American Society of Pharmacognosy

ASP2020 Younger Members Virtual Symposium
#ASP2020YM

Tuesday August 11, 2020

1:00 PM – 1:10 PM — Welcoming Remarks
Co-Chairs – Jaclyn Winter, Karen VanderMolen and C. Benjamin Naman

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Session I – New Methods and Informatics
Chair: Joseph Egan
Moderator: Jaclyn Winter

1:10 PM – 1:15 PM — Session Chair Remarks

1:15 PM – 1:40 PM — K-01
Michelle Schorn (Wageningen University)
The Paired Omics Data Platform: Standardized Links Between Genomic and Metabolomic Data for Integrative Mining

1:40 PM – 1:55 PM — C-01
Hongyan Ma (University Of Oklahoma)
Lickety-Split Ligand-Affinity-Based Molecular Angling System (LLAMAS): A Strategy for Detecting and Dereplicating DNA-Binding Biomolecules from Complex Natural Product Mixtures

1:55 PM – 2:10 PM — C-02
Raphael Reher (University Of California San Diego)
Improved High Throughput Methods for Natural Products Discovery

2:10 PM – 2:25 PM — C-03
Manead Khin (University Of North Carolina at Greensboro)
Integration of Bioinformatics and Bioassay-Guided Fractionation to Correlate Antimicrobial Compounds to Observed Bioactivity: A Case Study on Salvia rosmarinus against MRSA

Session II - Pharmacognosy Bioprospecting
Chair: Eduardo Caro Diaz
Moderator: C. Benjamin Naman

2:35 PM – 2:40PM	Session Chair Remarks
2:40 PM – 3:05 PM	K-02 **Shamsunnahar Khushi** (University Of Queensland) *Discovery of Unprecedented Classes of Molecules from a Library of Southern Australian Marine Sponges Guided by Molecular Networking*
3:05 PM – 3:20 PM	C-04 **Luděk Sehnal** (Recetox, Masaryk University, Brno) *Antarctic Microbial Biobank: A New Resource for Biodiversity Conservation, Research and Bioprospecting of Polar Microbes*
3:20 PM – 3:35 PM	C-05 **Riley Kirk** (University Of Rhode Island) Unnarmicin D, an Anti-Inflammatory Cyanobacterial Metabolite with Delta and Mu Opioid Binding Activity Discovered Via a Pipeline Approach Designed to Target Neurotherapeutics.
3:35 PM – 3:50 PM	C-06 **Ali Ramadan Elnaas** (Griffith University) *Discovery of a Natural Product that Binds to the Mycobacterium Tuberculosis Protein Rv1466 Using Native Mass Spectrometry*

4:00 PM – 5:00 PM **Panel I – Careers in Academia**

William Gerwick (University of California - San Diego)

Amy Lane (University of North Florida and ASP PUI Committee)

C. Benjamin Naman (Ningbo University)

Huzefa Raja (University of North Carolina at Greensboro)

Patrick Still (California State University, Dominguez Hills)

Wednesday August 12, 2020

1:00 PM – 1:05 PM	Welcoming Remarks Co-Chairs – Jaclyn Winter, Karen VanderMolen and C. Benjamin Naman

1:05 PM – 2:05 PM	**Panel II – Careers in Industry** **Steve Bobzin** (Central Coast Agriculture LLC) **Michael Kernan** (Gilead Science) **Shichang Miao** (ChemoCentryx Inc.) **Sandra Morris** (Johnson & Johnson) **Karen VanderMolen** (The Procter & Gamble Company)

Session III – Chemical Ecology
Chair: Skylar Carlson
Moderator: Karen VanderMolen

2:10 PM – 2:15 PM	Session Chair Remarks
2:15 PM – 2:40 PM	K-03 **Gordon Luu (**University Of Illinois At Chicago) Complex Community Metabolome Interactions from the Cheese Rind-Derived Microbiome
2:40 PM – 2:55 PM	C-07 **Ria Kidner** (Indiana University) *Uncovering Molecular Cues that Drive a Unique Symbiotic Relationship Between Biomphalaria glabrata and Capsaspora owczarzaki: A Potential Agent Against Schistosomiasis*
2:55 PM – 3:10 PM	C-08 **Daniel May (**University Of Wisconsin – Madison) *Chemical Weapons in Escovopsis, the Fungal Parasite of Fungus-Growing Ants*
3:10 PM – 3:25 PM	C-09 **Jack Ganley (**Duke University) *Investigation of Bacterial-Produced Small Molecules within the Mosquito Gut Microbiome*

Session IV - Biosynthesis
Chair: Jie Li
Moderator: Jaclyn Winter

3:45 PM – 3:50PM	Session Chair Remarks
3:50 PM – 4:15PM	K-04 **Shannon Ohlemacher** (National Institutes of Health) *Discovery, Biosynthesis, and Self-Resistance Mechanism of a Novel Polyhydroxylated Tetramic Acid Natural Product with Antimicrobial Activity*
4:15 PM – 4:30 PM	C-10 **Jason Hedges** (University Of British Columbia *Discovery and Reconstitution of the Biosynthetic Pathway to the Nitroimidazole Antibiotic Azomycin*
4:30 PM – 4:45 PM	C-11 **Trevor Purdy** (University Of California, San Diego *Discovery and Biosynthesis of Tetrachlorizine Reveals Enzymatic Benzylic Dehydrogenation via an ortho-Quinone Methide*
4:45 PM – 5:00 PM	C-12 **Lindsay Caesar** (Northwestern University) *Heterologous Expression of the Unusual Terreazepine Biosynthetic Gene Cluster Reveals a Promising Approach for Identifying New Chemical Scaffolds*

Thursday August 13, 2020

1:00 PM – 1:05 PM	Welcoming Remarks Co-Chairs – Jaclyn Winter, Karen VanderMolen and C. Benjamin Naman

