BIOMATERIALS IN DRUG DELIVERY SYSTEMS

2014 Indo-American Frontiers of Engineering Symposium

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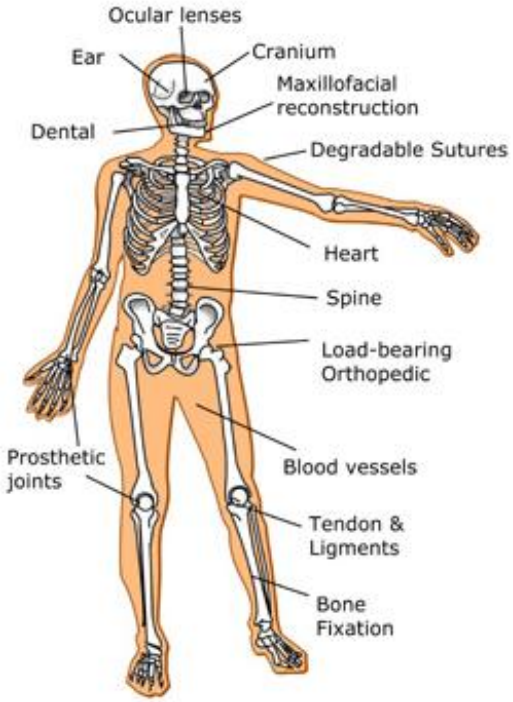
Outline

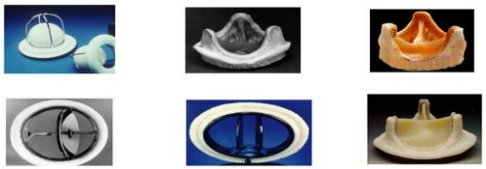
- Biomaterials
- Applications of biomaterials
- Drug delivery
- Recent developments through examples
- Conclusions & Future challenges

What are biomaterials?

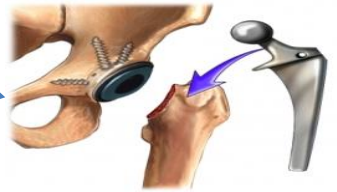
A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems (Williams, 1987)



Intraocular lens



Heart Valves



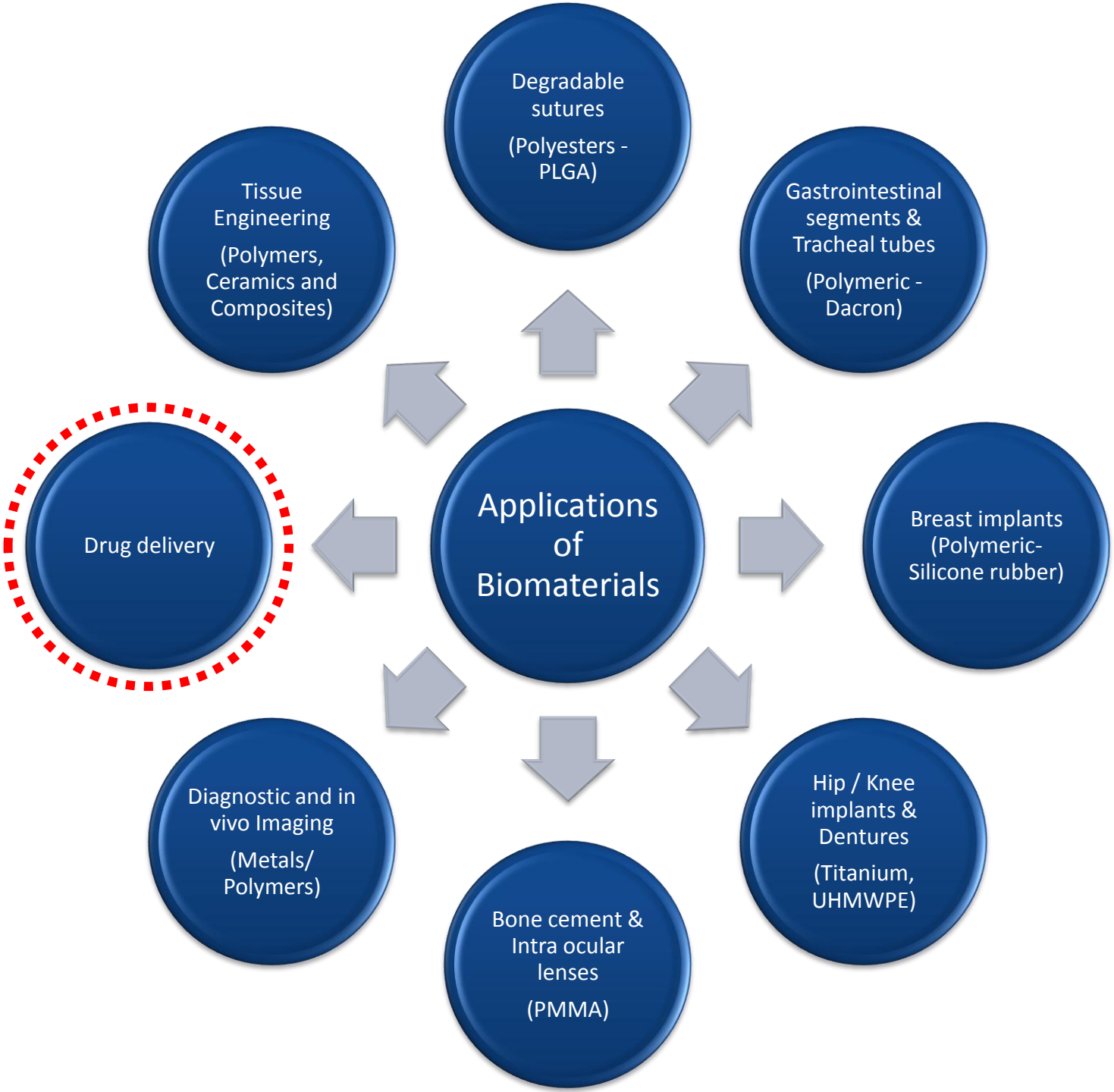
Hip Replacement

Vascular Graft

Williams, D.F.,

Proceedings of a Consensus Conference of the European Society for Biomaterials, England, 1987.

Image courtesy: MIT OCW


Applications of Biomaterials
Degradable sutures (Polyesters - PLGA)
Gastrointestinal segments & Tracheal tubes (Polymeric - Dacron)
Breast implants (Polymeric- Silicone rubber)
Hip / Knee implants & Dentures (Titanium, UHMWPE)
Bone cement & Intra ocular lenses (PMMA)
Diagnostic and in vivo Imaging (Metals/ Polymers)
Drug delivery
Tissue Engineering (Polymers, Ceramics and Composites)

Drug Delivery

‘Drug delivery’ involves the design and development of intelligent cargo carrier systems that can deliver their cargo (pharmaceutical/biological agent) to specific parts (organs/tissues/cells) in the human body on demand with control on the rate of delivery

Cargo

Small Molecules

DNA

RNA

Protein/peptide

Vehicle/Carrier

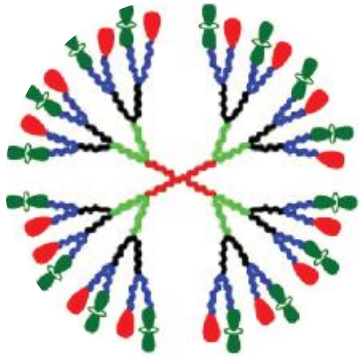
Polymeric

Lipid

Inorganic

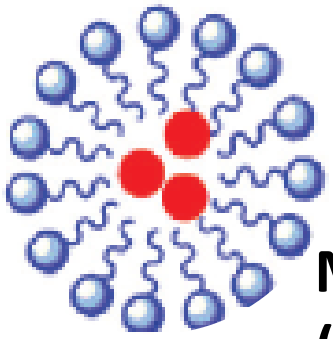
Drug delivery vehicles

Dendrimers (1-10nm)

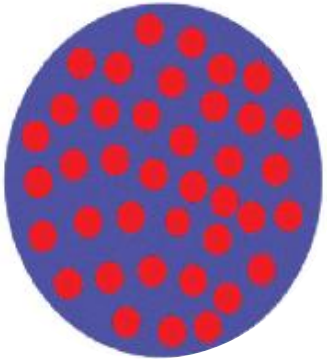


Polymer drug conjugates (6-15nm)

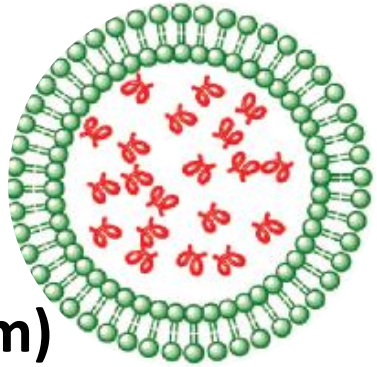
Micelles (≈ 20 nm)



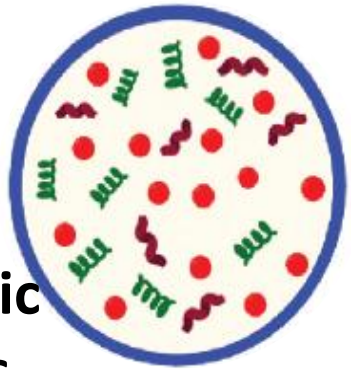
Polymeric Particles (> 25 nm)



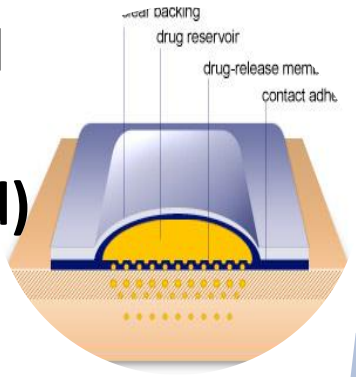
Liposomes (40 - 400 nm)



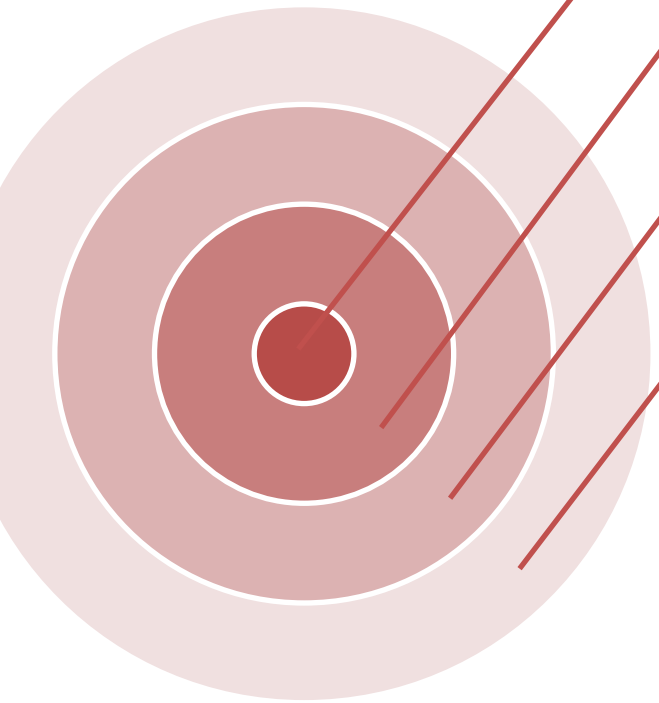
Polymeric Capsules (10 – 1000 nm)



