



# TISSUEGEN

TISSUEGEN PROPRIETARY

# Latest Advancement in Extrusion Technology for Drug Delivery Applications

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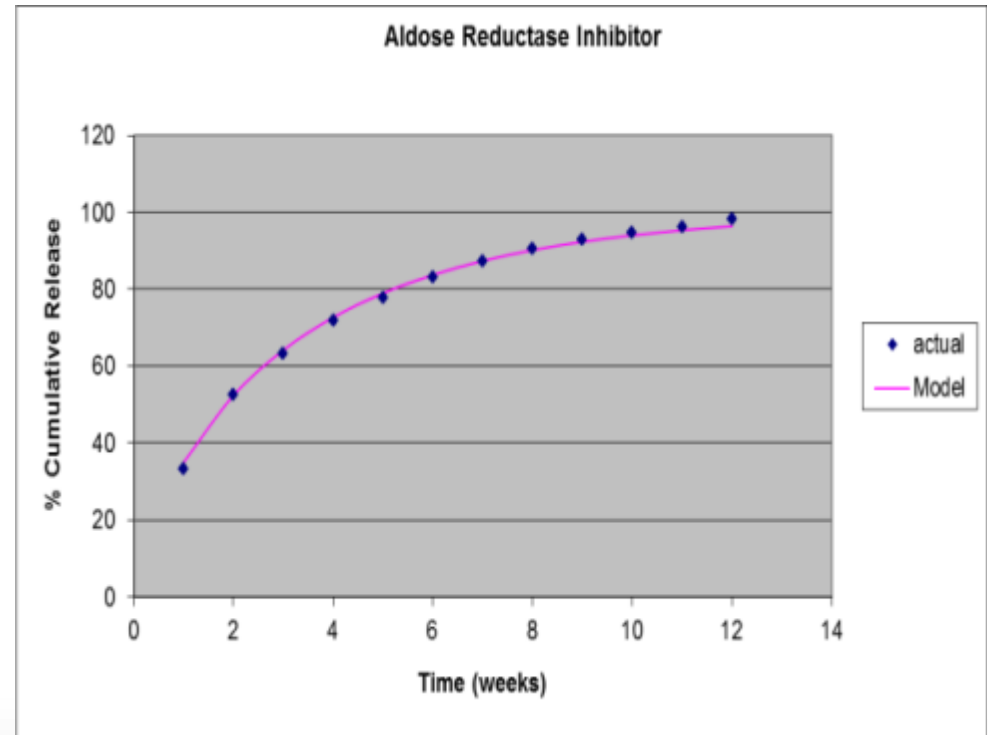
# Overview

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- Drug delivery from fiber
- Fiber manufacturing methods
- Novel extrusion method for drug loading
  - Drugs
  - Polymers
  - Release studies
- Medical applications
- Commercial availability

# Implantable Drug Delivery

- Advantages
  - Slow sustained release
  - Avoid high toxic levels
  - May be site specific
  - Patient compliance
- Many Formats
  - Gels
  - Nanoparticles
  - Microspheres
  - Fibers



# Advantages of Fibers

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- Mechanically strong
- Remain in place
- Readily explanted
- Highly uniform diameter and drug concentration
- Slower release than spheres of same diameter
- Coatings and complex geometries
- Readily mass produced

# Fiber Manufacturing Methods

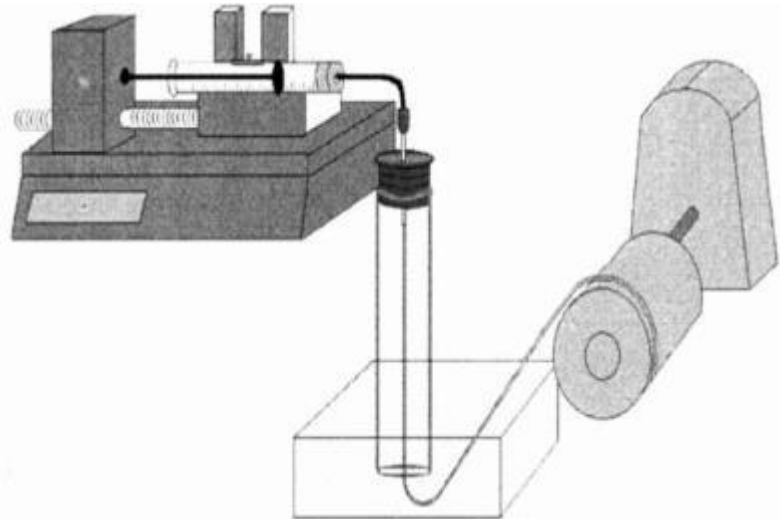
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- **Melt Extrusion**
  - High temperature melt and high shear stress
  - Relatively low cost
  - Limited drugs due to process
- **Electrospinning**
  - Non-woven sheets, filters, and membranes not individual fibers
  - Harsh organic solvents
  - Wider range of drugs
- **Wet Extrusion**
  - Extremely strong fibers
  - Harsh organic solvents
  - Widest range of drugs including pharmaceuticals and biologically-derived agents

