INTERACTIONS BETWEEN DRUG PROPERTIES AND HOST FACTORS: *ADAPTIVE MECHANISMS*

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INTRODUCTION

- Drug-induced liver injury (DILI) is a multifactorial disorder
- Certain drug properties are associated with severe clinical hepatotoxicity
- Drug-induced ALT elevations in <0.001% to 20% prescriptions
  - Most resolve
  - Non-progressive chronic liver enzyme elevation
  - Rare serious liver injury, acute liver failure
- Drug and host: two key players in determining DILI risks

- *What determines DILI risk, phenotypes and outcomes?*

DRUG-HOST INTERPLAY IN HUMAN HEPATOTOXICITY
- CONCEPT -

- Interplay of specific drug and host attributes
  - Cellular, molecular levels
  - Injury process
  - Inflammation
  - Immunological responses
  - Tissue regeneration
- Determine individual susceptibility to specific drug (or drug class), phenotype, and outcome

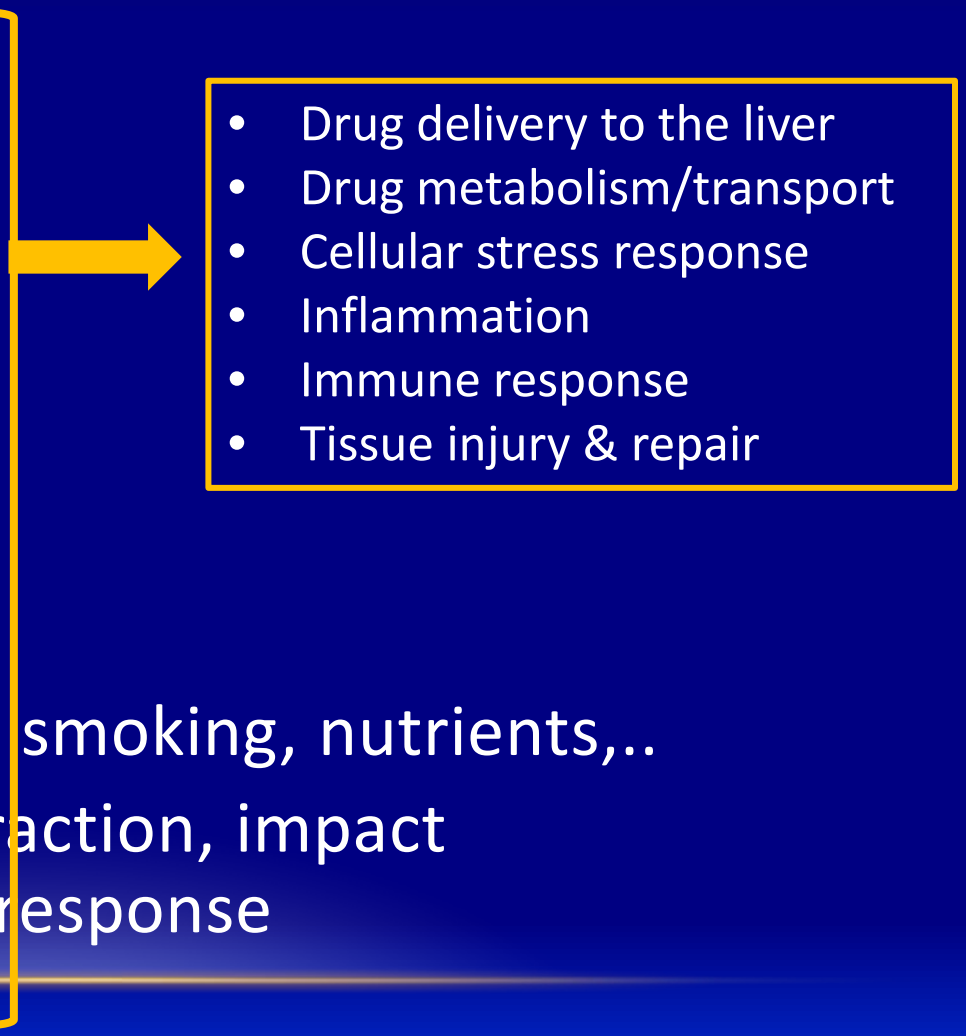
J Hep. 63: 503, 2015

DRUG'S MULTIFACETED PROPERTIES

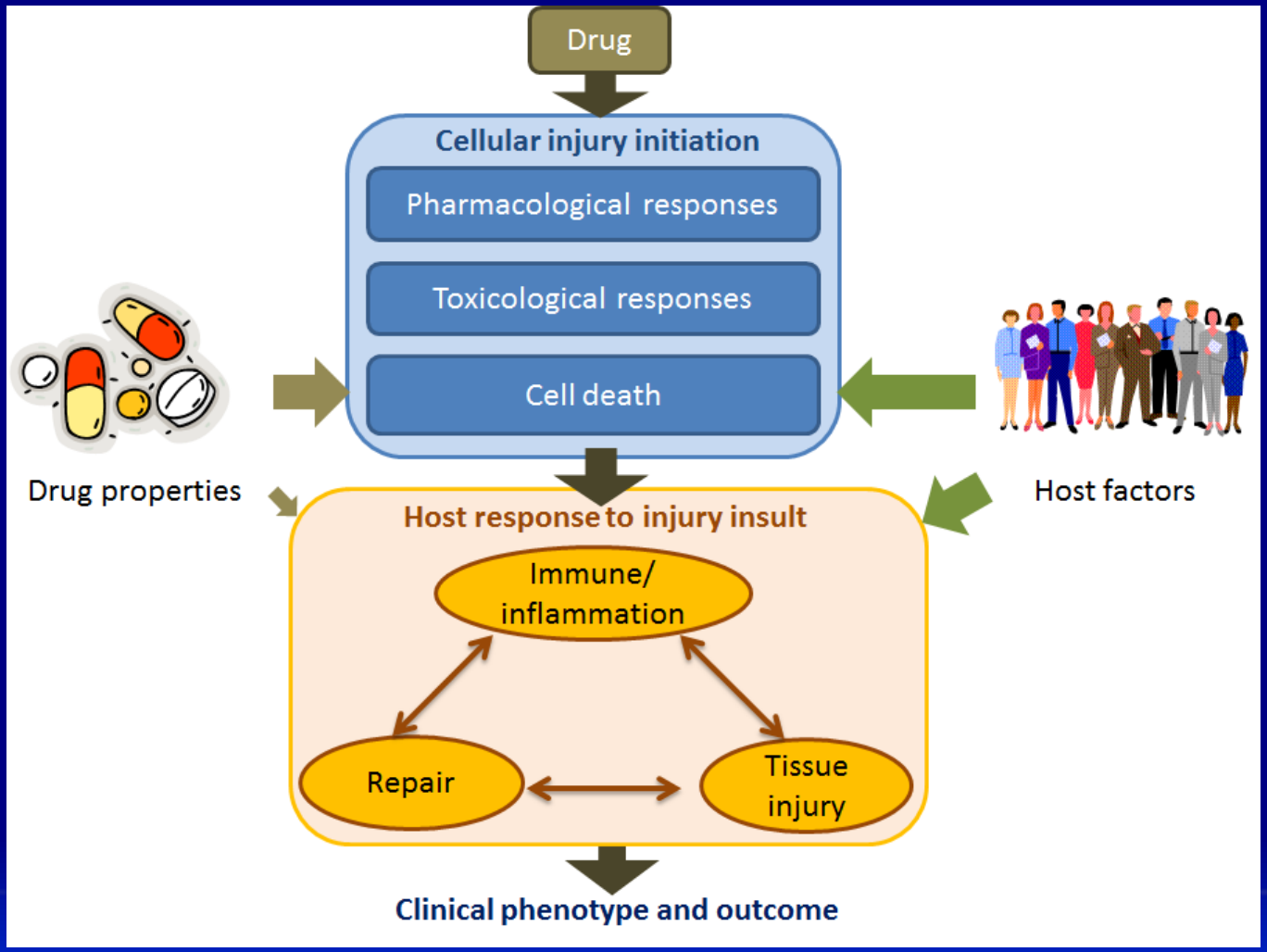
- Physiochemical: molecular weight, lipophilicity, solubility
- Pharmacological: dose, metabolism, elimination, protein binding
- Toxicological: reactive metabolite formation, mitochondrial toxicity, oxidative stress
- Targeted biophysiological: therapeutic class
- Off-target biophysiologial: cellular biology, injury/repair, immune response, visceral blood flow
- Immunological: some drugs induce specific immunoreactions

