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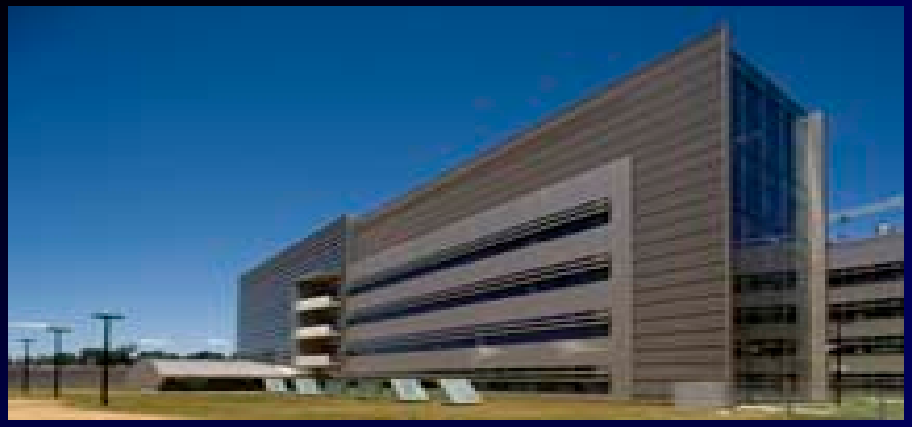

Drug-induced immune injuries

Why these are important

March 19, 2015

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The views being presented are my own and not an official position of the FDA

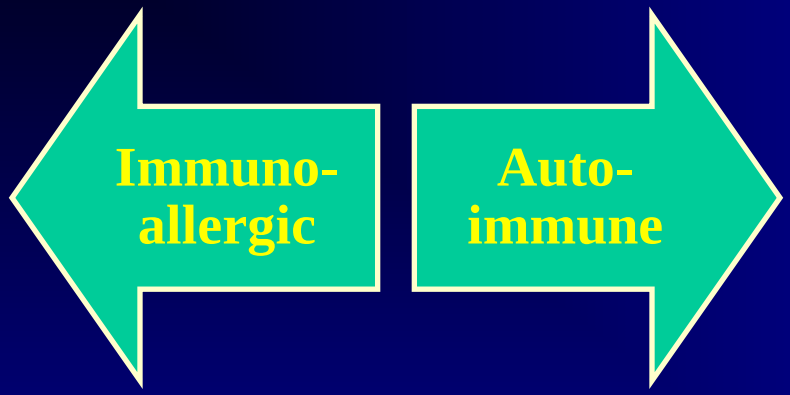
Overview of Presentation

- Drug-induced Immune Injury: Challenges in Definitions & Regulatory Implications
  - product labeling & risk management
- Drug-induced Autoimmunity & Autoimmune Hepatitis: Accounting for diverse phenotypes & mechanisms
  - susceptibility factors & markers
  - new cancer drugs with risk of DIAI & AIH
  - future directions in assessing drug causality

Immune Injury Caused by Therapeutic Drugs

Targets: drug-associated antigens or self

- Onset within 1-8 wks of treatment; can be as short as 1-2 days
- Multiple organs can be affected
- Multiple types of hypersensitivity
- Fever, rash, eosinophilia common in some forms
- Re-challenge has significant risk



Reaction Pathways

- Onset after prolonged treatment
- Sub-acute or chronic organ injury
- Characteristic range of affected organs can depend on the specific drug
- Characteristic autoantibody profiles for certain drugs, but many overlap

Drugs & Hypersensitivity Reactions*

FDA Postmarketing Safety Alerts: 1996-2014

Chlormezanone	**SJS/TEN**	***Withdrawal***
Lamotrigine	**SCAR**	***Boxed Warning***
	Aseptic Meningitis	***Warning***
Valdecoxib	**SCAR**	***Withdrawal***
Abarelix	**Immed Hypersens**	***Withdrawal***
Abacavir	**Multiorg Hypersens**	***Boxed Warning***
Carbamazepine	**SJS/TEN**	***Boxed Warning***
Omalizumab	**Anaphylaxis**	***Boxed Warning***
Phenytoin	**SJS/TEN/DRESS**	***Modified Warning***
Ansenapine	**Anaphylaxis**	***Warning***
Daptomycin	**Eosin Pneumonia**	***Warning***
Telaprevir	**SJS/TEN/DRESS**	***Boxed Warning***
Acetaminophen	**SJS/TEN/AGEP**	***Warning***
Ziprasidone	**SCAR/DRESS**	***Warning***
Benzoyl Peroxide, or Salicylate (Topicals)	**Immediate Hypersensitivity**	***OTC Communications***