# Wet Extrusion

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- Developed in 1850's
- Polymer solution
- Coagulating bath
- Harsh organic solvents
- Fiber drawn (stretched)
- Low shear stress
- Room temperature



“Technique Paper for Wet-Spinning Poly(L-lactic acid) and Poly(DL-lactide-co-glycolide) Monofilament Fibers.” *Tissue Engineering* 9(6): 1323-30 (2003)

# Solvent Issue for Drug Loading

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- Harsh organic solvents
- Very few drugs can survive extrusion
- Must remove residual solvents from fiber



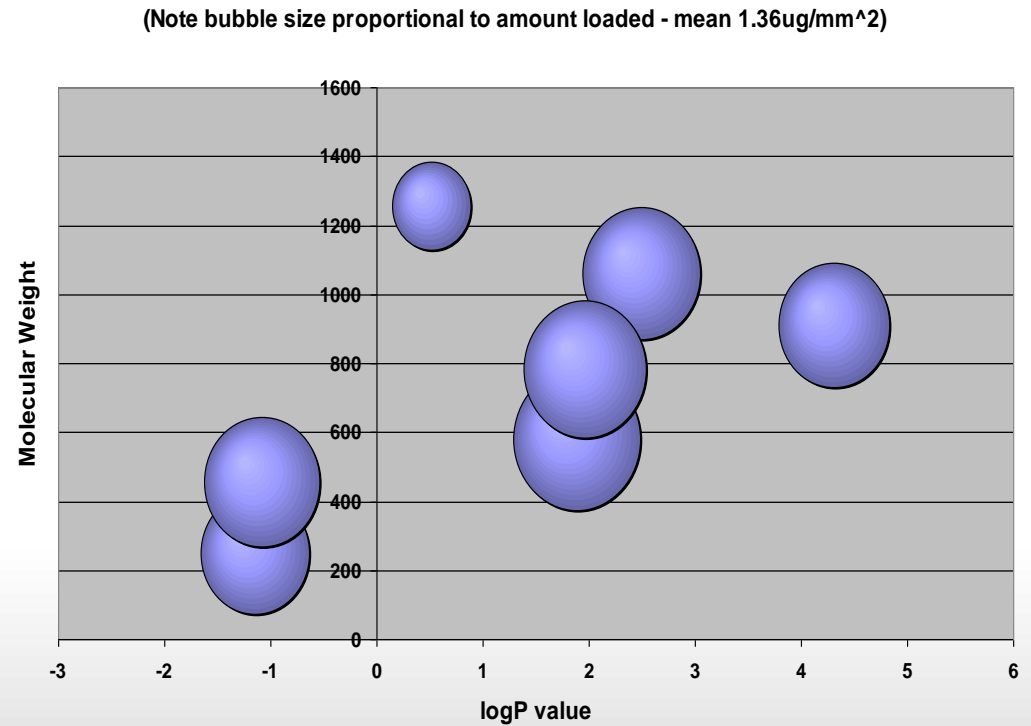
# The Solution is the Solution

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- Drug loading process
  - Isolation
  - Excipients
  - Create protective bubble for drug within harsh solvent bath
  - Extrude drug-loaded polymer
  - Post-process to remove residual solvents
- Enables loading broadest range of drugs
  - Pharmaceuticals
  - Biologically-derived agents

