

The background of the slide features a stylized, glowing blue human spine on the right side, with numerous circular, glowing blue cells of varying sizes scattered throughout the scene, suggesting a biological or medical theme.

 **BIOTIME**

 **ORTHOCYTE**
CORPORATION

Tailoring effective stem cell therapies for the aging spine

Francois Binette PhD
Vice President Research and
Business Development

Tailoring effective stem cell therapies for the aging spine



Today's presentation



Opportunity/Unmet need → The Challenge

Our Technologies → diverse osteochondral progenitors, biomaterials delivery

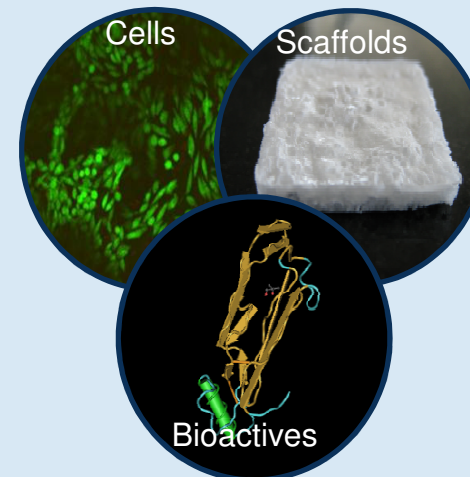
Our Strategy → Tailoring Our Approach

OrthoCyte Corporation

An orthopedic-focused regenerative medicine subsidiary of BioTime Inc

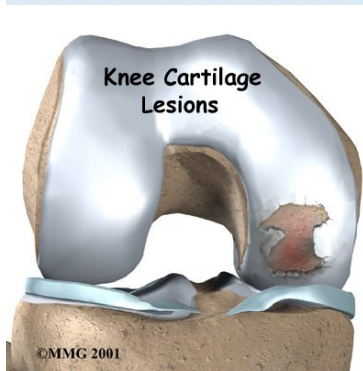
OncoCyte Corporation Cancer diagnostics and anti-cancer therapies	
Cell Cure Neurosciences Ltd. Age-related macular degeneration (AMD)	
OrthoCyte Corporation Orthopedic indications	
ReCyte Therapeutics, Inc. Reversal of developmental aging of cells Embryonic progenitor cells for age-related vascular disorders	
ES Cell International PTE Ltd. Clinical-grade master stem cell banks	
LifeMap Sciences, Inc. Stem cell data base	
BioTime Asia, Ltd. BioTime products for Asia market	

- Orthopedics:
“Medical specialty concerned with the skeleton and its associated structures”
→ Bone
→ Soft tissues: cartilage, disc, tendons, ligaments
- Regenerative Medicine:
“process of replacing or regenerating human cells, tissues or organs to restore or establish normal function”

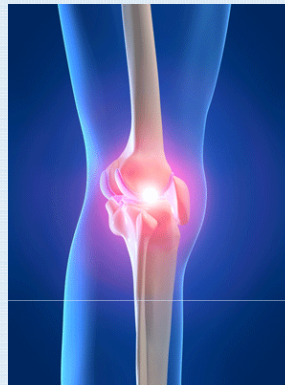


Orthopedic Regenerative Medicine a different value proposition

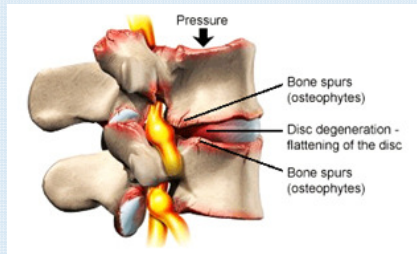
Accelerating regenerative medicine for the largest health economic burden in modern societies



