Pieter Cullis
Professor, University of British Columbia
Health Summit 2025 Vancouver, Canada

The Future of Medicine

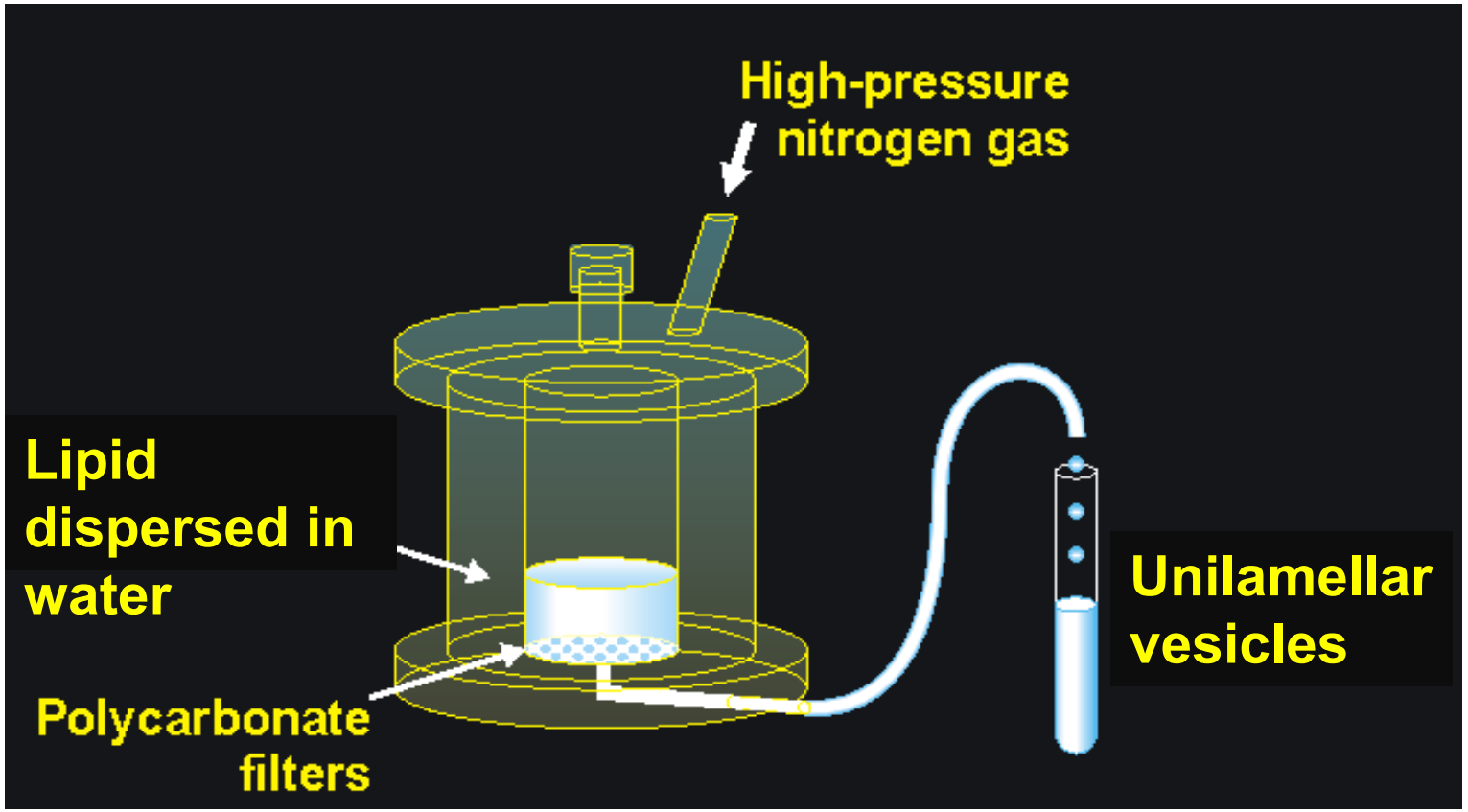
Conflicts of Interest
Precision NanoSystems: Founder
Acuitas Therapeutics: Founder
NanoVation Therapeutics: Founder and Chair
Molecular You: Founder and Chair

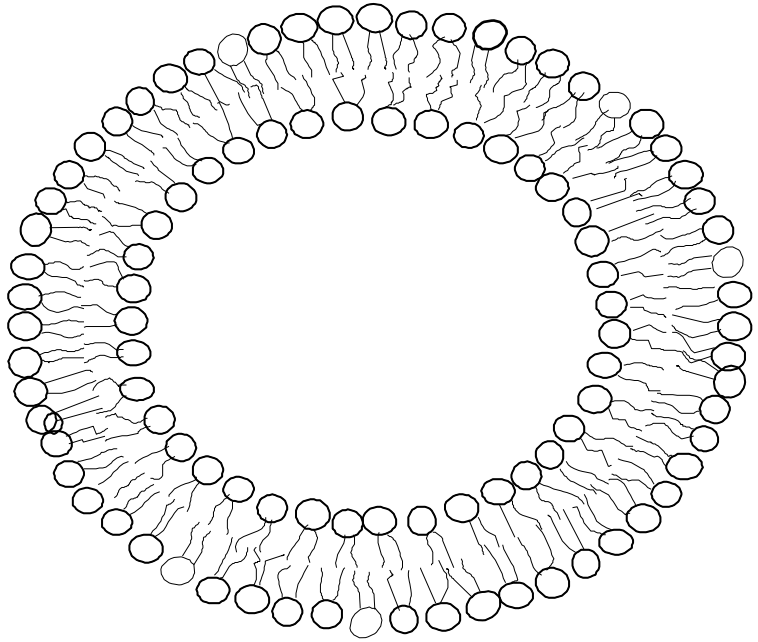
Honouring The Legacy of Pieter Cullis??
I'm Not Dead Yet!!

But it did get me thinking: what have I done with my life??

1) Starting companies: 1984-present
2) Delivery of cancer drugs: 1985-present
3) Delivery of nucleic acid-based drugs: 1996-present
    a) Onpattro and Comirnaty
    b) Personalized gene therapies
4) Personalized preventive medicine: 2010-present

What Got Me Hooked on Starting Companies? Lipex Biomembranes!





Liposome

In 1984 we invented a device for making unilamellar liposomes. We called this device the Extruder

We Formed Lipex Biomembranes to Market the Extruder

Lipex was formed by me and four postdocs in my lab in 1985;

We knew companies must have a Board of Directors!

Pieter Cullis | Mick Hope | Tom Madden

Lawrence Mayer | Marcel Bally

The Board

I was Chairman of the Board!

We Also Knew That Companies Had to Have a Mission Statement

Lipex Biomembranes mission statement:

Free beer every Friday and parties whenever possible!

Lipex Biomembranes: Purveyors of Extruders and Fine Parties!

The Extruder Was (and is) a Best-Seller!

Over 3,000 Extruders sold

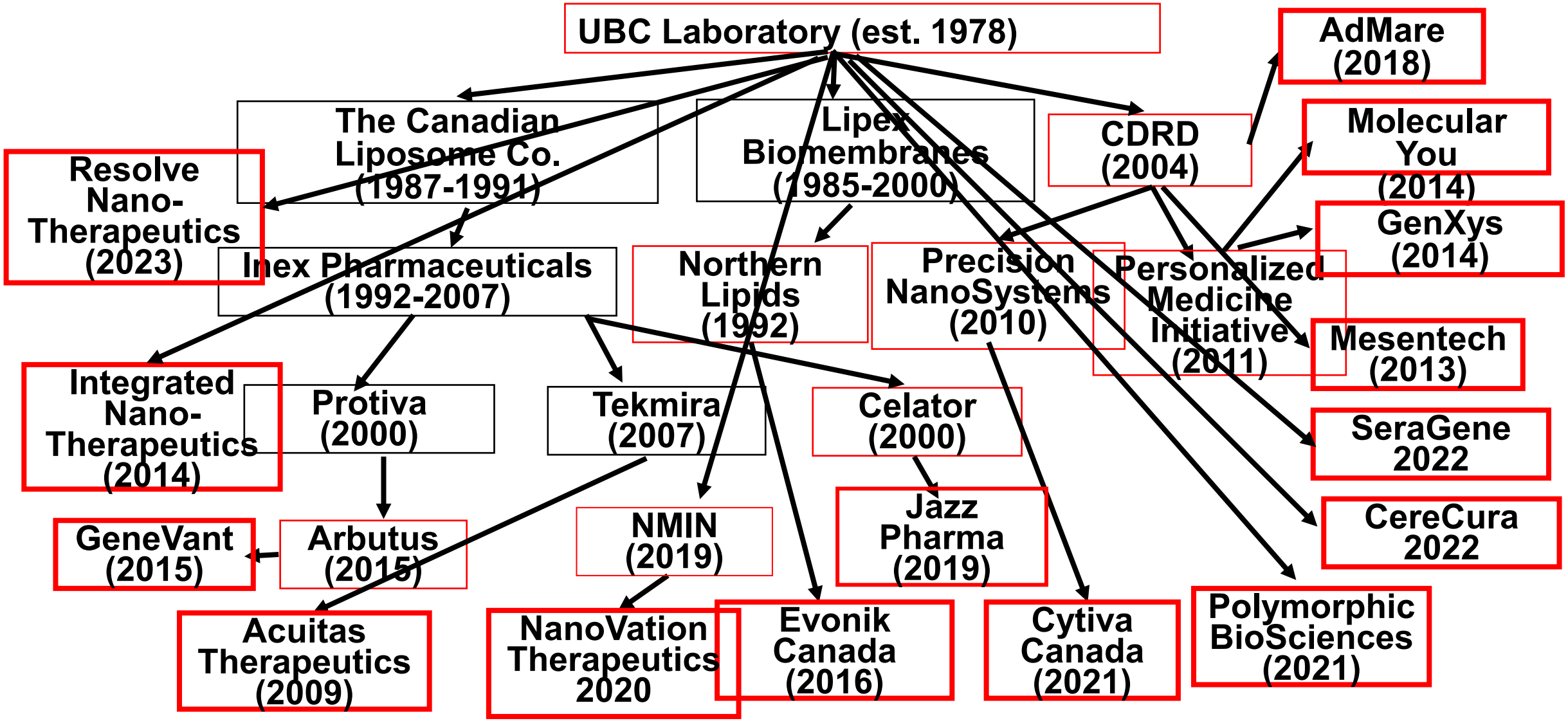
Total sales 1986-2024: > $50M

Free beer every Friday forever!

The Royal Lipex Ballet!

Decided that every serious company has to support the Arts!

Starting Companies Was Clearly a Lot of Fun And One Thing Led to Another….



Now 14 companies that employ more than 500 people in the Vancouver area..

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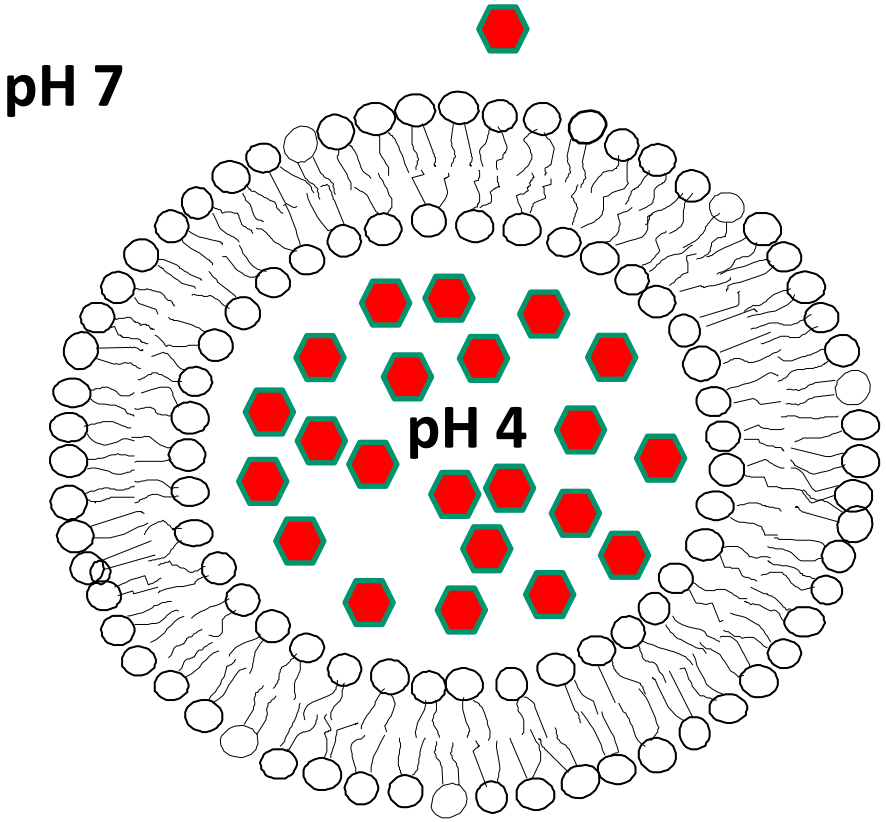
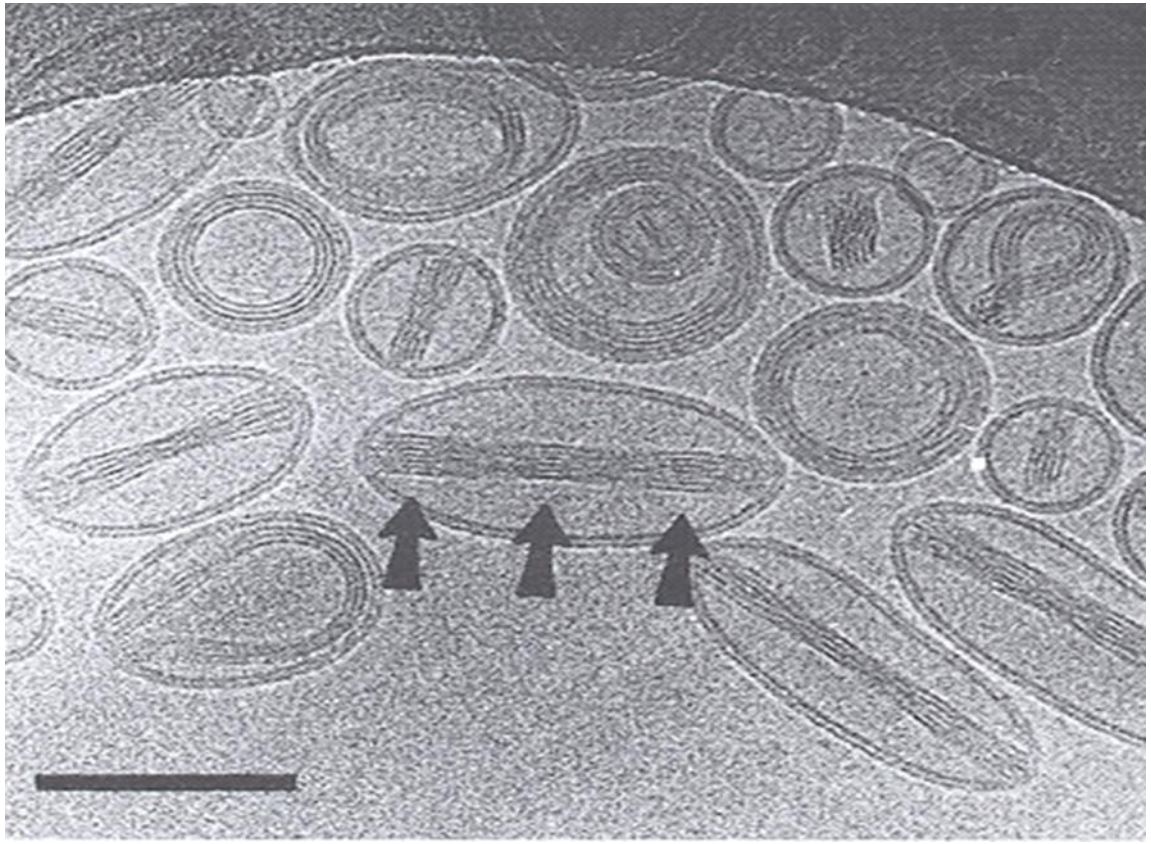
In 1985 Discovered We Could Load Anticancer Drugs Into Liposomes Exhibiting a pH Gradient



Weak base drugs will accumulate in liposomes exhibiting a pH gradient (inside acidic)



