



Nanotechnology Approaches for Crossing the Blood Brain Barrier

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A Working Definition of Nanotechnology

Nanotechnologies are engineered materials or devices whose smallest functional organization over which there is some degree of control in at least one dimension is on the nanometer scale.

... resulting in functional properties unique to the engineered technology not necessarily shared by its constituent elements.

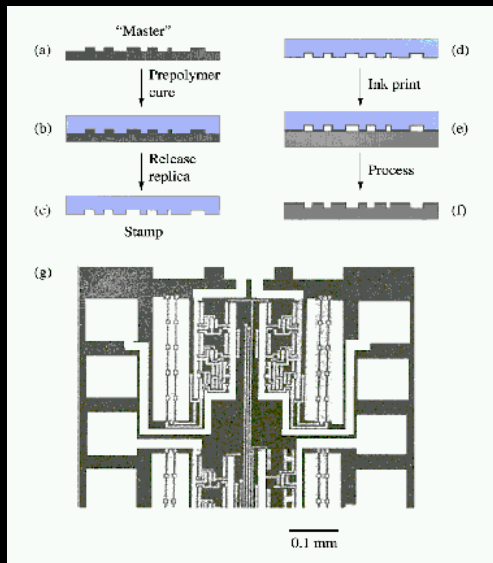
A Working Definition of Nanomedicine

Understanding, preventing, and treating diseases using tools, materials, and approaches that take advantage of and operate at the nanoscale.

NIH Nanomedicine Roadmap Initiative meeting, May 4, 2004

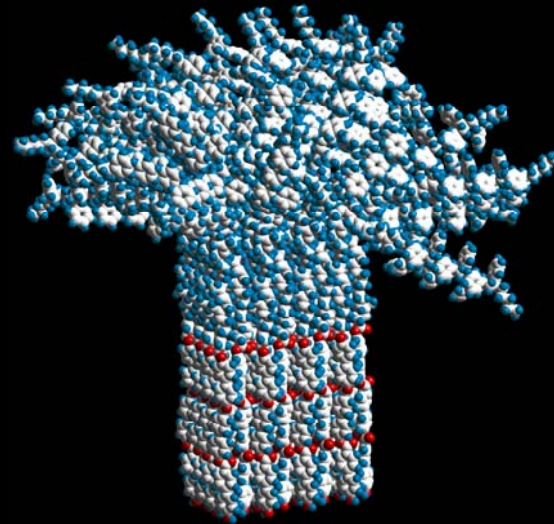
Synthetic Approaches to Nanotechnology

Top Down Approach:
Machining or etching
techniques (e.g. micro-
contact printing)



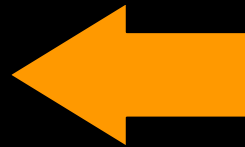
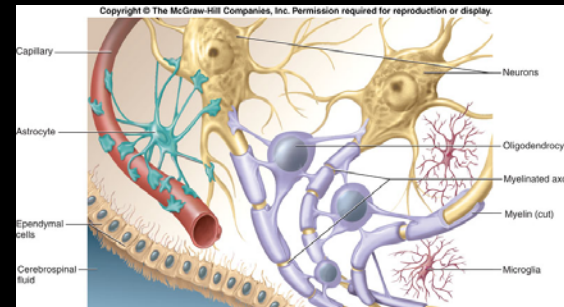
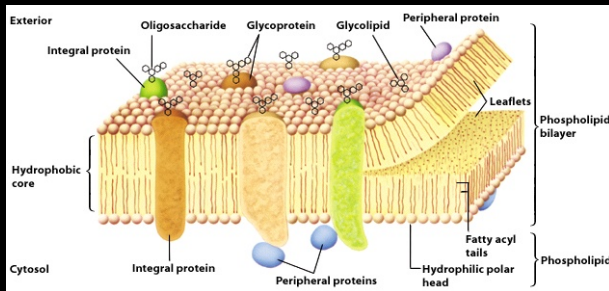
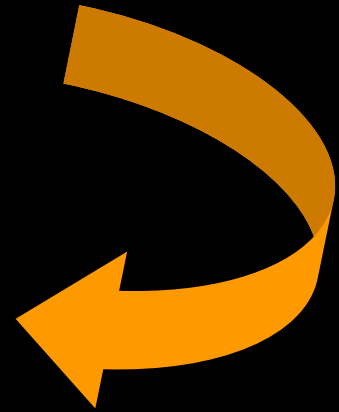
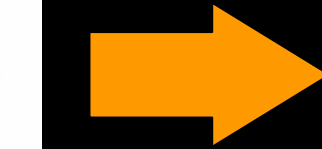
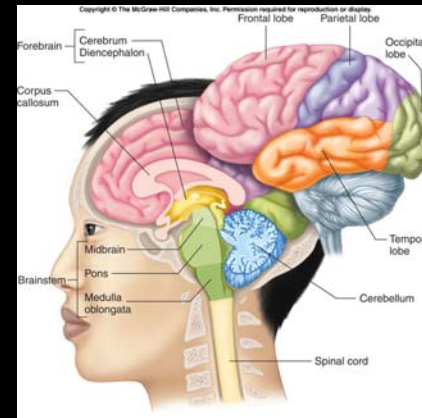
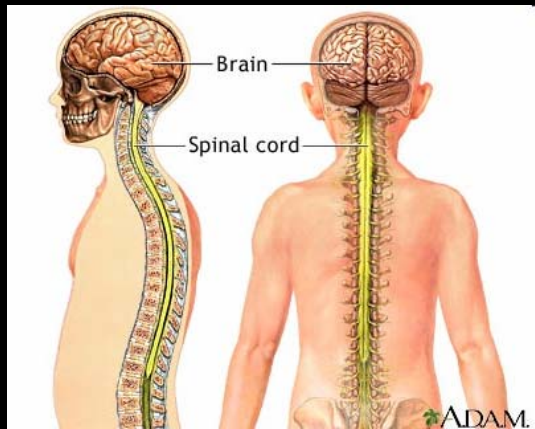
Biebuyck, et al., *IBM J. of Res. and Dev.*
41 159 (1997)

