U.S. Department of Health and Human Services

National Institutes of Health

National Heart Lung and Blood Institute

Nanotechnology Research Across the NIH

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Division of Cardiovascular Diseases

Nanoscale Science and Engineering
2007 NSF Grantees Conference
Arlington (VA), December 5, 2007

Overview

- Summary of programs supporting nanotechnology research at NIH
- Examples of NIH-supported nanotechnology research
  - Fundamental nanoscale research and tools
  - Diagnostics
  - Therapeutics
    - Drug delivery
    - Tissue engineering
    - Devices

NIH Support for Nanoscience and Nanotechnology Research

- Investigator-initiated grants
- BECON (Bioengineering Consortium) programs
- Institute programs
  - NHLBI Programs of Excellence in Nanotechnology
  - NCI Alliance for Nanotechnology in Cancer
    - Centers
    - Platforms
    - Training
    - Nanotechnology Characterization Lab (with FDA and NIST)
  - NIEHS
    - NTP
    - Joint solicitations
- NIH Roadmap Nanomedicine Initiative

Nanotechnology Research Support at NIH

Program announcements issued through BECON:

- Nanoscience and Nanotechnology in Biology and Medicine
- Bioengineering Nanotechnology Initiative (SBIR)

- Exploratory/Developmental Bioengineering Research Grants
- Bioengineering Research Grants
- Bioengineering Research Partnerships
- Mentored Quantitative Research Career Development (K25)

- *Awards under these programs are listed on the BECON web site: www.becon.nih.gov/nano.htm*

Nanotechnology Research Support at NIH

Nanoscience and Nanotechnology in Biology & Medicine

- i) create structures, devices & systems with novel properties to understand biological processes or for disease detection, therapy, or prevention; ii) fabricate and test devices to detect and analyze nanoscale entities of relevance to biomedicine; iii) study biological systems at the nanoscale to develop nanotechnologies and nanostructured materials for use in biomedicine
- Encourages team approach to nanotechnology research
- R01 (research project)
- R21 (exploratory/developmental) if << preliminary data and potential for groundbreaking impact. ≤3 years, $125k/yr DC
- Application Receipt: Current iteration expired Oct 22 2007

- http://grants.nih.gov/grants/guide/pa-files/PAR-07-270.html

Nanotechnology Research Support at NIH

Bioengineering Nanotechnology Initiative - SBIR/STTR

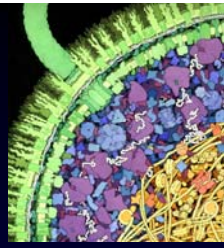
- Encourages team approach to nanotechnology research
- Phase I may request up to 2 years, $200,000 per year
- Phase II may request up to 3 years, $400,000 per year
- Applications Receipt per SBIR:
  April 5, August 5 and December 5
- Competes with other SBIR applications

- http://grants.nih.gov/grants/guide/pa-files/PA-06-008.html
- http://grants.nih.gov/grants/guide/pa-files/PA-06-009.html

NHLBI Programs of Excellence in Nanotechnology

- The Programs of Excellence in Nanotechnology represent NHLBI's flagship nanotechnology activity
- The PENs create multidisciplinary teams to develop and apply nanotechnology solutions to the diagnosis and treatment of heart, lung, blood and sleep disorders
- NHLBI funded 4 multidisciplinary PENs in spring 2005, committing $54 million over 5 years
  - Gang Bao — Emory University/Georgia Tech
  - Jeffery Smith — Burnham Institute/UCSB
  - Ralph Weissleder — Mass General Hospital/Harvard/MIT
  - Karen Wooley — Washington University/UCSF/UCSB
- The PENs include a significant training component including courses taught across the different institutions with video links

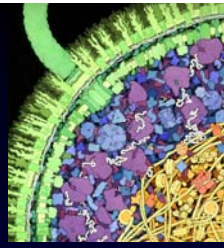
NIH Nanomedicine Roadmap Initiative



The overarching goal is to create the *conceptual and literal interface* between biology and medical devices at the scale of biomolecular processes

- Characterize quantitatively the physical and chemical properties of molecules and nanomachinery in cells
- Gain an understanding of the engineering principles used in living cells to "build" molecules, molecular complexes, organelles, cells, and tissues
- Use this knowledge of properties and design principles to develop new technologies, and engineer devices and hybrid structures, for repairing tissues and for preventing and curing disease

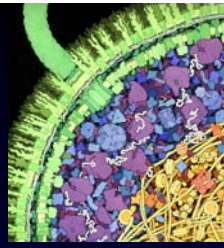
NIH Nanomedicine Roadmap Initiative



- The program seeks substantial leaps beyond current capabilities, and encourages a higher level of risk

- Nanomedicine Roadmap Initiative projects should depart from established, ongoing projects and should propose truly novel approaches and break new scientific and technical ground. A primary programmatic objective is to stimulate new ideas and directions that would not be likely to receive funding in routine grant solicitations

Nanomedicine Development Centers
Collaborative Network



Center for Protein Folding Machinery
Baylor College of Medicine

Nanomedicine Center for Mechanics in Regenerative Medicine
Columbia University

Engineering Cellular Control: Synthetic Signaling and Motility Systems
University of California San Francisco

National Center for Design of Biomimetic Nanoconductors
University of Illinois Urbana-Champaign

Nanomedicine Center for Nucleoprotein Machines
Georgia Tech

Phi29 DNA-Packaging Motor for Nanomedicine
Purdue University

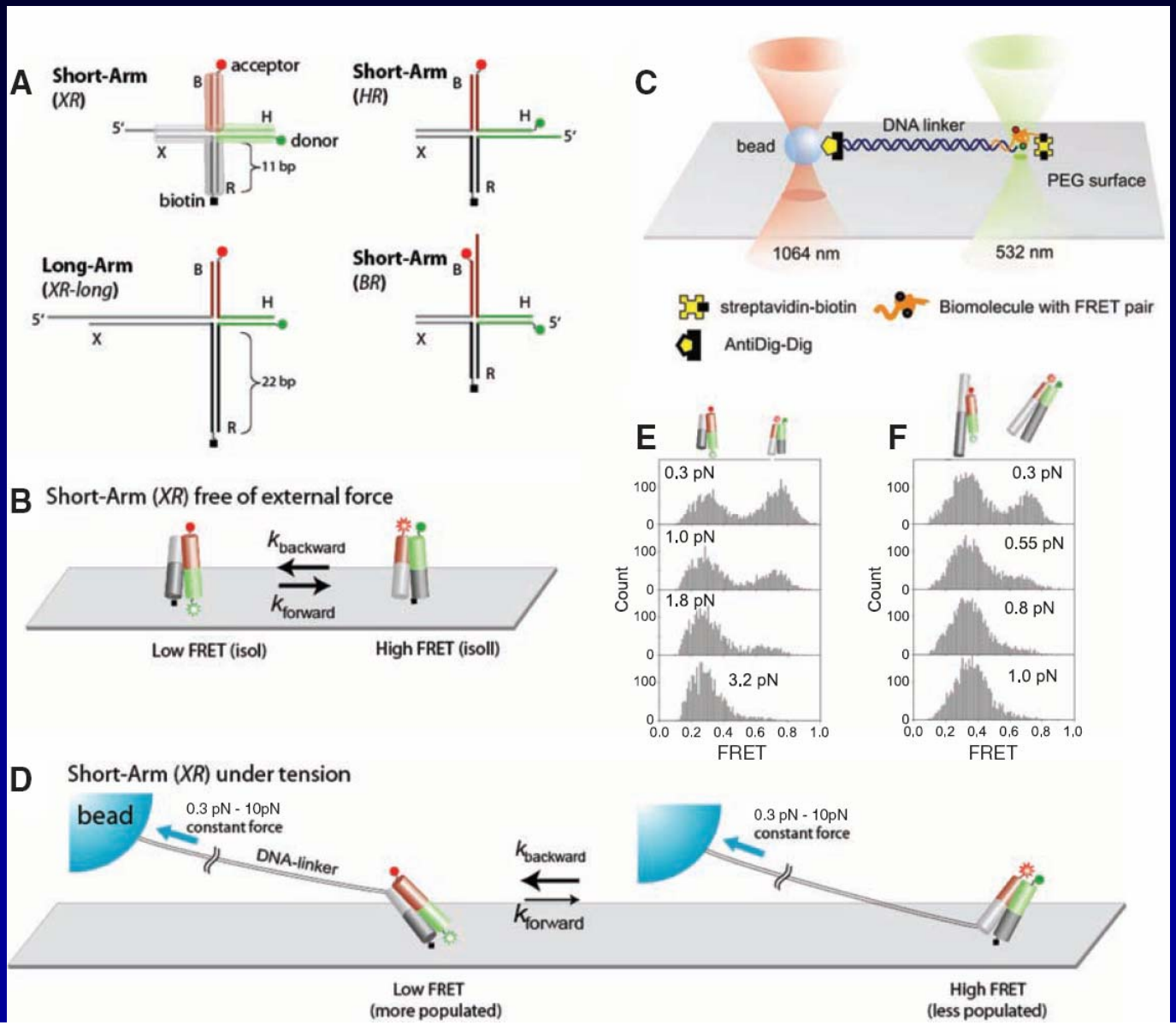
The Center for Systemic Control of Cyto-Networks
University of California, LA

