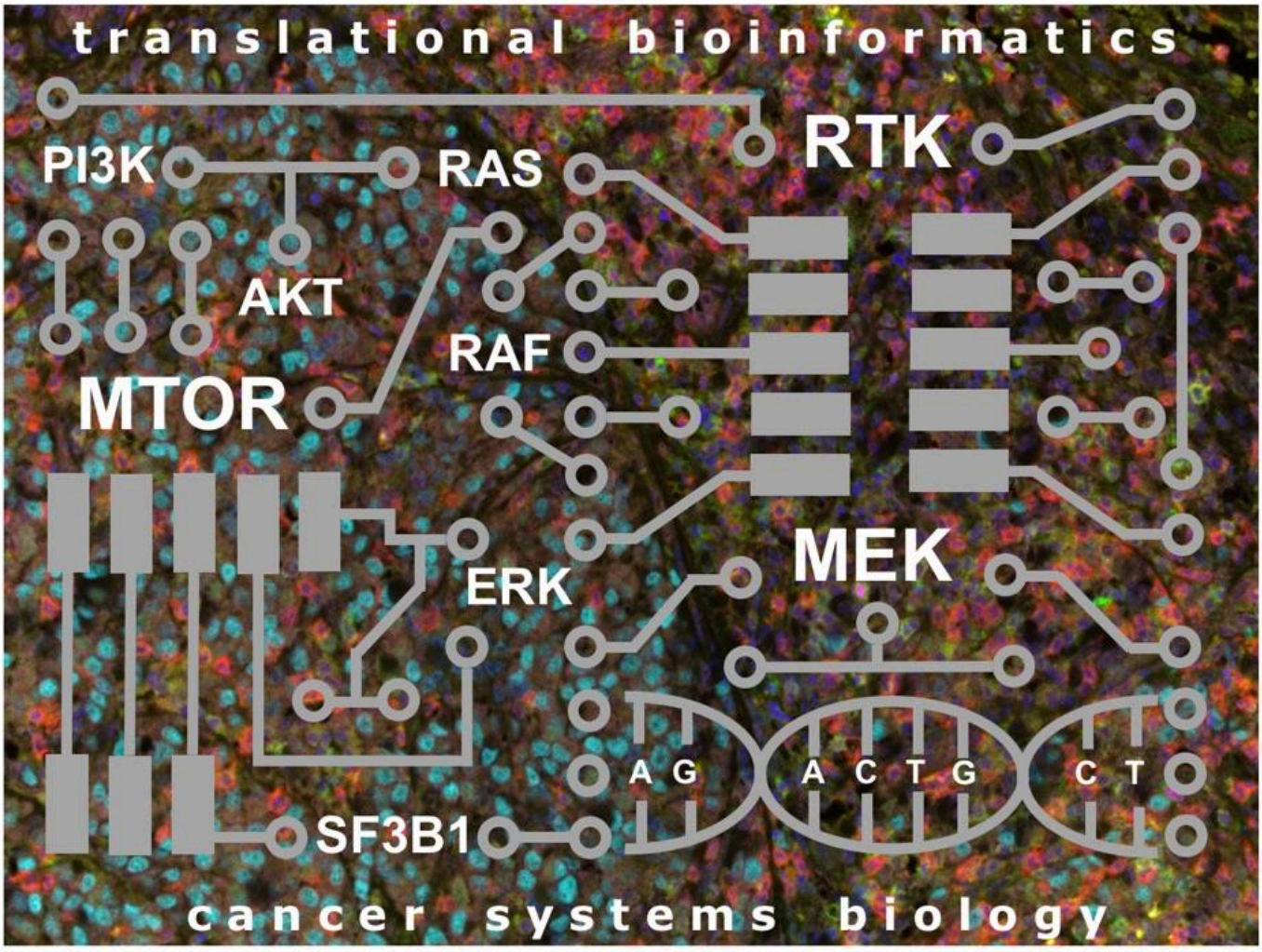
T A N | L A B



http://tanlab.ucdenver.edu

2017

A YEAR IN REVIEW


stroom
SPIDER-MAN

Dear Colleagues and Friends,

As 2017 draws to a close, we should take time to reflect on the accomplishments of the past year and look to the opportunities ahead of us. This past year has been filled with many challenges and substantial accomplishments.

In this past year, we collaborated with our cancer research colleagues and made some advances in the understanding of cancer biology. Specifically, we identified new drivers and targets in mucosal melanoma, a rare subtype of melanoma that has a different mutational landscape than cutaneous melanoma (sun-exposed). We continued to study the kinase signaling networks in cancer, and utilizing this knowledge to target kinase dependency in cancer cells, as well as overcoming resistance mechanisms to kinase inhibitors. We also explored new therapeutics (e.g. targeting protein NEDDylation and translation) in preclinical cancer models. In collaboration with our colleagues, we identified new cross-talk signaling in cancer stem cells; and identified cancer-associated fibroblasts that regulate treatment responses in breast cancer. You can read more details about these exciting results in the Research Highlight section. We presented our research at international conferences, and published the methods and findings in scientific journals. We developed a new Biomedical Data Science Graduate Certificate Program to train the next-generation biomedical data scientists.

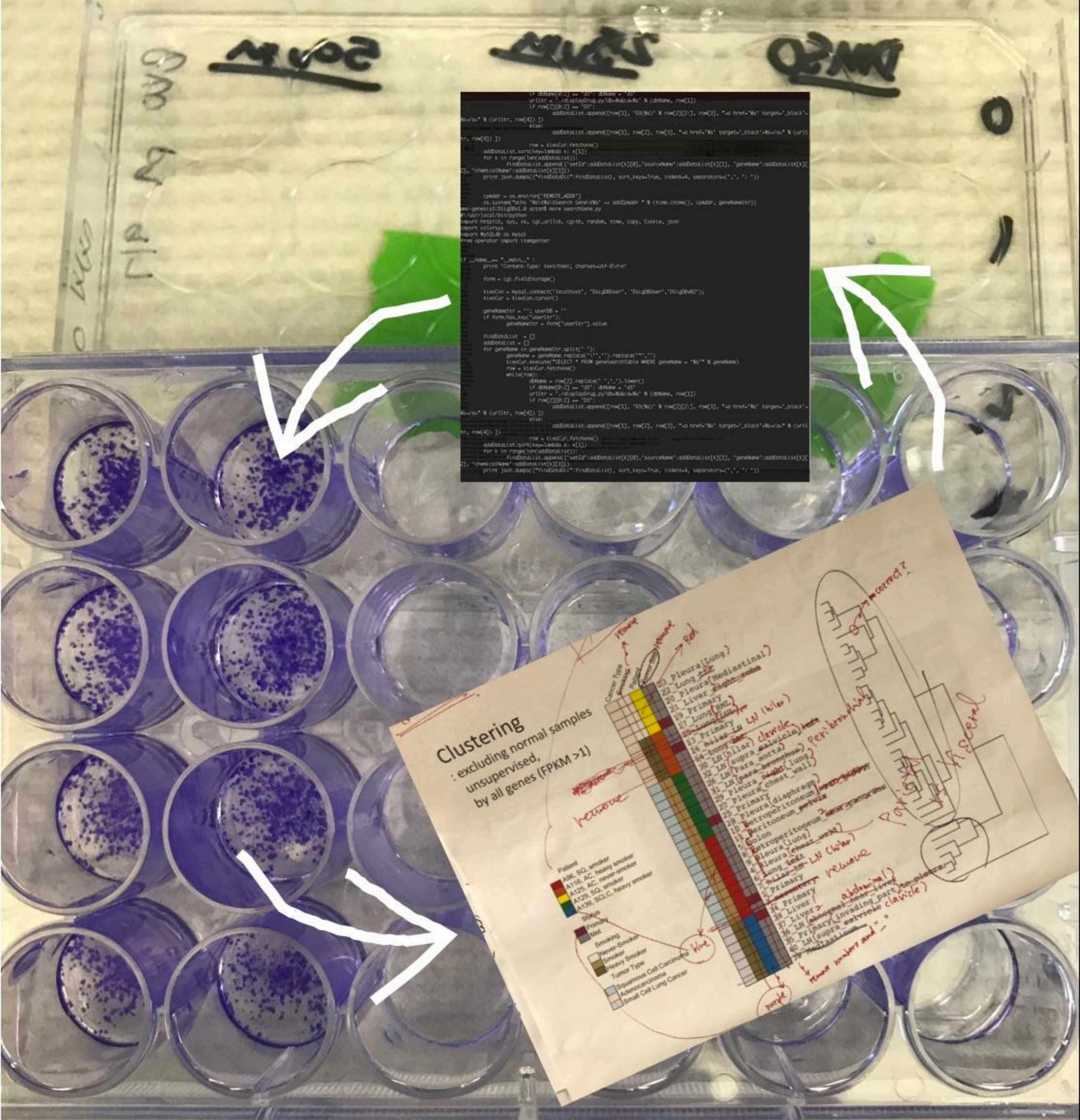
As for the personnel in our lab, we welcome Dr. **Hyunmin Kim** (Feb) and Dr. **Ilyssa Summer** (June) joining our lab as Senior Research Instructor and Post-doctoral Research Fellow, respectively. Congratulations to **Jihye Kim** as she is promoted to Assistant Professor – Research in February. We hosted **Georgia Philips** as a Cancer Center Summer Fellow in our lab. We also hosted **Bernard Lee** from the Cancer Research Malaysia as a visiting student. We bid farewell and wish good luck to **Amy Kreienkamp** and **Paul Francoeur** this year. Amy started her residency training at the Medical School of Washington University St. Louis and Paul entered his graduate study in the Joint CMU-Pitts Computational Biology Program. We are very happy to host our guests and friends this year visiting us, Prof. **Jaewoo Kang** (Korea University), Prof. **Sok Ching Cheong** (Cancer Research Malaysia), Dr. **Kyubum Lee** (Korea University), Dr. **Paul Huang** (Institute of Cancer Research, London, UK) and Dr. **Junbai Wang** (University of Oslo, Norway).

The **Tan Lab** has much to celebrate in 2017. I want to personally thank all of the lab members for their dedication to their research projects, and to our wonderful collaborators in supporting our ongoing research. I really enjoy working with you and looking forward for another exciting year. I wish you and your families a healthy and fulfilling New Year!

Best Wishes,

Aik Choon Tan, Ph.D.

