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Chula Vaccine Research Center
Faculty of Medicine, Chulalongkorn University

HPV Therapeutic Vaccine

Rational and Challenges

Kiat Ruxrungtham

Chula Vaccine Research Center, and
School of Global Health,
Chulalongkorn University

2nd WHO/MPP Asian mRNA Vaccine RnD Consortia Meeting
Singapore 18-19 March 2024

HPV Vaccine

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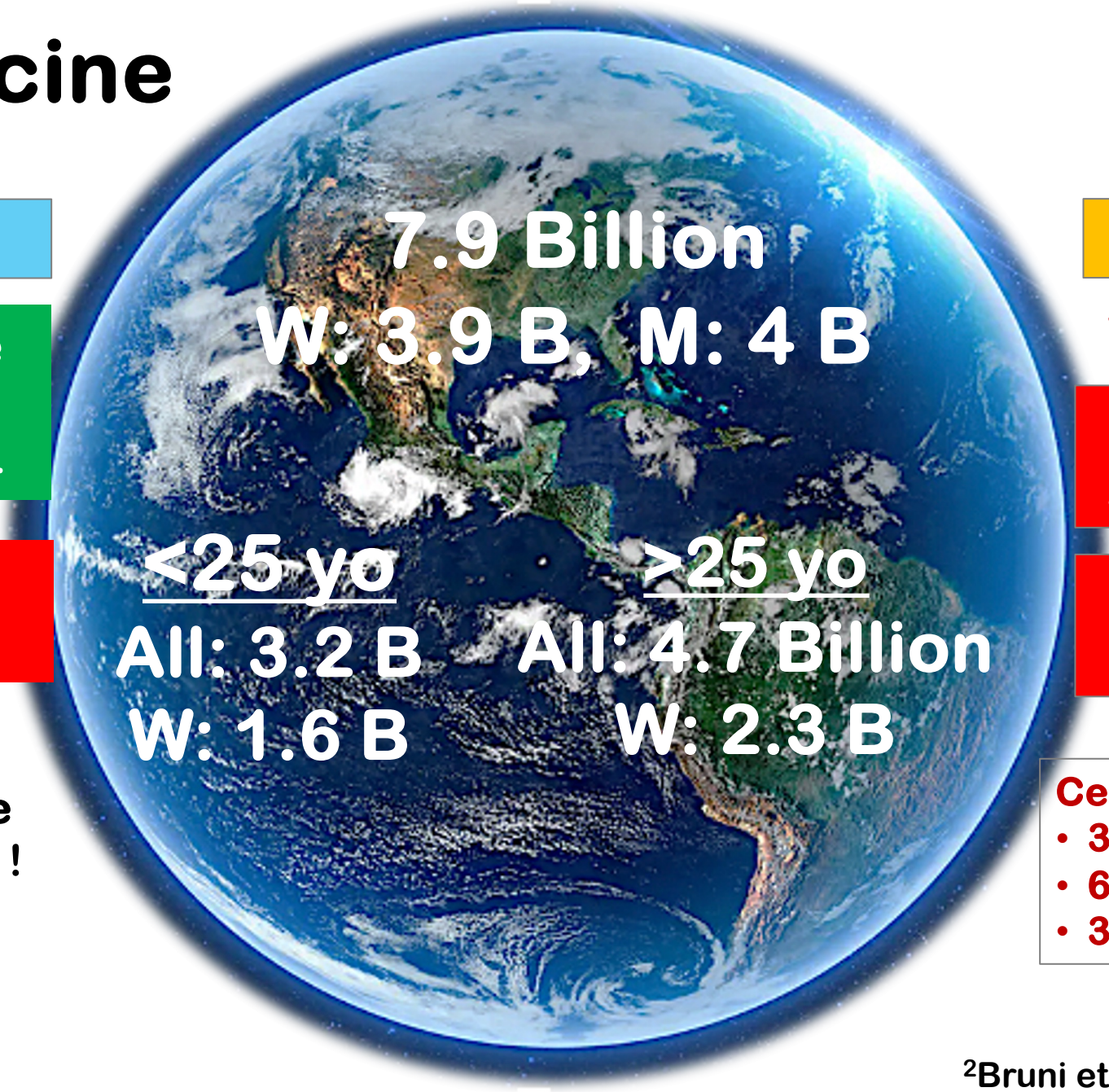
PREVENTIVE

Highly Efffective HPV Vaccine
Avialable since 2014

Global 2022[1]
21 % coverage !!

L1-VLP
Affordable Vaccine
Is definitely needed !



THERAPEUTIC

Vaccine- not available

291 Million Women are HPV DNA carriers

21% men are HR-HPV Infected[2]

Cervical Cancer
- **3.1%** of all cancers
- **604,127** new cases
- **341,831** deaths annually

[1]WHO, July 2023

[2]Bruni et al. Lancet Global Health 202

Timeline of the Development and Use

The **value of therapeutic HPV vaccines** will be **higher** when the **timeline** to develop and implement them **is shorter**

One model found that **a 10-year delay** in introduction of a therapeutic vaccine from 2030 to 2040

resulted in a **45% decrease** in the number

of **deaths averted** by 2070

Any Promising Proof-of-Concept Clinical Trials of HPV Therapeutic Vaccines ?

