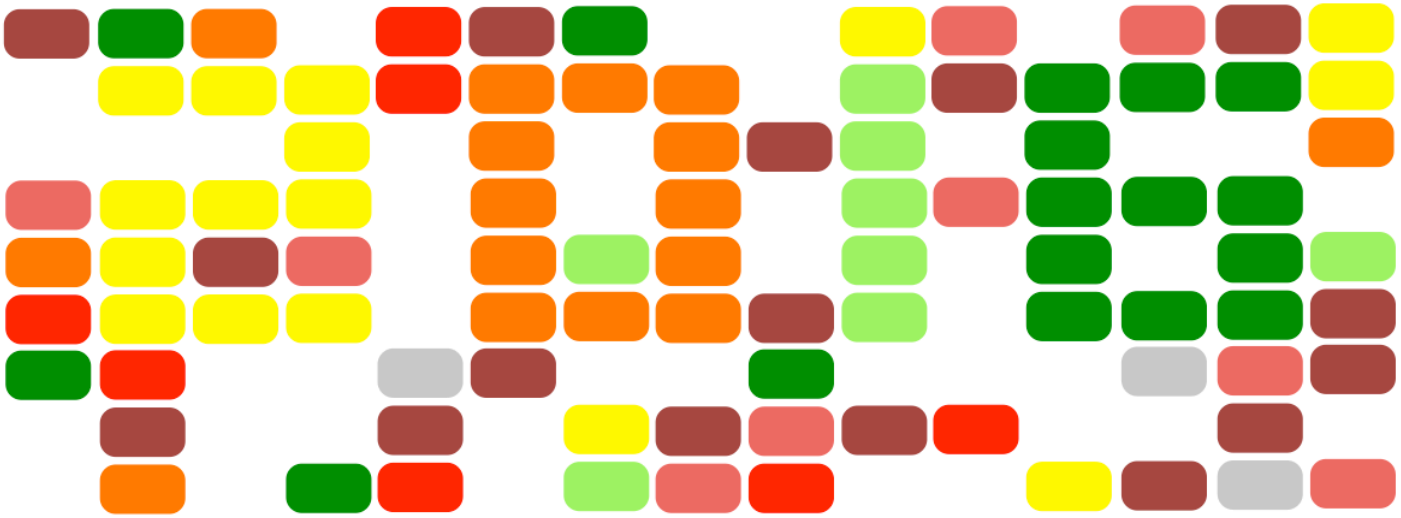


A REVIEW OF 2016

ONE YEAR
366 DAYS
TEN STORIES

TAN | LAB

http://tanlab.ucdenver.edu

Dear Colleagues and Friends,

As 2016 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.

The **Tan Lab** has much to celebrate in 2016. 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!

Personnel: We welcome **Kelsey Wuensch** and **Paul Francoeur** to join our lab as graduate student (Cancer Biology Graduate Program) and research assistant, respectively. Congratulations to **Jennifer Hintzsche** as she is promoted to **Research Associate** (Oct). We hosted two rotation/project students: **Mindy Szeto** (MSTP) and **Callie Federer** (Computational Bioscience) in our lab. We bid farewell and wish good luck to **Karen Ryall** and **Peter Klacuk** this year. Karen joined a company as data scientist and Peter is starting his Medical School here in CU. We also hosted our collaborator Dr. **Paul Huang** (Institute of Cancer Research, London, UK) and Prof. **Jaewoo Kang** (Korea University) for their visits in our lab.

Tan Lab Members (Aug 2016). (L-R) Minjae Yoo, Jimin Shin, Karen Ryall, Kelsey Wuensch, Brian Jackson, Jihye Kim, Paul Francoeur, AC, Jennifer Hintzsche.

2016 RESEARCH HIGHLIGHTS OF TAN | LAB

Extracts from selected articles published this year

IMPACT: WHOLE-EXOME SEQUENCING ANALYSIS PIPELINE TO ID CANCER VARIANTS AND MATCH PATIENTS TO DRUGS

(**Hintzsche et al**, ***Journal of the American Medical Informatics Association***, 2016, 23(4): 721-730)