Session V – Ethnobotany
Chair: Joshua Kellogg
Moderator: Karen VanderMolen

1:05 PM – 1:10 PM	Session Chair Remarks
1:10 PM – 1:35 PM	K-05 **Caitlin Risener** (Emory University) *A Clerodane Diterpene from Callicarpa americana Resensitizes Methicillin-Resistant Staphylococcus aureus to -Lactam Antibiotics*
1:35 PM – 1:50 PM	C-13 **Jessica Furner-Pardoe** (University Of Warwick) *Anti-biofilm activity of 1,000-year-old-remedy requires the combination of multiple ingredients.*
1:50 PM – 2:05 PM	C-14 **Kristelle Hughes** (University Of French Polynesia) *Polynesian Cosmetopoeia as Hair Loss Treatment: LC-MS/MS Molecular Networks for Metabolites Identification and Their Targets in Hair Growth-Inducing Signaling Pathways*
2:05 PM – 2:20 PM	C-15 **Mohammad Omar Faruque** (University of Chittagong) *Demystifying Bangladeshi Ethnomedicines with Modern Approaches: Congea Tomentosa as a Source of Potential Anti-Microbial and Anti-Cancer Agents*

Session VI - Medicinal Chemistry and Pharmacology
Chair: Fatma Al-Awadhi
Moderator: C. Benjamin Naman

2:30 PM – 2:35 PM	Session Chair Remarks
2:35 PM – 3:00 PM	K-06 **Charles Fermaintt** (University of Texas - Health Science Center San Antonio) *Dual Immunogenic and Triple-Negative Breast Cancer Selective Daphnane-Type Diterpenoids*
3:00 PM – 3:15 PM	C-16 **Victoria Klein** (University Of California, Santa Cruz) *Identifying the Cellular Target of Cordyheptapeptide A and Synthetic Derivatives*
3:15 PM – 3:30 PM	C-17 **Amanda Christine Maldonado** (University Of Illinois At Chicago *Eupenifeldin, a Novel Bistropolone Secondary Metabolite,May Act to Induce Apoptotic Events in High-Grade Serous Ovarian Cancer*
3:30 PM – 3:45 PM	C-18 **Mahsa Khoshbakht** (Oregon State University) New Chalanilines A from *Chalara* sp. Fungi and Total Synthesis of Chalaniline B'
3:55 PM – 4:55 PM	**Panel III - Current Events and Impactful Careers Away From Lab Benches** **Dominique Carter** (US Department of Agriculture USDA) **Cheryl Hogue** (Chemical & Engineering News) **Craig Hopp** (National Center for Complementary and Integrative Health, National Institutes of Health) **Sabine Kuhn** (Retired Marketing Manager for CAS (Chemical Abstracts Service); Pedal with Pete Foundation **Nicholas Oberlies**, University of North Carolina at Greensboro and President of ASP
4:55 PM – 5:00 PM	**Program Conclusion** - Jaclyn Winter, Karen VanderMolen, C. Benjamin Naman and Nicholas Oberlies

We hope to see you next year at the ASP Annual Meeting in Grand Rapids, Michigan! http://aspmeetings.pharmacognosy.us/

ASP2020 Younger Members Virtual Symposium
Abstract Book

Keynote Speakers

K-01 – Michelle Schorn

The Paired Omics Data Platform: Standardized Links between Genomic and Metabolomic Data for Integrative Mining

Michelle A. Schorn[1], Stefan Verhoeven[2], Lars Ridder[2], Florian Huber[2], Pieter C. Dorrestein[3], Marnix H. Medema[4], Justin J.J. van der Hooft[4]. [1]Laboratory of Microbiology, Department of Agricultural and Food Sciences, Wageningen University, Wageningen, the Netherlands, [2]Netherlands eScience Center, Amsterdam, the Netherlands, [3]Collaborative Mass Spectromatry Innovation Center, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, USA, [4]Bioinformatics Group, Department of Plant Sciences, Wageningen University, Wageningen, the Netherlands

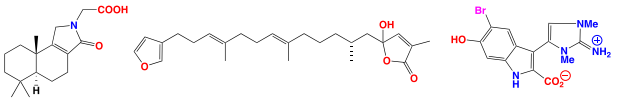
Genomics and metabolomics are widely used to explore microbial and plant biosynthetic diversity. Integrating these types of data from paired samples holds great promise for accelerating natural product discovery by mutually informing each other. However, while many paired (meta)genomes and metabolomes have become publicly available, connections between these datasets remain undocumented, and the same is true for links between biosynthetic gene clusters and mass spectra of their metabolic products. This precludes scientists from exploiting paired data to discover new connections between genes and molecules. Here, we introduce the Paired Omics Data Platform (https://pairedomicsdata.bioinformatics.nl/), a community effort to systematically document links between metabolome and (meta)genome samples, and between gene clusters and MS/MS spectra. Seeded with >4,500 genome-metabolome links, the platform enables transferring structural knowledge between omics types and more efficiently linking products to producers. Thus, it paves the way towards large-scale computationally-guided natural product analysis.

K-02 – Shamsunnahar Khushi

Discovery of Unprecedented Classes of Molecules from a Library of Southern Australian Marine Sponges Guided by Molecular Networking

Khushi, S.[1], Salim, A. A.[1] and Capon, R. J.[1]. [1]Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, University of Queensland, QLD 4072, Australia

A global natural product social (GNPS) molecular network guided search of a library of ×960 southern Australian marine sponge extracts successfully detected two southern Australian marine sponges, as sources of two new classes of compounds. Detailed chemical analysis of a *Dysidea* sp. extract led to isolation of dysidealactams A–F (**1.1**–**1.6**) and dysidealactones A–B (**1.7**–**1.8**); and a *Cacospongia* sp. extract led to isolation of cacolides A-L (**2.1**–**2.12**) and cacolic acids A-C (**2.13**–**2.15**). Additionally, this molecular network effectively identified a *Geodia* sp. sponge as a new source of a rare class of indolo-imidazole alkaloids. Further chemical analysis of this sponge extract led to the isolation of the new trachycladindoles H–M (**3.8**–**3.13**). In addition to expanding knowledge of marine natural products, this study demonstrates the value of applying GNPS molecular networking to map chemical diversity and prioritize the selection of marine sponge extracts for more detailed chemical analysis.



dysidealactam A (**1.1**) cacolides A (**2.1**) trachycladindole H (**3.8**)

K-03 –Gordon Luu

Complex Community Metabolome Interactions from the Cheese Rind-Derived Microbiome

Gordon T. Luu[1], Jessica L. Cleary-Little[1], Emily C. Pierce[2], Rachel J. Dutton[2], Laura M. Sanchez[1]. [1]Department of Pharmaceutical Science, University of Illinois at Chicago, Chicago, IL, 60612, USA, [2]Division of Biological Sciences, University of California, San Diego, La Jolla, CA, 92093, USA.

