UNC ESHELMAN SCHOOL OF PHARMACY

UNC LINEBERGER

Academic Drug Discovery and Chemical Biology: A Tale of Two Targets

Stephen V. Frye, Ph.D.
Professor & Director
Center for Integrative Chemical Biology & Drug Discovery
University of North Carolina Chapel Hill

SGC

www.pharmacy.unc.edu/cicbdd

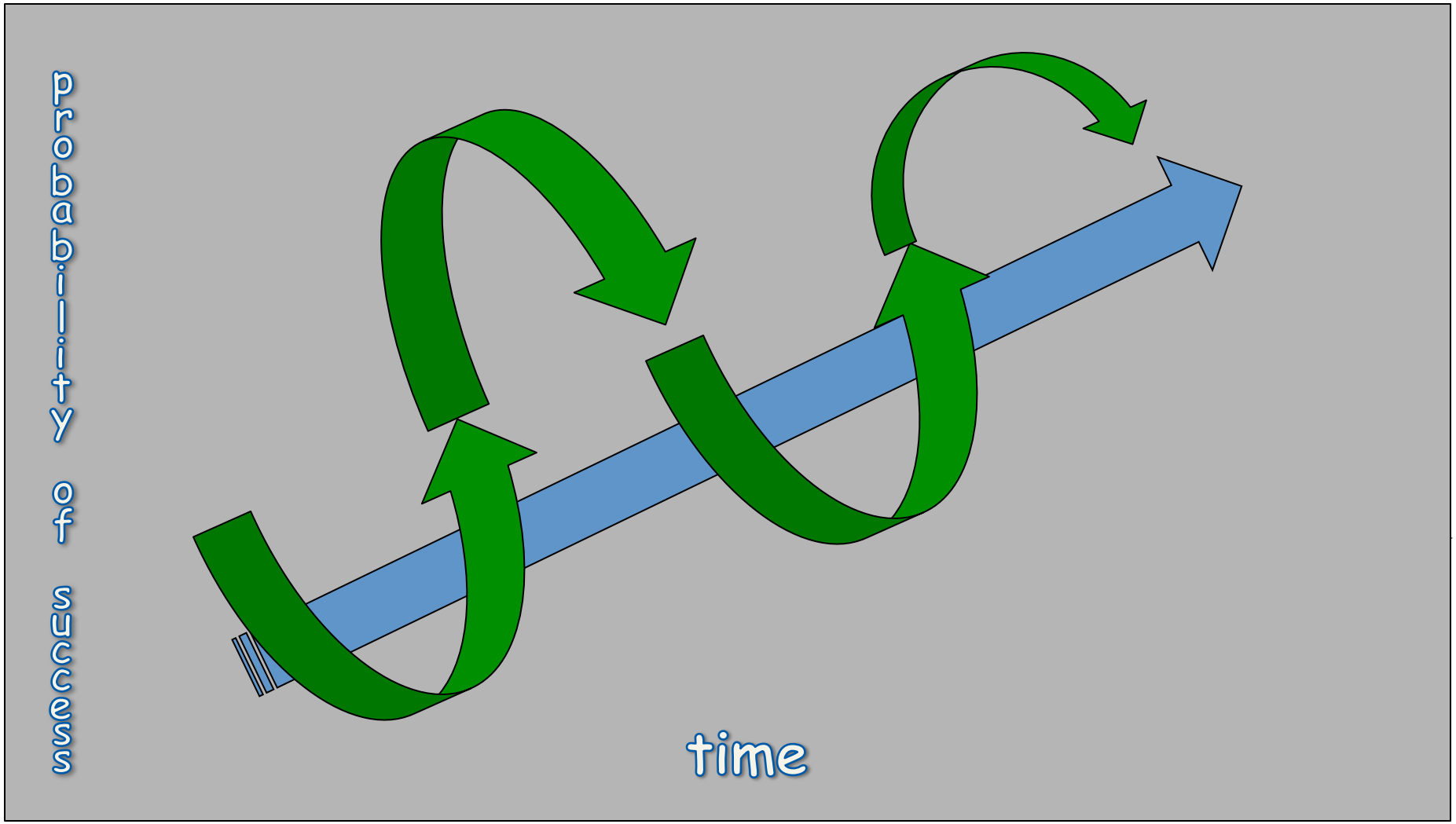
Outline

- Why Academic Drug Discovery?
- Mer Kinase Discovery Project
- Chemical Probes for Methyl-Lysine Readers

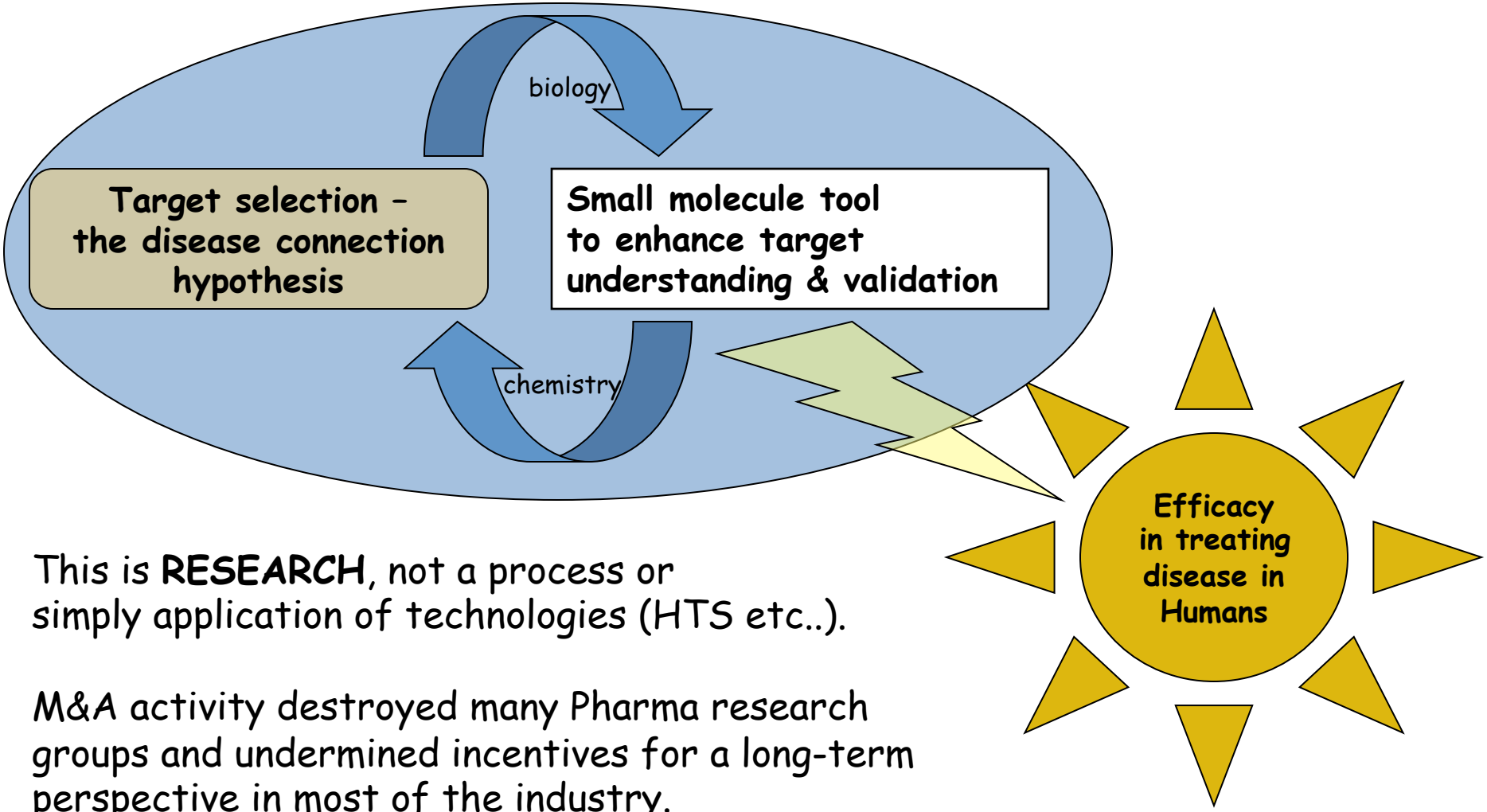
Conflict of Interest Statement

- A company (Meryx Inc.) to progress the mer kinase inhibitor discovery work has been formed to advance a candidate toward the clinic.
- Shelley Earp, Doug Graham and I are founders of this company.

Drug Discovery – what can be done better in academia?



Drug Discovery – what can be done better in academia?



This is **RESEARCH**, not a process or simply application of technologies (HTS etc..).

M&A activity destroyed many Pharma research groups and undermined incentives for a long-term perspective in most of the industry.

DISCOVERY of Mer TK Inhibitors

>1100 Compounds, >4 Years of Work


Shelley Earp


Doug Graham


Bill Janzen


Dmitri Kireev


Xiaodong Wang

A great collaboration

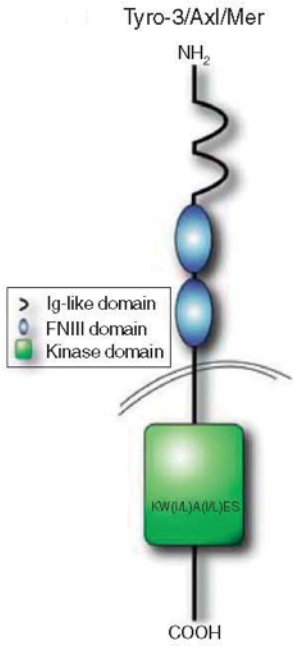
Chemistry & In vitro assays: CICBDD,
Biology: Earp and Graham labs
Funding: NCI NexT Program

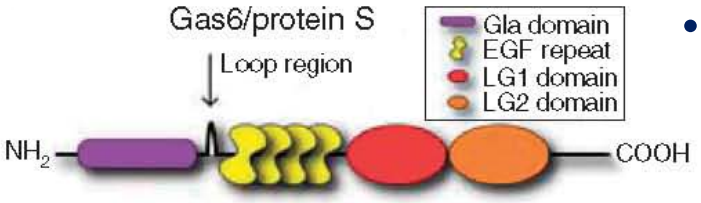
University of Colorado
Anschutz Medical Campus

UNC LINEBERGER

Mer Receptor Tyrosine Kinase

Member of TAM family of RTKs

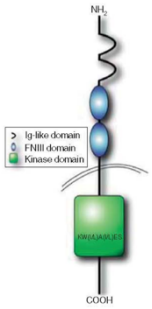




- Normal expression in:
  - Macrophages – NK, dendritic cells
  - Epithelial tissues
  - Reproductive tissues
- Physiologic function:
  - Phosphatidyl serine responsive
  - Protein ligands bind apoptotic cells
  - Binding triggers ingestion and suppresses inflammatory cytokines
- Aberrantly expressed in cancer:
  - Acute Leukemia – ALL & AML
  - Solid tumors – melanoma, NSCLC, GBM, etc.
- Oncogenic function:
  - Survival signaling – anti-apoptosis
  - Chemoresistance
  - Motility and invasion
  - Immune suppression in the tumor microenvironment

Mer TK: A Dual Target in Cancer

Mer TK



Mer over-expressed in tumor cells e.g., leukemia, lung cancer, melanoma, GBM

Survival signal

Combination w/ chemotherapy and targeted agents

Mer TK Inhibitors Reverse survival & chemoresistance

Mer TKIs could have a dual anti-cancer effect

Expressed in tumor macrophages e.g., breast & lung cancer

Suppresses tumor immunity

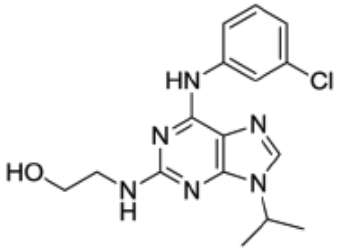
Mer TK Inhibitors Stimulate innate anti-tumor immunity

Combination w/ immuno-therapy and targeted agents

MerTKI Leads: Structure based hit design

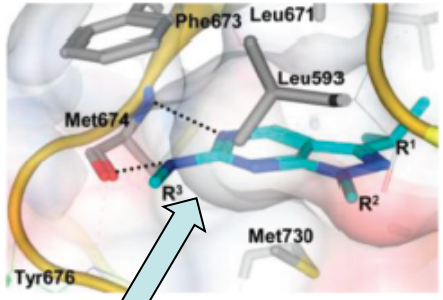
ACS Medicinal Chemistry Letters Letter

a

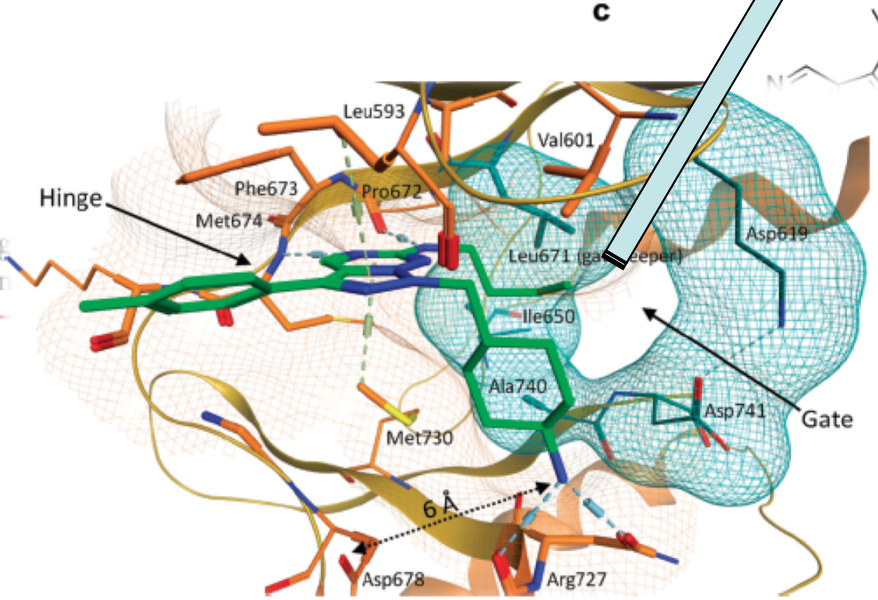


Compound-52

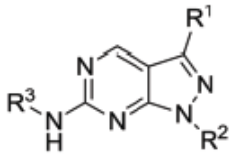
b



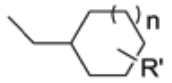
c

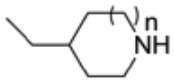


d



R^1 = alkyl, alkene, Ar

R^2 =  n = 0, 1, 2; R' = OH, NH_2, etc.



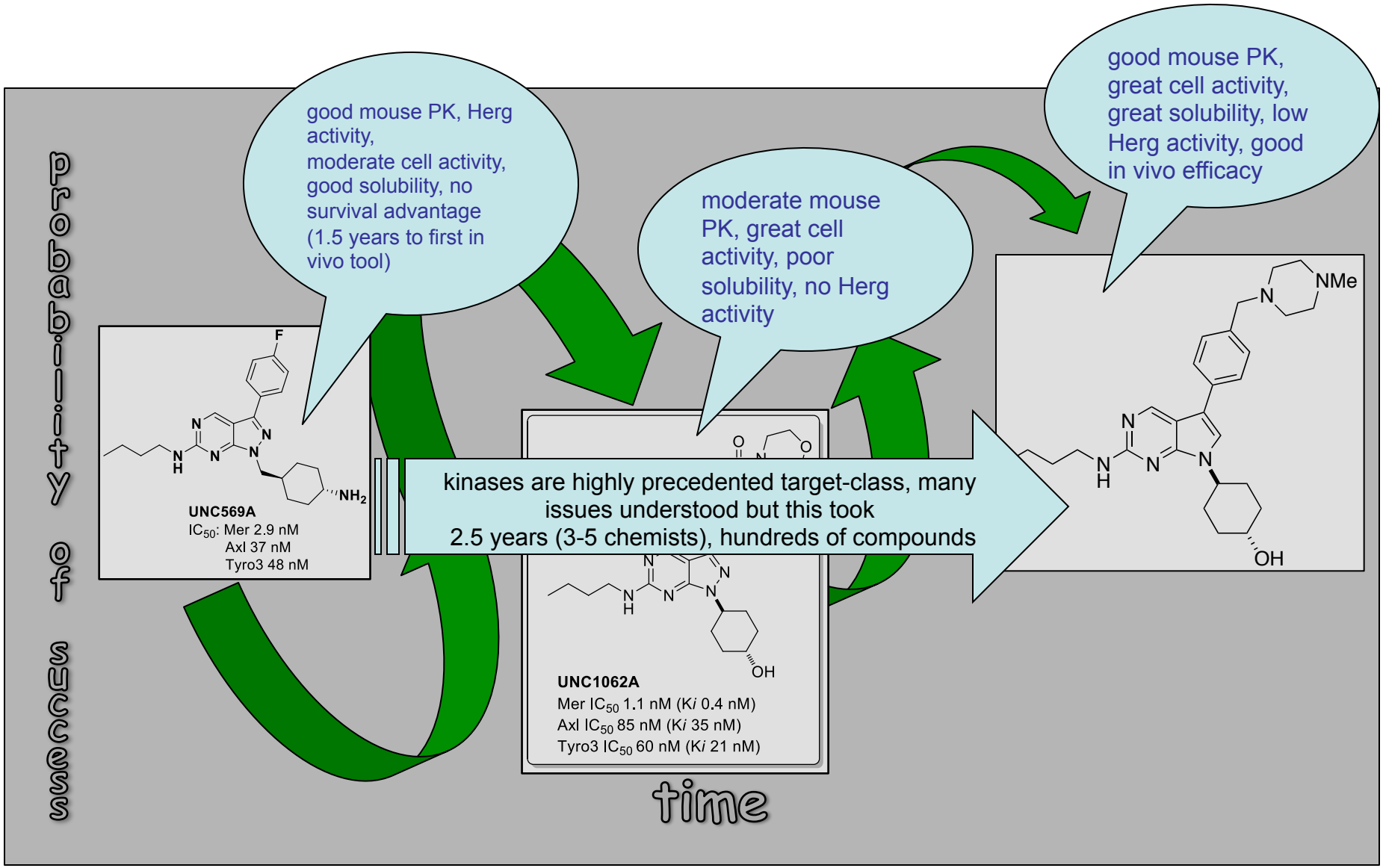
n = 0, 1, 2

R^3 = substituted alkyl chains

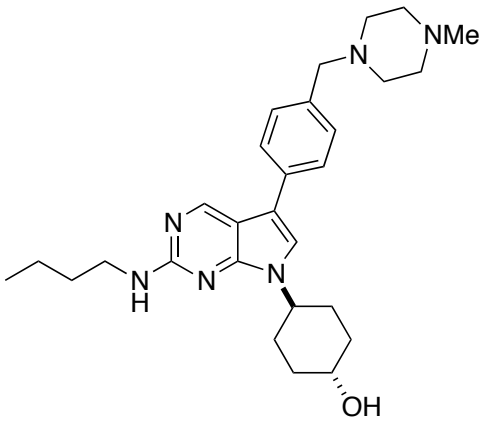
Fig… 1 in the X-ray structure of Mer; (c) chemical structure of 1; (d) design of ca… d.