With the advancement of next-generation sequencing technologies, it is becoming common practice to obtain somatic variants from whole-exome sequencing (WES) for individual cancer patients. However, there is a disconnect between finding a patient's relevant molecular profile and predicting actionable therapeutics. We have developed **IMPACT** (**I**ntegrating **M**olecular **P**rofiles with **AC**tionable **T**herapeutics), a novel WES analysis pipeline that links variants detected from WES to actionable therapeutics. The IMPACT pipeline contains four analytical modules: detecting somatic variants, calling copy number alterations, predicting drugs against deleterious variants, and analyzing tumor heterogeneity. We tested the IMPACT pipeline on whole-exome sequencing data in The Cancer Genome Atlas (TCGA) lung adenocarcinoma samples with known EGFR mutations, and correctly detected these mutations. We also used IMPACT to analyze melanoma patient tumor samples before treatment, after BRAF-inhibitor treatment, and after BRAF- and MEK-inhibitor treatment. For the melanoma patient samples, we identified NRAS p.Q61K as an acquired resistance mutation to BRAF-inhibitor treatment. We also identified CDKN2A deletion as a novel acquired resistance mutation to BRAFi/MEKi inhibition. The IMPACT analysis pipeline predicts these somatic variants to actionable therapeutics. We observed the clonal dynamic in the tumor samples after various treatments. We showed that IMPACT not only helped in successful prioritization of clinically relevant variants but also linked these variations to possible targeted therapies. In summary, we demonstrated that IMPACT as a new bioinformatics strategy to delineate candidate somatic variants and actionable therapies from WES data. This approach can be applied to other patient tumor samples to discover effective drug targets for personalized medicine. Read the accompanying press release from the University of Colorado Cancer Center (http://goo.gl/tDrgVZ) and GenomeWeb interview (http://goo.gl/IOUfSx). We have used IMPACT pipeline to analyze > 700 WES in 2016. **IMPACT** is publicly available at http://tanlab.ucdenver.edu/IMPACT.

IMPACT: a whole-exome sequencing analysis pipeline for integrating molecular profiles with actionable therapeutics in clinical samples

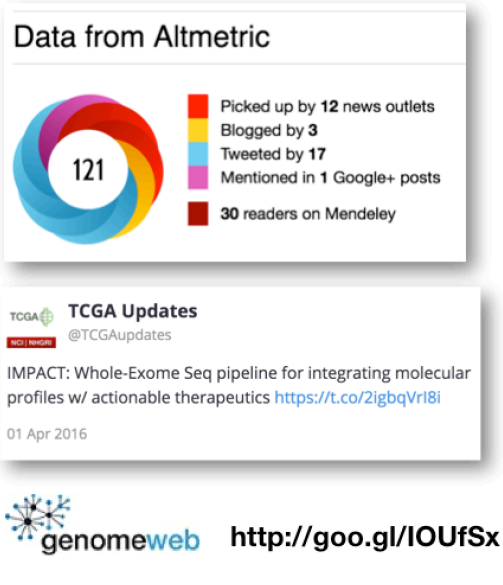
RECEIVED 31 August 2015
REVISED 18 December 2015
ACCEPTED 1 February 2016

AMIA OXFORD UNIVERSITY PRESS

Jennifer Hintzsche,[1] Jihye Kim,[1,7] Vinod Yadav,[2] Carol Amato,[1] Steven E Robinson,[1] Eric Seelenfreund,[1] Yiqun Shellman,[3,7] Joshua Wisell,[4,7] Allison Applegate,[1] Martin McCarter,[5,7] Neil Box,[3,7] John Tentler,[1,7] Subhajyoti De,[2,6,7] William A Robinson,[1,7,*] Aik Choon Tan[1,6,7,*]

