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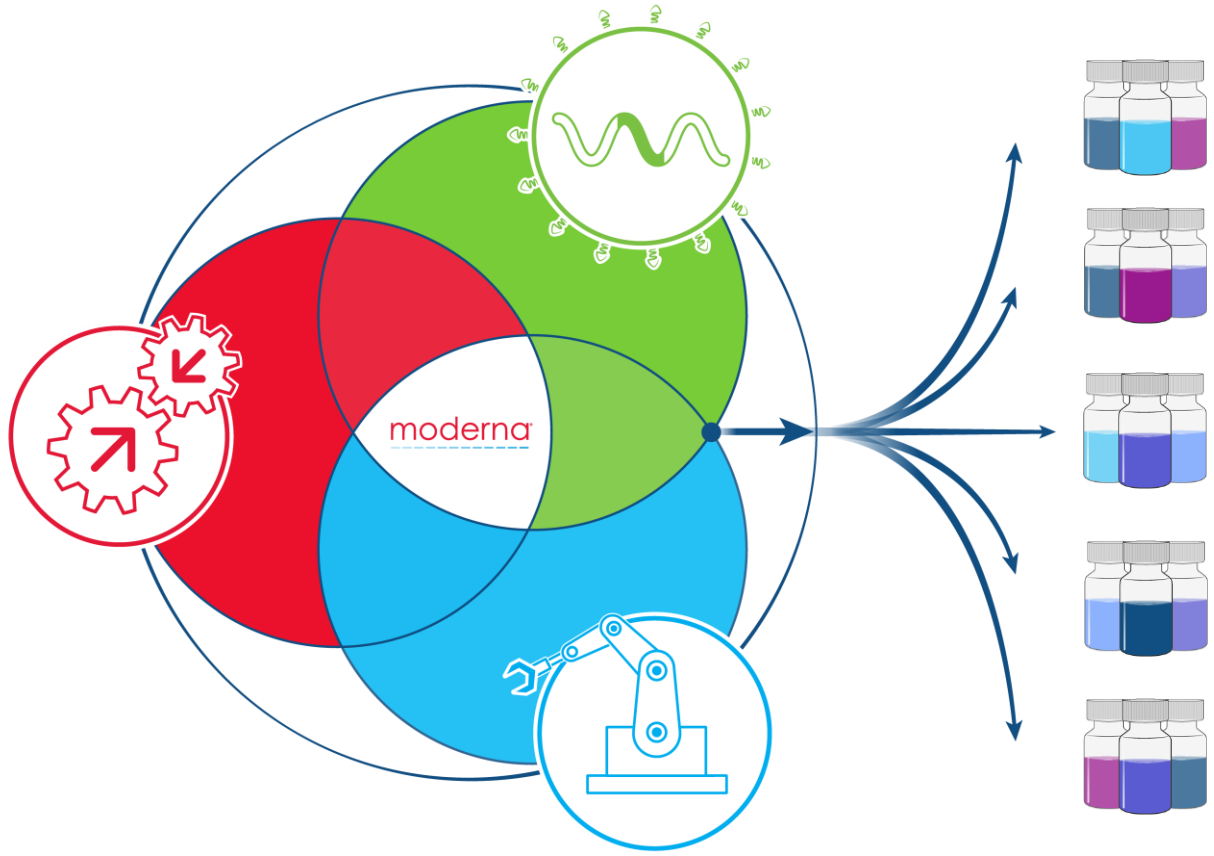

Annual R&D Day

Thursday, September 9th

Forward-looking statements and Disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding: the Company's development of the Moderna COVID-19 Vaccine (mRNA-1273); its efforts to continue developing vaccines against COVID-19, including efforts to develop vaccines against variant strains of SARS-CoV-2 and for booster doses; the ability of the Moderna COVID-19 Vaccine to provide protection against COVID-19 over time and to trigger an antibody response against variants of concern; the potential for booster doses of the Moderna COVID-19 Vaccine and variant-specific vaccine candidates to trigger neutralizing antibodies; the need for boosters against COVID-19 and the timing of that need; the safety profile associated with COVID-19 booster candidates; the ability for the Moderna COVID-19 Vaccine to be used as a booster in individuals who received a different vaccine for their primary series; the enrollment, conduct and timing of clinical trials for programs in the Company's pipeline, including its vaccine candidates against COVID-19, seasonal flu, CMV, RSV, HIV and EBV; the ability to expand the Company's portfolio of development programs; the potential to combine different vaccines into a single dose; the ability to use mRNA to enable combination therapeutics personalized for individual tumors and patients; the potential for mRNA medicines to address various diseases with unmet medical need; the potential markets associated with commercial vaccines; the scalability of the Company and its ability to bring potential medicines to market; the potential for establishing proof of concept in exploratory modalities; investments to facilitate the manufacturing of doses of the Moderna COVID-19 Vaccine; the ability of the Company to leverage mRNA vaccines manufacturing speed and scale; and the Company's commercial rights to its development candidates. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "could," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others, those risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

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Moderna COVID-19 Vaccine: Authorized Use & Important Safety Information

Authorized Use in the United States:

Moderna COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

Important Safety Information:

- Do not administer the Moderna COVID-19 Vaccine to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of the Moderna COVID-19 Vaccine.
- Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine. Monitor Moderna COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html).
- Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose.
- Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be in place to avoid injury from fainting.
- Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished response to the Moderna COVID-19 Vaccine.
- The Moderna COVID-19 Vaccine may not protect all vaccine recipients.
- Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site.
- The following adverse reactions have been reported following administration of the Moderna COVID-19 Vaccine during mass vaccination outside of clinical trials: (i) severe allergic reactions, including anaphylaxis, and (ii) myocarditis and pericarditis
- Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion.
- There are no data available on the interchangeability of the Moderna COVID-19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Moderna COVID-19 Vaccine should receive a second dose of Moderna COVID-19 Vaccine to complete the vaccination series.
- Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Moderna COVID-19 Vaccine.
- Vaccination providers must complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS, call 1-800-822-7967. The reports should include the words “Moderna COVID- 19 Vaccine EUA” in the description section of the report.

Click for Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Full EUA Prescribing Information for more information.

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Software uses a binary system

Binary System

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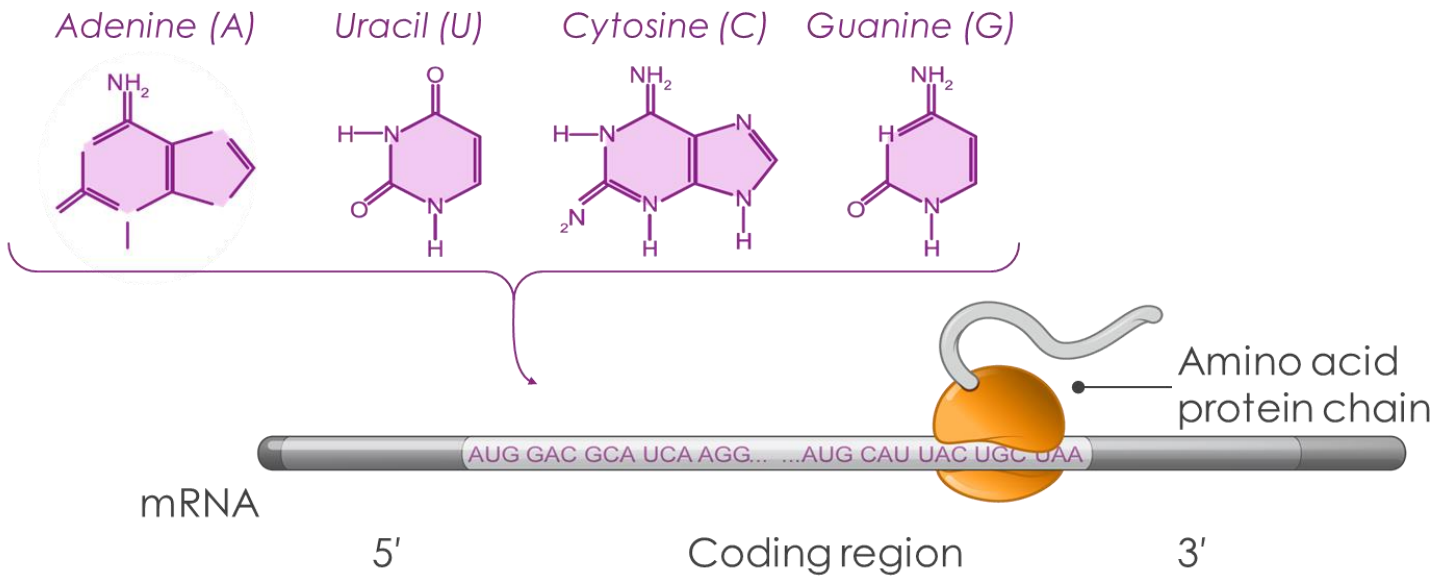
Life uses a quaternary system

Binary System

Quaternary System



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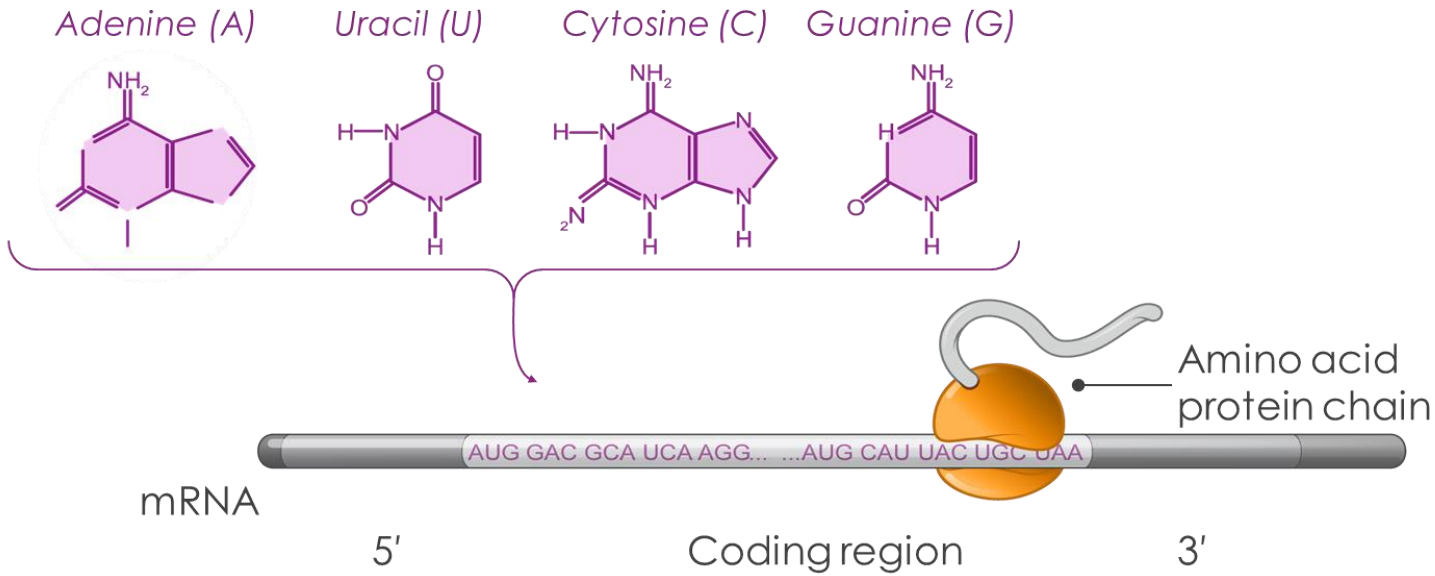
Life uses a quaternary system

Binary System

Quaternary System



mRNA is an information molecule

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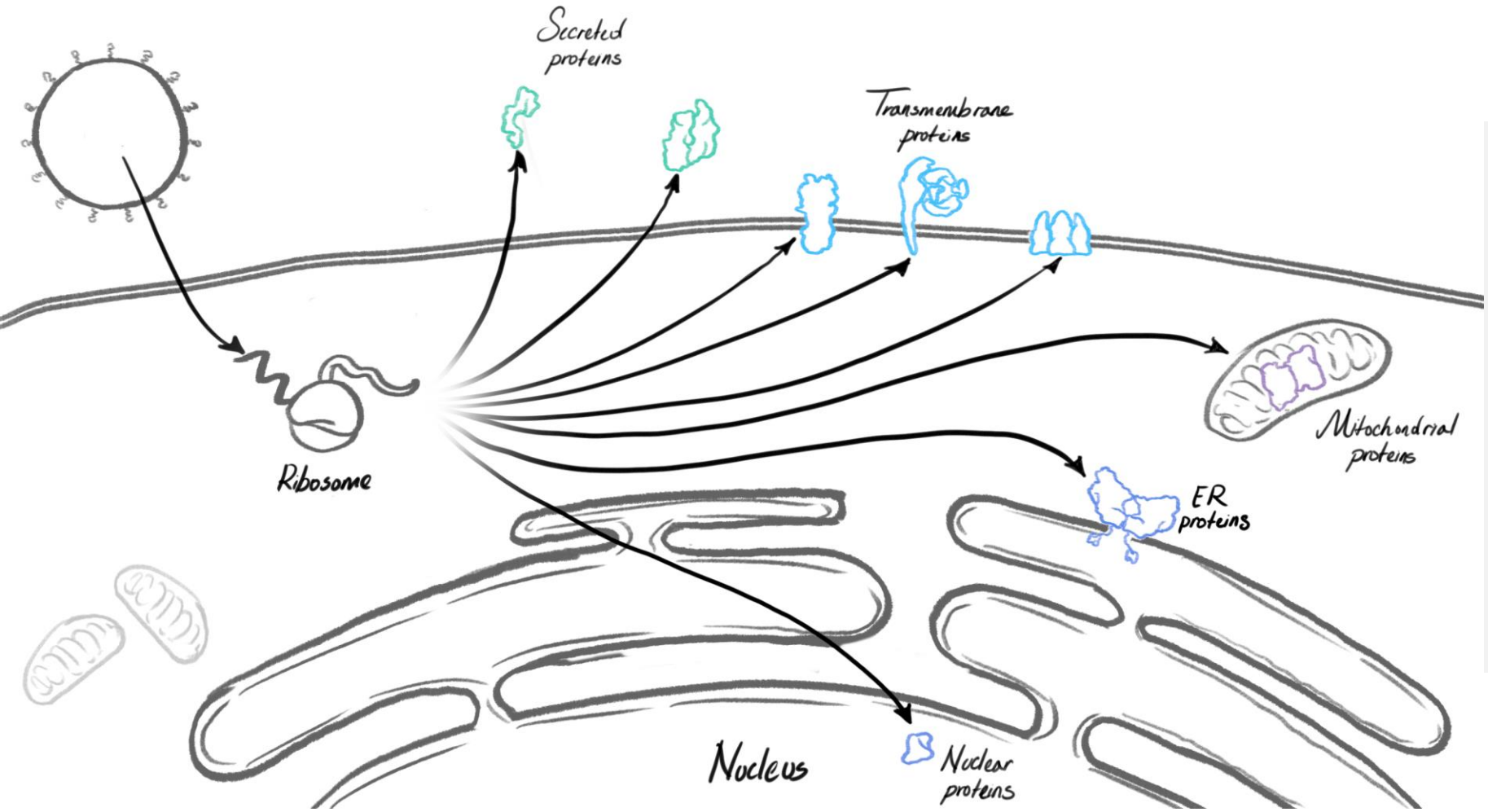
mRNA is a new class of medicines



1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology

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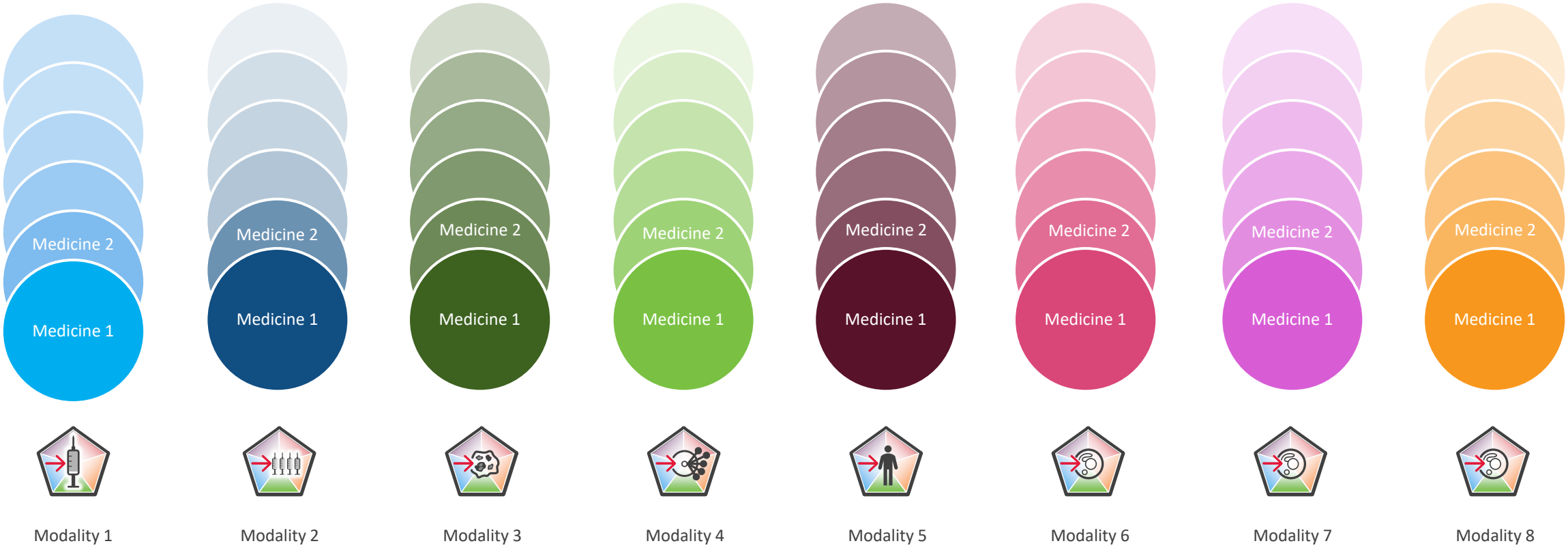
Moderna's vision for mRNA science

1 mRNA is an information molecule

2 Invest in science to invent novel ways to deliver mRNA into various cell types – each will be a new application, which we call a modality



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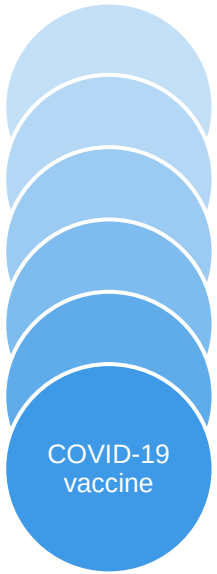
Moderna in 2021

— COMMERCIAL —

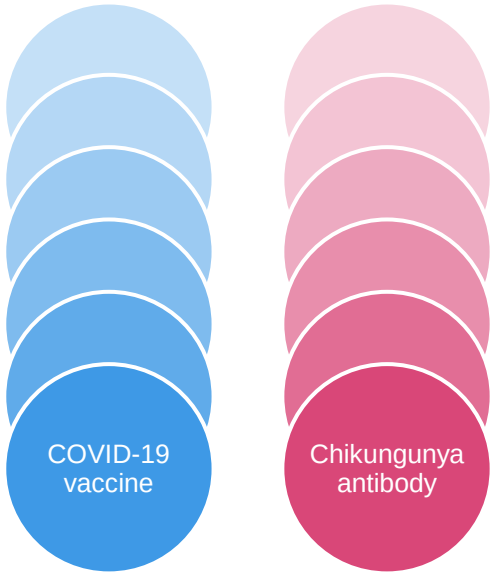


Prophylactic
vaccines

Moderna in 2021

COMMERCIAL — DEVELOPMENT

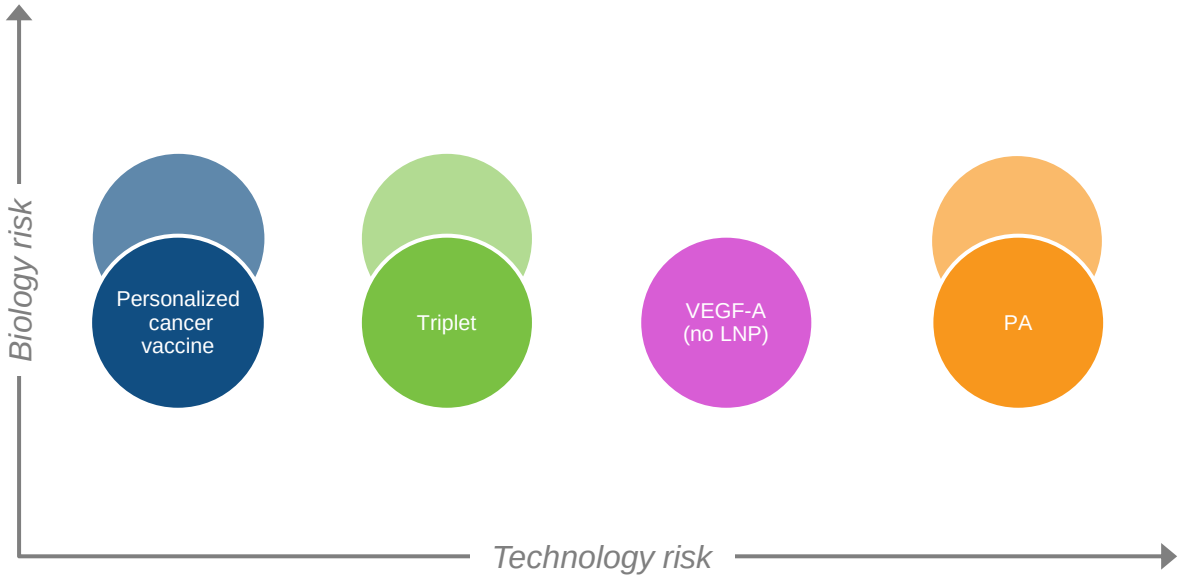
Core Modalities



Prophylactic vaccines

Systemic secreted & cell surface therapeutics

Exploratory Modalities



Cancer vaccines

Intratumoral immuno-oncology

Localized regenerative therapeutics

Systemic intracellular therapeutics

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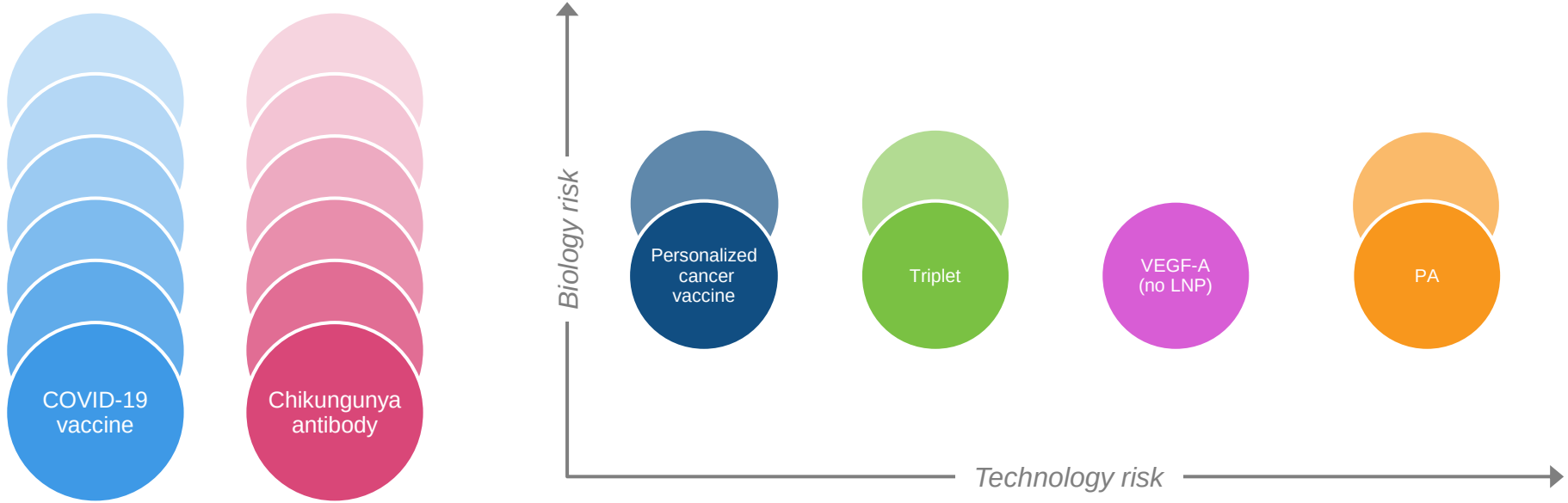
Moderna in 2021

COMMERCIAL — DEVELOPMENT — RESEARCH

Core Modalities

Exploratory Modalities

Future Modalities



Prophylactic vaccines

Systemic secreted & cell surface therapeutics

Cancer vaccines

Intratumoral immuno-oncology

Localized regenerative therapeutics

Systemic intracellular therapeutics

Lung

Stem cells

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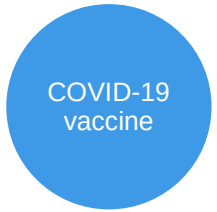
Some believe Moderna is just a COVID-19 vaccine company



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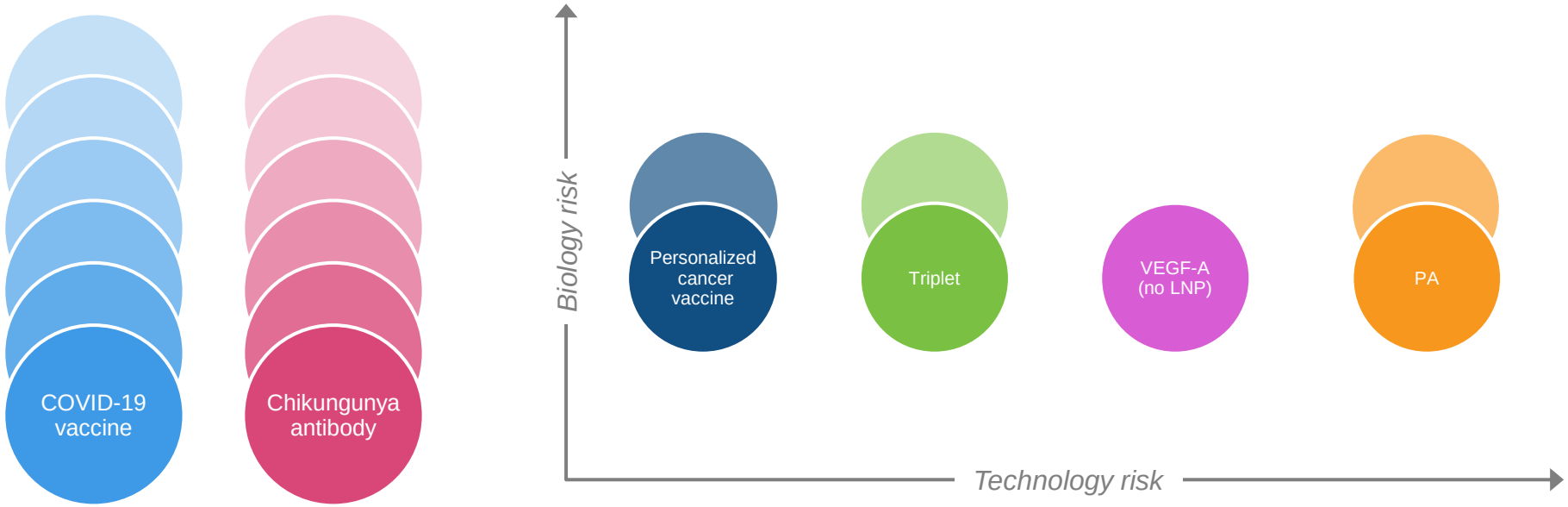
Moderna is an information-medicine based platform company

COMMERCIAL — DEVELOPMENT — RESEARCH

Core Modalities

Exploratory Modalities

Future Modalities



Prophylactic vaccines

Systemic secreted & cell surface therapeutics

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Moderna's product strategy

1	Bring to market a **pan-respiratory annual booster vaccine** (which we will continuously customize)
2	Bring to market **first-in-class vaccines for complex viruses**
3	Bring to market **therapeutics based on mRNA-encoded proteins**
4	Bring to market **therapeutics based on mRNA-encoded gene editing enzymes**

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Our vision for pan-respiratory annual booster vaccines

A single dose annual booster which is customized…

Time

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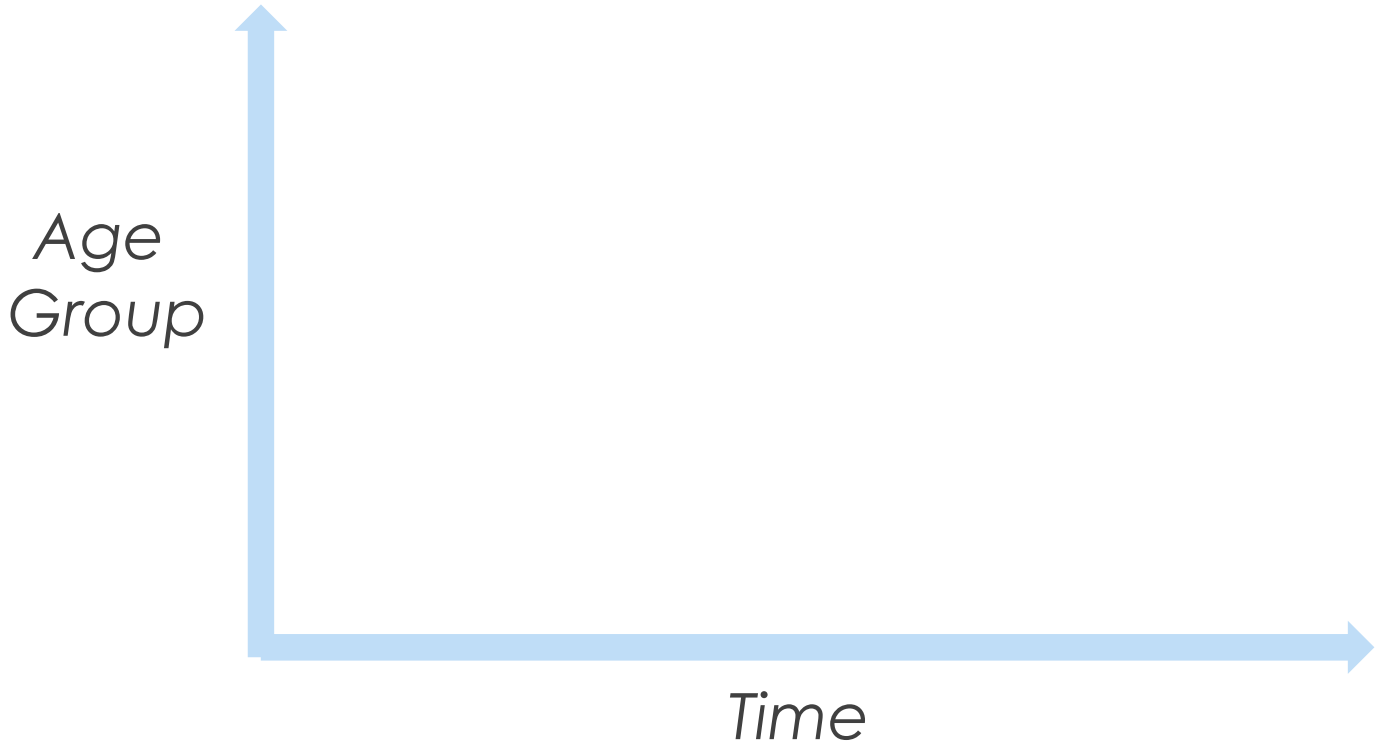
Our vision for pan-respiratory annual booster vaccines

A single dose annual booster which is customized…



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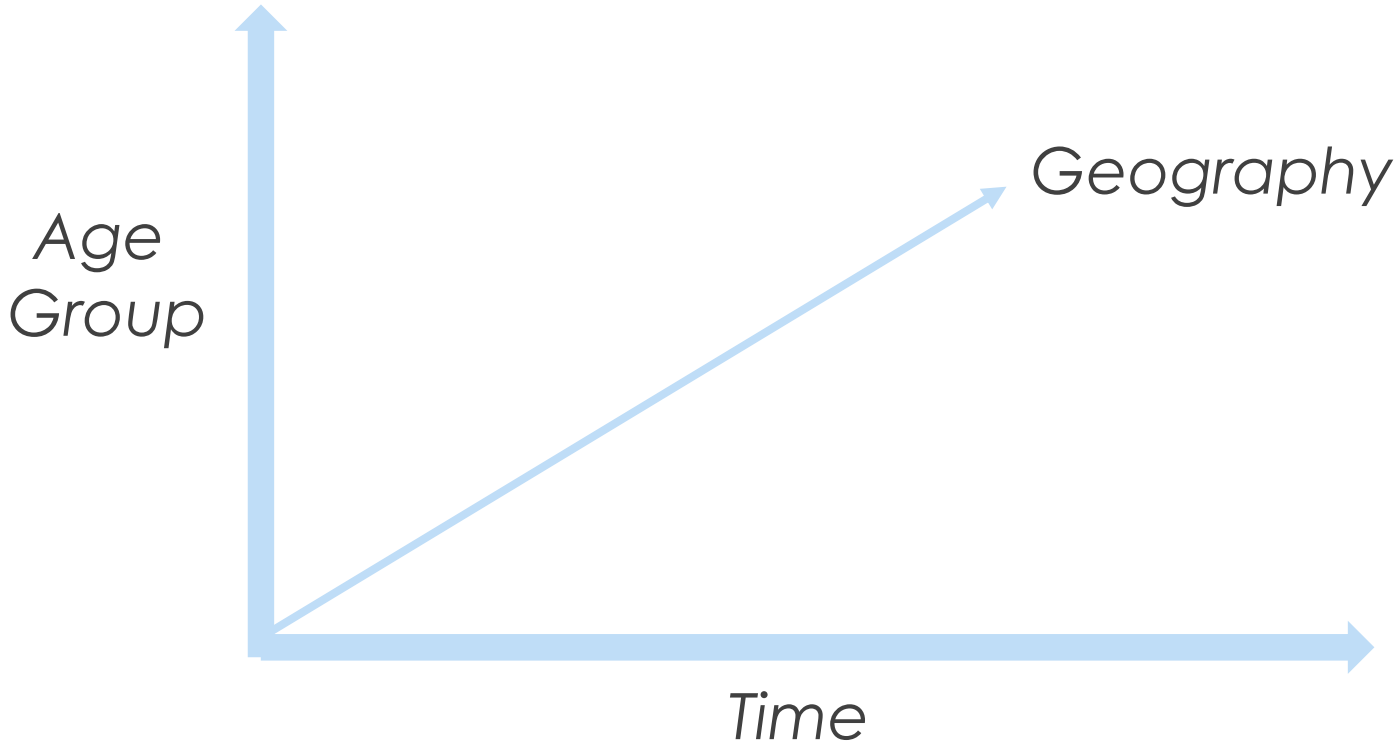
Our vision for pan-respiratory annual booster vaccines

A single dose annual booster which is customized…



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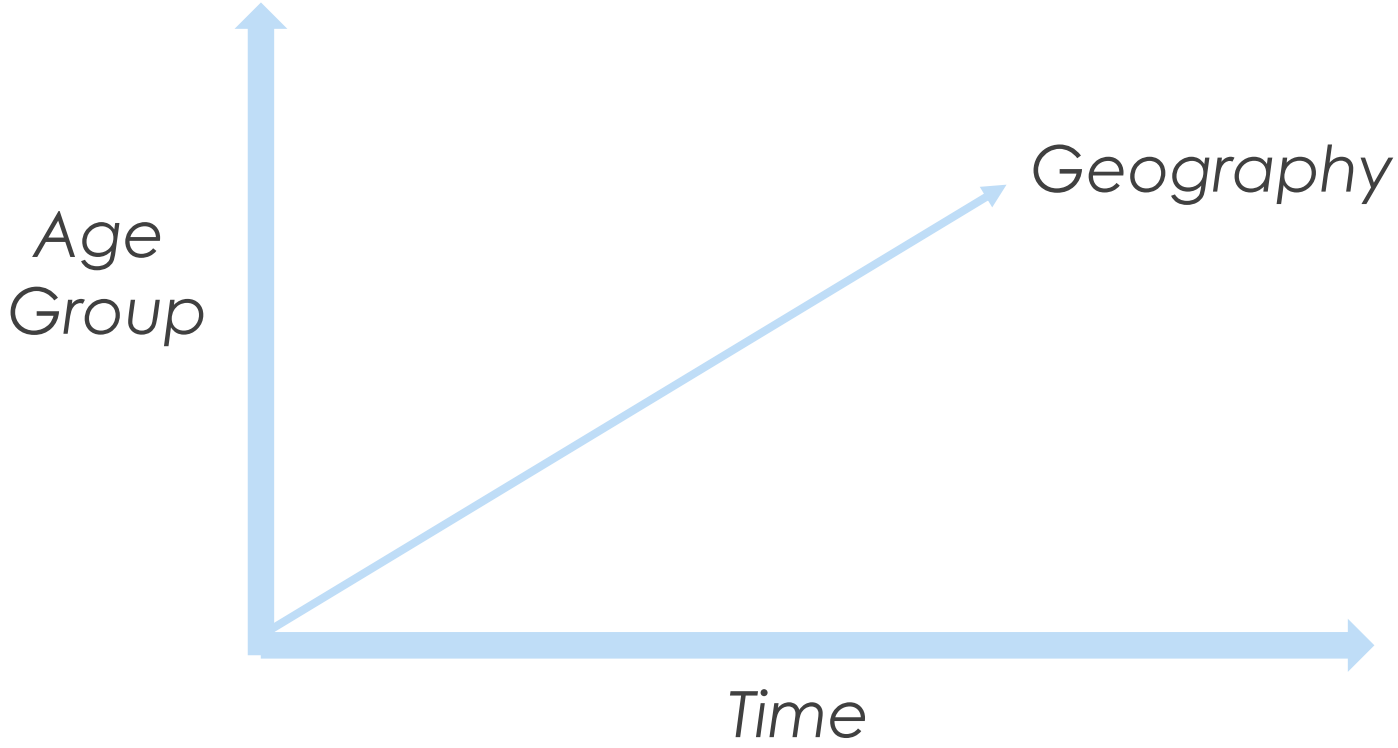

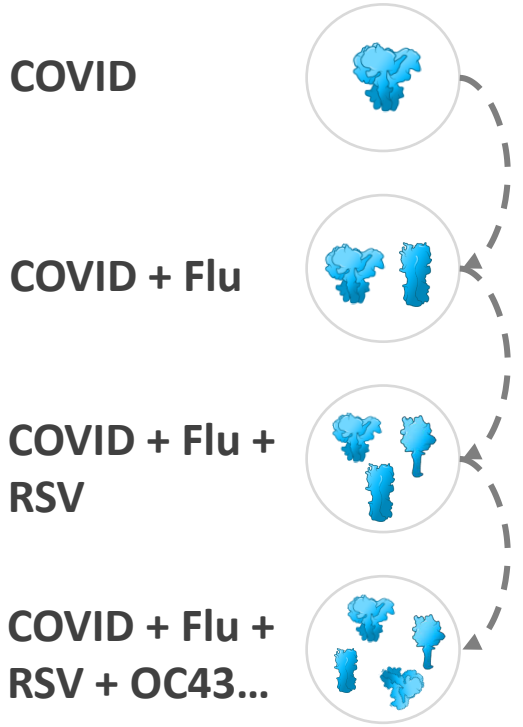

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Respiratory viruses are a leading cause of many hospitalizations and deaths

Location/ Population	Top respiratory viruses	Hospitalizations	Deaths	Estimate
U.S. only	Influenza	404,646	21,909	2019-2020 flu season
U.S. only	Resp. syncytial virus (RSV)	235,000	14,000	Annual estimates
OECD markets, **65+ years old**	OC43	175,000	10,000	Annual estimates
U.S. only, **<5 years old**	Metapneumovirus (HMPV)	28,000	ND	Annual estimates
U.S. only, **<5 years old**	Parainfluenza virus(PIV3)	12,000	ND	Annual estimates

ND = No Data

CDC, https://www.cdc.gov/flu/about/burden/2019-2020.html
CDC, https://emergency.cdc.gov/han/2021/han00443.asp
Sieling. Influenza Other Respi Viruses. 2021; 00:1, Rae. Potential Costs of Coronavirus Treatment for People with Employer Coverage. 2020. Peterson-KFF Health System Tracker, Kozak. Journal of Clinical Virology. 2020; 126:104338, Fischer. Lancet Microbe. 2021; doi.org/10.1016/S2666-5247(20)30221-4, Gilca. J Infect Dis. 2020; jiaa477

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A pan-respiratory annual booster vaccine represents a large opportunity for Moderna

How big will the market be?

- In 2019, the flu market was greater than 500M doses

How much share could we own?

- We believe Moderna could be first to market with a COVID + Flu + RSV booster vaccine
  - Quadrivalent seasonal Flu candidate (mRNA-1010) is in the clinic and is preparing for Phase 2/3 study
  - RSV vaccine (mRNA-1345) had positive Phase 1 results and we are preparing for a Phase 2/3 study

What value could we create?

- A single vaccine to cover multiple viruses
- Compliance with a pan-respiratory annual booster drives value for payors
- Convenience to the consumer (1 vs. 3 injections) drives preference
- Reduction in vaccine administration cost to the healthcare system (1 vs. 3 injections)

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Moderna's Respiratory Vaccines (Pipeline 1/3)

11 respiratory vaccine programs in the clinic

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Prophylactic vaccines: Adults	COVID-19 vaccine	mRNA-1273						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
	Flu vaccine	mRNA-1010	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	**mRNA-1073**	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	mRNA-1345			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	mRNA-1273	KidCOVE					Worldwide
	Pediatric RSV vaccine	mRNA-1345	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	mRNA-1653						Worldwide
	Pediatric RSV + hMPV vaccine	**mRNA-1365**						Worldwide

New development candidates

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Moderna's product strategy

1	Bring to market a **pan-respiratory annual booster vaccine** (which we will continuously customize)
2	Bring to market **first-in-class vaccines for complex viruses**
3	Bring to market **therapeutics based on mRNA-encoded proteins**
4	Bring to market **therapeutics based on mRNA-encoded gene editing enzymes**

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Moderna's Other Vaccines (Pipeline 2/3)

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Prophylactic vaccines	CMV vaccine	**mRNA-1647**				Phase 3 prep		Worldwide
	EBV prophylactic vaccine **EBV therapeutic vaccine**	**mRNA-1189**						Worldwide
		mRNA-1195						Worldwide
	Zika vaccine	**mRNA-1893**						Worldwide ***BARDA** funded*
	HIV vaccine	**mRNA-1644**	Open IND					Worldwide ***IAVI/others** funded*
		mRNA-1574						Worldwide ***BMGF/NIAID/ others** funded*
	Nipah vaccine	**mRNA-1215**						Worldwide ***NIH** funded*

New development candidates

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Moderna's product strategy

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2	Bring to market **first-in-class vaccines for complex viruses**
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Moderna's Therapeutics (Pipeline 3/3)

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	**mRNA-1944**						Worldwide ***DARPA** funded*
	IL-2 *Autoimmune disorders*	**mRNA-6231**						Worldwide
	Relaxin *Heart failure*	**mRNA-0184**						Worldwide
	PD-L1 *Autoimmune hepatitis*	**mRNA-6981**						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	**mRNA-4157**						50-50 global profit sharing with **Merck**
	KRAS vaccine	**mRNA-5671**						50-50 global profit sharing with **Merck**
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	**mRNA-2752**						Worldwide
	IL-12 *Solid tumors*	**MEDI1191**						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	**AZD8601**						**AZ** to pay milestones and royalties
Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	**mRNA-3927**						Worldwide
	Methylmalonic Acidemia (MMA)	**mRNA-3705**						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	**mRNA-3745**	**Open IND**					Worldwide
	Phenylketonuria (PKU)	**mRNA-3283**						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	**mRNA-3351**						Provided to **ILCM** free of charge

New development candidates

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Today's speakers from Moderna

Stephen Hoge, M.D.

President

Paul Burton, M.D., Ph.D., F.A.C.C., M.R.C.S.

Chief Medical Officer

Jacqueline Miller, M.D.

Senior Vice President, Therapeutic Area Head, Infectious Diseases

Praveen Aanur, M.B.B.S, M.P.H

Vice President, Therapeutic Area Head, Oncology

Ruchira Glaser, M.D., M.S.

Senior Vice President, Therapeutic Area Head, Cardiovascular, Rare Diseases & Autoimmune

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Today's agenda

Opening Remarks	**Stéphane Bancel**, *Chief Executive Officer*
Platform, Modalities & Therapeutic Area Overview	**Stephen Hoge, M.D.**, *President*
Review of COVID-19 Vaccine Real-World Experience	**Paul Burton, M.D., Ph.D., F.A.C.C., M.R.C.S.**, *Chief Medical Officer*
Infectious Diseases	**Jacqueline Miller, M.D.**, *Senior Vice President, Infectious Diseases* *Vaccines against acute respiratory infections* *Vaccines against persistent infections*
Break	
Oncology	**Praveen Aanur, MBBS, MPH,** *Vice President, Oncology* **Ignacio Melero Bermejo, M.D.**, *Clinica Universidad de Navarra*
Rare Diseases, Autoimmune Diseases & Cardiovascular Diseases	**Ruchira Glaser, M.D., M.S.,** *Senior Vice President, Cardiovascular, Rare Diseases & Autoimmune*
Conclusion	**Stéphane Bancel**, *Chief Executive Officer*
Q&A	

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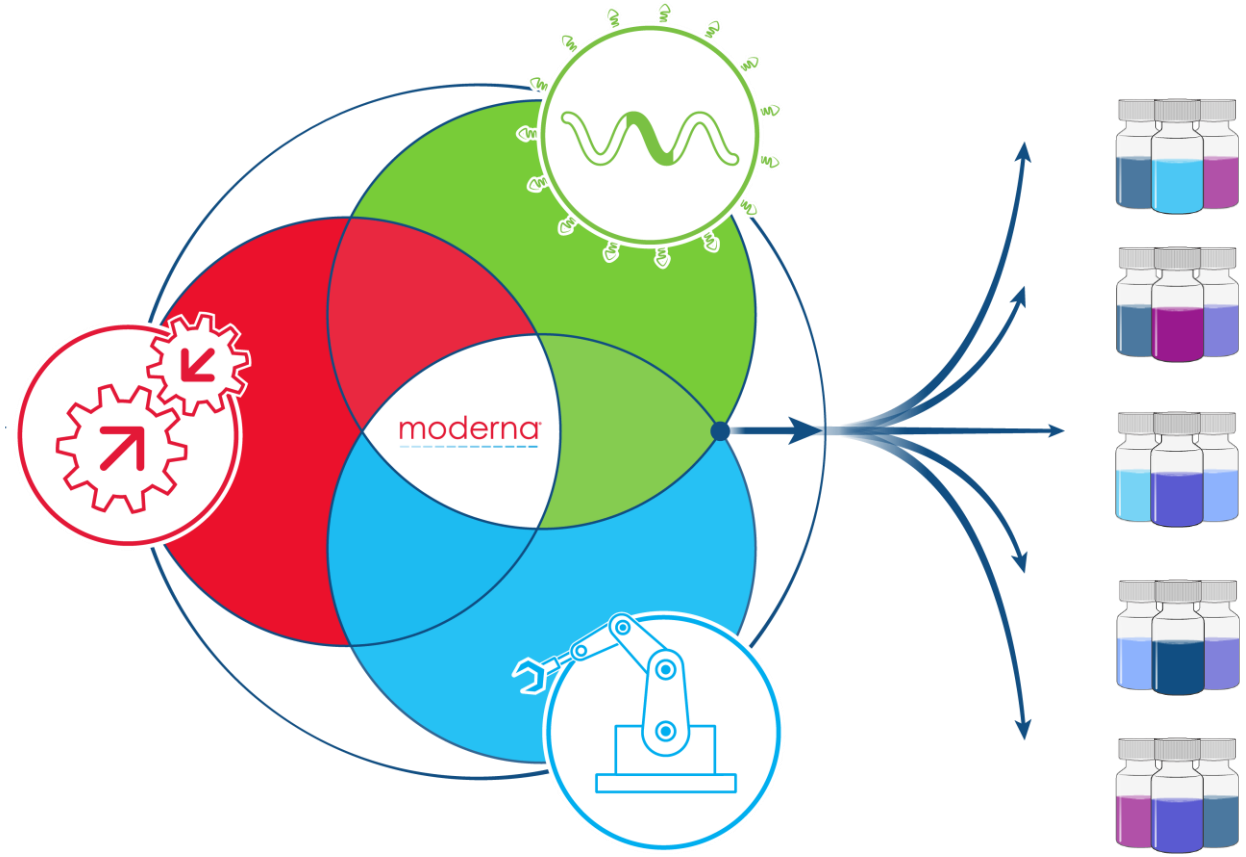
Platform, modalities & therapeutic area overview

Stephen Hoge, M.D.
President



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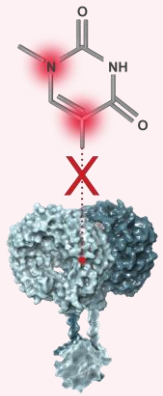
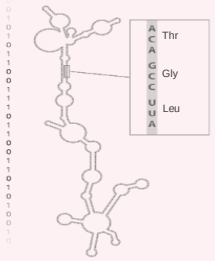
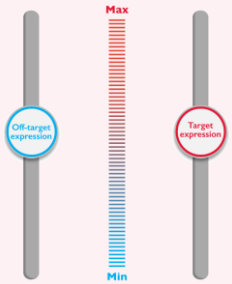
Key components of our platform

mRNA

- Chemistry
- Sequence engineering
- Targeting elements

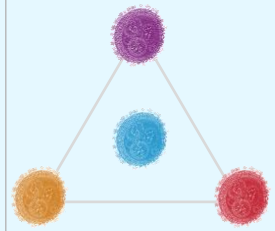


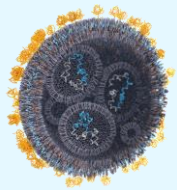




Delivery

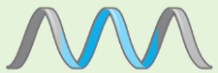
- Chemistry
- Composition
- Surface properties

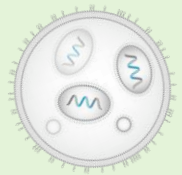




Process

- mRNA
- LNP





Our platform incorporates the advancements and inventions we've made and continue to make in mRNA science, delivery technologies and manufacturing processes

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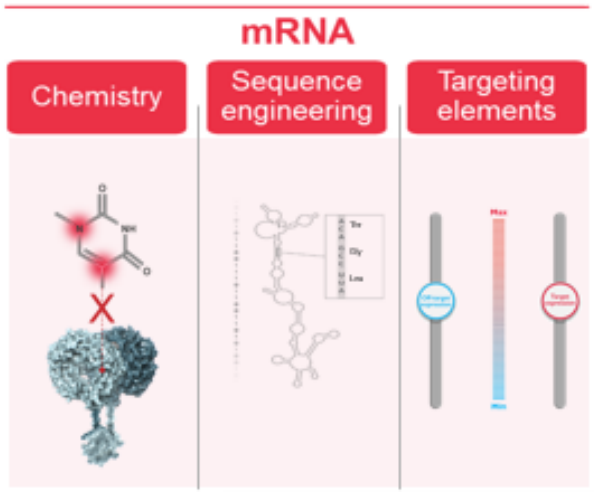
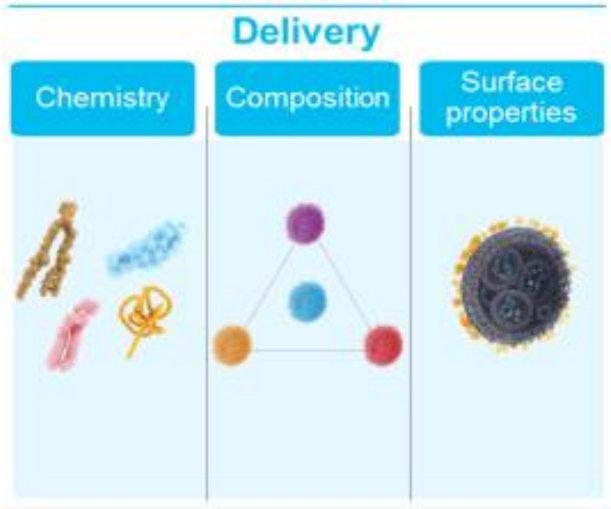
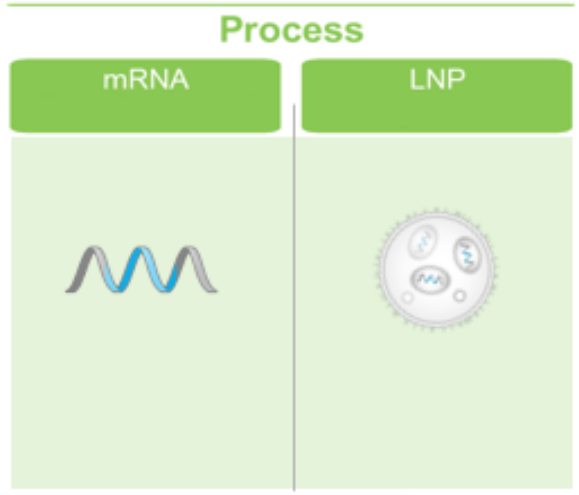
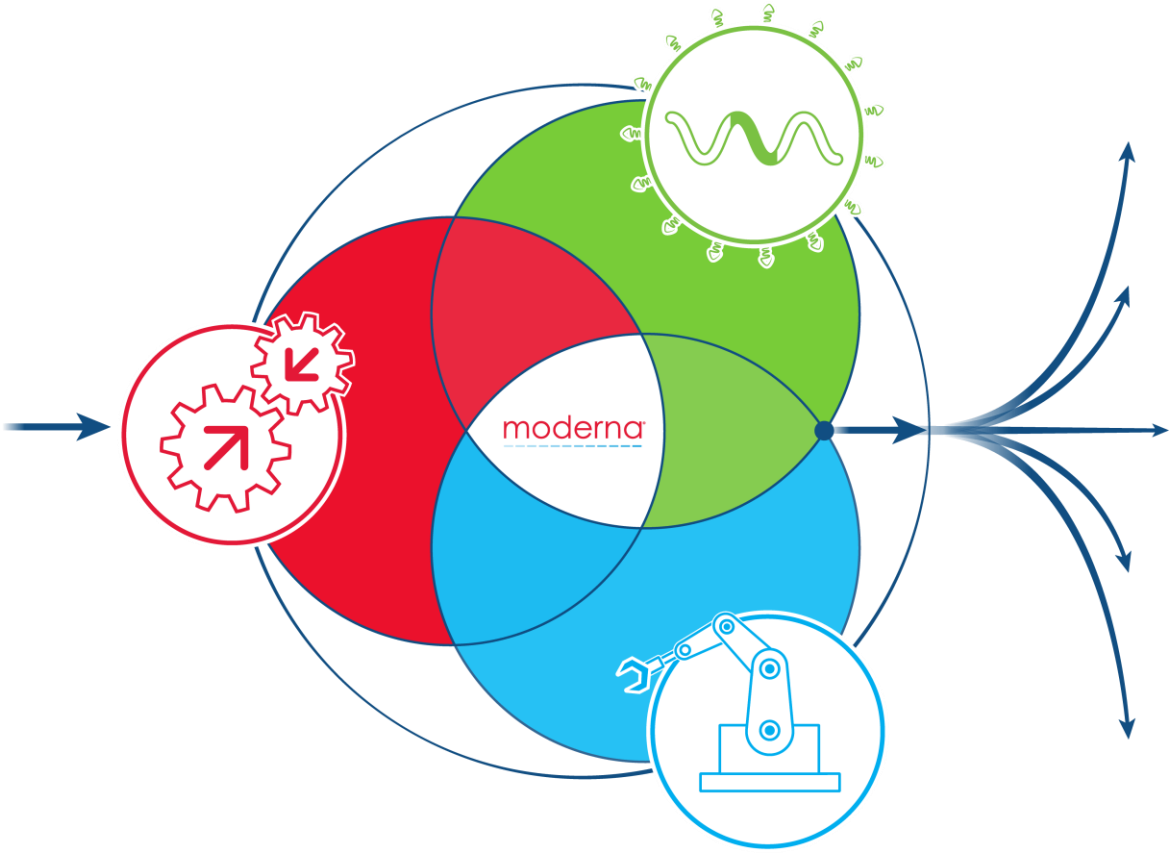
The integration of the components and the processes of our platform enable the development of mRNA medicines









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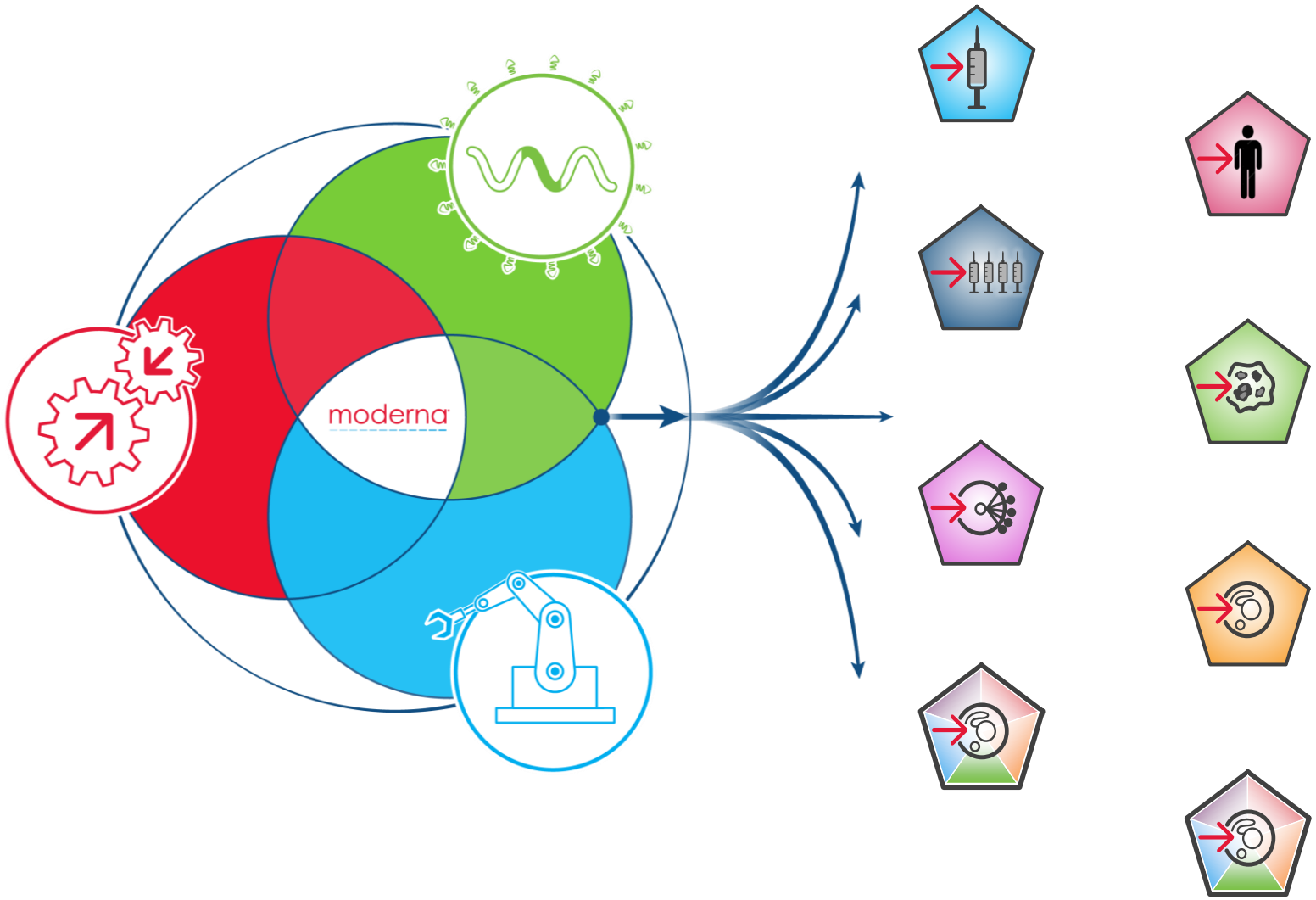
Moderna modalities are applications of our platform



