Background Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine malignancy that accounts for 15% of lung cancer diagnoses. The severity of this disease is exacerbated by the fact that there are few therapeutic options, which mostly offer limited clinical benefit, culminating in a 5-year survival rate of

Methods To identify transcriptional subtypes, we used non-negative matrix factorization of gene expression data from 81 SCLC tumors and identified four subtypes largely based on differential expression of the transcription factors ASCL1, NEUROD1, and POU2F3. We hypothesized that these subtypes may underlie unique therapeutic vulnerabilities. We examined differential expression of genes that encode surface-expressed proteins that may be targetable by reagents such as therapeutic antibodies or antibody-drug conjugates (ADCs).

Results Our four subtypes are defined either by high expression of ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P), or an absence of those transcription factors and instead a prevalence of immunological factors (SCLC-Inflamed, SCLC-I). We curated a list of approximately 60 candidate genes encoding surface proteins that are differentially expressed across the four subtypes. Within these 60 candidates, we have identified a few specific to each subtype for which there exist clinically available, targeted ADCs. The most prevalent subtype, SCLC-A, showed high expression of targets such as DLL3 (SCLC-A) and CEACAM5 (SCLC-A). SCLC-N highly expressed SSTR2, a somatostatin receptor that is being actively targeted in SCLC clinical trials. The two non-neuroendocrine subtypes, SCLC-P and SCLC-I shared some common hits such as the NK cell ligand MICA and B7H6. All of the identified and highlighted hits have been or are actively being pursued in clinical trials, highlighting the importance of understanding their expression levels pre- and post-treatment so that novel therapies can be developed that will be effective over the course of disease progression.

Conclusions The underlying biology defining our four identified subtypes of SCLC has revealed a striking number of targetable, differentially expressed surface protein encoding genes many of which already have clinically available reagents that could be repurposed for treatment of SCLC on a subtype-specific basis.

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Immunotherapy toxicities

PROFILING OF DONOR-SPECIFIC IMMUNE EFFECTOR SIGNATURES IN RESPONSE TO RITUXIMAB IN A HUMAN WHOLE BLOOD LOOP ASSAY USING BLOOD FROM CLL PATIENTS

1Mohamed Eltahir, Erika Fletcher, 2Linn Dynesius, 3Justina Jarblad, 1Martin Lord, 1Ida Olsson, 1Mikaela Zekarias, 3Xiaojie Yu, 4Mark Cragg, 5Caroline Hammarstom, 5Kerstin Olofsson, 1Mohamed Eltahir, 1Erika Fletcher, 2Linn Dynesius, 2Justina Jarblad, 1Martin Lord, 1Ida Olsson, 1Mikaela Zekarias, 3Xiaojie Yu, 4Mark Cragg, 5Caroline Hammarstom, 5Kerstin Olofsson

1University of Southampton, Southampton, UK; 2Immuneed AB, Uppsala, Sweden; 3University of Southampton, Southampton, UK; 4Clinical Trial Consultants AB, Uppsala, Sweden; 5Uppsala University Hospital, Uppsala, Sweden

Background Rituximab is widely used in the treatment of haematological malignancies, including chronic lymphoid leukaemia (CLL), the most common leukaemia in adults. However, some patients, especially those with high tumour burden, develop cytokine release syndrome (CRS). It is likely that more patients will develop therapy-linked CRS in the future due to the implementation of other immunotherapeutics, such as CAR T-cell, for many malignancies. Current methods for CRS risk assessment are limited, hence there is a need to develop new methods.

Methods To better recapitulate an in vivo setting, we implemented the unique human whole blood ‘loop’ system (figure 1)1 to study patient-specific immune responses to rituximab in blood derived from CLL patients.

Results Upon rituximab infusion, both complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) profiles were evident in CLL patient blood, coincident with CLL cell depletion. Whereas B cell depletion is induced in healthy persons in the blood loop, only patients display B cell depletion coupled with CRS. With the exception of one donor who lacked NK cells, all other five patients displayed variable B cell depletion along with CRS profile. Additionally, inhibition of CDC or ADCC via either inhibitors or antibody Fc modification resulted in skewing of the immune killing mechanism consistent with published literature.

Conclusions Herein we have shown that the human whole blood loop model can be applied using blood from a specific indication to build a disease-specific CRS and immune activation profiling ex vivo system. Other therapeutic antibodies used for other indications may benefit from antibody characterization in a similar setting.

REFERENCE


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PREDICTION OF SEVERE IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS ON IMMUNE CHECKPOINT INHIBITORS: STUDY OF A POPULATION LEVEL INSURANCE CLAIMS DATABASE FROM THE UNITED STATES

1Mark Kálnich, William Murphy*, Shannon Wongvilai, Varthan Pahalayants, Kun-Hsing Yu, Feicheng Wang, Leyre Zubiri, Vivek Narahbhain, Alexander Gusev, Shrinivas Kwaitra, Kerry Reynolds, Yevgeniy Semenov. 1Harvard Medical School, Boston, MA, USA; 2Johns Hopkins School of Medicine, Baltimore, MD, USA; 3Dana-Farber Cancer Institute, Boston, MA, USA; 4Massachusetts General Hospital, Boston, MA, USA; 5Johns Hopkins University, Baltimore, MD, USA

1Mark Kálnich, William Murphy*, Shannon Wongvilai, Varthan Pahalayants, Kun-Hsing Yu, Feicheng Wang, Leyre Zubiri, Vivek Narahbhain, Alexander Gusev, Shrinivas Kwaitra, Kerry Reynolds, Yevgeniy Semenov. 1Harvard Medical School, Boston, MA, USA; 2Johns Hopkins School of Medicine, Baltimore, MD, USA; 3Dana-Farber Cancer Institute, Boston, MA, USA; 4Massachusetts General Hospital, Boston, MA, USA; 5Johns Hopkins University, Baltimore, MD, USA

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