Therapeutic HPV-Vaccine Trial Results

from Past to Present

- **Limited evidence** of therapeutic vaccine efficacy in patients with **advanced, recurrent, or metastatic** HPV-mediated malignancies
- Most of the **double blinded RCTs** demonstrate that therapeutic HPV vaccination **either trends towards efficacy or is effective** in patients with **cervical intraepithelial neoplasia (CIN)**

Yan et al. Curr Otolaryngology Report, Feb 2023

HPV therapeutic vaccine in Precancerous and Cancers

Early Landmark Trials Results (Non-RCT, single arm)

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Vaccine Type	Vaccine - antigens	Study Phase	Sample size	Published	Eligibility	Regression Vaccine vs Placebo
DNA GX188E	HPV16/18 E6/E7+FLT3L	I	**9**	2014	**CIN3**	**9 months:** 7/9 with complete regression + viral clearance
Peptides ISA101	HPV16 E6/E7 epitopes	II	**8**	2009	**HPV6 VIN3**	**12 months:** 79% clinical response (15/19) 47% complete response (9/19)
Protien TA-CIN	HPV16 L2/E6/E7	II	**15**	2010	**VIN2/3**	**5 months** 58% complete regression (11/19)
Viral Vector TA-HPV	HPV16/18 E6/E7	I/II	**22**	1996	**Invasive Cervical CA**	**15-21 months** 2/8 disease-free
Bacterial Vector ADXS11-001	HPV16 E7	I	**19**	2009	**A/R Cervical CA**	100% Flu-like syndrome 40% grade 3 AEs 1/15 with partial response

Yan et al. Curr Otolaryngology Report 2023: 11(1)

HPV Therapeutic Vaccine in CIN2/3
RCT-placebo-controlled Results

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Vaccine Type	Vaccine - antigens	Study Phase	Sample size Vac/Placebo	Route	Eligibility	Regression Vac vs Pla
DNA VGX-3100	HPV16/18 E6/E7	IIb	**125 : 42**	IM-EP	HPV16/18 CIN2/3	**9 months:** 49 % vs 30 %, p=0.034
DNA ZYC101a	HPV16 E6/E7	II	**53 : 58 : 50**	IM Lateral Thigh	HPV CIN2/3	**6 months:** 43% vs 27%, p=0.12 (ns)
Viral Vector TG4001	HPV16 E6/E7 (+ IL12)	II	**136 : 70**	SQ	HPV16 CIN2/3	**6 months** HPV16 mono-infection: 18% vs 4%, p<0.05
Peptide CVLP-L1E7	VLP HPV16 L1-E7	NR	**14 : 12 : 13**	SQ Upper arm	HPV16 CIN2/3	**6 months** 39% vs 24%, p=ns

Remark: number of given doses: 3-4, Vac=vaccine, Pla =Placebo

Yan et al. Curr Otolaryngology Report 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vaccination against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia

Gemma G. Kenter, M.D., Ph.D., Marij J.P. Welters, Ph.D.,
A. Rob P.M. Valentijn, Ph.D., Margriet J.G. Lowik,
Dorien M.A. Berends-van der Meer, Annelies P.G. Vloon, Farah Essahsah,
Lorraine M. Fathers, Rienk Offringa, Ph.D., Jan Wouter Drijfhout, Ph.D.,
Amon R. Wafelman, Ph.D., Jaap Oostendorp, Ph.D., Gert Jan Fleuren, M.D., Ph.D.,
Sjoerd H. van der Burg, Ph.D., and Cornelis J.M. Melief, M.D., Ph.D.

Kenter et al NEJM 2009

Study Design:

- **N=20** women with HPV-16–positive, grade 3 vulvar intraepithelial neoplasia(**VIN3**)
- **Vaccine**: a mix of long peptides from the **HPV-16 E6 and E7** in incomplete Freund's adjuvant.
- **Route: SQ** at 3-wk intervals, each time in a different arm or leg x 3-4 times
- **The end points** were clinical and HPV-16–specific T-cell responses.

HPV16 E6/E7 peptide vaccine trial in **VIN3** Results

RESULTS

The most common adverse events were local swelling in 100% of the patients and fever in 64% of the patients; none of these events exceeded grade 2 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute. At 3 months after the last vaccination, 12 of 20 patients (60%; 95% confidence interval [CI], 36 to 81) had clinical responses and reported relief of symptoms. Five women had complete regression of the lesions, and HPV-16 was no longer detectable in four of them. At 12 months of follow-up, 15 of 19 patients had clinical responses (79%; 95% CI, 54 to 94), with a complete response in 9 of 19 patients (47%; 95% CI, 24 to 71). The complete-response rate was maintained at 24 months of follow-up. All patients had vaccine-induced T-cell responses, and post hoc analyses suggested that patients with a complete response at 3 months had a significantly stronger interferon-γ–associated proliferative CD4+ T-cell response and a broad response of CD8+ interferon-γ T cells than did patients without a complete response.

CONCLUSIONS

Clinical responses in women with HPV-16–positive, grade 3 vulvar intraepithelial neoplasia can be achieved by vaccination with a synthetic long-peptide vaccine against the HPV-16 oncoproteins E6 and E7. Complete responses appear to be correlated with induction of HPV-16–specific immunity.

