



SEVOFLURANE AND DESFLURANE HEPATOTOXICITY

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DISCLOSURES

- MCGRAW – HILL EDUCATION
 - ON-LINE PODCASTS/LECTURES
- INVENTION DISCLOSURE: RECOGNITION OF CRITICAL CYP2E1 EPITOPES, US PATENT NUMBER: 9,339,531, ISSUE DATE: 5/17/2016.

AT THE COMPLETION OF THIS LECTURE

- **COMPREHEND** THE PREVALENCE OF HEPATOTOXICITY ASSOCIATED WITH SEVOFLURANE AND OTHER HALOGENATED ANESTHETICS.
- **REVIEW** ACCEPTED MECHANISMS OF HEPATOTOXICITY FROM SEVOFLURANE AND DESFLURANE AS WELL AS METHODS FOR CONFIRMATION OF THE DIAGNOSIS.
- **RECOGNIZE** GAPS IN KNOWLEDGE SURROUNDING THE PREVALENCE AND MECHANISMS OF SEVOFLURANE AND DESFLURANE HEPATOTOXICITY AND BEGIN TO DISCUSS HOW THESE GAPS MAY BE ADDRESSED.



BACKGROUND

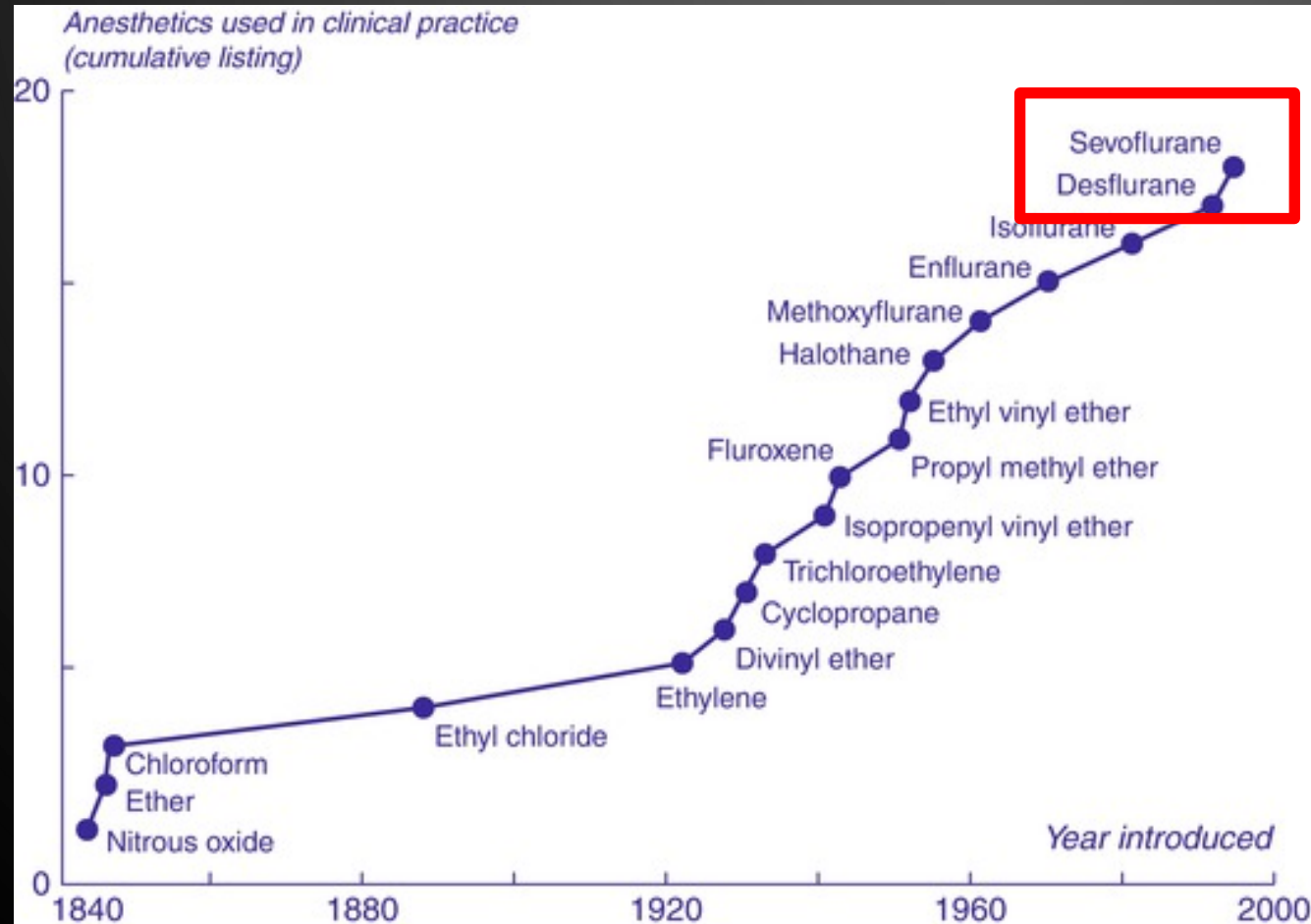
LIVER DISEASE

- LIVER DISEASE AND CIRRHOSIS ARE THE SIXTH MOST COMMON CAUSE OF DEATH IN ADULTS BETWEEN THE AGES OF 25 AND 64 (NATIONAL CENTER FOR HEALTH STATISTICS, 2014).
- LIVER-RELATED MORTALITY IN THE UNITED STATES MAY BE UNDERESTIMATED (ASRANI ET AL., 2013).

LIVER DISEASE

- DRUG-INDUCED HEPATITIS IS A LEADING CAUSE OF LIVER FAILURE AND IS THE MOST COMMON REASON AN APPROVED MEDICATION IS REMOVED FROM THE CONSUMER MARKET (BELL AND CHALASANI, 2009).
- MANY TYPES OF DRUG-INDUCED HEPATITIS ARE BELIEVED TO BE IMMUNE-MEDIATED.

