



PERSONALIZED mRNA CANCER VACCINES

CANCER ENGINEERING: THE CONVERGENCE OF ENGINEERING AND HEALTH TO ADVANCE CANCER RESEARCH AND CARE. MAY 20-21, 2025, NATIONAL ACADEMY OF SCIENCES, WASHINGTON, D.C.

John P. Cooke MD PhD
Founding Director, Center for RNA Therapeutics
Professor and Chair, Dept of CV Sciences
Houston Methodist Research Institute



Disclosures



- **Inventor** on mRNA technologies assigned to Stanford University, and to HMH
- **Founder** of ChromeX Bio and PeakRNA which are developing mRNA and circRNA therapies
- **Member of SAB** of Humann, Fibralign, JanOne, Avenna Therapeutics, NTX
- **PI** on sponsored research agreements with Avita Inc., VGXI Inc., TriLink

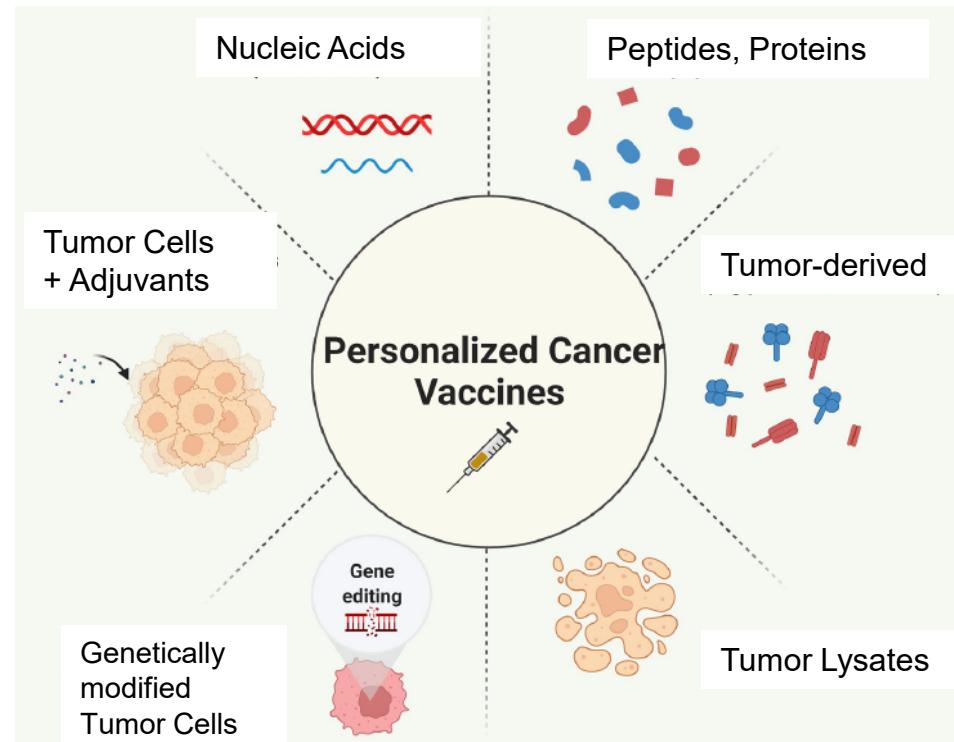
Convergence of engineering with RNA innovation will radically change how drugs are developed and distributed.

- Limitless potential of RNA therapeutics, combined with manufacturing advances, will enable hospital-based, personalized precision medicine that is affordable and accessible.
- Technology of mRNA cancer vaccines, combined with deployable manufacturing units, will facilitate hospital-based point-of-care treatment