Associate Professor of Bioinformatics/Medicine
Director, Translational Bioinformatics and
Cancer Systems Biology Laboratory
Co-Director, Data Science Core,
Colorado Lung Cancer SPORE
Director, Biomedical Data Science
Graduate Certificate Program

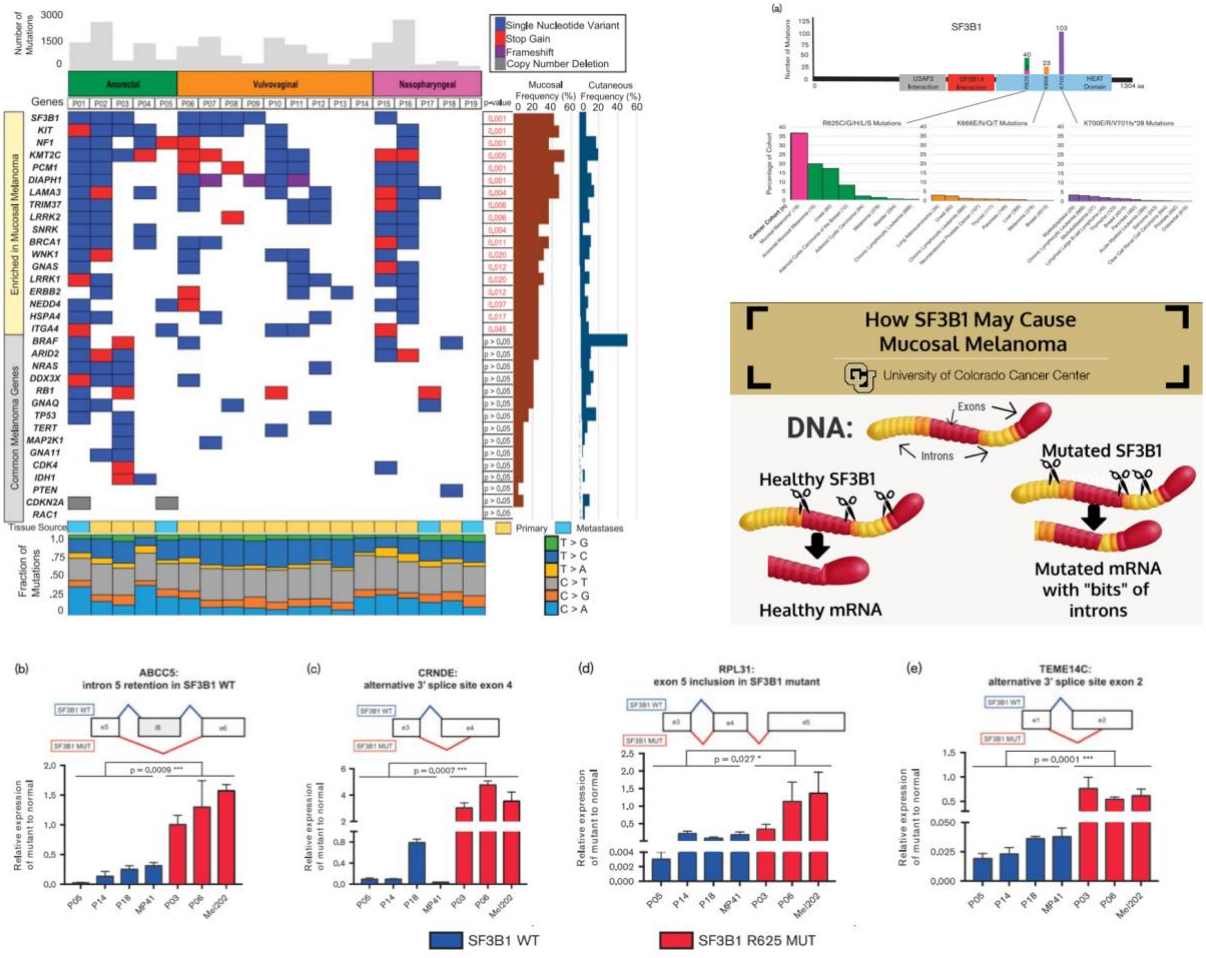


RESEARCH HIGHLIGHTS

IDENTIFYING NEW DRIVERS AND TARGETS IN MUCOSAL MELANOMA

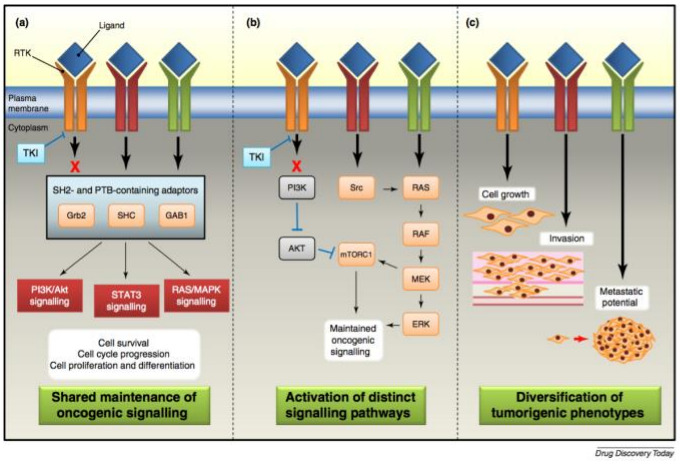
(**Hintzsche et al**, ***Melanoma Research***, 2017, 27: 189-199)

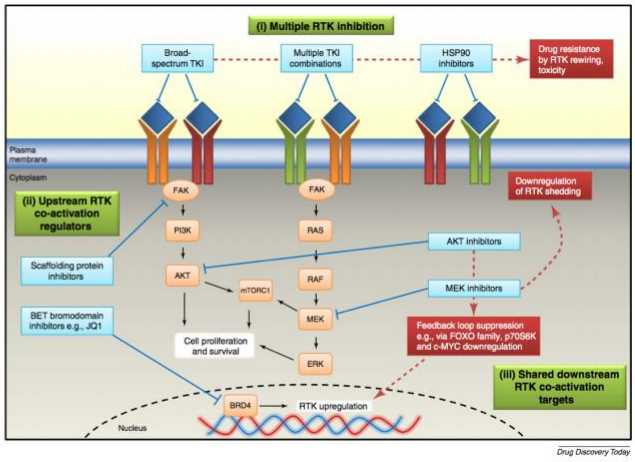
Mucosal melanomas are a rare subtype of melanoma, arising in mucosal tissues, which have a very poor prognosis due to the lack of effective targeted therapies. This study aimed to better understand the molecular landscape of these cancers and find potential new therapeutic targets. Whole-exome sequencing was performed on mucosal melanomas from 19 patients and 135 sun-exposed cutaneous melanomas, with matched peripheral blood samples when available. Mutational profiles were compared between mucosal subgroups and sun-exposed cutaneous melanomas. Comparisons of molecular profiles identified 161 genes enriched in mucosal melanoma ($P<0.05$). KIT and NF1 were frequently co-mutated (32%) in the mucosal subgroup, with a significantly higher incidence than that in cutaneous melanoma (4%). Recurrent SF3B1 R625H/S/C mutations were identified and validated in 7 of 19 (37%) mucosal melanoma patients. Mutations in the spliceosome pathway were found to be enriched in mucosal melanomas when compared with cutaneous melanomas. Alternative splicing in four genes were observed in SF3B1-mutant samples compared with the wild-type samples. This study identified potential new therapeutic targets for mucosal melanoma, including co-mutation of NF1 and KIT, and recurrent R625 mutations in SF3B1. This is the first report of SF3B1 R625 mutations in vulvovaginal mucosal melanoma, with the largest whole-exome sequencing project of mucosal melanomas to date. The results here also indicated that the mutations in SF3B1 lead to alternative splicing in multiple genes. These findings expand our knowledge of this rare disease. Here is a press release covered by the University of Colorado Cancer Center: https://tinyurl.com/yayqn4dq.



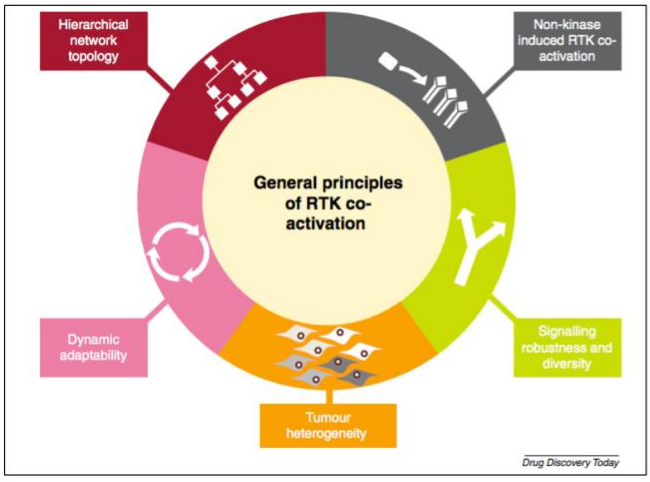
EXPLOITING RECEPTOR TYROSINE KINASE CO-ACTIVATION FOR CANCER THERAPY

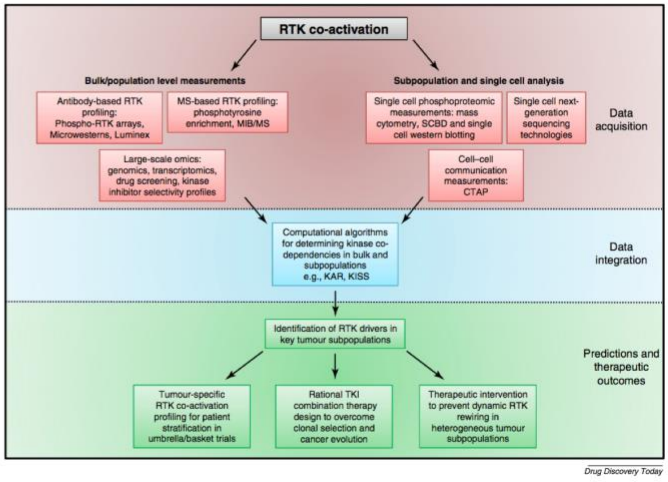
(**Tan, Vyse and Huang**, ***Drug Discovery Today***, 2017, 22: 72-84)





Oncogenic signaling by receptor tyrosine kinases (RTKs) is a causative driver in cancer initiation and progression. There is an increasing consensus that RTKs rarely act in isolation but rather cooperate as networks of multiple receptors that undergo extensive crosstalk – a concept known as RTK co-activation. It is therefore no longer sufficient to view RTKs as single entities; instead these receptors should be investigated as part of complex networks working in a concerted fashion. This review summarizes the general principles of RTK co-activation and discusses approaches to exploit this phenomenon in cancer therapy and drug discovery. Five key principles of RTK co-activation were described in details: dynamic adaptability, hierarchical network topology, non-kinase induced RTK co-activation, signaling robustness and diversity, and tumor heterogeneity. We also provide some reviews on computational strategies to predict kinase co-dependencies, especially on the methods by integrating drug screening data and kinase inhibitor selectivity profiles. We offer a perspective on the implications of RTK co-activation on tumor heterogeneity and cancer evolution and conclude by surveying emerging computational and experimental approaches that will provide insights into RTK co-activation biology and deliver new developments in effective cancer therapies. Read this review at https://tinyurl.com/yb366fbj.

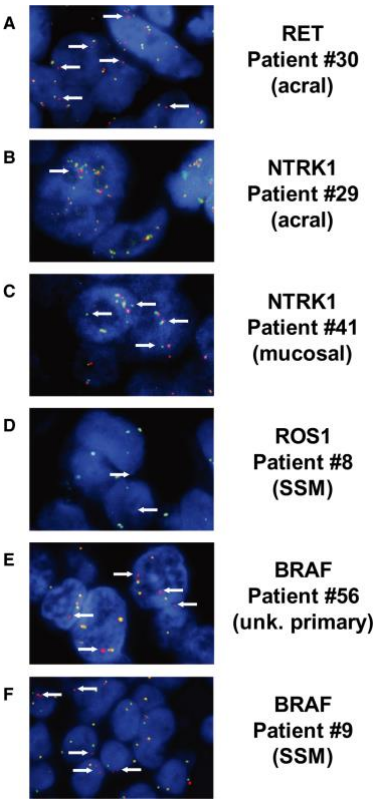




KINASE GENE FUSIONS IN DEFINED SUBSETS OF MELANOMA

(**Turner, Couts et al**, ***Pigment Cell & Melanoma Research***, 2017, 30: 53-62)

Genomic rearrangements resulting in activating kinase fusions have been increasingly described in a number of cancers including malignant melanoma, but their frequency in specific melanoma subtypes has not been reported. We used break-apart fluorescence in situ hybridization (FISH) to identify genomic rearrangements in tissues from 59 patients with various types of malignant melanoma including acral lentiginous, mucosal, superficial spreading, and nodular. We identified four genomic rearrangements involving the genes BRAF, RET, and ROS1. Of these, three were confirmed by Immunohistochemistry (IHC) or sequencing and one was found to be an ARMC10-BRAF fusion that has not been previously reported in melanoma. These fusions occurred in different subtypes of melanoma but all in tumors lacking known driver mutations. Our data suggest gene fusions are more common than previously thought and should be further explored particularly in melanomas lacking known driver mutations.



