Applied Pharmaceutical Chemistry 2017

Thursday, April 6

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In May 2011, the U.S. Food and Drug Administration (FDA) approved Vertex's first medicine, a treatment for hepatitis C. In 2012, Vertex received approval for our first medicine for cystic fibrosis in the U.S., Europe and Canada. Vertex received U.S. approval of our second medicine for cystic fibrosis in 2015. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening disease

Vertex has continually been recognized as one of the industry's top workplaces by leading publications such as Science Magazine, The Boston Globe, Boston Business Journal and the San Diego Business Journal.

ORGANIZER'S WELCOME

Welcome to the 2017 Applied Pharmaceutical Chemistry Conference. Our organizers have gathered another excellent group of speakers for the eighth annual APC conference. The program is arranged to incorporate extensive audience participation and discussion. We encourage attendees to take full advantage of the opportunity to engage in discussion in order to receive the maximum benefit from the APC experience.

Thank you for your participation.

ORGANIZING COMMITTEE

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Conference Chair: Adam Gilbert, Pfizer

Conference Chair Elect: Andreas Goutopoulos, EMD Serono

Committee Members

Susan Ashwell, Forma Therapeutics
Eamon Comer, Broad Institute
Siva Dandapani, Biogen
Simon Giroux, Vertex
Matt Hayward, Pfizer
Richard Heidebrecht, Sigilon
Benoit Moreau, Tarveda Therapeutics
Eric Schwartz, Celgene

APC 2017 CONFERENCE AGENDA

Thursday, April 6

7:30 - 8:30 REGISTRATION & BREAKFAST

8:30 - 8:40 **Conference Opening**
Adam Gilbert, Pfizer

SESSION I: COVALENT APPROACHES / CHEMOPROTEOMICS

8:40 - 8:45 **Session Introduction and Plenary Speaker Introduction**
Benoit Moreau, Tarveda Therapeutics

8:45 - 9:30 **Plenary Lecture**
Activity-Based Proteomics – Protein and Ligand Discovery on a Global Scale
Benjamin Cravatt, Scripps

9:30 - 10:00 **Design of a JAK3 Specific Inhibitor Allowing for the Interrogation of JAK3 Signaling in Humans**
Atli Thorarensen, Pfizer

10:00 - 10:30 **The Endocannabinoid System: Therapeutic Opportunities**
Alexandros Makriyannis, Northeastern University

10:30 - 10:50 Break

SESSION II: CHEMICAL BIOLOGY

10:50 - 10:55 **Session Introduction**
Siva Dandapani, Biogen

10:55 - 11:25 **Applications of Sulfonyl Fluorides in Drug Discovery and Chemical Biology**
Hua Xu, Pfizer

11:25 - 11:55 **Getting to Know Your Target**
Erik Hett, Merck

11:55 - 12:55 Lunch

12:55 - 1:00 **Plenary Speaker Introduction**
Adam Gilbert, Pfizer

1:00 - 1:45 **Discovery of PF-06747775: A Next Generation Irreversible EGFR Inhibitor Targeting the T790M Resistance and Activating Mutations in NSCLC**
Tony Wood, Pfizer

SESSION III: HUMAN DOSE PREDICTIONS

1:45 - 1:50 **Session Introduction**
Simon Giroux, Vertex

1:50 - 2:20 **Minimizing Human Dose and Plasma Levels of Drugs: Progress and Pitfalls**
Mike DeNinno, Vertex

2:20 - 2:50 **Integrated Approach to Predicting Human PK Parameters**
Sekhar Surapaneni, Celgene

2:50 - 3:10 Break

SESSION IV: PHENOTYPIC APPROACHES / PHENOTYPIC ASSAYS

3:10 - 3:15 **Session Introduction**
Andreas Goutopoulos, EMD Serono

3:15 - 3:45 **VX-787 (JNJ872): A Novel, First-in-Class, Orally Bioavailable Azaindole Inhibitor of Influenza PB2**
Michael Clark, Vertex

3:45 - 4:15 **Curing by Maturing: A Phenotypic Differentiation Screen Identifies a New Target in the Treatment of Patients with Acute Myeloid Leukemia**
David Sykes, MGH/Harvard