Transdermal Patches (Macro sized)



Challenges in Drug Delivery

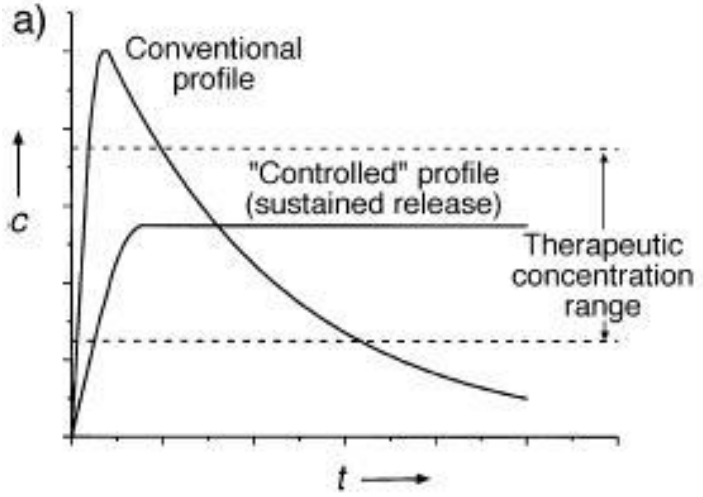


4 **Crossing Cellular Barriers**

3 **Crossing Tissue Barriers**

2 **Targeted Delivery**

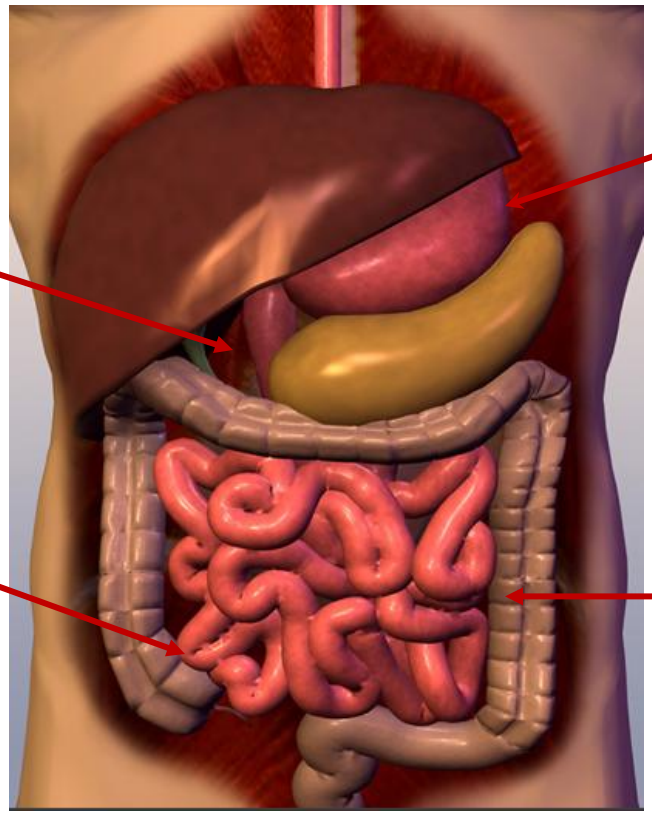
1 **Controlled Drug Release**



Aggarwal P., Advanced Drug Delivery Reviews 2009.

Controlled Drug Release in Colon

- **For treatment of colon diseases such as Inflammatory bowel disease, amoebic dysentery, Crohn's disease and ulcerative colitis**
- **To delay drug absorption after oral intake of the drug**
- **Protect drugs from harsh acidic environment of the stomach**



Duodenam
pH = 6 - 7
Microbiota = 10^4 CFU/g

Stomach
pH = 1 - 3
Microbiota = 10^2 CFU/g

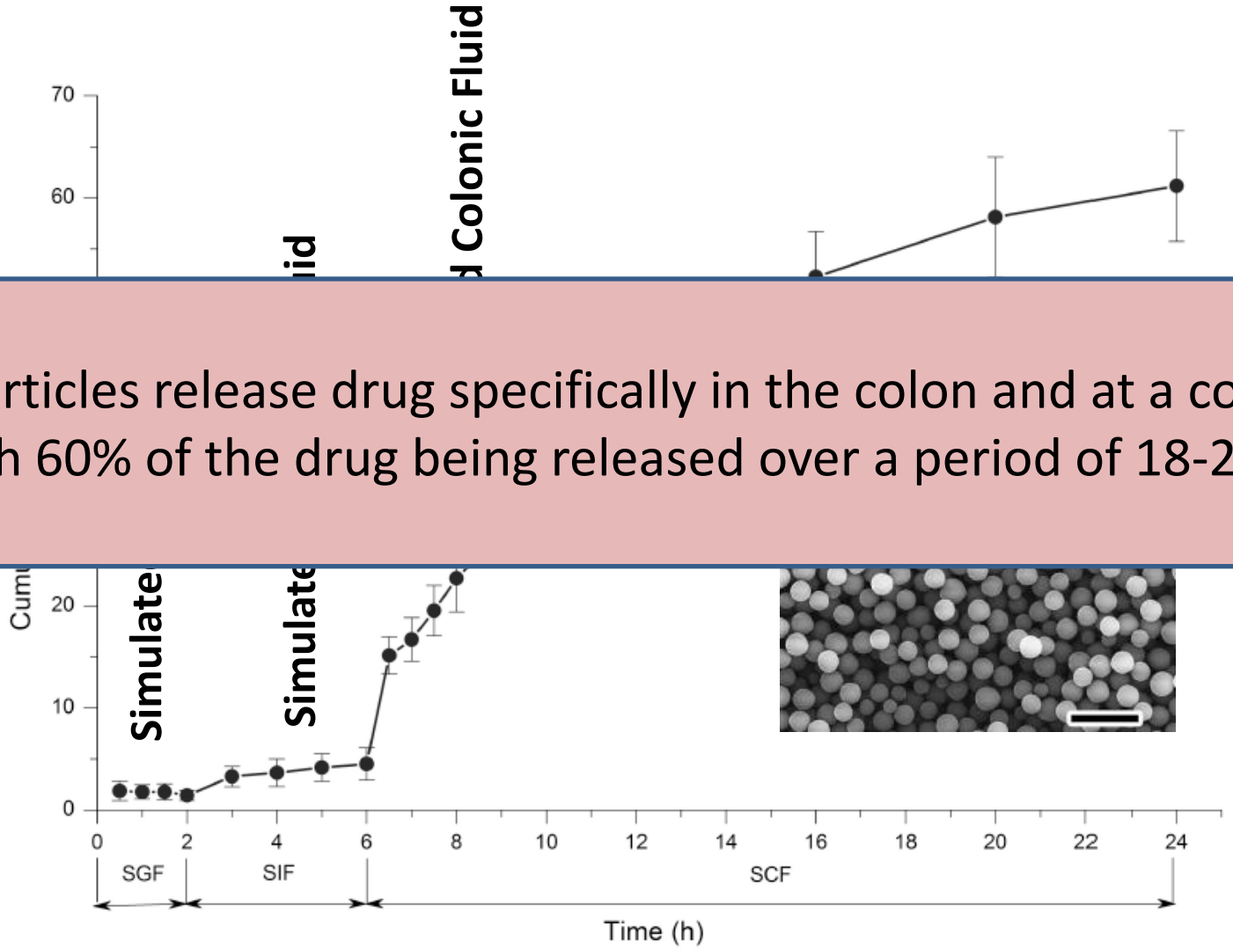
Ileo-caecal region
pH = 6 – 8
Microbiota = 10^7 CFU/g

Colon
pH = 5.8 – 7.4
Microbiota = 10^{11} – 10^{12} CFU/g

Enzymes secreted: Inulinase

Maroni A. et. al., Advanced Drug Delivery Reviews 2012.

