SCREENING FOR DRUGS TO PROMOTE OR INHIBIT MREG-INDUCED TREG DEVELOPMENT

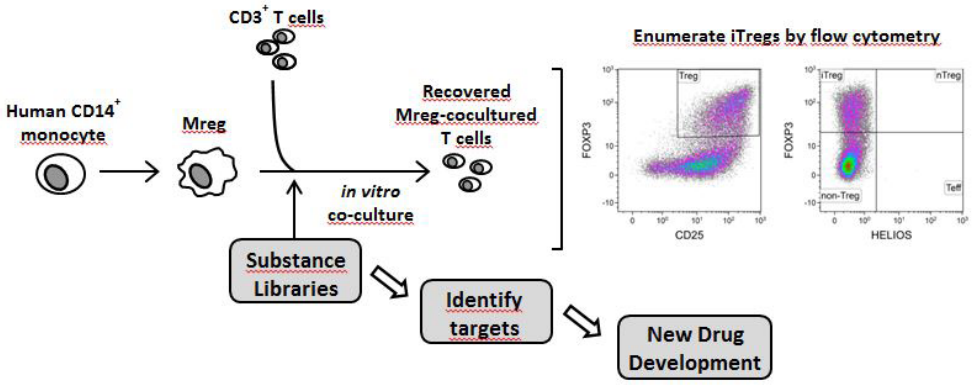
Reference No. B77143

CHALLENGE

Regulatory macrophages (Mregs) are crucial to establishment and maintenance of peripheral immunological tolerance [1]. A highly specialized function of Mregs is efficient conversion of naive T cells into TIGIT+ FoxP3+ induced Tregs, which themselves play essential roles in controlling immunological responses in health and disease [2]. The reciprocal interactions of human Mregs and T cell subsets are mediated by multiple, non-redundant molecular pathways that are not fully characterized. Currently, there are no drugs to specifically target development of function of iTregs in clinical use; however, therapeutic agents that target these pathways could have wide-ranging applications. Drugs capable of enhancing Mreg-induced iTreg responses could be useful in treating of autoimmune diseases, chronic inflammatory conditions or transplant rejection. Conversely, drugs that suppress Mreg-iTreg interaction could be useful in treatment of cancer [3]. This technology now provides a way to investigate the effect of drugs on human Mreg-driven generation of iTregs.

INNOVATION

This assay system has been optimized as a platform for mid-throughput screening of substances that enhance or suppress TIGIT+ FoxP3+ Treg induction by human Mregs. It enables an unbiased approach to discovery of novel mechanisms controlling human iTreg development, stability and function, as well as identifying potential drug targets or drug substances. Assay performance has been characterized extensively and pilot screens of small drug libraries have been technically successful. Using a flow cytometry-based read-out generates very rich and reproducible datasets, which include information about CD4+ and CD8+ non-Tregs, as well as Treg subets. The assay has been used as a basic research tool for investigating dose-response relationships for small drug molecules, antibodies and soluble recombinant proteins [2].



COMMERCIAL OPPORTUNITIES

This screening technology is designed to **identify drugs substances and/or drug targets** that enhance or suppress Mreg-mediated iTreg generation. The assay system has been carefully optimized to ensure reproducibility and to reduce sample processing times and costs. To date, the platform has only been used for small-scale applications; however, the assay could be easily scaled-out for **mid- or high-throughput drug screening**. This technically simple, biologically complex assay system opens the possibility of discovering novel drugs or drug targets relevant to the t**reatment of autoimmune diseases, prevention of transplant rejection and cancer therapy.**

DEVELOPMENT STATUS

Proof-of-concept *in vitro*

REFERENCE:

[1] Molecular Therapy. 2013, Feb 1; 21(2):409. doi: 10.1038/mt.2012.168 [2] Nature Communications. 2018, July 20; 9(1):2858. doi: 10.1038/s41467-018-05167-8. [3] Blood Advances. 2017, Jun 7; 1(14):947. doi: 10.1182/bloodadvances.2017006858.

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