Kenter et al NEJM 2009

HPV-VIN3 patients

Response Rate at 12 months:

79% clinical response (15/19)

47% complete response (9/19)

Post-hoc analysis

T-cell responses may play important roles in complete response

Adverse Events:

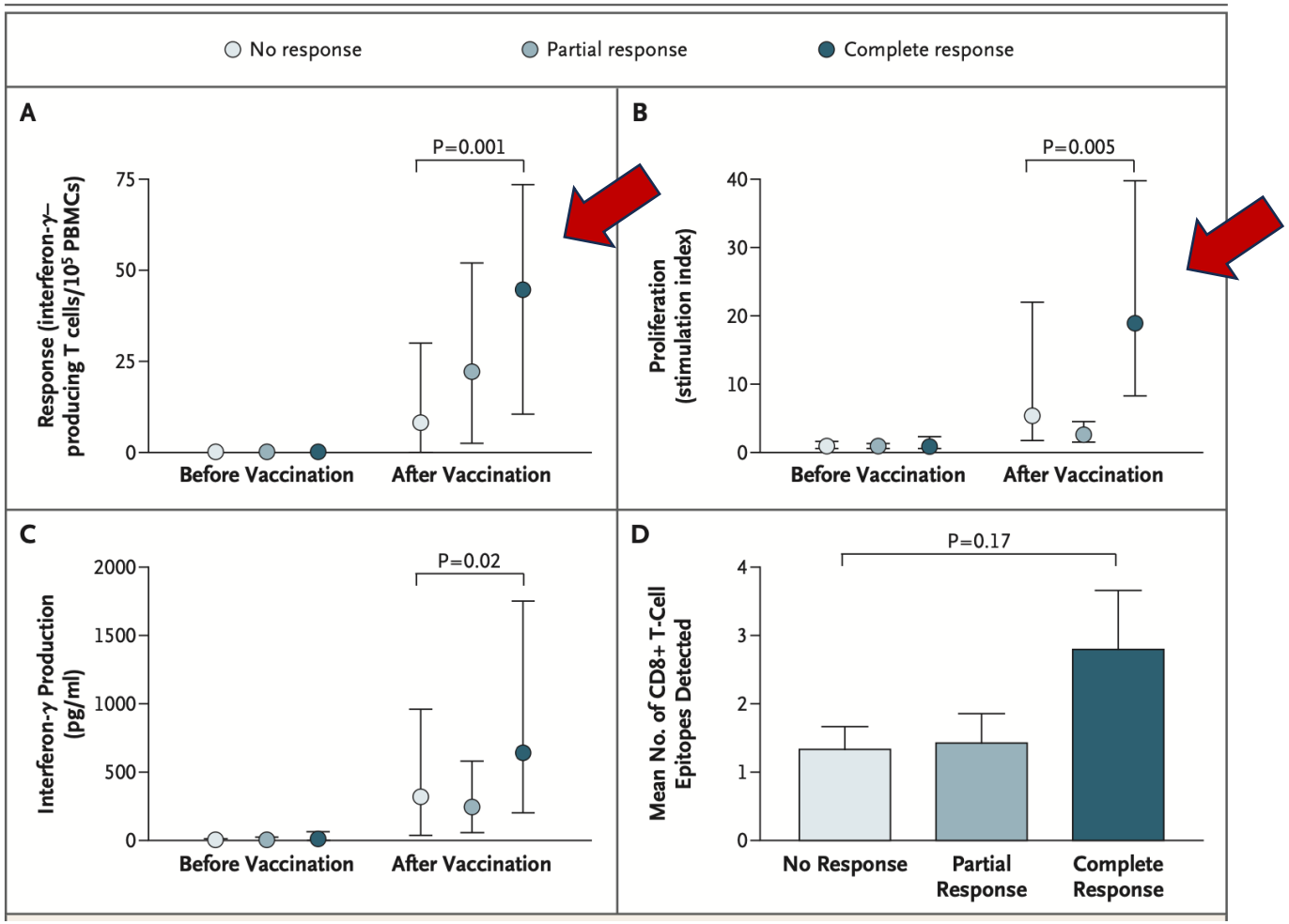
Local swelling 100%

Fever 64%

All <grade 2 AES

**Adjuvant*: Incomplete Freund's Adjuvant*

Immune Response before and after Vaccination



- All patients had vaccine-induced T-cell responses
- Post hoc analyses suggested that patients with a complete response at 3 months had a significantly stronger interferon- γ–associated proliferative CD4+ T-cell response and a broad response of CD8+ interferon-γ T cells than did patients without a complete response.

