Blood Products Advisory Committee
November 4, 2021 Meeting Presentation

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Overview of the Plasma Derivatives Branch Research Program

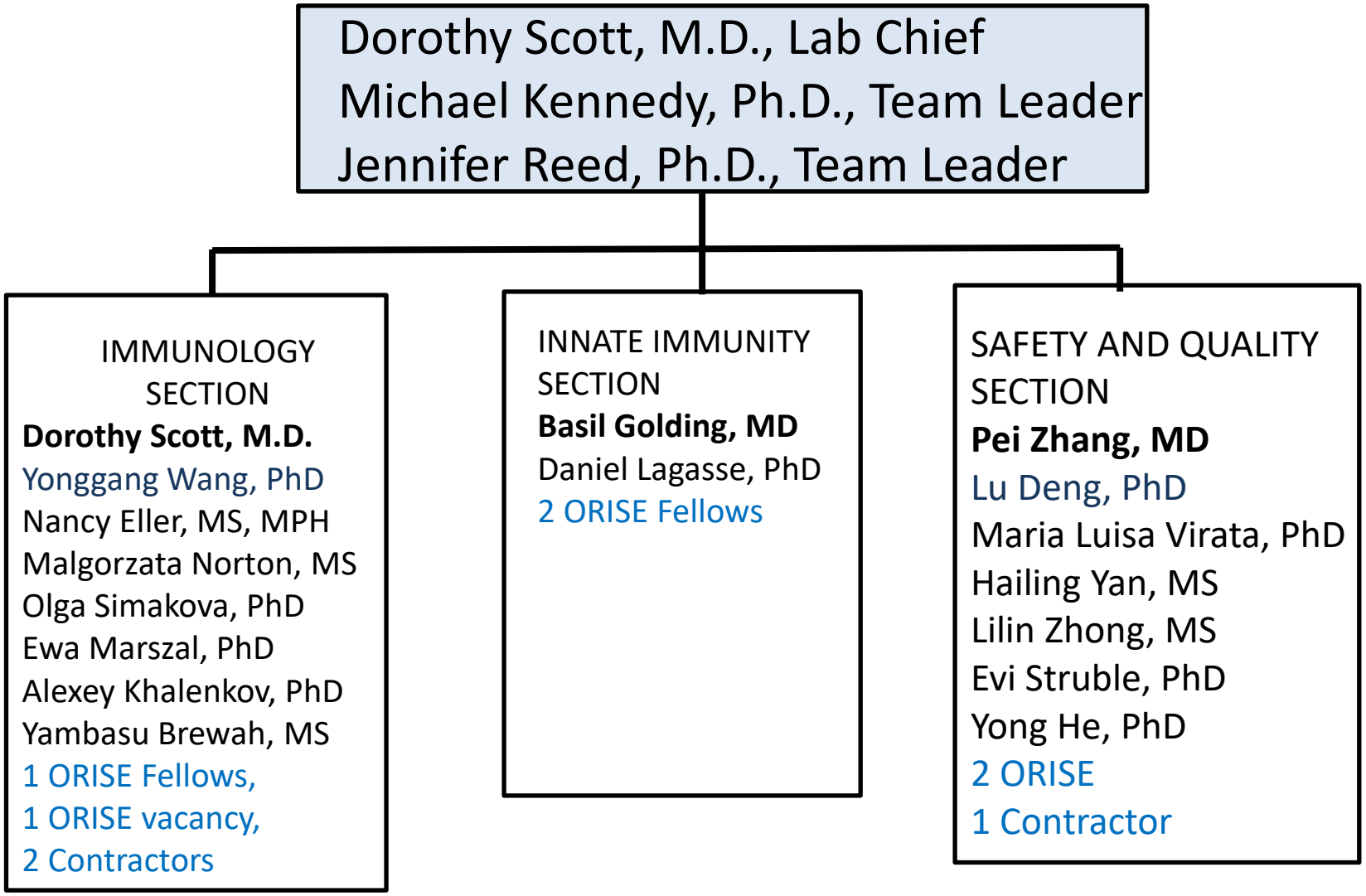
Blood Products Advisory Committee
November 4, 2021

Dorothy Scott, M.D.
Chief, Plasma Derivatives Branch

PDB Mission Statement

To meet the public health needs for safe and effective products by performing high quality research that directly impacts the safety, effectiveness and availability of Plasma Derivatives.

Plasma Derivatives Branch



U.S. FOOD & DRUG ADMINISTRATION

PDB Site Visit April 22, 2021; BPAC November 4, 2021

Project 1: New Approach for Treating Hemophiliacs with Inhibitors Using Fc-fusion proteins and NK Cells

Project 2: Dosing Considerations for use of Hyperimmune SARS-CoV-2 Immune Globulin in Treatment of Covid-19

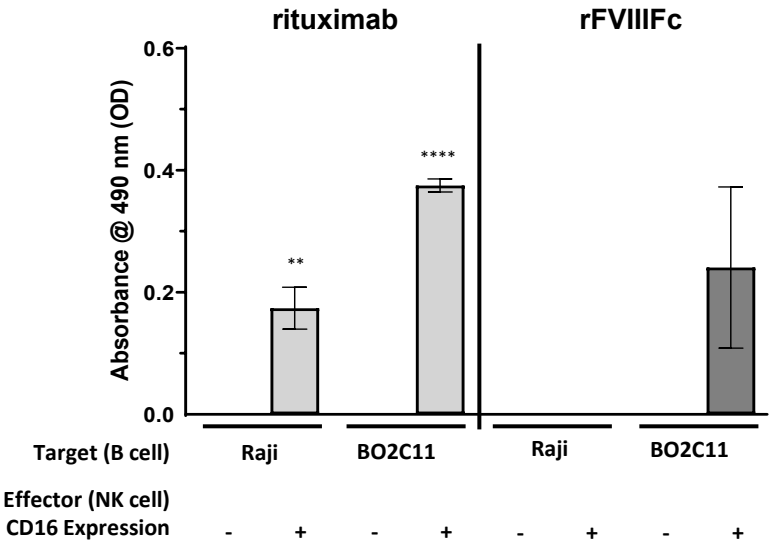
Basil Golding, M.D.

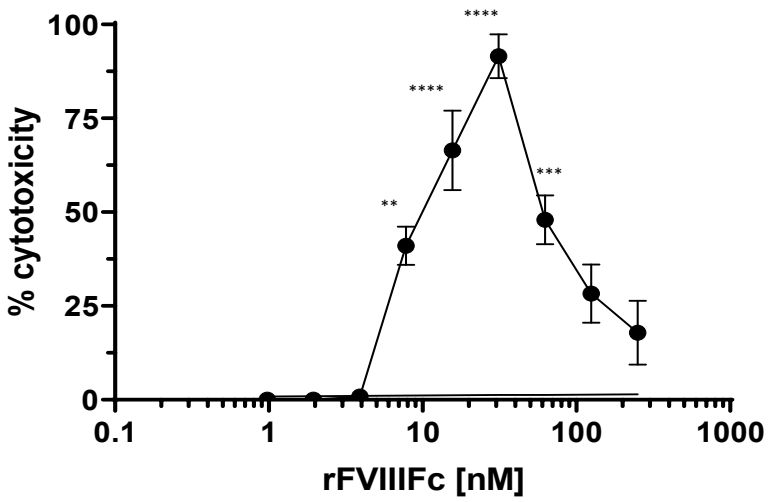
Project 1: Outline

Experiments showing that FVIII-Fc:

