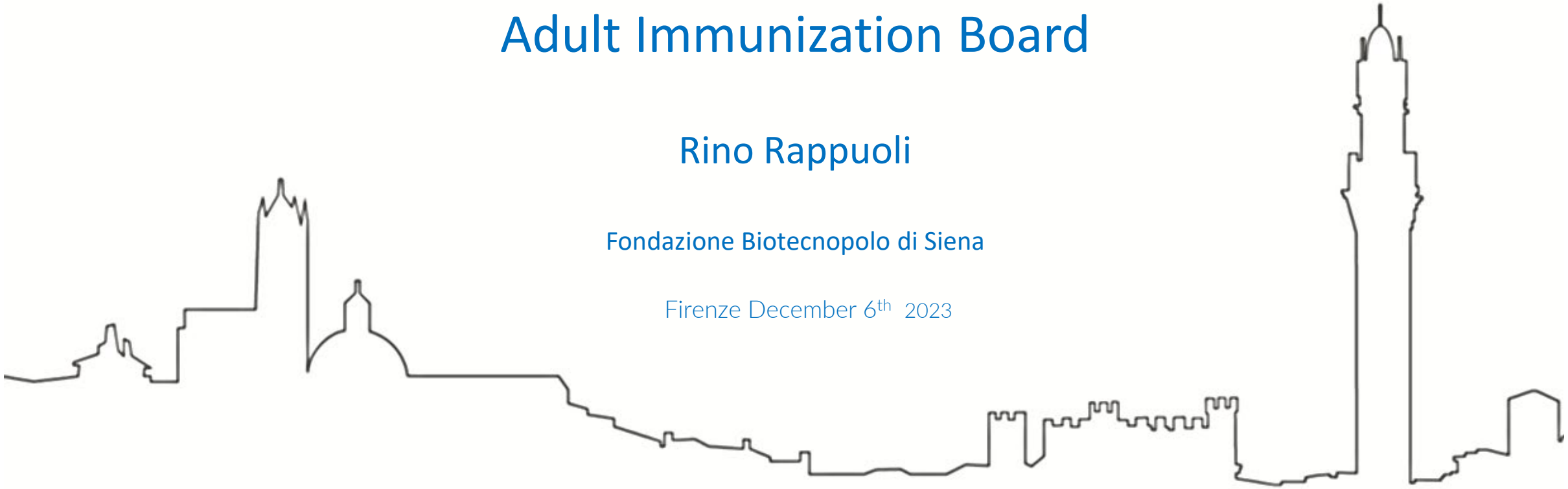
New Platforms and Technologies to develop adult vaccines