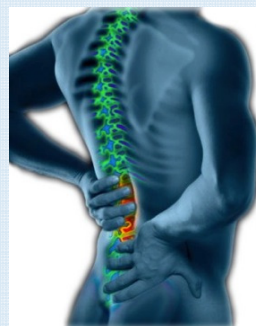
Cartilage damage



Knee Pain/OA



Intervertebral Disc Damage



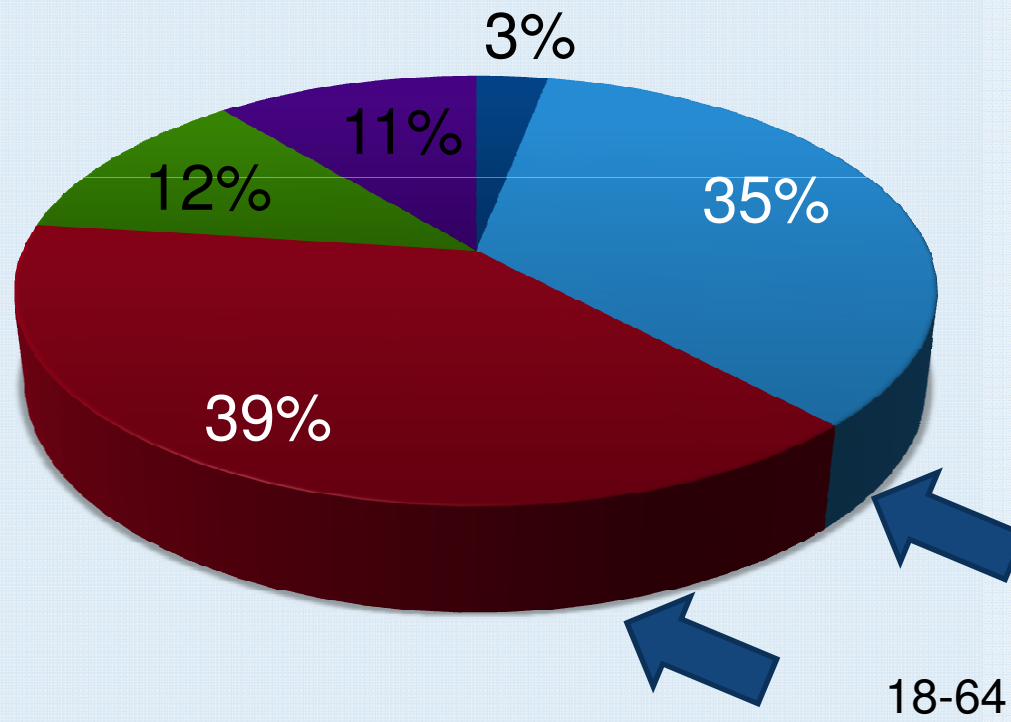
Back Pain/DDD

- Prevalence:
 - Affects nearly everybody
- Pathophysiology:
 - Insult to avascular tissue → does not heal
 - Chronic, irreversible
 - Soft tissue and Bone involvement
- Standard of care:
 - No treatment option between Tylenol™ and invasive risky surgery

CBP is largest health-economic burden

Back pain: largest impact on productivity and wages loss

■ <18 ■ 18-44 ■ 45-64 ■ 65-74 ■ 75 over



→ Direct Medical Cost
193.9 billion

→ Earning loss, indirect
22.4 billion

2005 National Health Interview Surveys

Several opportunities to intervene?

Targeting Disc and Bone tissue for Degenerative disc disease



Insult/inflammation

Matrix break down

Cell/tissue loss

Structural collapse

Disease Progression

Early Stage



Late Stage



LARGE THERAPEUTIC GAP



Inflammation modulation

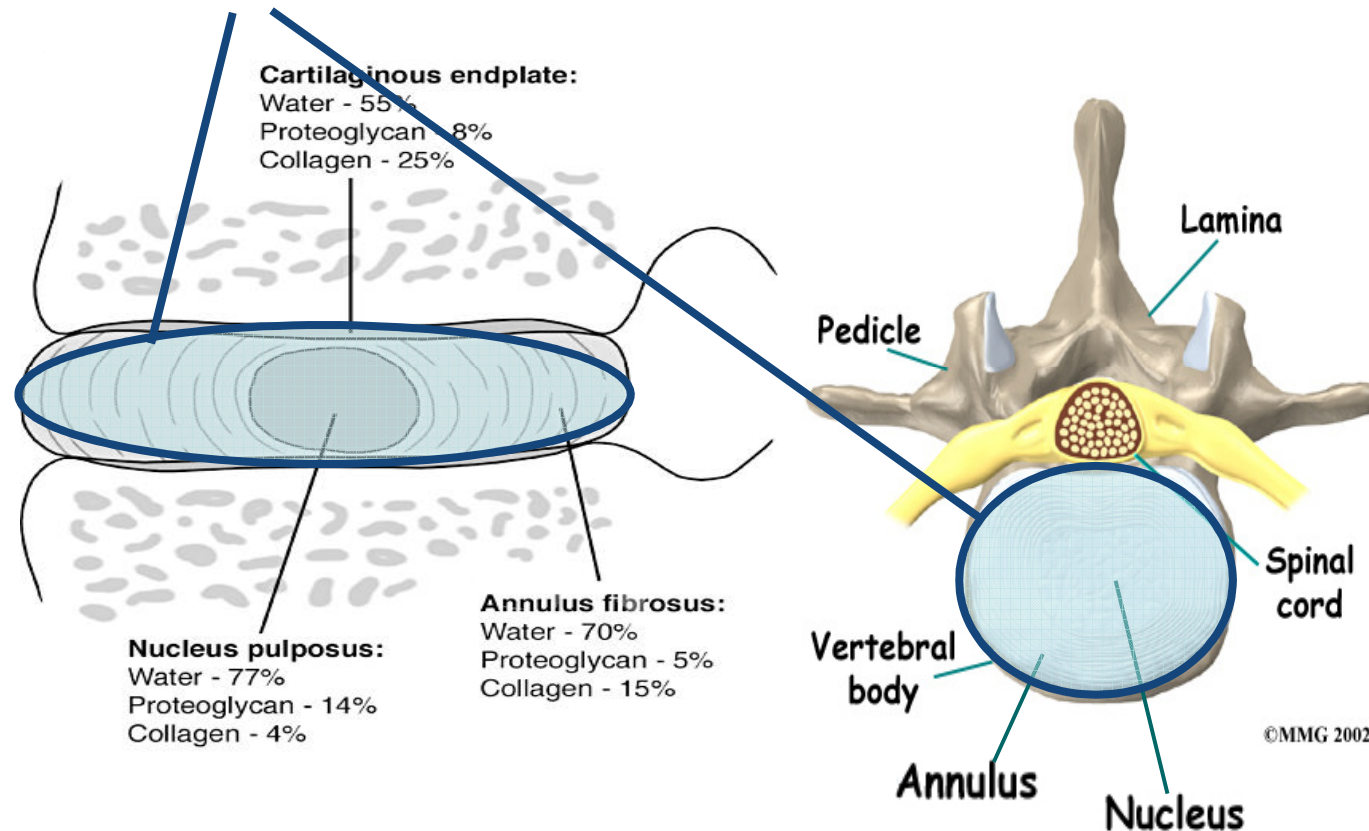
Block catabolic/increase anabolic

Replenish disc cells

Induce bone fusion

Traditional pharma approach won't work: a regenerative medicine opportunity

Almost completely devoid of vascular support



→ requirement for enabling: intradiscal delivery system

→ allogenic cells may be possible

Market size¹/opportunity² for proposed bone and disc repair are real

Indication	Incidence Prevalence	Product: ASP \$/unit	Market size \$MM	Market Opportunity
Bone Fractures + Spinal Fusions	300k + 600k = 900k/yr	Ceramic-based Bone Graft substitutes: 1000	WW 2010: 546 US 2010: 172	900MM
		rhBMPs : 5000	WW 2010: 865 US 2010: 826	4.5B
Chronic back pain: Discogenic	10MM/yr	Fusion/TDR: \$25K-50K <u>2000-5000 for Biologic?</u>	High scenario	20-50B