UNDERSTANDING RESISTANCE MECHANISM OF RET-INHIBITION IN RET-FUSION NSCLC

(**Nelson-Taylor et al**, ***Molecular Cancer Therapeutics***, 2017, 16: 1623-1633)

Oncogenic rearrangements in RET are present in 1-2% of lung adenocarcinoma (LAD) patients. Ponatinib is a multi-kinase inhibitor with low-nanomolar potency against the RET kinase domain. Here, we demonstrate that ponatinib exhibits potent anti-proliferative activity in RET fusion positive LC-2/ad LAD cells and inhibits phosphorylation of the RET fusion protein and signaling through ERK1/2 and AKT. Using distinct dose-escalation strategies, two ponatinib-resistant LC-2/ad cell lines, PR1 and PR2, were derived. PR1 and PR2 cell lines retained expression, but not phosphorylation of the RET fusion and lacked evidence of a resistance mutation in the RET kinase domain. Both resistant lines retained activation of the MAPK pathway. Next-generation RNA sequencing revealed an oncogenic NRAS p.Q61K mutation in the PR1 cell. PR1 cell proliferation was preferentially sensitive to siRNA knockdown of NRAS compared to knockdown of RET, more sensitive to MEK inhibition than the parental line, and NRAS-dependence was maintained in the absence of chronic RET inhibition. Expression of NRAS p.Q61K in RET fusion expressing TPC1 cells conferred resistance to ponatinib. PR2 cells exhibited increased expression of EGFR and AXL. EGFR inhibition decreased cell proliferation and phosphorylation of ERK1/2 and AKT in PR2 cells but not LC-2/ad cells. Although AXL inhibition enhanced PR2 sensitivity to afatinib, it was unable to decrease cell proliferation by itself. Thus, EGFR and AXL cooperatively rescued signaling from RET inhibition in the PR2 cells. Collectively, these findings demonstrate that resistance to ponatinib in RET-rearranged LAD is mediated by bypass signaling mechanisms that result in restored RAS/MAPK activation.

UNDERSTANDING RESPONSES AND RESISTANCE MECHANISMS OF AURORA AND ANGIOGENIC KINASE INHIBITOR IN P53-MUTANT TRIPLE-NEGATIVE BREAST CANCER

(**Ionkina et al**, ***Frontiers in Oncology***, 2017, 7: Article 94)

Triple-negative breast cancer (TNBC) is a subtype associated with poor prognosis and for which there are limited therapeutic options. The purpose of this study was to evaluate the efficacy of ENMD-2076 in p53-mutated TNBC patient-derived xenograft (PDX) models and describe patterns of terminal cell fate in models demonstrating sensitivity, intrinsic resistance, and acquired resistance to ENMD-2076. p53-mutated, TNBC PDX models were treated with ENMD-2076 and evaluated for mechanisms of sensitivity or resistance to treatment. Correlative tissue testing was performed on tumor tissue to assess for markers of proliferation, apoptosis, senescence, and pathways of resistance after treatment and at the time of acquired resistance. Sensitivity to ENMD-2076 200 mg/kg daily was associated with induction of apoptosis while models exhibiting intrinsic or acquired resistance to treatment presented with a senescent phenotype. Response to ENMD-2076 was accompanied by an increase in p53 and p73 levels, even within the background of mutant p53. Treatment with ENMD-2076 resulted in a decrease in pAurA and an increase in pHH3. We observed a TNBC subtype switch from the luminal androgen receptor to the basal-like subtype at acquired resistance. ENMD-2076 has antitumor activity in preclinical models of p53-mutated TNBC. Increased levels of p53 and p73 correlated with sensitivity whereas senescence was associated with resistance to ENMD-2076. The novel finding of a TNBC subtype switch at time of acquired resistance may provide mechanistic insights into the biologic effects of selective pressure of anticancer treatments on TNBC. ENMD-2076 is currently being evaluated in a Phase 2 clinical trial in patients with metastatic, previously treated TNBC where these biologic correlates can be further explored.

A GENOME-WIDE LOSS-OF-FUNCTION SCREEN IDENTIFIES SLC26A2 AS A NOVEL MEDIATOR OF TRAIL RESISTANCE

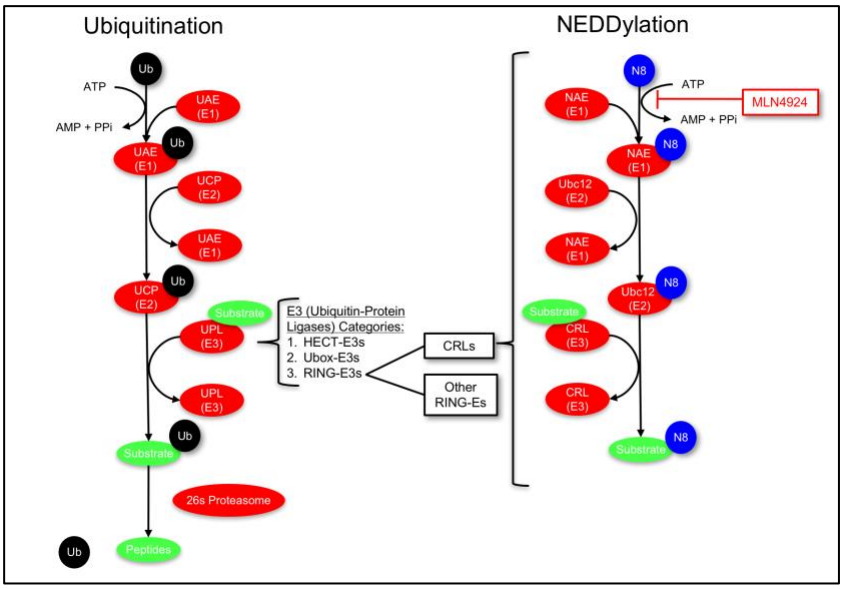
(**Dimberg, Towers et al**, ***Molecular Cancer Research***, 2017, 15: 382 – 394)

TRAIL is a potent death-inducing ligand that mediates apoptosis through the extrinsic pathway and serves as an important endogenous tumor suppressor mechanism. Because tumor cells are often killed by TRAIL and normal cells are not, drugs that activate the TRAIL pathway have been thought to have potential clinical value. However, to date, most TRAIL-related clinical trials have largely failed due to the tumor cells having intrinsic or acquired resistance to TRAIL-induced apoptosis. Previous studies to identify resistance mechanisms have focused on targeted analysis of the canonical apoptosis pathway and other known regulators of TRAIL receptor signaling. To identify novel mechanisms of TRAIL resistance in an unbiased way, we performed a genome-wide shRNA screen for genes that regulate TRAIL sensitivity in sublines that had been selected for acquired TRAIL resistance. This screen identified previously unknown mediators of TRAIL resistance including angiotensin II receptor 2, Crk-like protein, T-Box Transcription Factor 2, and solute carrier family 26 member 2 (SLC26A2). SLC26A2 downregulates the TRAIL receptors, DR4 and DR5, and this downregulation is associated with resistance to TRAIL. Its expression is high in numerous tumor types compared with normal cells, and in breast cancer, SLC26A2 is associated with a significant decrease in relapse-free survival. **Implication:** Our results shed light on novel resistance mechanisms that could affect the efficacy of TRAIL agonist therapies and highlight the possibility of using these proteins as biomarkers to identify TRAIL-resistant tumors, or as potential therapeutic targets in combination with TRAIL.

EVALUATING NEW DRUGS IN PRE-CLINICAL CANCER MODELS

Wong et al, Targeting the protein ubiquitination machinery in melanoma by the NEDD8-activating enzyme inhibitor Pevonedistat (MLN4924)**.** ***Investigational New Drugs***, 2017, 35(1): 11-25.

The neddylation pathway conjugates NEDD8 to cullin-RING ligases and controls the proteasomal degradation of specific proteins involved in essential cell processes. Pevonedistat (MLN4924) is a selective small molecule targeting the NEDD8-activating enzyme (NAE) and inhibits an early step in neddylation, resulting in DNA re-replication, cell cycle arrest and death. We investigated the anti-tumor potential of pevonedistat in preclinical models of melanoma.



Scarborough et al, AZ1366: An inhibitor of tankyrase and the canonical Wnt pathway that limits the persistence of non-small cell lung cancer cells following EGFR inhibition**.** ***Clinical Cancer Research*****,** 2017, 23(6): 1531-1541.

Non–small cell lung cancer (NSCLC) is the most common form of cancer worldwide. Despite progress in the treatment of NSCLC driven by alterations in signaling through the EGFR gene, the prognosis for patients with these mutations generally remains poor and new therapeutic strategies are urgently needed. Recent efforts have identified the canonical Wnt/β-catenin pathway as a means of persistence for EGFR-driven NSCLCs treated with EGFR-inhibitors. Here, we show that co-treatment of these cancers with an EGFR inhibitor and AZ1366, a novel tankyrase inhibitor which effectively reduces signaling through the Wnt/β-catenin pathway, induces tumor cell senescence, reduces tumor growth, and increases survival in a subset of cell lines that can undergo Wnt pathway modulation. These data strongly support further evaluation of tankyrase inhibitors as a co-treatment strategy for EGFR-driven NSCLC.

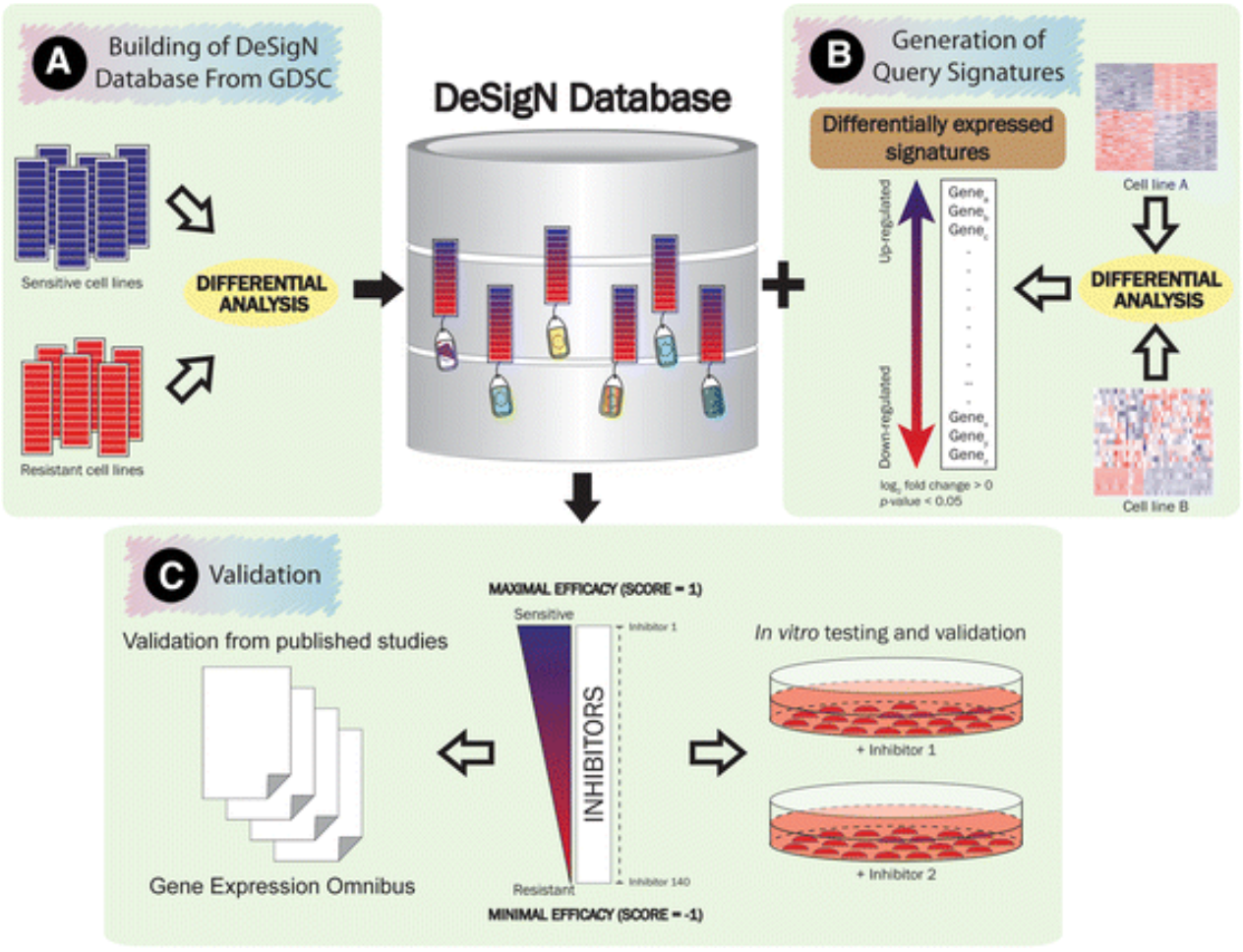
Scott et al, Evaluation of the efficacy of dasatinib, a Src/Abl inhibitor, in colorectal cancer cell lines and explant mouse model. ***PLoS ONE***, 2017, 12(11):e0187173.