Moderna Modalities:

- A grouping of development candidates with **shared technologies and product features** (engineered mRNA, LNP delivery and manufacturing processes)
- Allows us to **manage technological risk** while leveraging mRNA as an information molecule

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Each modality has several candidates in development addressing one of five therapeutic areas

We have development candidates in the clinic across **five** therapeutic areas

- Infectious diseases
- Oncology
- Cardio-vascular
- Rare diseases
- Autoimmune diseases

37 Development Programs across 34 Development Candidates[1]
(compared to 23 development candidates last year, with many more on the way…)

We have **six** modalities in the clinic and **two** in research leveraging different delivery technologies

(1) Includes separate COVID-19 Vaccine (mRNA-1273) programs in development for adults, pediatrics & adolescents and separate RSV vaccine (mRNA-1345) programs in development for adults and pediatrics

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Having many development candidates creates *network effects* for our platform

mRNA could be a new class of medicines

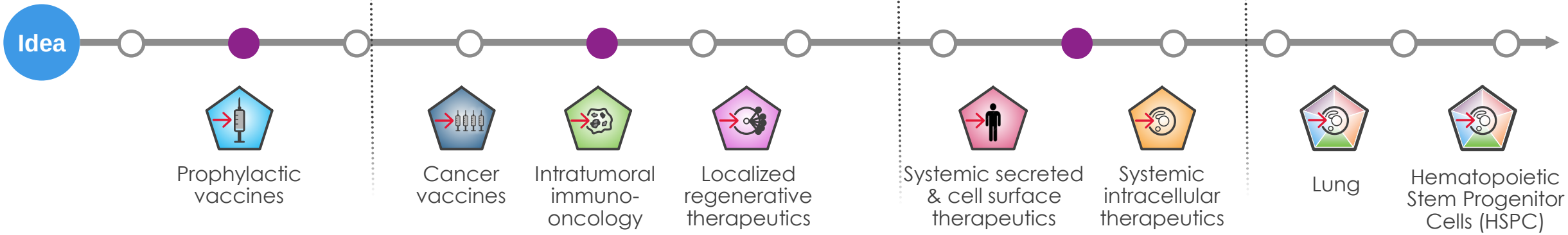
Started with prophylactic vaccines (lower technical hurdles)

Leveraged prophylactic vaccines LNP to **elicit T cell response**

Expanded into local therapeutic applications (after demonstration of local protein expression)

Expanded into systemic delivery of mRNA to encode secreted or intracellular proteins

Two modalities in research using new delivery techniques



The value and utility of our platform increases as we have more development candidates and modalities

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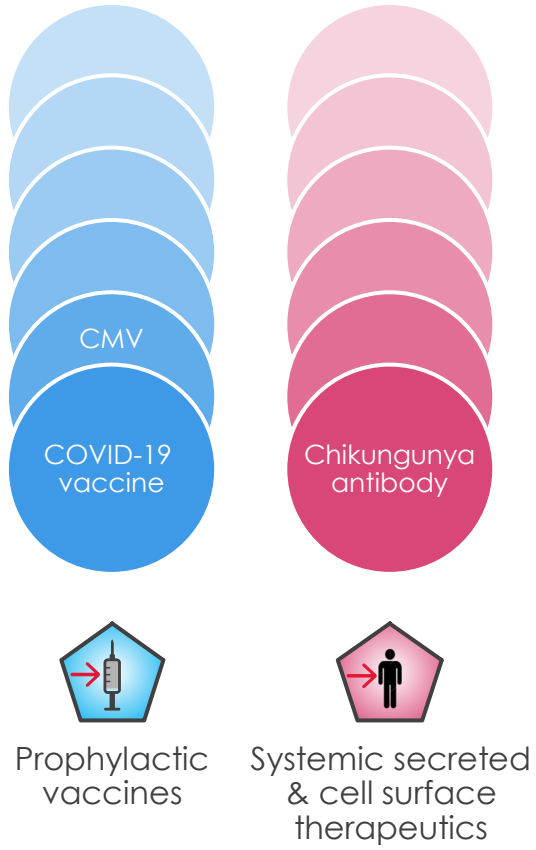
Advantages of modality development

- ✓ Data from sentinel programs in each modality **can de-risk the application of the technology**
- ✓ If the proof-of-concept clinical data are achieved, we can **accelerate investments and clinical programs**
- ✓ **We created Core Modalities in 2019** following positive Phase 1 clinical data sets

Core Modalities



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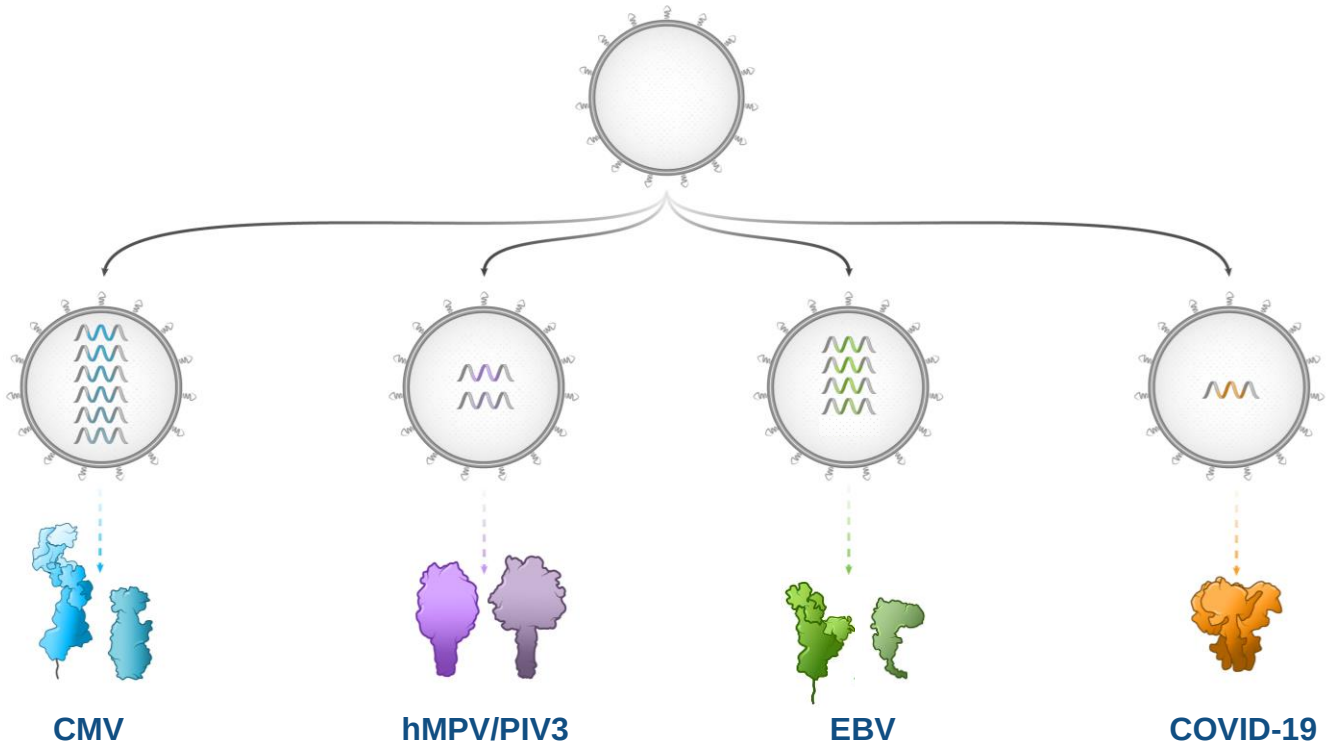
Prophylactic vaccines modality is an example of how we accelerate development of core modalities

With positive proof-of-concept data from our CMV vaccine program, **we invested more and invested faster to develop additional mRNA vaccines** in our prophylactic vaccines modality

Next steps in our prophylactic vaccines modality:

- **COVID-19**: Ongoing booster/variant studies
- **Flu & RSV**: Phase 2/3 preparation ongoing
- **CMV**: Plan to start a Phase 3 in 2021
- **Zika**: Phase 2 vaccine ongoing
- **hMPV/PIV3**: Phase 1 ongoing
- **New combos**: COVID-19/Flu and RSV/HMPV preclinical development ongoing
- **EBV, HIV and Nipah**: In preclinical development
- **More vaccines** in development



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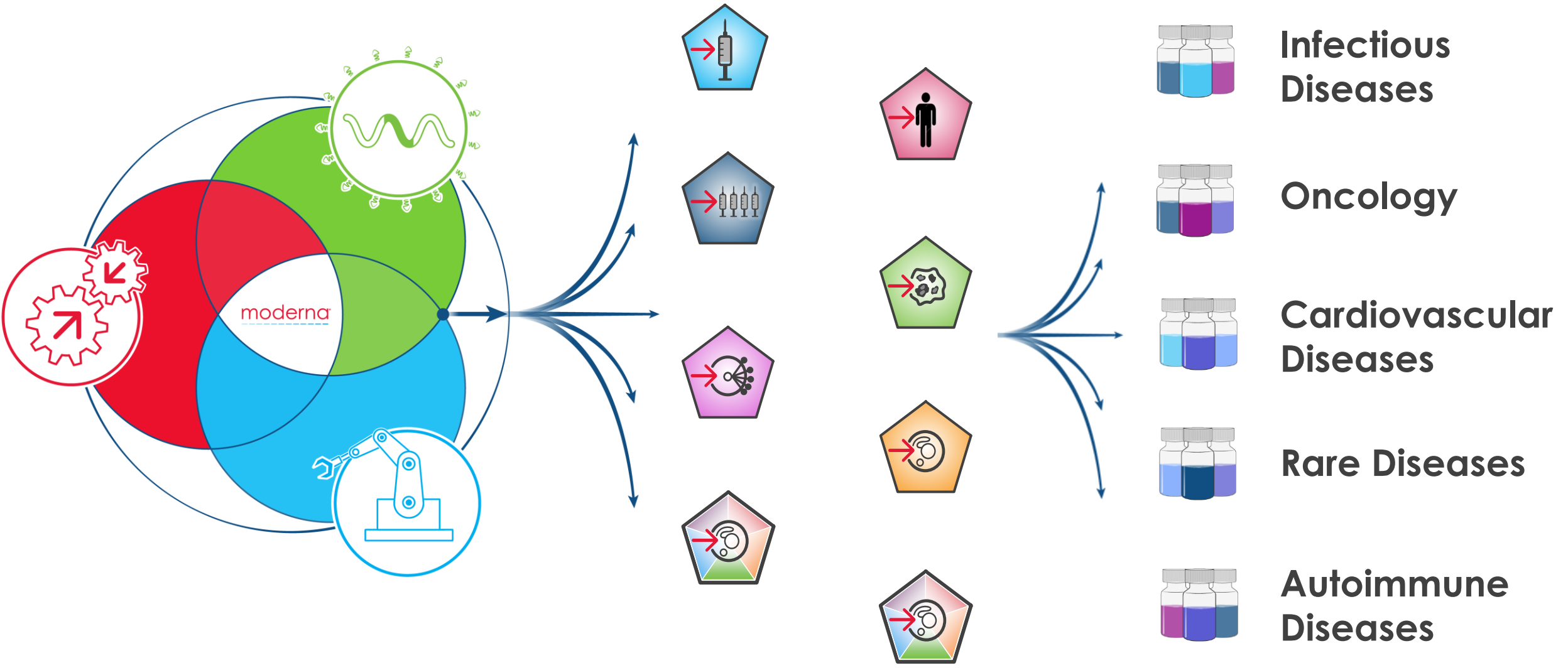
Linking our platform, Moderna modalities & therapeutic areas



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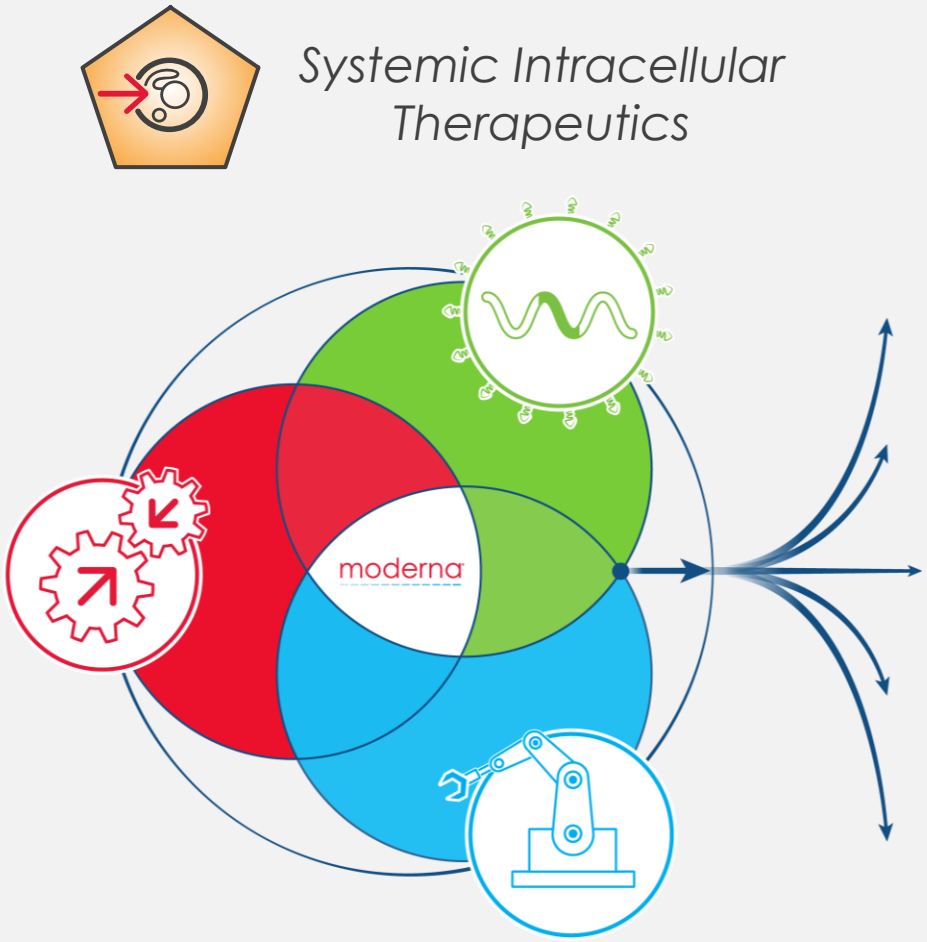
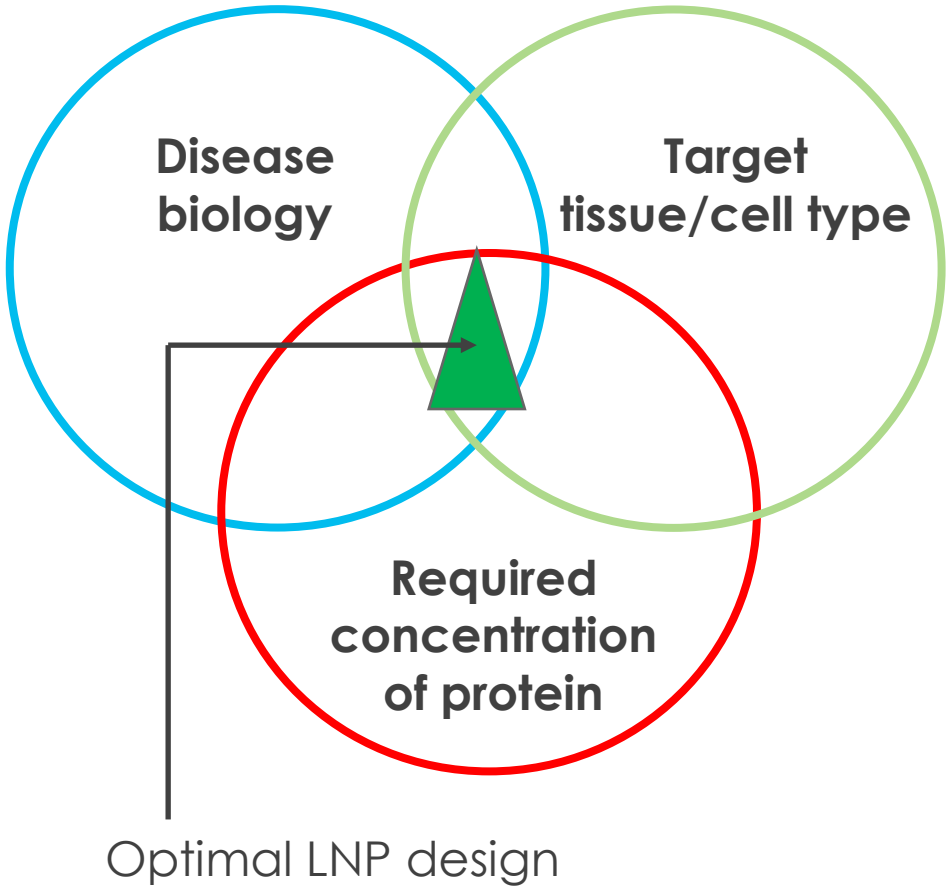
Systemic intracellular modalities is an example of how we approach exploratory modalities





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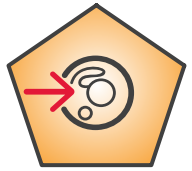
Our systemic intracellular modality comprises three different delivery systems across four different rare diseases



Systemic Intracellular Therapeutics

Therapeutic LNP Used	IV-LNP 1	IV-LNP 2	IV-LNP 3
Range of Diseases	PA, MMA	PKU	GSD1A

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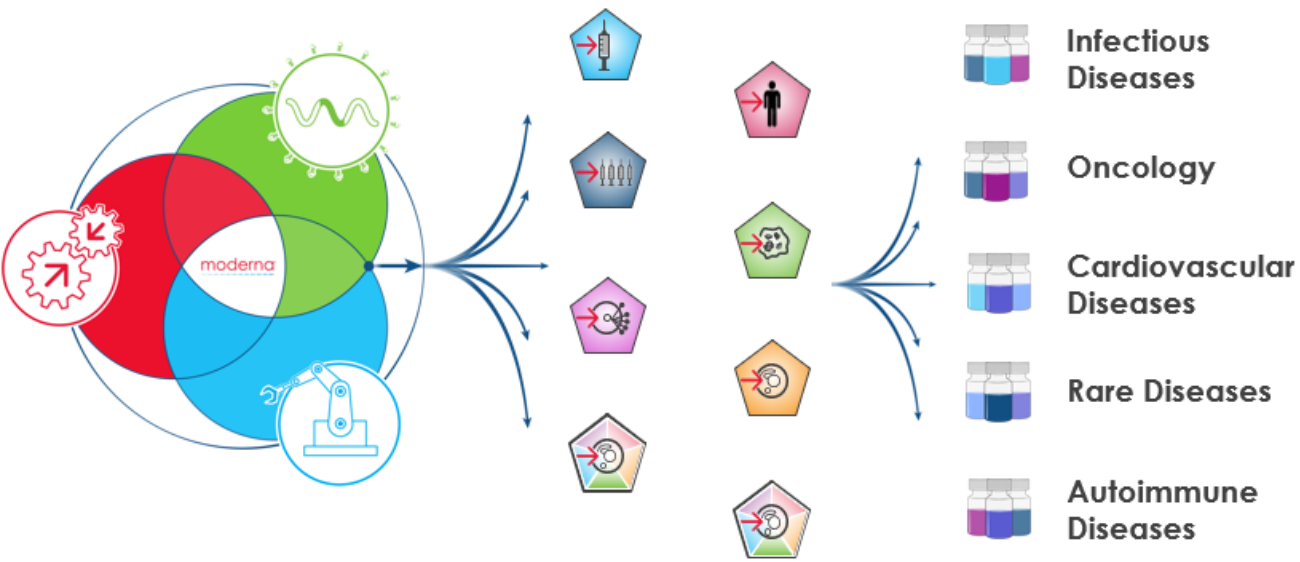
Moderna Genomics (MGX) vision is to be a leader in large, complex genomic editing

MGX will leverage Moderna's current mRNA + LNP platform, but will also **pursue novel technology** within nucleic acids



Eric Huang, Ph.D.
Chief Scientific Officer,
Moderna Genomics

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Review of COVID-19 Vaccine Real-World Experience

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Paul Burton, M.D., Ph.D., F.A.C.C., M.R.C.S.

Chief Medical Officer

The Data Discussed Today

The real-world evidence data has been generated and published entirely independently of Moderna. Moderna has not sponsored nor supported these analyses or publications

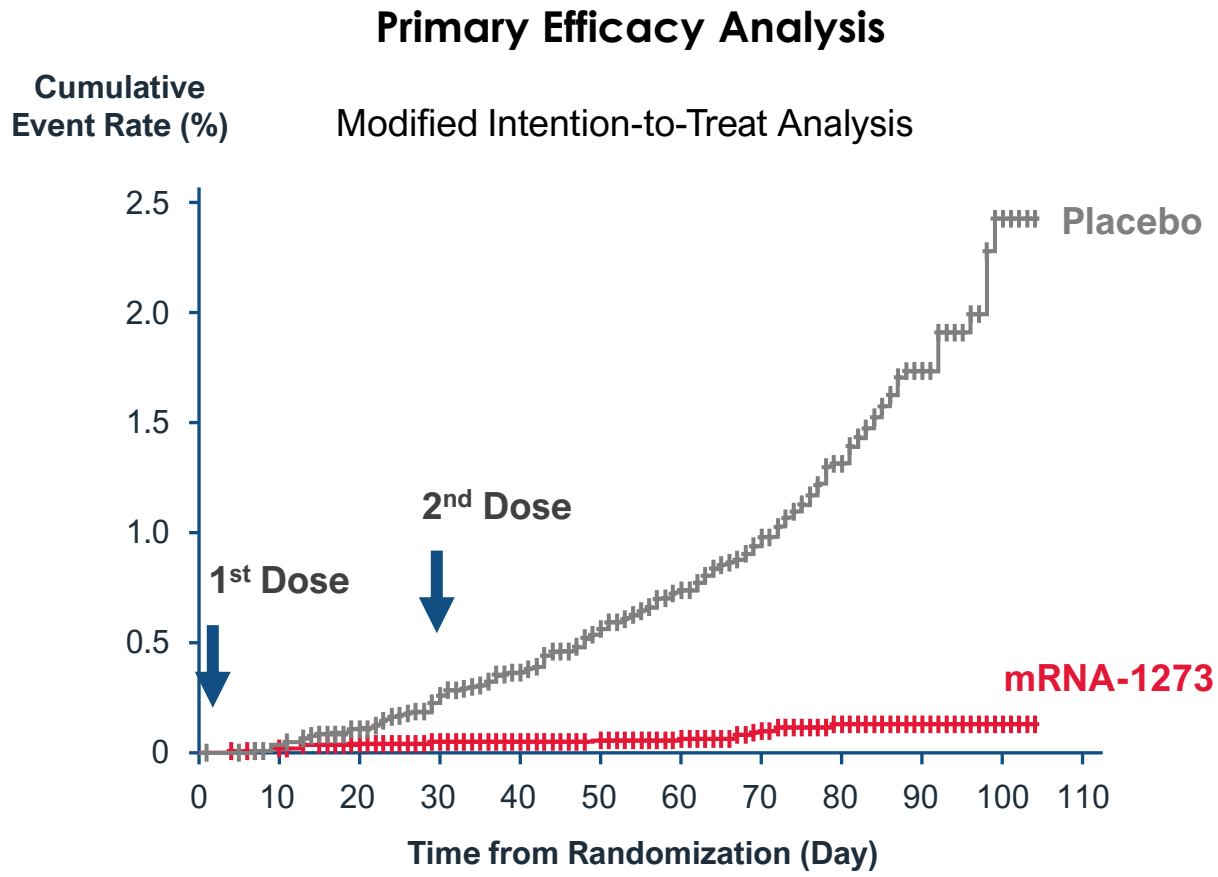
We will comment only on the mRNA-1273 data

Given the speed with which investigators and scientists are generating data regarding COVID-19, some of these data are published on preprint servers. These publications have yet to be peer reviewed in medical journals

Emergency Use Authorization received after Phase 3 COVE study primary efficacy analysis

Vaccine efficacy against COVID-19 was **94.1%**

Vaccine efficacy against severe COVID-19 was **100%**



Baden, Lindsey, et al. "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine," New England Journal of Medicine (04 Feb. 2021), https://www.nejm.org/doi/full/10.1056/NEJMoa2035389

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Final analysis of Phase 3 COVE Study demonstrates vaccine efficacy of 93%

- **COVE Study vaccine efficacy** (95% CI) by primary and secondary endpoints at final analysis[1]:
  - Against **COVID-19: 93.2%** (91.0-94.8)*
  - Against **severe COVID-19: 98.2%** (92.8-99.6)*
  - Against **death caused by COVID-19: 100%** (NE-100.0)

- Sub-group analyses are consistent across different populations

- Safety profile based on extended safety follow up is consistent with Phase 3 COVE study primary results and consistent across population sub-groups

(1) Analysis per protocol set, median follow-up of 5.3 months
* Based on Adjudication Committee assessments

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Review of COVID-19 Vaccine Real-World Experience

Translating Science In Real World Outcomes: COVID-19

1. General Population and Variants
2. Immunocompromised Patients

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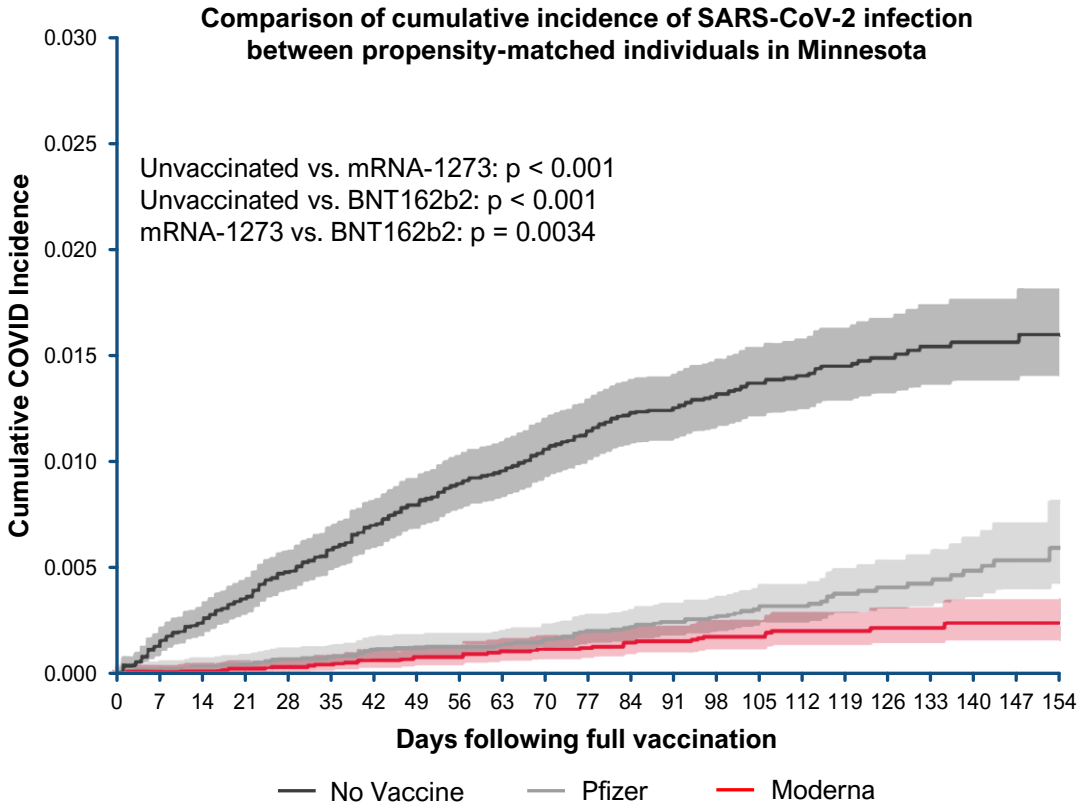
Recent analysis of the Mayo Clinic database shows 76% estimated vaccine efficacy of mRNA-1273 in the face of the Delta VOC



Time period	State	mRNA-1273 Incidence Rate Event/Person-Days [Per 1000 Person-Days] (# Individuals Contributing)	BNT162b2 Incidence Rate Event/Person-Days [Per 1000 Person-Days] (# Individuals Contributing)	IRR mRNA-1273/ BNT162b2 (95% CI)
On or after the 14 days following the second dose (in July only)	Minnesota	15/627756.0 [0.024] (n = 21079)	38/652459.0 [0.058] (n = 21946)	0.41 (0.21, 0.76)
	Florida	26/100940.0 [0.26] (n = 3379)	70/106535.0 [0.66] (n = 3583)	0.39 (0.24, 0.62)
	Wisconsin	9/187855.0 [0.048] (n = 6284)	18/198532.0 [0.091] (n = 6644)	0.53 (0.21, 1.2)
	Arizona	5/95238.0 [0.053] (n = 3182)	10/96602.0 [0.1] (n = 3228)	0.51 (0.14, 1.6)
	Iowa	0/22590.0 [0] (n = 753)	1/24368 [0.041] (n = 813)	0 (0, 42)
	All States	58/1065321.0 [0.054] (n = 35710)	138/1112136.0 [0.12] (n = 37337)	0.44 (0.32, 0.6)

Assessed the overall effectiveness of each vaccine by comparing the cumulative incidence of infection in each vaccinated cohort compared to the matched unvaccinated cohort. We also assessed the relative effectiveness of each vaccine (i.e., incidence rate of infection in the mRNA-1273 cohort compared to the BNT162b2 cohort).
Results based on real world data. This was not a head-to-head randomized trial designed to compare the vaccines. Therefore, no comparative conclusions should be drawn.
Puranik A et al., preprint, https://doi.org/10.1101/2021.08.06.21261707

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Among a vaccinated population in Qatar, mRNA-1273 demonstrated effectiveness at preventing COVID-19 Delta infection

	≥14 days after first dose and no second dose					≥14 days after second dose				
	Cases* (PCR-positive)		Controls* (PCR-negative)		Effectiveness in % (95% CI)†	Cases* (PCR-positive)		Controls* (PCR-negative)		Effectiveness in % (95% CI)†
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against infection										
BNT162b2	19	1602	52	1569	64.2 (38.1-80.1)	209	1621	397	1433	53.5 (43.9-61.4)
mRNA-1273	11	1629	51	1589	79.0 (58.9-90.1)	22	1644	135	1531	84.8 (75.9-90.8)
BNT162b2 or mRNA-1273	31	1700	96	1635	68.9 (52.7-80.1)	231	1728	466	1493	57.2 (48.9-64.1)

*Cases and controls were matched one-to-one by sex, 10-year age group, nationality, reason for PCR testing, and calendar week of PCR test.
†Vaccine effectiveness was estimated using the test-negative, case-control study design.
§Exact confidence levels were not possible with zero count cells. Confidence intervals were calculated using the Cornfield method.

Results based on real world data. This was not a head-to-head randomized trial designed to compare the vaccines. Therefore, no comparative conclusions should be drawn.
Tang P et. al., Preprint, 2021, https://doi.org/10.1101/2021.08.11.21261885

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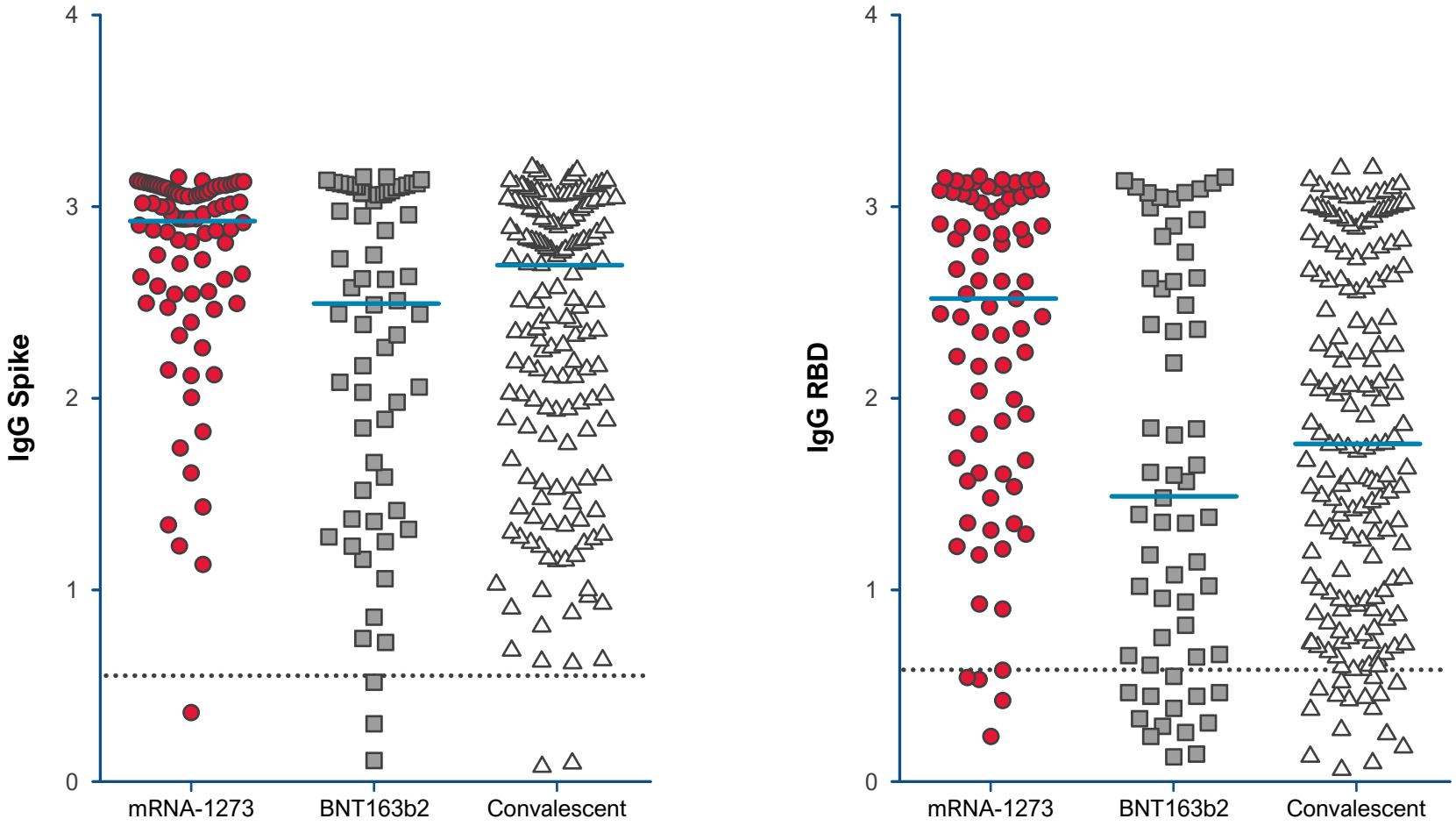
Among nursing home residents tested 3-5 months post immunization mRNA-1273 provides robust antibody titers



Blue bars indicate median values. Dotted lines represent the level of detection.
Results based on real world data. This was not a head-to-head randomized trial designed to compare the vaccines. Therefore, no comparative conclusions should be drawn.
Breznik et al., preprint, https://doi.org/10.1101/2021.08.17.21262152

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Review of COVID-19 Vaccine Real-World Experience

Translating Science In Real World Outcomes: COVID-19

1. General Population and Variants
2. Immunocompromised Patients

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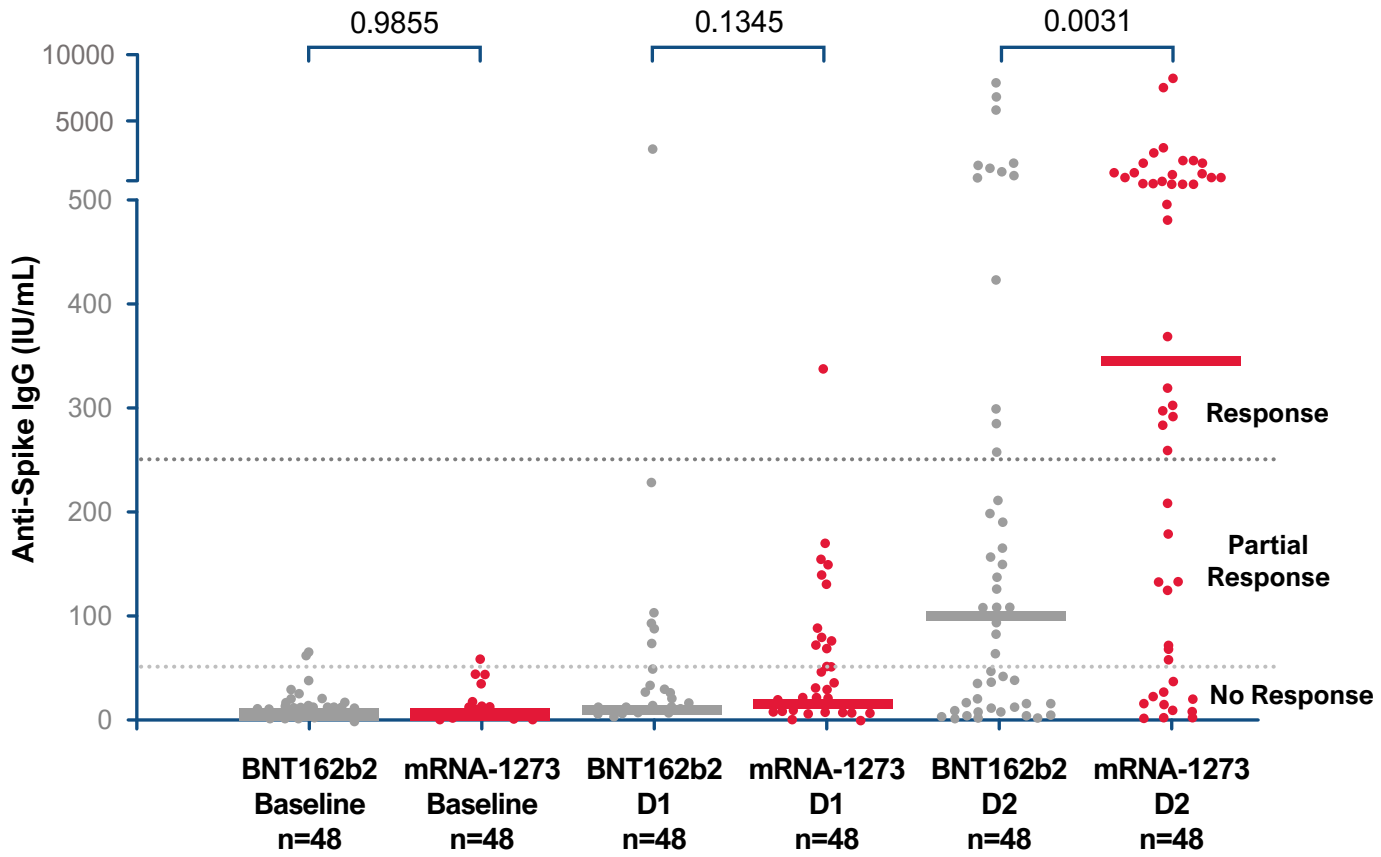
In multiple myeloma, mRNA-1273 induces antibody titers and CD4+ T-cell activation

63% Of Multiple Myeloma Patients Who Receive **mRNA-1273** Generate Anti-Spike Antibodies



*within Vaccine Groups

Results based on real world data. This was not a head-to-head randomized trial designed to compare the vaccines. Therefore, no comparative conclusions should be drawn

Stampfer S et. al., , "Response to mRNA vaccination for COVID-19 among patients with multiple myeloma," *Leukemia,* 2021, https://doi.org/10.1038/s41375-021-01354-7

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In a wide variety of hematological cancer patients use of mRNA-1273 is associated with a robust immune response

In univariate as well as multivariate logistic regression analysis the **use of mRNA-1273**, is associated with the **development of an immune response to vaccination**

Models of the Association between Vaccine Type and Immune Response

	Odds Ratios (95% CI)	P value
Model 1 (n = 845) COVID-19 Vaccination Type **(mRNA-1273)**	1.50 (1.12, 2.00)	**0.007**
Model 2 (n = 844) COVID-19 Vaccination Type **(mRNA-1273)**	1.48 (1.06, 2.06)	**0.021**
Model 3 (n = 844) COVID-19 Vaccination Type **(mRNA-1273)**	1.73 (1.24, 2.42)	**0.001**

Greenberger L et. al., Cancer Cell, 2021, https://doi.org/10.1016/j.ccell.2021.07.012

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Use of mRNA-1273 in organ transplant patients: antibody generation

Demographic and Clinical Characteristics of Study Participants, Stratified by Immune Response to the 2 Doses of SARS-CoV-2 mRNA Vaccine

	No. (%) by postvaccination antibody response			*P* value
	Dose 1- Dose 2-	Dose 1- Dose 2+	Dose 1+ Dose 2+	
No.	301 (46)	259 (39)	98 (15)	
Vaccine				
mRNA-1273 (Moderna)	124 (40)	116 (38)	**67 (22)**	<0.001
BNT162b2 (Pfizer-BioNTech)	175 (51)	138 (40)	29 (8)	

Results based on real world data. This was not a head-to-head randomized trial designed to compare the vaccines. Therefore, no comparative conclusions should be drawn.
Boyarsky B et. al., JAMA (June), 2021, https://doi.org/10.1001/jama.2021.7489

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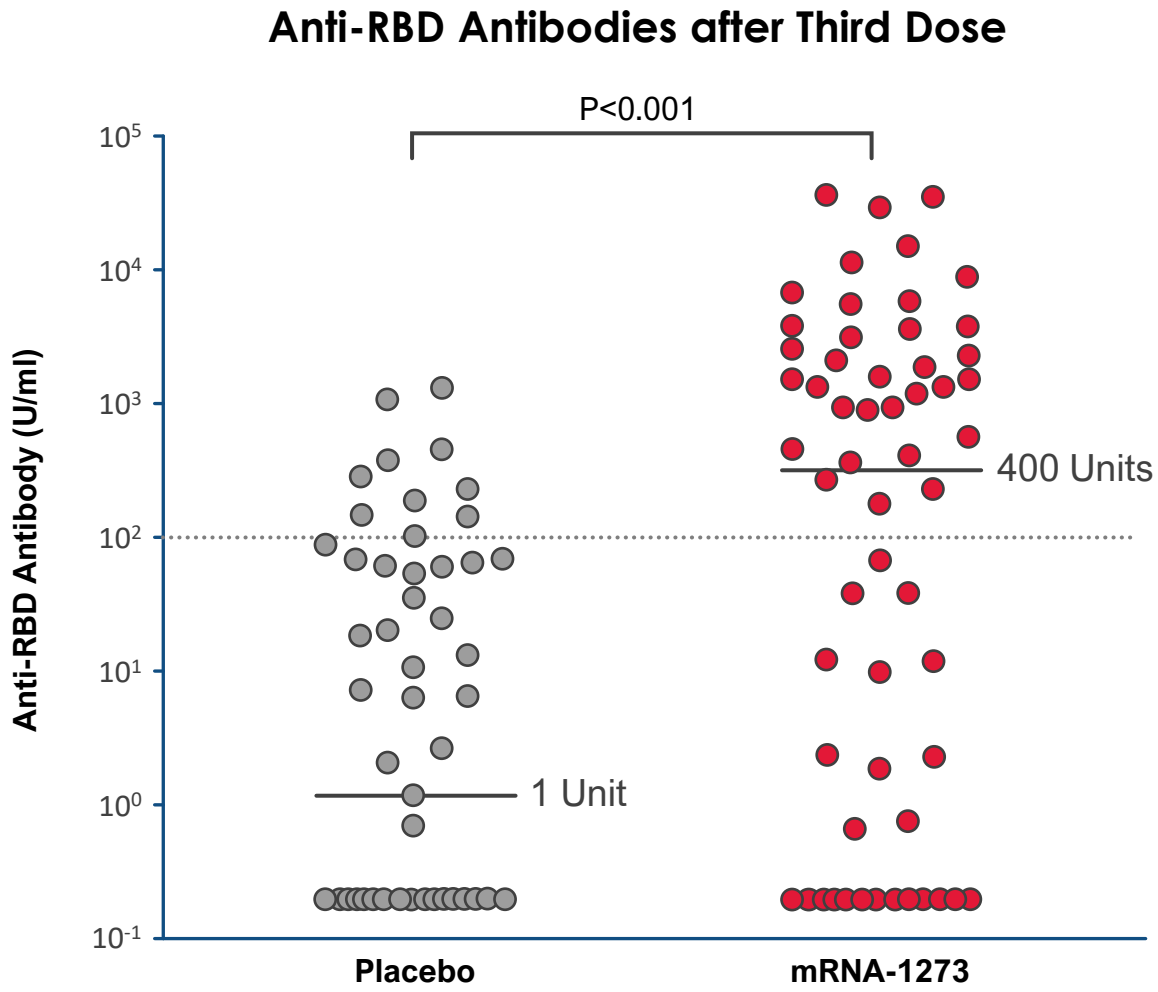
A third dose of mRNA-1273 enhanced anti-COVID-19 immune response in a randomized control trial of 120 solid organ transplant patients



Hall, V et al., NEJM 2021, https://doi.org/10.1056/NEJMc2111462

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Among kidney transplant or renal dialysis patients use of mRNA-1273 is associated with generation of an antibody response

- In dialysis patients, antibodies against the receptor binding domain (RDB; suggestive for neutralization) were detected in **97% of patients with mRNA-1273** (P < 0.001)
- In the kidney transplant patients, seroconversion rate **with mRNA-1273 was 49%** (p < 0.001)

Factors	Category	DP	KTR	MP
Vaccine Type	% of group number	95% of 1136	42% of 333	99% of 134
mRNA-1273	% of group number	**97% of 936**	**49% of 234**	**99% of 95**
BNT162b2 mRNA	% of group number	88% of 200*	26% of 99*	97% of 39

MP = Medical Personnel; DP = Dialysis Patients; KTR = Kidney Transplant Recipient; IS means immunosuppresion CNI = Calcineurin-Inhibitor; MMF-MPA = mycophenolate mofetil or myocophenolic acid; mTOR-*I* = mTOR-inhibitors; CS = glucocorticosteroids; T2 = 8 weeks after first vaccination.
Vaccination response rates in drug combinations of less than 10 patients were reported as n.a.
*statistical significance using p < 0.001 compared to other vaccine type

Results based on real world data. This was not a head-to-head randomized trial designed to compare the vaccines. Therefore, no comparative conclusions should be drawn.
Stumpf J et. al., Lancet Regional Health, 2021, https://doi.org/10.1016/j.lanepe.2021.100178

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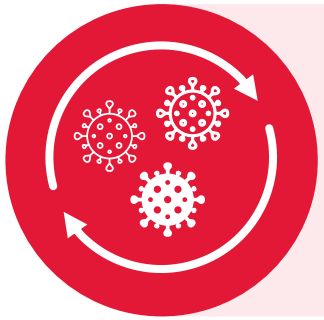
Key takeaways

Phase 3 COVE study demonstrated **vaccine efficacy of >93% at 6 months**

Real world studies suggest that mRNA-1273 retains robust vaccine effectiveness and protection against COVID-19



In real world studies mRNA-1273 shows protection against infection from Delta **variant of concern**

In **hard to treat patient groups** such as those with hematological cancers, solid organ transplantation and renal dialysis, mRNA-1273 shown to elicit an immune response

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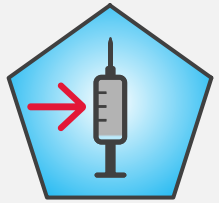

Prophylactic vaccines

Infectious Diseases

Jacqueline Miller, M.D.

Senior Vice President, Infectious Diseases

Moderna's respiratory vaccines: COVID-19

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Adults	COVID-19 vaccine	mRNA-1273						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
Prophylactic vaccines	Flu vaccine	mRNA-1010	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	mRNA-1073	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	mRNA-1345			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	mRNA-1273	KidCOVE					Worldwide
	Pediatric RSV vaccine	mRNA-1345	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	mRNA-1653						Worldwide
	Pediatric RSV + hMPV vaccine	mRNA-1365						Worldwide

New development candidates

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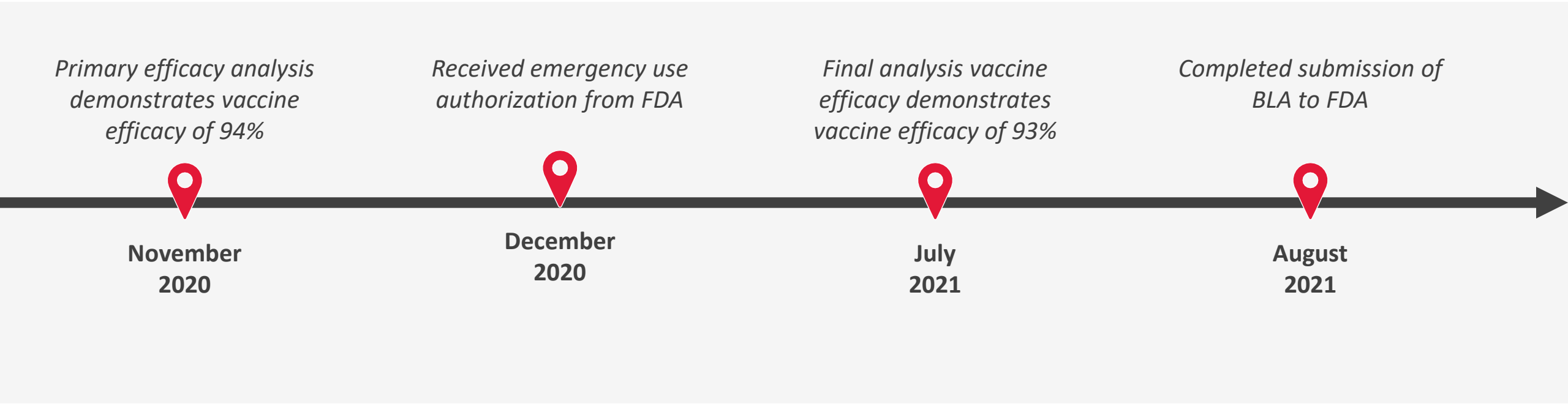
Moderna COVID-19 Vaccine
Review of where we are in adults ≥18 years of age



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Moderna COVID-19 Vaccine efficacy is durable through six months after the second dose[1]

Primary series (100 µg) Currently authorized for a two-dose vaccination series (second dose 28 days after first dose) in adults ≥18 years

Completed BLA filing based on Phase 3 COVE study final analysis showing 93% efficacy

First COVID-19 Occurrence[2]	VE (%) (95% CI)[3]
≥14 days after dose 2*	**93.1%** (90.9, 94.9)
≥14 days after dose 2 to <2 months after dose 2*	**91.8%** (86.9, 95.1)
≥ 2 months after dose 2 to <4 months after dose 2*	**94.0%** (91.2, 96.1)
≥4 months after dose 2**	**92.4%** (84.3, 96.8)

(1) Analysis per protocol set, median follow-up of 5.3 months
(2) COVID-19 cases based on adjudication committee assessments; 1 month = 28 days
(3) VE and 95% confidence interval (CI) are based on the exact method conditional on the total number of cases adjusting for person-years using the Poisson distribution for the time period.
* Subjects who were not at risk (cases or censored at prior time period(s)) are excluded from the analysis of this time period
** To earliest of study discontinuation, PDV/unblinding, or data cutoff date of 3/26/2021, longest follow up to 241 days

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Moderna COVID-19 Vaccine (mRNA-1273) third dose overview

Third dose (100 µg) Currently authorized for a third dose for immunocompromised populations in adults ≥18 years

Real world evidence shows immune response in immunocompromised patients

- ✓ In multiple myeloma, mRNA-1273 induces antibody titers and CD4+ T-cell activation
- ✓ In a wide variety of hematological cancer patients use of mRNA-1273 is associated with a robust immune response
- ✓ A third dose of mRNA-1273 enhanced anti-COVID-19 immune response in a randomized control trial of 120 solid organ transplant patients

Phase 3 COVE Transplant Study ongoing

Stampfer S et. al., , "Response to mRNA vaccination for COVID-19 among patients with multiple myeloma," *Leukemia,* 2021, https://doi.org/10.1038/s41375-021-01354-7
Greenberger L et. al., Cancer Cell, 2021, https://doi.org/10.1016/j.ccell.2021.07.012
Hall, V et al., NEJM 2021, https://doi.org/10.1056/NEJMc2111462

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Overview of Moderna COVID-19 Vaccine (mRNA-1273) in adolescents (P203)

Overview

- Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety and effectiveness of mRNA-1273 in **healthy adolescents 12 to <18 years of age**

Data updates

- Primary endpoint of non-inferior immunogenicity versus the Phase 3 study adult comparator group was met
- No cases of COVID-19 observed after two doses of vaccine using the primary case definition, consistent with a vaccine efficacy of 100%
- Safety and tolerability generally consistent with Phase 3 COVE study in adults

Regulatory Updates

- Authorized for adolescents in United Kingdom, European Union, Japan, Canada, Switzerland, Taiwan, Saudi Arabia, Australia and the Philippines
- Data submitted in United States and other countries

TeenCove STUDY™

Trial Design

100 µg mRNA-1273
N=2,486

Placebo
N=1,240

Ali, Keshaf, et al. "Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents," *NEJM* (August 2021), https://doi.org/10.1056/NEJMoa2109522

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Overview of Moderna COVID-19 Vaccine (mRNA-1273) in children (P204)

Overview

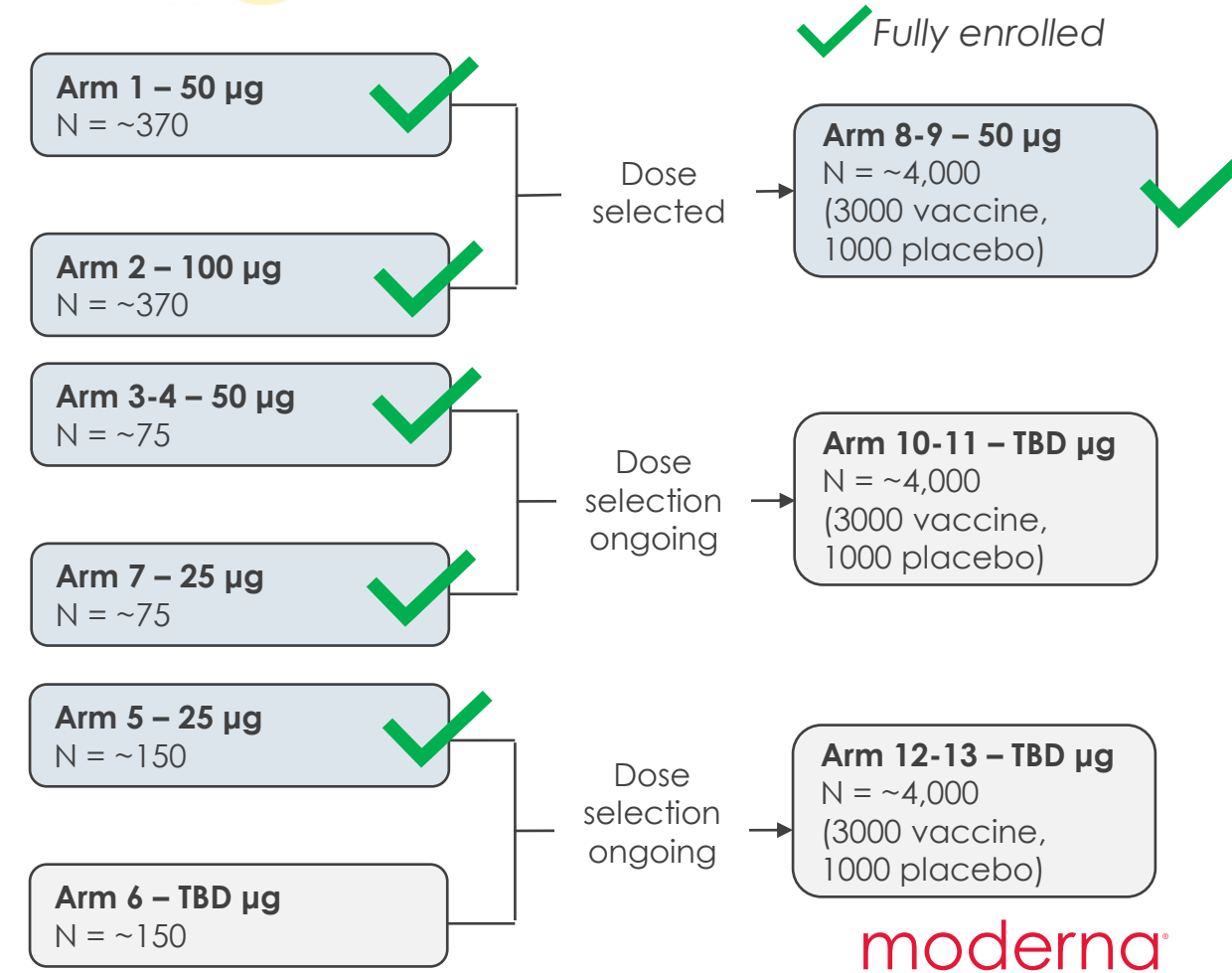
- Phase 2/3 expansion study to evaluate the safety and effective of mRNA-1273 in children aged 6 months to less than 12 years ongoing
  - 2-part, open-label, dose-escalation, age de-escalation, randomized, observer-blind, placebo-controlled

Updates

- We selected a dose and expanded enrollment in the 6 years to less than 12 years old cohort, and Part 2 of the study (Arms 8 & 9) is fully enrolled (N=4,000)
- Dose selection studies are still underway for 2 to <6 years old and 6 months to <2 years

KidCove STUDY™

Trial Design



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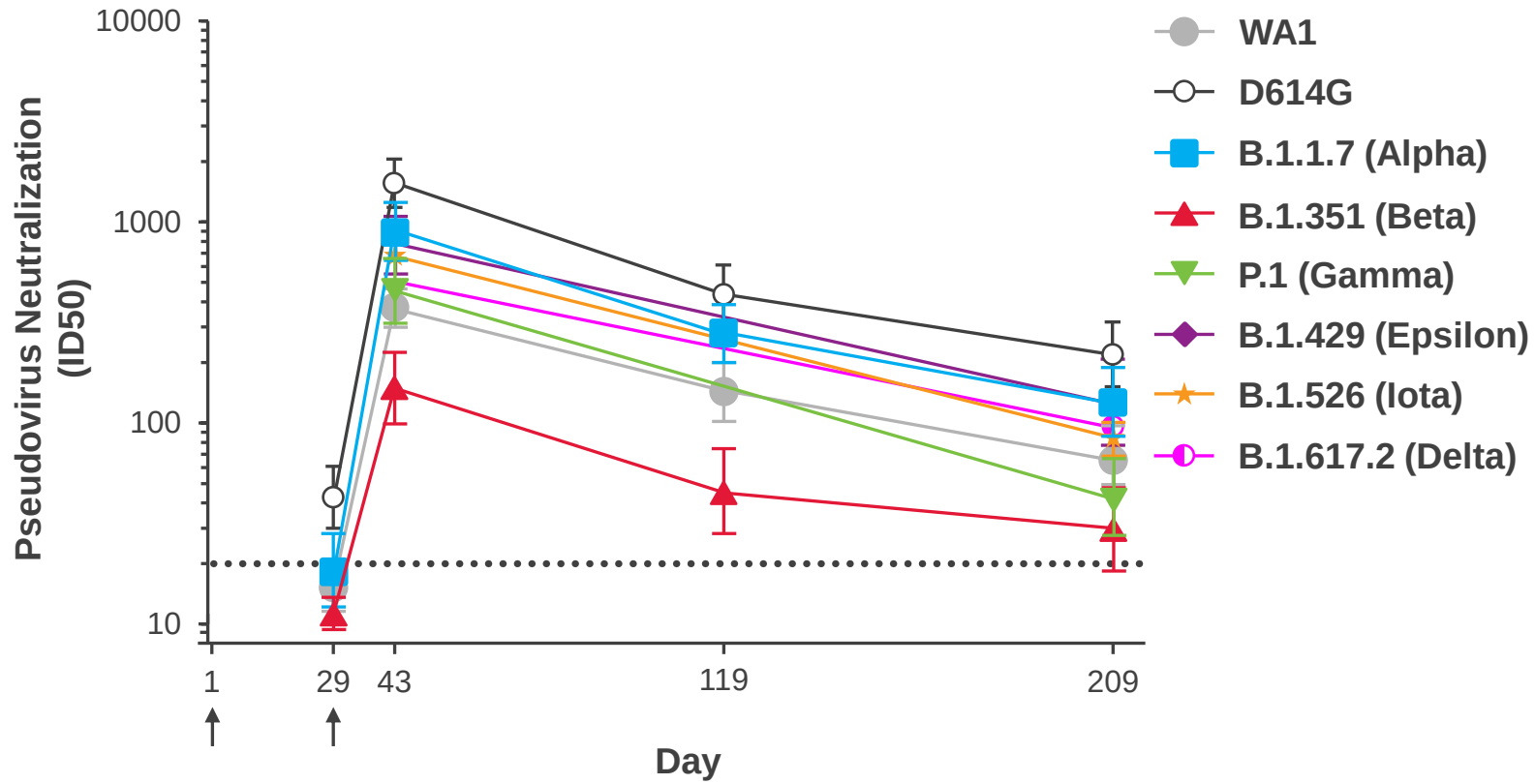
Summary of antibody persistence against ancestral strain and variants of concerns 6 months after Dose 2 (P101 sponsored by NIH)



Pseudovirus neutralization, expressed as 50% inhibitory dilution (ID50). Dotted line, limit of detection (>20). Pseudoviruses included WA1, D614G, B.1.1.7, B.1.351, P.1, B.1.429, B.1.526, and B.1.617.2.
A. Pegu et al., Science 10.1126/science.abj4176 (2021).

