DiscGenics™

The Next Generation in Spinal Therapeutics

Considerations for Patient Variability in a Low Back Pain Trial using an Allogeneic Cell Therapy

Exploring Sources of Variability Related to the Clinical Translation of Regenerative Engineering Products – a Workshop

October 18, 2018

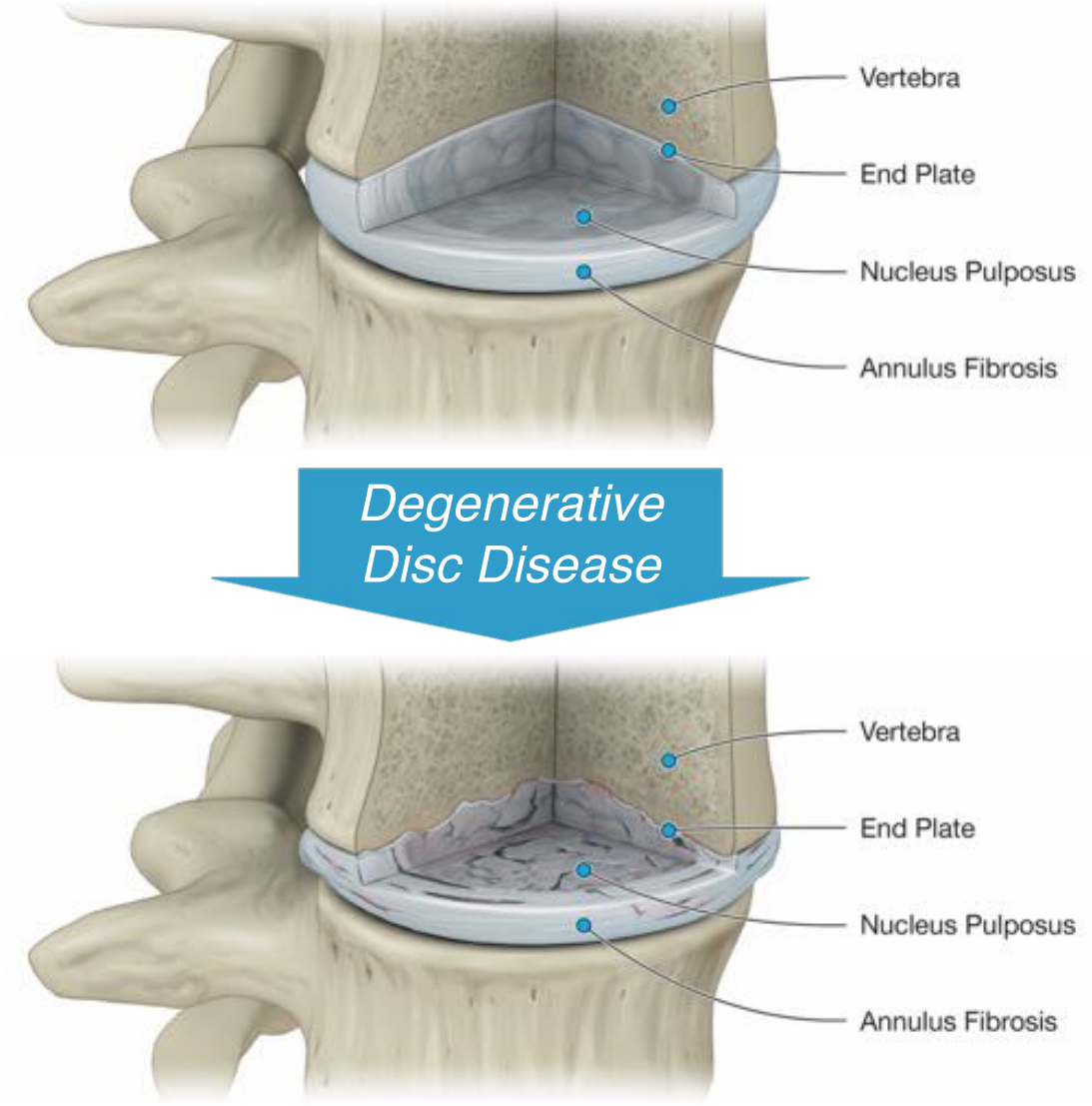
National Academy of Sciences Building, Washington DC