Harder et al, Brusatol overcomes chemoresistance through inhibition of protein translation. ***Molecular Carcinogenesis***, 2017, 56(5): 1493-1500.

DeSigN: A NEW WEB TOOL FOR CONNECTING GENE EXPRESSION WITH THERAPEUTICS

(**Lee et al**, ***BMC Genomics***, 2017, 18(Suppl 1):934)

We developed DeSigN, a web-based tool for predicting drug efficacy against cancer cell lines using gene expression patterns. The algorithm correlates phenotype-specific gene signatures derived from differentially expressed genes with pre-defined gene expression profiles associated with drug response data (IC50) from 140 drugs. DeSigN successfully predicted the right drug sensitivity outcome in four published GEO studies. Additionally, it predicted bosutinib, a Src/Abl kinase inhibitor, as a sensitive inhibitor for oral squamous cell carcinoma (OSCC) cell lines. In vitro validation of bosutinib in OSCC cell lines demonstrated that indeed, these cell lines were sensitive to bosutinib with IC50 of 0.8–1.2 μM. As further confirmation, we demonstrated experimentally that bosutinib has anti-proliferative activity in OSCC cell lines, demonstrating that DeSigN was able to robustly predict drug that could be beneficial for tumor control. DeSigN is a robust method that is useful for the identification of candidate drugs using an input gene signature obtained from gene expression analysis. This user-friendly platform could be used to identify drugs with unanticipated efficacy against cancer cell lines of interest, and therefore could be used for the repurposing of drugs, thus improving the efficiency of drug development. The DeSigN website is freely available at http://design.cancerresearch.my/.



FIBROBLAST SUBTYPES REGULATE RESPONSIVENESS OF LUMINAL BREAST CANCER TO ESTROGEN

(**Brechbuhl et al**, ***Clinical Cancer Research***, 2017, 23: 1710 – 1721)

Estrogen receptor (ER)–positive breast cancer is the most common subtype. Targeting ER is an effective therapy, but development of anti-endocrine resistance remains a major cause of treatment failure. Attempts to uncover and therapeutically target mechanisms of anti-endocrine resistance have focused mainly on tumor-intrinsic traits. Here, we identify two subtypes of cancer-associated fibroblasts (CAF), based on their CD146 expression. We further show that CAF subtypes differentially contribute to tumoral ER expression and tamoxifen sensitivity. $CD146^{neg}$ CAFs enforce ER-independent growth and mediate tamoxifen resistance by activating receptor tyrosine kinase pathways. Furthermore, the CAF subtypes predict treatment response and patient outcomes. We believe that these findings have clear clinical implications and support a direct role for the tumor microenvironment in modulating response to anti-endocrine therapy. Insight into CAF–tumor interactions and recognition of CAF subtypes in breast cancer could lead to further improvements in personalized care.

REGULATION OF HEAD AND NECK SQUAMOUS CANCER STEM CELLS BY PI3K AND SOX2

(**Keysar, Le et al**, ***Journal of the National Cancer Institute***, 2017, 109(1): djw189)

We have an incomplete understanding of the differences between cancer stem cells (CSCs) in human papillomavirus–positive (HPV-positive) and –negative (HPV-negative) head and neck squamous cell cancer (HNSCC). The PI3K pathway has the most frequent activating genetic events in HNSCC (especially HPV-positive driven), but the differential signaling between CSCs and non-CSCs is also unknown. We addressed these unresolved questions using CSCs identified from 10 HNSCC patient-derived xenografts (PDXs). Sorted populations were serially passaged in nude mice to evaluate tumorigenicity and tumor recapitulation. The transcription profile of HNSCC CSCs was characterized by mRNA sequencing, and the susceptibility of CSCs to therapy was investigated using an in vivo model. CSCs were enriched by high aldehyde dehydrogenase (ALDH) activity and CD44 expression and were similar between HPV-positive and HPV-negative cases. CSCs were resistant to conventional therapy and had PI3K/mTOR pathway overexpression, and PI3K inhibition in vivo decreased their tumorigenicity. PI3K/mTOR directly regulated SOX2 protein levels, and SOX2 in turn activated ALDH1A1 expression and ALDH activity. SOX2 enhanced sphere and tumor growth and therapy resistance. SOX2 expression prompted mesenchymal-to-epithelial transition (MET) by inducing CDH1 followed by asymmetric division and proliferation, which contributed to tumor formation. The molecular link between PI3K activation and CSC properties found in this study provides insights into therapeutic strategies for HNSCC. Constitutive expression of SOX2 in HNSCC cells generates a CSC-like population that enables CSC studies.

PUBLICATIONS

Publications: We published 18 papers for this past year and we have accrued more than 1100 citations in 2017 related to the publications of our lab. We look forward for another productive year! Go Tan Lab!

1. **Tan AC**, Vyse S, Huang PH. (2017). Exploiting Receptor Tyrosine Kinase Co-activation for Cancer Therapy. ***Drug Discovery Today*.** 22(1): 72-84. [PMID: 27452454]
2. Murakami A, Wang L, Kalhorn S, Schraml P, Rathmell WK, **Tan AC**, Nemenoff R, Stenmark K, Jiang BH, Reyland ME, Heasley L, Hu CJ. (2017). Context-dependent role for chromatin remodeling component PBRM1/BAF180 in clear cell renal cell carcinoma. ***Oncogenesis*.** 6: e287. [PMID: 28092369]
3. Lee BKB, Tiong KH, Chang JK, Liew CS, Abdul Rahman ZA, **Tan AC**, Khang TF, Cheong SC. (2017). DeSigN: connecting gene expression with therapeutics for drug repurposing and development. ***BMC Genomics***. 18(Suppl 1): 934. [PMID: 28198666]
4. Keysar SB, Le PH, Miller B, **Jackson BC**, Eagles JR, Nieto C, **Kim J**, Tang B, Glogowska MJ, Morton JJ, Padilla-Just N, Gomez K, Warnock E, Reisinger J, Arcaroli JJ, Messersmith WA, Wakefield LM, Gao D, **Tan AC**, Serracino H, Vasiliou V, Roop DR, Wang XJ, Jimeno A. (2017). Regulation of Head and Neck Squamous Cancer Stem Cells by PI3K and SOX2. ***Journal of the National Cancer Institute*.** 109(1): djw189. [PMID: 27634934]
5. Turner J*, Couts K*, Sheren J, Saichaemchan S, Ariyawutyakorn W, Avolio I, Cabral E, Glogowska M, Amato C, Robinson S, **Hintzsche J**, Applegate A, Seelenfreund E, Gonzalez R, Wells K, Bagby S, Tentler J, **Tan AC**, Wisell J, Varella-Garcia M, Robinson WA. (2017). Kinase Gene Fusions in Defined Subsets of Melanoma. ***Pigment Cell & Melanoma Research***. 30(1):53-62. [PMID: 27864876]
6. Wong KM, Micel L, **Selby H**, **Tan AC**, Pitts TM, Bagby S, Spreafico A, **Klauck P**, Blakemore S, Smith P, McDonald A, Berger A, Tentler J, Eckhardt SG. (2017). Targeting the Protein Ubiquitination Machinery in Melanoma by the NEDD8-Activating Enzyme Inhibitor Pevonedistat (MLN4924). ***Investigational New Drugs*.** 35(1): 11-25. [PMID: 27783255]
7. Scarborough HA, Helfrich BA, Casas-Selves M, Schuller AG, Grosskurth SE, **Kim J**, **Tan AC**, Chan DC, Zhang Z, Zaberezhnyy V, Bunn PA, DeGregori J. (2017). AZ1366: An inhibitor of tankyrase and the canonical Wnt pathway that limits the persistence of non-small cell lung cancer cells following EGFR inhibition. ***Clinical Cancer Research*.** 23(6): 1531-1541. [PMID: 27663586]
8. Brechbuhl HM, Finlay-Schultz J, Yamamoto TM, Gillen AE, Cittelly DM, **Tan AC**, Sams S, Pillai MM, Elias AD, Robinson WA, Sartorius CA, Kabos P. (2017). Fibroblast Subtypes Regulate Responsiveness of Luminal Breast Cancer to Estrogen. ***Clinical Cancer Research*.** 23(7): 1710-1721. [PMID: 27702820] [COVER]
9. Smith Jr BJ, **Hintzsche JD**, Amato CM, **Tan AC**, Wells KR, Applegate AJ, Gonzalez RT, Barr JR, Robinson WA. (2017). Systematic Analysis of Whole Exome Sequencing Determines RET G691S Polymorphis, as Germline Variant in Melanoma. ***Marshall Journal of Medicine*.** 3(2): Article 10. [PDF]
10. Harder B, Tian W, La Clair JJ, **Tan AC**, Ooi A, Chapman E, Zhang DD. (2017). Brusatol overcomes chemoresistance through inhibition of protein translation. ***Molecular Carcinogenesis***. 56(5): 1493-1500. [PMID: 28019675]

11. Dimberg LY*, Towers CG*, Behbakht K, Hotz TJ, **Kim J**, Fosmire S, Porter CC, **Tan AC**, Thorburn A, Ford HL. (2017). A genome-wide loss-of-function screen identifies SLC26A2 as a novel mediator of TRAIL resistance. ***Molecular Cancer Research*.** 15(4): 382-394. [PMID: 28108622]

12. **Hintzsche JD**, Gorden NT, Amato CM, **Kim J**, **Wuensch KE**, Robinson SE, Applegate AJ, Couts KL, Medina TM, Wells KR, Wisell JA, McCarter MD, Box NF, Shellman YG, Gonzalez RC, Lewis KD, Tentler JJ, **Tan AC**[@], Robinson WA[@]. (2017). Whole Exome Sequencing Identifies Recurrent SF3B1 R625 Mutation and Co-Mutation of NF1 and KIT in Mucosal Melanoma. ***Melanoma Research***. 27(3):189-199. [PMID: 28296713] [[@]Co-corresponding authors.]

