Pieter Cullis
Professor, University of British Columbia
Health Summit 2026 Vancouver, Canada

The Future of Medicine is Personalized, Precision Medicine

How Can We Make It Happen?

Conflicts of Interest
Precision NanoSystems: Founder
Acuitas Therapeutics: Founder
NanoVation Therapeutics: Founder and Chair
Molecular You: Founder and Chair

Outline

How can we make personalized medicine happen?

- The Personalized Medicine Initiative 2011-2017
- The start-up approach: Precision diagnostics
  - Molecular You
  - GenXys
- The start-up approach: The clinical interface
  - Polymorphic BioSciences: data collection and analysis
  - Connect Health: The Longevity 100
- The start-up approach: Personalized medicines
  - Aurion Therapeutics: Personalized cancer drugs (small molecules)
  - Background: Gene Therapy
  - Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies

Our First Attempt 2011-2017….

The Personalized Medicine Initiative

An Organization Formed to Introduce Personalized, Precision Medicine Into the Population

pmi

Personalized
Medicine Initiative

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

We Did a Lot of Work…

- **2011-12:** Established consensus, wrote business plan, raised initial funding
- **2013-14:** Identified lead projects, raised funding for them, formed start-ups where possible
- **2015:** Held first PMI Summit conference, produced Roadmap 1.0 and associated recommendations
- **2015-16:** Focused on achieving molecular profiling capabilities through Molecular You Corporation
- **2017:** Focused on implementation of molecular profiling in priority disease and performance enhancement cohorts
- **2017:** Held second PMI Summit conference, produced Roadmap 2.0 and associated recommendations….

We Produced Advisory Documents…

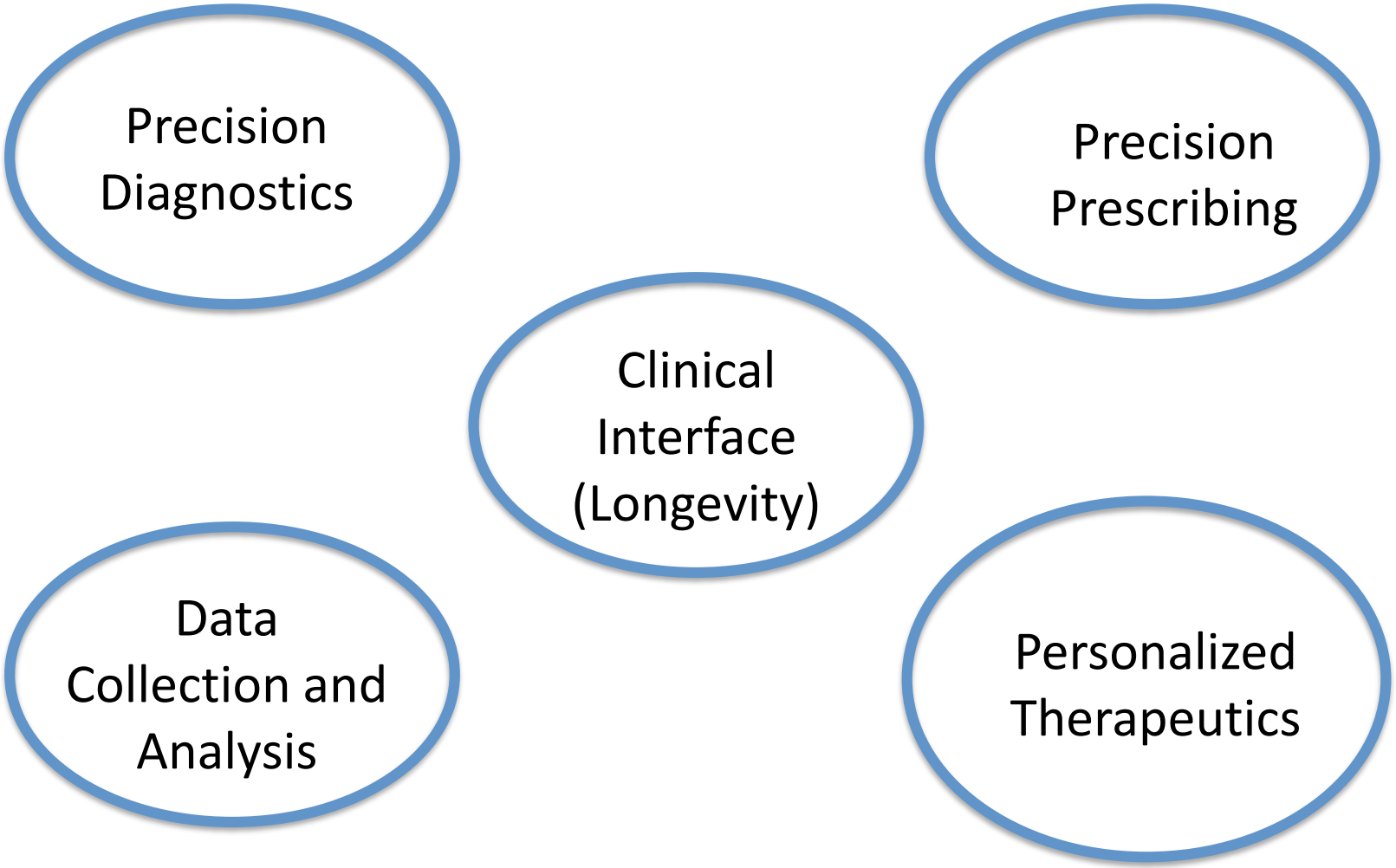
June 2017 we produced Roadmap 2.0: The Time Is Now For Personalized Medicine In British Columbia (produced in collaboration with PwC, LSBC, Genome BC, UBC, CDRD, PROOF…)

Recommendations:

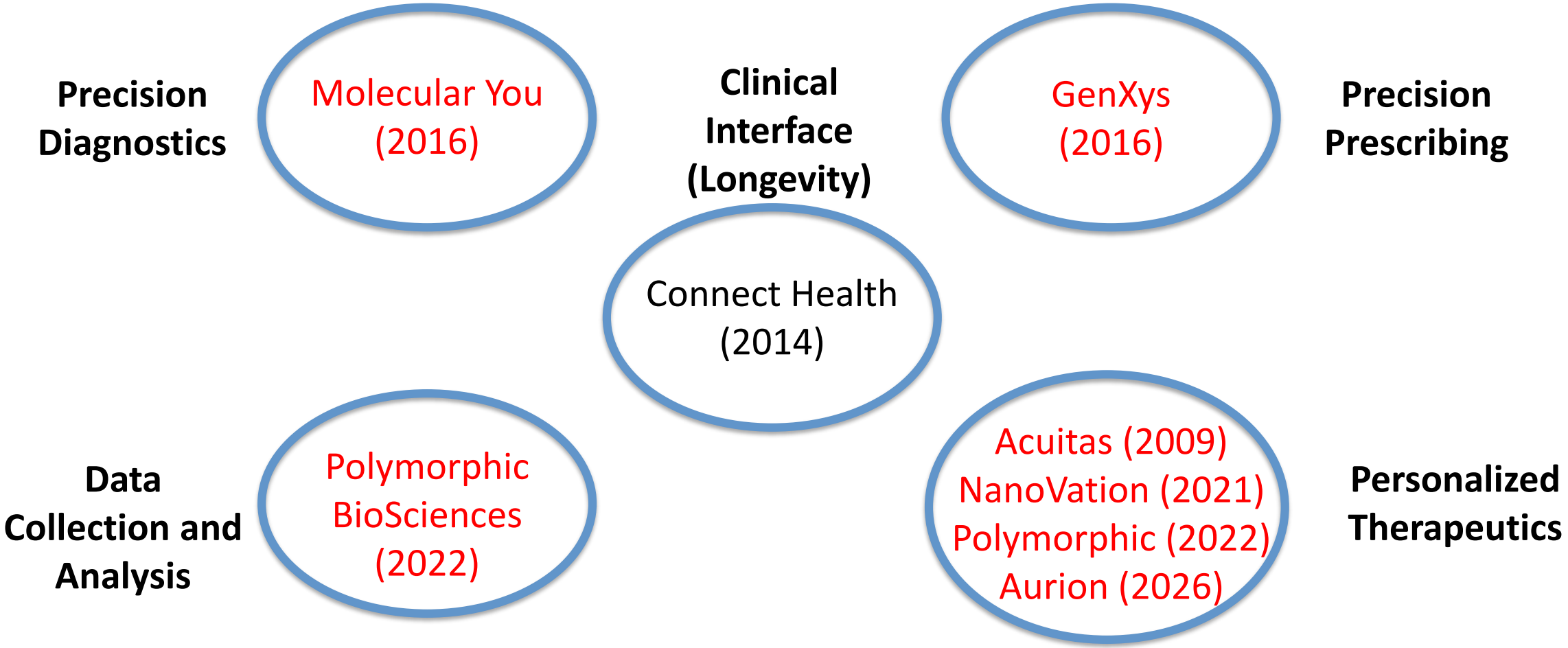
1. **The BC government should make a leadership commitment to personalized medicine**
2. **We should establish an umbrella organization to catalyse and implement personalized medicine**
3. **We should build on established strengths in personalized medicine**
4. **We should construct a unique 25,000 person Omics database in high cost/morbidity/mortality diseases**

But we could not get any support from the BC Government or healthcare authorities. So in early 2018 we decided to build the infrastructure required for personalized medicine through start-up enterprises…

What Were The Priorities?



We Have Founded More Than Seven Start-Up Companies in Vancouver to Enable Implementation of Personalized Medicine



Molecular You, Connect Health and Polymorphic are presenting elsewhere in this conference

Outline

How can we make personalized medicine happen?

- The Personalized Medicine Initiative 2011-2017
- **The start-up approach: Precision diagnostics**
  - **Molecular You**
  - **GenXys**
- The start-up approach: The clinical interface
  - Polymorphic BioSciences: data collection and analysis
  - Connect Health: The Longevity 100
- The start-up approach: Personalized medicines
  - Aurion Therapeutics: Personalized cancer drugs (small molecules)
  - Background: Gene Therapy
  - Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies

Precision Diagnostics: Molecular You

Enabling Predictive Health through AI-Assisted Multi-omic Analysis

Jim Kean
Chief Executive Officer
Rob Fraser
Chief Scientific Officer

A two-sided solution:

Blood Test + Interpretation

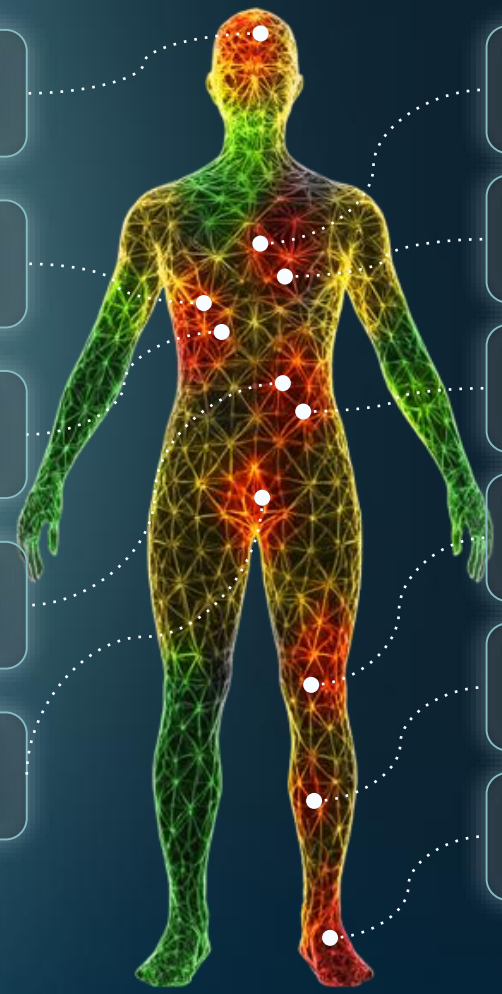
- A single vial of blood
- Proprietary assay platform
- Laboratory Developed Test
  (CLIA / COLA (US)/ ISO-15189 (International)
- 288 Metabolomic and Proteomic biomarkers and growing
- AI & Data Technology platform

288
biomarkers

molecular you

The most **Comprehensive** Health Risk Analysis

- 1 — Vial of blood (250 uL)
- 88% — Avg. Predictive Value
- 288 — High Value Biomarkers
- 1K+ — Biomarkers in Development



- Cognitive Function
- Lung Function
- Liver Function
- Metabolic Health
- Reproductive Function
- Inflammatory Function
- Cardiovascular Function
- Kidney Function
- Immune Function
- Coagulation Function
- Gout

Cancers

- Breast
- Colorectal
- Esophageal
- Ovarian
- Lung
- Pancreatic
- NSCLC
- Melanoma

Precision Prescribing: GenXys

Scaling AI Enhanced Precision Prescribing

Clinical context

Therapy selection

Access & approval

Actionable insight

An orchestration model for precision prescribing

Speaker

Bernard Esquivel MD, Ph.D., MHA

CEO, GenXys

The Prescribing Status Quo Leads to
Dangerous, Costly, and Fragmented Care

Treatment delays hinder clinical outcomes

- **85% of prior authorizations** for specialty medications cause delays (AMA, 2023) **causing 75M patients to be impacted annually**

Inefficient use of clinical resources

- Physicians spend **14.6 hours/week** on PAs, costing **$35B** annually (CAQH, 2022). (PA-prior authorization)

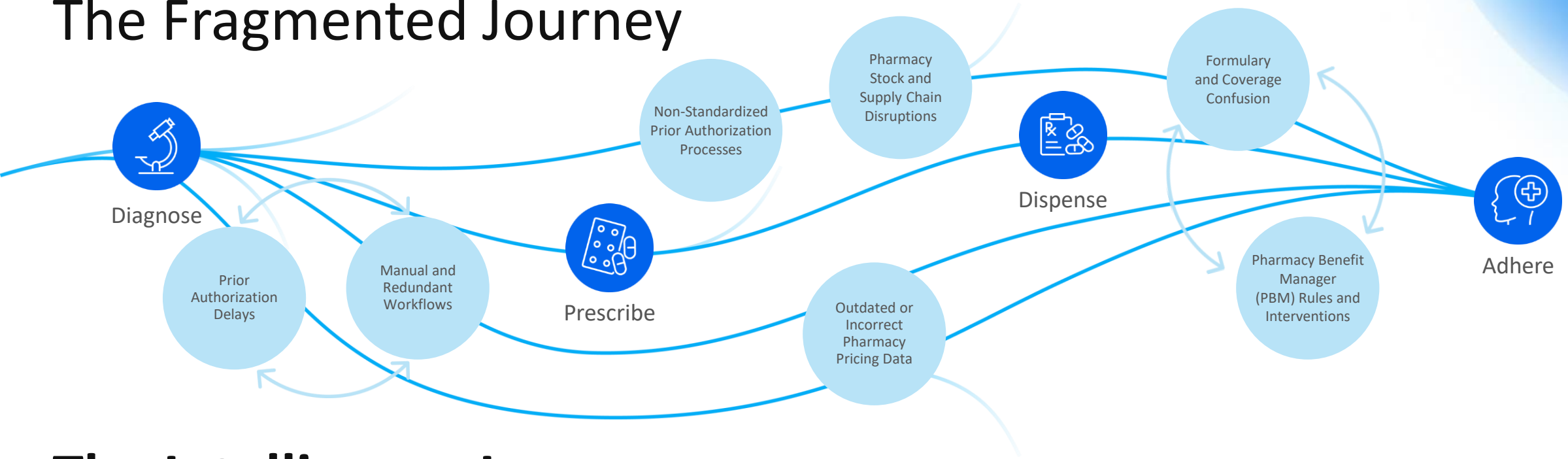
Avoidable health and safety risks

- Adverse drug events cause **1.3M ER visits** and 350K hospitalizations .
- They are the **4th cause of death (CDC, 2023)**.

