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status of patients, but invasive candidiasis and paracoccidioidomycosis have affected immunocompetent individuals due to the virulence factors of fungi that subvert the host immune response. T cells are essential to control the invasive candidiasis and paracoccidioidomycosis and the effector activity of T cells is required in the site of infection, which can be modulated by C. albicans and P. brasiliensis to promote the establishment and progression of infection. Then, the technology of chimeric antigen receptor (CAR) can redirect T cells to target fungi in the site of infection, and our group developed a novel CAR that targets a carbohydrate available on the cell surface of C. albicans hyphae and yeast form of P. brasiliensis.

**Methods, Results & Conclusion:** The novel CAR is designed M-CAR and its coding sequence is into lentiviral vector, moreover M-CAR has a FLAG-tag on the extracellular domain, the CD3 molecule as hinge/transmembrane domain, and the activation motifs of CD137 and CD3ζ molecules as signal transduction domains. Lentiviral particles containing the coding sequence of M-CAR were made in HEK 293T cells after transient transfection, and the titer of 1.55x10^8 TU/ml of lentiviral particles was quantified after transduction of Jurkat cells. These cells were modified with M-CAR using a multiplicity of infection (MOI) of 3, 5, 10 or 20. The CAR expression increased in a MOI dependent-manner, whereas the cell viability was optimal between MOI of 1 and 5. M-CAR Jurkat cells were incubated with yeast or hyphae forms of C. albicans (fungi/cells ratio of 1:1) or P. brasiliensis (fungi/cells ratio of 1:1; 1:5; 1:10) for 24 and 48 h. M-CAR Jurkat cells secreted high levels of IL-2 in the presence of hyphae form of C. albicans and its yeast form was not recognized by M-CAR. M-CAR Jurkat cells also recognized P. brasiliensis as evidenced by high levels of IL-2 quantified in the cell supernatant of co-culture between modified cells and fungi. These data open new perspectives to evaluate the capacity of M-CAR to recognize other species of fungi.
day 28 (end of study). 18 patients had mild-to-severe ARDS and 16/18 (88.8%) completely recovered within few days. The cytokine storm was resolved in all discharged patients as shown by laboratory and 30 cytokine/chemokine measurements (Fig. 1 shows pro-inflammatory cytokines). Conclusion: Allocetra showed excellent safety profile and promising results regarding resolution of inflammation and respiratory failure. A double blind large comparative study in this population is now recruiting patients in 3 countries.

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NOVEL STRATEGIES TO ENHANCE THE SAFETY OF CAR T CELL IMMUNOTHERAPY: THE IMSAVAR PROJECT
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Keywords: CAR T cells, cytokine release syndrome, safety assessment.

Background & Aim: Adoptive immunotherapy with CAR T cells is a transformative treatment in hematology but can be associated with significant toxicity from e.g. cytokine release syndrome (CRS). Non-clinical testing to assess CRS is not standardized and there is a strong medical need to establish algorithms assessing the propensity of novel CAR T cell products inducing CRS and other toxicities. imSAVAR – immune safety avatar – is an EU Innovative Medicines Initiative project that tackles this challenge in a joint academia-industry consortium seeking to establish a platform for assessing the utility of innovative non-clinical models and endpoints for enhancing the safety assessment of e.g. CAR T cells.

Methods, Results & Conclusion: A key deliverable is the development of a conceptual map of CRS pathogenesis as an immune-related adverse outcome pathway (irAOP) comprising key molecular and cellular events identified through a systematic literature review on pathophysiology and clinical occurrence of CRS after CAR T cell therapy. To each event existing and emerging non-clinical assays were allocated. imSAVAR is engaging all stakeholders in CAR-T immunotherapy, including clinicians, scientists, model developers, bioinformaticians, data analysts as well as patients through surveys and workshops for patients and health care professionals. We established a roadmap for studies establishing a new set of non-clinical assays and endpoints that will be validated incorporating the feedback from multi-stakeholder workshops to help mitigate clinical safety concerns. To this end, an experimental campaign was conducted with n=3 CAR T cell products in n=5 test systems from within the consortium. Test systems available in imSAVAR include in vitro co-culture assays, in vivo models, genomic approaches, and organ-on-a-chip models. All data will be correlated with clinical data to identify optimal non-clinical assays for enhancing assessment and prediction of CRS. imSAVAR established an irAOP that will enable the development and validation of novel non-clinical assays that aim to enhance the characterization of CAR T cell associated CRS during non-clinical development. This effort is ultimately anticipated to enhance the safety assessment of therapeutic CAR T cell products, thus potentially accelerating patient access to CAR T cell products.

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REAL-NEOsplice, A NOVEL BIOINFORMATICS PIPELINE FOR IDENTIFICATION AND PRIORITIZATION OF NEOANTIGENS FROM ABERRANT RNA SPlicing ISOFORMS
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Keywords: Neoantigen, Splicing, Bioinformatics.

Background & Aim: Cancer neoantigen vaccines are among the most promising next generation immunotherapy agents. Neoantigens arise from protein-altering somatic mutations. Multiple bioinformatics frameworks, including our own REAL-neo {Ren et al.} pipeline, have been developed to identify neoantigens from single nucleotide mutations, small INDELs, and gene fusions. However, the identification of neoantigens from aberrant RNA splicing events, which is another rich source of neoantigens, has been analytically difficult. Accurate identification and prioritization of splicing neoantigens from short read RNA-seq data has been challenging due to the absence of full-length transcriptome profiles. Here, we present a computational pipeline, REAL-neoSplice.

Methods, Results & Conclusion: REAL-neoSplice leverages somatic splice site mutations detected in tumor exomes to predict splicing acceptor and donor gain and loss, as well as the consequent aberrant splicing isoforms. In addition, REAL-neoSplice discovers de novo splicing isoforms without underlying DNA splice site mut-