Bench, Biosphere & Beyond

2nd Annual Manitoba Chemistry Symposium

MCS2019

May 3-4, 2019

Brandon University

Event Outline: Fri. May 3rd

9:00 – 9:55	Registration Opens	
9:55 – 10:00	Opening remarks	**Dr. David Docherty**, President & Vice Chancellor, Brandon University **Dr. Vincent Chen,** MCS2019 Co-Chair, Brandon University
Chair B. Hill **10:00 – 10:25**	**Dr. Bernadette Ardelli**	*The Genome Sequence of a Bodonid Kinetoplastid: Cryptobia Salmositica*
10:25 – 10:50	**Dr. John Sorensen**	*Exploring Natural Product Biosynthesis in Lichen Fungi*
10:50 – 11:15	**Dr. Vincent Chen**	*Proteome-wide Identification of Oncometabolite-Protein Binding for Cancer Metabolism Studies*
11:15 – 11:25	Coffee Break	
Chair B. Hill **11:25 – 11:50**	**Dr. Christian Kuss**	*On the Importance of Inactive Battery Materials*
11:50 – 12:35	**Dr. Phil De Luna**	*Renewable electrosynthesis of chemicals and fuels from CO_2*
12:35 – 13:40	Lunch Break	Please enjoy our local restaurants.
Chair J. Ritch **13:40 – 14:35**	**Dr. Georg Schreckenbach**	*Chemistry at the Bottom of the Periodic Table: Theoretical Actinide Molecular Sciences*
14:25 – 14:50	**Dr. Eric Bushnell**	*A DFT study of the Capture and Release of Carbon Dioxide by Benzyl-Disulfide, -Diselenide and -Ditelluride*
14:50 – 15:35	**Dr. Joshua Hollet**	*Alternative models from a deeper understanding of electronic structure*
15:35 – 15:45	Coffee Break	
Chair E. Bushnell **15:45 – 16:10**	**Dr. Jamie Ritch**	*Cationic Selenium Compounds as Lewis Acids*
16:10 – 16:35	**Dr. Oleg Krokhin**	*Modeling Peptide Interaction with Hydrophilic Surfaces: Peptide Retention Prediction in HILIC*
16:35 – 17:00	**Dr. Micheal Eze**	*Indigenous Nutrition and Health: Intensify Chemical Research*
17:00 – 17:30	Break. Poster Set Up	
17:30 – 18:30	**Poster Session**	
18:30 – 19:30	Dinner	Please collect posters after dinner
19:30	Depart for Bowling	
20:00 – 21:30	Bowling	
21:30 – 22:30	Drinks	

Event Outline: Sat. May 4th

8:45 – 8:55	Coffee & Danish	
8:55 – 9:00	Opening Remarks	
Chair V.Chen		
9:00 – 9:45	**Dr. Ned Budisa**	*Chemical Synthetic Biology and the Expansion of the Genetic Code*
9:45 – 10:30	**Dr. Leonard Foster**	*Hypothesis Testing with Proteomics: Applications in Forensics and Biomedical Research*
10:30 – 10:40	Break	
Chair E. Bushnell		
10:40 – 11:25	**Dr. Tao Huan**	*Multi-Modal Metabolomics Data Integration for In-Depth Biological Interpretation*
11:25 – 11:50	**Dr. Sabine Kuss**	*Versatile Electrochemical Sensing Platform for Bacteria*
11:50 – 12:15	**Dr. Tabitha Wood**	*Evaluating the Effect of Substrate Ortho- and Meta-substitution Upon the Truce-Smiles Rearrangement*
12:15 – 12:40	**Dr. Vladimir Kubyshkin**	*Design of Hydrophobic Peptides Based on Extended Peptide Conformation*
12:40 – 13:00	Lunch: Assorted Sandwiches & Soups	
Graduate talks Chair E. Bushnell	Please allow for 1-3 minutes for questions	
13:00 – 13:15	**Ismael Elayan**	*The Bimolecular Catalytic Transformation of Methyl Vinyl Ketone Oxide: A DFT Study*
13:15 – 13:30	**Milan Teraiya**	*Proteomics of Temozolomide Resistant Glioma.*
Undergraduate talks Chair J.Ritch/T.Wood	Please allow for 1-3 minutes for questions	
13:30 – 13:45	**Spencer Ferbers**	*Phytochemical Studies on Anacardium occidentale and Chromolaena odorata*
13:45 – 14:00	**Robert Ortiz**	*Synthesis and Characterization of Hybrid Phenanthridine-Carbene (N^C) Ligands and their Transition Metal Complexes*
14:00 – 14:15	**Jesse Schmidt**	*Synthesis and Characterization of Novel Pseudo-Octahedral Iron Complexes of Bis-Phenanthridine Ligands*
14:15 – 14:30	**Syeda Yousra Irshad**	*Extraction and Isolation of Compounds from Carissa Apaca*
14:30 – 14:45	Trainee Poster/Oral Prizes, Closing Remarks, Acknowledgments, MCS2019 Group Photo	Award presentations

Poster Presentations: Fri. May 3th

#	Name	Title	Category	Trainee
1	Kiran Krishnamurthy	**Nuclear Magnetic Resonance Studies of HIV-1 Tat-Protein at Physiological pH**	Biochemistry	Graduate
2	Yuhua Fang	**An Optimized PARP-1 Enzymatic Assay for Screening Small Molecules as Potential PARP-1 Inhibitors**	Biochemistry	Graduate
3	Billy Vuong	**Hypoxia-Activated SN-38: Targeting Hypoxic Tumors**	Biochemistry	Graduate
4	Aisha Majeed	**Phytochemical studies on Sapium integerrimum**	Biochemistry	Graduate
5	Tanner Blesener	**Electron Transfer Properties of Ferrocene-BODIPY-Fullerene NIR Absorbing Triads**	Organic	Graduate
6	Chukwuebuka Onyema	**α-GLUCOSIDASE INHIBITING NATURAL PRODUCTS FROM CHROMOLAENA ODORATA**	Organic	Graduate
7	Francesca Valentini	**Spectroelectrochemical characterization of KuQuinones anions.**	Organic	Graduate
8	Paul Szymanski	**A One-pot, Microwave-assisted Synthesis for Aryl Urea and Carbamate Analogues Using Benzoyl Chloride and HOSA**	Organic	Graduate
9	Arun Krishnamurthy	**Network Structure of Nuclear Waste glasses at Canister-Centerline Temperature**	Inorganic	Graduate
10	Robert Ortiz	**Synthesis and Characterization of Hybrid Phenanthridine-Carbene (N^C) Ligands and their Transition Metal Complexes**	Inorganic	Undergraduate
11	Jesse Schmidt	**Synthesis and Characterization of Novel Pseudo-Octahedral Iron Complexes of Bis-Phenanthridine Ligands**	Inorganic	Undergraduate
12	Harjasmin Mander	**Synthesis of Forskolin Derivatives as Selective Activators of Adenylyl Cyclase 6**	Biochemistry	Undergraduate
13	Baldeep Sidhu	**Electrochemical Hydrogenation of Unsaturated N-Heterocyclic Substrates**	Organic	Undergraduate
14	Uriah Wolf	**Phytochemical Studies on Anacardium Occidentale**	Organic	Undergraduate
15	Matthew Polo P. Marcalinas	**Synthesis of hypoxanthine-3-N-oxide derivatives: Chemical alarm signalling pheromone in ostariophysan fishes**	Organic	Undergraduate
16	Rachel Willim	**Truce-Smiles Rearrangement: The Synthesis of Benzamide Derivatives from Amide Precursors**	Organic	Undergraduate
17	Caitlin Le	**Metabo-Proteomic Landscape of IDH R132H Mutation: 2-Hydroyglutarate Competitively Inhibits Phosphoserine Amino Transferase 1**	Biochemistry	Undergraduate
18	Cassidy Baumung	**Determining the Function of the Natively Disordered and Post-Translationally Modified N-terminus of the Bowen-Conradi Syndrome Protein Emg1**	Biochemistry	Undergraduate
19	Jessica Li	**Towards the Stratification of Canadian Glioma Patient Subpopulations Using Oncometabolite Levels**	Analytical	Undergraduate
20	Gurleen Cheema	**Phytochemical Studies on Methanolic Extract of Roots of Carissa Opaca**	Organic	Undergraduate
21	Bianca Zinzombe	**Exploration of Cationic Selenium Compounds**	Inorganic	Undergraduate

Contents

“Bench, Biosphere & Beyond”

The MCS 2019 conference takes place at Brandon University under the theme “Bench, Biosphere & Beyond”. This theme represents the importance of chemical research and the role chemical research has in shaping our society and environment. As such, presenters are welcome in any area of chemistry, including (but not limited to) organic, analytical, physical, inorganic, biochemistry, chemical biology, environmental chemistry, life sciences/health, chemical education, agriculture and pharmaceutical industry. In addition to the oral presentations on Friday and Saturday, we will host poster presentations on Friday evening followed by a social event. There will be undergraduate and graduate student competitions and prizes for both oral and poster presentations. Mingling will be encouraged during the poster session/reception on Friday evening.