Unnecessary denials by Payers add costs to the system

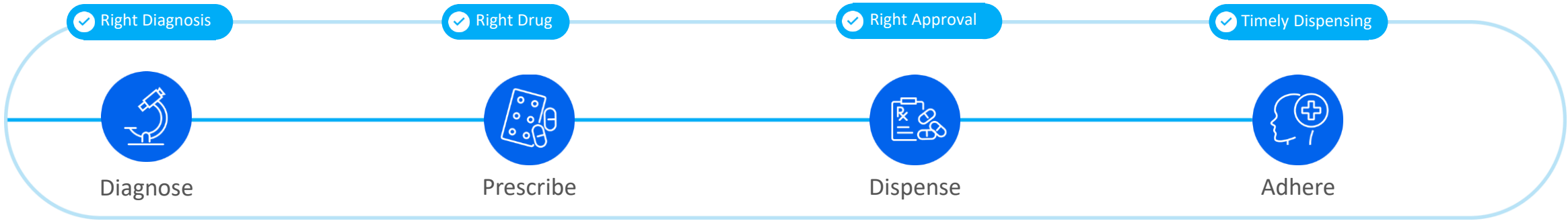
- 54% of denials are eventually overturned, causing **~$10B of waste to the system.**

The Fragmented Journey



The Intelligence Layer

End-to-end infrastructure to unify the prescribing process



Outline

How can we make personalized medicine happen?

- The Personalized Medicine Initiative 2011-2017
- The start-up approach: Precision diagnostics
  - Molecular You
  - GenXys
- **The start-up approach: The clinical interface**
  - **Polymorphic BioSciences: data collection and analysis**
  - **Connect Health: The Longevity 100**
- The start-up approach: Personalized medicines
  - Aurion Therapeutics: Personalized cancer drugs (small molecules)
  - Background: Gene Therapy
  - Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies

The Clinical Interface (Longevity)
Data Collection and Analysis: Polymorphic BioSciences

The clinical interface problem

Longevity clinics are **data-rich** (labs, imaging, body composition, hormones, wearables, genomics).

The data is **fragmented, static and siloed,** so clinics can't ask questions of their data

- and often don't even know **what questions are possible**.

Multimodal data requires automated data extraction and AI-assisted analysis

Typical Datasets	
Patient medical history	ECGs/ECHO cardiograms
LifeLabs clinical testing	Prenuvo MRI
Cleveland heart data	Dutch DUTCH (Dried Urine Test for Comprehensive Hormones)
DEXA Scan	GI-MAP stool test
InBody body composition	Molecular You

Polymorphic is Developing a Clinical Data Platform Called PALM

Polymorphic Biosciences

What does PALM provide?

- **Step 1 — Aggregate & Structure Longitudinal Data**
- **Step 2 — Generate Actionable Clinical Insights**
- **Step 3 — Build a Real-World Outcomes Intelligence Network**
- **Step 4 — Establish the Data Infrastructure for Precision Preventive Medicine**

The Clinical Interface
Connect Health

DR. LAWRENCE CHENG

MD, CCFP(EM), MPH
Medical Director & Co-Founder

DR. ASHLEY RISKIN

BSc, MD, CCFP
Clinical Director & Co-Founder

EMILY O'LOUGHLIN

CEO

Connect Health: A premier centre for longevity medicine

Connect Health and The Longevity 100 Program
A science-driven clinical framework for longevity therapies

A variety of interventions are potentially beneficial for improving healthspan and decreasing disease risk

- **Supplements**
  - Vitamin D — associations with lower mortality
  - NMN / NAD+ boosters — human metabolic data; preclinical longevity signals
  - Fish oil / DHA — mortality and cardiometabolic associations
  - Glucosamine — prospective mortality and complication data
  - Creatine — improved strength and performance in older adults
  - Urolithin A — human trial showing improved muscle / mitochondrial biomarkers
  - Taurine / glycine — strong preclinical aging biology rationale
- **Vaccines / preventive interventions**
  - COVID-19 vaccination — 25% lower all-cause mortality (National Study, France)
  - Shingles vaccination — lower cardiovascular event risk
- **Repurposed Drugs**
  - Metformin
  - GLP-1 agonists
  - SGLT2 inhibitors
  - Statins
  - Rapamycin
  - Dasatinib / senolytics
  - Aspirin — longevity and cancer-related outcome data in selected settings

The Longevity 100 program will assess the health/longevity benefits of these anti-aging agents for a select cohort of patients

Outline

How can we make personalized medicine happen?

- The Personalized Medicine Initiative 2011-2017
- The start-up approach: Precision diagnostics
  - Molecular You
  - GenXys
- The start-up approach: The clinical interface
  - Polymorphic BioSciences: data collection and analysis
  - Connect Health: The Longevity 100
- **The start-up approach: Personalized medicines**
  - **Aurion Therapeutics: Personalized cancer drugs (small molecules)**
  - **Background: Gene Therapy**
  - **Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies**

Personalized Medicines

We need a new generation of pharmaceuticals in order to have truly personalized therapeutics:

- **First generation pharmaceuticals: small molecule drugs**
  - Usually treat symptoms, not underlying disease
  - Efficacy limited by toxic side effects
  - Cost >$1B; >10 years to develop
  - One-size-fits all medicines
- **Second generation pharmaceuticals: biologics**
  - Limited number of diseases (e.g. only extracellular targets for mAb)
  - Cost >$1B; >10 years to develop
  - Resistance may develop

These drugs take too long to develop and cost too much to be truly personalized

Personalized Medicines

Requirements:

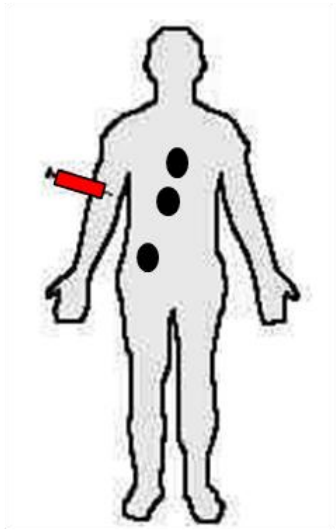
- Can be devised quickly (3 months or less) to treat terminal diseases
- Non-toxic
- Relatively inexpensive
- Highly specific
- Potentially able to treat/cure most human diseases

Solutions:

- Delivery systems that deliver small molecule drugs more specifically to sites of disease
- Delivery systems that enable gene therapies. Such therapeutics have the potential to treat/cure most human diseases

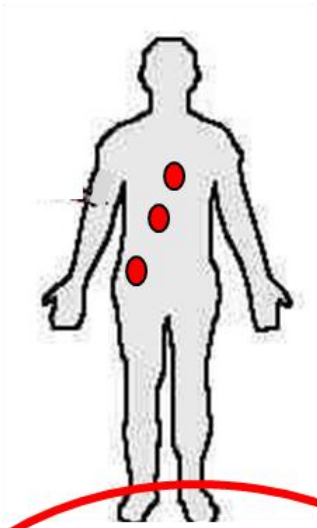
Lipid nanoparticle delivery systems will enable these medicines…

How Can Anti-Cancer Drugs be Personalized?

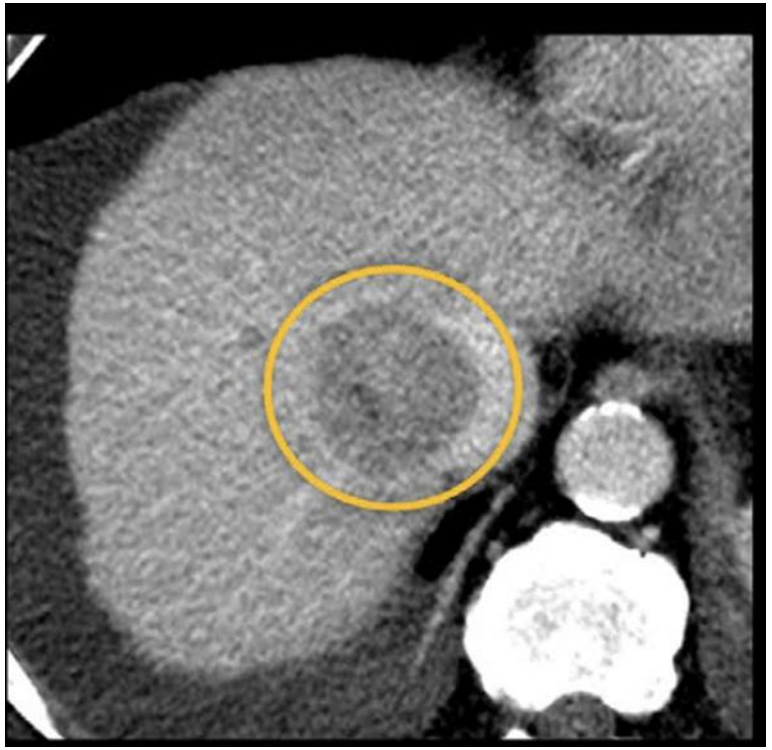


Patient with cancer

Less than 0.01% of cancer drug goes to disease site



Need drug delivery systems to enhance delivery to disease sites and protect sensitive tissues

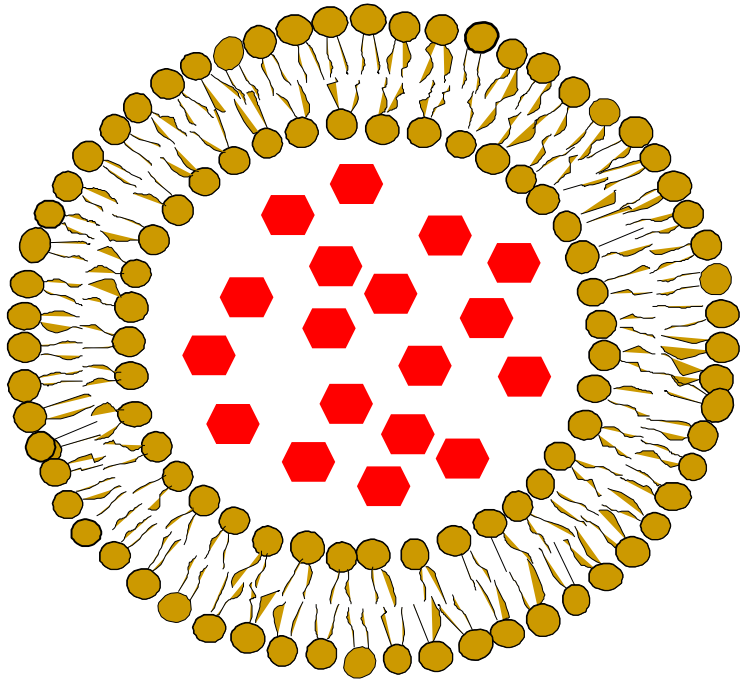


CT scan revealing tumour in a patient's liver.
Need delivery systems that deliver cancer drugs to that site

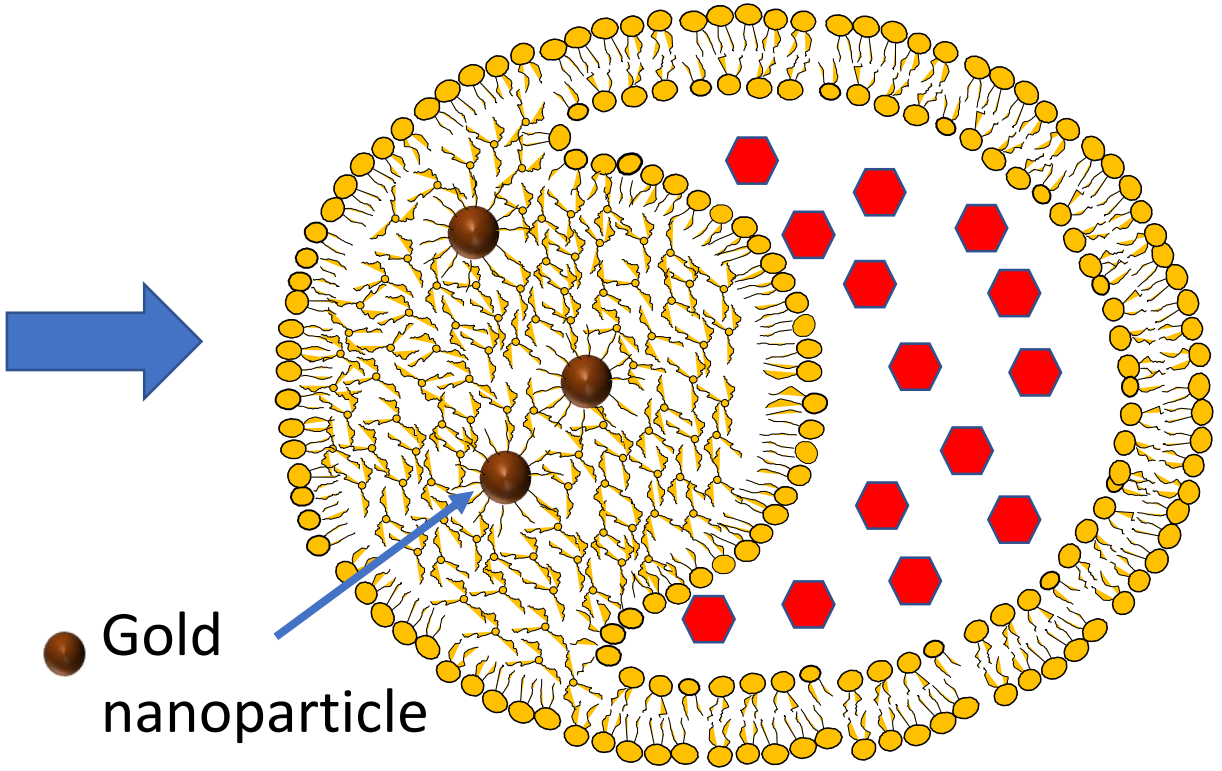
By delivering them more specifically to the sites of disease!

