1st International Symposium on Mathematical and Computational Oncology (ISMCO'19)

October 14-16, 2019, Lake Tahoe, Nevada, USA

Contents

Registration Desk Hours:

Sunday 4pm – 6pm
Monday – Wednesday 8:00am – 5:00pm

Monday, October 14th

9:00–10:00	*Keynote:* ***Ron Bose***, **Washington University School of Medicine, USA** (Emerald Bay 1-2-3)	
10:10-11:10	**Spatio-temporal tumor modeling and simulation** Chair: Russell Rockne (Emerald Bay 1-2-3)	
	10:10	Towards Model-based Characterization of Biomechanical Growth Phenotypes *Daniel Abler, Philippe Büchler and Russell Rockne*
	10:30	Population modeling of tumor growth curves, the reduced Gompertz model and prediction of the age of a tumor *Cristina Vaghi, Anne Rodallec, Raphaelle Fanciullino, Joseph Ciccolini, Jonathan Mochel, Michalis Mastri, John Ebos, Clair Poignard and Sebastien Benzekry*
	10:50	3D Spatio Temporal Modeling of Tumor Growth and Metabolism through Genome Scale Network Reconstructions using COMETS *Darshi Shah, Dr. Ilija Dukovski and Dr. Daniel Segre*
11:10-11:30	*Coffee Break*	
11:30-12:10	**Precision medicine and immuno-oncology** Chair: TBD (Emerald Bay 1-2-3)	
	11:30	Exploring the Dynamics of Leukemogenesis using Time-series Sequencing Data to Identify Leukemia Associated miRs *David Frankhouser, Russell Rockne, Sergio Branciamore, Denis O'Meally, Ya-Huei Kuo and Guido Marcucci*
	11:50	Large-scale modeling of class I peptide-HLA complexes using APE-Gen *Dinler Antunes, Jayvee Abella, Sarah Hall-Swan, Mark Moll, Gregory Lizée and Lydia Kavraki*
12:10-1:30	*Lunch* (on your own)	
1:30-2:30	*Keynote:* ***Yuval Kluger***, **Yale School of Medicine, USA** (Emerald Bay 1-2-3)	
2:40-3:40	**General cancer computational biology** Chair: Takis Benos (Emerald Bay 1-2-3)	
	2:40	Mathematical modeling of cancer recurrence caused by premalignant lesions formed before the first treatment *Mitsuaki Takaki and Hiroshi Haeno*
	3:00	Evaluation of flow cytometry automated gating pipeline on a large-scale lymphoma dataset *Margaret Hannum, Sophia Roshal, Sary El Daker, Olivier Elemento, Ahmet Dogan, Mikhail Roshal and Venkatraman Seshan*
	3:20	Breast cancer cell line transcriptional profiling at single cell resolution *Fangyuan Chen, Kai Ding, Nolan Priedigkeit, Ashuvinee Elangovan, Steffi Oesterreich and Adrian Lee*
3:40-4:00	*Coffee Break*	
4:00-5:30	**Discussion Panel** Moderator: George Vasmatzis (Emerald Bay 1-2-3)	
	Validation models (3D, PDX, etc) Are genomics really needed and if yes how comprehensive? George Vasmatzis (moderator), Panos Anastasiadis, Ron Bose, Russel Rockne, Parvesh Kumar	

