Overcoming Anti-PEG Antibody Responses – A Novel PEOZ-lipid That Fails to Elicit an Immune Response to the Polymer-lipid in mRNA-LNP Formulations

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December 2024 Non-confidential Presentation
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Today's Messaging:

- Consecutive cohort studies show that anaphylaxis occurs at an unusually high incidence rate in patients receiving the approved mRNA vaccines; current data suggest this is ***not*** classically characterized IgE-mediated (mast cell degranulation)

- The high titers of anti-PEG IgM & IgG that are boosted by the vaccines bind to LNPs, form membrane complex and activate complement, and induce structural changes in the LNP (leak payload, allow access to serum components)
  - Activation of the complement cascade may also result in anaphylaxis

- The high titers of IgM & IgG are associated with first-exposure loss of efficacy for some PEGylated therapies (notably PEGrFVIII as a replacement therapy for Hemophilia A)

- The Serina LNP Laboratory has identified a PEOZ-lipid that is capable of replacing the PEG-lipid in standard LNP formulations
  - And fails to elicit an immune response to the PEOZ-lipid on repeat dosing

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Balancing immunogenicity and reactogenicity

Review

KSBMB
Korean Society for Biochemistry and Molecular Biology

www.nature.com/emm

REVIEW ARTICLE OPEN

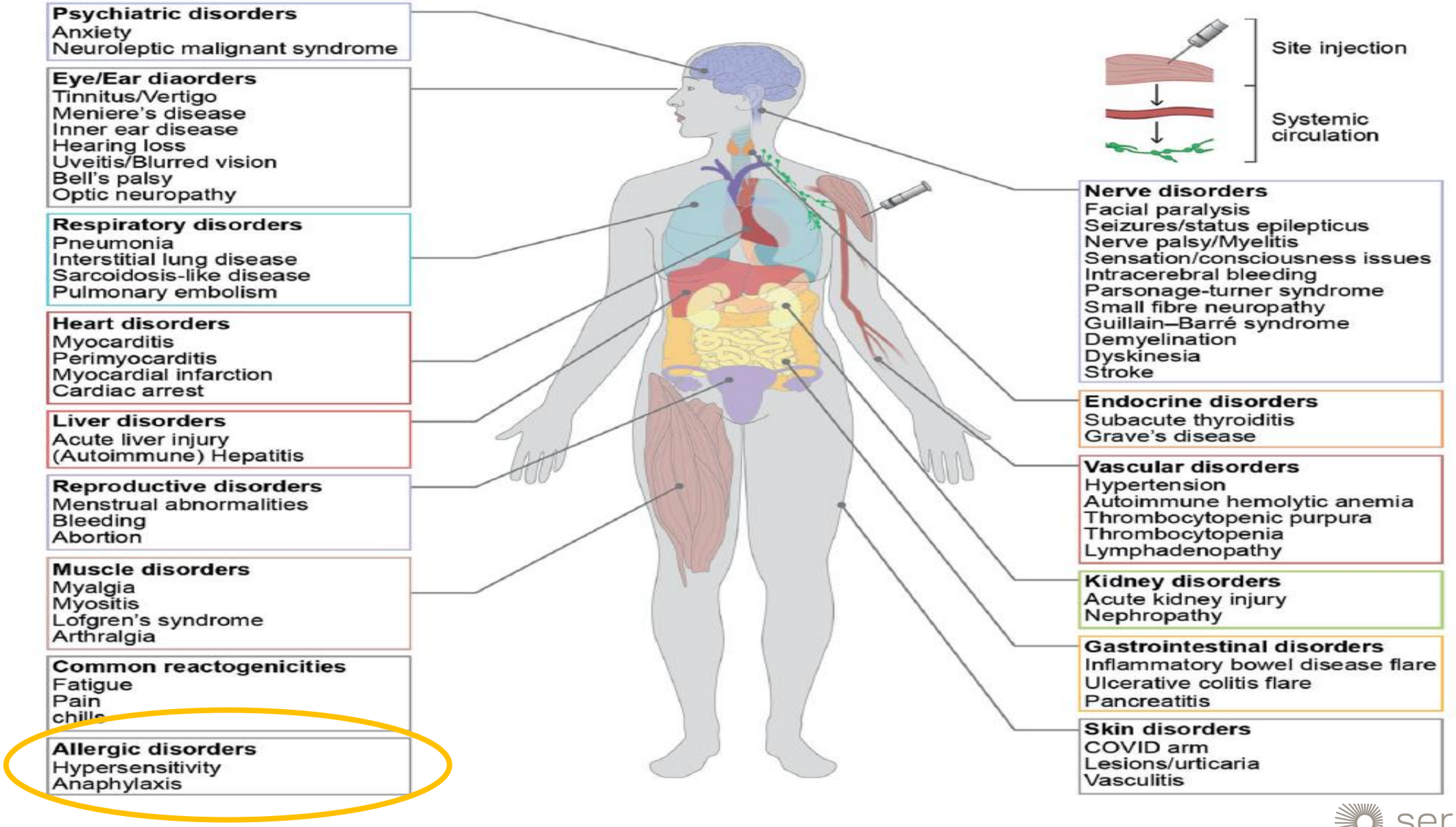
Check for updates

Knife's edge: Balancing immunogenicity and reactogenicity in mRNA vaccines

Jisun Lee[1,6], Matthew C. Woodruff[2,3,6], Eui Ho Kim[4]✉ and Jae-Hwan Nam[1,5]✉

Balancing immunogenicity and reactogenicity

List of adverse events reported with the mRNA vaccines



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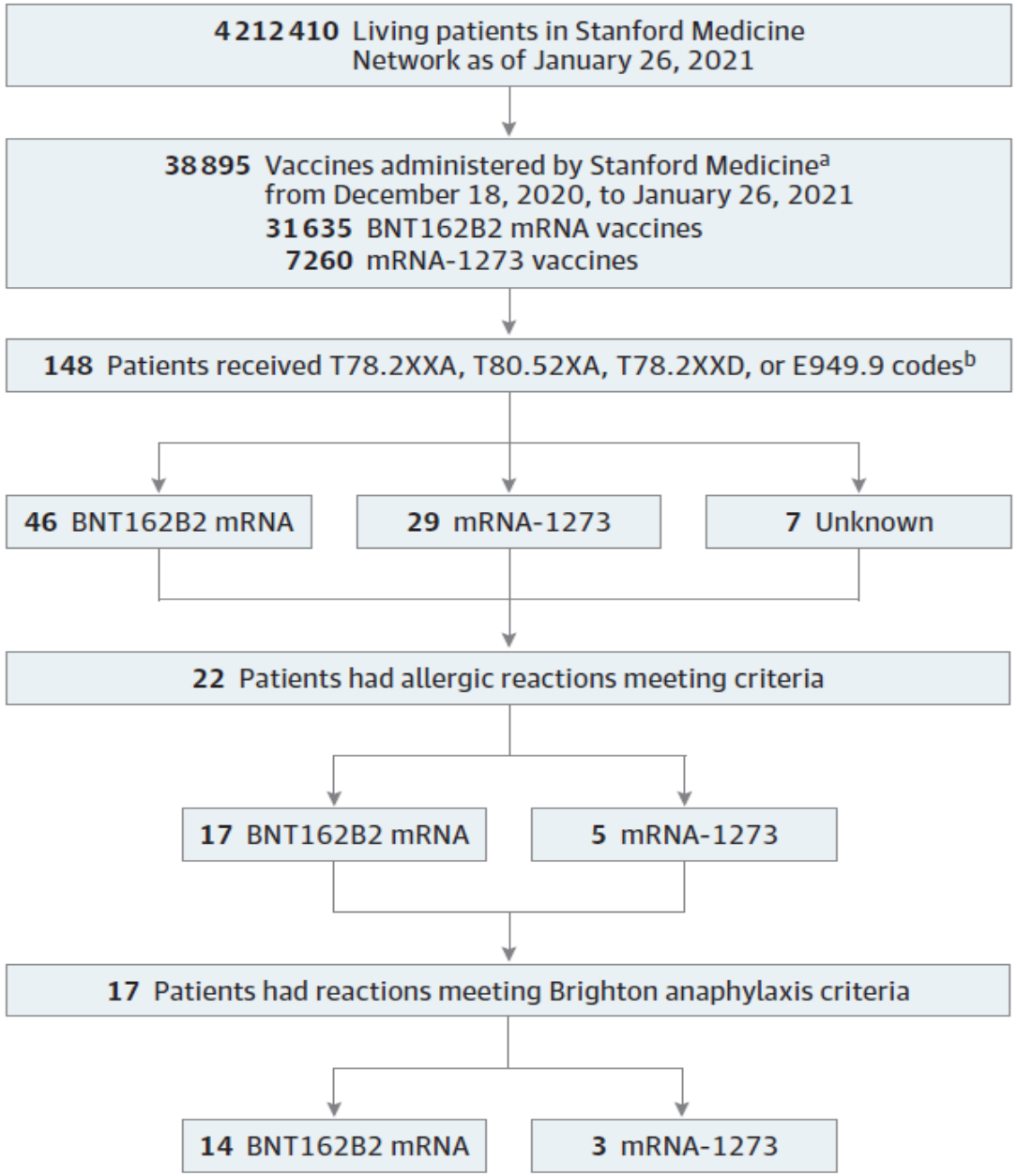
In A Consecutive Cohort Study in Stanford Medical Center Network



Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. *JAMA Network Open.* 2021;4(9):e2125524.

