Imperial College London

“Emerging technologies for vaccines and biotherapeutics"

Robin Shattock

10th APS International PharmSci Conference

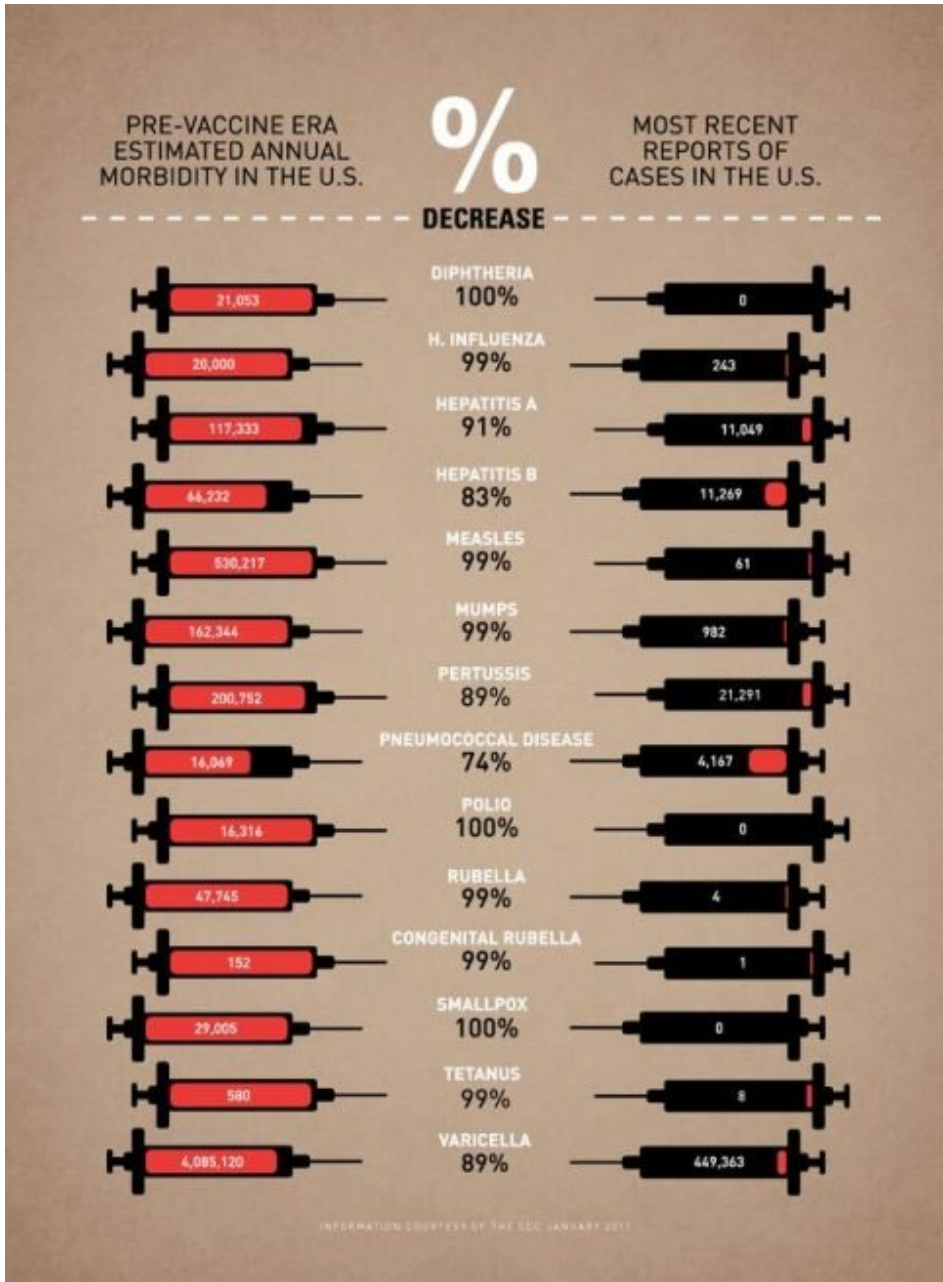
Greenwich 2019

Vaccination, one of the most effective medical intervention ever introduced

- So far prevented >3.0 billion disease cases
  >500 million deaths
- 2011-2020 vaccines will prevent
  - 25 million deaths
    - 2.5 million/year
    - 7000/day
    - 300/hour
    - 5/min

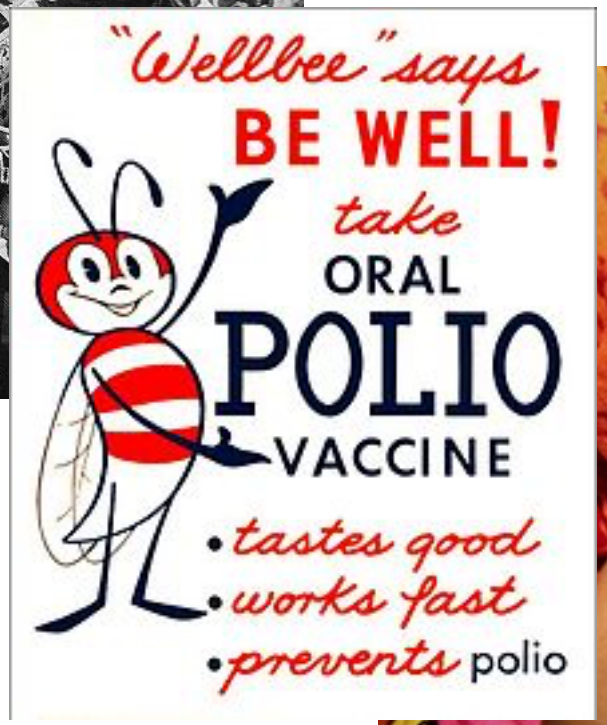
Yet most vaccines for Low and middle incomes are targeted at <$1

WHO Global Action Plan
http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/index.html)



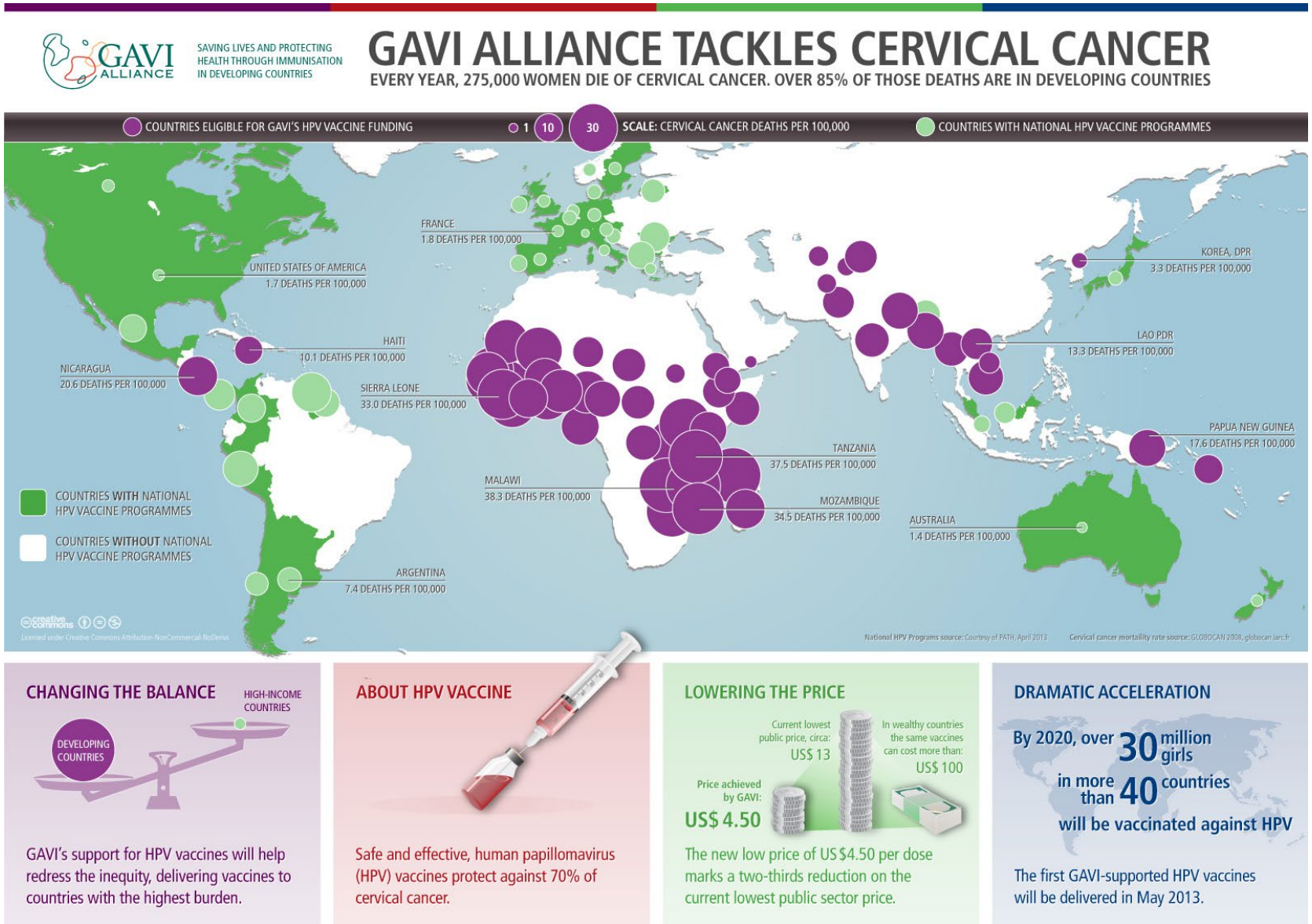
Smallpox, one of the deadliest and most contagious diseases known to humankind

Smallpox killed over half a billion people in the 20th century alone — three times the number of deaths from all of the century's wars combined.



Soon to be eliminated?

Could be eliminated?

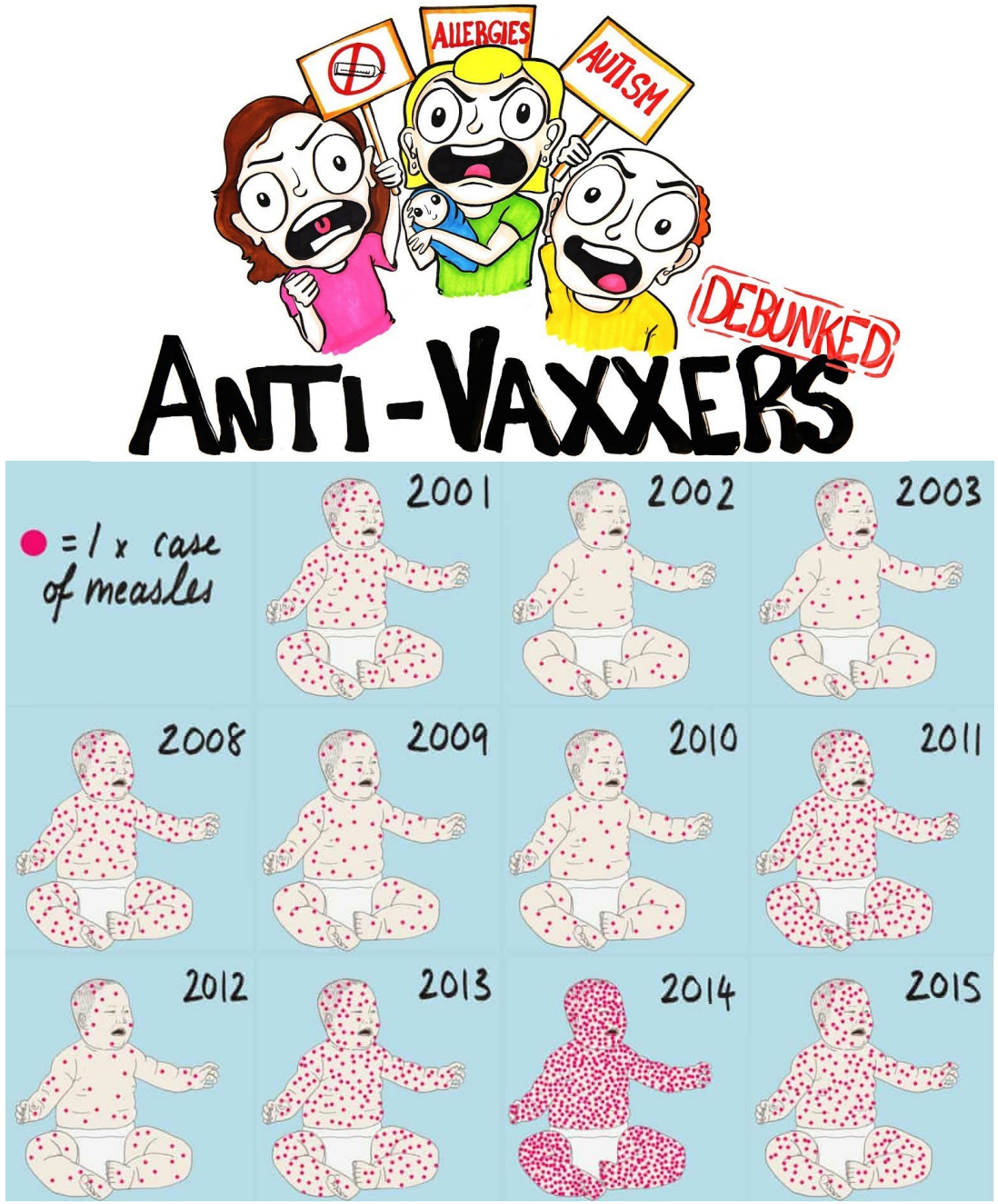


These are the 10 biggest threats to global health in 2019

Based on rankings from the World Health Organization

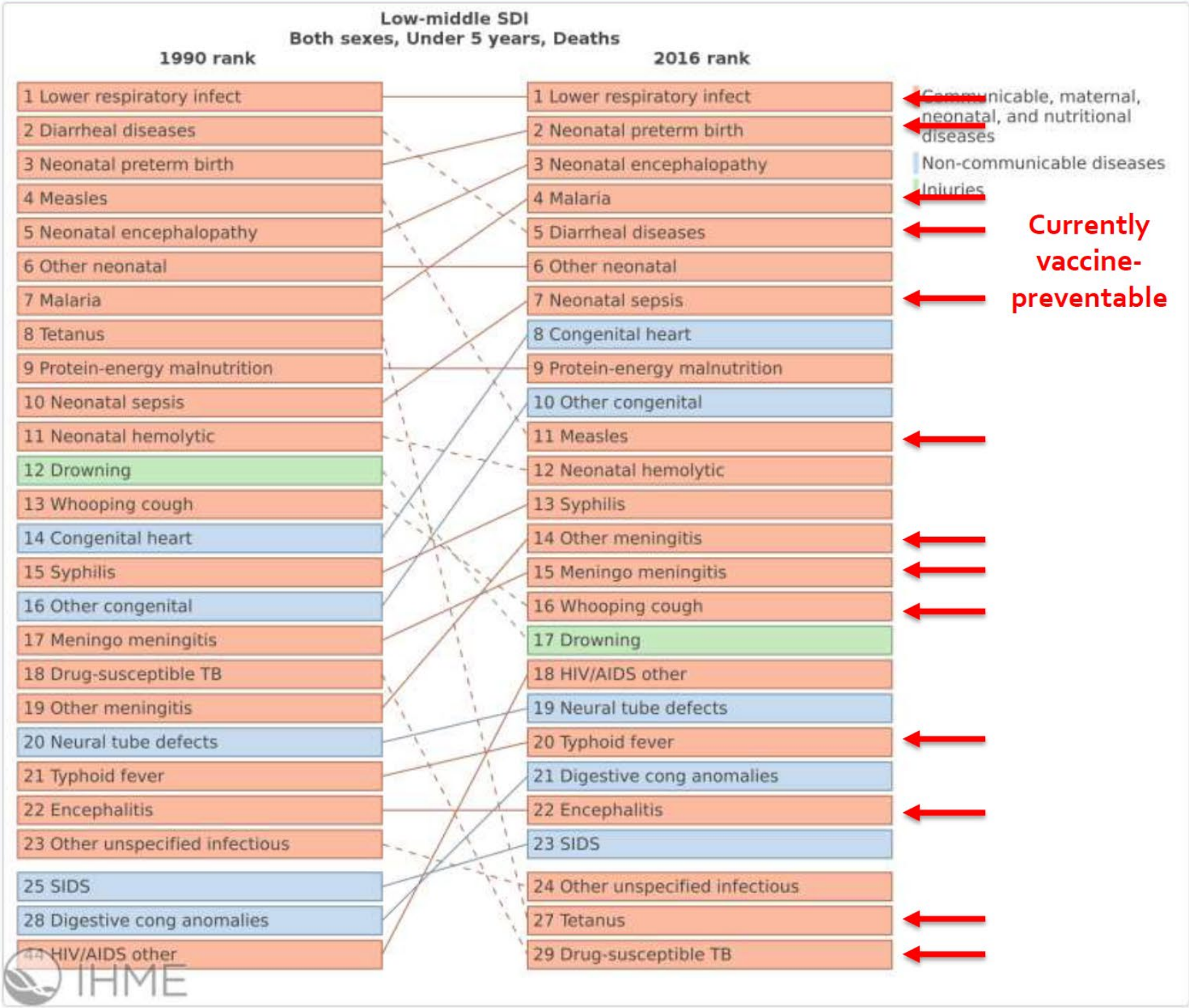
1. Air pollution and climate change
2. Noncommunicable diseases
3. Global influenza pandemic
4. Fragile and vulnerable settings
5. Antimicrobial resistance
6. Ebola and other high-threat pathogens
7. Weak primary healthcare
8. Vaccine hesitancy
9. Dengue fever
10. HIV

