南加州華裔教授會

CHINESE AMERICAN FACULTY ASSOCIATION
SOUTHERN CALIFORNIA
WWW.CAFASC.ORG

46th Annual Convention
第四十六屆年會

May 6, 2017
Quiet Cannon Conference Center
Second floor, Sunset Room
901 Via San Clemente, Montebello, CA 90640

科 技 處

駐洛杉磯台北經濟文化辦事處科技組

Science and Technology Division, Taipei Economic and Cultural Office in Los Angeles, Republic of China

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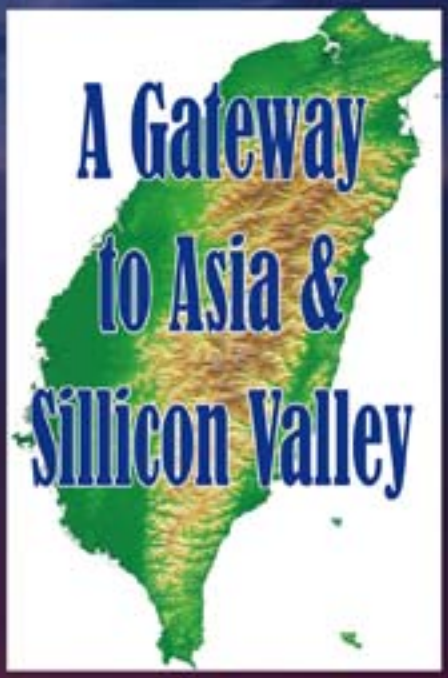

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Chinese American Faculty Association of Southern California

46th Annual Convention
Saturday, May 6th, 2017
Quite Cannon Restaurant
901 Via San Clemente, Montebello, CA 90640

Social Hour and Registration		6:20 pm
Dinner		7:00 pm
Welcome	Elizabeth Budde	潘莉華
Inauguration of New President & Officers	Elizabeth Budde	潘莉華
CAFA Foundation President Report	Shiuan Chen	陳 瑄
Introduction to Keynote Speaker	Elizabeth Budde	潘莉華

Keynote Speech

Dr. **Anthony H. C. Huang**
University of California, Riverside
GMO crops/food

Awards Presentation	Elizabeth Budde	潘莉華
Achievement Award Presentation		
Service Award Presentation		
Faculty Grant Presentation	Chia-en Chang	陳嘉恩
Student Scholarship Presentation	Yi Cheng	鄭怡
Master of Ceremony	Joseph Chao	趙孝祖

Keynote Speech

GMO crops/food

Dr. Anthony H. C. Huang, B.S., Ph.D.

黃煥中 博士

Anthony Huang is Professor in Department of Botany and Plant Sciences at the University of California, Riverside (1988-present). He was Director of the Institute of Plant and Microbial Biology, Academia Sinica, Taiwan (1/2010-12/2012). He was born in China, raised in Hong Kong (high schooling at Queen's College), college-educated in Taiwan (National Taiwan U.) and granted Ph.D. by the U. of California, Santa Cruz. Afterward, he was a faculty member at the University of South Carolina (-1988). His research has centered on the cell and molecular biology of plants, including seed oils and proteins, pollen formation and male sterility, and photosynthesis. He has been active in voluntary teaching and giving public lectures, which have included *The Fascination of Life* (a course for 5th and 6th graders in Gifted and Talented Program at a local school, 4 years), a crash course of *AP Biology* at a local high school (weekends, one semester), *Plants and Human Affairs* (a formal course for senior citizens, 1 quarter), *Biofuels--Facts and Myths*, *Molecular Farming*, *What Cooking Oils You Should Use* and *GMO crops/food*.

The lecture *GMO crops/food* at the CAFA-SC convention will describe the initiation, advances, present status and projected future of GMO crops/food. Evolving policies in dealing with GMO by different nations, especially the U.S., will be explained. Public opinions on GMO will be assessed. The lecture will contain no hardcore science, with the intention that those in the audience without a science background will comprehend most/all of the contents.

2017 ACHIEVEMENT AWARD RECIPIENT

Dr. Shiuan Chen, Ph. D.

陳瑄 博士

Dr. Chen received his bachelor degree from National Taiwan Ocean University and doctoral degree from the University of Hawaii. He is currently the Chair and Professor of Department of Cancer Biology, Beckman Research Institute of City of Hope, Duarte, California. Dr. Chen is recognized for his contributions in the functional characterization of aromatase in breast cancer and in the understanding of aromatase inhibitor (AI) response in breast cancer treatment. Aromatase is the protein that makes estrogen. Dr. Chen is also known for his research on the demonstration of anti-cancer properties of grape seed extract, mushrooms, pomegranate, and blueberries against breast cancer and prostate cancer. Importantly, he has successfully translated his research findings into several clinical trials. Furthermore, his group at City of Hope has recently developed a high throughput screening system, AroER Tri-Screen™, for identifying the testing chemicals that target estrogen receptor (ER) and aromatase. This screening system has been approved by the Tox21 program, NIH, for screening anti-aromatase endocrine disrupting chemicals (EDCs). Dr. Chen has served as the Chair of a 2007 Gordon Research Conference on Hormone Action in Development & Cancer and the Chair of the Ninth International Aromatase (2008) conference. He is also a co-organizer of the Taiwan Aromatase Conference in 2009. In 2012, he was inducted to the Portrait Gallery of Scientific Achievement for his scientific contributions at City of Hope. Furthermore, he was invited to be a member of the International Chinese Medicine Consortium, National Cancer Institute, USA. In 2015, Dr. Chen was awarded with a 4.8 million dollars from NIH/NIEHS/NCI for a five-year grant to study the impact of environment exposures during menopausal transition on the promotion of breast cancer. In 2016, he starts to serve as a mentor/contact for the Dragon Gate Program, Taiwan. Dr. Chen has published 243 papers and has mentored 10 graduate students, 32 research and surgical fellows, and several junior faculty members.