The incidence rate of anaphylaxis meeting Brighton anaphylaxis criteria was 1:2,287

(the incidence of anaphylaxis with flu vaccine is ~ 1:2,000,000)

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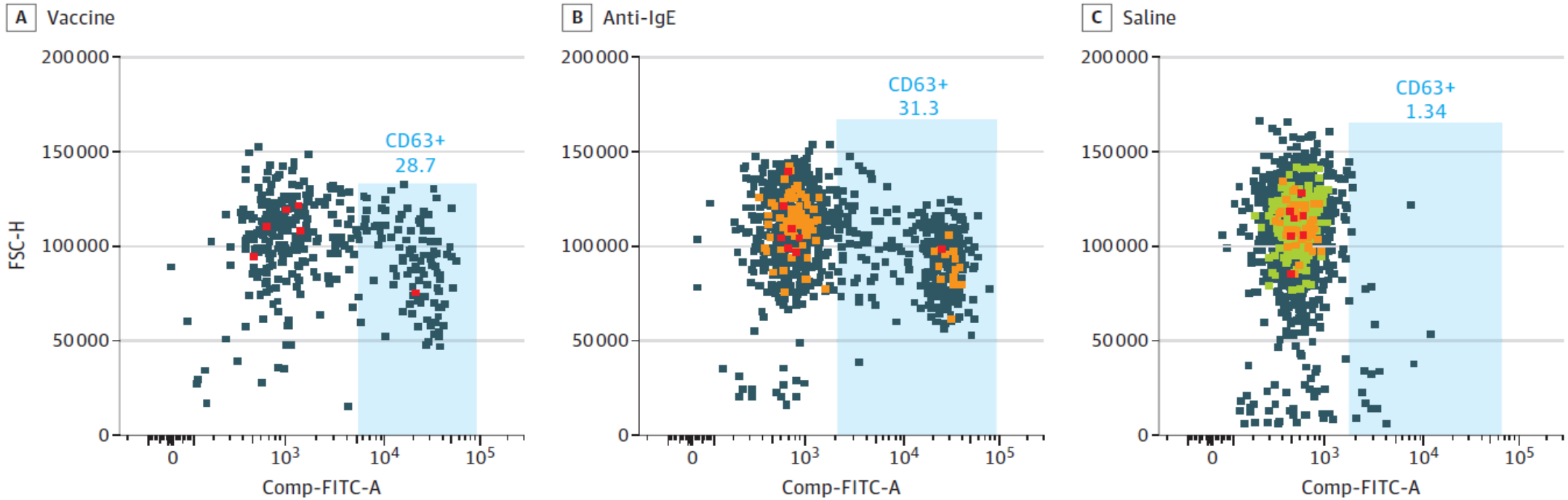
Figure 2. Basophil Activation Testing (BAT) Assay on Example Participant Using Vaccine, Anti-Immunoglobulin E (IgE), and Saline



BAT assay on example participant with allergic reaction to the vaccine. Color indicates intensity of forward scatter and gated cells, with red being greater than orange; orange greater than green, and green greater than blue. FSC-H indicates forward side scatter-height; Comp-FITC-A, compensation–fluorescein isothiocyanate–area.

Eleven of the seventeen patients consented to additional studies. BAT assays revealed that patients with anaphylaxis gated activated CD63+ basophils in the presence of vaccine (A), PEG (not shown) - but not saline (C)

The Anti-IgE panel (B) is the positive control

IgG-mediated degranulation of basophils may lead to release of PAF, one of the most potent anaphylatoxins known

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Is PEG the culprit ? Yes.

MAIN OUTCOMES AND MEASURES Allergic reactions were graded using standard definitions, including Brighton criteria. Skin prick testing was conducted to polyethylene glycol (PEG) and polysorbate 80 (P80). Histamine (1 mg/mL) and filtered saline (negative control) were used for internal validation. Basophil activation testing after stimulation for 30 minutes at 37 °C was also conducted. Concentrations of immunoglobulin (Ig) G and IgE antibodies to PEG were obtained to determine possible mechanisms.

RESULTS Of 22 patients (20 [91%] women; mean [SD] age, 40.9 [10.3] years; 15 [68%] with clinical allergy history), 17 (77%) met Brighton anaphylaxis criteria. All reactions fully resolved. Of patients who underwent skin prick tests, 0 of 11 tested positive to PEG, 0 of 11 tested positive to P80, and 1 of 10 (10%) tested positive to the same brand of mRNA vaccine used to vaccinate that individual. Among these same participants, 10 of 11 (91%) had positive basophil activation test results to PEG and 11 of 11 (100%) had positive basophil activation test results to their administered mRNA vaccine. No PEG IgE was detected; instead, PEG IgG was found in tested individuals who had an allergy to the vaccine.

10 of 11 patients had positive basophil activation tests to PEG

11 of 11 patients had positive basophil activation tests to the administered vaccine

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We've seen this before …

The Regado Bioscience story

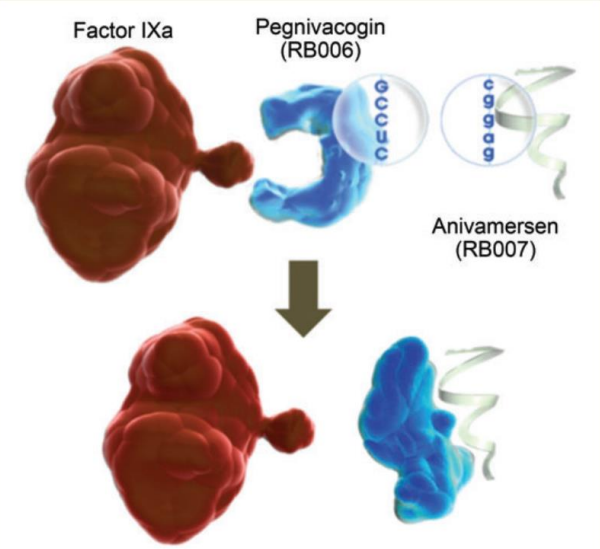

Figure 1 The REG1 anticoagulation system, consisting of pegnivacogin (RB006) and its complementary controlling agent anivamersen (RB007).

- The REG1 system was a rationally-designed strategy to replace the anticoagulant heparin in the cardiac catheterization lab as an adjunct to percutaneous coronary artery procedures
- Pegnivacogin (RB006) was a 40 kDa methoxy-PEG attached to an aptamer that could completely inhibit Factor IXa in ~ 1 minute @ 1 mg/kg (64 mg PEG)
- The anti-aptamer Anivamersen (PB007) was shown to provide prompt reversal of anticoagulation in ~ 1 minute
- RADAR – a dose-ranging Phase 2a study in ACS to determine the optimal dose of pegnivocogen to (a) achieve anticoagulation, and (b) to reverse anticoagulation promptly with the anti-aptamer to prevent subsequent bleeding (sheath removal). The trial enrolled 640 patients (2013-2016; n=479 across four doses of anivamersen, n=161 heparin) before the trial was halted due to three serious adverse events that occurred within minutes of infusion …

Pre-existing anti–polyethylene glycol antibody linked to first-exposure allergic reactions to pegnivacogin, a PEGylated RNA aptamer

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MAY 2016

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TABLE I. Subjects experiencing SARs in RADAR

Patient ID	Onset (min)	Symptoms	Treatment	Resolution (h)	Allergy history
602-004	5	GI, D, P, H	IVF, H1, IVV, S	6	2 mo prior diffuse urticaria to unknown agent
406-003	25	D	S, H1, H2	0.4	Contrast dye, hay fever
418-008	5	P, D, H	S, H1, H2, IVF, IVV, I, Inh	1144	Recent allergy to β-blockers and steroids

D, Dermal; *GI*, gastrointestinal; *H*, hypotension; *H1*, H1 blocker; *H2*, H2 blocker; *I*, intubation; *Inh*, inhalers; *IVV*, intravenous vasopressors; *IVF*, intravenous fluid resuscitation; *P*, pulmonary; *S*, steroids.

- All three patients were female with a history of allergic reactions
- The onset of these SAEs occurred within minutes of the infusion
- Quality review of the nonhuman primate studies revealed no aggregation, degradation or evidence of inflammatory cytokine release
- There was no evidence of complement activation in vitro or in vivo
- Blinded testing of a causal association of the SAEs in half the RADAR patients revealed an association with high titers of IgG against PEG and first-exposure adverse reactions
- This was the first study to demonstrate a causal relationship between pre-exposure anti-PEG antibodies and serious adverse events

Pre-existing anti–polyethylene glycol antibody linked to first-exposure allergic reactions to pegnivacogin, a PEGylated RNA aptamer

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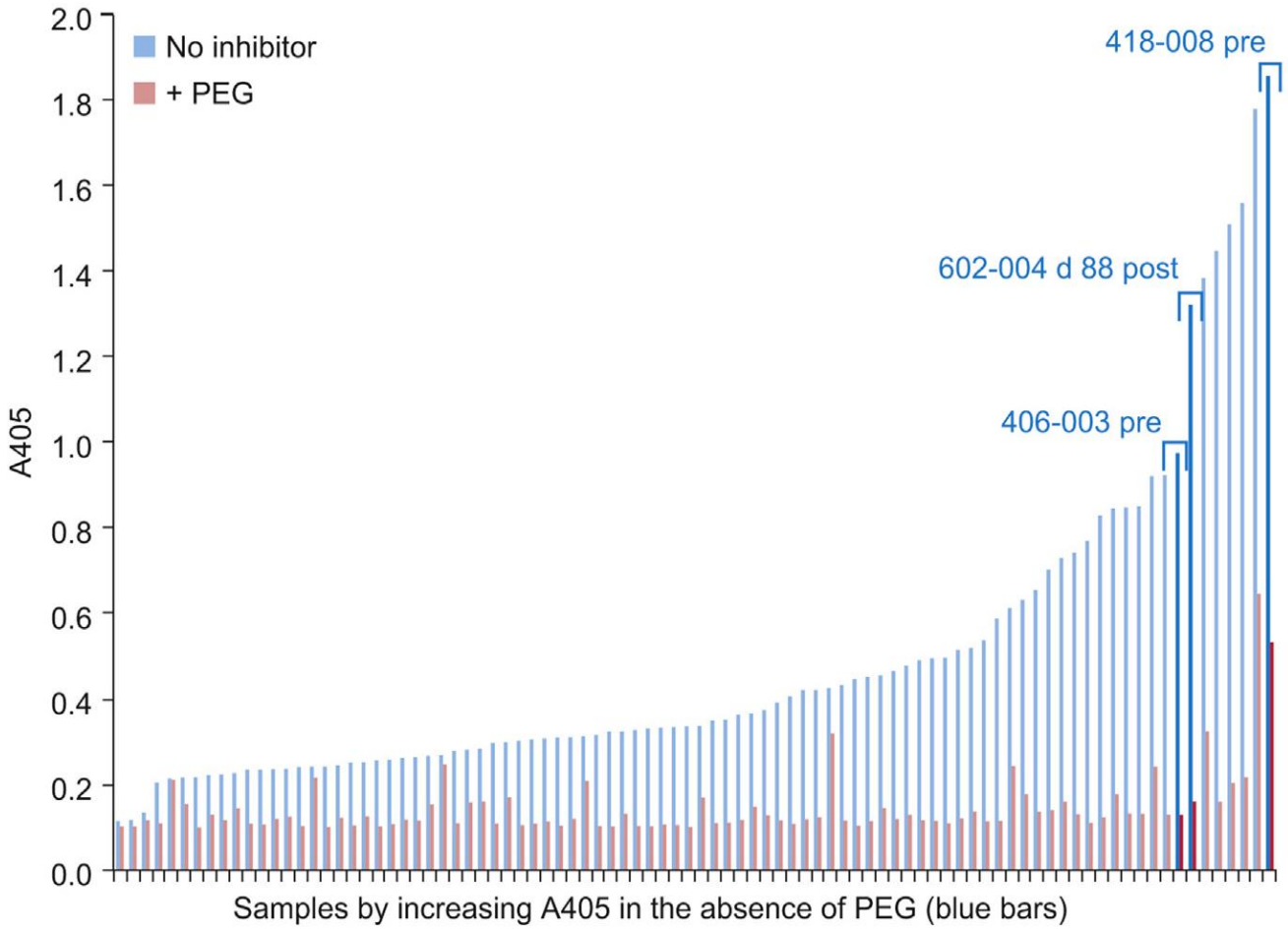