1: Kalomara information: Orthopedic biomaterials 2011, Millennium research group: US market for orthopedic biomaterials 2009

2: Based on Cassidy, Spine 2005, Hestbaek, E Spine J. 2003

Tailoring effective stem cell therapies for the aging spine



Content



Opportunity/Unmet need → The Challenge

Our Technologies → diverse osteochondral progenitors, biomaterials delivery

Our Strategy → Tailoring Our Approach

PureStem®: The most diversified stem cell portfolio for orthopedics

Combines broad applicability of ESCs with defined targeted utility of adult MSCs

Enhanced attributes

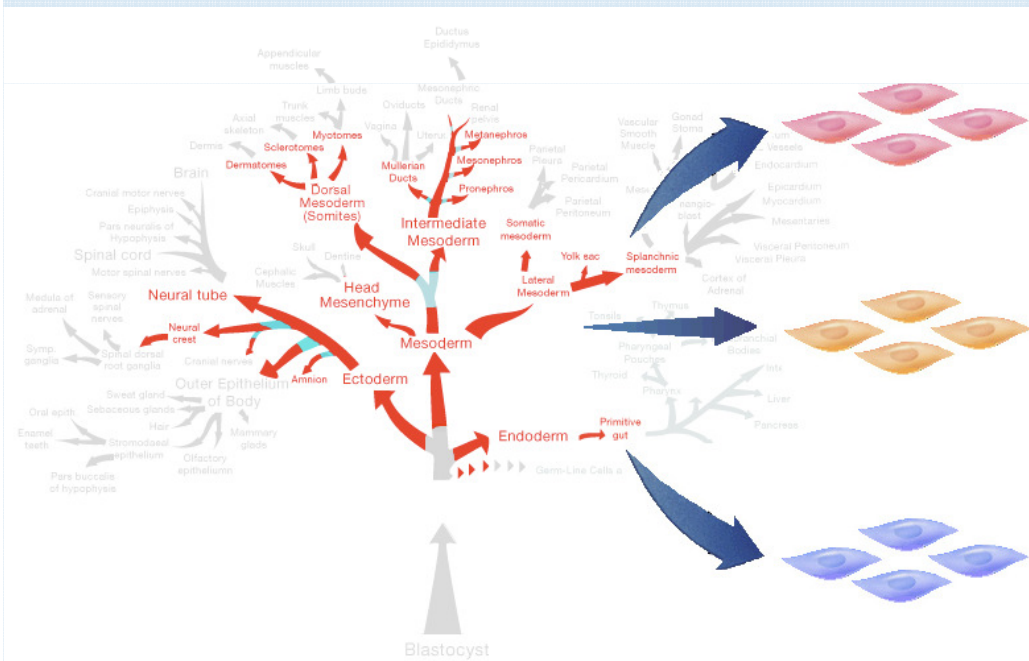
→ Diversity

→ Purity

→ Identity

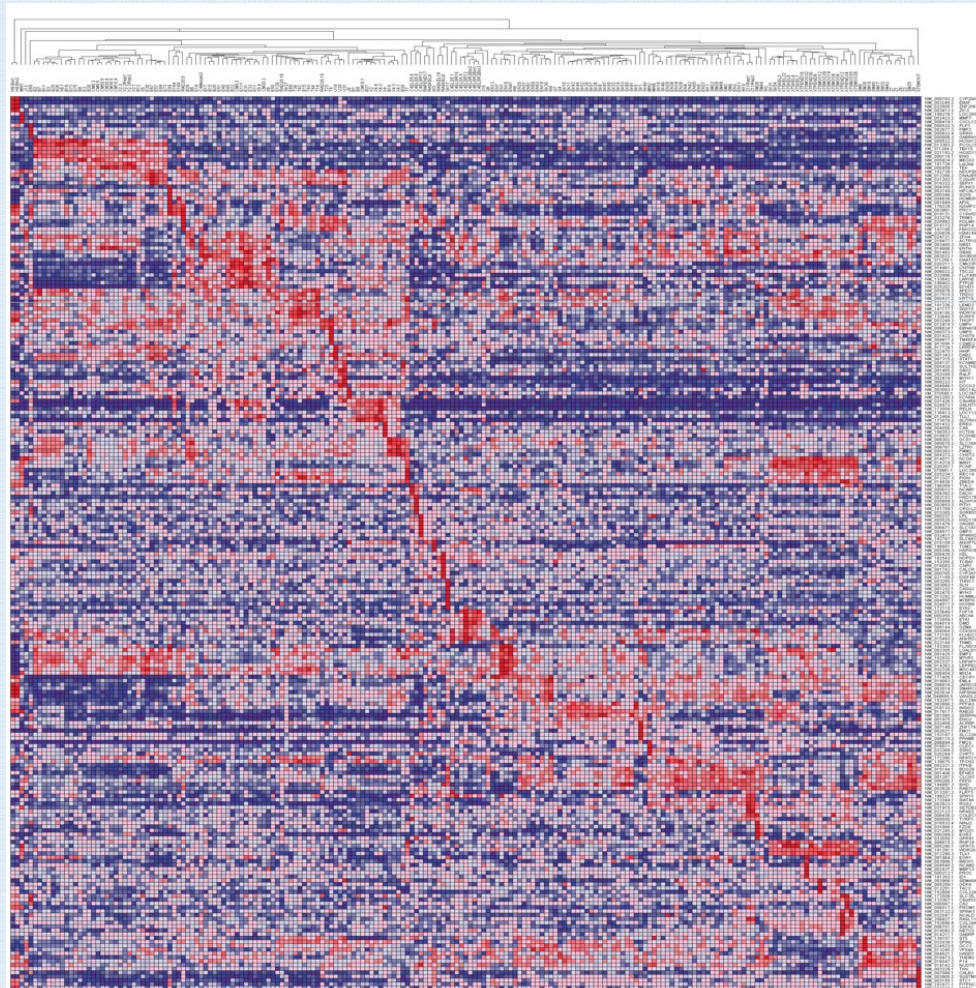
→ Potency

→ Scalability



PureStem[®]: Clonally derived progenitors from embryonic origin

Broad stem cell therapy portfolio



Enhanced attributes

- Diversity
