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Applied Translational Medicine

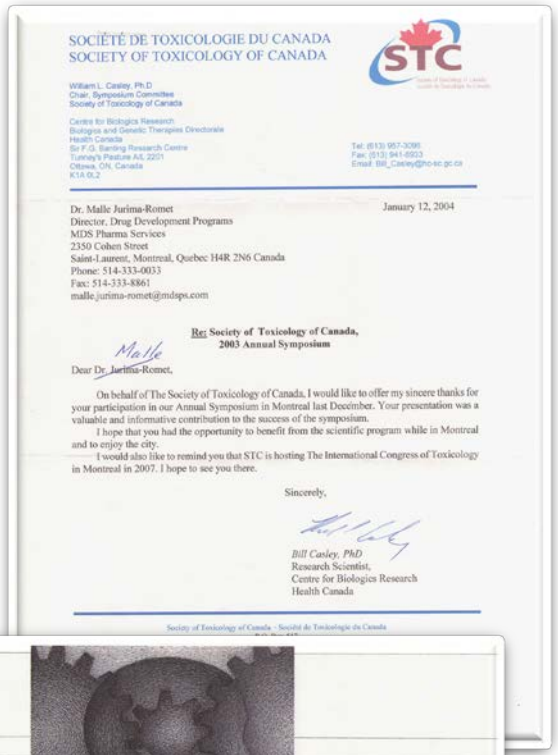
Assessing Safety Risk in Early Clinical Studies: Science or Art?

J. Fred Pritchard, PhD

Vice President, Global Drug Development

Right Brain <–> Left Brain
Art <–> Science

Malle's Legacy



SOCIÉTÉ DE TOXICOLOGIE DU CANADA
SOCIETY OF TOXICOLOGY OF CANADA

STC

William L. Casley, Ph.D
Chair, Symposium Committee
Society of Toxicology of Canada

Centre for Biologics Research
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Health Canada
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January 12, 2004

Dr. Malle Jurima-Romet
Director, Drug Development Programs
MDS Pharma Services
2350 Cohen Street
Saint-Laurent, Montreal, Quebec H4R 2N6 Canada
Phone: 514-333-0033
Fax: 514-333-8861
malle.jurima-romet@mdsps.com

Re: Society of Toxicology of Canada, 2003 Annual Symposium

Malle

Dear Dr. Jurima-Romet,

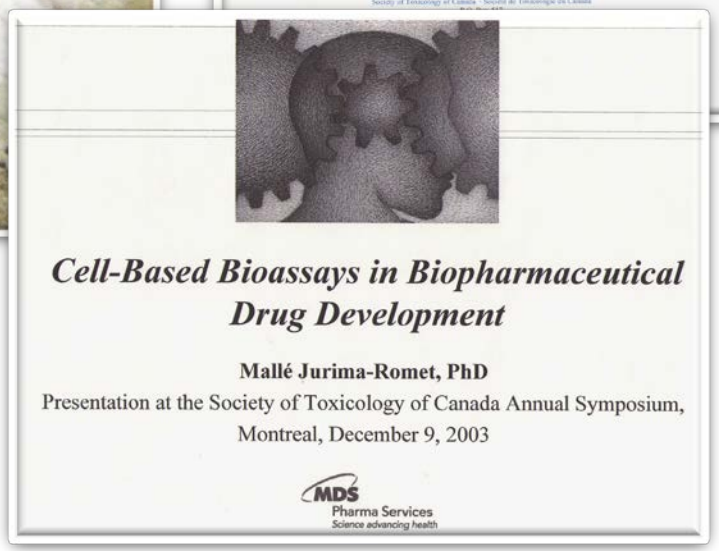
On behalf of The Society of Toxicology of Canada, I would like to offer my sincere thanks for your participation in our Annual Symposium in Montreal last December. Your presentation was a valuable and informative contribution to the success of the symposium.

I hope that you had the opportunity to benefit from the scientific program while in Montreal and to enjoy the city.

I would also like to remind you that STC is hosting The International Congress of Toxicology in Montreal in 2007. I hope to see you there.

