Getting to the bottom of PFAS-induced immune dysfunction

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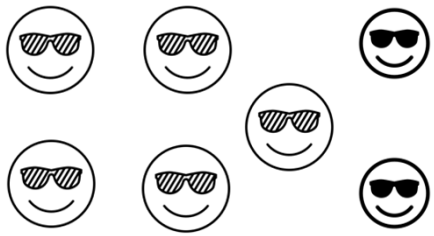
Potential conflicts of interest

I currently am funded to study immune system effects of PFAS (sources of funding: North Carolina Policy Collaboratory & NC General Assembly, US EPA/Oregon State University (83948101), NIEHS/NC State University (1 P42 ES031009-01), NC State University (Center for Human Health and the Environment).

I currently am a member of the U.S. EPA PFAS Science Advisory Board and have served as an external peer-reviewer for some of the documents used to support assertions in this slide set.

I often speak publicly about my understanding of PFAS toxicity, serve/have served as a plaintiff's expert witness, advocate for the need to protect the public from their exposures to PFAS, and am a proponent of the essential use concept and the class approach for PFAS management.

The DeWitt Lab



Current lab members:

Qing Hu (Research specialist), Dr. Tracey Woodlief (Research instructor), Krystal Taylor, Aya Ahmed (doctoral students), five undergraduate students, and two high school students.

Current sources of DeWitt laboratory funding for PFAS:

- NC General Assembly via the North Carolina Policy Collaboratory
- US EPA/Oregon State University (83948101)
- NIEHS/NC State University (1 P42 ES031009-01)