*Partial list

Drug-induced Autoimmune Reactions

*FDA Approved Product Labels **

Minocycline	**AI Syndromes, AIH**	***Warnings***
Nitrofurantoin	**Hepatotoxicity, CAH**	***Warning***
Procainamide	**Lupus-like syndrome**	***Boxed Warning***
Hydralazine	**Lupus-like syndrome**	***Warning***
	Hypersensitive reactions	***Adverse Reactions***
Interferon β-1a	**AI Disorders, DILI**	***Warnings***
	Anaphylaxis	
Infliximab	**Hepatotoxicity, AIH**	***Warnings***
	Lupus –like syndrome	
	Hypersensitivity	
Metreleptin	**AI Disorders, AIH**	***Warnings***
	Hypersensitivity	
Ipilimumab	**Immune Mediated AR Hepatitis**	***Warnings***
Pembrolizumab	**Immune Mediated AR Hepatitis**	***Warnings***

*Partial list

Drug-induced Immune Injury
Regulatory Science Objectives

- Universal categorical criteria of reaction types needed
  - Should have practical utility for HCPs & patients
- Reliable risk assessment of drug in each individual required for optimal treatment
- Effective procedures to monitor patients and manage immune reactions
- Post-market surveillance strategies to tally & evaluate events
- Consistent AE descriptions & instructions to manage risk in product labels & other tools of communication

Immune Injury - *Challenge 1*

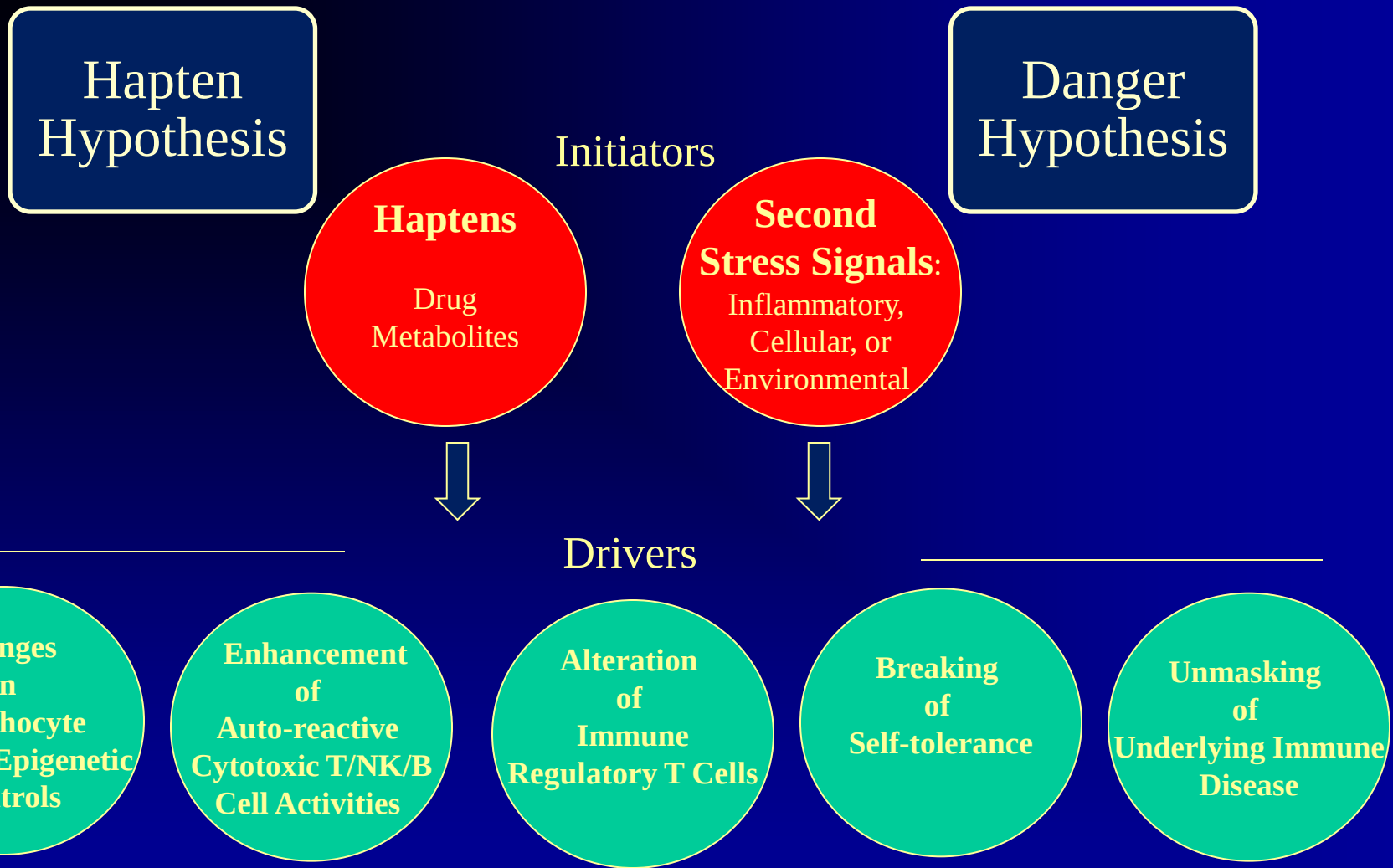
Multiple drug reactions associated with specific agents