Kenter et al NEJM 2009

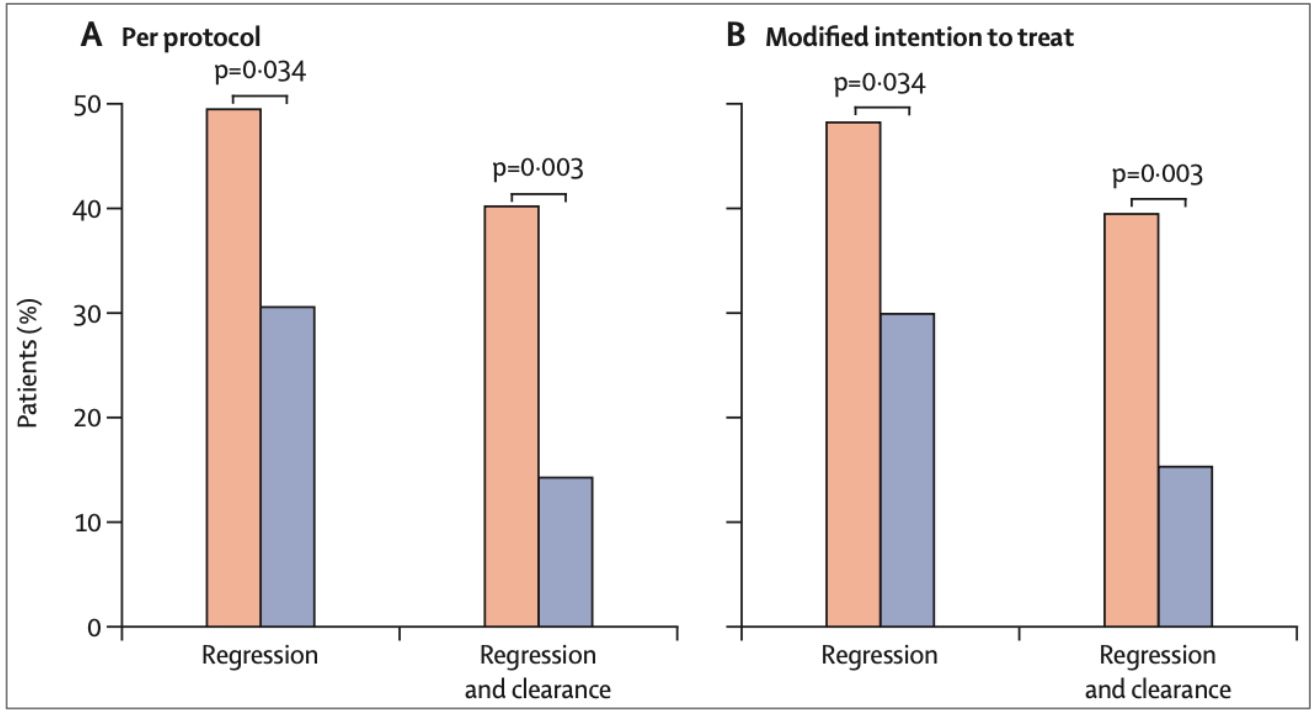
Trimble et al. **Lancet** 2015

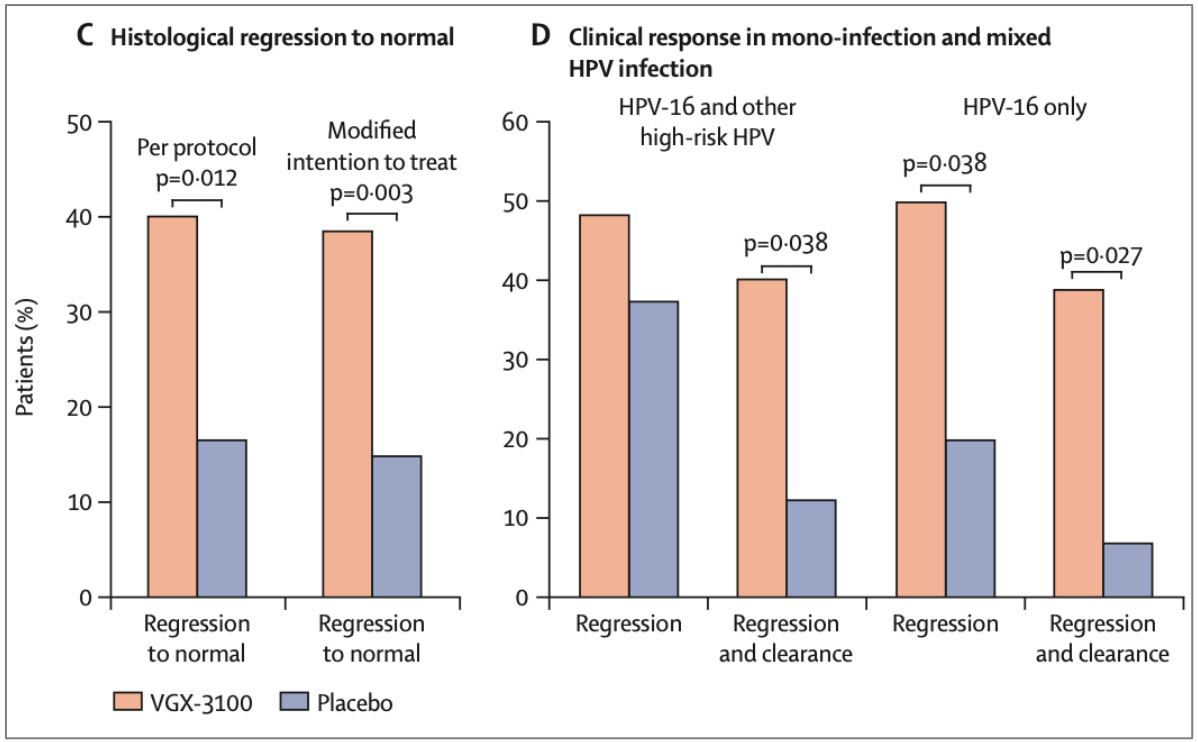
Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial

Cornelia L Trimble, Matthew P Morrow, Kimberly A Kraynyak, Xuefei Shen, Michael Dallas, Jian Yan, Lance Edwards, R Lamar Parker, Lynette Denny, Mary Giffear, Ami Shah Brown, Kathleen Marcozzi-Pierce, Divya Shah, Anna M Slager, Albert J Sylvester, Amir Khan, Kate E Broderick, Robert J Juba, Timothy A Herring, Jean Boyer, Jessica Lee, Niranjan Y Sardesai, David B Weiner, Mark L Bagarazzi