The logo is meant to visually connect the three universities, University of Winnipeg, University of Manitoba, and Brandon University as partners in this endeavor. Cyclohexane rings were selected as a readily recognized chemical symbol. The colors (red, gold and blue) are representative of the institutions, being the primary colors of each school. The circles connect not only the three institutions, but also the various disciplines that connect chemistry and science. MCS logo was developed by the University of Winnipeg Marketing and Communications Department.

Committees

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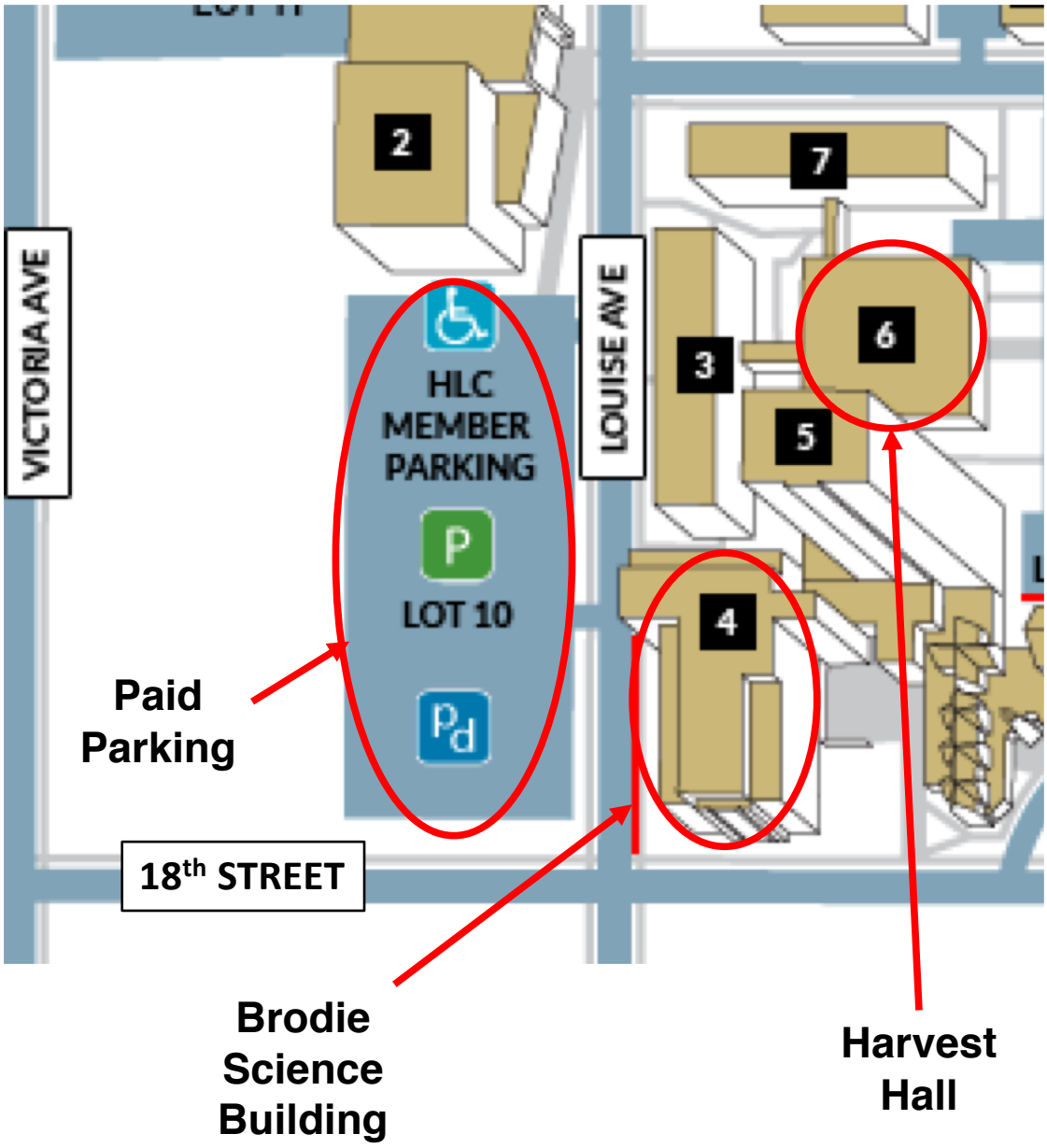
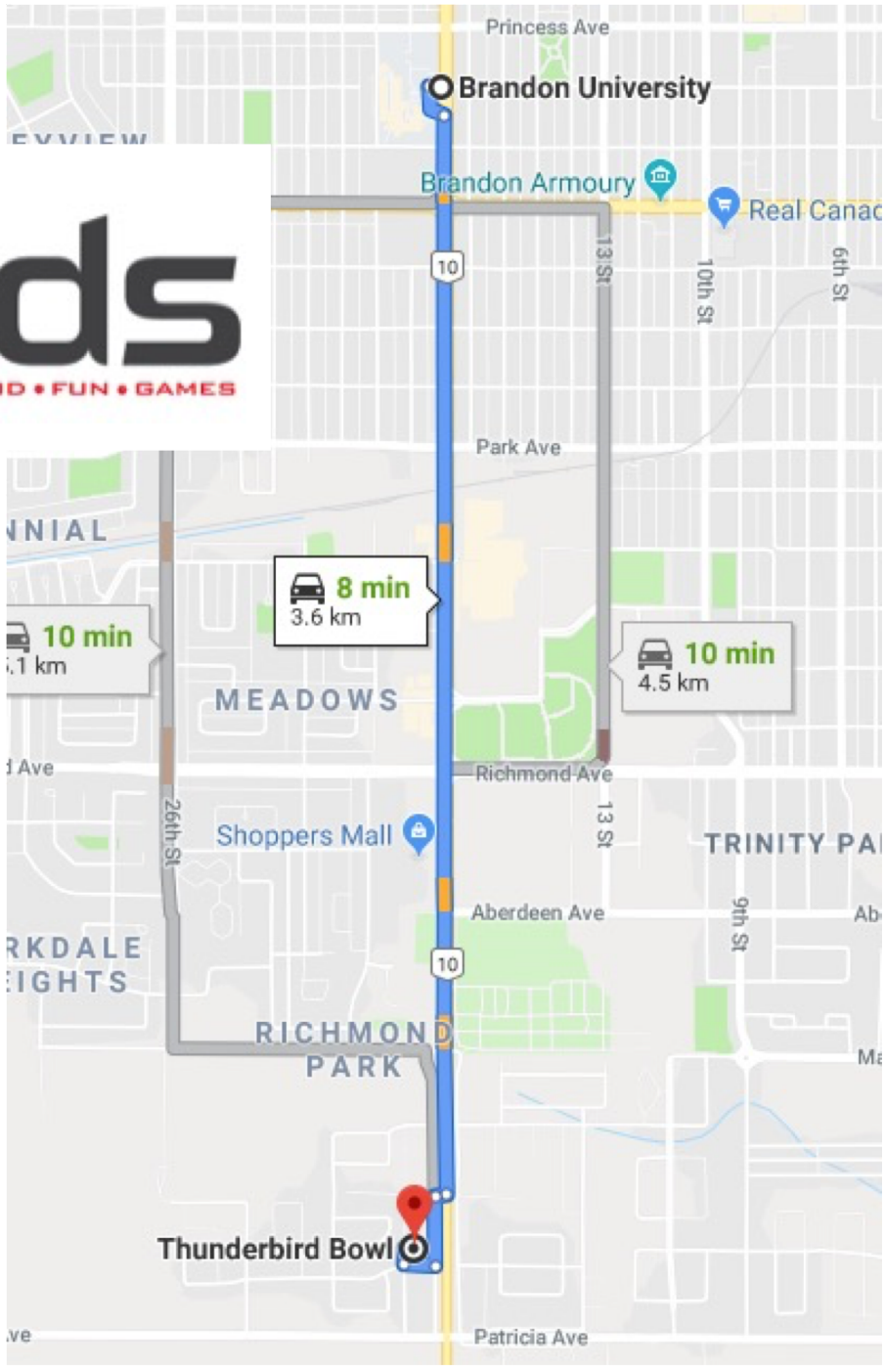
Campus Map



