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Translating Science to Medicine

Oncology Drug Development: Phase I Case Studies in Healthy Volunteers

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Overview

- Tobacco – cancer - biomarkers of exposure
- Interesting science – using healthy normal volunteers to mimic the diseased state
- Celerion's early phase oncology small molecule experience in healthy normal volunteers
  - Case studies

Smoke/Vape

The lesser of 2 evils?

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Tobacco Use Is the Single Largest Preventable Cause of Death in the US

Cancer – bladder, cervix, esophagus, kidney, larynx, leukemia, lung, oral cavity, pancreas, stomach

Cardiovascular disease – atherosclerosis, stroke, coronary heart disease

Respiratory disease – COPD, pneumonia, impaired lung development and growth, impaired pulmonary function, poor asthma control

Reproductive effects – SIDS, infertility, low birth weight, pregnancy complications

Others – cataracts, diminished health status, low bone density, hip fractures, peptic ulcer disease

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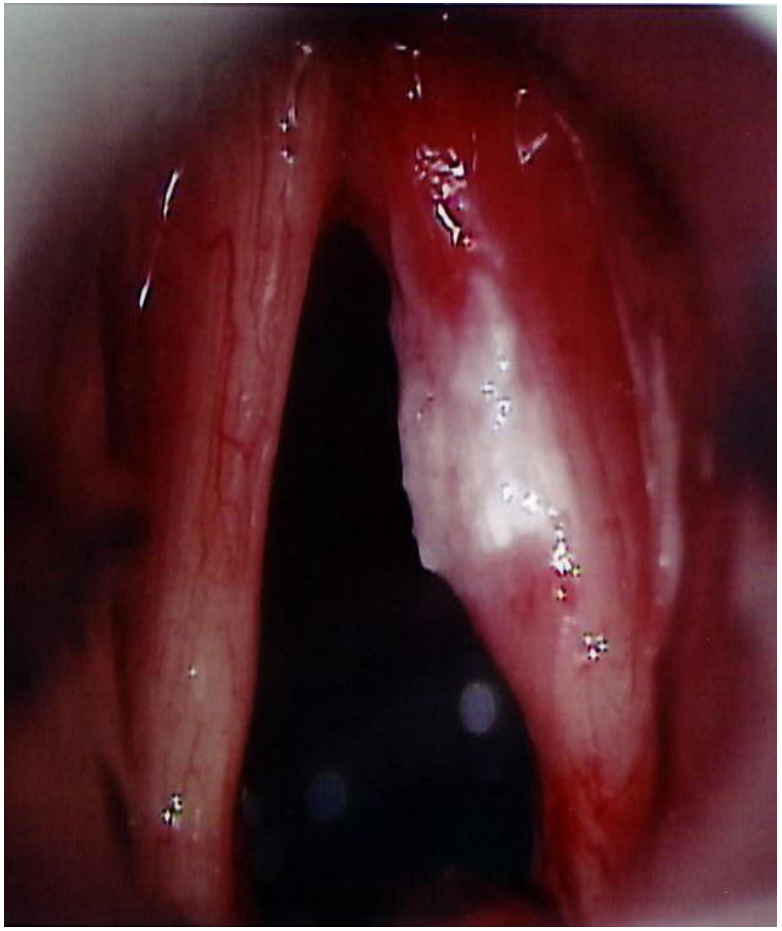
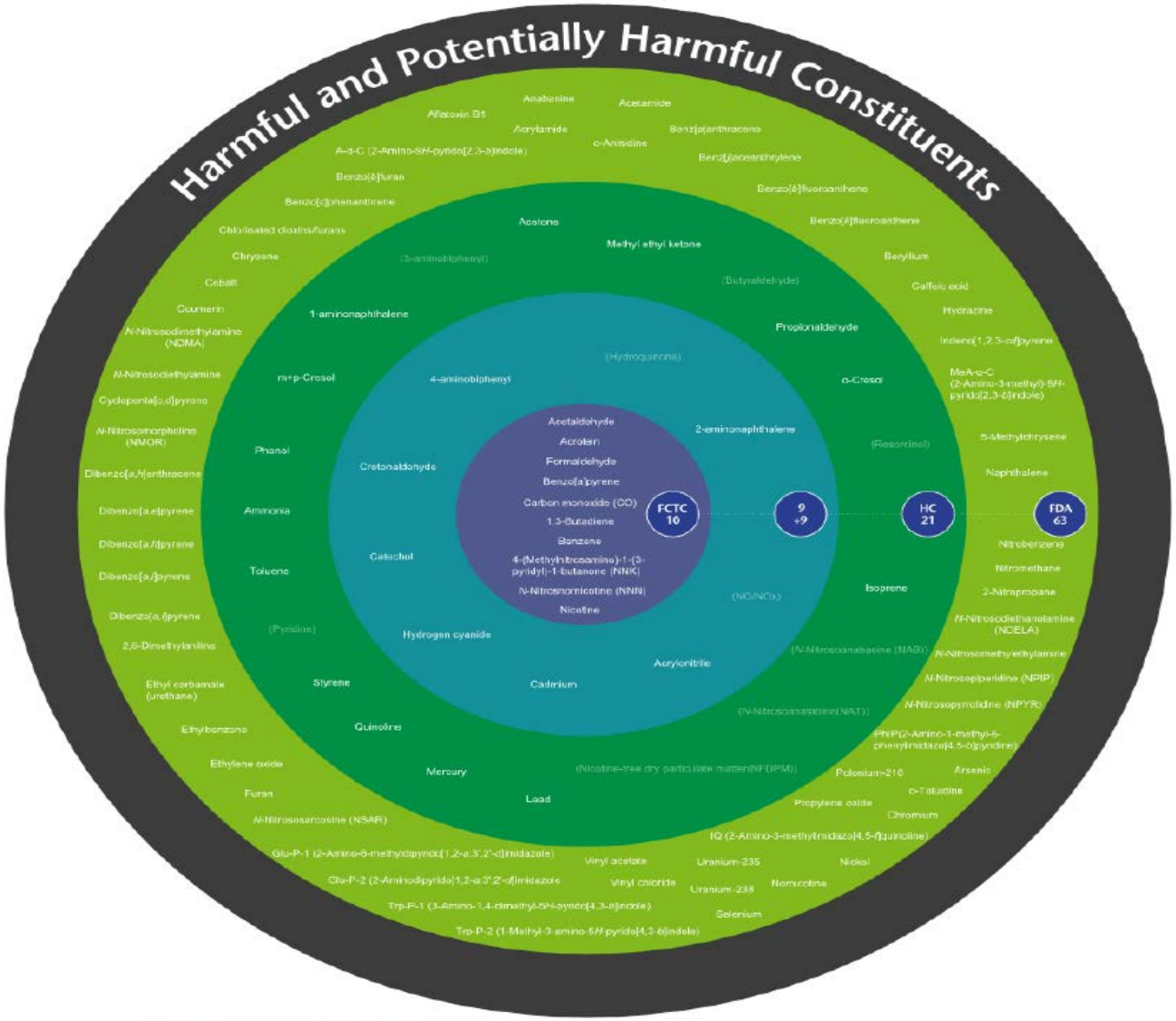
Cancer of the Voice Box - Larynx