- Some agents (e.g. minocycline) can induce immuno-allergic or autoimmune injuries (AI) in different individuals
- Variable temporal features, severity & affected organs are observed in different patients, even with same injury type
  - e.g. *minocycline* AI includes drug-induced lupus, AIH &/or autoimmune thyroiditis; *lamotrigine* hypersensitivity can affect different organs (skin, liver, meninges)
  - Inter-individual differences are hard to predict. Hypothesized co-determinants include:
    - HLA polymorphisms ± other genomic effects
    - Pre-existing Ag-specific auto-reactive T cell clones
    - Danger signals associated with different organs

Drug-Induced Autoimmune Injury
'Classical' Categories

- Drug-induced lupus erythematosus (DILE)
  - arthralgia, serositis, lymphadenopathy, subacute & chronic cutaneous SLE
- Rash
- Autoimmune Hepatitis (AIH)
- Colitis
- Endocrinopathies
  - thyroiditis, adrenal insufficiency, hypopituitarism

Drug-induced Autoimmune Injury



Drugs/biologics & risk for drug-induced lupus*

RISK LEVEL	DRUGS
HIGH (>1%)	Procainamide (20%), Hydralazine (5-10%)
MEDIUM (<1%)	Quinidine
LOW (<<1%)	Methyldopa, Acebutol, Captopril, Minocycline, INH, Chlorpromazine, Carbamazepine, Propylthiouracil, D-Penicillamine, Sulfasalazine
VERY LOW	Nitrofurantoin, Sulfasalazine, Clonidine, Minoxidil, Pindolol. Prazosin, Chlorprothixene, Phenelzine, Lithium Carbonate, Enalapril, Labetalol, Phenytoin, Ethosuximide, Primidone, Trimethadione, Phenylbutazone, Chlorthalidone, Hydrochorothiazide, Atorvastatin, Fluvastatin, Lovastatin, Simvastatin, Pravastatin, Infliximab, Etanarcept, Adalimumab, IFN-α, IFN-1β, Il-2

*** Representative (Incomplete) List; X. Xiao & C. Chang, J Autoimm. 2014; RL Rubin, Toxicol. 2005**

Drugs/biologics & risk for drug-induced AIH*

CAUSAL LINK	DRUGS
+++	Tienilic Acid, Oxyphenisatin, Methyldopa, Dihydralazine, Minocycline, Nitrofurantoin, Clometacine, Propylthiouracil, Diclofenac, INH, Infliximab, IFN-α, IFN-β
++	Fenofibrate Statins, Etanercept, Adalimumab, Indomethacin, Meloxicam, Terbenafine, Imatinib, Atomoxetine, Pemoline, Phenprocoumon, Doxycyline, Germander, Morinda Citrifolia

