Introduction

- Nucleus/Disc Repair Techniques:
  - (I) Cellular therapy
  - (II) Growth factor therapy
  - (III) Gene therapy

IVD

• NUCLEUS PULPOSUS
  – 2 cells types derived from distinct embryonic sources (maintain ECM homeostasis):
    – (1) Notochord cells
      • notochordal remnant
      • generally disappear by age 20
    – (2) Chondrocytic disc cells
      • derived from axial mesoderm
  – Homeostasis: balance between anabolism and catabolism of disc cells and the ECM they produce.

Disc Repair

• 3 main mechanisms:
    • Boost native chondrocytic cell production by up-regulating production of anabolic ECM proteins, down-regulate catabolic factors.
  – II. Gene therapy: transfer of genetic material.
    • Boost native chondrocytic cell production by inserting genetic material to maintain/restore ECM.
  – III. Cell therapy: exogenous injection of cells.
    • Introduction of exogenous cells to augment/replenish ECM.
      – Stem, native disc and chondrocyte cells

Cell Therapy

• Notochordal cells
  – Allogeneic: embryonic human NP, soon after birth these cells diminish rapidly.
• Chondrocytes
  – Autologous: mature
  – Allogeneic: juvenile
• Mesenchymal stem cells
  – Autologous: bone marrow/adipose
  – Allogeneic: embryonic/adult/umbilical
Disc Repair

- Cell therapy: Mechanism
  - (1) Cell harvest
  - (2) Cell expansion
    - Musculoskeletal cell therapies generally introduce 5-10 million cells/defect; cells are expanded by growing in monolayer to encourage proliferation.
  - (3) Add scaffold/carryer
    - Hyaluronic acid, fibrin, silk, collagen
  - (4) Insertion
    - Ideally minimally invasive with percutaneous needle

Cell Therapy

- Donor Cells
- Cell expansion
- Carrier
- Percutaneous Injection

CNSA Disc Repair IND Experience

- NuQu – Phase I
  - Juvenile chondrocyte nucleus repair
  - 2 sites: CNSA/Ken Pettine MD
  - 15 pts: prospective
  - Thrombin/fibrinogen carrier
- Mesoblast – Phase II
  - Stem cell nucleus repair
  - 100 pts: prospective, randomized, placebo
  - Allogeneic mesenchymal stem cells
  - Hyaluronic acid carrier

CNSA Disc Repair IND Experience

• NuQu – Phase II
  - “A Phase II, Randomized, Double Blind, Placebo Controlled Study Evaluating the Treatment of Degenerative Lumbar Discs with Allogeneic Cultural Chondrocytes.”
  - 44 pts: (22 juvenile cartilage cells, 22 placebo), 1 year follow-up
  - Lead study site

• Mesoblast – Phase III
  - “A Prospective, Multicenter, Double-blind, Controlled Study Evaluating Safety and Preliminary Efficacy of a Single Injection of Adult Allogeneic Mesenchymal precursor Cells Combined with Hyaluronic in Subjects with Chronic Discogenic Lumbar Back Pain.”
  - Prospective, randomized, placebo, blinded
  - Initiated Q4 2014

Stem Cells: Mesoblast

• Mesoblast study (NCT01290367)
  - “A Prospective, Multicenter, Double-blind, Controlled Study Evaluating Safety and Preliminary Efficacy of a Single Injection of Adult Allogeneic Mesenchymal precursor Cells Combined with Hyaluronic in Subjects with Chronic Discogenic Lumbar Back Pain.”
  - Indications: early/mod lumbar DDD
  - Allogenic mesenchymal precursor (MPC) cells
    • Bone marrow (iliac crest) derived mesenchymal stem cells.

