Pieter Cullis
Professor, University of BC
Vancouver, Canada

Conflicts of Interest

Precision NanoSystems: Co-Founder
Acuitas Therapeutics: Co-Founder and Chairman
Molecular You: Co-Founder and Chairman
GenXys Healthcare: Co-Founder
Innovation as a Driver for Personalized Medicine in British Columbia

BC is becoming a leading innovator in two important forms of personalized medicine:

- Using molecular level information about an individual to maintain health
  - Achievements by companies formed by the Personalized Medicine Initiative
- Use molecular level information about an individual to develop personalized therapies to treat their disease
  - Achievements by companies developing precision medicines-nanomedicines
The Personalized Medicine Initiative
An Organization Formed to Introduce Personalized, Precision Medicine Into the Population

2011-2017
The PMI Founders

Pieter Cullis, PhD
Chair – PMI
CSO & Cofounder – Molecular You
Professor & Director – Life Sciences Institute, UBC

Martin Dawes, MD, MB.BS
CEO & Cofounder – GenXys Health
Professor & Head – Family Practice, UBC

Rob Fraser, PhD
COO – PMI
CEO & Cofounder – Molecular You

David Huntsman, MD
CSO & Cofounder – Contextual Genomics
Professor – BC Cancer Agency, UBC

Bruce McManus, MD, PhD
CEO – PROOF Centre
Professor – Institute for Heart + Lung Health, UBC

James Russell, MD
CMO & Cofounder – Cyon Therapeutics
Professor – Centre for Heart Lung Innovation, UBC
The Future of Healthcare: Personalized Medicine Based on Molecular Profiling

Well people, ill people

Molecular data-clouds for each individual

Precise diagnoses
Individualized therapies
Better matching of treatment to disease
Identification of new biomarkers/targets associated with disease
Early detection
Effective preventive medicine
There Are Irresistible Forces Driving Personalized Medicine Based on Molecular Profiling

1. Rapid technological change (inexpensive molecular level analyses, advances in data science to interpret that data)

2. Patient safety (adverse reactions to prescribed drugs are the 4th leading cause of death)

3. Drug efficacy ( >50% of drugs don’t work for individuals they are prescribed for)

4. Preventive medicine (need individualized, definitive data to avoid trending toward disease)

5. Consumer demand: want better ways to treat disease and maintain health!
Objectives of the PMI

1. Encourage a political/public commitment to personalized medicine

2. Establish coalition of healthcare, academic, industry & patients to promote personalized medicine

3. Take advantage of near-term opportunities for implementation and commercialization of personalized medicine

4. Construct an Omic database for British Columbians suffering from high cost/morbidity disorders
What Did The PMI Achieve?

1. Encourage a political/public commitment to personalized medicine
   - “The Personalized Medicine Revolution: How Diagnosing and Treating Disease are About to Change Forever” (Cullis, 2015)
   - PMI website; PMI public talks, media coverage
   - Personalized Medicine Summit June 7-9, 2015; Personalized Medicine Summit June 11-13, 2017

2. Establish coalition of healthcare, academic, industry & patients to promote personalized medicine
   - The PMI assembled a coalition of stakeholders (LSBC, Genome BC, CDRD, PROOF, UBC etc)
   - Roadmaps 1.0 and 2.0 for introducing personalized medicine in BC
What Did The PMI Achieve?

3) Take advantage of near-term opportunities for implementation and commercialization of personalized medicine

➢ The PMI initiated five major projects (*pharmacogenomics*; personalized cancer chemotherapy; biomarkers for autism; *microbiome* analyses; *Omic* profiling for disease identification)

➢ The PMI catalyzed formation of four companies

4) Construct an *Omic* database for British Columbians suffering from high cost/morbidity disorders

➢ The PMI established comprehensive *Omic* molecular profiling capabilities through Molecular You

➢ **NEED TO ESTABLISH DATABASE TO STUDY 25,000 BRITISH COLUMBIANS SUFFERING FROM HIGH COST/HIGH MORBIDITY/MORTALITY DISEASES**
The PMI Catalyzed Formation of Four Personalized Medicine Start-ups

