Intramuscular Injection of Stem Cell-Derived Secretomes for Treatment of Muscle Atrophy Related to Knee Osteoarthritis: A Phase 1/2A Clinical Trial

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Study performed at University of California, Irvine

Disclosures

DW

- Research Support: Immunis, Vericel
- Consultant: Stryker, Newclip, Arthrex, Vericel, Cartilage Inc
- Stock: Cartilage Inc, Overture Resurfacing
- Committee Member: AOSSM, AAOS, ICRS, WOA

GN, EC, NB, HK

- Employees of Immunis

Introduction

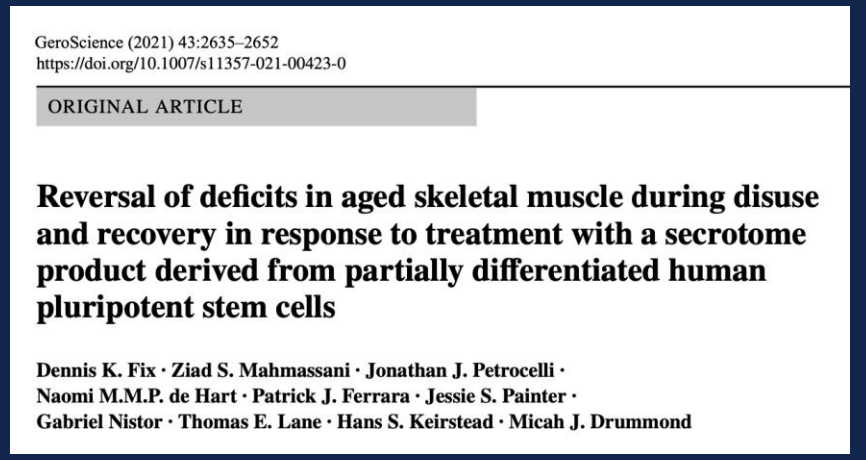
- **Quadriceps muscle weakness has been shown to correlate with symptoms of pain and dysfunction attributed to knee osteoarthritis (OA).[1,2]**

- **IMMUNA (Immunis, Inc) is a secretome product derived from partially differentiated pluripotent stem cells that contains a multitude of pro-myogenic factors involved in immunomodulation, cytoskeleton remodeling, and growth factor-mediated cellular signaling**
  - Follistatin and Follistatin-Like 1 are inhibitors of Myostatin and Activin A, which limit skeletal muscle mass and reduce the ability of muscle to regenerate in response to injury
  - Fetuin A is a generic TGFb suppressor and immune modulator that is likely effective for increasing muscle mass and strength

Multiplex ELISA

Target	SA100680	SA100681	SA100682
Fetuin A	582,856.5	672,420.1	304,696.1
OPN	129,872.9	136,029.2	155,570.4
IGFBP-4	125,591.3	133,417.6	109,953.8
MMP-1	97,830.1	84,864.0	100,381.9
TSP-1	86,652.9	72,765.4	80,479.5
GROa / CXCL1	77,071.2	66,823.6	43,306.0
Follistatin	62,432.2	36,391.7	49,457.3
MMP-10	60,700.1	43,130.1	44,950.7
Follistatin-like 1	25,257.6	28,838.1	24,294.5
bIG-H3	19,167.0	23,895.6	20,269.9
hCGb	16,033.8	74,766.7	12,884.2
RGM-B	11,779.9	10,268.8	9,075.3
VEGF	4,614.6	4,078.3	3,841.7
Cripto-1	4,479.1	4,495.9	4,332.0
HGF	3,422.9	2,425.4	1,146.4
BMP-5	3,035.1	6,020.6	6,440.0
bFGF	2,267.4	2,135.2	2,057.9
IGF-2	2,234.4	1,740.0	1,995.1
PDGF-AA	2,055.4	2,122.1	2,101.9
FGF-19	1,417.0	1,691.4	1,195.8
WISP-1	954.9	1,897.6	1,354.1

Introduction



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ORIGINAL ARTICLE

Reversal of deficits in aged skeletal muscle during disuse and recovery in response to treatment with a secrotome product derived from partially differentiated human pluripotent stem cells

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- **IND-Enabling efficacy studies[3] confirmed that IMMUNA:**
  - Prevents age- and disuse-associated decrease in muscle mass, strength, and fiber cross-sectional area
  - Prevents age- and disuse-associated increase in muscle fibrosis
  - Increased rodent muscle cell growth
  - Increased human muscle myotube area and myonuclear fusion in a dose-dependent manner

- **Clinical Rationale: Knee OA → muscle atrophy → worsening knee pain and dysfunction**

