MIT DEPARTMENT OF BIOLOGY

Biology Undergraduate Research Symposium 2015

January 29th | 12–5 pm | 68-181

12:00 pm Opening Remarks

12:10–1:10 pm	1:25–2:25 pm	2:40–3:40 pm	3:55–4:40 pm
Luke Koblan Golub Lab	**Jennifer Halford** Krieger Lab	**Sung Won Cho** Sabatini Lab	**Max Baas-Thomas** Littleton Lab
Meghan Torrence Vander Heiden Lab	**Joanne Zhou** Tonegawa Lab	**Lakshmi Subbaraj** Jacks Lab	**Preeti Singhal** Bhatia Lab
Sharon Kim Amon Lab	**Alycia Gardner** Samson Lab	**Jeff Chen** Ploegh Lab	**Adelaide Tovar** Irvine Lab
Julie Ko Amon Lab	**Kyle Lathem** Weiss Lab	**Choah Kim** Sabatini Lab	

4:45 pm Closing Remarks

All are welcome!

Refreshments will be served.

Contents

Understanding Selectivity and Potency of Drug Action from Serine Hydrolases to Epigenetic Machinery

Luke W. Koblan, Daniel A. Bachovchin, Christopher J. Ott,
James E. Bradner, Todd R. Golub, Eric S. Lander
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As the effectors of biological function, proteins are the canonical targets for therapeutic intervention. Proteins regulate cellular activities and their hydrophobic clefts present druggable targets ranging from the regulators of the epigenome to proteases. The development of rationally designed, novel therapeutics hinges on understanding the delicate balance between potency and selectivity for drugs. We therefore developed a novel high-throughput platform for enzyme superfamily-wide inhibitor selectivity profiling. This technology quickly and reproducibly identified previously known inhibitor interactions (like Sitagliptin with dipeptidyl peptidase-IV, DPP4), but importantly identified hundreds of unknown interactions, including several with potential therapeutic benefit. One such example is our finding that the prolylcarboxypeptidase (PRCP) inhibitor Telaprevir, but not Boceprevir, has an off-target interaction with an epithelium-specific protein, CELA1. This interaction may explain epithelial lesions associated with Telaprevir, confirming that characterization of off-target effects is an important facet in the creation of safe and effective therapeutics. Understanding drug selectivity is not the only requirement for developing good drugs. Thus, in a related project, we sought to understand an emerging drug target class- the bromodomains. We began this work by studying the activity of the BET bromodomain inhibitor, JQ1. This small molecule inhibitor disrupts the binding of a reader of histone acetylation marks, BRD4, to chromatin. BRD4 normally recruits P-TEFb to promoters; however, administration of JQ1 impairs P-TEFb's ability to up-regulate transcription. This mechanism generates efficacy without toxicity in a number of biological contexts because it mediates cell-state transitions that are upregulated in diseased cells. The powerful outcomes of drugging BRD4 inspired us to characterize the chromatin binding of other bromodomain-containing proteins. Each of these proteins plays a unique role in transcriptional regulation that could ostensibly be drugged just as BRD4 is drugged by JQ1. I believe that combining inhibitor development with comprehensive target characterization is the future of drug discovery.

Faculty Supervisor: Eric S. Lander
Research Supervisors: Todd R. Golub & James E. Bradner
Postdoctoral Mentors: Daniel A. Bachovchin & Christopher J. Ott

Investigating Branched Chain Amino Acid Metabolism in Mutant *Kras*-Driven Tumors of Different Tissue Origins

Meghan Torrence, Jared Mayers, Matthew Vander Heiden
Broad Metabolite Profiling Platform, Dana-Farber Cancer Institute,
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In collaboration with researchers at the Dana Farber Cancer Institute and the Broad Institute, we recently identified plasma elevations of the three branched-chain amino acids (BCAAs) isoleucine, leucine, and valine to be associated with early stage pancreatic ductal adenocarcinoma (PDAC) in humans. We further showed that elevated amounts of BCAAs were present in the plasma of mice with early-stage pancreatic cancer and demonstrate that these elevations were derived from increased whole-body protein breakdown. Interestingly, and in contrast to our findings in PDAC, plasma BCAAs are significantly decreased in mice with early stage non-small cell lung cancer (NSCLC) also driven by mutant *Kras* expression. Based on these data, I have been investigating the contributions of BCAA catabolism to tumor progression in both PDAC and NSCLC models with the hypothesis that the same oncogenic mutations in different tissue contexts drive in different metabolic dependencies. To address this possibility, I am combining a variety of stable-isotope tracing approaches as well as using the CRISPR Cas-9 system to knock-out branched-chain amino acid transaminases 1 and 2 (BCAT) and also branched-chain keto acid dehydrogenase E1A (BCKDHA), both critical for BCAA catabolism, *in vitro* and *in vivo* to observe effects on tumor metabolism and growth.