1. GenXys Health Care Systems
2. Contextual Genomics
3. Microbiome Insights
4. Molecular You Corporation

These companies have raised >$20M, now employ ~100 people and have substantially added to BC’s capabilities in personalized medicine
Contextual Genomics: Matching Cancer Therapy to the Individual

We empower clinical labs to deploy cancer genomic tests in their facilities

Founded and led by international leaders in cancer genomics and bioinformatics, Contextual Genomics delivers End-to-End solutions to clinical laboratories that harness the genomic data of cancer patients to improve patient diagnosis and present expanded treatment options to oncologists and patients.

Our End-to-End solutions are NGS *liquid* and *tissue* biopsy assays that detect mutations in cancer, and are designed to be clinically actionable, clinical grade (CAP, CLIA validated), and cost effective. A proprietary state-of-the-art cloud based bioinformatics platform (CGiRP) that alleviates the need for our partner laboratories to invest in any additional R&D and software development is an integral part of our offering. All our solutions are embedded with leading, proprietary molecular quality assurance tools, enabling laboratory partners to effectively support their cancer physicians and patients.
Microbiome Insights: The Gut Health Test

Bringing Experience and Clarity to Your Microbiome Analysis
Leading the way in precision prescribing

GenXys provides the world’s most comprehensive precision prescribing software to solve healthcare’s most pressing challenges. Our precision prescribing software and pharmacogenetic solutions prevent adverse drug reactions, a leading cause of death in developed countries, and personalize drug selection to increase drug efficacy. Powering every prescription with our software improves medication safety, increases drug efficacy and reduces healthcare costs.
Molecular You measures thousands of biomarkers to identify health trends and develop individual health action plans.

**Metabolites**
Metabolites are the clues left behind by your body – the indicators of your inner workings. We test for over 85 metabolites: sugar, acids, fats & neurotransmitters that contribute to your energy, metabolism, muscle & organ function, brain & heart health.

**Environment & Diet**
We test for over 60 metals, minerals, nutrients & toxins. The analysis of your blood can uncover dietary imbalances and environmental exposure. These markers impact bone & brain development, liver function, skin & cardiovascular health.

**Genetics**
Genes are like a blueprint – they define many of your characteristics. We can identify over 25,000 genetic variants, which span 6,000 genes. These can help identify your health and medication risks.

**Pharmacogenetics**
We provide a personalized medication profile which shows risk of adverse or unwanted side effects to many common medications.

**Proteins**
The state of your blood proteins impacts your health and health risks significantly. We test over 130 proteins that can tell you about inflammation, immunity & oxidation; blood clotting & bone function.

**Health & Lifestyle History**
We integrate your self-reported history into our analysis to give us more insight and context. We look at your family history, medical conditions, medications, supplements, nutrition, exercise and environment.
Objectives of the PMI

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2. Establish coalition of healthcare, academic, industry & patients to promote personalized medicine

3. Take advantage of near-term opportunities for implementation and commercialization of personalized medicine

4. Construct an Omic database for British Columbians suffering from high cost/morbidity disorders
The Database Would Drive Discovery and Innovation And Establish BC as a Major Power in the Personalized Medicine Revolution!

The tools to do this are in place: Digital Supercluster project??
Innovation as a Driver for Personalized Medicine in British Columbia

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BC is a Global Leader in Nanomedicines

| Nanomedicines for Systemic (i.v) Administration Approved in USA and/or Europe |
|---|---|---|---|---|
| **Name** | **Encapsulated Drug** | **Indication** | **Year Approved** | **Company** |
| AmBisome | amphotericin B | Fungal infections | 1990 (EU), 1997 (USA) | Gilead |
| DaunoXome | daunorubicin | Kaposi’s sarcoma | 1996 (EU, USA) | Galen |
| Amphotec | amphotericin B | Invasive aspergillosis | 1996 (USA) | Intermune |
| Abelcet | amphotericin B | Aspergillosis | 1995 (USA) | Enzon |
| Myocet | doxorubicin | Breast cancer | 2000 (EU) | Cephalon |
| Visudyne | verteporphan | Macular degeneration | 2000 (USA) | QLT |
| Marqibo | vincristine | Leukemia (ALL) | 2012 (USA) | Spectrum |
| Vyxeos | cytarabine | Leukemia (AML) | 2017 (USA) | Jazz |
| Onpattro | TTR siRNA | hATTR amyloidosis | 2018 (USA, EU) | Alnylam |

BC researchers have developed six of the ten approved nanomedicines worldwide.
How Did BC Become a Leader in Nanomedicines?