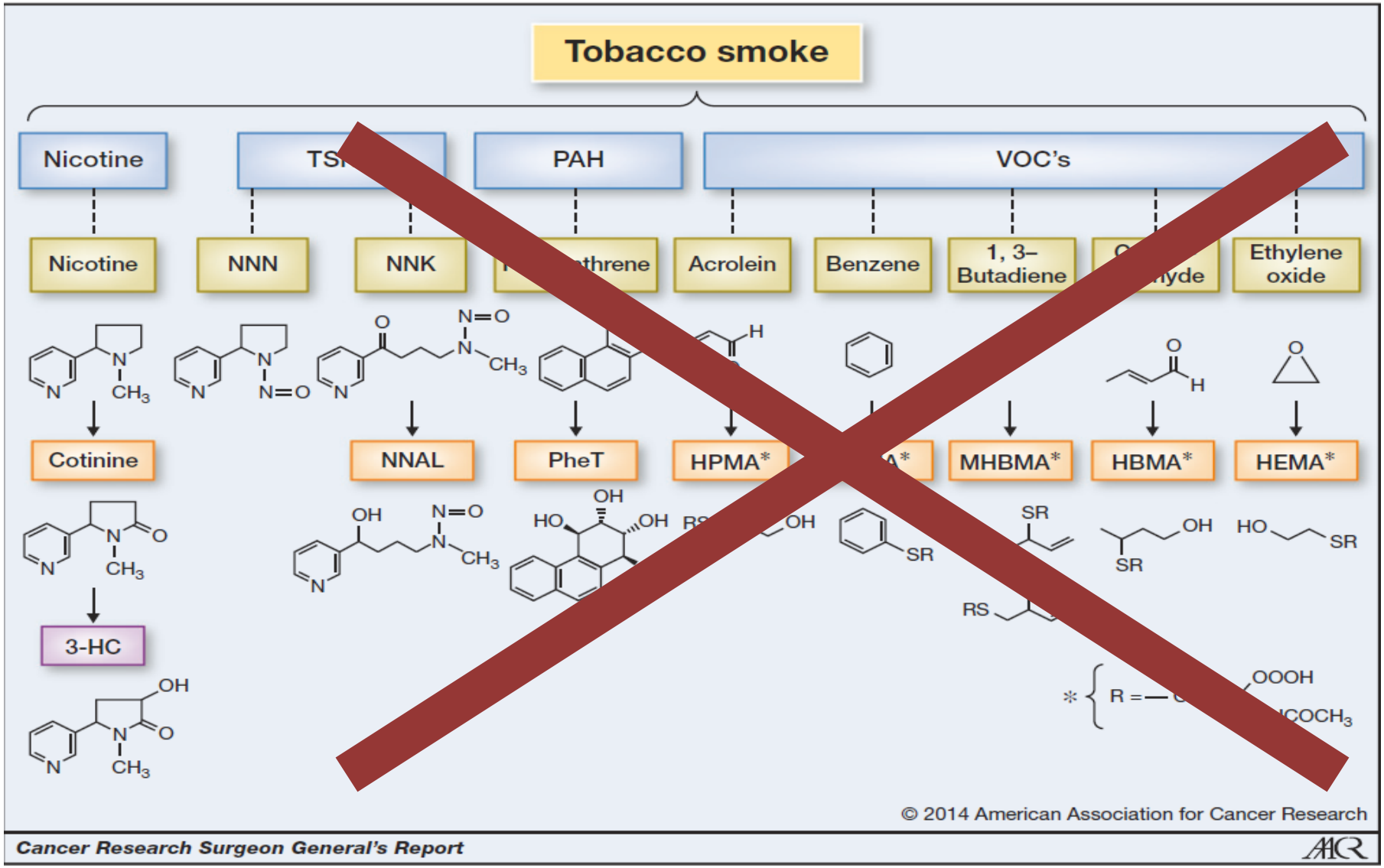


- Traditional Therapy
  - Surgery
  - Laser Therapy
  - Radiation Therapy
  - Chemotherapy
    - Typically parenteral admin
    - Non-specific target
    - Serious dose- and duration-limited Aes
    - Can produce 2ndary malignancies

Cigarette Smoke Components



Cigarette Smoke Components



Common Endpoints: Biomarkers of Exposure

Exposure Component	Measured Analyte
BLOOD	
Nicotine	Nicotine, cotinine, trans-3'-Hydroxycotinine
Carbon monoxide	Carboxyhemoglobin
URINE	
1,3-Butadiene	Dihydroxybutylmercapturic acid, monohydroxybutenylmercapturic acid
Acrolein	3-Hydroxypropylmercapturic acid
Aldehydes	Acetaldehyde, formaldehyde
Benzene	S-phenyl mercapturic acid
Benzo[a]pyrene	3-hydroxybenzo[a]pyrene
Crotonaldehyde	3-Hydroxy-1-methylpropylmercapturic acid
Nicotine Equivalence	Nicotine, cotinine, trans-3'-hydroxycotinine, nicotine-N-glucuronide, cotinine-N-glucuronide, trans-3'-hydroxycotinine-O-glucuronide
Pyrene	1-Hydroxypyrene
Tobacco-Specific Nitrosamines	NNAL, NNN, NAB, NAT
Polyaromatic Hydrocarbons	1- and 2-hydroxynaphthalene; 2-hydroxyfluorene; 1-, 2-, 3-, 4-, and 9-hydroxyphenanthrene
Aromatic Amines	3- and 4-aminobiphenyl, o-toludine, 2-aminonaphthalene
Urine Mutagenicity	Ames Test

Forced Switch Study in Smokers

- Forced-switch parallel proof-of-concept study
- Assessed exposure to biomarkers of tobacco exposure following short-term ad libitum use of 3 electronic products vs dual (regular + electronic) vs cessation.
- Baseline measurements - regular cigarettes on Day -1
- Switch - Post-product use measurements Days 1-6
- Change from baseline in biomarkers of exposure presented after 5 days

