TRANSFORMING INSTITUTIONS
BY **GENDERING** CONTENTS
AND GAINING EQUALITY IN **RESEARCH**

IN SUPREMÆ DIGNITATIS 1343

GENERE E SCIENZA TRA RICERCA E INNOVAZIONE

IL CONTRIBUTO DEI PROGETTI EUROPEI DELLE UNIVERSITÀ ITALIANE

La prospettiva di genere nella ricerca farmacologica

Eleonora Da Pozzo

Claudia Martini

Dipartimento di Farmacia

Università di Pisa

DIPARTIMENTO FARMACIA

Evento formativo organizzato dal Progetto Europeo TRIGGER in collaborazione con la Conferenza Nazionale degli Organismi di Parità delle Università Italiane

5-6 APRILE 2017

TRIGGER

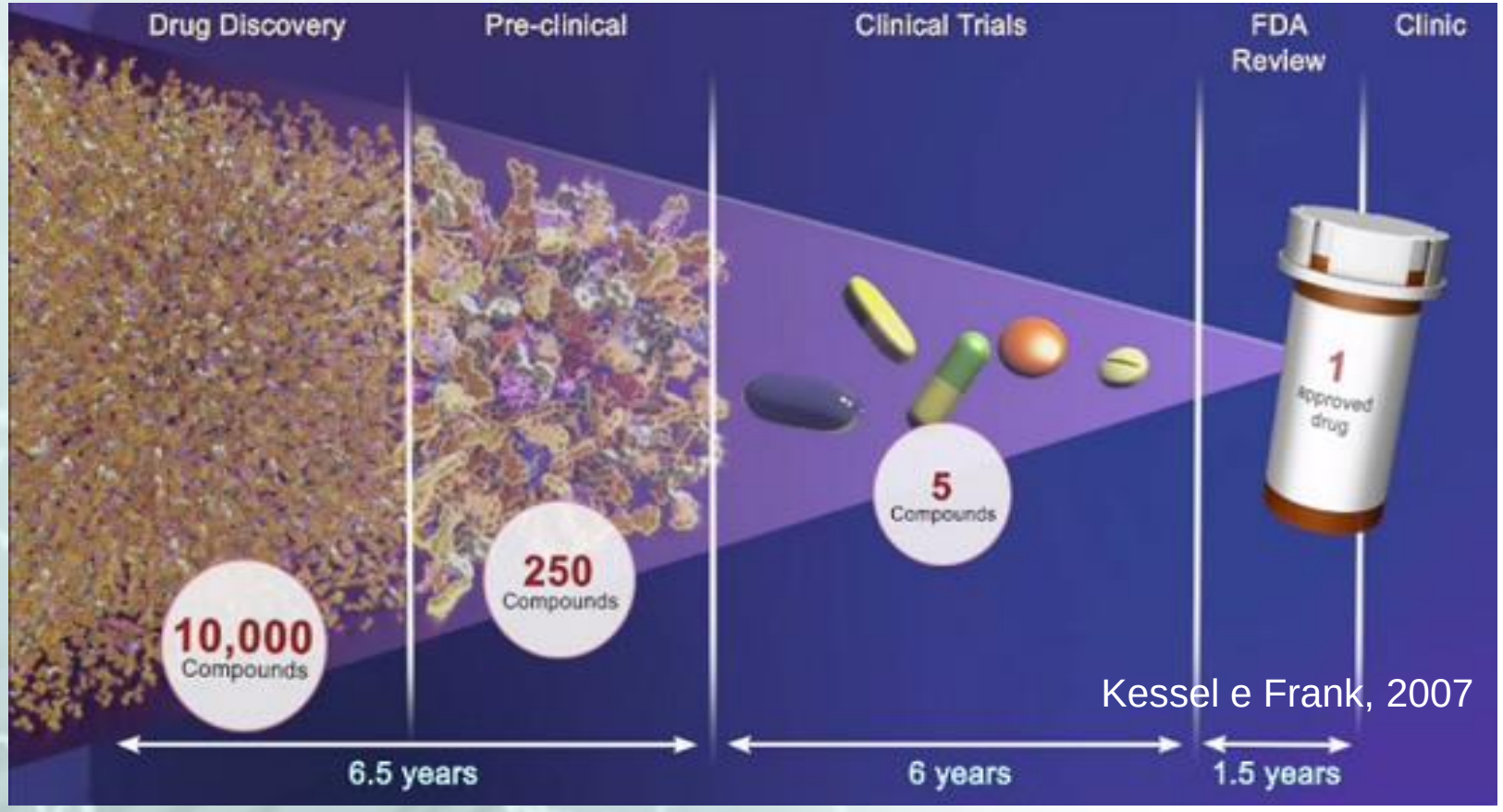
TRANSFORMING INSTITUTIONS BY **GENDERING** CONTENTS AND GAINING EQUALITY IN **RESEARCH**

Aims

TRIGGER aims to promote systemic interventions with an impact at all levels of research institutions. Integrated actions will be implemented in all universities to address the different aspects of gender inequality in science, covering:

- the working environment, culture (formal and informal) and the rules (explicit and tacit) of the research world;
- the scientific leadership;
- the content and methods of scientific research, with regard to the size and gender impacts (**gendering of research practices**).