ABSTRACT

Objective Currently, there is a disconnect between finding a patient's relevant molecular profile and predicting actionable therapeutics. Here we develop and implement the Integrating Molecular Profiles with Actionable Therapeutics (IMPACT) analysis pipeline, linking variants detected from whole-exome sequencing (WES) to actionable therapeutics.
Methods and materials The IMPACT pipeline contains 4 analytical modules: detecting somatic variants, calling copy number alterations, predicting drugs against deleterious variants, and analyzing tumor heterogeneity. We tested the IMPACT pipeline on whole-exome sequencing data in The Cancer Genome Atlas (TCGA) lung adenocarcinoma samples with known EGFR mutations. We also used IMPACT to analyze melanoma patient tumor samples before treatment, after BRAF-inhibitor treatment, and after BRAF- and MEK-inhibitor treatment.
Results IMPACT Food and Drug Administration (FDA) correctly identified known EGFR mutations in the TCGA lung adenocarcinoma samples. IMPACT linked these EGFR mutations to the appropriate FDA-approved EGFR inhibitors. For the melanoma patient samples, we identified NRAS p.Q61K as an acquired resistance mutation to BRAF-inhibitor treatment. We also identified CDKN2A deletion as a novel acquired resistance mutation to BRAFi/MEKi inhibition. The IMPACT analysis pipeline predicts these somatic variants to actionable therapeutics. We observed the clonal dynamic in the tumor samples after various treatments. We showed that IMPACT not only helped in successful prioritization of clinically relevant variants but also linked these variations to possible targeted therapies.
Conclusion IMPACT provides a new bioinformatics strategy to delineate candidate somatic variants and actionable therapies. This approach can be applied to other patient tumor samples to discover effective drug targets for personalized medicine.
IMPACT is publicly available at http://tanlab.ucdenver.edu/IMPACT.



Data from Altmetric

121

Picked up by **12** news outlets
Blogged by **3**
Tweeted by **17**
Mentioned in **1** Google+ posts
30 readers on Mendeley

TCGA Updates
@TCGAupdates

IMPACT: Whole-Exome Seq pipeline for integrating molecular profiles w/ actionable therapeutics https://t.co/2igbqVrI8i

01 Apr 2016

genomeweb **http://goo.gl/IOUfSx**

BRONCO: MANUAL CURATED FULL-TEXT CORPUS FOR CANCER GENE-VARIANT-DISEASE-DRUG RELATIONS


DATABASE

Database, 2016, 1–13
doi: 10.1093/database/baw043
Original article

Original article

BRONCO: Biomedical entity Relation ONcology COrpus for extracting gene-variant-disease-drug relations

Kyubum Lee[1], Sunwon Lee[1], Sungjoon Park[1], Sunkyu Kim[1], Suhkyung Kim[1], Kwanghun Choi[1], Aik Choon Tan[2,*] and Jaewoo Kang[1,*]

[1]Department of Computer Science and Engineering, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul, 02841 Korea and [2]Translational Bioinformatics and Cancer Systems Biology Laboratory, Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, 12801 East 17th Avenue Aurora, CO 80045, USA

*Corresponding author: Email: kangj@korea.ac.kr, Correspondence may also be addressed to Aik Choon Tan. Email: aikchoon.tan@ucdenver.edu

Citation details: Lee,K., Lee,S., Park,S. *et al.* BRONCO: Biomedical entity Relation ONcology COrpus for extracting gene-variant-disease-drug relations. *Database* (2016) Vol. 2016: article ID baw043; doi:10.1093/database/baw043

Received 3 October 2015; Revised 9 March 2016; Accepted 9 March 2016

Comprehensive knowledge of genomic variants in a biological context is key for precision medicine. As next-generation sequencing technologies improve, the amount of literature containing genomic variant data, such as new functions or related phenotypes, rapidly increases. Many researchers focus on creating an improved automated biomedical natural language processing method that extracts useful variants and their functional information from the literature. However, there is no gold-standard data set that contains texts annotated with variants and their related functions. To overcome these limitations, we introduce a Biomedical entity Relation ONcology COrpus (BRONCO) that contains more than 400 variants and their relations with genes, diseases, drugs and cell lines in the context of cancer and anti-tumor drug screening research. The variants and their relations were manually extracted from 108 full-text articles. BRONCO can be utilized to evaluate and train new methods used for extracting biomedical entity relations from full-text publications, and thus be a valuable resource to the biomedical text mining research community. BRONCO is freely available at http://infos.korea.ac.kr/bronco. The Denver Broncos (the American Football team) also won the 50th Super Bowl (Champion) this year! Go BRONCO(s)! This is a collaborative research with Prof. **Jaewoo Kang** lab at the Korea University.