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- The IgGs in these patients were shown to bind linear PEG and branched PEG, presented as either methoxyPEG or hydroxyPEG (PEG diol)
- The anti-PEG IgG titers ranged from 1:120 to 1:3100
- The anti-PEG antibodies also bound PEGloticase (Krystexxa, refractory gout) and PEGylated adenosine deaminase (ADA deficiency)
- Unblinding of coded samples from 31 patients in RADAR revealed all three patients were at the high end of the ELISA (figure left)
- None of the IgGs bound the un-PEGylated aptamer
- ~ 36% of the patients in RADAR had A405 cutoffs in the ELISA (arbitrarily chosen at 0.2) suggesting they had detectable levels of antibodies to PEG
- The REG1 system was advanced into a pivotal Phase 3 trial (REGULATE PCI); target enrolment 13,200 ACS patients

We've seen this before …

The Regado Bioscience story

TABLE I. Incidence of allergic reactions within 24 hours by treatment arm

Type of allergic reaction	Bivalirudin (n = 1601)	Pegnivacogin (n = 1605)	Total (N = 3206)	OR (95% CI)
Any allergic reaction	10 (0.62)	24 (1.5)	34 (1.06)	2.4 (1.2-5.1)
Serious allergic reaction	1 (0.06)	10 (0.62)	11 (0.34)	10.0 (1.3-78.5)
Severe allergic reaction	4 (0.25)	18 (1.12)	22 (0.69)	4.5 (1.5-13.4)
Nonsevere allergic reaction	6 (0.37)	6 (0.37)	12 (0.37)	1.0 (0.3-3.1)
Anaphylaxis	1 (0.06)	10 (0.62)	11 (0.34)	10.0 (1.3-78.5)
Allergic reaction onset <1 h after study drug dosing	2 (0.12)	16 (1.0)	18 (0.56)	8.1 (1.9-35.1)
Severe allergic reaction onset <1 h after study drug dosing	1 (0.06)	12 (0.74)	13 (0.40)	12.1 (1.6-92.8)

Data presented as n (%). Bivalirudin was the reference group in the calculation of OR.
OR, Odds ratio.

Pre-existing anti-PEG antibodies are associated with severe immediate allergic reactions to pegnivacogin, a PEGylated aptamer

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- The trial was halted due to an excess of SAEs in the Pegnivacogen arm vs Bivalirudin; included one fatality
- Of the 16 patients who developed SAEs in < 1 hr in the Pegnivacogen arm 15 (94%) had high titer IgGs to PEG
- **The authors speculated that anti-PEG IgG-mediated basophil degranulation was the likely cause of severe immediate allergic reactions**
- **Note – these SAEs occurred in the absence of known mechanisms of immunization against PEG**

Does vaccination induce high titers of anti-PEG antibodies ?

Review of recent literature

Anti-PEG Antibodies Boosted in Humans by SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine

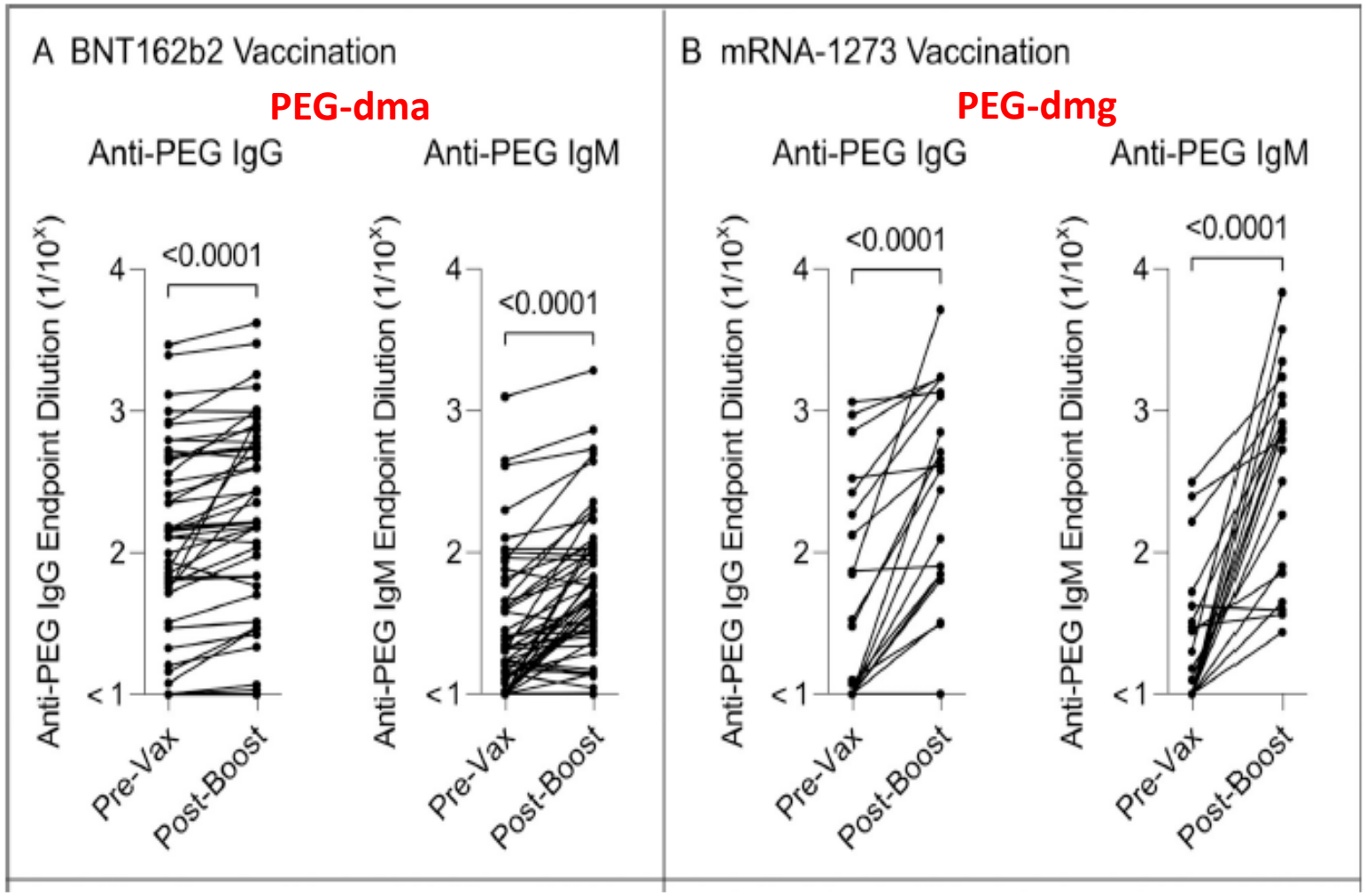
Yi Ju,* Wen Shi Lee, Emily H. Pilkington, Hannah G. Kelly, Shiyao Li, Kevin J. Selva, Kathleen M. Wragg, Kanta Subbarao, Thi H. O. Nguyen, Louise C. Rowntree, Lilith F. Allen, Katherine Bond, Deborah A. Williamson, Nghia P. Truong, Magdalena Plebanski, Katherine Kedzierska, Siddhartha Mahanty, Amy W. Chung, Frank Caruso, Adam K. Wheatley, Jennifer A. Juno, and Stephen J. Kent*

Cite This: *ACS Nano* 2022, 16, 11769–11780

Read Online

Does vaccination induce high titers of anti-PEG antibodies ?

Absolutely. But there are differences between Pfizer/BioNTech vs Moderna.