Drug development



14 aa

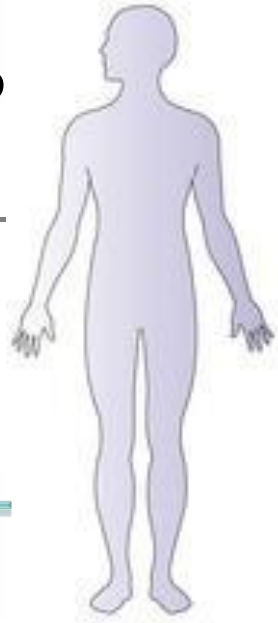
AIFA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 aa

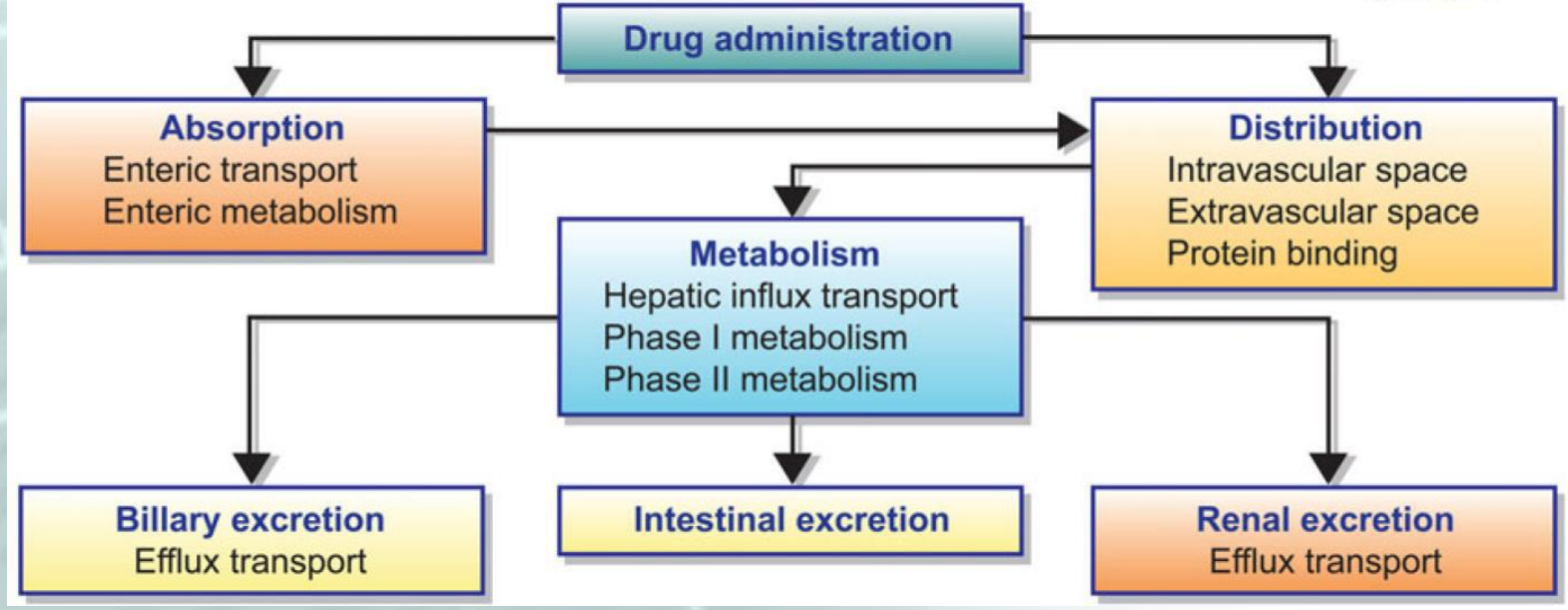
Why the potential drugs fail?

CLINICAL TRIAL



PK

- Absorption
- Distribution
- Metabolism
- Elimination



Among factors that cause interpatient variability in drug disposition and drug response…

Absorption:
- Slower GI motility and transit time
- Lower gastric acid secretion
- Less drug enzymes and transporters
- Lower absorption rates

Body composition:
- Lower BW, organ size and blood flow

Distribution:
- Greater body fat and lower body water content (Higher Vd for lipophilic drugs, Lower Vd for water-soluble drugs)
- Less α1-acid glycoprotein
- Lower cardiac output

Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

Other Factors:
- Differences in BW, cardiac output, plasma volume and regional blood flow

Metabolism

CYP Enzyme	Enzyme Activity
1A2	M > W
2A6	W > M
2B6	W > M
2C9	M = W
2C19	M = W
2D6	Mostly W > M
3A4	Mostly W > M
UDP-glucuronosyltransferases (UGTs)	M > W
Sulfotransferases	M > W
N-acetyltransferases	M < W
Methyltransferases	M > W

European Heart Journal (2015) **36**, 2677–2680

Physiologic reference values for drug distribution studies (and therefore dosage) are those related to **a person of 70 Kg** (Rescigno and Thakur, 1990).

