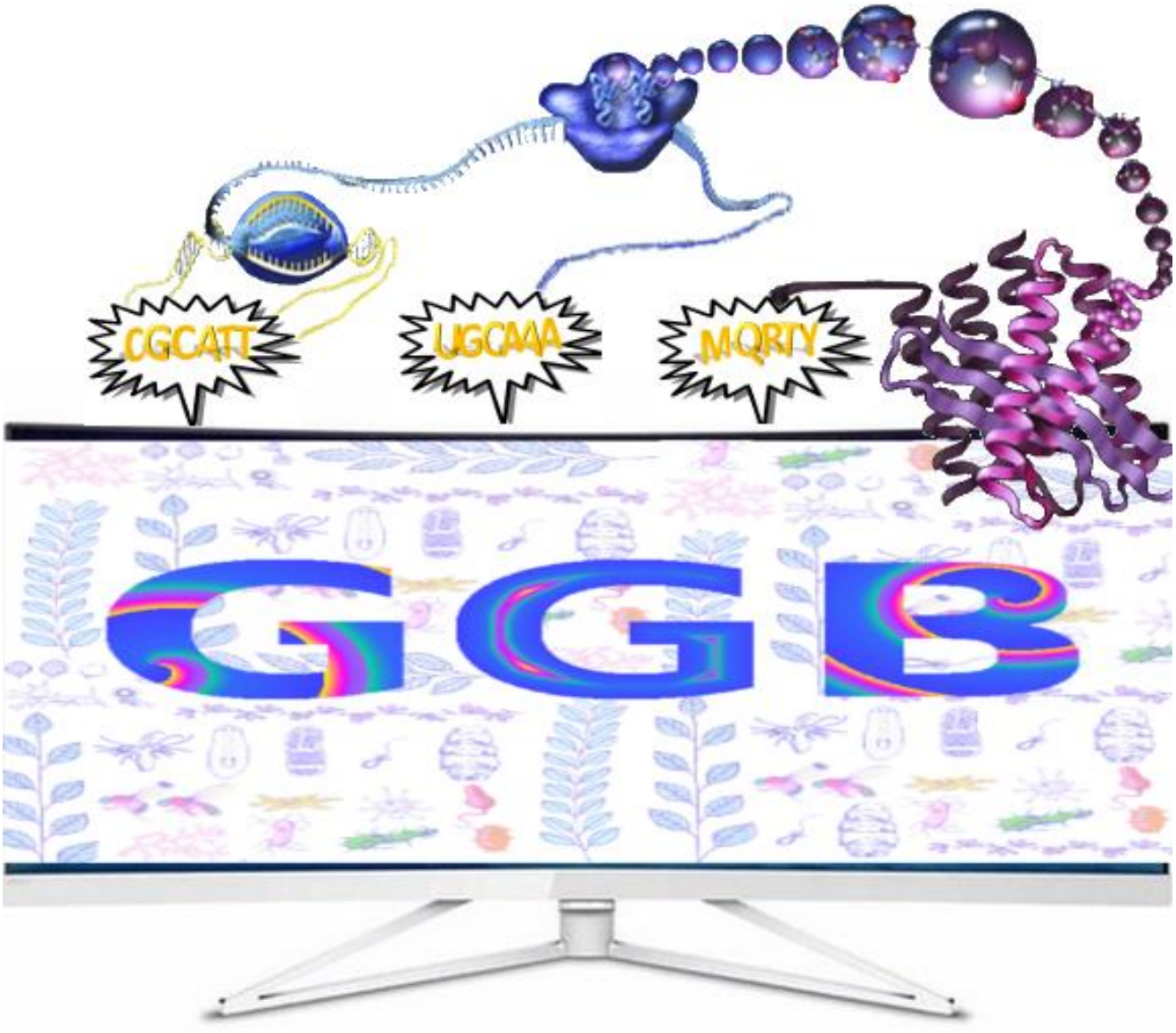
Genetics, Genomics, and Bioinformatics Program

