Building a NEW Cancer Therapy

PACYLEX
ACCELERATING THE PACE OF CANCER CARE

Michael J. Weickert, PhD Michael.Weickert@pacylex.com

Pacylex Overview

New Cancer Mechanism:
Recently discovered mechanism of cancer proliferation exposed a new therapeutic target

New Drug:
First-in-kind, oral, small molecule drug for this target

- Lead drug PCLX-001 is water soluble and >90% orally bioavailable
- Predictive diagnostic test identifies cancer patients with key biomarker associated with target (personalized medicine)

Proof in Blood Cancers:
Eliminates tumors in 4 different mouse models of leukemia and lymphoma including one human drug-resistant tumor model; >10x more potent than ibrutinib or desatinib

Proof in Solid Tumor Cancers:
Inhibits tumor growth in mouse models of Breast and Lung cancer

Traction:
Accepted into Merck Accelerator, closed initial Seed round funds, 14-day tox dosing completed in rat and dog, pre-IND meeting completed, 3 Canadian clinical sites lined up, in discussions with MD Anderson Cancer Center in US for AML Phase 1, Phase 1 protocol written, CRO ready

Timeline in Drug Development:
IND and initial clinical dosing in < 1 year; follow precedent for 3-4 year clinical development and approval (Fast Track, Orphan eligible)

TEAM
CEO Michael J. Weickert, PhD
CSO Luc G. Berthiaume, PhD
CMO John Mackey, MD, FRCPC
COO Ryan Heit, MSc, MBA

FOUNDED : 2012
Non-dilutive capital to date - >$6M
Founder & Seed capital ~$2M

PROJECT STATUS: Pre-IND

COMPLETED: Animal efficacy, PK/PD, Biomarker monoclonal antibody, 14d tox, ADME studies, pre-IND meeting

NEXT STEPS: GLP tox studies (Late '19), IND (early '20), Phase I/IIa study (mid-'20)

SEEKING: $3 million to initiate Phase I clinical trials & expand indications, $25+ million to finish initial Phase II

PACYLEX
ACCELERATING THE PACE OF CANCER CARE

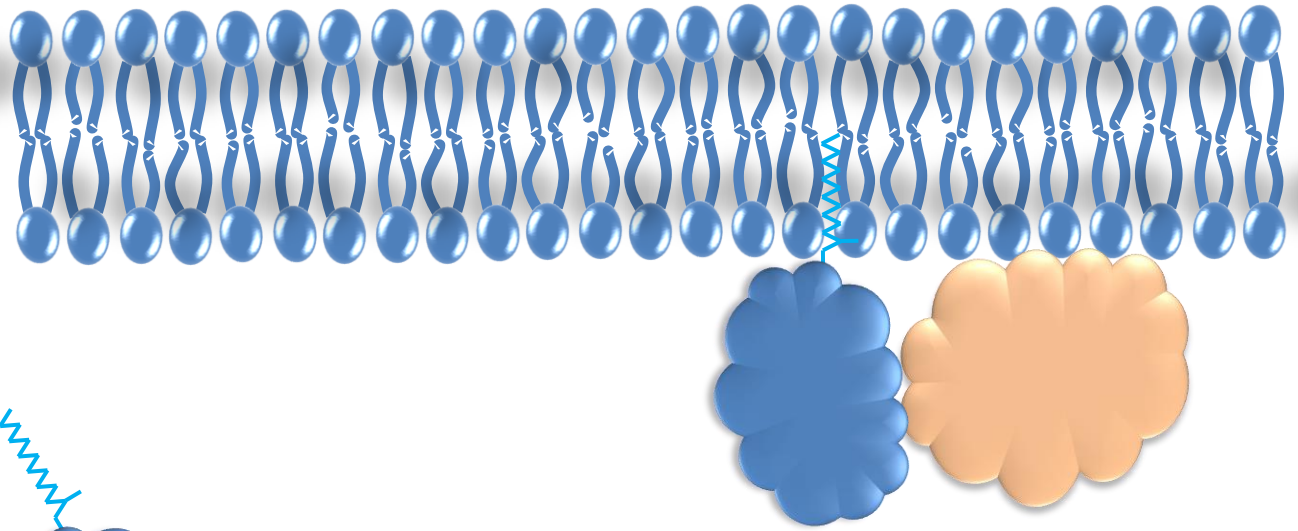
Myristoylation helps ~200 proteins attach to cell membranes to enable control of growth and metabolism

myristate

+ enzymes: NMT1 or NMT2

=

Protein

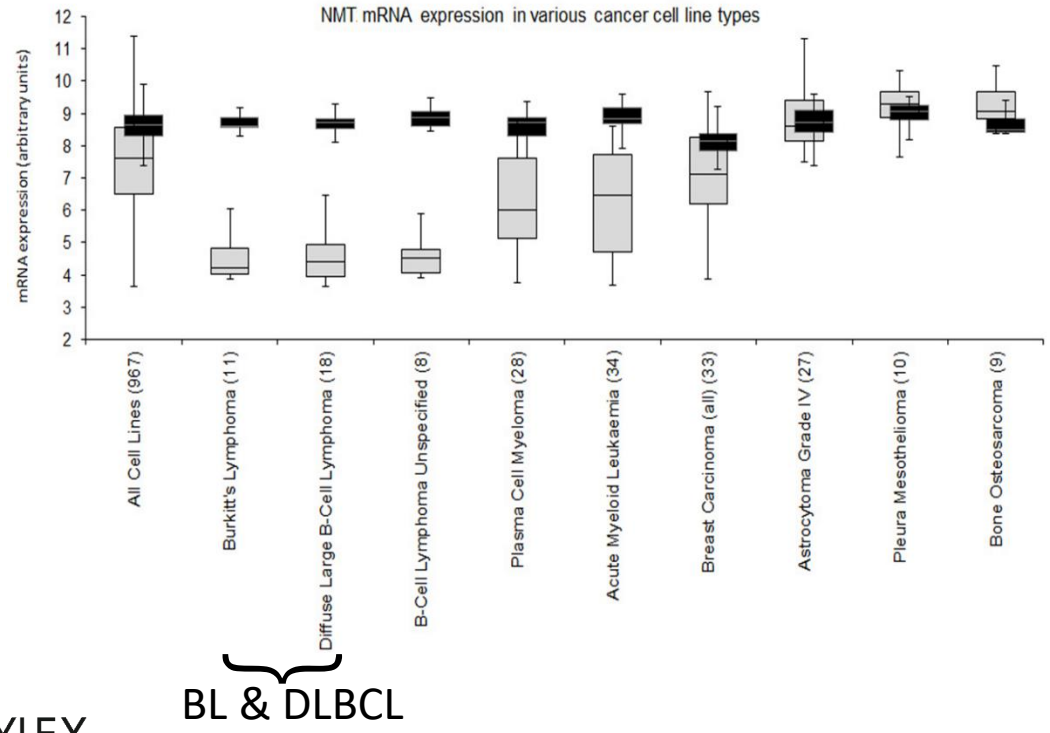


~200 proteins - most involved in homeostasis:
Control of normal growth and metabolism,
Typically through protein-protein interactions
in membrane complexes

PACYLEX
ACCELERATING THE PACE OF CANCER CARE

NMT2 expression is lost in numerous cancer types, is the lowest in lymphoma and is NOT compensated by an increase in NMT1 expression

