Castellvi Spine
Current FDA Trials: Disc Regeneration

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DISCLOSURE

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- Spine Wave: Consultant/Stock/Royalties
- Spinal Kinetics: Stock
- Medtronic: Consultant
- Globus Medical: Consultant
- DiscGenics: Consultant/Stock
- Premia Spine: Consultant
- United HealthCare: Spine Advisory Board
- *All disc repair procedures are investigational*.

Introduction

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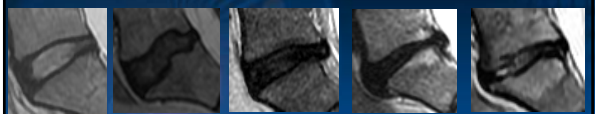
- *Nucleus/Disc Repair Techniques:*
  - (I) Cellular therapy
  - (II) Growth factor therapy
  - (III) Gene therapy



Grade 1 Grade 2 Grade 3 Grade 4 Grade 5

Pfirrmann CS, Boos N, et al: Magnetic resonance imaging classification of lumbar intervertebral disc degeneration. *Spine 26*:1873-78,2001

IVD

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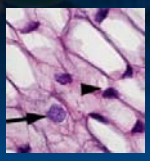
- **NUCLEUS PULPOSUS**
  - 2 cells types derived from distinct embryonic sources (maintain ECM homeostasis):
  - (1) ***Notochord cells***
    - notochordal remnant
    - generally disappear by age 20
  - (2) ***Chondrocytic disc cells***
    - derived from axial mesoderm



  - *Homeostasis:* balance between anabolism and catabolism of disc cells and the ECM they produce.

Disc Repair

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- 3 main mechanisms:
  - I. ***Growth factors:*** exogenous protein injection.
    - 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

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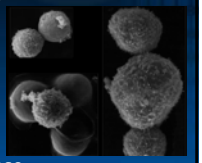
- Notochordal cells
  - Allogeneic: embryonic human NP, soon after birth these cells diminish rapidly.
- Chondrocytes
  - Autologous: mature
  - Allogeneic: juvenile
- Mesenchymal stem cells
  - Autologous: bone marrow/adipose
  - Allogeneic: embryonic/adult/umbilical



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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/carrier
    - Hyaluronic acid, fibrin, silk, collagen
  - (4) Insertion
    - Ideally minimally invasive with percutaneous needle

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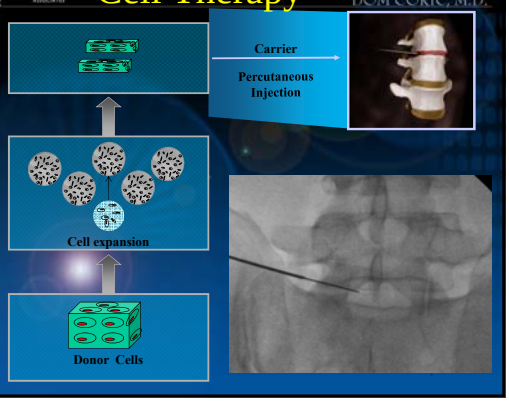
Cell Therapy



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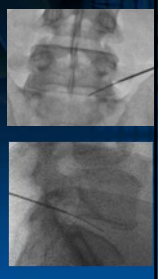
CNSA Disc Repair IND Experience

- *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



Coric D, Pettine K, Sumich A, Boltes MO: Prospective Study of Disc Repair with NuQu® Allogeneic Chondrocytes. *J Neurosurg-Spine 18*:36-42, 2013

CNSA Disc Repair IND Experience

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- *NuQu – Phase II*
  - 'A Phase II, Randomized, Double Blind, Placebo Controlled Study Evaluating the Treatment of Degenerative Lumbar Discs with Allogeneic Cultured 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 Hyaluronan in Subjects with Chronic Discogenic Lumbar Back Pain.'
  - Prospective, randomized, placebo, blinded
  - Initiated Q4 2014

Stem Cells: Mesoblast

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- 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 Hyaluronan 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

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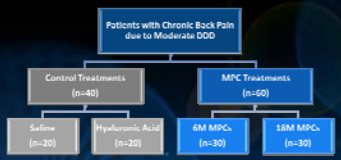

- Prospective, multi-center, randomized, double-blind, controlled study
  - *Patients and radiographic evaluators blinded to treatment*
- Follow-up: 1, 3, 6, 12, 24 & 36 months
  - Safety Evaluations
    - Adverse Events
    - Treatment Failure (Surgical & Injection Interventions)
    - Immunological Testing
    - Blood chemistry & inflammatory markers
    - Radiographic
      - Heterotopic ossification
      - Disc degeneration
  - Efficacy Evaluations
    - Radiographic Changes
      - MRI
      - X-ray & Stability
    - Lower Back and Leg Pain measured by VAS Score
    - Oswestry Disability Index (ODI)
    - SF-36
    - Work Productivity & Activity Index (WPAI)
    - Medication usage