(**Lee et al**, ***DATABASE***, 2016, 2016:baw043)

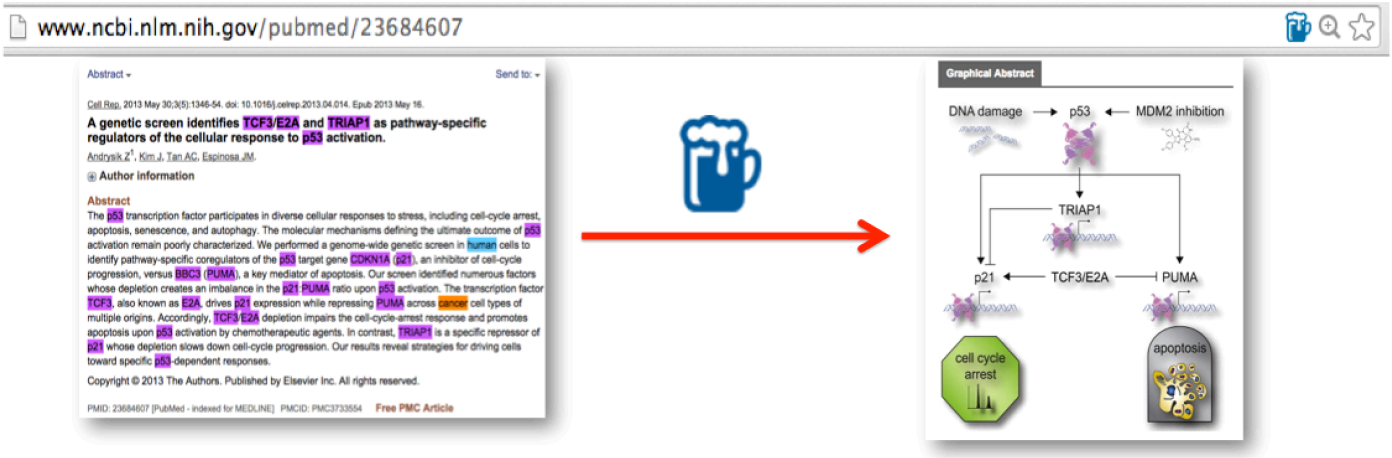
BEST: NEXT-GENERATION BIOMEDICAL ENTITY SEARCH TOOL FOR KNOWLEDGE DISCOVERY FROM BIOMEDICAL LITERATURE

(**Lee, Kim et al**, ***PLOS ONE***, 2016, 11(10): e016468)

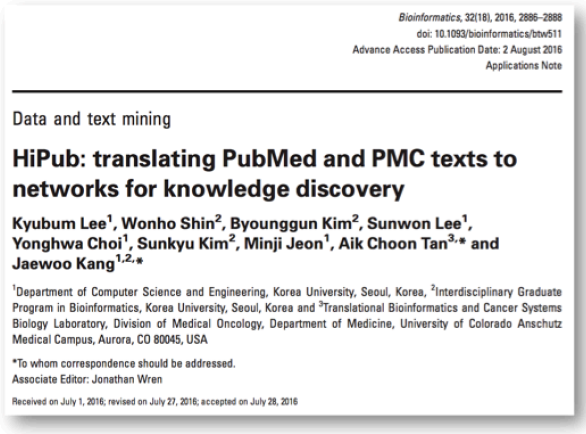
As the volume of publications rapidly increases, searching for relevant information from the literature becomes more challenging. To complement standard search engines such as PubMed, it is desirable to have an advanced search tool that directly returns relevant biomedical entities such as targets, drugs, and mutations rather than a long list of articles. Some existing tools submit a query to PubMed and process retrieved abstracts to extract information at query time, resulting in a slow response time and limited coverage of only a fraction of the PubMed corpus. Other tools preprocess the PubMed corpus to speed up the response time; however, they are not constantly updated, and thus produce outdated results. Further, most existing tools cannot process sophisticated queries such as searches for mutations that co-occur with query terms in the literature. To address these problems, we introduce BEST, a biomedical entity search tool. BEST returns, as a result, a list of 10 different types of biomedical entities including genes, diseases, drugs, targets, transcription factors, miRNAs, and mutations that are relevant to a user's query. To the best of our knowledge, BEST is the only system that processes free text queries and returns up-to-date results in real time including mutation information in the results. BEST is freely accessible at http://best.korea.ac.kr. This is another collaborative research with Prof. **Kang** lab at the Korea University.

