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Executive Director, A\*STAR Infectious Diseases Labs



# A\*STAR's Mission and Vision



## MISSION

We advance science and develop innovative technology to further economic growth and improve lives

## VISION

A global leader in science, technology and open innovation

# A\*STAR's Research Institutes

1970 - 2000	2000 - 2010	2010 - Present
National Metrology Centre (NMC)	Bio-informatics Institute (BII)	Advanced Remanufacturing and Technology Centre (ARTC)
Institute of Microelectronics (IME)	Genome Institute of Singapore (GIS)	A*STAR Skin Research Labs (A*SRL)
Singapore Institute of Manufacturing Technology (SIMTech)	Institute for Infocomm Research (I <sup>2</sup> R)	A*STAR Infectious Diseases (ID) Labs
Institute of Materials Research & Engineering (IMRE)	Singapore Institute for Clinical Sciences (SICS)	Singapore Institute for Food & Biotechnology Innovation (SIFBI)
Institute of High Performance Computing (IHPC)	Singapore Immunology Network (SIgN)	Institute of Sustainability for Chemicals, Energy and Environment (ISCE2) <sup>2</sup>
Institute of Molecular & Cell Biology (IMCB)		
Bioprocessing Technology Institute (BTI)		
		<div>8 SERC Research Institutes</div> <div>9 BMRC Research Institutes</div>

<sup>2</sup> ISCE<sup>2</sup> is a re-organisation of A\*STAR's former Institute of Chemical and Engineering Sciences, which was established in the 2000s



# Core BMRC capability stack

BMRC manages 9 Research Institutes which carry out a spectrum of R&D activities, ranging across knowledge creation, enabling capabilities, large scale programmes, and industry-oriented activities.

**IMCB**



**Molecular & Cell  
Biology,  
Neurometabolism**

**GIS**



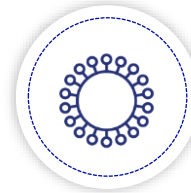
**Genomics &  
other "omics"**

**SIgN**



**Immunology**

**A\*IDL**



**Infectious  
Diseases**

**BII**



**Bioinformatics**

**A\*SRL**



**Skin Health**

**SIFBI**



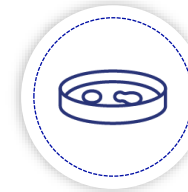
**Food Sciences**

**SICS**



**Life Course Human  
Potential Research**

**BTI**



**Bioprocessing &  
Biomanufacturing**

## Our Vision

Lead the global fight against Infectious Diseases  
to protect lives and society

## Our Mission

Driving scientific excellence in Infectious  
Diseases research with translation to  
impact on Practice and Policies for Better  
Health and Economic Outcomes



# ID Labs has 3 key research pillars supported by cross cutting epidemic preparedness capabilities

ID Labs' research pillars addresses growing Infectious Diseases threats and key public health concerns of Singapore and the region