Low Back Pain: A Global Health Problem

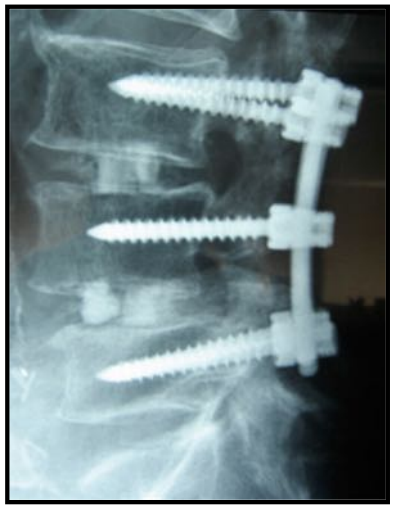
- Affects approx. ¼ of global population
- Imposes major financial burden on healthcare system
  - >$100B annual U.S. spend
- Leading cause of disability worldwide
- Can lead to:
  - Missed work
  - Lost wages
  - Addiction to pain medication, including opioids
- Void of curative treatment options

Degenerative Disc Disease (DDD)

- Major cause of low back pain
- Progressive breakdown of discs between the vertebrae
- Complex etiology (inflammation, breakdown of extracellular matrix, etc.) makes DDD difficult to treat



Disease Progression & Treatment Options



Fusion surgery (>$100,000)

Adjacent Level Disease

Injury, genetics, etc.

Degenerative Disc Disease

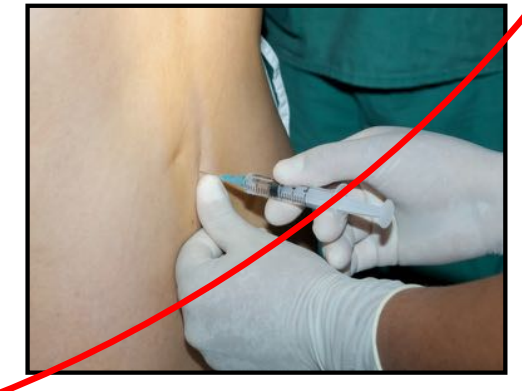
- *Pain meds (NSAIDS, opioids)*
- *Physical therapy*
- *Steroid injections*
- *Ablation*
- *Chiropractic/ alternative care*

Mild Stages

Moderate Stages

- *"Just buying time"*
- *Continued degeneration*
- *Mild stage treatments*

Severe Stages



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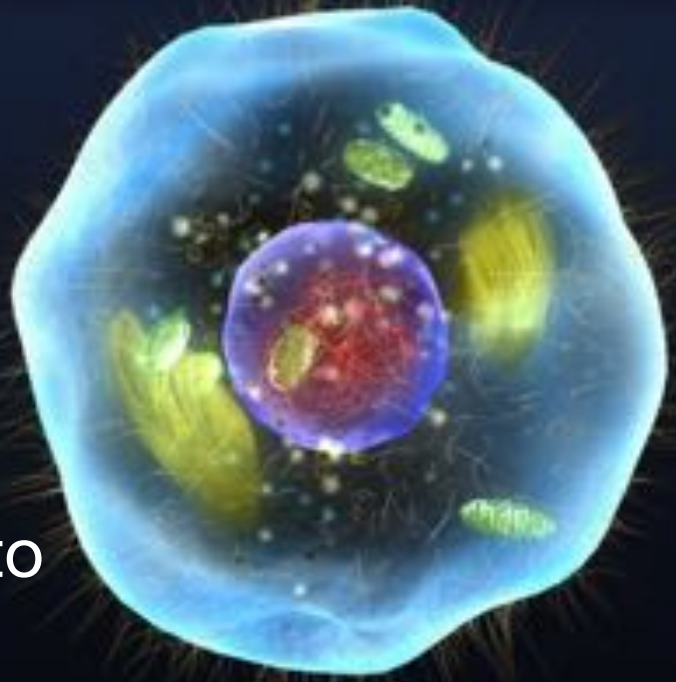
Cell Therapy: The Cell as “Drug”