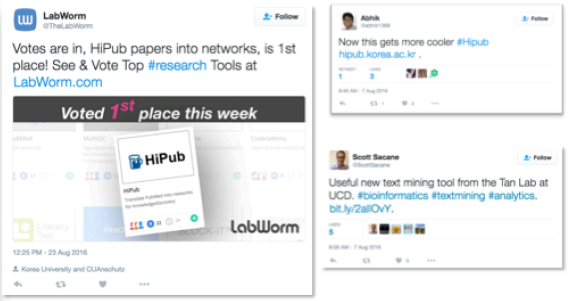
HiPub: TRANSLATING PUBMED AND PMC TEXTS TO NETWORKS FOR KNOWLEDGE DISCOVERY

(**Lee et al**, ***Bioinformatics***, 2016, 32(18): 2886-2888)



Every biomedical research paper is a story about the interactions between genes, proteins or drugs in a specific biological context. New hypotheses could be formulated by mining these papers follow by performing new sets of experiments to validate (or refute) hypotheses in the knowledge discovery process. However, the volume and rate of current biomedical publications are far larger and more rapid than our ability to extract and use them in this knowledge discovery cycle. It is impossible for researchers to manually go through all the records to extract relevant information for their research. To address these challenges, we developed HiPub, a novel Chrome browser plug-in that automatically highlights, annotates and translates biomedical entities (e.g. genes, proteins, drugs and diseases) from texts into networks for knowledge discovery. The text mining technology was based on the combination of BEST search engine and PubTator; whereas the visualization component is best on BEReX (Jeon et al, Bioinformatics 2014). HiPub provides functional enrichment analysis, and link-out option for users to further explore the interactions between biomedical entities. Since its publication, HiPub has been downloaded by >700 users to assist their research. HiPub is freely available in http://hipub.korea.ac.kr. Read a related press release on HiPub in http://goo.gl/OehO06. We hope that HiPub will be a practical tool that bridges the text mining and biomedical research communities. We will continue to enhance the functionality of HiPub in 2017. Stay tuned!

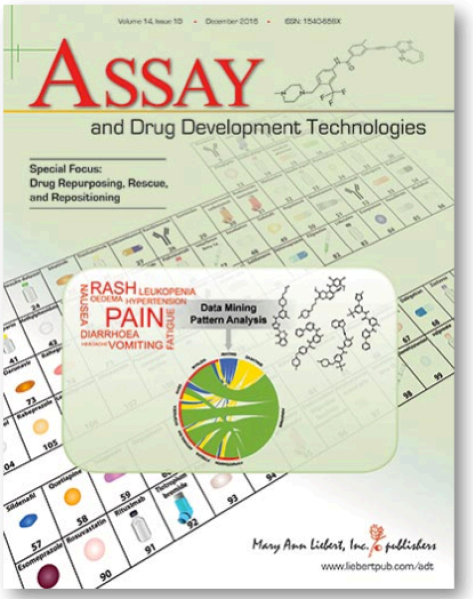


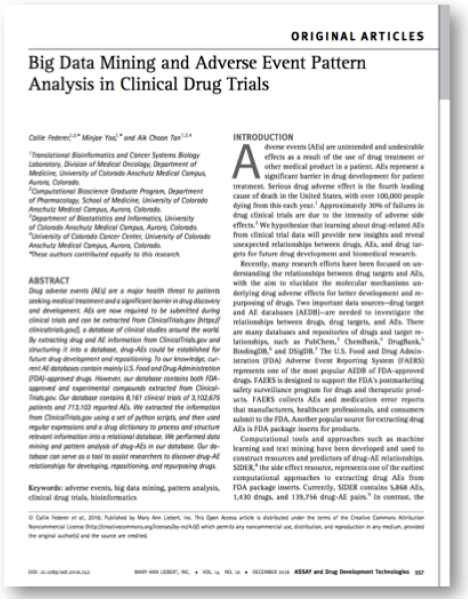


BIG DATA MINING OF DRUG – ADVERSE EVENT RELATIONSHIPS FROM CLINICAL DRUG TRIALS

(**Federer et al**, ***ASSAY and Drug Development Technologies***, 2016, 14(10): 557-566)

Serious drug adverse effect (AE) is the fourth leading cause of death in the United States, with over 100,000 people dying from this each year. Trial data reported in ClinicalTrials.gov are a new source of big data for biomedical research, as ClinicalTrials.gov currently holds more than 217,000 studies in its registry. To understand the patterns of AEs reported in clinical trials, we performed "big data mining" on the published results from the ClinicalTrials.gov website. We extracted drug-AE relationships from 8,161 clinical trials, in which more than 3 million individuals participated. A total of 1,248 drugs and a total of 31,267 AEs were extracted from these trials. The AEs extracted from these trials span across 26 AE categories. To facilitate data analysis, we have developed AEDB to store and manage the drugs and AEs extracted from ClinicalTrials.gov. We performed PRRs for comparing the AEs of five common kinase inhibitors with those of other drugs in the database. We found that the signal in the AEs with higher frequencies and the results were corroborated by published studies. Our database can serve as a tool to assist researchers in discovering drug-AE relationships for developing, repositioning, and repurposing drugs. Our paper was selected as the **COVER** for the ***ASSAY and Drug Development Technologies*** Special Issue of Drug Repurposing, Rescue and Repositioning!