Liposomes loaded with doxorubicin, a common anticancer drug

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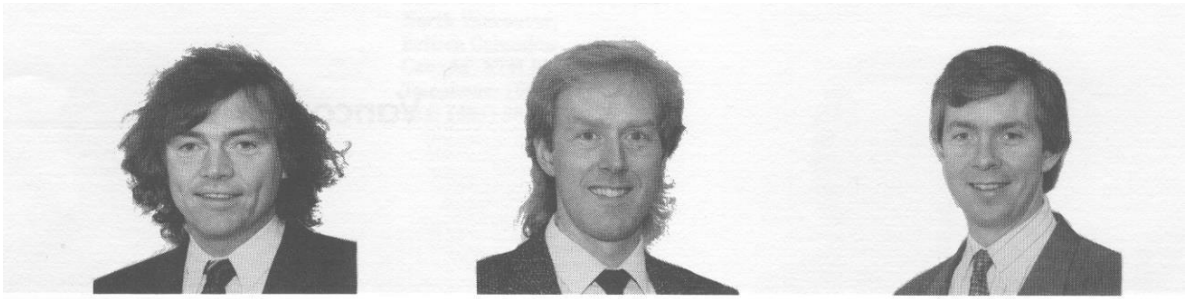
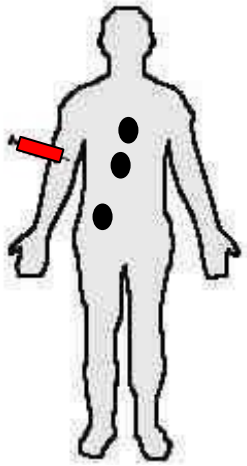
So In 1992 We Founded A Company (Inex Pharmaceuticals) To Use These Liposomes To Improve Delivery Of Cancer Drugs To Tumours



Pieter Cullis Mick Hope Tom Madden

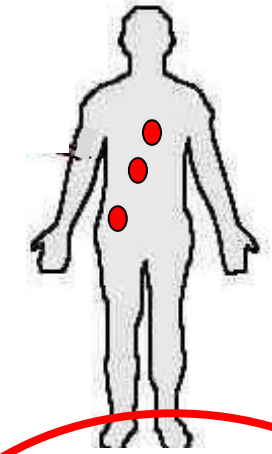
Lawrence Mayer Marcel Bally

Me and four postdocs in my group in 1990…



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

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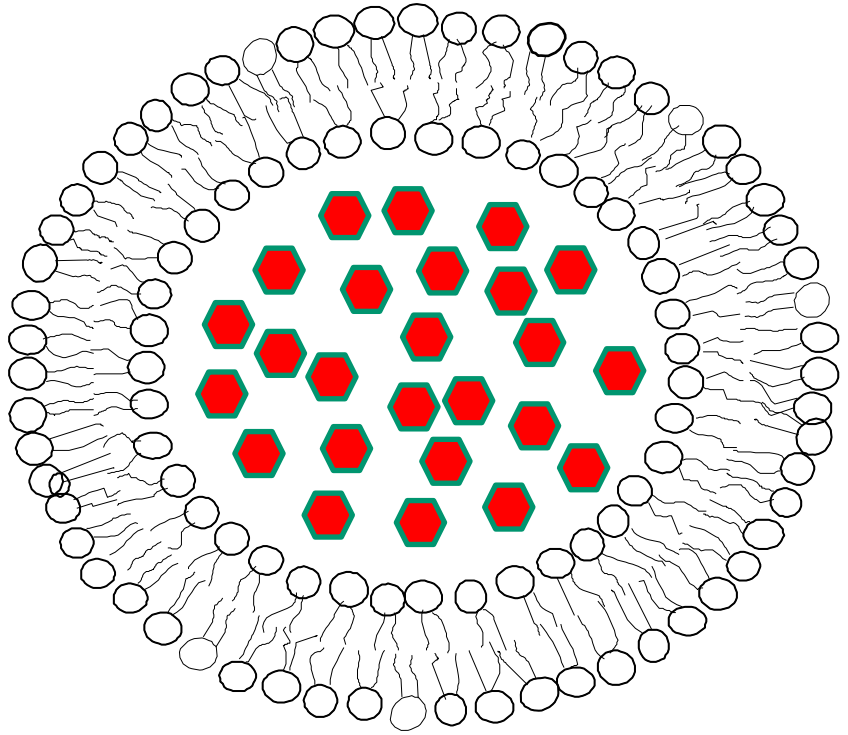
These Efforts Resulted in Two Nanomedicines That Were Approved For Clinical Use By the US FDA and the European EMA

Liposomal doxorubicin (Myocet) approved for treatment of metastatic breast cancer in 2000

Liposomal vincristine (Marqibo) approved for treatment of acute lymphoblastic leukemia in 2012



Liposomal encapsulation results in reduction in toxicity and/or improvements in efficacy but is not curative

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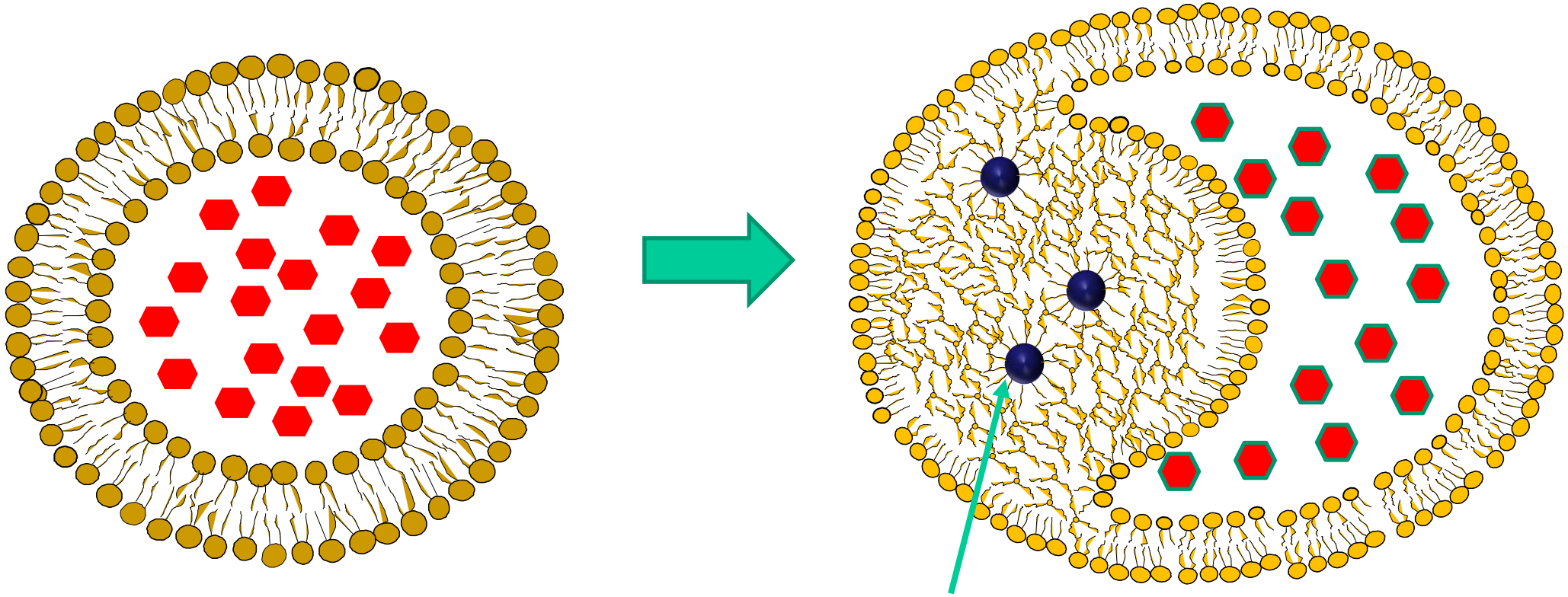
We Are Still Working On Ways To Improve Delivery To Tumour Sites 30 Years Later…

Have developed hybrid delivery systems for triggered release of anticancer drugs



Iron oxide nanoparticle

Gold nanoparticle

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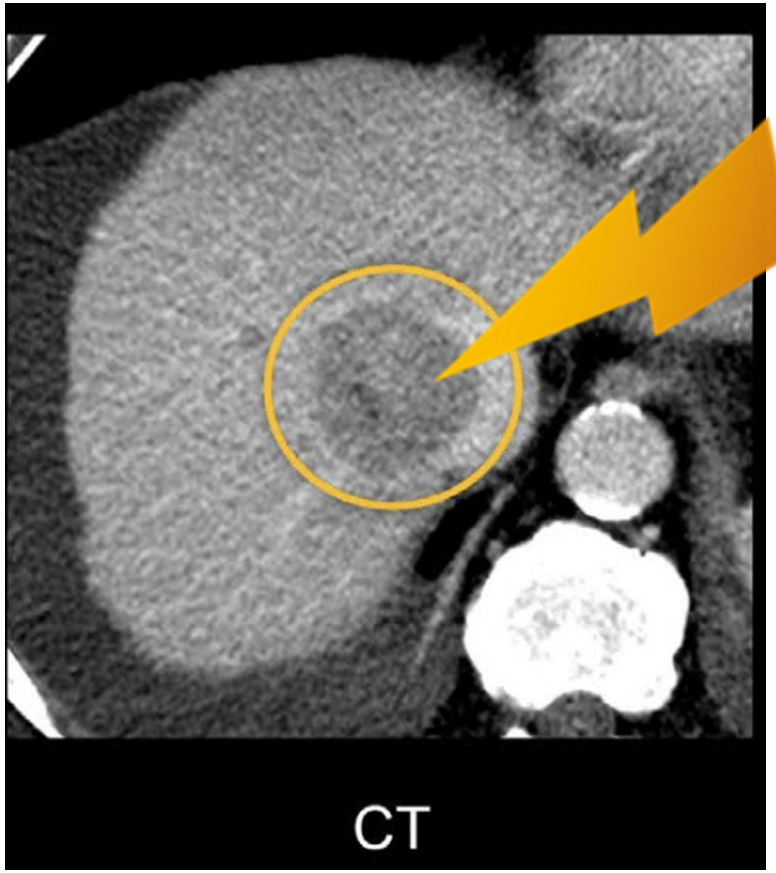
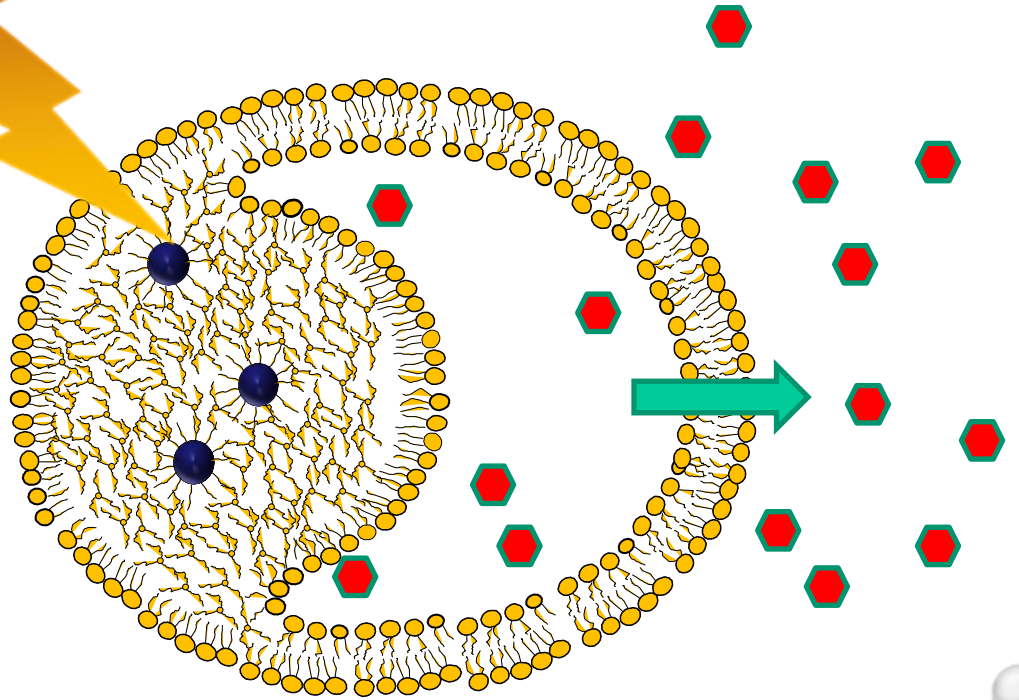
Are Aiming at Triggered Release Systems So That Cancer Drugs Are Only Released In The Region Of The Tumour

Focused RF, Laser, HIFU



Liver tumour



Long-circulating hybrid LNP

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Honouring The Legacy of Pieter Cullis??
I'm Not Dead Yet!!

1) Starting companies: 1984-present
2) Delivery of cancer drugs: 1985-present
    a) Still working hard at it
3) Delivery of nucleic acid-based drugs: 1996-present
    a) Onpattro and Comirnaty
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4) Personalized preventive medicine: 2010-present

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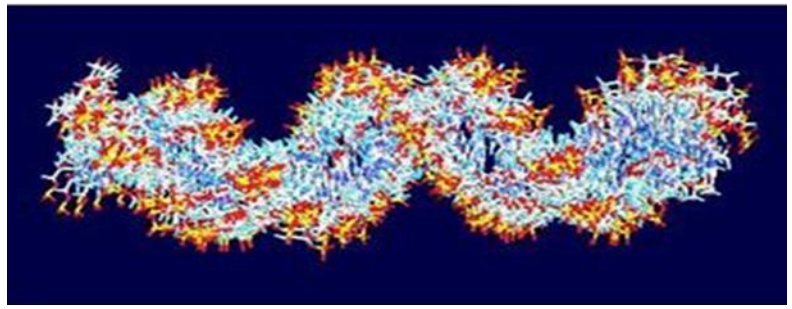
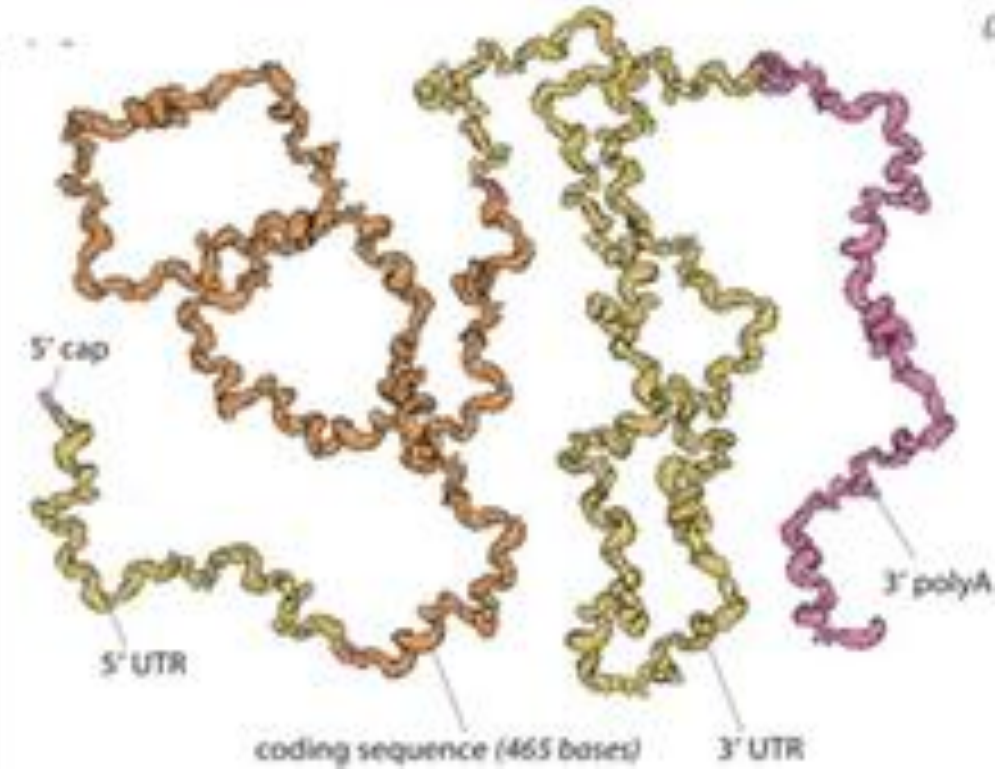
What Nucleic Acid-Based Drugs Do We Want to Deliver?