Anti-PEG Abs were present in 71% of patients prior to vaccination

Moderna vaccination induced a much higher titer of both IgG and IgM post-boost than the Pfizer vaccination

Moderna mean-fold change in titers were 13.1 (IgG) and 68.5 (IgM)

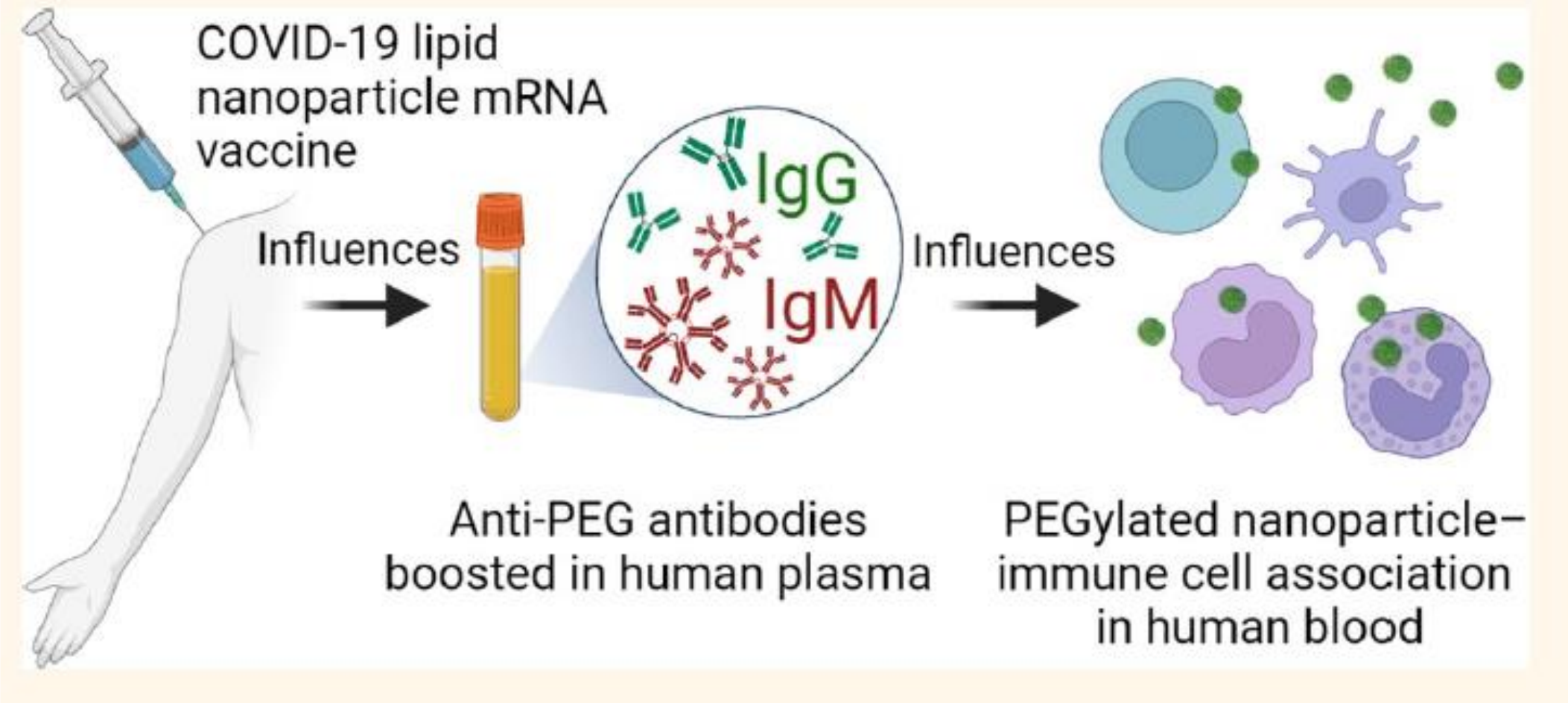
Pfizer mean-fold change in titers were 1.78 (IgG) and 2.64 (IgM)

PEG-dmg vs PEG-dma: 100 ug vs 30 ug dosing

*Note – both PEG-lipids in the vaccines have a methoxy-PEG at the terminus. Note that despite other literature to the contrary, this results in binding of C1q to antibodies boosted by the Moderna vaccine.

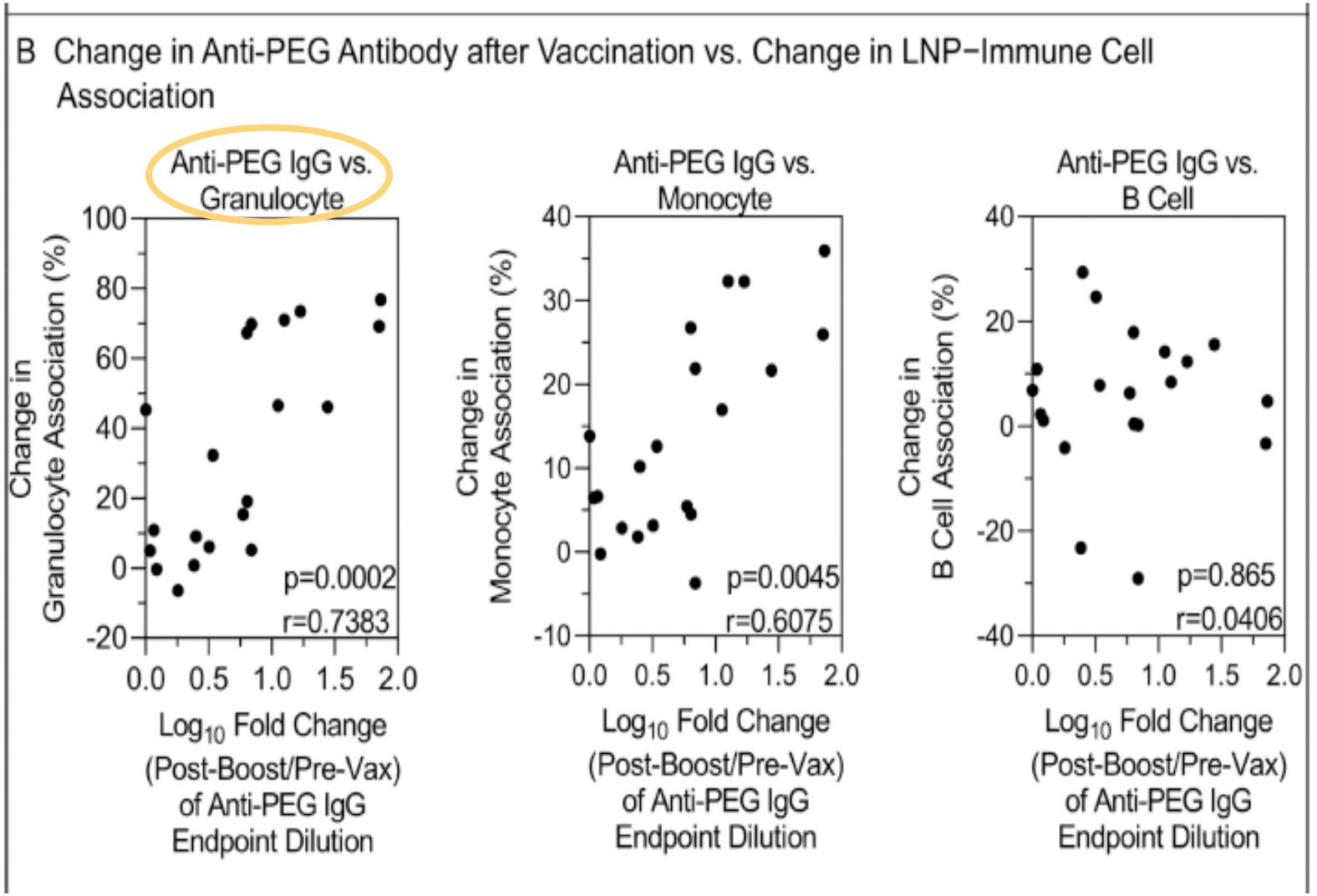
Does vaccination induce high titers of anti-PEG antibodies ?

Do these antibodies bind to immune cells ?



Does vaccination lead to binding of nanoparticles to immune cells ?

High titers of anti-PEG IgG bind to granulocytes & monocytes



The high titers of anti-PEG IgG lead to association of Onpattro nanoparticles to the granulocyte and monocyte populations of immune cells in the plasma (Onpattro is a PEG-dmg LNP)

Degranulation of granulocytes (basophils) can occur in the presence of antigen when bound by IgG on the surface of the cells

Does vaccination lead to complement activation ?

It is clear that the anti-PEG antibodies bind complement … but do they compromise the LNP (study 2022) ?

Anti-PEG antibodies compromise the integrity of PEGylated lipid-based nanoparticles *via* complement

Mariona Estapé Senti [a,b,g,1], Caroline A. de Jongh [a,b,1], Kim Dijkxhoorn [a], Johan J.F. Verhoef [b], Janos Szebeni [c,d,e], Gert Storm [b,f], C. Erik Hack [a], Raymond M. Schiffelers [g], Marcel H. Fens [b,1,*], Peter Boross [a,1]

In this study, we investigated the consequences and mechanisms of complement activation by anti-PEG antibodies interacting with different types of PEGylated lipid-based nanoparticles. By using both liposomes loaded with different (model) drugs and LNPs loaded with mRNA, we demonstrate that complement activation triggered by anti-PEG antibodies can compromise the bilayer/surface integrity, leading to premature drug release or exposure of their mRNA contents to serum proteins. Anti-PEG antibodies also can induce deposition of complement fragments onto the surface of PEGylated lipid-based nanoparticles and induce the release of fluid phase complement activation products.

Does complement activation lead to anaphylaxis ?