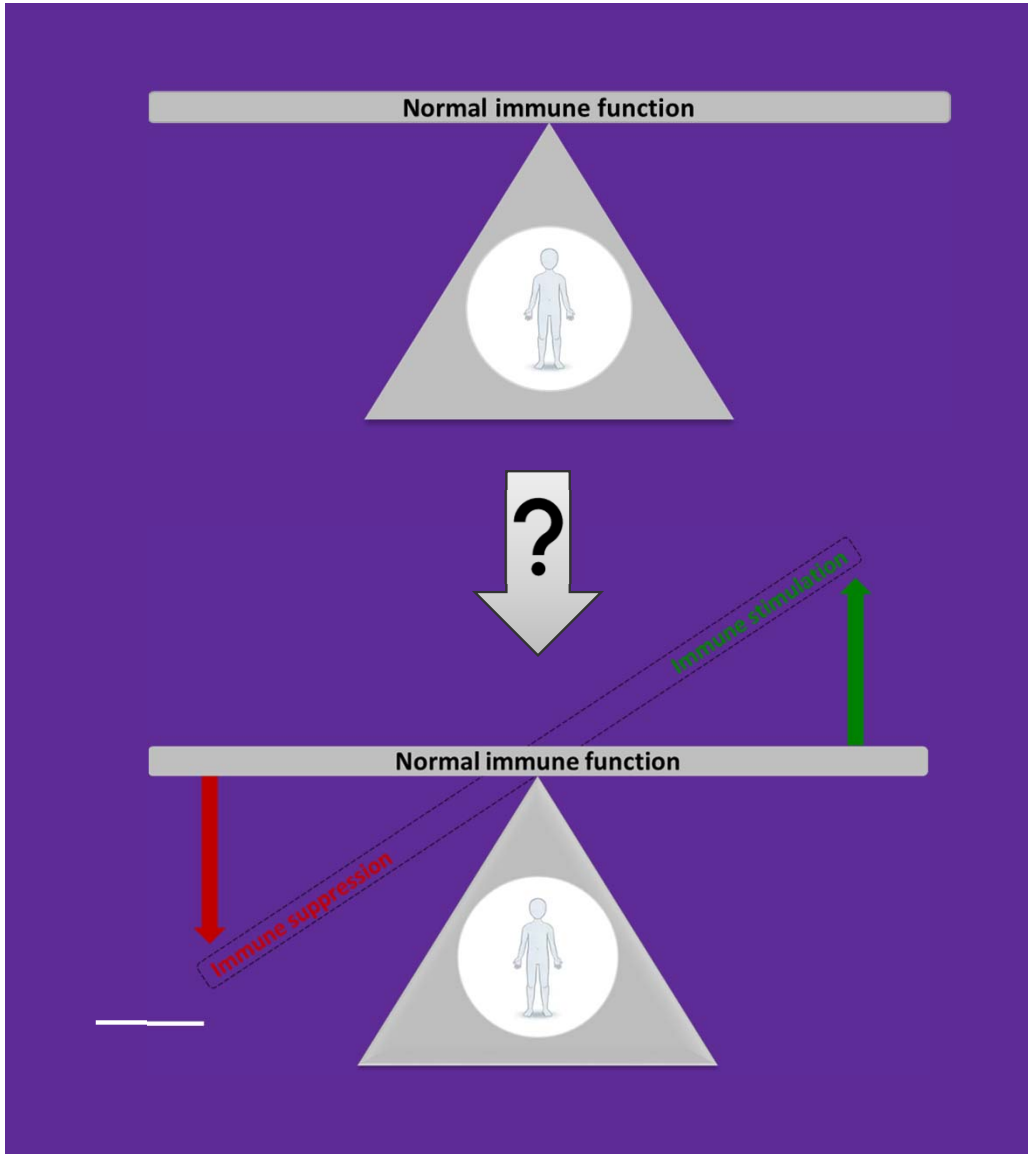
NORTH CAROLINA PFAS Testing Network

Srp Superfund Research Program

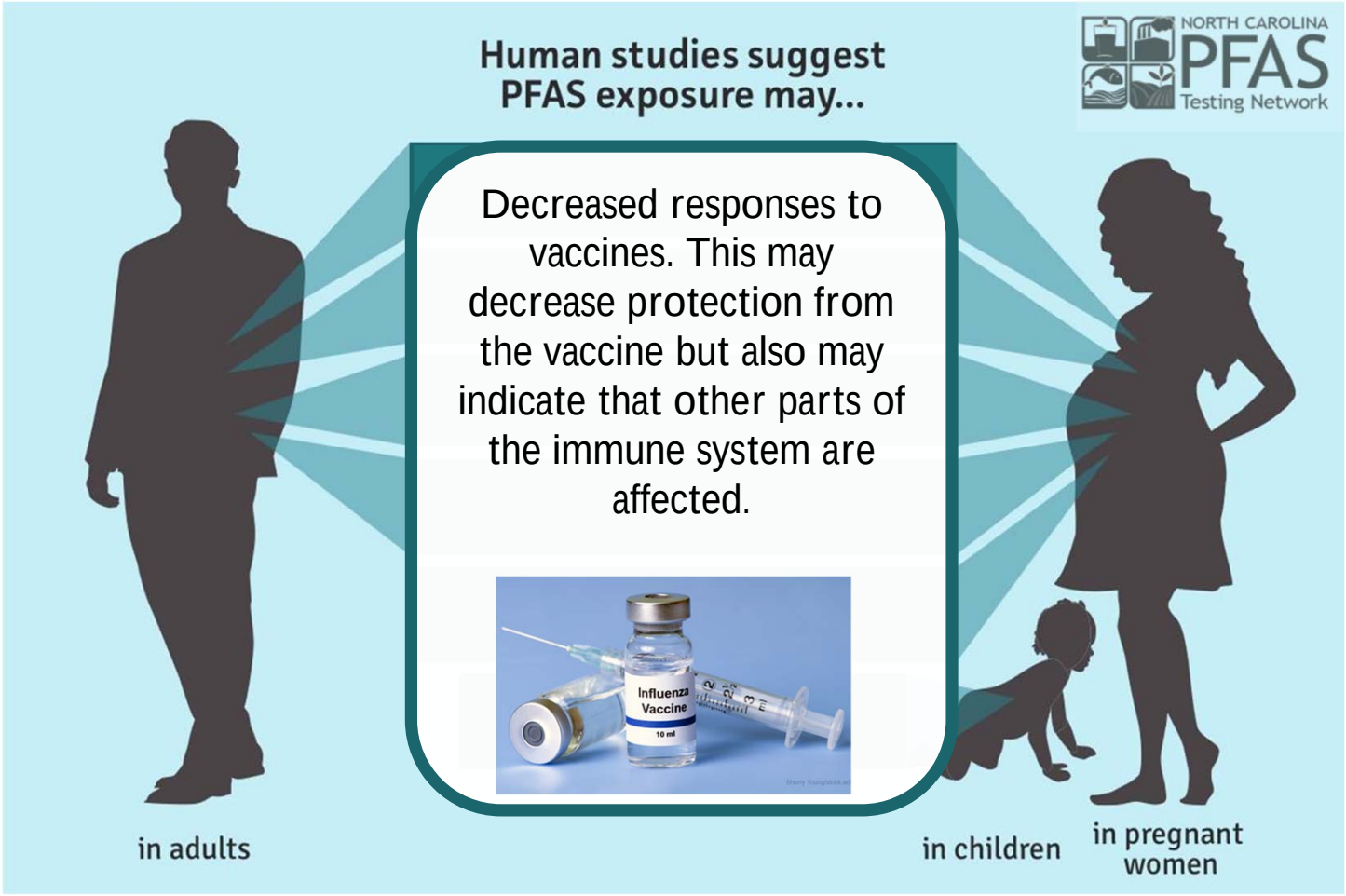
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

GLOBAL PFAS SCIENCE PANEL

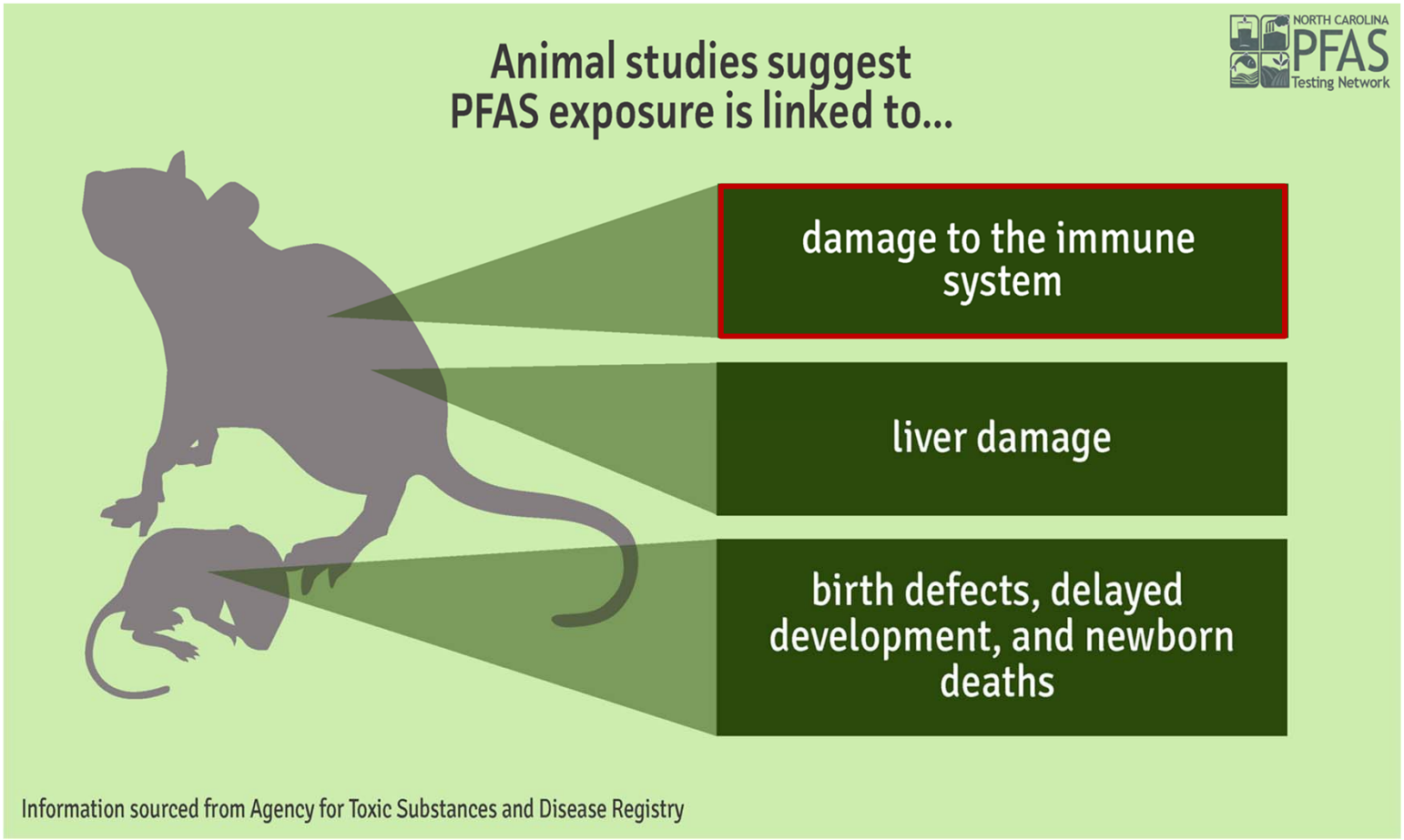
Why are we concerned about effects of PFAS exposure on the immune system?



PFAS immunotoxicity



PFAS immunotoxicity



Weighing of the evidence

Table 6. Evidence Profile of the Main Findings for PFOA Immunotoxicity

INITIAL CONFIDENCE for each body of evidence (# of studies)	Factors decreasing confidence "---" if no concern; "↓" if serious concern to downgrade confidence					Factors increasing confidence "---" if not present; "↑" if sufficient to upgrade confidence				FINAL CONFIDENCE RATING
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose Response	Residual Confounding	Consistency Species/Model	
Immunotoxicity Based on Evidence for Suppression of the Antibody Response										
Human										
Initial Moderate (4 prospective studies)[a]	---	---	---	---	---	---	---	---	---	**Moderate**
Initial Low (2 cross-sectional studies)[b]	---	---	---	---	---	---	---	---	---	**Low**
Confidence Across Human Bodies of Evidence	No change for considering across study designs									**Moderate**
Animal										
Initial High (7 mammal studies)	↓	---	---	---	---	---	↑	---	---	**High**

References:

Human: Granum (2013)[a], Grandjean (2012)[a], Kielsen (2016)[b], Looker (2014)[a], Mogensen (2015)[a], Stein (2016)[b]

Animal: DeWitt (2008, 2009a, 2016), Hu (2010), Loveless (2008), Vetvicka (2013), Yang (2002a)

National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)

Note that I was an external reviewer during the development of this document.

