Novel one-component ionizable amphiphilic Janus dendrimers (IAJD) as a delivery platform for efficient mRNA vaccine development

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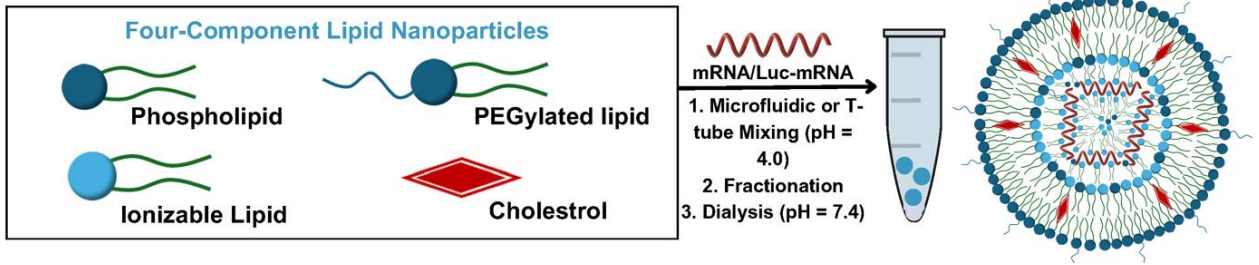
July 14, 2025

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

Four-component LNP vs one-component IAJD Nanoparticles

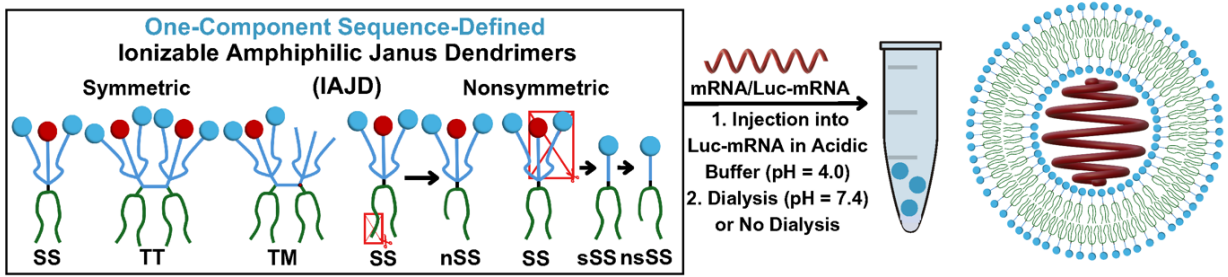
Four-Component Ionizable Lipid Nanoparticles (LNPs)



LNPs

- Four components;
- Microfluidics
- PEG adverse reaction
- Storage at -80℃

One-Component Ionizable amphiphilic Janus dendrimers (IAJDs)

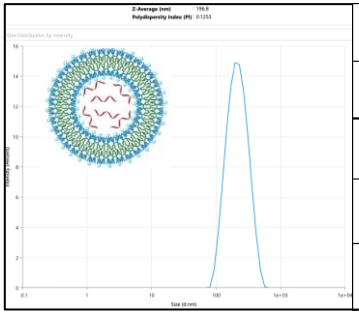


IAJDs

- One component
- Simple mixing
- No PEG
- Stable at 4°C for over 6 months
- Less cost and fast in production

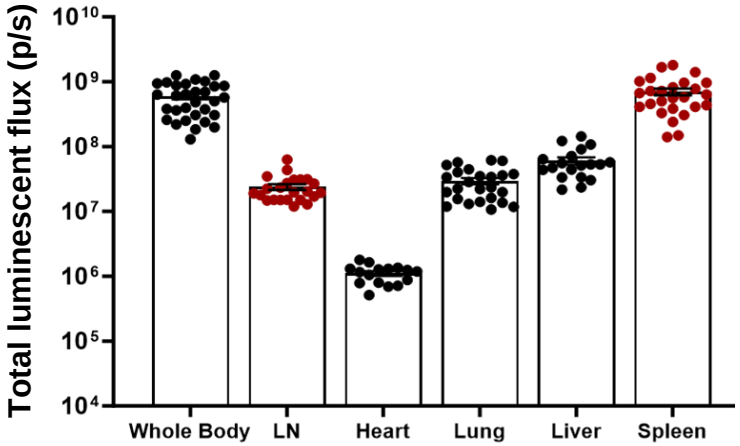
Luc mRNA-IAJD97 targeted delivery to the spleen

