Νανοσυστήματα για χορήγηση/στόχευση Φαρμάκων

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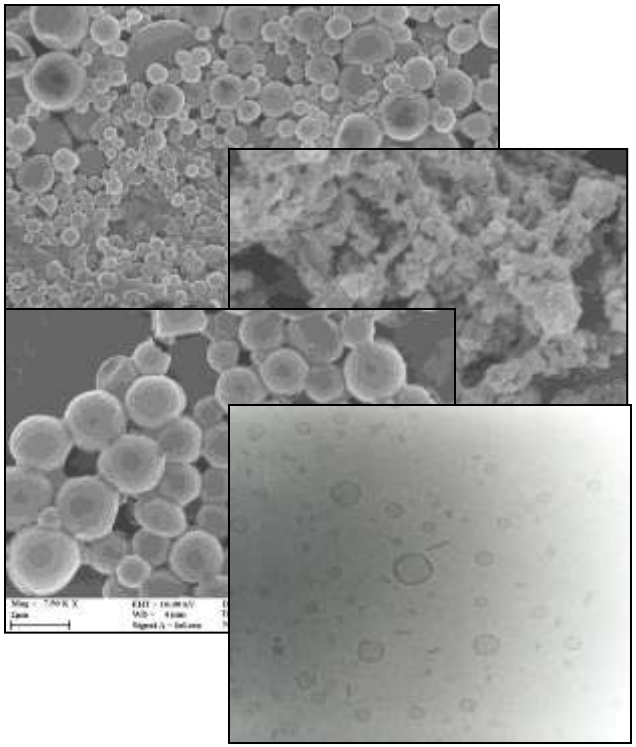
Nanosystems for Controlled Drug Delivery and Targeting - Nanomedicines



Applications:

✓Drug Delivery/Targeting
✓Controlled Release Rate- Protection - Stability
✓Targeting specific cell types → [↑ **Activity** ↓ **Toxicity**]
✓Solubility enhancement
✓Permeability enhancement / Barriers

Administration routes:

i.v., i.m., per os,
Lungs-Alveolar (nebulization)- Mucosal, Ocular (intravitreal)
Dermal/transdermal (elastic vesicles)

SHIVA *Selection and development of microbicides for mucosal use to prevent sexual HIV transmission /acquisition FP6 IP(Contract n°:503162)*

NAD *Nanoparticles for Therapy and Diagnosis of Alzheimer Disease FP7 CP-IP 212043-2*

INTEREG *– Intereg III-GREECE-ITALY "Establishment of a Network for Advanced Biomaterials*

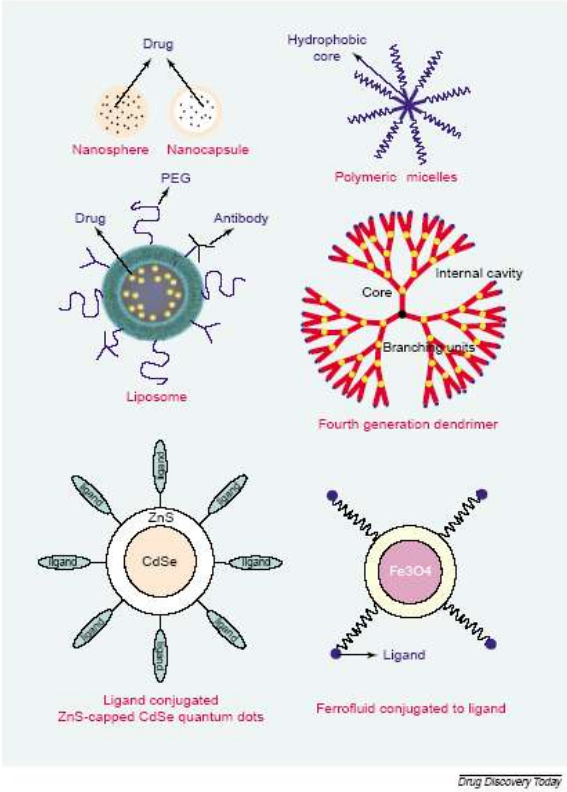
GalenosNetwork
Euro-PhD
in Advanced Drug Delivery

2007 - 2013

INTERREG III

ΝΑΝΟΣΥΣΤΗΜΑΤΑ ΜΕΤΑΦΟΡΑΣ ΦΑΡΜΑΚΩΝ

- Nano-Particulate systems ranging in size between 10 nm – 200 nm, which can encapsulate or incorporate drugs and carry them exactly to their site of action.
  - Nano/micro particles (or spheres)
    - Polymeric
    - Lipidic (SLN)
  - Nano/micro capsules
  - Liposomes
- Recently (mainly for diagnosis):
  - Quantum Dots
  - Iron Oxide NPs
  - Carbon Nanotubes



from S. K. Sahoo and V. Labhasetwar, Drug Discovery Today, 8, 1112 (2003), with permission by Elsevier

