

# REGENERATIVE MEDICINE IN UROGYNECOLOGY

An experimental study in rats of  
MPEG-PLGA scaffolds, trophic factors,  
muscle-derived cells and muscle tissue

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- Danish National Advanced Technology Foundation
  - "Stem cells – repair of damaged tissue"
  - Other participants:
    - University Hospital Aarhus, Dept. Of Orthopedic Surgery
    - University of Copenhagen – Farma
    - Coloplast A/S
- The Capital Region of Denmark
  - Study fee to the Faculty

# Outline

- Background
- Animal study, part I
- Animal study, part II
- Conclusion and perspectives

# Pelvic organ prolapse

- Biological or synthetic, permanent implants
- Tenuous evidence for efficacy
- High rate of complications (10%):
  - Erosions, pain, infection, vaginal shrinkage
- Alternatives needed!



# Regenerative medicine

- Aim: Creating functional tissues
- *Tissue engineering*
  - Biologically active molecules/trophic factors
  - Cell-based therapies (stem cells)
  - Often involves use of scaffolds

# *In vitro* cultured cells

- Increased regulatory demands, autumn 2007
- Inhibits cost-effectiveness in treatment of benign disorders
- New concepts needed in regenerative medicine

# Muscle fiber fragments

- AUTOLOGOUS
- Fresh
  - No *in vitro* culturing
  - No need for advanced facilities
  - Time sparing
- Contain naturally occurring muscle stem cells

# Outline

- Background
- ***Animal study, part I***
- Animal study, part II
- Conclusion and perspectives

# Animal study, part I

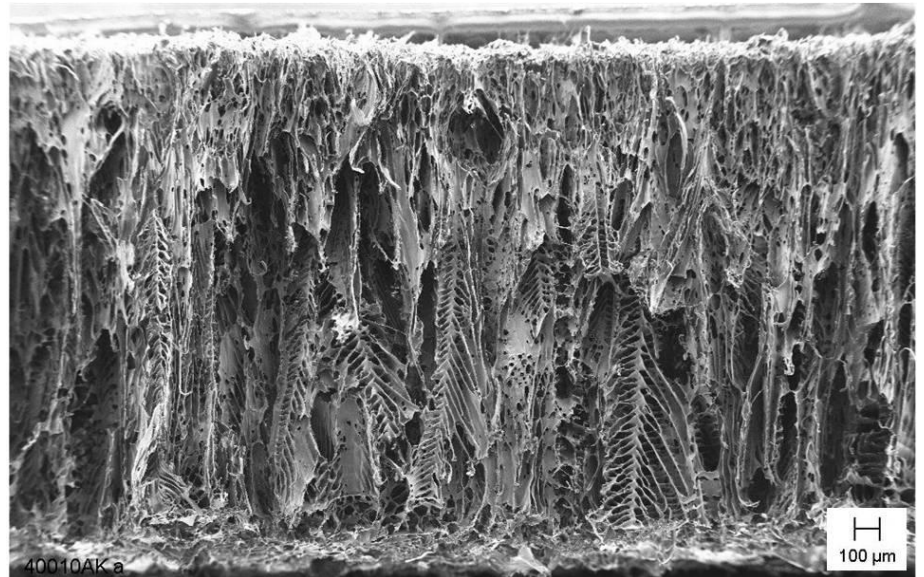
- Aim:
  - Biocompatibility and tissue regeneration of MPEG-PLGA scaffold
    - Plain
    - With Extra-Cellular Matrix (ECM)
    - With estrogen
- Approved by Danish Animal Experiments Inspectorate

# Scaffold

- MPEG-PLGA

MethoxyPolyEthyleneGlycol-Poly(Lactic-co-Glycolic Acid)

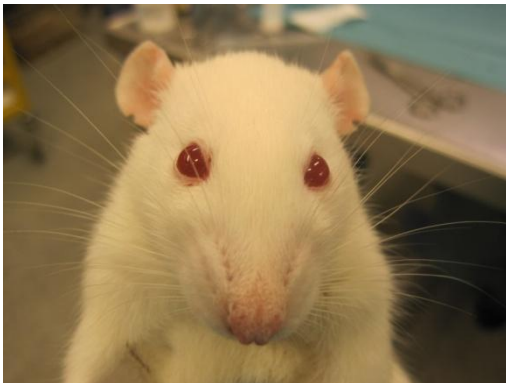
- Can be enriched and serve as carrier for trophic factors and cells
- Synthetic
- *Biodegradable*