2017 SERVICE AWARD RECIPIE

Dr. Yuan Yuan

袁 媛 博士

Yuan Yuan MD PhD is an assistant professor specializing in breast oncology at the City of Hope Medical Center. She currently serves as principle investigator for multiple investigator-initiated phase I/II clinical trials in TNBC, including a novel androgen receptor (AR) targeted therapy in combination with immune check point inhibitor pembrolizumab, for which Dr. Yuan has pioneered. She was awarded Phase I Foundation Award in March 2017 to study correlative science of this novel clinical trial.

Her research interests are bi-fold. For her work in triple negative breast cancer, she focuses on translational and clinical studies investigating novel therapeutics in triple negative breast cancer (TNBC). Dr. Yuan is a current recipient of an NIH K-12 Paul Calabresi Career Development Award for Clinical Oncology (K-12). She was awarded the STOP CANCER Career Development Award supporting her translational research in TNBC tumor evolution. To develop subtype-directed and PI3K-targeted TNBC therapeutic trials, I have formed collaboration with multiple collaborators at City of Hope in TNBC *in vitro* and *in vivo* models and cell biology research. Our recent work combining eribulin and everolimus in mouse models of TNBC was presented at San Antonio Breast Cancer Symposium (SABCS) 2015. Most recently, her study in paired primary and metastatic TNBC genomic study was presented at SABCS 2016. She has strong interest in pursue translational research understanding how to better precision medicine in the population of metastatic breast cancer. She have recently published on "genomic mutation driven therapy in patients with metastatic breast cancer- a single center experience".

For the aging research, she received NIH R03 grant studying peripheral blood biomarkers of aging and its association with patient's physical function and chemotherapy tolerance with the guidance of her mentor Dr. Arti Hurria. She is currently leading an investigator initiated clinical trial in geriatric population: phase II study of Neratinib, a novel tyrosine kinase inhibitor of human epidermal growth factor receptor 2 (HER-2) in patient 60 and older with HER2 amplified or mutated breast cancer. Primary clinical objective of this trial is to study the safety and toxicity profile of neratinib in older adults. Her recent manuscript titled "The association of pro-inflammatory (IL-6, CRP) and coagulation (D-Dimer) markers with functional status in women with breast cancer pre-chemotherapy" has been accepted for publication (The Oncologist). Dr. Yuan also served as President of the CAFA in 2015-2016.

CAFA Faculty Development Grant

The Robert T. Poe and the CAFA Faculty Development Grants are aimed to support CAFA faculty members in their scholarly pursuit. The grants cover a range of expenses: minor equipment, materials, student hires, manuscript preparation, and proposal preparation. The amount awarded to each grant will depend on the proposal and can be a maximum of $2,000. Preference will be given to junior faculty members.

This year CAFA received excellent proposals covering several fields. All the proposals deserve recognition and financial assistance. Due to funding limitation, we are only able to fund the following three most meritorious proposals.

1. **Robert T Poe award**
   Recipient: Dr. Haofei Zhang, Assistant Professor
   Department of Chemistry, University of California Riverside

   Project Title: ***Compositional Gradients in Organic Aerosol Particles***

Abstract: This project aims to develop a novel method to probe the compositional gradients during chemical transformation of organic aerosols (OA) upon evaporation, condensation of semi-volatile and low-volatile organic vapors, and gas-phase and heterogeneous oxidation. We proposes to perform laboratory evaporation/condensation/oxidation experiments of atmospherically relevant primary OA (POA) and secondary OA (SOA) using a newly designed tandem flow reactor system. The chemical composition at different particle probing depths, will be measured using a comprehensive set of advanced mass.

2. **Recipient: Dr. Aimei Yang, Assistant Professor**
   Annenberg School for Communication and Journalism, University of Southern California

   Project Title: ***The network dynamic of grassroots social movement and corporate-sponsored social activism: Digital advocacy of the fracking issue in the United States***

Abstract: Organizations are ideological entities. This observation is especially true for social movement organizations (SMOs) that are infused with ideologies and are important agents that uphold and promote ideologies. Recently, the digital space has become an increasingly important battle ground for SMOs with competing ideologies to advocate for their own causes and counter the arguments of adversaries. The current study focuses on two opposing movements: the grassroots anti-fracking (hydraulic fracturing) social movement that is led by environmental NGOs and local community groups, and the pro-fracking social movement that is powered by corporations and corporate front-groups. The study will collect hyperlink network data, twitter conversation data, and organizational attribute data on two groups of SMOs. Exponential random graph models (ERGMs) will be used to model tie formation patterns in the network and test theory-driven hypotheses.

3. **Recipient: Dr. Ling Li, Assistant Professor**
   Division of Hematopoietic Stem Cells and Leukemia Research, City of Hope Medical Center

   Project Title: ***Role of arginine methylation in maintenance of FLT3-ITD positive AML leukemia stem cells***