NDC for the Optical Control of Biological Function
University of California / LBNL

Examples of NIH-funded research

Fundamental Science

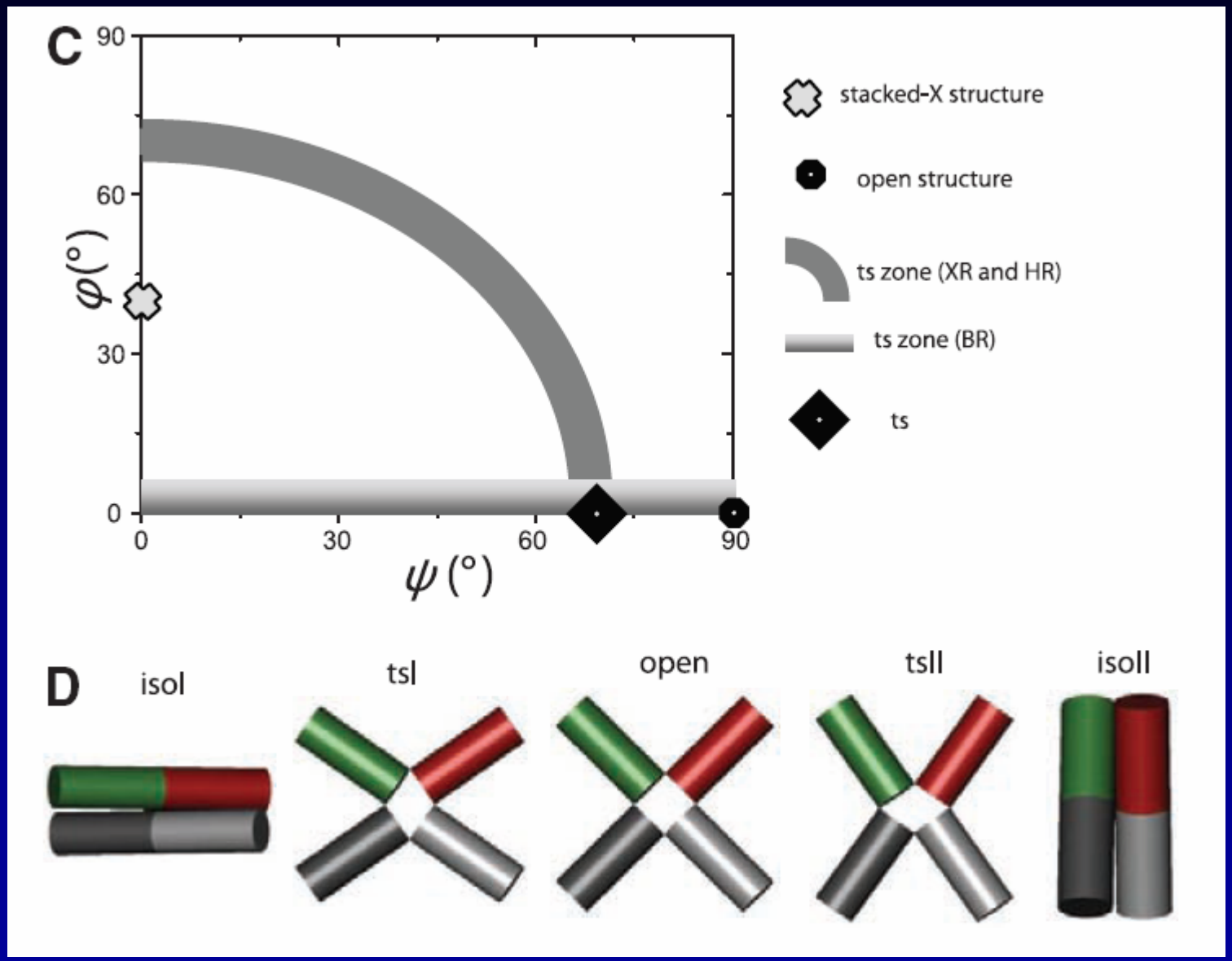
Mapping 2-D reaction landscape of the Holliday junction



Taekjip Ha Science 2007

Funded NIGMS/NSF

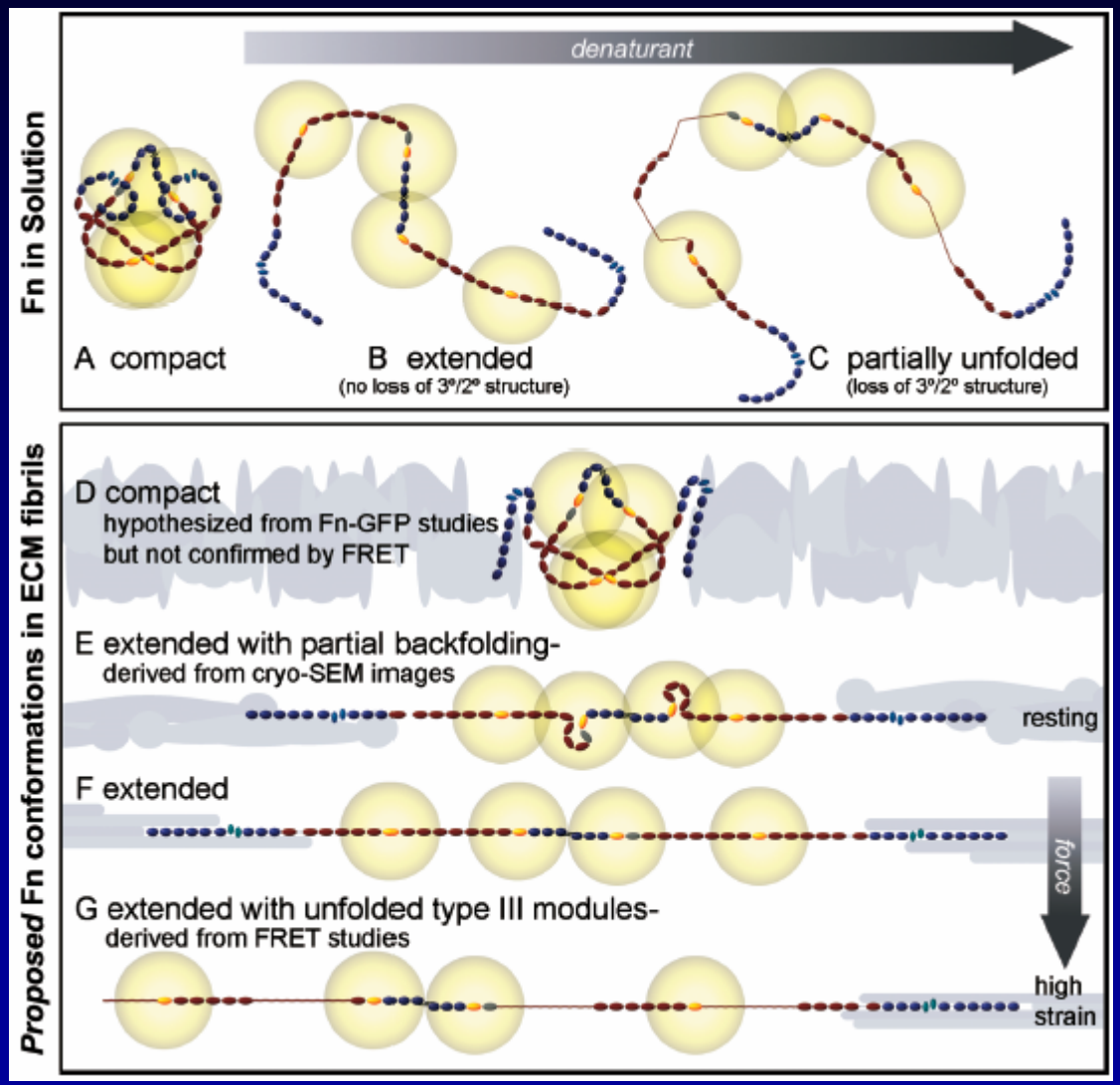
Mapping 2-D reaction landscape of the Holliday junction



