XVII International Workshop on Chronic Lymphocytic Leukemia (CLL) 2017, New York

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In May 2017, I attended the XVII International Workshop on chronic lymphocytic leukaemia (iwCLL) in New York's Times Square. For more than 30 years, the iwCLL has grown from a small group of specialist Consultant Haematologists to a large international group of multidisciplinary professionals focused on improving the understanding and treatment of CLL. Patients with CLL have a variable disease course influenced by different factors. This conference was a well-designed 3-day event with talks from clinical healthcare professionals, research scientists and diagnostic geneticists for an update of the new concepts emerging from clinic and laboratory-based research about the pathobiology and treatment of this still incurable disease.

A number of very interesting talks were presented but some of the highlights including a talk titled "What is the cell of origin of CLL" by Olivier Bernard PhD, from the Institut Gustave Roussy, Paris. Bernard stated that, like many adult myeloid malignancies, CLL develops from a pre-leukemic phase and that "early" mutations in CLL affect B-cell differentiation/maturation as well as contribute to growth/survival of the tumour clone.

Chris Oakes, from The Ohio State University, Columbus, USA talked about "New Insights Revealed by Epigenetic Studies in CLL" and discussed the divergent epigenetic patterns seen in patients with CLL and showed that it was possible to link certain epitypes to disease features such as *IGHV* mutation status and prognostic clinical outcomes. The patterns of methylation, shown to be largely derived from founder cells, can evolve over time and this usually corresponds to the acquisition of driver mutations.

Genetic evolution in CLL was also discussed by Dan Landau, MD, PhD, from Weill Cornell Medical College, New York who's talk on "The Origin of CLL Evolution" focussed on intra-tumour heterogeneity in CLL and the impact of treatment on clonal evolution. In 2013, Landau *et al.*[1] found that the presence of a sub-clonal driver mutation was an independent risk factor for rapid disease progression. In a later study, they reported that 97% of CLLs showed significant clonal evolution in relapse and that evolution frequently involves the expansion of a sub-clone that could be retrospectively detected in the pre-treatment sample[2]. To the audience, Landau presented the idea that the future of treatment for patients with CLL, and possibly other cancers, would include mathematical modelling to temporally map the dynamics of sub-clonal mutations present even at diagnosis to allow for bespoke administration of therapies for patients according to their mutational signatures.

In spite of many new advances in understanding CLL pathobiology, it is clear that disruptions of *TP53* (17p13) are still an important prognostic indicator for this disease; they have been associated with a poor prognosis, a short time to progression, an early need for treatment, and dismal outcome mainly due to refractoriness to standard chemoimmunotherapy treatment[3,4,5,6]. Recent studies have shown that patients with a *TP53* disruption significantly benefit from non-chemotherapy approaches with agents acting independently of the p53 pathway and it is recommended that *TP53* status is assessed prior to therapy by European and British recommendations for CLL[7,8]. Work published by Rossi *et al.* (2014) dispelled the

dogma that the size of the clone with a *TP53* disruption must be greater than 10-20% of leukaemic cells to be clinically significant through demonstrating that small *TP53* mutated sub-clones detected by ultra-deep next generation sequencing (NGS) (variant allele frequency <1%; with no apparent cut-off) have the same unfavourable prognostic impact as clonal *TP53* defects present in a higher proportion of cells[9].The pathogenic effect of these sub-clonal mutations was indicated by the observation that they are positively selected to become the most dominant leukaemic population at the time of CLL relapse due to resistance to chemoimmunotherapy. However, there is currently a lack of prospective clinical trial data on the significance of low level (<10% VAF) mutations in CLL and as such, the iwCLL and the European research initiative on CLL (ERIC) consortium recommend that mutations in *TP53* are only reported when detected above 10% VAF. This presents a challenging ethical dilemma for diagnostic laboratories that sequence this gene using NGS technologies which can detect mutations down to 1% VAF, especially when mutations detected are known pathogenic mutations frequently reported.

The conference provided presenters an opportunity to share critical updates and allowed attendees to actively engage with presenters, make important connections and gain insight into the latest treatment strategies. There was also a feeling that many of the attendees had been working together as a community in spite of the modern challenges of competitive research environments. This conference provided a fantastic opportunity to present the work that my colleagues and I have completed for the implementation of *TP53* mutation testing by next generation sequencing for patients with CLL and I must sincerely thank the ACGS for part-funding my attendance through the ACGS travel fund.

References
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New York, New York!