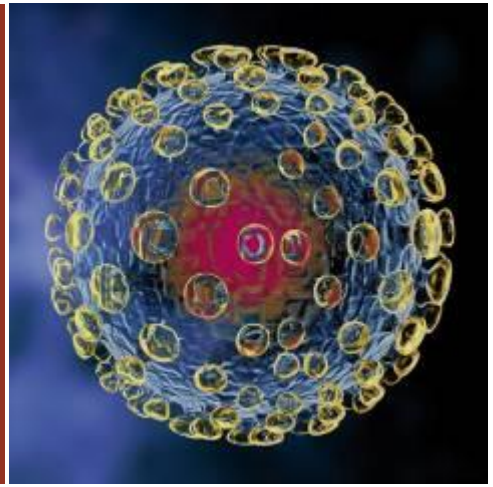
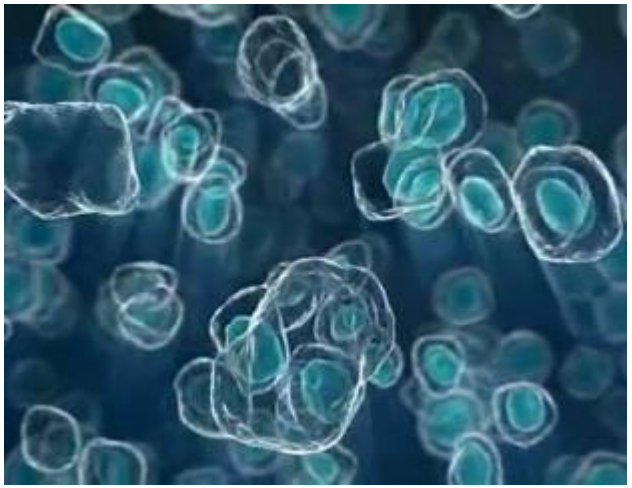


Synthetic Vaccinology at Novartis

Philip R. Dormitzer, MD, PhD

Head of US Research, Global Head of Virology, Vice President
Novartis Vaccines and Diagnostics

The National Academy of Sciences Forum on Synthetic Biology
October 21, 2013. The Keck Center, Washington, DC

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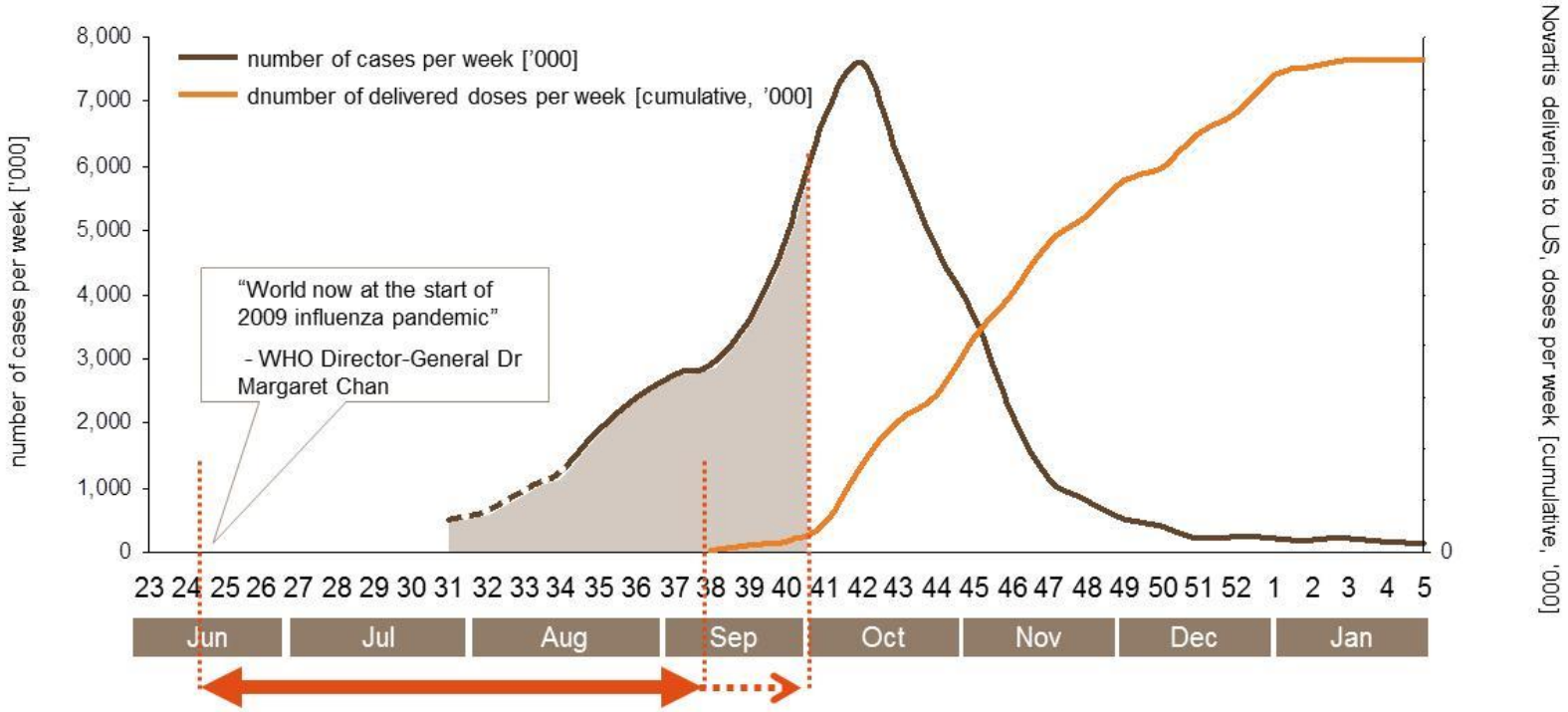
2009 pandemic response fastest ever but too slow