Phase 1/2A clinical trial

- **Primary objective: To evaluate the safety of IMMUNA treatment in study participants with muscle atrophy related to knee OA**

- **Secondary objectives:**
  - To evaluate the safety and tolerability after 4 wks of treatment with IMMUNA in study participants with muscle atrophy related to knee OA
  - To evaluate stiffness and physical functioning of the knee joint after 4 wks of treatment with IMMUNA in study participants with muscle atrophy related to knee OA

Methods – Inclusion & Exclusion Criteria

Inclusion criteria

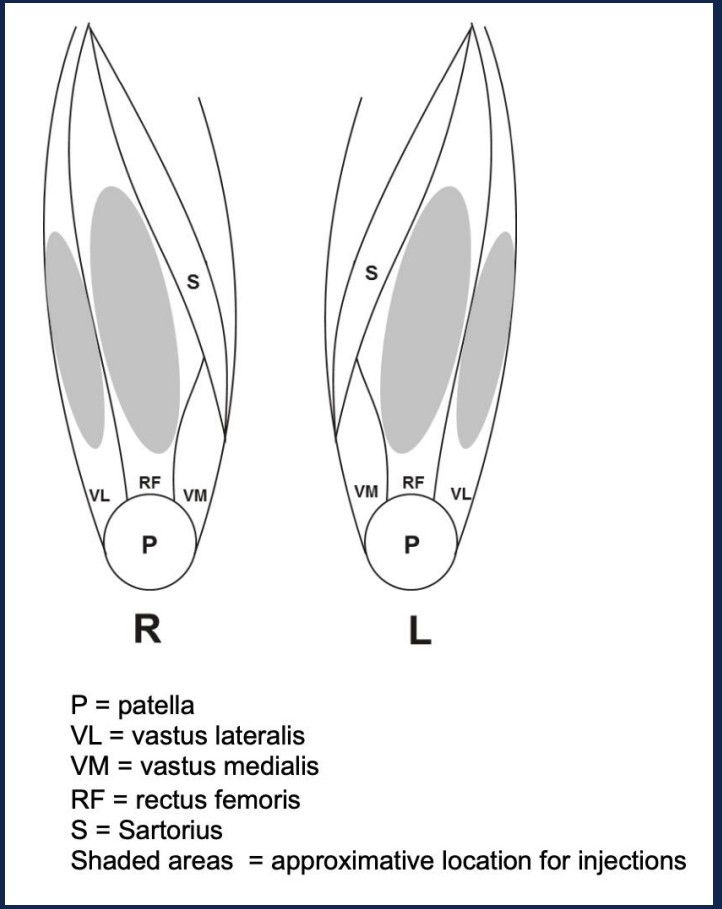
- ☐ Age 50 to 75 years at the time of signing the informed consent.
- ☐ Body mass index (BMI) of < 40kg/m2.
- ☐ Mild to moderate osteoarthritis (Kellgren-Lawrence [KL] grade 1 to 3) on affected knee.
- ☐ Able to ambulate >50 feet unassisted.
- ☐ Quadriceps weakness (<7.5 N/kg/m^2).
- ☐ Undergone and failed at least one 3-month or longer treatment regimen (ie, activity modification, weight loss, physical therapy, anti-inflammatory medications, or injection therapy) within 2 years prior to the Screening visit.

Exclusion criteria

- ☐ Moderate to severe OA (defined as KL grade >3) on contralateral knee.
- ☐ Prior total knee arthroplasty on affected limb.
- ☐ Known hypersensitivity to any components of IMMUNA .
- ☐ Current or past history (within 10 years) of smoking.
- ☐ Chronic alcohol or drug abuse within the previous 3 months as judged by an Investigator.
- ☐ Current or past history of malignancy (10y) excluding non-melanoma skin cancer.
- ☐ Uncontrolled co-morbidities including diabetes (hemoglobin A1c level >7.0), Hypertension (resting heart rate >100 bpm, systolic blood pressure >170 mmHg, or diastolic blood pressure >90 mmHg), Cardiovascular disease, Asthma, or COPD.
- ☐ Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
- ☐ Neurological, Vascular, or Cardiac condition that limits function, or in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
- ☐ Use of systemic oral or intravenous steroids within 6 months of Screening visit.
- ☐ Received injection of intra-articular cortisone or visco-supplementation product (eg, Synvisc®) within 3 months prior to first IMMUNA dose.
- ☐ Use of narcotic pain medications or synthetic opioids (eg, tramadol) within 28 days prior to first IMMUNA dose.
- ☐ A change in medication to manage co-morbid conditions within 1 month of Screening visit.
- ☐ Administration of a live, attenuated vaccine[1] within 28 days of first IMMUNA dose, or anticipation that such vaccine will be required during the study.
- ☐ Use of any investigational drug within 28 days or 5 half-lives (if known), whichever is longer, prior to first IMMUNA dose.

