

Stony Brook Symposium
Chemical Synthesis in Life Sciences

June 5-6, 2015

Charles B. Wang Center, Stony Brook University

Celebrating the Achievements of

Professor Iwao Ojima

Distinguished Professor, State University of New York
Director, Institute of Chemical Biology and Drug Discovery
Stony Brook University

On the Occasion of His 70th Birthday



Stony Brook University

<https://you.stonybrook.edu/symposiumchemicalsynthesis/>

Iwao Ojima

*Distinguished Professor, State University of New York
Director, Institute of Chemical Biology and Drug Discovery (ICB&DD)
Stony Brook University*



Iwao Ojima received his B.S. (1968), M.S. (1970), and Ph.D. (1973) degrees from the University of Tokyo, Japan. He joined the Sagami Institute of Chemical Research and held a position as Senior Research Fellow until 1983.

He joined the faculty at the Department of Chemistry, State University of New York at Stony Brook first as Associate Professor (1983), was promoted to Professor (1984), Leading Professor (1991), and then to University Distinguished Professor (1995). He served as the Department Chairman from 1997 to 2003. He serves as the founding Director for the Institute of Chemical Biology and Drug Discovery (ICB&DD) at Stony Brook from 2003. Also, he was a Visiting Professor at the Université Claude Bernard Lyon I, France (1989), The University of Tokyo, Japan (1996), The Scripps Research Institute, La Jolla, CA (1997), and Université de Paris XI, BIOCIS, Châtenay-Malabry, France (1997).

His research interests include medicinal chemistry and chemical biology (anticancer agents, tumor-targeted drug delivery, antibacterial agents, enzyme inhibitors), catalytic asymmetric synthesis, organic synthesis by means of organometallic reagents and catalysts, peptidomimetics, β -lactam chemistry (applications of the β -lactam synthon method), and organofluorine chemistry (fluoroamino acids and peptides, fluorotoxoids, medicinal applications). He has

published more than 440 papers and reviews in leading journals and more than 100 patents granted, edited 8 books (SciFinder lists >900 publications to his credits; Google Scholar indicates h-index of 65, total citation >19,900), and he has given more than 125 Plenary and Invited Lectures in international conferences and symposia by April 2015.

He is a recipient of the Arthur C. Cope Scholar Award (1994), the E. B. Hershberg Award (for important discovery of medicinally active substances) (2001) and the ACS Award for Creative Work in Fluorine Chemistry (2013) from the American Chemical Society; The Chemical Society of Japan Award (for distinguished achievements) (1999) from the Chemical Society of Japan; Outstanding Inventor Award (2002) from the Research Foundation of the State University of New York. He was inducted into the Medicinal Chemistry Hall of Fame, American Chemical Society (2006).

He is an elected Fellow of the J. S. Guggenheim Memorial Foundation (1995~), the American Association for the Advancement of Science (1997~), The New York Academy of Sciences (2000~), the American Chemical Society (2010~), and National Academy of Inventors (2014~).

He has served in various advisory committees for National Institutes of Health (National Cancer Institute, National Institute of Allergy and Infectious Diseases, National Institute of General Medical Sciences), National Science Foundation and the U.S. Department of Energy. He has served as a member of the Executive Committee for the Division of Organic Chemistry and the Long Range Planning Committee for the Division of Medicinal Chemistry, American Chemical Society. He has also been serving as an External Advisory Board for the Cluster of Excellence, "Cells in Motion", at the University of Muenster, Germany.

He has served and has been serving as Editorial Advisory Board member of *Journal of Organic Chemistry*, *Organometallics*, *Journal of Molecular Catalysis*, *Chemistry Letters*, *Current Topics in Medicinal Chemistry* (current), *Medicinal Chemistry* (current), *Letters in Drug Design & Discovery* (current), *Bulletin of the Chemical Society of Japan* (current), and *Anti-Cancer Agents in Medicinal Chemistry* (current). He has also served as the Guest Editor for thematic issues of the *Journal of Medicinal Chemistry*, *Accounts of Chemical Research*, and *Current Topics in Medicinal Chemistry*. In addition, he serves as the Senior Editor of "Future Medicinal Chemistry".

During his tenure at the State University of New York at Stony Brook and Stony Brook University, he has advised 64 postdoctoral research associates/fellows, 112 graduate students (58 Ph.D. degrees and 33 M.S. degrees), 92 undergraduate research students, 12 visiting scientists, and 50 high school summer research students by April 2015.

Stony Brook Symposium on
“Chemical Synthesis in Life Sciences”
June 5-6, 2015, Charles B. Wang Center, Stony Brook University
Celebrating the Achievements of Professor Iwao Ojima On the Occasion of His 70th Birthday

Symposium Sessions and Speakers

Friday, June 5

9:00 am to 9:15 am

Opening Remarks

Dr. Michael L. Miller (Chair of the Organizing Committee)

Dr. David Conover, Vice-President for Research, Stony Brook University

Dr. Nicole Sampson, Chair, Department of Chemistry, Stony Brook University

9:15 am to 9:55 am

Opening Lecture

Moderator: Dr. Michael L. Miller

Dr. Makoto Fujita – *Professor, Department of Applied Chemistry, Graduate School of Engineering, University of Tokyo, Japan*

“Crystalline Sponge Method for Synthetic and Pharmaceutical Studies”

9:55 am to 12:00 pm

Session I (Medicinal Chemistry and Chemical Biology)

Moderator: Dr. Antonella Pepe

Dr. Scott D. Kuduk*** – *Director of Chemistry, Novira Therapeutics*

“Evolution of M1 Receptor Selective Positive Allosteric Modulators for the Treatment of Alzheimer’s Disease”

Dr. Bibia Heidmann** – *Senior Laboratory Head, Actelion Pharmaceuticals, Switzerland*

“Discovery of Highly Potent Dual Orexin Receptor Antagonists via Scaffold Hopping Approach”

Dr. Hauh-Jyun (Candy) Chen** – *Professor, Department of Chemistry and Biochemistry, National Chung Cheng University, Taiwan*

“Trace Analysis of DNA and Protein Adducts in Humans by Mass Spectrometry”

Dr. Tadashi Honda** – *Research Professor, Department of Chemistry and Institute of Chemical Biology and Drug Discovery, Stony Brook University*

“Michael Acceptors as Nrf2 Activators for the Treatment of Inflammatory Diseases – From Bardoxolone Methyl to Monocyclic Cyanoenones”

Dr. Zihao Hua* – *Medicinal Chemist, Amgen Inc.*

“Structure-based Design of Potent and Selective Tankyrase Inhibitors to Target the Wnt Pathway”

12:00 pm to 1:00 pm

Lunch

Chapel (*invited speakers and faculty only*) Zodiac Gallery (*students*)

1:00 pm to 3:00 pm

Session II (Drug Design, Discovery and Development)

Moderator: Dr. Bruno Chapsal

Dr. Songnian Lin** – *Principal Scientist and Project Leader, Merck Research Laboratories*

“Discovery of a Novel and Potent Glucagon Receptor Antagonist for the Treatment of Type II Diabetes”

Dr. Michael L. Miller** – *Leader, New Effector Program, ImmunoGen, Inc.*

“Design, Synthesis and Evaluation of a Novel Class of Potent DNA-Alkylating Agents for Use in Antibody-Drug Conjugates (ADCs)”

Dr. Masakatsu Eguchi** – *Chief of Chemistry, JW Theriac Pharmaceutical*

“Peptidomimetics in Drug Discovery: The Progress Since the Last Meeting”

Dr. Tao Wang* – *Principal Scientist, Biogen*

“Discovery of Potent, Selective Trk and JAK1/2 Kinase Inhibitors for Treatment of Cancer and Myeloproliferative Neoplasms”

Dr. Claude Commandeur* – *Medicinal Chemistry Team Leader, Research and Development Department, Selvita, A.A., Poland*

“Design of MELK Covalent Inhibitors”

3:00 pm to 3:30 pm

Coffee Break and Poster Session
Theater Lobby

3:30 pm to 5:00 pm

Session III (Chemistry and Multifaceted Career Development)

Panel Discussion:

Dr. Elke Schoffers (Moderator) – Professor, Western Michigan University
“Beyond the Lab Coat – Scientists as Educators and Citizens”

Dr. Subrata Chakravarty – Chief Science and Technology Officer, Hope4Cancer Institute
“Tales of a Meandering Scientist”

Dr. Elizabeth P. Cormier – Chemist, Center for Veterinary Medicine, US Food and Drug Administration
“Chemists, Chemistry, and the FDA: Building Quality into Drug Manufacturing”