- Vaccine only available in substantial quantities after the 2nd pandemic wave peak

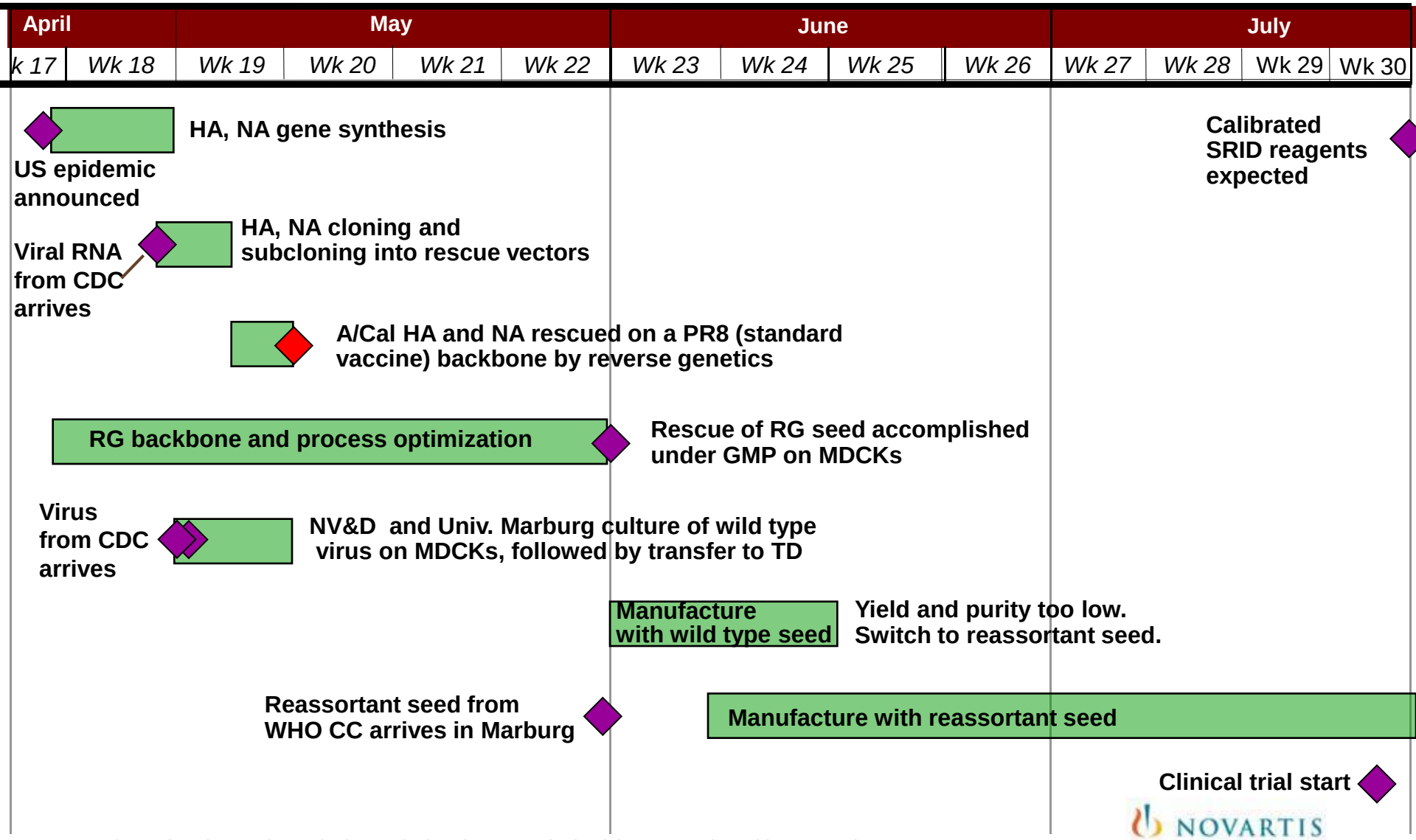


Close to 40% of cases occurred in a time when no meaningful vaccine quantities were avaiable