Access to Harvest Hall can be gained through Brodie Science Building

Bowling

T-Birds
FOOD • FUN • GAMES



- **2140 Currie Blvd, Brandon, MB** [204-727-2695]

Abstracts

Listed in alphabetical order of last name

The genome sequence of a Bodonid Kinetoplastid: *Cryptobia salmositica* (Kinetoplastida: Euglenozoa)

Bernadette Ardelli

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Cryptobia salmositica is a bodonid kinetoplastid and a close relative of the trypanosomatid parasites, which cause such human diseases as African sleeping sickness, leishmaniasis and Chagas disease. The genome data were determined using both Illumina-HiSeq and Pac-Bio strategies. Some of the assembled sequences extend into the subtelomeric regions and contains the molecular machinery for antigenic variation. Both strands contain long, nonoverlapping gene clusters that are probably transcribed as polycistrons, then subsequently trans-spliced and polyadenylated, similar to other kinetoplastids. Homologs of components of actin- and tubulin-based cytoskeleton are present with six members of the tubulin superfamily identified. The parasite possesses a full complement of candidate genes necessary for the uptake and degradation of glucose via glycolysis or the pentose phosphate shunt and the tricarboxylic acid (TCA) cycle. Few hexose transporters are present. A fully functional mitochondrial electron transport system and adenosine triphosphate (ATP) synthase is present. The sequenced genome reveals similarities with other TriTryps as well as some unique features.

Determining the Function of the Natively Disordered and Post-Translationally Modified N-terminus of the Bowen-Conradi Syndrome Protein Emg1

Cassidy Baumung

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The ribosomal RNA small subunit methyltransferase Emg1 plays a crucial role in the assembly of the small subunit (SSU) of the ribosome. This is done through its membership in the SSU processome, a 6 MDa ribonucleoprotein complex that is responsible for most processing steps in the assembly of the SSU of the ribosome. An Emg1 mutation has been identified as the key factor causing Bowen-Conradi Syndrome (BCS), a rare genetic disease affecting Hutterite communities of Canadian prairie regions. BCS is part of a growing family of ribosome assembly disorders called ribosomopathies. Our lab discovered that the N-terminal region of Emg1 is natively disordered and heavily post-translationally modified by phosphorylation, acetylation, ubiquitination, SUMOylation, and NEDDylation. It is hypothesized that this post-translationally modified and natively disordered region plays an unknown functional and regulatory role in Emg1. As the BCS Emg1 mutation is within close proximity of the disorderd region, we also ponder whether or not this further modulates the function of the disorderd region. Consequently, we aim to characterize the function of the disordered and heavily post-translationally modified N-terminus of Emg1 protein and to determine the effects of the BCS mutation on the stability and post-translational modifications of the protein. To achieve this, all methods will use a yeast model system of BCS in which the endogenous chromosomal protein can be genetically depleted and WT, BCS, and other Emg1 variants are epitope-tagged and constitutively expressed from a plasmid. We will use a cyclohexamide chase assay to determine the stability of the BCS protein relative to its WT counterpart. The function of the natively disordered region will be assessed using a series of truncation mutants, assaying them for their protein stability, ability to complement the WT protein, as well as protein-protein interactions and ribosome assembly. The function of post-translational modifications will be determined by mutational analysis and the creation of phosphomimetics, with changes in post-translational modifications between WT and BCS Emg1 assessed using post-translational modification-specific antibodies and co-immunoprecipitations. We anticipate confirming that the BCS mutation leads to protein destabilization and a decrease in protein abundance along with a change in post-translational modifications. Ultimately, the resulting discoveries on the function of these post-translational modifications will give us a deeper understanding of the molecular mechanisms of the Emg1 protein allowing us to better understand its molecular role in the pathogenesis of BCS.

Electron Transfer Properties of Ferrocene-BODIPY-Fullerene NIR Absorbing Triads

Tanner Blesener

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Boron dipyromethane (BODIPY) dye has intense excitation and emission peaks, high solubility in organic solvents, as well as high fluorescence quantum yields which have made them a very popular fluorophore. Ferrocene-BODIPY-fullerene triads were synthesized and characterized by 1D and 2D NMR, UV-Vis, steady-state fluorescence spectroscopy, high-resolution mass spectrometry, and X-ray crystallography. The redox properties of these donor-antennae-acceptor triads were probed using electrochemical (CV and DPV) approaches and spectroelectrochemistry. The photophysical properties of these triads were also investigated by transient absorption spectroscopy in both UV-vis and NIR spectral regions.

1) Y. V. Zatsikha, E. Maligaspe, A. A. Purchel, N. O. Didukh, Y. Wang, Y. P. Kovtun, D. A. Blank, V. N. Nemykin, Inorg. Chem. 2015, 54, 7915-7928.; 2) N. O. Didukh, Y. V. Zatsikha, G. T. Rohde, T. S. Blesener, V. P. Yakubovskyi, Y. P. Kovtun, V. N. Nemykin, Chem. Commun. 2016, 52, 11563-11566

A DFT study of the Capture and Release of Carbon Dioxide by Benzyl-Disulfide, -Diselenide and -Ditelluride.

Eric Bushnell

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Rising levels of CO_2 concentration and its contribution to climate change is one of the greatest issues our planet faces today. This is why the minimization of carbon emissions is the focus of many researchers today. In the present work a density functional theory (DFT) approach was used to investigate the ability of benzyl-disulfide, benzyl-diselenide and benzyl-ditelluride to act as a carbon capture and storage (CCS) technology. In addition to varying the chalcogen atom we have modeled the reaction in several solvent systems. Specifically, water, acetonitrile, and diethyl ether were chosen to investigate the effect of varying solvent polarity on the reaction. Key results will be presented.

Phytochemical Studies on Methanolic Extract of Roots of Carissa Opaca

Gurleen Cheema

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An understanding of the ethnopharmacological properties plants has led to the discovery of effective drug-like compounds that can be used in clinical practices. The project was designed to isolate and study the phytochemical constituents of the roots of plant Carissa opaca. Our detailed phytochemical studies on methanolic extract of roots of this plant using chromatography, 1H-NMR, 13C-NMR, and 2D-NMR spectroscopy afforded three compounds;6-methoxy-7-hydroxycoumarin (Compound A), 7β(H),10β-eudesm-4-en-3-on-11-ol (Compound B), and a flavonoid (Compound C). Structure of the flavonoid and the antioxidant, antibacterial and anti-enzymatic activities of the compounds are yet to be investigated.

Proteome-wide Identification of Oncometabolite-Protein Binding for Cancer Metabolism Studies

Vincent Chen

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Metabolite-protein interactions control a variety of cellular processes and represent the largest fraction of molecules in the cell. However, our understanding of how metabolites regulate proteins far lags behind our understanding of associations of proteins with other classes of biomolecules, such as interactions between protein-protein and DNA-protein. Thus far, most protein-metabolite interactions have been discovered via hypothesis-driven methods. These methods are typically laborious and time consuming. Here, we demonstrate a chemoproteomic workflows involving the identification of metabolite-protein interactions utilizing high-throughput identification of peptides by LC-MS/MS. In this study, we examine the interactions of the oncometabolite 2-hydroxygluaterate (2HG) that is produced by clinically relevant mutations in the enzyme isocitrate dehydrogenase 1 (IDH R132H). Our results identify the interaction of 2HG with phosphoserine amino transferase 1 (PSAT1). Further biochemical analysis suggests 2HG competitively competes with natural substrates for the PSAT1 active site, thereby reducing the overall . Our data reveals functional insights into the mechanisms of chemical communication and metabolic reprograming that is intimately associated with a number of cancers. Our data identifies metabolic pathways for possible future therapeutic design.

