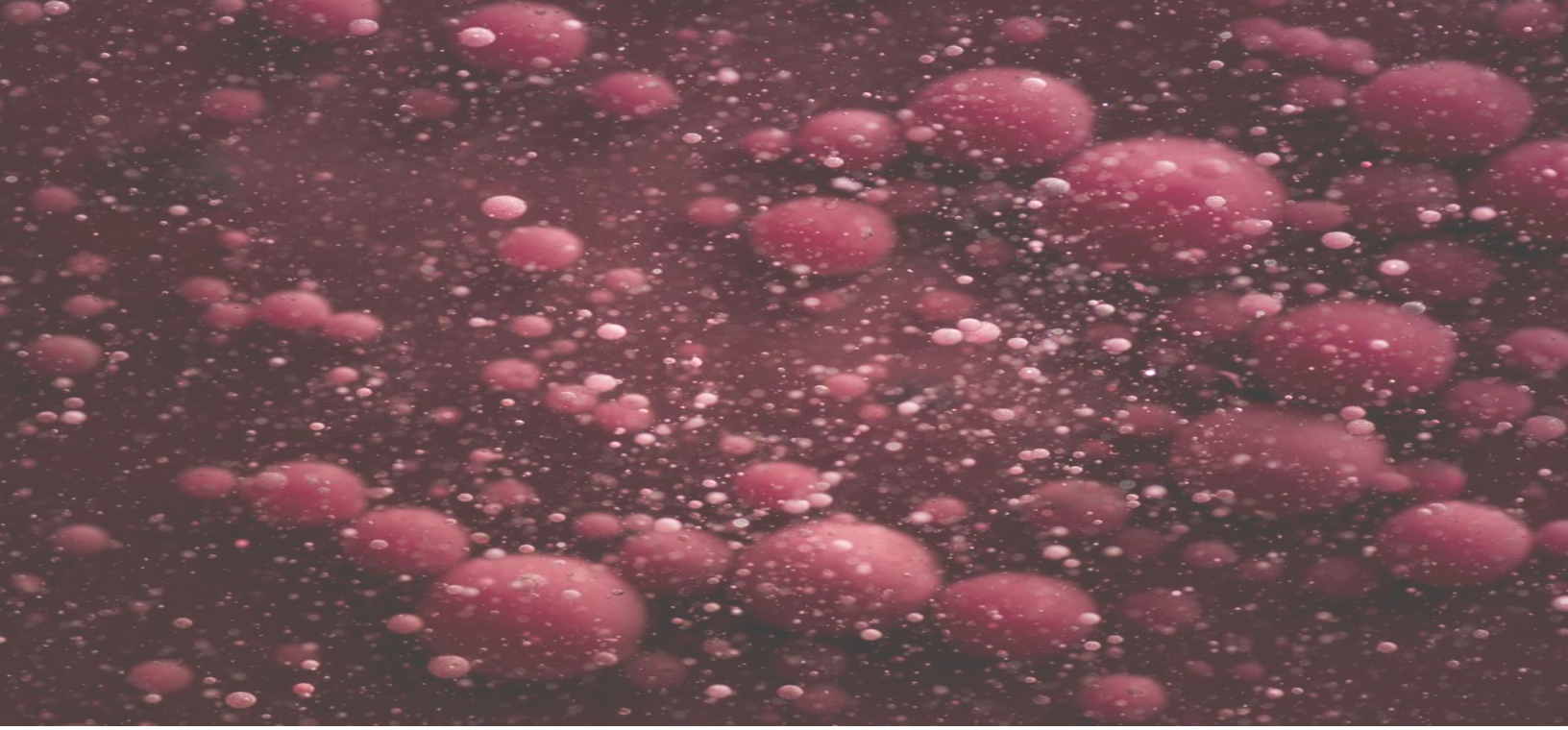


Sager Strong Foundation

2022 Progress Report

V FOUNDATION
Victory Over Cancer

Assessing the Canine Model of Acute Leukemia | Awarded December 2019

Anne Avery, Ph.D., DVM/VMD | *Funded in partnership with The Leukemia & Lymphoma Society's PedAL initiative and the Wine Celebration Fund-A-Need*

Scope

Acute myeloid leukemia is a cancer of bone marrow cells. It can be difficult to treat, particularly in young patients. The disease can differ from one patient to another, depending on the kinds of mutations that are found in the cancer cell. Different mutations may respond to different treatments. Dogs also develop acute leukemia. In this species, the outcomes are dismal, with most dogs being euthanized within days of the diagnosis because of poor quality of life.