Adult Immunization Board

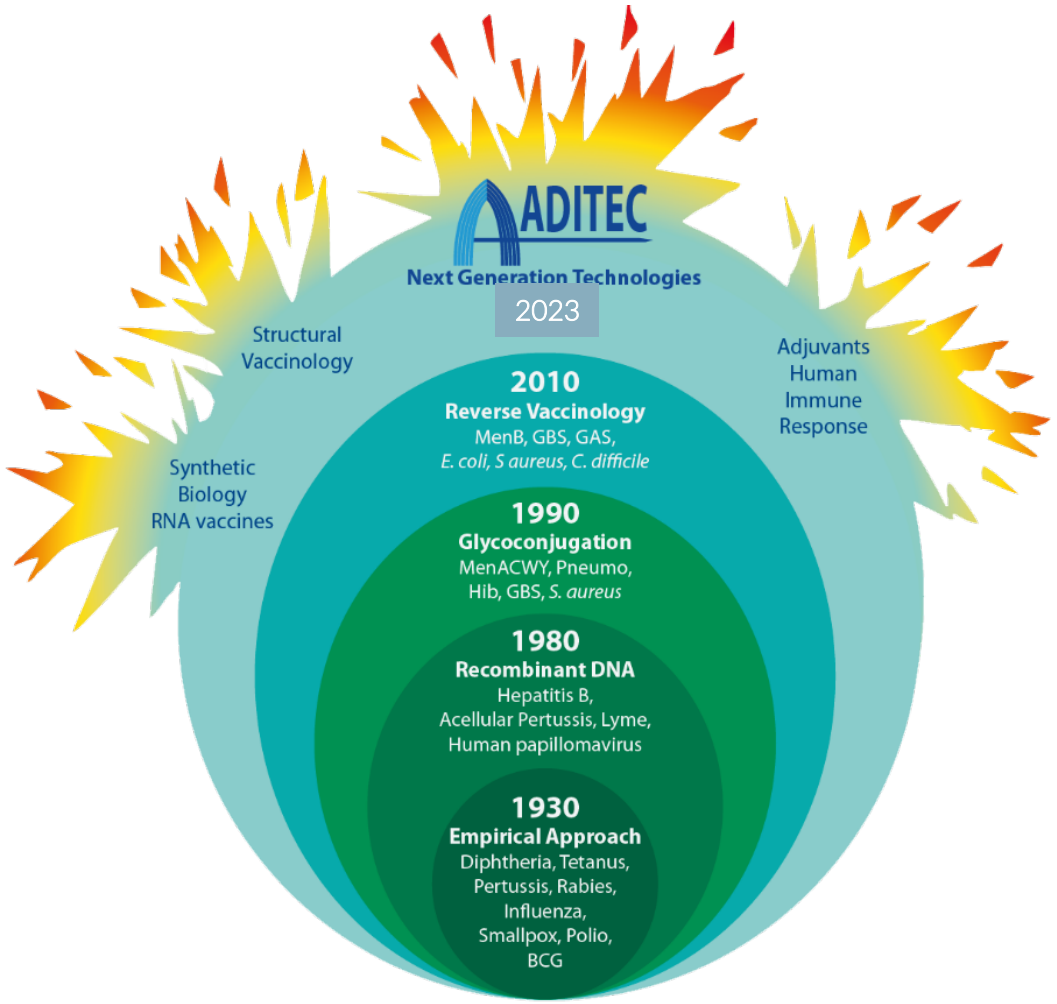
Rino Rappuoli

Fondazione Biotecnopolo di Siena

Firenze December 6th 2023



Vaccine Technolgies



The vaccine field has been tranformed

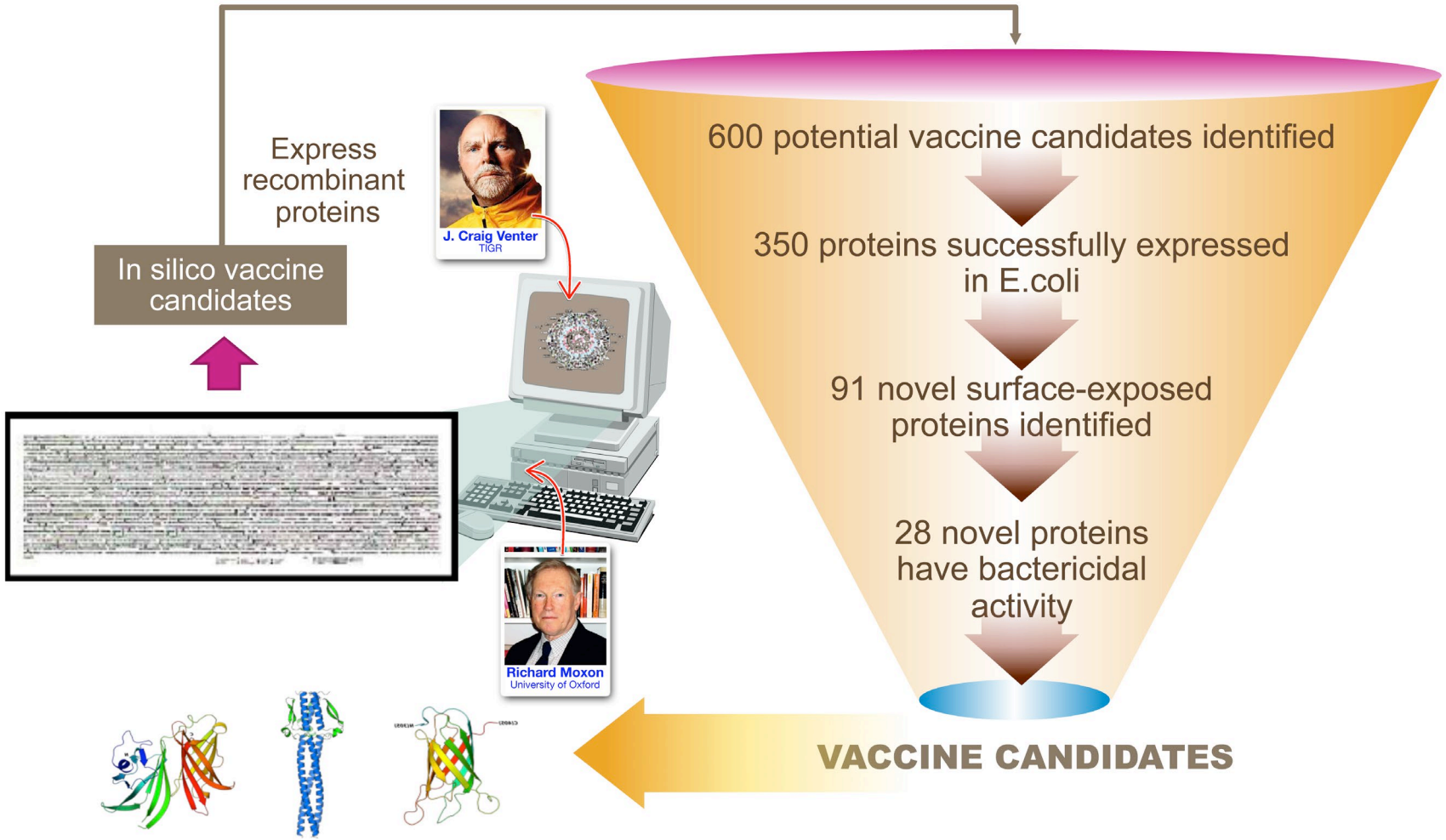
- Reverse Vaccinology
- Structural Vaccinology
- Synthetic biology

Reverse Vaccinology

the beginning of big data and high throughput

Reverse Vaccinology

genomics, the new technology made the meningococcus B vaccine possible



Science AAAS

Identification of Vaccine Candidates Against Serogroup B Meningococcus by Whole-Genome Sequencing
Mariagrazia Pizza, *et al.*
Science **287**, 1816 (2000);
DOI: 10.1126/science.287.5459.1816