Altezza	185 centimetri
Peso	70 Kg
Sesso	Femmina
Calcola BMI	
IL TUO BMI è	20.45 kg/m^2
ed è	Normopeso

But women generally have

- average weight and stature inferior to men
- higher percentage of fat
- minor gastric secretion and lower rate of gastric emptying
- reduced intestinal motility
- minor hepatic biotransformation
- reduced glomerular filtration rate

It is intuitive that the dose determined by clinical trial is NOT calibrated to the body of a woman.

The need to diversify medications or dosages between men and women becomes an essential element in therapeutic protocol.

Table 2 Sex-related differences in drug pharmacokinetic parameters

Drug class	Outcomes in females
Anaesthetics: propofol	Plasma propofol levels decline more rapidly in W at the end of infusion
Alcohol	Lower gastric alcohol dehydrogenase activity in W. Higher plasma concentrations in W as compared with M following an equivalent drink
Antidepressants	Higher AUC and C_{max} in W
H1-antihistamines	Slower metabolism and elimination in W
Antipsychotic drugs[a]	Higher plasma levels and Vd and lower Cl in W. Reduce the dosage in W or increase dosage in M. Olanzapine is more rapidly eliminated in M than in W
Aspirin	Bioavailability and plasma levels of aspirin and salicylate are higher in W possibly due to lower activity of aspirin esterase, larger Vd and lower Cl in W than in M. Differences disappear with OCP
Benzodiazepines	Lower initial plasma levels due to larger Vd, and possibly higher Cl, in W. OC reduce their Cl. Higher plasma levels of free diazepam in W
Beta-receptor agonists	W are less sensitive
Beta blockers: metoprolol, propranolol	W have higher plasma levels due to a smaller Vd and slower Cl. Drug exposure to metoprolol increases by OC
	Renal Cl of atenolol and metoprolol increases during P due to enhanced hepatic metabolism
Calcium channel blockers	Faster Cl of verapamil, and nifedipine in W. Increased bioavailability and decreased clearance of oral verapamil in W compared with M
Digoxin	W have higher serum digoxin concentrations due to reduced Vd and lower Cl. Drug Cl increases during P
Glucocorticoids	Oral Cl and Vd of prednisolone are higher in M. Prednisolone clearance was reduced by OC
Heparin	W had higher plasma levels and APTT values than M due to a lower Cl
Iron	Oral absorption of iron is greater in W than in M
Isosorbide mononitrate	W had significantly higher serum plasma concentrations compared with men, probably due to the lower body weights in females
Labetalol	Labetalol concentrations are 80% higher in W
Lidocaine	W has a larger Vd and may require a higher i.v. bolus dose than M. Higher free plasma levels in W receiving OCP, as alpha 1-acid glycoprotein levels are reduced by oestrogens
μ-opioid (OP3) receptor agonists[b]	Slower onset and offset of action in W
Neuromuscular blocking drugs[c]	Lower Vd, higher plasma levels, faster onset and prolonged duration in W due to the higher body fat and lower Vd
Paracetamol	Lower plasma levels and higher Cl in M due to increased activity of the glucuronidation pathway. OCP increase drug clearance
Procainamide	Plasma levels are higher (30%) in W due to a lower BMI and Vd
Quinidine	Plasma protein binding decreases during P
Selective serotonin reuptake inhibitors[d]	W present higher plasma levels, probably related to sex-related activity of various CYP enzymes
Statins	Higher plasma levels of lovastatin and simvastatin in W
Theophylline	Metabolism is faster and half-life is shorter in W than in M. Plasma protein binding decreases and the Vd increases during P
Torasemide	Higher C_{max} and lower Cl in W than in M
Tricyclic antidepressants	Free plasma concentrations of imipramine, clomipramine, and nortriptyline are higher during pregnancy
Verapamil	W display faster Cl of verapamil after i.v. administration probably due to the higher activity of CYP3A4 or lower activity of P-gp; lower Cl in W after oral administration
Vorapaxar	C_{max} and AUC are 30% higher in women but no dose adjustment is required
Warfarin	Higher free plasma levels in W
Zolpidem	Plasma levels and AUC are higher, and Cl is lower in W

References are presented in Supplementary material online, *Table S2*.

AUC, area under the curve; BMI, body mass index; Cl, clearance; C_{max}, peak plasma drug concentrations; CYP, cytochrome P450 isoforms; i.v., intravenous; M, men; OC, oral contraceptives; P, pregnancy; P-gp, P-glycoprotein; Vd, volume of distribution; W, women.

aOlanzapine, clozapine, pimozide, haloperidol.

bFentanyl, morphine, pentazocine, ramifentanil.

cAtracurium, pancuronium, rocuronium vecuronium.

dCitalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

Table 3 **Sex differences in drug pharmacodynamics**

Drug class	Outcomes
Alcohol	Higher vulnerability of W to acute and chronic complications of alcoholism
Anaesthetics: propofol	W are less sensitive to propofol. W wake up faster and require higher doses than M for the same effect
ACEIs	No mortality benefit in W with asymptomatic LV systolic dysfunction
Antidepressants	W respond better to selective serotonin/noradrenaline uptake inhibitors. M respond better to TCA and MAO inhibitors than W
Antipsychotic drugs	More effective in W. They require lower doses to control symptoms
Aspirin	Higher protective effect against stroke in W and against MI in M. Aspirin is more active in male platelets. Aspirin resistance is more frequent in W
Benzodiazepines	Diazepam impairs psychomotor skills to a greater extent in W. They should be initiated at lower dosages in W
Beta blockers	Greater reduction in blood pressure and heart rate in W treated with metoprolol and propranolol
Digoxin	W with HF have an increased risk of mortality on digoxin therapy. W require lower doses and lower plasma levels (< 0.8 ng/mL)
Glucocortioids	Females are more sensitive to the effects of methylprednisolone
Heparin	W had increased partial thromboplastin time, even after weight-adjusted dosing, suggesting an increased sensitivity
Ibuprofen	Less effective in W
Lidocaine	W may require a higher i.v. bolus doses to achieve the same plasma levels
μ-opioid (OP3) and κ* (OP2) receptor agonists[a]	W experience more pain and are more sensitive to opioid receptor agonists. M require 30–60% greater dose of morphine and κ receptor agonists for the same pain relief
Neuromuscular blocking drugs[b]	W are more sensitive and require lower (20–30%) doses than M due to a smaller Vd. If a rapid onset of action is required the dose should be increased in M
Paracetamol	W displayed lower Cl and Vd compared with M. OCP increase drug Cl
rt-PA	W with acute ischaemic stroke obtain more benefit from rt-PA than M
SSRIs[c]	W respond better than M, being the preferred therapy
Verapamil	Greater reduction in blood pressure and heart rate in W
Warfarin	W need less warfarin per week than M. Doses should be modified to reduce the risk of excessive anticoagulation in W
Zolpidem	The recommended initial dose is lower in W

References are presented in Supplementary material online, *Table S3*.

ACEIs, angiotensin-converting enzyme inhibitors; Cl, clearance; E, oestrogens; HF, heart failure; i.v., intravenous; LV, left ventricular; M, men; MAO, monoamine oxidase; MI, myocardial infarction; OCP, oral contraceptives; rt-PA, recombinant tissue plasminogen activator; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; Vd, volume of distribution; W, women.

[a]Alfentanyl, butorphanol*, fentanyl, morphine, nalbuphine* pentazocine*, remifentanyl.

[b]Atracurium, pancuronium, rocuronium and vecuronium.

[c]Citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

*refers to κ (OP2) receptor agonists.

Table 4 **Examples of sex differences in adverse drug reactions**

Drug class	Outcomes in females
Analgesic drugs	W report more adverse effects to perioperative analgesic drugs
Anaphylactic shock	Anaphylactic shock induced by neuromuscular blocking agents, hypnotics, opioids and benzodiazepines is more frequent in W
Anaesthetic drugs	W are more prone to ADR postoperatively
Angiotensin converting enzyme inhibitors	Dry cough is 2 to 3 times more frequent in W. No gender preference for angioedema/urticaria
Anorectics	Cardiac valvulopathy is more frequent in W exposed to phentermine, dexfenfluramine, or fenfluramine
Antiarrhythmic drugs	Higher risk of QT prolongation and TdP in W
Anticoagulants	More frequent and severe bleedings in W
H1-Antihistamines	W are more vulnerable to sedation and drowsiness
Antiplatelets	More frequent and severe bleedings in W
Antipsychotics	W present more extrapyramidal and anticholinergic effects and QTc prolongation. M reported more sexual problems
Aspirin	Increased risk of bleeding in W. More ulcer complications in M
Beta blockers	Enhanced BP lowering and heart rate reduction with metoprolol in W
Benzodiazepines	Diazepam impaired the psychomotor skills more in W than in M. Dependency is more frequent in W
Calcium channel blockers	Higher risk of oedema in W. Women taking OCP and diazepam during menstruation become relatively intoxicated
Digoxin	Higher mortality in W with HF. Digoxin plasma levels < 0.8 ng/mL are recommended in W
Diuretics	Higher rates of hospitalizations due to hypo-osmolarity, hypokalaemia and hyponatraemia and higher risk of arrhythmias in W
Drug-induced TdP	W have a longer QTc intervals and development of TdP more frequently than M
GPIIb/IIIa inhibitors	W experience more bleeding than M
Heparin	W present higher bleeding risk
Opioid receptor agonists	W experience more ADRs (nausea and vomiting, respiratory depression) despite smaller dose requirements for pain control
NSAIDs	M display a higher prevalence of ADRs than W
Paracetamol	Acute liver failure due to paracetamol overdose is more common in W
Procainamide	Systemic lupus erythematosus more common in W
Skin diseases	W > M (systemic lupus erythematosus and photosensitivity)
Statins	Myopathy is more frequent in older W with low body weight
Thiazides	More hyponatraemia and hypokalaemia in W
Thiazolidinediones	Double the risk of fractures among diabetic W, but not among M
Thrombolytics	Higher risk of bleeding and intracranial haemorrhagic in W
Unfractioned heparin	W develop higher plasma levels and higher bleeding risk
Zolpidem	To reduce the risk of morning-after activity impairment decrease the dose of zolpidem by 50% in W

References are presented in Supplementary material online, *Table S4*.