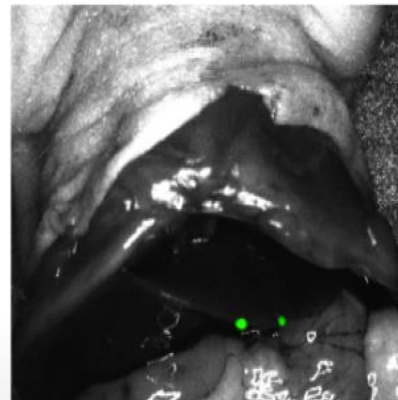
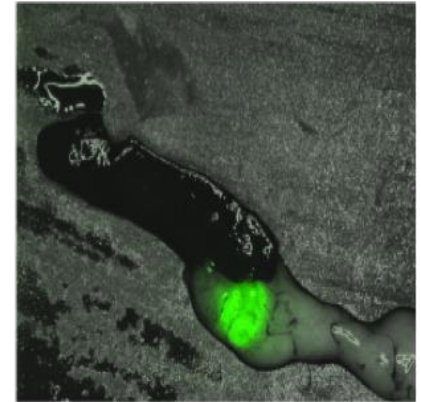
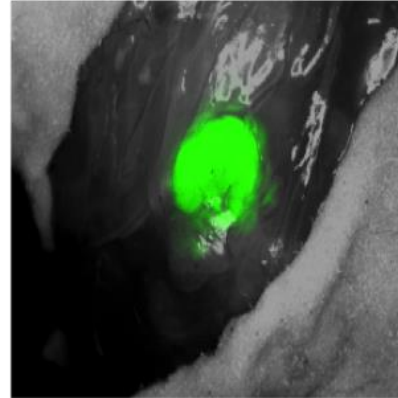
# Pharmaceuticals

- Broad water solubility
  - Hydrophobic
  - Hydrophilic
- Broad molecular weight
  - Antibiotics
  - Antimicrobials
  - Cancer remediation



# Biologically-derived Agents

- Proteins
  - BDNF
  - GDNF
  - NGF
  - VEGF
  - BSA
  - Collagen
  - Lysozyme
  - Matrigel
  - Fab fragment of IgG
- DNA
  - $\beta$ -galactosidase adenovirus)



# Polymers

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- Polymer requirements
  - Both solvent and non-solvent must exist
  - Combination of solvent and non-solvent must be miscible
- Synthetic biodegradable polymers
  - Poly(L-lactic acid) (“PLLA”)
  - Poly(D,L-lactic acid) (“PDLLA”)
  - Poly(lactic acid-co-glycolic acid) (“PLGA”)
  - Poly(p-dioxanone) (“PDO” also referred to as “PDS”)
  - Blends with poly( $\epsilon$ -caprolactone) (“PCL”)
- Biopolymers
  - Chitosan and chitosan/alginate blends
  - Silk and silk blended with synthetic polymers

# Fiber Conformations

- Diverse formats
  - Hollow
  - Gel-filled core
  - Core sheath
  - Over-the-wire
  - Multi-lumen
- Broad range of sizes
  - Circular monofilament (~10  $\mu\text{m}$  to 1 mm diameter)
  - Ribbon fiber (0.1 mm x 1 mm shown)



