Daniel Friedman from King's College London was awarded an award to attend the American Society for Hematology (ASH) conference virtually in December 2021. Daniel presented a poster of his most recent data along with an oral summary examining intraclonal heterogeneity in CLL entitled '*identification of a novel proliferating cell fraction in CLL with high expression of IgM and chemokine receptors'*.

"Although attending virtually the online platform was well designed to easily reach out and interact with other groups and discuss experimental methodology/findings etc. The amount of novel research was huge at ASH making it difficult to choose from a host of great talks! I have chosen key presentations which particularly appealed to me – I have focused on talks on new molecular insights into CLL."

Dr Hassan – Moores Cancer centre, San Diego
Using Mass spectrometry their research has shed light on the mechanism underlying the observation that enhanced ROR1 in CLL cells leads to enhanced leukemogenesis in TCL1 mice. They show that Wnt5a induces ROR1 to couple with DOCK2 forming intracellular heterodimers inducing tyrosine phosphorylation of DOCK2 which in turn recruits the cytoplasmic adaptor protein Grb2 and SOS1 to ROR1, which enhances Ras and ERK1/2 activation leading to activation and proliferation of CLL cells.

Elisa ten Hacken – Dana Farber Institute
Using a novel setup of a multiplexed CRISPR based mouse model to elucidate genetic signatures underlying Richter's transformation (RS), her research showed that TP53 mutation is an essential RS driver in CLL. Mutated TP53 is mechanistically linked to *Mga* and *Chd2* mutations with reduced capacity to respond to interferons *in vitro*.

Chiorazzi group – Feinstein institute, NY
Following on from previous work on the intraclonal heterogeneity of CLL cells in the periphery, analysis of further subfractions in patients using incorporated deuterium as a measure of proliferation demonstrated that the proliferating fraction ($CXCR4^{lo}CD5^{hi}$) contained the highest amount of incorporated deuterium followed by the $CXCR4^{lo}CD5^{lo}$, $CXCR4^{hi}CD5^{hi}$ and $CXCR4^{hi}CD5^{lo}$. Additionally, by looking at subfractions before and after ibrutinib treatment they show that fraction most impacted by treatment are the proliferating fractions with both a reduction in cell size and surface IgM.

Hui Jin - Pukou CLL Centre, China
Using single cell RNA sequencing to examine both ibrutinib-resistant and ibrutinib-sensitive CLL cells in the bulk peripheral blood cells, two candidate genes Galectin-1 (*LGALS1*) and lymphocyte-activating gene 3 (*LAG3*) were identified to contribute towards ibrutinib-resistance and poor survival in CLL patients. Chronic exposure of ibrutinib *in vitro* resulted in upregulation of *LGALS1* and *LAG3*, whilst addition of an LGALS1 inhibitor inhibited the growth of ibrutinib-resistant CLL cells highlighting potential new gene candidates for therapeutic targeting.

Shanye Yin, Dana Farber Institute
Really interesting work highlighted the critical role of methylation deregulation in the pathogenesis of CLL. Generation of a conditional knock out with B cell restricted homozygous deletion of the DNA methyltrasferase *DNMT3a* resulted in the development of $CD19^{+}CD5^{+}$ B cells. RNAseq in these knockout cells revealed an enrichment of oncogenic signalling with an increase in Wnt signaling and Notch activation revealing a role for the *DNMT3a* in the generation of CLL.

Jaewoong Lee, Yale University
Marcus Muschens' group show that the cytoplasmic tail of CD25 and one of the three chains of the IL-2R signals in B cells in a monomeric fashion showing recruitment either to the BCR or

transforming oncogenes within lipid rafts in B-ALL, CLL and mantle cell lymphoma. They demonstrate in oncogenic B cells that CD25 plays a distinct signalling role in maintaining homeostasis of oncogenic signalling by recruitment of PKCδ and adaptor proteins which provide scaffolding platforms for the inhibitory phosphatases SHIP1 and SHP1 and provide negative feedback to the BCR signalling thus preventing B cell exhaustion.