Tuesday, October 15th

9:00–10:00	*Keynote:* ***Susan Perkins, National Cancer Institute, USA*** (Emerald Bay 1-2-3)	
10:10-11:10	**Special Trak: Tumor evolvability and intra-tumor heterogeneity** Chair: Ernesto Lima (Emerald Bay 1-2-3)	
	10:10	Tumor Growth Model Calibration and Selection Using Triple Negative Breast Cancer Cell Lines *Anna Claudia M Resende, Ernesto Augusto Bueno Da Fonseca Lima, Regina C Almeida, Matthew T Mckenna and Thomas E Yankeelov*
	10:30	Phylogenies Derived from Matched Transcriptome Reveal the Evolution of Cell Populations and Temporal Order of Perturbed Pathways in Breast Cancer Brain Metastases *Yifeng Tao, Haoyun Lei, Adrian Lee, Jian Ma and Russell Schwartz*
	10:50	Modeling the evolution of ploidy in a resource restricted environment *Gregory Kimmel, Jill Barnholtz-Sloan, Hanlee Ji, Philipp Altrock and Noemi Andor*
11:10-11:30	*Coffee Break*	
11:30-12:10	**Imaging and Scientific visualization for cancer research** Chair: George Bebis (Emerald Bay 1-2-3)	
	11:30	OncoCast: an improved interface for survival analysis using genomic data *Axel Martin, Ronglai Shen, Gregory Riely and Andy Ni*
	11:50	cmIF: A Python Library for Scalable Multiplex Imaging Pipelines *Jennifer Eng, Elmar Bucher, Elliot Gray, Lydia Grace Campbell, Guillaume Thibault, Summer Gibbs, Koei Chin, Young Hwan Chang and Joe Gray*
12:10-1:30	*Lunch* (on your own)	
1:30-2:30	*Keynote:* ***Trachette Jackson, University of Michigan, USA*** (Emerald Bay 1-2-3)	
2:40-3:40	**Statistical methods and data mining for cancer research** Chair: TBD (Emerald Bay 1-2-3)	
	2:40	An Outcome Weighted Learning Approach for Identifying Clinically Relevant Patient Subgroups from Large-scale Sequencing Data *Arshi Arora, Adam B. Olshen, Venkatraman E. Seshan, and Ronglai Shen*
	3:00	Accurate and Flexible Bayesian Mutation Call from Multi-Regional Tumor Samples *Takuya Moriyama, Seiya Imoto, Satoru Miyano and Rui Yamaguchi*
	3:20	Flexible data trimming for different machine learning methods in omics-based personalized oncology *Victor Tkachev, Anton Buzdin and Nikolay Borisov*
3:40-4:00	*Coffee Break*	
4:00-4:40	**Anticancer Drug Development** Chair: TBD (Emerald Bay 1-2-3)	
	4:00	Chemotherapy Radiosensitiziation for High Risk Prostate Cancer: From Concept to Clinical Trial to Changing the Standard of Care *Parvesh Kumar (Invited)*
	4:20	Computational modeling identifies optimal use of EGFR tyrosine kinase inhibitors for lung cancer patients with EGFR mutations *Hiroshi Haeno and Susumu Kobayashi*
8:00-9:00	*Banquet Keynote:* ***Panos Anastasiadis & George Vasmatzis, Mayo Clinic, USA*** (Tallac)	

Wednesday, October 16th

9:00–10:00	*Keynote:* ***Nikolaos Zacharakis, National Cancer Institute, USA*** (Emerald Bay 1-2-3)	
10:10-11:10	**Systems biology and networks** Chair: Alfred Schissler (Emerald Bay 1-2-3)	
	10:10	Mathematical modeling of hematopoietic system and data analysis of single-HSC transplantation. *Shoya Iwanami, Ryo Yamamoto, Shingo Iwami and Hiroshi Haeno*
	10:30	A single-subject method to detect pathways enriched with alternatively spliced genes *Alfred Schissler, Dillon Aberasturi, Colleen Kenost and Yves Lussier*
	10:50	Organoid models of mammographic density for investigating biological processes *Bahram Parvin (Invited)*
11:10-11:30	*Coffee Break*	
11:30-12:10	**Systems biology and networks (cont'd)** Chair: Alfred Schissler (Emerald Bay 1-2-3)	
	11:30	Computational analysis of mass spec proteomics data *Yanji Xu(Invited)*
	11:50	
12:10-1:30	*Lunch* (on your own)	
1:30-2:30	*Keynote:* ***Ben Raphael, Princeton University, USA*** (Emerald Bay 1-2-3)	

	Tutorial
2:40-4:40	**Current methods and open challenges for structural modeling in cancer immunotherapy** Instructors: Antunes Dinler, Abella Jayvee, Lydia Kavraki, Rigo Mauricio (Emerald Bay 1-2-3)
4:40-5:00	*Coffee Break*
5:00-7:00	**Current methods and open challenges for structural modeling in cancer immunotherapy (cont'd)** Instructors: Antunes Dinler, Abella Jayvee, Lydia Kavraki, Rigo Mauricio (Emerald Bay 1-2-3)