Data extracted from www.CCLE.org



*

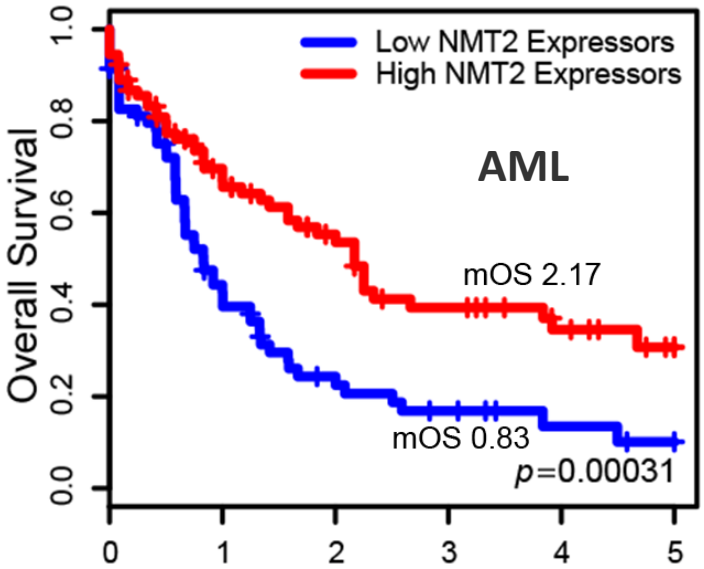
NMT1: Black

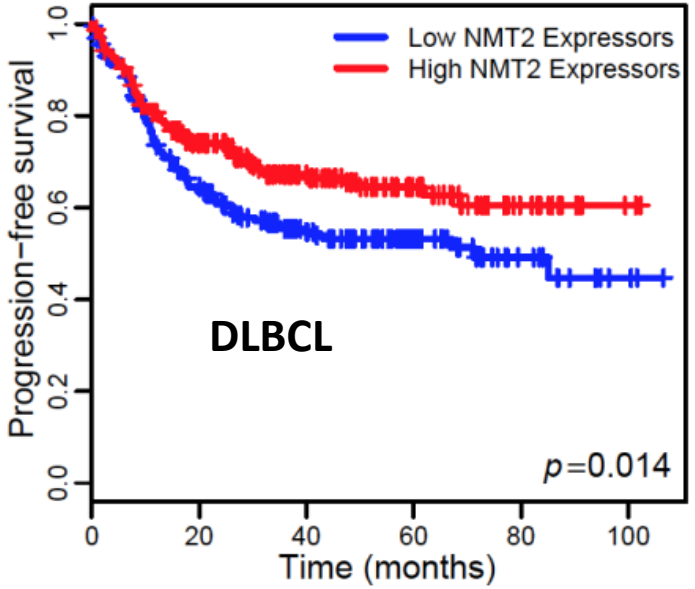
NMT2: Grey

*same trend seen in tumours

PACYLEX
ACCELERATING THE PACE OF CANCER CARE

Low NMT2 associated with higher mortality in patients with leukemia (AML) and lymphoma (DLBCL)

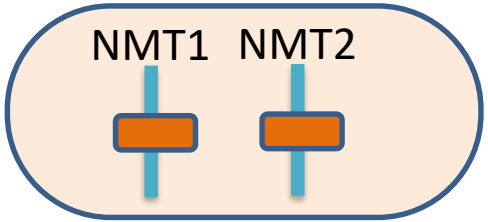




AML = Acute Myelogenous Leukemia; DLBCL = Diffuse large B-cell lymphoma (DLBCL); NMT = n-myristoyltransferase

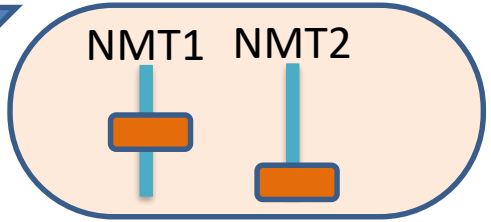
NMT2 may be a cancer switch

Normal NMT level = normal cell growth and metabolism



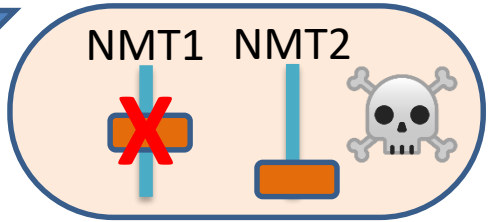
NMT = enzymes that modify proteins involved in growth and metabolism - to reach their active biological location

NMT2 switched off = uncontrolled cell growth = **cancer**



Happens in 19 different types of cancer, most often in blood cancer

BUT if you give these cancer cells an NMT inhibitor drug…



…the cancer cells die via apoptosis while normal cells are unaffected

Lead Drug = PCLX-001: Developed for Wellcome Trust program to treat African sleeping sickness

Part of a family of NMT-inhibitor drugs developed by University of Dundee (UK)

- $6M support from Wellcome Trust (UK medical charity)

Originally developed to treat African Sleeping Sickness

- Drug doesn't cross the blood brain barrier
- Unable to eradicate reservoir of parasites in brain so disease always came back
- Project cancelled

Published in top journal Nature in 2010

nature Vol 464|1 April 2010|doi:10.1038/nature08893

ARTICLES

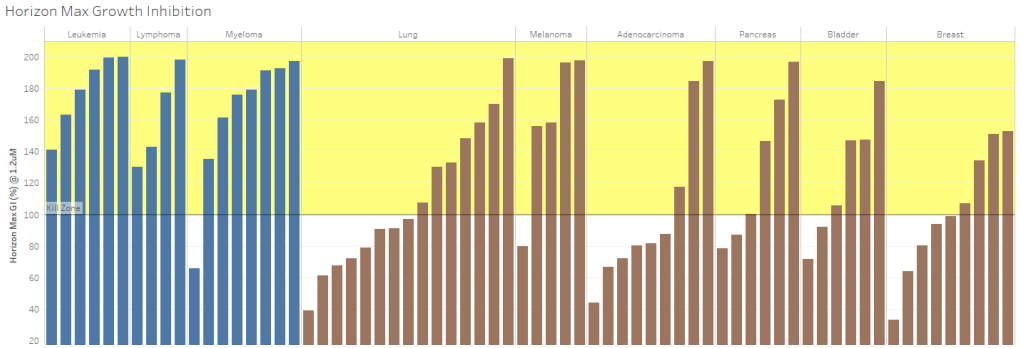
N-myristoyltransferase inhibitors as new leads to treat sleeping sickness

Julie A. Frearson[1], Stephen Brand[1], Stuart P. McElroy[1], Laura A. T. Cleghorn[1], Ondrej Smid[1], Laste Stojanovski[1], Helen P. Price[4], M. Lucia S. Guther[1], Leah S. Torrie[1], David A. Robinson[1], Irene Hallyburton[1], Chidochangu P. Mpamhanga[1], James A. Brannigan[3], Anthony J. Wilkinson[3], Michael Hodgkinson[4], Raymond Hui[5], Wei Qiu[5], Olawale G. Raimi[2], Daan M. F. van Aalten[2], Ruth Brenk[1], Ian H. Gilbert[1], Kevin D. Read[1], Alan H. Fairlamb[1], Michael A. J. Ferguson[1], Deborah F. Smith[4] & Paul G. Wyatt[1]

Pacylex licensed entire drug family and is repurposing a different molecule, with ideal properties for human NMTs, for cancer

PACYLEX
ACCELERATING THE PACE OF CANCER CARE

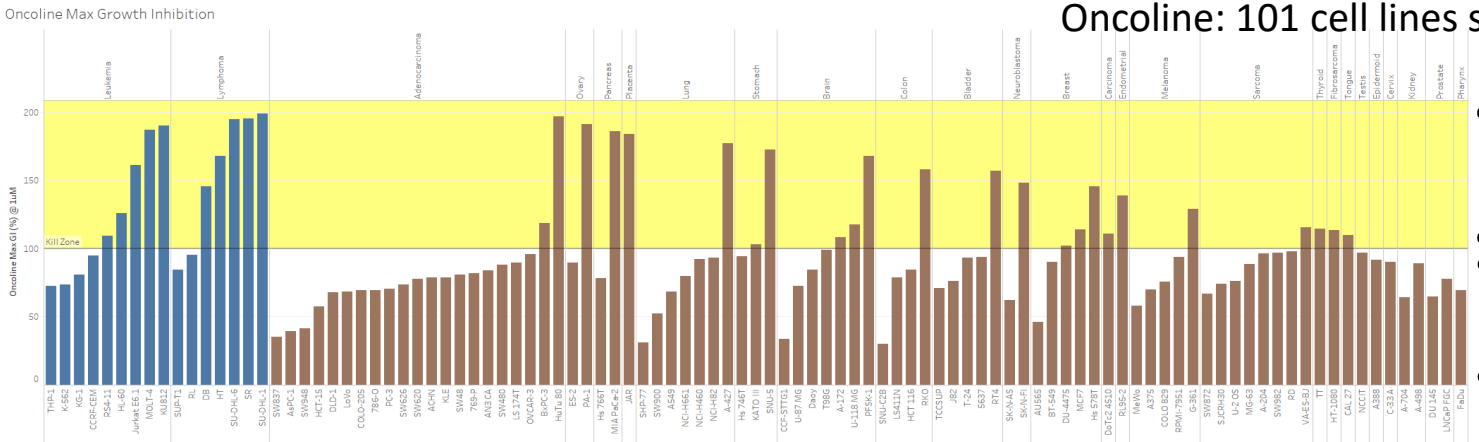
Robotic screen analysis of PCLX-001 mediated cell growth inhibition (GI) on 169 cell lines sorted by cancer type suggests hematological cancer cell lines are more vulnerable to NMT inhibition