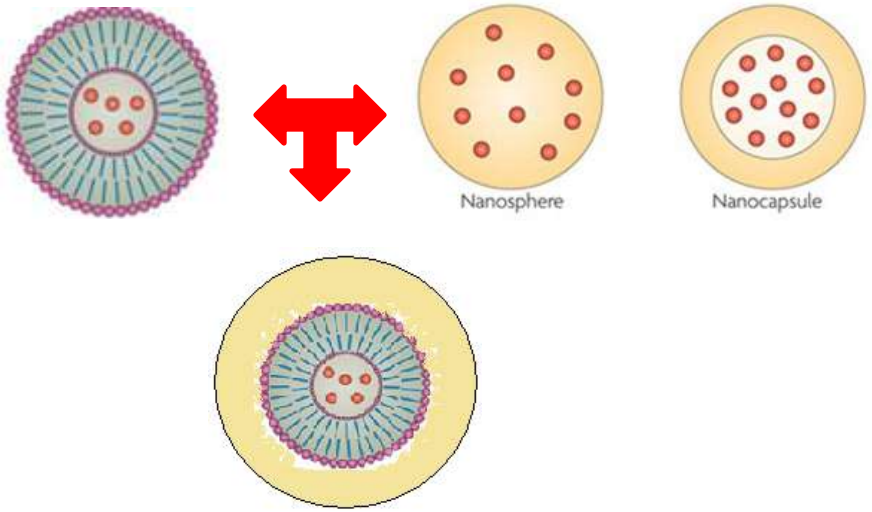
ΠΡΟΥΠΟΘΕΣΕΙΣ ΓΙΑ ΧΡΗΣΗ

- Ability to associate (incorporate or entrap) sufficient quantities of drugs.
- Easy Tailoring, ex. Antibody or ligand conjugation [for targeting] on NP surface

- Non-Toxic
- Minimum antigenicity.
- Biodegradable
- Biocompatible (haemocompatible)

- Retention of drug (after in vivo administration) at least until the Nps reach the site of action

- Proper control of drug release (depending on the specific therapeutic application plan)



Εφαρμογές:

✓**Drug Delivery/Targeting**

✓Controlled Release Rate-Protection - Stability

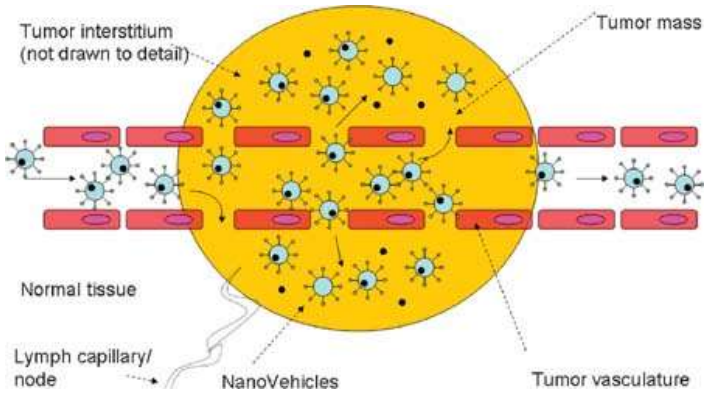
✓Targeting specific cell types →

[↑ **Activity** ↓ **Toxicity**]

✓Solubility enhancement

✓**Permeability enhancement / Barriers**

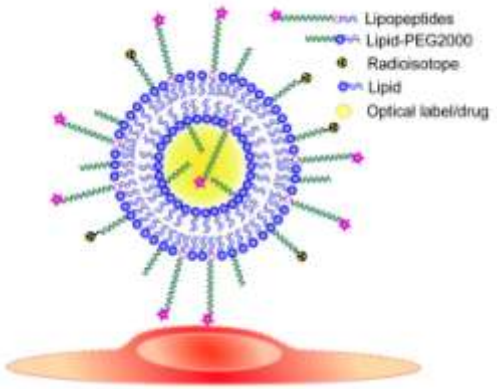
Φαινόμενο Αυξημένης Διαπερατότητας και συγκράτησης: Due to EPR effect nanosized particles (< 200 nm) are good carriers for anti-cancer drugs



•Sufficient circulation time (in vivo stability)

Coat with hydrophilic molecules (PEG, other Polymers, gangliosides (GM1), sugars (polysialic acid), etc)

•↑Binding affinity (decoration with appropriate ligand)



RECENT RESEARCH PROJECTS

- **Nanoparticles for diagnosis and therapy of Alzheimer Disease (NAD –FP7)**
- Liposomal formulations for Controlled release-Drug-eluting stents (*for performance & haemo/ biocompatibility improvement* –Intereg Program)
- Liposomal formulations of arsenic-containing compounds for therapy of cancer (coll. Dept. Chem/Patras)
- Development of liposomal formulations of a microbicide MC1220 for vaginal administration (for preventing sexual transmission of HIV) (FP6 IP project SHIVA)
- Controlled release DDS for intravitreal delivery (coll. School of Medicine / University of Crete)
- Rifampicin-loaded liposomes or polymeric microspheres for targeting alveolar macrophages (2 Early stage Marie Curie grants-FP6)
- Liposome entrapping polymeric films [PFs] (Early stage Marie Curie grant-FP6) –Controlling drug or intact vesicle release from PFs

AD is the most common neurodegenerative disease caused by the formation of senile plagues in the brain. Amyloid protein (A*β*) is a self-assemble peptide and presents the main constituent of these plagues.