Methods - Administration

- Total of 8 intramuscular injections (25G needle) over a 4-wk period (2 injections/week)
- Alternating injection sites between the ipsilateral rectus femoris and vastus lateralis
- Site injection and dose recorded on Case Report Form diagram (right)



Methods

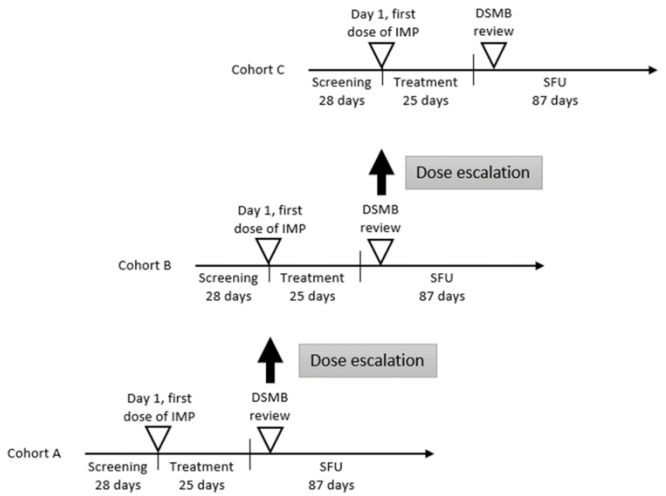
Trial Schema

Phase 1/2A 3+3 design
Dose escalation
DLT/AE

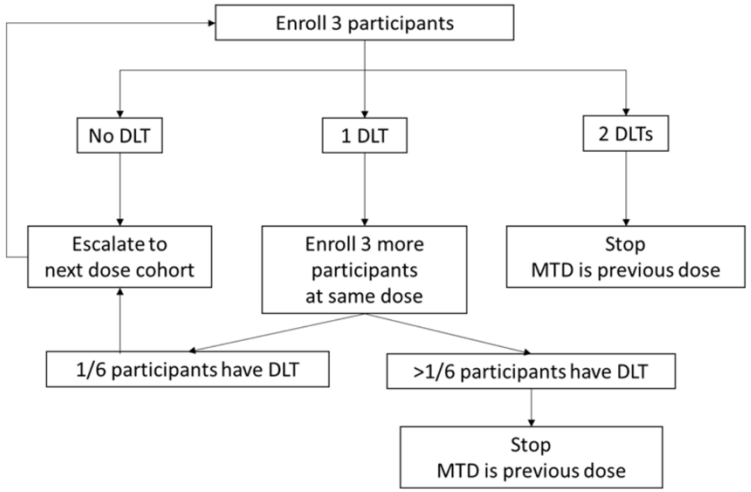
3 to 6 participants per cohort:

- Cohort A: 225µg (0.5 mL)
- Cohort B: 450 µg (1.0 mL)
- Cohort C: 900 µg (2 mL)

- **Screening Period:**
  4 weeks, ending on Day -1
- **Treatment Period:**
  4 weeks (Day 1 through Day 25)
- **SFU Period:**
  3 months (Day 26 through Day 112)



Dose Escalation Decision Making



DLT (Dose Limiting Toxicity) is defined as any AE related to IMMUNA :

- Grade 2 (Moderate) unresolved within 48 hours post-injection, Or
- Any Grade 3, 4, or 5 (Severe, Life-threatening, or Fatal) during any time of treatment

