Cellvation

A Majority-Owned Subsidiary of Fortress Biotech

January 2025

Investment Highlights

1. Novel Bioreactor for Enhancing Potency of Cellular Therapies
2. In Vitro & In Vivo Proof of Concept Established in Multiple Cell Types
3. Enhanced Potency Based on Established Matrices (↑PGO, ↑IDO, ↓TNFα, ↓Tcells)
4. Ability to Use 2-5X Fewer Cells Than Conventional (Clinical) Doses
5. Results in Proprietary (Off-the-Shelf) Cell Types with COGS Reduced by Up to 75%
6. Clinical Development in Rare Pediatric Disease & Other Inflammatory Conditions
7. Robust Global IP Portfolio Targeting $13B Global Cell Therapy Market

Cellvation

Overview

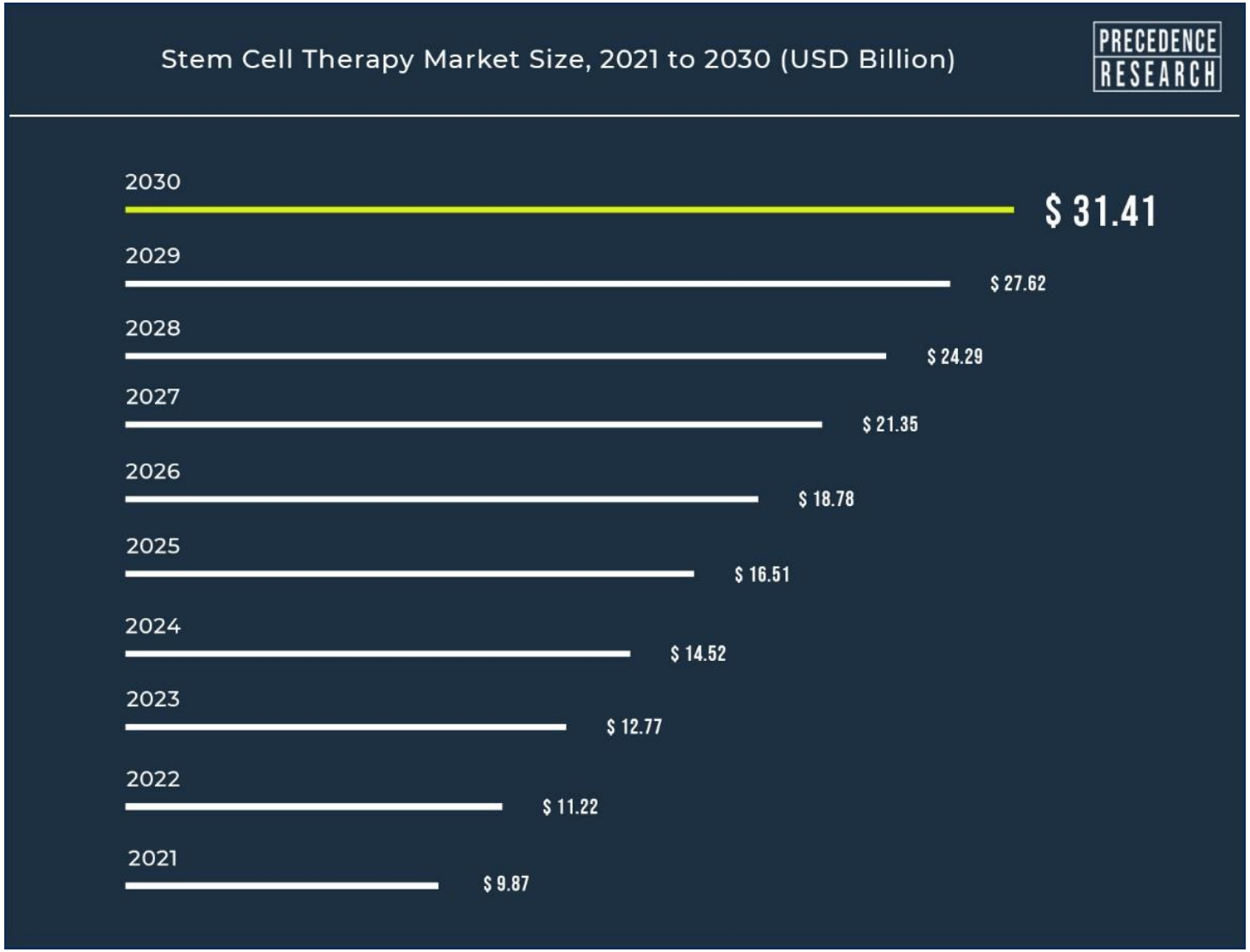
- **Novel Cellular Therapeutics for Inflammatory Conditions**
  - Based on Research from University of Texas Health Science Center (Houston)

- **<u>CEVA-D</u> (Mechano-Transduction Device)**
  - Shear Stress Up-Regulates Anti-Inflammatory Gene Programs
    - Ability to use fewer, more potent cells for *any* cell therapy
    - Substantially reduces COGS (vs. conventional MSCs)
  - Proof of Concept Completed *In Vitro*, *In Vivo*
    - Tested with Adipose, Amniotic Fluid, Bone Marrow
    - Mechano-Transduced Cells More Effective at Lower Dose

- **<u>CEVA101</u> (Next Gen Cell Product)**
  - "Off-the-Shelf" Mechano-Transduced MSCs
  - Upregulated Anti-Inflammatory Gene Programs
    - More Effective @ Substantially Lower Dose
  - Initial Indication(s): rGVHD, Crohn's, ARDS, CHF

Global Stem Cell Market

- Global Stem Cell Therapy Market Estimated at $11B in 2022, Expected to Reach $31.5B by 2030
- Pharma with Increased Interest In Stem Cell Therapy Based on Number and Size of Biotech Deals
- Expanding Clinical Applications in Cardiac, Neurological and Autoimmune Disorders
- Increased Adoption, Growing Investment in R&D, Favorable (Global) Regulatory Environment



Development Pipeline

CEVA-101 (Mechano-Transduced Cells)	Pre-Clinical	Phase 1	Phase 2	Phase 3	Market Potential
Steroid-Refractory Pediatric Graft Versus Host Disease					$2.7B Global Market in 2023
Crohn's Disease					$10B Global Market in 2023
Acute Respiratory Distress Syndrome					$3B Global Market in 2023
Congestive Heart Failure					$7B Global Market in 2023
Chronic Low Back Pain					$10B Global Market in 2023
Other Inflammatory Conditions					>$5B Potential

CEVA-D: Enhanced Potency Reduces COGS

- Enhanced potency based on established matrix
  - PGE2 production
  - IDO production
  - TNFα suppression
  - T cell proliferation suppression
- Increased potency translates into
  - Decreased COGS based on lower dosing requirements
  - Potential to expand into other indications
- Dosing of MSCs typically in the 2-10 million cells / kilogram range
- Data generated to-date demonstrates a 2-5X dose reduction
  - Using potency assays of PGE2 production and/or TFNα suppression
- COGS of ~US$20,000 per billion cells (or 10M cells per kilogram for 100 kilograms)
  - Based on estimated cost of cells from major supplier (Rooster Bio)
  - COGS could conservatively be reduced to $4,000 per dose

CEVA-101: Proprietary Cell Product
Initial Indication: Refractory Pediatric Acute GvHD

- Children with steroid-refractory acute graft versus host disease (SR-aGVHD)

- Treatment Options
  - Corticosteroids are first-line therapy for aGVHD
  - Only one approved treatment for disease refractory to steroids
  - No approved treatment in the US for children under 12 years old

- Burden of Illness
  - Acute GVHD is a life-threatening complication
  - Occurs in ~50% of patients receiving allogeneic bone marrow transplants (BMTs)
  - Acute GVHD primarily affects skin, GI tract, and liver
  - Steroid-refractory aGVHD is associated with mortality rates as high as 90%
  - Significant costs associated with extended hospital stays

- Market Opportunity
  - More than 30,000 allogeneic BMTs performed globally (>20K US/EU) annually, ~20% pediatric
  - >4,000 allogeneic BMTs in children and adolescents in US
  - >5,000 allogeneic BMTs in children and adolescents in China

CEVA-101: Proprietary Cell Product
Initial Indication: Refractory Pediatric Acute GvHD (cont.)