>200 distinct lines
- Purity
- Identity
- Potency
- Scalability

PureStem®: Clonally derived progenitors from embryonic origin

Broad stem cell therapy portfolio

Enhanced attributes

→ Diversity

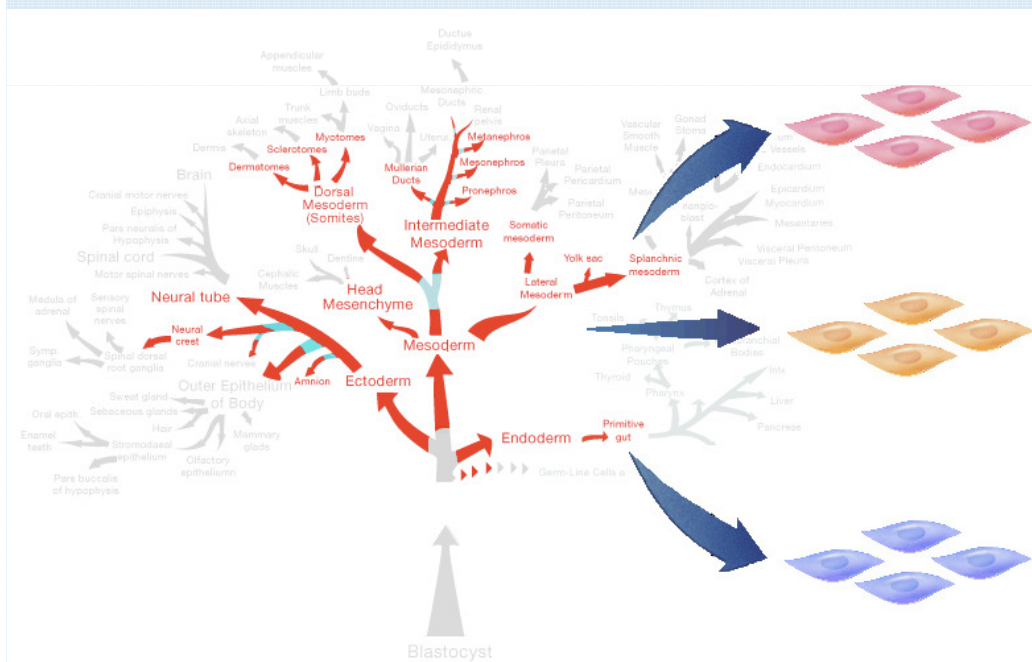
→ Purity

Clonally derived

→ Identity

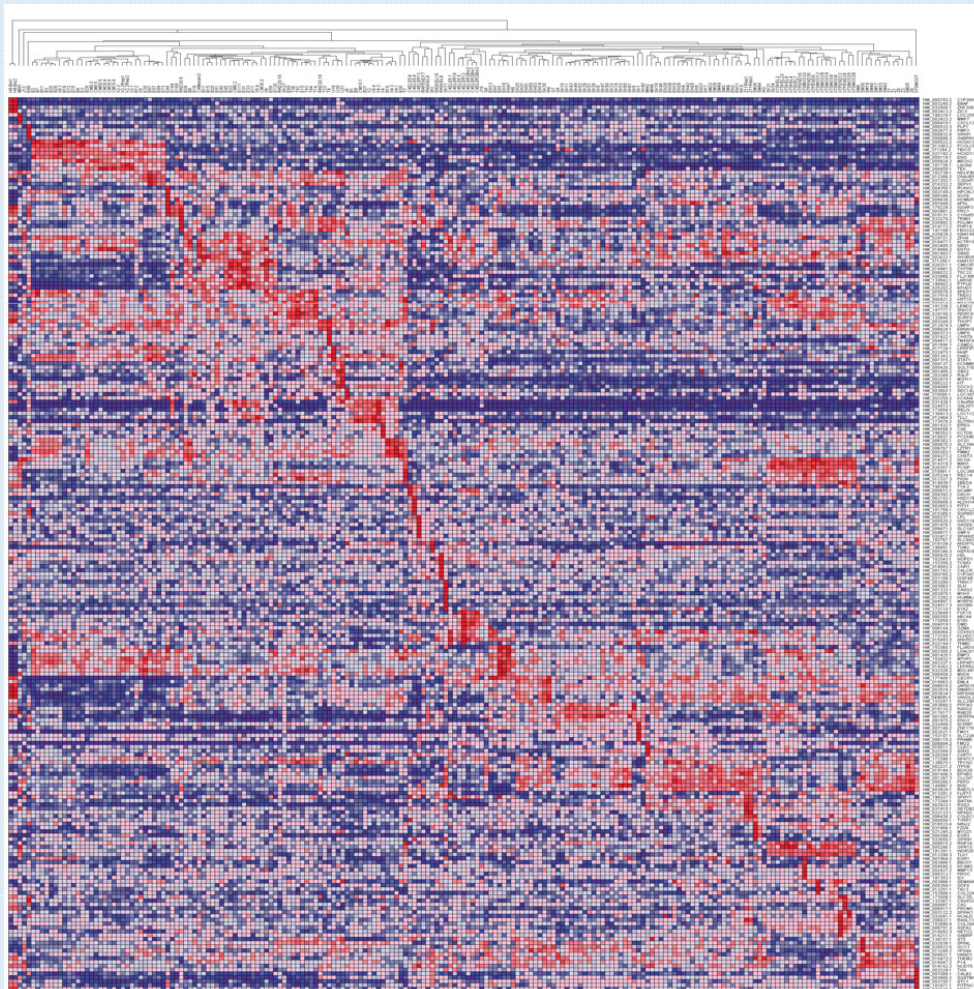
→ Potency

→ Scalability



PureStem[®]: Clonally derived progenitors from embryonic origin

Broad stem cell therapy portfolio

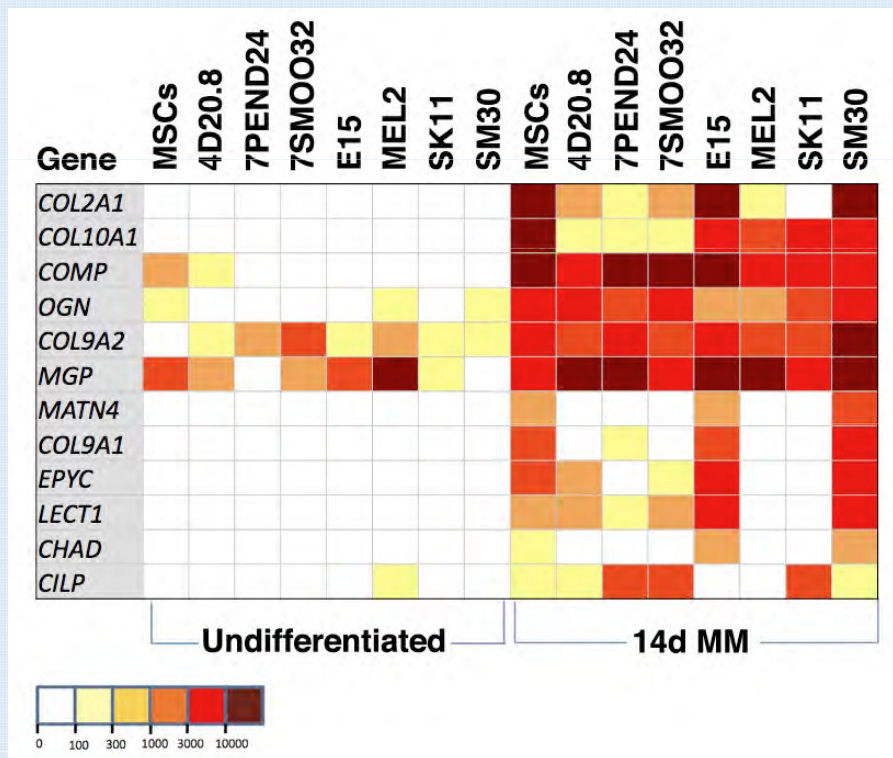


Enhanced attributes

- Diversity
- Purity
- Identity
All micro arrayed
- Potency
- Scalability

PureStem[®]: Clonally derived progenitors from embryonic origin

Broad stem cell therapy portfolio



→ Diversity

→ Purity

→ Identity

→ Potency

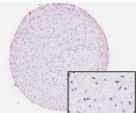
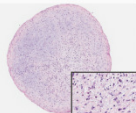
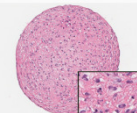
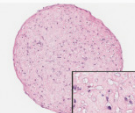
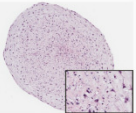
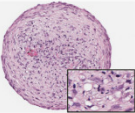
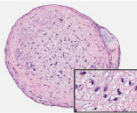
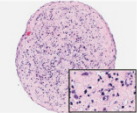
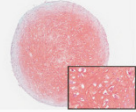
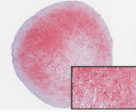
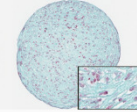
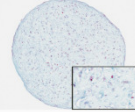
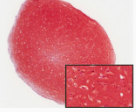
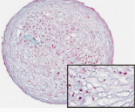
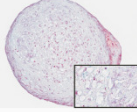
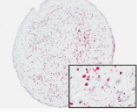
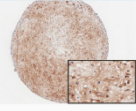
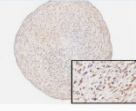
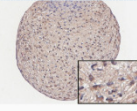
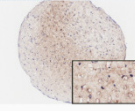
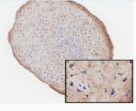
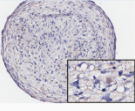
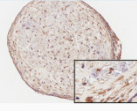
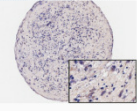
Selectable attributes