*** Representative (Incomplete) List; X. Xiao & C. Chang, J Autoimm. 2014; RL Rubin, Toxicol. 2005**

Autoimmune Injury – *Challenge 2*

Genetic susceptibility markers are limited

DILE

- HLA DR-4 (*Hydralazine*)
- Slow Acetylator Status (*Hydralazine*)
- Complement C-4 Null status (*Procainamide*)
- Female Gender (*Hydralazine*, *Procainamide*)
- HLA-DR0301 (*Sulfasalazine*)
- HLA-DQB1: Y30 (*Minocycline*)
- HLA-DR-2 or HLA-DR-4 (*Minocycline*)

AIH

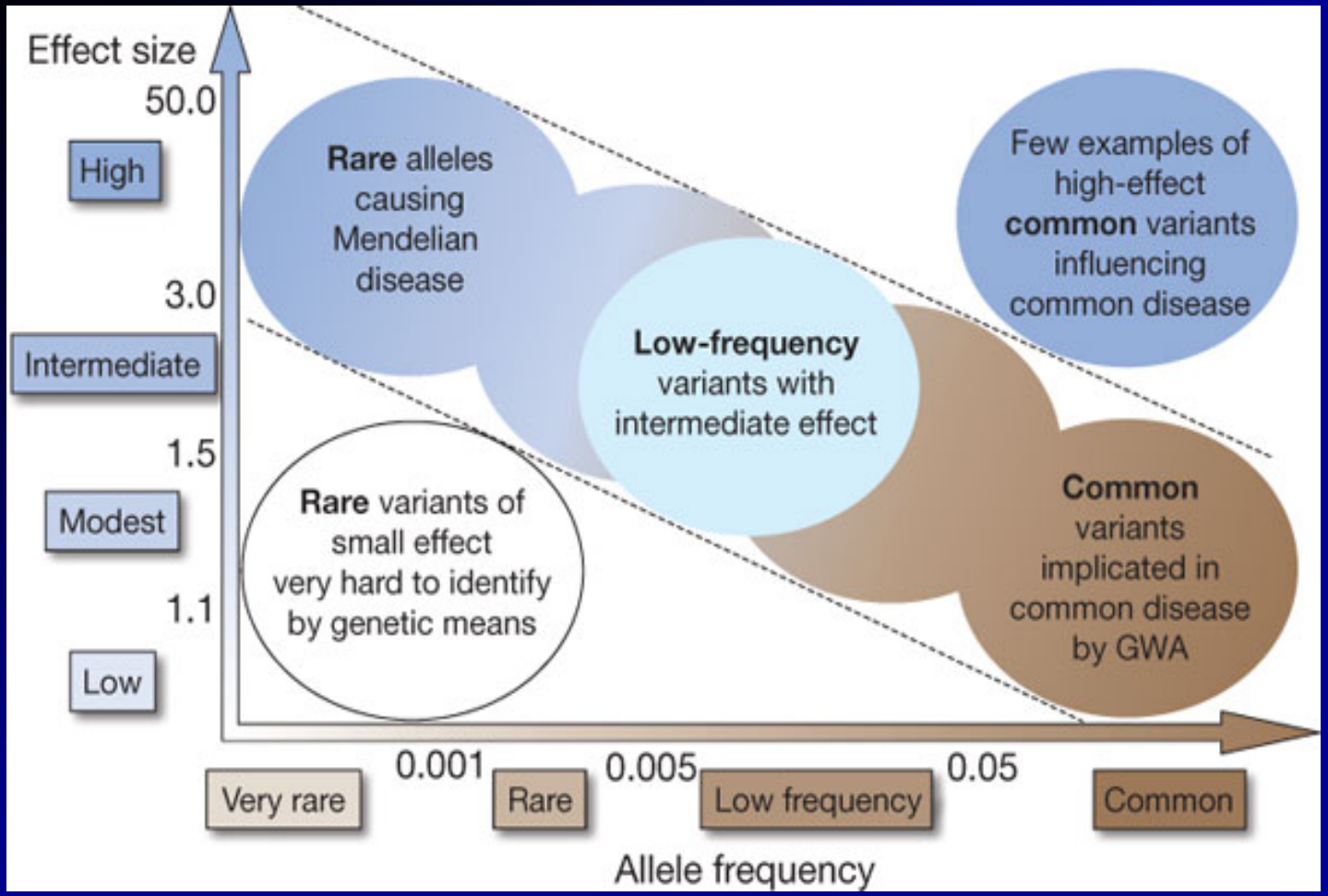
- A3, B8, DRB03*301, DQB1*0201, DR3 (Idiopathic AIH). Whether same risk markers for DIAIH, undefined.