4:15 - 4:45 **Phenotypic Drug Discovery in SMA: Parallel Efforts in Preclinical Development and Target Identification**
Susanne Swalley, Novartis

4:45 - 5:45 **EVENING RECEPTION hosted by The Boston Society**

ABSTRACTS

SESSION I: COVALENT APPROACHES / CHEMOPROTEOMICS

PLENARY

Activity-Based Proteomics – Protein and Ligand Discovery on a Global Scale

Benjamin Cravatt, The Scripps Research Institute

Genome sequencing projects have revealed that eukaryotic and prokaryotic organisms universally possess a huge number of uncharacterized proteins. The functional annotation of these proteins should enrich our knowledge of the biochemical pathways that support human physiology and disease, as well as lead to the discovery of new therapeutic targets. To address these problems, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Prominent among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map the activity state of large numbers of proteins in parallel. In this lecture, I will describe the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease. I will also discuss the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

Design of a JAK3 Specific Inhibitor Allowing for the Interrogation of JAK3 Signaling in Humans

Atli Thorarensen, Pfizer

Significant work has been dedicated to the discovery of JAK kinase inhibitors resulting in several compounds entering clinical development and two FDA approved NMEs. However, despite significant effort during the past two decades, identification of highly selective JAK3 inhibitors has eluded the scientific community. A significant effort within our research organization has resulted in the identification of the first orally active JAK3 specific inhibitor, which achieves JAK isoform specificity through covalent interaction with a unique JAK3 residue Cys-909. The relatively rapid resynthesis rate of the JAK3 enzyme presented a unique challenge in the design of covalent inhibitors with appropriate pharmacodynamics properties coupled with limited unwanted off-target reactivity. This effort resulted in the identification of PF-06651600, a potent and low clearance compound with demonstrated in vivo efficacy. The favorable efficacy and safety profile of this specific JAK3 inhibitor led to its evaluation in several human clinical studies.

The Endocannabinoid System: Therapeutic Opportunities

Alexandros Makriyannis, Northeastern University

The endocannabinoid system includes the CB1 and CB2 cannabinoid receptors, two families of endocannabinoid ligands represented by 2-arachidonoyl ethanolamide (anandamide) and 2-arachidonoylglycerol (2AG), as well as a number of enzymes involved in their biosynthesis or their hydrophilic deactivation. Over the past twenty-five years, my laboratory has been involved in work aimed at studying the endocannabinoid system as a target for therapeutic medications. We have designed and synthesized a variety of cannabinergic ligands that have found great utility as pharmacological and biochemical probes within the scientific community, as well as novel drug leads, some of which are currently in late preclinical trials. In addition to developing novel ligands, my laboratory has also been involved in the biochemical and biophysical characterization of the cannabinergic targets (GPCRs and enzymes) through the combined use of biochemical and biophysical approaches and judiciously designed covalent ligands. This approach, which we have designated as Ligand Assisted Protein Structure (LAPS) was used to study the ligand-receptor motifs involved in CB1/CB2 activation.

I shall discuss the use of LAPS to obtain detailed

structural information on the complexes of CB1 and CB2 receptors with key cannabinergic ligands. Our work allows us to understand the basis of CB1/CB2 functional selectivity and opens the door for the design of novel compounds with improved pharmacological profiles.

This research is supported by grants from NIH/NIDA DA009158 and DA003801

SESSION II: CHEMICAL BIOLOGY

Applications of Sulfonyl Fluorides in Drug Discovery and Chemical Biology
Hua Xu, Pfizer

Sulfonyl fluorides are privileged warheads for chemical biology, as they possess a good balance of biocompatibility, stability and reactivity. They modify nucleophilic residues in a context-specific manner. In addition, sulfonyl fluorides introduce a minimal perturbation of physiochemical properties. Given these advantages, we have designed and utilized sulfonyl fluoride probes for various applications in drug discovery and chemical biology, for instance, target engagement, selectivity, and binding site elucidation. A few recent examples will be presented in this talk.

