Profiling biologics in circulating human whole blood

Functional and safety assessments of biologics prior to first-in-human (FIH) is key to understand the mode-of-action and safety profile. We have made use of an ex-vivo whole blood assay for its potential in assessment of antibody-based drug candidates.

Therapeutic monoclonal antibodies are biological drugs developed for the treatment of human diseases such as cancer, autoimmune diseases, and inflammatory related heart-problems along with geriatric diseases. Apart from the therapeutic effect, monoclonal antibodies can cause unexpected side effects such as activation of immune cells and release of factors that collectively induce a severe systemic immune activation, called cytokine release syndrome (CRS). The affected patient experience chills, muscle- and joint-aches, fever, nausea, vomiting and in severe cases breathing difficulties and organ failures. Because of these side effects, such as CRS, all biological drugs require safety testing before a FIH trial can take place.

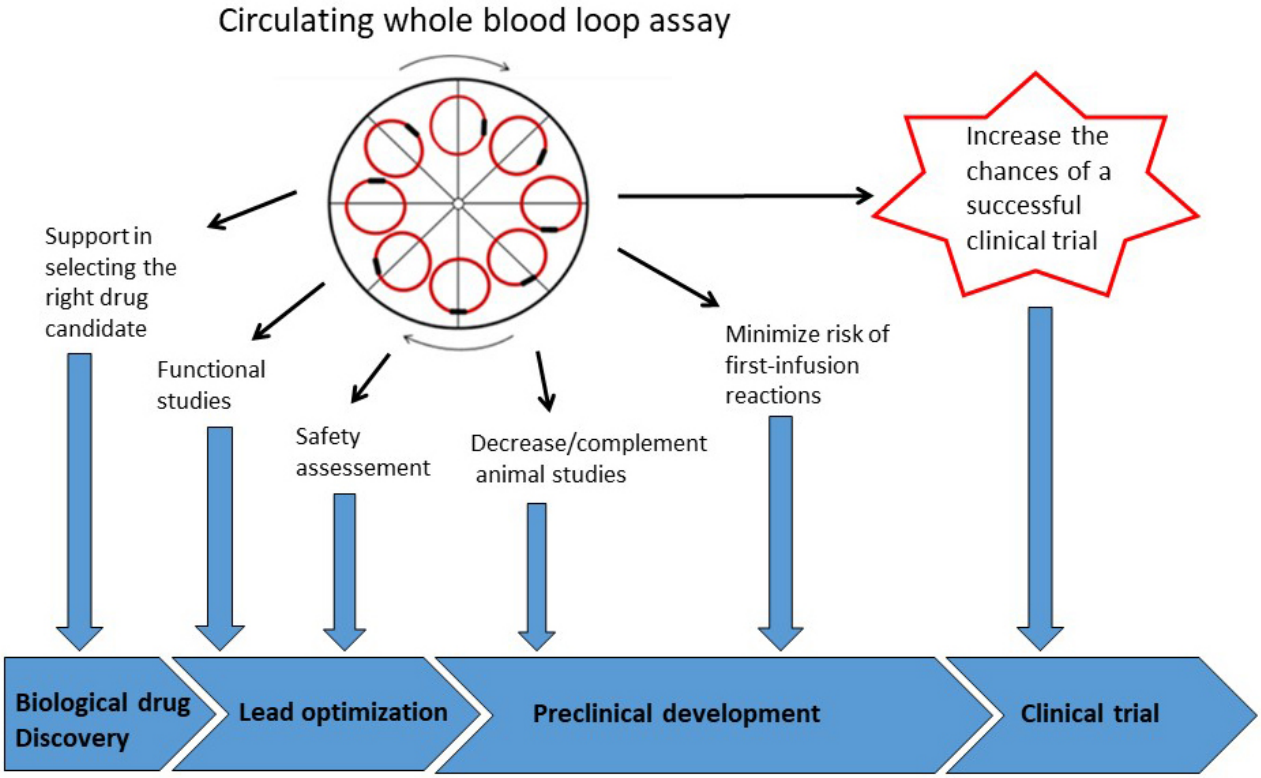

Fig. 1. Illustration of how profiling of biological drugs in circulating whole blood can improve the chances of a successful clinical trial.

The safety of biological drugs is today tested in animal models and by use of plate-based assays

with human blood or selected blood cells. The advantage of standard plate-based assays, over animal studies, is that they contain human cells; however, the drawback is the absence of one or several factors that are present in circulating blood in the human body. The absence of blood factors that may be involved in causing the side effect reduces the predictive power of these assays and it is therefore essential that alternative methods are developed.

A modified Chandler loop model is a whole blood assay historically used to study the interaction of blood with materials and related immune responses. In this assay, the blood is constantly circulating and with minimal anti-coagulants, all the blood factors are intact mimicking blood in the human body and therefore comprise a breath of an immune response that cannot be mimicked in plate-assay setups.

In the recently published work by our group we validated the loop assay for its potential to predict side effects, such as CRS, induced by monoclonal antibodies. Monoclonal antibodies that cause CRS in humans also induced a CRS-like profile in the loop assay and monoclonal antibodies that do not prevalent cause CRS in humans did not induce a CRS-like profile in the loop assay. In other words, the responses seen in the loop assay resembles the safety profile of humans treated with these monoclonal antibodies, supporting the potential of the loop assay as a powerful screening tool for risks of CRS.

The therapeutic effect of monoclonal antibodies is through binding a target cell can have an antagonistic, agonistic, blocking or cell depleting net effect. The killing of a target cell that a monoclonal antibody has bound to can occur through two major mechanisms that both are uniquely present in the loop assay, i.e. antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. By specifically blocking the different mechanisms in the loop assay, the responsible mechanism of target cell killing was identified for antibodies, which are known to induce killing of their target cells.

With the possibility to study all components in circulating human blood the Chandler loop model can provide a unique and welcomed tool to assess the safety and function of biological drugs. In addition, monoclonal and multi-specific antibodies can be evaluated for cellular binding properties in such model system. With better understanding of the drug candidates, the likelihood of choosing the best candidate for successful treatment of human disease is greatly improved.

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Publication

Extracorporeal human whole blood in motion, as a tool to predict first-infusion reactions and

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