Courtesy of Hyun Bae, MD

Stem Cells: Mesoblast

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- 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
    - MPCs – 18 million: N=30
    - MPCs – 6 million: N=30
    - Hyaluronic acid: N=20
    - Saline: N=20

Stem Cells: Mesoblast

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

PHASE II STUDY

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- *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)

VAS

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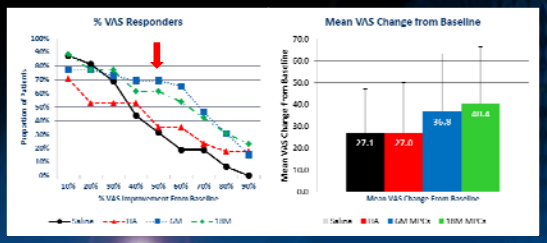

- 6M and 18M MPCs treated groups performed similarly and the saline and HA control groups performed similarly
- The 6M MPC group had 69.2%, the 18M MPC group had 61.5% of patients achieving at least 50% reduction in VAS back pain while the Saline group had only 31.3% and the HA group had 35. 3% (p = 0.036)
- Mean reduction from baseline in the VAS low back pain was 40.4 for 18M group, 36.8 for 6M group, 27.0 for pooled controls (p=0.11 for 6M vs. pooled control and p=0.046 for 18M vs. pooled control)
- Large differences around the mean reflect responder vs. non-responder outcomes

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PHASE II STUDY

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- *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)

ODI

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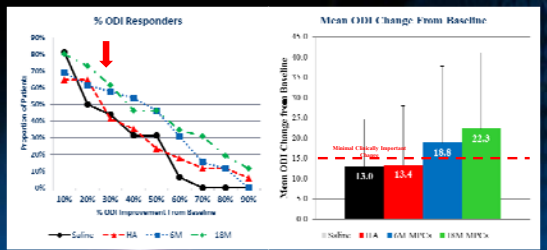
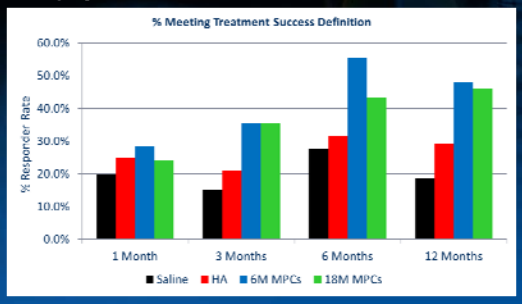


- 6M (57.7%) and 18M (61.5%) had a greater % of patients with a minimally important clinical difference (MCID) ≥30% reduction in ODI compared to Saline (43.8%) & HA (41.2%) at 12 months
- 6M (46.2%) and 18M (46.2%) had a greater % of patients with ≥50% reduction in ODI compared to Saline (31.3%) & HA (23.5%) at 12 months
- Mean reduction from baseline in the ODI was 43% for 18M group, 35% for 6M group, 30% 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

MPCs groups show sustained treatment effect relative to controls over 12 months



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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.

Coric D, Pettine K, Sumich A, Boltes MO: Prospective Study of Disc Repair with NuQu® Allogeneic Chondrocytes. *J Neurosurg-Spine 18*:36-42, 2013

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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)

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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.

Pre-op	*6 mths*	*2 yrs*	
NRS: 5.7	→ 3.8	→ 2.5	(p=0.0036)
ODI: 53.3	→ 26.9	→ 14.3	(p<0.0001)
SF-36:35.5	→ 43.4	→ 29.2	(p=0.0014)

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Cartilage Cells: NuQu

- *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)

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Cartilage Cells: NuQu

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

SF-36 Pre-op	*6 mths*	*2 yrs*
NuQu:37.1	→ 40.8	→ 44.1
Saline:36.2	→ 41.2	→ 40.3

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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.

VAS	Pre-op	6 mths	2 yrs
NuQu:	72.7	46.8	37.5
Saline:	74.6	49	46.2

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Cartilage Cells: NuQu

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

ODI	Pre-op	6 mths	2 yrs
NuQu:	48	29.8	22.1
Saline:	50.7	33.5	32.8

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Cartilage Cells: NuQu

- *Phase II results:* CLINICAL
  - Composite success (min 50% improvement VAS and 15 point improvement in ODI, no further surgical intervention).

Composite Success:	1yr	2 yrs	
NuQu:	50%	45.5%	(p=0.618) 1yr
Saline:	50%	36.4%	(p=0.380) 2yrs

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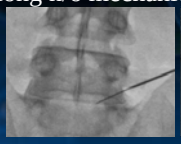
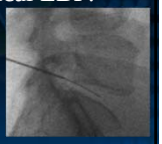
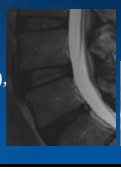
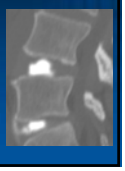
Disc Repair for DDD

- 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.





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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.

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THANK YOU!