CDD WEBINAR

Interdisciplinary Pathways In Medicine- from Neurodegenerative to Oncology Disease Research And Drug Discovery

FRANK LEE, PH.D.
Scientific Associate,
Krembil Research Institute

MARK A REED, PH.D.
Chief Science Officer,
Treventis Corporation

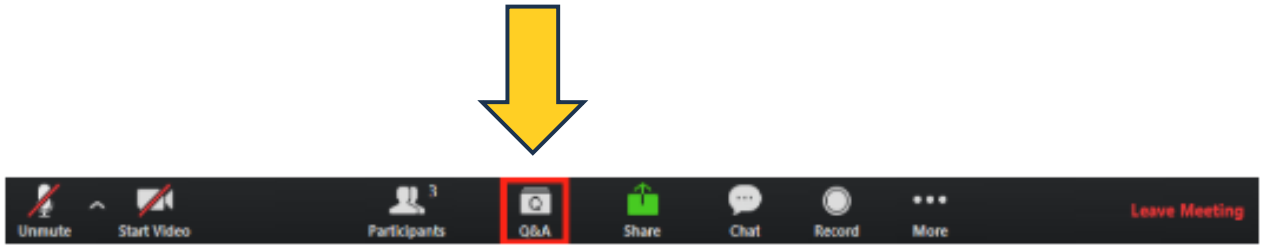
ERIC GIFFORD, PH.D.
Business Development Consultant
Collborative Drug Discovery

LIVE
Thursday, March 21 2024
8:00 AM (PDT) | 11:00 (EDT) 3:00 (GMT)

CDD VAULT®
Complexity Simplified

Have a question to ask our panel?

Open the ZOOM Q&A and type in your question during the webinar



We will reserve time and answer as many questions as we can at the end

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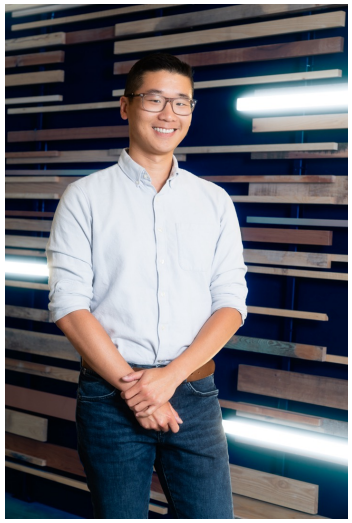
Complexity Simplified

Dr. Mark A. Reed

- 2018–present – Staff Scientist II and Director, **Centre for Medicinal Chemistry and Drug Discovery (CMCDD)**, Krembil Research Institute, UHN, Toronto
- 2023–present – Assistant Professor **Department of Chemistry, University of Toronto**
- 2019–present – Assistant Professor Department of **Pharmacology and Toxicology and Department of Chemistry, University of Toronto**
- 2008–present – Co-founder and CSO, **Treventis Corporation**
- 2003–2008 – Senior Scientist, Medicinal Chemistry, **ICOS Corporation**, Seattle, WA and **Schering Plough Research Institute**, Cambridge, MA
- 2000–2003 – Postdoctoral Fellow, Queen's University, Canada. (**Organic chemistry - Aromatic Lithiation)**
- 1996–2000 – Ph.D., University of Sussex, UK**. (Organic Chemistry - Total Synthesis)**

Dr. C. Frank Lee



UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Krembil Relentless.

- 2020–present – Scientific Associate II, **Centre for Medicinal Chemistry and Drug Discovery (CMCDD)**, Krembil Research Institute, University Health Network (UHN), Canada
- 2018–2020 – Postdoctoral Fellow, **Centre for Medicinal Chemistry and Drug Discovery (CMCDD)**, Krembil Research Institute, University Health Network (UHN), Canada
- 2013–2018 – Ph.D., University of Toronto, Canada **(Organic Chemistry – Organoboron methodology & Macrocyclic peptides)**
- 2009–2013 – B.Sc.H., Queen's University, Canada **(Organic chemistry- Aromatic Lithiation, Total Synthesis)**

TREVENTIS™ CORPORATION

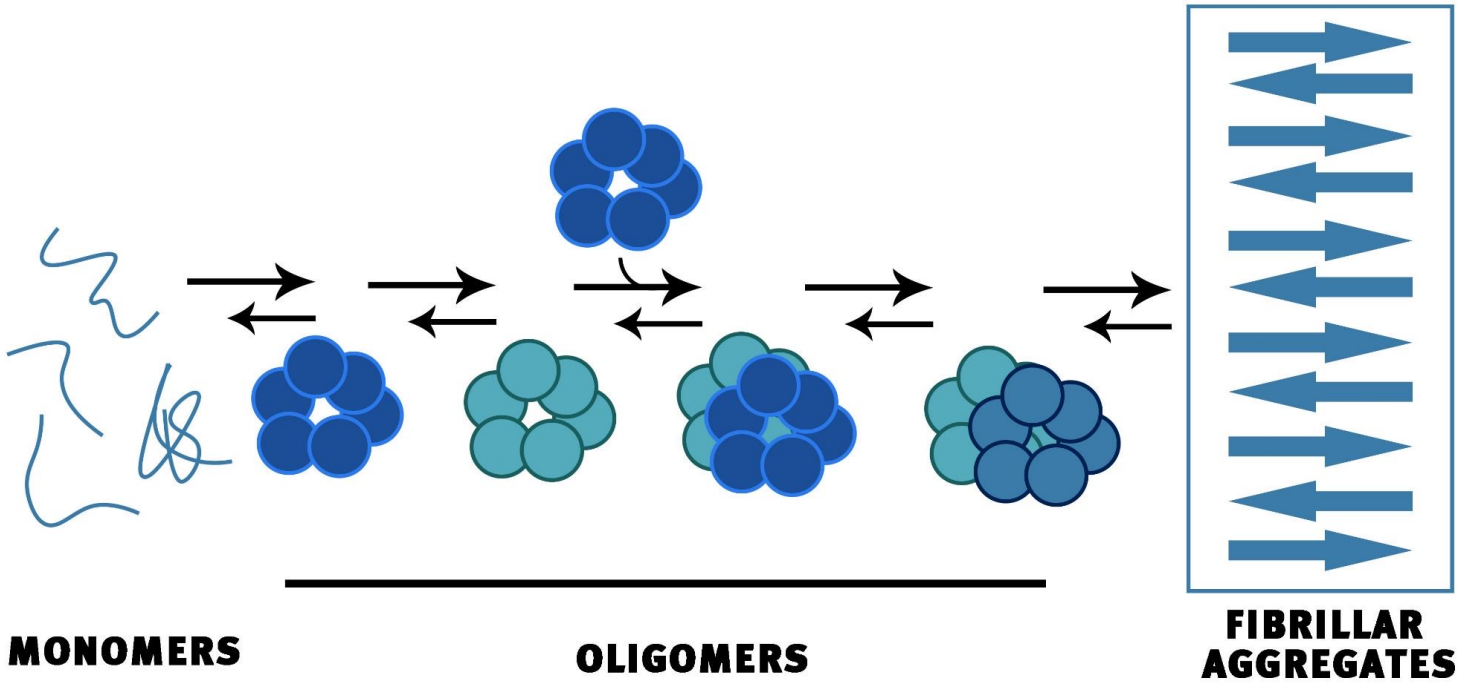
Targeting Protein Misfolding Disorders: Discovery of small oligomerization inhibitors for the treatment of neurodegeneration

