Reactive Species in Inflammation, Infection & Disease

Participants

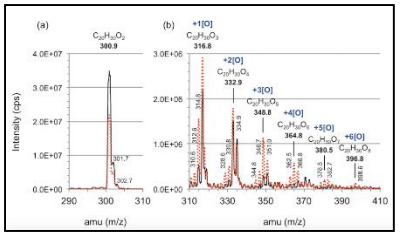
PI: Dr. Rita K. Upmacis

Students:

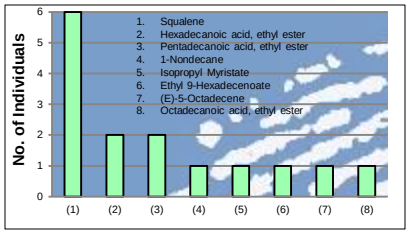
Travis Korosh (2012)
Kelsey D. Jordan (2014)
Steven J. Miller (2015)
Ivelisse Dyson (2015)
Justine Wu (2015)
Solmaz Azimi (2016)
Joy Tugbiyele (2016)
Amani Basaeed (2016)

Collaborators:

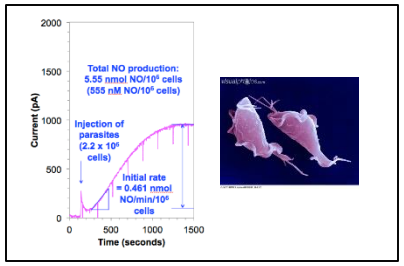
Dr. Nigel Yarlett - Pace University
Dr. Demos Athanasopoulos - Pace University
Dr. Josh Palmer - Columbia University
Patrick Quinlivan - Columbia University



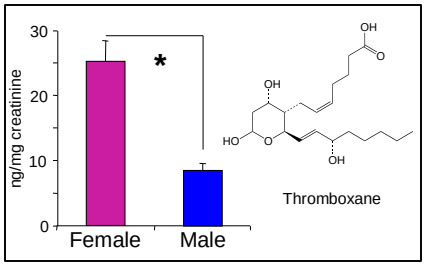
1. **Fatty acid oxidation: 6 oxygen atoms add to fish oil.**



2. **Fingerprint oils analyzed by GC-MS.**



3. **NO production by *T. vaginalis*.**



4. **Female mice produce more urinary thrombxane B_2.**

Goals

Objective: To understand the role of fatty acids, reactive oxygen and nitrogen species in inflammation, infection and disease. A better understanding will lead to the development of alternative therapeutic approaches.

Funding: Start-Up Funds, Undergraduate Research Awards, Dyson College and Provost's Summer Research Funding.

Research Foci

Idea #1: Fatty acids, found in fish oil, readily oxidize in air and modulate parasite activity.

Idea #2: The fatty acid composition of a fingermark or latent fingerprint (which may also contain sweat and other possibly discerning contaminants) provides identifying information.

Idea #3: The parasite *Trichomonas vaginalis* produces nitric oxide (NO).

Idea #4: Gender differences in fatty acid (prostaglandin) production may indicate a requirement for different treatment options in males and females during disease.

Synthesis of Metal Complexes as Anti-Parasitic Drugs or Catalysts

Participants

PI: Dr. Rita K. Upmacis

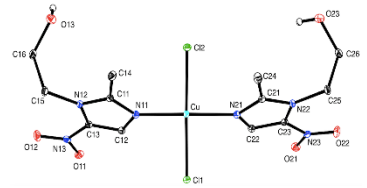
Students:

Justine Wu (2015)
Joy Tugbiyele (2016)
Kaltrina Mulosmani (2017)
Solmaz Azimi (2016)
Tyler Brescia (2017)

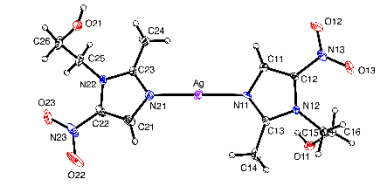
Collaborators:

Dr. Nigel Yarlett, Dr. Demos Athanasopoulos (Pace University)
Dr. Josh Palmer, Dr. Shivani Gulati, Patrick Quinlivan (Columbia University)

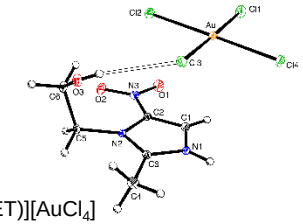
X-Ray Crystal Structures of Metal Complexes.