Bottom Up Approach: Molecular
self-assembly



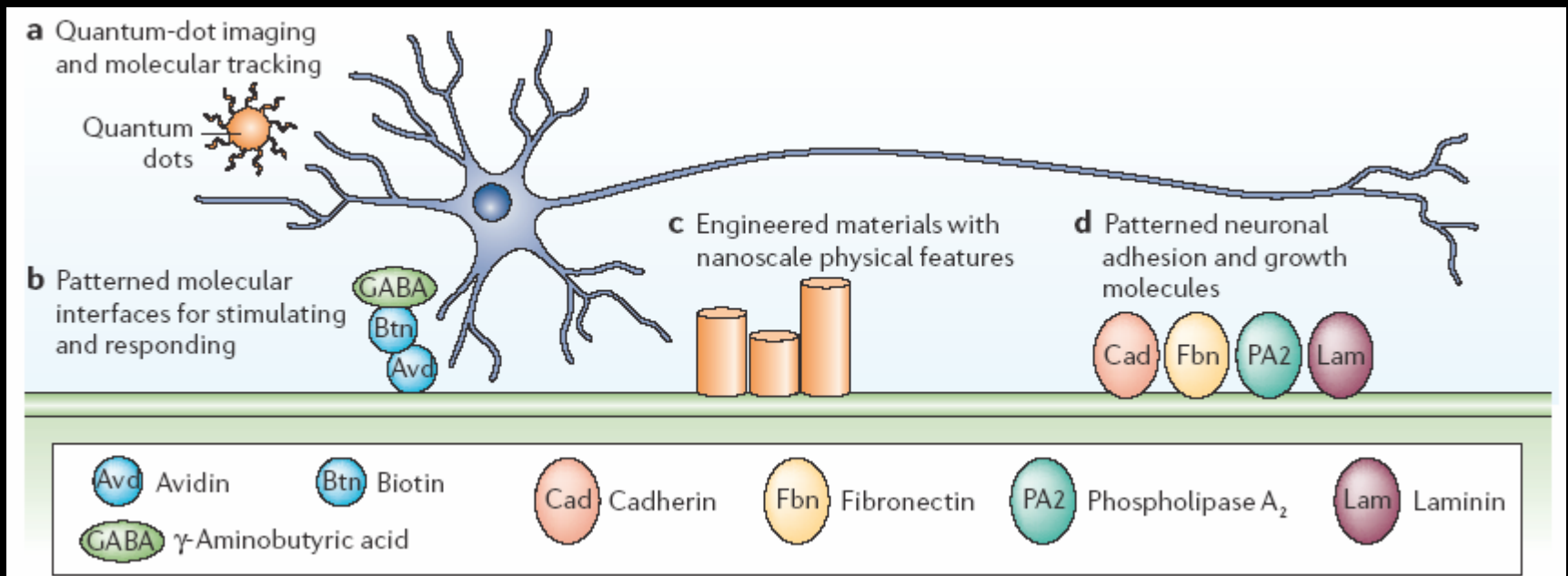
Stupp, et al., *Science* 276 384 (1997)

The Potential of Nanotechnology: Interacting with cells and tissues at a fundamental molecular level