Dr. Zhaoyang (Paul) Li – Partner, DLA Piper, LLP
“IP Commercialization: Trends and Issues”

Dr. Deric Geng – Patent Attorney, WilmerHale, LLP
“From Bench to Bar: An Introduction to a Career in Patent Law for Chemists”

Dr. An Vu – Senior Chemist, Center for Tobacco Products (CTP)
“The Role of Chemists at FDA’s Center for Tobacco Products”

Dr. Cecilia F. Oderda – Free-Lance Clinical Project Manager, Nestlé Research Center, Italy
“Clinical Project Managers: Chemists on the Other End of New Drugs’ Development Process”

5:00 pm to 6:00 pm

Poster Session

6:15 pm to 7:00 pm

Reception (SAC Ballroom B)

7:00 pm to 9:30 pm

Banquet (SAC Ballroom A)

Saturday, June 6

9:10 am to 12:00 Noon

Session IV (Organic Synthesis and Synthetic Methods)

Moderator: Dr. Scott D. Kuduk

9:10 am to 10:20 am

Dr. Thierry Brigaud** – Professor, University of Cergy-Pontoise, France
“Fluorine Chemistry: From Asymmetric Synthesis to Peptides”

Dr. Vadim A. Soloshonok** – Ikerbasque Research Professor, University of Basque Country, Spain;
Visiting Professor, Department of Chemistry, Stony Brook University

“New Reagents for Installation of CF₃, CF₂ and Quaternary CF Groups”

Dr. Wen-Hua Chiou* – Associate Professor, National Tsing Hua University, Taiwan

“Enantiomeric Synthesis of Piperidine, Indolizidine and Dendrobatid Alkaloid Epibatidine”

10:20 am to 10:40 am

Coffee Break
Theater Lobby

10:40 am to 11:50 am

Dr. Louis Fensterbank** – Professor, Department of Chemistry, Pierre and Marie Curie University, France
“Some New Stories about Gold (I) and Related Catalyses”

Dr. Chung-Ming Sun** – Department of Applied Chemistry, National Chiao-Tung University, Taiwan
“Design and Synthesis of Novel *N*-Methyl *D*-aspartate (NMDA) Receptor Modulators for the Therapeutic Utility in Schizophrenia”

Dr. Greta Varchi* – Head, Chemistry and Nanotechnology, Healthcare Unit, ISOF, Italy

“Nano-biomaterials for Cancer Treatment and Wound Healing Management: a Light Triggered Implemented Approach”

12:00 pm to 12:55 pm

Lunch and Poster Session
Chapel (invited speakers and faculty only) Zodiac Gallery (students)

1:00 pm to 3:00 pm

Session V (Chemical Synthesis in Industries)

Moderator: Dr. Leila Abrous

Dr. Stephen Brandstadter*** – *Principal Investigator, DuPont Fluorochemicals Research & Development*
“The Fluorochemical Enterprise 2015: Renewal and Reinvention”

Dr. Matthew Zhao** – *Senior Director in Process Chemistry, Lexicon Pharmaceuticals*
“Process Development of LX4211, SGLT1/SGLT2 Dual Inhibitor for the Treatment of Diabetes”

Dr. Masaki Fujiwara** – *Electronic Materials Sales Department, Central Glass Company, Ltd., Japan*
“Fluorine Chemical Synthesis at Central Glass”

Dr. Koji Kato* – *Manager, Marketing and Sales Division, Tosoh F-Tech, Inc., Japan*
“Industrial Synthesis of 5-(Trifluoromethyl)uracil and its Derivatives”

Dr. Jin Chen* – *Senior Research Scientist at Corporate Research & Engineering, Kimberly-Clark Corporation*, “Chemical Synthesis in Consumer Products”

3:00 pm to 3:45 pm

Coffee Break and Poster Session

Theater Lobby

3:45 pm to 4:45 pm

Closing Lecture

Moderator: Dr. Michael L. Miller

Dr. Iwao Ojima – *University Distinguished Professor, Department of Chemistry, and Director, Institute of Chemical Biology and Drug Discovery, Stony Brook University*

“Quest for Scientific Excitement at the Multidisciplinary Interface of Chemistry and Biology”

5:00 pm to 6:30 pm

Farewell Reception

Theater Lobby

***** Plenary Speaker, ** Keynote Speaker, * Invited Speaker**

Time allocation: Plenary Speaker 30 minutes, Keynote Speaker 25 minutes, Invited Speaker 20 minutes

Speakers



Dr. Makoto Fujita was born in 1957 in Tokyo, Japan. He is currently Professor of Department of Applied Chemistry, Graduate School of Engineering, The University of Tokyo, Japan. He received his Ph. D. degree from Tokyo Institute of Technology in 1987. After working in Chiba University (1988-1997, as Assistant Professor, Lecturer, and then Associate Professor), Institute for Molecular Science (IMS) at Okazaki (1997-1999), and Nagoya University (1999-2002, as Full Professor), he moved to the current position in 2002. He was appointed as a Visiting Professor at POSTECH during 2012-2014. He is also an Honorary Professor at the Department of Chemistry, Renmin University of China. He is a recipient of SSOCJ Incentive Award in Synthetic Organic Chemistry (1994), The CSJ Award for Creative Work (2000), IBM Science Award (2001), International Izatt-Christensen Award (2004), Japan Society of Coordination Chemistry Award (2010), Leo Ezaki Prize (2010), Thomson-Reuter Research Front Award (2012), The Chemical Society of Japan (CSJ) Award (2013), ACS Arthur C. Cope Scholar Award (2013), ISNSCE 2014 Nanoprize (2014), Medal with Purple Ribbon (2014), Fred Basolo Medal (Northwestern University) (2014).

“Crystalline Sponge Method for Synthetic and Pharmaceutical Studies”

The crystalline sponge method is a technique for X-ray single crystal diffraction (SCD) analysis that does not require the crystallization of the sample.^{1,2} In this method, tiny crystals of porous complexes are soaked in the solution of a target, where the complexes can absorb the target molecules. The crystallographic analysis clearly determines the absorbed guest structures along with the host frameworks. As the SCD analysis is carried out with only one tiny crystal, the required sample amount is of the nano-to-microgram order. With chiral guests, the space group of the crystal turned into chiral, enabling the determination of absolute configuration of the guests from the anomalous scattering from the host ZnI₂ component. We demonstrate that even ~50 ng of a sample is enough to be analyzed. In this talk, a focus will be on the updated crystalline sponge method emphasizing the synthetic and pharmaceutical application as well as on the scope and limitation. ³



Dr. Scott Kuduk obtained his B.S. and Ph.D. degrees at the State University of New York at Stony Brook under the guidance of Professor Iwao Ojima. He joined the Merck Research Laboratories (MRL) in 1999 after completing postdoctoral studies with Professor Samuel Danishefsky at the Memorial Sloan-Kettering Institute for Cancer Research. At Merck, he was a Director of Medicinal Chemistry, where his research has dealt with the

design of novel therapeutic agents for the treatment of pain, sleep, schizophrenia, Alzheimer's, and HIV. Toward this end, he has worked on numerous ion channel, enzyme inhibitor, and GPCR antagonist/modulator programs leading to the discovery of 11 clinical candidates across four discovery programs. After 15 years at MRL, he joined Novira Therapeutics, a biotechnology company focused on the discovery of novel antiviral agents for the treatment of Hepatitis B. as Director of Chemistry.

“Evolution of M1 Receptor Selective Positive Allosteric Modulators for the Treatment of Alzheimer's Disease”

Identification of new mechanisms to treat the neurodegenerative effects of Alzheimer's disease (AD) represents a major unmet medical need. One approach to ameliorate the cognitive decline in AD has been to target the neurons of the basal forebrain cholinergic system via activation of the M1 muscarinic receptor. Non-selective M1 muscarinic agonists have previously shown positive cognitive effects on in AD patients, but were limited due to cholinergic adverse events thought to be mediated by activation of the M2 to M5 sub-types. One strategy to confer selectivity for M1 is to identify a positive allosteric modulator, which would target an allosteric site on the M1 receptor rather than the highly conserved orthosteric acetylcholine binding site. This presentation describes the chemical evolution of HTS lead quinolone carboxylic acid BQCA into a highly selective Quinolizidinone carboxylic acid M1 positive allosteric modulators with good pharmacokinetic and *in vivo* properties.