Taekjip Ha Science 2007

Funded NIGMS/NSF

Force-Induced Unfolding of Fibronectin



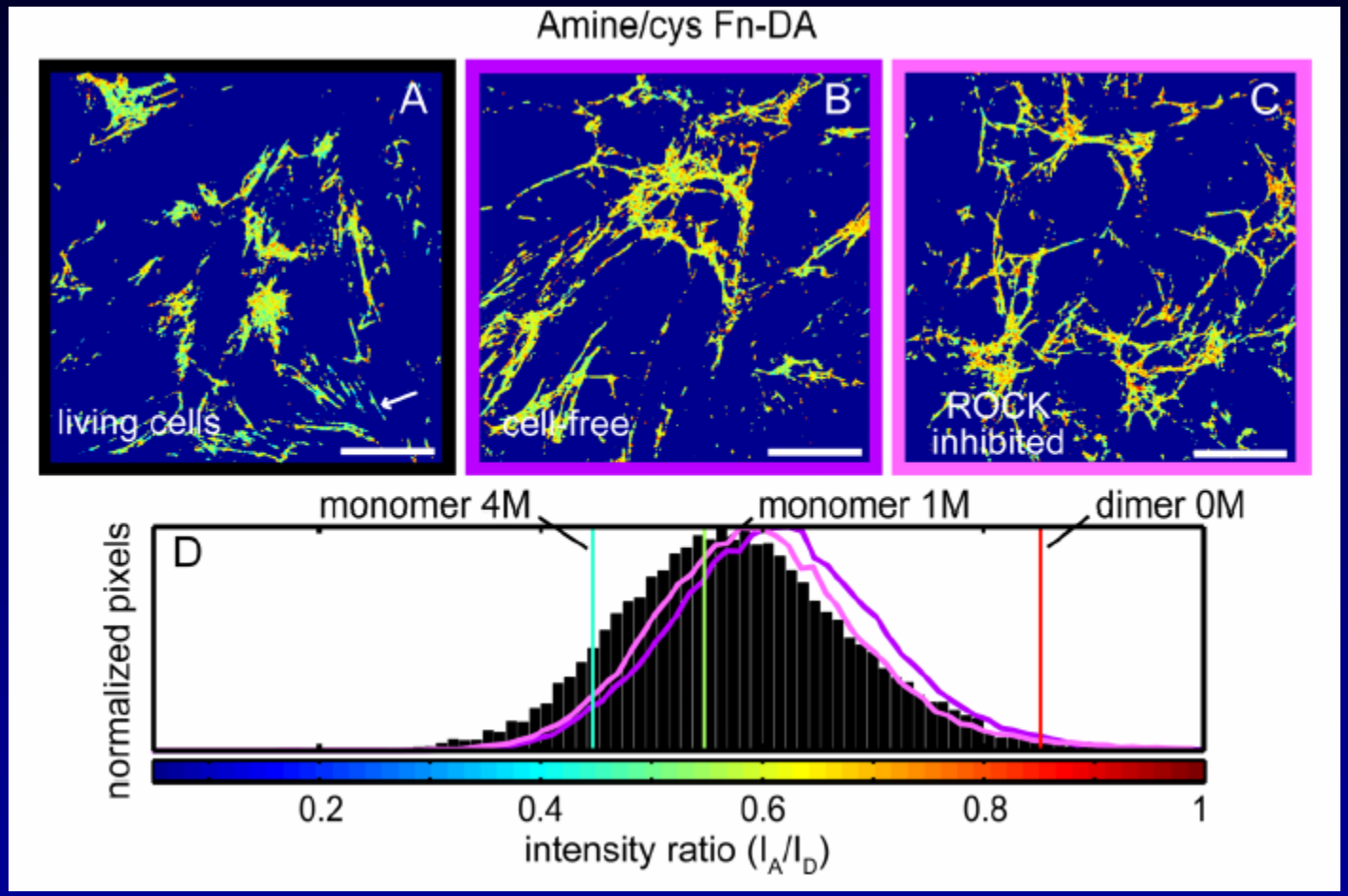
Used 2 FRET labeling schemes to assess elongation and unfolding