Targeting A*β* in the blood

Recent studies have demonstrated the affinity of A*β* for curcumin [1,2]. It has been suggested that liposomal formulations functionalized with these molecules can be used for the treatment of AD by sequestering A*β* from the circulating blood [3]. In this study we examined the possibility to prepare curcumine-decorated liposomes by a click chemistry technique.

References:

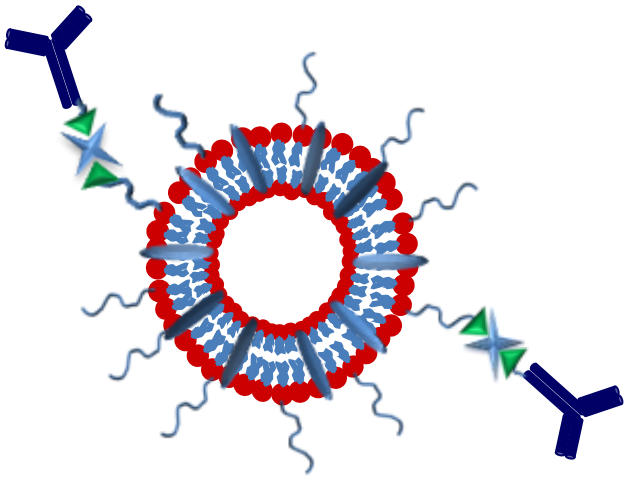
[1] Ono K, Hasegawa K, Naiki H, Yamada M. Curcumine has potent antiamyloidegenic effects for Alzheimers beta-amyloid fibrils in vitro. J. Neurosci Res 2004; 75:742 -750

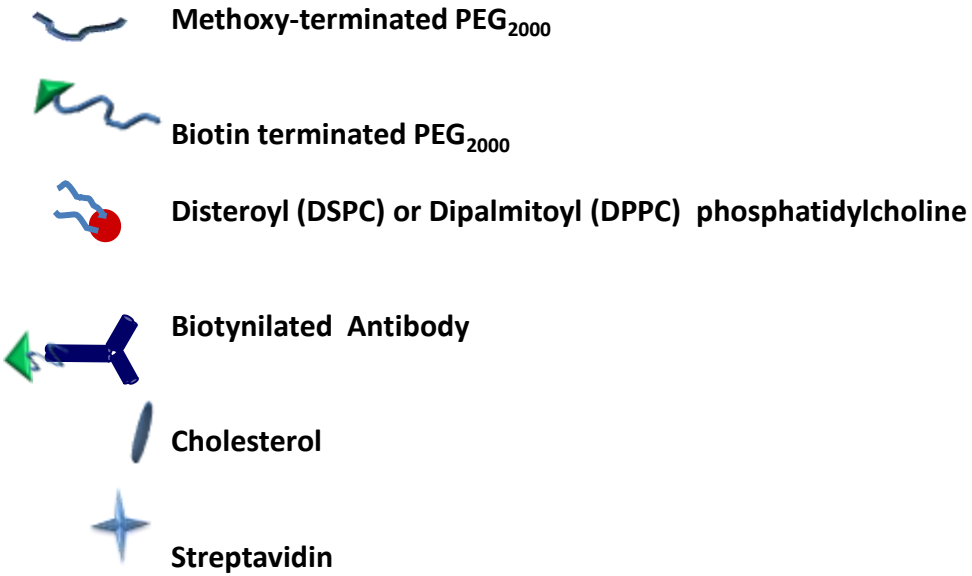
[2] Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 2005; 280:5892-5901

[3] Sagare A, Deane R, Bell RD, et al. Clearance of amyloid- by circulating lipoprotein receptors. Nature Medicine 2007; 13: 1029 - 1031