HOST FACTORS

- Genetic variants
- Race/ethnicity
- Age
- Gender
- Sex hormones
- Co-morbidity
- Co-medications
- Environmental: alcohol, smoking, nutrients,..
- Gut flora: gut-liver interaction, impact immune/inflammatory response



PRELIMINARY CONCEPTUAL FRAMEWORK FOR DRUG-HOST INTERACTION



J Hep. 63: 503, 2015 (Modified)

DEFINITION OF '*ADAPTATION*'

- Adaptation: diverse host responses to minimize toxic cellular insults, inflammation, and tissue injury, leading to the resolution of cellular stress, cellular dysfunction, inflammation and tissue damage.
  - Cellular stress responses
  - Inflammation/immune response
  - Tissue injury/repair
- Compromised adaptation results in clinically significant DILI and may lead to serious clinical outcomes

OUTLINE

- Drug-host interaction in:
  - Cellular stress responses
  - Inflammation/Immune response
  - Injury/Repair
- Future investigations of DILI drug-host interactions
  - Experimental
  - Clinical
  - Bi-directional translation in research network

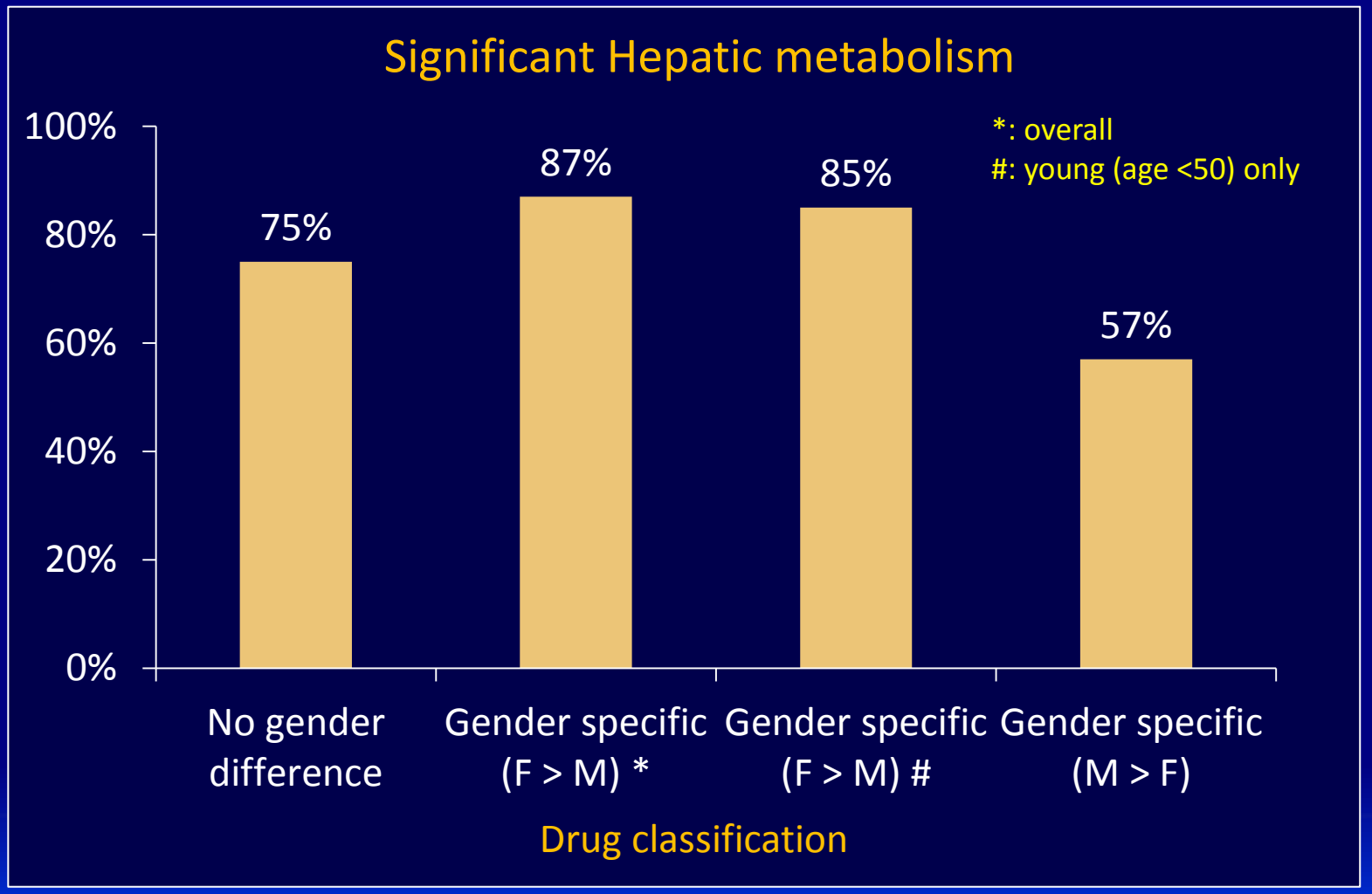
DRUG-HOST INTERACTION IN CELLULAR STRESS RESPONSE