Amine/cysteine FRET – Assess extended/unfolded state

Cysteine/cysteine FRET – Quaternary structure

Viola Vogel PLoS Biology 2007
Funded by NIH Roadmap Nanomedicine

Force-Induced Unfolding of Fibronectin



Cell extraction or ROCK Inhibition lead to partial refolding

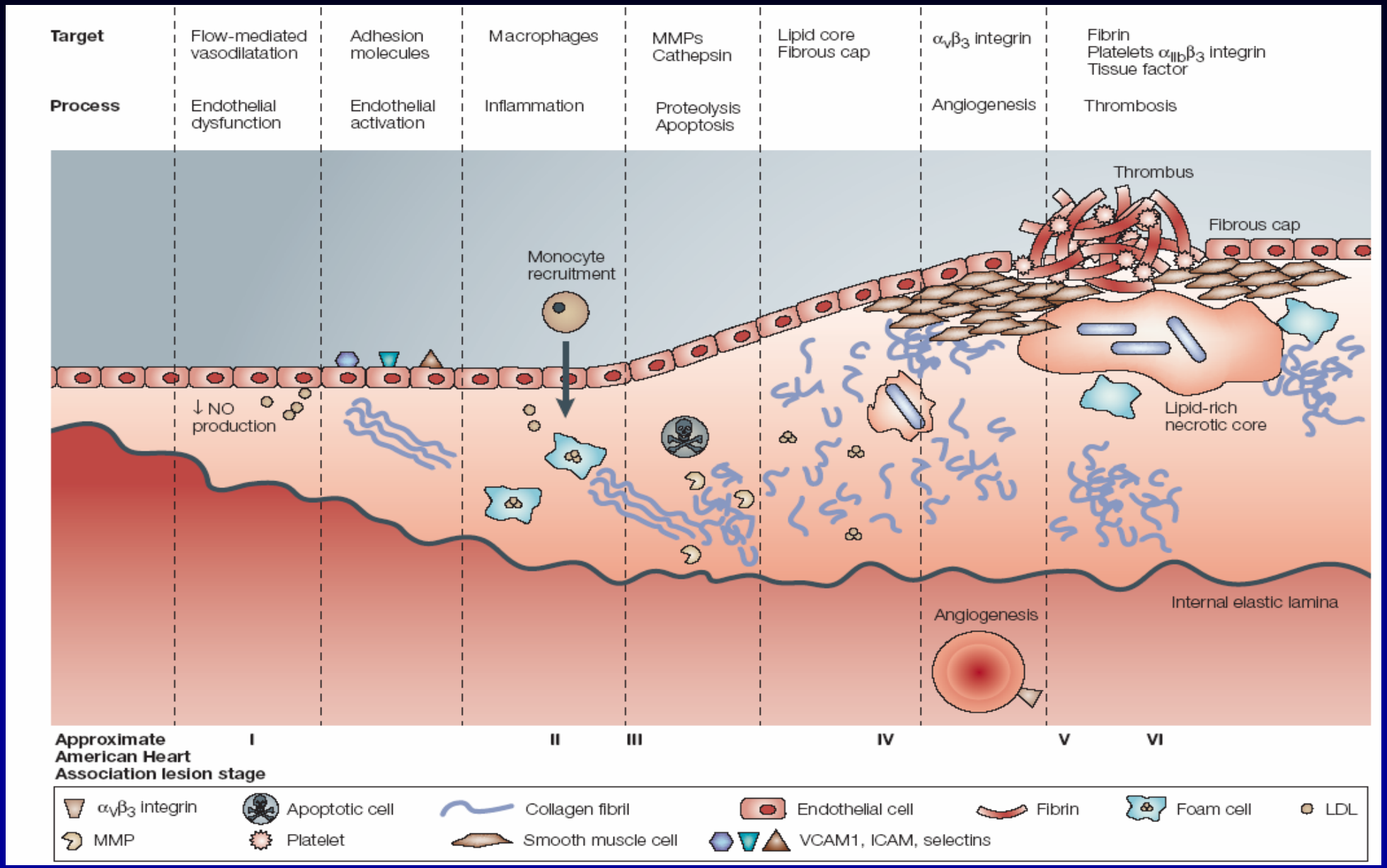
Fn found in a range of conformations

No evidence for compact folded state

Viola Vogel PLoS Biology 2007
Funded by NIH Roadmap Nanomedicine

Diagnostics

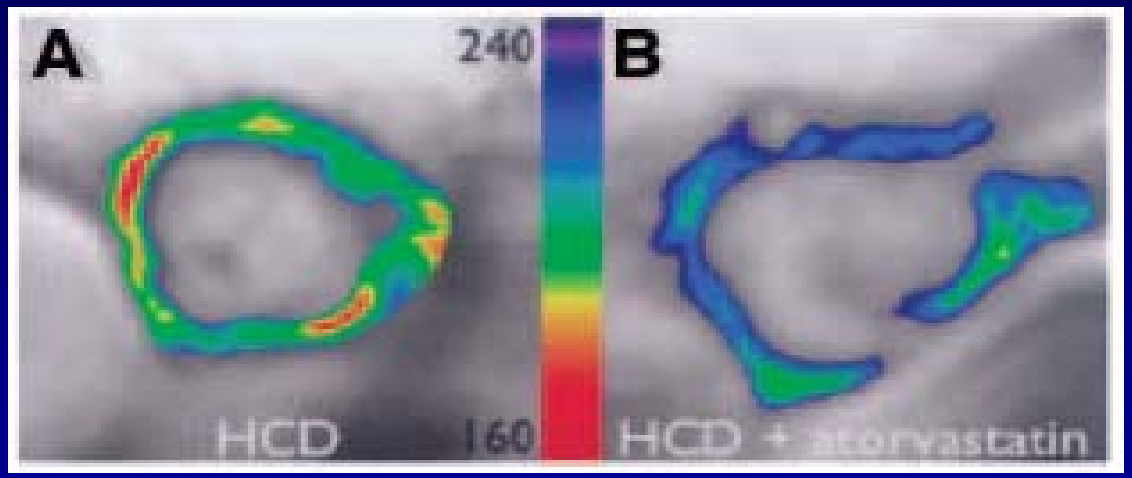
Imaging Targets in Atherosclerosis



Choudhury et al Nat Rev Drug Discov 2004

Imaging Atheroma with Nanoparticles

Recent work from the Weissleder group imaged atheroma in apoE-/- mice using in vivo MRI and nanoparticles targeted to VCAM-1 by a novel high affinity peptide



Aortas of ApoE-/- mice fed a high cholesterol diet showed MR signal enhancement after injection of VCAM-1 targeted nanoparticles (left). Treatment with statin for 8 weeks reduced nanoparticle deposition (right) and VCAM-1 expression

Nahrendorf et al, Circulation Oct 2006
Weissleder PEN

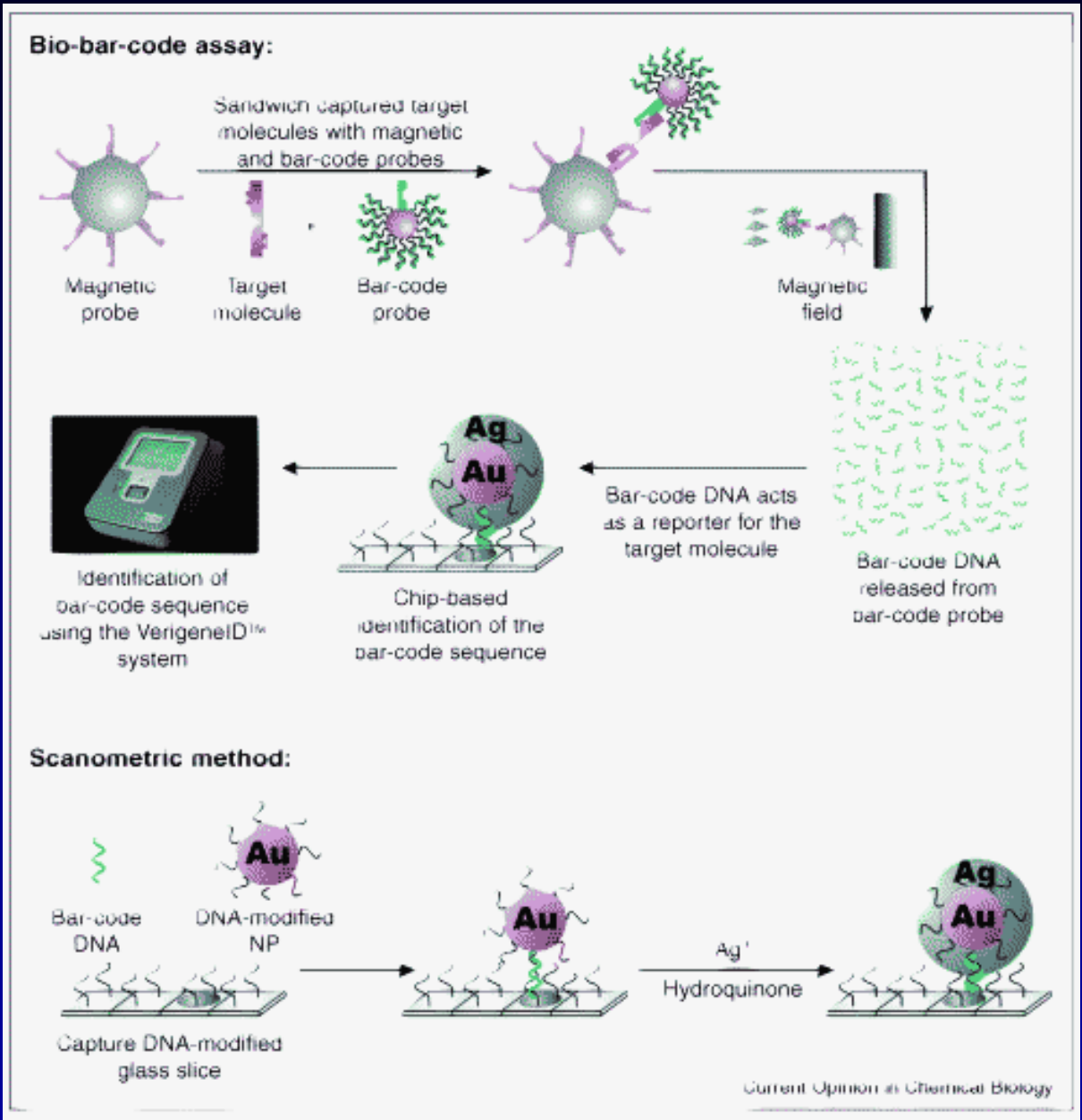
In Vitro Diagnostics

- Nanotechnology and microfluidics are expected to play a major role in the proliferation of next-generation integrated point-of-care diagnostic devices
- The availability of fast, multiplexed POC devices will enable personalized medicine through:
  - Genotyping to permit tailored drug prescription (e.g. BiDil) or dosing (e.g. warfarin)
  - Biomarker measurement for diagnostics or for rapid monitoring of treatment efficacy

Nanotechnology Approaches to Diagnostics

- There are a large number of competing technologies being developed:
  - Nanoparticle-based bio-barcode assays with electrochemical or optical detection
  - Label-free measurements based on direct detection of binding to nanocantilevers, nanowires, nanotubes
- Success will depend on a number of factors:
  - Ease of integration of sample preparation, diagnostics
  - Speed
  - Cost
  - Reliability, specificity
  - Capacity for multiplexing, concomitant measurement of multiple species (DNA, RNA, protein)