Huang, X. et al. Structural insights into the inhibited states of the Mer receptor tyrosine kinase. *J Struct Biol* **165**, 88-96 (2009).

Liu, J. *et al.* Discovery of Novel Small Molecule Mer Kinase Inhibitors for the Treatment of Pediatric Acute Lymphoblastic Leukemia. *ACS Med Chem Lett* **3**, 129-134 (2012).


probability of success
good mouse PK, Herg activity, moderate cell activity, good solubility, no survival advantage (1.5 years to first in vivo tool)
moderate mouse PK, great cell activity, poor solubility, no Herg activity
good mouse PK, great cell activity, great solubility, low Herg activity, good in vivo efficacy
UNC569A
IC50: Mer 2.9 nM
Axl 37 nM
Tyro3 48 nM
kinases are highly precedented target-class, many issues understood but this took
2.5 years (3-5 chemists), hundreds of compounds
UNC1062A
Mer IC50 1.1 nM (Ki 0.4 nM)
Axl IC50 85 nM (Ki 35 nM)
Tyro3 IC50 60 nM (Ki 21 nM)
time

UNC2025: Potent Mer TK Inhibitor



Carna Biosciences tested
@100nM against 305 kinases, IC50's for >50% I

MW	446
tPSA	66.7
cLogP	4.78
LE	0.36
SEI	14
LipE	4.4
freely soluble in saline	

TAM Family Activity		
Mer	0.74 nM	(Ki 0.16 nM)
FLT3	0.84 nM	(Ki 0.71 nM)
Axl	17 nM	(Ki 15 nM)
Tyro3	25 nM	(Ki 5.1 nM)

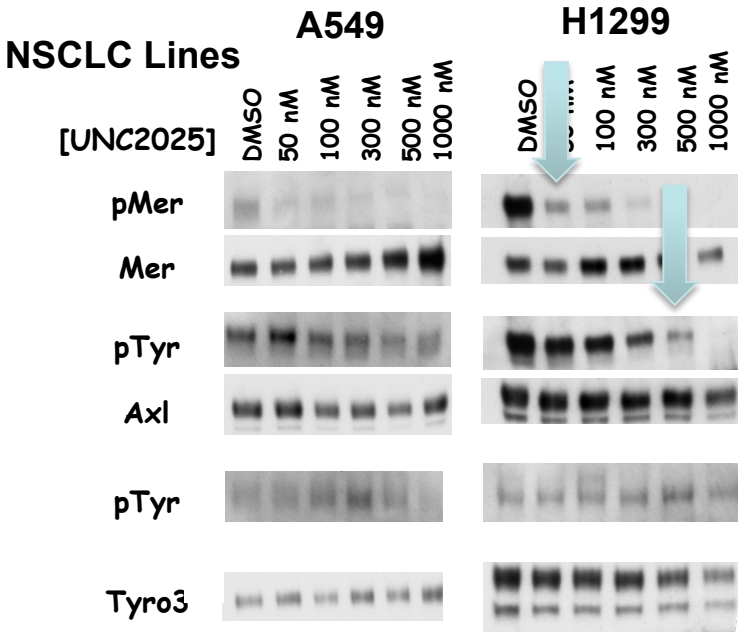
hERG	>20 uM

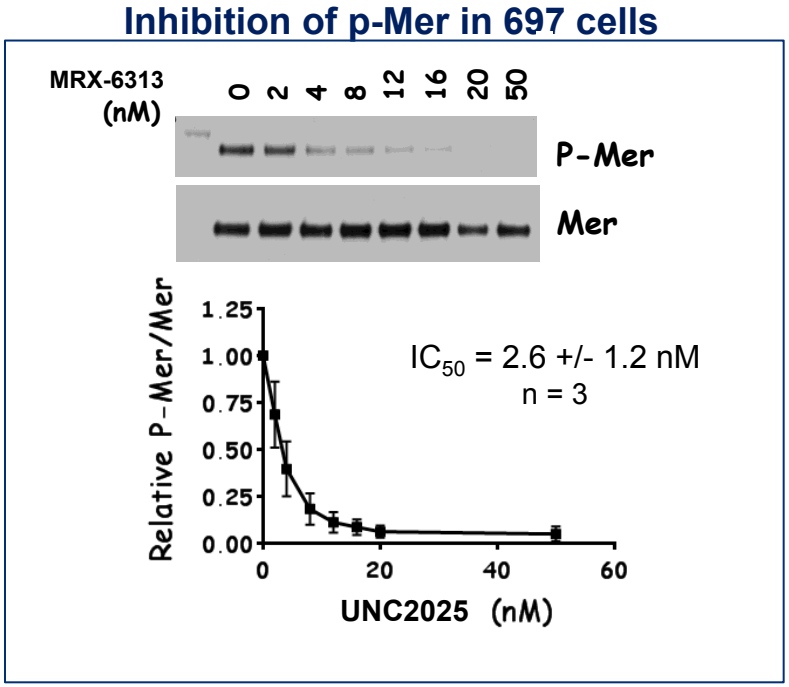
Can Axl be a sentinel for "off-target" kinase activity?

Selectivity Concerns

- What hypothesis are you testing?
  - most important issue
- Will off-target activity compromise safety & developability?
  - we rarely know what the ‘anti-targets’ are
    - Herg
    - 5HT2b agonism
    - p450’s
  - Some ‘multikinase’ inhibitors are quite toxic

UNC2025: Potent Cellular Mer TK Inhibitor



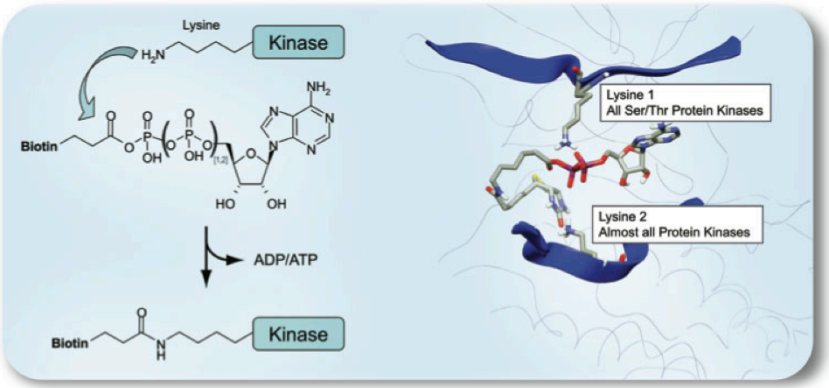


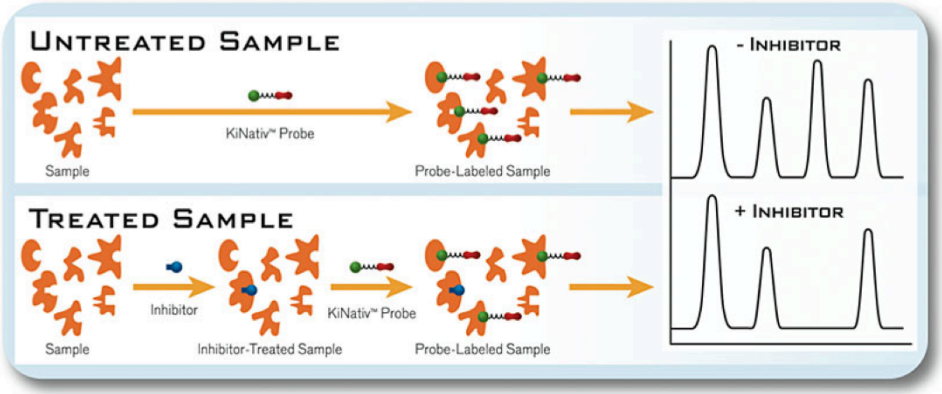
	TAM Family Activity	
Mer	0.74 nM	(Ki 0.16 nM)
FLT3	0.84 nM	(Ki 0.71 nM)
Axl	17 nM	(Ki 15 nM)
Tyro3	25 nM	(Ki 5.1 nM)

- cellular IC_{50}'s right shifted by 10-20 fold
- 50 nM Mer = 500 nM Axl $\geq$1 μM Tyro3
- If this relationship holds for other kinases, in vivo effects will be dominated by Mer and Flt3

Can Axl be a sentinel for "off-target" kinase activity?

Kinome Cellular Profiling of MRX-6313





- 697 cellular lysate [500uL of a 5mg/mL stock]
- +/- MRX-6313 for 15 minutes [0, 0.1, 1.0, 10, 100, 1000nM]
- Add reactive ADP or ATP probes [5uM-10 min]
- Denature protein to stop reaction
- Digest with Trypsin
- Enrich probe labeled peptides with streptavidin
- Purified elute was analyzed by LC MS/MS [quadruplicate]

Preliminary conclusions:

- Mer is the kinase most potently protected from labeling by UNC2025 with ADP and ATP reagent (700 pM and 50 pM IC_{50}, respectively)
- Axl not observed (Tyro3 peptides are redundant with Mer, so not distinguishable). Flt3 was not significantly protected – we do not understand this result.
- ADP detected kinase IC_{50}'s correlate better with Carna data than ATP
  - more analysis underway
- NCI: "work confirms the team's finding that UNC2025 preferentially inhibits MERTK"

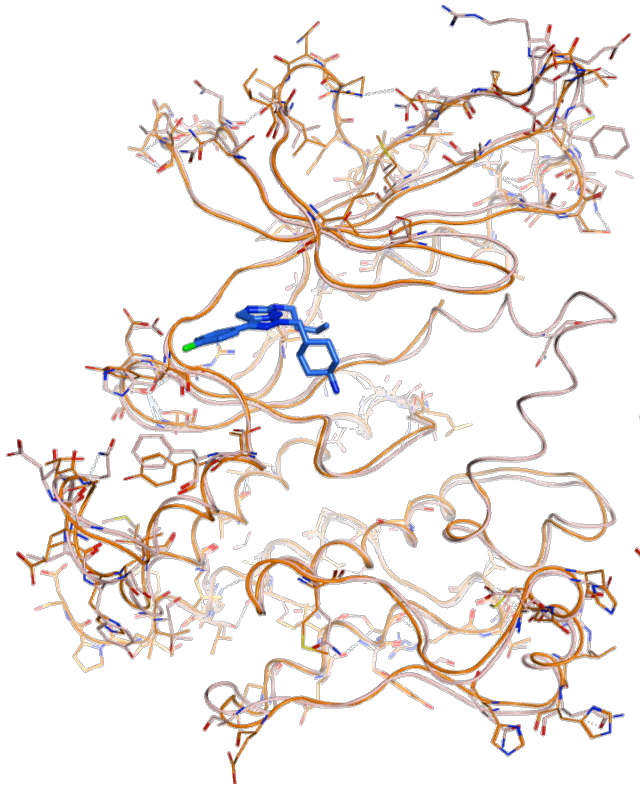
Trevor Glaros
Dianne Newton

SAIC®
Frederick

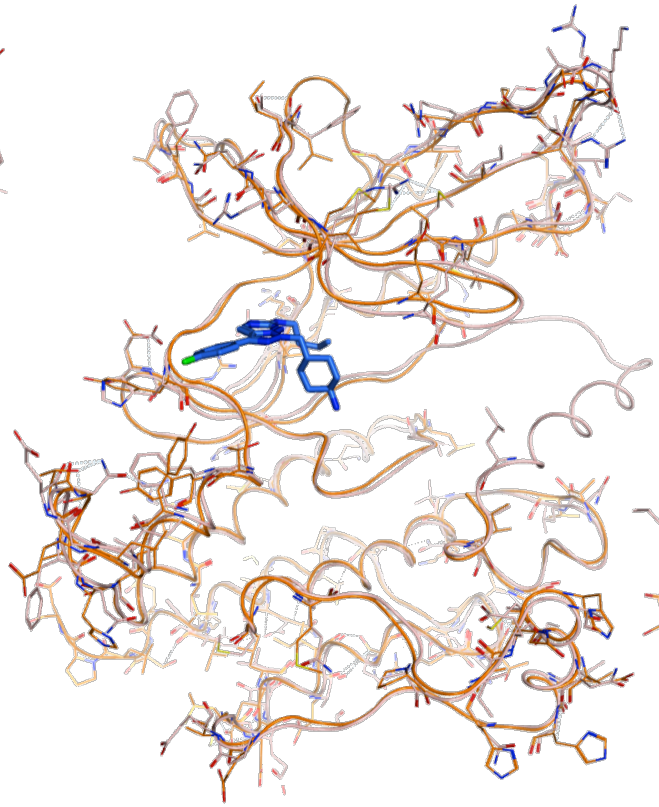
Patricelli, Matthew P. *et al.* In Situ Kinase Profiling Reveals Functionally Relevant Properties of Native Kinases. *Chemistry & Biology* **18**, 699-710, (2011).

Selectivity: Identity and Divergent Side-chains

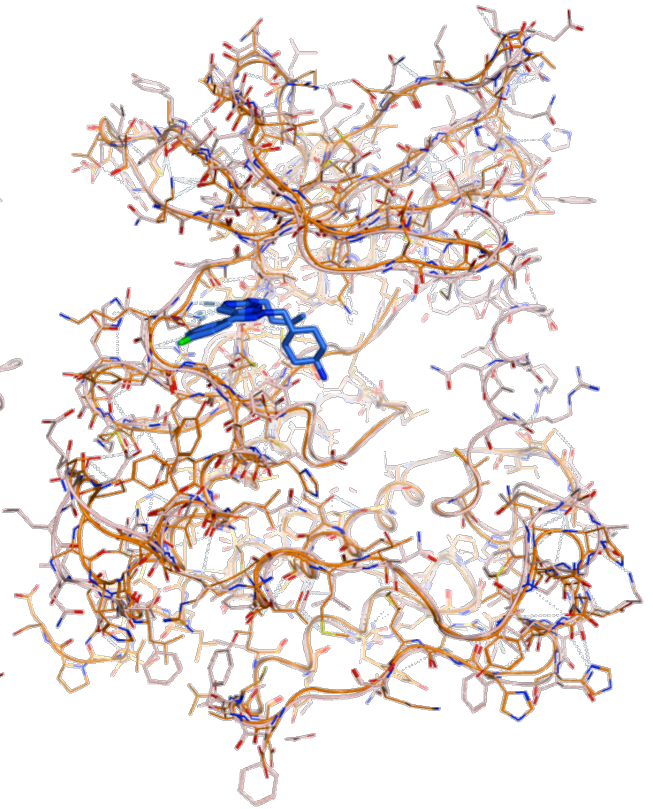
Axl (~60%)



Tyro3 (~52%)