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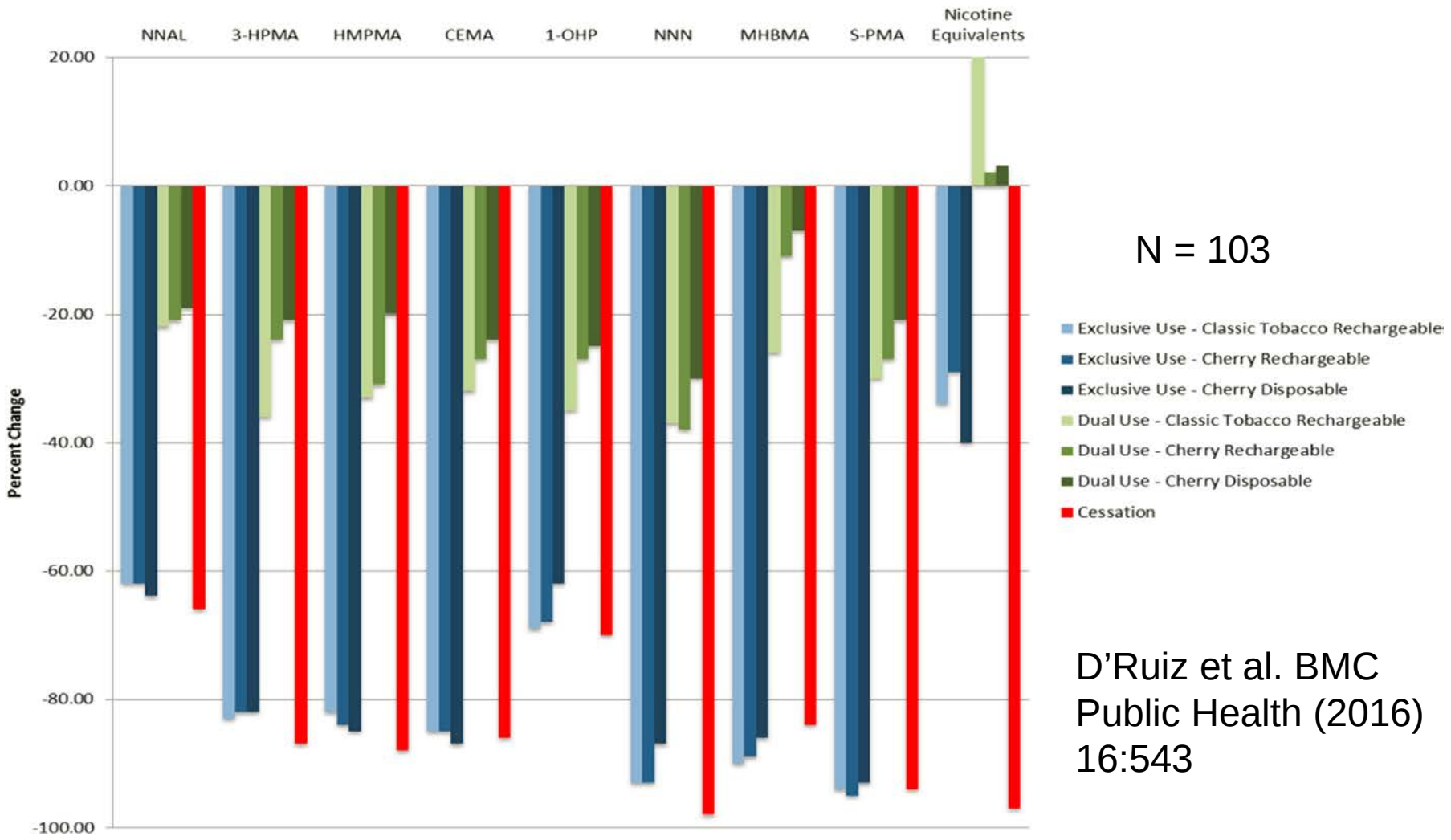
Change in Urine Biomarkers of Exposure After 5 Days



N = 103

D'Ruiz et al. BMC Public Health (2016) 16:543

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Tobacco Product Risk Continuum

CONVENTIONAL CIGARETTES

TOBACCO HEATING PRODUCTS (THPs)

LOW-TOXICANT SMOKELESS TOBACCO

VAPOUR PRODUCTS (E-CIGARETTES)

