Allogeneic NK-1R+ MSCs in Development for Acute Respiratory Distress Syndrome Secondary to COVID 19

Peter Altman, PhD
BioCardia, Inc.
Chief Executive Officer
NASDAQ: BCDA

Presentation Content and Forward-Looking Statements

Presentation Content

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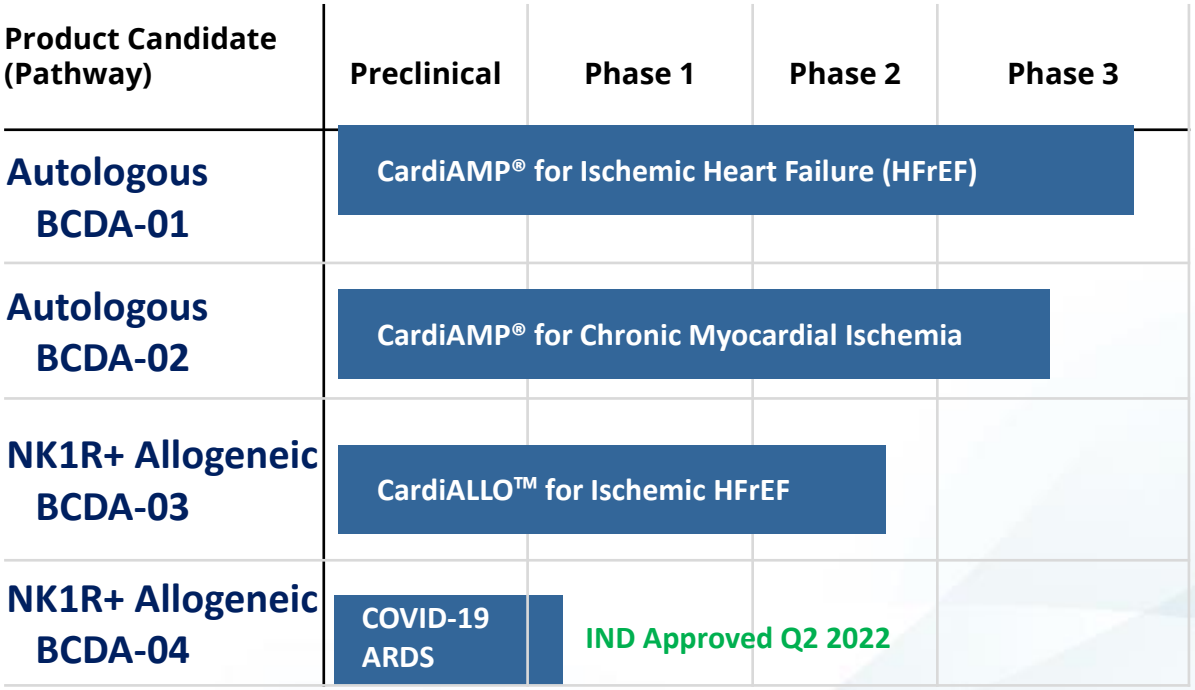
Pipeline of Autologous and Allogeneic Cell Therapies for Cardiovascular and Pulmonary Diseases



Allogeneic MSC History

The isolation and culture expansion of human bone marrow MSCs were reported in 1992 and their infusion into patients was begun as early as 1993 as reported in 1995.

Over the past 25 years the infusion procedures have exhibited an excellent safety profile, so much so in 2019, there were over 950 registered MSC clinical trials listed with the FDA.

Haynesworth, S. E., Goshima, J., Goldberg, V. M. & Caplan, A. I. Characterization of cells with osteogenic potential from human bone marrow. *Bone* **13**, 81–88 (1992).

Lazarus, H. M., Haynesworth, S. E., Gerson, S. L., Rosenthal, N. S. & Caplan, A. I. Ex vivo expansion and subsequent infusion of human bone marrow-derived stromal progenitor cells (mesenchymal progenitor cells): implications for therapeutic use. *Bone Marrow Transpl.* **16**, 557–564 (1995).

Pittenger, M.F., Discher, D.E., Péault, B.M. *et al.* Mesenchymal stem cell perspective: cell biology to clinical progress. *npj Regen Med* **4,** 22 (2019).