Study Design

• Prospective, multi-center, randomized, double-blind, controlled study
  - Patients and radiographic evaluators blinded to treatment

• Safety Evaluations
  - Adverse Events
  - Treatment Failure (Surgical & Injection Interventions)
  - Immunological Testing
  - Blood chemistry & inflammatory markers
  - Radiographic
    • Heterotopic ossification
    • Disc degeneration

• Efficacy Evaluations
  - Radiographic Changes
  - VAS Score
  - Oswestry Disability Index (ODI)
  - SF-36
  - Work Productivity & Activity Index (WPAI)
  - Medication usage

 courtesy of Hyun Bae, MD
Stem Cells: Mesoblast

• Phase II IND Study
  – 13 sites (US and Australia), 100 patients
  – Single level, early DDD
    • <30% loss of disc space ht
  – Clinical indices: VAS, ODI
    • MPC – 18 million: N=30
    • MPC – 6 million: N=30
    • Hyaluronic acid: N=20
    • Saline: N=20

Stem Cells: Mesoblast

• Phase II results (12 months):
  • Less opioids for pain control.
  • Greater radiographically defined disc stability.
  • Less additional surgical and nonsurgical interventions.

PHASE II STUDY

• Mesoblast results (12 months):
  • VAS
    • Significantly greater mean reduction in pain scores.
      • 18 million MPC: 40 point reduction (p=0.046)
      • 6 million MPC: 37 point reduction (p=0.11)
    • Significantly greater proportion of pts with >50% reduction in pain.
      • 18 million MPC: 62% (p=0.038)
      • 6 million MPC: 69% (p=0.009)
    • Significantly greater proportion of pts with minimal residual LBP (VAS <20)
      • 18 million MPC: 42% (p=0.05)
      • 6 million MPC: 59% (p=0.01)
• 6M and 18M MPC treated groups performed similarly and the saline and HA control groups performed similarly.
• The 6M MPC group had 69.2%, the 18M MPC group had 61.5% of patients achieving at least 50% reduction in VAS back pain while the saline group had only 13.2% and the HA group had 32.7% (p = 0.036).
• Mean reduction from baseline in the VAS low back pain was 8.4 for 6M group, 7.5 for 18M group, 6.8 for pooled controls (HA and saline), 4.4 for HA group, and 4.3 for the 18M vs. pooled control.
• Large differences around the mean reflect responder vs. non-responder outcomes.

PHASE II STUDY
• Mesoblast results (12 months):
  • ODI
    • Greater mean reduction in disability scores.
      • 18 million MPC: 43% reduction (p = 0.09)
      • 6 million MPC: 35% point reduction (p = 0.11)
    • Greater proportion of pts achieving minimal residual functional disability (ODI <20)
      • 18 million MPC: 39% (p = 0.14)
      • 6 million MPC: 36% (p = 0.14)
  • 6M (57.7%) and 18M (61.5%) had a greater % of patients with a minimally important clinical difference (MCID) ≥30% reduction in ODI compared to saline 43.8% & HA 41.2% at 12 months.
  • 6M (46.2%) and 18M (46.2%) had a greater % of patients with ≥50% reduction in ODI compared to saline 31.3% & HA 23.5% at 12 months.
  • Mean reduction from baseline in the ODI was 40.4 for 18M group, 36.8 for 6M group, 27.0 for HA and 28% for saline (p = 0.09 for 18M vs. saline).
  • Mean ODI change from baseline exceeds the FDA accepted Minimal Clinically Important Difference (MCID) for the MPC treated groups, but does not exceed it for the MPC control groups.
  • Large differences around the mean reflect responder vs. non-responder outcomes.

Courtesy of Hyun Bae, MD
Composite Endpoint for Treatment Success
50% VAS back pain reduction; AND 15 point ODI improvement; AND no intervention at the treated level

Cartilage Cells: NuQu

- NuQu: Juvenile cartilage cells
  - Phase I: 15 pts - prospective, non-randomized.
  - Phase II: 44 pts - prospective, randomized, blinded, placebo-controlled.
- Pts with discogenic back pain secondary to mild/moderate degenerative disc disease (DDD) L2-S1.
  - Fibrin glue carrier.