BOTH OF THE MODERN HALOGENATED ANESTHETICS HAVE BEEN ASSOCIATED WITH HEPATOTOXICITY



Frost E.A.M. (2015) A Review of Mechanisms of Inhalational Anesthetic Agents. In: Kaye A., Kaye A., Urman R. (eds) Essentials of Pharmacology for Anesthesia, Pain Medicine, and Critical Care. Springer, New York, NY

BACKGROUND SUMMARY

- LIVER-RELATED MORTALITY IS AT AN ALL TIME HIGH IN THE US
- THE BURDEN OF DISEASE ASSOCIATED WITH THE LIVER MAY BE UNDERESTIMATED
- IMMUNE-MEDIATED HEPATITIS IS A FINAL COMMON MECHANISM THAT FOLLOWS MANY FORMS OF LIVER INJURY
- DESFLURANE AND SEVOFLURANE HAVE BEEN ASSOCIATED WITH HEPATOTOXICITY

The background is a dark gray gradient. In the top-left and bottom-right corners, there are several realistic-looking bubbles of various sizes, some overlapping, with highlights and shadows that give them a three-dimensional appearance.

**WHAT IS THE INCIDENCE OR PREVALENCE OF
HEPATOTOXICITY ASSOCIATED WITH
DESFLURANE OR SEVOFLURANE?**

DESFLURANE

- INTRODUCED IN 1993
- PREVALENCE OF HEPATOTOXICITY: 1 IN 10 MILLION
 - STACHNIK J. INHALED ANESTHETIC AGENTS. AM J HEALTH SYSTPHARM 2006; 63: 623–34.
- REPORTED CASES OF HEPATOTOXICITY: **FIVE**

Year	Age/ Sex	Procedure	Prior exposure	POD Onset	Elevated LFTs	Infectious rule out	CYP2E1 or TFA testing	Outcome
1995	65y/o F	Thyroid ectomy	Yes	14	Yes	Yes	Yes	survival
1999	37y/o F	Tibial fx	Yes	12	Yes	Yes	Yes	survival
2005	81 y/o F	Hemi- colectomy	Yes	6	Yes	Yes	No	survival
2007	15 mo M	Nissen	Yes	2	Yes	Yes	No	survival
2018	54y/o F	Sleeve gastrec- tomy	Yes	1	Yes	Yes	No	survival

SEVOFLURANE

- INTRODUCED IN 1999
- INCIDENCE OR PREVALENCE OF HEPATOTOXICITY: UNKNOWN
 - STACHNIK J. INHALED ANESTHETIC AGENTS. AM J HEALTH SYSTPHARM 2006; 63: 623–34.
- REPORTED CASES: **NINE**

Year	Age/ Sex	Procedure	Prior exposure	POD Onset	Elevated LFTs	Infectious rule out	CYP2E1 or TFA testing	Outcome
1991	infant	Extra digit	No	15	Yes	Yes	No	Unk
2007	75y/o F	AVR	Yes (4)	2	Yes	Unk	No	Death
2007	69y/o M	vascular	Yes (twice in 2 days)	1	Yes	Yes	No	Death
2010	66 y/o F	Lymph node 2 weeks after mastec tomy	Yes (twice in 2 days)	15	Yes	Yes	No	Death
2010	37y/o M	abdominal	Unk	3	Yes	EBV	No	survival
2010	47y/o F	Renal transplant	Unk	2	Yes	Unk	No	Death
2012	24 y/o F	colectomy	Weeks apart	8wks	Yes	Yes	Yes	survival
2012	38 y/o M	Hand reconstruct ion	No	8mos.	Yes	Yes	Yes	survival
2012	30 y/o F	crani	No	8wks	Yes	Yes	Yes	survival

SUMMARY:
**THE INCIDENCE OR PREVALENCE OF DESFLURANE
HEPATOTOXICITY IS 1 IN 10 MILLION**

- DESFLURANE HEPATOTOXICITY HAS BEEN REPORTED AT LEAST 5
TIMES
 - **80%** OF CASES WERE IN FEMALE PATIENTS
 - **20%** OF CASES WERE IN MALE PATIENTS
 - **ALL** REPORTED CASES HAVE **SURVIVED**

SUMMARY: THE INCIDENCE OR PREVALENCE OF SEVOFLURANE HEPATOTOXICITY IS UNCLEAR

- SEVOFLURANE HEPATOTOXICITY HAS BEEN REPORTED AT LEAST **9 TIMES**
 - **55%** OF CASES WERE IN FEMALE PATIENTS
 - **33%** OF CASES WERE IN MALE PATIENTS
 - IN **11%** OF CASES THE SEX WAS UNKNOWN
 - **DEATH** OCCURRED IN **44%** OF PATIENTS AND **OF THE PATIENTS THAT DIED, ALL WERE FEMALE.**

SUMMARY: IF METABOLISM IS THE KEY....

- **WHY DID HEPATOTOXICITY OCCUR WITH DESFLURANE AND SEVOFLURANE?**
- **ARE THERE SUSCEPTIBLE PERSONS OR CONDITIONS THAT INCREASE SUSCEPTIBILITY DESFLURANE OR SEVOFLURANE HEPATOTOXICITY?**

