Scientists reactivate immune

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Scientists at the Gladstone Institute of Virology and Immunology (GIVI) and the University of California, San Francisco (UCSF) have found that therapy can be used to stimulate the production of vital immune cells, called “T- cells,” in adults with HIV infection.

HIV disease destroys T-cells, leading to collapse of the immune system and severe infection. The thymus gland, which produces T-cells, gradually loses function over time (a process called “involution”) and becomes mostly inactive during adulthood. Because the thymus gland does not function well in adults, it is difficult for HIV-infected adults to make new T-cells. Thus, therapies that stimulate the thymus to produce new T-cells could help HIV-infected patients to rebuild their embattled immune systems.

Although it has been long assumed that the thymus cannot be reactivated in humans, research published in the March issue of the *Journal of Clinical Investigation*, shows that the thymus can be stimulated to produce more T-cells. This study is the first to show that pharmacologic therapies can be used to enhance human thymic function.

“These results represent new proof-of-principle findings that thymic involution can be reversed in humans” said Laura Napolitano, MD, lead author of the study, an Assistant Investigator at Gladstone and Assistant Professor of Medicine at UCSF. “Improved T-cell production may be helpful for some medical conditions such as HIV disease or bone marrow transplantation. These findings contribute new information to our understanding of T-cell production and are also an important step to

determine whether immune therapies might someday benefit patients who need more T-cells."

Based on promising animal studies suggesting that growth hormone (GH) enhances thymic function in aged mice, Gladstone and UCSF investigators conducted a prospective randomized research study that yielded an exciting observation: GH increased thymic mass and T-cells in humans. The investigators studied 22 HIV-infected adults for 2 years. One half of study participants were randomly assigned to continue their usual HIV therapy and to receive GH in the first year ("GH Arm"), and the other half continued their usual HIV therapy without GH treatment ("Control Arm"). In the second year of the study, Control Arm participants received GH, and GH Arm participants were studied off GH. Immune analyses were performed regularly in all study participants. The thymus was assessed by computed tomography (CT) scans, and the numbers and types of immune cells in the blood were determined by an advanced method called multiparameter flow cytometry.

All study participants had been receiving effective HIV therapy for at least one year (average duration of HIV therapy was approximately 3 years) with good suppression of the virus. Despite effective therapy, they still had an unusually low number of "CD4" T-cells, a type of T cell that is essential for normal immune function. At the start of the study, the patients in the two arms did not differ in average duration of effective HIV therapy, amount of HIV in the blood, age, thymic mass or in a large number of important immunologic measurements.

The results were very encouraging. Napolitano's team found that GH treatment markedly increased thymic mass and appeared to double the number of newly made T-cells. On average, GH receipt was associated with a 30% increase in CD4 T-cells (2.4 fold higher than no GH). These gains continued to increase at least 3 months beyond GH discontinuation and appeared to persist for at least one year after GH discontinuation.

“The findings of this study are exciting,” said senior author Joseph M. McCune, a Professor of Medicine at UCSF, “and dispel the previously-held notion that the thymus cannot be summoned into action later in life. If these findings bear out in larger studies, this news should be of particular interest to those in need of new T-cells, for instance, adults with HIV disease or other forms of T cell depletion.”

“However,” both Napolitano and McCune cautioned, “GH should not be used as a treatment for immune purposes in HIV disease or in any other individuals at this time, unless this treatment occurs within a research study. More research is needed to learn whether stimulating the production of new T-cells actually provides a health benefit.

–“We have shown an increase in the quantity of T-cells, but must also determine whether a recovered thymus produces good quality T-cells that provide satisfactory immune protection.” Napolitano added, “This was a relatively small study of carefully selected adults receiving effective therapy for HIV infection and our findings may not apply to the majority of individuals.”

While the sample in this study is relatively small, Napolitano said a larger, multi-center study conducted by the AIDS Clinical Trial Group (ACTG) has yielded similar results in preliminary analyses and is expected to report these results in the future. “The ACTG study will provide additional data that will add to our understanding of GH effects on the immune system,” said Napolitano who is also a member of the ACTG Team conducting the multi-center study.

“GH is a protein hormone that acts upon mosT-cells of the body, which can result in several side effects,” stated Napolitano. “We are interested in learning the specific way that GH affects the thymus so that therapy can be more narrowly directed to the thymus.

Source: Gladstone Institutes