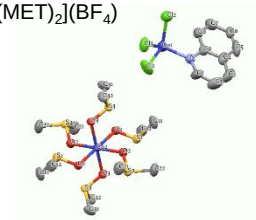
(i) $Cu(MET)_2Cl_2$•MeOH



(ii) $[Ag(MET)_2](BF_4)$



(iii) $[H(MET)][AuCl_4]$



(iv) $[Co(II)(DMSO)_6][Co(II)Cl_3quinoline]_2$

Overall Goal/Purpose

To prepare and characterize metal complexes that have not previously been observed and to examine their activity as anti-parasitic drugs or catalysts.

Funding:

Start-Up Funds, Undergraduate Research Awards, Dyson College and Provost's Summer Research Funding.

Specific Research Aims

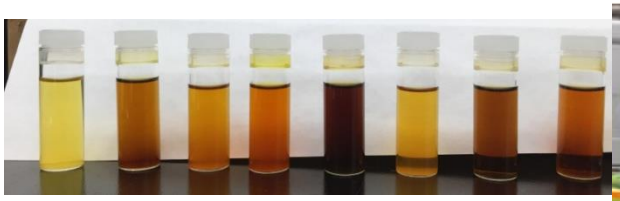
Our aim has been to prepare metal-metronidazole (MET) complexes containing Cu, Ag and Au, that have not previously been observed. These complexes were characterized by X-ray diffraction as (i) $Cu(MET)_2Cl_2$•MeOH, (ii) $[Ag(MET)_2](BF_4)$, and (iii) $[H(MET)][AuCl_4]$. The Cu(II)-MET complex showed anti-parasitic activity against *T. vaginalis* suggesting a role for metal-MET complexes in combating trichomoniasis.

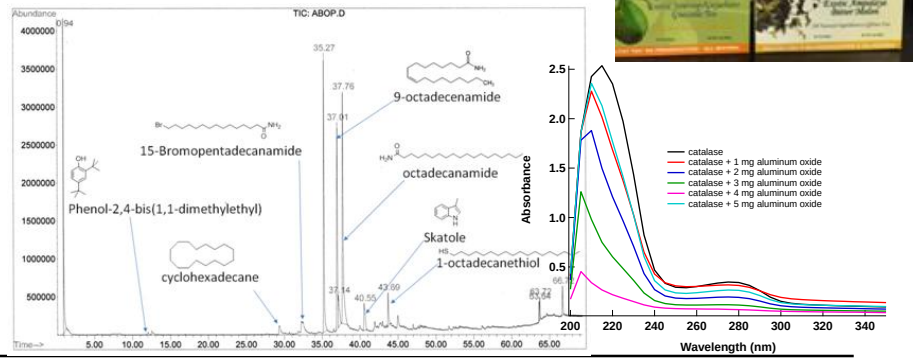
We have recently prepared a metal-quinoline complex, characterized as (iv) $[Co(II)(DMSO)_6][Co(II)Cl_3quinoline]_2$ that will be examined for catalytic activity.

Analysis of Chemicals of Medical and Environmental Concern

Participants

PI: Dr. Elmer-Rico E. Mojica
Students:
Jahaira Zapata
Amanda Villaggi
Tyler Nolan
Josephine Farshi
Lauren Reilly
Lyric Wyan
Gwen Iannone





Goals

To analyze and characterize chemicals of medical use from nutraceutical products (bee products, tea samples) to nanomaterials and of environmental concern (emerging contaminants such as pharmaceuticals) using different instrumental methods.

To develop new methods for analysis of these chemicals

Funding: Start-up Fund, Scholarly Research Grant. NSF-BOP

Research Foci

Idea #1: Limited studies have been done on the nutraceutical products that are readily available for the consumers with claims of extra health benefits and the effect of nanomaterials in biological systems.

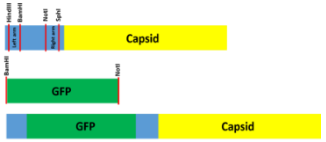
Idea #2: Knowing the chemical composition and the fate and transport of emerging contaminants found in Hudson River is of great concern on how it will impact the communities around the river system.

