TAN | LAB

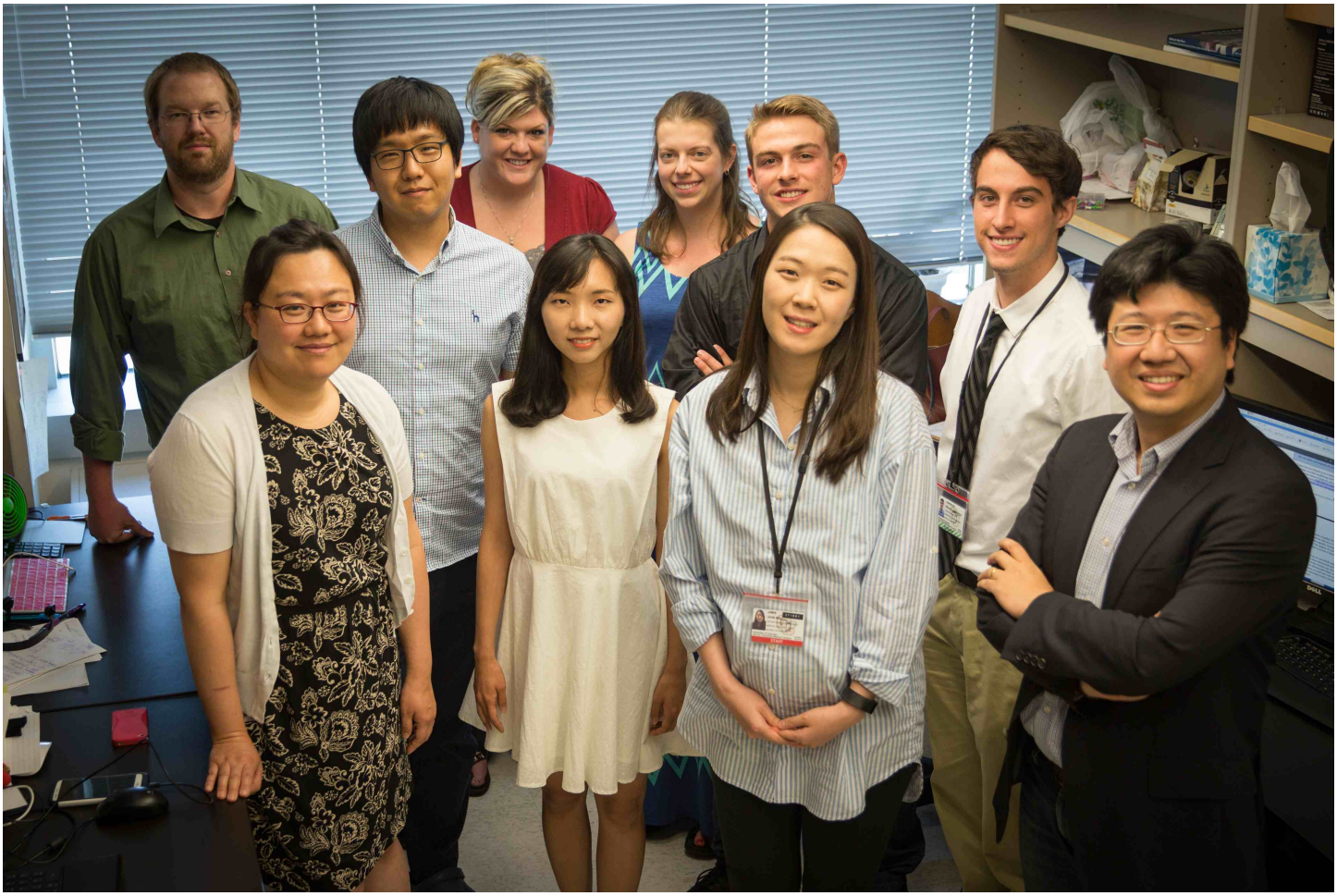
A REVIEW OF 2015

http://tanlab.ucdenver.edu

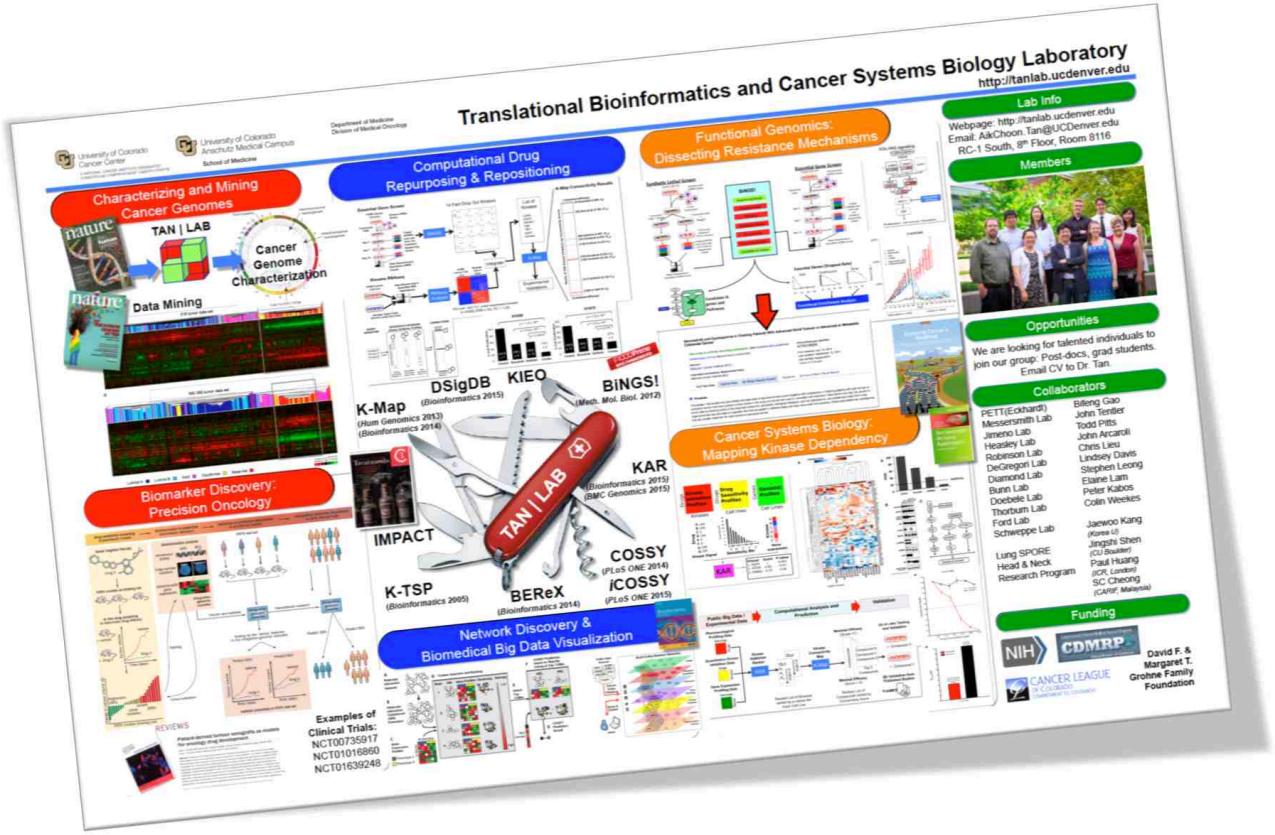
Dear Colleagues and Friends,

As 2015 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. The **Tan Lab** has much to celebrate in 2015.

Personnel: We welcome **Jennifer Hintzsche** (Jan 2015) and **Brian Jackson** (May 2015) as new post-doctoral research fellows in our lab. Jenn and Brian will be focusing on melanoma and head and neck cancer genomics, respectively. We hosted two visiting Ph.D. students from Prof. **Jaewoo Kang**'s lab at Korea University, **Kyubum Lee** (Aug 2014 – Feb 2015) and **Minji Jeon** (Mar 2015 – Aug 2015). Kyubum is developing new computational tools and resources to extract gene-variant-disease relations from full-text publications. Minji is devising new bioinformatics methods to predict drug responses from multiple omics data. We also hosted two Cancer Center Summer Fellows, **Harrison Pielke-Lombardo** (Applied Mathematics, University of Colorado-Boulder) and **Ryan Hays** (Computational Biology, Massachusetts Institute of Technology), in our lab. We also have the opportunity to host Prof. **Dong-Hoon Shin** (Oct 2014 – June 2015) from the Seoul National University while he is doing his sabbatical leave in learning bioinformatics in our lab.

