

Myelodysplastic Syndromes (MDS) are diverse, clonal stem cell disorders characterized by bone marrow failure and an increased risk of transformation to acute myeloid leukemia (AML). Incidence of MDS (as well as AML) increases with age and disease is incurable with current therapies except bone marrow transplantation. Frequency of MDS increases with age to approximately 20 new cases each year per 100,000 individuals over 65. MDS represents important health problem contributing to premature mortality, particularly in the areas with growing elderly population. MDS are fatal diseases in the majority of patients, with high morbidity and mortality rates. In addition, observed 5-year survival rate can be as low as 29%. New therapies are urgently needed. In AML there has been no progress in therapeutic agents and strategies for over thirty years. One exception is the Acute Promyelocytic Leukemia (APL), which has been effectively treated with combination of all-*trans*-retinoic acid (ATRA), a derivative of vitamin A, and either chemotherapy or Arsenic Trioxide. Remarkably, the cure rate in APL approaches almost 100%. The key objective set out in our research is to extend this success of using ATRA as a therapeutic agent to MDS and other AML subtypes.

We have recently discovered that combined therapy with the all-*trans*-retinoic acid, (ATRA) and an anti-depressant (TCP, tranylcypromine) have potent anti-leukemic activity in the laboratory. Both of these drugs are licensed for other disease states. Using novel genomic technologies we plan to understand better the mechanism of ATRA/TCP action and plan to re-purpose these orally available, cheap and non-cytotoxic treatments for patients with MDS and AML, who are in desperate need of more effective and safer therapies.