Exploiting a Virus to Cure a Parasitic Disease

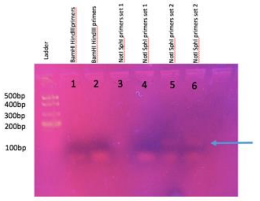
- Nigel Yarlett † *
- Mary Morada *
- Cho Chan † *
- Gabrel Samantha †

Dept Chemistry/Phys Sciences †; Haskins Laboratories *

Grant from The Grand Challenges

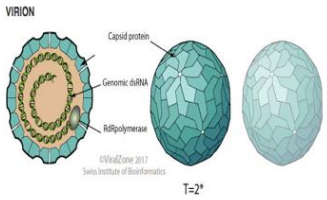


GFP-capsid construct: BamH1/Not1 restriction sites on the GFP, cloned into the capsid RNA using Sph1/HindIII sites.



The amplified construct was confirmed by 3% agarose GC resulting in 130 bp band using Not1/Sph1 primer set 2

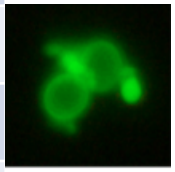
- *Cryptosporidium parvum* and *C. hominis* harbor a RNA virus known as *Cryspovirus*
- The role of the virus in growth and survival of *C. parvum* is unknown.
- To study this we plan to produce a GFP-taged cryspovirus.



The virus has a non enveloped capsid with icosahedral geometry (T=2); A linear, segmented dsRNA genome coding for two proteins.

Inhibitors of reverse transcriptase were effective in removing Cryspovirus which also resulted in a significant reduction of *C. Parvum*. This data suggests that C. parvum is dependent upon the virus and antiviral therapy is a potential tratment for cryptosporidosis

antiviral	Conc (µM)	% Inhibition		
		HCT-8	Cpv-capsid	*C. parvum*
zidovudine	3.0	0	100	99.9
acyclovir	111	0	100	98.0
lamivudine	9.1	97	100	85



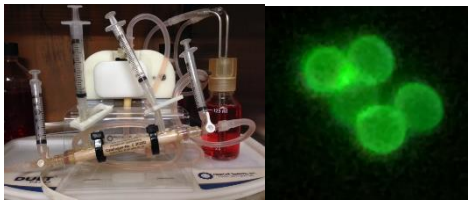
Chemotherapy of Pediatric Diarrheal Disease

- Nigel Yarlett † *
- Mary Morada *
- Mohini Gobin ✦

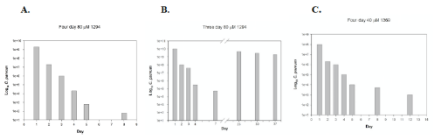
Dept Chemistry/Phys Sciences †; Haskins Laboratories *; Dept Biology ✦

Grant from the Bill and Melinda Gates Foundation

- 1.7 billion cases of pediatric diarrhea annually.
- Second cause of death in children under 5 years.
- Cryptosporidia sp. is a commonly diagnosed cause.
- No therapy exists for pediatric cryptosporidosis.
- This project aims to improve methods to study the parasite aiding the development and implementation of new chemotherapeutic agents to cure this disease.



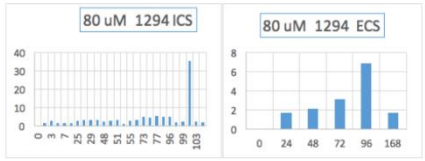
Far left: In vitro culture system enables the analysis of potential drugs under conditions that mimic the gut.
Left: Parasites from the culture stained fl-mAb.



Using the culture system a series of bump kinase inhibitors were tested under varying conditions.

compound	concentration (μM)	days of treatment	Log reduction oocysts (days post treatment)	Fig No.
1294	20	3	1(4)	
1294	80	4	7(4)*	Fig 5A
1294	80	3	5(4)†	Fig 5B
1517	80	4	0(4)	
1369	40	4	5(8)	Fig 5C

80 μM/day of UW1294 for 4 days Was the most effective dose.



Partitioning of UW1294 between the extracapillary space (gut) and the intracapillary space (blood capillary).

- A continuous in vitro culture method was developed using Hollow Fiber Technology.
- Potential chemotherapeutic agents were tested using this culture method.
- pharmacokinetic and pharmaco-dynamic measurements enable the determination of dose required to maintain a curative threshold over time.