Abstract: Acute myeloid leukemia (AML) is a lethal hematological malignancy with a 5 year overall survival of only 23%. AML is propagated by small populations of leukemia stem cells (LSCs), which are chemo-resistant relative to more mature leukemic cells, and thus are potential sources of disease relapse on discontinuation of treatment. As a heterogeneous disease, the most frequent somatic mutation (seen in 20-25% of patients) in AML is internal tandem duplication (ITD) of the FMS-like tyrosine kinase-3 (FLT3), a feature associated with significant increased relapse risk suggesting presence of persistent FLT3-ITD$^+$ AML LSC. FLT3-ITD lesion in AML LSCs promotes constitutive FLT3 activation and aberrant downstream proliferation and survival signaling, and thus is an attractive therapeutic target. Several FLT3 tyrosine kinase inhibitors (TKIs), including AC220, have been examined in clinical trials. Their clinical effects are often transient due to the incomplete inhibition of aberrant FLT3 signal, leading to survival of FLT3-ITD$^+$ LSC. Thus there is a great interest in developing novel approaches that combine current FLT3 TKI with other agents to achieve sustained remission and fully eradicate FLT3-ITD$^+$ AML LSCs. It is vital to thoroughly understand molecular mechanisms maintaining FLT3 activation in the presence of TKIs. During the project period, we aim to 1) to define the role of FLT3 arginine methylation at R972/R973 in maintenance of FLT3-ITD$^+$ AML LSC using a FLT3-ITD and AML1-ETO double-hit murine leukemia model; 2) to determine the effects of arginine methylation inhibitor enhances elimination of FLT3-ITD$^+$ LSC in combination with AC220 using double-hit murine AML model and primary human AML xenografts.

2017 CAFA Student Scholarship Recipients

1. Hung-To Chen Scholarship

Recipient: Isabel Qi 齊靖寧

Isabel Qi is a student at UCLA double majoring in Atmospheric, Oceanic, and Environmental Sciences and Geography with GPA 3.9. She is interested in the role of cities in curbing climate change, so she plans to pursue a graduate program in urban studies and study in foreign cities. Her experience of living in Beijing and her involvement in the Chinese American community have helped her develop a passion for community advocacy and an interest in interracial relations.

2. Professor Shanmin Li Memorial Scholarship

Recipient: Halah Elsahhar 王曉月

Halah is currently a fourth year Chinese major at the University of California, Riverside with GPA3.7. Growing up with a Taiwanese mother and an Egyptian father, Halah became fascinated with the Chinese language when her mother started teaching her how to speak the language when she was a child. She has spent half of her third year at UC Riverside studying abroad in Taiwan at National Taiwan University with the goal of perfecting her Chinese skills. When Halah graduates, she plans to get her Masters in Fine Arts (**M.F.A.**) and continue to use her B.A. in Chinese to improve her creatively.

3. General Li-Jen Fang Memorial Scholarship

Recipient: Dennis Woo 胡竣傑

Born and raised in San Francisco, Dennis Woo is a classically-trained singer and grade eight pianist. In 2008, Gavin Newsom proclaimed February 22nd "Dennis Woo Day," acknowledging the then eleven-year-old for his community service and leadership through music and the arts. Woo has also earned the President's Education Award, New Generation of Leadership Award, and Lions Club International Leadership Award to name a few. Having performed throughout California and Nevada since the age of four, Woo has sung for the United States Citizenship and Immigration Services and United States Postal Service. In addition to his native languages, Teochew and Hokkien (Taiwanese), Woo learned Cantonese and Mandarin before learning English. A second-year student majoring in Applied and Computational Mathematics at the University of Southern California with GPA 3.78, Woo is a Dornsife Ambassador, Orientation Leader, and the External Community Chair for the Asian Pacific American Student Assembly. Formerly a Research Assistant at the Annenberg School for Communication and Journalism, Woo will be joining the Advocacy branch of Undergraduate Student Government next year. Passionate about the intersection of diversity, technology, and community coalition, Woo has interned at Salesforce and VMware in the last two summers, and he will return to San Francisco to intern at Sony as a Program Manager for PlayStation this summer. Woo is also the Assistant Director for the AT&T Autumn Moon Festival, one of the largest cultural celebrations in the San Francisco Bay Area with 100,000+ annual attendees.

4. Chi-Yue Lin Memorial Scholarship

Recipient: Eddie Lin

Eddie Lin is currently a second year electrical engineering student at Cal Poly Pomona with GPA 3.91. Ever since he was a kid, he has always had a passion for building things. One of his favorite toys as a child was Legos. Something as simple as small building bricks allowed him to express his passion. As he grew older, he also grew to love electronics, and especially computers. With these interests, he knew electrical engineering was meant for him, and he is glad to have chosen this major. His classes have introduced him to new topics that have inspired him hobbies. For example, he would like to get more into tinkering with hobby electronics and learning new programming languages. His classes have also been very interesting and rewarding, and he finds himself learning new things every day. He is excited to see what the future will hold, and what he will be able to build!

Research Reports of Year 2016
Faculty Grant Recipients

1. Recipient: Ming Lee Tang, 鄧明莉, Ph.D. Assistant Professor
Department of Chemistry and Materials Science & Engineering, University of California, Riverside. Tel: 951-827-5964. Email: mltang@ucr.edu

Project title: ***An Upconverting Hybrid Platform For Transforming Bioimaging***

The Tang group's mission is to exploit the multi-excitonic processes inherent in organic semiconductors and semiconducting nanocrystals (NCs), to potentially harvest all the sun's light. This is achieved by the design, synthesis and characterization of novel hybrid organic-inorganic materials for energy applications. Emphasis is on the synthesis of tailor-made organic ligands designed to control, enhance or mediate charge or energy transfer for photon management in optoelectronic devices.

This group discovered a new molecular-nanocrystal system for photon upconversion that can potentially have significant impact in several fields. Such a system can increase the efficiency of solar cells by 15%, and thus provide an inexpensive way to address the high cost. If used for bioimaging, it may offer all the advantages of two-photon emission (TPE) microscopy at a fraction of the cost. In contrast to TPE, which requires expensive femtosecond pulsed lasers and laser scanners (and is thus a serial technique), the proposed technique will use cw lasers and provide wide field imaging capabilities. If successful, the low excitation power densities and simultaneous recording of all fluorophores within the field of view will address current bottlenecks for long-duration imaging of thick tissues, e.g. organs like the brain. Excitement about our upconversion research is palpable- Times Magazine, the Huffington Post, the Aspen Institute, Engadget, TechnoFAQ, the EE Times, etc. have highlighted or covered this work.