Cancer Vaccines, Modalities

Three Modalities

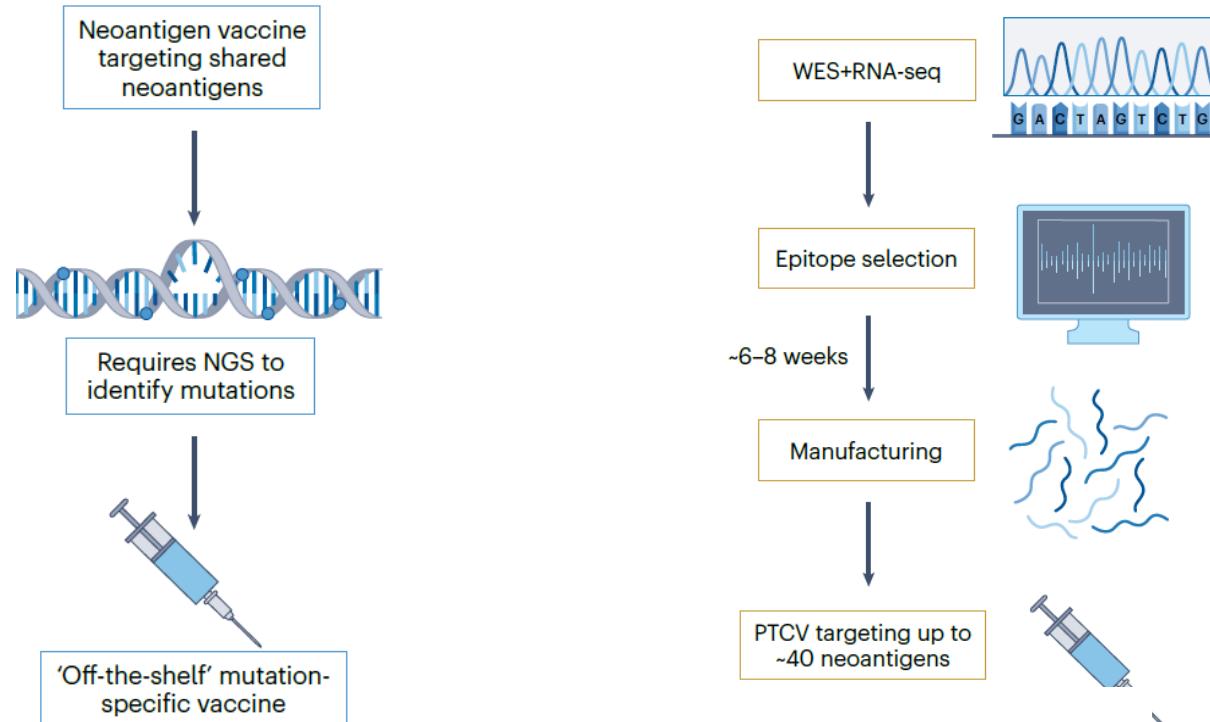
1. Tumor cells (genetically modified, lysates)
2. Proteins or peptides
3. Nucleic acids