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Administration of a 3rd dose of 50 µg of mRNA-1273 to persons who previously received a 50 µg or 100 µg primary series of mRNA-1273 (Study 201B)

Study	N	Previous Dose of mRNA-1273 Doses 1 & 2	Dose 3	Interval between Doses 2 & 3
201B (boost with mRNA-1273)	173	50 µg	50 µg	≥ 6 months
	171	100 µg	50 µg	
301 Immunogenicity Subset	1055	100 µg (primary series only)	NA	NA

- Evaluation of safety & immunogenicity against regulatory guidance for registration of booster doses
- Primary analysis based on Day 29 post-dose 3
- Results compared to Day 29 post-dose 2 in subset of subjects in pivotal efficacy trial (COVE)

NA: Not applicable

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Immune response after mRNA-1273 p201 Part B 50 µg booster dose vs. after primary series (stratified by age group)

	Pseudovirus Neutralizing Antibody ID50 All ages		Pseudovirus Neutralizing Antibody ID50 18 – <65		Pseudovirus Neutralizing Antibody ID50 65+	
	P201 Part B (N=295)	P301 Random Sub-Cohort (N=1055)	P201 Part B (N=219)	P301 Random Sub-Cohort (N=700)	P201 Part B (N=74)	P301 Random Sub-Cohort (N=355)
Baseline GMT	*125.7*	*9.6*	*145.6*	*9.8*	*82.5*	*9.4*
28 days after booster dose (P201 Part B) or completion of primary series						
GMT- observed	1892.7	1081.1	1940.4	1206.6	1761.8	871.2
GLSM- model based estimate for GMT 95% CI	1768.0 1586.4, 1970.2	1032.7 974.2, 1094.7				
Ratio of GMT (P201 Part B vs. P301)	**1.75**		**1.61**		**2.02**	
Ratio of GLSM (P201 Part B vs. P301) 95% CI	**1.7** **1.5, 1.9**					
Seroresponse Rate 95% CI	265 /294 **(90.1)** 86.1, 93.3	1033 /1050 **(98.4)** 97.4, 99.1	194/218 (89.0) 84.1, 92.8	686/697 (98.4) 97.2, 99.2	71/76 (93.4) 85.3, 97.8	347/353 (98.3) 96.3, 99.4
Difference in SSR (P201 Part B - P301) 95% CI	-8.2 -12.2, -5.2		-9.4		-4.9	

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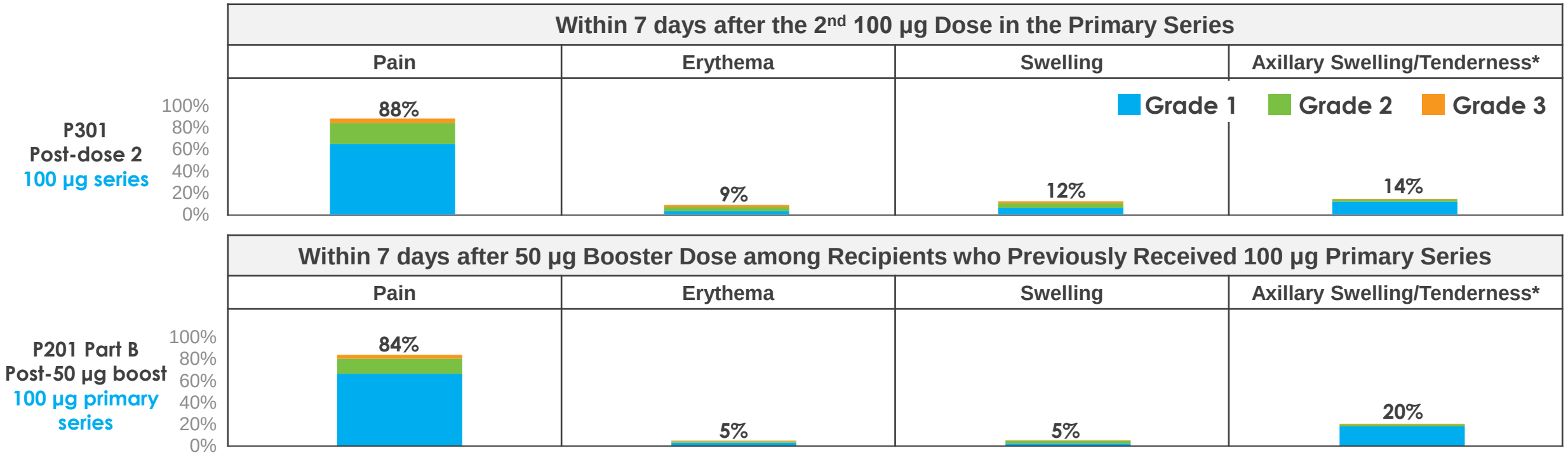
Summary of solicited local adverse reactions within 7 days of vaccination P201 Part B compared to COVE participants (Study 201B)



There were no local Grade 4 solicited reactions

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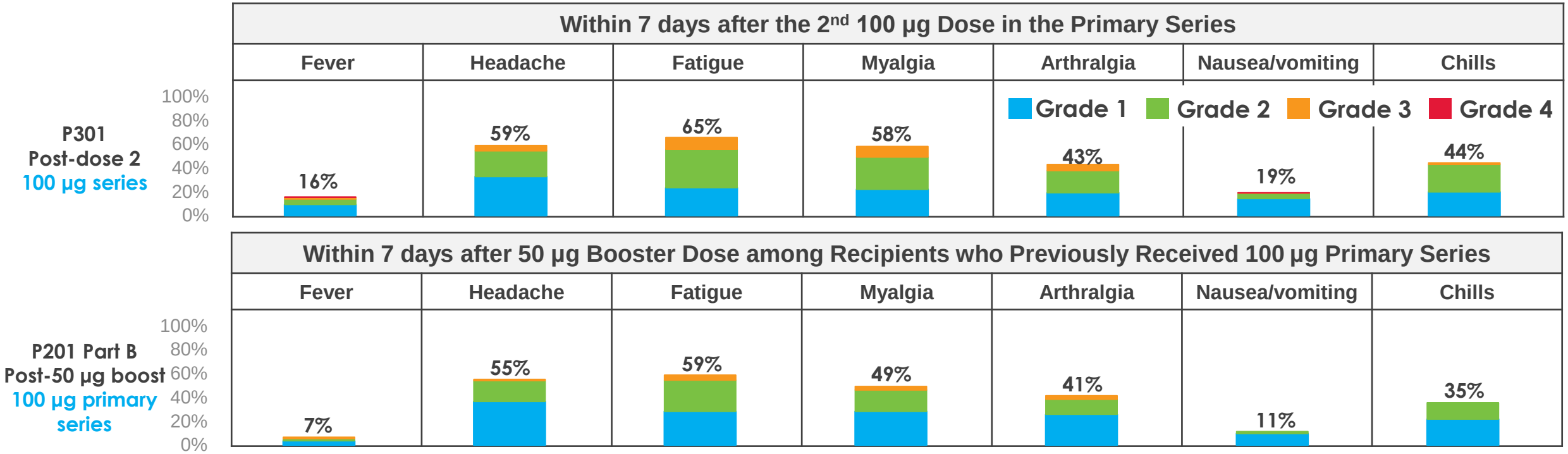
Summary of solicited systemic adverse reactions within 7 days of vaccination P201 Part B compared to COVE participants (Study 201B)



No deaths, severe AEs, or SAEs were reported

Grade 4 fever & nausea/vomiting occurred in <0.1% of subjects in P301

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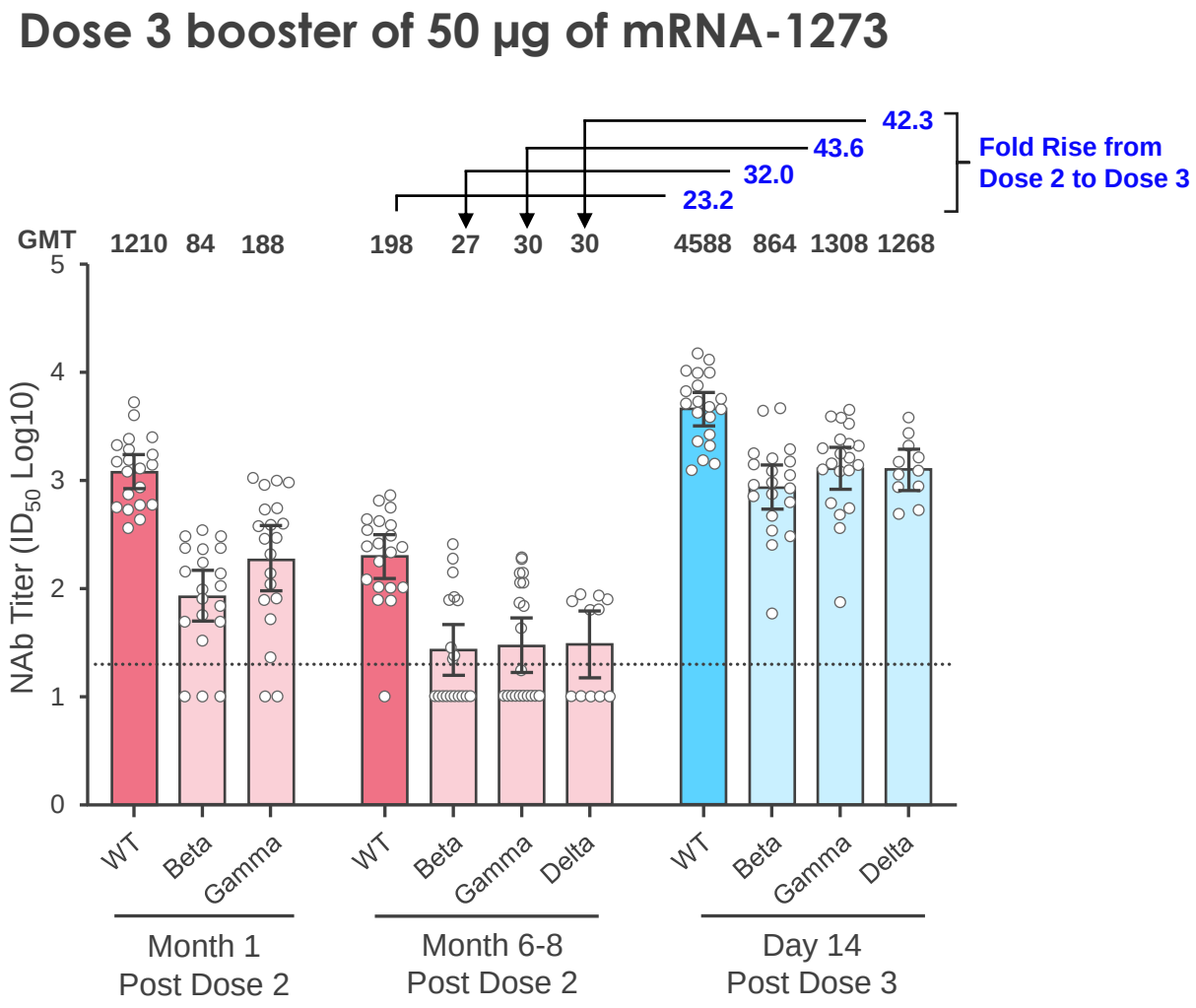
Exploratory assay comparison against broader VOCs 14 days post-dose 3 for 50 µg of mRNA-1273 (P201C; N=11-20)



Exploratory assay (VSV-based) with strong correlation to validated assay for WT and Beta (R^2 of 0.92 and 0.94, respectively)

Neutralizing titers against ancestral strain remained above GMT; against VOCs GMTs waned substantially by 6 months post-dose 2

Dose 3 (50 µg) booster increased GMT for Beta (32-fold), Gamma (43.6-fold) and Delta (42.3-fold) VOCs

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50 µg third dose / booster summary

- 50 µg third dose/ boosters induce neutralizing antibodies that are significantly higher than at Day 29 after Dose 2 in Phase 3 COVE
  - 50 µg resulted in a 17-fold increase over pre-booster titers in P201
- 50 µg third dose/ booster titers were comparable between younger and older adult cohorts
- The safety and tolerability profile of 50 µg third dose/boosters was similar to the second dose in the COVE study
- 50 µg third dose/ booster has been submitted for Emergency Use Authorization (EUA) to the U.S. FDA and Conditional Marketing Approval (CMA) with the European Medicines Agency (EMA)
- 100 µg third dose has been issued EUA for the immunocompromised population

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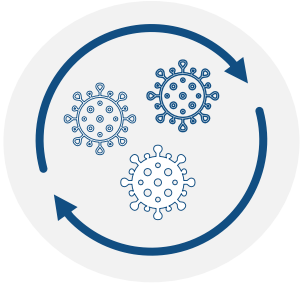
Moderna COVID variant booster vaccines against future variants

Variant Boosters

- We have four development candidates against variants of concern
  - Three of them are in the clinic (mRNA-1273.351/-617/-211)
  - mRNA-1273.213 is preparing to enter the clinic

Today: Moderna's COVID-19 vaccine (mRNA-1273) is effective against today's variants of concern



Future: Anticipating how the virus could evolve by developing multivalent candidates combining VOCs

If that changes…

Developing existing variant-specific candidates:

I. mRNA-1273.351 (Beta variant, B.1.351)

II. mRNA-1273.617 (Delta variant, B.1.617.2)

Anticipating future variants (multivalent candidates):

III. mRNA-1273.211 (Beta variant + Wild-type)

IV. mRNA-1273.213 (Beta variant + Delta variant)

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Moderna's respiratory vaccines: Flu

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Adults	COVID-19 vaccine	mRNA-1273						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
Prophylactic vaccines	Flu vaccine	**mRNA-1010**	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	**mRNA-1073**	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	**mRNA-1345**			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	mRNA-1273	KidCOVE					Worldwide
	Pediatric RSV vaccine	mRNA-1345	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	mRNA-1653						Worldwide
	Pediatric RSV + hMPV vaccine	**mRNA-1365**						**Worldwide**

New development candidates

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Moderna's development strategy

mRNA may have two advantages over traditional influenza vaccines:

- Potential for improved efficacy, given mRNA technology
- Increased manufacturing speed, potentially allowing for more rapid strain change in case of antigenic drift

Speed to Market

mRNA-1010

- Quadrivalent seasonal flu vaccine
- Targets WHO recommendations, such as A H1N1, H3N2 and influenza B Yamagata and Victoria lineages

Next Generation Products

mRNA-1020 & mRNA-1030

- Aim to add additional antigens, such as NA antigens
- Increased flexibility in targeting circulating strains and updating strains more often

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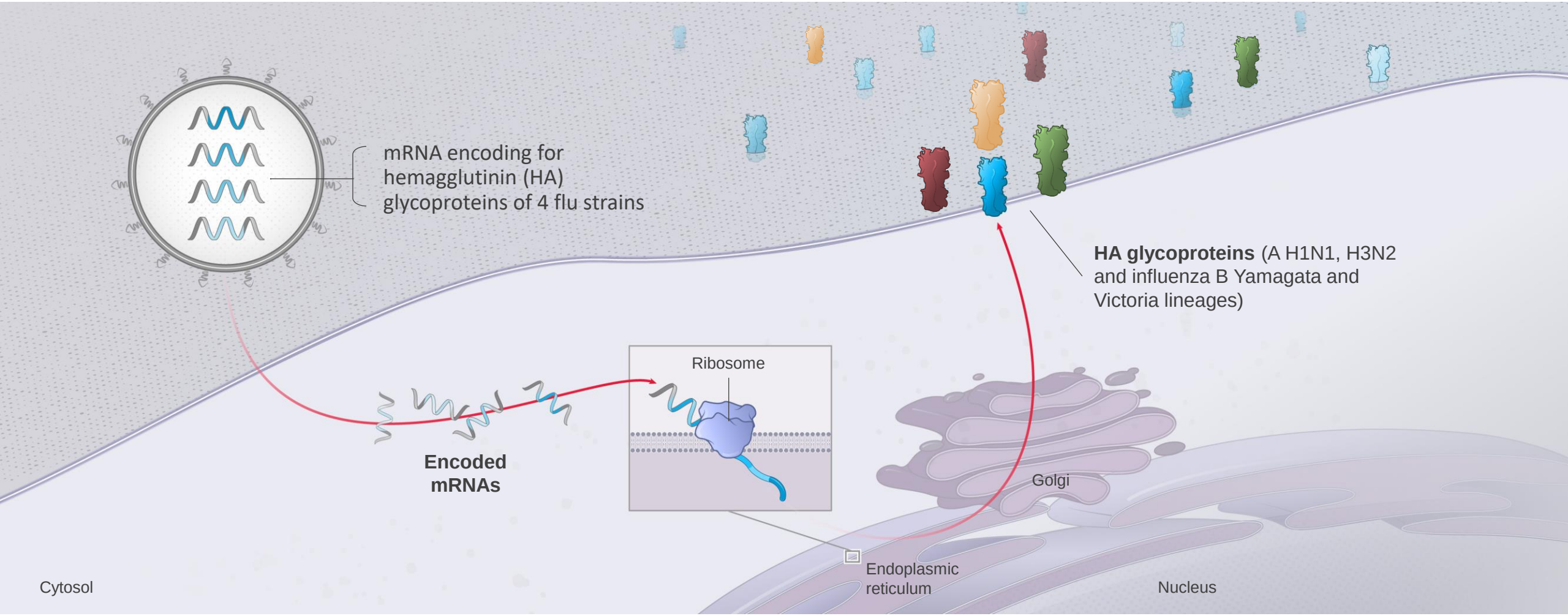
Quadrivalent seasonal flu vaccine (mRNA-1010)



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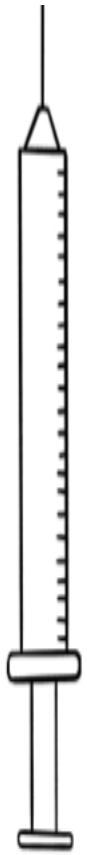
Influenza market overview



- Worldwide, influenza leads to **3-5M severe cases** of flu and **290-650K flu-related respiratory deaths annually**[1]
- In the US, the estimated average **economic burden of flu is ~$11 billion** per year[2]
- **500M+ doses** of seasonal influenza vaccines were administered in 2019[3]
- Currently **approved vaccines are ~40-60%** effective and face significant challenges from strain mismatch and antigenic drift[4]
- An improvement in vaccine efficacy has the potential to **increase the current $5-6B influenza market**

(1) World Health Organization. Influenza (Seasonal). WHO. 2018. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).
(2) Putri W et al. Economic burden of seasonal influenza in the United States. *Vaccine* 2018; 36(27):3960-3966.
(3) WHO, Global Vaccine Market Report (December 2020)
(4) Centers for Disease Control and Prevention. Vaccine Effectiveness: How Well Do the Flu Vaccines Work? Available at: https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm.

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Quadrivalent seasonal flu vaccine (mRNA-1010) Phase 1 fully enrolled

Overview

- Evaluating safety and reactogenicity of 3 different dose levels of the mRNA influenza vaccine
- Parallel enrollment of 18-49 years and ≥ 50 years age groups
- Single dose vaccine

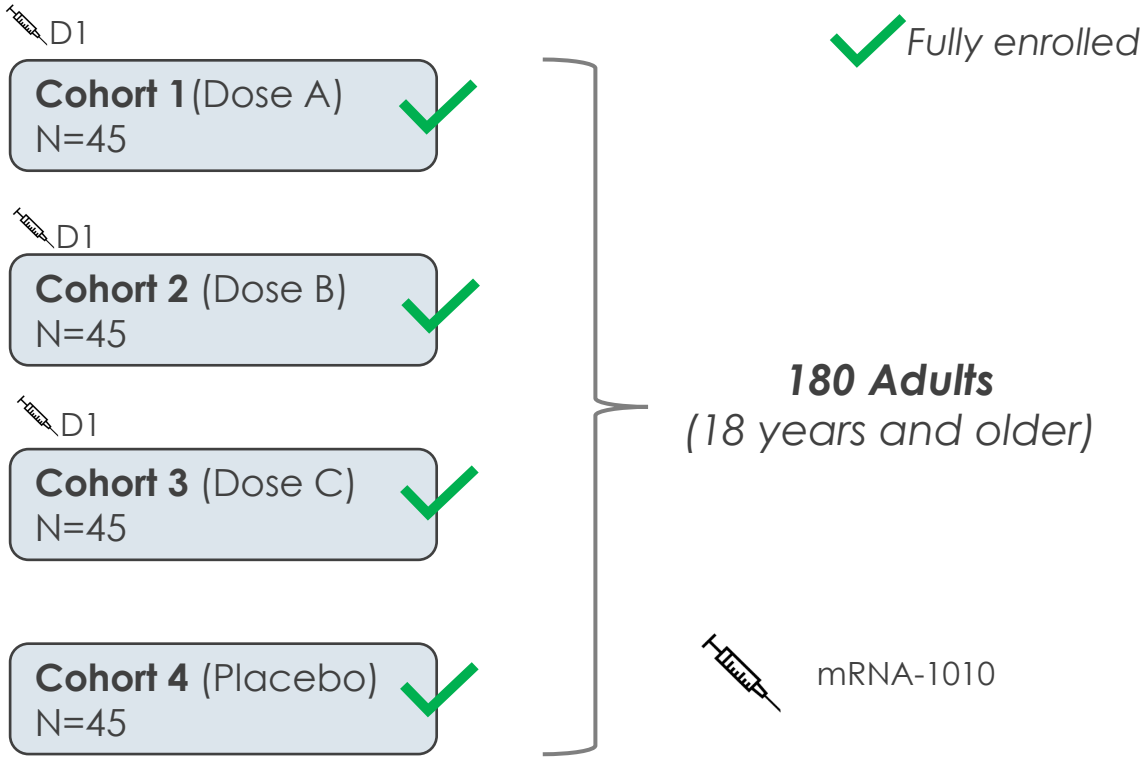
Outcome Measures

- Safety and immunogenicity

Trial progress

- All cohorts fully enrolled

Phase 1 Trial Design



Each cohort has an initial stage (n=9) followed by expansion stage (n=36)
Expansion from initial to expansion stage enrollment) is triggered by the Internal Safety Team (IST)

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Next generation influenza vaccines (mRNA-1020 & mRNA-1030)

Development Plan

Currently in preclinical development studies

Parallel development along with mRNA-1010

Working on adding **additional influenza antigens, such as neuraminidase,** in order to provide the broadest coverage

Aim to leverage mRNA vaccines manufacturing speed and scale to **make vaccines closer to the flu season**

Work with WHO on surveillance techniques to **potentially choose strains closer to the ones circulating in the hemisphere**

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Moderna's respiratory vaccines: RSV

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Adults	COVID-19 vaccine	mRNA-1273						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
Prophylactic vaccines	Flu vaccine	mRNA-1010	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	mRNA-1073	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	**mRNA-1345**			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	mRNA-1273	KidCOVE					Worldwide
	Pediatric RSV vaccine	**mRNA-1345**	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	mRNA-1653						Worldwide
	Pediatric RSV + hMPV vaccine	mRNA-1365						Worldwide

New development candidates

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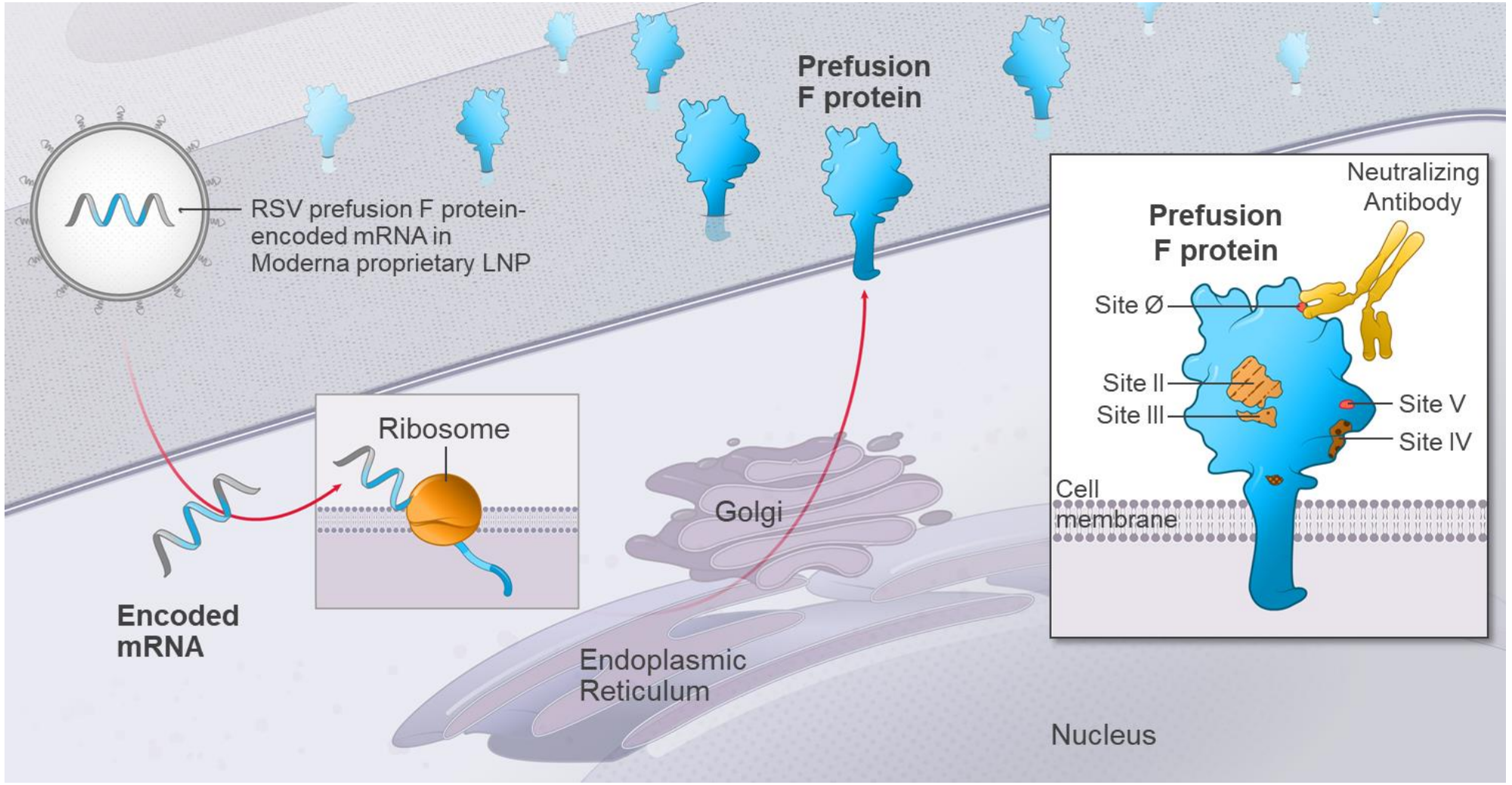
RSV vaccine (mRNA-1345) encodes for a stabilized prefusion F glycoprotein



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RSV is the leading cause of respiratory illness in young children and older adults are at high risk for severe RSV infections

Disease burden in pediatrics

- Hospitalization rate in children <5 years old in the U.S.: ~3:1000[1]
- Annually over 2 million medically attended RSV infections in children <5 years old in the U.S., more than 86,000 are hospitalized[2]
- Pediatric RSV results in an estimated ~$2 billion in annual medical costs in the U.S.
- Almost all children will have had an RSV infection by their second birthday[3]

Disease burden in older adults

- There are ~177,000 hospitalizations in adults 65+ due to RSV in the U.S. each year, and ~14,000 deaths[4]
- Globally it is estimated that there are ~1.5 million episodes of acute respiratory tract infection and ~336,000 hospitalizations related to RSV each year[5]
- RSV in older adults results in an estimated >$3 billion in annual medical costs in the U.S. each year

RSV infection sequelae (Infancy, childhood, adulthood)

- Fevers
- Nasal congestion
- Breathing difficulties
- Wheezing
- Chest congestion
- Bronchiolitis
- Pneumonia
- Cardiovascular complications

(1) Rha, Brian, et al. "Respiratory Syncytial Virus-Associated Hospitalizations Among Young Children: 2015-2016," *Pediatrics* (Jul. 2020), https://pubmed.ncbi.nlm.nih.gov/32546583/
(2) Eiland, Lea. "Respiratory Syncytial Virus: Diagnosis, Treatment and Prevention," *J Pediatr Pharmacol Ther.* (Apr-Jun 2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461981/
(3) Respiratory Syncytial Virus Infection (RSV), CDC, https://www.cdc.gov/rsv/about/symptoms.html
(4) RSV in Older Adults and Adults with Chronic Medical Conditions, CDC, https://www.cdc.gov/rsv/high-risk/older-adults.html
(5) Shi, Ting, et al. "Global Disease Burden Estimates of Respiratory Syncytial Virus," *J Infect Dis.* (07 Oct 2020), https://pubmed.ncbi.nlm.nih.gov/30880339/

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RSV vaccine (mRNA-1345) Phase 1 ongoing in pediatric and adult populations

Overview

- Evaluating the tolerability and reactogenicity of mRNA-1345 in younger adults, older adults, children and women of child-bearing potential

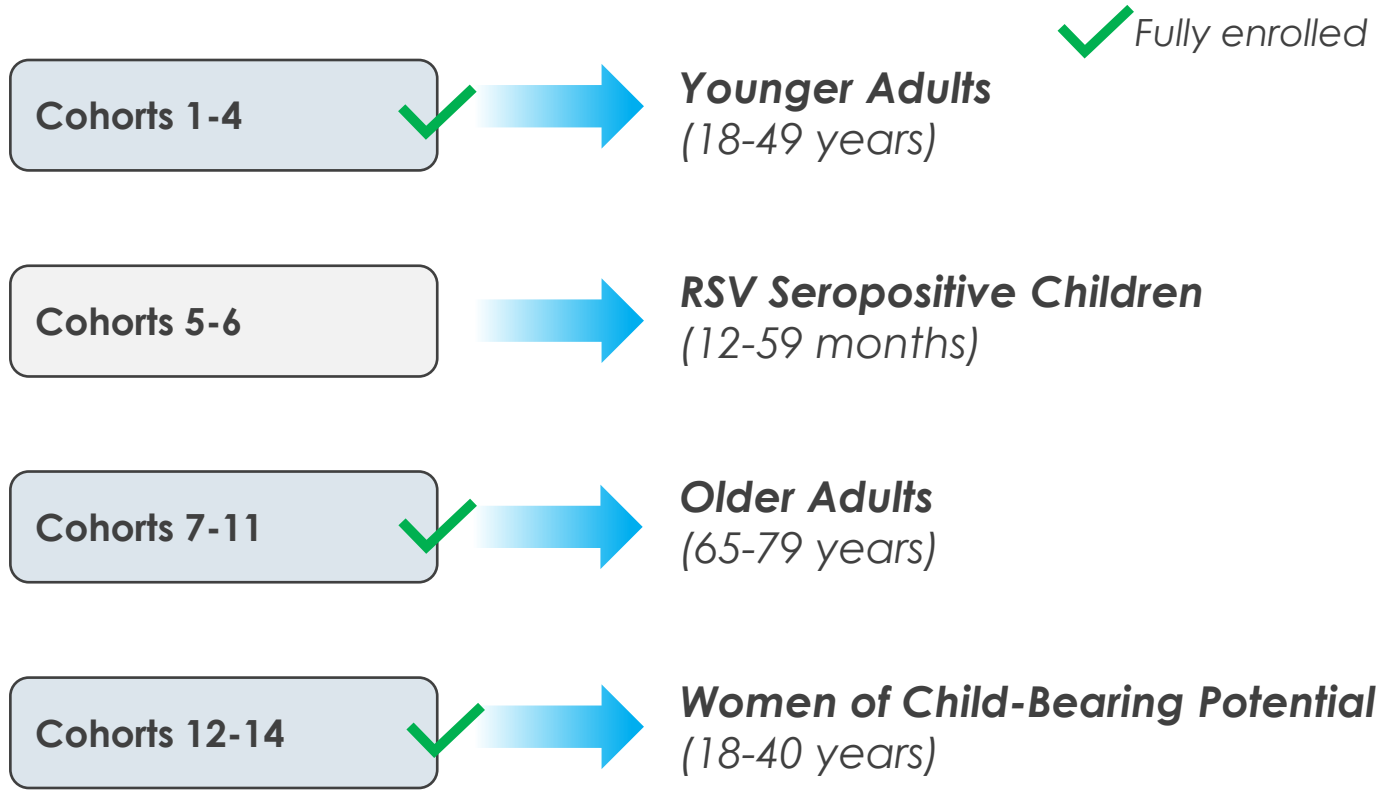
Outcome Measures

- Safety and immunogenicity
  - Neutralizing antibody titers against RSV

Trial progress

- Younger adults, older adults and women of child-bearing potential cohorts are all fully enrolled
- Enrollment ongoing in cohort 5 (RSV seropositive children)

Phase 1 Trial Design – Ongoing in four different populations



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Review of Phase 1 interim data in younger adults (presented in April 2021)

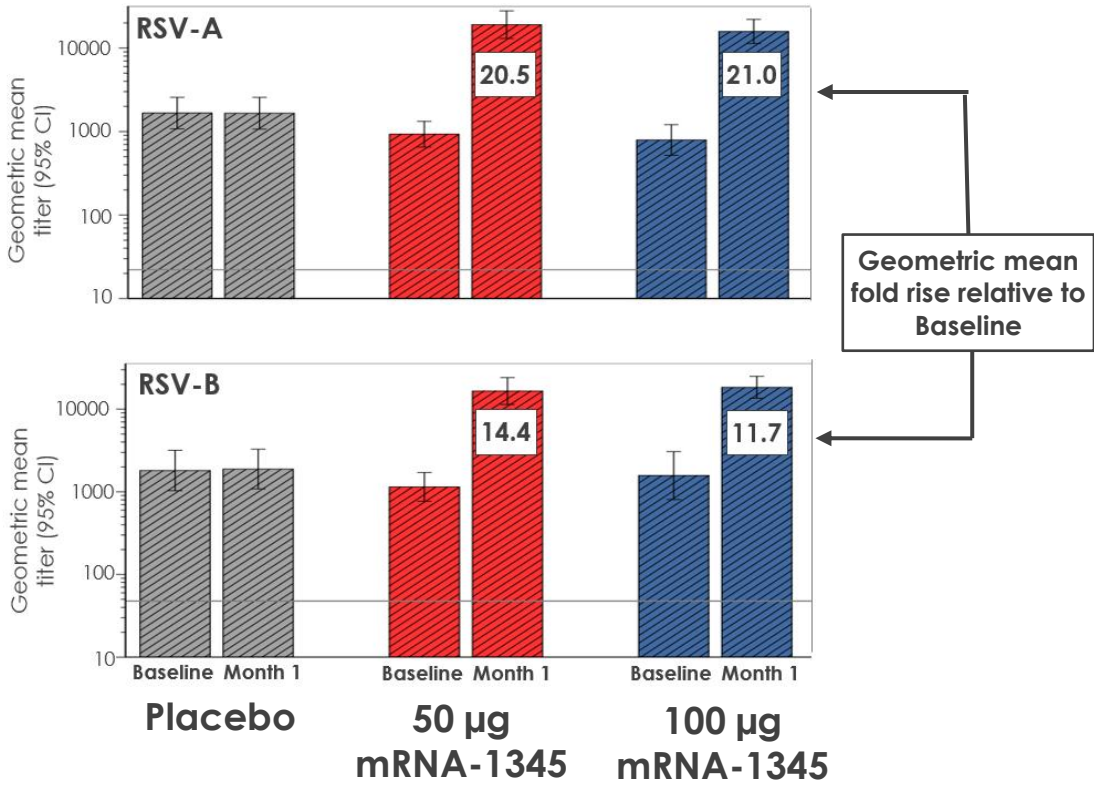
Safety

- A single mRNA-1345 vaccination of 50 µg or 100 µg was generally well-tolerated in younger adults
- Most common solicited adverse reaction was injection site pain and most common systemic solicited adverse reactions were headache fatigue and myalgia (majority occurred within 1-3 days after vaccination and resolved after 1-4 days)

Immunogenicity

- At month 1, the geometric mean fold rise in neutralizing antibody relative to baseline was at least 20.5 for RSV-A and at least 11.7 for RSV-B

RSV Neutralizing Antibody



Interim data, Per-Protocol analysis set
N = 10 for placebo, 18 for 50 µg and 19 for 100 µg

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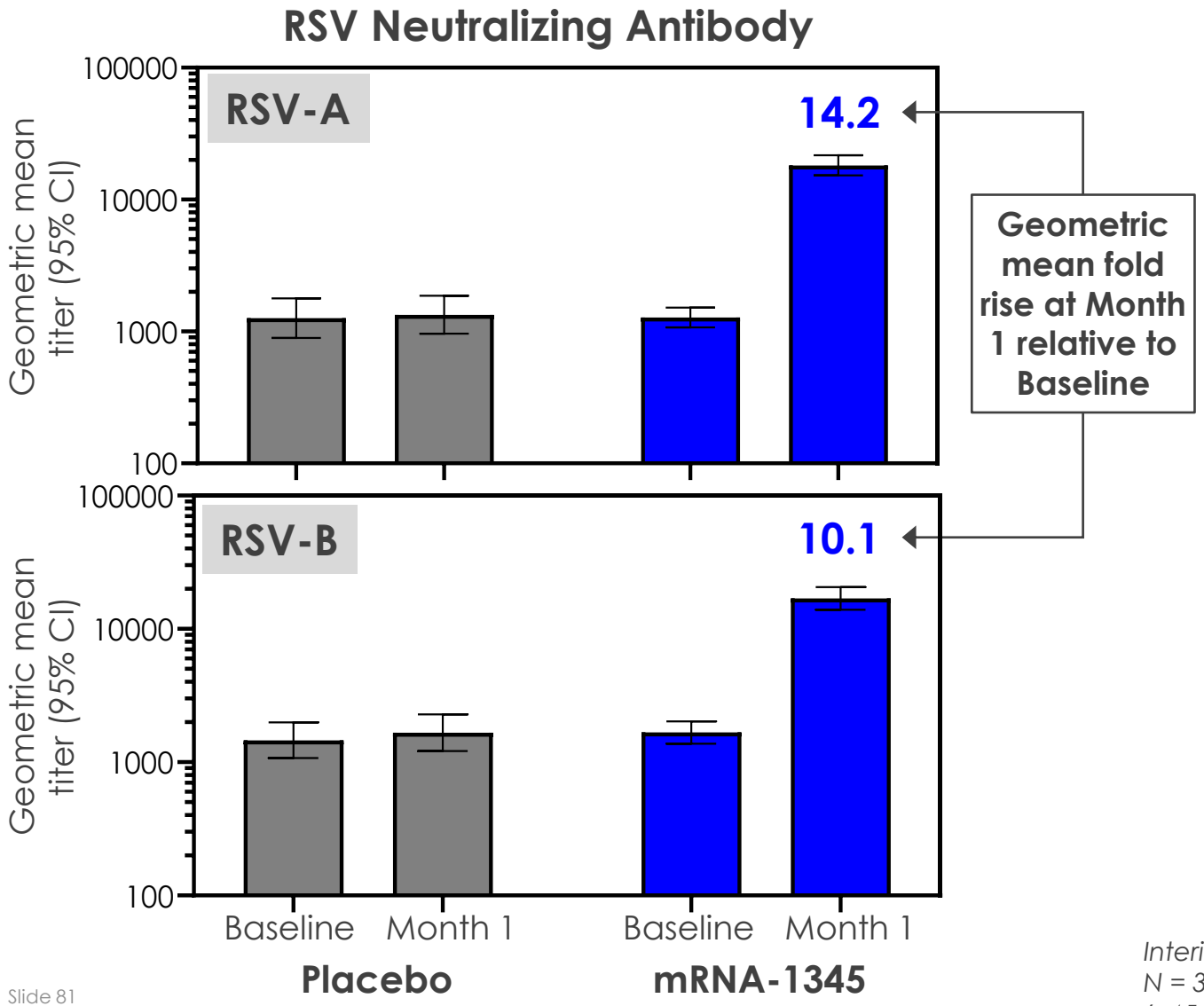
In older adults, mRNA-1345 boosts RSV neutralizing antibodies



- Neutralizing antibodies were confirmed to be present at baseline in all subjects, as expected
- A single mRNA-1345 vaccination of 50, 100 or 200 µg boosted neutralizing antibody titers against RSV-A ~14-fold and RSV-B ~10-fold
- Data are pooled across dose levels because there was not a significant difference between doses
- A single mRNA-1345 vaccination of 50, 100 or 200 µg was well tolerated in older adults through Month 1

Interim data, Per-Protocol analysis set.
N = 34 for placebo, N = 135 for mRNA-1345
(~45 per 50, 100 and 200 µg dose level)

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Preparing for Phase 2/3 RSV trial in older adults

- Aiming to start Phase 2/3 by the end of 2021
- Global trial; locations influenced by RSV epidemiology
- Placebo-controlled, case-driven design
- Primary endpoints will be safety and vaccine efficacy
- Study is in adults ≥ 60 years of age
- Expect to enroll 34,000 participants, subject to agreement with regulatory authorities

We received FDA Fast Track designation for older adults

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Moderna's respiratory vaccines: Pediatric hMPV + PIV3

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Adults	COVID-19 vaccine	mRNA-1273						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
Prophylactic vaccines	Flu vaccine	mRNA-1010	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	mRNA-1073	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	mRNA-1345			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	mRNA-1273	KidCOVE					Worldwide
	Pediatric RSV vaccine	mRNA-1345	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	mRNA-1653						Worldwide
	Pediatric RSV + hMPV vaccine	mRNA-1365						Worldwide

New development candidates

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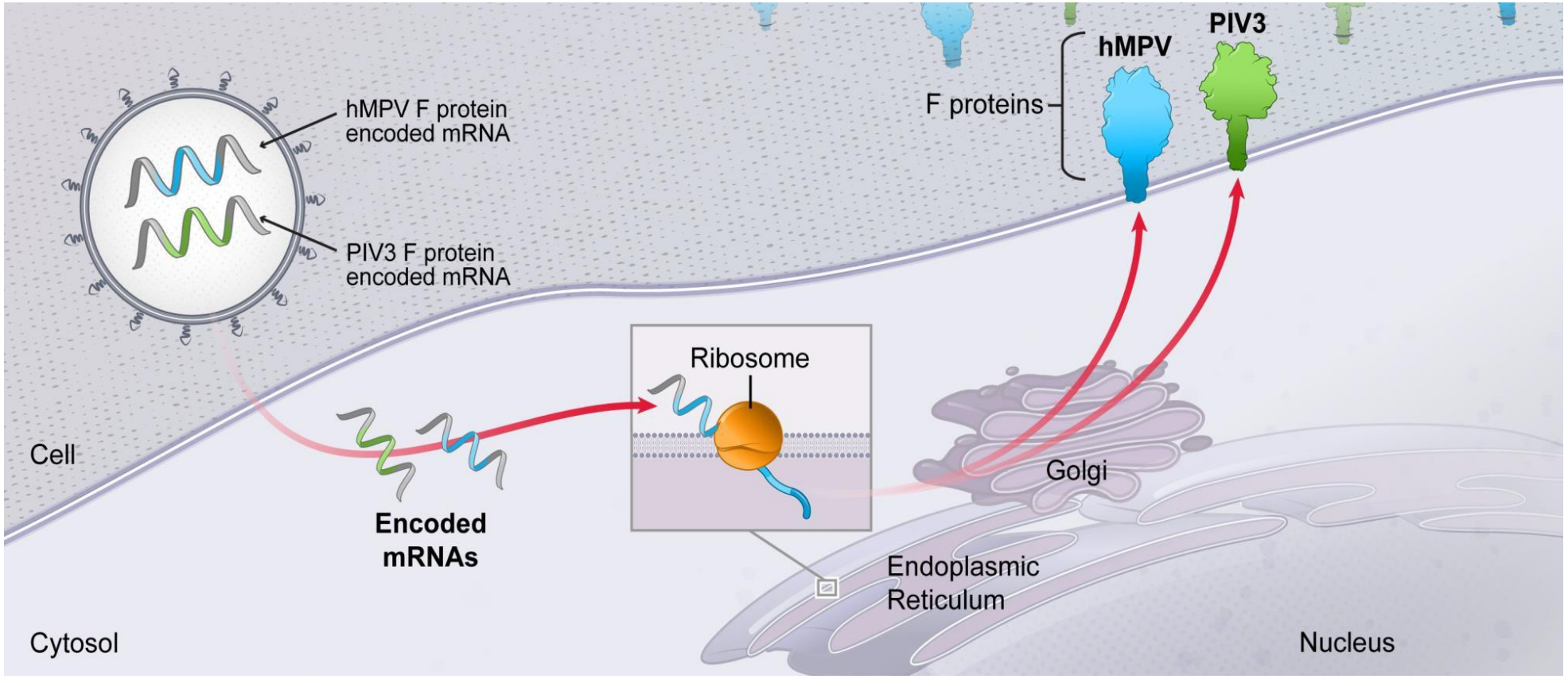
hMPV/PIV3 vaccine (mRNA-1653) combines mRNAs encoding antigens from two different viruses



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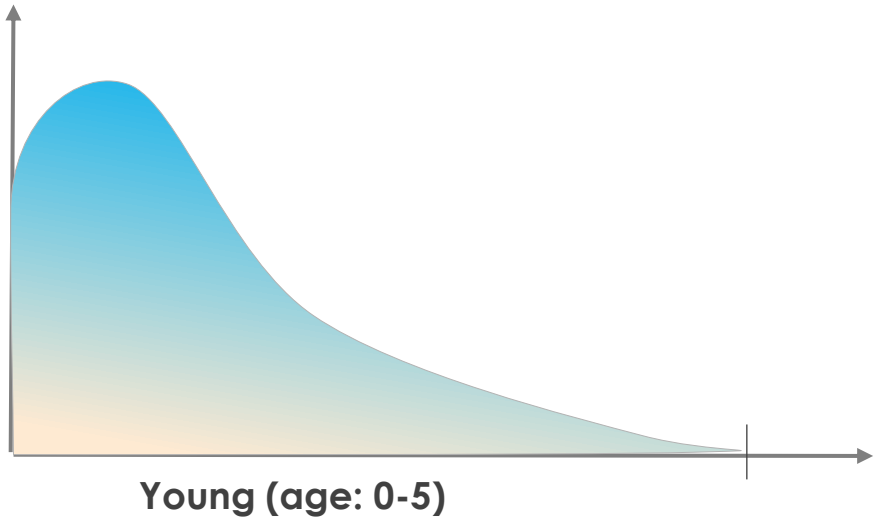
Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) represent a high unmet need in young children

Burden of hMPV/PIV3
(illustrative)



Most hMPV or PIV3-associated hospitalizations in children occur under 2 years old

Hospitalization rates in children < 5 years old in the U.S.:

- hMPV: 1.2 per 1,000
- PIV3: 0.5 per 1,000

hMPV/PIV3 infection sequelae:

- High fever
- Otitis media
- Thick nasal discharge
- Breathing difficulties, coughing
- Croup
- Pneumonia
- Bronchiolitis

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Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) represent a high unmet need in young children

Overview

- To evaluate the safety and immunogenicity of mRNA-1653 when administered to adults and to children 12-59 months of age with serologic evidence of prior exposure to hMPV and PIV3

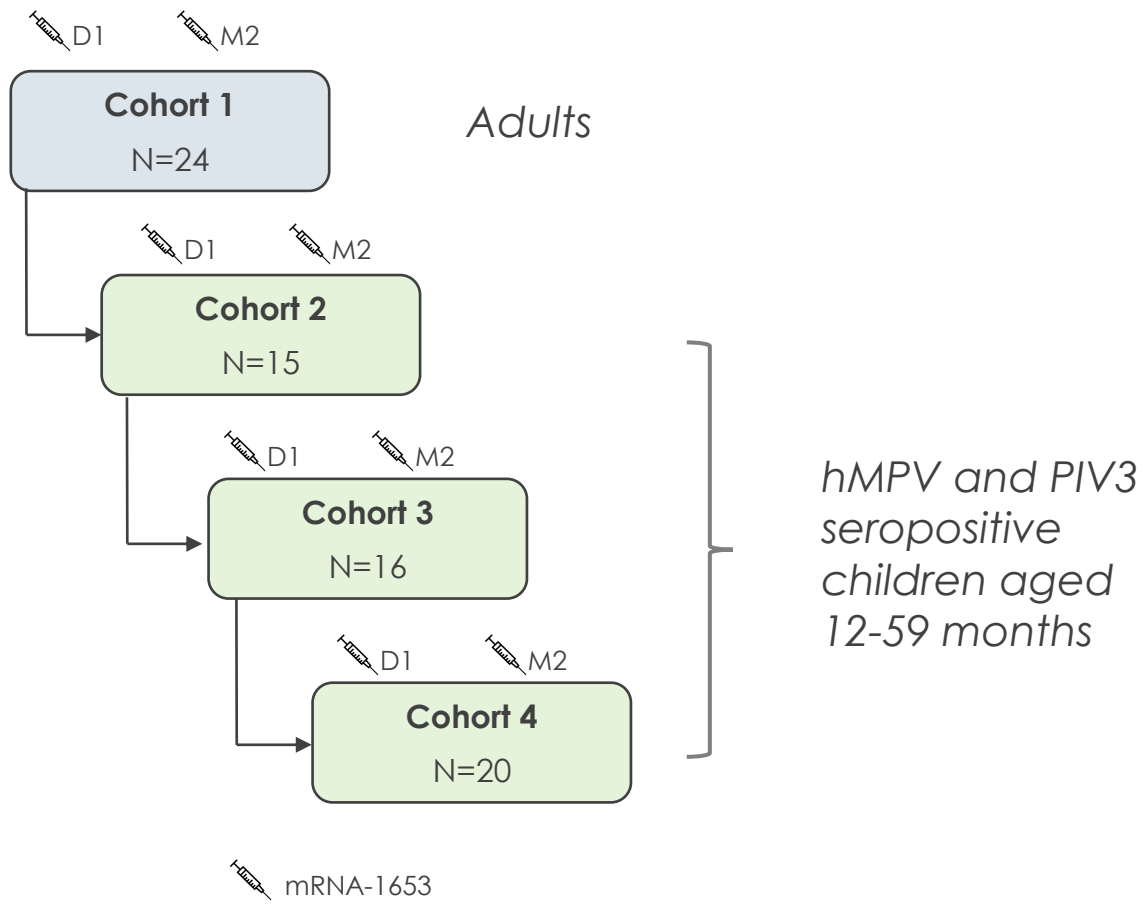
Outcome Measures

- Safety and immunogenicity
  - Neutralizing antibodies against hMPV and PIV3

Trial progress

- Interim data from the adult cohort in this study corroborated the data shared in 2019 from our first Phase 1 study (hMPV and PIV3 neutralization titers were boosted ~6X and ~3X baseline, respectively)
- Recent interim data also show that mRNA-1653 boosts hMPV and PIV3 titers in seropositive children; These data will be presented a medical conference

Phase 1 trial design



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Moderna's respiratory vaccines: Combinations

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Adults	COVID-19 vaccine	mRNA-1273						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
Prophylactic vaccines	Flu vaccine	mRNA-1010	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	**mRNA-1073**	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	mRNA-1345			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	mRNA-1273	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	mRNA-1273	KidCOVE					Worldwide
	Pediatric RSV vaccine	mRNA-1345	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	mRNA-1653						Worldwide
	Pediatric RSV + hMPV vaccine	**mRNA-1365**						**Worldwide**

New development candidates

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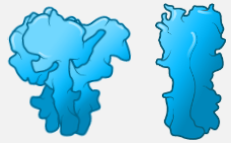
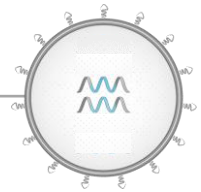
Announcing two new combination vaccines are progressing towards the clinic

COVID/Flu
mRNA-1073



RSV/hMPV
mRNA-1365



Combination mRNA vaccines against acute respiratory infections

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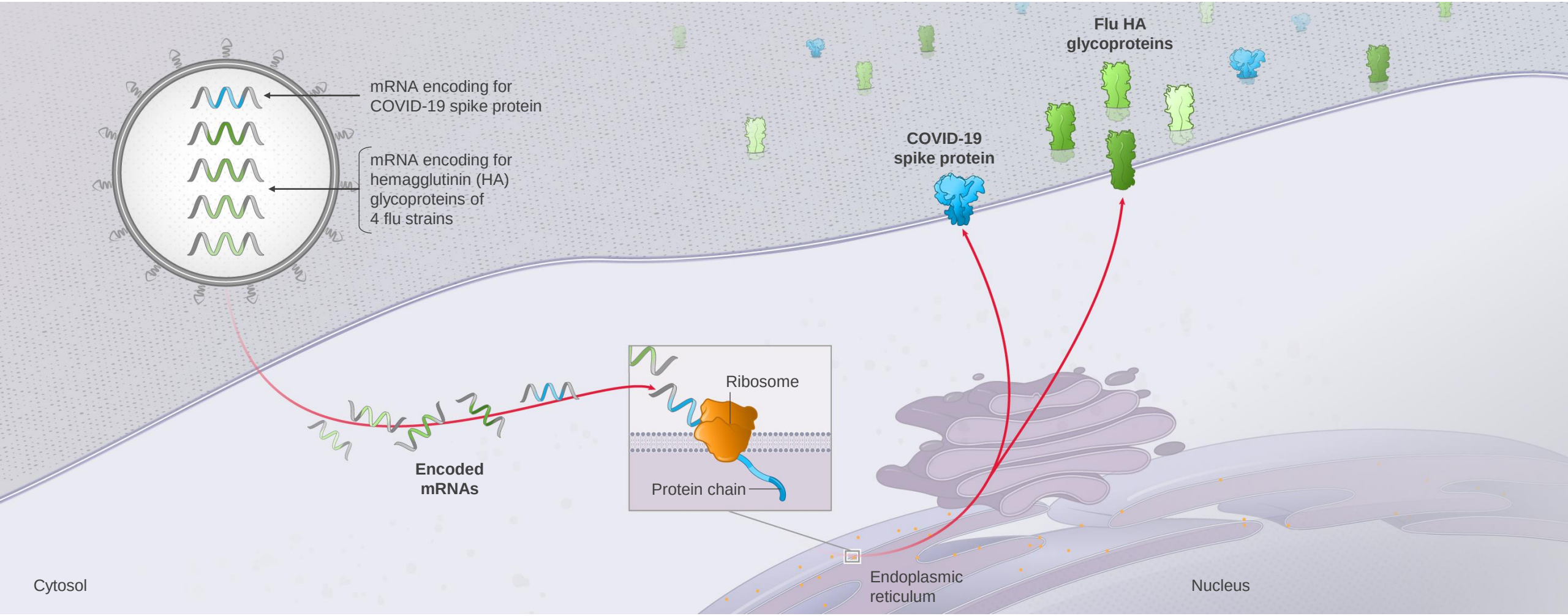
mRNA-1073 encodes for the COVID-19 spike protein and Flu HA glycoproteins