Use of cells as the active ingredient



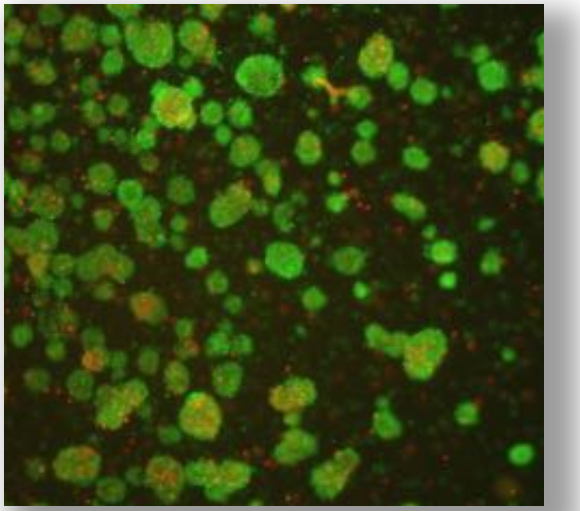
Perform role of diseased or missing cells

Generate chemical cues to influence local microenvironment

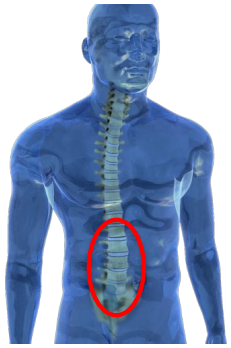
Respond to local microenvironment

Our Solution: Discogenic Cells

- Therapeutic progenitor cells engineered to address complex environment of degenerated disc
- Derived from donor adult disc tissue (allogeneic), to treat disc tissue (homologous use)
- Dual hypothesized mechanism: regenerative & anti-inflammatory
- Protected by 24 issued patents and 15 pending patents; trade secret protected



Green – live Discogenic Cells



A single donor produces thousands of doses

Off-the-Shelf Cell Therapy Product

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Two-Part Cell Manufacturing Process

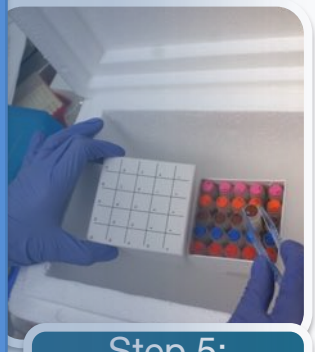
Check Point #2:

Potency: Cell number and cell viability; therapeutic capacity (make matrix, anti-inflammatory)

Safety: Sterility, mycoplasma, virus testing, residual raw materials

Identity and purity: Flow cytometry, endotoxin

- Sampling plan designed to ensure sufficient data
- Test on each lot upon release, subset of lots to determine stability
- *To date, 20+ donors show consistent release profile*