mRNA Cancer Vaccines, Types

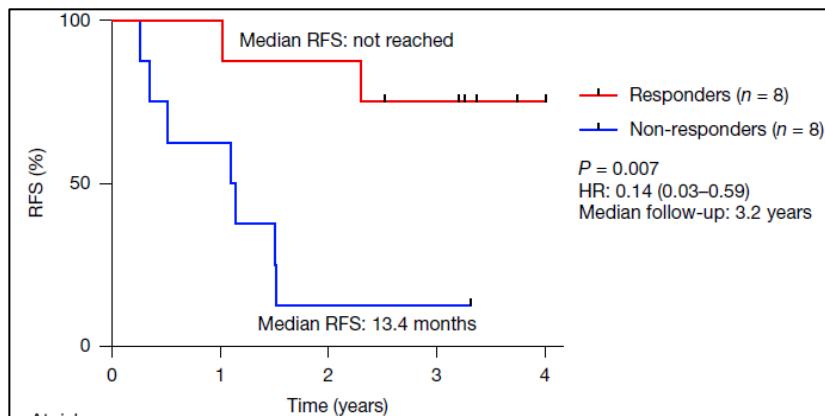
Two Types

1. Shared neoantigens (public neoantigens or Off-the-Shelf)
2. Personalized neoantigens

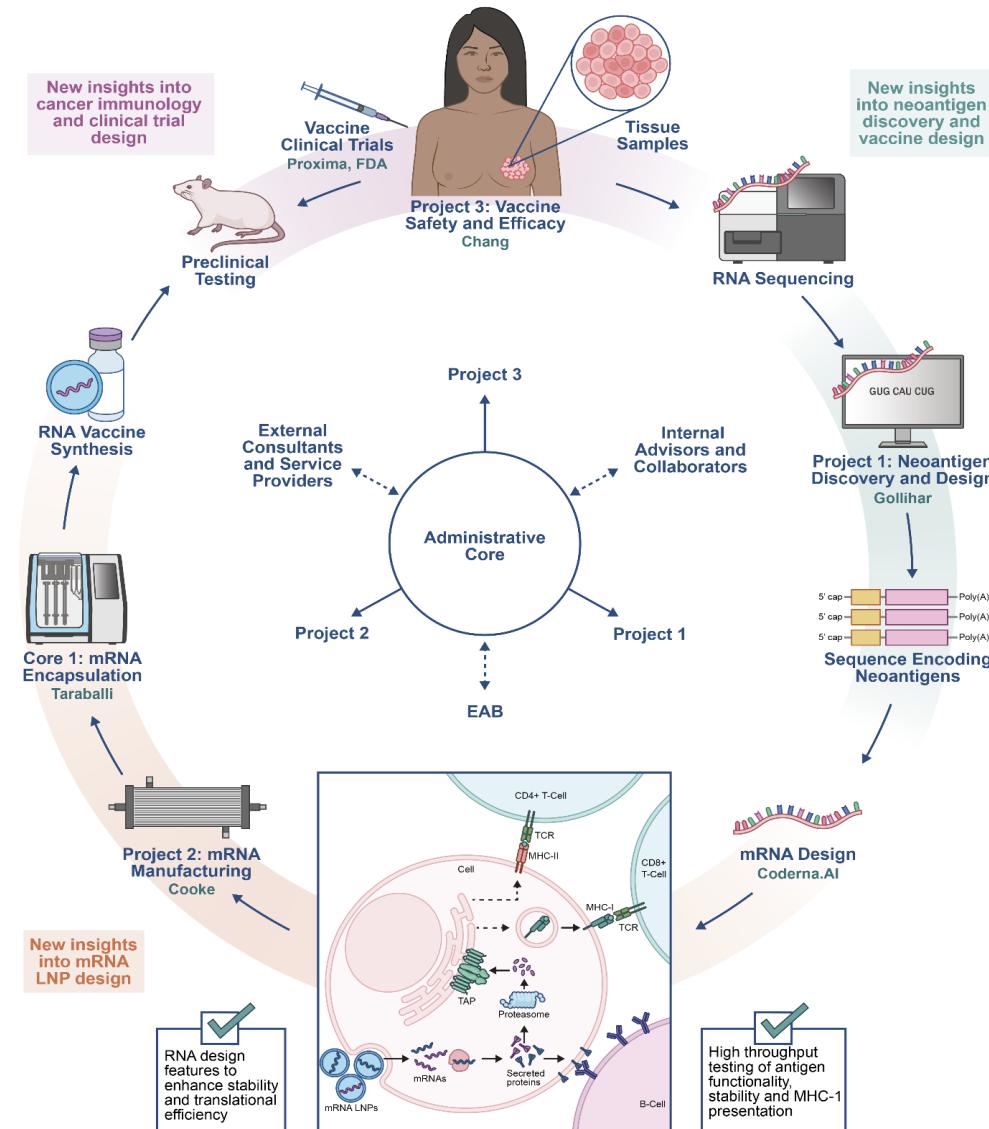


Article

RNA neoantigen vaccines prime long-lived CD8⁺ T cells in pancreatic cancer



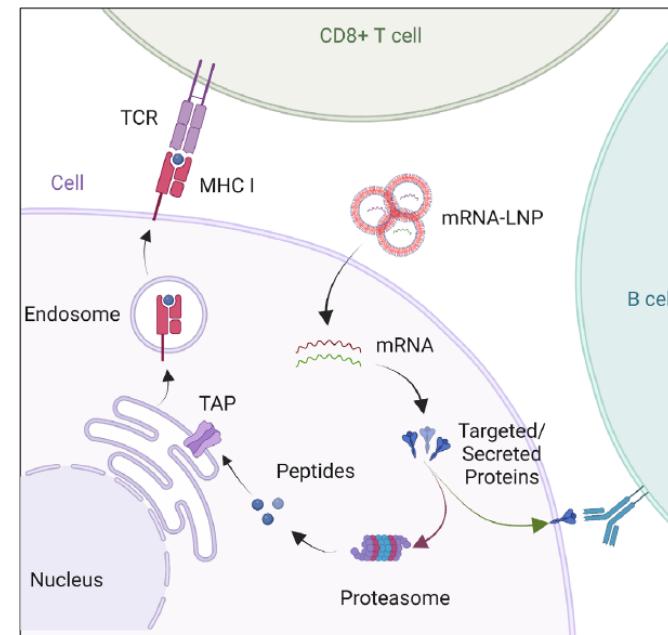
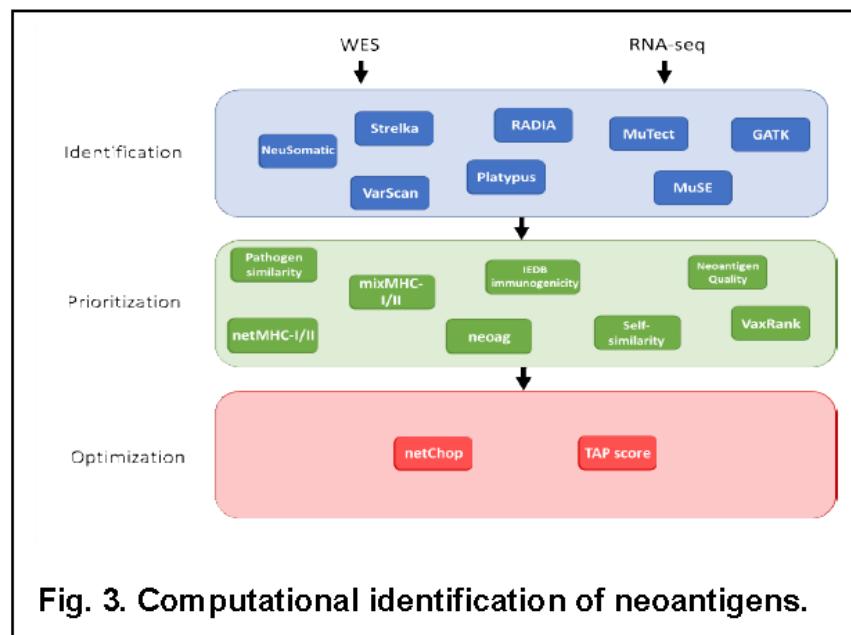
Personalized mRNA Cancer Vaccine Program at HMH



Antigen Design

AI/ML assisted computational design of tumor neoantigen vaccines.

- Computational platform to identify, prioritize, optimize neoantigens
- HMH licensed several vaccine designs to pharma in 2024 against viral pathogens.
- Early evidence of success in a humanized mouse model of triple negative breast cancer.



Antigen Optimization and Validation

Optimize and Validate tumor neoantigen expression.

- Cell lines expressing 95% of the MHC1 and MHC2 monoallelic alleles in the US population.
- Immunopeptidomic studies guide optimization; validate MHC presentation.
- Optimization includes modifications of signal sequences to enhance cellular processing of the neoantigens, sequences targeting cell surface expression, as well as oligomerization motifs.

