mRNA科學：
從當前成功邁向無限未來

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大綱

- mRNA 技術平臺與莫德納
- mRNA 疫苗的安全性&常見迷思
- mRNA 技術的未來-疫苗
- mRNA 技術的未來-罕見疾病與腫瘤

➢mRNA 技術平臺與莫德納

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Moderna的重要時刻

2010
Moderna Incorporates
Moderna's name combines the words "modified" and "RNA", which happens to contain the word "modern."

2011
Operations started
Moderna begins research into the production of mRNA medicines. Stéphane Bancel joins as founding CEO.

2014
Expansion
New headquarters and labs open in Cambridge, Massachusetts.

2015
First human dose of flu vaccine
Moderna initiates first-in-human dose of an mRNA vaccine (mRNA-1440), an H10N8 flu vaccine candidate.

2016
New lease signed
Lease signed to build 200,000 sq ft GMP mRNA clinical manufacturing facility in Norwood, MA

2017
First human dose of multivalent vaccine
Moderna initiates first-in-human dosing for mRNA-1653, a combination vaccine with the potential to protect against more than one disease – human metapneumovirus (hMPV virus) and parainfluenza virus.

2018
New facility opens
Moderna opens its state-of-the-art clinical development site in Norwood, MA.

2019
First antibody encoded by mRNA
Moderna announces dosing of the first antibody encoded by mRNA in a clinical trial.

2020
CDC recommendation
The U.S. Centers for Disease Control and Prevention votes to recommend the use of the Moderna COVID-19 vaccine in people 18 years of age and older in the U.S.

2022
Moderna receives full approval for COVID-19 vaccine & RSV vaccine by U.S. FDA
The U.S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for SPIKEVAX (COVID-19 Vaccine, mRNA) to prevent COVID-19 in individuals 18 years of age and older in the U.S.

mRNA 有什麼功能？

傳遞訊息：DNA → mRNA → 蛋白質

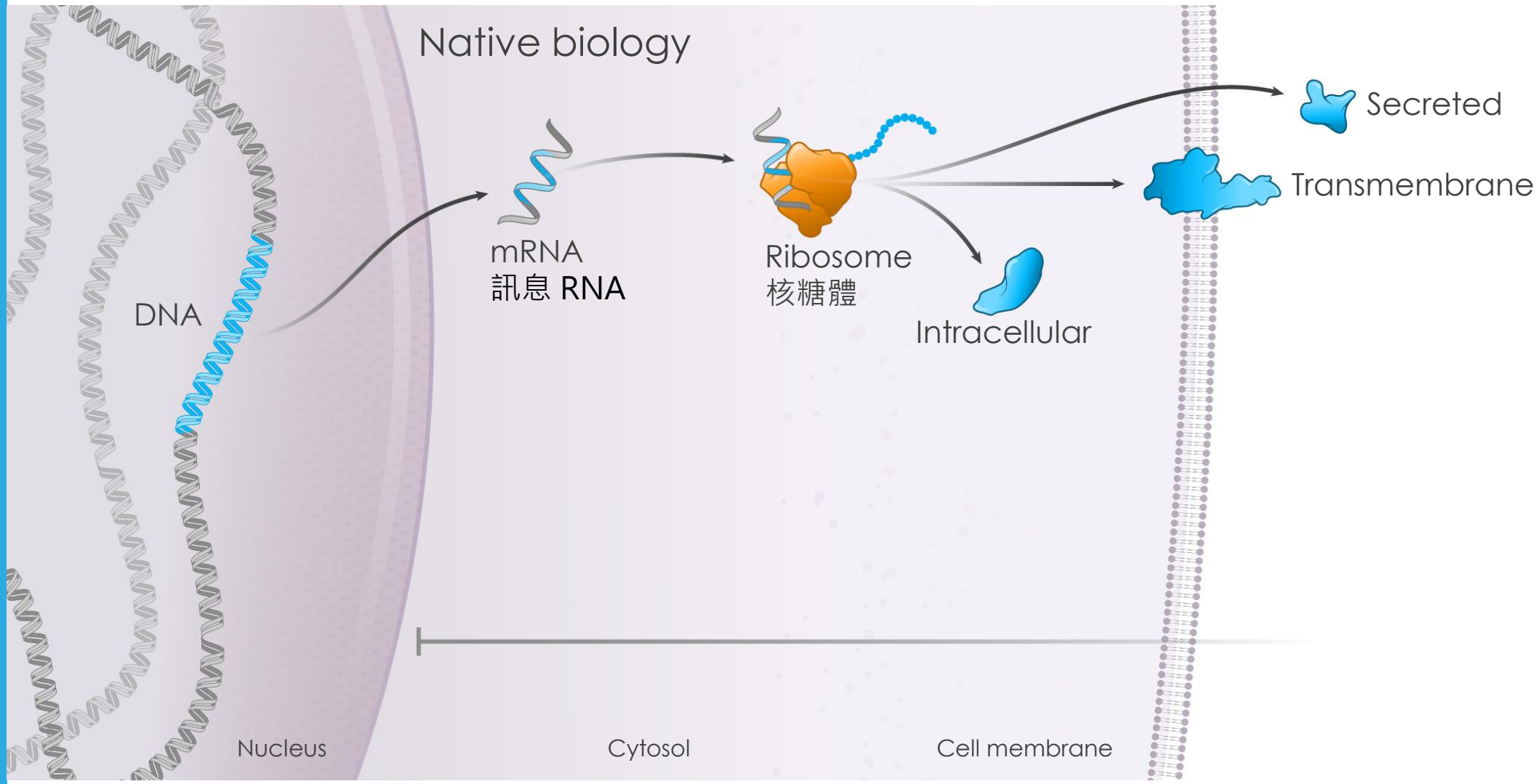
mRNA 稱為訊息 RNA，**負責把 DNA 轉化後的遺傳訊息，攜帶到細胞中製造蛋白質的工廠**，
工廠會依照 mRNA 的訊息內容，製造出各種功能的蛋白質[1]

人體細胞是一座蛋白質工廠

DNA = Deoxyribonucleic Acid; mRNA = Messenger Ribonucleic Acid

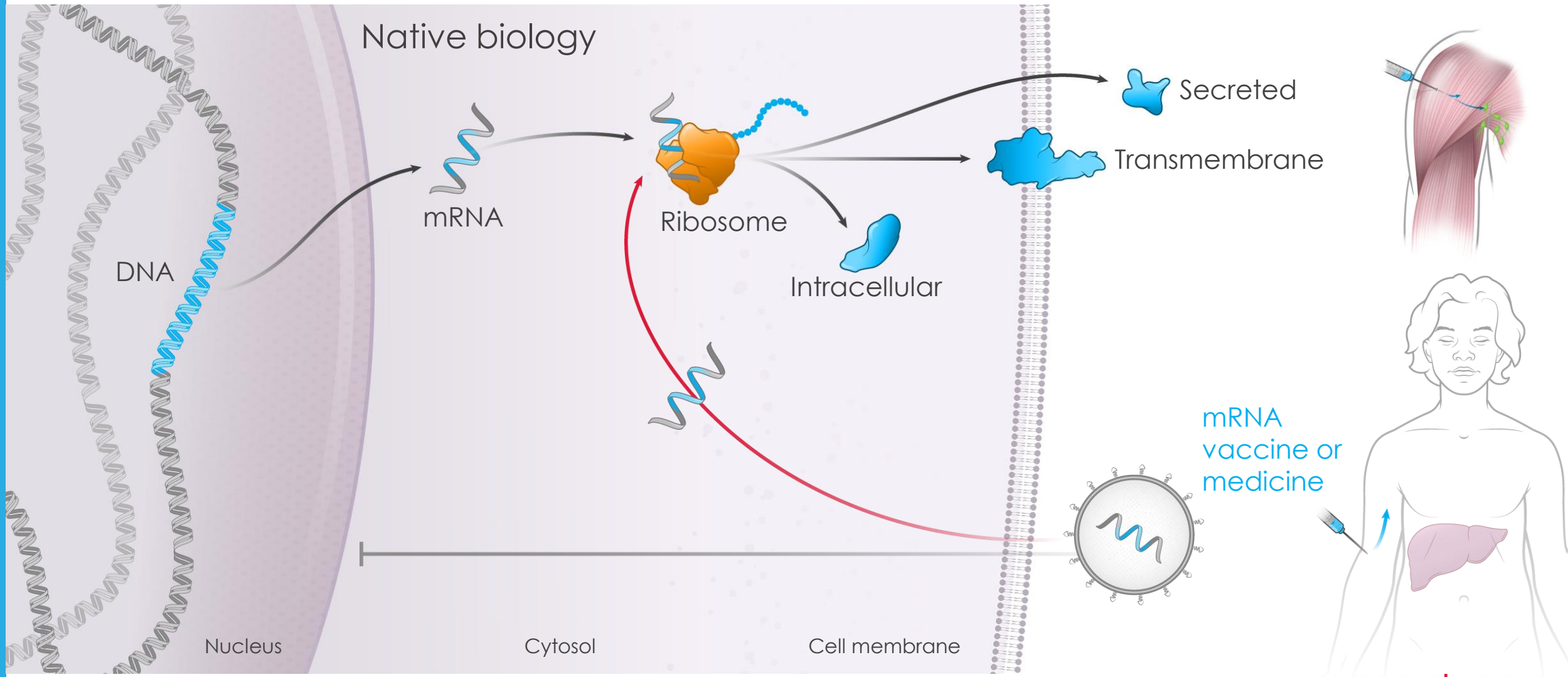
Reference :
1. Clancy S., et al. Nature Education. 2008. 1(1):101

mRNA疫苗和藥物是利用人體的細胞機制來產生藥用蛋白[1]