The cheese rind microbiome has proven to be a useful model system for studying microbial interactions due to its simplified diversity, lab-cultivability, and the ease with which the cheese rind can be simulated. However, little is known about the molecules involved in signaling interactions that these microbes utilize for inter-kingdom communication within the community during colonization of the cheese rind. Two fungi (*Scopulariopsis* sp. JB370, *Penicillium solitum*) and three bacteria (*Hafnia* sp. JB132, *Pseudomonas psychrophila* JB418, *Escherichia coli* K12) are of interest to us. Here, *E. coli* K12 is a model for food borne pathogens, and all other species are native cheese rind microbes. Using mass spectrometry-based untargeted metabolomics on tripartite fungus-bacterium-bacterium synthetic communities, we compared the metabolomic profiles to those of pairwise fungus-bacterium communities and fungal and bacterial monocultures to identify new fungal secondary metabolites responsible for community interactions. Tripartite microbial communities allow us to identify and validate metabolite roles in community formation and growth over time.

K-04 – Shannon Ohlemacher

Discovery, Biosynthesis, and Self-Resistance Mechanism of a Novel Polyhydroxylated Tetramic Acid Natural Product with Antimicrobial Activity

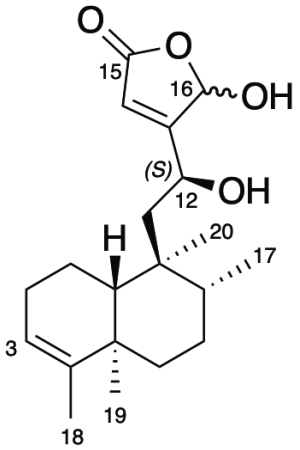
Shannon I. Ohlemacher, Hongbing Liu, Gengxiang Zhao, Carole A. Bewley Natural Products Chemistry Section, Laboratory of Bioorganic Chemistry, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

Antimicrobial resistance is a growing public health threat that is further exacerbated by the dwindling number of compounds in the development pipeline. Towards discovering new natural products with antimicrobial activity, we isolated actinomycetes from North American desert soil and used antibiotic resistance to filter the collection for understudied taxa. Two *Amycolatopsis* strains from different geographic locations were identified that produce a novel polyhydroxylated tetramic acid natural product with potent minimum inhibitory concentrations (MICs) against *Candida albicans* and Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin- resistant *Enterococcus* (VRE). The strains also produce a glycosylated derivative that is inactive against all organisms tested. The planar structures were elucidated by tandem mass spectrometry (MS/MS) and 1D and 2D NMR methods, including ^{1}H-^{1}H and ^{13}C-^{13}C COSY, HSQC, HMBC, and ROESY. Whole genome sequencing of the two producing strains revealed a 158 kb biosynthetic gene cluster (BGC) containing a 23-module mixed NRPS-PKS pathway responsible for their biosynthesis. Glycosylation appears to be a self-protection mechanism used by the producing strains, based on the activities of a glycosyltransferase and secreted glycosyl hydrolase encoded in the BGC. To our knowledge, this is the first instance of glycosylation as a self-protection mechanism identified outside the macrolide class of antibiotics.

K-05 – Caitlin Risener

A Clerodane Diterpene from *Callicarpa americana* Resensitizes Methicillin-Resistant *Staphylococcus aureus* to ß-Lactam Antibiotics

Micah Dettweiler[1], Roberta J. Melander[2], Gina Porras[3], Caitlin Risener[4], Lewis Marquez[4], Tharanga Samarakoon[5], Christian Melander[2], Cassandra L. Quave[1,3,4*] [1]Emory University, Department of Dermatology, 615 Michael St., Whitehead 105L, Atlanta, GA 30322, [2]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556, [3]Emory University, Center for the Study of Human Health, 1557 Dickey Drive, Anthropology 306, Atlanta, GA 30322, [4]Emory University, Molecular and Systems Pharmacology Program, 615 Michael St., Whitehead 115, Atlanta, GA 30322, [5]Emory University Herbarium, 1462 Clifton Road, Atlanta, GA 30322*



The rise of antibiotic resistance presents a significant healthcare challenge and precludes the use of many otherwise valuable antibiotics. One potential solution to this problem is the use of antibiotics in combination with resistance-modifying agents, compounds that act synergistically with existing antibiotics to resensitize previously resistant bacteria. In this study, 12(*S*),16ξ-dihydroxycleroda-3,13-dien-15,16-olide, a clerodane diterpene isolated from the medicinal plant *Callicarpa americana*, was found to synergize with oxacillin and meropenem against methicillin-resistant *Staphylococcus aureu*s. This synergy was confirmed by checkerboard for oxacillin (FICI = 0.125) and meropenem (FICI = 0.094). Additionally, time-kill assays were performed with oxacillin and a sub-inhibitory dose of 12(*S*),16ξ-dihydroxycleroda-3,13-dien-15,16-olide causing the effective concentration of oxacillin to fall below the susceptibility breakpoint for *S. aureus*, a > 32-fold decrease in both cases.