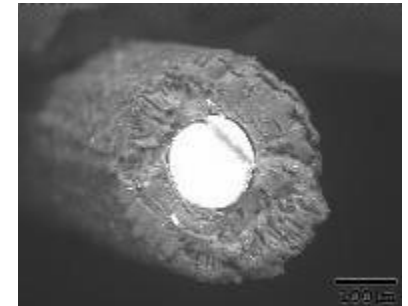
Hollow



Gel-Filled Core



Core Sheath



Over-the-Wire

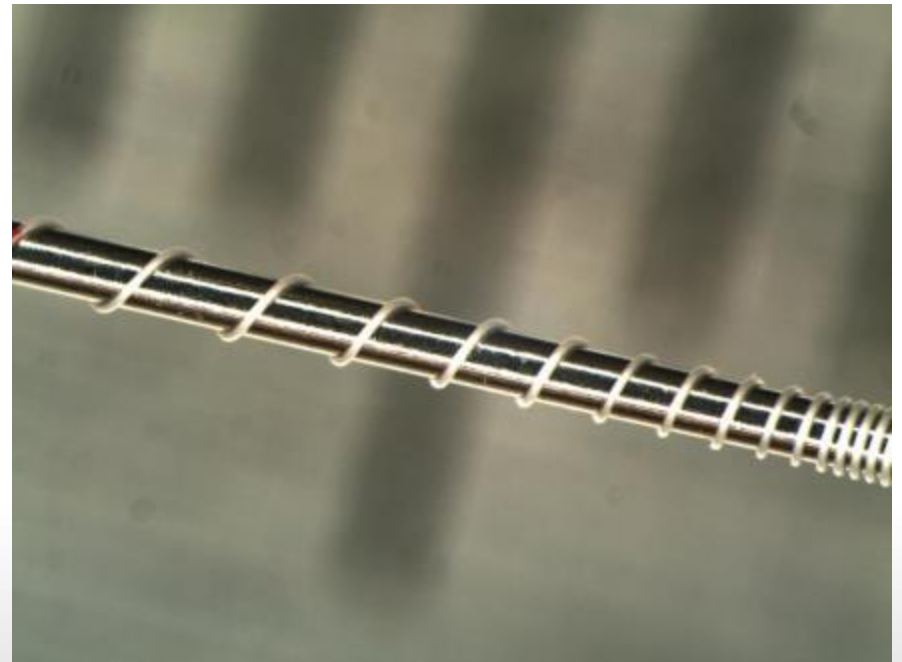


Cross Section of Ribbon Fiber

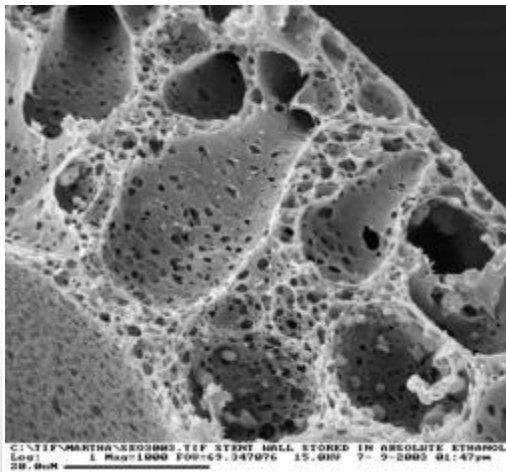
# Coil Delivery Format

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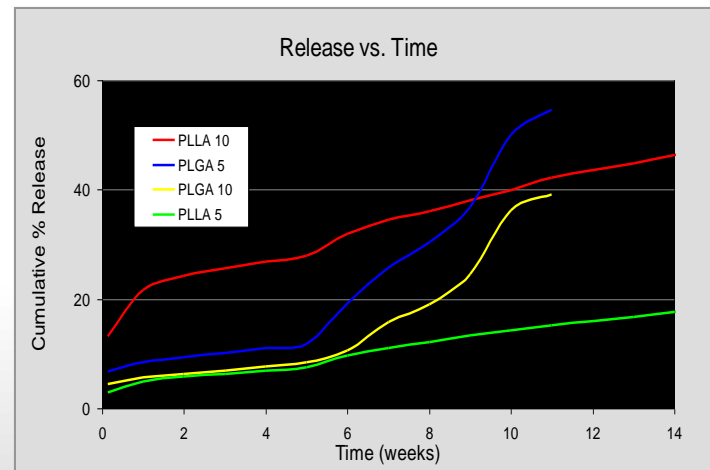
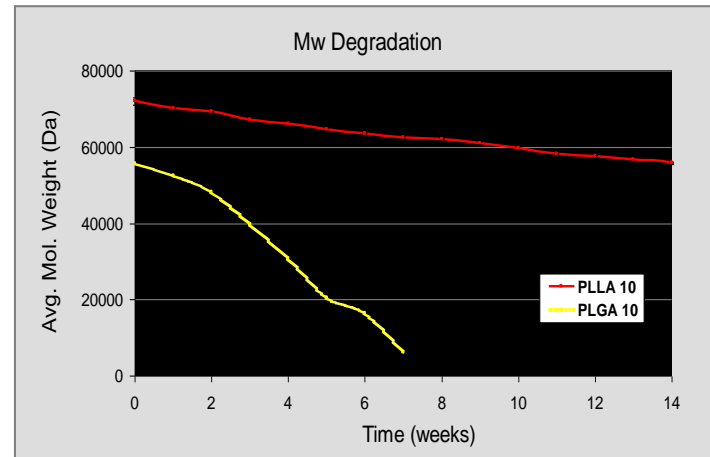
- Directs cells to migrate through specified pathways.
- Guided by concentration gradient introduced by continuously variable pitched coil



