

Potency Assay Development for CAP-1002: An Allogeneic Cell Therapy in Phase 3 Clinical Trial for DMD

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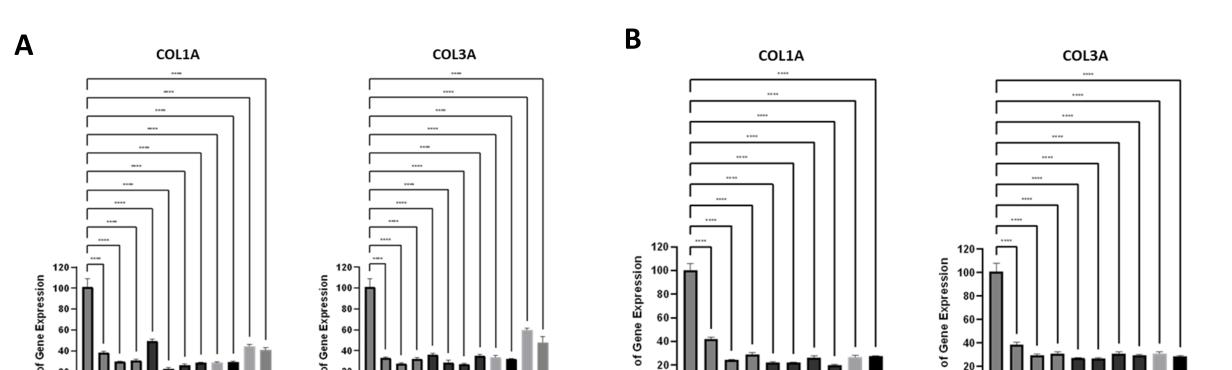
Abstract

Duchenne muscular dystrophy (DMD) is a severe, progressive, X-linked disease affecting both skeletal and cardiac muscle with severely reduced life expectancy. More than 80% of patients with DMD are non-ambulatory after the first decade. DMD triggers fibrosis, inflammation, and a maladaptive immune response. CAP-1002, the core technology product of Capricor consists of allogeneic cardiosphere-derived cells or CDCs, has been shown to be safe in multiple clinical trials and effective in reducing deterioration of upper limb function in patients with late stage DMD in a randomized, double-blind, placebo-controlled Phase 2 trial (HOPE-2). In accordance with the potential mechanism of action and clinical efficacy data for CAP-1002, the following assays were developed to better define CAP-1002 product identity and potency: 1) antifibrotic activity via fibroblast production of collagen using a co-culture system; 2) analysis of β-catenin in CAP-1002 cells and non-CAP-1002 cells, 3) analysis of CAP-1002 identity using a qRT-PCR panel generating from RNAseq data, 4) analysis of CAP-1002 clinical potency by RNA sequencing of CAP-1002 cells and non-CAP-1002 cells. Multiple CAP-1002 lots which were shown to be clinically potent were tested together with non-CAP-1002 cells as negative controls. Our results showed that the anti-fibrotic activity as demonstrated by the reduction in collagen expression induced by multiple CAP-1002 lots is consistent with clinical potency. At the same time, elevated β-catenin expression was detected by ELISA for all the clinical potent CAP-1002 lots. Finally, using RNAseq data from 20 potent CAP-1002 lots with known clinical efficacy and 16 non-CAP-1002 cell lines, a differentially expressed model was established, which could be used for CAP-1002 potency testing for all future CAP-1002 lots. This RNA profile identified a set of genes including HSPA6, IL6 and CXCL8, which gave the most different expression between CAP-1002 and non-CAP-1002 cells and could be used for CAP-1002 cell identity. Together these data support the use of these new assays for CAP-1002 product identity and potency.

Results

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Sample Name	Correlation p<0.00001	Sample Classification			
Potent Lot 1	0.9944	Potent	٦		
Potent Lot 2	0.9942	Potent			
Potent Lot 3	0.9928	Potent			
Potent Lot 4 Potent Lot 5	0.9919	Potent Potent			
Potent Lot 6	0.9876	Potent			
Potent Lot 7	0.9869	Potent			
Potent Lot 8	0.986	Potent			
Potent Lot 9	0.9843	Potent			
Potent Lot 10	0.977	Potent	}	- CAP-1002	2
Potent Lot 11 Potent Lot 12	0.9735	Potent Potent			
Potent Lot 12	0.9675	Potent			
Potent Lot 14	0.9654	Potent			
Potent Lot 15	0.9653	Potent			
Potent Lot 16	0.9626	Potent			
Potent Lot 17 Potent Lot 18	0.9608	Potent Potent			
Potent Lot 19	0.9244	Potent			
Potent Lot 20	0.9119	Potent	L		
Cardiac Endothelial Cells Lot 1	0.8965	Non-Potent	٦		
aHDF Lot 1	0.8929	Non-Potent			
Cardiac Fibroblast Lot 1 Cardiac Smooth Muscle	0.8907	Non-Potent Non-Potent			
Cardiac Endothelial Cells Lot 2	0.887	Non-Potent			
MSC Lot 1	0.8836	Non-Potent			
aHDF Lot 2	0.8834	Non-Potent			
MSC Lot 2	0.8605	Non-Potent	l	Non-	
Cardiac Fibroblast Lot 2	0.7396	Non-Potent	ſ	CAP-1002	2
Human aortic smooth muscle cells (HASMC-1 Human atrial cardiac fibroblasts (HACF-1)	0.649	Non-Potent Non-Potent			
HEK293	0.5889	Non-Potent			
MSC Lot 3	0.5572	Non-Potent			
Human aortic endothelial cells (HAEC-1)	0.5106	Non-Potent			
aHDF Lot 3	0.4037	Non-Potent			
THP-1	0.3594	Non-Potent			
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Sample Name	Correlation p<0.00001	Sample Classification			
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Figure 1.CAP-1002 conditioned media (CM) from 11 lots (including 4 clinical lots and 1 repeat lot) significantly reduced the collagen gene expression (COL1A, COL3A) in fibroblasts after co-culture. Non-conditioned media (media control) was used as a control. COL1A and COL3A gene expression analysis was evaluated by qRT-PCR. Assay was performed in triplicate with data shown as average \pm SD of assay triplicates. **** p < 0.0001, *** $p \le 0.0005$, ** $p \le 0.001$.