KEYNOTE TALK

Monday, October 14, 2019 at 9am
(Emerald Bay 1-2-3)

Breast Cancer Genomics: Tackling Complexity with Functional Genomics and Patient-Derived Organoids

Ron Bose
Washington University School of Medicine
USA

Abstract: Breast cancer is a heterogeneous disease with multiple molecular subtypes and three major clinical subtypes: hormone receptor positive, HER2 positive, and triple negative breast cancer. These three clinical subtypes are very important because they determine the drugs used for patient treatment. Cellular, molecular, and genomic understanding of breast cancer has resulted in new treatments for breast cancer. In 2019, the FDA approved an oral PIK3CA inhibitor for PIK3CA mutated, hormone receptor positive, Stage IV breast cancer and immunotherapy for triple negative, Stage IV breast cancer. Major challenges facing future research on breast cancer and other cancers are: 1) Interpreting genome sequencing results to better understand the effects and significance of new or under-characterized mutations, and 2) having platforms for rapid biological testing of hypotheses. I will provide examples of how my laboratory is trying to address both of these challenges.

Speaker Bio-Sketch: Dr. Ron Bose is a breast cancer specialist and a breast cancer researcher at the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. He is board certified in Medical Oncology and Internal Medicine. He received his MD and PhD degrees from Cornell University. He performed medical training at the top hospitals in the country, including Oncology training at The Johns Hopkins Hospital in Maryland and Memorial Sloan-Kettering Cancer Center in New York City and Internal Medicine residency at Barnes-Jewish Hospital. He joined the faculty of Siteman Cancer Center in 2007 and has received many awards including being named the Susan G. Komen for the Cure - St. Louis, Health Professional of the Year in 2013 and being elected to the prestigious academic medicine society, the American Society for Clinical Investigation (ASCI), in 2017. His research focuses on the HER2 gene in breast cancer and his lab uses genome sequencing, high throughput protein measurements, and 2D and 3D tissue culture methods to study HER2. He is funded by the National Institutes of Health and the Department of Defense Breast Cancer Research Program.

KEYNOTE TALK

Monday, October 14, 2019 at 1:30pm
(Emerald Bay 1-2-3)

High dimensional unsupervised approaches for dealing with heterogeneity of cell populations and proliferation of algorithmic tools

Yuval Kluger
Yale University School of Medicine
USA

Abstract: Revealing the clonal composition of a single tumor is essential for identifying cell subpopulations with metastatic potential in primary tumors or with resistance to therapies in metastatic tumors. Bulk sequencing technologies provide only an overview of the aggregate of numerous cells. We propose an evolutionary framework for deconvolving data from a bulk genome-wide experiment to infer the composition, abundance and evolutionary paths of the underlying cell subpopulations of a tumor. With advances in high throughput single cell techniques, we can in principle resolve these issues. However, these techniques introduce new challenges such as analyzing datasets of millions of cells, batch effects, missing values etc. We provide several algorithmic solutions for some of these challenges. Finally, a key challenge in bioinformatics is how to rank and combine the possibly conflicting predictions of several algorithms, of unknown reliability. We provide new mathematical insights of striking conceptual simplicity that explain mutual relationships between independent classifiers/algorithms. These insights enable the design of efficient, robust and reliable methods to rank the classifiers performances and construct improved predictions in the absence of ground truth.

Speaker Bio-Sketch: Yuval Kluger has been working in the broad fields of bioinformatics, machine learning, and dynamics of quantum fields. His main contributions to date relate to development of spectral methods for unsupervised learning, cell specific regulatory networks, algorithms for analyzing genomics and epigenomics sequencing data, algorithms for detecting and characterizing biomarkers in high dimensional assays, and non-equilibrium quantum field theory models.

KEYNOTE TALK

Tuesday, October 15, 2019 at 9am
(Emerald Bay 1-2-3)

Career Development Opportunities: The Government Can Help!

Susan Perkins
National Cancer Institute
USA

Abstract: The National Cancer Institute is committed to the training and support of the next generation of cancer researchers. The NCI funds training at extramural institutions across the nation, using funding mechanisms that include fellowships, career development awards, and institutional training grants. This session will provide a broad overview of this wide range of opportunities, with an emphasis on some new NCI programs for early-stage investigators, as well as some tips and tools for applicants.