Luc mRNA-IAJD97 characterization

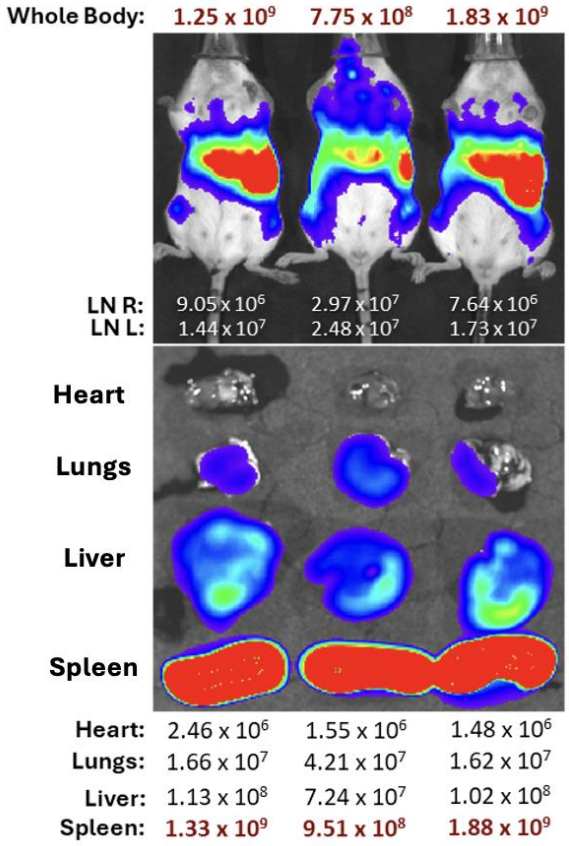


Size, nm	195 ± 7 n=23
PDI	0.130 ± 0.012 n=29
Encapsulation efficiency, %	96.7 ± 1.6 n=7
pKa	8.22 ± 0.01 n=3
Zeta potential, mV	23.0 ± 3.3 n=5