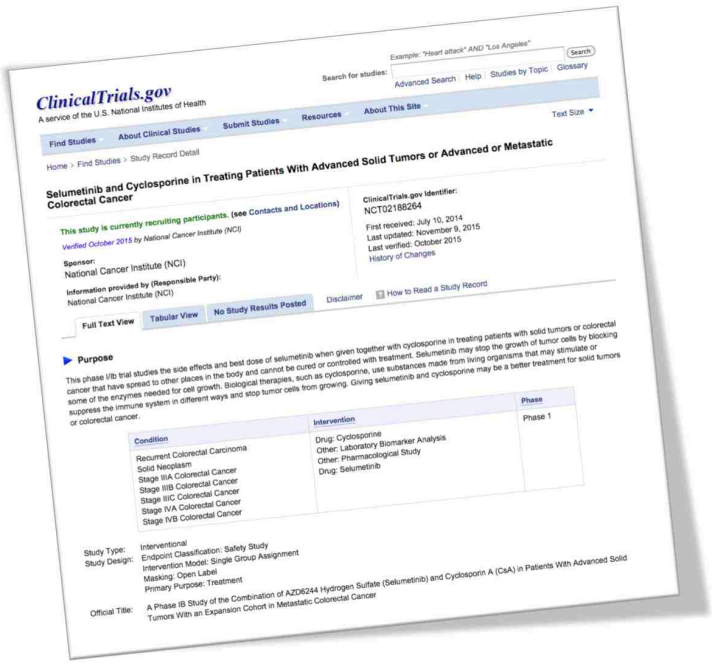


Tan Lab (Summer 2015): *Back (L-R)*: Brian, Jenn and Karen. *Middle (L-R)*: Minjae, Ryan and Harrison. *Front (L-R)*: Jihye, Minji, Jimin and AC.



Tan Lab Poster 2015.

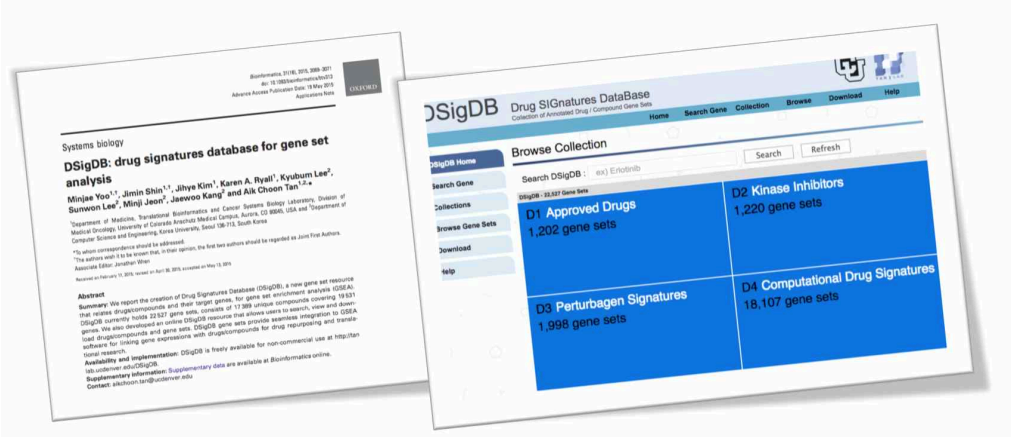
Research: We continued to participate in and contribute to several high impact cancer research projects. In collaboration with the **PETT** lab members (**Eckhardt**, **Pitts**, **Tentler**, **Leong**, **Lieu**), we performed genome-wide synthetic lethality screens to identify rational combination partner with Selumetinib in KRAS-mutant colorectal cancer (CRC). Using a novel bioinformatics platform BiNGS! (developed by **Jihye** and **AC**) for the analysis of synthetic lethal screens together with integrating the results with unbiased gene set enrichment analysis, we unraveled the non-canonical Wnt/Ca++ signaling pathway as a potential mediator of resistance to Selumetinib. This key finding led to an evaluation of the rational combination of selumetinib and WNT pathway modulators (cyclosporin A) and demonstrated synergistic antiproliferative effects in *in vitro* and *in vivo* models of CRC. Importantly, this combination not only showed tumor growth inhibition but also tumor regression in the more clinically relevant patient-derived tumor xenograft (PDX) models of KRAS-mutant CRC. These results strengthen the hypothesis that targeting both the MEK and Wnt pathways may be a clinically effective rational combination strategy for patients with metastatic CRC. More importantly, this study has now translated into a Phase I/IB clinical trial as an Investigator Initiated Trial at the University of Colorado Cancer Center Clinic (clinicaltrials.gov#: NCT02188264).



This year, we have developed and published several novel computational tools for translational bioinformatics and cancer systems biology research.