Annual Symposium 2018

Genomics Auditorium

Tuesday, September 18th



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Annual Symposium 2018

Genomics Auditorium

Tuesday, September 18th

08:30-09:15AM **NEW STUDENT ORIENTATION**

09:15-10:15AM **BREAKFAST AND REGISTRATION**
(Genomics Lobby)

10:15-11:30AM **SESSION I**

10:15AM DR. XUEMEI CHEN
Opening Remarks

10:30AM ELIZABETH DEYETT
Talk: Fungal Ecology of the Endophytic Grapevine Microbiome

10:45AM ALEJANDRO NAVARRO
Flash Talk: 5th time is the charm. Hopefully.

10:50AM SAWYER MASONJONES
Talk: Population variation in post-harvest rot Rhizopus stolonifer

11:05AM STEVEN ABEL
Flash Talk: Defining the molecular architecture of malaria parasite chromatin complexes by cross-linking based mass spectrometry and structural modeling

11:10AM LICHAO LI
Talk: The Roles of An RNA Polyphosphatase PIR-1 in RNA interference

11:25AM ARAFAT RAHMAN
Flash Talk: Addressing questions on rhizobia's nodulating but non-nitrogen-fixing genetics

11:30AM SHORT BREAK

11:40AM PROSPECTIVE ADVISOR TALK

12:40-02:00PM **LUNCH BREAK**

02:00-03:45PM **SESSION II**

02:00PM TIANTIAN YE
Talk: Statistical modeling of allele-specific chromatin structure

02:15PM LE ZHANG
Flash Talk: Variant Safety Assessment in Parkinson's Disease Stem Cell Therapy

02:20PM EMRE AKSOY
Talk: microRNA regulation in the fatbody tissue of the disease vector *Aedes Aegypti*

02:35PM THEODORE KATARAS
Flash Talk: Automatic Image Segmentation Strategies from Fluorescent Microscopy in Neuroimmunology

02:40PM JAMES RANDOLPH
Talk: Identification of a Novel Endogenous Small RNA Pathway Specifically Targeting the 3' UTRs of mRNAs

02:55PM SARAH BOBARDT
Flash Talk: Endocannabinoids in Soil-based Helminths

03:00PM SHORT BREAK

03:10PM MIKKAL BLICK
Talk: The Influence of Nutrient Condition on Developmental Timing in Drosophila

03:25PM RUI LIU
Flash Talk: Effect of diet on human gut microbiome and vibrio cholerae infection

03:30PM JEFF LI
Talk: Discovering the novel interactions between nonsense mediated RNA decay and DNA damage response

03:45-04:45PM **POSTER SESSION & RECEPTION**
(GENOMICS LOBBY)

04:45-05:00PM **AWARD GIVING CEREMONY & CONCLUDING REMARKS**

Presentations from GGB Students

Talks, Flash-Talks, and Posters

Talks

1. Fungal Ecology of the Endophytic Grapevine Microbiome

Elizabeth Deyett, Rolshausen Lab

Host-microbe-pathogen interactions are highly dynamic and are poorly understood especially in the context of agricultural cropping systems. However, advances in sequencing technologies have revealed how vitally important microbial diversity and communities are for plant health. This work builds upon host-microbiome knowledge by identifying the fungal microbiome fingerprint associated with grapevine in the context of Pierce's Disease (PD). The aim of this project is to study microbial community temporal and spatial dynamics in PD-symptomatic and asymptomatic bicompartments of grapevines. The overarching goal is to identify biocontrol agents and anti-Xylella bioactive natural molecules of microbial origin for preventative and curative control strategies for PD, respectively. The discovery of novel natural microbes to combat pathogens using "Omics" technologies could be an alternative approach to limit the risks of pesticide resistance, increase crop productivity, and support of sustainable agriculture.

