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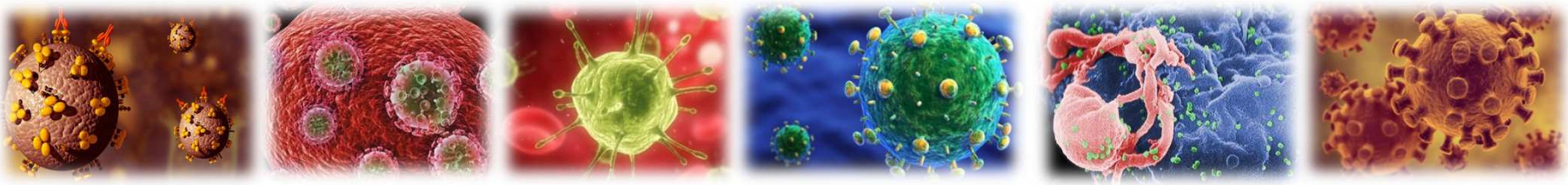
From Traditional to New-Generation Vaccines: Can We Overcome the Impossible?

Anan Jongkaewwattana, Ph.D

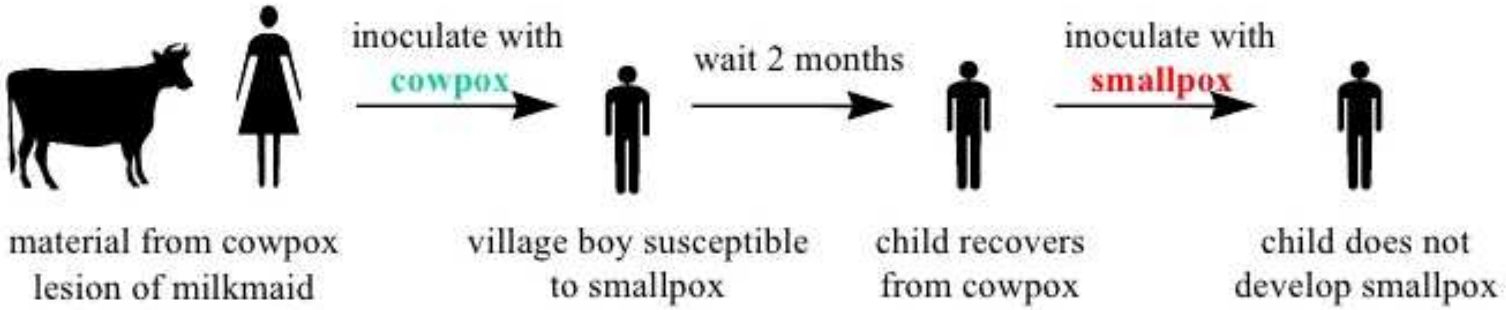
Virology and Antibody Technology Research Unit
BIOTEC, NSTDA



"Immunization is the strategy of stimulating the host's defense against a specific pathogen to establish immunological memory and thus protect against the consequences of infection".

Conceptual basis for traditional vaccine development

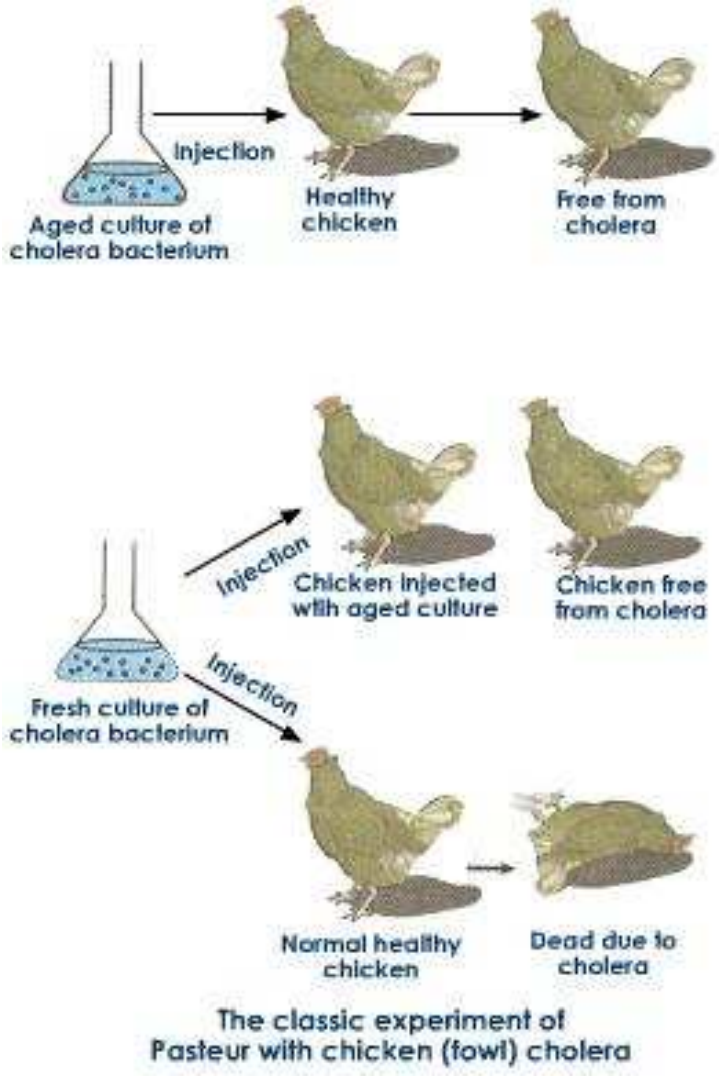
Mimic Natural Infection → **Recapitulate Natural Immunity**



Edward Jenner (1749-1823)

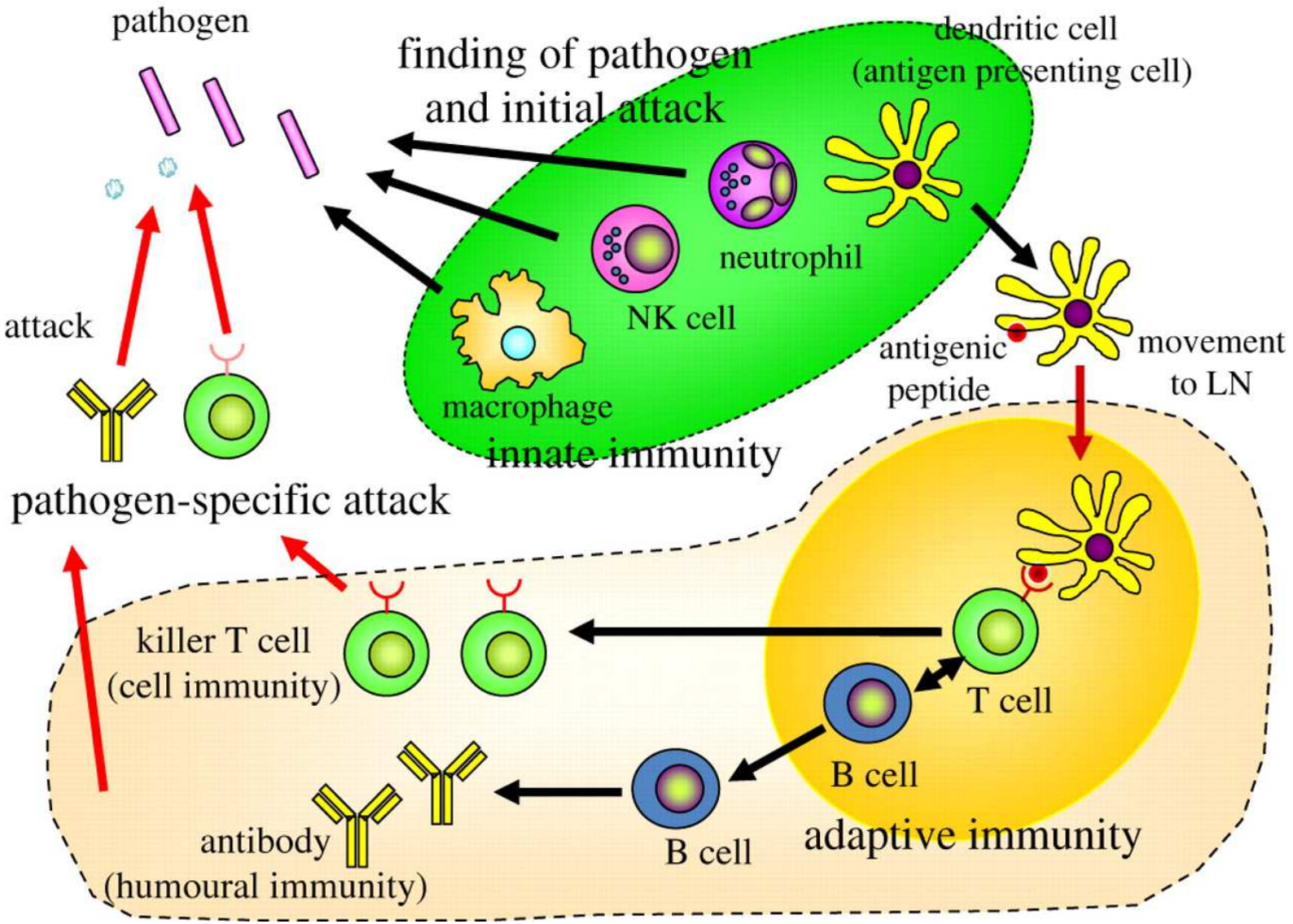
Isolate – Inactivate - Inject

Louis Pasteur (1811-1895)