ACEIs, angiotensin-converting enzyme inhibitors; ADR, adverse drug reactions; BP, blood pressure; CV, cardiovascular; E: oestrogens; GP, glycoprotein; HF, heart failure; M, men; NSAIDs, non-steroidal anti-inflammatory drugs; OCP, oral contraceptives; QTc, corrected QT interval; TdP, torsades de pointes; W, women.

Women present a greater (1.5–1.7-fold) incidence of ADRs and they tend to be more severe than in men requiring more often hospital admissions.[7,23,26,36,276–282] Specifically, women have a higher risk of drug-induced torsades de pointes (TdP), hepatotoxicity and skin diseases, bleeding complications with anticoagulants, platelet antiaggregants and thrombolytics, electrolyte abnormalities with diuretics, myopathy with statins and cough, and rise in creatinine with ACEIs[12,17,26,36,42,44,61,185,186,237,263,276–282] (*Table 4*). This is in line with the evidence that 8 of 10 drugs dropped out from US market between 1997 and 2000 posed greater health risks for women than for men.[283]

EUROPEAN SOCIETY OF CARDIOLOGY®
European Heart Journal - Cardiovascular Pharmacotherapy (2017) **0**, 1–7
doi:10.1093/ehjcvp/pvw042

The reasons for the higher incidence of ADRs are unclear, but may result from (i) increased polypharmacy, as women consume more drugs than men, including over-the-counter medications and herbal remedies, which increases the risk of ADRs from drug–drug interactions[11,36]; (ii) differences in prescribing guideline-based drug therapy[2]; (iii) sex-related differences in PD (alterations in drug-target expression and/or in signal transduction pathways), immunological and hormonal factors.[26] However, sex-related differences can be explained simply because women present higher drug plasma levels than men due to lower clearance and/or smaller Vd and if doses are not corrected for body weight, women are more frequently overdosed than men.[18,19]

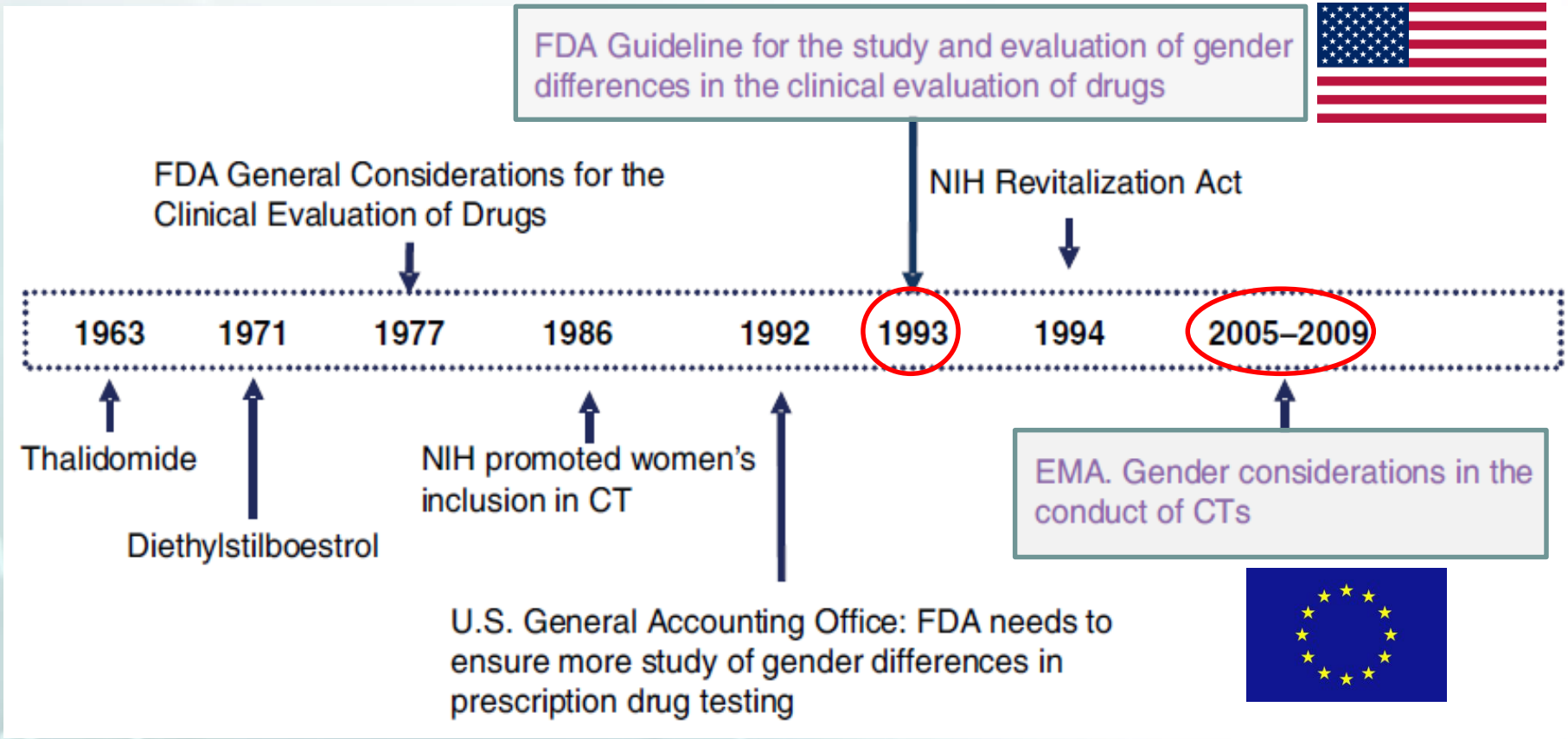
Why?

