**Revealing Immunomodulatory Properties of Implants Using a Human Whole Blood Test System**

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**Background:** Implants have become indispensable in oral and maxillofacial surgery, resulting in constant development of new implants with improved biological and immunomodulatory properties (e.g., barrier membranes). Although a variety of *in vitro* test systems exists, making reliable predictions of implant-related responses *in vivo* remains a major problem. This is mostly related to the limited complexity of the test systems (compared to *in vivo* conditions). Here, we present a proof-of-concept study of a whole-blood test system that provides insights into not only immunocompatibility but also immunomodulatory processes of biomaterials.

**Methods:** All tested barrier membranes were cut to fit into inert reaction tubes. Subsequently the tubes were filled with 2 ml of a proprietary cell culture medium ± immune cell stimulus (LPS/TStim) and 1 ml fresh human whole blood from healthy volunteers. The assembled tubes were incubated for 48 hours at 37 °C in an occasionally rotated system to increase immune cell contacts with the materials. Nelfilcon A, that turned out to induce donor-dependent immune cell activation, was used as a material control and LPS/TStim-treated tubes as stimulation control. After incubation, supernatants were analysed using multiplexed cytokine analysis (Luminex™) or Enzyme-linked Immunosorbent Assay (ELISA).

**Results:** The incubation of barrier membranes in unstimulated human whole blood cultures resulted in a characteristic activation profile for the collagen-based BioGide® membranes as well as for the control material Nelfilcon A. Interestingly, incubating BioGide membranes in LPS/TStim stimulated human whole blood cultures, mimicking an inflammatory environment, resulted in a significant decrease of some cytokines (TNFα, IFNγ, IL-4 and IL-12p70), whereas typical chemotactic mediators (IL-8, MCP-1 and MIP-1α) further increased. Similar values were found, but to a lesser extent, for the also collagen-based OSSIX Plus membrane. This finding was not related to adsorption properties of the collagen, but more likely to anti-inflammatory mediators such as TGF-b1, released by whole blood ingredients or the membranes themselves.

**Conclusion:** This novel human whole blood test system represents an *in vivo*-like complexity compared to most other *in vitro* test systems. This provides a highly reliable method to sensitively detect immunomodulatory effects and complex reaction profiles of implant materials such as barrier membranes after contact with human whole blood.

Access to such insights during implant development can help to identify positive immunomodulatory effects (e.g. on wound healing) but also reveal undesired material properties at an early stage, resulting in significant time and cost savings.