Engineering tendon repair

Mark S Thompson
Oxford Mechanobiology Group
Institute of Biomedical Engineering,
University of Oxford

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Achilles tendon

- Largest tendon in the body
- Huge forces – 3.8 kN
  - Millions of cycles
  - Strength ~ 120 MPa

Fukashiro et al 1993 Clin Biomech

http://www.ibme.ox.ac.uk/mechanobiology
Tendon rupture
Current treatments

http://www.ibme.ox.ac.uk/mechanobiology
Current treatment outcome

- Healing outcomes
  - Re-rupture rate 5 – 15%

![Graph showing mechanical function over time with re-rupture rates marked at 4 months]
Engineering tendon repair

- Clinical demands:
  - Accelerate healing
  - Personalize treatment

- Oxford platelet tendon group
  - Lab studies
  - New, objective outcome measure
  - Pilot clinical study
Platelets for tendon healing

- Platelet rich concentrate (PRC)
  - Cells vital for clotting
  - Packed with over 30 growth factors

- Cheap, simple preparation
  - Low infection risk
  - Increases tendon cell proliferation, collagen synthesis

(Akeda et al., 2006, Schnabel et al., 2007)
Tendon cell protection: ciprofloxacin

http://www.ibme.ox.ac.uk/mechanobiology

Culture medium  Ciprofloxacin  Ciprofloxacin+PRC

Tendon cell protection: hypoxia

- Total hypoxia (0.1% oxygen) induced tenocyte apoptosis after 48hrs
- PRC reduces cell death
Tendon cell protection: hypoxia

0% FCS

48hrs

PRC (10%)

48 hrs

Normoxia

Hypoxia (0.1% O₂)


http://www.ibme.ox.ac.uk/mechanobiology
Tendon cell migration: “wound healing”

Scratch Area

Control | PRC

<table>
<thead>
<tr>
<th>Cell coverage of wound region after 72 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>35</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>

Objective outcome measure

- Ultrasound – widely used for tendon imaging
- Strain imaging
  - Image correlation - estimate tissue displacement
  - Algorithm developed for breast cancer detection

Kadour and Noble 2009 IEEE Trans Ultrason
Computer controlled instrumented foot motion

http://www.ibme.ox.ac.uk/mechanobiology
Correlation of image kernels

- Normalised cross-correlation (NCC) maximised
- Displacement estimated
- Strain derived
FUSE: B-Mode

Achilles Tendon

Fat Pad

FHL
FUSE: PC controlled motion

http://www.ibme.ox.ac.uk/mechanobiology
Strain values from images

- Average Strain in A (Achilles tendon)
- Average Strain in B (Fat pad)
Healthy volunteers: Strain plot

http://www.ibme.ox.ac.uk/mechanobiology
Clinical Trial

- **PATH** = Platelet rich plasma in Accelerated Tendo-Achilles Healing

- a parallel double arm, Patient-blinded individually randomised controlled trial

- **Hypothesis**
  - PRC local application in the tendon rupture gap leads to accelerated healing and faster return to normal function than standard treatment alone.
Clinical Trial: Conservative arm

- Ultrasound to measure rupture gap size in equinus
- Gap < 5 mm
  - Standard cast, randomised PRC percutaneously
Clinical Trial: Operative arm

- Ultrasound to measure rupture gap size in equinus
- Gap > 5 mm
  - Surgical repair, randomised application of PRC
Methods

- PRC Analysis
  - Platelet Function
  - Platelet count
- Functional outcome measures
  - Patient reported outcome – questionnaires
- Functional Ultrasound Elastography (FUSE)
- Follow up: 1, 3, 6, 8, 12, 24 weeks
- Mixed linear regression model. Significance level 0.05. SPSS (PAWS 18.0)
## PATH RCT: recruitment

![Image](http://www.ibme.ox.ac.uk/mechanobiology)

<table>
<thead>
<tr>
<th></th>
<th>Operative arm</th>
<th>Conservative arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>37.5 ± 8.8</td>
<td>41.7±7.1</td>
</tr>
<tr>
<td>Sex</td>
<td>5 males</td>
<td>6 males</td>
</tr>
<tr>
<td></td>
<td>5 females</td>
<td>4 females</td>
</tr>
<tr>
<td>SAE</td>
<td>1 DVT (control)</td>
<td>1 partial-rerupture (control)</td>
</tr>
<tr>
<td>Infection</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Average rupture gap</td>
<td>12.4mm</td>
<td>3.2mm</td>
</tr>
<tr>
<td>Rupture location</td>
<td>4.8cm</td>
<td>4.1cm</td>
</tr>
</tbody>
</table>
PRC Function

- Cell surface marker for activated platelet function - CD62p
- Expression measured using flow cytometry

<table>
<thead>
<tr>
<th>n = 9</th>
<th>Before Thrombin Mean ± S.D</th>
<th>After Thrombin Mean ± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Platelets %</td>
<td>7.43±6.5</td>
<td>68.42 ± 4.52</td>
</tr>
<tr>
<td>Resting Platelets %</td>
<td>92.57±4.1</td>
<td>31.58±3.82</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
### PRC: Platelet count

<table>
<thead>
<tr>
<th></th>
<th>Initial Blood (60 mL)</th>
<th>PRP (8 mL)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT (x 1000/µL)</td>
<td>220.03 ± 48.58</td>
<td>1044.89 ± 302.00</td>
<td>4.74 ± 0.73</td>
</tr>
<tr>
<td>WBC (x 1000/µL)</td>
<td>5.49 ± 1.43</td>
<td>11.9 ± 7.01</td>
<td>2.16 ± 0.90</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>32.87 ± 2.95</td>
<td>6.81 ± 1.59</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Mean ± S.D.; n = 9
Results: Patient reported (ATRS)

$y = 12.6x - 3.8$
$R^2 = 0.96$

$y = 9.5x - 7.9$
$R^2 = 0.91$

Differences significant from week 6.
Mixed linear regression significant to better than 0.001
Results: Patient reported (VISA)

y = 11.4x – 8.7  
R² = 0.89

y = 8.0x - 5.7  
R² = 0.69

Differences significant from week 6.  
Mixed linear regression significant to better than 0.001

http://www.ibme.ox.ac.uk/mechanobiology
Strain imaging - rupture

- B-mode – training required to identify rupture
- Strain imaging – rupture clear

http://www.ibme.ox.ac.uk/mechanobiology
Strain images

- Preliminary results

Ruptured tendon week 0

Ruptured tendon week 12
FUSE: Preliminary Results

Strain index progression is significantly better in PRP group (p 0.031)
Summary

- Platelets protect tendon cells from damage
- New objective, functional outcome measure
- Preliminary findings:
  PRC in Achilles tendon rupture *may* lead to:
  - Faster regeneration
  - Improved pain
  - Faster return to function
- However, for desired statistical power in pragmatic settings, a multi-centre clinical trial is required.
- Modelling and data from foot motion device estimate material properties of tendon
Acknowledgements

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