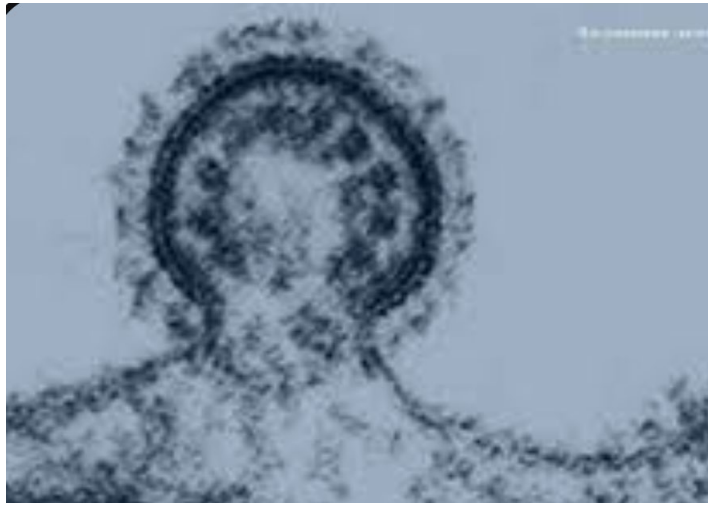
Structural Vaccinology

high throughput structure biology

Structural Vaccinology

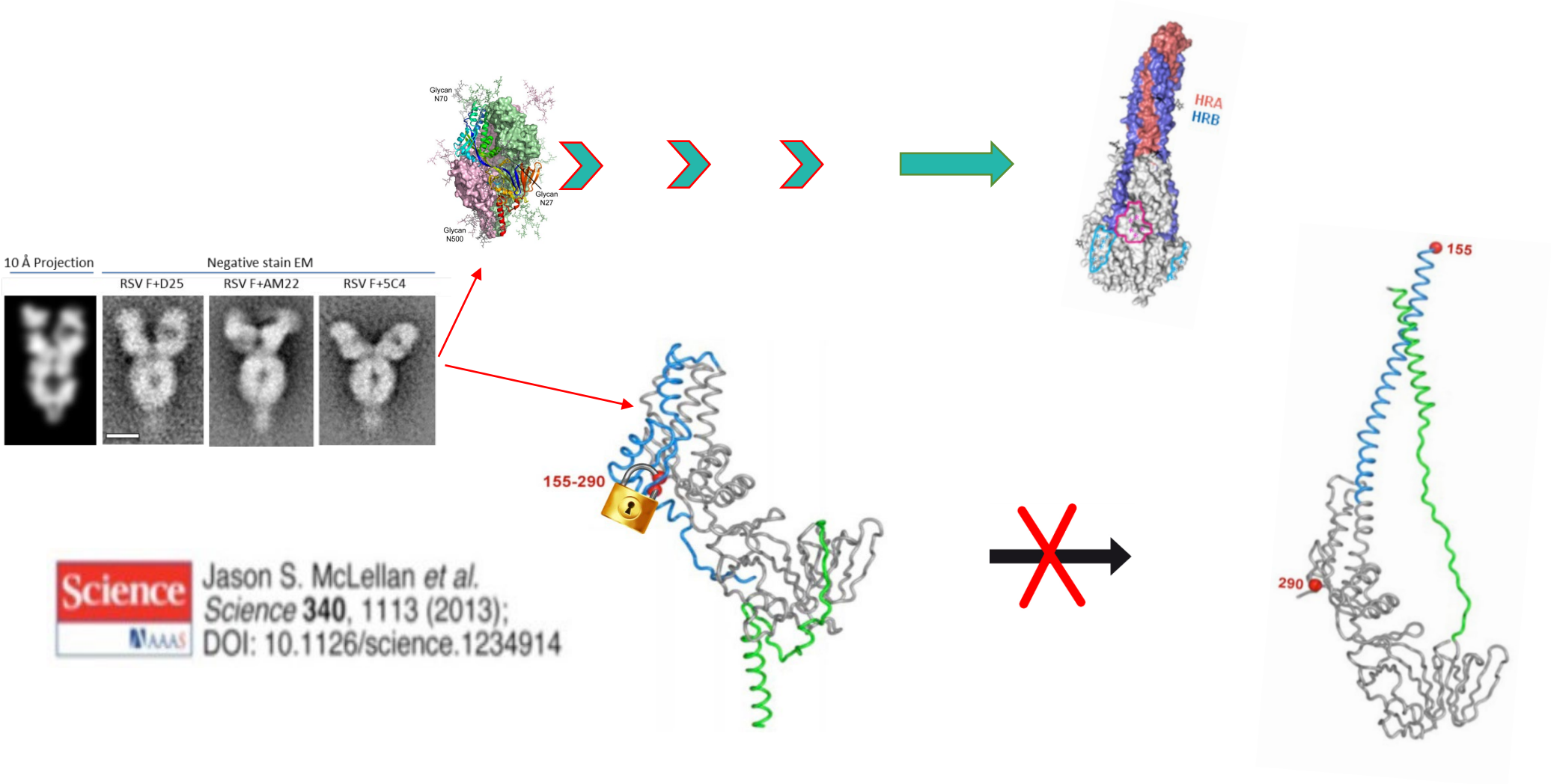
Respiratory Syncitial virus

RSV



Structural Vaccinology

in the case of RSV allowed the development of an impossible vaccine



Science
AAAS

Jason S. McLellan *et al.*
Science **340**, 1113 (2013);
DOI: 10.1126/science.1234914

2023 the year of **RSV**

2 vaccines approved
for 60 years and older

FDA NEWS RELEASE

FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine

for Individuals 60 Years of Age and Older

1 vaccine approved
for pregnant women

FDA NEWS RELEASE

FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in Infants

1 monoclonal antibody
Approved for babies

FDA NEWS RELEASE

FDA Approves New Drug to Prevent RSV in Babies and Toddlers

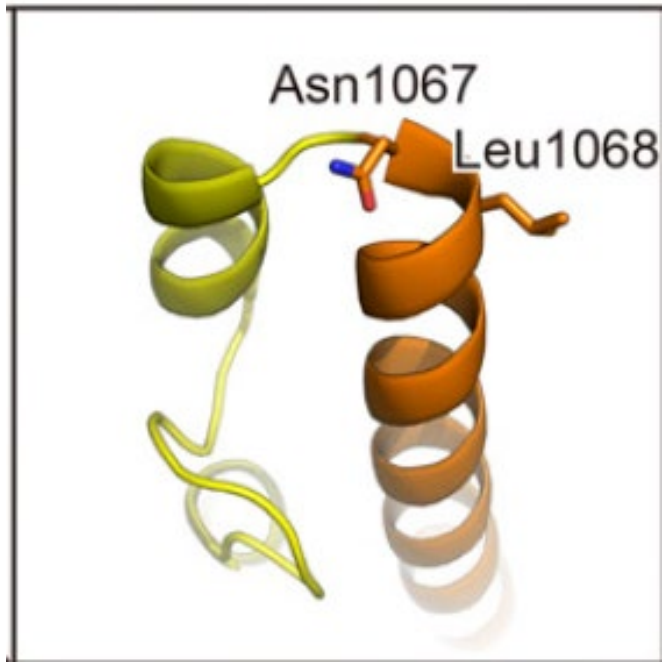
Return to
Passive immunization

erc

Stabilizing the prefusion spike protein of MERS in 2017 the prototype of SARS-CoV-2 vaccine

Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen

Jesper Pallesen[a,1], Nianshuang Wang[b,1,2], Kizzmekia S. Corbett[c,1], Daniel Wrapp[b], Robert N. Kirchdoerfer[a], Hannah L. Turner[a], Christopher A. Cottrell[a], Michelle M. Becker[d], Lingshu Wang[e], Wei Shi[e], Wing-Pui Kong[e], Erica L. Andres[d], Arminja N. Kettenbach[b,f], Mark R. Denison[d,g], James D. Chappell[d], Barney S. Graham[c], Andrew B. Ward[a,2], and Jason S. McLellan[b,2]