Source: World Health Organization



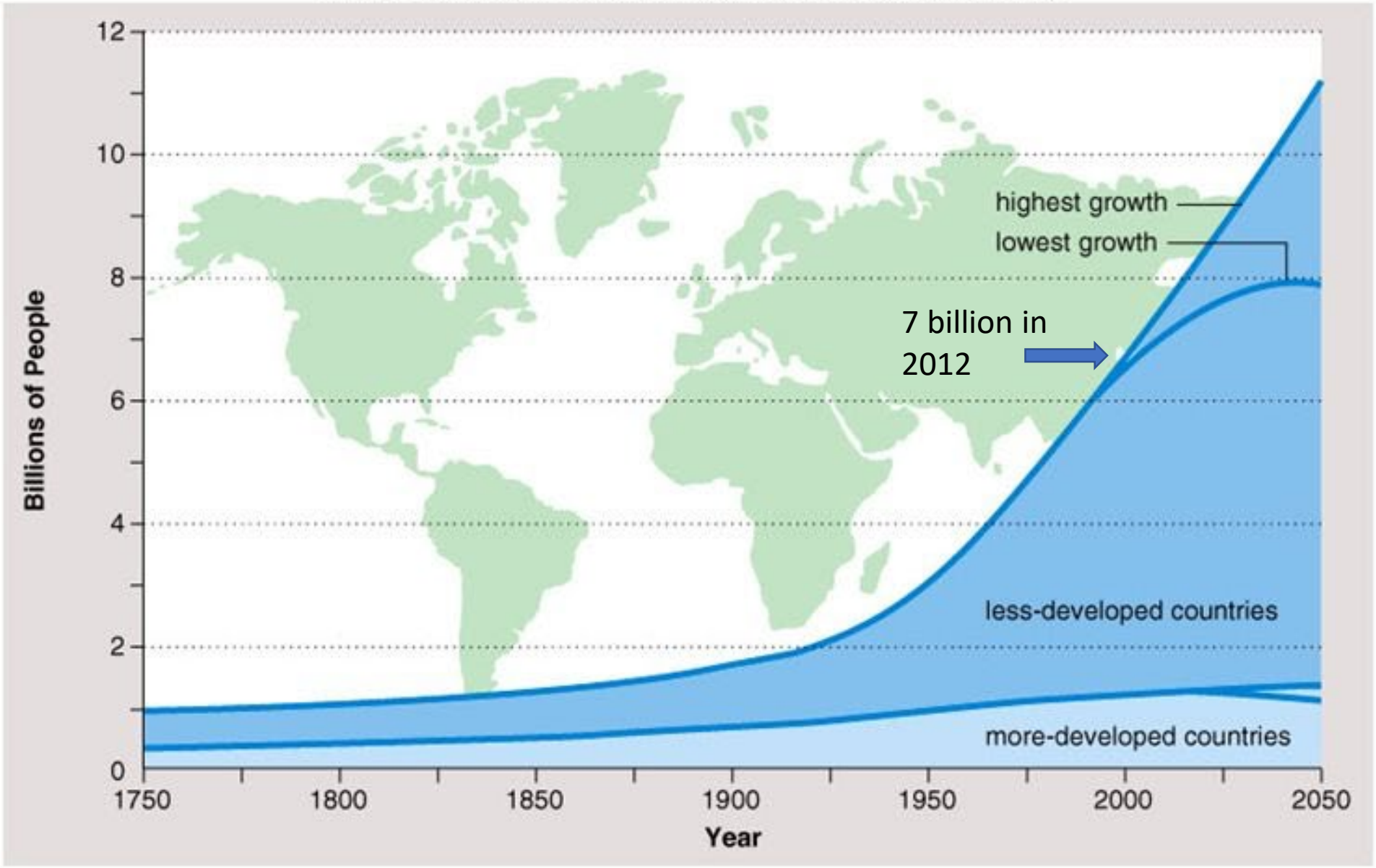
Under 5 deaths 1990 to 2016

Low-middle SDI countries (incl India)



- Socio-demographic Index (SDI) is a function of **development** based on income per capita, average educational attainment, and fertility rates of all areas in the GBD study.

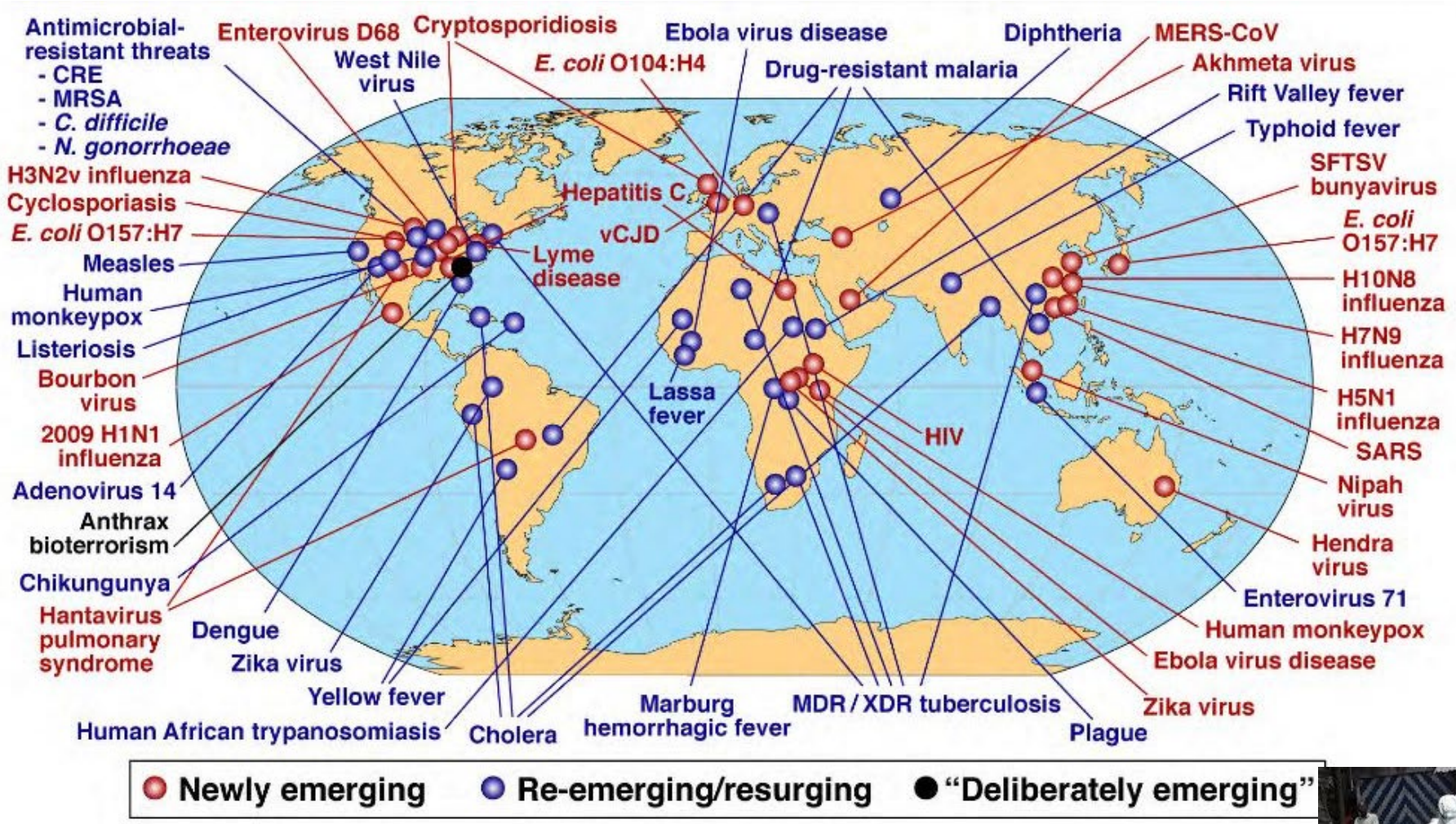
Responding to developing world vaccine needs

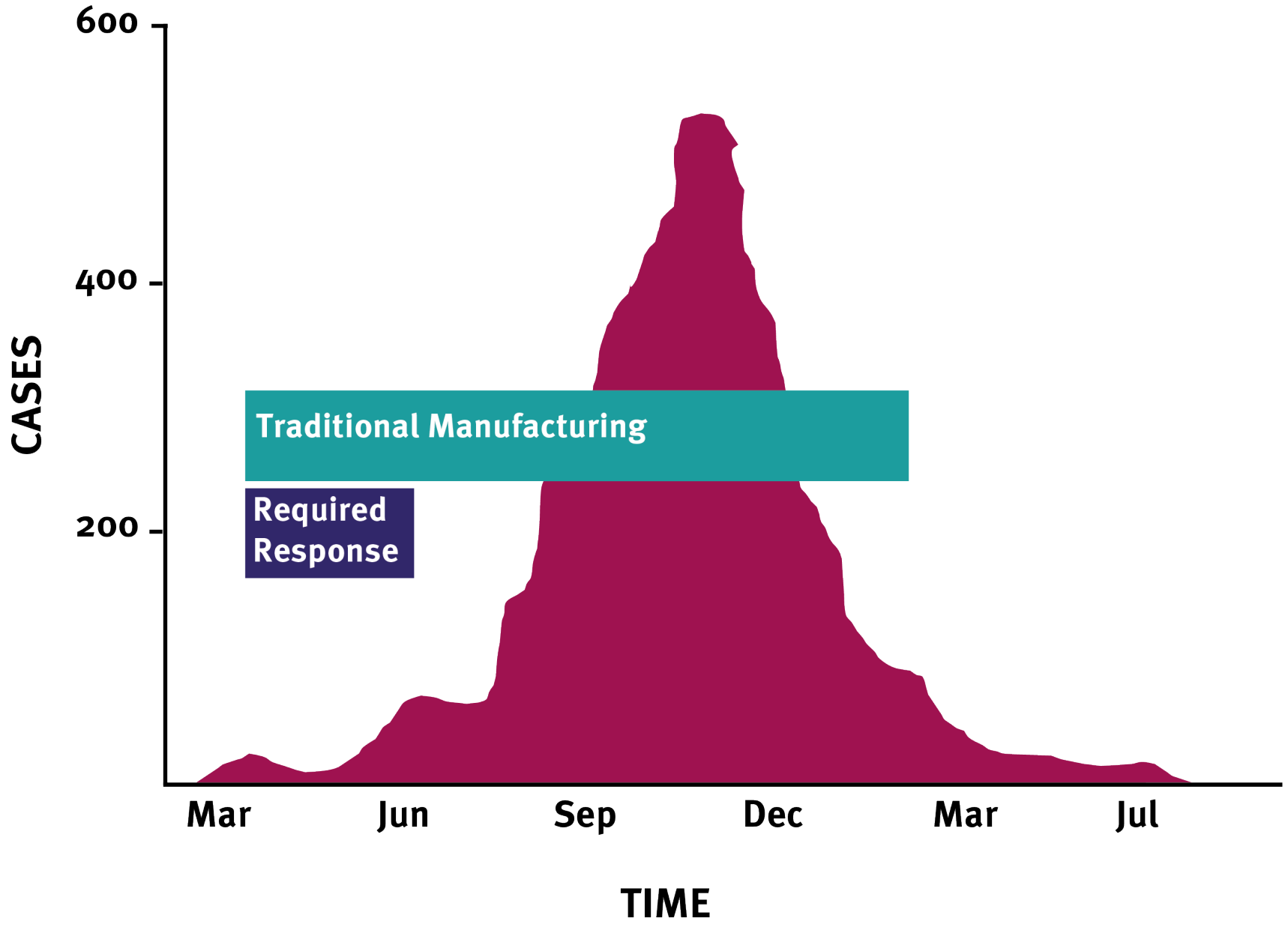


Most EPI vaccines cost less than $1 per dose

- No margins for reinvestment in R&D required for development of new vaccines

Responsive to the treat of emerging and re-emerging infections




600
400
200
CASES
Traditional Manufacturing
Required Response
Mar
Jun
Sep
Dec
Mar
Jul
TIME


HANIFA TOWERS
PRUDENTIAL
Okusoma kwomwanawo okuteeseteese?
ROYAL PLAZA
MAJESTIC PLAZA
STANDARD