Luciferase expression biodistribution

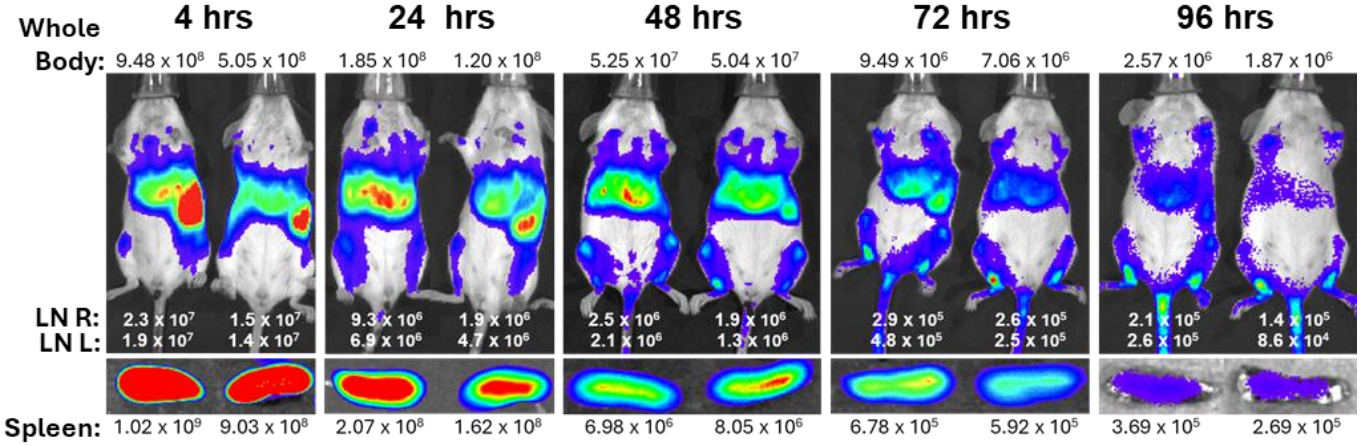


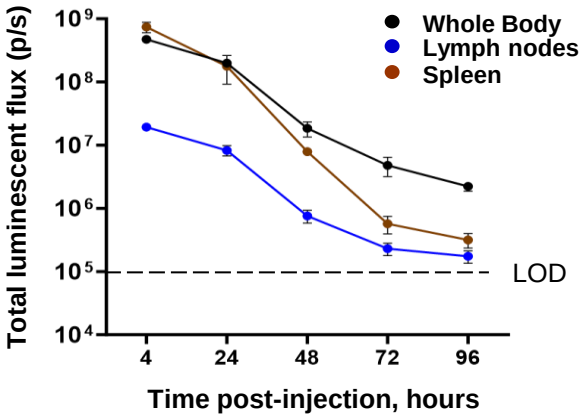
In Vivo Imaging System (IVIS)



- DNPs were formulated by simple mixing of Luc mRNA and IAJD97.
- Injection dose: 5 µg per mouse.
- Strongest luciferase expression observed in the spleen.
- In Vivo Imaging System (IVIS) images show luciferase expression in the whole body (top) and organs (bottom) 4 h post-IV injection.
- BLI data quantified as total flux (p/s) from ROI