Speakers



Dr. Bibia Heidmann received her Ph.D. from the University of Paris XI, Curie Institute at Orsay, France under the direction of Dr. David S. Grierson (2002). She was a Postdoctoral Research Associate at the State University of New York at Stony Brook under the supervision of Professor Iwao Ojima (2003-2004). She joined Nero3D and then Speedel, working on central nervous system disorders and cardiovascular diseases (2004-2008). In 2009, she joined

Actelion Pharmaceuticals, where she worked on various projects covering different fields such as antimalarial, sleep disorders and epilepsy. Towards this end she worked on enzyme inhibitors, GPCR modulators and ion channels. Her work successfully delivered 1 clinical candidate that already successfully finished Phase I clinical trials and 2 preclinical candidates that are planned to enter into man by the end of 2015. Her achievements in those different fields were acknowledged by three “Actelion Preclinical Candidate” awards and with the “Actelion Sabbatical Research Award”. She was appointed Project Team Leader in the CNS department in April 2013 where she is currently leading a project in neurodegenerative diseases.

“Discovery of Highly Potent Dual Orexin Receptor Antagonists via Scaffold Hopping Approach”

Insomnia is a widespread condition characterized by difficulty to initiate and/or to maintain restorative sleep. Among many debilitating side effects, insomnia can lead to excessive fatigue, poor work performance, and driving impairments. The physical and psychological distress of people suffering from insomnia as well as the lack of treatments that improve restorative sleep without the usual dependency or next day impairment side effects led to intensive research in the field. The orexin system is an evolutionarily conserved neuropeptide–receptor system that acts as a central regulator of wakefulness. The system consists of two GPCRs, the orexin-1 and the orexin-2 receptors, expressed in diverse regions of the brain and two peptide agonists orexin-A and orexin-B, produced in the lateral hypothalamus. Two dual orexin receptor antagonists (DORA) have been studied in clinical trials for the treatment of sleep disorders. In patients, both compounds dose-dependently increased sleep efficiency and total sleep time. We report here the identification of novel starting points as DORA following a scaffold hopping approach. We also describe the structural optimization of one scaffold into CNS penetrant DORA that decreased wakefulness and increased non-REM and REM sleep while maintaining physiological sleep architectures in rat and dog electro-encephalography/electro-myography (EEG/EMG) experiments.



Dr. Hauh-Jyun Candy Chen is a Professor in the department of Chemistry and Biochemistry at National Chung Cheng University (NCCU) in Taiwan. She received her B.S. degree in Chemistry from National Cheng Kung University (NCKU) in Taiwan (1983) and Ph.D. degree in Organic Chemistry from State University of New York at Stony Brook (1988) under the supervision of Prof. Iwao Ojima. After postdoctoral work at the National Institutes of Health and the Rockefeller University, she joined American Health Foundation where she was later promoted to Associate Research Scientist, a tenure-track position. From 1997–2004, she held the positions of Assistant through Full Professor at the National Chung Cheng University, Taiwan. Her research interests started from medicinal chemistry to toxicological chemistry, and shifted to bioanalytical chemistry. She has developed several mass spectrometry-based analytical methods for DNA and protein adducts.

Dr. Chen received the Outstanding Research Award in 2005 from NCCU. She served as an executive officer of the Taiwanese Society for Mass Spectrometry (TSMS) in the periods of 2007-2009 and 2012-2015. In 2014, she served as the Chair of the Female Chemist Organization. In 2014, she was elected as the Distinguished Alumni from the Chemistry Department of NCKU.

“Trace Analysis of DNA and Protein Adducts in Humans by Mass Spectrometry”

Human are constantly exposed to endogenous and exogenous chemicals capable of reacting with biomolecules such as DNA and proteins. DNA adduction plays a critical role in the initiation stage of carcinogenesis. Analysis of DNA adducts provide feasible biomarkers of DNA damage in vivo. Because DNA adducts are present in trace amounts and the matrix containing them are complex, highly sensitive and specific assays are demanded. We have developed mass spectrometry-based assays in human urine, saliva, blood, and tissues of various DNA adducts derived from endogenous oxidation and exogenous sources. Incorporation of stable isotopes of the target analytes as internal standards grants accurate quantification of these adducts. Nanoflow ultraperformance liquid chromatography coupled with nanospray. Modifications of proteins can lead to alteration of protein functions. Posttranslational modifications (PTMs) in human hemoglobin, including nitration, oxidation, chlorination, bromination, and glutathionylation, were characterized by high-resolution mass spectrometry. Only one drop of blood is required to quantify the extents of these modifications, which are used to assess the degree of oxidative stress in patients with cancer and with diabetes mellitus.

Speakers



Dr. Tadashi Honda was born in Japan in 1951. He graduated from the University of Tokyo in 1974 and earned his Master's degree in 1976 and Ph.D. in 1979 from the University of Tokyo. In 1979, he joined Suntory Institute for Biomedical Research and was involved in the discovery of anti-cancer drugs based on natural product models. Amongst several anti-cancer drug candidates that he invented during his pharmaceutical career at

Suntory, 2 α -L-arabinopyranosyl-9-hydroxyellipticinium bromide (SUN4599) was evaluated in phase II clinical trials for the treatment of solid tumors, but failed due to hepatotoxicity. In 1991, he was invited to the Central Pharmaceutical Research Institute at Japan Tobacco Inc. as a Chief Senior Research Scientist. In 1995, he joined the Department of Chemistry at Dartmouth College as a research faculty. He has been engaged in the development of new anti-inflammatory and cytoprotective agents by modifications of naturally occurring pentacyclic triterpenoids. Currently, bardoxolone methyl (BARD) has been evaluated in phase 2 clinical trials for the treatment of pulmonary arterial hypertension (PAH) in the United States and diabetic nephropathy in Japan. In 2010, he joined the Department of Chemistry (as a Research Professor) and ICB&DD at the State University of New York at Stony Brook.

“Michael Acceptors as Nrf2 Activators for the Treatment of Inflammatory Diseases – From Bardoxolone Methyl to Monocyclic Cyanoenones”

Bardoxolone methyl (BARD, a pentacyclic triterpenoid), one of the most potent Nrf2 activator, is expected to be a new class of anti-inflammatory and cytoprotective drug. Currently, BARD has been evaluated on phase 2 clinical studies for the treatment of diabetic nephropathy, for which the therapeutics are unmet medical needs, in Japan and pulmonary arterial hypertension (PAH) in the United States.

A tricyclic compound, TBE-31, which is another highly potent Nrf2 activator, is expected to be a second generation drug for the treatment of diabetic nephropathy because TBE-31 has various features which BARD does not have. For example, TBE-31 significantly and dose-dependently increases glomerular filtration rate (GFR) in Ang II-treated rats and even reverses the Ang II effect on GFR at 50 $\mu\text{mol/kg}$, while RTA405 (an analogue of BARD) increases at three times higher dosage (193 $\mu\text{mol/kg}$) but does not abolish the Ang II effect.

To explore reversible covalent drugs, which bind with protein targets but not permanently, monocyclic, bicyclic, and tricyclic compounds containing a cyanoenone as an electrophilic fragment, were synthesized and evaluated as Nrf2 activators. Notably, monocycles MCE-1 and 31 show the highest potency, which are approaching the potency of CDDO whose methyl ester is BARD.



Dr. Zihao Hua received his Bachelor of Science degree at Peking University in China and his Ph.D. at the State University of New York at Stony Brook. From 2004 – 2006, Dr. Hua performed his postdoctoral research at the Memorial Sloan-Kettering Cancer Center under the mentorship of Professor Samuel Danishefsky. From 2007 to the present, Dr. Hua has been working at Amgen Inc. as a medicinal chemist at its Cambridge, MA research site.

“Structure-based Design of Potent and Selective Tankyrase Inhibitors to Target the Wnt Pathway”

The evolutionarily conserved Wnt/ β -catenin (canonical) signaling transduction pathway plays a critical role in embryonic development and maintenance of homeostasis in mature tissues. Tankyrases are proteins in the poly-ADP-ribose polymerase (PARP) family. They have been shown to directly bind to axin proteins, which negatively regulate the Wnt pathway by promoting β -catenin degradation. Inhibition of tankyrases may offer a novel approach to the treatment of APC-mutant colorectal cancer. The hit compound was identified as an inhibitor of tankyrase through a combination of substructure searching of the Amgen compound collection based on a minimal binding pharmacophore hypothesis and high-throughput screening. Structure-based optimization of the hit compound led to the identification of more potent and selective tankyrase inhibitors with improved pharmacokinetic properties in rodents, which are well suited as tool compounds for further *in vivo* validation studies.