Horizon: 68 cell lines screened

Cell death

Growth inhibition



Oncoline: 101 cell lines screened

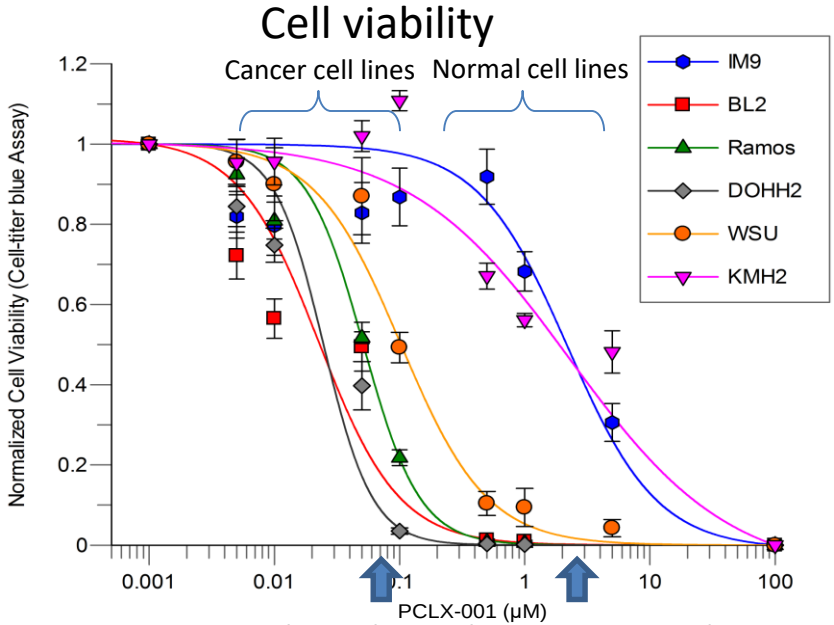
Cell death

Growth inhibition

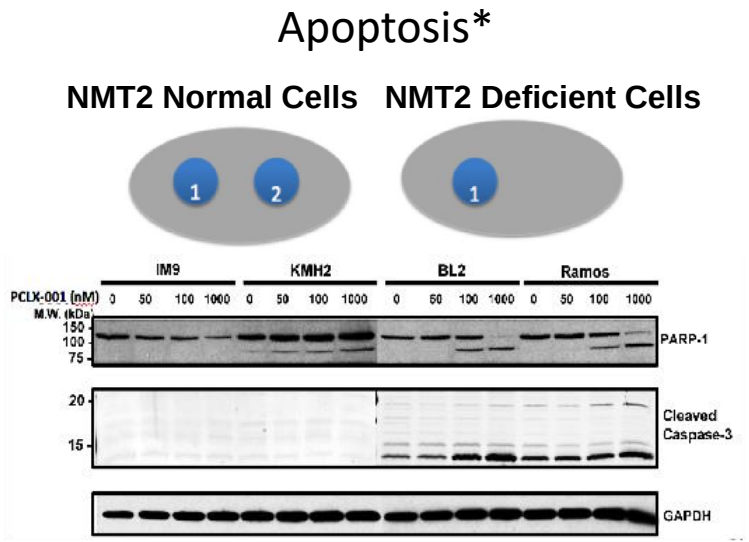
PACYLEX
ACCELERATING THE PACE OF CANCER CARE

PCLX-001 selectively kills cancer cell lines deficient in NMT2 by turning on apoptosis (cell death)

PCLX-001 selectively kills cancer cells deficient in NMT2 at a drug concentration to which normal cells are insensitive by disabling myristoylation which initiates apoptosis



PCLX-001 has a large therapeutic window



*indicated by cleaved PARP-1 and caspase-3

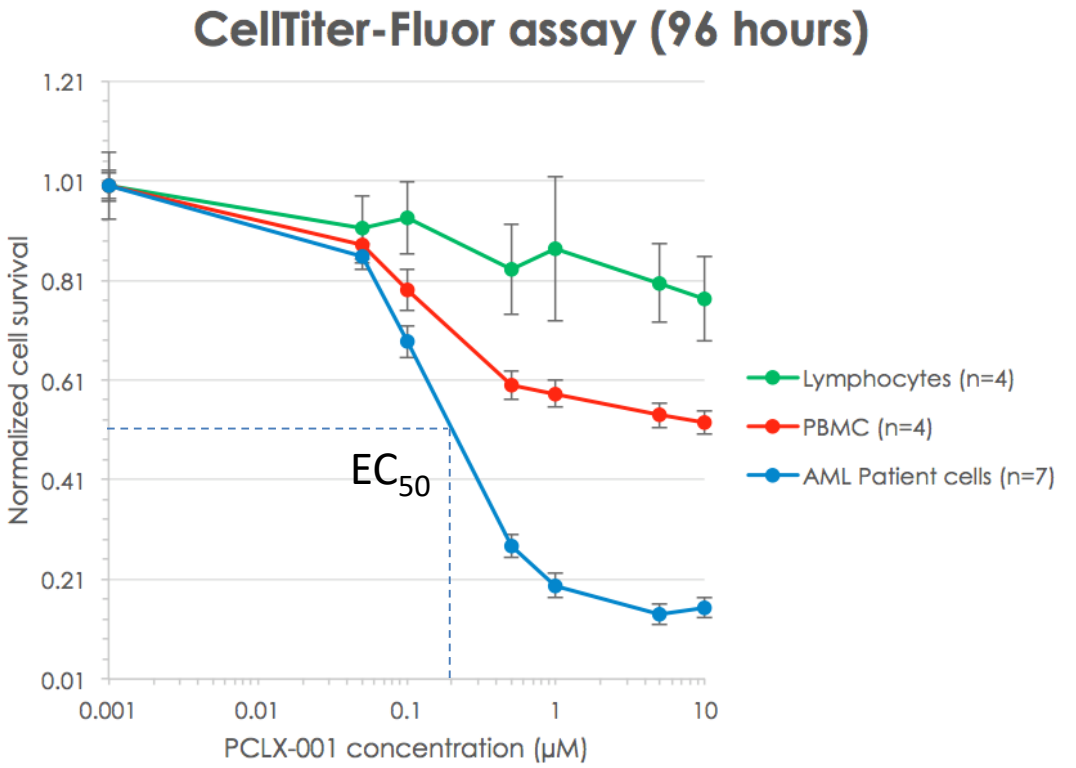
PACYLEX
ACCELERATING THE PACE OF CANCER CARE

PCLX-001 selectively kills cancer cells from patients: AML cells are >50 X more sensitive than normal cells

Normal and patient cancer cells treated with PCLX-001 for 96h then viability tested

AML cancer cells from patients are at least 50x more sensitive to PCLX-001 *ex vivo* (7 patients shown) than normal peripheral blood monocytic cells (PBMCs) or freshly isolated human monocytes (Lymphocytes).