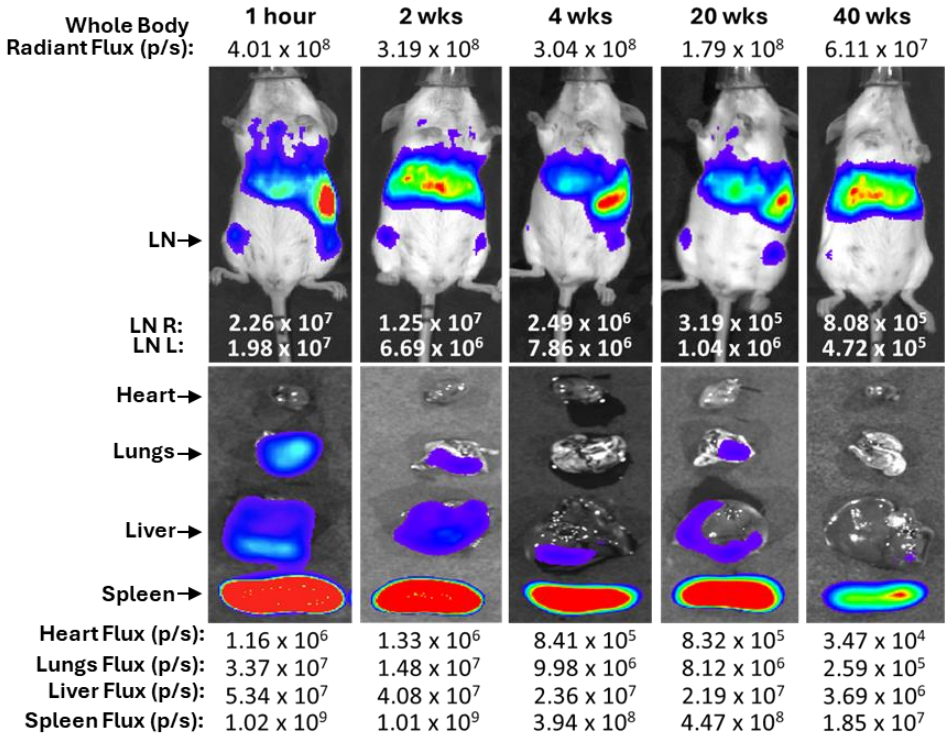
Persistence of Luc mRNA-IAJD97

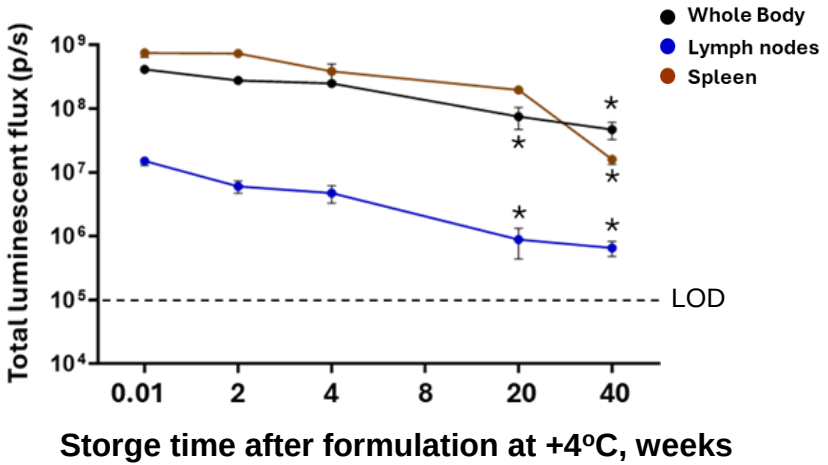




- 5 µg Luc mRNA-IAJD97 per mouse was injected.
- Luciferase expression persisted for at least 96 hours *in vivo.*
- Luminescence values that were below 1×10⁵ total flux (p/s) were considered below the limit of detection (dash line).

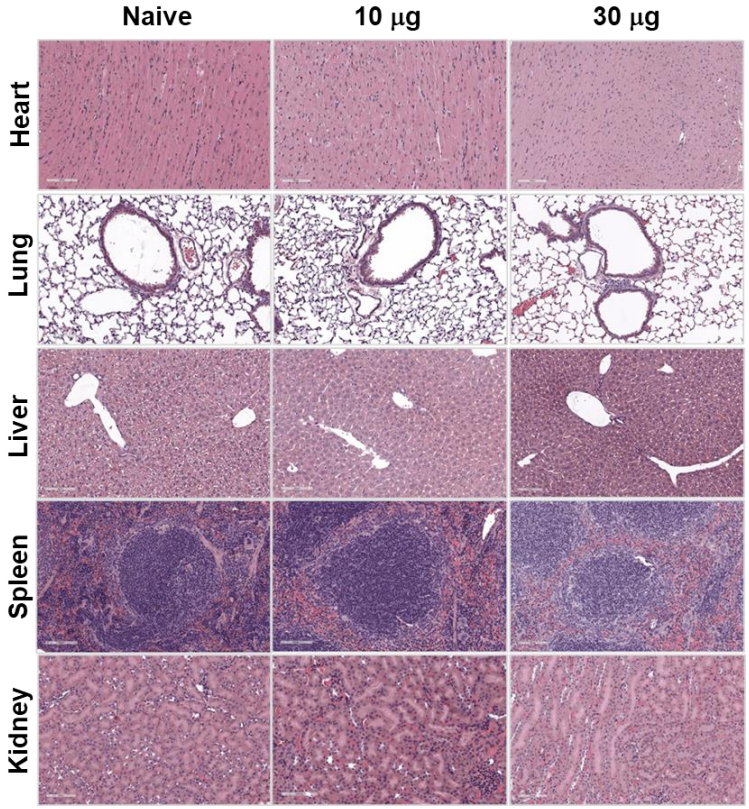
Stability of Luc mRNA-IAJD97

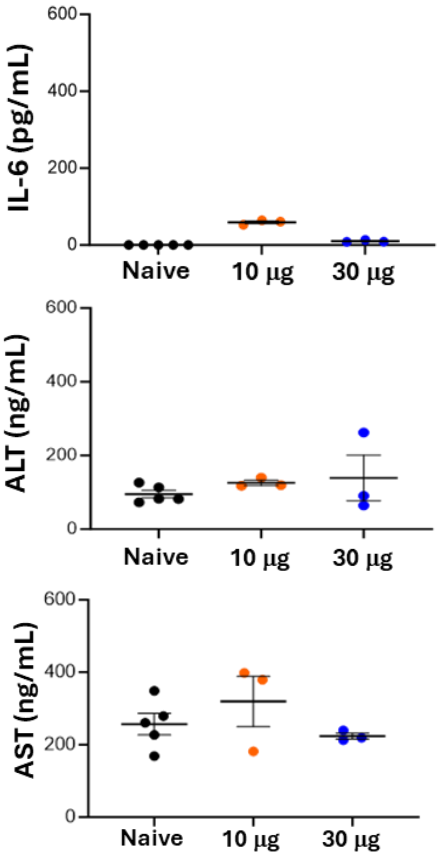




- 5 µg Luc mRNA-IAJD97 per mouse was injected. BLI data are shown as total flux (p/s).
- Stability of Luc mRNA-IAJD97 was maintained after storage at +4℃ for up to 20 weeks.
- Luminescence values that were below 1×10⁵ total flux (p/s) were considered below the limit of detection (dash line).