$330 billion

Emerging innovative technologies

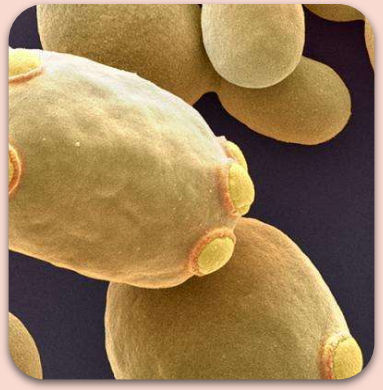
RNA

Rapid

Low cost

Synthetic and cell-free

Immature



Yeast

Easy scale-up and high yield

Low risk of contamination

Human glycosylation challenging

Baculovirus

Thermostable

Rapid

Feasible scale-up

Technologically complex

GMMA

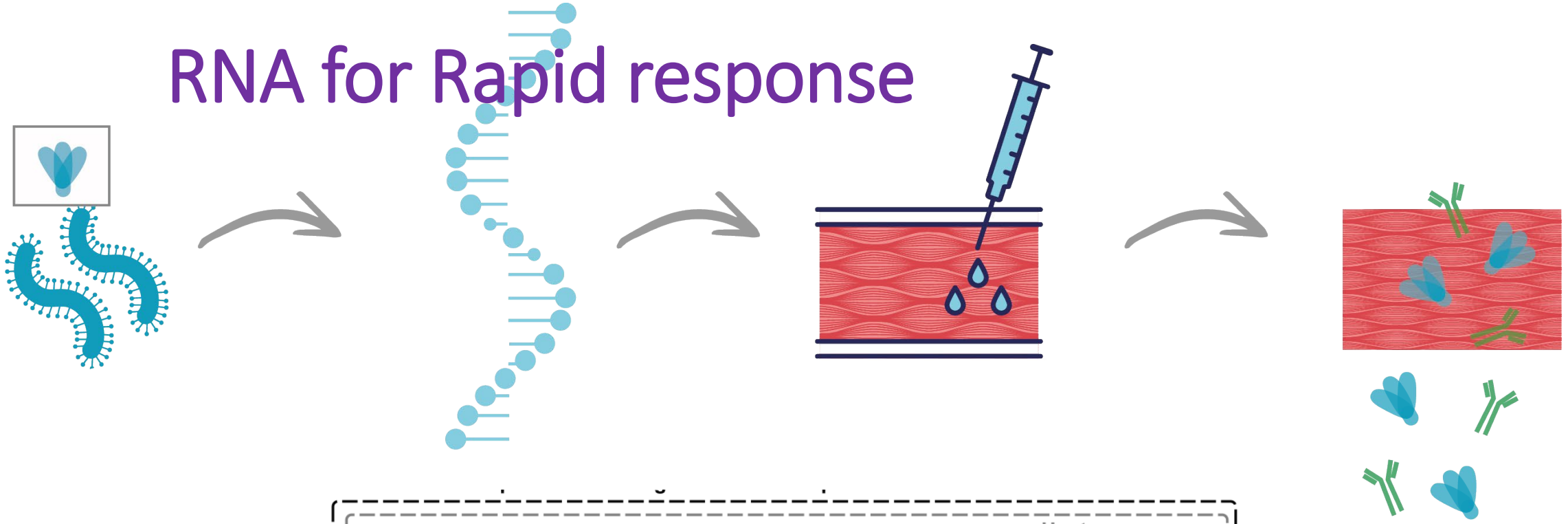
Easy scale-up

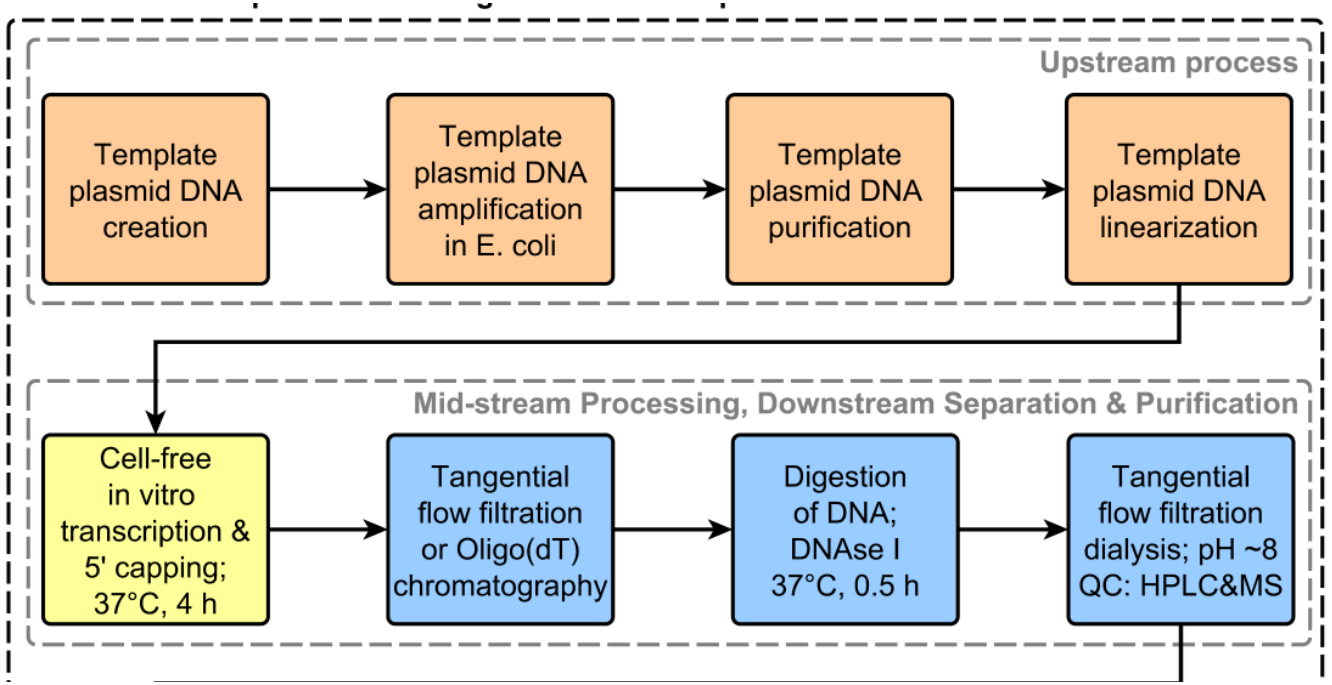
Mature

Slow

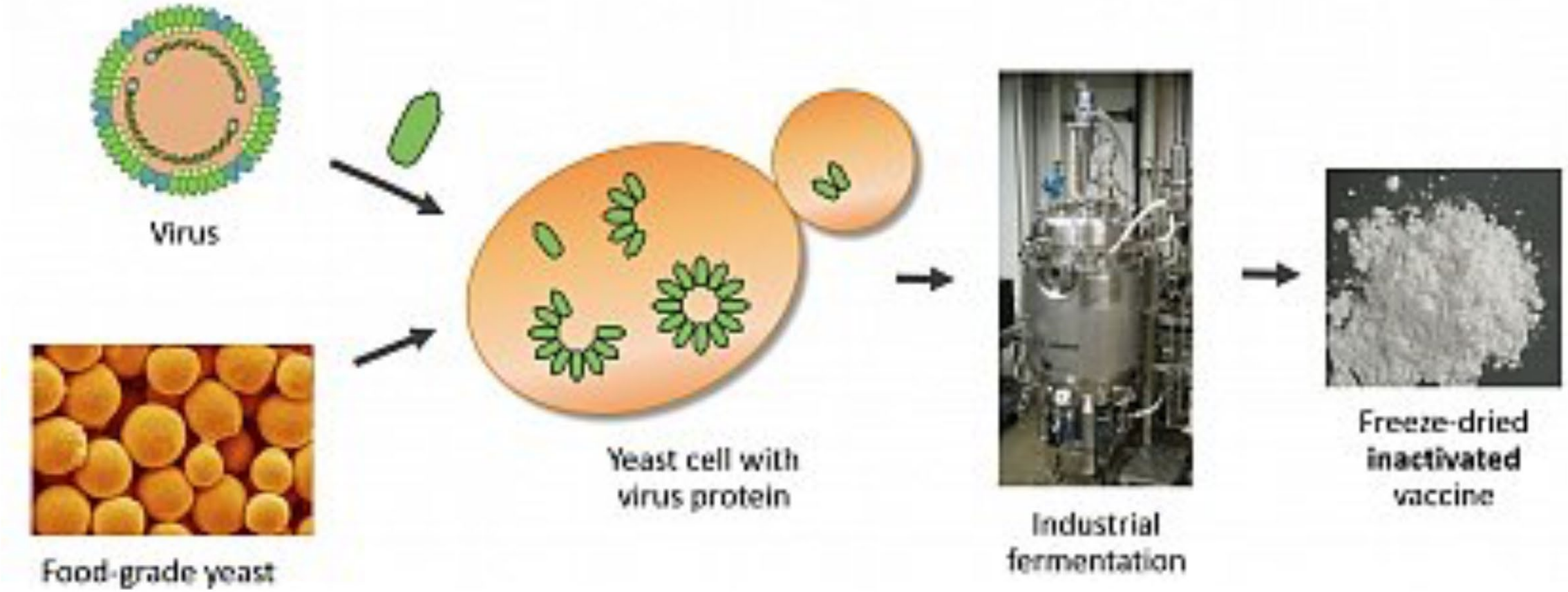
Purification challenging

RNA for Rapid response



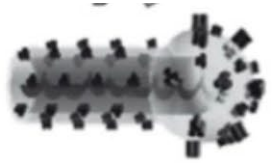


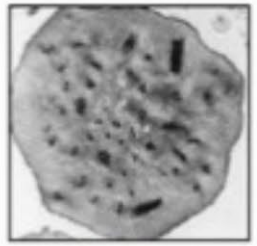
Engineering enhanced yeast based expression platforms



Developing “super-strains for optimal expression and human glycosylation

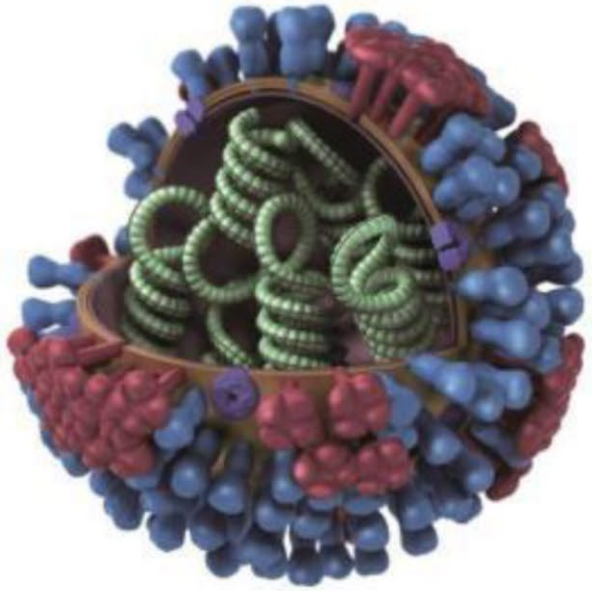
Engineering insect cell culture for efficient VLP production





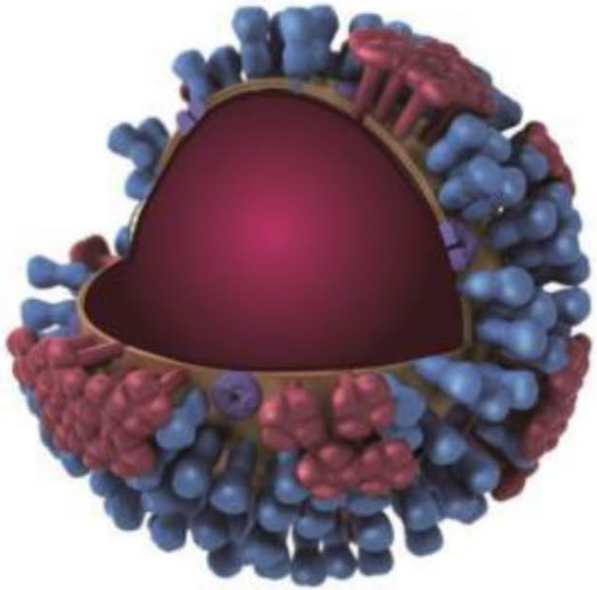
Baculovirus expression vector system (BEVS)

Influenza Virus

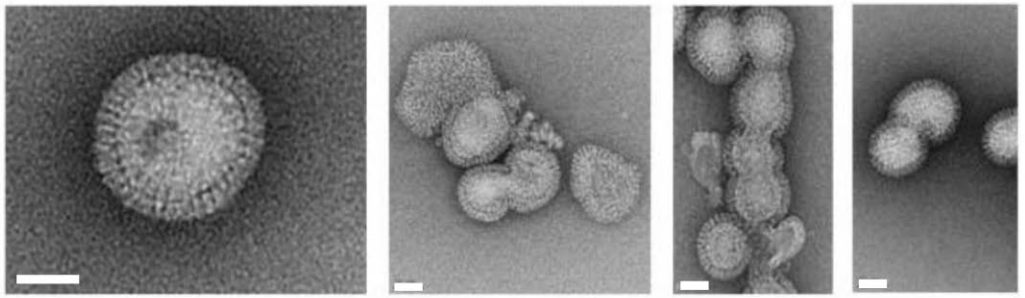


infectious

Synthetic Influenza Virus Like Particle (VLP)

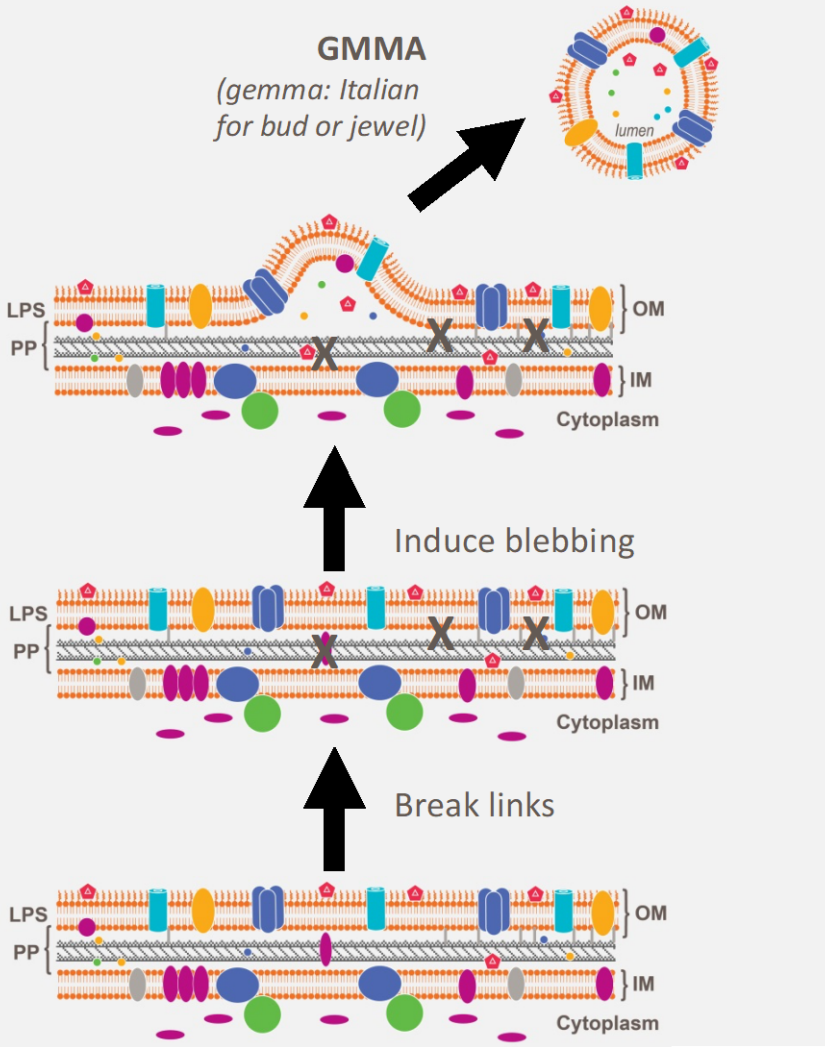


safe

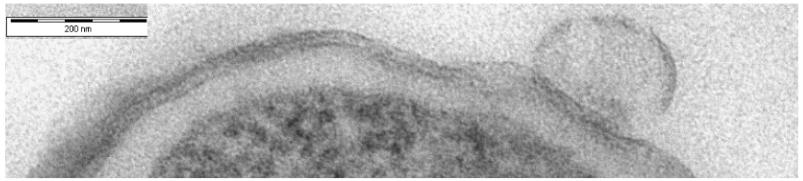


Sari-Ak et al.,**Meth. Miol. Biol.** 2018

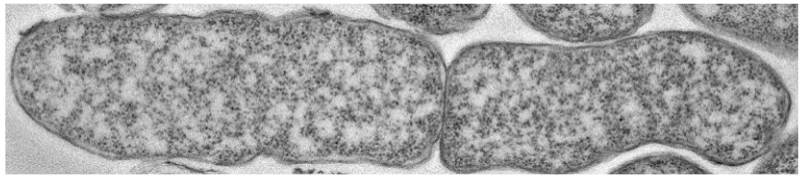
Exploiting enhanced membrane particles for bacterial vaccines



- GMMA are released yielding pure source of outer membrane
  - Similar size to virus-like particles
  - Contain PAMPs: naturally adjuvanting
  - Multiple antigens are presented in their natural environment and conformation

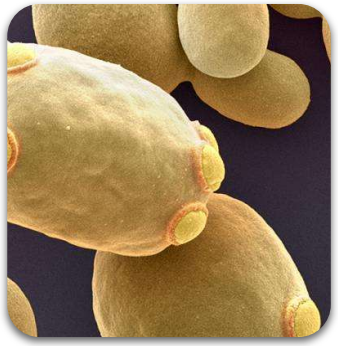


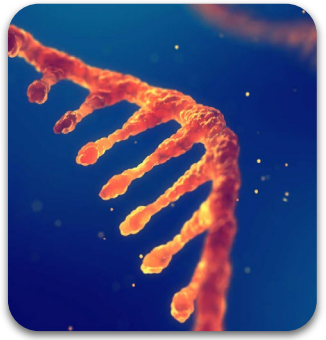
- Genetic modifications trick bacteria into shedding outer membranes



Eleonora Meloni &Taddei Anna Rita C.I.M.E. Institute, Università della Tuscia

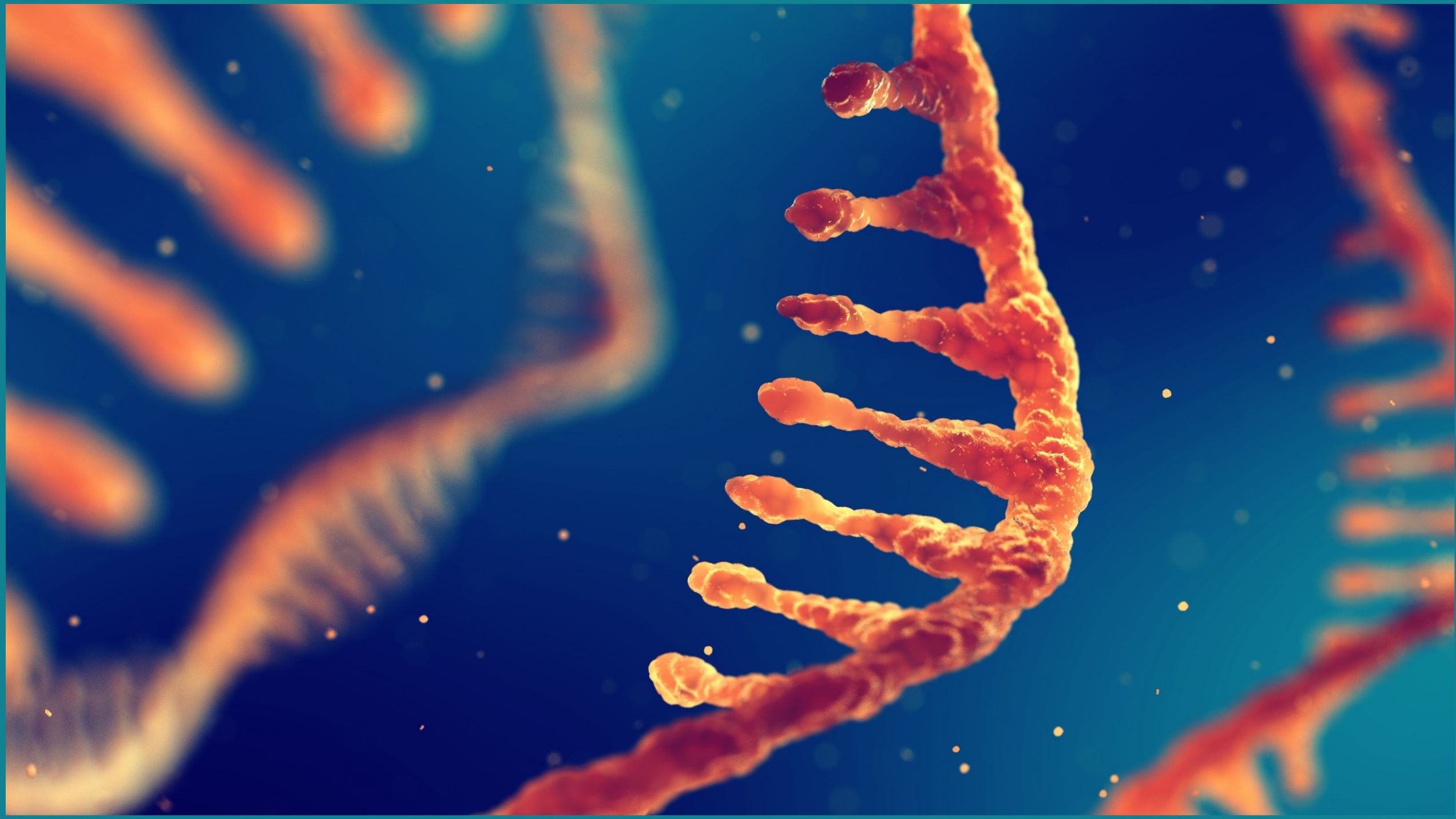
Feasibility and Risk Assessment



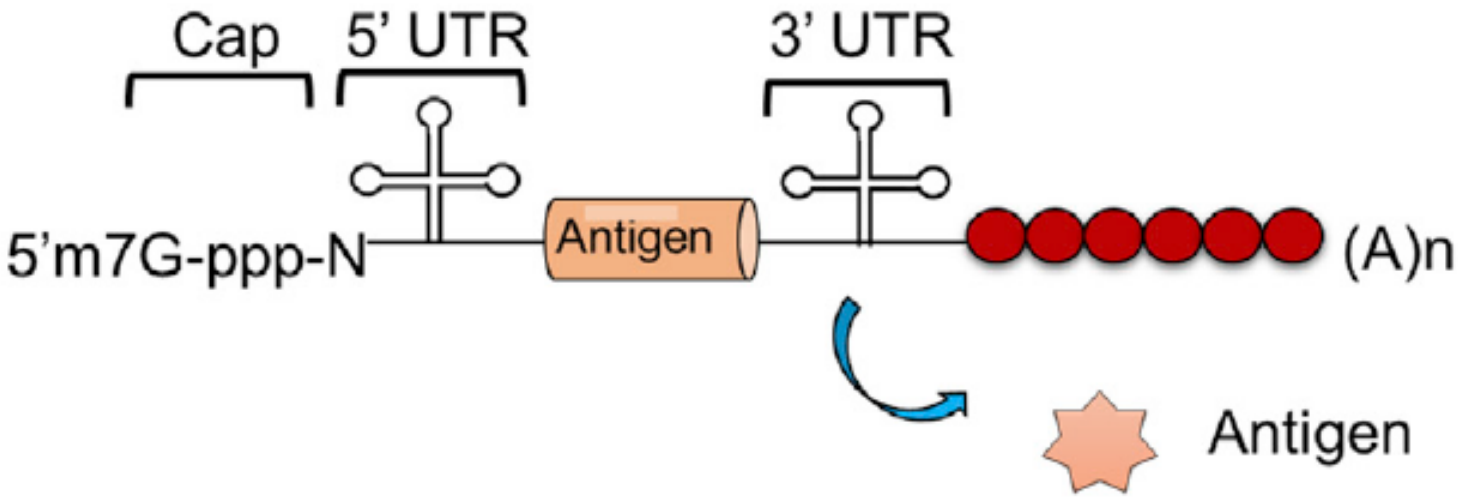



Platform[a]	metric	Yeast platform	ADDomer platform	GMMA platform	RNA platform
1	Technology readiness	2	3	5	4
2	Technological complexity	3	1	5	2
3	Ease of scale-up and −out	4	2	5	3
4	Flexibility[b]	3	3	2	4
5	Thermo-stability of product	3	5	3	2
6	Speed of response	1	4	2	5
Sum: overall feasibility and risk estimate[c]		16	18	22	20