1. **DSigDB**. Drug Signatures Database (DSigDB) is a new gene set resource that relates drugs/compounds and their target genes, for gene set enrichment analysis. DSigDB currently holds 22,527 gene sets, consists of 17,389 unique compounds covering 19,531 genes. We also developed an online DSigDB resource that allows users to search, view, and download drugs/compounds and gene sets. DSigDB gene sets provide seamless integration to GSEA software for linking gene expressions with drugs/compounds for drug repurposing and translational research. DSigDB is freely available for non-commercial use at http://tanlab.ucdenver.edu/DSigDB.

   Reference: Yoo M*, Shin J*, Kim J, Ryall KA, Lee K, Lee S, Jeon M, Kang J, Tan AC. (2015). DSigDB: Drug Signatures Database for Gene Set Analysis. ***Bioinformatics***. 31(18): 3069-3071. [PMID: 25990557].



Left: DSigDB paper published in Bioinformatics. Right: DSigDB web resource (http://tanlab.ucdenver.edu/DSigDB).

2. **KAR**. Kinase Addiction Ranker (KAR) is an algorithm that integrates high-throughput drug screening data, comprehensive kinase inhibition data and gene expression profiles to identify kinase dependency in cancer cells. KAR is available to download at: http://tanlab.ucdenver.edu/KAR/. We illustrated the integration of **KAR** and **K-Map** in dissecting kinase dependency and predicting drugs in triple negative breast cancer.

   Reference: Ryall KA, Shin J, Yoo M, Hinz TK, Kim J, Kang J, Heasley LE, Tan AC. (2015). Identifying kinase dependency in cancer cells by integrating high-throughput drug screening and kinase inhibition data. ***Bioinformatics***. 31(23):3799-3806. [PMID: 26206305].
   Ryall KA, Kim J, Klauck PJ, Shin J, Yoo M, Ionkina A, Pitts TM, Tentler JJ, Diamond JR, Eckhardt SG, Heasley LE, Kang J, Tan AC. (2015). An integrated bioinformatics analysis to dissect kinase dependency in triple negative breast cancer. ***BMC Genomics***. 16 (Suppl 12):S2. [PMID: 26681397].

Left: KAR paper published in Bioinformatics. Right: Integrating KAR and K-MAP for TNBC research.

3. **iCOSSY**. COntext-Specific Subnetwork discoverY. COSSY is an algorithm to discover important subnetworks differentiating between two phenotypes (context). It automatically finds differentially expressed subnetworks of closely interacting molecules from molecular interaction networks (such as KEGG or STRING) using gene expression profiles. This is the first non-greedy approach of its kind. COSSY works for any interaction network regardless of the network topology. iCOSSY is a web server that finds subnetworks that are differentially expressed in two phenotypes, based on the concept of COSSY. Users can upload their gene expression datasets, and discover important subnetworks of closely interacting molecules to differentiate between two phenotypes (context). They can also interactively visualize the resulting subnetworks. iCOSSY can be accessed at: http://icossy.korea.ac.kr/.


PLOS ONE

RESEARCH ARTICLE

iCOSSY: An Online Tool for Context-Specific Subnetwork Discovery from Gene Expression Data

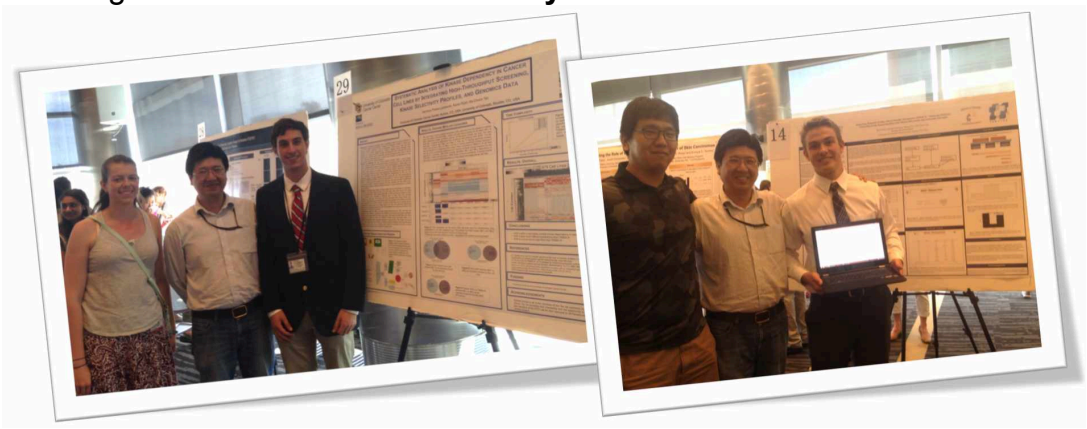
Abstract

Introduction

Reference: Saha A, Jeon M, Tan AC, Kang J. (2015). iCOSSY: an online tool for context-specific subnetwork discovery from gene expression data. PLoS ONE. 10(7): e0131656. [PMID: 26147457].