Speaker Bio-Sketch: Dr. Perkins is Acting Chief of the Cancer Training Branch of the Center for Cancer Training at the National Cancer Institute. She received her BS in biochemistry from North Carolina State University and her doctorate in physiology from the University of Virginia, with further postdoctoral training in neuroendocrine physiology during fellowships at Stanford University and the Johns Hopkins University. She was recruited to NCI in 1990, first as a Senior Staff Fellow and then as an Investigator in what is now the NCI Center for Cancer Research (CCR). Her research interests focused on the development of animal models to study cancer preventive strategies and interactions among nutritional factors, hormones, and genetic susceptibility to cancer. Subsequently, she was concurrently Associate Director of the NCI Cancer Prevention Fellowship Program and a member of the NCI CCR Laboratory of Biosystems and Cancer (2000-2006) and then a Research Assistant Professor in the Department of Nutritional Sciences at the University of Texas at Austin. Dr. Perkins returned to NCI as a Program Director in the Cancer Training Branch in 2010. Her grants portfolio has included all types of NCI-supported training awards: fellowships, individual career development (K) awards, and T32 and R25 institutional training grants.

KEYNOTE TALK

Tuesday, October 15, 2019 at 1:30pm
(Emerald Bay 1-2-3)

Converting Cancer Revelations into Effective Treatments with the Aid of Multiscale Modeling

Trachette L Jackson
University of Michigan
USA

Abstract: Increased understanding of the molecular drivers of tumor initiation and progression has led to targeted manipulation of intracellular signaling pathways for patient-specific therapeutic benefit. In this talk, we outline a multiscale modeling strategy for linking intracellular signaling pathways critical to cell proliferation and apoptosis; receptor-ligand binding on the cell surface that triggers these intracellular signaling cascades; and population-level tumor growth dynamics and response to treatments targeting these pathways. Integration of these tiers of information is precisely the level of detail required to uncover possible hidden mechanisms that mediate both expected and potentially counterintuitive therapeutic effects of novel, targeted therapeutics on the multiple cell types responsible for tumor progression. We demonstrate the predictive therapeutic power of our multiscale computational approach with two specific examples. The first considers treatments targeting VEGF and its receptors. In this case, it is difficult to tease out the differential anti-angiogenic and anti-tumor effects of drug combinations experimentally due to the dynamic crosstalk between tumor cells and vascular endothelial cells, which impacts critical aspects of tumorigenesis, independent of angiogenesis. Our model predicts that certain therapeutic combinations result in antagonism in vivo, but not in vitro. In the second example, our computational approach is used to study the therapeutic impact of Tocilizumab, a competitive IL-6R inhibitor, on tumor growth and cancer stem cell fraction, alone and in combination with the traditional chemotherapeutic agent, Cisplatin. Targeting critical regulators of the cancer stem cell phenotype to overcome their acute influence on tumor growth is a promising new strategy for cancer treatment. Our results suggest that nonintuitive dose scheduling strategies will optimize the synergy of combination therapy. Both examples show that this predictive modeling framework can serve to evaluate strategies for signaling pathway modulation rapidly and can provide a basis for proposing optimized
dose scheduling for combination treatments involving targeted therapeutics.

Speaker Bio-Sketch: Trachette L. Jackson earned her Ph.D. in Applied Mathematics from the University of Washington. She conducted postdoctoral research at the Institute for Mathematics and its Applications (IMA) and Duke University and is currently a Professor of Mathematics at the University of Michigan. Dr. Jackson specializes in Computational Cancer Research or Mathematical Oncology. Motivated by addressing critical challenges associated with cancer therapeutics, developing multiscale mathematical models is the aim of much of Dr. Jackson's research. These models are designed to optimize the use of anticancer agents that specifically target active molecular pathways that cancer cells use to promote their growth and survival. Dr. Jackson is an award-winning educator and scholar who has received honors for her accomplishments in both areas. In 2003, she became the second African American woman to receive the prestigious Alfred P. Sloan Research Award in Mathematics; in 2005 she received the James S. McDonnell 21st Century Scientist Award; in 2008 Diverse Magazine honored her as one of the year's Emerging Scholars. In 2010 she received the Blackwell-Tapia Prize, which biannually recognizes a mathematician for both their research achievements and for their contributions to addressing diversity in mathematics. Dr. Jackson has built her

career on collaborative research and educational activities that cut across traditional disciplinary boundaries and envisions that this type of team science will eventually change the face of cancer research.