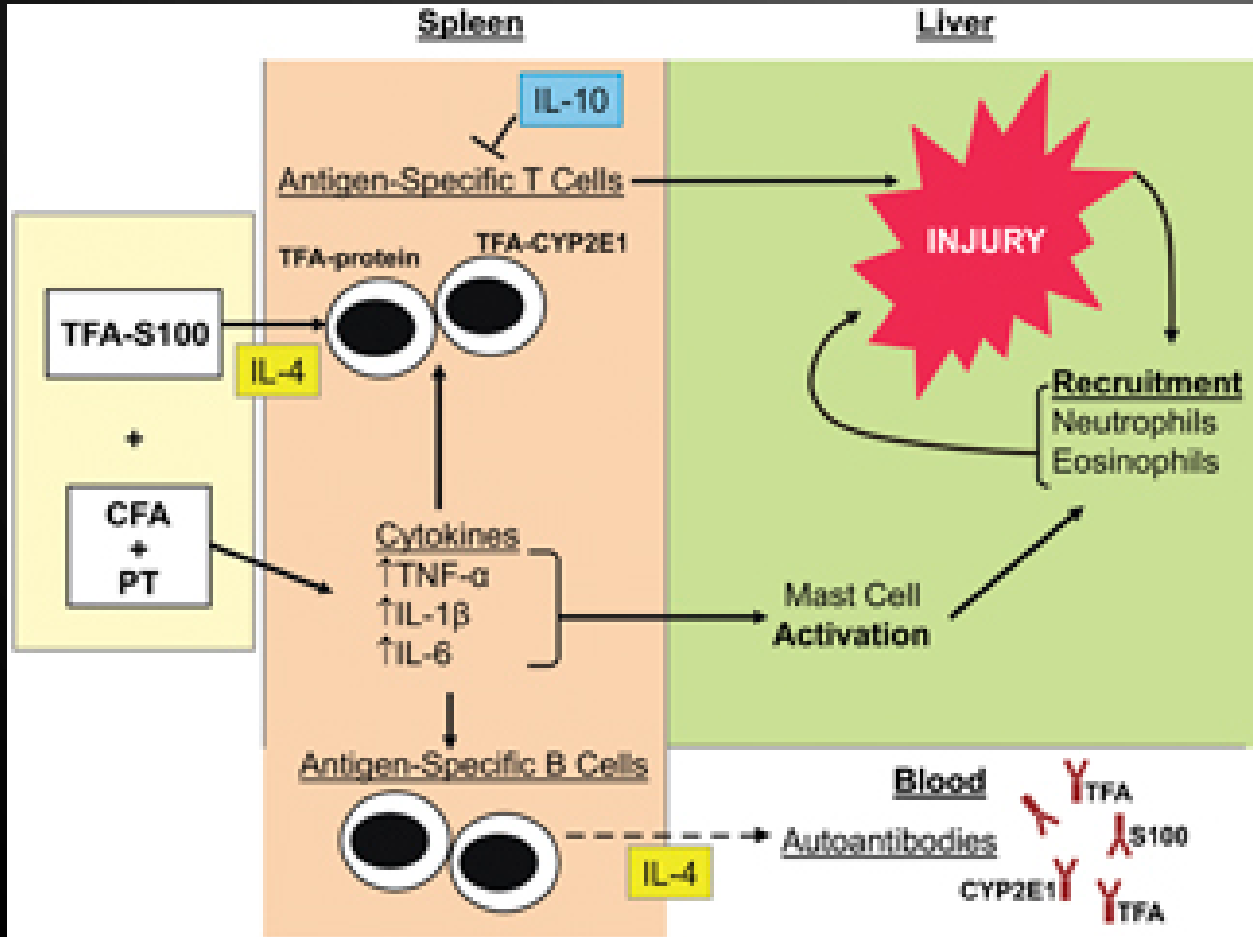
The background is a dark, almost black, gradient. It is decorated with numerous bubbles of various sizes, some appearing as bright highlights and others as soft, out-of-focus shapes. The bubbles are scattered across the frame, with a higher concentration in the top-left and bottom-right corners.

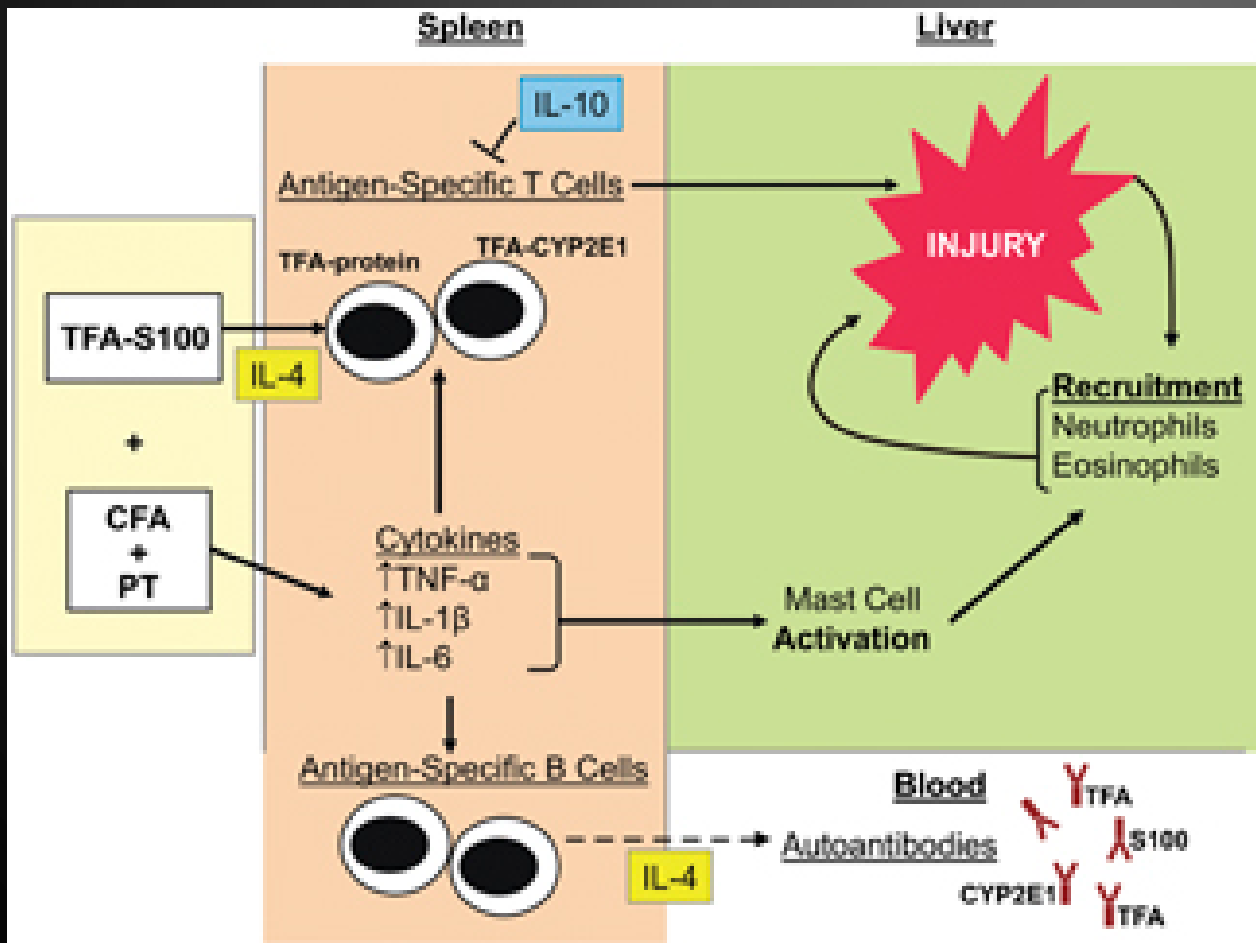
**WHAT ARE THE ACCEPTED MECHANISMS OF
HEPATOTOXICITY FROM SEVOFLURANE AND
METHODS FOR CONFIRMATION OF THE DIAGNOSIS.**