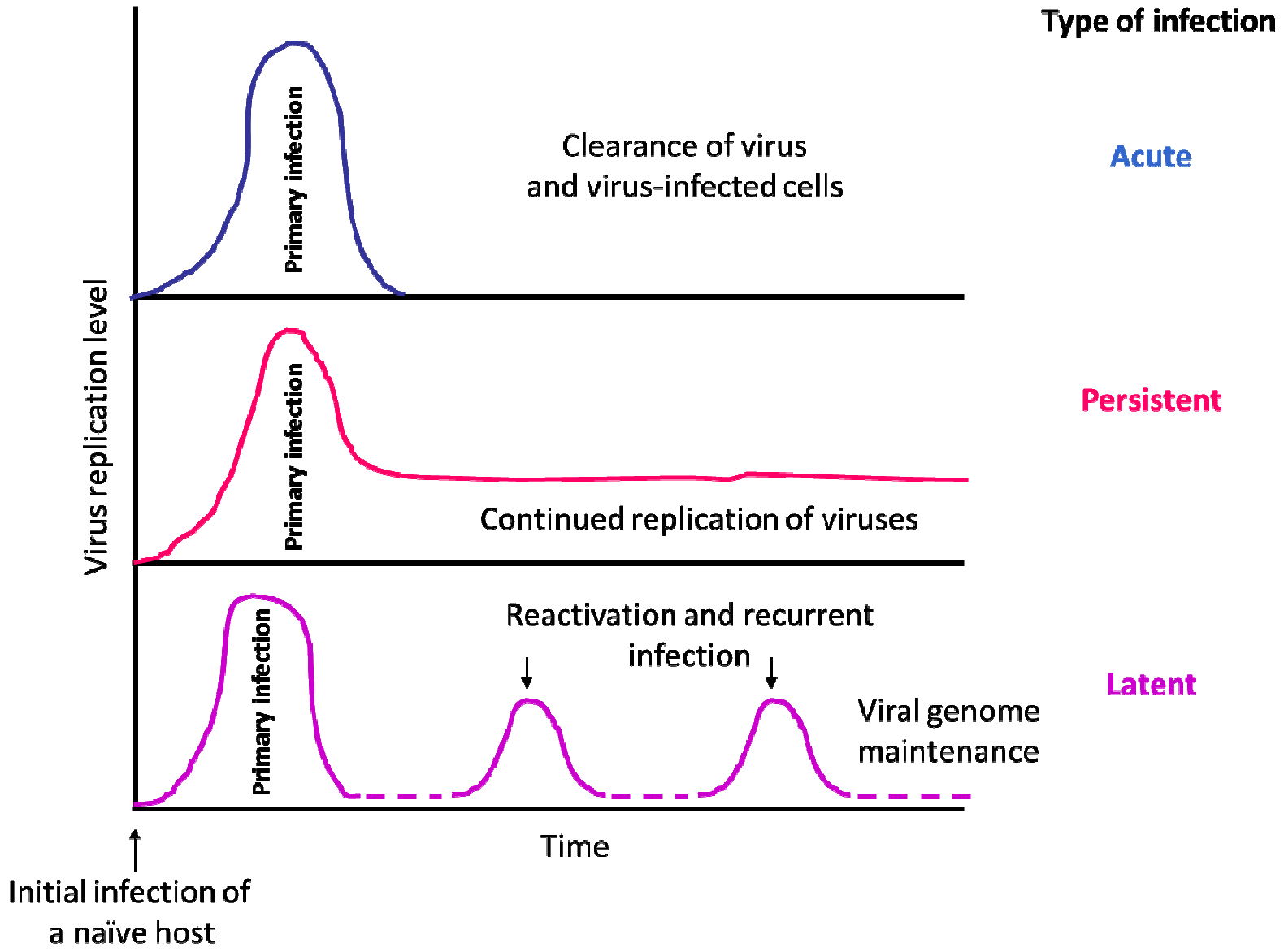


The classic experiment of Pasteur with chicken (fowl) cholera

Innate and Adaptive immunity: The Concept



Outcomes of virus infection can vary

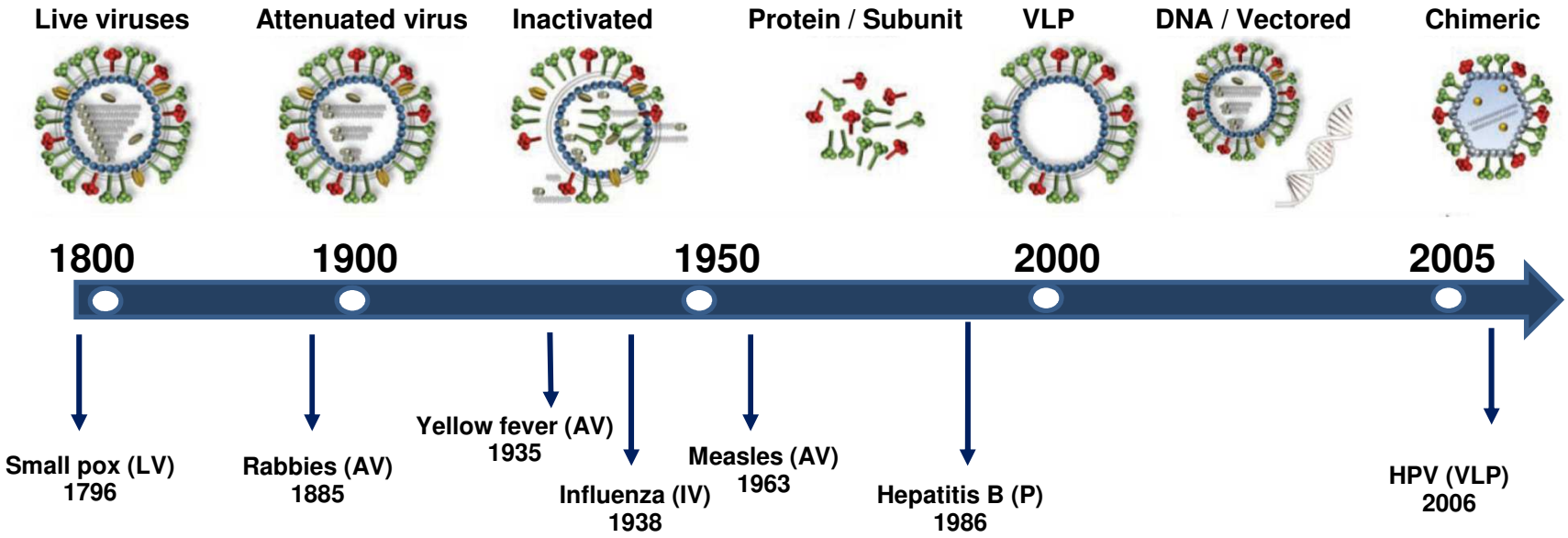


Class I Pathogen
Infects narrow age range
Host exhibits spontaneous recovery
Host generates long lasting protective immunity
Priming with wild-type or attenuated pathogen induces protection
Genetically stable with limited antigenic variation
Immune responses are directed to multiple epitopes
Ex: Measles, mumps, rubella, diphtheria, Canine distemper, rabies, poliovirus