We continued to contribute and collaborate with the **PETT** and **Messersmith** labs (colorectal cancer), **Jimeno** Lab (head and neck cancer), **DeGregori** Lab (cancer and aging), **Heasley** Lab (FGFR signaling), **Diamond** Lab (triple negative breast cancer), **Ford** Lab (SIX1/EMT), **Robinson** Lab (melanoma), **Schweppe** Lab (thyroid cancer), **Thorburn** lab (autophagy and cancer). We have established new collaboration with **Paul Huang** (**Institute of Cancer Research, London, UK**) in the understanding of kinase reprogramming in cancer as a resistance mechanism to targeted therapies. We continued to collaborate with Prof. **Jaewoo Kang** at the Korea University in developing new computational tools for extracting highly relevant and precise entity-relations from literature. We also continued to collaborate with Prof. **Sok Ching Cheong** at the Cancer Research Malaysia in identifying new druggable targets in oral cancer. We look forward to these exciting collaborations in the coming years!

Presentations: Our Cancer Center Summer Fellows, **Harrison** and **Ryan** presented their research at the annual fellows poster day. **Harrison** was working with **Karen Ryall** to systematically characterize the kinase-dependency in a large panel of cancer cell lines using Kinase Addiction Ranker (**KAR**). **Ryan** was working with **Jenn** to develop a web portal for integrating and visualizing melanoma genomics data. Congratulations to **Harrison** and **Ryan**!



Left: Karen, AC and Harrison with his poster. *Right*: Minjae, AC and Ryan with his poster.

AC has presented our research to several Korean universities (Korea University, Korea University Medical Center, Soongsil University, Sookmyung Women's University) as a visiting professor of the Korea University.

Karen presented the integration of KAR and K-Map paper at the the 1st Joint Conference of Genome Informatics Workshop (GIW) and International Conference on Bioinformatics (InCOB) in Tokyo, Japan. This is Karen's first trip to Asia, and she visited Korea University (Prof. **Jaewoo Kang**'s lab) en-route to Tokyo. **AC** also attended the conference and experienced the earthquake in Japan.

Left: Karen presenting at the GIW/InCOB 2015. *Middle*: Tokyo view from Odaiba. *Right*: Earthquake.

Grants and Funding: **Jenn** and **Karen** were awarded research grants from the Cancer League of Colorado. Following the tradition of the Tan lab, both of them have the chance to celebrate with a sparkling "juice". For the CLC project, Jenn will be researching the resistance mechanisms of drug combination in melanoma. Karen will be studying the kinome reprogramming in non-small cell lung cancer upon drug treatment. We thank the Cancer League of Colorado for their continuous supports to our research.

Left: Jenn getting some helps from Jaewoo and Bryan in opening up her bottle, first-timer. *Right*: Karen is very careful in opening up her bottle.

AC and **Paul Huang** received an international exchange grant from the Royal Society to initiate collaborative research between our labs. We would like to congratulate to our valuable collaborators on securing new grants this past year: **Scott Cramer** (R21), **Stephen Malkoski** (R21), and **Andrew Thorburn** (R01). We will continue to write and submit proposals for this coming year! We also like to acknowledge the generous support from the David F. and Margaret T. Grohne Family Foundation to our research. Thank you for supporting our research!

***Publications*:** This past year, we have published 20 papers. According to Google Scholar, we have accrued more than 800 citations in 2015 related to the publications of our lab. We look forward for another productive year! Go Tan Lab!

1. Song EK, Tai W, Messersmith WA, Bagby S, Purkey A, Quackenbush KS, Pitts TM, Wang G+, Blatchford P, Yahn R, Kaplan J, **Tan AC**, Atreya CE , Eckhardt G, Kelley RK, Venook A, Kwak EL, Ryan D, Arcaroli JJ. (2015). Potent antitumor activity of cabozantinib, a c-MET and VEGFR2 inhibitor, in a colorectal cancer patient-derived tumor explant model. ***International Journal of Cancer***. 136(8):1967-1975. [PMID: 25242168]. [PMCID: PMC4323738]

2. Micel LN, Tentler JJ, **Tan AC**, Selby HM+, Brunkow KL, Robertson KM, Davis SL, Klauck PJ+, Pitts TM, Gangolli E, Fabrey R, O'Connell SM, Vincent PW, Eckhardt SG. (2015). Antitumor Activity of the MEK Inhibitor TAK-733 Against Melanoma Cell Lines and Patient-Derived Tumor Explants. ***Molecular Cancer Therapeutics***. 14(2): 317-325. [PMID: 25376610].