- Initial Clinical Design

- Inclusion Criteria
  - Male and female, ages of 2 months and 17 years
  - Confirmed aGVHD following BMT
  - Failed to respond to treatment with systemic corticosteroid therapy
  - Grades C and D aGVHD involving the skin, liver and/or gastrointestinal (GI) tract OR
  - Grade B aGVHD involving the liver and/or GI tract, with or without concomitant skin disease

- Number of Patients & Design
  - Single Arm (Open Label) Trial in ~20 patients
  - Initial Therapy: IV CEVA-101 at dose TBD twice per week, for each of four consecutive weeks
  - Continued Therapy: eligible participants to receive add'l once per week infusion for four weeks
    - Twice per week for four consecutive weeks if aGVHD persists or flares

- Endpoints
  - Primary Outcome: Overall Response Rate 28 Days after Initiation of Therapy
    - Complete Response: resolution of aGVHD in all organs
    - Partial Response: organ improvement of at least one stage w/o worsening of other organs
  - Secondary Outcome: Overall Survival at Day 100

Proprietary Bioreactor and Novel Cells
Key Data & Technical Details

CEVA-D & CEVA101: Key Publication

STEM CELLS®

REGENERATIVE MEDICINE

Biomechanical Forces Promote Immune Regulatory Function of Bone Marrow Mesenchymal Stromal Cells

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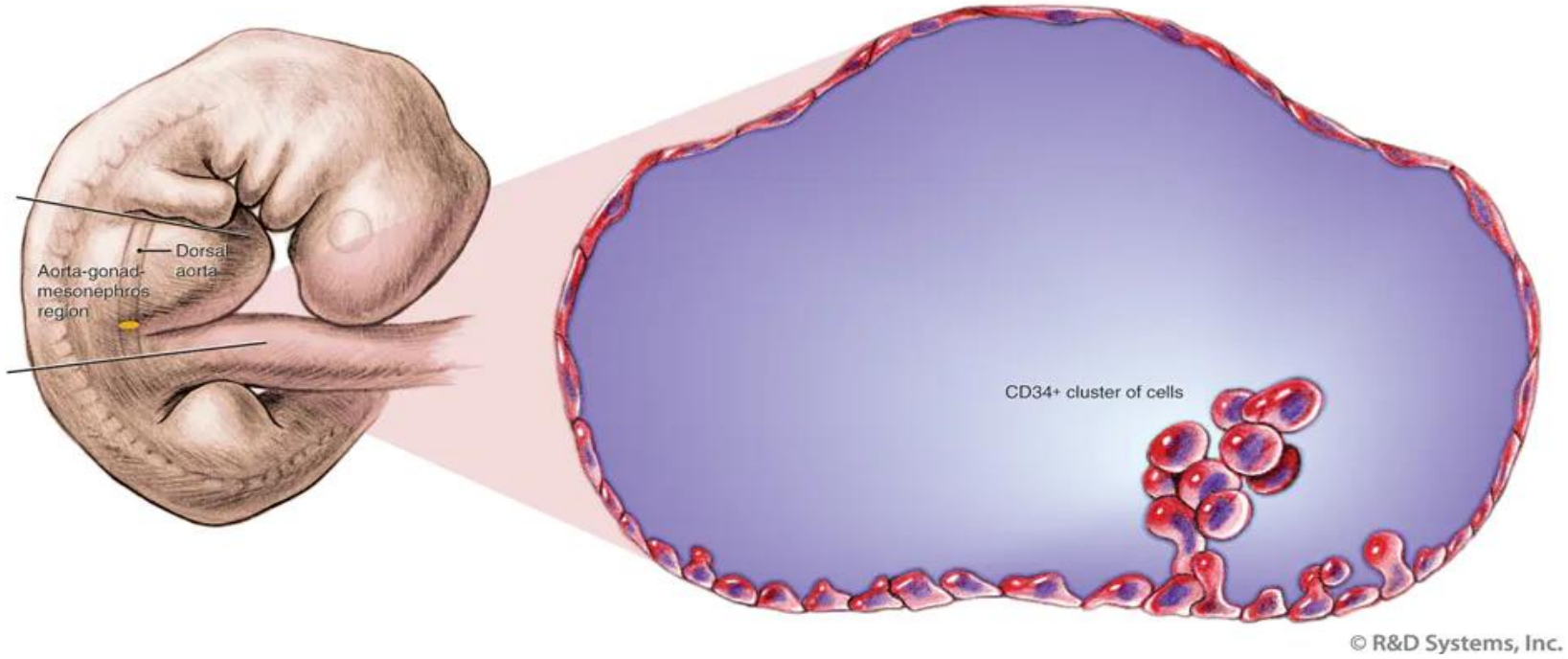
- Wall Shear Stress (WSS) Stimulates Anti-Inflammatory Mediators
  - Promotes Signaling To Suppress TNF-α
  - Improves Therapeutic Efficacy of MSCs in Rat Model of TBI