Krembil Relentless.

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Centre for Medicinal Chemistry and Drug Discovery (CMCDD): Early-stage translation research within Canada largest research hospital

Proteinopathies: Intrinsically Disordered Proteins (IDPs)

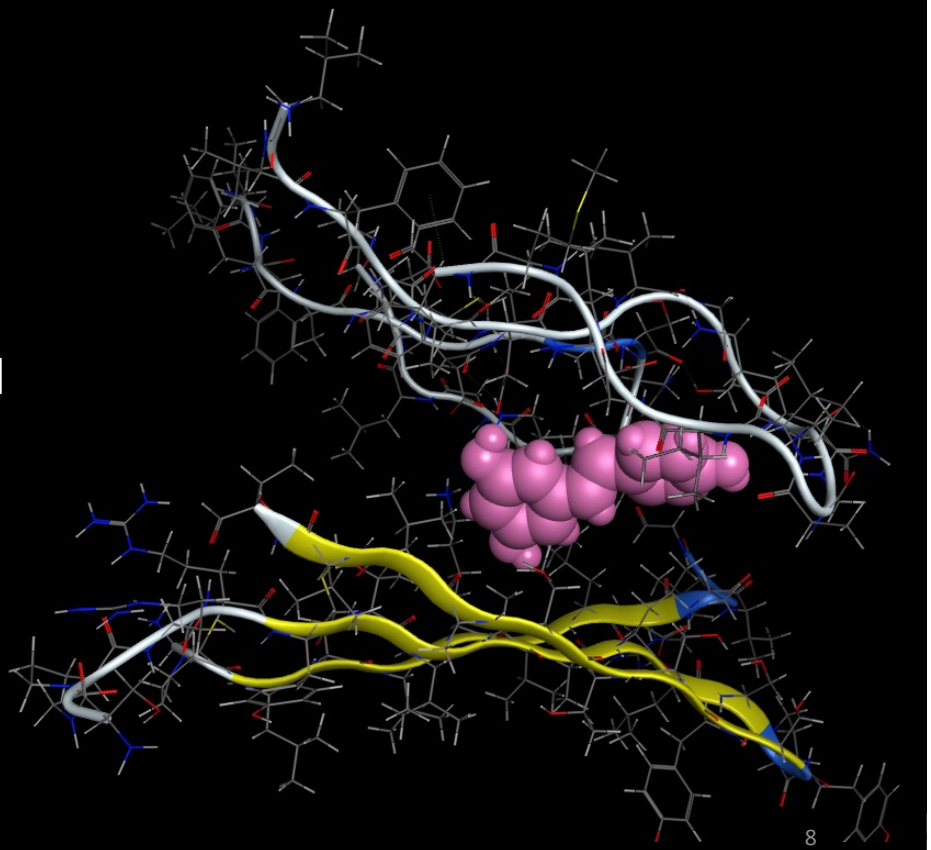


Pathogenic

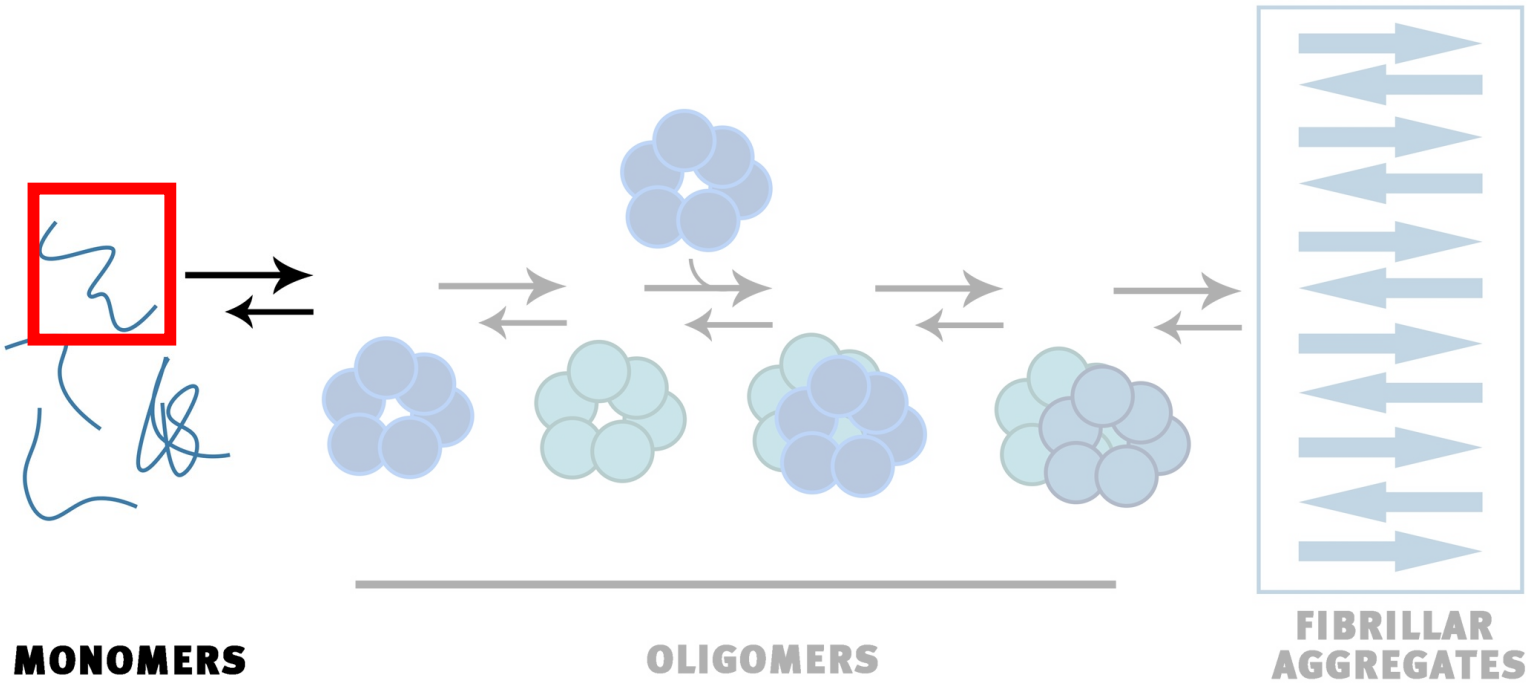
TREVENTIS™ CORPORATION

Common Conformational Morphology – CCM

- IDPs
  - No X-ray structures; solution NMR only
  - SBDD not possible
- HTS difficult due protein/ assay nature
- Technology: *In silico* model of protein misfolding, the Common Conformational Morphology (CCM)
  - An *in silico* model based on epitope commonality between multiple misfolding amyloidogenic proteins (e.g, A Syn, Aβ, tau).
  - Used to build “surrogate crystal structures” of incipient oligomers.



Target: Common Conformational Morphology – CCM



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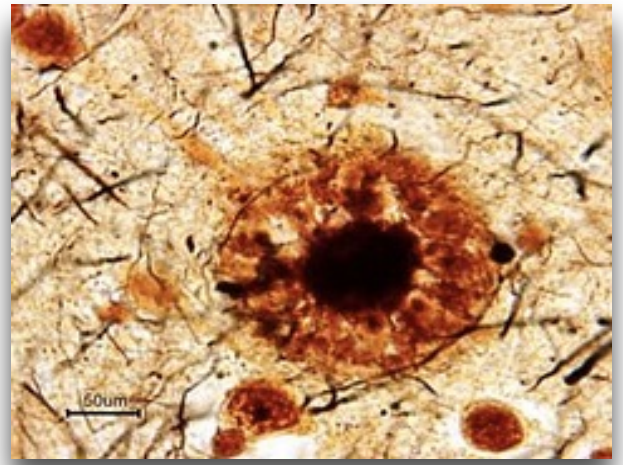
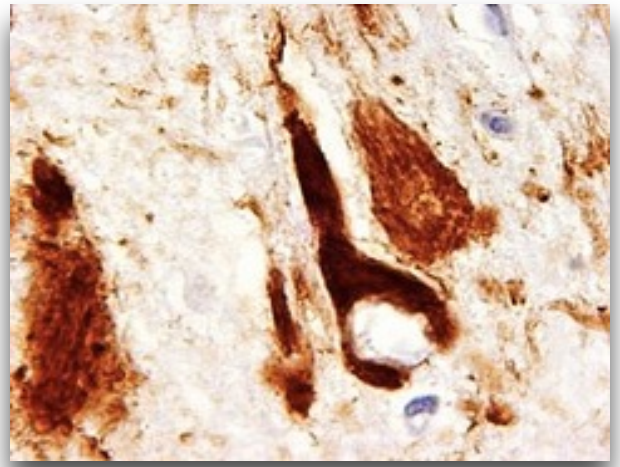