Sincerely,

Bill Casley, PhD
Research Scientist,
Centre for Biologics Research
Health Canada

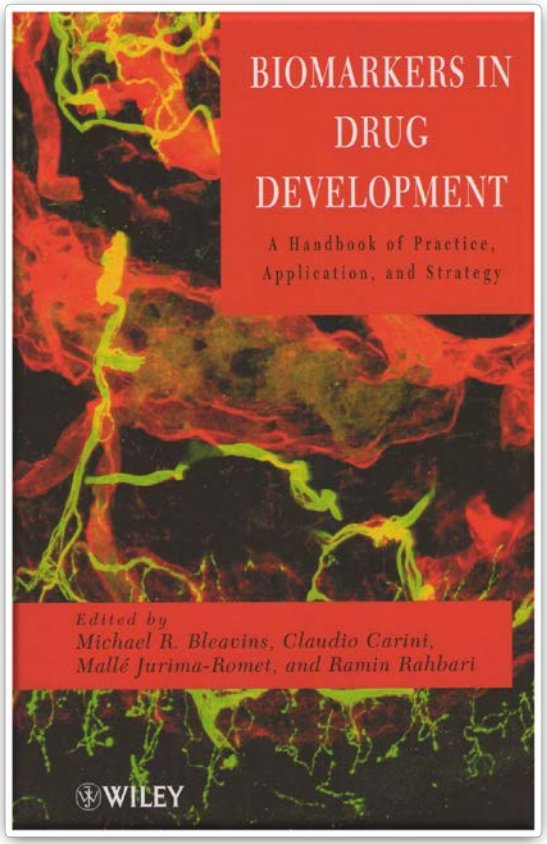


Cell-Based Bioassays in Biopharmaceutical Drug Development

Mallé Jurima-Romet, PhD

Presentation at the Society of Toxicology of Canada Annual Symposium,
Montreal, December 9, 2003

MDS Pharma Services
Science advancing health



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Questions

- How is early clinical research changing?
- How good are we in predicting safety for early clinical research and ultimately for marketed drugs?
  - Focus on role of safety biomarkers (Malle's interest)
  - No focus on CNS safety testing (no time)
- What are some recent examples of addressing the relevance of preclinical toxicology findings in early clinical studies?
  - Cardiac safety
  - Testicular toxicity
- What are important areas for future innovation in establishing the safety of new drug candidates in early studies in humans?

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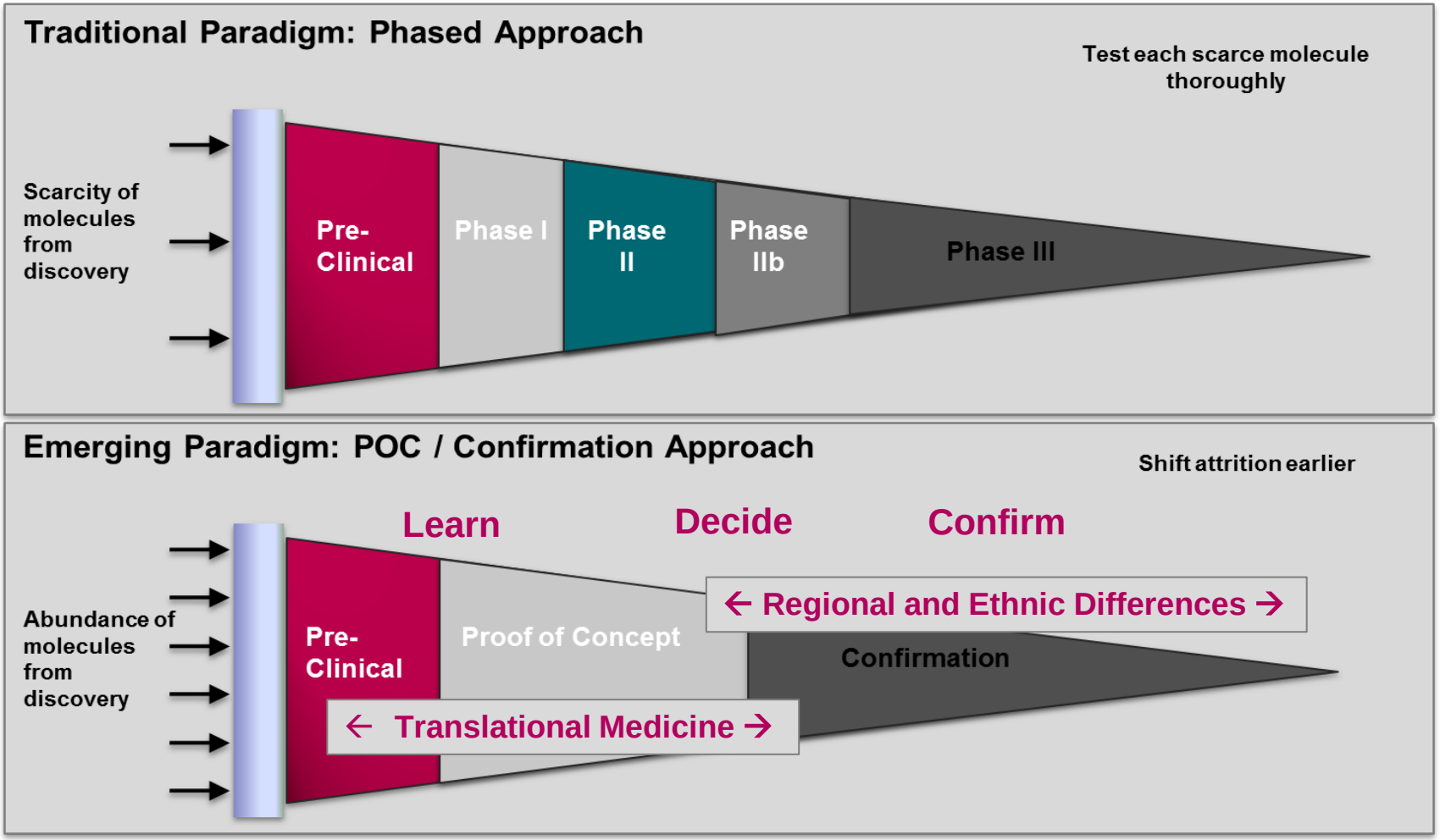
Changing Paradigm