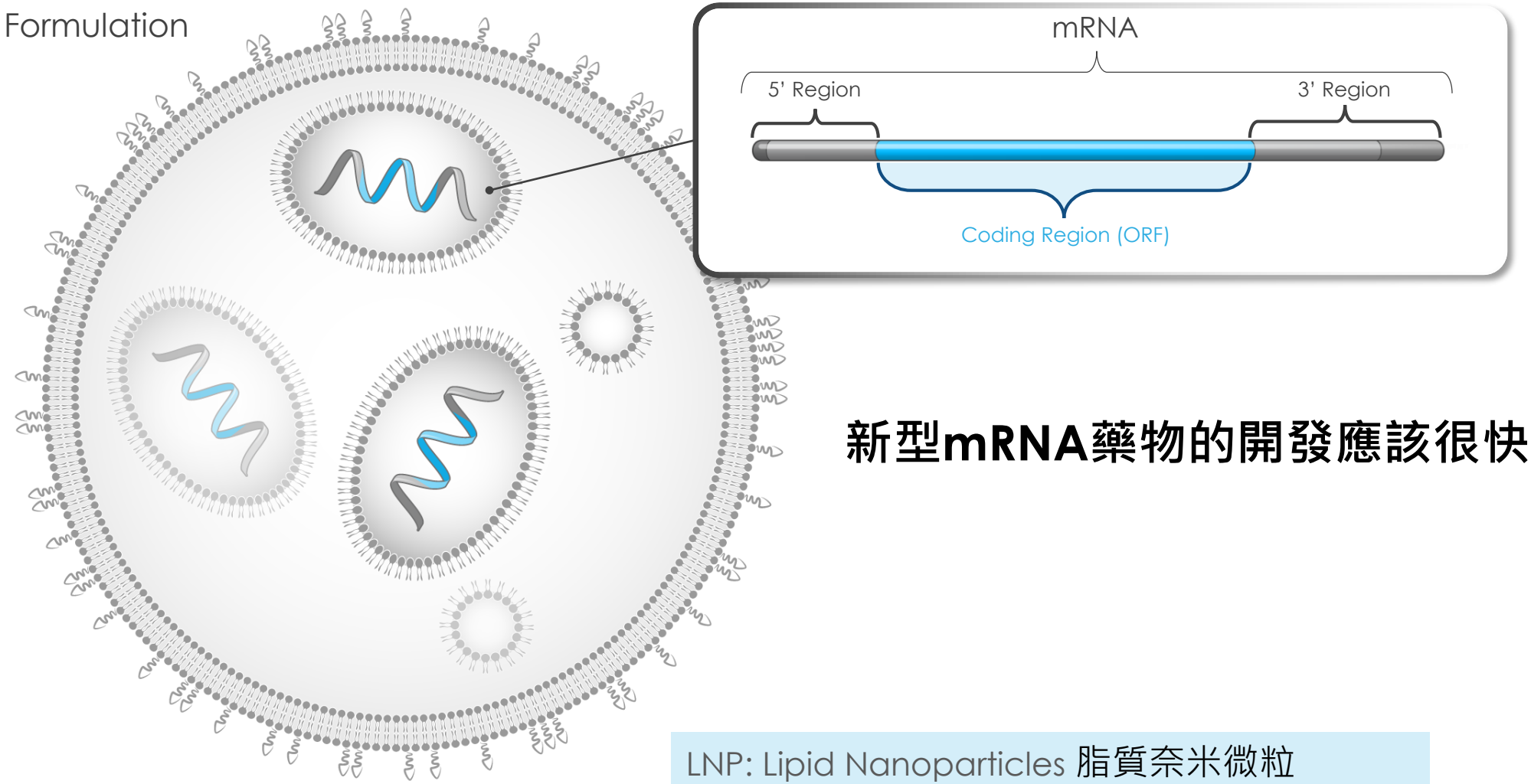
1. Adapted from Pardi N, et al. *Nat Rev Drug Discov* 2018;17:261–79.

mRNA疫苗和藥物是利用人體的細胞機制來產生藥用蛋白[1]



1. Adapted from Pardi N, et al. *Nat Rev Drug Discov* 2018;17:261–79.

mRNA藥物是一項平台技術-
它們的作用就像軟體， 不同mRNA藥物之間僅在編碼區域有所不同

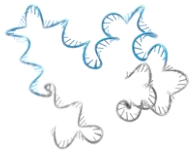


新型mRNA藥物的開發應該很快!

LNP: Lipid Nanoparticles 脂質奈米微粒

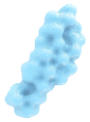
1. Adapted from Pardi N, et al. *Nat Rev Drug Discov* 2018;17:261–79.

LNPs 的所有關鍵成分都是可生物降解的



mRNA
- Contains all naturally occurring nucleotides, including modified Uridine
- Eliminated by endogenous mRNA decay machinery

Ionizable lipid (RNA binding lipid)
- Readily breaks down to saturated fatty acids ready for elimination



Cholesterol
- Widely present in the human body

Distearoyl phosphatidylcholine (DSPC)
- Core phospholipid component of cell membranes

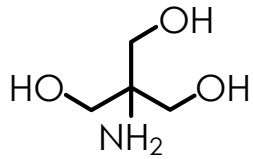
Polyethylene glycol (PEG) lipid
- Rapidly digested into two fatty acids and a 2k PEG polymer, which is found in numerous consumer products from toothpaste to Tylenol®

Water

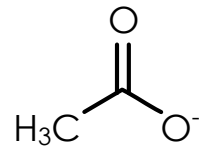
Sucrose
蔗糖

Sodium Chloride

The only other components are water, sugar, salt, & GRAS pharmaceutical buffers



Tris buffer
Approved IV drug
Approved as excipient



Acetate
GRAS

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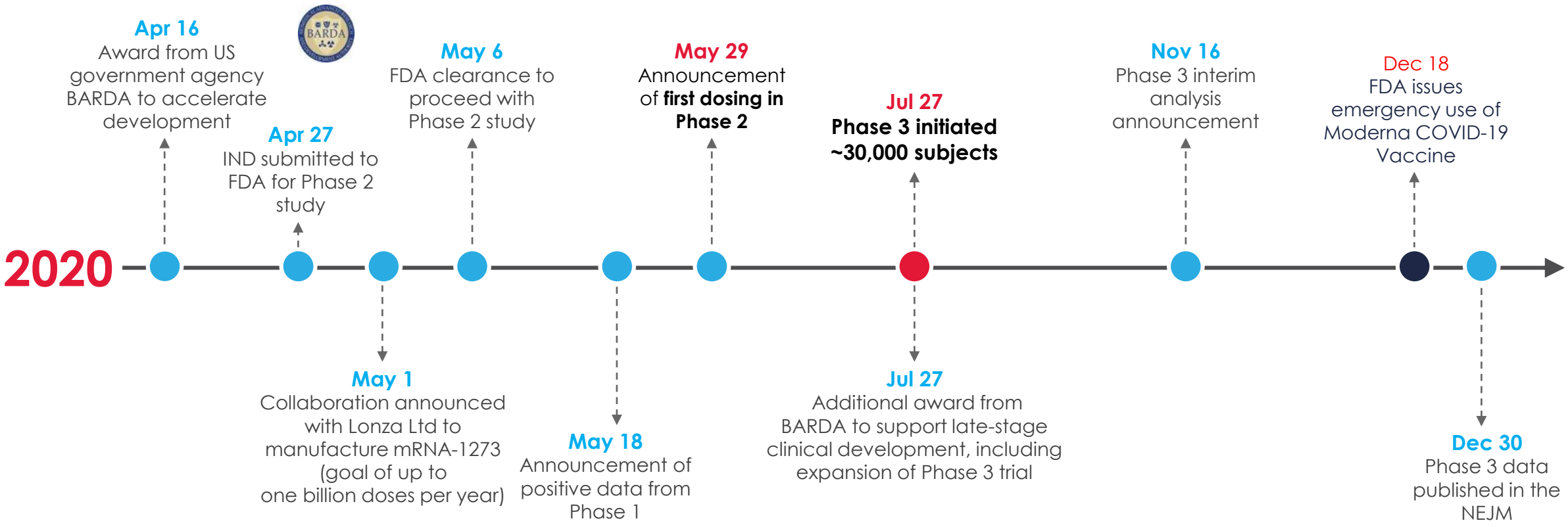
Moderna COVID-19疫苗：從首次臨床研究到首次授權的時間軸[1]



Novel mRNA vaccine technology was the platform with the fastest development timelines[2]

BARDA, Biomedical Advanced Research and Development Authority

1. Baden LR, et al; COVE Study Group. *N Engl J Med* 2021;384:403–16; 2. National Academy of Medicine 2022. Vaccine Research and Development to Advance Pandemic and Seasonal Influenza Preparedness and Response: Lessons from COVID-19. Washington, DC: The National Academies Press. https://doi.org/10.17226/26282

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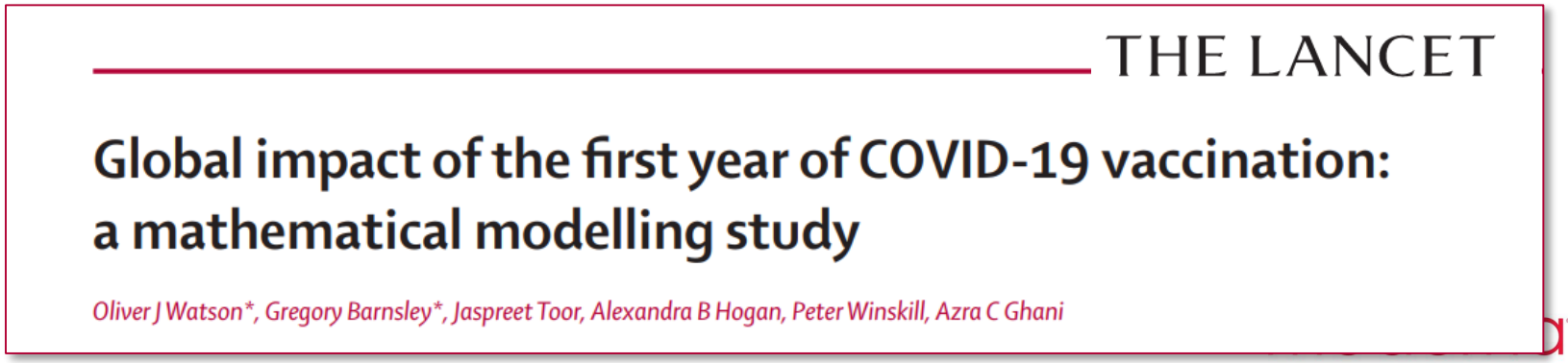
"Based on official reported COVID-19 deaths, we estimated that **vaccinations prevented**…**19.8 million**…**deaths from COVID-19**… representing a global reduction of **63%** in total deaths during the **first year** of COVID-19 vaccination"

根據官方報告的COVID-19死亡數據，在COVID-19疫苗接種的**第一年內**，全球總死亡人數減少了**63%**

我們估計疫苗接種防止了…**1980萬**…例COVID-19死亡…


THE LANCET

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

Oliver J Watson*, Gregory Barnsley*, Jaspreet Toor, Alexandra B Hogan, Peter Winskill, Azra C Ghani

Watson OJ, et al. *Lancet Infect Dis* 2022;22:1293–1302.