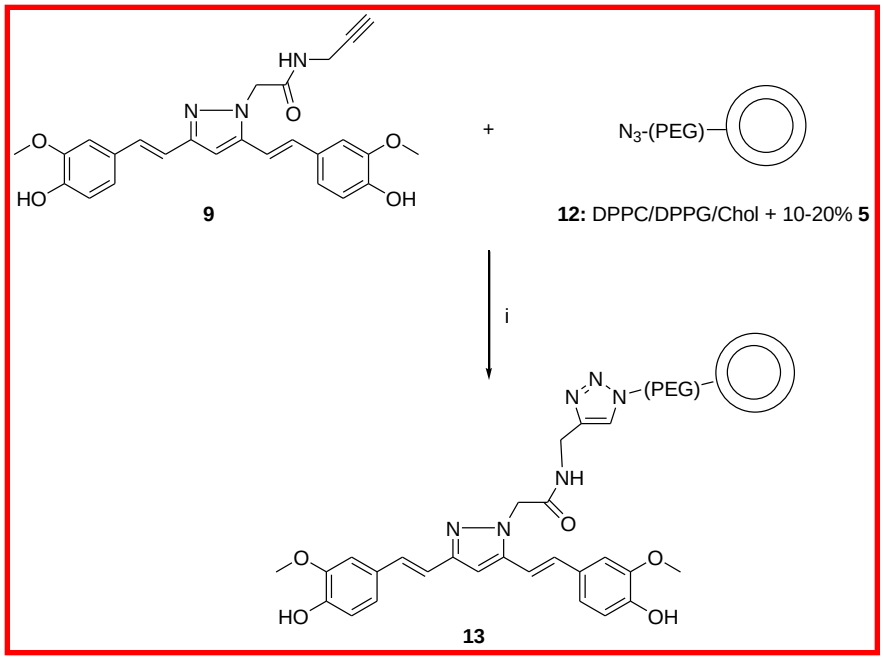
Development of Immunoliposomes for targeting the Blood Brain Barrier and/or Abeta peptides

Purpose: *To target the endothelial cells of the Blood-Brain Barrier based (transferrin receptor) or Aβ aggregates*





Other possibilities: Maleimide/SATA reaction; Amide bond formation; Thiol/thiol bond; Click chemistry method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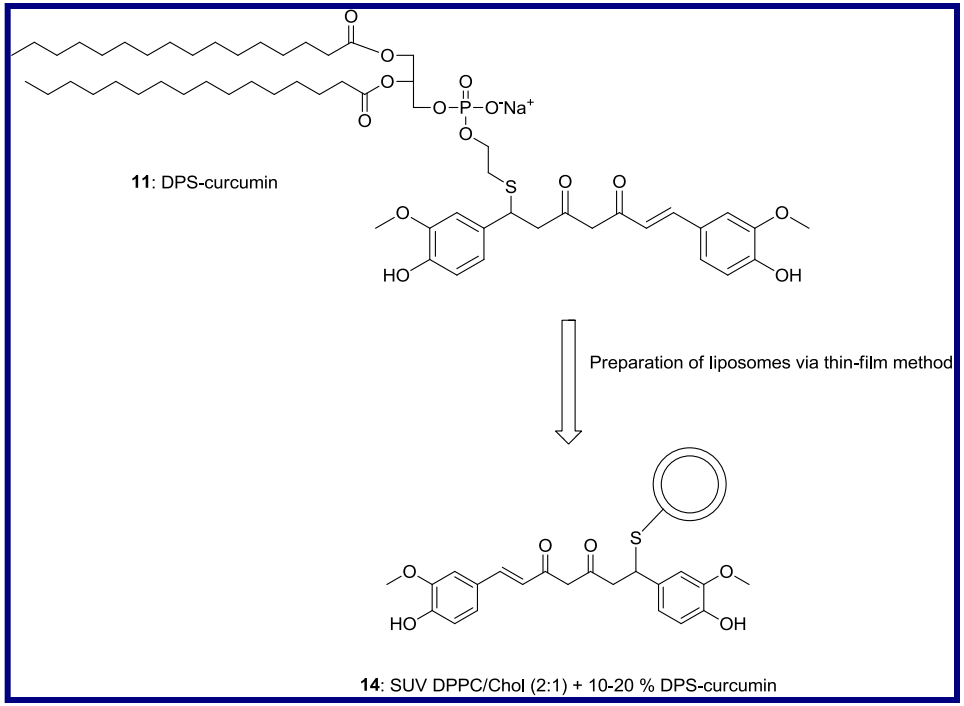
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11: DPS-curcumin
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Preparation of liposomes via thin-film method
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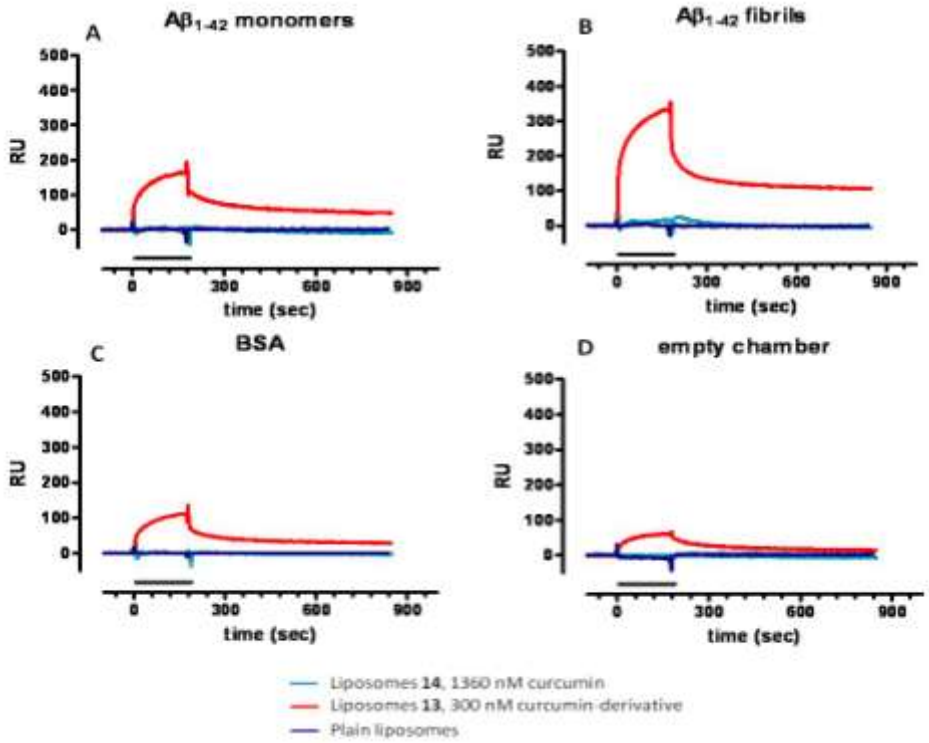
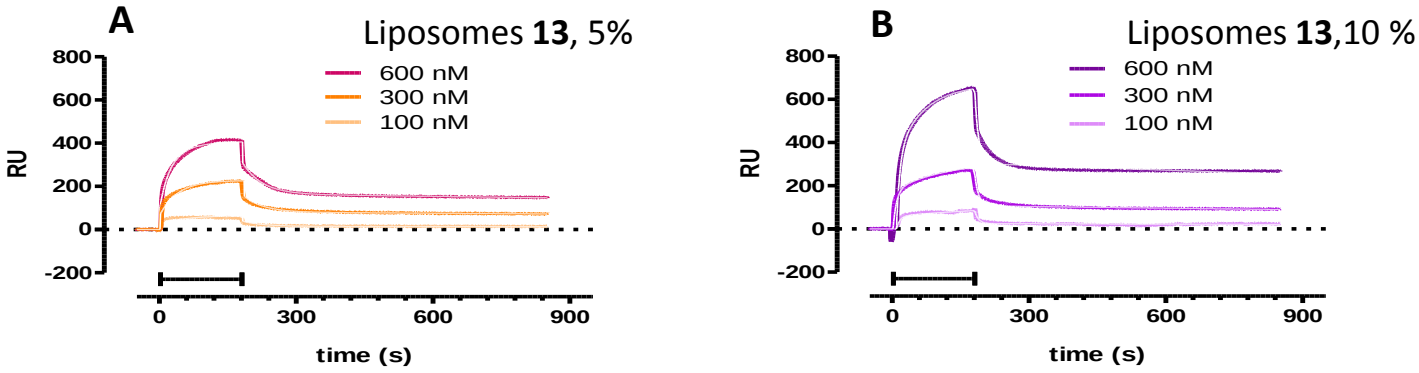
14: SUV DPPC/Chol (2:1) + 10-20 % DPS-curcumin



