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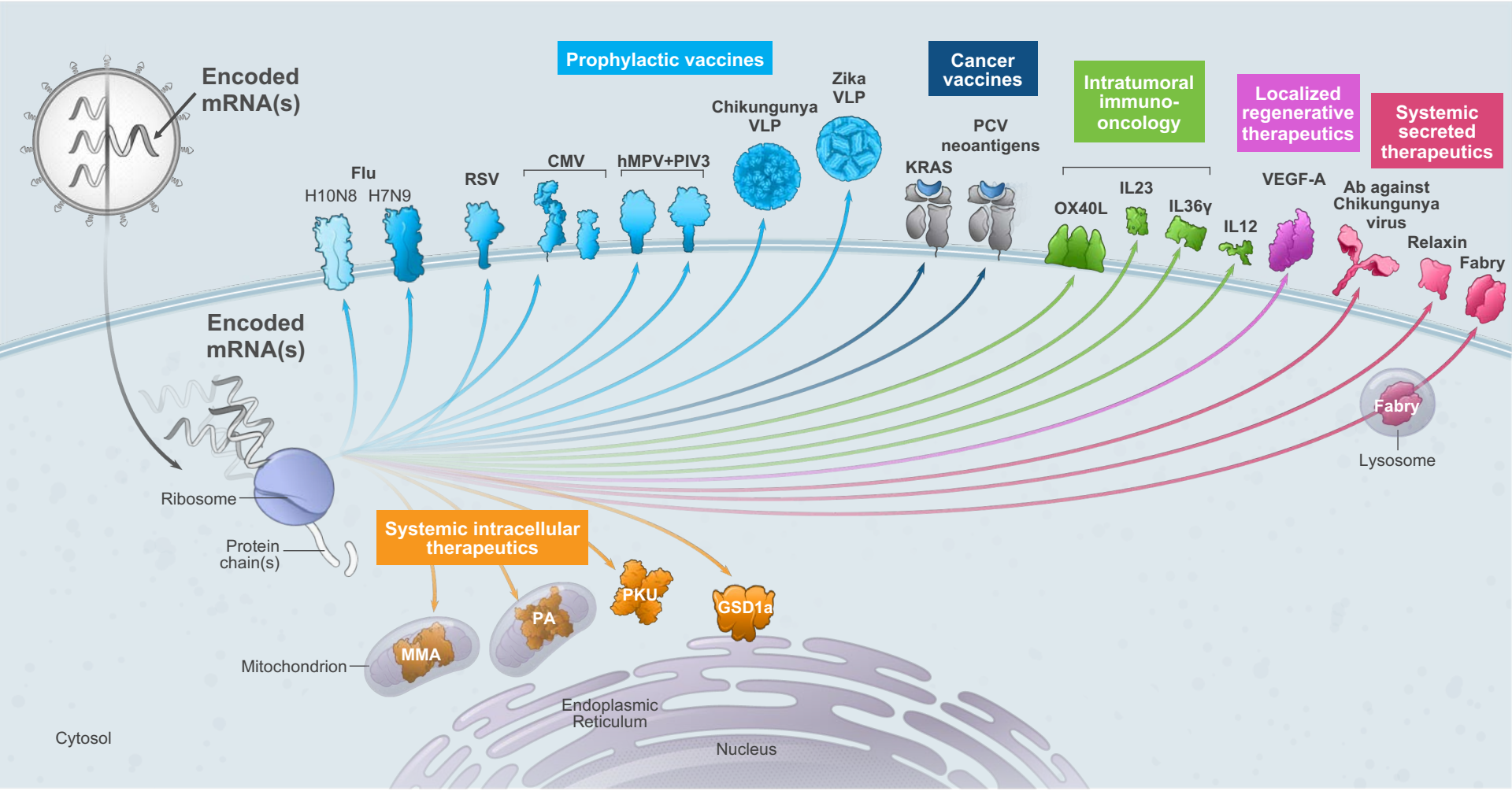
R&D Day
September 12, 2019



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Welcome and Introduction

Stéphane Bancel

Chief Executive Officer

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended including, but not limited to, statements concerning: the potential approval and commercial launch of Moderna's development candidates, including CMV vaccine (mRNA-1647); Moderna's belief that Phase 1 clinical data from mRNA-1944 provides support for the continued development of Moderna's rare disease therapeutic modality; clinical program next steps; development candidate activities; future clinical study commencement, progression, enrollment, and conclusion, including the Phase 2 clinical study start and Phase 3 preparation for mRNA-1647; manufacturing capacity and scalability; regulatory submissions and approvals; risk management; estimates and forward-looking projections with respect to Moderna or its anticipated future performance or events, including the commercial opportunity and gross margins for mRNA-1647. In some cases, forward-looking statements can be identified by terminology such as "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: preclinical and clinical development is lengthy and uncertain, especially for a new category of medicines such as mRNA, and therefore Moderna's preclinical programs or development candidates may be delayed, terminated, or may never advance to or in the clinic; no mRNA drug has been approved in this new potential class of medicines, and may never be approved; mRNA drug development has substantial clinical development and regulatory risks due to the novel and unprecedented nature of this new class of medicines; and those described 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 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 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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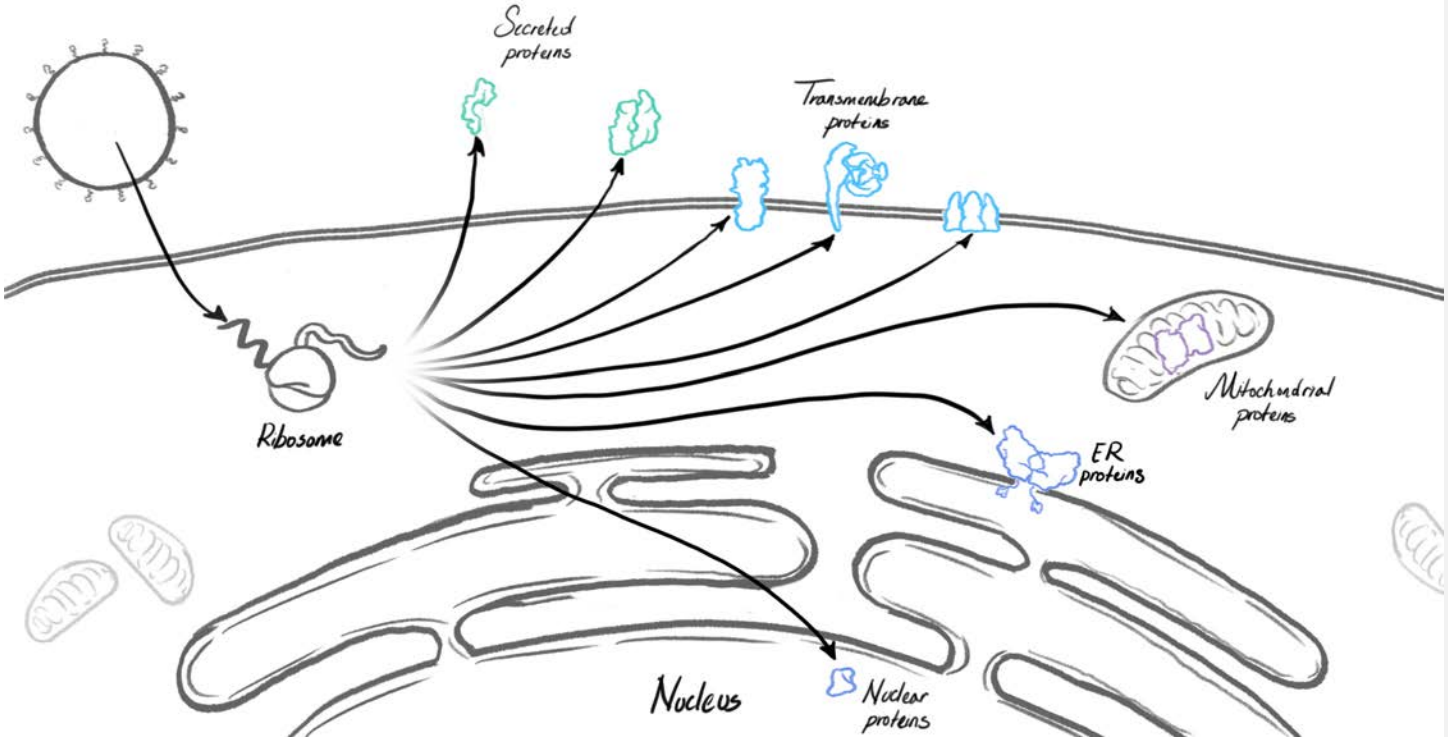
mRNA as a potential new class of medicines



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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Risk management is essential to building a new class of medicines

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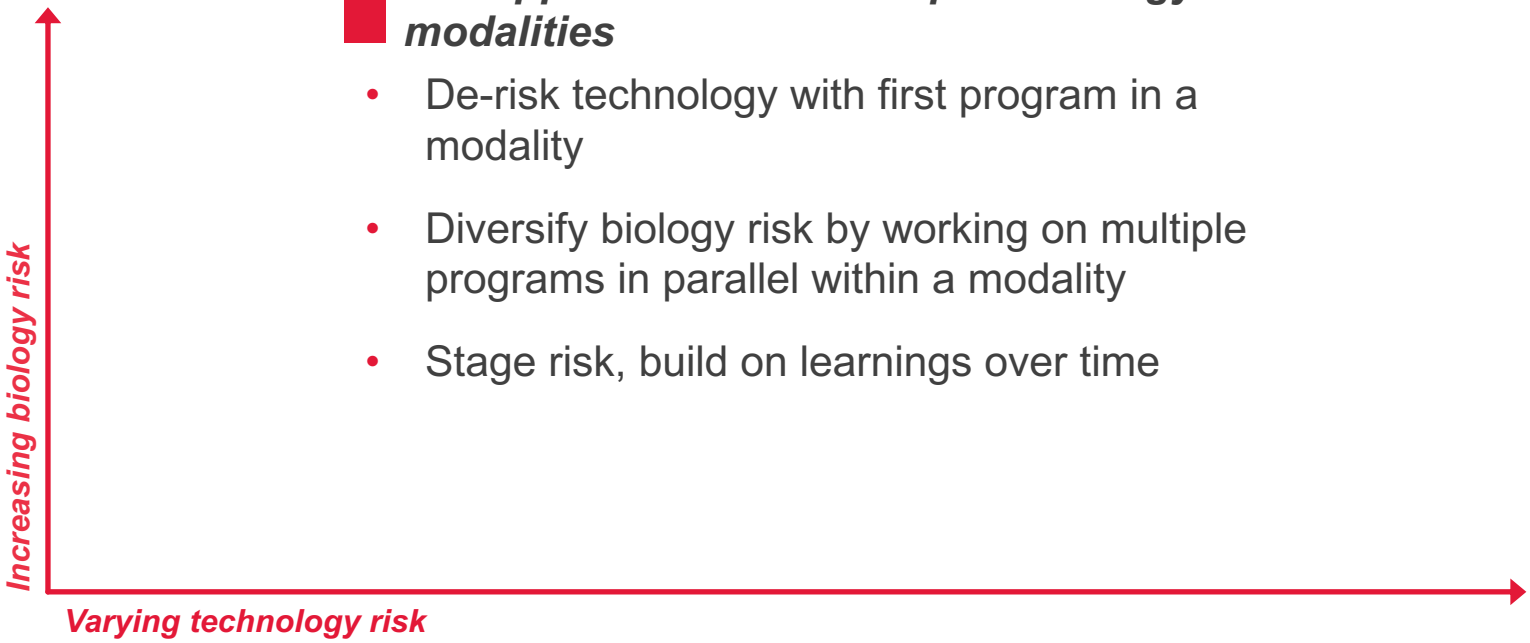
Risk management is essential to building a new class of medicines

Our approach is to develop technology modalities

- De-risk technology with first program in a modality
- Diversify biology risk by working on multiple programs in parallel within a modality
- Stage risk, build on learnings over time



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Risk management is essential to building a new class of medicines

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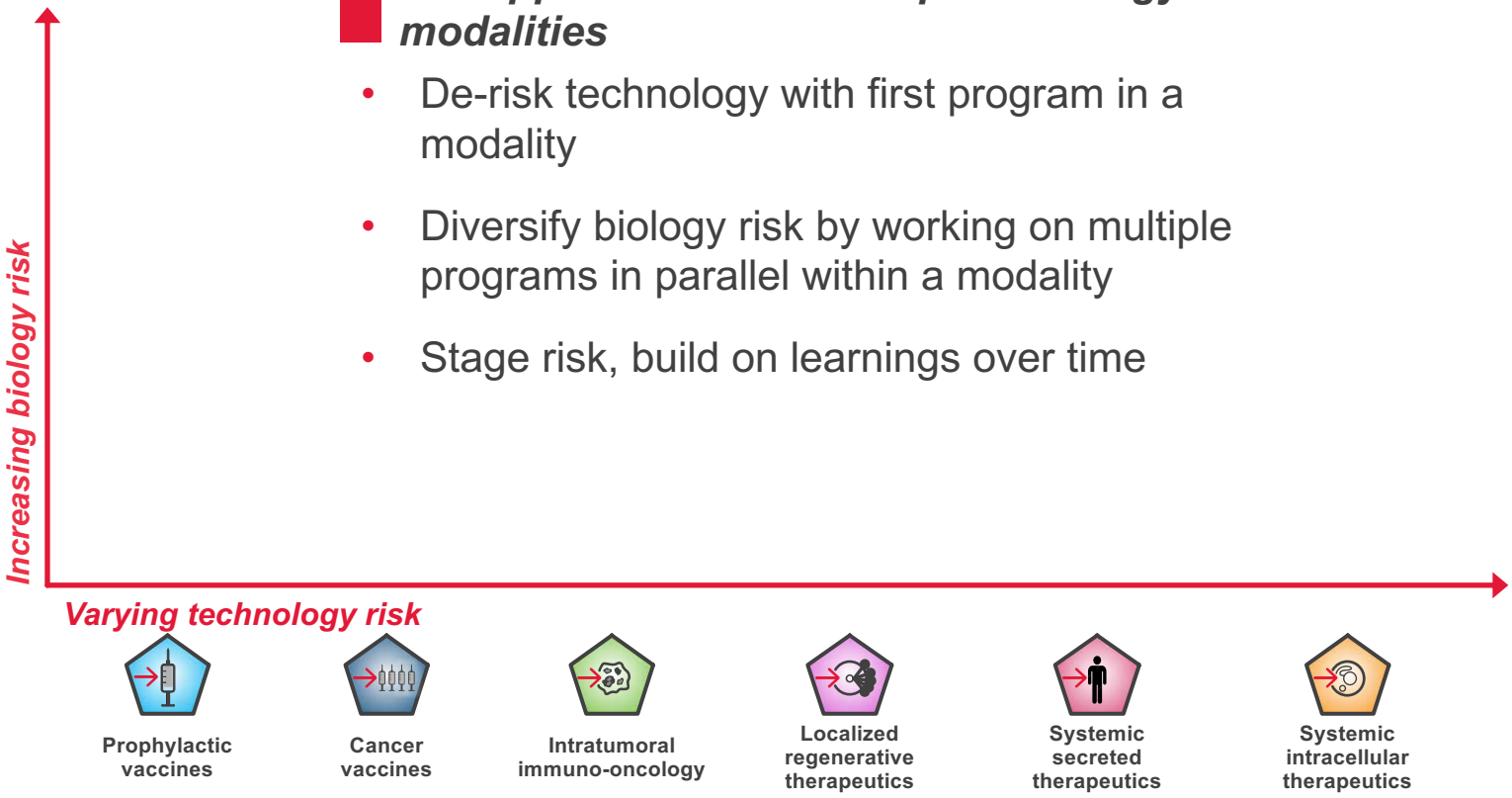

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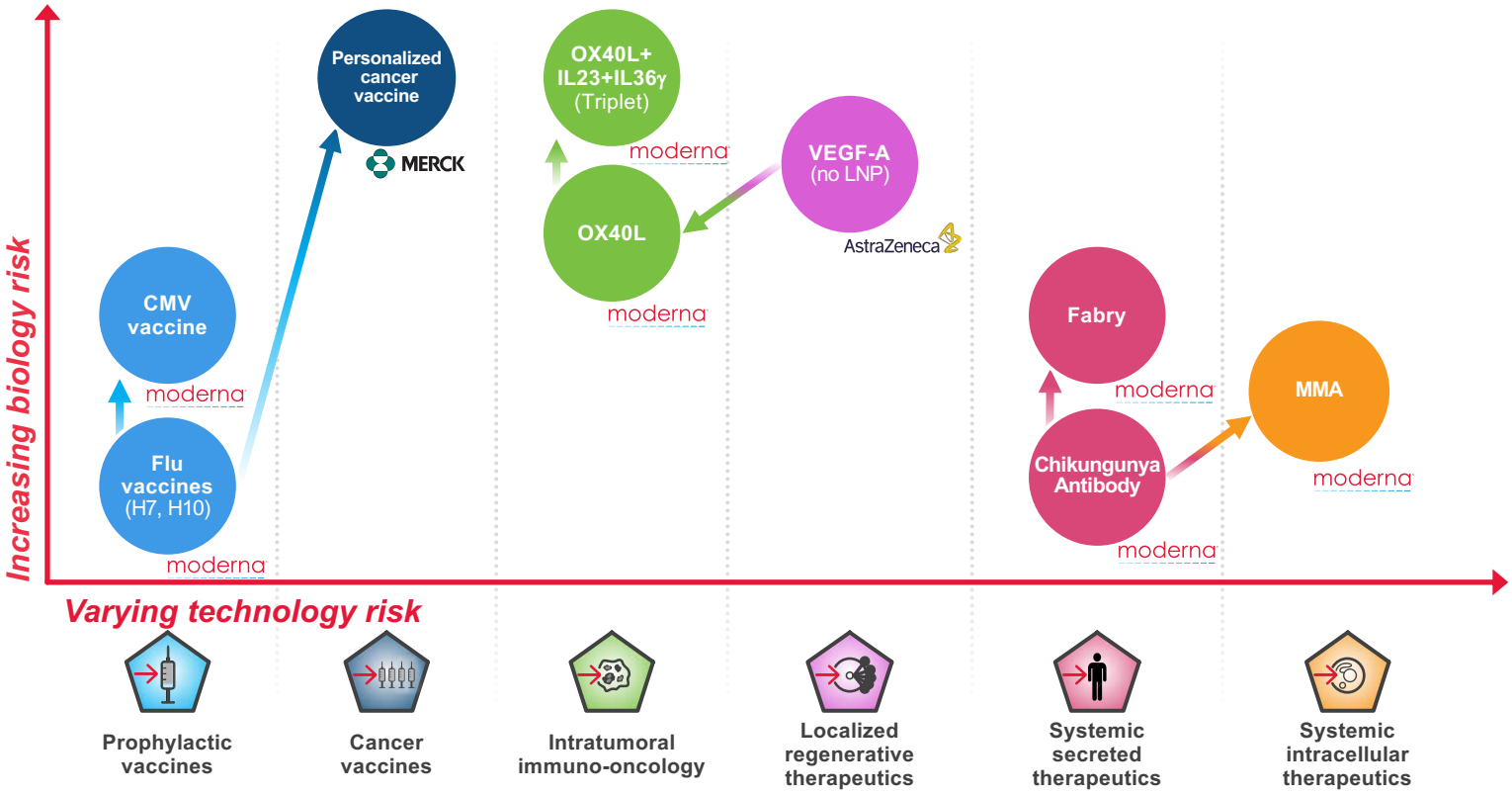
Risk management is essential to building a new class of medicines



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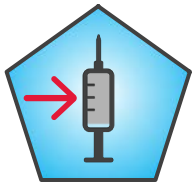
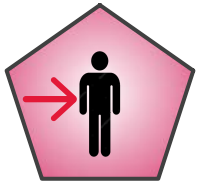
Two important positive clinical milestones in two modalities announced today



Cytomegalovirus (CMV) vaccine (mRNA-1647)

- Positive interim phase 1 data
- Successfully immunized seronegatives and boosted seropositives
- Generally well tolerated
- Phase 2 to start in the near term
- Preparations underway for the phase 3
- Moderna owns the global commercial rights to mRNA-1647



Antibody against Chikungunya virus (mRNA-1944)

- Positive phase 1 data
- Observed dose dependent protein expression
- Achieved expected therapeutic levels at a well tolerated dose (0.3mg/kg)
- Observed expected translation from NHP to human

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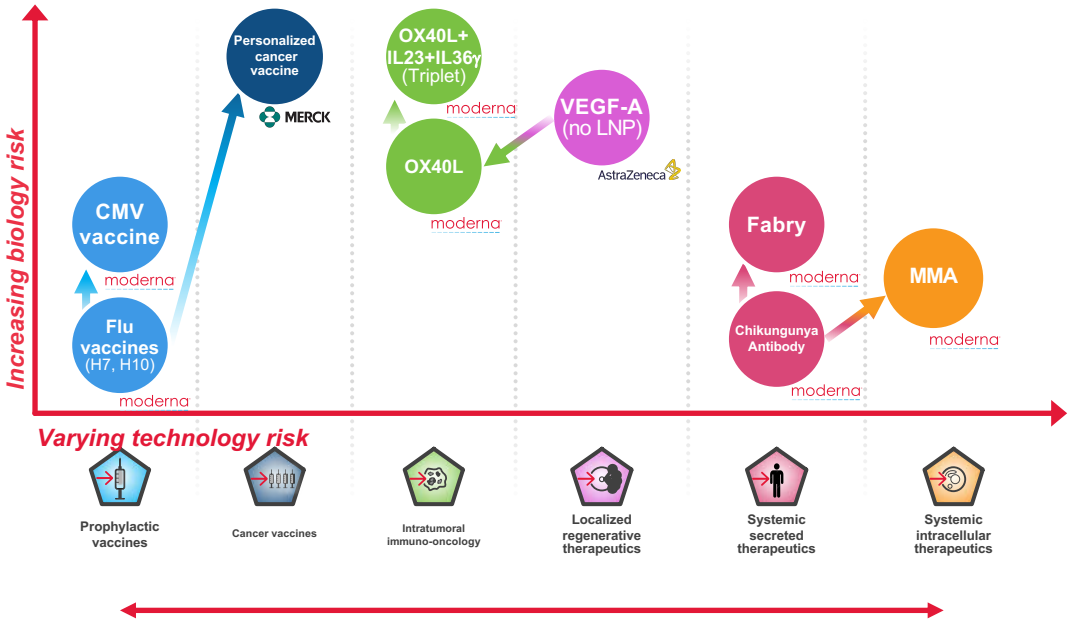
Body of clinical data from Moderna's platform to date

- Moderna platform investments in research, manufacturing and clinical have enabled 16 investigational medicines to start clinical trials in the last 3.5 years
- We have enrolled more than 1,300 subjects and patients across five modalities.
- We have administered repeat doses to patients through multiple cycles in our immuno-oncology programs (OX40L & PCV)
- Across 5 modalities we have shown that our development candidates:
  - have an acceptable safety profile and are generally well tolerated*
  - result in consistent protein expression**
  - encode functional proteins
  - translate from preclinical models to humans



*Common Adverse Events by Modality - Prophylactic Vaccines: injection site pain, myalgia, and fatigue; Cancer Vaccines: for PCV, the most common grade 2 adverse events were fatigue, soreness at the injection site, colitis, and myalgias; Intratumoral Immuno-Oncology: for OX40L, multiple grade 2 and a single grade 3 transient reversible injection related reactions; Localized Regenerative Therapeutics: for VEGF-A, mild injection-site reactions; and Systemic Secreted Therapeutics: see the section below titled Systemic Therapeutics – Secreted and Intracellular.

**Only mRNA-1325, our initial Zika vaccine did not elicit desired pharmacologic effect

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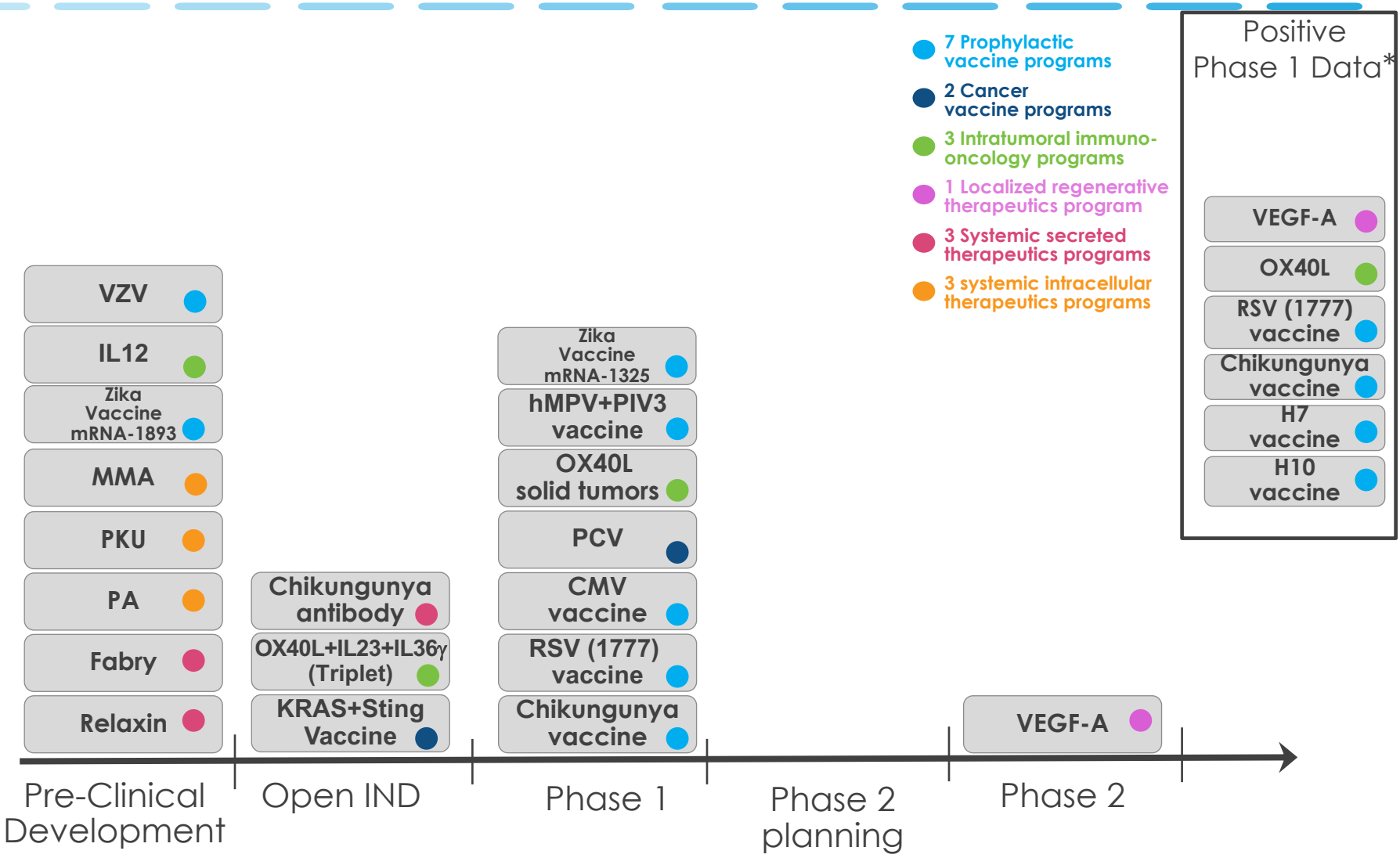
Moderna's development pipeline at IPO



*Data in some cases are interim; positive data means the data warrant continued advancement within a trial or for further development

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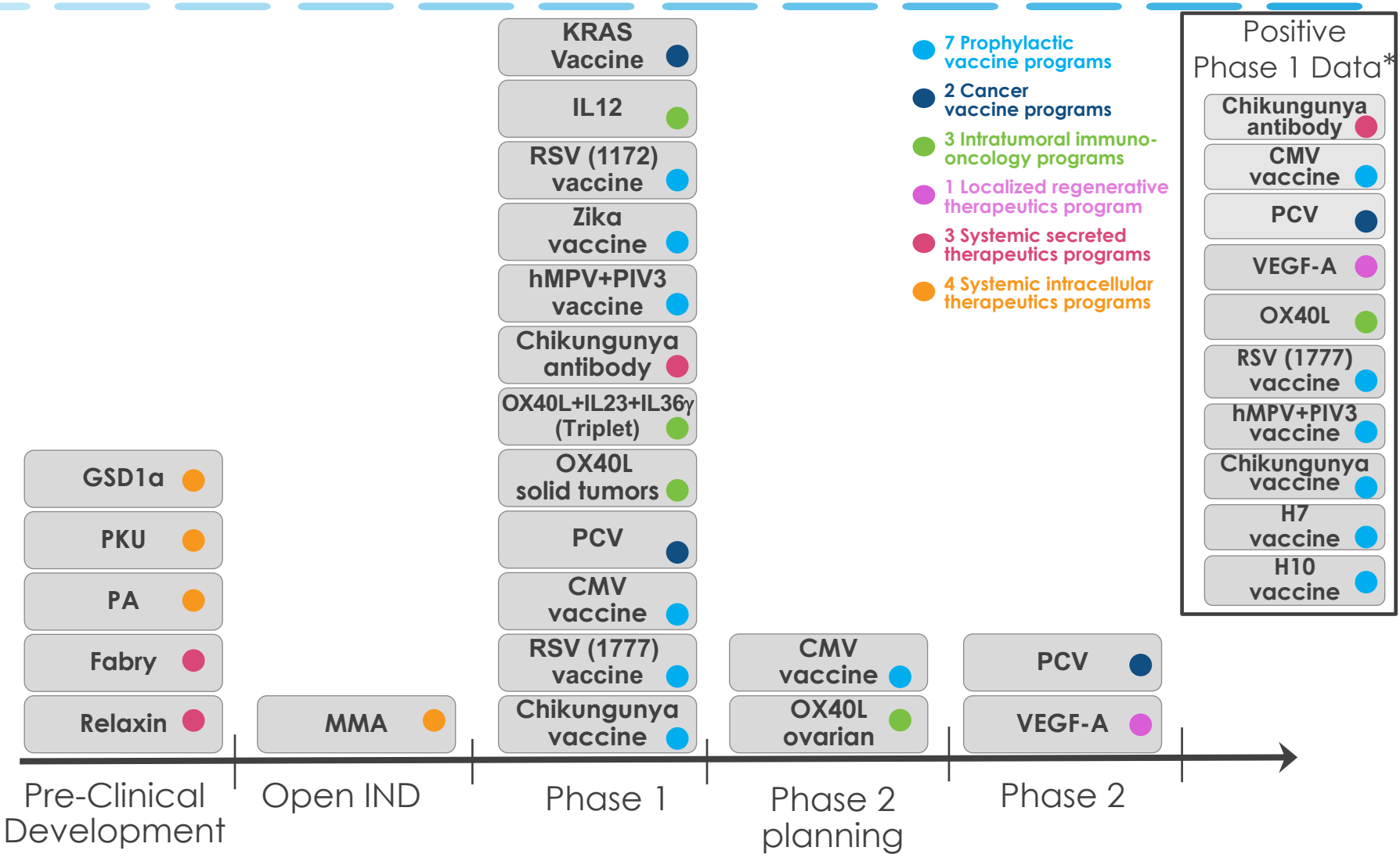
Moderna's development pipeline today (9 months since IPO)



*Data in some cases are interim; positive data means the data warrant continued advancement within a trial or for further development

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Moderna in September 2019

Pipeline

4
In or preparing for Ph 2

12
Ph 1 trials ongoing

10
Positive Ph1 readouts: 6 vaccines, PCV, OX40L, VEGF, Chik ab

Programs in Development

4
Vaccines for major unmet needs

- CMV preparing Phase 2
- hMPV+PIV3 – positive interim Ph 1 data
- RSV and Zika in Ph 1

5
Immuno-Oncology

- PCV in Ph 2
- OX40L preparing for Ph 2 cohort
- Triplet, IL2, KRAS in Ph 1

5
Rare Disease

- First systemic therapeutic: Chik antibody: positive Ph 1
- MMA – Ph 1 actively recruiting
- PA, PKU, Fabry & GSD1a in GLP Tox

Foundations

>1,300
Healthy volunteers and patients enrolled

>800
employees

A fully-integrated
200,000
sq. ft.
GMP site operational in Norwood, MA

Leading Biopharma Partners

MERCK
AstraZeneca
VERTEX

$1.44 bn
of cash, cash equivalents, as of June 30, 2019 (unaudited)

R&D Day 2019 agenda

September 12, 2019

Sign-in, Coffee, Breakfast		*7:30–8:30 AM*	*60 min*
Introduction	*Stéphane Bancel*	*8:30–8:40 AM*	*10 min*
CMV	*Tal Zaks, MD, PhD* *Sallie Permar, MD, PhD, Duke University School of Medicine* *Tal Zaks, MD, PhD* *Juan Andres* *Mark Schleiss, MD, University of Minnesota* *Laura Riley, MD, Weill Cornell Medical College* *Stéphane Bancel*	*8:40–10:00 AM*	*80 min*
Q&A		*10:00–10:30 AM*	*30 min*
Break		*10:30–10:40AM*	*10 min*
Immuno-oncology	*Tal Zaks, MD, PhD* *Keith Flaherty, MD, Massachusetts General Hospital*	*10:40–11:10 AM*	*30 min*
Antibody against Chikungunya virus	*Tal Zaks, MD, PhD*	*11:10–11:50AM*	*40 min*
Methylmalonic acidemia	*Gregory Enns, MD, Stanford University*	*11:50–12:20 AM*	*30 min*
Conclusion	*Stéphane Bancel*	*12:20–12:30 PM*	*10 min*
Q&A	*Moderna Team*	*12:30–1:00 PM*	*30 min*
Lunch			

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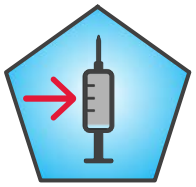
Prophylactic vaccines

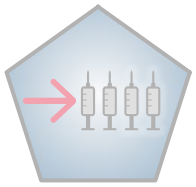
Tal Zaks, MD, PhD

Chief Medical Officer

Progress by modality

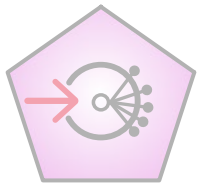


Prophylactic vaccines

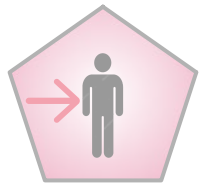


Cancer vaccines

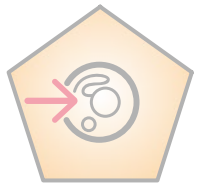
Intratumoral immuno-oncology



Localized regenerative therapeutics



Systemic secreted therapeutics



Systemic intracellular therapeutics

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Prophylactic Vaccines

Modality	ID #	Program	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Prophylactic vaccines – Commercial programs	**mRNA-1647**	CMV vaccine					Worldwide
	mRNA-1172/ Merck V172	RSV vaccine					Merck to pay milestones and royalties
	mRNA-1777	RSV vaccine					
	mRNA-1653	hMPV+PIV3 vaccine					Worldwide
	mRNA-1893	Zika vaccine					Worldwide *BARDA funded*
Prophylactic vaccines- Global health programs	**mRNA-1851**	Influenza H7N9 vaccine					Worldwide *Advancing subject to funding*
	mRNA-1440	Influenza H10N8 vaccine					Worldwide *Advancing subject to funding*
	mRNA-1388	Chikungunya vaccine					Worldwide *Advancing subject to funding*

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Our mRNA platform has significant advantages for the development of infectious disease vaccines

*mRNA **mimics natural infection** to activate the immune system and achieve a potentially potent response*

***Multiple** mRNAs in one vaccine for more compelling product profiles*

***Faster discovery**, ability to respond rapidly to emerging pandemic threats*

*Single process and **single, multi-product facility** for all vaccines*

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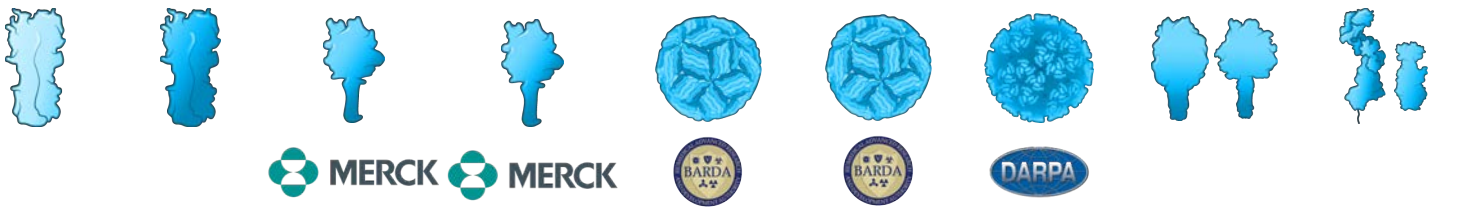
Progress in the prophylactic vaccines platform to date

		H10N8 mRNA-1440	H7N9 mRNA-1851	RSV mRNA-1777	RSV mRNA-1172	Zika mRNA-1325	Zika mRNA-1893	Chik mRNA-1388	hMPV+PIV3 mRNA-1653	CMV mRNA-1647
Clinical	*Immunogenicity at sufficient levels to warrant further study*	✓	✓	✓	*Ongoing*	✗	*Ongoing*	✓	✓	✓
Clinical	*Clinical safety and tolerability*	✓	✓	✓	*Ongoing*	✓	*Ongoing*	✓	✓	✓
Preclinical	*Dose dependent pharmacology*	✓	✓	✓	✓	✓	✓	✓	✓	✓
Preclinical	*NHP protein expression*	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prophylactic vaccines										



Positive readouts from six prophylactic vaccines

Phase 1 safety and immunogenicity data (H10N8, H7N9, RSV, Chikungunya virus, hMPV+PIV3, CMV)

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Prophylactic Vaccines

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	mRNA-1388	Chikungunya vaccine					Worldwide *Advancing subject to funding*

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Congenital CMV infection and the global need for a vaccine