LICENSED MEDICINAL PRODUCTS

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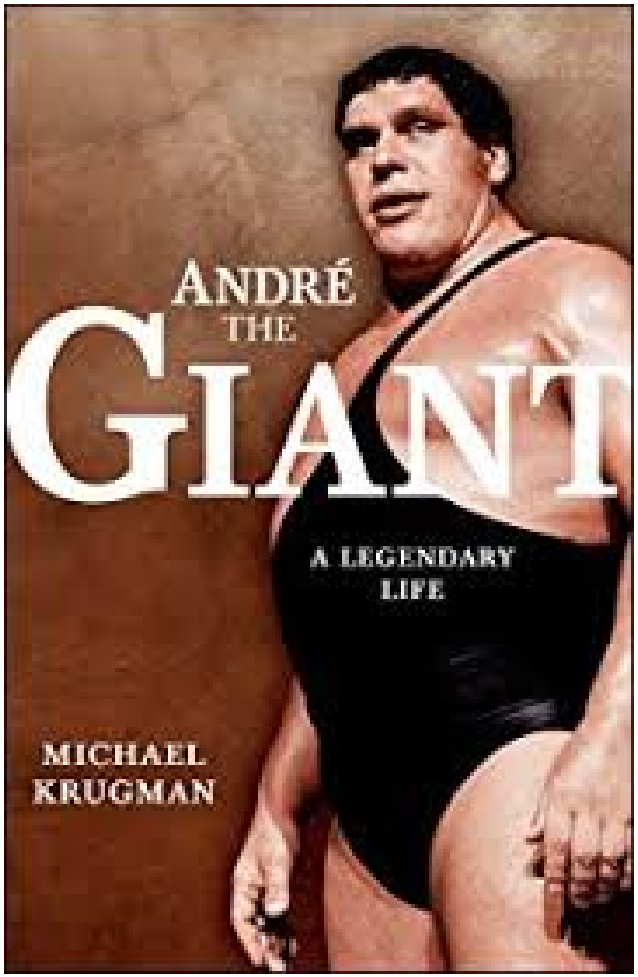
Impact of Tobacco Use

- Tobacco induces CYP1A
- Constitutive activity of CYP1A low in normal individuals, however substantially upregulated
- If preclinical testing suggests CYP1A catalyzed metabolism: Consider testing in vivo, impact of smoking status on PK in early clinical pharmacology study before Phase II/III
- Mitigates risk of treatment failure in cancer patients who continue to smoke during treatment