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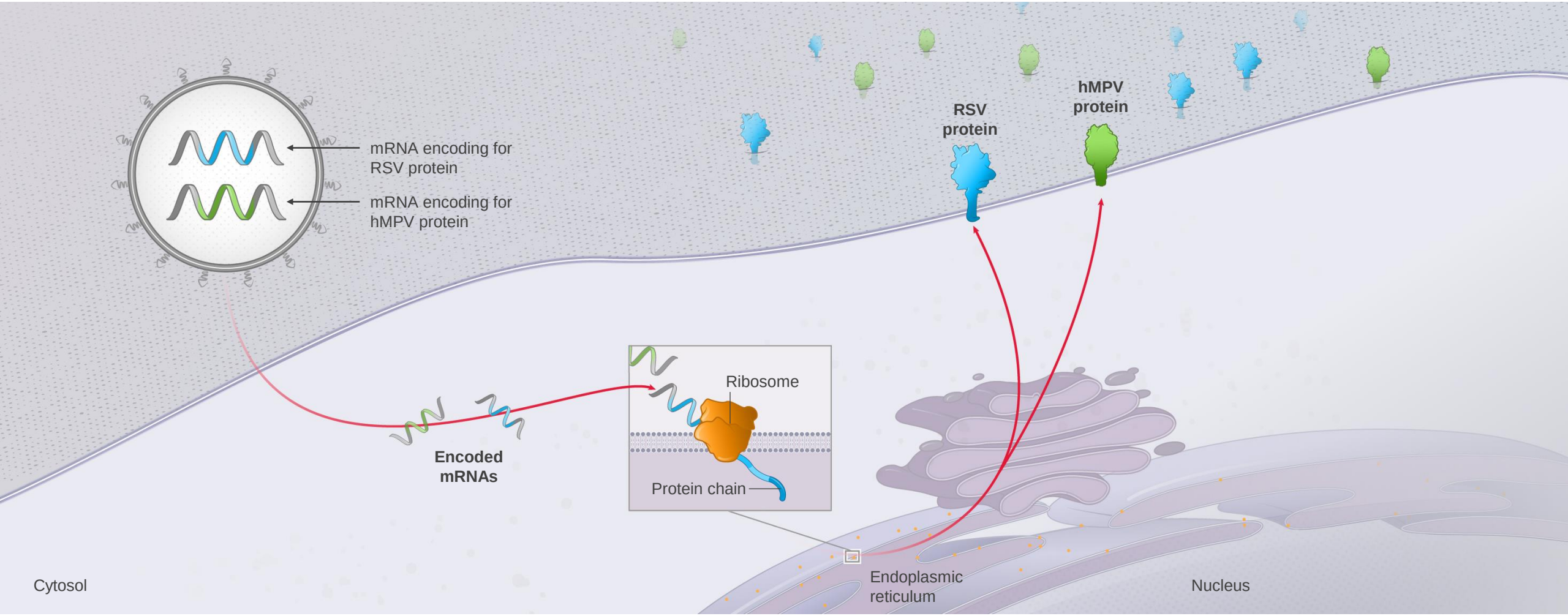
mRNA-1365 encodes for a RSV prefusion F glycoprotein and a hMPV F protein



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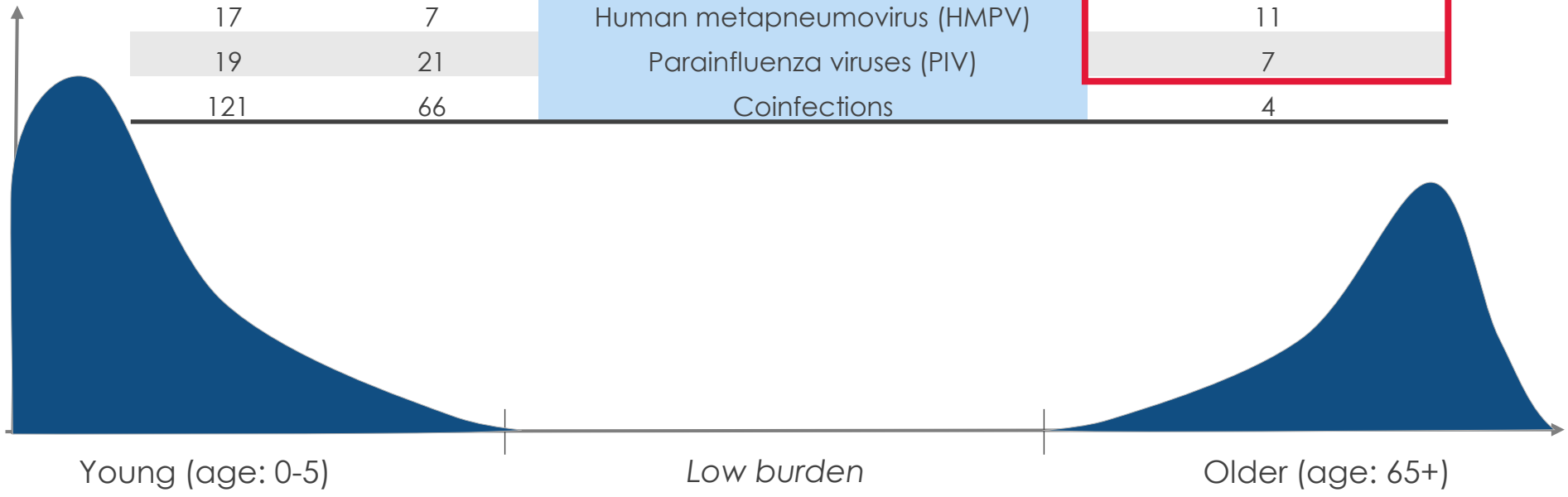
Respiratory virus disease burden is greatest in the young and the old

***Within Season Outpatient* Acute Respiratory Infection**
Attack Rate per 1,000
(Kaiser Permanente WA, N=2,767, 11/18/18-4/20/19)

<2 years	2-4 years	Respiratory Virus	≥65 years
54	64	Influenza A (H1, H3)	32
107	59	Respiratory syncytial virus (RSV)	19
6	23	Human coronavirus (HCoV)	18
33	8	Human rhinovirus (HRV)	12
17	7	Human metapneumovirus (HMPV)	11
19	21	Parainfluenza viruses (PIV)	7
121	66	Coinfections	4

Burden of Respiratory Viruses
(illustrative)



ARI: Acute respiratory infection.
Jackson, Michael et al. "Incidence of Medically Attended Acute Respiratory Illnesses Due to Respiratory Viruses Across the Life Course During the 2018/19 Influenza Season," Clinical Infectious Diseases (16 Feb. 2021), 2021; https://doi.org/10.1093/cid/ciab131

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We are developing combination vaccines against the respiratory viruses with greatest public health impact

Developing vaccines against respiratory viruses with greatest public health impact

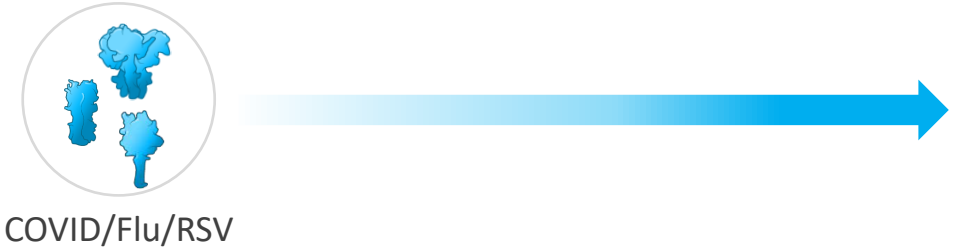
Combination vaccines may lead to:

- Higher compliance
- Better uptake
- Larger benefit to healthcare system

Clinical trials ongoing

Preparing for clinical trials

In research



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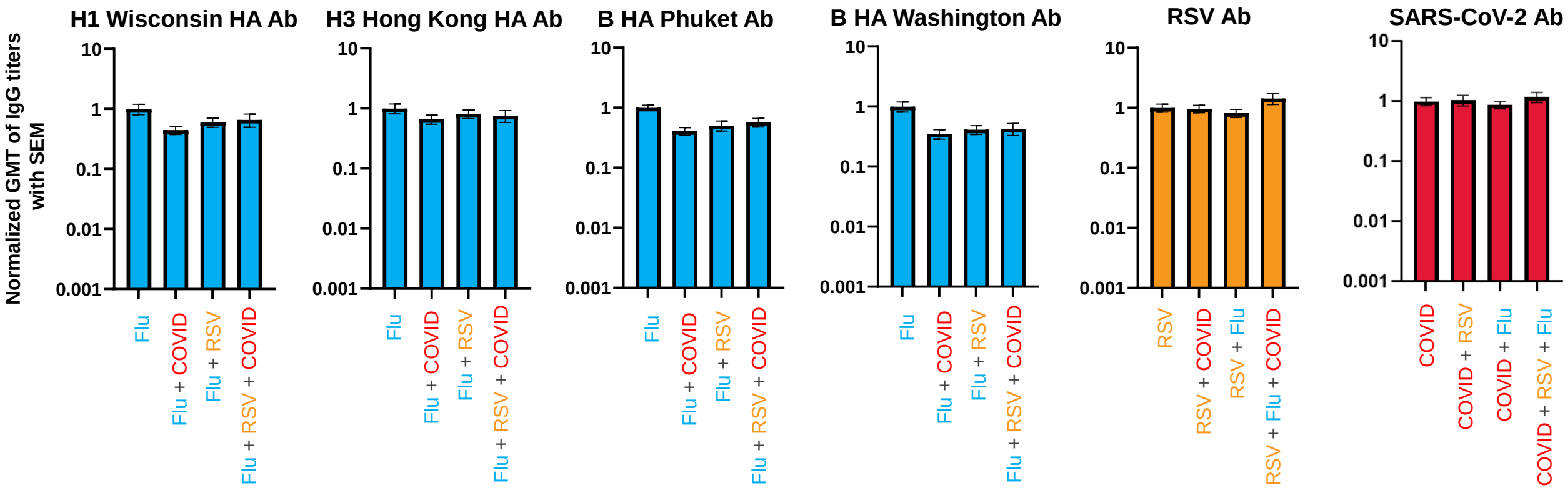
A Flu, RSV and SARS-CoV-2 combo vaccine induces robust antibody responses to all components in mice

Flu vaccine (mRNA-1010) encodes for **4 antigens** (HA)	COVID-19 vaccine (mRNA-1273) encodes for **1 antigen** (spike protein)	RSV vaccine (mRNA-1345) encodes for **1 antigen** (prefusion F protein)

or mRNA-1010 + mRNA-1345 + mRNA-1273



Species: Mice; Shots on Day 0 and Day 21; Results from Day 36

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Moderna's other vaccines: CMV

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Prophylactic vaccines	CMV vaccine	**mRNA-1647**				Phase 3 prep		Worldwide
	EBV vaccine **EBV therapeutic vaccine**	**mRNA-1189**						Worldwide
		mRNA-1195						Worldwide
	Zika vaccine	**mRNA-1893**						Worldwide ***BARDA** funded*
	HIV vaccine	**mRNA-1644**	Open IND					Worldwide ***IAVI/others** funded*
		mRNA-1574						Worldwide ***BMGF/NIAID/ others** funded*
	Nipah vaccine	**mRNA-1215**						Worldwide ***NIH** funded*

New development candidates

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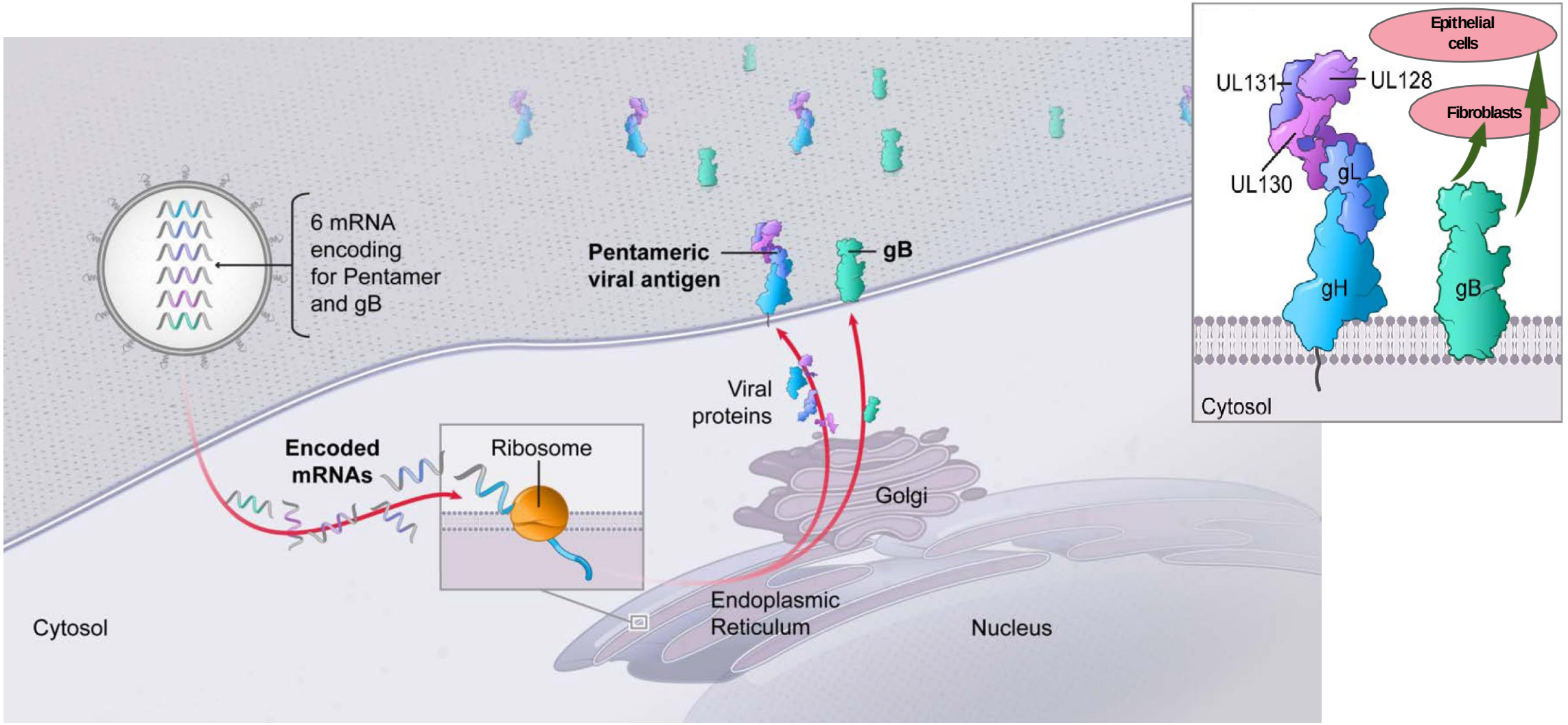
CMV vaccine (mRNA-1647) includes six mRNA sequences



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Cytomegalovirus (CMV) Overview

- Cytomegalovirus: **CMV is a common infection and is the leading cause of birth defects in the US**
  - About 1 out of every 200 infants in the US are born with congenital CMV infection[1] (20,000-30,000 infants born annually in the US)[2]

- **Disease burden**: Significant impact on survivors, families, caregivers and health systems[3]
  - An estimated 10% - 15% of newborns with congenital CMV infection are severely ill at birth
  - Approximately 4% - 12% of children with symptomatic CMV will die in their first year of life, and 70% - 80% will survive to suffer lifelong disabilities

- **Unmet need**: No approved CMV vaccine

CMV infection sequelae[4,5]	
Neonatal period	Jaundice Microcephaly Hearing loss Vision loss Seizures Low birth weight
Infancy, childhood, adulthood	Deafness/Hearing loss Neurodevelopmental delay Seizures

(1) https://www.cdc.gov/cmv/clinical/congenital-cmv.html
(2) Britt W. Cytomegalovirus. In: Remington JS, Klein JO, Wilson CB, Baker, CJ, eds. Infectious Diseases of the Fetus and Newborn Infant. 7th ed. Philadelphia: W.B. Saunders Company; 2011: pp 704-753
(3) Boppana et al. Symptomatic congenital cytomegalovirus infection: Neonatal morbidity and mortality, Pediatric Infectious Disease Journal, 1992
(4) Manicklal et al, The silent global burden of congenital cytomegalovirus, Clinical Microbiology Reviews, 2013
(5) Lopez et al, The impact of cytomegalovirus reactivation and its treatment on the course of inflammatory bowel disease, AP&T, 2014

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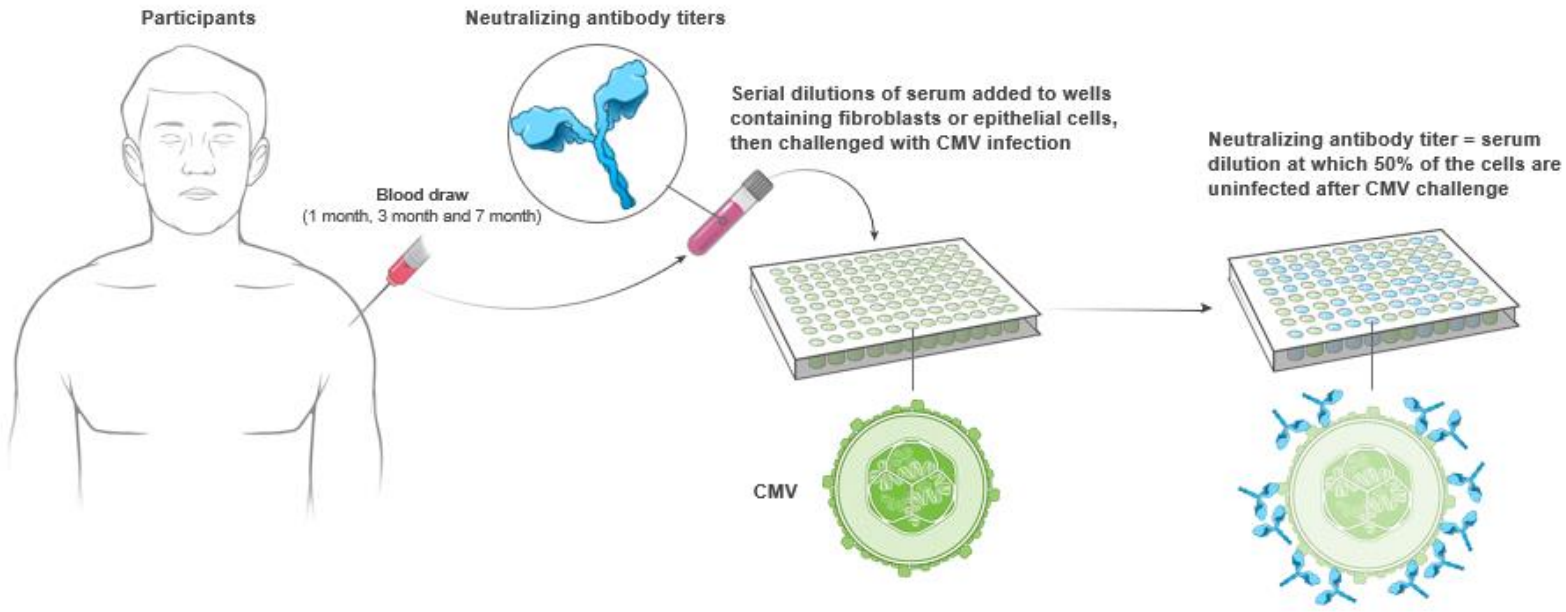
Phase 3 CMV trial to start in 2021

- Expected to enroll ~8,000 participants across ~150 sites in the U.S., Europe and APAC
- Pivotal Phase 3 trial will test the 100 µg dose level
- Primary objective is demonstration of vaccine efficacy to prevent CMV infection
- Primary efficacy analysis will be triggered based on accrual of seroconversion cases; meeting the primary objective will be the basis for filing
- Seroconversion will be determined using an assay containing non-vaccine antigens



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Moderna's other vaccines: EBV vaccine

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	EBV vaccine **EBV therapeutic vaccine**	mRNA-1189						Worldwide
		mRNA-1195						Worldwide
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		mRNA-1574						Worldwide ***BMGF/NIAID/ others** funded*
	Nipah vaccine	mRNA-1215						Worldwide ***NIH** funded*

New development candidates

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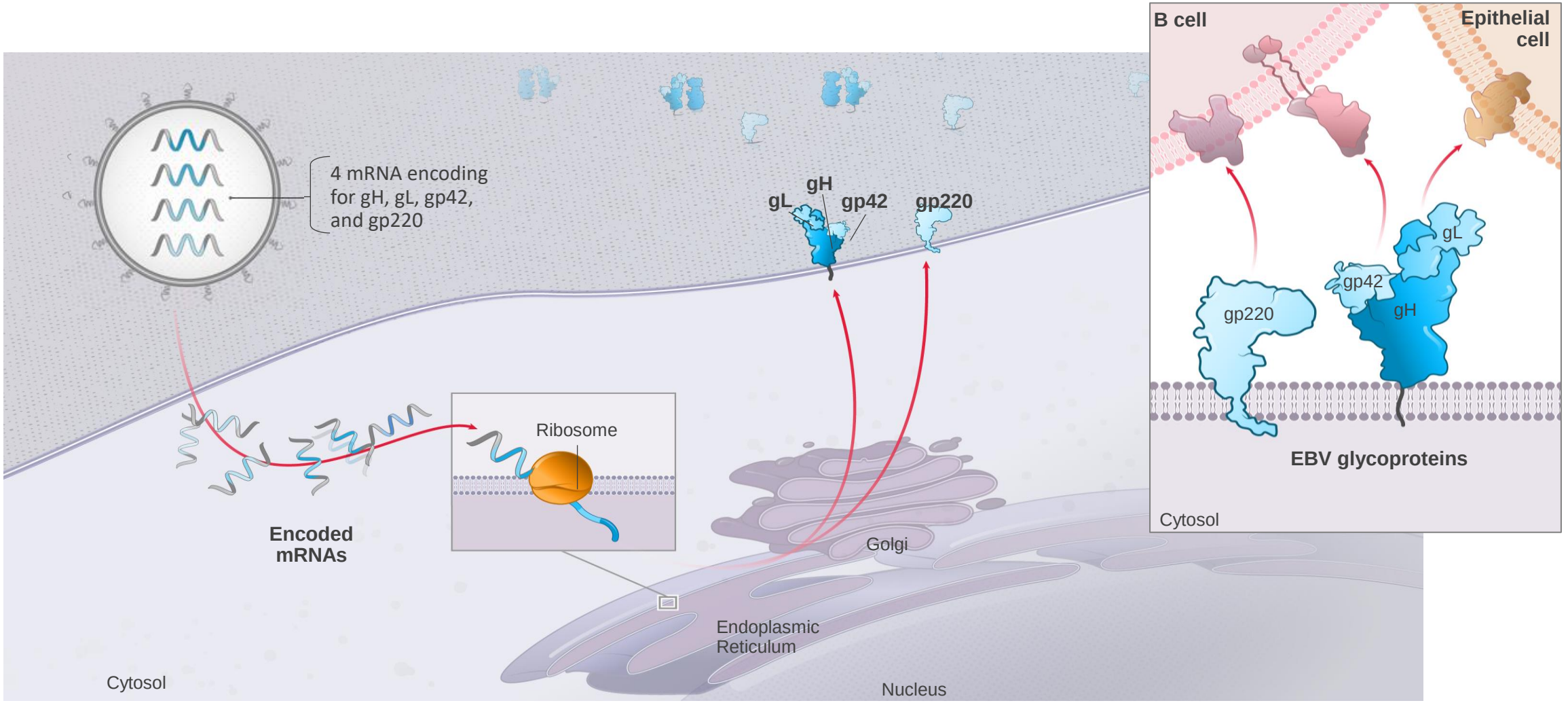
EBV vaccine (mRNA-1189) encodes for four antigens



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Epstein-Barr virus (EBV) is a major cause of infectious mononucleosis (IM) and also associated risks to other long-term medical conditions

- EBV is a member of the herpesvirus family that includes CMV, HSV and VZV, is spread through bodily fluids (e.g., saliva) and contracted primarily by young children and adolescents
- EBV is a major cause of infectious mononucleosis (IM) in the U.S., accounting for over 90% of the ~1+ million cases annually
  - IM symptoms includes sore throat, lymphadenopathy, fever, body aches, fatigue and splenic rupture (rare complication)
- EBV reactivation has also been linked to long-COVID

Age

<20 years of age

EBV Infection

~90% EBV prevalence in the U.S.

Lifetime associated risks:

- Increased risk of developing multiple sclerosis by ~4-10 fold
- Associated with certain lymphoproliferative disorders
- Higher risk of developing cancers and autoimmune diseases

Saade A et al, Infect Dis Now (2021), https://doi.org/10.1016/j.idnow.2021.07.005
Jacobs M et al, Mult Scler. (2020), https://doi.org/10.1177/1352458520907901

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EBV vaccine (mRNA-1189) aims to start a Phase 1 in 2021

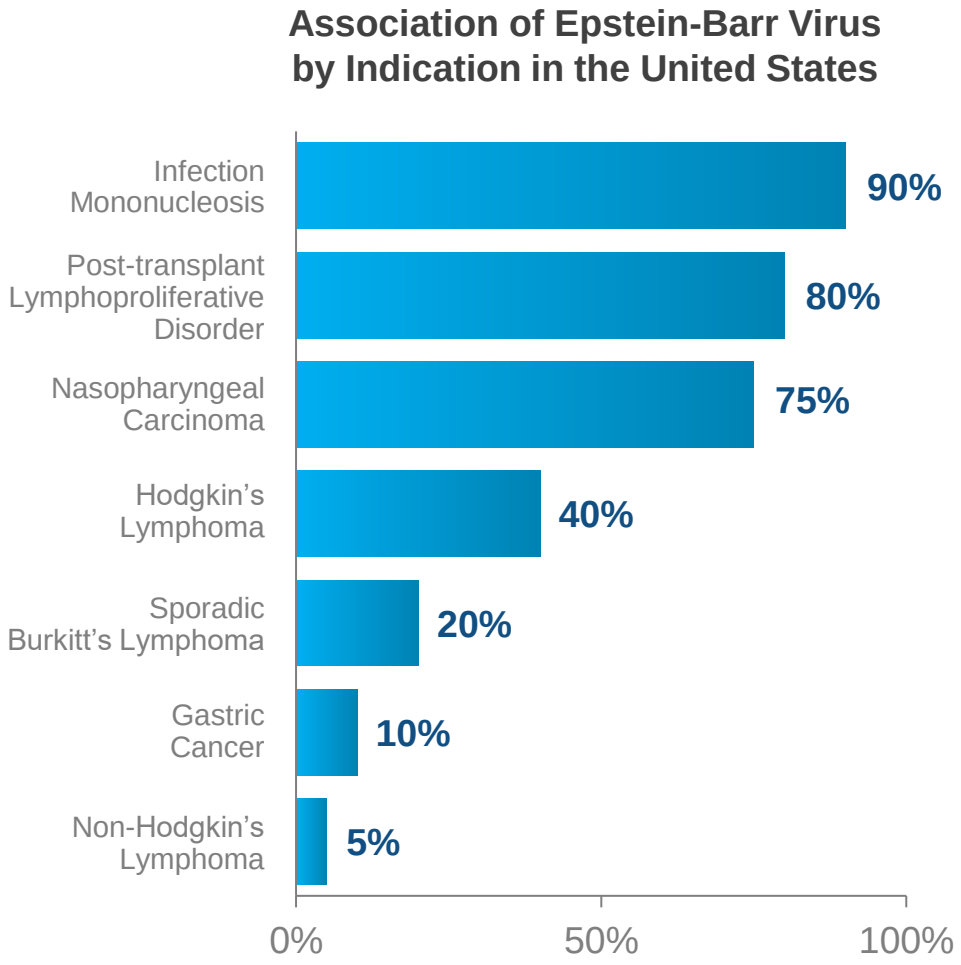
Prophylactic Vaccine (mRNA-1189)

- We believe that our vaccine has the potential to induce **protection in both cell types** (inhibiting viral entry into B cells and epithelial cells)
- **Primary Indications**:
  - Aim to reduce the rate of IM
- **Potential future indications**
  - Prevent EBV infection
  - Long COVID (subject to additional research)
- We aim to **start a Phase 1 clinical trial in 2021**

EBV therapeutic vaccine (mRNA-1195) in preclinical development

EBV Therapeutic Vaccine (mRNA-1195)

- To prevent longer term sequelae of EBV infection
- Encodes for additional antigens
- Indications
  - Post-transplant lymphoproliferative disease (80% of PTLD cases can be attributed to EBV)
- Other potential indications (subject to additional research)
  - Multiple sclerosis
  - Long COVID
- In preclinical development



Gequelin, Lucian, et al. *Rev Bras Hematol Hemoter* (2011), https://doi.org/10.5581/1516-8484.20110103

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Today's agenda

Opening Remarks	**Stéphane Bancel**, *Chief Executive Officer*
Platform, Modalities & Therapeutic Area Overview	**Stephen Hoge, M.D.**, *President*
Review of COVID-19 Vaccine Real-World Experience	**Paul Burton, M.D., Ph.D., F.A.C.C., M.R.C.S.**, *Chief Medical Officer*
Infectious Diseases	**Jacqueline Miller, M.D.**, *Senior Vice President, Infectious Diseases* *Vaccines against acute respiratory infections* *Vaccines against persistent infections*
Break	
Oncology	**Praveen Aanur, MBBS, MPH,** *Vice President, Oncology* **Ignacio Melero Bermejo, M.D.**, *Clinica Universidad de Navarra*
Rare Diseases, Autoimmune Diseases & Cardiovascular Diseases	**Ruchira Glaser, M.D., M.S.,** *Senior Vice President, Cardiovascular, Rare Diseases & Autoimmune*
Conclusion	**Stéphane Bancel**, *Chief Executive Officer*
Q&A	

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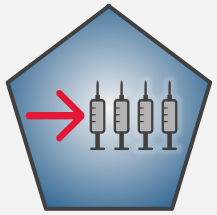
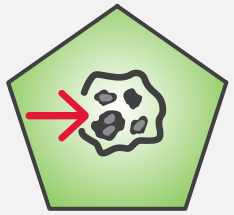


Cancer Vaccines



Intratumoral
Immuno-Oncology

Oncology

Praveen Aanur MBBS, MPH

Vice President, Therapeutic
Area Head, Oncology

Moderna's therapeutics: Oncology

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with **Merck**
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						**AZ** to pay milestones and royalties
	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
Systemic Intracellular Therapeutics	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge

New development candidates

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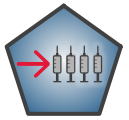
mRNA opportunity in immuno-oncology

Combining with PD1/PDL1 inhibitors to improve the benefit to patients

Immuno-oncology today

- Powerful antitumor responses can be achieved by activating antigen specific T cells
- Checkpoint inhibitors available to unleash tumor-reactive T cells and provide significant benefit to a subset of patients
- However, majority of patients with epithelial cancers **do not respond fully or at all to checkpoint inhibitors**



Cancer vaccines

- Our vaccines focused on expressing neoantigens found in a particular cancer
- Potential to improve efficacy of checkpoint inhibitors by increasing number and antitumor activity of T cells that recognize neoantigens

Intratumoral immuno-oncology

- Focused on activating T cells and transforming the tumor micro-environment to drive anti-cancer response
- In combination with checkpoint inhibitors

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Moderna's therapeutics: PCV

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
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	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to ILCM free of charge

New development candidates

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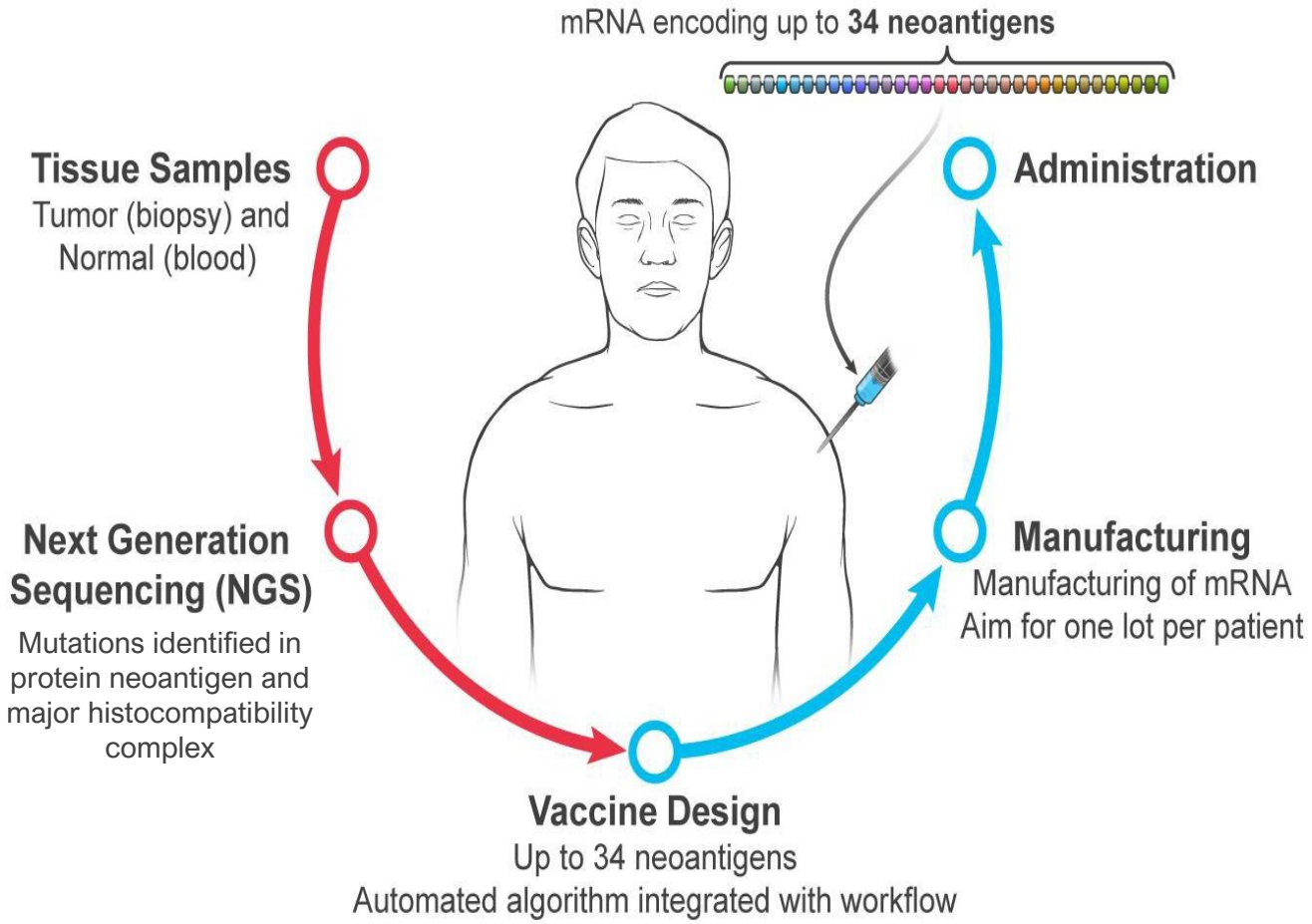
Personalized cancer vaccine (mRNA-4157)

Designed to target an individual patient's unique tumor mutations

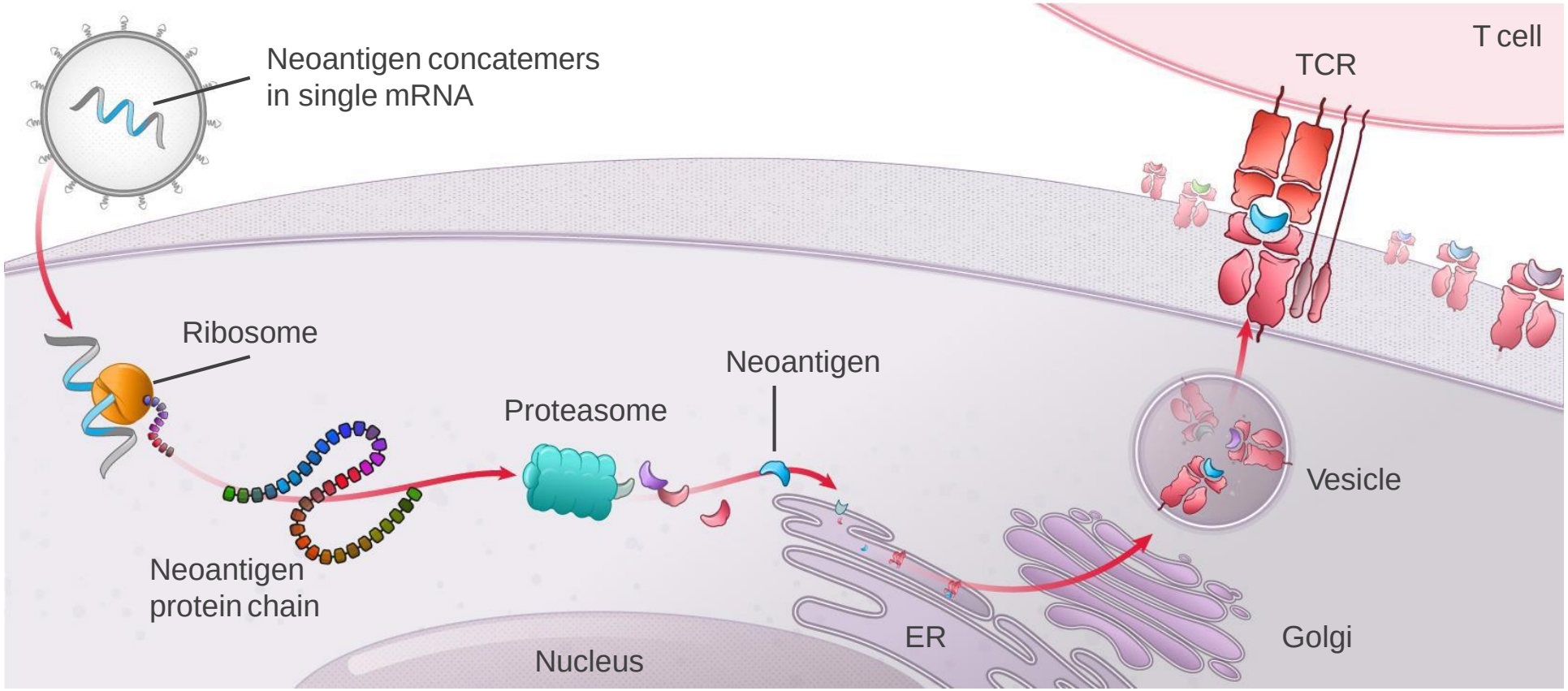


Personalized drug design

Rapid turnaround times

Needle-to-needle in just **weeks**

PCV vaccine (mRNA-4157) elicits T cells required for curative cancer therapy



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Personalized cancer vaccine (mRNA-4157) is ongoing in both Phase 1 and Phase 2 trials simultaneously

Phase 1 Trial Overview

- Assessing safety, tolerability and immunogenicity as monotherapy and in combination with pembrolizumab (KEYTRUDA®)
- Identify a safe Ph 2 dose
- Encouraging early signal observed in (HPV-) Head and neck squamous cell carcinomas (HNSCC)[1,2]
  - Cohort expanded from 10 to 40 patients
  - Currently enrolling expanded cohort

Phase 2 Trial Overview

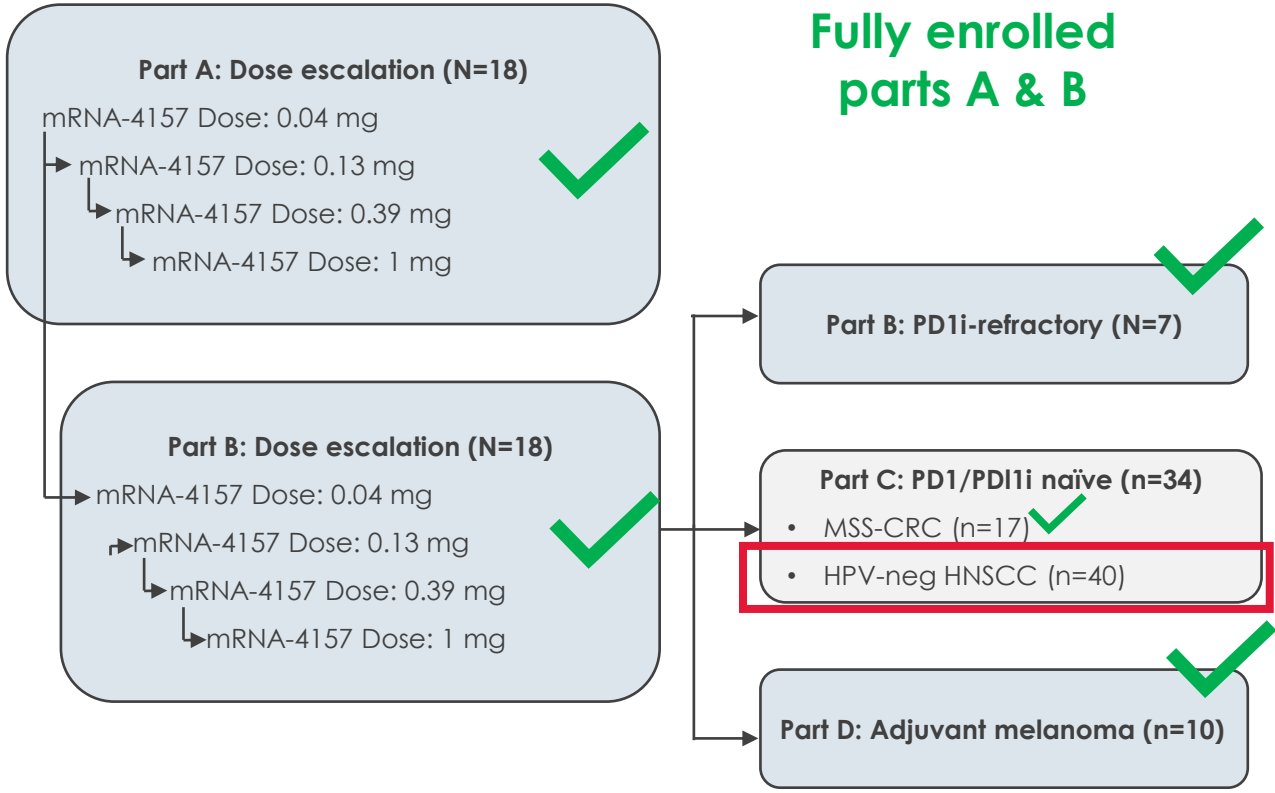
- Randomized controlled study: PCV + pembrolizumab (KEYTRUDA®) vs. pembrolizumab alone (2:1)
- High Risk Resected Melanoma Patients
- Primary endpoint = recurrence free survival at 12 months
- N~150 (Fully enrolled)

1. Data presented at SITC 2020. Data cutoff as of Oct 01, 2020
2. https://investors.modernatx.com/static-files/a79f9ce0-02f6-4ea8-8a8b-2d9f4ddcc531

Expanded Phase 1 Head and neck squamous cell carcinomas (HNSCC) cohort following encouraging early signal

Phase 1 Trial Overview

- Assessing safety, tolerability and immunogenicity as monotherapy and in combination with pembrolizumab
- Dose escalation to determine Ph 2 dose level
- Encouraging early signal observed in (HPV-) Head and neck squamous cell carcinomas (HNSCC)[1,2]
  - Cohort expanded from 10 to 40 patients
  - Currently enrolling expanded cohort



HPV: Human papillomavirus
HNSCC: Head and neck squamous cell carcinomas

1. Data presented at SITC 2020. Data cutoff as of Oct 01, 2020
2. https://investors.modernatx.com/static-files/a79f9ce0-02f6-4ea8-8a8b-2d9f4ddcc531

Encouraging early signal in checkpoint inhibitor (CPI) naïve HPV(-) HNSCC patients receiving mRNA-4157 + pembrolizumab (data presented at SITC 2020)

Best Overall Response

	HPV(-) HNSCC (n=10*)
Best overall response	
Complete Response (CR)	2
Partial Response (PR)	3
Stable Disease (SD)	4
Progressive Disease (PD)	1
Overall response rate (ORR)	50%
Disease control rate (DCR)	90%
Median progression-free survival (mPFS)	9.8 months
Median duration of response (mDOR)	Not reached

*4 additional patients started pembrolizumab dosing but progressed and came off study prior to the start of vaccine dosing.

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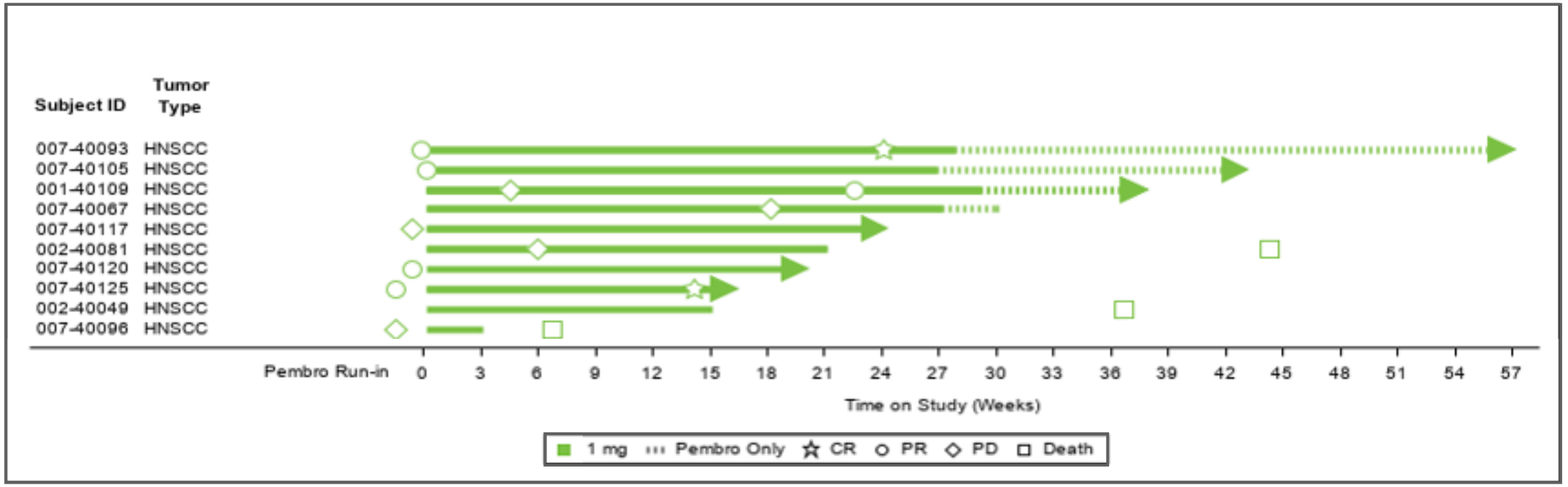
Encouraging early signal in checkpoint inhibitor (CPI) naïve HPV(-) HNSCC patients receiving mRNA-4157 + pembrolizumab (data presented at SITC 2020)

Time on Study Swimmer Plot



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Encouraging early signal in checkpoint inhibitor (CPI) naïve HPV(-) HNSCC patients receiving mRNA-4157 + pembrolizumab (data presented at SITC 2020)

%Change from Baseline Spider Plot

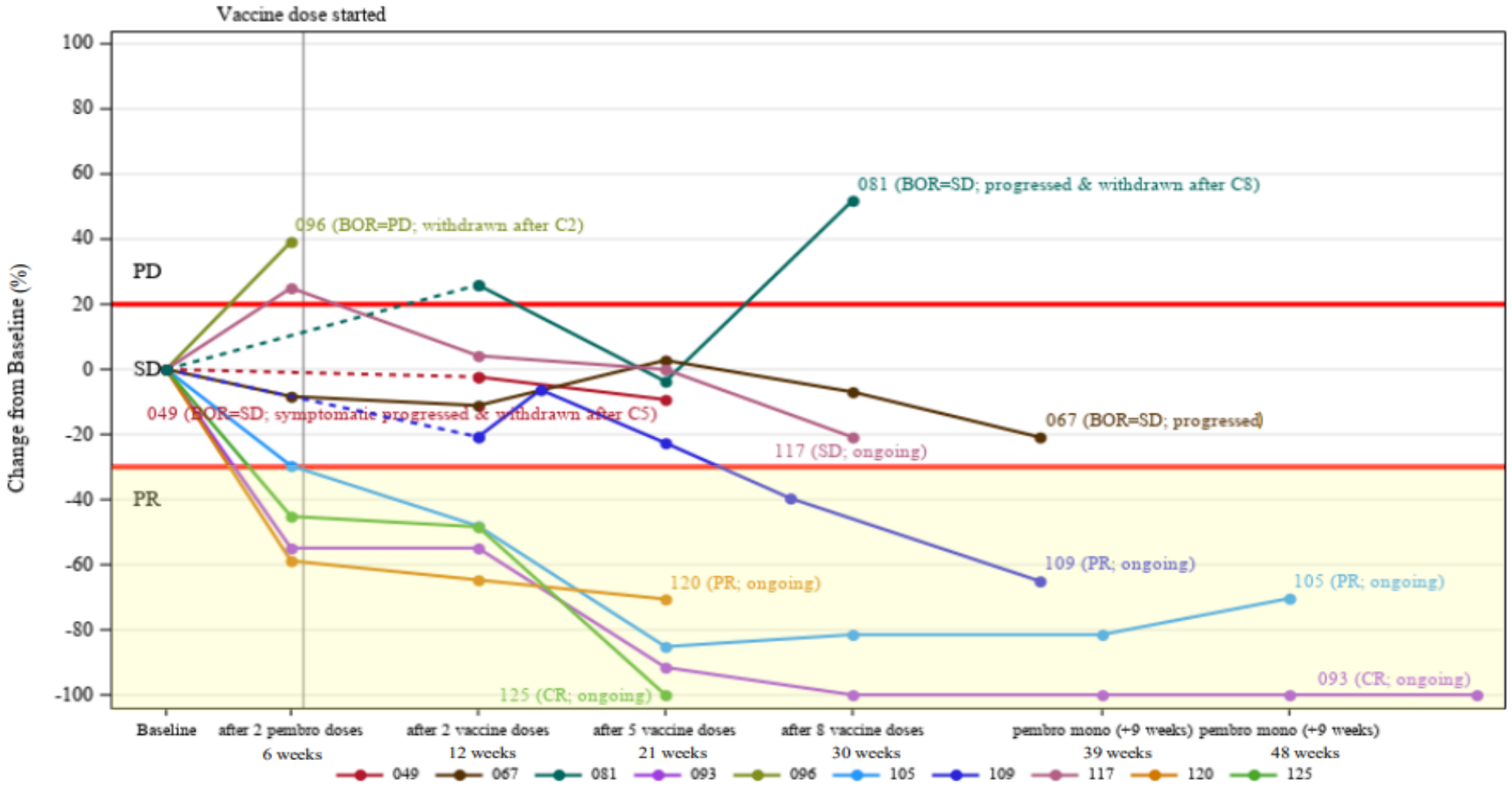
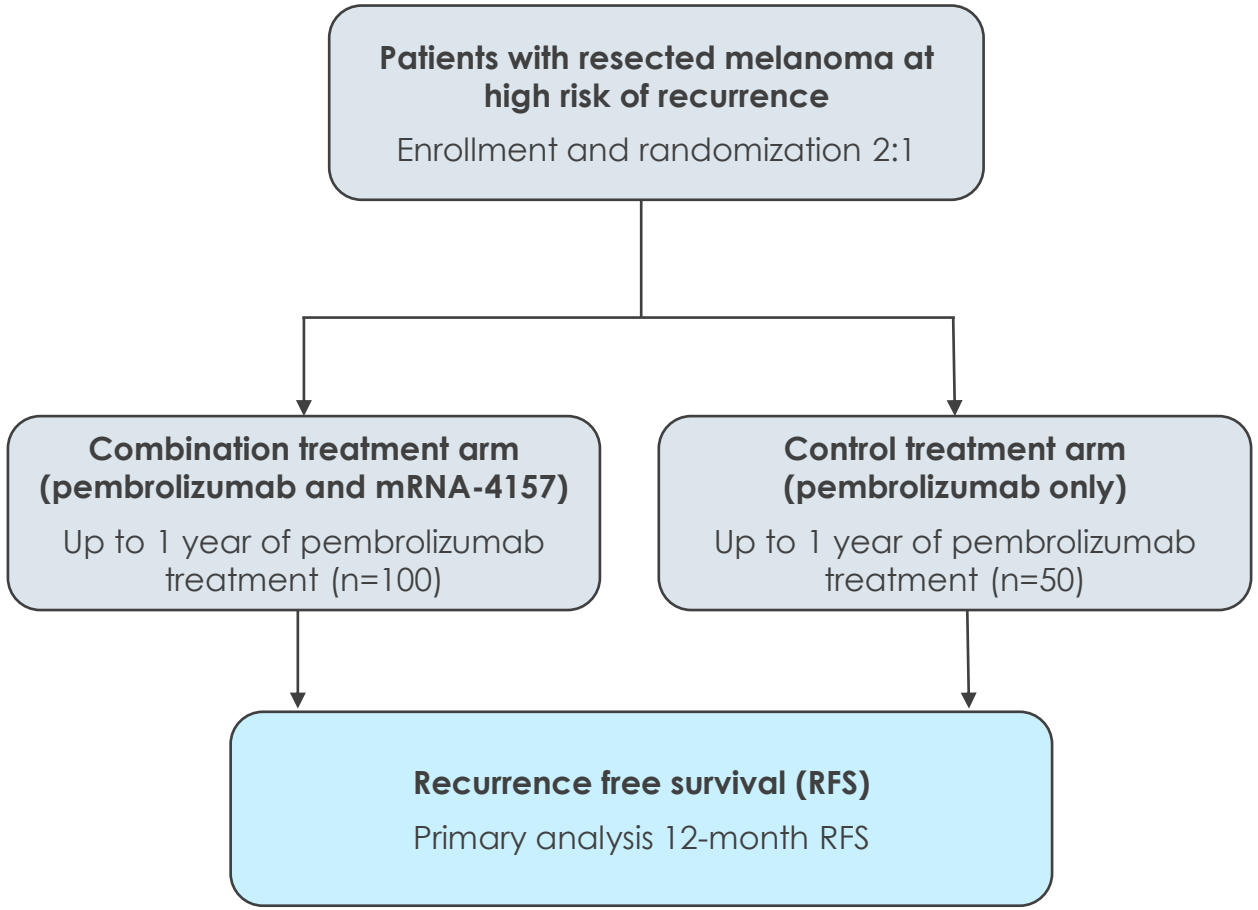


Figure 1-1: Four out of five responding patients achieved PR after 2 doses of pembrolizumab prior to the start of vaccine administration. Two PRs converted to CR after the addition of vaccine. Patient 109's tumor burden was decreasing but then started to progress until 2 doses of the vaccine were given, and then subsequently achieved a PR. Patient 067 also had started to progress until after the 5th dose of the vaccine, then ultimately had a discordant CR in the neck while progressing in the lung (vaccine was manufactured from the genetic sequencing of the dermal neck disease). Patient 117 progressed on monotherapy pembrolizumab until vaccine was started and tumor burden continues to decrease.