Scanning Electron Microscopy

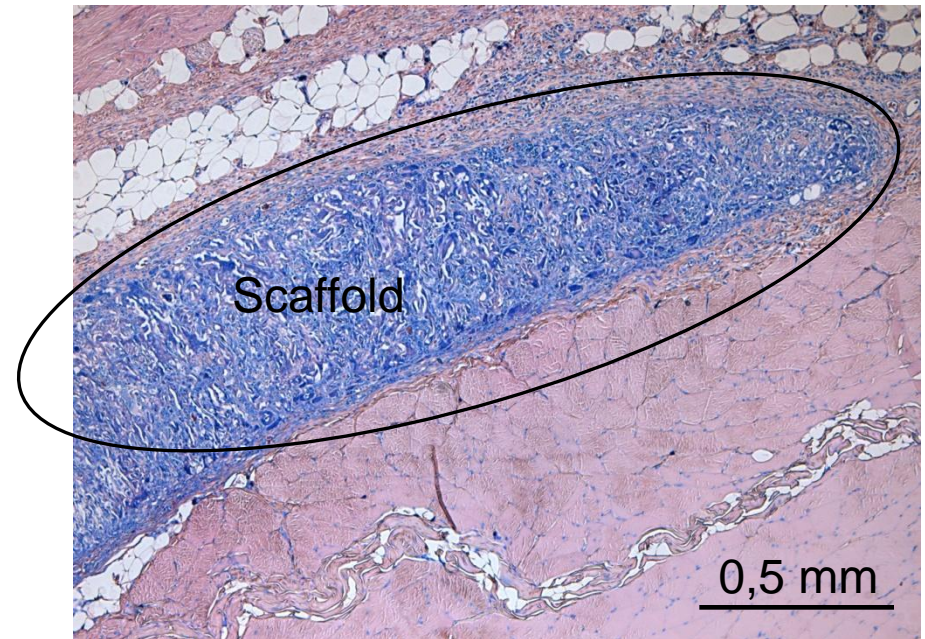
# Materials and Methods

- Retired breeder rats
- Abdominal subcutaneous implantation
- MPEG-PLGA scaffold
  - Plain
  - With Extra-Cellular Matrix
  - With estrogen
- Scaffold: 10 x 20 x 1 mm
- 10 of each preparation
- Tissue harvest: 3 and 8 weeks



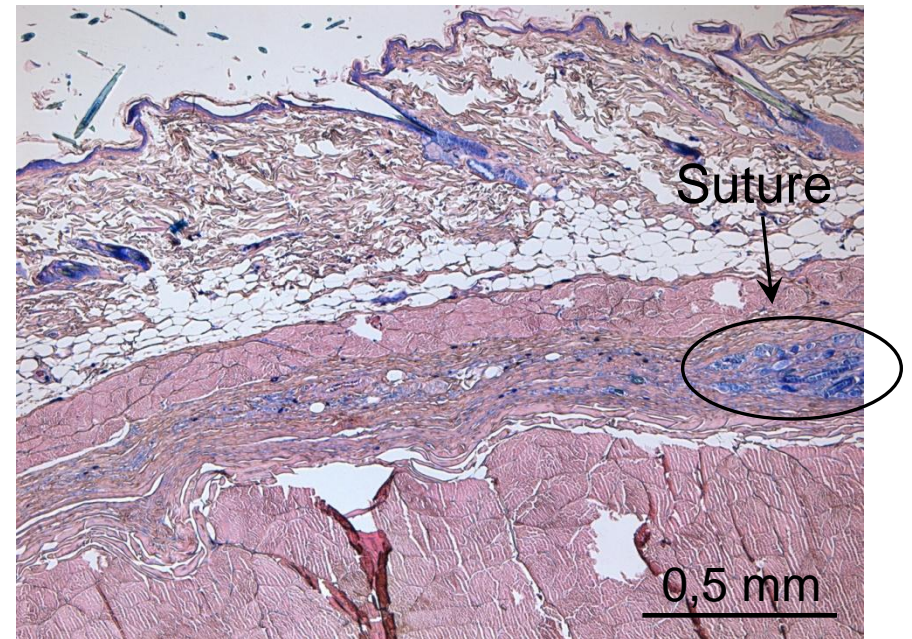
# Results 3 weeks

- Massive cellular in-growth
- Higher in ECM-enriched scaffolds than plain scaffolds
- No significant differences in other parameters