K-06 – Charles Fermaintt

Dual Immunogenic and Triple-Negative Breast Cancer Selective Daphnane-Type Diterpenoids

Charles S. Fermaintt[1], Shengxin Cai [3,4], Leila Takahashi- Ruiz[1], Barry R. O'Keefe [5,6], Robert H. Cichewicz[3,4], Susan L. Mooberry[1,2], and April L. Risinger[1,2], [1]Department of Pharmacology and [2]Mays Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, [3]Department of Chemistry and Biochemistry and [4]Natural Products Discovery Group, University of Oklahoma, Norman, OK USA, [5]Natural Products Branch, Division of Cancer Treatment and Diagnosis, and [6]Molecular Targets Laboratory, Center for Cancer Research, National Cancer Institute, Frederick, MD, USA.

Triple-negative breast cancer (TNBC) lacks effective treatment options due to the absence of estrogen, progesterone and HER2 receptors. Immunotherapy is emerging as a promising therapeutic alternative for TNBC, particularly with combination chemotherapy and immune checkpoint inhibition. However, the response rate of metastatic TNBC patients to this combination therapy remains under 50% suggesting that new approaches are needed. We initiated a screen to identify natural product extracts that promote differentiation of THP-1 human monocytes into macrophages as a measure of immune activation. In parallel, we screened these same extracts for selective cytotoxicity towards TNBC cell lines that represent molecularly distinct subtypes of this heterogenous disease. We identified an NCI extract that caused THP- 1 differentiation, upregulated expression of antitumor cytokines, and displayed potent and selective cytotoxicity towards cell lines belonging to the basal-like 2 (BL2) TNBC subtype. Three diterpenes were identified that promoted both immunogenic and selective cytotoxic effects. The diterpenoid ester yuanhuacine stood out as the most potent, therefore we isolated 7 additional bioactive yuanhuacine analogs from *Daphne genkwa*. Structure activity relationships among these compounds revealed that the C6-7 epoxide contributes toward the potency of this compound class for both THP-1 differentiation and BL2 selective cytotoxicity, suggesting a common mechanism that is being further explored. In summary, we have implemented a multipronged screening strategy to identify natural product extracts and fractions that possess both selective cytotoxicity to molecularly distinct TNBC subtypes as well as the induction of antitumor-associated immunogenic signaling that could have benefit in the treatment of TNBC.

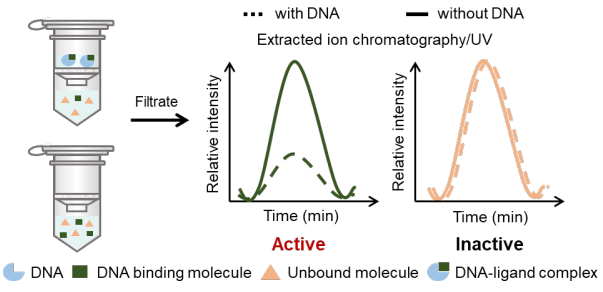
Contributed Speakers

C-01 – Hongyan Ma

Lickety-Split Ligand-Affinity-Based Molecular Angling System (LLAMAS): A Strategy for Detecting and Dereplicating DNA-Binding Biomolecules from Complex Natural Product Mixtures

Hongyan Ma[1,2], Shengxin Cai[1,2], and Robert H. Cichewicz[1,2]. [1]Department of Chemistry and Biochemistry [2]Institute for Natural Products Applications and Research Technologies, The University of Oklahoma, Norman, OK.

The lack of tools to directly pinpoint the bioactive molecules in complex crude natural product extracts/fractions is currently a painful challenge in the discovery of new bioactive natural products. To address this problem, the Lickety-Split Ligand-Affinity-Based Molecular Angling System (LLAMAS), which is a high-throughput, ultrafiltration-LC-PDA-MS/MS-based DNA binding assay, coupled with modern dereplication tools (e.g. GNPS and DNP), was established for efficient identification and dereplication of DNA binding agents in complex natural product mixtures. With this method, seven DNA binding candidates, including berberine, palmatine, coptisine, fangchinoline, tetrandrine, daurisoline, and dauricine were efficiently detected and identified through high-throughput screening of an NCI library of 332 traditional Chinese medicinal plant extracts. The results demonstrate that LLAMAS is an adaptable tool that enables the efficient identification and dereplication of DNA binding molecules directly from complex compound mixtures in the early stage of natural product discovery.



C-02 – Raphael Reher

Improved High Throughput Methods for Natural Products Discovery

Raphael Reher[1], Daniel Petras[2], Hyunwoo Kim[1], Chen Zhang[1,3], Kelsey L. Alexander[1], Louis-Felix Nothias[2], Mingxun Wang[2], Eduardo Caro-Diaz[4], Benjamin C. Naman[5], Garrison W. Cottrell[3], Pieter C. Dorrestein[2], William H. Gerwick[1,2]. [1]Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, La Jolla, California, USA, [2]Department of Computer Science and Engineering, UC San Diego, La Jolla, CA, USA, [3]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California, USA, [4]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California 92093, [5]College of Food and Pharmaceutical Sciences, Ningbo University, Zhejiang, China.

While still the single most important source of drug leads, natural products (NPs) discovery is costly and too slow for many pharmaceutical industry settings. To accelerate this process, several MS- and NMR-based methods have been developed, such as Molecular Networking (gnps.ucsd.edu) and SMART 2.0 (smart.ucsd.edu), respectively. These methods rapidly identify known as well as putatively new analogues of bioactive NPs. In the current study, crude cyanobacterial fractions of a *Rivularia* sp. field collection from Puerto Rico were analysed by molecular networking and deep learning-based CANOPUS and SMART 2.0, and suggested the occurrence of several 3-amino-6-hydroxy-2-piperidone (AHP)-containing cyclic depsipeptides. Screening the crude fractions versus four serine proteases via native mass spectrometry, we detected ca. 30 putative AHP-containing depsipeptides and measured their binding affinity profiles towards α-chymptrypsin, trypsin, proteinase K, and porcine elastase in only 40 minutes (each enzyme takes 10 minutes). Targeted isolation and structure elucidation of the major compound yielded the new AHP-peptide, rivulariapeptolide 1155; it is among the most potent elastase-inhibitors known (IC_{50} = 550 pM).

