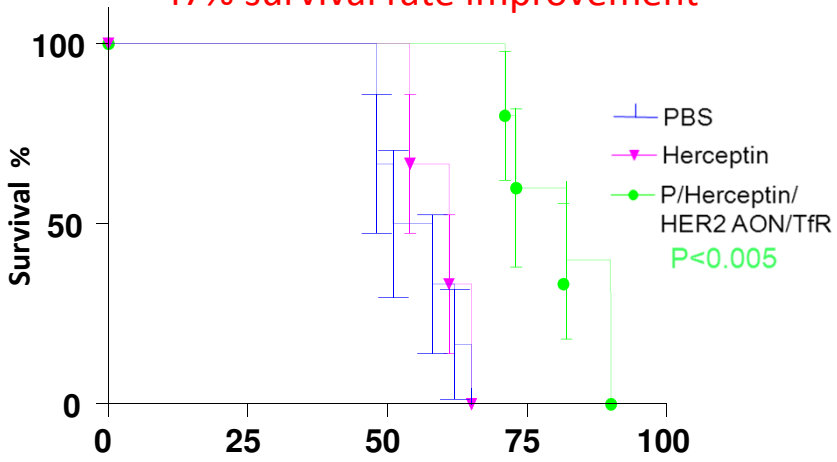
Primary **Triple Negative Breast Cancer**



Brain metastases

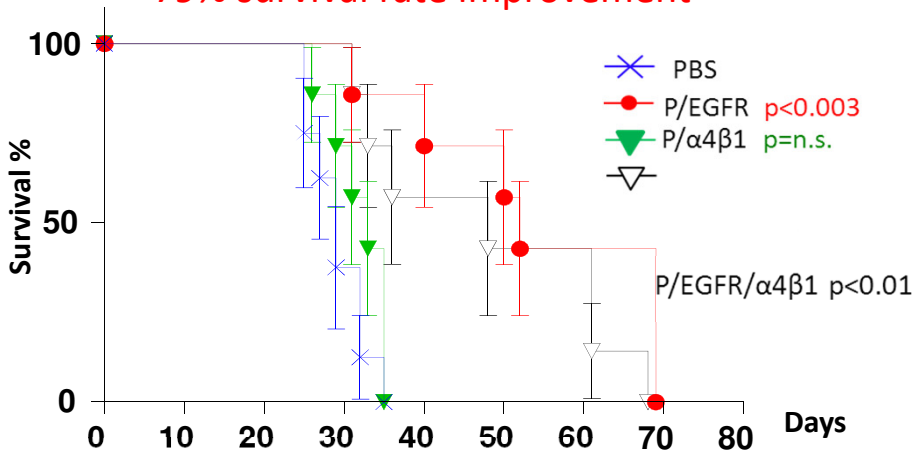
Metastatic **HER2-Positive Breast Cancer**

47% survival rate improvement



Metastatic **Triple Negative Breast Cancer**

79% survival rate improvement



High potential for drug delivery

High potential for personal treatment of malignancies

Replacement of antibody by affinity peptide: Pro and Contra

Pro	Contra
Multiple peptides per conjugate	Less affinity to bind to target
Robust structure	Absence of Fc and biological activity
Small size for slender shape of polymeric nanoconjugate	Less passive tissue targeting (EPR)
Increased diffusibility Deep tissue penetration	Low Stability/reduced longevity in plasma
Reduced immunogenicity Humanization not required	Possibility of unscheduled side reactions
Possibility of multivalency	Tendency for aggregation
Chemical fabrication	
Easy packaging and delivery. Decreased overall MW of nanodrug and less injectable drug volumen	