- The EC_{50} of PCLX-001 in AML patient cells is ~200nM
- The EC_{50} of PCLX-001 in normal PBMC cells is > 10 µM (10,000nM)
- PCLX-001 is at least 50-fold more lethal to AML cancer cells than normal **PBMC** and >>50-fold than lymphocytes



PACYLEX
ACCELERATING THE PACE OF CANCER CARE

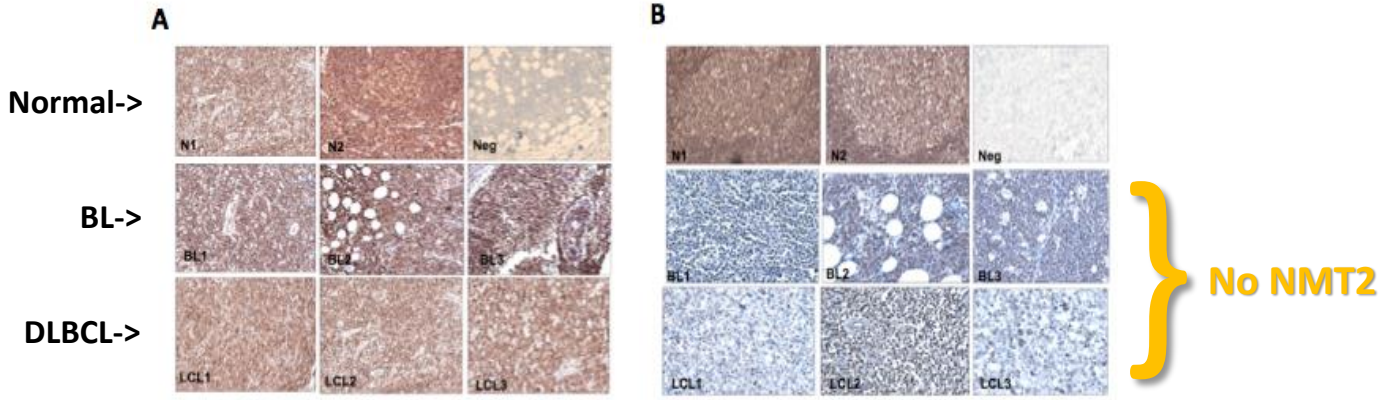
Tests enable the identification of patients with NMT2-deficient cancers

Patient selection strategy: Tumour biopsy → IHC or RNA-ISH → Identify Patients with NMT2-deficient tumours

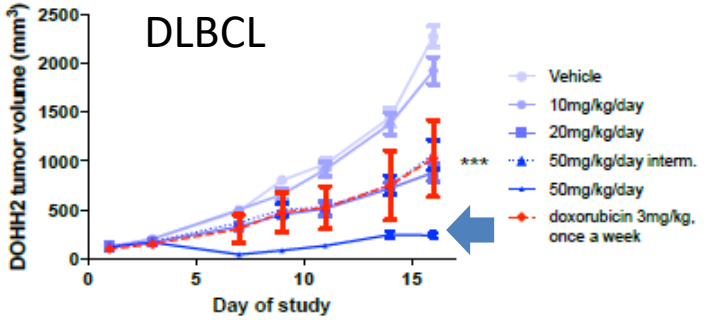
IHC

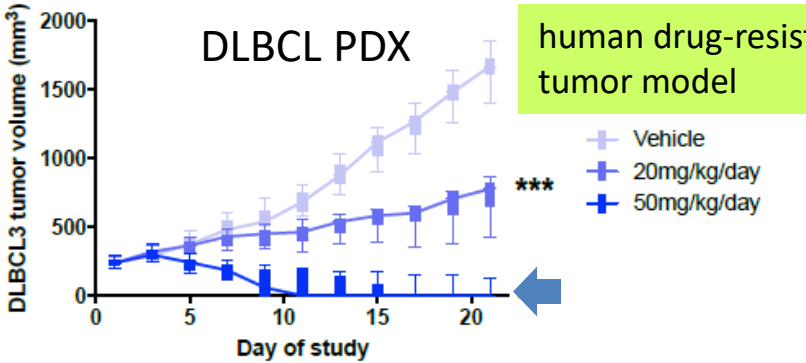
A. NMT1 staining

B. NMT2 staining

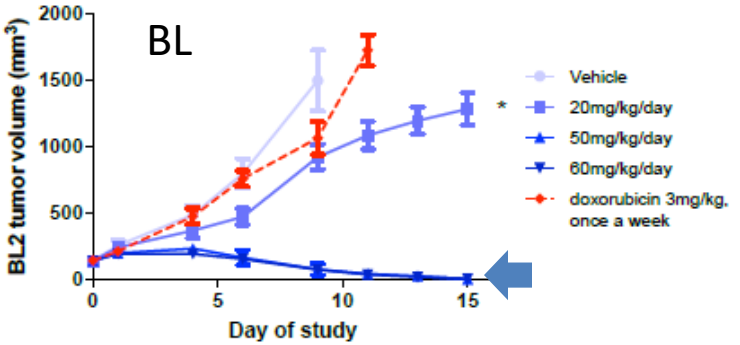


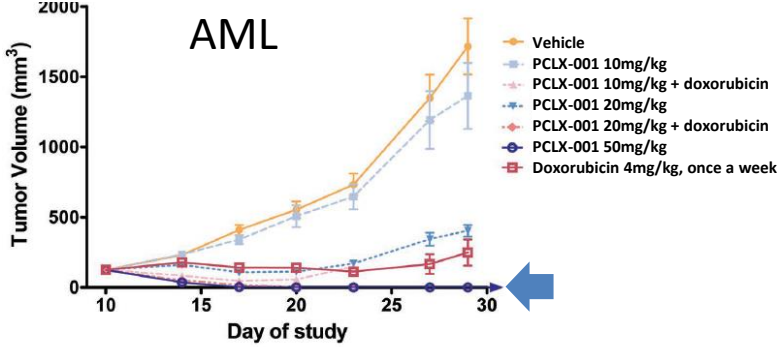
PCLX-001 eliminates tumors in leukemia and lymphoma xenograft models including patient-derived tumors