Getting to Know Your Target
Erik Hett, Biogen

Cellular phenotypic screens are a powerful way to uncover novel biology and discover druggable targets and chemical matter. One of the main bottlenecks for this approach, as opposed to target-based screening, is determining the mechanism of action of lead hits. Current approaches include using proteomics, RNAi, RNAseq, chemical probes, and in silico studies. I will share an example where we have utilized chemical proteomics and RNAi to unveil the mechanism of a small molecule hit from a phenotypic screen.

SESSION III: HUMAN DOSE PREDICTIONS

Minimizing Human Dose and Plasma Levels of Drugs: Progress and Pitfalls
Mike DeNinno, Vertex

There are numerous examples where first-in-class drugs have lost significant market share after introduction of best-in-class agents from competitors. The advantages of a best-in-class drug can be manifold including improved efficacy, better safety profile or more convenient dosing regimens. The human dose, and total and free plasma levels, can play a role in all of these best-in-class drug attributes. In this talk, I will address how focusing on a holistic approach toward lowering human dose may lead medicinal chemists in a different direction with their SAR. Importantly, a deep understanding of confounding factors must be mastered to improve the odds of success.

Integrated Approach to Predicting Human PK Parameters
Sekhar Surapaneni, Celgene

Prediction of human pharmacokinetic parameters and human dose projections is important for selection of clinical candidate and planning FIH studies. However, prediction of human PK and dose projection is challenging and complex, and multiple approaches have been adopted for accurately projecting human PK parameters and doses. The presentation discusses the purpose and various approaches to predicting human PK; and presents successes and limitations of these approaches.

SESSION IV: PHENOTYPIC APPROACHES / PHENOTYPIC ASSAYS

VX-787 (JNJ872): A Novel, First-in-Class, Orally Bioavailable Azaindole Inhibitor of Influenza PB2
Michael Clark, Vertex

In our effort to develop agents for the treatment of influenza, a phenotypic screening approach utilizing a cell protection assay identified a series of azaindole based inhibitors of the cap-snatching function of the PB2 subunit of the influenza A viral polymerase complex. Using a bDNA viral replication assay in cells as a direct measure of antiviral activity, we discovered a set of cyclohexyl carboxylic acid analogs, highlighted by VX-787 (JNJ872). VX-787 shows strong potency versus multiple influenza-A strains, including pandemic 2009 H1N1 and avian H5N1 flu strains, and shows an efficacy profile in a mouse influenza model even when treatment was administered 48h post infection. VX-787 represents a first-in-class, orally bioavailable, novel compound that offers potential for the treatment of both pandemic and seasonal influenza and has a distinct advantage over the current standard of care treatments including potency, efficacy and extended treatment window. This presentation will also highlight the newly disclosed backup PB2 inhibitor, VX-353.

Curing by Maturing: A Phenotypic Differentiation Screen Identifies a New Target in the Treatment of Patients with Acute Myeloid Leukemia
David Sykes, Massachusetts General Hospital Cancer Center

Adults diagnosed with acute myeloid leukemia (AML) have a five-year survival rate of 25%. Despite advances in understanding the genetics of this disease, the chemotherapy standard of care remains unchanged since 1973. In contrast to cytotoxic chemotherapy, differentiation therapy drives leukemia cells to mature and to overcome their differentiation blockade, pushing cells to a stage of maturation where they lose potential as leukemia stem cells.

Towards the goal of developing differentiation therapy, we engineered a cell line where development was arrested at the early myeloblast stage – a stage common across the spectrum of AML subtypes. This model permitted a rapid assessment of differentiation, and a phenotypic flow cytometry screen to identify compounds that overcome differentiation arrest.

Our strongest hits were identified as inhibitors of the enzyme dihydroorotate dehydrogenase (DHODH). DHODH is involved in de novo uridine synthesis. Inhibition of DHODH results in myeloid differentiation, resulting in a decreased leukemia burden and a depletion of leukemia stem cells. Remarkably, DHODH is neither overexpressed nor mutated in hematologic malignancies. However, normal cells can tolerate inhibition of DHODH and transient pyrimidine starvation while leukemic cells cannot, demonstrating a 'metabolic therapeutic window'.

The immediate availability of DHODH inhibitors will permit the rapid transition from pre-clinical models to the evaluation of DHODH inhibitors in the treatment of patients with acute myeloid leukemia.