BANQUET KEYNOTE TALK

Tuesday, October 15, 2019 at 8:00pm
(Tallac)

Application of Functional Genomics to Oncology Practice: Opportunities, Successes, Failures and Barriers

Panos Anastasiadis & George Vasmatzis
Mayo Clinic
USA

Abstract: Radical improvement in cancer care can be accomplished by individualizing patient management via the application of genomics and functional model systems into clinical practice. Recent breakthroughs in immunotherapy (i.e. checkpoint inhibitors) and targeted therapies (i.e. NTRK inhibitors) have shown that therapy of advanced cancers might become agnostic to the organ of origin, arguing for a more individualized approach to patient care. Emerging genomics technologies, data integration and visualization platforms are powerful tools to determine the state of the individual's tumor and point to tailored treatments. Furthermore, an efficient combination of comprehensive genomics with 3D microcancer functional model systems can further refine treatment decisions. However, applying such disruptive technologies in clinical practice is not trivial. Regulatory, financial and clinical barriers will be discussed.

Speaker Bio-Sketch: Dr. Anastasiadis is the Chair of the enterprise-wide Department of Cancer Biology, co-director of the Cell Biology Program at the Mayo Clinic Cancer Center, and executive member of the Center for Biomedical Discovery. He is also a professor and consultant in the Department of Cancer Biology. Dr. Anastasiadis is widely recognized for his work in the cell-cell adhesion field, has served in several NIH study sections as member and Chair, and more recently serves on the R35 MIRA study section at NIGMS. His research program focuses on cell-cell adhesion signaling events, regulation of Rho GTPases during cell adhesion, transformed cell growth and/or migration, as well as the establishment of cell polarity in adherent and migrating cells. Published papers in Nature Medicine, Nature Cell Biology, Journal of Cell Biology and Cancer Research demonstrate the laboratory's high impact research. Related to cell adhesion, his lab recently reported the crosstalk between apical cell-cell junctions and the RNAi machinery to regulate the expression and localization of select miRNAs and mRNAs in order to inhibit epithelial cell growth. As a result of his pre-clinical work, Dr. Anastasiadis is involved in multiple translational and clinical studies. Finally, in collaboration with the Center for Individualized Medicine he has also launched the Ex Vivo project in multiple cancer types and across Mayo Clinic sites.

Speaker Bio-Sketch: Dr. Vasmatzis is the co-director of the Biomarker Discovery Program, within the Center for Individualized Medicine. He is also an Associate professor and consultant in the Department of Molecular Medicine and a member of the Mayo Clinic Cancer Center. His research program consists of bioinformatics specialists, molecular biologists, epidemiologists, and pathologists. By training and experience, Dr. Vasmatzis has a unique set of skills in engineering, computational

biology, bioinformatics and genomics. He recognizes the critical importance that each team member plays to the success of a given project or that of a program as a whole. He works tirelessly to maintain a team spirit. This team has demonstrated success in discovery and translation of several biomarkers as well as developing evidence-based models that should help clinicians stratify (cancer) patients in order to provide each individual with the appropriate care. Published papers in Journal of Clinical Oncology, Cancer Research and BLOOD further demonstrate the laboratory's discovery, validation, and translation capabilities. With the recent advances in Next Generation Sequencing (NGS) technologies his laboratory have been engaging in massive sequencing to scan the genome of cancer cells for abnormalities that can be used for clinical purposes such as diagnosis and stratification of patients for optimal treatment. He has developed MPseq, an accurate and inexpensive whole genome sequencing platform that has been used to detect structural variants. MPseq is a combination of a protocol and algorisms that can deliver a detailed description of all DNA rearrangements at a resolution that can show how individual genes are disturbed thus providing necessary novel insight for correct clinical interpretation.