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

Major Reasons for Drug Attrition

PMC Full Text: Br J Pharmacol Jun 2011: 163(4):675-693
Doi: 10.1111/j.1476-5381.2011.01255x

Figure 2

Phase	Non-clinical	Phase I	Phase I-III	Phase III/ Post-approval	Post-approval	Post-approval	Post-approval
Information	Causes of attrition	Serious ADRs	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale	Withdrawal from sale
Source	Car (2006)	Sibille et al. (1998)	Olson et al. (2000)	BioPrint®	Budnitz et al. (2006)	Fung et al., (2001)	Stevens & Baker (2009)
Sample Size	88 CDs stopped	1,015 subjects	82 CDs stopped	1,138 drugs	21,298 patients	121 drugs	47 drugs
Cardiovascular	27%	9%	21%	36%	15%	9%	45%
Hepatotoxicity	8%	7%	21%	13%	0%	26%	32%

0% 1 - 10% 10-20% >20%

Critical Preclinical Information for Early Clinical Research

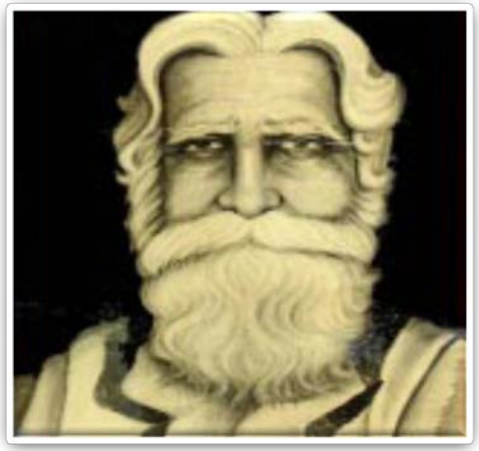
- Objectives of First-in-Human (FIH) studies:
  - **Establish if drug elicits acute, treatment-limiting adverse events**
  - Define ADME properties
  - Identify influences for future patient exposure
- Preclinical information used to:
  - Justify why humans should receive drug based on pharmacology
  - Determine “maximum recommended starting dose (MRSD) and dose escalation strategy based on the no-observed-adverse-effect-level and human equivalent dose calculations from most sensitive tox species
  - **Identify potential target organs of acute and chronic toxicity – potential sensitive biomarkers of effect**
  - Understand relationship between systemic exposure and dose based on toxicokinetic data.
  - Predict potential for drug-drug interactions

Definition of a Biomarker

“a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic invention”

Atkinson AJ et al. (2001) Clin Pharmacol Ther 69: 89-95.

First Diagnostic Biomarker?



Sushruta (clinician in India, 600 B.C.)

Recorded that urine of diabetic patients attracted ants

= Diagnostic biomarker for diabetes

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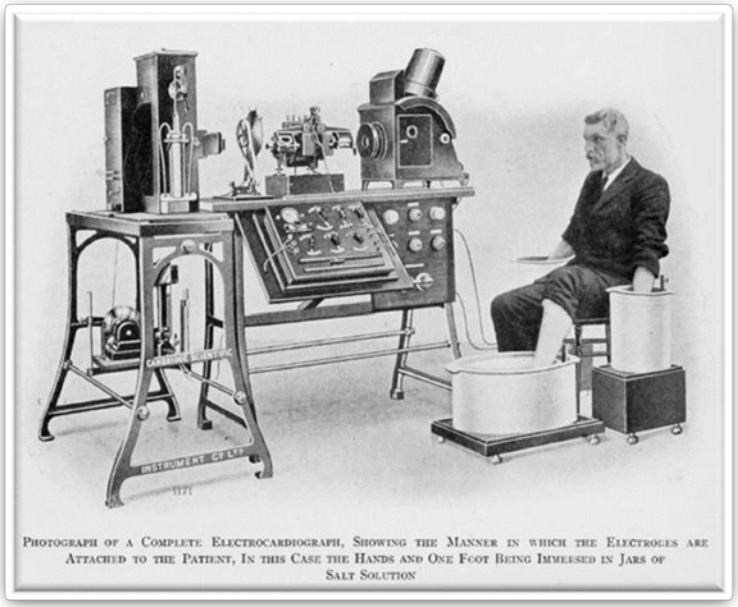
Safety Biomarkers

