Clinical translation of an mRNA cancer vaccine adjuvanted with alpha-galactosylceramide

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FACULTY OF PHARMACEUTICAL SCIENCES

Laboratory for General Biochemistry and Physical Pharmacy

nanomedicines & biophotonics

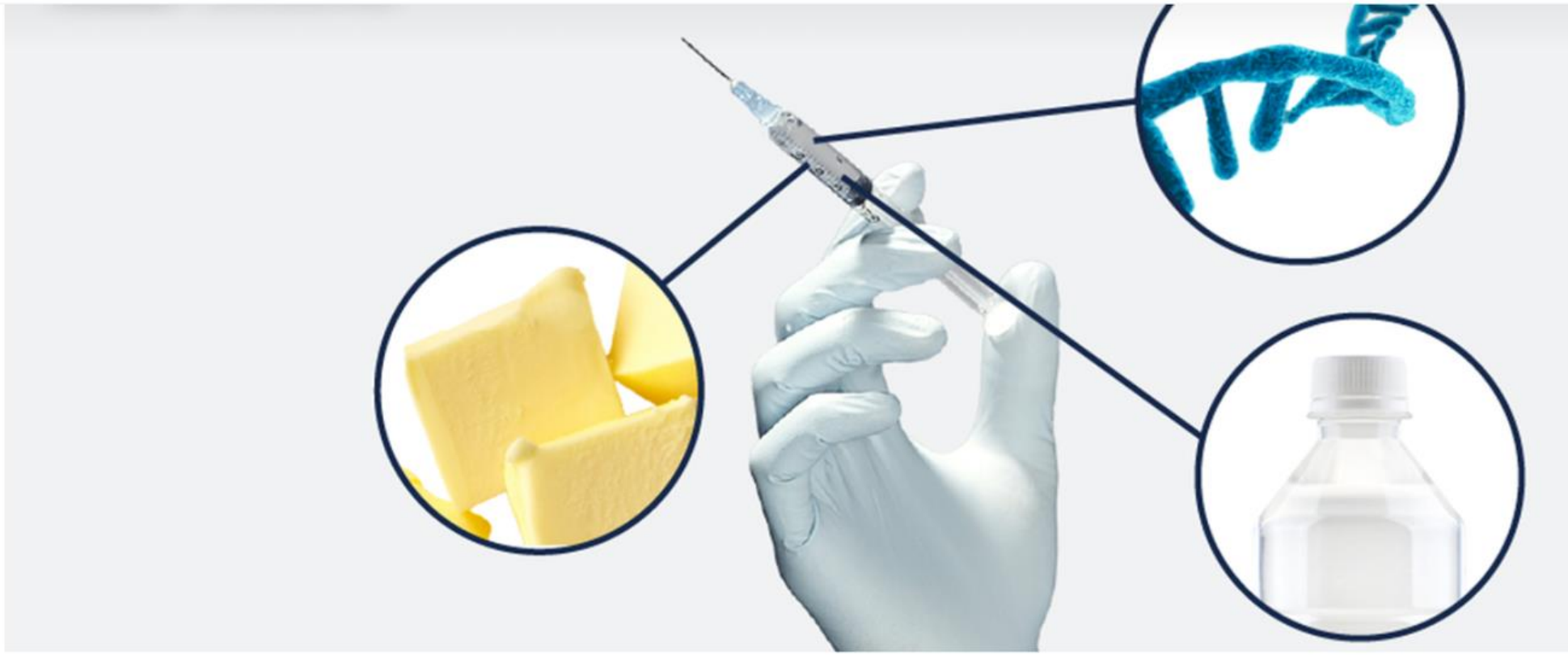
CRIG

Table 3. Total cumulative number of health outcomes averted by BNT162b2, and associated cost-savings.

Outcomes	"Low" scenario	Base case	"High" scenario
Symptomatic cases, *n*	5,033,511	8,663,085	13,853,033
Deaths, *n*	45,760	111,380	202,797
Outpatient cases, *n*	4,771,447	7,973,287	12,590,046
Hospitalizations, *n*	262,065	689,797	1,262,987
General ward without IMV	*189,680*	*501,191*	*918,794*
General ward with IMV	*12,401*	*32,104*	*58,512*
ICU without IMV	*24,876*	*65,279*	*119,376*
ICU with IMV	*35,108*	*91,223*	*166,305*
QALY lost, discounted	489,548	1,144,091	2,056,257
Cost outcomes, USD			
Direct costs (billions)	$12.7	$30.4	$57.4
Productivity loss (billions)	$22.4	$43.7	$73.3

Abbreviations. ICU, intensive care unit; IMV, invasive mechanical ventilation; LY, life year; QALY, quality-adjusted life year; USD, United States dollar.