Bio-barcode Assay

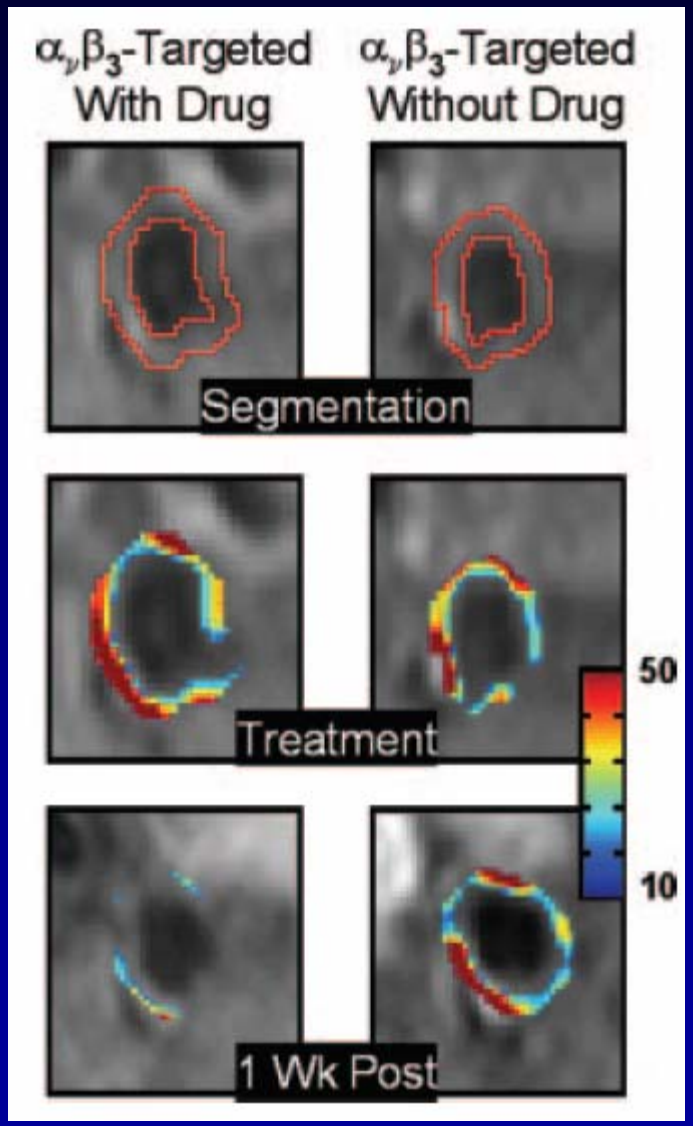


Cheng Curr Opin Chem Biol 2006

Therapeutics

Drug delivery

Anti-Angiogenic Effects of Fumagillin Nanoparticles in Atherosclerotic Rabbits



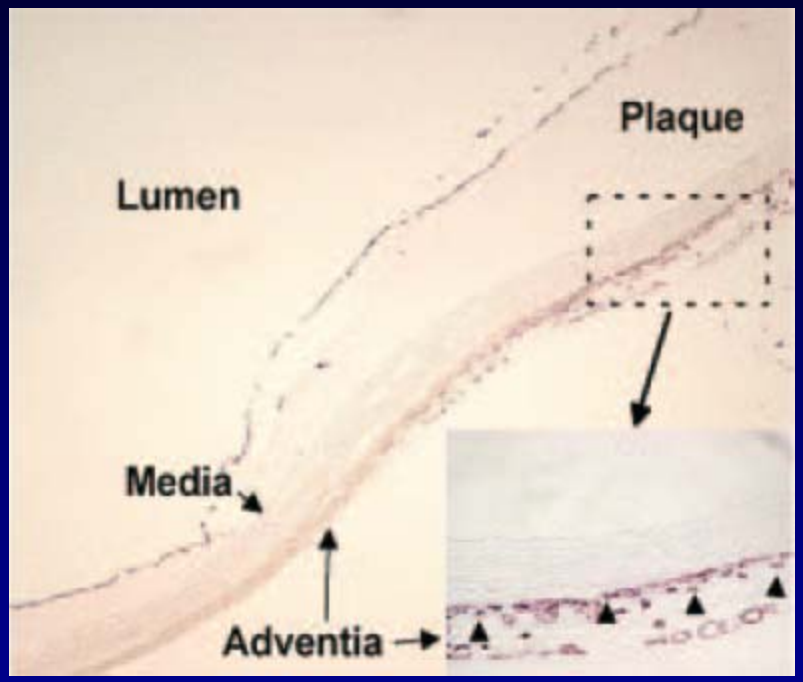
- Multifunctional perfluorocarbon nanoparticles are targeted to new vasa vasorum using a peptidomimetic vitronectin antagonist

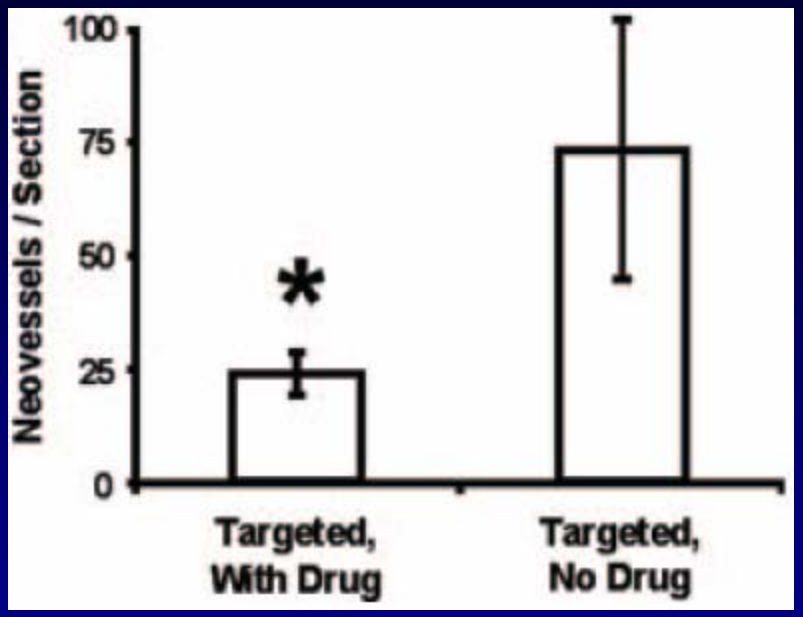
- The nanoparticles contain gadolinium for MR imaging, and the anti-angiogenic drug fumagillin

- Rabbits treated with the targeted fumagillin nanoparticles show decreased nanoparticle binding, consistent with loss of vasa vasorum

Greg Lanza ***Arterioscler Thromb Vasc Biol 2006***

Anti-Angiogenic Effects of Fumagillin Nanoparticles in Atherosclerotic Rabbits



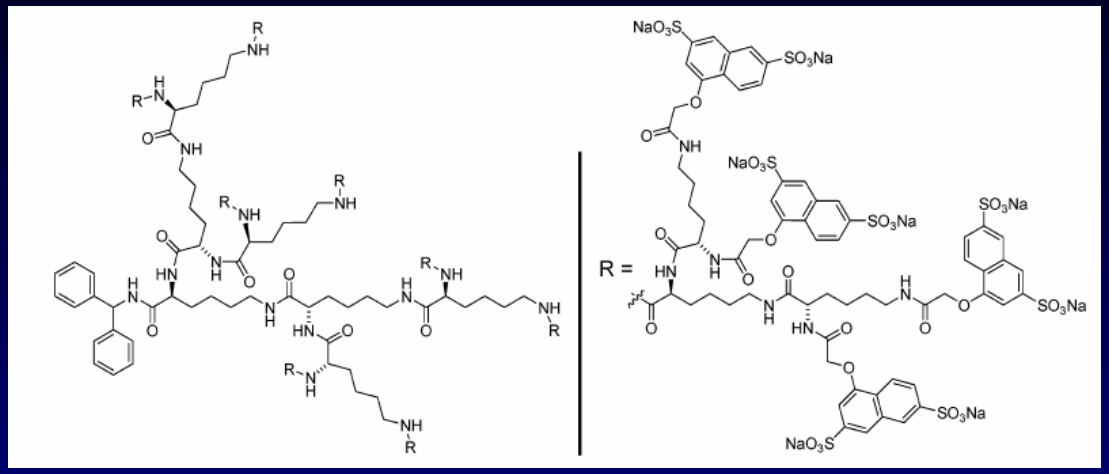


Histological staining confirmed that the neovessels were primarily associated with plaque thickening, and that fumagillin decreased neovessel density

