Stem Cell Research in Urology

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Professor of Urology
Director of Aikens CURE-UAB
Oakland University William Beaumont
School of Medicine
Royal Oak, Michigan

Academic Journey
- University of Michigan: Residency
- Columbia University: Fellowship
- Thomas Jefferson University: (1990-1996)
- University of Pittsburgh: (1997-2007)
- NIH funding: P01, R01, U01, T32, K12, K08, R43+44

Why Research at Beaumont?

Stress Urinary Incontinence

From Bed Side to Bench Top and Back
- Muscle Biopsy
- MDC
- Autologous Injection
- Culture
Autologous Muscle Derived Stem Cells

- Plasticity
- Low tumorigenicity
- Simple biopsy
- Ages 18 to 85
- Stable myofibers

Skeletal Muscle Cell Isolation

Muscle biopsy
Enzymatic digestion
Muscle Derived Stem Cells
Committed skeletal myoblasts

Pre-plating 6
Muscle biopsy
After 1 h
After 24 h (repeated 4 times)

Qu-Petersen et al., J Cell Biology, 157: 851-64, 2002.

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- Enzymatic digestion
- Muscle biopsy
- Pre-plating technique

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Muscle Derived Stem Cells

- Fibroblasts

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Maximum Readings in Bladder and Urethra During Sneezing

Proximal

Maximum responses (cmH2O)

10
20
30
40
50
60
70
80

Intravesical

Intraurethral

Middle

Distal

Mean ± SEM from 5 rats

Kano et al., Am J Phy 287: F434, 2004

Injection of AMDCs

Female Urethra Histology

Urethral Sphincter Region: smooth and striated muscle layers surrounding submucosa

Injection targets the striated muscle layer of the urethral sphincter complex

Jankowski et al, Am J Phy 2005

Technology Transfer and Licensing

Cook MyoSite

56,000 s.f. GMP facility

40 employees

Over $50M investment

Two Phase 3 global trials ongoing
Clinical Trial

- Eight women with SUI at Sunnybrook and Women’s Health Science Centre, Department of Urology at the University of Toronto
- Protocol approved by IRB and Health Canada
- The injection technique evolved during the initial set of patients
- A dosage of 18-22 x 10^6 autologous MDC was used

Muscle Biopsy

- Shipped on dry ice
- Ready for injection
- Excellent cell survival/recovery

International Shipping

Results

- 8 / 8 have completed at 12 months of follow-up
- Mean follow up 17 (range 3-24) months
- Improvement in SUI was seen by objective and/or subjective measures in 5 of 8 women with 1 achieving total continence
- Onset of improvement was noted between 3-8 months after injection
AUTOLOGOUS MUSCLE-DERIVED CELLS AS A THERAPY FOR STRESS URINARY INCONTINENCE (SUI): A RANDOMIZED, BLINDED TRIAL


Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Mean (range)</th>
<th>All Patients n = 38</th>
<th>Low Dose n = 23 ≤ 16 million cells</th>
<th>High Dose n = 15 ≥ 32 million cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 (30-73)</td>
<td>51 (41-73)</td>
<td>49 (30-70)</td>
</tr>
<tr>
<td>Stress Leaks*</td>
<td>4.5 (0-17)</td>
<td>5.3 (0-17)</td>
<td>3.3 (0-9)</td>
</tr>
<tr>
<td>UDI-6§</td>
<td>45 (17-92)</td>
<td>47 (17-92)</td>
<td>51 (17-83)</td>
</tr>
<tr>
<td>UIQ-7§</td>
<td>34 (0-76)</td>
<td>32 (0-57)</td>
<td>38 (19-76)</td>
</tr>
</tbody>
</table>

No significant differences in baseline characteristics between low and high dose groups.

* Although all patients met inclusion criteria, 7 patients reported no baseline stress leaks.
§ Both UDI-6 and UIQ-7 use a 0 – 100 scale, with lower values indicating better quality of life.

Patients Reporting 0 or 1 Stress Leaks Over 3 Days

The percentage of high dose patients reporting 0 or 1 stress leak significantly increased from B to 18 M.

Percentage of Patients Reporting Satisfaction

The percentage of high dose patients reporting satisfaction significantly increased.