CHARACTERISTICS OF IMMUNE-MEDIATED HEPATOTOXICITY FROM ANESTHETICS

- FEMALE
- URTICARIA OR SKIN RASH, SUGGESTING A DRUG ALLERGY
- EOSINOPHILIA
- SERUM AUTOANTIBODIES TO CYTOCHROME P450 2E1 (CYP2E1)
- SERUM ANTI-DRUG METABOLITE (TFA)
- LIVER INFLAMMATION ± FULMINANT LIVER FAILURE
- MILD OR MODERATE INCREASES IN LIVER ENZYMES
- FAMILY HISTORY OF AUTOIMMUNE DISEASE

WE NOW KNOW THIS.....

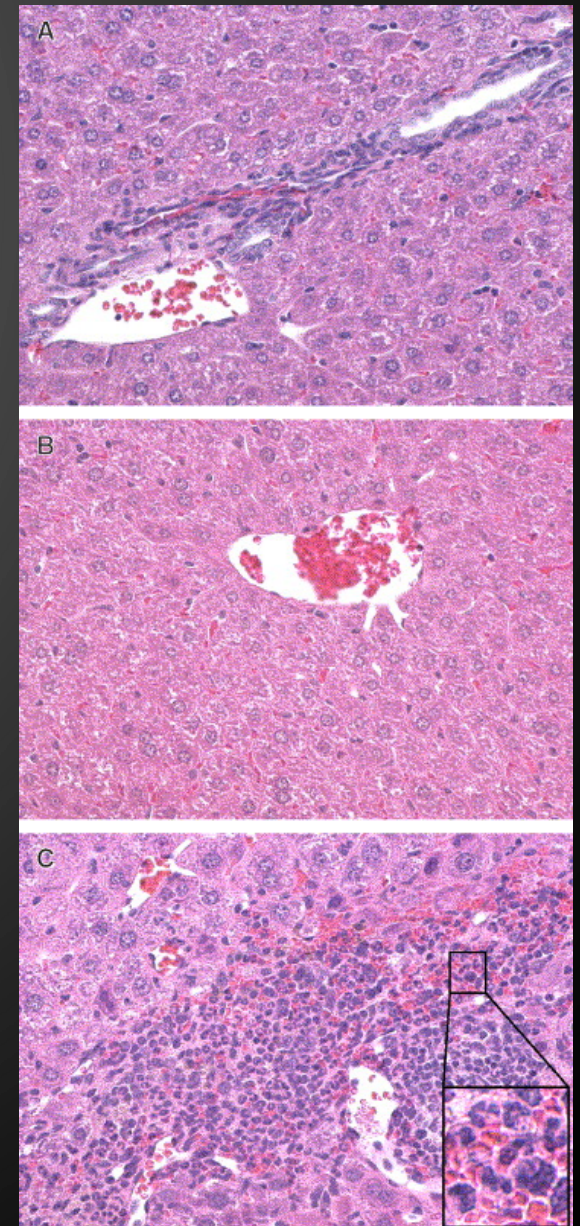




**CFA
(viral
Mimic)**

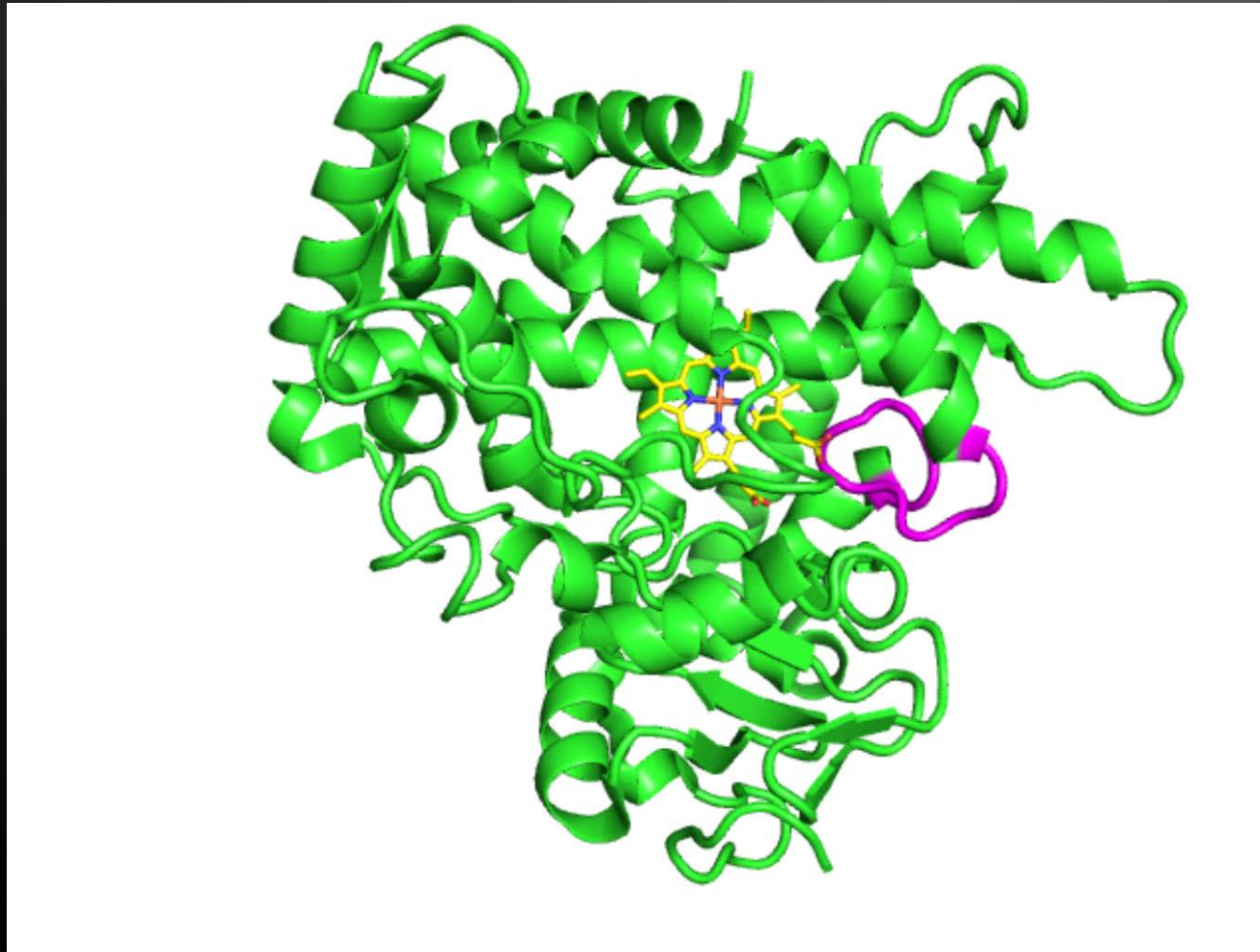
**S100
(liver
Proteins)**

**CFA
+
TFA-S100**



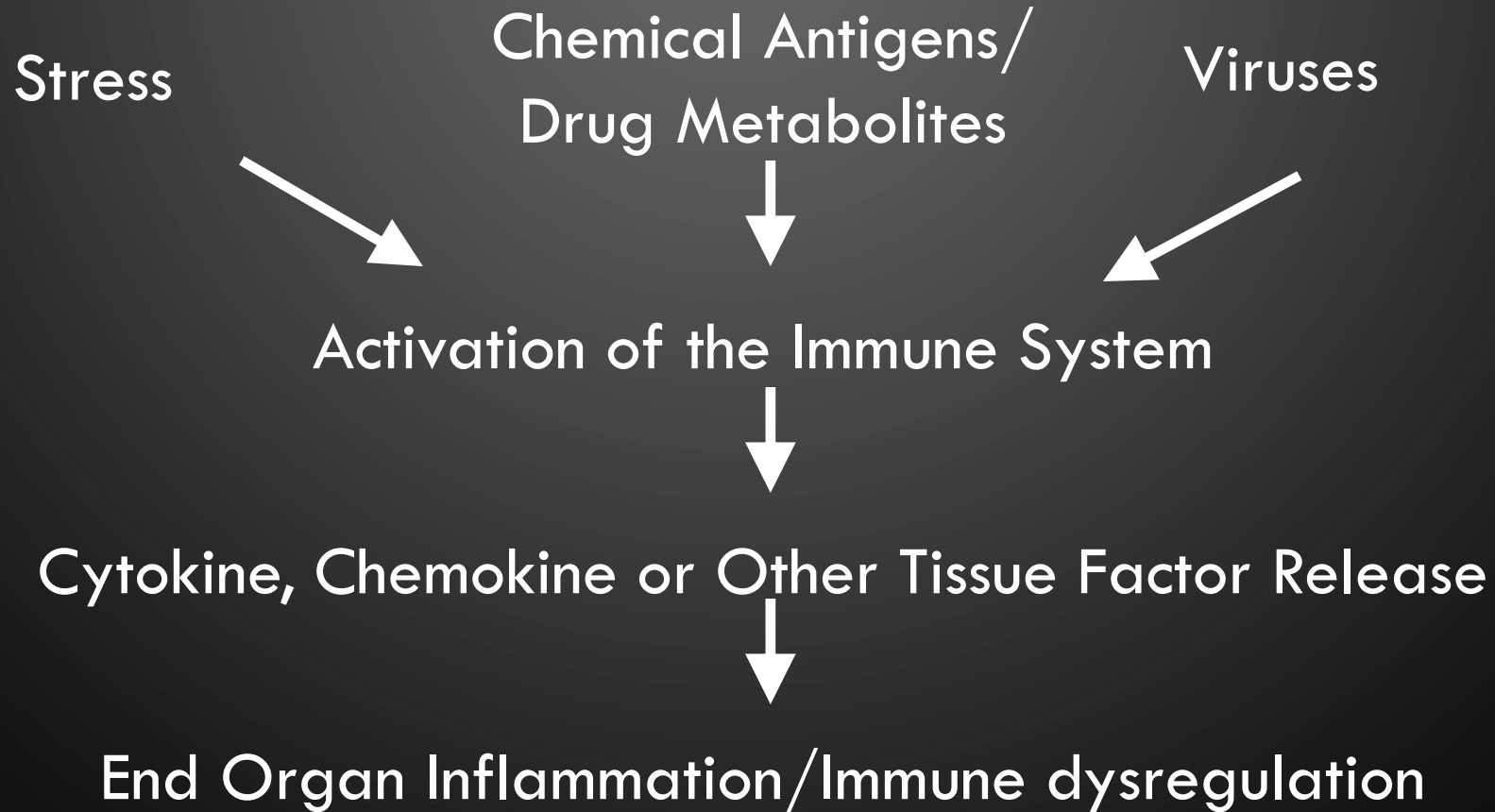
WE ALSO KNOW THIS.....