Lack of toxicity with Luc mRNA-IAJD97 delivery

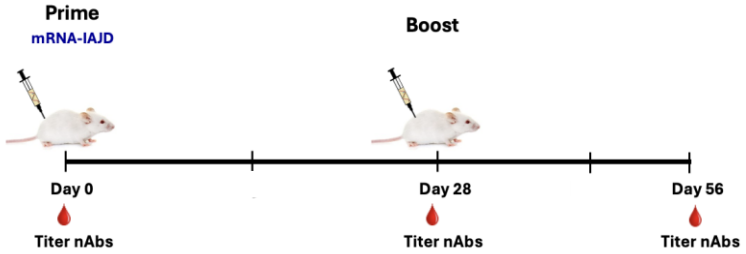




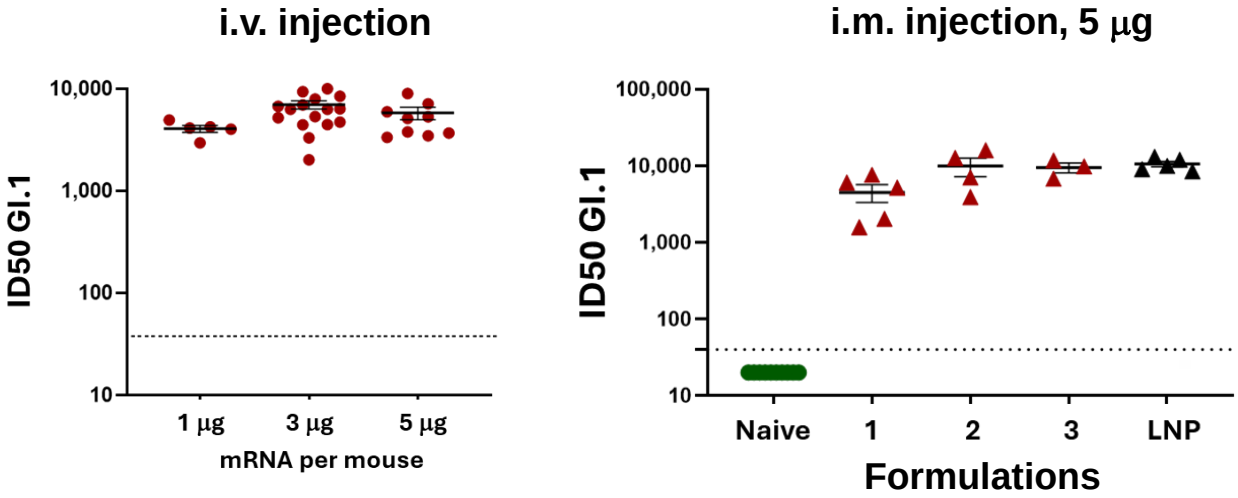
- BALB/c mice were injected with 10 and 30 µg of Luc mRNA-IAJD97.
- Serum and organs were collected 24 hours post-injection.
- No pathological alterations observed in hearts, lungs, liver, spleen, or kidney at any dose.
- No significant increases in serum IL-6, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), key markers of liver health, were observed when compared with naïve mice.

In this study we use norovirus mRNA capsid protein as a proof of concept for the potential use of one-component IAJD97 as a novel and efficient platform for vaccine delivery