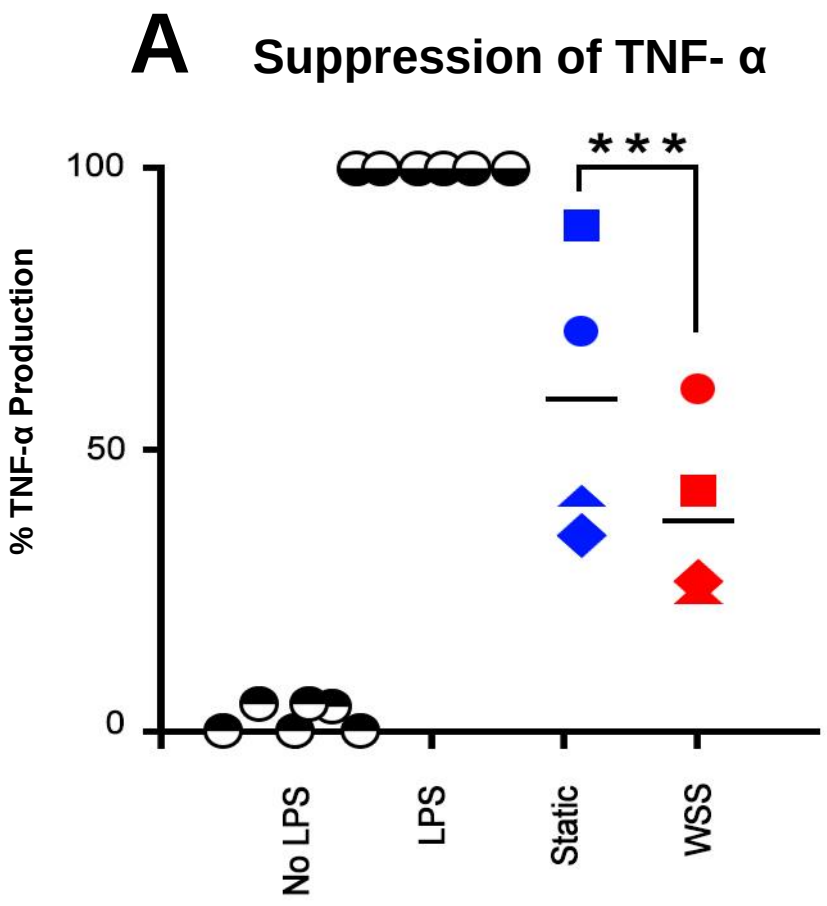
CEVA-D: Rationale

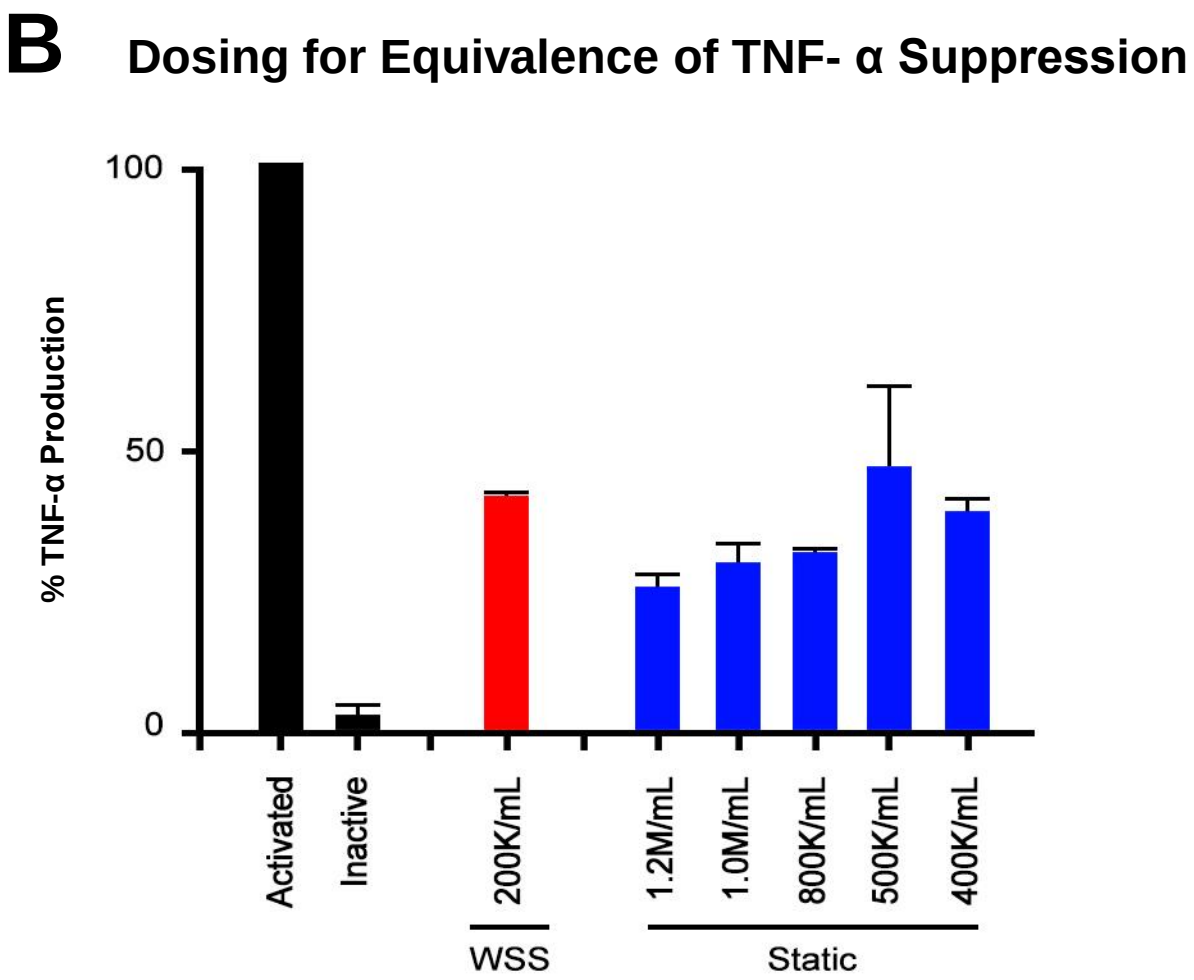
- Create a biological enhancement during the manufacturing process
- Stem cells start out in embryologic aorta-gonad-mesonephros
- Subjected to shear stress that up-regulates specific gene programs



Concept observed for HSCs in Daly Lab

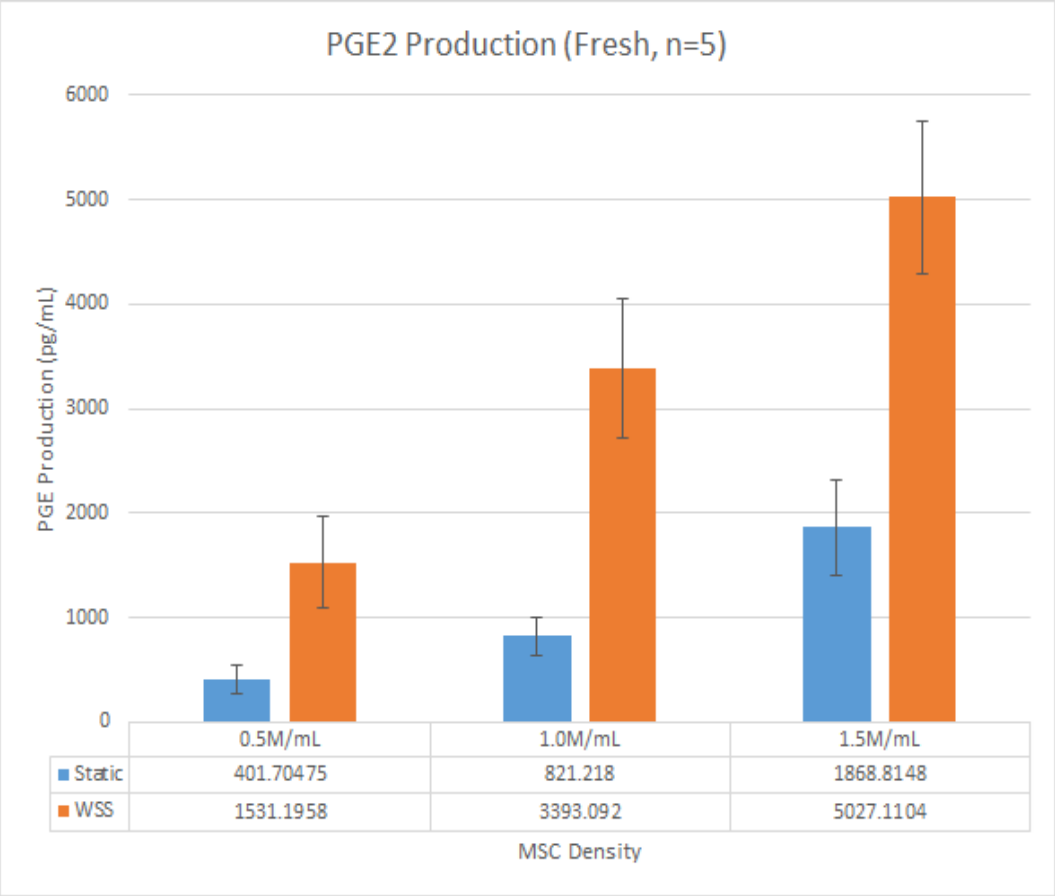
CEVA-D: Conditioned Cells More Effective @ Lower Dose (published)