Step 5:
Final Formulation of Drug Product

Cryopreserve Intermediate Cell

Check point #1

Cryopreserve Final Allogeneic Cell Therapy Product

Check point #2

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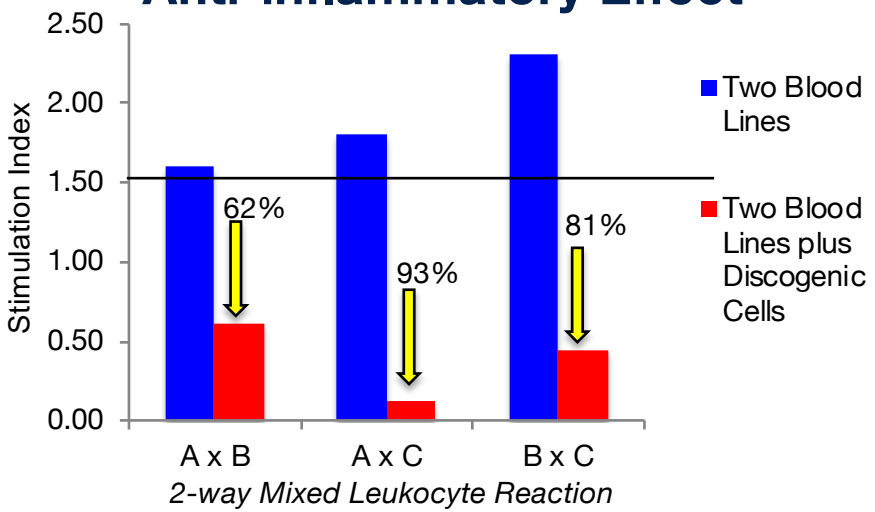
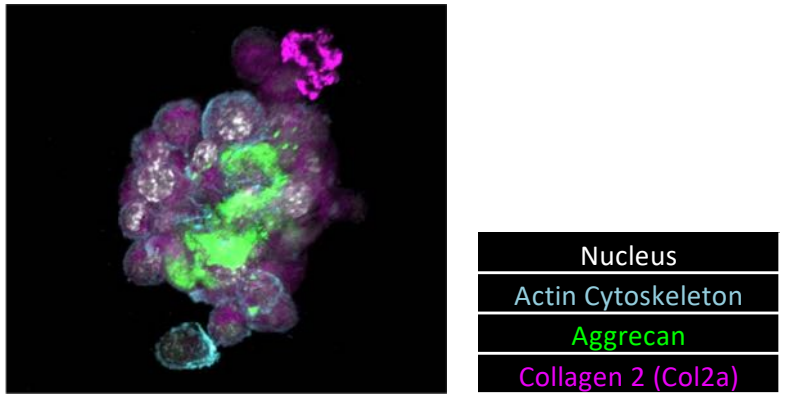
Characterization of Discogenic Cells

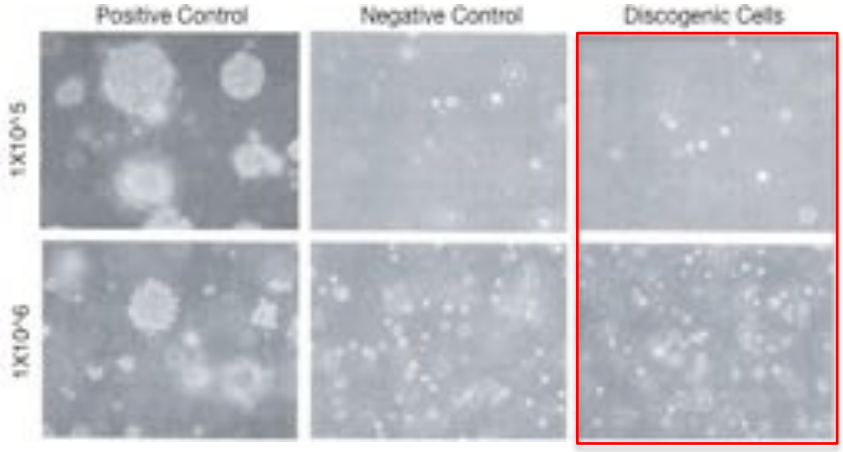
Anti-inflammatory Effect



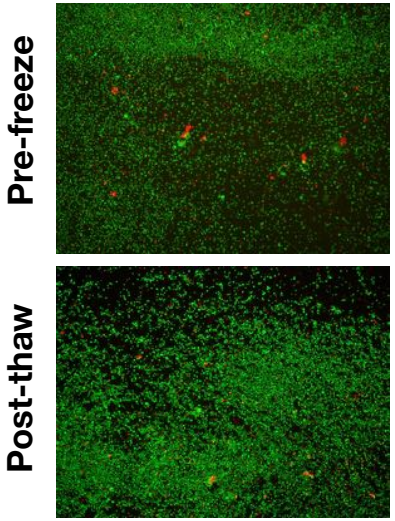
Produces Extracellular Matrix of the Disc