➢mRNA 疫苗的安全性&常見迷思

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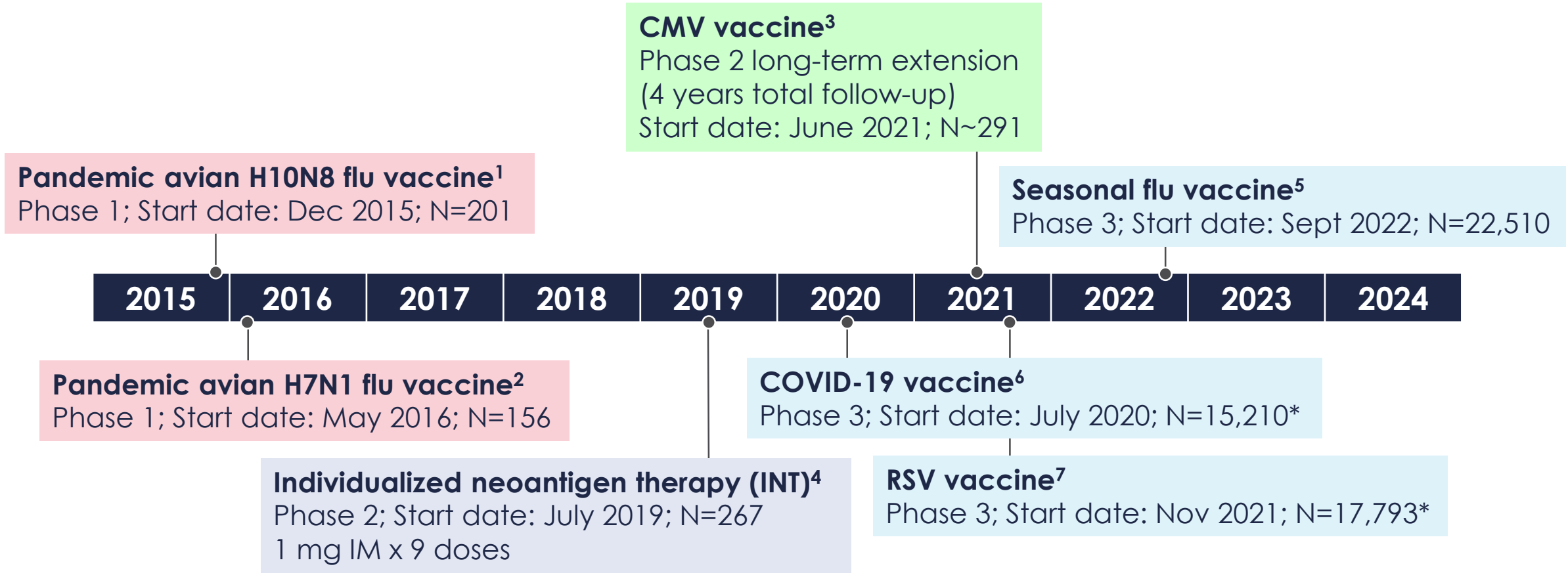
Moderna的mRNA相關人類研究開始自2015年



Extensive data from clinical trials and real-world use have not identified any new safety concerns beyond those observed during initial testing

*Intervention arm only.

1. ClinicalTrials.gov. NCT03076385; 2. NCT03345043; 3. NCT04975893; 4. NCT03897881; 5. NCT05566639; 6. Baden LR, et al. *N Engl J Med* 2021;384:403-416; 7. Wilson E, et al. *N Engl J Med* 2023;389:2233–44.

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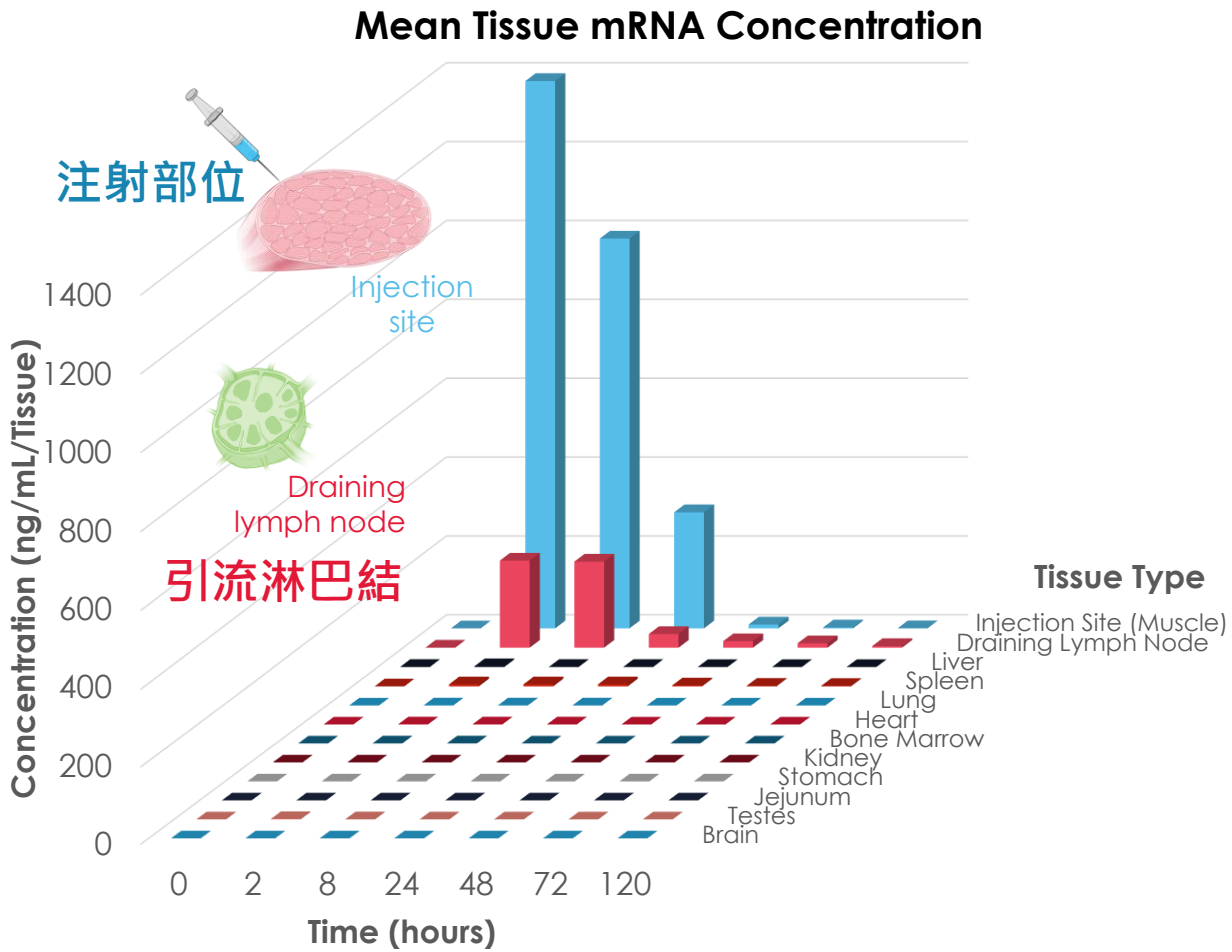
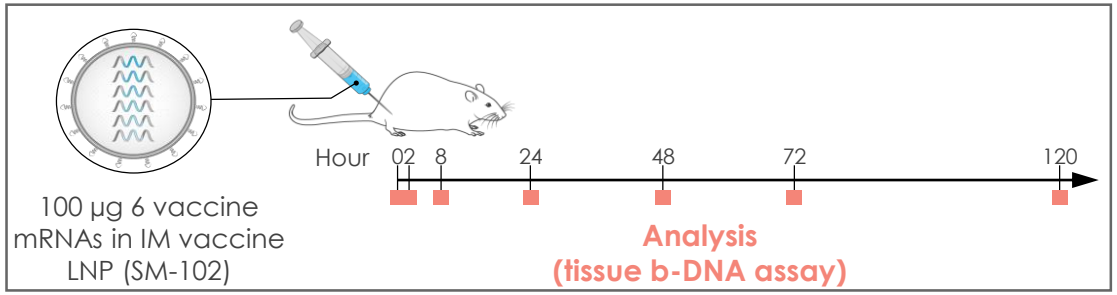
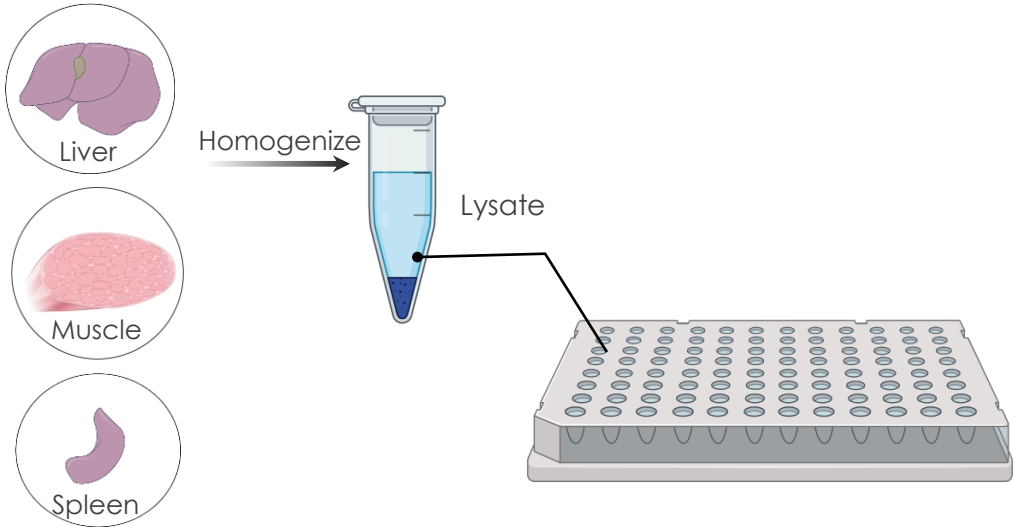
在動物試驗中， mRNA在肌肉注射後的生物分佈主要集中於注射部位和附近的引流淋巴結， 約在24至28小時後幾乎無法偵測到







IM, intramuscular; LNP, lipid nanoparticle.