- stimulates activation of NK cells
- the activated NK cells can target FVIII-specific B cells

Project 1: rFVIIIFc induces BO2C11 (FVIII-specific B-cell) lysis through interactions with CD16^{+} NK cells





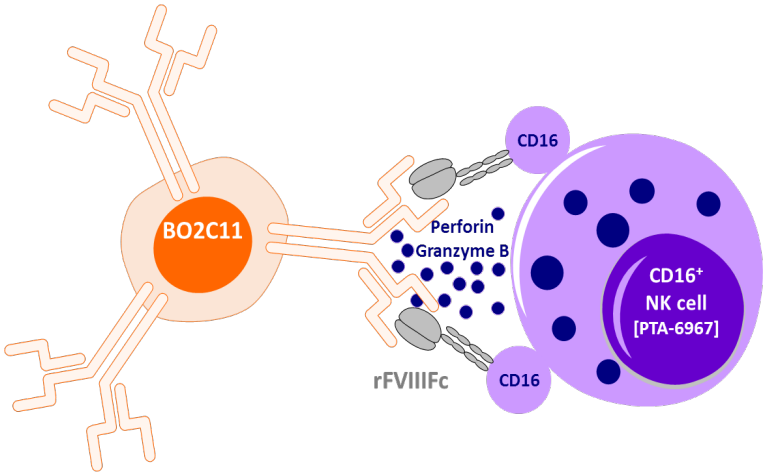
- rFVIIIFc induces specific lysis of anti-FVIII B cells
- Peak of rFVIIIFc-induced lysis ~ 25 nM

25 nM FVIII hyper-physiological → could be achieved during high-dose ITI regimens (200 IU/kg/day)

Lagassé, H.A. Daniel ; Hopkins, Louis B ; Jankowski, Wojciech ; Jacquemin, Marc G ; Sauna, Zuben E ; Golding, Basil. Frontiers in Immunology, 2021-06-28, Vol.12, p.692157-692157

Project 1: Conclusions

- rFVIIIFc activates CD16^{+} NK cells
  - induces IFNγ secretion
  - induces degranulation and cytolytic granzyme B/perforin release
- rFVIIIFc induces IFNγ secretion from primary PBMCs and NK cells
  - associated with high-affinity CD16 158V allotype
- rFVIIIFc induces FVIII-specific B cell (BO2C11) lysis through interactions with CD16^{+} NK cells



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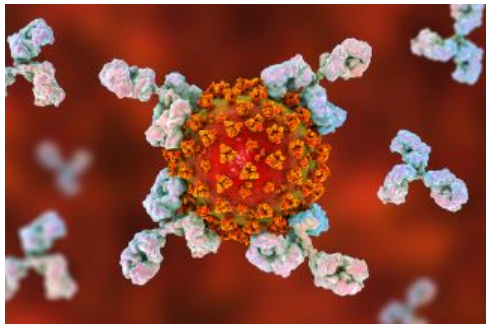
PROJECT 2: Dosing Considerations for Antibodies against Covid-19

Hypothesis:

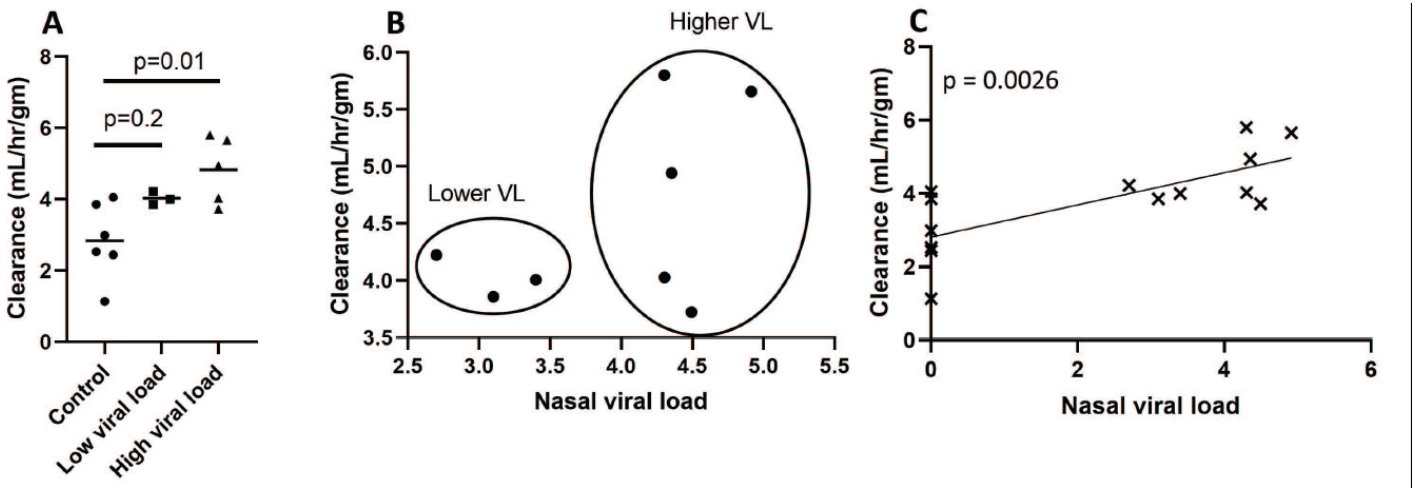
In order to achieve optimal dosing viral load needs to be taken into account



Million A. Tegenge[1] · Iftekhar Mahmood[2] · Evi Struble[3] · Basil Golding[3]

Nov. 2020 Drugs in R&D (2021) 21:1–8

PROJECT 2: A higher viral load leads to increased antibody clearance



D

	Low nasal viral load (n =3)	High nasal viral load (n =5)	% Mean Difference
AUC $_{(0\text{-last hr})}$ (% x hr)[a]	7773 ± 432	5206 ± 1328	-33
AUC $_{(0\text{-}\infty)}$ (%x hr)	9940 ± 449	8546 ± 1720	-14
Clearance (mL/hr/gm)[b]	4.0 ± 0.2	4.8 ± 0.9	21
Clearance (mL/hr/gm)[c]	5.2 ± 0.3	8.0 ± 1.6	55
V_{ss} (mL/gm)	328 ± 37	409 ± 35	24

[a]IgG concentrations were percent of the initial observed concentrations within 1-1.5 hours.
[b]Calculated based on AUC $_{(0\text{-}\infty)}$, [c]calculated based on AUC $_{(0\text{-last hr})}$.

CB Stauft, M Tegenge, S Khurana, Y Lee, P Selvaraj, H Golding, Tony Wang and B Golding. Clin. Inf. Dis. *In Press.*

Project 2:

Conclusions

- Virus presence reduces antibody concentration due to immune complex clearance
- Viral load needs to be taken into account when treating patients with Covid-19 with hyperimmune SARS-CoV-2 IG

Evaluation and Characterization of Neutralizing Antibodies Against Viruses Relevant to Blood-derived Products

Pei Zhang

Regulatory Relevance of the Research

- To develop and evaluate technologies, reagents, and standards that may improve the chemistry, manufacturing and controls (CMC) of plasma-derived immunoglobulin products.

