Abstract Submission Form

Title:	**Human umbilical cord-derived mesenchymal stem cells in combination with small extracellular vesicles improve survival and dramatically reduce fibrosis and cirrhosis in Wistar rats receiving CCL4**
Background	Umbilical cord-derived mesenchymal stem cells (UC-MSCs) exert potential anti-inflammatory properties and in previous studies have shown anti-fibrotic effects in animal models of liver fibrosis and cirrhosis. In this proof-of-concept, first in animal study, we examined the effect of human UC-MSCs combined with small extracellular vesicles (SEVs) on liver fibrosis in a rat model of fibrosis and cirrhosis.
Methods	Human UC-MSCs were cultured via a xenofree, explant process with modifications to passage 3 and SEVs were obtained from supernatant of the cultured UC-MSCs. Two groups, each of 14 Wistar male rats, aged 7-8 weeks, received oral CCL4 with olive oil (1ml/kg) twice weekly for a total of 6 weeks from week 1 to week 6. Starting at week 4, after all animals in both groups received 6 induction doses of CCL4, one group of 14 animals received three weekly IV doses of UC-MSC + SEV at a dose of 1 million MSCs and 5 billion SEV each. All animals alive at week 7 were sacrificed. 14 animals who received CCL4 alone from weeks 4-7 were control animals. The primary objectives were to examine the survival differences between two groups of animals and the effect of UC-MSC + SEV on fibrosis stage by Trichrome and Sirius Red.
Results	Six animals in the control group died before week 6 whereas all 14 animals in the US-MSC + SEV were alive at week 6. The survival difference at 6 weeks was significant between two groups (100% with UC-MSC + SEV vs 57%, p=0.0066). The necropsy of 6 dead animals in the control group showed cirrhosis in all 6 animals. The comparison between 8 animals in the control group and 14 animals receiving US-MSC + SEV is shown in Table1. Notably, liver fibrosis stage by both Trichrome and Sirius Red was significantly lower in the UC-MSC + SEV group. While there were no animals in the UC-MSC + SEV group had cirrhosis, there were 12 animals in the control group with cirrhosis. There were corresponding favorable liver biochemistry and liver immunohistochemistry changes in the UC-MSC +SEV group (Table).
Conclusion	Human UC-MSCs cultured to passage 3 in combination with SEV significantly improved the survival of the animals receiving low-dose CCL4. UC-MSC + SEV dramatically reduced the development of fibrosis and cirrhosis induced by CCL4. Further studies are needed to validate our observations and to test the

combination of UC-MSC + SEV in other animal models and in humans with fibrotic liver diseases and liver failure.

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Table: Selected characteristics of CCL4 fed animals with and without US-MSC + SEV treatment

	CCL4 (N=8) (Mean±S.E)	CCL4 UC-MSC+ SEV (N=14) (Mean±S.E)	P. Value
Body weight(gm)	404.500 ±14.6470	429.357± 14.2785	0.271
Feed intake(gm)	21.750 ±1.1378	26.929 ±0.9677	0.003
Liver Index (g/100g of BW)	5.3924 ±0.18765	4.0001 ±0.09214	0.0001
Serum AST (U/L)	215.663 ±16.0369	220.393± 16.2959	0.851
Serum ALT (U/L)	214.850± 37.5172	97.214 ±5.2280	0.001
Serum ALP (U/L)	396.350±39.0886	270.171 ±27.3007	0.014
Serum Total Bilirubin (mg/dL)	0.2013 ±0.01093	0.1857 ±0.01147	0.381
Liver Histology			
- Fibrosis by Masson trichome	3.929±0.0714	1.071±0.2864	0.0001
- Fibrosis by Sirus red	3.929±0.0714	1.000±0.2568	0.0001
- Cirrhosis %	85%	0	0.0001
Liver IHC			
-Liver Collagen	3.429±0.1727	1.214±0.1869	0.0001
-Liver a-SMA	3.571±0.1373	0.714±0.1634	0.0001
-Liver CK18	1.964±0.2312	0.250±0.0869	0.0001
-Liver CK19	2.464±0.1333	0.179±0.0664	0.0001
Mortality (%)	**43**	**0**	**0.007**

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Funding Source: No Funding Source

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Category: Liver Fibrogenesis and Non-Parenchymal Cell Biology

Liver Fibrogenesis and Non-Parenchymal Cell Biology Subtopic: Clinical and Translational Fibrosis Research

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