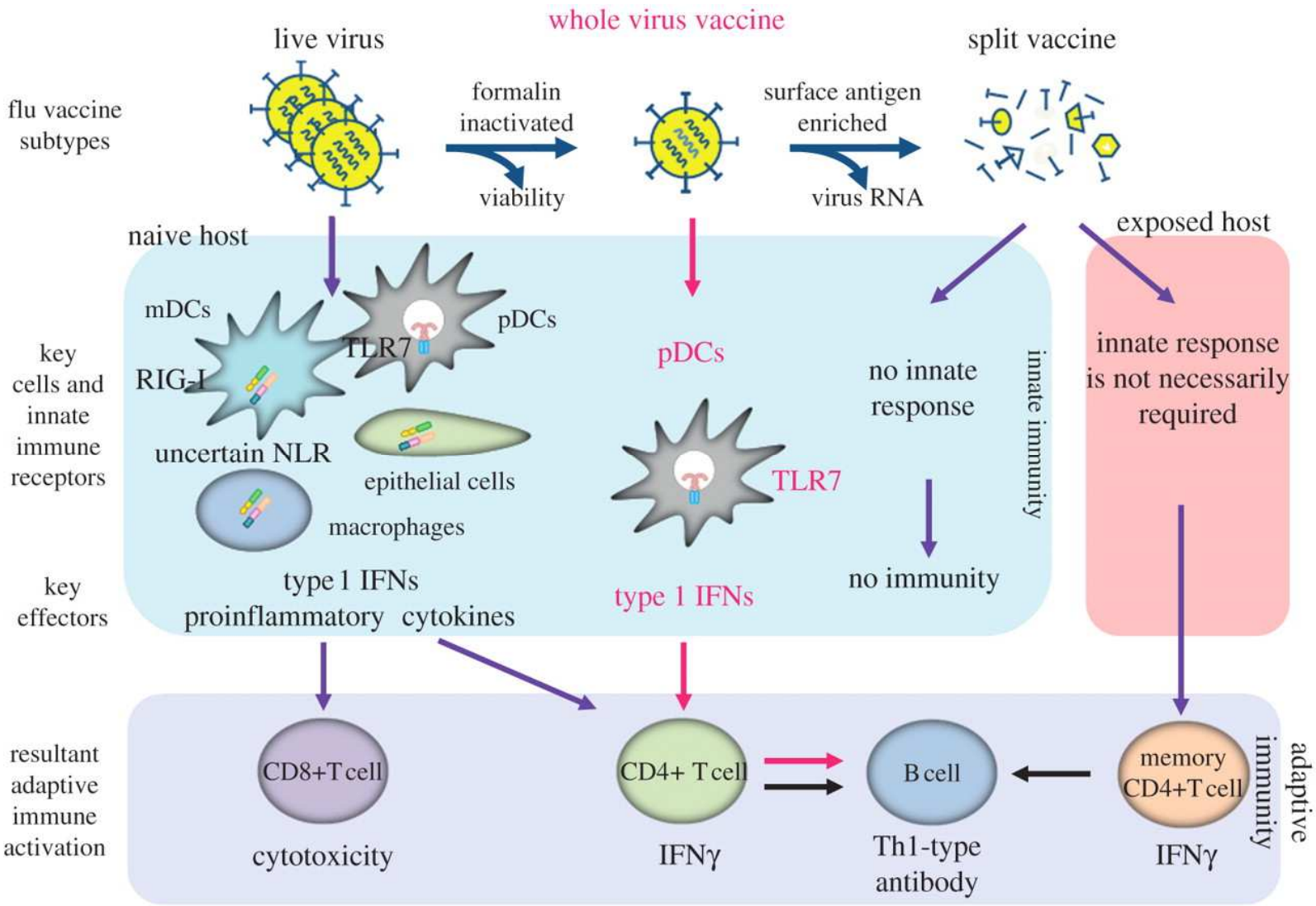
Technological milestones

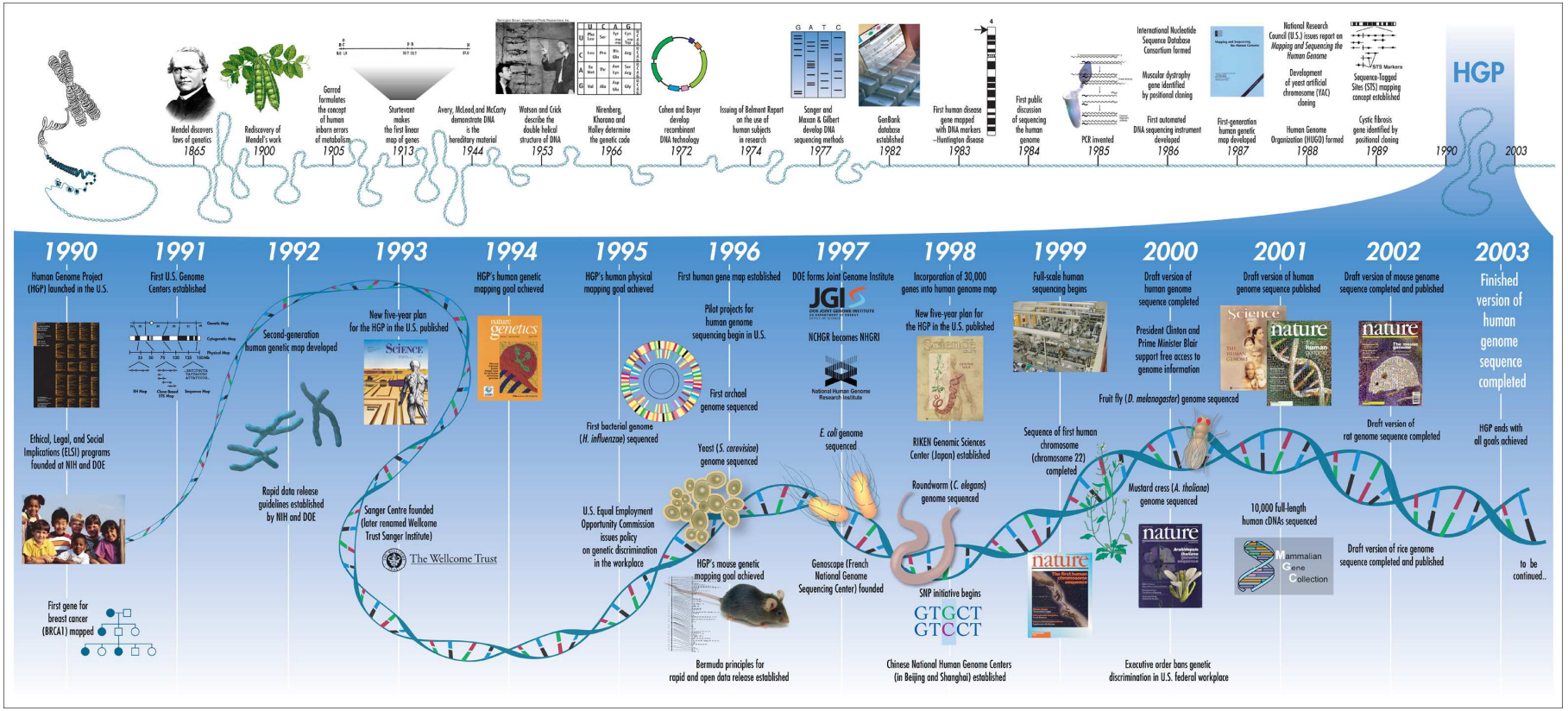
Experimental Sciences 18-19th Century Inoculation	Tissue Culture – 1930s Eggs, Animal cell culture	Recombinant DNA – 1980s Sequencing Cloning PCR Gene Delivery	Synthetic Biology – 2000s DNA and Peptide Synthesis