Aurion Therapeutics

We recently founded Aurion Therapeutics to develop triggered release LNPs for targeted delivery of small molecule drugs



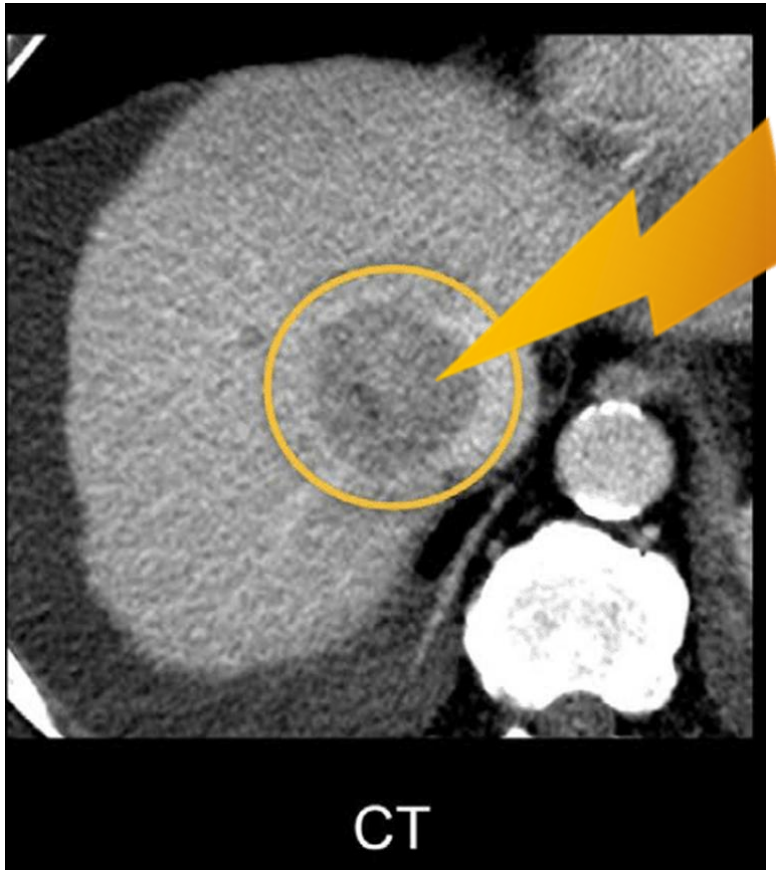
In the 1980s we developed liposomal systems containing cancer drugs; got two products approved by the FDA



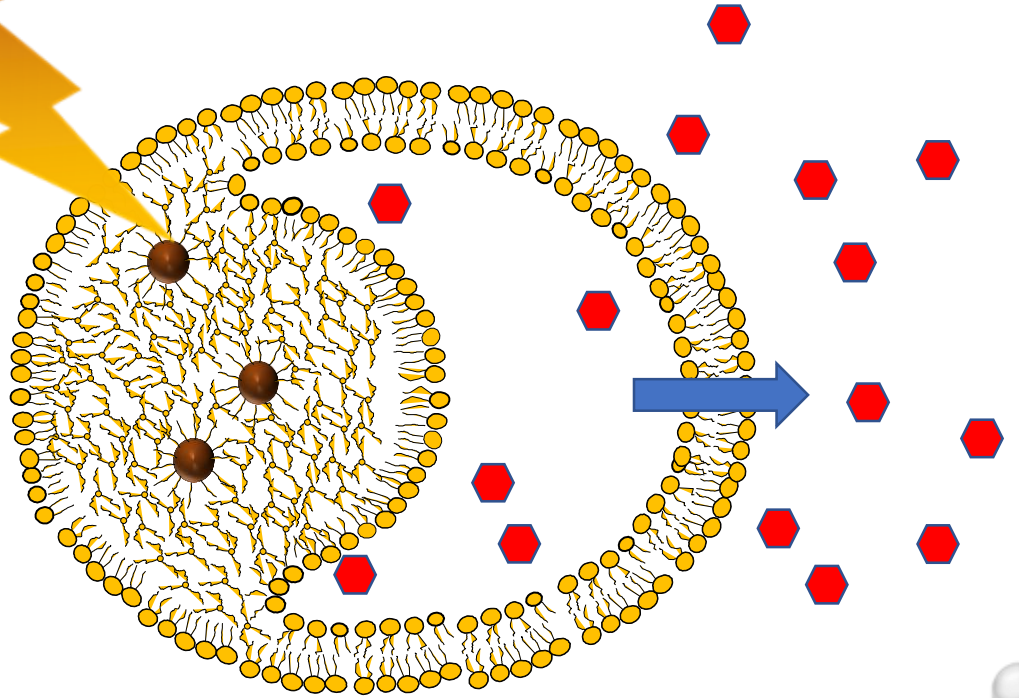
Recently we have developed hybrid systems that contain both cancer drugs and gold nanoparticles (GNP)

Aurion's Triggered Release System is Designed So That Chemotherapeutic Drugs Are Only Released In The Region Of The Tumour

Focused Pulsed Laser



Liver tumour



Long-circulating hybrid LNP

Not quite working yet but we are getting close..

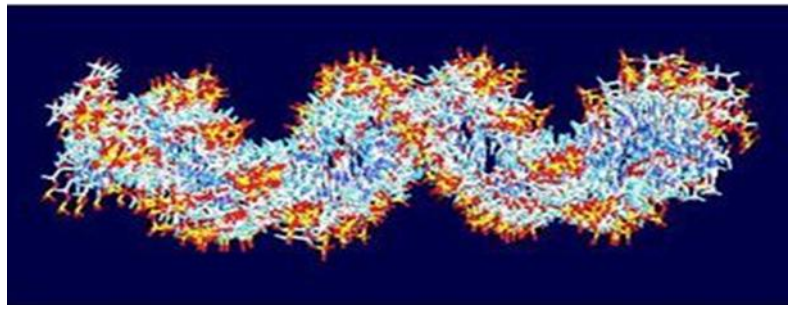
Outline

How can we make personalized medicine happen?

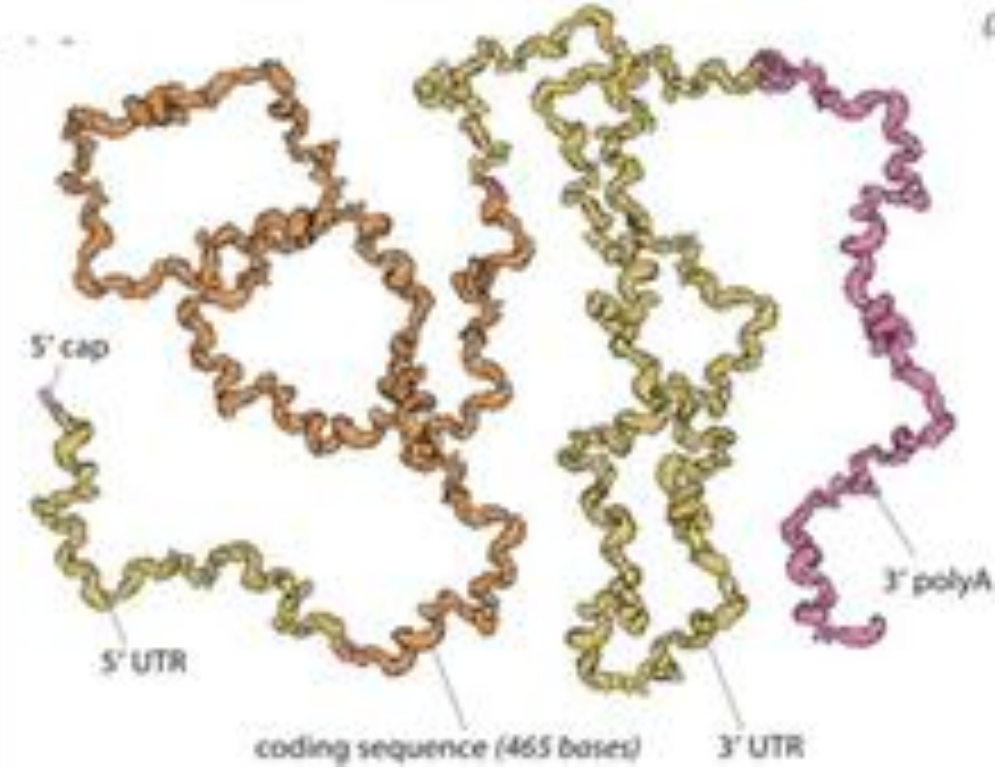
- The Personalized Medicine Initiative 2011-2017
- The start-up approach: Precision diagnostics
  - Molecular You
  - GenXys
- The start-up approach: The clinical interface
  - Polymorphic BioSciences: data collection and analysis
  - Connect Health: The Longevity 100
- The start-up approach: Personalized medicines
  - Aurion Therapeutics: Personalized cancer drugs (small molecules)
  - **Background: Gene therapies**
  - Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies

Background: Gene Therapies

Nucleic-acid based drugs can potentially treat most human diseases



siRNA: to inhibit production of any protein you want (e.g. an oncogene causing cancer)

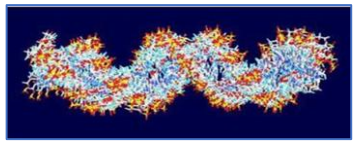


mRNA: to produce any protein you want (e.g. a clotting protein that a hemophiliac needs, or a viral protein for a vaccine)

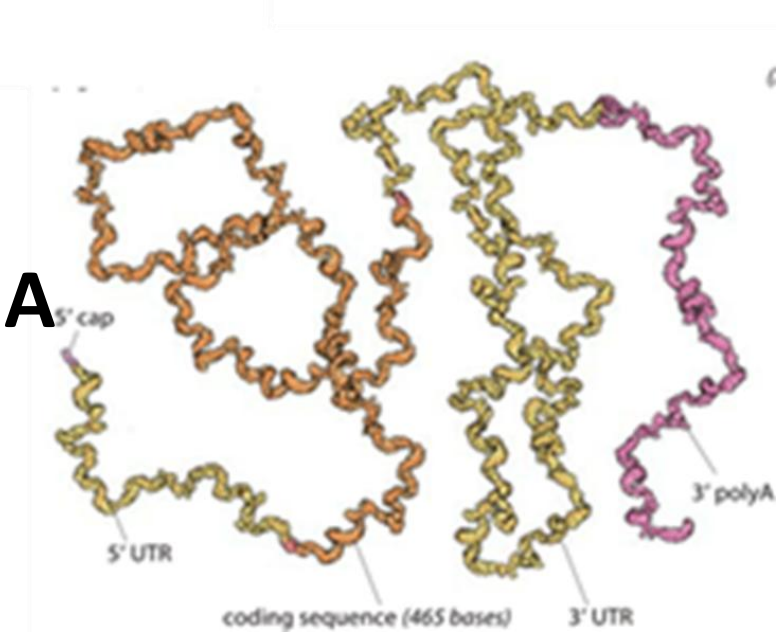
xxx

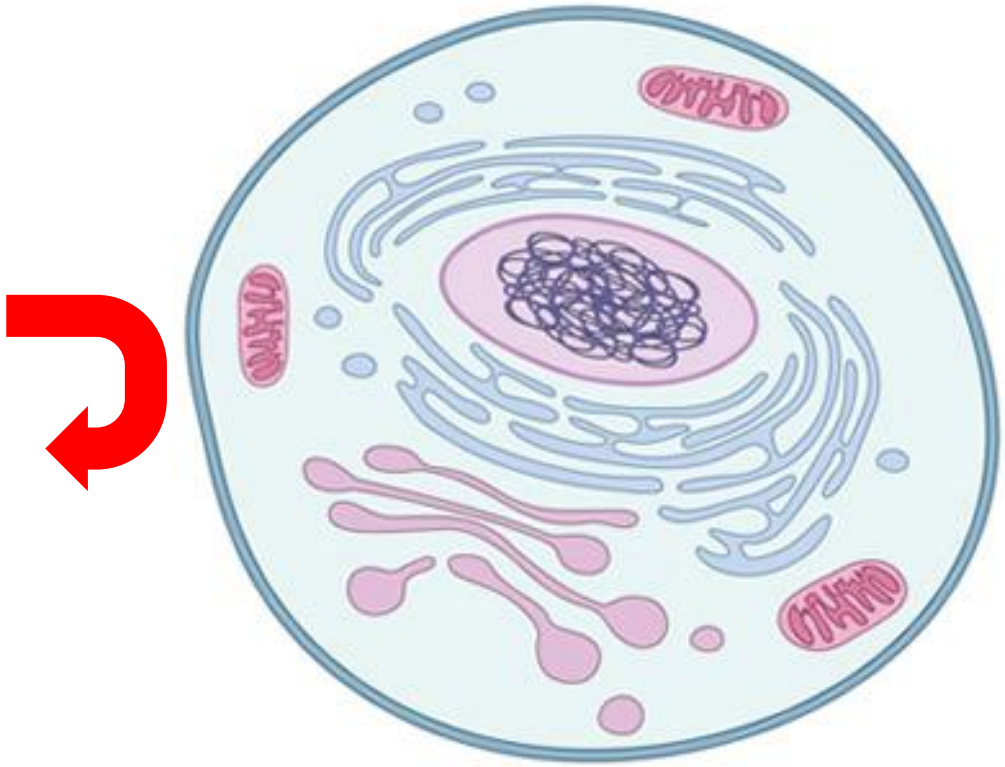
But siRNA and mRNA Molecules Can't Get Into Cells on Their Own