DRUG-HOST INTERACTION IN CELLULAR STRESS RESPONSE

COVALENT BINDING-PROTEIN DAMAGE & REPAIR/DEGRADATION

Drug	Host
Extensive liver metabolism • Atorvastatin • Disulfiram • Terbinafine	**Alterations in drug metabolizing enzymes** • Female sex ↑ • Inducers/inhibitors ↑↓
Reactive metabolite formation • APAP • Isoniazid • Phenytoin • Carbamazepine	**Protein repair & degradation** • Thioredoxin • Thioredoxin reductace • Glutathione reductase • Methionine sulfoxide reductase • Lysosomal functions • Aging

INTERPLAY OF GENDER, AGE AND DRUG PROPERTIES IN DRUG-INDUCED LIVER INJURY: ANALYSIS OF ADVERSE EVENT REPORTING AT WHO VIGIBASE™



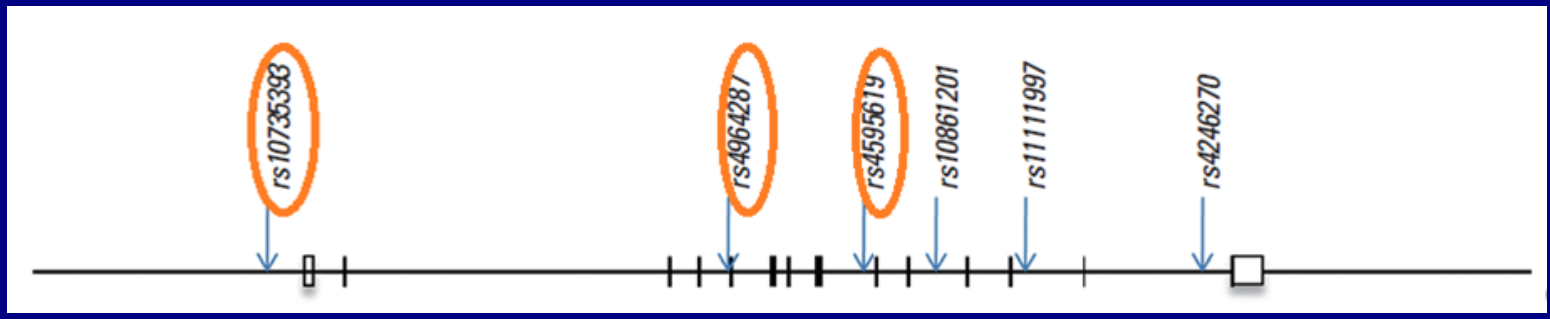
(DDW 2015)