Renewable Electrosynthesis of Chemicals and Fuels From CO_2

Phil De Luna

Program Director | Directeur de Programme
Energy Materials Challenge Program | Programme Défi (Matériaux énergétiques)
National Research Council Canada | Conseil National de Recherches Canada
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Today many of the world's chemicals are produced from fossil fuel–derived feedstocks. Electrochemical conversion of carbon dioxide into chemical feedstocks offers a way to turn waste emissions into valuable products, closing the carbon loop. When coupled to renewable sources of electricity, these products can be made with a net negative carbon emissions footprint, helping to sequester CO_2 into usable goods. This talk describes recent progress on nanostructured catalysts for CO_2 conversion, their integration into prototype systems, and a new collaborative research program at the NRC for renewable fuels and chemicals.

The Bimolecular Catalytic Transformation of Methyl Vinyl Ketone Oxide: A DFT Study

Ismael Elayan

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The bimolecular reactions of the dominant Criegee Intermediate that results from the ozonolysis of isoprene, methyl vinyl ketone oxide (MVK-OO), has been studied. The reactions investigated include H_2O, H_2S, NH_3, their dimer forms, and NH_2CH_3 to form a hydroperoxide. Furthermore, the interchange of the molecule's dimers to different asymmetric molecules, e.g. (H_2O…H_2S), (H_2S…NH_3), and (NH_3…H_2O) has been investigated. The reactions occur with low free energies of activation ($\Delta G‡$) that do not exceed 70 kJ mol-1. The presence of other molecules in the H_2O and NH_3 reactions exhibit a similar effect of reducing the energy barrier; a catalytic behavior. The former reactions decrease by 20 kJ mol^{-1} while the latter by 14 kJ mol-1. In contrast to these reactions, the presence of other molecules in H_2S reactions increases the calculated $\Delta G‡$ values by 22 kJ mol^{-1}. Interestingly, the calculations of MVK-OO + NH_2CH_3 predict $\Delta G‡$ = 26 kJ mol^{-1}, lower than the catalyzed reactions of H_2O, H_2S, and NH_3. Including a catalyst in NH_2CH_3 reactions leads to negligible effects on the energy, except for the (NH_2CH_3…H_2O) reaction, where the $\Delta G‡$ is reduced by 10 kJ mol-1 to 16 kJ mol^{-1}. The formation of a carbonyl hydroperoxide (MVK-OO + CH_2O_2) is predicted to be the least favorable pathway with $\Delta G‡$ values in the range of 61 to 69 kJ mol^{-1}, at different levels of theory.

Indigenous Nutrition and Health: Intensify Chemical Research

Michael Eze

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We as living beings should remain in tune with the ecosystem in which we belong, as implied in the Indigenous “Holistic View of Health and Wellness.” This is consistent with the “Let Food be thy medicine and medicine be thy food” dictum enunciated by Hippocrates. As thermodynamic “open systems”, avoiding polluting the ecosystem guarantees its sacrosanctity and ensures that we derive fresh foods, clean air and water therefrom; and establish homeostasis, thereby keeping the body’s chemistry optimized. Issues currently plaguing the health of Indigenous peoples may relate to aspects of the violation of the Holistic view. To address this requires concerted efforts in varied aspects of chemical research: Commonalities in the chemical species participating in the operation and control of metabolic reactions in both disease and healthy states. Thus the new direction should address reactive oxygen species (ROS), reactive nitrogen species (RNS), advanced glycation end-products (AGEs), and others present in normal individuals, and in diverse and numerous infectious diseases, as well as in chronic [diabetes and complications; cancer; degenerative diseases (Alzheimer’s, Parkinson’s, cardiovascular)] diseases; and other states of ill-health. Investigating the role and mechanism of traditional Indigenous resources as remedies would be relevant. Ultimately, isolation of active ingredients and formulation of remedies therefrom, as per recent successes in the field, should be the end game.

An Optimized PARP-1 Enzymatic Assay for Screening Small Molecules as Potential PARP-1 Inhibitors

Yuhua Fang

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PARP-1 belongs to the Poly(ADP-Ribose)polymerase (PARP) family and is involved in DNA repair. Inhibition of PARP-1 enhances chemotherapy effects by blocking the repair of DNA damage caused by chemotherapeutic agents. While some PARP inhibitors have been proved by the FDA, we are still interested in developing novel PARP inhibitors with better potency and selectivity. Methods using commercially available assay kits to screen small molecules as potential PARP-1 inhibitors are expensive and cannot be used to screen more than a couple of compounds at one time. A fluorescent enzymatic assay was reported in several papers using chemical quantitation of NAD+. Given the problem experienced when repeating this PARP assay, we have further improved and optimized the assay by reforming protocols for PARP-1 enzyme, activated DNA, NAD+ and the wavelength for detecting fluorophore. Compared to the old one, our assay possesses a wider detecting range, higher sensitivity. Meanwhile, with some novel molecules that we synthesized tested in the assay, using PJ-34 and phenanthridinone as standard groups, it shows that the assay produces consistent and trustworthy results and is highly robust towards different kinds of small molecules.

Phytochemical Studies on Anacardium occidentale and Chromolaena odorata

Spencer Ferbers

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Type 2 diabetes is a silent killer that affects over 2 billion people worldwide and often goes unnoticed. It can cause strokes, heart attacks and kidney failure in those who suffer from the disease. Alpha-glucosidase is a membrane-bound enzyme in the small intestines that breaks down sugars into the blood. The hyperactivity of alpha-glucosidase results in postprandial hyperglycemia, also referred to as type 2 diabetes. Potent alpha-glucosidase inhibitors are used to treat type 2 diabetes as well as other sugar regulated diseases such as HIV, cancer and obesity by reducing the amount of glucose absorbed in the stomach and thus reducing hyperglycemia. However, the alpha-glucosidase inhibitors currently on the market produce many unwanted side effects, such as flatulence and diarrhea. The purpose of this research was to isolate and determine the structure of potential alpha-glucosidase inhibitors in Anacardium occidentale and Chromolaena odorata that do not produce these side effects. A. occidentale and C. odorata are plants that are used in folk medicine in Nigeria to treat diabetic-like symptoms and have recently been tested to be active in inhibiting alpha-glucosidase. In order to isolate these compounds, column chromatography and various types of thin-layer chromatography were used. Once compounds were isolated, different types of carbon and proton nuclear magnetic resonance spectroscopies were used to determine the structure of these compounds. A future study is to perform bioassays on the isolated compounds to test their biological activity in inhibiting alpha-glucosidase and as a potential pharmaceutical.

Hypothesis Testing with Proteomics: Applications in Forensics and Biomedical Research

Leonard Foster

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I will discuss two vignettes of how we have applied proteomics, one in forensics and one to understand the fundamental biology behind tissue structure/function:

1. We were approached by the RCMP to help determine if the blood of a deceased child contained snake venom. The species of a putative snake was unknown. The blood sample had been stored at 4°C for ~6 months, without protease inhibitors, so was a sub-optimal sample for proteomics. We used all the pre-fractionation strategies available to us at the time, creating 80 samples for LC-MS/MS. The data were searched against a database of all human proteins plus all Uniprot sequences retrieved by a “Serpente venom” query. We were able to confirm that several venom proteins were present in the blood, which subsequently led to a charge and an arrest.

2. Cellular processes arise from the dynamic organization of proteins in networks of physical interactions. Mapping the complete network of biologically relevant protein-protein interactions, the interactome, has therefore been a central objective of high-throughput biology. Yet, because widely used methods for high-throughput interaction discovery rely on heterologous expression or genetically manipulated cell lines, the dynamics of protein interactions across physiological contexts are poorly understood. Here, we use a quantitative proteomic approach combining protein correlation profiling with stable isotope labelling of mammals (PCP-SILAM) to map the interactomes of seven mouse tissues. The resulting maps provide the first proteome-scale survey of interactome dynamics across mammalian tissues, revealing over 27,000 unique interactions with an accuracy comparable to the highest-quality human screens. We identify systematic suppression of cross-talk between the evolutionarily ancient housekeeping interactome and younger, tissue-specific modules. Rewiring of protein interactions across tissues is widespread, and is poorly predicted by gene expression or coexpression. Rewired proteins are tightly regulated by multiple cellular mechanisms and implicated in disease. Our study opens up new avenues to uncover regulatory mechanisms that shape in vivo interactome responses to physiological and pathophysiological stimuli in mammalian systems.