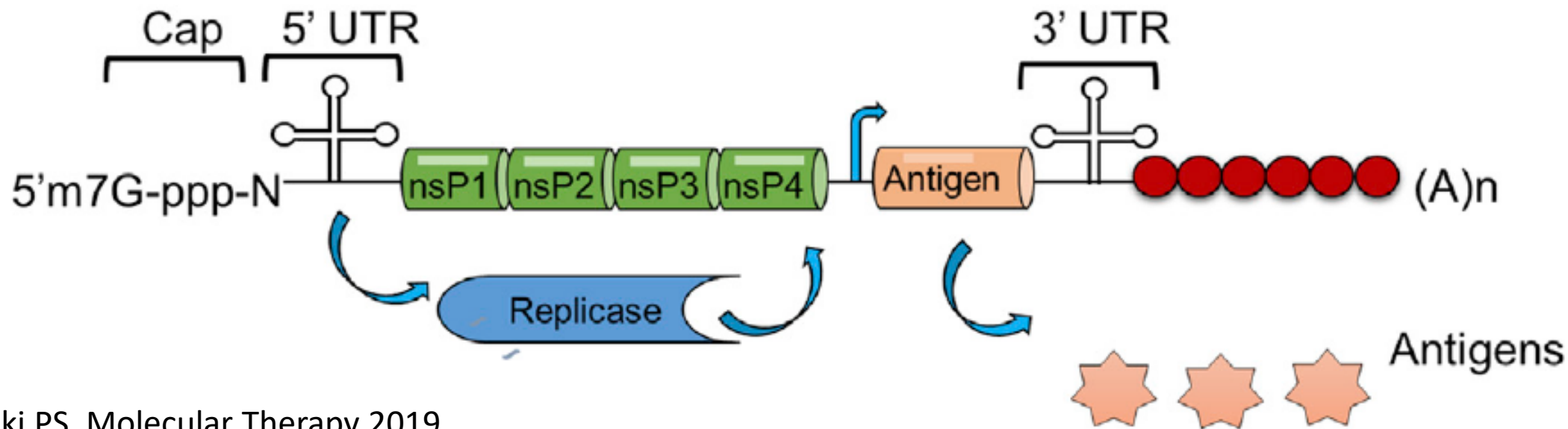
Kis Z. et al, Biotechnol J. 2019



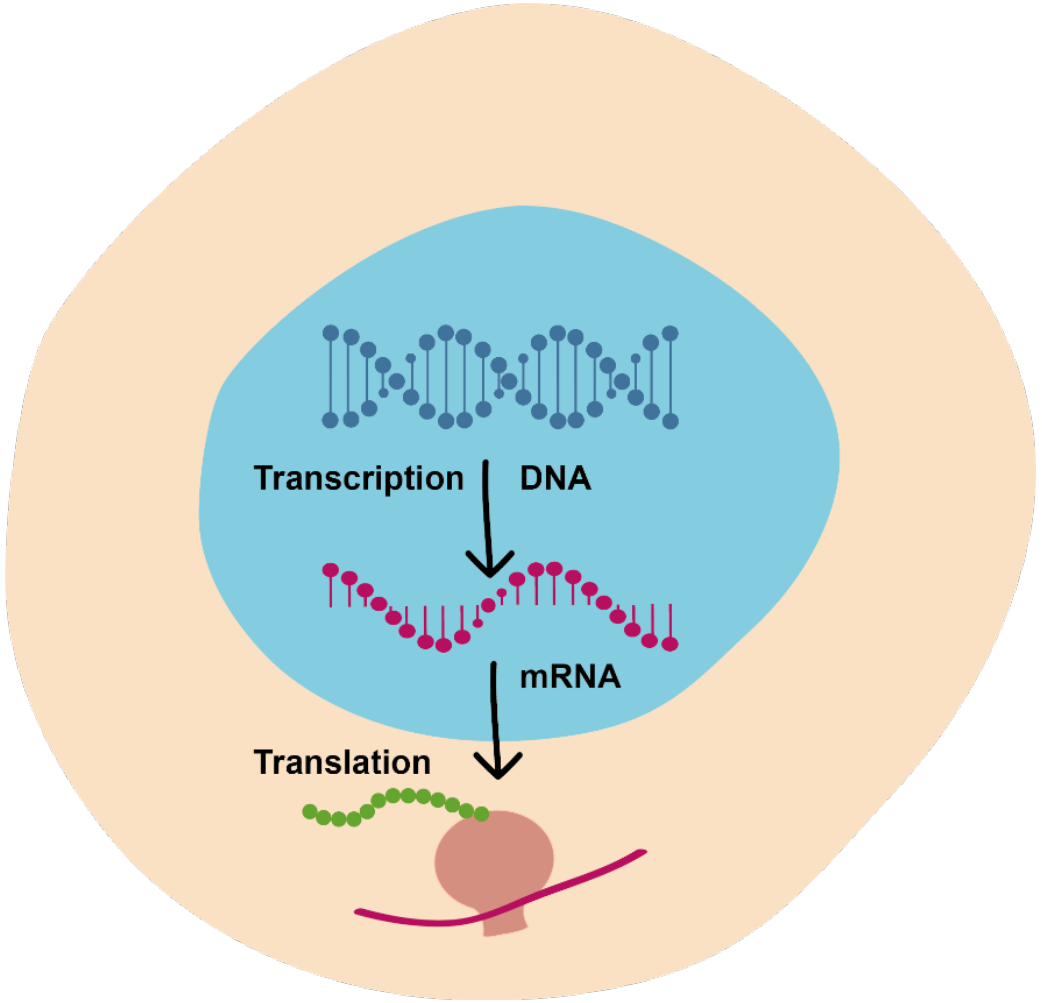
Conventional non-amplifying mRNA

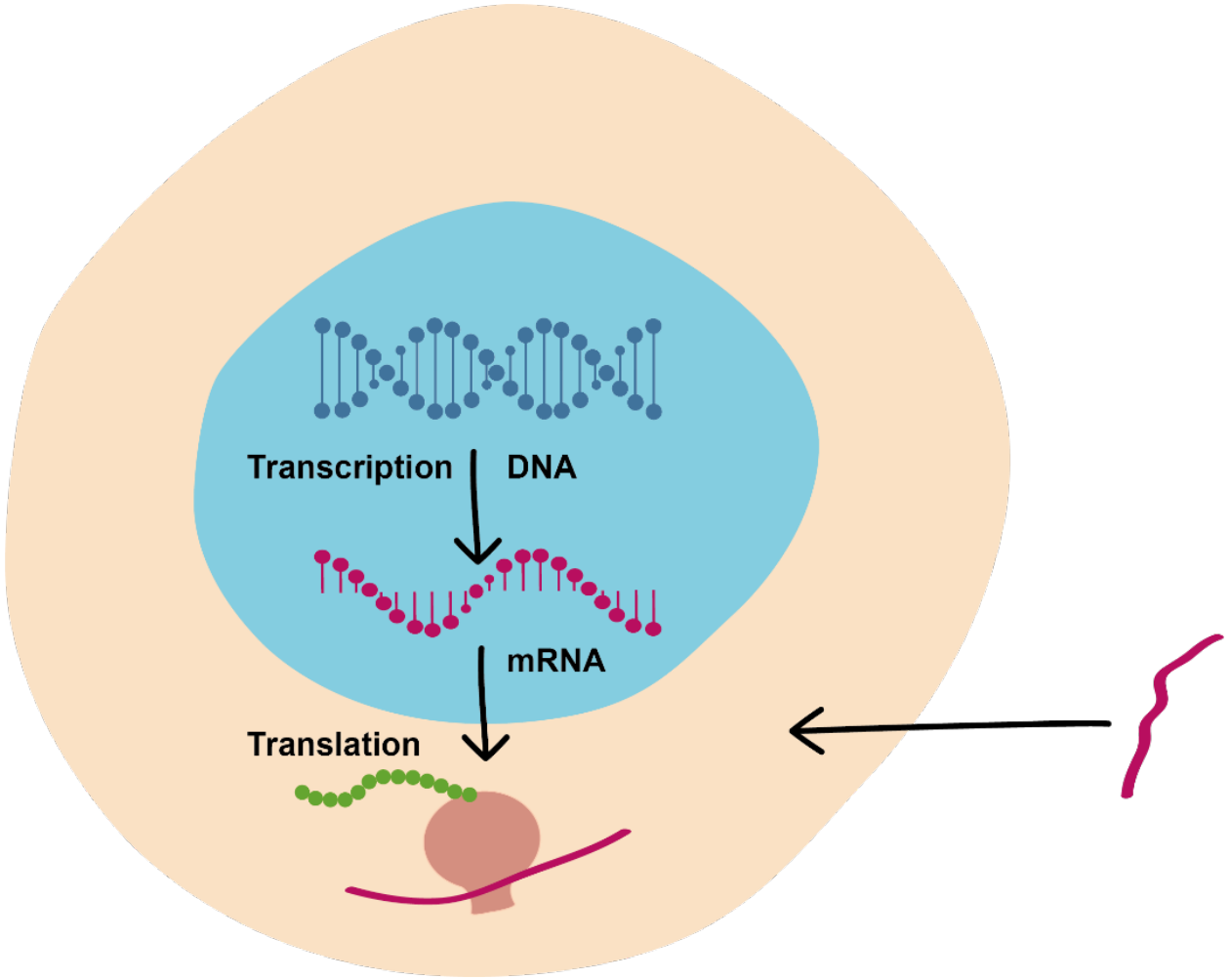


Self-amplifying mRNA (replicon)



