McMaster University

Centre for Discovery in Cancer Research

CENTRE FOR DISCOVERY IN CANCER RESEARCH

2023 RESEARCH DAY SYMPOSIUM

FRIDAY SEPTEMBER 22, 2023

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AGENDA

WELCOME!

SEPTEMBER 22, 2023

Welcome to the 2023 Research Day Symposium for the Centre for Discovery in Cancer Research (CDCR)! Our dedicated researchers and trainees have been hard at work over the past year, and we cannot wait to present our groundbreaking research to you. Thank you for joining us on this exciting day.

VENUE

McMaster Innovation Park
175 Longwood Rd S, Hamilton, ON L8P 0A1

WIFI

Network: MIP-Internet
Password: Connect@MIP

8:30 - 9:05 AM	BREAKFAST & REGISTRATION	ATRIUM
9:05 - 9:10 AM	WELCOME & INTRODUCTIONS - Sheila Singh, CDCR Director	CONFERENCE ROOMS
9:10 - 9:15 AM	HOUSEKEEPING & INTRODUCTIONS - Anthony Rullo	CONFERENCE ROOMS
9:15 - 10:00 AM	ORAL PRESENTATIONS William Maich: *uPAR as a novel immunotherapeutic target in recurrent Glioblastoma* Ana Portillo: *Human γδ T cells expanded long term with feeder cells expressing membrane bound IL-21 exert high antigen independent anti-tumor function* Hanad Adan: *The role of Kaiso in TGF-beta mediated epithelial-to-mesenchymal transition (EMT) in TNBC*	CONFERENCE ROOMS
10:00 - 10:30 AM	COFFEE BREAK	ATRIUM
10:30 - 11:00 AM	ORAL PRESENTATIONS Karolina Krygier: *Reprogramming Non-Specific Serum Antibodies with a Covalent Immune Recruiter for Targeted Tumor Immumotherapy* Misaal Mehboob: *Investigating the cytotoxicity of expanded NK and CD70-targeting CAR-NK cells against brain tumour cells*	CONFERENCE ROOMS
11:00 - 11:30 AM	RAPID FIRE PRESENTATIONS Stefan Custers: *Targeting lipid metabolism as a potent therapeutic target in MYC-amplified group 3 medulloblastoma* Maria Davola: *Pre-clinical studies of oncolytic BHV-1 in humanized mouse cancer models* Lindyann Lessey: *Kaiso and p120ctn in intestinal diseases* Mandeep Marway: *In Vitro Glioblastoma Model for Monocyte Migration using iFlowPlate™* Ronak Moftakhari: *Role of Lipocalins in Lipid Integrity and Survival of Growth-Arrested Chicken Embryo Fibroblasts* Stephanie Ali Fairbairn: *The Role of Kaiso in Quadruple-Negative Breast Cancer (QNBC)* Arthur Srayeddin: *Development of Covalent Antibody Labeling T-cell Recruiters as a Universal Cancer Therapeutic* Alannah Wilson: *Bone-Marrow Microenvironment Contributes to Venetoclax Resistance in Acute Myeloid Leukemia* Tomas Frankovich: *Reversible covalent immune recruiters allow selective and tunable engagement of immune machinery*	CONFERENCE ROOMS

11:30 - 1:00 PM

LUNCH & POSTER PRESENTATIONS

ATRIUM

Sandra Hwang: *Investigating the Functional Roles of Covalent Immune Recruiters in Immune Activation and Tumour Cell Killing*

Agata Kieliszek: *Intratumoral Delivery of Chimeric Antigen Receptor-T Cells Targeting CD133 Effectively Treats Brain Metastases*

Holly Edward: *Using Outcome Measures to Assess Physical Mobility in Young Adults with Cancer During Chemotherapy: A Scoping Review*

Alisha Anand: *Inhibiting Elements of the Proteosome Recovery Pathway Sensitizes Cells to Proteosome Inhibitors in Glioblastoma*

Dorisa Meng: *Pharmacological and Non-pharmaceutical interventions for Cancer-related Pain Management: a scoping review of Cochrane reviews*

Kabir Siraj: *Integrated platform for high-throughput investigation of cancer ecosystem evolution*

Zoya Adeel: *Screening small molecules to identify anti-cancer engineered T cell boosting agents*

Preyansh Patel: *Characterizing the role of GEM1 in Chicken Embryo Fibroblasts*

Vanshika Khaitan: *The role of master RNA regulators in glioblastoma progression*

Anish Puri: *Role of uPAR in Standard-of-Care resistance and recurrence in Glioblastoma*

Clare Morris: *Developing a TIL product for universal vaccination-based boosting in ACT*

Enzo Baracuhy: *Elucidating the role of non-replicating particles in bovine herpesvirus-1 immunotherapy*

Siddhaarth Varatharajan: *Validation of Candidate Compounds from a Screen of Epigenetic Inhibitors in Acute Myeloid Leukemia*

Olga Cormier: *Development of Bovine herpesvirus - 1 as part of a broad spectrum viral-mediated immunotherapy*

1:00 - 2:00 PM

KEYNOTE PRESENTATION

ATRIUM

Professor John Bell: *Synthetic Virology Strategies to Create Cancer Therapeutics*

2:00 - 2:45 PM

ORAL PRESENTATIONS

CONFERENCE ROOMS

Kanwaldeep Singh: *Venetoclax and LSD1 inhibitor Bomedemstat synergistically target cellular metabolism in Acute Myeloid Leukemia*

Allyson Moore: *IL-15 is required for optimal anti-tumor activity of Vγ9Vδ2 T cells against glioblastoma*

Emily Hartung: *Role of myeloid transcription factor networks in the response of normal and malignant stem cells to LSD1 inhibition*

2:45 - 3:15 PM

COFFEE BREAK

ATRIUM

3:15 - 3:45 PM

INTERVIEW WITH PROF. JOHN BELL & DR. SHEILA SINGH

ATRIUM

3:45 - 4:15 PM

AWARDS CEREMONY

ATRIUM

Trivia Prize Winner

Poster Presentation Award Winner

Rapid Fire Presentation Award Winner

Oral Presentation Award Winners

Cindy Lee Graham Award Winner

Alexander Janke Memorial Scholarship in Brain Cancer Research Award Winner

KEYNOTE SPEAKER

JOHN BELL
PhD

"SYNTHETIC VIROLOGY STRATEGIES TO CREATE CANCER THERAPEUTICS"

Dr. John Bell received his PhD from McMaster University in 1982. In the three years that followed, he trained as a post-doctoral fellow at the University of Ottawa and then at the Medical Research Council in London, England. Dr. Bell began his independent research career at McGill University in 1986 and moved to the University of Ottawa, Department of Medicine, in 1989. He is a member of the Centre for Cancer Therapeutics at The Ottawa Hospital Cancer Centre, a Senior Scientist with the Ottawa Hospital Research Institute and Professor of Medicine at the University of Ottawa. He is the Director of the Canadian Oncolytic Virus Consortium supported by a Terry Fox Program Project Grant and is the Scientific Director of BioCanRx, a Network of Centres of Excellence that aims to bring novel immune stimulating therapies to cancer patients across Canada. His research program has focused on the development of novel viral and cell-based therapeutics for the treatment of cancer. Dr. Bell is a Fellow of the Royal Society of Canada.

ORAL PRESENTATIONS

WILLIAM MAICH

TITLE: uPAR as a novel immunotherapeutic target in recurrent Glioblastoma

AUTHORS: William Maich, Vaseem Shaikh, Anish Puri, Mathieu Seyfrid, Alisha Anand, Sabra Salim, Chitra Venugopal, Martin Rossotti, Chirayu Chokshi, Neil Savage, Daniel Mobilio, Kevin Henry, Sheila Singh

OBJECTIVE/INTRODUCTION: Glioblastoma is the most common adult malignant brain tumor with an average survival of less than 15 months, and a five-year survival rate of 6.8%, despite an aggressive Standard-of-Care involving maximal surgical resection and chemo-radiotherapy with Temozolomide. It is imperative to develop novel therapies that (1) target brain tumor initiating cells (BTICs), the source of tumor formation and heterogeneity, and (2) can target and overcome GBMs immunosuppressive microenvironment. Chimeric Antigen Receptor (CAR) T cells are a promising therapeutic modality to specifically target cell-surface tumor associated antigens. To this end we have identified uPAR, a cell surface BTIC marker and receptor for urokinase with major roles in tumor formation and progression, as a promising immunotherapeutic target in recurrent GBM.

METHODS: We identified uPAR through a pipeline involving RNA sequencing and N-glycocapture proteomics of primary and recurrent GBM samples. Target validation was performed by Fluorescent Activated Cell Sorting and CRISPR-Cas9 gene knockout in vitro, and survival and tumor burden studies in vivo. Additionally, we developed and validated novel single domain antibodies against uPAR.

RESULTS: uPAR is highly expressed in multiple recurrent GBM samples, and with minimal uPAR expression in primary GBM samples and normal tissues. Data in recurrent GBM samples show that genetic aberration of uPAR expression drastically inhibits proliferation and sphere formation capacity in BTICs, which is indicative of tumorigenicity, and provides a significant survival advantage in vivo. Anti-uPAR CAR T cells are being developed and optimized in vitro and in vivo to induce cytotoxicity against rGBM samples. Additionally, we found that uPAR is highly expressed on immunosuppressive macrophages in vitro.

CONCLUSIONS: We identify a unique immunotherapeutic target, uPAR, present not only on recurrent GBM BTICs, but in the tumor microenvironment as well. This provides a unique opportunity to build a novel CAR T therapy for recurrent GBM patients with very few options.