Cartilage Cells: NuQu

- Phase I Pilot Study
- Levels:
  - L3-4: 2
  - L4-5: 1
  - L5-S1: 12
- Injection duration: Avg=11.6 s (Range 5-32s)
- Injection amount: Avg=1.4cc (Range 1-1.6cc)
  - Est # of viable cells 6.75-13.5 million cells/cc
- Intradiscal press: Avg=92.4 psi (Range 60-101)
Cartilage Cells: NuQu

- **Phase I results: CLINICAL**
  - Mean preoperative pain (NRS), disability (ODI) and function (SF-36) scores improved significantly at six months and were maintained through 2 years.

<table>
<thead>
<tr>
<th></th>
<th>Pre-op</th>
<th>6 mths</th>
<th>2 yrs</th>
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<tbody>
<tr>
<td>NRS</td>
<td>5.7</td>
<td>3.8</td>
<td>2.5</td>
</tr>
<tr>
<td>ODI</td>
<td>53.3</td>
<td>26.9</td>
<td>14.3</td>
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<tr>
<td>SF-36</td>
<td>35.5</td>
<td>43.4</td>
<td>29.2</td>
</tr>
</tbody>
</table>

(p=0.0036)  (p<0.0001)  (p=0.0014)

- **Phase II IND Study**
  - Levels:
    - L3-4:  5
    - L4-5:  15
    - L5-S1: 24
  - Injection amount: Avg=1.8cc (Range 1-2cc)
  - Est # of viable cells 6.75-13.5 million cells/cc
  - Intradiscal press: Avg=57.3 psi (Range 20-100)

- **Phase II results: CLINICAL**
  - Mean preoperative function (SF-36) scores improved significantly at six months and were maintained through 2 years in both groups.

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Pre-op</th>
<th>6 mths</th>
<th>2 yrs</th>
</tr>
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<tbody>
<tr>
<td>NuQu</td>
<td>37.1</td>
<td>40.8</td>
<td>44.1</td>
</tr>
<tr>
<td>Saline</td>
<td>36.2</td>
<td>41.2</td>
<td>40.3</td>
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Cartilage Cells: NuQu

- **Phase II results: CLINICAL**
  - Mean preoperative pain (VAS) scores improved significantly at six months and were maintained through 2 years in both groups.

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<tr>
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<th>2 yrs</th>
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<tbody>
<tr>
<td>NuQu:</td>
<td>46.8</td>
<td>37.5</td>
</tr>
<tr>
<td>Saline:</td>
<td>49</td>
<td>46.2</td>
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- Mean preoperative pain disability (ODI) scores improved significantly at six months and were maintained through 2 years.

<table>
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<tr>
<th></th>
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<th>2 yrs</th>
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<tbody>
<tr>
<td>NuQu:</td>
<td>29.8</td>
<td>22.1</td>
</tr>
<tr>
<td>Saline:</td>
<td>33.5</td>
<td>32.8</td>
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</table>

- Composite success (min 50% improvement VAS and 15 point improvement in ODI, no further surgical intervention).

<table>
<thead>
<tr>
<th></th>
<th>1yr</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NuQu:</td>
<td>50%</td>
<td>45.5% (p=0.618)</td>
</tr>
<tr>
<td>Saline:</td>
<td>50%</td>
<td>36.4% (p=0.380)</td>
</tr>
</tbody>
</table>
Disc Repair for DDD

• CH: Pt is 40 yo with long h/o mechanical LBP.
  – NuQu procedure
  – 7 in, 22-gauge.
  – 1.4 cc injection, 12s.
  – Max press= 82 psi.
  – Pt now 1 yr postop resolution of chronic mechanical LBP (16 mnths), no narcotics, VAS=1.

Conclusion

• Disc repair is both a minimally invasive as well as motion preserving technique to treat symptomatic degenerative disc disease earlier and less invasively.
• Stem cells for disc regeneration:
  – The jury is still out.
  – Safe: Yes
  – Efficacious: ?
• Early clinical results are equivocal, Mesoblast Phase III trial is ongoing.

THANK YOU!