KEYNOTE TALK

Wednesday, October 16, 2019 at 9am
(Emerald Bay 1-2-3)

Recognition of non-synonymous somatic mutations by Tumor Infiltrating Lymphocytes (TIL) in metastatic Breast Cancer

Nikos Zacharakis
National Cancer Institute
USA

Abstract: Adoptive transfer of tumor infiltrating lymphocytes (TIL) can mediate long-term durable regression in patients with metastatic melanoma, a type of cancer which is characterized by a high number of mutated genes and pronounced lymphocytic infiltrate. Common epithelial cancers, including breast cancer, express far fewer somatic mutations than melanoma and the level of reactive TIL is limited. This pilot study investigated the ability to identify personalized non-synonymous somatic mutations in metastatic breast cancer lesions, to grow TIL that recognize the products of these mutations, and to adoptively transfer these TIL into patients with metastatic breast cancer, refractory to other treatments. Metastatic and primary tumor lesions from thirty one patients with breast cancer were studied in the Surgery branch, NCI, NIH and all of them were found to contain and express mutated genes (range: 4-1788 , median: 99). TIL recognized at least one (range: 1-10, median: 3) mutated product in 21 of 32 the patients (66%). Five evaluable patients with metastatic breast cancer, refractory to prior multiple lines of treatment, were treated with enriched mutation-reactive TIL in our ongoing pilot clinical trial. The immunogenicity of mutations in the majority of the patients with metastatic breast cancer can be the platform for an adoptive T cell transfer therapeutic approach targeting those mutated genes.

Speaker Bio-Sketch: Nikolaos Zacharakis received his bachelor degree in Chemistry, from the University of Patras, Greece, followed by a Master of Science degree in Medicinal Chemistry from the same university. He earned his Ph.D. in Microbiology and Immunology from Temple University in Philadelphia, USA. In 2015, he joined Dr. Steven Rosenberg's group in Surgery Branch, NCI, NIH, where he remains until today. Dr. Zacharakis recently received the 2019 Federal Technology Transfer award by the Center of Cancer Research, NCI. The immune system and in particular, the biology of T lymphocytes has been in the center of Dr. Zacharakis research interests. In the earlier stages of his career, he investigated the T cell involvement in autoimmune diseases like Multiple Sclerosis and Scleroderma, whereas, in the recent years, the focus of his research is on the tumor immunology of Breast cancer. Dr. Zacharakis examines the potential of tumor infiltrating T cells to fight metastatic lesions in advanced stages of the disease. Specifically, he is investigating the presence of immunogenic somatic mutations in patients with metastatic breast cancer and whether these mutations can be a sufficient target of T cells, aiming to the tumor killing. To ultimately evaluate the potential of those T cells, they are adoptively transferred into patients with breast cancer, as part of the clinical trials conducted in the NCI. Dr. Zacharakis believes that fully harnessing the powers of the immune system will be the key element in the fight against the disease and that immunotherapy can be in the frontline of therapy in cancer.

KEYNOTE TALK

Wednesday, October 16, 2019 at 1:30pm
(Emerald Bay 1-2-3)

Inferring Tumor Evolution from Bulk and Single-cell Sequencing Data

Ben Raphael
Princeton University
USA

Abstract: Cancer is an evolutionary process driven by somatic mutations that accumulate in a population of cells. These mutations provide markers to infer the ancestral relationships between cells of a tumor, to describe populations of cells that are sensitive/resistant to treatment, or to study migrations between a primary tumor and distant metastases. However, such phylogenetic analyses are complicated by specific features of cancer sequencing data such as heterogeneous mixtures of cells present in bulk tumor sequencing data, undersampling in single-cell sequencing data, and large-scale genome rearrangements. In this talk, I will describe algorithms to address several problems in tumor evolution including: the inference of seeding patterns of metastases; the identification of copy number aberrations and whole-genome duplications in multi-sample sequencing data; and the integrated analysis of single-nucleotide mutations and copy number aberrations in single-cell sequencing data.