# Tunable Drug Delivery



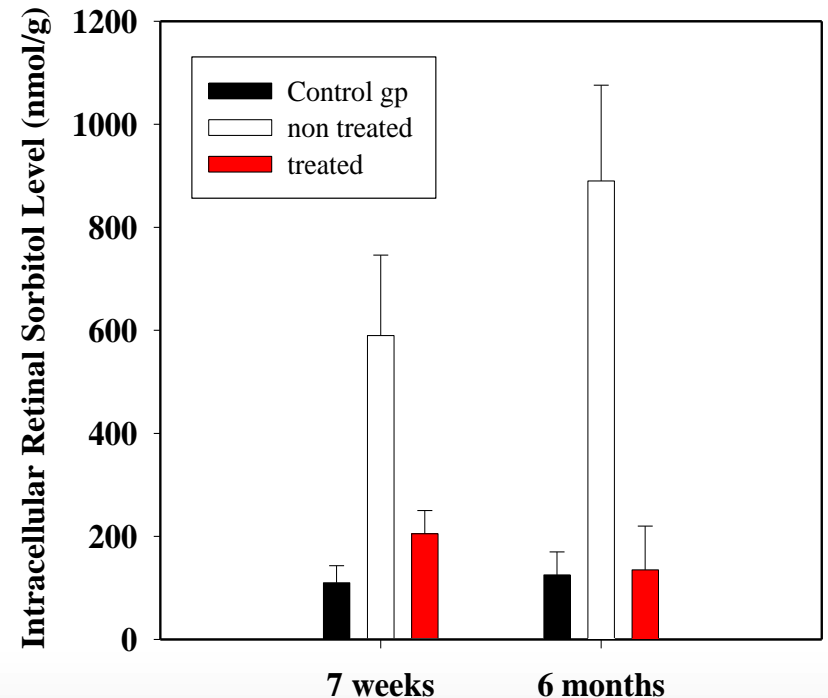
← 20 μm →



# ARI Loaded Fiber

## *In Vivo* Animal Study

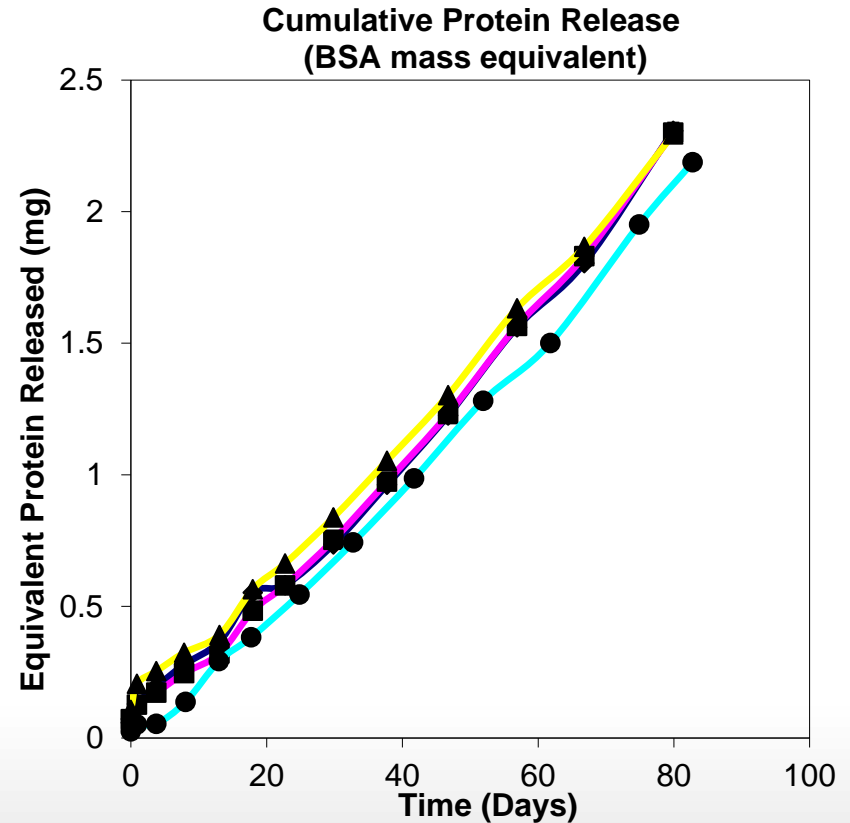
- Monofilament fiber loaded with Aldose Reductase Inhibitor (ARI)
- ARI blocks conversion of glucose to sorbitol—potential cause of blindness in diabetic patients
- One eye of diabetic rats implanted with ARI fiber compared with untreated eye in same animal and age-matched, normal healthy rats
- Single dose over 6 months resulted in 5-fold reduction of diabetic state indicators
- Demonstrated potential diabetic retinopathy treatment