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截止到2023年底，Moderna的mRNA疫苗

- 全球生產和銷售已經超過17億劑
- 預計截至2023年12月底，全球已接種超過10億劑

Expert Rev Vaccines;. 2024 Sep 13. doi: 10.1080/14760584.2024.2402955.

➢mRNA 疫苗常見迷思

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迷思1

打過mRNA疫苗就一勞永逸，不需要再打加強針

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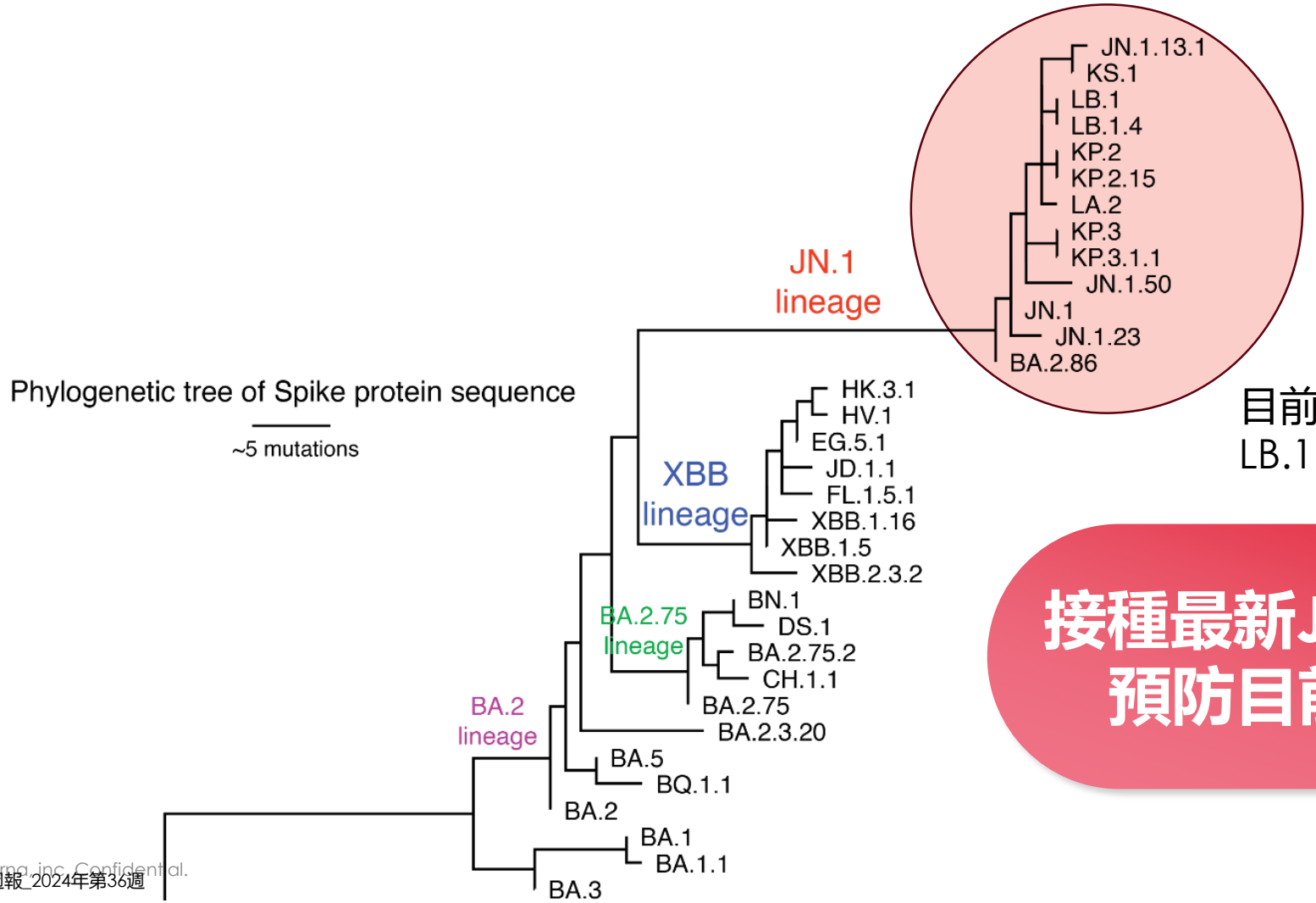
新冠病毒至今仍持續變異
目前流行的變異株為JN.1及其子代變異株



目前本土病例以
LB.1、KP.3.3、KP.2、JN.1等居多

接種最新JN.1新冠疫苗可以
預防目前流行的變異株

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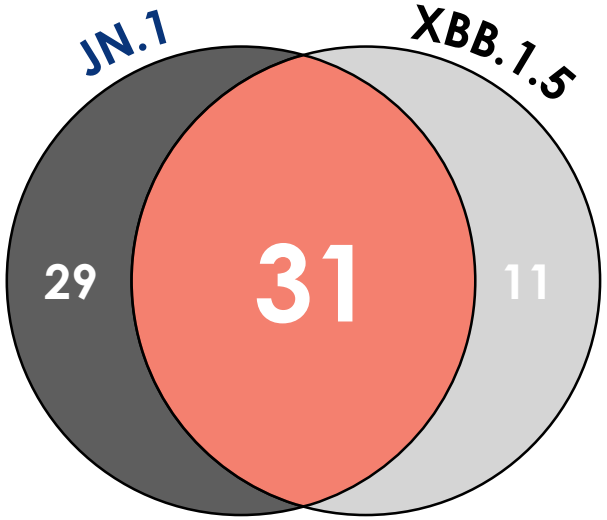
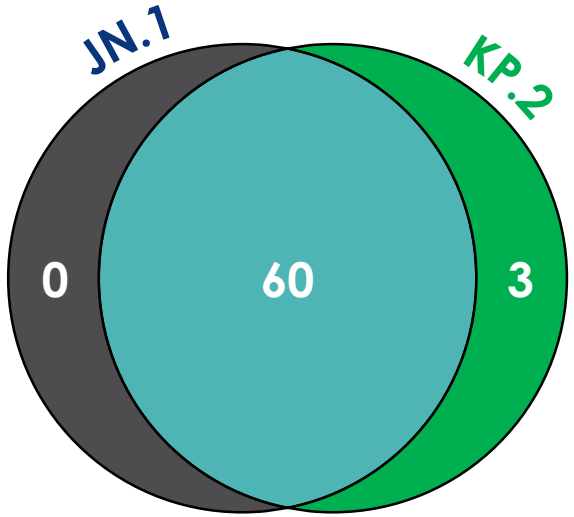
世界衛生組織WHO:
當新冠病毒變異太大,就需要更新疫苗來更新抗體