ANA PORTILLO

TITLE: Human γδ T cells expanded long term with feeder cells expressing membrane bound IL-21exert high antigen independent anti-tumor function

AUTHORS: Ana Portillo, Misaal Mehboob, Ali Ashkar

OBJECTIVE/INTRODUCTION: γδ T cells are unconventional T cells which do not require antigen presentation by MHC class I to mediate tumor cell killing, making them a good candidate for allogenic adoptive cell therapy. While Vδ2+ γδ T cells are the most prominent in peripheral blood, the less prevalent non-Vδ2 subsets have shown superior tumor killing. However, difficulties in expanding non-Vδ2+ γδ T cells to high numbers has limited their clinical use. Here, we evaluated the use of K562 feeder cells expressing membrane-bound IL-21 (K562-mb-IL-21) for long term expansion and activation of non-VD2+ γδ T cells.

METHODS: We expanded γδ T cells from healthy donor peripheral blood and tracked their proportion and fold expansion for five weeks in each culture. We then assessed expanded γδ T cell in vitro cytotoxicity, degranulation, and IFN-γ production against breast cancer and ovarian cancer cell lines. We also examined their cytotoxicity and nutrient receptor expression within the immunosuppressive ovarian cancer ascites tumor microenvironment (TME) in vitro. Lastly, we assessed the anti-tumor function of γδ T cells in an adoptive transfer setting using an OVCAR8 xenograft model of human ovarian cancer.

RESULTS: We found that expanded γδ T cells were primarily non-Vδ2+ subsets and expressed higher levels of NK cell activation receptors compared to freshly isolated γδ T cells. Additionally, expanded γδ T cells displayed innate cytotoxicity against all the tumor targets tested but surprisingly did not degranulate or produce IFN-γ. We also found that expanded γδ T cells retained their cytotoxic function and nutrient receptor expression in the ascites TME. Finally, we show that expanded γδ T cells significantly reduced tumor burden in vivo.

CONCLUSIONS: Overall, we demonstrate the anti-tumor potential of γδ T cells expanded with K562-mb-IL-21 cells but need to further characterize their anti-tumor functions to maximize their therapeutic potential.

HANAD ADAN

TITLE: The role of Kaiso in TGF-beta mediated epithelial-to-mesenchymal transition (EMT) in TNBC

AUTHORS: Hanad Adan, Juliet Daniel

OBJECTIVE/INTRODUCTION: Triple-negative breast cancer (TNBC) is the most difficult to treat breast cancer subtype due to its aggressive and highly metastatic nature. Increasing evidence implicates the dual-specificity transcription factor, Kaiso, in TNBC's increased metastatic potential. In our mouse xenograft models, Kaiso-depleted TNBC cells formed little to no metastatic lesions in the lung or liver compared to parental Kaiso-expressing TNBC cells. Furthermore, several studies have correlated increased nuclear Kaiso localization with tumors of a higher histological grade and poorer survival. Unfortunately, the mechanism underlying Kaiso's role in TNBC aggressiveness remains unknown. We recently identified a positive feedback loop between Kaiso and Transforming Growth Factor Beta (TGFβ) signaling, which also participates in breast cancer progression. We aim to examine this Kaiso-TGFβ feedback loop to elucidate Kaiso's mechanism of action in TNBC aggressiveness and metastasis.

METHODS: We will examine Kaiso's transcriptional role in regulating expression of the TGFβ receptors by conducting a promoter-reporter analyses using a luciferase reporter system and site-directed mutagenesis of the promoter to generate promoter mutations. This will allow us to identify critical regulatory elements within the TGFβ receptor promoter that are recognized and bound by Kaiso. We will also determine if Kaiso is a target of TGFβ signaling (specifically the TGFβ downstream transcription factors SMAD2/3 and ZEB1) using Chromatin immunoprecipitation (ChIP)-PCR, western blotting and qRT-PCR.

RESULTS: Our results to date demonstrate that TNBC cell lines treated with TGFβ1 exhibit increased Kaiso expression. Additionally, upon TGFβ1 treatment, SMAD2/3 associates with the Kaiso promoter, suggesting that Kaiso may be a downstream target of TGFβ signaling. Kaiso also modulated the expression of TGFβ signaling effectors.

CONCLUSIONS: Our data indicate that Kaiso is a downstream target of TGFβ signaling and may also be an upstream regulator of the pathway. To further examine Kaiso's role in TNBC aggressiveness and metastasis, we plan to investigate this Kaiso-TGFβ feedback loop.

KAROLINA KRYGIER

TITLE: Reprogramming Non-Specific Serum Antibodies with a Covalent Immune Recruiter for Targeted Tumor Immumotherapy

AUTHORS: Karolina Krygier, Anthony Rullo

OBJECTIVE/INTRODUCTION: Antibodies recognize and target foreign substances for immune-mediated clearance. IgG mediated degradation proceeds through antibody dependent cellular cytotoxicity (ADCC) and/or antibody dependent cellular phagocytosis (ADCP) through various Fc receptor interactions. Due to the highly specific nature of antibodies, their use as a host protein in bioconjugation protocols remains of considerable interest for the development of novel targeted therapeutics and diagnostic probes. For example, in situ formation of antibody-drug conjugates (ADCs) using covalent antibody recruiting molecules (cARMs) remains a powerful strategy for cancer immunotherapy. Bifunctional cARMs contain an antibody-binding domain (ABD) and a target-binding domain (TBD) to bridge a "ternary complex" at the tumor cell surface. By templating these complexes, cARMs allow for immune recognition and clearance via Fc:FcR interactions. However, cARMs are limited in their efficacy with low antigen expressing tumors and are limited in their ability to target only one endogenous antibody source, and thus the titers of said antibody. Using our covalent immune proximity-inducing strategy, we propose to explore how a pan IgG binding peptide incorporated into a covalent immune recruiter (CIR) mediates immune recognition of tumors.

METHODS: We have synthesized a CIR that consists of an IgG binding peptide equipped with a reactive electrophile and urokinase-type plasminogen activator receptor (uPAR) TBD. Validation of anti-tumor function in ADCP assays will be investigated using uPAR+/- cancer cell lines. Furthermore, tumor growth kinetics, mouse survival, and immune cell tumor infiltration will be measured using xenograft mouse breast tumor models.

RESULTS: As a proof of concept, we have demonstrated the selective and irreversible covalent modification of human serum IgG antibodies ex vivo. We have also investigated the kinetic labeling of antibody via fluorescent SDS-PAGE and binding of antibody-CIR to uPAR receptors using bio-layer interferometry.

CONCLUSIONS: Using our CIR technology, we demonstrate a broadly applicable technique to covalently reprogram endogenous antibodies for targeted tumor immunotherapy.

MISAAL MEHBOOB

TITLE: Investigating the cytotoxicity of expanded NK and CD70-targeting CAR-NK cells against brain tumour cells

AUTHORS: Misaal Mehboob, Matthew Rätsep, Ana Portillo, Meisam N. Kararoudi, Sheila K. Singh, Ali. A. Ashkar

OBJECTIVE/INTRODUCTION: Glioblastoma multiforme (GBM) and medulloblastoma (MB) are aggressive metastatic brain cancers that demonstrate low to very poor long-term patient survival, despite surgical and chemo-radiotherapeutic interventions. Chimeric antigen receptor (CAR) immunotherapy, which involves engineering immune cells to target specific tumour antigens, is a promising avenue of treatment. Given the key role that CD70 plays in the recurrence and aggressiveness of glioblastoma, anti-CD70 CAR-Natural Killer (CAR-NK) cells may be valuable in targeting these treatment-resistant brain tumours. Here, we will evaluate the in vitro cytotoxicity of ex vivo expanded peripheral blood NK cells and CD70-targeting CAR-NK cells against GBM and MB.

METHODS: Peripheral blood-derived human NK cells and anti-CD70 CAR-NK cells were expanded using K562 cells expressing membrane-bound IL-21 and exogenously delivered IL-2. Anti-CD70 CAR-NK cells were constructed by delivering the anti-CD70 CAR insert into expanded NK cells using an adeno-associated viral vector and CRISPR/Cas9 editing. The in vitro cytotoxicity of ex vivo expanded NK cells was then assessed in response to the U-118 MG grade IV glioblastoma/astrocytoma and D425 group 3 medulloblastoma cancer cell lines.

RESULTS: Ex vivo expanded NK cells demonstrate cytotoxicity against the U-118 and D425 GBM and MB cancer cell lines, respectively. Expansion led to the rapid surface expression of CD70 on anti-CD70 CAR-NK cells. This led to a depletion of CD70-expressing anti-CD70 CAR-NK cells, potentially through CAR-NK cell-mediated killing. To address this, we generated CD70 knock-out anti-CD70 CAR-NK cells, which successfully expanded in culture.

CONCLUSIONS: We demonstrate the anti-tumour potential of ex vivo expanded NK cells against GBM and MB cancer cell lines. We also demonstrate the successful expansion of CD70 knock-out CAR-NK cells. We next want to test the in vitro and in vivo efficacy of CD70 knock-out CAR-NK cells against GBM and MB cancer cell lines and primary cells to harness their immunotherapeutic potential.

KANWALDEEP SINGH

TITLE: Venetoclax and LSD1 inhibitor Bomedemstat synergistically target cellular metabolism in Acute Myeloid Leukemia

AUTHORS: Kanwaldeep Singh, Emily Hartung, Christina Muhs, Islam Alshamleh, Maria Kleppe, Hugh Y. Rienhoff, Harald Schwalbe, Tobias Berg

OBJECTIVE/INTRODUCTION: Acute myeloid leukemia (AML) is a hematological neoplasm with poor clinical outcomes. Venetoclax has demonstrated activity against a range of hematologic malignancies and combinations of Venetoclax with HMA or cytarabine have demonstrated superior activity in clinical trials. However, resistance is a common feature that limits the potential of these combinations. Thus, there is an unmet need to improve the clinical efficacy of Venetoclax combinations in the treatment of AML. Lysine-specific demethylase 1 (LSD1) inhibition has shown activity in AML by inducing differentiation and by targeting leukemic stem cells. We have therefore studied if LSD1 inhibition could enhance efficacy of Venetoclax in AML. of ex vivo expanded peripheral blood NK cells and CD70-targeting CAR-NK cells against GBM and MB.