Weighing of the evidence

Table 8. Evidence Profile of the Main Findings for PFOS Immunotoxicity

INITIAL CONFIDENCE for each body of evidence (# of studies)	Factors decreasing confidence "---" if no concern; "↓" if serious concern to downgrade confidence					Factors increasing confidence "---" if not present; "↑" if sufficient to upgrade confidence				FINAL CONFIDENCE RATING
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose Response	Residual Confounding	Consistency Species/Model	
Immunotoxicity Based on Evidence for Suppression of the Antibody Response										
Human										
Initial Moderate (4 prospective studies)[a]	---	---	---	---	---	---	---	---	---	**Moderate**
Initial Low (2 cross-sectional studies)[b]	---	---	---	---	---	---	---	---	---	**Low**
Confidence Across Human Bodies of Evidence	No change for considering across study designs									**Moderate**
Animal										
Initial High (8 mammal studies)	↓	---	---	---	---	---	↑	---	---	**High**

References:

Human: Granum (2013)[a], Grandjean (2012)[a], Kielsen (2016)[b], Looker (2014)[a], Mogensen (2015)[a], Stein (2016)[b]

Animal: Dong (2009b, 2011), Keil (2008), Lefebvre (2008), Peden-Adams (2008), Qazi (2010b), Vetvicka (2013), Zheng (2009)

National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)

Note that I was an external reviewer during the development of this document.

Weighing of the evidence

Table 7. PFOA Main Immune Effects Summary Table						
Category of Immune Response	Immune Outcomes	Confidence Ratings in the Body of Evidence		Level of Evidence in the Body of Evidence		Hazard Conclusion
		Human	Animal	Human	Animal	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	Presumed to be an Immune Hazard to Humans

Table 9. PFOS Main Immune Effects Summary Table						
Category of Immune Response	Immune Outcomes	Confidence Ratings in the Body of Evidence		Level of Evidence in the Body of Evidence		Hazard Conclusion
		Human	Animal	Human	Animal	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	Presumed to be an Immune Hazard to Humans

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NTP MONOGRAPH ON IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)

Weighing of the evidence

Other immune effects supported the NTP's weight-of-evidence classification for PFOA and PFOS:

- Increased hypersensitivity-related outcomes.
- Suppression of innate immune responses (i.e., NK cell function).
- Alterations in disease resistance/infectious disease outcomes.
- Findings of autoimmunity.

These findings indicate that PFAS (as represented by PFOA and PFOS) can have multiple effects on the immune system.

National Toxicology Program
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NTP MONOGRAPH ON IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR PERFLUOROOCTANE SULFONATE (PFOS)

Weighing of the evidence

Reference doses for recommended maximum contaminant level goals (MCLGs) by the U.S. EPA are currently based on risks immunotoxicity as represented by impacts of PFAS exposure on vaccine responses in children.

The RfD selected for PFOA is 1.5×10^{-9} mg/kg-day based on the critical effect of decreased serum anti-tetanus antibody concentration in children.

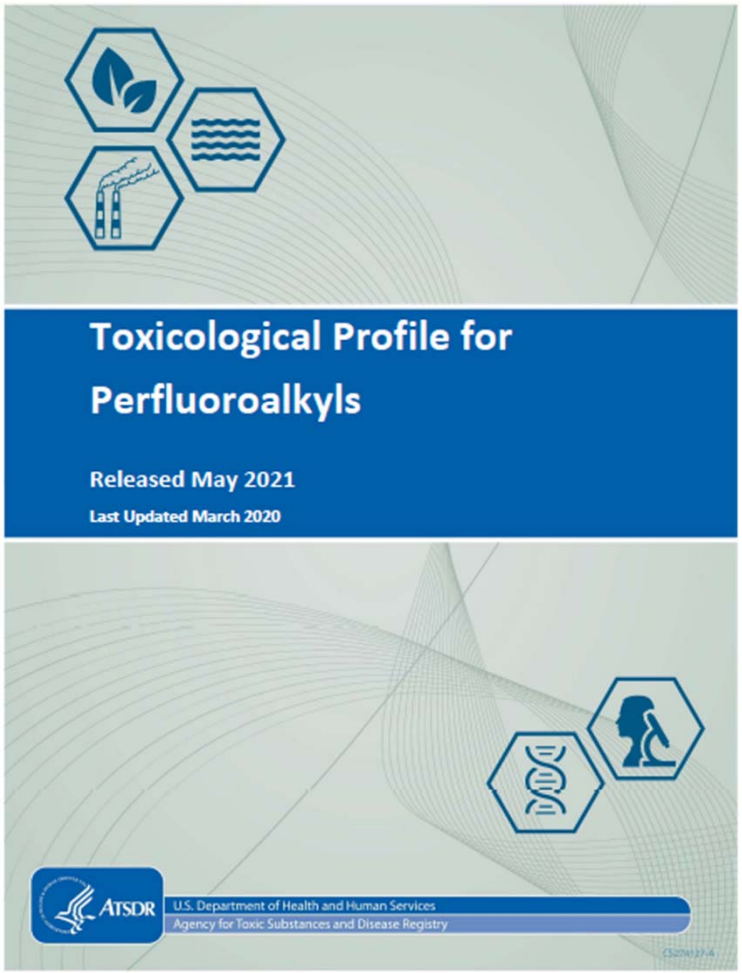
The RfD selected for PFOS is 7.9×10^{-9} mg/kg-day based on the critical effect of decreased serum anti-diphtheria antibody concentration in children.

EXTERNAL PEER REVIEW DRAFT
Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) (CASRN 335-67-1) in Drinking Water

EXTERNAL PEER REVIEW DRAFT
Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) (CASRN 1763-23-1) in Drinking Water

Note that I am serving as a member of the EPA PFAS Science Advisory Board and the Board is currently reviewing these maximum contaminant level goals.

Weighing of the evidence



Statement on Potential Intersection between PFAS Exposure and COVID-19:

CDC/ATSDR understands that many of the communities we are engaged with are concerned about how PFAS exposure may affect their risk of COVID-19 infection. We agree that this is an important question.