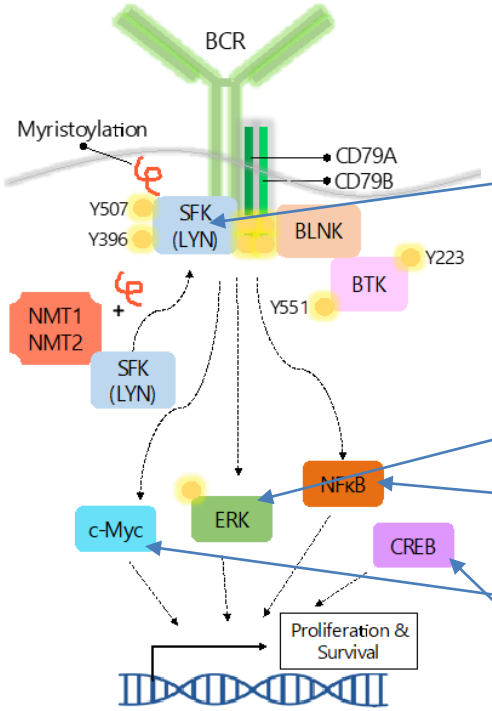
human drug-resistant tumor model

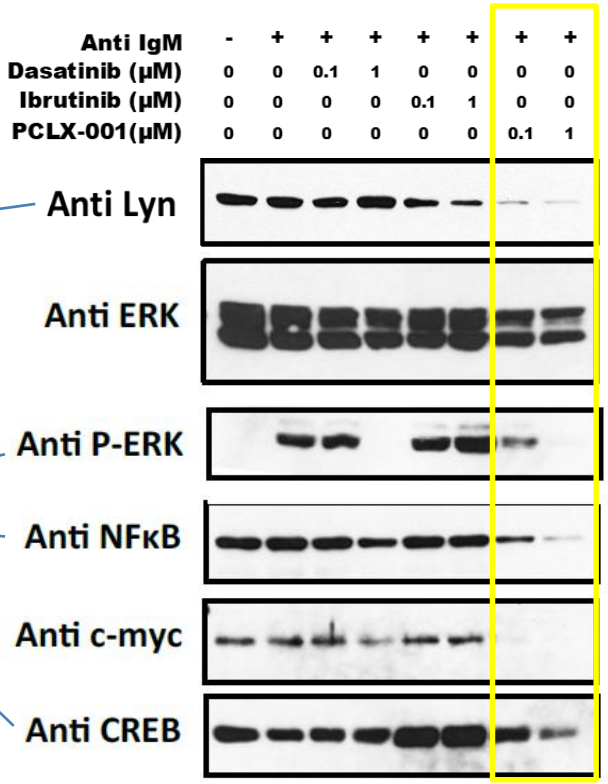


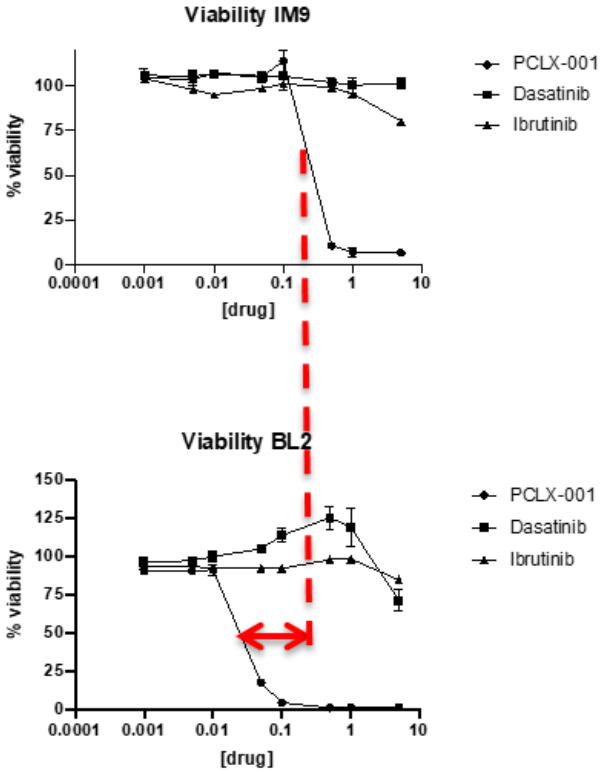


NHL – non Hodgkin's Lymphoma DLBCL Diffuse large B-cell lymphoma
BL – Burkitt's Lymphoma AML - Acute Myelogenous Leukemia (AML)

MOA in lymphoma: PCLX-001 inhibits BCR signaling leading to apoptosis in BL2 cells (>10x potency of dasatinib and ibrutinib)



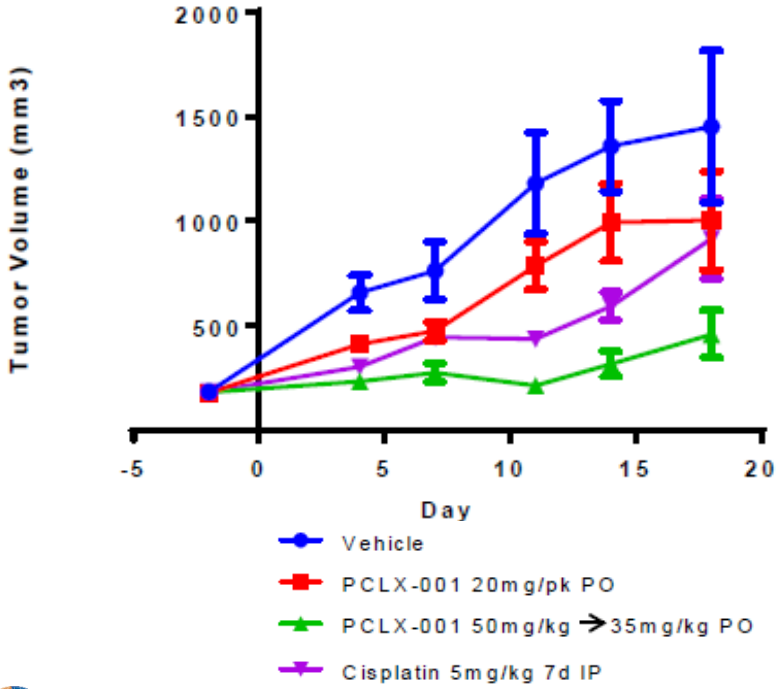




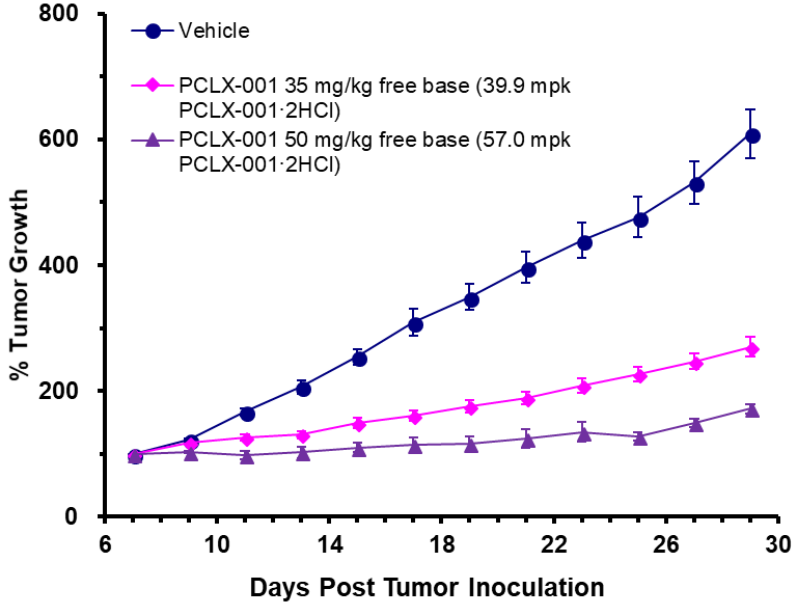
PACYLEX
ACCELERATING THE PACE OF CANCER CARE

PCLX-001 inhibits tumor growth in lung and breast cancer xenograft models (PDX)

Small Cell Lung Cancer Xenograft Model



Human Breast Cancer Xenograft Model

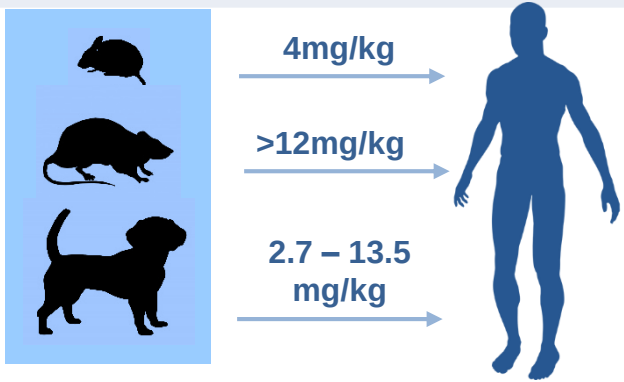


PACYLEX
ACCELERATING THE PACE OF CANCER CARE

Toxicology progress - clear path to IND

Species	Duration	Doses (mg/kg)	Findings
Rat	Acute (1)	100, 1,000	No noteworthy signs at 100 except low monocytes and lymphocytes in 1 rat. At 1,000mg/kg, significant effects on blood and GI including 1 animal death
Dog	Acute (1)	10, 50	Vomiting, GI bleeding and body weight loss in 1 animal (of 2) at 50mg/kg
Rat	14-days	10, 25, 75	No dose limiting toxicity, slightly lower weights in some 75mg/kg dose – drug exposure declines from d1 to d14
Dog	14-days	5, 25	Fatal toxicity in 3-5 days at 25mg/kg dose, slight body wt. loss for 5mg/kg in drug and control animals, no change in drug exposure from d1 to d14

50mg/kg effective dose in mice =
4mg/kg target in humans
= 25mg/kg in rats; ~7mg/kg in dogs



Work performed at:
citoxlab
A Charles River Company

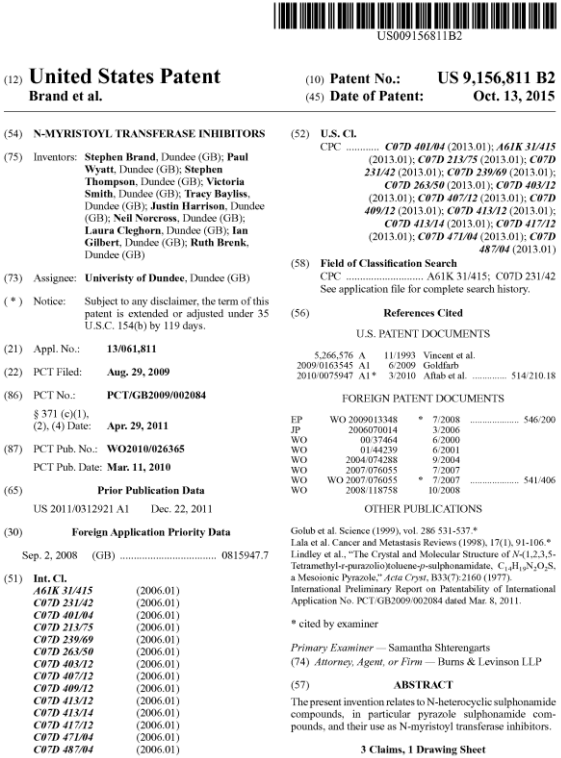
PACYLEX
ACCELERATING THE PACE OF CANCER CARE