METHODS: We have studied the effect of co-treatment with Venetoclax and LSD1 inhibitor Bomedemstat on cell proliferation, metabolite abundance and functional cellular bioenergetics using NMR spectrometry and Seahorse extracellular flux analyzer in human AML cell lines, murine AML models and primary AML patient samples. Further, we have studied the efficacy of this drug combination in vivo in patient-derived xenograft (PDX) AML models. We are currently analyzing the effect of co-treatment with these two compounds using single-cell RNA-seq and ATAC-seq, and bulk RNA-seq on AML cell line and primary AML patient samples to study pathways differentially regulated by these treatments.

RESULTS: Venetoclax and Bomdemstat co-treatment showed a significant synergistic reduction in cell proliferation along with synergistic reduction in various metabolic pathways in different in vitro AML models. We further explored the efficacy of the co-treatment in vivo and found that the drug combination significantly reduced the leukemic burden in bone marrow and spleen in the PDX AML model. Initial preliminary analyses of single-cell multiomics RNA-seq data suggest that the co-treatment leads to the downregulation of metabolic pathways.

CONCLUSIONS: Our results show that LSD1 inhibitor and Venetoclax synergistically reduce cell proliferation by targeting cellular metabolism making this combination a promising new treatment approach.

ALLYSON MOORE

TITLE: IL-15 is required for optimal anti-tumor activity of Vγ9Vδ2 T cells against glioblastoma

AUTHORS: Allyson E. Moore, Nickolas Serniuck, Arya Afsahi, Hayley Nault, Chitra Venugopal, Sheila K. Singh, Jonathan L. Bramson

OBJECTIVE/INTRODUCTION: Glioblastoma (GBM) is a clinical unmet need that could benefit from adoptive therapy with engineered T cells. Gamma-delta (γδ) T cells are a promising cellular substrate as they naturally possess the ability to target GBM using endogenous cytotoxicity receptors. Furthermore, γδ T cells have an MHC-unrestricted TCR, allowing for transfer to unrelated recipients without risk of graft-vs-host disease. We hypothesize that genetic engineering will enable the production of γδ T cells with optimized anti-GBM activity and enhanced cellular fitness. Here, we investigated γδ T cell anti-GBM activity and explored the role IL-15 plays in important effector functions to inform our engineering strategy.

METHODS: Human Vγ9Vδ2 (γδ) T cells were expanded from PBMCs using Zoledronate, IL-2 and IL-15, and engineered with lentiviruses encoding DAP12-associated synthetic antigen receptors (SARs). γδ T cells were co-cultured with primary GBM cells +/- IL-15 to assess various effector functions.

RESULTS: Non-engineered γδ T cells displayed robust cytotoxicity against primary GBM cells but failed to proliferate and produce cytokine. Engineering γδ T cells with DAP12-associated SARs targeting GBM antigens (CD133, HER-2, IL13Ra2) greatly augmented cytotoxicity and production of inflammatory cytokines upon co-culture with GBM cells, however, SAR-γδ T cells still failed to proliferate. Inclusion of IL-15 in γδ T cell/GBM co-cultures enhanced γδ T cell cytotoxicity, survival, and promoted robust proliferation, which was further amplified by the presence of a SAR. Engineering γδ T cells with IL-15 transgenes did not reproduce the enhancement observed with supplementary IL-15, therefore, we are exploring the biological consequences of IL-15 supplementation to identify engineering strategies that can recapitulate the effect intrinsically.

CONCLUSIONS: The presence of IL-15 during the γδ T cell-GBM cell interaction is required for maximal anti-tumor activity. Recapitulating the role of IL-15 and its associated signalling at the tumour site may be necessary to unleash the full potential of γδ T cells.

EMILY HARTUNG

TITLE: Role of myeloid transcription factor networks in the response of normal and malignant stem cells to LSD1 inhibition

AUTHORS: Emily Hartung, Kanwaldeep Singh, Tobias Berg

OBJECTIVE/INTRODUCTION: Epigenetic modulation to treat Acute Myeloid Leukemia (AML) is promising in clinical trials and understanding how targeted epigenetic modulators, such as LSD1 inhibitors, can affect both normal and malignant cells is crucial for implementation into clinical practice. There are opposing effects of LSD1 inhibition (LSD1i) in normal hematopoiesis versus leukemia which are poorly understood.

METHODS: We treated normal murine stem cells (LSK-sorted) or retrovirally-induced AML cells (Hoxa9/Meis1, H9M) with LSD1 inhibitors (IMG-7289 [1μM] or GSK-LSD1 [100nM]) for 5 days. The phenotype was assessed via flow cytometry using markers: CD45+EPCR+CD150+CD48-(ESLAM), c-Kit, Sca-1. We generated murine AML cells with a knockout (KO) of myeloid transcription factor IRF8, cultured with LSD1i and assessed for differentiation via flow cytometry using markers c-Kit, Sca-1, CD11b, and Ly6G. Gene expression levels of key myeloid transcription factors (PU.1, GFI1/1B) were determined via qPCR.

RESULTS: At day 5, the cKIT+EPCR+ population was increased by 35% ($p \leq 0.001$) in treated LSK-sorted cells. At day 5 of treatment in H9M or H9M IRF8 KO cells: the proportion of c-Kit+ cells is decreased by 60% for the H9M ($p \leq 0.0001$) and 50% for H9M IRF8 KO ($p \leq 0.0001$); the Sca-1+ population increased in H9M, no change in the IRF8 KO condition ($p \leq 0.001$); the CD11b+ population (mature myeloid) expands in H9M, this effect was dampened in IRF8 KO ($p \leq 0.0001$). qPCR analysis indicated that GFI1 was downregulated in both the WT and IRF8 KO cells ($p \leq 0.0001$ and $p \leq 0.001$ respectively), GFI1B was upregulated in the KO cells ($p \leq 0.05$) after treatment.

CONCLUSIONS: Treatment of LSK-sorted BM cells with LSD1i ex vivo leads to phenotypic stem cell expansion. In leukemic cells we find a reduction in phenotypic stem cells with this treatment. The differentiation induced by LSD1i is modulated by a deficiency of IRF8. After further in vivo validation, this model will provide an excellent platform to study the functional effect of LSD1 inhibition on normal and malignant cells using single-cell approaches.

STEFAN CUSTERS

TITLE: Targeting lipid metabolism as a potent therapeutic target in MYC-amplified group 3 medulloblastoma

AUTHORS: Stefan Custers, William D. Gwynne, Laura Escudero, Yujin Suk, Iqra Chaudhry, Jeremy K Chan, Andrew T Quaile, Chitra Venugopal, J. Rafael Montenegro-Burke, Sheila K. Singh

OBJECTIVE/INTRODUCTION: Medulloblastoma (MB) is the most common pediatric brain tumor comprising of four subgroups: WNT, SHH, Group 3 (G3) and Group 4 (G4). Improved standard of care has led to a greatly improved patient survival. However, 30% of patients still succumb to the disease and survivors are plagued with lifelong neuro-cognitive and neuro-developmental disorders. MYC-amplified G3MB is a highly aggressive subgroup with a high frequency of metastasis and recurrence, leading to a bleak prognosis. Molecular understanding of G3MB is lacking and improved treatment options are urgently needed. Recent studies suggest a role for reprogrammed lipid metabolism, especially at recurrence, and may prove to be a viable treatment option.

METHODS: We compared the lipidome profile of patient-derived G3MB cells and human neural stem cells (hNSC) by using liquid chromatography-mass spectrometry (LC-MS). Genetic and pharmacological studies in vitro and in vivo were employed to understand and exploit the reprogrammed metabolome in G3MB as a therapeutic vulnerability.

RESULTS: We identified a class of lipids whose differential abundance in G3MB renders these tumor cells sensitive to chemical inhibition of their biosynthesis. Pharmacological and genetic inhibition of an enzyme involved in lipid metabolism (target-A) completely abolishes self-renewal and proliferation in vitro. However, supplementing cell culturing media with its lipid product fully restores these effects. Genetic knockout of target-A in G3MB cells significantly prolongs survival and reduced tumor burden in vivo. Moreover, administration of a target-A specific small molecule inhibitor reduced tumor burden in vivo (Survival studies are ongoing). RNA-seq analysis of G3MB treated with the specific target-A small inhibitor or DMSO is being employed to unravel its mediated mechanisms and will be further validated.

CONCLUSIONS: Together, these data suggest that enzymes regulating lipid metabolism in G3MB represent potential targets for therapeutic translation.

MARIA DAVOLA

TITLE: Pre-clinical studies of oncolytic BHV-1 in humanized mouse cancer models

AUTHORS: Davola ME, Cormier O, Lepard M, Collins S, Gillgrass A, Mossman K

OBJECTIVE/INTRODUCTION: Among the many cancer immunotherapies being developed, oncolytic viruses (OVs) are gaining traction as potent clinical agents with the ability to turn immune cold tumors into hot, allowing other immunotherapies, such as immune checkpoint inhibitors (ICI), to be more effective. We have developed an OV therapy based on oncolytic bovine herpesvirus-1 (oBHV-1) which has performed excellently in pre-clinical syngeneic models. However, due to differences in innate and adaptive immunity between mice and humans, even syngeneic models have limitations. Humanized mice (hu-mice) are immunodeficient mice that develop a human immune system when reconstituted with human hematopoietic stem cells (HSCs). Basic hu-mouse models still have limitations due to human leukocyte antigen (HLA) mismatch between the human immune cells and mouse tissues. To address these limitations, we used NRG mice that express human HLA-A2.1 (NRG-A2) and cord blood CD34+ HSCs with the same HLA type. Compared to normal hu-NRGs, our hu-NRG.A2s develop more fully functional CD8+ T cell subsets making it an improved model to bridge between pre-clinical and clinical studies.

METHODS: Recently, we successfully established humanized models of colorectal and pancreatic cancer with fully HLA match using human cancer cell lines expressing HLA-A2.1.

RESULTS: In both models, we observed striking tumor control when mice are treated with our previously established combination regimen of oBHV-1, low-dose mitomycin c and ICI. Similar to our previous studies in a syngeneic melanoma model, our combination regimen induces tumor infiltration of CD8+ T cells with high ratio cytotoxic : regulatory T cells.