SALLIE PERMAR, MD, PHD

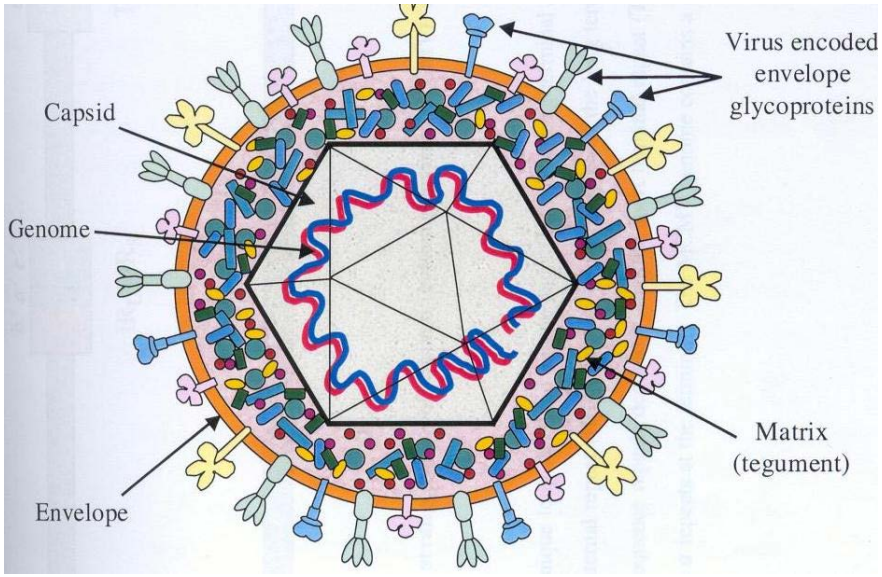
ASSOCIATE DEAN OF PHYSICIAN SCIENTIST DEVELOPMENT

PROFESSOR, PEDIATRICS, IMMUNOLOGY, MOLECULAR GENETICS AND MICROBIOLOGY

DUKE UNIVERSITY SCHOOL OF MEDICINE

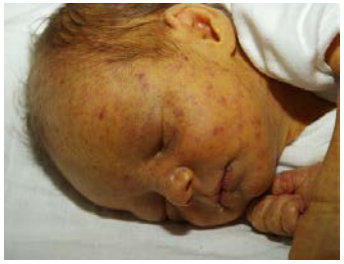
CMV: The Virus

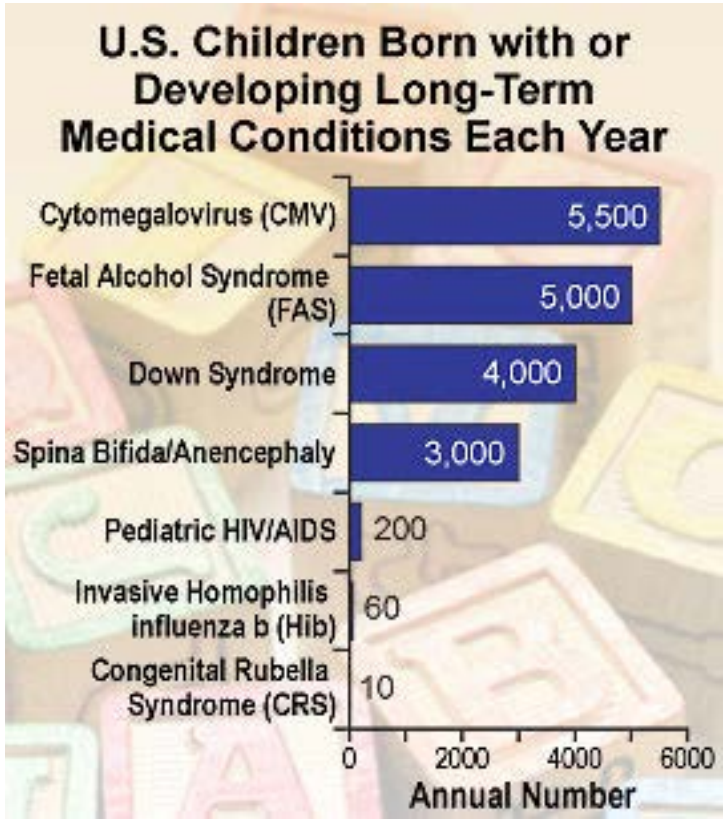
- Large double-stranded DNA virus
- Herpes virus family (Zoster, HSV, EBV)
- Infection usually mild or asymptomatic
- Remains latent in host cells
- Most adults worldwide are infected with CMV



Congenital CMV Disease Burden

- 1 in 150 live births have congenital CMV, worldwide
- Most common infectious cause of birth defects
  - 20% of affected infants will have long term deficits
  - 25% of infant hearing loss
- Annual US burden: $4 billion

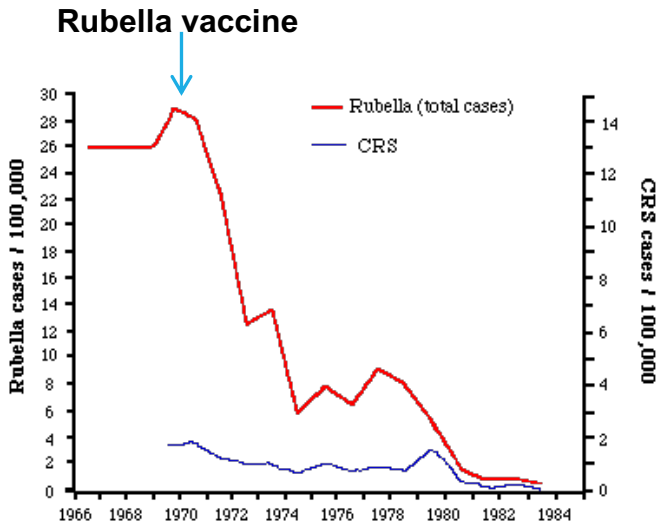




Fowler 1992, Cannon 2009, Yamamoto 2010, IOM

Need for a maternal vaccine against CMV

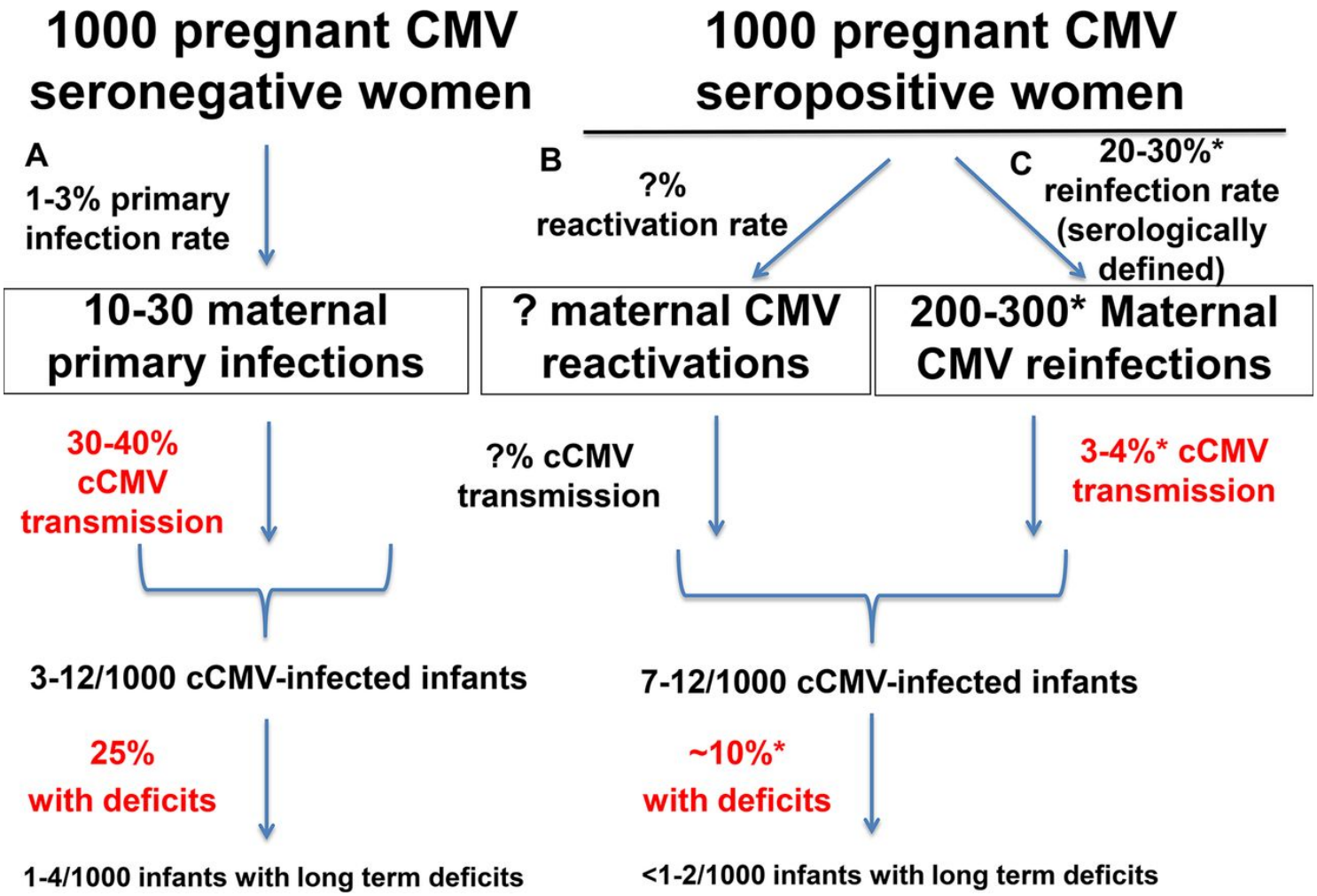
- Vaccine that can elicit protective immune responses prior to pregnancy needed to eliminate congenital CMV
- Top priority for 20 yrs
- Success of Rubella vaccine
- Eliminated congenital rubella syndrome in the Americas



"Introduction of the highly-effective rubella vaccine in 1969 led to the closure of schools for the deaf and blind due to lack of children needing these services"

- Sam Katz, MD

Unlike Rubella, natural immunity is not completely protective in congenital CMV

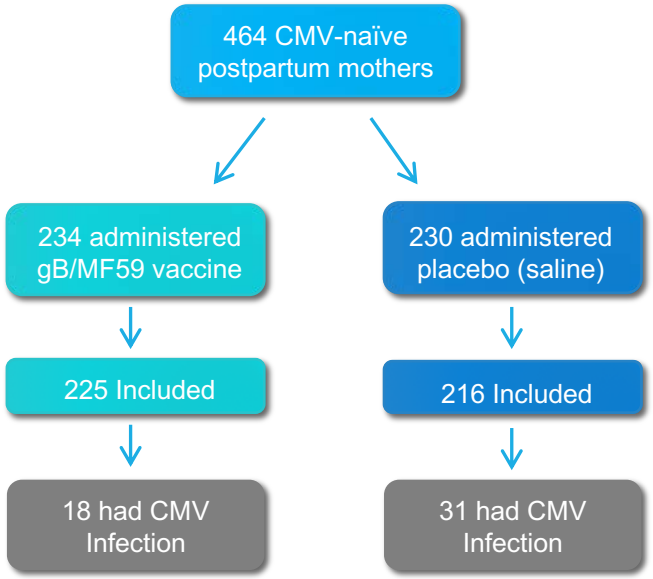


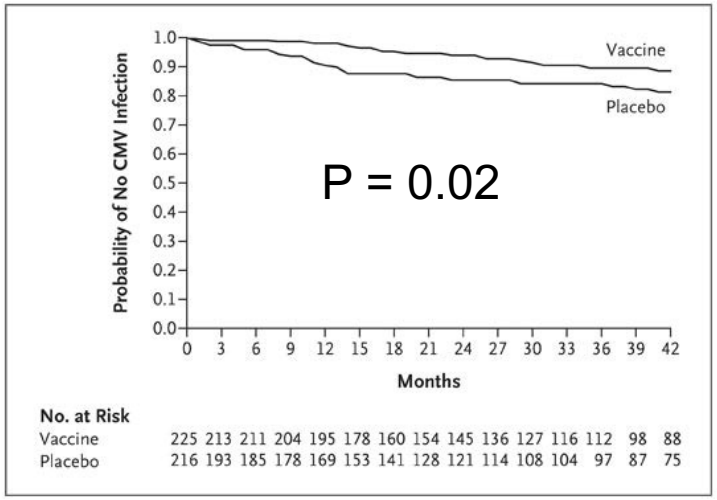
Sallie R. Permar et al. J. Virol. 2018;

Leruez-Ville, Clin Infect Dis 2017; 65:398–404

Phase 2 CMV Vaccine Trial: gB/MF59 trial in postpartum women

- Most efficacious HCMV vaccine trial to-date
- Population of seronegative, postpartum US women
- Immunized with **gB** (Sanofi) (20µg) + **MF59** squalene adjuvant (Novartis) at 0, 1, 6 months
- Primary Endpoint: Time to HCMV *acquisition*

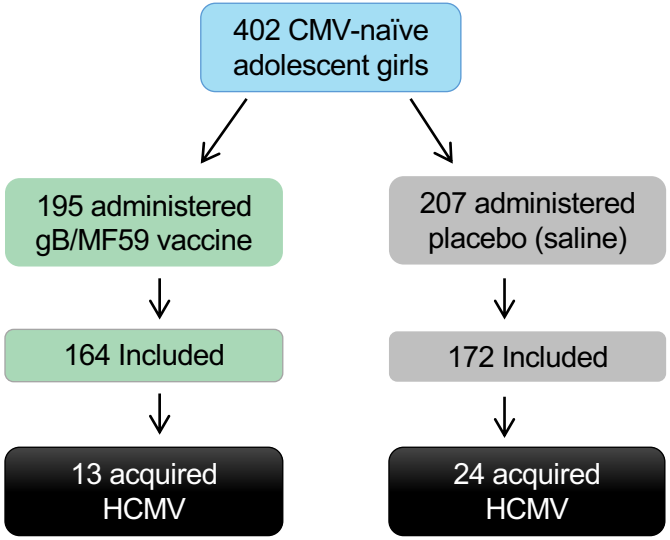


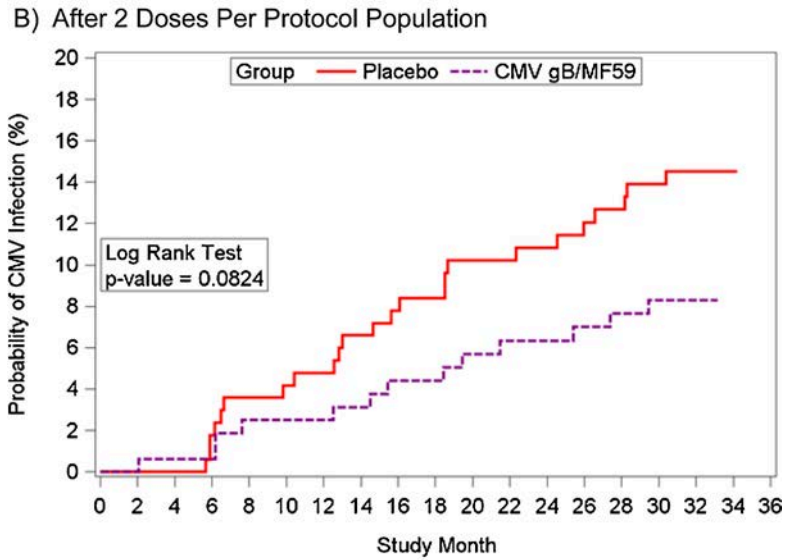


→50% Efficacy in preventing maternal primary infection

Phase 2 CMV Vaccine Trial: gB/MF59 trial in adolescents girls

- Identical study design and Sanofi **gB/MF59** vaccine
- Seronegative US girls age 12-17



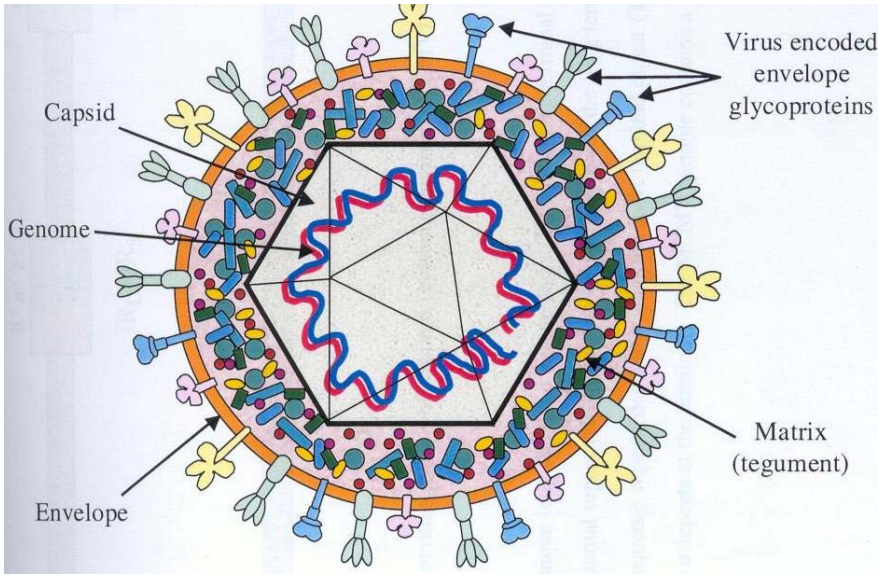


→ 45% efficacy in preventing primary infection after 2 doses (p=0.08)

David Bernstein
Walla Dempsy, VTEU
Chip Walter
Kathy Edwards

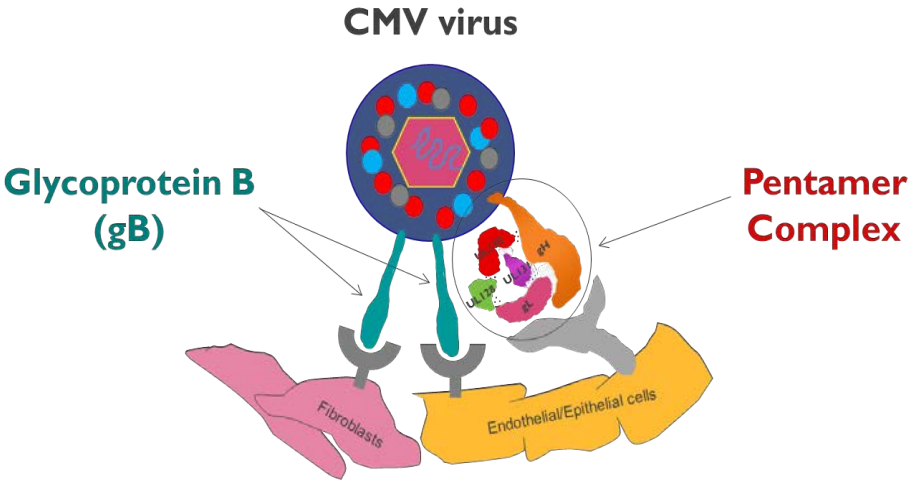
Why have previous vaccine efforts failed?

- Virus has coevolved with human immune system for millions of years
- Frequent exposure to high levels of virus in mucosal fluids
- Live attenuated vaccination did not impede virus acquisition, and carries risk of congenital infection
- Subunit vaccines only partially protective

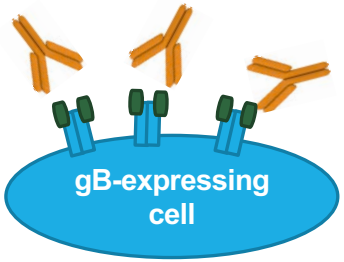


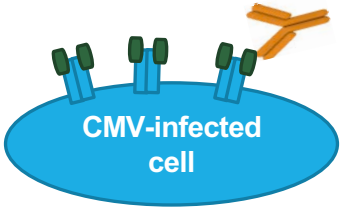
Immune Correlates of Protection Against cCMV Infection

- Neutralization antibody titer, IgG avidity correlated with protection against congenital transmission
  - Boppana, *J Infect Dis* 1995;171:1115–1121]
- Neutralization in epithelial cells associated with reduced congenital CMV transmission
  - Bialas *J Infect Dis* 2016; 214:1916 –1923
- gB-directed antibodies associated with prevention of infant CMV acquisition and block placental trophoblast infection
  - Saccocio *J Infect Dis* 2019
- Induction of T cell responses remains a goal for eliminating CMV-infected cells and support B cell responses

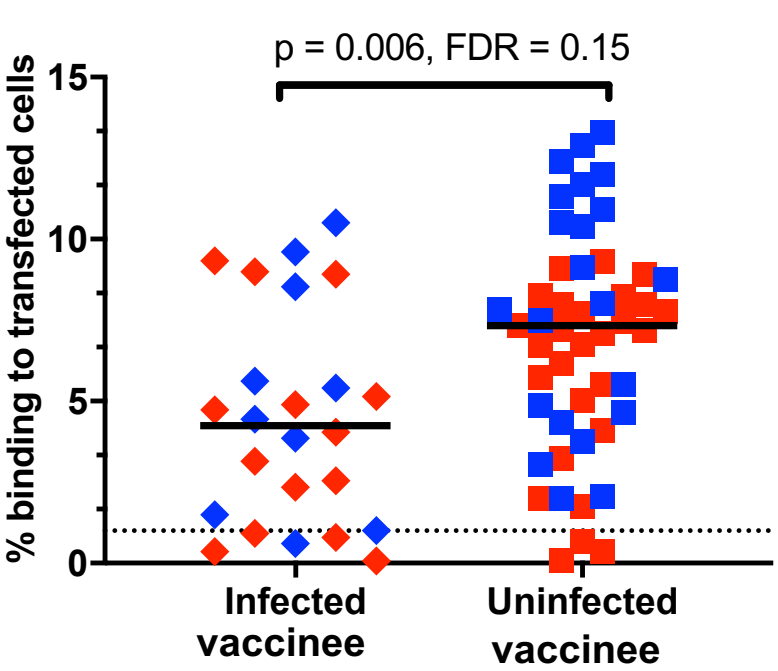


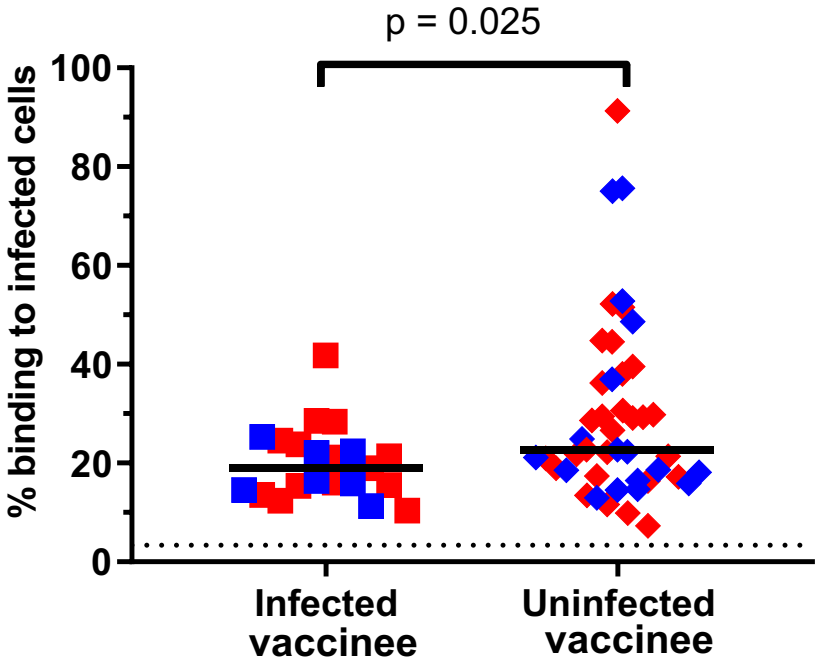
gB-transfected cell binding identified as an immune correlate of protection for the gB/MF59 vaccine





Adolescent
Postpartum



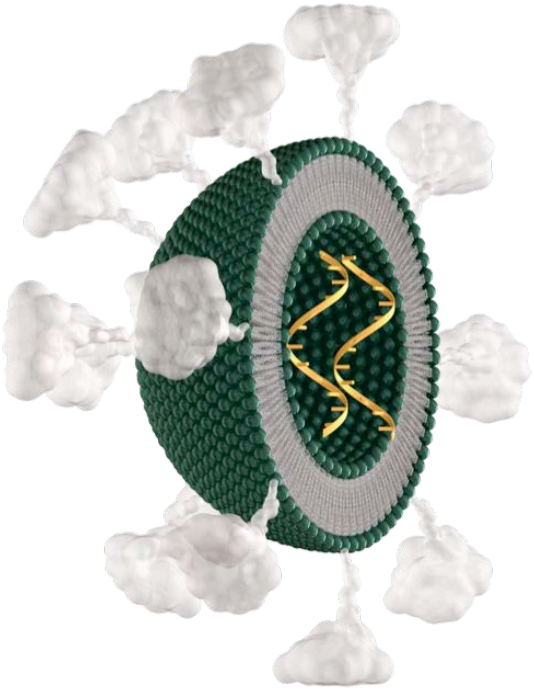


Permar et al, IHW 2019, unpublished

Why mRNA?

(1) Extremely robust, durable antibody responses

→ Antibody titers after a single immunization with modified mRNA-LNPs exceeds durability achieved by traditional subunit, vector, or DNA vaccine platforms



(1) Cell surface associated Pentamer and gB expression

(3) Limited immune exposure to cytoplasmic glycoprotein components (AD3)

Summary

- CMV vaccine is highly needed to prevent the most common infectious cause of birth defects and brain damage
- Natural immunity is only partially protective against cCMV
- Novel platforms needed to effectively induce immunity that is distinct from that of natural immunity
- mRNA will express antigens on the surface of a cell, mimicking infected cells

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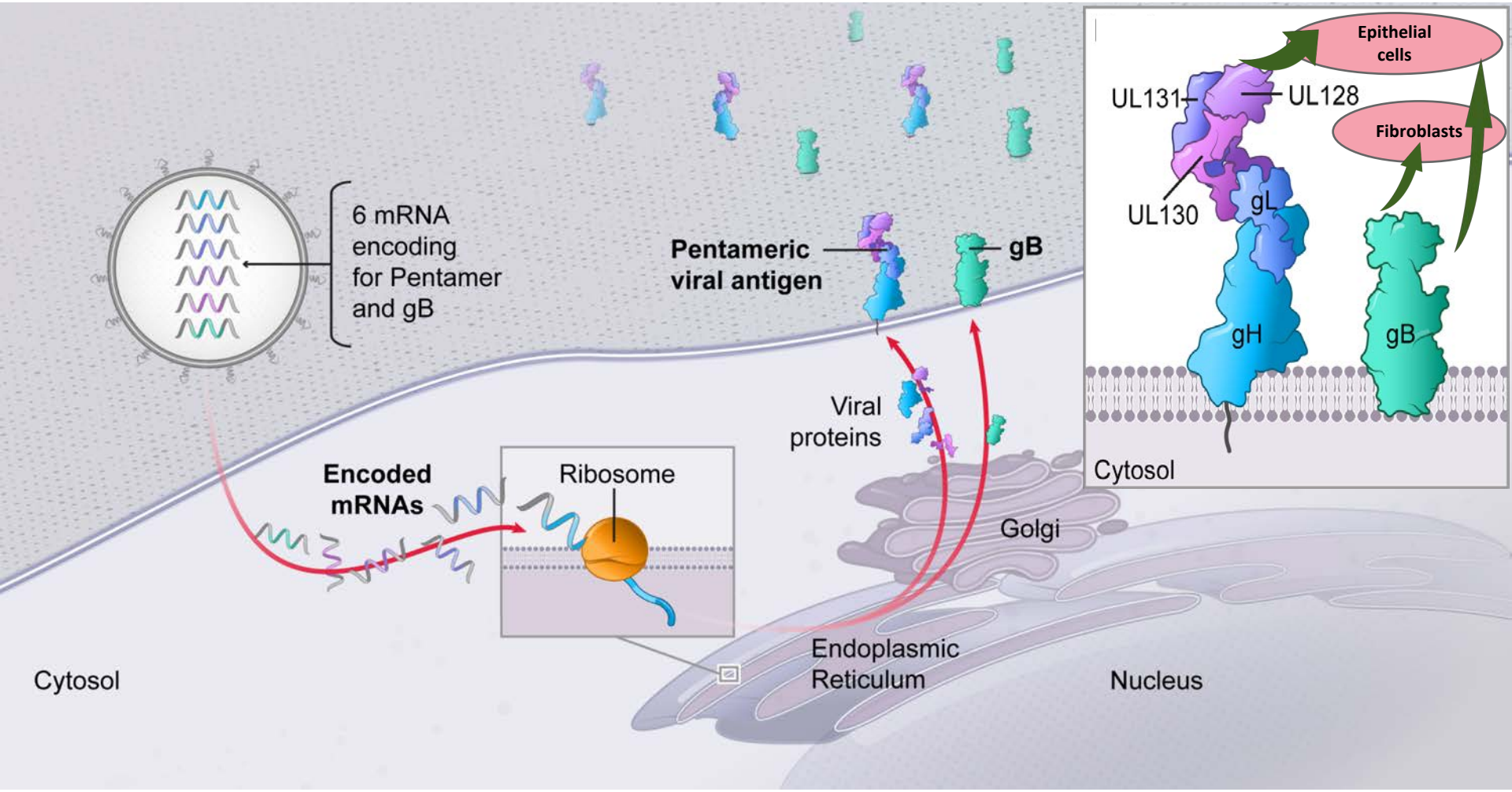
Cytomegalovirus (CMV) vaccine (mRNA-1647): Review of interim phase 1 data

Tal Zaks, MD, PhD

Chief Medical Officer

Congenital CMV vaccine includes 6 mRNAs

5 encode the Pentamer, 6th encodes gB antigen



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CMV vaccine (mRNA-1647)

Phase 1 trial design

Key Objective:

- To assess the safety, reactogenicity, and immunogenicity of different dose levels of mRNA-1647

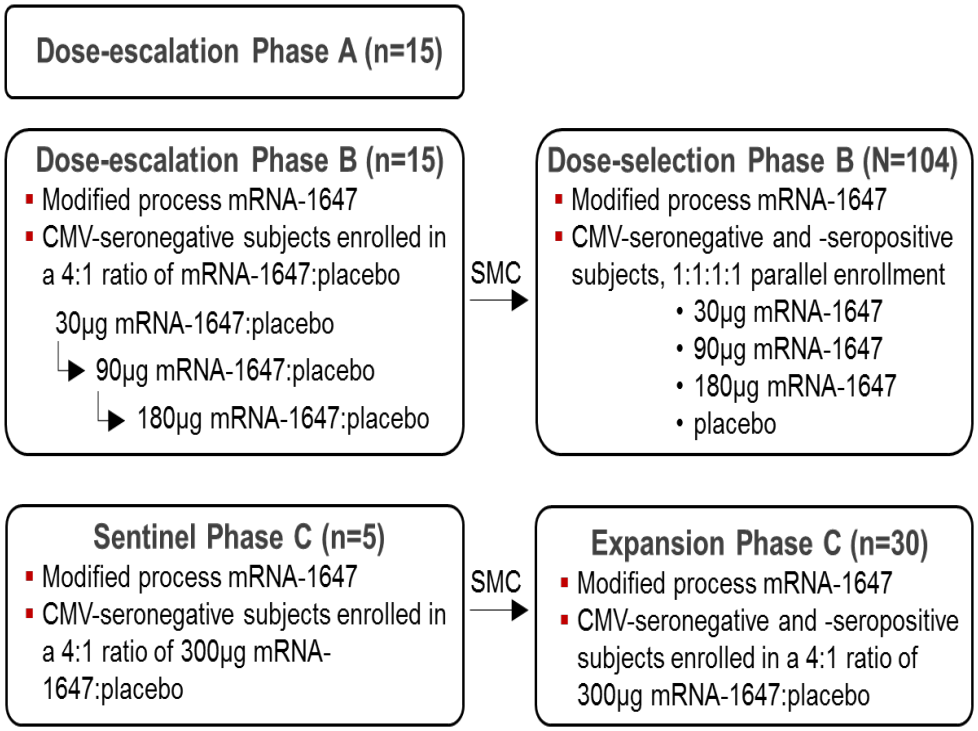
Primary endpoint: **Safety**

Secondary endpoints:

- **Neutralizing antibodies against CMV infection of epithelial cells and fibroblasts**
- Binding antibodies to gB and Pentamer antigens

Trial progress:

- FSFV: December 2017
- Enrollment completed June 2019 (N=169)
- Phase B – **2nd vaccination completed May 2019; interim data available**
- Phase B – 3rd vaccination completed August 2019; interim data not yet available
- Phase C – 2nd vaccination completed August 2019; interim data not yet available



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CMV Vaccine (mRNA-1647) Phase 1 Interim Analysis

Immunogenicity in CMV-seronegative participants, per-protocol set

Variable	Neutralizing Antibodies Against Epithelial Cell Infection			
	Placebo	30 µg	90 µg	180 µg
Baseline GMT	8	8	8	8
GMT post 1st vaccination	8	37	708	1,387
GMT post 2nd vaccination	12	3,263	15,305	30,743
GMT/benchmark ratio	---	0.6	2.7	5.5
	CMV-seropositive GMT benchmark = 5,588			

Variable	Neutralizing Antibodies Against Fibroblast Infection			
	Placebo	30 µg	90 µg	180 µg
Baseline GMT	8	8	8	8
GMT post 1st vaccination	8	8	24	10
GMT post 2nd vaccination	10	305	1,141	1,264
GMT/benchmark ratio	---	0.2	0.9	1.0
	CMV-seropositive GMT benchmark = 1,295			

GMT = geometric mean titer; CMV-seropositive benchmark values derived from baseline values of all CMV-seropositive participants

	Subject n at each timepoint			
	Placebo	30 µg	90 µg	180 µg
Baseline	13	17	13	15
Post 1st vaccination	12	17	10	15
Post 2nd vaccination	11	14	12	12

- Seronegative subjects successfully immunized to generate neutralizing titers against CMV
- Dose-related increase in neutralizing antibodies
- After the 2nd vaccination, GMTs of the 90 µg and 180 µg dose levels achieved or exceeded the CMV-seropositive benchmark

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CMV Vaccine (mRNA-1647) Phase 1 Interim Analysis

Immunogenicity in CMV-seropositive participants, per-protocol set

Variable	Neutralizing Antibodies Against Epithelial Cell Infection			
	Placebo	30 µg	90 µg	180 µg
Baseline GMT (Benchmark = 5,588)	8,169	3,614	5,634	5,700
GMT post 1st vaccination	7,890	24,752	39,020	52,775
GMT post 2nd vaccination	7,490	47,435	62,400	119,829
GMR post 2nd vaccination	0.9	13.2	9.9	19.4
Variable	**Neutralizing Antibodies Against Fibroblast Infection**			
	Placebo	30 µg	90 µg	180 µg
Baseline GMT (Benchmark = 1,295)	1,298	1,094	1,458	1,371
GMT post 1st vaccination	1,278	2,654	3,885	3,879
GMT post 2nd vaccination	1,451	2,935	3,891	5,578
GMR post 2nd vaccination	1.1	2.3	3.0	4.1

GMT = geometric mean titer; GMR = geometric mean ratio, defined here as the average of the ratio between Baseline/post 2nd vaccination for each participant

Subject n at each timepoint

	Placebo	30 µg	90 µg	180 µg
Baseline	14	13	12	13
Post 1st vaccination	14	13	12	13
Post 2nd vaccination	12	10	9	9

- Seropositive subjects effectively boosted beyond levels seen in natural infection
- Dose-related increase in neutralizing antibody titers
- mRNA-1647 boosted neutralizing antibody titers against epithelial cells to 10-fold or higher in all treatment groups

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CMV vaccine (mRNA-1647) Phase 1 Interim Analysis

Solicited adverse events (AE) post 2nd vaccination, solicited safety set

		CMV Serostatus at Baseline							
		CMV-seronegative				CMV-seropositive			
		Placebo n=13	30 µg n=15	90 µg n=16	180 µg n=15	Placebo n=13	30 µg n=12	90 µg n=11	180 µg n=11
Local AEs	**Pain**	-	11 (73%) -	13 (81%) 2 (13)	12 (80%) 2 (13)	-	9 (75%) 1 (8)	8 (73%) -	10 (91%) 3 (27)
	Redness	-	-	-	3 (21) -	-	-	-	2 (18) 1 (9)
	Swelling	-	-	-	-	-	-	-	1 (9) -
Most common systemic AEs	**Headache**	3 (23) -	5 (33) -	10 (63) -	9 (60) 2 (13)	2 (15) -	4 (33) 1 (8)	4 (36) -	9 (82) 2 (18)
	Fatigue	2 (15) -	5 (33) 1 (7)	8 (50) 1 (6)	11 (73) 1 (7)	1 (8) -	7 (58) 3 (25)	7 (64) 1 (9)	8 (73) 3 (27)
	Myalgia	1 (8) -	5 (33) 1 (7)	8 (50) 3 (19)	11 (73) 2 (13)	-	5 (42) 4 (33)	7 (64) 1 (9)	7 (64) 2 (18)
	Chills	1 (8) -	3 (20) 1 (7)	7 (43) 1 (6)	11 (73) 3 (20)	-	6 (50) 1 (8)	7 (64) 1 (9)	9 (82) 3 (27)
	Fever	-	3 (20) -	3 (19) 1 (6)	5 (33) -	-	2 (17) -	6 (55) 3 (27)	6 (55) 2 (18)

Values represent n (%) participants reporting each AE, red text=grade 3 AEs

- Solicited AEs after the second vaccination higher than after the first vaccination
- After the first vaccination, AEs higher in the seropositives relative to seronegatives
- One event triggered Study Pause: asymptomatic Grade 4 elevation in partial thromboplastin time (PTT) at 7 days post 2nd vaccination in a subject with Grade 1 PTT elevations throughout study, PTT normal on repeat testing
- No vaccine-related serious adverse events (SAEs)