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)

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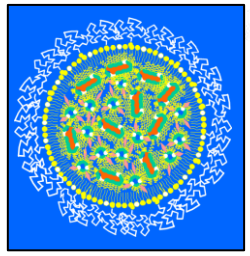
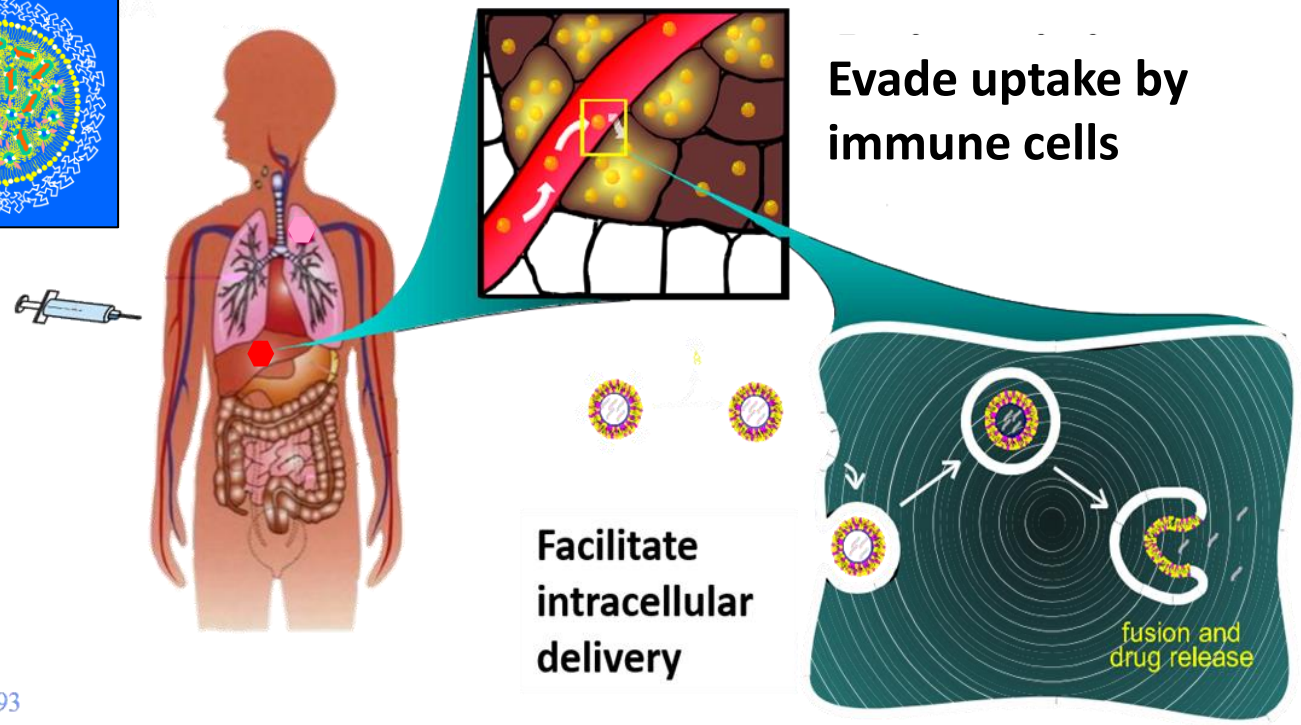
In 2000 We Developed Ways of Encapsulating Nucleic Acid-Based Drugs Into Lipid Nanoparticles

Package RNA in LNP





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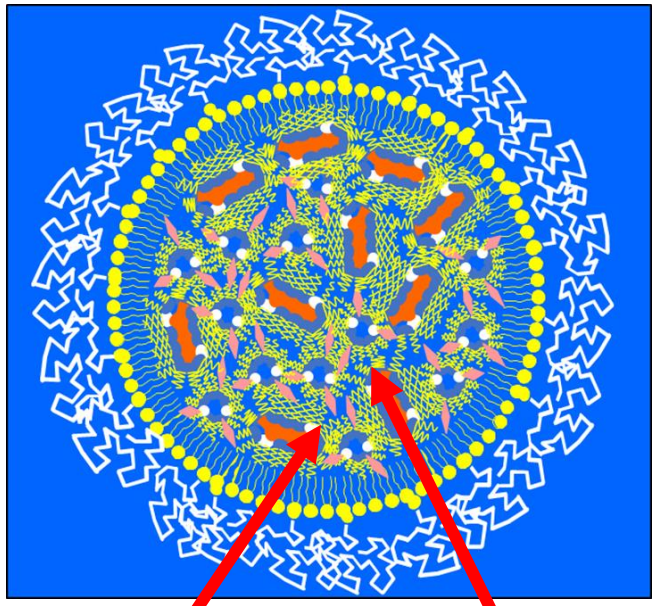
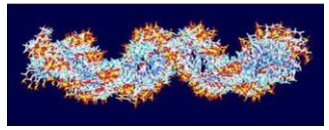
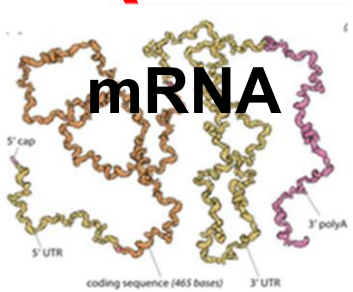


siRNA



mRNA



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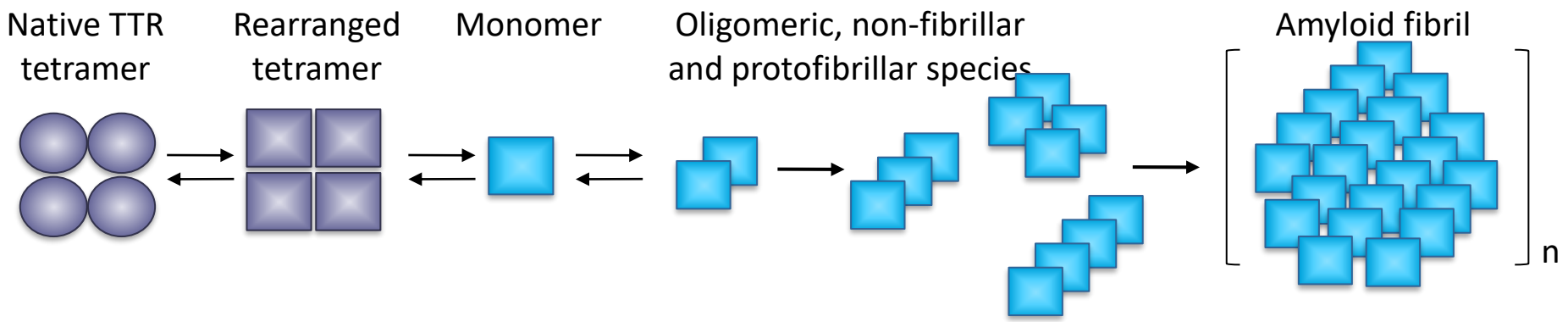
In 2012 We Developed an LNP siRNA System to Treat A Rare Disease Called Hereditary Amyloid Transthyretin (hATTR) Amyloidosis



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

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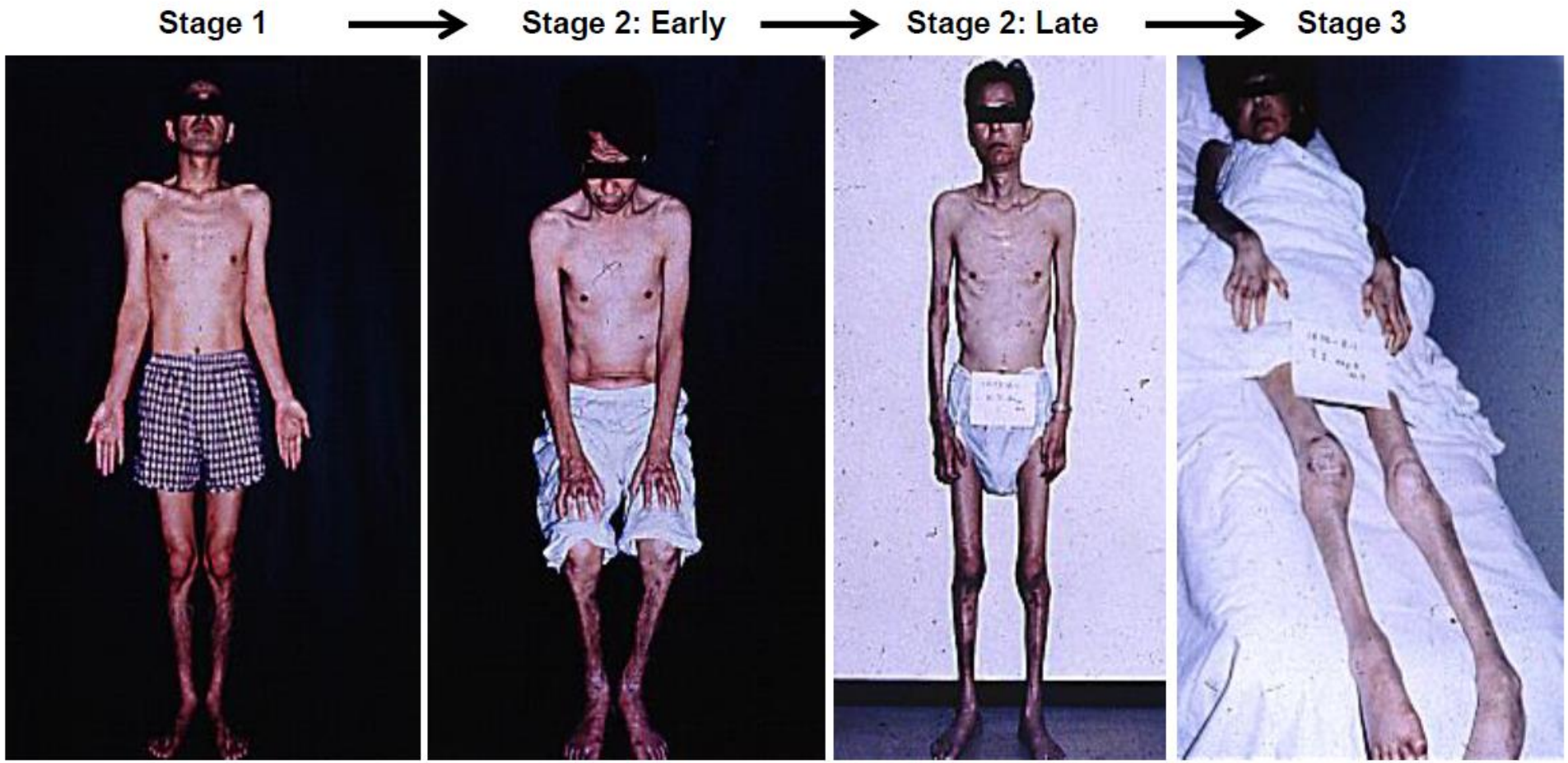
hATTR Amyloidosis: A Rapidly Progressing Disease Usually Fatal Within Five Years of Diagnosis



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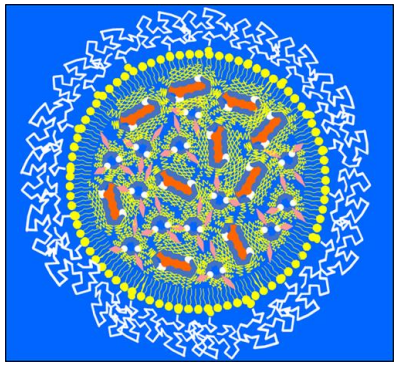
Used LNP siRNA to Inhibit Production of Transthyretin in the Liver



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 disease.
Approved by FDA in Aug, 2018.

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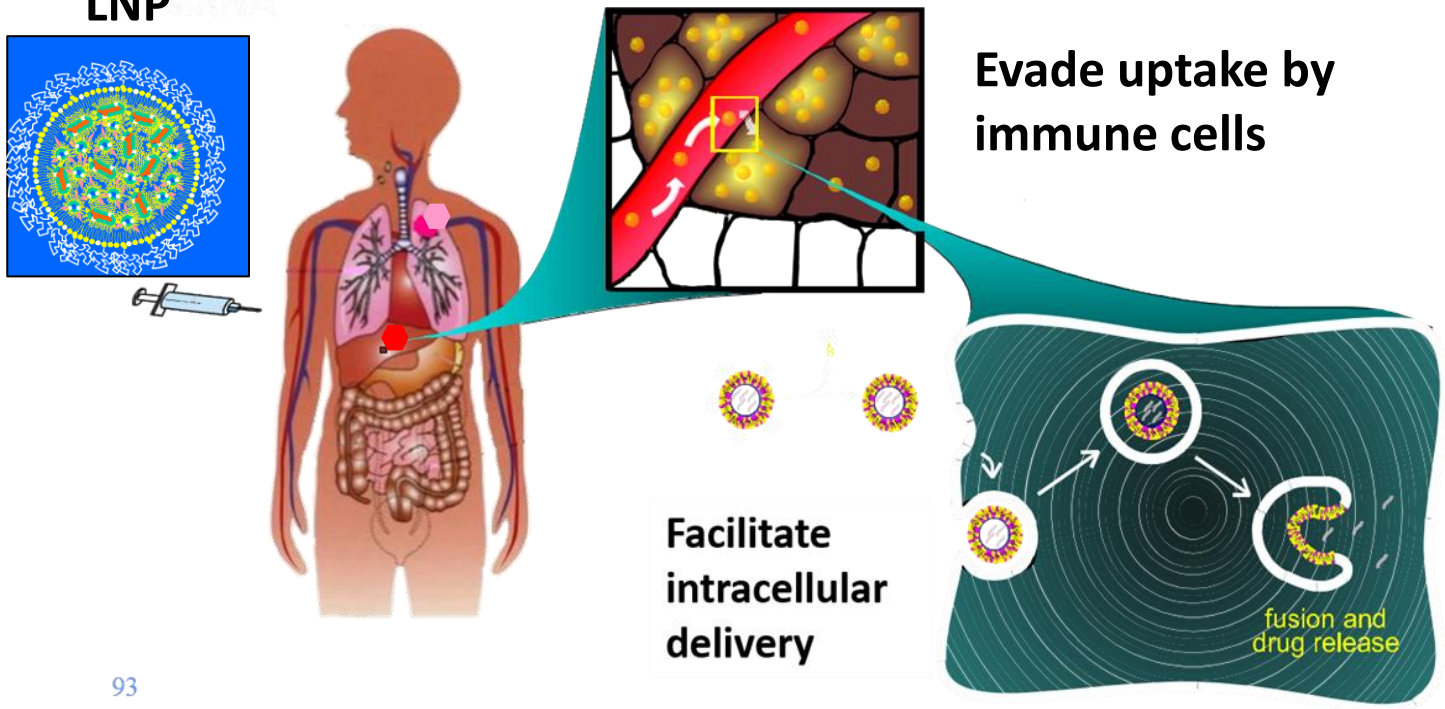
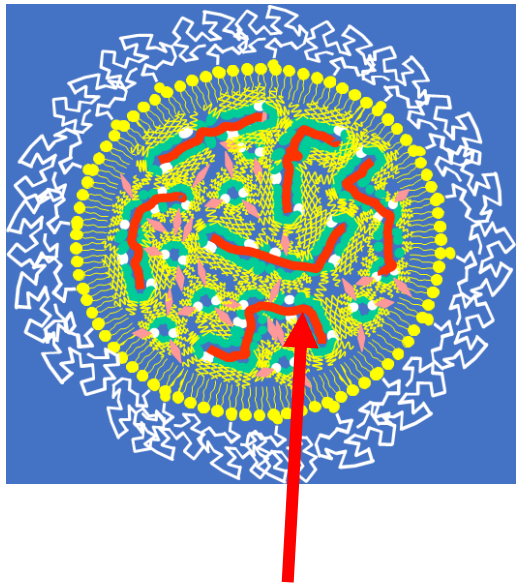
In 2013 We (Acuitas) Asked If We Can Deliver siRNA to Silence a Gene in the Liver, Can We Deliver mRNA to Express a Gene in the Liver?

