Advances in Biologics and Stem Cells for Sexual Dysfunction

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Disclosures

• 2011 - started treating urologic conditions with biologic injectables

• 2013 - 2014 - successful feasibility studies for PD and ED

• 2014 - UroStem and UroCellZ Research founded to provide greater access, research, and education of biologics to urologists

Founder of UroCellZ Research

- Advisory board of 21 leaders in Sexual Medicine dedicated to researching and finding a safe and effective biologic treatment
Stem Cells

- Stem cells are undifferentiated cells that can differentiate into specialized cells
- Promote vasculogenesis and wound healing
  - Vasculogenesis: de novo development of blood vessels from endothelial progenitor cells (EPCs)
  - Angiogenesis: reorganization of endothelial cells from preexisting blood vessels
Stem Cells

- Bone Marrow - Mesenchymal Stem Cells (MSC’s)
- Adipose-derived stem and regenerative cells (ADRC’s)
- Placental Derived Stem Cells
Biologics

- Amniotic Fluid
- Amniotic Membrane
- Umbilical Cord
- Platelet Rich Plasma
Placenta amnion

Placenta amnion epithelial stem cells

Synthesis

Endoderm

Mesoder

Ectoderm

Lung

Pancreas

Thymus

Bone

Fat

Neural cells

Skin
Female Sexual Dysfunction - PRP

- Roy - 2014 -

- 11 pts, underwent PRP injections
  - 7 of 11 patients had improvement in FSD
  - 2 pts were overstimulated
- 40% placebo effect in FSD
- Needs more research

- What to inject
- Where?
  - Clitoris?
  - G-Spot?
  - Glands?
Stem-cell therapy for erectile dysfunction
Maarten Albersena, Ching-Shwun Linb, Tom Lue 2013

“The convincing results acquired in the animal studies worldwide provide great hope that we can cure patients with ED, or at least render PDE5i-nonresponders responsive to oral medication, within the next decade.”
Male Sexual Dysfunction
2014

Advances in Stem Cell Therapy for Erectile Dysfunction
Ching-Shwun Lin
Knupppe Molecular Urology Laboratory, Department of Urology, School of Medicine, University of California, San Francisco, CA 94143-0738, USA
2014

— All 35 studies reported improved erectile function with SC transplantation in ED patients or animal models.
Stem Cell Therapy for Erectile Dysfunction of Cavernous Nerve Injury Rats: A Systematic Review and Meta-Analysis

Haitao Shan, Fengzhi Chen, Tao Zhang, Shuhua He, Le Xu, Anyang Wei 2015

— This study is the first meta-analysis to evaluate the effect of stem cell therapy on ED rat models with CNI. This analysis shows that the studies with rats are valid and can predict outcomes of pre-clinical studies. Moreover, the results show that stem cell therapy is safe and can lead to improved ICP/MAP. Future studies should simultaneously focus on nerve regeneration and vascular cell recovery. The synergistic effect of multiple growth factors or agent administration in stem cell transplantation should be considered as beneficial strategies to obtain preferable effects.
It is evident that stem cells can provide a realistic therapeutic modality for the treatment of ED. The preclinical work using rat models for the various disease processes responsible for ED has enabled researchers to elucidate the mechanisms that underlie their therapeutic potential (Table 1). BM-MSCs and ADSCs have demonstrated a paracrine effect on surrounding smooth muscle, neurons, and endothelium, promoting regeneration. MDSCs, on the other hand, have been shown to improve erectile function through stem cell differentiation and cavernosal tissue incorporation. UDSCs enhance erectile function through a unique paracrine effect, which may offer the most convenient and noninvasive source for future studies. As for TSCSs, NCSCs, and EPCs, it is still unclear what specific role they might have in a field dominated by BM-MSCs and ADSCs. The next step, however, will be to find the most efficient means of utilizing gene transfer, growth factors, acellular scaffolds, and even the endogenous stem cells of the penis to create a maximally effective therapy.
While generally demonstrating favorable treatment outcome, these studies, including our own, have so far not been able to explain why cells injected into the cavernosum can treat the underlying diseases.