## The 3 research pillars of ID Labs

### Vector-Borne Diseases



### Respiratory Diseases



### Antimicrobial Resistance



## Epidemic Preparedness Capabilities

**Biomarkers  
Discovery**

**BSL-3  
facility**

**Pathogen  
Evolution**

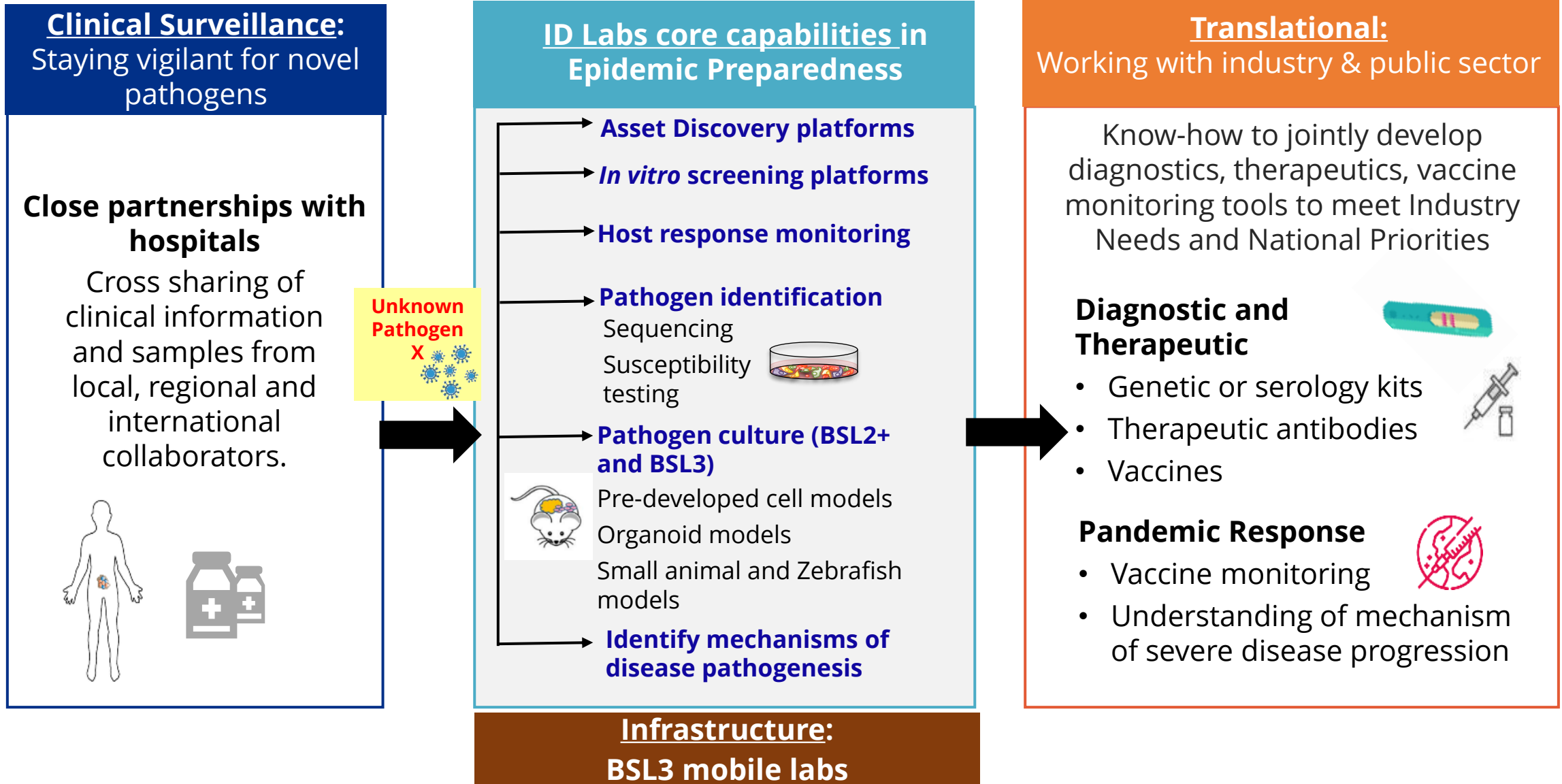
**Diagnostic  
Development**

**Vaccine  
Therapeutics  
Development**

**Vaccine  
monitoring**

**Animal  
models**

# Translating our basic research and core capabilities to meet industry and public sector needs



# ID Labs capabilities value add to the early stages of the vaccine & therapeutics development process in Infectious Diseases

## Phase 1: Discovery

### Vaccine Antigen discovery

- Protein subunits (epitopes)
- Live Attenuated
- Nucleic Acid (saRNA)

### Asset discovery platforms

- Host directed therapies
- Defective viral genomes
- Phage therapy
- Microfluidics antibody discovery
- Viral evolution modelling
- Candida screening platform

### In-vitro screening assays

- Cell based assays
- Live culture assays
- Drug susceptibility assays
- Phage display assays

## Phase 2: Pre-Clinical

### Efficacy and mechanistic studies

- High throughput zebrafish models
- Mouse infection models
- Vaccine Immunoprofiling

### Vaccine and adjuvant immunomonitoring

- Whole blood immunophenotyping (neutralising antibodies, T-cell, B-cells, cytokines)
- Adjuvant effects and adaptive response

### Pathogen culture and identification (BSL2+ and BSL3)

## Phase 3: Clinical Trials

## Phase 4: Regulatory & Approval

## Phase 5: Mfg & Scale up

## Phase 6: Quality Control



# ID Labs' core capabilities: vaccine immuno-monitoring expertise and technologies

## SARS-CoV-2

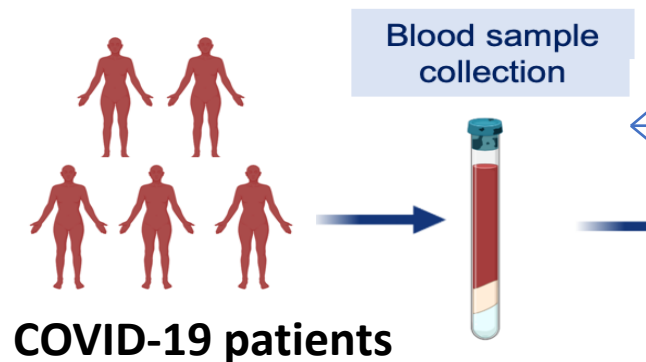
Examining vaccine-induced immunity responses



Antibody Response of Heterologous vs Homologous mRNA Vaccine Boosters Against the SARS-CoV-2 Omicron Variant: Interim Results from the PRIBIVAC Study, A Randomized Clinical Trial

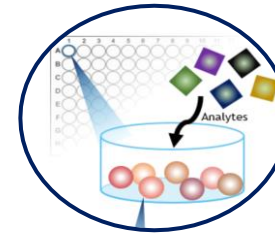
35 Pages • Posted: 16 Mar 2022

<https://ssrn.com/abstract=4056669>

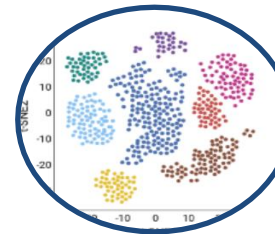


Leveraging our **suite of comprehensive Immuno-monitoring technologies** for whole blood immunophenotyping that can be deployed to **discover unique biomarkers correlating to disease severity and understanding of vaccine immune response**