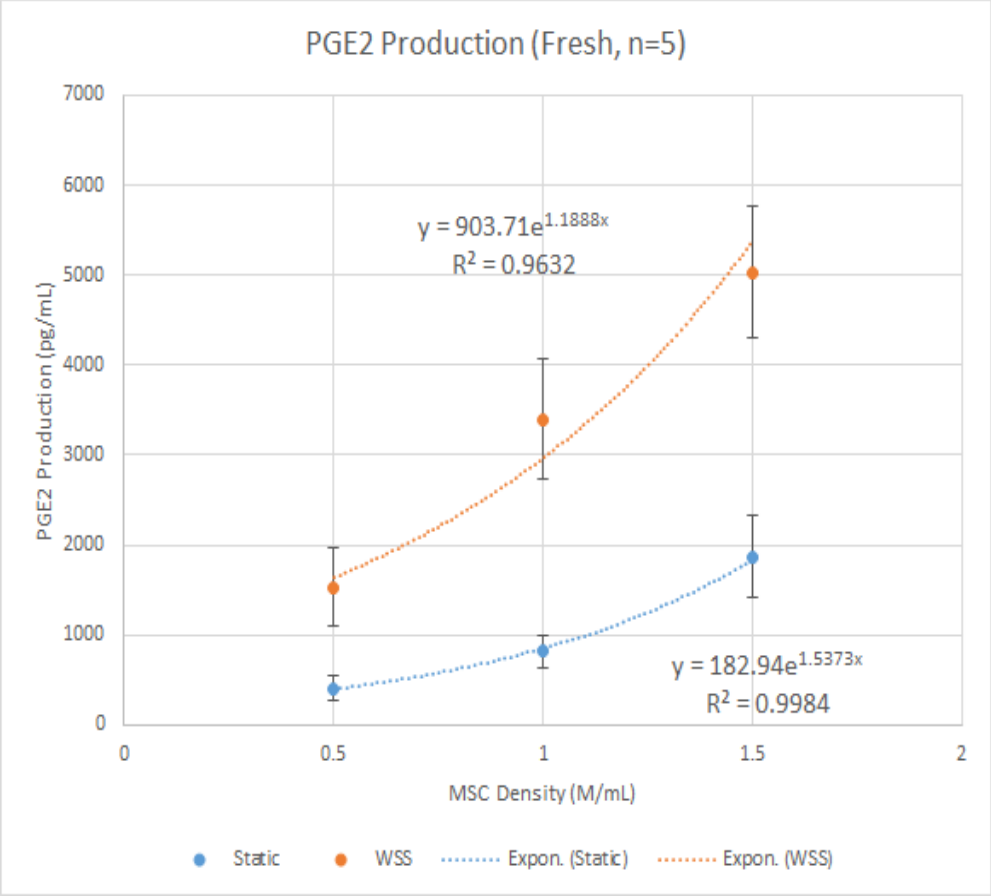


CEVA-D: Increases PGE_2 Production

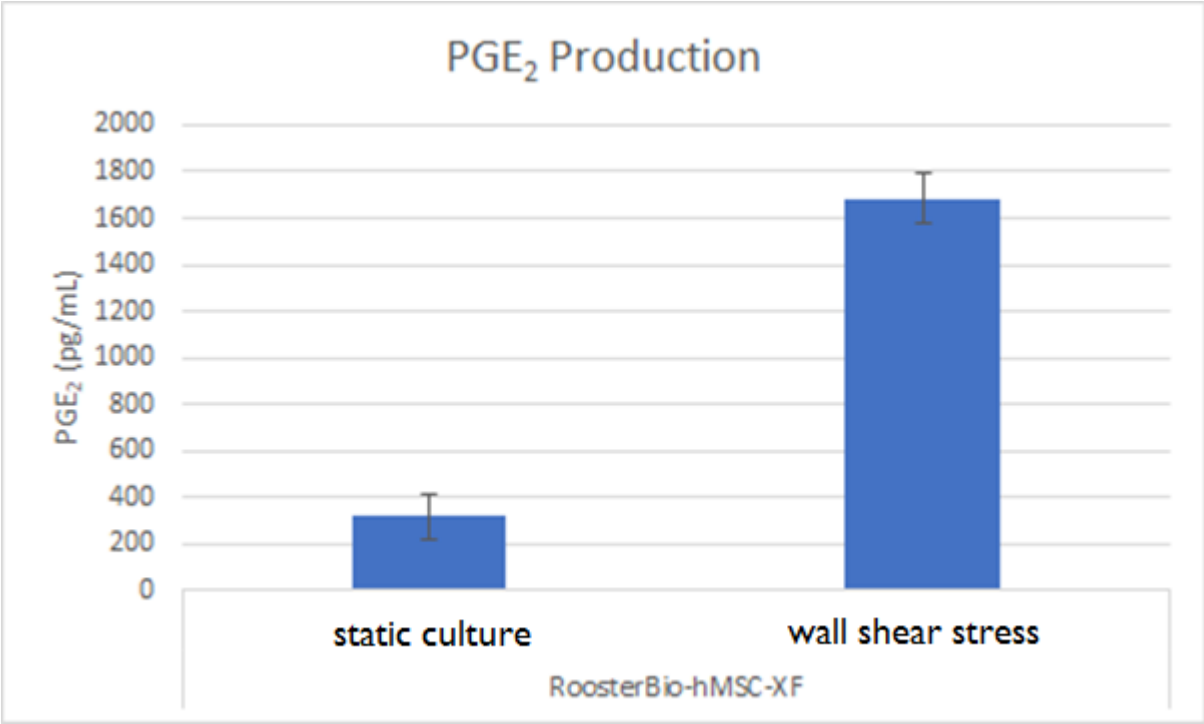
- 3x Increase in PGE_2 Production
  - Cells treated for three hours in CEVA-D bioreactor
  - PGE_2 : established marker for MSCs efficacy

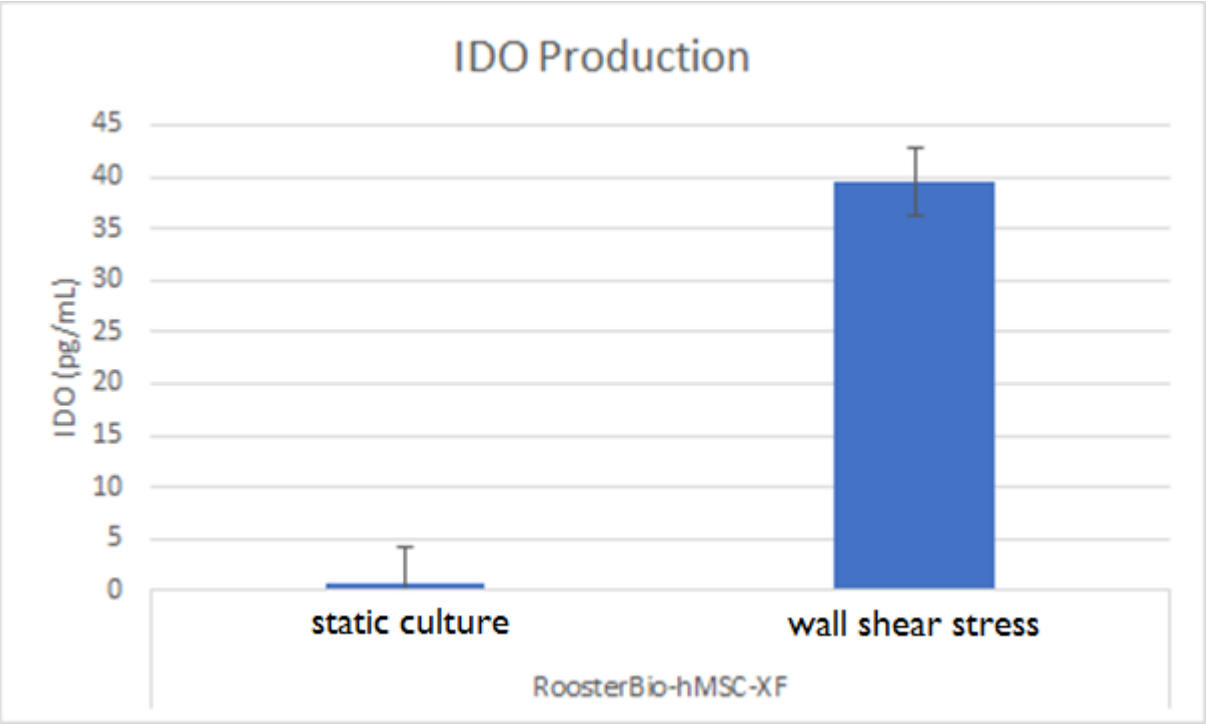


	0.5M/mL	1.0M/mL	1.5M/mL
Static	401.70475	821.218	1868.8148
WSS	1531.1958	3393.092	5027.1104



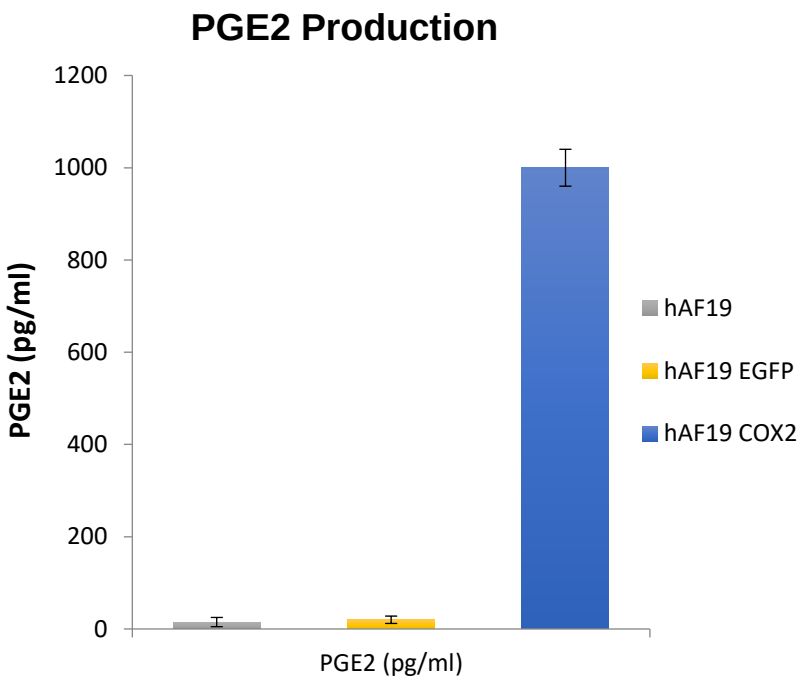
CEVA-D: Increases PGE_2 and IDO Production