C-03 – Manead Khin

Integration of Bioinformatics and Bioassay-guided Fractionation to Correlate Antimicrobial Compounds to Observed Bioactivity: A Case Study on *Salvia rosmarinus* against MRSA

Manead Khin[1], Sonja L. Knowles[1], Derick D. Jones Jr.[1], William J. Crandall[1], Nicholas H. Oberlies[1] and Nadja B. Cech[1]. [1]Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC 27402

Natural products have been a primary source of medicines throughout the history of human existence. It is estimated that close to 70% of drugs on the market are derived from natural products. Traditionally, bioassay-guided fractionation has been the gold standard for isolating antimicrobial compounds from natural products. Oftentimes, this process has to go through multiple rounds of fractionation in order to successfully isolate antimicrobial compounds and cannot pinpoint the compound most related to the bioactivity. To refine the protocol, bioinformatic analysis in the form of orthogonal partial least squares-discriminant analysis (OPLS-DA), in combination with bioassay-guided fractionation, was utilized to study *Salvia rosmarinus* (rosemary). This procedure allowed (1) efficient identification of the accurate masses of antimicrobial compounds and (2) correlation of these compounds to the observed bioactivities. All *S. rosmarinus* fractions were analyzed using UPLC-HRMS and tested for bioactivities against methicillin-resistant *Staphylococcus aureus* (MRSA). As a result, three antimicrobial compounds most related to the bioactivity against MRSA (micromeric acid, oleanolic acid, ursolic acid) were identified by ^{1}H NMR and MS-MS analyses, with ursolic acid being the one most correlated to the overall bioactivity.

C-04 - Luděk Sehnal

Antarctic Microbial Biobank: A New Resource for Biodiversity Conservation, Research and Bioprospecting of Polar Microbes

Luděk Sehnal[1], Sarah E. Ongley[2], Lucie Bláhová[1], Stanislav Smatana[1,3], Jakub Javůrek[4], Caitlin S. Romanis[2], Brett A. Neilan[2], Klára Hilscherová[1]. [1] RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic, [2] School of Environmental and Life Sciences, University of Newcastle, Callaghan, New South Wales, Australia, [3] Brno University of Technology, Faculty of Information Technology, IT4Innovations Centre of Excellence, 61266 Brno, Czech Republic, [4] TESCAN ORSAY HOLDING a.s., Brno, Czech Republic

Knowledge about polar microbes and the specialized metabolites that contribute to the survival of cyanobacteria that thrive in the Antarctic is significantly under-studied. Hence, we have established the Antarctic Microbial Biobank (AMB), for the sustainable research and bioprospecting of polar microbes. Taxonomic and biochemical analysis of biological samples collected from James Ross Island, Antarctic led to the identification of several novel cyanobacterial species within the microbial mats and culture collection. We also detected saxitoxin and a variety of retinoids, for the first time, in Antarctic microbial mats, as well as detected the presence of homologs of various natural product biosynthetic genes. These results suggest that the AMB represents a rich source of microbial and biochemical diversity. This biobank will advance the study of polar microbial ecophysiology and facilitate the discovery of biotechnologically valuable enzymes and specialized metabolites. Importantly, the AMB adheres to the principles of 'sustainable research activity' outlined in the Antarctic Treaty of 1959.

C-05 – Riley Kirk

Unnarmicin D, an Anti-Inflammatory Cyanobacterial Metabolite with Delta and Mu Opioid Binding Activity Discovered Via a Pipeline Approach Designed to Target Neurotherapeutics

Riley D. Kirk, Kassie Picard, Joe Christian, Shelby Johnson, Brenton DeBoef, Matthew J. Bertin Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy; Department of Chemistry, The University of Rhode Island, Kingston, RI 02881, United States

To combat the bottlenecks in early-stage drug discovery, a pipeline to identify neuropharmacological therapeutic candidates using *in silico*, *in vitro*, and receptor specific assays was devised. A library of pure compounds isolated from the cyanobacteria *Trichodesmium thiebautii* was evaluated using this approach. *In silico* analysis of drug likeliness and *in vitro* permeability analysis using the parallel artificial membrane permeability assay (PAMPA) highlighted multiple metabolites of interest with potential blood-brain barrier (BBB) permeability. Murine microglia were used to assess if these BBB permeable compounds could reduce nitric oxide levels after LPS induced inflammation. Compounds that significantly lowered NO levels were further analyzed for the ability to modulate inflammatory cytokines TNFα, IL-6, and sTLR-2 in the cellular supernatant. The nontoxic metabolite unnarmicin D was identified as an early candidate and it was further evaluated due to its moderate permeability in the PAMPA assay, promising ADME data, modulation of all cytokines tested, and prediction as an opioid receptor ligand. Molecular modeling of unnarmicin D to the mu and delta opioid receptor showed binding potential for both opioid targets. *In vitro* binding assays validated this pipeline showing micromolar binding affinity for both the delta and mu opioid receptors opening the potential for further analysis of unnarmicin D derivatives for the treatment of pain and neuroinflammation related diseases.