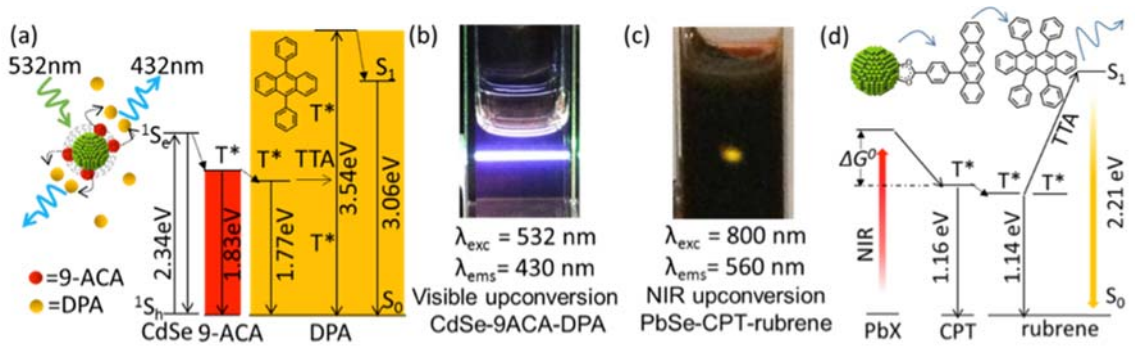

Figure 1. (a) Schematic illustration of the energy transfer for CdSe/9-ACA (9-anthracene carboxylic acid) /DPA (diphenylanthracene) based photon upconversion of green to violet light. The green arrow indicates the photoexcitation of sensitizer CdSe nanocrystals (NCs, green ball). Energy is transferred to the transmitter, i.e. the bound 9-ACA ligands (red ball), and then to the annihilator DPA (yellow ball), followed by the annihilation between two triplet DPA molecules and subsequent emission from the singlet state of DPA (blue arrow). The same process for the upconversion of near-infrared (NIR) light is shown in (d), with PbX (X=S or Se), CPT (carboxylic phenyl tetracene) and rubrene as the sensitizer, transmitter and annihilator respectively. (b) Photograph of visible upconversion in a cuvette containing CdSe/9-ACA/DPA, with the excitation by a cw 532 nm green laser and 430 nm violet emission. (c) Photograph of NIR upconversion in a cuvette containing PbSe/rubrene. The sample is excited with a cw 800 nm laser, and the yellow emission at 560 nm can be seen. (a), (b) and (c) are reproduced with

permission from the American Chemical Society. (d) is reproduced with permission from the The Royal Society of Chemistry.

The key concept of this novel system is the use of a nanocrystal to absorb light and transfer the energy to a triplet state of a molecule. Two triplets then combine to emit light of higher energy. The beauty of this system is the tunability of both the nanocrystal light absorber and molecular fluorophore. This allows upconversion to be engineered between arbitrary wavelengths for various applications. Such a system has not been realized before. This general platform has inherent advantages over conventional molecular and the rare-earth based upconversion systems. Efficiency in the lanthanide systems is hampered by their small absorption cross-sections. In contrast, the nanocrystal absorber has molar absorption cross-sections typically an order of magnitude larger than the best organic fluorophores. Nanocrystals can also absorb in the infrared, where molecules generally do so very poorly, if at all. Currently, the group has achieved a relatively high quantum efficiency of 15% at visible wavelengths, for the conversion of green photons to blue photons. A fundamental understanding of the elementary steps in this interfacial energy transfer has enabled similarly high efficiencies in the infrared (9%), to create visible light from near infrared photons. Importantly, this quantum yield (QY) is achieved at sub-solar fluxes (meaning it is compatible with sunlight), at excitation densities $\sim 10^6$ below that required for the state of the art lanthanide compounds.

Current work is focused on obtaining a molecular level understanding of triplet energy transfer (TET) between semiconductor nanocrystals (NCs) and conjugated molecules because this is a key factor limiting the upconversion QY. Presently, the upconversion QYs are a factor of 3 or 4 below the maximum imposed by the finite value of the efficiency of triplet-triplet annihilation. Emphasis is on the design of transmitters to tune the molecular energetics, photophysics, binding affinity, stability and energy offsets with respect to the NC donor, so as to enhance electronic communication between the NC donors and the emitter. For example, by tuning the functional groups and side chains on the conjugated core, transmitter ligands can be designed to minimize vibrational losses and maximize both the driving force for TET and orbital overlap with the NC donor. Other improvements in the upconversion QYs could arise from alternative nanocrystal sensitizers or annihilators, or nanocrystal surface passivation. Kinetic data obtained from transient absorption and time resolved photoluminescence measurements complement the steady-state photon upconversion experiments and structural characterization conducted in parallel.

Fundamental structure-property relationships governing energy transfer between semiconductor nanocrystals and organic semiconductors will be ironed out. The knowledge gained can be applied to molecularly engineer efficient singlet fission. Ultimately, this understanding will allow sunlight to be utilized efficiently in photocatalysis and photovoltaics whether with photon up- or down-conversion. This will lead to the exciting development of an efficient, solid-state, upconverting platform that can harness the entire solar spectrum for cheaper solar cells or more efficient photocatalysts.