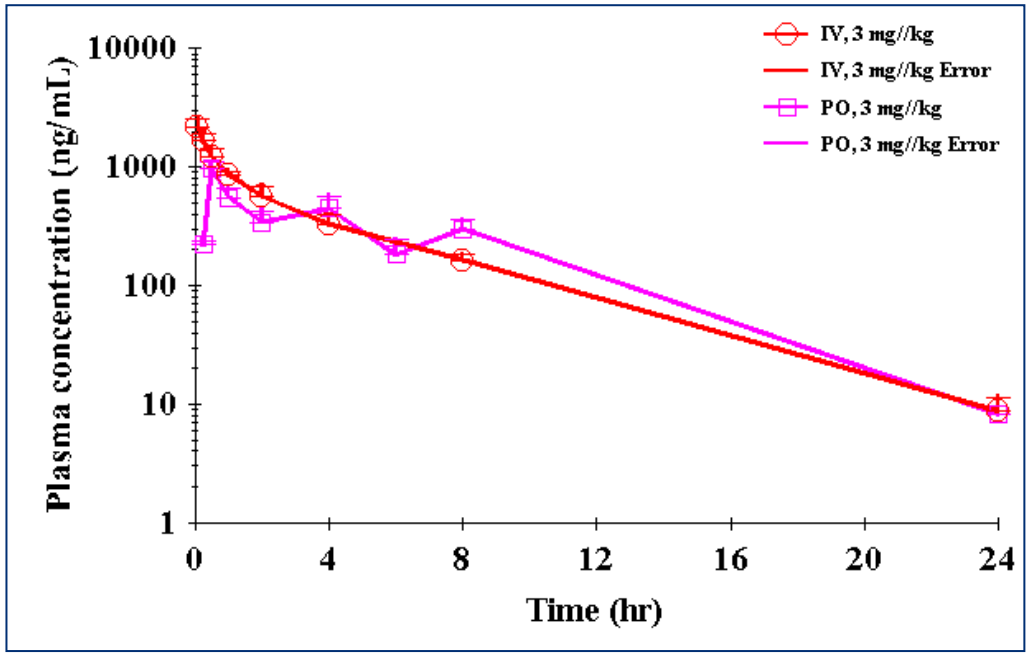
FLT3 (~26%)



IC_{50} Mer 1.5 nM
Axl 94 nM
Tyro3 86 nM
FLT3 270 nM

IC_{50} Mer 1.1 nM
Axl 2.4 nM
Tyro3 6.3 nM
Flt3 95 nM

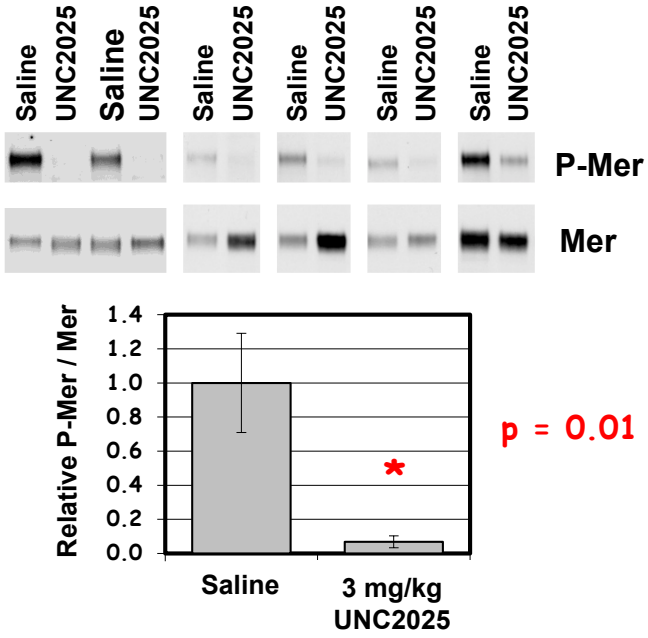
UNC2025: Mouse Pharmacokinetics



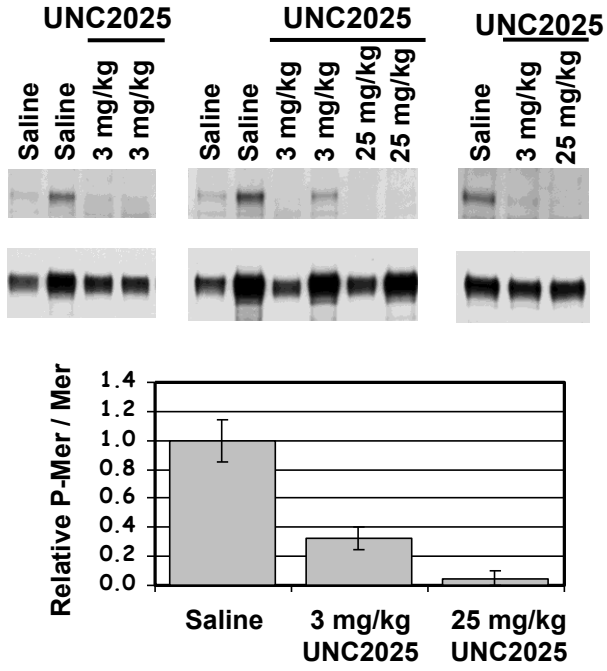
PO Cmax	1.75 uM
T1/2	3.8 h
%F	100

Dose (mg/kg)	Route	T1/2 (h)	Tmax (h)	Cmax (μM)	AUC_{last} (h*μM)	Vss (L/Kg)	CL (mL/min/kg)	% F
3.0	IV	3.8	-	4.36	9.78	2.33	9.22	
3.0	PO	-	0.50	1.75	9.79	-	-	100

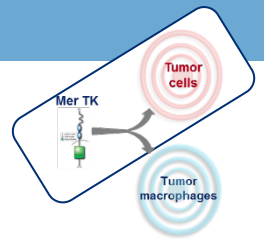
UNC2025 Pharmacodynamics: Potent Inhibition of p-Mer in Bone Marrow Leukemia Cells



x0.5 hours Post-Treatment

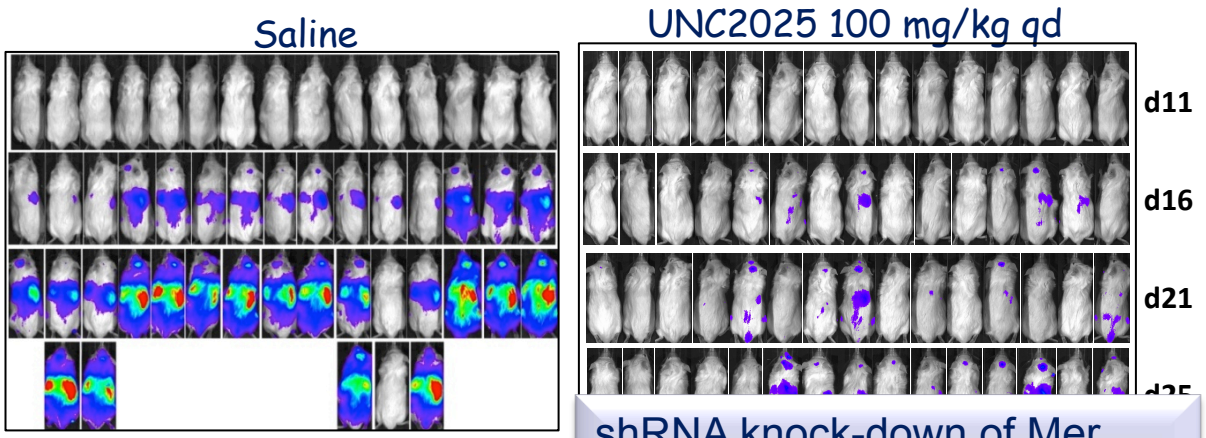


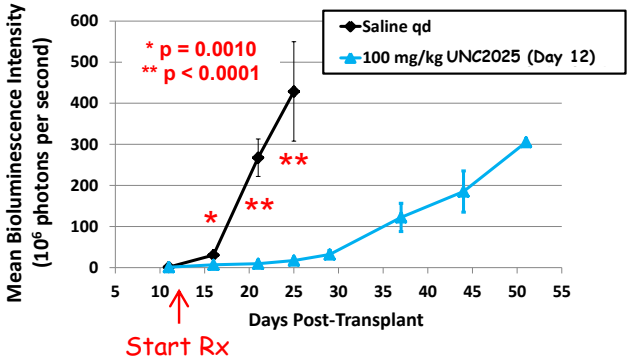
x12 hours Post-Treatment



UNC2025: Active in Established Leukemia

Mer TK over-expressed in B ALL 697 cells

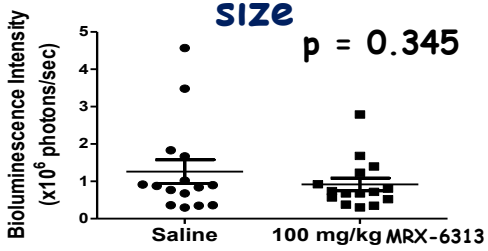


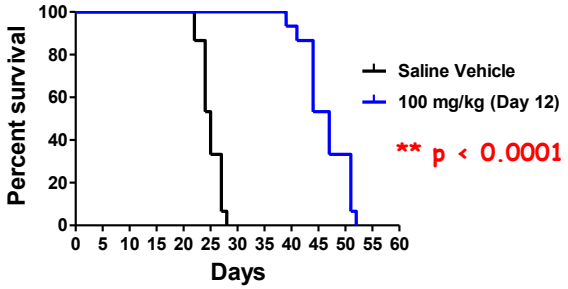


shRNA knock-down of Mer inhibits growth of:

- ALL – similar effects to TKI
- AML
- melanoma
- lung cancer

Pre-treatment tumor size





Rx started on day 12 post-transplant
n=15

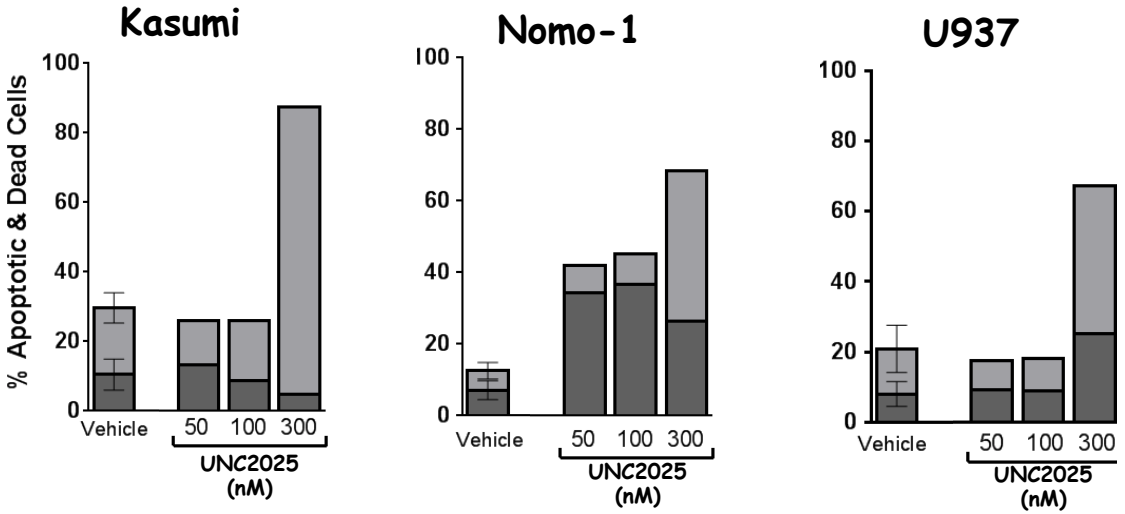
Graham Lab

	Median Survival
Saline	25 days
UNC2025	47 days

University of Colorado Anschutz Medical Campus

NSG mice (immunocompromised) + 697 + Luciferase + 100 mg/kg UNC 2025 qd

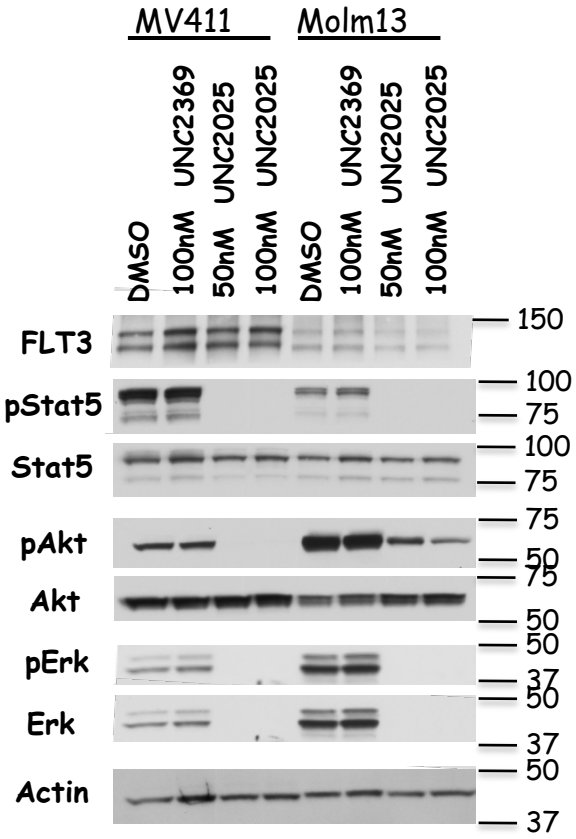
UNC2025 Induces Apoptosis in Mer-Expressing AML Cell Lines

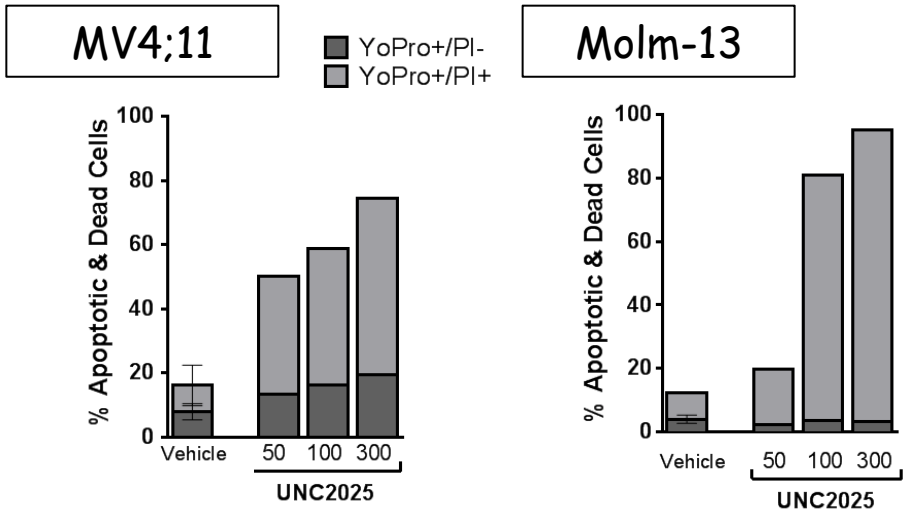


Cell cultures were treated with UNC2025 or vehicle for 72 hrs.

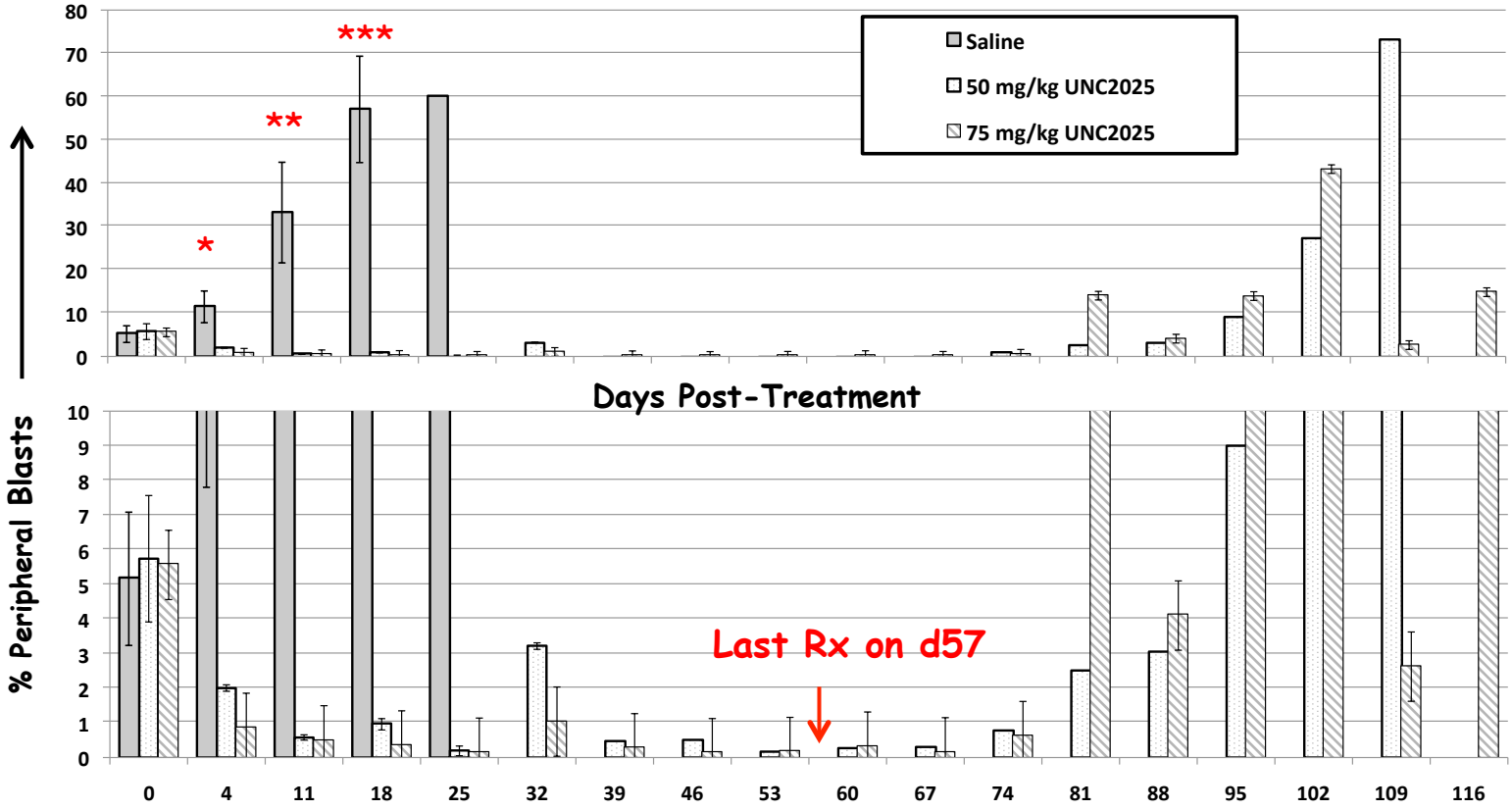
Apoptotic & dead cells were detected by flow cytometry after staining with YoPro®-1-iodide & propidium iodide.

