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Dear Editors of Clinical and Experimental Immunology

Per this paper concerning genesis of new therapy for LONG COVID with convalescent plasma from survivors, it is well known that there have been numerous very disappointing results of Convalescent Plasma Therapy (CPT) *in active infections with COVID-19*.

A question is how to account for this, given the huge history of *seeming* benefit of CPT in a variety of instances over more than the past 100 years.

We have published some reasoning *based on our experimental evidence* (Philip Askenase, **COVID-19 Therapy With Mesenchymal Stromal Cells (MSC) and Convalescent  Plasma Likely Depend on Exosomes; Do the exosomes in convalescent plasma antagonize the weak immune antibodies? Editorial Review**, *Jo Extracellular Vesicles,* [Volume10, Issue 1](https://onlinelibrary.wiley.com/toc/20013078/2020/10/1), October 2020,e12004, pages 1-19).

**Here is the reasoning in sum:**

In CPT there is a collision between desirable viral resistance promoting developed hyper immune antibodies and undesirable convalescent exosomes that act to suppress the “over the top ”cellular immunity of the acute infection by inhibiting antigen presenting cells (APC) and cytokine producing effector T cells (our work, see attached power point presentation and references below).

These inhibiting exosomes are appropriate to convalescence, but when given early in infection may interfere with endogenous early developing profitable innate mononuclear APC and acquired-immune T cell mediated anti-viral IFN-g driven responses.

**Knowing that there is growing interest in the Covid Long Haulers** that go on with significant clinical syndromes after successfully dealing with the viral infection, I raise the possibility that CPT containing the potential of broadly Ag-specific suppressive exosomes, might be considered for possible effective treatment of the COVID-19 Long Hauler Syndromes. We argue that syndrome are due to residual COVID antigens perhaps complexed in remnants of neutrophil extracellular traps of the acute infection to which there is an aberrant immune response or remaining positive immune acting antigen specific exosomes The convalescent plasma inhibiting exosomes should certainly be superior compared the purported value of vaccines, as there would be an influence on multiple Ag-specific responses, beyond just to the viral spike protein solely brought by the vaccine.

The question for you is how to progress towards publication of this proposed point of view manuscript hoping to stimulate moving towards trials of LONG COVID treatment with convalescent plasma vs. normal plasma

Warmly

Phil A.

PS: Also attached below is the exosome part of my CV to show my expertise in this emerging area.

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**PHILIP W. ASKENASE, MD**

**PUBLICATIONS ON EXOSOME EXTRACELLULAR VESICLES IN IMMUNITY, NEURO INJURY,**

**CUTANEOUS INFLAMMATION, AND GENERAL BIOLOGY**

**ORIGINAL PEER REVIEWED PAPERS** (numbers to the left are from my complete CV)

192. [Bryniarski K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bryniarski%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23727037)1, [Ptak W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ptak%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Jayakumar A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jayakumar%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Püllmann K](https://www.ncbi.nlm.nih.gov/pubmed/?term=P%C3%BCllmann%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Caplan MJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Caplan%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Chairoungdua A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chairoungdua%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Lu J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lu%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Adams BD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Adams%20BD%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Sikora E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sikora%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Nazimek K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nazimek%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Marquez S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Marquez%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Kleinstein SH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kleinstein%20SH%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Sangwung P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sangwung%20P%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Iwakiri Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Iwakiri%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Delgato E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Delgato%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Redegeld F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Redegeld%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Blokhuis BR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Blokhuis%20BR%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Wojcikowski J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wojcikowski%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Daniel AW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Daniel%20AW%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Groot Kormelink T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Groot%20Kormelink%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23727037), [Askenase PW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Askenase%20PW%5BAuthor%5D&cauthor=true&cauthor_uid=23727037). **Antigen-specific, antibody-coated, exosome-like nanovesicles deliver suppressor T-cell microRNA-150 to effector T cells to inhibit contact sensitivity**. [*J Allergy Clin Immunol.*](https://www.ncbi.nlm.nih.gov/pubmed/23727037) 2013 Jul;132(1):170-81.

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198. Karen L. Lankford, Edgardo J. Arroyo, Katarzyna Nazimek, Krzysztof Bryniarski,Philip W Askenase**,** and Jeffery D. Kocsis, **Intravenously Delivered Mesenchymal Stem Cell-Derived Exosomes Specifically Target M2-type Macrophages of the Injured Spinal Cord**.[*PLoS One.*](https://www.ncbi.nlm.nih.gov/pubmed/29293592/) 2018 Jan 2;13(1):e0190358. doi: 10.1371/journal.pone.0190358.

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207. Katarzyna Nazimek, Eugenio Bustos-Morán, Noelia Blas-Rus, Bernadeta Nowak, Justyna Totoń-Żurańska, Michał Seweryn, Magdalena Wąsik, Paweł Wołkow, Philip W. Askenase, Francisco Sánchez-Madrid, and Krzysztof Bryniarski.**Regulation in vivo at the level of the immune synapse, by a circuit of primary orally administered exosomes delivering miRNA-150, then induce secondary exosomes in a circuit of multiple APC-connected T cells**. Submitted to JCI, March 2021,

209. Masahito Nakazaki, Tomonori Morita, Karen L. Lankford, Philip W Askenase, and Jeffery D. Kocsis, **Exosomes released by systemically delivered MSCs target M2 macrophages that upregulate TGF-β linked to microvascular stabilization and functional recovery in spinal cord injury,** Submitted to Nature Communications, April 2021.

**INVITED AND OTHER REVIEW PAPERS**

1. Groot Kormelink T, Askenase, PW, and Redegeld, FA, **Immunobiology of Antigen-Specific Immunoglobulin Free Light Chains in Chronic Inflammatory Diseases,** *Current Pharmaceutical Design*, vol 18, , 2012.
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65. Philip W. Askenase, **Exosome Extracellular Vesicles: A Vehicle for Simultaneous Immune and Genetic Therapy**, *Microbiology, Immunology and Pathology* Volume 2(1): 1–3, 2020

66**.** Philip W. Askenase, **Perspective: Viva la Natural Extracellular Vesicles, Naturally occurring exosomes are ideal for therapies-and are better for the job than artificial nanoparticles** . *Nature Outlook*, Issue on Extracellular RNA and Exosomes, *NATURE*, Vol 582, 18 June 2020, page S5

67. Philip W. Askenase, **Ancient Origin and Properties of Natural Exosomes Contribute to Their Therapeutic Superiority Compared to Artificial Nanoparticles**, *Int. J. Mol. Sci.* 2021, 22, 1429. <https://doi.org/10.3390/ijms22031429>

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69. Philip W. Askenase, **Exosomes Provide Unappreciated Carrier Effects That Assist Transfers of Their miRNA to Targeted Cells; I. They are “The Elephant in the Room**,” In Press at *RNA Biology*, 2-30-20. doi: 10.1111/j.1758-2229.2012.00348.x.