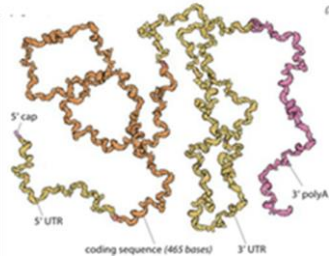
Package mRNA in LNP



mRNA expresses a protein



mRNA



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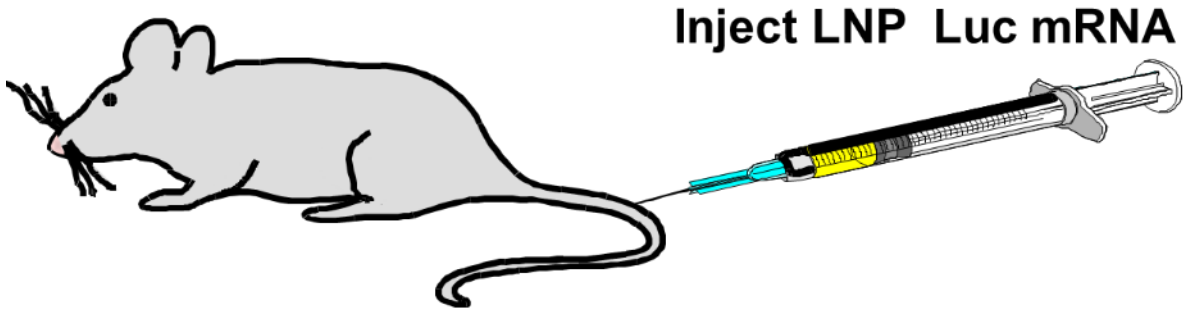
It Worked! LNP mRNA Formulations Could Give Rise to High Levels of Gene Expression in the Liver



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**

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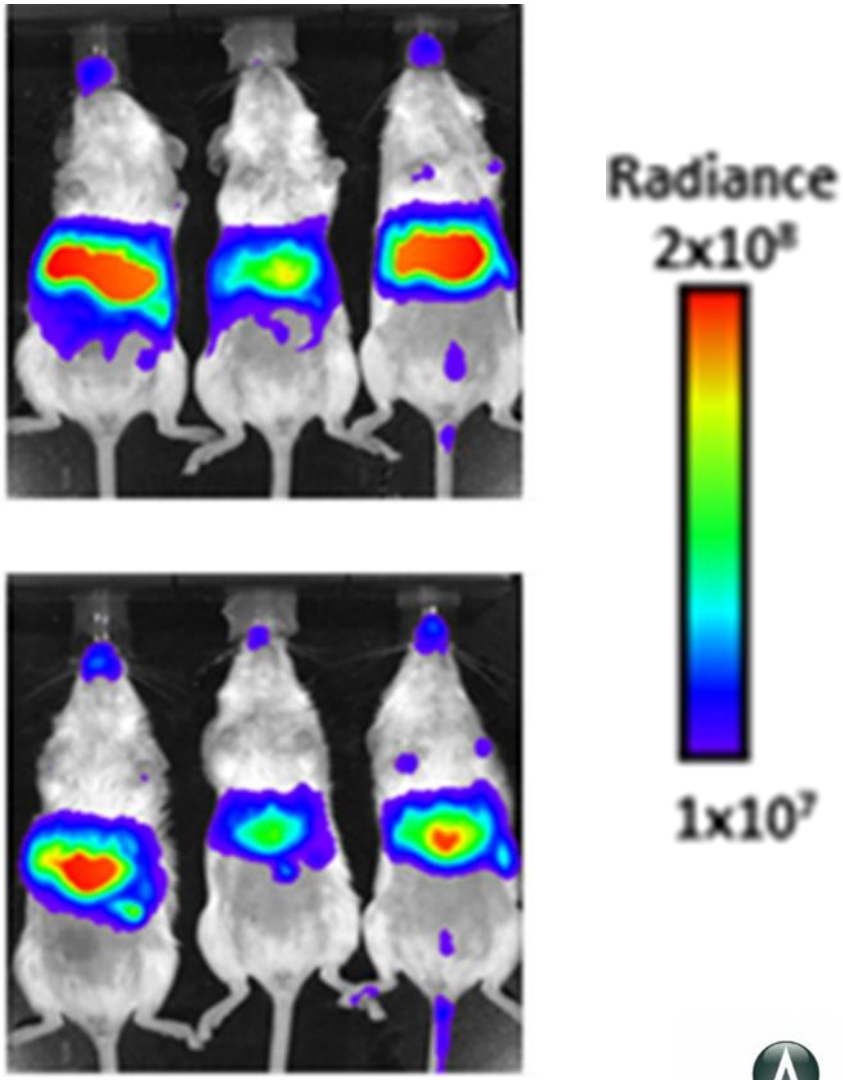

IVIS Imaging

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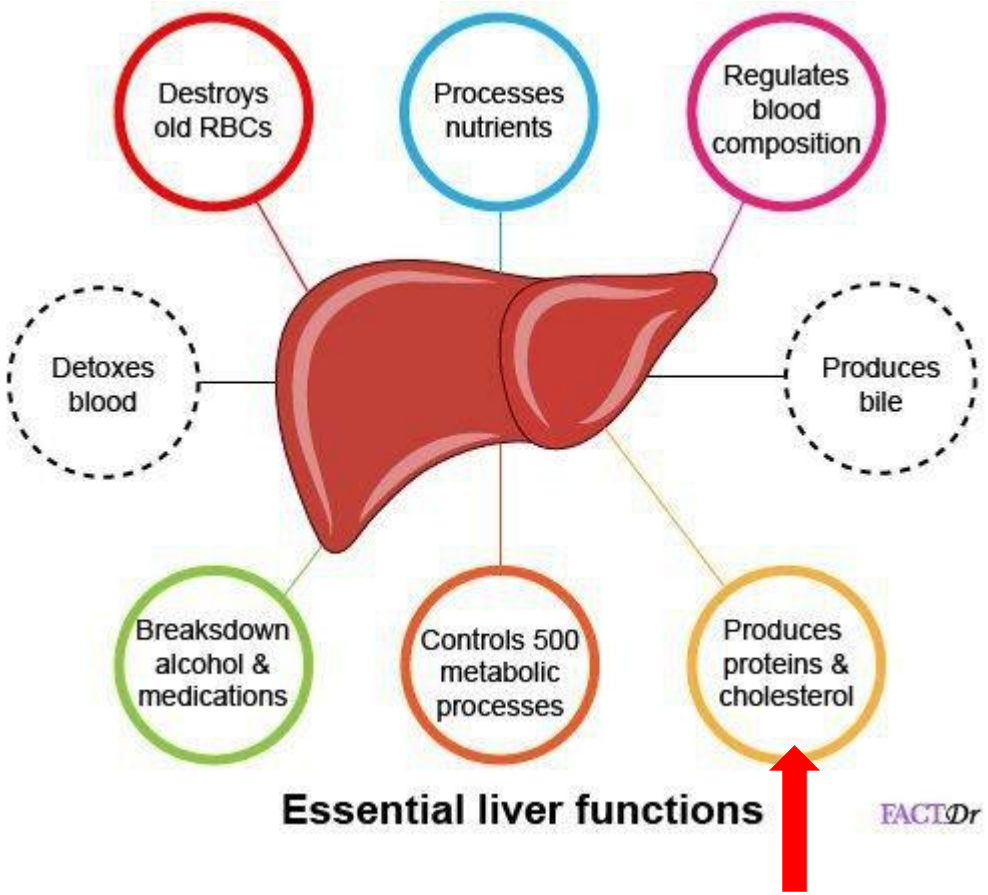
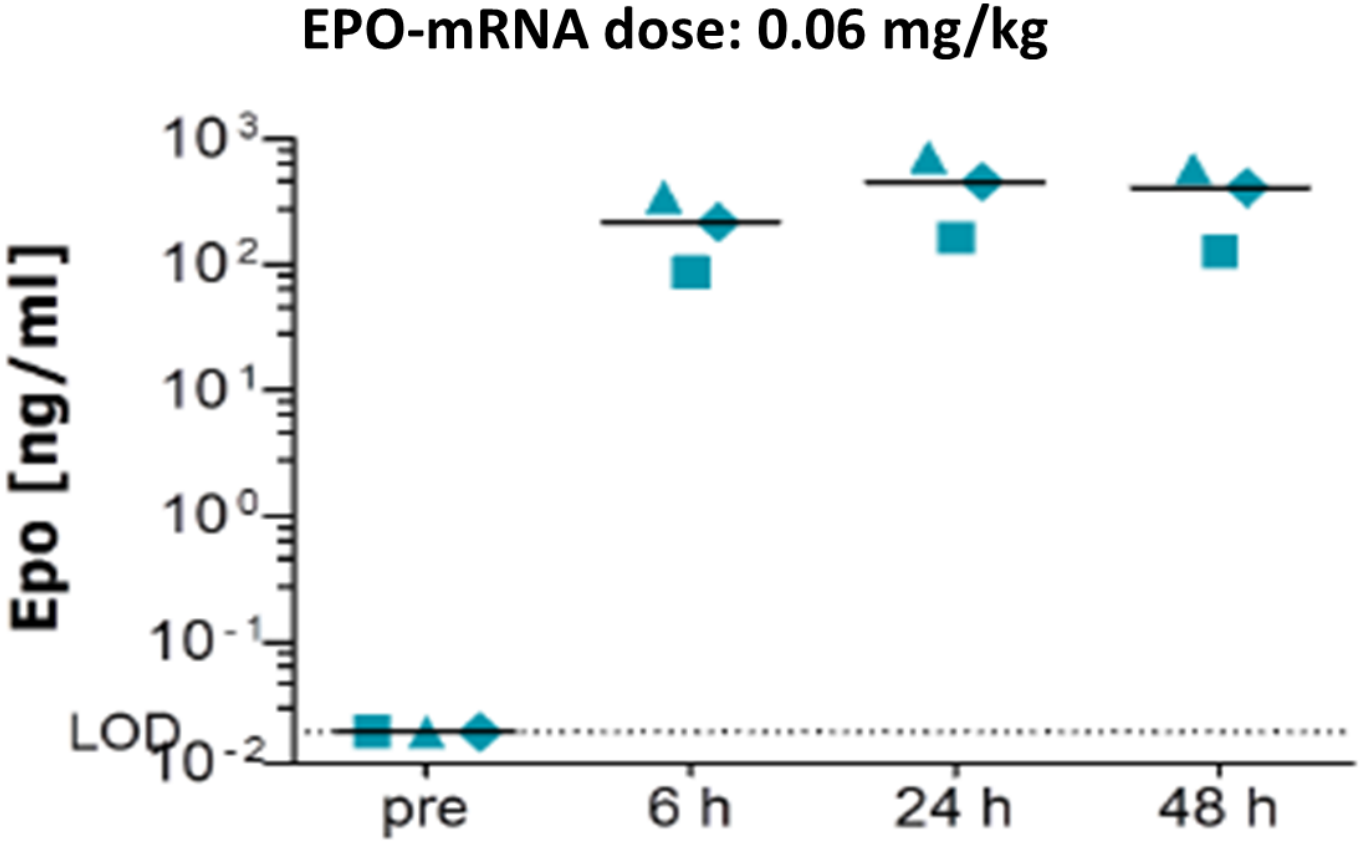
Found That We Could Make the Liver Make Any Protein We Wanted by Injecting LNPs Containing mRNA Coding for That Protein



The liver produces most of the proteins in your body



Injected pigs with LNP mRNA coding for erythropoietin

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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?"

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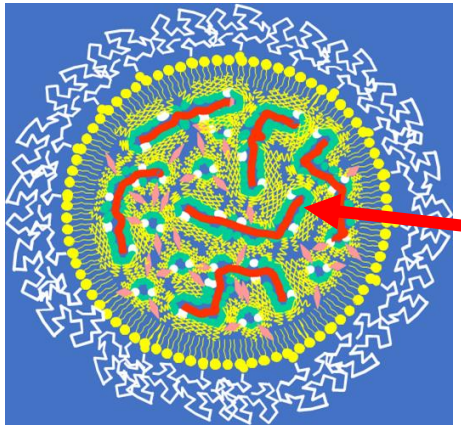
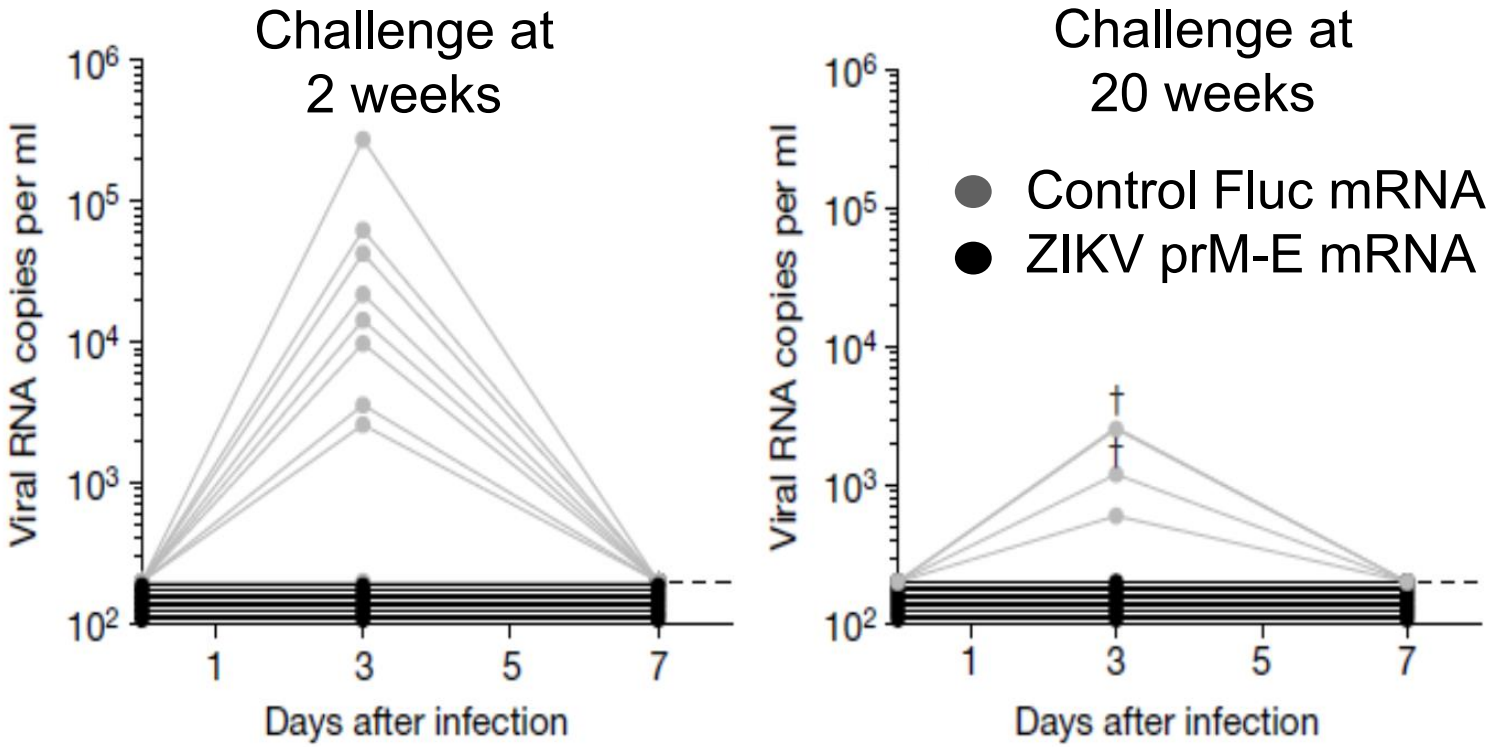
Found That An LNP Containing mRNA Coding for a Surface Protein on Zika Virus Provided Total Protection Against Zika Virus Infection

Microcephaly



LNP mRNA



mRNA coding for ZIKV prM-E (Zika virus pre-membrane and envelope glycoprotein)

Suddenly we were in the vaccine business..