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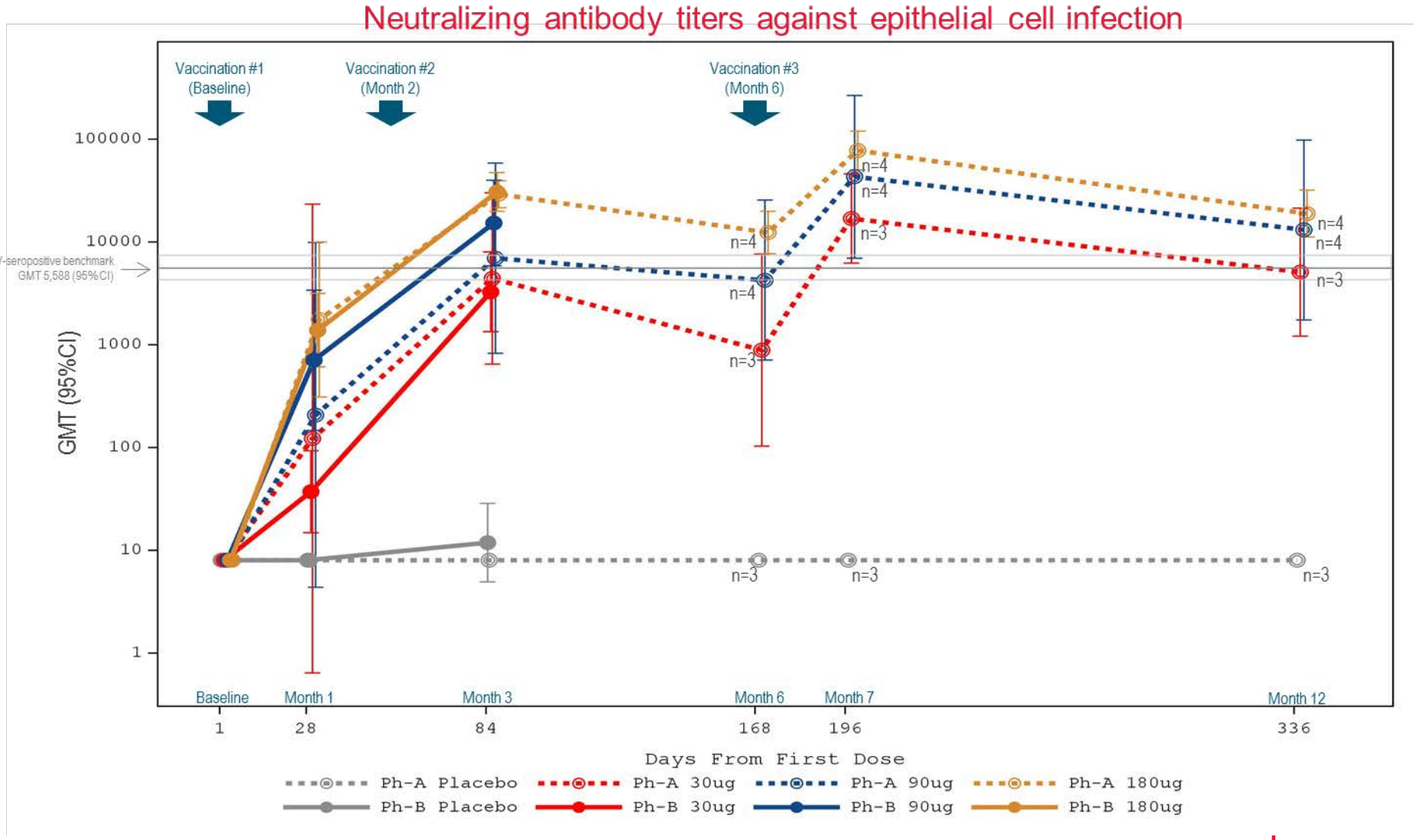
CMV vaccine (mRNA-1647) Phase 1 Interim Analysis

Durable immunogenicity demonstrated in initial cohort followed to one year



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CMV vaccine (mRNA-1647)

Phase 2 study to be initiated in the near term

STUDY DESIGN

A phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation trial to evaluate the safety and immunogenicity of Cytomegalovirus vaccine mRNA-1647 in healthy adults

- **Evaluate intended phase 3 formulation (same LNP) at 3 dose levels (50µg, 100µg, 150µg)**
- **N = 252** adult females and males 18 – 40yrs of age
  - 180 CMV-seronegative
  - 72 CMV-seropositive
- **Vaccination schedule**: 0, 2, 6 months
- **Randomization**: 3:1 mRNA-1647 vs placebo
- **US sites only**: up to 12 clinical investigator sites
- **First interim analysis**: safety and immunogenicity through 1 month after 2nd vaccination

= *Selected investigator site location*

STUDY STATUS

- Protocol finalized and under review with FDA
- Core vendors and suppliers on-board:
  - PPD selected as clinical contract research organization (CRO)
  - Other key vendors selected, including expanded, new partnerships for critical study activities
- Investigator selection and initiation progressing well with robust interest in the program:
  - Clinical site feasibility complete
  - On-site investigator qualification visits complete
  - 12 clinical investigator sites selected, including back-up sites as risk mitigation to slow enrollment rates

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CMV vaccine (mRNA-1647)

Phase 3 pivotal trial preparations are underway

- Solicited and received Type C meeting feedback from FDA
- Primary endpoint: prevention of primary CMV infection in a population that includes women of child bearing age (WOCBA)
- We believe we can achieve this objective with a trial with <8,000 subjects
- Country and site feasibility: outreach to 285 sites in 18 countries across North America, Europe and Asia Pac with robust positive response, feasibility assessments continue

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CMV vaccine supply plans for late stage development and commercialization

Juan Andres

Chief Technical Development, Manufacturing, Quality Officer

Moderna's Internal Manufacturing Site, Norwood MA

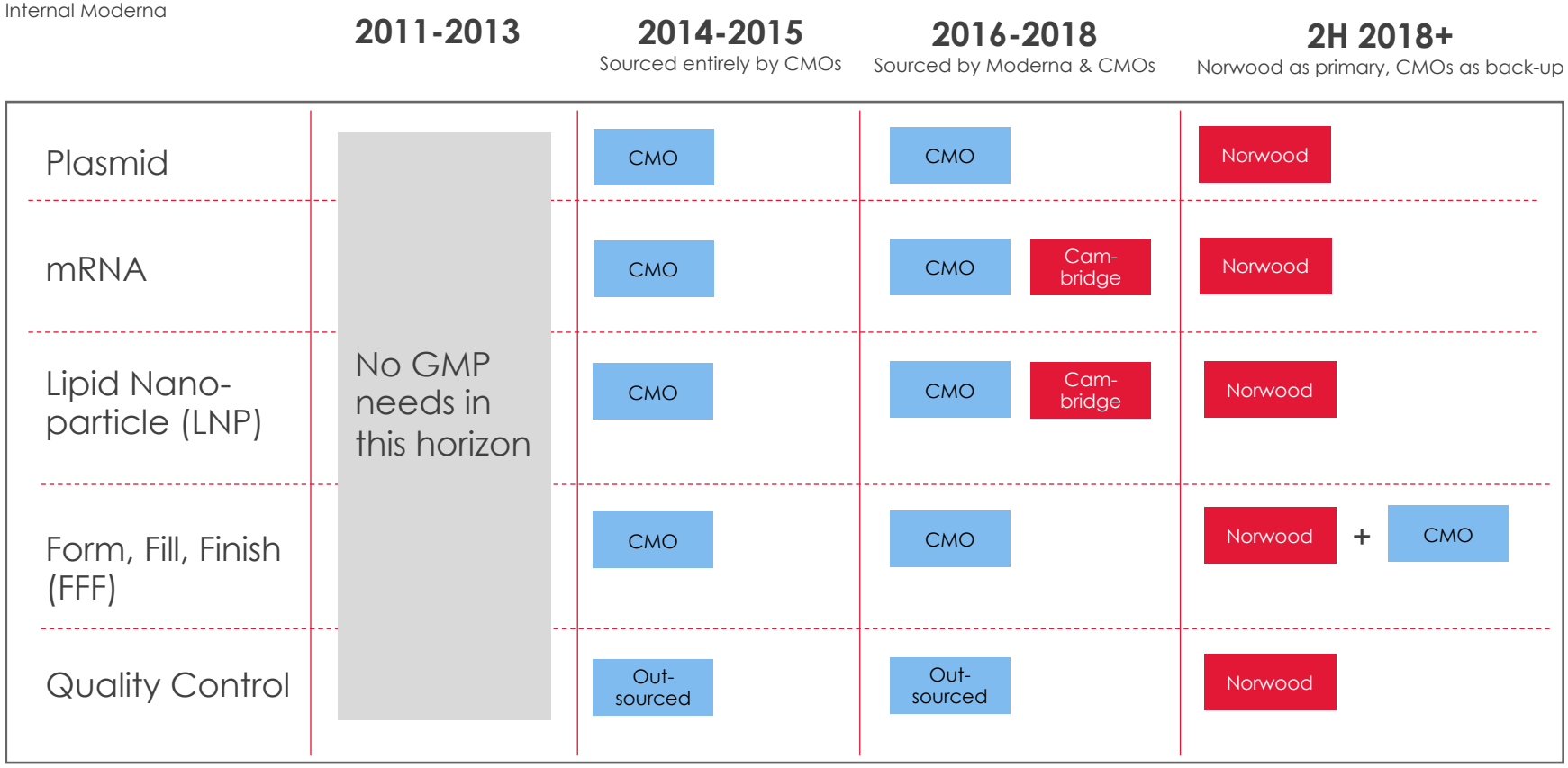
- Built and operationalized in 22 months
- Pre-clinical, clinical & personalized cancer vaccine production
- 1st clinical batch manufactured in Aug '18, 70 batches manufactured to date


Mobius

Internalizing manufacturing to enable focus on quality, speed and scale

External/ CMO

Internal Moderna



Norwood now provides the scalability we need for our growing pipeline

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Manufacturing in Norwood brings a competitive advantage to CMV vaccine (mRNA-1647)

mRNA technology :

- Platform allows similar manufacturing process across all products
- Process improvements implemented fast to platform processes
- Cell-free process to make mRNA
- Less future capital investment

Enables fast scale up

Cost at economical scale (anticipated 90+ % Gross Margin for mRNA-1647 in US)

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CMV vials already produced for phase 2 trial

- Same lyophilized image intended for phase 3
- Norwood site can produce mRNA and LNP for phase 3
- Norwood site can support commercial launch (FFF to be done at CMO)
- Potential for >10+ million doses/year from Norwood

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Cytomegalovirus (CMV) vaccines: Where do we stand?

Mark Schleiss, MD

Co-Director, Center for Infectious Diseases and Microbiology Translational Research
University of Minnesota

Cytomegalovirus Vaccines 2019: Where do we Stand? What do we Need to Learn?

Mark R. Schleiss, MD

Center for Infectious Diseases and Microbiology Translational Research

University of Minnesota

schleiss@umn.edu

September 12, 2019

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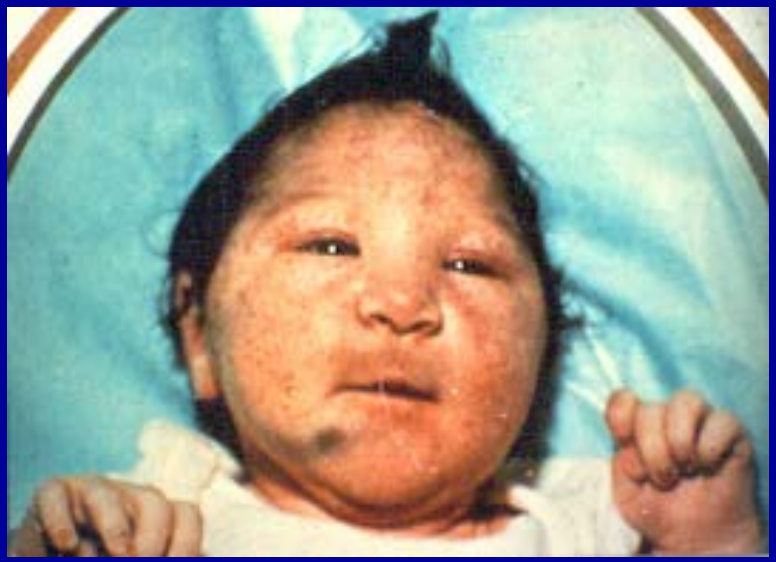
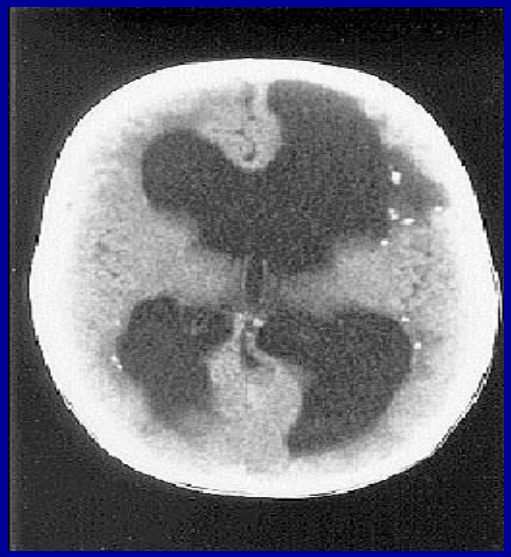
University of Minnesota
Driven to Discover®

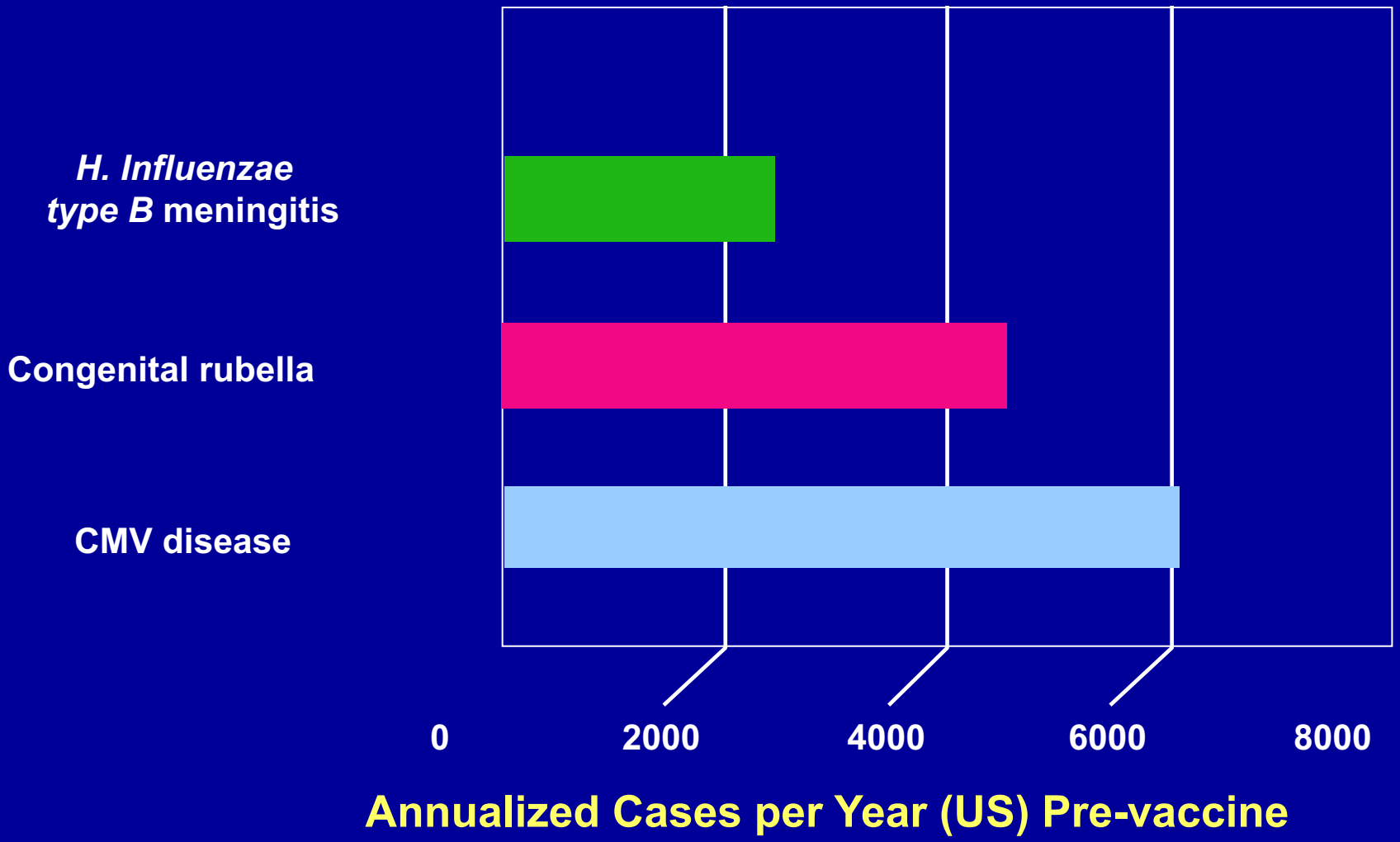
Congenital Cytomegalovirus Infection

- Most common disabling pediatric infection
- Mental retardation, developmental delay, seizures, cerebral palsy, microcephaly, neuronal migration defects
- Major infectious cause of sensorineural hearing loss





Infectious Causes of Neurologic Damage in Infancy



Annual Estimated Impact of Congenital CMV Infection and Disease in Europe and the United States

Category of Infants	Total
Total number of live births/yr	8,600,000
Average rate of congenital CMV infection (%)	0.7
Total number of newborns with CMV infection	60,200
Number with symptomatic infection (12.7%)	7,645
Number with fatal disease (~4%)	306
Number of survivors with sequelae (40-58%)	3058-4434
Number with asymptomatic infection (87.3%)	52,555
Number with sequelae (13.5%)	7,095
Total number with sequelae or death	**10,459-11,835**

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Kenneson, Rev Med Virol 2007;17:253-76
Boppana, N Engl J Med, 2011;364:2111-8

Evidence of Effectiveness of Preconception Immunity in Protection of the Fetus

- Immunity induced by prior CMV in seropositive women of childbearing age protects against secondary infection

  Adler, J Infect Dis, 1995; 171:26

- Preconception immunity associated with a 69% reduction in risk transmission to fetus

  Fowler, JAMA, 2003; 289:1008

- Risk of fetal infection during documented primary maternal infection of **30-40%** compared to **~1%** in seropositives

  Stagno, N Engl J Med 1982; 306:945-949

  Britt, J Virol 2017; 91:15

- Tremendous economic potential would be realized by CMV vaccine capable of preventing congenital infection

  Stratton et al, IOM Report, 1999

  Arvin, Clin Infect Dis. 2004;39(2):233-9

CMV Vaccine

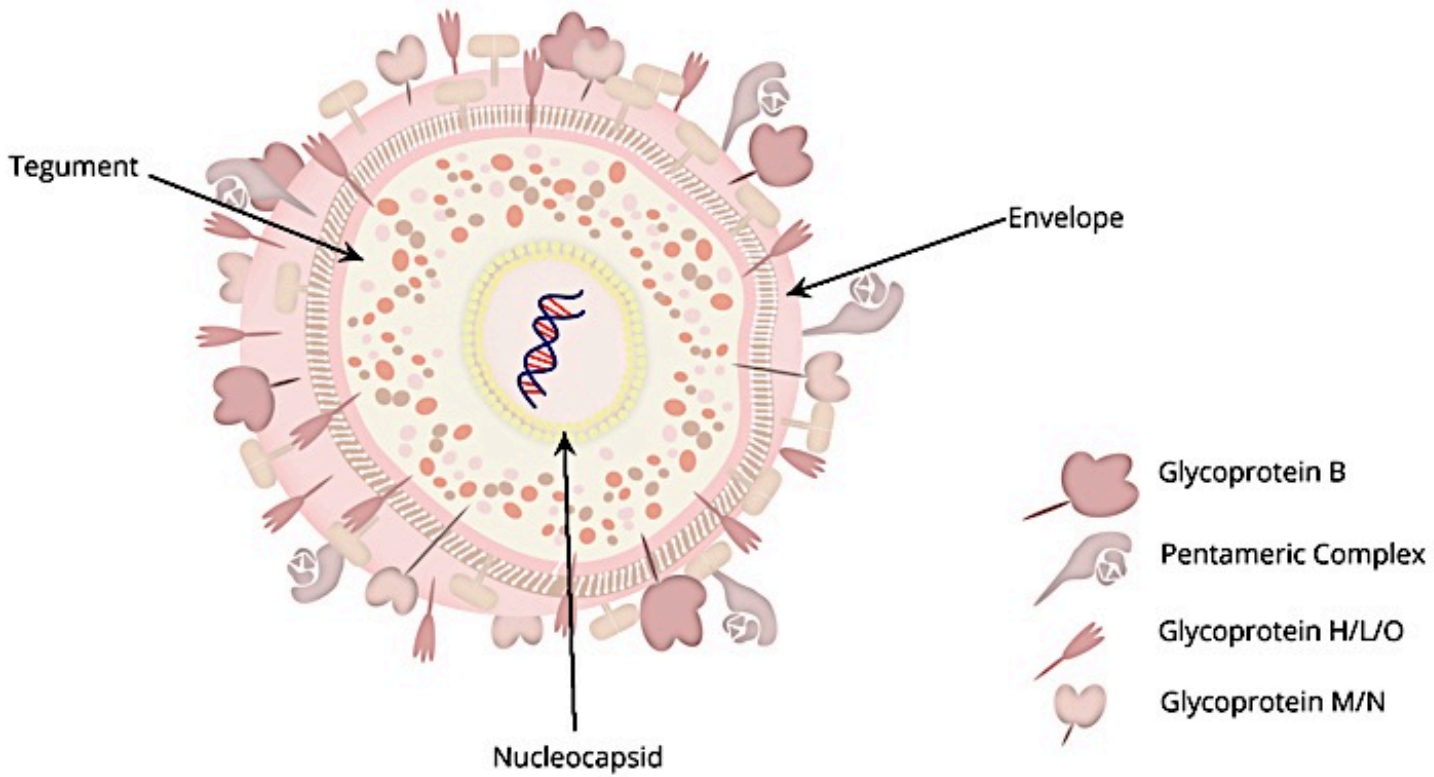
If there is evidence that immunity is protective, why is a CMV vaccine such a “difficult” vaccine?

Four Unmet Challenges

Challenge 1

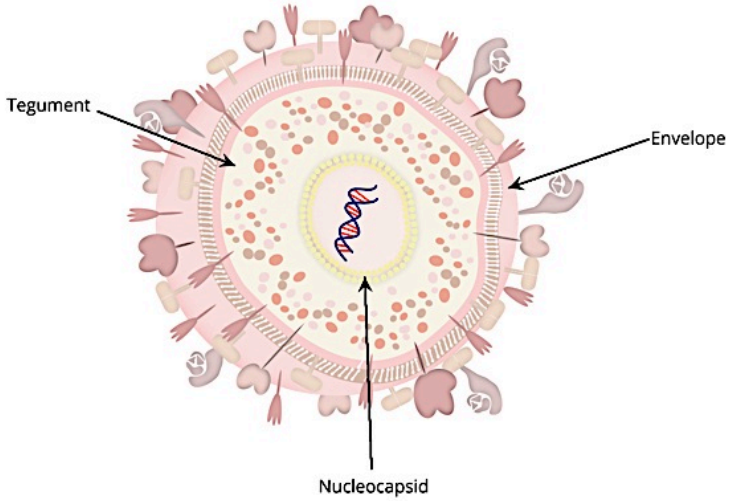
Uncertainty Regarding Correlate(s) of Protective Immunity at the Maternal/Fetal Interface

Viral Particle is Complex…



http://cmv.umn.edu/about-cmv

CMV Gene Product	Rationale for Inclusion
Envelope Glycoproteins	
gB	Major target of neutralizing antibodies; target of CTLs; cornerstone of CMV vaccine development programmes; demonstrated efficacy as subunit vaccine in clinical trials
gH/gL	Important target of neutralizing antibodies; target of CTLs
gH, gL, UL128-131 (Pentamer)	Pentameric Complex (PC) of gH/gL/UL128/UL130/UL131 on viral envelope; target of neutralizing antibodies; antibodies neutralize CMV infection at epithelial and endothelial cell surfaces; current focus of clinical trials (in combination with gB)
gH, gL, gO (Trimer)	Target of neutralizing antibody; antibodies to block cell entry/fusion?
gM/gN	Target of antibody neutralizing antibody responses; has not been tested as CMV subunit vaccine; hypervariability of gN in clinical isolates suggests this protein is under immune selective pressure
Structural proteins	
pp65	Major target of CTLs; target of non-neutralizing antibody responses; has been evaluated (in combination with gB) in clinical trials
pp150, pp28	Target of CTLs and antibody responses; no data available from clinical trials
pp50	Target of CTLs; no data available from clinical trials
pp71, pp52	Targets of antibody responses; no data available from clinical trials
Nonstructural proteins	
IE1	Important target of CTLs; target of non-neutralizing antibody responses; has been evaluated (alone, or in combination with gB and UL83 (pp65) in clinical trials



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Other Preclinical CMV Vaccine Strategies

- Modified vaccinia virus Ankara (MVA)
- “Dense Body” vaccines
- Polyepitope vaccines
- Soluble pentamer vaccine (CHO)
- Messenger RNA vaccines (Moderna)
- SynCon® vaccine platform

Challenge 2

Safety and Regulatory Concerns About Live, Attenuated CMV Vaccines

CMV Vaccines In Clinical Trials: Live Attenuated and "DISC" Vaccines

Live Attenuated and Disabled Virus Vaccines	
AD169 vaccine	• Elicited CMV-specific antibodies in seronegative vaccine recipients • Significant injection-site and systemic reactogenicity
Towne vaccine (± rhIL12)	• Elicits humoral and cellular immune responses • Favorable safety profile; no evidence for latency or viral shedding in recipients • Reduced CMV disease but not infection in renal transplant recipients • Augmented immunogenicity with recombinant IL-12 in Phase I studies
Towne/Toledo chimera vaccines	• Favorable safety profile; no evidence for latency or viral shedding in CMV seropositive subjects • Attenuated compared to Toledo strain of HCMV • No efficacy data available; studies in seronegatives in progress
V160–001 replication-defective vaccine	• AD169 backbone with restoration of UL128/130/131 PC components • Rendered replication-incompetent by inclusion of ddFKBP/Shld1 • Administered with alum-based adjuvant • Phase I studies ongoing

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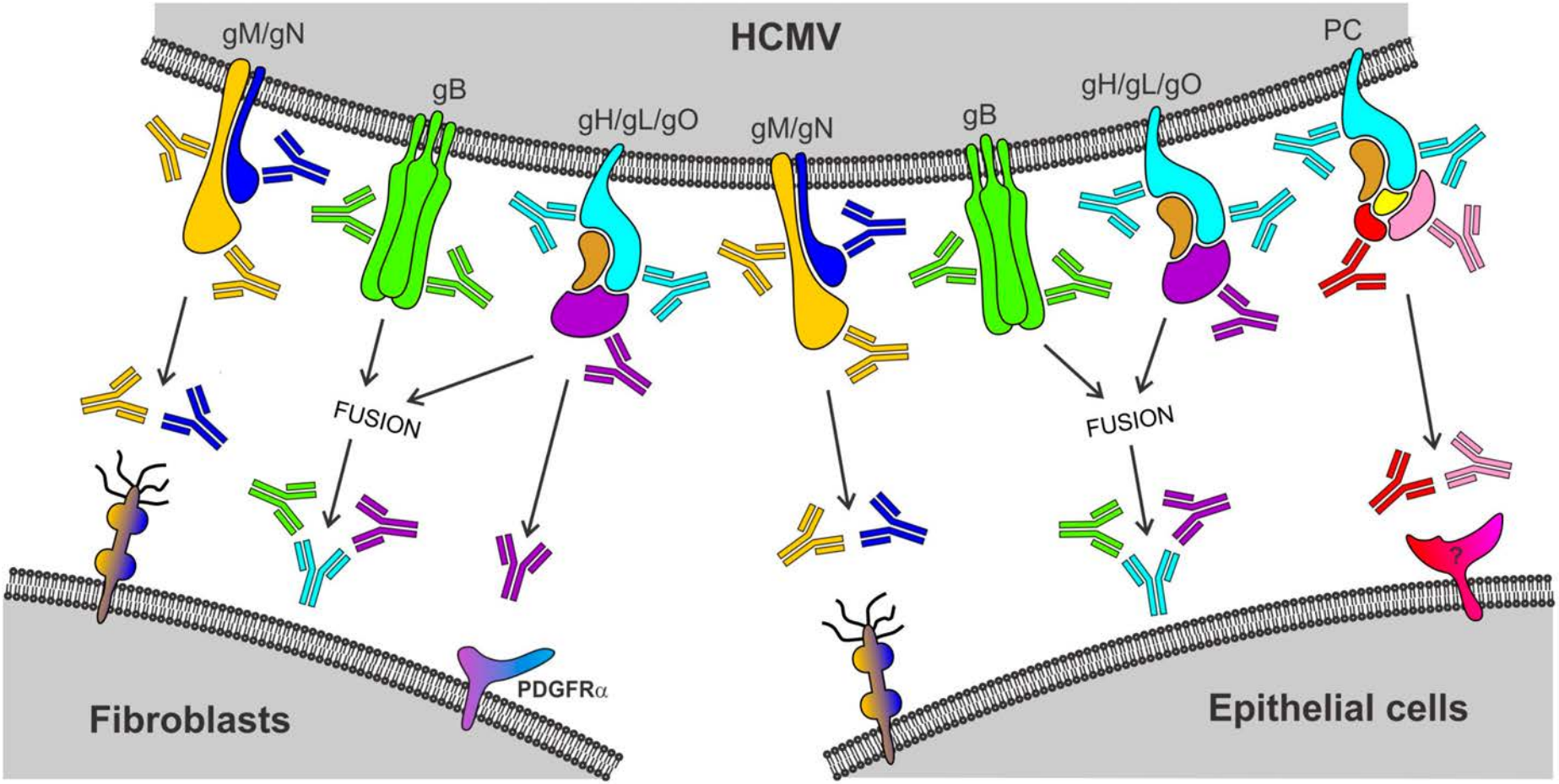
Schleiss and Plotkin, 2017, *Vaccines*



Vaccines 2017, 5(4), 39; https://doi.org/10.3390/vaccines5040039

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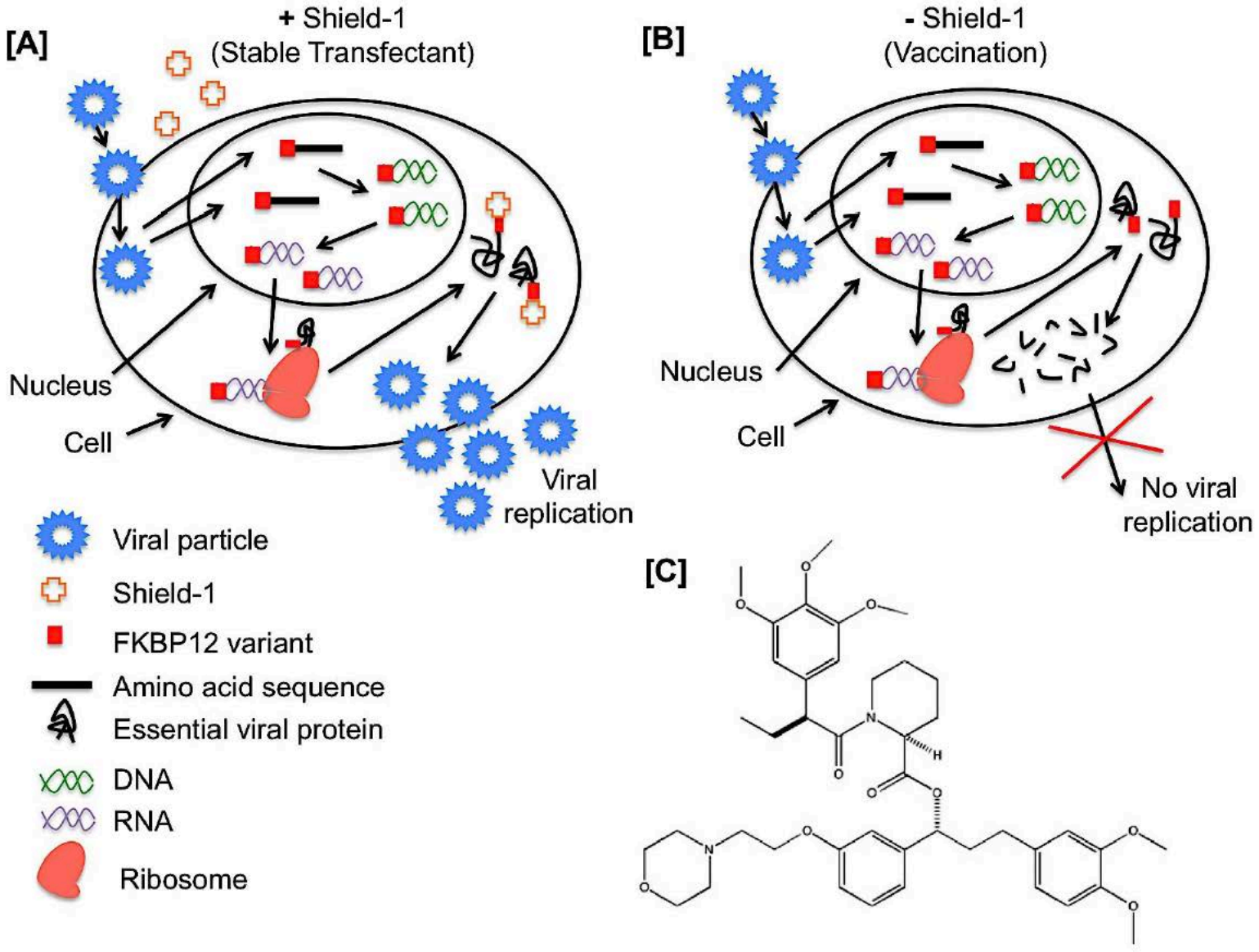
Cytomegalovirus Vaccine (V160) in Healthy Adults (V160-001)

- AD169-like virus with repair of frame-shift mutation in ORF encoding UL131, restoring epithelial tropism and pentameric complex formation
- Virus rendered conditionally replication-defective (FKBP/CMV protein fusion) and propagated in presence of stabilizing protein
- Produced in retinal pigment epithelial cells
- Multiple arms, dose range, with or without with or without proprietary aluminum phosphate adjuvant (MAPA) by IM or ID
- Seropositive and seronegative

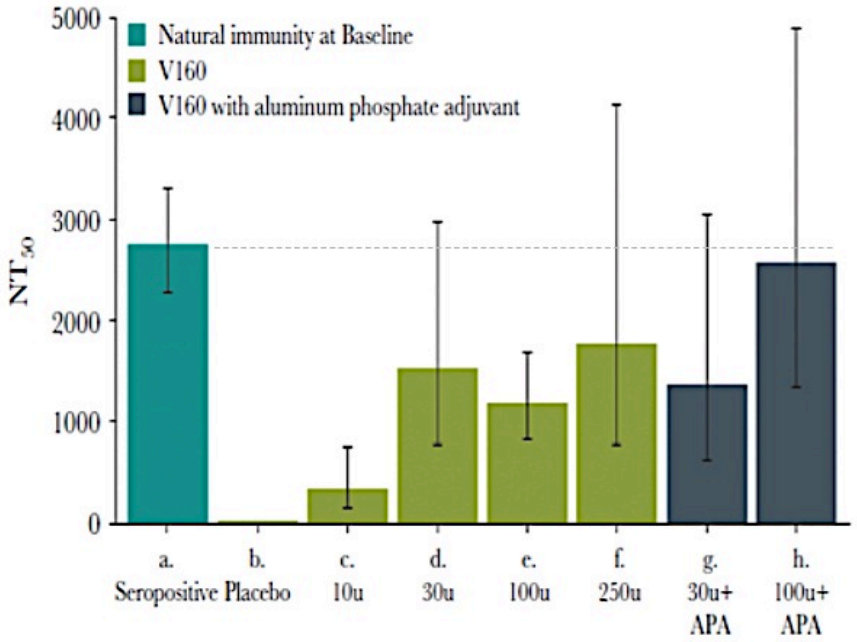
Fu, et al. Vaccine 30, 7469-7474 (2012)
Fu, et al. Vaccine 32, 2525-2533 (2014)
Adler, et al. JID 220, 411-419 (2019)



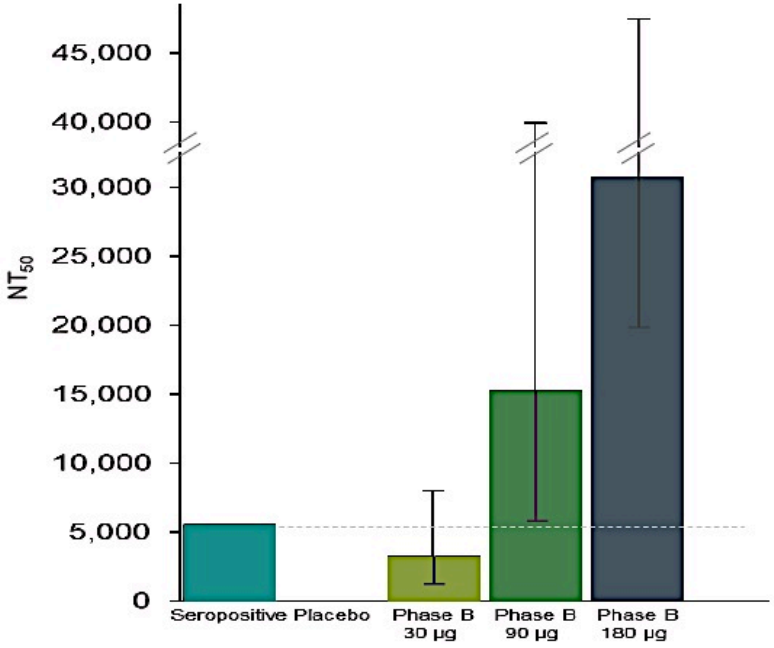
Anderholm Drugs. 2016;76(17):1625-1645
Wang et al., Science Translational Medicine 2016: 8(362), 362ra145

Comparison of emerging clinical data showing epithelial neutralization by replication defective and mRNA vaccine approaches

Adler et al, J Inf Dis 2019;220:411–9
Month 7 (1 month after the **3rd vaccination**)



mRNA-1647
Month 3 (1 month after the **2nd vaccination**)



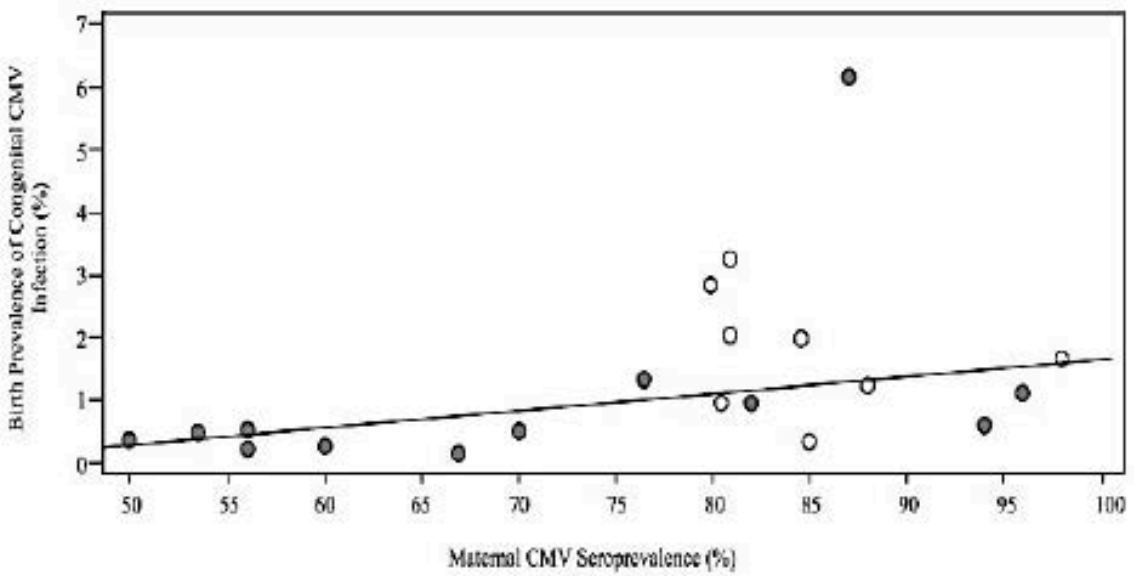
- Both vaccines approach or exceed seropositive controls in respect study
- 3-vaccination schedule for V160 (0,1,6); 2-vaccination for mRNA1647 (0,2)

Seropositive = baseline GMT of seropositive individuals in the trial

Challenge 3

Target Population for CMV Vaccine and the Issue of Transmission in the Setting of Re-Infection

Most Congenital CMV Infections Occur in the Context of Preconception Immunity and Maternal Re-Infection



Kenneson and Cannon, Rev. Med. Virol. 2007; 17: 253–2760

The NEW ENGLAND JOURNAL of MEDICINE

CIDMTR Center for Infectious Diseases & Microbiology Translational Research

ORIGINAL ARTICLE

Intrauterine Transmission of Cytomegalovirus to Infants of Women with Preconceptional Immunity

Suresh B. Boppana, M.D., Lisa B. Rivera, M.P.H., M.B.A., Karen B. Fowler, Dr.P.H., Michael Mach, Ph.D., and William J. Britt, M.D.