	Preclinical	Clinical	Comment
Cardiac Rhythm	In vitro Ik_r In vivo QTc (ICH S7B)	ECGs in FIH/FIP Thorough QTc Study (ICH E14)	Robust ECGs in FIH → waiver of TQT?
Myocardial Injury			
Acute renal tubular injury			
Acute glomerular and renal tubular injury affecting reabsorption			
Liver Injury			
Testicular Toxicity			

Evolution of ECG Assessment

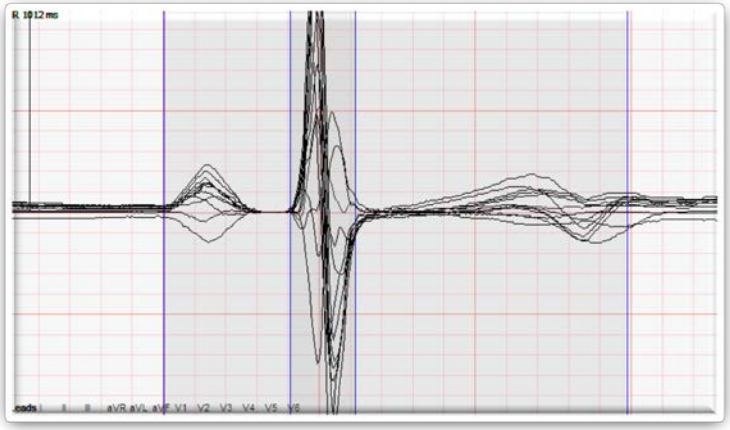


PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

1902 – First published ECG

1971 – Early Holter Monitor

2011 – Digital Bluetooth Holter Monitor



High definition digital analysis (accurate and fast)

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Torsades de Pointes Pathogenesis