Kowalski PS, Molecular Therapy 2019


Transcription
DNA
mRNA
Translation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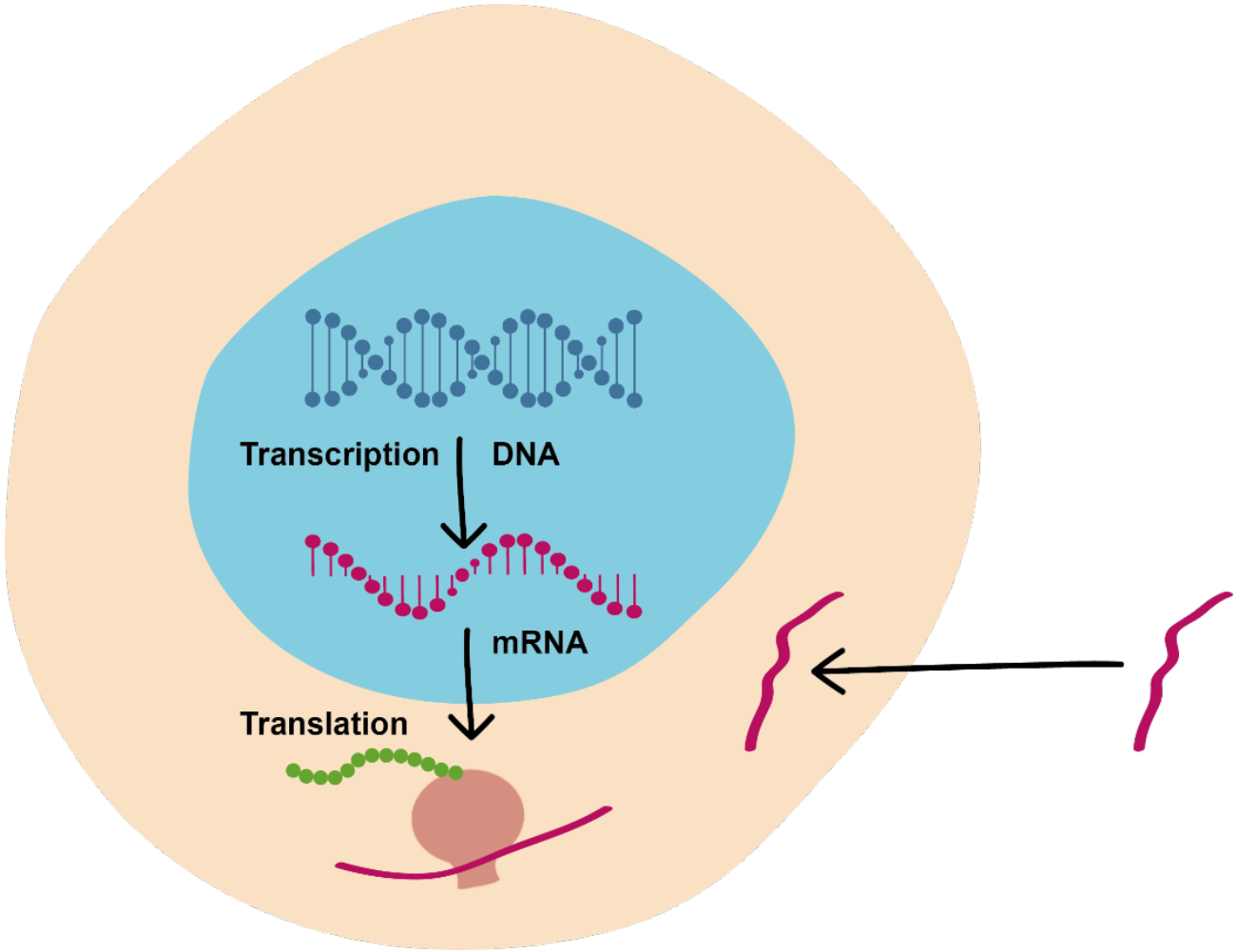
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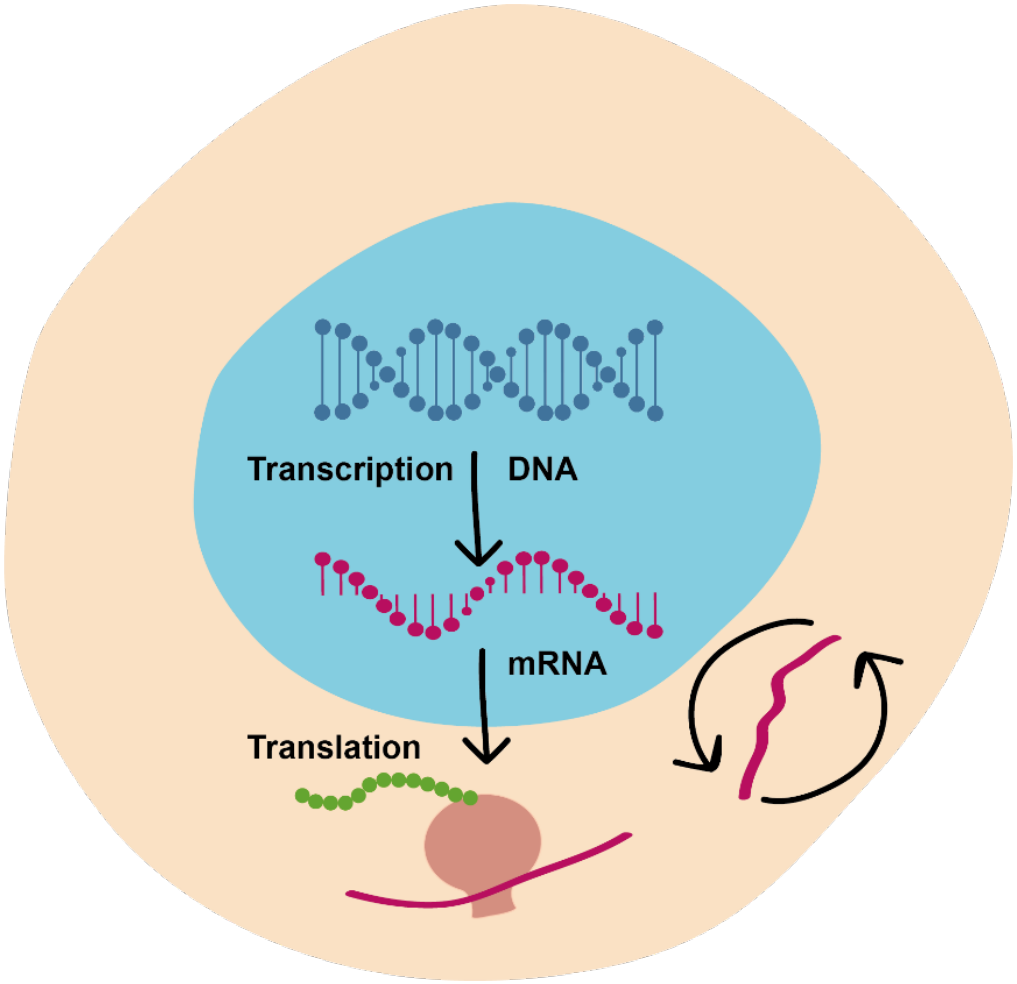
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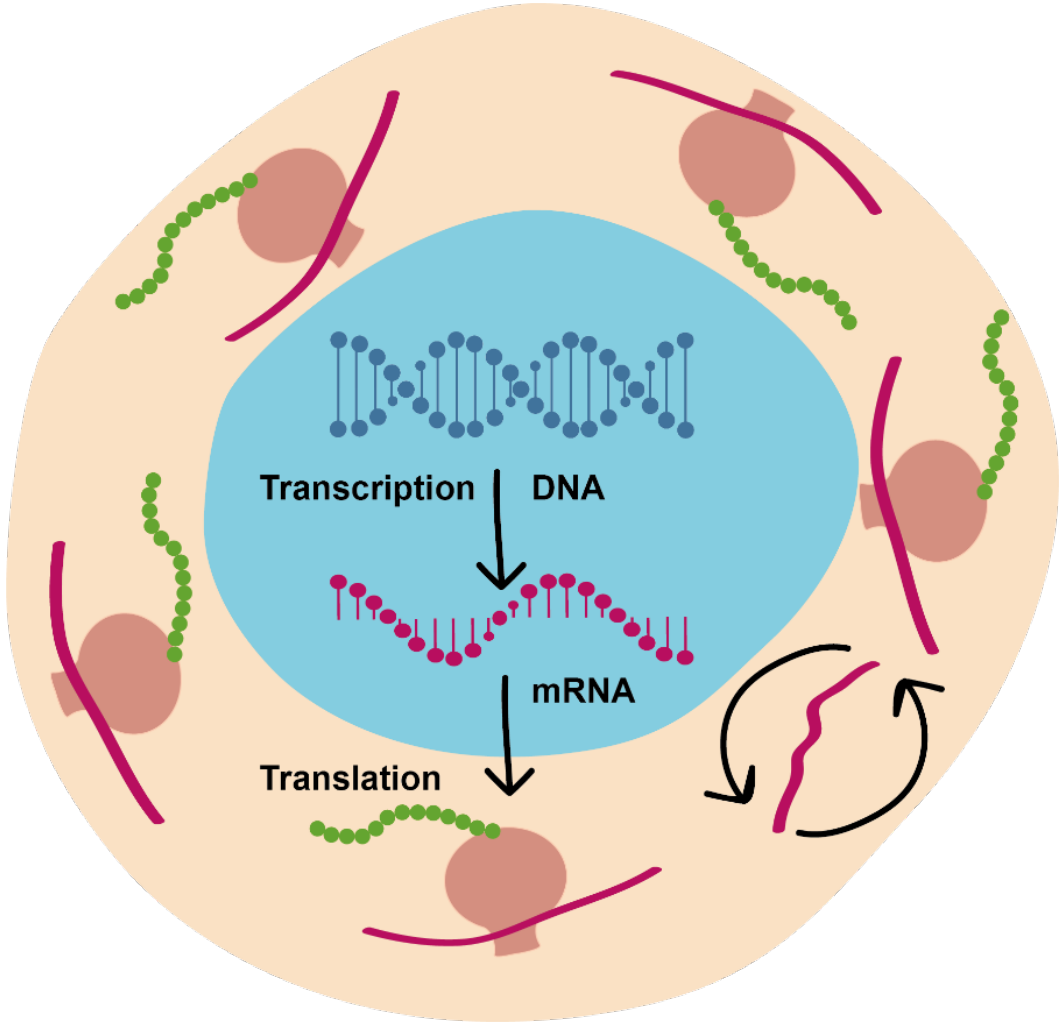
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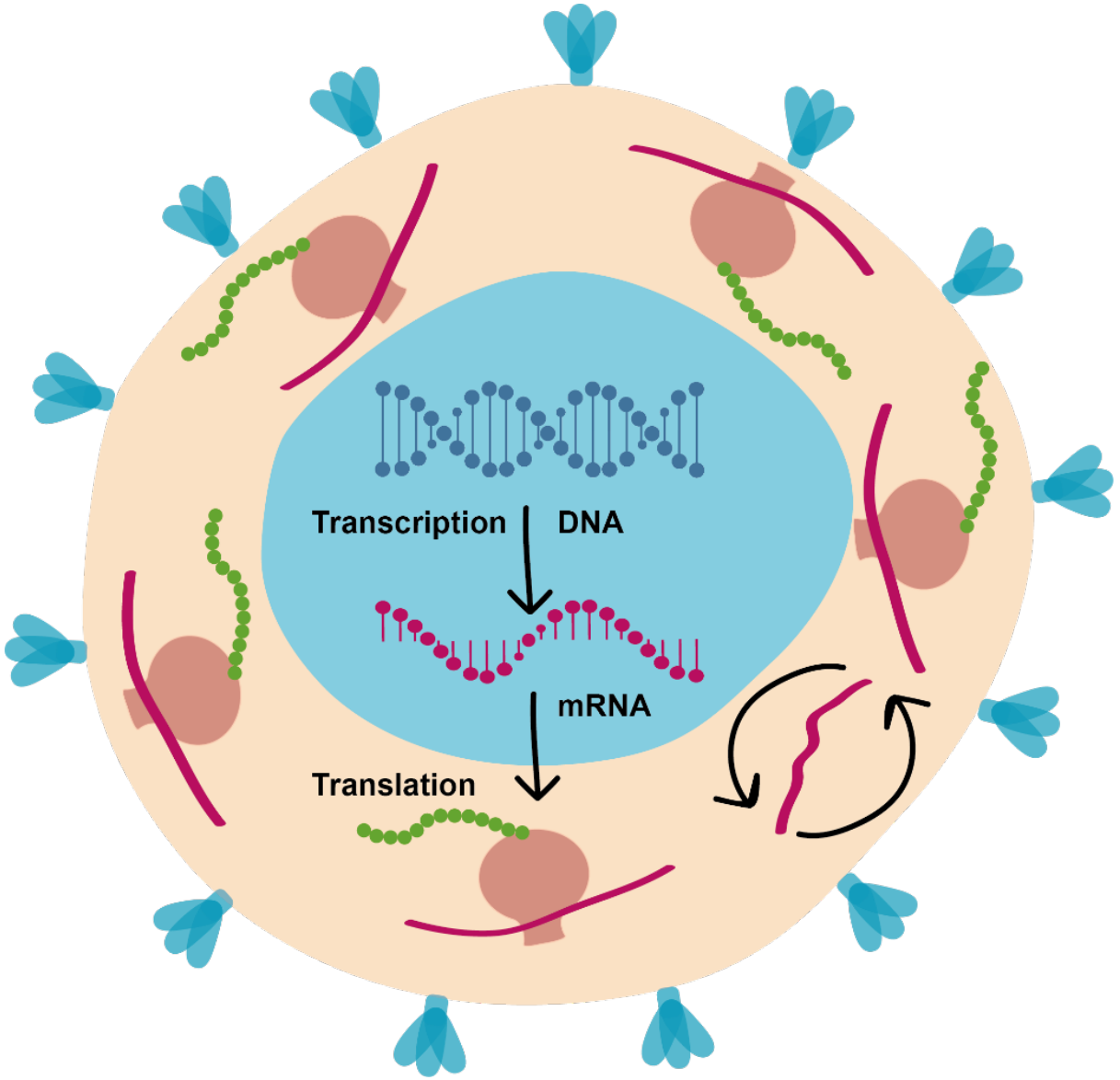
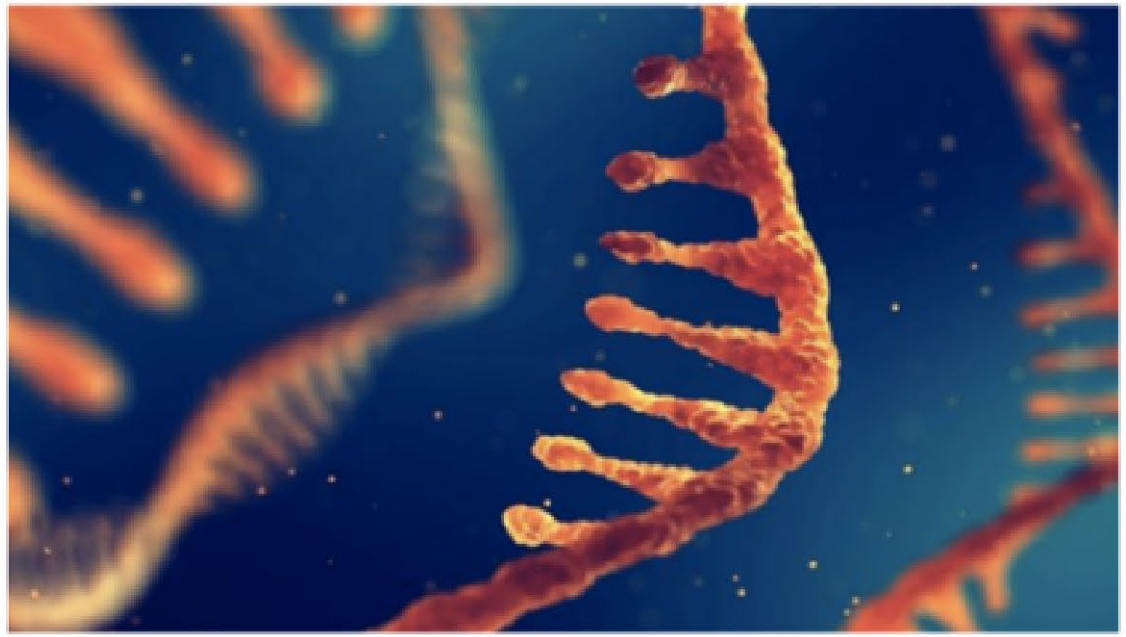
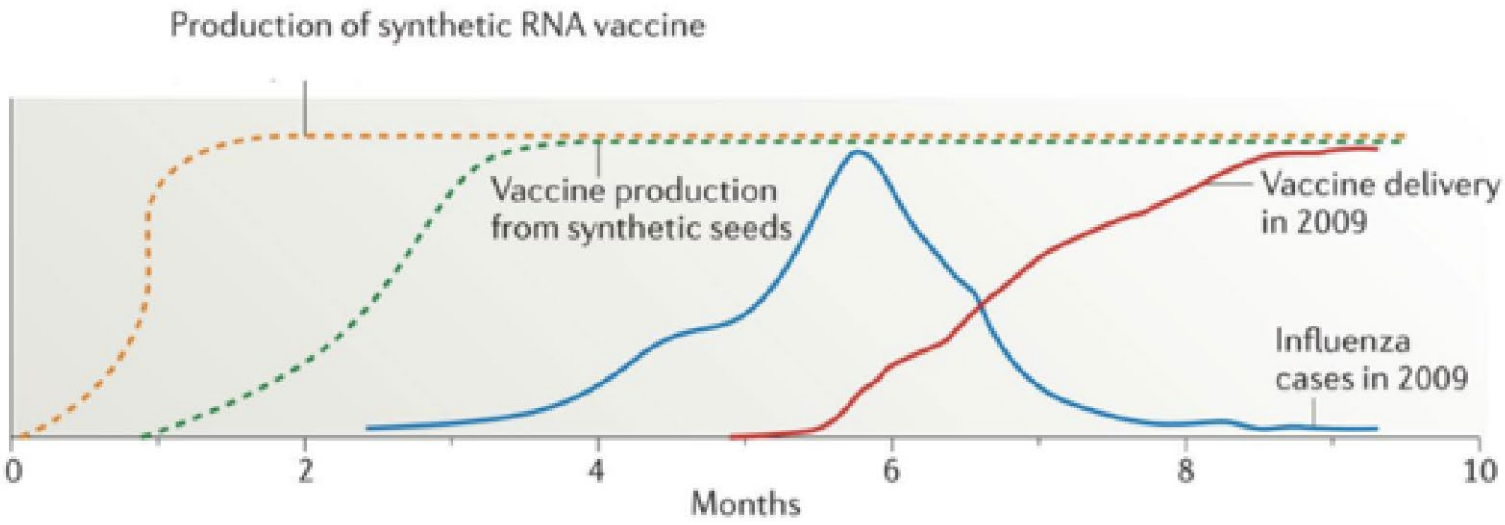
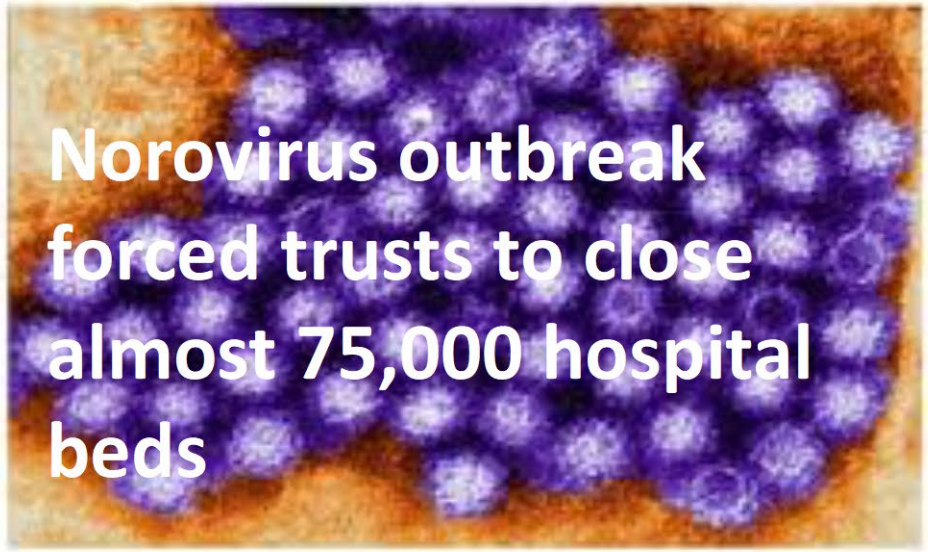

Transcription
DNA
mRNA
Translation

Establishing RNA based vaccines for rapid response





SUNDAY EXPRESS

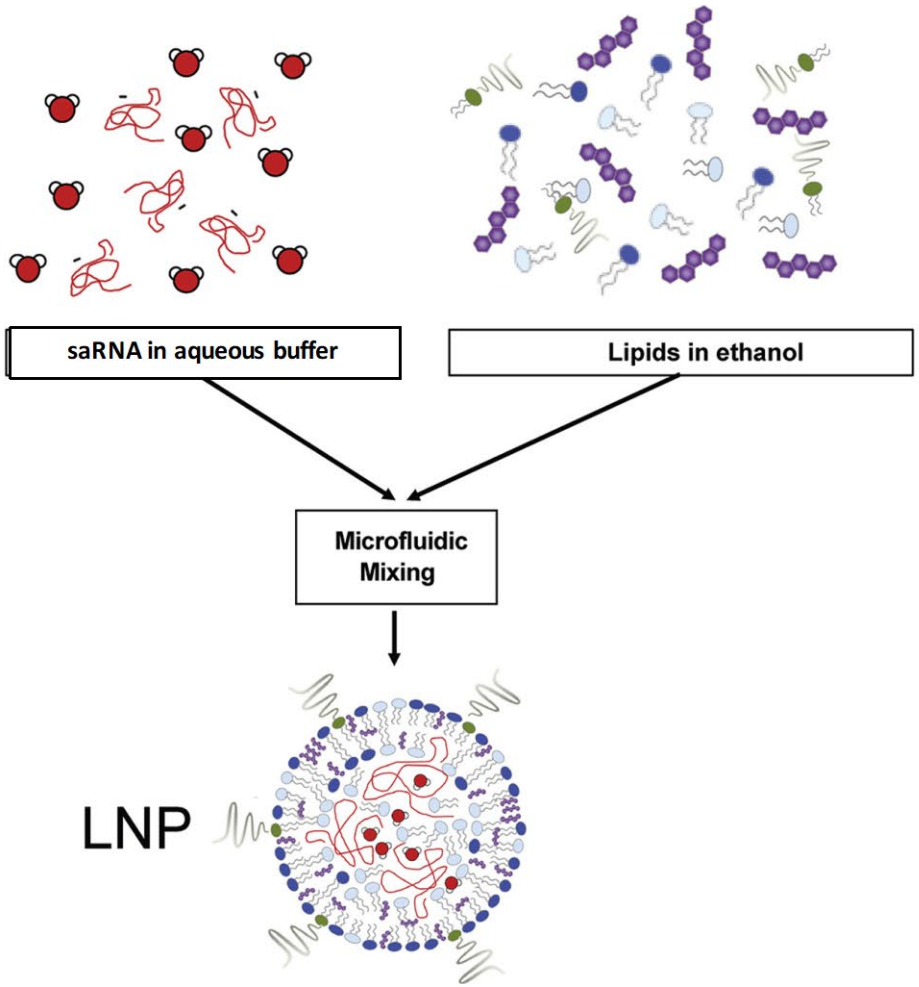


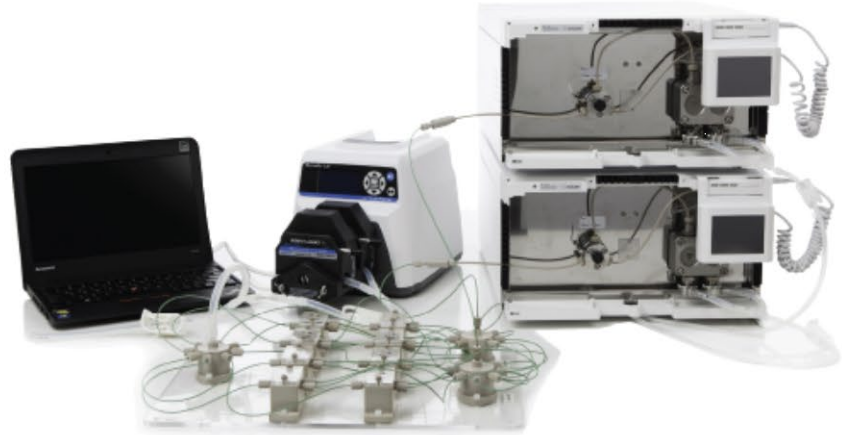
The flu jab DOESN'T work: Officials admit that a vaccine already dished out to thousands of patients may be targeting the wrong strain