N Engl J Med 2001; 344:1366-1371 | May 3, 2001 | DOI: 10.1056/NEJM200105033441804

A

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          15                  34
          |                   |
. . . TVYLLSHLPSQRYGADAAEEALDPHAFHLLLNTYGRPIRFLRENTT . . .   AD169
. . . . . C . . . . . L . S . . . E . I . . P . . *K . . . . . . . . . . . . . . . . . . . .   Towne
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B

Maternal Serologic Reactivity				Acquisition of New Antibody Specificity	Sequence Homology	Predicted Amino Acid Sequences of the Amino-Terminal Region of Glycoprotein H from CMV Isolates from Seven Infected Infants
BEFORE PREGNANCY		AT DELIVERY				
AP86	TO86	AP86	TO86			15 34
Negative	Positive	Positive	Positive	Yes	AP86	YLLSHLPSQRYGADAAEEALDPHAFHLLLNTYGRPIRFLRENTT
Positive	Negative	Positive	Positive	Yes	TO86	CLLSHLLSSRYGAEAIEEPLD*KAFHLLLNTYGRPIRFLRENTT
Negative	Positive	Positive	Positive	Yes	AP86	YLLSHLPSQRYGADAAEEALDPHAFHLLLNTYGRPIRFLRENTT
Negative	Negative	Positive	Negative	Yes	AP86	YLLSHLPSQRYGADAAEEALDPHAFHLLLNTYGRPIRFLRENTT
Positive	Positive	Positive	Positive	No	TO86	CLLSHLLSSRYGAEAIEEPLD*KAFHLLLNTYGRPIRFLRENTT
Negative	Positive	Negative	Positive	No	TO86	CLLSHLLSSRYGAEAIEEPLD*KAFHLLLNTYGRPIRFLRENTT
Positive	Negative	Positive	Negative	No	AP86	YLLSHLPSQRYGADAAEEALDPHAFHLLLNTYGRPIRFLRENTT

Table 2 Power analysis for Phase III efficacy trials for the prevention of congenital CMV disease by immunizing seronegative women by study endpoint

Endpoint	Vaccine efficacy = 80%			Vaccine efficacy = 50%		
	Rate for placebo arm (%)	Rate for vaccine arm (%)	Total no. of subjects needed	Rate for placebo arm (%)	Rate for vaccine arm (%)	Total no. of subjects needed
Maternal infection	50*	10	48	50*	25	130
	12	2.4	264	12	6	776
Transmission	4	1	976	4	2	2476
to the fetus	3	0.075	1310	3	1.5	3326
	2	0.5	1976	2	1	5028
	1	0.25	3404	1	0.5	10 128
Disease in the	0.4	0.08	8542	0.04	0.02	25 434
newborn	0.2	0.04	17 154	0.2	0.1	50 940

Assumes an equal number of vaccine and placebo subjects with an alpha of 0.05 and a beta of 0.8. Calculated by the method of Fleiss.[47]

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Adler, British Medical Bulletin 2013; 107: 57–68

Proposed endpoints for CMV vaccine clinical trials in different target populations

Target Population	Objectives	Endpoint
Children <2 yrs of age	Prevent maternal and congenital CMV infection by removing an important source of maternal infections. Prevent primary CMV infection which may have long-term deleterious consequences to the host	Rate of CMV infection in vaccinees.
Adolescent girls	Prevent infection in future mothers and their children (preventing congenital infection) Prevent primary CMV infection which may have long-term deleterious consequences to the host	Rate of CMV infection in vaccinees.
Women of childbearing age (women likely to become pregnant)	Prevent maternal and congenital CMV infection	~~Rate of CMV infection in vaccinees.~~ Rate of cCMV infection in their children.
Hematopoetic stem cell transplant recipients	Prevent CMV disease by reducing the rate of occurrence of surrogate markers	Prevention of CMV viremia (and associated antiviral use) Composite endpoints including CMV disease
Solid organ transplant recipients	Prevent CMV disease	Prevention of CMV-associated disease (including CMV syndrome) Prevention of CMV viremia (and associated

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Krause et al., Vaccine. 2013 Dec 17; 32(1): 4–10.

Employing a Cytomegalovirus Vaccine

- All seronegative adolescents age 12
- Girls 11-13 years of age (MCV4/TdAcP/HPV)
- Seronegative women (seropositives?)
- SOT recipients
- HSCT donors/recipients
- All infants (universal)
- Will transplacental immunity ameliorate CMV disease in infants even if transmission occurs?

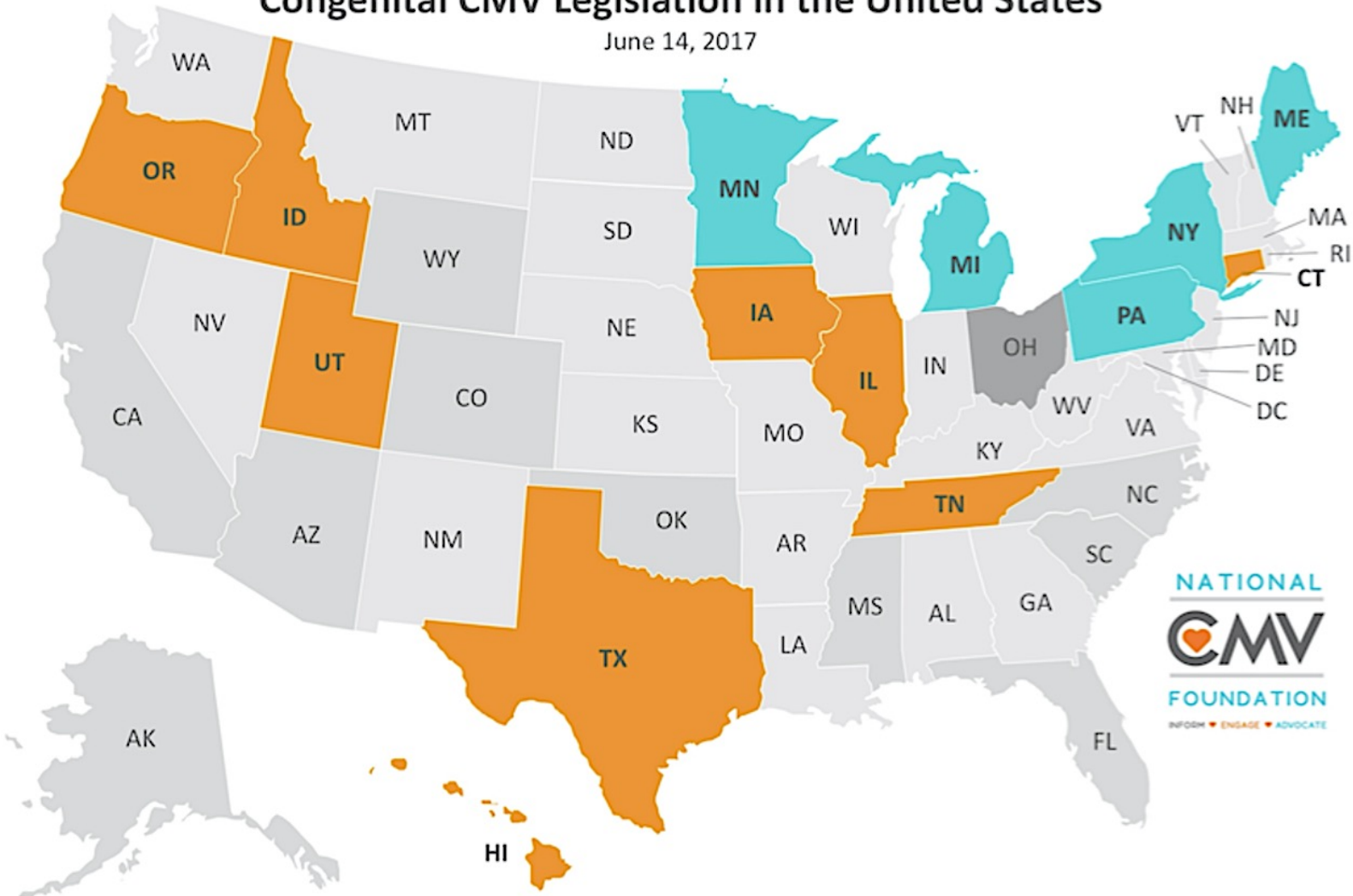
Stratton et al, 1999, IOM Report
Griffiths, Vaccine. 2001;19(11-12):1356-62

Challenge 4

Increase Knowledge and Awareness of the Problem of Congenital CMV and Enlist Parents in Advocacy for CMV Research

Congenital CMV Legislation in the United States

June 14, 2017



Key: Law enacted Law proposed Law drafted Stakeholder interest in legislation

https://www.youtube.com/watch?v=qEc0jncqBQQ

Conclusions

- There is a major public health need for a vaccine against cytomegalovirus infection, particularly congenital CMV
- A variety of protein and DNA subunit, vectored vaccines, and live attenuated vaccines are in clinical trials
- A better understanding of: 1) the correlates of protection of the fetus; 2) the problems of re-infection and viral immune evasion; 3) the issue of safety of live, attenuated vaccines is needed; 4) increased knowledge and awareness of CMV

Acknowledgements

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- Anders Lilja
- Klaus Orlinger

Leah Henriksen

Kelly Fenton

NICHD
NIAID
March of Dimes

Cytomegalovirus (CMV): An Obstetrician's Perspective on CMV vaccine

Laura Riley , MD

Obstetrician and Gynecologist-in-Chief
New York-Presbyterian Hospital

Chair of the Department of Obstetrics and Gynecology; Professor of Clinical Obstetrics and Gynecology
Weill Cornell Medical Colle

Weill Cornell Medicine
Obstetrics & Gynecology

An Ob's Perspective on the CMV Vaccine

Laura E. Riley, M.D
Given Foundation Professor and Chair
Obstetrician and Gynecologist -in-Chief
New York Presbyterian Hospital

Epidemiologic factors related to CMV:

- Seropositivity : 40-90% of women ages 15 – 44 years
- Seropositivity increases with **demographic factors**: lower SES, contact with children <3 yrs, black or Mexican ethnicity, age >25-30 yrs, higher parity, residence in developing country
- Multiple routes of transmission (nonsexual contact, sexual exposure, transfusion, organ transplant, multiple bodily fluids)

Annual Seroconversion Rates

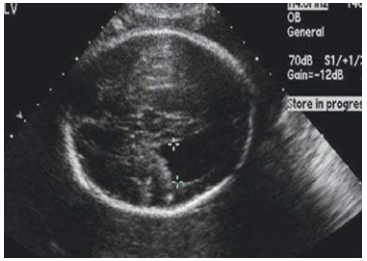
- Pregnant Women: 2.3% (95% CI 2.1- 2.4 %)
- Healthcare Workers: 2.3 % (95% CI 1.9 – 2.9%)
- Daycare Providers: 8.5% (95% CI 6.1 - 11.6%)
- Parents of a Child:
  - Non-shedding: 2.1% (95% CI 0.3 – 6.8%)
  - Shedding: 24% (95% CI 18-30%)

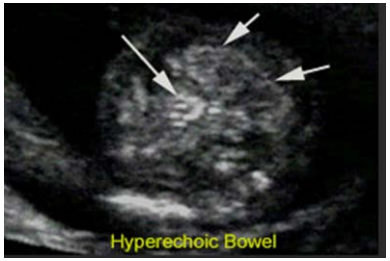
Hyde et al Rev Med Virol 2010; 20; 311

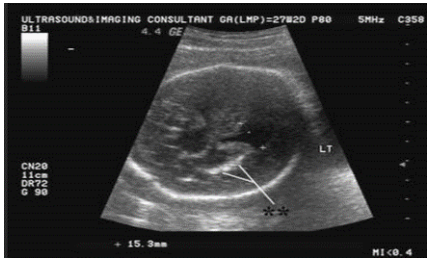
Maternal CMV disease

- Primary CMV - may be symptomatic
- Reactivation of latent CMV – no symptoms
- Reinfection with different strain - may or may not have symptoms

- Current recommendations to test for maternal CMV:
  - Mothers with mono-like illness
  - Fetuses with anomalies or findings c/w congenital CMV







M-F Transmission Rate (Primary maternal disease)

Preconception period (2 months – 3 weeks prior to conception)	5.2%
Periconception period (3 weeks – 3 weeks after conception)	16.4%
First Trimester (4 weeks – 12 weeks)	36.5%
Second Trimester	40. 1%
Third Trimester	65.0%

Picone et al. Prenat Diagn 2013; 33: 751

Timing of maternal infection is important!

Study of 248 Primary Maternal Infection Newborn symptoms

• preconception (1-10 weeks before LMP)	0/24
• periconception (1 week prior to LMP – 4 to 6 weeks)	1/29
• 1st trimester (5-13 and 6 weeks)	7/83
• 2nd trimester	4/76
• 3rd trimester	0/36

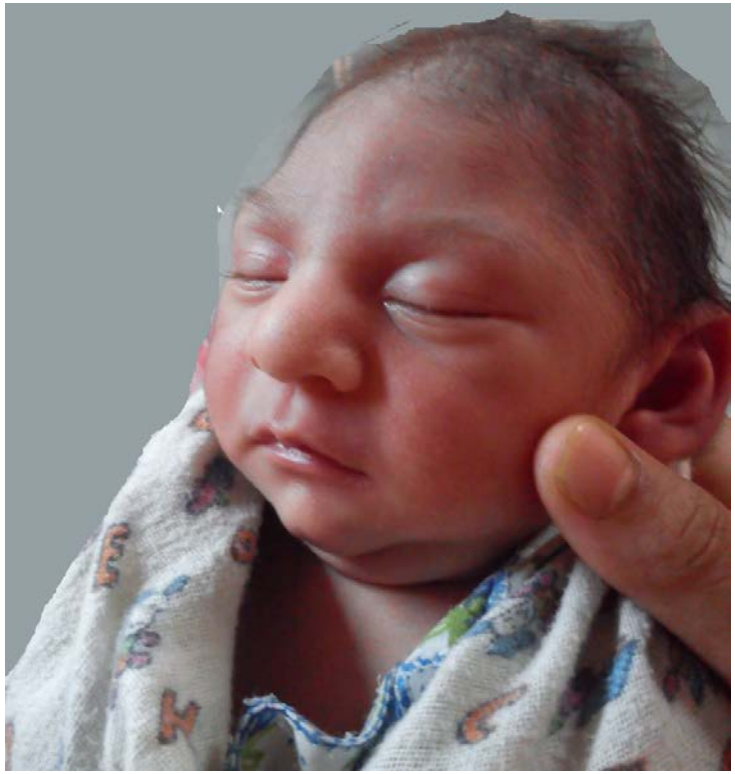
Enders et al. J Clin Virol 2011; 52:244

M-F Transmission Rate

If mother has reactivated or infection with a new strain:

0.15-2%

Severity of disease: unchanged



Mussi-Pinhata et al. JID 2018; 218:1200
Fowler et al. NEJM 1992; 326:663

M-F transmission w/ reactivated or reinfection of CMV

- "The true impact of recurrent maternal infection on both the incidence of congenital CMV infection and the long-term neurologic deficits in children ..is not known."

- Diagnosis of non-primary disease is difficult using CMV-IgG, CMV-IgM, CMV IgG avidity and maternal viremia yields variability despite known fetal infection.

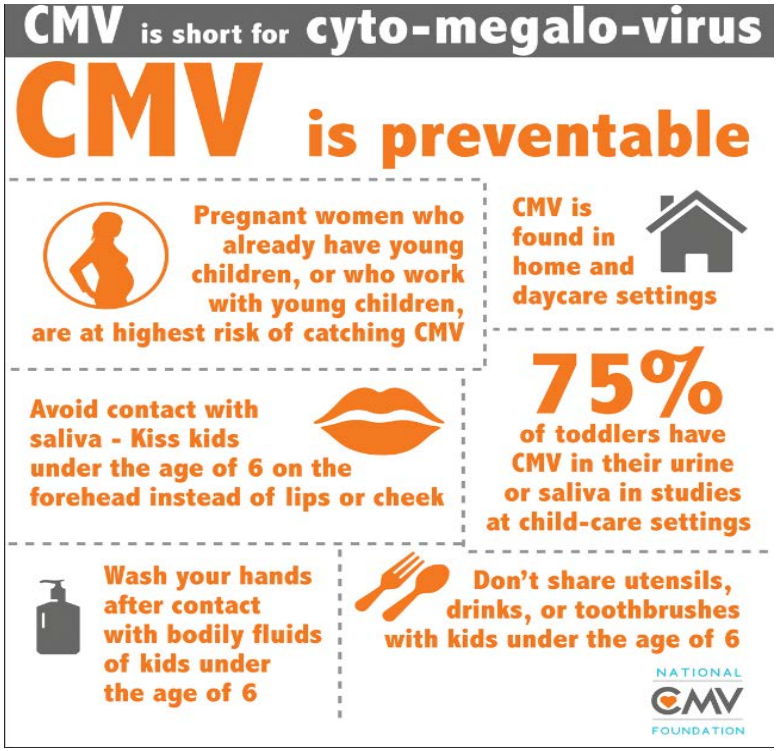
Boppana et al. Pediatrics 1999; 104: 55.
Picone et al. J Matern Fetal Neonatal Med; 2017: 30(2): 224.

Current Prevention Strategies

- No routine screening
- Education about personal hygiene, avoid kissing less than 6 years old, sharing food etc., clean surfaces
- Breastfeeding benefits “outweigh” risks
- If recent infection, wait 6 months

Vauloup-Fellous et al. J Clin Virol 2009;46 Suppl 4:S49

Public awareness:



Current Treatment Strategies

- CMV IVIG - doesn't work!

ORIGINAL ARTICLE

Passive Immunization during Pregnancy for Congenital Cytomegalovirus Infection

Giovanni Nigro, M.D., Stuart P. Adler, M.D., Renato La Torre, M.D., and Al M. Best, Ph.D. for the Congenital Cytomegalovirus Collaborating Group*

ORIGINAL ARTICLE

A Randomized Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus

Maria Grazia Revello, M.D., Tiziana Lazzarotto, Ph.D., Brunella Guerra, M.D., Arsenio Spinillo, M.D., Enrico Ferrazzi, M.D., Alessandra Kustermann, M.D., Secondo Guaschino, M.D., Patrizia Vergani, M.D., Tullia Todros, M.D., Tiziana Frusca, M.D., Alessia Arossa, M.D., Milena Furione, M.D., et al., for the CHIP Study Group*

- Antiviral medications – focused on ameliorating symptoms of congenital CMV rather than prevention of congenital disease

This Ob's Perspective on a CMV Vaccine:

- Safety
- Efficacy
- Durability
- Much needed intervention for the most common congenital viral infection affecting 20,000-40,000 newborns/yr in U.S.

Selected references:

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- Staras SA et al. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. Clin Infect Dis. 2006;43(9):1143.
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- Picone O et al. Cytomegalovirus non-primary infection during pregnancy. Can serology help with diagnosis? J Matern Fetal Neonatal Med. 2017;30(2):224.
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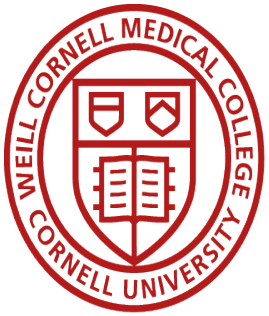
- Mussi-Pinhata MM et al. Seroconversion for Cytomegalovirus Infection During Pregnancy and Fetal Infection in a Highly Seropositive Population: "The BraCHS Study". J Infect Dis. 2018;218(8):1200.



Weill Cornell Medicine

Obstetrics & Gynecology

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CMV commercial opportunity

Stéphane Bancel

Chief Executive Officer

Our development plan for our CMV vaccine mRNA-1647

- Preparing for the pivotal phase 3 trial
- Near-term initiation of the dose-confirmation phase 2 (supply and clinical operations preparation is already advanced)
- Rapid phase 2 with 252 healthy subjects and a three-month interim analysis (IA) endpoint
- Phase 3 to demonstrate prevention of CMV infection in a sub-8,000 participant study in healthy women

CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine

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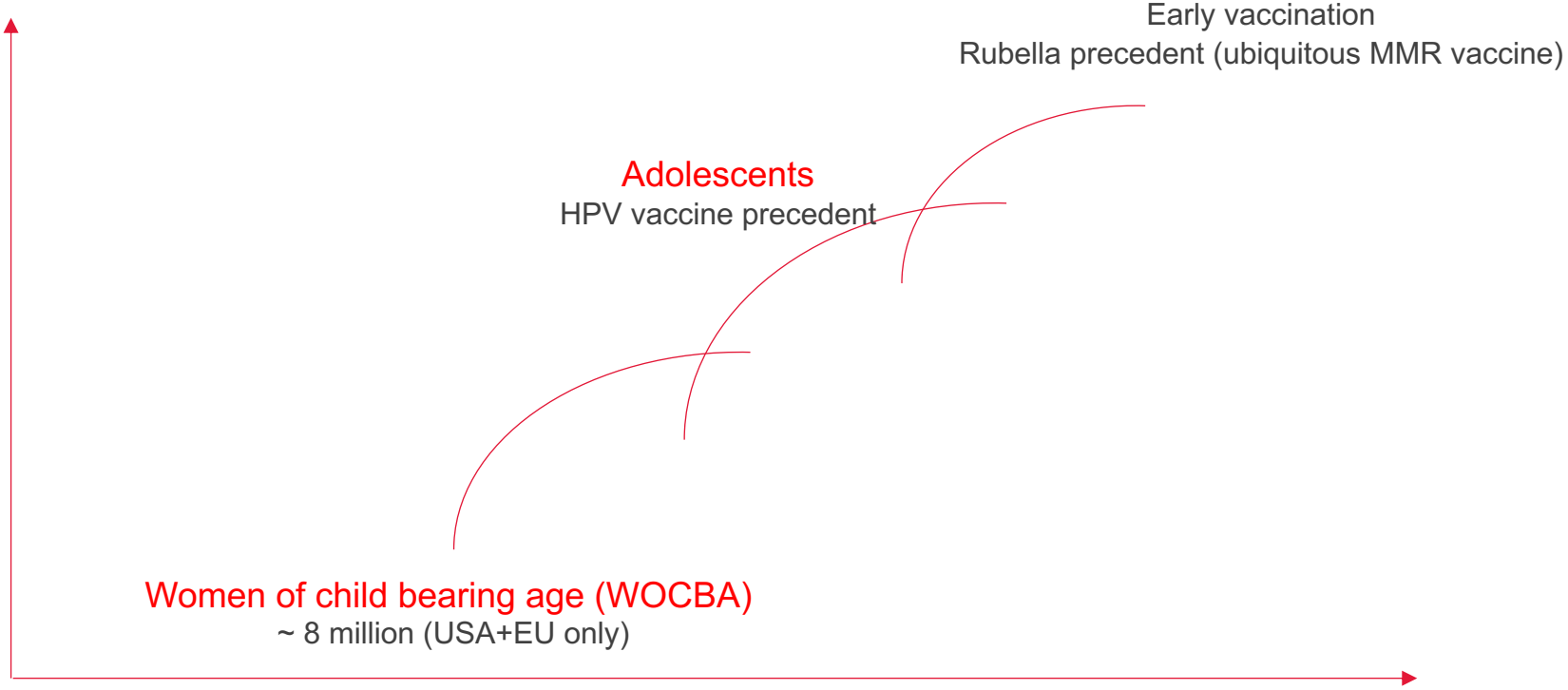
CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity



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CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity
- Total addressable market could be as high as 40-70 million vaccinations per year

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CMV vaccine infant cohort opportunity size

2030 Birth Cohort Opportunity Size

Region	Births
U.S.	~3.6 M
Europe	~5.4 M
Japan	~0.9 M
10% of China	~1.4 M
10% of India	~2.5 M
10% of ROW	~8.8 M
Total	**~22.6 M**

Accessible male & female birth cohort **exceeding 20 million** around the anticipated time of potential launch

2040 Birth Cohort Opportunity Size

Region	Births
U.S.	~3.7 M
Europe	~4.7 M
Japan	~0.9 M
25% of China	~3.4 M
25% of India	~6.3 M
25% of ROW	~22.3 M
Total	**~41.3 M**

10 years later, improved market access expands the cohort to **over 40 million**

2050 Birth Cohort Opportunity Size

Region	Births
U.S.	~3.7 M
Europe	~4.7 M
Japan	~0.9 M
50% of China	~6.6 M
50% of India	~12.7 M
50% of ROW	~44.7 M
Total	**~73.3 M**

Further market maturation grows the addressable cohort to **more than 70 million** by 2050

Source: UN Population Division; INED; UNICEF.

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CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity
- Total addressable market could be as high as 70 million vaccinations per year
- Focused sales effort: OBGYN and Pediatricians

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CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
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- Total addressable market could be as high as 70 million vaccinations per year
- Focused sales effort: OBGYN and Pediatricians
- Opportunity to leverage social media during Phase 3 for pre-launch activities to educate a motivated initial target population, women of childbearing age (WOCBA)

We aim to raise CMV awareness in the medical community and the public to accelerate trial recruitment and launch uptake

Strategic Initiatives	Description	Beneficial to Trial Recruitment
1 Partner with national and regional CMV advocacy groups	• Establishing early relationships with advocacy groups to influence policy and guidelines	✓
2 Educate OB/GYNs, pediatricians, and PCPs about congenital CMV infection	• Educating physicians in the near term, particularly with PCPs who have limited awareness	✓
3 Distribute educational materials to key populations through physicians	• Informational pamphlets on risks of congenital CMV infection and current prevention tactics can be distributed through OB/GYN, pediatrician, and PCP offices to engage key populations	✓
4 Leverage online platforms to raise CMV awareness in key populations	• Additional raising of awareness of CMV and its consequences in key populations	✓
5 Promote awareness of mRNA-1647	• Emphasizing antibody titer profile of mRNA-1647	○

Source: ClearView

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CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity
- Total addressable market could be as high as 70 million vaccinations per year
- Focused sales effort: OBGYN and Pediatricians
- Opportunity to leverage social media during Phase 3 for pre-launch activities to educate a motivated initial target population, women of childbearing age (WOCBA)
- Pricing power for innovative vaccines due to value proposition (GARDASIL* US pricing=$450)

*GARDASIL ® is a registered trademark of Merck & Co., Inc.

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- Vaccine sales are annuity-like, scaling with population growth
- Innovative vaccines have EBIT margins of approximately 50%

Moderna owns global commercial rights to mRNA-1647

*GARDASIL ® is a registered trademark of Merck & Co., Inc.

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Q&A

R&D Day 2019 agenda

September 12, 2019

Sign-in, Coffee, Breakfast		*7:30–8:30 AM*	*60 min*
Introduction	*Stéphane Bancel*	*8:30–8:40 AM*	*10 min*
CMV	*Tal Zaks, MD, PhD* *Sallie Permar, MD, PhD, Duke University School of Medicine* *Tal Zaks, MD, PhD* *Juan Andres* *Mark Schleiss, MD, University of Minnesota* *Laura Riley, MD, Weill Cornell Medical College* *Stéphane Bancel*	*8:40–10:00 AM*	*80 min*
Q&A		*10:00–10:30 AM*	*30 min*
Break		*10:30–10:40AM*	*10 min*
Immuno-oncology	*Tal Zaks, MD, PhD* *Keith Flaherty, MD, Massachusetts General Hospital*	*10:40–11:10 AM*	*30 min*
Antibody against Chikungunya virus	*Tal Zaks, MD, PhD*	*11:10–11:50AM*	*40 min*
Methylmalonic acidemia	*Gregory Enns, MD, Stanford University*	*11:50–12:20 AM*	*30 min*
Conclusion	*Stéphane Bancel*	*12:20–12:30 PM*	*10 min*
Q&A	*Moderna Team*	*12:30–1:00 PM*	*30 min*
Lunch			

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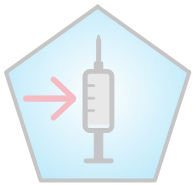
Cancer vaccines and Intratumoral immuno-oncology

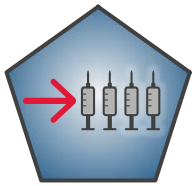
Tal Zaks, MD, PhD

Chief Medical Officer

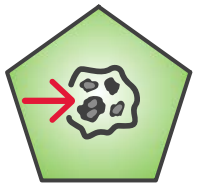
Modalities



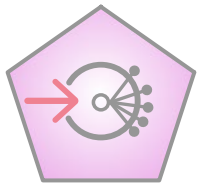
Prophylactic vaccines



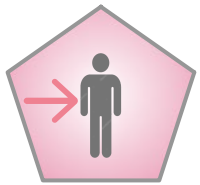
Cancer vaccines



Intratumoral immuno-oncology



Localized regenerative therapeutics



Systemic secreted therapeutics

Systemic intracellular therapeutics

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Cancer Vaccines

Modality	Program #	Program *Indication*	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Cancer vaccines	**mRNA-4157**	Personalized cancer vaccine (PCV)					50-50 global profit sharing with Merck
	NCI-4650	Personalized cancer vaccine (PCV)					
	mRNA-5671 V941	KRAS vaccine *CRC, NSCLC, pancreatic cancer*					50-50 global profit sharing with Merck

Note: NCI-4650 differs from mRNA-4157 in its neoantigen selection process

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mRNA advantages in immuno-oncology

- ***Natural cellular processing*** *(antigen presentation, membrane proteins)*
- ***Combinations*** *(neoantigens, immuno-stimulatory agents)*
- ***Single process*** *and single, multi-product facility enables* ***rapid production*** *and economies of scale*
- ***Transient, localized*** *immuno-stimulatory effect at the tumor site*
- *mRNA sequences can be engineered to* ***reduce off-target effects***

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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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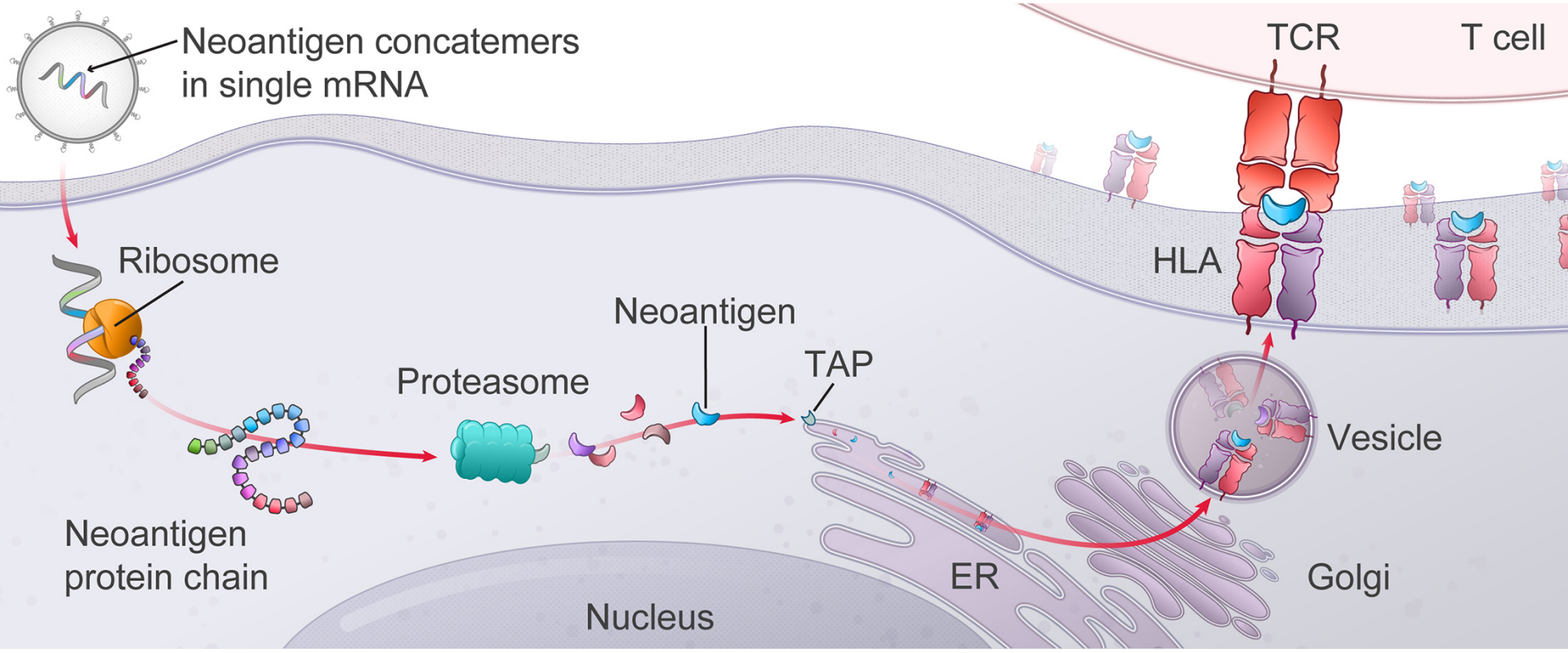
Moderna's mRNA vaccines elicit T cell activation for curative intent cancer therapy



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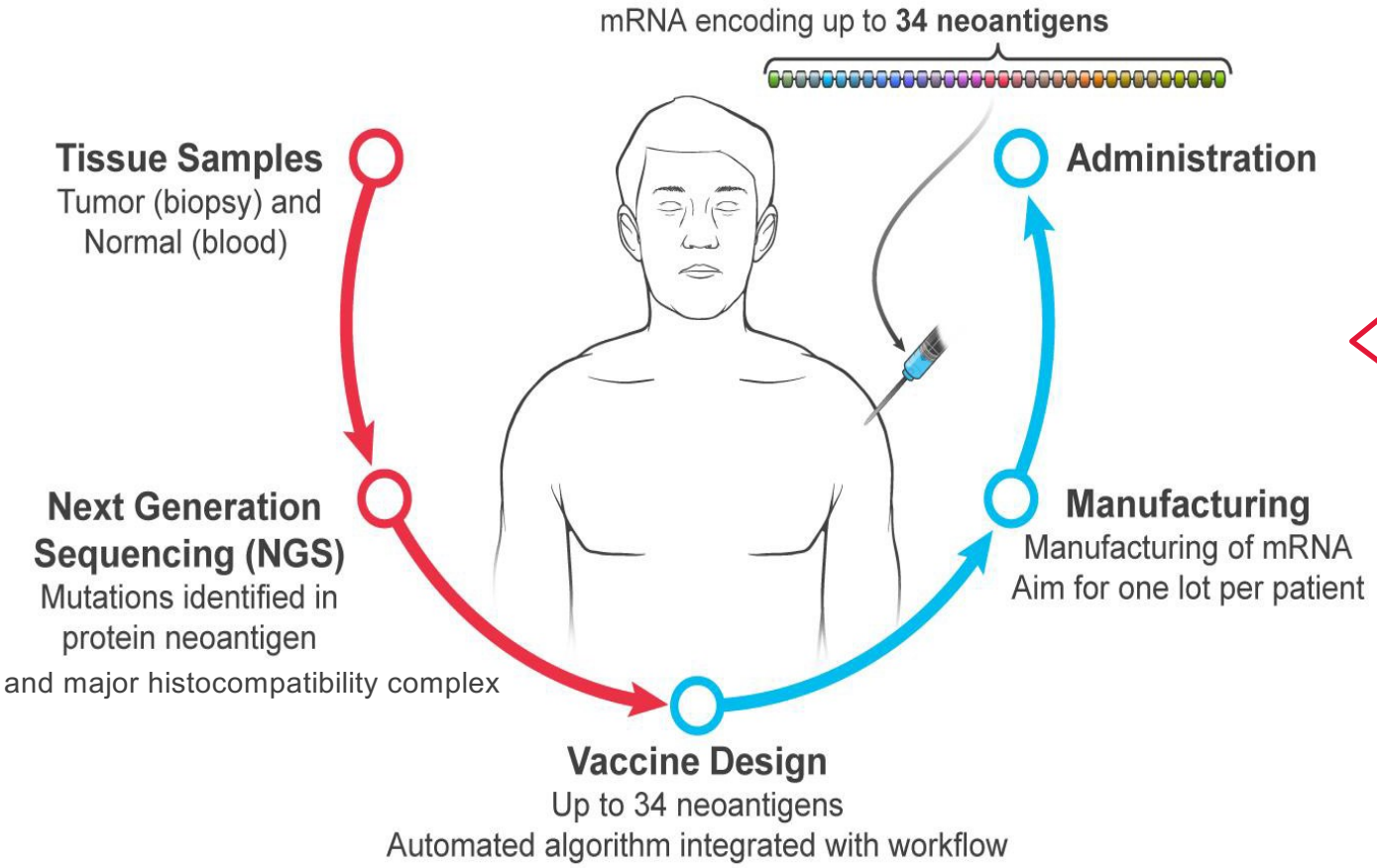
Personalized cancer vaccine (mRNA-4157)