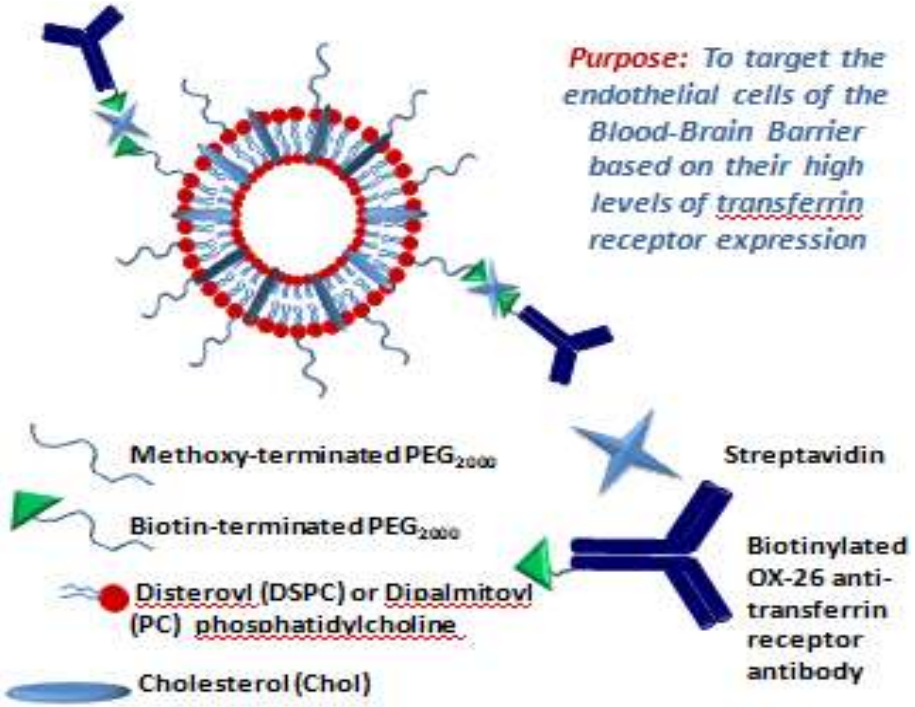
Curcumin-decorated Nanoliposomes with very high affinity for Amyloid-β1-42 peptide
Biomaterials in press

Spyridon Mourtas, Mara Canovi, Cristiano Zona, Dario Aurilia, Anna Niarakis, Barbara La Ferla, Mario Salmona, Francesco Nicotra, Marco Gobbi, Sophia G. Antimisiaris



AD is the most common neurodegenerative disease caused by the formation of senile plagues in the brain. Amyloid protein (A*β*) is a self-assemble peptide and presents the main constituent of these plagues.