ORIGINAL ARTICLES

Big Data Mining and Adverse Event Pattern Analysis in Clinical Drug Trials

NOVEL PRECLINICAL MODELS FOR CANCER RESEARCH

(**Morton *et al***, ***Oncogene***, 2016, 35: 290-300; **Hidayatullah Fadlullah et al**, ***Oncotarget***, 2016, 7(19):27802-27818, **Bagby *et al***, ***The Journal of Visualized Experiments***, 2016, 115: e54393.)

Patient-derived xenografts (PDXs) and cancer cell lines are important preclinical models to study the relationships between genomic alterations of tumors, and therapeutic dependencies. In collaboration with the **Jimeno** lab, we have developed XactMice – a novel humanizing mouse bone marrow that enables microenvironment reconstitution in head and neck cancer PDX models (Morton et al ***Oncogene*** 2016). We also collaborated with the Oral Cancer Team (Prof. **Sok Ching Cheong**) in the Cancer Research Malaysia for generating and characterizing a new panel of oral cancer cell lines as preclinical model in this disease (Hidayatullah Fadlullah et al ***Oncotarget*** 2016). We also published a video on the generation and maintenance of PDX for developmental therapeutics (Bagby et al ***JoVE*** 2016), check out the cool video (http://goo.gl/G0QkvC)!

SPREADING OF BREAST CANCER RISK PREDICTED BY TWO GENES

(**Todd, Ryall, Vyse et al**, ***Oncotarget***, 2016, 14(10): 557-566)


Katie Gibbons

August 18 2016, 12:01am, The Times

THE TIMES

Risk of breast cancer spreading predicted by two genes

Scientists have found that a pattern of activity in two genes determines whether a woman is more likely to die from breast cancer within ten years

ISTOCKPHOTO

THE TIMES (http://goo.gl/VAw3uh).

Tumor cell-extracellular matrix (ECM) interactions are fundamental for discrete steps in breast cancer progression. In particular, cancer cell adhesion to ECM proteins present in the microenvironment is critical for accelerating tumor growth and facilitating metastatic spread. A gene expression signature that defines a subset of cell lines displaying impaired adhesion to laminin was identified through a systematic phenotypic screen of a panel of human HER2 amplified breast cancer cell lines across six ECM proteins commonly deregulated in breast cancer. Cells with impaired laminin adhesion showed an enrichment in genes associated with cell motility and molecular pathways linked to cytokine signaling and inflammation. Evaluation of this gene set in the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) cohort of 1,964 patients identifies the F12 and STC2 genes as independent prognostic factors for overall survival in breast cancer. Our study demonstrates the potential of in vitro cell adhesion screens as a novel approach for identifying prognostic factors for disease outcome. This is a collaborative research with Dr. Paul Huang and his team at the Institute of Cancer Research, London, UK. Read more about this in **THE TIMES** (http://goo.gl/VAw3uh).

NEW DRUG COMBINATION TO TARGET MALIGNANT RHABDOID TUMORS

(**Wong, Todd, et al**, ***Cell Reports***, 2016, 17(5):1265-1275.)


theguardian

Cancer research

The Guardian (http://goo.gl/8JjNPJ)

Scientists find 'chink in armour' of aggressive childhood cancer

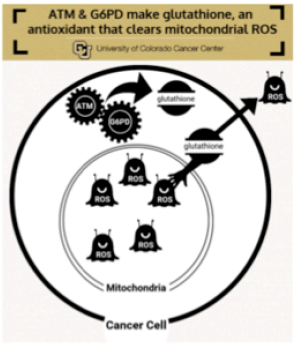
Researchers believe they have found way to treat malignant rhabdoid tumours, which can kill children within months of diagnosis

Grace Kelly was diagnosed with malignant rhabdoid tumours two years ago and 'went from being a happy, healthy schoolgirl to passing away within three weeks', her mother said. Photograph: Grace Kelly Ladybird Trust