2. Recipient: Jianming Xie, 謝建明, Ph.D. Assistance Professor
Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Tel: (323)442-2341, Email: jianminx@usc.edu

Project title: ***Mechanistic studies of CAR T-cell recognition and activation***

Background and Significance:

Engineering T cells to express chimeric antigen receptors (CARs) has emerged as a promising strategy for cancer treatment. However, most tumor-associated antigens (TAAs) are also expressed on normal cells (albeit at a lower level), leading to a severe and potentially life-threatening adverse effect known as the "on-target/off-tumor" toxicity. Therefore, there is a critical need for a new strategy to design CAR-T cells capable of distinguishing tumor cells from normal cells based on their different antigen densities. CARs are artificial receptors typically consisting of an antibody-derived extracellular antigen-binding domain (often a single-chain variable fragment, scFv) and a T-cell-originated intracellular signaling domain (such as CD3ζ, CD28, and/or 4-1BB). As distinct from conventional T cell receptors (TCRs) which recognize peptide-MHC (pMHC) complexes with a low affinity (K_D = 1-100 μM), CARs recognize antigens independently of pMHCs and have a wide range of affinities. Our hypothesis is that the minimal antigen density required for CAR-T cell activation is at least partially determined by the affinity of CAR-antigen recognition. Previous studies assessed the effects of CAR affinities on T-cell activation by generating multiple CAR-T cells with various affinities for a common TAA (e.g., ErBB2 or EGFR). However, the results are mostly inconclusive because the ranges of TAA densities and CAR affinities attained in these studies were limited, and the various CARs could recognize different epitopes of the same antigen which can also impact CAR-T cell activation. To overcome these limitations, we have devised a novel chemical strategy that utilizes the small 2,4-dinitrophenyl (DNP) moiety as a model CAR antigen. Our strategy is advantageous for the following three reasons. (1) Dozens of anti-DNP antibodies with varying affinities are readily available for CAR design. (2) CARs derived from these antibodies recognize the same DNP moiety and thus there is no variation associated with epitope locations. (3) Unlike typical CAR antigens which require the use of lentiviral or retroviral systems for cell-surface expression, DNP can simply be engineered on the cell surface by chemical conjugation. By varying the concentration of DNP reagents, a wide range of DNP densities can be easily attained. The overall objective of our proposed research is to develop and apply such a DNP-based CAR-T platform for a precise understanding of the effects of CAR affinities on the sensitivity and magnitude of CAR-T cell activation.

Results and Discussion:

Development and validation of anti-DNP CAR-T cells. The Jurkat human T-cell line has been used to express anti-DNP CARs in our initial study. As shown in Fig. 1A, the anti-DNP CAR consists of an N-terminal HA-tag (for the ease of detection), an anti-DNP scFv derived from a mouse antibody, a CD8 hinge and transmembrane domain (TM), and an intracellular CD28/CD3ζ signaling domain. Jurkat cells expressing anti-DNP CARs were generated by the lentiviral gene delivery system. The expression of

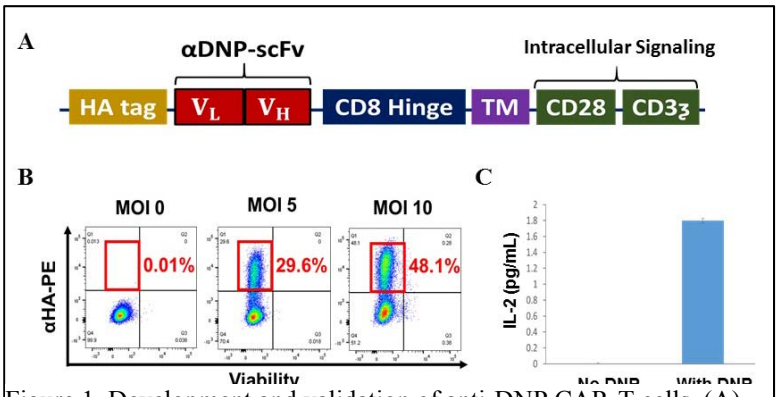

Figure 1. Development and validation of anti-DNP CAR-T cells. (A) Components of the anti-DNP CAR. (B) Verification of CAR expression by HA-tag staining. (C) Verification of the recognition and activation of anti-DNP CAR-T cells.

anti-DNP CARs was confirmed by fluorescent staining with PE anti-HA antibody (Fig. 1B). The recognition and activation of anti-DNP CAR-T cells were validated by a series of T-cell activation assays. Specifically, the K562 leukemia cells modified with DNP (by cell-surface modification) were used as the target cell and co-cultured with the anti-DNP CAR-T cells. Interleukin-2 (IL-2) production was measured by enzyme-linked immunosorbent assay (ELISA). The result showed that the activation of anti-DNP CAR-T cells generated above was dependent on the presence of DNP on the surface of K562 cells (Fig. 1C). The DNP-dependent activation was further verified by other assays, including pERK phosphorylation and CD69 upregulation (data not shown). Additionally, the Jurkat anti-DNP CAR-T cells were further sorted to a purity greater than 97% for subsequent experiments.

Generation of DNP-modified target cells. To systematically study the correlation among CAR affinities, antigen densities, and T-cell activation, we need to obtain the target cells presenting a wide range of DNP densities. To achieve this goal, we utilized DNP-NHS to nonspecifically conjugate the DNP moiety to the surfaces of K562 cells, and the DNP density was determined by fluorescence staining using PE anti-DNP antibody followed by measuring the average fluorescence intensity of these cells. By this method, we were able to attain a wide variety of DNP densities, ranging from a few hundred to over one million DNP moieties per cell (Fig. 2A).

Correlation among CAR affinities, antigen densities, and T-cell activation. Next, we attempted to assess the impacts of CAR affinities and antigen densities on CAR-T cell activation. In preliminary results we generated two types of Jurkat anti-DNP CAR-T cells with different affinities. Using the DNP-modified K562 cells as the target cell, we found that the low-affinity CAR-T cells exhibited lower overall activity than the high-affinity CAR-T cells, though we did not see a significant difference in the minimal DNP densities required for the activation of these two anti-DNP CAR-T cells (Fig. 2B).