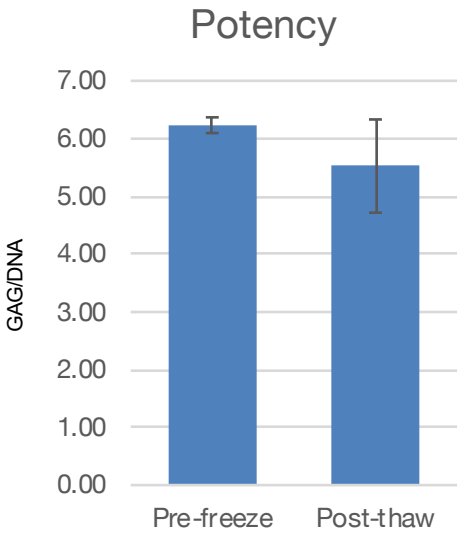
Non-Tumor Forming



Robust through Cryopreservation



Green: Alive
Red: Dead



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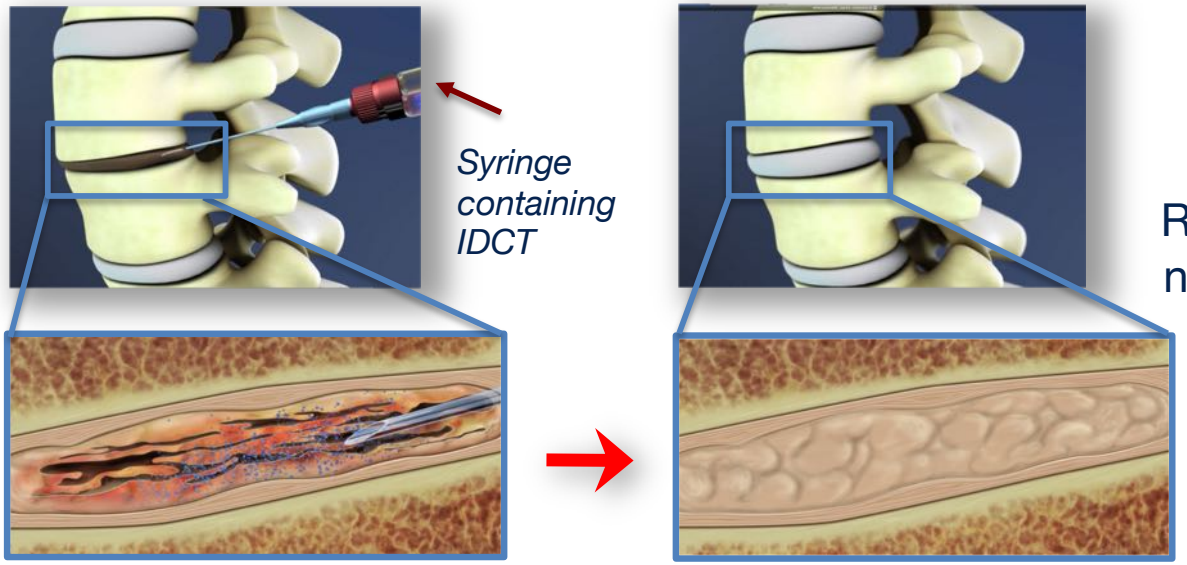
First Product Candidate: Injectable Disc Cell Therapy (IDCT) for DDD

- Allogeneic (donor-derived), non-invasive cell therapy
- Comprised of proprietary Discogenic Cells & viscous delivery vehicle

Potential Benefits of IDCT	
Cost-effective	Compared to ineffective conservative care or eventual fusion surgery
Non-surgical	Easy to administer, does not take up OR time, cost savings for healthcare system
Off-the-shelf	Frozen product means no complex patient-specific logistics

Treatment:
IDCT is injected into the disc percutaneously (non-surgical)