# Results 8 weeks

- No differences
- All scaffolds disappeared
- No harmful reactions in tissue



# Conclusion

- MPEG-PLGA scaffold
  - Very biocompatible
  - Left no traces behind in the tissue
- MPEG-PLGA alone, or combined with ECM or estrogen, is hardly a candidate scaffold for reinforcement in pelvic reconstructive surgery

# Outline

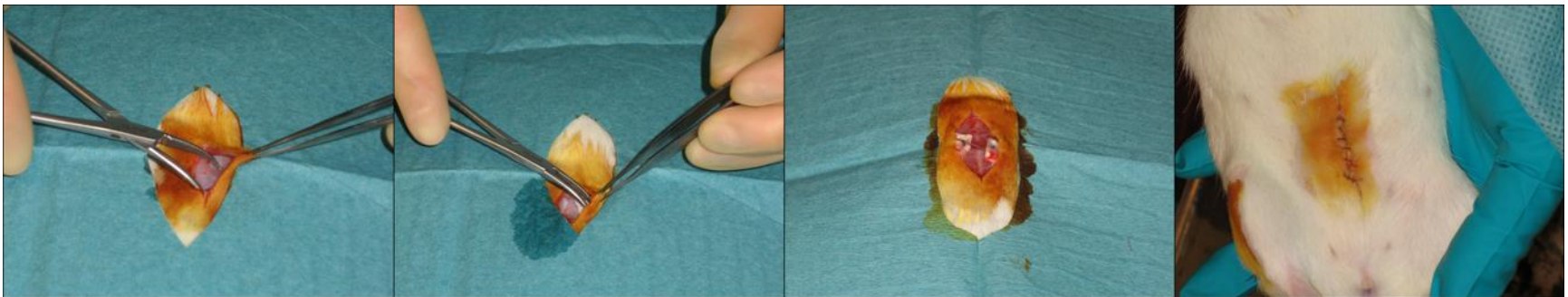
- Background
- Animal study, part I
- ***Animal study, part II***
- Conclusion and perspectives

# Animal study, part II

- Aim:
  - Potential within regenerative medicine?
    - MPEG-PLGA scaffold seeded with cultured muscle-derived cells
    - MPEG-PLGA scaffold seeded with fresh muscle fiber fragments
- Approved by Danish Animal Experiments Inspectorate