CYP2E1

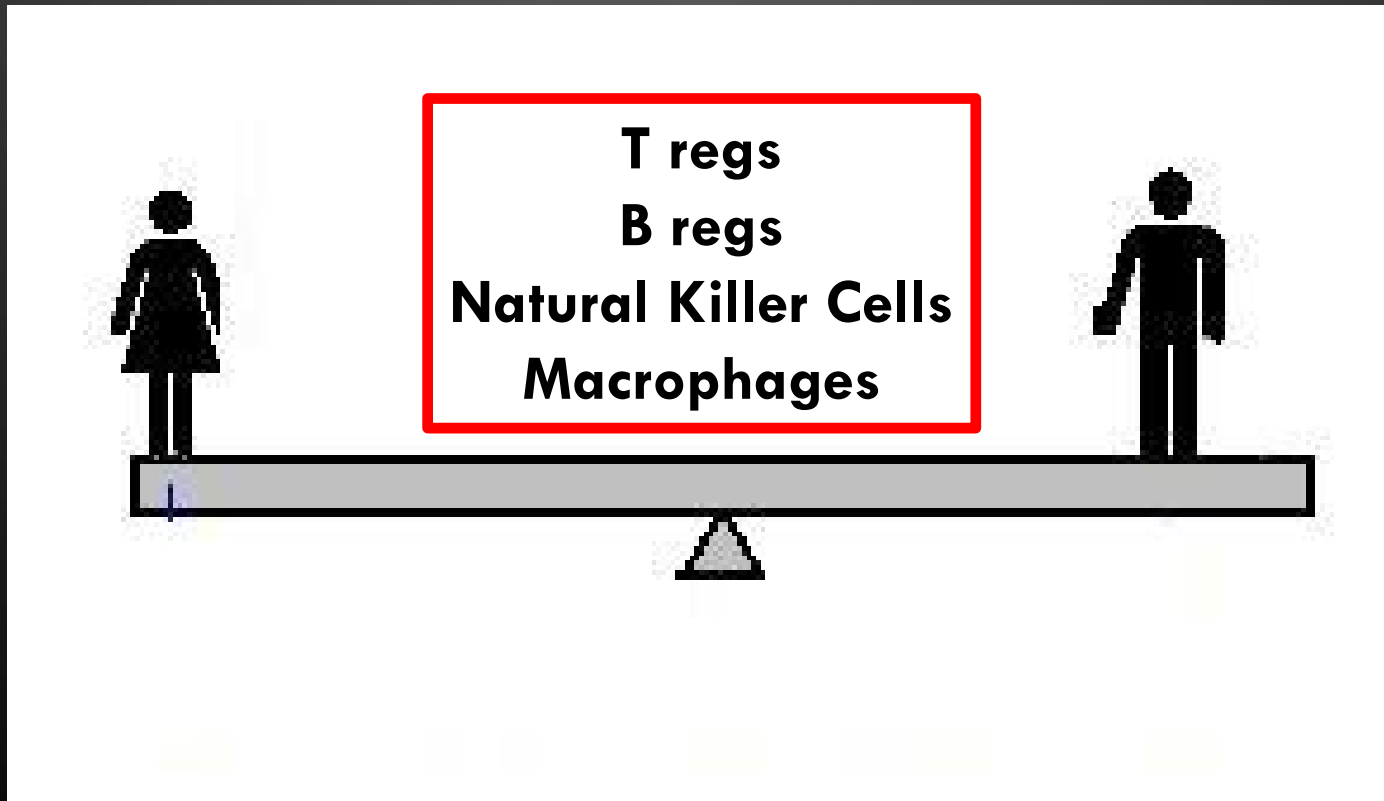


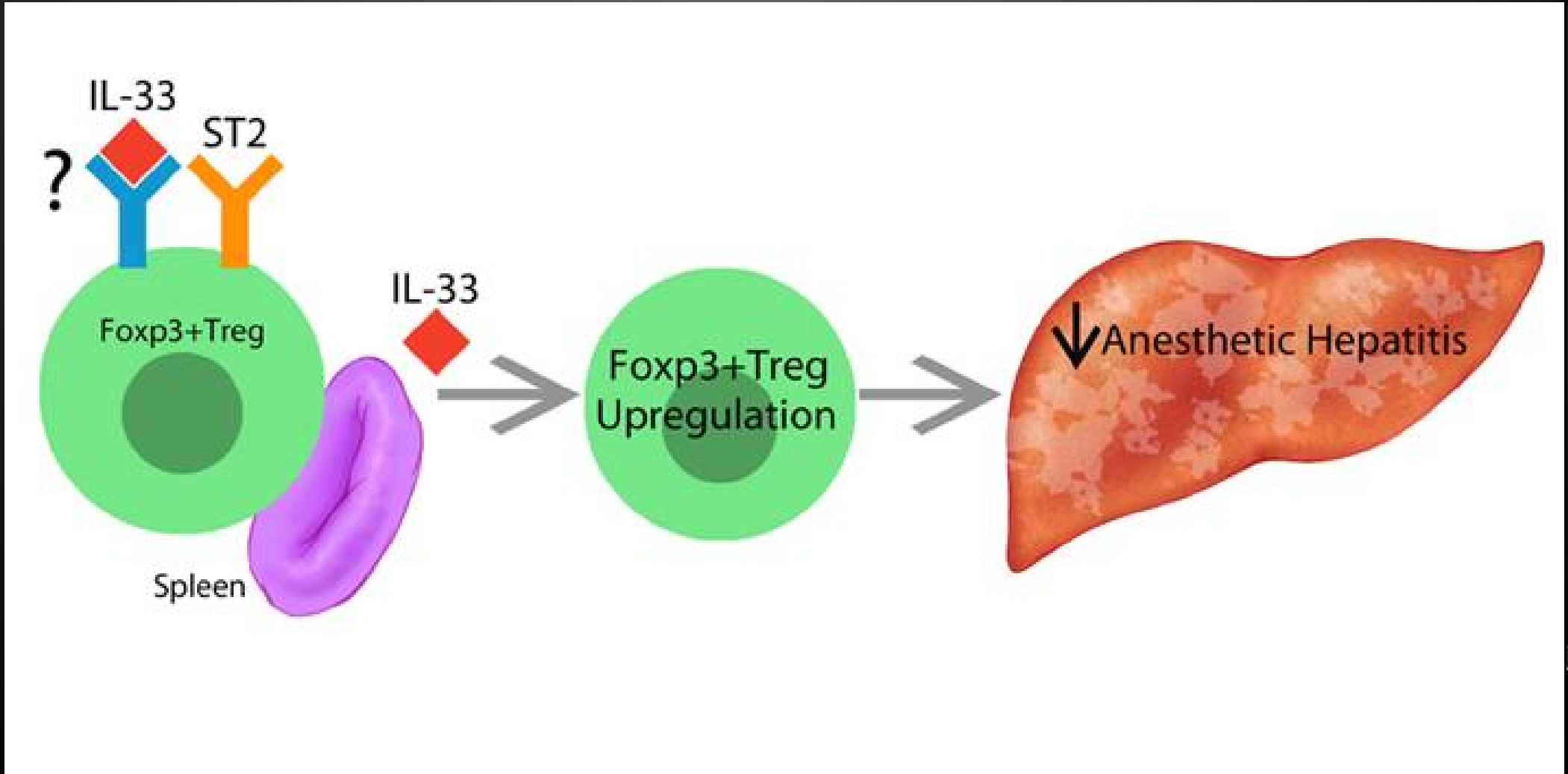
McCarthy E, et al., mSphere, 2018

SUMMARY: IMMUNE-MEDIATED HEPATOTOXICITY