Drugs for Neglected Diseases

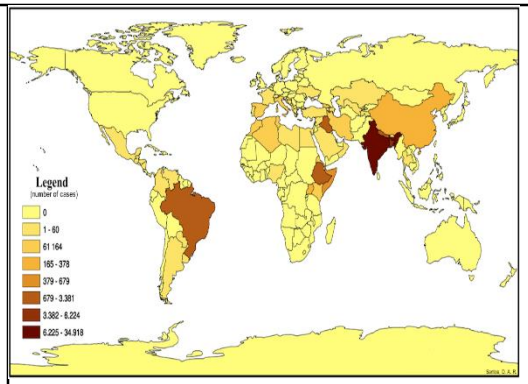
Participants

P.I. Dr. Zhaohua Dai (Pace)

Pace Students: Kyle van Tiehoven
Julia Fatum
Tsai-Hua Lee

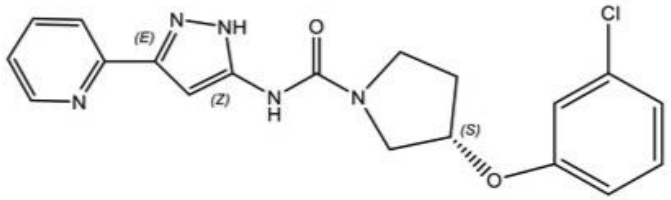
Collaborators: Dr. Nigel Yarlett
DNDi Consortium

Press release:
https://www.dndi.org/2017/media-centre/press-releases/universities-drug-discovery-neglected-diseases/



IC_{50} *L. Infantum*
0.08944 μM

65 time better than Original Pfizer compound



Goals: To develop an effective cure for *Leishmaniasis*

Funding: Pace
Possibly DNDi

Research Foci

Idea #1

Synthesis of multiple drug candidates

Idea #2

Test their effectiveness

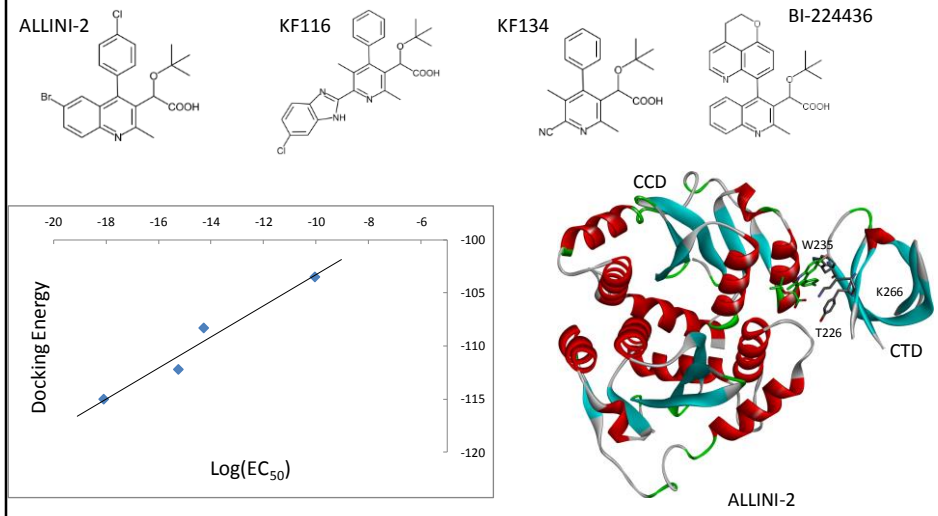
Idea #3

Elucidating drug mechanism, structure-activity relationship

Elucidating the Mechanism of Drug-induced HIV-1 Integrase Multimerization

Participants
P.I. Dr. Nanjie Deng (Pace)
Collaborators:
Dr. Ron Levy (Temple Univ.)
Dr. Mamuka Kvaratskhelia (Univ. of Colorado)

Pace Students: Jeffrey Cruz, Yinxin Zhao, Iqra Ahmed, Tsai-hua Lee



Background: The allosteric inhibitors of the HIV-1 Integrase exert their therapeutic activity by inducing multimerization of the Integrase. However, the underlying mechanism of this process remains elusive.

Goals: Using molecular modeling to study the HIV-1 Integrase multimerization.

Funding: National Institute of Health

Publications:

"Allosteric HIV-1 integrase inhibitors promote aberrant protein multimerization by directly mediating inter-subunit interactions: Structural and thermodynamic modeling studies."

