Metabolic profiling of CAR-T cell production process

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ABSTRACT

In recent years, adoptive cell therapies (ACT), including Chimeric Antigen Receptor T (CAR-T)[1] and T-cell receptor (TCR) therapy[2] have revolutionized treatment approaches in cancer immunotherapy. CAR-T cell therapy, cleared for use by regulatory agencies in just 2017, involves genetic engineering of immune cells (T lymphocytes) to express a synthetic Chimeric Antigen Receptor (CAR), redirecting them to seek and specifically destroy cancerous cells in patient's body. CAR-T cell therapy has already proven to be a successful clinical treatment for haematological malignancies, including leukaemia, lymphoma and multiple myeloma[3]. However, despite its great potential and positive outcomes, CAR-T cell therapy remains a very expensive treatment for the general public and faces challenges, such as life-threatening toxicities (e.g., cytokine release syndrome), potential loss of target antigen, exhaustion of tumour-infiltrating T cells upon entering solid tumours and relatively low rates of durable responses[4]. Moreover, complexities arising from centralized manufacturing facilities, inflexible production processes and clinical utilization strategies restrict patients' access to CAR-T therapy and influence the therapeutic outcome. Therefore, a comprehensive characterization of CAR-T cell production process would enable the optimization and standardization of the process, the development of automated systems for consistent high-yield CAR-T cell production and the identification of biomarkers for sensitive process monitoring.

In the H2020 AIDPATH ("Artificial Intelligence-driven, Decentralized Production for Advanced Therapies in the Hospital") project #101016909, our group aims at the use of metabolic profiling to characterize different CAR-T cell production setups and provide high-throughput data complimenting the current bioprocess measurement set. Metabolomics has not been extensively used in CAR-T cell bioprocess development and analysis, so the project is contributing novel omic data to further our understanding of the process. In this presentation, we will show and discuss results from (a) the endo-metabolomic analysis of samples obtained from the CliniMACS Prodigy system in a clinical trial carried out at the Fundacio de Recerca Clinic Barcelona (FRCB) partner and (b) the exo-metabolomic analysis of samples from G-Rex system in different media, obtained in collaboration with UCL and CellGenix partners.

KEYWORDS: CAR-T cell therapy, metabolomics, bioreactor engineering, cell culture engineering, systems immunology

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