Personalized cancer vaccine (mRNA-4157) Phase 2 trial is now fully enrolled

Phase 2 Trial Overview

- Randomized, placebo controlled, PCV + pembrolizumab (KEYTRUDA®) vs. pembrolizumab alone (2:1)
- Resected Melanoma patients - high recurrence risk
- Primary endpoint = recurrence free survival at 12 months
- N~150 (Fully enrolled)



Moderna's therapeutics: OX40L/IL-23/IL-36γ (Triplet)

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New development candidates

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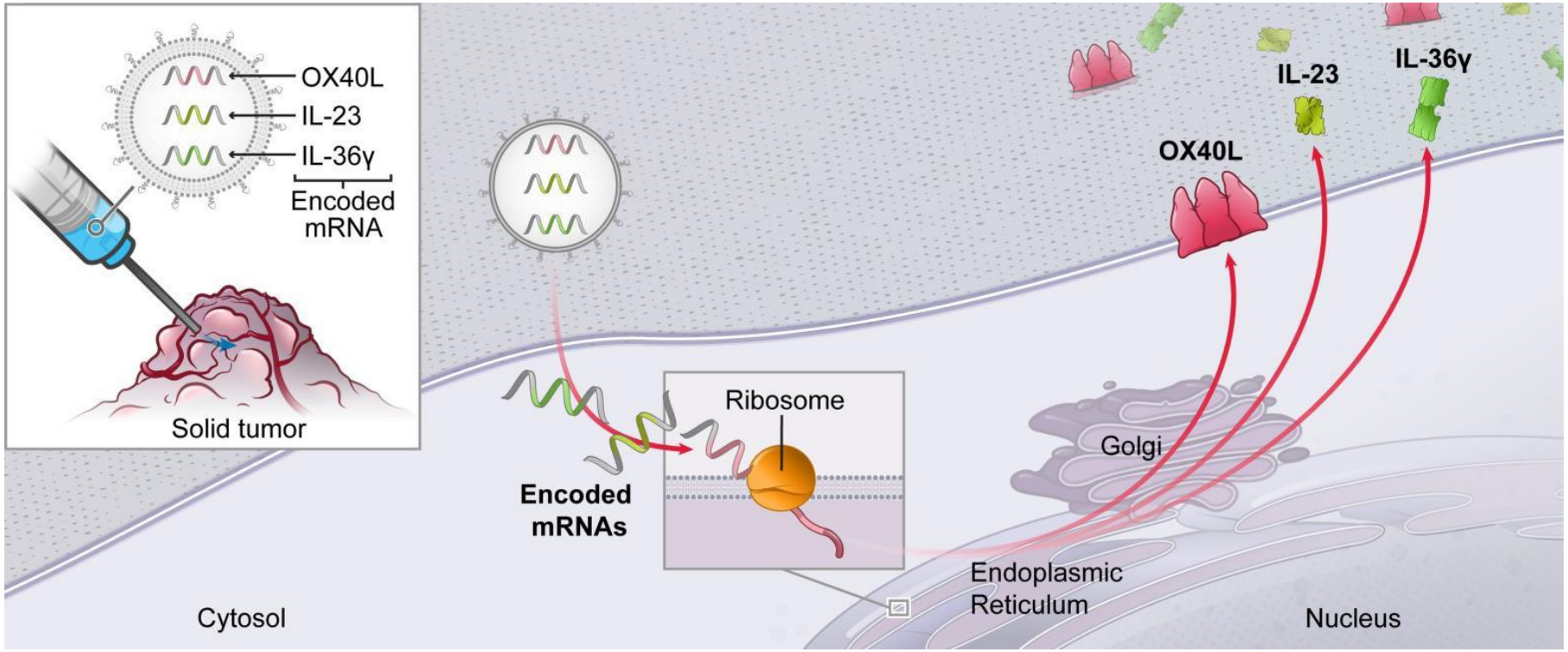
OX40L/IL-23/IL-36γ (mRNA-2752) overview

Moderna's technology enables novel combinations of targets
Intratumoral delivery may enable delivery of targets locally that are too toxic systemically



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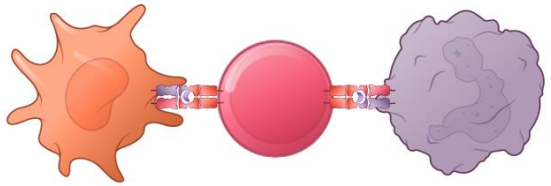
Immune modulation with OX40L, IL-23, IL-36γ



Dendritic Cell | T Cell | Cancer Cell

	OX40L	IL-23	IL-36γ
	Transmembrane T cell co-stimulatory protein	**Proinflammatory cytokine of the IL-12 family** • Reported to prime DC • Activates other cells that bridge innate to adaptive immunity (NKT, ILCs, gd T cells)	**Proinflammatory cytokine of the IL-1 family** • Acts on DCs to promote maturation and ↑ cytokine/chemokines
	• Promotes Th1, Th2, Th9; suppresses Treg • Enhances expansion and survival of CD4 and CD8 T cells → promotes memory	• Expands and maintains Th17 • Acts on antigen experienced T cells	• Enhances T cell proliferation, Th1, Th9 differentiation
	• Preclinical monotherapy efficacy established and reported	• Preclinical monotherapy efficacy established and reported • Clear role in human barrier immunity and inflammatory disease	• Reported to preclinically enhance anti-cancer immunity • Clear role in human barrier immunity and inflammatory disease

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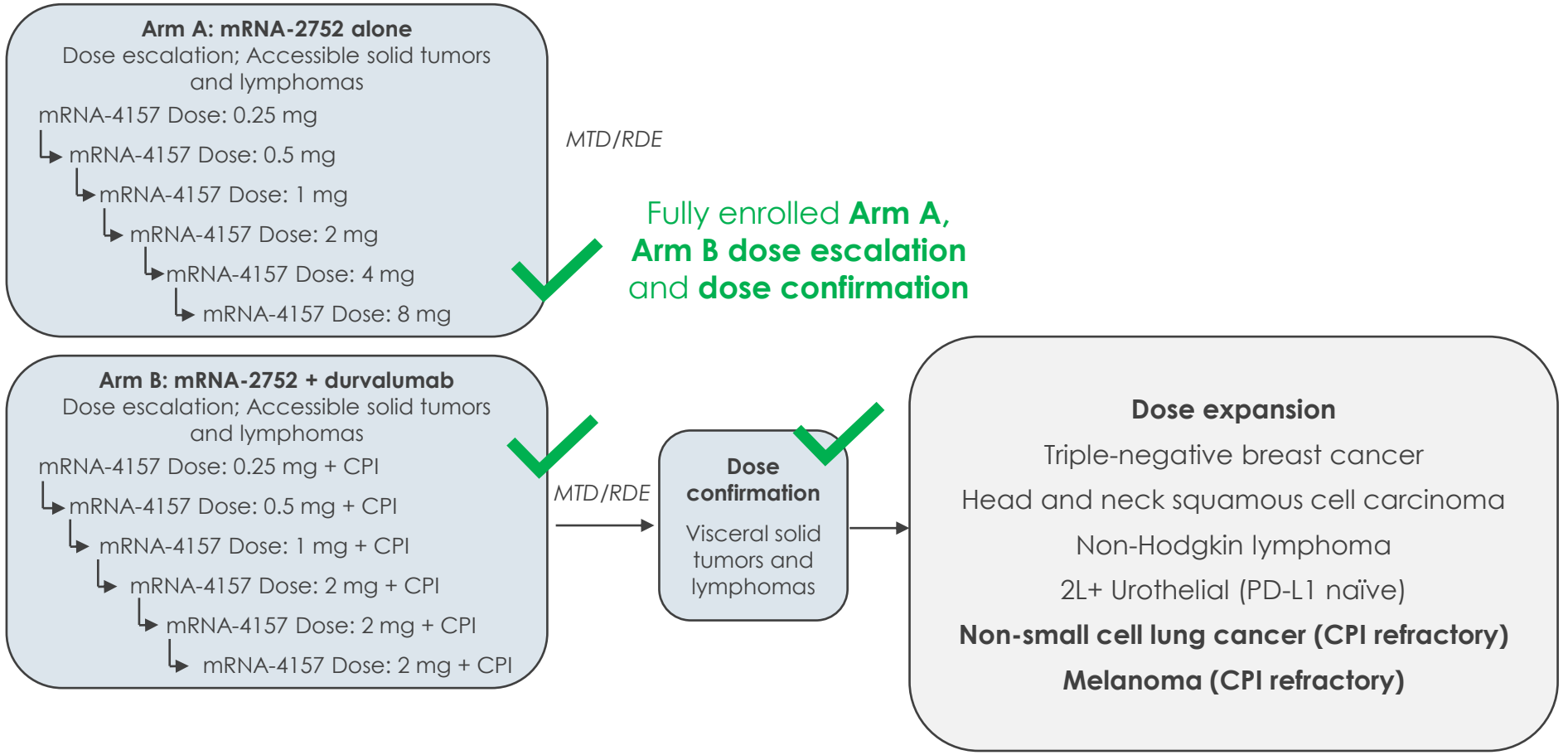
OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

Phase 1 ongoing; patients dosed in combination with durvalumab



Key Objectives

- Evaluate safety and tolerability of mRNA-2752 administered alone and in combination with PD-L1 inhibitor
- Define maximum tolerated dose (MTD) and recommended dose for expansion for mRNA-2752 alone and in combination with durvalumab
- Secondary Objectives: (1) Anti-tumor activity, (2) Protein expression in tumors and (3) Pharmacokinetics

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OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

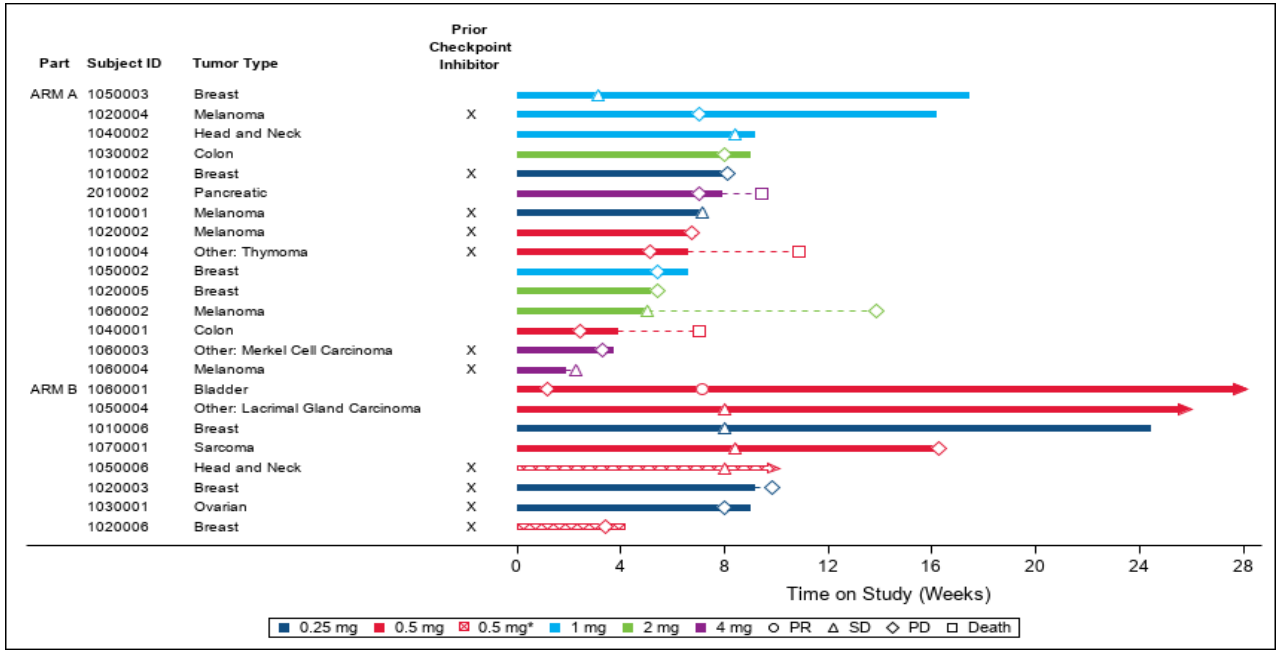
Preliminary Safety and Efficacy Data(ASCO 2020)

mRNA-2752-P101 Safety Data

Related Adverse Events*				
	Arm A		Arm B	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Injection site erythema	6	-	3	-
Injection site pain	6	-	2	-
Pyrexia	5	1**		
Chills	3	1**		
Fatigue	3	1**		
Alanine aminotransferase increased	2	-		
Aspartate aminotransferase increased	2	-		
Back pain	2	-		
Rash maculo-popular	2	-		
Injection site reaction	-	1**		
Malaise	-	1**		

*Treatment-related AEs reported once per patient. **All Gr 3 events observed in 1 patient @ 4mg dose
AEs: ≥ 2 patients (grade 1-2), ≥ 1 patient (grade 3), No Gr 4 or 5 AEs were reported

mRNA-2752-P101 Swimmer plot: per RECIST 1.1



17 patients on Arm A with duration on study up to 16 weeks. 12 patients on Arm B up to 28 weeks on study and continuing at time of data cutoff.

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High unmet medical need in checkpoint inhibitor (CPI) refractory melanoma

CPI refractory melanoma presents a **high unmet medical need with low survival rates**

- 8000 patients/year and no approved treatment
- mPFS 2-4.7 months

	ORR	Median PFS
KEYNOTE-002 (Pembro)	**22%**	2.9 months
CheckMate-037 (Nivo)	**27%**	3.1 months
Ipi/Nivo post Pembro (Zimmer et al. 2017)	**16%**	2.0 months
Low-dose Ipi + Pembro (n=70) (Olson et al, 2020, ASCO#10004)	**31%**	4.7 months

Target Population: Both primary refractory and secondary acquired resistance with progression on prior CPI as most recent treatment

- Primary CPI resistance: estimated ~40-65% pts
- Secondary acquired resistance: 39-43% pts at 3 years

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OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

- ✓ iTu mRNA-2752 as monotherapy and in combination with durvalumab is **tolerable at all dose levels studied**
- ✓ mRNA-2752 is associated with **tumor shrinkage** in **both injected** and **non-injected lesions** in both monotherapy and in combination
- ✓ These data **support the ongoing testing** of the mRNA-2752/durvalumab combination in Arm B of the Phase I study
  - Update to be shared at SITC 2021

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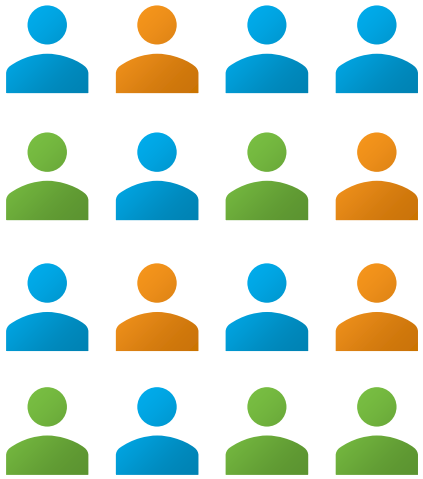
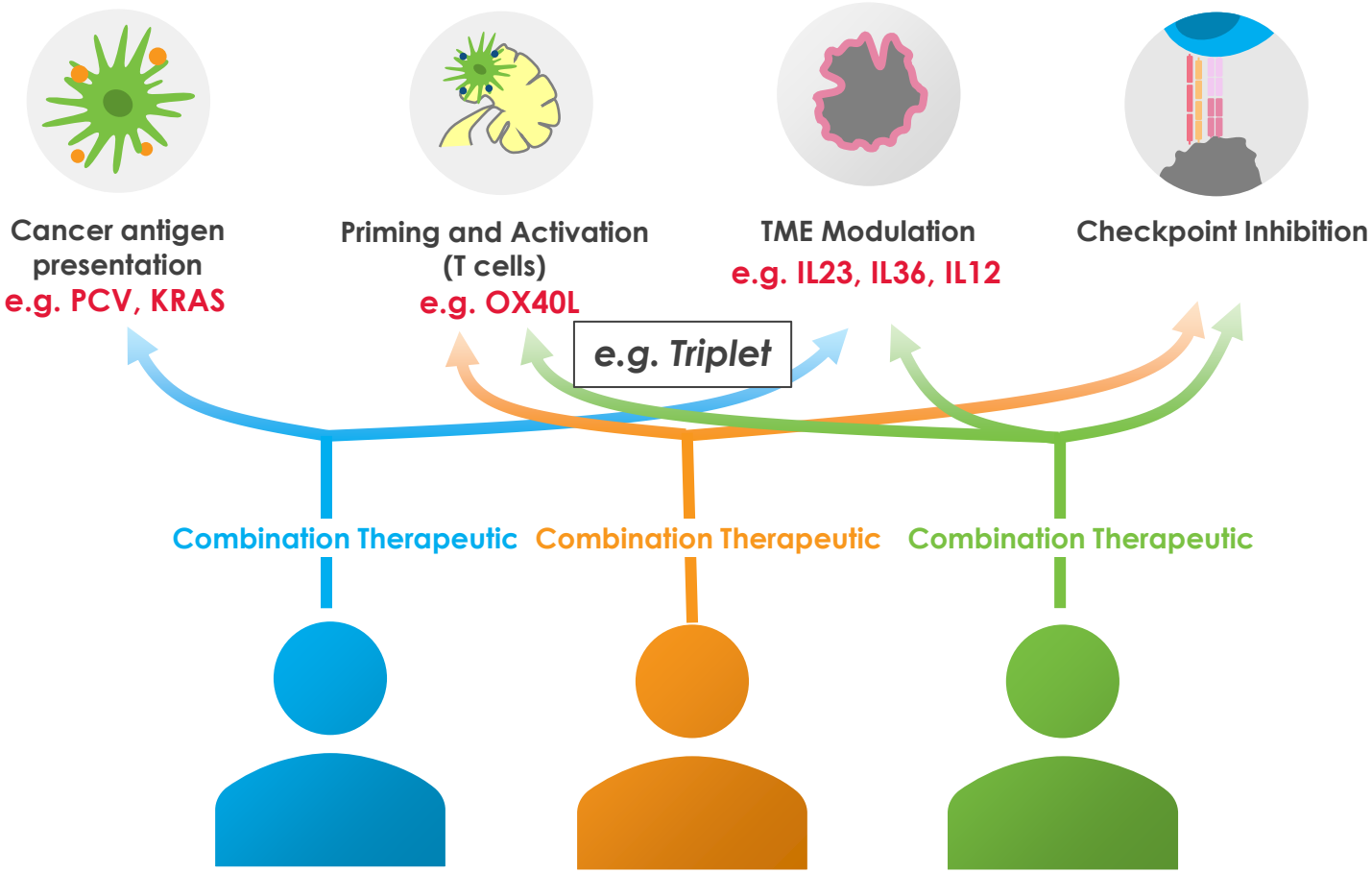
We believe mRNA will enable combination therapies personalized for individual tumors and patients

Response prediction based on immune signatures…



…is expected to lead to a rational combination of multiple IO approaches



Tailored treatment

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Moderna's therapeutics: IL-12

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with Merck
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with Merck
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						AZ to pay milestones and royalties
Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to ILCM free of charge

New development candidates

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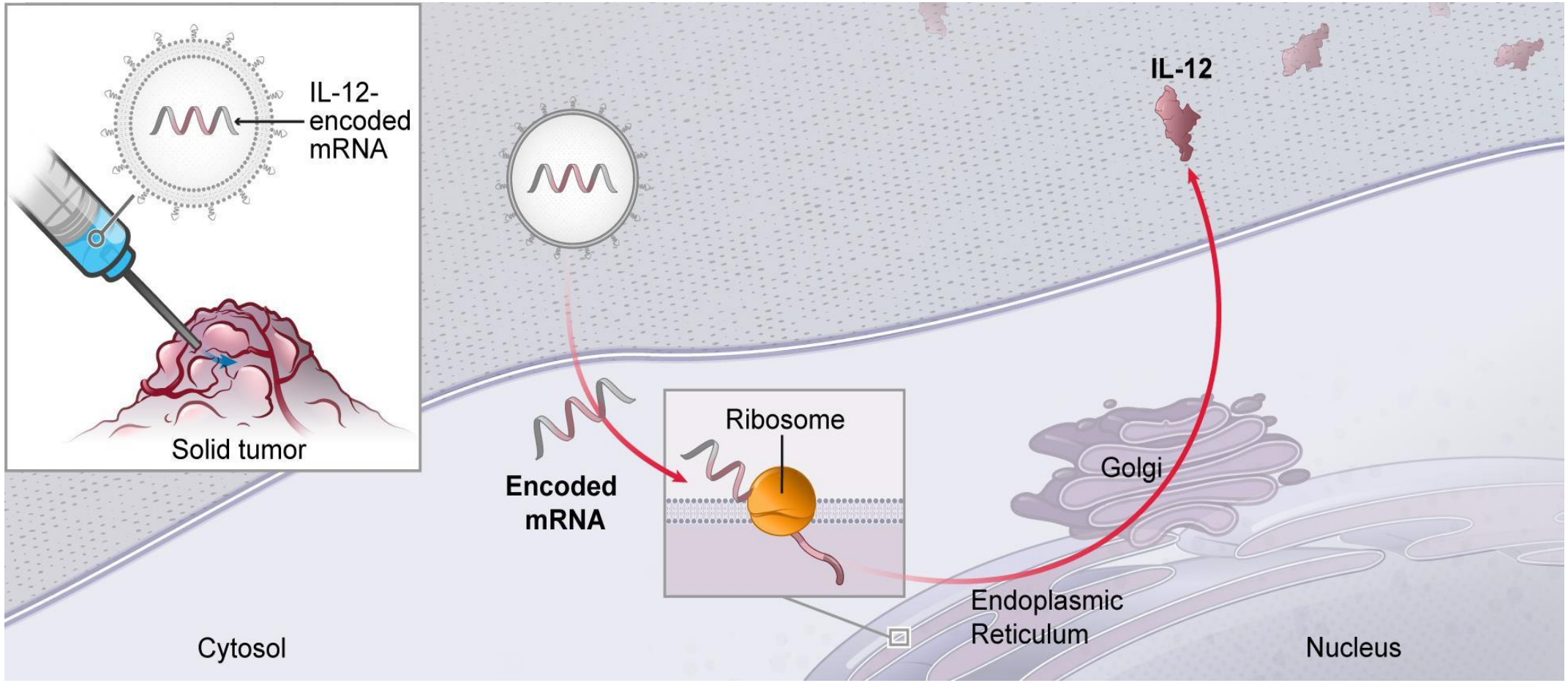
mRNA-encoding IL-12 (MEDI1191)

mRNA-encoded cytokine to activate tumor microenvironment



Dr. Ignacio Melero Bermejo

Co-Director and Professor,
Department of Immunology and Immunotherapy,
Clinica Universidad de Navarra (Spain)

Graduated (1988) in Medicine from the University of Navarra and a Ph.D. (1994), with an extraordinary doctorate award, from the Autonomous University of Madrid. He specialized in Immunology at the Hospital Universitario de la Princesa (Madrid, 1993). He worked for four years in the research center for Bristol Myers Squibb in Seattle (USA)

Co-director of the Immunology and Immunotherapy Service since 2015

Senior researcher at the Center for Applied Medical Research (CIMA)

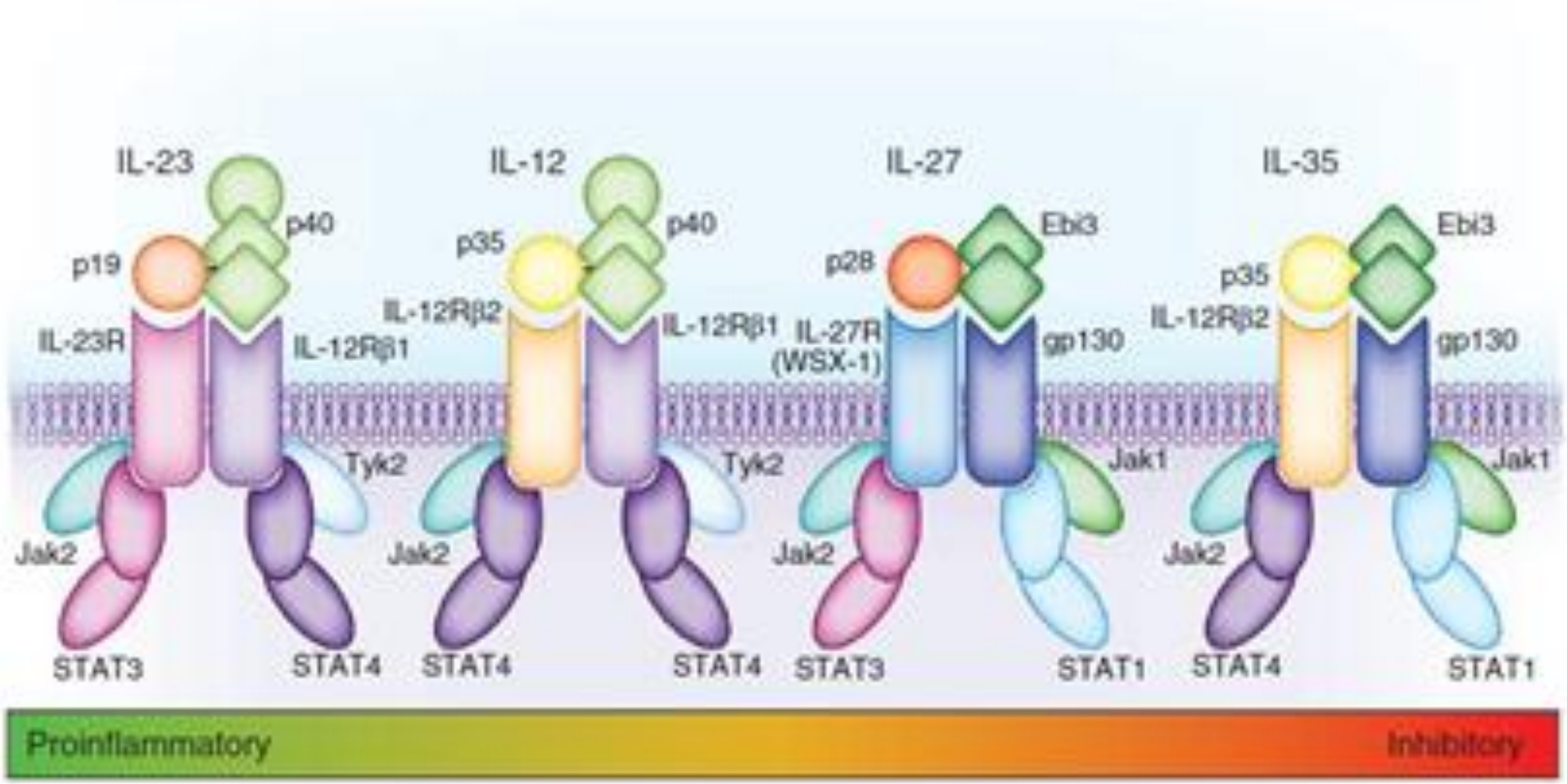
Research focus on cancer immunology and immunotherapy with a translational approach from experimental models to clinical trials.
He has conducted more than 40 clinical trials as principal investigator

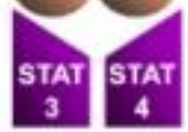
moderna

Interleukin-12 based immunotherapy of cancer

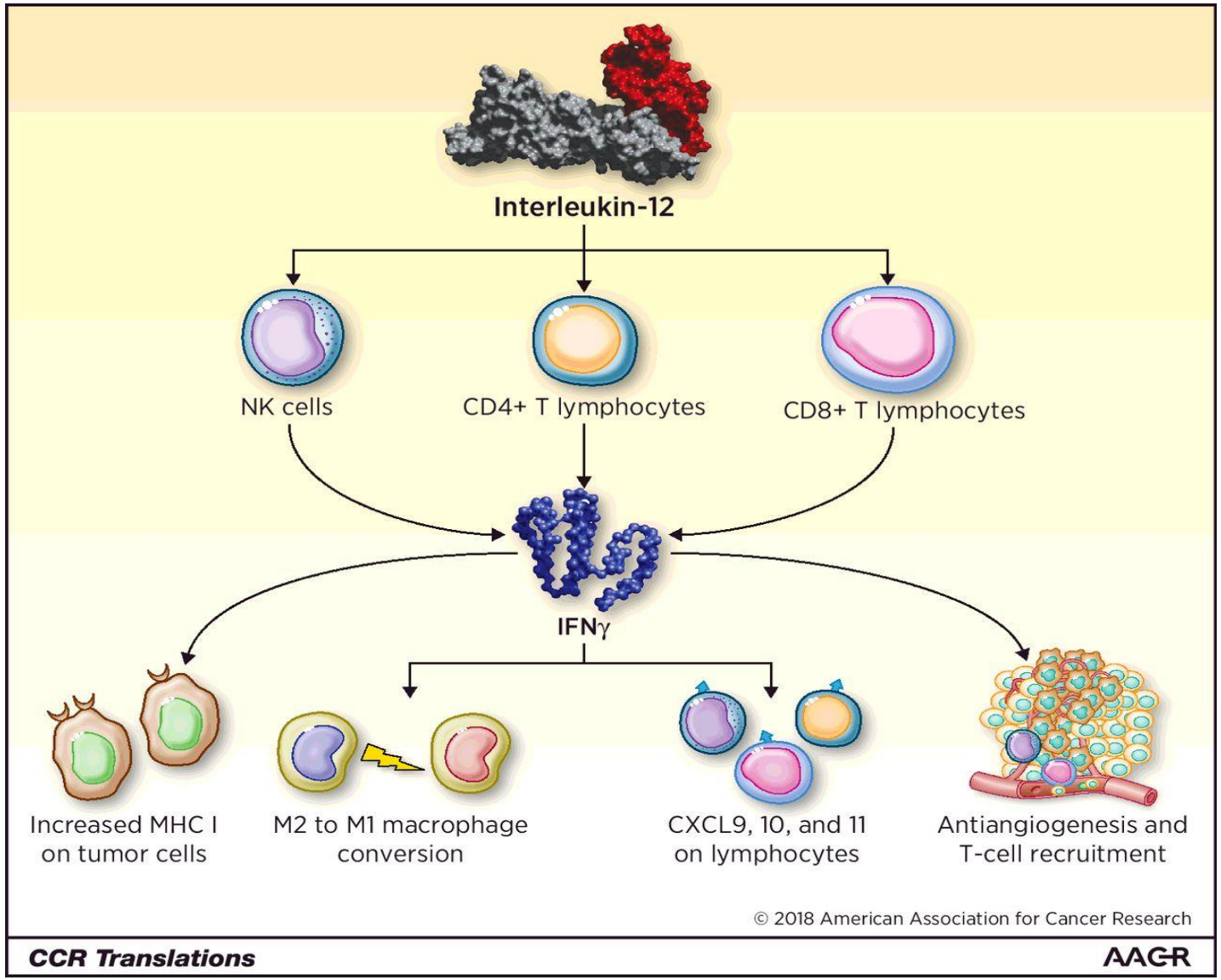
Ignacio Melero
imelero@unav.es

Interleukin-12 family



	IL-12	IL-23	IL-27	IL-35
Cytokines				
Receptors				
Kinases				
Vital STATs				
Also phos-phorylated	STAT 1/3/5	STAT 1/5	STAT 4/5	?
Cells that Produce	DCs, monocytes macrophages, B cells	DCs, monocytes macrophages, B cells	DCs, monocytes macrophages, B cells	Foxp3$^+$ T_{regs}, Others?
Cells that Respond	Naïve T cells Th1 cells NK cells	Memory T cells Th1 & Th17 cells NK cells	T cells Th1 cells NK cells	T cells, Others?
Function	Th1 activation Th1 maintenance Blocks Th2	Th1 activation Th17 polarization & proliferation	Th1 cell proliferation Skewing effector T cell lineages Blocks Th17	Inhibits T cell proliferation Additional?

Mechanisms of action of IL12.



Pedro Berraondo et al. Clin Cancer Res 2018;24:2716-2718

Clinical Cancer Research
AACR American Association for Cancer Research

Antitumor and Antimetastatic Activity of Interleukin 12 against Murine Tumors

By Michael J. Brunda,* Leopoldo Luistro,* Rajeev R. Warrier,‡ Rosemary B. Wright,* Brian R. Hubbard,§ Molly Murphy,§ Stanley F. Wolf,§ and Maurice K. Gately‡

*From the Departments of *Oncology and ‡Inflammation/Autoimmune Diseases, Hoffmann-La Roche Inc., Nutley, New Jersey 07110; and §Genetics Institute Inc., Cambridge, Massachusetts 02140*

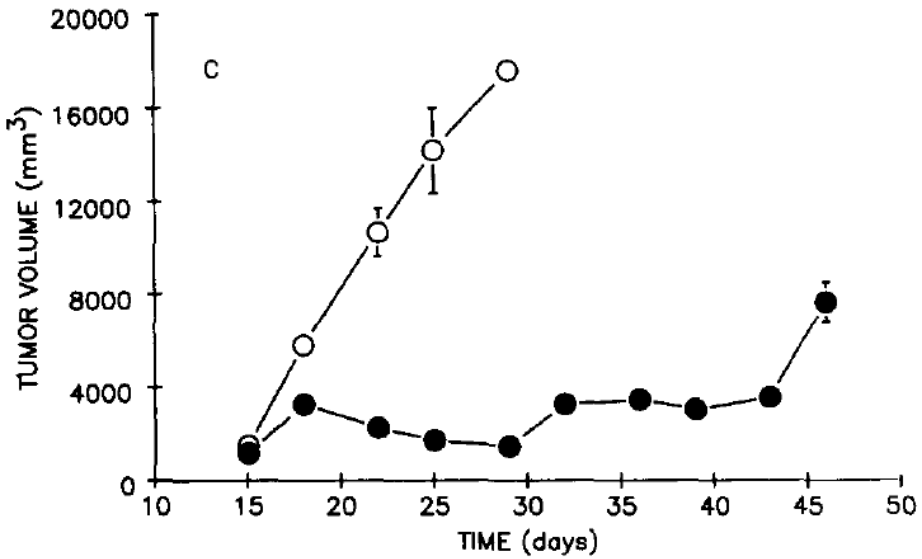


Figure 2. Inhibition of subcutaneous growth of B16F10 tumors. (*A*) Mice were injected subcutaneously with 10^6 B16F10 cells on day 0 and intraperitoneal treatment with diluent (○—○) or 5 μg (●—●), 1 μg (△—△), 0.1 μg (▲—▲), or 0.01 μg (□—□) of IL-12 was initiated on day 7. Mice were treated five times per week until animals were killed

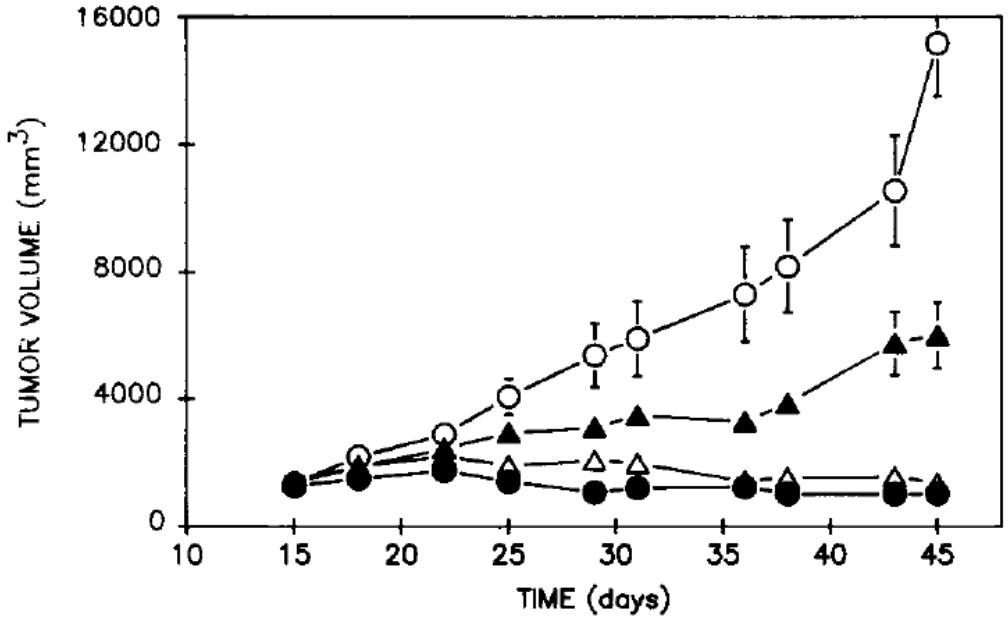


Figure 8. Effect of depletion of $CD4^+$ or $CD8^+$ T cells on antitumor efficacy of IL-12. Mice were injected subcutaneously with 10^6 Renca tumor cells on day 0 and intraperitoneal treatment five times per week until the end of the experiment with diluent (○—○) or 1 μg IL-12 (●—●) was

Phase I Evaluation of Intravenous Recombinant Human Interleukin 12 in Patients with Advanced Malignancies[1]

Michael B. Atkins,[2] Michael J. Robertson, Michael Gordon, Michael T. Lotze, Michelle DeCoste, Jon S. DuBois, Jerome Ritz, Alan B. Sandler, Howard D. Edington, Pamela D. Garzone, James W. Mier, Christine M. Canning, Linda Battiato, Hideaki Tahara, and Matthew L. Sherman

Tupper Research Institute and the Division of Hematology/Oncology, Tufts-New England Medical Center, Boston, Massachusetts 02111 [M. B. A., J. S. D., J. W. M.]; Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, Massachusetts 02115 [M. J. R., J. R., C. M. C.]; Division of Hematology/Oncology, Indiana University School of Medicine, Indianapolis, Indiana 46202 [M. G., A. B. S., L. B.]; Department of Surgical Oncology, Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania 15261 [M. T. L., H. D. E., H. T.]; and Genetics Institute, Inc., Cambridge, Massachusetts 02140 [M. D., P. D. G., M. L. S.]

ABSTRACT

A Phase I dose escalation trial of i.v. administered recombinant human interleukin 12 (rhIL-12) was performed to determine its toxicity, maximum tolerated dose (MTD), pharmacokinetics, and biological and potential antineoplastic effects. Cohorts of four to six patients with advanced cancer, Karnofsky performance ≥70%, and normal organ function received escalating doses (3–1000 ng/kg/day) of rhIL-12 (Genetics Institute, Inc.) by bolus i.v. injection once as an inpatient and then, after a 2-week rest period, once daily for five days every 3 weeks as an outpatient. Therapy was withheld for grade 3 toxicity (grade 4 hyperbilirubinemia or neutropenia), and dose escalation was halted if three of six patients experienced a dose-limiting toxicity (DLT). After establishment of the MTD, eight more patients were enrolled to further assess the safety, pharmacokinetics, and immunobiology of this dose.

Forty patients were enrolled, including 20 with renal cancer, 12 with melanoma, and 5 with colon cancer; 25 patients had received prior systemic therapy. Common toxicities included fever/chills, fatigue, nausea, vomiting, and headache. Fever was first observed at the 3 ng/kg dose level, typically occurred 8–12 h after rhIL-12 administration, and was incompletely suppressed with nonsteroidal anti-inflammatory drugs. Routine laboratory changes included anemia, neutropenia, lymphopenia, hyperglycemia, thrombocytopenia, and hypoalbuminemia. DLTs included oral stomatitis and liver function test abnormalities, predominantly elevated transaminases, which occurred in three of four patients at the 1000 ng/kg dose level. The 500 ng/kg dose level was determined to be the MTD. This dose, administered by this schedule, was associated with asymptomatic hepatic function test abnormalities in three patients and an onstudy death due to *Clostridia perfringens* septicemia but was otherwise well tolerated by the 14 patients treated in the dose escalation and safety phases. The $T_{1/2}$ elimination of rhIL-12 was calculated to be 5.3–9.6 h. Biological effects included dose-dependent increases in circulating IFN-γ, which exhibited attenuation with subsequent cycles. Serum neopterin rose in a reproducible fashion regardless of dose or cycle. Tumor necrosis factor α was not detected by ELISA. One of 40 patients developed a low titer antibody to rhIL-12. Lymphopenia was observed at all dose levels, with recovery occurring within several days of completing treatment without rebound lymphocytosis. There was one partial response (renal cell cancer) and one transient complete response (melanoma), both in previously untreated patients. Four additional patients received all proposed treatment without disease progression. rhIL-12 administered according to this schedule is biologically and clinically active at doses tolerable by most patients in an outpatient setting. Nonetheless, additional Phase I studies examining different schedules and the mechanisms of the specific DLTs are indicated before proceeding to Phase II testing.

INTRODUCTION

IL-12[3] is a heterodimeric cytokine with potent immunoregulatory activity. It was initially given the names natural killer cell stimulatory factor and cytotoxic lymphocyte maturation factor (1, 2) based on its stimulatory effects on these cytolytic lymphokine populations. The cDNAs encoding the two IL-12 subunits are unrelated and encode for two distinct proteins having molecular masses of approximately 35 and 40 kDa (3, 4). The p35 subunit is distantly related to IL-6, granulocyte colony-stimulating factor, and

Table 1. Clinical studies of systemic IL-12 alone

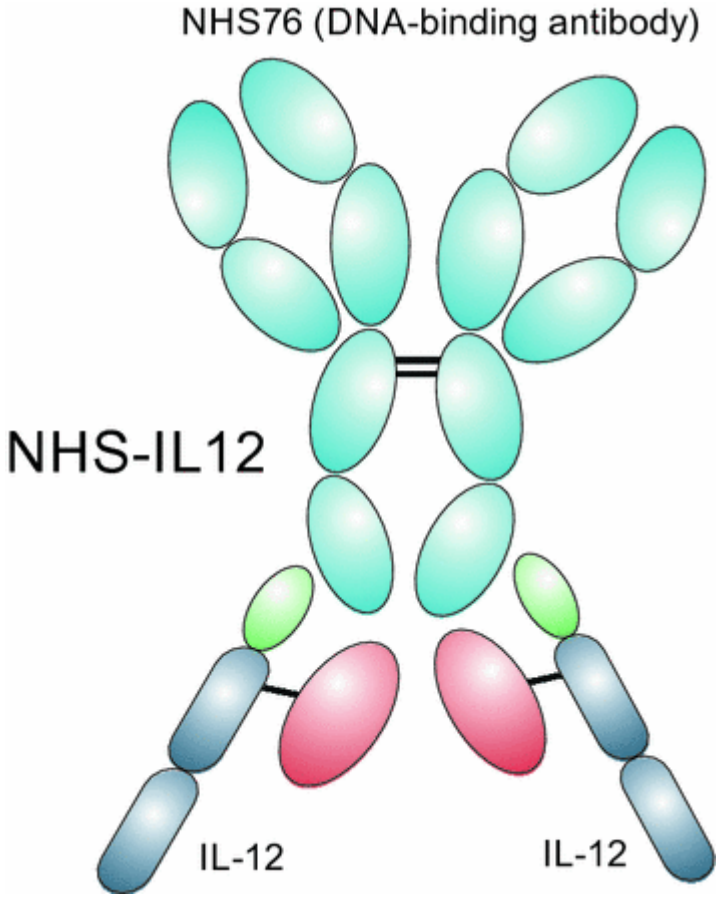
Tumors	Route of administration	Patients (*n*)	Objective response	Immune modulation	Angiogenesis-related effects
Different solid tumors*	i.v.	40	5%	Dose-dependent ↑ sIFN-γ; peak at 24-48 h after IL-12 ↓ $CD4^+/CD8^+$ and $CD16^+$ cells; nadir at 24 h after IL-12 ↑ of NK cell adhesion molecules (CD2, LFA-1)	ND
Melanoma*	s.c.	10	0% (three minor responses)	↑ sIFN-γ within 24 h after the first IL-12 injection ↑ IL-10 during the second cycle Lymphopenia and CD4/CD8 ratio inversion ↓ CD16+cells 24 h after the first injection ↑ Frequency of antitumor CTL precursors Tumor infiltration by CD8+ memory T cells	↓ Urine bFGF in two of three patients with minor responses
Renal cell carcinoma*	s.c.	51	2%	↑ sIFN-γ with peak level at 24 h after the first maintenance dose	ND
Cutaneous T cell lymphoma*	s.c. or intralesionally	10	56%	↑ $CD8^+$ and/or $TIA\text{-}1^+$ T cells in skin biopsy from regressing lesions	ND
Melanoma, renal cell carcinoma*	i.v.	28	3%	Induction of IFN-γ, IL-15 and IL-18, maintained in patients with tumor regression or prolonged disease stabilization	ND
Renal cell carcinoma †	s.c.	30	7%	↑ sIFN-γ, IL-10 and neopterin, maintained in cycle 2	ND
Abdominal tumors*	i.p.	29	7%	↑ Peritoneal $CD3^+$ and ↓ $CD14^+$ cells	↓ bFGF and VEGF in tumor
Head-neck carcinoma*	Intratumoral	10	ND	↑ $CD56^+$ NK cells in the primary tumor High IFN-γ mRNA expression at lymph node level	ND
AIDS-related Kaposi's sarcoma*	s.c.	34	50% (71% at highest doses)	↑ sIFN-γ after first dose, persisting after week 4	↑ sIP-10 after the first dose, persisting after week 4
Mycosis fungoides †	s.c.	23	43%	ND	ND
Non–Hodgkin's lymphoma and Hodgkin's lymphoma †	i.v. or s.c.	42	21% ‡	↑ Circulating $CD8^+$ T cells	↓ sVEGF and sbFGF in 37% of patients

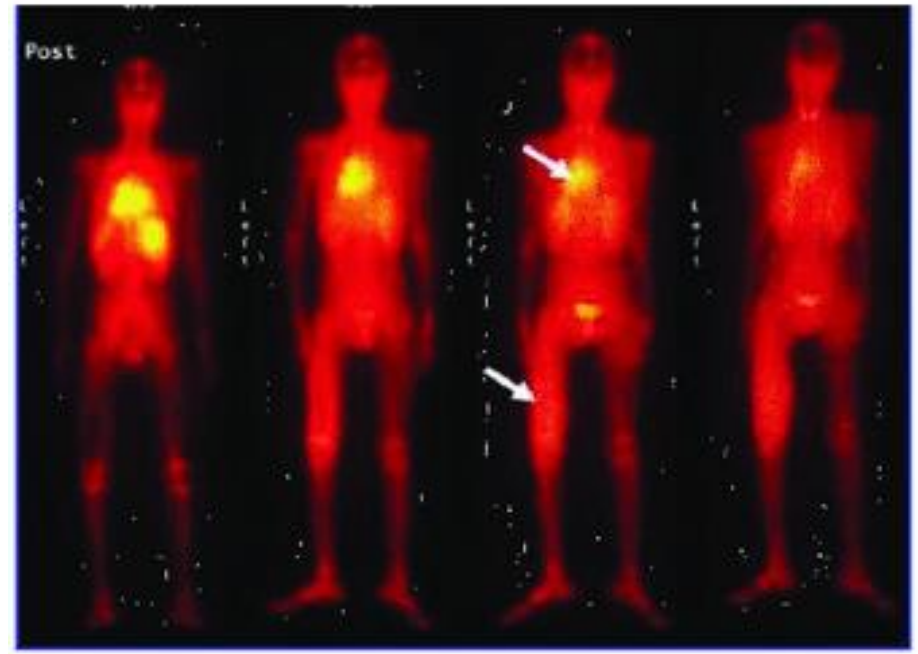
Table 2. Clinical studies of systemic IL-12 in combination with vaccines, other cytokines, or antitumor monoclonal antibodies

Tumors	Combined treatment	Patients (*n*)	Objective response	Immune modulation	Angiogenesis-related effects	Refs.
Melanoma*	gp100 and tyrosinase peptides	48	ND	Age-specific immune response against the peptide vaccine, as shown by ↑IFN-γ release in most patients	ND	(70)
	Melan-A/Mart-1 and influenza peptides	28	8%	↑ sIFN-γ within 24 h after the first IL-12 injection	ND	(71)
	Melan-A/Mart-1 peptide-pulsed PBMC†	20	10%	↑ IFN-γ–producing T cells directed to Melan-A/Mart-1 after vaccination	ND	(72)
Melanoma, renal cell carcinoma*	IL-2	28	11%	↑ IFN-γ production and expansion of NK cells	↑ IP-10 production	(73)
	IFN-α2b	26	11%	CD80 and IFN-γ induction in PBMCs of selected patients by RT-PCR	RT-PCR on PBMCs showed induction of IP-10 and IFN-γ in selected patients	(74)
HER2+ tumors*	Trastuzumab	15	6%	↑ IFN-γ production by NK cells in responsive or stable patients; associated with IFN-γ gene polymorphism	↑ sMIP-1α, TNF-α and IP-10	(75)

Systemic IL-12 has not ever been combined with an anti-PD-1 agent in humans

Considering the loop: IL-12……..IFNgamma…….PD-L1


NHS76 (DNA-binding antibody)
NHS-IL12
IL-12
IL-12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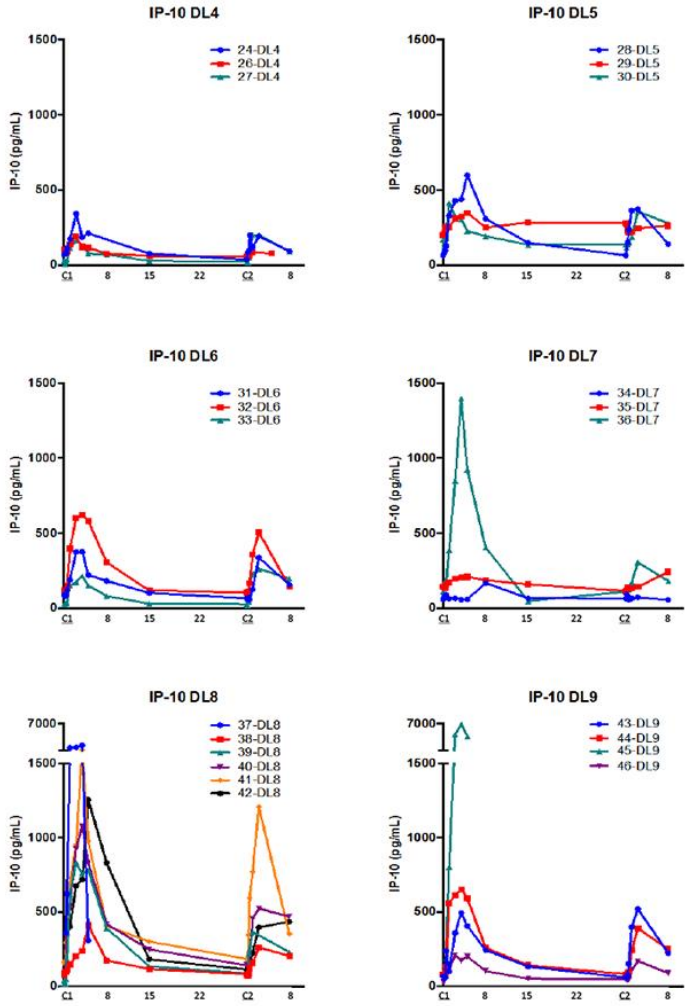

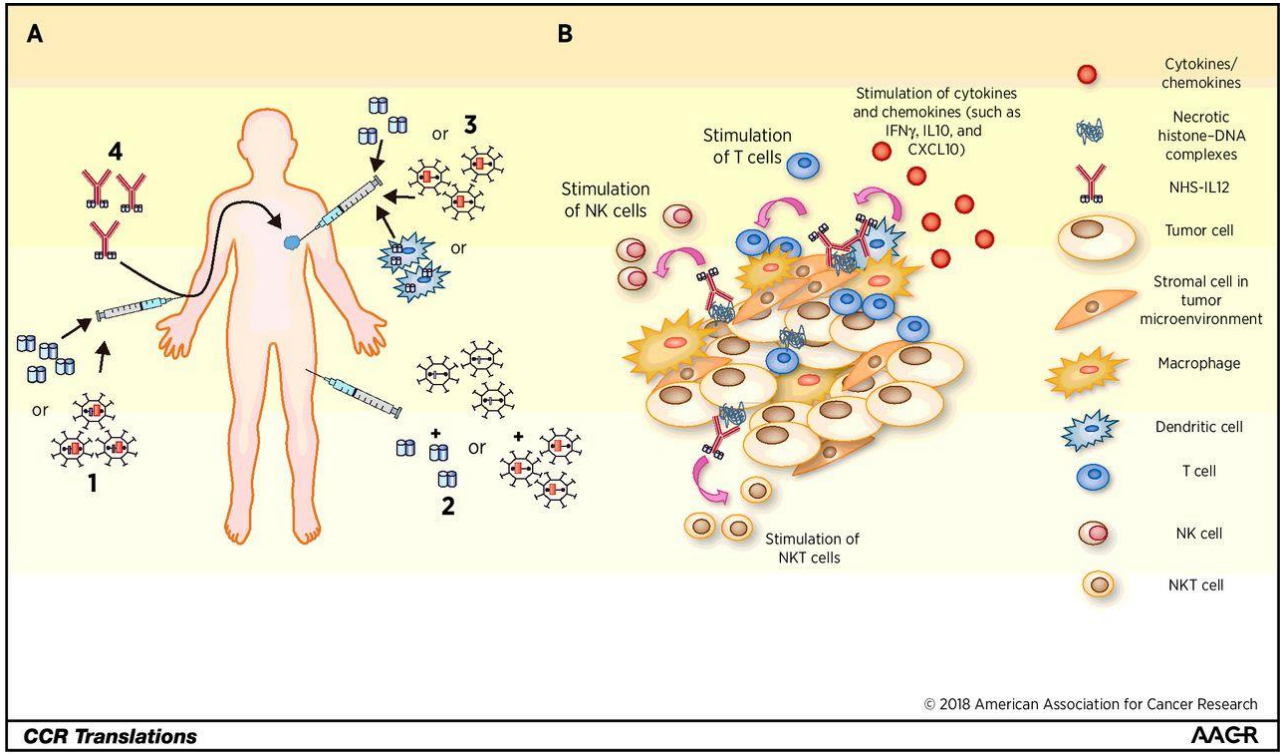

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A Phase Ib Study to Evaluate the Safety, Tolerability, and Pharmacokinetics (PK) of Avelumab in Combination With M9241(NHS-IL12) (JAVELIN IL-12) (COMBO)

study is the responsibility of the study sponsor and investigators. Listing a study by the U.S. Federal Government. Read our disclaimer for details.

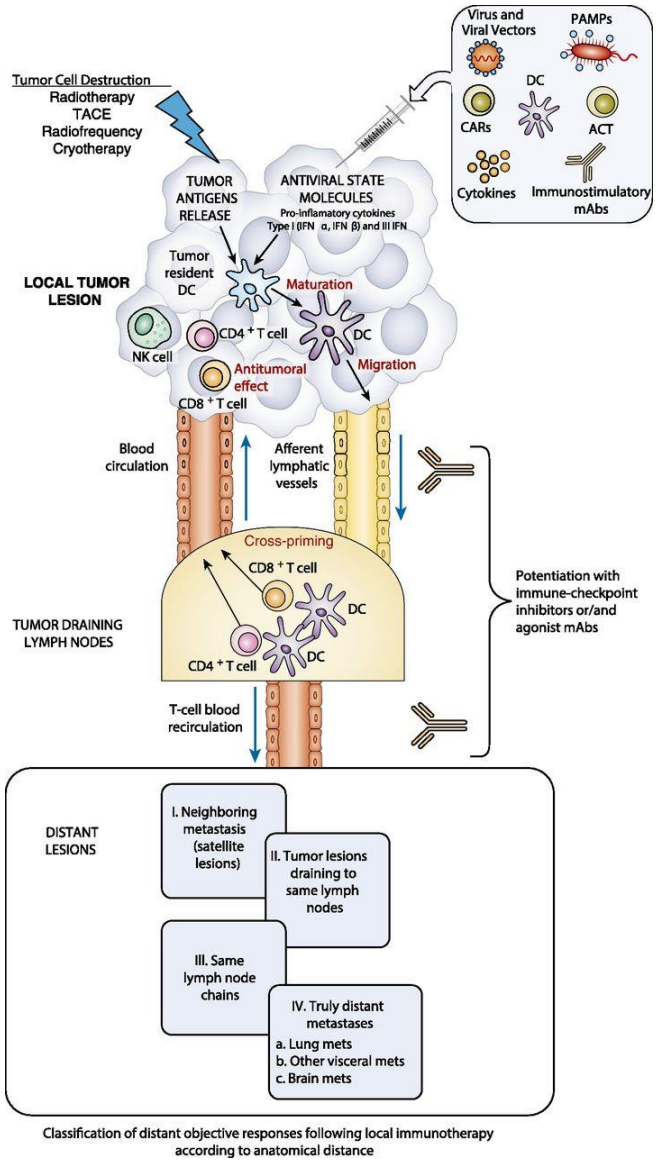
ClinicalTrials.gov Identifier: NCT02994953

Recruitment Status : Terminated (The study got discontinued due to lack of efficacy)
First Posted : December 16, 2016
Last Update Posted : December 17, 2020

INTERLEUKIN-12 a case for intratumoral or localized approaches?

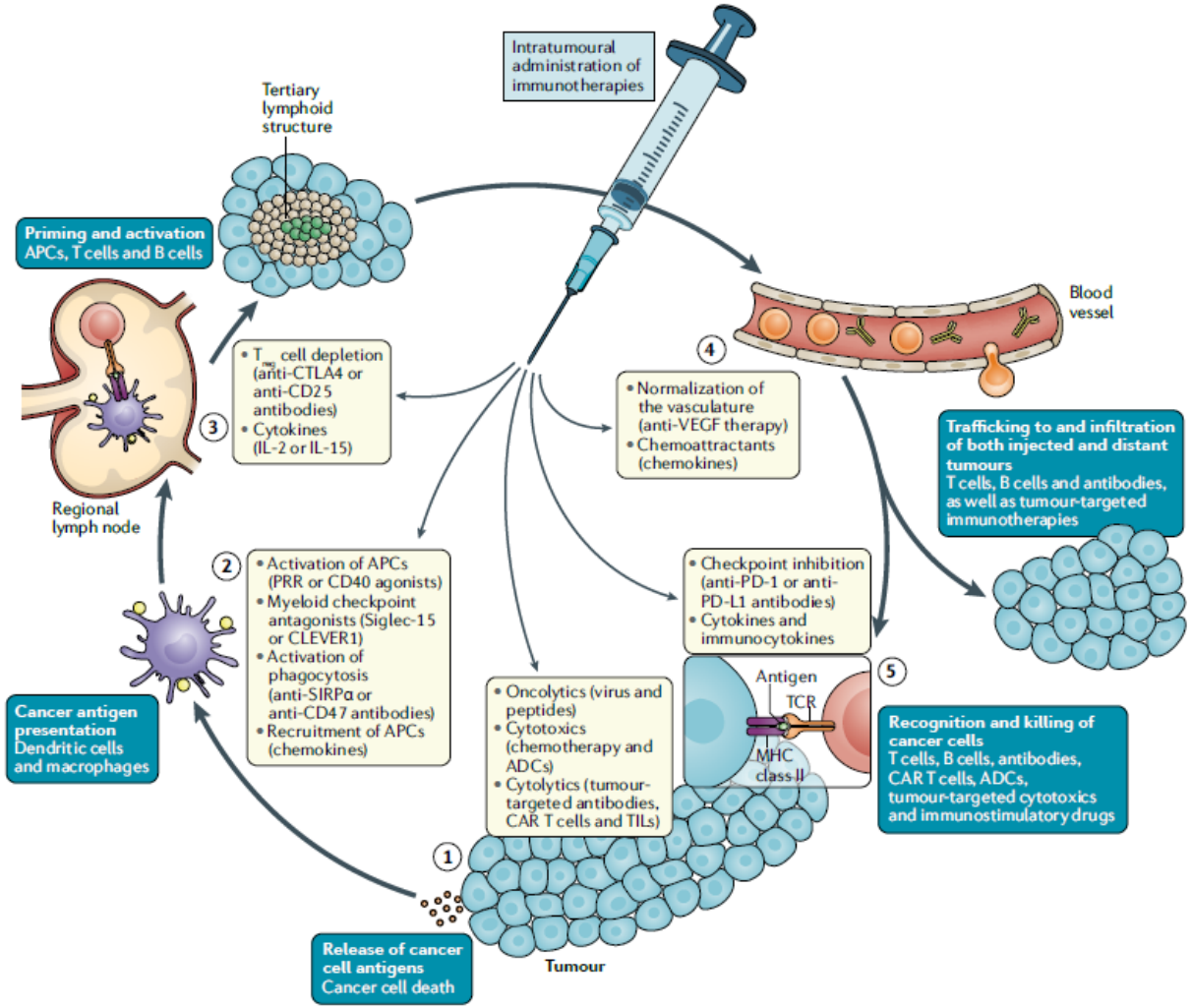
Local Gene therapy?

Concept of local immunotherapy with systemic (abscopal) effect.