Genetic Variations in *TXNRD1* as Potential Predictors of Drug-Induced Liver Injury

Jae-Woo Kwon,[1,2] Eun-Soon Shin,[3] Jong-Eun Lee,[3] Sang-Heon Kim,[4] Sang-Hoon Kim,[5] Young-Koo Jee,[6] Yoon-Keun Kim,[7] Hae-Sim Park,[8] Kyung-Up Min,[1,2] Heung-Woo Park,[1,2*]; The Adverse Drug Reaction Research Group in Korea

- 118 DILI cases
- Causal drugs: 57.6% anti-TB drugs, 18.6% antibiotics , 5.9% anti-epileptic drugs
- 7 SNPS of thioredoxin reductase 1 gene
- No associations with any of 7 SNPs
- Significant association with a TTA haplotype (below)

TXNRD1



Haplotype	Case n=118 (236 haplotypes)	Control n=120 (240 haplotypes)
TCG	127 (53.8%)	128 (53.3%)
TTA	73 (30.9%)	47 (19.6%)
GCA	34 (14.4%)	42 (17.5%)

Dysregulation of protein degradation pathways may mediate the liver injury and phospholipidosis associated with a cationic amphiphilic antibiotic drug

Merrie Mosedale [a], Hong Wu [b], C. Lisa Kurtz [a], Stephen P. Schmidt [b], Karissa Adkins [b,*,1], Alison H. Harrill [a,c,1]

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[c] University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA

Drug (PF-04287881)
7-day exposure

↓

Mouse diversity panel
(34 strains)

↓

Elevated serum ALT (88%)
Hepatocellular hypertrophy
Hepatocellular single cell necrosis
Kupffer cell vacuolation (phospholipidosis)

→ mRNA expression

- Resistant strains
- Susceptible strains

Differentially expressed pathways

- Protein ubiquitination pathway
- Drug transport, phospholipid metabolism, lysosomal function