Innovation!

- Lipex Biomembranes 1985
- Inex Pharmaceuticals 1992
- Northern Lipids 1992
- Protiva Biotherapeutics 2001
- Celator 2001
- Acuitas Therapeutics 2009
- Precision NanoSystems 2011
siRNA for silencing disease causing genes (Acuitas, my UBC laboratory, Alnylam-Boston)

mRNA for expressing therapeutic proteins

Gene editing techniques (e.g. CRISPR Cas9) for correcting defective/pathological genes

Genetic drugs have the potential to treat essentially all human diseases, but they need delivery systems
Hereditary Amyloid Transthyretin (hATTR) Amyloidosis

TTR is a tetrameric protein that is primarily expressed in the liver and transports serum retinol binding protein (RBP)

Native TTR tetramer  Rearranged tetramer  Monomer  Oligomeric, non-fibrillar and protofibrillar species  Amyloid fibril

hATTR amyloidosis is a fatal, multisystem disease caused by extracellular deposits of TTR amyloid

- ~100 mutations in the TTR gene lead to amyloid deposition in:
  - Nerves: ~10,000 patients
  - Heart: ~40,000 patients
- Liver transplant only current therapy
hATTR Amyloidosis: A Fatal Multi-Systemic Disease Causing Neuropathy and Cardiomyopathy Due to Liver-Derived TTR

CNS
Dementia
Seizures etc

GI
Nausea, vomiting
Diarrhea
Weight loss

Kidney failure

Carpal tunnel

Vision impairment

Neuropathy
Sexual dysfunction
Sweating abnormalities

Cardiac problems
Cardiomyopathy
Palpitations, arrhythmia
Edema

Neuropathies
Neuropathic pain
Numbness, tingling
Muscle weakness
Difficulty walking
hATTR Amyloidoisis: A Rapidly Progressing Disease Usually Fatal Within Five Years of Diagnosis

Stage 1 → Stage 2: Early → Stage 2: Late → Stage 3
LNP TTR siRNA: The Hypothesis

Production of mutant and wild type TTR

Unstable circulating TTR tetramers reduced

Organ deposition of amyloid fibrils prevented, clearance promoted

Stabilization and recovery from cardiomyopathy, neuropathy

A potentially simple solution to a devastating disease
Need Delivery System That Can Deliver RNA to the Liver and Into the Cytoplasm of Target Cells

Package siRNA in LNP

Enhanced delivery to disease sites

Intracellular delivery in target cells

This was a challenge!
Developed a Lipid Nanoparticle (LNP) System That Could Deliver the siRNA
Clinical Development Program of Patisiran, An Investigational RNAi Therapeutic for hATTR Amyloidosis

**Phase 1**
- **March 2012**
- Completed
- Healthy Volunteers
- Positive results in human healthy volunteers (N=17)
  - Single dose
  - 0.01–0.5 mg/kg by 60 min IV infusion

**Phase 2**
- Completed
- hATTR
- Positive multi-dose results in adult patients with hATTR amyloidosis (N=29)
  - Multiple doses
  - Multiple schedules: q3w vs q4w
  - Multiple infusion rates and premed regimens

**Phase 2 OLE**
- Completed
- hATTR
- Positive results in adult patients with hATTR amyloidosis with polyneuropathy who participated in the Phase 2 study (N=27)
  - 0.3 mg/kg every 3 weeks by IV infusion for up to 2 years
  - Premedication: original → reduced

**Phase 3**
- **August 2017**
- Completed
- APOLLO
- hATTR
- Adults with hATTR amyloidosis with polyneuropathy (N=225)
  - 0.3 mg/kg every 3 weeks by IV infusion for 18 months
  - Randomized, double-blind, placebo-controlled