Alzheimer's Disease



Intracellular neurofibrillary tangles

Tau – 441 amino acids,
Intrinsically disordered protein



Extracellular plaques

Aβ - 40/42 amino acids,
Intrinsically disordered protein

Discovery of a Dual Aβ/tau Oligomer Inhibitor

TREVENTIS™ CORPORATION

In Vitro Pharmacology

Biotin-tau 4R2N ELISA
Biotin-Aβ42 ELISA
SDS PAGE (cell free)

Counter Screens

Tublin assembly
DLS
IDP selectivity

MoA

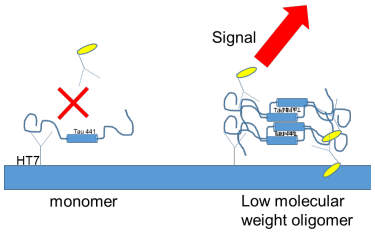
TRESI-HDX/Native-MS

ADMET: Property Based Lead Optimization

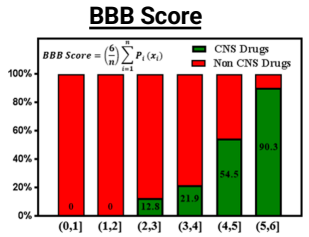
- BBB score, LogD/ Kinetic Sol.
- MDR1-MDCK, Caco2 (Permeability; PgP ER)
- M/R/H Hepatocytes/ microsomal clearance) Rat PK (cassette/ discrete) Kp,uu (Total and free drug brain exposure)

Target Engagement (PK-PD)

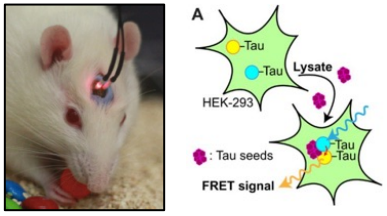
tau: rTg4510 murine; quant. otau in cortex; FRET- based biosensor/HTRF
Aβ42: APP/PS1 murine; oAβ42 ISF microdialysis; ELISA



LeVine, H. *Anal. Biochem,* **356**, 265–72, (2006)