N. Deng, A Hoyte, Y Mansour, M Mohamed, J Fuchs, A Engelman, M Kvaratskhelia, R Levy *Protein Science*, 25, 1911, (2016)

RGK inhibition of Ca^{2+} channels: implications for neurological and cardiovascular disease

The ion channel lab

PI: Zafir Buraei, PhD

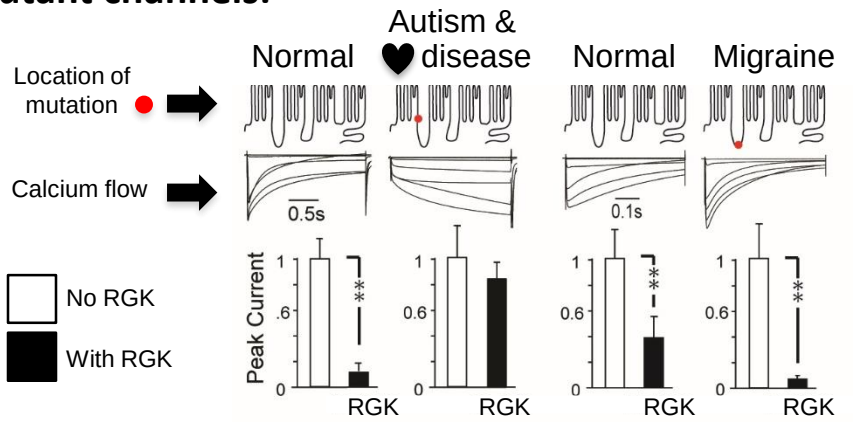
Undergraduates:

Salma Allam,
Emily Hirowski,
Melanie Franco
Laura Yorke

Graduate Student:

Elizabeth Rafikian

RGK proteins differentially control normal *vs* mutant channels:



Various Neurological and Cardiovascular disease are caused by mutations in calcium channels that disrupt the flow of Ca^{2+} ions into nerve and heart cells.

We found that RGK proteins, which normally block calcium channels, are not able to block mutant channels that cause autism and cardiac disease. We are now investigating the molecular and cellular mechanisms by which **RGKs serve as exacerbating factors for these and other human diseases.**

We received funding to study three broad aims:

1. Test the hypothesis that RGKs differentially inhibit normal channels vs. channels associated with disease.

2. Investigate the effects of RGKs on calcium channels in the presence of blood pressure and other calcium channel drugs.

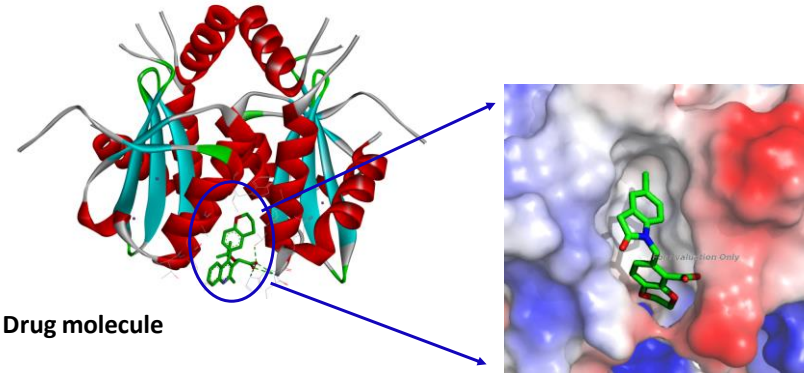
3. Investigate whether RGKs have differing effects on the presence of normal vs mutant calcium channels on the cell surface.

Research was supported by NIH and the National Institute Of General Medical Sciences; Award Number R15GM124013 to Z.B.

Drug Discovery Targeting HIV-1 Integrase for Developing HIV/AIDS Therapy

Participants
P.I. Dr. Nanjie Deng (Pace)
Collaborators:
Dr. Ron Levy (Temple Univ.)
Dr. Mamuka Kvaratskhelia (Univ. of Colorado)

Pace Students: Jeffrey Cruz, Yinxin Zhao, Iqra Ahmed, Tsai-hua Lee



Computer simulations are performed using the high performance computers at Pace to guide the discovery of novel drug molecules

Background: About 40 million people world wide are currently infected with HIV/AIDS; half of them will develop drug resistance.

Goals: Design and optimize novel drug molecule candidates that inhibit the AIDS virus.

Funding: National Institute of Health, Scholarly Research Fund (Pace)

Publications:

"Comparing Alchemical and Physical Pathways Methods for Computing the Absolute Binding Free Energy of Charged Ligands: Allosteric Inhibitors of HIV-1 Integrase"