Designed to target an individual patient's unique tumor mutations



- Partnered with Merck (Keytruda combo)
- Interim Phase 1 data presented at ASCO 2019
- Dosed for up to 9 cycles
- Randomized Phase 2 trial in adjuvant melanoma started

Personalized Cancer Vaccines

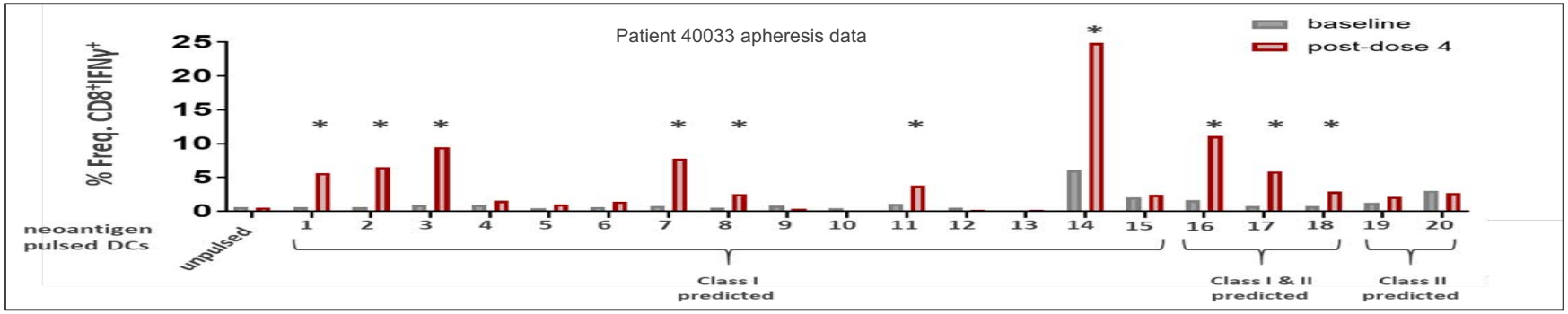
mRNA-4157: Phase 1 data

Clinical & regulatory update

- Continuing to enroll patients in phase 1 safety, tolerability and immunogenicity trial monotherapy and in combination with pembrolizumab
- Part C&D: Continuing to enroll patients
- Interim safety, tolerability immunogenicity data presented at ASCO 2019[1]
- First patients consented for phase 2 Randomized Controlled Trial

Select clinical data[1]

- **Safety:** mRNA-4157 is well tolerated at all dose levels studied with no DLTs reported. No mRNA-4157 related grade 3/4 AE or SAE was reported. The most common grade 2 adverse events were fatigue, soreness at the injection site, colitis and myalgias.
- **Activity:** Neoantigen specific CD8 T-cell responses were detected in 10 out of 18 class I neoantigens in patient 40033, the first patient dosed at 1 mg who underwent apheresis. 100% of positive CD8 T-cell responses post vaccination were to neoantigens with a high predicted binding affinity of <500 nm



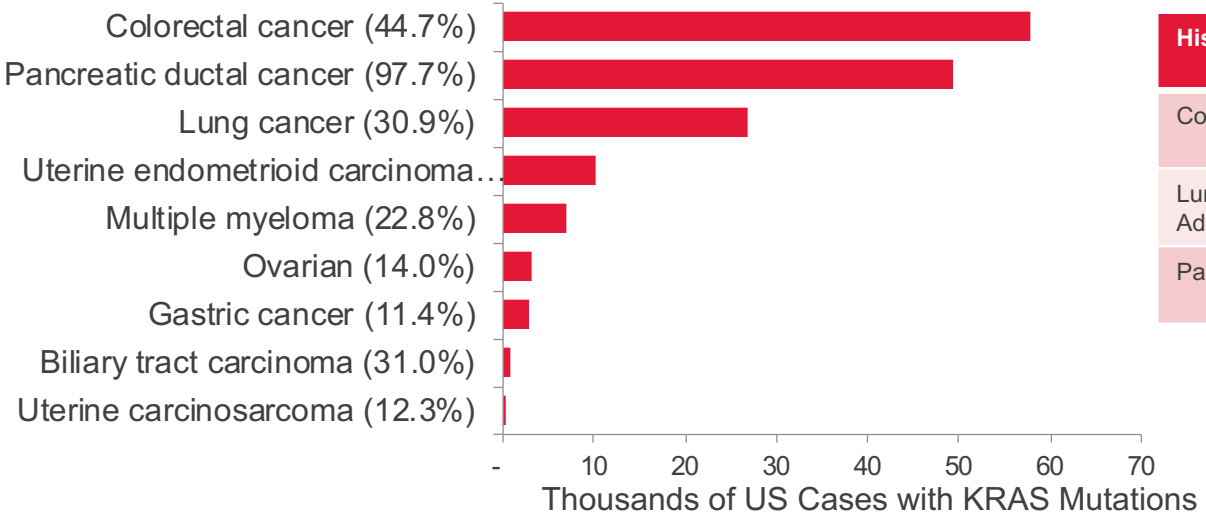
- **Early clinical:** Clinical responses have been seen in 6 out of 20 patients treated with mRNA-4157/pembrolizumab combination. Of these 6 patients, 2 responses have been seen in patients previously treated with PD-(L)1 inhibitor and 1 patient achieved CR prior to vaccination

[1] Data cutoff as of May 10, 2019

KRAS opportunity: mutation is present in >20% of human cancers

- KRAS is a key regulator of cell proliferation and survival; mutations cause dysregulated cell proliferation
- One of the most frequently mutated oncogenes in human cancers
- Mutations found principally in pancreatic cancer, lung cancer, and colorectal cancer
- Most prevalent KRAS mutations G12D, G12V, G13D, and G12C 80-90% of KRAS mutations

KRAS Mutation Prevalence (% with KRAS mutation)



Percentage of KRAS mutation type by histology

Histology	G12C	G12D	G13D	G12V
Colorectal	3%	13%	7%	9%
Lung Adenocarcinoma	13%	4%	1%	5%
Pancreatic	1%	34%	<1%	28%

Patients whose tumors harbor KRAS mutations have worse outcomes

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KRAS Vaccine

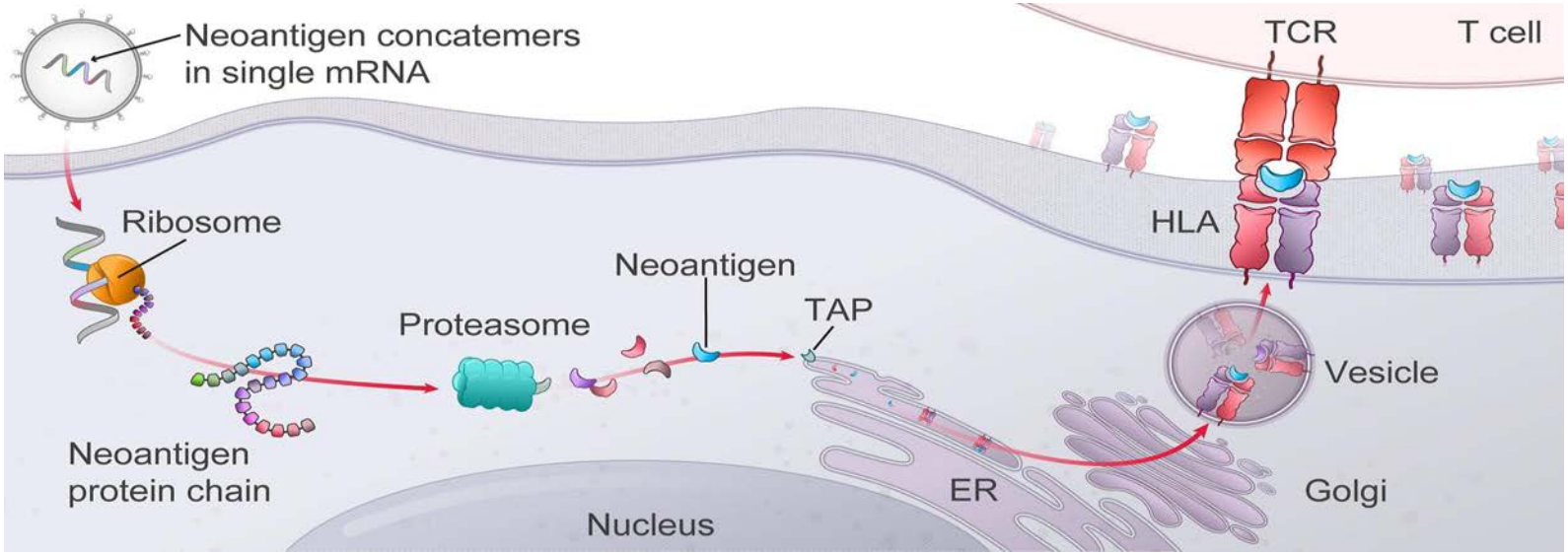
mRNA-5671/Merck V941:

KRAS Overview:

- KRAS is a key regulator of cell proliferation and survival; mutations cause dysregulated cell proliferation
- One of the most frequently mutated oncogenes in human cancers; mutation is present in >20% of human cancers
- Mutations found principally in pancreatic, lung and colorectal cancers
- Recognition of mutated KRAS epitopes by T-cells can lead to cancer cell regression as proven by adoptive T-cell transfer[1]

mRNA-5671/Merck V941:

- Codes for the four most prevalent KRAS mutations G12D, G12V, G13D, and G12C covering 80-90% of KRAS mutations



[1] T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer, NEJM, Eric Tran, Ph.D., et al.

KRASvaccine (mRNA-5671)/Merck V941

Patients dosed in Phase 1 trial

Phase 1 study overview

—A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/Merck V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma

—Selecting for HLA subtypes (HLA-A*1101 and/or HLA-C*0802) most likely to respond

Intratumoral Immuno-Oncology

Modality	Program #	Program *Indication*	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Intratumoral immuno-oncology	**mRNA-2416**	OX40L *Solid tumors/lymphoma* *Advanced ovarian Cancer*					Worldwide
	mRNA-2752	OX40L+IL23+IL36γ (Triplet) *Solid tumors/lymphoma*					Worldwide
	MEDI1191	IL12 *Solid tumors*					50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales

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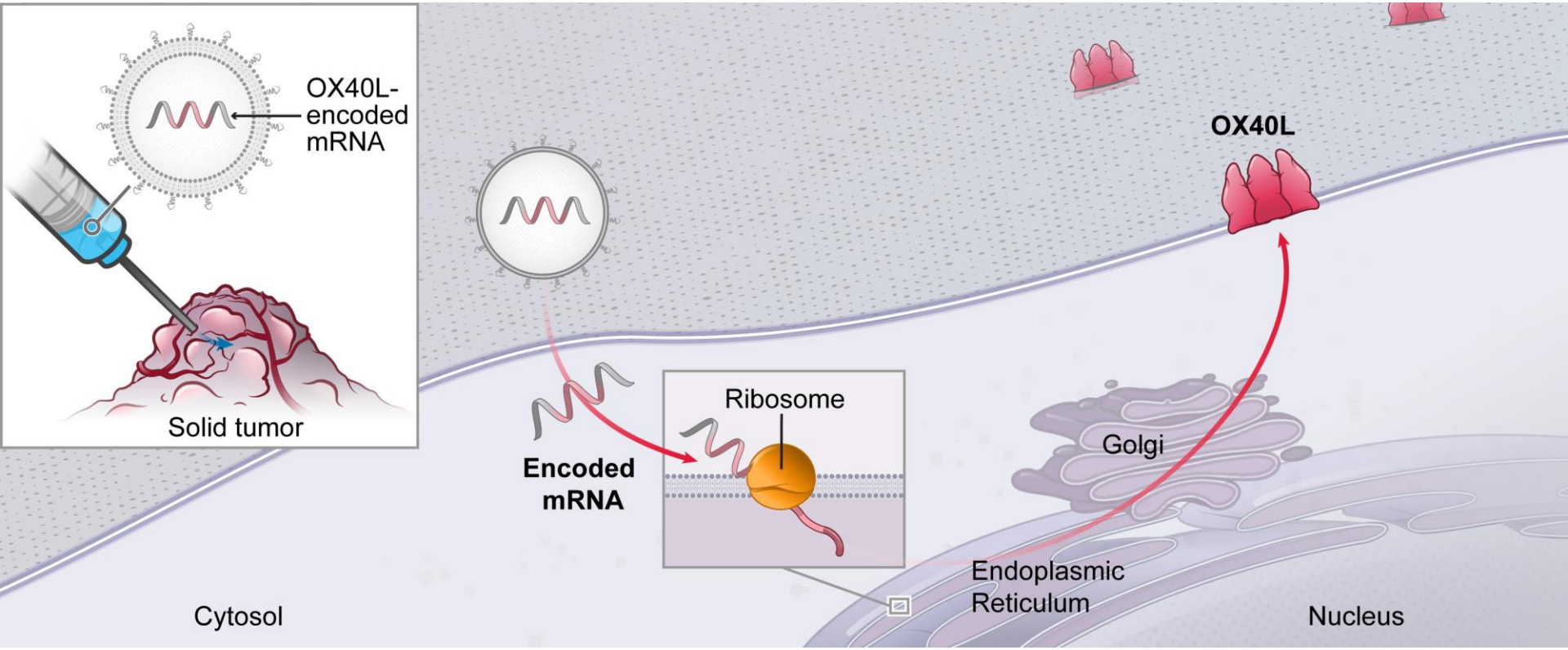
OX40L (mRNA-2416)

OX40L Overview:

- OX40L is a potent co-stimulator, which promotes T-cell proliferation and enhanced survival in the presence of antigen

mRNA-2416:

- mRNA-2416 encodes for OX40L, which is a membrane protein that we believe cannot be manufactured by recombinant technologies



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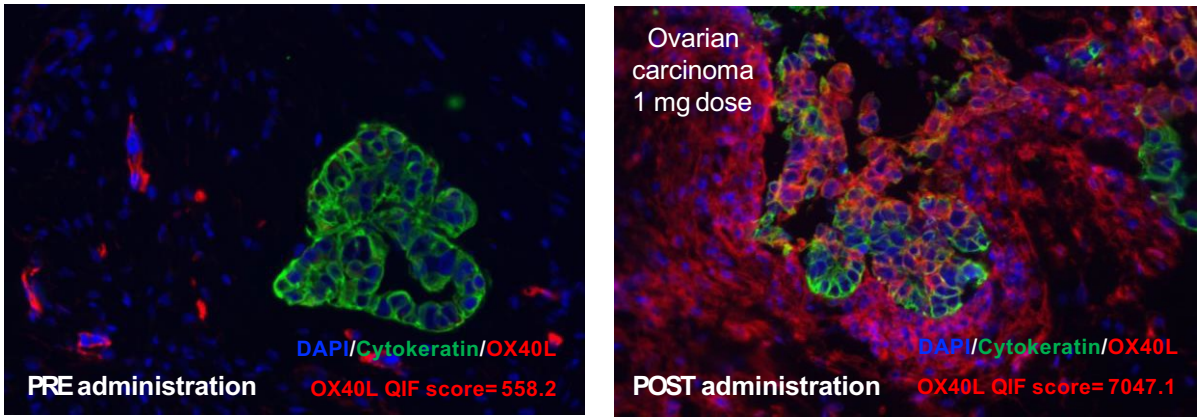
OX40L (mRNA-2416)

OX40L expression demonstrated: progressing to phase 2 cohort

Clinical:

- Interim analysis SITC 2018: mRNA-2416 is tolerable at all dose levels studied with no DLTs reported and the majority of AE's being grade 1 or 2
- A clear increase in OX40L protein expression from mRNA-2416 was observed in both tumor and stromal regions in three out of the five post-treatment biopsies collected from injected tumors
- Repeat dosing through 12 doses (6 cycles) continues at highest levels (8mg) in phase 1
- Phase 2 cohort in patients with ovarian cancer, including in combination with durvalumab is being prepared



OX40L protein production in tumor cells of an injected lesion of a patient with ovarian cancer

moderna

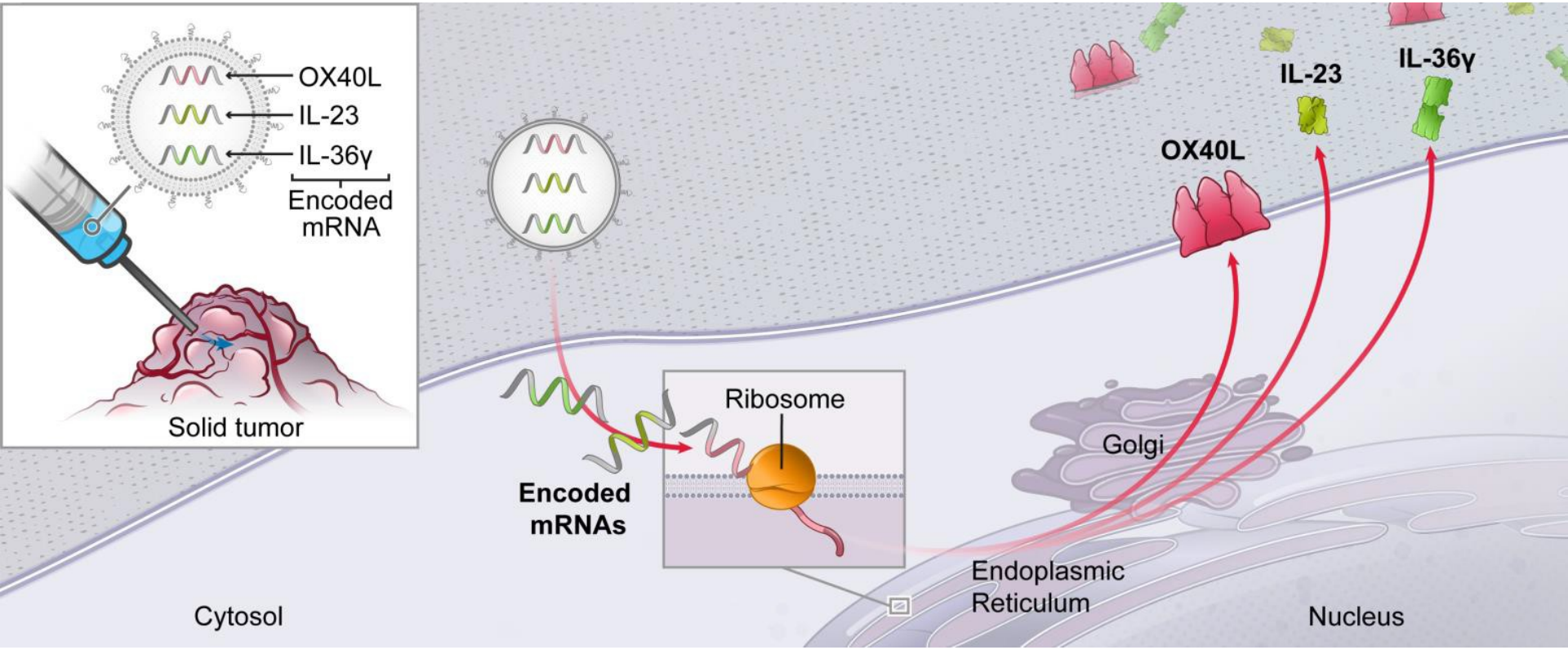
OX40L+IL23+IL36γ (Triplet) (mRNA-2752)

OX40L+IL23+IL36γ (Triplet) Overview:

- OX40L powerful co-stimulatory protein that enhances T-cell expansion, function and memory formation
- IL23 and IL36γ have established roles in mediating immune responses

mRNA-2752:

- mRNA-2752 encodes for OX40L which is a membrane protein and secreted pro-inflammatory cytokines IL-23 and Il-36γ



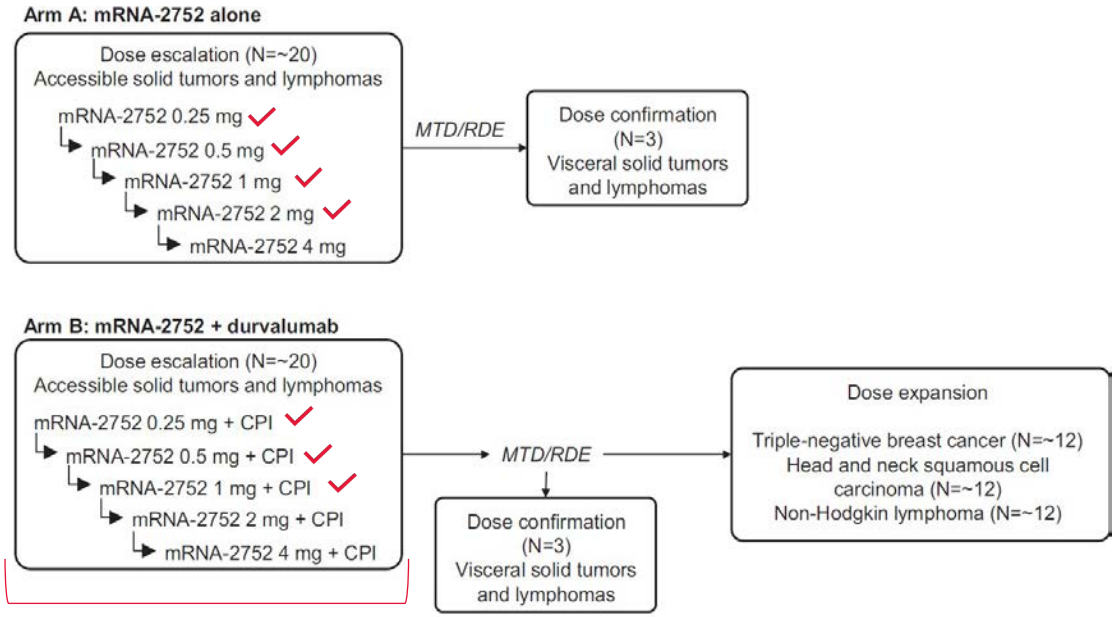
moderna

OX40L+IL23+IL36γ (Triplet) (mRNA-2752)

Phase 1 ongoing; First patient dosed in combination durvalumab

Key Objectives

- Evaluate safety and tolerability of mRNA-2752 administered alone and in combination with checkpoint inhibitors
- Define MTD and recommended dose for expansion for mRNA-2752 alone and in combination with durvalumab
- Intended to assess:
  - Anti-tumor activity
  - Protein expression in tumors
  - Pharmacokinetics



Patients dosed in combination arm

moderna

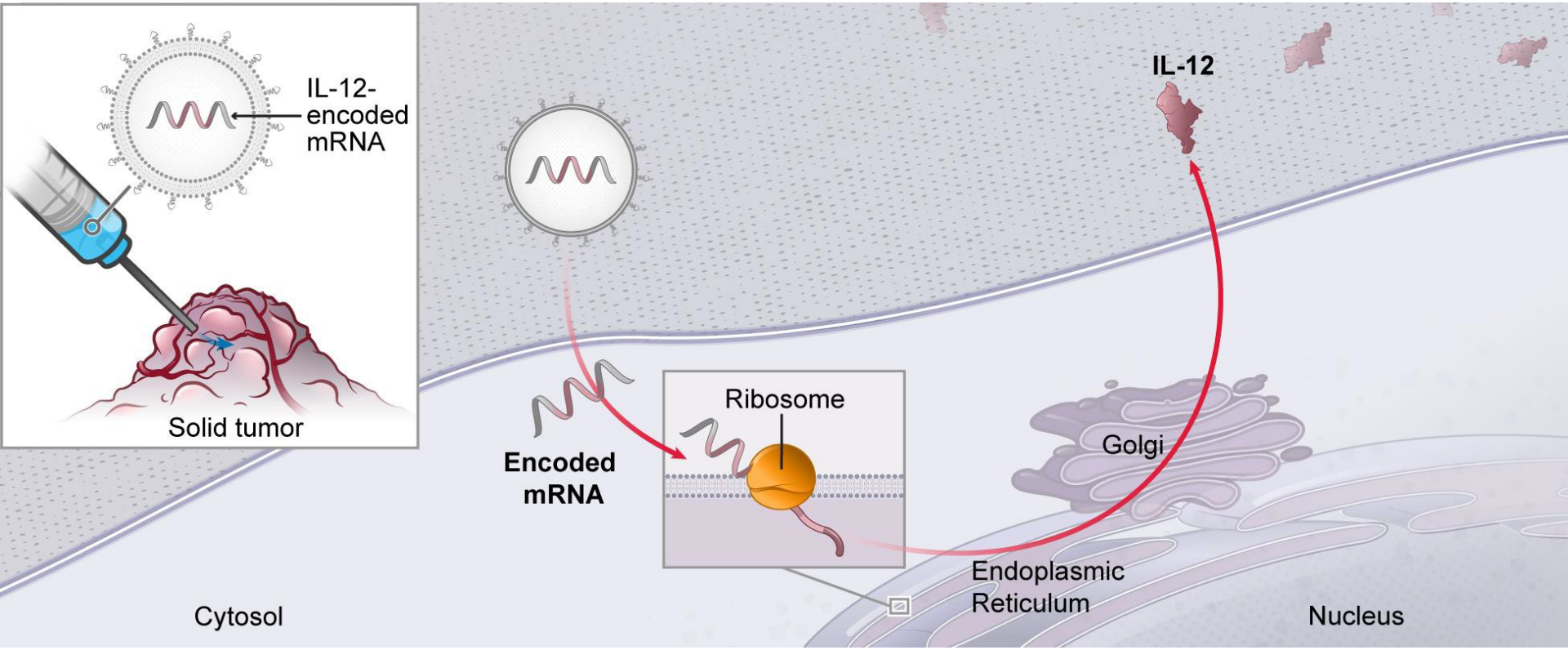
IL12 (MEDI1191)

IL12 Overview:

- IL12 is a potent immune modulator associated with type 1 immune response and production of interferon gamma

MEDI1191:

- Encodes for IL12, a secreted cytokine that acts locally in the tumor microenvironment (TME)



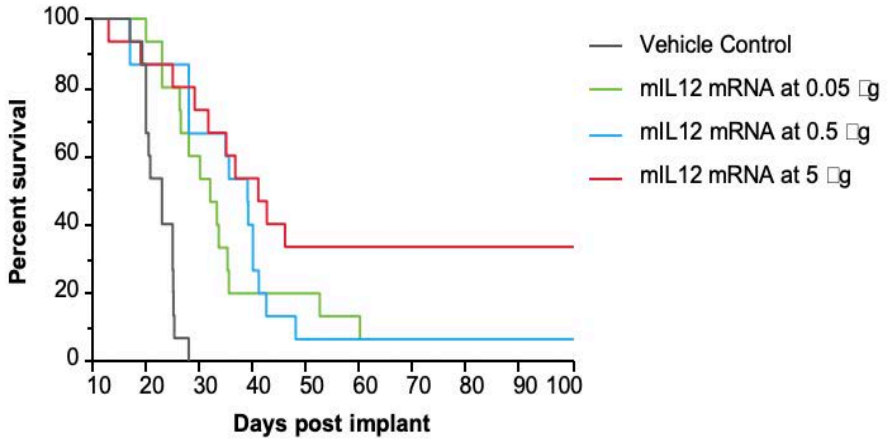
moderna

IL12 (MEDI1191)

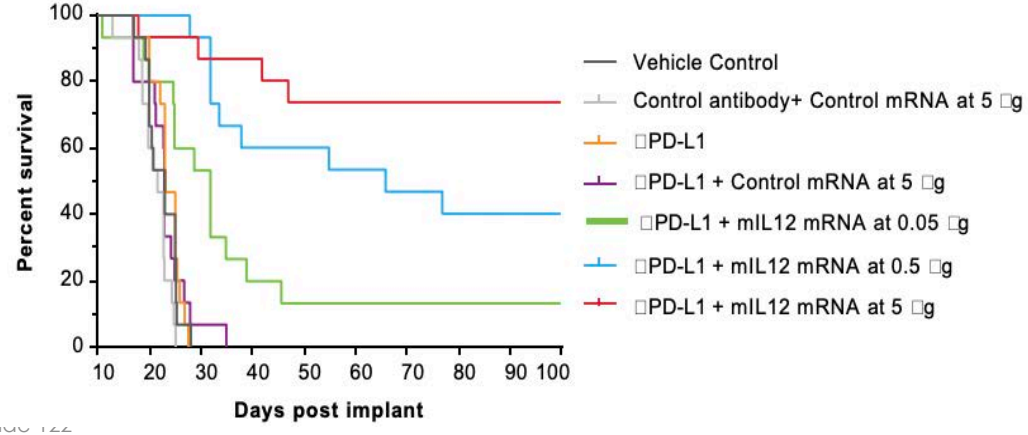
First patient dosed in phase 1

Preclinical:

Approximately 30% complete responders with highest dose tested for mIL12 mRNA in MC38 mouse model study



□70% complete responders at highest tested dose for mouse IL12 mRNA with □PD-L1 antibody in MC38 mouse model study



Clinical:

- Phase 1, open-label, multicenter, dose escalation and expansion study of MEDI1191 administered intratumorally as monotherapy and in combination with durvalumab in subjects with advanced solid tumors
- Key objectives to evaluate safety and tolerability in monotherapy and combination arms and objective response rate in patients within expansion arms
- First patient dosed with IL12 monotherapy in phase 1 trial

Immunoncology

Keith T. Flaherty, MD

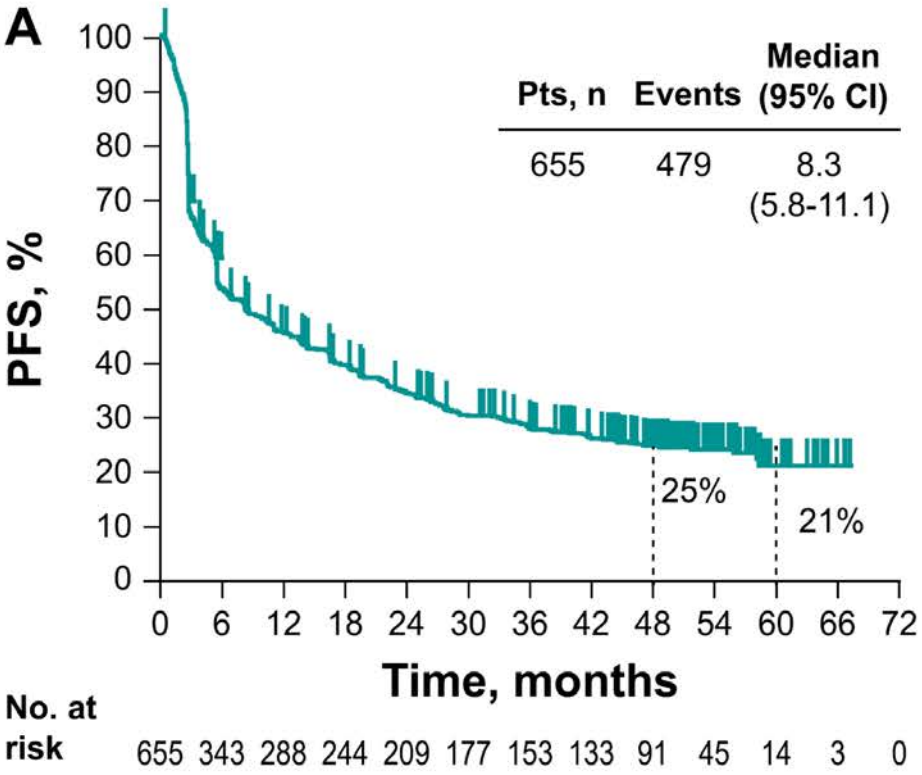
Director of Henri and Belinda Termeer Center for Targeted Therapy, Cancer Center;
Director of Clinical Research, Cancer Center
Massachusetts General Hospital

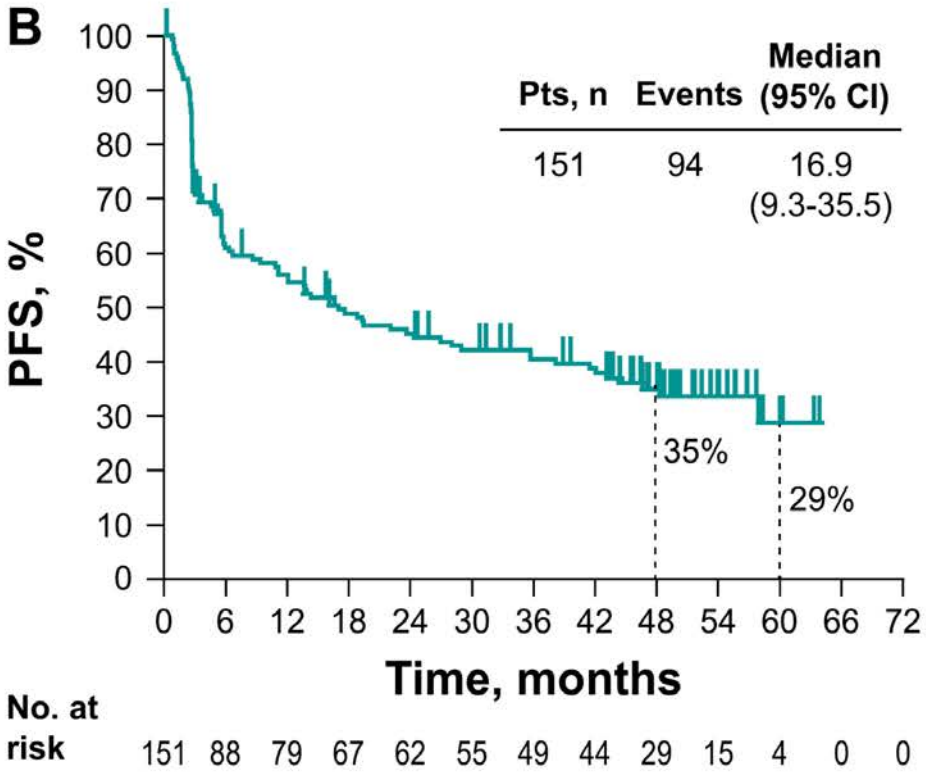
The remaining unmet need: the aftermath of the PD-1/PD-L1 revolution

Keith T. Flaherty, M.D.

