“Epigenetic Mechanisms of the Mixed Lineage Leukemia 1 (MLL1) Protein in Human Leukemogenesis Mediated by Specific Interactions with the PAF Transcription Elongation Complex”

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Abstract: MLL1 fusion proteins cause aggressive acute childhood and adult leukemias that respond poorly to treatment. The maintenance of HOX gene expression in hematopoietic progenitor cells is necessary for MLL1-mediated leukemogenesis, but specific molecular details of how this occurs are unknown. We recently have found a specific interaction between the CXXC domain of MLL1 and its fusion proteins and the PAF1 subunit of the PAF transcription elongation complex. This suggests that HOX gene expression in MLL1-mediated leukemia may be maintained via the PAF complex and the activity of interacting effector proteins. The broad aims of this proposal are: (i) to elucidate the structural basis of the PAF1-MLL1 interaction, (ii) to detail the mechanism of action of MLL1 fusion proteins through PAF-dependent functions of fusion protein complexes and/or through effects of MLL1 fusion protein complexes on other PAF-mediated functions in transcription, and (iii) to determine whether the PAF1-MLL1 interaction is important for leukemogenesis *in vivo*. Several complementary approaches will be taken to this fundamental, cancer-related problem. These include: high resolution x-ray crystallographic analysis of the PAF1-MLL1 interface, identification and functional analysis of mutations that selectively disrupt the MLL1-PAF1 interaction, mechanistic analyses of PAF and MLL1 fusion protein complexes in biochemically defined *in vitro* transcription assays, RNAi and chromatin immunoprecipitation assays to assess functions on endogenous target genes, and bone marrow transformation assays and mouse leukemia models. Dissecting these molecular mechanisms will provide the necessary details needed for targeted therapies not only for MLL1 mediated leukemias, but also more generally for the broader range of HOX gene induced human leukemias.