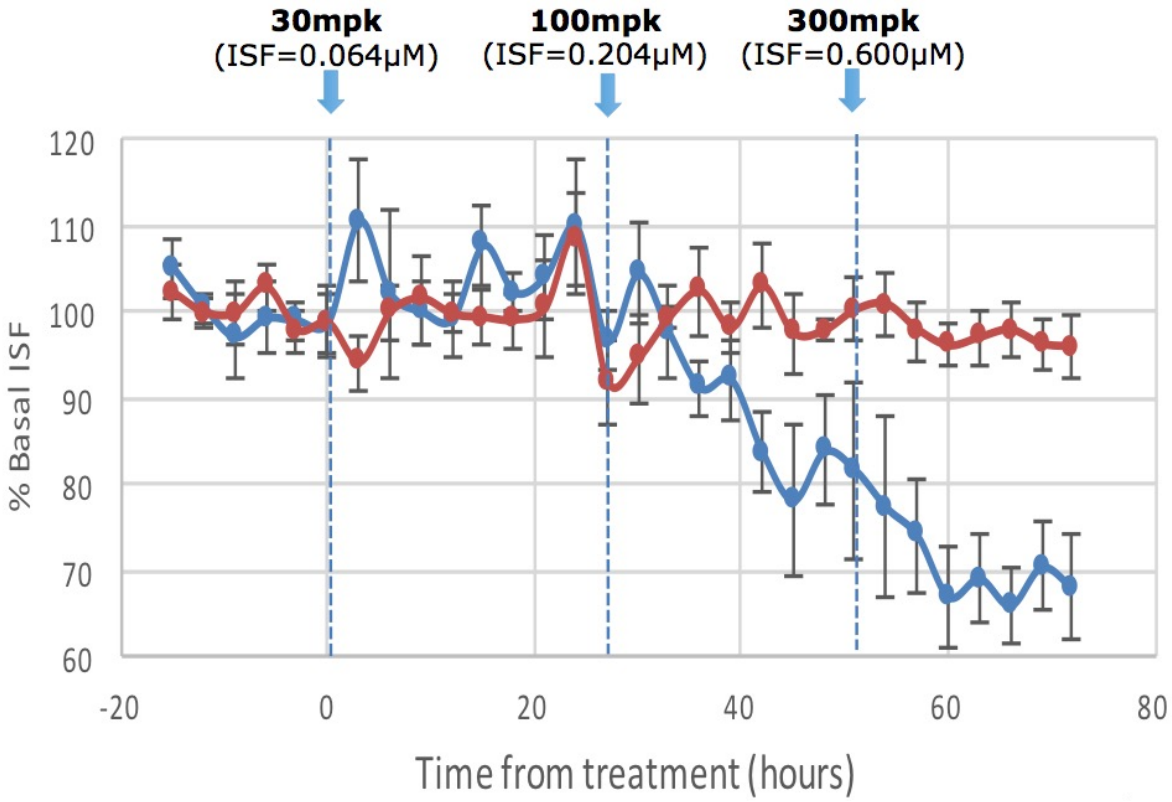


Gupta, M. et al., *JMedChem,* **62,** 9824-36, (2019).



Cirrito, J.R. et al., *J. Neurosci* **23,** 8844, (2003)

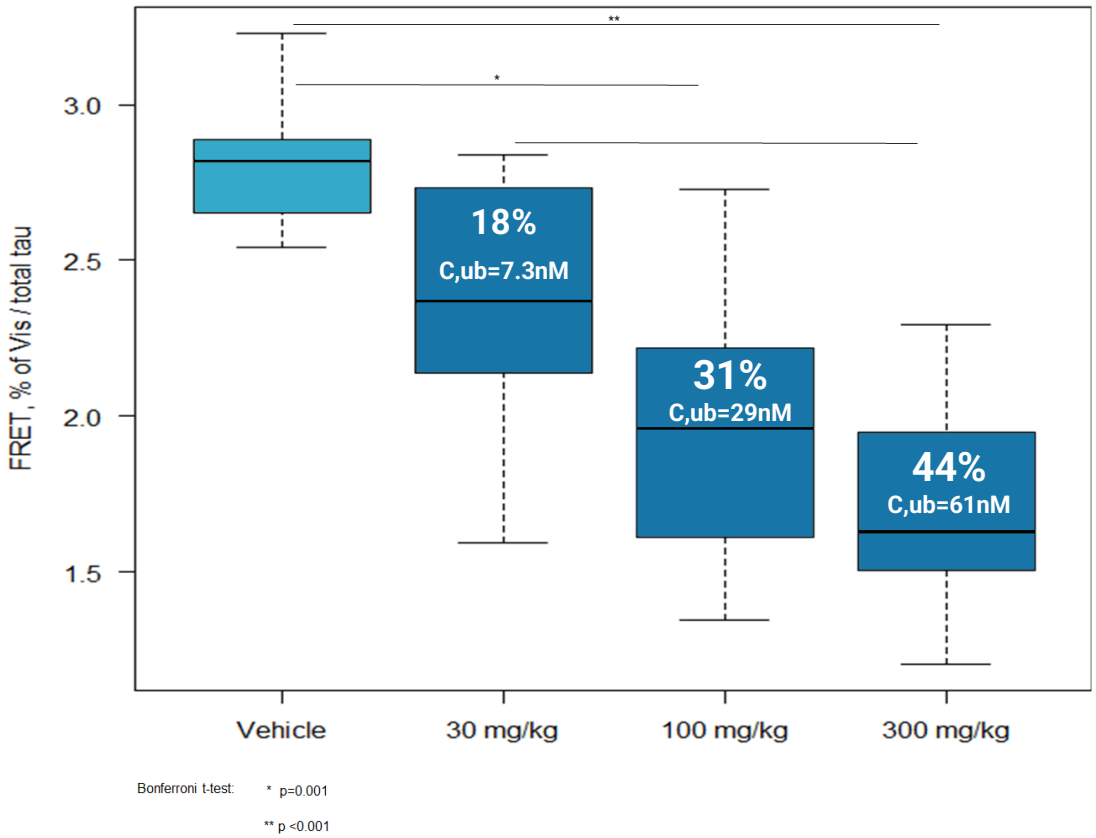
Aβ Oligomer Target Engagement



- TRV101 in TgAPP.PS1 (n=8): 1000 Kda MWCO Microdialysis/ELISA (ISF)
- APP/PS1 mice, 12 months old
- P.O. / Q.D. in the same animals
  - 30mg/kg on day 1
  - 100mg/kg on day 2
  - 300mg/kg day 3
- Interstitial fluid sampled via micro-dialysis probe every 2-3 hours
- Aβ Oligomers analyzed by ELISA
- Study conducted by John Cirrito University of Washington St Louis