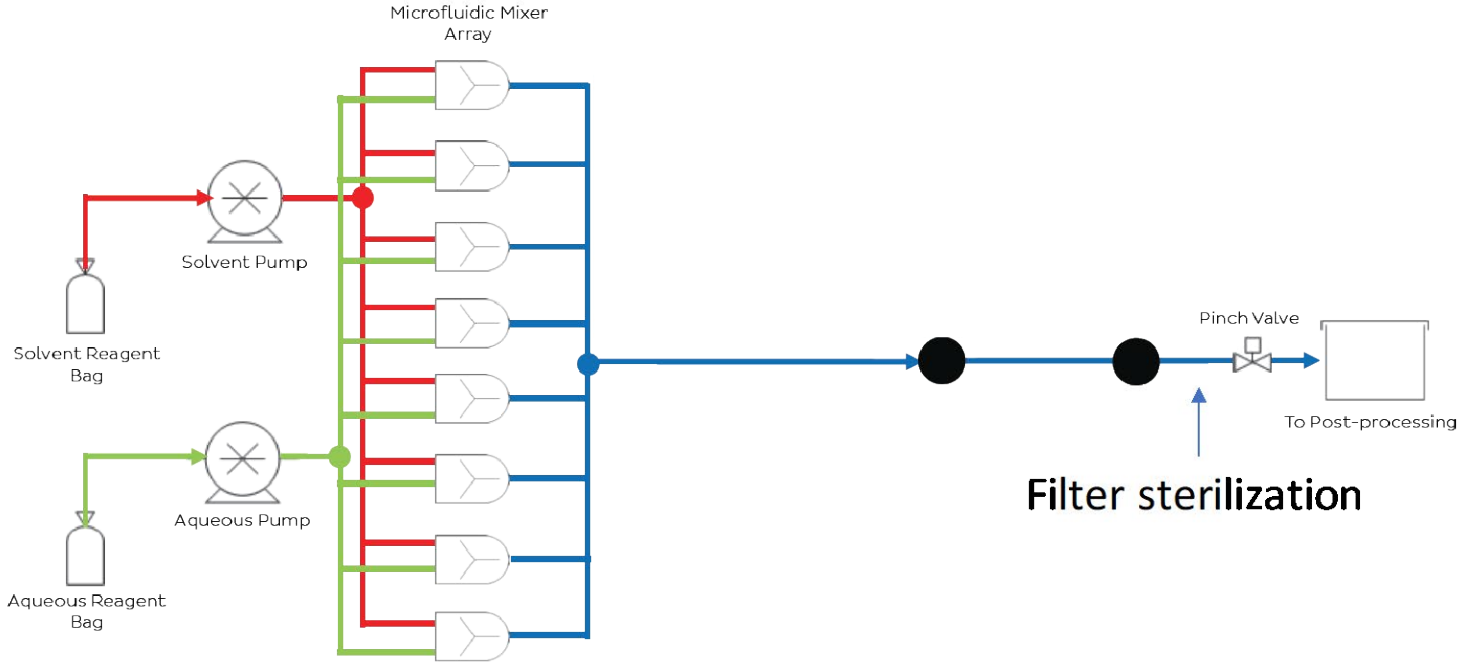
BIOTERRORISM.NEWS

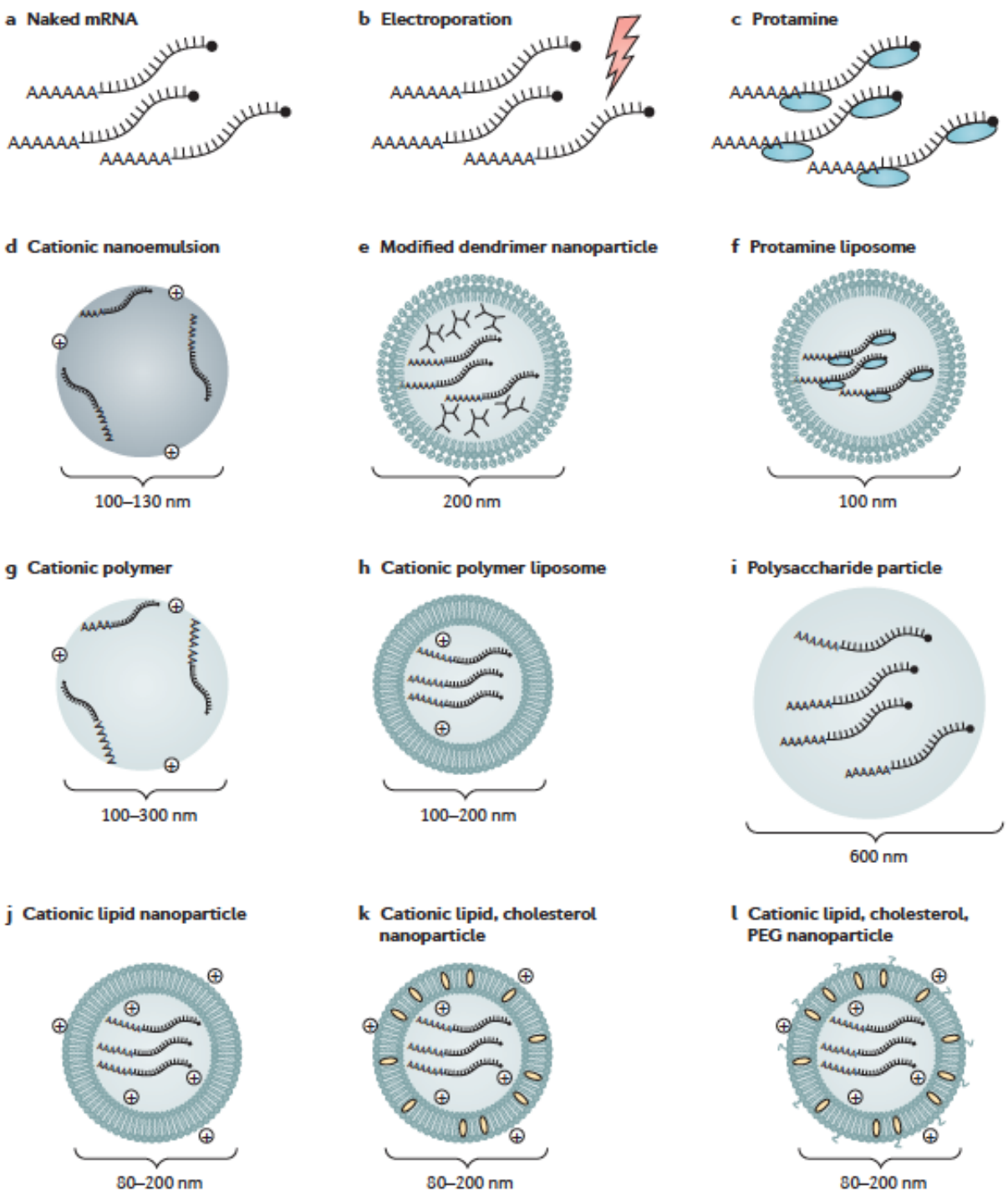
theguardian

How is saRNA formulated?





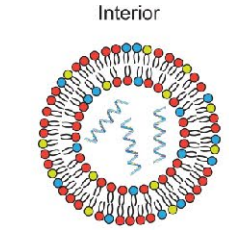


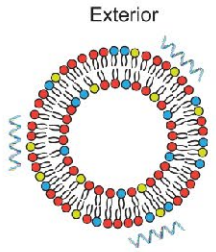


Pardi N, et al. Nature Reviews Drug discovery 2018

Blakney Ak, Gene Therapy 2019

Inside-out?

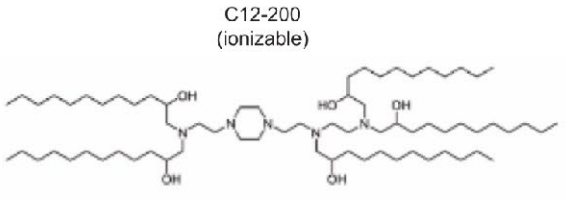


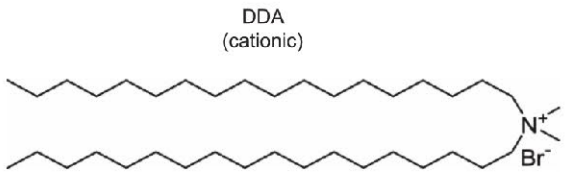


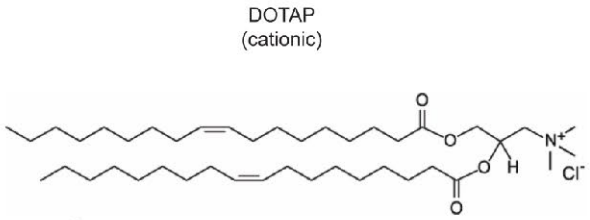
Complexing Lipid

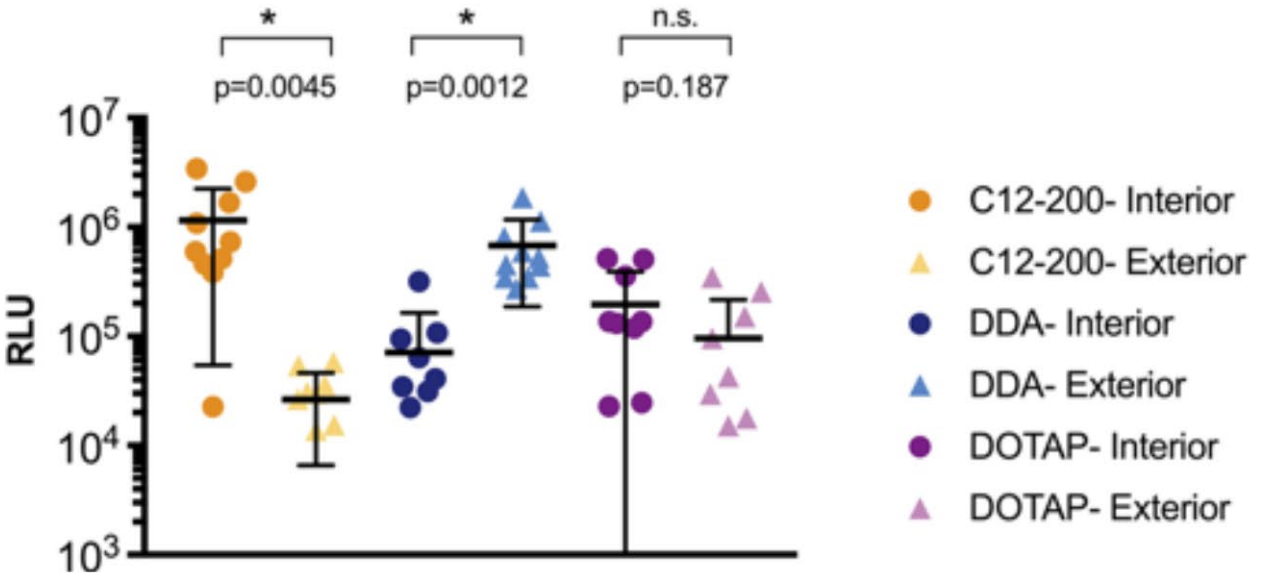
DOPE

Cholesterol









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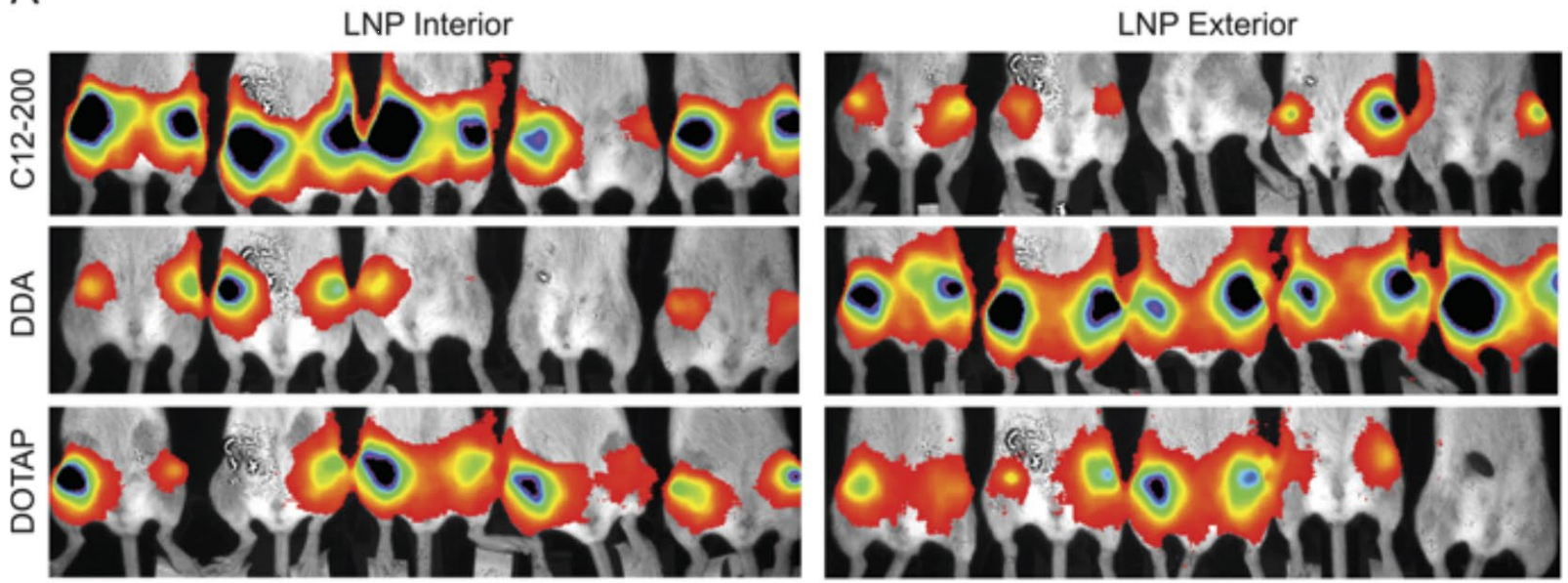
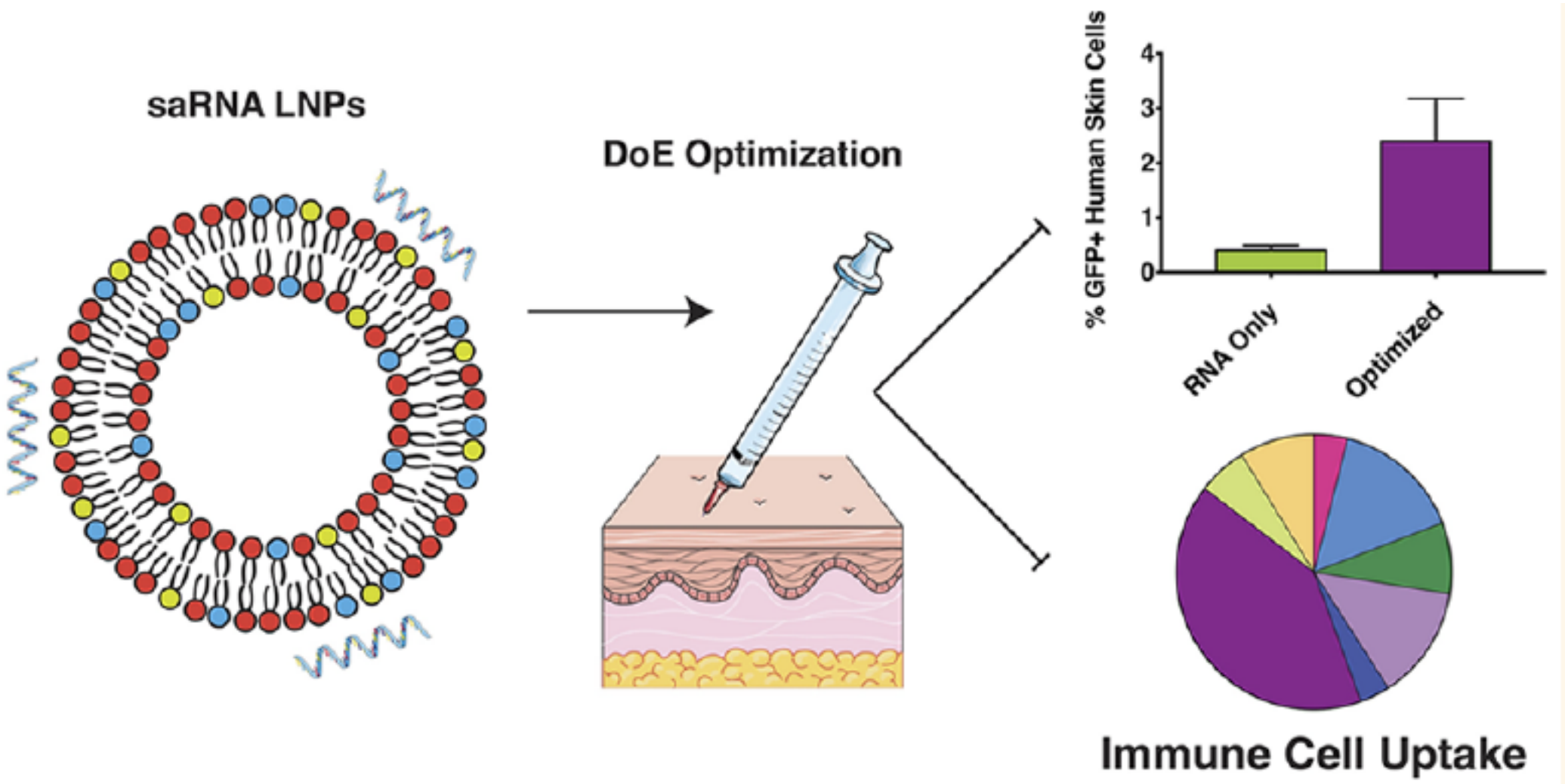
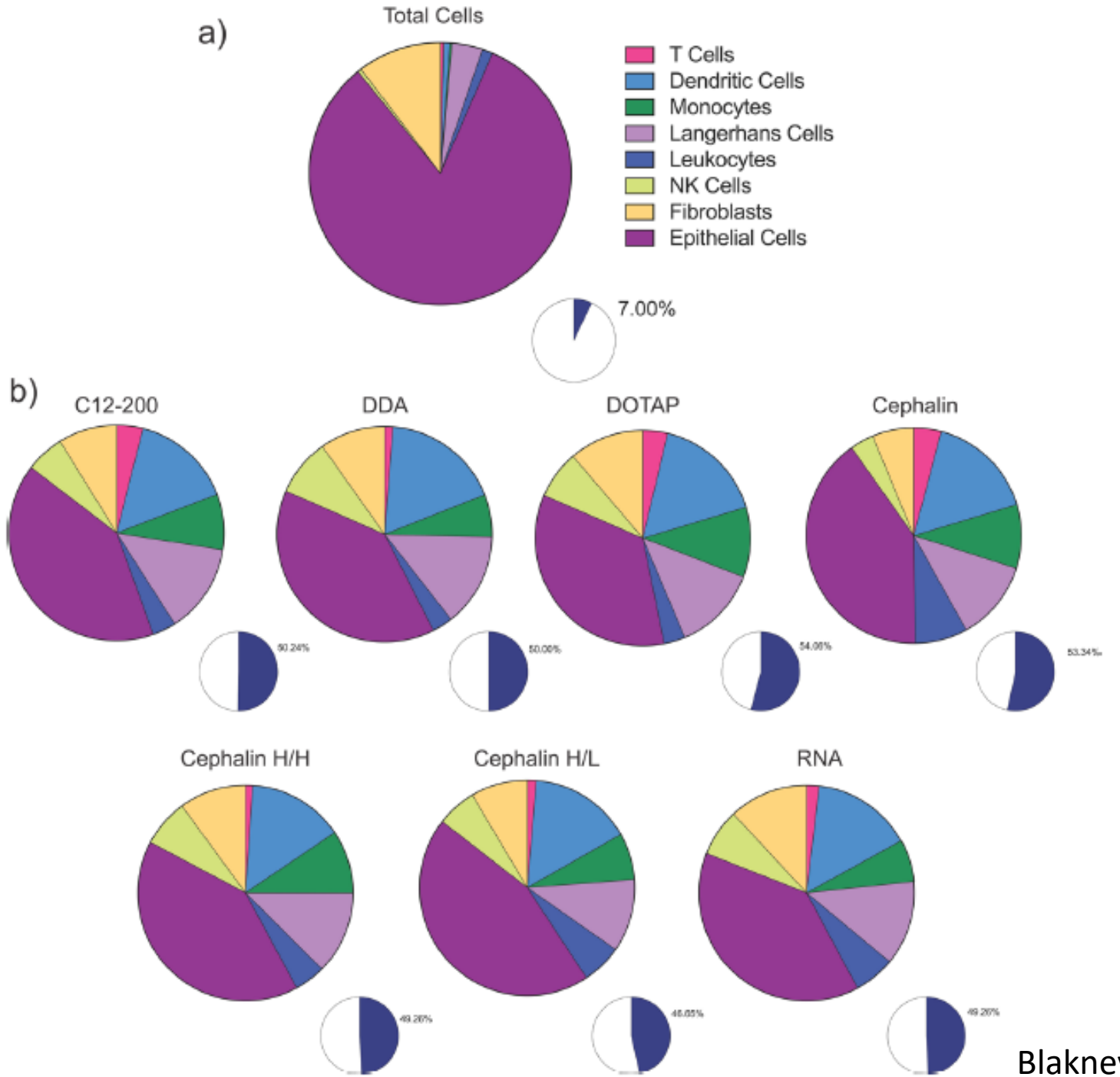