Speaker Bio-Sketch: Ben Raphael is a Professor of Computer Science at Princeton University. His research focuses on the design and application of novel algorithms for the interpretation of biological data. Recent areas of emphasis include cancer evolution, network/pathway analysis of genetic variants, and structural variation in human and cancer genomes. His group's algorithms have been used in multiple projects from The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). He is the recipient of the Alfred P. Sloan Research Fellowship, the NSF CAREER award, and a Career Award at the Scientific Interface from the Burroughs Wellcome Fund.

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Organizers:

- Antunes Dinler, Rice University, USA
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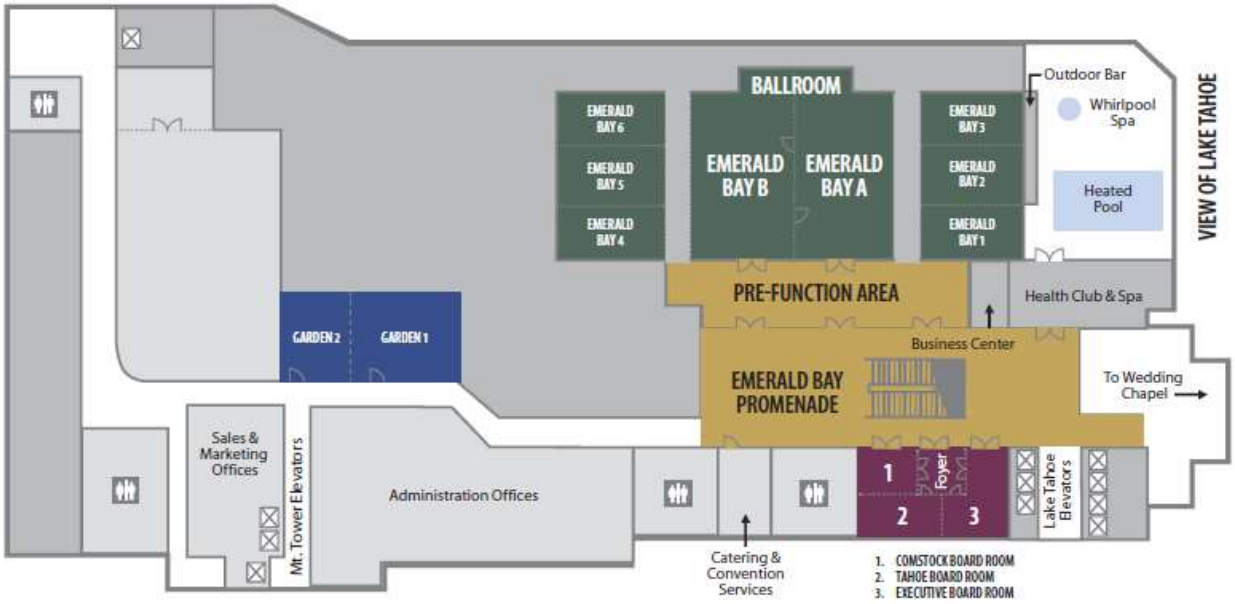
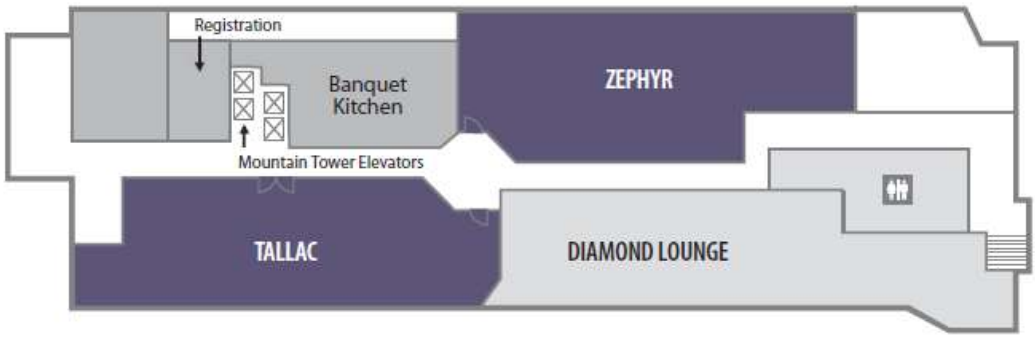


TWELFTH FLOOR

PANORAMIC VIEW OF LAKE TAHOE



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