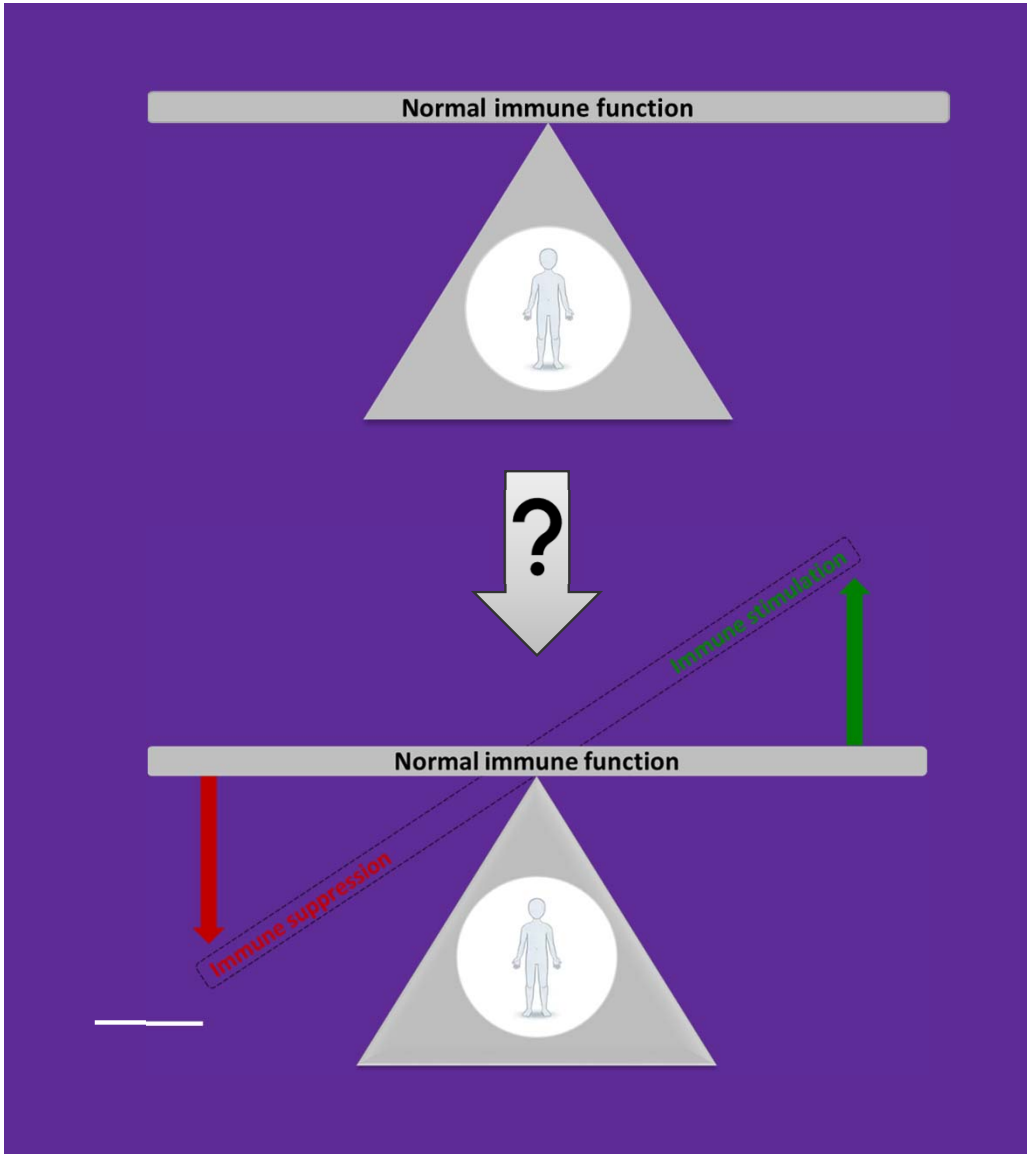
CDC/ATSDR recognizes that exposure to high levels of PFAS may impact the immune system. There is evidence from human and animal studies that PFAS exposure may reduce antibody responses to vaccines (Grandjean et al., 2017, Looker et al., 2014), and may reduce infectious disease resistance (NTP, 2016). Because COVID-19 is a new public health concern, there is still much we don't know. More research is needed to understand how PFAS exposure may affect illness from COVID-19.

References:

1. Grandjean P, Heilmann C, Weihe P, et al. Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. J Immunotoxicol. 2017;14(1):188-195. doi:10.1080/1547691X.2017.1360968
2. Looker C, Luster MI, Calafat AM, et al. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. Toxicol Sci. 2014;138(1):76-88. doi:10.1093/toxsci/kft269
3. NTP (National Toxicology Program). 2016. Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf

CDC ATSDR AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

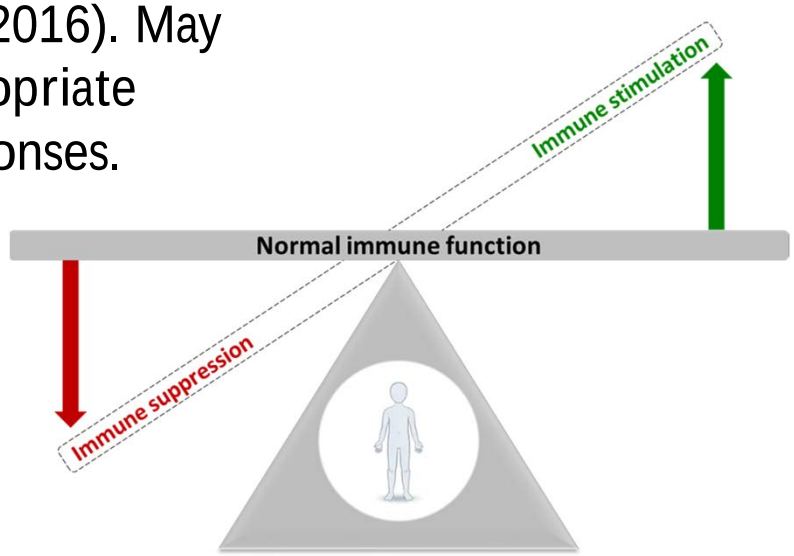
How is immune suppression measured?



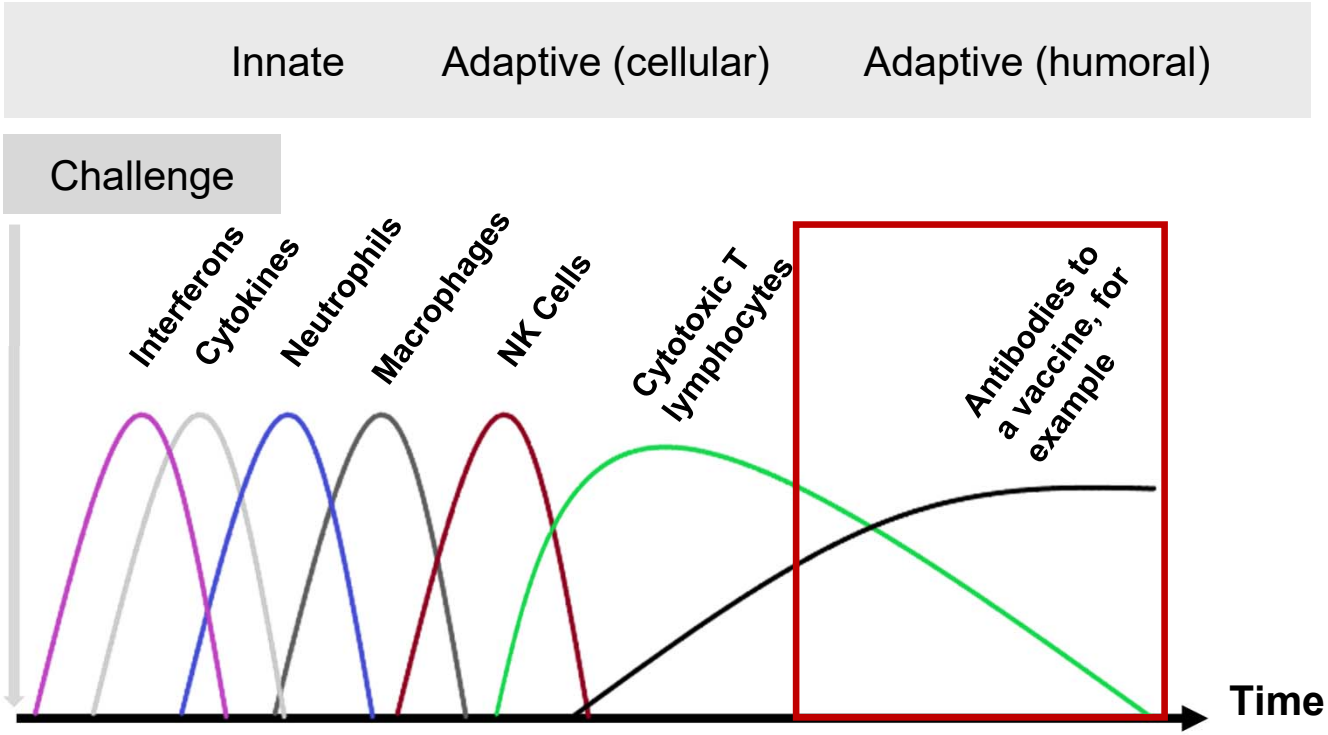
A focus on immune suppression

Immune suppression:
A reduced ability of the immune system to respond to a challenge from a level considered normal, regardless of whether clinical disease results (DeWitt et al., 2016). May also include inappropriate inflammatory responses.