tau Oligomer Target Engagement

TRV 201 in rTg4510 (n=12):
Cortex lysate – FRET otau biosensor



Bonferroni t-test: * p=0.001

** p <0.001

Current Status

- CCM Discovery Engine: Enables identification of druggable sites on IDPs for virtual screening against multiple targets
- Target Engagement: Dose dependent reduction in vivo of OAβ and Otau
- PCC identification (Aβ/tau): ~1500 NCEs in lead series, high CNS exposure (10-20X fold over PoC compounds); heterocycles developed for de-risking and supporting robust IP portfolio.
  PCC selected - IND enabling studies underway
- Translational : Multiple chronic model studies underway and biomarker discovery

WHO WE ARE

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab Michener Institute

4	12	6	5	1	2
Hospital Sites	Medical Programs	Research Institutes	Collaborative Centres	Education Institute	Foundations

RESEARCH AT UHN

RESEARCH INSTITUTES

Krembil Research Institute
arthritis | vision | neuroscience

McEwen Stem Cell Institute
cell-based regenerative therapies

KITE Research Institute
rehabilitation science

The Institute for Education Research
health care education

Princess Margaret Cancer Centre
cancer

Toronto General Hospital Research Institute
cardiovascular | respiratory and critical care | metabolism | infection and immunity | communities of health

RESEARCH AT UHN

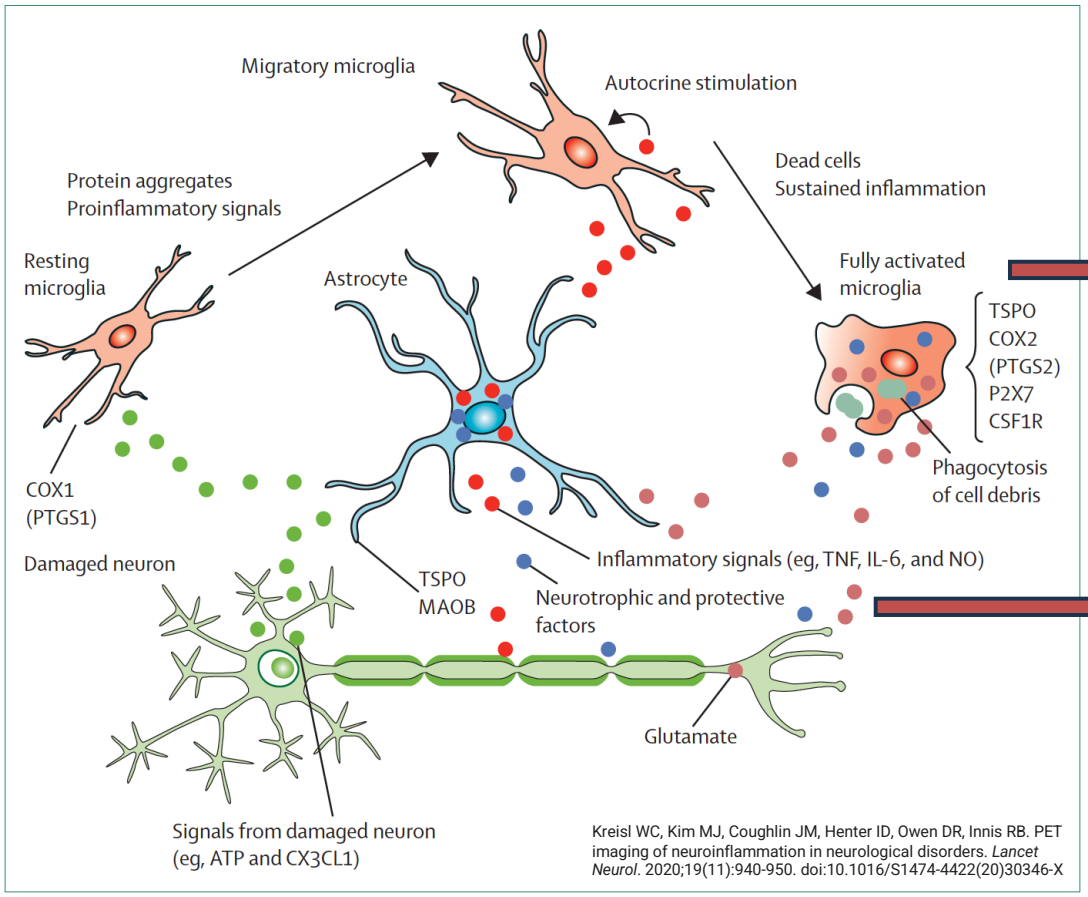
Centre for Medicinal Chemistry & Drug Discovery (CMCDD)

- Established at Krembil in 2018 to identify druggable targets from novel disease biology
- 10 medicinal chemists
- 30 collaborations at UHN and academic institutes across Canada
- Oncology, Neurology, Ophthalmology, Arthritis and Metabolic diseases
- Foster UHN institute collaborations based on therapeutic targets