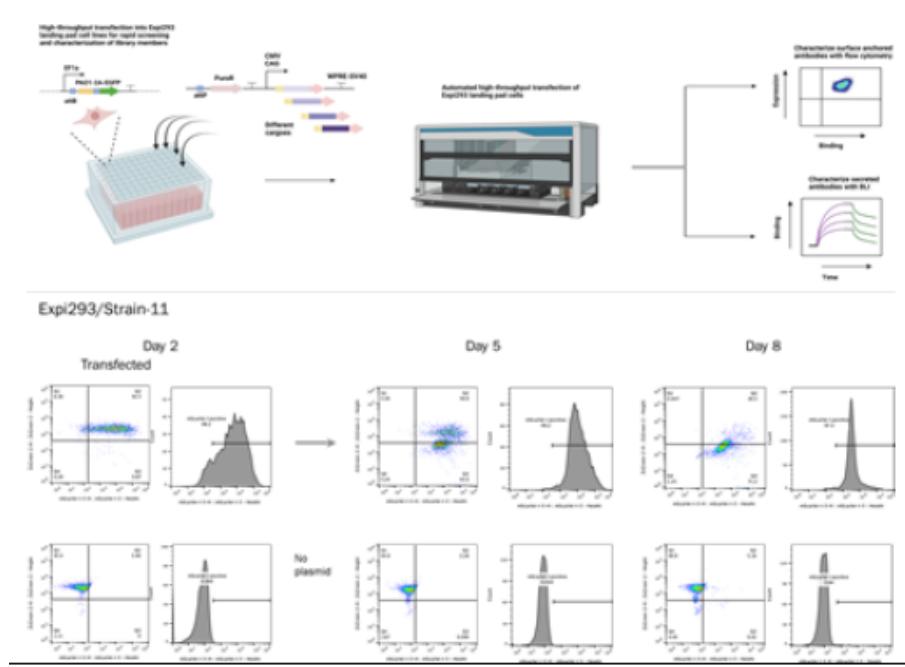


Figure 7 Stable cell line screening and high efficiency integration of cargos.

Synthesis and QC of mRNA vaccine

Synthesis, Validation and Distribution of Drug Product.

- AA sequence converted into NT sequence designed for codon optimality
- Highly defined master cell bank with starting plasmid for incorporation of ORF .
- Linearization of plasmid and IVT follow cGMP SOPs in an ISO5 clean room
- QC studies of Drug Substance
- Encapsulation
- QC of Drug Product; Fill and finish

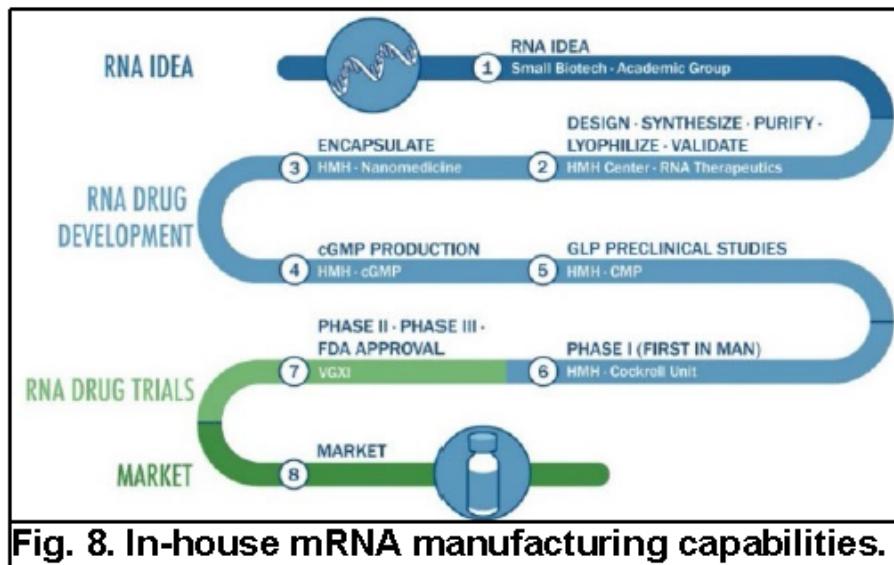
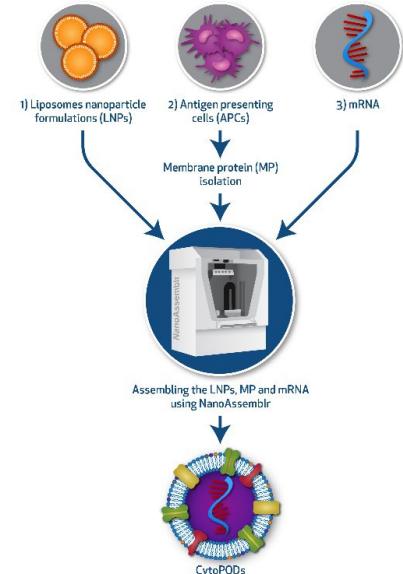
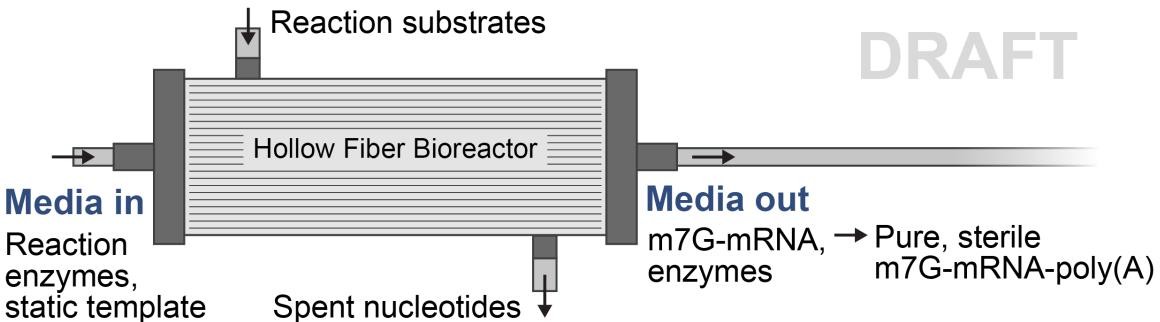