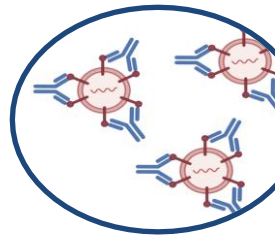
## Immuno-monitoring technologies



*Multiplex cytokine profiling*



*High-dimensional Immunophenotyping*



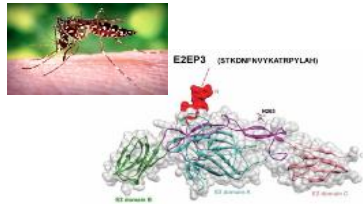
*S-flow based assay*

Identify Severity Signature

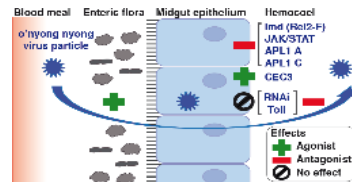
# Leading Efforts by ID Labs in Vaccine Development & Target Discovery

## Emerging and Neglected (Alphaviruses)

### Chikungunya



### O'nyong'nyong virus



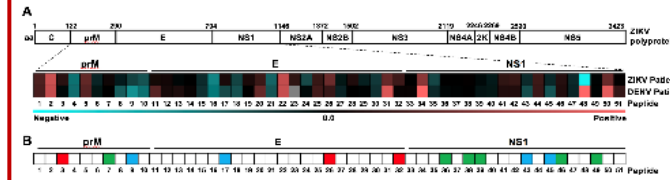
Candidates:  
epitope,  
attenuated

## Flaviviruses

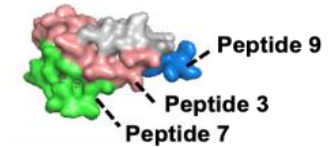


### Zika

### Dengue



**6 common flavivirus, 3 ZIKV-specific and 4 DENV-specific epitopes**



Candidates:  
epitope,  
saRNA

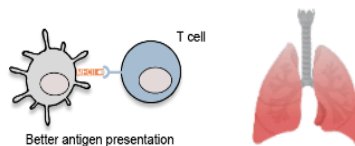
## Persistent Global Threat

### Malaria



Targets: new  
sporozoites and  
blood stage targets

### Tuberculosis

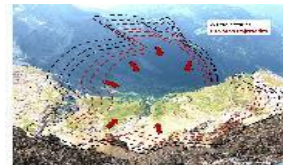


Candidates:  
TB subunit

## Enteroviruses, influenza

### Influenza

### Next gen Polio



Candidates: attenuate RNA  
viruses by altering their  
evolutionary potential

## Aquaculture vaccines



### Scale drop disease

### Lates Calcarifer Herpesvirus

### Viral Nervous Necrosis



Asian seabass (*Lates calcarifer*)

Candidates:  
epitopes,  
saRNA

# Applications of ID Labs capabilities in antiviral screening and biomarkers discovery for therapeutics and diagnostics

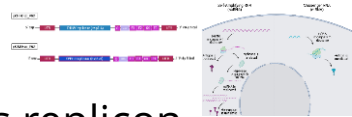
## *In vitro* screening assays

Viral cell-based reporter systems

Alphavirus replicon screening assays

Live viral quantification and detection assays

Viral Neutralisation assays

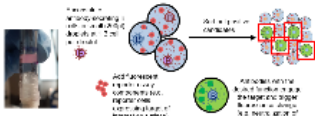


## Asset discovery platforms

Defective viral genomes therapeutics platform

Microfluidics antibody discovery

Viral evolution modelling



## Efficacy & Mechanistic studies

Mouse models – CHIKV, Zika, Dengue and other alphaviruses and flaviviruses

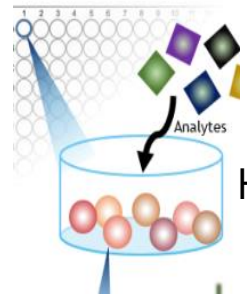


Patient samples

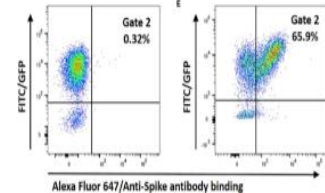
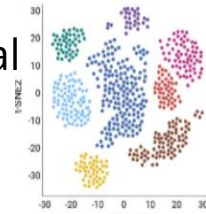


## Immunoprofiling

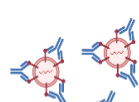
Multiplex cytokine profiling



High dimensional immuno-phenotyping



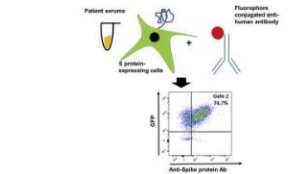
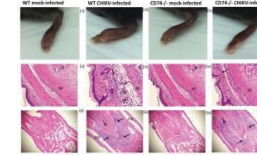
Neutralizing & total antibody response