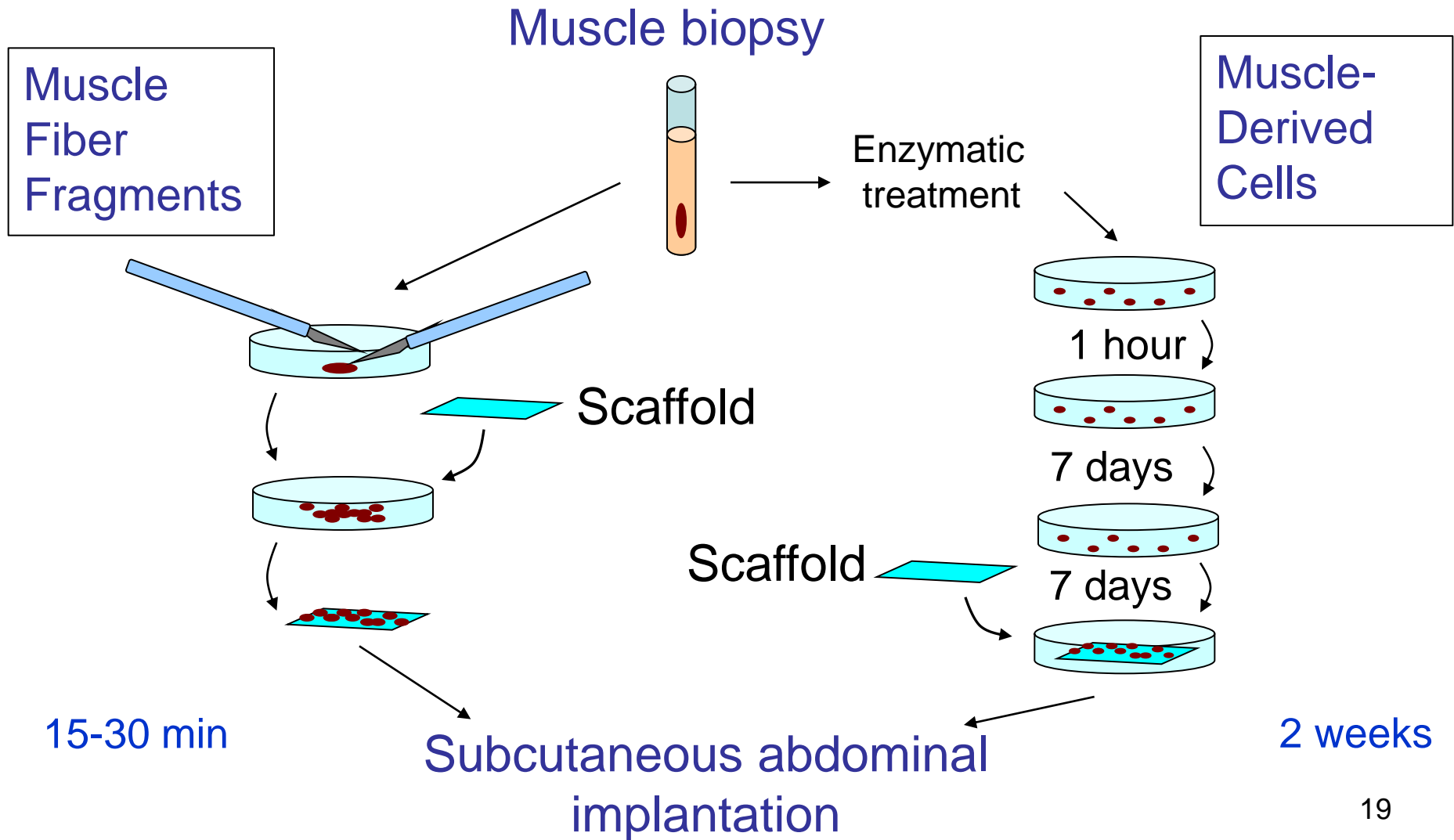
# Materials and Methods

- MPEG-PLGA scaffold
  - With cultured muscle-derived cells
  - With fresh muscle fiber fragments
- Scaffold: 10 x 20 x 1 mm
- 10 of each preparation
- 2 muscle biopsies (4 mm each)