Development partners engaged

- Merck Invention Accelerator, Edmonton, 2018
- CRO engaged (TRIO)
- Phase I clinical sites
- Draft Protocol complete for DLBCL and solid tumors
- Pre-IND meeting response August 15 defined IND path
- MD Anderson - parallel Phase 1 in AML
- Accepted and advanced in 2019-2020 Creative Destruction Lab Health West cohort

Issued patents with growing portfolio

- Exclusively licensed 3 issued API patents
  - N-myristoyl transferase inhibitors - WO 2010026365 A1
    - Issued: EP 2323987 A1 and US 9,156,811 B2
    - Issued: US 9,828,346 B2
- Synthetic lethality and the treatment of cancer (‘580) - PCT/CA2012/000696 (Priority date 2011/07/22), in National filing phase in AU & NZ, BR, CN, IL, KR, MX, SG, ZA, EP, US, and CA, and issued in Japan (2014-520475) and Russia (2014101787);
- Synthetic lethality and the treatment of cancer (‘581) - PCT/CA2013/050821 (Priority date 2012/10/30), issued in South Africa (2015/02280), Japan (2015-538225), Israel (238481) and Russia (2015118294) and pending/under examination in AU & NZ, BR, CN, KR, MX, SG, EP, US, and CA;
- Epigenetic silencing of NMT2 (‘313) – PCT/CA2016/050846 (Priority date 2015/07/17), published in US, EU and Japan.
- Counsel = Borden, Ladner, and Gervais LLP



US009156811B2

(12) **United States Patent**
Brand et al.

(10) **Patent No.: US 9,156,811 B2**
(45) **Date of Patent: Oct. 13, 2015**

(54) **N-MYRISTOYL TRANSFERASE INHIBITORS**

(75) Inventors: **Stephen Brand**, Dundee (GB); **Paul Wyatt**, Dundee (GB); **Stephen Thompson**, Dundee (GB); **Victoria Smith**, Dundee (GB); **Tracy Bayliss**, Dundee (GB); **Justin Harrison**, Dundee (GB); **Neil Norcross**, Dundee (GB); **Laura Clegborn**, Dundee (GB); **Ian Gilbert**, Dundee (GB); **Ruth Brenk**, Dundee (GB)

(73) Assignee: **Univeristy of Dundee**, Dundee (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 119 days.

(21) Appl. No.: **13/061,811**

(22) PCT Filed: **Aug. 29, 2009**

(86) PCT No.: **PCT/GB2009/002084**
§ 371 (c)(1),
(2), (4) Date: **Apr. 29, 2011**

(87) PCT Pub. No.: **WO2010/026365**
PCT Pub. Date: **Mar. 11, 2010**

(65) **Prior Publication Data**
US 2011/0312921 A1 Dec. 22, 2011

(30) **Foreign Application Priority Data**
Sep. 2, 2008 (GB) 0815947.7

(51) **Int. Cl.**

A61K 31/415	(2006.01)
C07D 231/42	(2006.01)
C07D 401/04	(2006.01)
C07D 213/75	(2006.01)
C07D 239/69	(2006.01)
C07D 263/50	(2006.01)
C07D 403/12	(2006.01)
C07D 407/12	(2006.01)
C07D 409/12	(2006.01)
C07D 413/12	(2006.01)
C07D 413/14	(2006.01)
C07D 417/12	(2006.01)
C07D 471/04	(2006.01)
C07D 487/04	(2006.01)

(52) **U.S. Cl.**
CPC ***C07D 401/04*** (2013.01); ***A61K 31/415*** (2013.01); ***C07D 213/75*** (2013.01); ***C07D 231/42*** (2013.01); ***C07D 239/69*** (2013.01); ***C07D 263/50*** (2013.01); ***C07D 403/12*** (2013.01); ***C07D 407/12*** (2013.01); ***C07D 409/12*** (2013.01); ***C07D 413/12*** (2013.01); ***C07D 413/14*** (2013.01); ***C07D 417/12*** (2013.01); ***C07D 471/04*** (2013.01); ***C07D 487/04*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/415; C07D 231/42
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,266,576	A	11/1993	Vincent et al.	
2009/0163545	A1	6/2009	Goldfarb	
2010/0075947	A1 *	3/2010	Aftab et al.	514/210.18

FOREIGN PATENT DOCUMENTS

EP	WO 2009013348	*	7/2008	546/200
JP	2006070014		3/2006	
WO	00/37464		6/2000	
WO	01/44239		6/2001	
WO	2004/074288		9/2004	
WO	2007/076055		7/2007	
WO	WO 2007/076055	*	7/2007	541/406
WO	2008/118758		10/2008	

OTHER PUBLICATIONS

Golub et al. Science (1999), vol. 286 531-537.*
Lala et al. Cancer and Metastasis Reviews (1998), 17(1), 91-106.*
Lindley et al., "The Crystal and Molecular Structure of *N*-(1,2,3,5-Tetramethyl-r-purazolio)toluene-*p*-sulphonamidate, $C_{17}H_{19}N_3O_2S$, a Mesoionic Pyrazole," *Acta Cryst.*, B33(7):2160 (1977).
International Preliminary Report on Patentability of International Application No. PCT/GB2009/002084 dated Mar. 8, 2011.

* cited by examiner

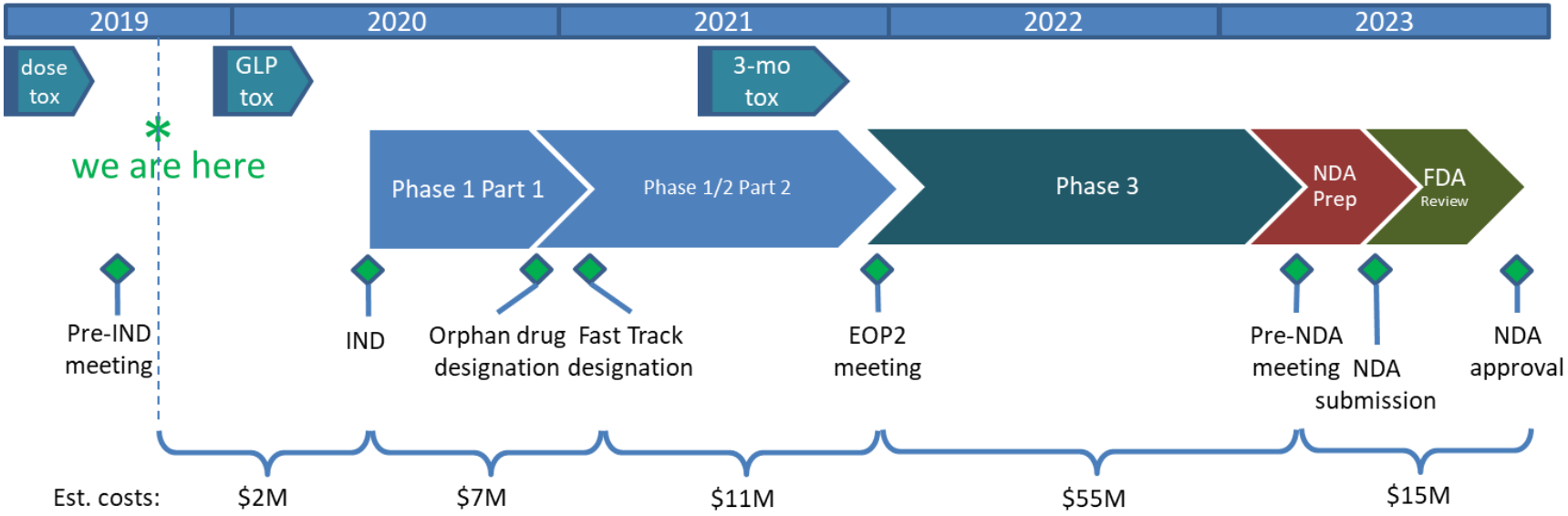
Primary Examiner — Samantha Shterengarts
(74) *Attorney, Agent, or Firm* — Burns & Levinson LLP

(57) **ABSTRACT**

The present invention relates to N-heterocyclic sulphonamide compounds, in particular pyrazole sulphonamide compounds, and their use as N-myristoyl transferase inhibitors.