JN.1 與 XBB.1.5



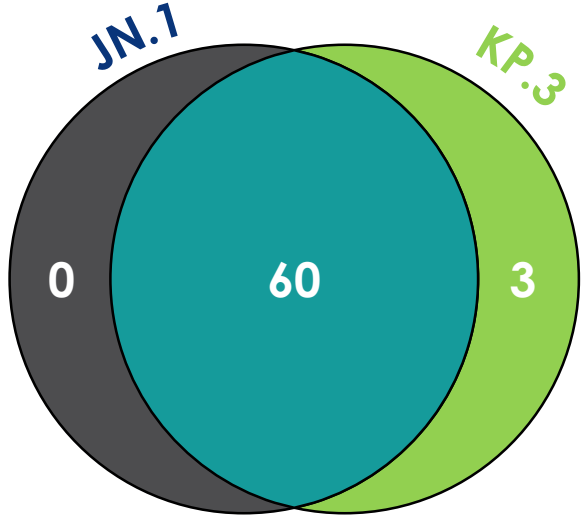
29 + 11 = **40個變異點**

JN.1 與 KP.2



0 + 3 = 3個變異點

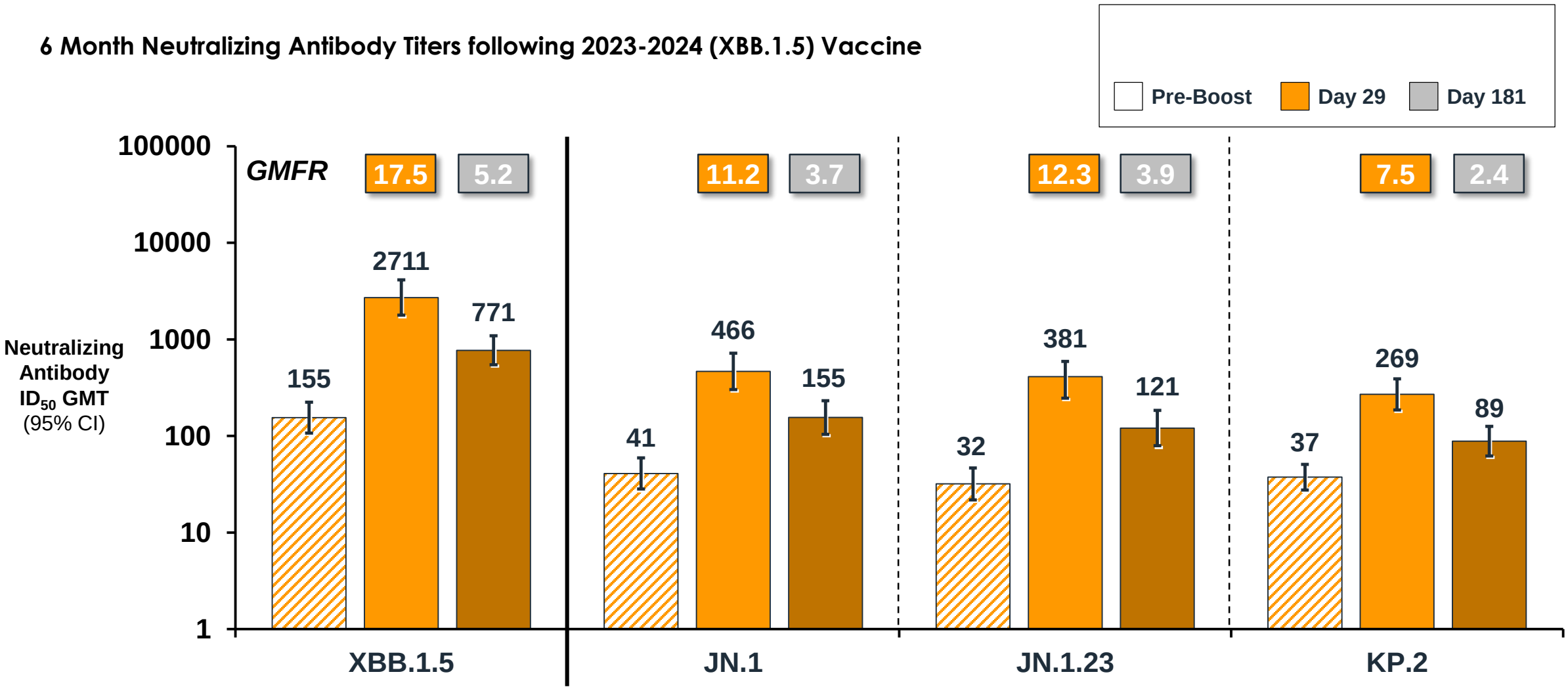
JN.1. 與 KP.3



0 + 3 = 3個變異點

無論過去有無接種過，
都需要接種最新JN.1新冠疫苗來對抗最新變異株

病毒持續變異+ 施打完6個月抗體會下降



- **Durable neutralizing responses for at least 6 months after XBB.1.5 vaccine**
- **Reduced response to JN.1 lineage variants at all timepoints**

迷思1

打過mRNA疫苗就一勞永逸，不需要再打加強針

正解：隨著時間推移和新變種出現，免疫力可能減弱，因此需定期接種以確保持續的保護力

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迷思2
接種mRNA疫苗會導致感染新冠病毒

正解：**mRNA 疫苗不含有活病毒，因此無法引發感染。它只是教導人體免疫系統辨識和攻擊新冠病毒**

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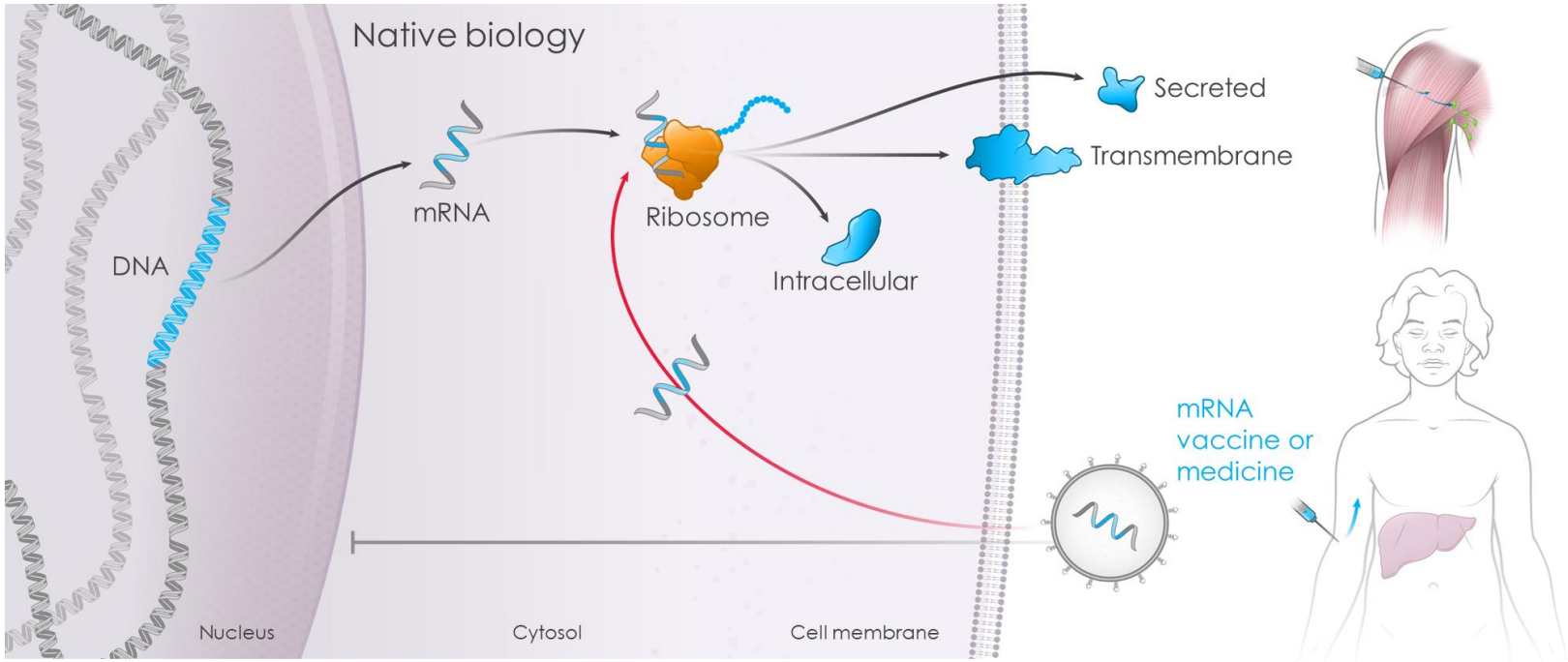
迷思3

mRNA 疫苗會改變人體的DNA



1. Adapted from Pardi N, et al. *Nat Rev Drug Discov* 2018;17:261–79.

正解：mRNA 疫苗不會進入細胞核，不會改變或影響人的DNA。疫苗的mRNA只是提供短暫的指令來製造刺突蛋白，觸發免疫反應，最終被細胞分解

迷思 4

接種mRNA疫苗會影響 生育、導致不孕，早產

在受孕前， 任一伴侶接種COVID-19疫苗與流產率之間未觀察到存在相關性

An Internet-based, prospective preconception cohort study of couples residing in the US and Canada. Data analyzed from 1815 female participants who conceived during **December 2020-November 2022**, including **1570 couples** with data on male partner vaccination

KEY FINDINGS

- 相比未接種的個體， 在懷孕前接種COVID-19疫苗的個體，流產率**略低**
- 置信區間大體上與疫苗接種對流產無影響的結果一致。
- 無論是女性還是男性伴侶的疫苗接種，結果相似。"

Associations between vaccination status at the estimated date of conception and rate of miscarriage

Vaccination Status at date of conception	N	#GW	# miscarriages (%)	Age adjusted IRR (95% CI)	PS-weighted IRR (95% CI)
Female partner vaccination					
Never vaccinated	455	5290	121 (26.6%)	Reference	Reference
Ever vaccinated	1360	15366	325 (23.9%)	0.88 (0.71, 1.08)	0.85 (0.63, 1.14)
Full primary sequence completed	1186	13088	290 (24.5%)	0.91 (0.73, 1.12)	0.89 (0.64, 1.23)
<3 mo before conception	339	4363	75 (22.1%)	0.77 (0.58, 1.03)	0.72 (0.51, 1.01)
Male partner vaccination (N=1570)					
Never vaccinated	427	5303	90 (21.1%)	Reference	Reference
Ever Vaccinated	1143	13227	263 (23.0%)	1.06 (0.84,1.35)	0.90 (0.56,1.44)
Full primary sequence completed	953	10717	225 (23.6%)	1.11 (0.86,1.41)	0.86 (0.53,1.40)

CI, confidence intervals; GW, gestational weeks; mo; months; IRR, incidence rate ratio; PS, propensity score

Yland JJ, et al *Hum Reprod*. 2023;38(12):2362-2372

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孕期中接種COVID-19疫苗的安全性：不會導致不良新生兒或孕婦不良事件

A **systematic review** and meta-analysis of 43 observational studies including pregnant individuals (**N=599,956**) **April 5, 2022 through May 25, 2022** evaluating the safety of COVID-19 vaccination during pregnancy

KEY FINDINGS

- 來自歐盟的24項研究、美洲地區的17項研究、西太平洋地區的2項研究。
- 本研究中孕期接種的疫苗主要是mRNA疫苗（74%為BNT162b2，24%為mRNA-1273，2%為其他），主要接種於妊娠的第二和第三期。
- 孕期接種COVID-19疫苗與**死產或新生兒死亡**的整體風險**降低**相關。
- 未觀察到孕期接種COVID-19疫苗會**導致**不良新生兒或孕婦不良事件

COVID-19 vaccination during pregnancy was associated with a reduced risk of stillbirth or neonatal death within 28 days after birth

Study or Subgroup	Vaccinated		Unvaccinated		Odds ratio IV, Random (95% CI)
	Events	Total	Events	Total	
Blakeway et al, 2022	0	133	1	399	1.00 (0.04, 24.57)
Dick et al, 2022	20	2305	33	3313	0.87 (0.50, 1.52)
Goldshtein et al, 2021	1	7530	2	7530	0.50 (0.05, 5.51)
Magnus et al, 2022	50	28506	338	129015	0.67 (0.50, 0.90)
Rottenstreich et al, 2022	5	712	5	1073	1.51 (0.44, 5.24)
Stock et al, 2022	25	5766	427	76690	0.78 (0.52, 1.17)
Theiler et al, 2021	0	140	6	1862	1.02 (0.06, 18.13)
Total events (95% CI)	101	45092	812	219882	0.74 (0.60,0.92)

CI, confidence interval; EU, European Union; IV, independent variable

Ding C, et al. *Front Public Health 2023;* 11:1044031. doi: 10.3389/fpubh.2023.1044031