2. Population variation in post-harvest rot Rhizopus stolonifera

Sawyer Masonjones, Stajich Lab

Globally postharvest diseases contributes to one third of food losses. Rhizopus stolonifer, a Mucoromycota fungus, causes postharvest soft rot in fruits and vegetables. Control is typically focused on quick harvesting, packing at cool temperatures combined with treatment of fungicides. However, many fungicides are not approved for direct use on fruits and understanding mechanisms of resistance development is limited. We are phenotyping and sequencing ~100 geographically and substrate diverse R. stolonifer strains. Strains have been cultured from California and Florida strawberries, from almond hulls from California orchards, from other California fruit farms. A subset are collected from around the world and obtained from culture stocks from the USDA-NRRL collection. Fungicide resistance varies among isolates with reduced sensitivity to Fludioxonil in some strains. Linear growth rates in race tubes at 12C, 23C, and 30C show significant differences among strains that originate from varied climates or isolation substrates. Whole genome sequencing is being performed on 250 strains from this collection and analysis of patterns of genetic variation was performed to test for evidence of population structure, demography, and association of genotype to phenotype, particularly fungicide resistance. Preliminary data from a geographically diverse subset of 70 samples identified more than ~20,000 SNPs across the 38 Mb genome. Variants were analyzed to scan for highly diverse gene loci, evidence of directional selection, or insertion/deletions of transposable elements. The strains group into 3 main clades, but no phylogeographic pattern has emerged yet. Initial GWAS show 3 loci potentially linked to fungicide resistance. Further sequencing will test robustness of these

potential sub-populations, examine genotype and phenotype correlations, and identify genetic loci with signatures of rapid evolutionary change.

3. The Roles of An RNA Polyphosphatase PIR-1 in RNA interference

Lichao Li, Gu Lab

RNA interference(RNAi) is a highly conserved process in eukaryotes that responsible for transposon silencing, gene regulation and antiviral response. During RNAi process, double- stranded RNAs (dsRNAs) are cleaved by Dicer into 20-26 nucleotides long primary short interfering RNAs (siRNAs). Then these primary siRNAs guide specific RNA binding proteins, Argonautes, to target mRNAs and recruit RNA-dependent RNA polymerases (RdRPs) to produce secondary siRNAs, for direct silencing of target mRNAs. Previous Dicer Immuno- precipitation discovered an RNA polyphosphatase PIR-1 interacting with Dicer, who may participate in RNAi but the mechanism is unrevealed. The project is to demonstrate the functions and mechanism of PIR-1 in RNAi pathways.

We firstly elucidated that the in vitro activity of C. elegans PIR-1 is to remove β and γ phosphates from the 5' end of triphosphorylated RNA molecule. Secondly we investigate the role of PIR-1 in antiviral RNAi. Orsay virus propagation enrichment in infected pir-1 null mutant suggests that PIR-1 is significant for antiviral RNAi response to Orsay virus. dsRNA extraction and strand-specific qPCR results show that viral dsRNAs are depleted in pir-1 null mutant but not in other RNAi deficient mutants such as rde-1, rde-3 or dcr-1, which indicated that PIR-1 is involved in dsRNAs processing. We are constructing pir-1;dcr-1double mutant and preparing pir-1 catalytic site mutant using CRISPR/Cas9 to understand the specific roles of PIR-1 in dsRNA stability and cleavage.

Thirdly, previous study revealed that PIR-1 is required for synthesis of endogenous siRNAs which targets self RNAs. We designed cloning method for endogenous siRNA precursors to investigate the roles of PIR-1 in endogenous RNAi pathways.

4. Statistical modeling of allele-specific chromatin structure

Tiantian Ye, Ma Lab

The Chromosome Conformation Capture technology coupling with high-throughput sequencing (Hi-C) technique has been widely applied to detect genome-wide chromosomal contacts and to study the principles of genome architecture. One challenging problem in Hi-C data analysis lays in the modeling of diploid genomes. Recently, heterozygous phased SNPs have been used to distinguish paired-end read between maternal and paternal chromosomes. However, for reads without SNPs information, we could not assign them to either chromosomes. Here, we developed a Zero-inflated Poisson Model with EM algorithm to assign the uncertain reads and reconstruct the allele-specific chromatin structures.