Fig. 8. In-house mRNA manufacturing capabilities.



Deployable Manufacturing Units for mRNA Vaccines

A BARDA-funded Collaboration between NTX Bio and HMRI
for Medical Countermeasures



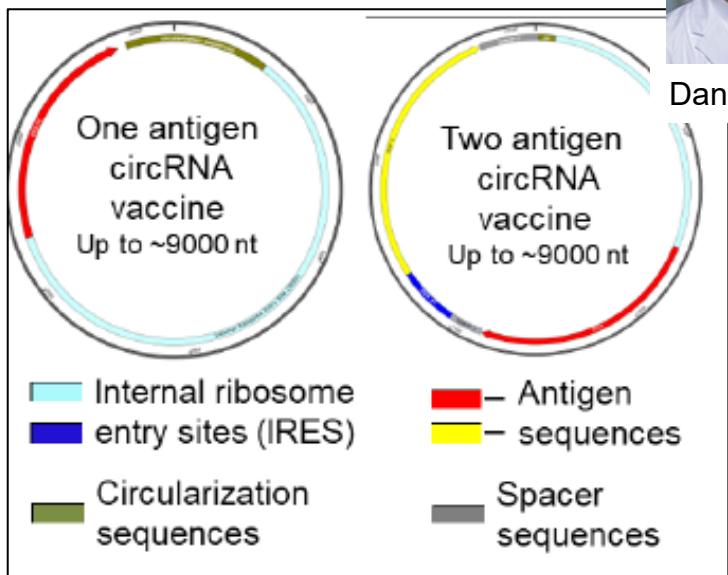
Innovation in mRNA Design

RNA Innovation.

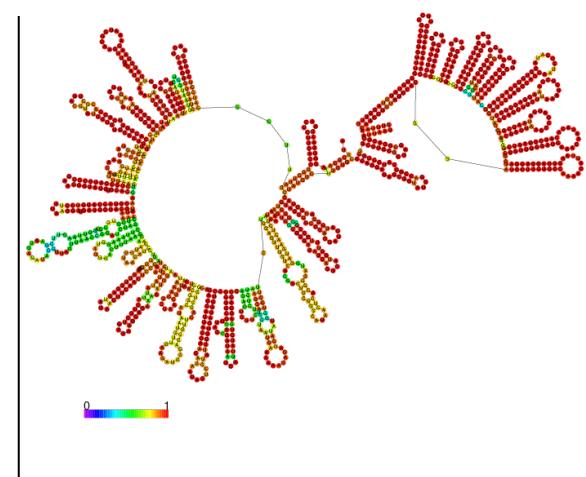
- Next-gen RNA constructs with greater stability, prolonged expression, reduced dosing.
- Circular RNA using a proprietary method also increases RNA stability and duration of expression
- RNA origami generates an mRNA structure with reduced free energy, greater stability, and greater expression exceeding the Linear Design algorithm.