Di Fusco et al. J. Medical Economics. 2022



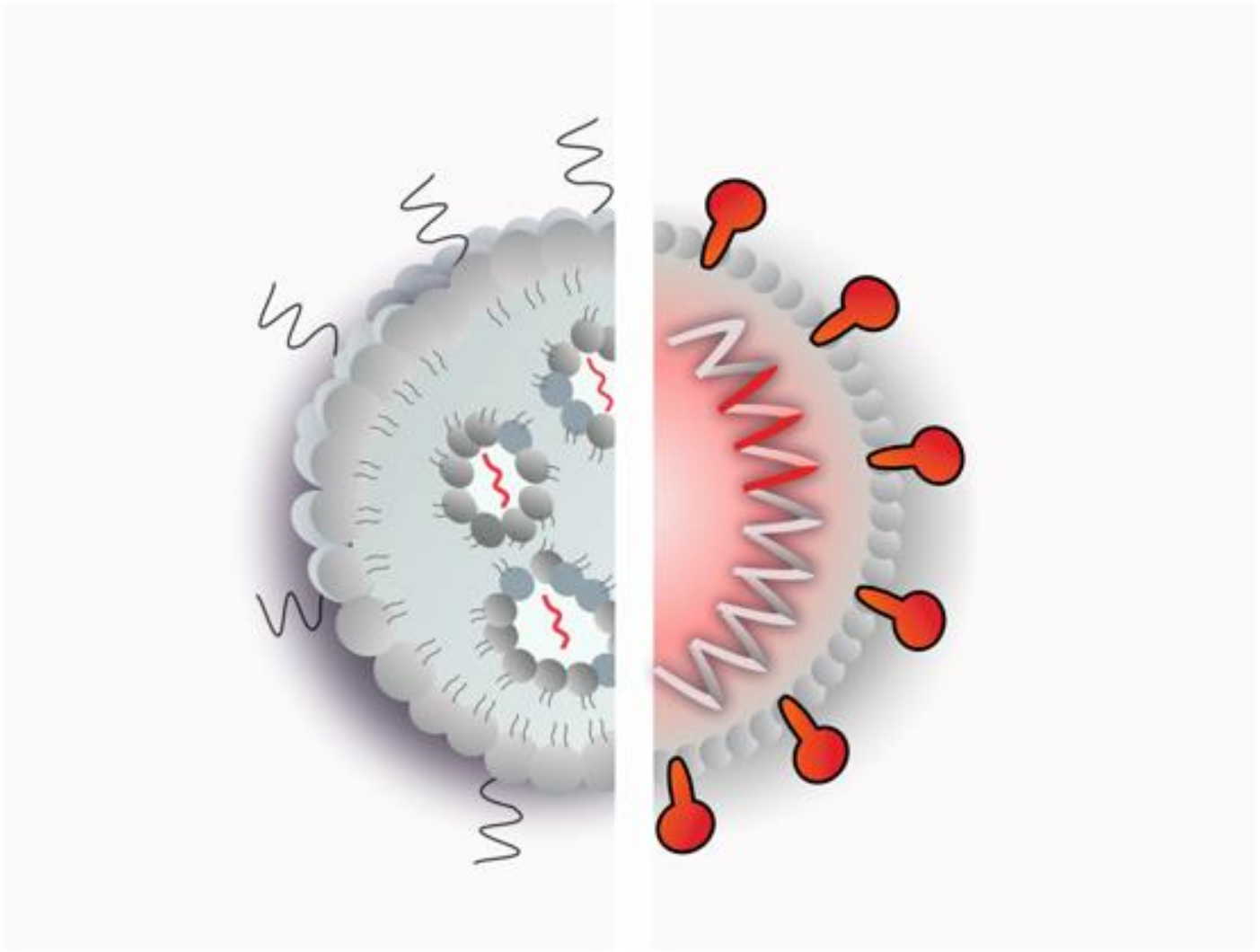
THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2023

Katalin Karikó Drew Weissman

"for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19"

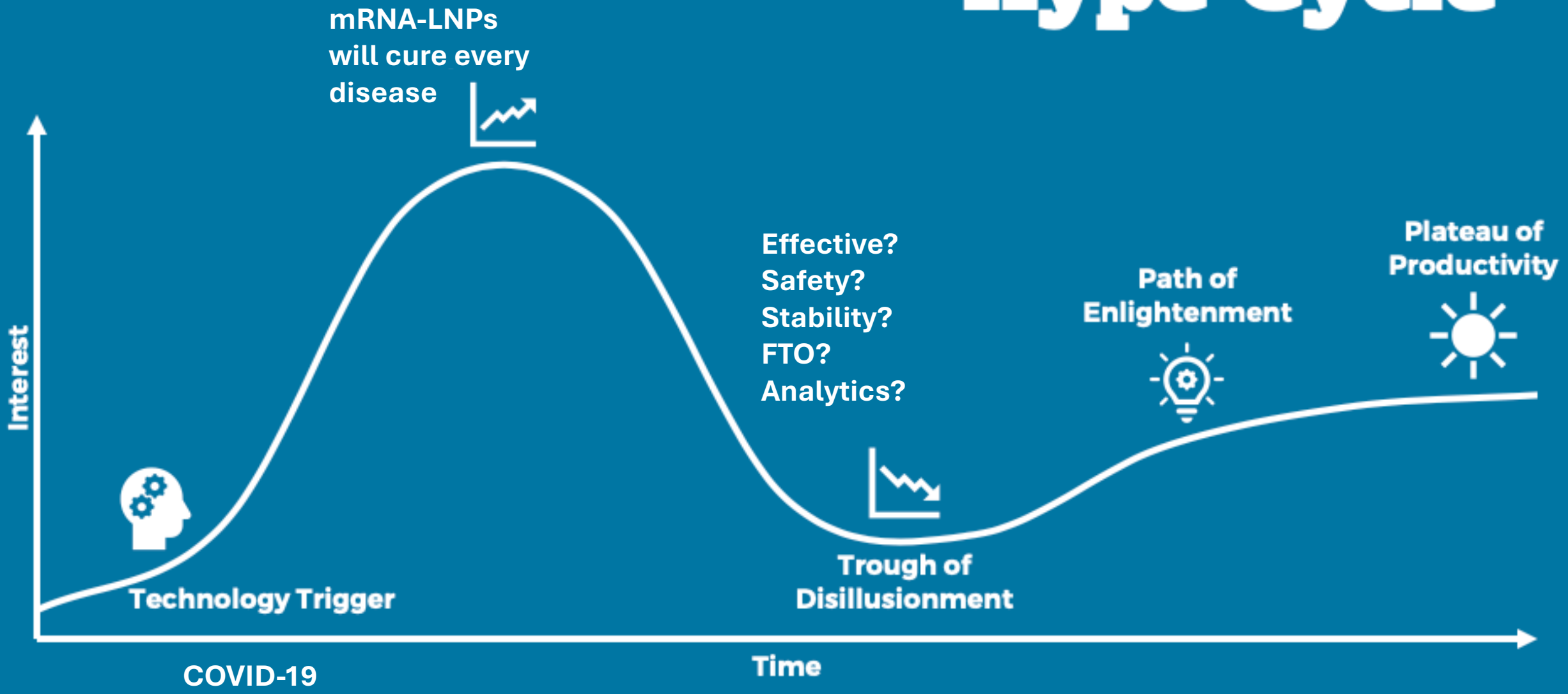
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