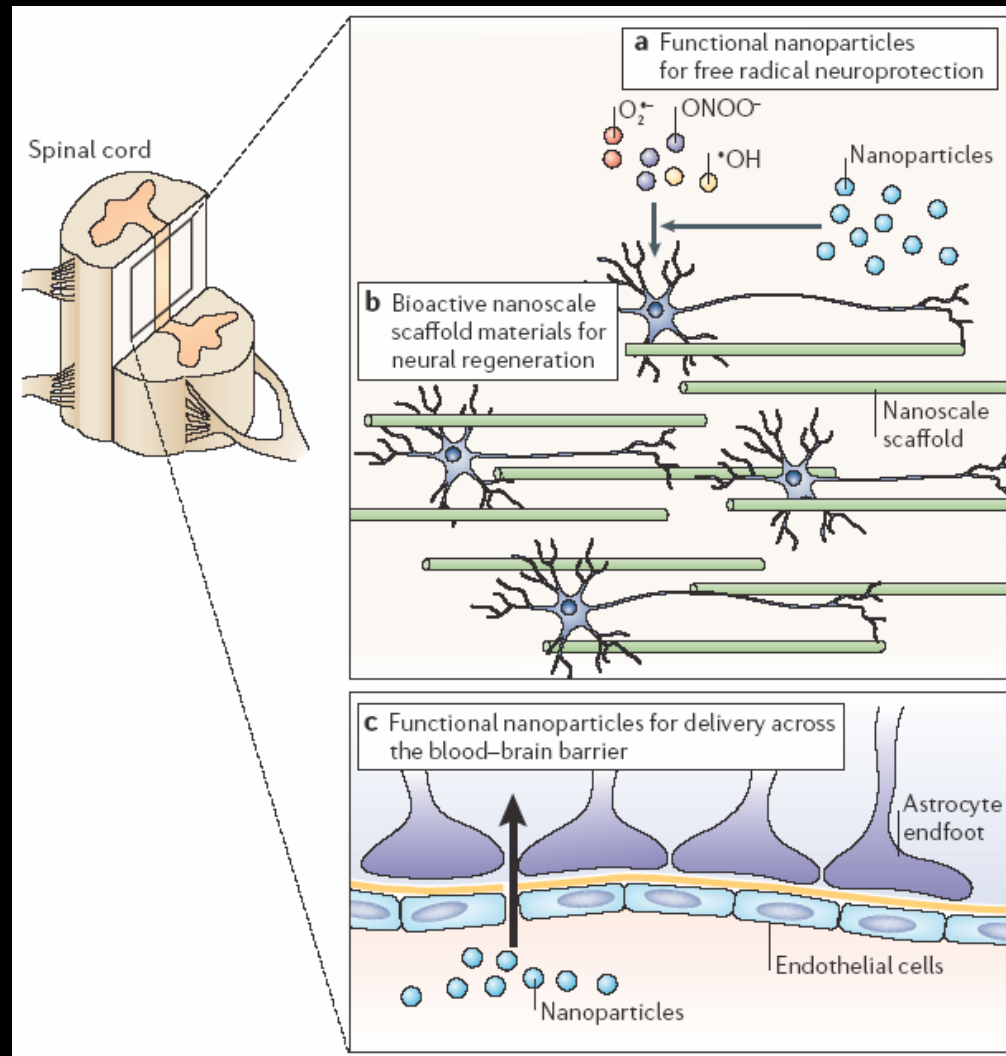


The nanoscale

Nanotechnology Applications to Basic Neuroscience



Nanotechnology Applications to Clinical Neuroscience



Challenges Faced by CNS Nanotechnologies

Involve the blood brain barrier in one way or another

- 4. Targeting to specific molecular elements (e.g. receptors, other proteins), in particular intracellular targets**
- 5. Highly restricted anatomical and functional access**
- 6. Multiple specific targeted effects and/or responses**
- 7. Optimization of desired integrated responses and minimization of local and systemic “side effects”**

The Ideal Nanoengineered Blood Brain Barrier Drug Delivery System

1. Systemic administration (e.g. IV, IP)
2. Find the CNS with minimal to negligible systemic side effects
3. Cross the blood brain barrier
4. Target specific cell populations in the CNS
5. Carry out its primary therapeutic function (e.g. kinetically timed release of an active compound)

Examples of Nanoengineered Blood Brain Barrier Drug Delivery System

polyethylene glycol (PEG) coated hexadecylcyanoacrylate nanospheres
target and accumulate in a rat model of gliosarcoma

poly(butylcyanoacrylate) nanoparticles coated with polysorbate 80
deliver the chemotherapeutic drug doxorubicin and other compounds