5. microRNA regulation in the fatbody tissue of the disease vector *Aedes aegypti*

Emre Aksoy, Raikhel Lab

6. Identification of a Novel Endogenous Small RNA Pathway Specifically Targeting the 3' UTRs of mRNAs

James Randolph, Gu Lab

We are reporting a novel WAGO small RNA pathway which specifically targets the 3' UTR of hundreds of functionally important genes. In C. elegans, endogenous small RNAs, 22G-RNAs, bind Argonautes to regulate almost all germline genes. There are two major 22G-RNA-mediated pathways in C. elegans germline cells: One is mediated by Argonaute CSR-1 and plays important roles in chromosome segregation and embryonic development; the other is mediated by multiple Argonautes, WAGOs, and play critical roles in silencing transposons, pseudogenes, viruses, and some functional genes. In all these small RNA pathways, 22G-RNAs are generated by RNA-dependent RNA polymerases (RdRPs) using mRNAs and other RNAs as templates. Usually these 22G-RNAs are generated from both coding regions and UTRs of RNAs. Here we are reporting a novel small RNA pathway which specifically targets the 3' UTRs of hundreds of genes, many of which have been well studied and play important roles in germline and embryonic development. Our preliminary results indicated that these genes are targeted both by CSR-1 and WAGO Argonautes. However, CSR-1 majorly targets the 5' UTR and coding regions, while the WAGO Argonautes only target the 3' UTRs. Interestingly, the WAGO-22Gs are not dependent on rde-3, which is usually required for generating 22Gs in other WAGO-dependent pathways including exogenous RNAi pathways. Our RNA-seq results suggest that these 22G-RNAs may be involved in silencing the target RNAs. We are currently using genetics, high-throughput sequencing and ribosome profiling to investigate why these small RNAs are only generated from the 3' UTR regions and if these small RNAs are involved in translation regulation. We are also analyzing if these 22G-RNAs affects miRNA-mediated gene regulation at the 3'UTR of RNAs, In all, we are reporting a novel WAGO-mediated 22G pathway which specifically targeting the 3'UTR of hundreds of functional genes and this pathway is different from the canonical WAGO pathway since RDE-3 is not required for the 22G biogenesis.

7. The Influence of Nutrient Condition on Developmental Timing in Drosophila

Mikkal Blick, Yamanaka Lab

The fruit fly Drosophila melanogaster goes through multiple life stages, with the release of the steroid hormone ecdysone being responsible for developmental transitions. The release of ecdysone causes a signaling cascade that triggers larval molts and pupariation. The release is controlled by multiple factors, including signaling from prothoracicotropic hormone (PTTH) secreting neurons. PTTH is known to play a role in the timing of ecdysone release prior to pupariation; ablation of the PTTH secreting neurons results in a developmental delay to pupariation. Determining what factors play a role in the release of PTTH would reveal some of the factors responsible for developmental timing in Drosophila. Previously our lab has shown that the neuropeptide hugin is also involved in developmental timing to pupariation. Both hugin mutant flies and hugin receptor mutant flies exhibit a developmental delay similar to the delay seen with PTTH neuron ablation. The hugin secreting neurons also show probable synaptic connections with the PTTH neurons and the hugin receptor mutant phenotype can be rescued by expressing the hugin receptor in the PTTH neurons. The hugin neurons are located in the subesophageal zone in the larval brain, which is known the be innervated by taste neurons. When

larvae are reared on a diet with limited amount of nutrients, the developmental delay seen in hugin mutant larvae is eliminated. Our results indicate that the hugin neurons respond to tastants and accelerate the cessation of the larval feeding period only when larvae are in a nutrient-rich environment, thereby minimizing the overgrowth caused by the consumption of excess amount of nutrients.