CONCLUSIONS: Overall, these findings show the great clinical potential of oBHV-1-mediated therapy for different hard-to-treat cancers. Current mechanistic studies to complete oBHV-1 pre-clinical package are underway.

LINDYANN LESSEY

TITLE: Kaiso and p120ctn in intestinal diseases

AUTHORS: Lindyann R. Lessey, Roopali Chaudhary, Juliet M. Daniel

OBJECTIVE/INTRODUCTION: Inflammatory bowel disease (IBD) is an incurable condition characterized by chronic inflammation of the gastrointestinal tract. Patients with IBD have an increased chance of developing Colitis-associated cancer (CAC), which is attributed as the cause of death in 10–15% of IBD patients. However, the molecular mechanisms underlying the IBD to CAC transition remain unknown. Our lab previously reported that intestinal- specific overexpression of the transcription factor Kaiso disturbs the intestinal epithelial barrier and induces a chronic intestinal inflammatory phenotype. Notably, loss of Kaiso's binding partner, p120ctn, in murine intestines, resulted in intestinal inflammation and adenoma formation. However, the role of Kaiso and p120ctn in IBD and CAC have not been explored. Since inflammation and genetic alterations drive progression from an inflammatory phenotype to hyperplasia and sometimes tumors, we hypothesize that Kaiso overexpression in conjunction with p120ctn depletion would induce severe intestinal inflammation and possibly CAC.

METHODS: To test this hypothesis, Kaiso overexpressing mice (KaisoTg) were mated with p120ctn conditional knock out (CKO) mice and intestinal tissues from the progeny (KaisoTg;p120CKO) were collected at 6 and 12 months post p120ctn loss. Intestinal tissues were stained with Hematoxylin and Eosin (H&E) and examined for intestinal inflammation and polyp formation by a pathologist, and protein expression was assessed using immunofluorescence, immunohistochemistry and western blot analysis.

RESULTS: Hematoxylin and Eosin (H&E) staining revealed increased hyperplasia and mass formation in 6 and 12-month-old mice respectively. Preliminary immunofluorescence staining also showed that p120ctn loss induced changes in E-cadherin, β-catenin and ZO-1 expression but no change in subcellular localization was observed.

CONCLUSIONS: Loss of p120ctn in KaisoTg mice leads to cell-cell adhesion defects that appears to exacerbate intestinal inflammation and lead to abnormal intestinal epithelial cell proliferation and hyperplasia.

MANDEEP MARWAY

TITLE: In Vitro Glioblastoma Model for Monocyte Migration using iFlowPlate™

AUTHORS: Mandeep Marway, Ryan Wylie, Boyang Zhang

OBJECTIVE/INTRODUCTION: Monocytes recruited from the bone marrow to the tumor site differentiate into tumor-associated macrophages (TAMs). TAMs play a key role in tumor progression and metastasis. Screening of monocyte-targeting therapies to prevent recruitment or differentiation to TAMs could prevent tumor progression. We are developing an in vitro drug screening tool to characterize monocyte infiltration across an endothelial barrier, through extracellular matrix environments towards embedded cancer spheroids. The iFlowPlate™ technology is a high-throughput screening platform, created on a 384-well plate containing 128 perfusable networks, each created by connecting 3 adjacent wells using a single channel allowing for the screening of drug combinations and sustained release drug delivery vehicles.

METHODS: Glioblastoma (BT935) spheroids were embedded into a fibrin hydrogel with a confluent layer of human umbilical vein endothelial cells (HUVECs) on the hydrogel surface. Barrier function was confirmed by quantifying the diffusion of 4 and 65 kDa dextran. Finally, monocytes were introduced above the barrier and migration was monitored using confocal microscopy.

RESULTS: HUVECs consistently form confluent monolayers within 5 days of seeding at 2x10^5 cells/mL on fibrin gel surfaces. CD31 and VE-cadherin immunofluorescence staining confirmed barrier formation, while dextran permeability confirmed barrier function. The model has been used to follow the real-time migration of monocytes under various conditions, showing monocyte migration only in the presence of cancer spheroids. This indicates that signaling pathways that encourage monocyte migration were established. We are now conducting cytokine release assays to identify chemotactic agents. Drug and delivery vehicle screening will be performed to inhibit and promote monocyte recruitment and differentiation.

CONCLUSIONS: The recruitment and differentiation of monocytes to TAMs in the tumor environment is an important question for drug screening. The iFlowPlate™ allows for visualizing monocyte recruitment, and screening for drugs to prevent recruitment and differentiation to TAMs.

RONAK MOFTAKHARI

TITLE: Role of Lipocalins in Lipid Integrity and Survival of Growth-Arrested Chicken Embryo Fibroblasts

AUTHORS: Ronak Moftakhari, PA Bédard

OBJECTIVE/INTRODUCTION: In response to oxygen deprivation, serum starvation and high cell density, chicken embryo fibroblasts (CEF) enter a reversible growth-arrest state called quiescence (G0). Quiescence can be defined by the expression growth arrest-specific gene (GAS) products that regulate cell-cycle arrest and promote cell viability. The quiescent state is critical for cancer stem cells but not much is known about the underlying factors that regulate this dormant state.
Based on these findings, we propose the following hypothesis:
1. Perturbations in the lipidome induces an adaptive response characterized by the C/EBPbeta-dependent activation of lipocalin expression
2. The expression of lipocalins prevent ROS formation and lipotoxicity-induced cell death
To test this hypothesis, we propose the following objectives:
1- Characterize the regulation of lipocalins in response to disturbances in lipid metabolism
2- Describe the role of lipocalins in lipid homeostasis and cell survival
3- Characterize the transcriptional regulation of lipocalin expression by C/EBPbeta inresponse to hypoxia

METHODS: Using chicken embryo fibroblast (CEF) we use a primary cell model to analyze the fundamental concepts of growth arrest state and the ability to regulate the cell cycle. Using several cell culture techniques we investigate the role of oxidative stress using several chemical inducers of ROS (tBHP) and inhibitors of fatty acid metabolism to investigate the role of lipid metabolism and lipid binding factors in regulating this key dormant state. Using Chromatin immunoprecipitation of DNA bound to C/EBPbeta, a key transcription factor of this response, we demonstrate the impact of downregualting lipid transport/regulation on this response and the key importance of lipid homeostasis to quiescence and GAS gene expression.

RESULTS: Our results show the downregulation of p20K or FABP4 enhances oxidative stress and cellular apoptosis in hypoxia. Furthermore, lipocalin mis-regulation ultimately impaired the GAS gene expression program regulated by CCAAT/enhancer binding protein (C/EBPbeta) in conditions of hypoxia. Additionally, the loss of lipocalins impairs the capacity of the cell to re-enter the cell cycle in normoxic conditions following oxidative stress. Lipid chaperones play a critical role in maintaining cellular homeostasis, but their precise activity and regulation is not well understood.

CONCLUSIONS: Thus, the gene expression program activated by C/EBP-beta functions to enhance cell survival, restore the cellular redox state and maintain lipid homeostasis. In this response, both p20K and FABP4 play a prominent and distinct role in mediating the adaptive response to the accumulation of lipid- and oxygen-radical production following oxygen deprivation. Impairing the expression of either will impede the adaptive capacity to restore redox homeostasis, further propagating ROS accumulation and oxidative stress that ultimately surpasses the threshold of tolerance and disrupts the co-regulation of both by C/EBPbeta.

STEPHANIE ALI FAIRBAIRN

TITLE: The Role of Kaiso in Quadruple-Negative Breast Cancer (QNBC)

AUTHORS: Stephanie Ali Fairbairn, Robert Cowan, Sailaja Golamari, Ryan Rattan, Juliet M. Daniel

OBJECTIVE/INTRODUCTION: Women of African ancestry (WAA) experience a disproportionate burden of the highly aggressive, triple-negative breast cancer (TNBC) subtype and high mortality rates compared to Caucasian women (CauW). Previous studies suggest that the transcription factor Kaiso may be linked to this racial disparity as it is highly expressed in TNBC and this correlates with increased metastasis and mortality in WAA TNBC patients. Recent studies revealed that African American TNBC tissues express less androgen receptor (AR) than CauW TNBC tissues, supporting the existence of the novel breast cancer (BCa) subtype – quadruple-negative breast cancer (QNBC). Women with AR-negative tumors have a shorter disease-free interval and worse overall survival (OS) than those with AR-positive tumors. Notably, in silico analysis revealed that high Kaiso and low AR expression correlated with poorer overall survival in BCa patients. Thus, we hypothesized that Kaiso expression is negatively correlated with AR expression, and high Kaiso and low AR may contribute to increased mortality in WAA with TNBC.

METHODS: To determine if Kaiso binds and regulates the AR promoter, minimal-promoter-reporter assays will be conducted to verify AR as a bona fide Kaiso target gene. Since immunohistochemistry analysis of our tissue microarrays revealed reduced and cytoplasmic AR expression in WAA compared to CauW, we will correlate AR expression with clinicopathological features and overall survival to discern the link between high Kaiso and low AR expression in TNBC racial disparities.

RESULTS: Preliminary immunoblot and qRT-PCR analyses revealed increased AR expression in Kaiso-depleted TNBC cells and chromatin immunoprecipitation (ChIP) data indicates that Kaiso associates with the AR promoter region.

CONCLUSIONS: Kaiso and AR may be relevant prognostic biomarkers for TNBC/QNBC patients, thus ongoing studies will seek to confirm that AR is a Kaiso target gene.