Cross-section of the target disc

Cross-section of a regenerated disc

Post-Treatment Hypothesis:
Reduced pain & normalized disc tissue

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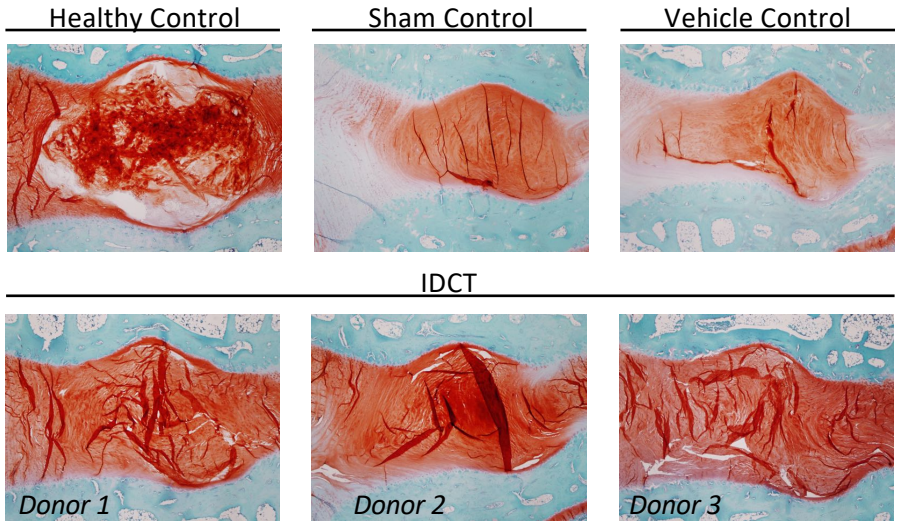
Preclinical Safety and Efficacy of IDCT in Animal Models

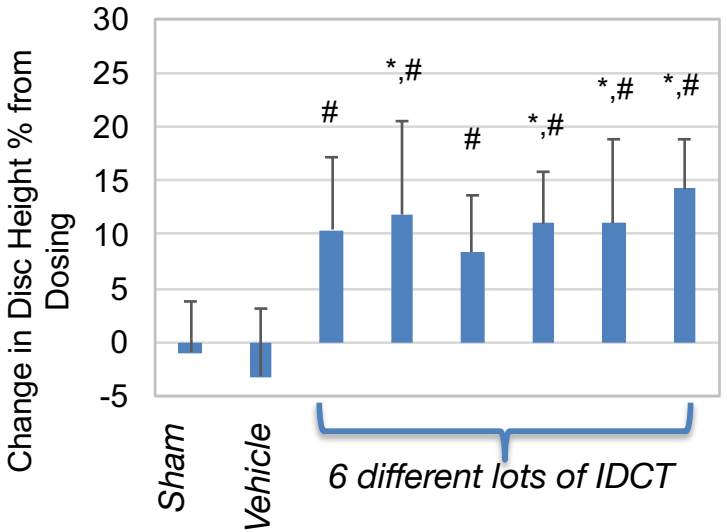
- Evaluated in 4 animal models across 13 studies
- Measured safety and bioactivity, acute and chronic timepoints
- No toxicity or safety issues identified, including similar parameters being evaluated in clinic
- Improvement in disc height, normalization of disc tissue found
- *Shown below:* 6 lots of IDCT evaluated in rabbit study (16 animals), found consistent bioactivity across donors

Cross-Section of Rabbit Discs



Safranin O

Disc Height Improved (X-ray measurements)