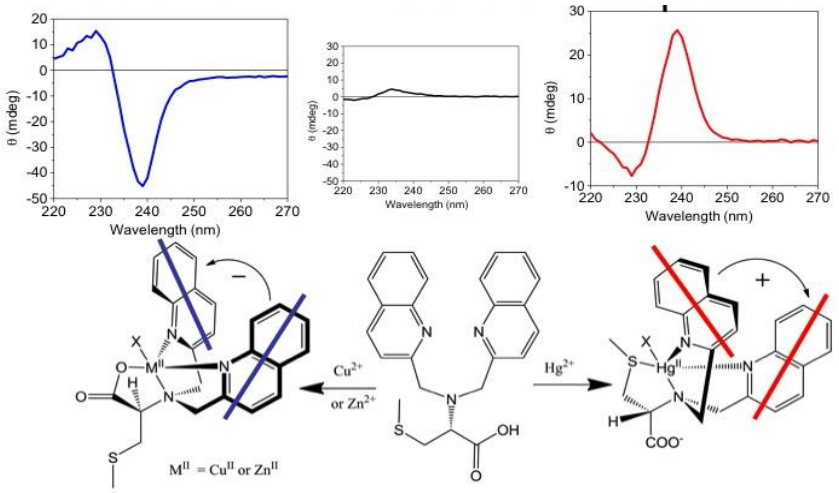
N. Deng, D. Cui, B. Zhang, J. Cruz, M. Kvaratskhelia, R Levy, *Journal of Computational Chemistry*, submitted

Chiral Recognition and Sensing

Participants

P.I. Dr. Zhaohua Dai (Pace)
Collaborators: Dr. J. W. Canary (NYU)
Dr. D. Athanasopoulos (Pace)

Pace Students: Amanda Mickley, Patrick Carney, Wenyao Zhang, Lyanne Valdez, David Mendoza, Jonathan Oswald, etc



Goals: To understand the chirality switching mechanism of nitrogen-containing tripodal compounds and develop chiroptical sensors for metal ions and catalysts for asymmetric syntheses.

Funding: Research Corporation, Petroleum Research Fund

Research Foci

Idea #1

Multimode chiroptical detection and imaging of mercury in biological samples

Idea #2

Asymmetric hydroxylation of hydrocarbon to make chiral alcohols

Idea #3

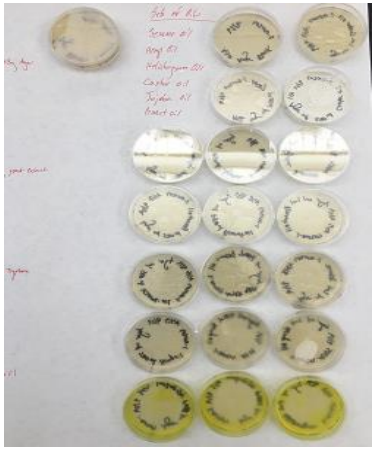
Switchable catalysis of aldol condensation to obtain different product at will using the same ligand with different metal ions

Synthesis and Investigation of a Novel Antimicrobial Surface Based on Agar

PI: JaimeLee Iolani Rizzo

Student: Aramis Sostre

Dept. of Chemistry & Physical Sciences, NYC



New surfaces tested against S. aureus

Presented at the National American Chemical Society,

San Francisco, CA

March 2017

The challenge to maintain a sterile environment and protect patients in a clinical setting has grown in the recent years, due to the exposure of microorganisms. Our work involves the utilization of Agar to incorporate and fuse with plants essentials oils in varying concentrations. Our work has demonstrated 52 samples that are positive against *S. aureus*.

RGK inhibition of Ca^{2+} channels: implications for neurological and cardiovascular disease

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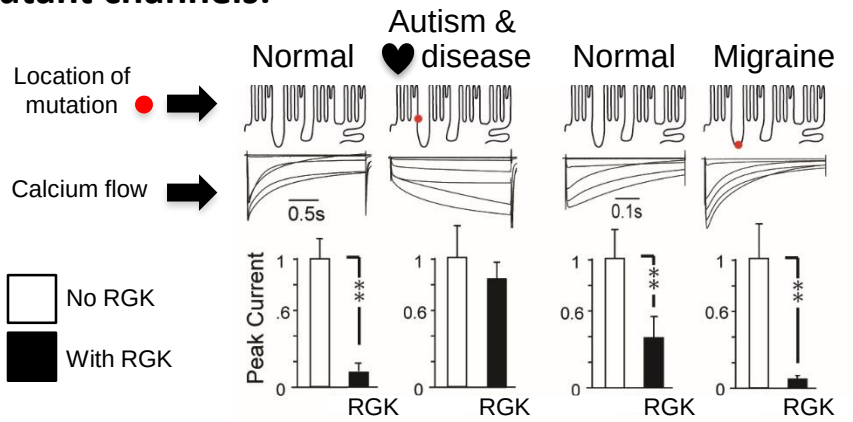

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