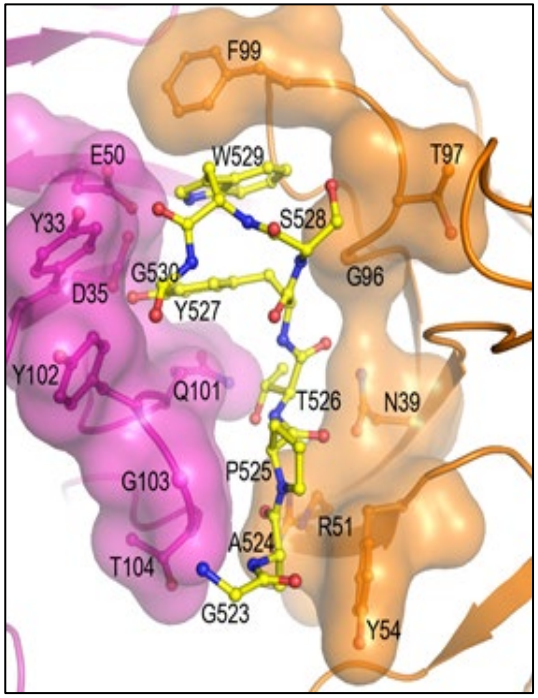
- To facilitate the improvement of immunoglobulin products to increase their clinical efficacy, specifically with virus-specific immunoglobulin products for immune prophylaxis.

- To help immunoglobulin manufacturers develop reliable assays for better product quality characterization, such as potency assays for virus-specific immunoglobulin products.

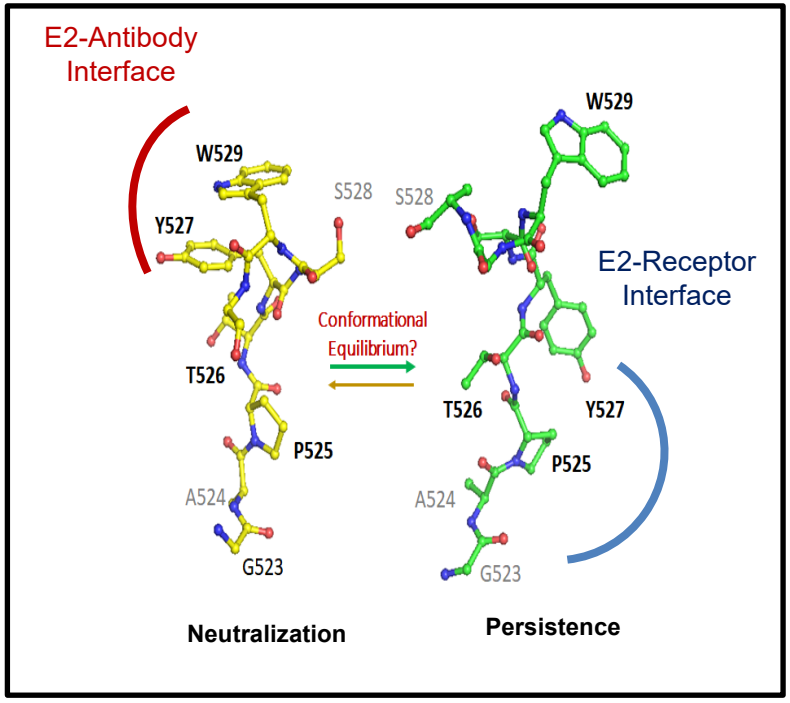
Project 1

Toward an Understanding of HCV Epitope Structural Dynamics: Implications for Antibody-Mediated Neutralization

Antibody-Epitope III Complex Structure



Conformational Changes at Epitope III on HCV E2 and their Potential Impact



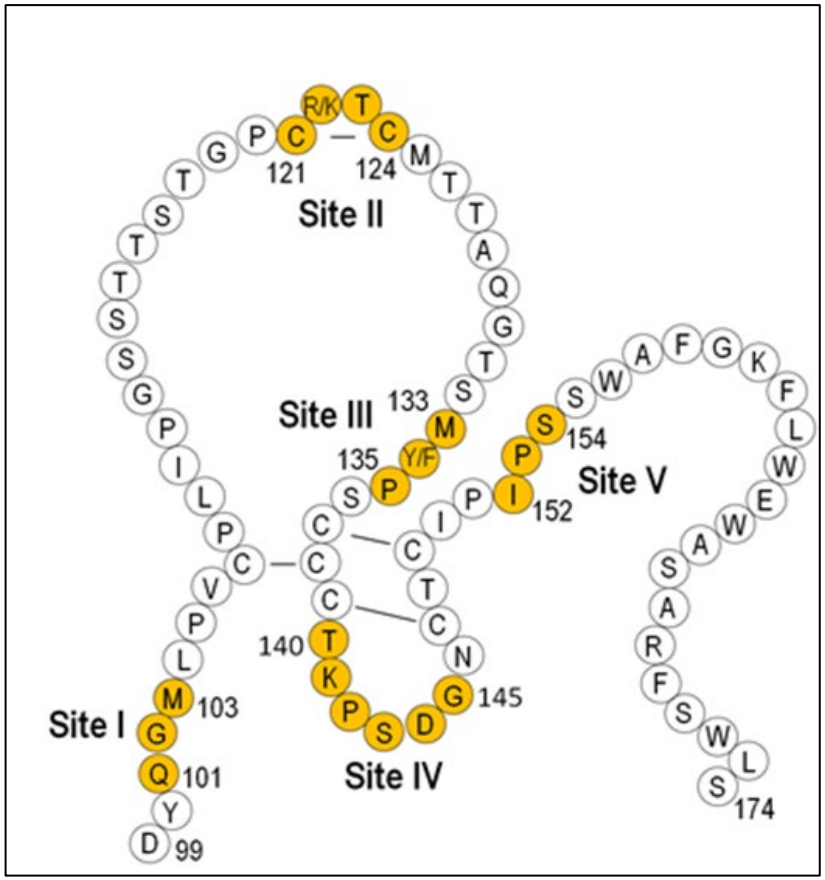
Conclusion: By changing its conformation, HCV E2 protein could avoid antibody recognition without varying its amino acid sequences and bind to host cell receptor CD81 for virus entry.

PNAS July 13, 2021 118 (28) e2104242118

Project 2

Multiple Epitopes of HBsAg Targeted by Human Plasma-Derived Immunoglobulins Coincide with Clinically Observed Escape Mutations

HBIG Antibody Binding Sites on HBsAg



Clinically Observed Mutations in HBsAg and their Impact

HBsAg	Mutation	Impact	Epitope
Q101	R	mAb	Site I
G102			
M103			
L104			
G119			Site II
P120	E/S/T	HBIG	
C121			
R/K122			
T123	N	mAb HBIG	
C124	R/Y		
T/M125			
T/I126	A/N/S	Vaccine HBIG	Site III
T127			
Q129	H/L	Vaccine HBIG	
G130	D/R		
T131			
S132			
M133	L	Vaccine HBIG	
Y/F134	N/R/S		
P135			
S136			
T140			Site IV
K141	E/I	mAb Vaccine	
P142	S		
S/T143	L	Vaccine HBIG	
D144	A/E		
G145	R/A		
N146			
I152			Site V
P153	A	Infectivity	
S154			

J Med Virol. 2021 Aug 18. doi: 10.1002/jmv.27278.