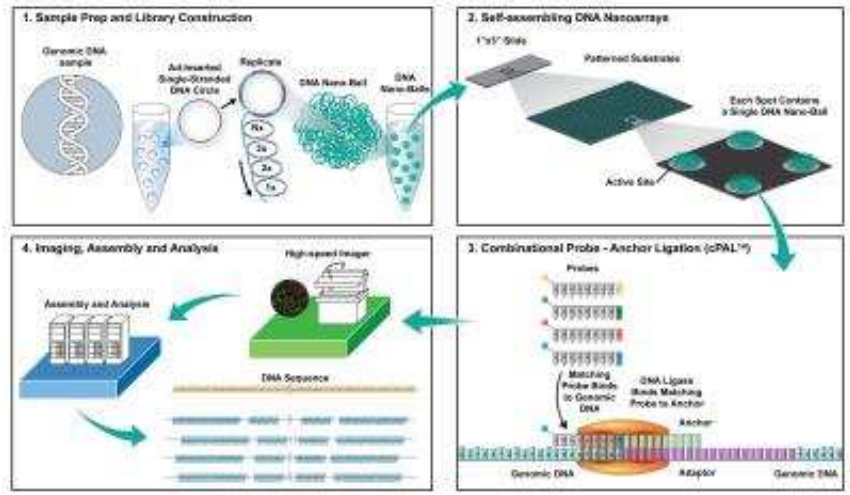
Vaccine types



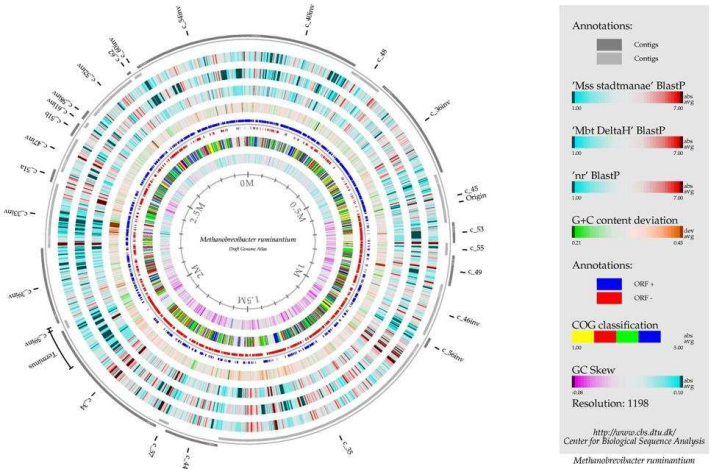
Each vaccine type has its pros and cons



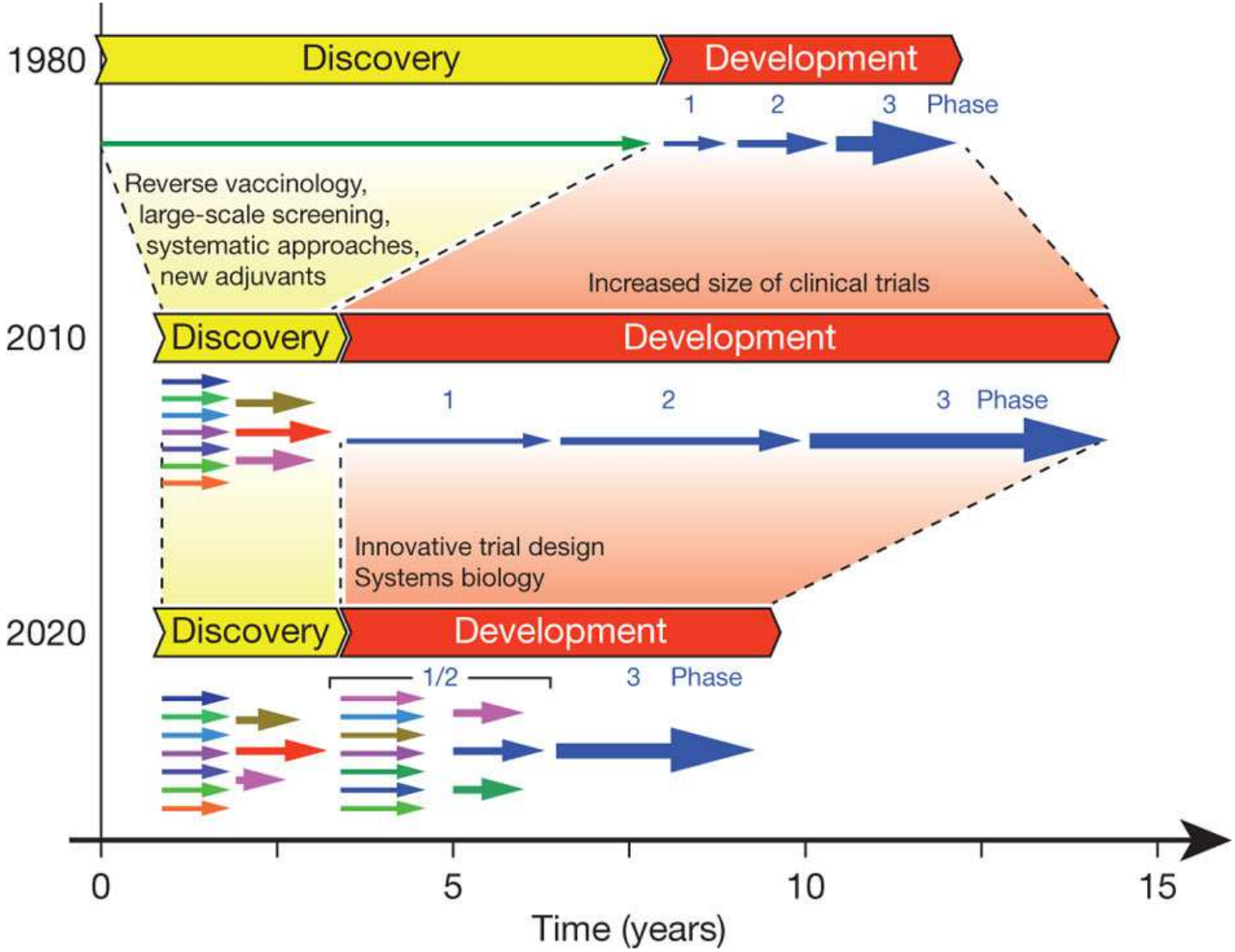




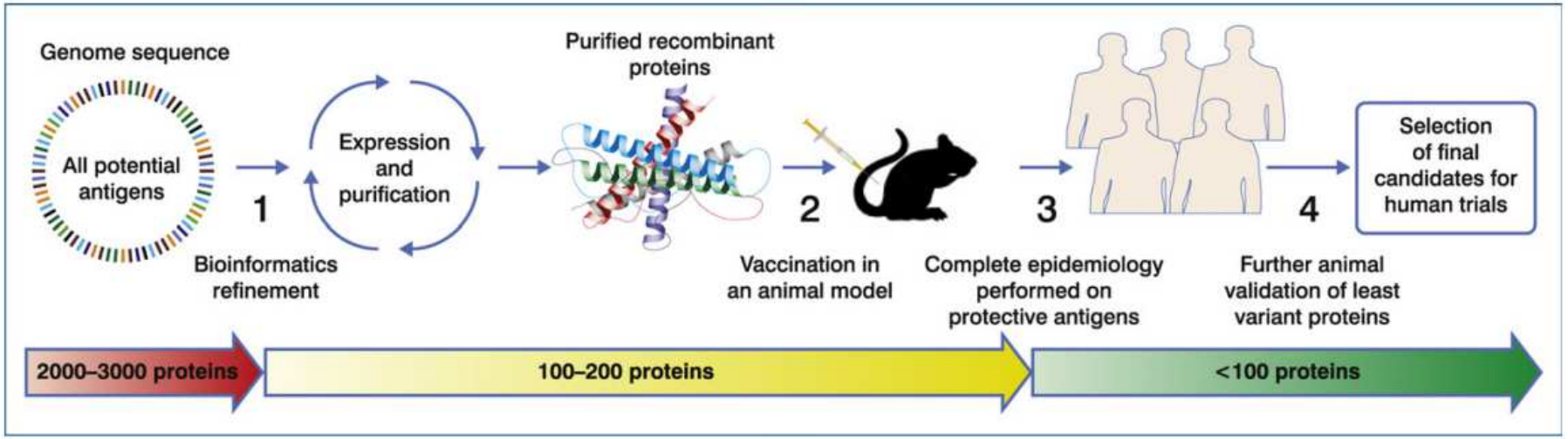
Complete Genomics' Sequencing Process

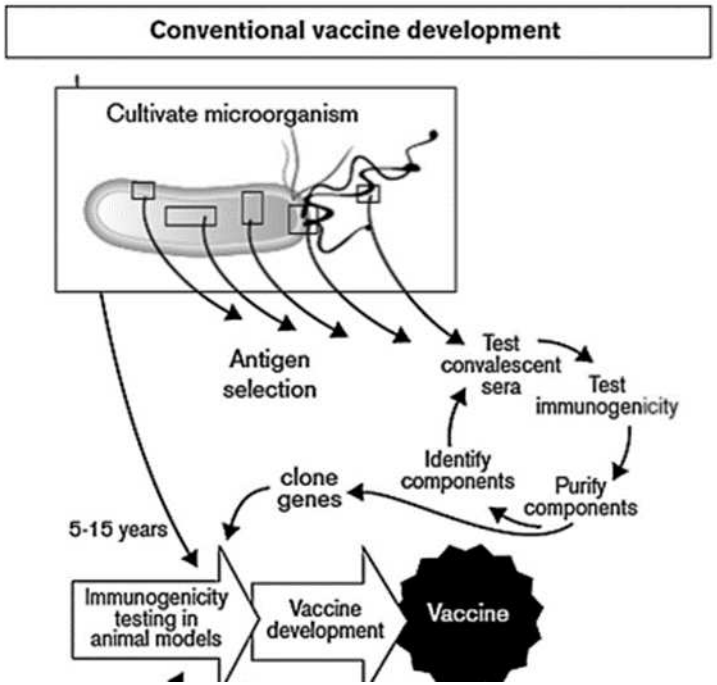


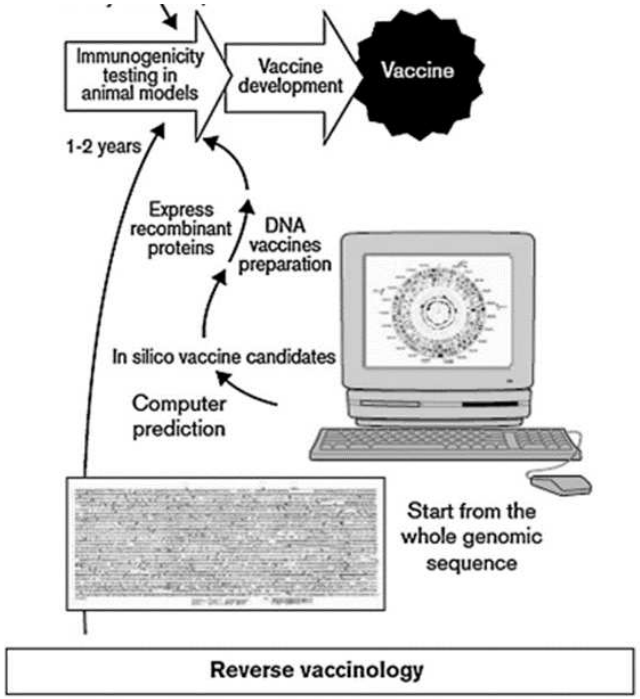
Evolution of vaccine development during the last 30 years