Lipid nanoparticles as most advanced non-viral delivery system



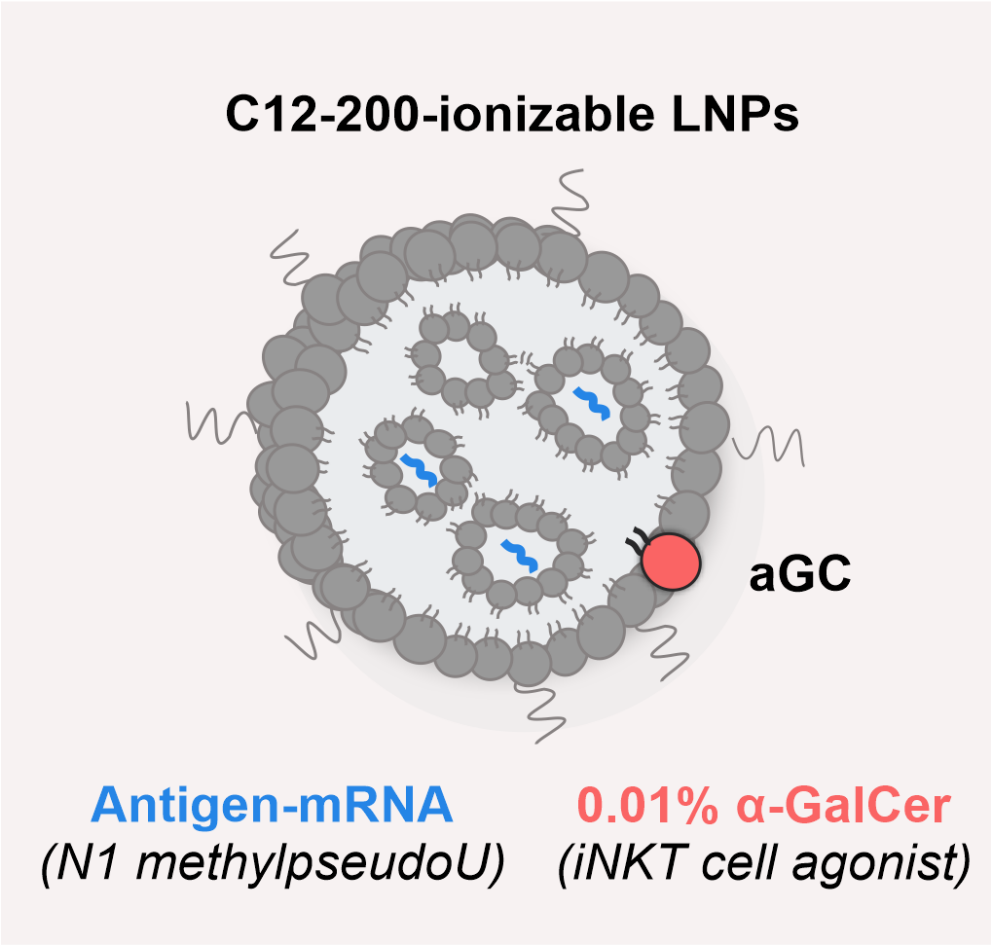
Ionizable lipid is the critical component that allows intracellular delivery

Hype Cycle


mRNA-LNPs will cure every disease
Effective?
Safety?
Stability?
FTO?
Analytics?
Path of Enlightenment
Plateau of Productivity
Interest
Technology Trigger
Trough of Disillusionment
COVID-19
Time

“Our lab wants to better understand how mRNA-LNPs work with the ultimate goal to develop vaccines with greater effectiveness and/or milder adverse events in the future”