Humoral immune response by Norovirus VP1 mRNA-IAJD97 vaccine

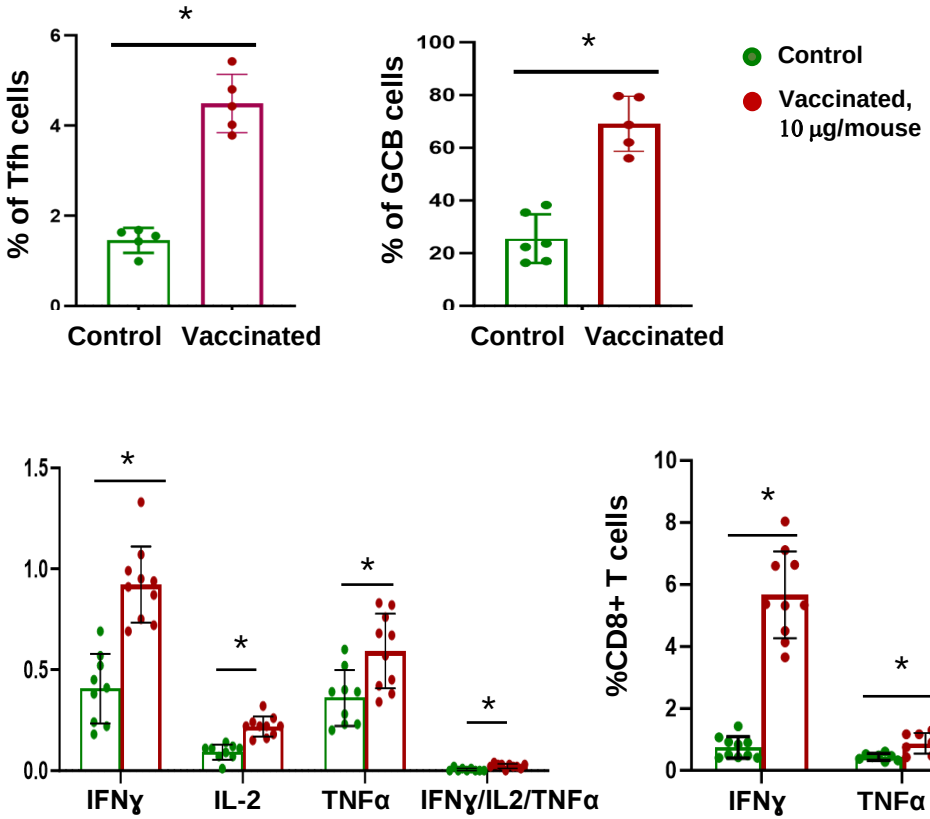


Neutralization Abs titer, Day 60



- Mice were immunized at day 0 and day 28 by i.v. or i.m. injection with GI.1 mRNA-IAJD97.
- Both i.v and i.m. routes induced high titers of neutralizing antibodies (nAbs).
- A dose of 1 μg GI.1 mRNA-IAJD97 was sufficient to trigger a robust nAb response with i.v. administration

Cellular immune response by Norovirus VP1 mRNA-IAJD97 vaccine



- Mice were immunized on Days 0 and 28 with GII.4 mRNA-IAJD97.
- Tfh and GCB cells, in inguinal and popliteal lymph nodes, were measured 7 days post-prime i.m. injection.
- Splenocytes were isolated 14 days post-boost, stimulated with GII.4 peptides pool and analyzed via multicolor flow cytometry.
- CD4+ T cells co-expressed antiviral cytokines: IFNγ, IL-2, and TNFα, highlighting a multifunctional response.

Conclusion

- The delivery platform, based on one-component ionizable amphiphilic Janus dendrimers (IAJD97), showed excellent stability and was well-tolerated in preclinical models.
- One–component IAJD97, formulated with Norovirus mRNA capsid protein, demonstrated strong potential as a novel and efficient platform for vaccine delivery.
- Both intravenous (IV) and intramuscular (IM) administration induced sustained humoral immune responses, with high levels of neutralizing antibodies.
- It effectively elicited robust cellular immune responses, including significant CD4+ and CD8+ T cell activation.
- **This proof-of-concept study demonstrates the ability of one-component IAJD to serve as a platform for efficient vaccine delivery.**

Acknowledgments

The Weissman Lab
Bringing mRNA therapeutics to the world

Drew Weissman Lab:

- Drew Weissman
- **Elena Atochina-Vasserman**
- Nathan Ona
- Jaclynn Meshanni
- Sydni Berkihiser
- Jessica Vasserman
- Sepideh Toshtzar
- Nathanael Moore
- Blair Williams
- Benjamin Nakagawa
- Ishana Baboo
- Xiomara Mercado-Lopez

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THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

❖ **Collaborators:**

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- Virgil Percec

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