The Giant


ANDRÉ
THE
GIANT
A LEGENDARY
LIFE
MICHAEL
KRUGMAN


Andre The Giant battles
Jake 'The Snake' Roberts.
— Toronto Sun photo

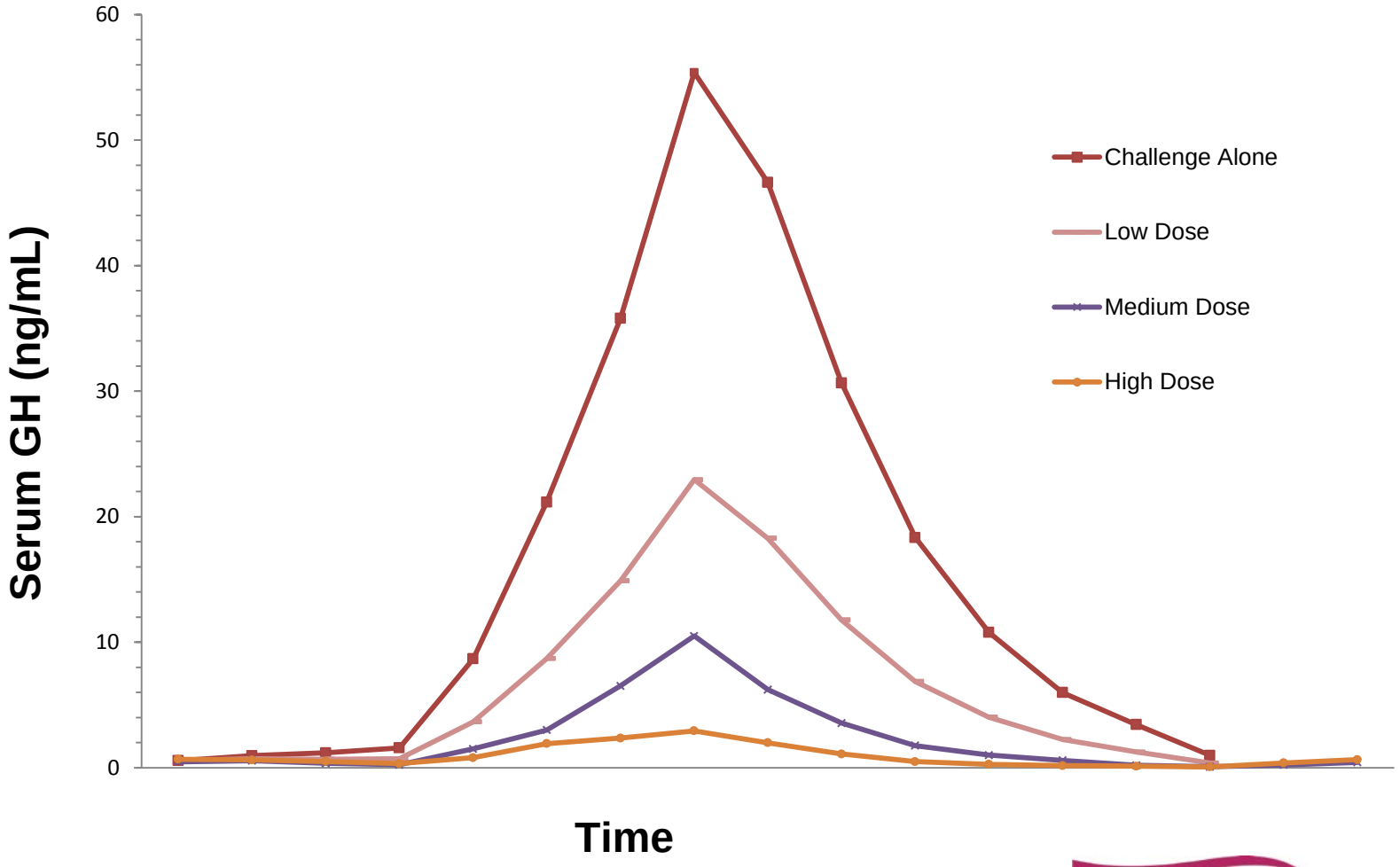
Acromegaly & Gigantism

- Usually caused by a noncancerous (benign) pituitary tumor – adenoma
- Overproduction of growth hormone
  - Tall stature, obesity
  - Macrocephaly
  - exaggerated growth of hands and feet, with thick fingers and toes
  - Coarse facial features
  - Wide spacing of the teeth
- Morbidity and mortality rates are high
  - Cardiovascular disorders
  - Cerebrovascular disorders
  - Respiratory disorders
  - Malignancies

Stimulation/Inhibition of GH

- Growth hormone-releasing hormone (GHRH)/arginine challenge (w/treatment/alone)
  - GHRH – IV bolus injection
  - Arginine Hydrochloride Injection – IV infusion over 30 minutes
- Somatostatin analogs used for therapy
  - Octreotide, Sandostatin, Somatuline
- Usual drug PK profiles (AUC, Cmax, Tmax, $T_{1/2}$)
- PD – after challenge (AUEC, Emax, Tmax)

Typical GH Profile Post-Challenge (Induced) & Treatment (Suppression)



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Early Phase Oncology Drug Development – Focus Change

Yesterday

Today

- Noncytotoxic oncology therapeutics
- Opportunity for HNS
- >60 studies (Celerion - since 2011) across variety of targets - VEGFR, EGFR, FGFR, MET, RET, BTK…
- FIH – SAD/MAD, DDI, NDA-enabling, BA, FE, Timing of meal, ADME, pH, TQT, cQT, RI, HI, Smoking effect, Palatability

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Novel Treatments in Oncology – Kinase Inhibitors

- Some kinase inhibitors are used to treat cancer
- Kinase inhibitors is a substance that blocks a type of enzyme called a kinase
- Human cells have many different kinases, and they help control important functions
  - cell signaling, metabolism, division, and survival
- Certain kinases are more active in some types of cancer cells and blocking them may help keep the cancer cells from growing
- Kinase inhibitors may also block the growth of new blood vessels that tumors need to grow

Kinase Inhibitors

- Inhibit Tyrosine/ Serine/ Threonine Kinases
- Most are orally bioavailable
- More specifically targeting overexpressed receptors and/or enzymes
- More selective for cancer cells vs. healthy cells
- Not without Adverse Event concerns
  - FIH starting dose