ARTHUR SRAYEDDIN

TITLE: Development of Covalent Antibody Labeling T-cell Recruiters as a Universal Cancer Therapeutic

AUTHORS: Srayeddin A, Bramson J, Rullo A

OBJECTIVE/INTRODUCTION: Cancer has a variety of immune suppressant mechanisms, some of which render T-cells ineffective. As an immunotherapeutic strategy, previous research demonstrated the modification of T-cell receptors (TCRs) to create chimeric antigen receptor (CAR) T-cells that target specific cancer cell antigens with high clinical efficacy. However, CAR T-cell therapy had an approximate relapse rate of 60% in large B cell lymphoma patients. This is attributed to cancer cells exhibiting varying cell surface antigens necessitating the development of novel CAR T-cells with compatible antigen binding regions. Problematically, access to the treatment is limited due to the complexity and excessive cost of manufacturing CAR T-cells. Previous work at the Rullo/Bramson labs saw the development of anti-dinitrophenol (DNP) scFv-expressing T-cells that can be selectively modified with covalent immune recruiters (CIRs) possessing a DNP hapten and a cancer targeting small molecule ligand to enhance T-cell direction to tumor targets. To expand upon this platform, we aim to decorate antibodies onto these T-cells, as opposed to small molecule ligands.

METHODS: The DNP-functionalized CIRs were synthetically modified to incorporate click handles. Using click chemistry, the facile attachment of the complementary click handles between the antibody and the DNP-functionalized CIRs allows for the modular recruitment of engineered T-cells to any biotinylated antibody. Functionalization of antibody with click handles will be tested via SDS-PAGE and MALDI/TOF. Recruitment of T-cells to tumor targeting antibodies and by extension tumor targets, will be validated using microscopy and flow cytometry.

RESULTS: We have successfully synthesized 5 T-cell labeling molecules. We were able to confirm that the biotin reactive handle labels biotinylated antibodies in a dose dependant manner. We are also performing a proof-of-concept experiment to validate the killing efficacy of antibody conjugated T-cells.

CONCLUSIONS: This approach will permit a diverse collection of antibodies to recruit T-cells to heterogeneous tumors, potentially increasing T-cell efficacy, and treatment accessibility.

ALANNAH WILSON

TITLE: Bone-Marrow Microenvironment Contributes to Venetoclax Resistance in Acute Myeloid Leukemia

AUTHORS: Alannah Wilson, Kanwaldeep Singh, Pradhariny Prabagaran, Tobias Berg

OBJECTIVE/INTRODUCTION: Acute myeloid leukemia (AML) in an aggressive hematological malignancy with poor prognosis due to treatment resistant relapse. Treatment with venetoclax, a BCL-2 inhibitor, has improved patient outcomes when used in combination with demethylating agents, but venetoclax-resistant relapse has been described. The leukemic BM niche is increasingly recognized as contributing to treatment resistance, however the cellular and molecular underpinnings of this chemoprotective effect remain poorly understood. This project aims to elucidate the role of the leukemic microenvironment in venetoclax- resistant AML and investigate the mechanism by which the microenvironment confers its effect.

METHODS: Using in vitro AML models including human and murine cell lines and primary patient samples, AML cells were cultured in standard mono-cultures or in co-culture with primary bone marrow mesenchymal stromal cells (BMSC) and treated with venetoclax for 96 hours. Mono- and co-cultures were assessed for cell viability using CellTiter Glo assays. Expression of apoptotic markers was analyzed by flow cytometry and expression of alternate anti-apoptotic proteins was assessed by western blotting.

RESULTS: Preliminary results indicate that co-culture with BMSC significantly increases the IC50 of venetoclax in two human AML cell lines, HL-60 and MOLM-13, suggesting induction of resistance. Accordingly, reduced expression of apoptotic cell surface markers is observed in co-cultured AML cells. Additionally, western blotting experiments have shown increased expression of an alternate anti-apoptotic protein MCL-1 in co-cultured AML cells, indicating a potential mechanism for microenvironment-induced venetoclax resistance. Indeed, preliminary experiments suggest that co-treatment with MCL-1 inhibitor Tapotoclax diminishes the protective effect of BMSC.

CONCLUSIONS: Overall, our results suggest that BMSC promote venetoclax resistance in AML. This research will further our understanding of the role of the leukemic microenvironment in treatment resistance and identify potential therapeutic avenues to reduce venetoclax resistance in AML.

TOMAS FRANKOVICH

TITLE: Reversible covalent immune recruiters allow selective and tunable engagement of immune machinery

AUTHORS: Tomas Frankovich, Anthony Rullo

OBJECTIVE/INTRODUCTION: Covalent Immune Recruiters (CIRs) are small molecule immunotherapies that link endogenous immune machinery to tumor targeting ligands through irreversible covalent bonds, enforcing immune-mediated tumor killing. Irreversible binding enhances the kinetic stability of the induced tumor-immune complex, allowing for robust immune activation. This project involves the synthesis of reversible CIRs (rCIRs) that bind to antibodies and immune cells with varying kinetic lifetimes. rCIRs consist of three domains: a dinitrophenyl (DNP) hapten that binds to immune machinery, a reversibly binding covalent moiety, and a small molecule or peptide target-binding domain. The reversible nature of rCIR binding minimizes potentially toxic off-target labelling effects observed with irreversible covalent binders. rCIRs also serve as chemical tools to probe basic immunological principles. Kinetic stability at the immune synapse is a major mechanism by which immune cells define activation thresholds and discriminate between self and non-self. By varying the structure of the reversible binding moiety, the kinetic stability of the rCIR-immune binding interaction can be modulated. The tunable nature of rCIR binding lifetime allows us to probe the kinetic requirements of immune activation.

METHODS: We synthesized a library of rCIRs using four different covalent chemistries and three different target-binding domains. We measured the residence time, selectivity, and specificity of rCIR-antibody binding using bio-layer interferometry and SDS-PAGE.

RESULTS: We demonstrated that rCIRs specifically and reversibly covalently engage anti-DNP antibodies. We characterized residence times of rCIR-antibody interactions ranging from > 10 minutes to < 1 second.

CONCLUSIONS: rCIRs engage immune machinery with high specificity and tunable kinetic properties. rCIRs have the potential to abrogate off-target binding observed with irreversible covalent constructs. Further efforts are underway to apply rCIRs to engineered T-cell therapies and to interrogate the kinetic requirements of T-cell activation.

SANDRA HWANG

TITLE: Investigating the Functional Roles of Covalent Immune Recruiters in Immune Activation and Tumour Cell Killing

AUTHORS: Sandra Hwang, Anthony Rullo

OBJECTIVE/INTRODUCTION: Proximity inducing molecules bridge together two entities to induce a biological phenomenon, such as redirecting immune cells to tumours leading to an immunotherapeutic response. For example, covalent immune recruiters (CIRs) are small molecules capable of binding to an immunological entity and a tumour target that can staple to either terminus through a covalent handle. This creates a stable complex capable of leading immune effector cells to recognize and bind to its tumour target, eliciting an immunotherapeutic response. CIRs have shown to increase phagocytosis of tumour targets and elevate activation of T-cell models, compared to non-stapling analogues. However, many unanswered questions remain regarding the therapeutic effects of CIRs in other aspects of cancer pathology. The objective of this study is to expand the platform of functional assays to allow further understanding into the immunotherapeutic advantages of CIRs.

METHODS: Two immune mechanisms of interest include antibody dependent cell cytotoxicity (ADCC) and macrophage activation through CD64 engagement. Upon CD64 binding, macrophages become activated leading to the release of reactive oxygen species (ROS), ultimately resulting in tumour killing. We are adopting a chemiluminescent assay to investigate the effects of CIRs on ROS production by macrophages. In addition, ADCC is a killing mechanism often used by natural killer (NK) cells to eliminate foreign entities. To investigate the ability of CIRs to induce or enhance ADCC, primary NK cells were first used to show efficacy of CIRs against prostate cancer cells. To further investigate this efficacy with higher throughput, and less variability we are using an NK92 transfected CD16 positive cell line.

RESULTS: Our preliminary data shows successful dose-dependent ROS production and ADCC using trastuzumab as a positive control.

CONCLUSIONS: Overall, the development and full optimization of these assays may provide important insights into the immunotherapeutic efficacy of our covalent proximity-inducing strategy.

AGATA KIELISZEK

TITLE: Intratumoral Delivery of Chimeric Antigen Receptor-T Cells Targeting CD133 Effectively Treats Brain Metastases

AUTHORS: Agata M. Kieliszek, Daniel Mobilio, Deepak Upreti, Darin Bloemberg, Zahra Alizada, Kui Zhai, Shawn C. Chafe, Parvez Vora, Chitra Venugopal, Sheila K. Singh

OBJECTIVE/INTRODUCTION: Brain metastases (BM) are mainly treated palliatively with an expected survival of less than 12 months post-diagnosis. In many solid tumors, the human neural stem cell marker glycoprotein CD133 is a marker of a tumor-initiating cell population that contributes to therapy resistance, relapse, and metastasis. To date, CD133 has been minimally investigated as a therapeutic target in BM, the most common and aggressive form of brain cancer in adults.

METHODS: Here, we use a variant of our previously described CD133 binder to generate second generation CD133-specific chimeric antigen receptor T cells (CAR-T) to demonstrate its specificity and efficacy against multiple patient-derived BM cell lines with variable CD133 antigen expression.

RESULTS: Using both lung- and colorectal-BM patient-derived xenograft models, we show that a CD133-targeting CAR-T cell therapy can evoke significant tumor reduction and survival advantage after a single dose, with complete remission observed in the colorectal-BM model.

CONCLUSIONS: In summary, these data suggest that CD133 plays a critical role in fueling the growth of BM, and immunotherapeutic targeting of this cell population is a feasible strategy to control the outgrowth of BM tumors that are otherwise limited to palliative care.

HOLLY EDWARD

TITLE: Using Outcome Measures to Assess Physical Mobility in Young Adults with Cancer During Chemotherapy: A Scoping Review

AUTHORS: Holly Edward, Jenna Smith-Turchyn

OBJECTIVE/INTRODUCTION: Young adults diagnosed with cancer are challenged with many unique obstacles throughout treatment and into life after cancer. Chemotherapy is a commonly prescribed anti-cancer treatment which can lead to a plethora of adverse side effects including loss of muscle mass and strength. Physical mobility can be considered as physical function and capabilities. Early detection of deteriorating physical mobility can lead to improved outcomes for survivors. The research questions we aimed to address are: 1) What mobility-focused outcome measures are currently being utilized for young adults with cancer receiving chemotherapy treatment? 2) Who is administering these measures? 3) How (i.e., what methods: in-person vs virtual) are these measures being used? 4) What timepoints of treatment are these measures being administered?