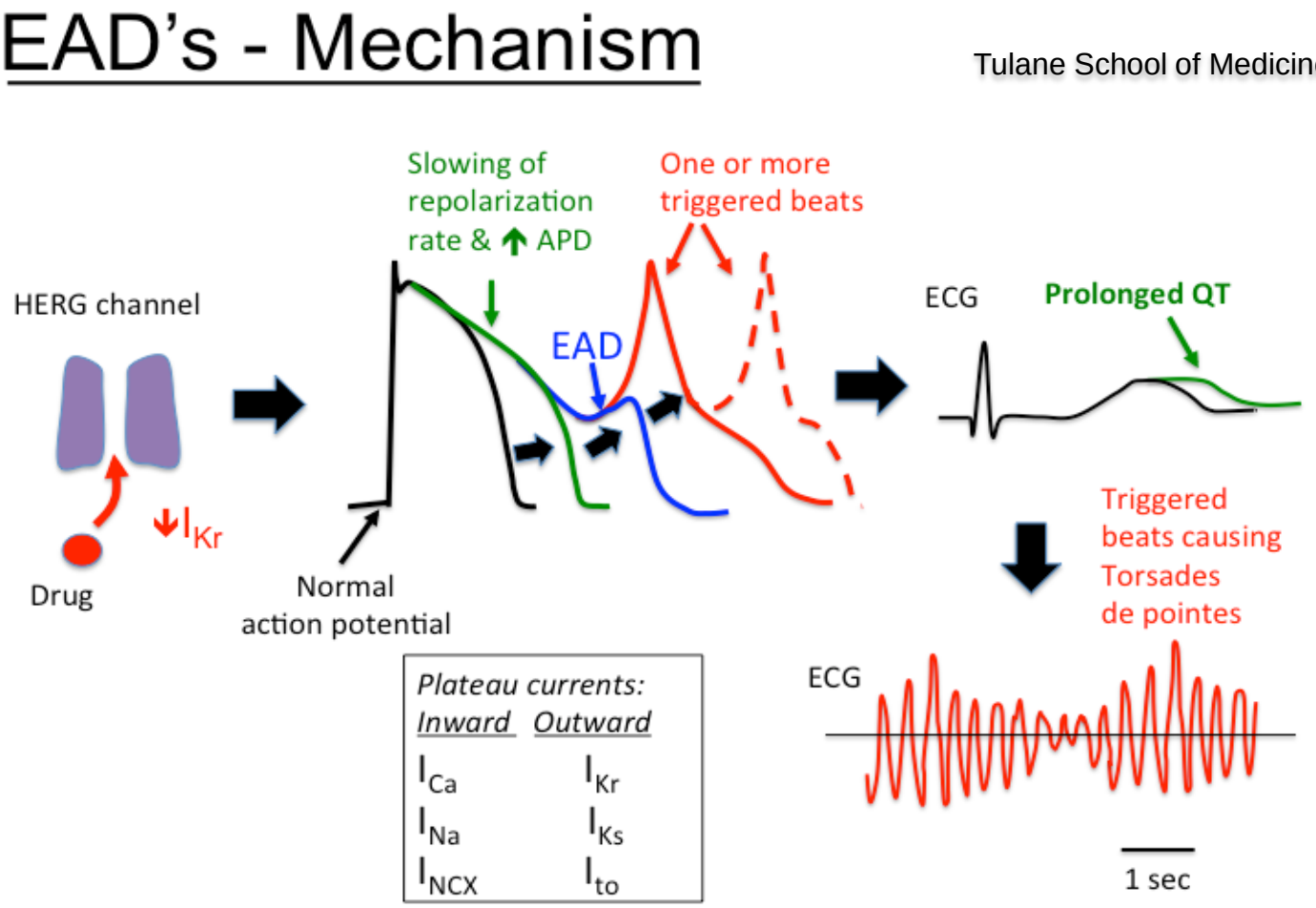
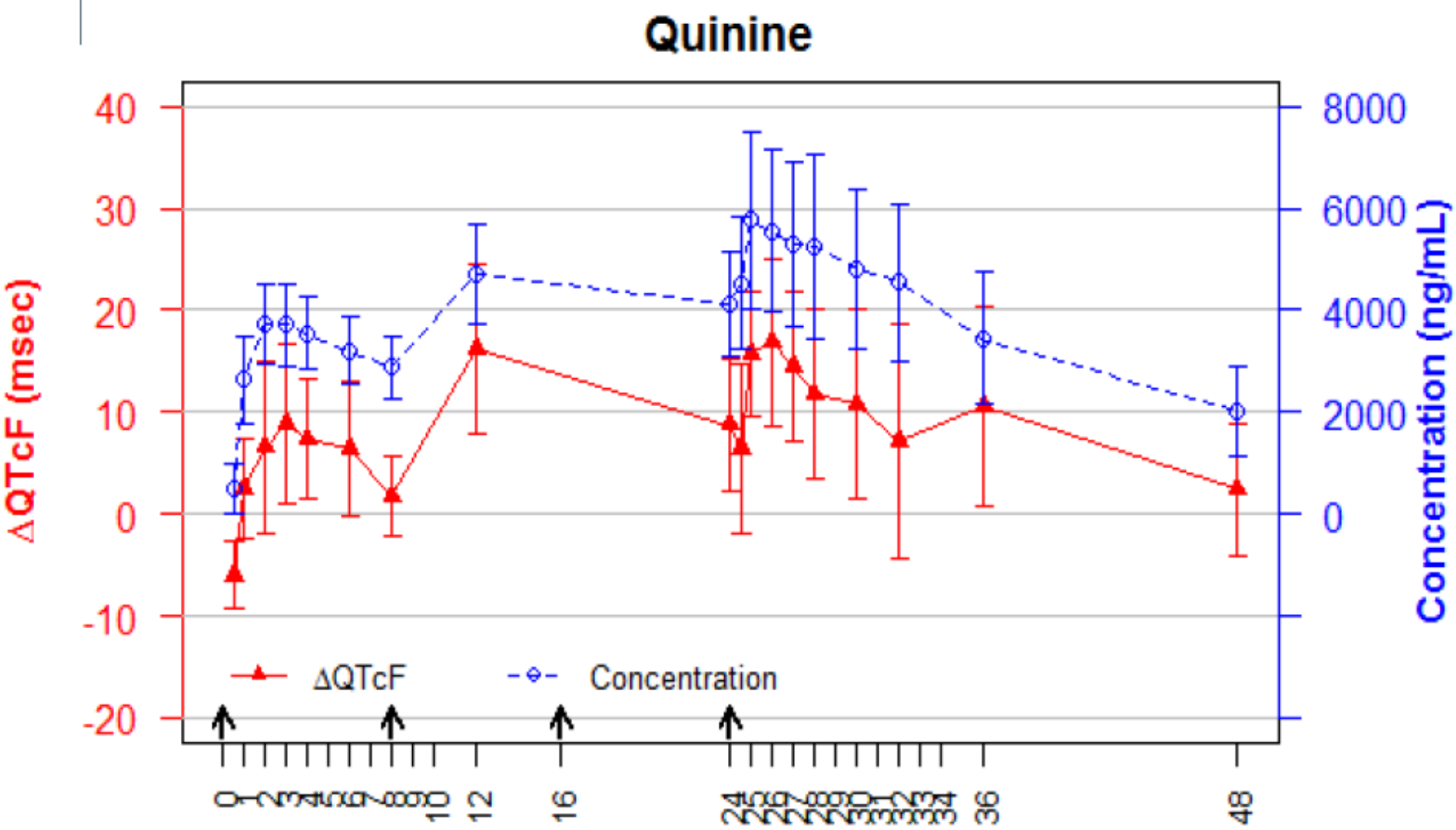