Portfolio

	Disease Indication/PI	Target Class	Pre-clinical Validation	Stage
Neurology/ Ophthalmology	Rett Syndrome and dementia - Neuroinflammation	Ion Channel	Genetic	Hit to lead
	Depression and dementia - Neuroinflammation	enzyme	Pharmacological	Lead Optimization
	Glaucoma and dementia – Neuroinflammation	unknown	Genetic/ Pharmacological	Receptor Identification
	Stroke, Spinal cord injury: Axonal Regeneration	Kinase	Genetic/ Pharmacological	Hit Finding
	BBB Integrity	Kinase	Genetic/ Pharmacological	Hit Finding
	Depression	Receptor	Genetic/ pharmacological	In Silico HTS
Oncology	AML	Kinase	Genetic/ Pharmacological	Hit to lead
	Radiation Fibrosis	Unknown	Genetic/ Pharmacological	Target ID
	Ovarian Cancer	Kinase	Genetic/ Pharmacological	Hit to lead
	BRCA1/2-mutant breast and ovarian cancer	E3 ligases	Genetic	Hit ID
	Pancreatic cancer	Receptor	Genetic	Assay development
	AML	Stress granule	Genetic	Structure Based Design
	Prostate Caner	transporter	Genetic	Hit to lead
Arthritis	Cartilage Degeneration	Transcription factor	Genetic	Hit finding
	Fibrosis/ myofibroblast activation	enzyme	Genetic/ Pharmacological	Hit ID
	Spondyloarthritis	Chemokine	Genetic/ Pharmacological	Hit to lead
Metabolic	NASH	enzyme	Genetic/ Pharmacological	Hit ID

Neuroinflammation: New Therapeutic Targets



Kreisl WC, Kim MJ, Coughlin JM, Henter ID, Owen DR, Innis RB. PET imaging of neuroinflammation in neurological disorders. *Lancet Neurol*. 2020;19(11):940-950. doi:10.1016/S1474-4422(20)30346-X

Lower Proinflammatory Phenotype:
TRPM2 Ion Channel (Dr. James Eubanks)

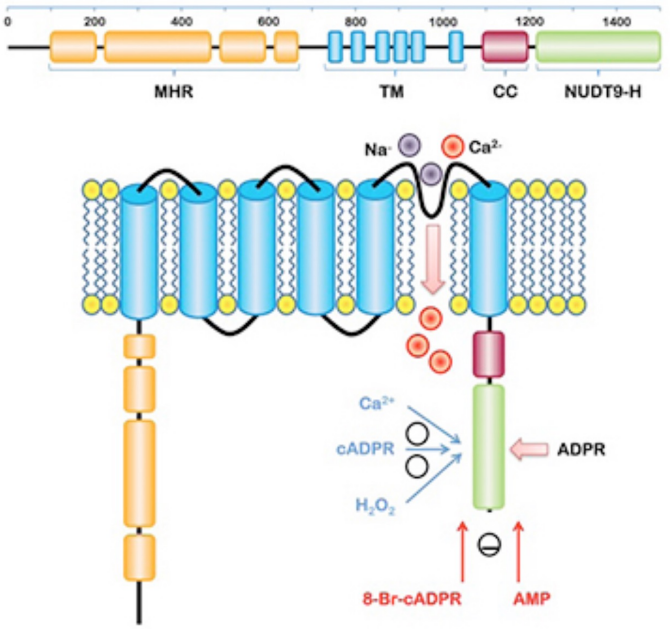
Dr. James Eubanks
- Senior Scientist, Krembil Research Institute, UHN
- Research Division Head, Krembil Research Institute, UHN

Enhance Neuroprotection:
Target Unknown (Dr. Jeremy Sivak)

Dr. Jeremy Sivak
- Senior Scientist & Glaucoma Research Chair, Krembil Research Institute, UHN and Associate Professor UofT School of Medicine
- 5+ years at Novartis leading multi-diciplenary ophthmalic drug discovery team

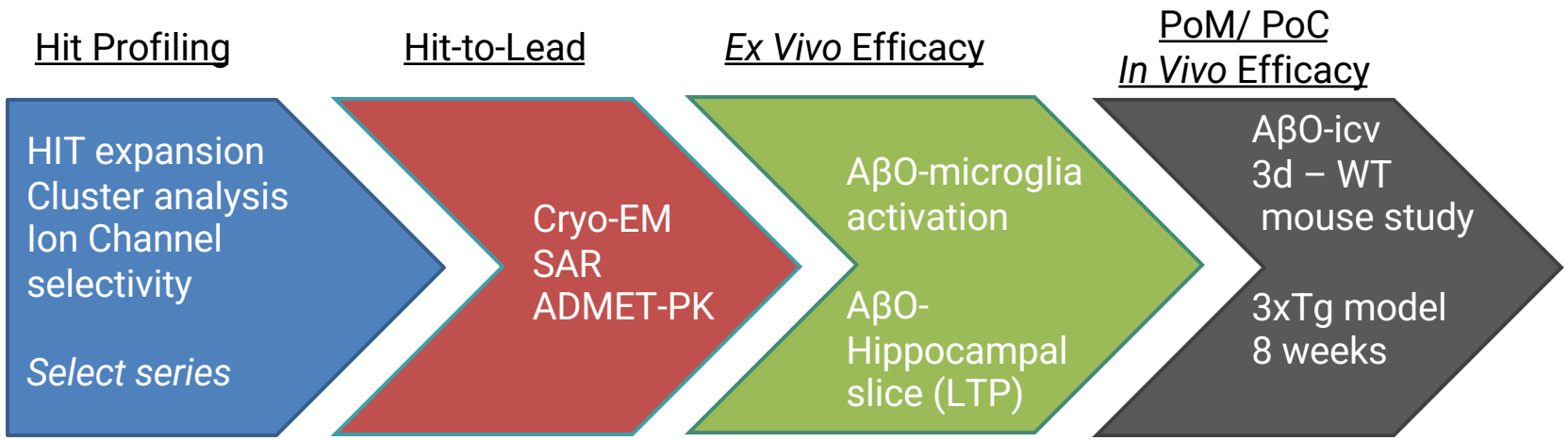
TRPM2 Ion Channel in Neuroinflammation

- **Member of Melastatin sub-group of TRP channel**
- **Redox sensing, non-selective cation channel** that allows **Ca^{2+} influx and efflux**
- **Functions as a surveillance receptor** in the brain, where it monitors local environments for signs of "stress"
- **Highly expressed in microglia**
- Under stress, **TRPM2 activates** and allows influx of Ca^{2+} → **pro-inflammatory cytokines**.
- **<u>TRPM2</u>** inhibition rescue AβO-induced microglia activation and hippocampal LTP