siRNA



mRNA

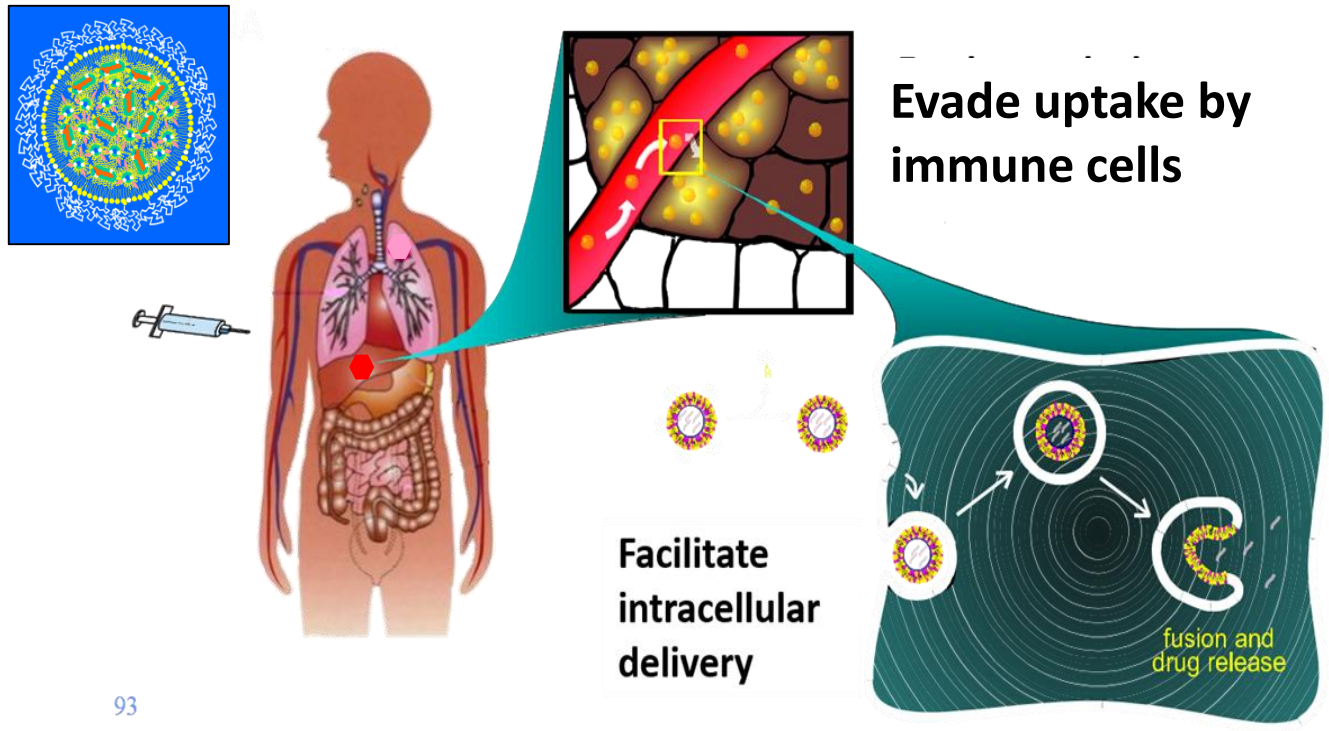




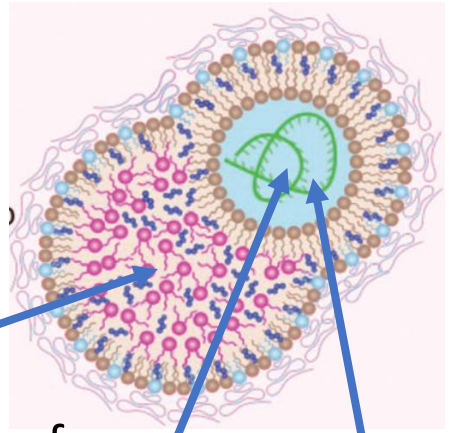
siRNA and mRNA need delivery systems….

In 2000 We Developed Lipid Nanoparticles Containing Nucleic Acid-Based Drugs That Could be Administered In Vivo

Package RNA in LNP



93

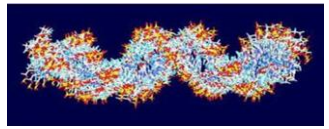


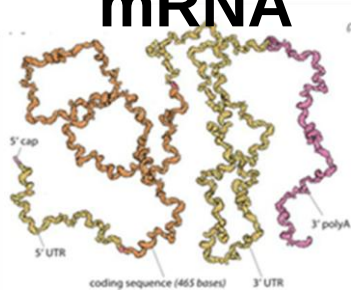
Oil core consisting of ionizable cationic lipids

LNP

mRNA

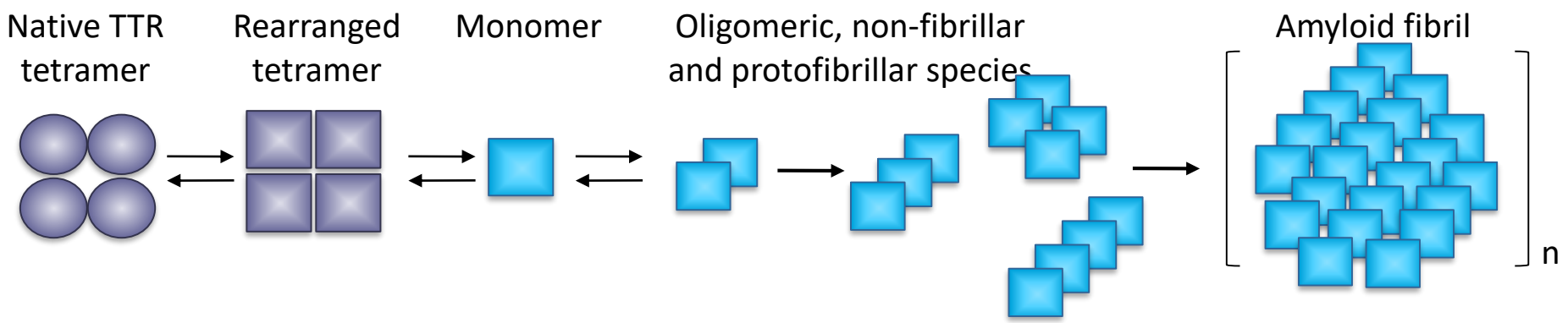
siRNA





xxx

In 2012 We Developed an LNP siRNA System to Treat A Rare Disease Called Hereditary Amyloid Transthyretin (hATTR) Amyloidosis



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

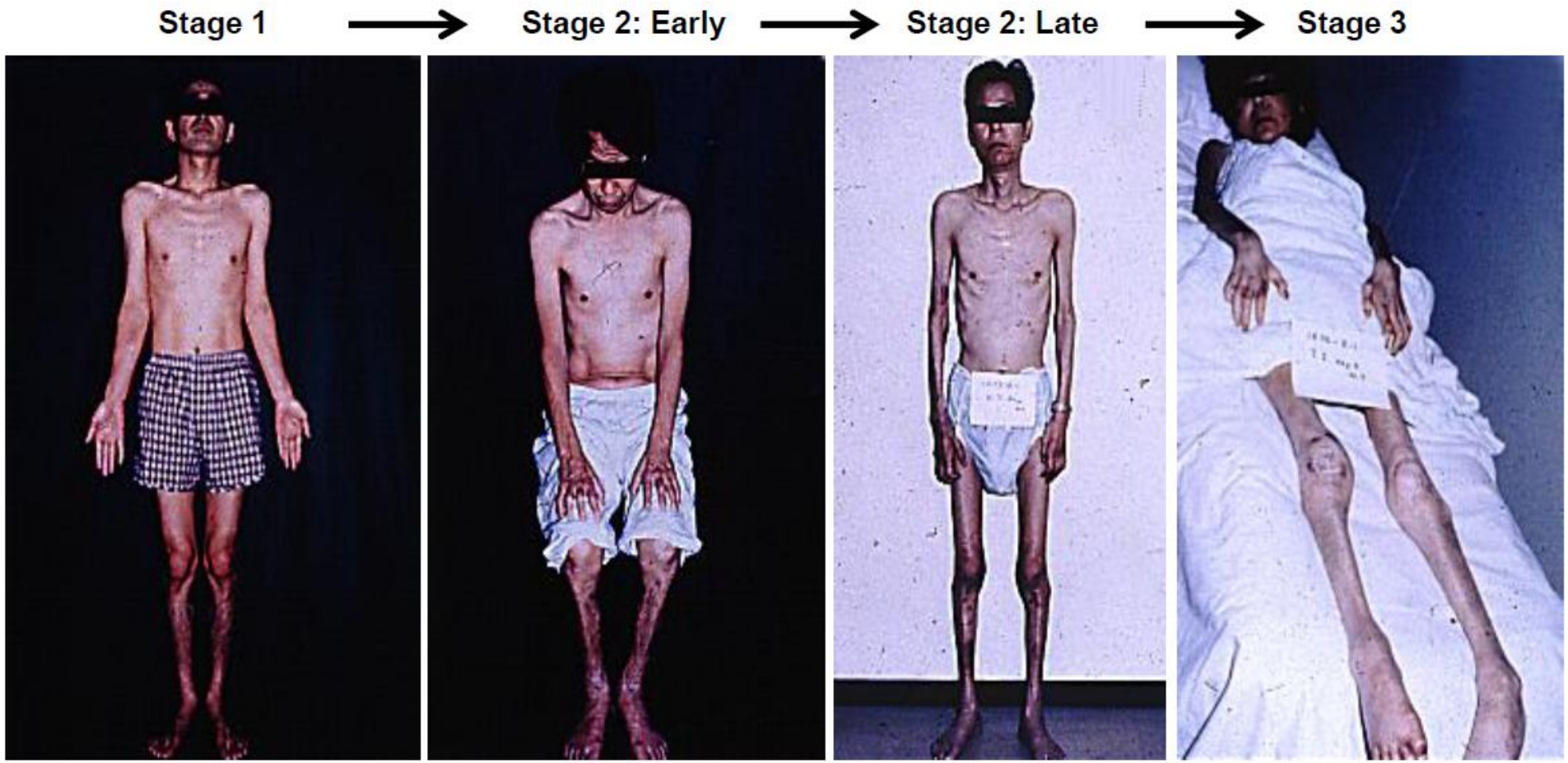
hATTR amyloidosis is a multisystem disease caused by extracellular deposits of TTR amyloid

- ~100 mutations in the TTR gene lead to amyloid deposition in:
  - Nerves : ~10,000 patients. extensive neuropathies
  - Heart: ~40,000 patients, cardiotoxicity leading to heart failure
- No effective therapy, usually fatal within five years of diagnosis

Mutations in TTR gene cause amyloid deposition in cardiac tissue and nervous tissue

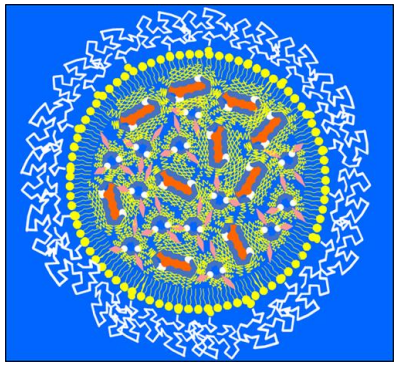
xxx

hATTR Amyloidosis: A Rapidly Progressing Disease Usually Fatal Within Five Years of Diagnosis



xxx

Used LNP siRNA to Inhibit Production of Transthyretin in the Liver



Use LNP containing siRNA to silence transthyretin (TTR) production in the liver

~~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

Entered clinical trials in 2013

A potentially simple solution to a devastating disease

xxx

LNP siTTR (Onpattro) Phase 3 Trial Results Announced September 20, 2017: Hit Primary Endpoint and All Secondary Endpoints!