DRUG-HOST INTERACTION IN CELLULAR STRESS RESPONSE

CELLULAR STRESS/ALTERED STRESS RESPONSE

Drug

Mitochondrial toxicity/oxidative stress

- Valproic acid
- APAP
- Troglitazone
- Flutamine
- Stavudine

ER stress

- Indomethacin
- Diclofenac
- Benzodiazepines
- Valproic acid
- APAP

Host

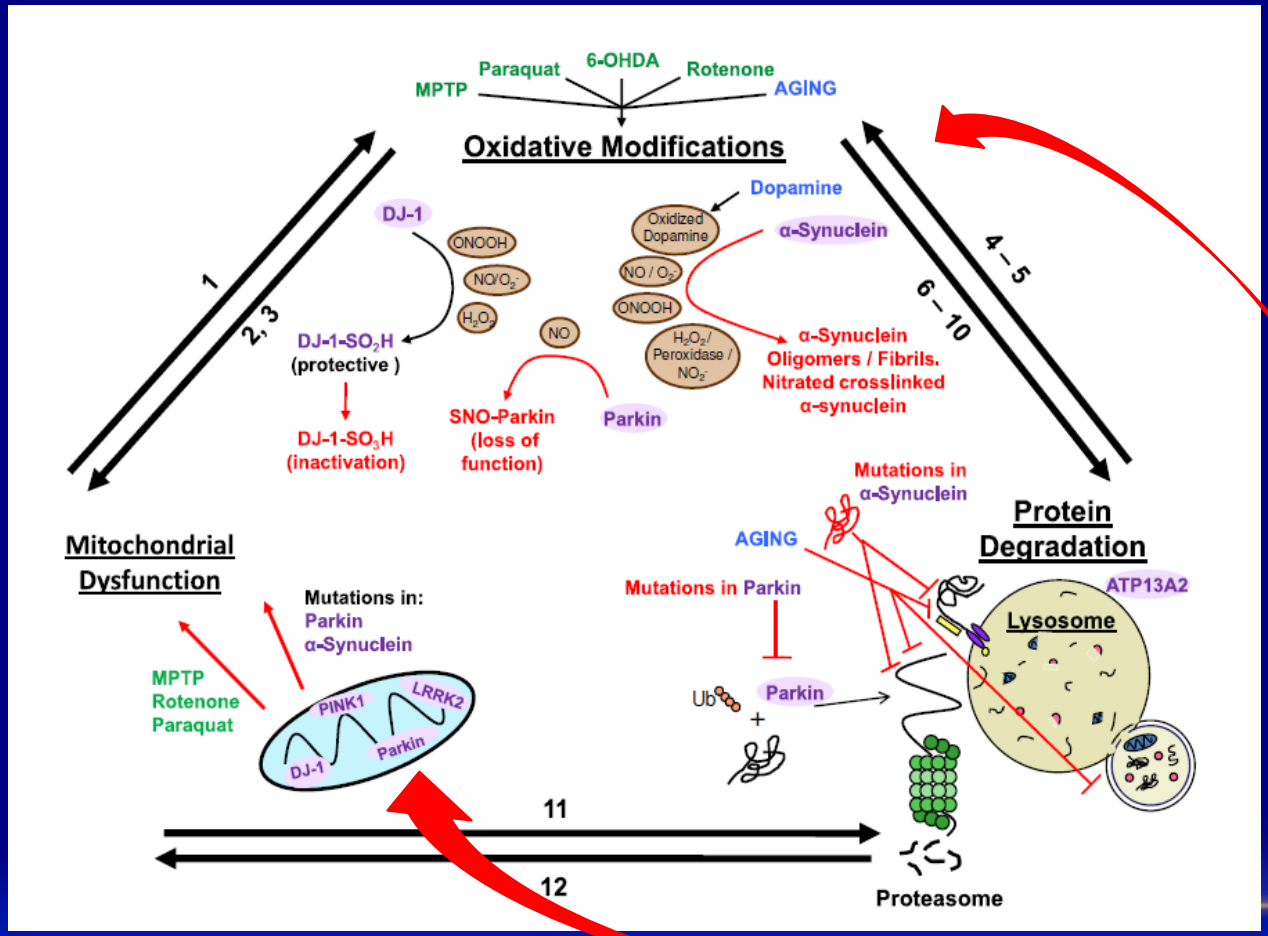
Altered stress responses

- Increased cellular oxidants
- Depleted antioxidants
- Fatty liver
- Impaired cellular protein repair/degradation
- Mitochondrial dysfunctions
- Impaired mt DNA repair

Altered ER stress response

- Pre-existing ER stress
- Medications to induce/ameliorate ER stress

RELATIONSHIP AMONG LYSOSOMAL DYSFUNCTION, OXIDATIVE STRESS, AND MITOCHONDRIAL DYSFUNCTION - A MODEL OF PARKINSON DISEASE



Impaired degradation of macromolecules and damaged organelle

(Molecular Neurodegradation 2009 4:24)

PHARMACOLOGICAL MODULATORS OF ER STRESS

Category	Drug	Mediator
mTOR inhibitors	Rapamycin	Autophagy ↑
		IRE1/JNK ↓
Chemical chaperones	4-PBA	GRP78 ↓, CHOP ↓
	TUDCA	Calcium efflux ↓
		eIF2α ↓, CHOP ↓
AMPK activators	Metformin	AMPK ↑
		AMPK ↑, PPARδ ↑
		eIF2α ↓, JNK ↓, IRS-1 ↓
	Salicylate/Salsalate	AMPK ↑
	AICAR	AMPK ↑
GLP-1 receptor agonists and DPP-4 inhibitors	Exenatide	PKA ↑, ATF4 ↑, BiP ↑, Bcl2 ↑, JunB ↑, SERCA ↑, Autophagy ↑
	Vildagliptin	C/EBPβ ↓
	Gemigliptin	Akt/PERK/CHOP ↓, IRE1α/JNK-p38 ↓
PPARs agonists	Fenofibrate	IRE1α/XBP1/JNK ↓, AMPK ↑, eNOS ↑
	Pioglitazone	SERCA ↑, SCD1 ↑
	GW1516	AMPK ↑, ERK1/2 ↓
		Autophagy ↑
ARBs	Valsartan	PUMA ↓, GRP78 ↓
	Losartan	PLC-IP3-calcium ↓
	Olmesartan	GRP78 ↓, CHOP ↓
	Telmisartan	GRP78 ↓, CHOP ↓