Malignant rhabdoid tumors (MRTs) are lethal pediatric cancers characterized by a deficiency in the SWI/SNF subunit SMARCB1. Here, we employ an integrated molecular profiling and chemical biology approach to demonstrate that the receptor tyrosine kinases (RTKs) PDGFRα and FGFR1 are coactivated in MRT cells and that dual blockade of these receptors has synergistic efficacy. Inhibitor combinations targeting both receptors and the dual inhibitor ponatinib suppress the AKT and ERK1/2 pathways leading to apoptosis. MRT cells that have acquired resistance to the PDGFRα inhibitor pazopanib are susceptible to FGFR inhibitors. We show that PDGFRα levels are regulated by SMARCB1 expression, and assessment of clinical specimens documents the expression of both PDGFRα and FGFR1 in rhabdoid tumor patients. Our findings support a therapeutic approach in cancers with SWI/SNF deficiencies by exploiting RTK coactivation dependencies. This is another collaborative research with Dr. Paul Huang and his team at the Institute of Cancer Research, London, UK. Read more about this in **THE GUARDIAN** (http://goo.gl/8JjNPJ).

ADDING OXIDATIVE STRESS TO FLT3 INHIBITION PROVES PROMISING COMBINATION AGAINST ACUTE MYELOID LEUKEMIA


ATM/G6PD-driven redox metabolism promotes FLT3 inhibitor resistance in acute myeloid leukemia

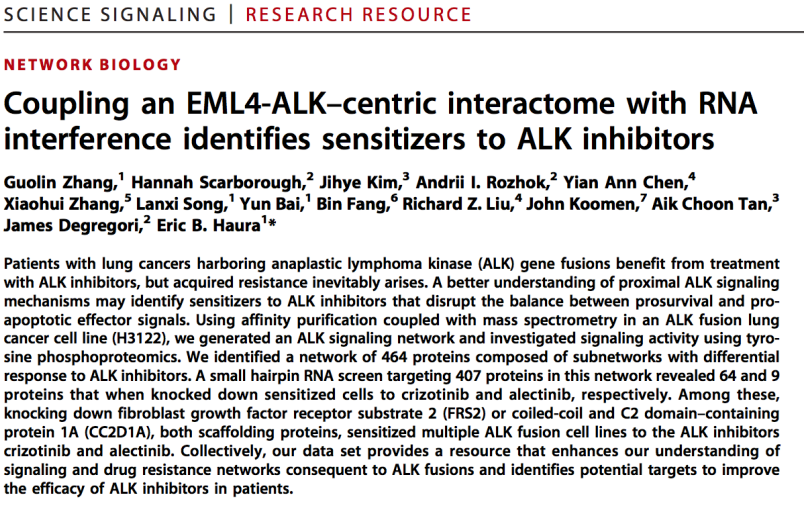


(**Gregory et al**, ***Proceedings of the National Academy of Sciences USA***, 2016, 113(43):E6669-E6678.)

Significance: FMS-like tyrosine kinase 3 (FLT3) inhibitors have shown impressive activity in clinical trials for acute myeloid leukemia (AML); however, these inhibitors invariably fail to achieve sustained remissions. Here we demonstrate that FLT3 inhibition causes severe deficiencies in redox metabolism and accumulation of reactive oxygen species (ROS) in the mitochondria of AML cells. We discovered that the metabolic regulators ataxia telangiectasia mutated and glucose 6-phosphate dehydrogenase help maintain antioxidant capacity and survival of a subpopulation of AML cells in the face of FLT3 inhibition. Inactivation of these factors escalates mitochondrial ROS and enhances AML cell eradication. Importantly, we show that the use of a drug that increases mitochondrial ROS enhances the efficacy of FLT3 inhibitor therapy, suggesting a combinatorial therapeutic strategy.
This is a collaborative research with the **DeGregori** lab at the University of Colorado Cancer Center. Read more of this in the University of Colorado Cancer Center Press Release (http://goo.gl/U62FHG).