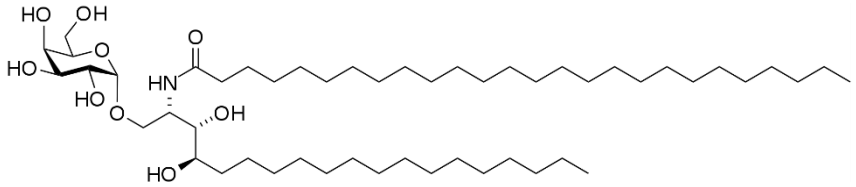
Galsomes: mRNA LNP vaccine adjuvanted with α-galactosylceramide



Co-encapsulation

- **Nucleoside modified mRNA encoding antigens**
  immunosilent -> limited type I IFN activity
  Increased stability and translation capacity

- **α-galactosylceramide (adjuvant)**
  Glycolipid antigen presented in CD1d pathway
  recognized by Natural Killer T cells (iNKT cells)

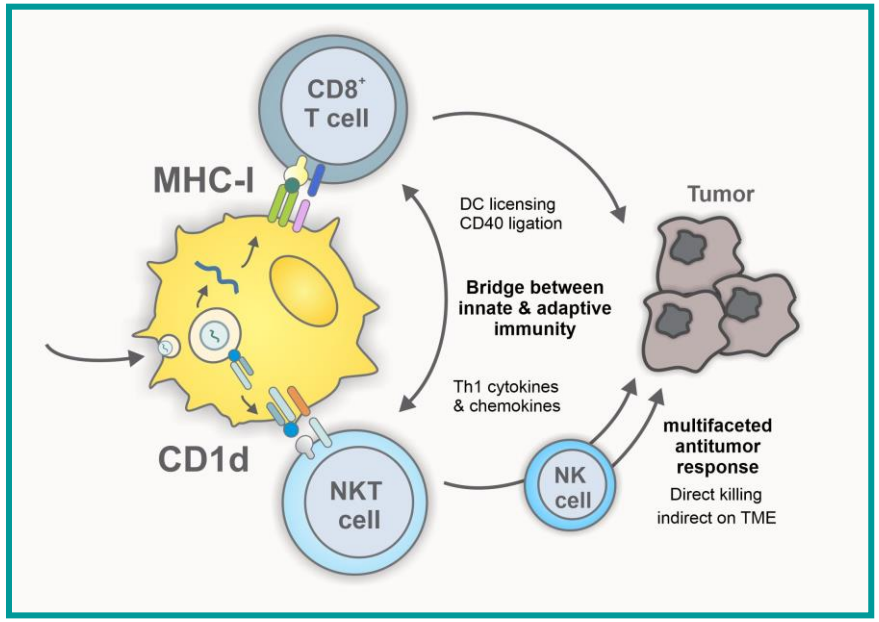


Verbeke, R. et al. ACS Nano 2019
WO2020058239A1

Exploring Galsomes as cancer therapeutics and bacterial vaccines

Lung cancer

Galsome-NEO ATMP



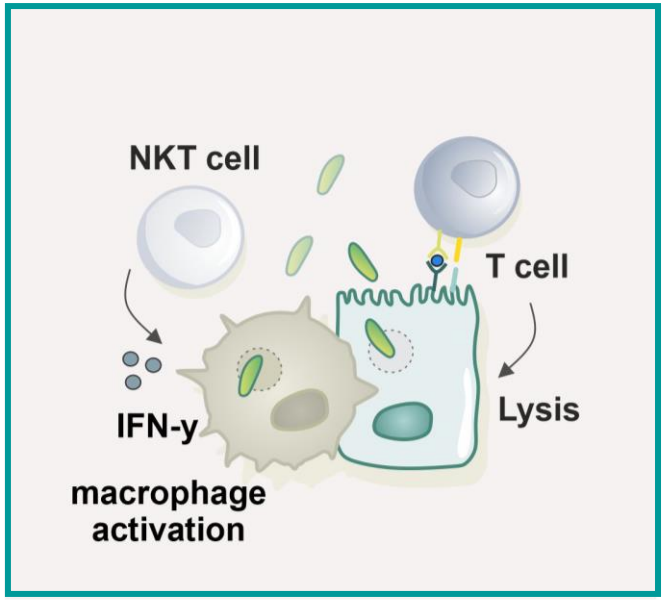
- Lung cancer patients have **lower % NKT cells**
- Activated NKT cells have **direct cytotoxic effects**
- Bystander activation of **NK cells**
- Galsome vaccination **depletes immunosuppressive cells in TME**