* Different than Sham
\# Different than vehicle

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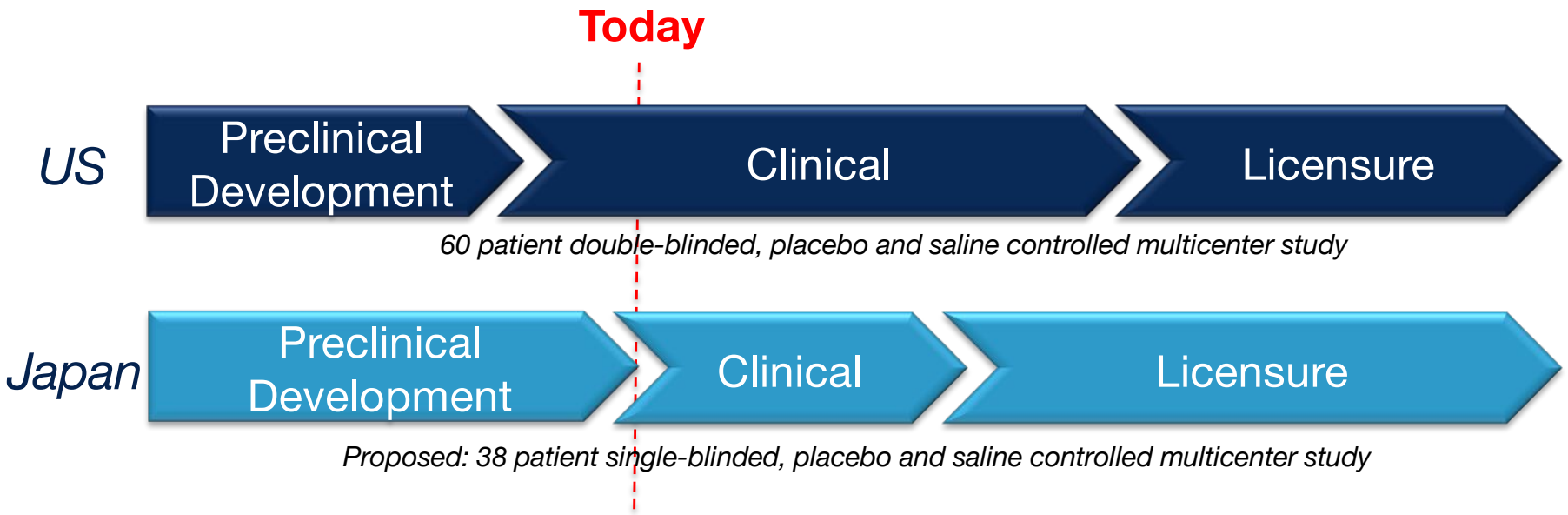
IDCT Regulatory Pathway

- Global footprint for clinical evaluation of IDCT
- Phase I/II U.S. clinical trial initiated Q1 2018
  - Biologic product regulated by FDA's CBER Office of Tissues & Advanced Therapies
- CTN submitted to Japanese PMDA



Follow-On Indications: Cervical DDD, Adjacent Level Disease & Herniated Discs

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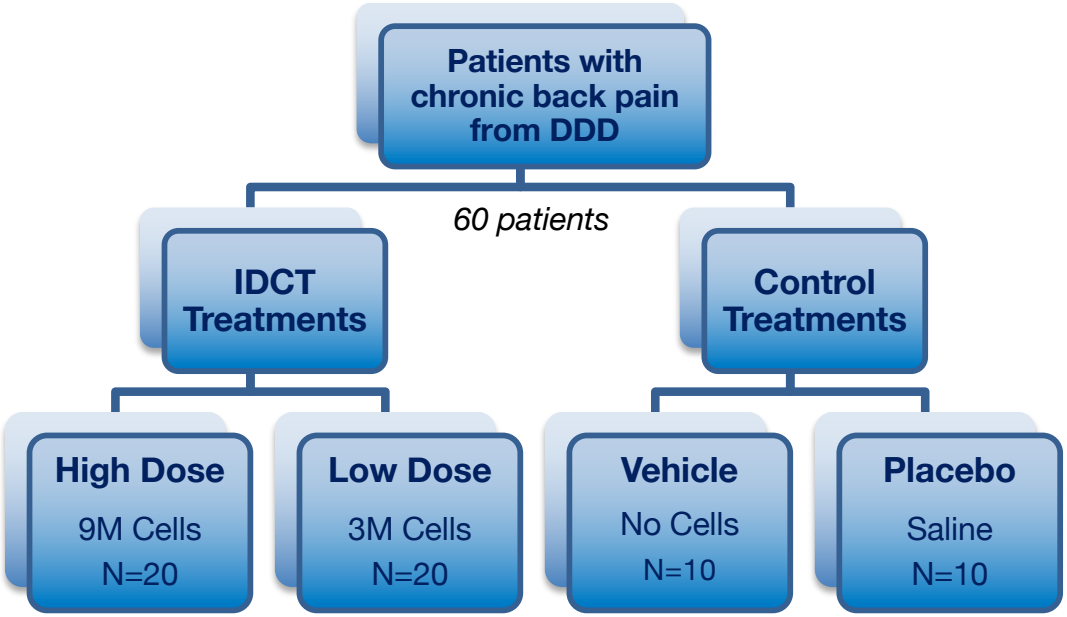
Clinical Evaluation of IDCT - US