NETWORKING ALK FOR COMBINATION THERAPIES IN LUNG CANCER

(**Zhang et al**, ***Science Signaling***, 2016, 9(450): rs12)


SCIENCE SIGNALING | RESEARCH RESOURCE

NETWORK BIOLOGY

Coupling an EML4-ALK–centric interactome with RNA interference identifies sensitizers to ALK inhibitors

Guolin Zhang,[1] Hannah Scarborough,[2] Jihye Kim,[3] Andrii I. Rozhok,[2] Yian Ann Chen,[4] Xiaohui Zhang,[5] Lanxi Song,[1] Yun Bai,[1] Bin Fang,[6] Richard Z. Liu,[4] John Koomen,[7] Aik Choon Tan,[3] James Degregori,[2] Eric B. Haura[1]*

Patients with lung cancers harboring anaplastic lymphoma kinase (ALK) gene fusions benefit from treatment with ALK inhibitors, but acquired resistance inevitably arises. A better understanding of proximal ALK signaling mechanisms may identify sensitizers to ALK inhibitors that disrupt the balance between prosurvival and pro-apoptotic effector signals. Using affinity purification coupled with mass spectrometry in an ALK fusion lung cancer cell line (H3122), we generated an ALK signaling network and investigated signaling activity using tyrosine phosphoproteomics. We identified a network of 464 proteins composed of subnetworks with differential response to ALK inhibitors. A small hairpin RNA screen targeting 407 proteins in this network revealed 64 and 9 proteins that when knocked down sensitized cells to crizotinib and alectinib, respectively. Among these, knocking down fibroblast growth factor receptor substrate 2 (FRS2) or coiled-coil and C2 domain–containing protein 1A (CC2D1A), both scaffolding proteins, sensitized multiple ALK fusion cell lines to the ALK inhibitors crizotinib and alectinib. Collectively, our data set provides a resource that enhances our understanding of signaling and drug resistance networks consequent to ALK fusions and identifies potential targets to improve the efficacy of ALK inhibitors in patients.

Summary from the *Science Signaling*: Some lung cancers have high activity of the kinase ALK as the result of rearrangements between the genes EML4 and ALK. ALK inhibitors are effective in some patients, but resistance to single-agent therapy is common. Using phosphoproteomics and an RNA interference screen, Zhang et al. derived a signaling network mediated by ALK in EML4-ALK–rearranged lung cancer cell lines. From this network, they identified many candidates that could sensitize cells to ALK inhibition. Indeed, knocking down either of two of these two proteins, the scaffolding proteins FRS2 and CC2D1A, sensitized cell lines to the ALK inhibitors crizotinib and alectinib. Thus, a clinical strategy that inhibits FRS2 or CC2D1A might enhance the efficacy of ALK inhibitors in some patients.
This is a collaborative research with Dr. **DeGregori** at the University of Colorado Cancer Center and Dr. **Eric Haura** and his team at the H. Lee Moffitt Cancer Center & Research Institute. Listen to the podcast about this research (http://goo.gl/FZF61H).

***Publications*:** We published 24 papers for this past year and we have accrued more than 900 citations in 2016 related to the publications of our lab. We look forward for another productive year! Go Tan Lab!

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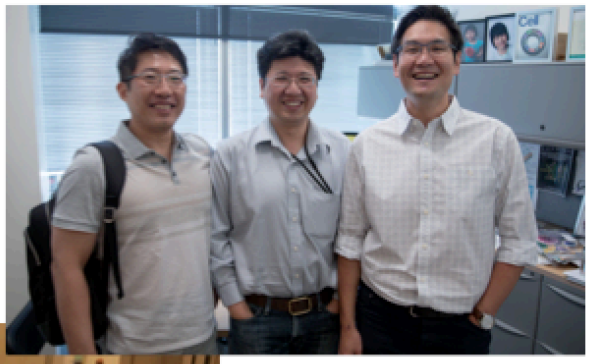
Lab Social Activities and Celebrations:

Sushi Lunch + Lab Meeting

Lunch @ Health Informatics Mini-Symposium



Jaewoo, AC and Paul

Annual Lab BBQ @ Seoul BBQ

Annual Lab Dim Sum @ Star Kitchen

With some good science in the works and the great collaborations with our colleagues, I am sure that 2017 will be another exciting and good year for the lab. I look forward to working together with you in the year ahead. Happy New Year!

Aik Choon Tan, Ph.D.
Associate Professor
Director, Translational Bioinformatics and Cancer Systems Biology Lab
December 31, 2016.

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

Aik Choon Tan, Ph.D.
Associate Professor of Bioinformatics
Translational Bioinformatics and Cancer Systems Biology Laboratory
Program for the Evaluation of Targeted Therapy
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