Classification of distant objective responses following local immunotherapy according to anatomical distance

M. Angela Aznar et al. J Immunol 2017;198:31-39



I. Melero et al. Nature reviews clinical oncology 2021

b SWOT analysis of intratumoural immunotherapy

Internal

Strengths
- Increased intratumoural bioavailability (therapeutic index)
- Lower systemic exposure, reducing the risk of irAEs
- Enables the use of multiple synergistic combinations

Weaknesses
- Requirements relating to logistics, staffing, beds and other resources need to be addressed to implement and increase the treatment capacity and quality in clinical trials of intratumoural immunotherapy
- Skilled radiologists or interventional radiologists are required for the treatment of deep-seated tumours

External

Opportunities
- Current boom in local immunotherapy studies, including first-in-human, phase I–III, industry-sponsored and academic trials
- Amenable to longitudinal and multisite studies
- Early pharmacodynamics readouts are possible

Threats
- Close coordination is needed to ensure the quality of clinical research
- Precision in data recording and reporting is required for both injected and non-injected lesions
- Appropriate radiological assessments are needed (such as itRECIST)

Phase I Trial of Intratumoral Injection of an Adenovirus Encoding Interleukin-12 for Advanced Digestive Tumors

Bruno Sangro, Guillermo Mazzolini, Juan Ruiz, Maite Herraiz, Jorge Quiroga, Ignacio Herrero, Alberto Benito, Javier Larrache, Jesus Pueyo, Jose Carlos Subtil, Cristina Olagüe, Josu Sola, Belén Sádaba, Carlos Lacasa, Ignacio Melero, Cheng Qian, and Jesus Prieto

A B S T R A C T

Purpose
To evaluate the feasibility and safety of intratumoral injection of an adenoviral vector encoding human interleukin-12 genes (Ad.IL-12) and secondarily, its biologic effect for the treatment of advanced digestive tumors.

Patients and Methods
Ad.IL-12 was administered in doses ranging from 2.5×10^{10} to 3×10^{12} viral particles, to seven cohorts of patients with advanced pancreatic, colorectal, or primary liver malignancies. Patients were thoroughly assessed for toxicity, and antitumor response was evaluated by imaging techniques, tumor biopsy, and hypersensitivity skin tests. Patients with stable disease and no serious adverse reactions were allowed to receive up to 3 monthly doses of Ad.IL-12.

Results
Twenty-one patients (nine with primary liver, five with colorectal, and seven with pancreatic cancers) received a total of 44 injections. Ad.IL-12 was well tolerated, and dose-limiting toxicity was not reached. Frequent but transient adverse reactions, including fever, malaise, sweating, and lymphopenia, seemed to be related to vector injection rather than to transgene expression. No cumulative toxicity was observed. In four of 10 assessable patients, a significant increase in tumor infiltration by effector immune cells was apparent. A partial objective remission of the injected tumor mass was observed in a patient with hepatocellular carcinoma. Stable disease was observed in 29% of patients, mainly those with primary liver cancer.

Conclusion
Intratumoral injection of up to 3×10^{12} viral particles of Ad.IL-12 to patients with advanced digestive malignancies is a feasible and well-tolerated procedure that exerts only mild antitumor effects.

J Clin Oncol 22:1389-1397. © 2004 by American Society of Clinical Oncology

Intratumoral Injection of Dendritic Cells Engineered to Secrete Interleukin-12 by Recombinant Adenovirus in Patients With Metastatic Gastrointestinal Carcinomas

Guillermo Mazzolini, Carlos Alfaro, Bruno Sangro, Esperanza Feijoó, Juan Ruiz, Alberto Benito, Iñigo Tirapu, Ainhoa Arina, Josu Sola, Maite Herraiz, Felipe Lucena, Cristina Olagüe, José Subtil, Jorge Quiroga, Ignacio Herrero, Belén Sádaba, Maurizio Bendandi, Cheng Qian, Jesús Prieto, and Ignacio Melero

A B S T R A C T

Purpose
To evaluate the feasibility and safety of intratumoral injection of autologous dendritic cells (DCs) transfected with an adenovirus encoding interleukin-12 genes (AFIL-12) for patients with metastatic gastrointestinal carcinomas. Secondarily, we have evaluated biologic effects and antitumoral activity.

Patients and Methods
Seventeen patients with metastatic pancreatic (n = 3), colorectal (n = 5), or primary liver (n = 9) malignancies entered the study. DCs were generated from CD14+ monocytes from leukapheresis, cultured and transfected with AFIL-12 before administration. Doses from 10×10^6 to 50×10^6 cells were escalated in three cohorts of patients. Patients received up to three doses at 21-day intervals.

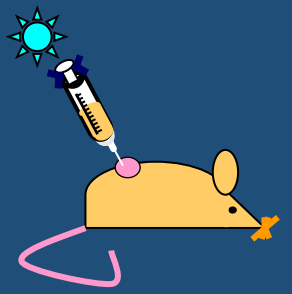
Results
Fifteen (88%) and 11 of 17 (65%) patients were assessable for toxicity and response, respectively. Intratumoral DC injections were mainly guided by ultrasound. Treatment was well tolerated. The most common side effects were lymphopenia, fever, and malaise. Interferon gamma and interleukin-6 serum concentrations were increased in 15 patients after each treatment, as well as peripheral blood natural killer activity in five patients. DC transfected with AFIL-12 stimulated a potent antibody response against adenoviral capsides. DC treatment induced a marked increase of infiltrating CD8+ T lymphocytes in three of 11 tumor biopsies analyzed. A partial response was observed in one patient with pancreatic carcinoma. Stable disease was observed in two patients and progression in eight patients, with two of the cases fast-progressing during treatment.

Conclusion
Intratumoral injection of DC transfected with an adenovirus encoding interleukin-12 to patients with metastatic gastrointestinal malignancies is feasible and well tolerated. Further studies are necessary to define and increase clinical efficacy.

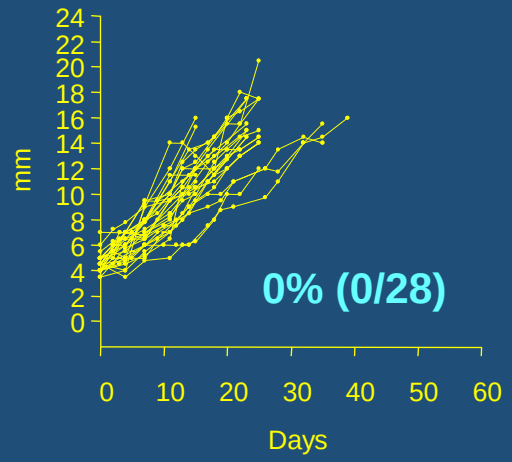
J Clin Oncol 23:999-1010. © 2005 by American Society of Clinical Oncology

ANTITUMOR EFFICACY OF SFV-IL12 IN scMC38

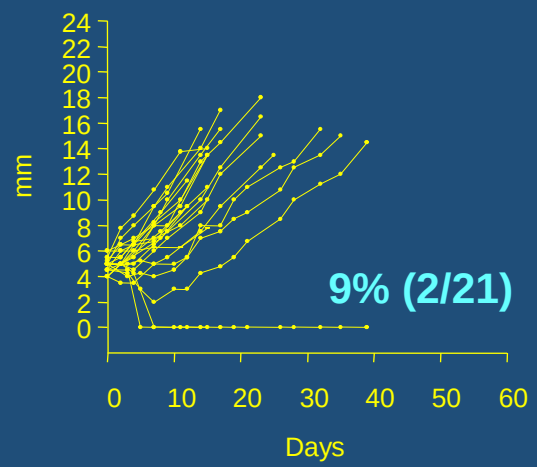
SFV-IL-12



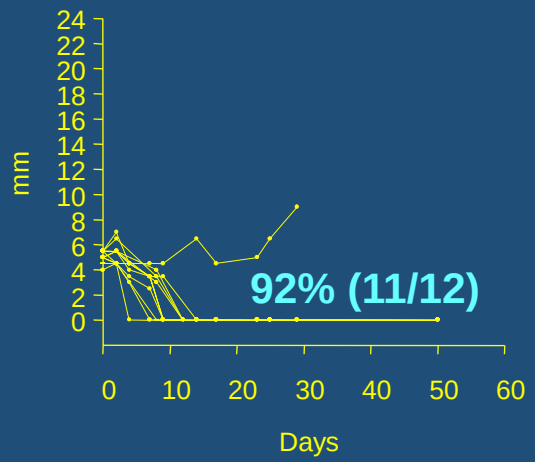
Saline



SFV-LacZ (10^8 pv)



SFV IL-12 (10^8 pv)



Rodriguez-Madoz et al. Mol Ther. 2005

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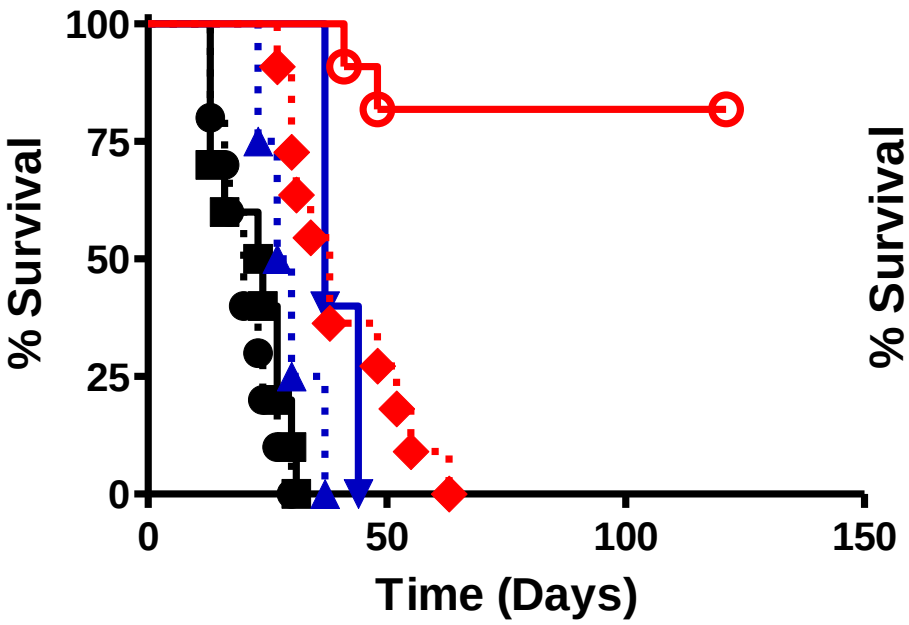
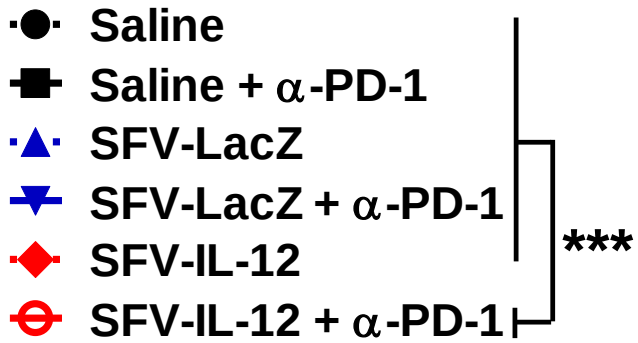
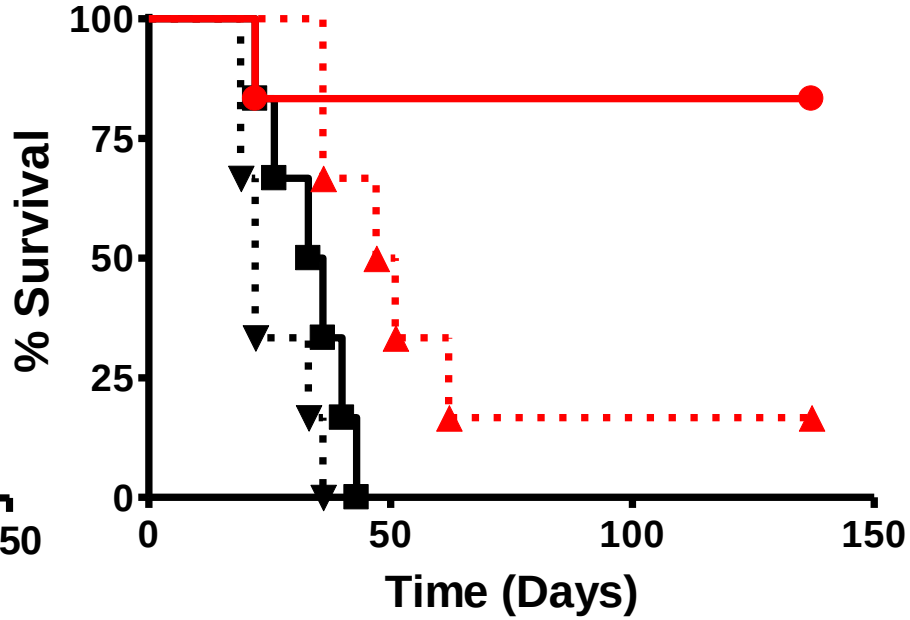
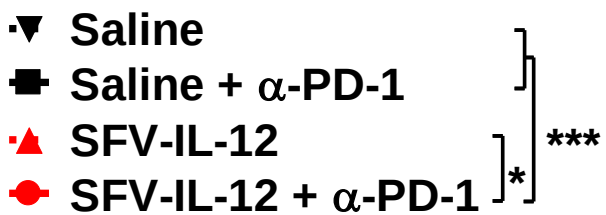




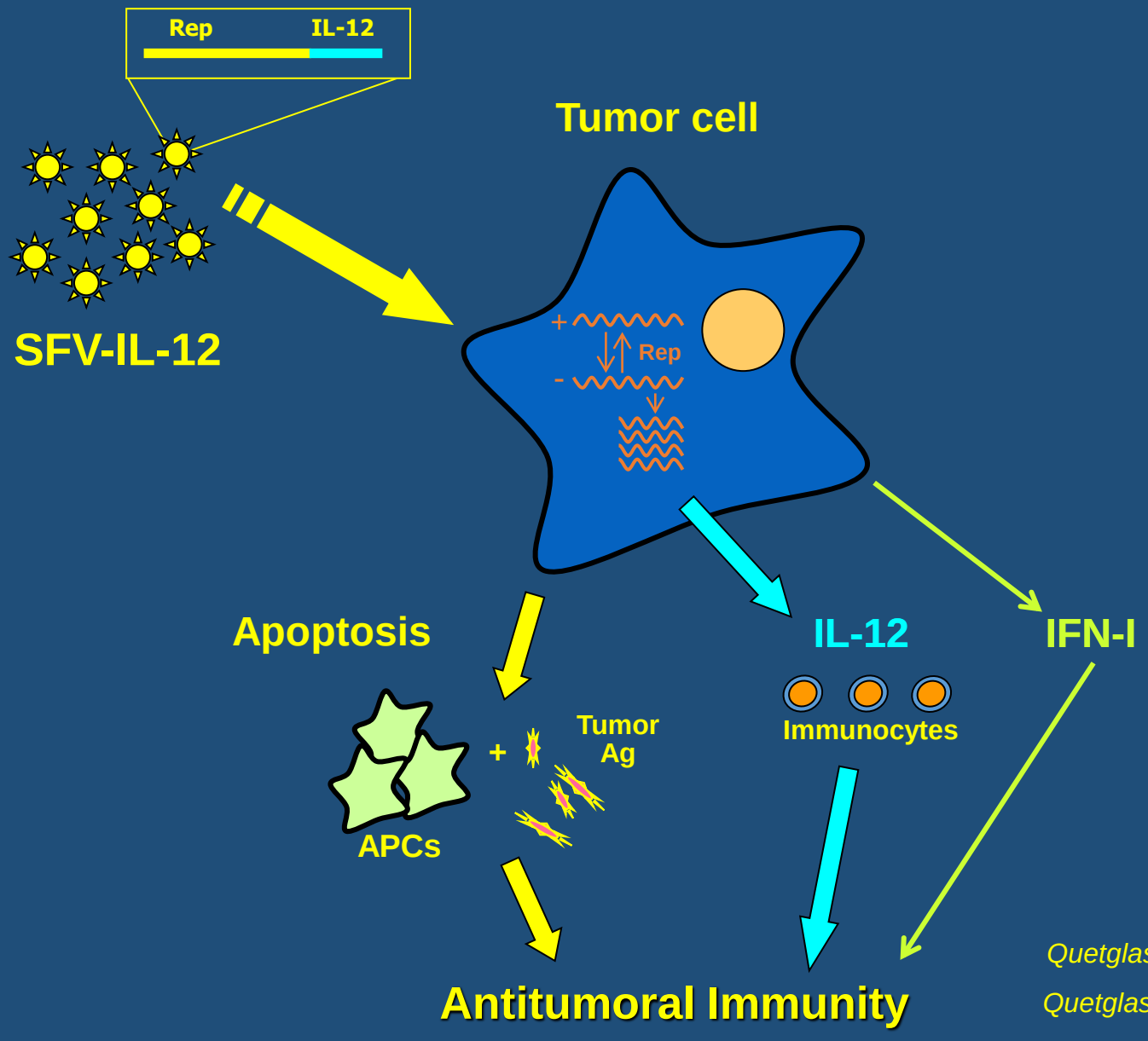
MC38





Quetglas et al., Cancer Immunol. Res. 2015

ANTITUMORAL MECHANISMS MEDIATED BY SFV

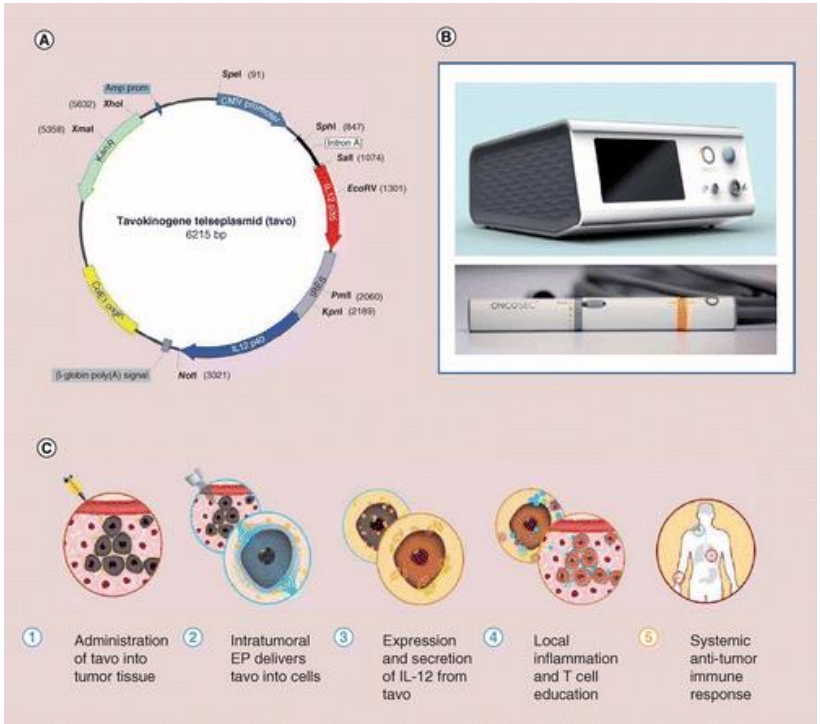


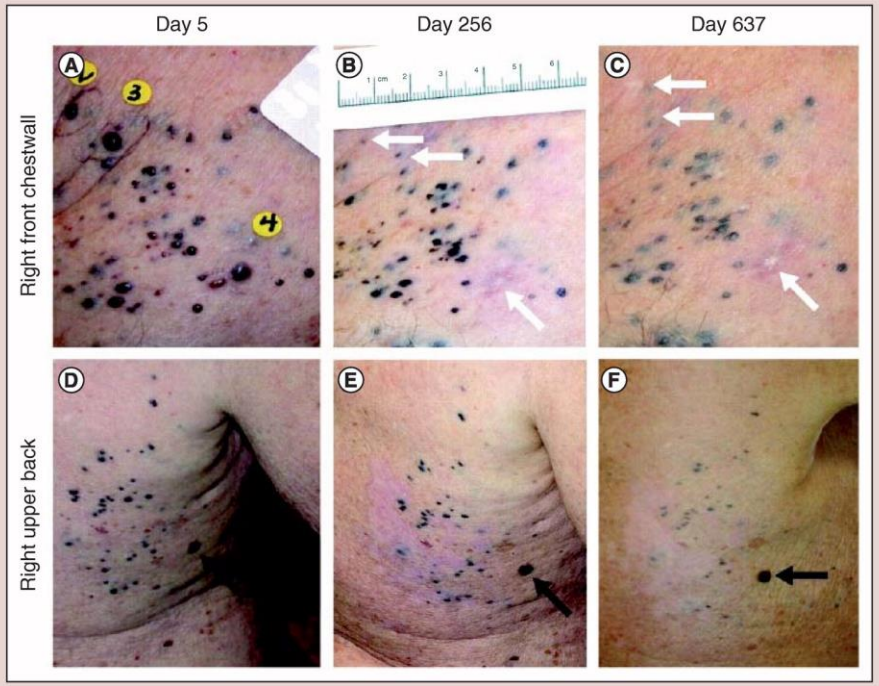
Quetglas, et al., Virus Res. 2010

Quetglas et al., Gene Ther. 2012

Melero et al. 2015

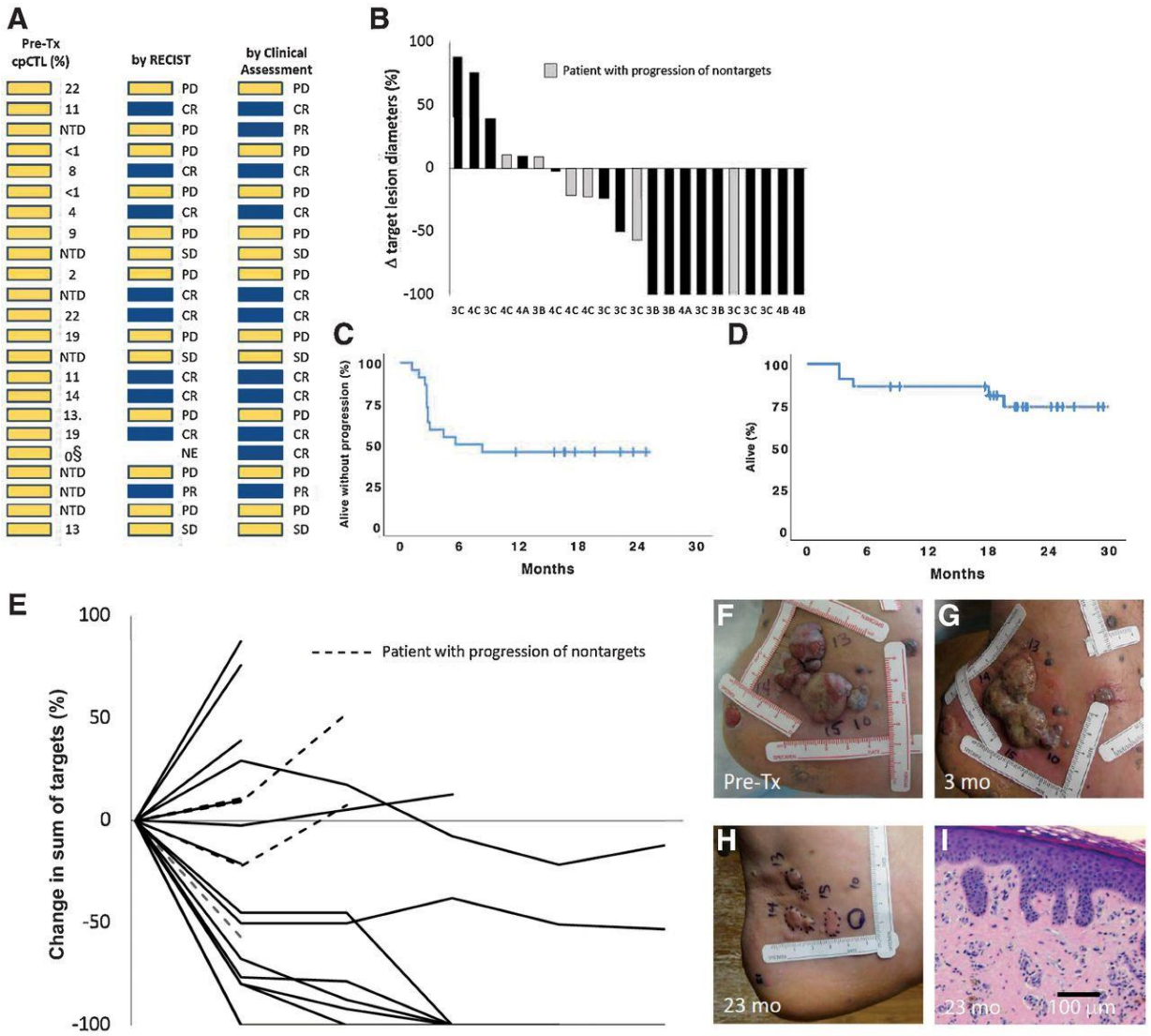
tavokinogene telseplasmid





In combination with Pembrolizumab

Individuals initiated the first cycle of i.t.-tavo-EP concurrently with the first injection of pembrolizumab, receiving both on day 1 of the first cycle. Pembrolizumab was administered on day 1 of each 3-week cycle. I.t.-tavo-EP was administered on days 1, 5, and 8 of every odd cycle (every 6 weeks; cycles 1, 3, 5, 7, etc.).



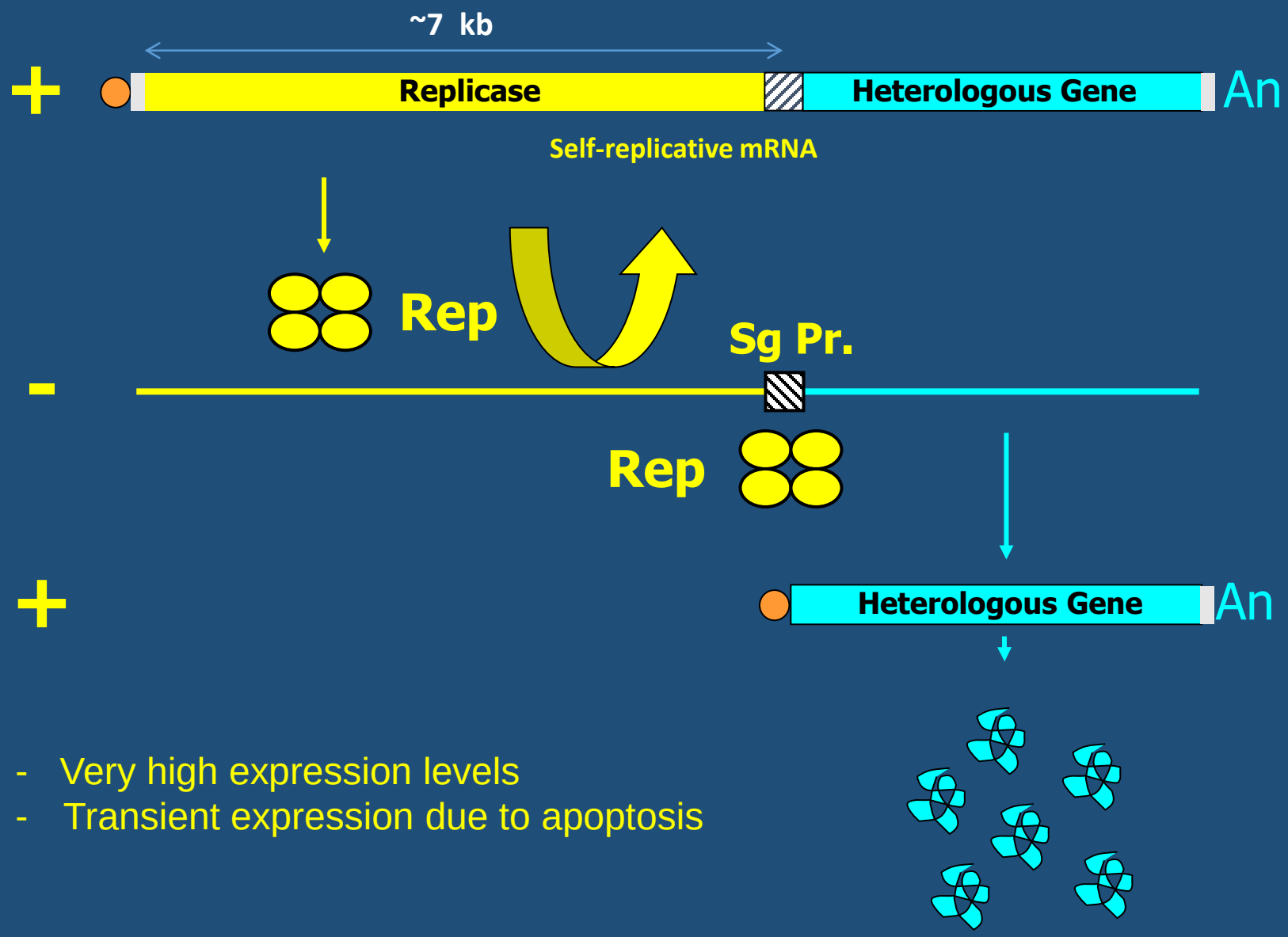
Alain P. Algazi et al. Clin Cancer Res 2020;26:2827-2837

LOCAL DELIVERY OF INTERLEUKIN-12

Delivery strategy	Description	Indications	Clinical trial identifier	Phase
Immunocytokines				
NHS-IL12	Fusion protein of IL-12 and antibody	Advanced solid tumors	NCT01417546	I
		Advanced solid tumors (*with avelumab*)	NCT02994953	I
Plasmid-based IL-12 delivery				
GEN-1	Lipopolymer containing pIL-12	Ovarian cancer (*with carboplatin and paclitaxel*)	NCT03393884	I/II
		Ovarian cancer	NCT02480374	I
Virus-based IL-12 delivery				
Ad5-yCD/mutTKSR39rep-hIL12	Oncolytic adenovirus-mediated cytotoxic and IL-12 gene therapy	Metastatic pancreatic cancer	NCT03281382	I
		Prostate cancer	NCT02555397	I
Ad-RTS-hIL-12	Inducible adenoviral vector engineered to express hIL-12	Pediatric brain tumor, diffuse intrinsic pontine glioma (*with veledimex*)	NCT03330197	I
		Recurrent/progressive glioblastoma (*with veledimex*)	NCT03679754	I
		R/P glioblastoma (*with veledimex and cemiplimab*)	NCT04006119	II
		Glioblastoma (*with veledimex and nivolumab*)	NCT03636477	I
		GBM, anaplastic oligoastrocytoma (*with veledimex*)	NCT02026271	I
M032	HSV-1 expressing IL-12	Recurrent/progressive glioma, anaplastic astrocytoma, or gliosarcoma	NCT02062827	I
Cell-based IL-12 delivery				
CAR-T therapy	Fourth generation CAR-T cells expressing IL-12 (and/or IL-7 and CCL19)	Nectin4-positive advanced malignant solid tumor	NCT03932565	I
mRNA-based IL-12 delivery				
SAR441000	mRNA encoding scIL-12, IL-15sushi, IFNα, and GM-CSF	Advanced solid tumors (± *cemiplimab*)	NCT03871348	I
MEDI1191	Lipid nanoparticles (LNP) encapsulating mRNA encoding IL-12	Advanced solid tumors (*with durvalumab*)	NCT03946800	I

G Nguyen
Frontiers in immunol

Replicon RNA vector RNA VECTOR

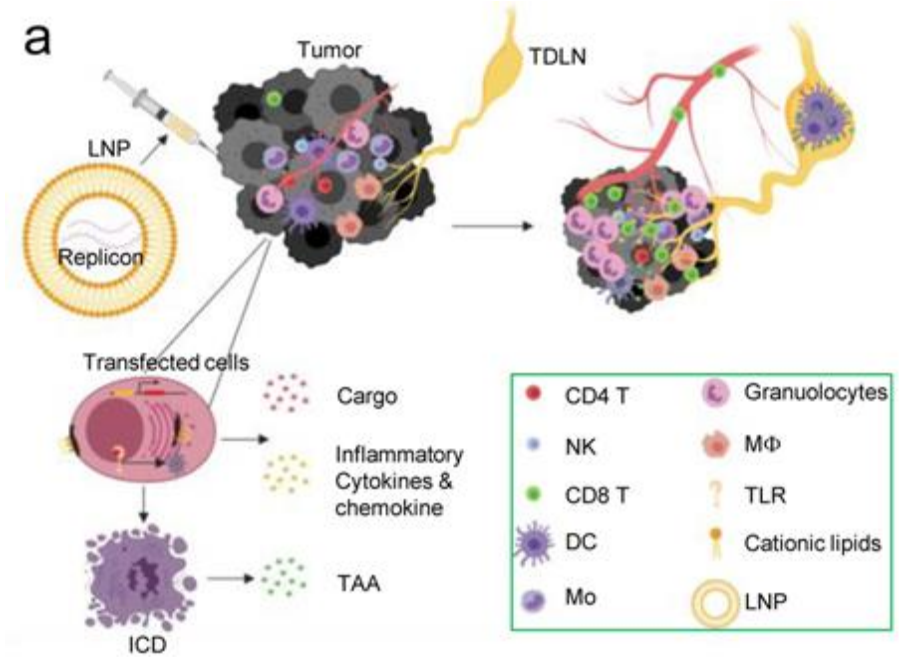


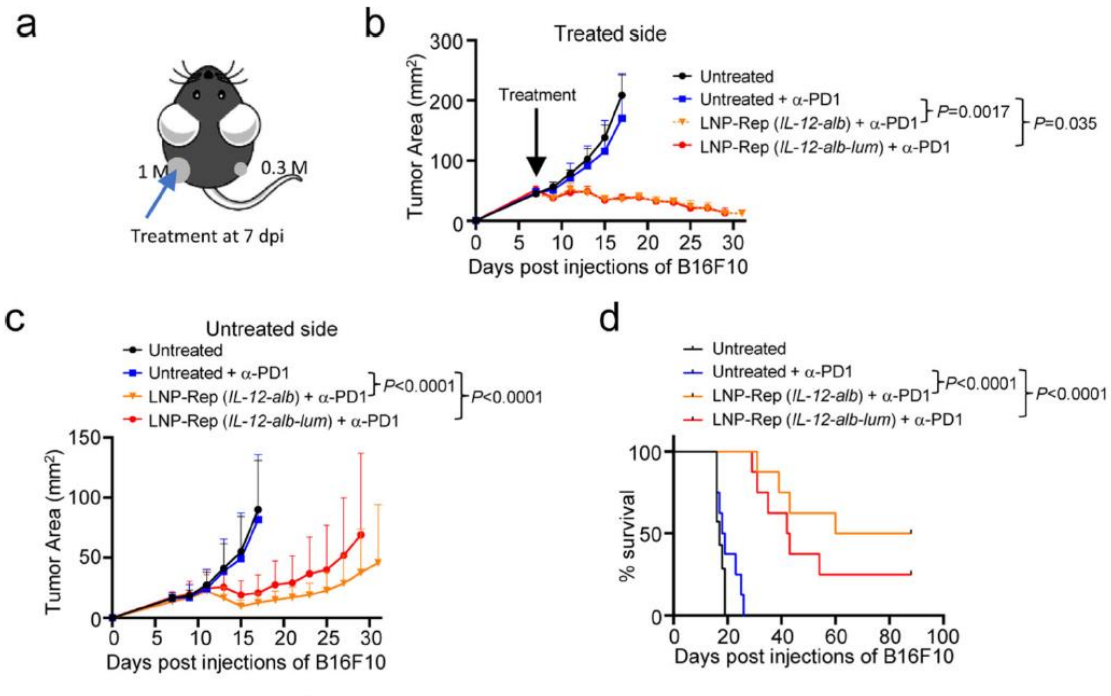
- Very high expression levels
- Transient expression due to apoptosis

Nat Cancer. 2020 September ; 1(9): 882–893. doi:10.1038/s43018-020-0095-6.

Multifunctional oncolytic nanoparticles deliver self-replicating IL-12 RNA to eliminate established tumors and prime systemic immunity

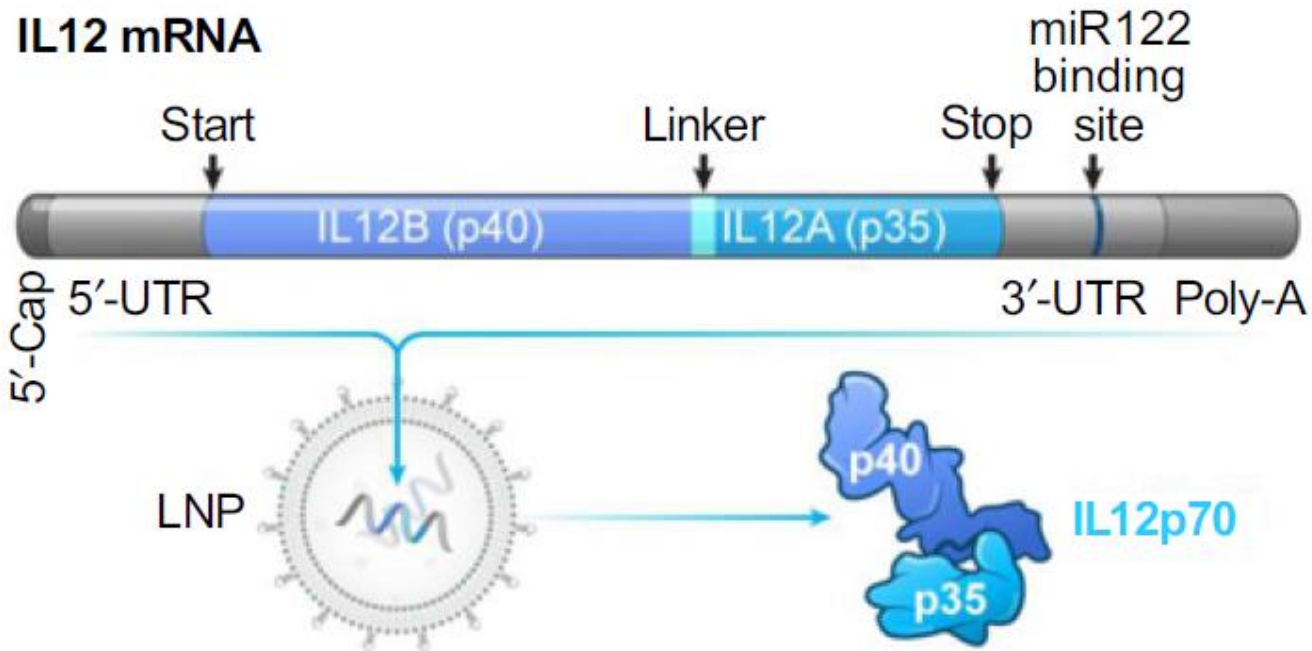
Yingzhong Li[1,2], Zhijun Su[2], Weiyu Zhao[4], Xinfu Zhang[4], Noor Momin[1,2], Chengxiang Zhang[4], K. Dane Wittrup[1,2,3], Yizhou Dong[*,4], Darrell J. Irvine[*,1,2,5,6,7], Ron Weiss[*,1,2]





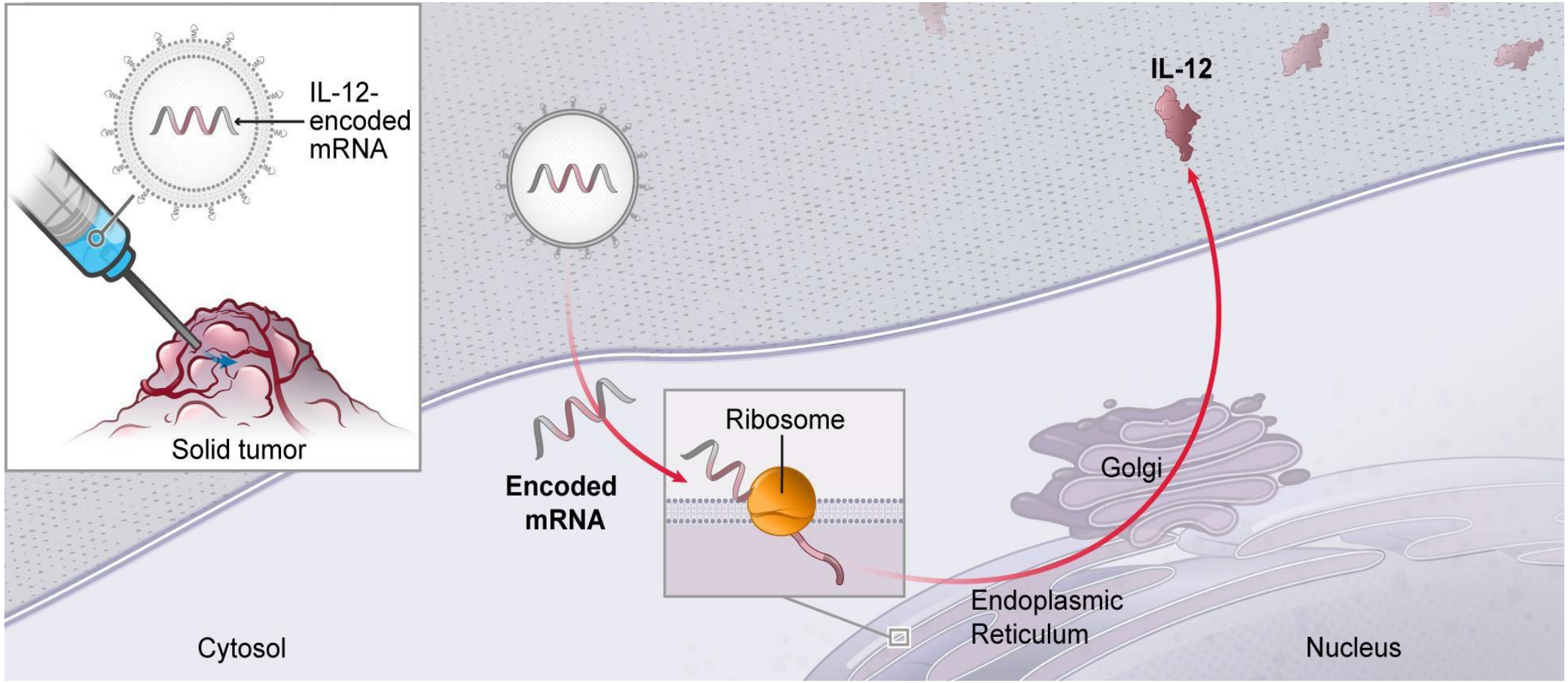
Intratumoral IL12 mRNA Therapy Promotes TH1 Transformation of the Tumor Microenvironment

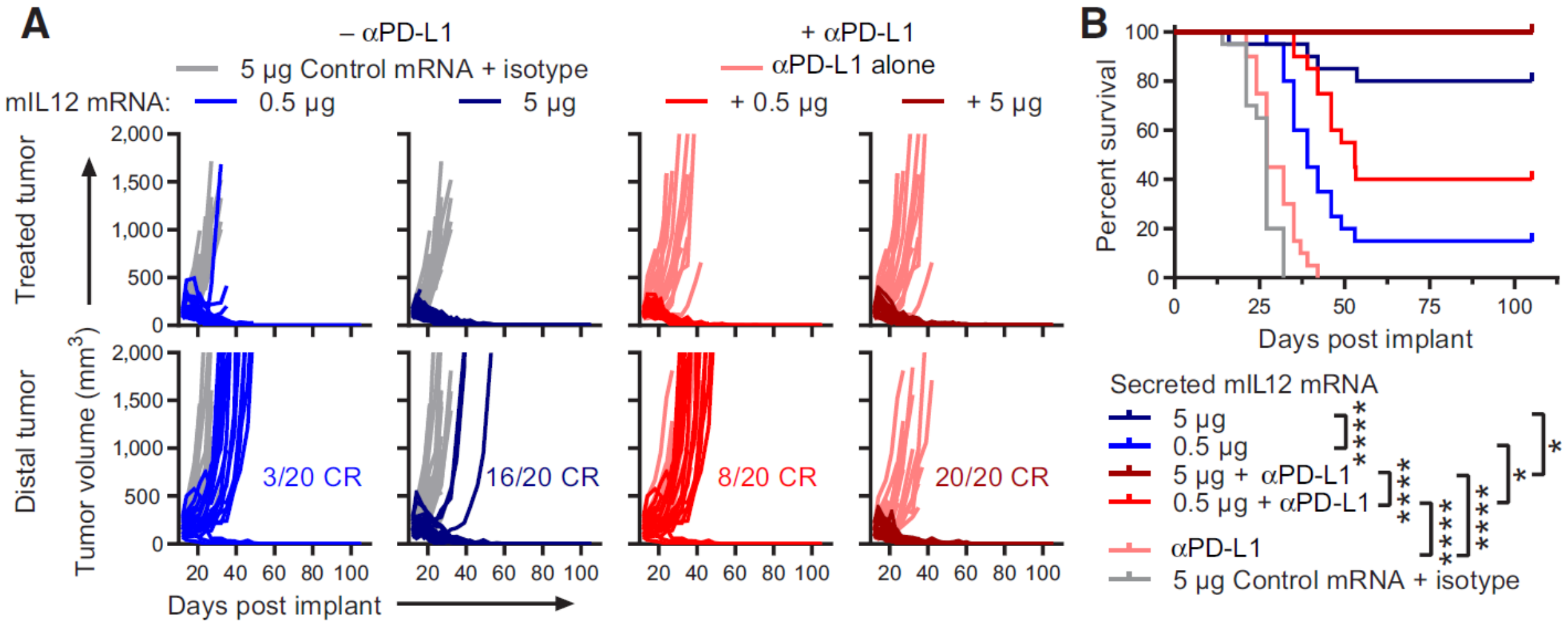
Susannah L. Hewitt[1], Dyane Bailey[1], John Zielinski[1], Ameya Apte[1], Faith Musenge[1], Russell Karp[1], Shannon Burke[2], Fabien Garcon[2], Ankita Mishra[1], Sushma Gurumurthy[1], Amanda Watkins[2], Kristen Arnold[1], James Moynihan[3], Eleanor Clancy-Thompson[3], Kathy Mulgrew[3], Grace Adjei[2], Katharina Deschler[2], Darren Potz[1], Gordon Moody[3], David A. Leinster[2], Steve Novick[2], Michal Sulikowski[2], Chris Bagnall[2], Philip Martin[3], Jean-Martin Lapointe[2], Han Si[3], Chris Morehouse[3], Maja Sedic[1], Robert W. Wilkinson[2], Ronald Herbst[3], Joshua P. Frederick[1], and Nadia Luheshi[2]



mRNA-encoding IL-12 (MEDI1191)

mRNA-encoded cytokine to activate tumor microenvironment




A
– αPD-L1
+ αPD-L1
5 µg Control mRNA + isotype
αPD-L1 alone
mIL12 mRNA:
0.5 µg
5 µg
+ 0.5 µg
+ 5 µg
Treated tumor
Distal tumor
Tumor volume (mm3)
2,000
1,500
1,000
500
0
20 40 60 80 100
Days post implant
3/20 CR
16/20 CR
8/20 CR
20/20 CR
B
Percent survival
100
80
60
40
20
0
0 25 50 75 100
Days post implant
Secreted mIL12 mRNA
5 µg
0.5 µg
5 µg + αPD-L1
0.5 µg + αPD-L1
αPD-L1
5 µg Control mRNA + isotype
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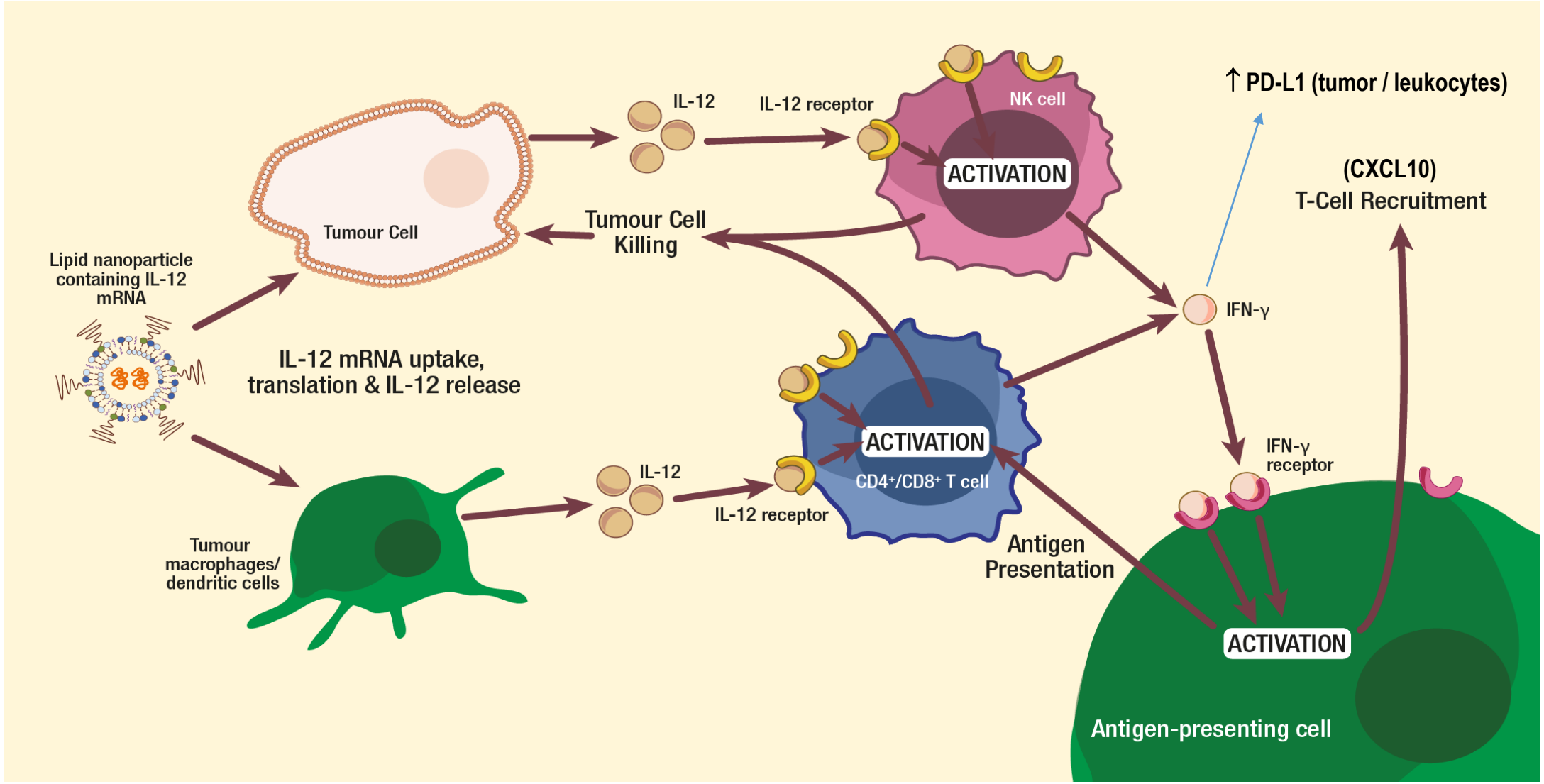
MEDI1191 (IL-12 mRNA) promotes antitumour immunity via multiple mechanisms



Hewitt SL, et al. *Clin Cancer Res.* 2020; 26(23):6284–6298

CD, cluster of differentiation; IFNγ, interferon gamma; IL-12, interleukin-12; mRNA, messenger ribonucleic acid; NK, natural killer.