Future Studies

For HCV, further studies will determine whether the current HBIG treatment could be improved by supplementing it with site-specific neutralizing monoclonal antibodies that target clinical observed mutations for control of HBV infections.

For HBV, further studies will determine whether the current HBIG treatment could be improved by supplementing it with site-specific neutralizing monoclonal antibodies that target clinical observed mutations for control of HBV infections.

For product improvement, further experiments will be designed, based on our data, to help immunoglobulin manufacturers to develop reliable assays for better product quality characterization, such as potency assays for virus-specific immunoglobulin products.

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Animal studies to assess immune globulin treatments when used during pregnancy

Evi Struble, Research Pharmacologist
OTAT/DPPT/PDB

Mission relevance

- FDA and CBER goals to conduct research to address challenges in the development and regulatory evaluation of biologics
  - Develop and evaluate technology and tools to support non-clinical assessment of medical products
  - Informs our advice on preclinical models to assess hyperimmune IGIV to prevent fetal infections, and to estimate dose ranges that may be effective in pregnant women

Maternal-Fetal Partition of HIG

- Hyperimmune IgG (HIG) proposed to treat the pregnant woman and to prevent vertical transmission of viral disease to the fetus
  - HBV, CMV, ZIKV

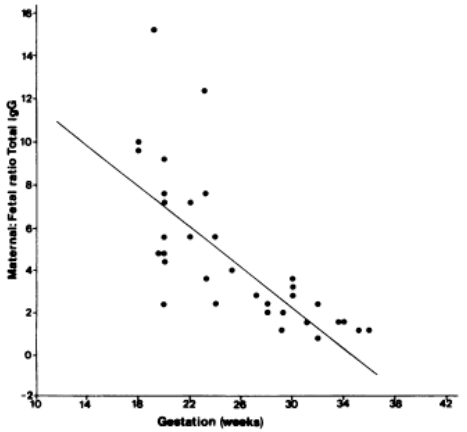


FIG. 1. Mother-to-fetus ratio of total IgG related to gestational age ($y = -0.46x + 16.4$; $r = 0.73$; $P < 0.0001$, $n = 34$).

- Placental transfer of IgG during the second and third trimesters
  - How does this affect the efficacy of HIG therapy in the pregnant woman?
  - Is HIG therapy during pregnancy effective in preventing vertical transmission of viral disease to the fetus/newborn?

Clinical data have not provided clear answers

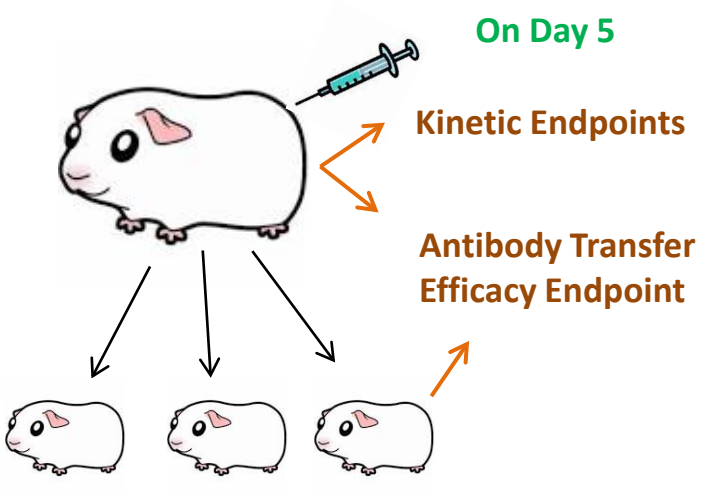
Garty, B.Z.; Ludomirsky, A.; Danon, Y.L.; Peter, J.B.; Douglas, S.D. Placental transfer of immunoglobulin G subclasses. *Clin Diagn Lab Immunol* **1994**, *1*, 667-669.

- Study 1: Evaluate placental transfer of HBIG in the timed pregnant guinea pig model
- Study 2: Towards Placenta-on-a Chip; in vitro studies to evaluate HIG therapies when used during pregnancy

1. Xu, Y.; He, Y.; Momben-Abolfath, S.; Eller, N.; Norton, M.; Zhang, P.; Scott, D.; Struble, E.B. Entry and Disposition of Zika Virus Immune Complexes in a Tissue Culture Model of the Maternal-Fetal Interface. *Vaccines (Basel)* **2021**, *9*, doi:10.3390/vaccines9020145.
2. Struble, E.B.; Murata, H.; Komatsu, T.; Scott, D. Immune Prophylaxis and Therapy for Human Cytomegalovirus Infection. *Int J Mol Sci* **2021**, *22*, doi:10.3390/ijms22168728.
3. Xu, Y.; Mahmood, I.; Zhong, L.; Zhang, P.; Struble, E.B. Passive Immunoprophylaxis for the Protection of the Mother and Her Baby: Insights from In Vivo Models of Antibody Transport. *J Immunol Res* **2017**, *2017*, 7373196, doi:10.1155/2017/7373196.
4. Wang, X.; Xu, Y.; Scott, D.E.; Murata, H.; Struble, E.B. Binding and neutralizing anti-cytomegalovirus activities in immune globulin products. *Biologicals* **2017**, *50*, 35-41, doi:10.1016/j.biologicals.2017.09.004.
5. Xu, Y.; Ma, L.; Norton, M.G.; Stuart, C.; Zhao, Z.; Toibero, D.; Dahlen, S.; Zhong, L.; Zhang, P.; Struble, E.B. Gestation age dependent transfer of human immunoglobulins across placenta in timed-pregnant guinea pigs. *Placenta* **2015**, *36*, 1370-1377, doi:10.1016/j.placenta.2015.10.018.

- Study 1: Evaluate placental transfer of HBIG in the timed pregnant guinea pig model
- Study 2: Towards Placenta-on-a Chip; in vitro studies to evaluate HIG therapies when used during pregnancy