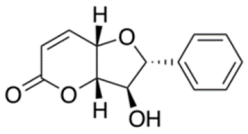
C-06 – Ali Elnaas

Discovery of a Natural Product that Binds to the *Mycobacterium Tuberculosis* Protein Rv1466 Using Native Mass Spectrometry

Ali R. Elnaas [1], Darren Grice [2], Jianying Han [1], Yunjiang Feng [1], Angela Di Capua [1], Tin Mak [1], Joseph A. Laureanti [3], Garry W. Buchko [4,5], Peter J. Myler [6], Gregory Cook [7], Ronald J. Quinn [1] and Miaomiao Liu [1,]*

Elucidation of the mechanism of action of compounds with cellular bioactivity is important for progressing compounds into future drug development. In recent years, phenotype-based drug discovery has been the dominant approach to drug discovery over target-based drug discovery, which relies on the knowledge of a specific drug target of a disease. Targeting an infectious disease via a high throughput phenotypic assay is still highly advantageous to identifying the compound's cellular activity. A fraction derived from the plant *Polyalthia* sp. showed activity against *Mycobacterium tuberculosis* at 62.5 μge/μL. A known compound altholactone, was identified from this fraction that showed activity towards *M. tuberculosis* at an minimum inhibitory concentration (MIC) of 64 μM. Retrospective analysis of a target-based against a TB proteome panel using native mass spectrometry, established that the active fraction was bound to the mycobacterial protein Rv1466 with an estimated pseudo Kd of 42.0 ± 6.1 μM. Our findings established Rv1466 as the potential molecular target of altholactone, which is responsible for the observed in vivo toxicity towards *M. tuberculosis*.

Altholactone



C-07 – Ria Kidner

Uncovering Molecular Cues That Drive a Unique Symbiotic Relationship Between *Biomphalaria glabrata* and *Capsaspora owczarzaki*: A Potential Agent Against Schistosomiasis

Ria Kidner[1], Núria Ros-Rocher[2], Catherine Gerdt[1], Iñaki Ruiz-Trillo[2], Joseph P. Gerdt[1]. [1]Department of Chemistry, Indiana University, Bloomington, IN 47405, USA. [2] Institut de Biologia Evolutiva (CSIC- Universitat Pompeu Fabra), Passeig Marítim de la Barceloneta 37-49, 08003 Barcelona, Catalonia, Spain

Mutualistic symbiosis is a remarkable phenomenon. All over the world there exist intricate biological relationships between diverse organisms. An underexplored symbiosis between the freshwater snail *Biomphalaria glabrata* and the unicellular protist *Capsaspora owczarzaki* presents a unique opportunity for the control of the neglected tropical disease Schistosomiasis. The parasitic disease agent, *Schistosoma mansoni*, relies on *Biomphalaria* as an intermediate host in its parasitic lifecycle. In contrast, *Capsaspora*, which was originally isolated from the snail's hemolymph, has been shown to swarm and kill *S. mansoni* parasites *in vitro*. Despite this interesting anti-parasitic activity, the relationship between *Capsaspora* and *Biomphalaria* is not well understood. We have discovered the first known phenotype *Capsaspora* displays in response to chemical cues released by its host: cell aggregation. Our lab strives to understand the molecular cues behind this distinctive behavior in an effort to characterize the symbiotic relationship. Through activity-guided fractionation, we discovered lipoproteins to be the putative cue causing *Capsaspora* aggregation. Further work in uncovering signaling pathways between these organisms may help to develop *Capsaspora* as a biocontrol agent against Schistosomiasis.

C-08 – Daniel May

Chemical Weapons in *Escovopsis*, the Fungal Parasite of Fungus-Growing Ants

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Evolutionary arms races are a common occurrence in host-parasite symbioses and can shape biocomplexity and diversity over evolutionary time. In instances where secondary metabolites facilitate the interactions of symbiotic partners, the chemical profiles of the participating organisms can similarly diversify. The ancient and diverse tribe of fungus-growing ants participate in a multipartite symbiosis with a basidiomycete that they cultivate as a food source, which is in turn parasitized by the ascomycete *Escovopsis*. This specialized mycoparasite is known to produce secondary metabolites that mediate interactions with other members of the symbiosis. However, studies to date have focused on *Escovopsis* from the most derived fungus-growing ant lineages, overlooking the full diversity of *Escovopsis*. We performed a comprehensive genomic and metabolomic analysis of *Escovopsis* strains from across the 50 mya phylogeny, which revealed a pattern of biosynthetic gene clusters and secondary metabolites that mirrored the evolution of the fungus-growing ants and their coevolved symbionts. For example, we identified two known insecticidal fungal metabolites, shearinines and destruxins, each with lineage specific distributions. Other uncharacterized secondary metabolites were also found to have both lineage specific and wide distribution patterns. Together, our results demonstrate that studying ancient symbiotic systems on an evolutionary time scale can facilitate the study and discovery of secondary metabolites.

C-09 – Jack Ganley

Investigation of Bacterial-Produced Small Molecules within the Mosquito Gut Microbiome

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Anopheles mosquitoes are the main vectors for the transmission of the *Plasmodium* parasite, the causal agent of malaria. Within the midgut of the mosquito, the *Plasmodium* parasite undergoes developmental changes and is exposed to the mosquito-gut microbiome. Despite many studies characterizing the bacterial populations within *Anopheles* midguts, there is little known about the microbiome small molecules produced. Through bioinformatics-, structure-, and coculture-guided discovery efforts, we have begun to characterize much of the biosynthetic space within this important ecological niche. In total, our efforts have discovered a novel group of antibacterial lipopeptide surfactants, antimalarial siderophores that influence mosquito reproduction, as well as uncovering bipartite bacterial-bacterial interactions that may be critical for establishing infection within the mosquito gut.

C-10 –Jason Hedges

Discovery and Reconstitution of the Biosynthetic Pathway to the Nitroimidazole Antibiotic Azomycin

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Nitroimidazoles have a broad range of biological properties and importantly are one of the primary tools for combating anaerobic bacterial infections. As is the case for many of the antibiotics in use today, the development of nitroimidazoles can be traced back to the discovery of the bacterially produced bioactive molecule azomycin (2-nitroimidazole). Despite azomycin being isolated over 60 years ago, the biosynthetic gene cluster that produces it was never identified. Through bioinformatics we identified a cryptic five gene cluster which appears to be broadly distributed amongst different strains of soil dwelling bacteria. We chose to investigate the activities of the enzymes encoded within this gene cluster through a series of *in vitro* experiments, through which we demonstrate that four of these enzymes are sufficient to convert the amino acid arginine into azomycin *in vitro*. Highlights of this biosynthetic pathway include uncommon oxidative chemistry mediated by pyridoxal phosphate and iron-dependent enzymes. By identifying the azomycin biosynthetic machinery we set the stage for the discovery of new azomycin derivatives and possibly other nitro-containing compounds.