Currently available chemotherapy is ineffective in this species. In this project, we will sequence DNA and RNA from 116 cases of naturally occurring acute leukemias in pet dogs. Our goal is to find mutations and gene expression patterns shared between dogs and people. Once these shared features are identified, new treatments can be devised, which can be tested first in dogs, and if successful, translated to humans. This approach offers a chance at better therapies in both species.

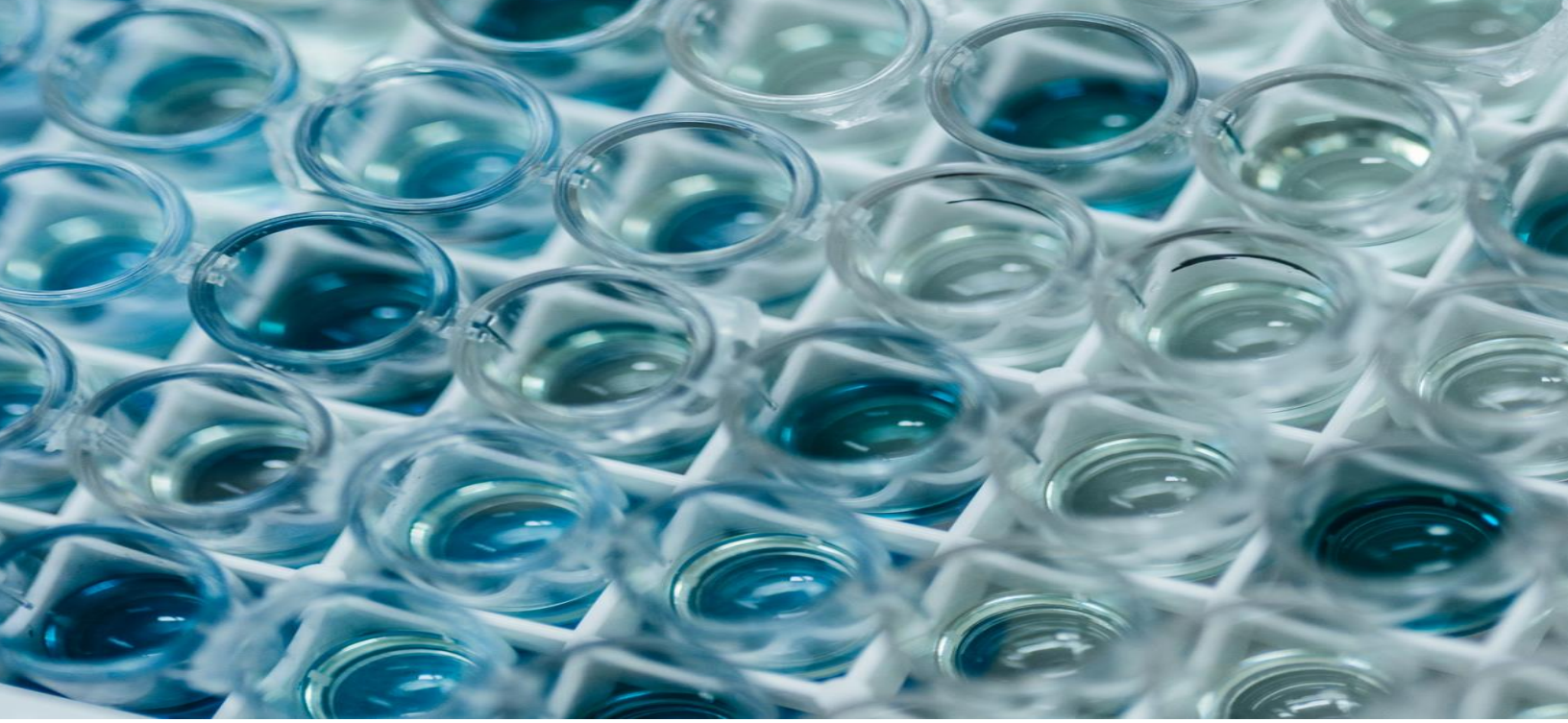
Updates

Year 1 is going according to schedule. As expected, it took most of a year to collect over 100 blood and bone marrow samples from dogs with acute myeloid leukemia, acute lymphoid leukemia and acute leukemia. RNA was extracted from these samples and also from control samples. All of the samples were shipped to the sequencing company (Novagene) in mid-October. Sequencing and preliminary analysis to be completed by mid-December, and then the data sets, contained on hard drives due to their enormous size, will be shipped from China to the U.S. where Dr. Anne Avery's team and co-investigators at Fred Hutchinson Cancer Research Center will collaborate for in-depth analysis to complete the three aims: transcriptome profiling, identify variants and fusion genes using RNA seq data and develop consensus criteria for assigning lineage to canine acute leukemias to establish similarities with human leukemia.

Anne Avery, Ph.D., DVM/VMD | Colorado State University, College of Veterinary Medicine

Anne Avery, Ph.D., DVM/VMD received her VMD from the University of Pennsylvania and a Ph.D. in Immunology from Cornell University. She was a post-doctorate fellow at the Dana-Farber Cancer Institute, Harvard Medical School, and she is currently a professor of immunology at Colorado State University, as well as the Director of the Clinical Hematopathology Laboratory.

Under the direction of Avery, the mission of the Clinical Hematopathology Laboratory is to aid veterinarians in the accurate diagnosis of hematologic malignancies, and to further our understanding of these diseases in canine and feline patients. These cases, and the follow up information generously provided by submitting clinics, have helped to better define breed trends in lymphoma and leukemia, factors involved in prognosis and to identify parallels between human and canine lymphoma.



"If I have learned anything through all of this, is that each and every day is a canvas waiting to be painted; an opportunity for love, for fun, for living, for learning."

- Craig Sager, 2016 ESPYs

Precisely Shaping the Intestinal Microbiome to Improve Cancer Therapy Outcomes

Ami Bhatt, M.D., Ph.D. | Awarded November 2018

Scope