METHODS: MEDLINE, CINAHL, EMBASE, EMCARE, and AMED were searched from inception to February 2023. Studies must have met the following criteria to be included: young adults (age 18-<40) living with cancer, receiving chemotherapy treatment, and measured any form of physical mobility during treatment. After duplicates were removed, two or more reviewers performed all screening and data extraction.

RESULTS: Four studies were included in this review. Most studies used self-reported physical activity logs. Each study administered a performance-based outcome measure which included the six-minute walk test, accelerometers, muscle strength tests and cycle ergometer testing. Timepoints of measurement were distributed across pre-administration, over the first seven days, weekly, and months into chemotherapy treatment. All assessments were conducted in-person, and no healthcare providers administered the outcome measures across all studies.

CONCLUSIONS: There is a scarcity of studies involving this patient population. Additional research is needed to explore how physical mobility changes throughout chemotherapy treatment. This will allow for the effectiveness of interventions aimed at reducing side effects as individuals transition from living with cancer to living beyond cancer to be examined.

ALISHA ANAND

TITLE: Inhibiting Elements of the Proteosome Recovery Pathway Sensitizes Cells to Proteosome Inhibitors in Glioblastoma

AUTHORS: Alisha Anand, Chirayu Chokshi, Benjamin Brakel, Vaseem Shaikh, Chitra Venugopal, Sheila Singh

OBJECTIVE/INTRODUCTION: The ubiquitin-proteosome pathway is upregulated in glioblastoma (GBM), leading to the degradation of critical proteins required for cell death. Thus, inhibiting proteosome activity and thereby promoting a cell death phenotype has been investigated extensively in GBM. Although preclinical data deemed proteosome inhibitors efficacious, clinical outcomes have been dismal. These shortcomings are attributed to an acquired resistance. Here we identify N-glycanase-1 (NGLY-1), DNA damage inducible 1 homolog 2 (DDI2) as a driver of resistance using genome wide CRISPR-Cas9 screening. NGLY-1 and DDI2 play important roles in modifying the transcription factor, Nuclear Factor Erythroid 2 Like 1 (NRF1), which upon modification, upregulates proteosome synthesis. Thus, we propose that inhibiting these components sensitizes GBM to proteosome inhibition.

METHODS: Using CRISPR/Cas9 technology, knockout cell lines (NGLY-1, NRF1, DDI2) were generated in patient-derived GBM cell lines. Knockout cell lines were tested with Marizomib (MZB), an irreversible proteosome inhibitor, and anti-tumor activity was evaluated using cell-viability, sphere formation, and proliferation assays. In vivo functional validation will be conducted by treating NSG mice with MZB post-intracranial engraftment with knockout or control cell lines. Mice will be monitored for survivorship and tumor volume. In collaboration with the Gunning lab, we will develop a novel NGLY-1 inhibitor that will be tested on patient-derived GBM cell lines. We will carry out the same experimental approaches to validate the efficacy of this NGLY-1 inhibitor when used in conjunction with MZB.

RESULTS: Genetic perturbation of NGLY-1, NRF1 and DDI2 in GBM attenuates cell proliferation, viability and self- renewal capacity in a dose dependent manner to MZB.

CONCLUSIONS: Targeting the proteosome rescue pathway shows promise for potentiating the effects of proteosome inhibitors for the treatment of GBM. The development of a novel NGLY-1 inhibitor could become an additional component to the standard therapy and potentially expand therapeutic options for the treatment of GBM.

DORISA MENG

TITLE: Pharmacological and Non-pharmaceutical interventions for Cancer-related Pain Management: a scoping review of Cochrane reviews

AUTHORS: Dorisa Meng, Roxanna Wang, Zhaoxia Li, Lucas Lorimer, Serena Wei, Fan Wang, Henry Kwon, Li Wang

OBJECTIVE/INTRODUCTION: Cancer is a leading cause of mortality in Canada. Cancer-related pain affects 40% to 70% of cancer patients and is associated with reduced quality of life with physical and psychological impairments. Despite the WHO recommended three-step analgesic ladder, cancer-related pain management is complicated due to differences in cancer treatments, cancer stages, pain causes, and comorbidities. There is no overall picture for cancer-related pain management. The objective is to assess and summarize the evidence from Cochrane systematic reviews regarding cancer-related pain management.

METHODS: We searched the Cochrane Database of Systematic Reviews in June 2023, for systematic reviews of RCTs reporting any pharmaceutical and non-pharmaceutical interventions for cancer-related pain management among cancer patients. Pain was the primary outcome. Secondary outcomes included quality of life, function or disability, sleep quality, mortality, cancer progress, and adverse events. Using standardized, pilot-tested forms, paired reviewers independently screened the title/abstracts and full-texts for eligibility, extracted data, and assessed quality of systematic reviews and quality of evidence using AMSTAR 2 and GRADE approach. Disagreements were resolved through discussion. We will narratively summarize the evidence of the effects of each type of interventions and associated quality and recommendations, if necessary, for different subgroups (e.g. type of cancer, cancer treatment, etc.).

RESULTS: Our literature search identified 3930 citations. We are in the process of identifying eligible reviews, extracting the data, and completing analyses. We will present the benefits and harms of the interventions for cancer-related pain management, based on the magnitude of the treatment effects and quality of evidence at the 2023 CDCR Research Day Symposium.

CONCLUSIONS: Our overview will be the first to systematically evaluate interventions for cancer-related pain management and associated quality of evidence and recommendations. In the future, we will conduct a network meta-analysis to rank the interventions for optimizing cancer pain management.

KABIR SIRAJ

TITLE: Integrated platform for high-throughput investigation of cancer ecosystem evolution

AUTHORS: Kabir Siraj, Mikhail Salnikov, Connor Clark-Baba, Alberto Torrez, Fuad Chowdhury, Vanshika Khaitan, Cole Nickason, Hong Han

OBJECTIVE/INTRODUCTION: Systematic dissection of coordinated gene regulation by in-depth multi-omics approaches is critical to revolutionize our understanding of mechanisms underlying complex human diseases, especially cancer – the leading cause of death in Canada. Cancer is increasingly viewed as a complex and rapidly evolving ecosystem, which involves dynamic interactions between malignant and non-malignant (i.e., microenvironment) compartments, such as crosstalk between tumor, immune, vascular, and diverse other surrounding tissue cell populations. Major challenges of treatment-resistant cancer include immense tumor heterogeneity and the rapid evolution of both tumor and microenvironment through time and therapy. The goal of our research is to develop and leverage the power of state-of-the-art, systematic experimental and computational approaches to understand coordinated multilayer gene regulatory networks that underlie the cancer ecosystem evolution.

METHODS: Our team has developed an innovative ultra-high-throughput single-cell multi-omics, highly multiplexed genetic/drug screening, and integrated bioinformatics platform to systematically reveal multilayer cellular and molecular mechanisms underlying treatment-resistant GBM and prostate cancer, and discover novel RNA-multimodal therapeutics.

RESULTS: We are currently establishing a highly efficient and cost-effective single-cell co-profiling (e.g., mutation-expression-splicing) approach, which allows in-depth profiling of millions of cells/nuclei per experiment. In addition, we have generated a list of over 2000 RNA-binding proteins for both bioinformatics and functional genomics (e.g., SPAR-seq) investigation of their roles in treatment-resistant GBM and prostate cancer.

CONCLUSIONS: Collectively, our study will link multilevel genetic information to provide deep mechanistic insights into treatment-resistant cancer. The framework and methodologies we build here are highly translatable to investigate diverse cancer types and models, facilitating the development of a new generation of therapies.

ZOYA ADEEL

TITLE: Screening small molecules to identify anti-cancer engineered T cell boosting agents

AUTHORS: Zoya Adeel, Princeton Luong, Jakob Magolan, Jonathan Bramson

OBJECTIVE/INTRODUCTION: T cells modified to express tumour-directed synthetic antigen receptors have shown remarkable clinical success in some cancers. Although T cell therapies have produced durable responses, some patients do not respond or produce long lasting effects. Approaches to enhance engineered T cell products have included the manipulation of activating costimulatory pathways, promoting the proliferation and survival of T cells. These pathways help to amplify and sustain T cell-mediated immune responses, ensuring robust anti-tumour activity. Our lab previously hypothesized that potentiating costimulation via small molecules may improve engineered T cell performance. This strategy has the added advantage of a manageable dosage protocol that can be discontinued if toxicities manifest. We formerly identified Ferutinin as a drug candidate with potent enhancement to T cell proliferation from a high-throughput screen of a large bio-active compound library. We hypothesized that the chemical modification of Ferutinin can improve its potency and drug-likeness. To this end, we employed a structure-activity relationship analysis to generate a small library of Ferutinin analogues (35+) that were synthesized in the Magolan lab.

METHODS: In this study, we set out to screen Ferutinin analogues to identify the compound(s) that improve engineered T cell function. To do so, we have generated engineered human T cells that target HER2 expressing solid tumour lines. We have evaluated their cytotoxic, proliferative, and survival capacity in the presence of a HER2+ tumour stimulus and Ferutinin analogues.

RESULTS: Preliminary functional screens have identified three Ferutinin analogues that enhance engineered T cell cytotoxicity and survival in vitro.

CONCLUSIONS: To validate our findings, we are developing a reporter-based proliferation assay that utilizes automated screening equipment. This screen will enable rapid testing of the compounds in different contexts, i.e., various antigen-binders, tumour targets, compound concentrations, and engineered T cell constructs. The findings of this study hold the potential of identifying a novel compound with engineered T cell boosting activity.