2nd TARGET: Targeting A*β* in the brain

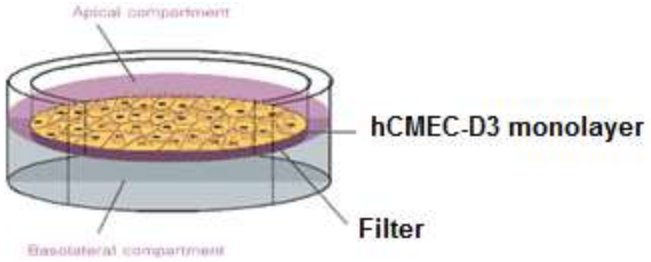


The hCMEC/ D3 cell line model

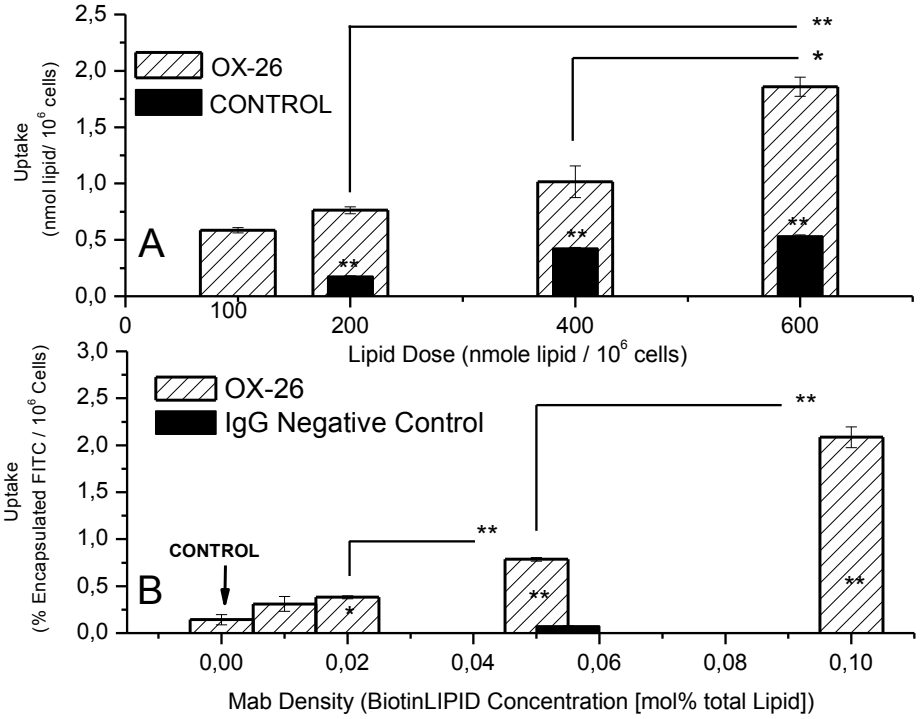
The hCMEC/D3 cell line is a well characterized human brain endothelial cell line, which has been demonstrated to mimic most of the basic characteristics of the BBB [*], even in the absence of co-cultured glial cells.

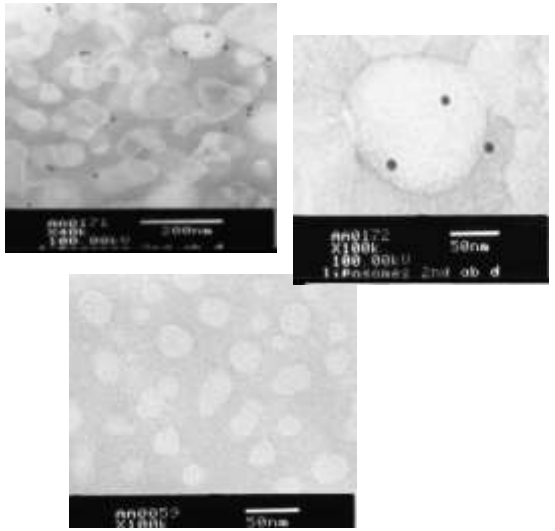
These cells have been demonstrated to form tight junctions