Drug-induced Autoimmune Injury

Genetic susceptibility markers

- **Individual loci:** Effects on overall risk are small
- **Multiple loci:** Combinatorial effects on overall risk are undefined

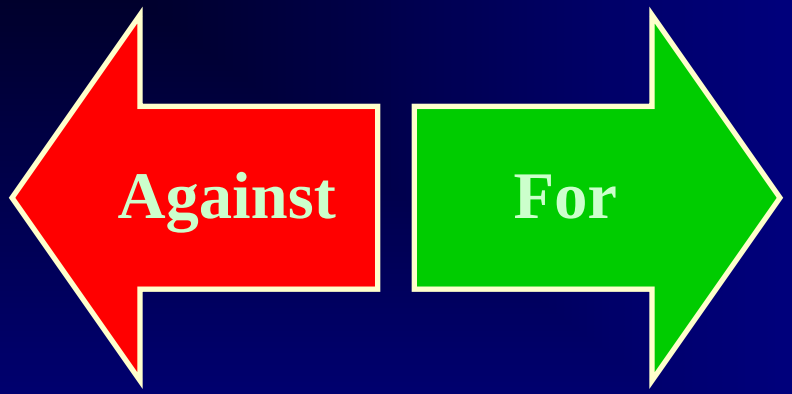
Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio)



TA Manolio *et al. Nature* 2009

When to pharmacogenetically screen?
Its all relative!

- Rare allele in key demographic group
- Test has low positive predictive value
- Result weakly impacts treatment benefits vs risks
- Other & inexpensive alternative treatments
- Low risk for severe HSR



- Common allele in key demographic group
- Test has high positive predictive value
- Result strongly impacts treatment benefits vs risks
- Few & expensive alternative treatments
- High risk for severe HSR

Autoantibodies - *Challenge 3*

Limitations as markers of drug-induced injury

- Why there are different antigenic cellular components & Ig isotypes among different auto-immune drug reactions is not understood

- High vs low titers of drug-induced autoantibodies does not predict clinical significance or severity of injury

Drug-Induced Autoantibodies & Injury

Drug	DILE Association	DILE Ag/Auto-Ab	AIH Association	AIH Ag/Auto-Ab	Other Rxn
Procainamide	++++	histone, histone-DNA, cardiolipin	-	N/A	
Hydralazine	++++	histone, ANCA histone-DNA	+	N/A	Vasculitis
Minocycline	++	ANA, pANCA, cardiolipin, ds-DNA, Ro/SSA	+++	ANA, pANCA	Thyroiditis
Nitrofurantoin	±	N/A	+++	ANA. SMA	
Methyldopa	++	ANA, histone	+++	ANA, SMA	Hemolytic Anemia
Infliximab	+	ds-DN A (IgM, IgG),cardiolipin	++	ANA, SMA ds-DNA	Vasculitis ILD Nephritis

Drug-Induced Autoantibodies & Injury

Drug	DILE Association	DILE Ag/Auto-Ab	AIH Association	AIH Ag/Auto-Ab	Other Rxn
Oxyphenisatin	-	-	+++	ANA, SMA	
Tienelic Acid	-	N/A	+++	CYP2C9 (LKM-2)	
Dihydralazine	+	ANA, MPO cardiolipin	+++	CYP1A2 (LM)	
Clometacine	-	N/A	++	ANA, SMA, DNA	
Ipilimumab	$\underline{+}$	N/A	+++		Colitis SCAR Other