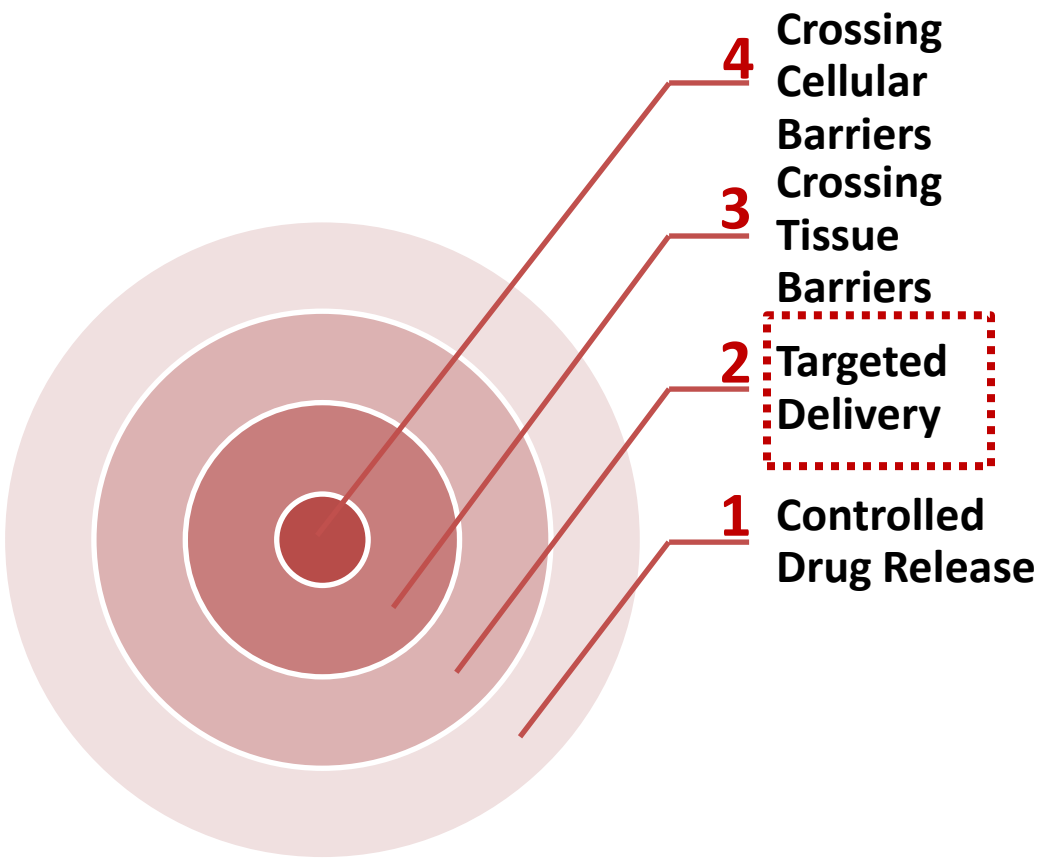
Controlled Release in Colon

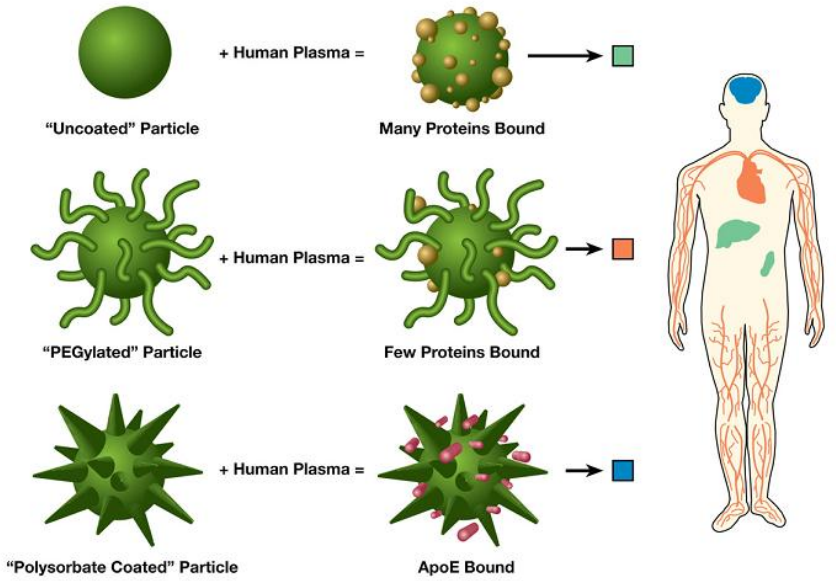


Inulin particles release drug specifically in the colon and at a controlled rate with 60% of the drug being released over a period of 18-20 hours

Katti et al., Unpublished Data (IIT Kanpur, India)

Challenges in Drug Delivery



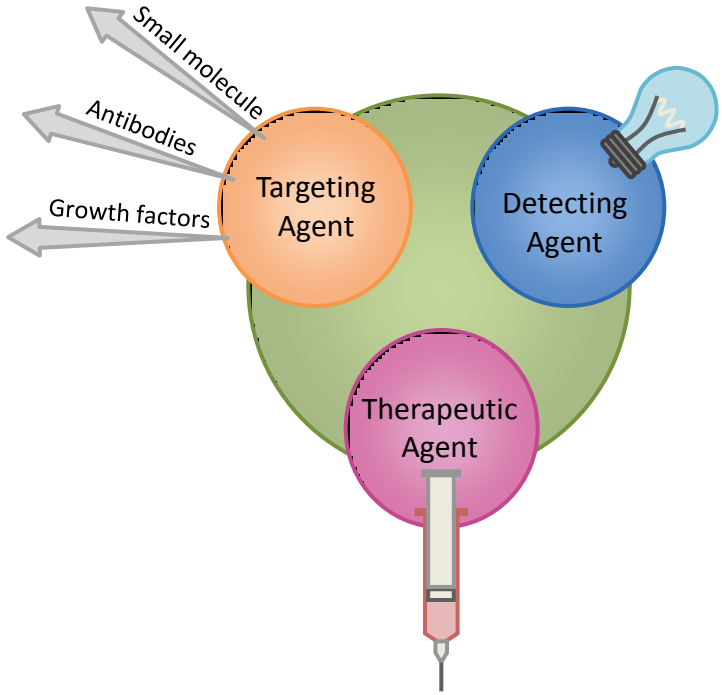


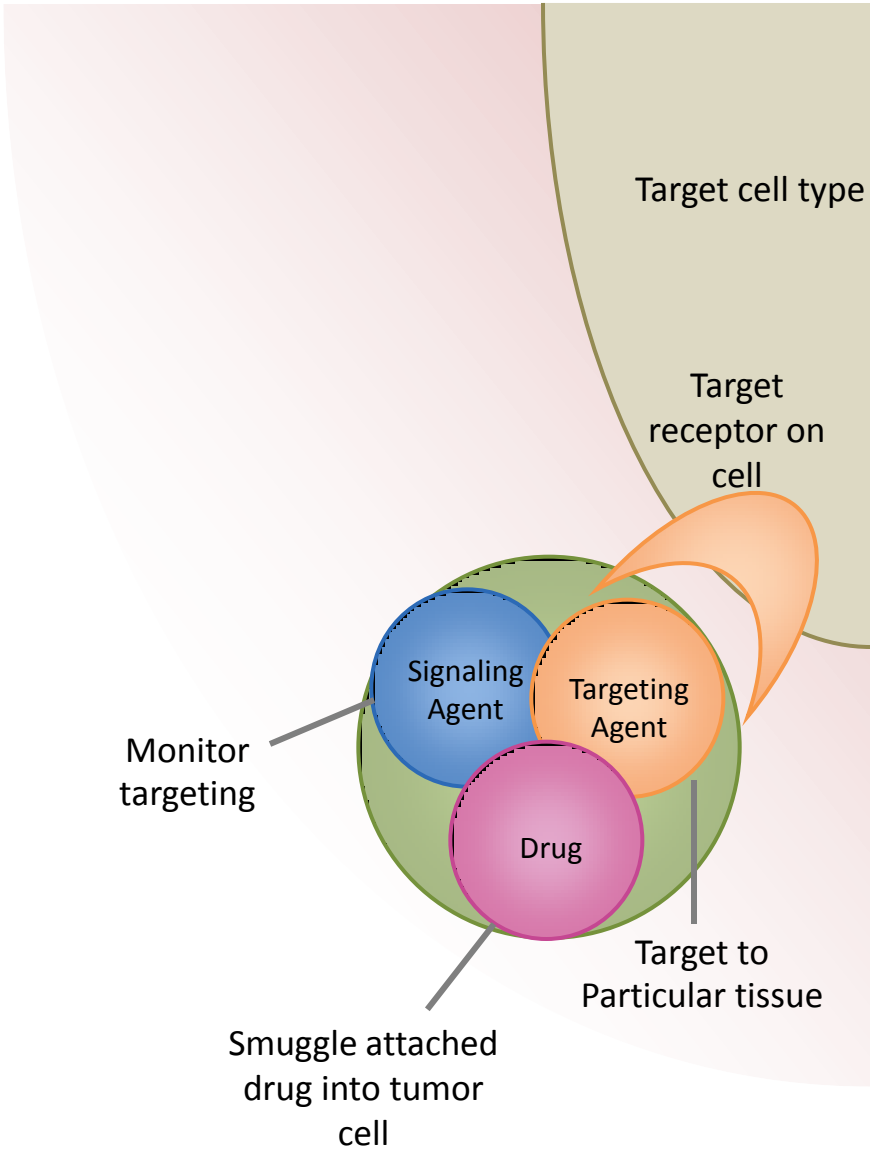
Aggarwal P., Advanced Drug Delivery Reviews 2009.

Targeted drug delivery

Following Tasks Can Be Performed Simultaneously

- Diseased cell recognition
- Reporting detection
- Diagnosis of disease state
- **Drug delivery**
- Reporting outcome of therapy





Cancer: A need for drug targeting

Cancer is a group of diseases in which cells divide and grow uncontrollably, and invade nearby parts of the body

Cancer Related Deaths

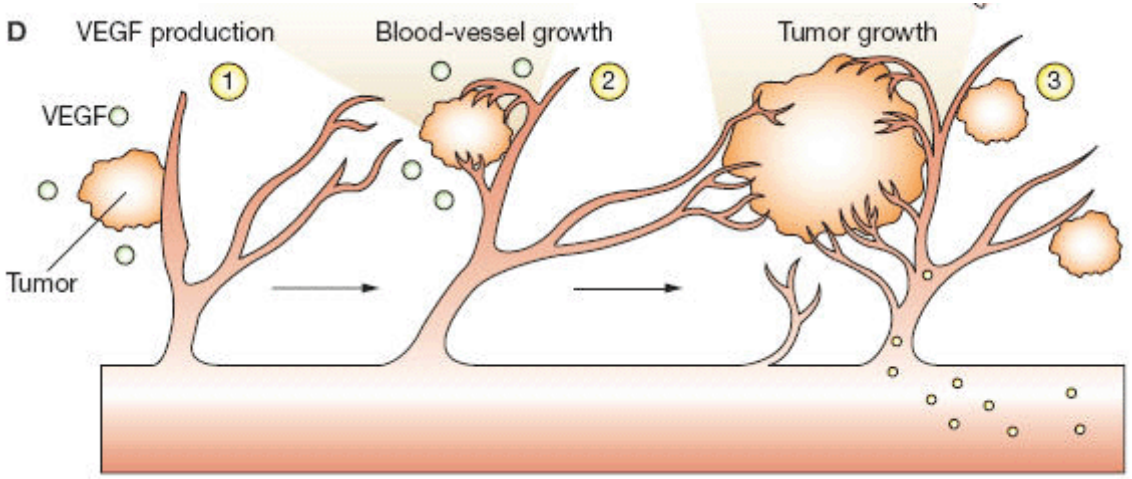
Worldwide	**8.2 Million**
USA	**0.58 Million**

Traditional chemotherapy has many side effects because it acts on all rapidly dividing cells of the body

Side effects may be reduced if the drugs are selectively targeted to tumor tissue rather than administered systemically

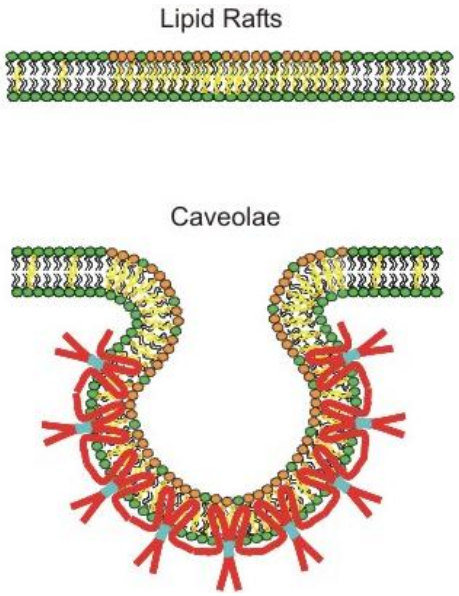
Cancer Facts and Figures 2014, American Cancer Society.