Phenotypic Drug Discovery in SMA: Parallel Efforts in Preclinical Development and Target Identification
Susanne Swalley, Novartis

Historically, phenotypic drug discovery has been a mainstay of drug development, enabling the discovery of numerous therapeutic molecules. This approach is particularly attractive when there are no known targets for treating a particular indication but knowledge of the molecular pathology of the disease is high. A key challenge, however, has always been the determination of the efficacy target. A recent success story will be presented, where our team progressed a small-molecule preclinical candidate to treat Spinal Muscular Atrophy (SMA) while simultaneously

elucidating the molecular mechanism of action. SMA is the most common genetic cause of pediatric mortality, caused by the loss of expression of the survival of motor neuron-1 (SMN1) gene. A duplicate copy of the gene (SMN2) is inefficiently spliced, producing a truncated and unstable protein. The molecules we discovered through phenotypic screening and subsequent extensive lead optimization efforts enhance SMN2 splicing in a sequence-selective manner, thereby elevating levels of full-length SMN protein and extending survival in a mouse model of severe SMA. The compounds act by stabilizing the transient double-strand RNA structure formed by the SMN2 pre-mRNA and U1 small nuclear ribonucleic protein (snRNP) complex. This novel mechanism validates the feasibility of small molecule-mediated, sequence-selective splice modulation and the potential for leveraging this strategy in other splicing diseases.

BIOGRAPHIES

Susan Ashwell, PhD, FORMA Therapeutics: Prior to joining FORMA Therapeutics, Sue was a Director in the Boston-based Oncology group of AstraZeneca where she had multiple roles including line and project leadership. Before AZ, she was a medicinal chemist with Wyeth-Ayerst Research in the CNS area. During her career she has been involved with a number of programs that have resulted in clinical candidates in the Oncology, CNS disorders and Inflammation therapeutic areas. Sue received her Ph.D. the University of Newcastle upon Tyne, prior to conducting postdoctoral research at the University of Illinois at Chicago and Imperial College, London.

Michael Clark, PhD, Vertex: Dr. Clark is a Director of Chemistry at Vertex Pharmaceuticals, Inc., at the Boston research site. At Vertex, he has directed medicinal chemistry efforts in the fields of virology, inflammation, neurology and oncology. Formerly, he was Director of Chemistry at Metastatix, Inc., in Atlanta, GA, and before that a stint at Procter & Gamble Pharmaceuticals in Cincinnati, OH. Dr. Clark received his BA in chemistry from Reed College in Portland, OR and Ph.D. in organic chemistry from Indiana University-Bloomington under the direction of Prof David Williams.

Siva Dandapani, Ph.D., Biogen: Dr. Siva Dandapani is a medicinal chemist at Biogen. Prior to joining to Biogen, he was at the Broad Institute of MIT and Harvard where his work focused on utilizing the power of modern organic synthesis for accessing novel compounds for screening collections, developing small molecule probes for advancing chemical biology and conducting medicinal chemistry optimization towards several antimicrobial drugs. Dr. Dandapani received his Ph.D. in chemistry from University of Pittsburgh and conducted post-doctoral research at Boston University. He has published over 40 papers in the areas of diversity-oriented synthesis and development of small molecule probes and drugs.

Michael DeNinno, PhD, Vertex: Dr. DeNinno is currently a Research Fellow II in the Medicinal Chemistry department at Vertex Pharmaceuticals where he has spent the last eight years at both the San Diego and Boston sites. Formally, he worked in the Cardiovascular and Metabolic Disease department at Pfizer Inc. in Groton, Connecticut for 18 years. Dr. DeNinno has worked in numerous therapeutic areas including cardiovascular, atherosclerosis, obesity, pain, cystic fibrosis and multiple sclerosis. He obtained a BS in chemistry from Providence College and a Ph.D. in organic chemistry from Yale University and has published and presented extensively in the areas of medicinal chemistry and organic synthesis.