Unfortunately, many of today drugs taken by women have not been or partially tested on the female population due to multiple reasons.

To prefer the uniformity of the sample to the gender translational of the result.

To avoid (i) the risk of exposing a childbearing age woman to no known effects, also in view of future pregnancies, and (ii) the risk, if it is presented pregnancy during the study, to expose the fetus to effects not known.

To avoid monthly hormone variability that makes females a more problematic model.



Glob Health Action 2014, **7**: 25484 - http://dx.doi.org/10.3402/gha.v7.25484

Developmental Biology

SCOTT F. GILBERT

Topic Number Search

9. Early Development in Vertebrates: Birds and Mammals

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PREVIOUS :: NEXT

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w to Use Search
Literature Cited

Sex Differences in Cell Divisions

As the technique of in vitro fertilization and implantation became widespread in the early 1990s, there were anecdotal reports that women who had undergone this procedure were delivering male babies at a higher than expected rate. Why

Pain. 2016 Feb;157 Suppl 1:S2-6. doi: 10.1097/j.pain.0000000000000389.

Sex differences in pain: a tale of two immune cells.

Mapplebeck JC[1], Beggs S, Salter MW.

The FASEB Journal • Review

Cell sex: a new look at cell fate studies

Angela Maselli,*,‡ Paola Matarrese,* Elisabetta Straface,* Silvia Canu,† Flavia Franconi,†,‡,1 and Walter Malorni*,1,2

Biochem Biophys Res Commun. 2017 Apr 29;486(2):431-437. doi: 10.1016/j.bbrc.2017.03.058. Epub 2017 Mar 16.

Differential sex-specific effects of oxygen toxicity in human umbilical vein endothelial cells.

Zhang Y[1], Lingappan K[2].

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Sex differences in resident immune cell phenotype underlie more efficient acute inflammatory responses in female mice

Ramona S. Scotland, Melanie J. Stables, Shimona Madalli, Peter Watson and Derek W. Gilroy

Blood 2011 118:5918-5927; doi: https://doi.org/10.1182/blood-2011-03-340281

Article Figures & Data Info & Metrics e-Letters PDF

Abstract

Females are protected against mortality arising from severe sepsi
precise mechanisms that confer this survival advantage in female
unclear. Resident leukocytes in resting tissues have a significant

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American Society of Hematolog
Self-Assessment Program
(ASH*SAP)

"cells from males and females can behave differently"

Handb Exp Pharmacol. 2012;(214):49-65. doi: 10.1007/978-3-642-30726-3_3.

Sex differences at cellular level: "cells have a sex".

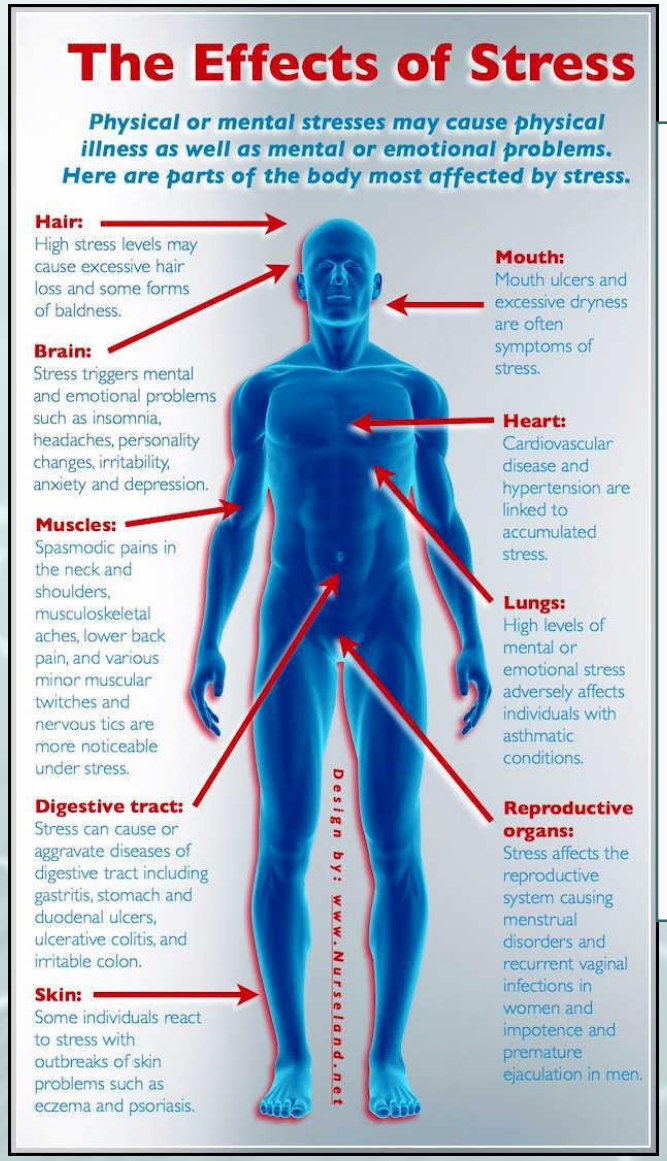
Straface E[1], Gambardella L, Brandani M, Malorni W.