Faculty Supervisor: Matthew Vander Heiden
Graduate Student Mentor: Jared Mayers

Fitness Cost of Stoichiometric Imbalance of Protein Complex Subunits on Budding Yeast

Sharon Kim, Stacie Dodgson, Angelika Amon
Koch Institute for Integrative Cancer Research,
Dept. of Biology, MIT, Cambridge, MA 02139 USA

Cells maintain protein homeostasis by synthesizing subunits of macromolecular complexes according to a defined stoichiometry. In aneuploid yeast cells, which harbor an extra copy of a chromosome, overexpression of subunits encoded on the extra chromosome results in stoichiometric imbalances. However, it has been found that some overexpressed subunits are attenuated by posttranslational degradation unlike other excess proteins, which are sequestered in aggregates. Such dosage compensation mechanisms likely impose a fitness cost on the cell. In this present study, we want to examine the fitness cost solely attributable to stoichiometric imbalances of complex subunits, which may contribute to the slow proliferation exhibited by aneuploid cells. As a preliminary analysis, we sought to isolate the fitness cost associated with the stoichiometric imbalance in two model complexes: yeast tubulin complex and human VHL-ElonginBC complex. Budding yeast cells expressing balanced subunit levels were competed against cells expressing unbalanced subunit levels to measure their relative fitness. Cells expressing more α-tubulin than β-tubulin exhibited decreased fitness compared to those expressing balanced levels of α- and β-tubulin. Cells only expressing VHL exhibited decreased fitness compared to those expressing both VHL and ElonginBC. This preliminary study suggests that there is an isolatable fitness cost associated with having unbalanced complex subunit levels.

Faculty Supervisor: Angelika Amon
Graduate Student Mentor: Stacie Dodgson

Aneuploidy Provides a Disadvantage to Human Colorectal Cancer Cells

Julie Ko, Jason Sheltzer, Angelika Amon
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While aneuploidy is largely believed to be beneficial to tumorigenesis, the effects of aneuploidy, both general and chromosome-specific, on cancer cells is still unclear. To examine the effects of aneuploidy on tumorigenesis, we compared the cancer-related phenotypes of the diploid, chromosomally-stable human colorectal cancer cell line HCT116, with derivatives of that line that were aneuploid for chromosomes 3, 5, or 8. We found that aneuploidy has a generally detrimental effect on cancerous phenotypes, including proliferation, colony forming ability, and anchorage-independent growth. However, some phenotypes appear to be specific to the aneuploid chromosome - the aneuploid line for chromosome 8 (HCT116 8/3) had remarkably similar in vitro growth to the euploid HCT116. Moreover, xenografts in nude mice showed that trisomy 5 (HCT116 5/3), but not the other aneuploid lines, grew tumors comparable to HCT116. Our results show that while the identity of the extra chromosome can change the severity of the phenotype, aneuploidy is in general detrimental to cancer cells.

Faculty Supervisor: Angelika Amon
Graduate Student Mentor: Jason Sheltzer

Uncovering the Mechanism by which a Cytoplasmic Adaptor Protein Regulates the Receptor for 'Good' Cholesterol (HDL) in the Liver