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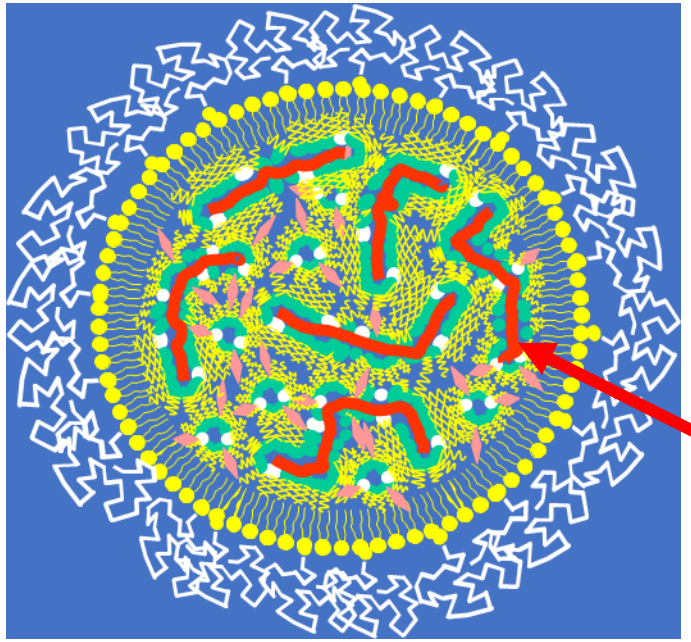
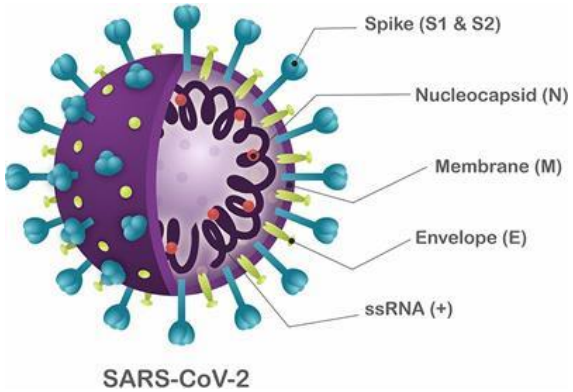
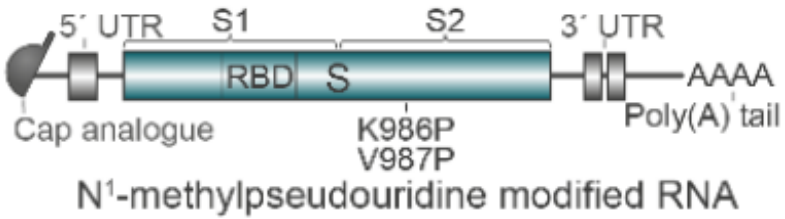
Pardi, Weissman et al. Nature 543, 248 (2017)

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

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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.

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The same LNP technology used for the vaccines can be used for gene therapies

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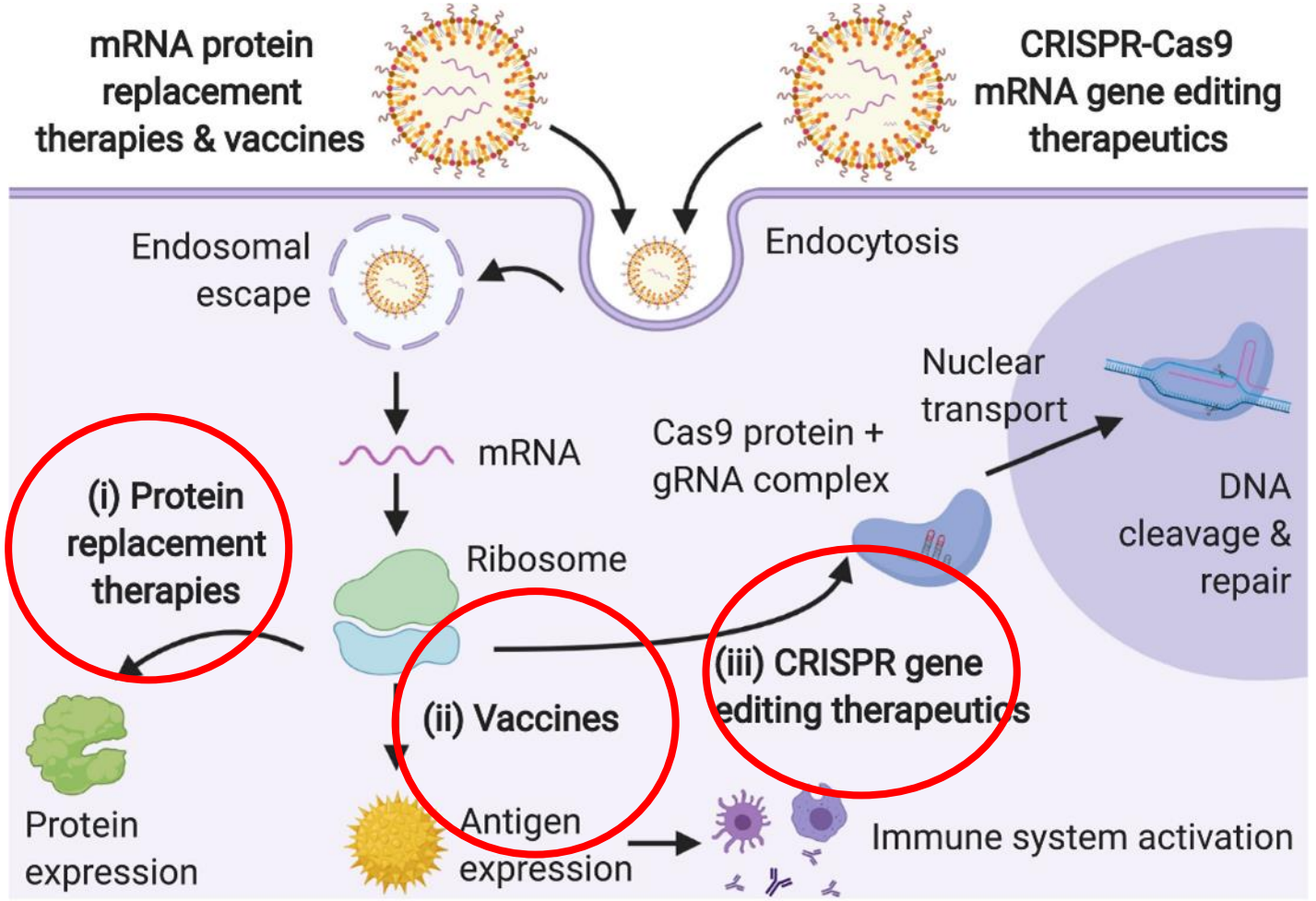
Personalized Gene Therapies: The Next Generation of Pharmaceuticals

First generation: small molecule drugs

Second generation: biologics

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

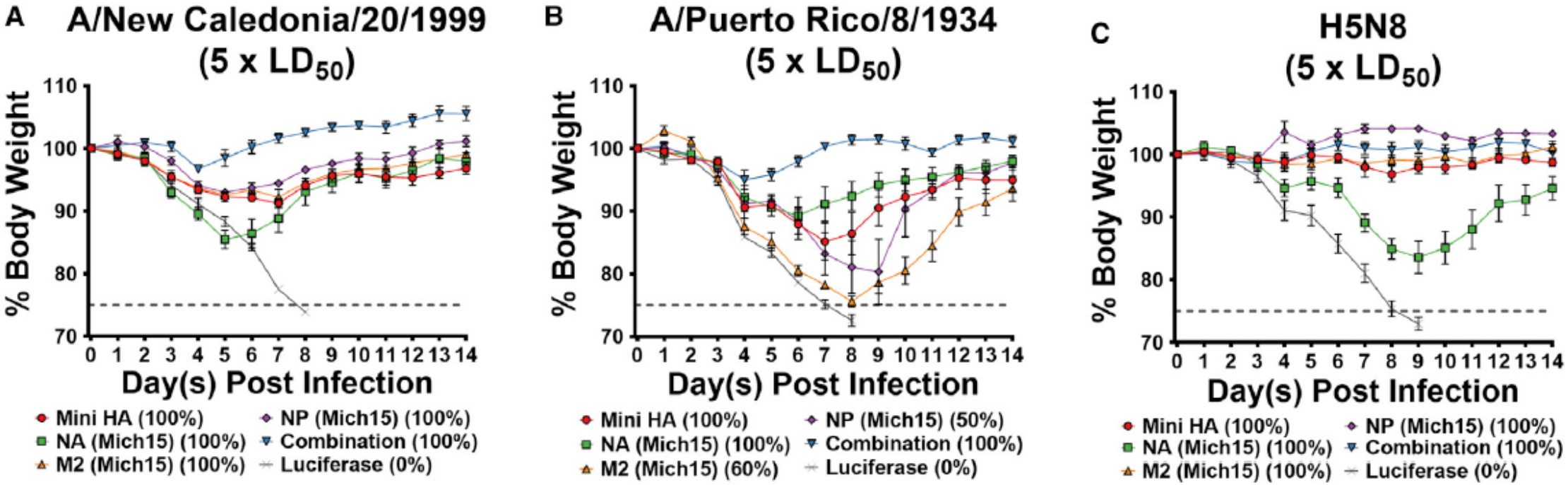


All of these gene therapies can be produced in a matter of weeks…

Enormous Number of Vaccine Applications: Universal Flu Vaccine

LNP combination (blue) contains mRNA coding for:

HA-hemagglutinin
NA-neuraminidase
M2-ion channel protein
NP-nucleoprotein



A single i.m. immunization with LNP encapsulated mRNA-encoded influenza virus antigens protects mice from challenge (5xLD_{50}) by a variety of influenza strains

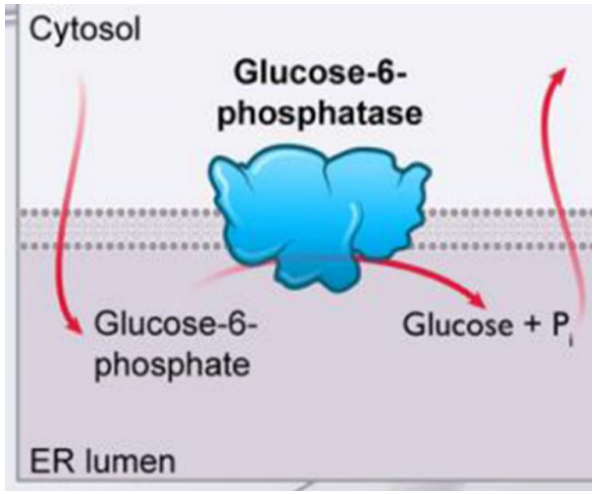
Freyn et al., Mol Ther. 2021

Enormous Number of Vaccine Applications for LNP mRNA Systems

Disease	Reference
Clostridioides difficile (C. Difficile)	Alameh, M.-G., et al. Science, 2024. https://doi.org/10.1126/science.adn4955
Influenza and SARS-CoV-2	Wang, Y., et al. bioRxiv 2024. https://doi.org/10.1101/2024.03.05.583547
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

Teatment

- **LNP G6P mRNA!**

Enormous Number of Applications for Rare Diseases

Propionic acidemia	Jiang et al. 2020 Nat. Comm. https://www.ncbi.nlm.nih.gov/pubmed/33087718
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
Thrombotic thrombocytopenic purpura	Liu-Chen et al., Sci. Rep. 2018 doi: 10.1038/s41598-018-26298-4
Argininosuccinic aciduria	Daly et al. Biomedicines 2023 DOI: 10.3390/biomedicines11061735

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

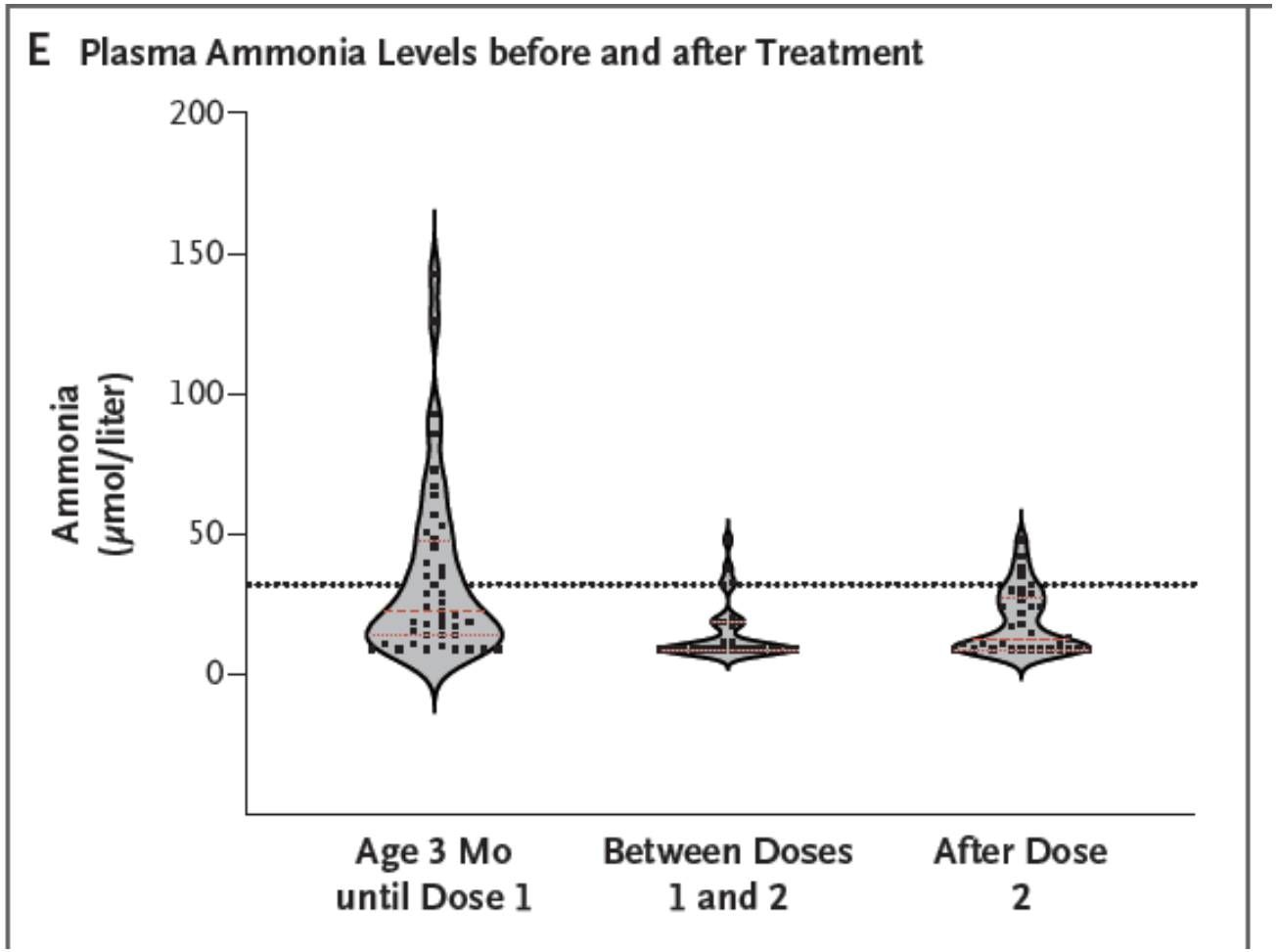
- CRISPR adenine base editor to correct mutation T→C
- gRNA, target adenine in the 8th position of protospacer sequence