36 Weeks Results

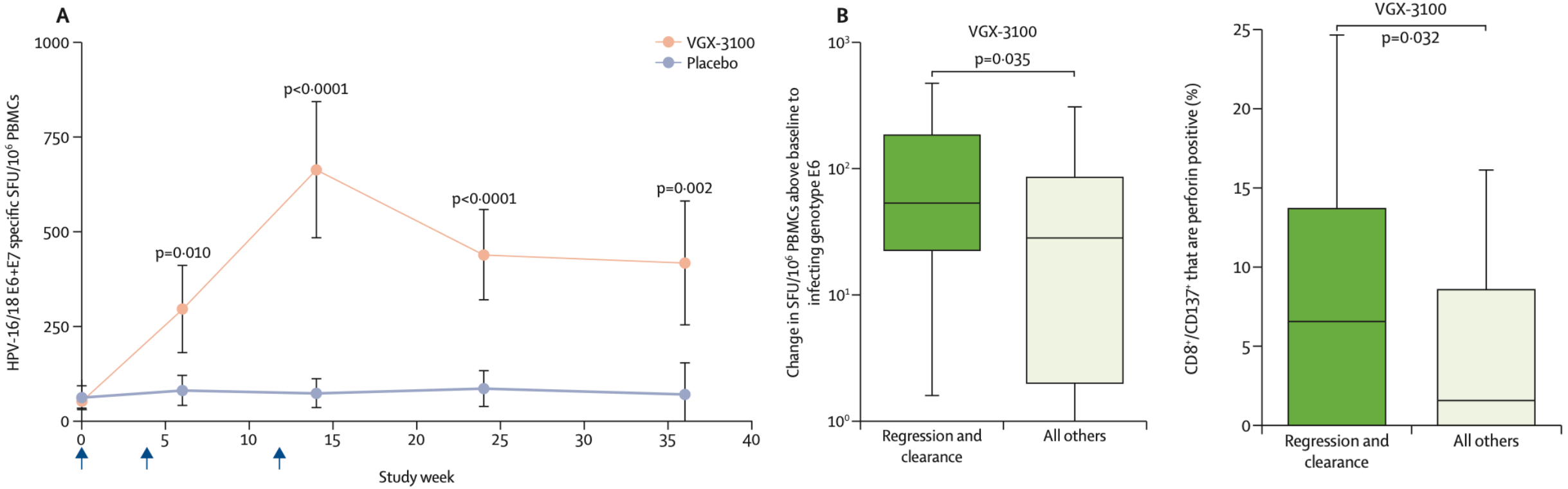
histopathological regression and viral clearance





Trimble et al. Lancet 2015

VGX-3001 Induced T-cell Responses that may associate with Regression/Clearance



Trimble et al. Lancet 2015

MVA Bovine E2 Vaccine

Rational of E2 Antigen Selection

- **E2** is negatively regulate Expression of E6/E7 proteins in infected cells
- **E2 protein** can also **promote cell arrest and apoptosis in** HeLa cells.
- **E2** induced macrophage antibody-dependent cytotoxicity that may enhance tumor/CIN regression

Rosales et al. Human Gene Therapy 2014

Phase 3 : non-RCT

N= 1356 patients (1176 female, 180 male) with intraepithelial lesions

-Female CIN 1-3 (25% CIN3) or condyloma

-Male - condyloma lesions.

Control: 166

Vaccine: MVA Bovine E2

Route: **Intralesional** /wk x 6 wk

Results

Complete regression rate

89% female patients

100% male patients

***HPV DNA clearance* : 83%**

Immune Responses

All developed antibodies and specific cytotoxic responses

Can E7 mRNA vaccine generate a better HPV16-tumor regression outcome vs the other platforms ?

Yes: In an Animal Model

CANCER VACCINES

Single immunizations of self-amplifying or non-replicating mRNA-LNP vaccines control HPV-associated tumors in mice

Jamile Ramos da Silva[1,2], Karine Bitencourt Rodrigues[1], Guilherme Formoso Pelegrin[1], Natiely Silva Sales[1], Hiromi Muramatsu[2,3], Mariângela de Oliveira Silva[1], Bruna F. M. M. Porchia[1,4,5], Ana Carolina Ramos Moreno[1], Luana Raposo M. M. Aps[1,5], Aléxia Adrianne Venceslau-Carvalho[1], István Tombácz[2], Wesley Luzetti Fotoran[6], Katalin Karikó[7], Paulo J. C. Lin[8], Ying K. Tam[8], Mariana de Oliveira Diniz[1], Norbert Pardi[2,3]*†, Luís Carlos de Souza Ferreira[1,9]*†

As mRNA vaccines have proved to be very successful in battling the coronavirus disease 2019 (COVID-19) pandemic, this new modality has attracted widespread interest for the development of potent vaccines against other infectious diseases and cancer. Cervical cancer caused by persistent human papillomavirus (HPV) infection is a major cause of cancer-related deaths in women, and the development of safe and effective therapeutic strategies is urgently needed. In the present study, we compared the performance of three different mRNA vaccine modalities to target tumors associated with HPV-16 infection in mice. We generated lipid nanoparticle (LNP)–encapsulated self-amplifying mRNA as well as unmodified and nucleoside-modified non-replicating mRNA vaccines encoding a chimeric protein derived from the fusion of the HPV-16 E7 oncoprotein and the herpes simplex virus type 1 glycoprotein D (gDE7). We demonstrated that single low-dose immunizations with any of the three gDE7 mRNA vaccines induced activation of E7-specific $CD8^+$ T cells, generated memory T cell responses capable of preventing tumor relapses, and eradicated subcutaneous tumors at different growth stages. In addition, the gDE7 mRNA-LNP vaccines induced potent tumor protection in two different orthotopic mouse tumor models after administration of a single vaccine dose. Last, comparative studies demonstrated that all three gDE7 mRNA-LNP vaccines proved to be superior to gDE7 DNA and gDE7 recombinant protein vaccines. Collectively, we demonstrated the immunogenicity and therapeutic efficacy of three different mRNA vaccines in extensive comparative experiments. Our data support further evaluation of these mRNA vaccines in clinical trials.