Outcomes

## Developing Immune-Based Diagnostics and Animal Models

- Novel CHKV/ O Nyong Nyong mouse models



- S-Flow Assay

## Understanding Disease Pathogenesis

- Understanding COVID-19 and Monkeypox

*nature reviews immunology*

The trinity of COVID-19: immunity, inflammation and intervention

Monkeypox: disease epidemiology, host immunity and clinical interventions

## Diagnosis & Treatment Strategies

- Discovery of biomarkers for differentiating febrile fevers and disease severity in dengue

*Clinical & Translational Immunology*

Systematic analysis of disease-specific immunological signatures in patients with febrile illness from Saudi Arabia

*Cell Reports Medicine*

Immune cell phenotypes associated with disease severity and long-term neutralizing antibody titers after natural dengue virus infection

- Defective viral genome based therapeutics

*nature communications*

Defective viral genomes as therapeutic interfering particles against flavivirus infection in mammalian and mosquito hosts



# Building capabilities in ID Labs to combat antimicrobial resistance, the silent pandemic

## Resistant Pathogens

### "ESKAPE" bacteria



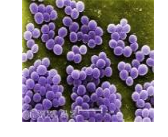
*Enterococcus faecium*



*Klebsiella pneumoniae*



*Acinetobacter baumannii*



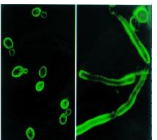
*Staphylococcus aureus*



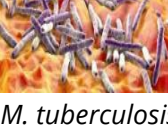
*Pseudomonas aeruginosa*



*Enterobacter spp.*

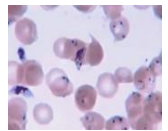


*Candida spp.*



*M. tuberculosis*

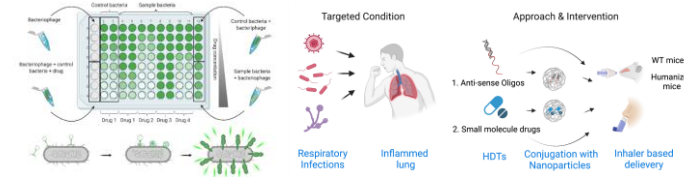
*Plasmodium spp.*



## ID Labs AMR Toolkit

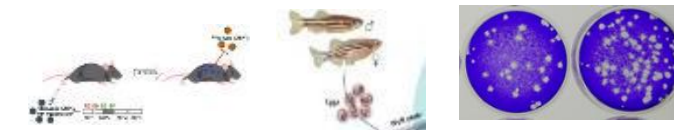
### Asset Discovery

- Microfluidics antibody discovery
- Host-directed therapies
- Phage therapy
- Candida screening platform



### Screening Assays

- *In vitro* cell cultures
- Drug susceptibility assays
- High throughput zebrafish & mouse infection models



Outcomes

## Mechanistic studies

- Explore genetic foundations of AMR, informing antibiotic development and drug discovery strategies

*The Journal of Infectious Diseases*

*The Journal of Infectious Diseases*

Integrative Genetic Manipulation of *Plasmodium cynomolgi* Reveals Multidrug Resistance-1 Y976F Associated With Increased In Vitro Susceptibility to Mefloquine

*HIVSA* *hivma*



A peptidoglycan storm caused by  $\beta$ -lactam antibiotic's action on host microbiota drives *Candida albicans* infection

## Novel treatment strategies

- Development of novel treatment strategies - antibiotics to which AMR has not yet evolved, host directed therapies

*Science* Translational Medicine

Metformin as adjunct antituberculosis therapy

LETTERS

<https://doi.org/10.1038/s41564-019-0381-1>

Antibody neutralization of microbiota-derived circulating peptidoglycan dampens inflammation and ameliorates autoimmunity