Adam Gilbert, PhD, Pfizer: Adam Gilbert is a Senior Director at Pfizer where leads Design and Synthesis Sciences – a medicinal chemistry group which focuses on new modalities and technologies in design, synthesis, molecular properties and purification. He received his B.A. in chemistry from Haverford College and his Ph.D. in organic chemistry from Columbia University. After a postdoctoral fellowship at the University of Chicago, he joined Medical Research Division of American Cyanamid in Pearl River, NY, which eventually became Wyeth Research. Adam joined Pfizer in 2010 in Groton, CT where he has worked on a diverse array of projects in tissue repair, neuroscience, immunology, metabolic diseases and oncology.

Simon Giroux, Ph.D., Vertex Pharmaceuticals: Dr. Simon Giroux received his Ph.D from the Université de Montreal in 2006 under the guidance of Prof. Stephen Hanessian. In 2007, he joined the laboratory of Prof. E.J. Corey at Harvard University as an NSERC postdoctoral fellow, working on steroidal natural product total synthesis. Since 2009, he his part of the Medicinal Chemistry Department at Vertex Pharmaceuticals and have contributed to

many drug discovery programs in infectious diseases, oncology, inflammation and more recently, pulmonary diseases. He is the author of more than 30 patents and publications.

Matthew Hayward, PhD, Pfizer: Matthew Hayward obtained his BA in Biochemistry from Connecticut College in 1989. During these formative years he worked in the labs of Dr. Bruce Branchini preparing novel analogues of firefly Luciferin. Inspired by his work there he continued his studies at Yale University, obtaining his Ph.D. under Prof. Alana Schepartz in 1995. At Yale Matt worked on several projects at the biology-chemistry interface. Following that, Matt joined the labs of Prof. Yoshito Kishi at Harvard as an NIH postdoctoral fellow. There he worked on and completed the first synthesis of Spongistatin A with fellow co-workers in the Kishi labs. He joined Pfizer in Groton in 1997. Since then he has been a medicinal chemist in the antibacterial, oncology, immunology, inflammation and neuroscience groups. Matt is currently an Associate Research Fellow in the Design and Synthesis Sciences group and is working on platform approaches that address medicinal chemistry issues that span multiple therapeutic areas. Matt's research interests include structure based drug design and kinase medicinal chemistry.

Richard Heidebrecht, Ph.D., Sigilon: Rich is the Director of Chemistry and Research at Sigilon, Inc. He received a bachelors degree in chemistry from Worcester Polytechnic Institute and completed his graduate work at Indiana University and the University of Texas at Austin. This work resulted in the total synthesis of a neodollabellane diterpene as well as a welwitindolinone alkaloid. Rich has worked at Pfizer, Merck, the Broad Institute, SciFluor Life Sciences and Preceres on diverse projects in human health and agriculture; and was on the project team that invented Tarceva®. He is currently at Sigilon, a company focused on immune privileged surface chemistry that enables implantable stealth biotechnology. He continues to consult on neglected diseases at the Harvard School of Public Health.

Erik Hett, PhD, Merck: Dr. Erik Hett received his Ph.D. from Harvard University in the lab of Dr. Eric Rubin, studying protein-protein interactions important for mycobacteria. His postdoctoral research was conducted in the lab of Dr. Deborah Hung at Harvard, Broad Institute and Massachusetts General Hospital, where he conducted phenotypic HTS and utilized chemoproteomics for target ID. He previously was a chemical biologist in the MedChem Department at Pfizer and led a chemical biology team in the mechanisms and pathways group at Biogen. He is currently the lead for the chemical microbiology team at Merck's Exploratory Sciences Center in Cambridge, MA.

Alexandros Makriyannis, Ph.D., Northeastern University: Alex Makriyannis is the George Behrakis Chair of Pharmaceutical Biotechnology at Northeastern University, Boston, MA, and is the Founder and Director of the Center for Drug Discovery. He is a highly successful medicinal chemist and is well recognized nationally and internationally for his important contributions in endocannabinoid research. Inventor of over 50 issued U.S. patents, Makriyannis played an important role in the discovery of this relatively newly characterized biochemical system that regulates many physiological functions including pain, neuroprotection, addiction, immunomodulation and cognition.

Over the past four decades, his laboratory has designed and synthesized some of the key pharmacological endocannabinoid probes that are widely used and serve as leads for the development of new medications. He has also made important contributions aimed at understanding the molecular basis of cannabinoid activity.

