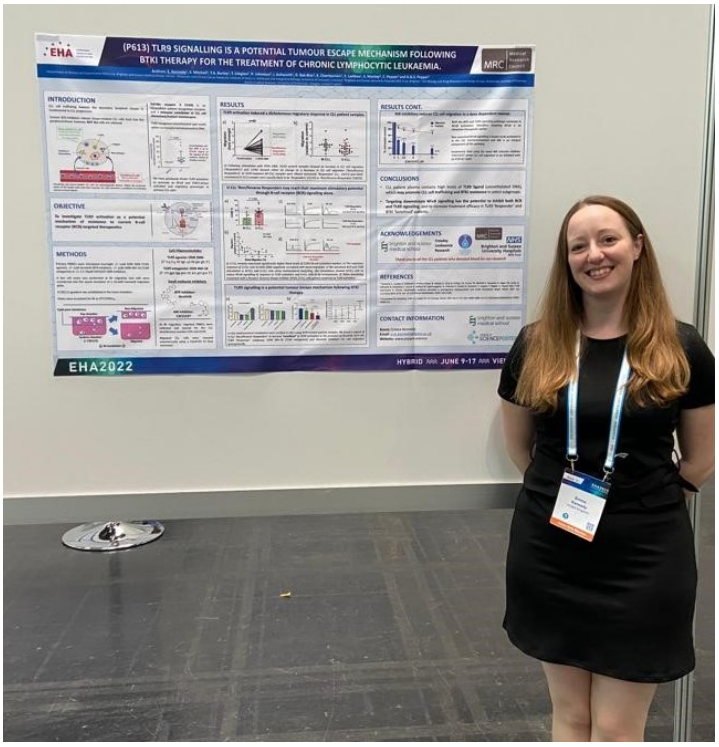
EHA 2022

I would like to thank the UK CLL Forum for funding my travel to the 30th European Hematology Association congress (EHA 2022), which was held in Vienna at the start of June. EHA 2022 comprised an extensive program of clinical and translational research, and whilst it would be impossible to individually acknowledge all of the wonderful speakers at this year's event, the following summary will concentrate on talks relating to microenvironmental interactions in CLL.

The main meeting was preceded by the YoungEHA Research Meeting in which Dr. Ernest Garguilo (Luxembourg Institute of Health) spoke about how 'Small extracellular vesicles in the leukemia microenvironment sustain CLL progression by hampering T cell-mediated anti-tumor immunity'. Garguilo described how CLL cells manipulate their environment by secreting extracellular vesicles, which are internalised by CD8+ T-cells. The contents of these vesicles induce transcriptomic, proteomic and metabolic changes in the CD8+ T-cells, reducing their ability to function and to induce an immune response against the malignant cells.

During the main meeting, Dr. Ingo Ringshausen (Wellcome-MRC Cambridge Stem Cell Institute, UK), emphasised the tumour promoting effects of tissue-resident mesenchymal stromal cells. In his fascinating talk, he described how direct contact between stromal and CLL cells results in a PKC-β/MAPK/BCL-xL-dependent mechanism of resistance to several CLL therapies (including venetoclax, Bendamustine and BCR-targeted agents). He then explained how PKC-β inhibition was found to alter the composition of adhesion molecules upon the stromal cell surface, resulting in the elimination of stromal-dependent MAPK signalling/BCL-XL expression in CLL tumour cells; PKC-β inhibitors were shown to synergise with the BCL-2 targeted agent venetoclax.

Dr. Dimitar Efremov (ICGB, Italy) presented an interesting overview of the interplay between genetic driver mutations and microenvironmental signals. Efremov explained how del9p21 is one of the most frequent genetic lesions to occur at the time of Richter's Transformation, and how it results in the loss of two negative regulators of G1/S phase progression (CDKN2A/CDKN2B). In the absence of this lesion, antigen-stimulated B-cell receptor activation both *promotes* entry into the G1 phase of the cell cycle, and *inhibits* further progression into S phase; the cell cycle therefore cannot advance without an additional co-stimulatory signal. Following the development of a del9p21 aberration, this G1/S barrier is removed, enabling antigen-stimulated BCR activation to induce 'co-stimulatory signal independent proliferation'. This was found to be reversed in the presence of the BCR-targeted Bruton's Tyrosine Kinase inhibitor (BTKi) ibrutinib

. 

EHA 2022 was my first 'in-person' experience of an international congress, and I was very excited to present my data in a face-to-face poster session; my poster was entitled: 'TLR9 signalling is a potential tumour escape mechanism following BTKi therapy for the treatment of chronic lymphocytic leukaemia'. CLL cell trafficking to the protective niches of the secondary lymphoid tissues, is fundamental to disease progression. Current BTKi's (e.g., ibrutinib), are extremely effective at releasing tissue-resident CLL cells back into the bloodstream, however, they notoriously fail to achieve a complete clearance. TLR9 is a pattern recognition receptor (specific for unmethylated CpG DNA) and can activate CLL cells independently of BCR signalling; our group have previously identified a pro-migratory role for TLR9 in primary CLL cells (Kennedy et al., 2021) and therefore believe it is an attractive candidate for a dual targeted approach to therapy. My poster expanded upon our previous findings, showing interpatient differences in the migratory response to TLR9 activation. We are currently investigating the effects of TLR9 signalling in ibrutinib-treated CLL cells and believe that TLR9 may act as a mechanism of BTKi resistance in select subgroups of CLL patients.

Interestingly, in a talk from Dr. Claudio Martinez (ICGB, Italy), it was suggested that the tumour-reducing effects of TLR inhibition were indirect. Martinez described an *in vivo* model in which inhibiting the downstream kinase IRAK4, resulted in a reduction of xenografted CLL cells within the spleen, yet disrupting IRAK4 by CRISPR/Cas9 genome editing, did not. This lead to the conclusion that TLR inhibition was important for impeding the actions of tumour promoting monocytes/macrophages, rather than the CLL cells themselves. Martinez even suggested that CLL

cells may not receive or rely on TLR signals; this was an interesting and thought-provoking contradiction to my own data.

Finally, a really positive addition to the program this year were two writing workshops for early career researchers covering ‘scientific writing’ and ‘grant writing’. I chose to attend the grant writing workshop which provided an interesting insight into how grant proposals are received and reviewed, and I feel I came away equipped with many useful tips and tricks to consider when planning future applications.

Many thanks once again to the UK CLL Forum for awarding my travel grant for the opportunity to attend EHA 2022.