Additional pathways to anaphylaxis include C5a anaphylatoxin

vaccines

MDPI

Article

Anaphylatoxin Complement 5a in Pfizer BNT162b2-Induced Immediate-Type Vaccine Hypersensitivity Reactions

Xin Rong Lim [1,*], Grace Yin Lai Chan [1], Justina Wei Lynn Tan [1], Carol Yee Leng Ng [1], Choon Guan Chua [1], Guat Bee Tan [2], Stephrene Seok Wei Chan [2], Kiat Hoe Ong [2], Ying Zhi Tan [3], Sarah Hui Zhen Tan [3], Claire Min Li Teo [1], Samuel Shang Ming Lee [1], Bernard Yu Hor Thong [1] and Bernard Pui Lam Leung [1,3]

The patients who developed anaphylaxis (n=10) were compared to non-reactors (n=67)

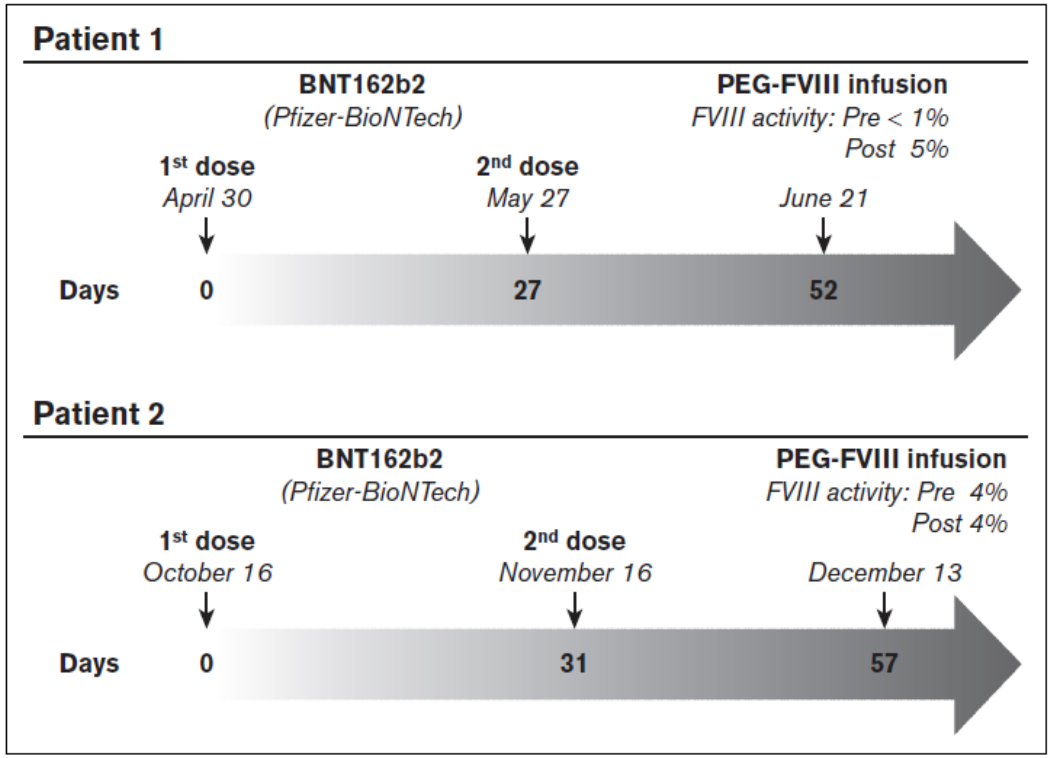
BAT assays were negative in 4 of the 10

The majority of patients had elevated C5a and Th-2 cytokines but were negative for elevated tryptase

The predominate antibody was an IgM to PEG, negative for IgE

Does vaccination alter response to PEGylated therapies ?

Yes.



- Both patients were stable (without bleeding events) on standard short-acting rFVIII
- Both patients were transitioned to the longer-acting PEGrFVIII formulation (Patient 1 - turoctocog alfa pegol; Patient 2 – damoctocog alfa pegol)
- Neither patient had pre-existing inhibitors of FVIII activity
- Neither patient responded adequately to the PEGrFVIII infusion
- Both patients were shown to have developed high titers of IgM to PEG; Patient 1 developed a low titer IgG to PEG with a persistent IgM to PEG out to one year
- There were no bleeding events and patients were transitioned back to their short-acting rFVIII therapies
- **A review of two small series of HA patients (n=43, n=84) suggests the incidence of anti-PEG antibodies that inhibit response to PEGylated rFVIII is ~ 1:20**

Reduced FVIII recovery associated with anti-FVIII PEG antibodies after BNT162b2 SARS-CoV-2 vaccination

Carla Valsecchi,[1] Roberta Gualtierotti,[1,2] Sara Arcudi,[2] Alessandro Ciavarella,[1,3] Lucia Schiavone,[1] Cristina Novembrino,[1] Simona Maria Siboni,[1] Pier Mannuccio Mannucci,[1] and Flora Peyvandi[1,2]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; [2]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy; and [3]Università degli Studi di Milano, Department of Biomedical Sciences for Health, Milan, Italy

Anti-PEG IgG & IgM alter response to ONPATTRO therapy

The loss of efficacy was linearly correlated with anti-PEG antibody levels

Amyloid

The Journal of Protein Folding Disorders

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iamy20

Anti-PEG antibodies associated with reduced therapeutic effect of patisiran in patients with hereditary transthyretin amyloidosis

Björn Pilebro, Jonas Wixner & Intissar Anan

This study followed the therapeutic response to ONPATTRO in patients in Vasterbotten County, Sweden (n=21)
In 7 of 21 patients there was an abnormal response to therapy - < 75% reduction compared to pre-treatment levels

Anti-PEG IgG & IgM alter response to ONPATTRO therapy

The loss of efficacy was linearly correlated with anti-PEG antibody levels

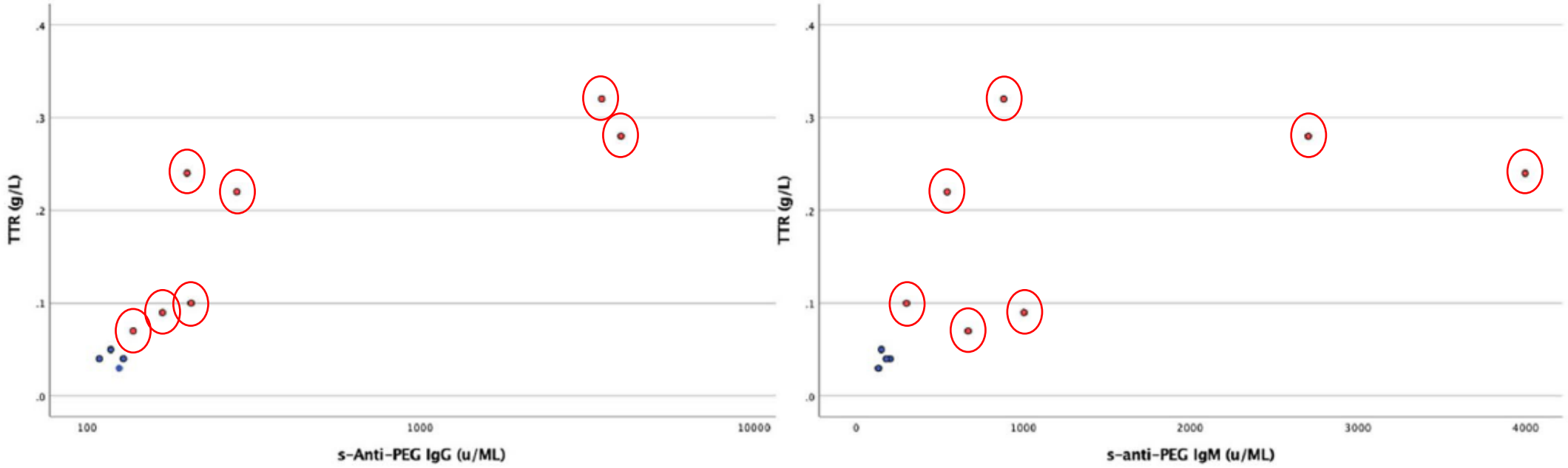


Figure 1. A. Association between s-TTR and s-anti-PEG. Patients with < 75% reduction on in s-TTR on patisiran marked as red and patients with > 75% reduction in blue.
For IgG spearman rank correlation coefficient: 0.91; $p=0.001$. For IgM. Spearman rank correlation coefficient: 0.82; $p=0.002$. s-TTR=s-transthyretin.

The loss of efficacy correlated with ELISA levels of anti-PEG IgG & IgM (p<0.001, p<0.002, respectively)
Patients were transitioned to vutrisiran with an enhanced therapeutic TTR response

Evaluation of Pfizer/BioNTech LNP in rat - PEG-dma

Rat immunogenicity study (The LNPs in this study employed ALC-0315 and ALC-0159 (Acuitas) at identical mol% for the published vaccine)

npj | vaccines

www.nature.com/npjvaccines

ARTICLE OPEN

Check for updates

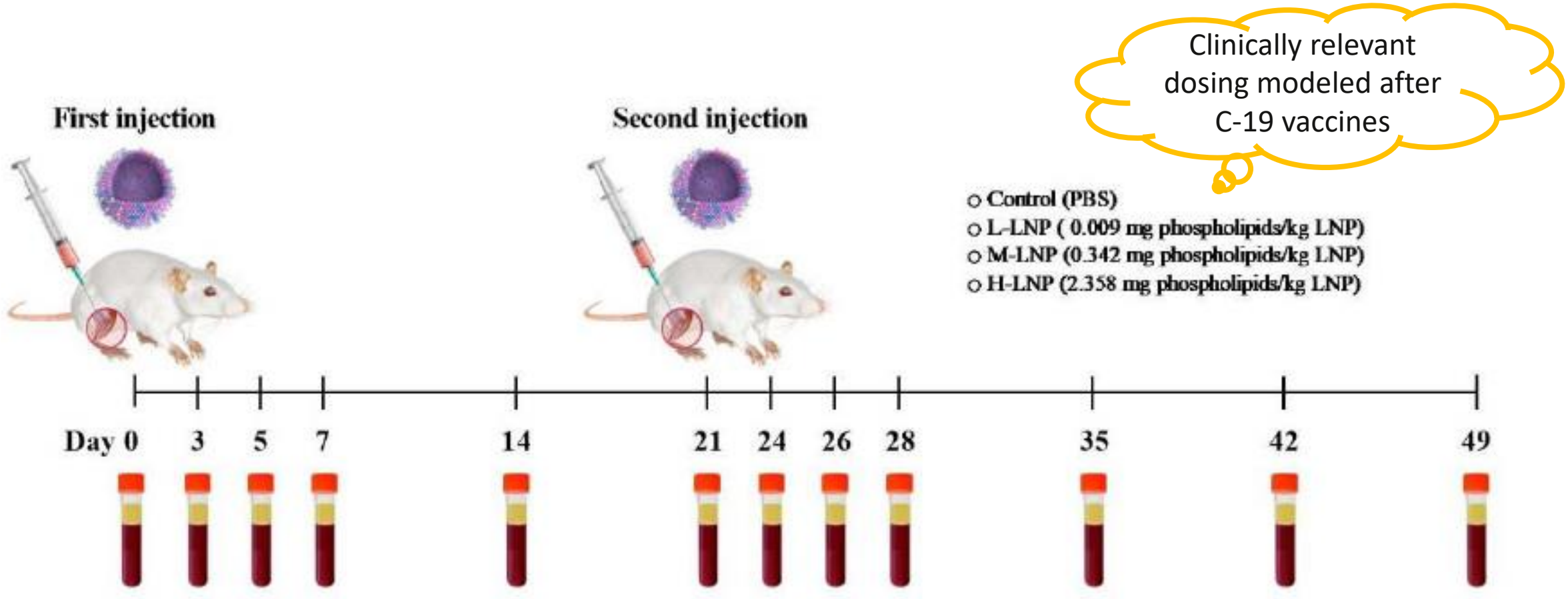
Polyethylene glycol (PEG)-associated immune responses triggered by clinically relevant lipid nanoparticles in rats