Greg Lanza ***Arterioscler Thromb Vasc Biol 2006***

Funded by NHLBI

Dendrimer-Based Antivirals - VivaGel

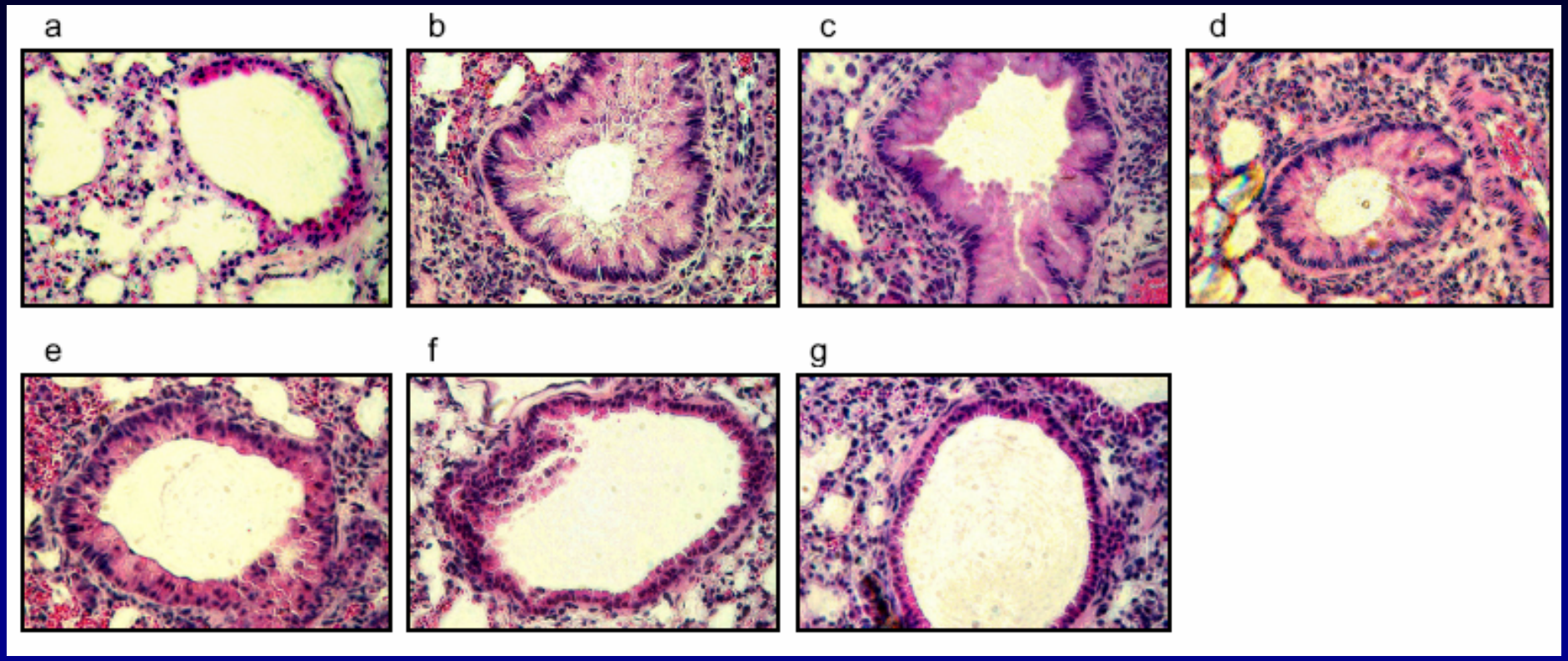


Chemical structure of SPL7013, the dendrimer antiviral in VivaGel

- *VivaGel has been shown to protect against genital herpes simplex in animal models*
- *In non-human primates, VivaGel is effective in blocking vaginal SHIV transmission*
- *Phase I trials in women have demonstrated the gel to be safe*
- *VivaGel is a promising microbicide candidate for a spectrum of sexually transmitted diseases*

Tom McCarthy Starpharma Supported by NIAID and NCRR

Nanoparticle-facilitated Asthma Treatment

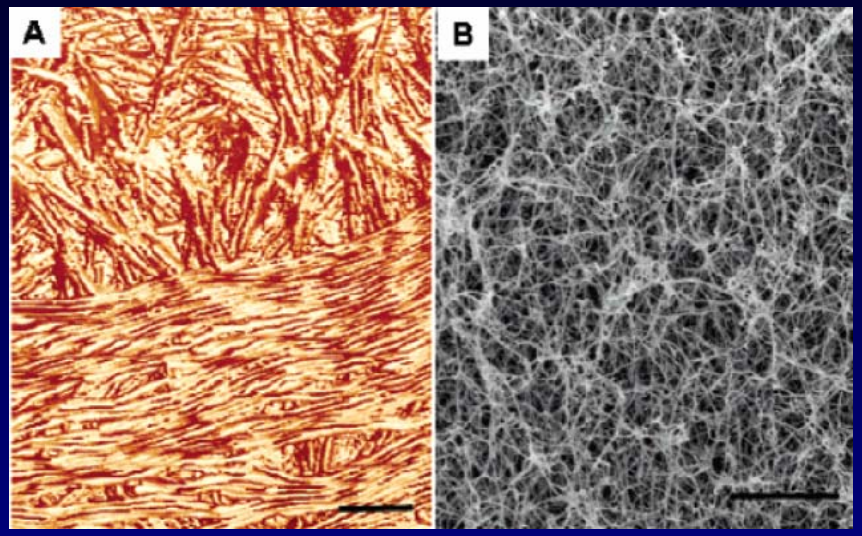


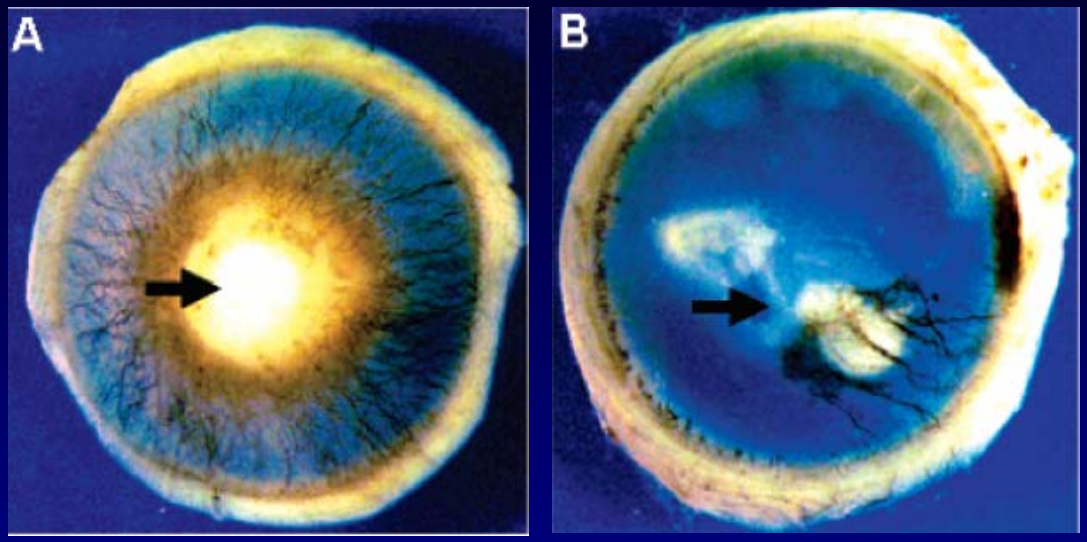
Binding of theophylline to thiolated chitosan nanoparticles enhances the anti-asthma effects of theophylline in antigen-challenged mice

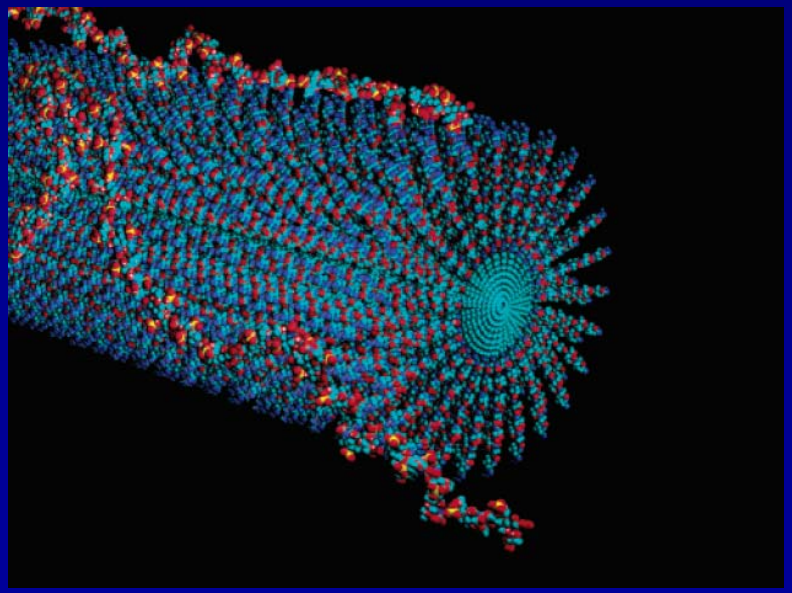
Shyam Mohapatra Respir Res 2006 Funded by NHLBI