Dr. Songnian Lin is a Principal Scientist and Project Leader at Merck Research Laboratories Kenilworth site in New Jersey. Dr. Lin was born and raised in a small village in southern China. In 1994, he earned his BS in Chemistry from the University of Science and Technology of China, and then pursued his graduate studies at the State University of New York at Stony Brook where he obtained his

Ph.D. in 1999. He stayed briefly as a post-doctoral research fellow with his Ph.D. supervisor Dr. Iwao Ojima to continue studying new organic methodology development with β -lactam and development of taxane-based antitumor agents. Early in 2000, Dr. Lin moved to Dr. Samuel Danishefsky's Laboratory at Memorial Sloan-Kettering Cancer center in New York City as an US Army Breast Cancer Research Fellow. He accomplished the first total syntheses of natural products TMC95 A & B (proteasome inhibitors) and Guanacastepene A (diterpene antibiotic) during his two-year tenure there. In March 2002, Dr. Lin was offered a Sr. Research Chemist position by the Merck Research Laboratories Rahway site, and in 2005 was promoted to Research Fellow and in 2009 to Sr. Research Fellow. In 2012, Dr. Lin was appointed as Director of Chemistry of the Merck Research Laboratories Kenilworth site, where he has been leading multi-discipline research teams in the area of drug discovery. Dr. Lin's research interests at Merck span across a wide range of disease areas, including diabetes, obesity, inflammation, hypertension, anemia, vaccine, etc. His current focus is development of peptide/protein biologics for the treatment of diabetes.

“Discovery of a Novel and Potent Glucagon Receptor Antagonist for the Treatment of Type II Diabetes”

Blood glucose levels are maintained by the balance of glucose production in the liver and glucose uptake in peripheral tissues. An inappropriately high rate of hepatic glucose production (HGP) is the predominant cause of fasting hyperglycemia and a major contributor to the postprandial hyperglycemia characteristic of type 2 Diabetes (T2DM). The glucagon receptor is predominantly located in the liver and upon activation stimulates hepatic glycogenolysis and gluconeogenesis. Studies in T2DM patients have demonstrated a causal role for glucagon in promoting excessive HGP. Glucagon receptor antagonists (GRAs) therefore have the potential to reduce HGP and be effective anti-diabetic agents. Clinical studies of GRAs MK-0893 and LY-2409021 have demonstrated the superior efficacy of GRAs in lowering blood glucose and reducing hemoglobin A1c. The goal of our research was to identify a structurally distinct backup to MK-0893. The synthesis and the SAR leading to the identification of a novel quinoline based potent GRA will be discussed.



Dr. Michael L. Miller received his PhD in Organic/Medicinal Chemistry from the University of Memphis under the direction of Partha S. Ray where he initially began working with highly potent compounds in the synthesis of both novel folic acid derivatives and a new class of aza-taxoids. In 1997-98, his work with the synthesis of pyrimidoazepine-based folates was recognized by the ACS Medicinal

Chemistry Division in the form of a National Fellowship. In 1998, he joined Professor Ojima's laboratory as a postdoc at the State University of New York at Stony Brook where he continued his work with potent molecules towards the design and synthesis of taxoids with potential applications across a broad range of therapeutic areas. During this time he was able to help lead a collaboration with ImmunoGen, Inc. to develop novel taxoids for use in Antibody-Drug Conjugates (ADCs). At the conclusion of his postdoc with Professor Ojima he joined ImmunoGen, Inc. in Cambridge, MA in 2000 to lead a New Effector Program with the goal of designing highly potent effector molecules to increase the application and therapeutic index of ADCs. In his 15 years at ImmunoGen, Inc. he has gained extensive knowledge in the design and synthesis of highly potent effector molecules, their properties in regards to conjugation with antibodies and the development of ADCs as therapeutics for the treatment of cancer. He currently lives in Framingham, MA with his wife Jennifer and their two children, Katherine and Andrew.

“Design, Synthesis and Evaluation of a Novel Class of Potent DNA-Alkylating Agents for Use in Antibody-Drug Conjugates (ADCs)”

There are currently over thirty Antibody-Drug Conjugates (ADCs) undergoing clinical evaluation, reflecting the interest in ADCs for the treatment of cancer. Most of these ADCs utilize a tubulin-interacting small molecule as their cytotoxic payload. In order to continue to extend the application of ADCs to more cancer types, there has been a strong need to develop cytotoxic payloads with other mechanisms of action. In light of this, we have designed and synthesized a new class of potent DNA-alkylating agents, “indolino-benzodiazepine dimers” (IGNs). These compounds are highly cytotoxic *in vitro* towards cancer cell lines, with IC_{50} values in the picomolar range. Linkable versions of IGN compounds have been synthesized and conjugated to monoclonal antibodies directed against tumor-associated antigens. These antibody-IGN conjugates display high antigen-specific potency *in vitro* and anti-tumor activity *in vivo* at non-toxic doses. The chemical design, synthesis and preclinical data for representative IGNs and their ADCs will be discussed.

Speakers



Dr. Masakatsu Eguchi received his B.S. degree in 1981 and M.S. degree in 1983 in pharmaceutical science from the Tokyo College of Pharmacy (now Tokyo University of Pharmacy and Life Science) working under Prof. Shoji Hara. His Ph.D. degree was granted from Brigham Young University, Department of Chemistry in 1990, where he worked under the late Prof. Bryant Rossiter. Subsequently, he did postdoctoral work at the State University of New York at Stony

Brook with Prof. Iwao Ojima ('90-'93) and Sandoz (now Novartis) with Dr. Russell Petter. In 1994, he joined Molecumetics Ltd. as a Senior Scientist and in 1999 he was promoted to Senior Research Fellow working on the design and combinatorial synthesis of peptidomimetics. In 2000, he moved to the Pacific Northwest Research Institute as a Staff Scientist with Prof. Michael Kahn and in 2004 continuously worked with him at the Institute of Chemical Genomics. In December 2005, he moved to CGEN Discovery (now JW Theriac Pharmaceutical) as Chief of Chemistry. He has held this position since then. He has been actively involved in drug discovery efforts for 20 years.

“Peptidomimetics in Drug Discovery: The Progress Since the Last Meeting”

We generated a library of bicyclic beta-turn mimetics with combinatorial solid-phase synthesis. Screening of the library using TOPFlash reporter assay led to the discovery of ICG-001. Structural modifications of ICG-001 were carried out, aiming for the development of anti-cancer agents, to produce more potent inhibitors of Wnt signaling pathway. Chemistry and biological activities of those compounds will be discussed



Dr. Tao Wang was raised in Tongling, Anhui in China. After obtaining a B.S. degree from University of Science and Technology of China (USTC) in 1994, he came to Stony Brook University and joined Professor Ojima's group the following year, working on beta-lactam and taxoid chemistry. Dr. Tao got his Ph.D. in 1999 and carried out his postdoc training in Professor Koji Nakanishi's group at Columbia University. After

a brief stay with 3-Dimensional Pharma (Cranbury, NJ), Dr. Tao joined the Oncology department of AstraZeneca (Waltham, MA) and in the following 10 years as a Principal Scientist led the teams to deliver three clinical candidates. Dr. Tao has been with Biogen since 2013 working in the areas of Immunology and Hematology. He lives in Sudbury (A town famous for its zip code 01776 and the oldest inn in the United States still in operation—Longfellow's Wayside Inn), MA with his wife Fei, a Stony Brook Alumni (B. A. 2000), daughter Rena and son Yifei. In his spare time, Dr. Tao likes biking with his children and reading.

“Discovery of Potent, Selective Trk and JAK1/2 Kinase Inhibitors for Treatment of Cancer and Myeloproliferative Neoplasms”

Trks are a family of receptor tyrosine kinases activated by neurotrophins. Recent discoveries on their cancer disease association have attracted more attention to discover small molecule inhibitors against this target. High-throughput screening identified a promising hit in the 4-aminopyrazolylpyrimidine chemotype. Initial optimization of the series led to nM potency Trk inhibitors. Further optimization using two strategies led to the discovery of AZ-23, a potent, orally bioavailable Trk A/B inhibitor. Two fusions on the central pyrimidine ring resulted in two 5/6-bicyclic series comprising either imidazo[4,5-*b*]pyridines or purines. Further optimization of these two fusion series led to compounds with pico-molar potencies against TrkA kinase in cellular assays and *in vivo* antitumor effects. The two Trk programs generated two clinical candidates AZD6918 and AZD7451 against cancer. Myeloproliferative neoplasms (MPNs) are a group of clonal hematopoietic stem cell disorders that have the potential to transform to acute myeloid leukemia (AML). A valine-to-phenylalanine change (V617F) in the pseudo-kinase domain was found in a majority of MPNs. Starting from our Trk compounds, we developed SAR to improve the JAK2 potency and to get away from JAK3 and Trks. This project progressed to generate AZD1480, a JAK1/2 inhibitor that entered in clinical development against MPNs and cancer.