13. Ionkina AA, Tentler JJ, **Kim J**, Capasso A, Pitts TM, **Ryall KA**, Howison RR, Kabos P, Sartorius CA, **Tan AC**, Eckhardt SG, Diamond JR. (2017). Efficacy and Molecular Mechanisms of Differentiated Response to the Aurora and Angiogenic Kinase Inhibitor ENMD-2076 in Preclinical Models of p53-Mutated Triple-Negative Breast Cancer. *Frontiers in Oncology*. 7: Article 94. [PDF]

14. Ohm AM, **Tan AC**, Heasley LE, Reyland ME. (2017). Co-dependency of PKCδ and K-Ras: Inverse association with cytotoxic drug sensitivity in KRAS mutant lung cancer. ***Oncogene*.** 36(30):4370-4378. [PMID: 28368426]

15. Nelson-Taylor SK, Le AT, **Yoo M**, Schubert L, Mishall KM, Doak A, Varella-Garcia M, **Tan AC**, Doebele RC. (2017). Resistance to RET-inhibition in RET-rearranged NSCLC is mediated by reactivation of RAS/MAPK signaling. ***Molecular Cancer Therapeutics***. 16(8):1623-1633. [PMID: 28500237]

16. Donson A, Apps J, Griesinger AM, Amani VA, Witt DA, Anderson RCE, Niazi TN, Grant G, Souweidane M, Johnston JM, Jackson EM, Kleinschmidt-DeMasters BK, Handler MH, **Tan AC**, Gore L, Virasemi A, Gonzalez-Meljem JM, Jacques TS, Martinez-Barbera JP, Foreman NK, Hankinson TC. (2017). Molecular analyses reveal inflammatory mediators in the solid component and cyst fluid of human adamantinomatous craniopharyngioma. ***Journal of Neuropathology and Experimental Neurology*.** 76(9): 779-788. [PMID: 28859336]

17. Zhang C, Liu Z, Bunker E, Ramirez A, Lee S, Peng Y, **Tan AC**, Eckhardt SG, Chapnick DA, Liu X. (2017). Sorafenib Targets the Mitochondrial Electron Transport Chain Complexes and ATP Synthase to Activate the PINK1-Parkin Pathway and Modulate Cellular Drug Response. ***Journal of Biological Chemistry*.** 292(36): 15105-15120. [PMID: 28673964]

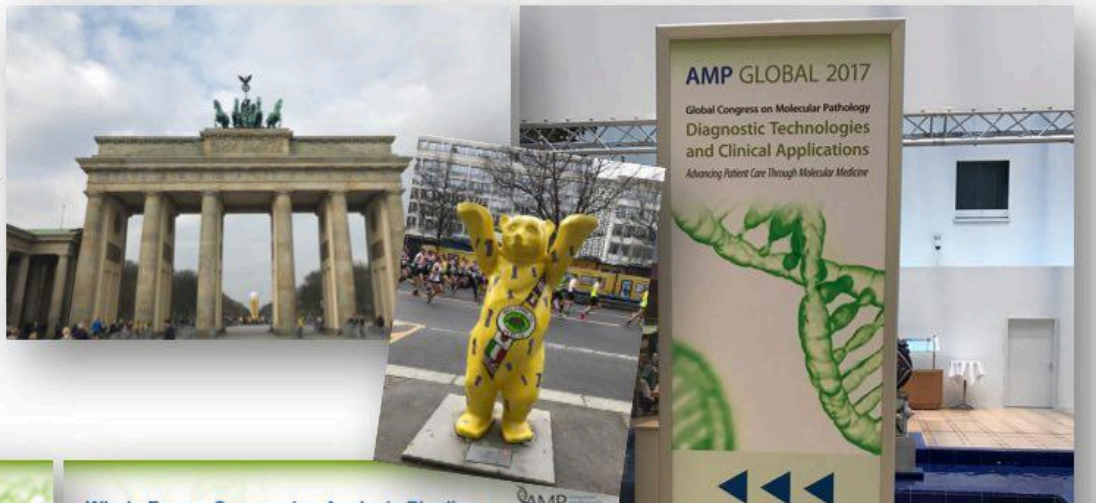
18. Scott AJ, Song EK, Bagby S, Purkey A, McCarter M, Gajdos C, Quackenbush KS, Cross B, Pitts TM, **Tan AC**, Eckhardt SG, Fenton H, Arcaroli J, Messersmith WA. (2017). Evaluation of the efficacy of dasatinib, a Src/Abl inhibitor, in colorectal cancer cell lines and explant mouse model. ***PLoS ONE*.** 12(11):e0187173. [PMID: 29091939]

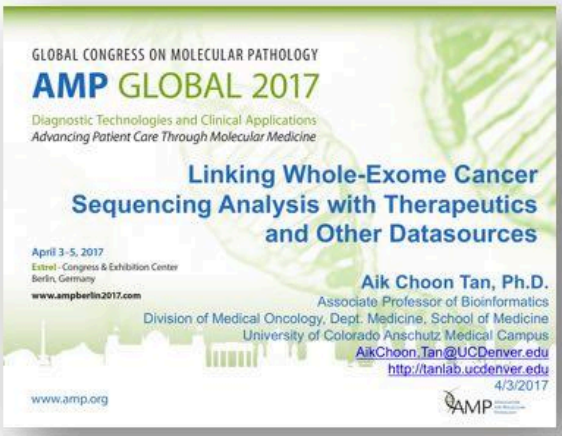
Together with Dr. Paul Huang, we co-edited and published the "***Kinase Signaling Networks***" in July 2017. Thanks to all the authors that have contributed to this book, and thanks to Paul for pushing this to finish line!

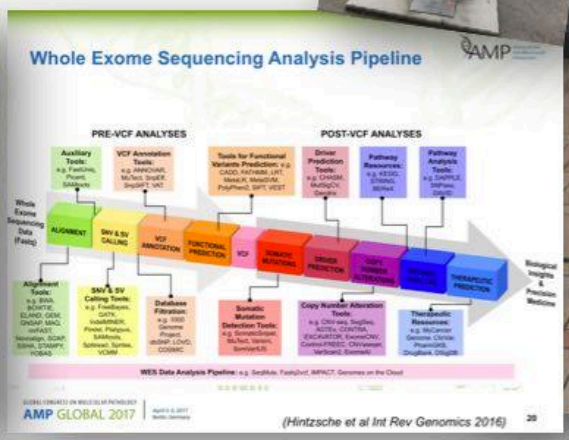

RESEARCH


OUTREACH

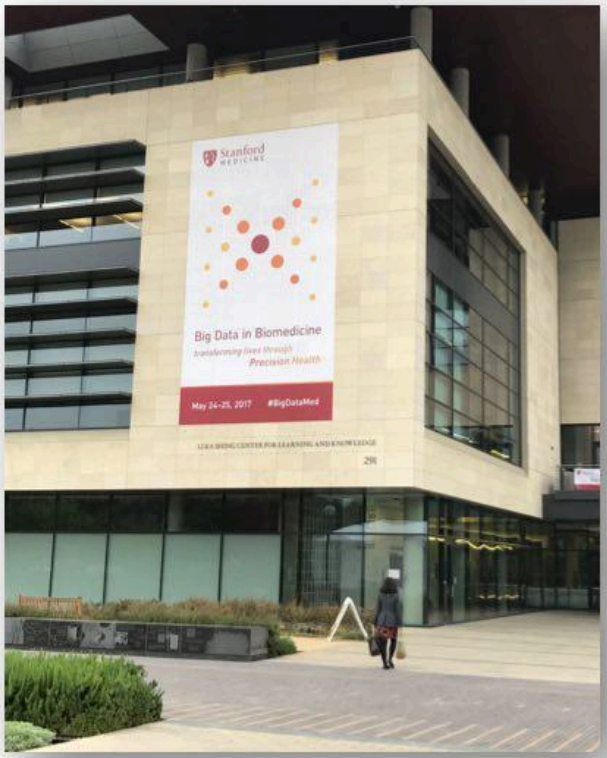
AC was invited to present at the Association of Molecular Pathology (AMP) Global Congress in Berlin (Apr 3 -5). He presented the current research in our lab of linking whole-exome sequencing with therapeutics pipeline.

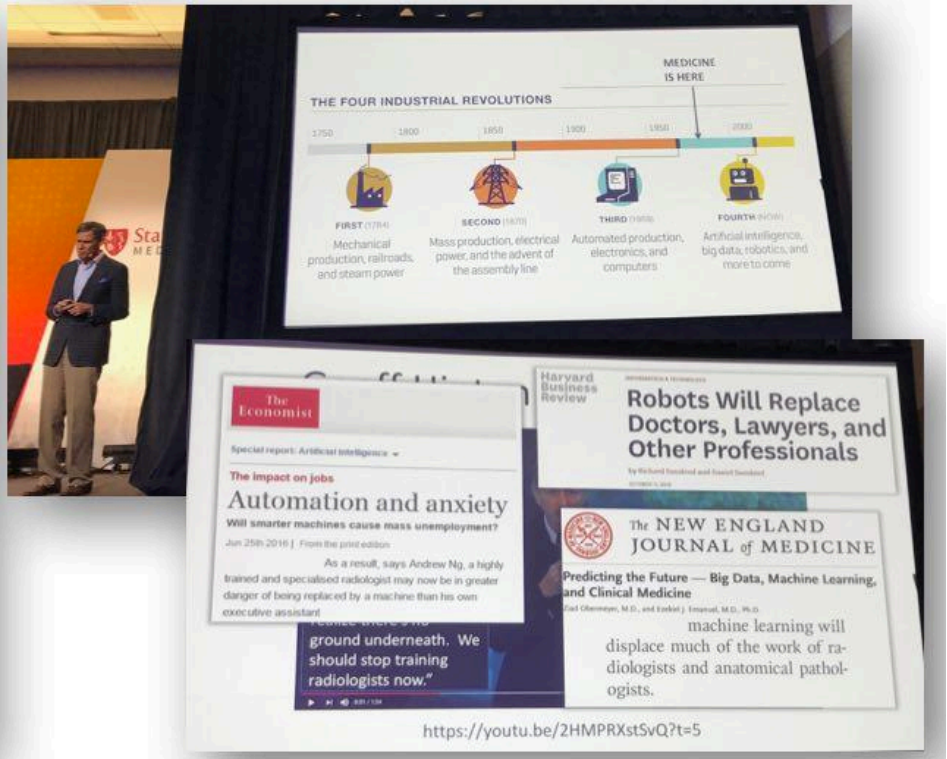






AC attended the Big Data in Biomedicine Conference in Stanford (May 24-25), and learned all new and exciting research of big data and machine learning approaches in medicine. A great conference to gain new ideas and networking!





Jenn, Jihye, Hyunmin and **AC** attended the 28th International Conference on Genome Informatics (GIW/BIOINFO 2017) in Seoul, Korea.

Jenn has a presentation in the GIW/BIOINFO 2017 Conference in Seoul, Korea.

Thanks to Prof. **Jaewoo Kang** and his lab for hosting us during GIW/BIOINFO 2017. Glad to have dinner with Prof. **Limsoon Wong**, conference co-chair.

Meeting up with Dr. **Sunghee Park** from Songsil University. Sunghee is AC's first Korean friend, they knew each other when they are still the graduate students in the University of Glasgow, Scotland!

We took the opportunity to visit a few research labs while we were in Seoul.

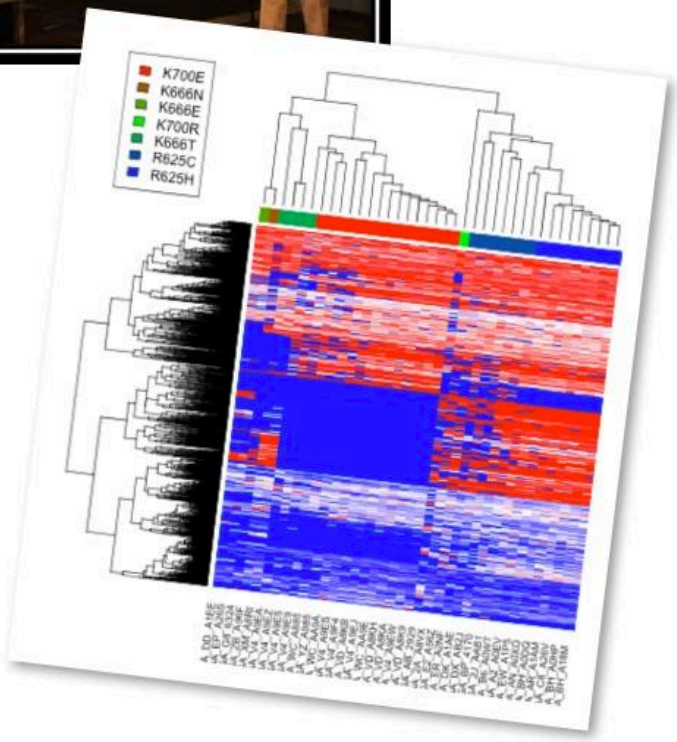
We visited the **Precision Medicine Center** at the **Seoul National University Bundang Hospital**. Thanks to Prof. **Choon-Taek Lee** and his team for hosting our visit. We were very impressed by the research conducted in SNUH and we look forward for future collaboration.

We also visited the **Center for Advanced Bioinformatics and Systems Medicine** at **Sookmyung Women's University**. Thanks to Prof. **Sukjoon Yoon** and his team for hosting our visit. We look forward for future collaboration with Prof. Yoon's team.

Finally, we met up with Prof. **Dong-Hoon Shin** (SNU), Dr. **Eunju Lee** (Asan Hospital), Dr. **Taek-Gu Lee** (Chungbuk National University Hospital), Dr. **Hui-Jeong Hwang** (Kyung Hee University) and **Jong Ha Hong** for dinner. It was great to meet up again! Thanks Dr. Shin for hosting us!