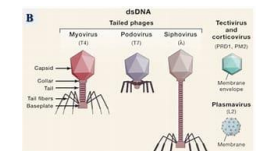
*nature microbiology*

## Surveillance and diagnostics

- Rapidly detect and react to AMR outbreaks

SCIENTIFIC REPORTS

Microchip-based ultrafast serodiagnostic assay for tuberculosis



Phage-based diagnostics

12

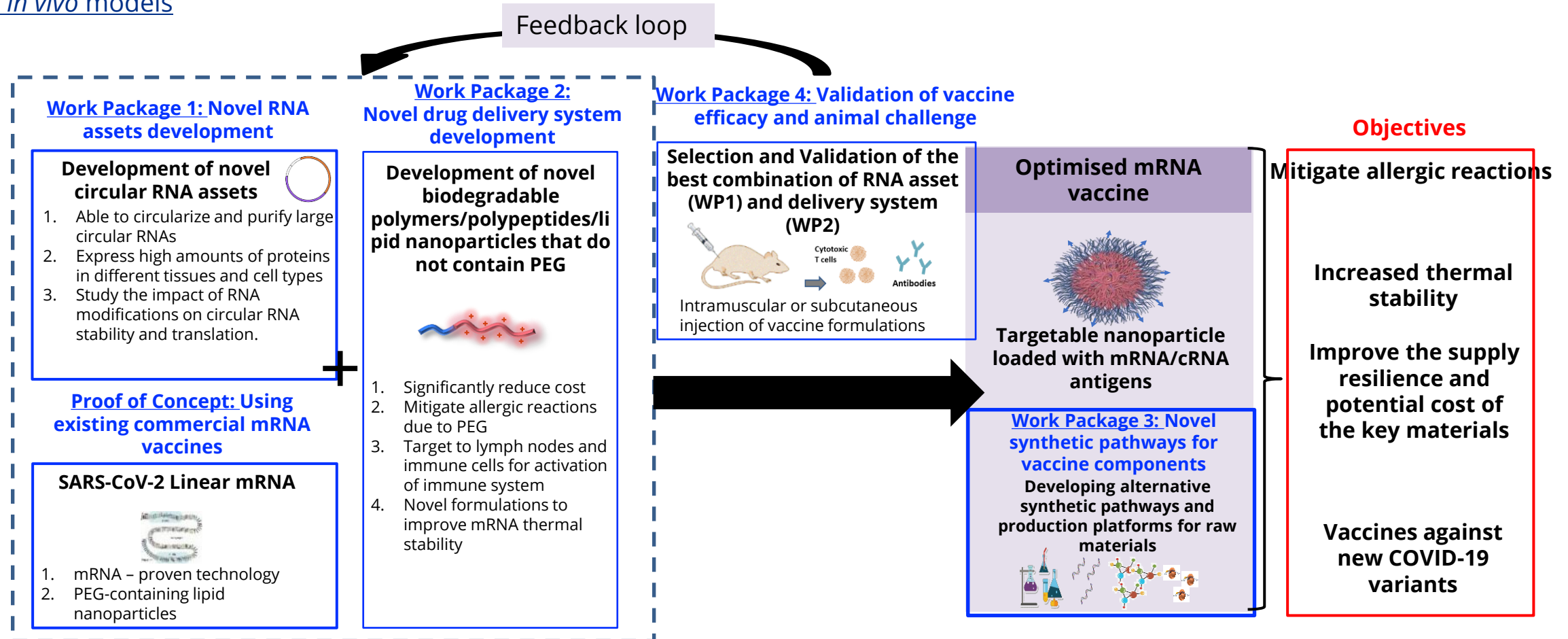




# NUCLEIC ACID THERAPEUTICS RESEARCH IN SINGAPORE/A\*STAR

# The Strategic Optimisation of mRNA vaccines for Preparedness of COVID-19 Variants Programme

The programme is a platform for the development of novel RNA vaccine technologies from discovery to novel encapsulation to proof of concept in *in vivo* models



ID Labs is the **host institution** for this multi-RI Programme to develop mRNA-based therapeutics



## **Nucleic Acids Therapeutics Initiative (NATi): A National Platform Hosted by A\*STAR**

### **Vision of NATi**

**Singapore to be the regional hub for NAT to achieve research and clinical translational excellence, strengthens resilience to future pandemics and supports a vibrant biotech ecosystem**

# NATi is a national platform to accelerate the translation of NAT Assets



**Dr Boon-Tong Koh**  
Executive Director, NATi  
Executive Director, BTI



## NAT Exchange

- Translational engine to drive RNA therapeutics into the clinic
- Build and develop delivery platforms to address industry challenges
- Partner with industry to co-develop platforms and avail validated technologies to support asset translation

## RNA Foundry

- Advance RNA manufacturing processes and technologies
- Production of pre-clinical and clinical-grade mRNA
- Partner with industry to co-develop and avail technology and manufacturing capacity