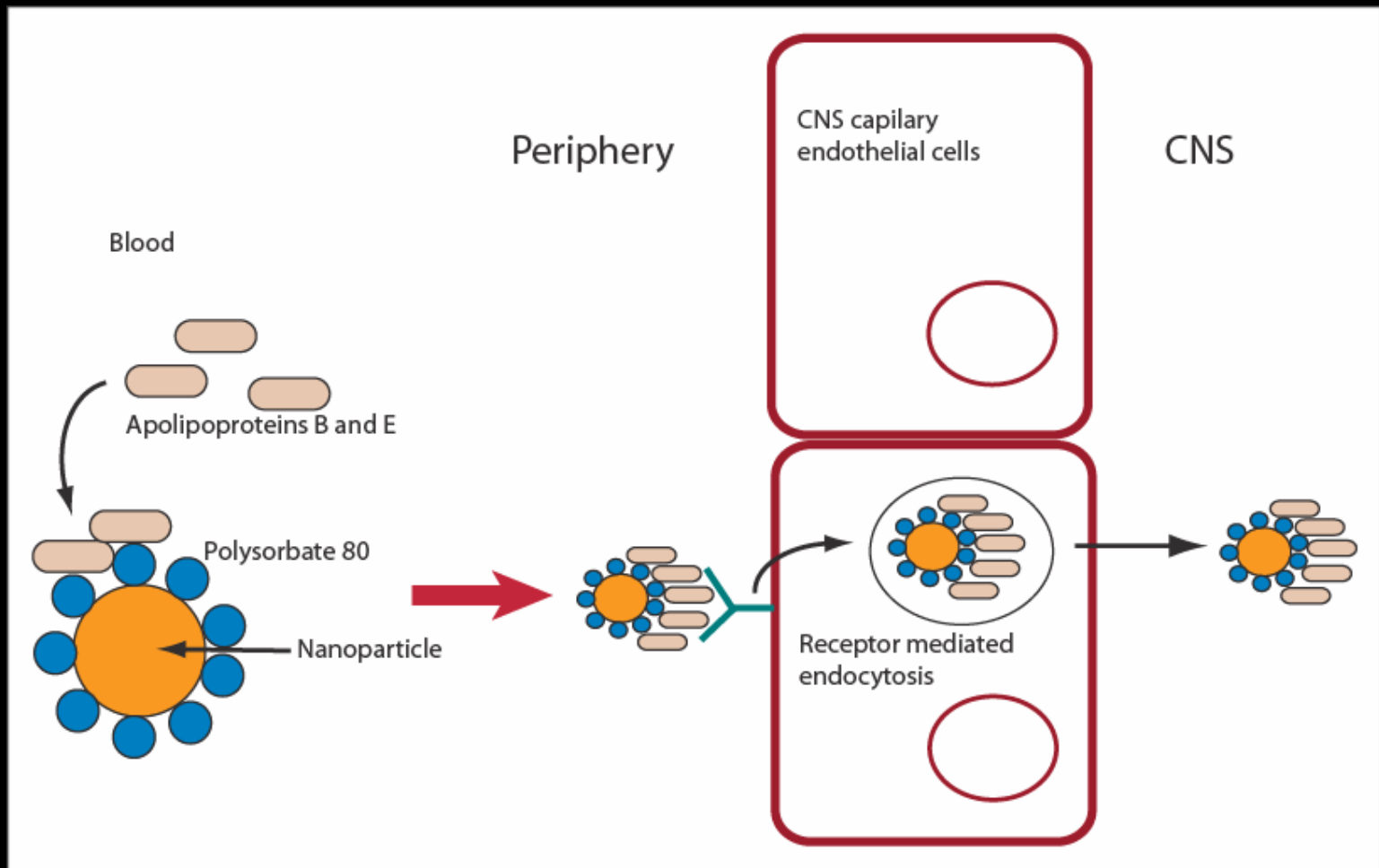
poly(butylcyanoacrylate) nanoparticles
deliver the analgesic dalargin

iron loaded lipid nanoparticles
potential use as a CNS specific MRI contrast agent