Dr. Claude Commandeur was born in 1976 in France. In 2003, he received his Ph.D. degree in organic chemistry under the supervision of Professor Max Malacria from Université Pierre et Marie Curie (Paris VI). After two years as a postdoctoral fellow at the State University of New York at Stony Brook under the supervision of Prof. Iwao Ojima, he joined IECB (Pessac, France) as a postdoctoral fellow (ARC) in the group of Dr. Michel

Laguerre. From 2007 to 2009, he worked as a postdoctoral fellow in the group of Professor Léon Ghosez in collaboration with Syngenta (Switzerland). He moved to Paris, first at the Institut Curie under the supervision of Dr. Jean-Claude Florent. He then joined the group of Professor Janine Cossy for a postdoctoral stay in collaboration with Laboratoires Pierre Fabre. Since 2013, he has been working as the Medicinal Chemistry Team Leader in the Research and Development Department at Selvita S.A. in Krakow, Poland with his wife Gosia, who is, in his own words, “Claude’s best discovery”.

“Design of MELK Covalent Inhibitors”

Triple Negative Breast Cancers (TNBCs) represent 10-20% of all breast cancers. TNBCs are biologically more aggressive and more likely to spread and recur. Less than 30% of women having metastatic TNBC survive 5 years. Furthermore, almost all die of TNBCs regardless adjuvant chemotherapy they received.

In recent studies, maternal embryonic leucine zipper kinase (MELK) has been identified as a novel oncogenic kinase that is highly overexpressed in several cancer types such as colon, breast and ovary. MELK is also overexpressed in TNBC and MELK knockdown significantly inhibits growth of breast cancer cell lines.

Up to date, the majority of kinase inhibitors are ATP-competitive. However, there has been renewed interest in the development of inhibitors that covalently bind to nucleophilic residues such as cysteine from ATP-binding pocket. Indeed, development of irreversible inhibitors presents several advantages such as improving efficiency, lowering required dosing and preventing drug resistance.

During this lecture, our recent achievements in developing both MELK ATP-competitive and covalent inhibitors, targeting a unique cysteine from the ATP-binding pocket will be presented.



Dr. Elke Schoffers is a native of Germany and received her undergraduate chemistry degree at the Johannes Gutenberg Universität in Mainz. Working under the supervision of Professor Iwao Ojima, she investigated asymmetric reactions of chiral β -lactam esters for her M.S. thesis before continuing her Ph.D. at Wayne State University under the supervision of Professor. C. R. Johnson with whom she completed her work in chemoenzymatic

synthesis. After studying (π -allyl)-molybdenum complexes as a postdoc at Case Western Reserve University with Professor A. J. Pearson, she started her independent career at Western Michigan University in Kalamazoo, Michigan. She is interested in the development of new synthetic methods, the synthesis of bioactive molecules and the design of ligands for catalysis.

“Beyond the Lab Coat – Scientists as Educators and Citizens”

As a university professor, much time is devoted to teaching lectures, overseeing laboratories and supervising undergraduate and graduate research students. However, this presentation will highlight my role outside these typical chemist roles by sharing my experience as an ACS Local Section Officer and the unusual paths this has led me on. I have organized outreach events for 20 to over 700 participants, some of which have included science poster sessions at a local bar, hands-on activities at a museum and combining “Chemistry & Culture” for several out-of-the-box activities. I will share my opinion on the role of service and the responsibilities of chemists when they don’t wear a lab coat

Speakers



Dr. Subrata Chakravarty has two Ph.D. degrees, one earned in India, and the second at the Department of Chemistry at Stony Brook University under the mentorship of Professor Iwao Ojima. After a postdoctoral stint in the same laboratory, Dr. Chakravarty moved to the San Diego biotech world as a medicinal and computational scientist at Idun Pharmaceuticals. He also worked at Valeant Pharmaceuticals, Accelrys and MannKind Corporation before

making a transition into management. He became the CEO of a startup natural supplements company where he stayed for 3 years. Since 2010, he has been the Chief Science and Technology Officer of the Hope4Cancer Institute, a leading natural cancer treatment clinic located in Baja California, Mexico. Besides his responsibilities in science, product and technology development, he is also a key member of the executive team driving policy decisions in areas of management, marketing, legal, administration and, most importantly, optimal patient care.

“Tales of a Meandering Scientist”

Is being worried about your future normal while going through the graduate school experience? How about we replace the word "worried" in that sentence by "terrified"? Dr. Chakravarty will highlight a powerful fact he learned from his experience: there is simply no value to being worried, let alone, being terrified. To highlight this concept, Dr. Chakravarty will use examples from the roller coaster journey that he started as a nerdy student in the Ojima laboratory. From there, he went on to become a scientist in "little" pharma and then quantum-leaped into management as the CEO of a startup nutritional company. Today, Dr. Chakravarty has found purpose in his current position as a senior executive in a cancer clinic, where he develops treatments for advanced cancer patients and overlooks the various aspects necessary to manage their recovery.



Dr. Elizabeth Pollina Cormier is a chemist for the US Food and Drug Administration's Center for Veterinary Medicine where she focuses on the evaluation of the various quality aspects of drug manufacturing. Dr. Cormier is recognized as an expert in the regulation of active pharmaceutical ingredients, and has served on several FDA-wide committees involved in the development of Agency policies for good manufacturing practices, contract manufacturing, and drug substances.

Throughout her ten years at the FDA, she has received numerous awards, including the FDA Centennial Honor Award for her contributions to the FDA and the public health.

“Chemists, Chemistry, and the FDA: Building Quality into Drug Manufacturing”

Prior to joining the FDA, Dr. Cormier received her bachelor's degree with honors in chemistry from Dartmouth College, during which time she conducted research at the State University of New York at Stony Brook and Merck Research Laboratories. And she was a Howard Hughes Medical Institute Undergraduate Fellow. She received her Ph.D. in organic chemistry from the University of Pennsylvania, where she developed novel synthetic methods using samarium(II) iodide in the laboratory of Dr. Gary Molander. Her interest in chemistry was sparked by her experiences in the Professor Iwao Ojima Group during which time she was a national finalist in the Westinghouse Science Talent Search (currently known as the Intel Science Talent Search).



Speakers



Dr. Zhaoyang (Paul) Li received his Bachelor of Science and Master of Science degrees from Nankai University in China in. He obtained his Ph.D. in chemistry from the University of South Carolina in Columbia, South Carolina. From 1994 – 1997, Dr. Li did his Postdoctoral research at the State University of New York at Stony Brook under the guidance of Professor Iwao Ojima. He then attended the J.D. Vanderbilt School of Law. He is currently a

partner in DLA Piper, LLP and specializes in life science IP and soft technical related IP issues including patent prosecution, licensing and commercialization. Dr. Li represents clients on complex IP matters, particularly those involving Chinese companies, including patent prosecution, patent infringement assessment opinions, patent right licensing agreements, patentability, and IP counseling and due diligence.

He also handles patent litigation for a variety of private and public companies that work in highly technical areas, including biotechnology, biopharmaceuticals, pharmaceuticals, stem cell technologies, including cell therapy such as tissue engineering, telecommunications and electronics, among others. He represents clients ranging from startup companies to top research institutions and giant multinational conglomerates.

He coordinates legal teams and facilitates their work on oil and gas projects as well as engineering, procurement and construction projects of Chinese state-owned enterprises (SOEs) and large companies in the private sector.

He helps companies navigate China IP strategies, strategies on salvaging and recapturing China IP patent rights and regaining IP advantageous positions in China. He also advises large and startup companies on trade secret issues and strategies in China. Dr. Li has extensive experience in assisting clients on small molecule pharmaceutical patent matters, including new chemical entity and formulation patents, and related paragraph IV certification issues in associated with new drug application (NDA) or abbreviated new drug application (ANDA) matters.

In 2014, he received recognition and has been listed as a recommended lawyer by the prestigious English legal directory The Legal 500 United States.

He was appointed by the US State Department as the US Intellectual Property Rights (IPR) speaker in the Greater China region to promote IPR protection and enforcement. He also serves as a special adviser to the Technology Commercialization Research Center for Nanjing University, which hosts training programs for companies in various Chinese sectors.

“IP Commercialization: Trends and Issues”

Dr. Li will discuss basic concepts of IP, IP commercialization elements by way of examples, and new trends and issues.