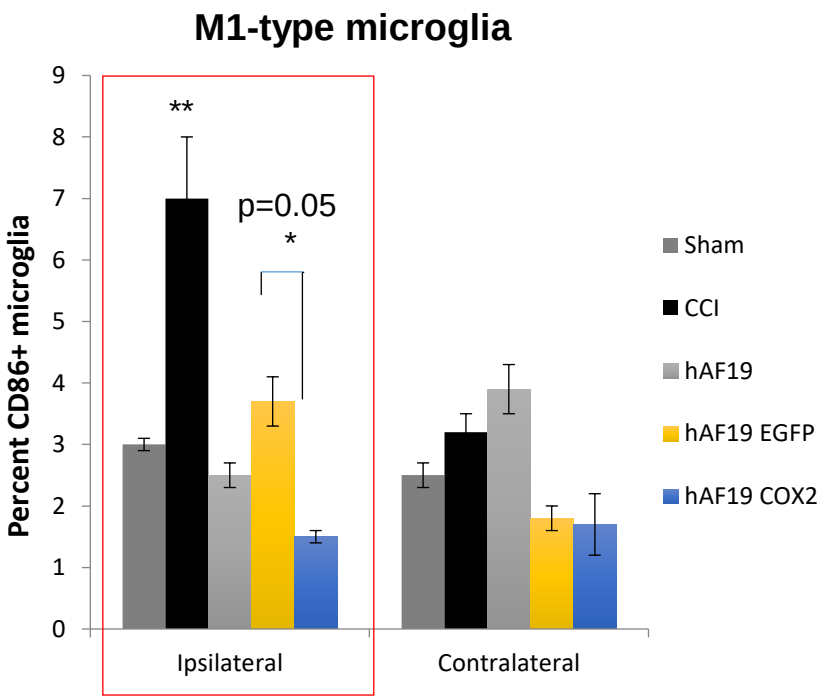




Importance of PGE_2 Expression

- Genetically engineered MSCs expressing PGE_2 better suppress microglial M1 polarization
- MAPCs suppress GVHD via PGE2 synthesis (Highfill et al, *Blood* 2009)





Kota et al. (2017) Stem Cells 35:1416-1430

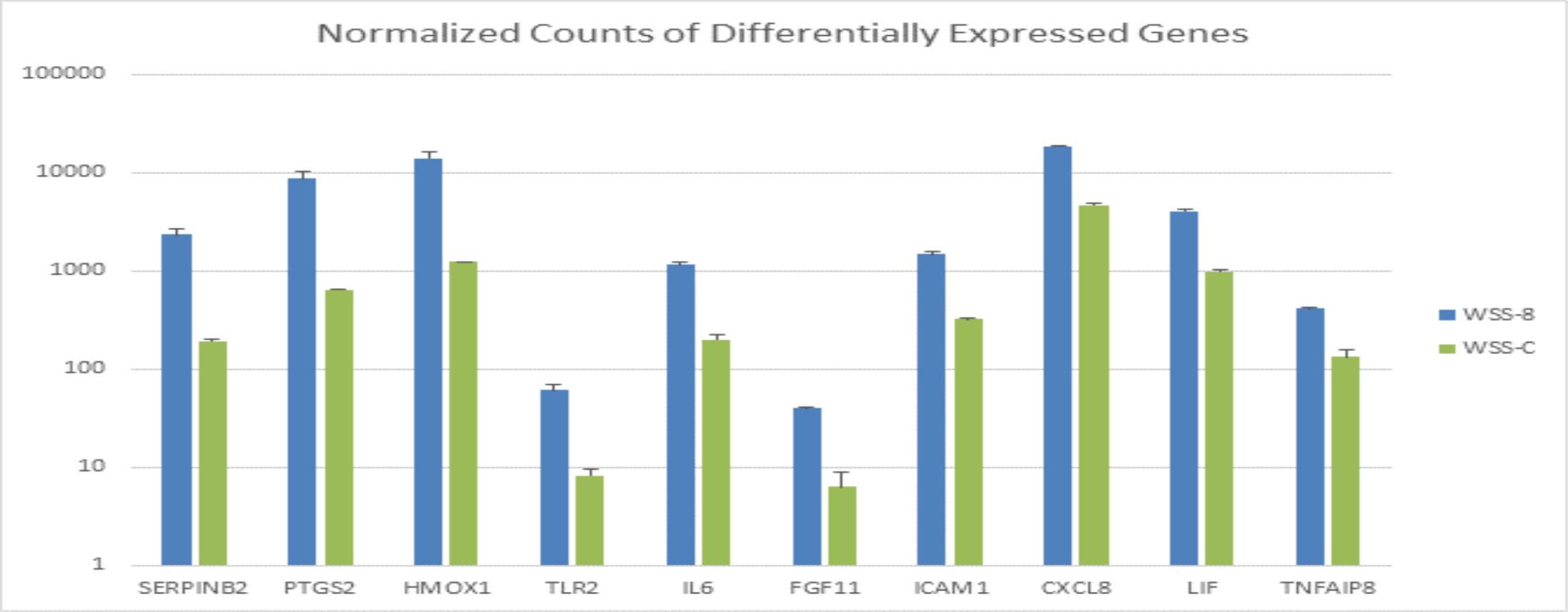
CEVA-101 vs. Static MSC

	Static-MSC					WSS-MSC				
	Media	TNF-α	IFN-γ	IL-1b	Combo	Media	TNF-α	IFN-γ	IL-1b	Combo
PGE_2 (pg/mL)	302.55 ± 55.33	459.61 ± 258.39	317.42 ± 19.93	331.33 ± 48.32	647.18 ± 290.60	1038.14 ± 336.90*	1351.23 ± 520.99*	1381.71 ± 680.51*	2427.72 ±311.15*	1610.97 ± 272.09*
HO-1 (pg/mL)	201.31 ± 29.73	151.49 ± 3.59	161.61 ± 10.29	172.55 ± 17.22	153.51 ± 29.77	3855.85 ± 158.00*	3967.68 ± 215.73*	4055.52 ± 275.17*	4428.55 ± 290.26*	3303.80 ± 238.97*
Rel. TNF-α Prod.	0.53 ± 0.23	N.D.	N.D.	N.D.	N.D.	0.17 ± 0.06*	N.D.	N.D.	N.D.	N.D.
Rel. IFN-γ Prod.	0.58 ± 0.03	N.D.	N.D.	N.D.	N.D.	0.59 ± 0.12	N.D.	N.D.	N.D.	N.D.

* Denotes significant difference from Static-MSC:Media

Data derived using cGMP compliant WJ-derived MSCs

CEVA-D Cells: Potency



**PTSG2 is COX2*
***TNFAIP8 isTSG6*

- RNA-Seq Demonstrates Enhanced Potency of CEVA101 Versus Static Cells
  - Log-fold increases in key anti-inflammatory signals
  - Confirms published pre-clinical data with cGMP compliant cell line

CEVA-D Cells: Characterization

- Consistent Expression of Key Cell Surface Markers After Mechano-Transduction
  - Repeated passages & differentiation often reduce anti-inflammatory potency

Sample	*CD34*	*CD73*	*CD90*	*CD105*	*CD146*
hBM-MSC 5204 (Research Grade Control) [p3]	0.17	99.99	99.93	99.08	100
RoosterBio hBM-MSC (GMP Grade Control) [p4]	0.06	100	99.89	99.72	99.86
RoosterBio hBM-MSC (CEVA-101) [p4]	0.11	99.93	99.79	99.58	99.89

CEVA-D: Sterility & Quality Control

- **Viability**
  - Release Criteria: >70.0%
  - Lot Average: 90.80%
- **Endotoxin Testing**
  - Release Criteria: <5.00 EU/mL
  - Lot Average: <1.00EU
- **14 Day Sterility Culture**
  - Release Criteria: Negative
  - Lot Average: Negative
- **Viable Cell Yield**
  - Release Criteria: >80.0%