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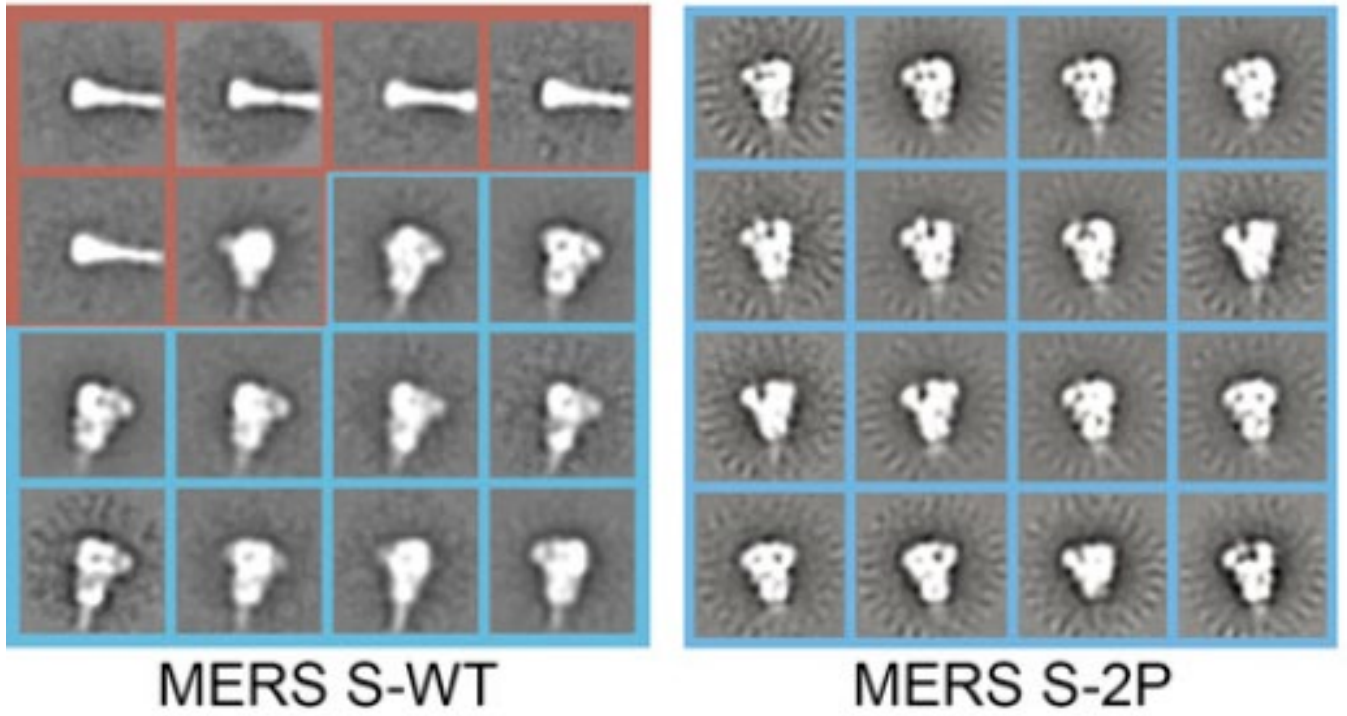


from

Reverse Vaccinology

to

Synthetic Biology

and

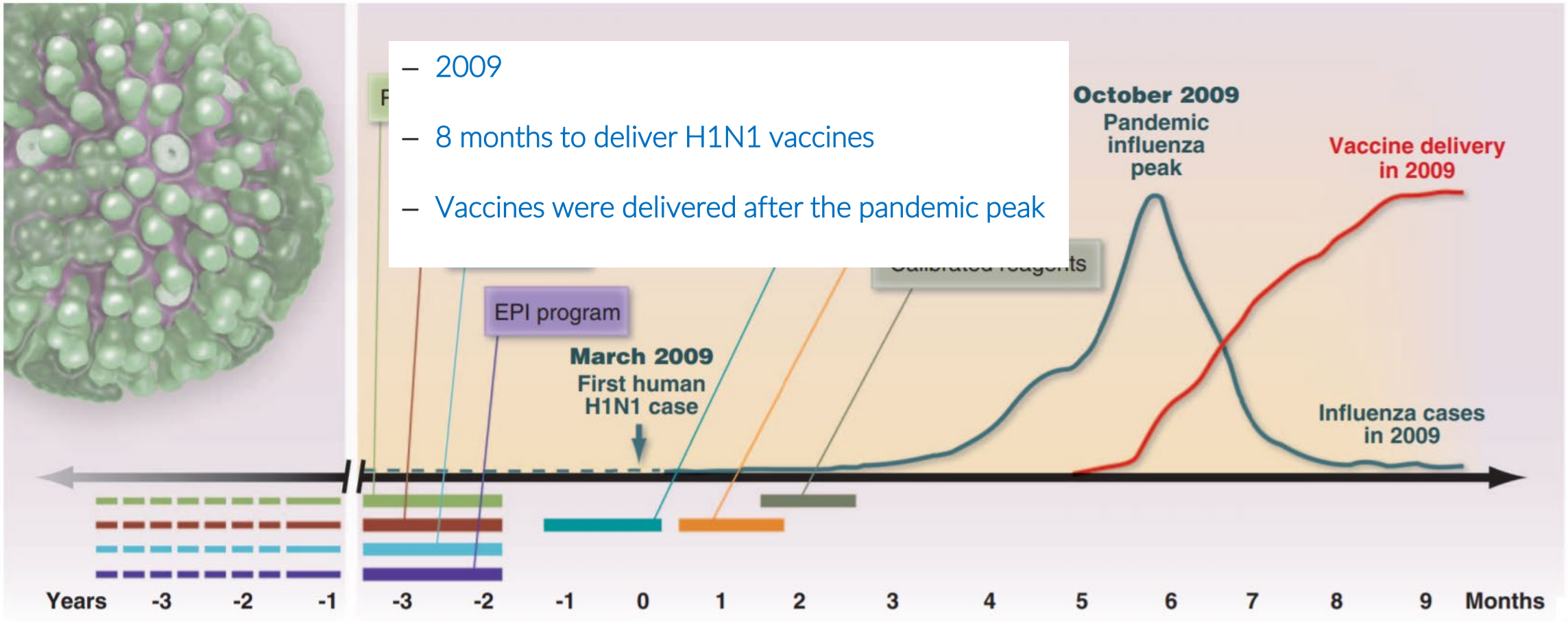
Digital Vaccinology

Science

Science **336** (6088), 1531-1533.
DOI: 10.1126/science.1221466

2009 Suine Influenza Pandemic

- 2009
- 8 months to deliver H1N1 vaccines
- Vaccines were delivered after the pandemic peak