Dan Kiss



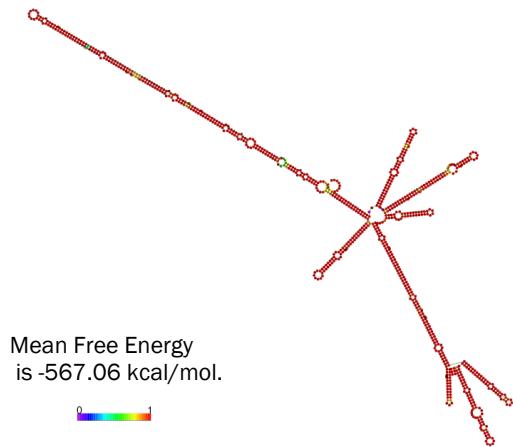
Ewan McCrae



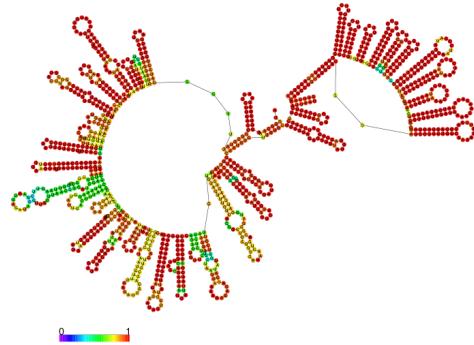
Origami Design

Origami RNA is more stable, makes more protein

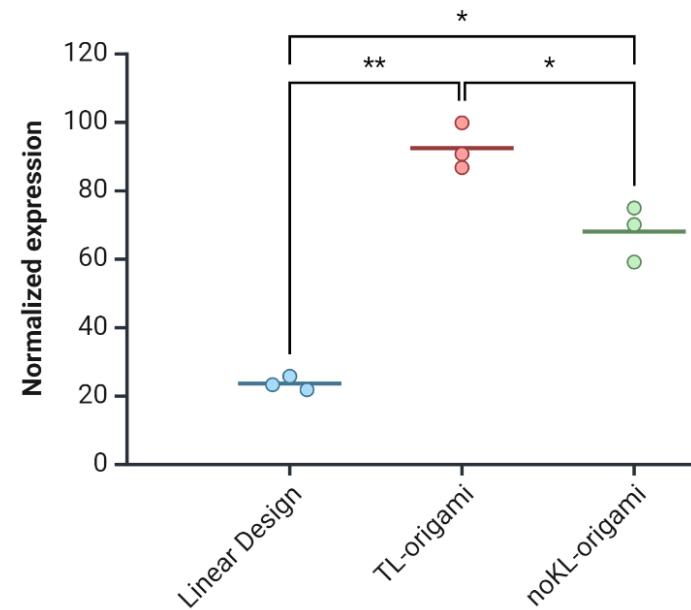
Coderna's Linear Design



HMH-origami design



Ewan McCrae



Personalized Cancer Vaccine in a Box



Hardware (NTX Bio)



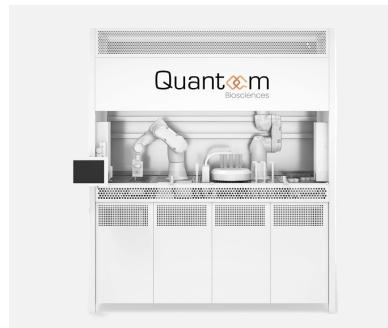
Generates Drug Substance

Software (HMH)



Designs Drug Substance

Companies generating cGMP devices:
Nutcracker Therapeutics; Curevac Printer;
Quantoom