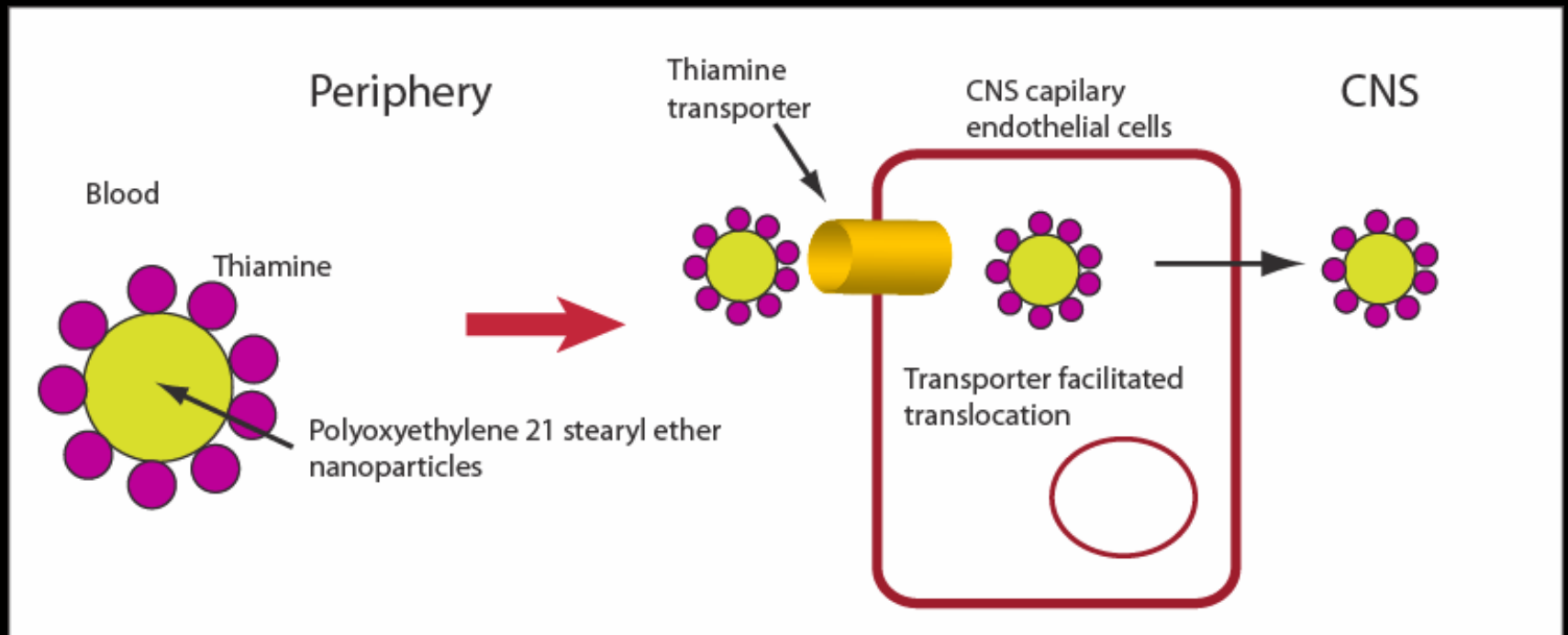
cross-linked polyethylene glycol and polyethylenimine nanogels
deliver oligonucleotides

polyethylene glycol immunoliposome nanoparticles
deliver genes for potential gene therapy