Immune stimulation:
Inappropriate immune responses to common substances, i.e., allergic hypersensitivity, or responses to self-antigens, i.e., autoimmunity (DeWitt et al., 2016). May also include inappropriate inflammatory responses.



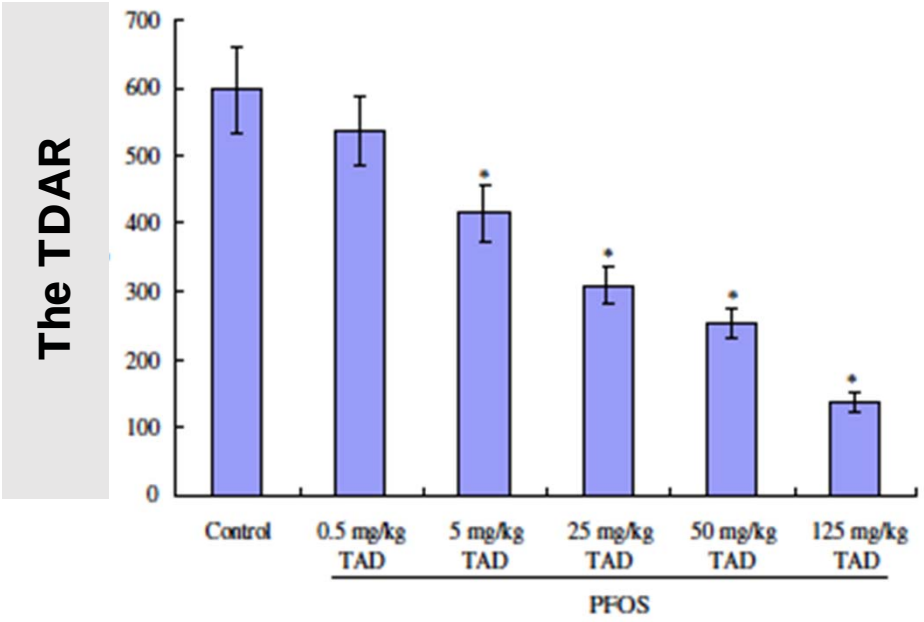
The “challenge” of a vaccine



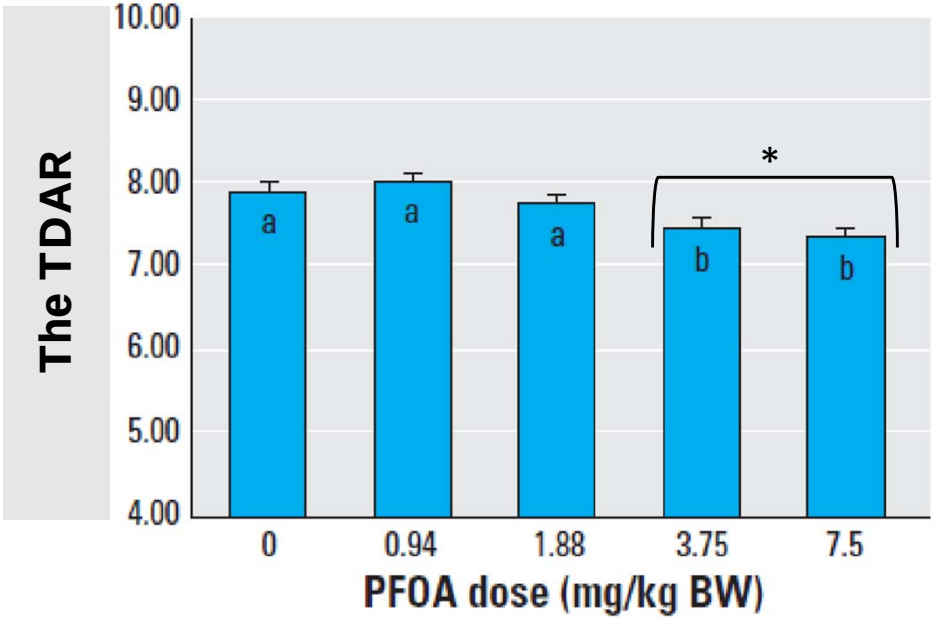
Antibody production is a *functional* outcome. The immune system is challenged and the response to that challenge is measured. This happens during a vaccination and it can be evaluated experimentally with “the T cell-dependent antibody response” or “the TDAR.”

Image information from: Burleson, 2015.

The TDAR in experimental models



Oral PFOS exposure in male C57BL/6 mice (60d of exposure) and measurement of **the TDAR**.



Oral PFOA exposure in female C57BL/6 mice (15d of exposure) and measurement of **the TDAR**.

PFOS data: Dong et al. 2009. PFOA data: DeWitt et al. 2008.