GENDER-ASSOCIATED DISEASES

Table 1 | *Gender disparity in some human pathologies*

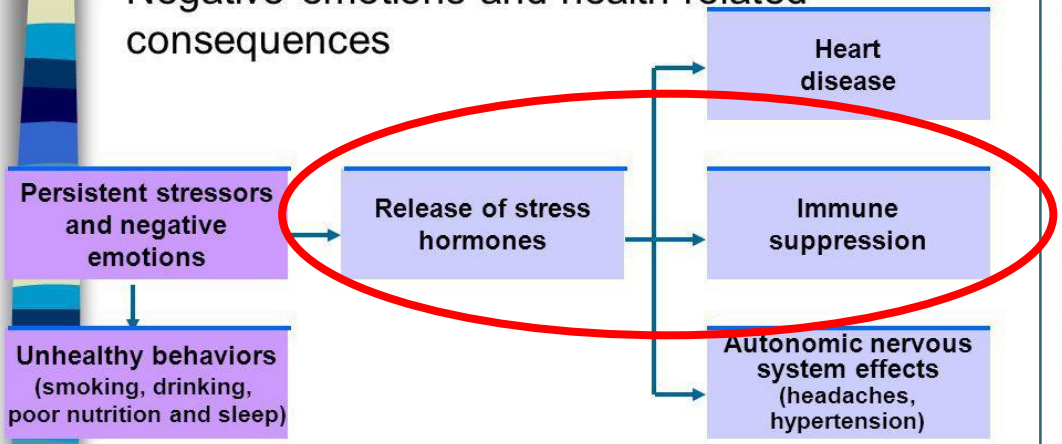
Pathology	Gender disparity
Cardiovascular disease	Delayed in women
Some forms of cancer	Differences in incidence, prognosis and response to therapy
Disability (bedridden)	Higher incidence in women
Other disabilities (sight, motion, hearing, speech)	Higher incidence in women
Rates of chronic disease	Higher incidence in women
Osteoarthritis/Arthritis	Higher incidence in women
Osteoporosis	Higher incidence in women
Hypertension	Higher incidence in men
Diabetes	Higher incidence in women
Depression and anxiety	Higher incidence in women
Senile dementia-Alzheimer's	Higher incidence in women
Autoimmune diseases	Higher incidence in women

Ann. Ist. Super. Sanità vol.48 n.3 Roma Jan. 2012



Stress and Disease

- Negative emotions and health-related consequences



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Sex differences in cell responses against stress

Hypothesis 1

Men and women respond to stress differently, with women experiencing greater sadness and anxiety, while men show a greater integration of reward motivation and emotional stress systems (Alcoholism, clinical and experimental research. 2008;32(7):1242-1250; Industrial Psychiatry Journal. 2011;20(1):4-10).

Furthermore, men and women manage stress differently and place a different level of importance on performing stress management techniques. Men report being less concerned about the management of stress and say they are able to manage it well, while women put more emphasis on the need to deal with stress, but feel they do not do it well enough (APA 2011).

Furthermore, both women and men are at risk for different types of stress-related disorders, with women at greater risk for depression and anxiety and men at greater risk for alcohol-use disorders (Alcoholism, clinical and experimental research. 2008;32(7):1242-1250).

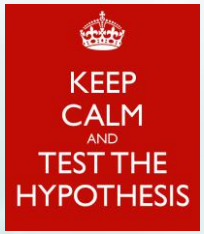
Hypothesis 2

These data suggests that the perception of stress is different between men and women, and that they differently react with stress, both psychologically and biologically. In order to have a better understanding in these gender behavioral differences, it could be interesting deepen the basic scientific knowledge about the gender-related mechanisms activated by stress. For these purposes, the use of simple in vitro models could facilitate the acquisition of knowledge about the pattern of stress responses. This understanding could open the door to new and more effective response strategies to prevent stress, or to manage stress efficaciously. The finding of suitable approaches, such as a different schedule of tasks or physical relaxation sessions, could permit women to achieve also those working positions that require a great ability to manage the stress.

"Sex differences and inflammation: an in vitro model for monitoring stress-mediated immune modulation."