Mechanisms of Action: Receptor Mediated Endocytosis

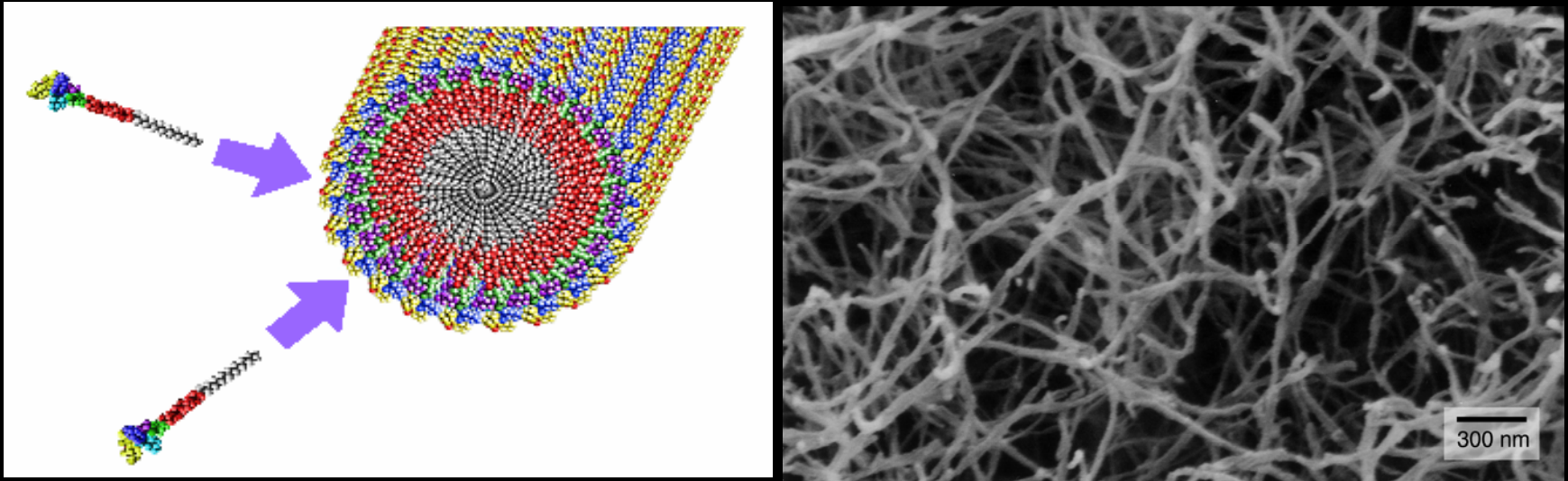


Mechanisms of Action: Transporter Facilitated Translocation



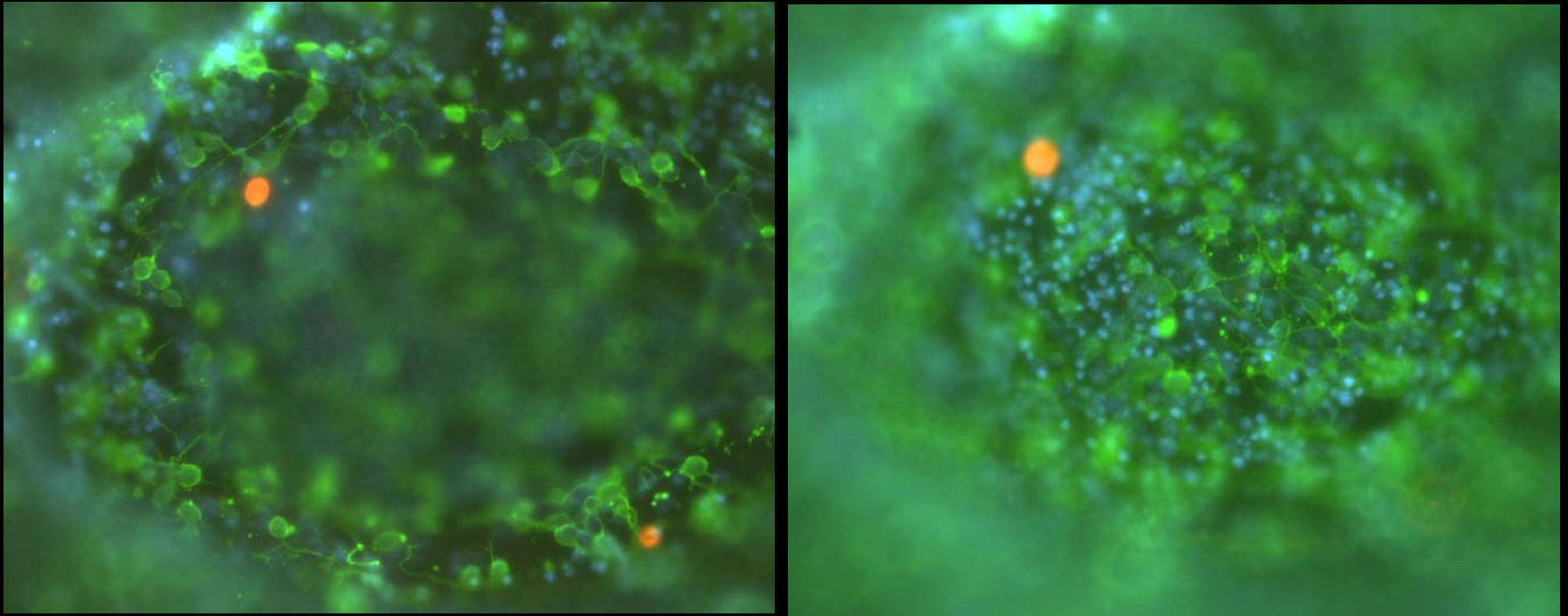
Nanoengineered delivery systems to the CNS that cross the blood brain barrier could also potentially deliver other therapeutic nanotechnologies ...

For Example: Peptide amphiphile molecules self-assemble into nanofiber networks ...