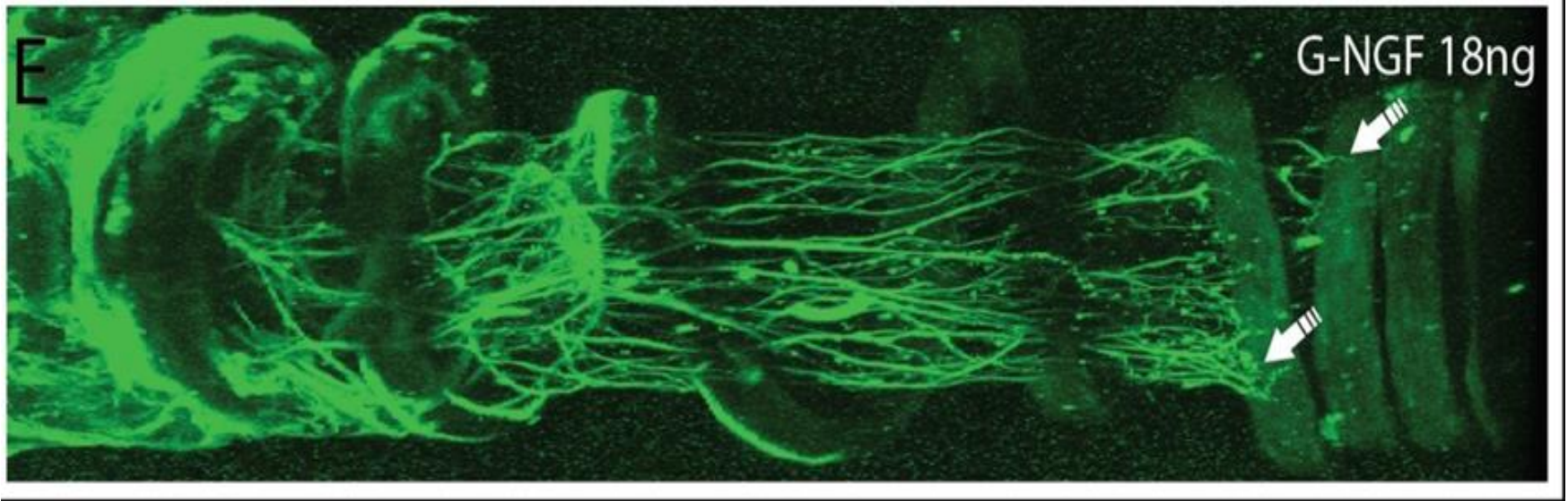
# Matrigel<sup>®</sup> Loaded Fiber *In Vitro* Release Assay

- Bi-component fiber loaded with Matrigel
- Matrigel resembles the complex extracellular environment found in many human tissues
- BSA used for calibration curve
- Cumulative release over 80 days
- Demonstrated linear protein release from fiber over extended period