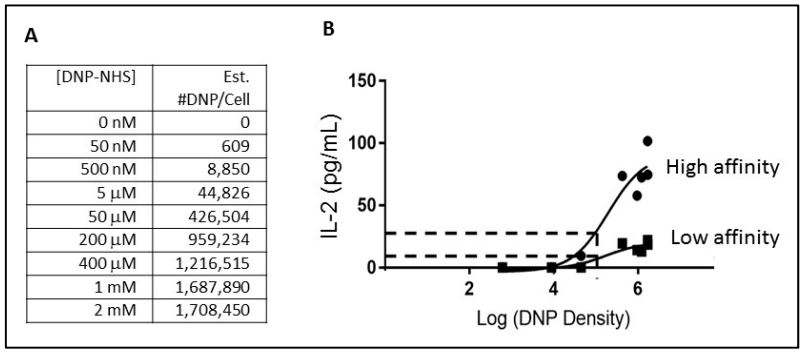

Figure 2. Determination of the correlation between CAR affinity and T-cell activation. (A) Cell surface DNP modification and quantification. (B) Comparison of IL-2 production by the high- and low-affinity anti-DNP CAR-T cells upon recognition of the DNP-modified K562 cells.

Expression, refolding, purification, and binding assays of αDNP scFvs. Previous studies have measured the affinities of anti-DNP antibodies, but the scFvs are expected to have decreased affinities. To quantify the affinity of anti-DNP scFvs used in our studies, we have optimized a protocol to express, refold, and purify anti-DNP scFvs. Briefly, anti-DNP scFvs were expressed in *E. coli* as an inclusion body, and refolded by a gradual dialysis method. Then the correctly folded scFvs were purified by gel filtration. We plan to measure their DNP-binding affinities by surface plasmon resonance (SPR) analysis.

Future Direction:

To fully assess the effects of CAR affinities, we plan to compare CAR-T cells with different affinities ranging from very low (in the micromolar range, i.e., similar to that of TCRs) to very high (in the sub-nanomolar range, i.e., similar to that of antibodies). So far we have developed and validated two anti-DNP CAR-T cells. Based on the anti-DNP antibodies of varying affinities already generated by previous researchers, we plan to select 3-4 additional antibodies and generate cognate CAR-T cells, respectively. Combining these anti-DNP CAR-T cells and the cell surface DNP modification method developed above,

we hope to elucidate the exact correlation among the CAR affinity, the threshold antigen density, and the magnitude of T-cell activation. Further, we will attempt to validate our findings using primary human T cells. Finally, we plan to quantify the densities of a variety of known tumor antigens on the surfaces of both tumor and normal cell surfaces, and use the knowledge obtained in our study to design next generation CAR-T cells with enhanced specificity for tumor cells.

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Project Title: ***Recreational physical activity and invasive epithelial ovarian cancer risk in the California Teachers Study***

Introduction. The American Cancer Society projected that about 22,440 women will be diagnosed with ovarian cancer in the United States (U.S.) in 2017. Approximately 14,080 U.S. women were expected to die from this disease in 2017, accounting for 5% of cancer deaths among U.S. women. Among gynecologic cancers, the mortality rate is highest for ovarian cancer. Despite its high mortality, the etiology of this lethal disease is not completely understood, in part because of possible differences by cell type, and also because the high death rate precludes inclusion of many women with ovarian cancer from case-control studies. Cohort studies do not suffer from this inability to include all cases of ovarian cancer occurring during a defined time period. One of the potential risk factors for ovarian cancer that are not well understood is recreational physical activity.

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer, accounting for around 90% of ovarian malignancies. As recreational physical activity is a modifiable factor, addressing this association with EOC would be important as if such an association exists it provides an opportunity for the prevention of EOC.

The California Teachers Study, a large cohort of female public school professionals (teachers, administrators, school nurses and psychologists, and computer specialists) collected detailed information on recreational physical activity, which offers an opportunity to study the possible association of EOC risk with recreational physical activity.

Methods: 106,269 women in the California Teachers Study, aged 22 to 84 years with no history of ovarian cancer at baseline (1995-1996), were followed from baseline through 2013; 619 were diagnosed with first primary invasive EOC. These women provided information at baseline on personal and family medical history, reproductive factors, use of menopausal hormone therapy, and lifestyle factors (including physical activity, daily sitting hours, diet, alcohol consumption, smoking, etc.). Information on recreational physical activity was collected for two intensity levels, strenuous (e.g., running, jogging, swimming laps, racquetball, aerobics, calisthenics, and cycling on hills) and moderate (e.g., brisk walking, golf, softball, volleyball, recreational tennis, and cycling on flat surfaces) during six time periods (high school, in age categories of 18-24, 25-34, 35-44 and 45-54 years, and physical activity during the 3 years prior to baseline). We fit multivariable Cox proportional hazards models to our data to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the HRs; the HR is a measure of the relative risk of EOC that is associated with long-term recreational physical activity (from high school through age 54 years or age at baseline, whichever was younger) and the relative risk for each of six specific time periods.