POLICY FORUM
Influenza: Options to Improve Pandemic Preparation
Rino Rappuoli[1]* and Philip R. Dormitzer[2]

Sunday March 31st 2013 Easter day

- Chinese CDC postes the sequence of an H7N9 avian influenza virus
- The virus had already killed 3 people, high risk of influenza pandemic
- Race for vaccine developement starts
- Virus had to be sent from China to CDC in Atlanta

Science Translational Medicine AAAS

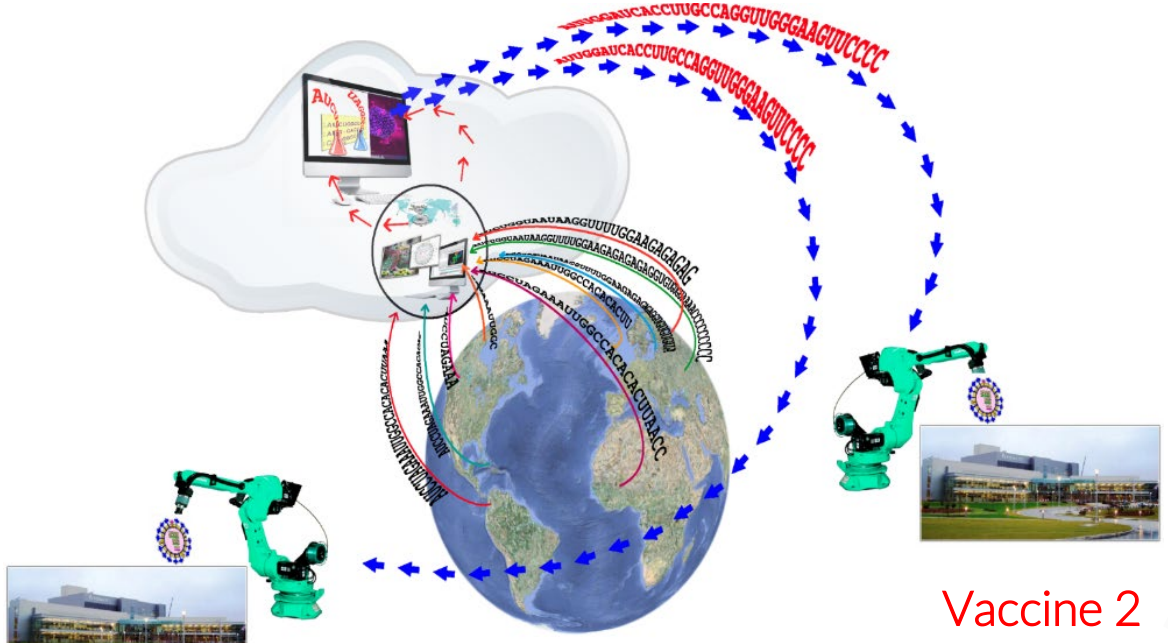
Synthetic Generation of Influenza Vaccine Viruses for Rapid Response to Pandemics
Philip R. Dormitzer *et al.*
Sci Transl Med **5**, 185ra68 (2013);
DOI: 10.1126/scitranslmed.3006368

Emerging Microbes and Infections (2013) 2, e52; doi:10.1038/emi.2013.54

www.nature.com/emi

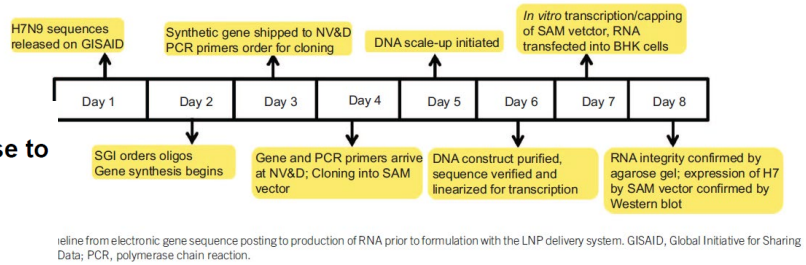
2013: Internet & Synthetic Biology-based Vaccines in One Week

In 2013 an RNA vaccine and a virus seed in one week
using information teleported by internet



Vaccine 1 whole virus

Vaccine 2 RNA vaccine



ıeline from electronic gene sequence posting to production of RNA prior to formulation with the LNP delivery system. GISAID, Global Initiative for Sharing Data; PCR, polymerase chain reaction.

Science Translational Medicine AAAS

Synthetic Generation of Influenza Vaccine Viruses for Rapid Response to Pandemics
Philip R. Dormitzer *et al.*
Sci Transl Med **5**, 185ra68 (2013);
DOI: 10.1126/scitranslmed.3006368