# NAT Exchange (NAT X) Overview

**NAT X** aims to **drive the research and development of RNA into the clinic** through:

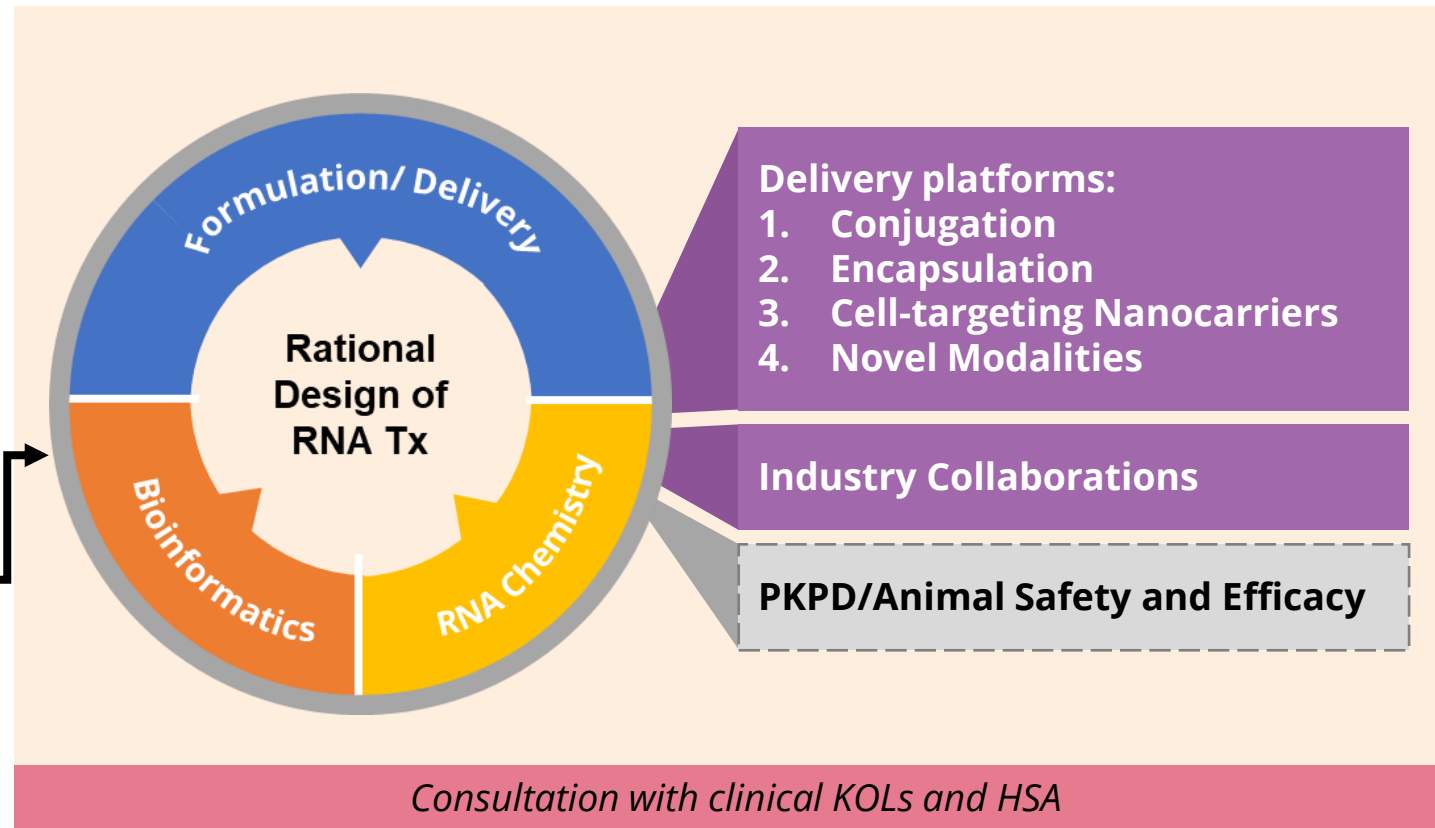
1. Supporting researchers' development of RNA therapeutics by **developing/partnering on enabling platforms** and developing alliances with clinical KOLs
2. Developing **new enabling technologies** to address clinical and industrial challenges

## Local/global assets/projects#:

1. RNA therapeutics, e.g., ASO, RNAi, mRNA, circRNA
2. Vaccines, e.g., cancer and infectious diseases
3. Editing, e.g., RNA-based CRISPR

*#May be supported by funding schemes, e.g., NIRBA, IAF-PP, STDR*

*Asset flow*



*Asset flow*

**Commercialisation  
vehicle/partners  
(e.g., out-license/  
spin-out)**

## Legend

Platforms to build/partner

Platforms to partner/buy

**KOLs:** Key Opinion Leaders, **PKPD:** Pharmacokinetic and Pharmacodynamic, **HSA:** Health Sciences Authority, **IAF-PP:** Industry Alignment Fund – Pre-positioning, **STDR:** Singapore Therapeutics Development Review

# Focus Areas in Delivery Technologies for NAT X

## Conjugation



### For small RNA delivery



Low bioavailability and rapid clearance



Explore chemical modifications and conjugates to enable targeted delivery and alternative routes of administration

## Encapsulation (Lipids, polymers, EVs)



### For large RNA delivery



Challenges in cytotoxicity, biodistribution, immunogenicity and stability



Develop and improve technologies to explore variations of component ratios and other additions, such as PEG and PBAE

## Cell-targeting Nanocarriers



### Integrates targeting ligands and nanocarriers



Lack of target specificity causing off-target side effects and lowered efficacy



Design and manipulate EV surfaces. Modulate composition of nanocarriers with high affinity targeting ligands and linkers.