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SR-BI, a receptor for HDL ('good' cholesterol), controls HDL metabolism and many physiologic and pathophysiologic processes. The expression and function of hepatic SR-BI depends on PDZK1, a four PDZ (PDZ1-4) domain-containing adaptor protein. *In vivo* complementation analysis of PDZK1 KO mice with wild-type (WT) and mutant PDZK1 transgenes showed that only two of PDZK1's PDZ domains, PDZ1 and PDZ4, are necessary for full regulation of hepatic SR-BI. The PDZ1 domain displays canonical binding to SR-BI's C-terminus and PDZ4 helps anchor PDZK1 to the plasma membrane, possibly by binding directly to inner leaflet lipids. We are using WT and putative membrane-binding-defective mutant PDZ4 proteins to characterize PDZ4's binding to inner leaflet mimetic liposomes *in vitro* and to determine if such binding is required for PDZ4 function *in vivo*. The structural integrity of the mutants, designed based on the X-ray structure of PDZ4, is assessed using Circular Dichroism (CD) and Isothermal Titration Calorimetry (ITC). Membrane binding in vitro is assessed using a robust Surface Plasmon Resonance (SPR) assay we have developed recently. Our CD studies show that one of our mutant PDZ4 proteins is unstable at body temperature (37°C) and thus unsuitable for functional studies in transgenic mice. Our *in vitro* SPR studies are designed to determine 1) which side chains on the surface of PDZ4 are required for binding to the inner plasma membrane mimetic liposomes and 2) which component(s) of the inner plasma membrane are required for PDZ4 binding. Preliminary studies suggest that a subset of anionic phospholipids in the membrane may bind directly to PDZ4. The results of our biophysical studies of the PDZ4-plasma membrane interaction will be discussed. Because PDZK1 is a scaffold/adaptor for multiple transmembrane proteins, including CFTR (mutated in cystic fibrosis), our studies may provide insights into the mechanisms controlling proteins in addition to SR-BI.

Faculty Supervisor: Monty Krieger
Research Mentor: Nadine Elowe

Activating Positive Memory Engrams Suppresses Depression-related Behavior

Joanne Zhou[1], Steve Ramirez[1], Xu Liu[1,2], Anthony Moffa[1], Roger L. Redondo[1,2], Susumu Tonegawa[1,2]
RIKEN-MIT Center for Neural Circuit Genetics at the Picower Institute for Learning and Memory[1], Dept. of Biology and Dept. of Brain and Cognitive Sciences, and Howard Hughes Medical Institute[2], MIT, Cambridge, MA 02139 USA

Stress-induced depression has increasingly pervaded much of modern life. Yet currently available treatments have yielded low efficacy, and the underlying neuronal mechanisms for rescuing depressive-like symptoms have remained unclear. Both stress and depression have been hypothesized to modulate hippocampal and behavioral functions that can be exhibited in animal models as quantifiable behavioral impairments, such as anhedonia and deficits in motivation. Here, we show that optogenetic activation of neurons previously involved in encoding positive memories is sufficient to alleviate depressive-like behavior in mouse behavioral models. A brain-wide histological investigation, and pharmacological and projection-specific optogenetic blockade experiments were performed. We found that glutamatergic activity in the hippocampus-amygdala-nucleus accumbens pathway was a crucial neurological circuit underlying this acute rescue. Moreover, chronic reactivation of positive hippocampal engrams alleviated depressive behavior at time points beyond the light stimulation epoch. By using light-activated control of specific memories in mouse models, our research presents the first glimpse into the role of positive memory reactivation in the context of stress-induced depressive symptoms.

Faculty Supervisor: Susumu Tonegawa
Graduate Student Mentor: Steve Ramirez

In vivo Quantification of 3,N^4-ethenocytosine Repair by the Nucleotide Excision Repair Pathway

Alycia M. Gardner[1], Isaac A. Chaim[2,3], Leona D. Samson[1,2,3,4]
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DNA repair pathways are essential to the maintenance of the cellular genome and the prevention of deleterious effects caused by compromised genomic integrity. The Nucleotide Excision Repair (NER) pathway functions in removing bulky DNA lesions from the genome. One type of bulky DNA lesion that has not been previously shown to be repaired by NER is 3,N^4-ethenocytosine (εC), which is a lesion known to occur in inflammation related cancers. In this study, we optimize reporters for use in a modified host cell reactivation assay that will allow characterization of etheno adduct repair. Using shRNA constructs to establish cell lines deficient in proteins in the NER pathway, we use a fluorescence-based, multiplexed host cell reactivation (FM-HCR) assay to quantify the repair of thymine dimers, εC, and 1,N^6-ethenoadenine (εA) lesions by Nucleotide Excision Repair in Mouse Embryonic Fibroblasts (MEFs) and LN229 glioblastoma cells. This study suggests that NER is involved in the repair of εC lesions, establishing a new mechanism of εC repair. It further suggests a new use for the FM-HCR assay as a functional test to phenotype knockdown of proteins involved in DNA repair.