Autoantibodies

Other Findings

- AutoAbs often detected in drug exposed patients w/o liver injury, e.g.
  - ***Procainamide:*** 80% develop ANA (dose-related)
  - ***Infliximab:*** 15% with RA develop α-ds-DNA Ab (IgM); 55% with IBD develop ANA, most after 1 or 2 infusions
- Some drug-specific autoimmune rxns associated with characteristic autoAb signatures, e.g.
  - ***Halothane:*** α-LKM-1 (CYP-2D6); ***Tienelic Acid:*** α-LKM-2 (CYP-2C9), ***Dihydralazine:*** α-LM (CYP1A2); ***Iproniazid:*** α-M6, ***Minocycline & Propylthiouracil:*** pANCA (MPO)
- Checkpoint inhibitor-induced autoimmune rxns not consistently tied to characteristic auto-Abs. Predictive tests of autoreactive T cells that target normal organs so far not established.

Autoimmune Injury – *Challenge 4*

Predicting drug effects not mediated by autoantibodies

- Enhanced autoreactive T cells *(Procainamide ; Hydralazine)*
  - Mechanism: ↓ DNA methyltranferase - results in ↑[LFA-1, CD-70 & perforin] that ↑TH-2 cell actions
- Reduced apoptosis *(TNF inhibitors; Minocycline)*
  - Mechanism: Accumulation of cellular debris due to decreased removal of organ cells – results in autoimmunity
- ↑TH-2 cytokines [incl. Il-4, Il-5, Il-6, Il-10, Il-13]*(TNF inhibitors)*
- Increased infections *(TNF inhibitors)*
- Disruption of Central Tolerance *(Procainamide hydroxylamine)*
  - Mechanism: Metabolite blocks positive thymic selection of maturing T cells

Inducing Autoimmunity – *Challenge 5*
Use of checkpoint inhibitors for oncotherapy

- Inhibitors of CTLA-4, PD-1 and PD-1 ligands: Linked to high risk for autoimmune organ injuries mediated by 'souped-up' auto-reactive T & NK? cells
- Characteristic auto-Abs not identified to date
- Autoimmune injuries: colitis > SCAR, hepatitis/ALF, endocrine organs, nephritis & other organs with comparatively short latencies after treatment initiation
- Risk levels for life-threatening AEs sufficiently high for valuable assessment in clinical efficacy trials
- Predictors surrounding susceptibility factors in different organs for optimal patient treatment planning & risk management will require more study