Verbeke, R. et al. ACS Nano 2019
Meulewaeter S. et al. JCR 2024

Enhanced cellular immunity
iNKT and NK activation
Effects on myeloid cells

Intracellular bacterial infections

Galsome vaccine



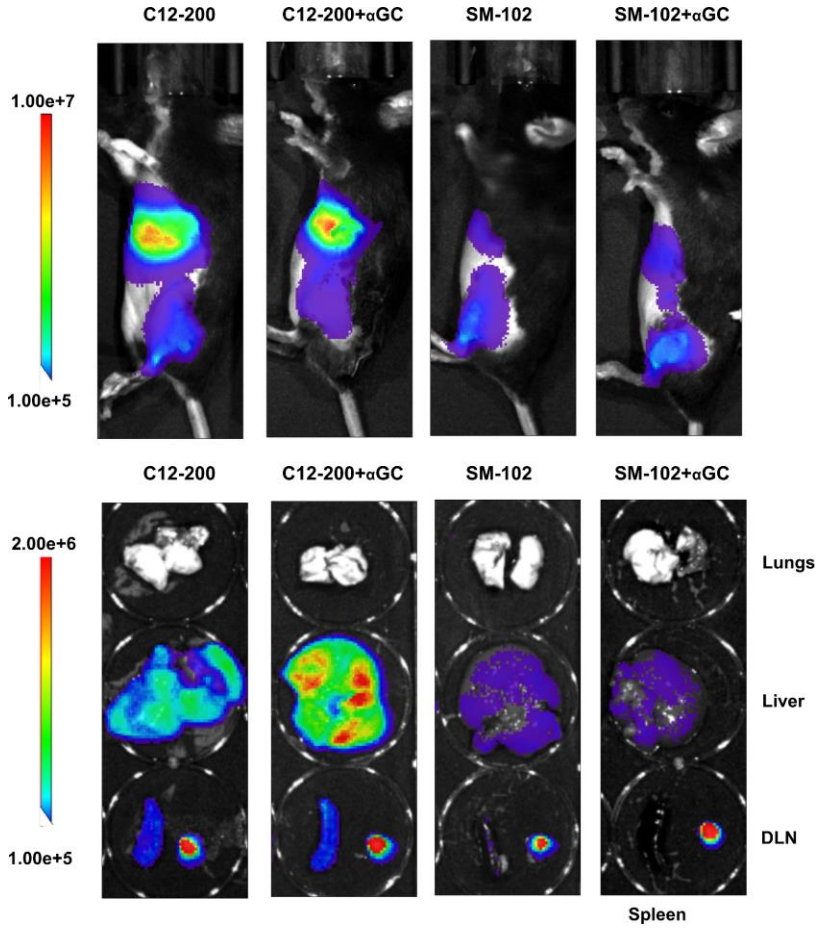
- **Mtb derived lipids (PIMs)** complex with **CD1d** to activate NKT cells during natural infection
- Active TB patients have **lower % NKT cells**
- Activated NKT cells have a **direct bactericidal effect** in mice
- Mice immunized with BCG or subunit vaccines + αGalCer are **better protected against Mtb**
- Galsome vaccination **depletes immunosuppressive cells**

Mayer. et al. Nat. Commun. 2024
Meulewaeter S. et al. JCR 2024
https://www.baxerna.eu/

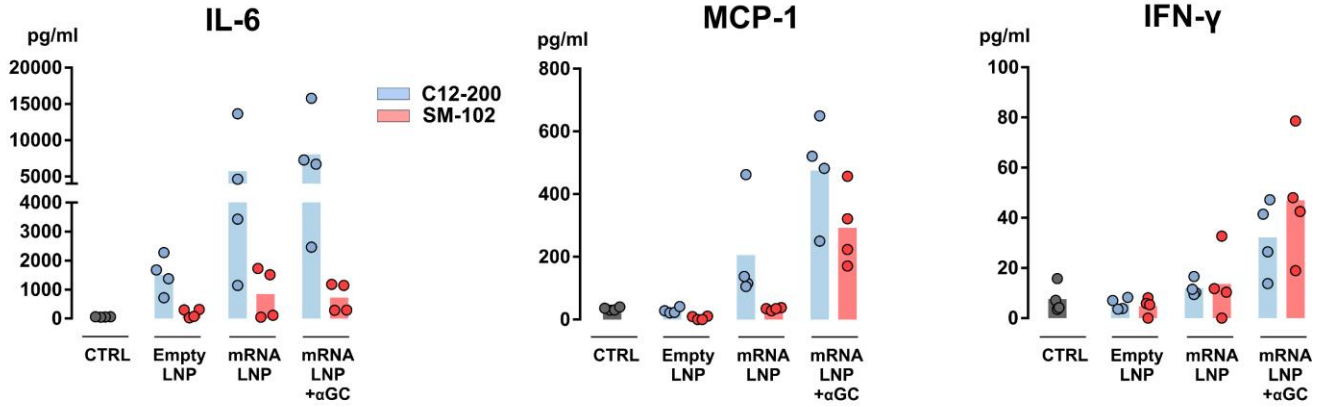
Kom op tegen Kanker

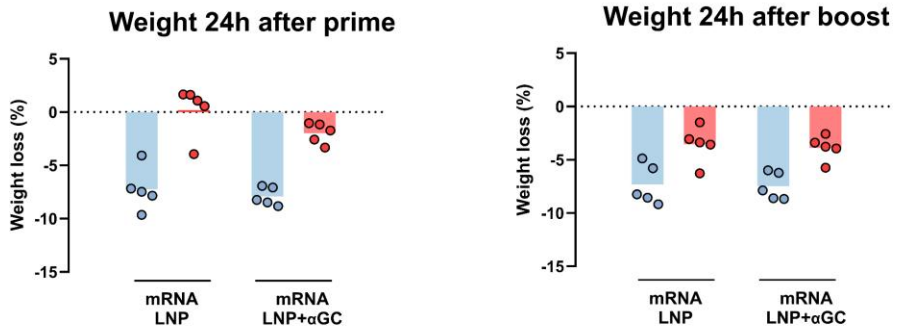
Funded by the European Union

Benchmark with Moderna's mRNA cancer vaccine platform



(6h post-injection of 2.5µg luciferase mRNA)