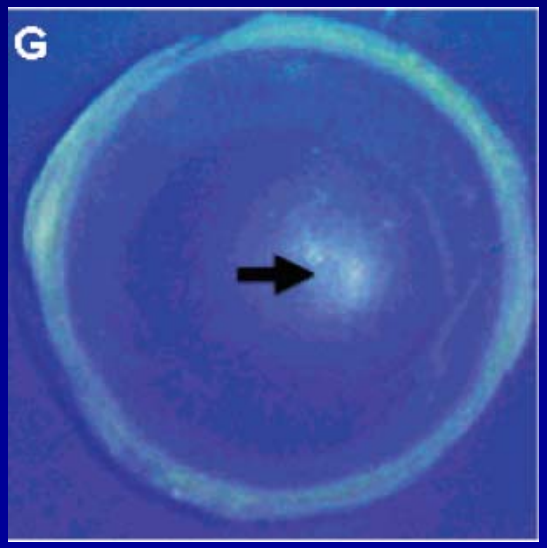
Tissue Engineering

Promoting Angiogenesis with Heparin Binding Nanostructures



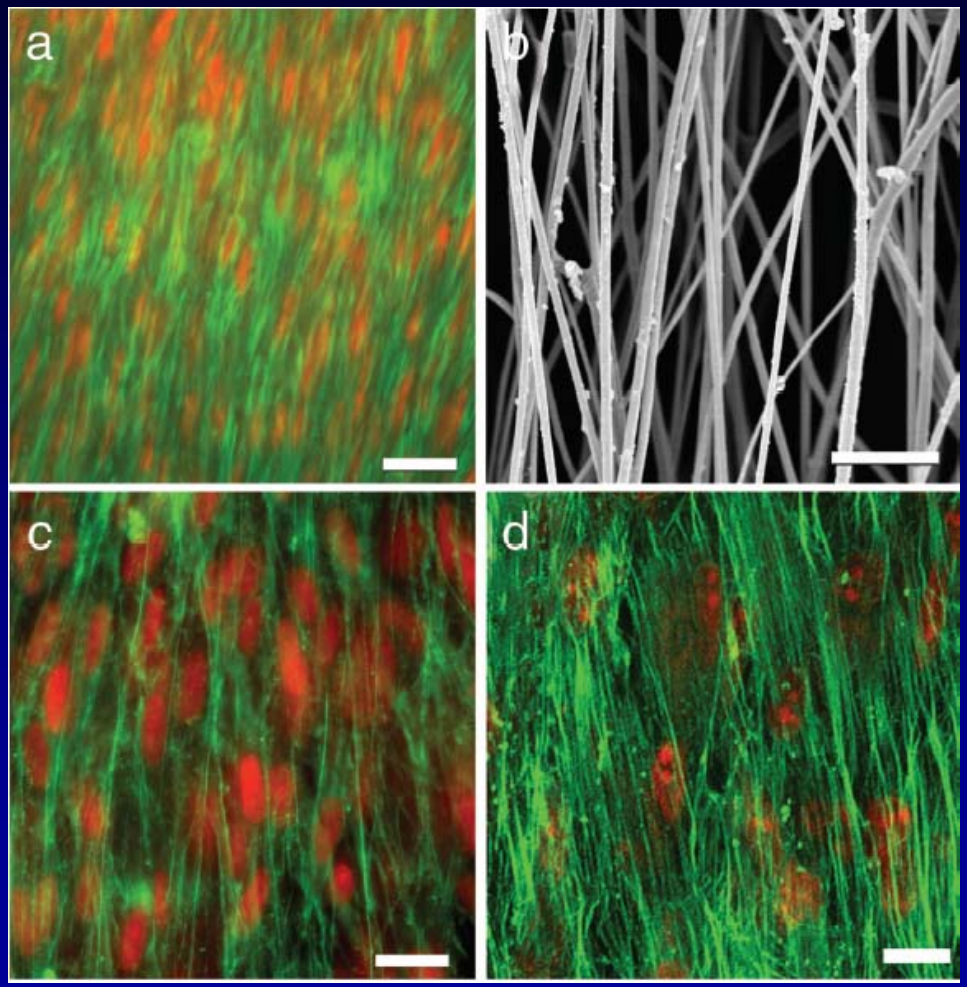


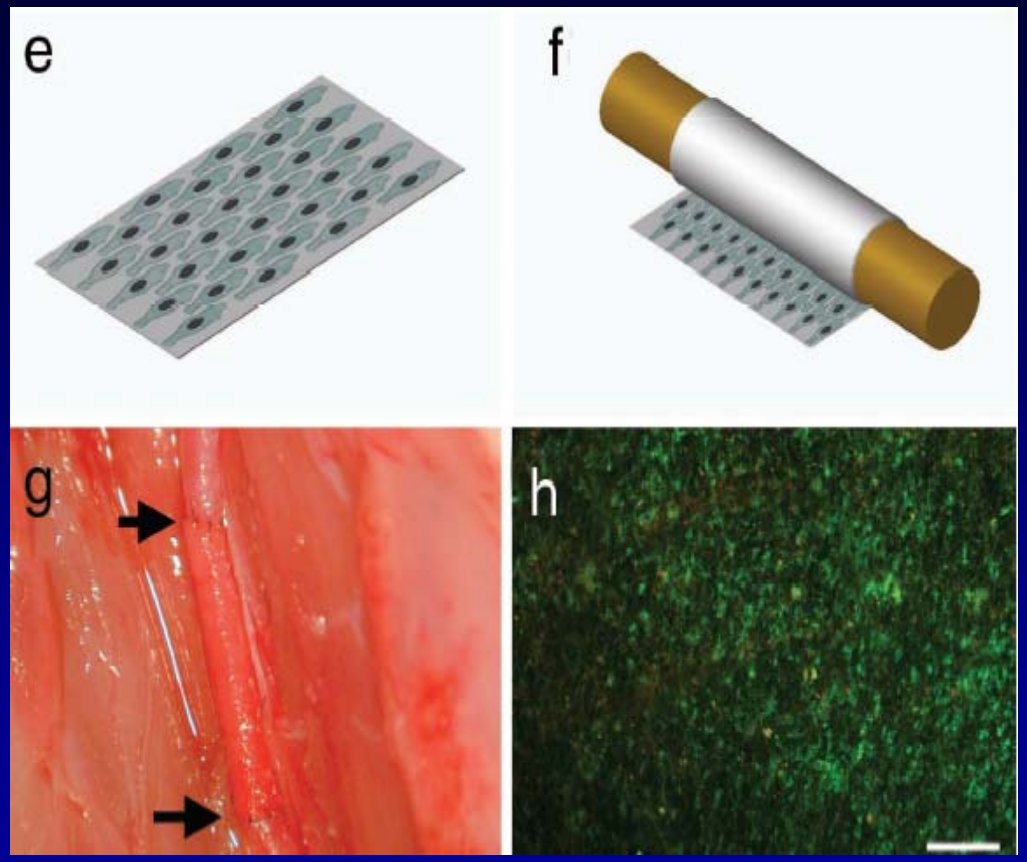




Sam Stupp Nano Letters 2007 NIBIB/NHLBI funding

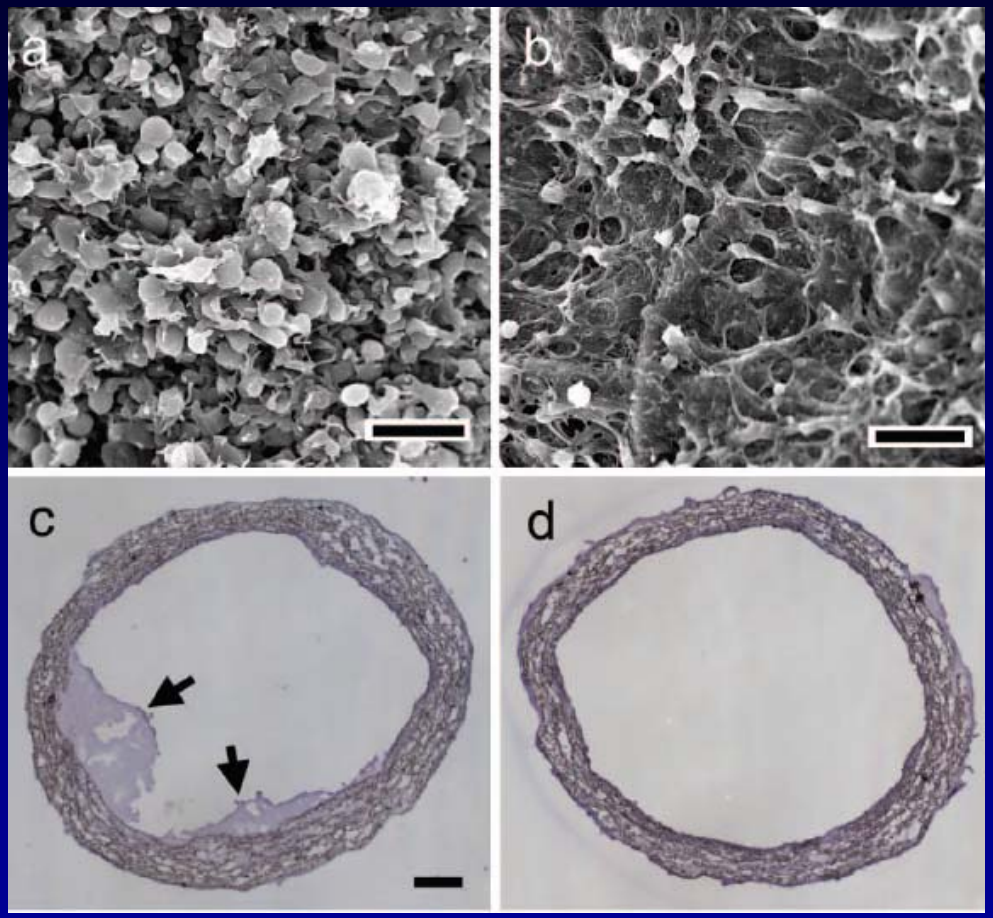
Nanofibrous Vascular Grafts



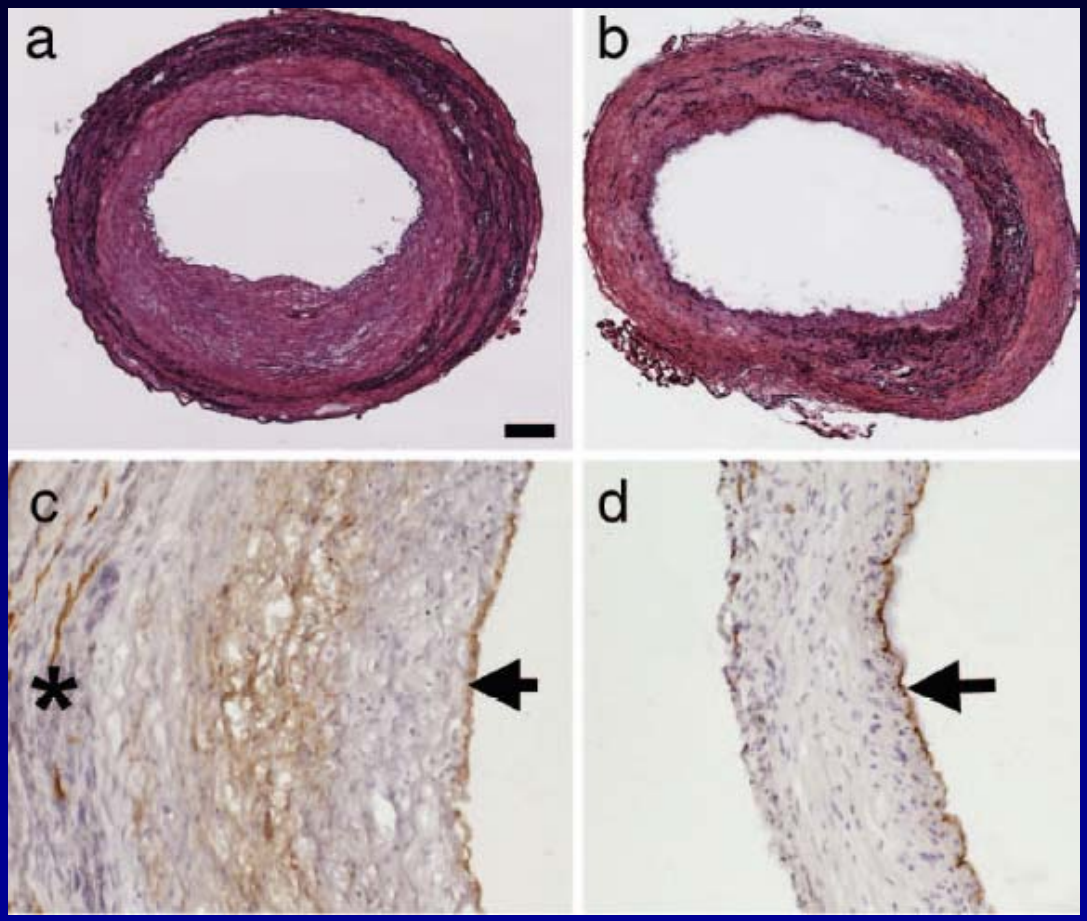


Song Li PNAS 2007 Funded by NHLBI