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

Plasma Ammonia Levels Come Under Control

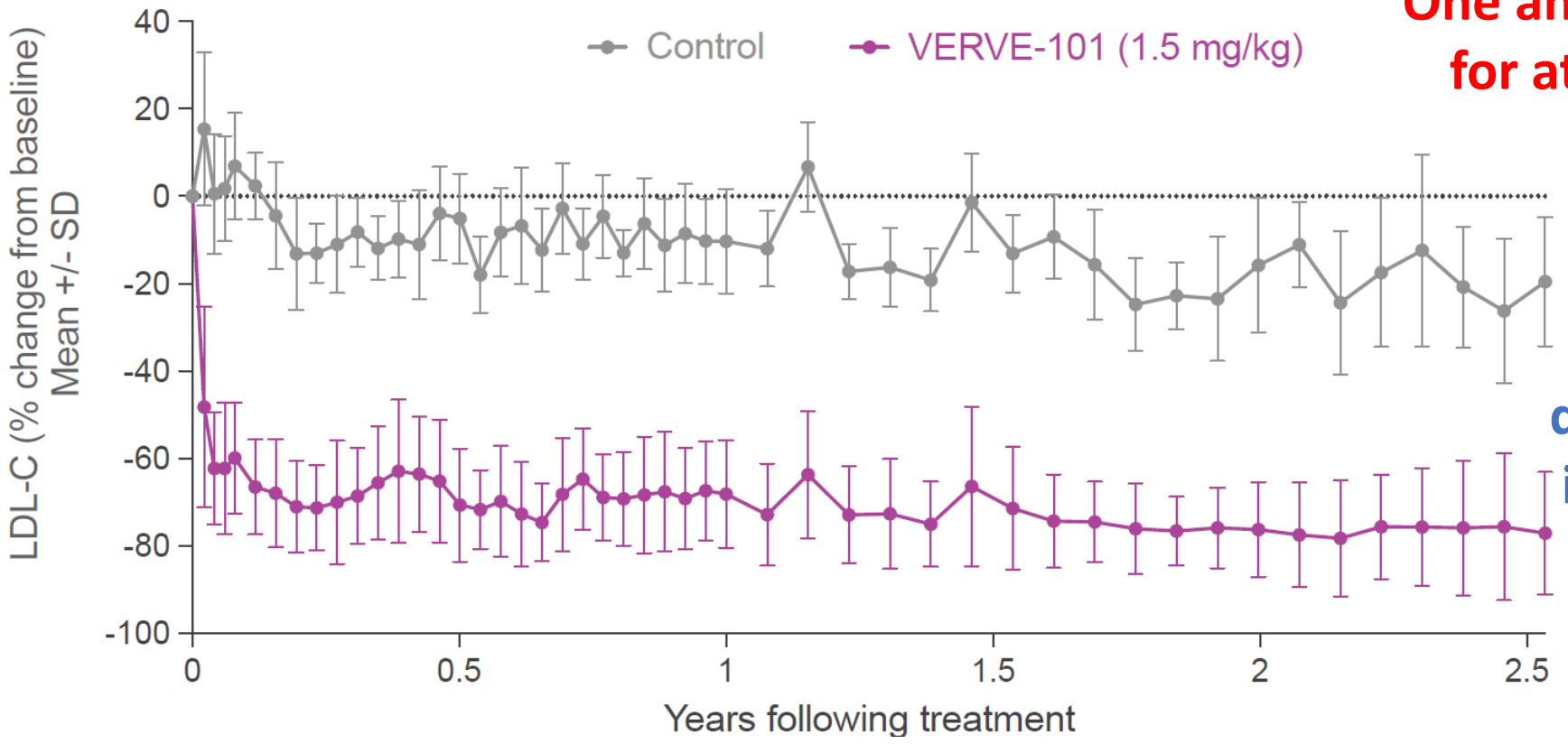


"We anticipate that rapid deployment of patient-specific gene editing therapies will become routine for many genetic diseases" (Musunuru et al. https://www.ncbi.nlm.nih.gov/pubmed/40373211)

Important Applications for Common Diseases

Example: Gene Editing Treatment for Cardiovascular Disease

In non-human primates, blood LDL-C observed to be durably lowered for 2.5 years following single infusion of VERVE-101



"One and done" therapy for atherosclerosis

Base editing of PCSK9 results in dose-dependent durable reductions in LDL-cholesterol

Essentially a vaccine to prevent heart disease, the major killer in the western world….

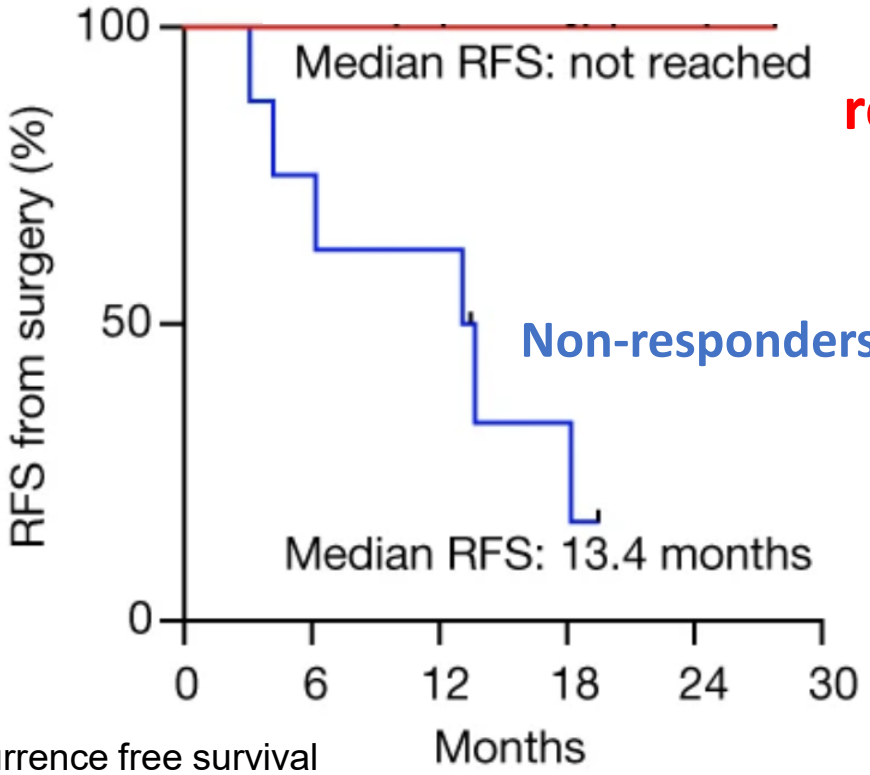
LNP mRNA Therapeutics Will Revolutionize Cancer Therapies

- **LNP mRNA therapeutic vaccines**: Biopsy tumour, identify mutations, select immunogenic peptides, code for them in mRNA, encapsulate in LNP, inject i.m. (melanoma, pancreatic….)
- **In vivo CAR-T therapies**: Identify antigen on cancer cells, code for receptor in mRNA, inject i.v. to transfect T cells (leukemias, lymphomas…)
- **Personalized mAb therapeutics**: identify antigen on cancer cells, code mRNA for mAb (heavy, light chains) inject i.v. to transfect hepatocytes (solid, liquid cancers)
- **LNP mRNA protein delivery:** Cytokine immunotherapies, expression of tumour suppressor genes…

These highly personalized therapeutics can be produced in real time (weeks) to help patients with terminal diseases….

LNP mRNA Vaccine: Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC)



RFS – recurrence free survival

Treatment:

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

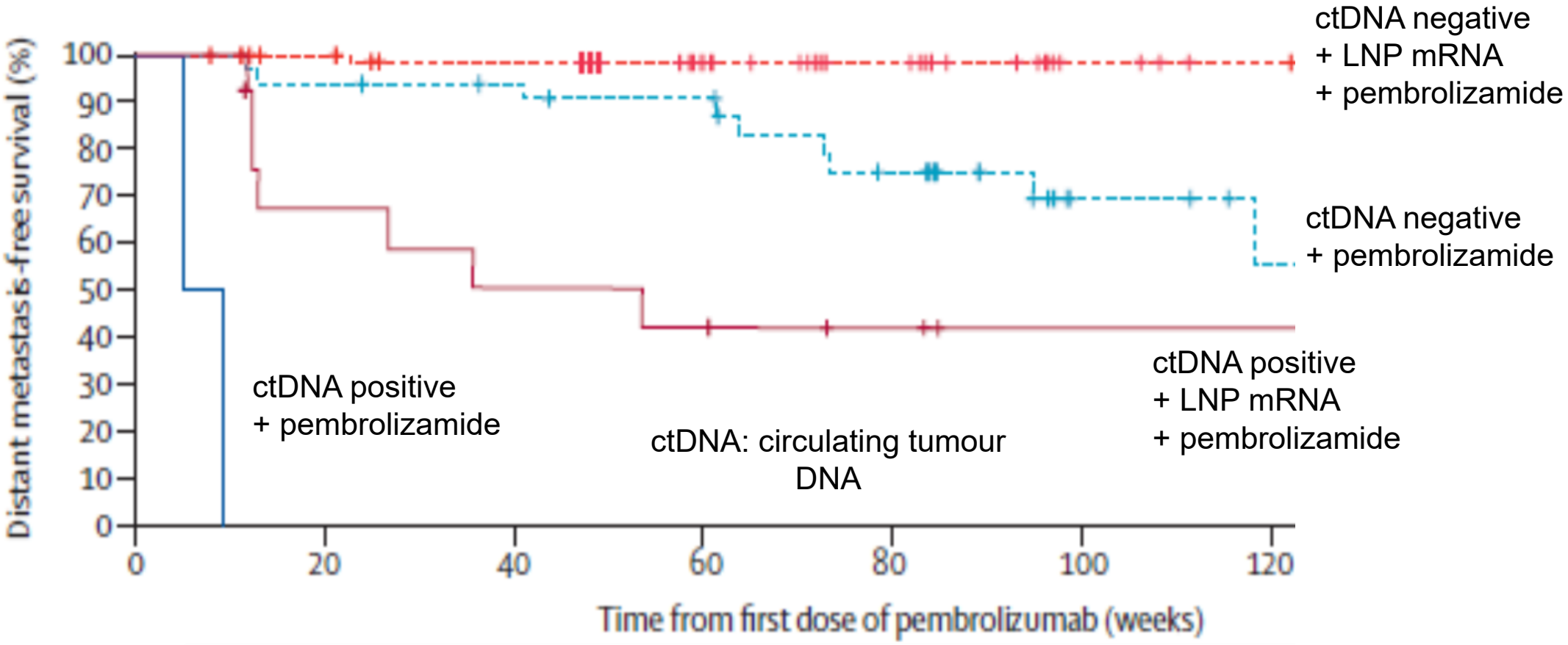
Outcomes:

- 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/Genentech Phase I Trial (NCT04161755)

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

LNP mRNA Vaccine: Melanoma



Weber et al Lancet 2024 https://www.ncbi.nlm.nih.gov/pubmed/38246194 Merck and Moderna

Moderna and Merck also reporting encouraging results for lung cancer LNP mRNA vaccines….

Over 30 LNP RNA Drugs in Phase II Studies or Beyond

Table 1 | Selected LNP-enabled RNA vaccines and therapeutics that have progressed beyond phase I clinical development

Drug or vaccine name	Developer(s)	Disease indication	Therapeutic class/strategy	Highest development stage	Trial identifier
Comirnaty (tozinameran)	BioNTech, Pfizer, Acuitas	SARS-CoV-2	Viral vaccine	Approved	N/A
SpikeVax (elasomeran)	Moderna	SARS-CoV-2	Viral vaccine	Approved	N/A
Onpattro (patisiran)	Alnylam, Inex/Tekmira, Acuitas	Transthyretin amyloidosis	Gene silencing	Approved	N/A
mRNA-4157	MSD and Moderna	Melanoma	Cancer vaccine	III	NCT05933577
MK-3475	MSD and Moderna	Non-small cell lung cancer	Cancer vaccine	III	NCT06077760
mRNA-1273	GlaxoSmith-Kline	Herpes zoster	Viral vaccine	III	NCT05047770
mRNA-1647	Moderna	Cytomegalovirus	Viral vaccine	III	NCT05085366
mRNA-1345	Moderna	Respiratory syncytial virus	Viral vaccine	III	NCT05330975
mRNA-1010	Moderna	Influenza	Viral vaccine	III	NCT05415462
qlRV	Pfizer	Influenza	Viral vaccine	III	NCT05540522
ARCT-810-03	Arcturus	OTC deficiency	Protein replacement	II	NCT05526066
AZD8601	AstraZeneca	Heart failure	Protein expression	II	NCT03370887
BMS-986263	BMS	Liver cirrhosis; liver fibrosis	Gene silencing	II	NCT03420768
BMS-986263	BMS	Liver cirrhosis; NASH	Gene silencing	II	NCT04267393
mRNA-4157	Moderna	Melanoma	Cancer vaccine	II	NCT03897881
mRNA-1647	Moderna	Cytomegalovirus	Viral vaccine	II	NCT04232280
mRNA-1893	Moderna	Zika virus	Viral vaccine	II	NCT04917861
mRNA-1345	Moderna	Respiratory syncytial virus	Viral vaccine	II	NCT06097299
ND-L02-s0201	Nitto Denko	Idiopathic pulmonary fibrosis	Gene silencing	II	NCT03538301
TKM-080301	Arbutus Biopharma	Hepatocellular carcinoma	Gene silencing	I/II	NCT02191878
BNT151	BioNTech	Solid tumours (advanced)	Immunotherapy	I/II	NCT04455620
BNT142	BioNTech	Solid tumours (advanced)	Bispecific antibody	I/II	NCT05262530
mRNA-3927	Moderna	Propionic acidaemia	Protein replacement	I/II	NCT04159103
mRNA-3705	Moderna	Methylmalonic acidaemia	Protein replacement	I/II	NCT04899310
mRNA-4359	Moderna	Solid tumours (advanced)	Cancer vaccine	I/II	NCT05533697
mRNA-1468	Moderna	Herpes zoster	Viral vaccine	I/II	NCT05701800
mRNA-1608	Moderna	Herpes simplex virus type 2	Viral vaccine	I/II	NCT06033261
OTX-2002	Omega Therapeutics	Liver cancer; multiple cancers	Epigenetic modifier	I/II	NCT05497453
LNP CL-0137	Sanofi	Respiratory syncytial virus	Viral vaccine	I/II	NCT05639894
MRT5005-101	Translate Bio	Cystic fibrosis	Protein replacement	I/II	NCT03375047

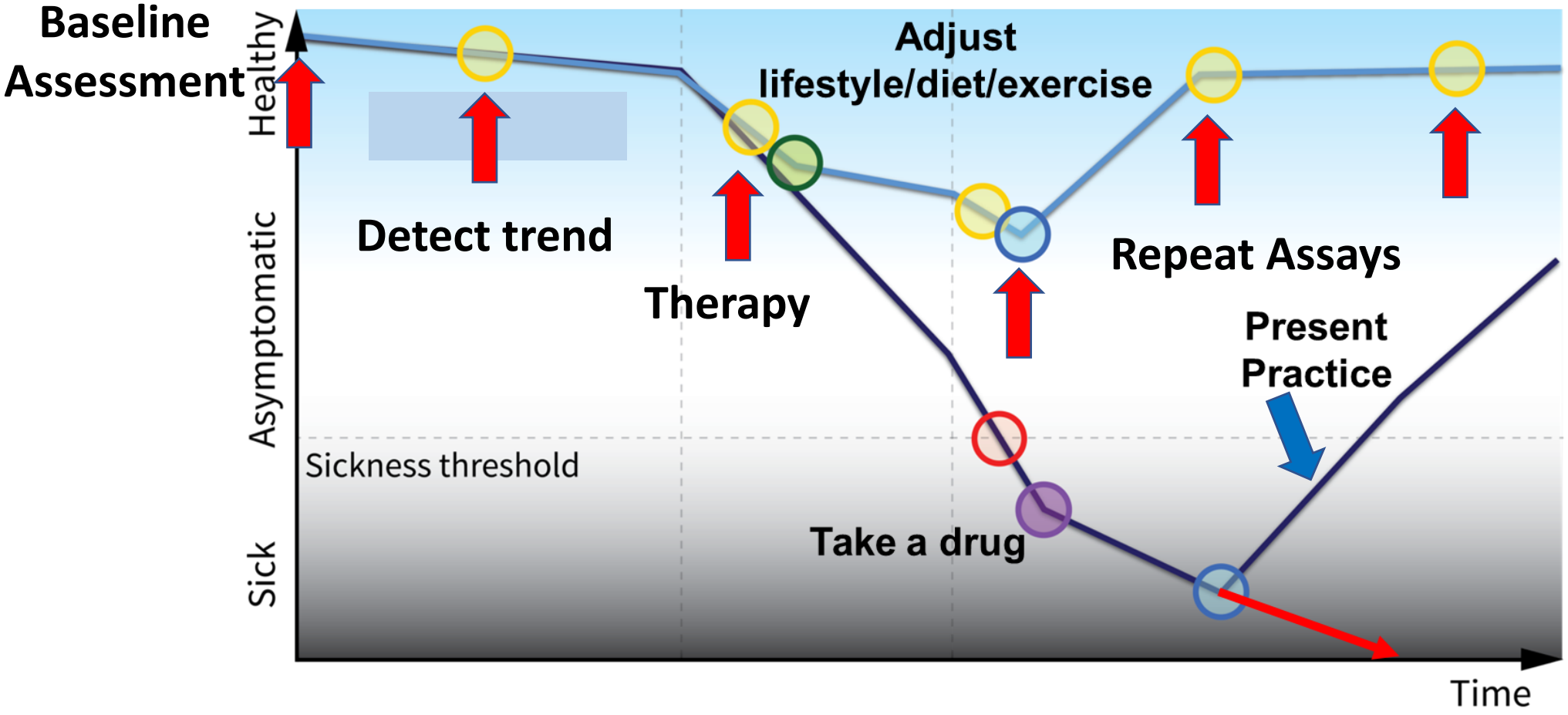
Over 400 LNP mRNA medicines in preclinical and clinical development….