Allogeneic MSC are Immunomodulatory ; Not Immune Privileged

MSCs produce extracellular vesicles, including exosomes, and a multitude of cytokines and growth factors that suppress immune responses by inhibiting B- and T-cell proliferation and monocyte maturation and by promoting generation of regulatory T cells and M2 macrophages.

Although MSCs cannot be considered truly immune privileged, rejection of allogeneic-MSCs occurs more slowly than rejection of other allogeneic cell types.

Prockop DJ. Concise review: two negative feedback loops place mesenchymal stem/stromal cells at the center of early regulators of inflammation. *Stem Cells.* 2013;31:2042–2046.

Allogeneic MSC vs. Autologous MSC Study

BioCardia co-sponsored the POSEIDON Trial comparing allogeneic and autologous MSC in the setting of heart failure.

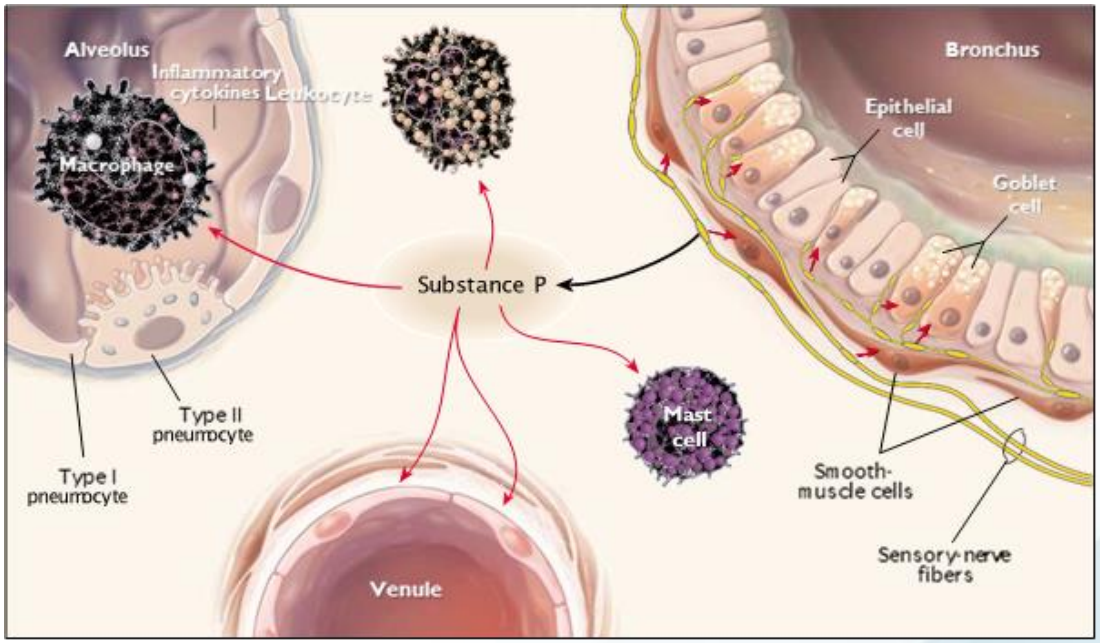
Results were compelling as there were no overt signs of rejection.

BioCardia CSO, Dr. Ian McNiece, led the manufacturing of the mesenchymal stem cells used in this and other published cardiac studies.

Hare JM, Fishman, JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Suncion VY, Tracy M, Ghersin E, Johnston PV, Brinker JA, Breton E, Davis-Sproul J, Schulman IH, Byrnes J, Mendizabal AM, Lowery MH, Rouy D, Altman P, Wong Po Foo C, Ruiz P, Amador A, Da Silva J, McNiece IK, Heldman AW. Comparison of Allogeneic vs Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy, The POSEIDON Randomized Trial, JAMA. 2012;308(22).