Dr. Deric Geng obtained his Ph.D. degree from the State University of New York at Stony Brook in 2002, where he designed and synthesized taxoid and taxane-free anticancer agents in Professor Iwao Ojima's laboratories. From 2002 to 2004, Dr. Geng was a US Army Breast Cancer Research Foundation Postdoctoral Fellow in Dr. Samuel Danishefsky's laboratory at the Memorial Sloan-Kettering Cancer Center in New York,

where he accomplished the total synthesis of anticancer agent aigialomycin D and worked as a part of a team to design and accomplish the total synthesis of fully synthetic gp120 glycopeptides as anti-HIV vaccine agents.

From 2004 to 2008, he was a Research Investigator at the Novartis Institute for Biomedical Research in Cambridge, Massachusetts. His primary research involved discovering drug-like molecules that modulated protein targets and pathways implicated in diabetes and metabolic diseases.

He is currently a patent attorney at WilmerHale, LLP. As a Senior Associate at WilmerHale, Dr. Geng focuses his practice on intellectual property law, specifically on U.S. and foreign patent prosecution, due diligence, prior art and patentability searches, freedom to operate analysis and patent litigation. Dr. Geng has helped a variety of start-up, mid-size and well-established clients in the chemical, pharmaceutical, biotechnology and energy industries to obtain patent protection in the US and foreign countries. Utilizing his core IP practice skills, Dr. Geng has also assisted clients in patent infringement litigations and trade secret litigations.

“From Bench to Bar: An introduction to A Career in Patent Law for Chemists”

Speakers



Dr. An Vu received his education in the South. In 1992, after completing high school, he attended Mercer University in Georgia and graduated with a B.S. in Chemistry. In 1997, he received his Ph.D. in Organic Chemistry from Emory University in Atlanta. He then worked with Professor Iwao Ojima as an NIH Postdoctoral Research Fellow at the State University of New York at Stony Brook. In 1999, he joined Wyeth Research in Collegeville,

Pennsylvania where he led a group of medicinal chemists to develop novel drug substances in diverse therapeutic areas including the central nervous system, women's health, oncology, and hormone and pain therapies. In 2011, Dr. Vu switched his career from drug discovery to regulatory compliance and worked for the FDA Center for Drug Evaluation and Research (CDER). As a drug compliance officer at CDER, he conducted current good manufacturing practice (CGMP) evaluations of drug manufacturing facilities and provided advice and guidance regarding conformance with CGMPs to drug manufacturers and other components within the FDA. With the passage of the Tobacco Control Act in 2009, Dr. Vu was recruited to the FDA's newly created Center for Tobacco Products (CTP) and brought with him a broad knowledge of the Food, Drug and Cosmetic Act, regulations, policies, and guidance. In his current position as a Senior Chemist at CTP, he reviews marketing applications and industry submissions, and evaluates tobacco research studies. He also provides scientific expertise to develop regulations and guidance for industry. In his free time, Dr. Vu enjoys traveling to fun places with his wife and two young daughters, Sophie and Cecily.

“The Role of Chemists at FDA's Center for Tobacco Products”

Prior to joining the FDA, I spent 11 years as a senior research chemist in the pharmaceutical industry. In 2011, I decided to pursue a different career path where I can apply my chemistry knowledge beyond the lab. In this panel discussion, I will share my experience about my career transition from a research chemist to a regulatory scientist. During the poster session, I will introduce the FDA Center for Tobacco Products (CTP) and discuss the role of chemists and the actions we take to reduce public health burden of tobacco use. In a separate poster, I will present a specific research project entitled *Polycyclic Aromatic Hydrocarbons in the Mainstream Smoke of Popular U.S. Cigarettes*.



Dr. Cecilia Fumero Oderda received her B.S. in Chemistry and Pharmaceutical Technologies in 1996 from the University of Torino (Italy). In 2000, she received her Ph.D. in Medicinal Chemistry from the State University of New York at Stony Brook working under Professor Iwao Ojima on a thesis entitled “SAR Study of Novel Taxoids for Macrophage Activation and MDR-Reversal Activity”. In 2003, she joined the Clinical Trial

Management department of Serono International in Geneva as Clinical Project Associate, and participated in various Phase IV studies and in two large international Phase III studies in the field of psoriasis. From 2005-2007, she was responsible for the Pre-clinical and Clinical Development and Regulatory Affairs Unit of Creabilis Therapeutics, a biotech startup in Italy. From 2007-2013, she worked as Clinical Project Manager for Genexion SA, a CRO in Geneva, Switzerland, where she was responsible for various multicenter clinical trials, ranging from Phase I to Phase III for autoimmune diseases and nutrition. Since 2013, she works as a free-lance Clinical Project Manager, mainly in collaboration with the Nestlé Research Center of Lausanne, Switzerland. She coordinates various multicenter clinical trials in the fields of infant nutrition and allergies.

“Clinical Project Managers: Chemists on the Other End of New Drugs' Development Process”

Chemists often offer their skills to pharmaceutical companies, in order to synthesize new molecules, some of which will eventually be developed and become marketed drugs. In some other cases, chemists might use their scientific knowledge to become Clinical Project Managers. After having successfully passed through a series of pre-clinical studies, a potential new drug begins the so-called “clinical development phase” which may take several years. It will initially undergo Phase I studies in healthy volunteers, followed by Phase II studies in a limited number of patients, and finally multicenter randomized Phase III trials involving an elevated number of patients, to prove beyond any doubts its efficacy and safety before registration. Clinical trials collect safety and efficacy data for health interventions, not only for drugs but also for diagnostics, devices and therapy protocols. Clinical studies involve a large variety of parties: medical writers, data managers, statisticians, medical officers, regulatory authorities, local monitors, investigational centers and their medical staff, financial and legal departments, external service providers and the clinical project manager (CPM). CPMs play a key role in the conduct and management of a clinical study. They are responsible for a clinical trial from the start-up activities (design, writing of the protocol and essential documents, selection of the investigational sites, submissions to regulatory authorities), through its active phase (subjects' recruitment, sites' monitoring, data collection), up to the closeout activities and the statistical report production. CPMs, by coordinating the activities of all parties involved, ensure the success of a clinical trial, while respecting the principles of good clinical practice, as well as project final budgets and timeline.



Dr. Thierry Brigaud is a professor at the University of Cergy-Pontoise (France). In 1990, he received his Ph.D. in Chemistry from the University Claude Bernard Lyon I (France) under the guidance of Professor Eliane Laurent working on nucleophilic fluorination in α position of an aromatic ring or a sulfur atom. In 1990, he joined the group of Professor Iwao Ojima at the State University of New York at Stony Brook working on asymmetric

synthesis of non-protein amino acids. In 1991, he joined the University of Reims-Champagne-Ardenne (France) as an Associate Professor where he defended his habilitation in 1999 on organofluorine-silicon-sulfur chemistry. In 2002, he joined the University of Cergy-pontoise (France) as a Full Professor. He is now the Head of the Biological Chemistry Laboratory of this university. His main interests are organofluorine chemistry, asymmetric synthesis, synthesis and biological applications of fluorinated amino acids and peptides.

“Fluorine Chemistry: From Asymmetric Synthesis to Peptides”

Fluorinated Oxazolidines (Fox) were found to be efficient chiral auxiliaries to perform highly stereoselective enolates alkylation, fluorination and hydroxylation reactions. This excellent stereoselectivity can be explained by fluorine-metal interactions. Fluorinated oxazolidines can also be used as starting materials for the preparation of trifluoromethylated enantiopure α - and β -amino acids (CF_3 -alanine, allylglycine, serine, proline, aspartic acid, pyroglutamic acid...). The incorporation of fluorinated unnatural amino acids into peptides may significantly modulate their physico-chemical and biological properties (hydrophobicity, control of the conformation, protease resistance...). Despite the strong deactivation of the nitrogen atom in α position of the trifluoromethyl group, we could proceed to the incorporation of these fluorinated amino acids into peptides. Some biological applications of these peptides will be presented (analgesic peptides, antimicrobial peptides...). Trifluoromethylated oxazolidines derived from serine can be considered as stable pseudoproline and constitute useful tools for the control of peptides conformations.