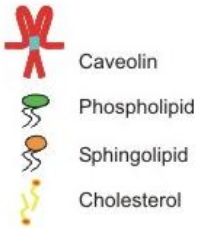
Targeting Drugs to Endothelial cells

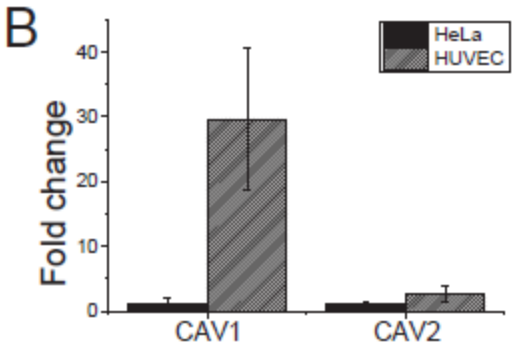


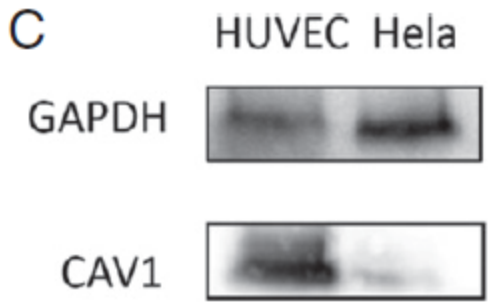
- Endothelial cells play a crucial role in tumor development
- Tumor survival is highly dependent on blood vessels which are comprised of endothelial cells
- Targeting endothelial cells may help in delivering therapeutics to tumor vasculature

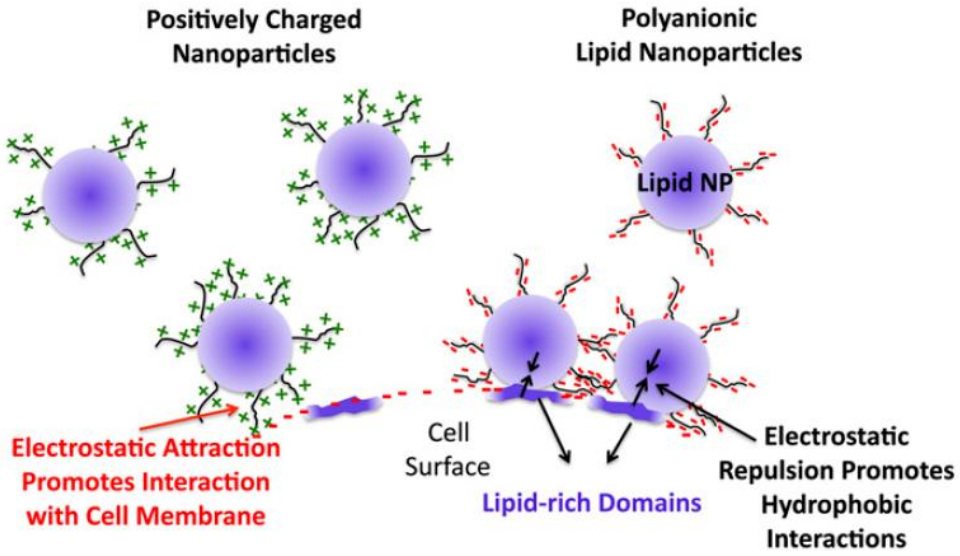
Targeting Endothelial Cells via Lipid Rafts





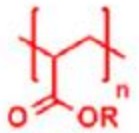
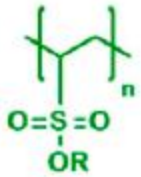
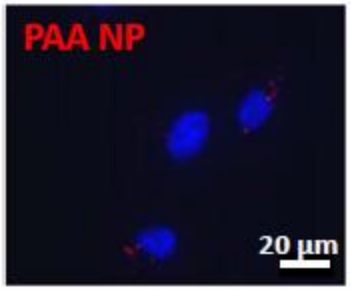
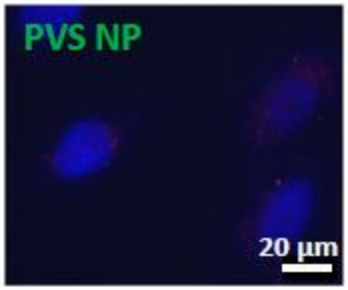
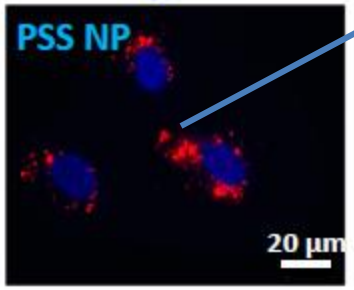






Shastri V.P. et al., PNAS 2014 (University of Freiburg, Germany).

Charge vs. Lipophilicity

Polyacrylic acid	Polyvinyl sulfonate	Polystyrene sulfonate
		
		

Nanoparticle uptake

Octanol Water

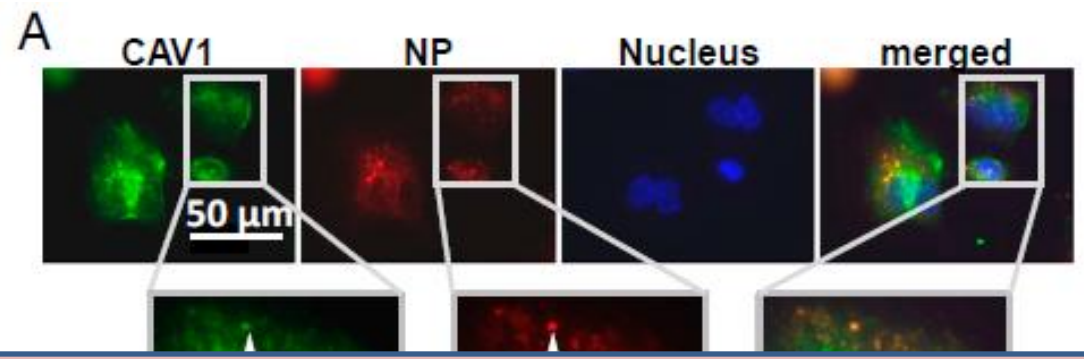
Partitioning Coefficient: ***-2.227*** ***-3.283*** ***-1.211***

Most Lipophilic

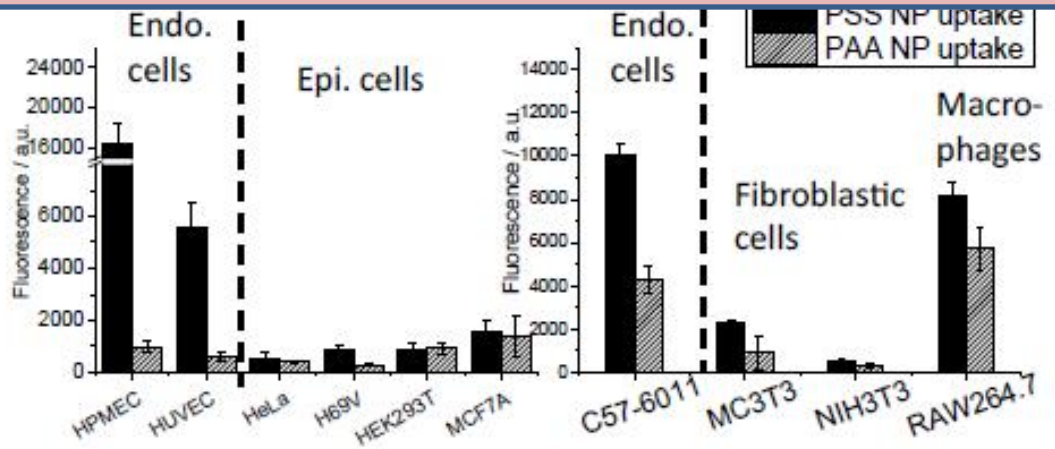
A value closer to zero indicates more lipophilicity

Shastri V.P. et al., PNAS 2014 (University of Freiburg, Germany).

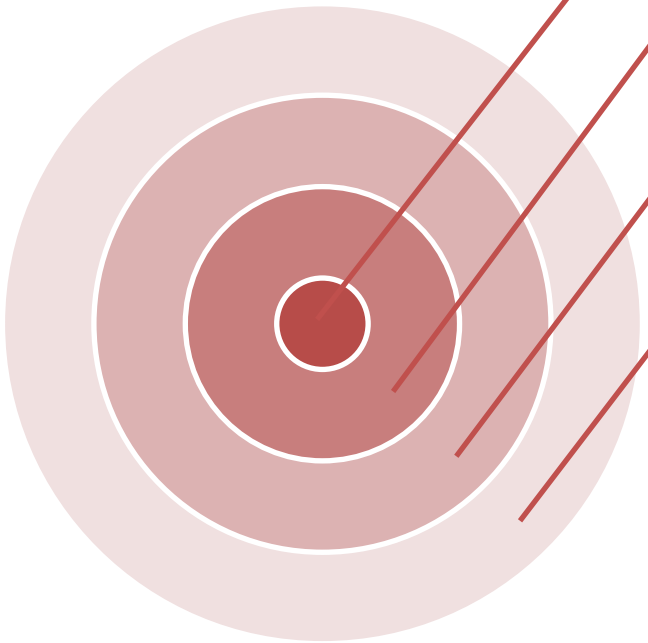
Specific Targeting to Endothelial Cells



Polystyrene sulfonate lipid nanoparticles are endocytosed in caveolin dependent manner specifically by endothelial cells over epithelial cell types