Source: source is: http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm and http://www.cdc.gov/flu/weekly/index.htm: As of Jan16, 2010 the CDC estimated that about 57 million people are infected with 2009 H1N1. weekly data on influenza positive tests reported to CDC by U.S. WHO/ NREVSS collaborating laboratories applied to CDC estimate to arrive at the weekly estimate for number of cases in the US.

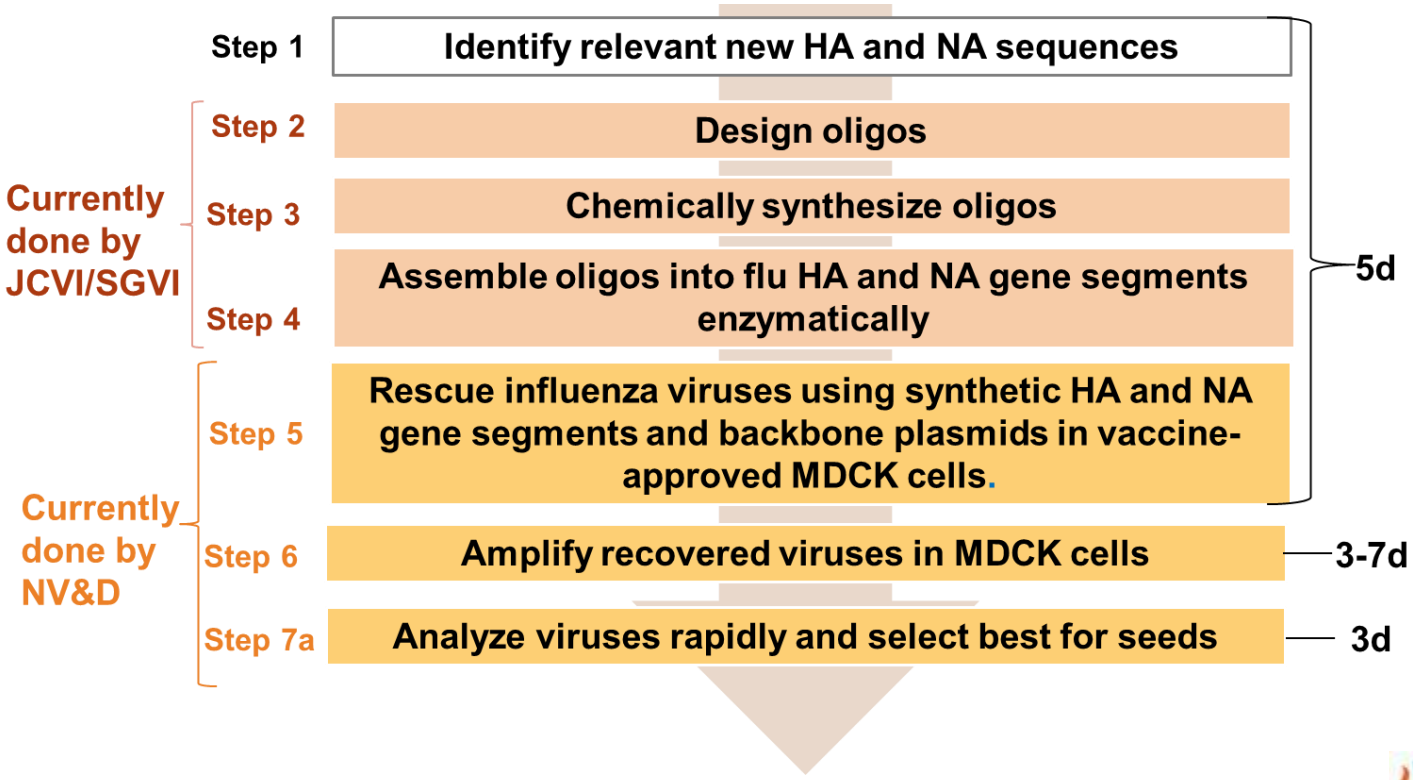
Early events in the NV&D response to H1N1v