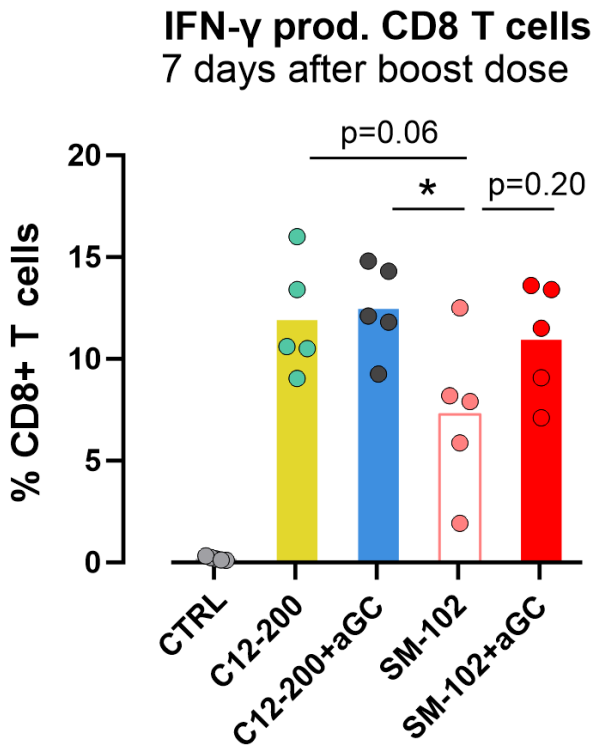




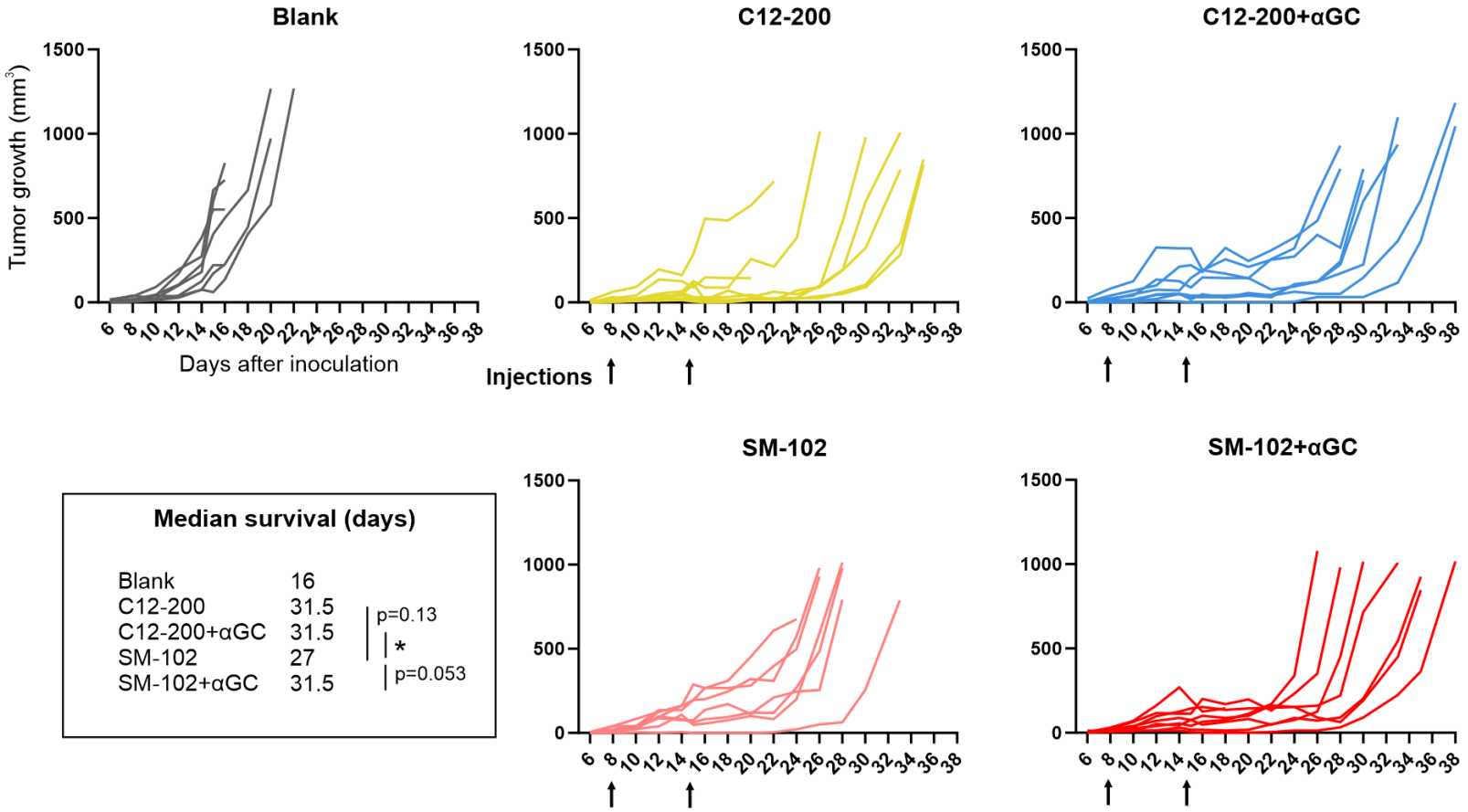
- C12-200 is more inflammatory than SM-102 (Moderna)
- C12-200 is slightly better in transfection than SM-102