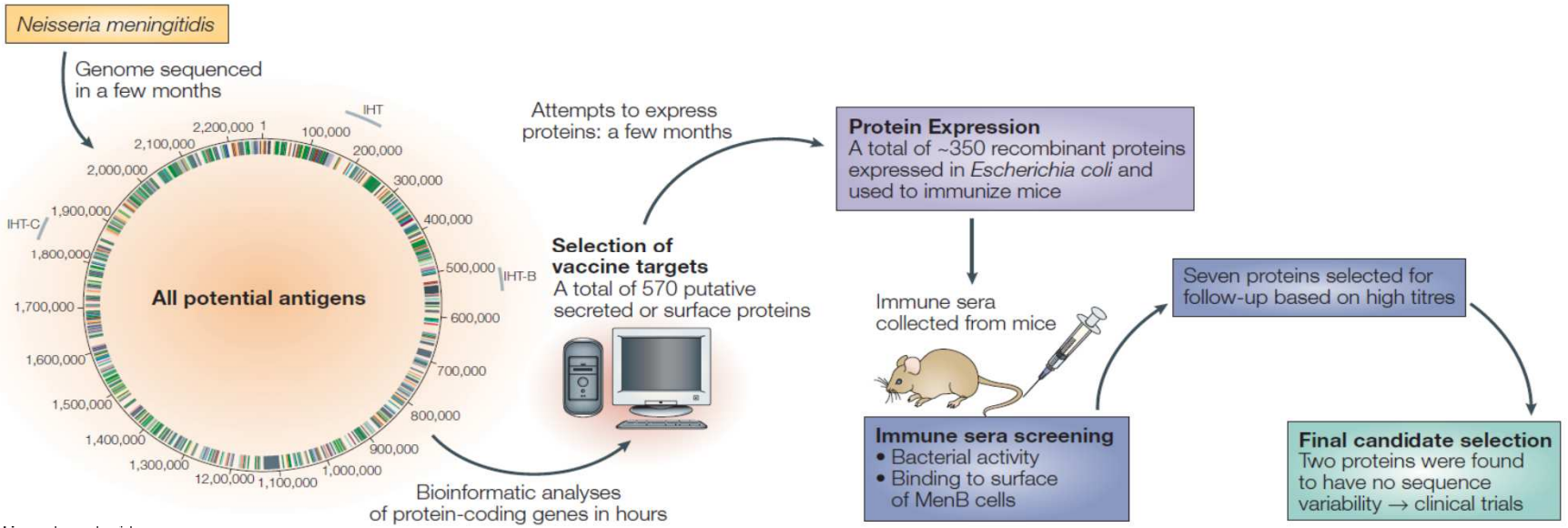
Reverse Vaccinology: The Concept

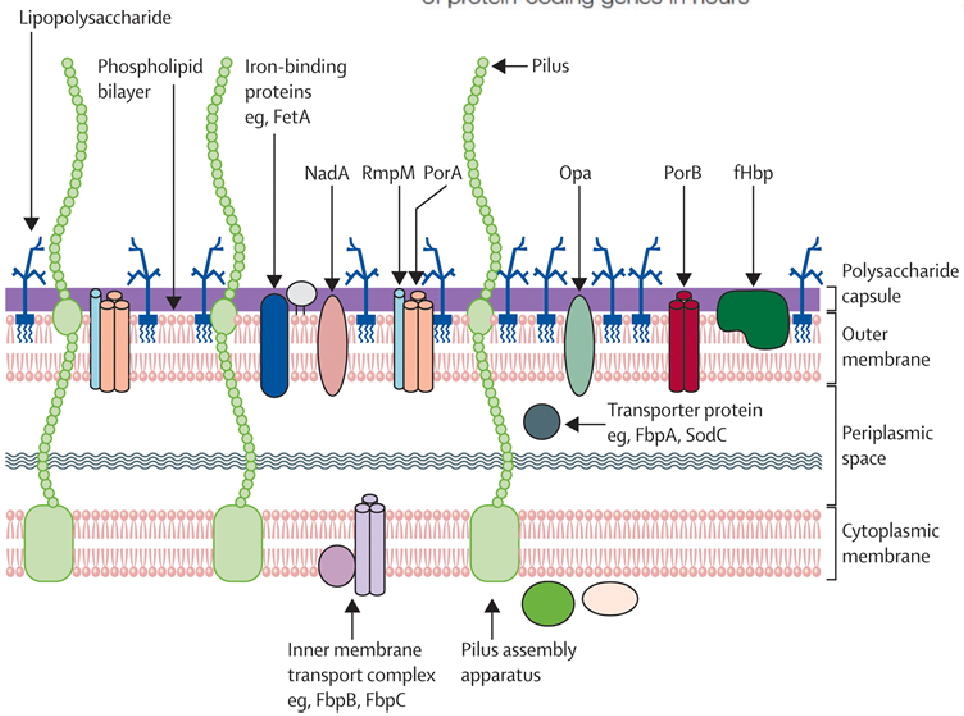


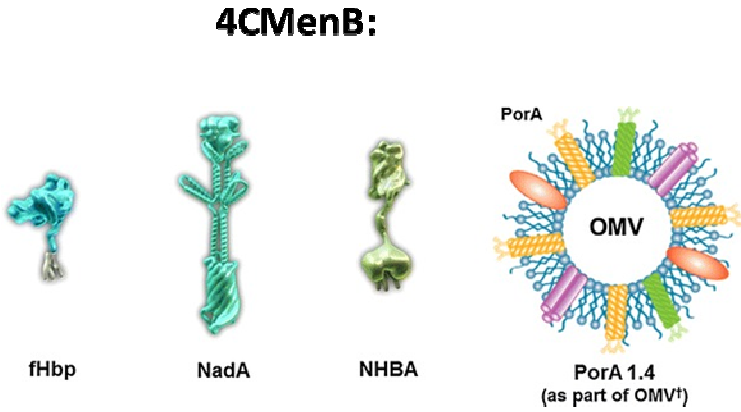




Reverse Vaccinology: The Application





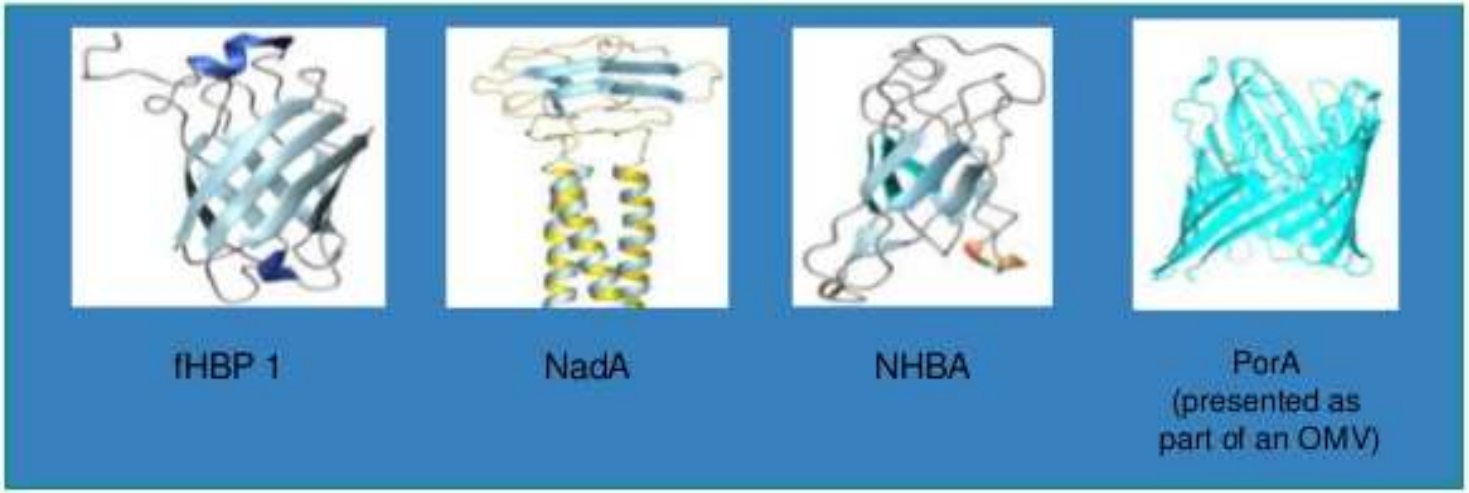


Public Health England

Novartis investigational MenB 4CMenB vaccine (Bexsero®)

- Bexsero (previously known as 4CMenB or rMenB+OMV) contains 4 main antigens.

- Three recombinant proteins discovered by genome mining/reverse vaccinology combined with OMV from the New Zealand outbreak strain (NZ 98/254).



http://www.inpharm.com/news/101223/novartis-meningococcal-vaccine-bexsero

Published March 28, 2016

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Perspective

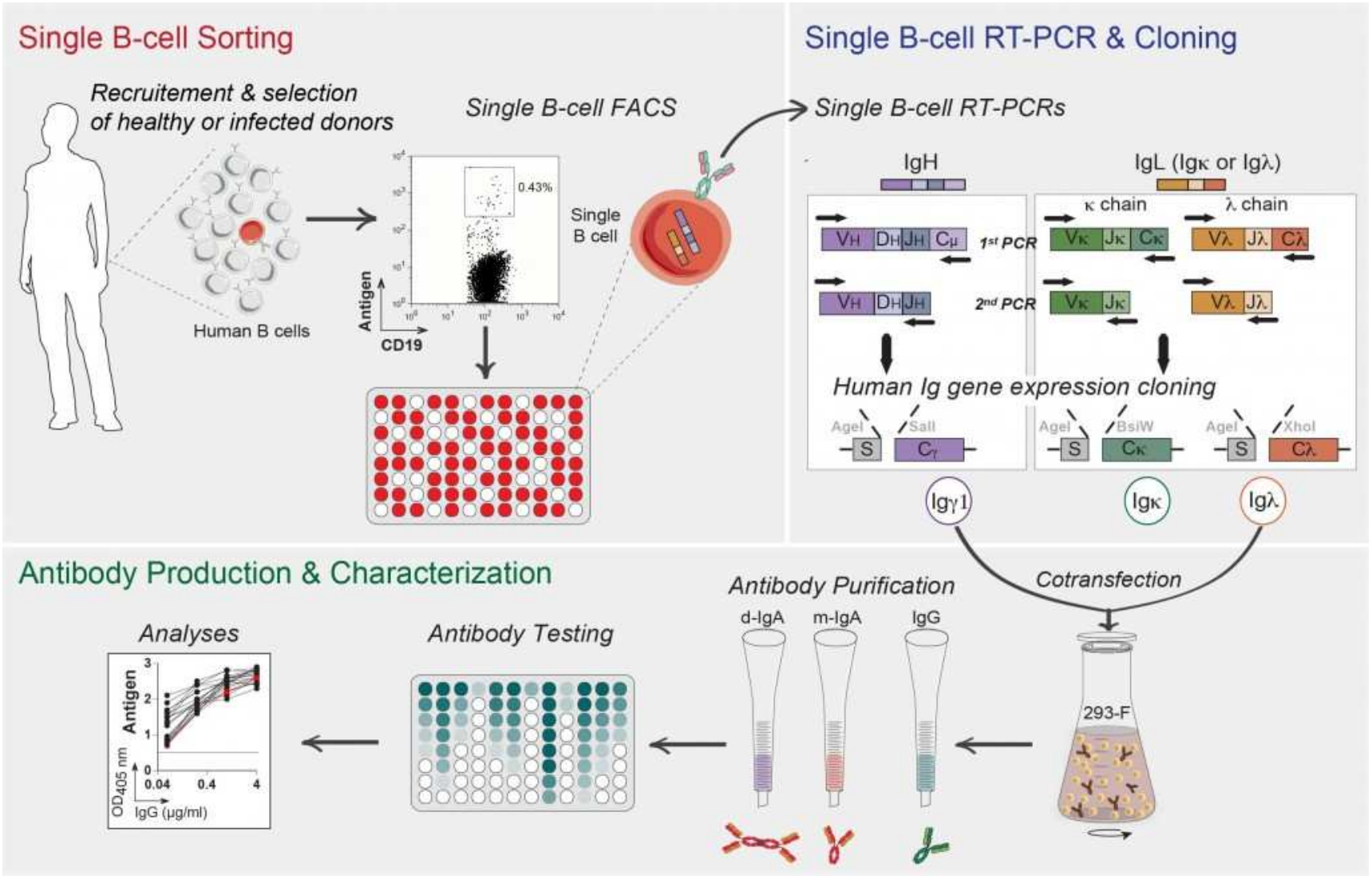
Reverse vaccinology 2.0: Human immunology instructs vaccine antigen design