UNC2025 Inhibits FLT3-dependent Downstream Signaling & Induces Apoptosis in Mer-Negative FLT3-ITD AML Cells





Treatment with UNC2025 decreases leukemia burden in a Mer +, FLT3-ITD+ AML patient sample xenograft model



TKI vs Saline

* p < 0.05
** p < 0.025
*** p < 0.003

n = 5

D. DeRyckere, A. Hill, & K. Minson

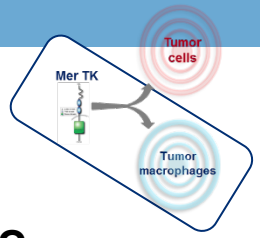
University of Colorado Anschutz Medical Campus

UNC LINEBERGER

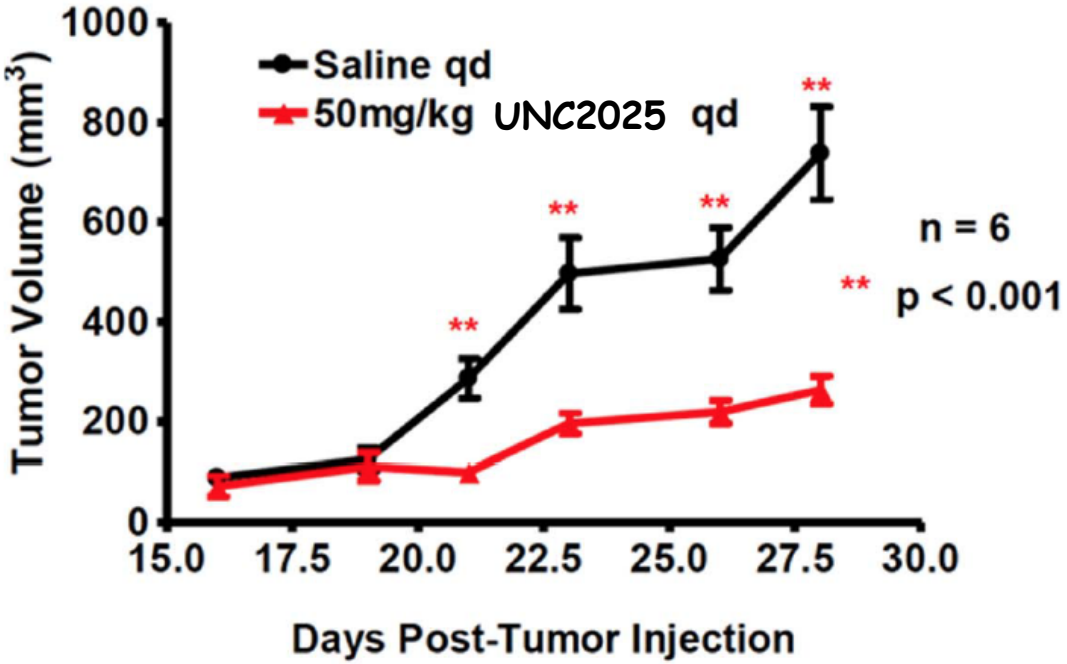
Studies Underway Using Immunocompetent Mice: Testing Mer TKIs with Immune Checkpoint Agents

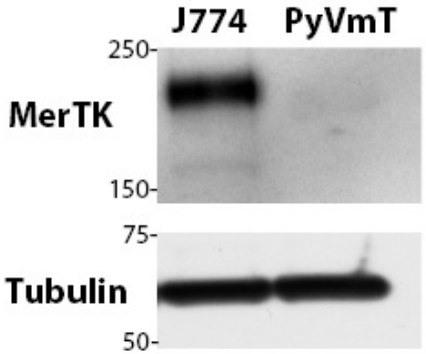
- **Breast Cancer Syngeneic Models**
  - PyVmT - Mer neg – C57/Bl6 - +/- anti-PD1-L and anti-CTLA4
  - NT2 HER2/Neu FVB mice +/- anti-PD1-L and anti-CTLA4
- **Melanoma**
  - B16 in C57/Bl6 Mer TKIs +/- anti-PD1-L/anti-CTLA4
  - Tria5 GEMM (Mer – tumor) Mer TKIs and anti PD1L
  - Combination with B-raf inhibition (synergistic in cells)
- **GEMMs – NSCLC**
  - Mer + and Mer – GEMMs
  - Mer TKIs +/- anti-PD1

Schlegel, J. *et al.* MERTK receptor tyrosine kinase is a therapeutic target in melanoma. *J Clin Invest* **123**, 2257-2267, doi:10.1172/JCI67816 (2013).



UNC2025:
Active in Mer TK-Negative Breast Cancer
Activity via immune modulation of tumor microenvironment?



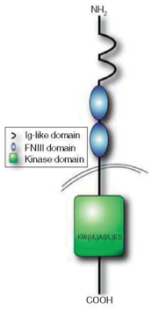


Graham lab

- Immune-Competent Orthotopic Model of Mer-Negative Breast Cancer
- Treatment from Day -2 to day 28; 50 mg/kg bid UNC2025 or vehicle

Mer TK: A Dual Target in Cancer

Mer TK



Mer over-expressed in tumor cells e.g., leukemia, lung cancer, melanoma, GBM

Survival signal

Combination w/ chemotherapy and targeted agents

Mer TK Inhibitors Reverse survival & chemoresistance

Mer TKIs could have a dual anti-cancer effect

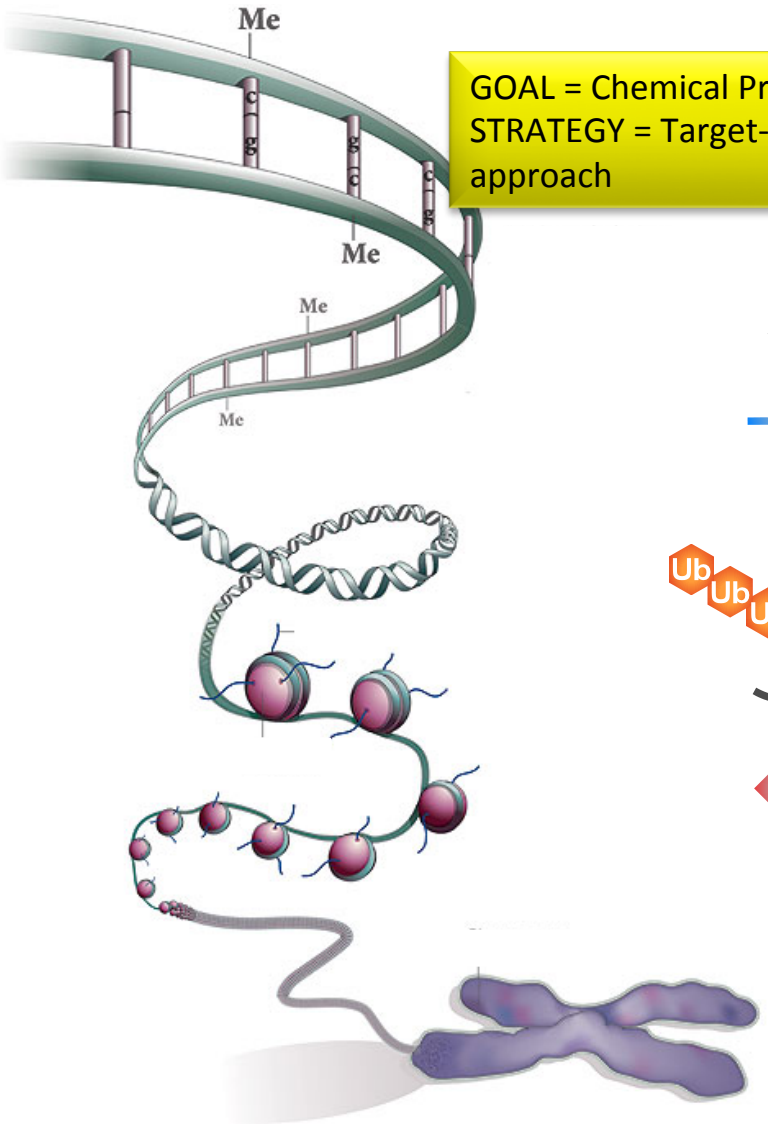
Expressed in tumor macrophages e.g., breast & lung cancer

Suppresses tumor immunity

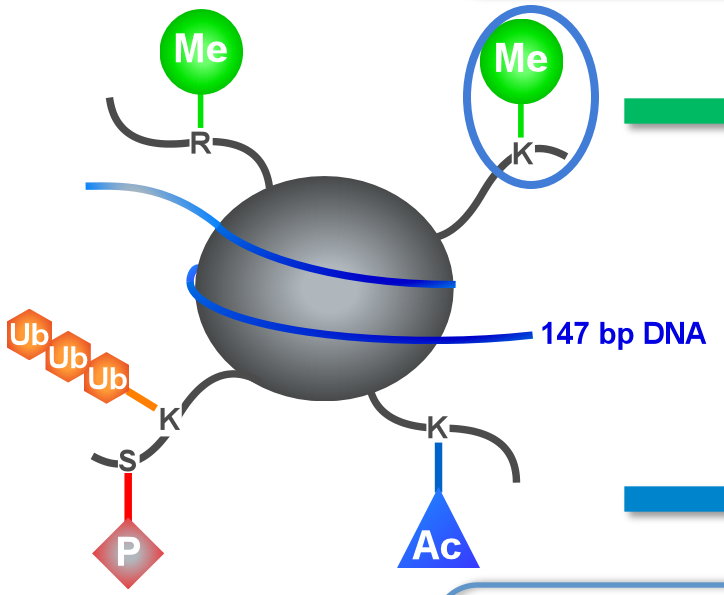
Mer TK Inhibitors Stimulate innate anti-tumor immunity

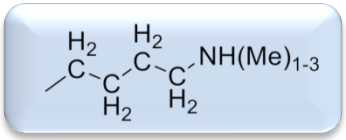
Combination w/ immuno-therapy and targeted agents

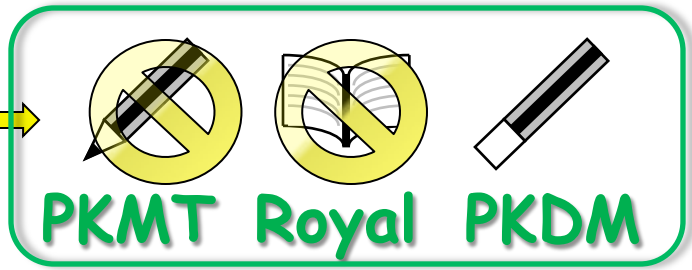
Chemical Biology of Chromatin Regulation



GOAL = Chemical Probes
STRATEGY = Target-class approach







SGC

Methyl-lysine Readers Implicated in Cancer

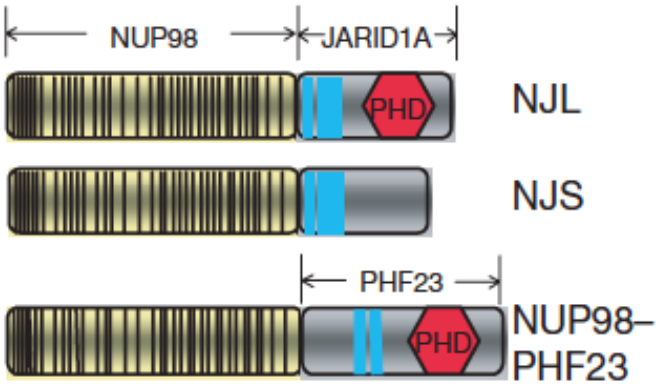
Vol 459|11 June 2009|doi:10.1038/nature08036 nature

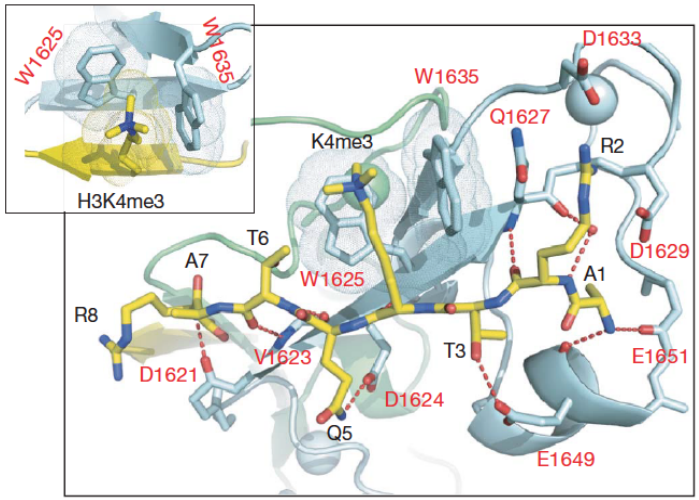
"Mutations in PHD fingers that abrogated H3K4me3 binding also abolished leukaemic transformation."

LETTERS

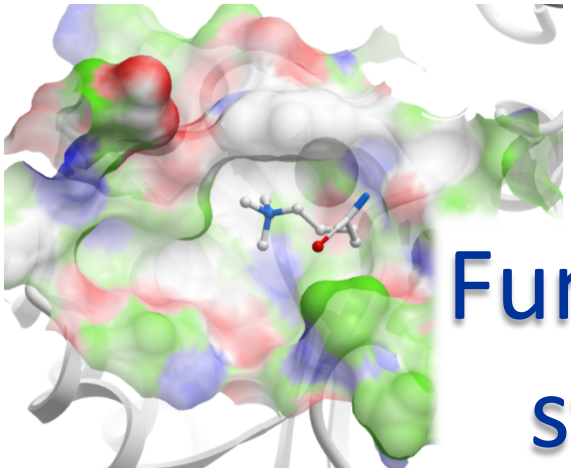
Haematopoietic malignancies caused by dysregulation of a chromatin-binding PHD finger

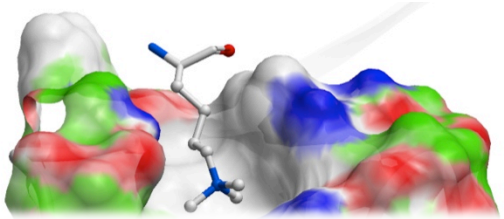
Gang G. Wang[1], Jikui Song[2], Zhanxin Wang[2], Holger L. Dormann[1], Fabio Casadio[1], Haitao Li[2], Jun-Li Luo[3], Dinshaw J. Patel[2] & C. David Allis[1]





Methyl-lysine Reader Families

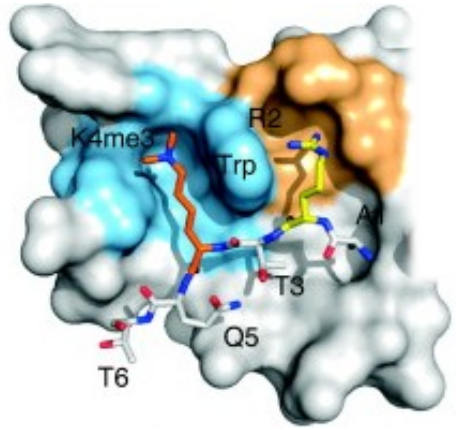




34 Chromo Domains (Kme3)

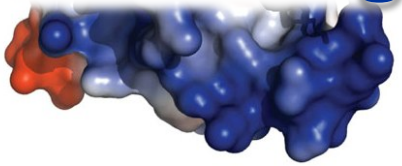
...ins (Kme1 & 2)

Functionally conserved, structurally diverse:

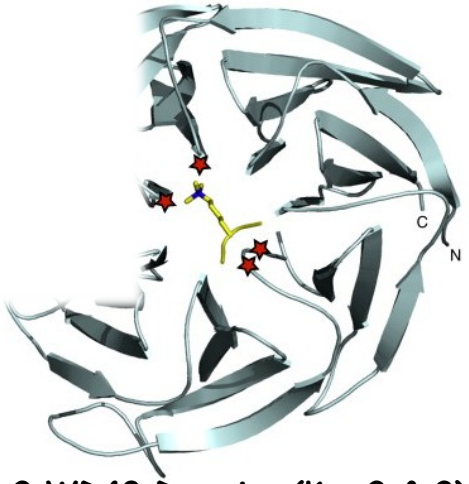


102 PHD Domains (Kme0-3)

No potent small molecule ligands

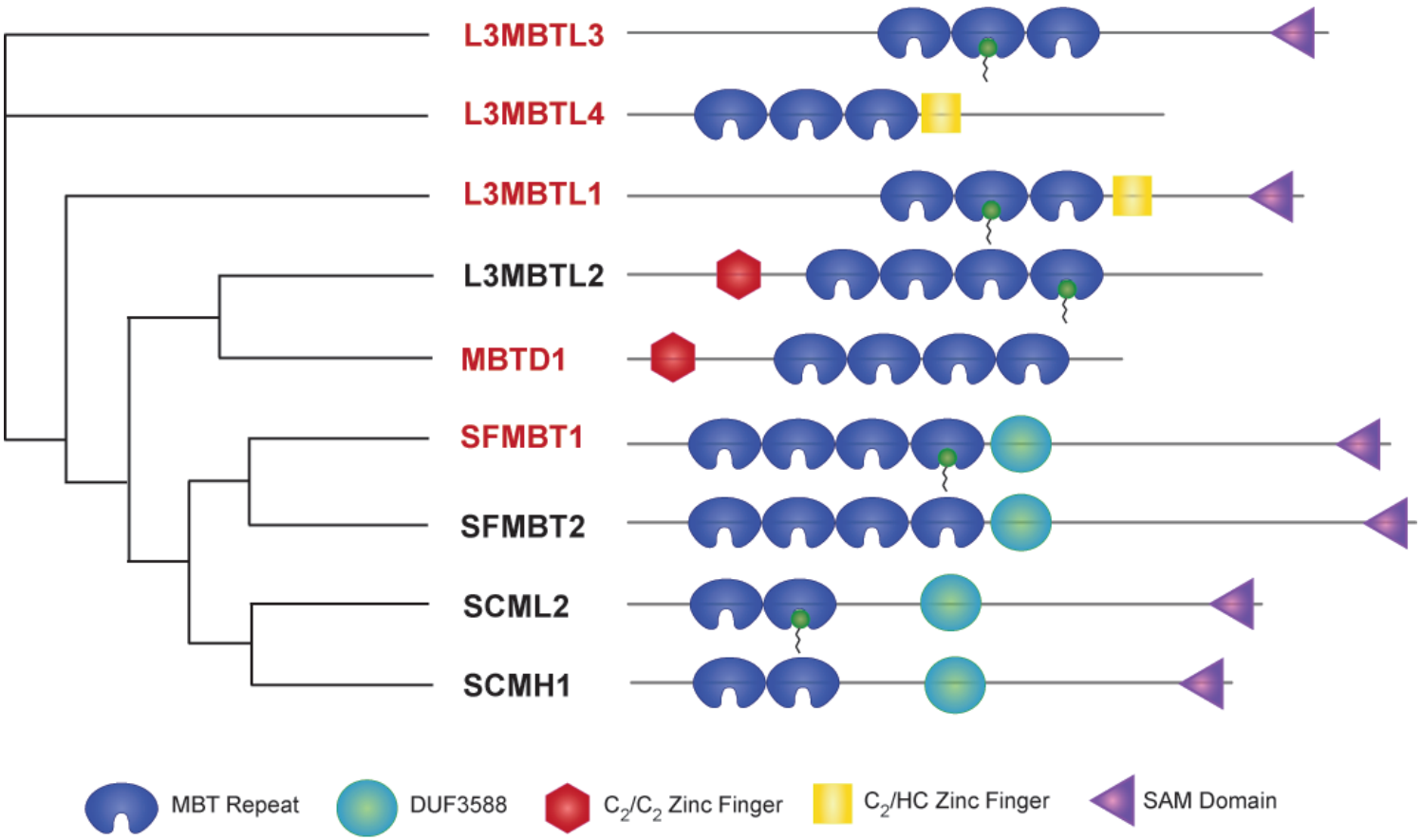


22 PWWP Domains (Kme3)



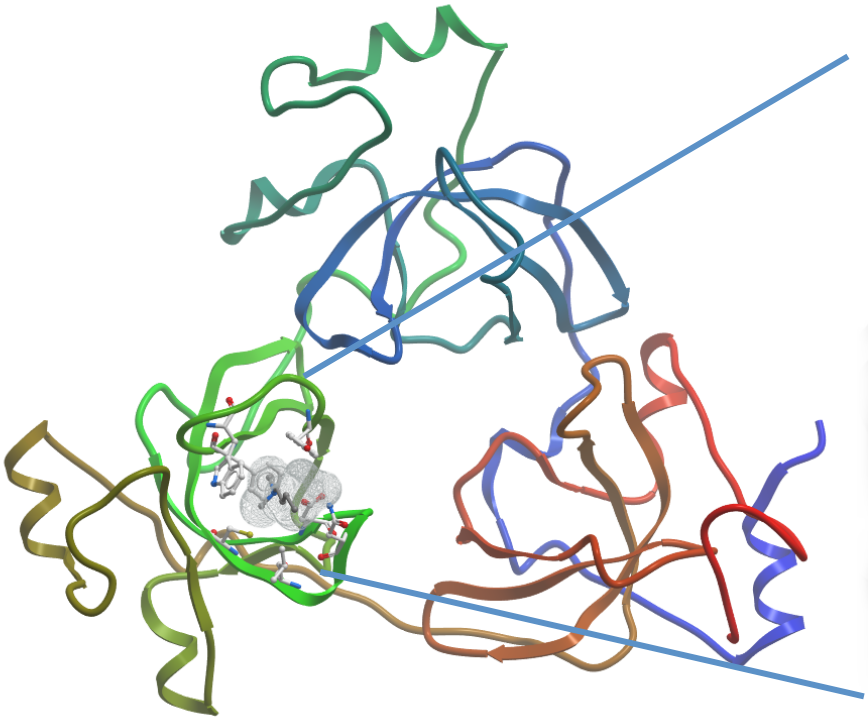
2 WD40 Domains (Kme2 & 3)

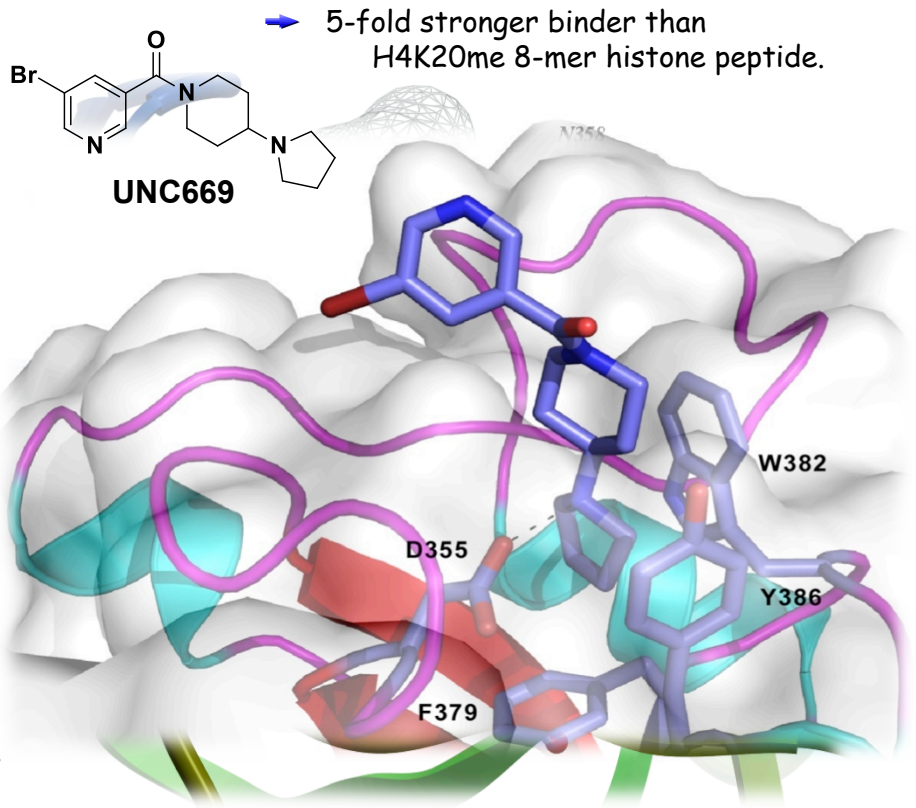
Phylogenetic Tree of Human MBT Proteins



Structural Biology of MBT Domains

- MBT domains recognize KMe_1 and KMe_2 in a sequence independent fashion
- Binding cavity is lined with aromatic residues, and the resulting cation-π interactions are major contributors to the binding along with an ion pair to an acidic residue



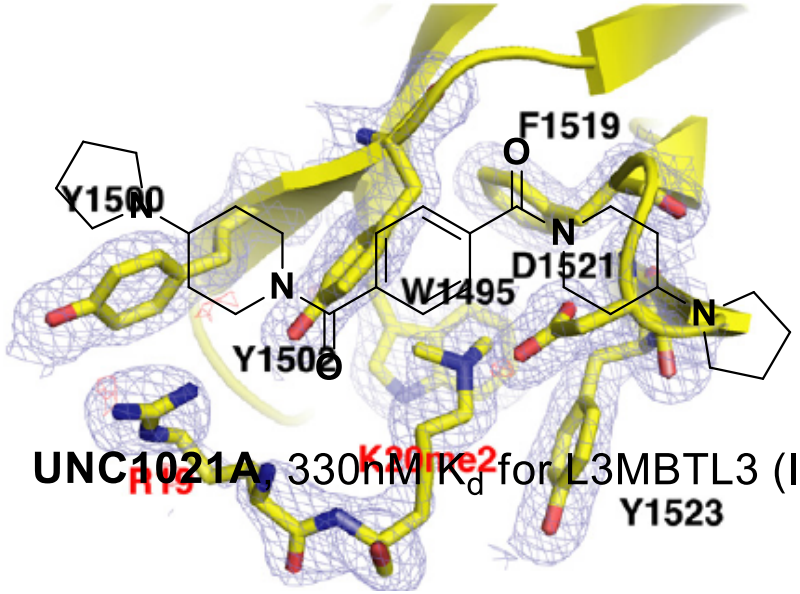


Wang, W.K. *et al. Malignant Brain Tumor Repeats: A Three-Leaved Propeller Architecture with Ligand/Peptide Binding Pockets. Structure 11*, 775-89 (**2003**)

J. Med. Chem. **2011**, *54*, 2504.
MedChemComm **2012**, *3*, 45.

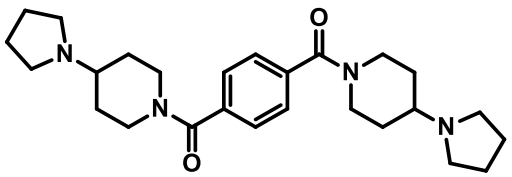
How to increase affinity?

- Change the target – tandem tudor domains (*e.g.* 53BP1, ca. 1 mM binder to H4K20me2) have two binding sites, maybe higher affinity is possible

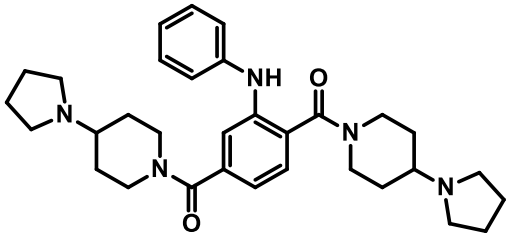


UNC1021A, 330nM K_d for L3MBTL3 (ITC)