Faculty Supervisor: Leona D. Samson
Graduate Student Mentor: Isaac Alexander Chaim

Engineered Mammalian Cell-Cell Communication Using Synthetic Exosomal miRNA

Kyle Lathem[1,2], Deepak Mishra[2,3], Ron Weiss[2,3,4]
Dept. of Biology[1], Synthetic Biology Center[2], Dept. of Biological Engineering[3], Dept. of Electrical Engineering and Computer Science[4], MIT, Cambridge, MA 02139 USA

Engineering complex behavior within a biological system requires specialized cell populations that coordinate their individual behaviors. One mechanism to achieve this coordination is through extracellular signals that result in changes in gene expression in the individual cell populations. In mammals, miRNA, mRNA, and proteins are naturally packaged within exosomes that are exchanged between cells. Incorporating synthetic signals into exosomes creates a platform for engineering intercellular communication. Informed by recently discovered sequence motifs1, we have designed eight variants of a well characterized mammalian-orthogonal miRNA which are expected to be selectively packaged into exosomes. We utilize a bead-based miRNA detection assay in conjunction with RT-PCR to quantify intracellular expression and exosomal packaging of the miRNA variants in HEK293 cells. Furthermore, we build and characterize a simple genetic network that changes gene expression in response to receiving miRNA. A functional synthetic miRNA communication platform will allow for the creation of more complex multicellular systems with coordinated behavior among multiple specialized cell populations.

[1] *Villarroya-Beltri, C. et al. (2013). Nature Communications, 4, 2980*

Faculty Supervisor: Ron Weiss
Graduate Mentor: Deepak Mishra

Small Molecule Inhibitors of Phosphoglycerate Dehydrogenase as Potential Agents for the Treatment of PHGDH-dependent Breast Cancers

Sung Won Cho, Michael Pacold, David Sabatini
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Estrogen receptor-negative (ER-negative) breast cancer accounts for more than half of deaths from breast cancer, the second most common cancer in American women. Therapeutic options are currently limited, but previous studies demonstrated that genetic knockdown of phosphoglycerate dehydrogenase (PHGDH) decreases proliferation in ER-negative breast cancer cells that overexpress PHGDH. Here, we detail the discovery of PHGDH Inhibitor #1, which suppressed PHGDH activity in enzymatic assays with IC_{50} < 5μM and reduced PHGDH-dependent ER-negative cell proliferation *in vitro* with EC_{50} < 20μM. Inhibitor #1 did not indiscriminately target dehydrogenases, as IC_{50} values were over 100μM for multiple dehydrogenases closely related to PHGDH. Inhibitor #1 decreased proliferation in three PHGDH-overexpressing cell lines and had minimal effects on two other cell lines with low PHGDH expression, indicating specificity of the compound. Inhibitor #1 is a proof of concept that small molecule inhibitors of PHGDH may be useful in future treatment of ER-negative breast cancers.

Faculty Supervisor: David Sabatini

Postdoc Mentor: Michael Pacold

Circadian Clock Disruption in Lung Tumorigenesis

Lakshmi Subbaraj, Thales Papagiannakopoulos, Tyler Jacks
Koch Institute for Integrative Cancer Research, Dept. of Biology, MIT, Cambridge, MA 02139 USA

Circadian clocks are molecular systems that allow organisms to adapt their behavior and physiology to anticipated environmental changes. Clock proteins such as the *Period* family (*Per*) regulate circadian clocks, located in the hypothalamus and peripheral organs, through transcriptional and post-translational negative feedback loops. Previous studies have shown that disruption of these rhythms leads to abnormal regulation of several cancer-associated hallmarks, such as cell cycle, DNA damage response, and metabolism. In this study, we examined the effects of cell autonomous oncogenic events on the regulation of circadian clocks using mouse models of non-small cell lung cancer driven by a constitutively active oncogenic $Kras^{G12D}$ allele. To understand changes in circadian rhythm oscillation patterns in lung tumors, we studied circadian clock protein levels over time. Analysis of pattern variations showed disruptions in the period and amplitude of circadian rhythm oscillation patterns associated with clock proteins *Arntl*, *Per2*, and *Cry1*. To visualize circadian oscillations *in vivo* and in real time, a luciferase reporting system (*Per2::Luc*) was used. Following the observations of circadian rhythm oscillation disruption, we began to functionally characterize various circadian clock regulated genes by disrupting circadian rhythm homeostasis. Using the CRISPR/Cas9-mediated genome editing system, loss-of-function mutations of core clock components were introduced in order to study mutant phenotypes. With this method, we successfully generated circadian clock gene knockouts in cell lines as well as in mouse models with a conditional oncogenic $Kras^{G12D}$ mutation. We anticipate that these tools will allow us to further elucidate the role of circadian rhythm disruption in lung tumorigenesis.