Human IGIV (HBIG) on GD21, 30, 40, 50, 60



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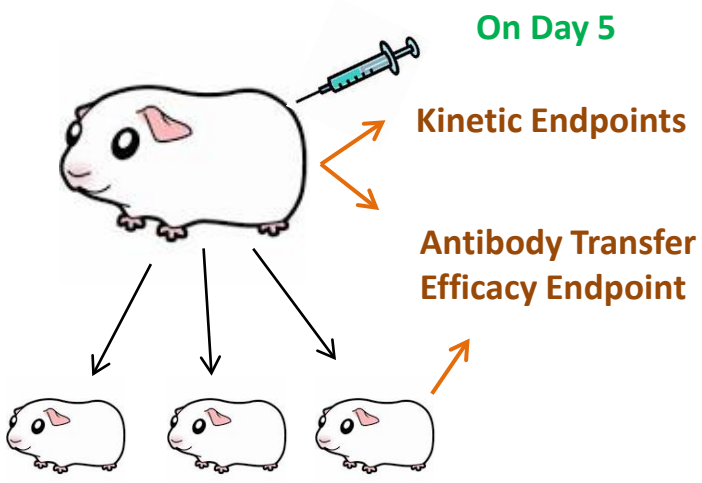
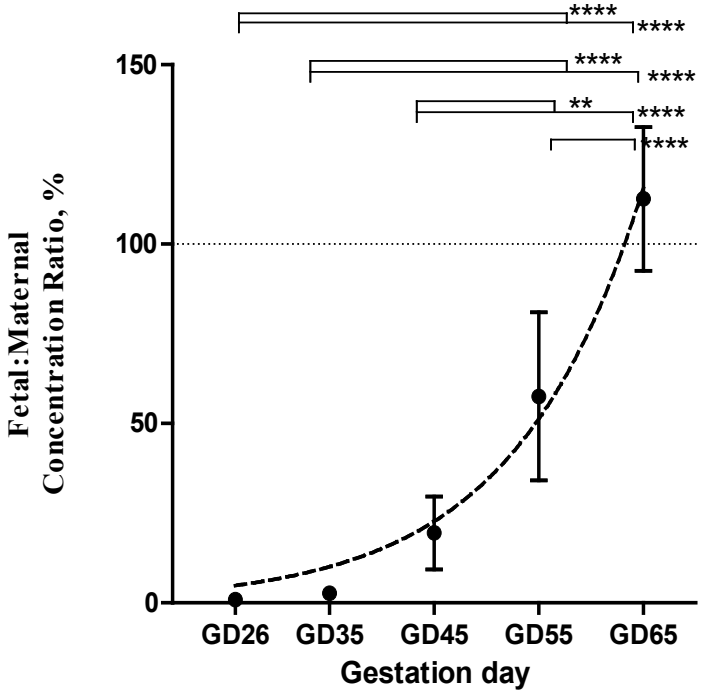
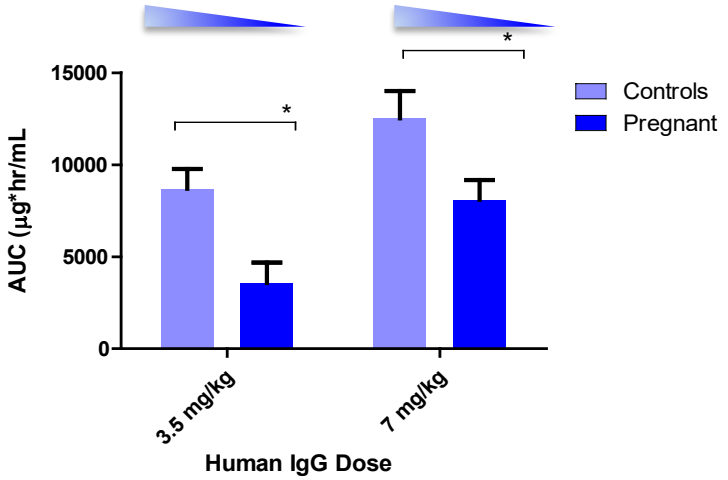




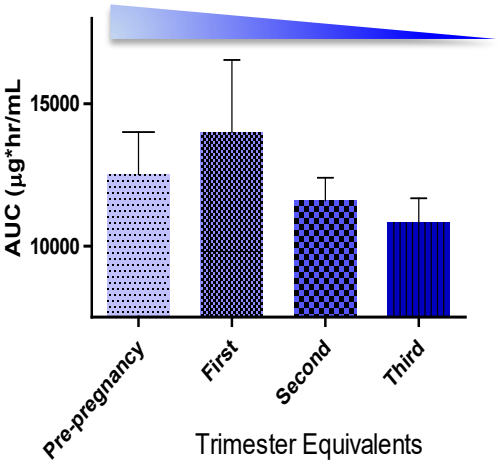
Transplacental transfer of human (h) IgG in n=4-7/group timed pregnant guinea pigs at different gestation ages. One way ANOVA with Bonferroni *post hoc* analysis was used to compare fetal:maternal ratios in each gestation age; **p<0.01, ****p<0.005; exponential fit shown by the broken line (R^2=0.87).

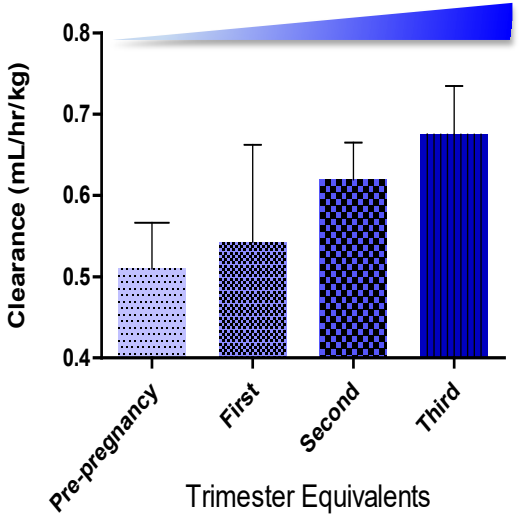
Xu, Ma, Norton, Stuart, Zhao, Toibero, Dahlen, Zhong, Zhang, Struble, Placenta. 2015 Dec;36(12):1370-7.

PK Properties of Human IgG: Therapeutic Change in Pregnancy



Xu, Mahmood, Zhong, Zhang, and Struble,
Journal of Immunology Research, Jan 2017





Conclusions

- Mother-to-fetus distribution of human IgG administered during pregnancy
  - contributes to a reduction of maternal exposure
  - exposes the fetus to progressively higher concentration with increased gestational age
  - results in fetal neutralizing activity against HBV associated with protection
- The potential for reduced maternal exposure, decreased half-life and increased clearance in pregnant woman should be taken into consideration on the selection of the dosing regimen during pregnancy.

Hemolytic Activity of Licensed Immune Globulins

Blood Products Advisory Committee

November 4, 2021

Dorothy Scott, M.D.

Yonggang Wang, PhD

Addressing Hemolytic Activity in IGIV Products

- Reports of hemolysis in IVIG recipients from products that passed direct hemagglutination test specification
- We developed a complement-mediated hemolysis assay (CDHA) for IVIG products
- Identified antibody subclasses in IVIG that mediate hemolytic activity

Mission Relevance

- CBER: Conduct research to address challenges in the development and regulatory evaluation of medical products
  - Develop and evaluate technology and tools to support non-clinical evaluation of medical products.

