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Title: Professor

Institution: U. T. M. D. Anderson Cancer Center

Name of Project: In-vitro Induced Immunosuppression in a Rotary Cell Culture System

Amount of Grant: [Redacted]

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The function of the innate immune system is to provide a first-line of defense against infectious organisms, via control of bacterial and viral growth using antigen nonspecific means. These nonspecific immune effectors include macrophages and NK cells, and certain cytokines elicited in response to "super antigens" on the infectious agents. This innate system usually keeps most infectious agents from rapidly growing while the adaptive immune system is generating a specific response complete with immunologic memory. Compelling evidence suggests that space flight results in various immunosuppressive effects, including reduced innate and adaptive immune responses. We were particularly concerned with reduced NK activity at landing, and have asked whether the microgravity component of space flight could be responsible for the previously observed NK defect. We have conclusively demonstrated that simulated microgravity as provided by the Synthecon bioreactors does not inhibit the NK function nor the IL-2 activation of lymphokine-activated killing (LAK). Interleukin-2 is the key cytokine responsible for activation of NK cells to express LAK, as well as to support differentiation of lymphocytes during adaptive immune responses. Therefore, we have disproved our original hypothesis based on poor NK in many of the astronauts upon landing.

During the course of our studies, however, we have found that aspects of the IL-2 signaling and sequela which are suboptimal or nonexistent, indicating that parts of the immune response are not functioning in the manner considered normal, at least based on those observed from flask cultures. The results we found include a lack of CD25 (IL-2Rα subchain) upregulation, which is needed for high affinity IL-2 signaling. The positive control of lymphocytes cultured with IL-2 in flasks consistently upregulated IL-2Rα. Further deficits include the lack of secondary cytokine induction in response to IL-2. Secondary cytokines required for amplification of the innate immune response. We tested for IL-1β, TNFα and IFNγ, and none were secreted after IL-2 stimulation in the bioreactors, but all were secreted from the parallel flask cultures. These tests were performed over various time points up to 8 days, and with several different donors.

Our future research is now directed to determine if mRNA for these cytokines and the IL-2Rα is expressed, and if not would suggest a transcriptional block. We are also testing the signal molecules themselves, and will look at the status of kinases believed to functional in the early response of the IL-2 driven-pathway. It is difficult to know if the bioreactor results actually represent real in vivo functioning, or whether the traditional flask cultures are realistic. To date we have accepted that the flask culture system for lymphocytes represented the "normal" human immune status most accurately, but we are questioning this.

There are no published articles as yet, although one manuscript is in preparation.