Challenges in Drug Delivery

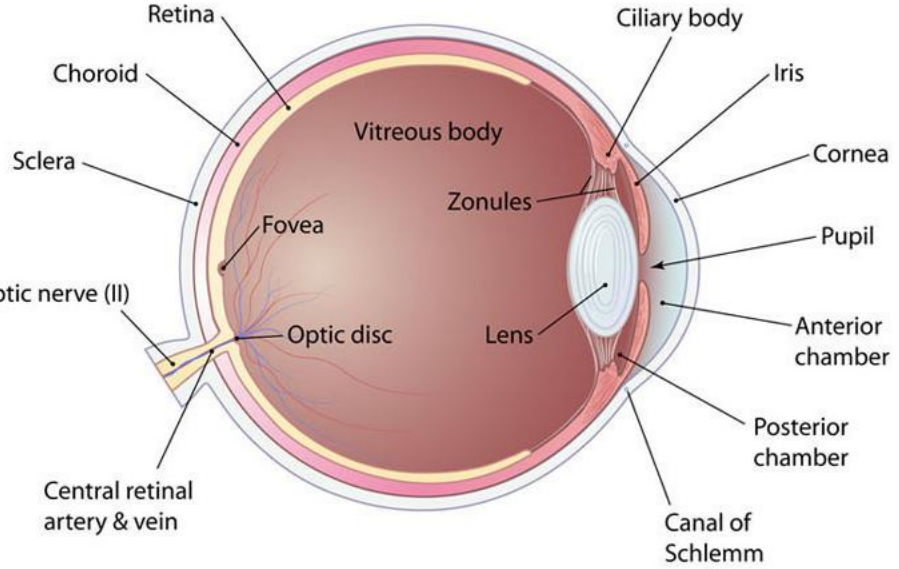


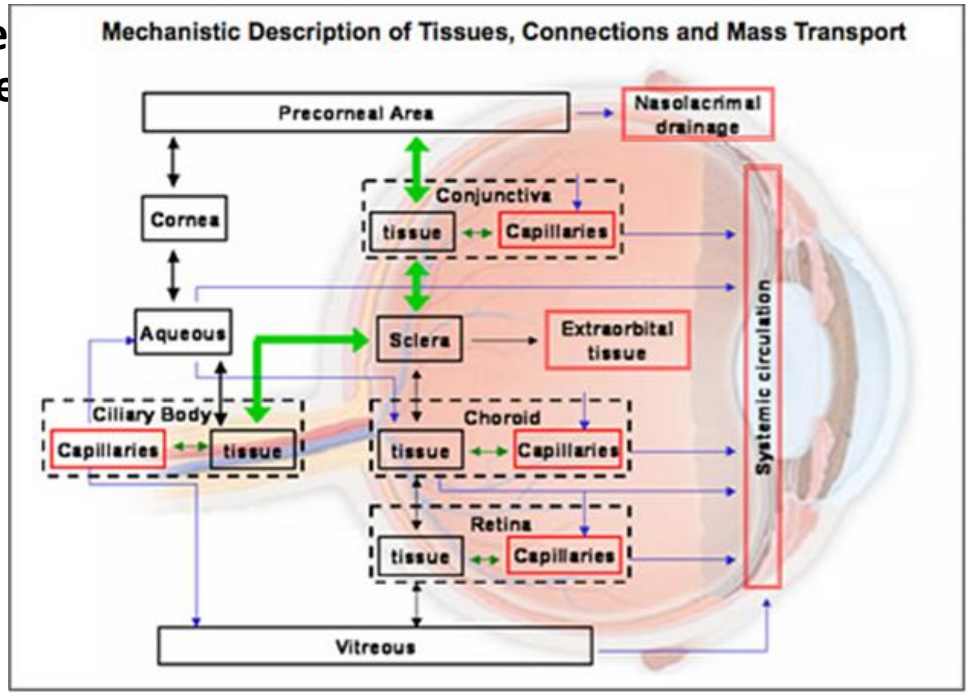
4 Crossing Cellular Barriers

3 Crossing Tissue Barriers

2 Targeted Delivery

1 Controlle Drug Rele



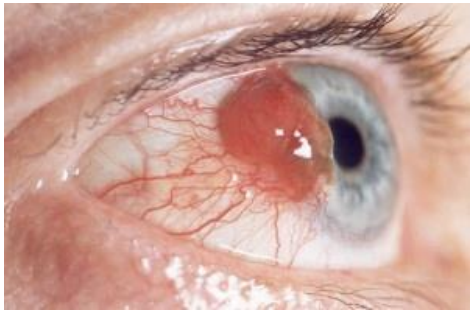


Aggarwal P., Advanced Drug Delivery Reviews 2009.

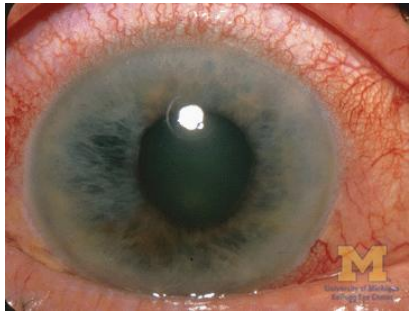
Need for Crossing Tissue Barriers: Eye

Posterior Eye Diseases

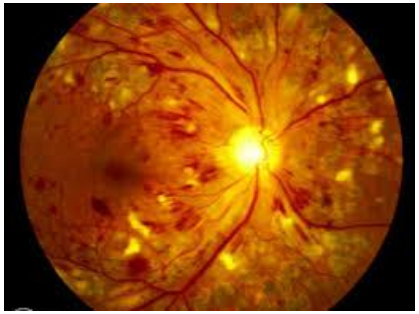
Scleratis
Sclera



Choroidal melanoma
Choroid



Glaucoma
Retina



Diabetic retinopathy
Retina

DISEASES	WORLD (In Millions)	INDIA (In Millions)
Visual impairment	285	53
Blind	39	78
Glaucoma	3.12	.55
Retinal Diseases	2.34	.45

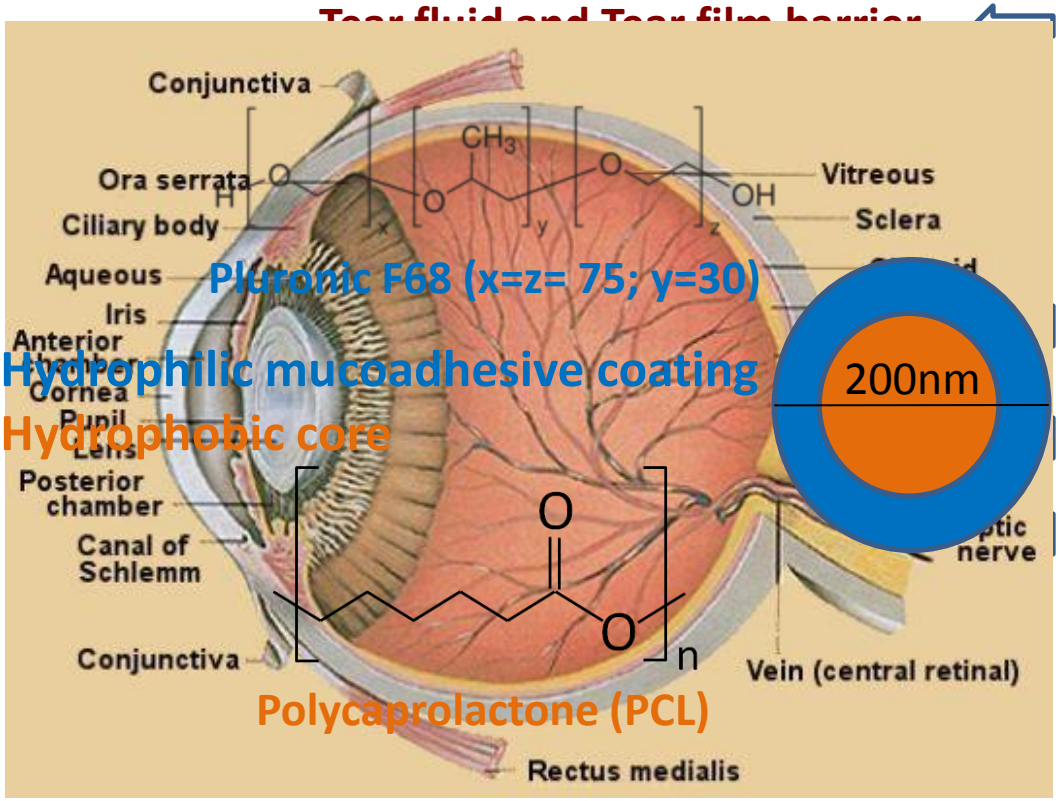
***Bulletin of the World Health Organization* , 2012, (1-14)**

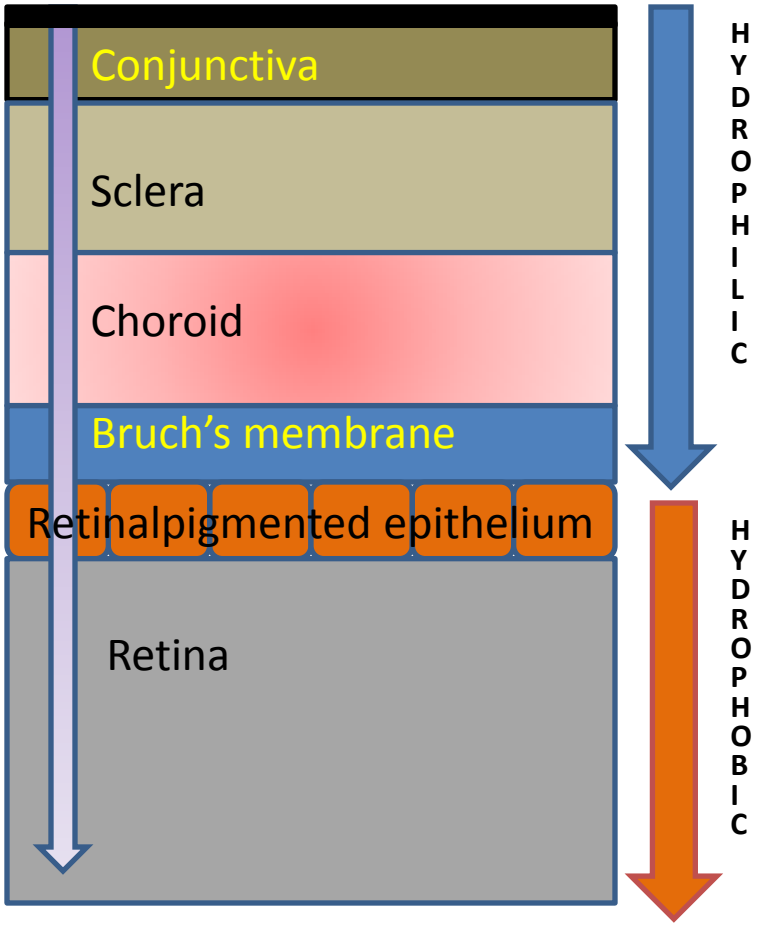
Current Drug Delivery Strategy to Eye

Side effects:

- Repeated injections can cause pain and discomfort
- Increase in intra ocular pressure and intraocular bleeding
- Increased chances of infection
- Possibility of retinal detachment