Allogeneic Neurokinin 1 Receptor Positive MSC Potential for Inflammatory Respiratory Disease

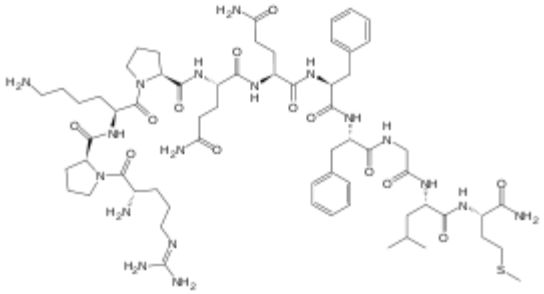
- The anti-inflammatory effects of MSCs have been well-documented and MSCs have been shown to reduce inflammation and injury in models of lung disease.
- The specific MSCs used in BioCardia's allogenic cell therapy are a unique population of MSCs which are NK1 receptor positive.
- NK1 receptor binds to substance P, an important neuropeptide associated with inflammation throughout the body and a primary mediator of inflammation in the airways.



NEJM 1997

1. Iter SS, Rojas M. Anti-inflammatory effects of mesenchymal stem cells: novel concept for future therapies. Expert Opin Biol Ther. 2008 May;8(5):569-81.
2. Colten HR, Krause JE. Pulmonary inflammation - a balancing act, N Engl J Med. 1997;336(15):1094-1096.
3. O'Connor TM, O'Connell J, O'Brien DI, Goode T , Bredin P, Shanahan F. The role of substance P in inflammatory disease, J Cell. 2004 March;201:167-180.

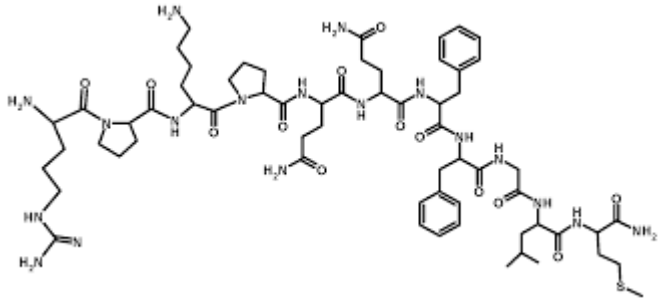
Substance P



- A peptide with 11 amino acid residues, family of tachykinin neuropeptides in the central and peripheral nervous systems.
- Initially, found to trigger smooth-muscle contraction.
- Later found involved in transmission of pain signals, regulation of BP, and stimulate secretion of endocrine and immune cells.
- A primary mediator of inflammation in the lungs.
- Responses to substance P mediated by NK-1R, a G protein-coupled receptor bearing seven transmembrane domains.

