Kendall And Taylor Atkinson
FOUNDATION
Fighting Fanconi Anemia...Enhancing The Lives Of Children

Research Funded by KATA

KATA has funded over 1.2 million dollars in Fanconi anemia research, including research into the causes, treatment and prevention of cancers particularly harmful to FA patients:

1. Comparative Genetic and Metastatic Potential Analyses of Head and Neck Squamous Cell Carcinomas from Wild-type and FANCC-Deficient Mice (Dr. Laura Hays, Oregon Health and Science University)

A study of squamous cell carcinoma in normal and FA mice to determine whether the tumors are biologically and/or genetically different. Dr. Hays' research uses gene arrays to classify and quantify chromosomal rearrangements in tumor cells to determine whether the mutations found in the FA tumors are genetically more unstable and have a higher malignant potential. Additionally, she will quantify the metastatic potential by injecting the oral cavity tumors derived from the normal and FA mice into the oral cavity of immune-competent mice and measure pulmonary metastases. This work will increase the understanding of carcinogenesis in head and neck cancer in FA patients.

2. Screening for Therapeutics in Models of Fanconi Anemia

A multi-institution (Harvard, University of Pennsylvania, Dana farber Cancer Institute and the University of Oregon) project involving the testing of small molecules on cancer prone mice **to discover drugs that can delay or prevent cancers in patients with Fanconi anemia — and in all of us. (Note: the National Institutes of Health in 2011 recognized the far reaching value of this initial FA research and gave the group a 10.7 million dollar grant to continue their work).**

3. "Gene Editing of Induced Pluripotent Stem Cells from Patients with FA"; also titled "Correction of Human FA-Induced Pluripotent Cells by Recombination" (Dr. Jakub Tolar M.D. Ph.D.)

A promising effort to identify an effective method of gene therapy which would safely correct the blood stem cells of FA patients. **The application to other diseases is unlimited.**

4. A Multicenter Trial of Hematopoietic Stem cell Transplantation for the Treatment of Patients with Fanconi Anemia Lacking a Genotypically Identical Donor, Using a Chemotherapy Only Cytoreduction with Busulfan, Cyclophosphamide and Fludarabine. (Memorial Sloan-Kettering Cancer Center)

What has been given for the treatment of FA in the past is to use a combination of low doses of radiation to the whole body and low doses of the chemotherapy drugs cyclophosphamide and fludarabine before the transplant. However, the use of radiation can, later on, increase the chances of getting a second cancer of the skin, head or the neck. These chances of a second cancer are higher than normal and more devastating in patients with FA. The purpose of this study is to find out if the doctors can use a chemotherapy drug called busulfan instead of the radiation. The goal of this study is to eliminate the short term and long term risks of the radiation.

5. Prevalence of FA Gene Germline Mutation in Young Adults with Head and Neck Cancer (MD Anderson Cancer Center)

A study at MD Anderson to see if young adults (under the age of 49) previously diagnosed with head & neck cancer but never diagnosed with FA might possibly also be FA patients. This research will help us know whether all young head and neck squamous cell cancer patients should be routinely tested for FA. If FA is diagnosed, it will help inform physicians how these patients should be treated (aggressive radiation/chemotherapy would not be appropriate).

6. Potential Therapeutic Use of Resveratrol for Head and Neck Carcinogenesis of Fanconi Anemia (Robert Sclafani, PhD)

A study conducted at the University of Colorado School of Medicine by Robert Sclafani, PhD; DNA repair processes may be weak or defective in many types of cancer (for all patients, not just those with FA). Resveratrol, a natural plant compound, has been shown to inhibit the growth of some cancer cells in vitro as well as tumor growth in animal models. When treated with this compound, head and neck squamous cancer cells and ovarian cancer cells (but not normal primary cells) died. Dr. Sclafani believes that since cancer cells lack normal DNA repair pathways, they are much more sensitive to resveratrol actions than normal cells. The proposal seeks to extend these findings to the setting of FA and to test whether resveratrol could be a safe, non-toxic, and inexpensive treatment to prevent or treat head and neck squamous cell carcinoma.

7. Fanconi Anemia and the Repair of DNA Protein Cross-Links (Harvard Medical School)

A study being conducted at Harvard Medical School by Johannes Walter, PhD. Recent studies from a laboratory in Cambridge, the United Kingdom, suggest that the inability to detoxify aldehydes may be a key problem in Fanconi anemia. Aldehydes are common carcinogens. They are constantly produced in the body as a result of cellular metabolism. Aldehydes also exist in the environment: formaldehyde and alcohol are common examples. Mice bred to have Fanconi anemia, coupled with an inability to detoxify aldehydes, developed aplastic anemia, leukemia, and developmental defects, similar to the problems experienced by FA patients. A study of FA patients in Japan showed that patients with an inability to detoxify aldehydes had a more severe form of this disease than patients without this additional defect. Dr. Johannes Walter at the Harvard Medical School is now examining how the FA pathway, when functioning normally, promotes the repair of aldehydeinduced DNA damage. He hopes that understanding the function of the FA pathway in the repair process will suggest how this repair could be stimulated even in the absence of a normal FA pathway. **FARF scientists believe that this work will lay the foundation for the development of rational therapeutic approaches.**

8. Novel Therapeutic Agents for the Treatment of Bone Marrow Failure in Fanconi Anemia

A study being conducted by Dr. Alan D'Andrea at Harvard University and the Dana-Farber Cancer Institute. The goal of this research is to find compounds that will help prevent bone marrow failure in individuals with FA and negate or delay the need for a bone marrow transplant. It has been established that one component of FA bone marrow failure is an increased incidence of and hypersensitivity to DNA damage. Therefore, Dr. D'Andrea screened approximately 6000 small molecules or drugs to find ones that protected FA skin cells in the laboratory from dying after DNA damage. He has narrowed the list of candidate drugs down to 10 and will now test to see if these small molecules or drugs protect FA blood and bone marrow cells from DNA damage.

9. Correcting Fanconi Anemia Mutations by CRISPR/Cas9 Genome Editing to Explore a Novel Therapeutic Strategy

A recent breakthrough in the technology called "gene editing" has provided the ability to efficiently mend mutations in Fanconi anemia genes in patient's own cells. This technology, called "CRISP/Cas9", enables the prevention of bone marrow failure in FA patients by autologous bone marrow transplantation with FA-corrected cells. It is believed that CRISP/Cas9 gene editing has great potential to provide clinical solutions, in particular for FA patients without matching donors. The research in this proposal will answer key questions about gene editing in FA-deficient cells as a first essential step towards the clinical translation of this technology to treat FA patients. The technology generated from this project could be used to correct mutated genes from a variety of different diseases, including cancer.