2017 International Visiting Scientist Award, BESST Program, Graduate School, University of Colorado Anschutz Medical Campus

Congratulation to **Kelsey** for being selected as an awardee for the International Visiting Scientist Award from the Graduate school. She visited Dr. **Rachael Natrajan**, our collaborator in the Institute of Cancer Research London in Oct/Nov for developing SF3B1 splicing signature in cancer. This is an ongoing collaboration with Dr. Natrajan's group. Thanks to Dr. Natrajan for hosting Kelsey!



ICR The Institute of Cancer Research

ROCKY 2017
Bioinformatics Conference

FIFTEENTH ROCKY MOUNTAIN BIOINFORMATICS CONFERENCE

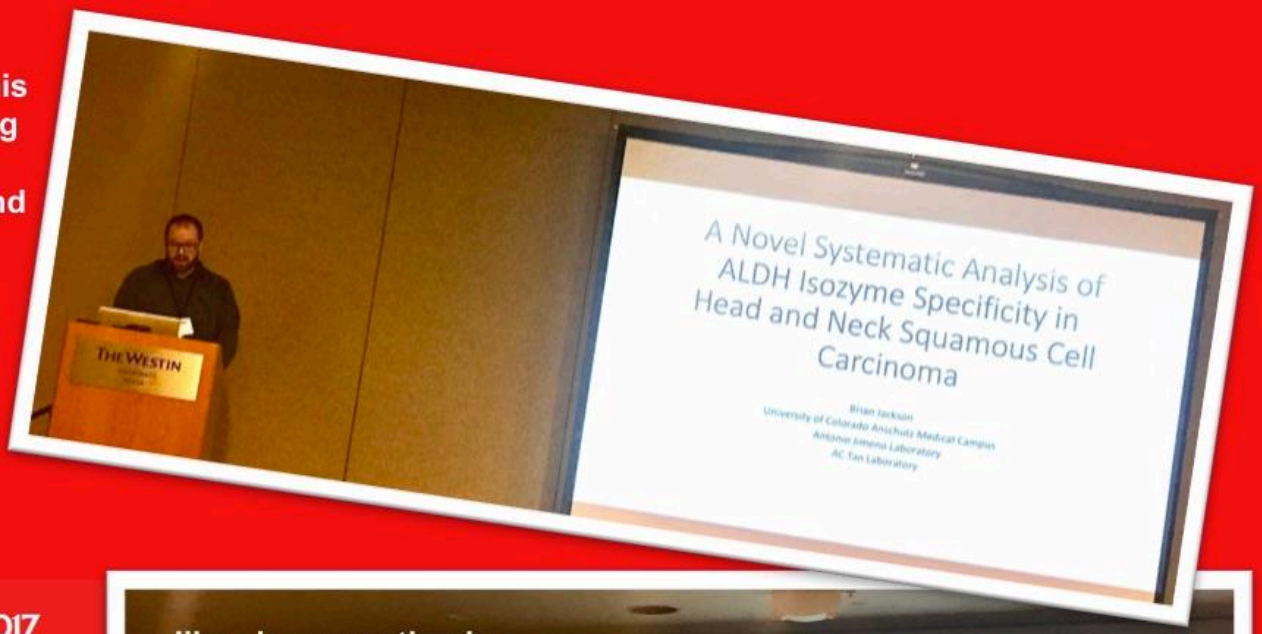
We attended the 15th Rocky Mountain Bioinformatics Conference in Snowmass Village where we presented our research to the scientific community!

The Tan Lab Big Family @ Snowmass Village, CO.

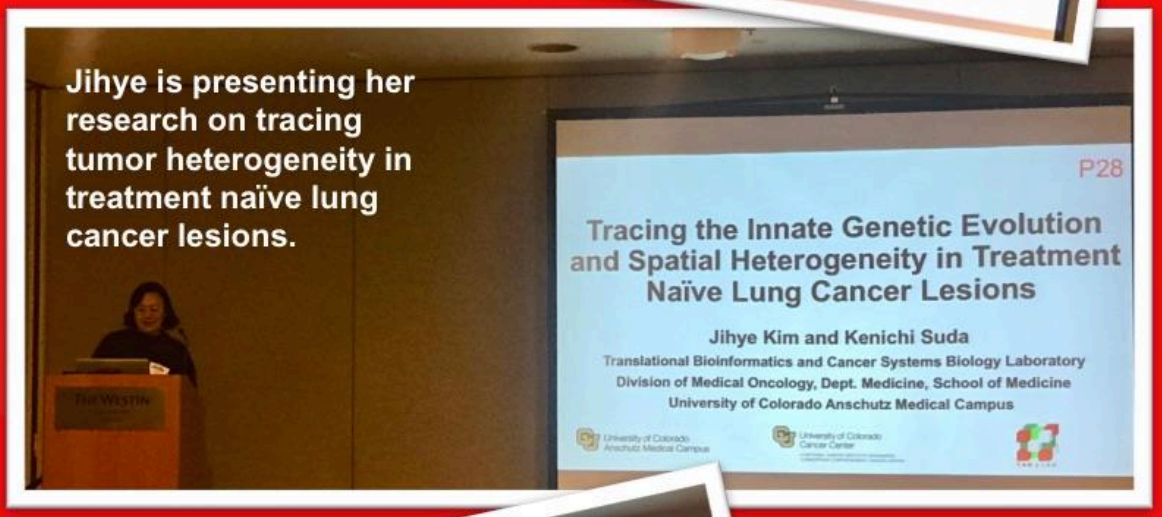
ROCKY 2017
Bioinformatics Conference

FIFTEENTH ROCKY MOUNTAIN BIOINFORMATICS CONFERENCE

Brian is presenting his research on analyzing ALDH isozyme specificity in head and neck cancer.

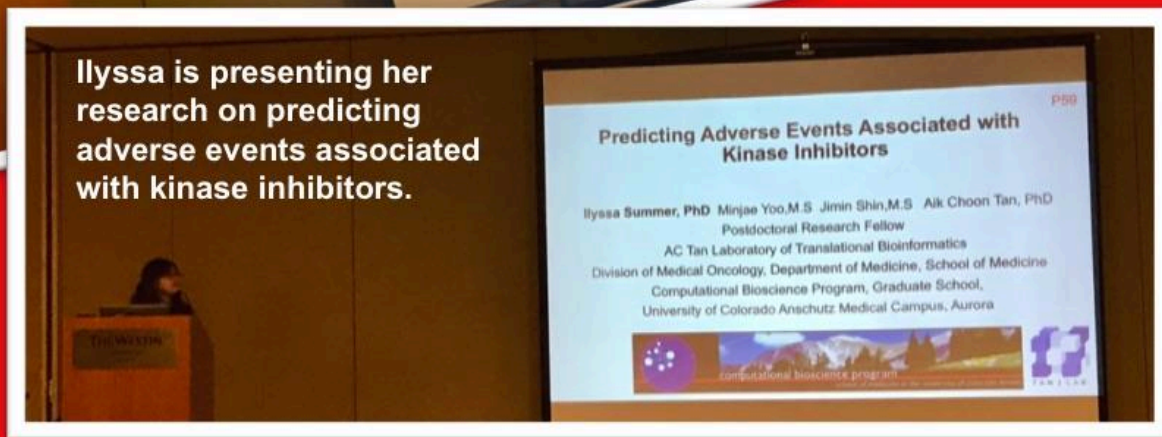


Jihye is presenting her research on tracing tumor heterogeneity in treatment naïve lung cancer lesions.



Jenn is presenting her new implementation of the IMPACT Web Portal.

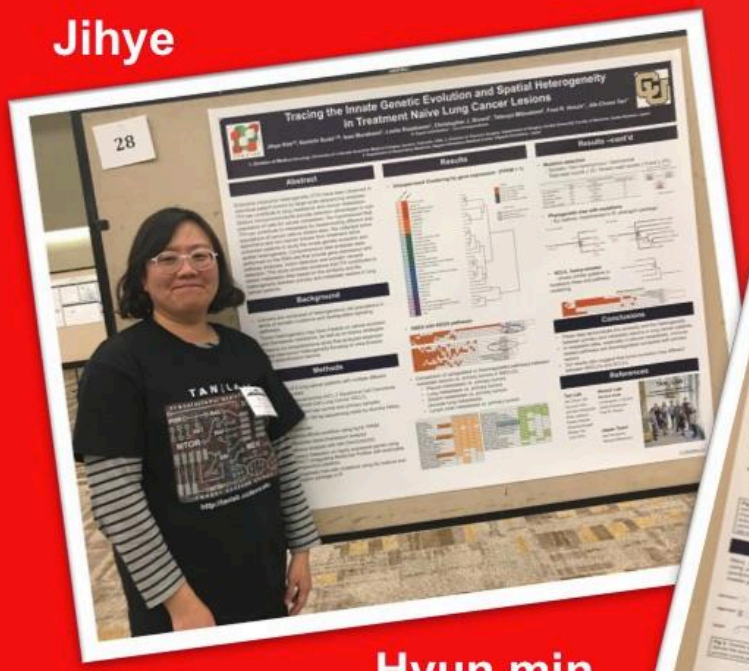
Ilyssa is presenting her research on predicting adverse events associated with kinase inhibitors.