Raghunatha P, Vosoughi A, Kauppinen TM, Jackson MF. Microglial NMDA receptors drive pro-inflammatory responses via PARP-1/TRMP2 signaling. *Glia*. 2020;68(7):1421-1434. doi:10.1002/glia.23790

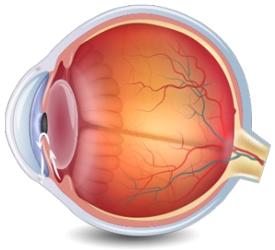
CNS-Penetrant TRPM2 Inhibitor Development



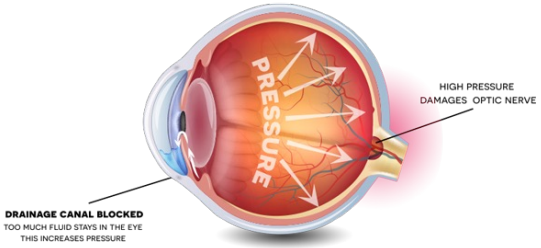
Glaucoma: A Neurodegenerative Disease

- Top cause of permanent blindness and growing (>80 million worldwide)
- Associated with many risk factors:
  - Intraocular pressure (IOP) the only current modifiable risk factor
  - IOP not associated with all cases
- **Neurodegenerative disease of retinal ganglion cells** (RGCs)
  - No direct treatment
  - Improved imaging has made clinical trials practical
  - Accessible to local delivery

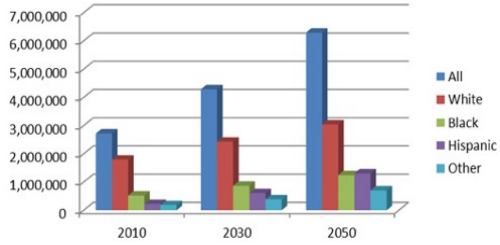
- **Goal**: target glaucoma through ***neuroprotection***



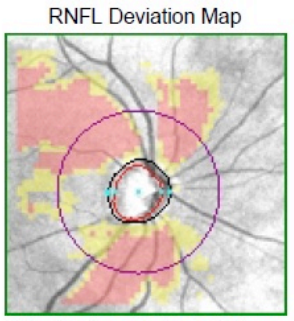
NORMAL EYE



GLAUCOMA

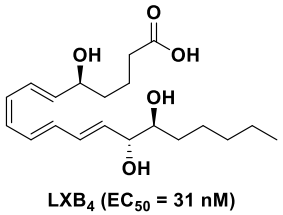


*National Eve Institute

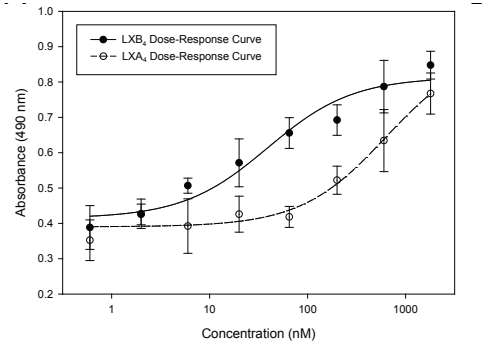


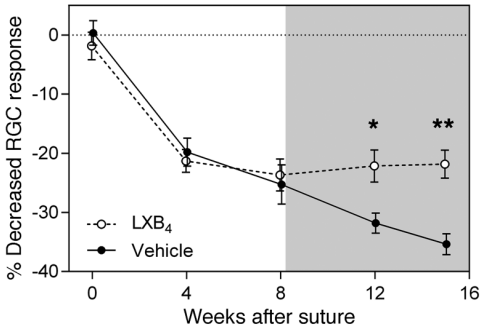
Livne-Bar, I.; Wei, J.; Liu, H.-H.; Alqawlaq, S.; Won, G.-J.; Tuccitto, A.; Gronert, K.; Flanagan, J. G.; Sivak, J. M. *J. Clin. Investig.* **2017**, *127*, 4403-4414; and references therein.
Nucci, C.; Martucci, A.; Giannini, C.; Morrone, L. A.; Bagetta, G.; Mancino, R. *Eye* **2018**, *32*, 938-945; and references therein.

LXB_4 Protects RGCs from Glaucoma Injury



LXB_4 (EC_{50} = 31 nM)





- **Sivak group discovered novel neuroprotective role of lipoxins**
- Lipoxins (LXA_4 and LXB_4): special pro-resolving lipid mediators (SPMs)
- Potent effectors of ***inflammation resolution***
  - Not well studied in retina or CNS
  - LXA_4 better understood and has an established receptor (GPCR)
  - LXB_4 less studied, and its **receptor is unknown**
  - LXB_4 (EC_{50} = 31nM) is ~20x more potent than LXA_4 (EC_{50} = 631 nM)
- LXB_4 treatment is efficacious in a 15-week chronic glaucoma model

LXB_4 target deconvolution strategies:

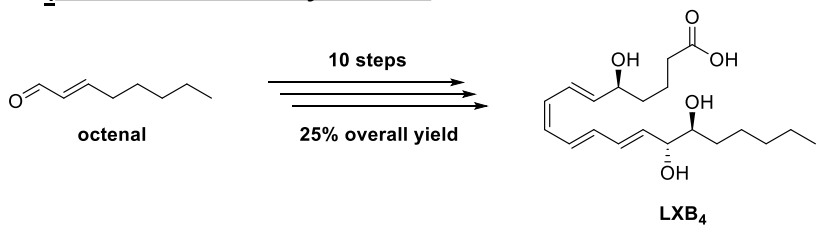
Photo Affinity Labelling (PALMS) (Evotec)

Tritiation in Cell Microarray (Retrogenix)

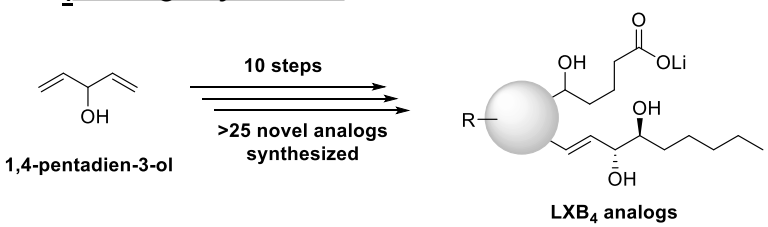
Livne-Bar, I.; Wei, J.; Liu, H.-H.; Alqawlaq, S.; Won, G.-J.; Tuccitto, A.; Gronert, K.; Flanagan, J. G.; Sivak, J. M. *J. Clin. Investig.* **2017**, *127*, 4403-4414; and references therein.