CEVA-D: Biology of Mechano-Transduced Cells

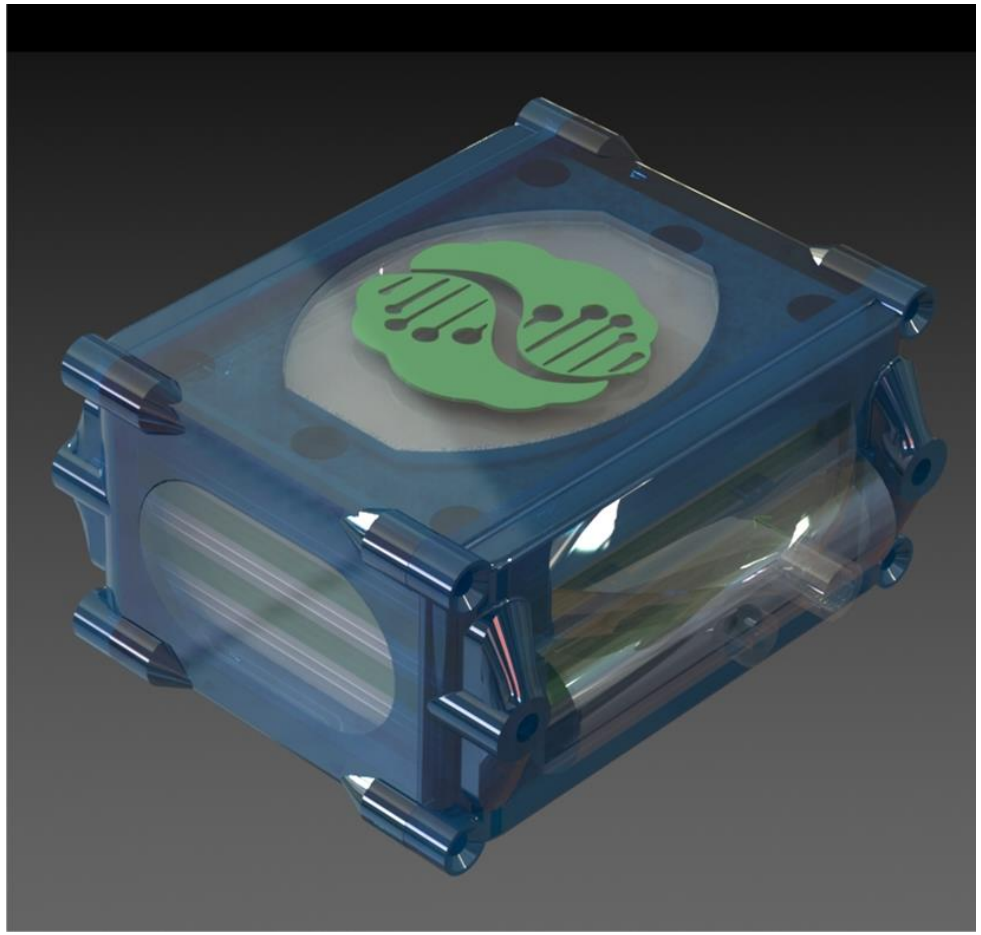
- Enhanced anti-inflammatory activity (Potency)
  - Broad set of gene programs up-regulated
  - Gain and loss of function of PGE2 confirms importance
- MSC Source Agnostic
- Reproduced under cGMP conditions, release
- Potency assays linked to outcomes in *in vivo models*

CEVA-D: Development Status and Intellectual Property

- 2D Device: functioning with defined manufacturing process
- 3D Device: in prototype development phase
- All devices and methods backed by robust IP protection
  - Methods & Apparatus for Conditioning Cell Populations
  - Issued / Allowed: Australia, China, Japan, Russia, US
  - Pending: Brazil, Canada, EP, Hong Kong, Israel, Korea
  - Earliest Expiration Date: 06/23/2036
  - *Broadest Claim: An apparatus comprising: an inlet fluid feed plate; a base plate; and a plurality of intermediate plates positioned between the inlet fluid feed plate and the base plate, wherein each of the plurality of intermediate plates comprises: a first end, a second end, a first side, and a second side; a distribution channel proximal to the first end; and a gathering channel proximal to the second end, wherein: the distribution channel extends between the first side and the second side of the intermediate plate; and the gathering channel extends between the first side and the second side of the intermediate plate.*

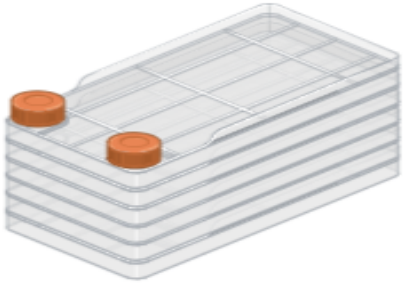
CEVA-D: Scale Up

- Production of Single Dose (CEVA101)
- Channel Dimensions: 7.50 x 8.00 x 0.04 cm
  - ~⅕ Clinical-scale
  - Seeding Density: 60k MSC / cm^2
- All parts designed for injection molding

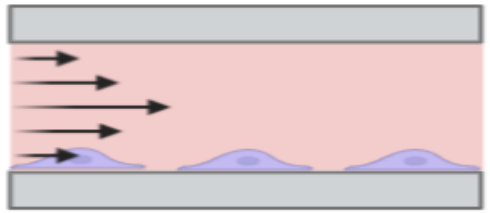


CEVA-D: Manufacturing Work-Flow

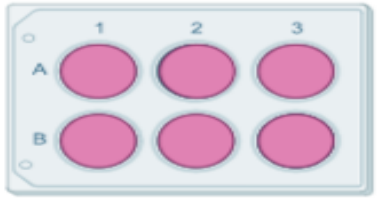
Cell Expansion → WSS Conditioning → Potency



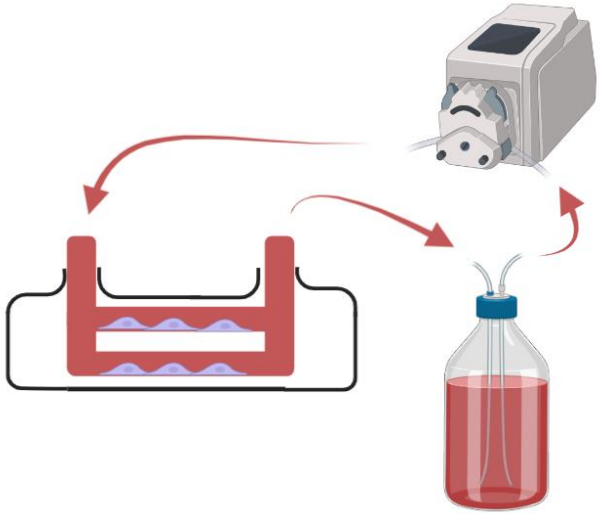
WJ-MSC Expansion in conventional tissue culture plastic up to passage 4