Massachusetts General Hospital Cancer Center

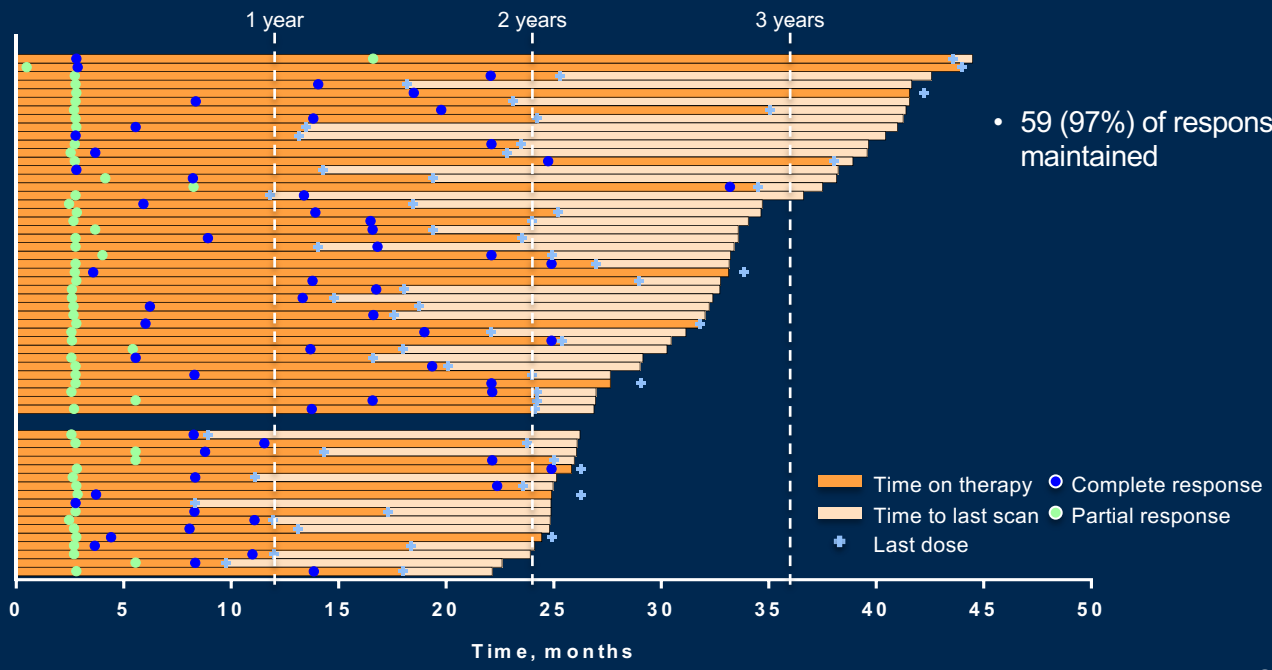
Kaplan-Meier Estimates of Progression-free Survival: Pembrolizumab





Hamid O et al. ASCO 2018

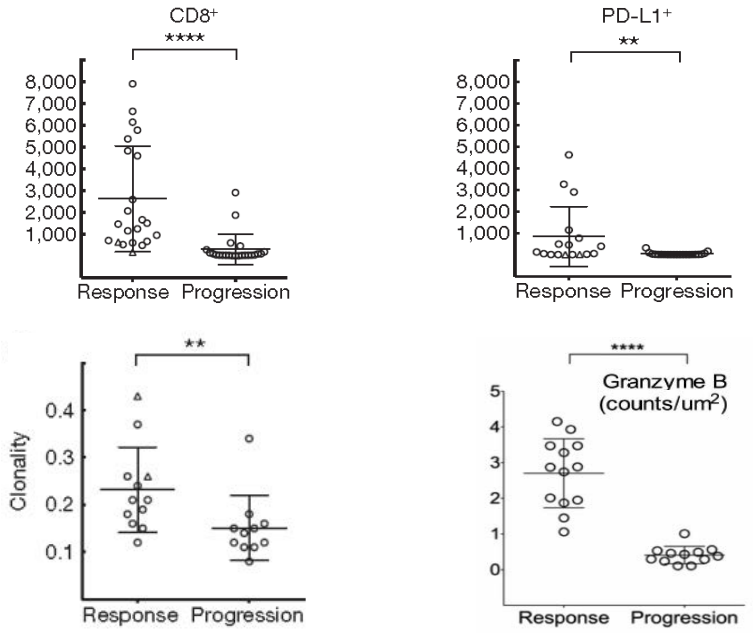
Complete Responders Who Stopped Pembrolizumab for Observation (N = 61)



- 59 (97%) of responses were maintained

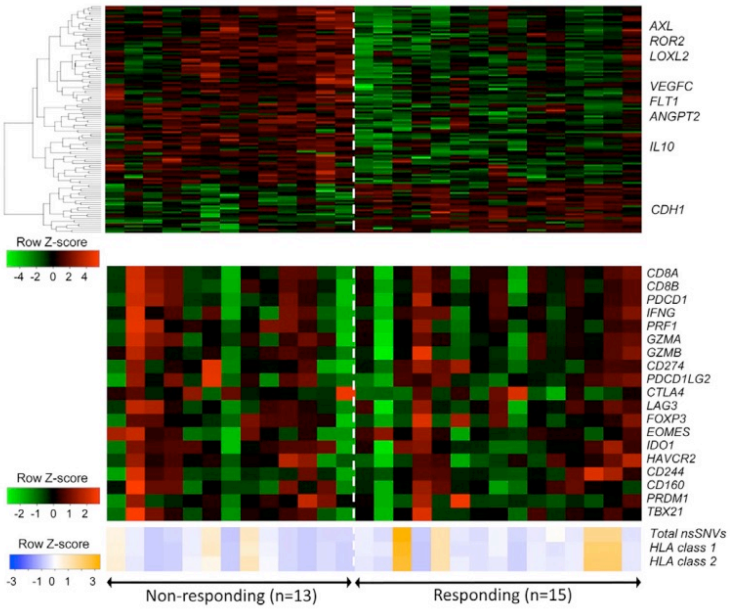
Robert et al. ASCO 2016

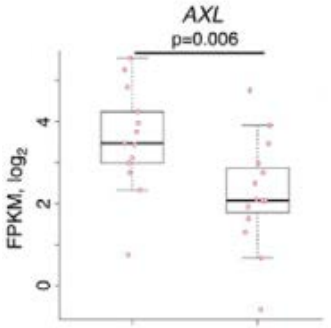
“Inflamed” tumors are more likely to respond to PD-1 antibody therapy



Tumeh P et al.
Nature 2014

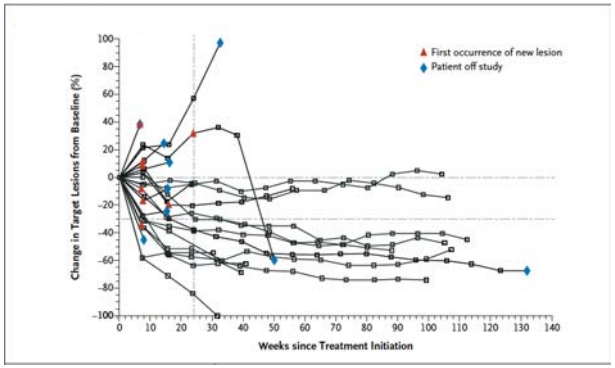
Tumor gene expression, but not immune checkpoints sorts response/non-response



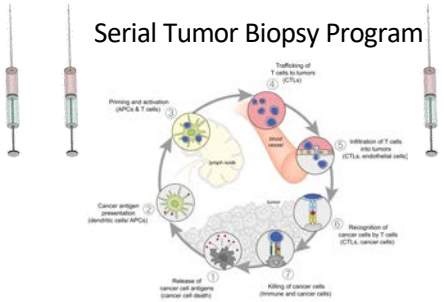


Hugo et al. Cell 2016

Interrogating mechanism of action & resistance

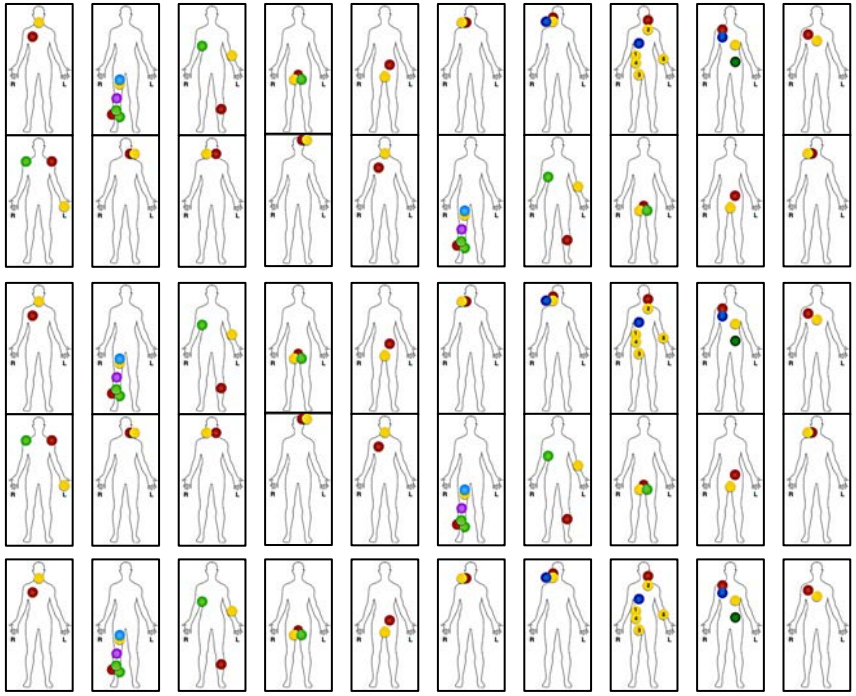


Serial Tumor Biopsy Program

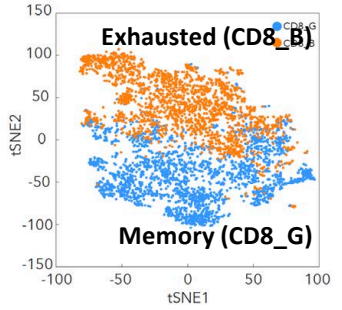


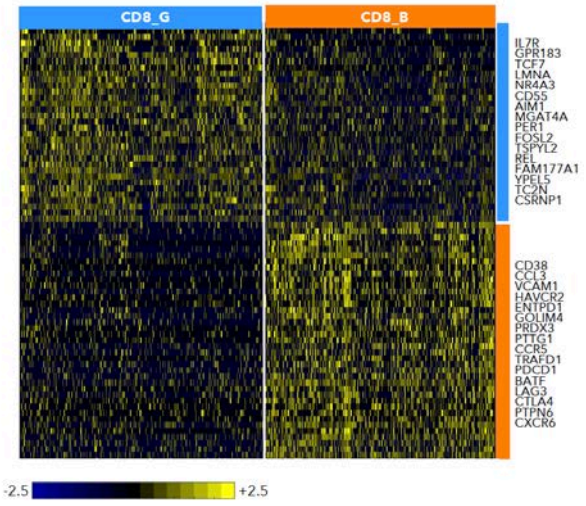
Rapid Autopsy Program

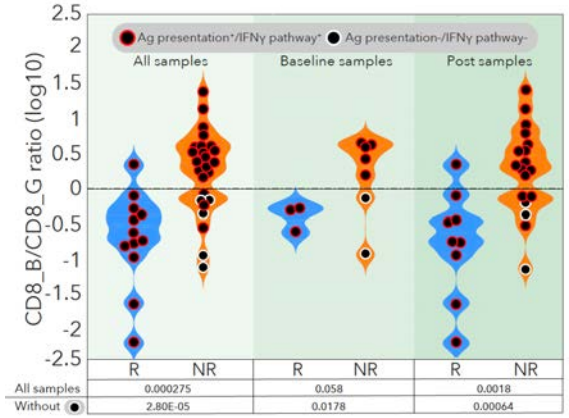
MGH Termeer Center checkpoint antibody serial biopsy cohort

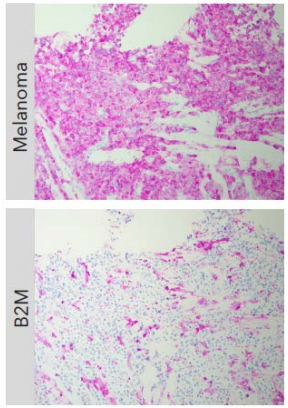


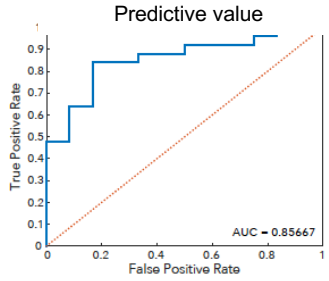
Two CD8⁺ T cell states associate with CPB response

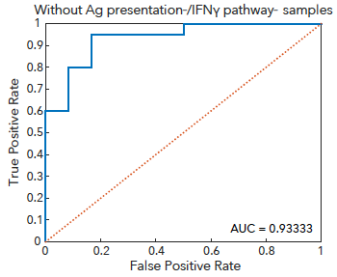






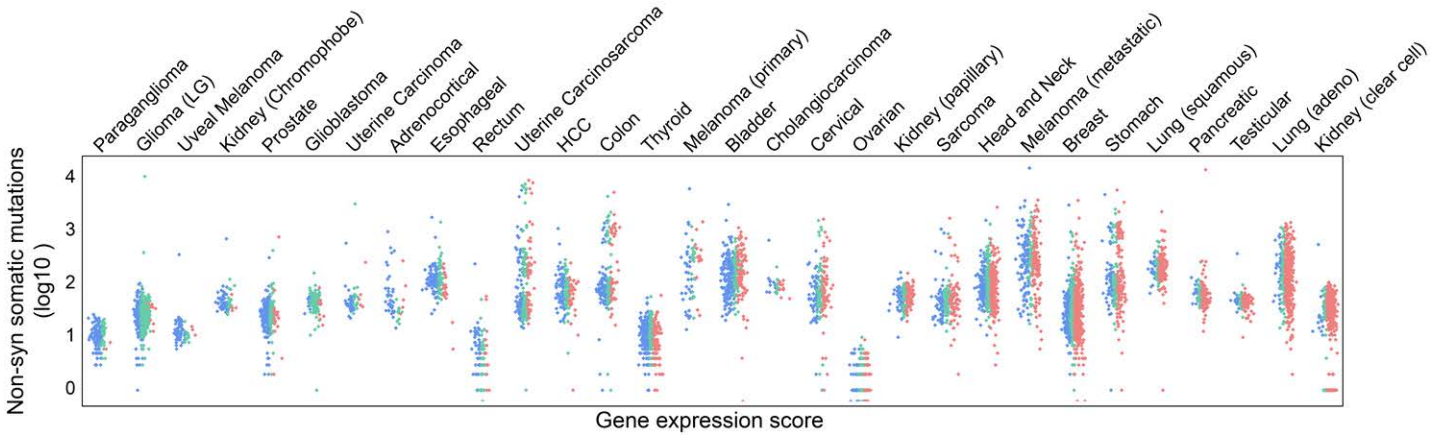






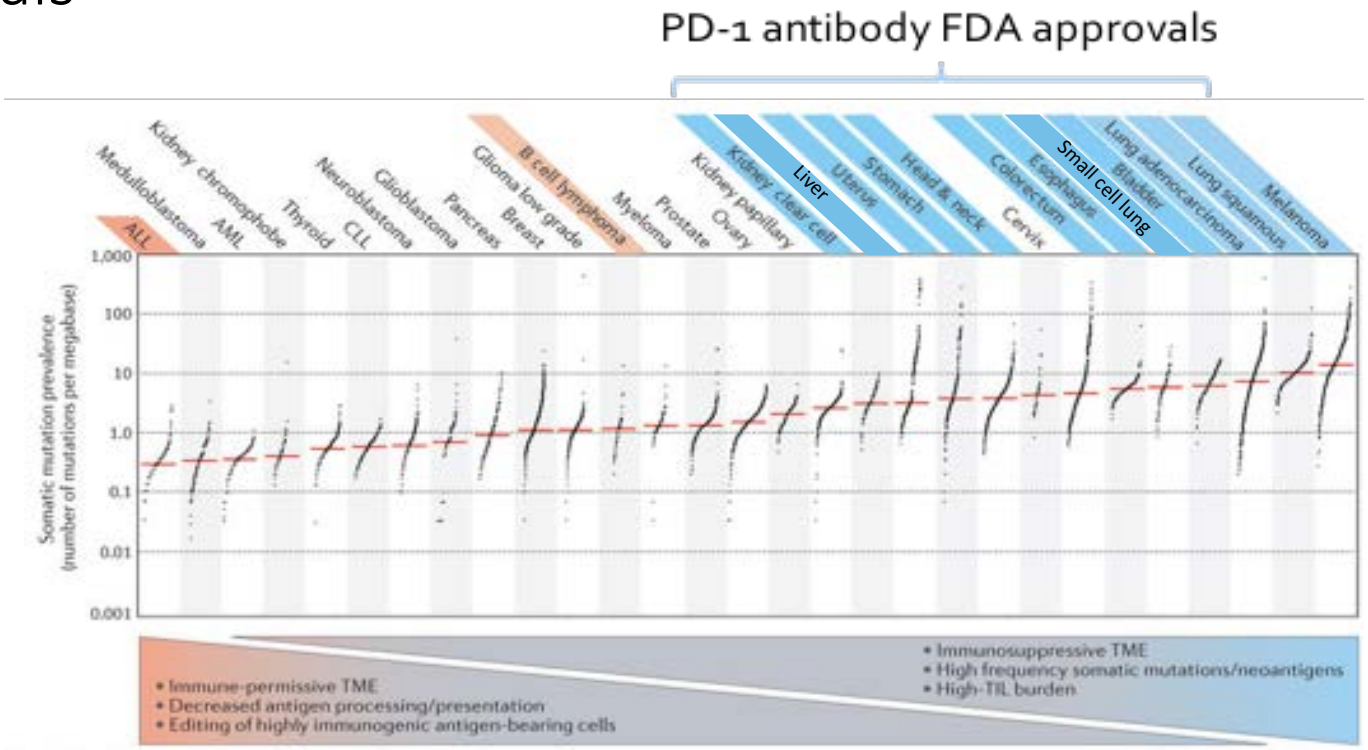
Sade-Feldman et al. *Cell* 2018

Mutational burden tightly correlates with T cell inflammation across cancer types



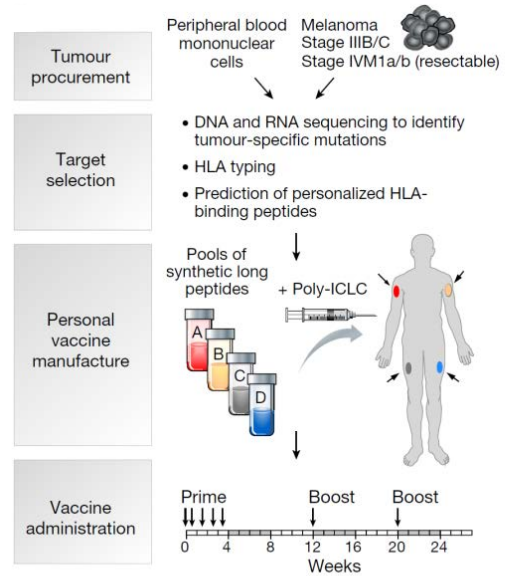
Luke and Spranger et al. PNAS 2016

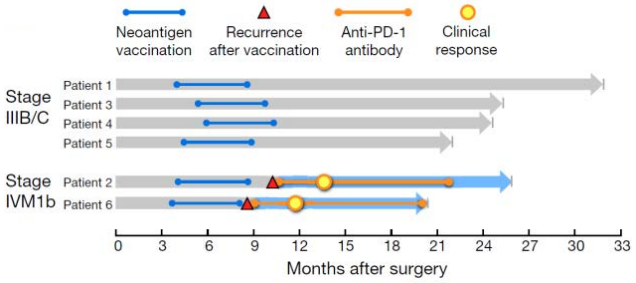
…and mutation burden correlates with response rates & approvals

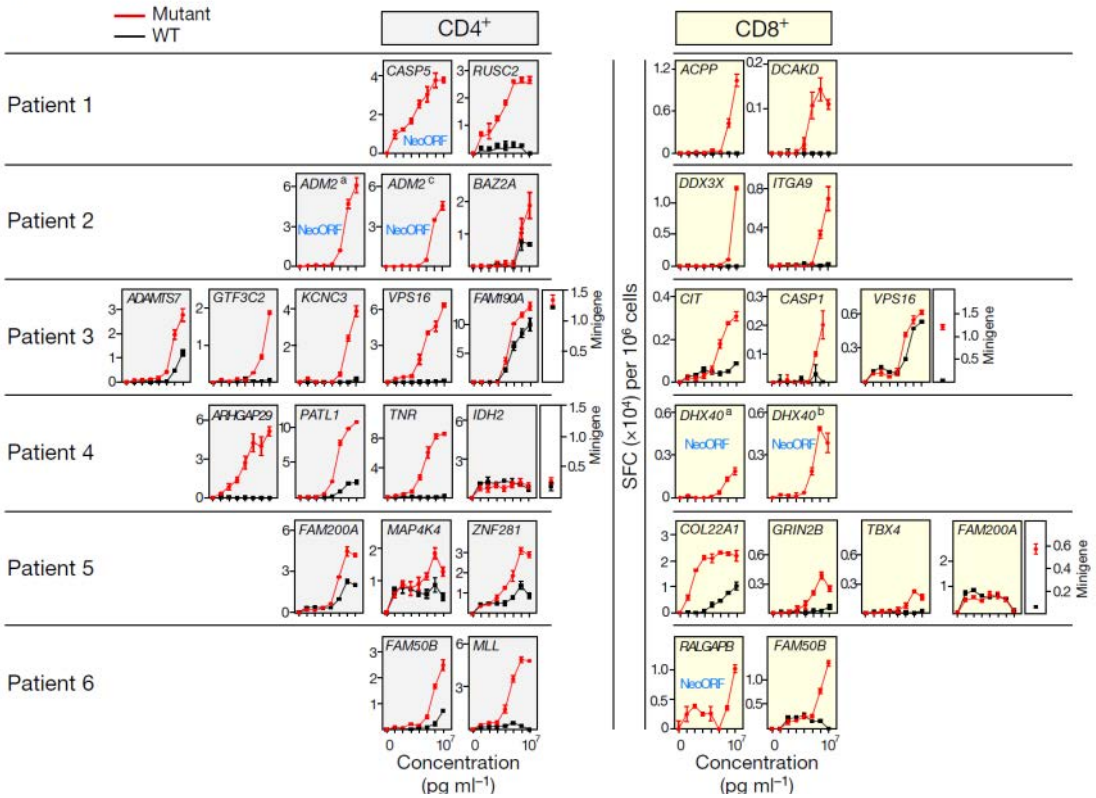


Adapted from Alexandrov et al. Nature 2013

Immunizing against mutated neoantigens







Ott et al. Nature 2018

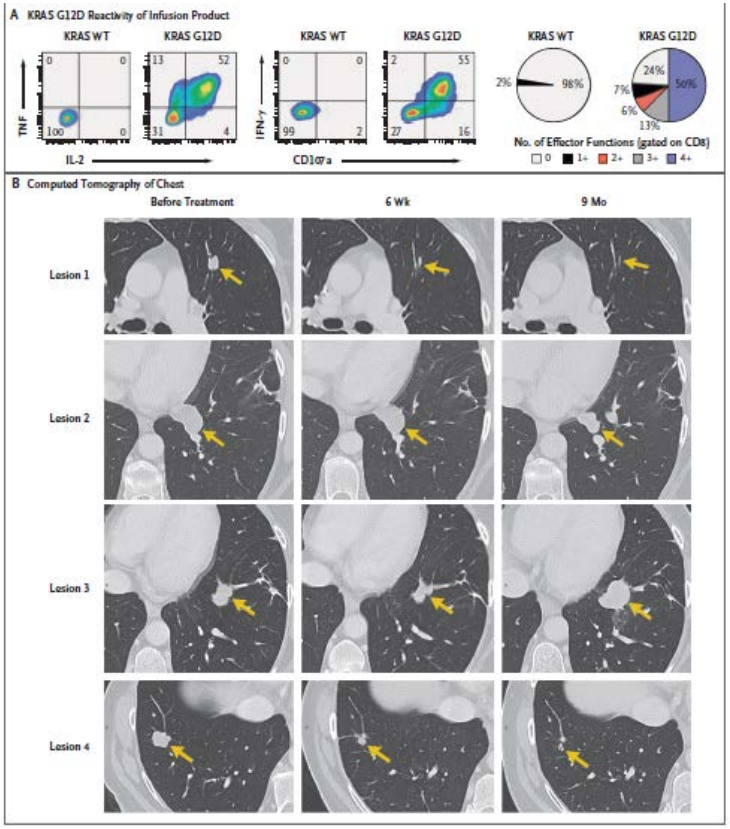
Anti-KRAS T cell transfer shows human efficacy (Rosenberg, NIH)

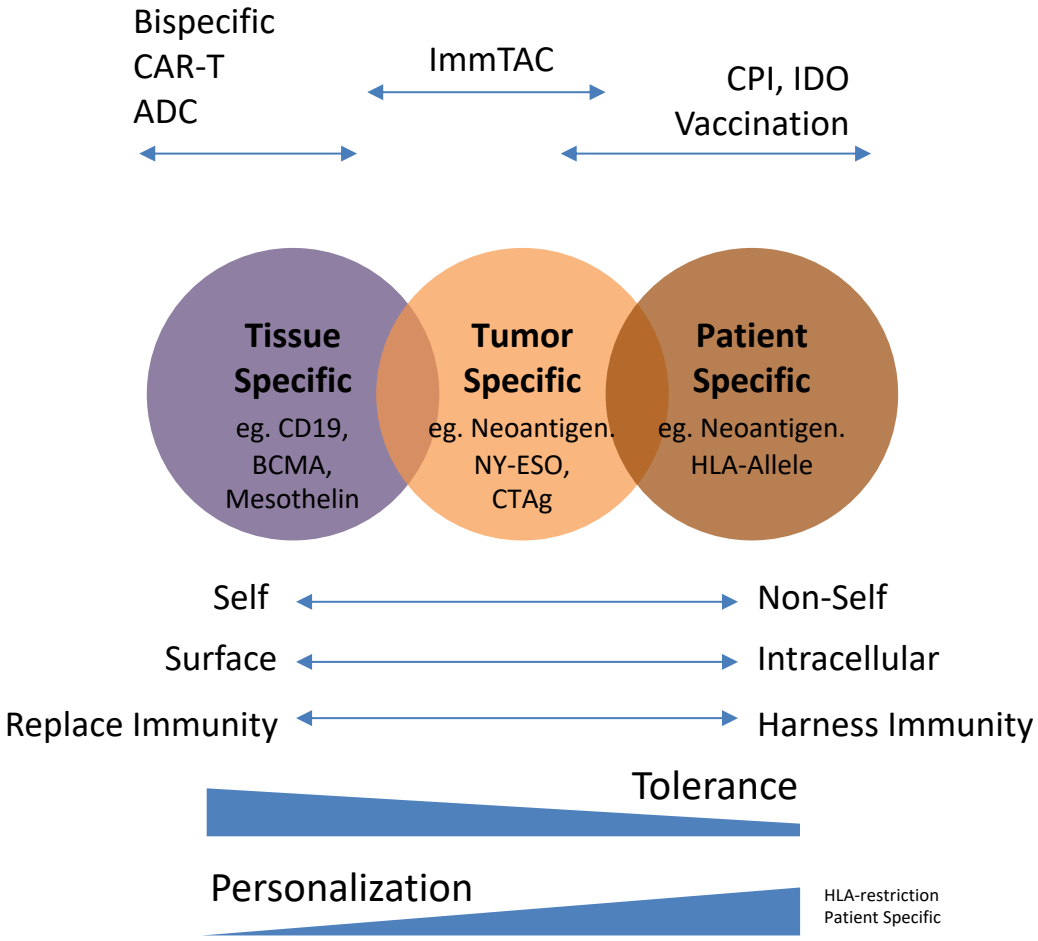
The NEW ENGLAND JOURNAL of MEDICINE

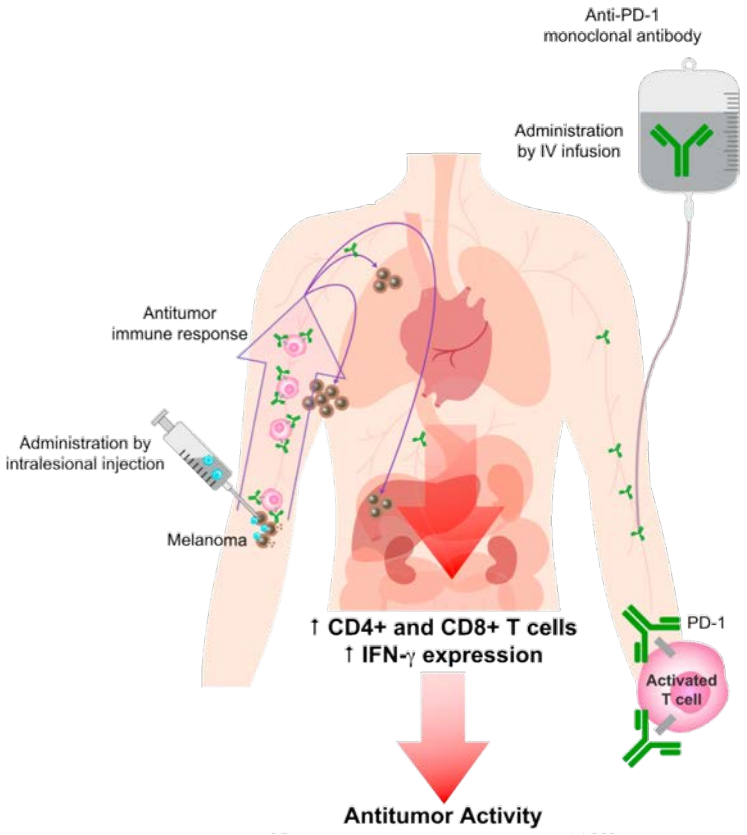
BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.



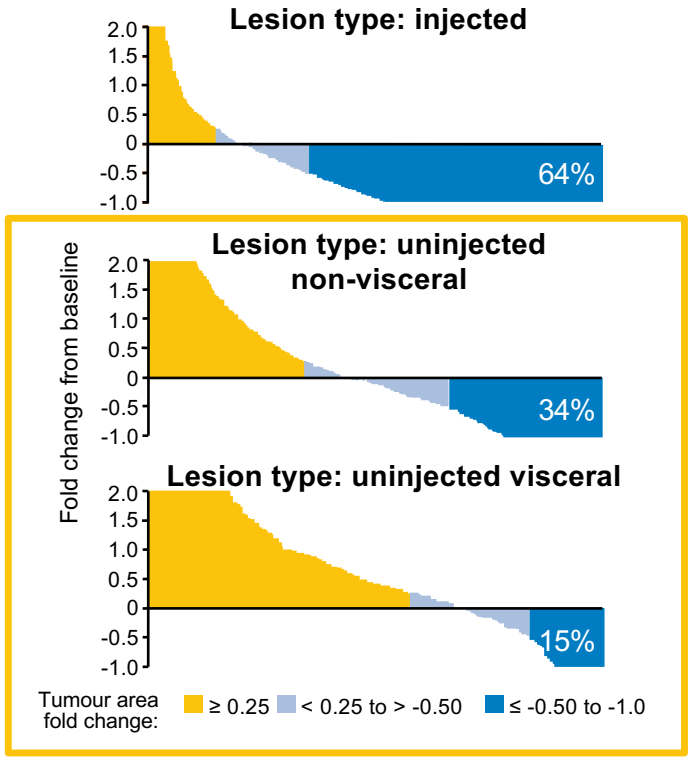

Bispecific
CAR-T
ADC
ImmTAC
CPI, IDO
Vaccination
Tissue Specific
eg. CD19, BCMA, Mesothelin
Tumor Specific
eg. Neoantigen. NY-ESO, CTAg
Patient Specific
eg. Neoantigen. HLA-Allele
Self
Non-Self
Surface
Intracellular
Replace Immunity
Harness Immunity
Tolerance
Personalization
HLA-restriction
Patient Specific



Class	Agent	Combination	Tumor type
PAMPs	CpG (CMP-001)	Pembrolizumab	Melanoma
	CpG (SD-101)	Pembrolizumab	Melanoma
	CpG (IMO-2125)	Ipilimumab	Melanoma
	STING agonists (ADU)	Ipilimumab	Solid tumors
Oncolytic viruses	T-VEC (HSV-1)	None	Melanoma
	T-VEC (HSV-1)	Ipilimumab	Melanoma
	T-VEC (HSV-1)	Pembrolizumab	Melanoma
	HF10 (HSV-1)	Ipilimumab	Melanoma
	Coxsackievirus A21	Ipilimumab	Melanoma
Cytokines	Vector encoded IL-12	None	Melanoma
Monoclonal AB	Ipilimumab	Nivolumab	Melanoma
Dendritic cells	INTUVAX (allo DC)	None	GISTS

Ribas, Cell, 2017

Summary of lesion-level and patient-level responses to T-VEC (ITT population)



Lesion, % n = 2116		Patient, % n = 277	
≥ 50% decrease	64	OR	32
100% decrease	47	CR	15

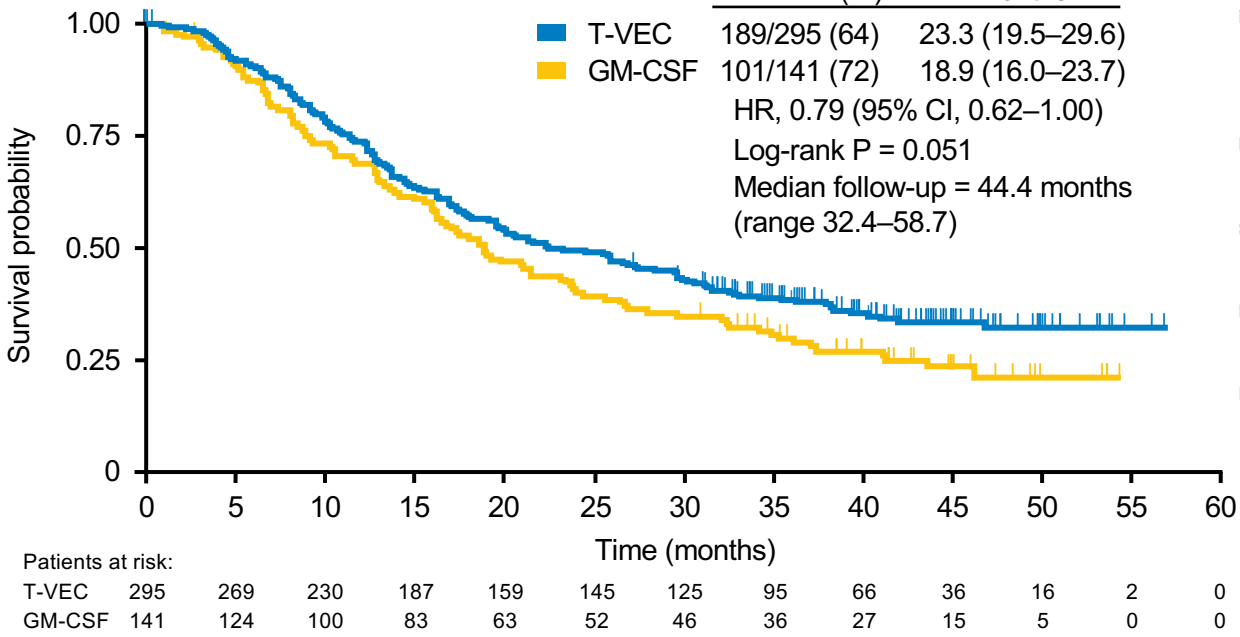
Lesion, % n = 981		Patient, % n = 177	
≥ 50% decrease	34	OR	18
100% decrease	22	CR	6

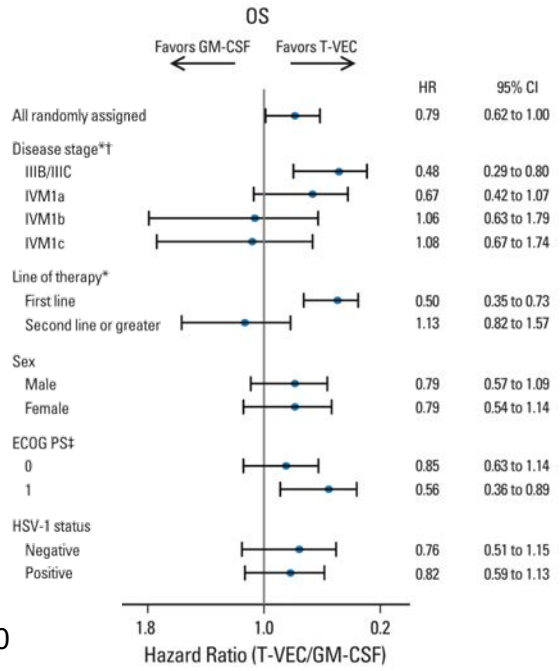
Lesion, % n = 177		Patient, % n = 79	
≥ 50% decrease	15	OR	14
100% decrease	9	CR	3

Adapted from Andtbacka RHI, et al. Ann Surg Oncol 2016;23:4169–77 (and supplementary appendix).

*Exclusion criteria of OPTiM limited the number and size of visceral metastases – please see slide notes for details. Vertical axis depicts maximal change in individual tumour lesion size (products of the 2 largest perpendicular diameters) from baseline. Lesions with ≥ 2 measurements recorded at 2 separate time points. Patients with ≥ 1 lesion(s) with ≥ 2 measurements recorded at 2 separate time points. Assessed by the investigators with modified WHO criteria.

OS data analysis (ITT population and subgroups)[1]



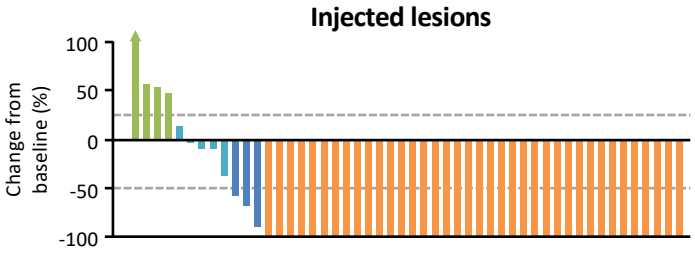


[1]Andtabacka, *JCO* 2015

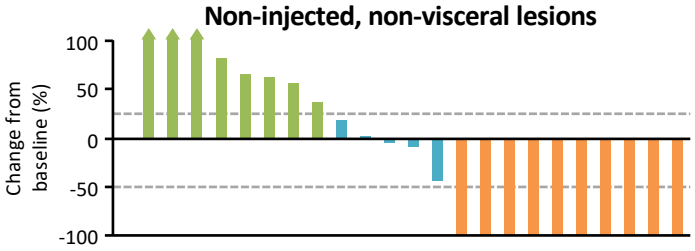
MUNICH 2018 ESMO congress

Adapted from Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

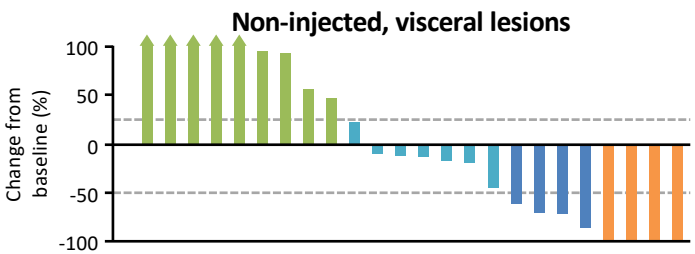
MASTERKEY-265 Phase 1b T-VEC/pembrolizumab – responses



Change in tumour area from baseline	n (%)
≥ 25%	4 (8)
< 25% to ≥ -50%	5 (10)
< -50% to ≥ -100%	3 (6)
< -100%	38 (76)



Change in tumour area from baseline	n (%)
≥ 25%	8 (34.8)
< 25% to ≥ -50%	5 (21.7)
< -50% to ≥ -100%	0
< -100%	10 (43.5)



Change in tumour area from baseline	n (%)
≥ 25%	9 (37.5)
< 25% to ≥ -50%	7 (29.2)
< -50% to ≥ -100%	4 (16.7)
< -100%	4 (16.7)

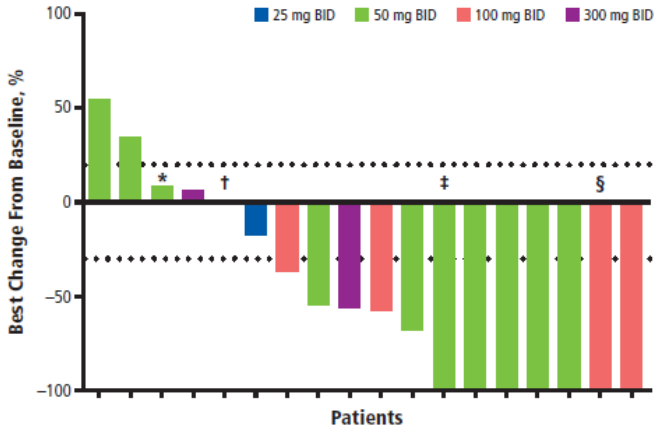
Tumour area change: ≥ 25% | < 25% to ≥ -50% | < -50% to ≥ - 100% | < -100

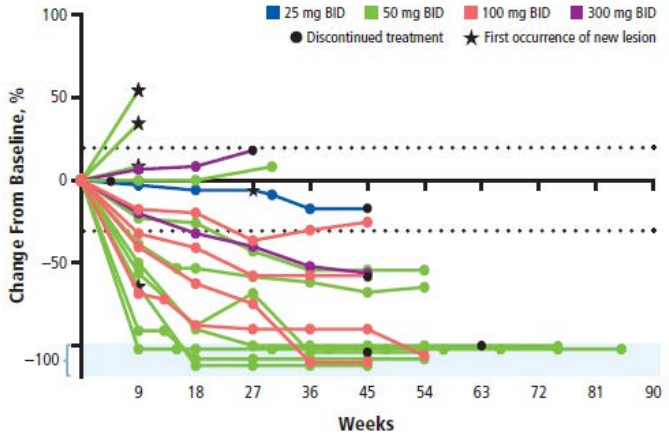
MASTERKEY-265 Phase 1b – responses seen in injected and non-injected lesions in 21 patients*

*Patients with Stage IIIB/C, IV M1a (n = 9) and with Stage IV M1b/c (n = 12)

Epacadostat + pembrolizumab

ECHO-202 phase 1 preliminary efficacy in melanoma (N=19)





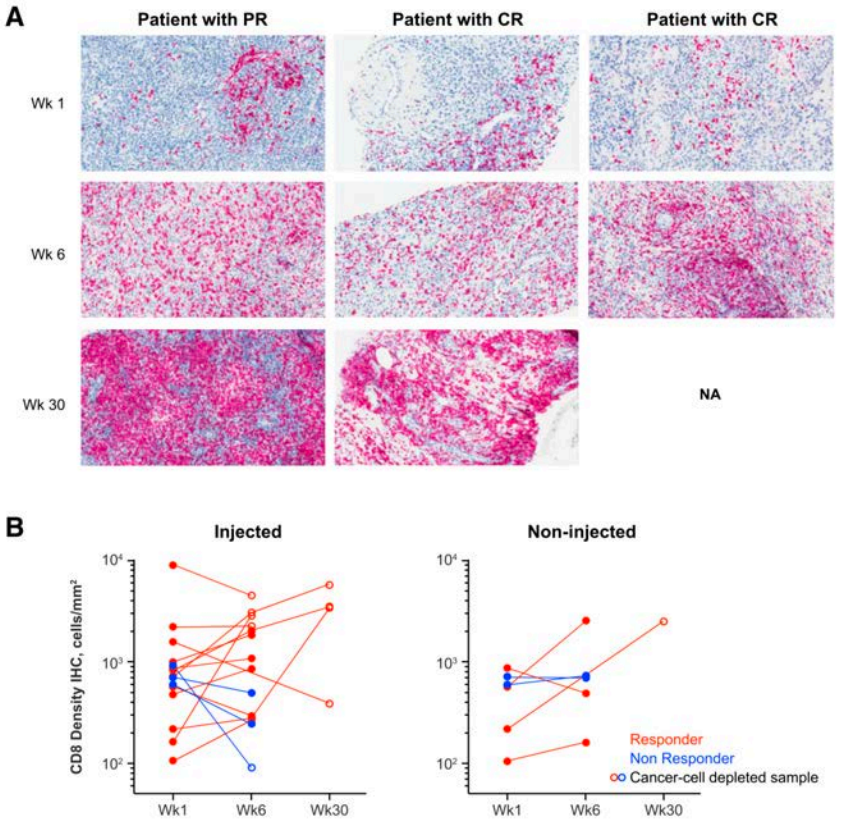
ORR = 58%, DCR = 74% by RECIST v1.1

Gangadhar TC, et al. ESMO 2016; poster #1110PD.