Emerging Microbes and Infections (2013) 2, e52; doi:10.1038/emi.2013.54

www.nature.com/emi

Shipping Information Instead of Viruses

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

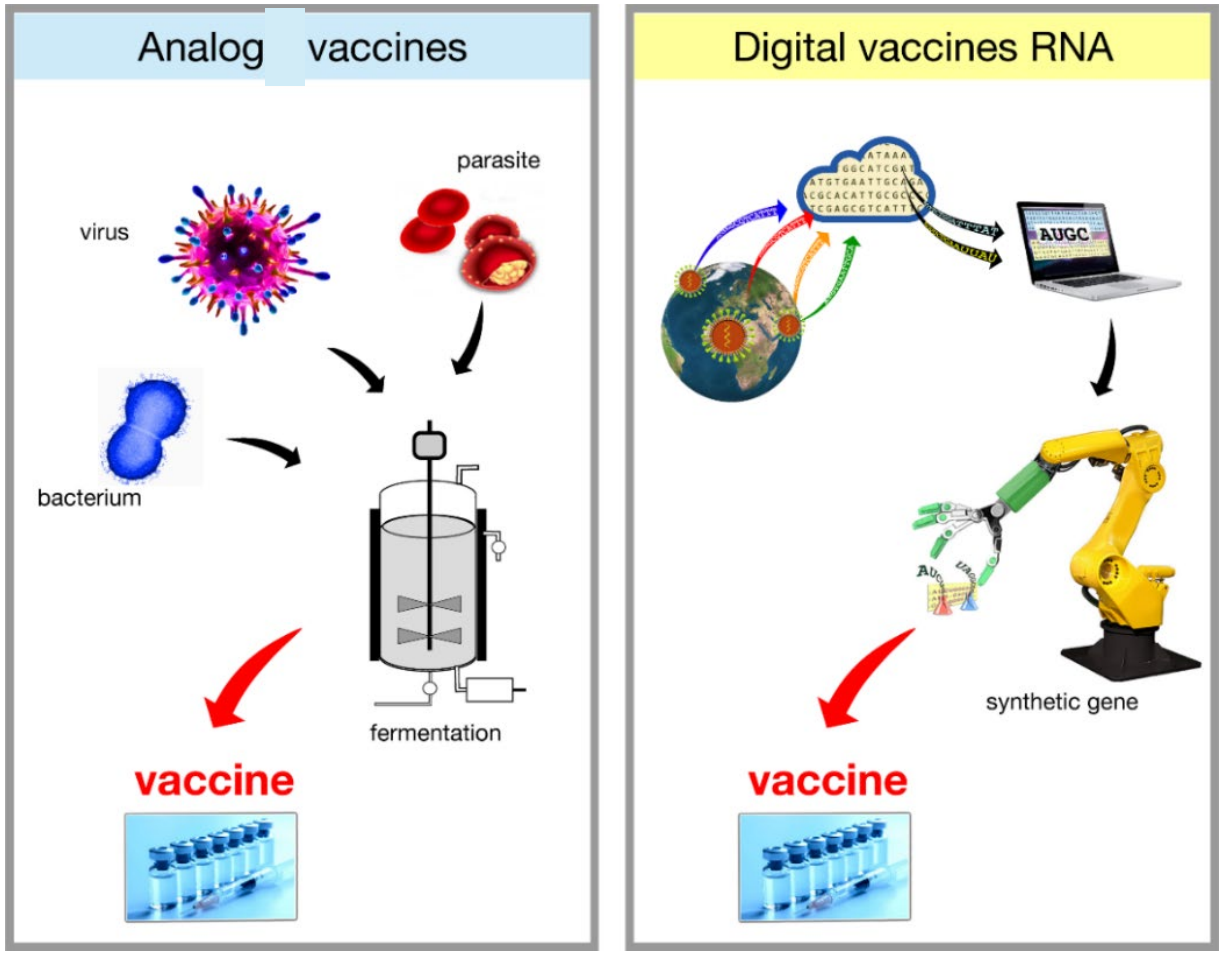
Synthesized HA and NA genes are rescued directly on high growth backbones and tested as potential vaccine seed viruses

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

2013 maked the transition from

Analog to Digital **Vaccines**



SCIENCE TRANSLATIONAL MEDICINE | VIEWPOINT

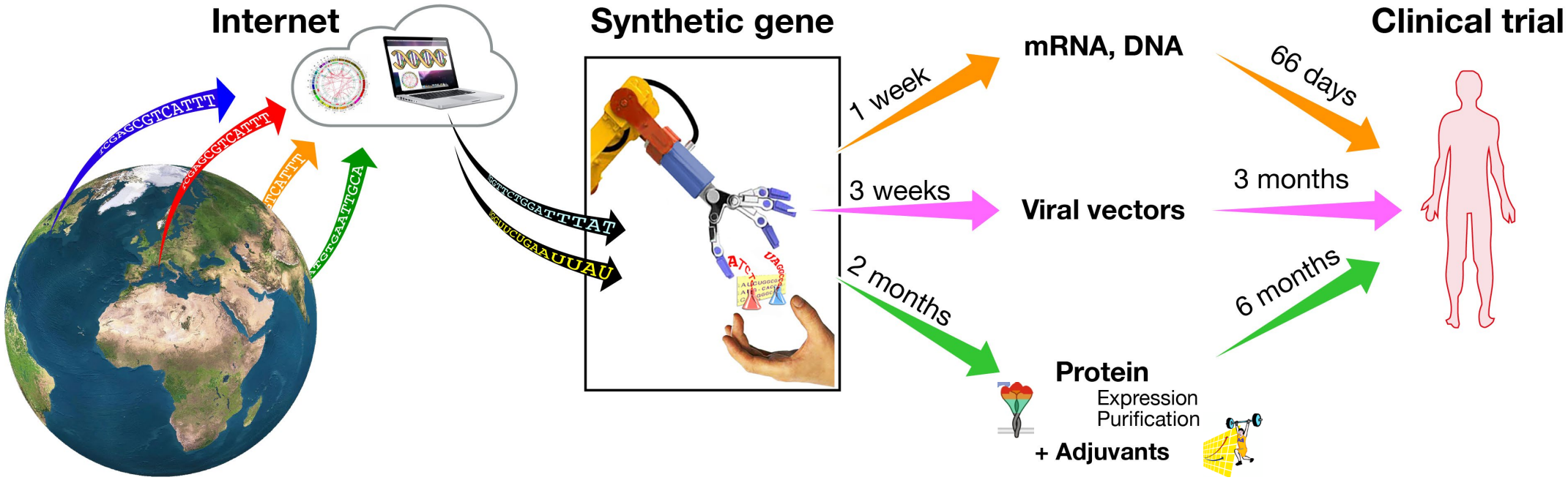
CORONAVIRUS

Vaccines 2020: The era of the digital vaccine is here

Mariagrazia Pizza, Simone Pecetta, Rino Rappuoli*

January 10th 2020 SARS-CoV-2 Sequence Posted in Internet

350 labs worldwide used the sequence to make synthetic genes



Vaccinology in the post–COVID-19 era

Rino Rappuoli[a,1], Ennio De Gregorio[a], Giuseppe Del Giudice[a], Sanjay Phogat[a], Simone Pecett
Mariagrazia Pizza[a], and Emmanuel Hanon[b]