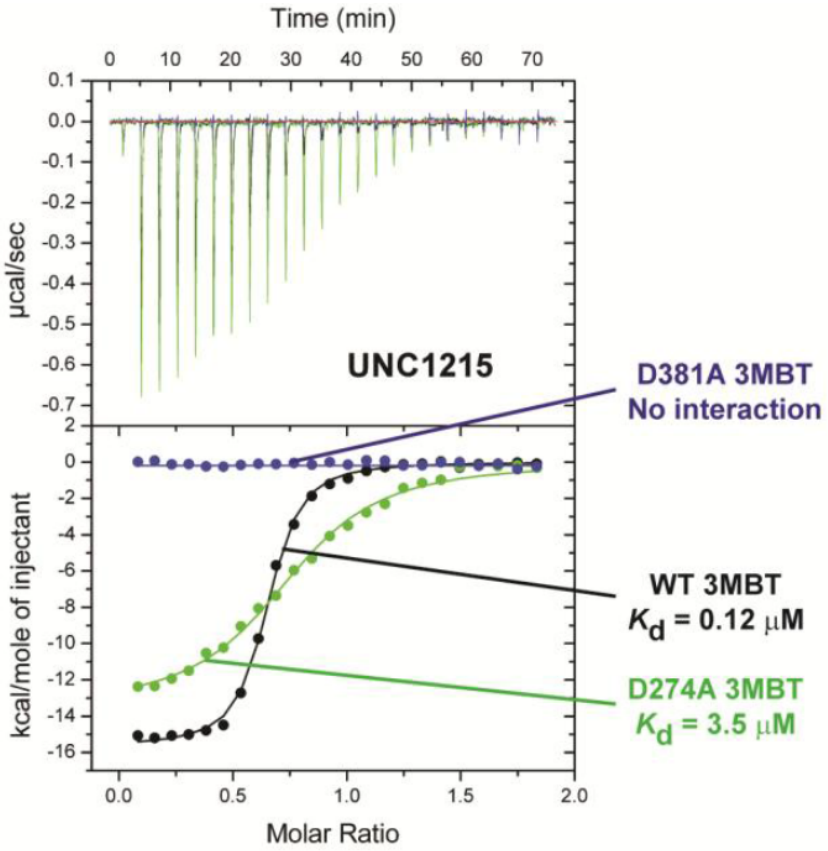
L3MBTL3 Small Molecule Inhibitors

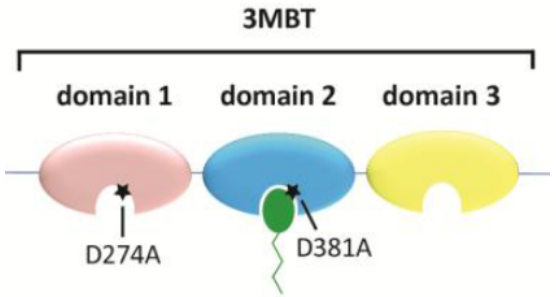


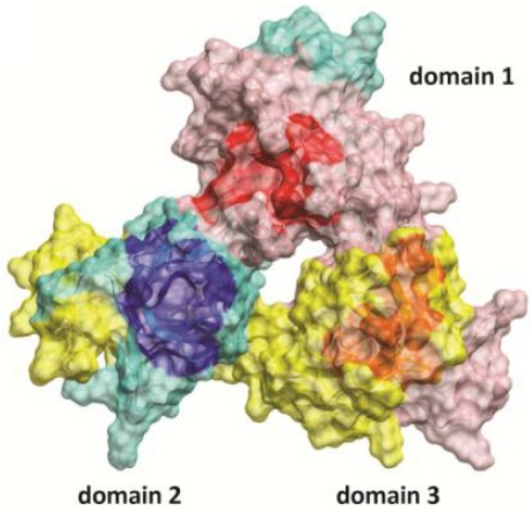
UNC1021



UNC1215

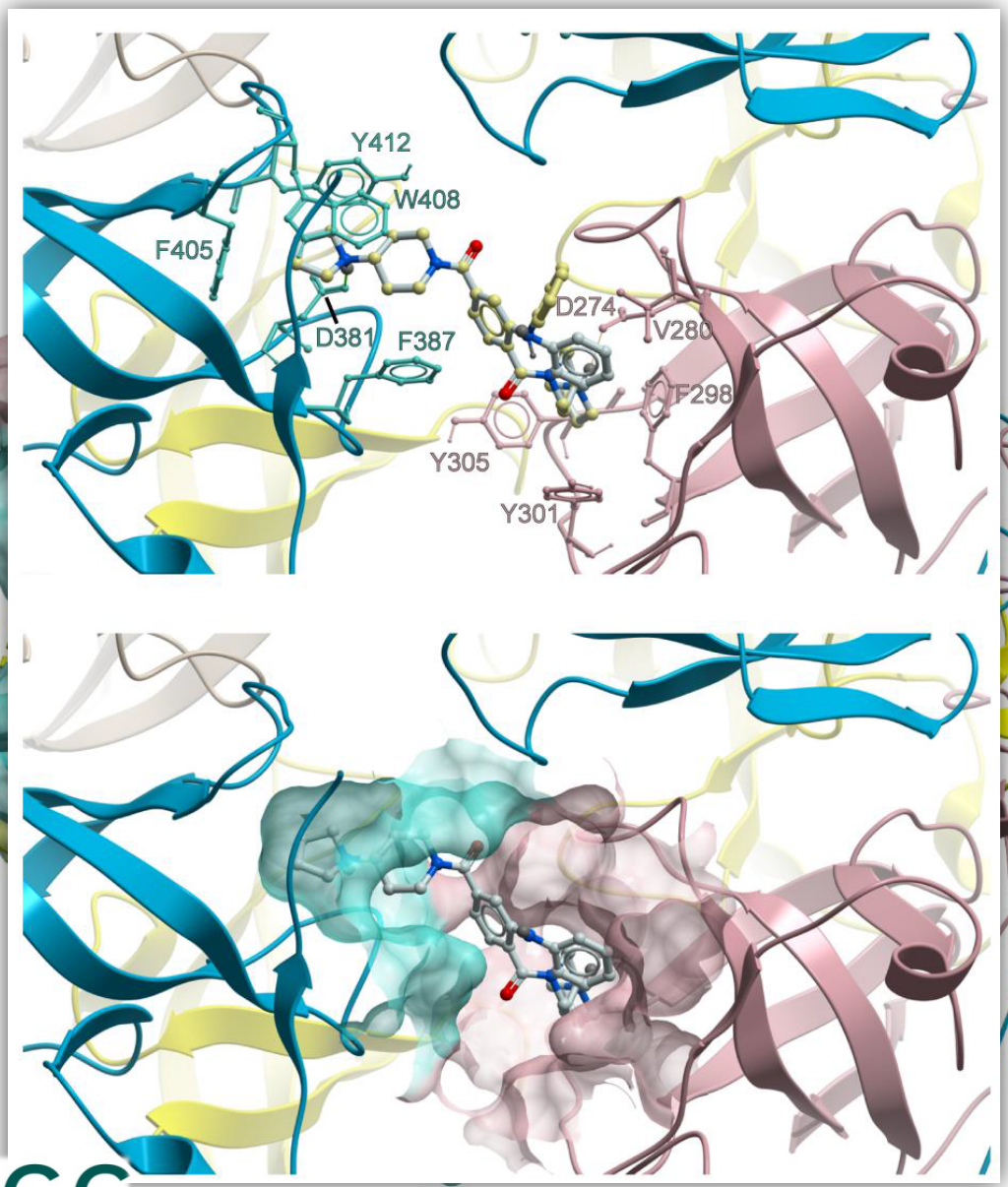


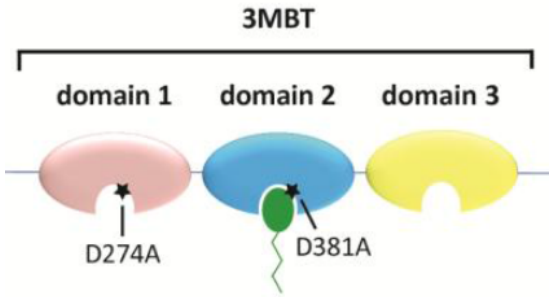




James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

L3MBTL3-UNC1215 Co-Crystal Structure



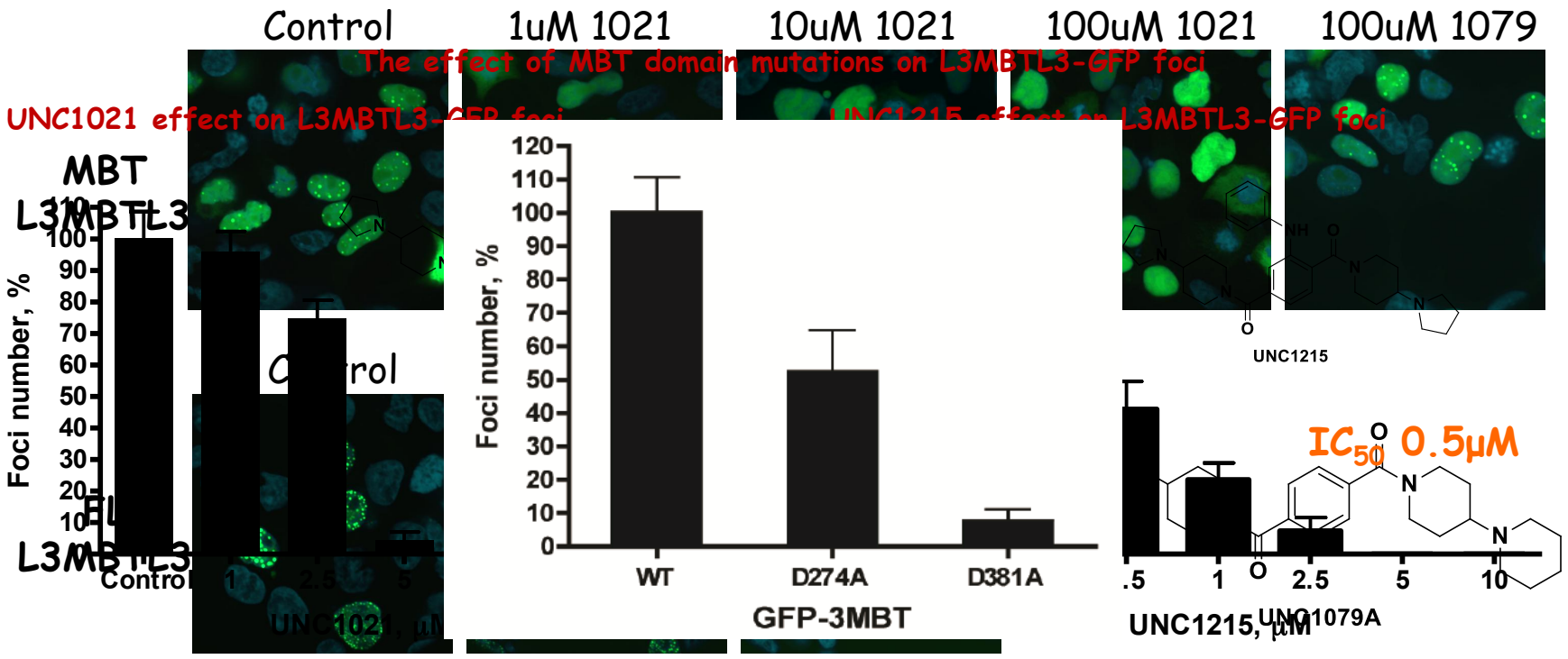


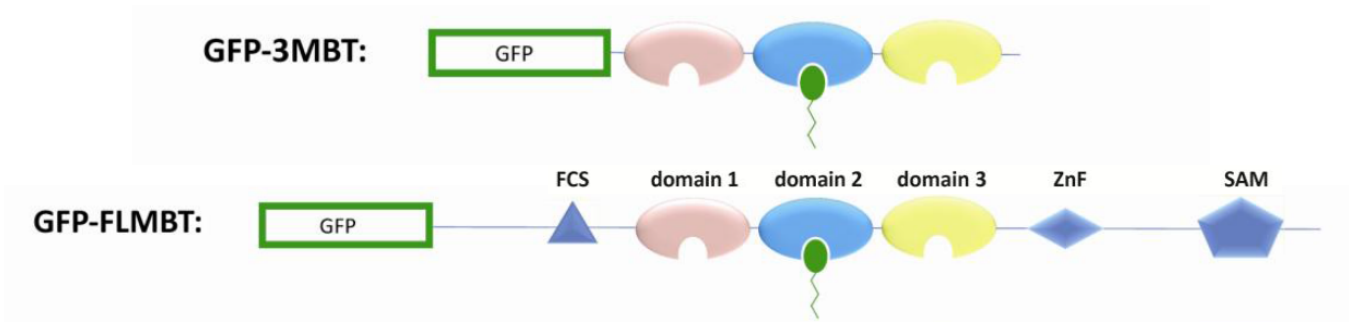
SGC

James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

GFP-L3MBTL3 Localization

L3MBTL3 inhibitors are effective at reducing MBT foci

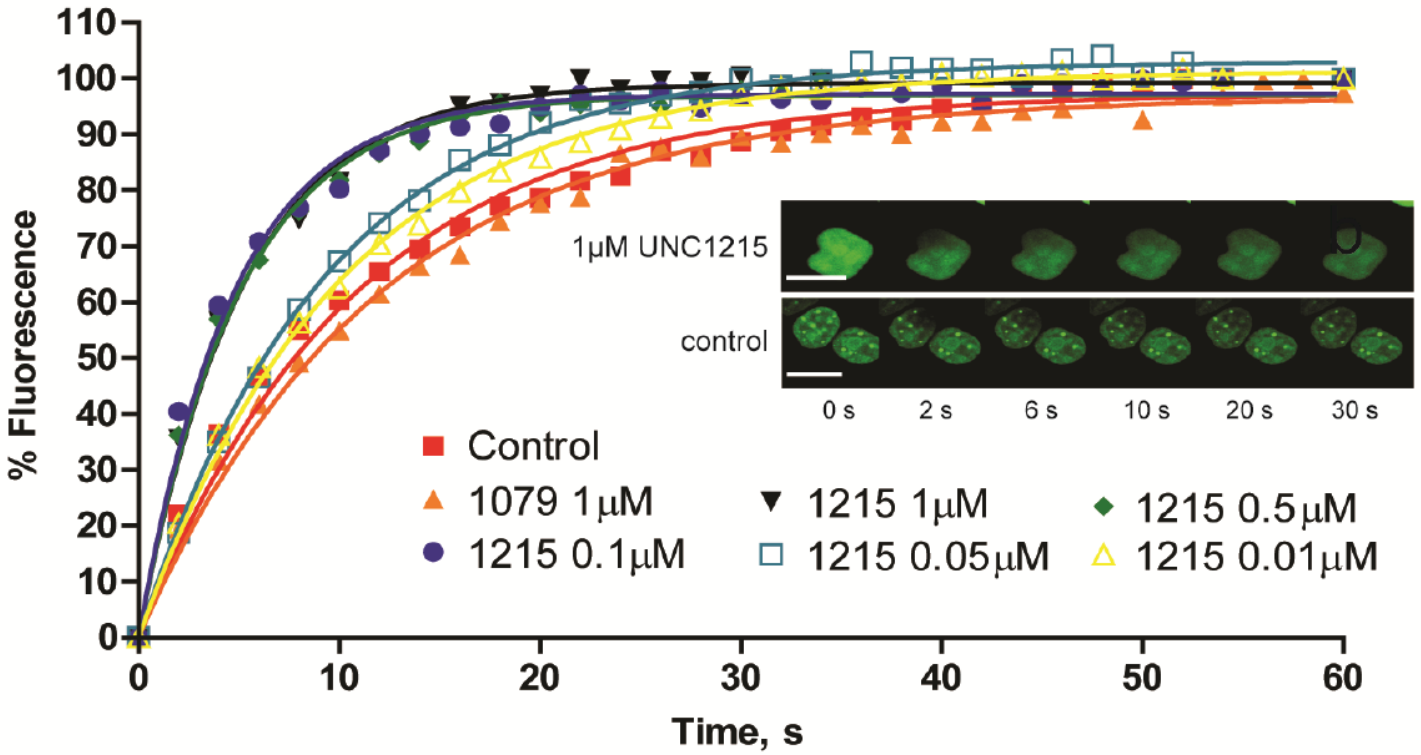




James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

GFP-L3MBTL3 FRAP

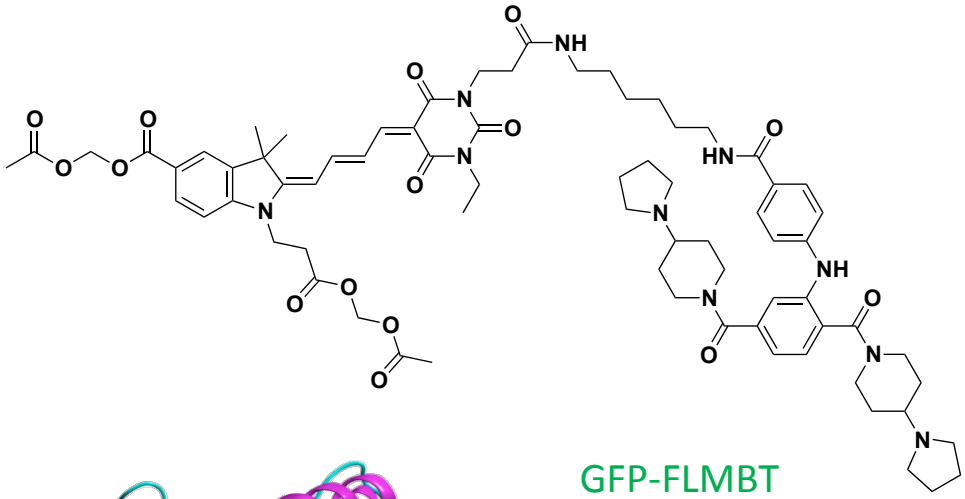
UNC1215 increases L3MBTL3 (MBT only) mobility in a dose response manner



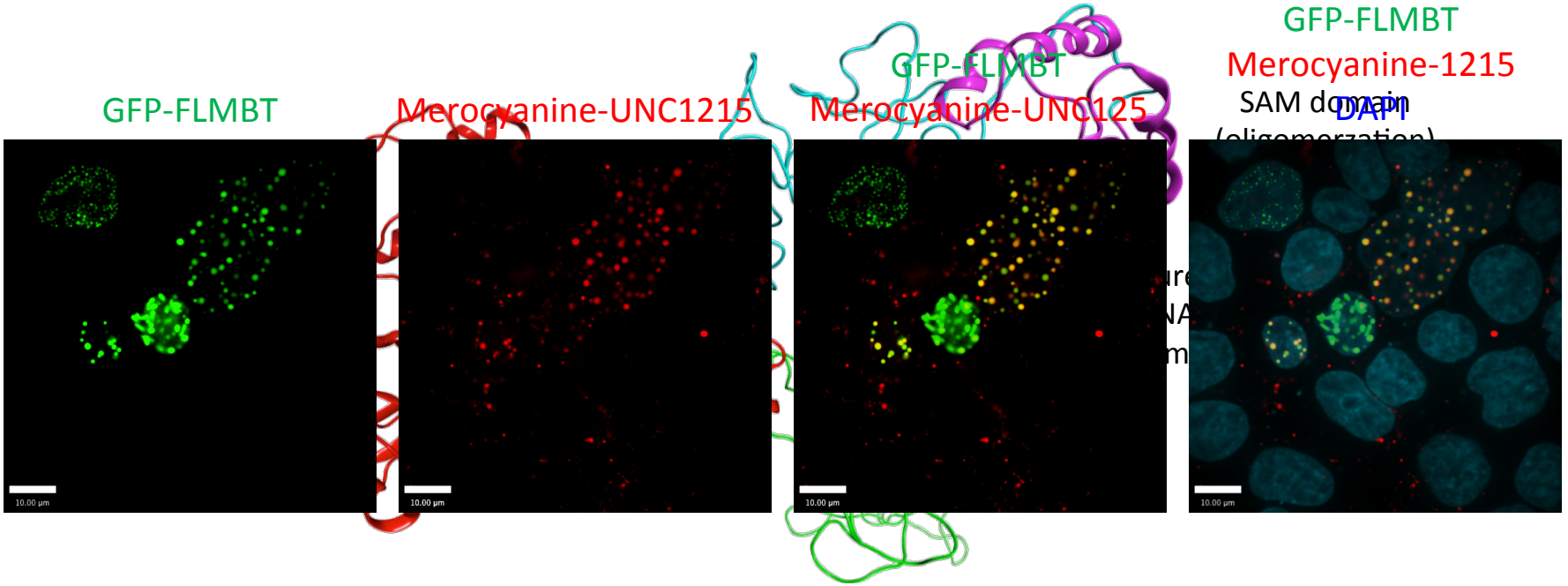
• L3MBTL3 D274A (domain 1) and D381A (domain 2) mutants have higher mobility than WT in FRAP assay in the context of both full length and MBT domain only proteins

James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

Fluorescent UNC1215



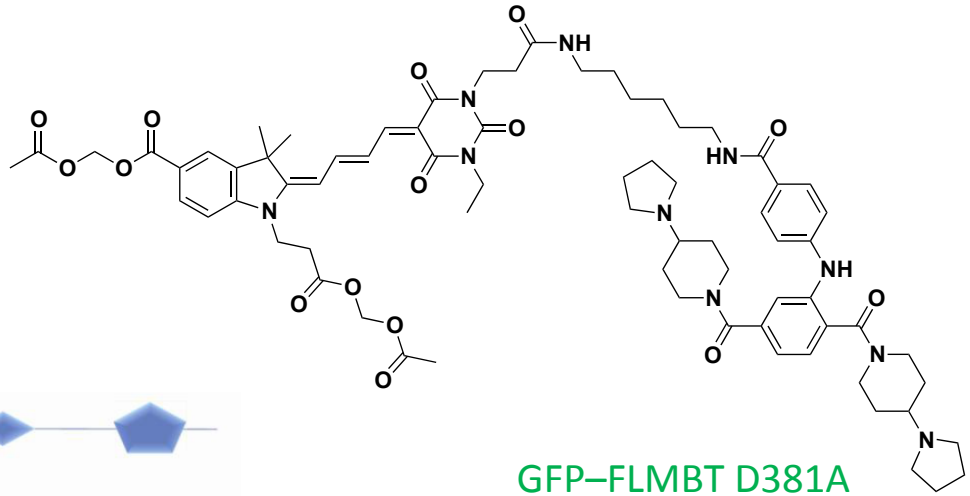
Does UNC1215 bind the full length L3MBTL3 protein?