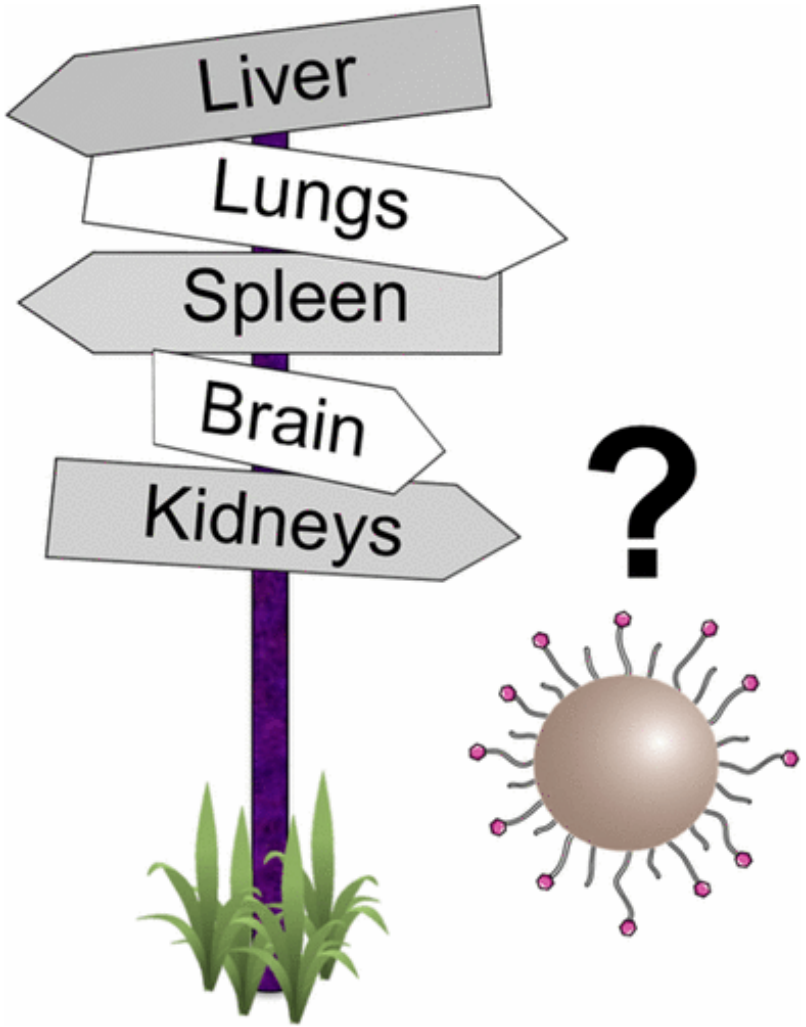


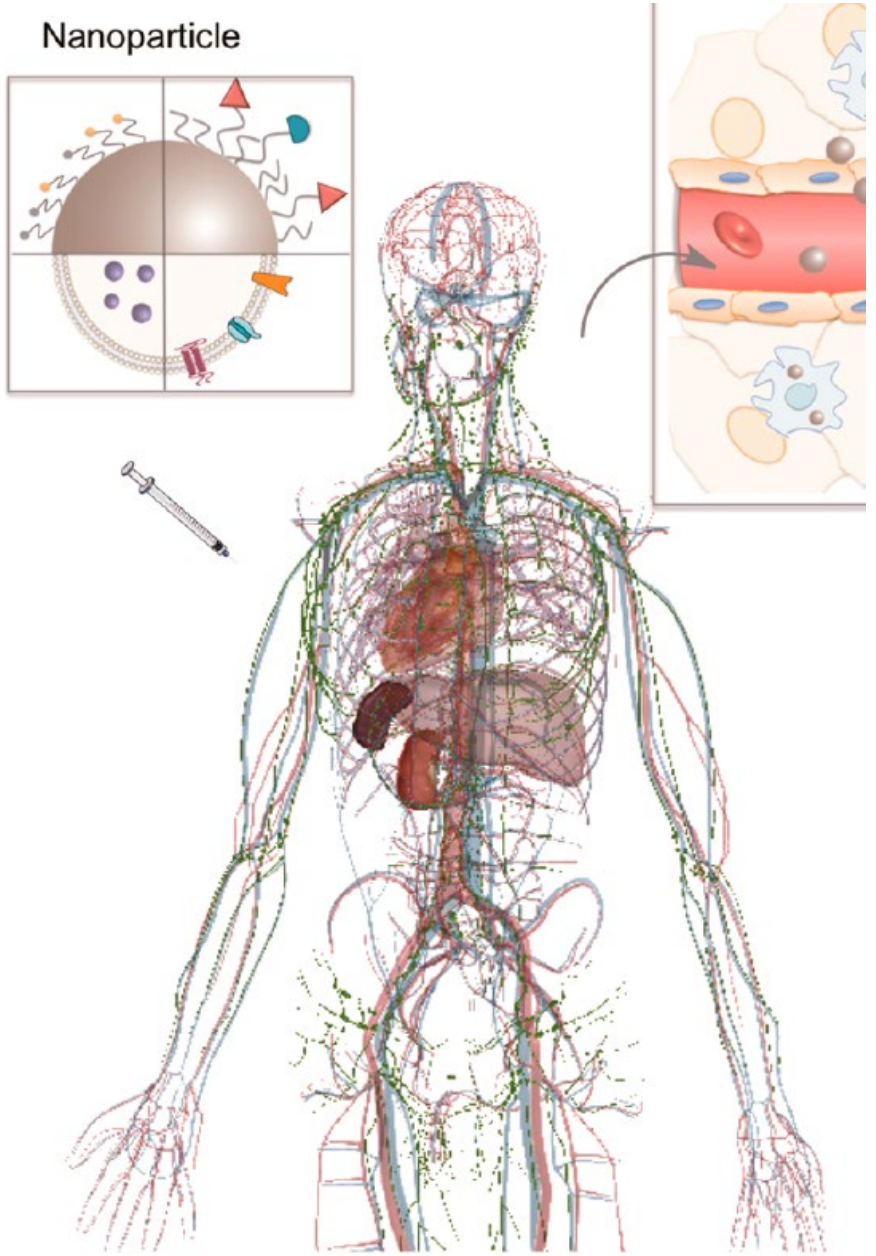
Blakney AK et al ACS Nano 2019



Blakney AK et al ACS Nano 2019

Targeting delivery?





Polo E, etal ACS Nano 2017

The long road to vaccination

Vaccines must be kept between 2-8ºC all the way from the factory to some of the most remote places on earth.

Source: MSF

3.8.2018

NEWS UPDATE

New Vision TV

ANOTHER EBOLA OUTBREAK IN CONGO

10th Ebola outbreak

Centralised versus decentralised manufacture

Single manufacturing plant

Economies of scale and volume
Hundreds of millions of doses
Standardised QC/QA
Applicable to complex manufacture (pneumococcal conjugate vaccine)
Global distribution
High up front capital costs
High personnel costs
Low flexibility

A toolbox of technologies, training, methodologies, and material designed to meet common needs among emerging vaccine manufacturers

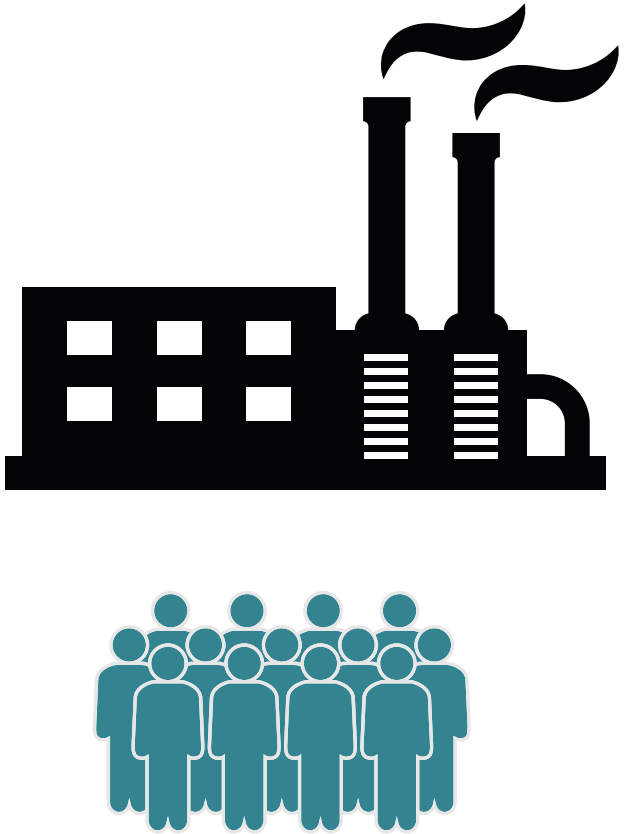
Central Hub

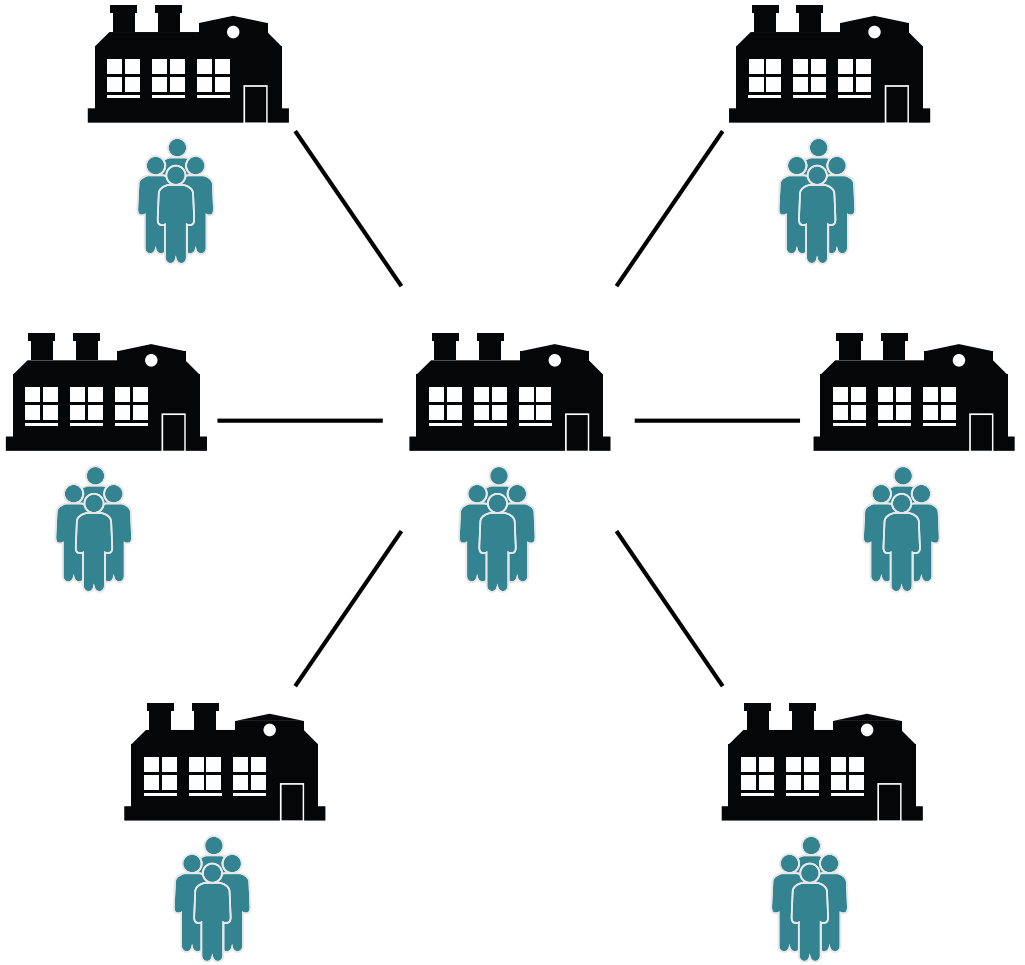
Up to millions of doses
National/regional
Neglected diseases
Rapid response to emerging and local infections
High flexibility