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迷思 4

接種mRNA疫苗會影響 生育、導致不孕，早產

正解：目前並無證據顯示mRNA疫苗會影響生育能力或導致不孕。多項研究已排除此可能性。

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迷思5

打完mRNA疫苗有心臟相關問題, 尤其是心肌炎/心包膜炎

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接種1劑、2劑或3劑mRNA-1273疫苗後罕見的心肌炎和心包炎事件

Retrospective review of the Moderna global safety database of adverse events **(N=477,932)**to determine the cumulative risk of myocarditis/pericarditis following vaccination with any mRNA-1273 dose (**2020-2022**)

KEY FINDINGS

- **在477,932例不良事件中，0.6%（n=3,017）為心肌炎/心包炎**
  - **•48.29%的心肌炎/心包炎事件已康復或正在康復中。**
  - **•1.5%的心肌炎/心包炎事件為致命事件**
- **心肌炎/心包炎的觀察與預期發生率（發生率比），第3劑相比第1劑和第2劑時最低**
  - 第1劑: 0.80 (95%CI: 0.7-0.93)
  - **第2劑: 2.71 (95%CI: 2.4-3.06)**
  - 第1劑: 0.73 (95%CI: 0.59-0.91)

Observed vs expected rates of myocarditis/myopericarditis in recipients of any mRNA-1273 dose

Demographic	Rate Ratio	95% CI
All recipients; All ages	1.03	(0.97-1.08)
Males; All ages	1.21	(1.14-1.29)
Females; All ages	0.69	(0.62-0.75)
All recipients; 12-17 years	0.92	(0.71-1.19)
All recipients; 25-39 years	**1.37**	(1.24-1.51)
All recipients; 50-64 years	0.4	(0.35-0.46)

CI, confidence interval; D1, dose 1; D2, dose 2; D3, dose 3

Straus W, et al. *Clin Infect Dis*. 2023;76(3).

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心肌炎為非常罕見, (好發在第二劑疫苗, 18-24 年輕男性) 並多為輕度

心肌炎和心包炎

Spikevax疫苗(原病毒株) 、Spikevax疫苗(雙價)的上市後安全數據與Spikevax疫苗(JN.1)相關，因為這些疫苗是使用相同的製程生產的。

接種Spikevax疫苗後，心肌炎和心包膜炎的風險會增加。大多數病例報告為 18 至 24 歲的年輕男性。

這些情況可能出現在接種疫苗的數日之後，主要發生在接種後14天內。與第一次接種疫苗相比，在接種第二劑疫苗後觀察到這些事件的頻率較高 (請參見第8 節)。

雖然有些病例需要重症加護協助或曾通報致命事件，但現有的短期追蹤資料顯示，大多數情況是輕度病症，經過治療和休息，病人大多可在短時間內康復。目前尚無關於潛在長期後遺症的資訊。

醫護人員應警惕心肌炎和心包膜炎的病徵和症狀。

若在接種 Spikevax疫苗後出現心肌炎或心包膜炎的症狀，例如(急性和持續性)胸痛、呼吸急促或心悸，應指導疫苗接種者務必立即就醫。

若發生上述情況，醫護人員應遵循臨床治療準則並/或會診專科醫師來診斷和治療。

心臟疾病	非常罕見 非常罕見(<1/10000)	心肌炎 心包膜炎

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迷思5

打完mRNA疫苗有心臟相關問題，尤其是心肌炎/心包膜炎

- 感染COVID-19後發生心肌炎/心包炎的風險比接種COVID-19疫苗後發生心肌炎/心包炎的風險**高3-5倍**。
- 接種COVID-19疫苗後發生心肌炎/心包炎的風險在青少年和年輕男性中較高，尤其是在接種**第2劑**疫苗後。
- 所有類型的COVID-19疫苗都曾報告過心肌炎/心包炎，但發生率極低。
- **WHO、FDA和CDC**強調，在所有年齡組中，mRNA疫苗的益處均大於其風險。

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Covid-19 疫苗不良事件通報資料報告 (截止113年9月30日)

衛生福利部食品藥物管理署

- 截至 113年 9月 30日 止 ，全國 共 施打 **2,619,302**劑 Moderna XBB.1.5疫苗 及 **324,813**劑 Novavax XBB.1.5疫苗
- 接獲疫苗不良事件通報 共 107件 及 13件 平均每 十萬 劑注射通報數 分別 約為 **4.1**件 及 **4.0**件 。
- 檢視接種死亡個案，包含1為男性及4位女性，個案年齡中位數74歲(範圍：47至81歲)。依器官系統分類檢視個案之死亡原因†，包括感染性疾病(敗血性休克、肺炎、菌血症)、心肌炎及急性呼吸衰竭；病史包括心血管疾病、內分泌疾病、腎臟及泌尿道疾病等
- **綜合目前疫苗不良事件通報資料之評估結果，尚未觀察到須 立即 採取相關措施之 COVID-19疫苗產品 安全疑慮。衛生福利部食品藥物管理署與全國藥物不良**

https://www.fda.gov.tw/tc/includes/GetFile.ashx?id=f638651998204509939&type=2&cid=47602

➢mRNA 技術的未來-疫苗

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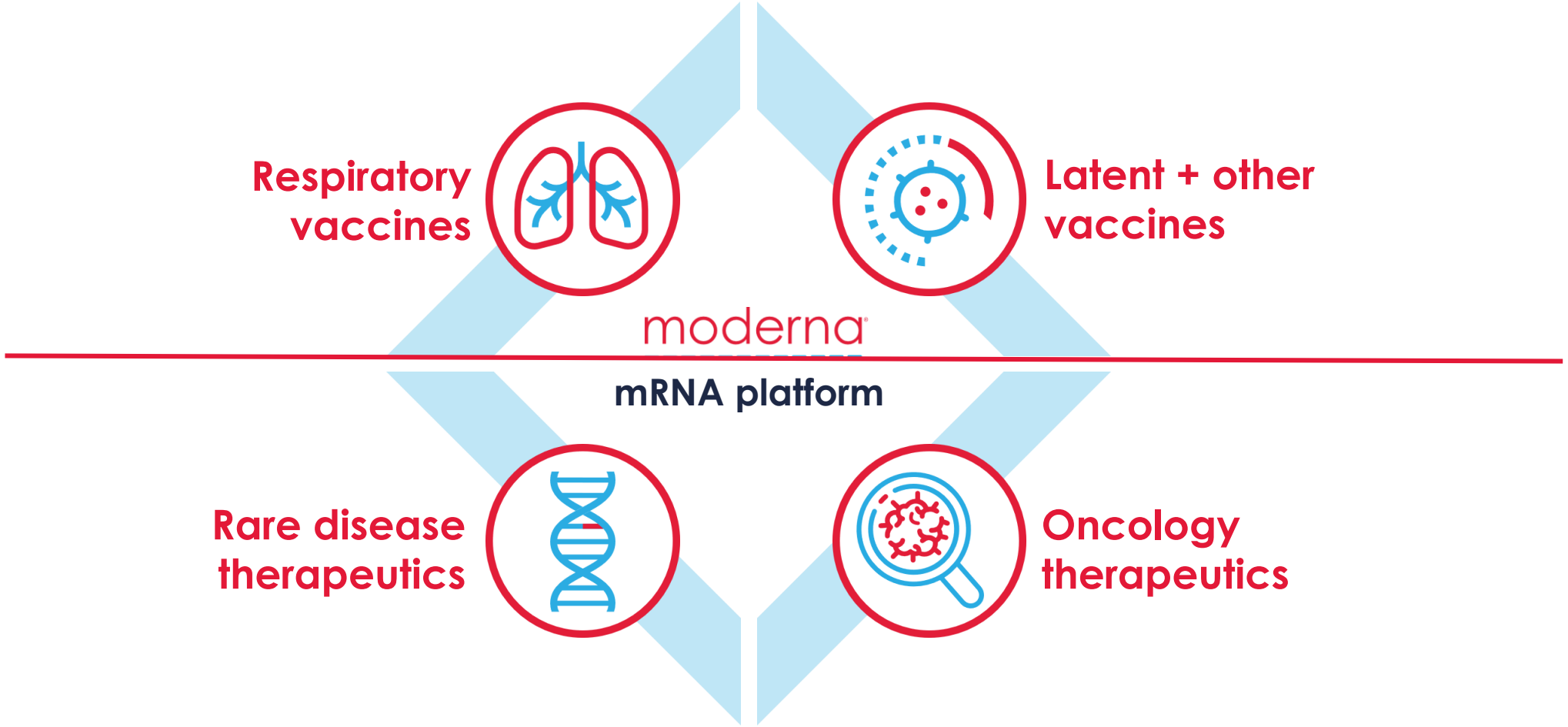
Moderna的未來產品組合

2Q24 updates in respiratory vaccines, oncology therapeutics, and rare disease therapeutics



呼吸道疫苗

RSV
呼吸道融合病毒
mRNA-1345

- 美國歐盟已批准
- 台灣2024

Flu
流感
mRNA-1010

Next-gen COVID
mRNA-1283

- 更低劑量，
- 更高的穩定性

Flu/COVID combo
組合疫苗
mRNA-1083

- 三期試驗達到主要終點
- 台灣參加亞洲試驗

1. EMA: European Medicines Agency

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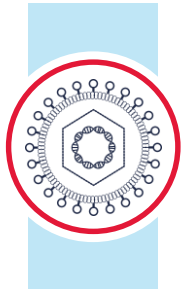
潛伏性 + 其他疫苗

CMV
巨細胞病毒

Most common infectious cause of birth defects in the U.S.; 1 in 200 babies in the U.S. are born with a congenital CMV infection



EBV
愛潑斯坦-巴爾病毒

Major cause of infectious mononucleosis (IM) in the U.S., accounting for over 90% of the estimated 150,000 cases annually[1], with potential sequelae

HSV
單純皰疹病毒

Herpes Simplex Virus Type 2 (HSV-2) infects ~13% of adults globally and is the primary cause of genital herpes[2]

VZV
水痘-帶狀皰疹病毒

Declining immunity in older adults decreases immunity against VZV, allowing reactivation of the herpes zoster virus