Generated virus in 17 days, made GMP 3 wks later, never used



With SGVI and JCVI, established a process for rapid generation of synthetic influenza viruses

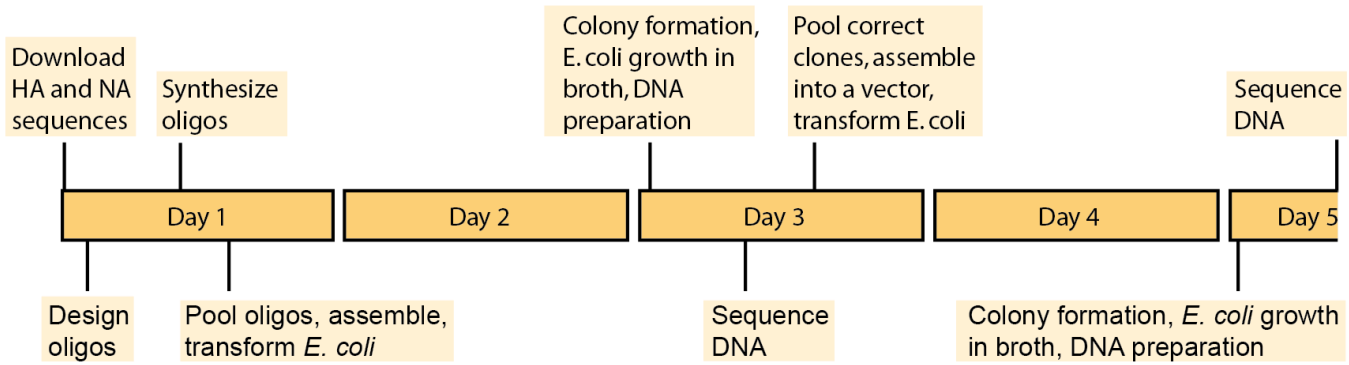
- Synthetic biology improves the ***speed*** of vaccine seed generation
- Enzymatic error correction improves the ***accuracy*** of seed generation
- Optimized backbones produce superior virus and HA ***yield***
- Process **robustness** shown by making >25 synthetic flu A and B virus strains



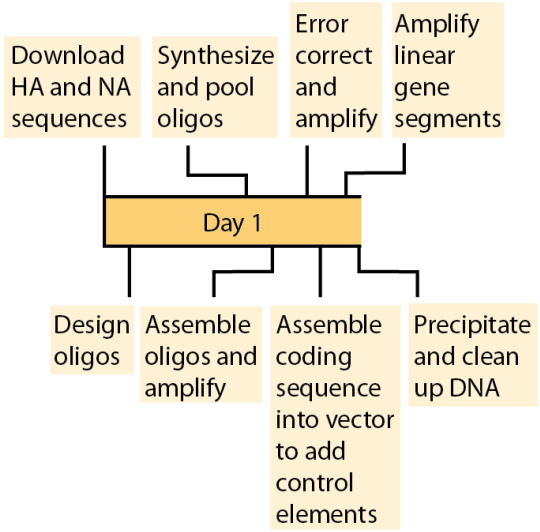
Improved gene assembly is the core advance

High fidelity enzymatic assembly and error correction

A.



B.



- Enzymatic gene assembly without cloning
- Enzymatic error correction degrades mismatched DNA
- High fidelity allows virus rescue in manufacturing cell line while sequence being confirmed
- Can be fully automated
- Rescuing many strains in parallel allows generation of a high yielding strain with the first synthesis
- Can accelerate any flu vaccine platform that requires strain changes