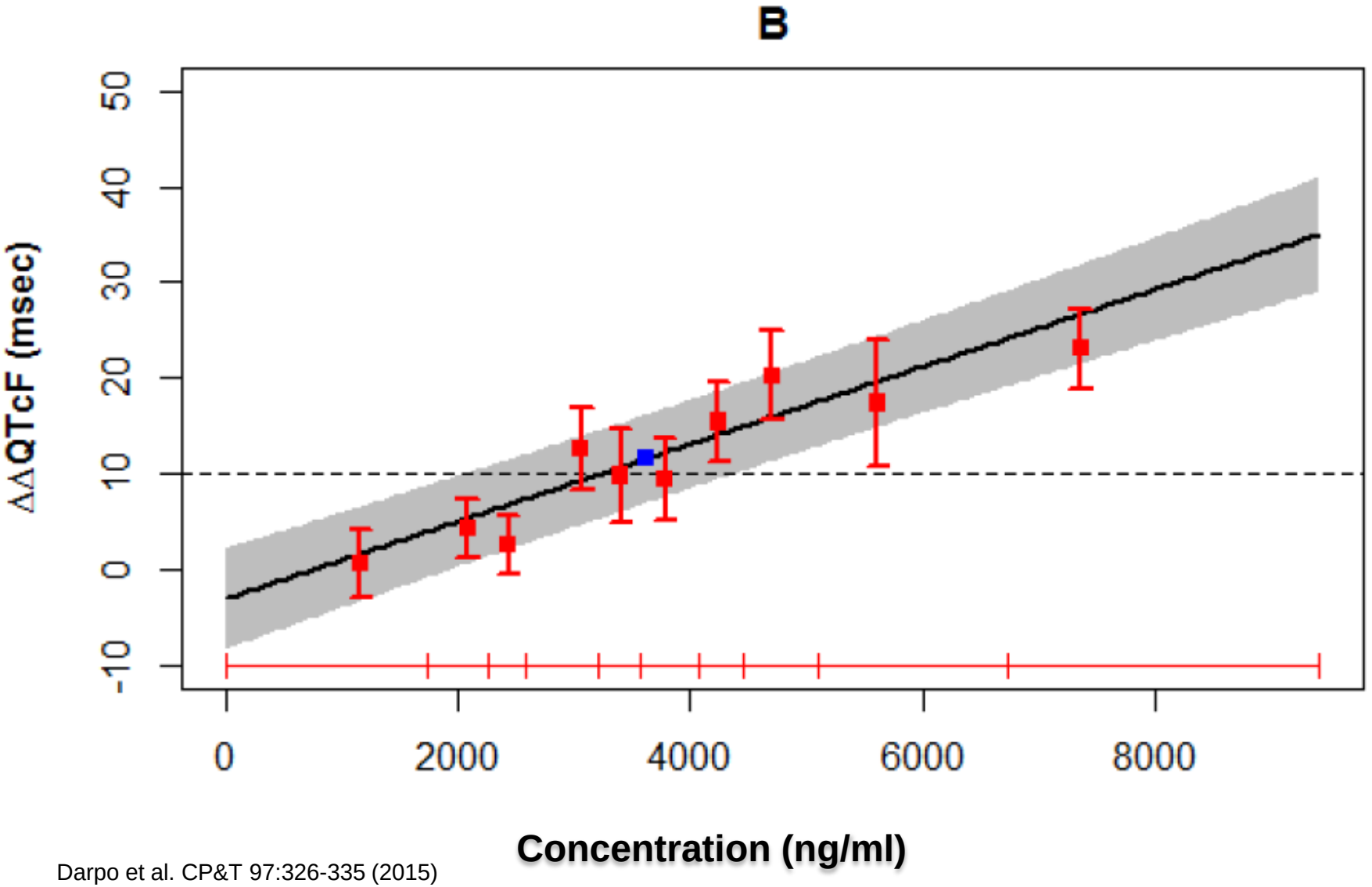
Figure 9. Mechanism of EAD formation & initiation of Torsade de pointes. Drug-induced blockade of the HERG channel reduces IKr amplitude, which in turn reduces net outward current during the plateau, and prolongation of the ventricular APD and QT interval in the ECG (green). If net inward currents during phase 3 become larger than outward currents, this can form an EAD (blue). These changes are typically heterogeneous and can create a substrate for producing triggered beats in multiple locations, resulting in a multifocal ventricular tachycardia. (Adapted from Kannankeril et al, 2010).