1. Example

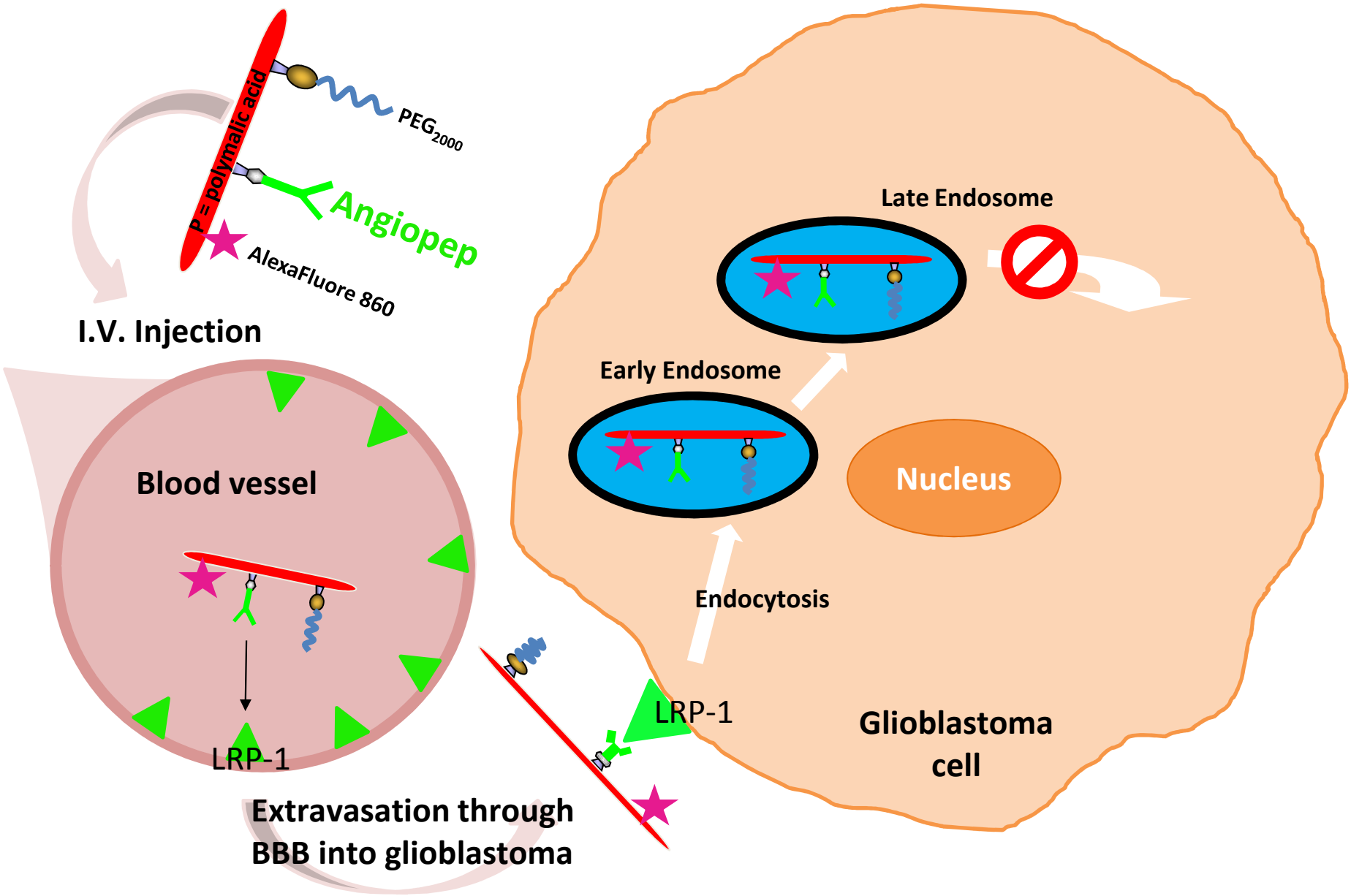
Targeting Brain tumor

Angiopep

Michel Demeule, et al. (2008) J Parm Exp Therapeut

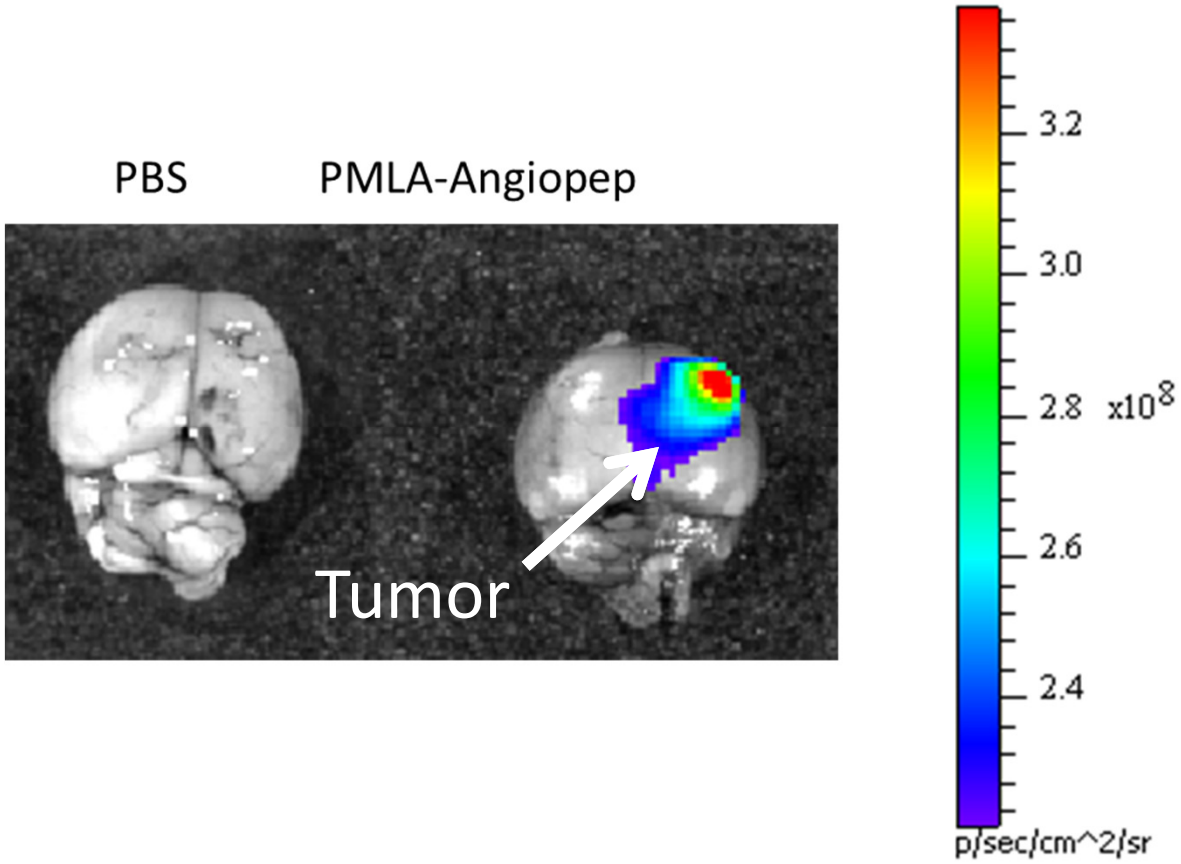
Target on BBB endothelial cells: LRP-1

Guangqing X and Liang-Shang G (2013) Int J Cell Biol



For Uptake and Imaging: P/PEG_{2000}-Angiopep(2%)/AlexaFluor 680 (0.5%)

Fluorescence Imaging of Glioblastoma-Nude Mouse Model



PMLSA-Angiopep-2: P/PEG2000-Angiopep(2%)/AlexaFluor 680

Specific problem with affinity peptides:

Self-association and aggregation because of:

- Electrostatic complementation
- Lipophilic amino acids

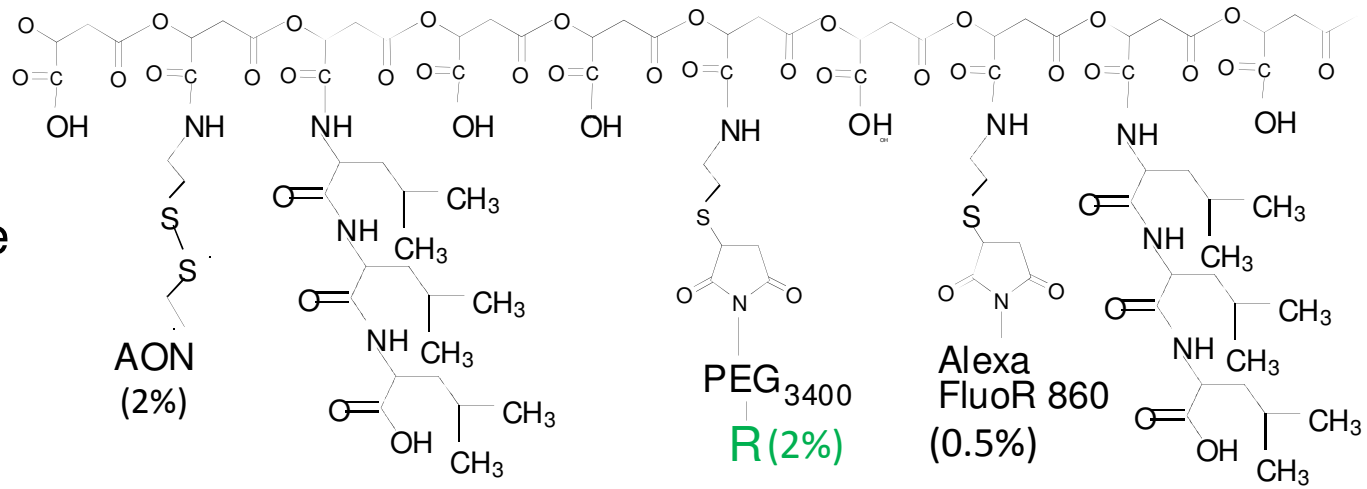
2. Example

AHNP

Target: HER2

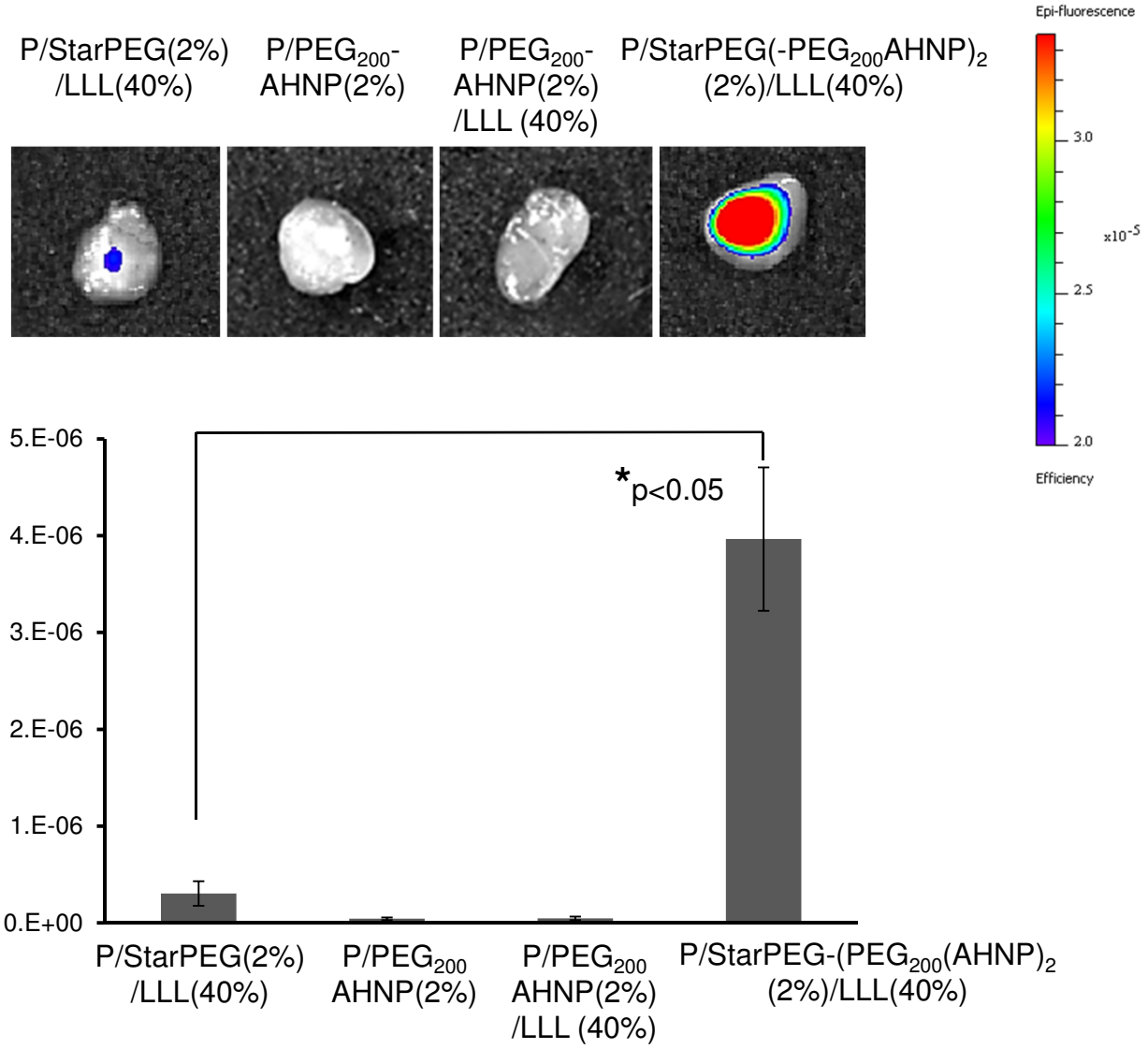
Ramachandran Murali et al. (2001) J Med Chem