Alternative models from a deeper understanding of electronic structure

Joshua Hollett

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Recently we devised an alternative, two-pronged, approach for modelling the electronic structure of atoms and molecules. More specifically it involves dividing electron correlation into to distinct components, static and dynamic. We have shown that this approach has the potential to be an efficient model of complex chemical systems. Key to the conception of such an approach is a thorough understanding of the correlated motion of electrons and the ability of existing methods to model different aspects of that correlation. This knowledge is extracted from many-electron wave functions with two-electron probability distributions, such as intracules. Our models can be further improved with a deeper understanding of correlated electron motion, facilitated by new two-electron probability distributions. Progress in this vein will be discussed.

Extraction and Isolation of compounds from Carissa apaca

Syeda Yousra Irshad

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Plants in their natural environment are exposed to diseases and other environmental factors. To overcome and fight against the disease-causing pathogens the plants produce a wide range of chemicals. These naturally occurring chemicals are diverse in their structures, with some possessing valuable medicinal application. Natural products have recently garnered interest in the drug discovery field. Diabetes, a metabolic condition which causes elevated blood glucose levels is a known target of drugs derived from natural sources. Increased expression of a-glucosidase levels-an enzyme which breaks downs polysaccharides into monosaccharides are inhibited by these compounds. Carissa apaca, native to Pakistan, has been shown to have great medicinal value. The natural products of the plant have been shown to treat various conditions including jaundice, hepatitis, asthma, and diabetes. My research is focused on phytochemical investigation of the plant's crude extract and isolation of several classes of compounds such as coumarin, terpenoids, and tannins among others using fractionating columns and running a preparative TLC to further purify the isolated compounds. The isolated compound will then be investigated for their respective mechanism of action in treating the afore mentioned diseases.

Multi-Modal Metabolomics Data Integration for In-Depth Biological Interpretation

Tao Huan

University of British Columbia, yousraali627@gmail.com

A comprehensive metabolomic study in a given biological sample can be achieved by analyzing the same sample set in orthogonal mass spectrometry (MS)-based analytical modes (i.e. multiple modes metabolomics). However, processing and interpreting biological information in multi-modal metabolomics presents a significant bioinformatic challenge, as it requires to integrate heterogenous metabolomic data sets generated from multiple analytical platforms. To address this challenge, we introduce multi-modal XCMS, an automated pathway/network analysis platform that can predict dysregulated metabolic pathways directly from multi-modal metabolomic data sets and perform multi-omic data integration for a systems-level understanding of the dysregulated pathways. This platform can automatically integrate many types of MS-based metabolomic data with no restrictions on the sample preparation, chromatographic separation, or MS detection.

Network Structure of Nuclear Waste glasses at Canister-Centerline Temperatures

Arun Krishnamurthy
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Commercial and prototype glasses for the immobilization of high-level radioactive waste have been comprehensively studied by a vast array of chemical and physical techniques. However, most of this work has been done at ambient temperatures, leaving relatively unexplored the higher- temperature regime at which radioactive glasses exist in the near term. Considering the importance of glass network structure in critical properties such as chemical durability and devitrification, we have used laser-heated nuclear magnetic resonance (NMR) spectroscopy to characterize several model nuclear glasses at temperatures up to 400°C. Compositions have been selected to evaluate the role of temperature in molybdenum retention within the glassy phase, encompassing simple borosilicates as well as more complex aluminoborophosphates and borosilicophosphates, which have been shown to significantly improve molybdenum and sulfur solubility. Magic-angle spinning NMR of ^{29}Si, ^{31}P, ^{27}Al, ^{11}B, ^{23}Na and ^{95}Mo provide complementary perspectives on the structural evolution of these glasses with temperature, revealing the limitations of studies done at ambient laboratory temperatures and providing a basis for more relevant property predictions.

Nuclear Magnetic Resonance Studies of HIV-1 Tat-Protein at Physiological pH

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The Human Immunodeficiency Virus-1 (HIV-1) Transactivator of transcription (Tat) protein is a 101-residue Intrinsically Disordered Protein (IDP) encoded by two exons. Tat binds to a stem-loop region at the 5'-end of newly transcribed viral RNA and the human Positive-Transcription Elongation Factorb (p-TEFb) consisting of Cyclin Dependent Kinase-9 and Cyclin T1. Phosphorylation of the C-terminal tail of RNA Polymerase and negative elongation factors results in enhanced viral transcription and successful virus production. Tat is also known to bind over 100 other human proteins by which it modulates several cellular processes including cell cycle, apoptosis, innate immunity, and others.

HIV-1 Tat protein has a high net positive charge, a high Cys content, a low content of hydrophobic residues and a low sequence complexity. It is highly soluble at pH 4 and has been extensively studied at acidic pH. Between pH 6 and pH 7, Tat NMR resonances broaden and disapper, and the protein precipitates from solution. To understand the role of this essential protein in enhancing transcription will require a study of its structure and dynamics in the presence of its binding partners at physiological pH. Thus, the aim of this research is to solubilize Tat at pH 7 and study the effects of binding partners on its structure and dynamics to gain insight into the mechanisms by which it functions.

We have used several approaches to solubilize Tat at neutral pH including the use of high concentrations of the natural hydrotrope ATP and high concentrations of metal ions. We will also report on investigations of the causes of the disappearing NMR resonances including the possibility of elevated H-exchange, ms-us conformational exchange, aggregation and precipitation. Both standard indirect detection NMR experiments and direct 13C and 15N detection NMR experiments have been explored and will be reported.

Design of hydrophobic peptides based on an extended peptide conformation

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Peptides are intrinsically polar structures due to the high polarity of the amide backbone. Therefore, installation of the hydrophobic motif on a peptide scaffold represents a particularly difficult task. Aggregation and denaturation are common problems associated with reconstitution of hydrophobic peptides in organic solvents and membrane models. To address these problems, over the past few years we explored the possibility to build a hydrophobic motif on a polyproline peptide scaffold, which folds into an extended type conformation, the polyproline-II helix. We were particularly intrigued by the fact that nature does not operate hydrophobic helices of this types, despite widespread presence of this secondary structure. Nonetheless, we demonstrated experimentally that by careful choice of the constitution hydrophobic amino acid, we could construct such peptides with astonishing hydrophobic properties. For example, the peptide construct can be made soluble in hexane, while it still maintains the secondary structure. Further success of our approach was demonstrated by designing a new type of transmembrane peptide elements and hyperstable collagen models. Application of the hydrophobic polyproline-II helical motif opens a new avenue in utilization of peptide structures under non-aqueous conditions. At the same time, our findings enable to address a series of fundamental questions in the fields of membrane biophysics and life evolution.

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On the importance of inactive battery materials

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Intercalation batteries, of which Lithium-ion batteries are the most successful representative, could be conceived with as little as three different materials: two active charge storing materials forming the electrodes and one electrolyte in between. These are the three fundamental battery materials and without them the battery is incomplete. Not surprisingly, most materials research is focusing on improving their intrinsic charge-storing properties - capacity, potential, conductivity. However, with very few exceptions, batteries require a lot more for optimal performance. Electrodes require conductive additives and binders to connect particles electronically and keep that connection over cycling. The liquid electrolyte is held within a porous separator, which is placed between the electrodes to avoid short circuiting. These and other materials contribute to the overall functioning of the battery, but don't take any active role in charge storage or cycling. This presentation will demonstrate the importance of the complex battery structure at the example of the lithium-ion cathode material $LiFePO_4$. Out of the intrinsic properties of this material, it is the conductivity that cannot be used to its full potential within current batteries. This leads to a reduction of charging speed from less than 10 seconds to tens of minutes. Given such performance loss when going from the intrinsic material properties to the overall battery performance, inactive battery components have been underappreciated in materials research to date. New work at the University of Manitoba will be presented, that explores conductive binders for intercalation electrodes that are expected to allow better use of the intrinsic capacity of electrode materials and enable the exploitation of otherwise abandoned high-energy-density electrode materials.

Versatile Electrochemical Sensing Platform for Bacteria

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Bacterial infections present one of the leading causes of mortality worldwide, resulting in an urgent need for sensitive, selective, cost-efficient, and easy-to-handle technologies to rapidly detect contaminations and infections with pathogens. The presented research reports a fully functional chemical-detection principle, addressing all of the above-mentioned requirements for a successful biosensing device. With the examples of *Escherichia coli* and *Neisseria gonorrheae*, we present an electrochemical biosensor based on the bacterial expression of cytochrome c oxidase for the selective detection of clinically relevant concentrations within seconds after pathogen immobilization. The generality of the biochemical reaction, as well as the easy substitution of target-specific antibodies make this concept applicable to a large number of different pathogenic bacteria. The successful transfer of this semidirect detection principle onto inexpensive, screen-printed electrodes for portable devices represents a potential major advance in the field of biosensor development.