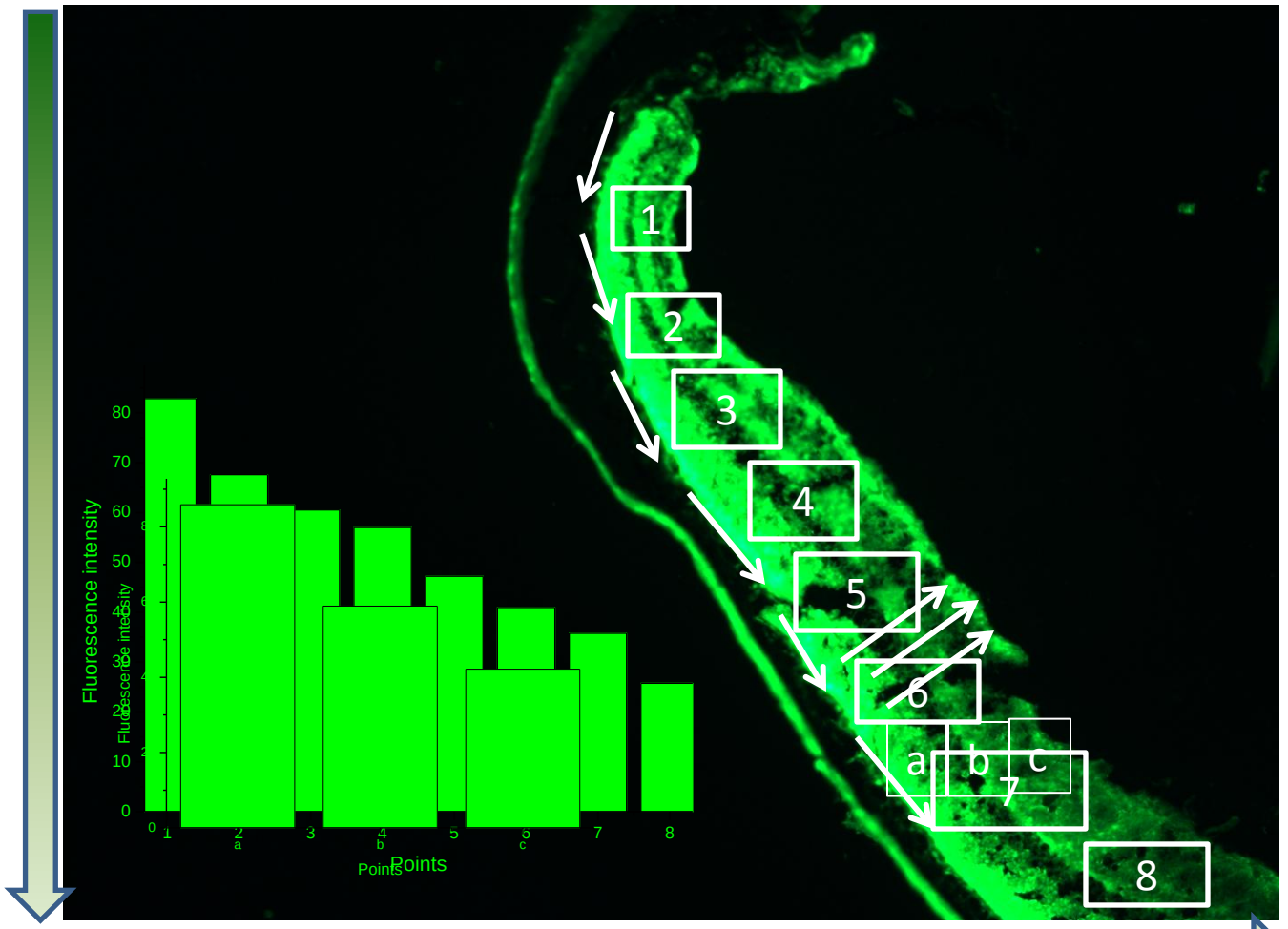
Crossing Tissue Barriers in the Eye

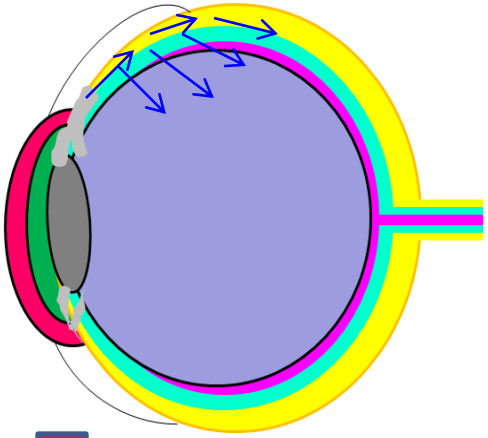




1. *Investigative Ophthalmology & Visual Science,* 38 (1997) 627-634
2. *Molecular Vision, 19 (2013) 1198-1210*
3. *Investigative Ophthalmology & Visual Science*, 47(2006) 4513-4522
4. *Investigative Ophthalmology & Visual Science,*46 (2005) 641-646

Pathway of Drug Delivery



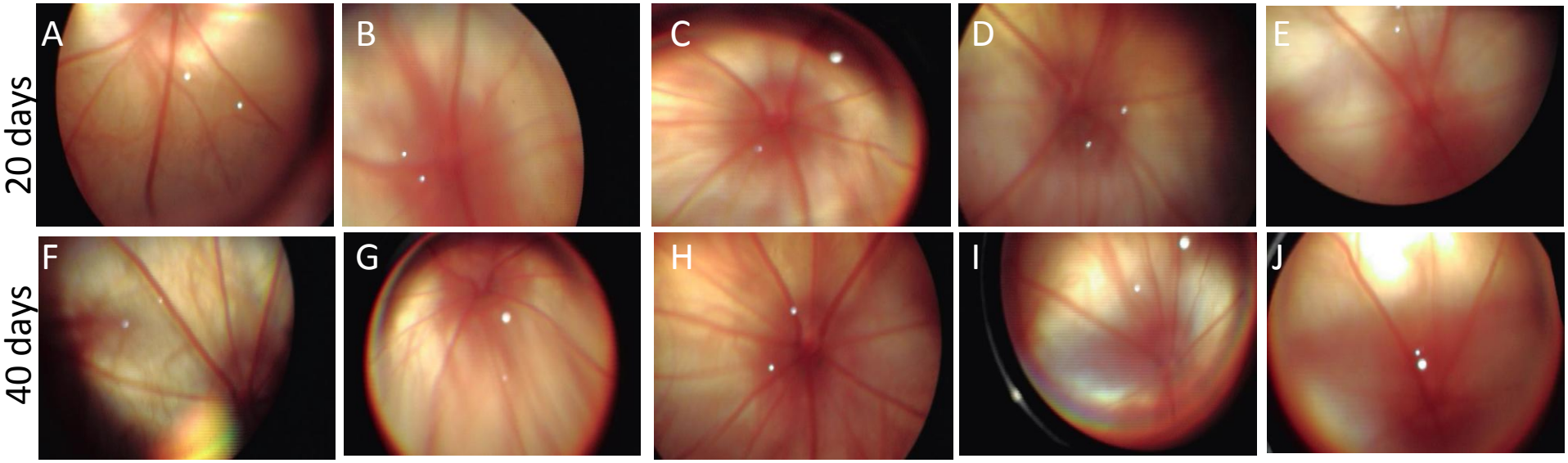


Cornea
Conjunctiva
Iris-ciliary body
Lens
Sclera
Choroid
Retina

Fluorescent image after permeability study

Katti et al., Unpublished Data (IIT Kanpur, India)

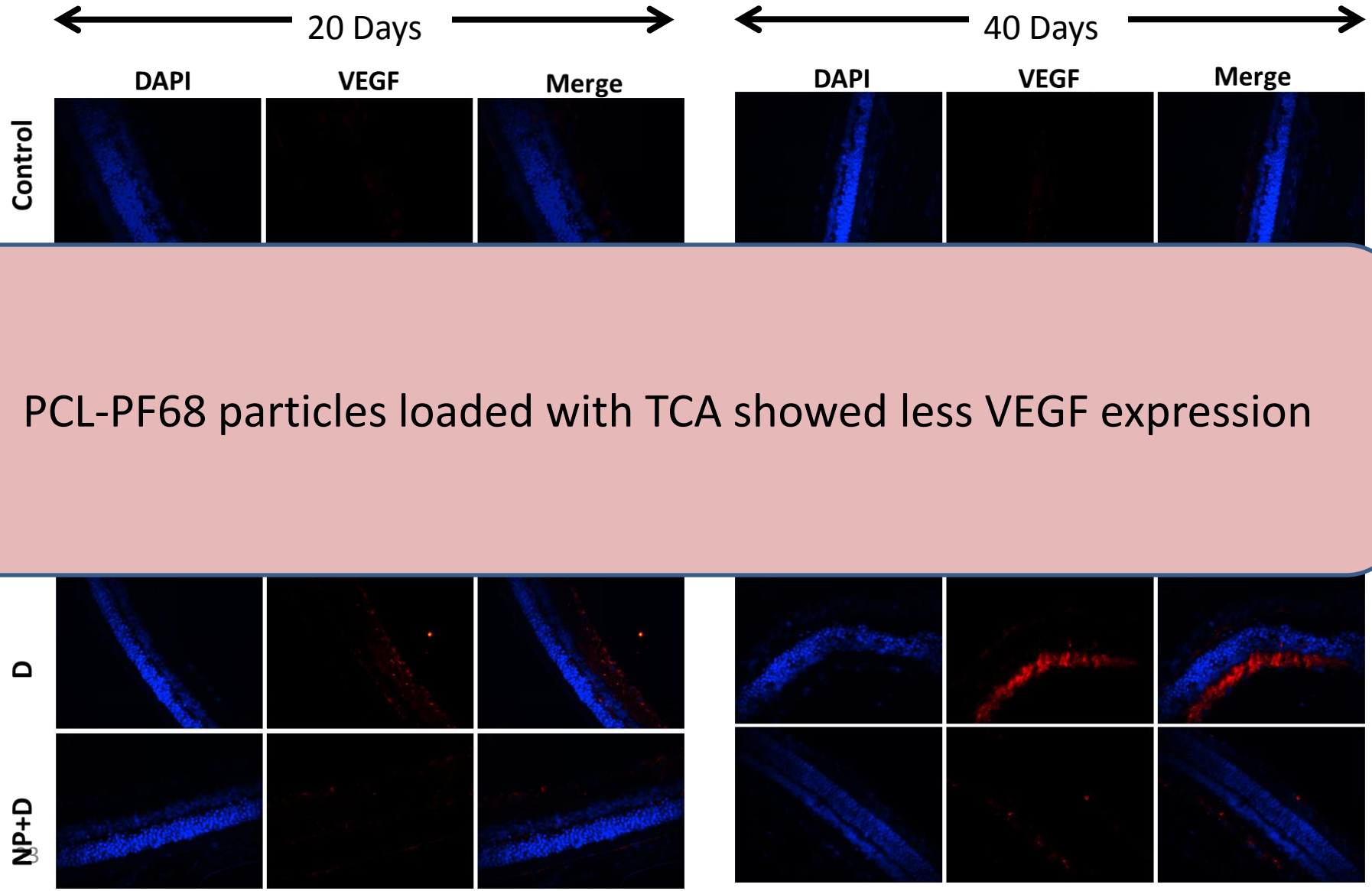
Pre-clinical Evaluation: Fundoscopy Study