Innovation and Quality - Cardiac Safety Research Consortium (IQ-CSRC) Study



Darpo et al. CP&T 97:326-335 (2015)

Quinine……"Positive" Drug



Darpo et al. CP&T 97:326-335 (2015)

QT Safety Challenges Remaining

- Discrepancies between non-clinical assays and clinical outcome
  - **False positives** - hERG blockers which are antiarrhythmic (Verapamil, Vanoxirene, Amiodarone)
  - **False negatives** - L-type Ca^{++}/late Na^{+} blockade, abnormal trafficking leading to proarrhythmia/TdP
- Metabolites, other ion channels
- QT measurement – variable methodology
- QT interval shortening

hERG – human Ether-a-go-go Related Gene

- Comprehensive In Vitro Pro-arrhythmia Assay (CiPA) Initative
  - Ion channel
    - Perform comprehensive tests (hERG plus 3 to 6 additional cardiac channels)
  - Stem cell-derived human cardiomyocytes
  - In silico modeling
  - Objective – Update ICH S7B

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Myocardial Injury	Histology cTnT, cTnI (dog, rat)	Cardiac tropinin (cTn)	LDH and CK lack specificity, sensitivity
Acute renal tubular injury			
Acute glomerular and renal tubular injury affecting reabsorption			
Liver Injury			
Testicular Toxicity			

Dramatic Example – HCV Drugs in Early Clinical Development

- **August 24, 2012**
  - Clinical testing of BMS-986094, a nucleotide polymerase inhibitor, was suspended after one study subject died of heart failure and 8 others were hospitalized due to heart and kidney toxicity. **Preclinical evidence of toxicity at high exposures in animals but biomarker indicators were seen in preclinical studies not seen in clinic**
- **August 27, 2012**
  - Partial clinical hold already on Phase IIb drug IDX184; clinical hold put on preclinical drug IDX19368. Both are nucleotide polymerase inhibitors which share the same active metabolite as BMS-986094
- **September 24, 2014**
  - Retrospective analysis showed evidence of cardiotoxicity in 14 of 34 patients enrolled in BMS-986094 Phase II study

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Liver Injury	Histology, Total bilirubin (specific), ALT (sensitive), AST, ALP, prothrombin time		Need markers for DILI (e.g. micro RNAs)
Testicular Toxicity			

Regulatory Action on Marketed Drugs due to DILI (1995-2010)*

Withdrawals (US* and/or other countries+)

troglitazone*
bromfenac*
trovofloxacin*
tilbroquinol+
pemoline+
tetrabamate+
ebrotidine+
nefazodone+
tolrestat+
droxicam+
niperotidine+
chlormezanone+
ximelegatran+
lumaricoxib+
gemtuzumab+

Restricted (US)

trovofloxacin
felbamate
pemoline

Boxed Warnings (US)

lamividine
leflunomide
propylthiouracil
lapatanib
pazopanib
sunitimib
tenofovir
tipranavir
tolcapone
bosentan
deferasirox
ambrisentan
acitretin
cytarabine
maraviroc
eltrombopa
acetaminophen (Rx)

*Partial List FDA/C-Path/PhRMA HepTox Steering Committee,15 March 2012

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Liver Injury	Histology, Total bilirubin (specific), ALT (sensitive), AST, ALP, prothrombin time		Need markers for DILI (e.g. micro RNAs)
Testicular Toxicity	Histology, LH, testosterone,	Semen analysis, Inhibin-B?	FSH inconsistent

Male Reproductive Safety – Preclinical Evaluation

- Preclinical general toxicology studies are the most frequent source of concern regarding the potential effect of a drug on the testis
- Concern is less likely to arise from the animal fertility study (usually carried out later in development)
- Preclinical toxicology studies may demonstrate testicular histopathological abnormalities in one species or in multiple species
- The is no single species that is best for prediction of human risk
- Abnormalities in any species may be a cause for concern

Testis is a Dual Organ in Function and Structure

- **Interstitial Compartment**
  - Endocrine Function
  - Leydig cell
  - Low metabolic rate
  - Fibroblast stem cells
  - Resistant to toxicity
- **Seminiferous Compartment**
  - Exocrine Function
  - Sertoli and germ cells
  - Active turnover rate
  - Spermatogonial stem cells
  - Exquisitely sensitive to toxicity