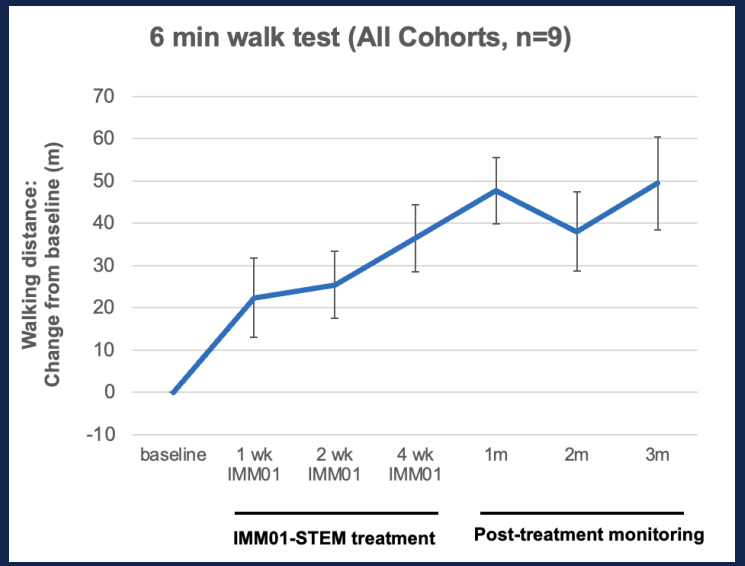
Results

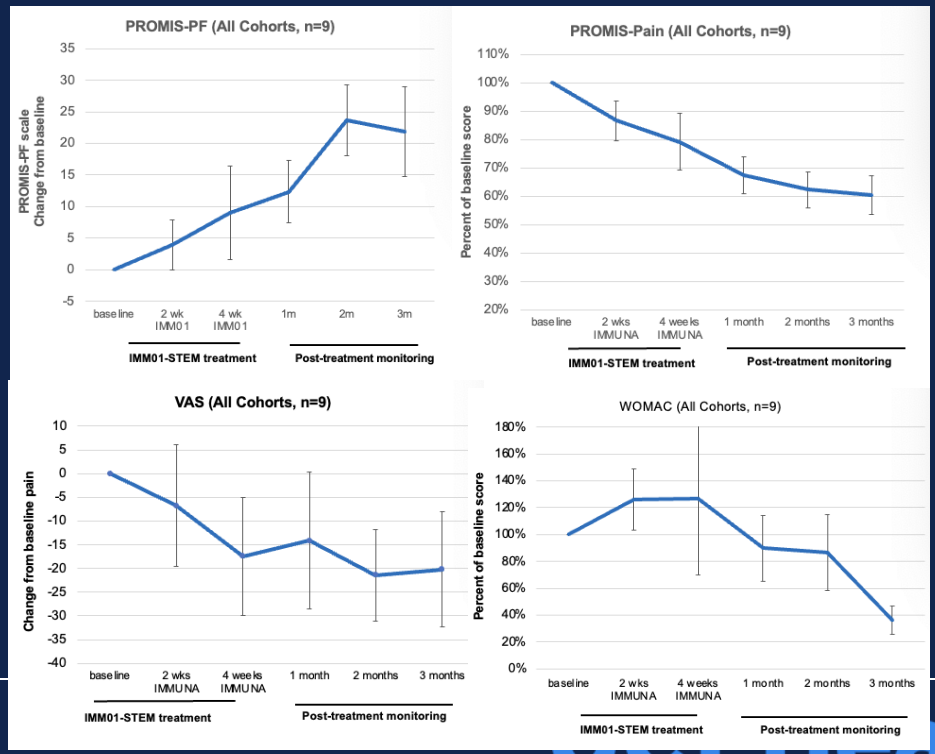
- **No serious AEs**
- **There were 9 adverse events reported**
  - 7 AEs (grade 1) were injection-site soreness/bruising or exacerbation of knee OA symptoms.
  - 1 AE was bloody emesis 3 months post-IMMUNA treatment in a patient with a history of gastric sleeve. 1 AE was asymptomatic hypokalemia likely related to side effect of a home medication. Both AEs were deemed unlikely related to IMMUNA treatment.

Characteristics		Cohort A	Cohort B	Cohort C	Trial total
Total Enrolled:		3	3	3	9
Age	Ages	73, 74, 59	70, 70, 74	70, 58, 60	Sum = 608
	Mean age	69	71	63	68
	Minimum age	59	70	58	58
	Maximum age	74	74	70	74
Gender	Male	0	1	1	2
	Female	3	2	2	7
Race	American Indian/Alaska Native	-	-	-	0
	Asian	-	-	1	1
	Black or African American	-	-	-	0
	Native Hawaiian or Other Pacific Islander	-	-	-	0
	White	2	3	2	7
	More than one race	-	-	-	0
	Unknown or not reported	1	-	-	1
KL Grade	2	2	2	3	7
	3	1	1	0	2

Results

- Mean quadriceps volumes and strength increased by 1.6% and 10.5%, respectively, in the treated leg
- Subjects showed clinically meaningful improvements in walking distance and speed on the 6-minute walk test ($p<0.005$)
- Patients reported clinically significant improvements in PROMIS-PF, PROMIS-pain, VAS, and WOMAC scores up to 3 months post-treatment
- No appreciable differences in patient outcomes were observed among the 3 doses tested





Discussion

- Results of this phase 1/2a study suggest that intramuscular IMMUNA injection treatment has a low rate of adverse reaction, warranting further study in a larger group of patients

- This initial cohort also showed early improvements in quadriceps strength, walking speed, and knee pain and function

- Clinical takeaway: This novel treatment represents a new paradigm for treating mild-to-moderate knee OA and may have applications for accelerating rehabilitation and reversing quadriceps atrophy after knee surgery

Thank You

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