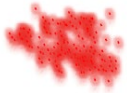
- OTAT: Enhance quality, consistency, and performance of advanced therapeutics through development of strategies and methods for improved…product characterization, including test methods, standards

Complement-Dependent Hemolysis Assay to Improve Detection of Hemolysins in IVIG

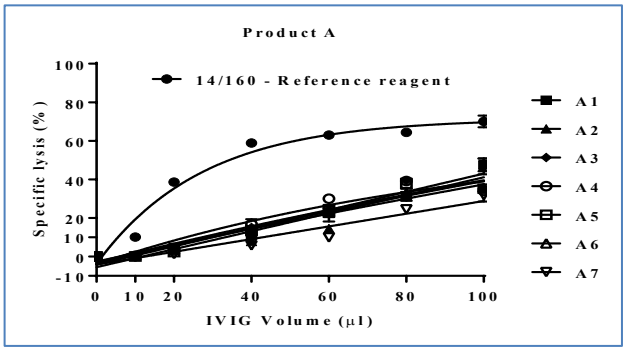
- Deficiencies of currently required direct hemagglutination assay (DHAT) for lot release
  - –Imprecision (~ 4-fold titer variation)
  - –Does not screen out hemolytic IVIG lots
  - –Subjective readout
  - –Replicates binding of antibody to RBC, but not functional activity
- Modification/modernization of classical methods to detect hemolytic activity in IVIG


Papain-treated RBC + IVIG incubation/wash → + human serum complement → OD 414 (hemoglobin)

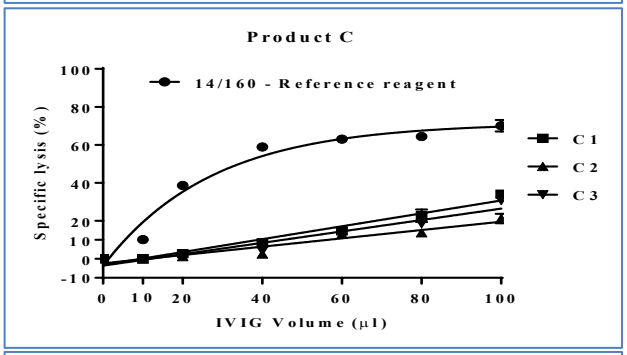




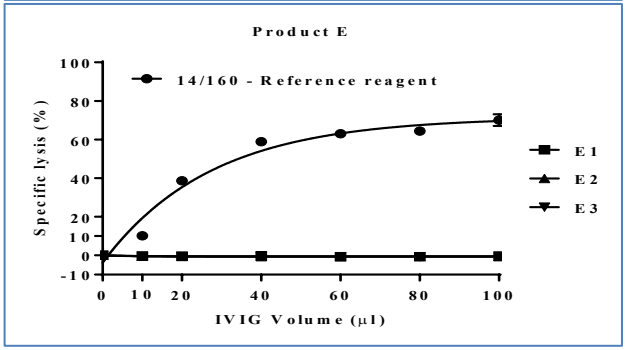
Hemolytic Activity of Different Products



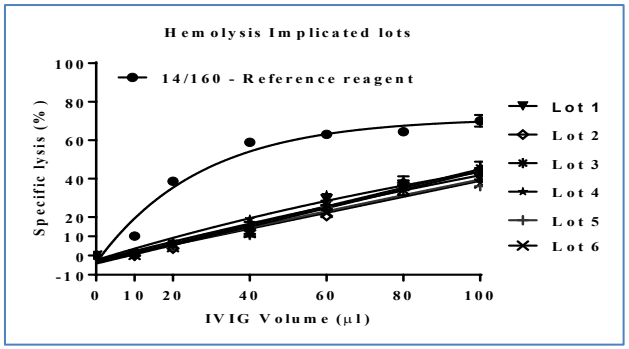
High
(Product A)



Medium
(Product C)



Undetectable
(Product E)



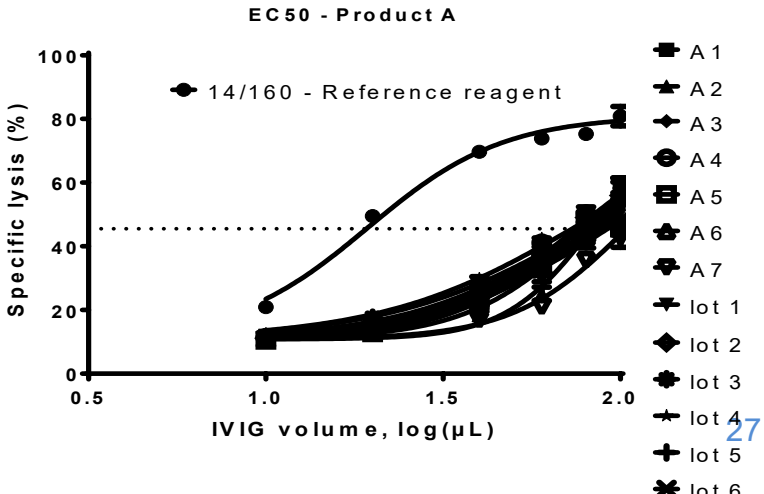
High (clinically
Significant)
(several products)

Hemolytic activity:

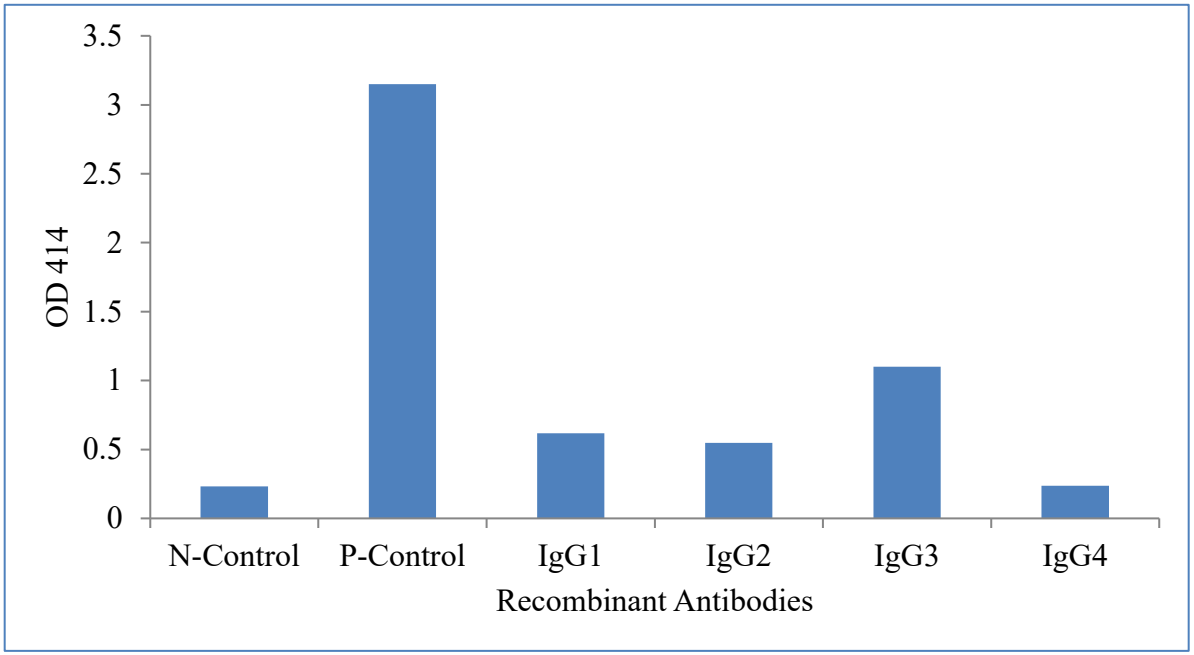
- Differs across product brands
- Consistent for individual products

CDHA testing:

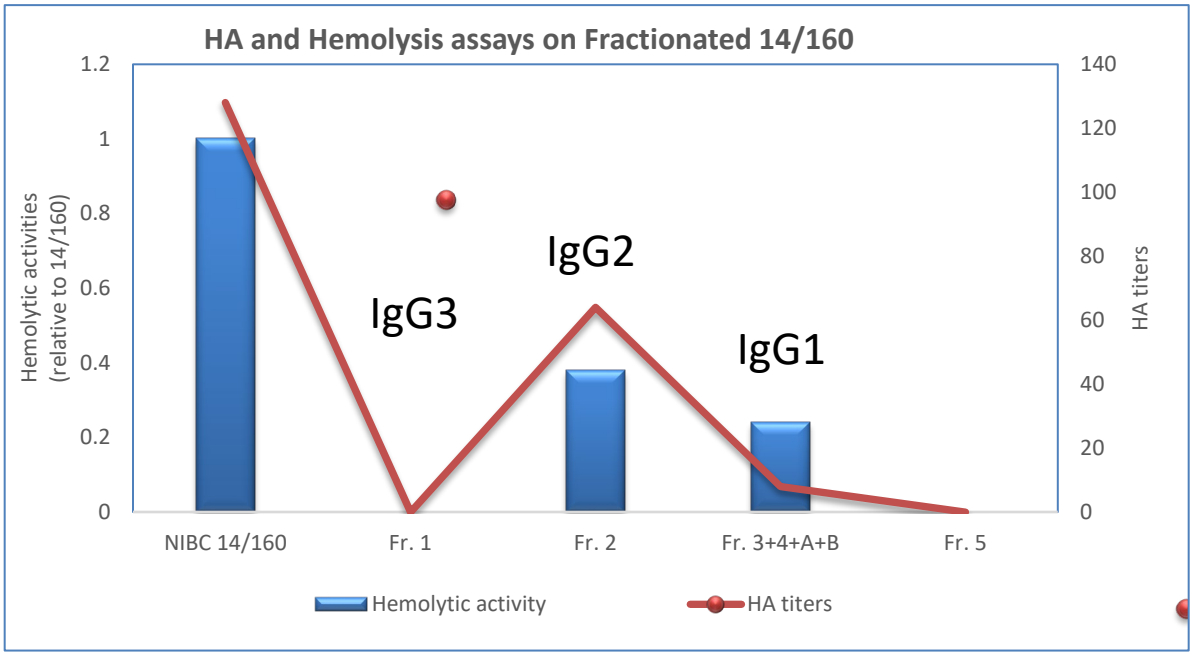
- Results are quantitative and reproducible
- Identified clinically hemolytic lots that passed direct agglutination testing



Contribution of IgG Antibody Subclasses to Hemolytic Activity



IgG3 has highest hemolytic activity among IgG subclass-switched recombinant anti-A antibodies



IgG2 purified from IVIG has highest hemolytic and hemagglutinating activity (clinically hemolytic lot)

Outcomes

- Product testing (CDHA and DHAT)
  - 7 pre-IND/IND products
  - 4 licensed products after major manufacturing changes
- In-house proficiency in standard DHAT
- Participation in WHO International standards and methods studies (anti-Rho(D) and Anti-A and Anti-B standards for IG products)
- Identified and assisted NIBSC to obtain a high titer anti-A/anti-B IVIG product for use as a reference standard (NIBSC 14/160)
- Manuscript submitted for CDHA method

Future Plans

- Develop a method to model cell-mediated extravascular hemolysis
  - Evaluate IgG subclass function, FcR binding, and role of inflammatory conditions in hemolytic/hemophagocytic activity
- Continue international standards work related to hemagglutinins and hemolysins
- Continue testing hemolytic activity of new IND products, and licensed products for surveillance and specific investigations

Treatment and Prophylaxis Efficacy of FLUIGIV in Murine Animal Models

Alexey Khalenkov, PhD

CBER/OTAT/DPPT/PDB

CBER's regulatory mission and Office research priorities

- **Increase preparedness for emerging threats and promote global public health**

Influenza A viruses are an emerging threat to the public health due to the high pandemic potential and annual mortality/morbidity toll.

This project addresses public health needs by evaluating hyper-immune anti-influenza IGIV (FLUIGIV) as a prophylactic and treatment option for lethal influenza disease challenge in murine animal models.

Specific goals for the FLUIGIV project

1) Study human hyperimmune globulin (FLUIGIV) against influenza A in normal (BALB/c) and immunocompromised (SCID) mice;

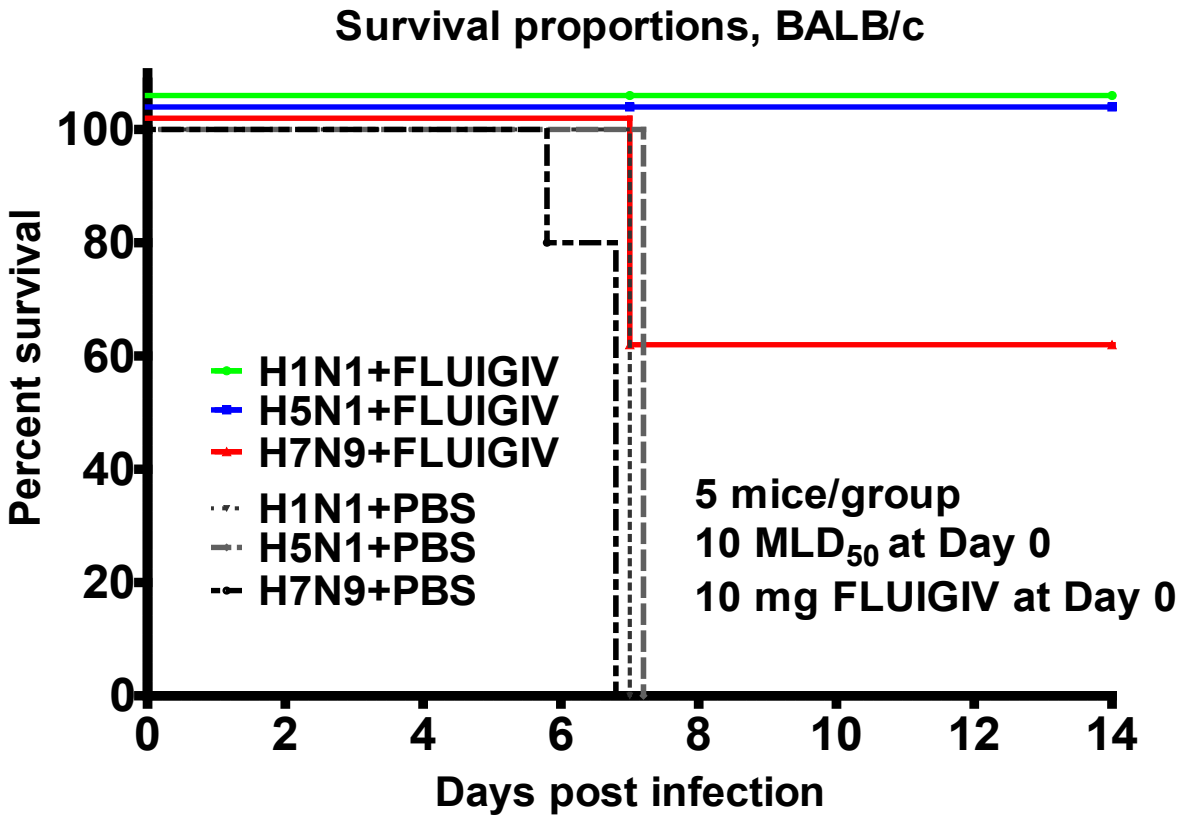
2) Evaluate FLUIGIV effects in pre-exposure prophylaxis and post-exposure treatment in SCID and BALB/c mice challenged with a lethal dose of 2009 pandemic H1N1 virus;