The vaccine response in people

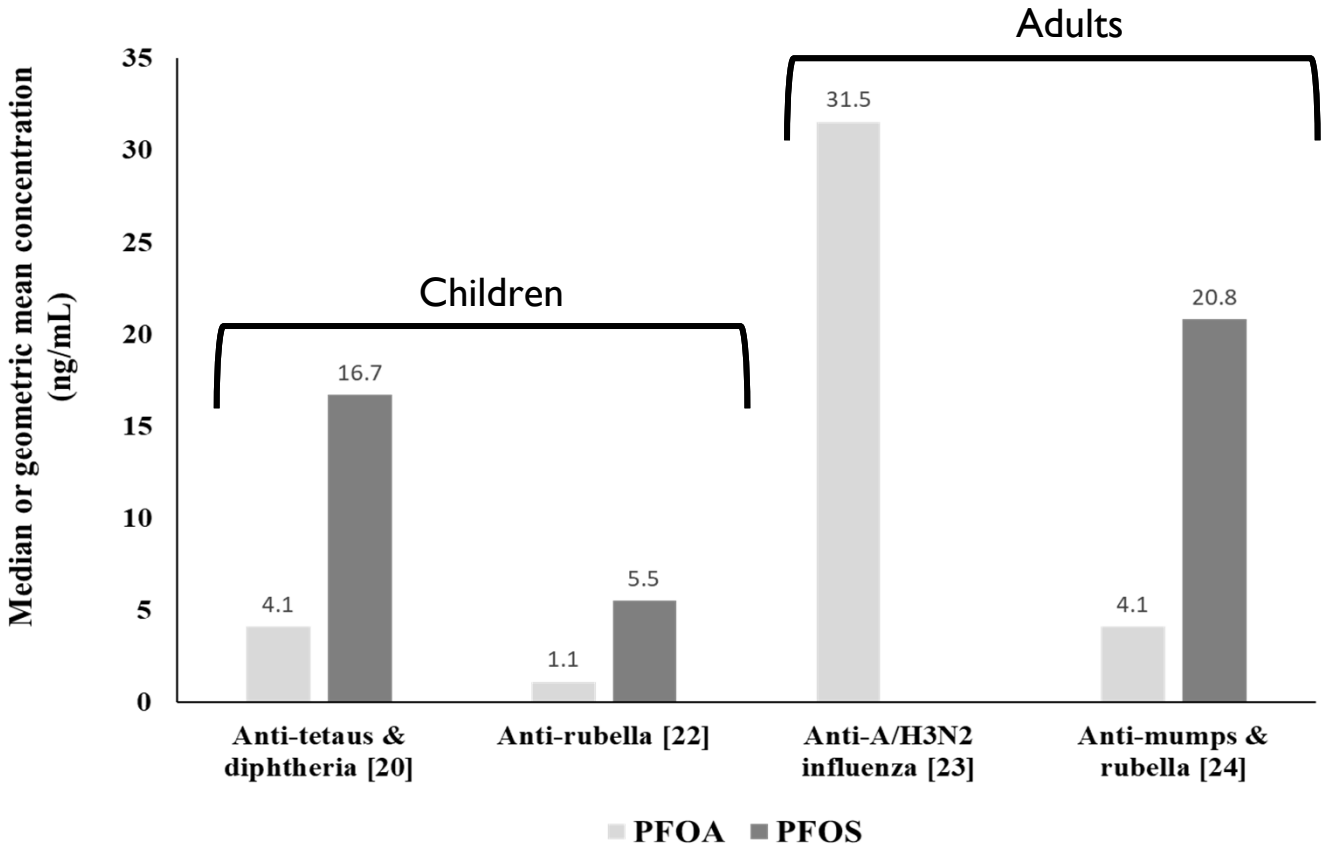
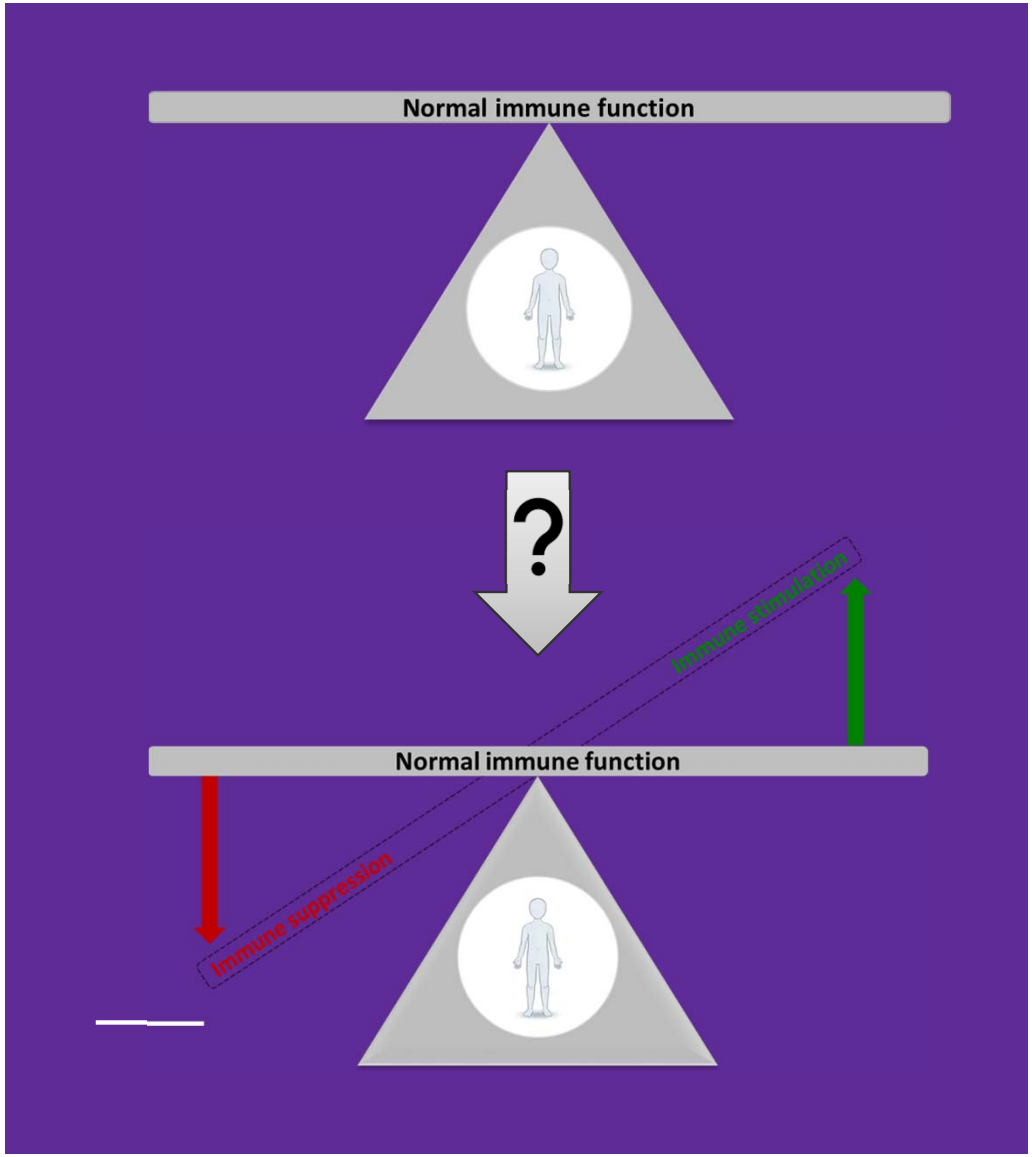
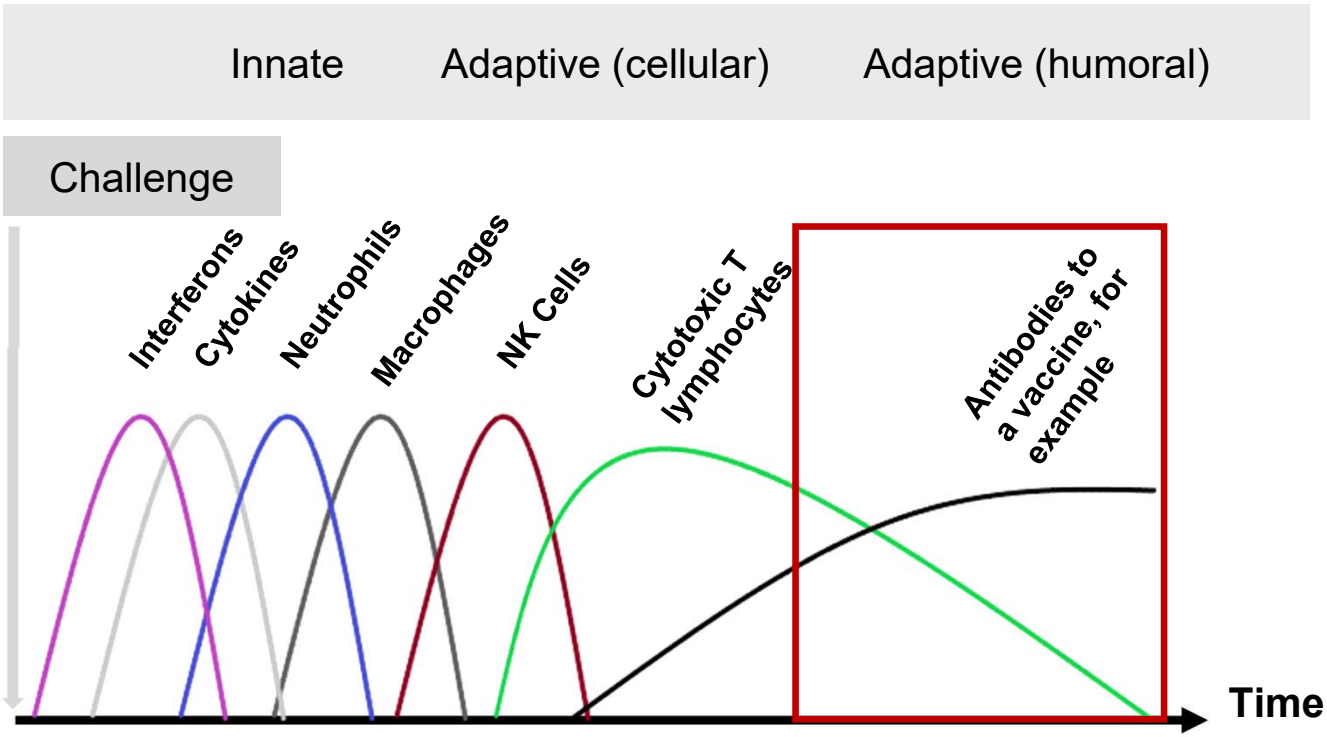