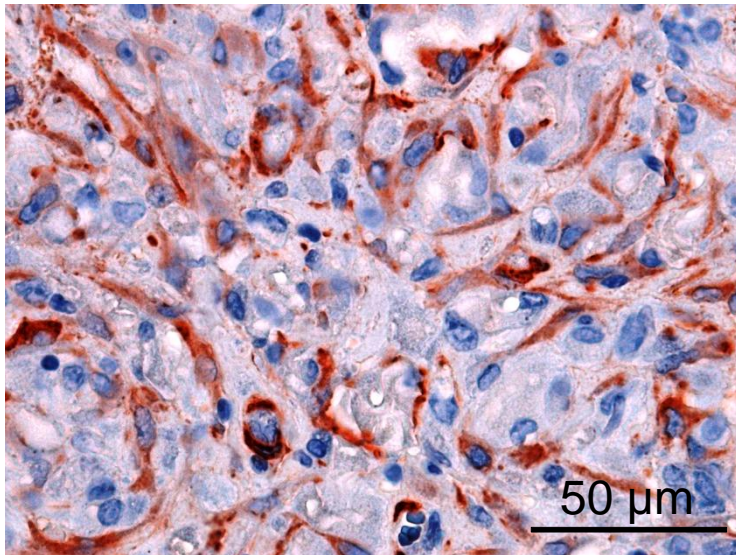
Implantation

# Method

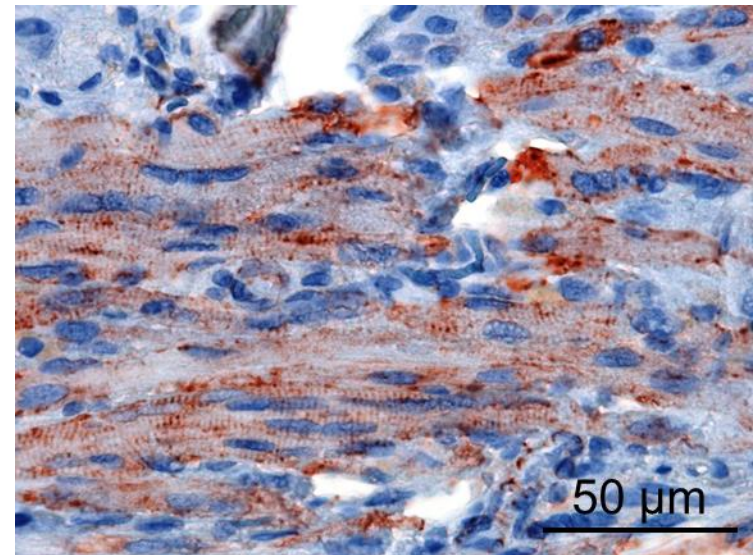


# Results 3 weeks

Muscle-derived cells:  
Single cells in scaffold



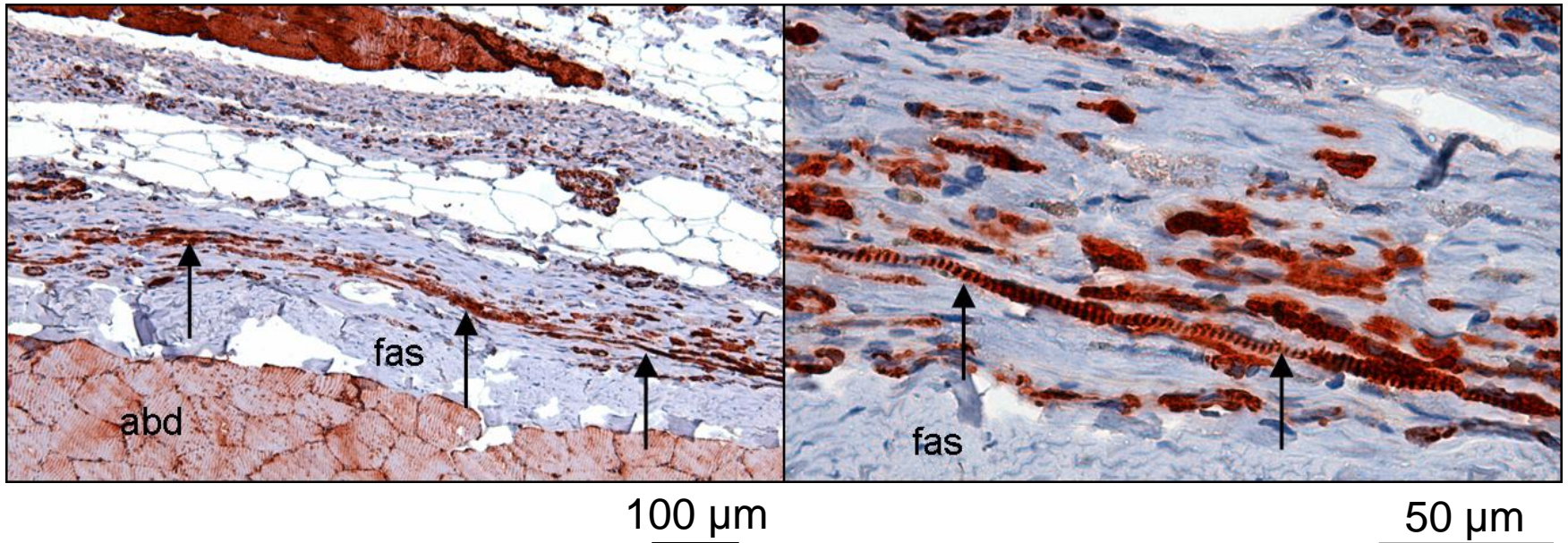
Muscle fiber fragments:  
Striated muscle tissue under scaffold



**Immunohistochemistry with desmin**

# Results 8 weeks

- Cultured muscle-derived cells and all scaffolds degraded
- Muscle fiber fragments generated striated muscle tissue:



**Immunohistochemistry with desmin**

# Conclusion

- Cultured muscle-derived cells compatible with MPEG-PLGA
  - But disappear when scaffold is degraded
- Striated muscle tissue created using muscle fiber fragments seeded on scaffold
  - At 3 and 8 weeks

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# Conclusion

Fresh muscle fiber fragments implanted on MPEG-PLGA scaffold...

...a promising new concept for pelvic floor regenerative medicine?

# Perspectives and future research

- Characterization of inherent cell types of fresh muscle fiber fragments
  - Standardization of mincing procedure
- Differentiation in a vaginal model
- Dose-response and long term studies
- Scaffolds – other type or shape?
- Randomized, controlled clinical studies

Thank you for your attention!

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# Thesis based on...

- I. Boennelycke M, Christensen L, Nielsen LF, Everland H, Lose G: **Tissue response to a new type of biomaterial implanted subcutaneously in rats.** Int Urogynecol J 2011;22:191–196
  
- II. Boennelycke M, Christensen L, Nielsen LF, Gräs S, Lose G: **Fresh muscle fiber fragments on a scaffold in rats - a new concept in urogynecology?** Am J Obstet Gynecol 2011;205(3):235.e10-4