8. Discovering the novel interactions between nonsense mediated RNA decay and DNA damage response

Jeff Li, Zheng Lab

Nonsense mediated RNA decay (NMD) plays an essential role in post transcriptional regulation. It is a surveillance mechanism that degrades potentially harmful NMD sensitive transcripts to maintain normal cellular function. In addition to serve as a passive surveillance mechanism in preventing aberrant expression of nonsense transcripts, increasing evidence suggests that NMD can actively integrate into various cellular processes such as alternative splicing, unfolded protein responses, amino acid deprivation, and other cellular stresses. Our most recent data indicates that NMD also interacts with DNA damage response (DDR) by upregulating γ-H2AX expression, a universal DNA damage marker. DDR describes all coping mechanisms that help cells maintain genome integrity from radiation, chemical exposure, cellular metabolism, replication errors, and other DNA damaging agents. When DDR fails, the damaged cells could undergo programmed cell death or proliferation. Understanding the relationship between NMD and DDR can be beneficial indeveloping novel DDR related gene therapies in the future.

Flash Talks

1. 5th time is the charm. Hopefully.
   Alejandro Navarro, Nugent Lab
2. Defining the molecular architecture of malaria parasite chromatin complexes by cross-linking based mass spectrometry and structural modeling
   Steven Abel, Le Roch Lab
3. Addressing questions on rhizobia's nodulating but non-nitrogen-fixing genetics
   Arafat Rahman, Sachs Lab
4. Variant Safety Assessment in Parkinson's Disease Stem Cell Therapy
   Le Zhang, Girke Lab
5. Automatic Image Segmentation Strategies from Fluorescent Microscopy in Neuroimmunology
   Theodore Kataras, Kaul Lab
6. Endocannabinoids in Soil-based Helminths
   Sarah Bobardt, Nair Lab
7. Effect of diet on human gut microbiome and Vibrio cholerae infection
   Rui Liu, Hsiao Lab

Posters

1. Investigating the function of mitochondrial glycolysis in Phytophthora and the identification of an associated transporter

Amy Boyd, Judelson Lab

The energy for cellular work is obtained from the bond energy of the nutrients an organism ingests. The bond energy of a variety of hexoses (6 carbon sugars) is released through a process called glycolysis. Glycolysis has 2 phases. The "investment" phase requires energy input from the cell and breaks down glucose into 3 carbon molecules. The "pay-off" phase rearranges the carbon skeletons and releases energy. The rearrangement of carbon skeletons provides precursors such as 3-phosphoglycerate for amino acids such as serine. Various forms of glycolysis exist as a result of the environmental realities of different organisms. In eukaryotic organisms, compartmentalization within plastids or mitochondria allows for multiple versions of glycolysis to exist. A distinct glycolytic pathway in stramenopiles containing only "pay-off" phase enzymes localizes to the mitochondria. I will investigate the function of the mitochondrial "pay-off" phase (MPP) in Phytophthora infestans and Phytophthora capsici, heterotrophic oomycetes, to clarify the selective advantage, if any, of MPP within the "SAR" supergroup. This investigation will also enhance understanding of central metabolic pathways within stramenopiles, many of whom are candidates for bioengineering for lipid biosynthesis. These investigations may also identify novel targets for more effective control of diseases caused by stramenopiles because MPP is a stramenopile specific pathway.