- Sex differences have been demonstrated in inflammatory processes (Journal of Inflammation 2010, 7:28).
- Cortisol, a marker of stress, showed different basal levels in male and female populations (for a review Psychoneuroendocrinology 2006, 31:151–178; Horm Behav. 2010, 57:35-45).
- In acute stress increased levels of cortisol and plasma cytokines, the molecules mainly involved in the inflammatory processes, have been reported (Nature Immunology 2015, 16: 448–457; Nature Reviews Immunology 2015, 15: 271–282; Brain, Behavior, and Immunity 2003, 17:373–383).

The purpose of the study is the in vitro investigation of sex-related differences in the stress-mediated immune modulation.

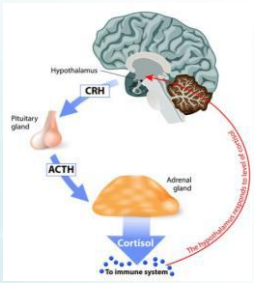


Experimental planning

human **lymphomonocytes** from male and female donors

Lipopolysaccharide (LPS)
and/or
Pokeweed Lectin

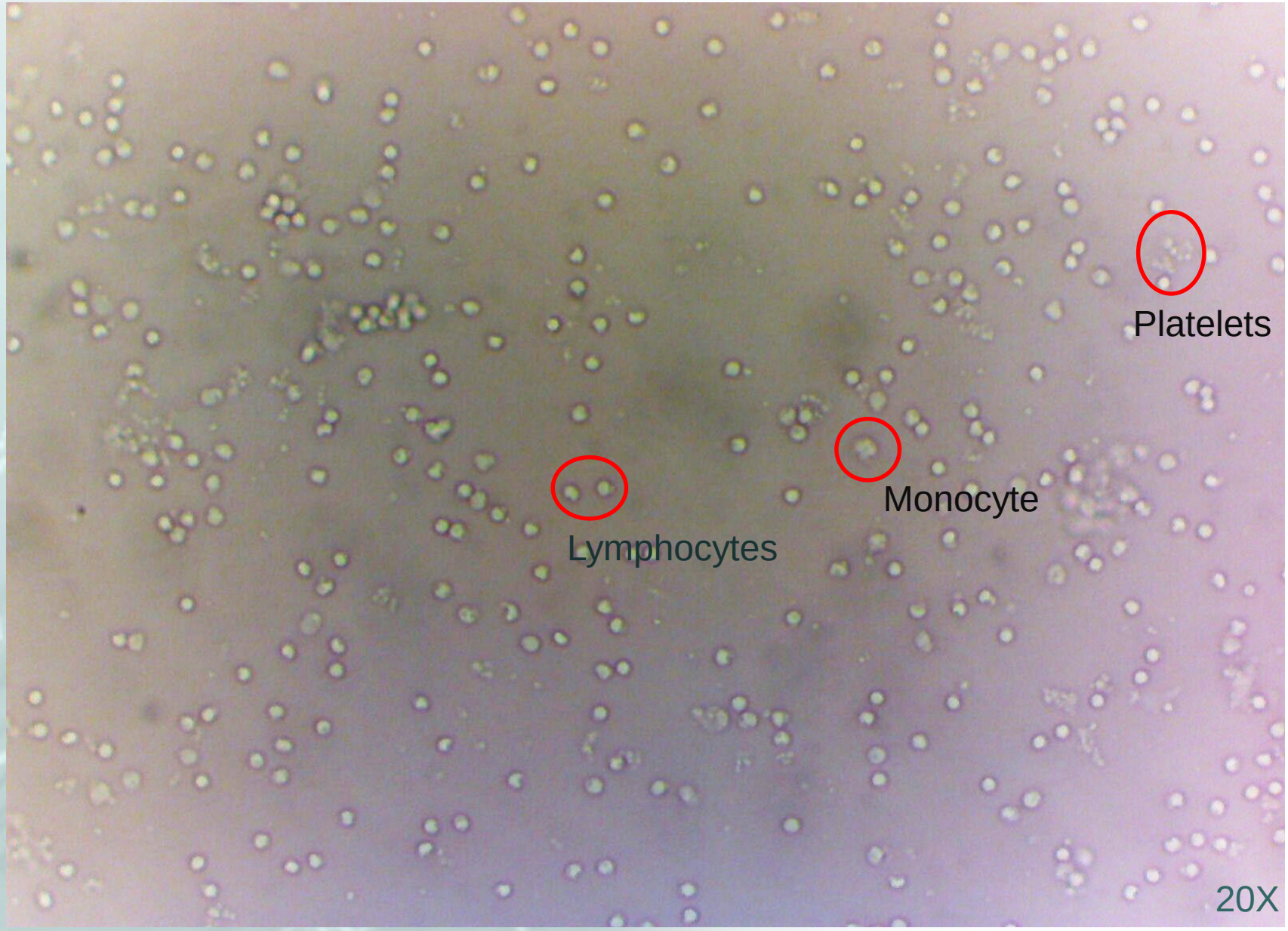
Cortisol → acute exposure (6 h)
Cortisol → chronic exposure (7 days)



pellet → RNA extraction and rtPCR → NFkB, IkB-α, IDO

surnatant → IL-1β, IL-2, IL-6 and IL-8
IL-10
IDO

Female, Hispanic, 21 y



work
in
progress