Dr. Vadim A. Soloshonok was born in 1961 in Ukraine. In 1983, he graduated from Kiev State University and in 1987 received his Ph.D. from the Ukrainian Academy of Sciences. In 1988-1990, he continued his education in Moscow with Professor Belokon, in 1992 in Milano with Professor Bravo and in 1994-1995 with Professor T. Hayashi in Sapporo as a JSPS Fellow. In 1995-1998, he received a permanent position in Nagoya Japan, but moved later (1998-

2001) to the USA to join the Professor Victor J. Hruby group in Tucson, Arizona. In 2001, he joined the faculty of the University of Oklahoma where he served as Associate Professor of Chemistry for almost 10 years. In 2011, he accepted an offer from Ikerbasque to move to the San Sebastian campus joining the faculty of the University of Basque Country, as a Ikerbasque Research Professor. He also holds a position of Visiting Professor in the Department of Chemistry, State University of New York at Stony Brook. He is a member of the international advisory editorial board of the *Journal of Fluorine Chemistry* (Elsevier, 2003-present), and a member of the editorial board and Synthesis Section Editor of *Amino Acids* (Springer, 2010-present). He is currently serving as a Past-Chair of the Division of Fluorine Chemistry of ACS. He is the author of 250+ research papers, 11 book-chapters, 10 patents and 6 books. His publications have generated >8,150 citations with a current h-index of 57. His major areas of research are asymmetric synthesis of amino acids, fluorine chemistry of biologically relevant compounds and self-disproportionation of enantiomers.

“New Reagents for Installation of CF_3 , CF_2 and Quaternary CF Groups”

The remarkable bearing of fluorine on modern pharmaceutical industry shaping up the future generations of healthcare products is well recognized. In particular, fluorine-containing drug candidates usually show improved efficacy, enhanced membrane permeability and, most importantly, significantly higher stability towards oxidative degradation. Currently the interest in the development of fluoro-organic methodology is at all-time high generating an exciting wealth of new chemistry. Considering pharmaceutical potential of fluorinated compounds, aspects of practicality and cost-per-structure become the key factors in the quality assessment of the newly developed synthetic methods. Consistent with our longstanding interest in synthesis of fluorinated biologically relevant compounds and the concept of operationally convenient conditions, during the last several years we were searching for new reactions and reagents roughly divided in three major projects: chemistry of (*R*)- and (*S*)-*N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimines as general reagents for convenient installation of 2,2,2-trifluoro-1-(amino)ethyl [$\text{CF}_3\text{-CH}(\text{NH})\text{-}$] pharmacophore group into biologically interesting organic compounds; unconventional, detrifluoroacetylative generation of di-fluoro- and quaternary C-F enolates; and perfluoro-3-ethyl-2,4-dimethyl-3-pentyl persistent radical as a new reagent for radical trifluoromethylation of aromatic compounds. The newest results obtained are presented in this lecture.



Wen-Hua Chiou obtained his Bachelor of Science degree in 1993 and his Master of Science degree in 1995 from National Tsing Hua University. In 2005, he received his Ph.D. from the State University of New York at Stony Brook (Advisor: Professor Iwao Ojima). In 2006, he performed his Postdoctoral research at OSI Pharmaceutical, Inc. and since 2011 he has served as an Associate Professor at National Tsing Hua University. Dr. Chiou's research

interests lie in the development of a new methodology involving cascade-typed reactions and the design of new organocatalysts for catalytic asymmetrical synthesis of intermediates.

“Enantiomeric Syntheses of Piperidine, Indolizidine and Dendrobatid Alkaloid Epibatidine”

We describe an efficient method for preparation of enantiopure 8-azabicyclo[3.2.1]octan-6-ol (+)-**1**, which is an crucial intermediate for the syntheses of piperidine, indolizidine alkaloids. In addition, an enantiomeric approach toward (-)-epibatidine and its derivatives has been described for the development of analgesics. In this research, we have also reported a general methodology to synthesize to a 5-substituted-2-chloro-pyridine derivative.



Dr. Louis Fensterbank was born in Poitiers in 1967 and raised in Tours. In 1990, while graduating from the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL), he joined the team of Prof. Scott Sieburth at SUNY Stony Brook, worked on silicon-tethered reactions and in 1993, obtained his Ph.D. In 1994, after a temporary Lecturer position at the Université Pierre & Marie Curie (UPMC), in 1995 he was appointed by the CNRS

as a Chargé de Recherche in Prof. Max Malacria's team. In 2004, he obtained a professor position at UPMC and in 2008, he was nominated to a Junior Member of the Institut Universitaire de France. In 2009, he was a Visiting Scientist at the Australian National University, Canberra. In 2014, he was awarded the Clavel-Lespiau Prize by the French Academy of Science for his work on organic synthesis.

His research interests concern the discovery of new molecular transformations relying on radical or organometallic processes and their applications to the synthesis of substrates with relevant properties (natural products, probes, ligands...). He has authored and co-authored more than 170 publications.

“Some New Stories about Gold (I) and Related Catalyses”

Our laboratory has been interested over the last ten years in the use of electrophilic complexes (Au, Pt, Ag, Ir) for the access to molecular complexity from readily available polyunsaturated precursors. We have explored applications for the total synthesis of natural products. Some of these transformations also lend themselves to their asymmetric version notably by using the chiral anion strategy. Interestingly, the electrophilic gold catalysis based on the carbene formation from the rearrangement of propargyl acetates can lead to a new type of polycyclopropanated polymers. Examples along these lines will be presented and discussed.



Dr. Chung-Ming Sun obtained his B.S. in Chemistry from Fu-Jen Catholic University of TAIWAN in 1986. He then completed his compulsory military service for two years before he moved to the United States to pursue his Ph.D. under the guidance of Professor Iwao Ojima at the State University of New York at Stony Brook. After his doctoral research, He joined CombiChem, Inc. (merged with DuPont Pharmaceutical) as a Research Scientist working on

the design and synthesis of G protein-coupled receptors antagonists. In 1996, after two years residence in San Diego, he decided to go back to Taiwan to start his own independent research at the National Dong Hwa University. Then in 2015, he moved to National Chiao-Tung University. His laboratory developed a new multidisciplinary synthetic approach comprising polymer support synthesis, microwave assisted synthesis, multicomponent condensation and C-H activation to facilitate scaffold-directed library synthesis with a set of advantages like rapid process, simple purification and structural diversity in one shot. Microwave irradiation greatly accelerates the rate of all reactions while polymer support facilitates purifications by simple precipitation technique. Multidisciplinary synthetic approach is an integrated concept that supports the coagulation of different disciplines of synthetic organic chemistry along with their advantages to facilitate drug discovery. This strategy dramatically increases the efficiency of overall multistep synthesis of G9a (an unique target for cancer stem cell) inhibitors.

“Design and Synthesis of Novel N-methyl D-aspartate (NMDA) Receptor Modulators for the Therapeutic Utility in Schizophrenia”

The increased DAO expression and activity in the postmortem brain of schizophrenic patients had been reported in literature. The D-amino acid oxidase inhibitors (DAOI) were suggested as a novel class of drugs for schizophrenia therapy. This project aims to identify inhibitors with novel chemical structures to against DAO and ultimately target to antipsychotic therapy. Thus, we envisioned a series of inhibitors that could interact with the distinct domains of DAO based on molecular modelling method. Accordingly, a lead compound NCTU #72 was identified to show cellular DAO inhibitory effect after high throughput screening. Another lead compound RS-D7 (a metabolite of RS-D7pro) from known drugs bank showed the highest DAO inhibition effects compared to all of known DAOI compounds in literature. Two USA provisional patents were granted for RS-D7 and NCTU #72. Diverse libraries for chemical structure optimization is based on the multidisciplinary synthetic strategy comprising one pot multi-component reaction, soluble support organic synthesis, microwave assisted organic synthesis and C-H functionalization to increase diversity. During this study, we expect to obtain repurposing DAOIs which may quickly apply for a clinical trial in near future. No commercially available medicines through these targets have as yet been approved by the FDA. This gap between knowing a novel target for therapy and needing small molecule inhibitors presents a major challenge for drug discovery and development.



Dr. Greta Varchi graduated from the University of Bologna in Industrial Chemistry in July 1997. Afterwards she spent six months as Visiting Researcher at the Department of Organic Chemistry, Fachbereich Chemie of the University of Marburg in Germany, under the supervision of Professor Paul Knochel. In 2001, she received her Ph.D. in Chemical Sciences from the University of Bologna in Italy. During her PhD study, she spent 6 months at the

Department of Chemistry of Ludwig Maximilian University of Munich in Germany. In January 2002, she joined the Institute of Organic Chemistry and Photoreactivity at the National Research Council area of Bologna. From 2003 – 2004, she was a Postdoctoral Research Associate at the Department of Organic Chemistry, State University of New York at Stony Brook under the supervision of Professor Iwao Ojima. Her current scientific activity spans from stereoselective synthesis of biologically active molecules to the preparation and characterization and tailored functionalization of nanomaterial for drug delivery and diagnosis purposes. She is the author of more than 50 scientific contributions in peer-reviewed journals and 3 international patents. Since 2014, she has been appointed as the Head of the “Chemistry and Nanotechnology for Healthcare Unit” at ISOF. She is the coordinator unit of two national projects funded by the Italian Association for Cancer Research and she is responsible for ISOF of the European Project NanoREG.