→ Scalability

Selectable Attributes and Diversity of Options

> 40 osteochondral progenitor PureStem®



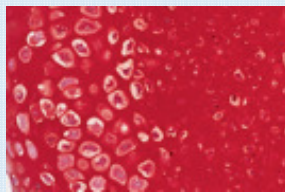
	MSCs	4D20.8	7PEND24	7SMO032	E15	MEL2	SK11	SM30
H&E								
Saf-O								
COL2								
	Restricted attributes	Optimized art. cartilage			Optimized disc cartilage		Optimized bone	

PureStem® Selectable Attributes

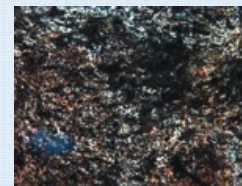
- MSCs = Restricted/no options
- PureStem® = multiple options for each indication

Tissue induction and Tissue regeneration

Additional selectable attributes for PureStem® lines

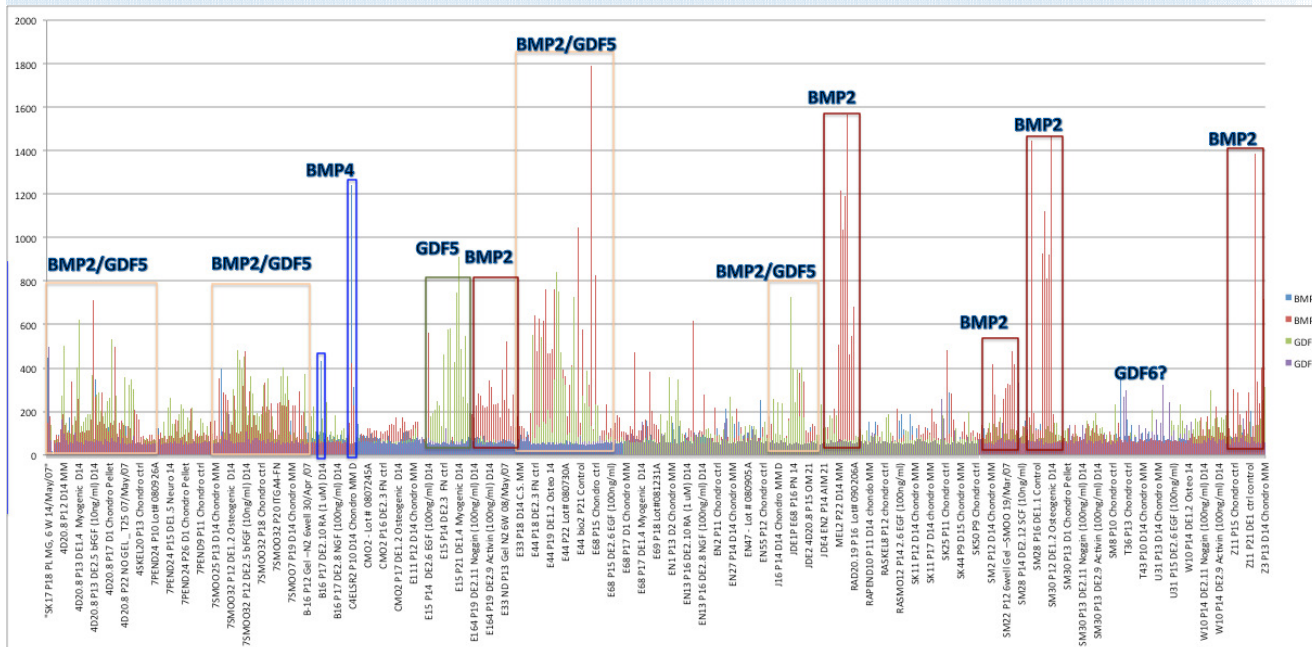


cartilage



bone

- Chondrogenic
- Osteogenic
- Cartilage induction
- Disc induction
- Bone induction