2. The Role of Influenza B Virus Nucleoprotein in Viral RNA Nuclear Import

Jerald Chavez, Rong Lab

Influenza A and B viruses cause seasonal epidemics, resulting in 250,000 to 600,000 annual deaths. Influenza B Virus (IBV) contributes significantly to total influenza annual morbidity as it is the dominant/co-dominant virus type during seasonal epidemics every 2-4 years in the United States. However, due to the lack of pandemic potential for B viruses, it is less studied than Influenza A Virus (IAV), which has hindered the understanding of the pathogenicity for influenza B viruses. The IBV nucleoprotein (NP) forms a viral ribonucleoprotein (vRNP) complex with the heterotrimeric viral polymerase and a viral genomic RNA segment (vRNA) which upon infection, requires nuclear import for viral RNA synthesis to begin. While IBV NP (BNP) is translocated to the nucleus, it's not clear whether BNP is involved in nuclear import of B vRNAs and what host proteins are involved. We recently identified Importin a4 (Impa4), a nuclear import subunit protein, as an interaction partner to BNP via a yeast two hybrid (Y2H) screen, and subsequently confirmed their interactions by Co-IP, suggesting BNP 's involvement in vRNP nuclear import. We hypothesize that the interaction between the Impa4 and BNP facilitates B vRNA nuclear entry. Here, we propose to define the domains involved in and required for both interaction between Impa4 and BNP, and determine its involvement in vRNA nuclear trafficking via in-vitro nuclear import assays.

3. Gene Expression Signature Search and Functional Enrichment Methods for Discovering Novel Modes of Action of Bioactive Compounds

Yuzhu Duan, Girke Lab

This project is about optimizing signature search and enrichment methods for the discovery of novel modes of action (MOA) of bioactive compounds from reference databases, such as LINCS, containing the genome-wide gene expression signatures (GESs) from tens of thousands of drug and genetic perturbations. The methods used by this prediction workflow can be divided into two major classes. First, gene expression signature search (GESS) methods are used to identify drugs that induce GESs similar to those of query GESs of interest. The queries can be drug- or disease-related GESs. Since the MOA of most drugs in the corresponding reference databases are known, the resulting associations are useful to gain insights into pharmacological and disease mechanisms and to develop novel drug repurposing approaches. Second, functional enrichment analysis (FEA) methods using Gene Ontology (GO) or pathway annotations have been developed to functionally interpret the vast number of GESS results generated by this project. The latter are composed of lists of drugs ranked by the similarity metric of the corresponding GESS method making the functional interpretation of their top ranking drugs challenging. Importantly, the FEA methods developed by this study also support the reconstruction of drug-target networks to guide the interpretation of the results

Characterization of Genome Content Variation in *Oryza sativa*

Christopher Fiscus, Koenig Lab

The resequencing of large numbers of natural accessions has enabled the comprehensive study of intraspecific genome variation. Existing methods to compare genomes using high-throughput sequencing reads are poorly suited for assessing variation in repetitive sequences. We propose a reference-free method to assess genome content variation based on counting K-mers in sequencing reads. Compared with existing methodologies, our method facilitates the analysis of highly repetitive sequences and is not dependent on sequence alignment or assembly. We use our method to analyze genome content in 50 accessions of *Oryza sativa* sampled from the 3K-RG dataset. We find that variation in repetitive sequences explain most of the genome content variation between accessions and discriminates between distinct subspecies.

4. Detecting Quantitative Trait Loci in Mice Bred for High Levels of Voluntary Wheel Running

David Hillis, Garland Lab

Understanding the biological basis of exercise behavior has become increasingly relevant for maintaining healthy lifestyles in humans and other mammals. Various quantitative genetic studies and artificial selection experiments have conclusively demonstrated substantial narrow-sense heritability for exercise behavior in both humans and laboratory rodents. One selection experiment with laboratory mice incorporates 4 replicate lines bred for high voluntary wheel running and 4 non-selected control lines. After 61 generations, the genomes of 80 mice (10 from each line) were fully sequenced and single nucleotide polymorphisms (SNPs) were identified. Using the Minimum Quadratic Variance Unbiased Estimation (MIVQUE) method (Xu and Garland 2017), we determined which SNPs are differentiated

between the 4 High Runner (HR) and 4 control lines. Results are compared with data from the MegaMUGA SNP chip published previously, and demonstrate similar regions of high differentiation, present on most chromosomes. Additionally, as expected, the higher resolution of the sequence data has produced additional promising SNPs outside these regions.