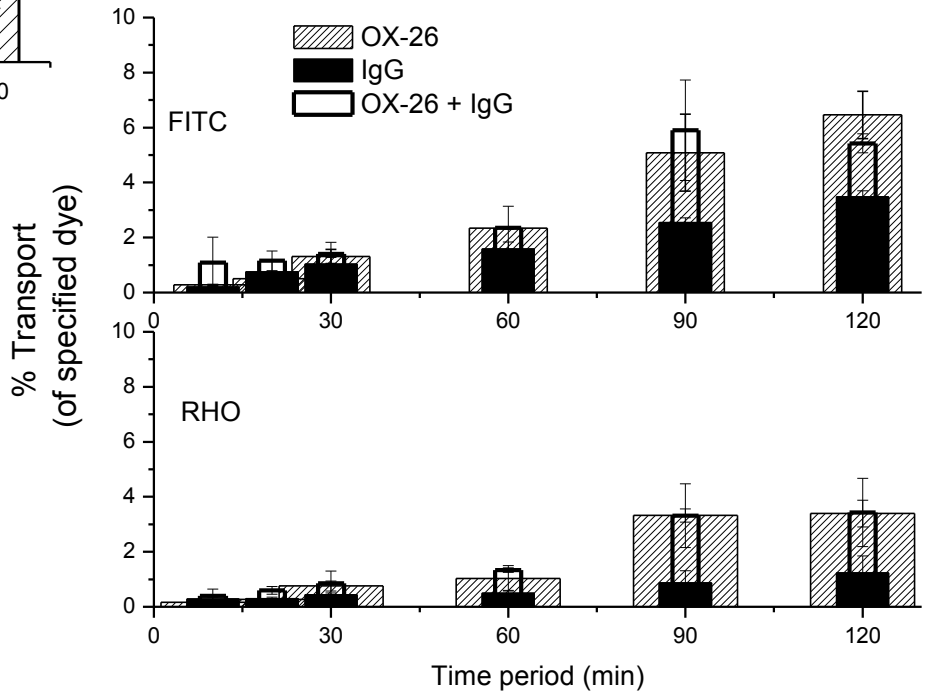
- Does not require co-culture system



*J Weksler B. B., Subileau E. A., Perriere N. et al. (2005) Blood-brain barrier-specific properties of a human adult brain endothelial cell line. FASEB J. 19, 1872–1874.
Poller,R. Gutman H. Krahenbuhl S. Weksler B. Romero I. Couraud P.O**. Tuffin G. Drewe J. Huwyler J. The human brain endothelial cell line hCMEC/D3 as a human blood-brain barrier model for drug transport studies. J. Neurochemistry, 2008, 107, 1358-1368.