T-VEC: Converting an immune desert into a T cell inflamed?

Data from MASTERKEY-265 phase Ib trial:[1]

- T cell infiltrate observed following T-VEC
- Injected and non injected lesions showed marked increase in CD8+ T cells
- Baseline biomarker
  - Baseline CD8+ T cells nor INF-γ signature were associated with response
- On treatment biomarker:
  - Responders had increased CD8+ T cells, elevated PD-L1 and IFN-γ signature after T-VEC
- This suggests T-VEC + PD-1 MoA involves reprogramming of the tumor µ-environment



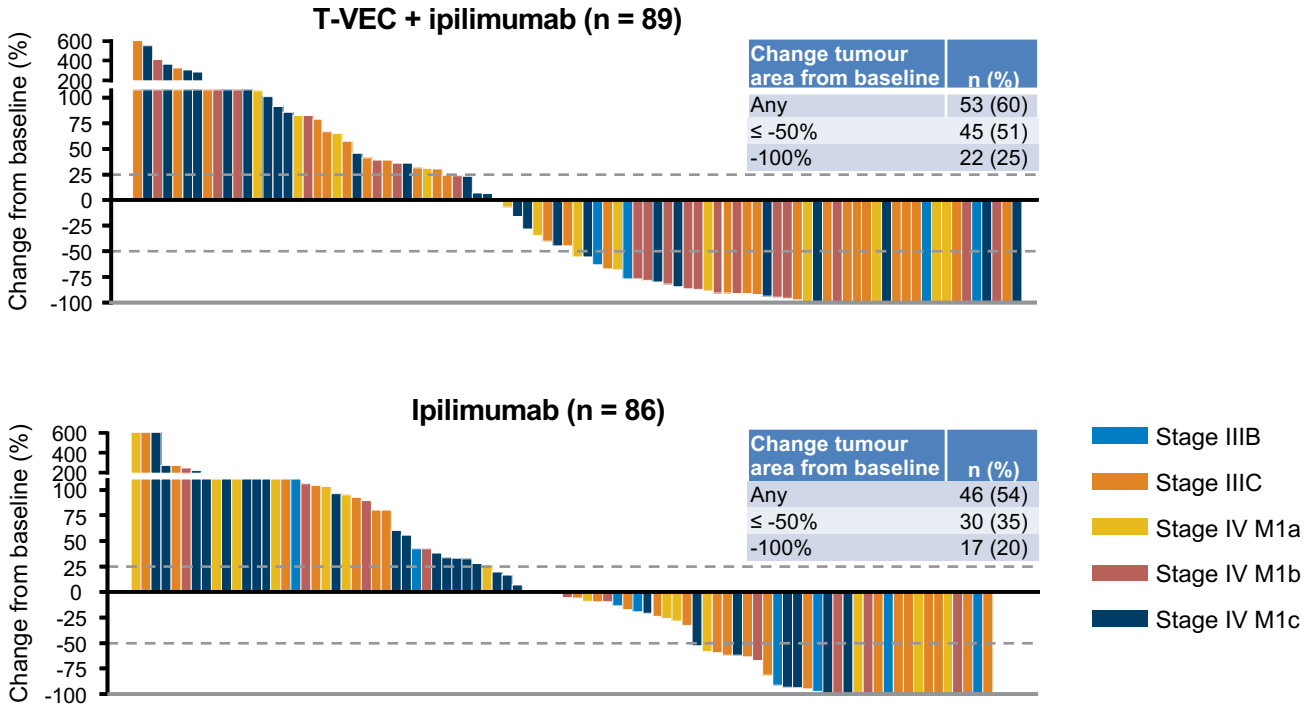
[1] Ribas, *Cell* 2017

Phase 2 T-VEC combination study with ipilimumab – best change in overall tumour area from baseline[1]

ORR 39%

P=0.002

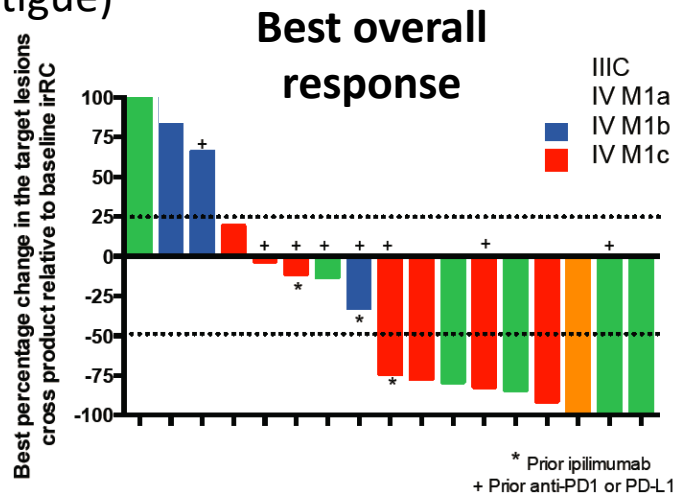
ORR 18%



[1] Chesney, *JCO* 2018

Phase 1b, CVA21 + ipilimumab MITCI study in Stage IIIC/IV unresectable melanoma: preliminary analysis of safety

- No DLTs have been reported in 18 patients who received treatment
- One Grade 3 or higher treatment-related AE was reported (ipilimumab-related fatigue)

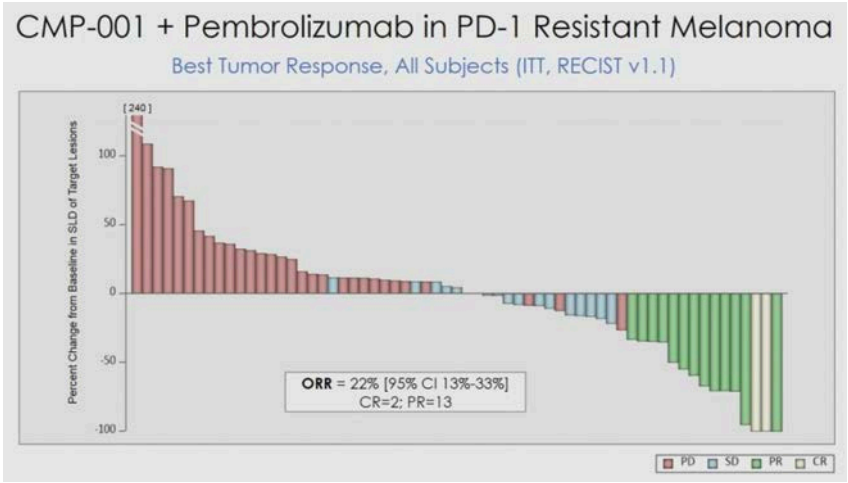


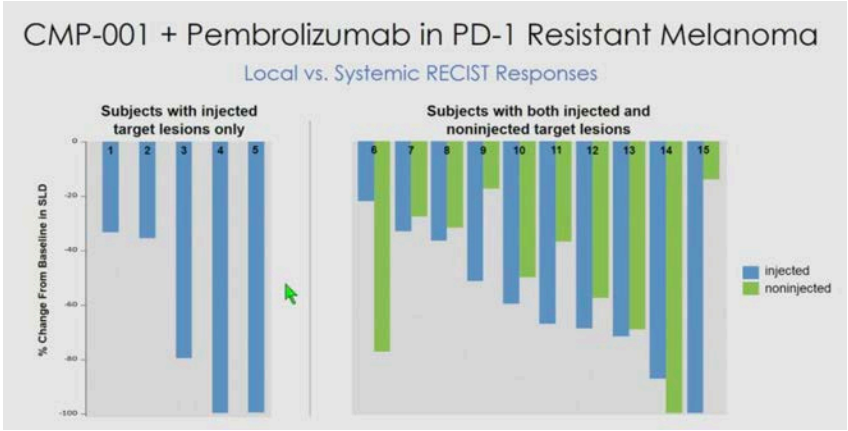
Response rate (irRC), n (%)*	
CR	3 (17.6)
PR	6 (35.3)
SD	5 (29.4)
BORR (CR + PR)	9 (52.9)†
DCR (CR + PR + SD)	14 (82.4)

*Intent-to-treat population: 17 patients evaluable for tumour assessment; †BORR in ipilimumab-naïve patients: 57.1%. BORR, best overall response rate.

TLR 9 agonist: CMP-001

- CMP-001 is a virus-like particle-packaged TLR-9 agonist
- Activity seen in melanoma patients having failed PD-1 mono or combo in the CMP-001-001 study[1]
- 69 subjects enrolled
  - ORR 22.5% for q1w (n=40) cohort
  - ORR 7.7% for q3w (n=13) cohort
  - ORR 33.3% for q1w (3 and 5 mg, n=18) cohort
  - Responses seen in non injected lesions
- TR part showed increase CD8+ infiltrate and PD-L1 expression

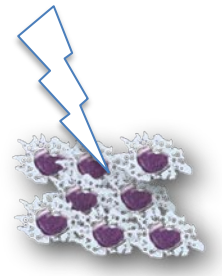




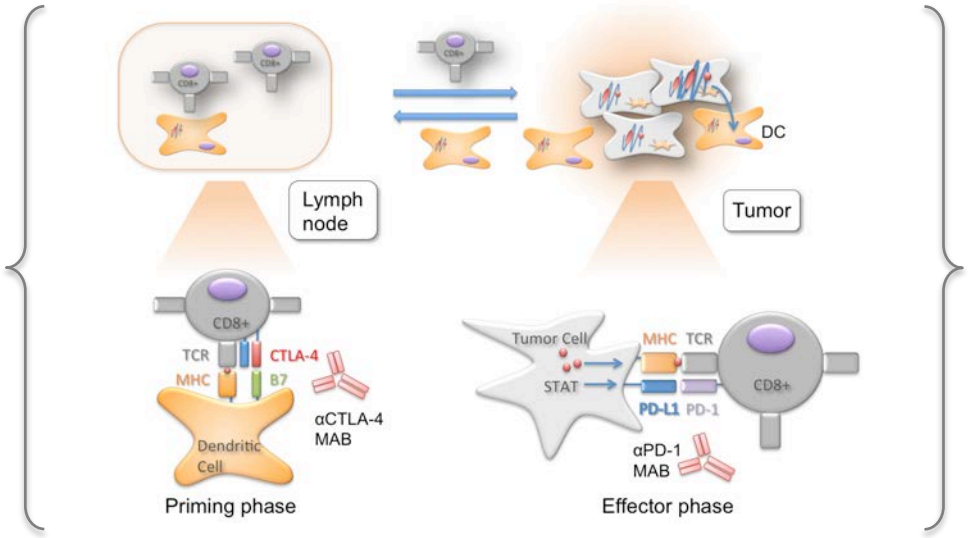
MUNICH 2018 ESMO congress

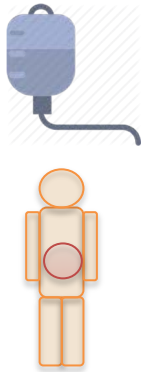
[1] Milhem, *AACR* 2018

Intratumor CTLA-4 combined with PD-1 combos



Intratumor CTLA-4 blockade





Systemic PD-1 blockade

NCT02857569:
65 melanoma
Patients (IGR)

→ R

- Ipi 3 (IV) + nivo 1 x4, followed by nivo 3 mg/kg q2w till PD
- Ipi 0.3 (IT) + nivo 1 x 4, followed by nivo 3 mg/kg q2w till PD

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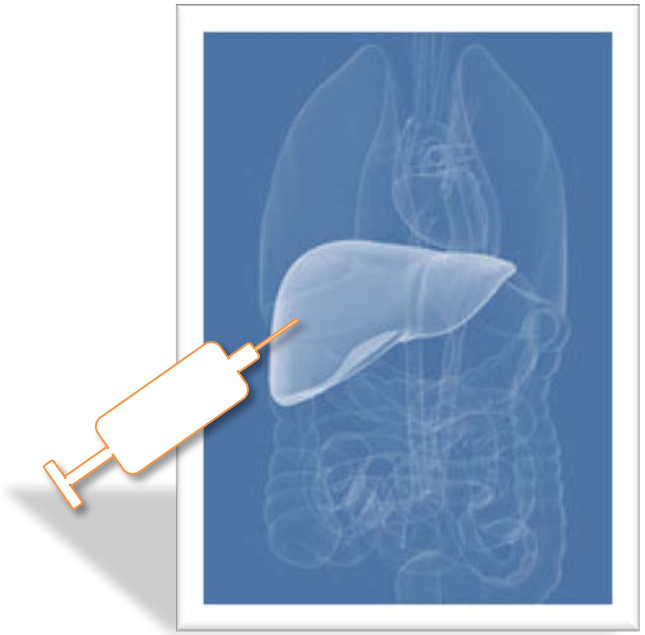
Injecting visceral disease?

- With advances in interventional radiology, most lesions become injectable
- Clinical trials looking at feasibility have started and results are eagerly awaited
- Examples:
  - Talimogene Laherparepvec for the Treatment of Peritoneal Surface Malignancies (NCT03663712)
  - Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Liver Tumors Alone and in Combination With Systemic Pembrolizumab (MASTERKEY-318)
  - …



Take-home messages

- Immunotherapy advances have been almost entirely on the basis of disrupting PD-1/PD-L1 interactions
- As predictive markers are elaborated for PD-1 antibody response prediction, it is increasingly clear what it lacking in non-responders
- Vaccines are receiving renewed interest as a means of reshaping T cell repertoire
- Intratumoral therapy has proven capable of influencing distant disease outcomes
- Moreso than systemic therapies, intratumor therapy platforms appear capable of remodeling the tumor-immune microenvironment with multiple interventions at once
- Intermediate markers of mechanistic effect (in tumors) are needed for both vaccines and intratumoral therapy

Acknowledgements

MGH Melanoma group

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David Lieb

Benchun Miao

Gyulnara Kasumova

Michelle Kim

Xue Bai

Patrick Kurpaska

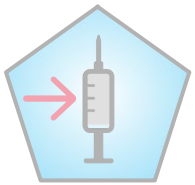
moderna®

Systemic Therapeutics - Secreted and Intracellular

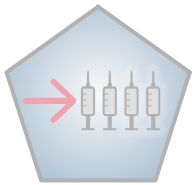
Tal Zaks, MD, PhD

Chief Medical Officer

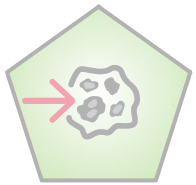
Progress by modality



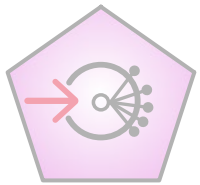
Prophylactic vaccines



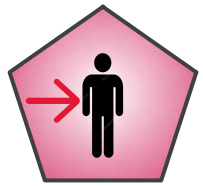
Cancer vaccines



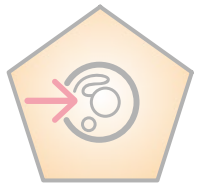
Intratumoral immuno-oncology



Localized regenerative therapeutics



Systemic secreted therapeutics



Systemic intracellular therapeutics

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Systemic secreted therapeutics

Modality	ID #	Program *Indication*	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Systemic secreted therapeutics	**mRNA-1944**	Antibody against Chikungunya virus					Worldwide *DARPA funded*
	AZD7970	Relaxin *Heart failure*					50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales
	mRNA-3630	α-GAL *Fabry disease*					Worldwide

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Systemic secreted therapeutics

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	mRNA-3630	α-GAL *Fabry disease*					Worldwide

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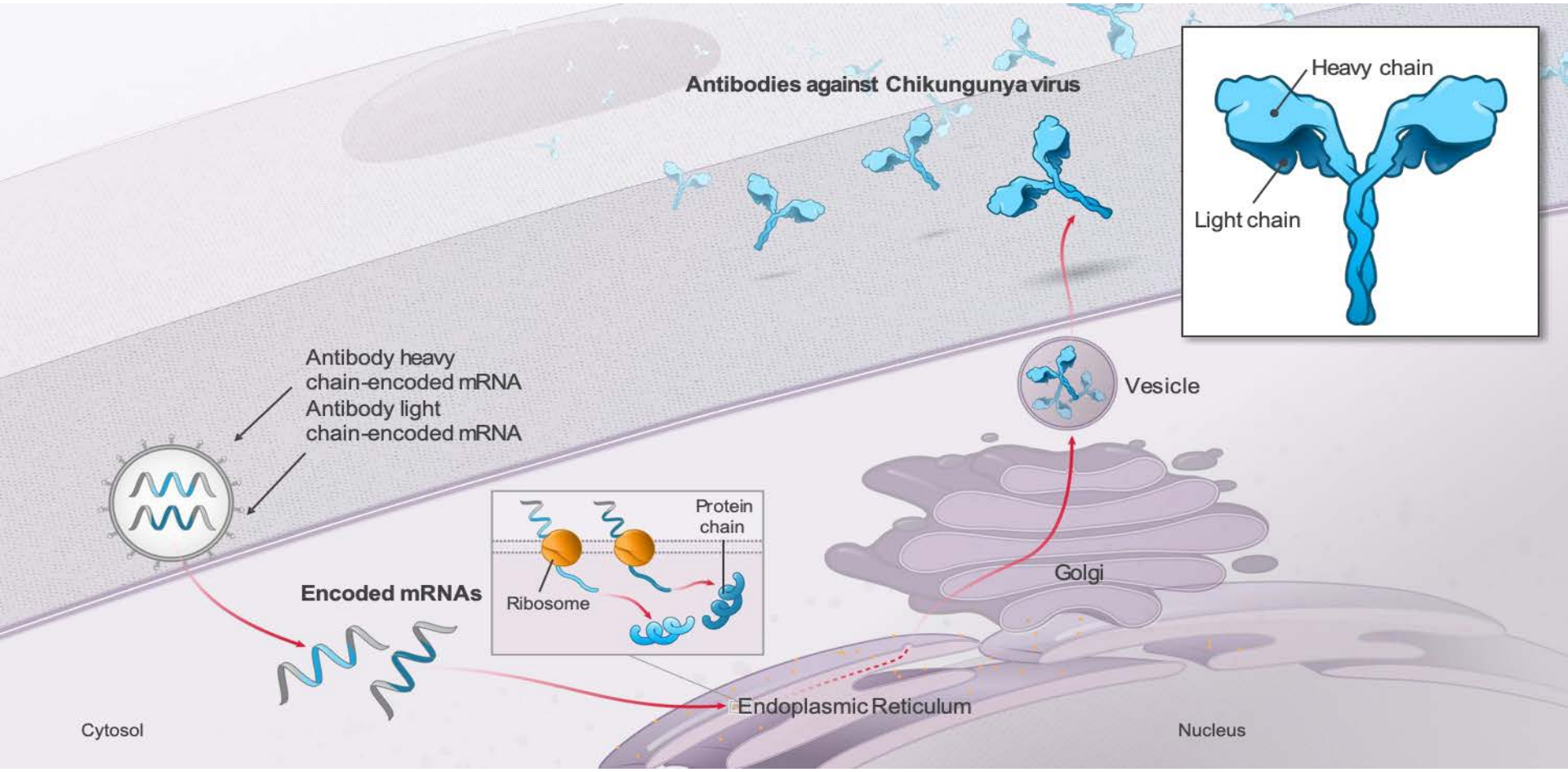
Antibody against Chikungunya virus (mRNA-1944)

mRNA-1944 contains two mRNAs that encode for the heavy and light chains of CHKV-24 antibody, which may confer passive immunity

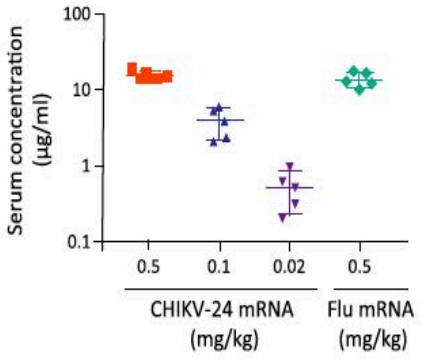


Antibody against Chikungunya virus (mRNA-1944)

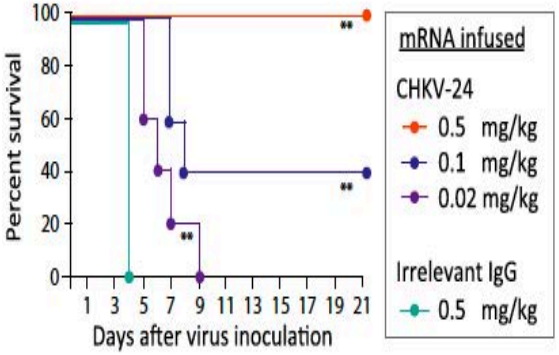
Preclinical evidence that mRNA-1944 encodes for functional antibody against Chikungunya virus

Species: Mouse

Expression of antibody against Chikungunya virus

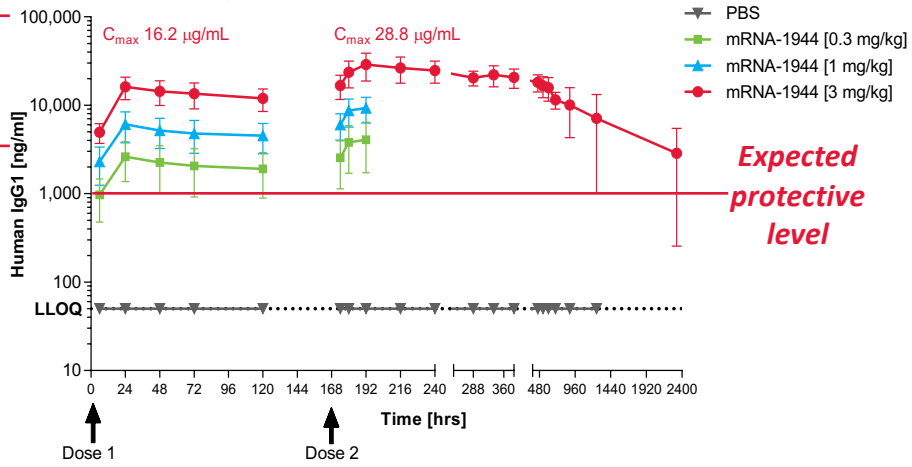


Survival after prophylactic vaccination with mRNA-1944



Species: NHP

Expression of antibody against Chikungunya virus with repeat dosing of mRNA-1944 in non-human primate study



Science Immunology MAY 2019

mRNA-1944 produces an antibody against Chikungunya virus that is

- Functional
- Protective
- Translates between pre-clinical species

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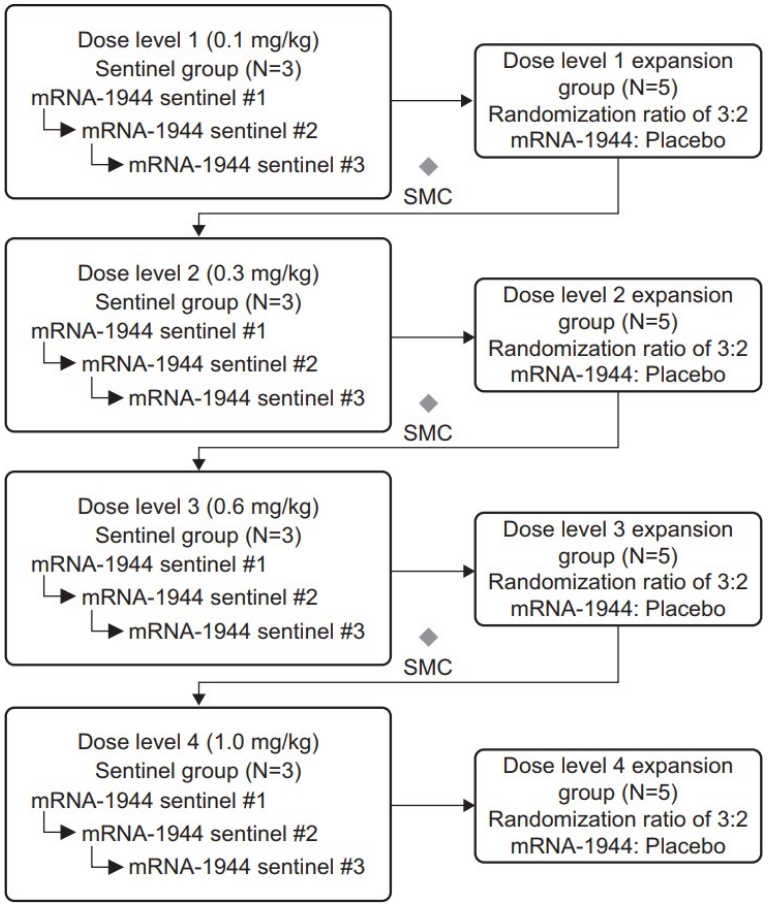
Antibody against Chikungunya virus (mRNA-1944)

Trial design

- Randomized, placebo-controlled, single ascending dose study in healthy adults
- All subjects received premedication with antihistamines
- No subjects received corticosteroids (permitted by protocol)

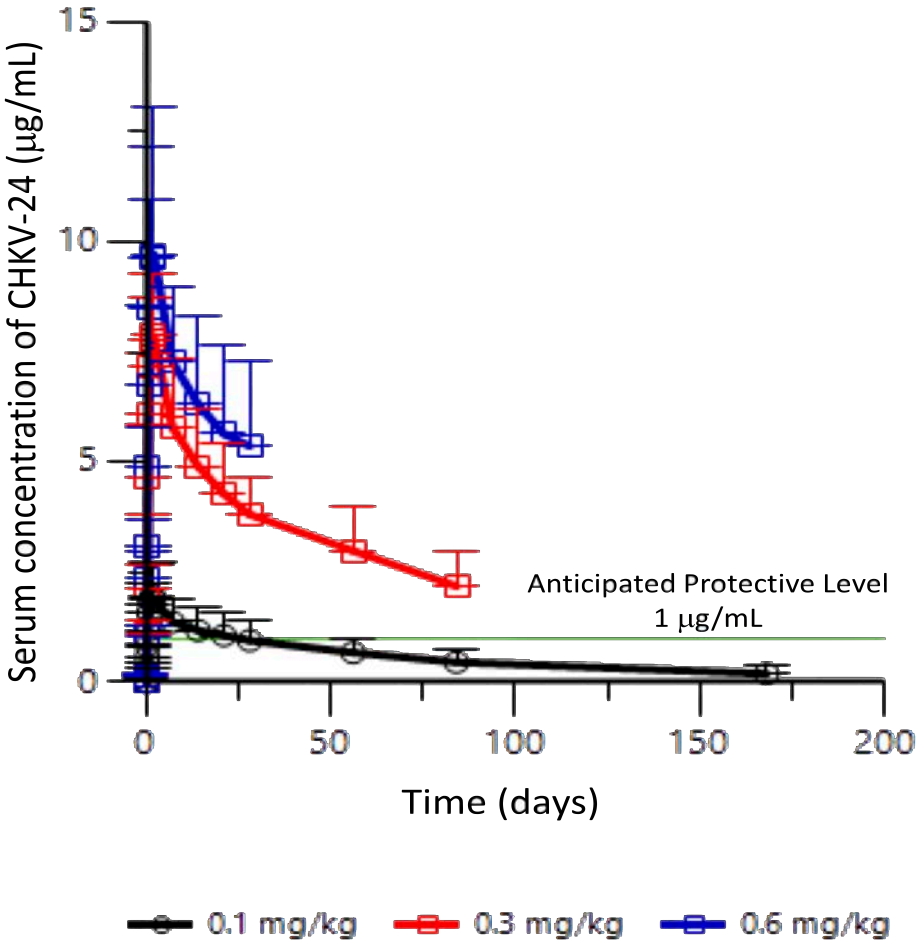
Key Objectives

- **Safety:** Evaluate safety and tolerability of escalating doses of mRNA-1944 administered via intravenous infusion
- **Translation of protein:** Evaluate pharmacology of mRNA-1944
- **Activity:** Determine ability of antibody to neutralize viral infection



Antibody against Chikungunya virus (mRNA-1944)

Protective antibody levels of >1µg/mL expected to endure at least 16 weeks at the middle dose of 0.3 mg/kg



Serum concentrations plotted as mean (+SD)
1 µg/mL indicates minimum concentration target

Cohort	0.1 mg/kg (N=6)	0.3 mg/kg (N=6)	0.6 mg/kg (N=4)
C_{max} (µg/mL)	2.0	7.9	10.2
C_{max} range (µg/mL)	1.1-3.1	6.3-10.0	7.0-14.2
C_{max} % CV	40.6%	18.2%	29.7%

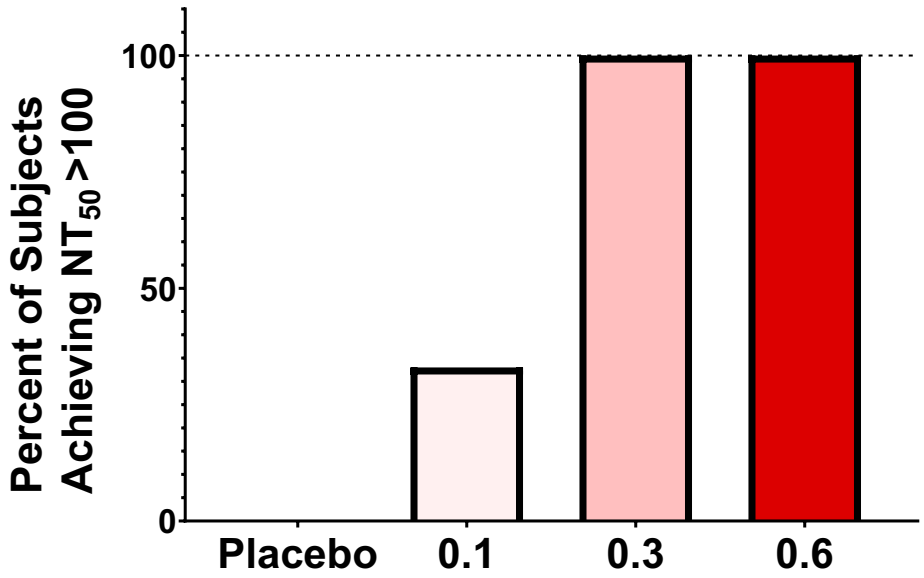
Pharmacology

- Administration of mRNA-1944 resulted in dose-related increase in levels of CHKV-24
- Half life ($t_{1/2}$) of antibody was 62 days
- Middle and high dose (0.3 and 0.6 mg/kg) projected to exceed 1 µg/mL target for at least 16 weeks

Antibody against Chikungunya virus (mRNA-1944)

mRNA-1944 driven protein expression results in functional antibody (CHKV-24)

Serum neutralization activity 48 hr after mRNA-1944 administration



N	6	6	6	4
GMT	<10	113	718	538

- Neutralizing antibody titers observed at all dose levels, indicating functional antibody production by mRNA-1944
- All placebo subjects below the lower limit of detection
- 100% of subjects administered 0.3 and 0.6 mg/kg had titers >100

Antibody against Chikungunya virus (mRNA-1944)

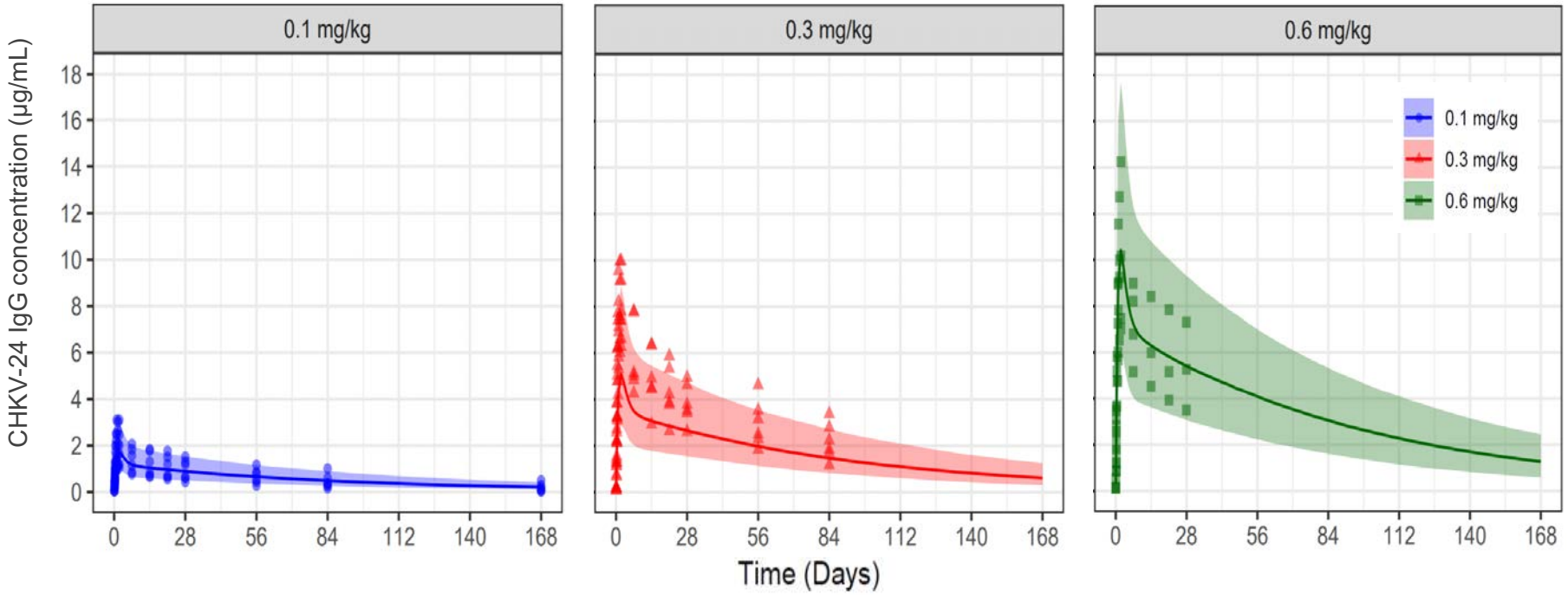
Summary of related adverse events

Cohort		Grade 1	Grade 2	Grade 3
Placebo (N=6)		None	None	None
mRNA-1944 0.1 mg/kg (N=6)		Feeling of warmth, transient (1)	None	None
mRNA-1944 0.3 mg/kg (N=6)		None	None	None
mRNA-1944 0.6 mg/kg (N=4)	*Subject 1*	Sinus tachycardia, fever, infusion associated shivering, lightheadedness, hypotension	None	None
	Subject 2	None	Nausea, emesis	None
	Subject 3	None	None	None
	Subject 4	Chills, headache, lightheadedness, gaseousness	EKG abnormal (T wave inversion), emesis, nausea, fever	Sinus tachycardia, elevated WBC

- All AEs were transient and resolved spontaneously without treatment
- No serious AEs in the study
- No meaningful changes in liver or kidney laboratory results

Antibody against Chikungunya virus (mRNA-1944)

Translation from preclinical species to humans



Solid line = Median predicted
Shaded area = 90% prediction interval
Symbols = Individual participant observations

Conclusions: mRNA-1944 achieved the target level of functional protein translation at a well tolerated dose

- Administration of mRNA-1944 resulted in dose-dependent increases in levels of antibody against Chikungunya (CHKV-24)
- Neutralizing antibodies were observed at all dose levels, indicating functional antibody production by mRNA-1944
- None of the participants treated with mRNA-1944 at the low (0.1 mg/kg) or middle (0.3 mg/kg) doses experienced significant adverse events (AEs). Three of the four participants at the high (0.6 mg/kg) dose had infusion related AEs, with the highest grade by subject being Grade 1 (n=1), Grade 2 (n=1) and Grade 3 (n=1)
- mRNA-1944 at 0.3 mg/kg and 0.6 mg/kg provides antibody levels that are expected to be protective against Chikungunya infection (>1 μg/mL) for at least 16 weeks, supporting further development.
- mRNA to protein translation in human was predicted by preclinical data

MRNA-1944 enables Moderna's systemic therapeutics

- For the first time, the systemic administration of an mRNA containing LNP has been demonstrated to produce a fully functional complex protein in humans
- Dose dependent pharmacology has been fully predicted from preclinical species with no loss of potency
- Target therapeutic concentrations have been achieved at a well tolerated dose in a healthy volunteer population

- We believe these data strongly support the continued development of our systemic rare disease therapeutic modality that targets both secreted and intracellular proteins