PCL-PF68 nanoparticles caused a decrease in neovascularization

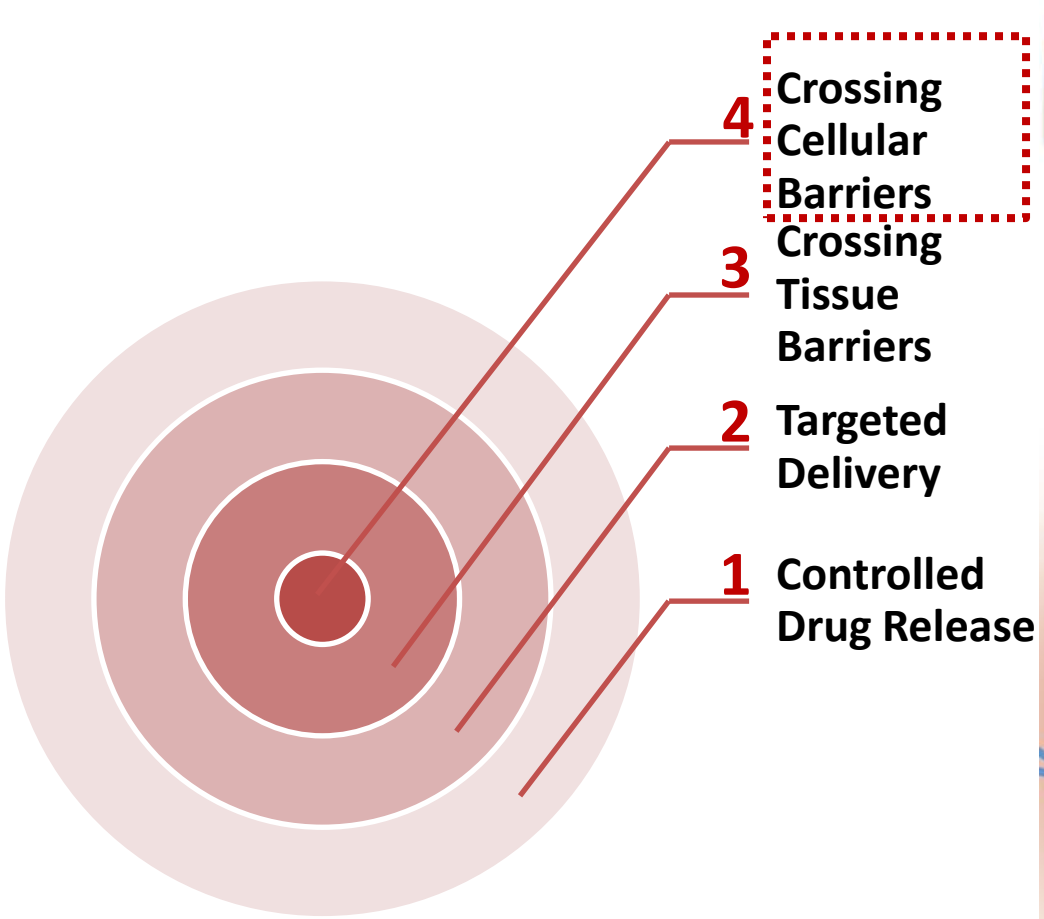
Katti et al., Unpublished Data (IIT Kanpur, India)

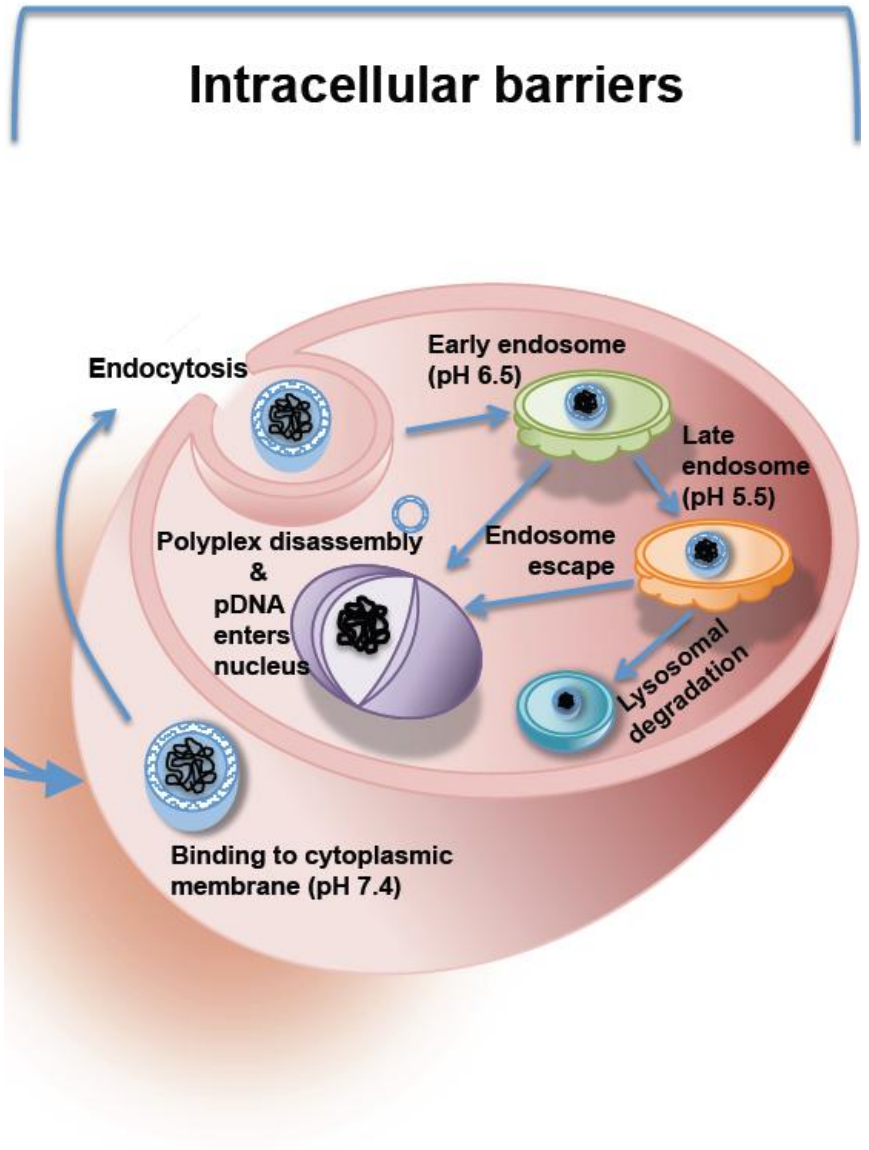
Immunohistochemistry : Anti-VEGF antibody staining



PCL-PF68 particles loaded with TCA showed less VEGF expression

Challenges in Drug Delivery

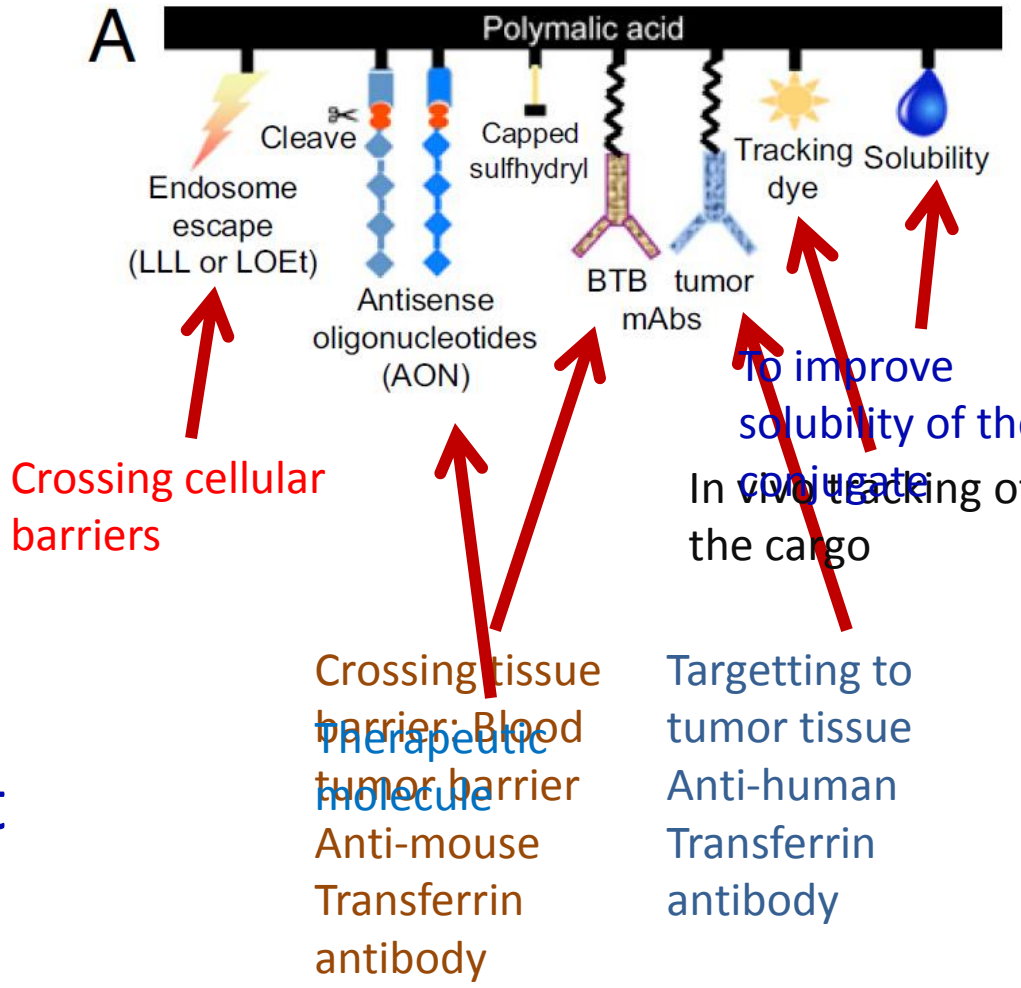




Aggarwal P., Advanced Drug Delivery Reviews 2009.

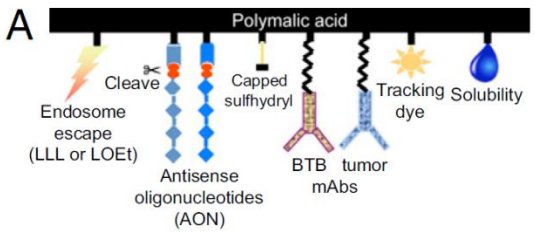
Reaching Target Tissue and Cells: Brain Tumor

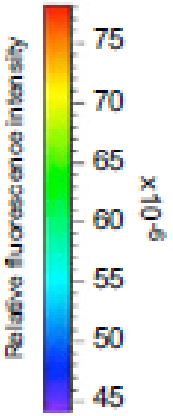
- Brain glioma most aggressive and lethal cancer
- Limited treatment strategies available
- Challenges: crossing blood brain barrier, building drug concentration without regional/systemic toxicity



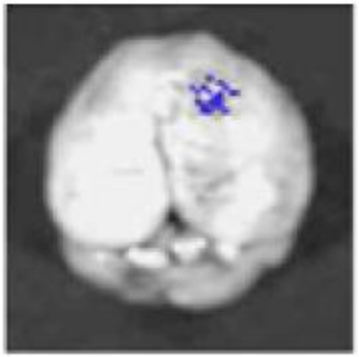
Ljubimova J.Y. et al., PNAS 2010 (Cedars Senai Medical Center, USA).