PNAS 2021 Vol. 118 No. 3 e2020368118

https://doi.org/10.1073/pnas.2020368118 | 1

Combining

Reverse Vaccinology & Digital Vaccinology

to Cure Cancer

First efficacious Cancer Vaccine reported

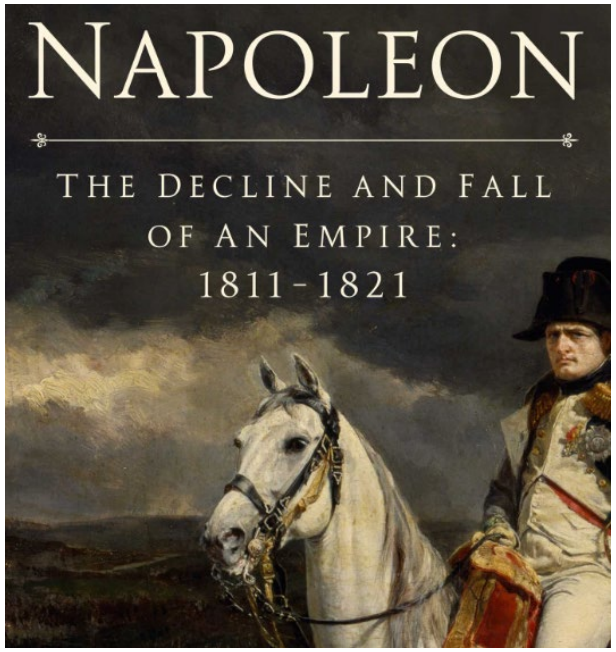
(press release from Merck/Moderna)

- People with melanoma stage 3 or 4 of the disease
  - 157 patients with surgically removed cancer
    - 50% of patients treated with checkpoint inhibitor
    - 50% of patients treated with checkpoint inhibitor + ***personalized mRNA vaccine containing 34 epitopes derived from the genome of the tumor of each patient***
- **Cancer vaccine reduced the risk of recurrencies or death by 65%**

WHO says COVID-19 is no longer a global health emergency

May 5th 2023

COVID-19 pandemic no longer constitutes a public health emergency



May 5th 1821

Death of Napoleon Bonaparte

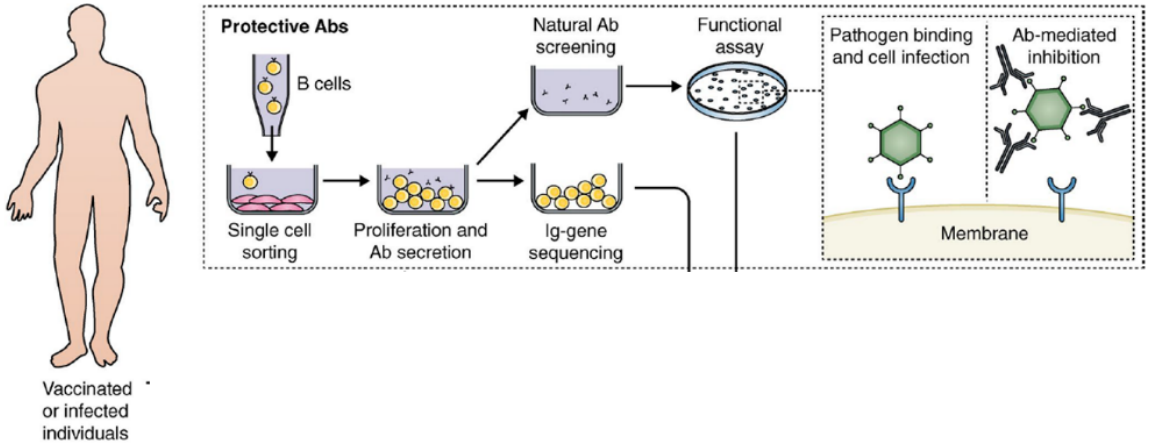
Manzoni wrote about Napoleon's death

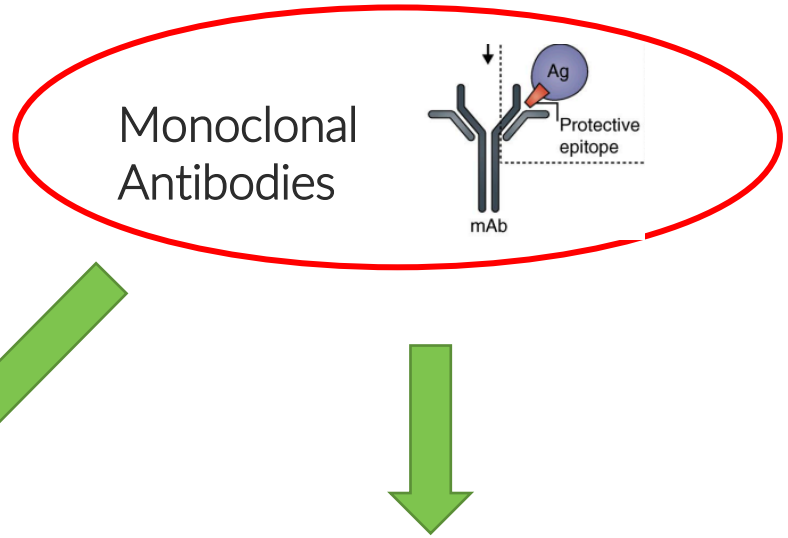
Ei fu. Siccome immobile, dato il fatal sospiro,stette la salma immemore orba di tanto spiro……..

così percossa, attònita la terra al nunzio sta

né sa quando una simile orma di piè mortale la sua cruenta polvere a calpestar verrà.

Reverse Vaccinology 2.0





Reverse vaccinology 2.0: Human immunology instructs vaccine antigen design

Rino Rappuoli, Matthew J. Bottomley, Ugo D'Oro, Oretta Finco, and Ennio De Gregorio

J Exp Med (2016) 213 (4): 469–481.

Vaccines
discovery of protective antigens
antigen structure
structure-based design

Monoclonal Antibodies
for prevention and therapy

AMR a silent pandemic

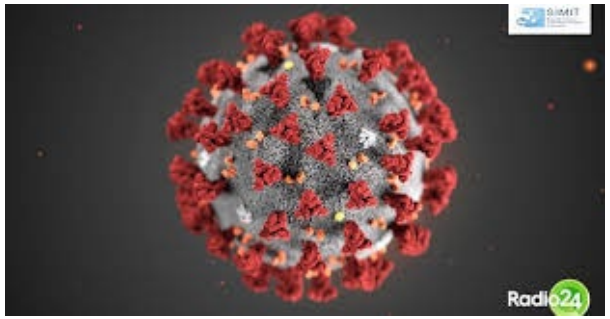
Killing 5 million per year

More than HIV and TB combined

bacteria are complex

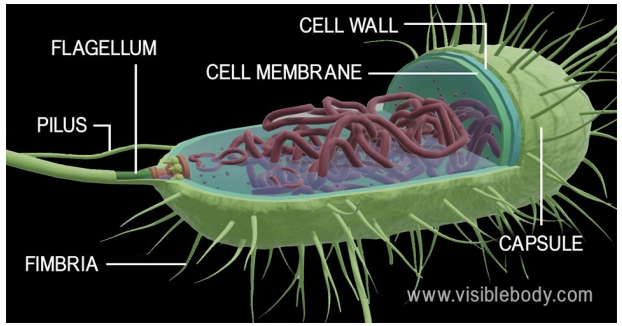
Vaccines and human monoclonals can help address AMR, but …