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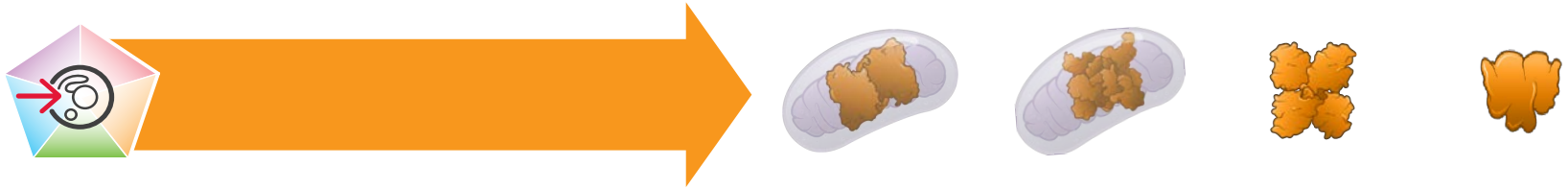
Progress in the systemic intracellular therapeutics modality to date

		Systemic intracellular therapeutics			
		MMA mRNA-3704	PA mRNA-3927	PKU mRNA-3283	GSD1a mRNA-3745
Clinical	*Phase 1/2 Recruiting patients*	✓			
Clinical	*IND Open*	✓			
Preclinical	*Natural history study initiated*	✓	✓	*N/A*	*N/A*
Preclinical	*Successful IND-enabling GLP toxicology studies*	✓	✓	*Ongoing*	*Ongoing*
Preclinical	*Pre-clinical activity and dose dependent pharmacology in animal models*	✓	✓	✓	✓



Sites open for MMA phase 1/2 trial and actively recruiting patients
MMA (mRNA-3704) utilizes the same LNP formulation as antibody against Chikungunya virus (mRNA-1944)

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Methylmalonic acidemia overview

Gregory Enns, MD

Professor of Pediatrics (Genetics) at the Lucile Salter Packard Children's Hospital

Stanford University

Methylmalonic Acidemia Overview

Gregory Enns, MD

Professor of Pediatrics

Director, Biochemical Genetics Program

Lucile Packard Children's Hospital

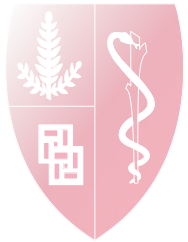
Stanford University

Disclosures

- Consultant – Moderna Therapeutics, Horizon Pharma
- Clinical trials – Aeglea Biotherapeutics, BioElectron, Moderna, Inc., Stealth Therapeutics
- DSMB – Biomarin, Audentes Therapeutics, Amicus, RegenxBio, Neurovia
- Co-Founder – Evvia Therapeutics

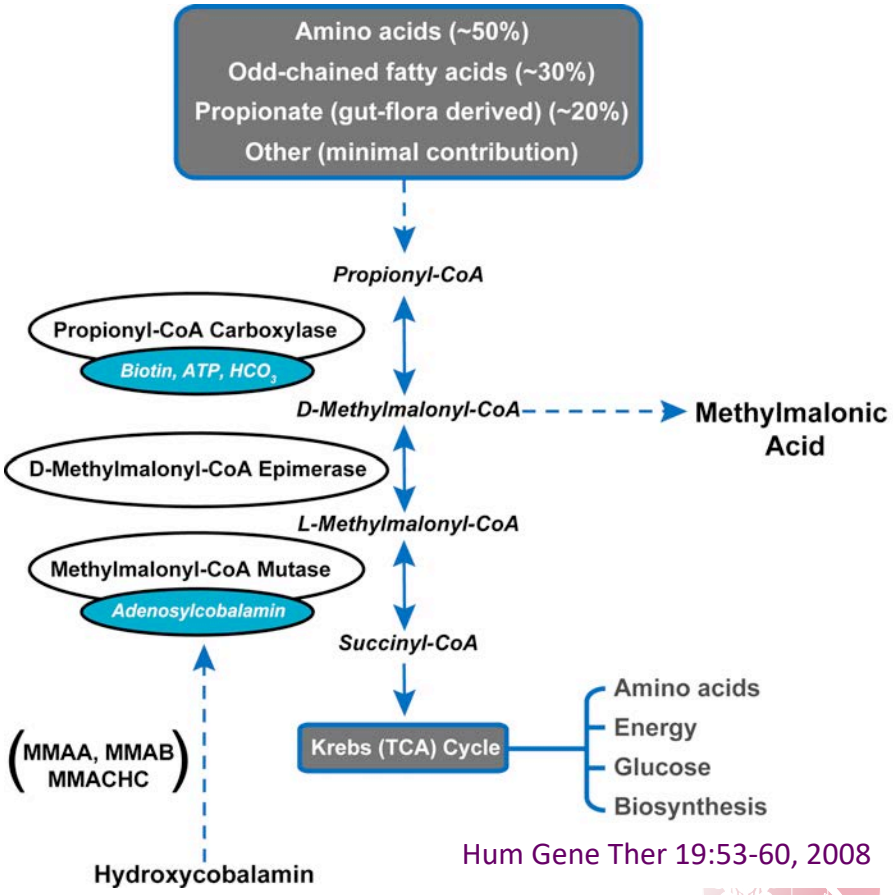
Methylmalonic Acidemia (MMA)

- Autosomal recessive
- Complete *(mut^0)* or partial *(mut$^-$)* decreased activity of methylmalonyl-CoA mutase
- Prevalence in North America ~1/50,000



Methylmalonyl-CoA mutase

- Nuclear encoded
- Mitochondrial localized
- Homodimer
- Requires 5'-deoxyadenosylcobalamin (Adocbl)



Hum Gene Ther 19:53-60, 2008

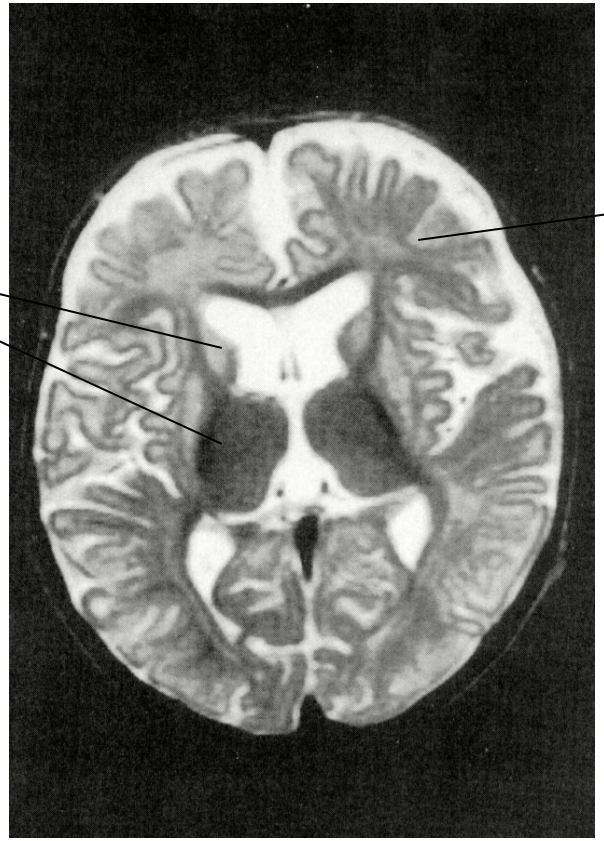
Table 3 Acute and chronic presentations of MMA/PA

Acute presentation	Chronic presentation
Neonatal sepsis-like picture, temperature instability, respiratory distress, hyperventilation	**Often episodic characteristic signs and symptoms**
Nervous system	**Nervous system**
• **Altered level of consciousness (from lethargy and somnolence to coma) mimicking encephalitis or drug intoxication**	• Hypotonia
	• **Developmental delay** (learning disabilities, intellectual disability)
• Acute encephalopathy	• **Movement disorders/dystonia**
• Seizures (in general not isolated but in the context of altered level of consciousness)	• Seizures
• Movement disorders (more frequent in PA)	• Optic atrophy
• Stroke-like episodes (more frequent in MMA)	• *Psychiatric symptoms (hallucinations, psychotic attacks)*
Gastrointestinal system	**Gastrointestinal system**
• **Vomiting and feeding difficulties**	• **Recurrent vomiting with ketoacidosis**
	• Abnormal feeding behavior (anorexia)
	• **Failure to thrive**
	• Constipation
	• Pancreatitis
Hematologic findings	**Hematologic findings**
• Neutropenia, pancytopenia	• Neutropenia, pancytopenia
	• *Secondary hemophagocytosis (rare)*
Heart	**Heart (more frequent in PA)**
• Acute cardiac failure (mostly on basis of cardiomyopathy)	• Cardiomyopathy
• Arrhythmias	• Prolonged QTc interval in ECG
	Kidney (more frequent in MMA)
	• **Chronic renal failure in MMA**
	Other
	• *Dermatitis*
	• *Hearing loss*

Orphanet J Rare Dis 9:130, 2014

BRAIN INJURY IN ORGANIC ACIDEMIAS

caudate and putamen hyperintensity

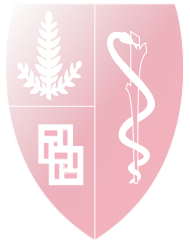


delayed myelination

Pediatr Res 40:404-9, 1996

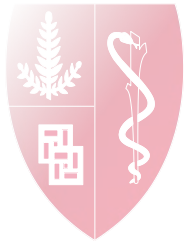
MMA Therapy

- Special low-protein diet
- Emergency/sick-day protocols
- Carnitine supplementation
- Vitamin B_{12} in some cases
- Dialysis – ↑NH_3, metabolic acidosis, renal failure
- Liver or combined liver/kidney transplantation
- Kidney transplantation



Gene Therapy with a Scalpel

- Liver transplantation
- Kidney transplantation
- Combined liver/kidney transplantation

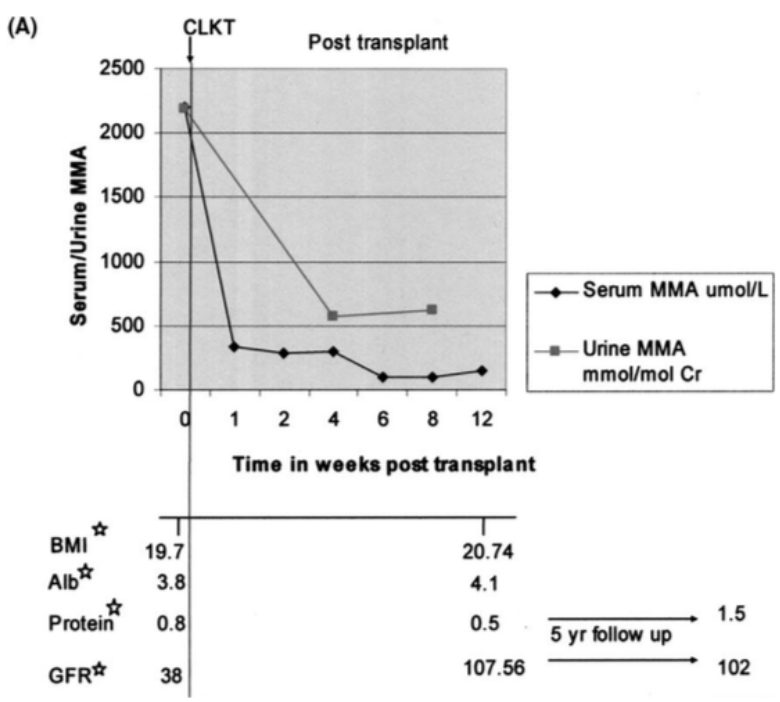


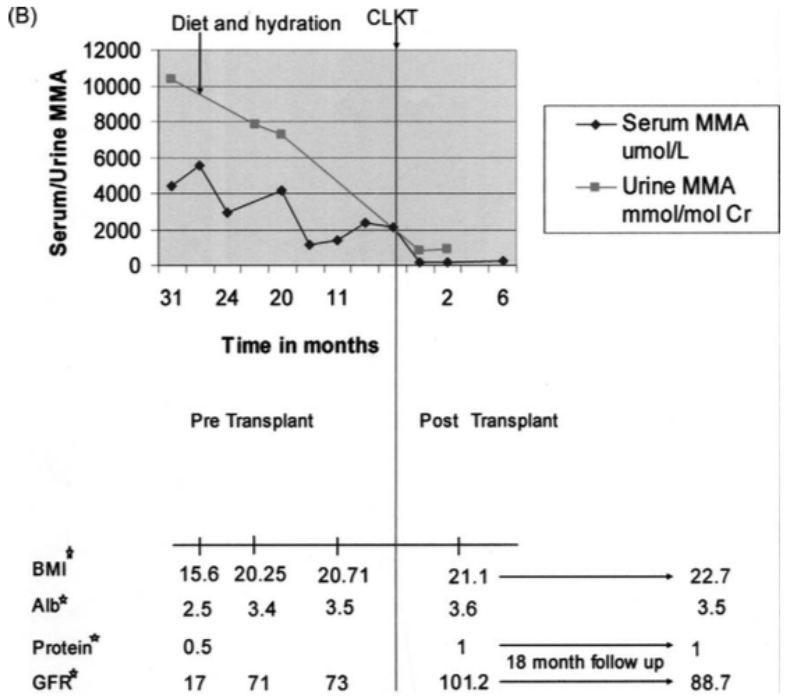
Combined liver-kidney transplantation in methylmalonic acidemia

W. G. van't Hoff, BSc, MD, MRCP, M. Dixon, BSc, SRD, J. Taylor, BM, MRCP, P. Mistry, PhD, MRCP, K. Rolles, MS, FRCS, L. Rees, MD, FRCP, and J. V. Leonard, PhD, FRCP

A 13-year-old boy with non-B12-responsive methylmalonic acidemia (MMA) had chronic renal failure. Hemodialysis led to symptomatic and biochemical improvement. He subsequently received a combined liver-kidney transplant. After 16 months of follow-up he has a normal lifestyle and a marked reduction in plasma and urine methylmalonate. (J Pediatr 1998;132:1043-4.)

Combined Liver-Kidney Transplantation in MMA





JIMD 28:517-524, 2005

LT or LKT for MMA

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Treatment of Methylmalonic Acidemia by Liver or Combined Liver-Kidney Transplantation

Anna-Kaisa Niemi, MD, PhD[1], Irene K. Kim, MD[2], Casey E. Krueger, PhD[3], Tina M. Cowan, PhD[4], Nancy Baugh, MS, RD[5], Rachel Farrell, MS[1,6], Clark A. Bonham, MD[2], Waldo Concepcion, MD[2], Carlos O. Esquivel, MD, PhD[2], and Gregory M. Enns, MB, ChB[1]

- Mean age for transplantation 8.75 ± 7 years (0.8-20.7 y)
- LKT 13.3 ± 4.9 years (5.9-20.7 y)
  - 88% underwent pre-operative hemodialysis
- LT 1.5 ± 0.9 years (0.8-3.3 y)

J Pediatr 166:1455-61, 2015

Postoperative period

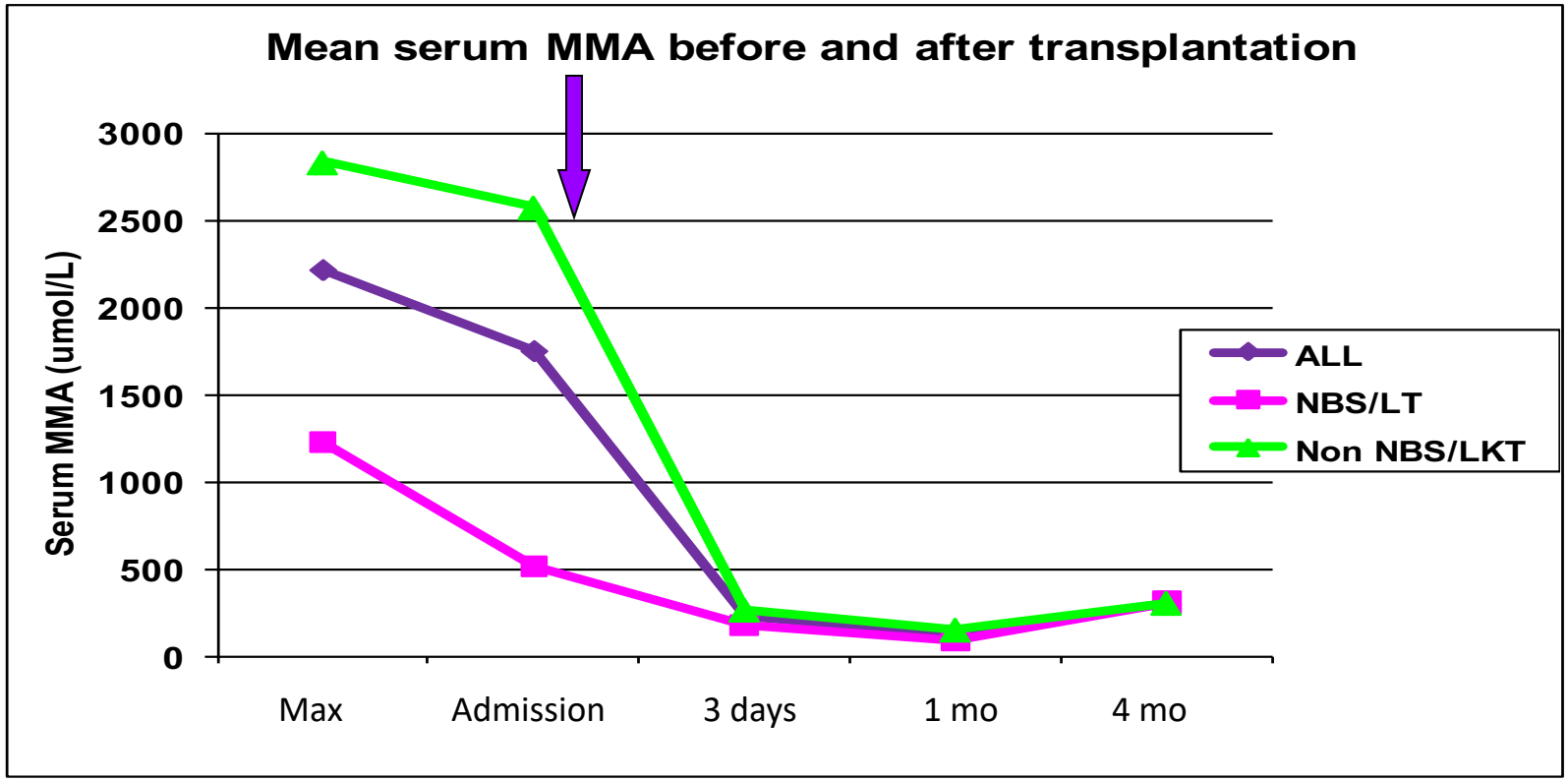
- Mean follow-up 3.3y

Patient survival	**100%**
Liver allograft survival	**93%** (hepatic artery thrombosis, n=1)
Kidney allograft survival	**100%**

Other clinical outcomes

- No hyperammonemia or metabolic acidosis
- Renal function normal on those with LT only
  - mean follow-up 1.1 years

J Pediatr 166:1455-61, 2015


Mean serum MMA before and after transplantation
Serum MMA (umol/L)
3000
2500
2000
1500
1000
500
0
Max
Admission
3 days
1 mo
4 mo
ALL
NBS/LT
Non NBS/LKT

Other clinical outcomes

- No hyperammonemia or metabolic acidosis
- Renal function normal on those with LT only
  - mean follow-up 1.1 years

Neurological outcomes

14

LT 6

Pretransplant:

1/6 global developmental delay

3/6 mild developmental delay

2/6 mild motor delay, otherwise age appropriate

Post:

3/5 gained motor skills

No neurological deterioration

LKT 8

Pretransplant:

4/8 global developmental delay

2/8 mild developmental delay

Post:

Maintained previous level

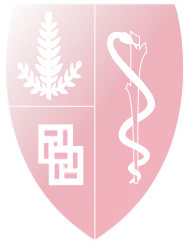
No neurological deterioration

Liver Transplantation Complications

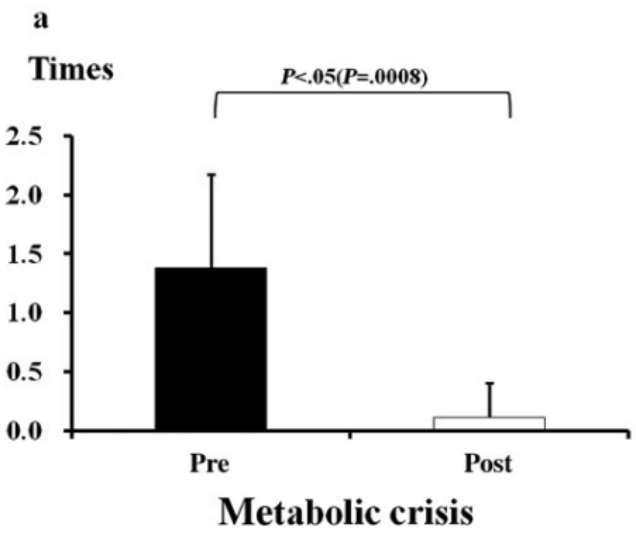
- Mortality
- Lactic acidemia
- Metabolic decompensation
- ‘Metabolic stroke’
- Graft rejection
- Post-op pancreatitis

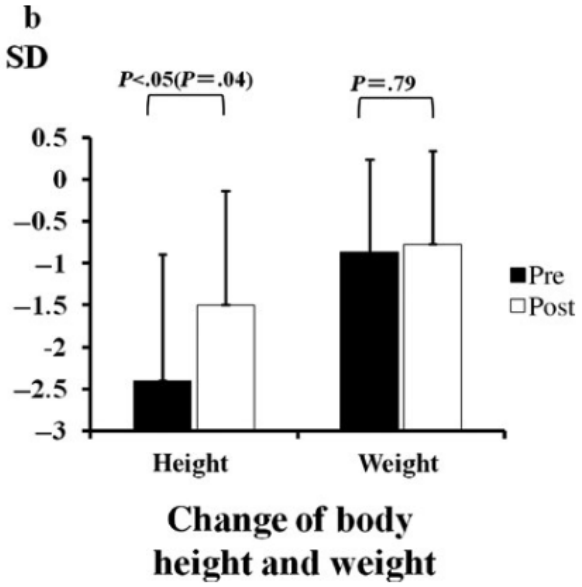
J Pediatr 140:261-3, 2002
Ther Apher Dial 15:488-92, 2011
J Pediatr 166:1455-61, 2015
Pediatr Anesth 26:694-702, 2016

- Immunosuppression complications
  - Diabetes
  - Hypertension
  - Seizures
  - Infections
  - Nephrotoxicity
- Surgical complications
  - Hepatic artery thrombosis
  - Subphrenic abscess
  - Splenic rupture



MMA Post-transplant Outcomes





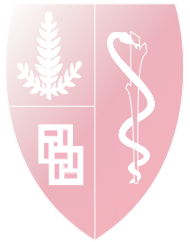
Persisting morbidity

- Biochemical abnormalities persist
- Renal insufficiency after LT
- Risk of metabolic strokes remains

Pediatr Transpl 20:1081-6, 2016

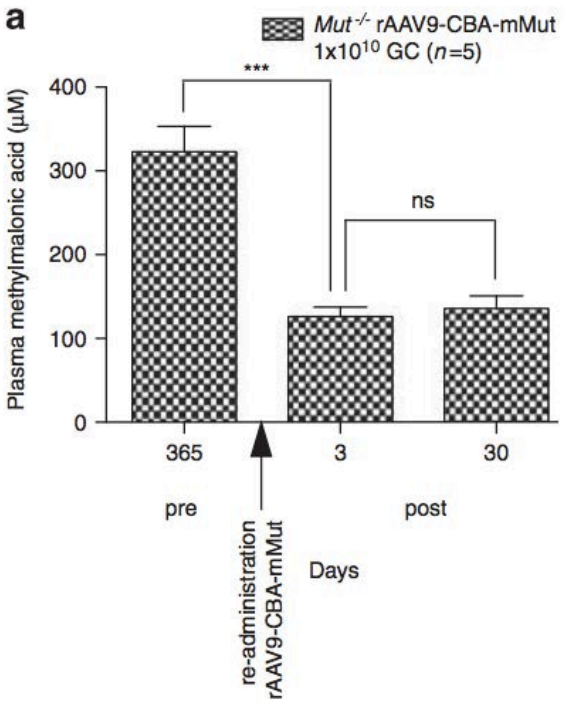
MMA Gene Therapies in Development

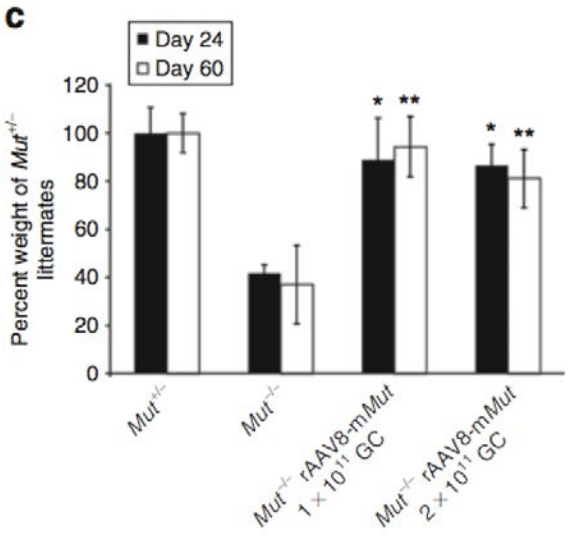
- Gene therapy
  - Transgenic model
  - Hepatic targeting > phenotypic correction
- AAV
  - Hepatic genotoxicity
  - Immune responses
    - Neutralizing antibodies



Gene Therapy (Pre-Clinical)

- Adenovirus, AAV, Lentivirus





Hum Gene Ther 19:53-60, 2008
Mol Ther 18:11-16, 2010
Gene Ther 29:385-91, 2012
Hum Gene Ther 25:529-38, 2014
Hum Gene Ther 25:837-43, 2014

mRNA Therapy

- No insertional mutagenesis
- Dose dependent pharmacology avoids constitutive gene activation
- No conventional ERT
- Lipid nanoparticles
  - Encapsulation
  - Biodegradable
  - Systemic delivery, liver targeting

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Cell Reports
Article

Systemic Messenger RNA Therapy as a Treatment for Methylmalonic Acidemia

Ding An,[1,3] Jessica L. Schneller,[2,3] Andrea Frassetto,[1] Shi Liang,[1] Xuling Zhu,[1] Ji-Sun Park,[1] Matt Theisen,[1] Sue-Jean Hong,[1] Jenny Zhou,[1] Raj Rajendran,[1] Becca Levy,[1] Rebecca Howell,[1] Gilles Besin,[1] Vladimir Presnyak,[1] Staci Sabnis,[1] Kerry E. Murphy-Benenato,[1] E. Sathyajith Kumarasinghe,[1] Timothy Salerno,[1] Cosmin Mihai,[1] Christine M. Lukacs,[1] Randy J. Chandler,[2] Lin T. Guey,[1] Charles P. Venditti,[2,4,*] and Paolo G.V. Martini[1,4,5,*]

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Research paper

Long-term efficacy and safety of mRNA therapy in two murine models of methylmalonic acidemia

Ding An, Andrea Frassetto, Eric Jacquinet, Marianne Eybye, Joseph Milano, Christine DeAntonis, Vi Nguyen, Rodrigo Laureano, Jaclyn Milton, Staci Sabnis, Christine M. Lukacs, Lin T. Guey *

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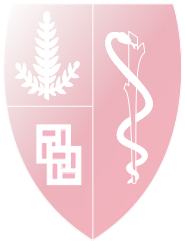
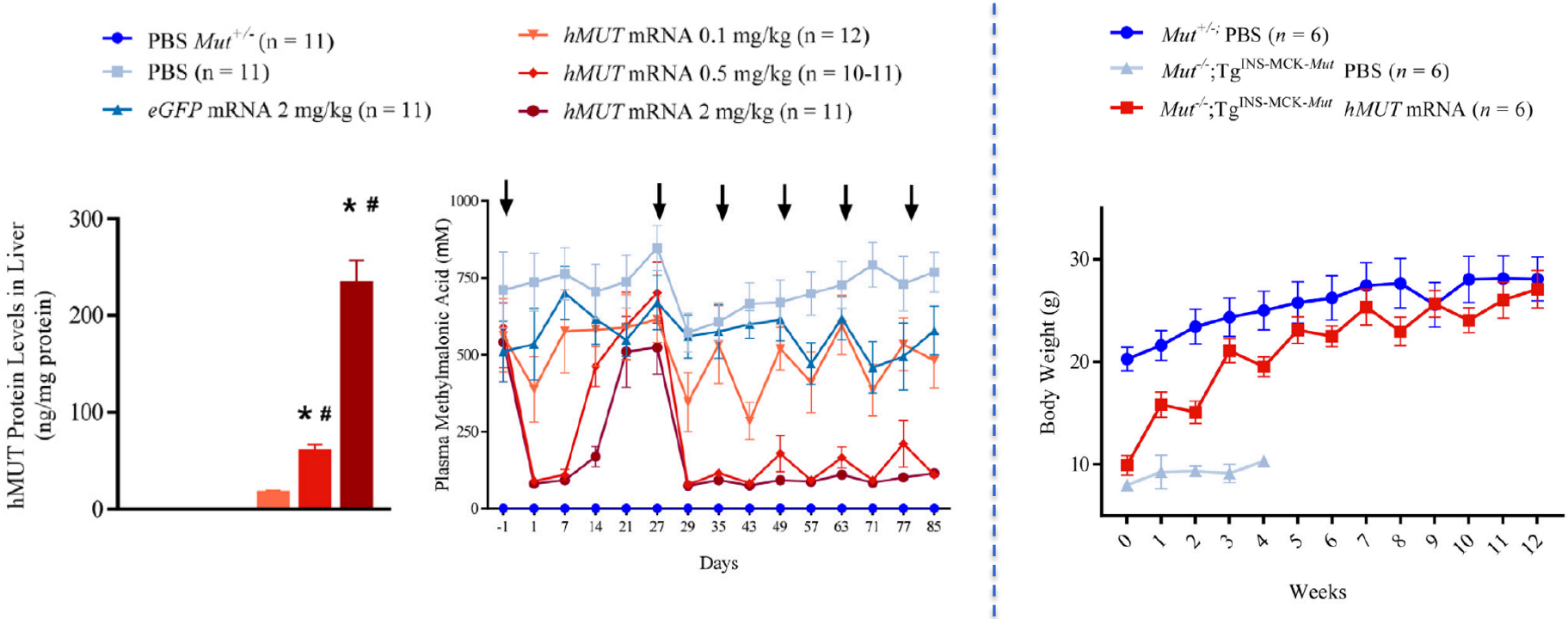
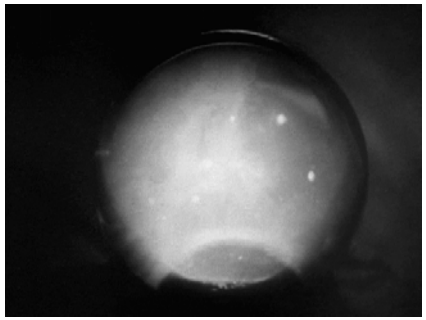


Improved Metabolism in *mut*$^{-}$ *and mut*^{0} MMA Mice after i.v. *hMUT* mRNA



Summary

- MMA *mut*^{0} associated with high morbidity/mortality
- Liver or combined liver/kidney transplantation
  - Decreased frequency of metabolic crises and hospitalizations
    Stabilization of neurological function
  - Liberalization of diet
  - Weight gain
  - Improved quality of life
- mRNA and gene therapies in development



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- Maria T. Millan, M.D.
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- Rachel Farrell
- Stanford Medical Genetics Residents, Genetic Counselors, RNs, RDs

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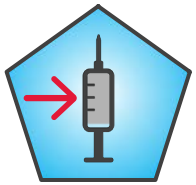
Conclusion

Stéphane Bancel

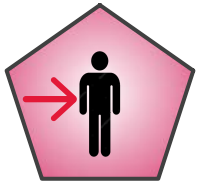
Chief Executive Officer

Two important positive clinical milestones in two modalities announced today



Cytomegalovirus (CMV) vaccine (mRNA-1647)

- Positive interim phase 1 data
- Successfully immunized seronegatives and boosted seropositives
- Generally well tolerated
- Phase 2 to start in the near term
- Preparations underway for the phase 3
- Moderna owns the global commercial rights to mRNA-1647



Antibody against Chikungunya virus (mRNA-1944)

- Positive phase 1 data
- Observed dose dependent protein expression
- Achieved expected therapeutic levels at a well tolerated dose (0.3mg/kg)
- Observed expected translation from NHP to human

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Moderna continues to mature and clinical data are validating the quality and relevance of our science

- 4 programs in or preparing for phase 2
- 10 positive phase 1 studies (6 vaccines, PCV, OX40, VEGF and Chikungunya antibody)
- 12 programs in phase 1
- Vaccine modality:
  - Six vaccines with positive phase 1 data, including CMV
  - CMV, RSV, hMPV+PIV3 in clinical trials, each as a potential blockbuster opportunity
- 5 I/O programs dosing patients in Phase 2 or Phase 1:
  - PCV and KRAS with Merck (50/50 global profit share)
  - IL12 with AstraZeneca (50/50 US profit share)
  - OX40L and Triplet wholly owned by Moderna
- Antibody against Chikungunya virus (mRNA-1944) phase 1 data validates:
  - mRNA approach for making a functional IgG antibody
  - LNP delivery technology shared by rare disease pipeline candidates

We believe innovative vaccines are a great business

	Me too vaccines (i.e., Tetanus, …)	Innovative vaccines (i.e., Prevnar, HPV…)	Public health vaccines (i.e., Yellow Fever…)
Pricing:	$	$$$	$
%EBIT:	10-25%	~50%	0-25%
	Moderna will <u>not</u> fund, but might partner	Moderna will fund or partner	Moderna will partner with governments and foundations to pursue social and public health goals

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Several vaccines have realized this value-add with strong, recurring revenues

Top selling vaccines, by 2024 projected sales

Vaccine	Indication	Company	Launch Year	2018 WW Sales	2024E WW Sales
Prevnar 13*	Pneumococcus	Pfizer	2000 (PCV7)	$5.8 bn	$6.7 bn
GARDASIL**	HPV	Merck	2006	$3.2 bn	$5.9 bn
SHINGRIX***	Herpes zoster	GSK	2017	$1.0 bn	$3.5 bn

Source: EvaluatePharma

*Prevnar 13 ® is a registered trademark of Wyeth LLC.
**GARDASIL ® is a registered trademark of Merck & Co., Inc.
***Shingrix is a registered trademark of GSK

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Our strategy for the mid-term

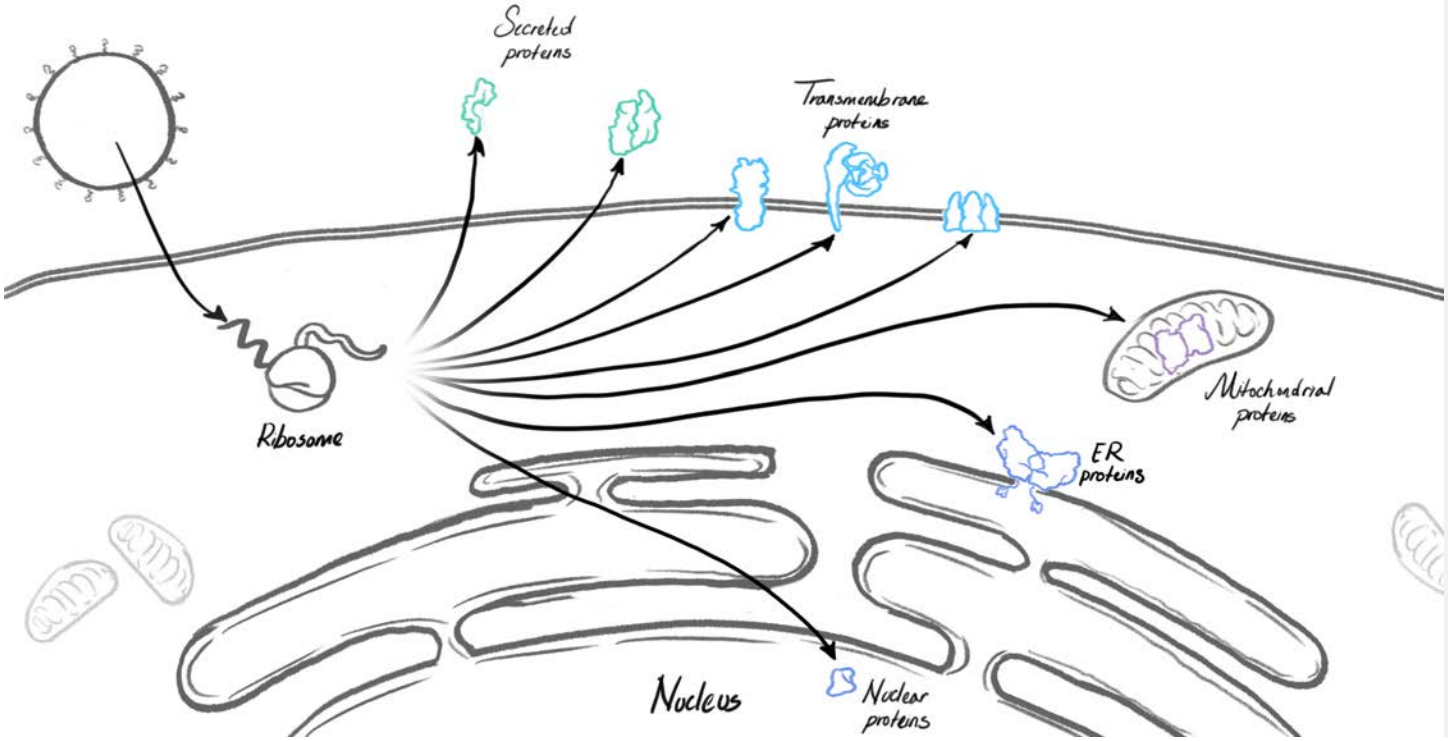
(1) Build a strong vaccine business based on innovative vaccines like CMV, RSV, hMPV+PIV3, Zika…

(2) Execute the clinical research plans on 5 I/O programs to potentially improve on PD1/PDL1 mono therapy

(3) Build a rare disease business, with an initial focus on metabolic diseases

(4) Expand into new therapeutic areas

Moderna's vision is intact: more than ever, we believe mRNA could be a potential 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

moderna

Our Mission

To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.

moderna®

Thank you