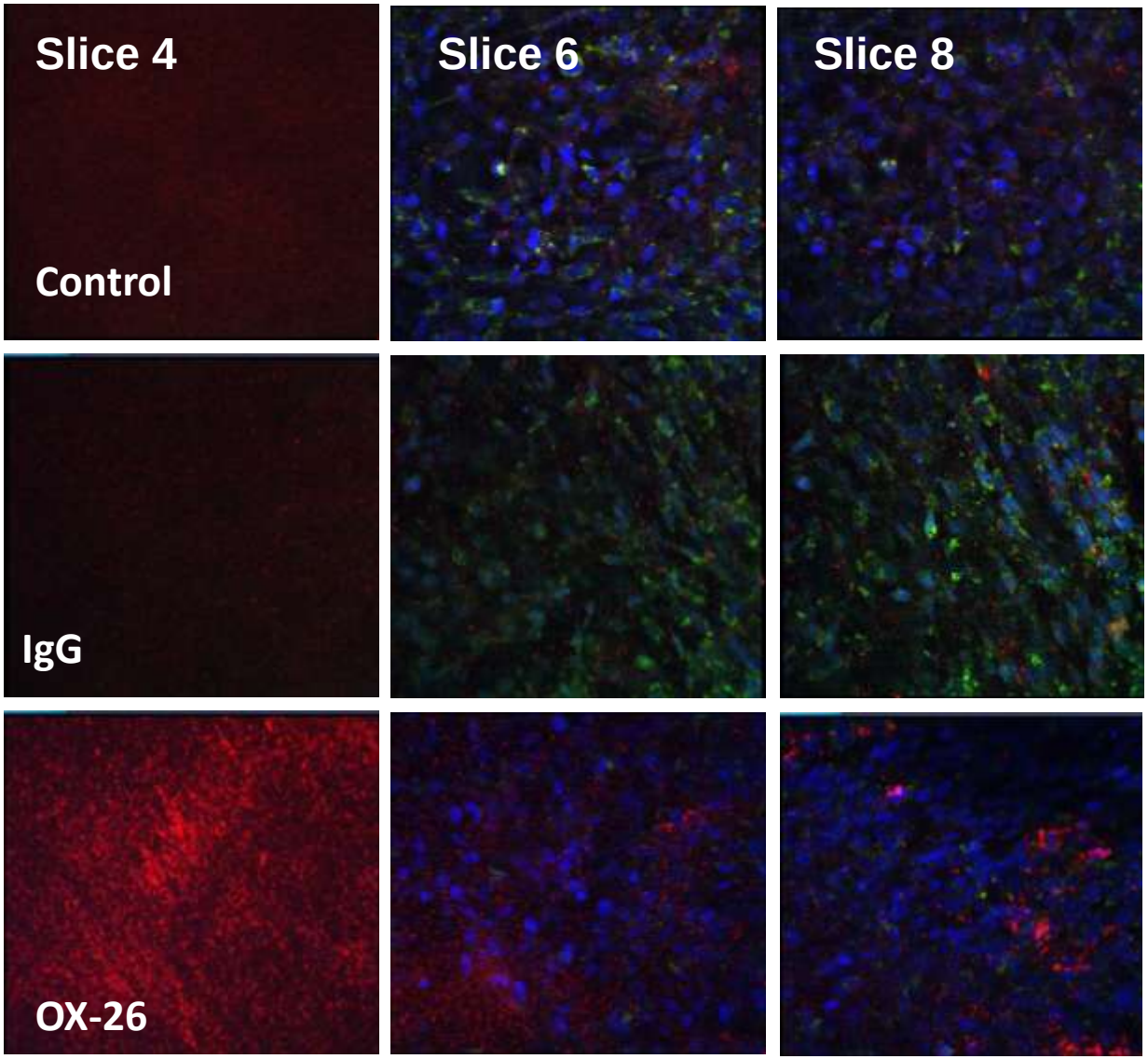




The new hCMEC/D3 cell line as a model for uptake and permeability studies of BBB-targeting nanoparticles. *Under publication*

Eleni Markoutsa[1], Georgios Pampalakis[1], Anna Niarakis[1], Ignacio A. Romero[2], Babette Weksler[2], Pierre-Olivier Couraud[2], Sophia G. Antimisiaris[1,3]*

[2]INSERM, 101 rue de Tolbiac, 75654 PARIS CEDEX 13, France



Confocal microscopy of hCMEC/D3 monolayers formed on transwell membranes.

Cells were treated with control liposomes (control), murine serum IgG immunoliposomes (IgG), and OX-26 immunoliposomes (OX-26). All liposomes are stained with lipid-Rhodamine (red) and encapsulate FITC (green). Nuclei are stained with DAPI (blue).

Each column represents different slices obtained under the confocal microscope (3.75 um/slice)

Equipment-Facilities

- **Equipment for nanoparticle preparation** (homogenizers, sonicators [bath & probe], mixers, incubators, rotor evaporators, lyophilizer, extruders, etc)
- **Equipment for nanoparticle characterization** (Chromatographic separation and fraction collectors, UV-VIS & Fluorimeters, automated-modular HPLC [diode array-FI] Shimatzu, DSC (Mettler Toledo), ultracentrifuge Sorvall etc)
- **Equipment for nanoparticle evaluation** [cell culture room, incubators, laminar hood, fluorescent microscope, small animal room, radioisotope facility]

Group members

Professors: S. G. Antimisiaris, P. Klepetsanis

Post-Doc Researchers: S. Mourtas, A. Niarakis, G. Pampalakis

Post-Grad. Students: E. Markoutsa, A. Skouras, G. Diamanti, K. Papadia

Recent Publications

- *Heparin incorporating liposomes as a delivery system of heparin from PET-covered metallic stents: Effect on haemocompatibility*, **Biomaterials**, 27:12, 2525-2533, 2006.
- *Integrity of liposomes in presence of cyclodextrins. Effect of liposome type and lipid composition*, **Int. J. Pharm** ,333 (1-2), pp. 167-176, 2007.
- *Liposomes for drug delivery to the lungs after nebulization*. **Eur. J. Pharmaceutics & Biopharmaceutics**, 67 (3), pp. 655-666, 2007.
- *PLGA, Chitosan or Chitosan-coated PLGA Microparticles for Alveolar Delivery? A comparative study of particle stability during nebulization*. **Colloids and Surfaces B: Biointerfaces,** 62 (2), pp. 220-231, 2008.
- *How liposome type, composition and loading concentration influence the rheological properties of a liposomal gel.* **J. Colloid & Inter. Scienc B: Biointerfaces,** 317 (2), pp. 611-619, 2008.
- *Release of Liposome-Encapsulated Calcein from Liposome Entrapping Gelatin-Carboxymethylcellulose Films: A Presentation of Different Possibilities*. **J. Nanoscience & Nanotechnology,** 8, 2249–2258 2008.
- *Chitosan-coated liposomes for delivery to lungs by nebulization*». **Colloids and Surfaces B: Biointerfaces** 71 (1), pp. 88-95 , 2009.
- "Complex gel formulations for topical drug administration: Rheological properties and aging", Invited contribution, **Langmuir**, 25: 15 8480-8488 2009.
- Arsonoliposomes for the potential treatment of medulloblastoma **Pharmaceutical Research** 26 (10), pp. 2237-2246 2009.
- Curcumin-decorated Nanoliposomes with very high affinity for Amyloid-β1-42 peptide **Biomaterials**, in press