Day 1

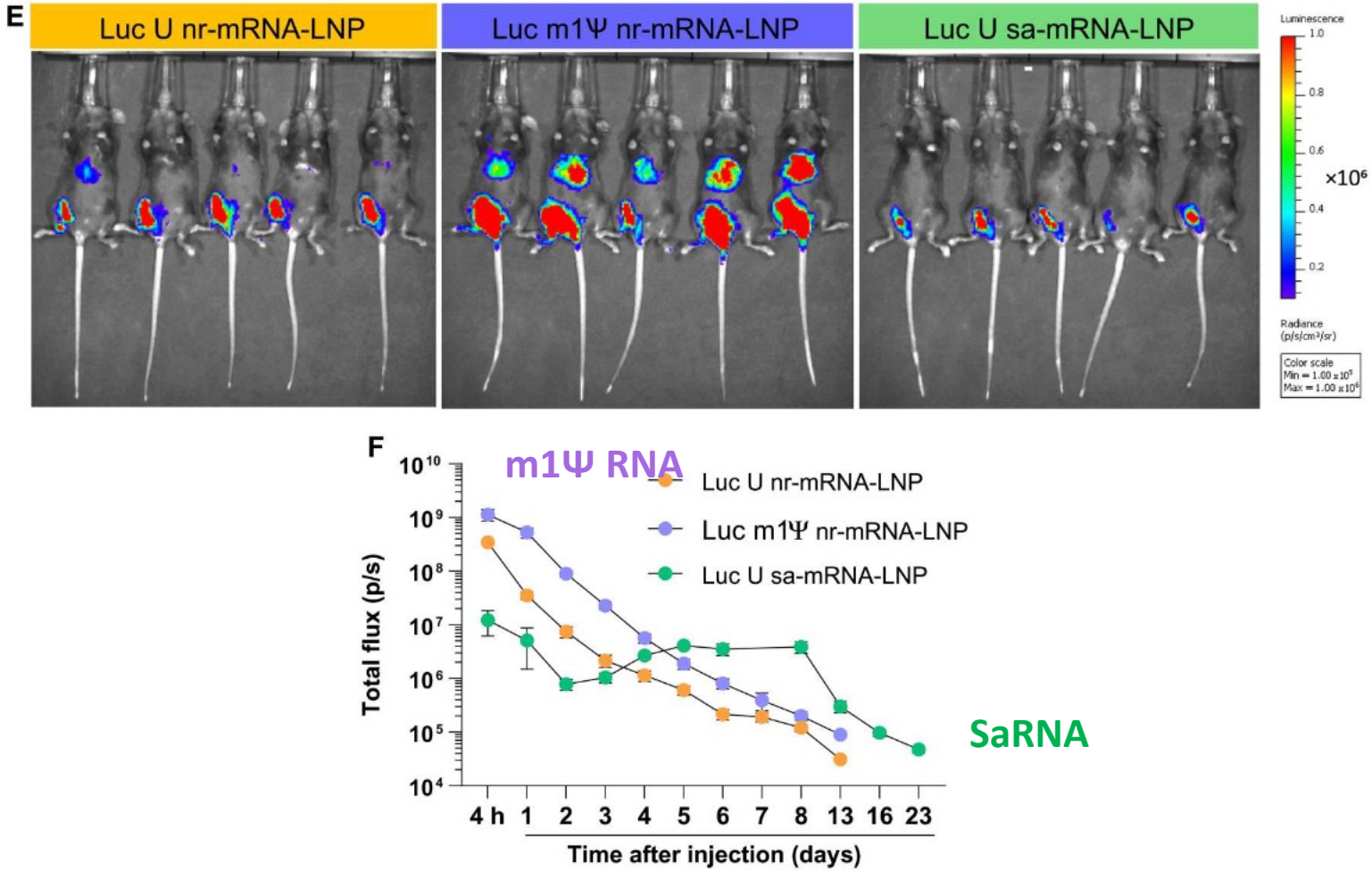