Metabo-proteomic Landscape of Clinical IDH Mutation: 2-Hydroyglutarate Competitively Inhibits Phosphoserine Amino Transferase 1

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Isocitrate dehydrogenase (IDH) is a NADP-dependent enzyme catalyzing the reversible oxidative decarboxylation reaction of isocitrate to alpha-ketoglutarate (KG). As a central regulator of the TCA cycle, metabolic intermediates produced by IDH are critical to maintaining energy balance, epigenetic control, oxidative stress and macromolecule production. Mutations in the IDH1/2 enzymes are common to glioma, and other malignancies (myeloid leukemia, cholangiocarcinoma). Approximately 85% of secondary glioblastomas (GBM) tumors harbor heterozygous IDH mutation, with the largest proportion of alterations characterized as 'hotspots' that target IDH catalytic core. Such changes result in the production and accumulation of the oncometabolite 2-hydroxyglutarate (2-HG) at exceedingly high levels (>1000x). Mechanisms of IDH mutation and signaling pathways downstream of 2-HG are poorly understood. Objectives: 1) access thermodynamics of mutant and WT IDH enzyme; 2) identify signaling pathways down-stream of 2HG to determine functional impact in glioma. Methods: A computational study of density functional theory cluster model was applied to PDB crystal structure of IDH to investigate the thermodynamic reaction balance associated with WT and IDH mutant. LN18 and HEK cell line expressing wild-type and mutant IDH and then collected for metabolic profiling. Protein-metabolite interaction screens were elucidated using limited proteolysis and LC-MS/MS to identify phosphoserine amino transferase 1 (PSAT1). Biochemical assays to measure PSAT1 activity were performed using recombinant expression, purification, and Western blotting methods. Results: Metabolomic analysis confirmed a significant increase of 2-HG in cells with IDH mutation. Of the TCA metabolites and amino acids monitored, no significant changes were observed suggest the TCA energetics remained unaltered. The computational approaches confirmed 2-HG is thermodynamically favored in IDH catalytic core mutations. PSAT1 was identified from proteomic data as an potential interactor or 2-HG with the functional inhibition of this enzyme demonstrated by biochemical assays. Discussion: GBM cells with IDH mutation have a high level of 2-HG, our data demonstrates high 2-HG levels interferes with the key metabolic enzyme PSAT1. As a key enzyme of serine metabolism, nucleotide synthesis, one-carbon metabolism, as well as cellular homeostasis our data provides avenues to investigate 'metabolic reprogramming' in cancer and therapeutic development. Functional assays to access the role PSAT1 inhibition (proliferation and migration) by 2HG are currently in are currently underway.

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Towards the Stratification of Canadian Glioma Patient Subpopulations Using Oncometabolite Levels

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Isocitrate dehydrogenases 1 and 2 (IDH1/2) are enzymes that catalyze the conversion of isocitrate to alpha-ketoglutarate (α-KG) in the tricarboxylic acid (TCA) cycle. Mutations in the active sites of these enzymes (eg. IDH R132H) alter their affinity for substrates, causing them to convert α-KG to the typically rare oncometabolite 2-hydroxyglutarate (2-HG). IDH mutations have been observed in several cancers, including nonepithelial melanoma, myeloid leukemia and glioma, specifically primary and secondary glioblastomas (GBM). In GBM, IDH mutations are paradoxically associated with an increased risk of tumorigenesis as well as increased survival of patients. 2-HG is hypothesized to be a biomarker of IDH status, which in turn may be used as a diagnostic and prognostic indicator. However, the mutational status of IDH mutation is not currently used by Canadian Clinicians, and in general, the role of 2-HG in metabolism is poorly understood. To help address these needs, we conducted a metabolomic analysis of human embryonic kidney (HEK) cells (IDH R132H and WT IDH control) to determine relative levels of 2-HG and a subset of TCA cycle intermediates. As anticipated, HPLC high-resolution QTOF mass spectrometry analysis showed a significant increase in 2-HG between wild-type and IDH mutant cells. However, TCA cycle metabolite levels did not significantly differ between cells harbouring wild-type and mutant IDH. These findings suggests IDH R132H mutation and increases in 2-HG do not significantly impact the energetic output of the TCA cycle. Moving forward, our procedures will be further benchmarked using LN18 human glioma cells (IDH R132H and wildtype) and patient derived cells. Global metabolomic analyses will be performed, and methods to accurately monitor 2-HG levels to take advantage of the clinical significance of the mutational status of IDH. With the aim of stratifying glioma patient populations, the overall goal is to develop a robust, readily accessible assay for the measurement of 2-HG in tissue, plasma and urine samples.

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Phytochemical studies on Sapium integerrimum

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Diabetes (especially type II diabetes) is affecting nearly 4 million people in the world. There are a number of hyperglycemic drugs available on the market to overcome this problem but all of them have different health related side effects. In order to minimize the side effects and enhance the curative nature researches have been made. In our lab we are investigating Sapium integerrimum, a medicinally important South African plant to discover a new anti-a-glucosidase inhibitors as potential lead compounds against type II diabetes. Our recent phytochemical studies have afforded coumarines, flavonoids and phorbol ester. Structures of these compounds were elucidated with the aid of extensive NMR mass spectroscopic studies. In this presentation, isolation and their structure elucidation with the help of NMR spectroscopic studies will be discussed.

Synthesis of Fr

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Adenylyl Cyclases (ACs) upon activation by the G-protein Gαs, catalyze the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). (1) The activation of this enzyme may play a crucial role in providing potential treatments for infants born with persistent pulmonary hypertension. (2) Adenylyl Cyclase 6 is localized to infant lung tissue where it functions as a vasodilator in vascular myocytes.(3) Previous studies have shown that hypoxia affects AC6 activity and results in deceased levels of cAMP. Through activation of A6C, the levels of cAMP can be increased to rescue hypoxic infants.(1) Forskolin; a major diterpene found in the roots of the Indian Coleus Forskolii plant, is a non-selective activator of AC that binds to the allosteric site and interacts with specific residues within the catalytic domain. (1) We hypothesize that through the derivatization of Forskolin with the reaction scheme below, the specificity for the 6th isoform of AC can be increased. The amines with various R groups can easily be protonated at physiological pH and therefore also help to increase the water solubility. Overall, through Forskolin derivatization, we can synthesize potential drugs as treatments for infants with persistent pulmonary hypertension.

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Synthesis of hypoxanthine-3-N-oxide derivatives: Chemical alarm signalling pheromone in ostariophysan fishes

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An interest in the ability of the molecule hypoxanthine-3-N-oxide (H3NO) to act as an alarm pheromone for ostariophysan fishes was investigated. H3NO is to be synthesized to provide an analytical standard in measuring its concentration in freshwater samples by HPLC. The synthesis of H3NO was conducted using two proposed schemes. A synthesis and characterization process using 6-methoxypurine and alternatively using 6-chloropurine involved in a two-step chemical oxidizing procedure. Spectral data was interpreted to characterize and qualitatively assess the favorable result of the synthetic procedures. An experimental yield was measured for the synthetic schemes using 6-methoxypurine and 6-chloropurine. Further additional study may incorporate the measurements of H3NO in natural water samples and to analyze the samples for derivatives of H3NO related to water pH changes. The structure of the derivatives may then be determined, and their synthesis may be attempted.

α-GLUCOSIDASE INHIBITING NATURAL PRODUCTS FROM CHROMOLAENA ODORATA

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Regardless of the alarming and persistent increase in the number of people globally affected by the Type II diabetes, there seems to be less natural curative measures except insulin and oral hypoglycaemic drugs (such as acarbose and magilitol) available to assist in tackling this issue. Both drugs work by inhibiting the activity of α-glucosidase, an enzyme involved in type II diabetes. Chromolaena Odorata, a medicinally important plant, is used to treat type II diabetes symptoms by traditional healers in Nigeria. The crude extract of this plant was active against α-glucosidase in our bioassay. Our recent phytochemical investigation of this plant resulted in the identification of flavonoids. Derivatization of isolated flavonoids by modified Williamson-ether synthesis using 7-hydroxycoumarin as base model was done. In this presentation, isolation and structure elucidation of isolated compounds and their derivatives with the aid of detailed one - and two dimensional NMR spectroscopy will be discussed. Additionally, we will also discuss the bioactivity of these phytochemicals.