GA Silva, *et. al.* (2004) *Science*. 303:1352

... which induce the rapid differentiation of neurons *in situ*



GA Silva, *et. al.* (2004) *Science*. 303:1352



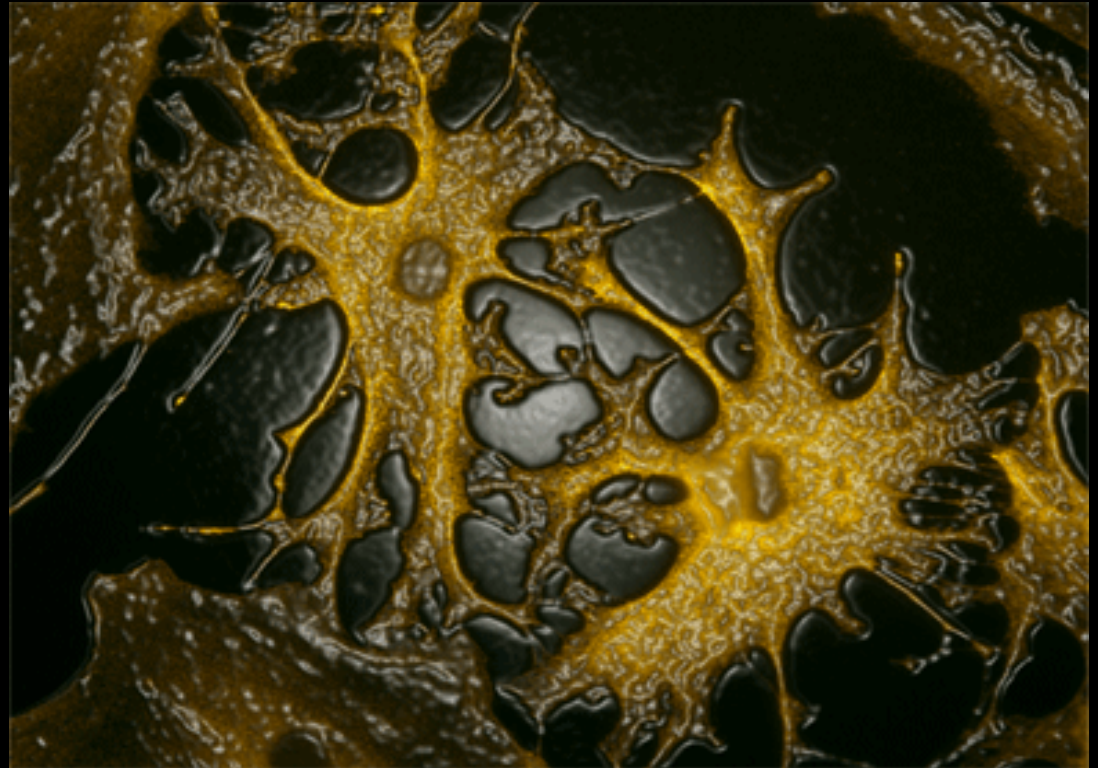
But only delivery method is invasively via direct injections into the CNS

Need a good systemic delivery system that can cross the blood brain barrier

Nanoengineered delivery systems to the CNS that cross the blood brain barrier would also benefit other areas of neurophysiology and neuropathology research ...

For Example: Delivery of specific cytological markers to determine cellular microanatomy *in vivo*

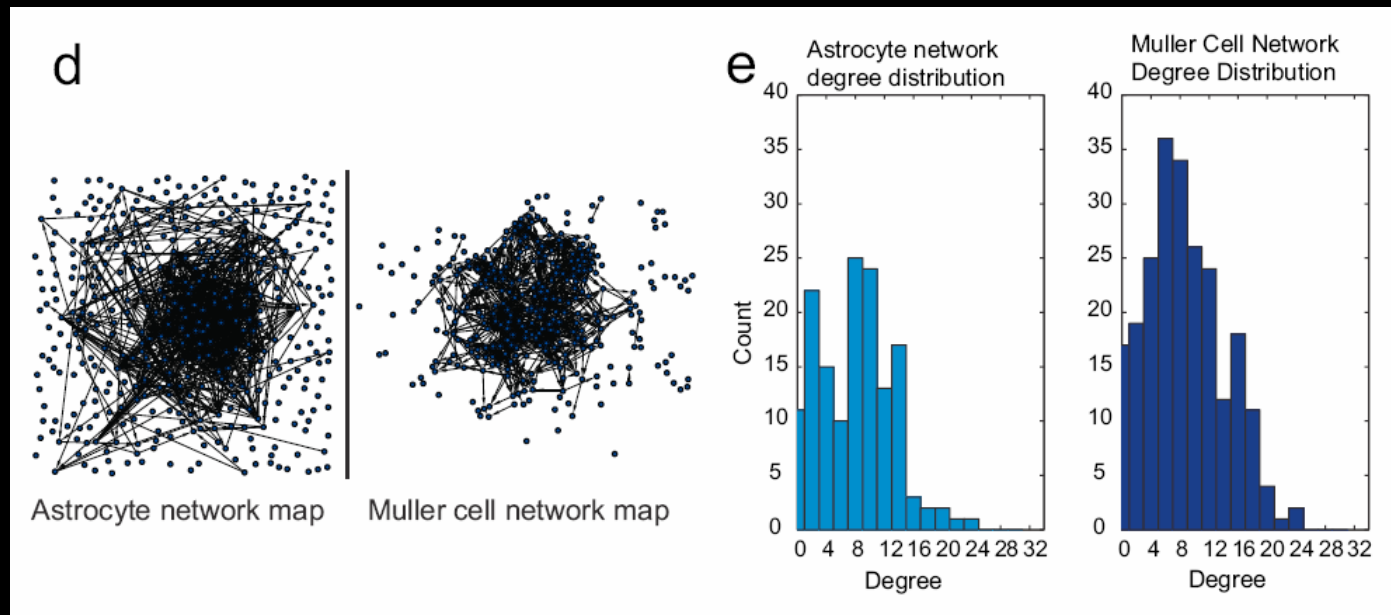
High resolution *in vitro* interactions between spinal cord astrocytes imaged using quantum dots



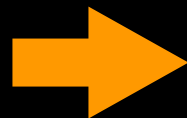
For Example: Delivery of signaling indicators to investigate functional network behavior *in vivo* ...