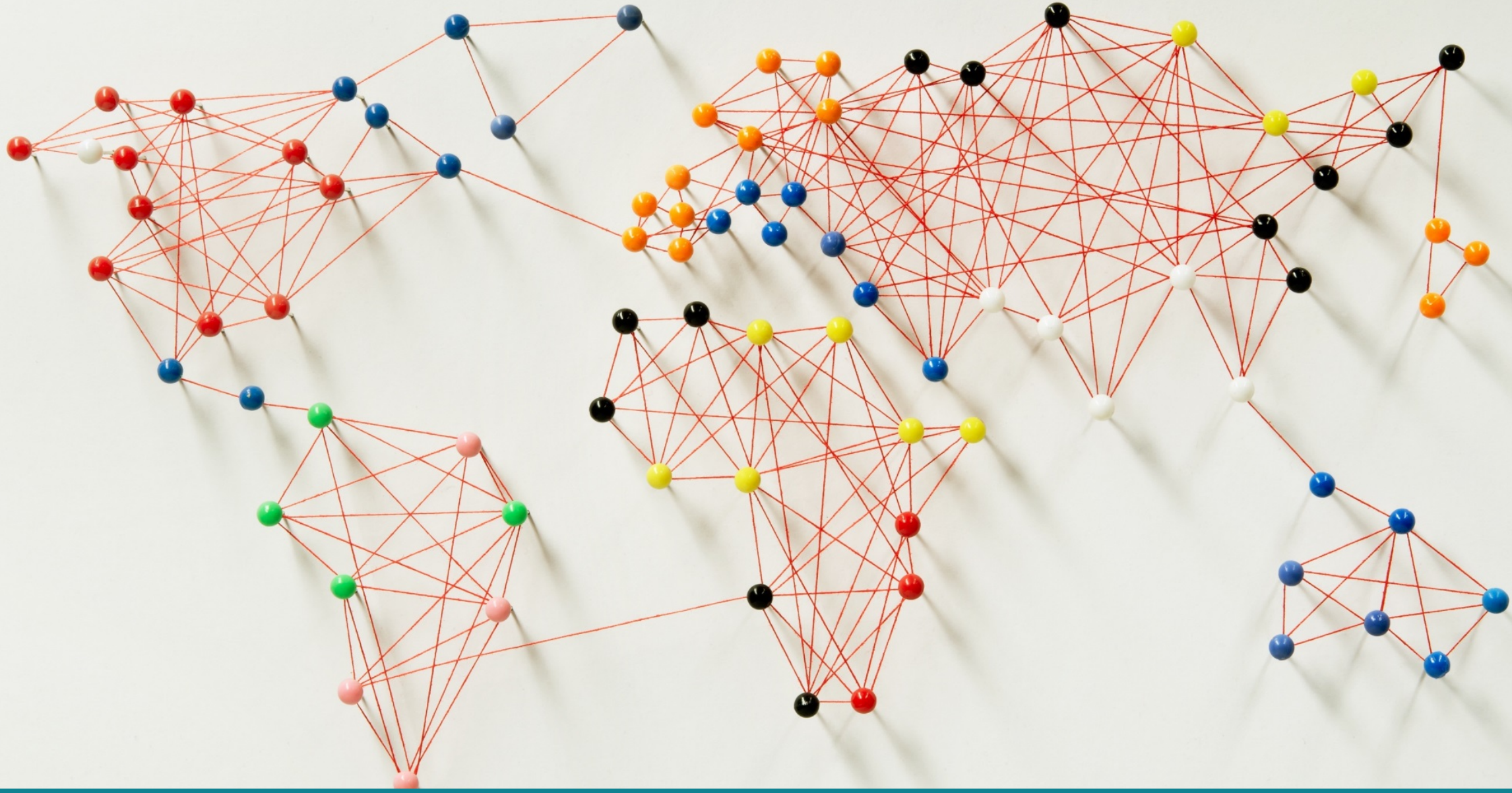
Staff/training
QMS
Equipment
Consumables
QA/QC testing

Licensing technology to regional facilities capable of cGMP, fill/finish labelling

Enhanced delivery: formulation, route, supply chain…



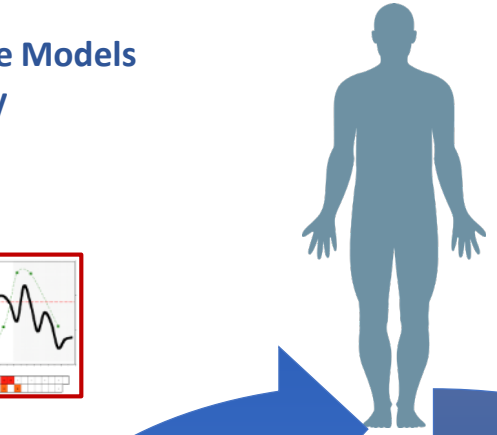




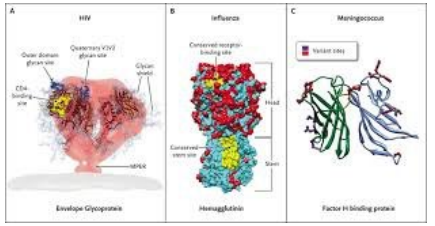
Clinically directed reverse vaccinology

Human Pathogen Challenge Models & Systems Biology

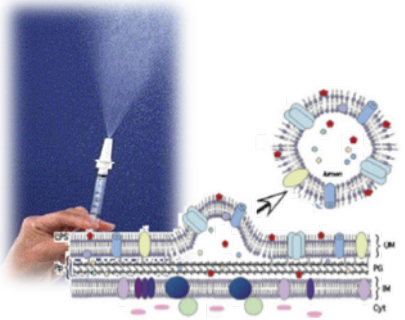
Systems Biology



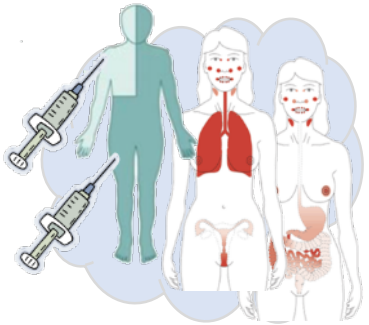
Rational immunogen design



New Technologies & Clinical Trials



Targeted Immunisation



Novel manufacturing platforms

Human challenge studies

Academic networks to:

- Support, develop and advocate the use of Human Infection Challenge
- Improve understanding of infections and the diseases they cause
- Enhance the development of new/better vaccines/treatments, focus on LMIC.

HIC-Vac

An innovative approach: Passive Immunity

THE FIND

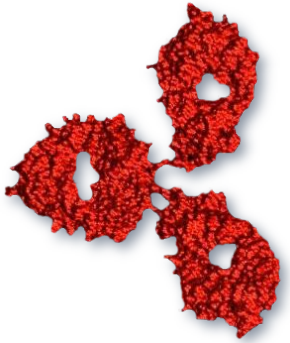
Multiple broadly protective antibodies

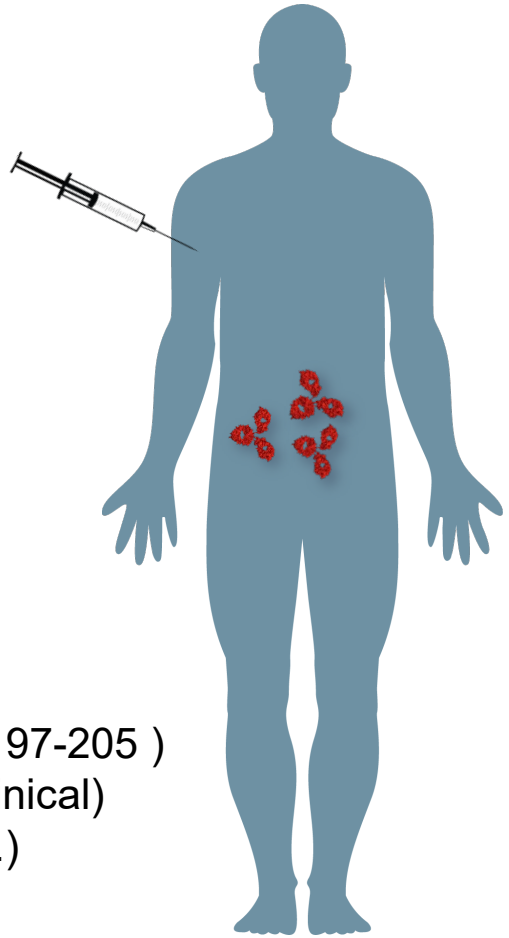
THE GOAL

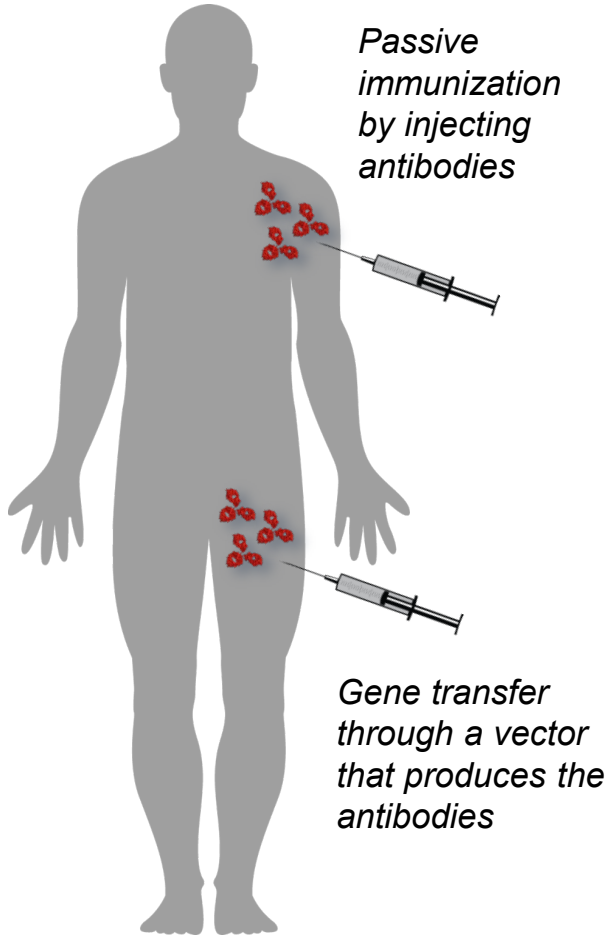
Elicit those antibodies through vaccination

INTERIM STEPS

Prove concept through …

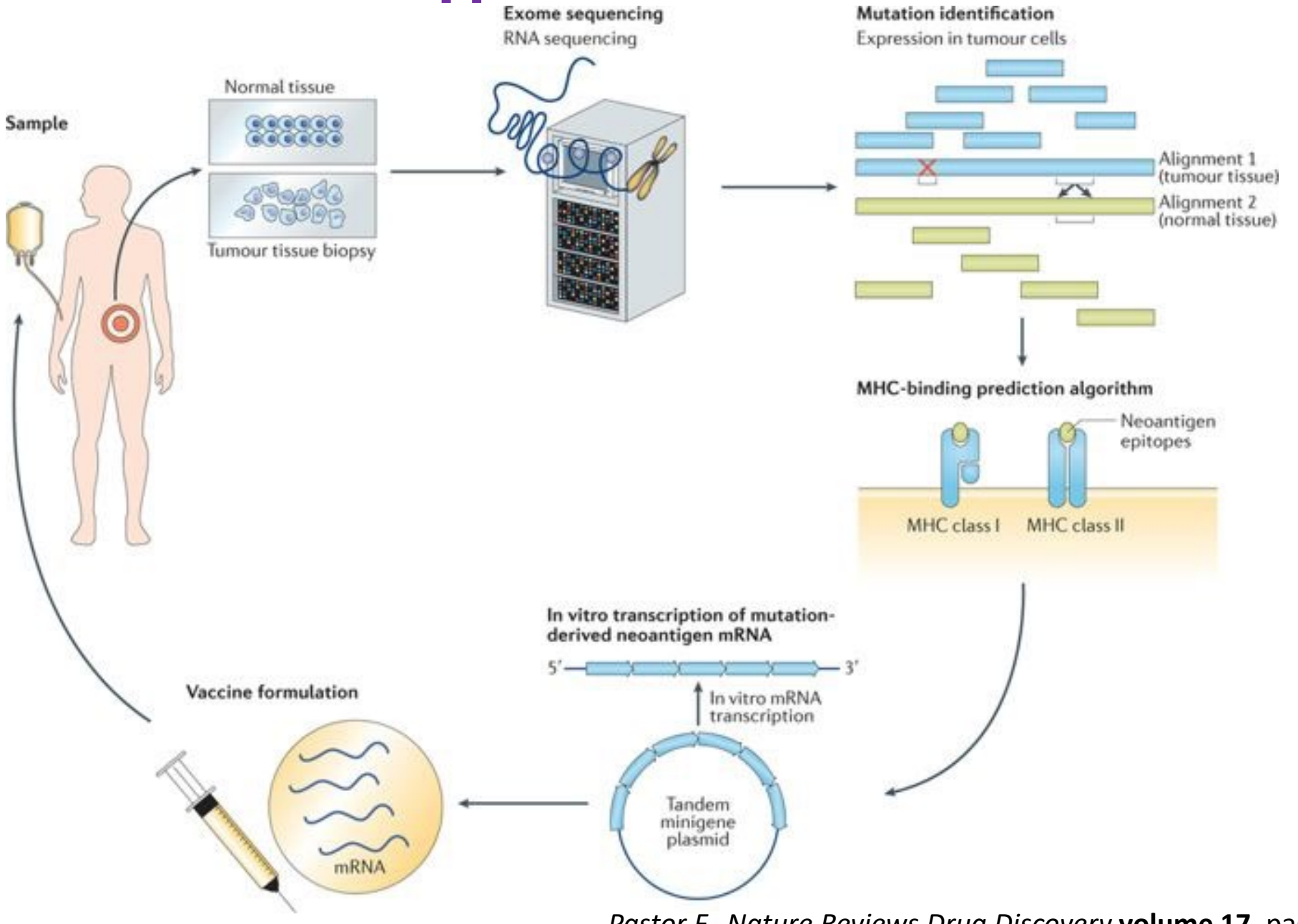




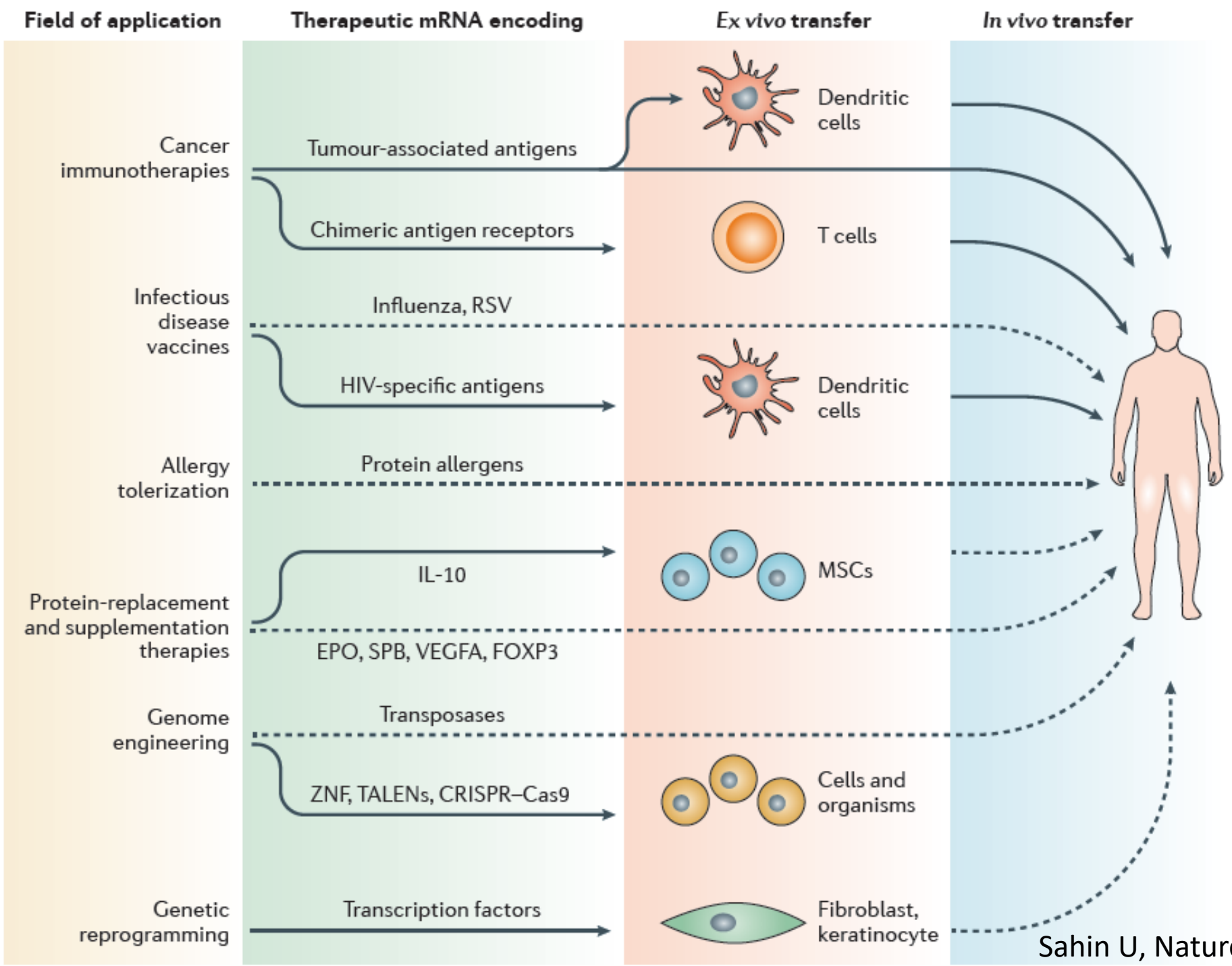


Therapeutic mAbs
C. difficile toxins (clinical)
(N Engl J Med 2010, 362:197-205)
Anti-alpha S.aureus (pre-clinical)
(J Mol Biol. 2015;427:1513.)

An innovative approach: Personalised Medicine



Pastor F,. Nature Reviews Drug Discovery **volume 17**, pages 751–767 (2018)



Sahin U, Nature Reviews Drug discovery 2014

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