Full-length GFP-L3MBTL3 co-localizes with merocyanine-UNC1215 in the nucleus, but not with the merocyanine dye alone

James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

Fluorescent UNC1215



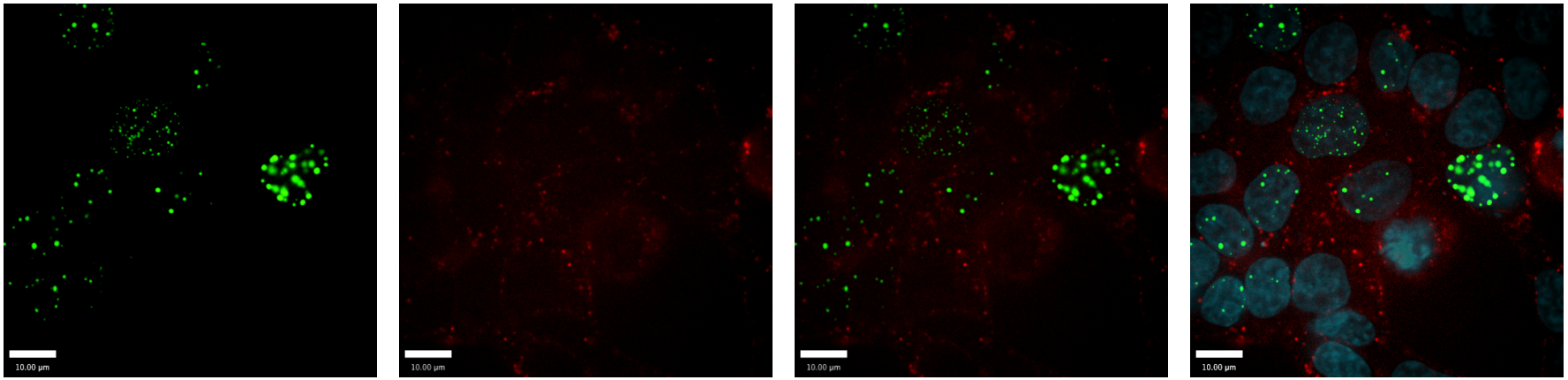
Does UNC1215 bind the full length L3MBTL3 protein?

GFP–FLMBT D381A
Merocyanine-1215
DAPI

GFP–FLMBT D381A
Merocyanine-UNC125

GFP–FLMBT D381A

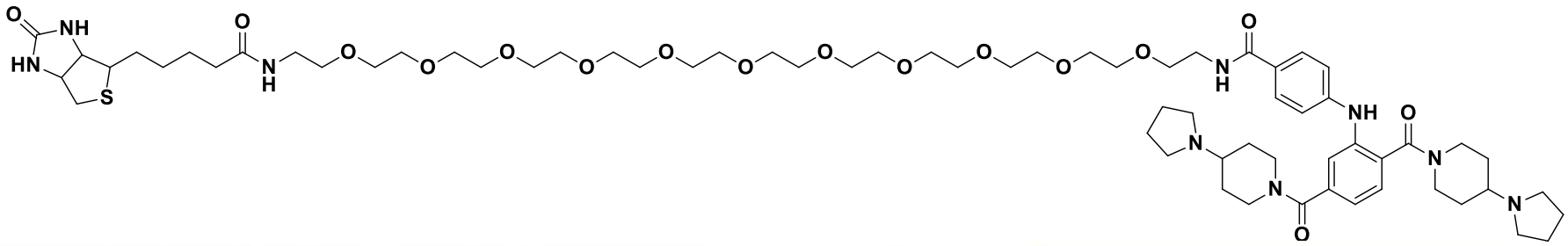
Merocyanine-UNC1215



Full-length GFP-L3MBTL3 domain 2 mutant does not co-localize with merocyanine-UNC1215

James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

UNC1215 Selectivity Profiling



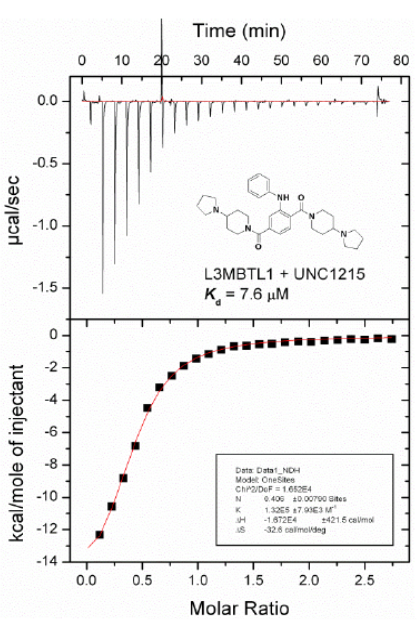
Alphascreen IC_{50} [μM]	L3MBTL1	L3MBTL3	L3MBTL4	SFMBT	MBTD1	CBX7	53BP1	UHRF1	PHF23	JARID1A
	MBT domains					Chromo Domain	Tudor Domains		PHD Fingers	
UNC1021	**3** (R^2 = 0.93, n = 44)	**0.04** (R^2 = 0.94, n = 44)	**16** (R^2 = 0.72, n = 35)	**> 30** (n = 33)	**11** (R^2 = 0.85, n = 29)	**> 30** (n = 31)	**17** (R^2 = 0.76, n = 45)	**>30** (n = 33)	**>30** (n = 6)	**>30** (n = 6)
UNC1215	**2** (R^2 = 0.93, n = 17)	**0.04** (R^2 = 0.93, n = 17)	**11** (R^2 = 0.63, n = 21)	**> 30** (n = 18)	**6** (R^2 = 0.71, n = 11)	**> 30** (n = 19)	**4** (R^2 = 0.90, n = 12)	**>30** (n = 18)	**>30** (n = 15)	**>30** (n = 15)
UNC1079	**> 30** (n = 6)	**21** (R^2 = 0.72, n = 6)	**>30** (n = 6)	**>30** (n = 5)	**3** (R^2 = 0.91, n = 5)	**>30** (n = 5)	**> 30** (n = 8)	**>30** (n = 5)	**>30** (n = 6)	**>30** (n = 6)

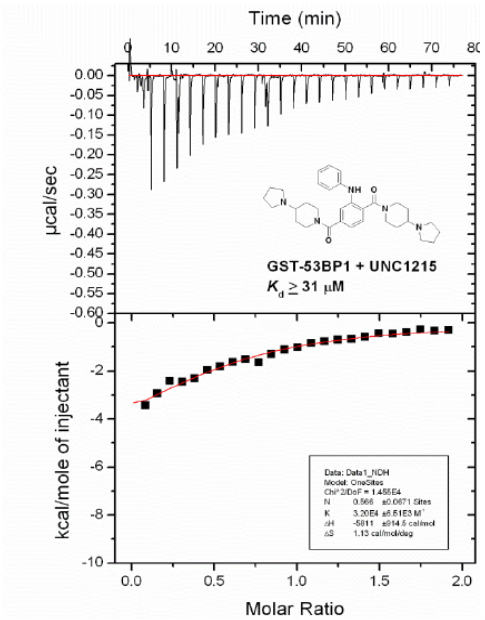
- All proteins (except MRG15) are binders of the H4K20me1-2 mark

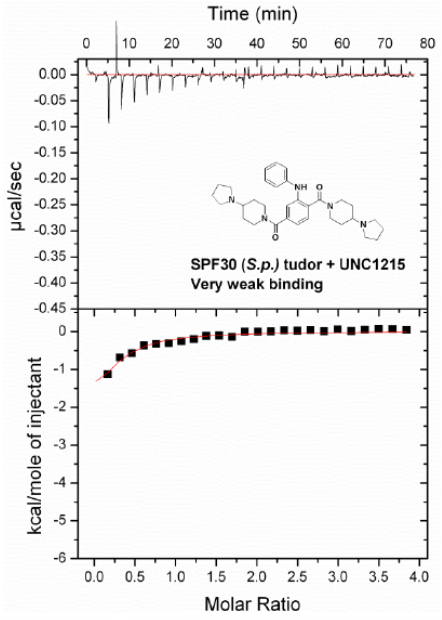
Bedford Lab, MD Anderson

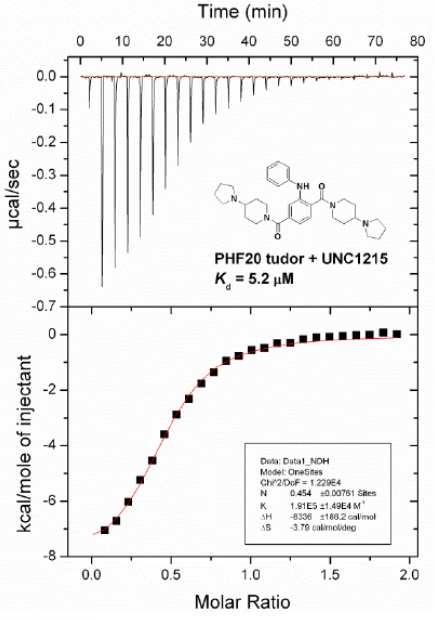
James, L. I. et al. *Nat. Chem. Biol.* **2013**, *3*, 184.

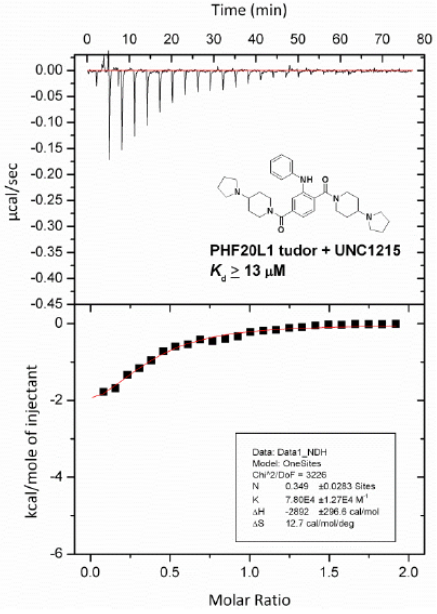
UNC1215 Selectivity Profiling

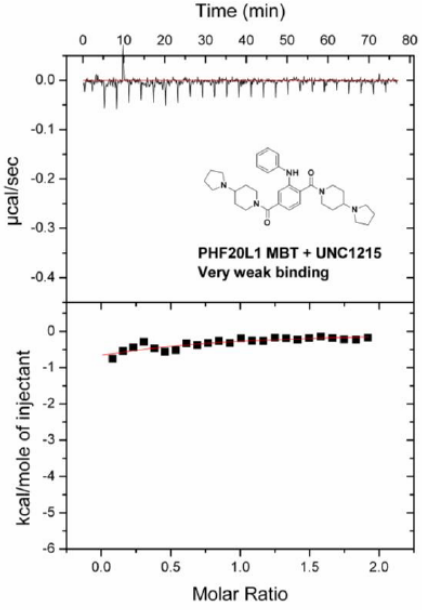


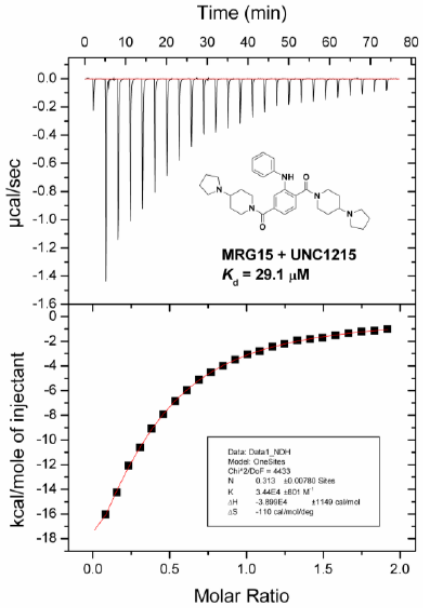












UNC1215 Selectivity profiling

Target Category	Target Activity		
Within methyl-lysine reader target family	**Target**	**IC_{50} (μM)[a]**	**K_d (μM)[b]**
	L3MBTL3	0.04	0.12
	L3MBTL1	2	9.4
	53BP1	4	> 31
	PHF20 Tudor	NT	5.6
	[illegible]	[illegible]	[illegible]
Histone methyltransferases	< 50% inhibition at 250 μM versus 10 targets[c]		
Bromodomains	T_m shift < 0.5 °C at 10 μM versus 12 targets[d]		
	[illegible]	[illegible]	[illegible]
	M2	0.072	30% at 30 μM[g]
	M3	0.89	NT
	M4	0.40	NT
	M5	4.3	NT
Kinase Selectivity Panel	< 15% inhibition at 10 μM versus 49 kinases		
	Target	% Inhibition at 10 μM	
	FLT3	64%	

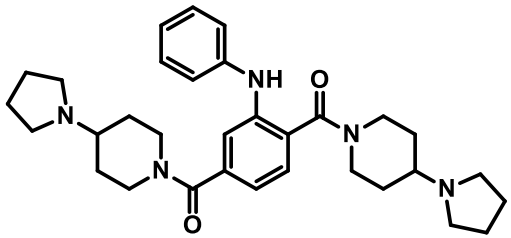
Non-toxic in cell titer glow assay in HEK293 cells up to 100 μM

"When one admits that nothing is certain one must, I think, also admit that some things are much more nearly certain than others."

Bertrand Russell

[a]Alphascreen assays results. [b]ITC results. [c]Radioactive SAM methyl transfer assay results. [d]Differential scanning fluorimetry results. [e]Radioligand binding assay results. [f]Ca^{2+} mobilization assay results. [g]cAMP biosensor assay results.

UNC1215's path to probedom



UNC1215

Quality Chemical Probes:

- Molecular profiling
- Mechanism of action
- Identity of the active species
- Proven utility as a probe
- Availability

Chen (UNC)
duced DNA
age repair

Jack Greenblatt
(U. Toronto)
Proteomics

Mark Bedford (MD Anderson)
Reader profiling
Chromatin Biology

Sean Taverna (Hopkins)
Tetrahymena

Hanno Hock (Harvard)
IR sensitivity in L3MBTL1 knockout MEF's

Bryan Roth (UNC)
CNS effects

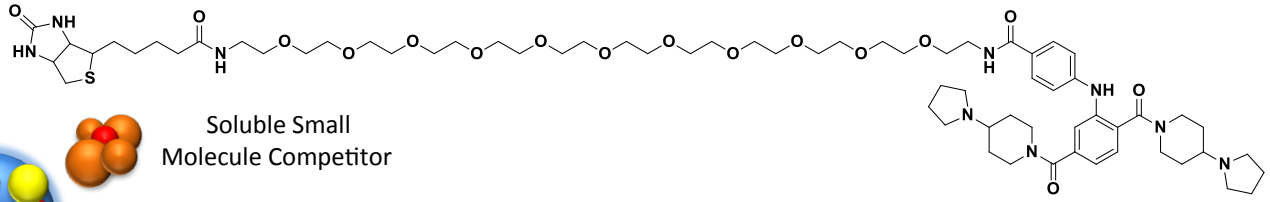
Brian Strahl (UNC)
Chromatin
Biochemistry

Eli Lilly
Open Innovation Drug Discovery

David Margolis (UNC)
Effects on HIV-1 latency

SGC

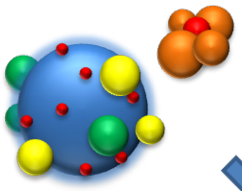
Understanding L3MBTL3 Function



Cell Culture

Regular (Light)

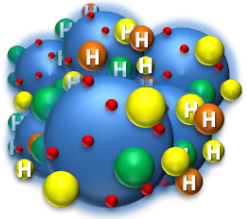
SILAC (Heavy)
Lysine-$^{13}C_6$ &
Arginine-$^{13}C_6{}^{15}N_4$



Soluble Small Molecule Competitor

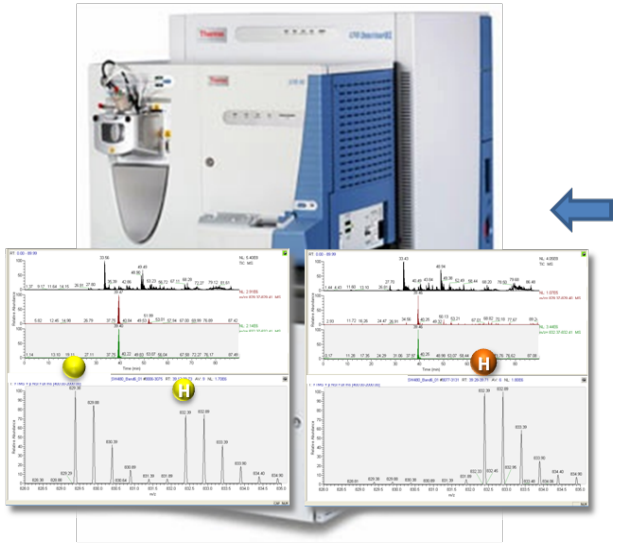
Affinity Enrichment

Wash
Mix 1:1



SDS PAGE

Excise Gel Bands
Tryptic Digestion



LC/MS/MS Data Acquisition

measuring differences in the ratio of SILAC (heavy):regular (light) proteins.