Primary Endpoint (18 mo.)		p-value
mNIS+7	Neuropathy improvement score better than placebo	9.26×10^{-24}

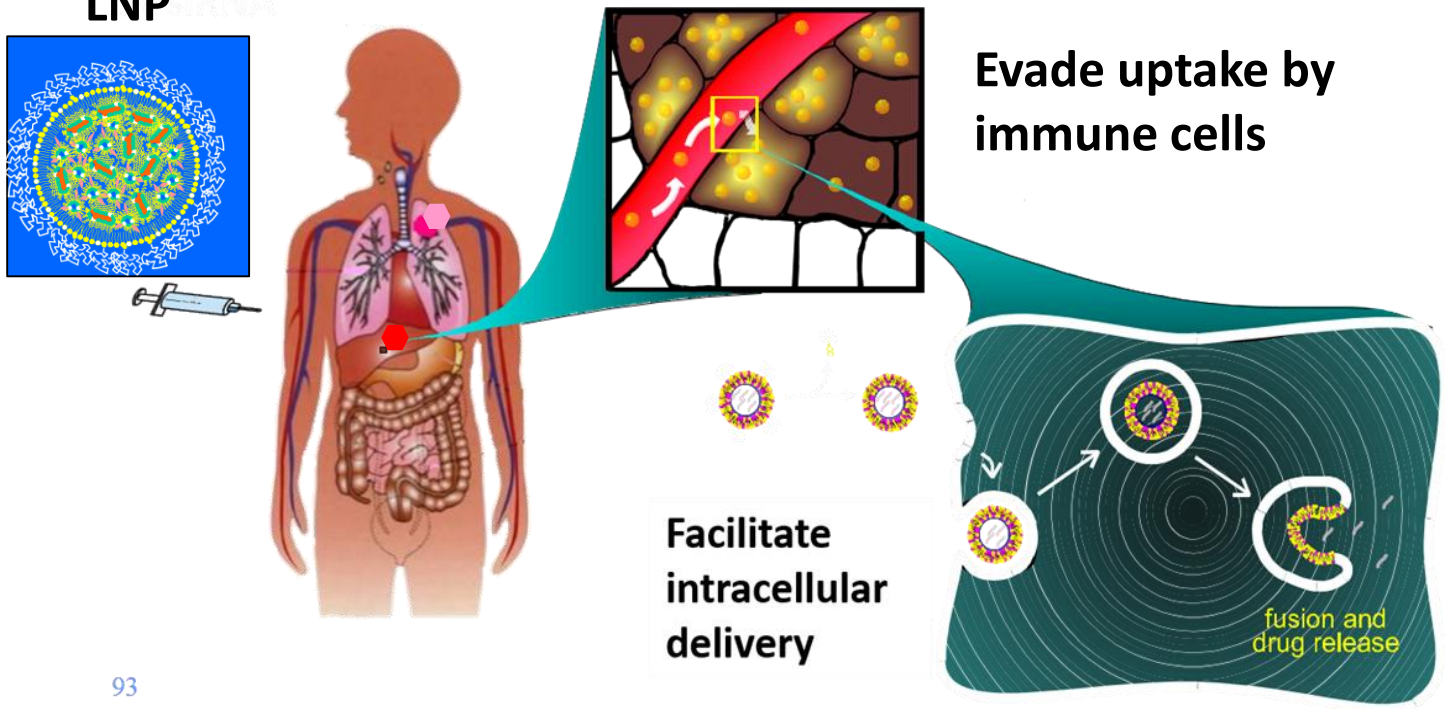
Secondary Endpoints (18 mo.)		p-value
Norfolk-QoL	Quality of life better than placebo	1.10×10^{-10}
NIS-W	Muscle strength better than placebo	1.40×10^{-13}
R-ODS	Overall disability scale better than placebo	4.07×10^{-16}
10MWT	Gait speed better than placebo	1.88×10^{-12}
mBMI	Nutritional status better than placebo	8.83×10^{-11}
COMPASS-31	Autonomic muscle function better than placebo	0.0008

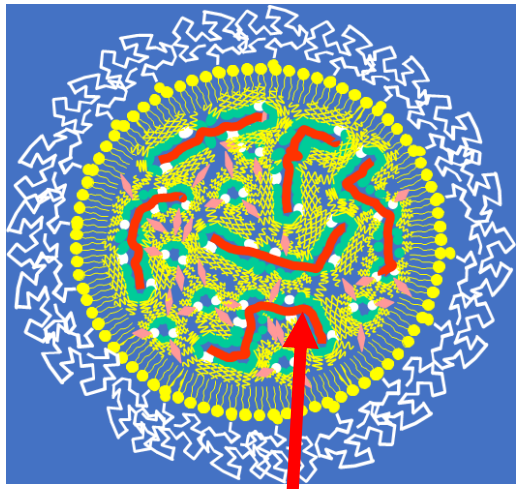
Onpattro is a curative therapy for a previously fatal rare genetic disease. Approved by FDA in Aug, 2018.

xxx

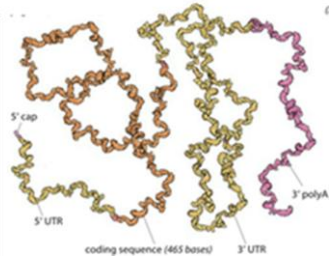
In 2013 We (Acuitas) Asked If We Can Deliver siRNA to Silence a Gene in the Liver, Can We Deliver mRNA to Express a Gene in the Liver?

Package mRNA in LNP





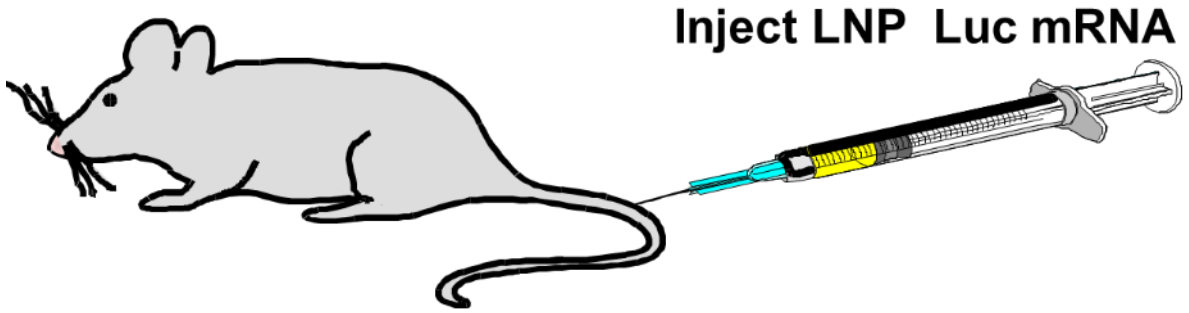
mRNA



93

xxx

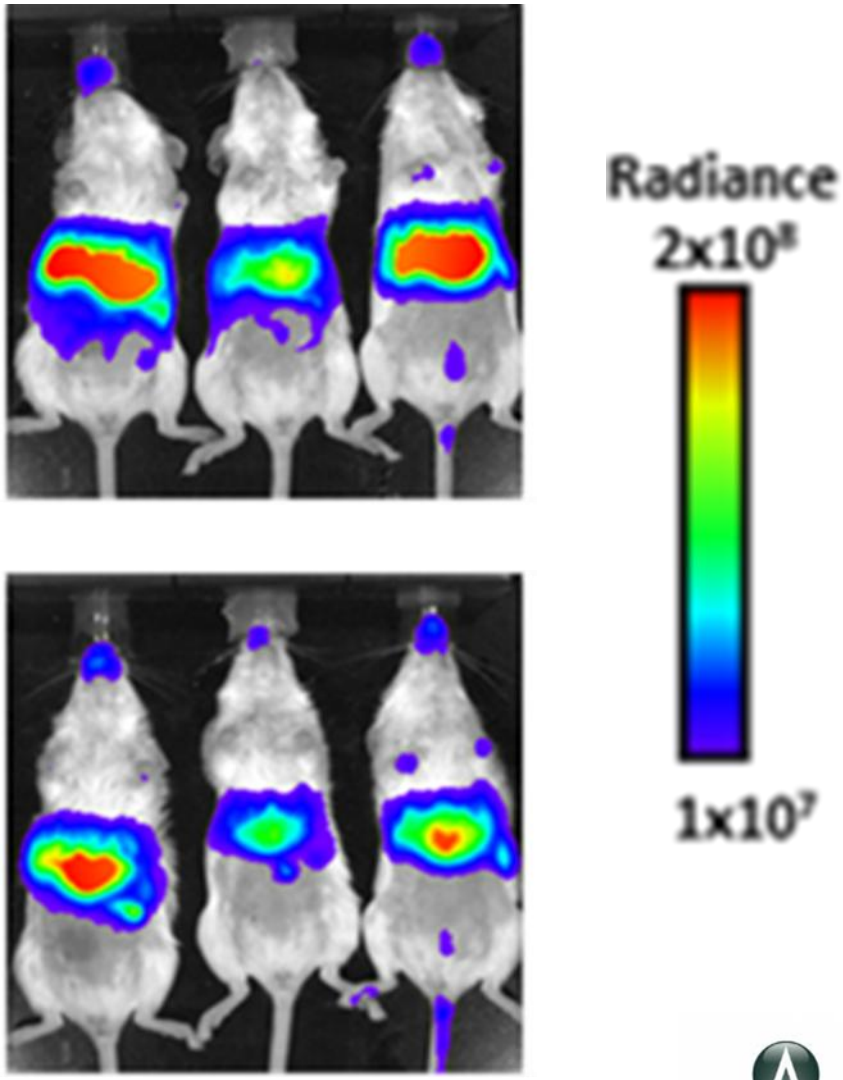
It Worked! LNP mRNA Formulations Could Give Rise to High Levels of Gene Expression in the Liver



Assay for Luciferase in liver

Time 0h	**Dose mice with LNP mRNA (range 0.01 to 10mg mRNA/kg body weight**
Time 4h	**Terminate mice, assay liver for Luciferase expression**
Lipid composition	**Ionizable cationic lipid/DSPC/cholesterol/PEG-lipid; usually 50/10/38.5/1.5; mol/mol**

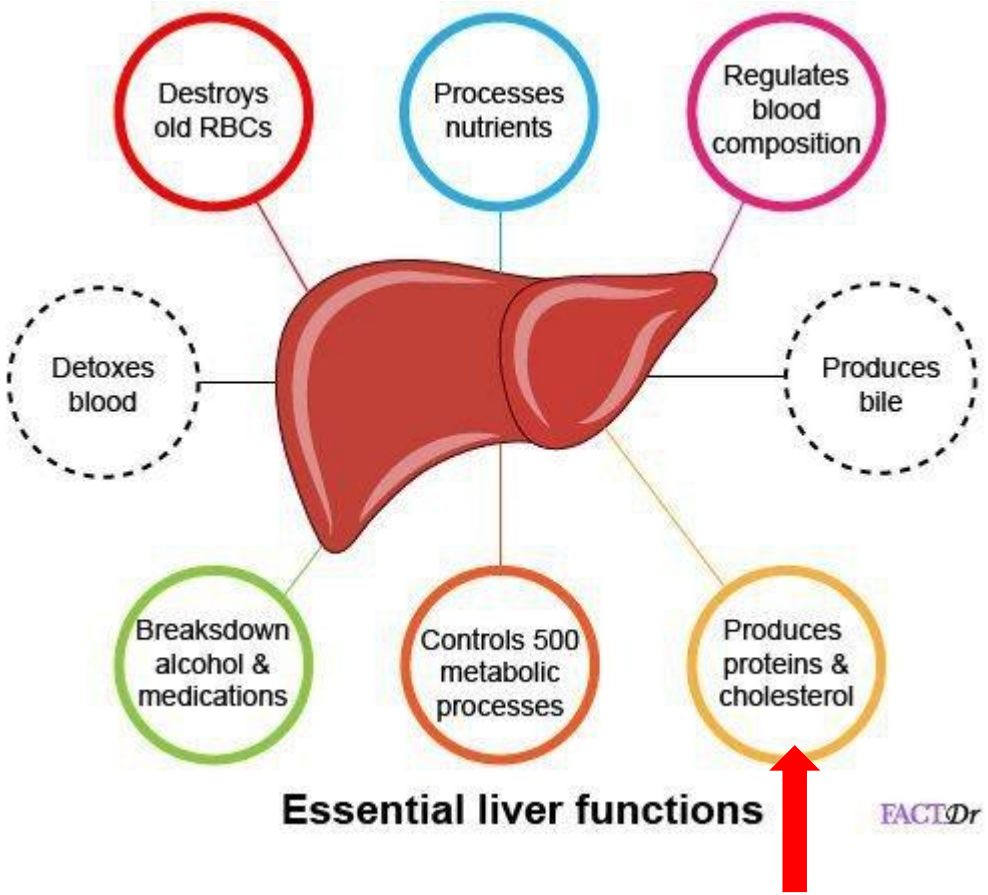
-



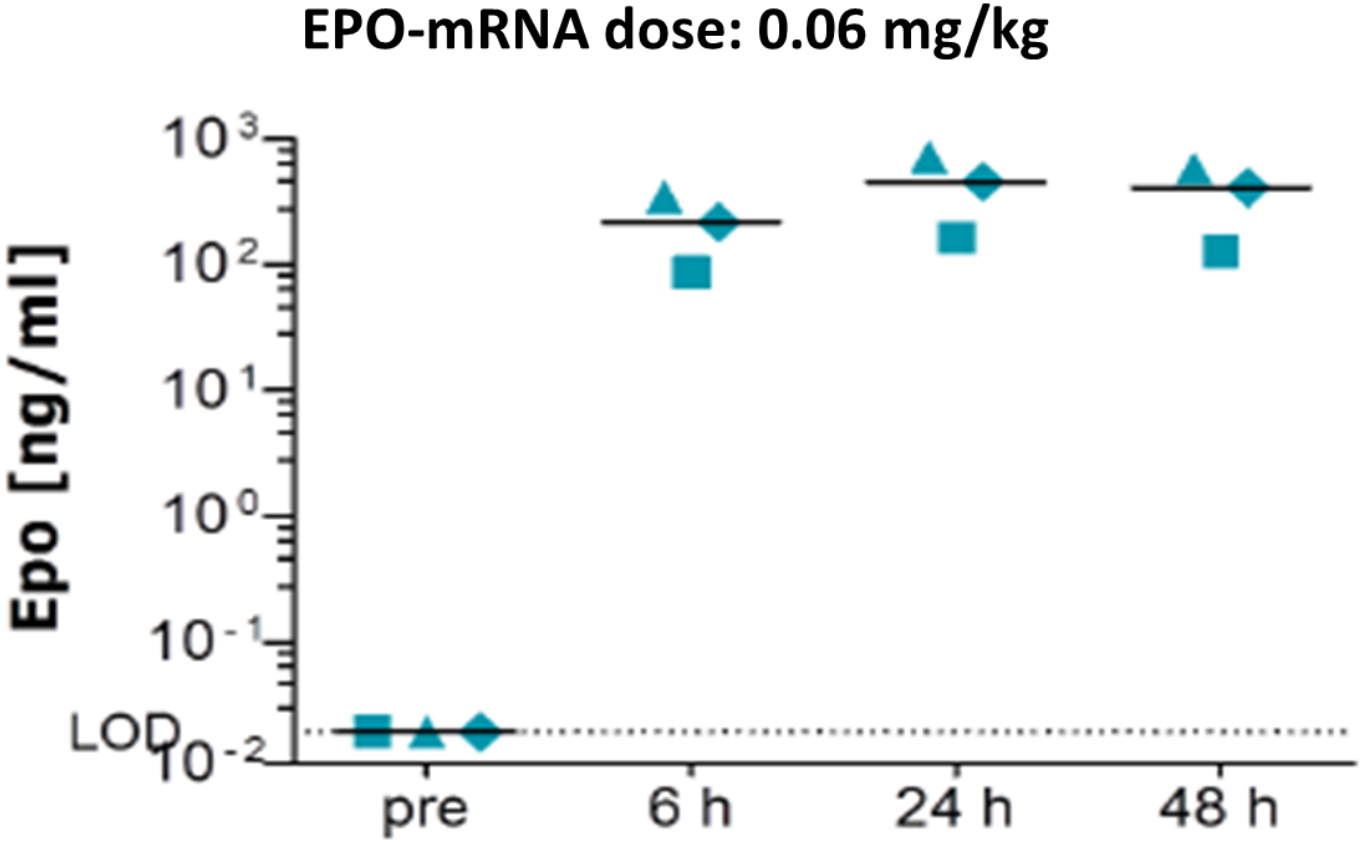
IVIS Imaging

xxx

Found That We Could Make the Liver Make Any Protein We Wanted by Injecting LNPs Containing mRNA Coding for That Protein