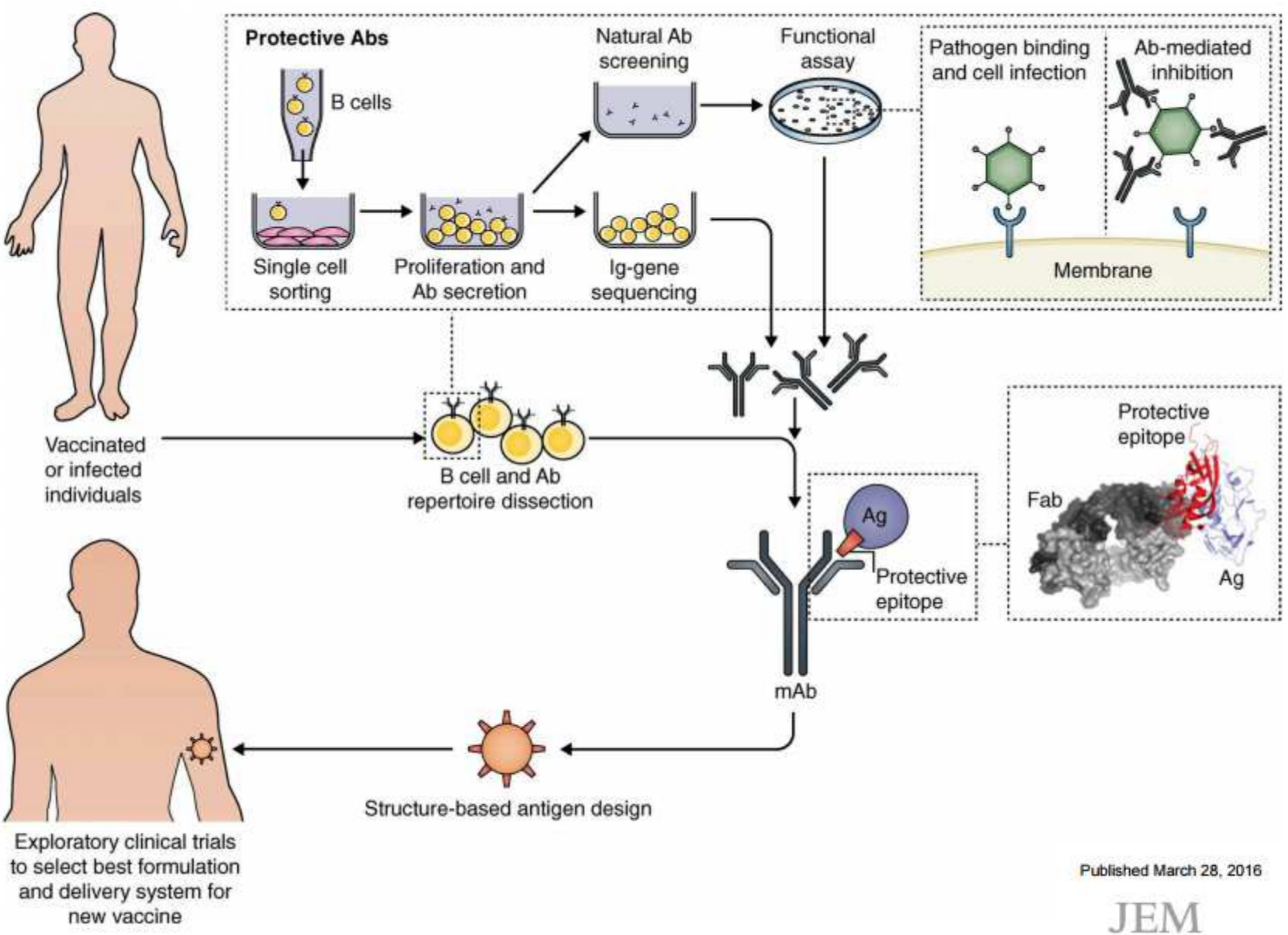
Rino Rappuoli, Matthew J. Bottomley, Ugo D'Oro, Oretta Finco, and Ennio De Gregorio

GlaxoSmithKline Vaccines S.r.l., 53100 Siena, Italy

Traditionally, vaccines have been developed by cultivating infectious agents and isolating the inactivated whole pathogen or some of its purified components. 20 years ago, reverse vaccinology enabled vaccine discovery and design based on information deriving from the sequence of microbial genomes rather than via the growth of pathogens. Today, the high throughput discovery of protective human antibodies, sequencing of the B cell repertoire, and the increasing structural characterization of protective antigens and epitopes provide the molecular and mechanistic understanding to drive the discovery of novel vaccines that were previously impossible. We are entering a "reverse vaccinology 2.0" era.

Accelerating Antibody Discovery by B cell cloning





Published March 28, 2016
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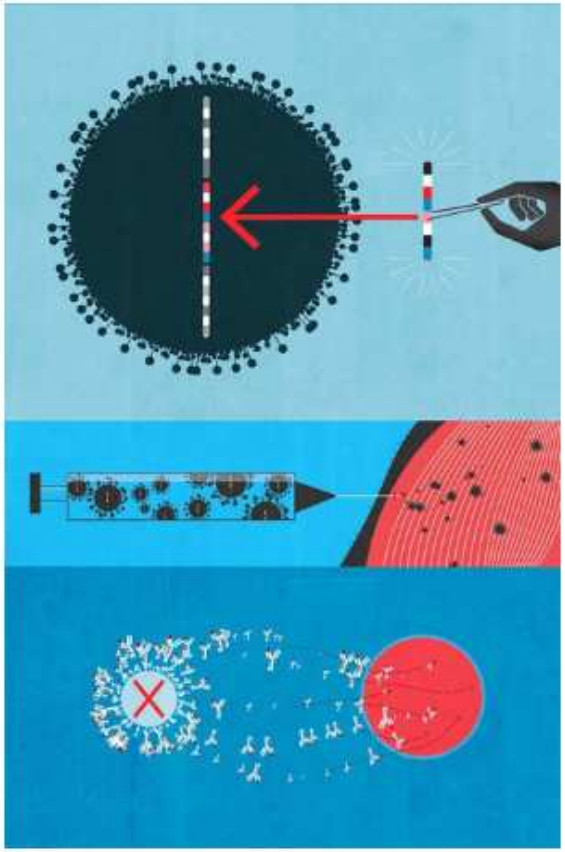
The New York Times

Protection Without a Vaccine

By CARL ZIMMER MARCH 9, 2015

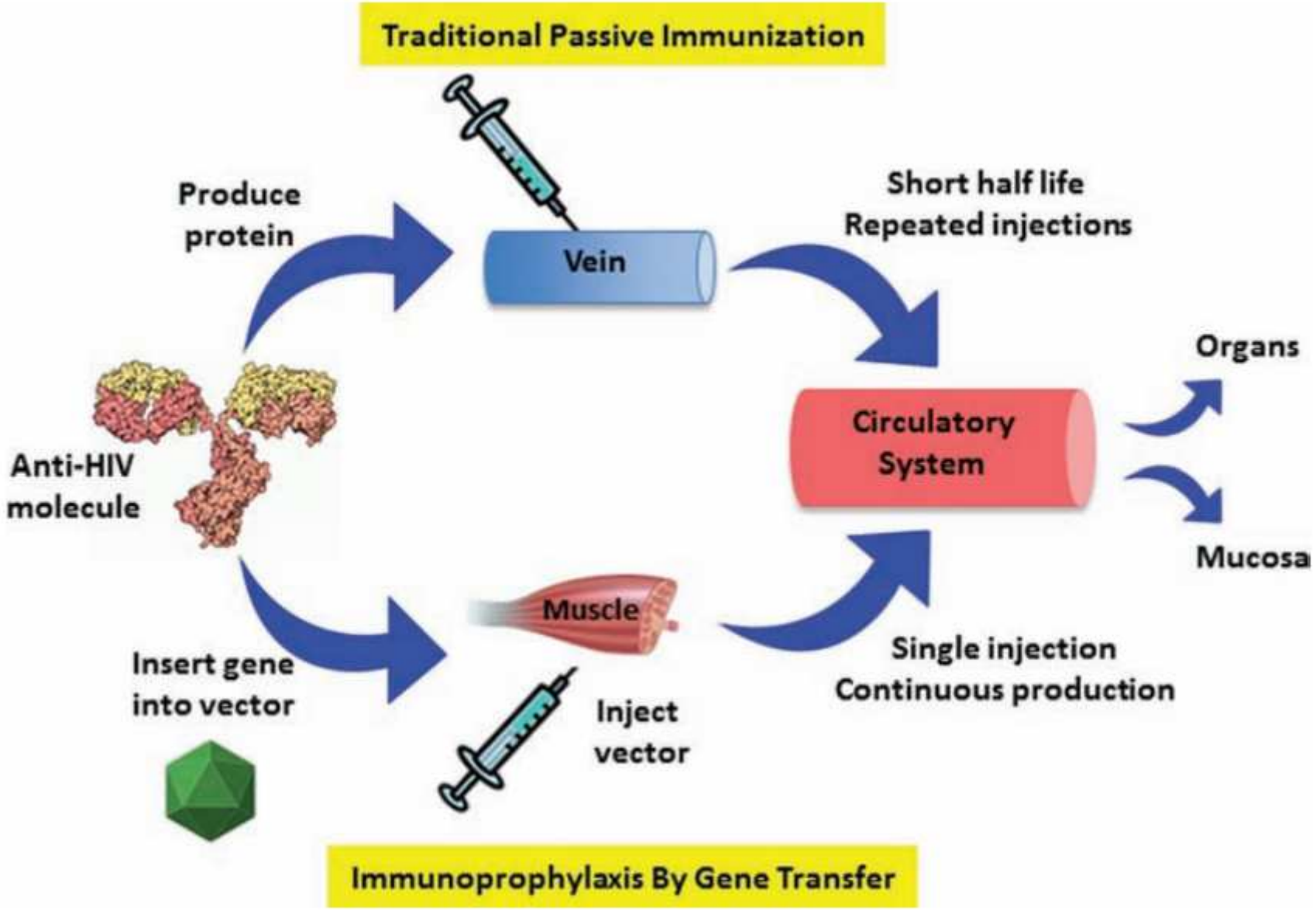


John Hersey

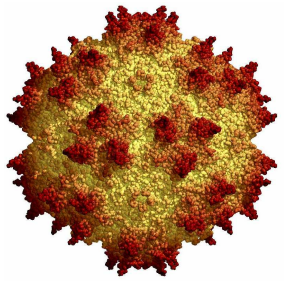
Last month, a team of scientists announced what could prove to be an enormous step forward in the fight against H.I.V.