Honouring The Legacy of Pieter Cullis??
I'm Not Dead Yet!!

1) Starting companies: 1984
2) Delivery of cancer drugs: 1985-present
3) Delivery of nucleic acid-based drugs: 1996-present
    a) Onpattro and Comirnaty
    b) Personalized gene therapies
4) Personalized preventive medicine: 2010-present

xxx

The Future of Medicine is Personalized Preventive Medicine to Prevent Disease Rather Than Treating Disease After You Are Ill



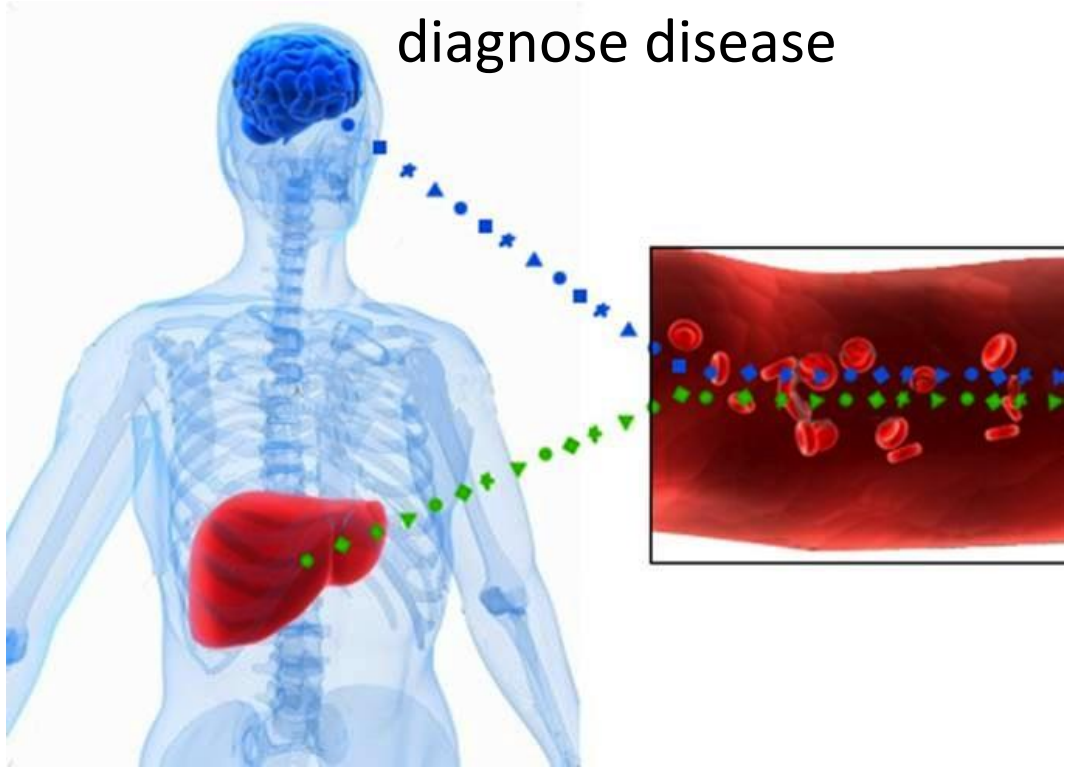
Preventive medicine requires advanced diagnostics and repeat assays to determine effectiveness of therapy..

The Protein and Metabolite Profile of Your Blood Provides Extensive Diagnostic Information

Each organ in your body secretes proteins and metabolites into the blood that can potentially be diagnostic for the health of that organ:

- Early detection of disease
- Monitor disease progression
- Monitor effects of therapy
- Detect re-occurrence of disease

Your blood contains many proteins and metabolites that can be used to detect and diagnose disease



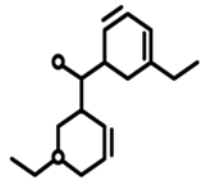
Mass spectrometry techniques allow many blood proteins and metabolites to be measured simultaneously and relatively inexpensively…

In 2014 We Founded Molecular You and Identified Over 200 Disease-Associated Blood Biomarkers

World's clinical and preclinical data on biomarkers associated with disease

~280 proteomic, metabolomic and environmental biomarkers identified that can be measured by mass spectrometry (~800 in 2025)

140 proteins



140 metabolites

molecular you PRECISION HEALTH

And Have Analyzed Various Disease Cohorts to Identify Risk Signatures Associated With These Diseases

Disease cohort

Omic profiles

AI

Use machine learning to compare Omic profiles of individuals in the disease cohort with healthy individuals **to identify risk signatures associated with the disease**

Molecular You Analyses Are Approaching 90% Accuracy For Predicting/Diagnosing Disease For Over 27 Diseases

Cognitive Function: Alzheimer Disease, Autism, Parkinson's

Cardiovascular Function: Atherosclerosis, Hypertension, etc

Metabolic Health: Type 2 Diabetes, Metabolic syndrome

Coagulation Function: Coagulopathies

Dietary Health: Inflammatory bowel disease

Immune Function: Multiple sclerosis, Rheumatoid Arthritis

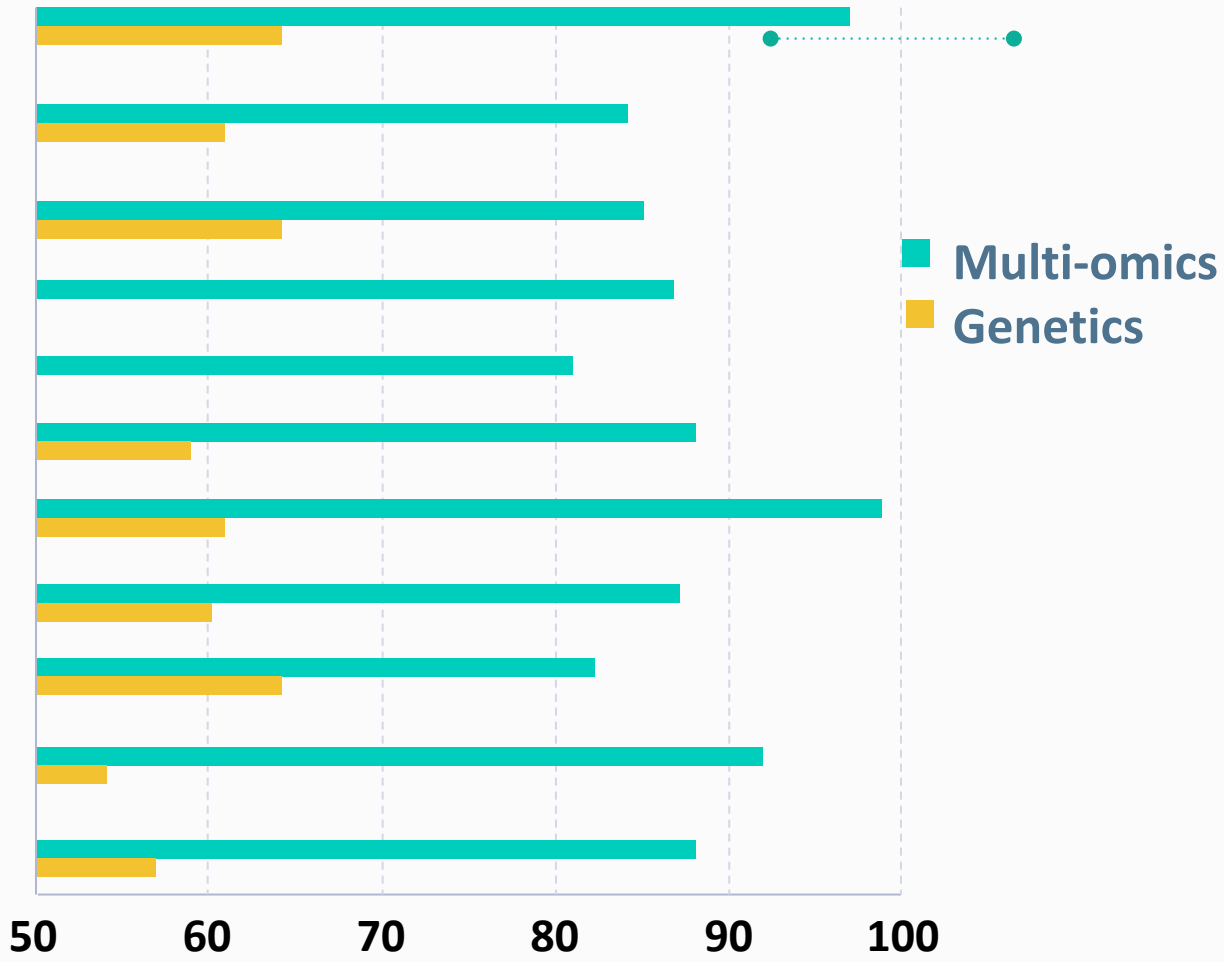
Kidney Function: Kidney Disease

Lung Function: Chronic Obstructive Pulmonary Disease

Liver Function: Liver Disease

Cancers: Breast, Lung, Colorectal, Pancreatic, Gastric cancers

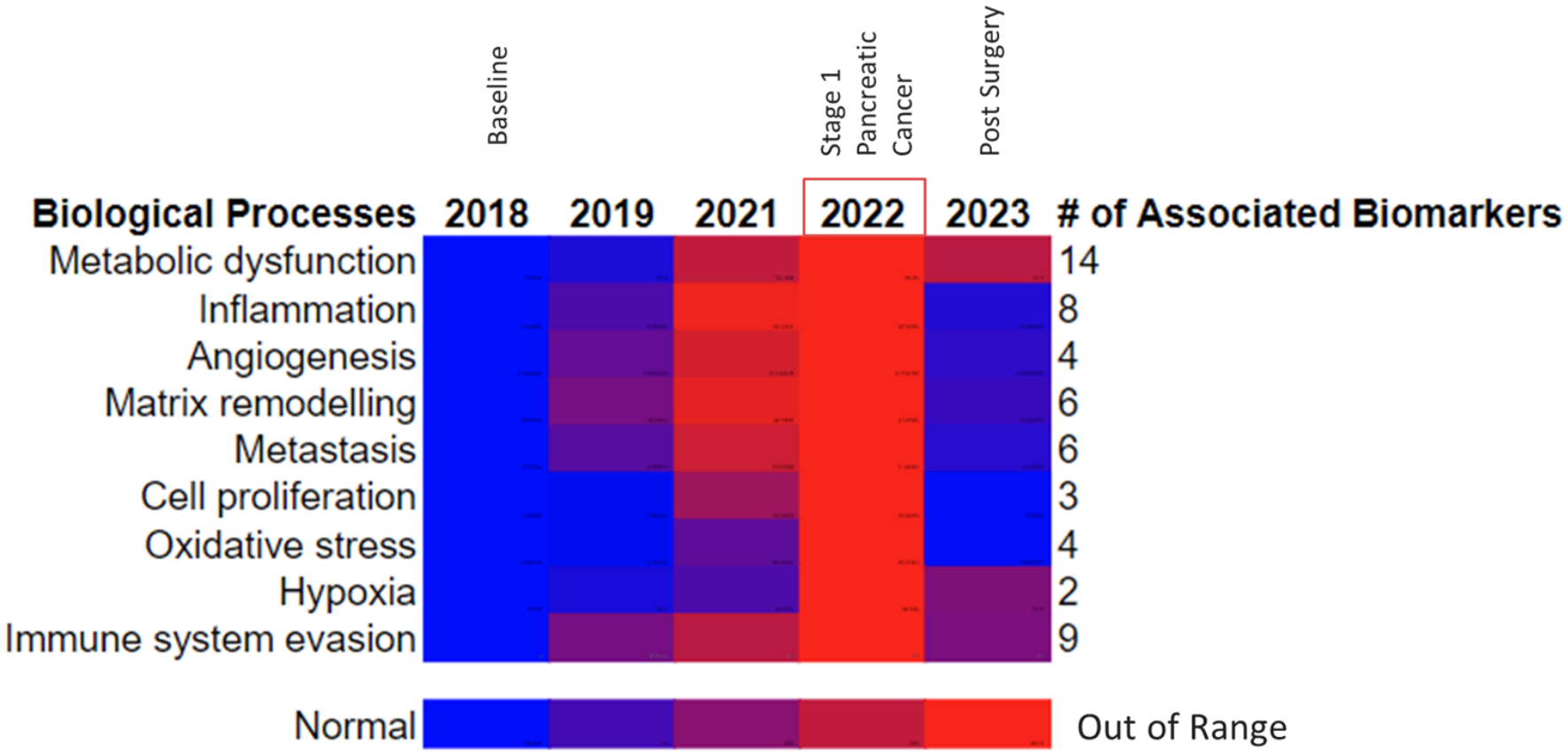
Reproductive Function: Polycystic Ovarian Syndrome



Will get more accurate as more data accumulated..

Patron J, Serra-Cayuela A, Han B, Li C, Wishart DS. Assessing the performance of genome-wide association studies for predicting disease risk. PLoS One. 2019 Dec 5;14(12):e0220215. doi: 10.1371/journal.pone.0220215. PMID: 31805043; PMCID: PMC6894795.

Longitudinal Omic Analyses Enable Early Detection of Disease: Pancreatic Cancer

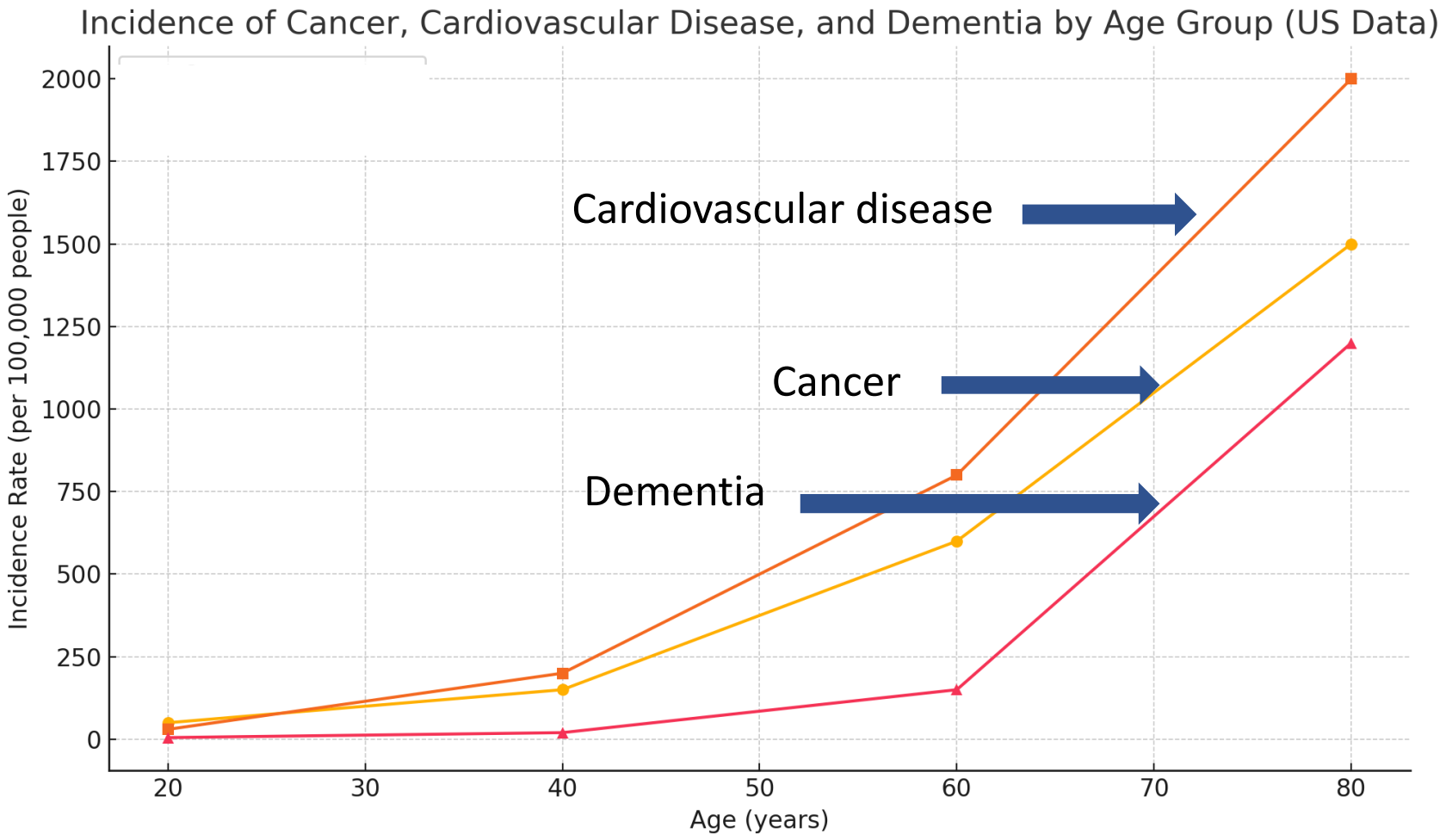


Yearly Omic analyses detected a rapid increase in pancreatic cancer-associated biomarkers enabling early detection (Stage 1) followed by normalization post-surgery

Preventive Medicine Will Eventually Require Strategies to Delay Aging

- Use Omic and other analyses to
  - Detect trends towards disease
  - Prescribe diet, exercise and supplements to address risks of disease
  - Ascertain whether therapeutic regime is working
- Develop personalized therapies to treat diseases that occur
- At some point none of these approaches will work anymore
  - **Have to address aging as the fundamental problem..**

Aging is the Dominant Risk Factor for Disease



90% of cancers occur in people over 50

By age 75 30% of us will have heart disease

If you manage to avoid cancer and heart disease, dementia awaits you!