# DRG Axons Responding to Coil Concentration Gradient

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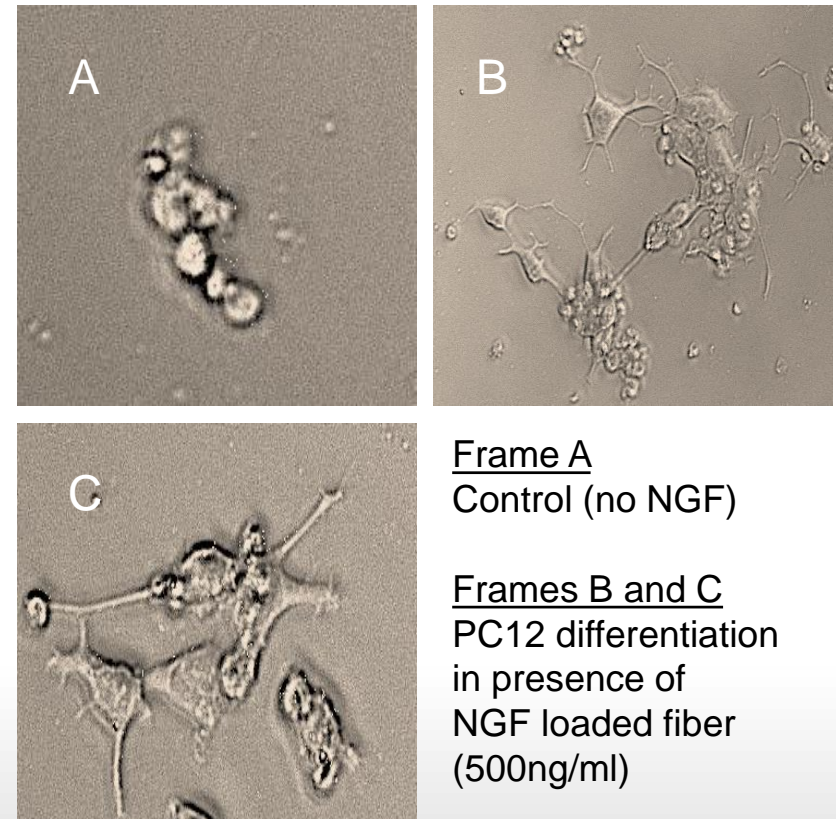


# NGF Loaded Fiber PC-12 Cell Assay

- Monofilament fiber loaded with Nerve Growth Factor (NGF)
- PC-12 cells sprout neurites in presence of biologically active NGF
- 5 cm and 10 cm samples of NGF loaded fiber in 96-well plate with PC-12 cells
- Demonstrated dose response

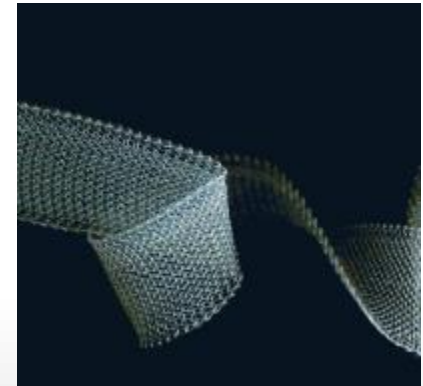
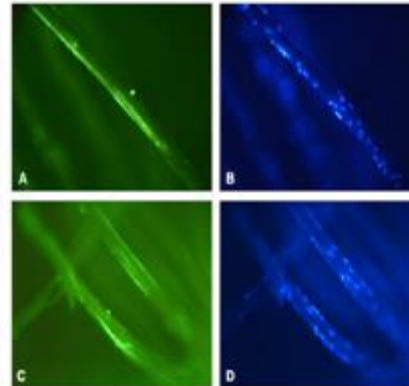
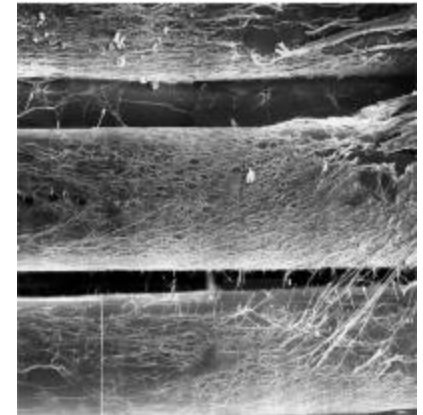
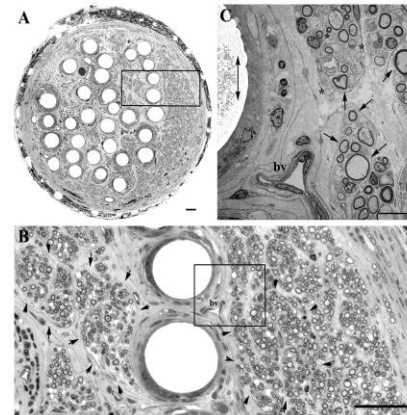
Fiber length	Avg. cell size
5 cm	96.13 $\mu\text{m}$
10 cm	120.93 $\mu\text{m}$
Control (no fiber)	15.09 $\mu\text{m}$

## Phase Contrast



# Medical Applications

- Advanced drug delivery
  - Retinal delivery
  - Solid tumor remediation
- Nerve regeneration
  - Long peripheral gaps
  - Spinal cord injury repair
- Tissue engineering
  - Premature cell differentiation
  - Small diameter vascular grafts
- Medical textiles
  - Hernia mesh
  - Pouches and slings
  - Tendon and ligament repair



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