Dormitzer *et al*., Sci Trans Med 5:185ra68, 2013

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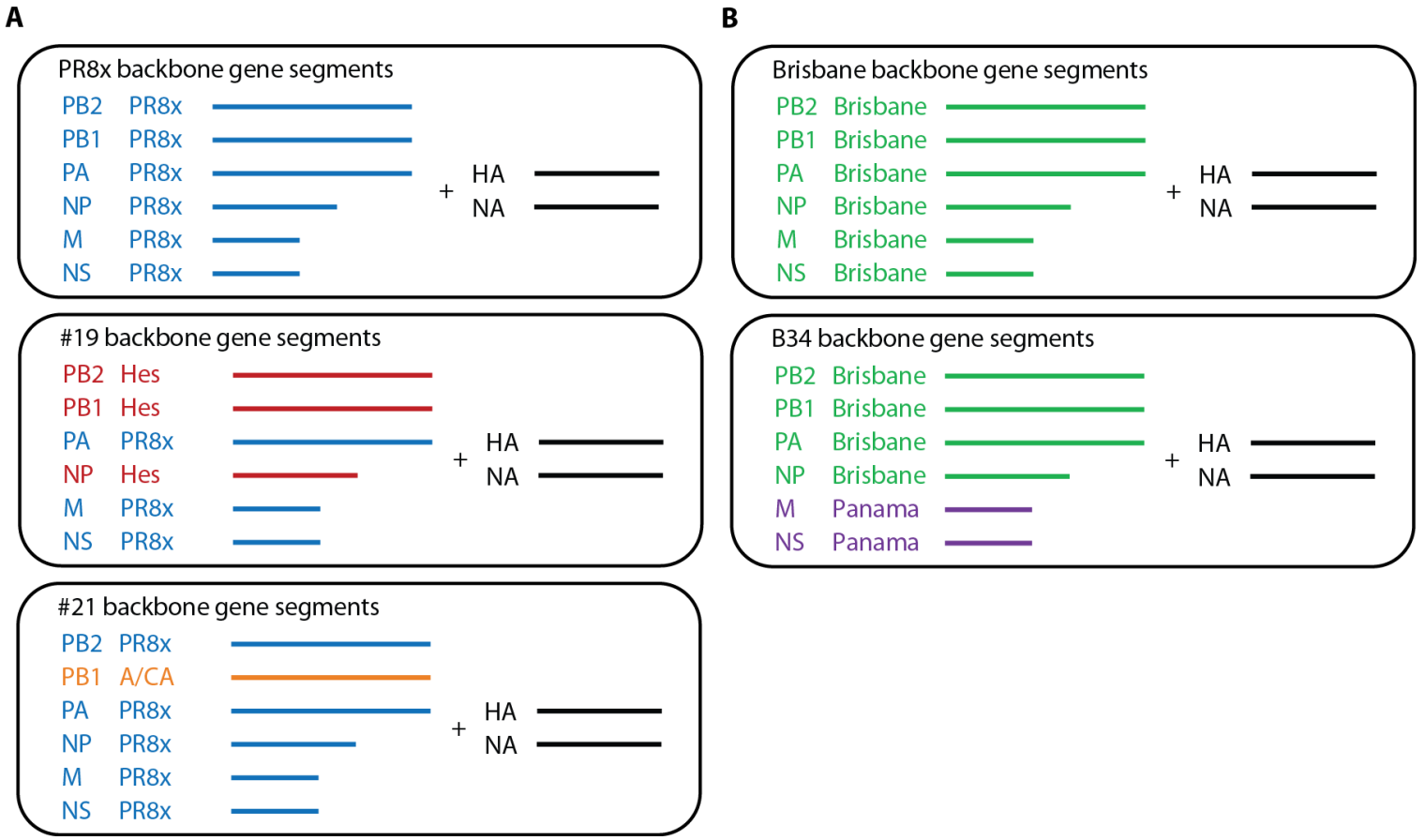
Alternative influenza vaccine backbones



- Can rescue directly on novel backbones for increased rescue efficiency and HA expression
- All genome segments from low pathogenicity strains

Dormitzer *et al.*, Sci Trans Med 5:185ra68, 2013

A panel of new vaccine backbones increases HA yield

Comparable yield increases in MDCK cells and eggs

Synthetic H1N1 strain	Reference strain	HA yield by ELISA (fold-increase)	HA yield by RP-HPLC (fold-increase)	Best backbone(s)
A/Christchurch/16/2010	NIB74	4.3 **	2.8	#21
A/Brisbane/10/2010	wild-type	6.9 ***	4.2	#21
A/Brisbane/59/2007	IVR-148	2.9	1.9	#21
A/Solomon/3/2006	IVR-145	6.4	1.8	#21
Synthetic H3N2 strain				
A/Victoria/361/2011	IVR-165	1.8	1.8	PR8x
A/Victoria/210/2009	X187	1.8 *	3.4	PR8x
A/Wisconsin/15/2009	X183	9.9	Ref. undetectable	#19
A/Uruguay/716/2007	X175C	1.4 *	1.4	#19
Synthetic H5N1 strain				
A/turkey/Turkey/1/2005	NIBRG23	2.1 *	3.8	#19, #21[b]
Synthetic H3N2v strain				
A/Indiana/8/2011	X213	n/a	2.4 ***	#21
Synthetic B-Yamagata strain				
B/Wisconsin/1/2010	wild-type	2.1	1.1	Brisbane
B/Brisbane/3/2007	wild-type	2.9	2.0	#B34
B/Florida/3/2006	wild-type	1.6	not tested	#B34
Synthetic B-Victoria strain				
B/Brisbane/60/2008	wild-type	1.0	1.5 **	Brisbane
B/Brisbane/32/2002	wild-type	2.3	1.8	Brisbane