Results: Overall, we saw no statistically significant association of EOC risk with long-term total (strenuous plus moderate), strenuous, or moderate recreational physical activity. However, among the many subgroups we evaluated we did find inverse associations among women whose consumption of daily dietary calories, total fat, or saturated fat, was below the median for women in the study. Among such women, long-term strenuous recreational physical activity was associated with lower risk of EOC, especially the non-serous subtype. This was not observed among women whose consumption of these dietary factors was equal to or above the median. For example, women with lower daily dietary saturated fat (<median [16.7 grams]) who were in the highest category (>4.0 hours/week/year) of long-term

strenuous recreational physical activity, EOC risk was 45% lower than among women whose exercise was in the lowest category (≤0.50 hours/week/year) (HR = 0.55, 95% CI = 0.36-0.83); their risk of non-serous EOC was 55% lower (HR = 0.45, 95% CI = 0.25-0.81). No such effect modification was observed for long-term moderate recreational physical activity. Moreover, the risk estimates for time-period-specific recreational physical activity were similar to those for long-term recreational physical activity.

Conclusions: Our data confirm the accumulating body of evidence from prospective epidemiologic studies showing no overall association between recreational physical activity and EOC. Although our data showed that strenuous recreational physical activity may decrease the risk of EOC, especially non-serous EOC, in women with lower daily intake of dietary calories, total fat, or saturated fat, these results may be spurious and due to chance. Such findings require confirmation in larger studies. Our findings suggest that strenuous recreational physical activity in combination with a healthy diet may be an important approach for lowering women's risk of EOC.

4. Recipient: Joseph Chao, 趙孝祖, M.D. Assistant Clinical Professor
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Project Title: ***Correlating Genome Wide Copy Number Alterations with MicroRNA Expression Profiling in Gastroesophageal Adenocarcinomas***

BACKGROUND/RATIONALE: Adenocarcinomas of the stomach and gastroesophageal junction account for a high proportion of worldwide cancer-related mortality. Efforts in comprehensive molecular characterization such as results from The Cancer Genome Atlas (TCGA) have demonstrated a multitude of gene copy number alterations that may serve as promising targets for novel therapeutics.[1] We have also recently presented preliminary data that whole genome microRNA sequencing profiles correlate with *HER2* gene amplification determined by traditional FISH techniques among 18 gastric cancer patient gastrectomy specimens identified from the City of Hope Biospecimen Repository.[2] Efforts have been ongoing to pursue microRNA sequencing of 48 additional patient gastrectomy specimens. Via traditional FISH, 5 cases are *HER2* amplified and 2 cases exhibit *MET* amplification. The support of the CAFA Faculty Development Grant enabled generation of pilot data using a whole genome copy number assay that will help elucidate the complex interplay between gene amplifications and microRNA expression profiles in gastric cancer.

RESEARCH PLAN: The City of Hope Cytogenetics Core recently obtained the powerful Affymetrix OncoScan™ platform, which enables whole genome analysis of solid tumors. It is capable of copy number detection of 891 cancer-related genes at 50-100 Kb resolution as well as detection of 74 frequent somatic mutations in 9 genes of interest (*BRAF, KRAS, EGFR, IDH1, IDH2, PTEN, PIK3CA, NRAS, TP53*). Genome wide coverage outside of the 891 cancer genes will also be provided at 300 Kb resolution along with genome wide LOH provided at 3-10 Mb resolution. It has been validated in highly degraded FFPE specimens providing the sensitivity needed in our patient samples obtained from the City of Hope Biospecimen Repository that may be over 20 years old. As a pilot project, we proposed assaying for whole genome copy number alterations of 4 gastric cancer samples among the 41 cases having completed microRNA sequencing in which traditional FISH did not reveal amplification of the oncogenes *HER2* and *MET*. Our data set has been clinically annotated for TNM staging as well as time to disease relapse after surgery with or without adjuvant chemotherapy and/or radiotherapy.

Table 1. Percentage LOH, genome change, and observed copy number alterations

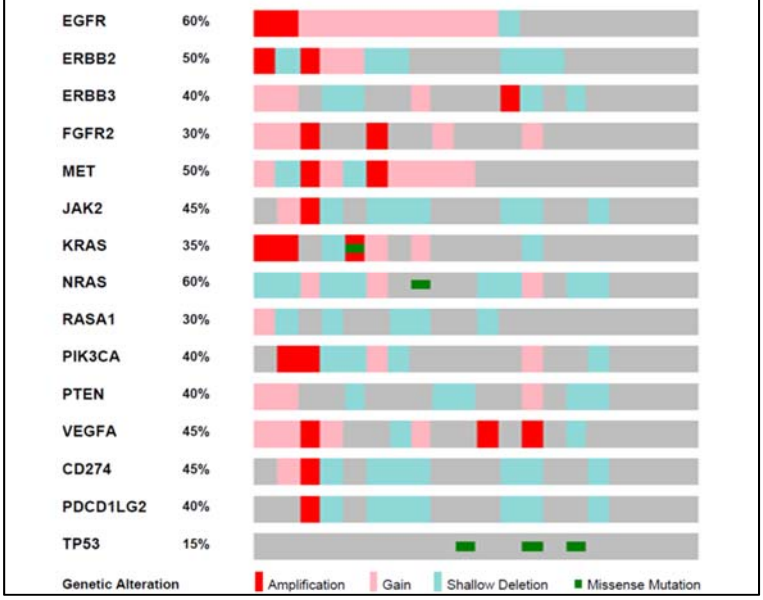
Deidentified Sample ID	Total Copy Number Aberrations	% LOH (loss of heterozygosity)	% Genome changed	
639634	7	0.7	0.2	Genomically Stable (GS)Tumors
42688	4	1.0	0.7	
106630	7	0.8	1.4	
967124	25	0.8	3.7	
114422	4	1.3	4.7	
129851	133	25.2	15.0	Tumors with CIN (chromosomal instability)
222940	67	22.6	15.7	
78580	66	3.0	17.2	
672	68	9.4	20.4	
375734	91	2.4	31.1	
135761	123	33.7	34.7	
42479	125	22.5	39.3	
269190	116	33.8	41.5	
573905	69	14.0	46.1	
4389	224	28.0	48.9	
687325	206	60.9	49.2	
226609	228	42.7	51.4	
406884	265	10.7	59.0	
149925	187	21.1	62.5	
9949	181	53.6	66.6	