Viruses are simple



Small genome
One target
One assay (neutralization)

Bacteria are complex



Large genome
hundreds targets
Many assays

The effort for AMR needs to be bigger and longer lasting than the one for Covid-19

NIH Priority list of viruses with pandemic potential

PANDEMIC POTENTIAL

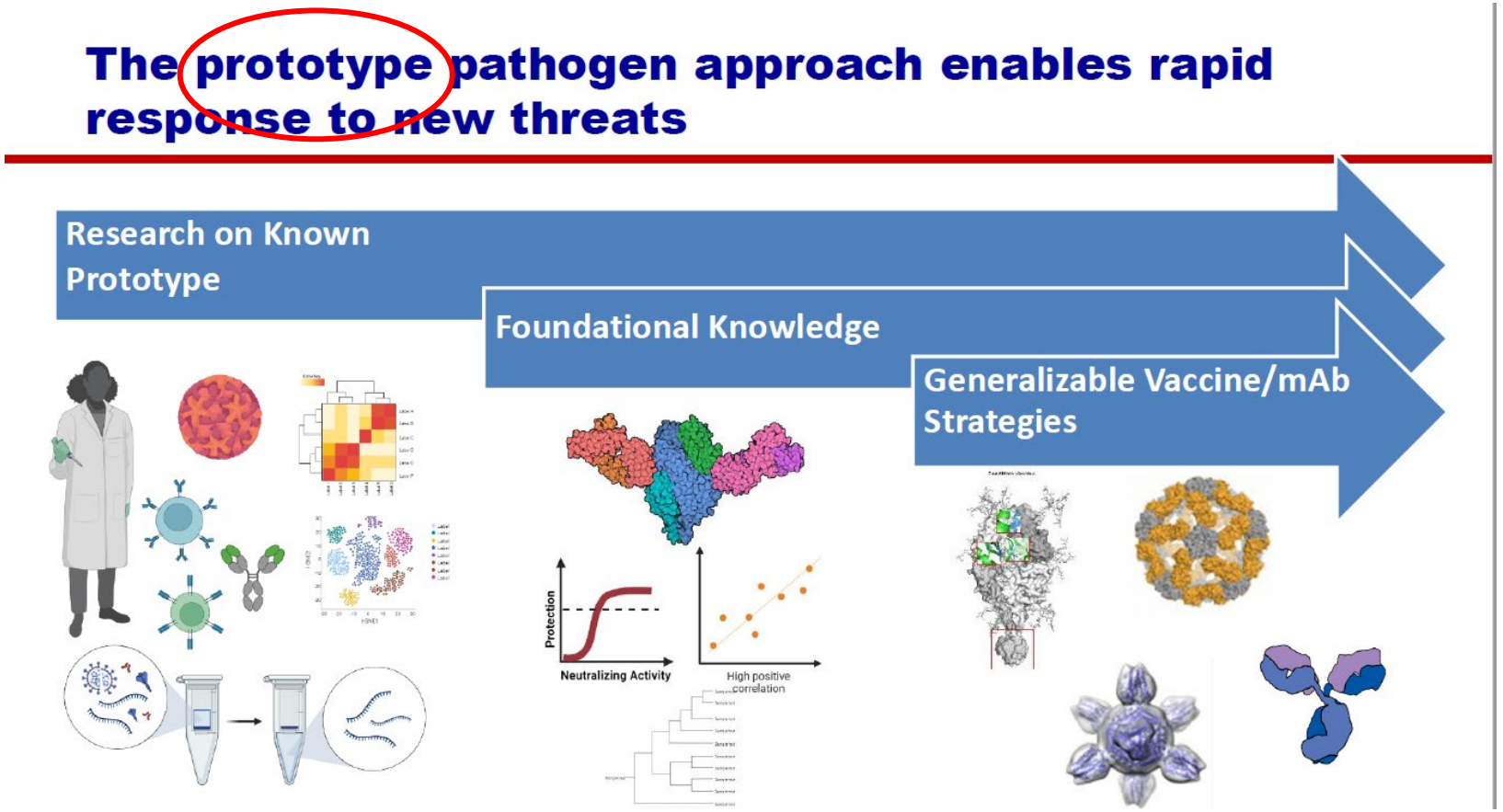
	HIGH	MODERATE	
HIGH	• ***Coronaviridae*** • ***Orthomyxoviridae***	• Hepadnaviridae* • Papillomaviridae* • Poxviridae* • Retroviridae	
MODERATE	• Bunyavirales • Arenaviridae • ***Filoviridae*** • ***Flaviviridae*** • ***Paramyxoviridae*** • ***Picornaviridae*** • Togaviridae	• Arteriviridae • ***Adenoviridae*** • Anelloviridae • Astroviridae • Bornaviridae • Caliciviridae • Hepeviridae	• Herpesviridae • Parvoviridae • Picobirnaviridae • Pneumoviridae • Polyomaviridae • ***Rhabdoviridae*** • Reoviridae

PROTOTYPE-APPROACH

Prototype Vaccines

Using Genome-Based Vaccine Discovery & Design

Image from NIH ReVAMPP



Genomes Antibodies ➡

Structures ➡ Structure-based vaccine design

Delivering vaccines in 100 days

a strategy of CEPI, NIH, G7

- Immediate reaction — 30 days
  - Sequence day 0
  - Vaccine design
  - Use prototype vaccine information
  - Precinical studies off critical path
  - Clinical batches

- Evidence Generation — 60 days
  - Clinical testing Phase 1-3
  - Use information from prototype vaccines
    - Dosing, safety, Correlates, CHIM studies
  - Innovative trial design
    - Adaptive and platform trials, digital twins

- Filing — 10 days
  - Safety and immunogenicity generated
  - Predefined benefit/risk authorization
  - Master file on vaccine platform
  - Accelerated authorization based on small & interim data
  - Continuous developer-regulator communication
  - Aligment between regulatory authorities

Grazie