- FDA allowed IND in 28 days
- Initiated in Q1 2018
- Patients with painful, single level lumbar DDD (Modified Pfirrmann 3-7, pain for 6 months and unresponsive to conservative care for 3 months)



Key Study Features:

- Prospective design
- Single injection
- Double-blind, vehicle and saline control
- Two doses
- Multicenter
- Outcomes: Safety and preliminary efficacy
- 1 year primary, 1 year extension

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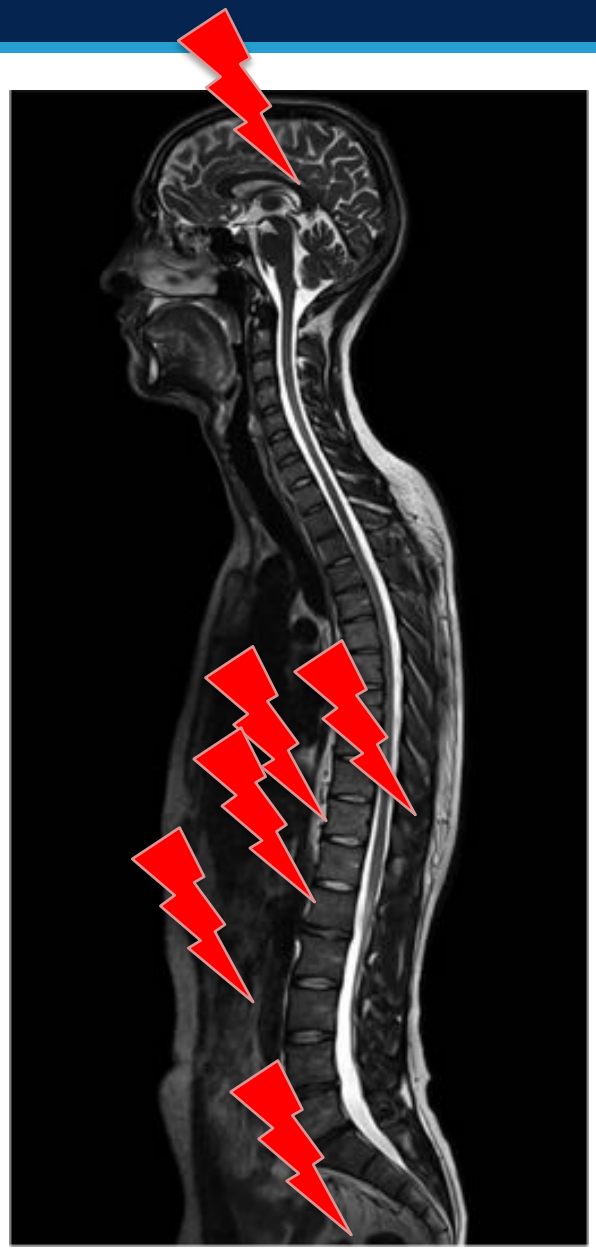
Finding the right patient

- Primary endpoint is Visual Analog Score (VAS) – measures pain
- Single Level Pain
- Back pain often accompanied by other pain, so in order to see ‘improvement’ must screen out patients with other pain
  - Another disc level
  - Facet pain
  - Leg pain
  - Radiculopathy
  - Muscular pain
  - Psychological issues
- Future evaluations may include such patients, but must screen out for sake of clinical trial evaluations



Next Steps for IDCT

- Process allows for manufacture of consistent cell population from different starting donor material
  - In vitro release testing on each lot
  - Animal study shows consistency across lots
- Must identify patients with one source of pain that comes from moderately degenerated disc
- Clinical trial in US is ongoing, with 5 patients included in study to date