FLUID DYNAMICS IN A NOVEL SINGLE-USE BIOREACTOR FOR PERSONALISED T-CELL THERAPIES

Gergana Atanasova, Dept. of Biochemical Engineering, University College London
gergana.atanasova.16@ucl.ac.uk
Andrea Ducci, Dept. of Mechanical Engineering, University College London
Martina Micheletti, Dept. of Biochemical Engineering, University College London

Key Words: CAR-T cell therapy, CliniMACS Prodigy®, Fluid dynamics, Mixing without an impeller

The complex nature of advanced personalised therapies requires the development of an incredibly robust manufacturing process that yields consistent final product quality despite patient-to-patient variability. Therefore, a lot of effort is focused on the design of novel, fully automated platforms that can accommodate the whole bioprocess in one closed system, using one or more single-use components.

One such platform, gaining momentum in clinical manufacturing, is the CliniMACS Prodigy® (Miltenyi Biotec). It is an all-in-one agitated system, tailored specifically to the manufacturing of CAR-T cell therapy; an autologous cell-based gene therapy given as a single-dose curative treatment for several forms of blood cancer [(1)]. At the core of the Prodigy's functionality is its bioreactor unit, the CentriCult™: a single-use cylindrical chamber, with no impeller or sparger, which rotates intermittently around its central axis to achieve agitation of the cell culture. Some work on intermittent agitation in stirred tanks has been published, suggesting that it may have beneficial effects for the cells [(2)], however no such studies have been done in geometries similar to the CentriCult™. Moreover, while the classical scenarios of non-linear spin-up and spin-down of a fluid in a rotating cylinder have been analytically and computationally examined by other disciplines [(3), (4)], these complex transient flows, an example of which is shown in Fig.1, have never been studied in the context of cell therapy manufacturing. As the cells spend most of the manufacturing time inside the CentriCult™ unit, understanding and optimising the fluid dynamics environment they are subject to is necessary for the successful translation of the process to this promising new platform.

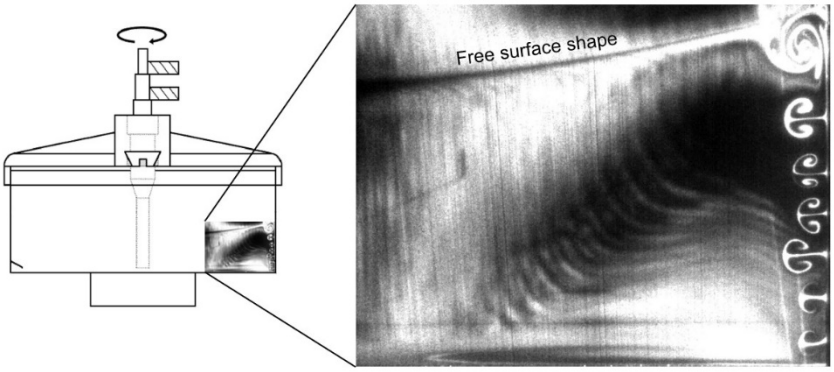

Figure 1 - An example of Taylor-Görtler vortices formed at the wall of a mimic of the CentriCult™ unit during spin-down to rest, visualised with fluorescent rhodamine dye

The current work aims to optimise the mixing efficiency of the single-use bioreactor unit through the design of improved rotation strategies, tailored specifically to the expansion and activation steps of the CAR-T manufacturing process. Different operating parameters, such as rotation speed, duration of spin-up and spin-down, and angular acceleration and deceleration, can significantly affect the flow patterns, secondary circulation and power input in the bioreactor. The effect of each was individually studied experimentally through Laser-Induced Fluorescence (LIF) and Particle Image Velocimetry (PIV), and then a combined agitation strategy was designed for optimal continuous micro- and macromixing during the expansion phase. The mixing efficiency of the new strategy is analysed using a colorimetric acid-base technique and is compared to that of the currently used agitation strategies preprogramed by the manufacturer (also referred to as 'shake' modes). Future work involves optimising the suspension efficiency of the bioreactor through a similar approach. The utilisation of the hereby described optimised 'shake' modes of the CentriCult™ can prove useful in the effort to achieve the desired cell densities in the new single-use bioreactor.

---

(1) Mock, U. et al. (2016), *Cytotherapy*, 18 (8), pp. 1002–1011.
(2) Samaras, J.J., Micheletti, M. and Ducci, A. (2019), *Chem. Eng. Technol.* 42 (8), pp. 1587–1593.
(3) Goller, H. and Ranov, T. (1968), *J. Basic Eng.*, 90, pp. 445–454.
(4) Kaiser, F. et al. (2020), *J. Fluid Mech.*, 885, A6