Faculty Supervisor: Tyler Jacks

Postdoc Mentor: Thales Papagiannakopoulos

Generation of Programmable Cell Lines and Single-domain Antibodies to Study the Inflammasome Response

Jeff Chen, Florian Schmidt, Hidde Ploegh
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Inflammasomes are large multi-protein complexes that respond to pathogenic infection in myeloid cells by activating Caspase-1, releasing pro-inflammatory cytokines such as IL-1β, and/or inducing an inflammatory form of cell death termed pyroptosis. Since whole bacterial infection can feed into multiple signaling pathways, we aimed to develop a clean system with which to study the inflammasome response in the absence of pathogenic infection. Using Tet-on lentiviral vectors, we generated several doxycycline-inducible THP-1 (human monocytic) cell lines programmed to express distinct bacterial needle proteins that are directly sensed by inflammasome receptors. We demonstrated that the expression of a single bacterial protein of fewer than 80 amino acids in differentiated THP-1 macrophages led to robust inflammasome activation, as evidenced by the proteolytic activation of Caspase-1 and the secretion of IL-1β. To generate additional tools to study the inflammasome response *in vivo*, we take advantage of the fact that animals in the Camelidae family naturally produce heavy chain-only antibodies, which can be further shrunk in the laboratory to a single 25kD variable domain of the heavy chain (VHH). We have cloned and expressed murine inflammasome components, which are used as baits in ongoing phage display experiments to select high-affinity binders from VHH libraries. It is hypothesized that reconstituted murine inflammasomes in 293T cells can be activated by the bacterial needle proteins described above, and that this activation can be blocked intracellularly by VHHs that target, for example, pro-Caspase-1. Since aberrant inflammasome activation is implicated in many diseases including flu and malaria infections, select VHHs can be tested for efficacy in animal models of these diseases.

Faculty Supervisor: Hidde Ploegh
Postdoc Mentor: Florian Schmidt

Beyond Intracellular Recycling: The Lysosome as a Signal Integration Site for a Major Growth Pathway

Choah Kim, Zhi-Yang Tsun, David M. Sabatini
Whitehead Institute, Dept. of Biology, MIT, Cambridge, MA 02139 USA

The lysosome has commonly been described as the waste or recycling bin of the cell, due to its digestive properties. However, recent research has identified the lysosome as the signal integration center of a major growth pathway, the mechanistic target of rapamycin (mTOR) pathway. This system integrates various cues, such as nutrients and growth factor signals, to control the balance of cell growth and recycling processes. Given the importance of these processes, it is not surprising that the mTOR pathway is deregulated in common diseases such as diabetes and cancer.

A system of switch-like GTPases regulate this critical pathway at the lysosomal surface. The Rag GTPases signal amino acid sufficiency and recruit mTOR complex1 (mTORC1) to the lysosome for pathway activation. We identified SLC38A9 as a candidate amino acid sensor that signals amino acid presence through the Rag GTPases. SLC38A9 is interesting because it appears to be a transceptor, an amino acid transporter with signaling properties. SLC38A9 binds amino acids via its transporter domain and signals their presence through its N-terminal Rag-binding domain.

Thus, the lysosome is not only a recycling bin, but has also emerged as a hub for signal integration for a major growth pathway.

Faculty Supervisor: David M. Sabatini
Graduate Student Mentor: Zhi-Yang Tsun

DShank Interacts with Trans-synaptic Adhesion Complexes to Regulate Synaptic Morphology

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Synapses are sites of communication between neurons and their target cells. For normal synaptic transmission, proteins on both sides of the synaptic cleft are organized into a structure capable of rapid signaling. Scaffolding proteins play a key role in this organization by bringing together binding partners. One family of scaffolding proteins is the postsynaptic Shank proteins. Shank recruits and regulates many other proteins, and its dysfunction or loss is linked to Autism Spectrum Disorders. In *Drosophila melanogaster*, a useful model organism for studying synapse formation and function, we created the first *DShank* deletion through imprecise excision of a transposable *Minos* element. We investigated its interactions with *neuroligin*, *neurexin*, *teneurin-a*, and *teneurin-m*, genes coding for trans-synaptic adhesion complex proteins. By creating double heterozygote combinations and evaluating their synaptic morphologies at the neuromuscular junction, we found evidence for genetic interactions between *DShank*, *dnlg-1* and *ten-a*. These results indicate DShank is likely to interact with these trans-synaptic components to properly organize normal synaptic connections.