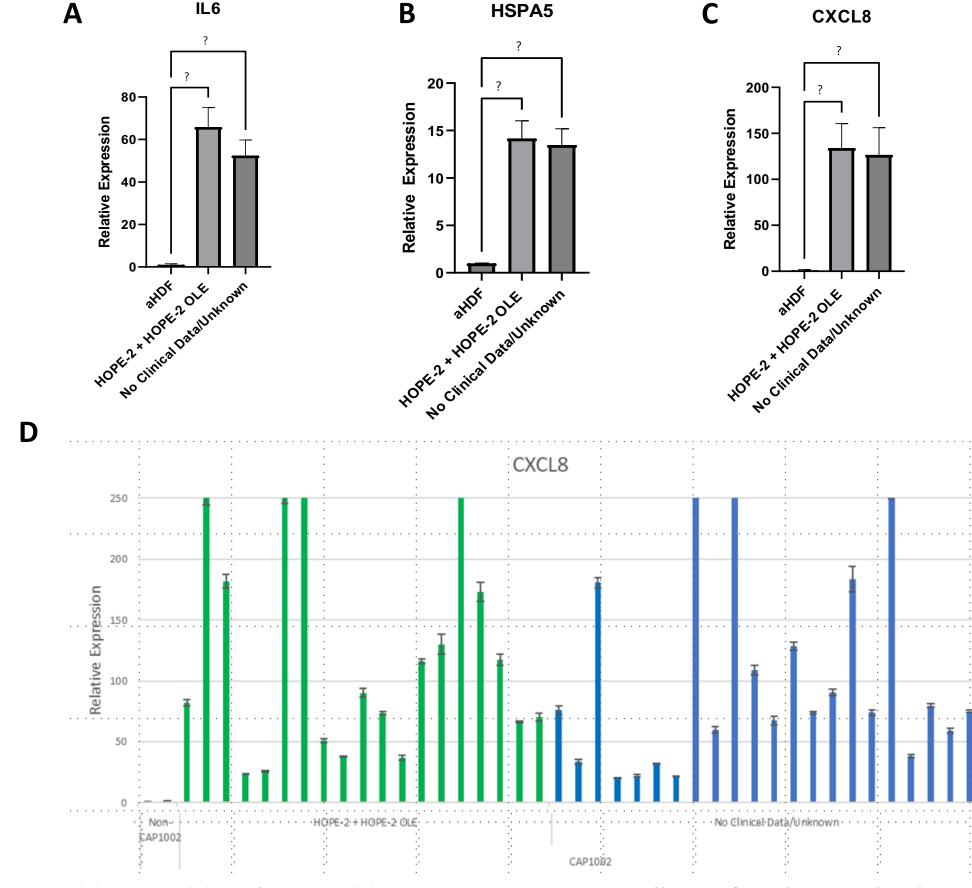


Figure 2. IL6 (A), HSPA5 (B), and CXCL8 (C) gene expression is statistically significantly upregulated in CAP-1002 cells,

re 3. (A) Gene expression profile data of clinically t CAP-1002 lots (green) and non-CAP-1002 cells ed as non-potent, red). CAP-1002 lots. Using the stringent, conservative model with a P value of 0001, 100% of known clinically potent CAPlots (highlighted green) rank higher than of "assumed non-potent", non-CAP-1002 (highlighted red). (B) Gene expression profile of clinically potent CAP-1002 lots (green) and CAP-1002 cells (labeled as non-potent, red). the model samples are duplicate RNA samples *were independently sequenced a second time* are shown in white. Test the model samples with poor quality RNA are labeled as "test the model".

including 19 CAP-1002 lots used in HOPE-2 or HOPE-2 OLE (middle bars) and CAP-1002 lots with unknown clinical efficacy (right bars), when compared to adult human dermal fibroblasts (aHDF, left bars). (D) CXCL8 gene expression is highly upregulated in 43 lots of CAP-1002, including 19 CAP-1002 lots used in HOPE-2 or HOPE-2 OLE (green bars), when compared to adult human dermal fibroblasts (aHDF, grey bars). CAP-1002 cells with unknown clinical efficacy are shown in blue bars.



- Conditional media (CM) collected from all eleven lots of CAP-1002 induced a statistically significant reduction in both COL1A and COL3A expression when compared to the non-conditioned media control, indicating that CAP-1002 may play a role in ameliorating fibrosis, which is a clear pathological feature observed in DMD patients.
- Expression of three genes, CXCL8, IL6 and HSPA5, is significantly upregulated in 41 lots of tested CAP-1002 cells compared with Non-CAP-1002 cells, suggesting that these genes could be potentially used for CAP-1002 cell identity.
- Differentially expressed gene (DE) model was built based on the RNAseq data from potent CAP-1002 cells (Used in HOPE 2 and HOPE 2 OLE) and non-CAP-1002 cells, which could be used to predict CAP-1002 potency.



• CAP-1002 is proprietary of Capricor Therapeutics, Inc (NASDAQ:CAPR)