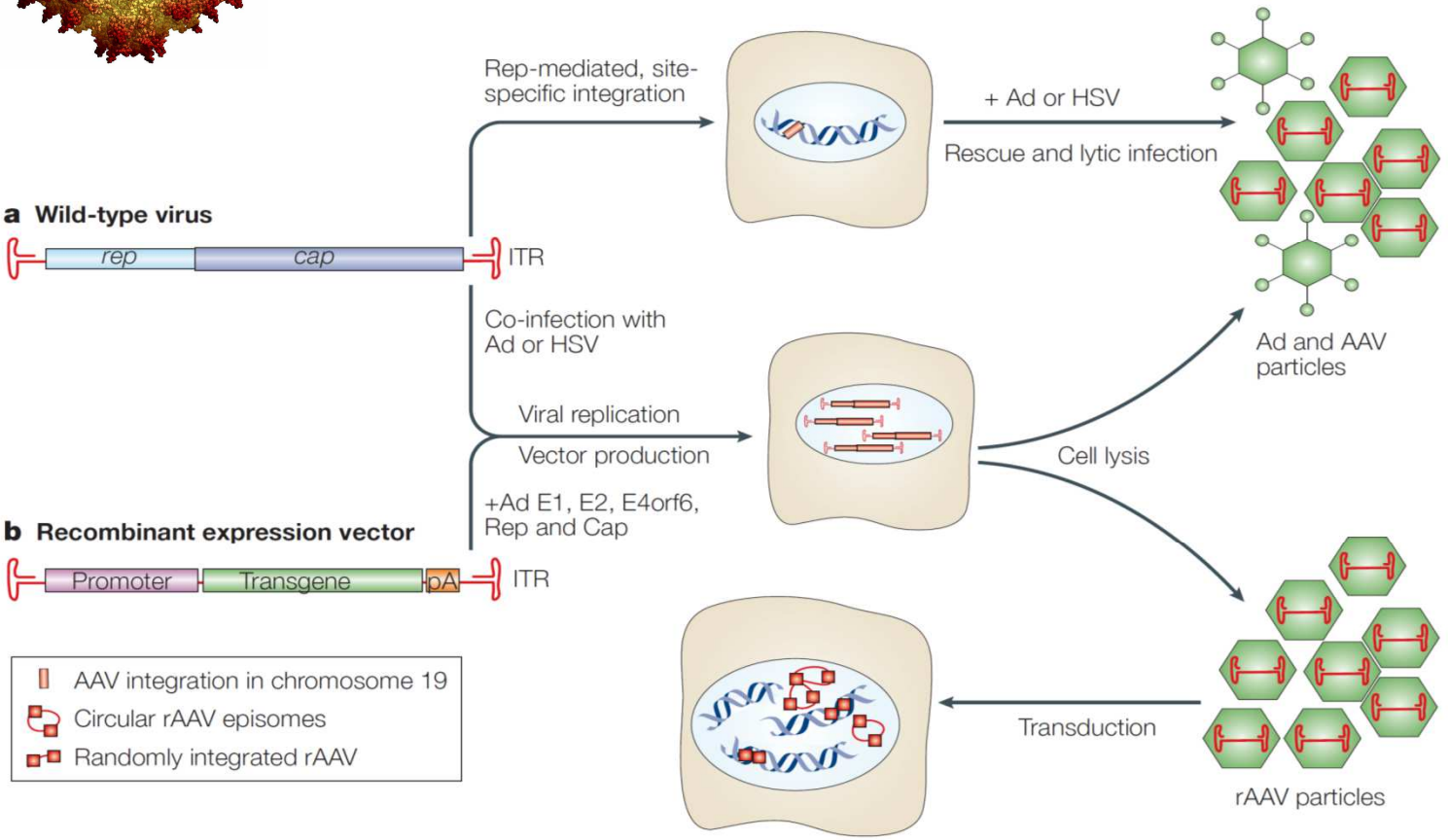
Scientists at Scripps Research Institute said they had developed an artificial antibody that, once in the blood, grabbed hold of the virus and inactivated it. The molecule can eliminate H.I.V. from infected monkeys and protect them from future infections.

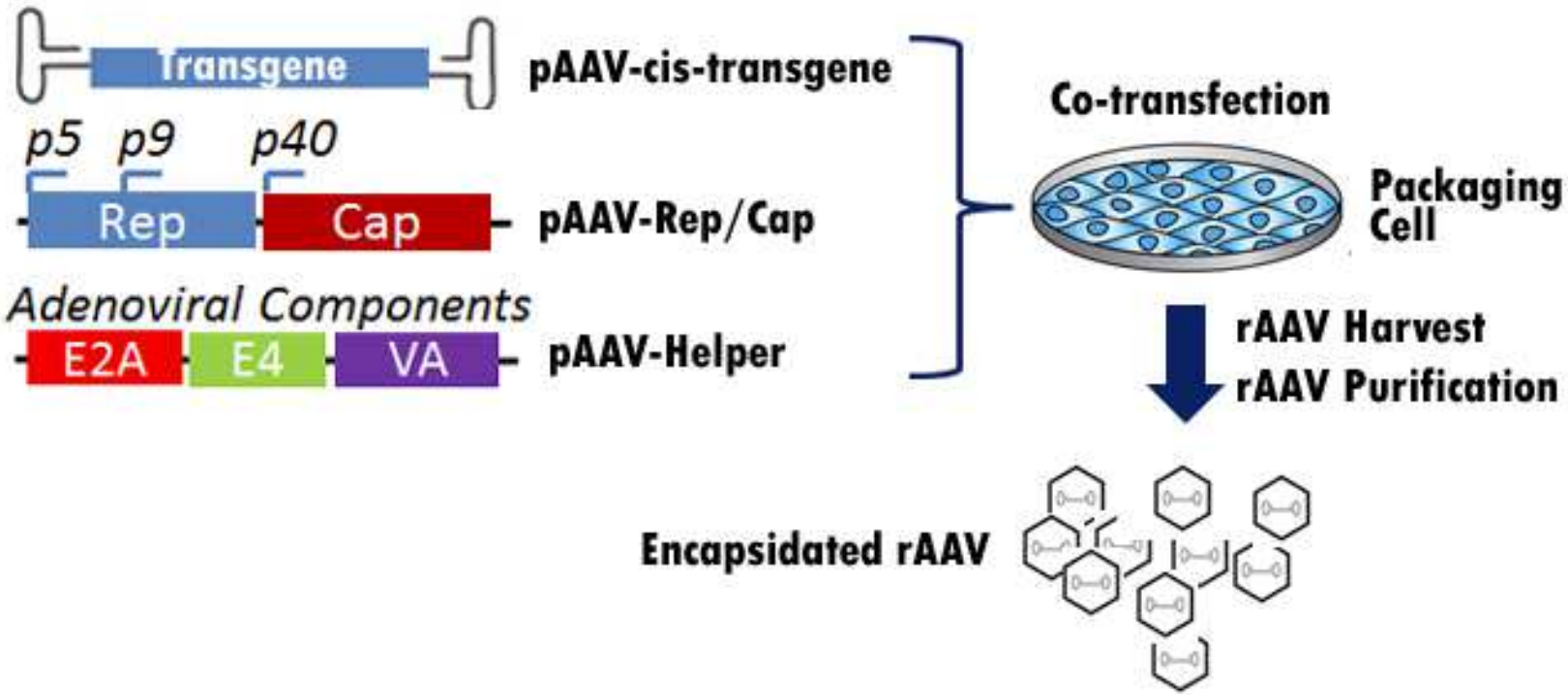
But this treatment is not a vaccine, not in any ordinary sense. By delivering synthetic genes into the muscles of the monkeys, the scientists are essentially re-engineering the animals to resist disease. Researchers are testing this novel approach not just against H.I.V., but also Ebola, malaria, influenza and hepatitis.