We Have to Find Ways of Adjusting Your Physiological Age

Chronological Age: The number of years since birth.

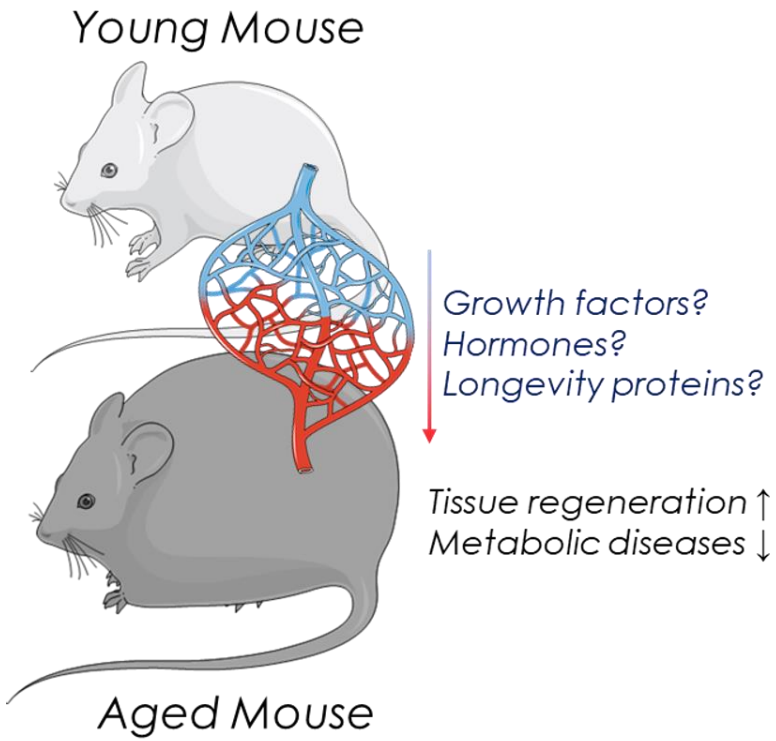
Physiological Age: How old your body appears to be based on its biological functioning.

Objective: Keep your physiological age below 50 to avoid/delay the diseases of old age

Can use Omic “clocks” to measure your physiological age and ascertain the effects of antiaging protocols

There Is Increasing Evidence That the Aging Process Can be Arrested or Even Reversed

Parabiosis: sharing the blood of a young mouse with an old mouse results in the old mouse becoming "younger" and the young mouse becoming "older"



There is an extensive literature supporting the rejuvenating effects of young blood	
1	Zhang et al. (2023). Multi-omic (epigenetic) rejuvenation and life span extension on exposure to youthful circulation. Nature Aging, 3(8), 948–964. https://doi.org/10.1038/s43587-023-00451-9
2	Ximerakis et al. Heterochronic parabiosis reprograms the mouse brain transcriptome by shifting aging signatures in multiple cell types. Nat Aging 3, 327–345 (2023). https://doi.org/10.1038/s43587-023-00373-6
3	Huang et al. (2018). A Young Blood Environment Decreases Aging of Senile Mice Kidneys. Journals of gerontology A 73 421 https://doi.org/10.1093/gerona/glx183
4	Katsimpardi et al. (2014). Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science 344 630 https://doi.org/10.1126/science.1251141
5	Loffredo et al. (2013) Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell, 153(4), 828–839. https://doi.org/10.1016/j.cell.2013.04.015
6	Suzuki et al. (2022). Evaluation of the effect of age of the younger mice on the rejuvenation of the older mice by heterochronic parabiosis. Aging, 14 2507 https://doi.org/10.18632/aging.203966
7	Sinha et al. (2014). Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science 344(6184), 649–652. https://doi.org/10.1126/science.1251152
8	Lagunas-Rangel, F.A. Aging insights from heterochronic parabiosis models. npj Aging 10, 38 (2024). https://doi.org/10.1038/s41514-024-00166-0
9	Villeda et al. (2014). Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nature medicine, 20(6), 659–663. https://doi.org/10.1038/nm.3569
10	Baht et al. Exposure to a youthful circulation rejuvenates bone repair through modulation of β-catenin. Nat Commun 6, 7131 (2015). https://doi.org/10.1038/ncomms8131

Parabiosis: young blood can make old mice younger. What factors cause this?

What Are the Factors in the Young Blood That Make Old Mice Younger?

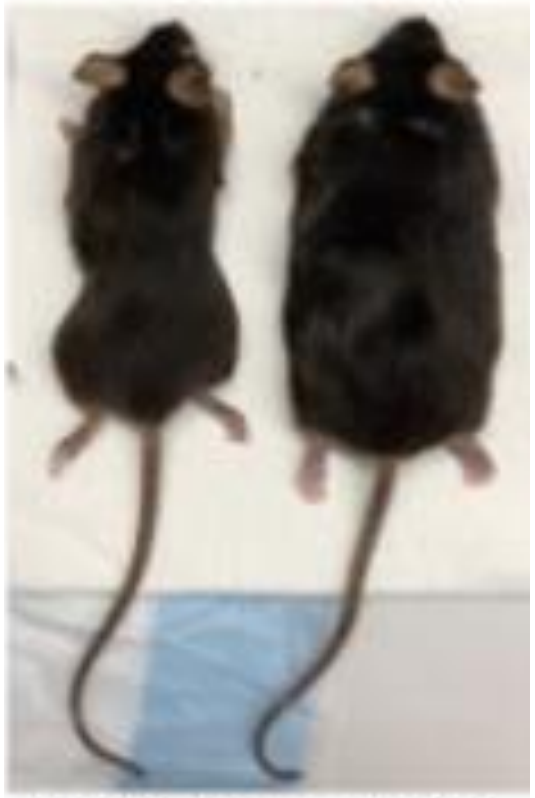
What are the drivers of this rejuvenating effect? Some leading contenders are "longevity" proteins such as GDF11, FGF21, Klotho, Heat shock factors, AMPK….

1) Schroer *et al.* **Platelet factors attenuate inflammation and rescue cognition in ageing.** *Nature* **620**, 1071–1079 (2023). https://doi.org/10.1038/s41586-023-06436-3
2) Erinjeri *et al.* **HSF-1 promotes longevity through ubiquilin-1-dependent mitochondrial network remodelling**. *Nat Commun* **15**, 9797 (2024). https://doi.org/10.1038/s41467-024-54136-x
3) Sousa-Victor, P., Neves, J., Cedron-Craft, W. *et al.* **MANF regulates metabolic and immune homeostasis in ageing and protects against liver damage**. *Nat Metab* **1**, 276–290 (2019). https://doi.org/10.1038/s42255-018-0023-6
4) Loffredo, F. S. et al. **Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy**. *Cell* **153**, 828–839 (2013). https://doi.org/10.1016/j.cell.2013.04.015
5) Sinha, M. et al., **Restoring Systemic GDF11 levels Reverses age-related dysfunction in mouse skeletal muscle.** Science 344, 649-652 (2014) https://doi.org/10.1126/science.1251152
6) Castner et al. **Longevity factor KLOTHO enhances cognition in aged nonhuman primates**. Nature Aging 3, 931-937 (2023) https://doi.org/10.1038/s43587-023-00441-x
7) Davidsohn et al. (2019). **A single combination gene therapy treats multiple age-related diseases.** *PNAS*, *116*(47), 23505–23511. https://doi.org/10.1073/pnas.1910073116 **(FGF21)**
8) Magrì *et al.* **AAV-mediated upregulation of VDAC1 rescues mitochondrial respiration in a SOD1 mouse model of inherited ALS.** *Cell Death Discov.* **10**, 178 (2024). https://doi.org/10.1038/s41420-024-01949-w
9) Li, M., Wang, Y., Wei, X. *et al.* **AMPK-PDZD8-GLS1 axis mediates calorie restriction-induced lifespan extension**. *Cell Res* **34**, 806–809 (2024). https://doi.org/10.1038/s41422-024-01021-3

Example: Expressing Longevity Genes Such As FGF21 In Mice (Liver) Reverses Age-Associated Conditions of Obesity, Diabetes, Heart Failure and Renal Failure

Davidson, Church et al. PNAS 116, 23505 (2019)

Mouse producing FGF21 and fed high fat diet (FGF21: Fibroblast growth factor 21, a hormone)



Mouse producing GFP and fed high fat diet (GFP: Green fluorescent protein, an easily measured reporter of gene expression)

Mice were transfected (i.v. administration)with adeno-associated virus (AAV) coding for FGF21 or GFP (control), resulting in production of FGF21 or GFP in the liver

There Are a Lot More Potential Longevity Proteins……

Longevity Factor	Primary Mechanism	Expected Benefits in Aged Cohorts	Primary Organs of Production
SIRT1-7 (Sirtuins 1-7)	Epigenetic regulation, mitochondrial health	Lifespan extension, metabolic improvement	Liver, Brain, Muscle, Kidney, Pancreas
FOXO3 (Forkhead Box O3)	Stress resistance, DNA repair	Increased lifespan, reduced oxidative damage	Brain, Liver, Muscle
AMPK (AMP-Activated Protein Kinase)	Energy homeostasis, autophagy	Enhanced mitochondrial function, lifespan extension	Liver, Muscle, Brain, Adipose Tissue
mTOR (Target of Rapamycin)	Growth regulation	Extended lifespan, i metabolic health	All cells, Liver, Muscle, Brain
Klotho (α-Klotho)	Phosphate metabolism, oxidative stress protection	Extended lifespan, improved kidney and vascular health	Kidney, Brain, Parathyroid Gland
GDF21 (Growth Differentiation Factor 21)	Metabolic control, mitochondrial health	Increased lifespan, reduced age-related metabolic decline	Liver, Adipose Tissue, Skeletal Muscle
FGF11 (Fibroblast Growth Factor 11)	Neuronal maintenance, metabolic regulation	Cognitive protection, neuroprotection	Brain, Central Nervous System
FGF21 (Fibroblast Growth Factor 21)	Metabolic regulation, stress resistance	Enhances metabolic health, promotes autophagy, reduces inflammation, lifespan extension	Liver, Adipose Tissue, Pancreas, Skeletal Muscle
GDF11 (Growth Differentiation Factor 11)	Tissue regeneration, vascular and neuroprotection	Improved muscle, brain, and heart function	Muscle, Heart, Blood
HSF1 (Heat Shock Factor 1)	Protein homeostasis, stress response	Lifespan extension, neuroprotection	All cells, Brain, Liver

Longevity Factor	Primary Mechanism	Expected Benefits in Aged Cohorts	Primary Organs of Production
PF4 (Platelet Factor 4)	Anti-inflammatory, immune regulation	Reduced inflammation, vascular health	Platelets
TGF-β (Transforming Growth Factor Beta)	Tissue repair, immune modulation	Rejuvenation effects, reduced inflammation	Immune Cells, Liver, Kidney
PDGF (Platelet-Derived Growth Factor)	Angiogenesis, tissue remodeling	Tissue repair, potential fibrosis prevention	Platelets, Endothelial Cells
TSP-1 (Thrombospondin-1)	Extracellular matrix remodeling	Reduced excessive angiogenesis, lifespan regulation	Platelets, Endothelial Cells
MANF (Mesencephalic Astrocyte-Derived Neurotrophic Factor)	Neuroprotection, ER stress response, inflammation control	Reduced neurodegeneration, improved metabolic and immune function	Brain, Pancreas, Liver
p53 (Tumor Suppressor Protein p53)	DNA damage response	Induces apoptosis in senescent cells	All cells
FOXO4 (Forkhead Box O4)	Stress response	Disrupts senescent cell survival (FOXO4-DRI)	Liver, Brain, Muscle
BCL-2 Family (BCL-XL, BAX, BAK)	Apoptosis regulators	Promotes or prevents senescent cell apoptosis	Immune cells, Liver
GDF11 (Growth Differentiation Factor 11)	Tissue rejuvenation	Improves stem cell function, reduces senescence markers	Muscle, Heart, Blood
NRF2 (Nuclear Factor Erythroid 2-Related Factor 2)	Antioxidant defense	Reduces oxidative stress-driven senescence	Liver, Lung, Brain
IL-10 (Interleukin-10)	Anti-inflammatory	Suppresses SASP factors	Immune cells
CXCL4 (PF4, Platelet Factor 4)	Platelet factor	Reduces immune-driven senescence	Platelets

How Could These Approaches Work in People?

There are increasingly accurate ways to measure your biological age:

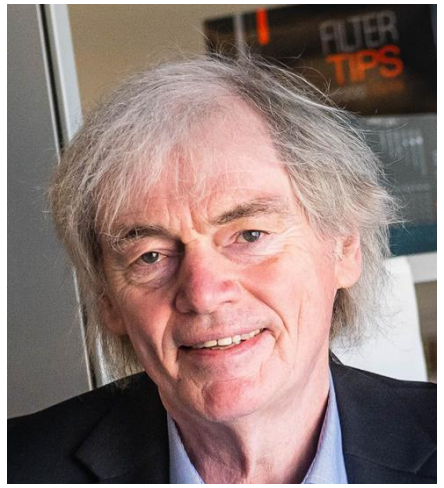
1) Proteomic age (Molecular You)
2) Epigenetic age
3) Telomere length
4) Blood biomarker age
5) Functional age

If your physiological age gets too high, devise a personalized LNP mRNA gene therapy to reduce the risk of age-related disease!

1) LNP mRNA to produce GDF11 in liver
2) LNP mRNA to produce FGF21 in liver
3) LNP mRNA to produce Klotho in liver, possibly kidney
4) LNP mRNA to produce AMPK in as many tissues as possible
5) LNP HSF1 to produce HSF1 in as many tissues as possible
6) Etc…

Honouring The Legacy of Pieter Cullis??

Hopefully More to Come!



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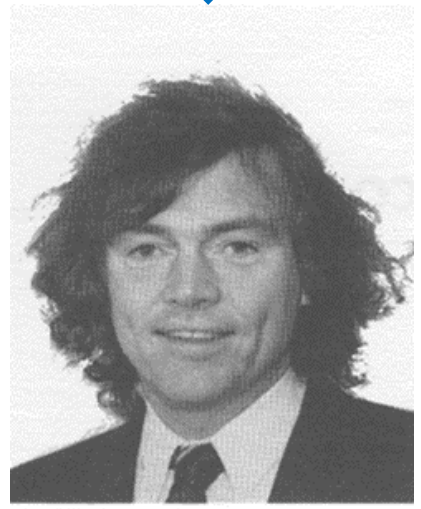

1) Starting companies: 1984
2) Delivery of cancer drugs: 1985-present
3) Delivery of nucleic acid-based drugs: 1996-present
    a) Onpattro and Comirnaty
    b) Personalized gene therapies
4) Personalized preventive medicine: 2010-present
5) **Anti-aging: 2025-**

xxx

The Future of Medicine

- **Preventive medicine using advanced Omic diagnostics**
  - To detect trends towards disease
  - To diagnose disease
  - To determine therapy
  - To determine whether therapy is working
- **Personalized gene therapies for diseases you have**
  - Treat disease with medicines that are individualized, non-toxic and very rapidly generated
- **Preventive medicine including therapies for aging**
  - Lifestyle changes/targeted therapeutics will only go so far to reverse trends towards disease
  - Need to develop gene therapies to delay/prevent aging to avoid the diseases of old age…

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