The liver produces most of the proteins in your body



Injected pigs with LNP mRNA coding for erythropoietin

xxx

Serendipity: We Were Approached in 2014 by Drew Weissman (U Penn) and Katalin Kariko (BioNTech) Who Needed a Delivery System for mRNA Vaccines

Drew Weissman

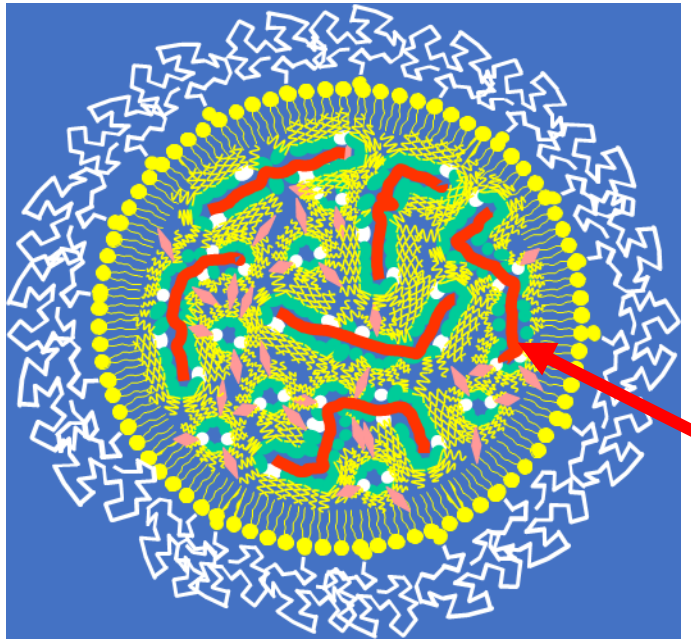
Katalin Kariko

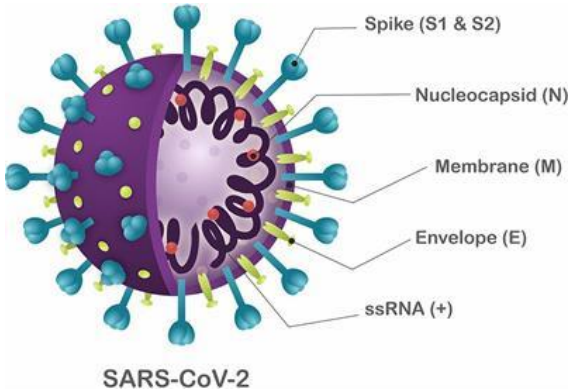
Drew Weissman and Katarin Kariko discovered that by modifying mRNA they could reduce toxicity and increase gene expression, wanted to use mRNA as a vaccine

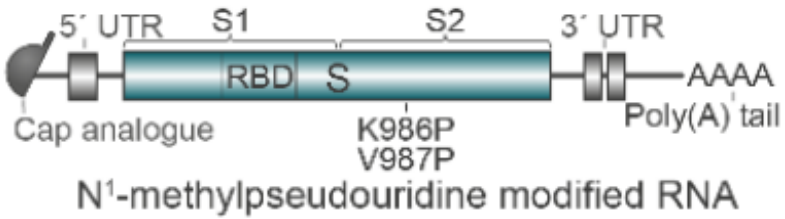
"We have a delivery problem. How do we get mRNA coding for viral proteins into muscle and immune cells in vivo?"

xxx

This Led to a Collaboration Between Acuitas and BioNTech (Germany) to Develop Comirnaty the Pfizer/BioNTech COVID-19 mRNA Vaccine







mRNA coding for the SARS-CoV-2 spike glycoprotein

Acuitas began working with BioNTech to develop influenza vaccines in 2018. BioNTech was also working with Pfizer on a flu vaccine. All efforts switched to a COVID-19 vaccine in February, 2020

xxx

Pfizer And BioNTech Conclude Phase 3 Study Of Covid-19 Vaccine Candidate in November 2020, Meeting All Primary Efficacy Endpoints

Press release Wednesday, November 18, 2020 - 06:59am

- Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose;170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group
- Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%
- Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved
- Data demonstrate vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%
- Companies plan to submit within days to the FDA for EUA and share data with other regulatory agencies around the globe
- The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021

Comirnaty approved by USA, UK, Canada, EU for emergency use December 2020

LNP mRNA played a major role in ending the COVID-19 pandemic.

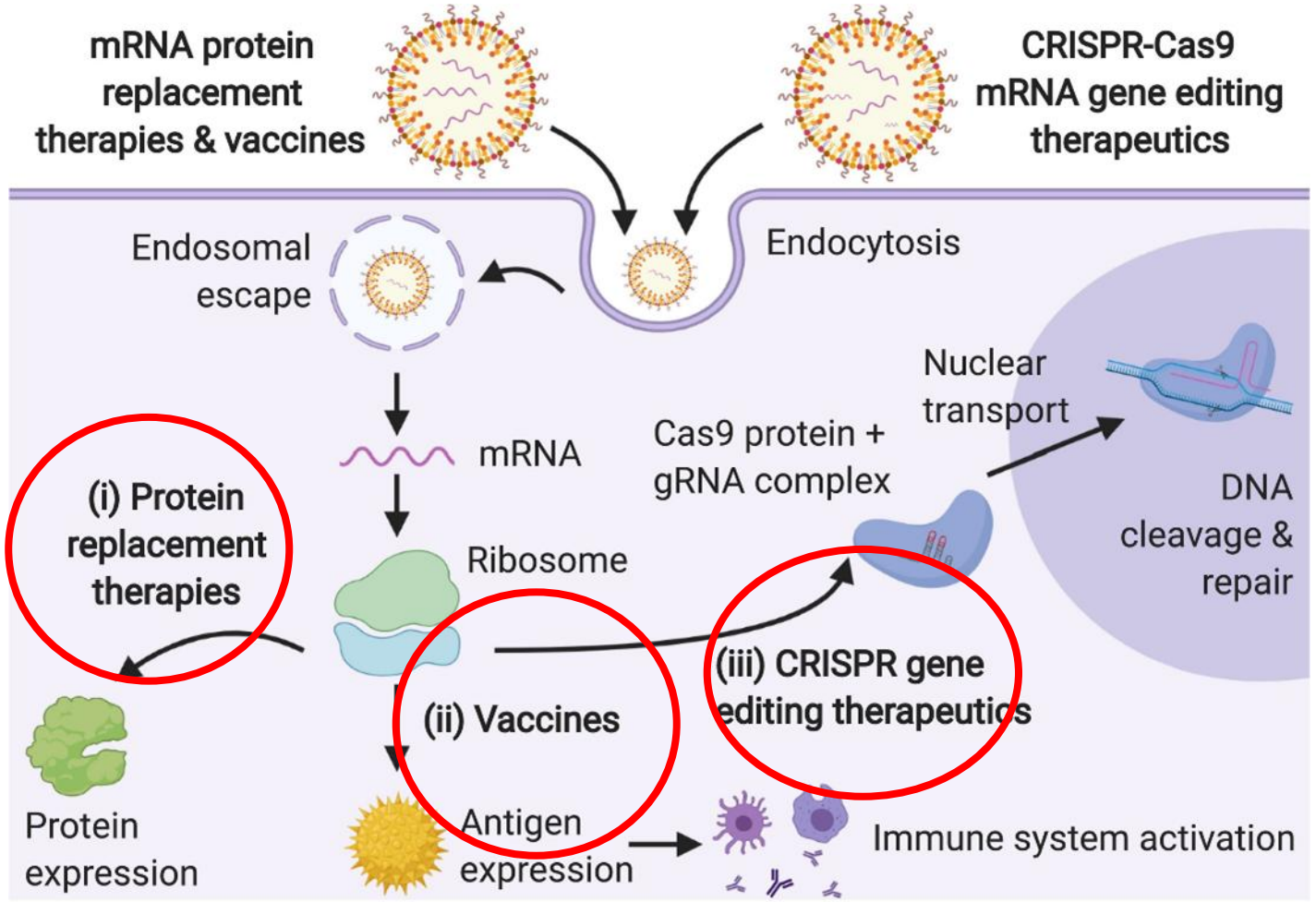
xxx

But The Therapeutic Applications of LNP RNA Systems Will Have Much Greater Impact Than Just The COVID-19 Vaccines…

First generation: small molecule drugs

Second generation: biologics

Third generation: LNP mRNA gene therapies for protein replacement therapies, vaccines and gene editing therapeutics



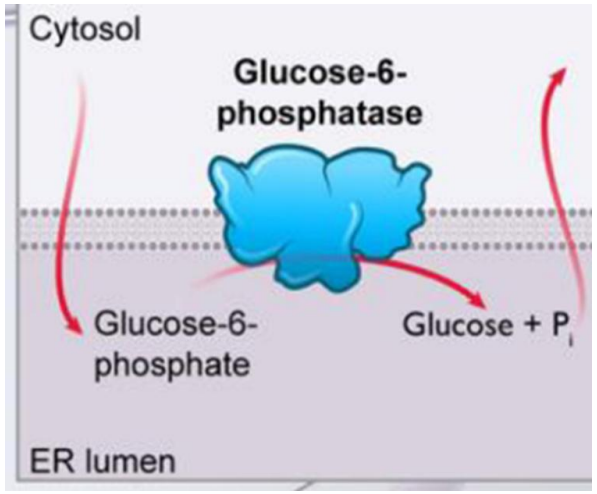
All of these gene therapies can be produced in a matter of weeks…

Enormous Number of Vaccine Applications for LNP mRNA Systems

Disease	Proof-of-Principle References
Clostridioides difficile (C. Difficile)	Alameh, M.-G., et al. Science, 2024. https://doi.org/10.1126/science.adn4955
Influenza and SARS-CoV-2	Freyn et al., Mol Ther.2020 https://pubmed.ncbi.nlm.nih.gov/32359470/
Lassa Virus	Hashizume, M. et al. bioRxiv 2023 https://doi.org/10.1101/2023.04.03.53531
Ebola Virus	Henao-Restrepo, A. M., et al. Journal of Infectious Diseases 2018 (https://doi.org/10.1093/infdis/jix478
Respiratory Syncytial Virus (RSV)	Reichmuth, A. M., et al. Frontiers in Immunology 2019 https://doi.org/10.3389/fimmu.2019.00594
Zika Virus	Pardi, N., et al. Nature 2017 https://doi.org/10.1038/nature21428
Herpes Simplex Virus 2 (HSV-2)	Zhang, R., et al. Nature Comm. 2020 https://doi.org/10.1038/s41467-020-19150-2
Human Cytomegalovirus (HCMV)	Pardi, N., et al. Nature Rev. Drug Discov. 2020 https://doi.org/10.1038/s41573-020-00092-5
Mpox (Monkeypox)	Sang et al. *Sig Transduct Target Ther* **8**, 172 (2023) https://doi.org/10.1038/s41392-023-01432-5
Avian Influenza (H5N1)	Krammer, F., et al. Virology 2023 https://doi.org/10.1186/s12985-023-02023-0
HIV	Haynes, B. F., et al. Vaccines 2021 https://doi.org/10.3390/vaccines9020134

Enormous Number of Applications of LNP mRNA Systems for Rare Genetic Diseases (~20% of All Diseases)

Example: Protein replacement to treat glycogen storage disease



Administer LNP containing mRNA coding for glucose-6-phosphatase

Cao et al. 2021 Nature Comms
https://www.ncbi.nlm.nih.gov/pubmed/34035281

Incidence

- 1 in 30,000 births

Symptoms

- Hypoglycemia (low blood sugar)
- Hepatomegaly (enlarged liver)
- Growth failure
- Lactic acidosis
- Muscle cramps, fatigue, and weakness
- Cardiomyopathy (in Pompe disease)
- Myoglobinuria (dark urine after exercise

Prognosis

- Without treatment death within 2 years

Treatment

- **LNP G6P mRNA!**

Enormous Number of Applications for Rare Genetic Diseases

Disease	Proof-of-Principle References
Methylmalonic acidemia	An, D., et al. Cell Reports 2017 https://doi.org/10.1016/j.celrep.2017.10.001
Acute intermittent porphyria	Jiang, L., et al. Nature Medicine 2018 https://doi.org/10.1038/s41591-018-0209-1
Haemophilia-B	Sahin et al., Gene Therapy 2016 https://doi.org/10.1038/gt.2016.46
Haemophilia-A	Jain, S. K. et al. Biomaterials Science 2024 https://doi.org/10.1039/D4BM00909F
Sickle cell anemia	Breda, L. et al. Science 2024 https://www.ncbi.nlm.nih.gov/pubmed/37499029
Arginase deficiency	Asrani, K. H. et al. RNA Biology 2018 https://doi.org/10.1080/15476286.2018.1475178
Cystic fibrosis	Bai, X. *et al. Nat Commun* 2024 https://doi.org/10.1038/s41467-024-51056-8
Phenylketonuria	Perez-Garcia et al. Molecular Therapy 2022 DOI: 10.1016/j.omtn.2022.02.020
Ornithine transcarbamylase deficiency	Yamazaki K. et al. Mol Ther Nucleic Acids. 2023 https://**doi**.org/**10.1016/j.omtn.2023.06.023**
Crigler-Najjar syndrome	Greig JA et al. Mol Ther Methods Clin Dev. 2023 https://**doi**.org/**10.1016/j.omtm.2023.02.007**
Citrullinemia	Cao et al., Mol Ther. 2019 https://doi: 10.1016/j.ymthe.2019.04.017
Alpha-1-antitrypsin deficiency	Karadagi, A. et al. *Sci Rep* **10**, 7052 (2020) https://doi.org/10.1038/s41598-020-64017-0
Hepatorenal tyrosinemia type 1	Cacicedo et al., 2022 Mol Ther Methods Clin Dev DOI: 10.1016/j.omtm.2022.07.006