ESMO TAT
VIRTUAL CONGRESS

Preliminary safety, antitumour activity and pharmacodynamic results of the Human Intratumoral Immunotherapy (HIT-IT) trial of MEDI1191 (mRNA IL-12) in patients with advanced solid tumours and superficial lesions

Omid Hamid, MD

Translational Research & ImmunoOncology

The Angeles Clinic and Research Institute

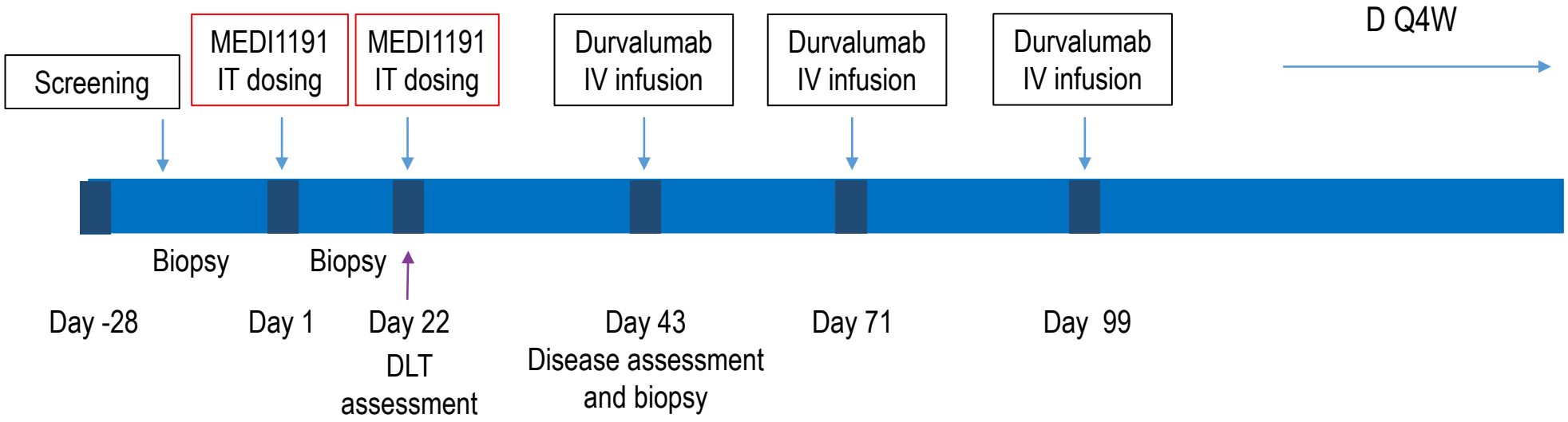
Omid Hamid[1], Matthew D. Hellmann[2], Benedito A. Carneiro[3], Thomas Marron[4], Vivek Subbiah[5], Inderjit Mehmi[1], Jim Eyles[6], Vincent Dubois[6], Benjamin Ridgway[7], Oday Hamid[7], Amaya Gascó Hernández[7]

[1]Medical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA;[2]Memorial Sloan Kettering Cancer Center, New York, NY, USA;[3]Lifespan Cancer Institute, Brown University, Providence, RI, USA; [4]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5]MD Anderson Cancer Center, Houston, TX, USA; [6]R&D Oncology, AstraZeneca, Cambridge, UK; [7]R&D Oncology, AstraZeneca, Gaithersburg, MD, USA

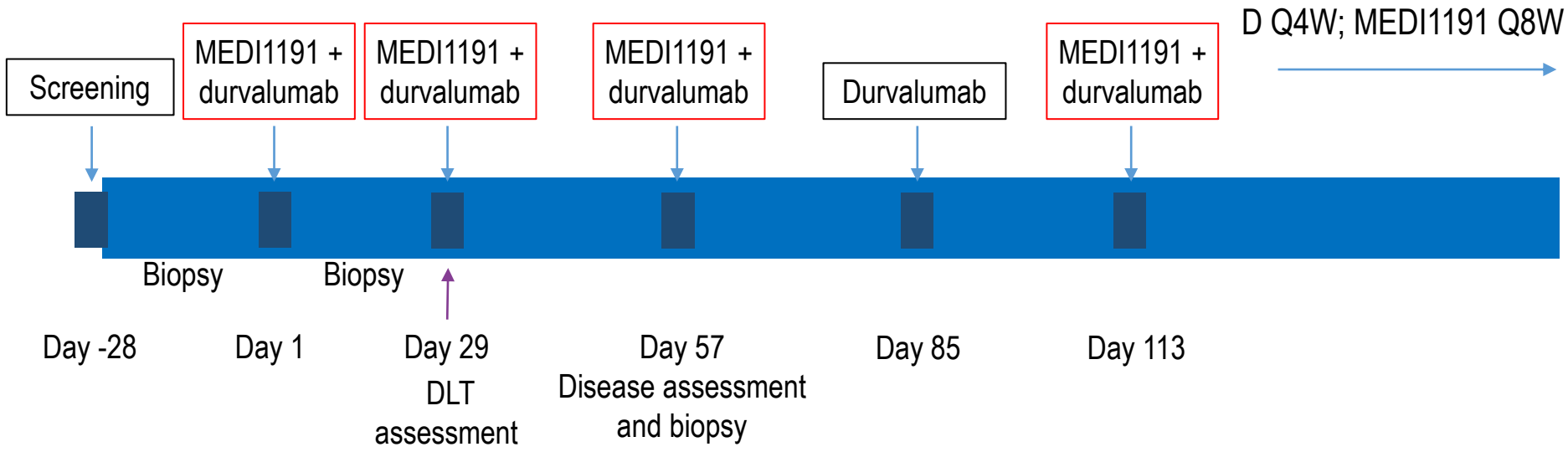
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Dosing scheme

Part 1A Sequential MEDI1191 + durvalumab

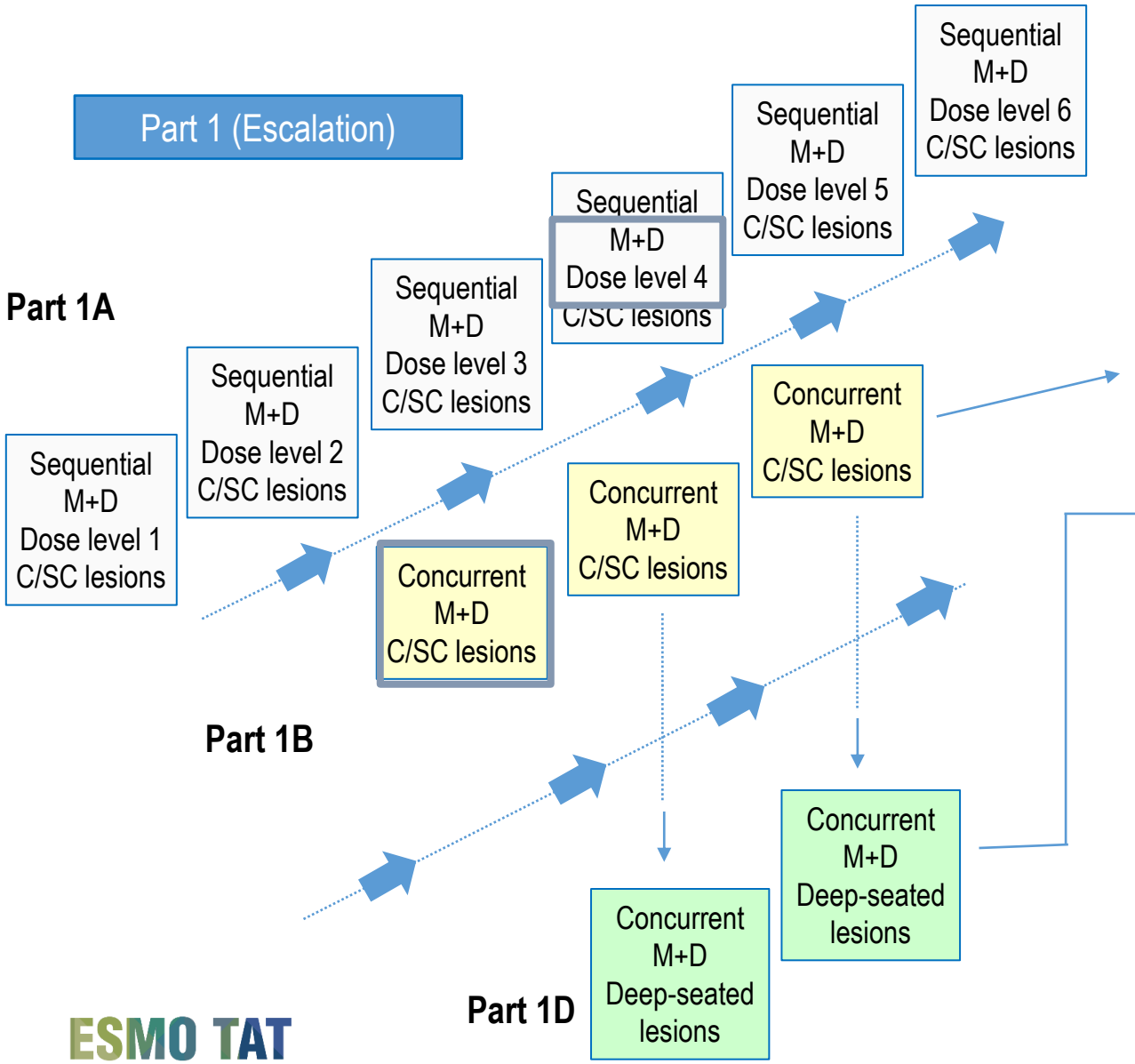


Part 1B and 1D Concurrent MEDI1191 + durvalumab



DLT, dose limiting toxicity

Study design



PD cohort

Part 2 (Expansion)
Other expansion cohorts will be based on efficacy

Concurrent MEDI1191 + durvalumab in NSCLC (C/SC/supraclavicular) n=10

Concurrent MEDI1191 + durvalumab in NSCLC (deep-seated) n=30

Key eligibility criteria

- ≥1 C/SC lesion or ≥2 deep-seated lesions suitable for IT injection, and ≥1 noninjected lesion measurable by RECIST v1.1
- Part 1: histologically or cytologically confirmed advanced solid tumours that have progressed on or are refractory to ≥1 line of standard systemic therapy for recurrent/metastatic disease*
- Part 2: histologically or cytologically confirmed locally advanced or metastatic NSCLC that has progressed on or is refractory to ≤2 lines of standard of care therapy for recurrent/metastatic disease, including anti-PD-1/PD-L1 and anti-CTLA-4 immunotherapy*

C, cutaneous; IT, intratumoural; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous
*A line of therapy is defined as systemic therapy given in the recurrent/metastatic setting with palliative intent

Patient characteristics and treatment exposure

		As Treated Population (N=10)
Sex, n (%)	Male / Female	8 (80) / 2 (20)
Mean age (range), years		51.7 (18–68)
Race, n (%)	White	7 (70.0)
	Asian	1 (10.0)
	Multiple/other	2 (20.0)
ECOG PS, n (%)	0 / 1	5 (50) / 5 (50)
Previous immunotherapy, n (%)	Any	6 (60.0)
	Previous PD-1 inhibitor therapy	5 (50.0)
	Previous PD-1 + CTLA-4 inhibitor combination therapy	1 (1.0)
Tumor type, n (%)	Head and neck squamous cell carcinoma	2 (20.0)
	Melanoma	2 (20.0)
	Colorectal cancer	1 (10.0)
	Non-small-cell lung cancer	1 (10.0)
	Gastric	1 (10.0)
	Other	3 (30.0)
Median number of doses of MEDI1191 (range)		2.0 (1.0, 2.0)
Median number of doses of durvalumab (range)		8.0 (4.0, 21.3)

Data cutoff: 28 Jan 2021

ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; SD, standard deviation, WHO, World Health Organization
*A line of therapy is defined as systemic therapy given in the recurrent/metastatic setting with palliative intent

Safety Summary: Part 1A MEDI1191 + durvalumab

- No DLTs
- No Grade ≥3 TRAEs or TR SAEs
- NR TESAEs: worsening constipation, oesophagitis, ascites (2x), gastric stenosis, sepsis

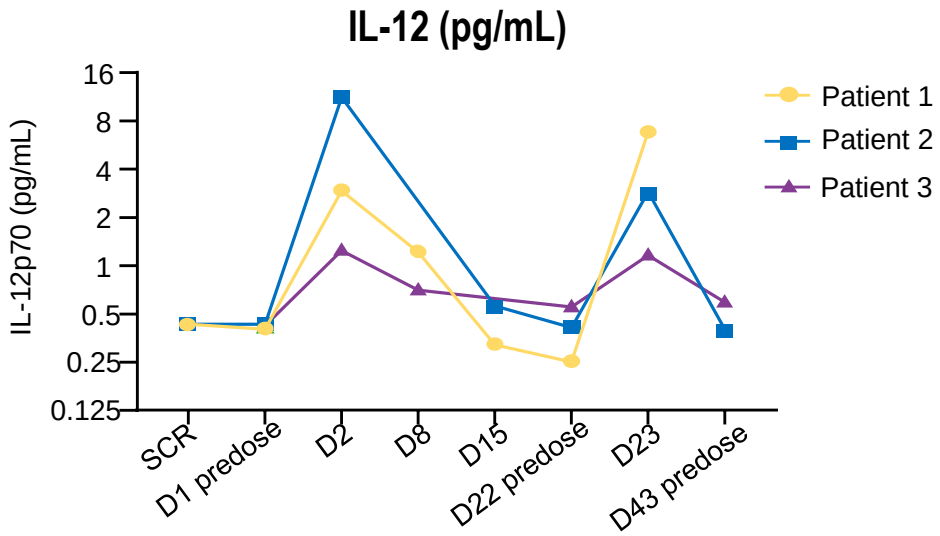
Treatment-emergent grade 3/4 AEs (none treatment-related)				
	Dose level 1 n=4	**Dose level 2 n=3**	**Dose level 3 n=3**	**Total N=10**
Patients with ≥1 event, n (%)	2 (50)	1 (33.3)	1 (33.3)	4 (40)
Abdominal pain	1 (25)	0	0	1 (10)
Ascites	1 (25)	0	1 (33)	2 (20)
Gastric stenosis	0	0	1 (33)	1 (10)
Oesophagitis	0	0	1 (33)	1 (10)
Fatigue	1 (25)	0	0	1 (10)
Hyponatraemia	1 (25)	0	0	1 (10)
Dyspnoea	1 (2.5)	0	0	1 (10)
Sepsis	0	1 (33)	0	1 (10)

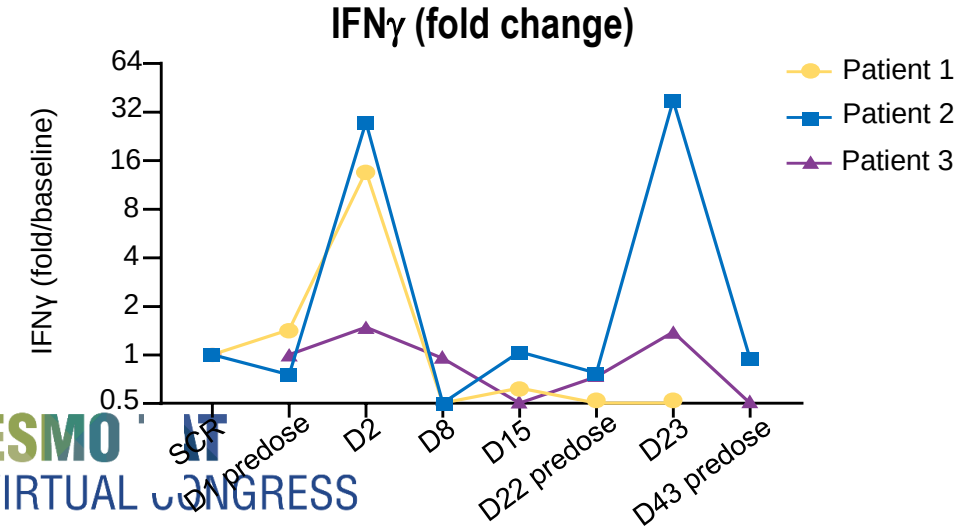
Data cutoff: 28 Jan 2021

NR TESAEs, non-related treatment-emergent serious adverse events; TRAEs, treatment-related AEs; TR SAEs, treatment-related serious adverse events

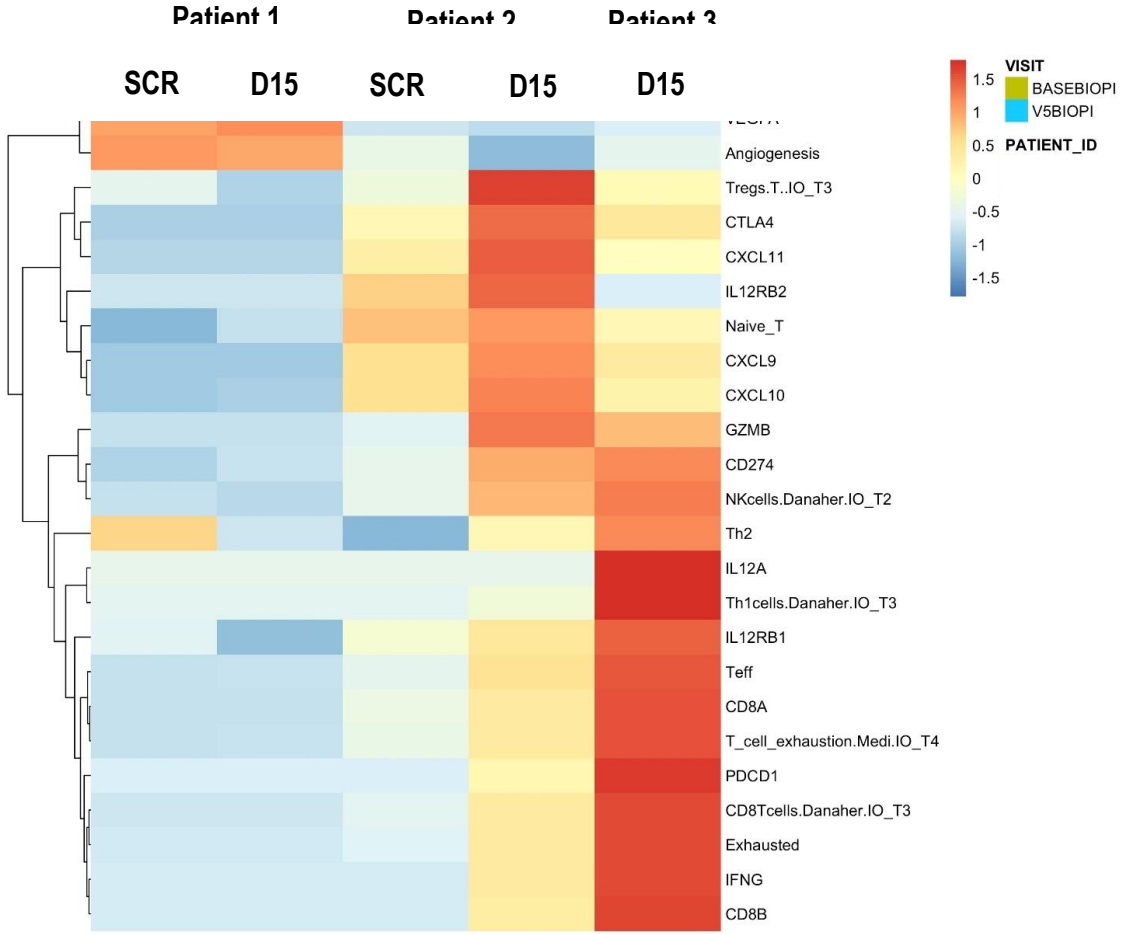
Part 1A Cohort 2: MEDI1191 induces pharmacodynamic changes in periphery and tumour consistent with proposed mechanism of action

Peripheral blood





Tumour

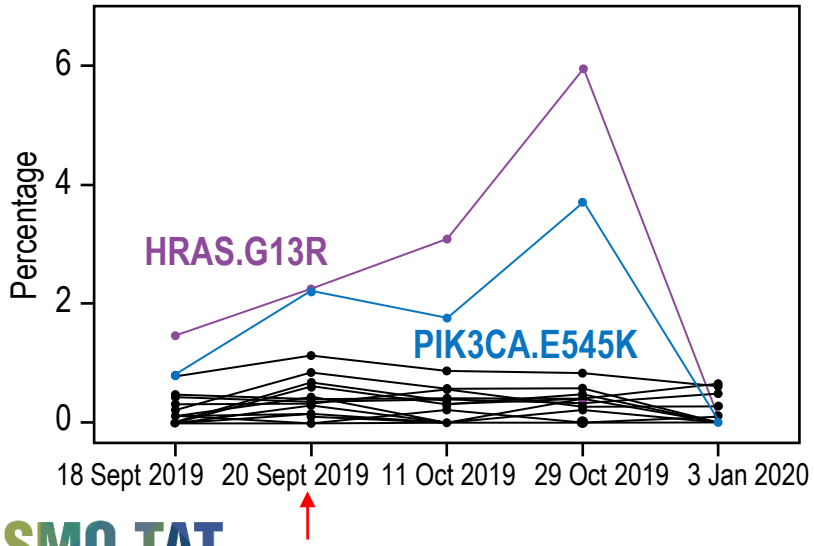


Red box = PR in melanoma pt; Data cutoff: 28 Jan 2021

ECOG PD, day; IFNγ, interferon gamma; IL-12, interleukin-12; SCR, screening

Partial response #1: Case summary

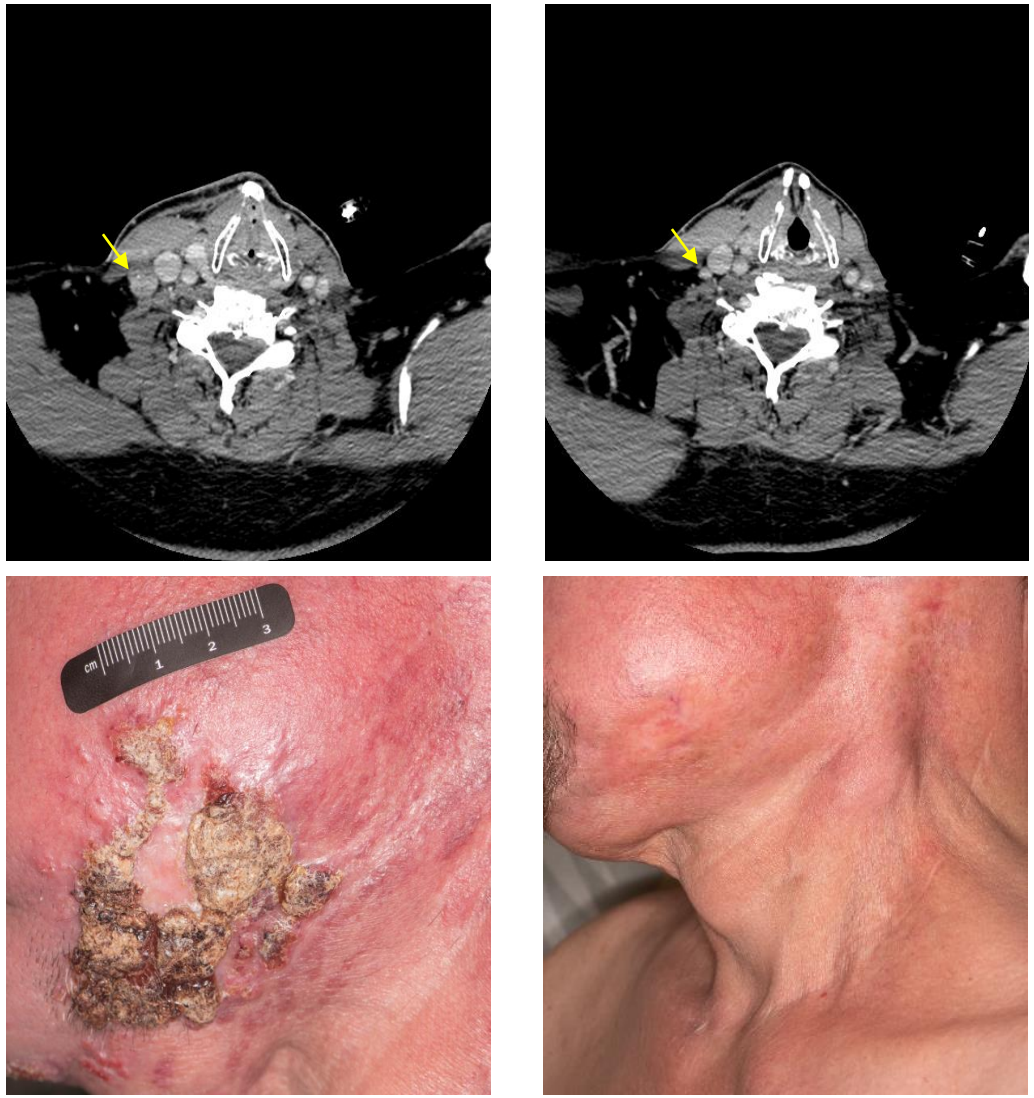
- 55-year-old male; ECOG PS 1
- Stage IVa HNSCC; PD-L1 negative
- Low tumour mutation burden (<20 muts/Mb) by ctDNA
- 4 prior regimens including nivolumab
- Part 1A Cohort 1: 1 cycle of MEDI1191 and 5 cycles of durvalumab on study
- Injected lesion: right cervical lymph node (20 Sept, 2019)
- **–58.7% change in size of target (noninjected) lesions along with shrinkage of injected (nontarget) lesions after 1 cycle of MEDI1191 and 4 cycles of durvalumab**



HRAS and PIK3CA driver mutations not detected at the last time point

16 Sept, 2019

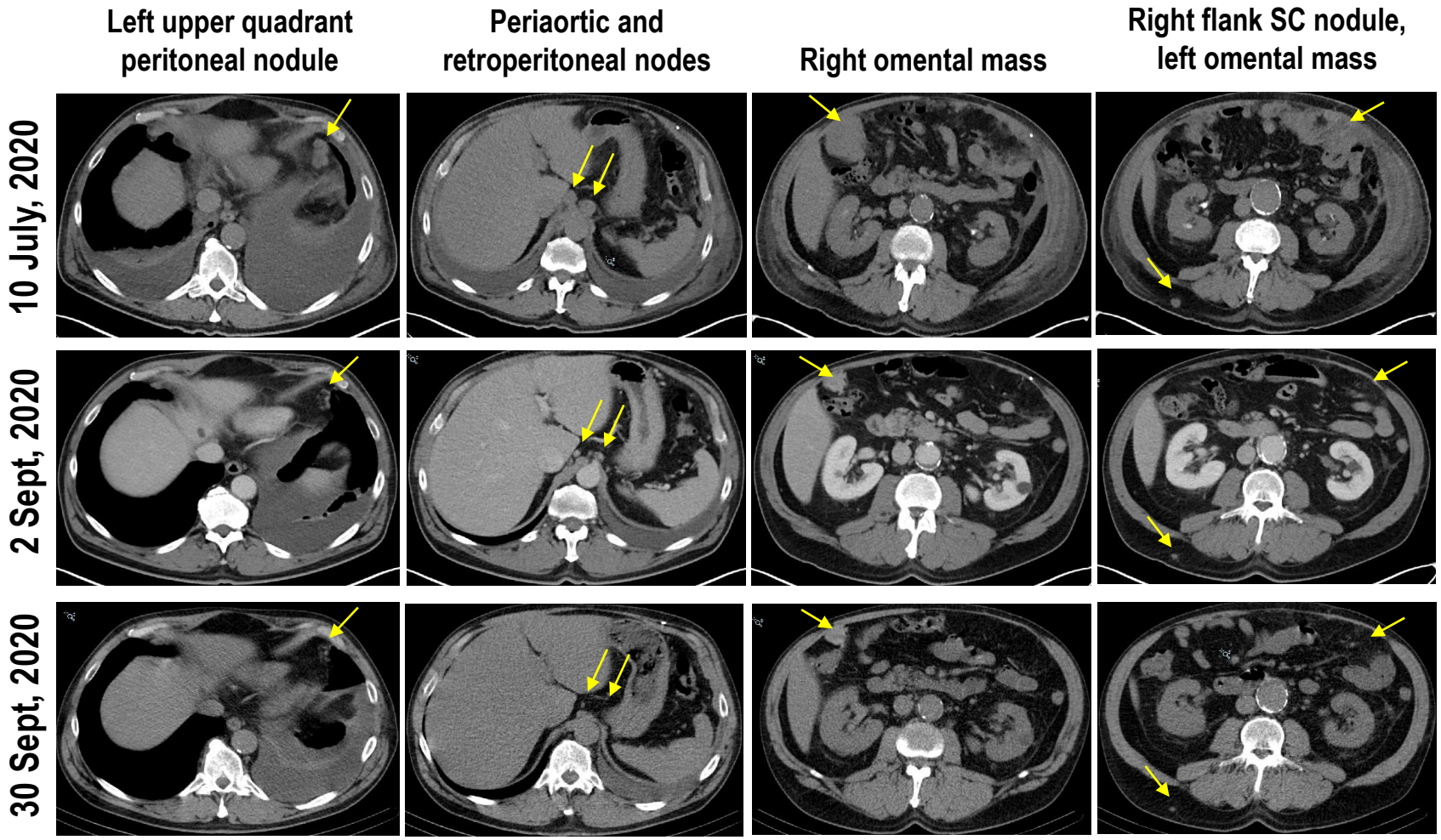
21 Feb, 2020 (after 4 cycles durvalumab)



ctDNA, circulating tumour DNA; HNSCC, head and neck squamous cell carcinoma; muts/Mb, mutations/megabase

Partial response #2: Case summary

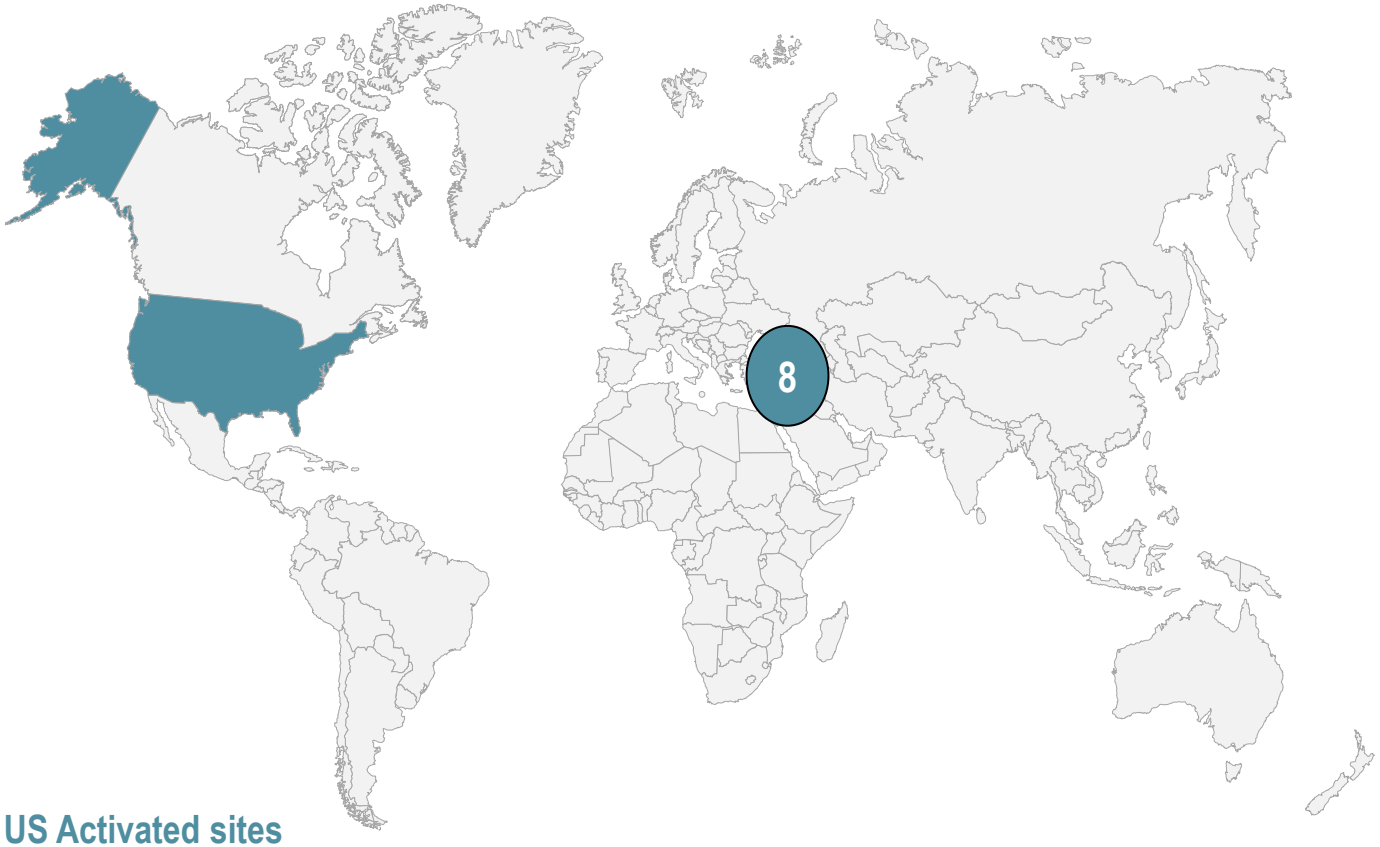
- 63-year-old male; ECOG PS 0
- Stage IV anal melanoma; PD-L1 negative
- Low tumour mutation burden (<20 muts/Mb) by ctDNA
- 3 prior regimens including nivolumab + ipilimumab and pembrolizumab monotherapy
- Part 1A Cohort 2: 2 cycles of MEDI1191 and 6 cycles of durvalumab on study
- Injected lesion: Left buttock SC nodule (20 July and 12 Aug, 2020)



- –61.2% change in size of noninjected (target lesions) along with shrinkage of nontarget (injected) lesions after 2 cycles of MEDI1191 and before first durvalumab dose

Conclusions

- Ten patients with advanced solid tumors and superficial lesions have been enrolled
- No dose-limiting toxicities; No $\geq$ grade 3 TRAEs
- Two PRs have been observed [HNSCC and melanoma]
- Both responders were previously PD-1 +/- CTLA4-treated
- Response in injected, local, and distant non-injected lesions
- Melanoma PR seen early with MEDI1191 alone
- Melanoma PR in correlative studies showed increase in IFN gamma, IL-12 , and inflammatory transcriptome
- Study ongoing, with the combination treatment to be tested in concurrent combination and in deep-seated lesions



US Activated sites

- MKSCC: M. Hellmann
- MDACC: V. Subbiah
- UCSD: S. Patel
- Mt Sinai NYC: T. Marron
- USC: A. El-Khoueiry
- Brown (Lifespan): B. Carneiro
- Montefiore: S. Goel
- Angeles Clinic: O. Hamid

Patients and

their families

Central facilities at

CIMA and CUN

EU FP7 & H2020

AECC

AICR

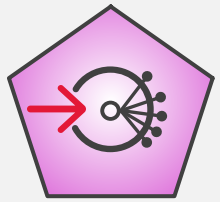
Fundación BBVA

Fundación CAN

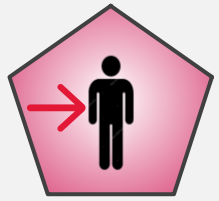
INDUSTRY

moderna

Systemic intracellular therapeutics



Localized regenerative therapeutics



Systemic secreted & cell surface therapeutics

Rare diseases

Cardiovascular

Autoimmune diseases

Ruchira Glaser, M.D., M.S.

Senior Vice President, Rare Disease and Autoimmune

Moderna's therapeutics: Rare diseases

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with **Merck**
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						**AZ** to pay milestones and royalties
Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge

New development candidates

moderna

Moderna's therapeutics: PA

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with **Merck**
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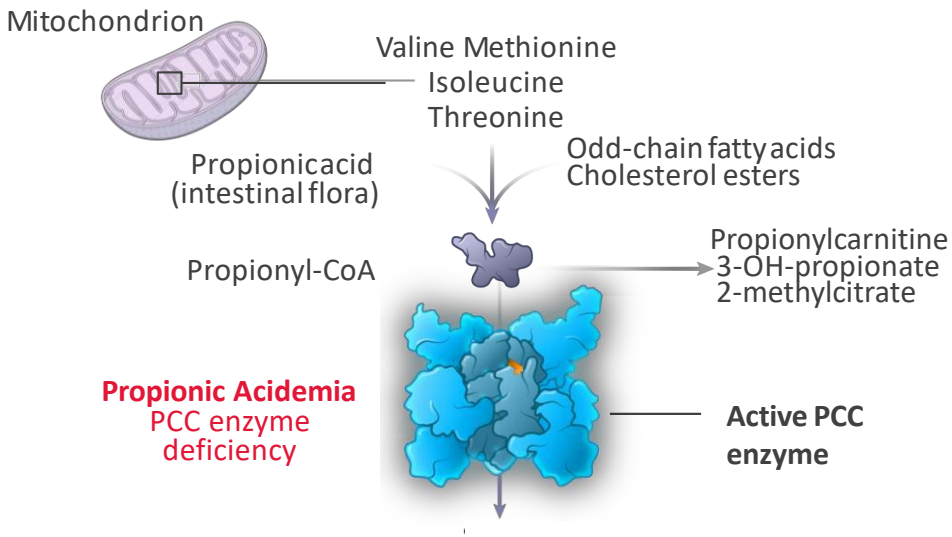
Systemic Intracellular Therapeutics	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge

New development candidates

moderna

PA therapy (mRNA-3927) encodes for an intracellular enzyme

- Propionic Acidemia (PA) **is a rare metabolic disorder**
  - Affects 1/20,000 to 1/250,000 individuals in various regions of the world
- **Changes in the *PCCA* and *PCCB* genes cause propionic acidemia**
  - These genes provide instructions for making two parts (subunits) of the propionyl-CoA carboxylase
  - Change in the *PCCA* or *PCCB* gene disrupt the function of the enzyme and prevent the normal breakdown of these molecules
- As a result, a substance called propionyl-CoA and other potentially **harmful compounds can build up to toxic levels** in the body; **buildup damages the brain and nervous system**, causing the serious health problems associated with propionic acidemia



Moderna's mRNA therapy for PA (mRNA-3927) encodes for two proteins that form the deficient enzyme

- PCCA (PA Type I)
- PCCB (PA Type II)

https://rarediseases.org/rare-diseases/propionic-acidemia/

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Propionic acidemia (PA) has significant morbidity and mortality and is without any approved therapies

- Primarily **a pediatric disease** with majority of cases presenting within 3 days of life, untreated may lead to coma and death

- **Treatment**: There is **no approved therapy for PA**
  - Standard of care included dietary and palliative measures
  - Liver transplant has been shown to improve biochemical and clinical outcomes

PA Clinical Manifestations

- Recurrent episodes of **life-threatening metabolic decompensations**
- **Progressive multi-organ damage**
  - Brain damage
  - Seizures
  - Intellectual disability
  - Inflammation of the pancreas (pancreatitis)
  - Chronic renal failure
  - Heart failure (cardiomyopathy); heart rhythm problems
  - Increased risk of having a metabolic stroke as early as a few weeks of age
  - Osteoporosis which can lead to fractures
  - Hematologic: reduced number of cells in blood (anemia, leukopenia, thrombocytopenia, pancytopenia)
  - Growth retardation
  - Severe vision problems

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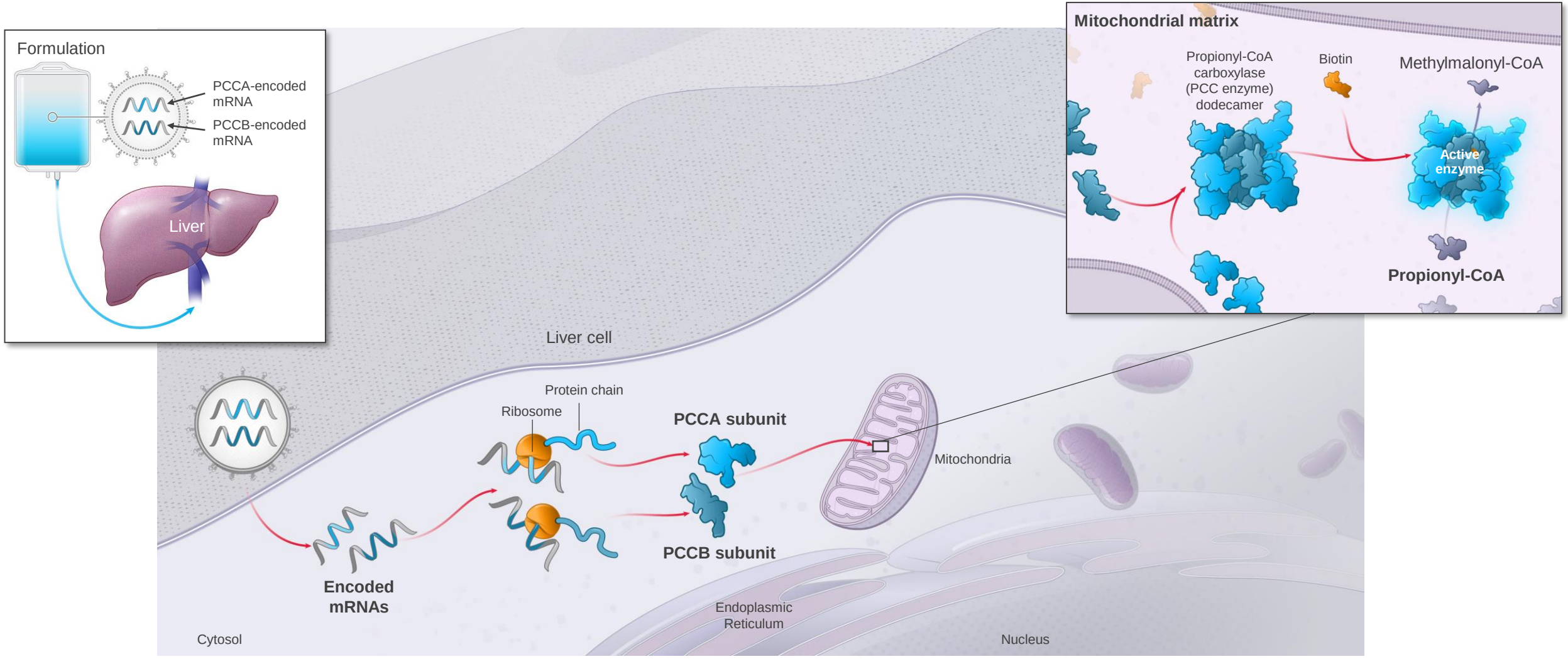
mRNA-3927 is a combination therapy encoding for PCCA and PCCB protein to form an active PCC enzyme (uses IV-LNP 1)



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Propionic acidemia (PA) ongoing in Phase 1/2 study

Key objective
- To evaluate the safety and pharmacology of mRNA-3927 in patients 1 year of age and older with propionic acidemia (PA)

Primary endpoint
- Safety
- Pharmacokinetics and Pharmacodynamics

Secondary endpoint
- Incidence and severity of adverse events (AEs)
- Change in plasma biomarkers: methylcitric acid (2-MC) and 3-Hydroxypropionic acid (3-HP)

Trial progress
- Phase 1/2 enrolling patients

Paramount study ongoing

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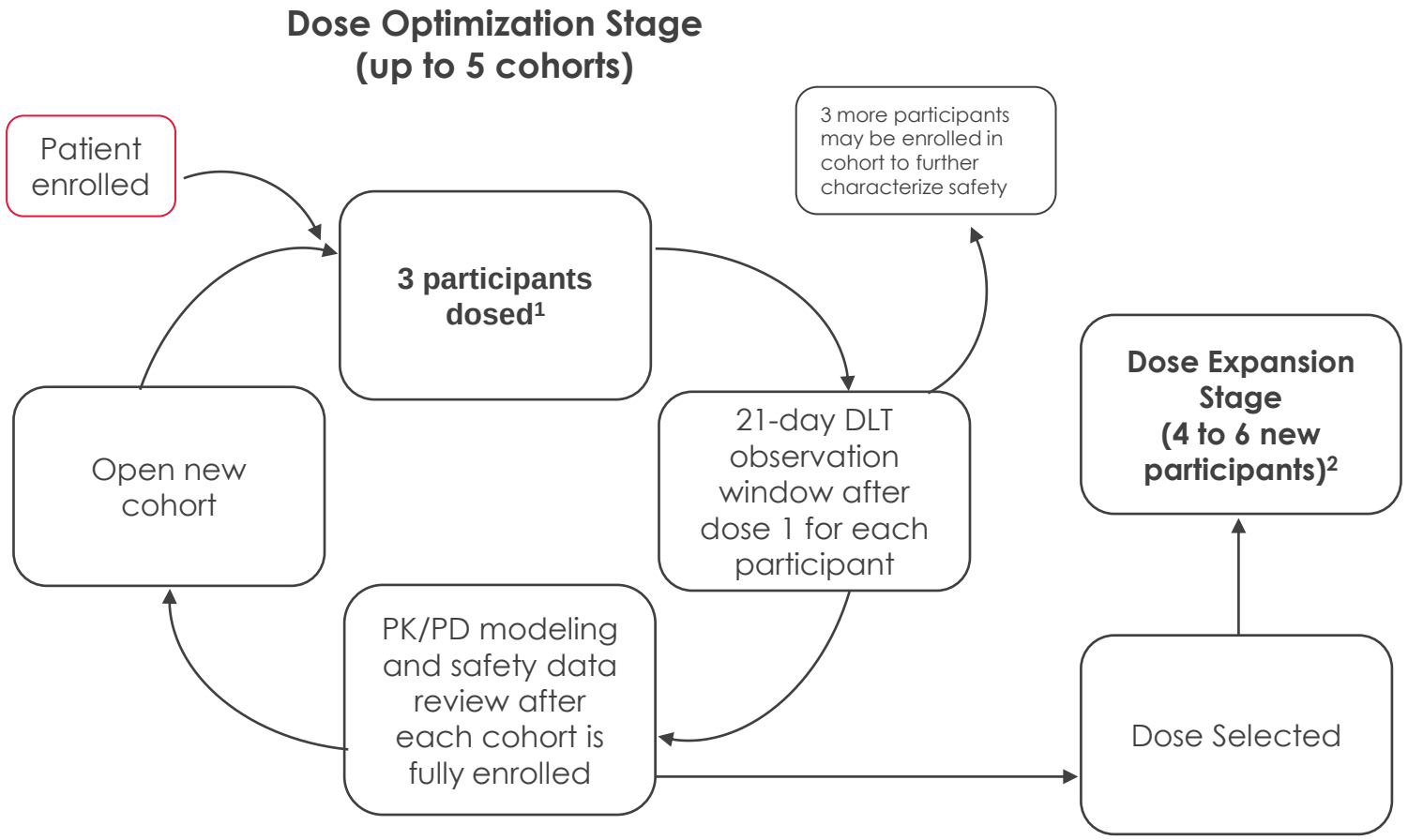
Propionic acidemia (mRNA-3927) Phase 1/2 Paramount Study



- Adaptive trial design
- Recruiting patients in Canada, United Kingdom and United States
- Multiple patients dosed; completed enrollment of cohort 1
- Looking for plasma biomarkers (methylcitric acid (2-MC) and 3-Hydroxypropionic acid (3-HP))

DLT = dose-limiting toxicity; PD = pharmacodynamic(s); PK – pharmacokinetic(s)
1. The first 2 participants will be ≥ 8 years of age
2. In the dose expansion stage, a minimum of 2 participants with each subtype (PCCA and PCCB) will be enrolled

Moderna's therapeutics: MMA

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with **Merck**
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						**AZ** to pay milestones and royalties
	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
Systemic Intracellular Therapeutics	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge

New development candidates

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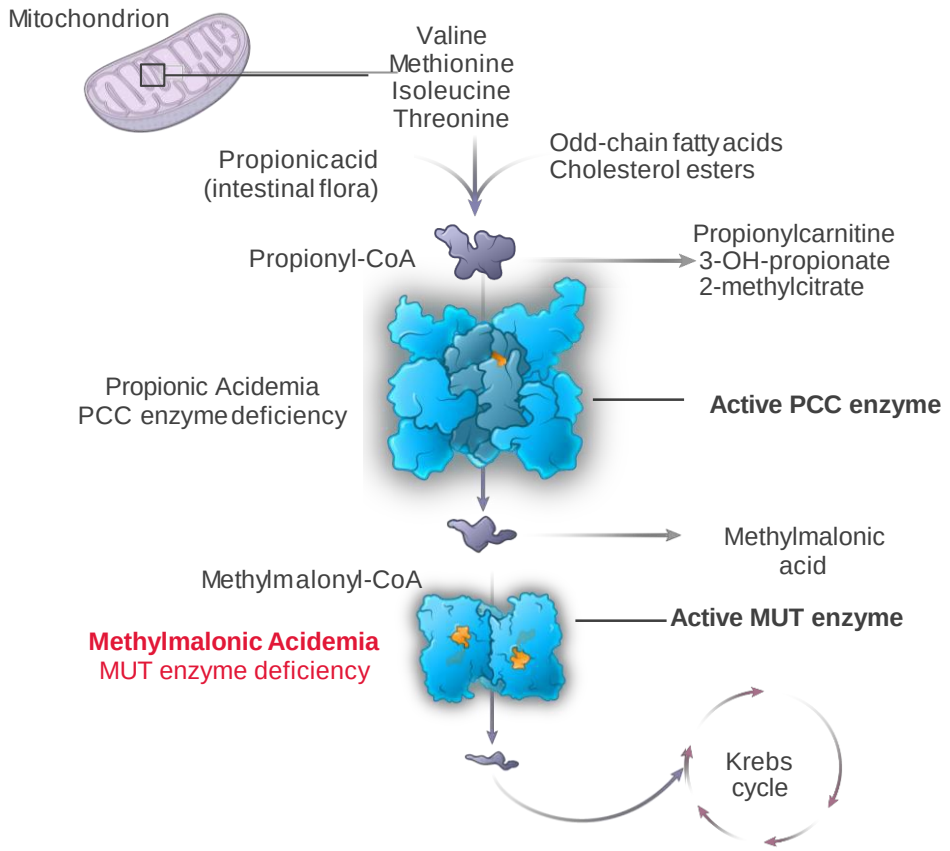
MMA therapy (mRNA-3705) encodes for the MUT enzyme

- Methylmalonic acidemia (MMA) refers to a rare, autosomal recessive acidemia
  - Affects 1/100,000 in various regions of the world (except in Middle East where it affects 6/100,000)
- It is caused by a defective or missing MUT enzyme (methylmalonic CoA mutase)
- **Changes in the *MMUT gene* causes methylmalonic acidemia**
  - Gene provides instructions for making an enzyme called methylmalonyl CoA mutase
  - Changes in the gene disrupt the function of the enzyme and prevent the normal breakdown of molecules



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Methylmalonic acidemia (MMA) has no approved therapies

- **Primarily a pediatric disease** with onset in early infancy; significant mortality and morbidity
- **Treatment:** There is no approved therapy for MMA
- **Current interventions include:**
  - Dietary restriction, cofactor therapy and carnitine
  - Liver and/or kidney transplant is the only effective treatment, even in infants (but transplant is not curative and is associated with mortality)

MMA Clinical Manifestations

- Recurrent episodes of **life-threatening metabolic decompensations**
- **Progressive multi-organ damage**
  - Brain damage
  - Seizures
  - Intellectual disability
  - Severe vision problems
  - Inflammation of the pancreas (pancreatitis)
  - Chronic renal failure
  - Heart failure (cardiomyopathy); heart rhythm problems
  - Increased risk of having a metabolic stroke as early as a few weeks of age
  - Osteoporosis which can lead to fractures
  - Hematologic: reduced number of cells in blood (anemia, leukopenia, thrombocytopenia, pancytopenia)
  - Growth retardation

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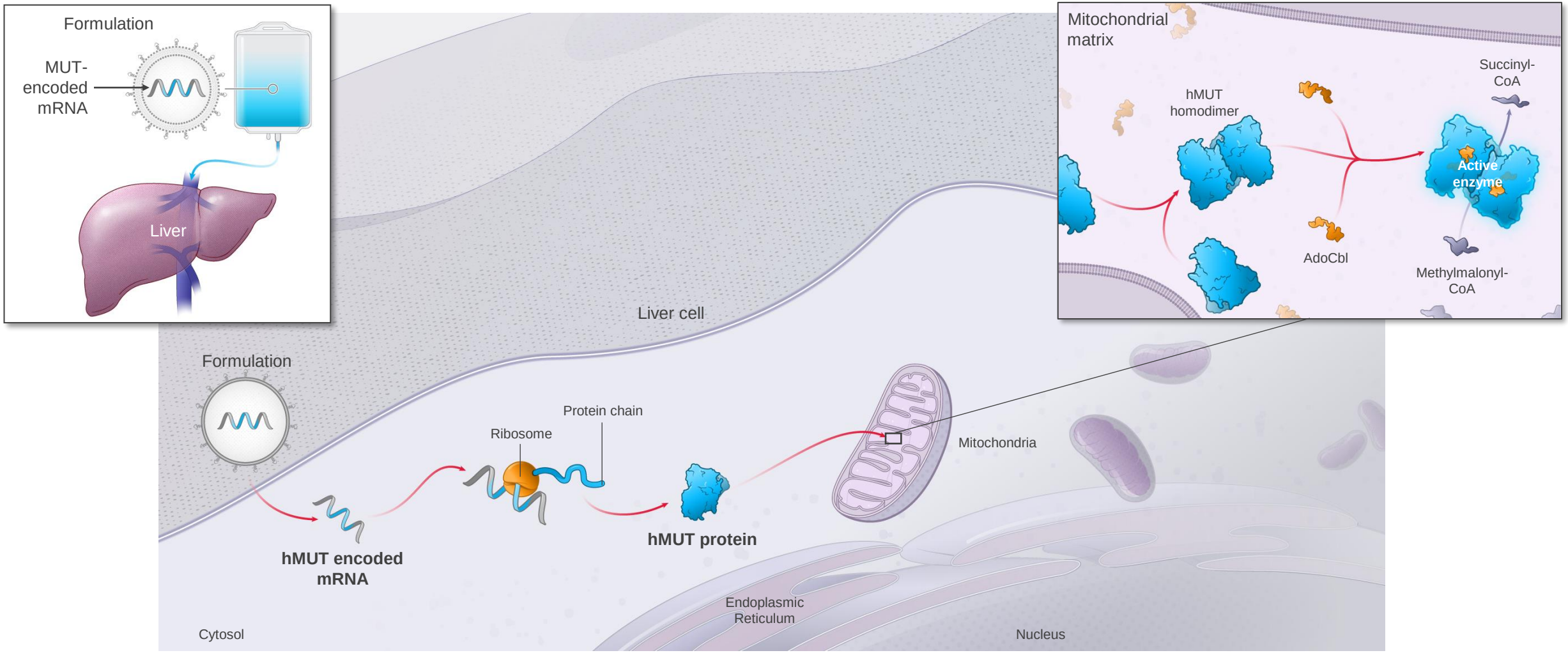
MMA therapy (mRNA-3705) encodes for the MUT enzyme (uses IV-LNP 1)



Note: AdoCbl = cofactor adenosylcobalamin

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Methylmalonic acidemia (MMA) ongoing in Phase 1/2 study

Key objective
- To evaluate the safety and pharmacology of mRNA-3705 in patients 1 year of age and older with methylmalonic acidemia (MMA)

Primary endpoint
- Safety
- Pharmacokinetics and Pharmacodynamics

Secondary endpoint
- Incidence and severity of adverse events (AEs)
- Change in plasma biomarkers: methylcitric acid (2-MC) and methylmalonic acid

Trial progress
- Phase 1/2 enrolling patients
- First patient dosed

Landmark study ongoing

landmark study

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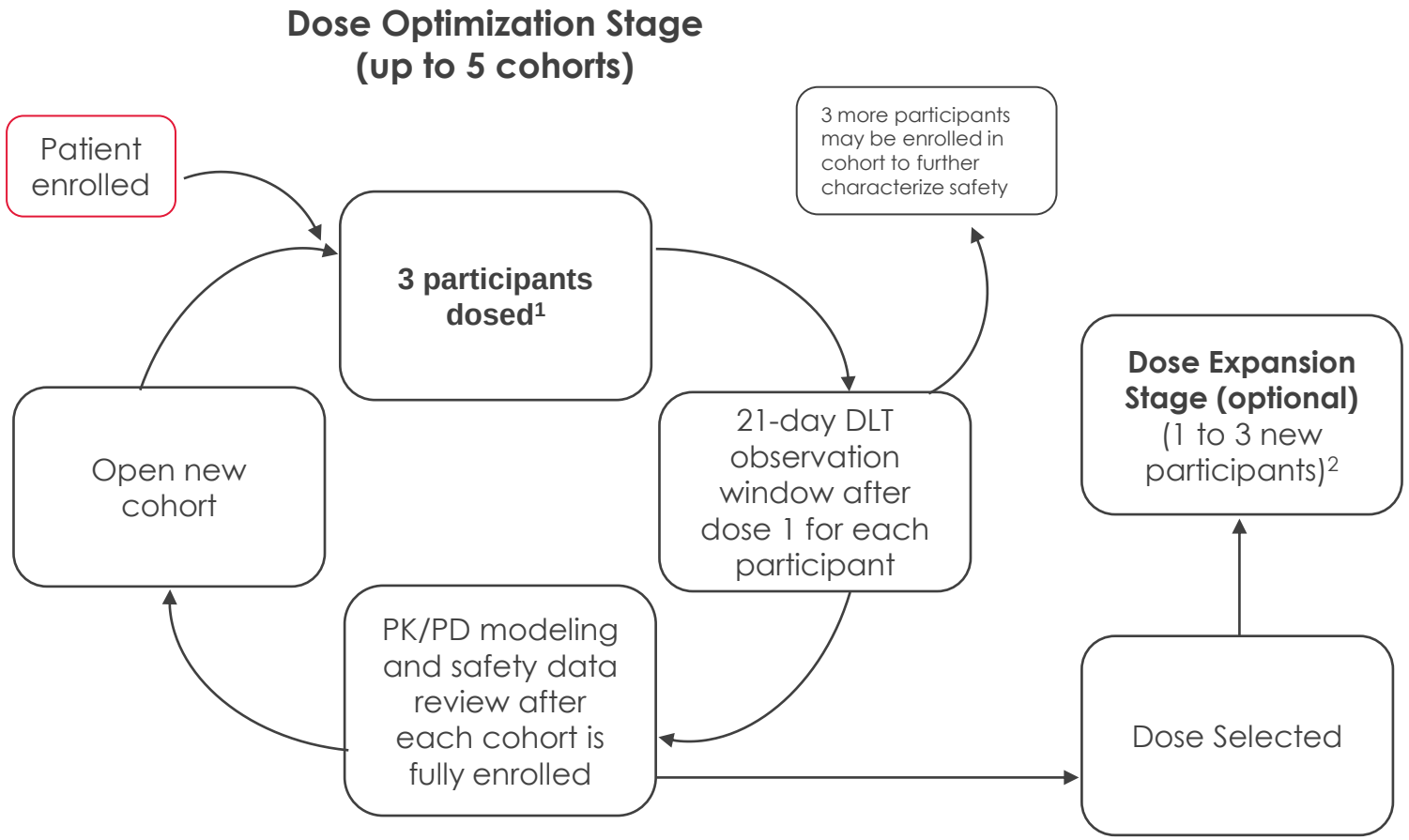
Methylmalonic acidemia (MMA) ongoing in Phase 1/2 study



- Adaptive trial design
- Recruiting patients in the United Kingdom and Canada
- Looking for change in plasma biomarker (methylcitric acid (2-MC) and methylmalonic acid

Abbreviations: DLT = dose-limiting toxicity; PD = pharmacodynamic; PK = pharmacokinetic
A DLT observation window only applies after Dose 1; events occurring thereafter (> 21 days after the first dose and Doses 2 through 10) will be recorded as adverse events (AEs)/serious adverse events (SAEs) but will not be considered DLTs.

Moderna's therapeutics: GSD1a

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with Merck
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with Merck
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						AZ to pay milestones and royalties
Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to ILCM free of charge

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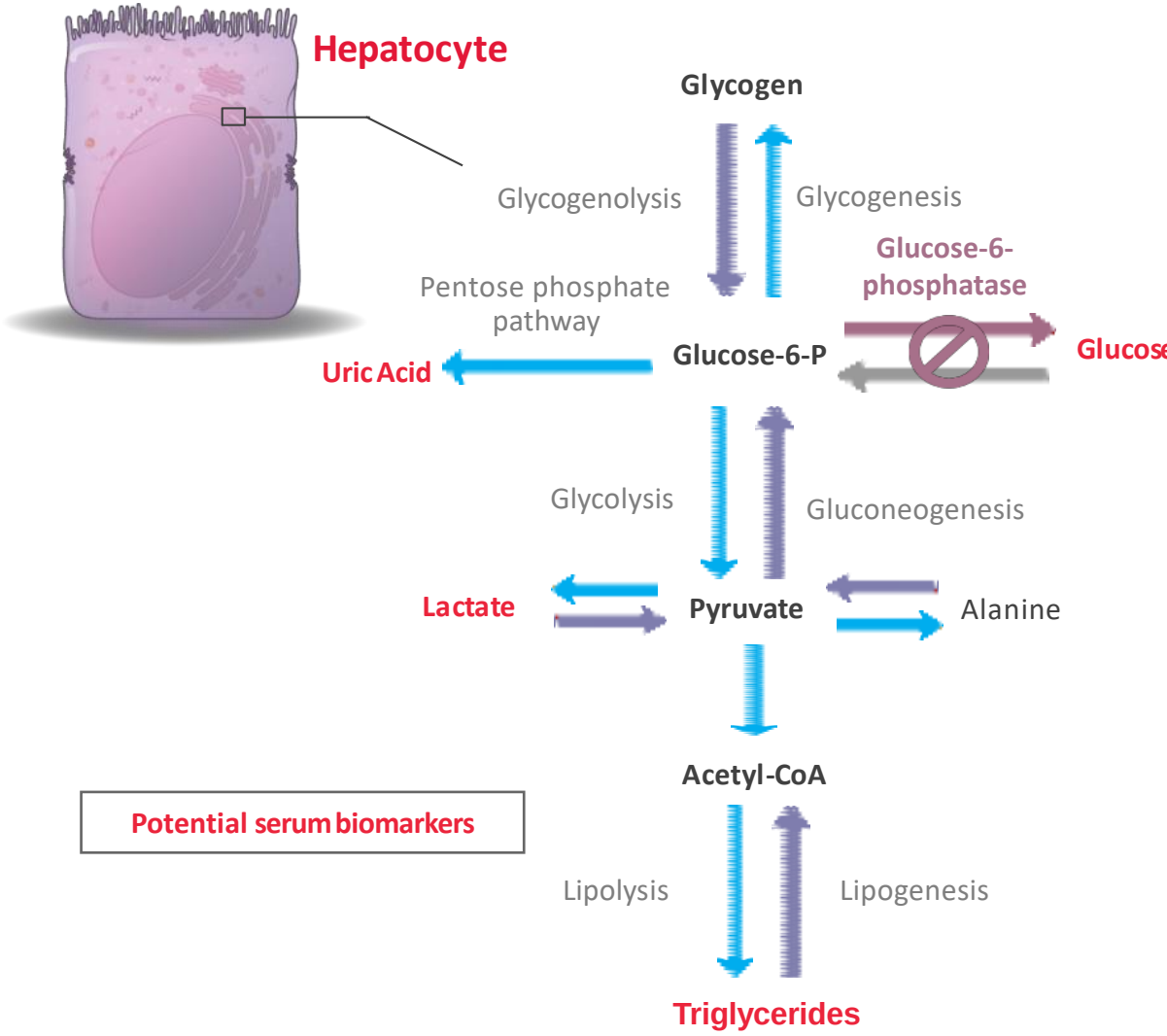
Glycogen storage disease type 1a therapy (mRNA-3745) encodes for the G6Pase enzyme

Glycogen storage disease type 1a (GSD1a) Overview

- GSD1a refers to a rare inherited metabolic disease resulting from a deficiency in the metabolism of glucose
- It is caused by mutations within the enzyme glucose 6-phosphatase, G6Pase



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Glycogen storage disease type 1a (GSD1a) has no approved therapies

- **Disease burden:**
  - Life-threatening hypoglycemia, long-term liver & kidney damage
  - Long-term hepatic complications are observed in 75% of adult patients of which 10% are at risk of malignant transformation into HCC
- **Prevalence:**
  - Incidence of ~1:100k live births[2]
  - 2,500 patients in US, and >4,000 patients in the EU[3]
- **Treatment:** There is no approved therapy for GSD1a
- **Current interventions include**:
  - Strict diet control; frequent consumption of uncooked cornstarch to improve hypoglycemia
  - Glycosade® (cornstarch for dietary management)
  - Liver/kidney transplantation

GSD1a sequelae
• Hypoglycemic seizures
• Cognitive impairment
• Hepatomegaly
• Hepatic adenomas
• Hepatocellular carcinoma (HCC)
• Renal disease
• Life-threatening hypoglycemia
• Growth retardation

(1) Cao, J., Choi, M., Guadagnin, E. et al. mRNA therapy restores euglycemia and prevents liver tumors in murine model of glycogen storage disease. Nat Commun 12, 3090 (2021). https://doi.org/10.1038/s41467-021-23318-2 (2) Froissart, Roseline et al. Glucose-6-phosphatase deficiency. Orphanet J Rare Dis. 2011 May 20;6:27. doi: 10.1186/1750-1172-6-27
(3) Based on estimated incidence of 1:100,000 (4) Kishnani, Priya, et al. Diagnosis and management of glycogen storage....Genet Med. 2014 Nov;16(11):e1. doi: 10.1038/gim.2014.128.