PREYANSH PATEL

TITLE: Characterizing the role of GEM1 in Chicken Embryo Fibroblasts

AUTHORS: Preyansh Patel

OBJECTIVE/INTRODUCTION: The cell cycle regulation is a complex and integral part of the cell. Various genes and proteins are involved in determining when the cell should continue proliferating or arrest the cell cycle. The cell can reversibly enter a quiescent state (G0) when the growth condition is unfavourable and re-enter the cell cycle once the condition has improved. A class of genes called growth-arrest specific (gas) genes are involved in mediating processes in the quiescent state. Some of the previously identified gas genes (p20K) is involved in mitigating oxidative stress caused by unfavourable growth condition in chicken embryo fibroblast (CEF). Transcriptome analysis have shown that GTP-binding protein overexpressed in skeletal muscle cells (GEM1) is upregulated under oxidative stress. GEM1 is a small monomeric GTPase signalling protein although its role and function is not fully characterized yet. Therefor the focus of this study is to determine candidacy of GEM1 as a gas gene and characterize the role of GEM1.

METHODS: The expression pattern of GEM1 is determined using western blot analysis. A shRNA was cloned into miRNA operon expression cassette (MOEC) in the RCASA vector to generate a knockdown construct for GEM1. Immunofluorescence microscopy is used to determine the localization of GEM1 within the cell.

RESULTS: Preliminary testing of GEM1 expression shows that it is primarily expressed in growth-arrested CEF under hypoxic, high cell density, and growth serum depleted conditions, all of which induces oxidative stress on CEF. Results for the knockdown expression of GEM1 is still in progress. Results for the localization of GEM1 is still in progress.

CONCLUSIONS: Research in progress.

VANSHIKA KHAITAN

TITLE: The role of master RNA regulators in glioblastoma progression

AUTHORS: Vanshika Khaitan, Alberto Torrez, Kabir Siraj, Hong Han

OBJECTIVE/INTRODUCTION: Glioblastoma (GBM) is the most common and lethal tumor affecting the adult nervous system. Despite maximal standard-of-care treatment, patients relapse within 7-9 months postdiagnosis and recurrent tumors are untreatable. Previous investigations of gene regulatory circuitry that controls GBM biology have largely focused on the roles of (epi)genetics, transcription, and translation. Recent high-throughput studies have demonstrated that alternative splicing (AS) represents an essential and widely acting gene regulatory layer, providing many opportunities to uncover new mechanisms and therapeutic targets. Over 95% of human multi-exon genes undergo AS, and misregulation of AS impacts every hallmark of cancer. However, AS regulation and its coordination with other gene regulatory layers to control GBM pathogenesis remain largely unexplored. This study aims to systematically characterize the role of coordinated RNA regulatory networks in the spatiotemporal regulation across different stages of GBM progression. We hypothesize that master RNA splicing regulators, such as MBNL1/2, and their regulated AS network play a critical role in controlling GBM cellular states, plasticity, as well as dynamic tumor and microenvironment interactions underlying GBM pathogenesis.

METHODS: Our previous study discovered MBNL proteins as conserved master regulators of a large network of stemness-differential AS events, which control different gene pathways, including key chromatin regulators and transcription factors. With the unique patient GBM samples and patient-derived models, we will use our newly established ultra-high-throughput single-cell co-profiling/multi-omics approaches to interrogate the role of the MBNL-regulated AS network and its coordination with other layers of gene regulation, including (epi) genetics and transcription to govern GBM progression, treatment response, and recurrence. Alongside the single-cell platform, MBNL1/2 knockout is performed in patient-derived primary and recurrent GBM models to further investigate the role of these proteins in GBM progression and interactions with the microenvironment. Together, these will provide novel insights into spatiotemporally coordinated RNA regulation during the GBM ecosystem evolution.

RESULTS: Research in progress.

CONCLUSIONS: Research in progress.

ANISH PURI

TITLE: Role of uPAR in Standard-of-Care resistance and recurrence in Glioblastoma

AUTHORS: Anish Puri, William Maich, Chitra Venugopal, Sheila Singh

OBJECTIVE/INTRODUCTION: Glioblastoma (GBM) is the most common primary malignant brain tumor of the central nervous system. The current Standard-of-Care treatment consists of gross surgical resection, followed by chemo-radiotherapy, but median survival remains at approximately 8 months. Recurrence after Standard-of-Care occurs in almost all cases and emphasizes the importance for exploring novel theraputic options to treat the reccurent tumor. Brain tumor initiating cells (BTICs) are a relevant and targetable niche within the tumor as they are believed to evade traditional therapy and initiate de novo reccurent tumor formation. We have identified that the urokinase receptor, uPAR, is significantly upregulated in BTICs of reccurent GBM. We set out to elucidate the role of uPAR in Standard-of-Care resistance and emergence from dormancy.

METHODS: Several patient-derived brain tumor cell lines were profiled for uPAR expression by flow cytometry. Subsequently, primary GBM cell lines were exposed to a 5 day in-vitro Standard-of-Care protocol which consisted of: 1) Treatment with Temozolomide at a concentration of 25 uM. 2) Incubation at 37 ° C for 1 hour. 3) Radiotherapy treatment of 1 gray (Gy) of radiation. The cells were allowed to recover for three days after which uPAR expression was measured by flow cytometry and compared against uPAR expression of the same cell line which recieved the control treatment.

RESULTS: Research in progress.

CONCLUSIONS: Research in progress.

CLARE MORRIS

TITLE: Developing a TIL product for universal vaccination-based boosting in ACT

AUTHORS: Claire Morris, Rebecca Burchett, Mira Ishak, Jonathan Bramson

OBJECTIVE/INTRODUCTION: Tumour infiltrating lymphocytes (TIL) are an attractive T cell product for ACT as they can offer a plethora of tumour specificT-cell receptors (TCRs) without prior knowledge of targetted tumour antigens. Unfortunately, current TIL-ACT methods involve intensive ex vivo expansion which can diminish the efficacy of the T cell product. To reduce the need for ex-vivo expansion, we have previously validated the combination of ACT with a vaccination-based "boost" through a synthetic receptor to promote in vivo expansion of engineered T cells derived from TCR transgenic mice. We hypothesize that TIL can be engineered with a synthetic receptor matched with a "boosting" vaccine to enable enhanced proliferation of TIL upon boosting antigen interaction. Uniting a vaccine with a matched synthetic receptor can create a universal combination where any TIL product can be minimally cultured, engineered and expanded in vivo by vaccination.

METHODS: Due to its proliferative capacity upon stimulation, we will use a chimeric antigen receptor (CAR) as the synthetic receptor for our vaccination boost. We are developing protocols for TIL isolation, culture, and engineering with a boosting CAR. To optimize protocols, we are using the syngeneic MC-38 tumour model and the CMS-5 tumour model. Tumour draining lymph node (TDLNs) derived T cells are also being engineered and assessed for tumour specificity and ability to proliferate through the boosting-CAR.

RESULTS: Research in progress.

CONCLUSIONS: Research in progress.

ENZO BARACUHY

TITLE: Elucidating the role of non-replicating particles in bovine herpesvirus-1 immunotherapy

AUTHORS: Enzo Baracuhy, Maria Davola, Olga Cormier, Susan Collins, Karen Mossman

OBJECTIVE/INTRODUCTION: Oncolytic viruses (OVs) are a promising approach for cancer treatment as they selectively target and kill cancer cells while also stimulating an immune response. Among OVs, Bovine herpesvirus type 1 (BHV-1) has several advantages, including not requiring virus replication to exhibit anti-cancer properties. We have demonstrated that binding and penetration of enveloped virus particles are sufficient to trigger intrinsic and innate immune signaling. In addition, we have published data showing mutated DNA-based OVs with lower replication in vitro exhibit strong anti-tumour activity in vivo. More recently, we have found that the chemotherapy drug mitomycin–which dampens BHV-1 replication in vitro–improves the efficacy of BHV-1 in vivo, suggesting that replication might hinder BHV-1's anti-cancer potential. Therefore, we hypothesize that replication-incompetent BHV-1 particles that can stimulate innate immune signaling in cancer cells will retain their efficacy in vivo. Such viral particles would also have an improved safety profile as this approach would avoid administering live biological agents to patients.

METHODS: Research in progress.

RESULTS: Our repeated qPCR experiments have shown that UV-inactivated (UVI) BHV-1 induces significantly stronger expression of interferon-stimulated genes (ISGs) compared to live BHV-1. Further experiments using an established transcriptome-profiling microarray will uncover the mechanisms underlying their differential immune activation. Lastly, we have planned an upcoming animal experiment that will compare the therapeutic efficacy of UVI and live BHV-1 together with immune activation and infiltration of different immune cell populations within the tumour.

CONCLUSIONS: Research in progress.

SIDDAARTH VARATHARAJAN

TITLE: Validation of Candidate Compounds from a Screen of Epigenetic Inhibitors in Acute Myeloid Leukemia

AUTHORS: Siddaarth Varatharajan, Lovette Chan, Kanwaldeep Singh, Tobias Berg

OBJECTIVE/INTRODUCTION: Acute Myeloid Leukemia is an aggressive hematological cancer characterized by proliferation and a differentiation arrest of myeloid progenitor cells in the bone marrow. While there has been a lot of development with many new drugs getting available in recent years outcomes are still fairly poor with less than 30 % long-term survival. New approaches including an integration of targeted therapies with allogeneic stem cell transplantation as well as combination treatments are therefore required.
Our lab has performed a screen for differentiation-inducing compounds with the SGC library of 82 compounds with epigenetic, metabolic and signaling targets in the highly resistant murine MN1 leukemia model. We identified a total of 5 compounds that exhibited differentiation effects (two of them against the same target). Therefore, it is of great interest to validate the compounds and understand their mechanism. As all compounds only exhibited a partial differentiation effect, we are further interested if the observed effects are additive and if these compounds synergize with other combination partners.