**Global OLE**
- Ongoing
- hATTR
- Adults with hATTR amyloidosis with polyneuropathy who participated in the Ph 2 OLE or Ph 3 study (N=211 enrolled)
  - 0.3 mg/kg every 3 weeks by IV infusion
  - Includes some patients with over 3 years treatment
Phase I Study Results (Healthy Volunteers)
Effective TTR Gene Silencing at Dose Levels of 0.15 mg siRNA/kg Body Weight

Selected a dose of 0.3 mg siRNA/kg body weight for subsequent trials
Apollo Patisiran Phase 3 Study

Design

N=225

Patient Population
- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT01960348

2:1 RANDOMIZATION

N=148
Patisiran
0.3 mg/kg IV q3W

or

N=77
Placebo
IV q3W

Primary Endpoint
- Change in mNIS+7 from baseline at 18 months

Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- R-ODS
- 10-meter walk
- mBMI
- COMPASS-31

mNIS+7: modified neuropathy impairment score; Norfolk QOL-DN: patients perception of diabetic neuropathy; R-ODS: Rasch-built Overall Disability Scale; COMPASS-31: Composite Autonomic Symptom Scale-31 (autonomic nervous system)
Apollo Patisiran Phase 3 Study Results: Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months

<table>
<thead>
<tr>
<th>TTR Change</th>
<th>Change from baseline at 9 months</th>
<th>Change from baseline at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (SEM) Serum TTR Knockdown</td>
<td>1.5% (4.47)</td>
<td>82.6% (1.36)</td>
</tr>
</tbody>
</table>
Apollo Patisiran Phase 3 Study Results: Improvement in Neural Impairment Score (mNIS+7)

Difference at 18 mos (Pati – PBO): -33.99
p-value: 9.26 ×10^{-24}
Apollo Patisiran Phase 3 Study: Improvement in Quality of Life (Norfolk QOL-DN)

- Placebo
  - Difference at 18mos (Pati – PBO): -21.1
  - p-value: $1.10 \times 10^{-10}$

- Patisiran
  -LS mean (SEM) change in Norfolk QOL-DN from baseline:
    - Baseline: 59.6 (5, 119)
    - 9 Months: -7.5 (1.52)
    - 18 Months: -6.7 (1.77)
Patisiran Phase 3 Trial Results Announced September 20, 2017: Hit Primary Endpoint and All Secondary Endpoints!

<table>
<thead>
<tr>
<th>Primary Endpoint (18 mo.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mNIS+7</td>
<td>9.26 x 10^{-24}</td>
</tr>
<tr>
<td>Neuropathy improvement score better than placebo</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoints (18 mo.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfolk-QoL</td>
<td>1.10 x 10^{-10}</td>
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<tr>
<td>Quality of life better than placebo</td>
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<tr>
<td>NIS-W</td>
<td>1.40 x 10^{-13}</td>
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<tr>
<td>Muscle strength better than placebo</td>
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<tr>
<td>R-ODS</td>
<td>4.07 x 10^{-16}</td>
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<tr>
<td>Overall disability scale better than placebo</td>
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<tr>
<td>10MWT</td>
<td>1.88 x 10^{-12}</td>
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<tr>
<td>Gait speed better than placebo</td>
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<tr>
<td>mBMI</td>
<td>8.83 x 10^{-11}</td>
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<tr>
<td>Nutritional status better than placebo</td>
<td></td>
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<tr>
<td>COMPASS-31</td>
<td>0.0008</td>
</tr>
<tr>
<td>Autonomic muscle function better than placebo</td>
<td></td>
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</tbody>
</table>
Patisiran (tradename Onpattro) approved by FDA Aug 10, 2018 for treatment of hATTR amyloidosis
First FDA approval of siRNA-based gene therapy drug

This is a big deal. Not only can we halt the progression of an hereditary disease, we can actually reverse the accumulated damage. Dramatically demonstrates the power of gene therapies.
Onpattro Predicted to Have Sales of $1B by 2023

Alnylam posts strong Onpattro sales as competition heats up

Dive Brief:

- Sales of Alnylam Pharmaceuticals’ rare disease drug Onpattro more than doubled between the fourth quarter of last year and the first three months of 2019, outstripping expectations and helping to ease worries of a slow start for the therapy.