Nanoconjugate
250-500 kDa

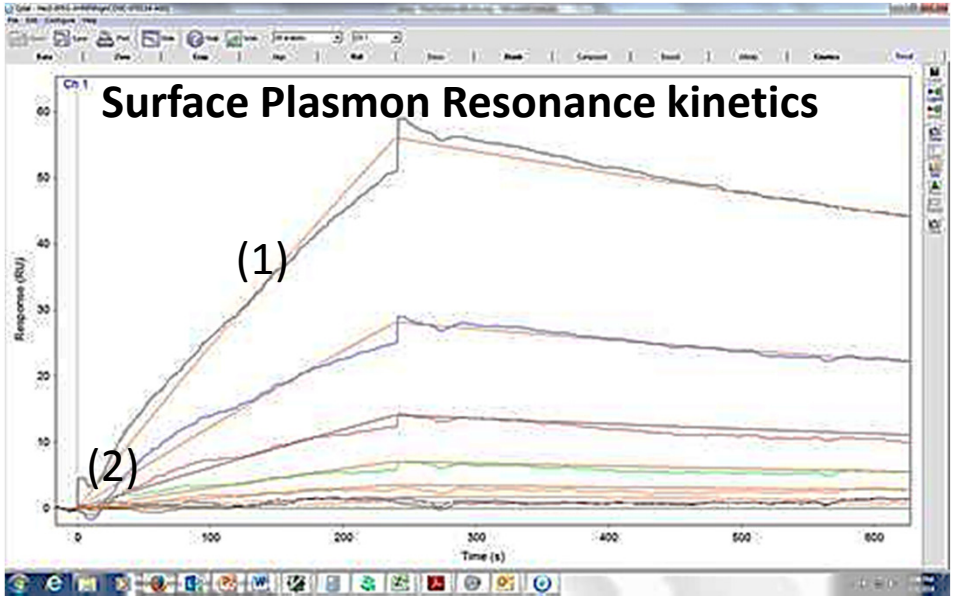


R = StarPEG(PEG_{200}AHNP)$_2$
10 kDa

In vivo Imaging of Subcutaneous BT-474 Human Breast Tumor on Nude Mice



* p-value calculated by Two-Tailed T-Test = 0.034



Rate limiting dissociation of self-aggregate

(1) $L_n \rightleftharpoons L_{n-1} + L$

L

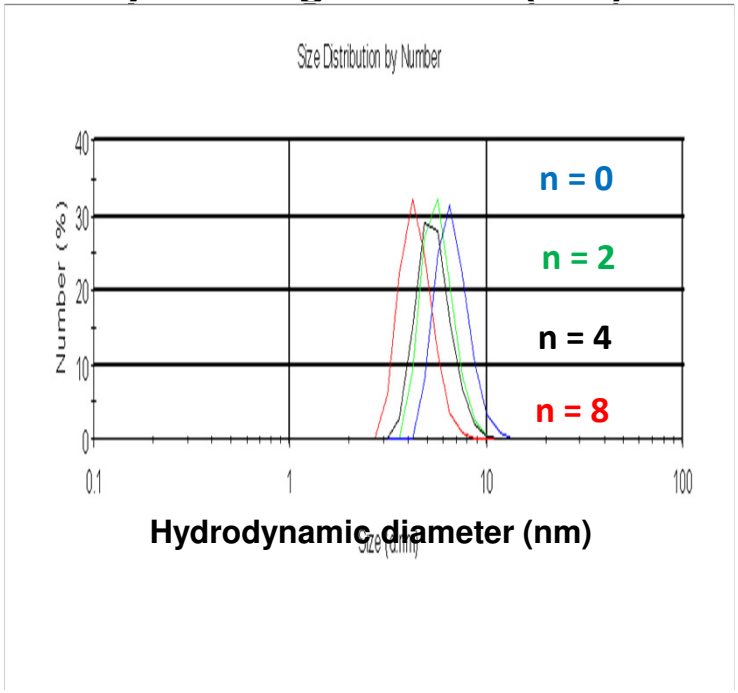
(2) $L + HER2 \rightleftharpoons HER2\text{-}L$

StarPEG(AHNP)$_n$

Surface Plasmon Resonance kinetic parameters

Code	k_{on} ($s^{-1}M^{-1}$)	k_{off} (10^{-3} sec-1)	Kd(10^{-6} M)
AHNP	800	0.42	0.52
StarPEG - AHNP2	118	0.54	4.6
StarPEG - AHNP4	1.5	0.62	41
StarPEG-AHNP6	n.d.	n.d.	n.d.
StarPEG-AHNP8	n.d.	n.d.	n.d.

Dynamic light scatter (DLS)



Conclusion:

(1) Polymalic acid is qualified for peptide targeting

(2) Need of appropriate linkers

Syntheses: Hui Ding
Imaging: Pallavi Gangalum

Martz Discovery Fund