Colten and Krause. *New Engl. J. Medicine*. 1997; 336: (April 10): 1094-6

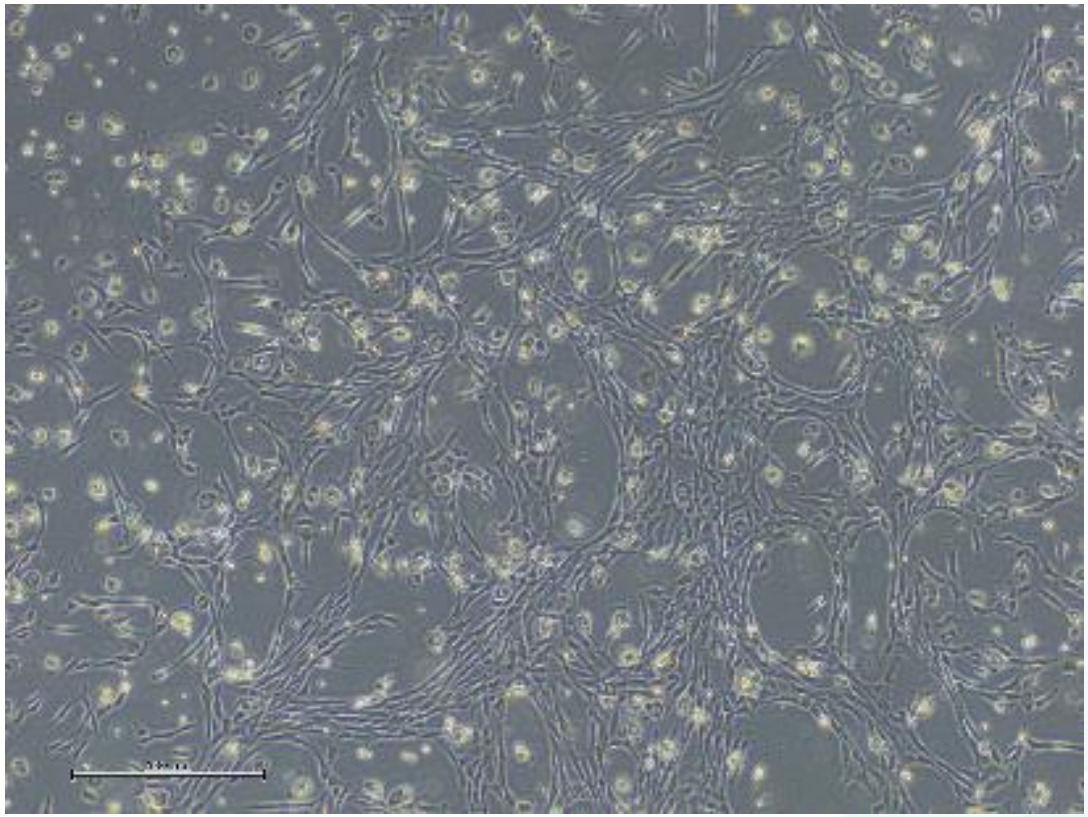
NK-1-R



Endogenous receptor for Substance P (SP) is neurokinin 1 receptor (NK1-R)

NK1-R is distributed over cytoplasmic membranes of many cell types (e.g., neurons, glia, endothelia of capillaries and lymphatics, fibroblasts, stem cells and white blood cells) in many tissues and organs.

NK-1-R+ MSC



Allogeneic Neurokinin 1 receptor positive (Nk1-R+) MSC

NK-1-R MSC

- Neurokinin 1 receptor (NK-1R) is expressed on subset of MSC precursors in bone marrow.
- Purification, using an antibody against NK-1R, enriches for CFU-F and decreases contaminating non-MSCs, (trypsin resistant non-plastic adherent cells and plastic-adherent cells).
- NK1R+ MSCs are highly proliferative in culture.
- Expansion of NK1-R+ MSCs purified from 50ml of bone marrow yields clinically relevant numbers of low passage MSCs.
- Culture expanded MSCs maintain NK1-R expression throughout expansion and even into later passages, indicating that NK1-R signaling could play a physiologically relevant role in MSC function. Additionally, NK-1R+ cell derived MSCs express standard MSC markers including CD105, CD93 and CD70.

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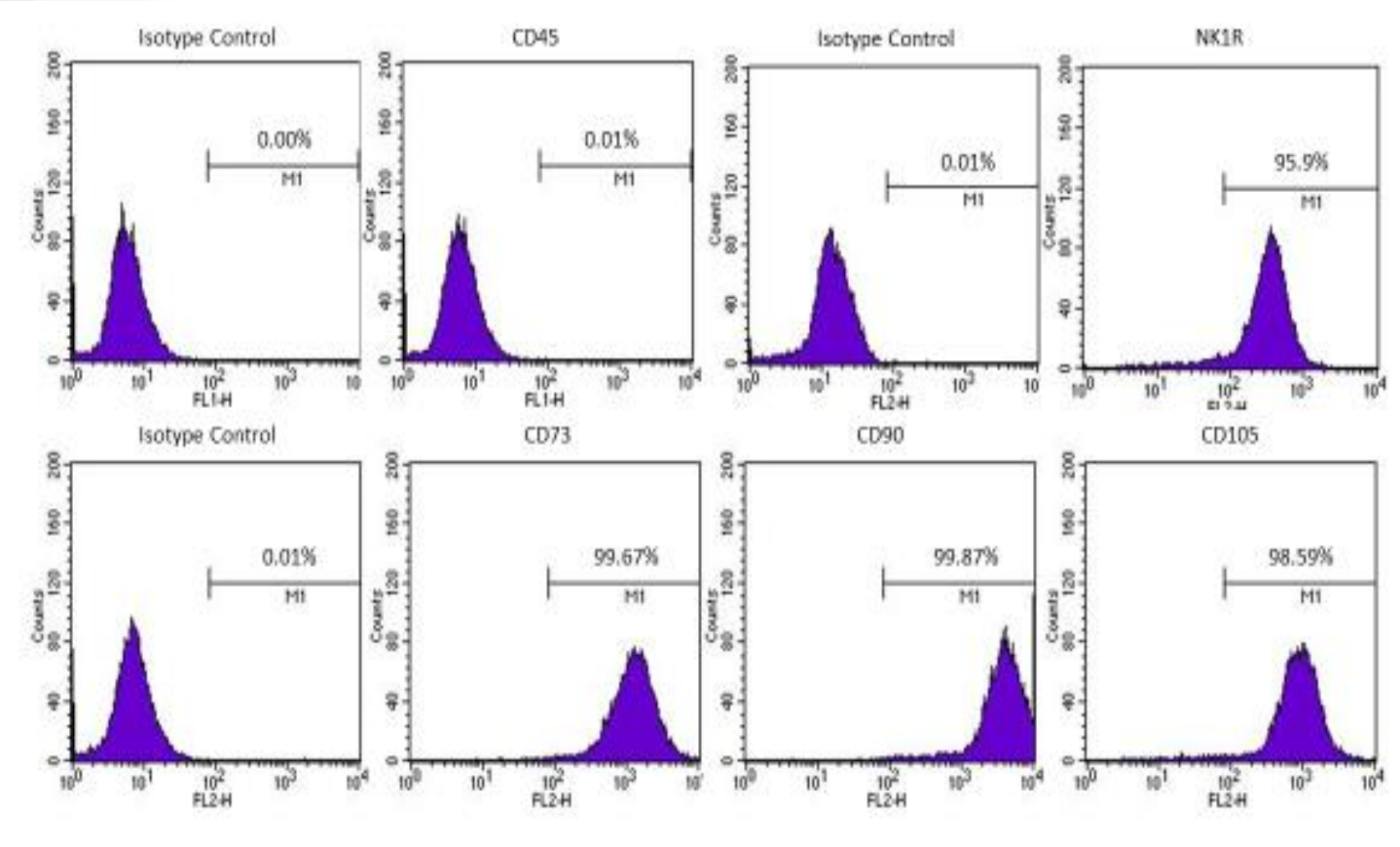
NK-1R+ CELLS ISOLATED FROM HUMAN BONE MARROW
Highly Expressed in Investigational Product After Multiple Passages