Reporting frequency of liver events↓ in VigiBase™

APAP, INH, VA

Int. J. Mol. Sci. 2016, 17, 192

DRUG-HOST INTERACTION IN INFLAMMATION & IMMUNE RESPONSE

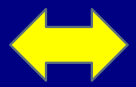
DRUG-HOST INTERACTION IN INFLAMMATION/IMMUNE RESPONSE

Hepatitis

- Ibuprofen
- Isoniazid
- ketoconazole

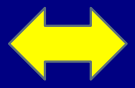
Pro/anti-inflammatory

- Genetic variants (IL-4, IL-10, IL-6, ..)
- Sex hormones (E2, P4, ..)
- Co-medications
- Altered microbiome
- Intestinal disease (hepatic LPS influx↑)
- Obesity



Immune-medicated

- Trimethoprim/sulfa-methoxazole
- Ciprofloxacin
- Halothane
- Amodiaquine



Immune response

- HLA variants
- Gender
- Sex hormones
- Immunomodulators
- Immunosuppressants

DRUG-HOST INTERACTION IN TISSUE INJURY & REPAIR

DRUG-HOST INTERACTION IN INJURY/REPAIR

Drug

Host

Hepatocyte necrosis

- APAP
- Diclofenac
- Flutamine

Apoptosis vs. necrosis

- Female sex → apoptosis?
- Impaired cellular energy supply → necrosis?

Altered tissue repair

- Aging ↓
- Histone acetylase / de-acetylase (Valproate, hydralazine deriv.) ↓
- ↓ FXR (reduced bile acid pool) ↓
- Co-medications ↓↑

Cholestatic injury

- Methyltestosterone
- Amoxicillin/Clavulanate
- Clarithromycin
- Azithromycin

Cholangiocyte injury/repair

- Male gender ?
- Estrogens?

FUTURE INVESTIGATIONS OF DRUG-HOST INTERACTIONS IN DILI

EXPERIMENTAL INVESTIGATIONS

Introduce biological variances to experimental designs (e.g., sex, sex hormones, age) to assess specific drug-host interactions

- Established DILI mouse models
- Human primary hepatocytes
- Engineered human liver models
- Organs-on-a-chip
- Induced pluripotent stem cells