Haiyang Wang[1,2,5], Yisha Wang[1,2,5], Changzheng Yuan[3,5], Xiao Xu[4], Wenbin Zhou[1,2], Yuhui Huang[3], Huan Lu[1,2], Yue Zheng[1,2], Gan Luo[1,2], Jia Shang[4] and Meihua Sui[1,2]✉

Nature Vaccines (2023)

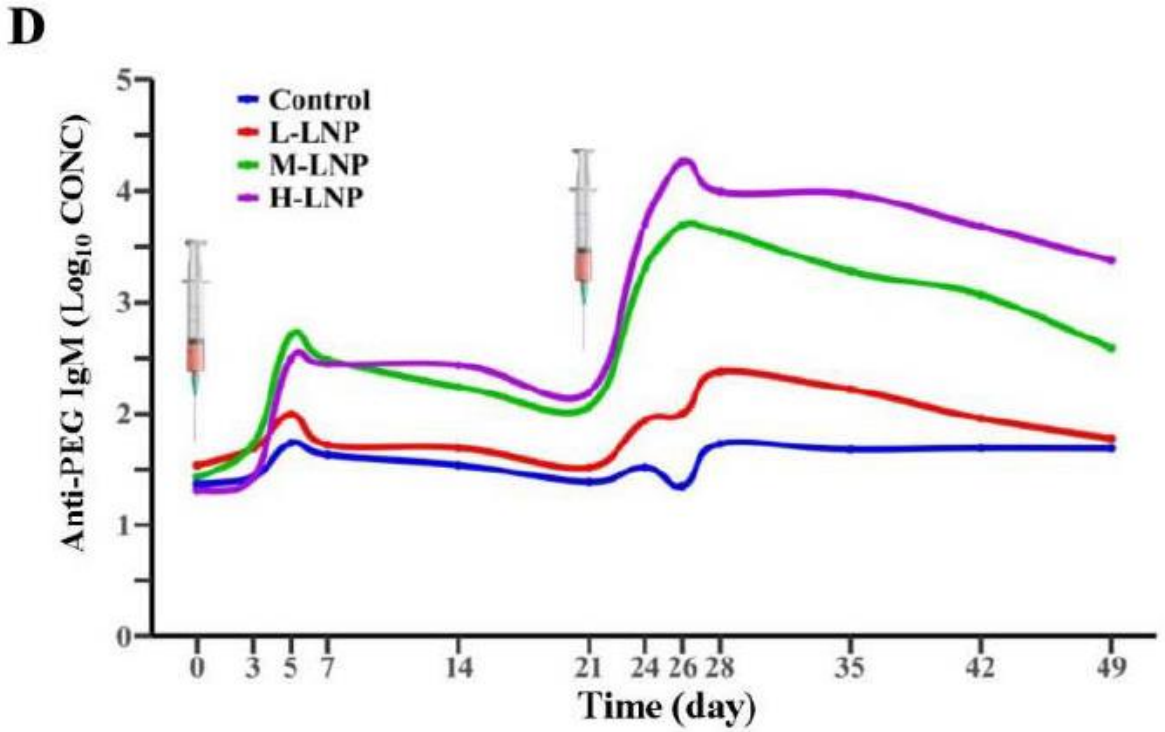
Does vaccination with clinically relevant LNPs lead to anti-PEG Abs

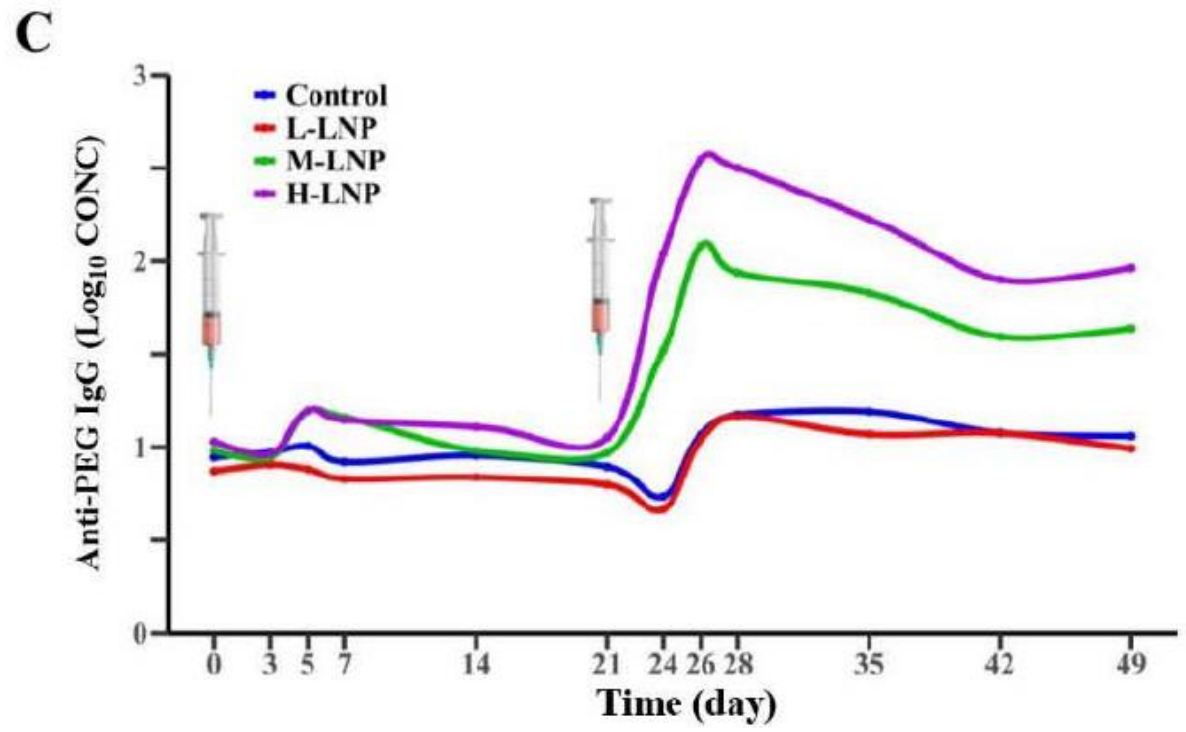
Rat immunogenicity study (Pfizer/BioNTech vaccine formulation)



Anti-PEG antibody induction in rat

Anti-PEG antibodies - IgM and IgG are both boosted (similar to human data)



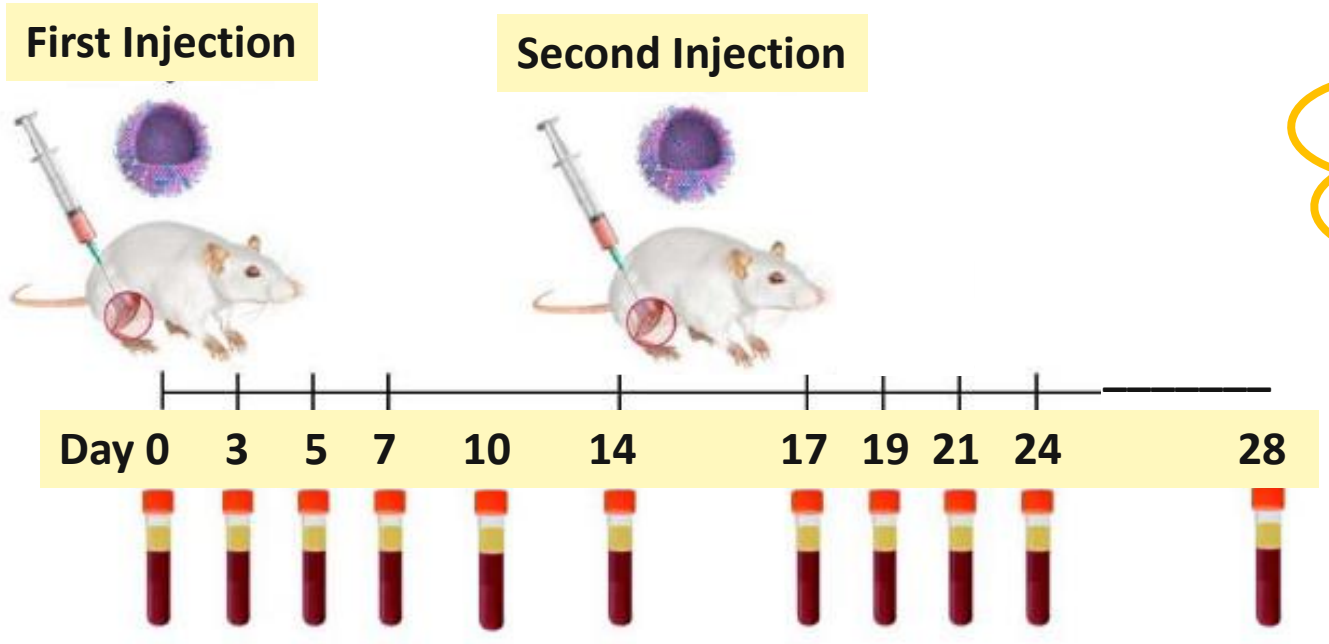


Both anti-PEG IgM and IgG antibodies are induced in the rat following vaccination of relevant doses of LNPs
Low levels of antibodies are produced by the Low Dose
Higher levels of anti-PEG antibodies are induced – and boosted – by the Mid Dose and High Dose