3. Fleenor CJ, Rozhok AI, Zaberezhnyy V, Mathew D, Kim J+, **Tan AC**, Bernstein ID, DeGregori J. (2015). Contrasting Roles for C/EBPalpha and Notch in Irradiation-Induced Multipotent Hematopoietic Progenitor Cell Defects. ***Stem Cells*.** 33(4):1345-1358. [PMID: 25546133]. [PMCID: PMC4376650]

4. Petillo D, Orey S, **Tan AC**, Forsgren L, Khoo SK. (2015). Parkinson's Disease-related Circulating microRNA Biomarkers - a Validation Study. ***AIMS Medical Science***. 2(1): 7-14.

5. Ryall KA+, **Tan AC**. (2015). Systems Biology Approaches For Advancing The Discovery Of Effective Drug Combinations. ***J. Cheminformatics***. 7:7. [PMID: 25741385]. [PMCID: PMC4348553][***Highly Accessed Article***]

6. Drasin DJ, Guarnier AL, Neelakantan D, Kim J+, Cabrera JH, Wang CA, Zaberezhnyy V, Gasparini P, Cascione L, Huebner K, **Tan AC**, Ford HL. (2015). Twist1-induced microRNA-424 reversibly drives mesenchymal programming while inhibiting tumor initiation. ***Cancer Research*** 75(9): 1908-1921. [PMID: 25716682]. [PMCID: PMC4417413]

7. Tentler JJ, Ionkina A, **Tan AC**, Newton TP, Pitts TM, Glogowska MJ, Kabos P, Sartorius CA, Sullivan KD, Espinosa JM, Eckhardt SG, Diamond JD. (2015). p53 Family Members Regulate Phenotypic Response to Aurora Kinase A Inhibition in Triple-Negative Breast Cancer. ***Molecular Cancer Therapeutics***. 4(5):1117-1129. [PMID: 25758253]. [PMCID: PMC4425647]

8. Kleczko EK, Kim J+, Keysar SB, Heasley LR, Eagles-Soukup J, Simon M, Marshall ME, Singleton KR, Jimeno A, **Tan AC**, Heasley LE. (2015). An Inducible TGFB2-TGFBR Pathway Modulates the Sensitivity of HNSCC Cells to Tyrosine Kinase Inhibitors Targeting Dominant Receptor Tyrosine Kinases. ***PLoS ONE***. 10(5):e0123600. [PMID: 25946135]. [PMCID: PMC4422719].

9. Yonekawa T, Gamez G, Kim J+, **Tan AC**, Thorburn J, Gump J, Thorburn A, Morgan MJ. (2015). RIP1 Negatively Regulates Basal Autophagic Flux through TFEB to Control Sensitivity to Apoptosis. ***EMBO Reports***. 16:700-708. [Epub ahead of print, Apr 23, 2015] [PMID: 25908842].

10. Yoo M+*, Shin J+*, Kim J+, Ryall KA+, Lee K, Lee S, Jeon M, Kang J, **Tan AC**. (2015). DSigDB: Drug Signatures Database for Gene Set Analysis. ***Bioinformatics***. 31(18):3069-3071. [PMID: 25990557].

11. Göke F, Franzen A, Hinz TK, Marek LA, Yoon P, Sharma R, Bode M, von Mäessenhausen A, Lankat-Buttgereit B, Göke A, Golletz C, Kirsten R, Boehm D, Vogel W, Kleczko EK, Eagles JR, Hirsch FR, Van Bremen T, Bootz F, Schröck A, Kim J+, **Tan AC**, Jimeno A, Heasley LE, Perner S. (2015). FGFR1 expression levels predict BGJ398-sensitivity of FGFR1-dependent head and neck squamous cell cancers. ***Clinical Cancer Research***. 21(19): 4356-4364. [PMID: 26015511].