Enormous Number of Applications for Rare Diseases
Example: Carbamoyl-Phosphate Synthetase 1 (CPS1) Deficiency

KJ Muldoon NY Times
May 15, 2025

CPS1 deficiency-a monogenic disease

- 1 in 1.3M incidence
- Caused by C → T variant in CPS1 gene
- Causes high ammonia in blood, lethal within months

LNP mRNA containing

- CRISPR adenine base editor to correct mutation T→C
- gRNA, target adenine in the 8th position of protospacer sequence

Doses

- Single patient IND approved FDA 6 months after birth
- Day 208 i.v. 0.1 mg mRNA/kg
- Day 230 i.v 0.3 mg mRNA/kg

World's first gene edited baby: LNP supplied by Acuitas Therapeutics

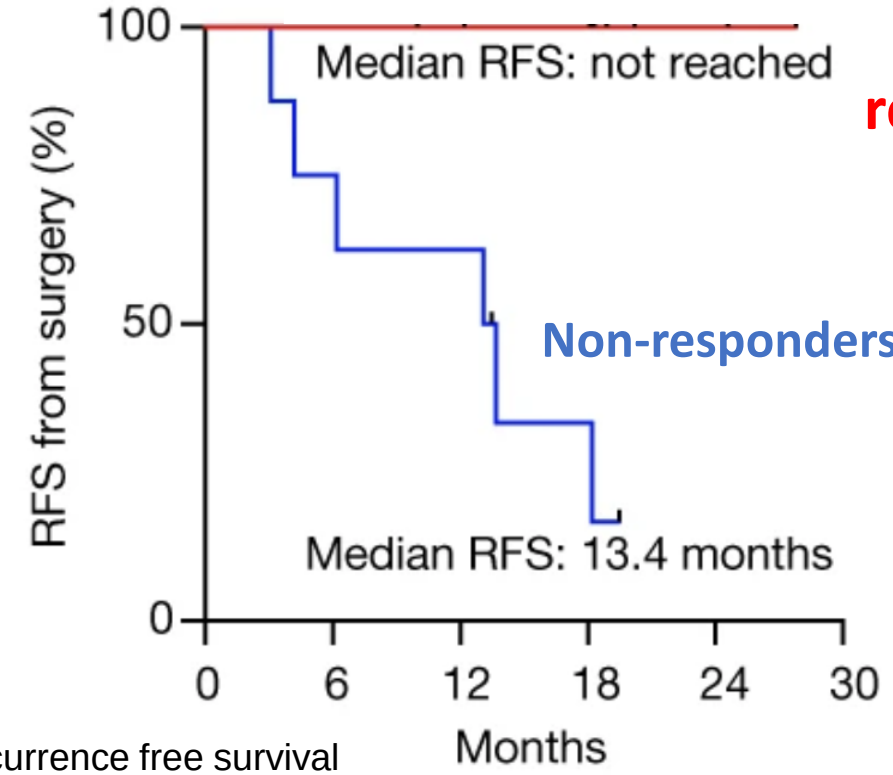
Enormous Number of Applications for Common Chronic Diseases

Disease	mRNA cargo	Proof-of-Principle References
Cancer: vaccines	mRNA Coding for neoantigens	Rojas et al . Nature 618, 144–150 (2023) https://www.ncbi.nlm.nih.gov/pubmed/37165196
Cancer: in vivo CAR-T	mRNA coding for CAR vs cancer cells	Billingsley et al., *Small*. 2024;20(11):e2304378. https://doi:10.1002/smll.202304378
Cancer: intratumoral injection	mRNA coding for cytokines	Hamouda et al., Nat. Comm. 2024 https://doi.org/10.1038/s41467-024-54877-9
Cardiac fibrosis	In vivo CAR-T vs FAP (fibroblast activating protein)	Rurik et al., Science (2022), https://www.science.org/doi/10.1126/science.abm0594
Osteoarthritis	FGF18 mRNA (rhFGF18)	Sun et al., Advanced Healthcare Materials (2024), https://pubmed.ncbi.nlm.nih.gov/39363784/
Cardiovascular/Hypercholesterolemia	Adenine base editor mRNA + PCSK9 gRNA (gene editing)	Musunuru K, et al. Nature. 2021;593:429-434. https://www.nature.com/articles/s41586-021-03534-y
Liver (metabolic/fibrosis) – NAFLD	HGF mRNA; EGF mRNA	Ceccarelli et al., Nature Communications (2021), https://www.nature.com/articles/s41467-021-20903-3
Chronic liver disease/steatosis/fibrosis	VEGFA mRNA	Rizvi et al., Cell Stem Cell (2023), https://pubmed.ncbi.nlm.nih.gov/38029740/
Inflammatory bowel	IL-10 mRNA	Rampado et al., Advanced Science (2025), https://doi/10.1002/advs.202408744
Kidney fibrosis	Relaxin-2 mRNA	Ding et al., Materials Today Bio (2023), 21:100716 https://pubmed.ncbi.nlm.nih.gov/37545557/

Enormous Number of Applications for Chronic Diseases

Example: LNP mRNA Cancer Vaccines

Pancreatic ductal adenocarcinoma (PDAC)



Vaccine responders

RFS – recurrence free survival

Treatment:

- Surgery
- + Immune checkpoint inhibitor (ICI)
  - atezolizumab: aPD-L1
- + mFOLFIRINOX Chemo
  - Oxaliplatin, Leucovorin, Irinotecan, 5-FU
- ± 20 neoantigens mRNA

Outcomes:

- 50% response rate (at least 1 neoAg)
- Responders repleted with vaccine-expanded T cells
- 18+ mo. RFS vs.13.4 mo. median RFS for non-responders

BioNTech/Genetech Phase I Trial (NCT04161755)

Similar encouraging results for melanoma and lung cancer from Merck and Moderna

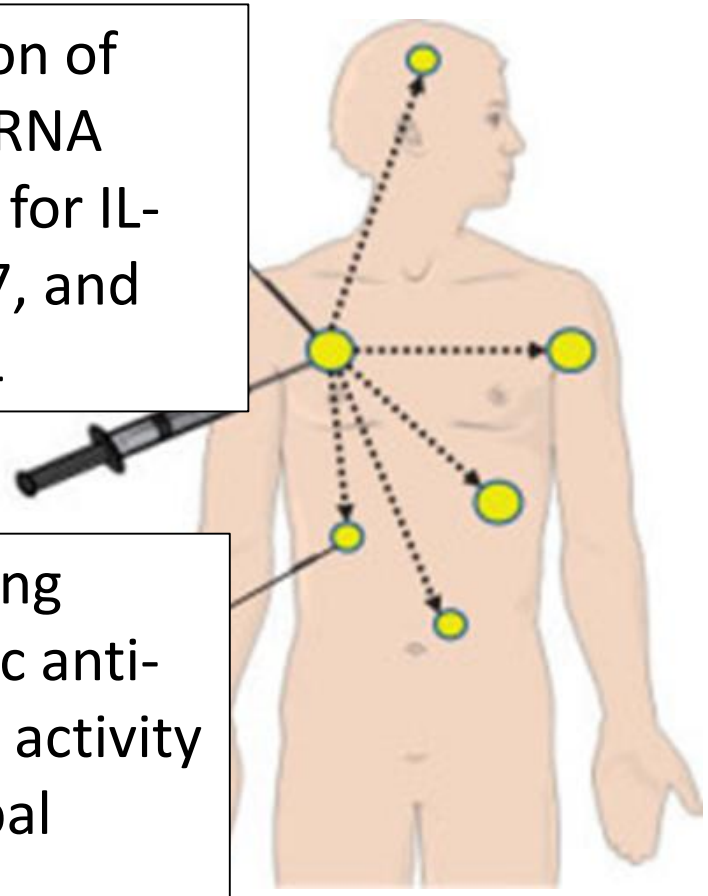
Rojas et al . *Nature* **618**, 144–150 (2023) https://www.ncbi.nlm.nih.gov/pubmed/37165196

Enormous Number of Applications for Chronic Diseases

Example: Direct Intra-Tumour (IT) Injection of LNP mRNA coding for immunostimulatory molecules

IT injections can render “cold” tumours susceptible to the immune system

Injection of LNP mRNA coding for IL-21, IL-7, and 4-1BBL



Activating systemic anti-tumour activity (abscopal effect)

IL-21: Enhances CD8 T-cell function, Increases proliferation and cytotoxicity

Helps generate long-lived memory T cells. Improves tumor cell killing

Supports B-cell responses

IL-7: Prevents T-cell death, Expands naïve and memory T cells

Maintains long-term T-cell pools

4-1BBL: Costimulatory surface ligand that strongly stimulates activated CD8 T cells. Enhances NK-cell activity and improves T-cell survival

Increases memory formation, reduces activation-induced cell death

Local expression of these agents dramatically reduces systemic toxicity

Can induce systemic anti-tumour immunity (abscopal effect).

Hamouda et al., Nat. Comm. 2024 https://doi.org/10.1038/s41467-024-54877-9

LNP mRNA Systems: The Next Generation of Pharmaceuticals That Are Able to Treat Most Human Diseases

Vaccines: such as the COVID-19 mRNA vaccines

Rare diseases: such as CPS1 deficiency

Cardiovascular disease: such as heart disease

Cancer: all forms; cancer vaccine, in vivo CAR-T, direct injection….

Neurological diseases: such as Parkinson’s or Alzheimer’s

All of these gene therapies can be produced in a time period of less than 3 months, relevant to those suffering from terminal diseases

How Can We Take Advantage of All These Opportunities?

Start-Up Tactics

We have founded a platform delivery company to provide LNP delivery systems with FTO for various applications

- NanoVation Therapeutics

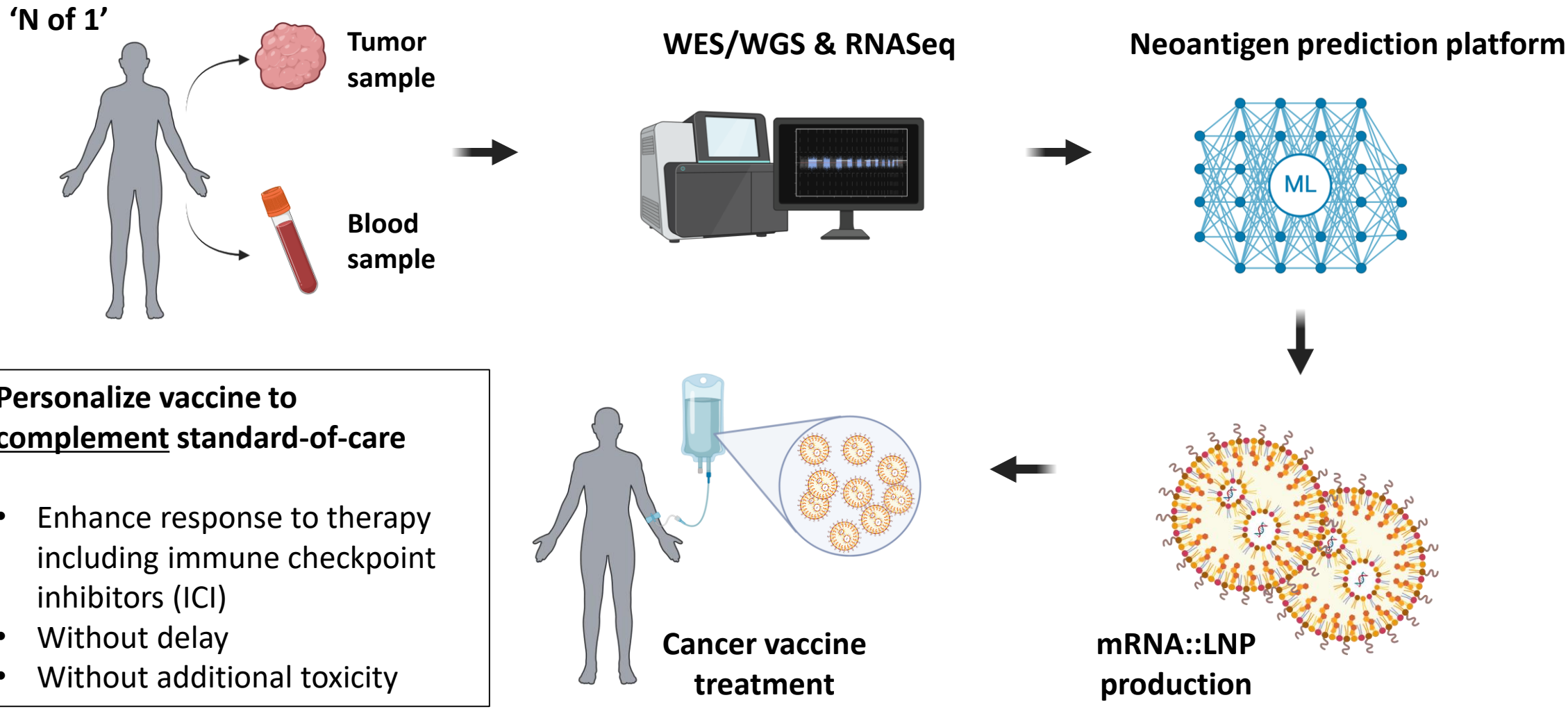
We are establishing the infrastructure for personalized cancer vaccines using academic resources

We have established an incubation company to gain PoP in first-in-human clinical trials for a variety of diseases

- Polymorphic BioSciences

Polymorphic will found companies based on clinical validation

We Are Establishing Infrastructure for Personalized Cancer Vaccines Through a Grant From Canada's Immuno-Engineering and Biomanufacturing Hub (CIEBH)