## Novel Modalities



### Future new/innovative modalities/platforms



**Challenge**



**Research focus**

Legend

**EVs:** Extracellular vesicles, **PEG:** Polyethylene glycol, **PBAEs:** Poly( $\beta$ -amino ester)

*Note: Focus areas may be subject to change*

# RNA Foundry – Aims and Overview

RNA Foundry aims to:

1. **Address clinical and industry problem statements** and **revolutionise RNA manufacturing** through the development of next-generation manufacturing technologies and processes
2. **Support translation of RNA assets** from scientists, clinicians and academics by producing pre-clinical- and clinical-grade formulated RNA

## Strategy for building RNA manufacturing capabilities in Singapore

**Build**

**Partner**

**Manufacturing technologies  
and processes**

**Research-grade  
formulated RNA**

**GMP-grade  
formulated RNA**

**To build R&D capabilities in technology  
development and RNA manufacturing**

**To produce research- and GMP-grade formulated RNA**

### R&D Manufacturing Programme

Potential areas:

- New RNA design
- Continuous IVT flow reaction
- Plasmid production
- Encapsulation technologies
- Cell free synthesis
- Formulation
- Enzyme engineering

- Strategic industry partners will avail their expertise and facilities to produce research- and GMP-grade formulated RNA
- Researchers can access this capability to translate their mRNA assets for pre-clinical and clinical studies

# Focus Areas in Manufacturing for RNA Foundry

## New RNA Design



- ⚠ Inherent instability and susceptibility to degradation by nucleases and oxidative damage
- 🔍 Improve protein translation and stability to reduce reactogenicity

## Plasmid Production



- ⚠ Supply chain constraints, poor scalability and low efficiency
- 🔍 Improve scalability and efficiency to reduce impact of supply chain disruptions

## Raw Material Synthesis



- ⚠ High cost and availability dependent on limited suppliers
- 🔍 Diversify raw materials to reduce reliance on suppliers to improve cost-effectiveness and build pandemic resilience

## Quality Control/Attributes



- ⚠ Lack standardised and well-defined quality control attributes
- 🔍 Develop analytical methods to characterise starting materials, intermediates and final products

## In-Vitro Transcription (IVT)



- ⚠ High cost, dsRNA by-product generation and high variability
- 🔍 Reduce dsRNA by-product generation by developing optimised protocols and/or novel T7 polymerase systems

## Purification



- ⚠ Highly variable output, low efficiency and recovery, poor scalability
- 🔍 Improve efficiency and scalability to maximise recovery to achieve high purity

## Encapsulation and Formulation



- ⚠ Thermal instability, allergenic and IP limitations
- 🔍 Develop novel/improved encapsulation technologies and explore alternate formulation strategies