Norovirus
諾羅病毒

A leading cause of diarrheal deaths globally

➢mRNA 技術的未來-罕見疾病與腫瘤

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罕見疾病與腫瘤與mRNA

			Ph 1	Ph 2	Ph 3	Commercial	
Individualized neoantigen therapy	Adjuvant melanoma	mRNA-4157					MERCK
	Adjuvant non-small cell lung cancer (NSCLC)	mRNA-4157					MERCK
	Cutaneous squamous cell carcinoma (cSCC)	mRNA-4157					MERCK
	Renal cell carcinoma (RCC)	mRNA-4157					MERCK
	Bladder cancer	mRNA-4157					MERCK

Rare Disease	Propionic academia (丙酸血症)
	Methylmalonic acidemia (甲基丙二酸血症)

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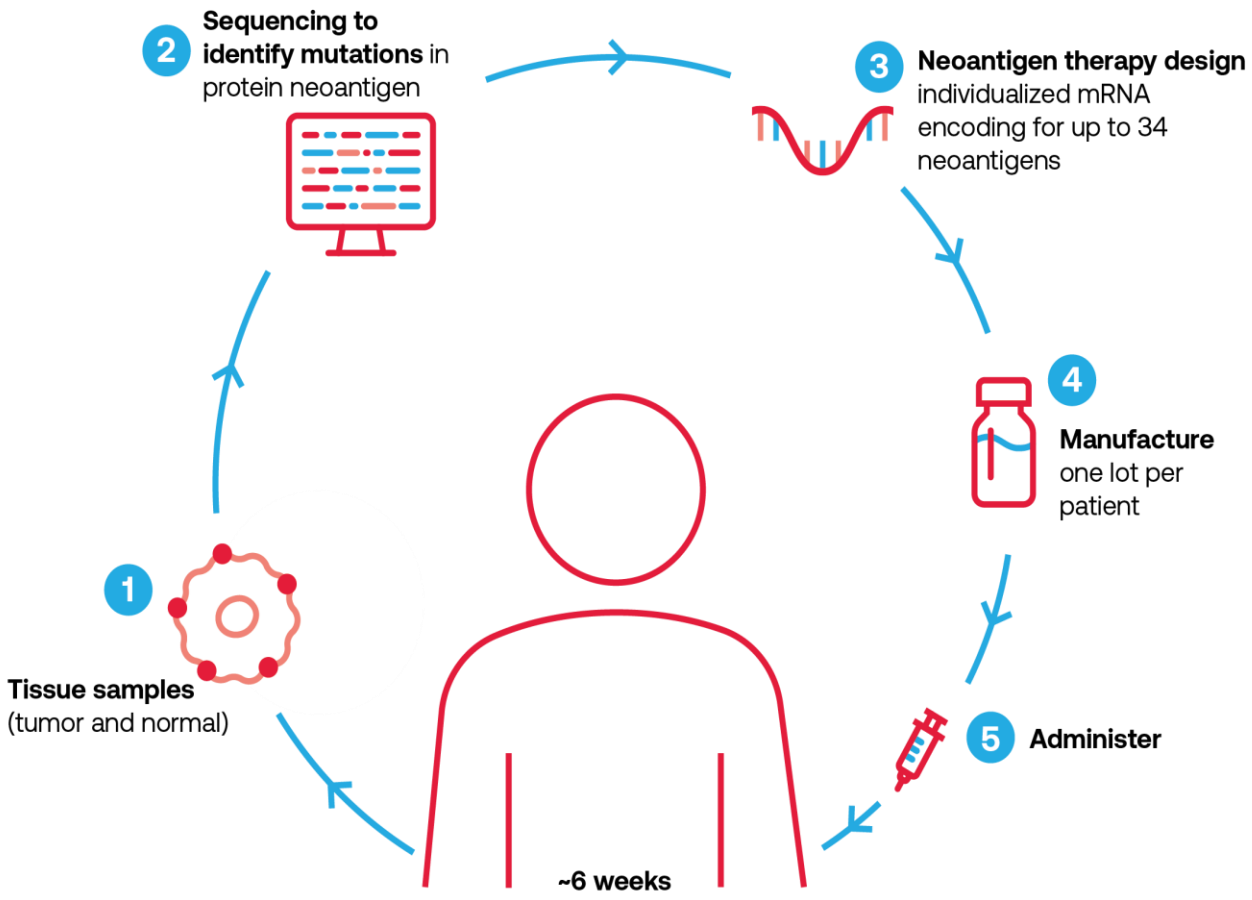
Oncology-Individualized Neoantigen Therapy (INT)*[1,2]
個體化新抗原療法-旨在針對單個患者的特有腫瘤突變



*Investigational therapy being jointly developed and commercialized by Merck and Moderna.

1. Xie N, et al. *Signal Transduct Target Ther* 2023;8:9; 2. Khattak A, et al. Presented at the American Association for Cancer Research (AACR) Annual Meeting; April 14-19, 2023; Orlando, FL, USA. Oral presentation CT001.

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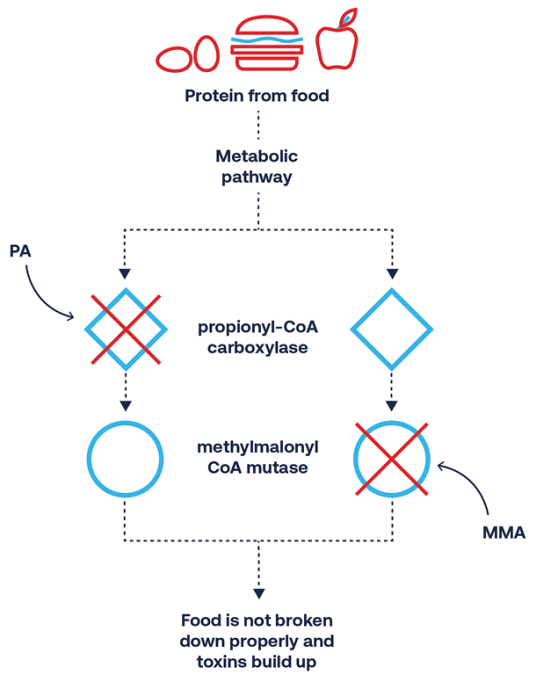
罕見疾病療法：MMA候選藥物（mRNA-3705）入選FDA START計劃

MMA: 甲基丙二酸血症

Methylmalonic acidemia

MMA is caused by a deficiency of the enzyme methylmalonyl CoA mutase protein which prevents the body from breaking down fats and proteins from food.



- mRNA-3705正在進行一期/二期研究，這是一項適應性、開放標籤研究，旨在評估其安全性和耐受性“
- START試點計劃是FDA的一項計劃，目的是加速針對罕見疾病未滿足醫療需求的新療法的開發

Summary

Summary

23,000

截至2024年10月獲得FDA批准的處方藥總數 [1]

100, 000

人體內的不同蛋白質的總數 [2]

1) FDA at a Glance, Oct. 2024; https://www.fda.gov/about-fda/economics-staff/fda-glance
2) https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/proteins/

Thank you

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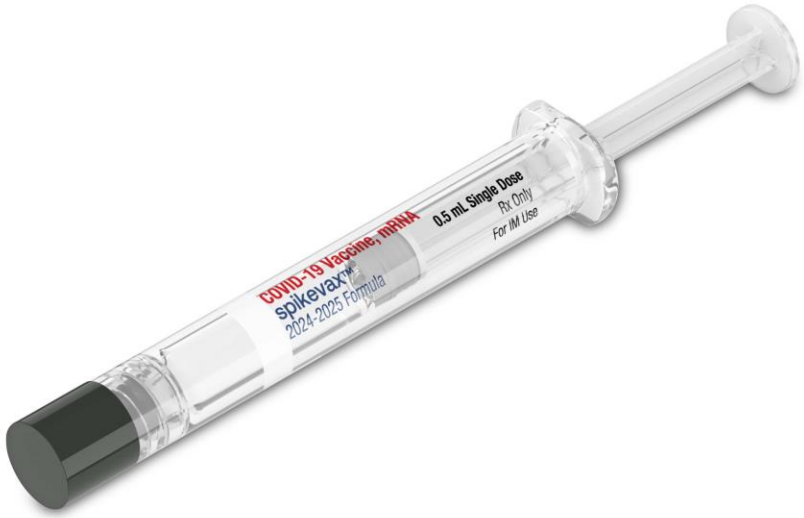
Spikevax JN.1，兩種劑型

spikevax® 世冠飛適®
mRNA-1273.167
COVID-19 mRNA Vaccine
by moderna

12歲以上

Pre-filled Syringe (PFS)
預充填注射針筒不含針頭
0.5 mL
12歲以上青少年和成人
單次使用



6個月以上
11歲

Multi-Doses Vail (MDV)
多次使用劑型，2.5 mL/瓶 (藍色塑膠蓋)
6個月以上-11歲
每次0.25mL, 共10劑

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接種過新冠疫苗者與前一劑間隔84天以上即可接種

◆ 接種時程與間隔：

年齡	COVID-19 疫苗接種史	接種方式	
		接種劑數	接種間隔
滿 6 個月至 4 歲	未曾接種 COVID-19 疫苗	2 劑	2 劑間隔 4 週以上
	曾接種 COVID-19 疫苗	1 劑	與前 1 劑間隔 12 週(84 天)以上
滿 5 歲以上	未曾接種 COVID-19 疫苗	1 劑	---
	曾接種 COVID-19 疫苗	1 劑	與前 1 劑間隔 12 週(84 天)以上

◆ 接種劑量：

包裝劑型	多劑型(玻璃小瓶，2.5 mL /瓶)	單劑型(預充填注射針筒，0.5 mL /支)
適用年齡	滿 6 個月至 11 歲	滿 12 歲以上
每劑	0.25mL (25mcg mRNA)	0.5mL (50mcg mRNA)