Traditional Passive Immunization
Produce protein
Vein
Short half life
Repeated injections
Organs
Circulatory System
Mucosa
Anti-HIV molecule
Muscle
Insert gene into vector
Inject vector
Single injection
Continuous production
Immunoprophylaxis By Gene Transfer

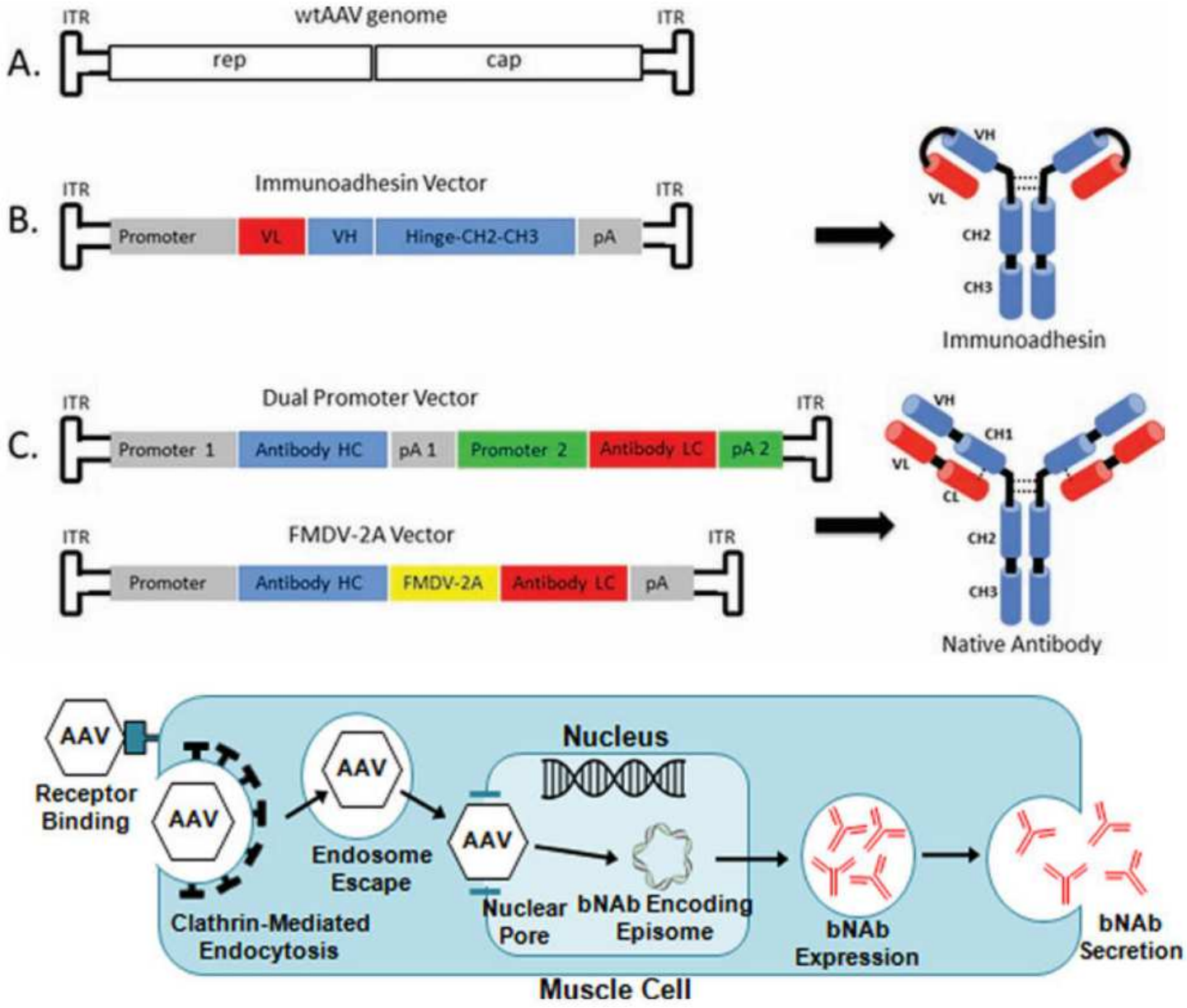
rAVV-based Technology






Transgene
pAAV-cis-transgene
p5
p9
p40
Rep
Cap
pAAV-Rep/Cap
Adenoviral Components
E2A
E4
VA
pAAV-Helper
Co-transfection
Packaging Cell
rAAV Harvest
rAAV Purification
Encapsidated rAAV

Engineering rAAV to deliver Nab *in vivo*



Generation of Neutralizing Activity against Human Immunodeficiency Virus Type 1 in Serum by Antibody Gene Transfer

Anne D. Lewis,[1] Ruju Chen,[1] David C. Montefiori,[2] Philip R. Johnson,[1,3,4]* and K. Reed Clark[1,3,4]†

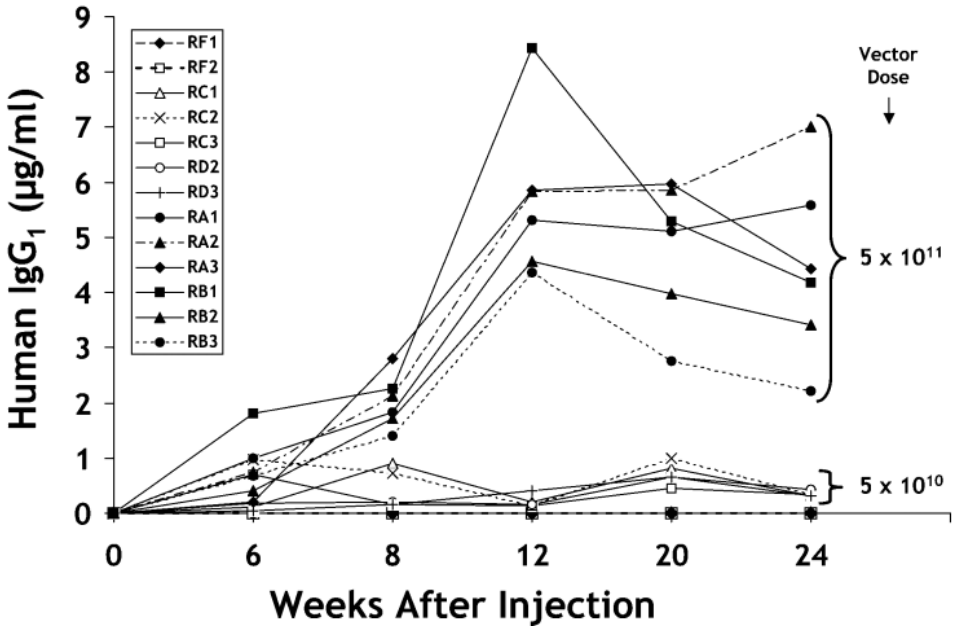
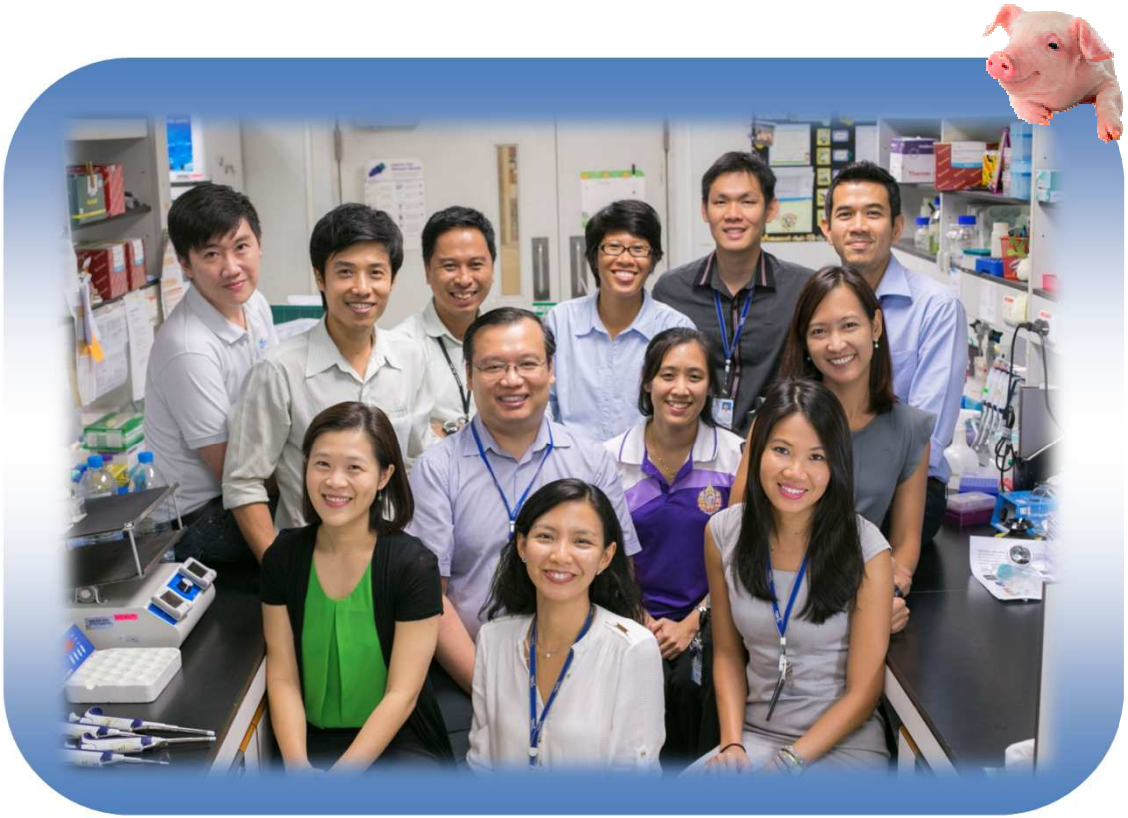


TABLE 4. Persistence of vector DNA in mouse muscle

Vector (dose)[a]	Mouse	Avg no. of genome copies/nucleus[b]
PBS	RF3	0.003
	RF4	0.012
rAAV/IgG1b12 (5×10^{10})	RC1	9.0
	RC2	5.5
	RC3	0.5
	RD2	1.2
	RD3	4.5
rAAV/IgG1b12 (5×10^{11})	RA1	42.5
	RA2	3.2
	RA3	20.0
	RB1	27.1
	RB2	0.4
	RB3	19.3

[a] Dose is measured as the DRP (see Materials and Methods).
[b] Values represent the average number of rAAV genomes per nucleus observed in the quadriceps muscles after rAAV injection. A total of 60 ng of muscle DNA (10,000 nucleus equivalents) was analyzed by quantitative Taqman PCR by using the CMV primer-probe set (see Materials and Methods). All samples were harvested 24 weeks after injection.



Virology and Cell Technology Laboratory

National Center for Genetic Engineering and Biotechnology (BIOTEC), NSTDA

Email: anan.jon@biotec.or.th

BIOTEC
a member of NSTDA

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NATIONAL CENTER FOR GENETIC ENGINEERING AND BIOTECHNOLOGY

Thank you

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