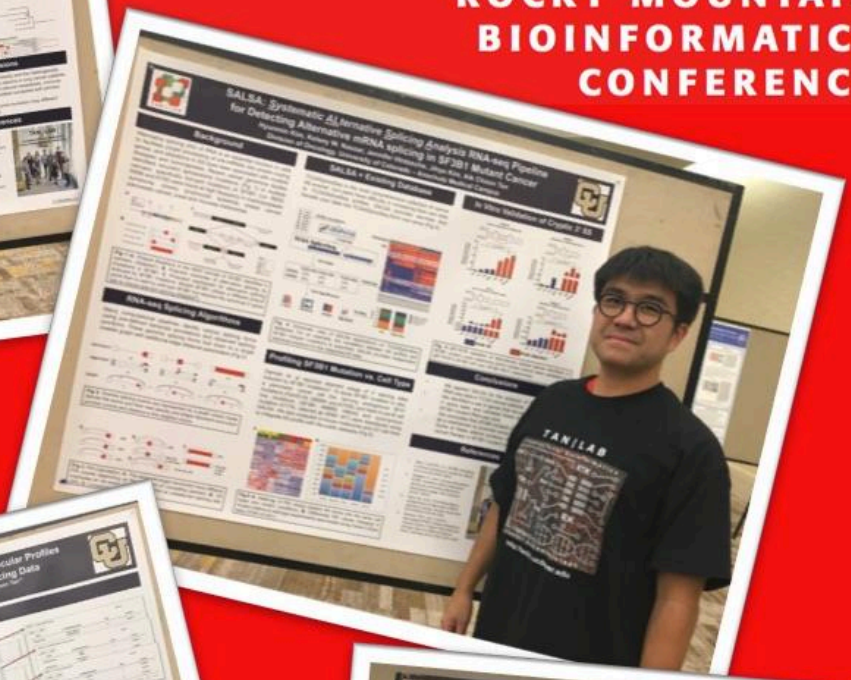
ROCKY 2017
Bioinformatics Conference

FIFTEENTH ROCKY MOUNTAIN BIOINFORMATICS CONFERENCE

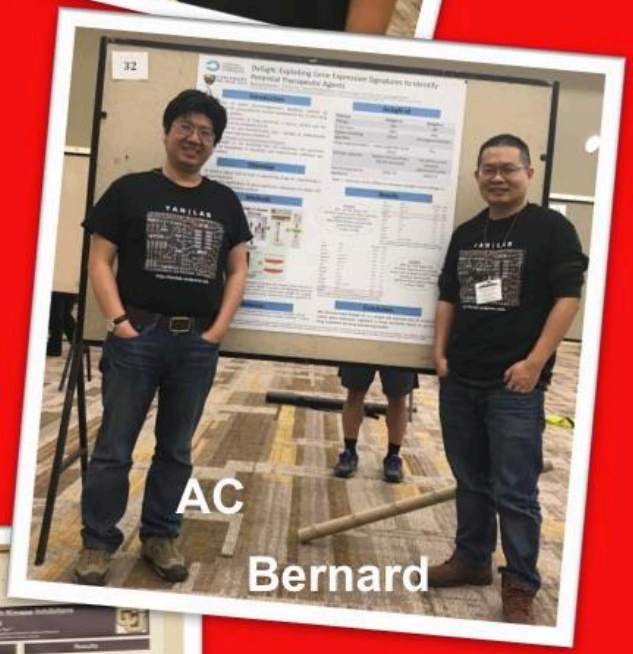
Jihye



Hyun min

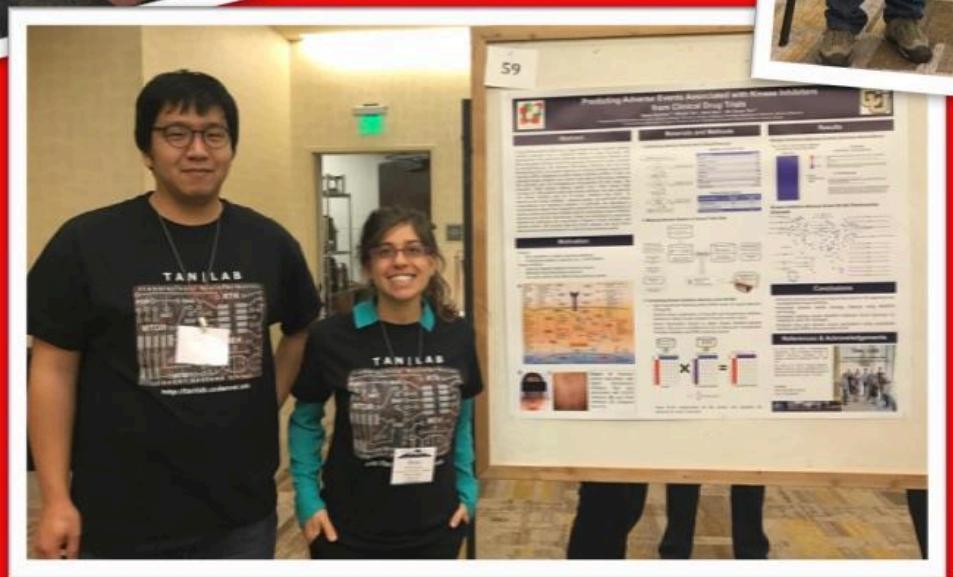


Jenn

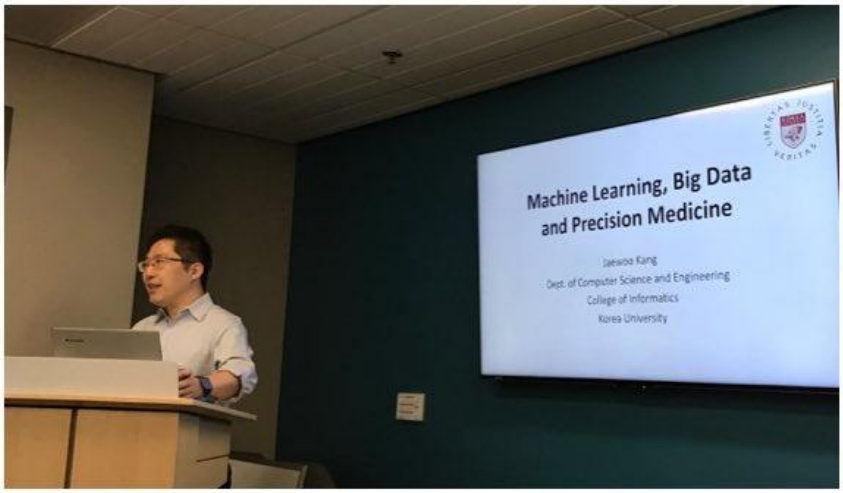


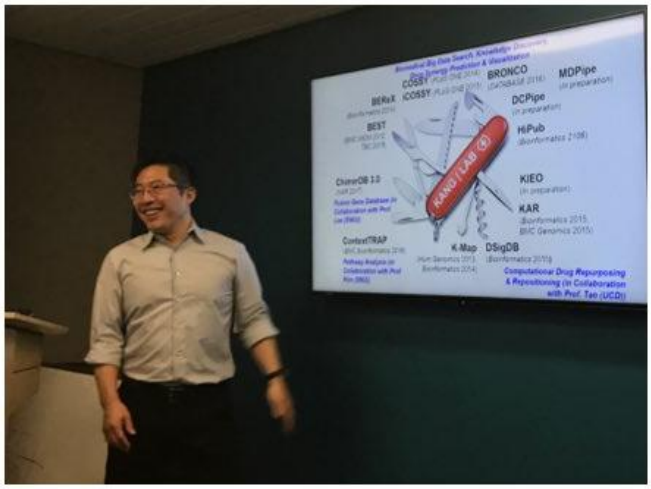
AC
Bernard

Minjae
&
Ilyssa



Special Guests & Friends Visiting the Tan Lab in 2017





Prof. **Jaewoo Kang**, our long time collaborator from Korea University delivered the seminar of “Machine Learning, Big Data and Precision Medicine” at the journal club.

Prof. **Sok Ching Cheong** from the Cancer Research Malaysia.

Dr. **Junbai Wang** from the Oslo University Hospital, Norwegian Radium Hospital.

Special Seminar

Dr. Kyubum Lee
Data Mining and Information Systems Lab
Korea University

Friday, July 7, 2017
11am – 12pm
RC1S 8107-8108

Text Mining Approaches for Knowledge Extraction from Biomedical Literature

Host:
Jihye Kim, Ph.D. & Aik Choon Tan, Ph.D.
jihye.kim@ucdenver.edu
Translational Bioinformatics and Cancer Systems Biology Lab
Division of Medical Oncology

Please contact Jihye if you would like to meet with the speaker.

Special Seminar

Dr. Junbai Wang
Senior Scientist
Pathology Departent
Oslo University Hospital - Norwegian Radium Hospital

Friday, July 17, 2017
4pm – 5pm
RC1S 8107-8108

Computational Genome Regulation in Cancer Research

Host:
Aik Choon Tan, Ph.D.
aikchoon.tan@ucdenver.edu
Translational Bioinformatics and Cancer Systems Biology Lab
Division of Medical Oncology

Please contact AC if you would like to meet with the speaker.

Special Seminar

Dr. Paul Huang
Team Leader,
Division of Cancer Biology
The Institute of Cancer Research, London, UK

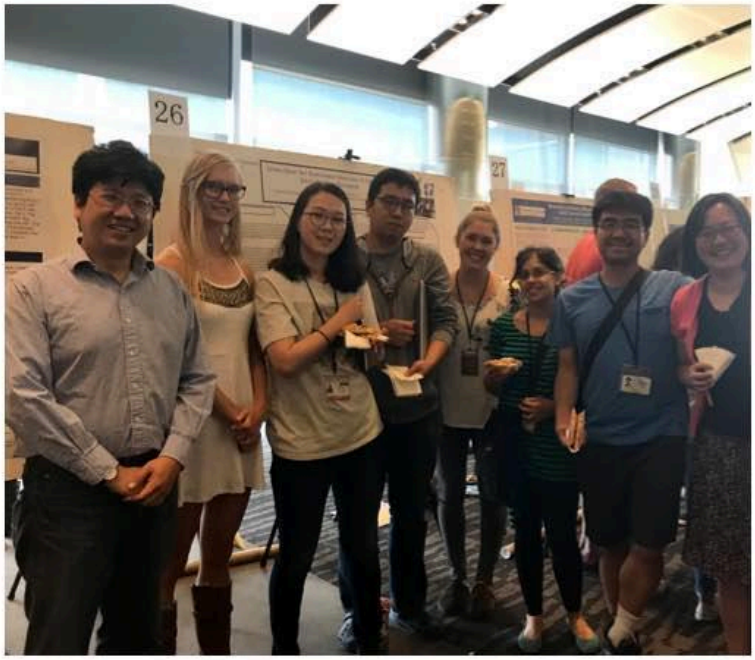
Thursday, October 19, 2017
12pm – 1pm
RC1S 8107-8108

Tackling Kinase Inhibitor Resistance: From Cancer Biology to Patient Outcomes

Host:
Aik Choon Tan, Ph.D.
aikchoon.tan@ucdenver.edu
Translational Bioinformatics and Cancer Systems Biology Lab
Division of Medical Oncology

University of Colorado Cancer Center
A NATIONAL CANCER INSTITUTE-DESIGNATED CONSORTIUM COMPREHENSIVE CANCER CENTER

We hosted **Georgia Philips** from the Computational Biology Program of Massachusetts Institute of Technology as the University of Colorado Cancer Center Summer Research Fellow in our lab. Her project was on identifying drug-induced gene expression changes from public microarray data. The Tan lab members showed up to support her poster presentation.



For education and training the next-generation biomedical data scientists, Dr. **Tzu Phang** and **AC** have developed the Biomedical Data Science Graduate Certificate Program. This is supported by Dr. **Inge Wefes**, Associate Dean of the Graduate School. We have eight students enrolled as our founding cohort of this program.

University of Colorado **Denver | Anschutz Medical Campus**

Biomedical Data Science Graduate Certificate Program

YOU WILL LEARN

- Learn the basics of computer programming.
- Locate, access, analyze and visualize biomedical data set using appropriate tools and programs.
- Understand and apply various machine learning techniques and data analytics for solving real world biological problems.
- Communicate effectively with biomedical researchers and computational data analysts in a team science environment.

Program Application Deadlines

The flexible one-year curriculum consists of 15 credits of core classes (12 credits can be transferred into selected Master's Programs)

We accept students in the fall semester only.

Domestic Student Deadline July 1
International Student Deadline January 2

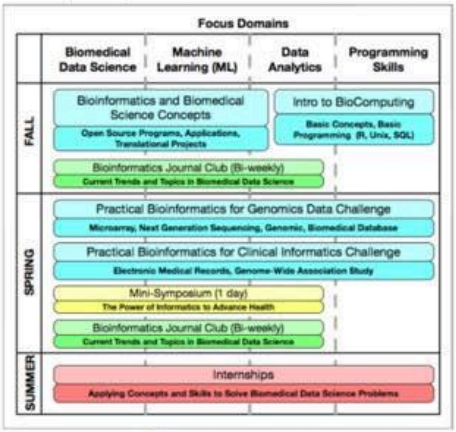
Apply Here!

YOUR OPPORTUNITY

Biomedical Data Science has become an integral part of biomedical research. Biomedical researchers with data science knowledge are advantaged on multiple fronts:

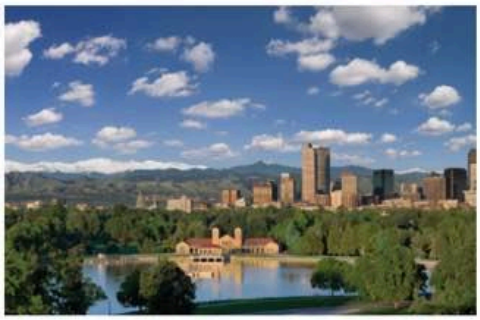
1. Are able to communicate constructively with Data scientists
2. Can analyze their own dataset
3. Can explore the large datasets available in the public domain, therefore missing an important opportunity to mine big data resources.

Therefore, training researcher the basics of data science is crucial to advance scientific discovery.