High resolution *in vitro* live cell imaging of functional signaling in spinal cord astrocytes networks

... for mapping the dynamic quantitative structure of functional neural networks with single cell resolution

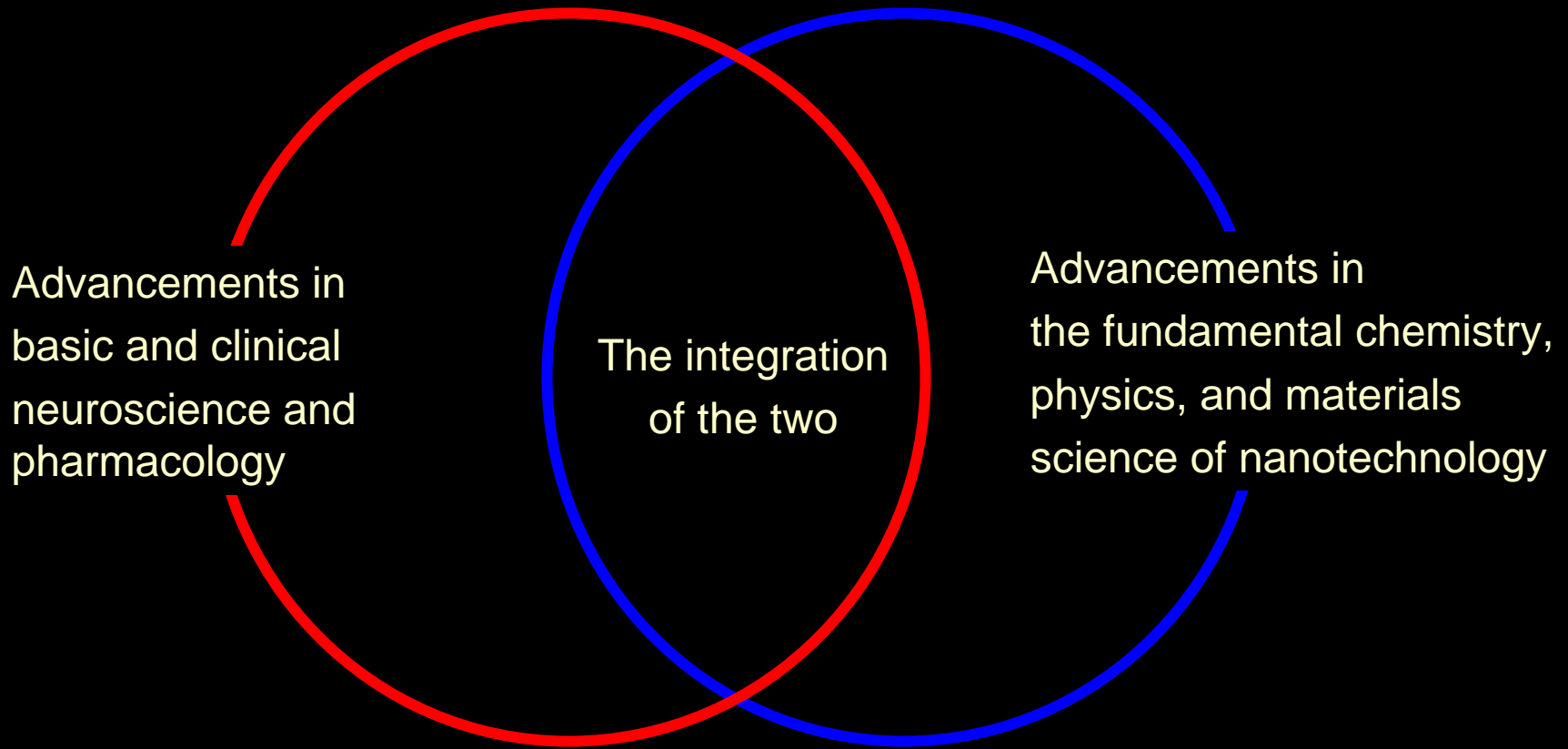


Network topology



Classification and characterization of networks in health and disease

Furthering Nanotechnology Approaches for Drug Delivery Across the Blood Brain Barrier



Acknowledgments and Collaborators

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