Mesenchymal Cells Reduce Graft Thrombosis



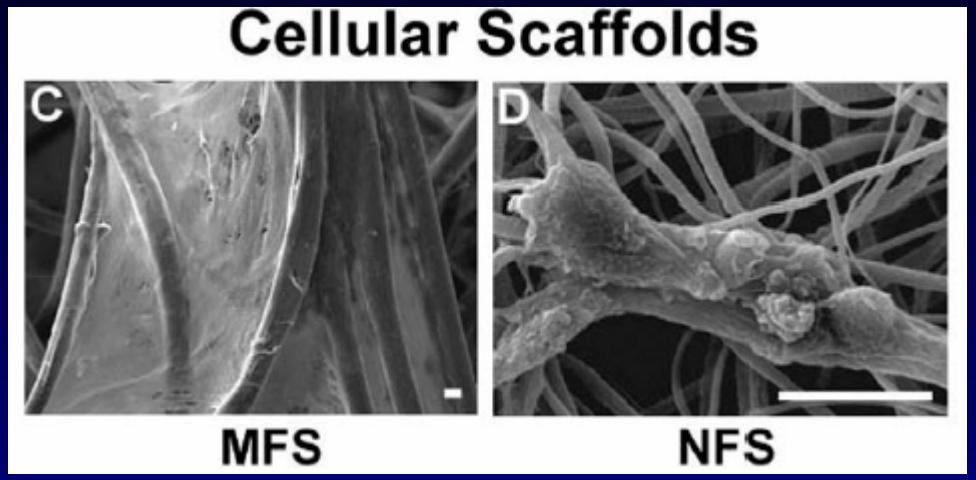
2 hours

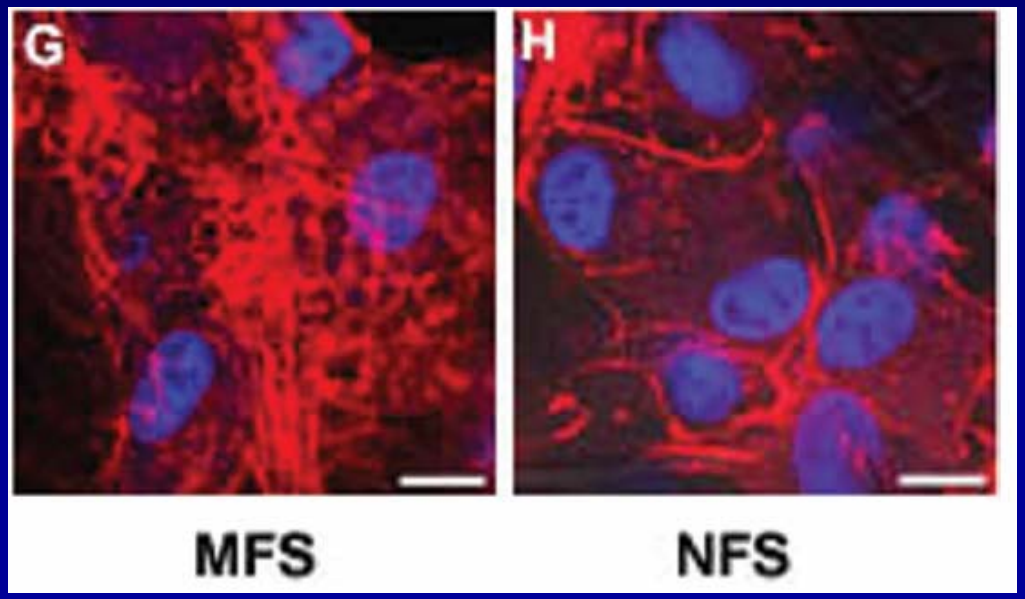


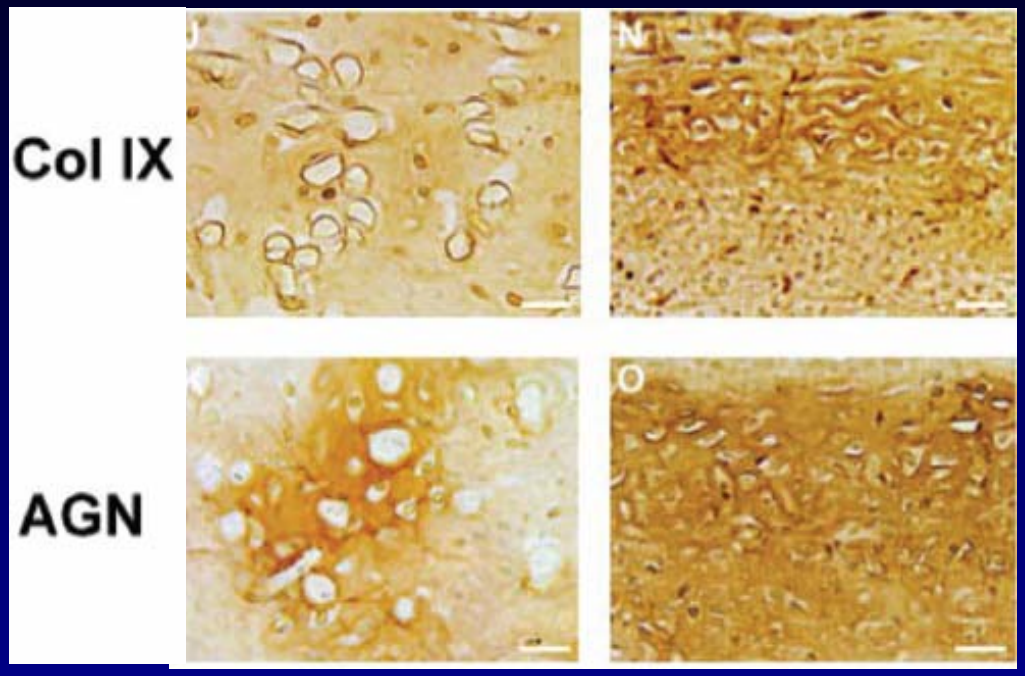
60 days

Song Li PNAS 2007

Nanofiber Scaffolds for Engineering Cartilage







Chondrocytes remain differentiated on nanofiber scaffolds, and display abundant ECM markers

Rocky Tuan Tissue Engineering 2006
NIAMS intramural funding