Building a **NEW** Cancer Therapy
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, FRCP
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
Myristoylation helps ~200 proteins attach to cell membranes to enable control of growth and metabolism.

Protein + enzymes: NMT1 or NMT2 = ~200 proteins - most involved in homeostasis: Control of normal growth and metabolism, Typically through protein-protein interactions in membrane complexes.
NMT2 expression is lost in numerous cancer types, is the lowest in lymphoma and is NOT compensated by an increase in NMT1 expression.

*same trend seen in tumours*

Data extracted from www.CCLE.org
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

NMT2 switched off = uncontrolled cell growth = cancer

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

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

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

...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

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

**Cell viability**

- Cancer cell lines
- Normal cell lines

**Apoptosis**

*indicated by cleaved PARP-1 and caspase-3
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 monocyotic 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
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**

- Normal
- BL
- DLBCL

**B. NMT2 staining**

- No NMT2

[Images of tissue samples showing staining patterns for A. NMT1 staining and B. NMT2 staining]
PCLX-001 eliminates tumors in leukemia and lymphoma xenograft models including patient-derived tumors

NHL – non Hodgkin’s 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)
PCLX-001 inhibits tumor growth in lung and breast cancer xenograft models (PDX)

Small Cell Lung Cancer Xenograft Model

Human Breast Cancer Xenograft Model
## Toxicology progress - clear path to IND

<table>
<thead>
<tr>
<th>Species</th>
<th>Duration</th>
<th>Doses (mg/kg)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Acute (1)</td>
<td>100, 1,000</td>
<td>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</td>
</tr>
<tr>
<td>Dog</td>
<td>Acute (1)</td>
<td>10, 50</td>
<td>Vomiting, GI bleeding and body weight loss in 1 animal (of 2) at 50mg/kg</td>
</tr>
<tr>
<td>Rat</td>
<td>14-days</td>
<td>10, 25, 75</td>
<td>No dose limiting toxicity, slightly lower weights in some 75mg/kg dose – drug exposure declines from d1 to d14</td>
</tr>
<tr>
<td>Dog</td>
<td>14-days</td>
<td>5, 25</td>
<td>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</td>
</tr>
</tbody>
</table>

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

Work performed at:

![Citoxlab](citoxlab.png)

PACYLEX
ACCELERATING THE PATH OF CANCER CARE
PACYLEX PHARMACEUTICALS

4mg/kg

>12mg/kg

2.7 – 13.5 mg/kg
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
• 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

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

Orphan and Fast Track accelerates drug development

Based on development and registration of Tagrisso 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**
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

**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

**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

**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)

**Naveen Pemmaraju, MD – Clinical Advisor**
Associate Professor in the Department of Leukemia, Division of Cancer Medicine

**David Jenish – Drug Development**
30+ years experience in research and process development for therapeutics

**Naveen Pemmaraju, MD – Clinical Advisor**
Associate Professor in the Department of Leukemia, Division of Cancer Medicine

**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

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#### 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
### Pacylex value dashboard consistently positive

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet need</td>
<td>low</td>
<td>very high</td>
</tr>
<tr>
<td>Market size</td>
<td>$100M</td>
<td>$1,000M</td>
</tr>
<tr>
<td>Market drivers</td>
<td>weak</td>
<td>very strong</td>
</tr>
<tr>
<td>Competition</td>
<td>strong</td>
<td>first in class</td>
</tr>
<tr>
<td>US Regulatory</td>
<td>std NDA</td>
<td>Orphan, Fast Track</td>
</tr>
<tr>
<td>Time to Mkt.</td>
<td>10yrs</td>
<td>3yrs</td>
</tr>
<tr>
<td>Cash to Mkt.</td>
<td>$500M</td>
<td>$100M</td>
</tr>
<tr>
<td>Team</td>
<td>weak</td>
<td>expert</td>
</tr>
<tr>
<td>IP</td>
<td>narrow</td>
<td>very broad; API</td>
</tr>
<tr>
<td>FTO</td>
<td>issues</td>
<td>clear</td>
</tr>
<tr>
<td>Corporate interest</td>
<td>low</td>
<td>very high</td>
</tr>
</tbody>
</table>
• **$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
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