Dormitzer *et al.*, Sci Trans Med 5:185ra68, 2013

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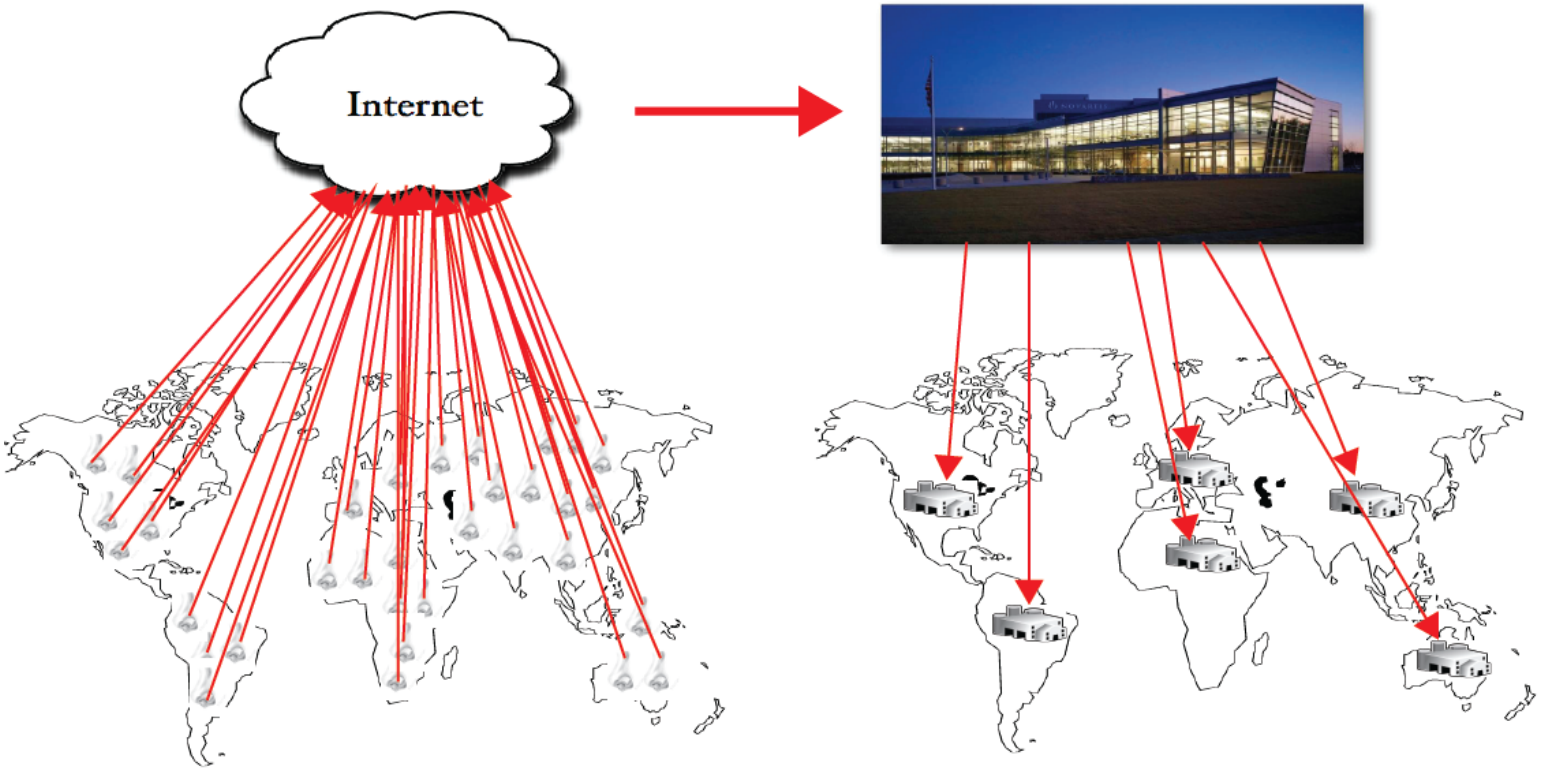
The emerging system

More rapid and reliable protection of the public from flu

Sequence data are posted on the web with open access and continuously monitored by algorthims to detect new antigenic variants

Synthesized HA and NA genes are rescued directly on high growth backbones and tested as potential vaccine seed viruses



National Inflenza Centers sequence flu genes directly from respiratory secretions

Seed viruses are shipped to additional manufacturing sites. When the technology matures, this shipment can also be replaced with electronic transfer and local synthesis