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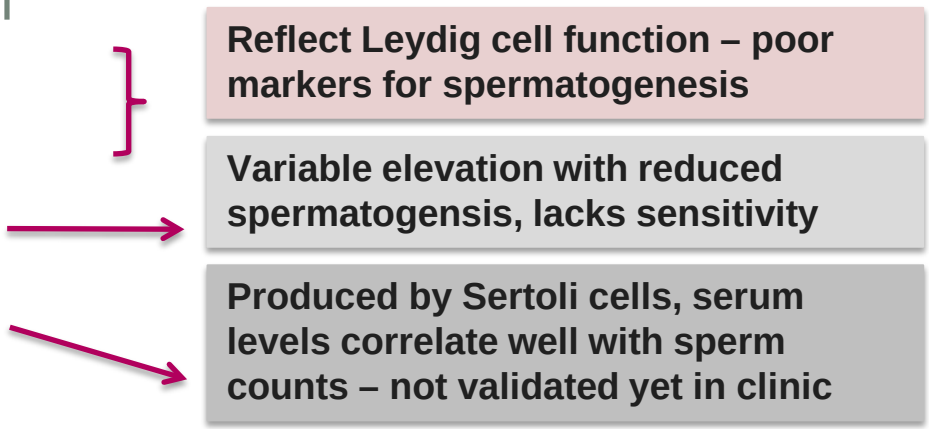
Evaluation of Spermatogenesis during Drug Development

- Hormonal Evaluation
  - LH
  - Testosterone
  - FSH
  - Inhibin B
- Advantages
  - Acceptable to subjects, no recruitment issues
  - Easily incorporated into clinical studies
- Semen Analysis
  - Sperm count, motility and morphology still best assessment in clinic despite challenges in obtaining good samples



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Case Study: Clinical Biomarkers of Testicular Safety Risk

- Novel anti-viral drug
- 1 month oral toxicity studies in rat and dog revealed histopathological changes in the testes
- Reproductive toxicity studies in rat demonstrated ↓fertility, ↓spermatogonia, ↑morphologically abnormal sperm
- Subsequent testicular toxicity studies were conducted in mice, rats, rabbits and monkeys
- Rat was the most sensitive species; histopath changes included degeneration of spermatocytes and dilatation of seminiferous tubules
- FDA placed a partial clinical hold on development

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How Do You Design a Clinical Study to Evaluate Testicular Safety?

- First, sponsor conducted a Phase I multiple dose safety
  - PK study in a healthy subject population of vasectomized males and postmenopausal women
  - Data used to select dose for testicular safety study
- Sperm concentration (biomarker) is the most commonly used endpoint
- Define “responder” as an individual with a 50% reduction in sperm concentration
- Non-inferiority analysis used
- Study duration must include at least one spermatogenic cycle, i.e. $\geq$ 90 days

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Other Key Considerations

- Goal is to reduce “noise” while having sufficient numbers to obtain a statistically valid result
- Control factors that contribute to variation
  - Limit # of sites to control geographical variation
  - Limit # of laboratories to control inter-laboratory variation
  - Multiple samples per time point
  - Control period of abstinence

The Chosen Design

- Phase I, randomized, double-blind, placebo-controlled, non-inferiority, multiple oral dose study in healthy male subjects
- Number of subjects: 110
- Primary endpoint: sperm conc. at Day 95
- Semen analysis conducted at baseline Day 65, Day 95 and Day 125
- 3 samples per time point 48-hour abstinence between samples; clinic confinement during sample collection periods
- 2 clinical sites; single laboratory conducted semen analysis
- DSMB reviewed semen and laboratory safety data at Day 65, 95 and 125

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Clinical Study Results

- Responder rate following drug treatment was not inferior to placebo re: semen biomarkers (sperm conc., motility and morphology)
- Drug and placebo were comparable re: endocrine biomarkers (LH, testosterone, FSH and inhibin B)
- Outcomes
  - 2012: FDA removed partial clinical hold
  - 2015: Drug approved for use in H5N1 (bird flu) in Japan. In Phase III development in US/Europe
  - 2015: Drug active against Ebola virus
- Impact – first study of its kind to evaluate the potential for testicular toxicity early in drug development – topic of an ASCPT workshop that Malle chaired in 2013

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Any Answers to Questions?

- How is early clinical research changing?
  - ***More information at CPoC – fail fast, fail early***
- How good are we in predicting safety for early research and ultimately for marketed drugs?
  - ***Doing better? But still not very good***
- Where are more right brain (creative) solutions needed in establishing the safety of new drug candidates in early studies in humans?
  - ***Specific human clinical markers for tissue damage***
    - ***Validating renal markers in clinical studies***
    - ***DILI, myocardial damage***
  - ***Specific marker imaging agents – functional MRI***
  - ***Validation of new human CNS function - safety tests***
  - ***Establishing a meaningful therapeutic index***