“Nano-biomaterials for Cancer Treatment and Wound Healing Management: a Light Triggered Implemented Approach”

Medicine is one of the disciplines that mostly benefited from the progress of nanotechnology in the last decades. Nano-sized systems offer the unique opportunity to combine different therapeutic features on the same compartment, allowing for the delivery of multi-cargo nano-sized objects with programmed/controlled functions.

Nanotechnological solutions for treatment of cancer and infection diseases are warranted and are expected to have major health and economic impacts in the next future. Moreover, the use of unconventional treatment modalities, such as light-triggered therapies, is very fascinating since light is a powerful mean for the local and non-invasive production of therapeutic agents at a desired site, through a controlled and timely dosage of the released species. Among light activated treatment modalities, Photo Dynamic Therapy (PDT) uses photosensitizers (PSs) that under irradiation react with ambient oxygen generating reactive oxygen species (ROS) able to inactivate bacteria or kill cancer cells via apoptotic and/or necrotic mechanisms. In this regard, we will report on our recent advances in the field of nano-biomaterials for cancer treatment and wound healing management, with particular reference to *albumin-based nanoparticles* and to wool *keratin-based matrices* (films or nanofibres).

Speakers



Dr. Stephan Brandstadter received his Ph.D. from Professor Iwao Ojima at the State University of New York at Stony Brook in 1989 and did his Post-Doctoral work with W.S. Johnson at Stanford University specializing in synthetic organic chemistry and methodology. In 1992, Dr. Brandstadter joined the Great Lakes Chemical Corporation as a Research Chemist in the fluorine chemicals business eventually becoming its Technology manager.

He continued in this role within the merger that formed the Chemtura Corporation. In 2008, he joined DuPont Fluorochemicals Research & Development as a Principal Investigator.

“The Fluorochemical Enterprise 2015: Renewal and Reinvention”

Since the beginning of the new millennial, the DuPont Fluorochemical Enterprise has been investing heavily in the new and exciting chemical technologies that will allow us to move into the future with safe, sustainable and environmentally friendly materials. These new materials will meet the demanding performance, value and capabilities that our customers have come to expect from our products. All of our organization’s research and development efforts have been focused on inventing, developing and producing these new materials safely and cost effectively. This lecture will describe some of these major initiatives and their target markets and applications and the progress we have made towards these goals.



Dr. Matthew Zhao obtained his BS in chemistry from Lanzhou University in 1985. He then moved to the US to pursue his PhD in Professor Iwao Ojima’s lab at the State University of New York at Stony Brook. His PhD research focused on the synthesis of azetidines and bis-azetidines via reduction of β -lactams and bis- β -lactams respectively. Another highlight of his research was on the asymmetric synthesis of α -hydroxy- β -lactams, useful for the introduction of

the side chain of taxol and its analogs. After obtaining his PhD in 1991, he did his postdoctoral research with Professor Leo Paquette at the Ohio State University working on the total synthesis of taxucin, a taxol analog. In 1993, he then joined the Process Research Department in Merck Research Laboratories at Rahway in New Jersey. He was involved in numerous process development projects including marketed drugs, Singulair for asthma and Emend for chemotherapy induced emesis. In 2007, he joined Lexicon Pharmaceuticals as an Associate Director in Chemical Development group. He is involved in the process development of a number of Lexicon’s drug candidates including LX1606, currently in Phase III trials for carcinoid syndrome and LX4211 for diabetes, the topic of his talk today. He is currently a Senior Director in Process Chemistry at Lexicon.

“Process Development of LX4211, SGLT1/SGLT2 Dual Inhibitor for the Treatment of Diabetes”

LX4211 is a drug candidate discovered at Lexicon for the treatment of diabetes. It is a first-in-class SGLT1/SGLT2 dual inhibitor that inhibits the absorption of glucose in the gut and reabsorption of glucose in the kidney. Phase 2 clinical trials for type I and type II diabetes has been successfully completed and LX4211 is now entering Phase III trials for type I diabetes. The process chemistry synthesis of LX4211 starts from L-xylose. It features a stereoselective ketone reduction, a high yielding stereoselective acetylation via kinetic dynamic resolution, a highly stereoselective Lewis acid promoted thiolation to give the penultimate triacetate intermediate. Finally, a global deprotection by treatment with catalytic amounts of sodium methoxide furnishes the final API in excellent yield. This process has been successfully implemented on a multi-hundred kilogram scale.



Dr. Masaki Fujiwara joined Central Glass, Chemical Research Center in 2000. He visited Professor Ojima's lab in 2001-2003 as a Research Scientist. He had been working on new fluoro-organic materials synthesis development at Central Glass in Tokyo Research, as well as in San Jose Lab in California. Now he belongs to the Electronic Materials Sales Department at the Head Quarters.

"Fluorine Chemical Synthesis at Central Glass"

Fluoro chemical's world demands increase 3.9% / year. The market in 2016 is estimated \$20billion. Central Glass co., Ltd. started its commercial production of hydrogen fluoride in 1974, And since then has continuously kept developing its own fluorine chemistry in the fields of inorganic, organic and polymer chemistry using various fluorination technologies based on HF, metal fluorides and elemental fluorine. It brings many kinds of "F"-application, such as anesthesia drugs or intermediates, alternative fluorocarbons, Li-ion battery electrolytes, and photo resist lithography materials, semiconductor process gas NF_3 etc.

The basic fluorination methods at Central Glass

We have 4 practical methods to introduce fluorine substituent in the molecule. (1) Halogen exchange reaction (HALEX reaction) of Chlorine substituent using HF, (2) Electrochemical fluorination of relatively activated hydrogen substituent by using HF, (3) Dehydroxy-fluorination of hydroxy group to fluorine substituent, (4) F_2 gas fluorination for inorganic fluoride synthesis. The overview of derivatization toward various fluoro-chemicals will be described. Recently we have developed a ehydroxyfluorination method by using sulfonyl fluoride (SO_2F_2). The new fluorination method can be applied various kind of -OH group substrate to introduce fluorine substituent with high regio or stereo selectivity. This time, our cost competitive application example to produce fluoro alkyl ester at pilot plant scale will be described.

Application of Rf- SO_3H toward the most advanced semi-conductor field

To utilize the effect of fluorine in the field of advanced semi conductor, we have recently developed a Photo Acid Generator (PAG) that is fluoro-alkyl organic sulfonium salt, which is used in the current lithography process. When PAG is irradiated by light source (ArF 193nm), acid generate to react with acid labile group (tert-ester) in resist polymer to release carboxylic acid parts. The acid regenerate to catalyze (chemically amplified lithography). The parts are dissoluble in basic developer ($\text{NMe}_4\text{OHaq.}$) to be rinsed away to make patterning. The nano meter scale control is one of the key factor to improve the quality of smooth patterning. Also, some other development "F" targets will be shown.



Koji Kato completed his Master's course in Chemistry at Sophia University (Tokyo, Japan) in 1985. After starting his career in Japan Halon Co. Ltd. (former name of Tosoh F-Tech Inc.) as a researcher, he joined Professor Iwao Ojima's laboratory at Stony Brook University as a Research Associate from 1986 to 1988. In 1990, he received his Ph.D. degree from Sophia University. From 1985-1998, he worked at Tosoh F-Tech research laboratory and studied organic synthesis and process development of organofluorine compounds. In 1998, he was transferred to the Marketing and Sales division and then became manager of that division.

"Industrial synthesis of 5-(Trifluoromethyl)uracil and its Derivatives."

Tosoh F-Tech, Inc. has been produced 5-(trifluoromethyl)uracil (TFU) from 1993. TFU is used as a key material for the synthesis of Trifluridine (anti-herpes eye drop, Viroptic® by GSK). Recently, Taiho Pharmaceutical Co. Ltd. launched Lonsurf® as the oral anticancer drug which is a mixture of Trifluridine and Tipitacil hydrochloride.

We produce TFU by building block synthesis from 3,3,3-Trifluoropropene which process was established by Professor Ojima's group at Sagami Institute of Chemical Research in Japan. I would like to describe here how we improved this process in a large scale and it would be a typical example of how to establish an industrial process.

I also would like to show a new process of TFU via direct trifluoromethylation of uracil and the synthesis of 2,4-substituted 5-(trifluoromethyl)pyrimidine

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