Examining a Novel Combination Approach in Treating Mutant p53-dependent CLL (Progress Report). Lead Investigator: Sean M. Post, Ph.D., University of Texas, MD Anderson Cancer Center

In December 2015, The CLL Foundation awarded Doctor Sean M. Post, Ph.D., of the MD Anderson Cancer Center in Houston a grant to investigate an approach to treating CLL patients whose cancer cells have an alteration or deletion of the p53 gene. CLL cells with p53 deletions are especially virulent, causing rapid disease progression and leaving patients with a poor prognosis for survival.

Ibrutinib, a drug that inhibits a B-cell receptor for CLL by suppressing Bruton's tyrosine kinase (BTK), has been approved for treatment of CLL patients with alterations of the p53 gene. Although this drug extends survival, it will not accomplish a complete remission and patients will relapse. Dr. Post used the Foundation's grant to determine whether the combination of ibrutinib with ABT-199, a BCL-2 inhibitor, would reduce the viability of CLL cells with a single p53 mutation and promote the death of such cells.

Dr. Post and his team started with a strain of mice susceptible to CLL and developed a sub-strain that lacked the p53 gene. Comparing the two genotypes, Dr. Post and his team determined that CLL progressed more rapidly in the mutant p53 mice, that such mice had diminished levels of a substance that contributed to the death of cancer cells, and that the mutant p53 mice provided an excellent preclinical platform for studying the progression of CLL. Leukemic B-cells from both mouse genotypes were collected, cultured, and tested with ibrutinib or ABT-199, alone or combined. Dr. Post and his team found that when the two drugs were used in combination they were highly effective at reducing cell viability regardless of mouse genotype. These findings demonstrate that the combination of drugs inhibiting BTK (ibrutinib) and BCL-2 (APT-199) has a potent effect against CLL and should be an effective treatment against the aggressive forms of CLL resulting from p53 mutations.

To determine whether the drug combination would be effective in live mice, Dr. Post needed to develop a way to shorten the time required to test the combination in mice with healthy immune systems. Dr. Post developed a way to transplant malignant B cells from the mutant p53 mice into healthy mice. This process has provided Dr. Post and his team with a preclinical platform for investigating the combination of ibrutinib and ABT in an *in vivo* setting.

Dr. Post presented his research to the European Hematology Association in June of 2017.