Considerations Before Testing Oncology Drugs in Healthy Subjects

General

- Mutagenicity/carcinogenicity
- Reproductive toxicity

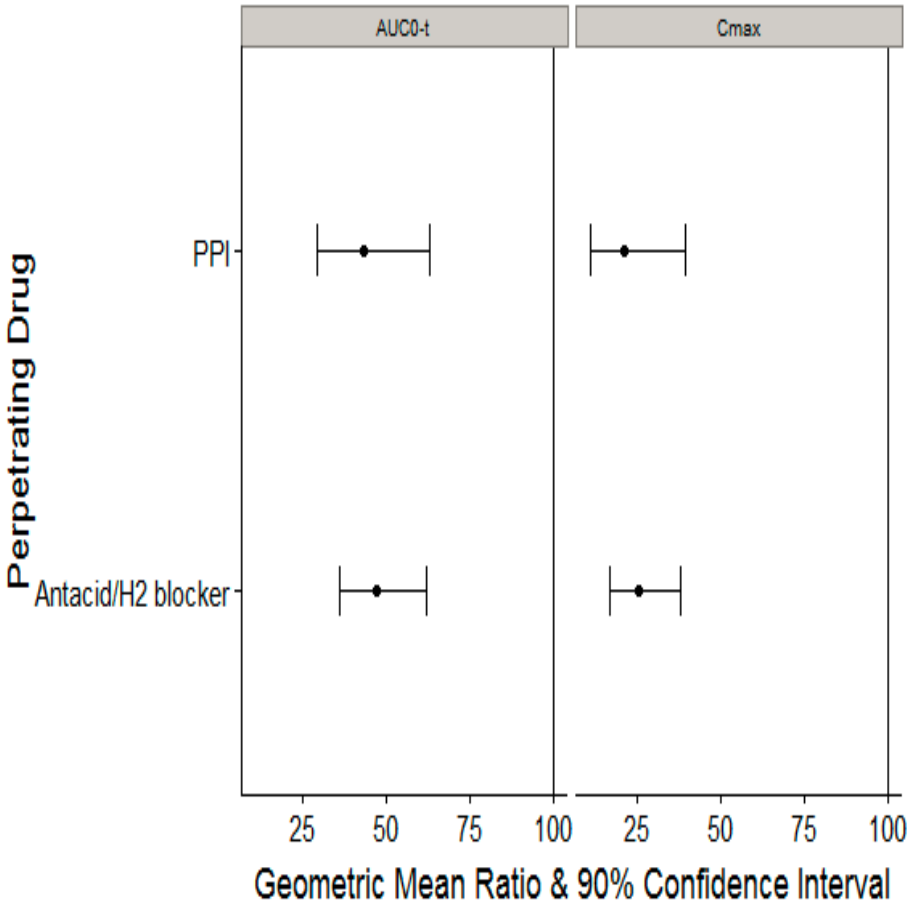
Class Specific Concerns

- Skin rashes and other cutaneous reactions
- Hepatotoxicity
- Cardiovascular safety
- Gastrointestinal irritation (nausea/vomiting)

Developing Oncology Products: Phase I Timeline/Cost

- Estimates range from at least 12-18 months for n=25 oncology patients
- Compared to 4-6 months for healthy normal subjects (HNS)
- Patients studies can cost into the millions
- Targeted therapies alter the risk vs. benefit ratio relative to cytotoxic agents
- Unless compound causes direct DNA damage, FDA typically allows dosing in HNS

To Consider - Acid-Reducing Agents on PK of TKI Class Compound



- Use of Acid-Reducing Agents in Cancer Patients ranges from 20-70% across cancer types
- Not a class effect
- Similar to food-effect
  - Test early before patient studies