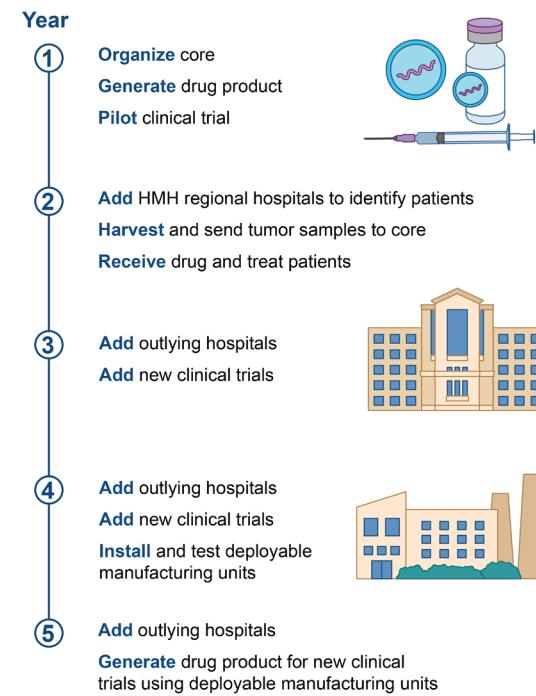
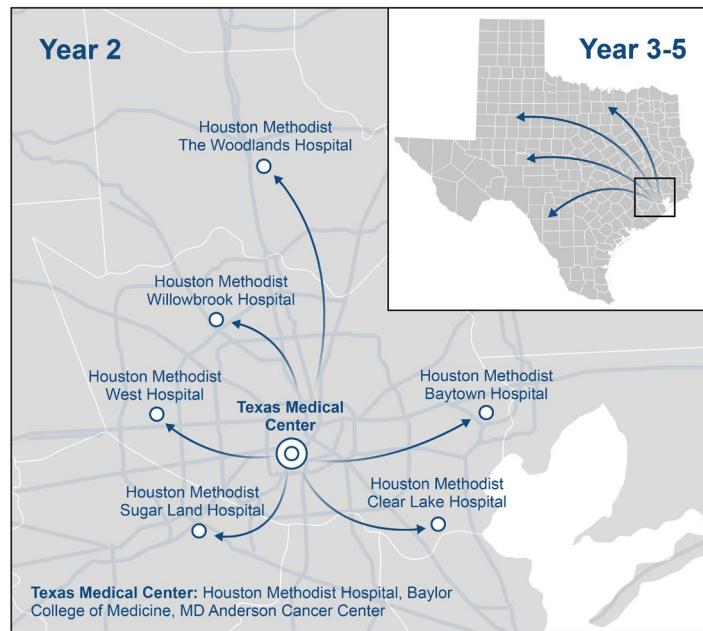
A Network for Personalized mRNA Cancer Vaccines

Year 1: Pilot study to determine the dose and frequency to induce an immune response,

Year 2: Add outlying HMH hospitals. Patients are identified, tumor samples sequenced at TMC facility; design, synthesis and validation of the PCV; cold chain transport to all hospitals.

Years 3-4: Hospitals outside of the HMH system are recruited.

Years 4-5: Introduce deployable manufacturing units to outlying hospitals. Design and synthesis at TMC facility of the linearized DNA template which is sent to outlying hospitals for on site generation of the drug product



Concluding Remarks

- RNA Therapeutic Applications Nearly Limitless
- Engineering Innovations will Democratize RNA Therapeutics
- A Paradigm Shift in Drug Development and Distribution To Increase Innovation, Accessibility and Affordability



U.S. Department of Defense

RNA TERT to Treat Radiation Injury



RNA TERT to protect against cosmic radiation



RNA Vaccines against Herpes virus



Deployable Manufacturing Unit for RNA Vaccines



National Institute of
Allergy and
Infectious Diseases

RNA vaccines against viral candidates for next
pandemic



CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS

RNA Constructs for Texas Cancer Research



Next Gen Platform for RNA Vaccines