BESST

Graduate School
UNIVERSITY OF COLORADO
DENVER | ANSCHUTZ MEDICAL CAMPUS

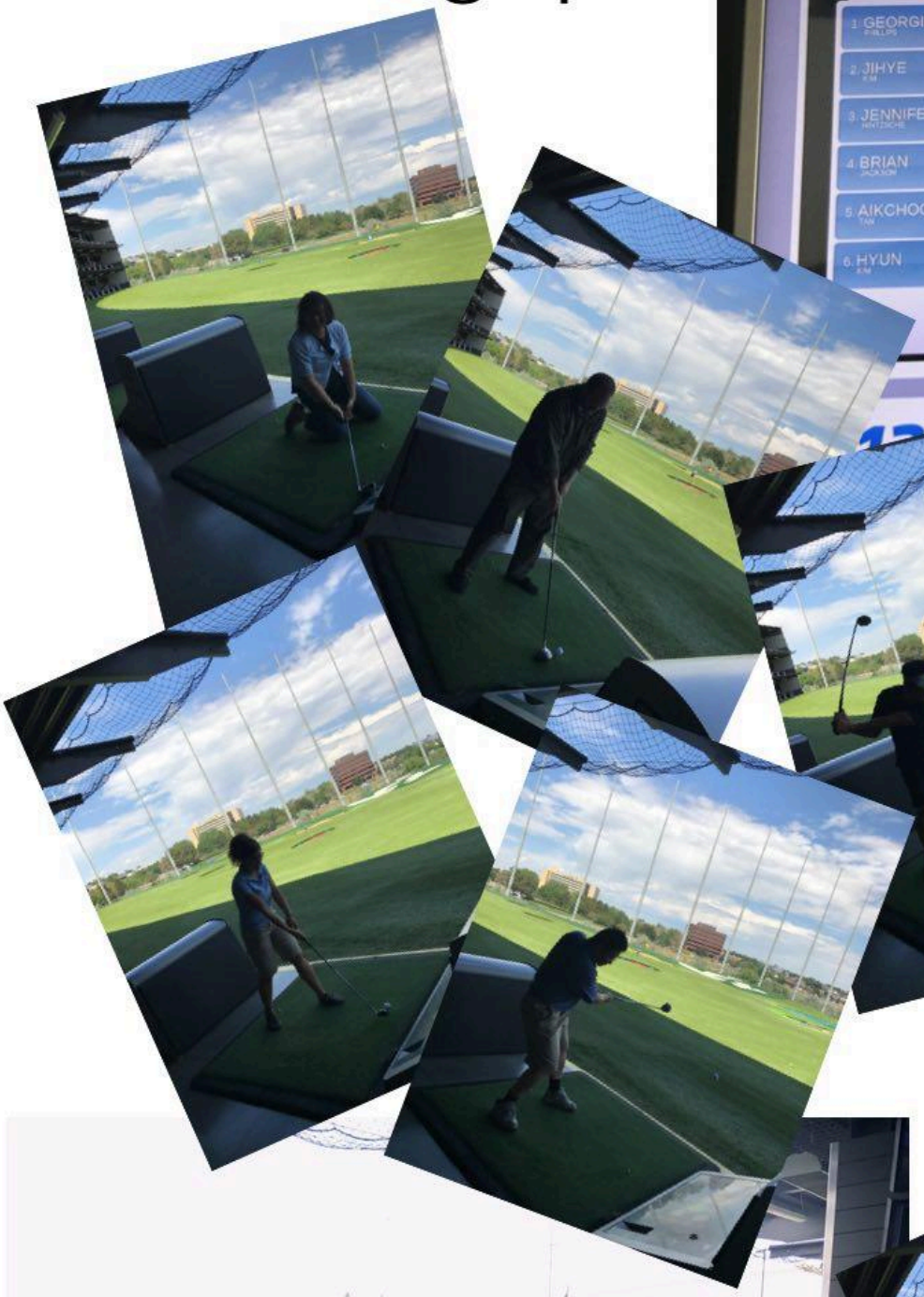


LAB SOCIAL ACTIVITIES, CELEBRATIONS & OUTINGS ;-)

Annual New Year Dinner

Lab Picnic

Tan Lab
Golf Tournament @ TopGolf



Prof. James Costello

Dr. Hyunmin Kim

Kelsey Wuensch

Dr. Kimberly Kanigel-Winner
(Costello Lab)

Dr. Jenn Hintzsche

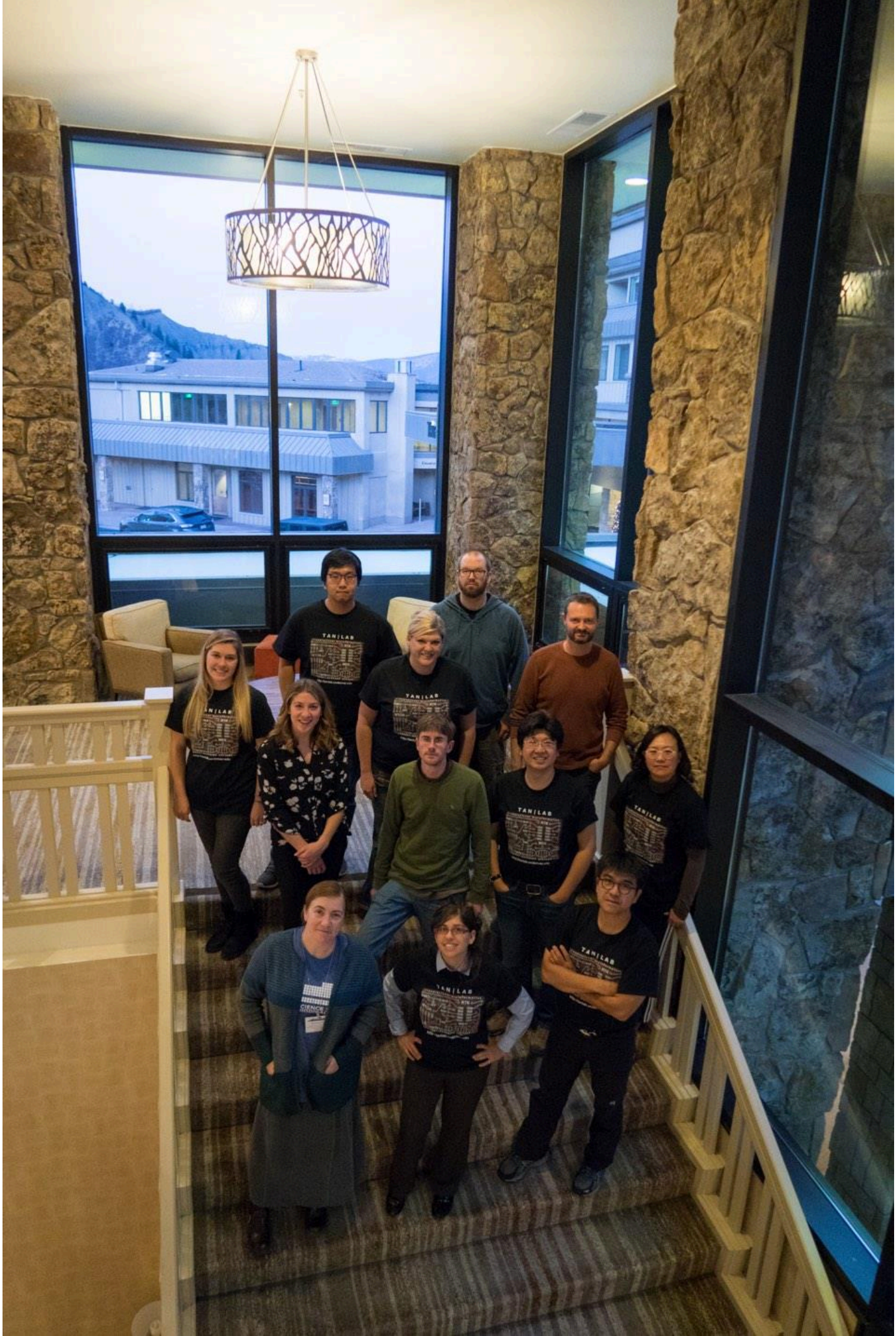
Dr. Brian Jackson

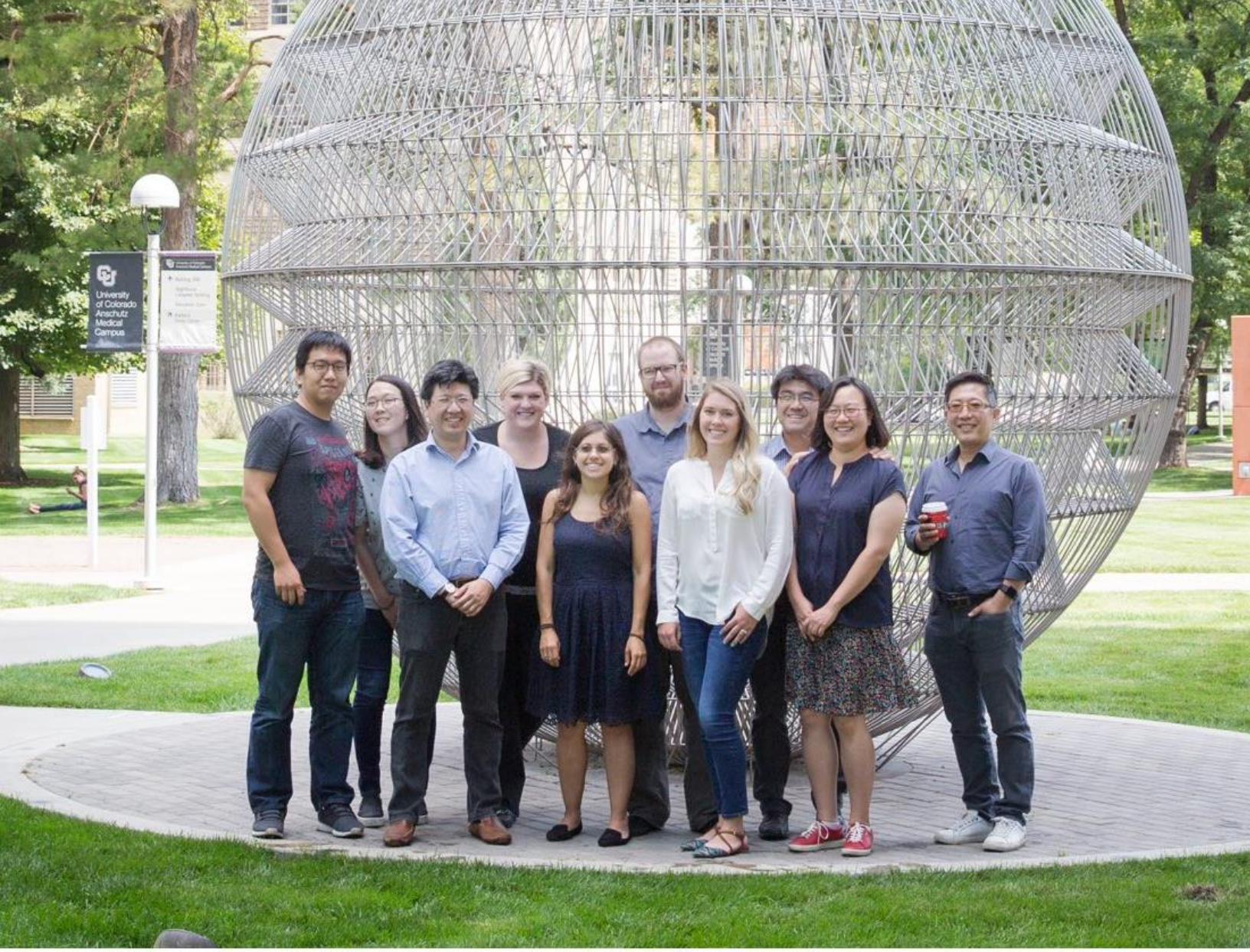
Dr. Ilyssa Summer

Dr. Brian Ross
(Costello Lab)

Rani Powers
(Costello Lab)

Joint Costello-Tan Lab Retreat
Snowmass Village, CO
Dec 9, 2017


TANILAB



Support Our Research and Contact Us

Aik Choon Tan, Ph.D.
Associate Professor of Bioinformatics
Translational Bioinformatics and Cancer Systems Biology Laboratory
Division of Medical Oncology, Department of Medicine,
School of Medicine, University of Colorado Anschutz Medical Campus
Mail Stop 8117
12801 E.17th Ave., L18-8116
Aurora CO 80045
Tel: 303.724.2520
Fax: 303.724.3889
Email: AikChoon.Tan@UCDenver.edu
Web: http://tanlab.ucdenver.edu