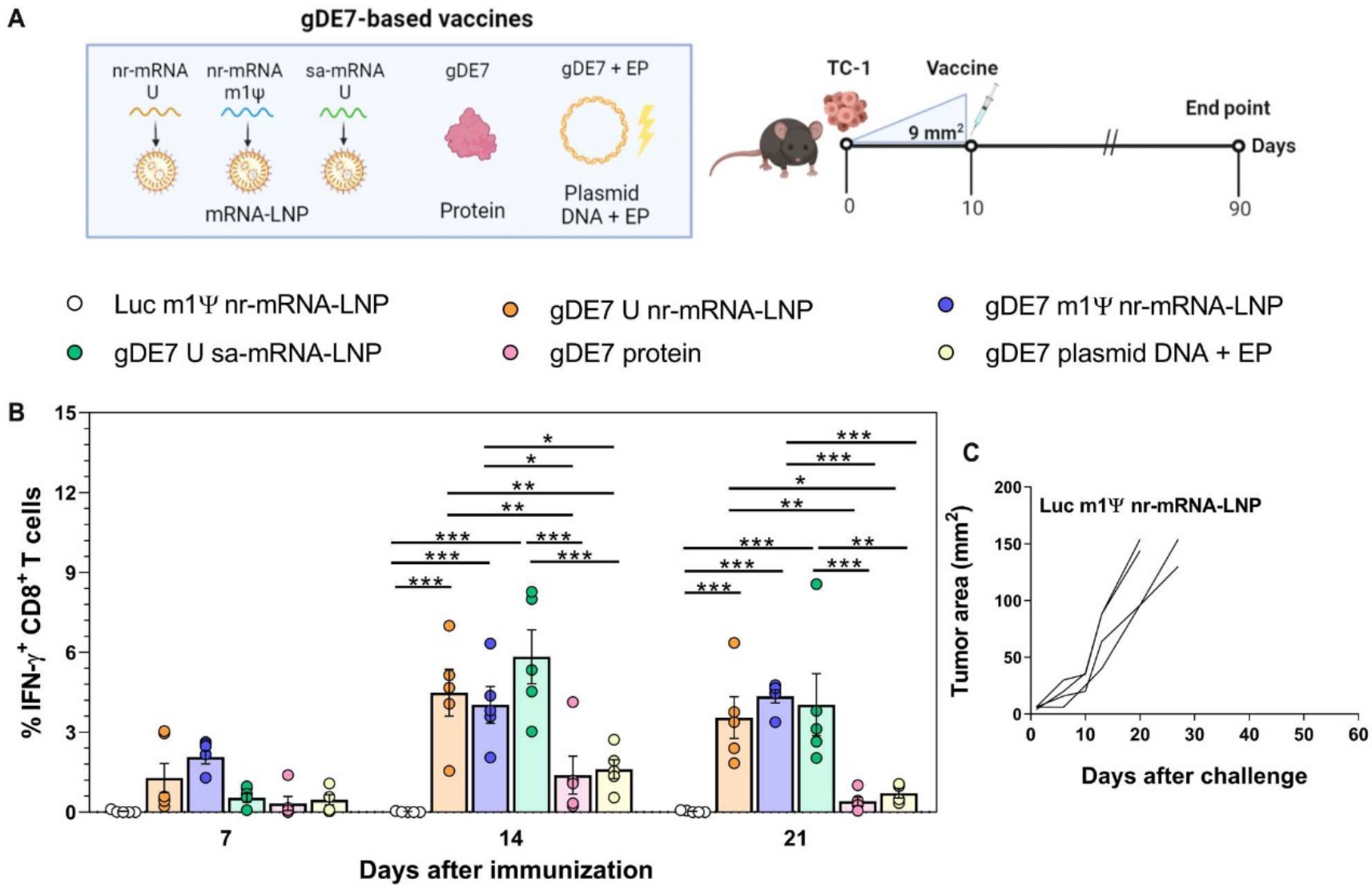
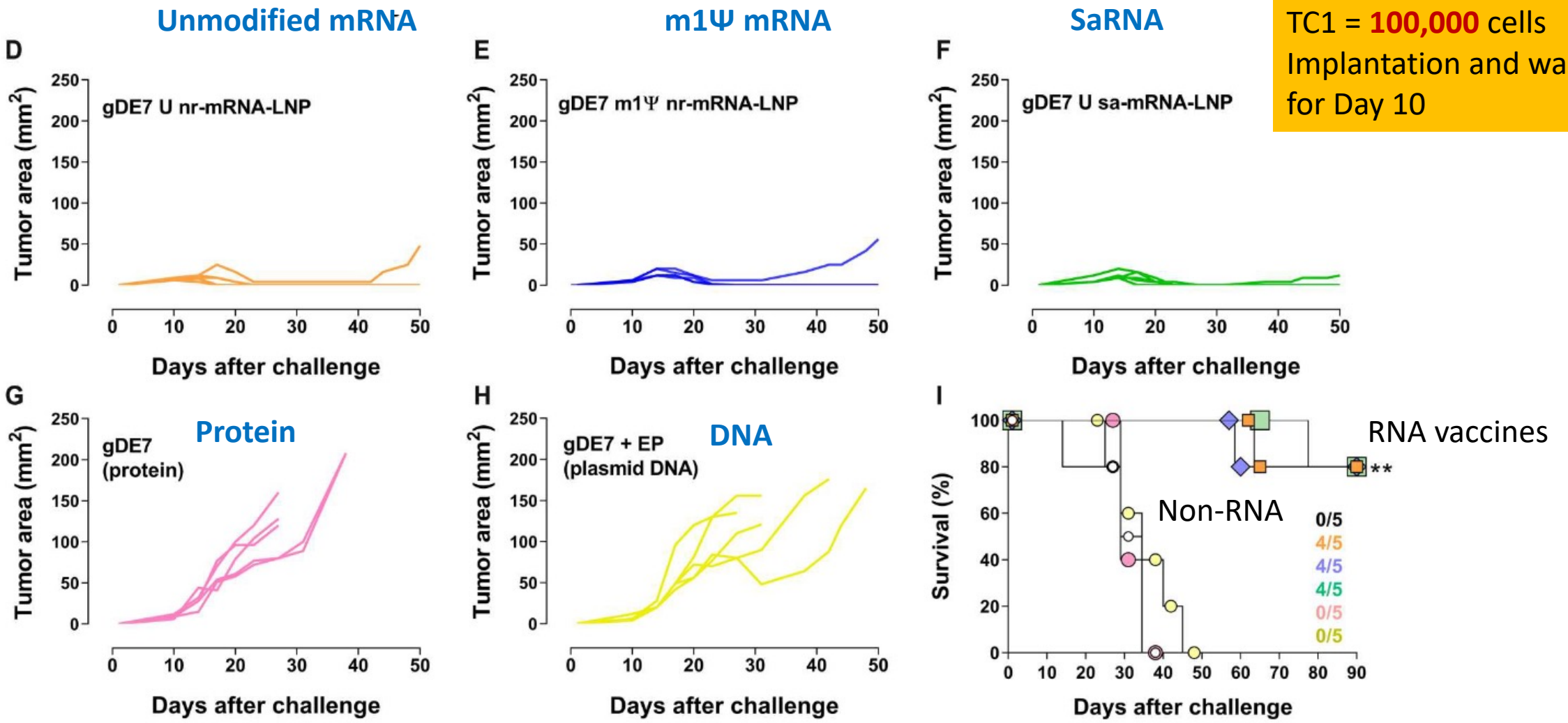


