Immunological Substance Testing on Human Lymphatic Microorganoids in vitro

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Pharmaceutical drugs and compounds used for consumer products may bear the risk of unexpected immunotoxicological effects such as sensitization, allergy, anaphylaxis or immunogenicity. Modern biopharmaceuticals of a high potency and target specificity like antibodies and cytokines need to be tested for their immune functionality before first-in-man application, with respect to therapeutical dose and exposition regiment.

Existing *in-vitro* tests and commonly used animal models do not reflect the complexity and specificity of the human immune system. However, novel humanized animal models have limitations in systemic reactions. Monolayer or suspended cell culture don't have tissue functionality and organ physiology and could not be used for long-term culture. In contrast, solid tissue biopsies, e.g. tonsil preparations of tonsillitis patients typically show inflammatory artefacts and degrade in long term culture due to damages induced by the preparation procedure.

The construction of tissue-like structures *in vitro*, so called "organoids" can overcome these limitations. Key structures of secondary lymphatic organs, e.g. lymph nodes or spleen are the primary lymphatic follicles and germinal centres, in particular in the "activated-state" of inflammation or infection. For the remodelling of lymphatic follicles, functional and structural cells, e.g. lymphoid cells (PBMC) and stromal cells need to be combined with biogenic or artificial matrices and scaffolds in a suitable 3D-environment. Tissue formation can be induced under controlled conditions.

A human lymph node model should be designed for the induction and monitoring of both, cellula r and humoral immune responses under operation of several weeks, long-term drug exposition and repeated doses. Cellular immunity is monitored e.g. by cytokine release patterns, and humoral immunity e.g. by analysis of B cell activation, plasma cell formation and antibody secretion profiles (IgM, IgG). Cellular composition and micro-organoid formation is analysed by flowcytometry, histology and *in-situ* imaging.