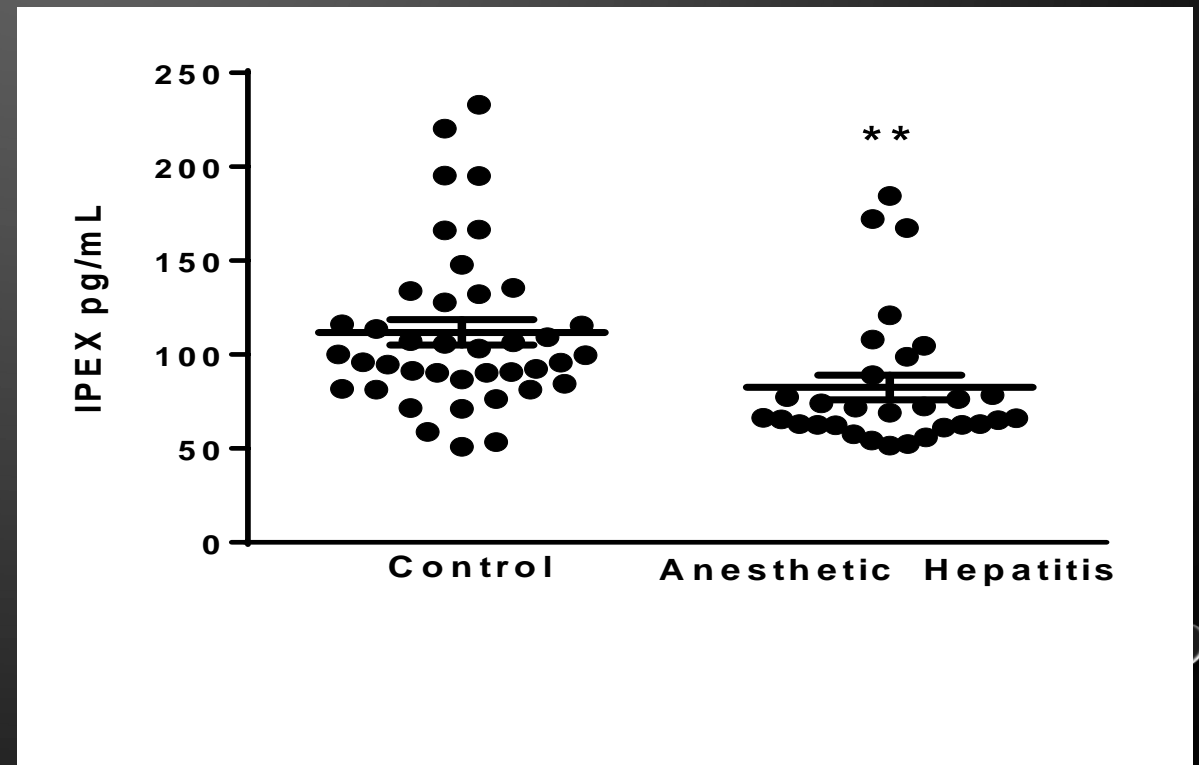
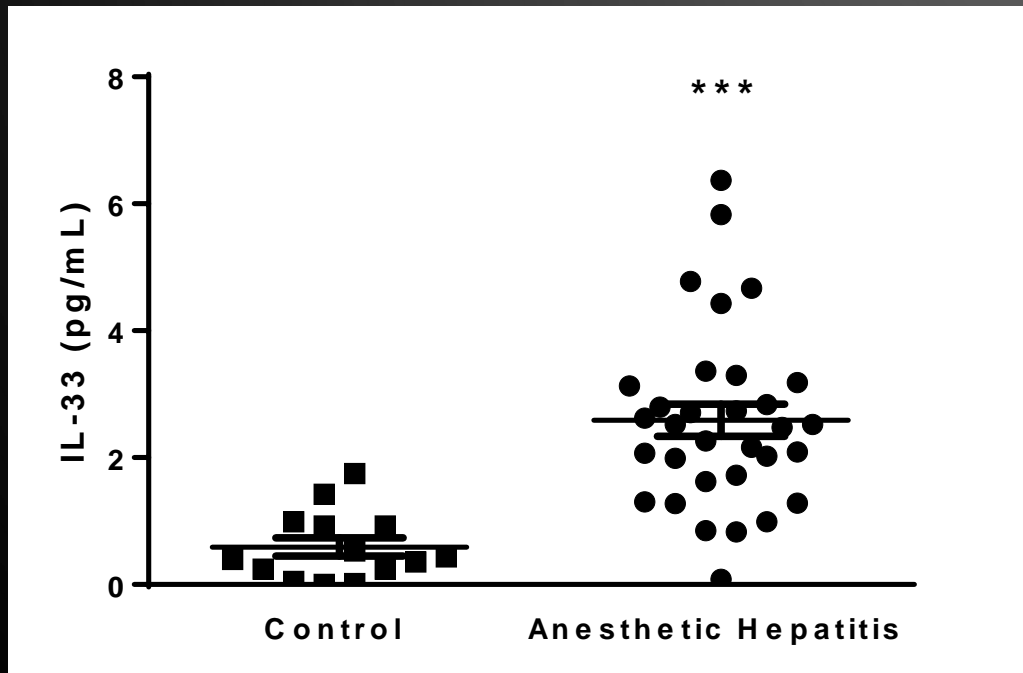


COULD REGULATORY CELLS BE UTILIZED TO REDUCE IMMUNE RESPONSES IN SEVOFLURANE OR DESFLURANE HEPATOTOXICITY?