PRECLINICAL RESEARCH FUNDED BY THE US NATIONAL INSTITUTES OF HEALTH CONSIDERED FEMALES AND MALES

COMMENT

ILLUSTRATION BY KATE SCOTT

NIH to balance sex in cell and animal studies

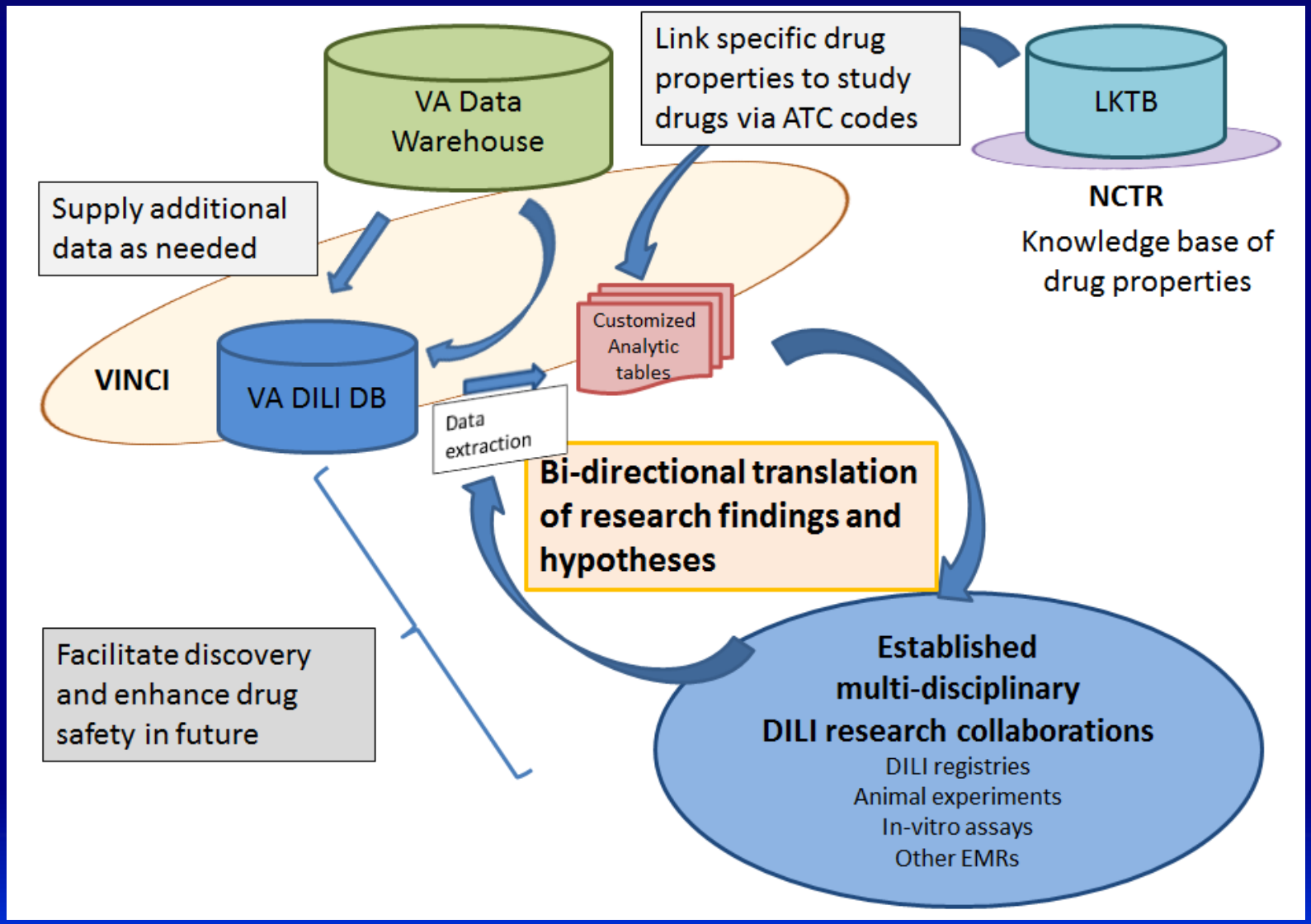
Janine A. Clayton and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

(Nature 509, 282-283, 2014)

CLINICAL INVESTIGATIONS

- Integration of drug properties in clinical/genetic analysis
- Further develop knowledge base of:
  - Drug properties (Liver Toxicity Knowledge Base, NCTR/FDA)
  - Degree of hepatotoxicity (DILIRank, Drug Discovery Today, *2016*)
  - Clinical phenotypes – unified resource?
- Implement new data-mining tools (e.g., topic modeling) - combine genetic and clinical data?
- Theoretical approach vs. unsupervised approach

DEVELOPMENT OF RESEARCH NETWORK SYNTHESIZING MULTIDISCIPLINARY RESEARCH FINDINGS IN DILI



VA HSRD: *HX001865-01A1 Suzuki*

SUMMARY

- Heterogeneity in risks, phenotypes, and outcomes of DILI may be explained by multilayered interplay of drug properties and host attributes in adaptive mechanisms
- Future investigations incorporating drug properties, biological variances, and their potential interactions in study designs will aid in better understanding of DILI pathobiology and facilitate future personalized drug safety

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Thank you for your attention