5. Nuclear receptor HNF4a plays a role in alternative splicing

Jose Martinez, Sladek Lab

Alternative splicing (AS) is increasingly being found to play an important role in gene expression. It can impact not only transcript diversity but also transcript levels, and it allows for a relatively low number of genes to encode for a much larger array of proteins which in turn lead to diversity of function, response to environmental and developmental cues and ultimately different phenotypes. The advent of Next Generation Sequencing (NGS) over a decade ago allowed for the generation of transcript data that makes determination of genome-scale alternative splicing possible. However, it has only been in the last couple of years that computational tools for identifying splicing events have become readily available. Here, we use an in vivo exon swap mouse model which expresses alternatively spliced transcripts from alternative promoters in the Hnf4a gene to compare two commonly used splicing analysis tools – rMATS and DEXSeq. We recently found that the alternative transcripts of HNF4a, a master regulator of liver-specific gene expression, not only cause a considerable alteration in gene expression but also interact in a differential fashion with an array of RNA processing proteins. Consistently, we identify hundreds of alternatively spliced transcripts between these two sets of mice. We also identify effects of fasting and circadian rhythms on splicing.

6. Regional and structural factors affecting WUSCHEL interaction

Albert Do, Gonehal Lab

Growth above ground in higher plants is coordinated through the shoot apical meristem. The meristem consists of a collection of undifferentiated stem cells surrounded by tissue which gradually begins to form the various structures of the plant at the outer fringes. The meristem is controlled by a complex web of pathways and regulatory molecules. Of especial importance is the network formed around the interaction of WUSCHEL and CLAVATA3, a transcription factor and peptide which take an antagonistic role towards each other; WUS pushing toward maintenance of stem cell identity while CLV3 pushes toward differentiation. Several avenues are being pursued to elucidate the finer details of this interaction. WUS target binding was investigated through gel shift assays comparing binding with CLV3 to the gene TAR2 and mutants. The migration patterns suggested the possible importance of TAAT core motifs found in the binding region. The structure surrounding the CLV3 binding region was probed via treatment with HDAC inhibitor trichostatin A, capable of potentially loosening the chromatin. Possible increased activity in a CLV3 marker indicated that the chromatin landscape around the WUS binding region played an important role in WUS/CLV3 regulation. WUS dynamics were further investigated through computational simulation of the network. WT dynamics have been replicated indicating that the simulation model may prove to be a valuable tool in visualizing and analyzing WUS properties which may be difficult to see in traditional experiments.

Prospective Advisor's Talk

1. **VENUGOPALA GONEHAL**
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   We utilize micro-genomics and live-imaging methods to decipher molecular and cellular networks underlying stem-cell homeostasis

2. **SIKA ZHENG**
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   Genetic regulation and molecular mechanisms of neural development and neurogenetic disorders

3. **HOWARD JUDELSON**
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   Molecular genetics of differentiation and pathogenesis in fungi

4. **ISGOUHI KALOSHIAN**
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   Molecular genetics of root-knot nematode and aphid resistance in tomato

5. **SYDNEY GLASSMAN**
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   My research focuses on understanding patterns and processes governing microbial diversity, and their ecosystem functions such as terrestrial symbioses and decomposition

6. **SIHEM CHELOUFI**
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   Stem cells, cancer and regenerative medicine, chromatin structure and regulatory RNAs

7. **JERNEJ MURN**
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   RNA and chromatin biochemistry, neurobiology, neural engineering, stem cells and cancer biology

8. **MARCUS KAUL**
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   Studying the role of lipocalin-2 and cysteinyl leukotrienes in HIV-associated neuronal injury and researching neuroprotection by IFN-beta in AIDS to characterize the neuroprotective effect of IFNβ against toxicity of HIV/gp120 using in vivo and in vitro models

Acknowledgements

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Food, Booking & Supervision: Julio Sosa