The boosted levels of IgM (~1.8) and IgG (~2.5) are remarkably consistent with the human data

Does vaccination with PEOZ-dma vs PEG-dma lead to different anti-PEG response

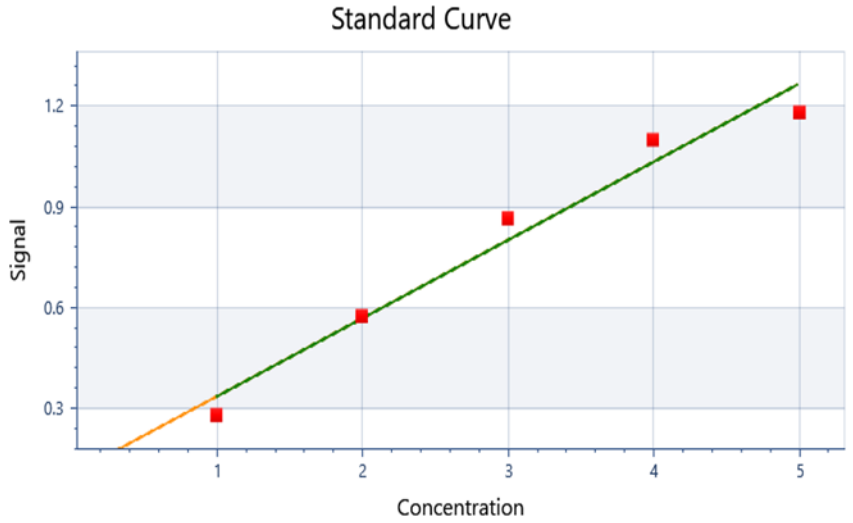
Serina study design to evaluate PEOZ-dma and PEG-dma



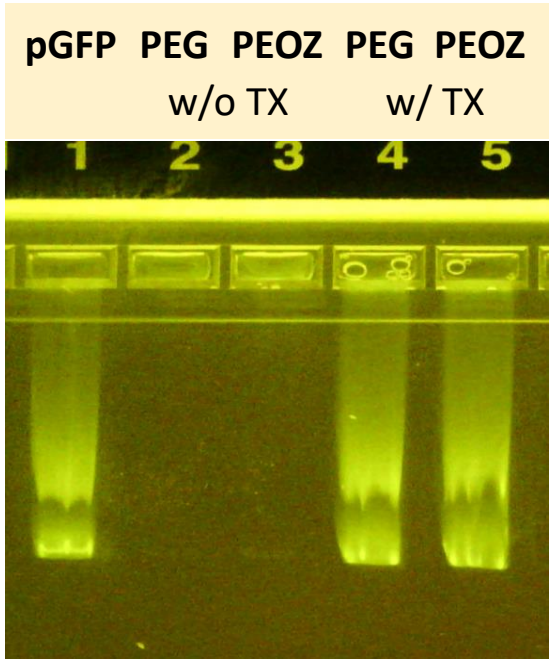
The High Dose – 2.0 mg phospholipid / kg body weight
The Mid Dose – 0.2 mg phospholipid / kg body weight

This study design dosed rats with two injections (two doses – mid & high) at a 14-day interval
The LNPs contained 1.6 mol% of the following polymer-lipids (a) PEOZ-dma **or** (b) PEG-dma (ALC-0159) with a DNA payload (GFP) that was evaluated in vitro for LNP biophysical properties (size, PDI, EE, transfection efficiency, osmolality)
Blood samples were taken at the indicated time points for CBC (day 0, 14 & 28), LFTs (day 0, 14 & 28) and ELISA determinations (all other days)

Phospholipid content, Particle size, Polydispersity, Zeta Potential & Encapsulation efficiency

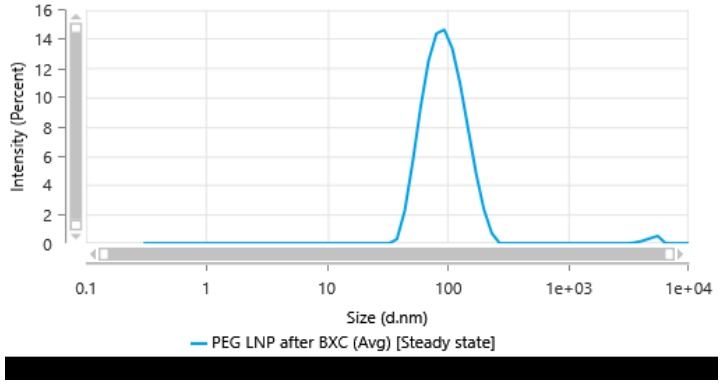


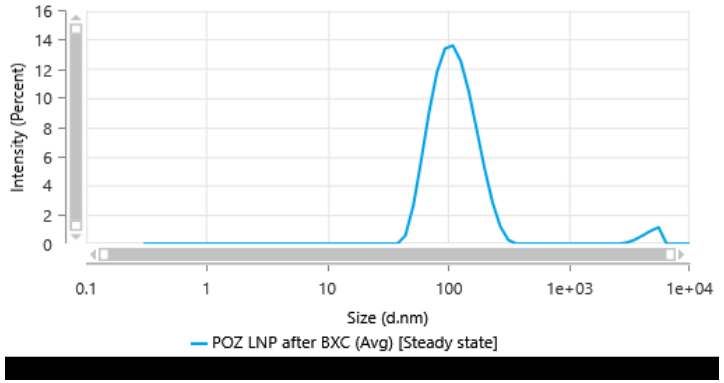
Phospholipid Standards



After Buffer Exchange in Tris-HCl, pH 7.1

Sample Name	Z-Average (nm)	Polydispersity Index (PI)	Zeta Potential (mV)	Encapsulation Efficiency
PEG LNP after BXC (Avg)	88.26	0.1592	-16.43	>98%
PEOZ LNP after BXC (Avg)	106.3	0.2099	-10.97	>98%

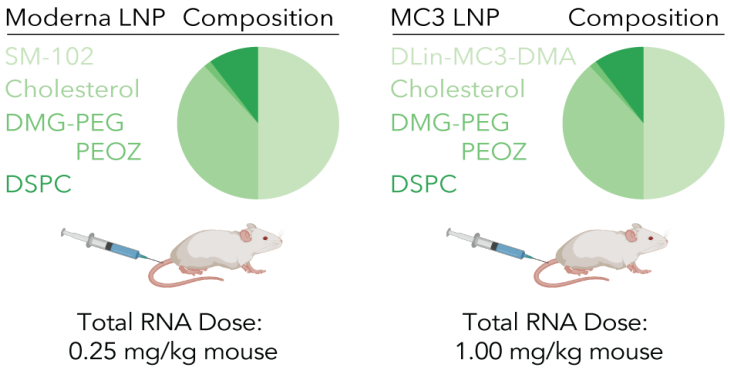




POZ-lipid LNPs Have Unique Properties – IV Infusion

LNPs which incorporate PEOZ-dmg selectively express the payload in macrophage (M) and dendritic (D) cells

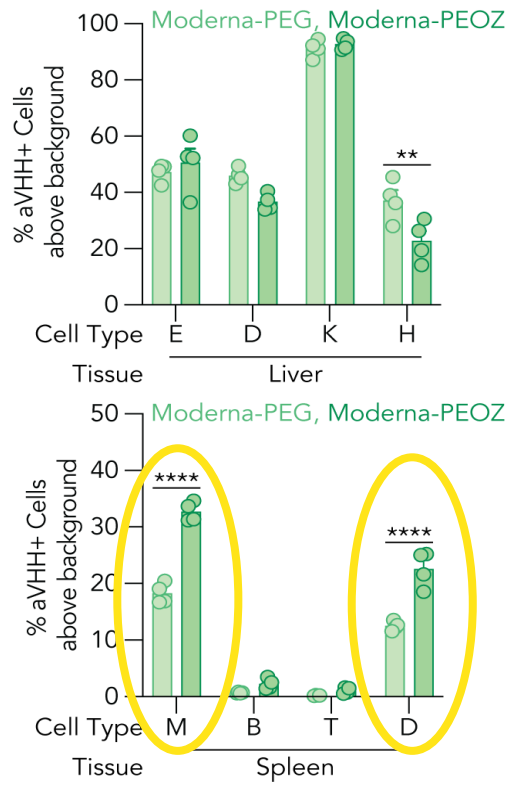
A



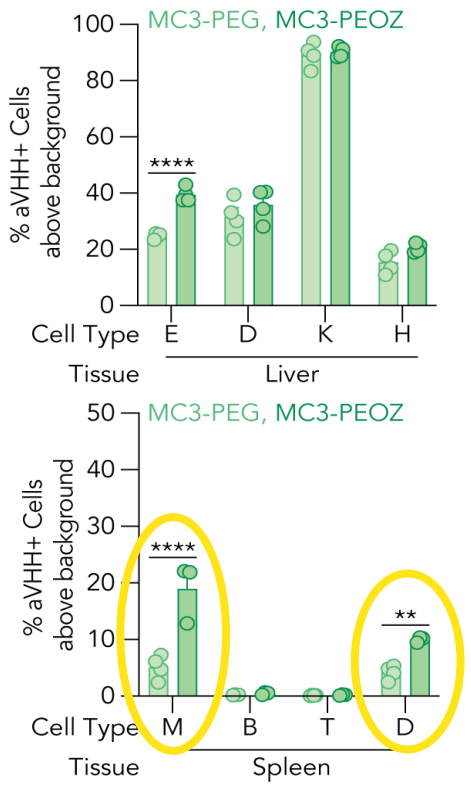
B

Cell Types
Endothelial (E): CD31+
Dendritic (D): CD45+, CD11c+
Macrophages (M): CD45+, CD11b+
Kupffer (K): CD45+, CD68+
B cells (B): CD19+
T cells (T): CD3+
Hepatocytes (H): CD31- / CD45-