The bacteria, viruses and fungi that live in us are our microbiome. The microbiome can change how cancer grows and how people respond to cancer therapies. We want to improve cancer patients' lives by improving their microbiomes. The usual ways to change the microbiome are through diet, antibiotics and by eating live bacteria in food. We completed an experiment to see if a special fiber can improve the human microbiome. This fiber is digested by specific bacteria in the gut – it is then turned into molecules that control the human immune system.

We gave 15 cancer patients this fiber to see if we can increase these immune system-controlling molecules. We compared the microbiomes of patients who received this fiber to the microbiomes of 16 patients who did not receive this fiber to see if there are any differences. Overall, their microbiomes are fairly similar to one another, as we expected, though there are some notable differences. The most important difference we found is that the patients have some differences in their microbiome after about five days of being exposed to this fiber. Next, we will try to figure out if and how this microbiome change can affect the immune systems of the patients as well. Once we understand how these fibers and our microbes change the immune system, we can figure out precise ways to use this knowledge to make the immune system work better. For example, we may be able to make cancer therapies, like immunotherapy, work better.

Updates

The first phase I clinical trial from this research showed that by adding a soluble fiber to the diet (fructooligosaccharide – FOS), patients did have some specific alterations in the microbiome. Further research is planned to determine the specific impact of these microbiome changes in response to this single fiber, as well as combinations of pre-biotics on the effectiveness of the body's immune cells. A phase 3 clinical trial is enrolling now.

The goal is to eventually introduce these most promising pre-biotics with a chemoimmunotherapeutic treatment (Hematopoietic cell transplantation (HCT)) to reduce some of the negative side effects patients experience due to hyperinflammation from HCT. Lack of access to the lab during the Covid-related shut-downs has slowed down some of this research, but it is back on track now.

Clinical Trials

1. Completed clinical trial - NCT02805075
2. Ongoing, phase 3 randomized controlled national trial

    300 subjects will be enrolled in the microbiome portion of this national, randomized controlled trial of Tac/MTX vs. post-HCT Cyclophosphamide for GVHD prophylaxis. The trial is currently enrolling at tons of sites around the USA and has enrolled >150 subjects to the microbiome portion of the study - NCT03959241. (V foundation PI, Bhatt, is one of five national co-chairs of this study.)