H:L ratio > 2:1 (target)

Experimental variations:

1. Active competitor
2. "Flip"
3. Inactive analog as competitor

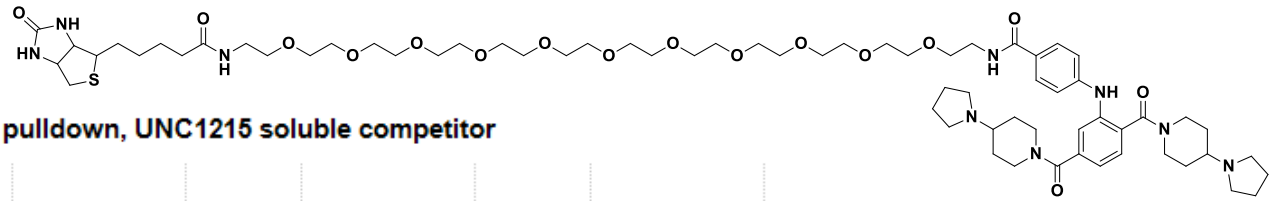
Candidate Proteins

1. Target / off-targets
2. Binding partners

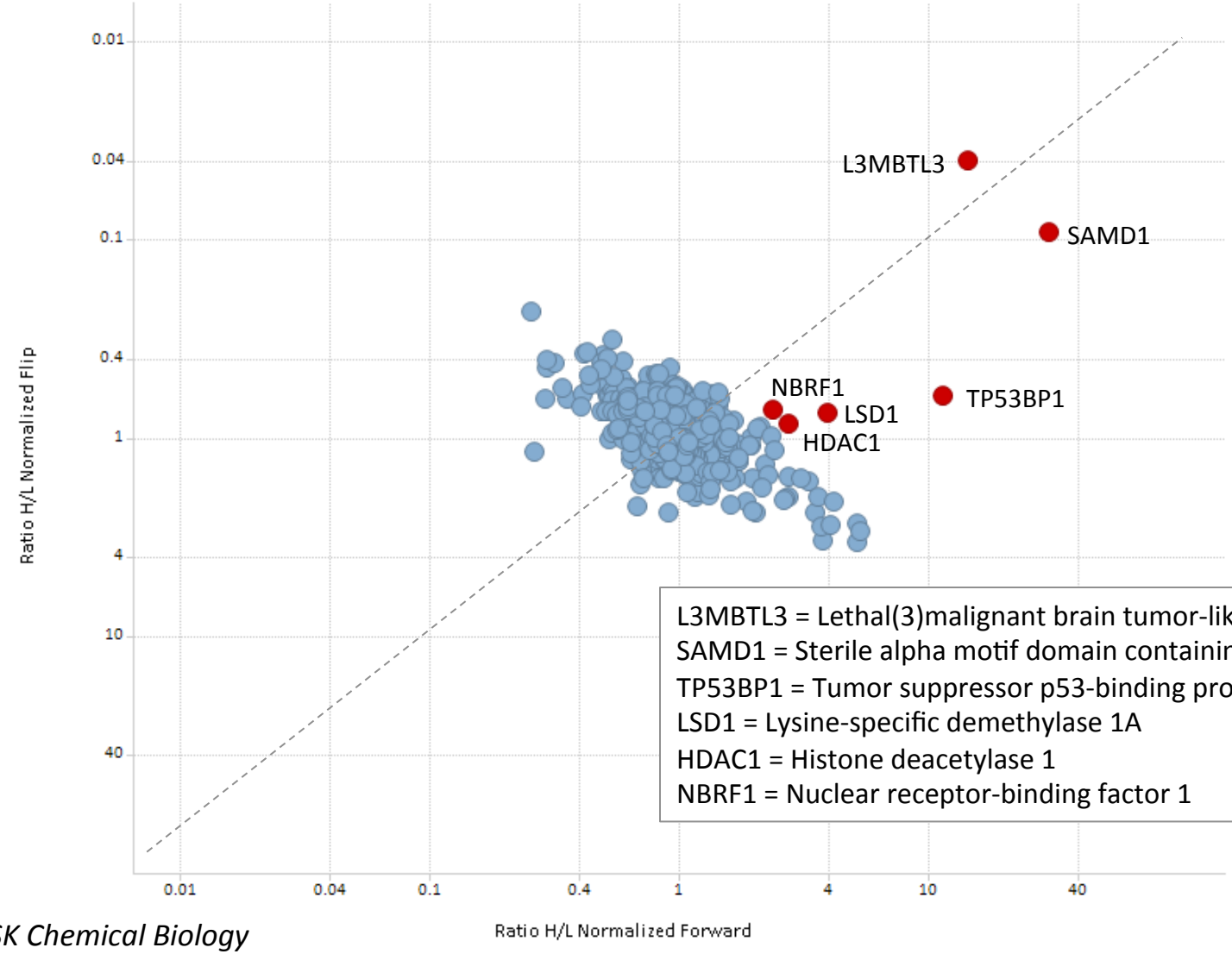
GSK Chemical Biology

Stable Isotope Labeling by Amino acids in Cell culture

Understanding L3MBTL3 Function



SILAC (G401 cells): Biotin-UNC1215 pulldown, UNC1215 soluble competitor

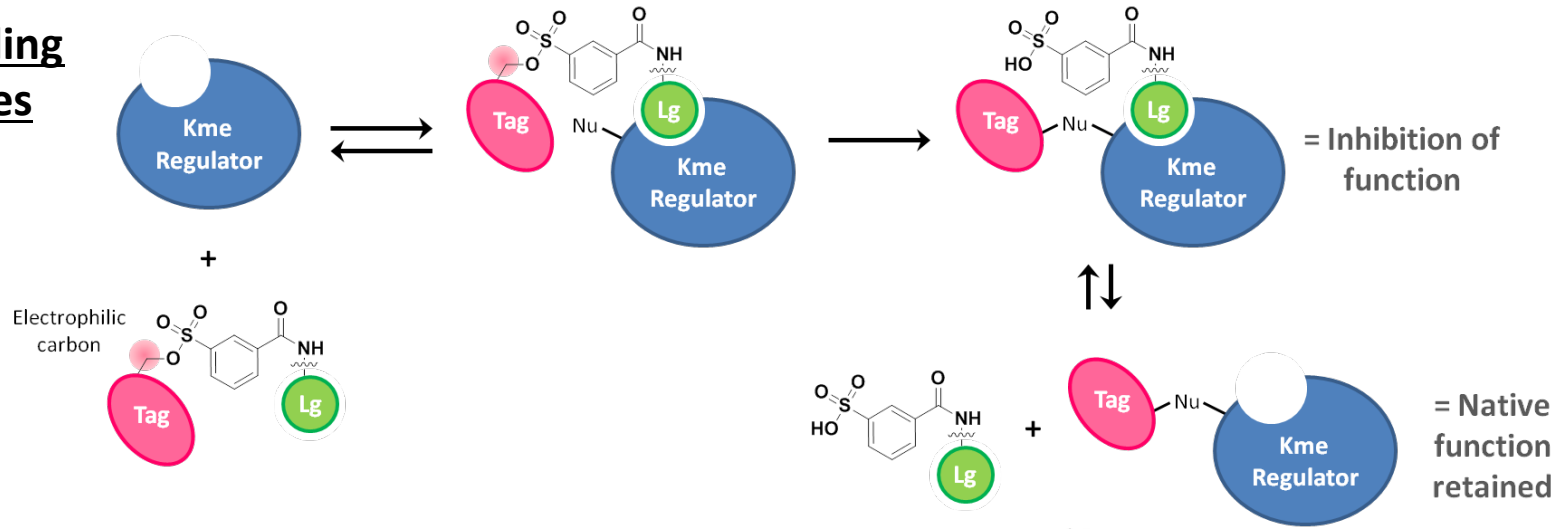


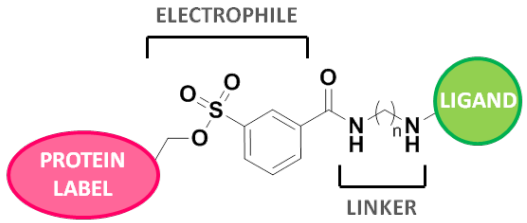
L3MBTL3 = Lethal(3)malignant brain tumor-like protein 3
SAMD1 = Sterile alpha motif domain containing protein 1
TP53BP1 = Tumor suppressor p53-binding protein 1
LSD1 = Lysine-specific demethylase 1A
HDAC1 = Histone deacetylase 1
NBRF1 = Nuclear receptor-binding factor 1

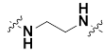
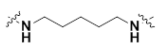
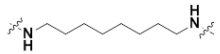
GSK Chemical Biology

Understanding L3MBTL3 Function

Affinity labeling technologies





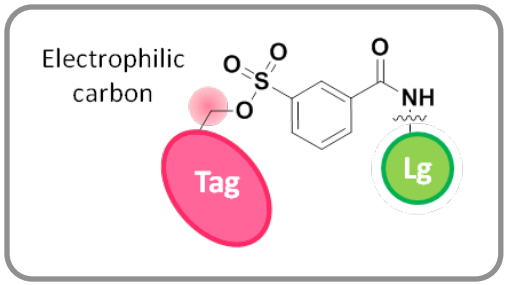
PROTEIN LABEL	ELECTROPHILE	LINKER	LIGAND
Biotin, Deuterated biotin	Tosylate (shown above)		Known compounds for Kme readers (L3MBTL3, L3MBTL1)
Fluorescent Dyes (coumarin, Mero76)	Acyl imidazole		Kme reader compounds in the pipeline (53BP1, UHRF1, CBX7, PHF23, JARID1A)
Photo-cross-linkers (diazirine), Dual biotin/cross-linkers			Known compounds for Kme writers (G9a, EZH2, DOT1L, SMYD2)
Azide			Kme writer compounds in the pipline (SETD8)

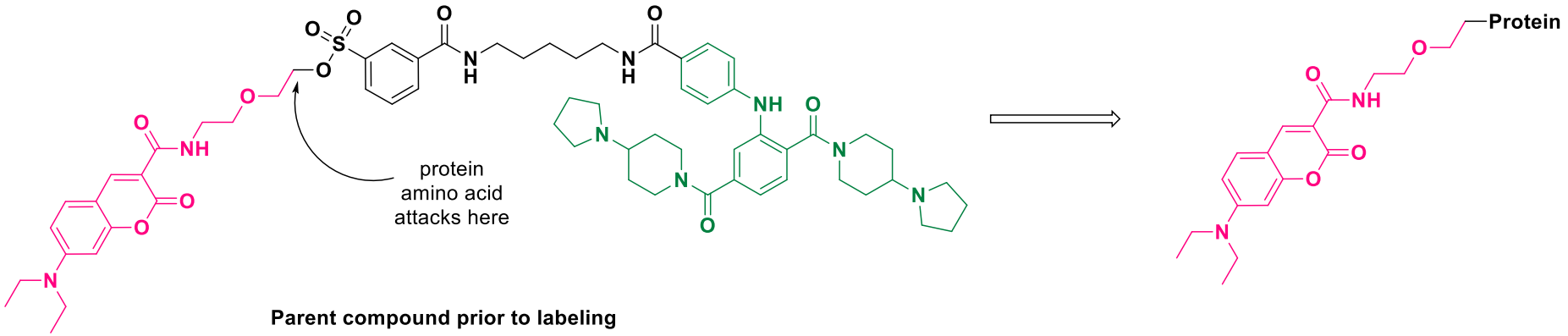
Goal: to covalently modify endogenous L3MBTL3 without genetic manipulation in a cellular context

1) Photo-cross-linking & MS experiments to identify protein-protein interactions
2) Confocal microscopy experiments to visualize protein localization
3) ChIP-seq experiments to analyze protein interactions with DNA without the need for protein specific antibodies

Understanding L3MBTL3 Function

Affinity labeling technologies

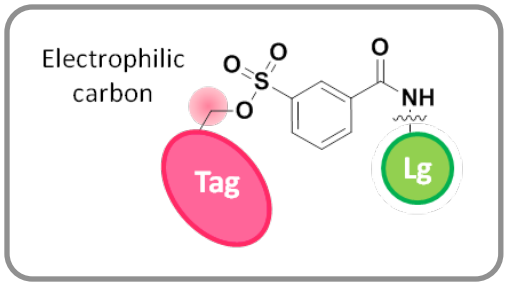




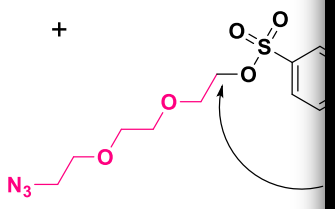
Parent compound prior to labeling

Understanding L3MBTL3 Function

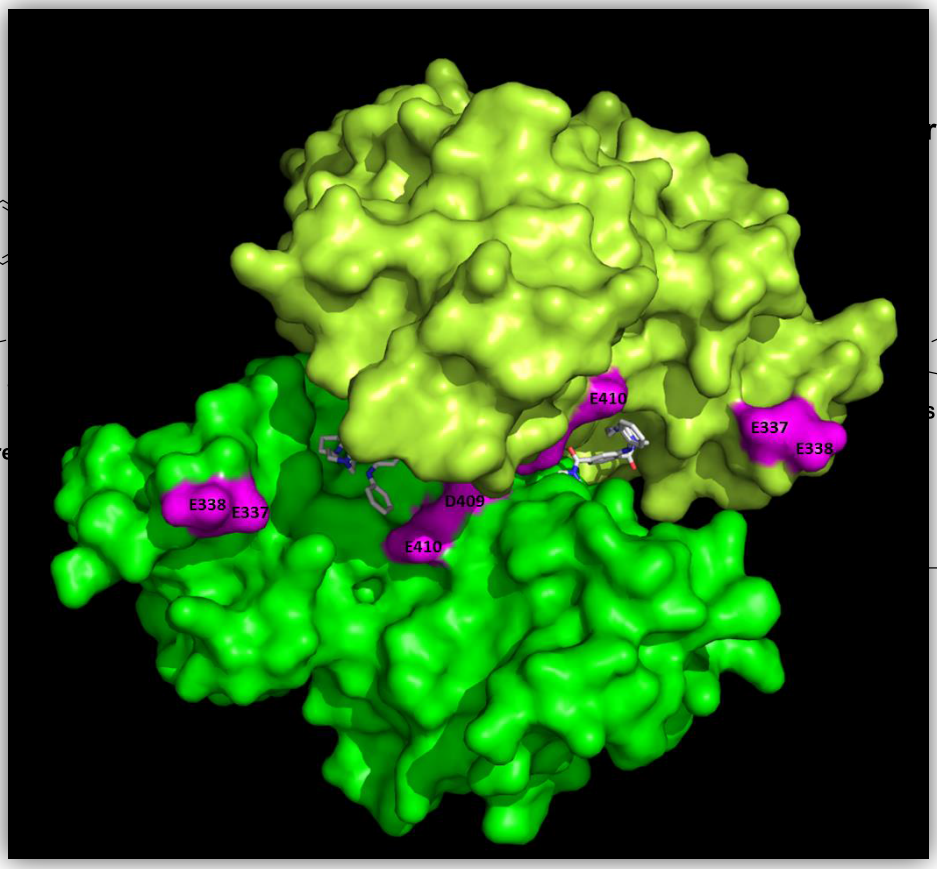
Affinity labeling technologies



protein +

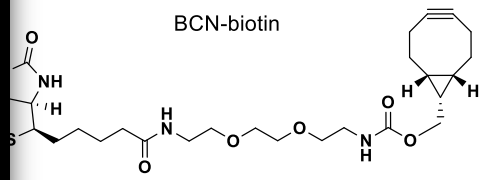


Pare



rotein

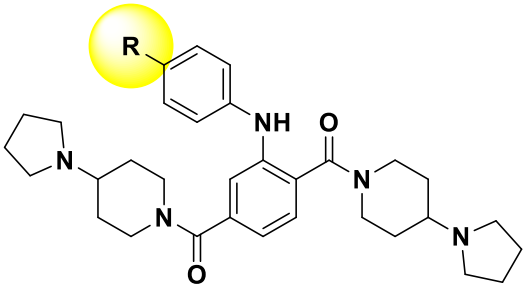
BCN-biotin



protein

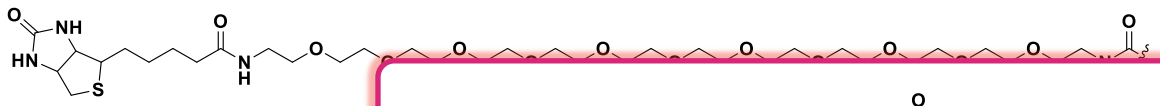
GSK Chemical Biology

Turning chemical probes into useful tools

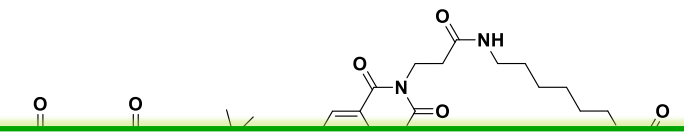


UNC1215:
Potent L3MBTL3 inhibitor

R =

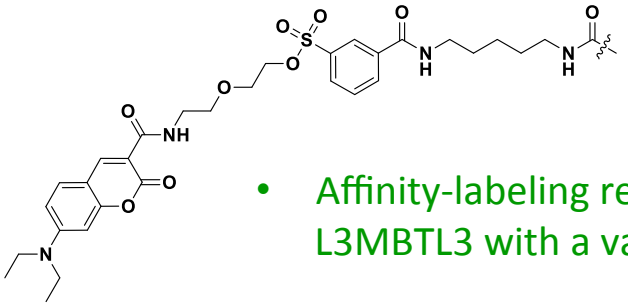


- Tagged reagent used to p
reader proteins



gent used to visualize
TL3 in cells

R =



- Affinity-labeling reagent used to covalently modify L3MBTL3 with a variety of chemical tags

MBT Acknowledgements

UNC CICBDD

Bill Janzen
Tim Wigle
Jian Jin
Martin Herold
Lindsey Ingerman James
Michelle Camerino
Brad Dickerson
Dmitri Kireev
Victoria Korboukh
Jacqueline Norris
Chris MacNevin (joint with Hahn Lab)

Funding

NIH: RC1, R01
Carolina Partnership/Lineberger Cancer Center

Structural Genomics Consortium, Toronto

Cheryl Arrowsmith
Peter Brown
Dalia Barsyte-Lovejoy
Liuba Krichevsky
Nan Zhong
Robert Lam
Matthieu Schapira
Abdellah Allali-Hassani
Masoud Vedadi
Valerie Campagna-Slater
Natalie Nady
Jinrong Min

MD Anderson

Mark Bedford

Stanford

Dennis Bua
Kaitlyn Coil
Or Gozani