3 Claims, 1 Drawing Sheet

Orphan and Fast Track accelerates drug development



Based on development and registration of TAGRISSO® osimertinib *for NSCLC*

Other recent examples:

- IDHIFA (enasidenib mesylate) approved in 47 mo.
- Jakafi from IND to approval in 55 mo.

***Clinical costs do not include CMC/manufacturing, regulatory costs or operating costs*

PACYLEX
ACCELERATING THE PACE OF CANCER CARE

Team well suited to developing new cancer therapy

Michael Weickert, PhD – CEO

CEO Sonescence, CEO SEA Medical Systems, CBO, Corium, Stratagent Life Sciences, Therashock, VP Development Auspex, Senior Program Executive, Nektar, Ligand, NCI/NIH

NEKTAR Ligand Corium

Naveen Pemmaraju, MD – Clinical Advisor

Associate Professor in the Department of Leukemia, Division of Cancer Medicine

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Luc Berthiaume, PhD – CSO

World leader in protein fatty acylation; Founder of Eusera and Pacylex; global distribution experience; 3 patents; commercialized antibody design and production

EUSERA

John Mackey, MD, FRCP – CMO

Director of clinical trials at the CCI; former Director of TRIO (International clinical trial organization, 200 people); founder of 3 companies; Extensive links to pharma

TRIO Translational Research In Oncology

Cross Cancer Institute ALBERTA CANCER FOUNDATION

David Jenish – Drug Development

30+ years experience in research and process development for therapeutics

PACYLEX ACCELERATING THE PACE OF CANCER CARE

Ryan Heit, MSc, MBA – COO

Technology and business development expert; 20+ companies assisted in early-stage commercialization; founder/co-founder of 4 companies; leads deal screening for VA Angels

Vanessa Grant - Counsel

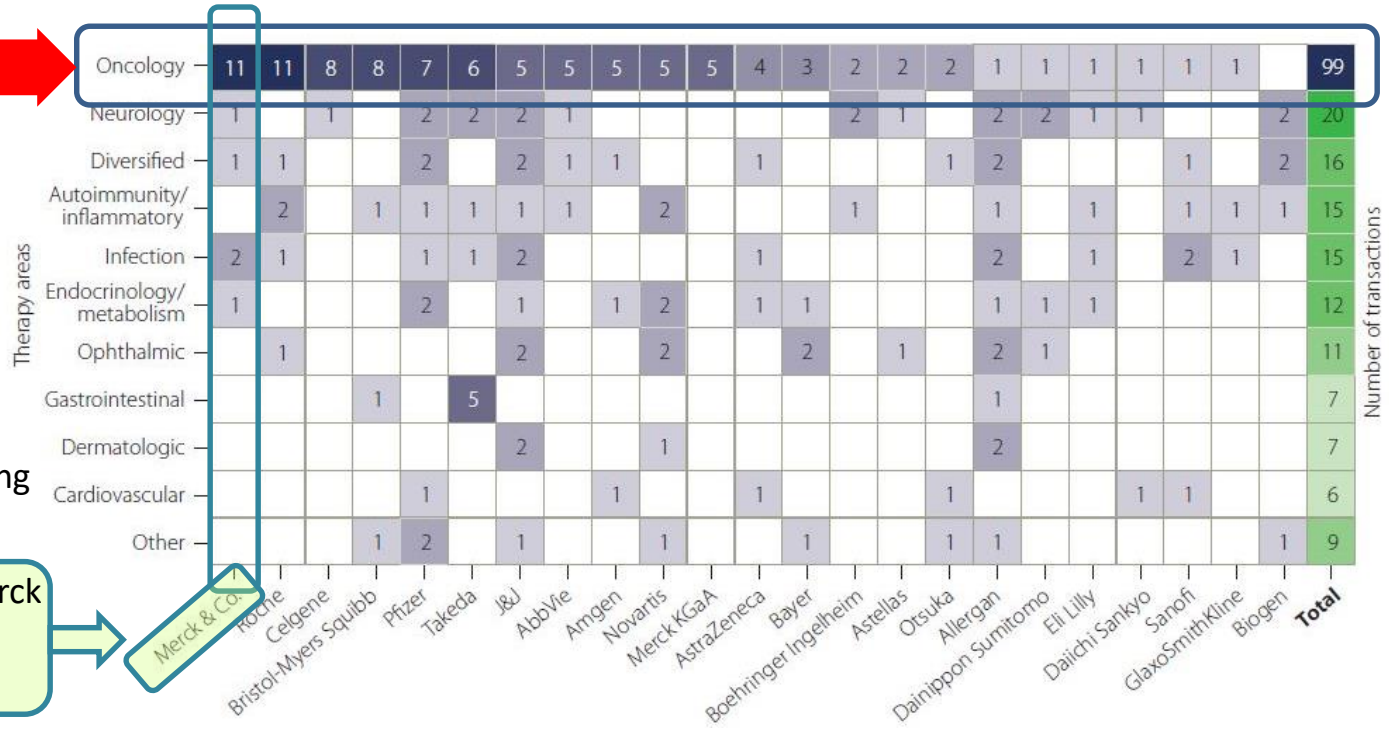
Counsel with Norton Rose Fulbright - expertise in mergers and acquisitions, corporate governance, private equity and venture capital. Led legal on largest Canadian biotech deal: Celgene option for TRPH-395 from Triphase Accelerator (2019; $980M)

Big pharma exit potential

Oncology is THE hot spot

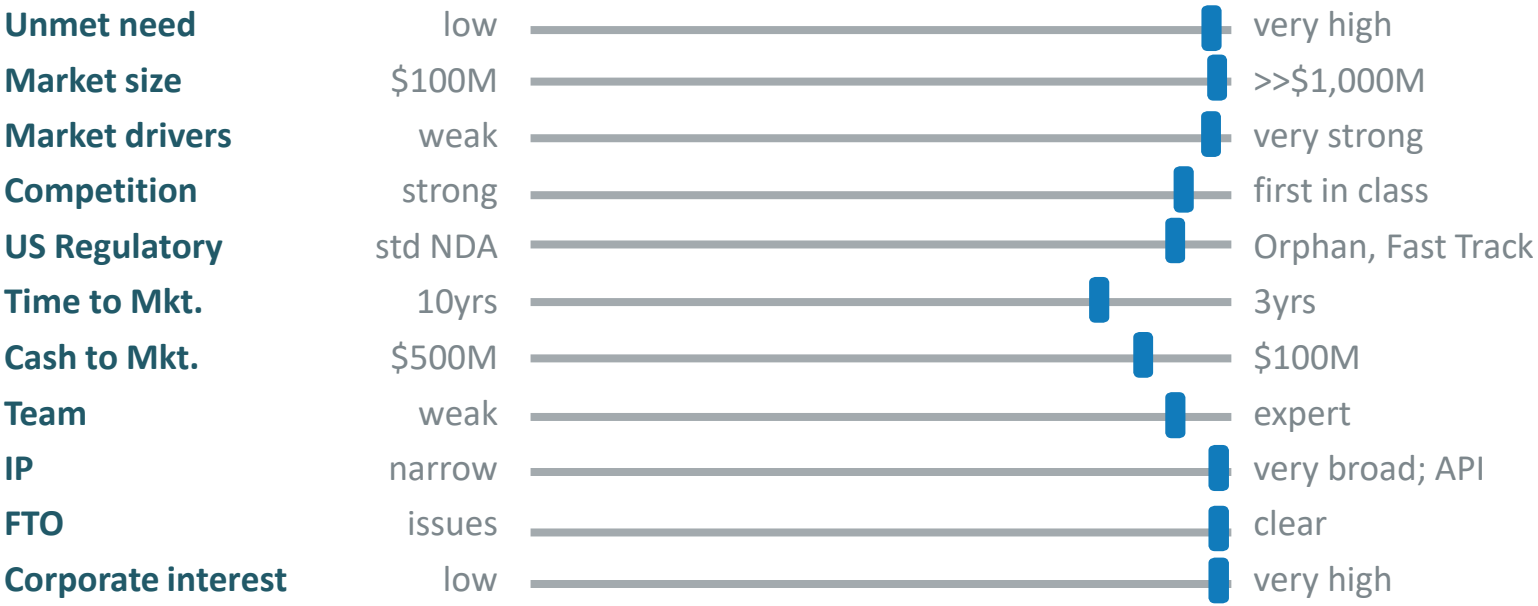
- Four of top ten pharmaceutical firms already engaged in discussions
- All want to see tox (next step – in progress)
- Pharma successful at replicating and confirming Pacylex results