Checkpoint Inhibitors

Post-market: Life-threatening autoimmune AEs

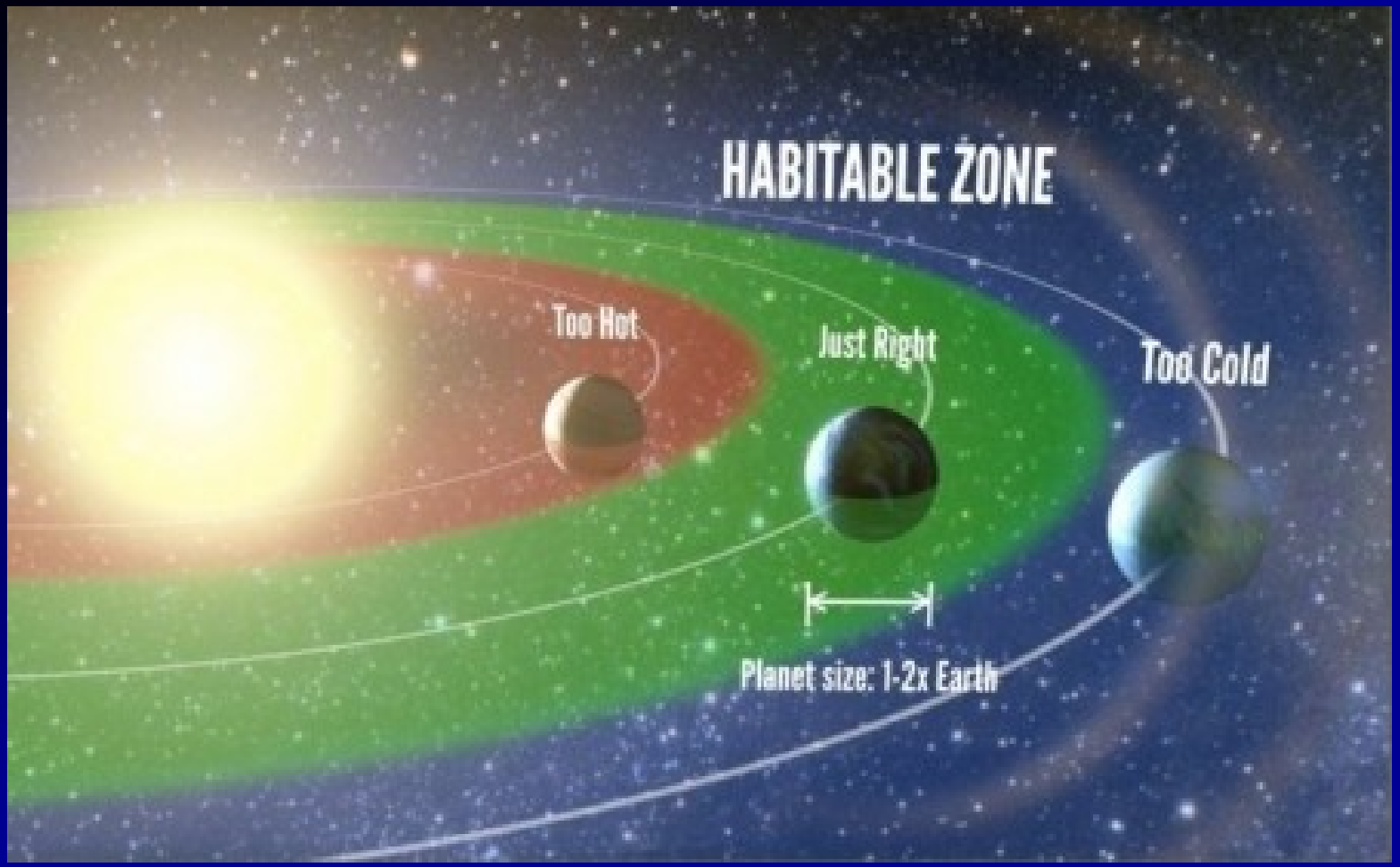
- In first 3 yrs of ipilimumab marketing – Serious AE reports submitted to FAERS (crude nos):
  - Colitis ~ 380 reports
    - Some reports of intestinal perforation
  - Autoimmune hepatitis &/or Hepatic Failure ~ 50 reports
    - Liver metastases (melanoma) often present
    - Onset after a small no of q3wk infusions
    - Some reports of fatal outcomes with rapidly deteriorating liver function

Checkpoint Inhibitors
Post-market AIH Cases of Interest: Example
60 yr old Male

- Melanoma metastases, brain & liver (2 lesions < 3cm, abd CT scan)
- Given 2 doses of *ipilimumab* (3mg/kg), 3 wks apart
- 3 wks after 2nd dose: Pt admitted with new onset weakness, diarrhea, tea colored urine & hepatic encephalopathy
  - ALT: 1704, AST: 3371, ALP: 886 (baseline: 84), T. Bili: 5.1, LDH, >2500, US: heterogeneous liver, IgG: 699, IgM: 72, ANA: 27 U (not elevated), Viral serology: unremarkable
  - Began po 80 mg Prednisone & Lactulose
- 2 d later: IV methylprednisolone 100 mg bid, N-AC & Rifaxamin; Serum liver tests worsened
- Pt died in liver failure 5 days after admission

Personalizing Use of Checkpoint Inhibitors

Aiming for an Autoimmune 'Goldilocks Zone'



Drug-Induced AIH
Future Assessment of Causality

- The broad range of clinical presentations & Rxn time-lines challenges the utility of a single algorithmic assessment of causality in suspected drug-induced auto-immunity or AIH
- Current RUCAM criteria of causality are not in alignment with a late onset, chronic AIH phenotype. Time /exposure effects, steroid responsiveness, histopathology & serology bear attention
- Matching specific auto-Abs with certain drug – induced injuries as an algorithmic criteria for causality may have utility, but requires case & control testing with validation studies
- In the future a set of RUCAM-like scales might be established that would be appropriate to align with particular drug-related AIH scenarios. Currently, expert opinion is a crucial tool in case assessment

FDA DILI website: www.fda.gov/Drugs/ScienceResearch/ResearchAreas