Synthesis and Characterization of Hybrid Phenanthridine-Carbene (N^C) Ligands and their Transition Metal Complexes

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Organic Light-Emitting Diodes (OLEDs) are being increasingly used in displays due to their efficiency in converting electrical energy to light. The emissive compound in the OLED determines the colour and efficiency of light emission. Much effort is going towards improving the emissive properties of OLEDs, which can help lower the energy needed to power displays, making them eco-friendlier and more cost friendly. Organometallic complexes are of specific interest for use as emissive components of OLEDs because in the presence of a heavy element, like transition metals, the probability of being able to populate triplet states by intersystem crossing will increase due to strong spin-orbit coupling. Access to the triplet states can increase the efficiency of OLEDs[1]. In this project, N-heterocyclic carbene ligands were synthesized with phenanthridine units and used to construct complexes with transition metals. Phenanthridine is an aromatic three ring system, with the middle ring containing a nitrogen atom. Combining π-accepting character from the phenanthridine with strong sigma donation from the carbene, it was anticipated to give organometallic complexes with potentially interesting emission properties due to a push-pull effect from the ligand. Complexes of iridium, palladium, silver and platinum were targeted, and the synthesized products were characterized by multinuclear NMR and single crystal X-ray diffraction. The absorbance and emission characteristics were probed by UV-VIS absorption and emission spectroscopy.

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Synthesis and Characterization of Hybrid Phenanthridine-Carbene (N^C) Ligands and their Transition Metal Complexes

Robert Ortiz (Poster)

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Hybrid ligands with an N-heterocyclic carbene (NHC) units have been of interest for many different applications. These hybrid NHC ligands have been found in organic light emitting diodes[1] and catalytic complexes[2]. The metal complexes of these ligands are of particular interest because the hybrid ligand generates a push-pull effect to the metal centre, donating electron density with one unit and accepting electron density with another. In this project phenanthridine, an aromatic three ring system containing a nitrogen on the middle ring, was used as the π-electron accepting unit and an NHC carbene was used as the σ-electron donor. Combining these two subunits on a ligand is expected to give potentially interesting complexes due to the push-pull effect generated. The synthesized hybrid proligand was used in various metalation reactions with target complexes of iridium, palladium, silver and platinum were. The synthesized products were characterized by multinuclear NMR and single crystal X-ray diffraction. Iridium and platinum complexes were targeted for their potential phosphorescent properties due to strong-spin orbit coupling in the heavy metal. Palladium complexes were targeted for their potential catalytic properties and silver complexes were targeted for their use in transmetallation reactions. The absorbance and emission characteristics were probed by UV-VIS absorption and emission spectroscopy.

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Cationic Selenium Compounds as Lewis Acids

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Heavy chalcogen-containing selenium and tellurium compounds are noted for their unique chemistry compared to the lighter congeners oxygen and sulfur. They have a number of applications including uses as catalysts, photovoltaic materials, and biomimetics. Our group is interested in studying the fundamental coordination chemistry of selenium-containing species to discover new ligand scaffolds and reactivity modes.

This presentation will discuss a new series of compounds featuring an organoselenium cation stabilized by a N-heterocyclic carbene ligand and varying anions. Reactivity, including an unusual anion-promoted decomposition reaction, will be discussed, in addition to characterization of these species by spectroscopic and crystallographic methods.

Chemistry at the Bottom of the Periodic Table: Theoretical Actinide Molecular Sciences

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Computational actinide chemistry is the application of the tools of computational chemistry to the actinides. We will begin by discussing our motivation for venturing in to this part of the periodic table, as well as some aspects of the computational methodology. We will then focus on selected applications; specifically:

(i) Inclusion complexes with macrocycles such as crown ethers or the famous 'pacman' ligand;

(ii) Mineral surface interactions: adsorbtion of uranyl species onto TiO_2 surfaces;

(iii) Interactions of actinides with 2D materials.

We will attempt to draw specific as well as general conclusions regarding methodology and the chemistry involved. Thus, we hope to illustrate the scope of questions that can be addressed, and the kind of unique insight that computational chemistry might provide for this part of the periodic table and beyond.

Synthesis and Characterization of Novel Pseudo-Octahedral Iron Complexes of Bis-Phenanthridine Ligands

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Visible light catalysis has been a long-standing topic of interest in chemistry, as light is an accessible and abundant source of energy. The same cannot be said for most catalysts used to harness light for synthesis, which typically contain iridium or ruthenium such as the widely used ruthenium (II) tris(2-2′-bipyridine) (= $Ru(bpy)_3^{2+}$). These metals are expensive and rare in the Earth's crust. To enhance sustainability, iron is being targeted to replace ruthenium in photoredox catalysis. Since both are group 8 metals, one could expect similar electronics and reactivity. However, the iron analogue of $Ru(bpy)_3^{2+}$, $Fe(bpy)_3^{2+}$, does not have the same advantageous excited state properties. The reactive excited state is quickly deactivated by relaxation to low-lying metal-centered states. In this project, a set of three pseudo-octahedral complexes containing bis-phenanthridine ligands were targeted for synthesis. Phenanthridine, a three-ring aromatic heterocycle, was used in designing ligands for its low-lying ϖ^* orbitals which can participate in charge transfer states and allow for longer lived excited states. Tridentate pincer ligands with phenanthridine imine character were synthesized and used to support an iron center. Physical properties of the complexes which are relevant to catalysis will be discussed.

Electrochemical Hydrogenation of Unsaturated N-Heterocyclic Substrates

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Hydrogenation is used extensively in industry. In the food industry, it has applications in the processing of vegetable oils where it converts liquid vegetable oils into solid or semi-solid fats, allowing control over melting point. In the petrochemical industry, hydrogenation is used to convert alkenes and aromatics into saturated alkanes (paraffins) and cycloalkanes (naphthenes) because alkenes tend to form hydroperoxides which can form gums that interfere with fuel handling equipment. In synthetic chemistry, asymmetric hydrogenation has implications in pharmaceuticals, agrochemicals, fragrances and flavouring. Substrates for hydrogenation are not limited to alkenes and alkynes, but they can also be aldehydes, imines and nitriles which are converted into the corresponding saturated compounds – alcohols and amines. Usually this process requires the use of H2 and complex catalysts. In this project, we are using three classes of N-heterocyclic compounds as substrates for hydrogenation – benzoxazines, alpha-ketoesters and benzoxazinones. Conventionally, the C=N and C=O bonds in these compounds can be hydrogenated with the addition of complex catalysts such as 1,1'-spirobiindane-7,7'-diol-derived chiral phosphoric acids. This research involves synthesizing these substrates, and electrochemically reducing their C=O and C=N bonds enantioselectively through a renewable method using weakly acidic conditions. We have also hydrogenated these substrates chemically using a known literature method so that the electrochemically hydrogenated product can be compared with chemically hydrogenated product.

Exploring natural product biosynthesis in lichen fungi

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Lichen fungi remain one of the most underdeveloped sources of novel bioactive natural products. This is in part this is due to challenges that result from the slow growth of the symbiotic organism. Our research program has identified over 40 biosynthetic gene clusters in the genome of the lichen Cladonia uncialis that appear to code for small molecule biosynthesis. A large number of these clusters have a gene that codes for a polyketide synthase. Numerous accessory genes, such as methyl transferases and hydroxylases, flank each of these polyketide synthase genes. Based on homology to genes characterized from non-lichen fungi we have been able to propose function for some of these gene clusters.

We have been using heterologous expression of lichen biosynthetic genes as a tool to assign function. This talk will present results on the heterologous expression of lichen biosynthetic genes in the non-lichen fungus Aspergillus oryzae. In addition, some of our efforts to get these genes functional in E. coli will be presented. This talk will outline the challenges that we have encountered and some of our recent strategies for overcoming them.