RESEARCH PROGRESS TO DATE: With the support provided by the CAFA faculty development award, in addition to the 4 samples originally proposed we have been able to perform the OncoScan assay on a total of 20 gastrectomy tumor samples to date. We are encouraged to see

among the 20 gastric adenocarcinomas, 5 cases demonstrate a very low percentage of genomic changes (<5%) and 15 cases exhibit a high percentage (15%-67%). This correlates very well to the proportion of gastric adenocarcinomas characterized as being either genomically stable or exhibiting chromosomal instability within the comprehensive molecular platforms carried out by the TCGA investigators. As such, even among these initial 20 cases, we believe we are capturing a representative sampling of the molecular heterogeneity that has become increasingly recognized to be inherent to gastric cancer.

Further analyses focusing on oncogenic drivers of interest do indicate that our case series possess a variety of alterations representative of putative driver mutations. Specifically, gene amplifications were noted in *EGFR*, *FGFR2*, *MET*, *KRAS*, and *PIK3CA*. Also provocative is identification of both *CD274* and *PDCD1LG2* co-amplification, which encode the immune checkpoint ligands PD-L1 and PD-L2 respectively. Of interest is denoting of *ERBB2*, *FGFR2*, *MET*, and *JAK2* co-amplification also existing in the same tumor specimen. These carry significant implications for ongoing efforts in immunotherapy and targeted drug development that combinatorial approaches are likely necessary to target co-existing driver mutations within the same tumor.

Figure 1. Genomic coverage of oncogenic drivers of interest



ONGOING RESEARCH EFFORTS: Twenty additional gastrectomy cancer samples are undergoing OncoScan analysis to broaden and add to the genomic landscape we have observed to date. We are also working with the City of Hope Cytogenetics core to pursue traditional FISH analyses to ascertain if there may be spatial intratumoral heterogeneity present among gene copy number gains and losses reported by the OncoScan assay. In addition, we will collaborate with fellow CAFA member Dr. Yate-Ching Yuan, Ph.D., director of the Bioinformatics Core facility at our institution. Raw miR-seq data has already been obtained for our 40 gastric cancer samples to date. With services of the Bioinformatics Core, we will perform comprehensive comparative analyses to ascertain the copy number and miRNA genomic landscape of our dataset with the public dataset of gastric cancers comprehensively profiled within the TCGA.

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2. Chao J, Kurata J, Chu P, et al. Gastric Cancer (GC) MicroRNA Expression Profiling Using a Next Generation (NGS) Approach Correlates with HER2 status. Keystone Symposia Conference: MicroRNAs and Noncoding RNAs in Cancer 2015:Abstract 1012.

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Project title: ***Define the Competence Windows for the Generation of Different Pancreatic Endocrine Cell Types in Human Pancreatic Progenitors***

The goal of this project is to develop a novel *in vitro* platform to create an individual human islet endocrine sub-types derived from a single human induced pluripotent stem cell (hiPSC) source. The overall goals of this proposal is to define the competence window of hPSCs to produce different endocrine cell types.

To monitor pancreatic endocrine progenitor cell differentiation in real-time, we established an hPSC H1 line carrying a NEUROG3-GFP-SMASH fusion protein construct. This construct introduces a GFP-tag to the endogenous NEUROG3 loci for NGN3 detection. The expression of NGN3 is critical for pancreatic endocrine cell commitment, and this reporter will allows us to quickly assess pancreatic endocrine differentiation in real time. While our preliminary study demonstrated that the *SMASH* technology does work in the culture condition (Fig1A,B), however, we encounter a difficulty to maintain this cell line in stem cells, as they spontaneously differentiated even in a defined stem cell culture condition. Thus we are in the processes of generating another cell line using similar approach. In order to combine with the capability to monitor beta cell maturation in real-time, we have obtained a hPSC line carrying a MAFA-T2A-mTomato reporter construct (Fig1C). The expression of MAFA is a strong indication of mature and functional beta cell phenotype. Our preliminary data indicated that MAFA-T2A-mTomato reporter construct faithfully represent Insulin+ beta-like cells at the final stage of pancreatic differentiation. The ability to follow the emergence and propagation of functional beta cells in real time, will also allow us to define endpoints for analyzing the presence of other endocrine cell types using immunohistochemical staining.

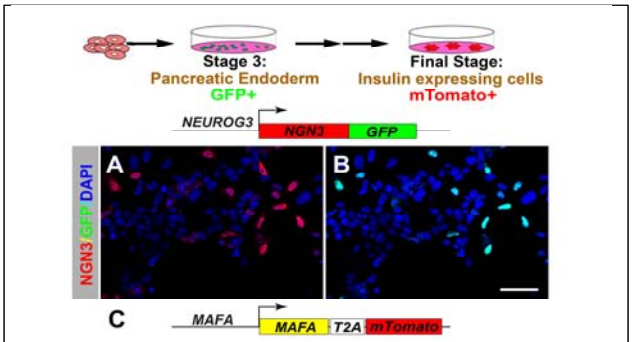

Figure 1. Determination of pancreatic differentiation efficiency and maturation using the NGN3-GFP fusion protein construct and MAFA-T2A-mTomato reporter IPSC lines. (A,B) GFP-tag faithfully report Ngn3-expressing cells in transiently transfected HepG2 cells. (C) A hPSC H1-line carrying a MAFA-T2A-mTomato reporter displays robust mTomato and Insulin expression at the final stage of pancreatic differentiation.

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