Fig. 1. Comparative evaluation of the translatability of sa-mRNAs and nr-mRNAs in vitro and in vivo. (**A** and **B**) HEK 293T cells (A) and human mo-DCs (B) were transfected with TransIT-complexed Luc mRNA. Cells were lysed at 1, 2, 3, 4, or 5 days after transfection, and Luc activity was measured (5000 cells per sample). Three independent experiments were performed using triplicates in each experiment. RLU, relative light unit. (**C** and **D**) HEK 293T cells (C) and human mo-DCs (D) were transfected with mRNAs encoding Luc or gDE7. Cells were collected 24 hours after transfection, and cell lysates were used to perform Western blotting for the detection of gDE7 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). (**E**) C57BL/6 mice were intramuscularly injected with 3 μg of Luc-encoding U nr-mRNA-LNP, m1Ψ nr-mRNA-LNP, or U sa-mRNA-LNP, and bioluminescence was measured. Representative images show luminescence 1 day after mRNA-LNP injection. (**F**) Quantification of luminescence expressed as photons per second (p/s). Means ± SEM are plotted for each group (n = 5 per group).


A
gDE7-based vaccines
nr-mRNA U
nr-mRNA m1ψ
sa-mRNA U
gDE7
gDE7 + EP
mRNA-LNP
Protein
Plasmid DNA + EP
TC-1
Vaccine
9 mm²
End point
Days
0
10
90
Luc m1Ψ nr-mRNA-LNP
gDE7 U nr-mRNA-LNP
gDE7 m1Ψ nr-mRNA-LNP
gDE7 U sa-mRNA-LNP
gDE7 protein
gDE7 plasmid DNA + EP
B
% IFN-γ⁺ CD8⁺ T cells
Days after immunization
7
14
21
C
Luc m1Ψ nr-mRNA-LNP
Tumor area (mm²)
Days after challenge

Can E7 mRNA vaccine generate a better HPV16-tumor regression outcome vs the other platforms ?

HPV-Tumor Model in Mice
TC1 = **100,000** cells
Implantation and waited for Day 10



HPV Therapeutic Vaccine

WHO Preferred-Product Profiles

WHO Preferred HPV Tx Vaccine TPPs

WHO/Draft for PDVAC review/V0.4/December2023

Parameter	Preferred characteristic
Indication	**For first-generation vaccines**: at a minimum type **16 and 18**, to **increase global public health value in**: - **regression** of cervical precancers AND/OR - **clearance** of additional oncogenic HPV type infections AND/OR - prolonged effects **against reinfection or recurrences**.
Target population	**Adult women** (e.g., ages 25 to 49 years), (Men ?, MSM)
Vaccine delivery strategy	Population-based delivery, with no requirement for a preceding screening test. OR Targeted vaccination based on positive test results.
Schedule	A **single dose** for primary immunization would be ideal. A two-dose primary schedule, and possible booster dosing: acceptable for first-generation vaccines.
Route	Parenteral or oral delivery.
Safety	A safety profile that is comparable to current WHO-recommended adult vaccines.
Efficacy	Relatively **high efficacy in clearing HPV type 16 and 18 infection** (e.g., **70-90%**) may be needed to drive broad population impact. Lower efficacies against HPV 16 and 18 infection could be acceptable in : efficacy in regressing precancers, cross-protection against other HPV types, or ongoing immune responses that could clear reinfections.
Concomitant use	Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines recommended for use.

Other general vaccine profiles

Product stability and storage	Stability under **refrigerated conditions (2–8°C**, the standard cold chain) for 24 months would be acceptable, but stability at room temperature **(20°C) would be ideal**
Concomitant use	Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines or with precancer treatments recommended for use.
Value assessment and affordability	The vaccine should be cost effective and have a favourable value assessment relative to existing cervical cancer prevention interventions. Dosage, regimen, and cost of goods amenable to affordable supply; price should not be a barrier to access in LMICs.
Prequalification and programmatic suitability	The vaccine should be pre-qualified according to the WHO process outlined.

WHO Preferred HPV Tx Vaccine Efficacy Profiles

What HPV Types should be included ?

- HPV types **16 and 18 account for 70%** of cervical precancers that progress to invasive cervical cancer. Therefore, minimally viable first-generation vaccines should include HPV 16 and 18.
- **Cross-protection against** cervical precancers associated with **additional** oncogenic **HPV types (e.g., 31, 33, 35, 45, 52, 58)** or clearance of associated HPV infection or low-grade cervical lesions would have added benefit.

Two HPV mRNA Vaccines in Clinical Trials

- **A Study in Subjects With Human Papillomavirus 16 or 18 Associated Cervical Intraepithelial Neoplasia Grade 2 or 3 (CIN2-3) -*Phase 1/2***

  ClinicalTrials.gov ID NCT06273553, Sponsor RinuaGene Biotechnology Co., Ltd., Last Update 2024-02-22

  Study Design: **3 dose** cohorts: **25µg,75µg and 150µg** x 2 weeks interval

- **A Clinical Trial Investigating the Safety, Tolerability, and Therapeutic Effects of BNT113 in Combination With Pembrolizumab Versus Pembrolizumab Alone for Patients With a Form of Head and Neck Cancer Positive for Human Papilloma Virus 16 and Expressing the Protein PD-L1 (AHEAD-MERIT) - *Phase 2***

  ClinicalTrials.gov ID NCT04534205; Sponsor BioNTech SE, Last Update 2024-03-15

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HPV Therapeutic Vaccine

WHO Preferred Product Profiles *to increase global public health value*

At Least covers
HPV16
HPV18

1. **Regression** of Cervical Precancers (CIN—3)
   AND/OR
2. **Clearance** of oncogenic HPV type infections
   AND/OR
3. Prolonged effects **against Reinfection or Recurrences**


คณะแพทยศาสตร์
FACULTY OF MEDICINE
Chulalongkorn University
โรงพยาบาลจุฬาลงกรณ์
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THANK YOU