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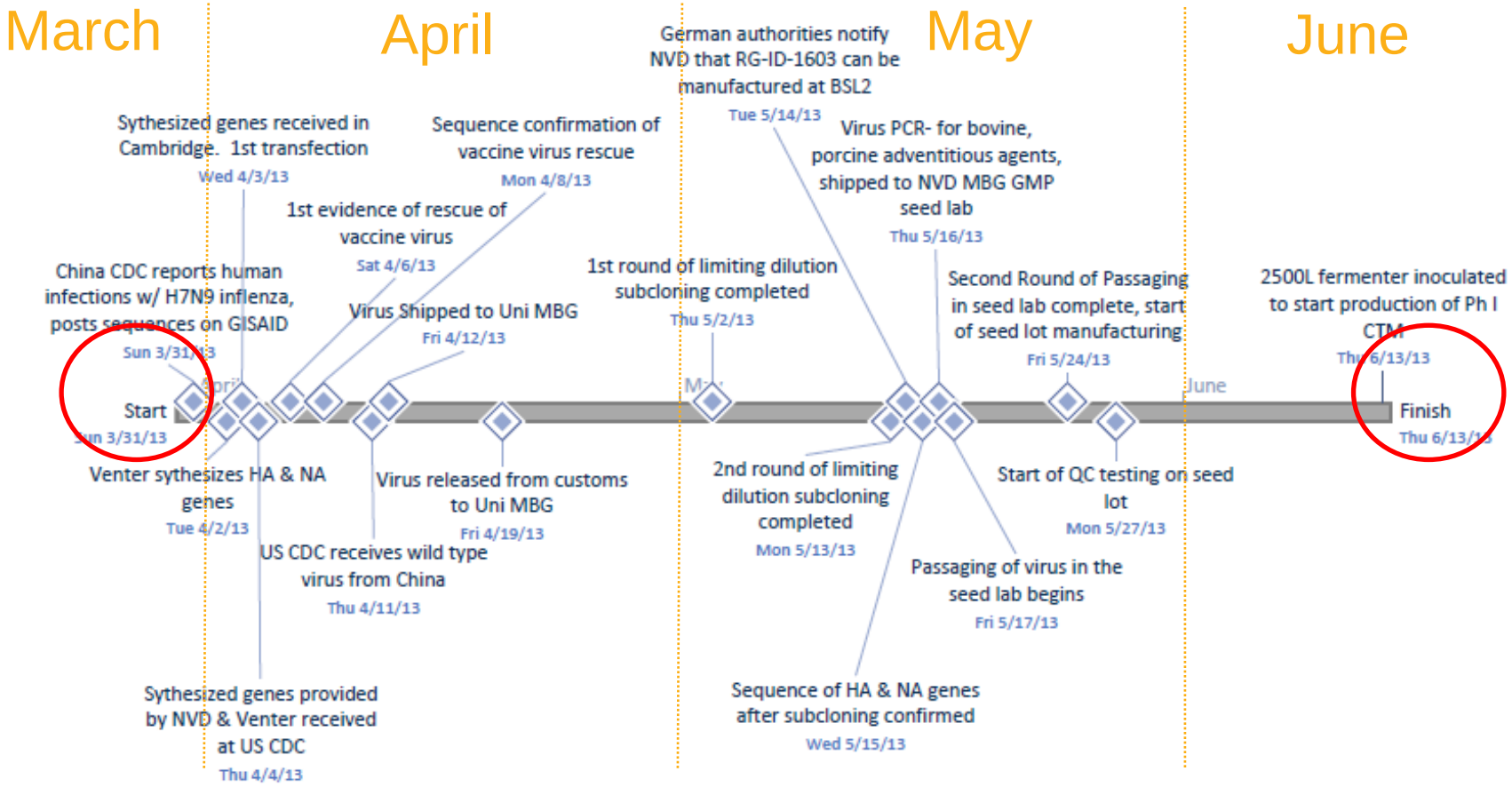
The Novartis H7N9 influenza vaccine response

Combining synthetic virus generation with flu cell culture platform



Synthetic virus rescue in collaboration with Synthetic Genomics Vaccines Inc.