Precisely Shaping the Intestinal Microbiome to Improve Cancer Therapy Outcomes | Ami Bhatt, M.D., Ph.D.

Technical Summary

Hematopoietic cell transplantation (HCT) is a chemoimmunotherapeutic treatment modality that has great potential – unfortunately, its overall contribution to improving patient mortality and morbidity has been greatly hampered by the very high rate of complications, known collectively as treatment-related mortality/morbidity (TRM). TRM occurs at rates that approach those of relapse in some diseases, yet there are significantly fewer studies aimed at improving outcomes for HCT patients by reducing TRM compared to reducing relapse. As additional immunotherapeutic strategies, such as checkpoint blockade and CAR-T cells, are applied in patients with hematological malignancies, we anticipate similarly high rates of TRM related to hyperinflammatory complications of these therapies. There is an abundance of evidence suggesting that the gut microbiota can regulate immunologic homeostasis. As such, precise microbiota manipulation may be a creative and innovative approach to mitigate the inflammatory complications of these types of therapies and may even improve the efficacy of these therapies.

To test the hypothesis that alteration of the microbiome can impact immune homeostasis, we completed a phase I clinical trial of prebiotics (fructooligosaccharide – FOS) in the peri-HCT setting. We used a prospective Bayesian Optimal Interval Design to define maximum tolerated dose, feasibility and toxicity of FOS for 15 HCT patients undergoing reduced-intensity transplantation. Additionally, we compared the stool microbiome composition and SCFA concentrations of longitudinally collected stool samples from HCT patients who received FOS to contemporaneous controls. FOS was found to be well-tolerated with only minimal side effects; intake was primarily limited by oral mucositis. No sustained significant differences in microbiome composition or SCFA concentrations were found between groups. Our findings demonstrate that FOS administration resulted in a statistically significant difference in microbiota composition at day 0 – i.e. the day of HCT (~five days after initiation of FOS) when compared to contemporaneous controls. The alterations in the microbiome are not sustained after day 0, suggesting that subsequent microbiota-altering interventions, such as antibiotics, likely have a stronger effect on the microbiota than FOS (Andermann et al, manuscript in preparation). Finally, we performed CyTOF on peripheral blood samples to quantify peripheral iNKT and T-reg cells (among other cell types) to understand how FOS impacted these immune cell populations (final analysis is ongoing).

In parallel work, we utilized the longitudinal stool from HCT patients to demonstrate that bacteria within the gut microbiota acquire antibiotic resistance in clinical timescales (Zlitni et al, *Genome Medicine* 2020). There is great enthusiasm in the field for microbiome-related research, and this represents one of the first translational research projects focused on harnessing the microbiota for improving cancer outcomes. This research allowed for us to develop a "blueprint" for future, larger studies that will enable careful mechanistic dissection of the immunological impacts of microbiota manipulation in a cancer population. This grant also enabled a post-doctoral fellow in our group (Dr. Tessa Andermann) to successfully transition to an Assistant Professor position and start her own research program, and also enabled our group to successfully compete for two NIH R01 awards.

Ami Bhatt, M.D., Ph.D. | Stanford University | Stanford, CA

Ami Bhatt, M.D., Ph.D., is an Assistant Professor of Medicine & Genetics at Stanford University. She received her M.D. and Ph.D. (Biochemistry & Molecular Biology) at the University of California San Francisco.. There she received the Fineberg Award for Excellence in Teaching and was inducted into Alpha Omega Alpha. She completed residency and chief residency in Internal Medicine at Brigham & Women's Hospital and was a fellow in Hematology/Oncology at the Dana-Farber Cancer Institute. Thereafter, she carried out her post-doctoral studies at the Broad Institute of Harvard and MIT.

In addition to her academic efforts, Bhatt is committed to improving cancer care, education and research in resource-limited settings. She is the Director of Global Oncology for the Center for Innovation in Global Health at Stanford University and has served as a visiting lecturer at the Tokyo Medical and Dental University, Trinity College in Dublin, Ireland, and the University of Botswana. She, along with Franklin Huang, is a co-founder and CEO of the non-profit organization Global Oncology (www.globaonc.org).

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