Within days of IC injection, ADSCs exited the penis and traveled preferentially to bone marrow.
Clinical Evidence
Encouraging Outcomes

• Erectile Dysfunction
  • Second human study in world
  • Podium Presentation at AUA 2014
  • Statistically Significant increase in blood flow
  • Published JAOA - 2016 - Zahalsky

• Peyronie’s Disease
  • First human study in world
  • Podium Presentation at SESAUA 2015
  • Statistically significant increase in blood flow
  • Decreased plaques size and number
  • Improved curvature
  • Published JAOA - 2015 - Zahalsky
PD35-05: Human urine-derived stem cells or their secretome alone facilitate functional recovery in a rat model of stress urinary incontinence Christine Tran*, Abhi Tangada, Cleveland, OH, Hualin Yi, Winston-Salem, NC, Brian Balog, Cleveland, OH, Yuanyuan Zhang, Winston-Salem, NC, Margot Damaser, Cleveland, OH

Abstract: PD35-05

there was no significant difference between both the striated and smooth muscle components of the urethral sphincter of VD + USC and VD + CCM animals

Conclusions - Intraperitoneal injection of USCs and their secretions facilitate recovery from SUI in a rat model, likely via paracrine effects.
PD35-07: Use of Stromal Vascular Fraction of Adipose Tissue in Patients with Vasculogenic Erectile Dysfunction: Evaluation of Clinical Effectiveness and Safety (Preliminary Results: Phases 1-2, 6 Months of Follow-up) NCT02472431 Michael Chalyy, Maya Epifanova, Alexander Krasnov*, Moscow, Russian Federation

— Abstract: PD35-07 - 6 patients

— Results - At 6 months after injection, all patients showed significant improvement in erectile function.
PD35-08: Effect of a single intracavernous injection of autologous adipose-derived stem cells on erectile dysfunction following radical prostatectomy. Martha Haahr*, Ditte Andersen, Charlotte Harken, Navid Toyserkani, Jens Ahm Sørensen, Per Damkier, Søren Sheikh, Lars Lund, Odense, Denmark

- Abstract: PD35-08 - 17 patients
- 73% recovered erectile function after 3 (IIEF3months=11 (5-22)) and 6 months
- No serious adverse events were reported.
Pre - SMS 2016 PRP

• No Clinical Data
• No Research - (reviews Clinicaltrials.gov)
• No Evidence it works
• Conceptually it should
Poster #146: The Efficacy of Platelet-Rich Plasma (PRP) as a Supplemental Therapy for the Treatment of Erectile Dysfunction (ED):

Initial Outcomes J.J. Bannoone poster

- IIEF improvement
- No complications
- Conceptually it should
The Treatment of Erectile Dysfunction in Men Post Radical Prostatectomy with Amniotic Fluid Injection

- 4 of 5 patients downgraded from Trimix to Sildenafil and are now able...
110 injections were administered to 70 patients at 4 facilities.

• There were no reported cases of transfusion reactions, acute rejection or chronic rejection from Amniotic Fluid injections.
• No cancers were newly diagnosed in the patients injected.
• There were no reported cases of Blood Born Pathogen Transmission, such as HIV or Hepatitis C, however no prescreening or post treatment screening was performed.
• Quantity of Amniotic Fluid injected did not appear to have a relationship to the frequency of complications.
• 6 patients reported ecchymosis (5.5%) for more than 5 days after one of their injections.
• There were 2 penile hematomas (1.8%). Neither required surgical intervention.
• No Corporal Ruptures
## Complication Chart

<table>
<thead>
<tr>
<th>COMPLICATIONS</th>
<th>AMOUNT</th>
<th>COMPLICATIONS</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corporal Rupture</td>
<td>0</td>
<td>New Onset of ED</td>
<td>0</td>
</tr>
<tr>
<td>Penile Fracture</td>
<td>0</td>
<td>Worsening of ED</td>
<td>0</td>
</tr>
<tr>
<td>Penile Hematoma</td>
<td>2 (1.8%)</td>
<td>Skin Discoloration</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Penile Infection</td>
<td>0</td>
<td>Localized Edema</td>
<td>0</td>
</tr>
<tr>
<td>Penile Swelling</td>
<td>0</td>
<td>Dyspareuina</td>
<td>0</td>
</tr>
<tr>
<td>Penile Pain</td>
<td>0</td>
<td>Injection Site Pruritus</td>
<td>0</td>
</tr>
<tr>
<td>Blood Blister</td>
<td>0</td>
<td>Development of Nodule / New Peyronie's Plaque</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Genital Pruritus</td>
<td>0</td>
<td>Suprapubic Pain</td>
<td>0</td>
</tr>
<tr>
<td>Painful Erection</td>
<td>1 (0.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesicles at Injection Site</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What Can We Use

• PRP
• Bone Marrow
• ADSC’s
• Amniotic Membranes
• Amniotic Fluid
Concentrated Autologous blood plasma enriched with platelets and growth factors

- platelet-derived growth factor
- transforming growth factor beta
- fibroblast growth factor
- insulin-like growth factor 1
- insulin-like growth factor 2
- vascular endothelial growth factor
- epidermal growth factor
- Interleukin 8
- keratinocyte growth factor
- connective tissue growth factor

Not all peoples growth factors are the same
Understanding Biologics

My Opinion

• I want to do what’s Legal
• I want to do what’s safe
• I want to know what’s in the injection