Reference

J. B. Hedges, K. S. Ryan, *Angew. Chem. Int. Ed.* **2019**, 58, 11647-11651.

C-11 – Trevor Purdy

Discovery and Biosynthesis of Tetrachlorizine Reveals Enzymatic Benzylic Dehydrogenation via an *ortho*-Quinone Methide

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Quinone methides are highly reactive chemical intermediates that are essential for the biosynthesis and bioactivity of many phenolic natural products. We recently discovered a new metabolic deviation of an *ortho*-quinone methide in an enzymatic benzylic dehydrogenation reaction that links two novel marine bacterial natural products, dihydrotetrachlorizine and tetrachlorizine. These dichloropyrrole-containing compounds were isolated from actinomycete strain AJS-327 that unexpectedly harbors in its genome a biosynthetic gene cluster of striking similarity to that of chlorizidine A, another marine alkaloid bearing a different carbon skeleton. Heterologous expression of the homologous flavin-dependent oxidoreductase enzyme Tcz9 confirmed its catalytic function as a dehydrogenase. Further chemoenzymatic derivatization with Tcz9 and Clz9 produced hydroxylated, dehydrogenated, and cyclized analogs of tetrachlorizine and chlorizidine, including a dearomatized chlorizidine analog with a stabilized *ortho*-quinone methide generated upon three successive oxidations.

C-12 – Lindsay Caesar

Heterologous Expression of the Unusual Terreazepine Biosynthetic Gene Cluster Reveals a Promising Approach for Identifying New Chemical Scaffolds

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Advances in genome sequencing have revitalized natural products discovery efforts, revealing the untapped biosynthetic potential of fungi; however, the time-consuming nature of experiments required to characterize new molecules often slows, discovery efforts. To direct resources towards biosynthetic gene clusters (BGCs) encoding novel chemical scaffolds, we utilized fungal artificial chromosomes (FACs). Using mass spectral profiles and structural clues provided by FAC-encoded gene clusters, we targeted a compound originating from an unusual BGC containing an indoleamine 2,3-dioxygenase (IDO). We isolated and characterized both enantiomers of the new molecule terreazepine, which contains a novel chemical scaffold resulting from cyclization of the IDO-supplied kynurenine. We also reveal the presence of hundreds of IDO-containing BGCs in fungi that have not yet been characterized. These discoveries illustrate that approaches targeting unusual biosynthetic machinery provide a promising avenue for targeted discovery of novel chemical scaffolds and their biosynthetic enzymes.

C-13 – Jessica Furner-Pardoe

Anti-Biofilm Activity of 1,000-Year-Old-Remedy Requires the Combination of Multiple Ingredients.

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Combatting the rise in resistance is one of the major challenges in modern science. Studying historical medical remedies could help reveal new antibiotics. Historical medical manuscripts prescribe complex preparations of several ingredients to treat infections, and it is suspected their efficacy may rely on creating a cocktail of natural products. A reconstructed 1000-year-old remedy, containing onion, garlic, wine and bile salts, was previously shown to kill methicillin-resistant *Staphylococcus aureus* in a mouse chronic wound model, and *Pseudomonas aeruginosa* in an *ex vivo* chronic lung infection model. Recently, we have shown this activity extends to biofilms of various ESKAPE pathogens, including *Acinetobacter baumannii*. This activity cannot be attributed to any single compound or any one ingredient in the mixture. In fact, all four ingredients were necessary to get full antibiofilm activity. To understand the remedy's activity at a chemical level, techniques including high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectroscopy (LCMS) have been used to identify antimicrobial molecules. Here, we will describe in detail the contribution of one garlic compound, allicin, to the remedy, as well as other potential contributors.

C-14 – Kristelle Hughes

Polynesian Cosmetopoeia as Hair Loss Treatment: LC-MS/MS Molecular Networks for Metabolites Identification and Their Targets in Hair Growth-Inducing Signaling Pathways

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Changes in the hair growth cycle including shortening of the anagen phase, premature ingression of the catagen phase and prolongation of the telogen phase, lead to hair loss. The Wnt/β-catenin pathway is crucial during anagen. When activated, dermal papilla cells signal surrounding epithelial cells and coordinate their migration thus promoting hair growth. FDA-approved synthetic drugs used to cure hair loss may induce side effects, *e.g.* tachycardia and fainting. Aiming to provide natural and sustainable hair loss alternative treatments, *Calophyllum inophyllum* L. and *Fagraea berteroana* A. Gray ex Benth., two plants traditionally used in French Polynesia for hair care, were studied for their potential bioactivity. The chemical composition of these plants via molecular networks and the mode of action of bioactive constituents regarding selected targets of the canonical Wnt pathway will be presented.

C-15 – Mohammad Omar Faruque

Demystifying Bangladeshi Ethnomedicines with Modern Approaches: *Congea Tomentosa* as a Source of Potential Anti-Microbial and Anti-Cancer Agent

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The traditional healers of indigenous communities of Bangladesh use several plant parts, with often unknown ingredients, for the treatment of cancers and microbial diseases. To investigate such treatments, we documented the traditional use of 276 ethnomedicinal plant species, utilising 292 informants of Bangladesh. Notably, 28 species were reported with new therapeutic uses and 13 species described have never been studied. Of these, *Congea tomentosa* was selected for *in-vitro* studies. Bioassay-guided screening led us to identify 10 compounds, and 5 compounds were isolated and identified. Among the isolated compounds, compound-2 displayed promising antimicrobial activity against tested microorganisms, while compound-4 significantly decreased the ratio of Bcl-2/Bax and increased the expression levels of cleaved caspases-9 and -3, suggested that compound-4 had the potential to induce apoptosis in U-251 cells, through activation of the intrinsic/mitochondrial pathway which might be triggered by the inhibition of Stat3 and Akt expression. Despite the ethnobotanical importance of *Congea tomentosa*, no chemical or biological studies have been published to date which support its traditional applications in Bangladesh. However, our study demonstrates the possible use of this plant in the treatment of cancers/microbial diseases, and support its traditional use.