Pre-clinical Study in Mice



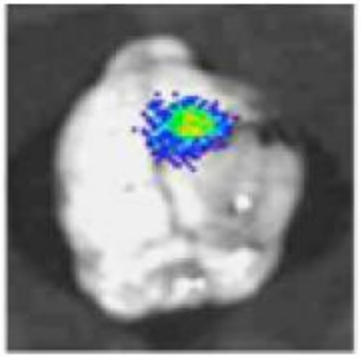


P/LLL/AON/Ms



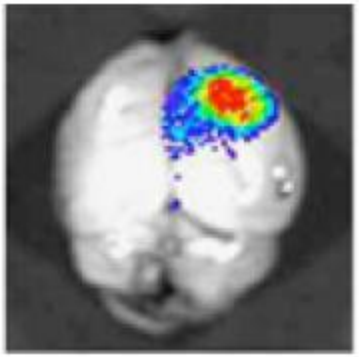
Anti Mouse Transferrin Antibody (Ms) **For crossing BTB alone**

P/LLL/AON/Hu



Anti Human Transferrin Antibody (Hu) **For targeting to tumor**

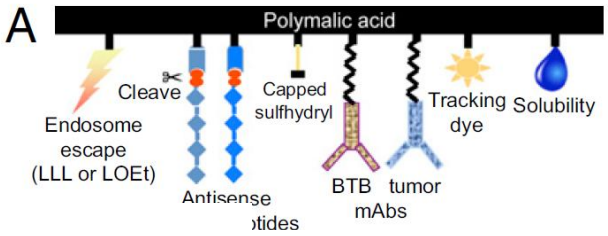
P/LLL/AON/Hu/Ms

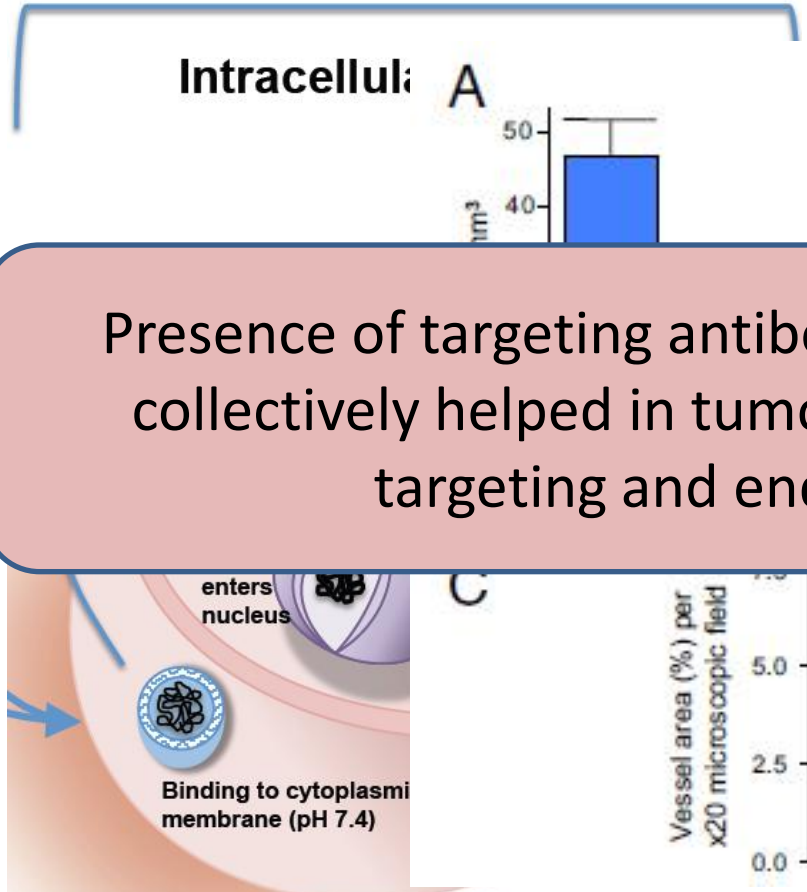


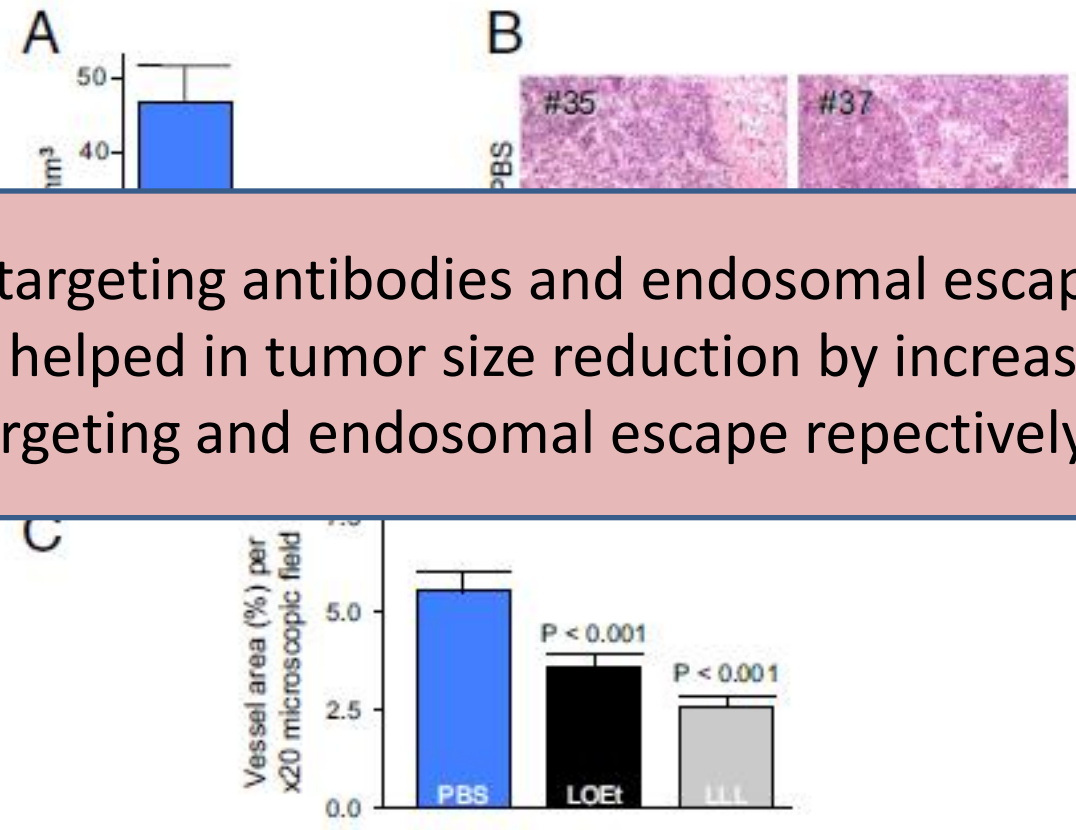
Combination of both Anti mouse and Anti human transferrin antibodies **Crossing BTB and targeting tumor tissue**

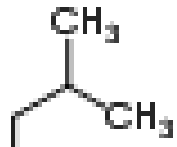
Ljubimova J.Y. et al., PNAS 2010 (Cedars Senai Medical Center, USA).

Crossing cellular barrier: Endosomal Escape









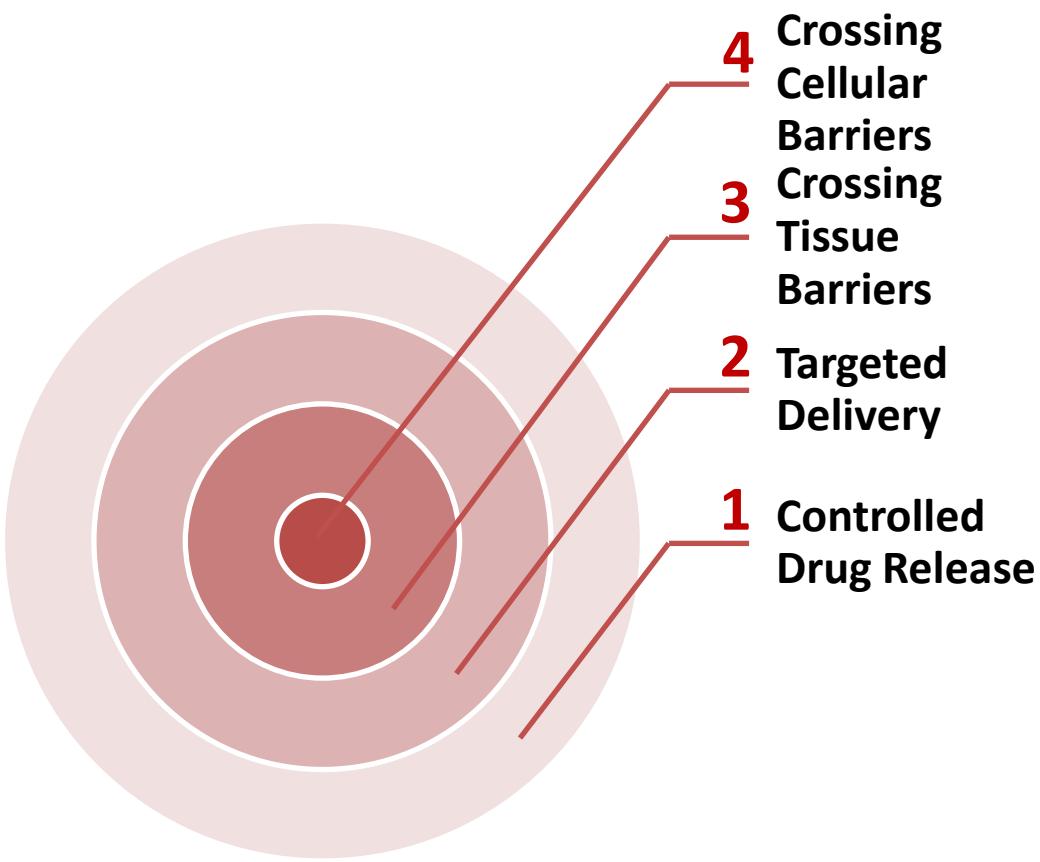
Presence of targeting antibodies and endosomal escape peptides collectively helped in tumor size reduction by increasing tumor targeting and endosomal escape repectively

- pH responsive
- governs hydrophobicity
- pKa 5.5

Control: NH_2 – Leu – Leu – Leu – Ethyl ester

Ljubimova J.Y. et al., PNAS 2010 (Cedars Senai Medical Center, USA).

Conclusions & Future Challenges



- Endosomal escape accompanied by lysosomal rupture may be associated with cytotoxicity
- Due to variation in tissue properties like size, results from small animals may not be directly extrapolated to humans
- Antibodies specific to a receptor does not always ensure cell specific targeting *in vivo*
- Simultaneous controlled release of hydrophilic and hydrophobic drugs has not been achieved

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Thank You!!!