He has been a creative pioneer in the field of chemical biology where he combined the use of medicinal chemistry, biochemistry, molecular biology and biophysics. His work is recognized for its high level of originality. Some of his compounds are in advanced preclinical trials for the treatment of metabolic disorders and liver function, neuropathic pain, addiction and neurodegenerative diseases.

Benoît Moreau, PhD, Tarveda Therapeutics: Dr. Benoît Moreau is Research Leader in Medicinal Chemistry at Tarveda Therapeutics, Watertown, MA where he works on the discovery of novel cancer therapeutics with targeted delivery. He has led research projects from their inception to clinical candidate identification and up to IND filing. Formerly, he was Research Scientist at Boehringer Ingelheim where he worked on the discovery of replication inhibitors of HCV, HIV and HCMV. Dr. Moreau received his B.Sc. and Ph.D. in chemistry from Université de Montréal and then joined Harvard University as a FQRNT postdoctoral fellow. His areas of expertise are project management, drug design, lead optimization,targeted delivery. He is a contributing author in over a dozen of scientific publications and over fifteen patents.

Eric Schwartz, Ph.D., Celgene: Dr. Schwartz received his B.S. degree in 1983 from Ohio State University, completed his Ph.D. with Ed Vedejs at the University of Wisconsin-Madison, and followed that with a post-doctoral stint at the University of Pittsburg in Dennis Curran's group. Eric started his industrial career in 1990 at Eisai Research Institute, later moving to positions of increasing responsibility at UCB Pharma, Biogen Idec, and Resolvyx Pharmaceuticals. In 2011 he joined Avila Therapeutics, which was acquired by Celgene in 2012. He is currently Executive Director of Chemistry and based in Cambridge, MA.

Susanne Swalley, Ph.D., Novartis: Susanne Swalley is an Investigator in the Chemical Biology and Therapeutics department at the Novartis Institutes for Biomedical Research. Trained as a chemist, her current research focuses on biochemical and biophysical approaches to target identification. Prior to Novartis, she was a scientist at Vertex Pharmaceuticals where she contributed to a wide variety of project teams on the evaluation and screening of new targets. Susanne graduated from Amherst College with bachelor's degrees in chemistry and music, and obtained a Ph.D. in chemistry from the California Institute of Technology with Dr. Peter Dervan. She completed her postdoctoral training at Harvard University in the laboratories of Dr. Don Wiley and Dr. Stephen Harrison with fellowships from the Damon Runyon-Walter Winchell Cancer Research Fund and the Charles A. King Trust.

David Sykes, MD, PhD, MGH/Harvard: David Sykes is a hematologist at the Massachusetts General Hospital Cancer Center and a post-doctoral fellow in the laboratory of Dr. David Scadden in the Center for Regenerative Medicine. David completed his undergraduate studies at the University of Alberta, Canada, and his MD/PhD as part of the Medical Scientist Training Program at the University of California San Diego. He was a resident and Chief resident in the MGH Department of Medicine and did his Hematology/Oncology fellowship in the combined MGH/Dana-Farber Cancer Institute training program. David has had a longstanding interest in understanding the normal processes of differentiation, elucidating how these processes are corrupted in the setting of leukemia, and identifying therapies to overcome differentiation arrest.

Atli Thorarensen, PhD, Pfizer: Dr. Thorarensen is a Research Fellow in medicinal chemistry working in the Immunoscience & Immunology research unit at Pfizer. In the past he has lead medicinal projects in several therapeutic areas including anti infective, allergy and respiratory, pain and inflammation. In the past few years his focus has been design of irreversible inhibitors as therapeutic targets for inflammation. Dr. Thorarensen

received his BS in chemistry from University of Iceland and a Ph.D. in organic chemistry from University of Illinois. He is the author of 48 publications and 26 patents.

Hua Xu, PhD, Pfizer: Dr. Hua Xu received his PhD in Chemistry from Stony Brook University in 2009. After conducting his post-doctoral research at Albert Einstein College of Medicine, he joined Pfizer as a chemical biologist in 2013. He received ACS Young Investigator Award in 2016. His current research interests are using chemical tools and technologies to investigate mode of action of drugs and understand drug occupancy in physiologically relevant systems.

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