Faculty Supervisor: J. Troy Littleton

Postdoc Mentor: Katie Harris

Delivery of Therapeutic siRNA via a Peptide-based Nanoparticle for Treatment of Ovarian Cancer

Preeti Singhal, Ester Kwon, Sangeeta Bhatia
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Ovarian cancer is the fifth leading cause of cancer-related deaths in women. Due to inadequate detection methods, a majority of cases are diagnosed at late stages after the cancer has metastasized, highlighting the need for innovation in ovarian cancer therapy. Loss-of-function mutations in ARID1A, a subunit of the mammalian SWI/SNF chromatin-remodeling complex, are prevalent in many ovarian cancers, and ARID1B is mutually exclusive to ARID1A. In the present studies, we validate ARID1B as a target for ARID1A loss-of-function ovarian cancer by studying the effects of RNAi-induced ARID1B knockdown in six different ovarian cancer and control cell lines. Of the six cell lines, OAW42 was found to be most sensitive to ARID1B knockdown. To apply ARID1B siRNA delivery to *in vivo* model in the future, we examined the efficacy of a peptide-based tumor penetrating nanoparticle (TPN) siRNA delivery carrier. The carrier was designed to target surface ligands enriched on ovarian cancer cells, such as NRP1, av integrins, and avb3 integrins, for optimal binding and internalization of siRNAs. Flow cytometric analysis showed that OAW42 cells were 70%, 98%, and 10% positive for NRP1, av, and avb3, respectively. A binding assay was performed to confirm the binding capacity of our TPN carrier to OAW cells, and the results demonstrated a significant increase in binding compared to LyP1, a control peptide. Furthermore, we tested the ability of the TPN carrier containing ARID1B siRNA to knockdown ARID1B in OAW42 cells. Western Blot analysis confirmed a ~40% decrease in ARID1B expression upon treatment with TPN ARID1B siRNAs. Taken together, these results suggest that our peptide-based siRNA delivery carrier is able to mediate targeted knockdown of ARID1B in OAW42 cells. Future studies will include testing the efficacy of the TPN siRNA carrier in *in vivo* xenograft models.

Faculty Supervisor: Sangeeta Bhatia

Postdoc Mentor: Ester Kwon

Developing an Improved Immunotherapy for Late-Stage Cancers by Engineered Immunomodulation

Adelaide Tovar, Gregory L. Szeto, Darrell J. Irvine

Koch Institute for Integrative Cancer Research, Dept. of Biology, MIT, Cambridge, MA 02139 USA

Recently developed immunotherapies targeting late-stage cancers have proven effective in many cases where first-line cancer therapies have failed. These new therapies specifically target some of the mechanisms that tumors use to evade the immune system, such as CTLA-4. One potential immunomodulatory strategy is targeting the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) which has been shown to mediate immune suppression and tolerance. Here we investigated whether IDO inhibition could prevent pulmonary metastasis. We employed intratracheally-instilled, micron-sized biopolymeric particles loaded with the IDO inhibitor CAY10581 to achieve sustained drug release and targeted inhibition in the lungs. After intravenous inoculation with B16F10 melanoma or 4T1 mammary gland carcinoma cells, mice that received IDO-inhibiting particles had decreased lung metastatic burden compared to mice delivered unloaded particles. Based on evidence showing that IDO functions as a resistance mechanism in α-CTLA-4 therapy, IDO inhibition and α-CTLA-4 therapy were combined to see if anti-metastatic effects could be enhanced. Contrary to the synergistic relationship that has been proposed by others, blocking both molecular targets did not lead to decreased pulmonary metastasis. Our study suggests a role for IDO in the progression of metastasis while also offering motivation for future investigation into the temporal relation between IDO and CTLA-4 activity.

Faculty Supervisor: Darrell Irvine

Postdoc Mentor: Greg Szeto