⚠ Challenge

🔍 Research focus

*Note: Focus areas may be subject to change*

Legend

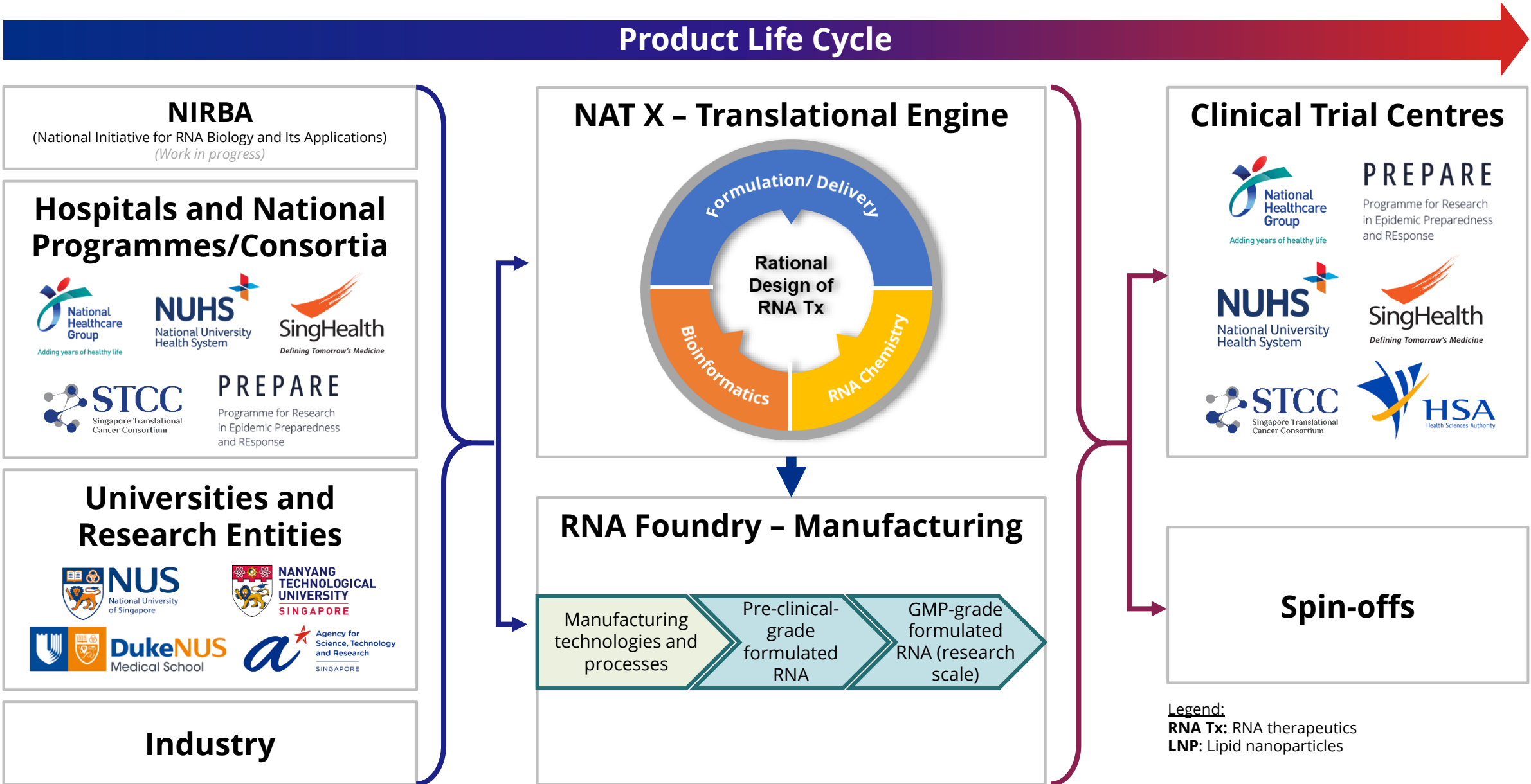
**mRNA:** Messenger RNA

**dsRNA:** Double-stranded RNA

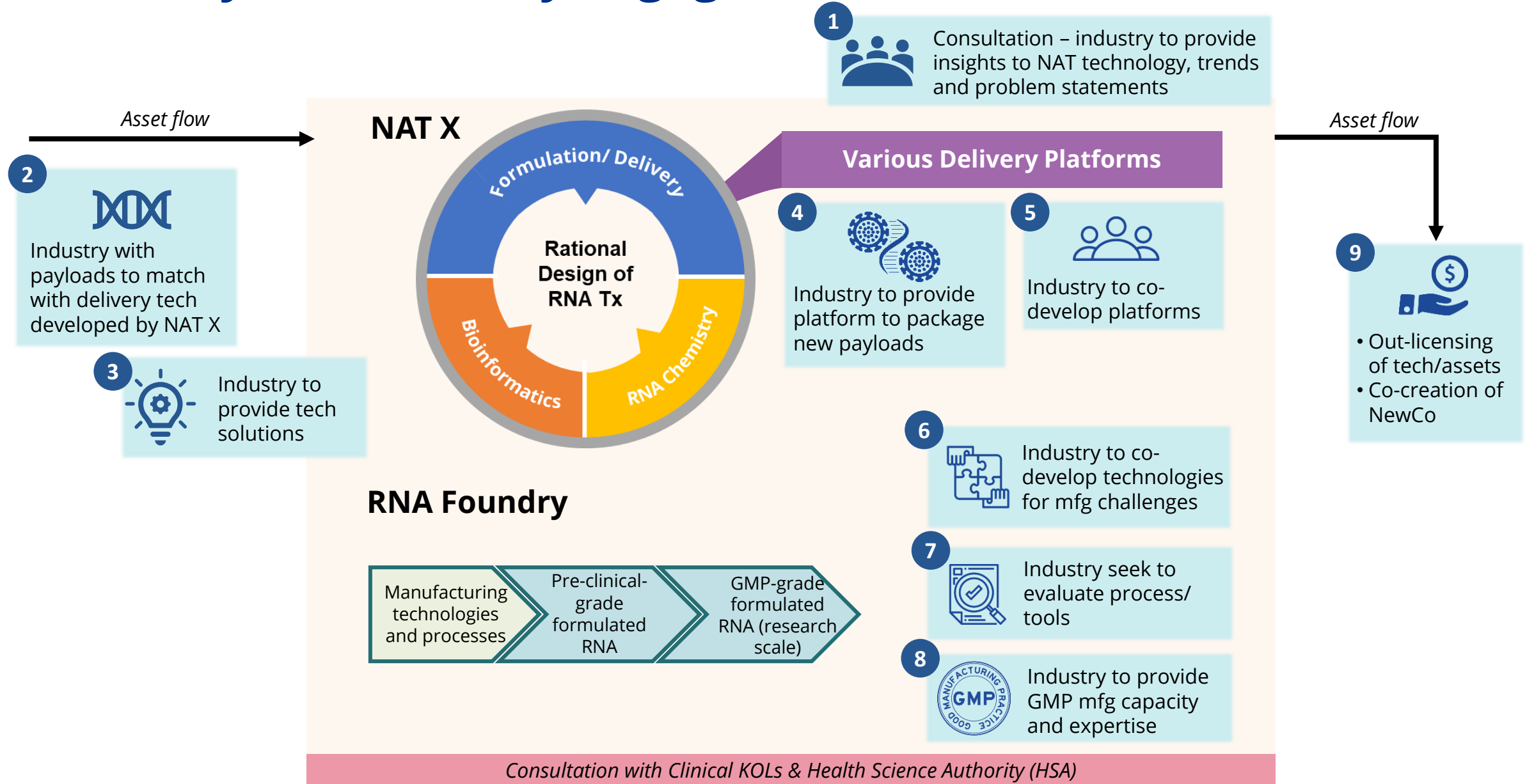
**IP:** Intellectual property



# Synergy of NATi in the Ecosystem



# 9 Pathways for Industry Engagement





# THANK YOU

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[www.a-star.edu.sg](http://www.a-star.edu.sg)