- By the end of the first quarter, more than 400 patients were on commercial treatment with Onpattro, which last year became the first RNA interference therapeutic to win U.S. approval. That figure was double what Alnylam reported at the end of 2018.
Gene Therapy is Becoming a Reality

The nanomedicine approach also applies to other kinds of gene therapy
LNP mRNA for expressing therapeutic proteins
• Protein replacement
• Vaccines
LNP containing gene editing constructs
• Correcting genetic defects
Vaccines: A Single Dose of LNP mRNA Coding For an HIV Antigen Provides Complete Protection Against HIV Infection

- For 30 μg Luc mRNA:
  - Weeks post challenge with JR-CSF:
    - Group 1: 10,000
    - Group 2: 1,000

- For 30 μg VRC01 mRNA:
  - Weeks post challenge with JR-CSF:
    - Group 1: 100
    - Group 2: 10
Vaccines: A Single Dose of LNP mRNA Coding For a Zika Virus Antigen Provides Complete Protection Against Zika Virus Infection
LNP mRNA Vaccines

- HIV
- Zika
- Universal influenza vaccine
- Malaria
- Cancer?
Gene Therapy is Becoming a Reality

Applications:
- LNP siRNA systems to silence any gene in hepatocytes
  - Soon: LNP siRNA systems to silence any gene in other tissues (immune cells, bone marrow, stem cells etc)
- LNP mRNA systems to produce any protein in hepatocytes
- LNP mRNA systems for many vaccine applications, possibly anticancer
- LNP CRISPR Cas9 systems for gene editing applications

All these advances have been materially assisted by BC-based companies
Genevant

Delivering solutions through RNA therapeutics.
A global leader in innovative solutions for the discovery, development, and manufacture of novel nanoparticle medicines.
Transferra Nanosciences Inc. (Formerly Northern Lipids)

**DRUG FORMULATION**
A wide range of pre-formulation services to support characterization of Active Pharmaceutical Ingredients (APIs) ...

Learn more about our Drug Formulation Services

**PROCESS DEVELOPMENT**
Manufacturing process development at small, intermediate and commercial scales with a focus on scalable, robust processes.
Learn more about our Process Development Services

**MANUFACTURING**
Production facility that supports the manufacture of lipid-based formulations under cGMP...

Learn more about our GMP Manufacturing Services

**ANALYTICAL**
Independent contract testing facility with extensive experience identifying and characterizing lipids, lipid derivatives and liposomal systems...

Learn more about our Analytical Services

**PRESS RELEASE**
Corporate Press  June 28, 2016

Evonik acquires Transferra Nanosciences Inc.
Evonik

Evonik expands North American contract development and manufacturing capabilities for advanced injectables

Evonik Vancouver Laboratories in Canada to double in size to meet growing demand for LNP formulation development and manufacturing processes
Celator Pharmaceuticals

Today's News

Jazz Pharmaceuticals To Acquire Vancouver-based Celator For $1.5 Billion ($30.25 Per Share)
Monday, June 6, 2016

Company Profile | Follow Company
NanoMedicines Innovation Network

UBC attracts over $40M to host Networks of Centres of Excellence in nanomedicines

April 16, 2019

The NanoMedicines Innovation Network (NMIN) has been awarded $18.5 million in new funding from the Networks of Centres of Excellence (NCE), a federal program that connects teams of scientists across Canada to collaborate on research with significant health, environmental and societal impacts. This funding is matched by more than $22 million from industry and other not-for-profit agencies.

The funding will maintain and extend Canada's standing as a leader in the development of nanomedicines — “smart” medicines that employ various forms of nanotechnology — to detect and treat cancer and many other acquired and hereditary diseases.
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Personalized Medicine in BC is Being Materially Assisted by a Strong Innovation Industry Infrastructure