Adverse Events After AMDC Injection

<table>
<thead>
<tr>
<th>AMDCs n = 38</th>
<th>UTI (treatment-related)</th>
<th>Acute urinary retention &lt; 7 days</th>
<th>Hematoma at biopsy site</th>
<th>Outlet obstruction</th>
<th>Hematuria (visible blood in urine)</th>
<th>Dysuria</th>
<th>Erosion, excreted or exposed material</th>
<th>Local urethral cramping and pain over 48 hrs</th>
<th>Urinary retention &gt; 7 days, unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3% (n = 2)</td>
<td>2.6% (n = 1)</td>
<td>2.6% (n = 1)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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TAP cGMP CompacT Automated Cell Culturing

- Greater reproducibility
- More efficiency
- Easy to schedule operations
TAP cGMP CompacT
Automated Cell Culturing

- Less variation Lot-to-Lot
- Increased production
- Less risk of operator contamination
- Fewer consumables

Safety and Potential Effectiveness of Cook MyoSite
Autologous Muscle Derived Cells for Treatment of Stress
Urinary Incontinence: Preliminary Results from a Dose
Escalation Study

Melissa Kaufman1, Roger Dmochowski1, Kenneth Peters2,
Leslie Carr3, Sender Herschorn3,
Melissa Fischer2, Larry Sirls2, Daniel Biller1,
Michael B Chancellor2

1. Vanderbilt University Medical Center
2. William Beaumont Hospital
3. Sunnybrook Health Sciences Centre

Baseline Characteristics

All patients had failed prior SUI treatment, including:
- Behavioral therapy (85.9%),
- Pharmacological therapy (32.8%),
- Surgical therapy (20.3%), and/or bulking agent injection (6.3%)

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<th>Characteristic</th>
<th>AMDC Dose Treatment Groups</th>
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<tr>
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<td>10 million (n=16)</td>
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<tr>
<td>Age (years)</td>
<td>55.6±2.8</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.4±1.3</td>
</tr>
<tr>
<td>3-day stress leaks</td>
<td>10.1±1.9</td>
</tr>
<tr>
<td>24-hr pad weight (g)</td>
<td>24.2±4.9</td>
</tr>
</tbody>
</table>

Improvement in 24-hour Pad Weight

Legend for all graphs:
- Baseline
- 1 Month
- 3 Months
- 6 Months
- 12 Months

NOTE: Complete 12-month follow-up data for the 10 and 200 million dose groups are not available.
Safety
Injection related AE: No serious AE, no retention requiring catheterization
Biopsy related AE: Hematoma (2/64) and bleeding requiring sutures (1/64)

Study Centers
Sunnybrook Health Science Center, Department of Urology, Toronto, ON, Canada
- Lesley K. Carr
- Sender Herschorn
- Ljiljana Petkovic
- Davina Buencamino

University of Calgary, Foothills Medical Center, Department of Obstetrics & Gynecology, Calgary, AB, Canada
- Colin Birch
- Magnus Murphy
- Lorel Dederer
- Carrey Maloney
- Sue Ross

William Beaumont Hospital, Dept. of Urology, Royal Oak, MI
- Kenneth Peters
- Larry Sida II
- Melissa Fisher
- Pradeep Nagaraju
- Deborah Hasenau
- Michael Chancellor

Vanderbilt University, Department of Urology, Nashville, TN
- Roger Dmochowski
- Melissa Kaufman
- Priya Padmanabhan
- Harriette M. Scarpero
- Daniel H Biller
- Renee M. Ward

Moving Forward
- Phase 3 prospective multicenter double blind randomized trial; Canada, EU and USA
- First male SUI compassionate IND
- Underactive bladder Indication:
  - 6 million people will develop underactive bladder (UAB)
  - No effective therapies for UAB

UnderActive Bladder is Common and Embarrassing
- Urinary incontinence is often thought of as the inability to hold in urine because of a weak or damaged sphincter or an overactive bladder. In fact, urinary retention or the inability to completely empty the bladder can also lead to bothersome urinary symptoms and incontinence. This is also known as underactive bladder or UAB.
- Existing therapeutic strategies leave much to be desired. Patients with the condition may need to use catheterization in order to drain the bladder. There is no effective drug treatment currently. UAB has no cure and has not received adequate research funding support.

What is Underactive Bladder (UAB)?

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Normal Heart Dilated Cardiomyopathy
Only Catheters and Diapers for UAB Today

FDA Compassionate IND Trial for UAB

Is the first underactive bladder symposium in the world. Supported by NIH R13 grant.

CURE-UAB is a 1.5-day meeting February 20-21, 2014, in Washington DC.

CURE-UAB will promote awareness, research, education and discussion of the UnderActive Bladder.

CURE-UAB will bring together leaders in urology, gynecology, geriatric, neurology, internal medicine, nursing and mentor future scientists and clinician.

CURE-UAB will be an assembly of stakeholders from regulatory agencies, patient advocacy groups, academia, industry, and NIH to ensure a comprehensive discussion.

Aikens-Diokno Center of Urologic Research Excellence in Underactive Bladder CURE-UAB

Mission: Steward basic research discoveries from discoveries to the time when external resources can fund clinical trials.

Goal: Becoming a world leader in creating and using knowledge that optimizes and enhance the management of age associated genito-urinary disorders.

My Journey from Clinician to Physician Scientist at Beaumont Innovation laboratory