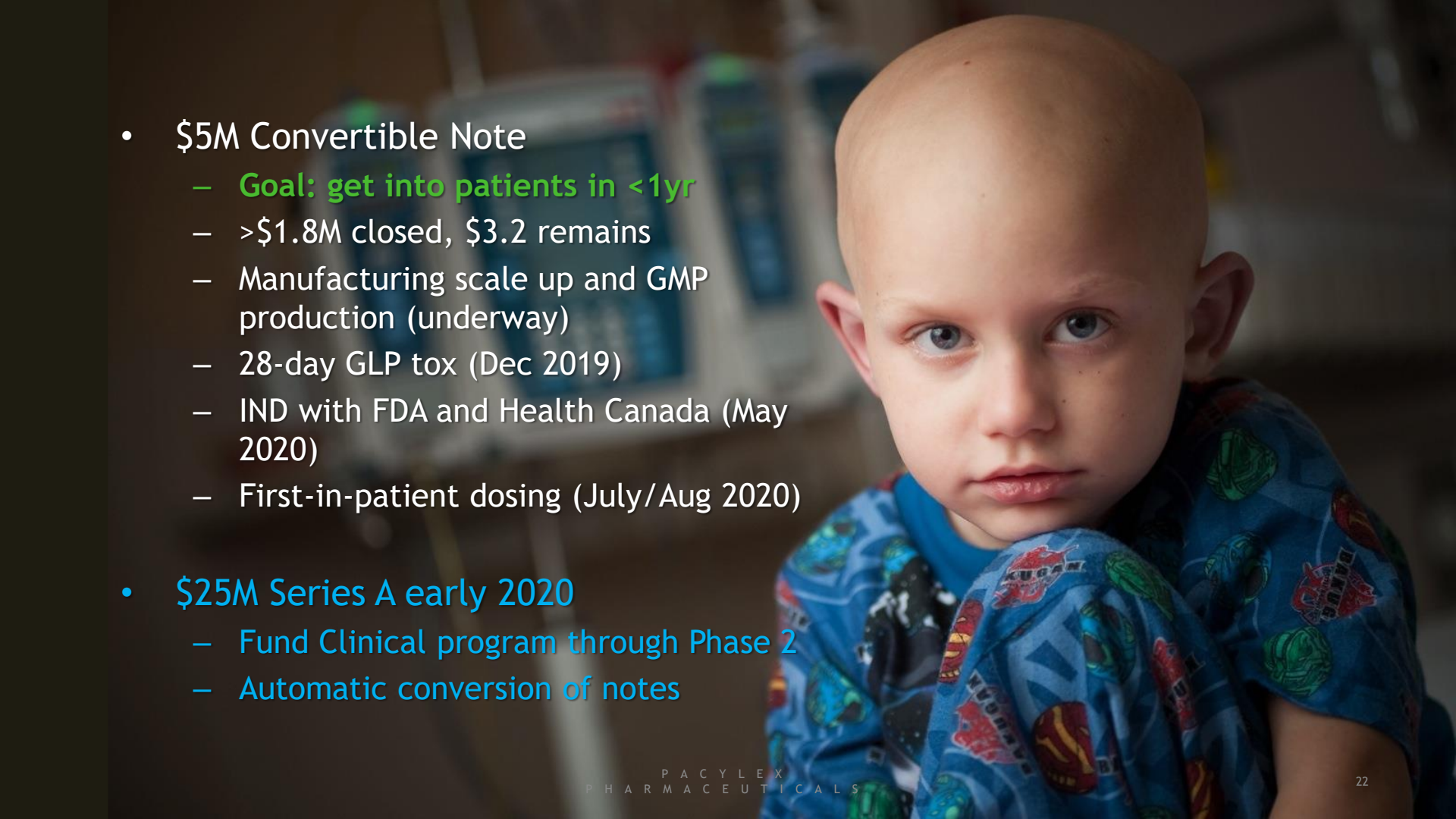
- 2018: Accepted into Merck Incubator in Edmonton, AB, Canada



BioPharma Dealmakers, Jun 09, 2017

Pacylex value dashboard consistently positive



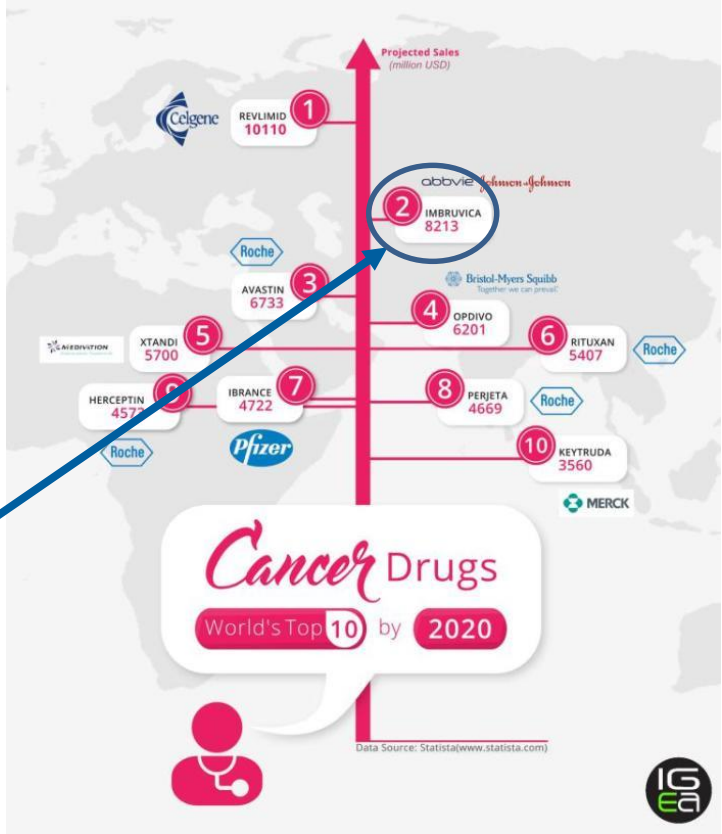


- $5M Convertible Note
  - Goal: get into patients in <1yr
  - >$1.8M closed, $3.2 remains
  - Manufacturing scale up and GMP production (underway)
  - 28-day GLP tox (Dec 2019)
  - IND with FDA and Health Canada (May 2020)
  - First-in-patient dosing (July/Aug 2020)
- $25M Series A early 2020
  - Fund Clinical program through Phase 2
  - Automatic conversion of notes

Key take home - Pacylex is potential blockbuster

- PCLX-001 is a genuine breakthrough
  - ✓ Oral
  - ✓ Activity against many blood and solid tumor cancers
  - ✓ New mechanism – not redundant with other products (synergy)
  - ✓ Tumor **killing** not tumor inhibiting
- Rapid development
  - ✓ On IND path with filing in 6-9mo
- Potential for early partnering or exit
  - ✓ >10x as potent as Ibrutinib (Imbruvica; **$4.4B** 2017) and Dasatinib (Sprycel; $2.3B 2017)

Making a real difference in cancer



PACYLEX
ACCELERATING THE PACE OF CANCER CARE

Contact Info

Michael Weickert, PhD
CEO
michael.weickert@pacylex.com
650-218-1840

Ryan Heit, MSc, MBA
COO
ryan.heit@pacylex.com
780-264-4295