C



D



- In vivo results are *reproducible* and *generalizable* to other LNP formulations
  - The initial observation that a PEOZ-lipid LNP selectively targets antigen-presenting cells (APC) gave nearly identical results on repeat study (Panel C)
  - When you change the LNP formulation from Moderna's cocktail (SM 102, DSPC, PEG-dmg, cholesterol, mRNA) to Onpattro's formulation (MC 3, DSPC, PEG-dmg, cholesterol, siRNA) and compare it to PEOZ-dmg – selective targeting of APCs is still present (Panel D)
- Selective targeting of APCs *in vivo* with a POZ-lipid vs PEG-lipid LNP is a novel observation

Anti-IgM antibodies to PEG-dma vs PEOZ-dma

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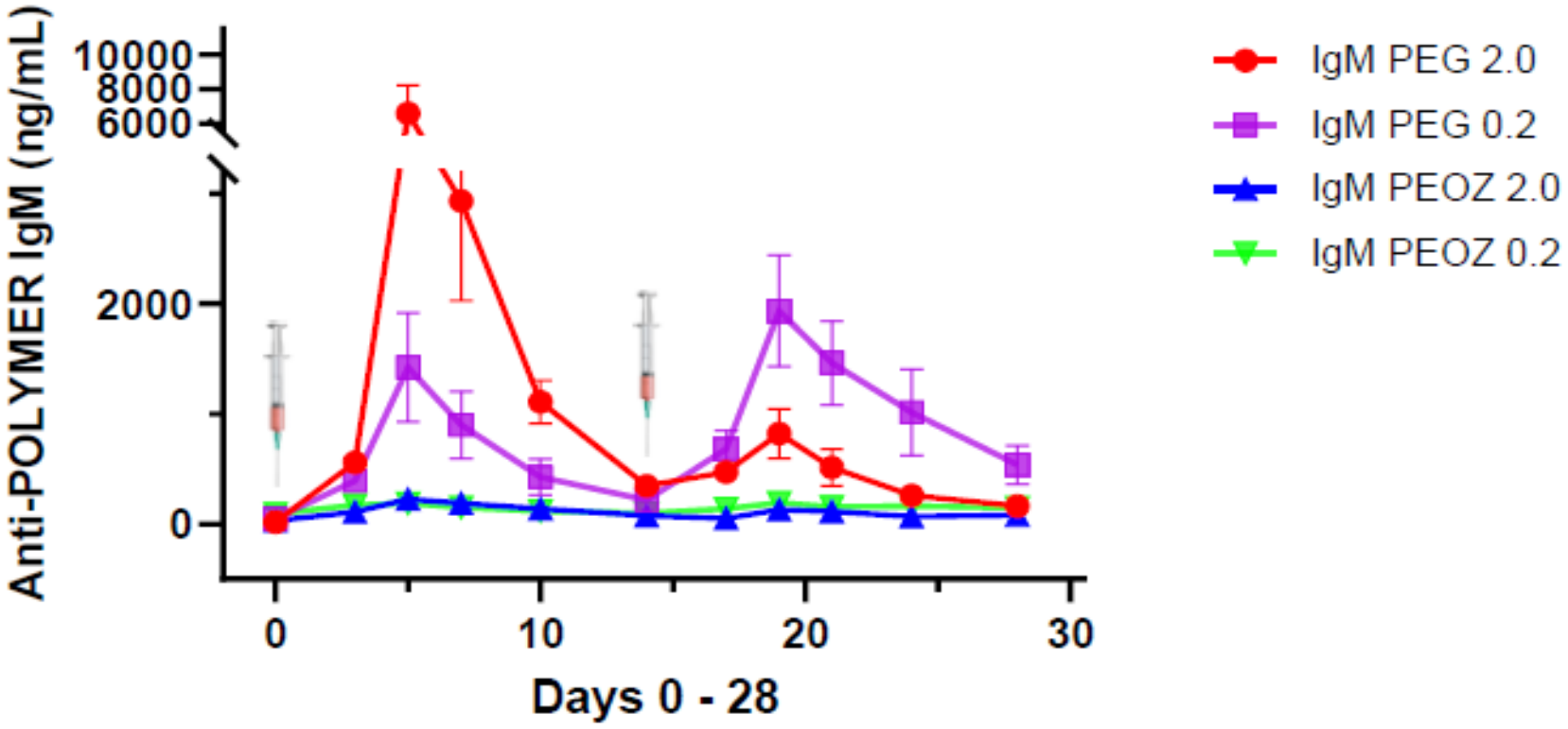
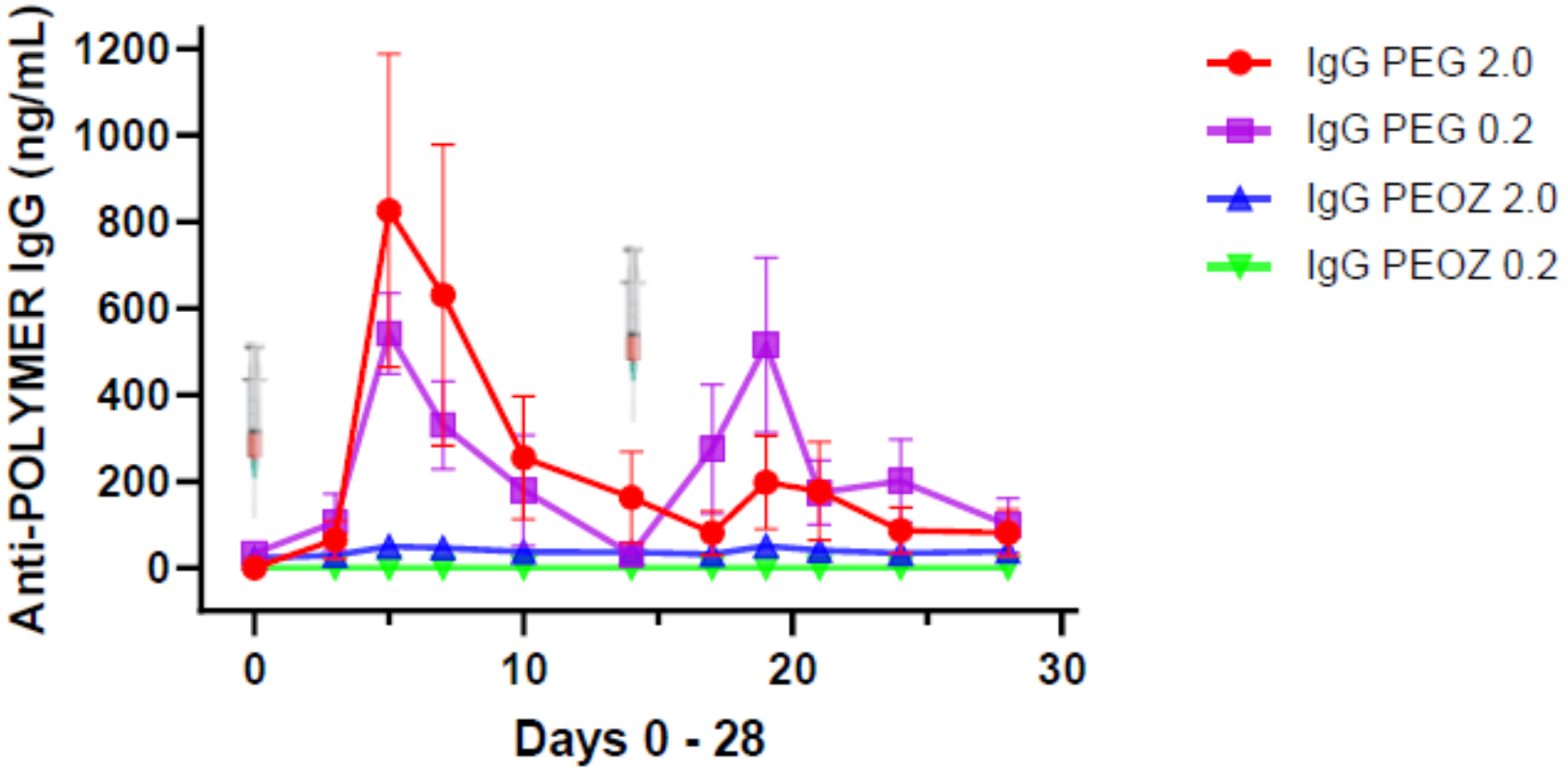


Anti-IgM antibodies are readily detected, and boosted, at the High Dose and Mid Dose when LNPs employing PEG-dma are injected (similar to published data)

LNPs prepared with PEOZ-dma failed to elicit an IgM response at either the High Dose or Mid Dose

Anti-IgG antibodies to PEG-dma vs PEOZ-dma

Serina LNP Laboratory



Anti-IgG antibodies are readily detected at both the High Dose and Mid Dose when LNPs employing PEG-dma are injected (similar to published data)

LNPs prepared with PEOZ-dma failed to elicit an IgG response at either the High Dose or Mid Dose

Today's Messages :

- Anaphylaxis to the vaccines appears to be primarily due to basophil degranulation, likely the result of high titer IgG (possibly IgM) to the PEG in the formulation
  - Now recognized as an uncommon mechanism of anaphylaxis, first described clinically ~ 15 years ago
- The high titers of IgM & IgG are associated with an increased incidence of reactogenicity (possibly other AEs), bind systemically administered LNPs, form membrane complex and activate complement
- High titers of IgM & IgG induced by the mRNA vaccines are capable of neutralizing the first exposure anticoagulant activity of PEGrFVIII in ~ 1:20 patients with Hemophilia A
- The vaccine community appears to be entrenched with PEG-lipids as the format … but the broader LNP community is evaluating alternatives
- The Serina LNP Laboratory has identified PEOZ-dma as a component for LNP formulations that produces LNPs virtually identical in biophysical properties to the PEG-dma LNP (Pfizer/BioNTech formulation)
  - **PEOZ-dma LNPs fail to elicit a detectable IgM or IgG immune response on repeat dosing**
  - **PEOZ-dma LNPs may provide a safe and effective alternative to PEG-lipid in LNP formulations**

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