Meulewaeter S. et al. JCR 2024

Benchmark with Moderna's mRNA cancer vaccine platform



B16-OVA melanoma model



Median survival (days)

Blank	16	
C12-200	31.5	p=0.13
C12-200+αGC	31.5	*
SM-102	27	p=0.053
SM-102+αGC	31.5	

Meulewaeter S. et al. JCR 2024

Development of an adjuvanted mRNA cancer vaccine

Kom op tegen Kanker

Partnered with
UZ Ghent (hospital)
B. Vandekerckhove
K. Vermaelen

Idea

Let's combine with adjuvantia

2015-2019

JCR 2017: Combi modif. RNA + MPLA in LPXs

1st gen. Galsomes

ACS Nano 2019 Combi modif. RNA + aGC in LPXs

2019-2024

Clinical-grade Galsomes

- Optimization of Galsome formulation
- GMP production process defined and validated (including release analytics)
- Pre-clinical toxicity evaluation
- Clinical design

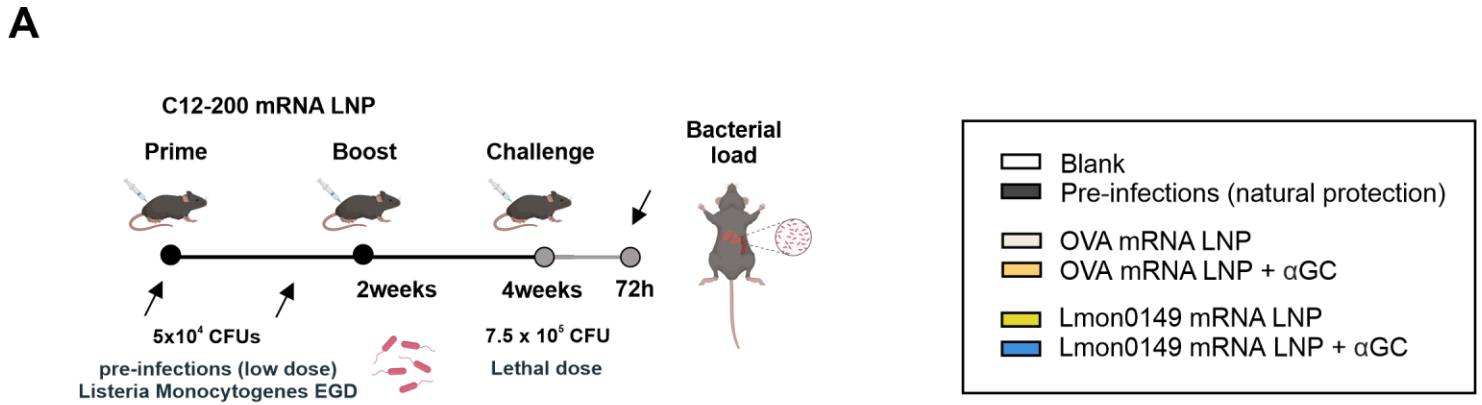
Investigational Medicinal Product Dossier

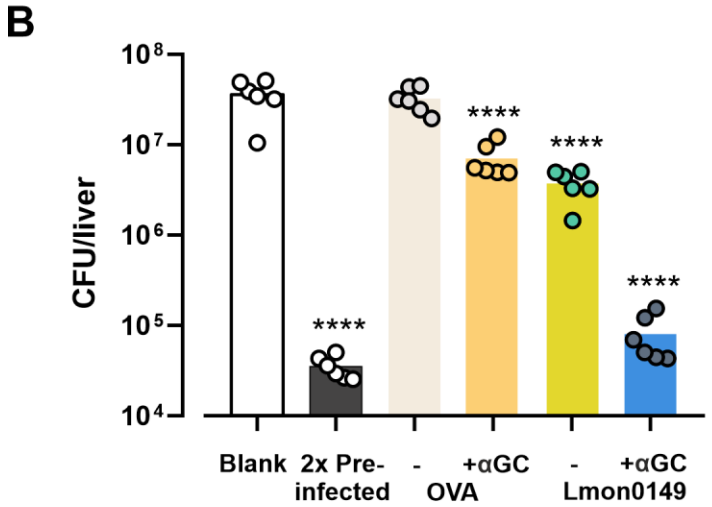
Phase I study

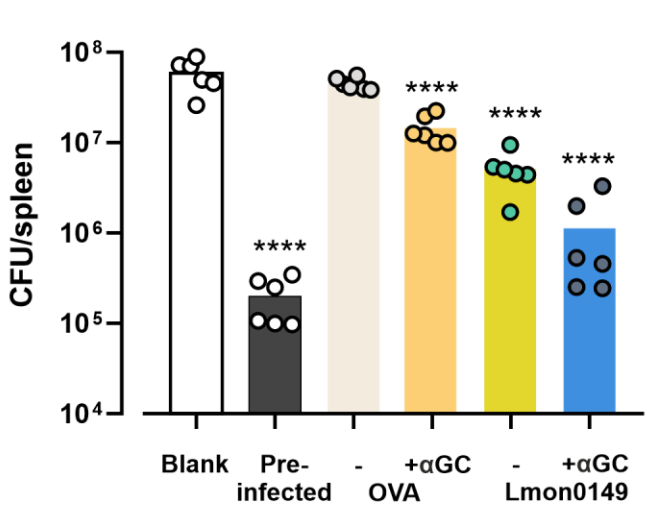
stage II-III NSCLC patients

- Dose escalation study
- Primary - safety evaluation
- Secondary - T cell read-out