Figure from: DeWitt et al. 2019.

What is my lab doing to understand PFAS-induced immune suppression?



PFAS immunotoxicity in the DeWitt Lab



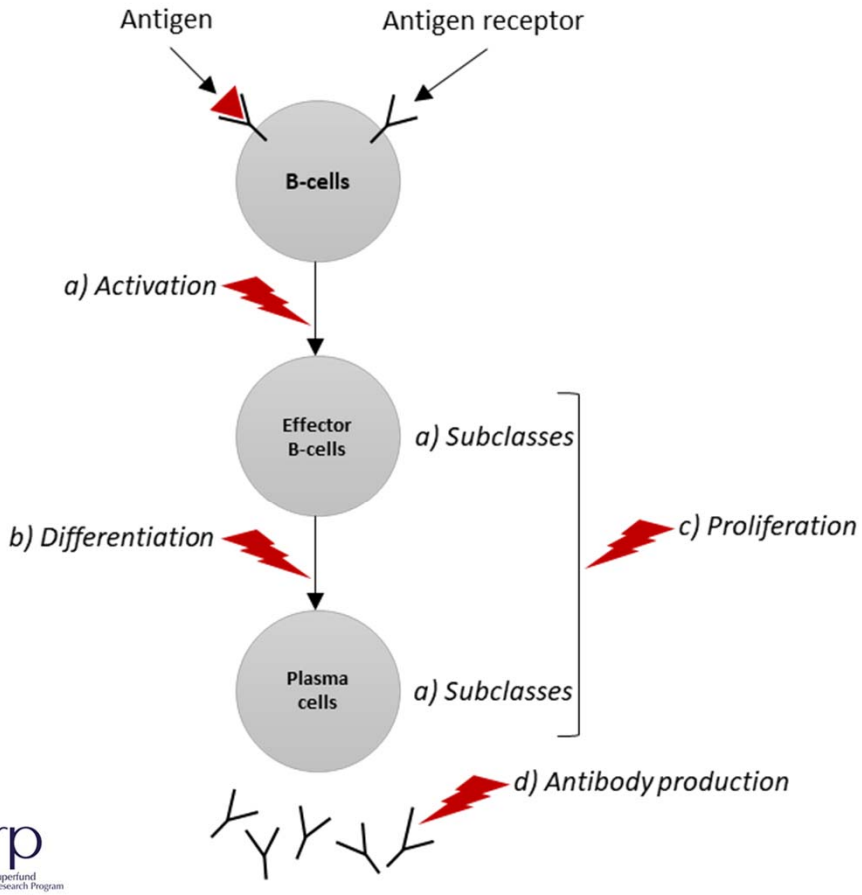
Our **descriptive immunotoxicological** studies are important first steps in uncovering deficits in how the immune system is able to function.

Evaluation of the TDAR

For PFAS detected in NC that are toxicologically understudied. These include the "perfluoroether acids" such as GenX, Nation byproduct 2, PFMOAA, other individual PFEAs and mixtures of these PFEAs.

NORTH CAROLINA PFAS Testing Network

PFAS immunotoxicity in the DeWitt Lab



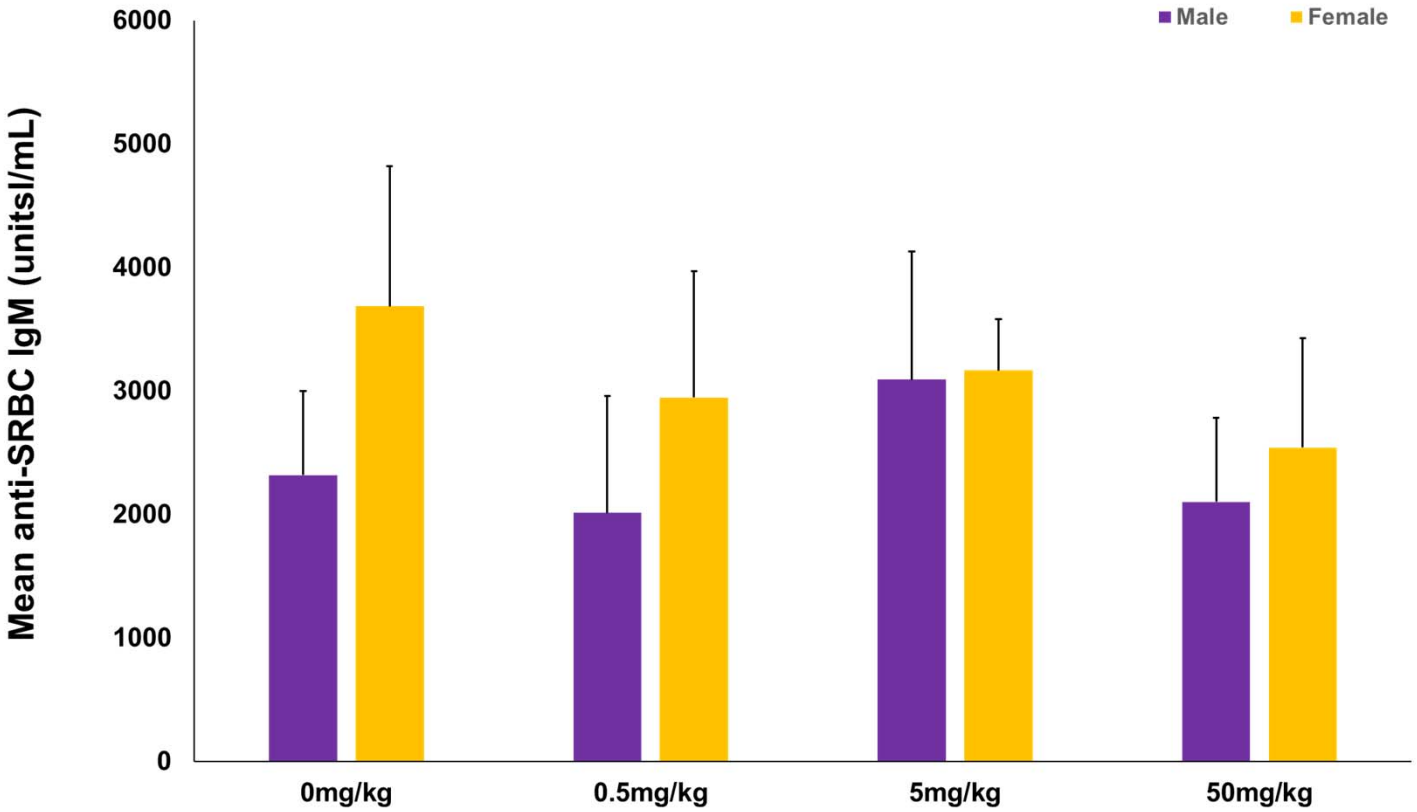
How does PFAS exposure affect the TDAR?