A One-pot, Microwave-assisted Synthesis for Aryl Urea and Carbamate Analogues Using Benzoyl Chloride and HOSA

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Ureas and carbamates are two functional groups which have found use in various industries. In particular, their multiple applications in medicine have made them especially valuable. These applications include antimicrobial activity, disease therapeutics, and drug design. A method frequently used to synthesize urea and carbamate compounds is the reaction of an isocyanate with an amine or alcohol. Unfortunately, isocyanates are not an ideal starting material due to their high toxicity, making them dangerous to handle. As a result, isocyanates are preferably generated as intermediates in situ by the intramolecular rearrangement of a precursor. One reaction pathway through which this can occur is known as the Lossen Rearrangement. The rearrangement proceeds following the deprotonation of a hydroxamic acid derivative. Unfortunately, hydroxamic acid derivatives are not readily available as starting materials. Therefore, a common approach is to form the hydroxamic acid derivative from simpler compounds, such as an acyl halide and hydroxylamine. However, a drawback of this approach is the formation of a hydroxamic acid intermediate which requires activation by a coupling reagent. In order to streamline the overall synthetic process, our research group has developed a robust, one-pot synthetic method for aryl ureas and carbamates which circumvents the formation of a hydroxamic acid intermediate by using hydroxylamine-O-sulfonic acid (HOSA) as one of the reagent. When combined with benzoyl chloride, HOSA allows phenylisocyanate to form without the occurrence of a hydroxamic acid intermediate. This eliminates the need for a coupling reagent and reduces the amount of time required for the synthetic procedure. Our synthetic method has been found to successfully produce several aryl urea and carbamate analogues, indicating its potential to act as a library synthesis for these compounds.

Proteomics of temozolomide resistant glioma

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Glioblastoma multiforme (GBM) grade IV is treated by surgical resection, radio- and chemotherapy. Radiotherapy and concomitant administration of temozolomide (TMZ) increases a median survival to 14.6 months. Post diagnosis, the primary cause of death in GBM is due to acquisition of drug resistance and the invasion of tumour cells. In initial phase of treatments, TMZ remains the clinically effective drug, however the increased exposure to the GBM patients leads to development of TMZ resistance in brain tumors. Despite the intense efforts the mechanism of TMZ resistance is inadequately understood. The present work highlights organellar proteomics to better understand the proteins that are differentially regulated with long term exposures to TMZ in GBM. The cell lines C6- wild type glioma and LN18- glioma were sub-cultured for the present study and resistant was developed against TMZ in LN18 cells. The subcellular fractions of mitochondria, cytosol and plasma membrane were prepared by using benchtop refrigerated centrifuge, and studied by quantitative proteomics using nano-liquid chromatography-electrospray ionization mass spectrometry (nLC-ESI-QTOF-MS, Agilent 6530 QTOF). Bioinformatics and statistical analysis tools include: TMHMM server 2.0, Mascot, Skyline and MaxQuant. Proteomics of subcellular fractionations obtained from controlled (CTR) and TMZ resistant glioma reveals differential expression of functional proteins. The label free quantitative approach is applied to subcellular fractionations of cytosol, mitochondria and plasma membrane and further association with TMZ will be discussed in detail. The outlined proteomic study features the functional proteins that highlights TMZ resistance in glioma, and future development of inhibitors or adjuvants to such enzymes can be a therapeutic benefit to the GBM patients by restoring the cytotoxicity of TMZ.

Spectroelectrochemical characterization of KuQuinones anions.

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KuQuinones (KuQ) are highly aromatic pentacyclic quinoid compounds synthesized in our lab [1]. These molecules show interesting electronic and electrochemical properties such as a broad absorption spectrum in the visible region and three reduction processes. In particular the first one has a favorable reduction potential with respect to simpler quinoid compounds. Due to these characteristics two appropriate KuQ's derivatives were used as photosensitizer in photoelectrochemical devices obtaining good results in terms of efficiency [2,3]. In order to fully characterize active reduced species of KuQs we are currently investigating their nature through spectroelectrochemical measurements. In this contribution, preliminary characterization of KuQuinones anions will be presented.

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Hypoxia-Activated SN-38: Targeting Hypoxic Tumors

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Solid tumours have the characteristic of being less oxygenated than normal tissue. Under hypoxic conditions, cancer cells display tendencies to metastasize, and are resistant to radiotherapy and chemotherapy.

Camptothecins are effective anti-cancer targets due to its ability to inhibit the enzyme topoisomerase I (topo I), which is involved in changing the winding states of DNA. Inhibition of topo I in cancer cells can lead DNA damage and cell death.

One of our initial efforts of developing tumour-targeting therapy, are C-10 substituted derivatives of a camptothecin analog (SN-38). We synthesized substituted 2-, 3-, and 4-nitrobenzyl derivatives as potential hypoxia-activated prodrugs. These work by cleavage of the nitrobenzyl group under hypoxic conditions, releasing the active drug SN-38. The derivatives have been evaluated for their cytotoxicity and topoisomerase I inhibition. All three derivatives had reduced toxicity towards human leukemia K562 cells compared to SN-38, validating a condition for prodrug action. Using an MTS assay, IC50's were found to be 3.0, 25.9, 12.2 and 58.0 nM for SN-38, 2-nitro-, 3-nitro- and 4-nitrobenzyl-C10-substituted-SN-38, respectively, representing an 8-, 4- and 19-fold decrease in cytotoxicity. A topo I inhibition assay showed that one of the analogs (4-nitrobenzyl) inhibited the ability of topo I to relax supercoiled pBR322 DNA, at a similar concentration to the clinically-approved active metabolite SN-38. Cyclic voltammetry was also performed to determine the reductive nature of the derivatives and used to determine the potential of these compounds to serve as hypoxia-targeting prodrugs. The electrochemical results showed validation for the first reduction step and as a proof-of-principle for the redox-futile cycle, the proposed mechanism of action.

Overall, the in vitro data suggests the nitrobenzyl derivatives of SN-38 have potential to act as hypoxia-activated prodrugs.

Truce-Smiles Rearrangement: The Synthesis of Benzamide Derivatives from Amide Precursors

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The Truce-Smiles rearrangement was studied in the synthesis of benzamide derivatives from amide precursors, utilizing directed-ortho metalation, lithium-halogen exchange, and acetyl-enolate anion formation as carbanion formation methods. Microwave-assisted synthesis of the benzamide precursor molecules was explored in comparison to conventional heating methods and the use of cyanuric chloride, as an activating agent for the reaction between carboxylic acid and an amine, was also utilized.

Phytochemical Studies on Anacardium Occidentale

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Anacardium occidentale was investigated due to its anti-diabetic, anti-bacterial and anti-fungal properties. In attempt to isolate which compounds give the plant these properties, leaves of the plant were extracted. To isolate and identify a compound that may act as an alternative treatment for Type 2 diabetes, several methods were used. Thin Layer Chromatography and Column Chromatography were conducted in various percentages of Ethyl Acetate ($C_4H_8O_2$) and Hexane (C_6H_{14}) to separate the compounds. Preparative TLC was used to purify the compound, along with 1H NMR, 13C NMR, HMBC, HSQC, HMQC, COSY and NOESY spectroscopy to assist with structural identification of the compound. To determine the biological properties that the compound processes, a bio-assay will be conducted on each of the pure isolated compounds. If time permits, synthesis will be performed to synthesize the compound and its derivatives. Bio-assay will also be conducted on the derivatives to identify any biological functions.

Evaluating the effect of substrate ortho- and meta-substitution upon the Truce-Smiles rearrangement

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The Truce-Smiles rearrangement is an intramolecular nucleophilic aromatic substitution reaction wherein a carbanion nucleophile substitutes at an aromatic electrophile. The reaction therefore achieves an aryl migration from, typically, a heteroatom to a carbon atom and can proceed via a classic SNAr mechanism. Consistent with the SNAr mechanism, strong electron-withdrawing substituents at the ortho- or para- positions of the migrating aryl ring can promote the reaction by stabilizing the Meisenheimer intermediate. We have found that sterically-demanding ortho-substituents on the migrating aromatic ring can accelerate the reaction further. We have also discovered that certain strong-electron withdrawing meta-substituents can stabilize the intermediate as well.

Exploration of Cationic Selenium Compounds

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Compared to other main group elements, selenium based catalysis is under-explored. Our group developed a new cationic selenium compound and explored its use as a potential catalyst for carbon-carbon coupling reactions. The coupling of 2-methylfuran with diphenylmethanol was done to investigate the ability of the selenium compound to act as a Lewis acidic catalyst. Analogues of this compound were prepared via anion exchange reactions, characterized and tested for air stability. The application of these potential catalysts in synthesis, specifically carbon-carbon coupling will be discussed in this presentation.

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