Proof of concept in Listeria Monocytogenes







Meulewaeter S. et al. JCR 2024

mRNA vaccines to tackle MDR bacteria – EU-funded project BAXERNA 2.0

Institut Pasteur

Demangel
Mycobacteria
Tuberculosis & Buruli Ulcer

Van der Henst & Muraille
Acinetobacter baumannii
AMR

VIB science meets life

ULB Université Libre de Bruxelles

VIB
Impens
MS Proteomics
Immunopeptidomics

VIB
Martens
MS Bio-IT
Immunopeptidomics

Antigen discovery

mRNA vaccine development

Breckpot
mRNA design
immunotherapy

Lentacker/De Smedt
mRNA vaccines
adjuvantia

Netea
trained immunity
innate immunity

Loré
vaccine mechanisms
In vivo models

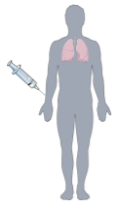
VUB Vrije Universiteit Brussel

Ghent University

Radboudumc

Karolinska Institutet

Ghent University
Vandekerckhove
GMP mRNA-LNP
production



Ghent University
Vermaelen
Pneumology
Tuberculosis

Ghent University
Leroux-Roels
Center for Vaccinology
Clinical trials

GMP unit Cell Therapy GENT

clinical trial

VFI Vaccine Formulation Institute — Analytical Methods

RheaVita — Vaccine lyophilization & storage

Quantoom Biosciences — Cheaper en local Vaccine production

Funded by the European Union

BAXERNA
Next-Generation Bacterial mRNA Vaccines
www.baxerna.eu

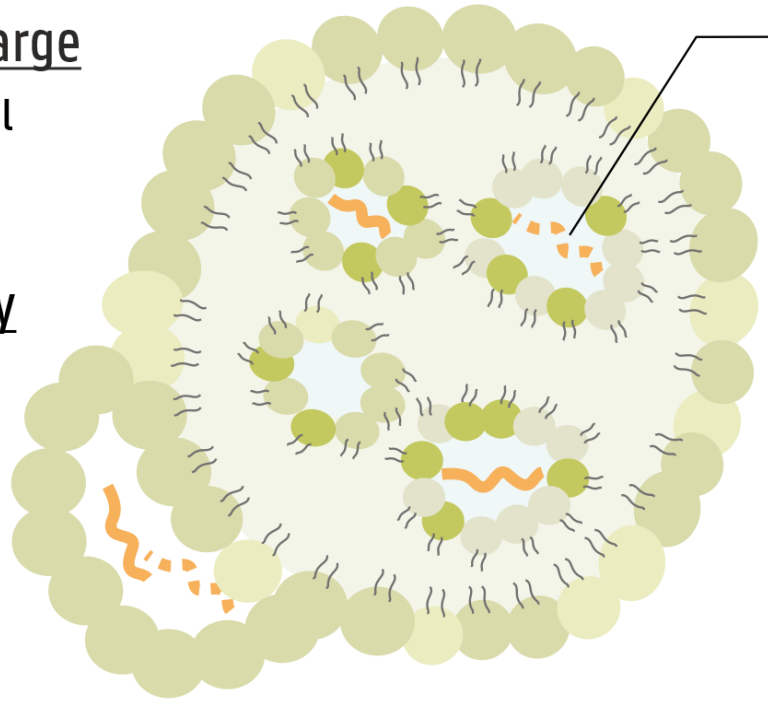
Advanced analytical toolbox for mRNA-LNP characterization

Size and surface charge

- DLS & zeta potential measurements

Morphology & heterogeneity

- Cryo-EM
- AF4-MALS/DLSUV/dRI
- µDSC



RNA content & loading

- Ribogreen
- Fragment analyzer
- AF4-MALS/DLS/UV/dRI
- FCS

Lipid composition

- UPLC-CAD

Quality and stability of formulations
Structure-activity relationships
Novel LNP formulations

Nanomedicine center

Mission

To offer cutting-edge pharmaceutical expertise and infrastructure to academic and industrial partners for the formulation of bio-therapeutics in nanoparticles from early discovery into first-in-human clinical trials.

Unique value

+20 years of expertise in nanomedicines and delivery of nucleic acids (since 1999)

Cutting edge infrastructure for analytical and biological characterization of nanomedicines

Close collaboration with Clinical GMP unit for small scale clinical production of mRNA-LNP vaccines (UZ Gent).

Our services

Consultation on formulation and delivery of bio-therapeutics

Formulation of bio-therapeutics in state-of-the art lipid nanoparticles

In-dept biological and analytical characterization of nanomedicines

gsk GlaxoSmithKline argenx Pfizer CEPI Quantoom Biosciences DROIA labs

vaxadvance

•Unites forces of **Nanomedicine center**, Good Manufacturing Practice (**GMP) Unit UZ Gent** and **Center for Vaccinology** (CEVAC)

•Vaxadvance provides **comprehensive services for the development, production and testing of novel mRNA vaccines** on the Ghent University Hospital campus

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Prof. Hristo Svilenov

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www.drugdelivery.be

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GHENT UNIVERSITY

CEPI

Kom op tegen Kanker

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fwo Research Foundation Flanders
Opening new horizons