12. Davis EM, Kim J+, Menasche B, Sheppard J, Liu X, **Tan AC**, Shen J. (2015). Comparative haploid genetic screens reveal divergent pathways in the biogenesis of glycophosphatidylinositol-anchored proteins. ***Cell Reports***. 11(11):1727-1736. [PMID: 26074080].

13. Davis SL, Robertson KM, Pitts TM, Tentler JJ, Bradshaw-Pierce EL, Klauck PJ+, Bagby SM, Hyatt SL, Selby HM+, Spreafico A, Ecsedy JA, Arcaroli JJ, Messersmith WA, **Tan AC**, Eckhardt SG. (2015). Combined inhibition of MEK and Aurora A kinase in KRAS/PIK3CA double-mutant colorectal cancer models. ***Frontiers in Pharmacology***. 6:120. [PMID: 26136684].

14. Saha A, Jeon M, **Tan AC**, Kang J. (2015). iCOSSY: an online tool for context-specific subnetwork discovery from gene expression data. ***PLoS ONE***. 10(7): e0131656. [PMID: 26147457].

15. Ryall KA+, Kim J+, Klauck PJ+, Shin J+, Yoo M+, Ionkina A, Pitts TM, Tentler JJ, Diamond JR, Eckhardt SG, Heasley LE, Kang J, **Tan AC**. (2015). An integrated bioinformatics analysis to dissect kinase dependency in triple negative breast cancer. ***BMC Genomics***. 16 (Suppl 12):S2. [PMID: 26681397].

16. Ryall KA+, Shin J+, Yoo M+, Hinz TK, Kim J+, Kang J, Heasley LE, **Tan AC**. (2015). Identifying kinase dependency in cancer cells by integrating high-throughput drug screening and kinase inhibition data. ***Bioinformatics***. 31(23):3799-3806. [PMID: 26206305].

17. Singleton KR, Hinz TK, Kleczko EK, Marek LA, Kwak J, Harp T, Kim J+, **Tan AC**, Heasley LE. (2015). Kinome RNAi Screens Reveal Synergistic Targeting of mTOR and FGFR1 Pathways for Treatment of Lung Cancer and HNSCC. ***Cancer Research***. 75(20): 4398-4406. [PMID: 26359452].

18. Lieu CH, Klauck PJ+, Henthron PK, Tentler JJ, **Tan AC**, Spreafico A, Selby HM+, Britt BC, Bagby SM, Arcaroli JJ, Messersmith WA, Pitts TM, Eckhardt SG. (2015). Antitumor Activity of a Potent MEK Inhibitor, TAK-733, Against Colorectal Cancer Cell Lines and Patient Derived Xenografts. ***Oncotarget***. 6(33):34561-34572. [PMID: 26439693].

19. Henry C, Casas-Selves M, Kim J+, Zaberezhnvv V, Aghili L, Daniel A, Jimenez L, Azam T, McNamee EN, Clambey E, Klawitter J, Serkova N, **Tan AC**, Dinarello C, DeGregori J. (2015). Aging-associated inflammation promotes selection for adaptive oncogenic events in B-progenitors. ***The Journal of Clinical Investigation***. 125(12):4666-4680. [PMID: 26551682].

20. Towers CG, Guarnieri AL, Micalizzi DS, Harrell JC, Gillen AE, Kim J+, Wang CA, Oliphant MUJ, Drasin DJ, Guney MA, Kabos P, Sartorius CA, **Tan AC**, Perou CM, Espinosa JM, Ford HL. (2015). The Six1 oncoprotein downregulates p53 via concomitant regulation of RPL26 and microRNA-27-a-3p. ***Nature Communications***. 6:10077. [PMID: 26687066].

Lab Social Activities and Celebrations: Dim sum lunch to celebrate the acceptance of DSigDB in *Bioinformatics*.

Left: Group picture, Cheers! *Right*: Dim sum, yummy!

Sushi dinner to celebrate the acceptance of two KAR papers: KAR method (*Bioinformatics*) and its applications in triple negative breast cancer (*BMC Genomics*). Karen presented the TNBC paper in the 1st Joint Conference of Genome Informatics Workshop (GIW) and International Conference on Bioinformatics (InCOB) in Tokyo, Japan.