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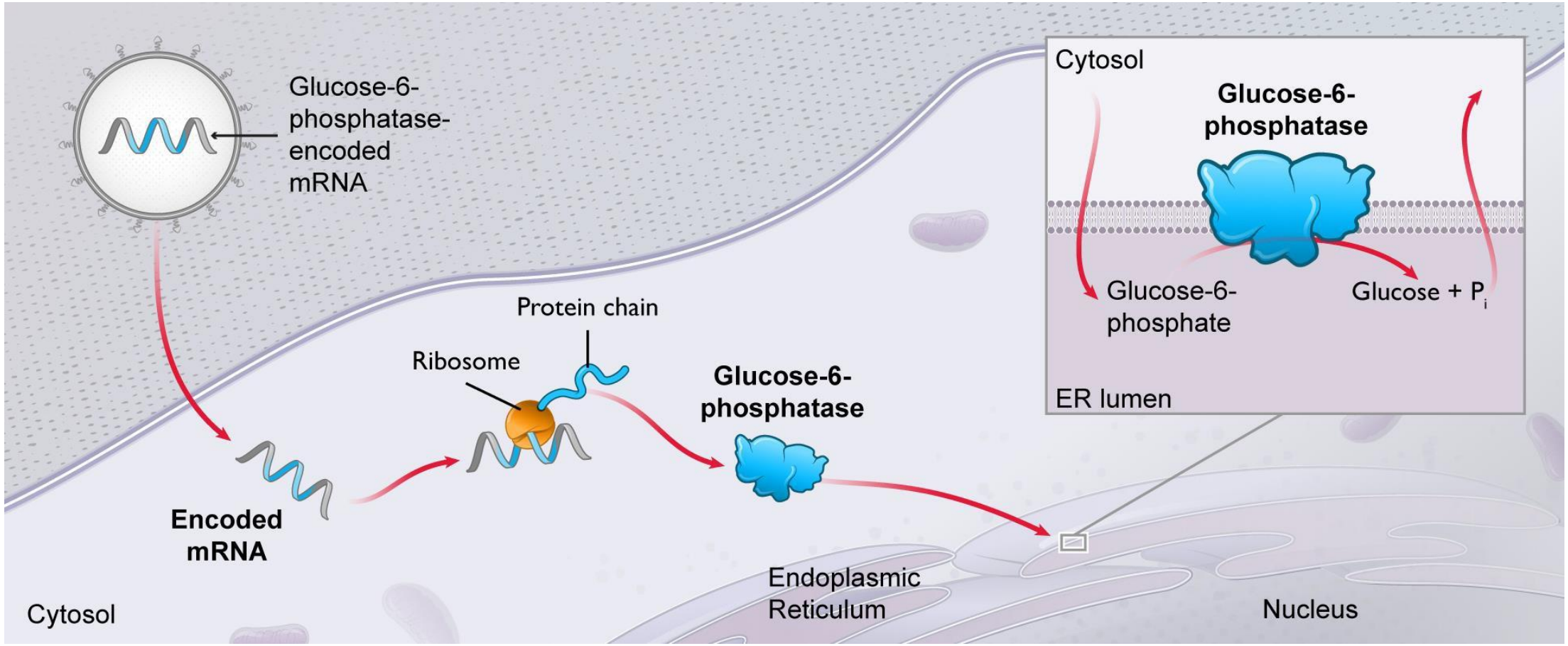
GSD1a therapy (mRNA-3745) encodes for the G6Pase enzyme localized to endoplasmic reticulum (uses IV LNP-2)



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GSD1a (mRNA-3745) is preparing for a Phase 1 study start

IND opened in August 2021

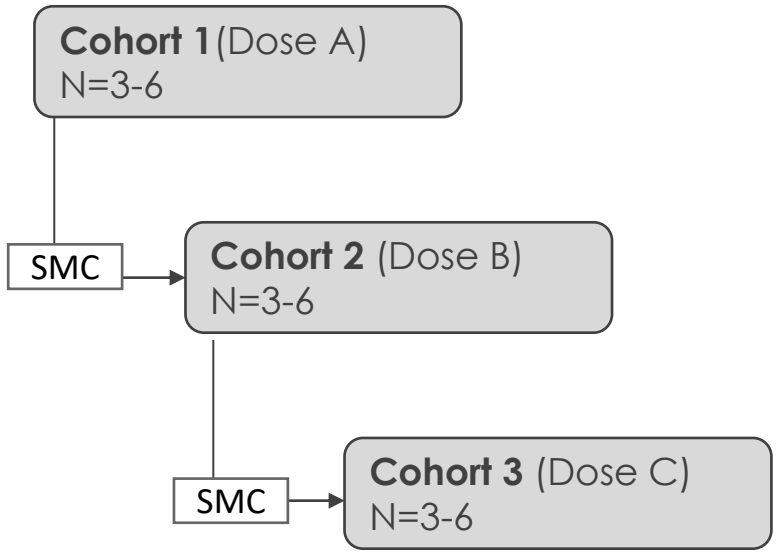
Key Objective

- To evaluate the safety and pharmacology of mRNA-3745 in patients 18 years of age and older with glycogen storage diseases type 1a
  - Safety
  - Changes in glucose metabolism assessed by fasting challenges and other serum biomarkers

Trial Progress

- IND opened in August 2021
- Site initiation ongoing

Phase 1 Trial Design



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Moderna's therapeutics: Autoimmune diseases

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	**mRNA-6231**						Worldwide
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	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge

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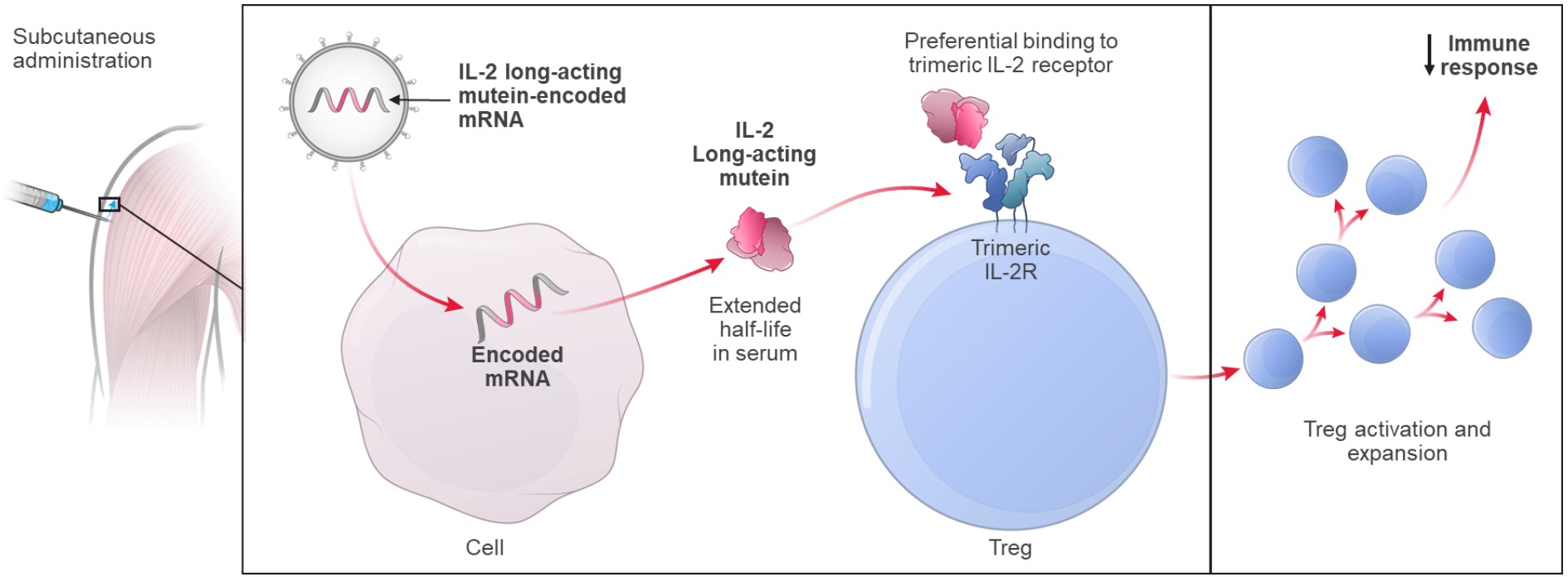
IL-2 (mRNA-6231) autoimmune therapy (uses IV-LNP 1)

- IL-2 is a cytokine that can stimulate the proliferation of T cells
- Modified IL-2 is longer acting and more selective for the high affinity IL-2 receptor which is expressed mainly by regulatory T cells
- mRNA-6231 encodes for modified IL-2



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IL-2 is a well validated target for a range of autoimmune conditions

Represents initial subcutaneous product for chronic use as a therapeutic for Moderna

- **IL-2 biology promotes immune tolerance** through the generation and maintenance of regulatory T cells, potentially without sacrificing the ability of the immune system to protect from opportunistic infections
  - **Selective Treg expansion has applications to many diseases,** and this is supported by a large body of published literature of clinical studies with low-dose IL-2
- Multiple IL-2 molecules in clinical development for a **range of autoimmune conditions, such as:** Inflammatory bowel disease (ulcerative colitis), psoriasis, systemic lupus erythematosus, graft-versus-host disease, autoimmune hepatitis, etc.
  - Clinical readouts from industry is expected to provide further mechanistic and early clinical evidence that chronic exposure to low-dose IL-2 may be beneficial in a variety of indications

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IL-2 autoimmune therapy (mRNA-6231) Phase 1 ongoing

Key Objectives

- The primary objectives of this study are to evaluate the safety and tolerability of escalating doses of a single subcutaneous (SC) administration of mRNA-6231

Primary Endpoints

- Safety

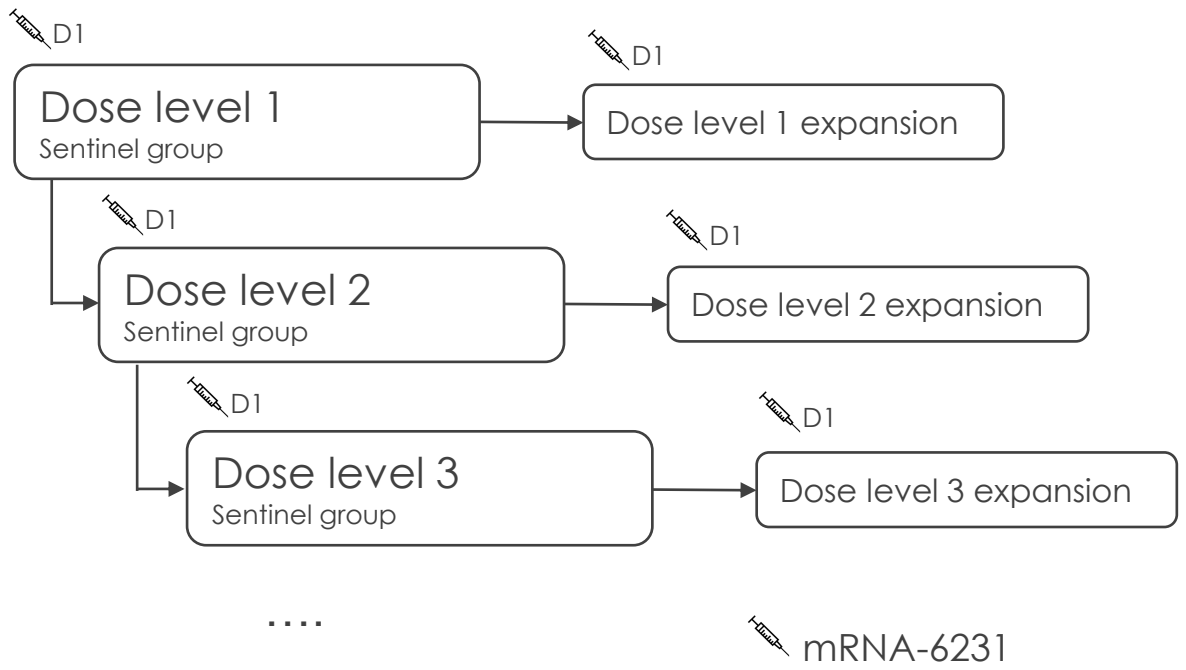
Secondary Endpoints

- Pharmacokinetics and pharmacodynamics

Trial Progress

- Phase 1 trial enrolling healthy volunteers (started in August 2021)

Phase 1 Dose Escalation Study
Adults ages 18-50 years



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Moderna's therapeutics: Cardiovascular diseases

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
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Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge

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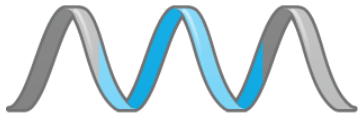
Moderna and AstraZeneca collaboration on VEGF-A (AZD8601)

AZD8601 Overview

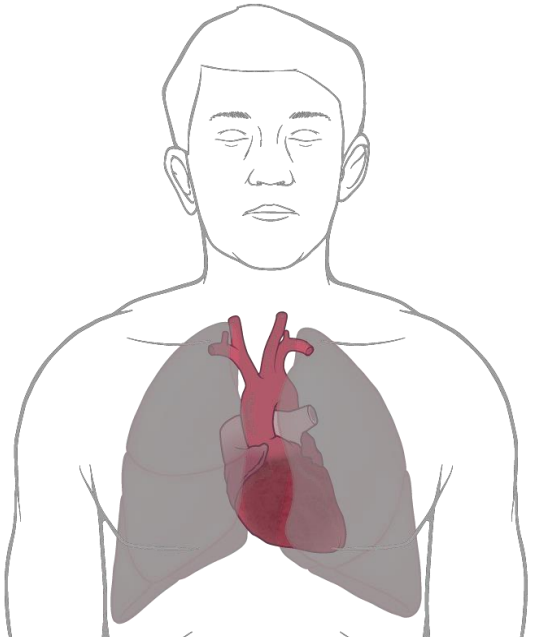
- **Locally administered mRNA encoding for VEGF-A** to promote recovery of cardiac function through partial tissue regeneration
- VEGF-A is a potent angiogenic factor that promotes **growth of blood vessels**
- **Currently only product in pipeline that is directly delivered** (without LNP)



mRNA encoding for VEGF-A
(formulated in biocompatible citrate-buffered saline)

Epicardial injections
(directly into heart)

Produces VEGF-A proteins



We believe mRNA medicines have the potential to address ischemic cardiovascular diseases

Coronary Artery Disease (CAD)

- Heart disease is the leading cause of death in the United States[1]
- Coronary artery disease, the primary cause of ischemic heart failure, affects the arteries providing blood supply to the cardiac muscle
- Coronary heart disease is the most common type of heart disease
  - Each year, nearly one million Americans suffer myocardial infarctions (MI) that are often fatal and at best lead to necrotic regions of myocardium that cause pathologic remodeling and arrhythmia
- About 18.2 million adults age 20 and older have CAD (about 6.7%) (in the U.S.)
- About 2 in 10 deaths from CAD happen in adults less than 65 years old (in the U.S.)

Leads to…

Myocardial Infarction
(heart attack)

Heart Failure
Due to heart damage or inadequate blood supply

1. CDC, Heart disease statistics, https://www.cdc.gov/heartdisease/statistics_maps.htm

Rationale for VEGF program

- **Coronary heart disease is caused by insufficient blood flow to the myocardium** because of atherosclerotic stenoses or blockages, in the main coronary arteries
- This condition can be treated by providing new blood flow to the ischemic muscle, such as coronary bypass surgery and angioplasty techniques
- **But these approaches are not possible for all patients**; there is an increasing group of severe angina pectoris patients (refractory angina) who cannot be treated with these conventional approaches
    - Patients who have myocardium that is alive but has insufficient blood flow may have chronic impaired left ventricular dysfunction
- **Those who cannot get complete revascularization would improve heart function if new blood flow could be restored**

Heart Failure Outcomes

- HF prognosis remains poor, with mortality estimated at 40% of patients at only 4 years from diagnosis
- This is worse than several common cancers
- HF is also tremendously expensive, representing 2–3% of national health expenditures in high-income countries, projected to more than doubling in the next 20 years

Giacca, M. Cardiac Regeneration After Myocardial Infarction: an Approachable Goal. *Curr Cardiol Rep* **22,** 122 (2020). https://doi.org/10.1007/s11886-020-01361-7

Roger VL. Epidemiology of heart failure. Circ Res. 2013;113(6):646–59

Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606–19

Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and National Burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1–25.

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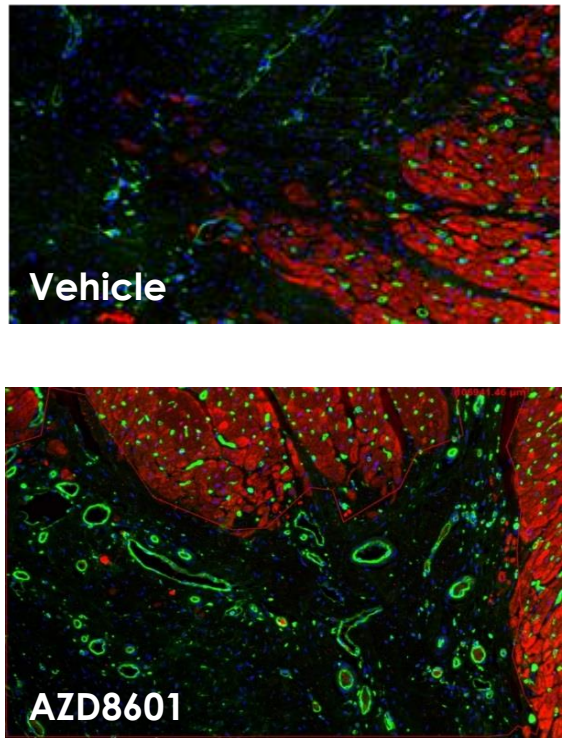
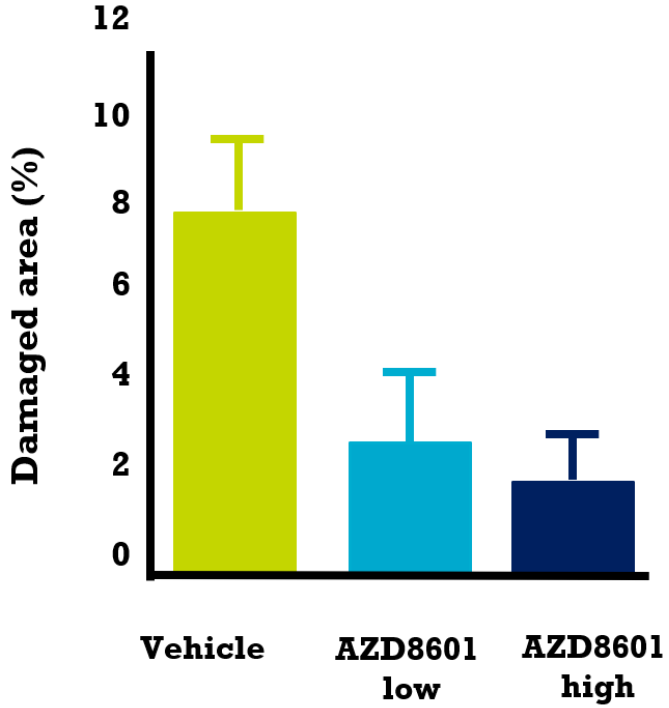
A single cardiac administration of VEGF-A mRNA improves cardiac function two months after MI in the Pig model

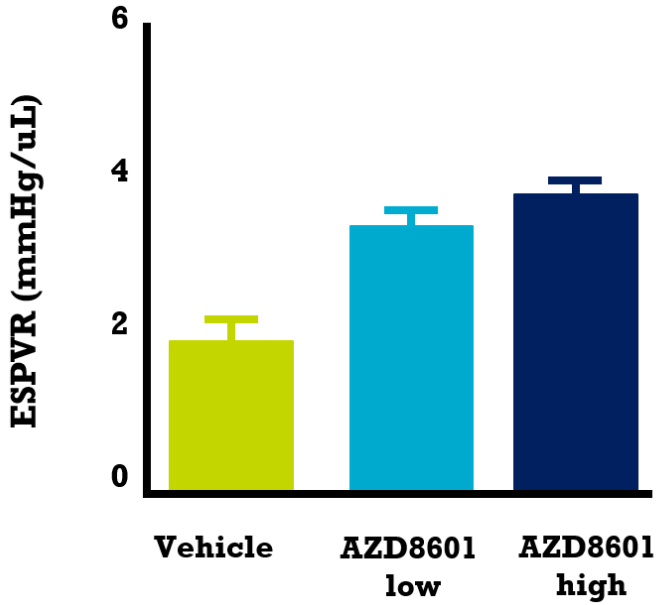
Regenerates blood vessels



Reduces heart damage



Restores heart function



Carlsson, Leif et al. "Biocompatible, Purified VEGF-A mRNA Improves Cardiac Function…" *Molecular Therapy,* 2018, https://doi.org/10.1016/j.omtm.2018.04.003

Phase 1 trial tested safety and suggested angiogenic potential

Phase 1 Study Overview

- Men with type 2 diabetes mellitus (T2DM) **received intradermal injections** of AZD8601 or placebo at randomized sites on the forearm
- **Safety**: Only treatment-related adverse events were mild injection-site reactions

Table 2 Adverse events

Study part (*n*): group (*n*)	Part A (*n* = 27): Placebo only[a] (*n* = 9)	Part A (*n* = 27): VEGF-A mRNA/placebo[a] (*n* = 18)	Part B (*n* = 15): VEGF-A mRNA/placebo[b] (*n* = 15)
Participants with any AE, *n* (%)	5 (55.6)	18 (100.0)	14 (93.3)
Causally treatment-related, *n* (%)	0	18 (100.0)	14 (93.3)
Treatment unrelated, *n* (%)	5 (55.6)	0	0
Participants with causally treatment-related AEs, *n* (%)			
Injection-site reaction [mild]	0	18 (100.0)	14 (93.3)
Participants with treatment-unrelated AEs, *n* (%)			
Injection-site reaction [mild]	1 (11.1)	0	0
Injection-site erythema [mild]	1 (11.1)	2 (11.1)	0
Asthenia [mild]	0	1 (5.6)	0
Tinea pedis [mild]	0	0	1 (6.7)
Arthropod bite [mild]	0	1 (5.6)	1 (6.7)
Injury [moderate]	0	1 (5.6)	0
Skin abrasion [mild]	0	1 (5.6)	0
Muscle spasms [mild]	0	1 (5.6)	0
Back pain [mild or moderate]	2 (22.2)	0	0
Myalgia [moderate]	0	0	1 (6.7)
Dizziness [mild]	0	1 (5.6)	0
Headache [mild]	1 (11.1)	0	0
Pruritus [mild]	0	1 (5.6)	0
Tooth extraction [mild]	0	1 (5.6)	0
Nasopharyngitis [moderate]	1 (11.1)	0	0

AE, adverse event; VEGF-A mRNA, vascular endothelial growth factor A modified messenger RNA
[a]VEGF-A mRNA/placebo, placebo/VEGF-A mRNA, or placebo/placebo at injection sites 1/2
[b]Randomized order of VEGF-A and placebo injections

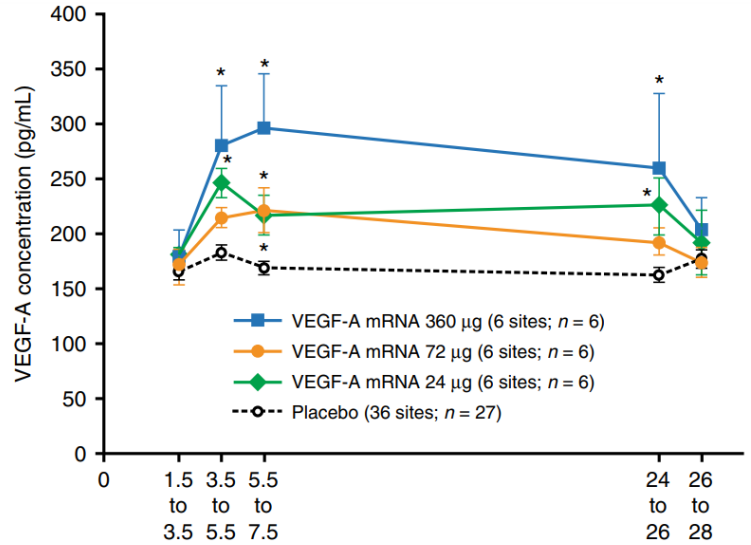
Gan, Li-Ming et al. "Intradermal delivery of modified mRNA…" *Nature Communications*, 2019, https://doi.org/10.1038/s41467-019-08852-4

Phase 1 trial tested safety and suggested angiogenic potential

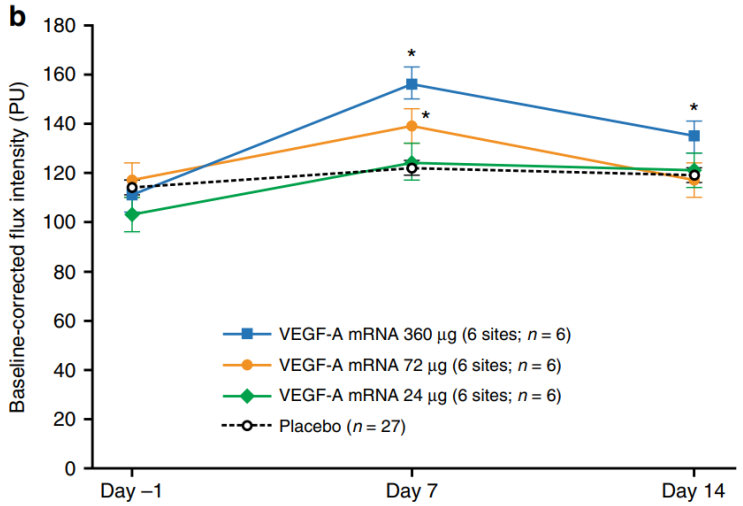
Phase 1 Study Efficacy Overview

- Enhancements in basal skin blood flow at 4 hours and 7 days post-administration were detected using laser Doppler fluximetry and imaging
- Intradermal VEGF-A mRNA led to local functional VEGF-A protein expression and transient skin blood flow enhancement
- **VEGF-A mRNA has potential for regenerative angiogenesis**

Mean VEGF-A protein levels in mRNA-treated sites were significantly elevated after administration



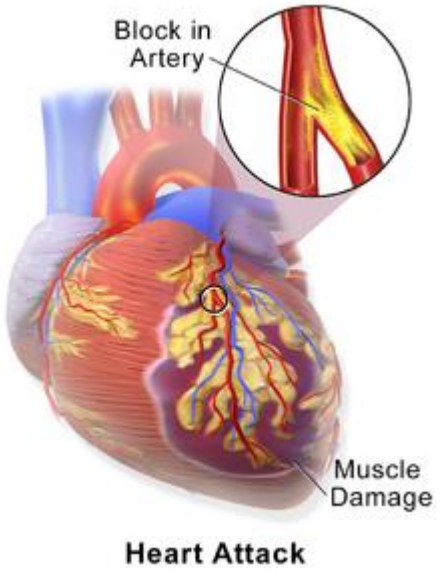
Enhanced basal skin blood flow



Gan, Li-Ming et al. "Intradermal delivery of modified mRNA…" *Nature Communications*, 2019, https://doi.org/10.1038/s41467-019-08852-4

VEGF-A has the potential to improve cardiovascular outcomes

A local, transient increase in VEGF-A protein levels in the heart has the potential to reduce morbidity and mortality in patients with heart failure with reduced ejection fraction and post-MI-cardiac dysfunction by improving cardiac perfusion and left ventricular ejection fraction



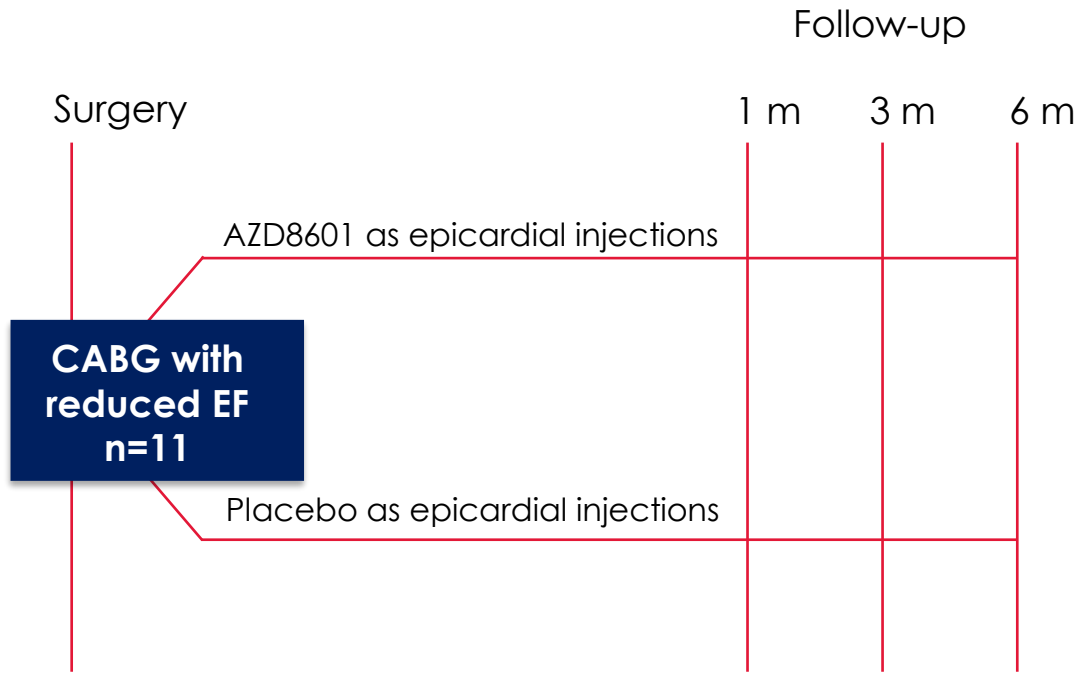
- Stimulate vessel regeneration to improve cardiovascular outcome
- VEGF-A protein is made within the cells and secreted into the neighboring microenvironment, mimicking the paracrine role of the protein

VEGF-A (AZD8601) Phase 2a focused on safety and efficacy

- Study performed in multiple European sites
- Primary endpoints
  - Safety & tolerability
- Exploratory endpoints
  - Blood flow, left ventricular end-diastolic and end-systolic volume, ejection fraction, and wall motion, and cardiac function
  - Clinical symptoms: NYHA functional class, SAQ, and KCCQ
  - Change in troponin T and NT-proBNP levels from baseline
  - VEGF-A protein concentration in plasma

Trial update

- Recruitment completed after enrollment of low dose cohort (n=11)



11 patients for elective bypass surgery

(originally planned for 12 patients in low dose cohort and 12 patients in high dose cohort)

CABG: Coronary artery bypass surgery
EF: Ejection fraction

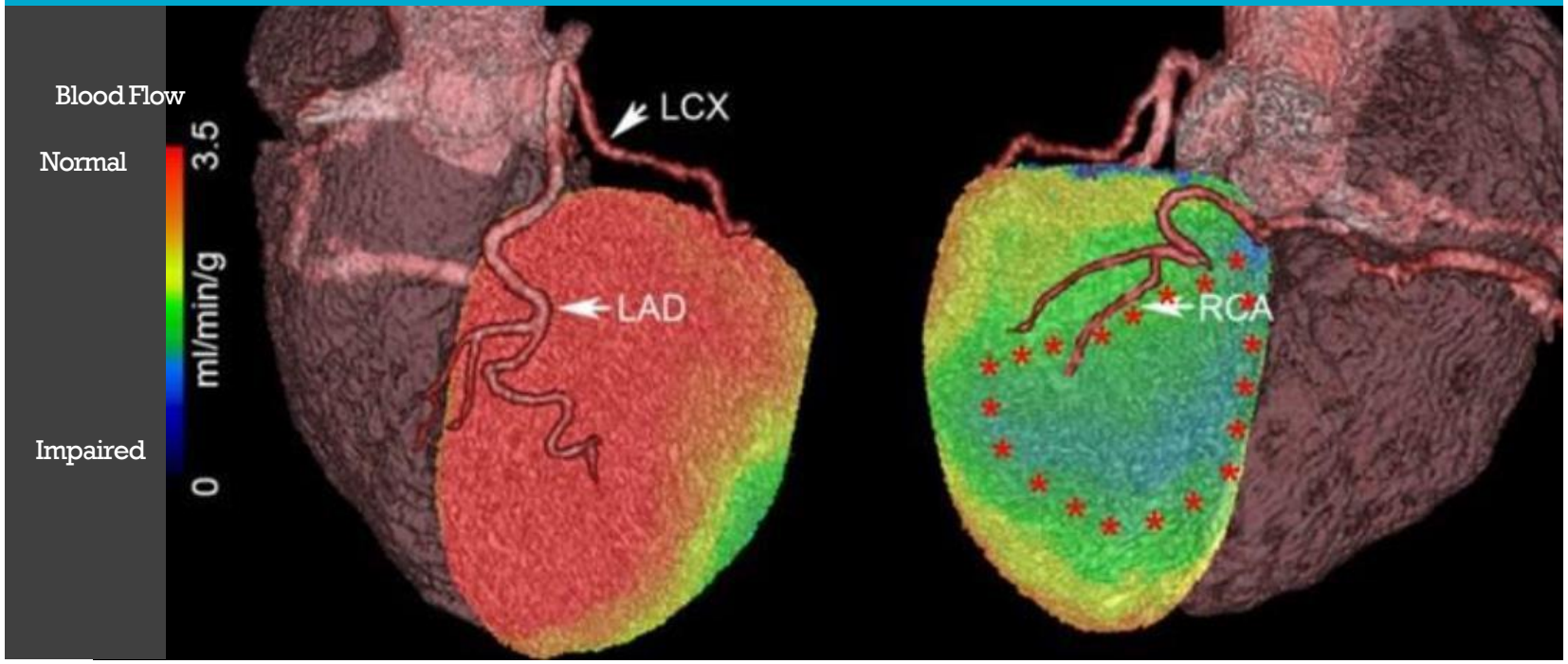
Antilla, Vesa et al. "Synthetic mRNA encoding VEGF-A…," *Molecular Therapy,* 2020. https://doi.org/10.1016/j.omtm.2020.05.030

Epicardial injections on coronary artery bypass surgery (CABG) patients

Administration overview

- AZD8601 3 mg or placebo administered as 30 epicardial injections in a 10-min extension of cardioplegia (the deliberate temporary stopping of the heart to permit heart surgery)

O^{15}-PET imaging is used to create tailored injection maps in patients



★ Injection sites in areas with impaired blood flow

Moderna's therapeutics: Relaxin

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	mRNA-1944						Worldwide *DARPA funded*
	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with Merck
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with Merck
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						AZ to pay milestones and royalties
Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic Acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen Storage Disease Type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	mRNA-3351						Provided to ILCM free of charge

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Relaxin is a naturally occurring hormone

Human relaxin-2 is a **naturally occurring hormone**, present in both men and women, that becomes elevated in pregnant women

It is a vasoactive peptide **associated with cardiovascular remodeling** – protects from vascular overwork, increases renal function, promotes cell growth and survival and maintains vessel structure

Subsequent studies have **implicated relaxin's role beyond pregnancy**, through vasodilatory, antifibrotic, anti-inflammatory and protective effects on multiple organs

Tietjens J, Teerlink JR. Serelaxin and acute heart failure. Heart. 2016 Jan;102(2):95-9
Adapted from Du et al. *Nat Rev Cardiol.* 2010;7:48-58

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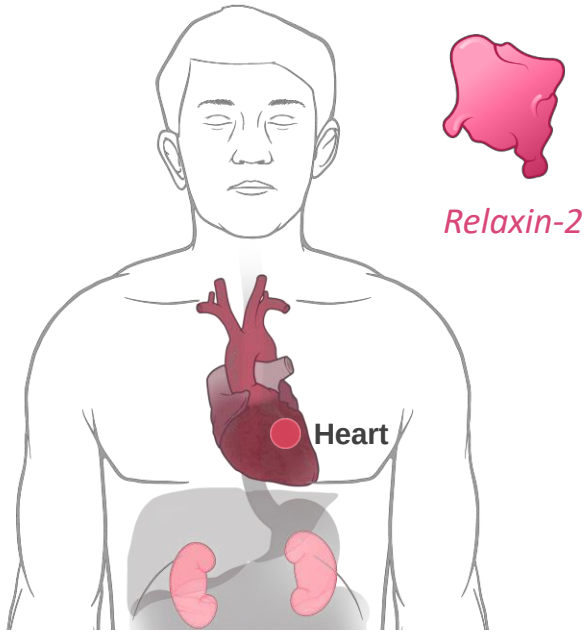
Evidence suggests relaxin has impact on cardiovascular disease



Relaxin-2

- **Relaxin activates a variety of pathways**, contributing to the reduction of oxidative stress, fibrosis, and inflammation
- Large body of evidence exists to support relaxin's clinical potential in several therapeutic areas, with its **impact on cardiovascular disease having been studied in both preclinical and clinical settings**

↓ Myocardial overload

↑ Renal function

↑ Cell preservation

↑ Extracellular matrix (ECM) remodeling

Tietjens J, Teerlink JR. Serelaxin and acute heart failure. Heart. 2016 Jan;102(2):95-9
Adapted from Du et al. *Nat Rev Cardiol.* 2010;7:48-58

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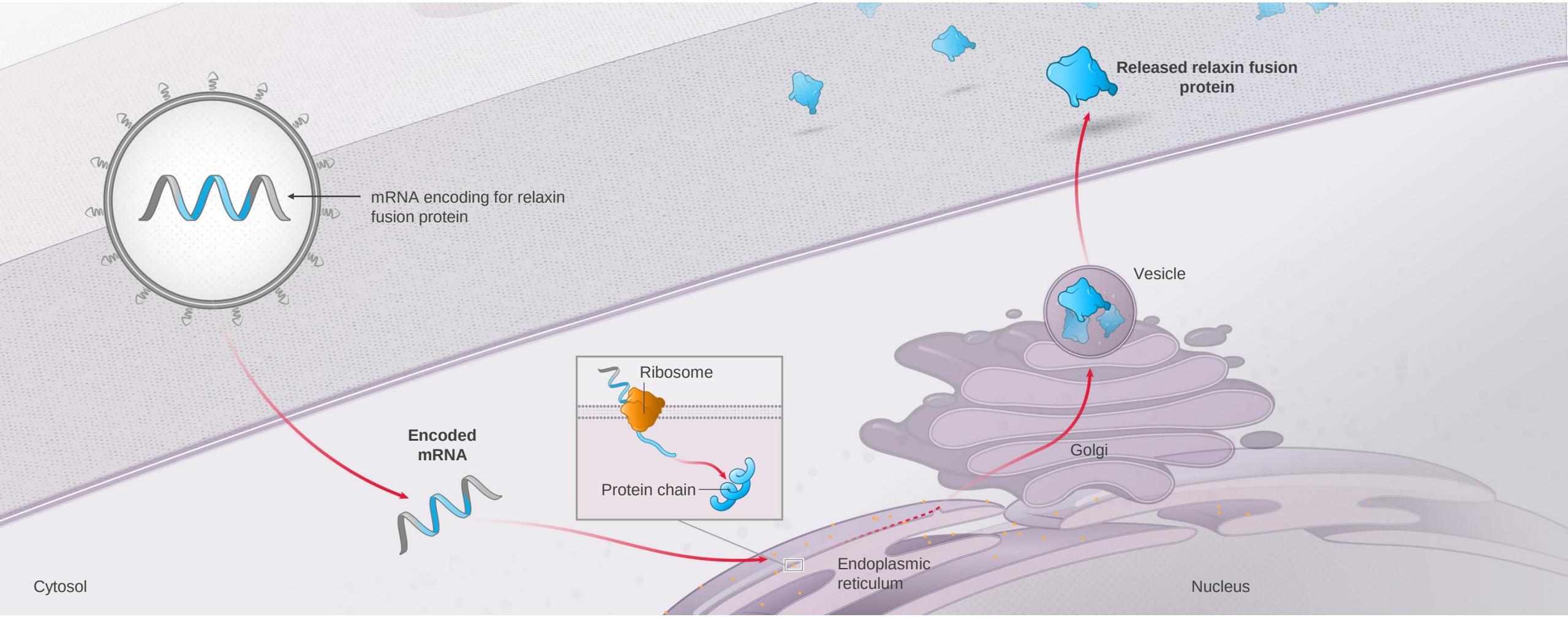
Relaxin therapy (mRNA-0184) encodes for relaxin fusion protein



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Moderna's relaxin program (mRNA-0184) is being developed to treat decompensated heart failure

- Acute heart failure (AHF) is defined as the new onset or worsening of symptoms and signs of heart failure (HF)
- In developed countries, HF has become a substantial public health problem, affecting 2% of the adult population
- AHF is the most frequent cause of unplanned hospital admission in patients of >65 years of age
- **Period after discharge is known as 'vulnerable phase' (2-3 months):**
  - 25% of patients readmitted within 30 days[1]
  - 30-day mortality rate of 5-10%[2,3]
  - 3-month readmission rates are ~30%[4,5,6]
  - Mortality is estimated at 25 – 30% at 1 year

– HF decompensation contributes to often permanent further decline in disease

Heart Failure Symptoms Outcomes
▪ Dyspnea (shortness of breath)
▪ Fatigue
▪ Pulmonary rales (abnormal crackling sounds)
▪ Peripheral oedema
▪ Distended jugular veins

(1) https://www.nature.com/articles/nrcardio.2015.14 (2) https://jamanetwork.com/journals/jama/fullarticle/185996 (3) https://www.sciencedirect.com/science/article/pii/S073510971001908X?via%3Dihub
(4) https://www.sciencedirect.com/science/article/pii/S0735109714002915?via%3Dihub (5) https://onlinelibrary.wiley.com/doi/10.1002/ejhf.566 (6) https://onlinelibrary.wiley.com/doi/10.1002/ejhf.1020

moderna

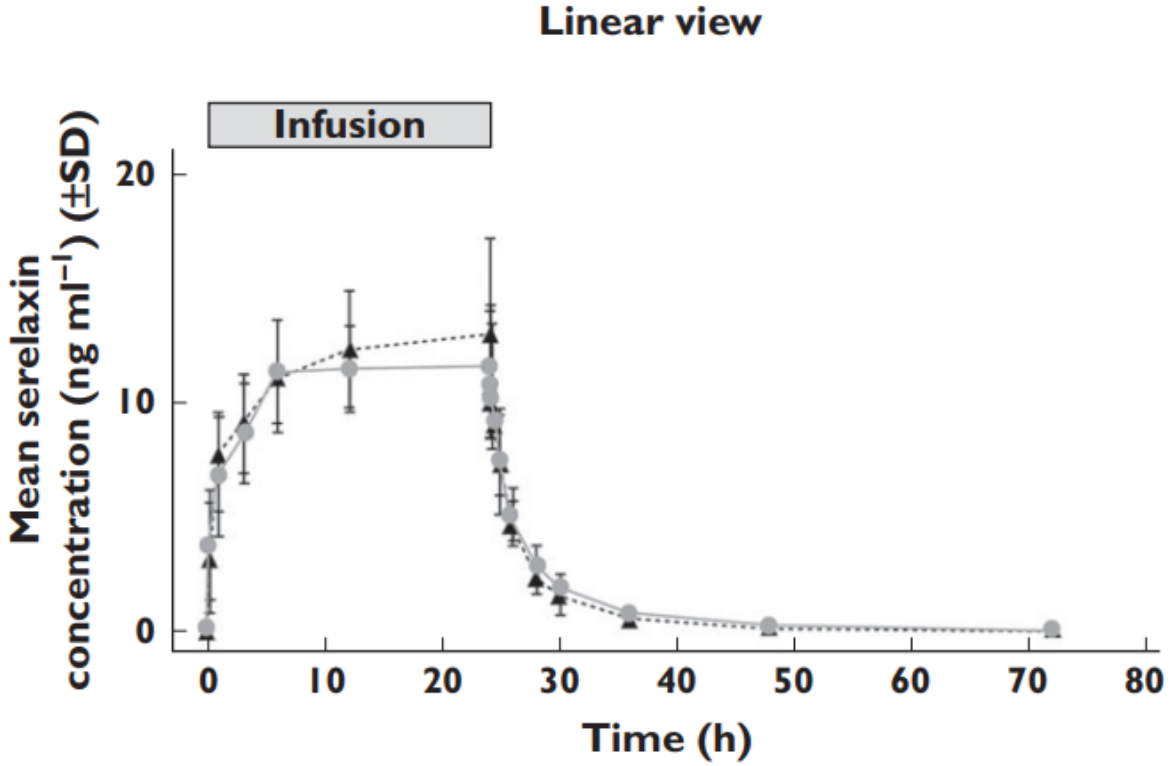
Longer duration relaxin and repeated infusions could allow for improved efficacy

Serelaxin (recombinant human relaxin-2) in a Phase 2/3 study

- Despite promising early results, the pivotal trial did not meet its primary endpoint

Recombinant relaxin-2

Serelaxin Serum Concentration – Time Profiles



Data shown as arithmetic mean with standard deviation in linear and semilogarithmic views for groups of patients with mild hepatic impairment compared with healthy controls

Kobalava, Zhanna et al. "Pharmacokinetics of serelaxin in patients with hepatic impairment: a single-dose, open-label, parallel group study," *BR J Clin Pharmacol,* (2015), https://doi.org/10.1111/bcp.12572

moderna

Longer duration relaxin and repeated infusions could allow for improved efficacy

Serelaxin (recombinant human relaxin-2) in a Phase 2/3 study

- Despite promising early results, the pivotal trial did not meet its primary endpoint

Moderna's technology and strategy may address these shortcomings through the following approaches:

- Long-acting form of relaxin has potential for extended disease impact
- Repeat acute/sub chronic dosing could extend the expected impact on cardiovascular disease (vs. single acute dosing with serelaxin)
- Indication strategy and trial design will prioritize an approach supporting clinical endpoints

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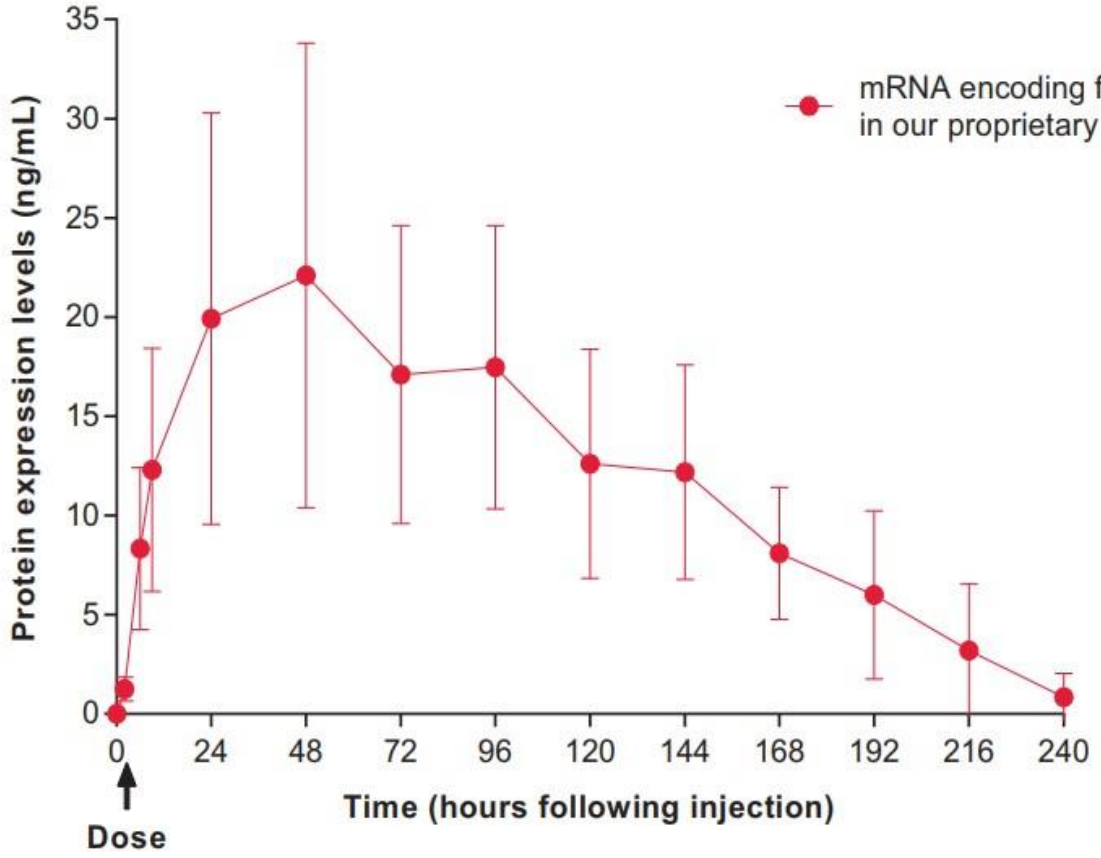
Previous relaxin collaboration saw protein expression in NHPs

- Preliminary protein expression data in non-human primates (NHPs) supports hypothesis of extended pharmacology relative to historical efforts with recombinant protein

- Advantages of mRNA delivery of relaxin fusion protein over earlier recombinant relaxin approaches:
  - Significantly increased half-life
  - No need for continuous IV infusion to maintain relaxin levels
  - Feasibility of repeat dosing

AZD7970: Protein expression up to 10 days in NHP



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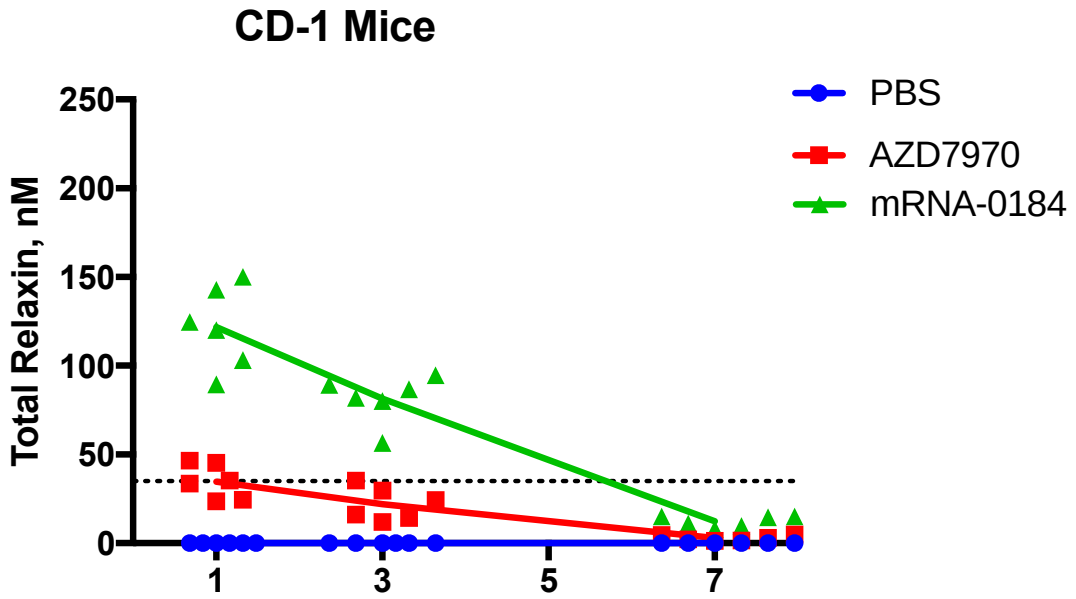
We are preparing to enter the clinic in chronic heart failure

Moderna's relaxin candidate (mRNA-0184)

- Introduction of a drug product with better pharmacology relative to AZD7970
- mRNA sequence engineered to increase protein expression and prolong half-life
- Additional NHP and preclinical studies ongoing
- Planning for a Phase 1 study in participants with chronic heart failure
  - Relaxin (mRNA-0184) to be administered after HF decompensation to bridge patients through the vulnerable period
  - Prior knowledge and use of biomarkers as clinical endpoints could help accelerate the overall development plan

Increase in expression observed in mice with mRNA-0184 vs. AZD7970 with sequence change



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We've been at this for ten years.

Our mRNA platform is a modern approach to medicine.

But it's just the beginning.

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Stéphane Bancel

Chief Executive Officer

The next 10 years…

1) We now know that Moderna's mRNA works

2) We have a unique cash position and growing (~$15B at the end of August)

3) We built the company from the beginning so it would be highly scalable because we knew if one medicine was going to get to market, then many would…

We are scaling the company so we can grow 10X

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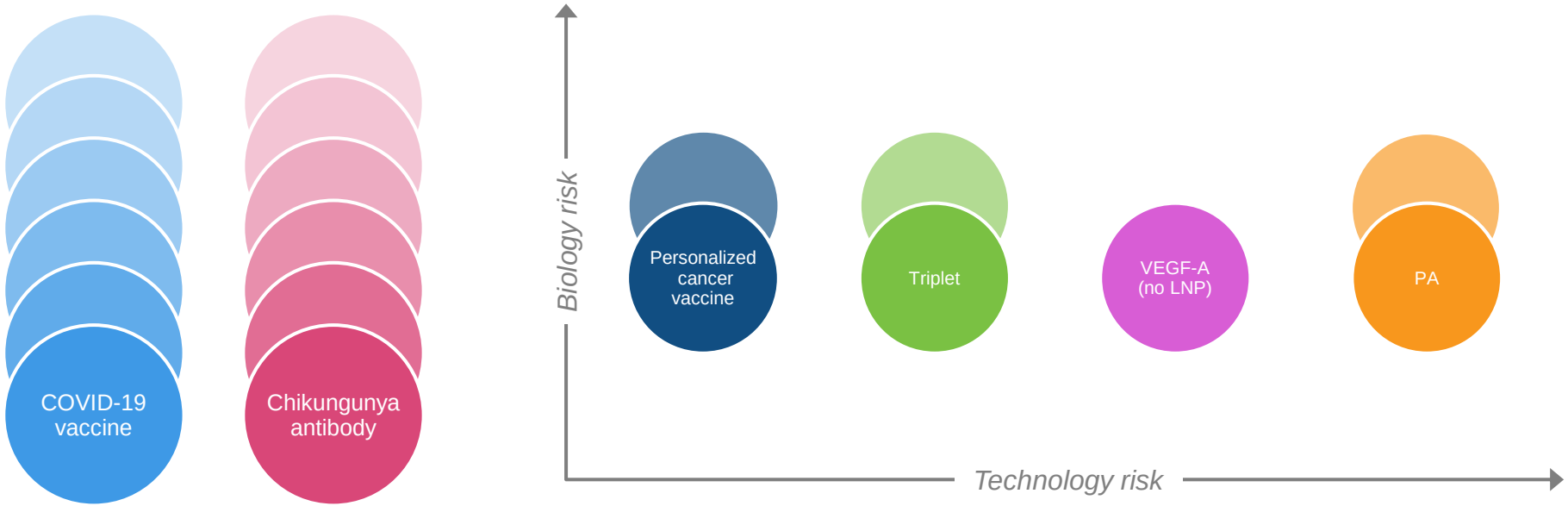
Moderna is an information-medicine based platform company

COMMERCIAL — DEVELOPMENT — RESEARCH

Core Modalities

Exploratory Modalities

Future Modalities



Prophylactic vaccines

Systemic secreted & cell surface therapeutics

Cancer vaccines

Intratumoral immuno-oncology

Localized regenerative therapeutics

Systemic intracellular therapeutics

Lung

Stem cells

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Moderna's product strategy

1	Bring to market a **pan-respiratory annual booster vaccine** (which we will continuously customize)
2	Bring to market **first-in-class vaccines for complex viruses**
3	Bring to market **therapeutics based on mRNA-encoded proteins**
4	Bring to market **therapeutics based on mRNA-encoded gene editing enzymes**

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Moderna's Respiratory Vaccines (Pipeline 1/3)

11 respiratory vaccine programs in the clinic

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Adults	COVID-19 vaccine	**mRNA-1273**						Worldwide
		mRNA-1273.351	Beta variant					Worldwide
		mRNA-1273.617	Delta variant					Worldwide
		mRNA-1273.211	Beta variant + wild-type					Worldwide
		mRNA-1273.213	Beta + Delta variant					Worldwide
		mRNA-1283	Next generation (2-5 °C)					Worldwide
Prophylactic vaccines	Flu vaccine	**mRNA-1010**	Phase 1/2		Phase 2/3 prep			Worldwide
		mRNA-1020						Worldwide
		mRNA-1030						Worldwide
	COVID + Flu vaccine	**mRNA-1073**	mRNA-1273 + mRNA-1010					Worldwide
	Older adults RSV vaccine	**mRNA-1345**			Phase 2/3 prep			Worldwide
Adolescents & Pediatrics	COVID-19 vaccine (adolescents)	**mRNA-1273**	TeenCOVE					Worldwide
	COVID-19 vaccine (pediatrics)	**mRNA-1273**	KidCOVE					Worldwide
	Pediatric RSV vaccine	**mRNA-1345**	Phase 1b					Worldwide
	Pediatric hMPV + PIV3 vaccine	**mRNA-1653**						Worldwide
	Pediatric RSV + hMPV vaccine	**mRNA-1365**						Worldwide

New development candidates

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Moderna's Other Vaccines (Pipeline 2/3)

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Prophylactic vaccines	CMV vaccine	**mRNA-1647**				Phase 3 prep		Worldwide
	EBV prophylactic vaccine **EBV therapeutic vaccine**	**mRNA-1189**						Worldwide
		mRNA-1195						Worldwide
	Zika vaccine	**mRNA-1893**						Worldwide ***BARDA** funded*
	HIV vaccine	**mRNA-1644**	Open IND					Worldwide ***IAVI/others** funded*
		mRNA-1574						Worldwide ***BMGF/NIAID/ others** funded*
	Nipah vaccine	**mRNA-1215**						Worldwide ***NIH** funded*

New development candidates

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Moderna's Therapeutics (Pipeline 3/3)

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Antibody against Chikungunya virus	**mRNA-1944**						Worldwide ***DARPA** funded*
	IL-2 *Autoimmune disorders*	**mRNA-6231**						Worldwide
	Relaxin *Heart failure*	**mRNA-0184**						Worldwide
	PD-L1 *Autoimmune hepatitis*	**mRNA-6981**						Worldwide
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	IL-12 *Solid tumors*	**MEDI1191**						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	**AZD8601**						**AZ** to pay milestones and royalties
Systemic Intracellular Therapeutics	Propionic Acidemia (PA)	**mRNA-3927**						Worldwide
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	Glycogen Storage Disease Type 1a (GSD1a)	**mRNA-3745**	**Open IND**					Worldwide
	Phenylketonuria (PKU)	**mRNA-3283**						Worldwide
	Crigler-Najjar Syndrome Type 1 (CN-1)	**mRNA-3351**						Provided to **ILCM** free of charge

New development candidates

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To scale Moderna 10X, we are investing in:

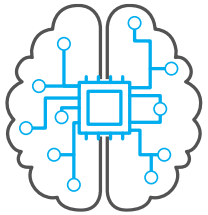
Talent

Hiring, training & growing people

Upgrading Moderna University

Digital & Robotics

2019-2021 digital investments expected to be over $250 million



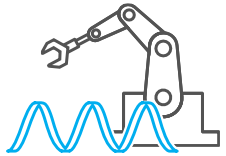
AI

We aim to make AI part of how we run the business

Launching an AI academy

Process Development

We are not done, we have just started



Manufacturing

Designing a fourth building in Norwood, MA

Building a new plant in Canada and in discussions with more countries

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Q&A