SAM® vaccines

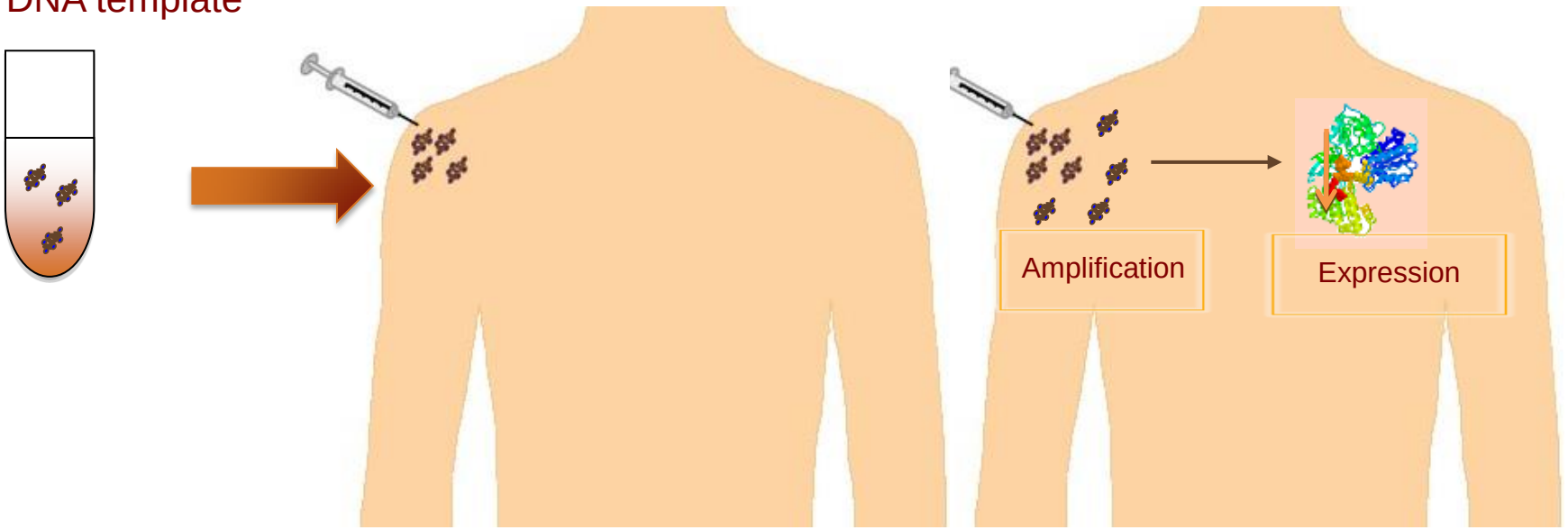
A disruptive synthetic RNA gene vaccine platform suitable for flu immunization

[1]Geall et al. (2012) Non-viral delivery of self-amplifying RNA vaccines. *PNAS* 109:14604-14609

RNA is enzymatically synthesized in vitro from a DNA template

RNA is delivered to cytoplasm of host cells, using NV&D proprietary delivery system

RNA self-amplifies in the vaccinee and expresses vaccine antigen or therapeutic molecule



- Combines the benefits of DNA immunization and viral vectors while eliminating the drawbacks of each
- Could allow very rapid generation of strain-specific vaccines

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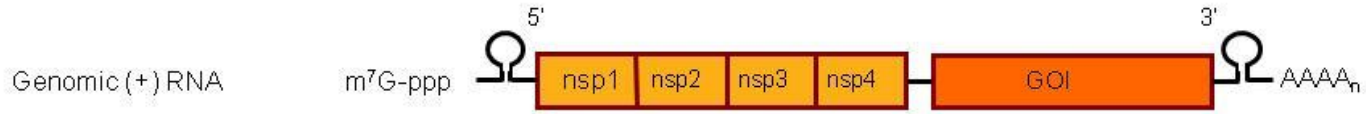
What is a self-amplifying mRNA (replicon)?



- Based on the genome of an alphavirus
  - Contains the genes encoding the non-structural proteins (nsp) that replicate RNA and allow protein expression
  - Lacks the genes required to make infectious viral particles (structural proteins)
  - We currently use RNAs derived from an alphavirus, but many other viral sources are feasible (flaviviruses, picornaviruses etc.)
- Gene of interest (GOI)
  - Structural proteins are replaced with gene encoding vaccine antigenic protein
  - Any viral or some bacterial antigens
  - Multiple proteins can be expressed from the self-amplifying RNA

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Conclusions

- Electronic data transmission combined with rapid and accurate gene synthesis is transforming the flu vaccine virus generation system
- The barriers to implementation are no longer primarily related to technical, synthetic biology challenges
  - Need transparency, accountability, and consistency in processes and decisions by agencies such as USDA, CDC, and FDA that support rapid responses to novel threats
  - Avoid unintended public health consequences of regulation intended to prevent misuse
  - Modernize other components of the system, such as potency release assays
  - Eliminate barriers to rapid, open virus gene sequence and antigenicity data sharing
  - Create a sustainable business model for implementation of this technology
- The current response to the H7N9 influenza outbreak is the first example of this technology in action
- Synthetic, self-amplifying mRNA vaccines and process automation are in the next wave of synthetic vaccinology