C-16 – Victoria Klein

Identifying the Cellular Target of Cordyheptapeptide A and Synthetic Derivatives

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Cyclic peptides have long been pursued for their rich structural diversity and continue to provide a bountiful source of bioactive scaffolds. Many cyclic peptide natural products are highly active in mammalian cells, prompting studies by our group and others into the factors that govern cell permeability in these large, non-"druglike" molecules. In the course of our studies into the relationship between molecular size and cell permeability, we synthesized and investigated the properties of cordyheptapeptide A (**1**). Originally isolated from *Cordyceps*, a fungal genus widely valued for its pharmaceutical potential, the cordyheptapeptide family, including cordyheptapeptide B and C, are reported to show toxicity toward bacteria, fungi, as well as a variety of cancer cell lines, mostly in the micromolar range. While a solution-phase total synthesis for **1** has been described, and its crystal structure has been solved, the biological target(s) and mechanism of action of **1** remain unknown. Here we describe a novel phenotypic activity for **1** and an efficient solid-phase synthesis approach that enabled a detailed investigation of structure-activity and structure-permeability relationships. Coupled with molecular dynamics simulations, we demonstrate that small modifications to both the backbone and side chains of a cyclic peptide can drastically affect both its permeability and bioactivity. Additionally, by combining two high-content screening assays with targeted pull-down assays, we identified its cellular target as the translation elongation factor eEF1A.

C-17 - Amanda Maldonado

Eupenifeldin, a novel bistropolone secondary metabolite, may act to induce apoptotic events in high-grade serous ovarian cancer

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High-grade serous ovarian cancer is the most common and aggressive form of ovarian cancer. There is an urgent need to develop novel drugs that could improve patient outcomes. Eupenifeldin was recently produced in large yields by the Oberlies lab, which allowed for extensive biological characterization. In three high-grade serous ovarian cancer cell lines (OVCAR3, OVCAR5, OVCAR8), eupenifeldin was found to have an IC_{50} of less than 10 nM, with a therapeutic index 10X lower in fallopian tube secretory epithelial cell lines (FTSEC), indicating that there may be a specificity for tumor cells. In a clonogenic assay, incubation of 10 nM eupenifeldin for 8 hours was found to significantly hinder the ability of these cells to undergo expansion 5-fold suggesting cytotoxicity. To evaluate if cell death occurred by apoptosis, the annexin-V/propidium iodine assay was performed. It was found that eupenifeldin induced early apoptotic events in OVCAR3 and OVCAR8. These findings were confirmed in a western blot by evaluating cleaved PARP. Future studies will test the changes in the mitochondrial membrane potential as a factor of mitochondrial integrity as well as the detection of caspase 3/7 activity upon treatment with eupenifeldin. Natural products with nM activity that induce apoptosis may provide new therapies for ovarian cancer.

C-18 – Mahsa Khoshbakht

New Chalanilines A from *Chalara* sp. Fungi and Total Synthesis of Chalaniline B

Mahsa Khoshbakht,[1] Jason Srey,[1] Donovon A. Adpressa,[1] Bongkotrat Thanaussavadate,[1] Yang Cao,[1] Paul R. Blakemore,[1] and Sandra Loesgen.*[1,2] [1]Department of Chemistry, Oregon State University, Corvallis, OR 97331, [2]Whitney Laboratory for Marine Bioscience, University of Florida, St. Augustine, FL 32080, USA.*

It was previously reported that perturbation of the endophytic ascomycete *Chalara sp.* 6661, producer of the isofusidienol class of antibiotics, with the histone deacetylase (HDAC) inhibitor vorinostat resulted in the production of new modified polyketides: chalaniline A (ChalA) and chalaniline B (ChalB). Both compounds incorporate an unusual anilino moiety which is derived from the vorinostat used to promote their biosynthesis. ChalA exhibits moderate cytotoxicity and ChalB shows potent activity against multi-drug resistant *Staphylococcus aureus*. The results of ongoing work to explore the chemistry and biology of the chalanilines via a combination of biochemical mutasynthesis and total synthesis will be presented. In part one of the lecture, the production, isolation, and structure elucidation (by NMR, MS) of six new chalaniline A analogs from *Chalara* cultures (0.5-2 mg/L yield) will be described (Figure 1). In each case, the new compound was obtained by incubating the fungus with a different vorinostat derivative. The various new vorinostats prepared for this purpose incorporate a sterically and electronically diverse range of anilino moieties. In part two of the lecture, the development of a successful elaboration of ChalB from 2-hydroxyxanthone by a route incorporating strategic oxidations followed by regioselective introduction of nitrogen- and carbon-based moieties to the resulting 1,3-dibromo-2,8-dihydroxyxanthone derivative, will be presented (Figure 2). With these results in hand, we are now poised to study biological SARs with the optimal method, either mutasynthesis (for ChalA) or chemical synthesis (for ChalB), being used to explore a given chalaniline chemotype.

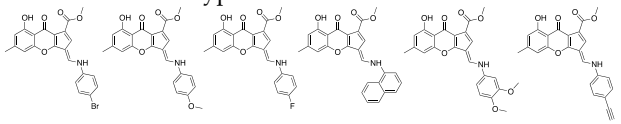

Figure 1. New chalaniline A compounds obtained from mutasynthesis with varied vorinostat analogs.

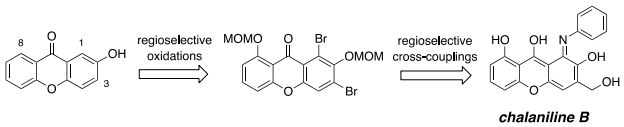

Figure 2. An overview of the total synthesis of chalaniline B from 2-hydroxyxanthone.

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