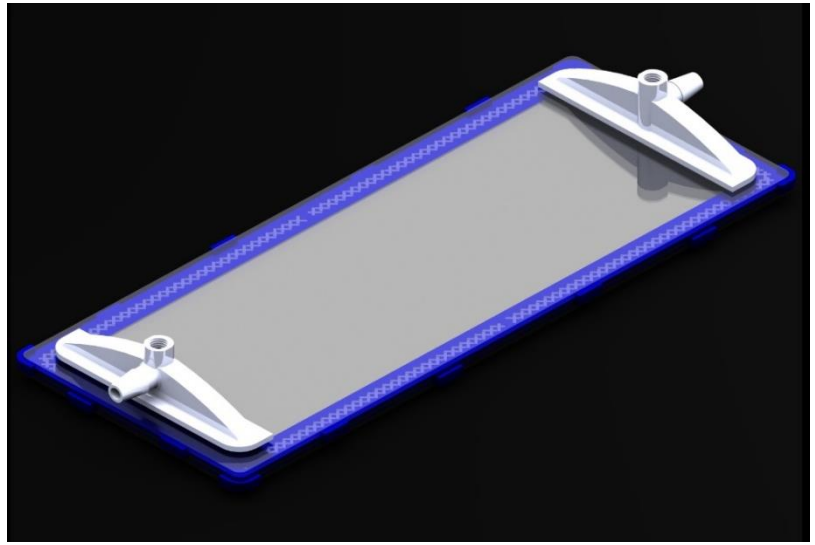


Conditioning of adherent MSC in bioreactor with 8 dyne/cm^2 for 3 hrs



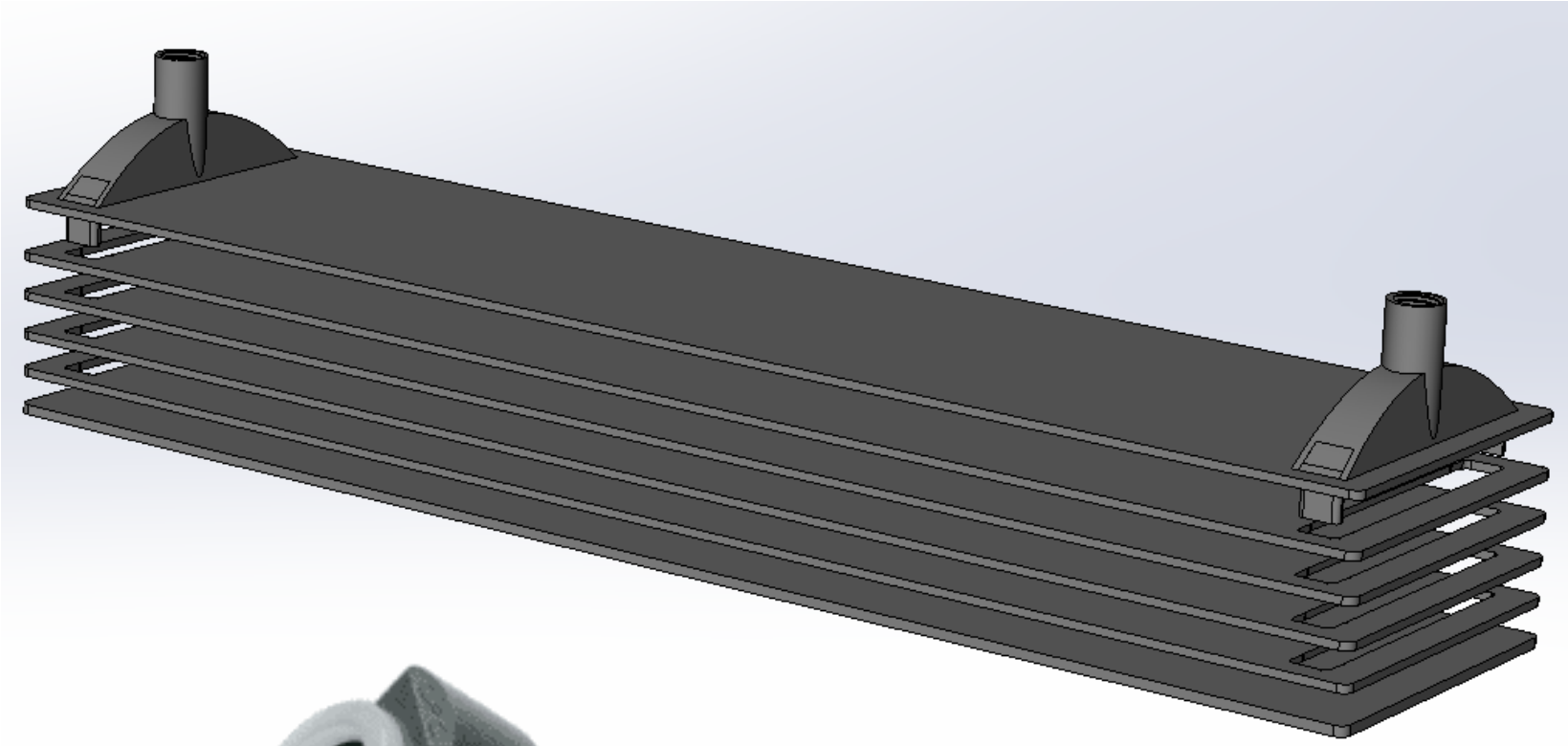
WSS-MSC & Static-MSC assessed via protein production, Splenocyte Co-Culture, & RNA-Seq



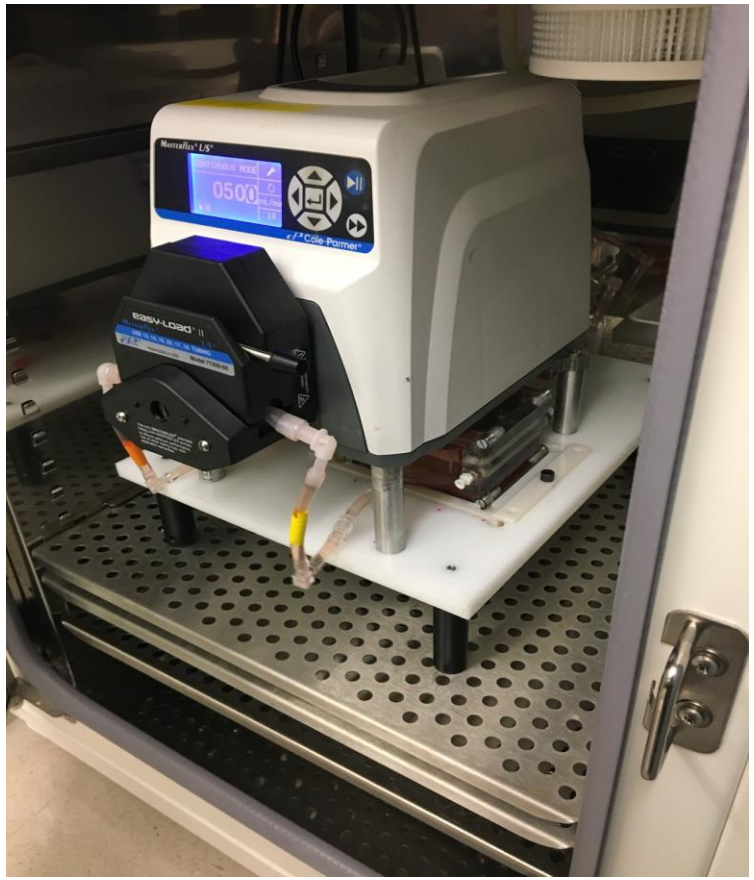


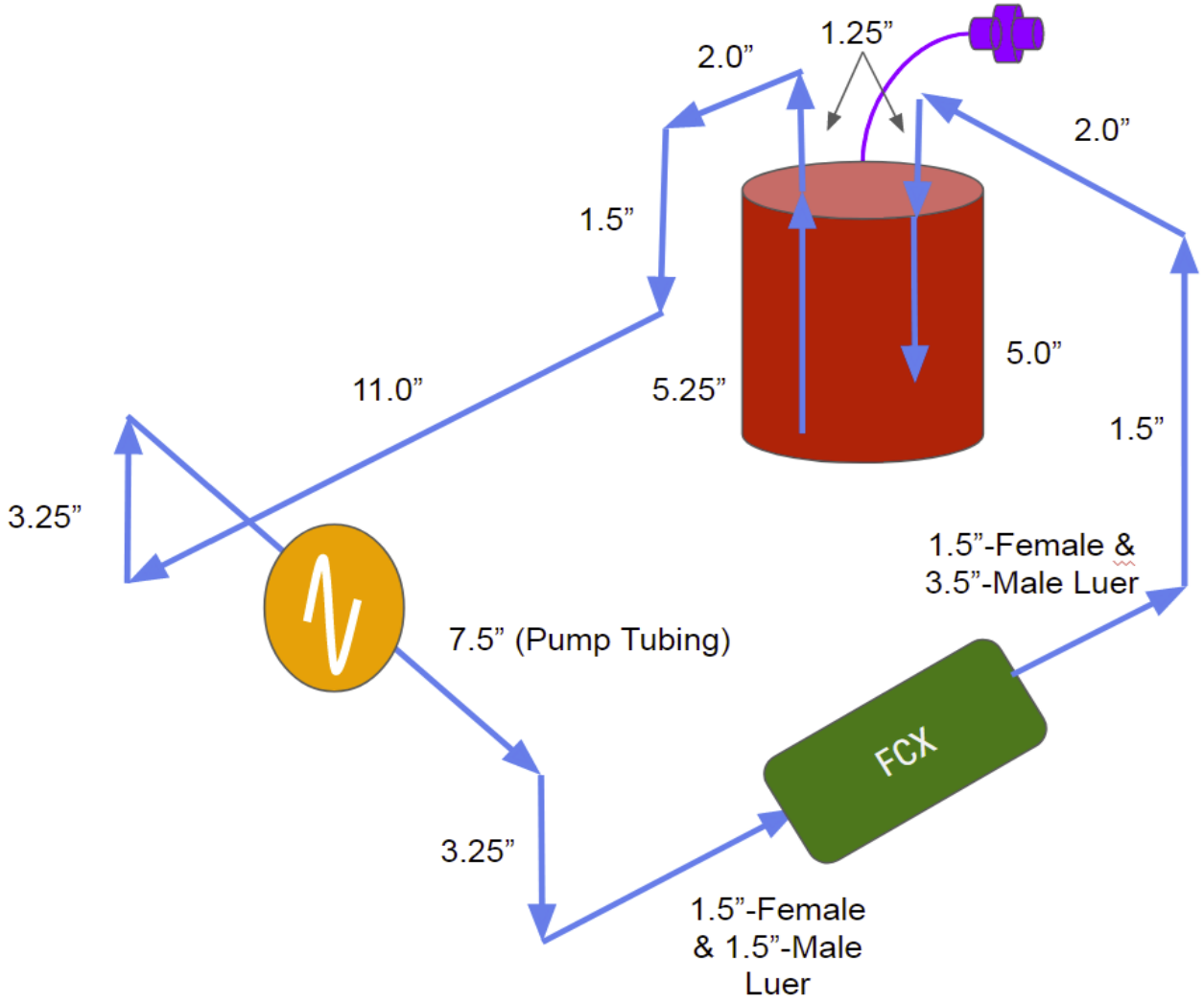
CEVA-D: Production Model

- Quick Connects
- Run 8X per pump
- 50 million cells @ 25k/cm^2
- 45 x 10 cm size