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NK-1R+ MSC Preclinical Studies Safety

IV treatment of NSG mice with human NK-1R+ MSC resulted in survival of all animals with no product related adverse events.

High doses of these MSCs do not appear to have negatively affected animal health.

IV NK-1R+ MSC Is Targeted Local Therapy for ARDS

Biodistribution of MSC after IV Infusion is Primarily in the Lungs

It has long been recognized that microspheres smaller than 15um to 20 um culture expanded mesenchymal stem cells (MSC) delivered intravascularly become trapped in the first capillary bed they meet as they don't readily pass through 5um to 9um capillaries.

For culture expanded cells, this has been described as "the lung barrier" in stem cell transplantation work targeted towards other organs using the intravenous route of administration.

This local retention of intravenously delivered culture expanded cells has advantages for where the local delivery target is the lungs as in the current clinical protocol.

Study to assess AllogeneiC Expanded human mesenchymal stem Cell therapy in patients recovering from COVID-19 Acute Respiratory Distress (ACE CARD)

Study Design

Phase I:
Experimental: Cohort 1
Low dose, 20M cells, 3 patients

Experimental: Cohort 2
Med dose, 100M cells, 3 patients

Experimental: Cohort 3
High dose, 200M cells, 3 patients

Subjects treated with allogeneicNK1R+MSC via IVinfusion
The study will follow the standard 3+3 design .

Phase IIa:
Experimental: Cohort 4
Maximum tolerated dose (from phase I) vs. placebo control, 24 patientsrandomized 1:1, patient and evaluator blinded (double-blinded).

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Initial Focus on Patients Recovering From ARDS Secondary to COVID-19

Patient must have:

- A laboratory-confirmed diagnosis of SARS-CoV-2 infection,
- recovered from moderate to severe Acute Respiratory Distress Syndrome, as determined by Berlin Criteria, and
- been weaned off the ventilator support.

Manufacturing NK1R+ Mesenchymal Stem Cells at BioCardia

- ISO-7 Controlled Environment Room certified and cell production ongoing to meet clinical studies ahead.
- Working towards first patient enrolled in Q3 2022.

Our NK1R+ MSC have great potential to be more potent MSCs in a unique post ventilator indication.

BIOCARDIA®

Thank you.

Peter Altman, PhD

Chief Executive Officer

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