METHODS: The aim of this project is to validate the compounds in various in vitro models. We will primarily use functional murine leukemia models as well as human AML cell lines in this context. We will determine the effect on proliferation by using the Celltiter Glo assay. We will further study differentiation by using flow cytometry-based read-outs such as the expression of immature markers like cKit and Sca1 as well as differentiation markers like CD11b and Ly6G. Follow up experiments will then focus on determining the effect on apoptosis induction using Annexin V staining. Once the effect of the inhibitors is confirmed, we will combine the inhibitors in these assays to determine if they exhibit synergistic or antagonistic effects when combined with each other as well as agents with known activity in AML.

RESULTS: Research in progress.

CONCLUSIONS: Research in progress.

OLGA CORMIER

TITLE: Development of Bovine herpesvirus - 1 as part of a broad spectrum viral-mediated immunotherapy

AUTHORS: Cormier O, Davola M, Collins S, Mossman K

OBJECTIVE/INTRODUCTION: Checkpoint (CP) immunotherapy continues to be a promising avenue for treatment of a wide variety of cancers. However immunologically cold tumours continue to present a major barrier to its widespread use. Major preclinical and clinical findings show that viral-mediated immunotherapy (previously oncolytic viruses (OVs)) can sensitize tumors to CP immunotherapy. Previously, our lab has identified Bovine Herpesvirus 1 (BHV-1) as a promising candidate for OV-mediated therapy when used in conjunction with low dose chemotherapy and CP. BHV-1 continues to be a promising candidate for therapy as it shows no seroconversion in humans, targets over 70% of the NCI60 panel, and more recently has been shown to induce immunogenic cell death in the tumour and induce the activation of CD8+ T cells in a syngeneic murine model of melanoma. When using low-dose chemotherapy mitomycin C (MMC) in conjunction with BHV-1 the tumour is sensitized to CP therapy through early recruitment of CD8+ T cells and the reduction of suppressive PD-1+ Tregs. The objective of the is to develop tools for further study of BHV-1 therapy efficacy in a variety of cancer models, and to understanding the underlying mechanism of action in each case with the ultimate goal being to improve efficacy and understand the precise mechanism of immune stimulation occurring in the tumour. This development includes cell and virus engineering, use of live cell imaging, transcriptional profiling as well as in vivo work with syngeneic models. We found effective ways to manipulate BHV-1 and relevant cell types, however the research is ongoing.

METHODS: Research in progress.

RESULTS: Research in progress.

CONCLUSIONS: Research in progress.

CINDY LEE GRAHAM MEMORIAL AWARD

WHO IS CINDY LEE GRAHAM?

Thomas Graham will always remember his wife Cindy as someone with the most beautiful smile. But he wants the world to remember her as someone whose dying wish was to donate herself, particularly her brain and spinal cord, to science, to save others from the deadly brain cancer that claimed her life.

And it is scientists at McMaster University whom Graham is trusting to keep alive his wife's legacy – and preserve the love they shared.

The cancer that killed the Guelph resident was a recurrent glioblastoma (GBM). The research manager died in February 2021, 21 months after being diagnosed. Most patients survive only 15 months after diagnosis, and it is a near-certain death sentence.

For McMaster University scientist Sheila Singh however, Cindy's cancer-ravaged brain and nervous system is worth its weight in gold, even as she feels haunted by her inability to save her. Singh and her team worked fast to fulfil their patient's final wish as preserving Cindy's stem cells quickly was important. They received the brain and spinal cord from McMaster's anatomy department within three hours of Cindy's death in Guelph.

"We work with harvesting live stem cells from brain tumour tissue, putting them into cultures to grow and 'passage' them into a renewable cell resource, called a cell line. When someone dies, their stem cells may only remain viable for up to 24 hours after death, and the sooner we are able to harvest them, the more viable the cells will be," said Singh, a professor of surgery at McMaster and pediatric neurosurgeon for Hamilton Health Sciences.

"The cure did not come soon enough for Cindy, but it is coming, and it will be dedicated to people like our patients. This is part of Cindy's true legacy and I know her husband and children will be very proud."

Next, Singh's team extracted the brain tumour stem cells and put them into cultures to grow in incubators. They also preserved tiny blocks of each tissue specimen in liquid nitrogen to freeze and later for sequencing and other lab studies. They catalogued and cultured all the tissues for nearly six hours, finally going home at midnight.

"It is amazing that all 10 samples passaged into 10 lines, we rarely get a 100 per cent hit rate for cell line development, unless the original cells were of extremely high viability," said Singh.

An entire organ system will allow Singh and her team to map out in detail the GBM and the mechanism behind it, building a comprehensive profile of a biological serial killer. Previous donations have typically only been small GBM tissue samples.

A recurring GBM is different from the originally cancer, spreads aggressively, does not respond to treatment and nearly always fatal. The tumour typically regrows from cancer stem cells that cannot be fully destroyed by traditional surgery, chemotherapy, nor radiotherapy. On average, GBM tumours regrow seven to nine months after diagnosis. The five-year survival rate for GBMs is only 5.5 to 6.8 per cent, according to figures released recently by Brain Cancer Canada.

"When it came time to realize Cindy was not going to recover, I and my students were devastated. We study this disease every day, trying to find a cure and it's a real blow to the whole research team every time we hear a patient is not going to survive," Singh added.

However, the organ gift will allow Singh to conduct research using CRISPR technology to map cancer cells' genetic makeup, that may mean GBMs are no longer a death sentence. Once identified, specific antibodies or immunotherapy can be deployed against GBM cells and halt their regrowth.

Cindy's death also represents a new beginning of sorts for Bruce Wainman, professor and director of McMaster's anatomy education program. He handled the donation and helped liaise with her family in making her last wish come true.

In doing so, this final gift breathed new life into McMaster's anatomy lab shuttered by the impact of COVID-19 and the restrictions of remote work. Despite those limitations, Wainman's team was prepared for Cindy's donation and quickly swung into action.

CINDY GRAHAM MEMORIAL AWARD FOR BRAIN AND CNS CANCER RESEARCH

Established in 2021 by Cindy Graham's family and friends to complement her donation of tissue upon her death and throughout her treatment for glioblastoma (GBM). It is hoped that through the support of talented graduate students Cindy will continue to inspire and provide hope. Cindy was committed to advancing research around GBM, participating in clinical trials and ultimately through the donation of her brain and spinal cord to research at McMaster University. McMaster scientists were given a unique opportunity to better understand GBM biology, the regulators of invasion and tumour spread, as well as immune system/immunotherapy responses and applications towards treatments.

To be awarded to a graduate student who has made significant contributions, or demonstrates a clear potential to do so, in brain or central nervous system cancer. The funds are to be awarded annually at the discretion of Dr. Sheila Singh in consultation with the Chair of the Department of Surgery.

PREVIOUS AWARD WINNERS

2021

CHIRAYU CHOKSHI

PHD CANDIDATE

2022

WILLIAM MAICH

PHD CANDIDATE

ALEXANDER JANKE MEMORIAL SCHOLARSHIP AWARD

WHO IS ALEXANDER JANKE?

Alexander Janke was a brave warrior who battled glioblastoma with a positive attitude for three years. He was a young chef with a passion for all things culinary who enjoyed preparing delicious meals for his restaurant patrons, friends and family. At the end of his life, he donated his brain and spinal cord to McMaster University for further research in glioblastoma. It is our hope that your contribution to brain cancer research will lead to a cure for glioblastoma.

Alexander obtained his degree in Culinary Arts from Niagara College in 2013 and returned to Waterloo, working at several restaurants until finding his home at Gilt Restaurant. At Gilt, he and Stephanie Rank created many wonderful tapas meals for the patrons. It was while working at Gilt that he had his first seizure caused by the brain tumour.

Shortly after starting his battle with glioblastoma, Alexander was easily recognizable with his shaved head and tattoos. Where did he go from there? He fought. He fought through treatment after treatment. He fought for more time to experience life's adventures. He fought for those who would receive the diagnosis after him by pushing the boundaries of his medical team for more treatment options, and more clinical trials. He fought for more time to cook, more holidays, and more birthdays. Most importantly, he fought for as much time as he could to make memories with his friends, family and to become an uncle.

Through the course of three surgeries, Alexander always maintained a positive attitude. The 29-year-old cancer warrior did a lot in those three years: baked sourdough bread, reconnected with family and friends, raised funds for brain cancer research, embraced simple truths about life that most of us take for granted: Be kind, don't give up!

Recipients of this grant will be individuals who can continue the fight Alexander wasn't able to finish. They will pursue further research for future patients, and find solutions to the many unanswered questions that surround the diagnosis and treatment of this aggressive disease.

ALEXANDER JANKE MEMORIAL SCHOLARSHIP IN BRAIN CANCER RESEARCH

Established in 2023 by Paul and Elizabeth Janke, and the family and friends of Alexander Janke. To be awarded to a graduate student who has made significant contributions, or demonstrates a clear potential to do so, in glioblastoma or other brain cancer research.

NOTES

McMaster University

Centre for Discovery in Cancer Research

THANK YOU

ADJUDICATION JUDGES:
Anthony Rullo
Hong Han
Juliet Daniel

ORAL & RAPID FIRE PRESENTATION JUDGES:
Ali Ashkar
Tobias Berg
Yonghong Wan

POSTER PRESENTATION JUDGES:
Chitra Venugopal
Joni Hammill
Leila Vahedi
Rob Cowan

MC:
Anthony Rullo

OPERATIONS TEAM:
Andrew Allen
Dana Radcliff
Paul Kutasi

VOLUNTEERS:
Anish Puri
Daniel Mobilio
Darlene Lane
Emily Hartung
Hanad Adan
Olga-Demetra Biziotis
Petar Miletic
Patrick Ang
Vanshika Khaitan

AUDIO/VISUAL:
Soundbox

VENUE:
McMaster Innovation Park (MIP)

CATERING:
McMaster Catering

FINANCIAL SUPPORT:
McMaster Vice-President Research Office

The CDCR and McMaster University recognize and acknowledge that we are located on the traditional territories of the Haudenosaunee and Anishinaabe nations. This territory, covered by the Upper Canada Treaties, is within the lands protected by the "Dish With One Spoon" Wampum agreement and is directly adjacent to the Haldimand Treaty territory.