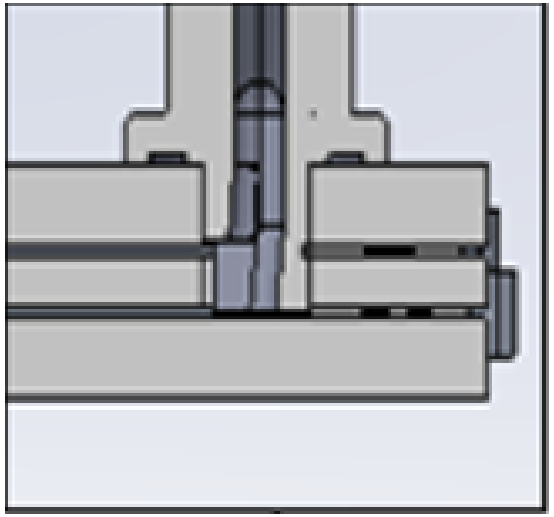
CEVA-D: Flow Loop





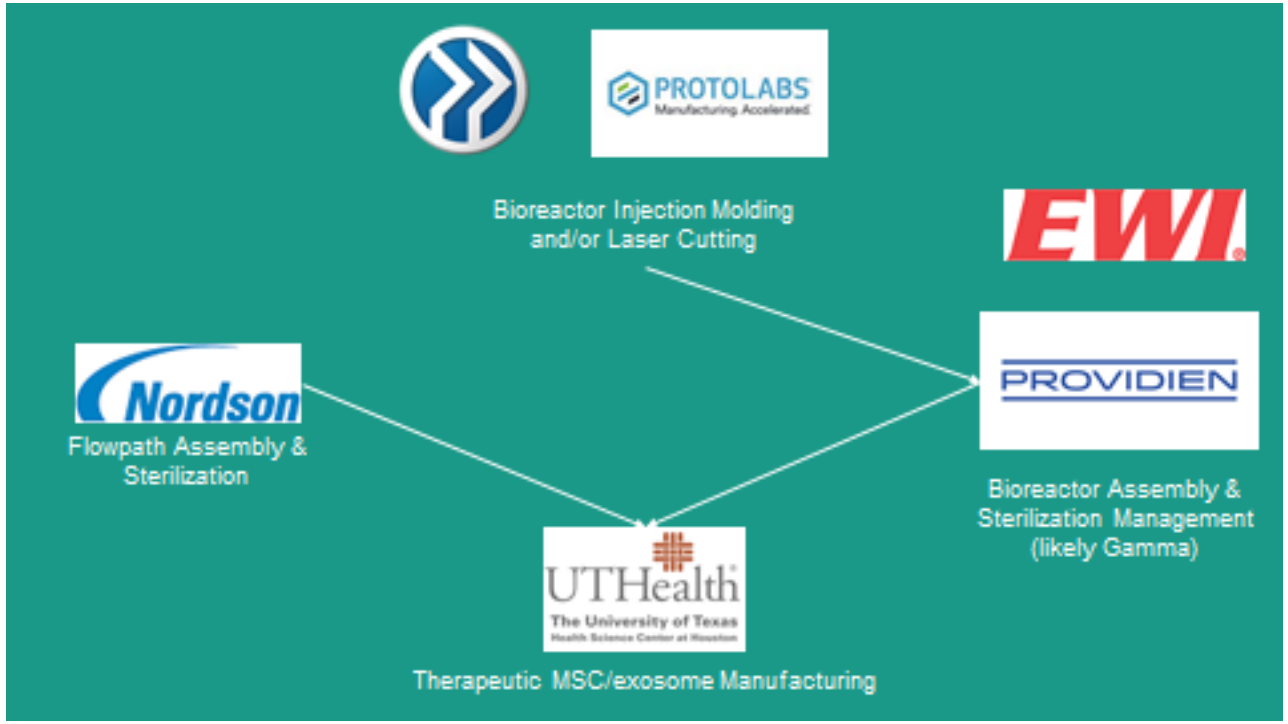
CEVA-D: Conditioning Schedule

- Conditioning Schedule
  - Fibronectin Coating: 12 hours
    - 10 ug/mL
  - Seeding: 4 hours
    - Can optimize for chosen cell line
  - Incubation: 15 hours
  - Flow Loop: 3 hours
  - TrypLE™ Harvest: 15 minutes



CEVA-D: Process for 2D Production

- Injection molding of casing
- Laser cutting of plates
- Laser welding
- Cleaning
- Sterilization (gamma, EtO)
- Packaging

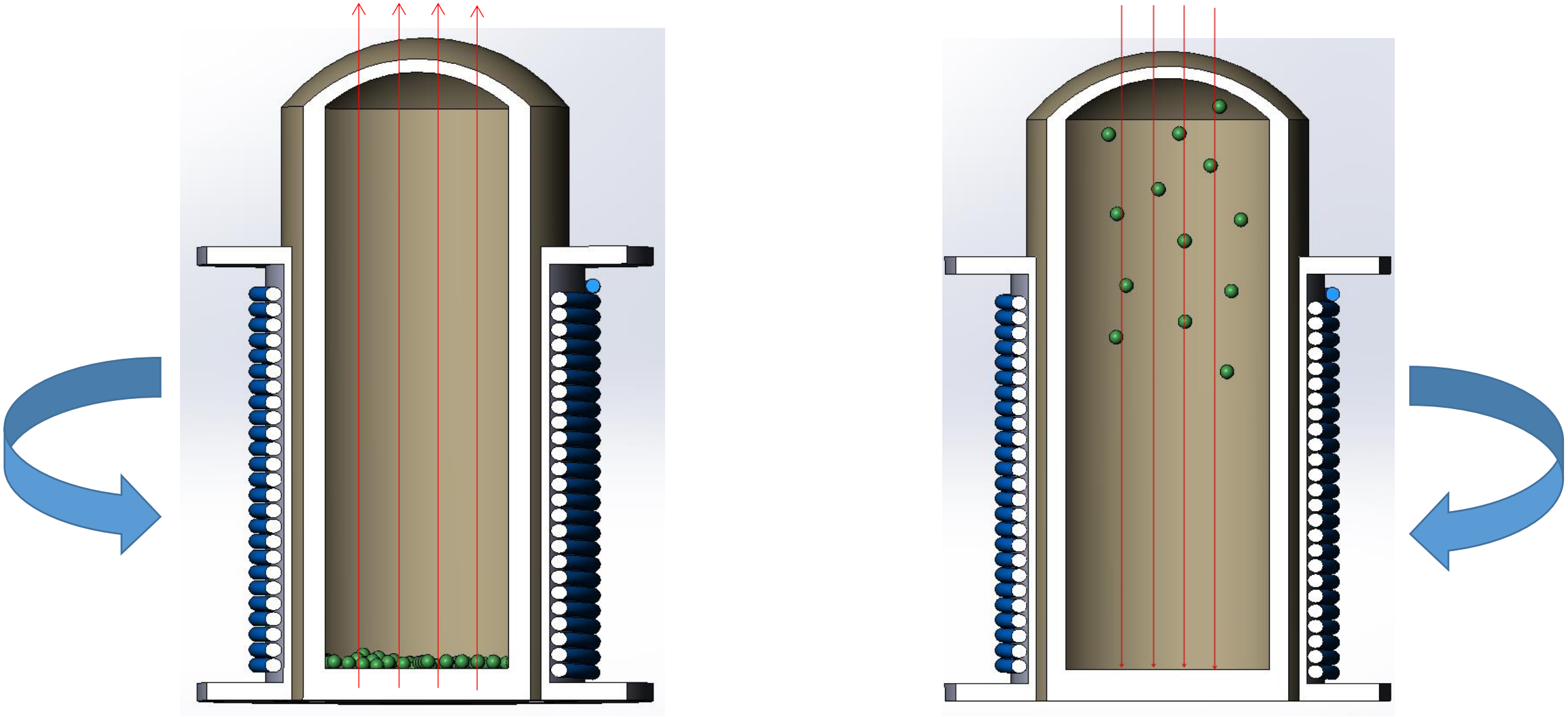


CEVA-D: 3D Scale-Up

- Rather than keeping cells still and moving fluid (2D), the opposite is done for 3D
- 3D cannot be accomplished with stirrer tank as beads and cells move with fluid
- Strategy based on use of magnetic beads with pulsatile current
  - Produces cell movement through the fluid
  - Generates shear stress in large-volume bioreactor

- No moving parts
- No cleaning or disinfection (simply discard canister after use)
- Programmable shear profiles

CEVA-D: 3D Process Rendering



- Magnetic beads (depicted in green) are coated with cells
- Spiral current (see blue arrows) creates magnetic field
- Magnetic field accelerates movement of beads and produces shear stress

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2. In Vitro & In Vivo Proof of Concept Established in Multiple Cell Types
3. Enhanced Potency Based on Established Matrices (↑PGO, ↑IDO, ↓TNFα, ↓Tcells)
4. Ability to Use 2-5X Fewer Cells Than Conventional (Clinical) Doses
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