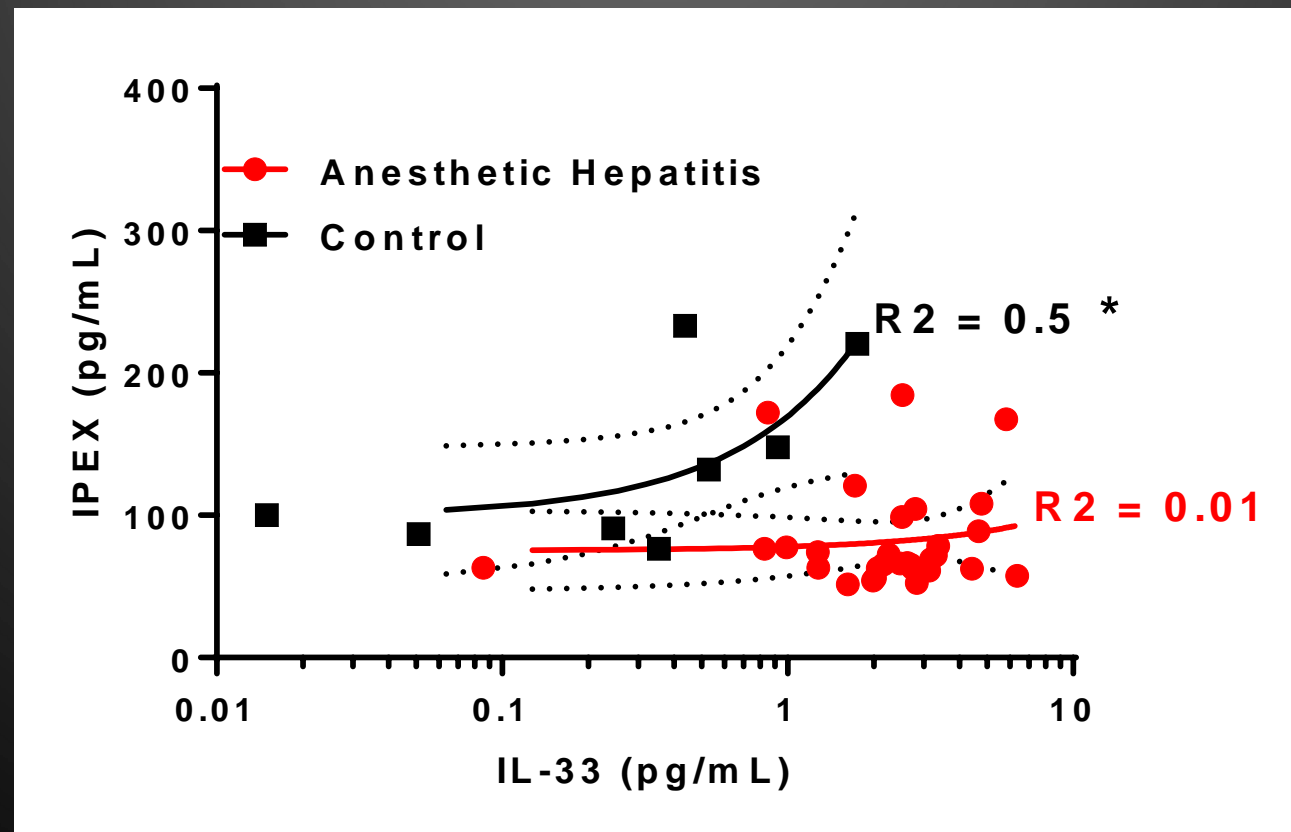




IN ANESTHETIC HEPATOTOXICITY, IL-33 IS UPREGULATED WHILE IPEX IS DOWN-REGULATED



DYSREGULATED IL-33- IPEX EXPRESSION PROMOTES ANESTHETIC HEPATOTOXICITY



**SUMMARY:
DEFICIENCY OF REGULATORY T CELLS INCREASES
HEPATOTOXICITY SEVERITY IN FEMALES**



The background is black with several translucent, reflective bubbles of various sizes scattered across the frame. The bubbles are most prominent in the top-left and bottom-right corners, with a few smaller ones in the top-right and bottom-left areas.

**WHAT ARE THE GAPS IN KNOWLEDGE
SURROUNDING THE PREVALENCE AND
MECHANISMS OF SEVOFLURANE HEPATOTOXICITY
AND CAN WE BEGIN TO DISCUSS HOW THEY MAY
BE ADDRESSED**

**WHAT IS THE INCIDENCE OR PREVALENCE OF
PERIOPERATIVE LIVER INJURY?**

**WHAT IS THE INCIDENCE OR PREVALENCE OF
SEVOFLURANE HEPATOTOXICITY?**

**IS SEVOFLURANE HEPATOTOXICITY MORE SEVERE
IN FEMALES?**

**COULD T REGULATORY CELL MARKERS BE
DEVELOPED AS CHECKPOINTS FOR SEVOFLURANE
OR DESFLURANE HEPATOTOXICITY ?**

Drug-induced hepatotoxicity: incidence of abnormal liver function tests consistent with volatile anaesthetic hepatitis in trauma patients

Jonathan Lin, David Moore, Brad Hockey, Rachel Di Lernia, Alexandra Gorelik, Danny Liew and Amanda Nicoll

Forty-seven (3%) of 1556 patients had abnormal post-operative liver biochemistry potentially attributable to volatile anaesthetic.

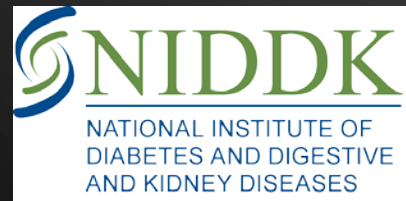
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CYP2E1 Epitope

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- Joonhee Cho, MD MS



REGULATORY T CELLS

- ZHAOXIA LI, MD, PHD
- JOONHEE CHO, MD MS
- LINA KIM, MS

Regulatory B cells

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- Maeva Nyandjo