One focus of our lab is on B cells, the cells that eventually transform to become antibody-secreting plasma cells.

Future Dr. Krystal Taylor is asking about how PFAS exposure affects subsets of B cells.

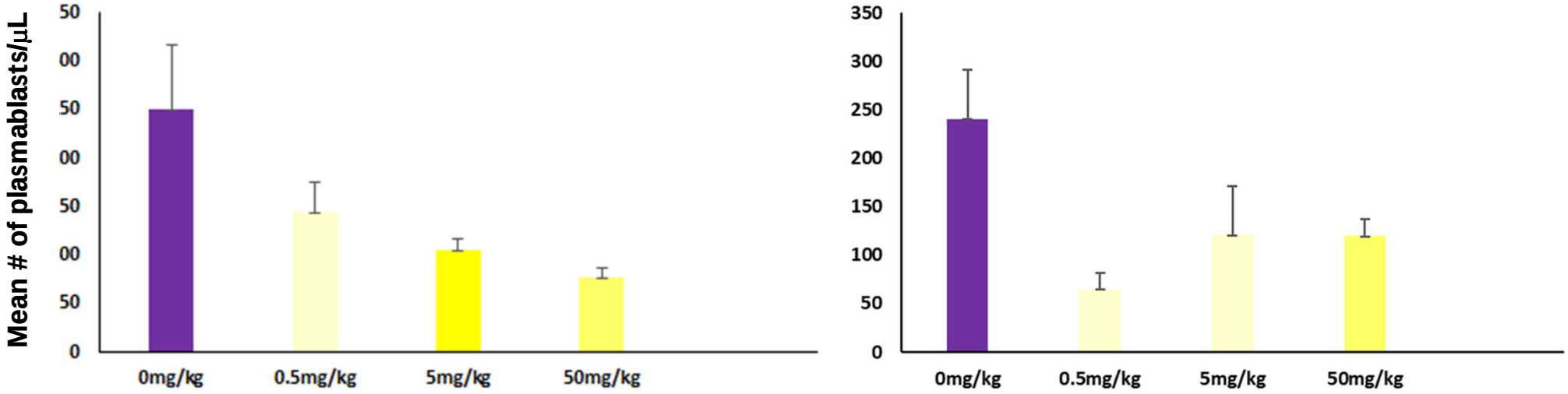
Source of funding: NIEHS/NC State University (1 P42 ES031009-01:
NC State University Center for Environmental and Human Health Effects of PFAS).

PFAS immunotoxicity in the DeWitt Lab



Male and female C57BL/6 mice orally exposed to PFHxA for 30 days had a redution in the TDAR (Males: ~13% and 9% reduction in 0.5 and 50 mg/kg dose groups. Females: 14-20% reduction in all dose groups).

PFAS immunotoxicity in the DeWitt Lab



Male and female C57BL/6 mice orally exposed to PFHxA for 30 days had a redution in the number of plasmablasts (pre-cursors to memory B cells and antibody-secreting plasma cells).

PFAS immunotoxicity in the DeWitt Lab

How does PFAS exposure affect the TDAR?

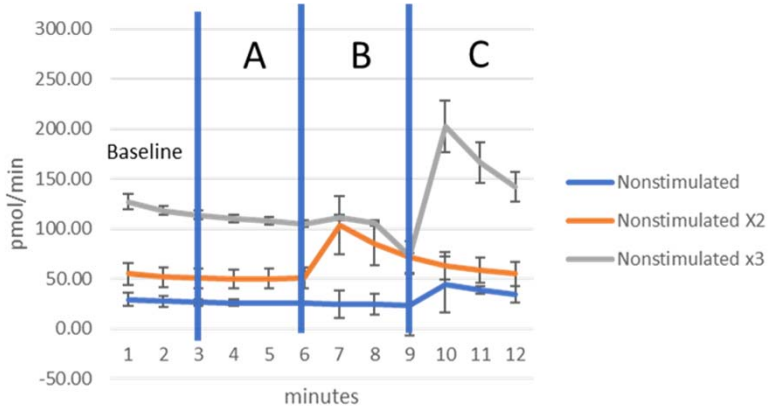
One focus of our lab is on B cells, the cells that eventually transform to become antibody-secreting plasma cells.

Dr. Tracey Woodlief Research Instructor is asking about how PFAS exposure affects how B cells use energy at the level of their mitochondria.

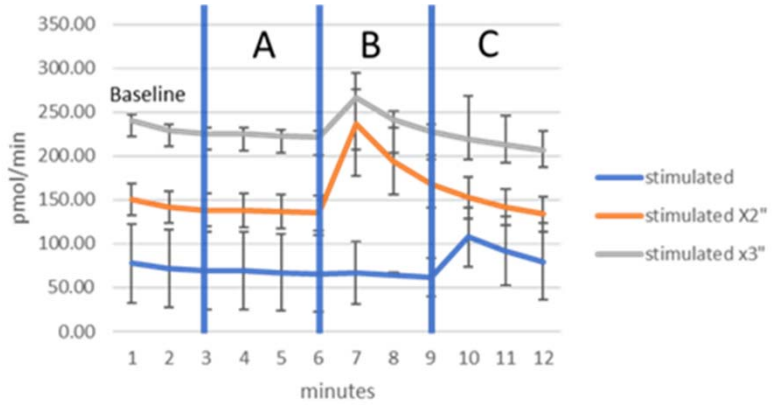
Source of funding: NIEHS/NC State University (1 P42 ES031009-01:
NC State University Center for Environmental and Human Health Effects of PFAS).

PFAS immunotoxicity in the DeWitt Lab

Non-stimulated cells (OCR)



Stimulated cells (OCR)



B cells are **unstimulated** in culture or **stimulated** with CD40 and IL4. Different lines = different B cell concentrations.

OCR: oxygen consumption rate in real time.

A, B, C panels = different concentrations of FCCP (disrupts ATP synthesis).

Final thought –

the risk of immunotoxicity from PFAS exposure is real

New Jersey & Michigan
MCL for PFOS in drinking water is based on suppression of the TDAR. Six states have RfDs for PFOS based on immune suppression.

European Food Safety Authority
Tolerable daily intake is based on epidemiological data linking *maternal* PFAS exposure with a decreased antibody responses to vaccines in their breastfed children.

ATSDR
Incorporated a modifying factor into its minimal risk level for PFOS citing concerns of the sensitivity of the immune system.

EPA
RfD for PFOA/PFOS MCLGs based on risk of immune suppression.

Source of (some) information: Post, 2020.

I welcome your questions!