3) Compare efficacy of different FLUIGIV treatment regimens with respect to:

- Timing relative to influenza challenge
- Single vs repeat dose regimens

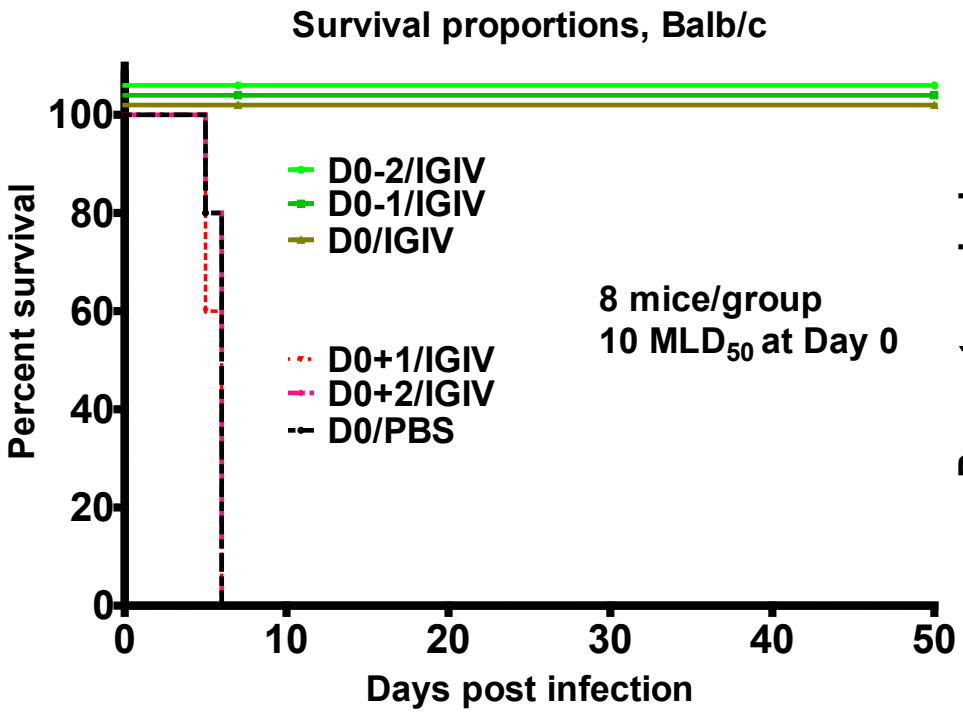
4) Assess FLUIGIV cross-reactivity and protection potential against highly pathogenic avian influenza (HPAI) strains.

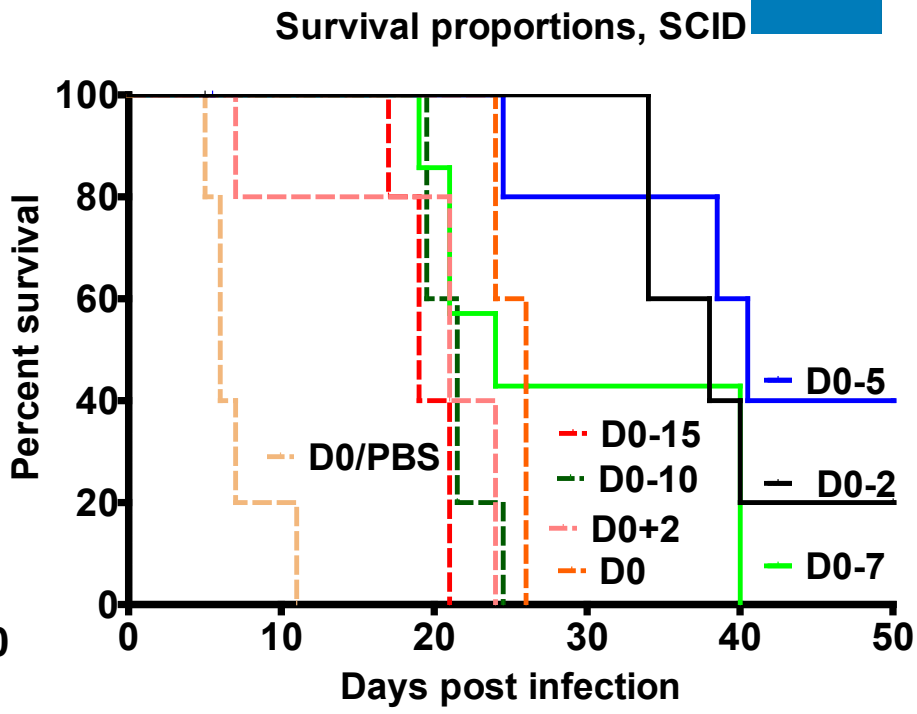
In Vivo Cross-reactivity of FLUIGIV with different pandemic influenza strains



- FLUIGIV protected 100% of animals in H1N1 and H5N1 group
- Partial protection was observed in H7N9 group

Time-dependent FLUIGIV prophylaxis/treatment in BALB/c and SCID mice





- Pre-exposure prophylaxis and D0 treatment fully protected BALB/c mice from lethal challenge
- Post-exposure treatment failed to protect BALB/c mice from lethal challenge

- Pre-exposure prophylaxis and post-exposure treatment prolonged survival in SCID mice in time-dependent manner, but did not provide protection from lethal challenge
- Partial protection in D0-5 and D0-2 groups in SCID mice observed

High-potency FLUIGIV Human Clinical Trial 2019

Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial

Richard T Davey Jr, Eduardo Fernández-Cruz*, Norman Markowitz*, Sarah Pett*, Abdel G Babiker, Deborah Wentworth, Surender Khurana, Nicole Engen, Fred Gordin, Mamta K Jain, Virginia Kan, Mark N Polizzotto, Paul Riska, Kiat Ruxrungtham, Zelalem Temesgen, Jens Lundgren, John H Beigel, H Clifford Lane, and James D Neaton, on behalf of the INSIGHT FLU-IVIG Study Group†*

Summary

Background Since the 1918 influenza pandemic, non-randomised studies and small clinical trials have suggested that convalescent plasma or anti-influenza hyperimmune intravenous immunoglobulin (hIVIG) might have clinical benefit for patients with influenza infection, but definitive data do not exist. We aimed to evaluate the safety and efficacy of hIVIG in a randomised controlled trial.

Lancet Respir Med 2019
Published Online
September 30, 2019
https://doi.org/10.1016/S2213-2600(19)30253-X

Results:

No difference in **the composite safety outcome of death, a serious adverse event, or a grade 3 or 4 adverse event between placebo and treatment groups.**

- BALB/c experimental data concur with the clinical trial results
- BALB/c results predict pre-exposure prophylaxis with FLUIGIV could be beneficial
- Based on SCID mouse experiments there could be potential benefits of FLUIGIV for treatment of severely immunocompromised patients infected with influenza A

Future studies

- Detailed PK/PD of the FLUIGIV in normal and SCID murine models.
- Evaluate host-dependent immunological determinants of protection, survival or failure to protect.
- Combination studies with currently approved drug therapies for influenza disease.

Thank you!