FDA

—My Opinion - FDA does not like physicians using Stem Cells that have not been studied
FDA Section 361 - Biologic Exemption

the PHS Act and 21 CFR Part 1271. An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria (21 CFR 1271.10(a)):

1) The HCT/P is minimally manipulated

2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;

3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article
What can we use:
Bone Marrow

• Bone Marrow - being investigated in Jordan and Korea
• Not realistic for Urologists to be drilling into the iliac
What can we use:
Fat - Adipose Derived Stem Cells

ADSC’s - being used

• legally in America - NO
  — more than minimal manipulation
  — not for homologous use

FDA has shut down some fat clinics

Why? Because of Stem Cells?
What can we use:
Stem Cell / Biologics Types

Tissue Reference Group from FDA website - 2008

• Autologous adipose tissue enzyme digested and processed for urinary incontinence and treatment of impotence is considered a biological product and not a 361 HCT/P because this is a non-homologous use. The tissue is recovered during one surgical procedure, then processed, and therefore the HCT/P is not exempt from the regulations under 21 CFR Part 1271.15(b).
What can we use:
Stem Cell / Biologics Types

- ADSC’s - being investigated
- Khera and Goldstein
  — Tissue Genesis
  — First and only Investigational Device Exemption (IDE) Study
What can we use:
Amniotic Membrane

- for wound covering
- more than minimal manipulation
- not for homologous use

Multiple manufacturers of these products have received letters from FDA stating these products are more than minimally manipulated.

Most of these products have claimed to have Stem Cells.
What can we use:
Amniotic Fluid

- FDA - Draft Guidance 2014 - HCT/P
  - Human Cell or Tissue Product
  - Nonstructural tissue that serves a biochemical role
- Minimally manipulated - Yes
- Homologous use - Yes
  - Made in the kidneys
  - Necessary for genitourinary system development
What can we use: Amniotic Fluid

• Not all amniotic fluid is created equal
  — 38-40 week live birth planned C-Sections
  — Maximize growth factors and anti-inflammatory factors
  — Freeze Process

— Some claim stem cells - then have changed marketing
## What can we use: Amniotic Fluid

<table>
<thead>
<tr>
<th>Growth Factors &amp; Cytokines</th>
<th>Abbreviation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte Growth Factor</td>
<td>HGF</td>
<td>Myogenesis, Wound Healing, Organ Regeneration</td>
</tr>
<tr>
<td>Epidermal Growth Factor</td>
<td>EGF</td>
<td>Cell Growth, Proliferation, Differentiation</td>
</tr>
<tr>
<td>Tumor Necrosis Factor - Alpha</td>
<td>TNF-α</td>
<td>Apoptosis, Angiogenesis</td>
</tr>
<tr>
<td>Chemokine</td>
<td>GRO- α</td>
<td>Angiogenesis, Wound Healing</td>
</tr>
<tr>
<td>Monocyte Chemo Attratanct Protein -1</td>
<td>MCP-1</td>
<td>Immune Modulation</td>
</tr>
<tr>
<td>Tissue Inhibitor of Metalloproteinases (1,2,3,4)</td>
<td>TIMP (1,2,3,4)</td>
<td>Growth Promotion</td>
</tr>
<tr>
<td>Insulin- Like Growth Factor (1,2)</td>
<td>IGF (1,2)</td>
<td>Cell Activation, Platelet Degranulation</td>
</tr>
<tr>
<td>IL1-Receptor Antagonist</td>
<td>IL1-RA</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Transforming Growth Factor (Alpha, Beta 1, Beta 2)</td>
<td>TGF (α,β1,β)</td>
<td>Proliferation, Differentiation, Immune Modulation</td>
</tr>
</tbody>
</table>
What can we use:
Amniotic Fluid
“SDF1 treatment facilitates axonal regeneration”

What can we use:
Amniotic Fluid

• Only Product with Safety data
• States exactly what is in it
• Does not claim to have stem cells
• Has results documenting improvement in Erectile Dysfunction
Low Intensity Shock Wave Therapy

Tom Lue - has shown it works by Reactivating a patients own Stem Cells in the Penis

- should eliminate concern over Stem Cells finding cancers and causing them to grow
  - multiple treatments of penis on a plate

If done incorrectly - leads to corporal fibrosis
BEFORE
After
Conclusions

Biologics are the Future of Erectile Dysfunction and Peyronie’s Disease

• Needs more research
  – What Growth Factors are best?
  – What Cells are best?
  – Is PRP good enough?
  – Autologous or Amniotic fluid based therapies?

Biologic Injections are the most promising development in the field of Male Sexual Dysfunction since the Invention of Viagra