Synthesis of LXB_4 & Aromatic Analogs

LXB_4 Natural Product Synthesis:



LXB_4 Analogs Synthesis:



Chemistry–A European Journal | Research Article
doi.org/10.1002/chem.202200360
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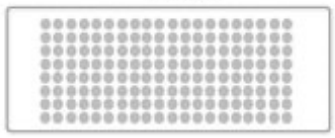
A Stereocontrolled Total Synthesis of Lipoxin B4 and its Biological Activity as a Pro-Resolving Lipid Mediator of Neuroinflammation

C. Frank Lee,[a] Carla E. Brown,[a] Alexander J. Nielsen,[a] Changmo Kim,[b, c, i] Izhar Livne-Bar,[b, c] Philip J. Parsons,[d] Christophe Boldron,[e] François Autelitano,[e] Donald F. Weaver,[f, g, h] Jeremy M. Sivak,[b, c, i] and Mark A. Reed*[a, j]

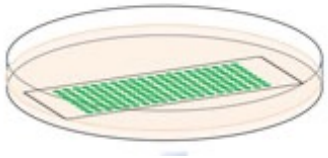
Lee, C. F.; Brown, C. E.; Nielsen, A. J.; Kim, C.; Livne-Bar, I.; Parsons, P. J.; Boldron, C.; Autelitano, F.; Weaver, D. F.; Sivak, J. M.; Reed, M. A. *Chem. Eur. J.* **2022**, *28*, e202200360.
Brown, C. E.; Lee, C. F.; Nielsen, A. J.; Sivak, J. M.; Reed, M. A. *Unpublished results; patent pending.*

LXB_4 Target Deconvolution

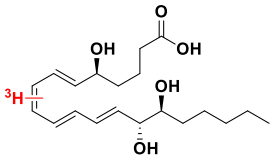
Cell microarray probe:



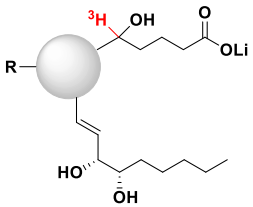
Expression vectors encoding >5000 membrane or secreted proteins arrayed



Cells grown on slides. Live cells overexpress each protein in distinct locations



^{3}H-LXB4

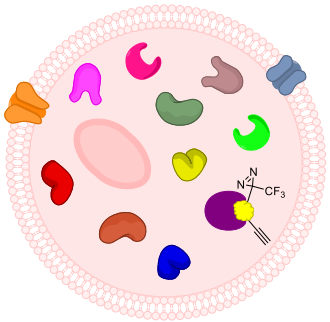


^{3}H-CMD15

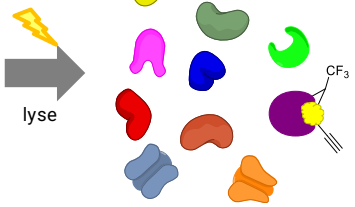
Cells treated with radiolabelled probes and washed

No targets detected

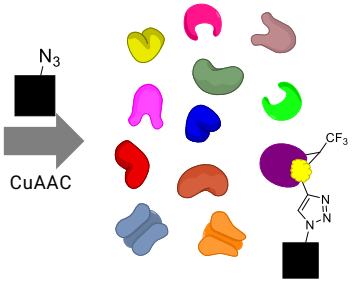
Photoaffinity labelling MS/MS (PALMS) probe:



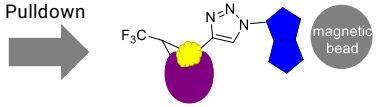
Live cells incubated with synthesized probe

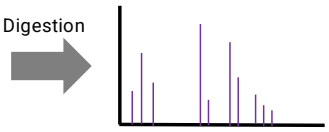


Photolabile diazirine crosslinks to target; lysed



Biotin/reporter installation via click chemistry





Target ID: Two targets of interest identified

Portfolio

	Disease Indication/PI	Target Class	Pre-clinical Validation	Stage
Neurology/ Ophthalmology	Rett Syndrome and dementia - Neuroinflammation	Ion Channel	Genetic	Hit to lead
	Depression and dementia - Neuroinflammation	enzyme	Pharmacological	Lead Optimization
	Glaucoma and dementia – Neuroinflammation	unknown	Genetic/ Pharmacological	Receptor Identification
	Stroke, Spinal cord injury: Axonal Regeneration	Kinase	Genetic/ Pharmacological	Hit Finding
	BBB Integrity	Kinase	Genetic/ Pharmacological	Hit Finding
	Depression	Receptor	Genetic/ pharmacological	In Silico HTS
Oncology	AML	Kinase	Genetic/ Pharmacological	Hit to lead
	Radiation Fibrosis	Unknown	Genetic/ Pharmacological	Target ID
	Ovarian Cancer	Kinase	Genetic/ Pharmacological	Hit to lead
	BRCA1/2-mutant breast and ovarian cancer	E3 ligases	Genetic	Hit ID
	Pancreatic cancer	Receptor	Genetic	Assay development
	AML	Stress granule	Genetic	Structure Based Design
	Prostate Caner	transporter	Genetic	Hit to lead
Arthritis	Cartilage Degeneration	Transcription factor	Genetic	Hit finding
	Fibrosis/ myofibroblast activation	enzyme	Genetic/ Pharmacological	Hit ID
	Spondyloarthritis	Chemokine	Genetic/ Pharmacological	Hit to lead
Metabolic	NASH	enzyme	Genetic/ Pharmacological	Hit ID

Acknowledgements

TREVENTIS

Senior Management

Christopher Barden
Mark Reed
Marcia Taylor
Donald Weaver

Chemistry

Leela Anagani
Scott Banfield
Christopher Barden
Kunal Keskar
Erhu Lu
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Dr. Anthony Joshua
Dr. Marianne Koritzinsky

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Questions?

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