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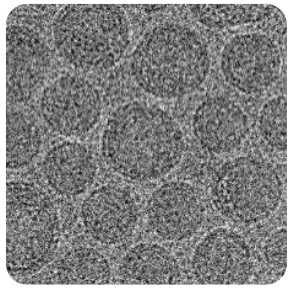
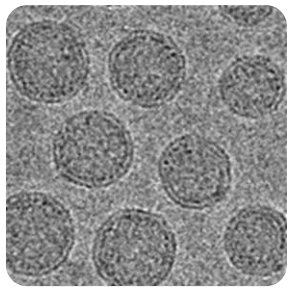
Moderna's five proprietary LNPs for different delivery goals[1]

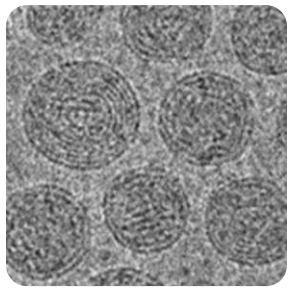
Prophylactic vaccines
Cancer vaccines
Intramuscular injection
IM LNP

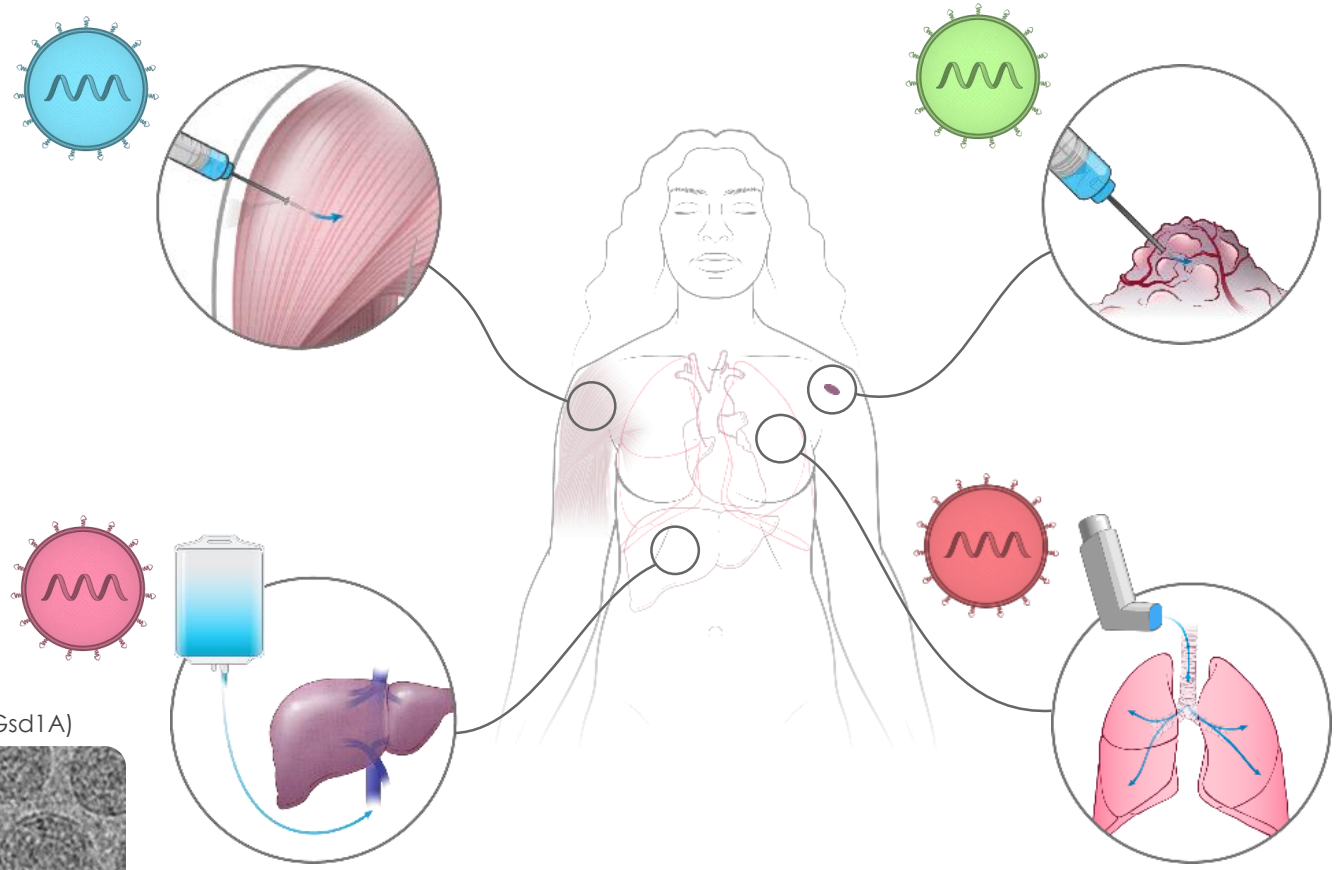


Systemic therapeutics
IV injection
IV LNP 1 (MMA, PA)

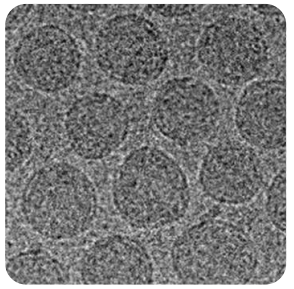


IV LNP 2 (Gsd1A)

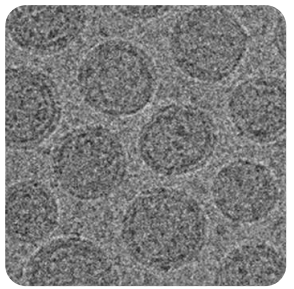




Intratumoral
Immuno-oncology
Intratumoral injection
ITu LNP



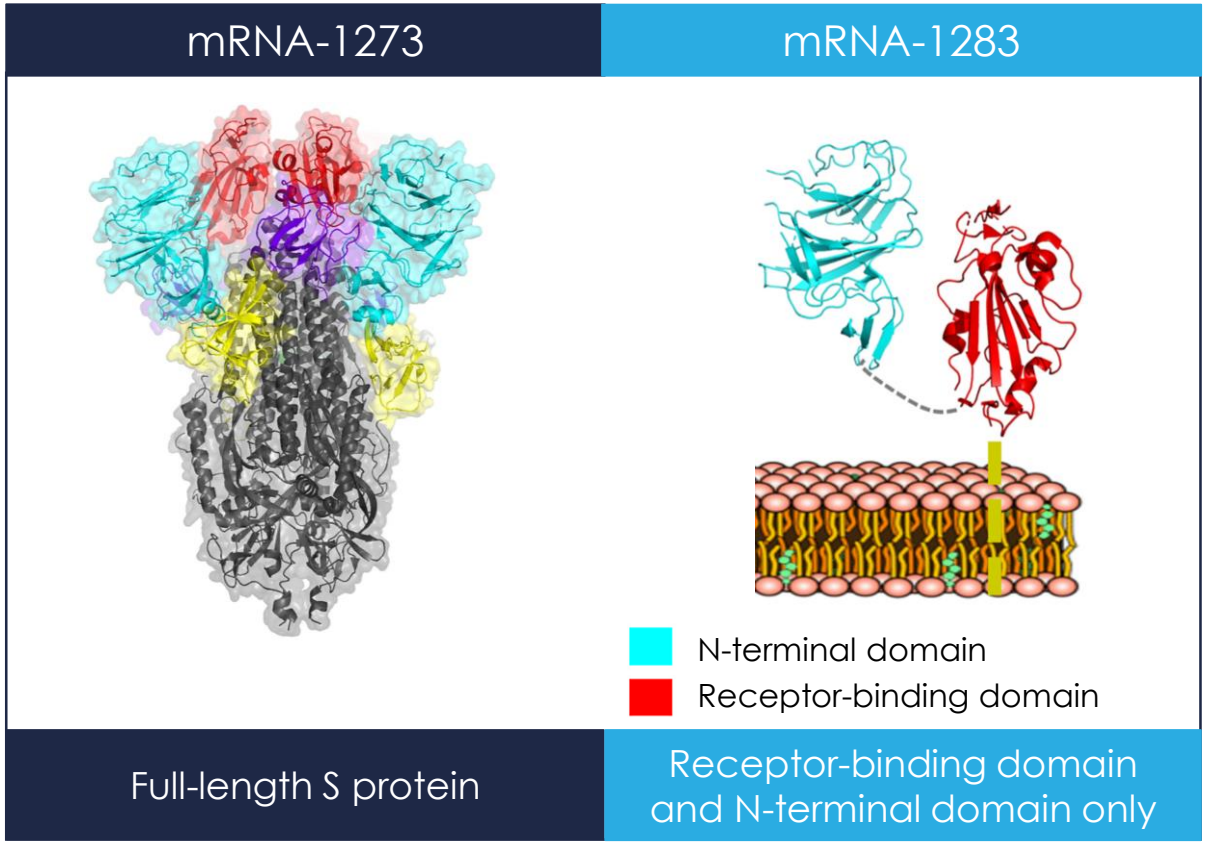
Inhaled pulmonary therapeutics
Inhaled delivery
Pulmonary LNP



1. Sabnis S, et al. Mol Ther 2018;26:1509–19; Hassett KJ, et al. Mol Ther Nucleic Acids 2019;15:1–11; Hassett KJ, et al. J Control Release 2021;335:237–46; Brader ML, et al. Biophys J 2021;120:2766–70; Cornebise M, et al. Adv Funct Mater 2022;32:2106727.

Next-generation COVID-19 vaccine (mRNA-1283)

- mRNA-based vaccines protect against COVID-19[1]
- The original mRNA-1273 vaccine encodes for the **full-length** SARS-CoV-2 spike
- mRNA-1283 is an investigational vaccine designed to encode for the immuno-dominant receptor-binding domain and N-terminal domain of the spike
  - Shorter mRNA with the potential for **enhanced thermostability**
  - **Elicits similar immune responses** compared to mRNA-1273[2]



1. Baden LR, et al. *N Engl J Med* 2021;384:403–16. 2. Stewart-Jones, et al. *Sci Transl Med* 2023;15:eadf4100.
Figure adapted from Stewart-Jones GBE, et al. Domain-based mRNA vaccines encoding spike protein N-terminal and receptor binding domains confer protection against SARS-CoV-2. *Sci Transl Med* 2023;15:eadf4100. Reprinted with permission from AAAS.

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