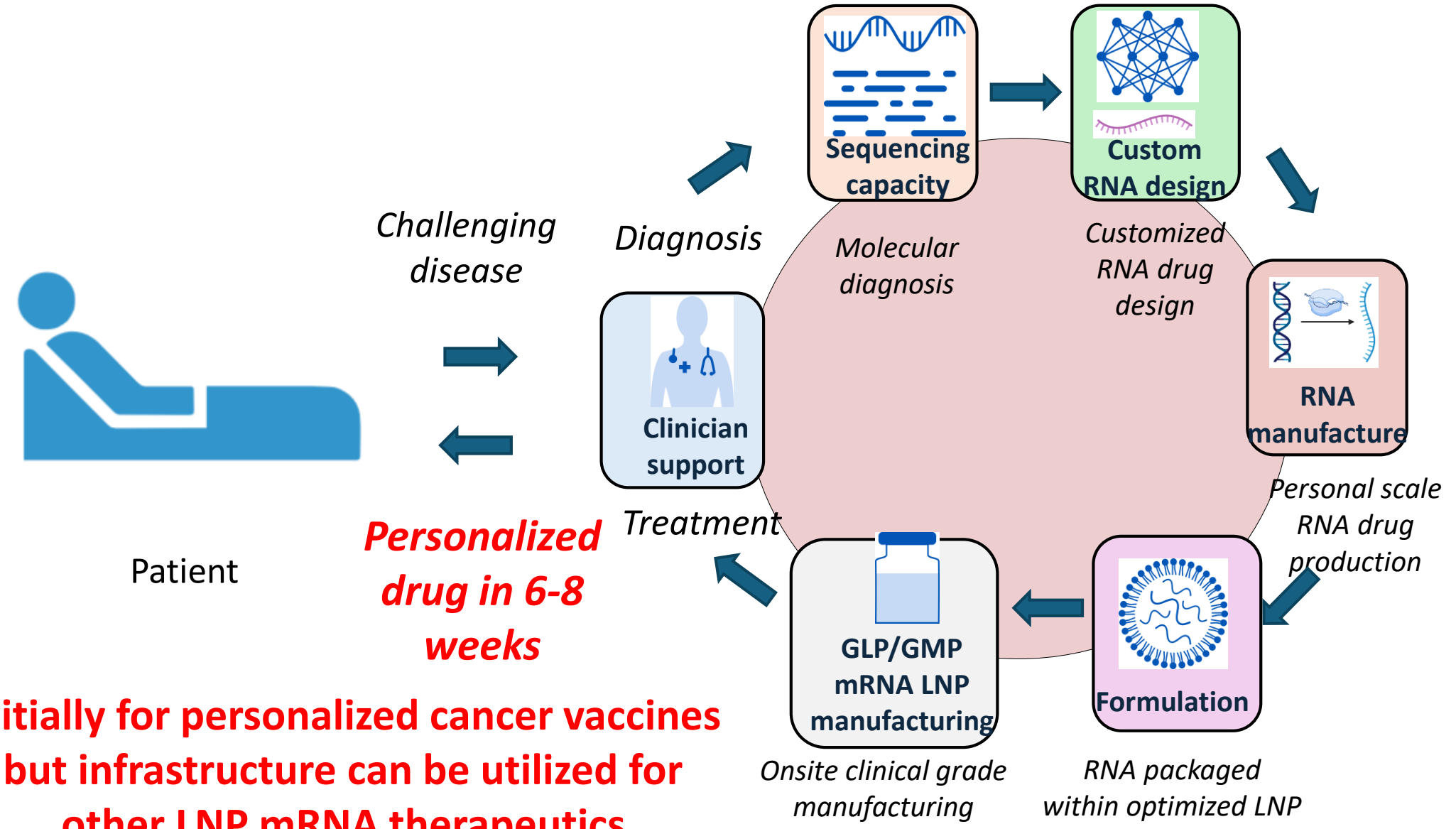


Personalize vaccine to <u>complement</u> standard-of-care

- Enhance response to therapy including immune checkpoint inhibitors (ICI)
- Without delay
- Without additional toxicity

Aim: In the clinic in 18 months

We Are Establishing LNP mRNA Design and Manufacturing Infrastructure at UBC and Associated Hospitals



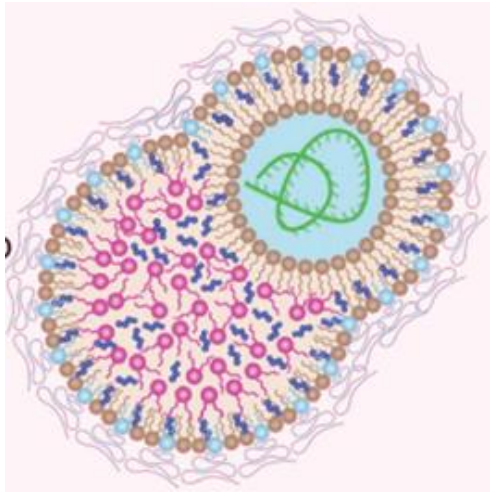
Initially for personalized cancer vaccines but infrastructure can be utilized for other LNP mRNA therapeutics

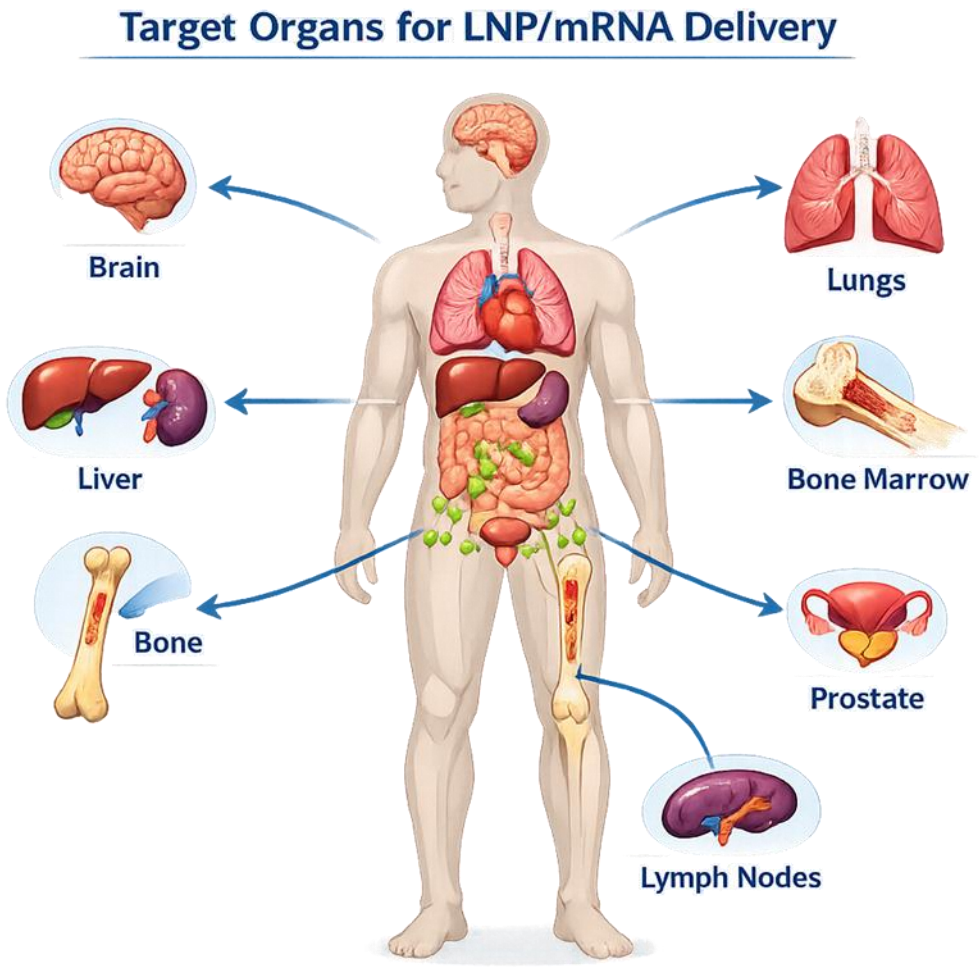
Outline

How can we make personalized medicine happen?

- The Personalized Medicine Initiative 2011-2017
- The start-up approach: Precision diagnostics
  - Molecular You
  - GenXys
- The start-up approach: The clinical interface
  - Polymorphic BioSciences: data collection and analysis
  - Connect Health: The Longevity 100
- The start-up approach: Personalized medicines
  - Aurion Therapeutics: Personalized cancer drugs (small molecules)
  - Background: Gene Therapy
  - **Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies**

We Formed NanoVation Therapeutics (NVTx) to Develop LNP Systems With FTO to Deliver Nucleic-Acid Based Drugs to Hepatic and Extra-Hepatic Tissues

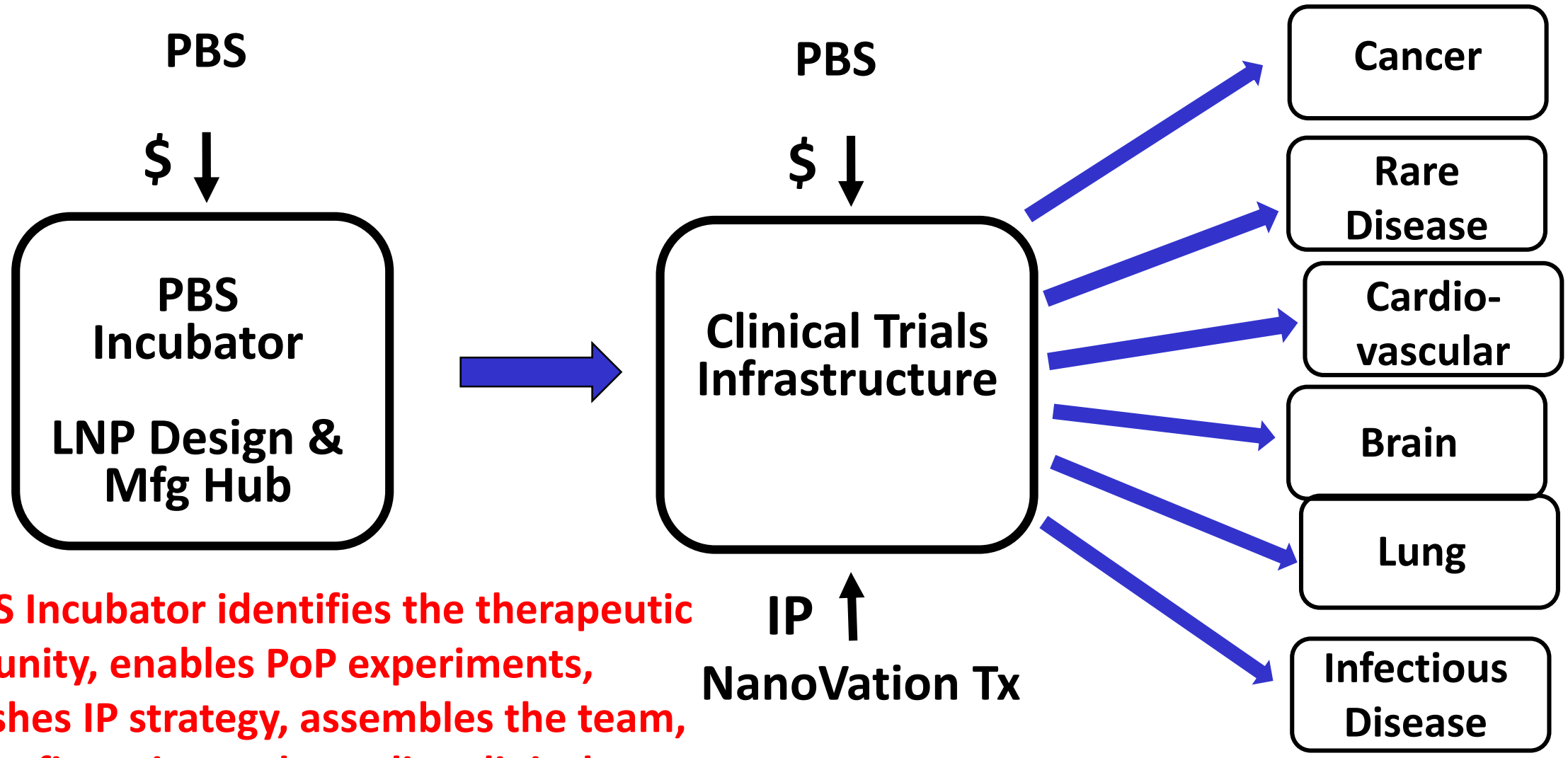




NanoVation

xxx

We Formed Polymorphic BioSciences (PBS) to Exploit Delivery Technology Developed by NanoVation Therapeutics For a Variety of Therapeutics



The PBS Incubator identifies the therapeutic opportunity, enables PoP experiments, establishes IP strategy, assembles the team, arranges financing and supplies clinical grade LNP RNA for clinical studies…

Polymorphic Has Six Companies in Stealth Mode

Technology Incubation

Polymorphic BioSciences

HexTwo Capital

$

NewCo

IP

NanoVation Therapeutics

Companies in "stealth" mode

- **Pneumonia (Resolve NTx)**
- **Personalized cancer vaccines**
- **Personalized chemotherapy**
- **Prostate cancer**
- **GMP manufacturing apparatus**
- **Longevity/ healthy aging**

xxx

Outline

- The Personalized Medicine Initiative 2011-2017
- The start-up approach: Precision diagnostics
  - Molecular You
  - GenXys
- The start-up approach: The clinical interface
  - Polymorphic BioSciences: data collection and analysis
  - Connect Health: The Longevity 100
- The start-up approach: Personalized medicines
  - Aurion Therapeutics: Personalized cancer drugs (small molecules)
  - Background: Gene therapies
  - Polymorphic BioSciences and NanoVation therapeutics: Personalized gene therapies

ACKNOWLEDGEMENTS

Acuitas

Mick Hope

Tom Madden

Steve Ansell

Ying Tam

Barb Mui

Paulo Lin

Sean Semple

Precision NanoSystems

James Taylor

Euan Ramsay

Lloyd Jeffs

Arbutus

Ammen Sandhu

Ian MacLachlan

James Heyes

Lorne Palmer

Alnylam

Mark Tracy

Akin Akinc

Martin Maier

Mano Manoharan

UBC Brain Research

Brian MacVicar

Ravi Rungta

NanoVation

Dominik Witzigmann

Jay Kulkarni

Marco Ciufolini

U. Penn

Drew Weissman

Molecular You

Rob Fraser

Ash Anwar

Christoph Borchers

David Wishart

UBC Biochemistry

Miffy Cheng

Genc Basha

Bin Zhao

Igor Zhigaltsev

Harrison Fan

Arash Momeni

Yao Zhang

Yan Mei

Tania Schluter

Nisha Chander

Jerry Leung