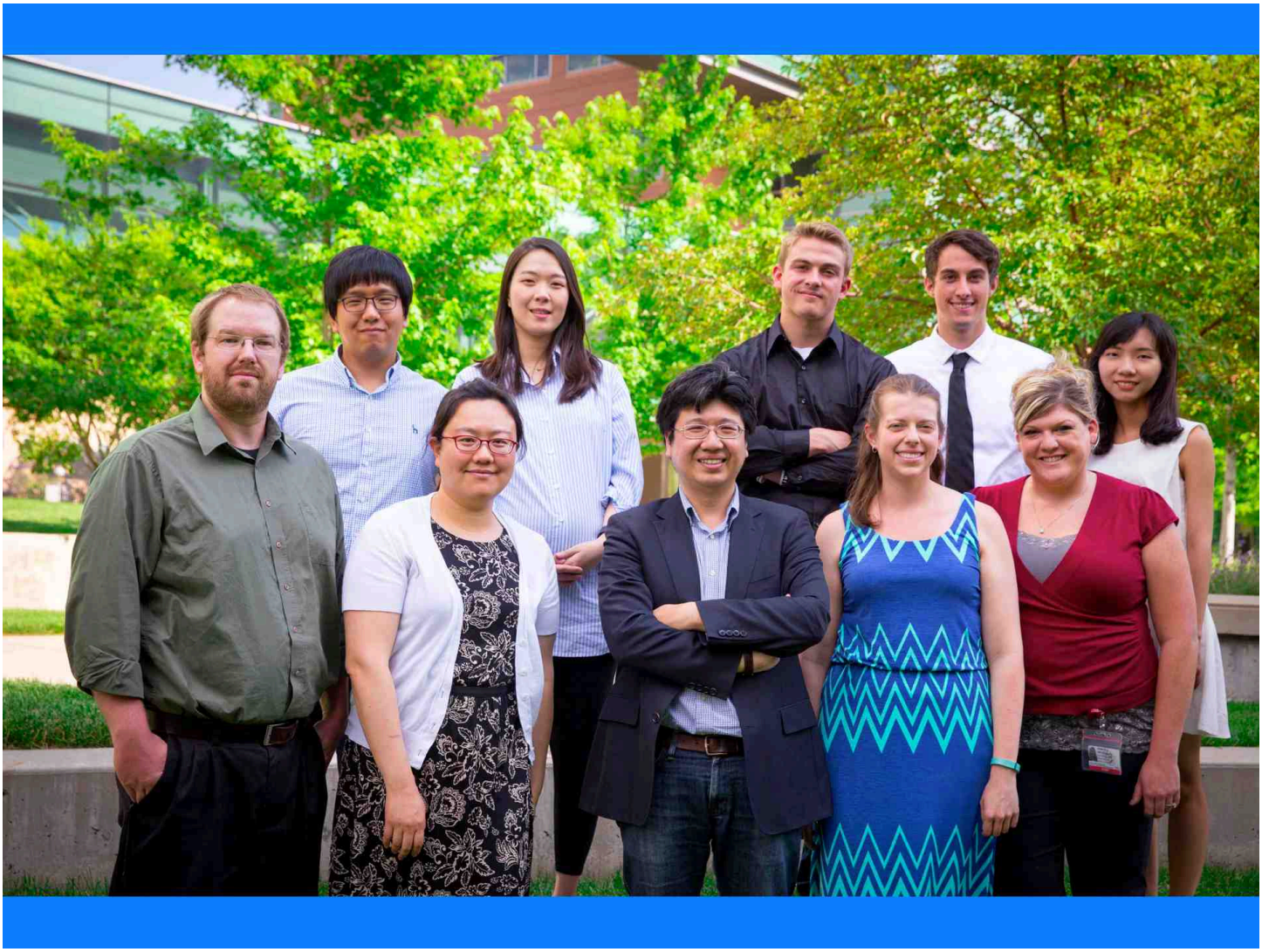
Left: Karen and Jimin. *Middle*: Sushi!! *Right*: Group picture, Cheers!

We also hosted farewell parties for: Kyubum (Mexican foods in Feb), Dr. Shin (Korea BBQ in June) and Minji (American BBQ in August).

Baby: **Minjae** and **Jimin** welcome their first baby boy **Jeremy Junho Yoo** in Sept 2015, Congratulations **Minjae** and **Jimin**!

With some good science in the works and the great collaborations with our colleagues, I am sure that 2016 will be another exciting and good year for the lab. Thank you all for your hard work and I look forward to working together with you in the year ahead.

Aik Choon Tan, Ph.D.
Associate Professor
Director, Translational Bioinformatics and Cancer Systems Biology Lab
December 30, 2015.



We only focus on the research that matters! The Tan Lab will continue to address challenging problems in cancer research by harnessing the power of big data and developing novel and innovative computational methods.

Support Our Research and Contact Us

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