PureStem[®]: Clonally derived progenitors from embryonic origin

Broad stem cell therapy portfolio

Enhanced attributes

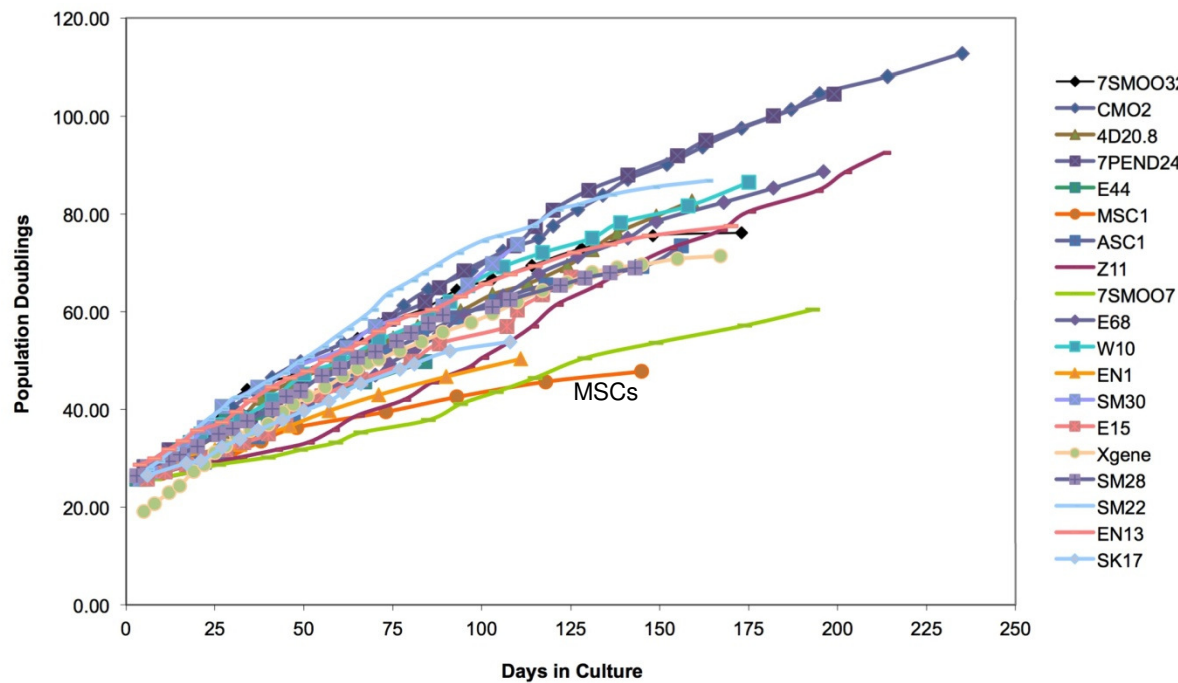
→ Diversity

→ Purity

→ Identity

→ Potency

→ Scalability
To > 100 pop. doublings



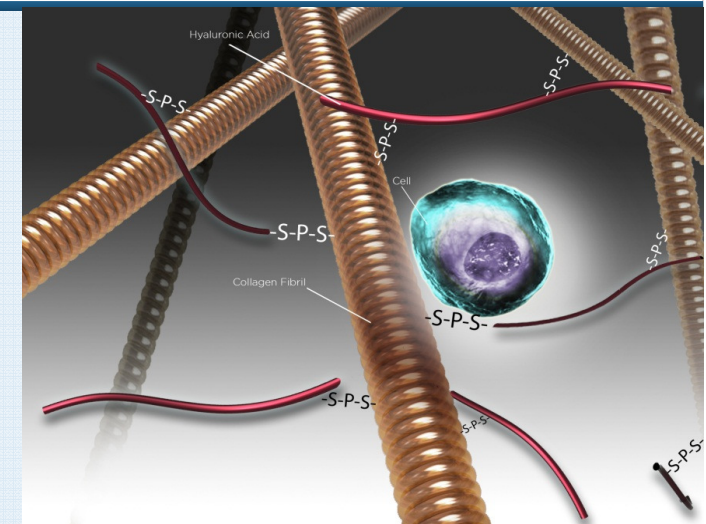
HyStem[®] Cell Delivery System

BIO TIME

Dynamic hydrogel enabling biomaterials

ORTHOCYTE CORPORATION

- Derived from naturally occurring biomolecules: Hyaluronic acid and collagen



- In situ gelling cell delivery system
 - Targeted delivery
 - Minimally invasive approach



Tailoring effective stem cell therapies for the aging spine

Content

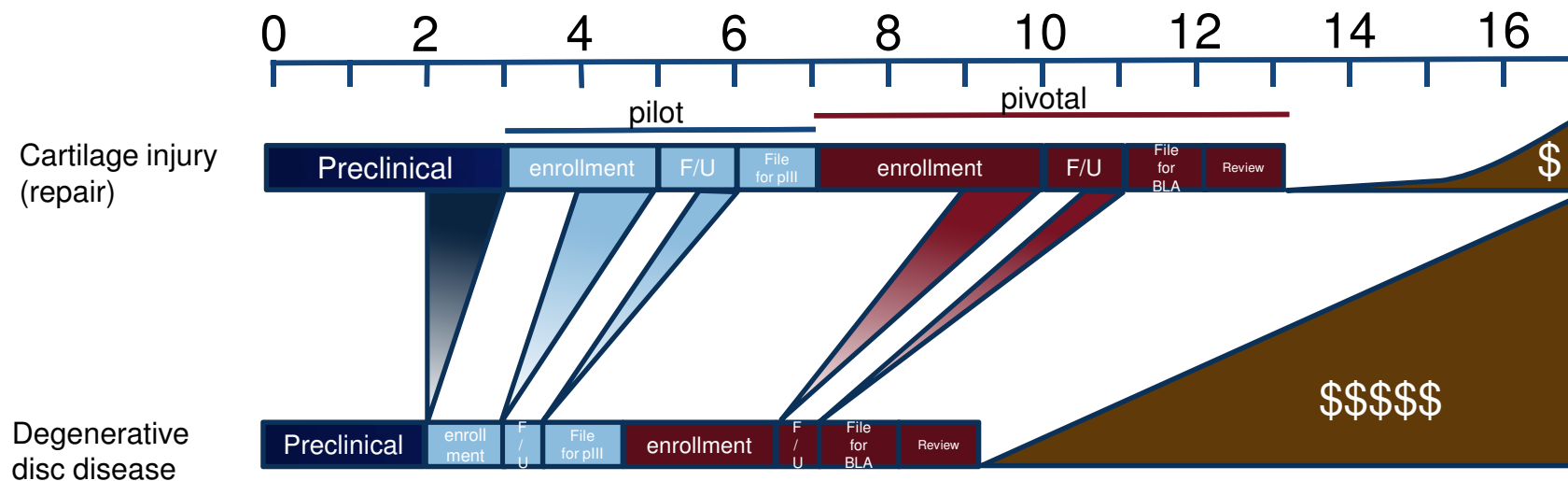
Opportunity/Unmet need → The Challenge

Our Technologies → diverse osteochondral progenitors, biomaterials delivery

Our Strategy → Tailoring Our Approach

Initial focus on back pain

	Preclinical		Clinical		Addressable patient pool	Health economics benefit
Cartilage injury (repair)	Goat/Horse	12 month follow up	Pain/function/structural	1 year	50000-300000	>3-5 years?
Degenerative disc disease	Rabbit	3 month follow up	Pain/function	6 months	1MM-10MM	1 year?



DDD = Cartilage Development - 4yr = 4 years faster growing income

The Therapeutic Opportunity

Early-stage target → disc repair

Late-stage target → bone induction



Insult/inflammation

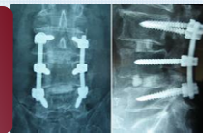
Matrix break down

Cell/tissue loss

Structural collapse



LARGE THERAPEUTIC GAP



Disease Progression

Early Stage



Late Stage

Orthocyte's Broad Opportunity

Therapeutic target

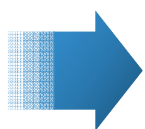
Balancing risk: near- and long-term opportunities in large markets

Near term: 12-24 months

DEVICES



HyStem



+ Ceramics



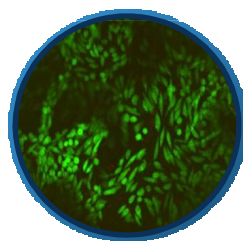
510 K Bone Graft

Bone repair

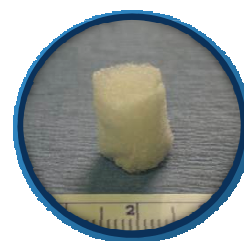
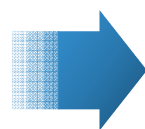
Long term: 3y to IND



BIOLOGICS



+ PureStem Bone



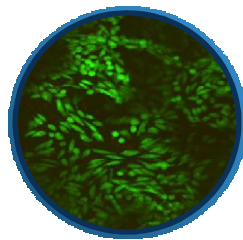
BLA Bioactive Spinal Fusion

Bone Induction

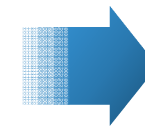
Long term: 3y to IND



BIOLOGICS



+ PureStem Disc

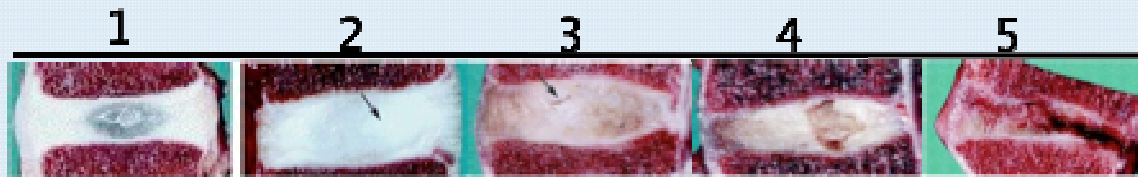


BLA Bioactive disc repair

Disc Repair

The therapeutic opportunity

PureStem® and HyStem® product pipeline addresses entire care continuum for disc degeneration



Slows down degradation

Induces residing cells

Replaces lost cells

Induces bone

Preserve/repair disc

Bone repair

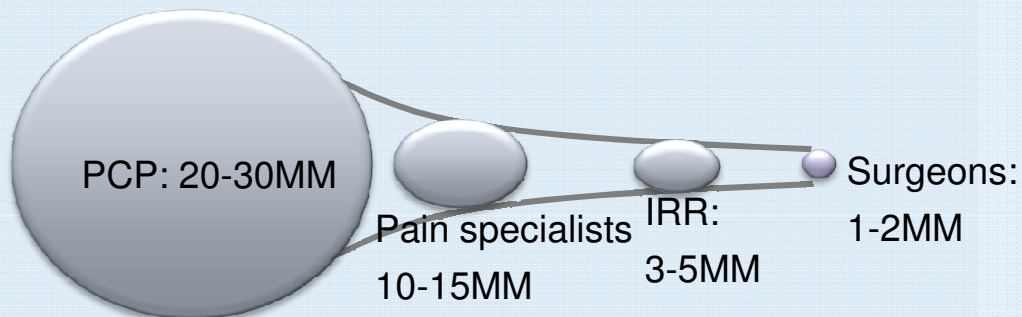
PureStem1 MMP inhibitors

PureStem2 Chondrogenic

PureStem3 Disc Regeneration

HyStem/PureStem4 Bone induction

Orthocyte's Broad Opportunity

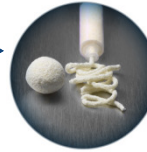


OrthoCyte Development Plan: balancing and sharing risk

1: Bone graft augmentation-Spine fusion/Trauma



FDA 510 (k)
CE



Sustained product launches: \$\$\$

2: Bone induction-Spine fusion/Trauma



FDA BLA

Pivotal clinical

3: Disc nucleus Augmentation



Pilot clinical

4: Disc repair



IND Enabling

2013

2014

2015

2016

2017

2018

2021

2022

OrthoCyte investment opportunity: De-risking regenerative medicine for Orthopedics



1. Best in class regenerative medicine portfolio for orthopedics: >40 distinct osteochondro-progenitor lines + Cell delivery biomaterial
2. Broad range of addressable therapeutic opportunities
3. Regenerative Medicine balanced risk: 510K → BLA

Most comprehensive orthobiologics portfolio to address largest orthopedic markets:
Entire chronic back pain care continuum

Balancing long-term blockbuster opportunities
with tangible near-term revenue-generating pipeline:

**ORTHOCYTE IS THE MOST PROMISING ORTHOBIOLOGICS
OPPORTUNITY TODAY**



Thank You!

Francois Binette

Vice President Research and Business
Development

fbINETTE@biotimemail.com

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