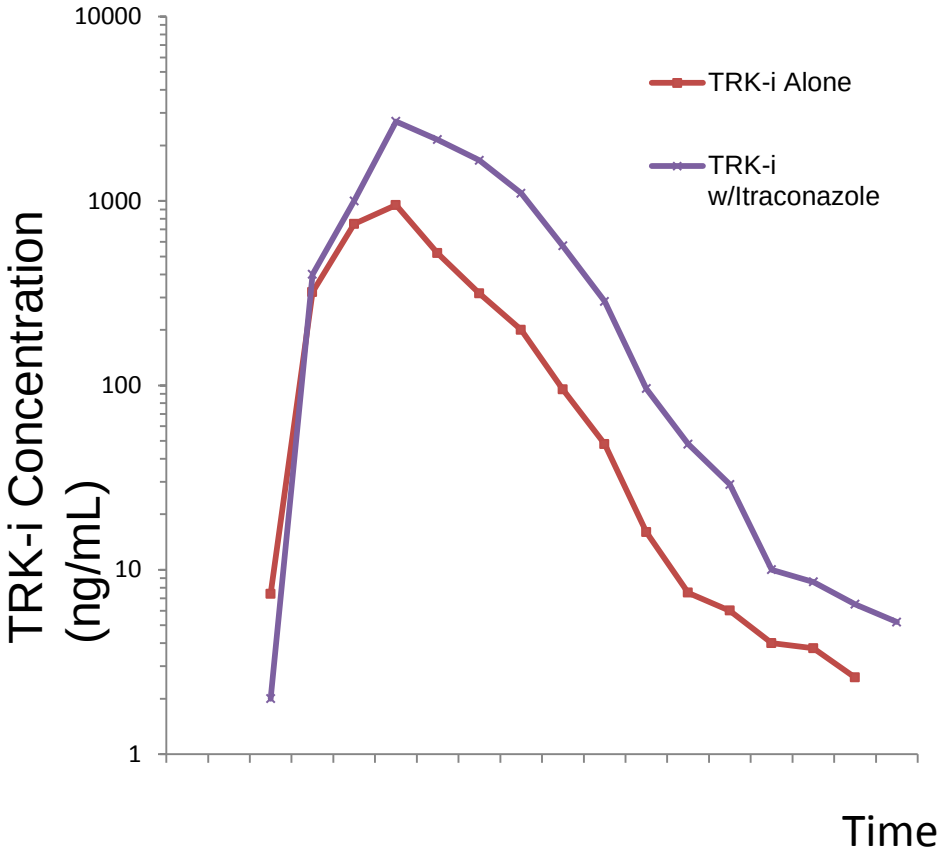
DDI - CYP3A4/P-gp Inhibition/Induction – Single Study

- Part A – Fixed Sequence
  - Drug SD – Itraconazole MD - Coadmin
- Dose Drug Day 1
  - Drug PK, washout
- Itraconazole MD, minimum 5 days and throughout sampling
- Co-admin Drug+Itraconazole on Day 5 or later
  - Drug PK

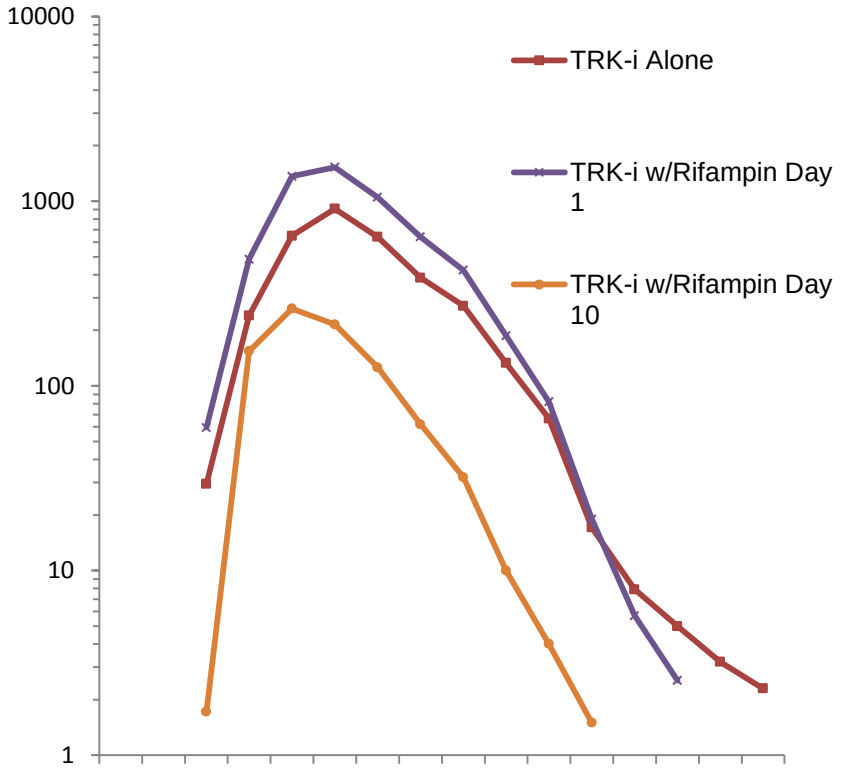
- Part B – Fixed Sequence
  - Drug SD – Rifampin MD Coadmin with Drug SD on Days 1 and 10
- Dose Drug Day 1
  - Drug PK, washout
- Coadmin Rifampin SD with Drug SD
  - Drug PK, washout if necessary
- Rifampin dosing for at least 10 days
- Co-admin Drug+Rifampin on Day 10 or later
  - Drug PK

DDI - CYP3A4/P-gp Inhibition/Induction

MD Itraconazole



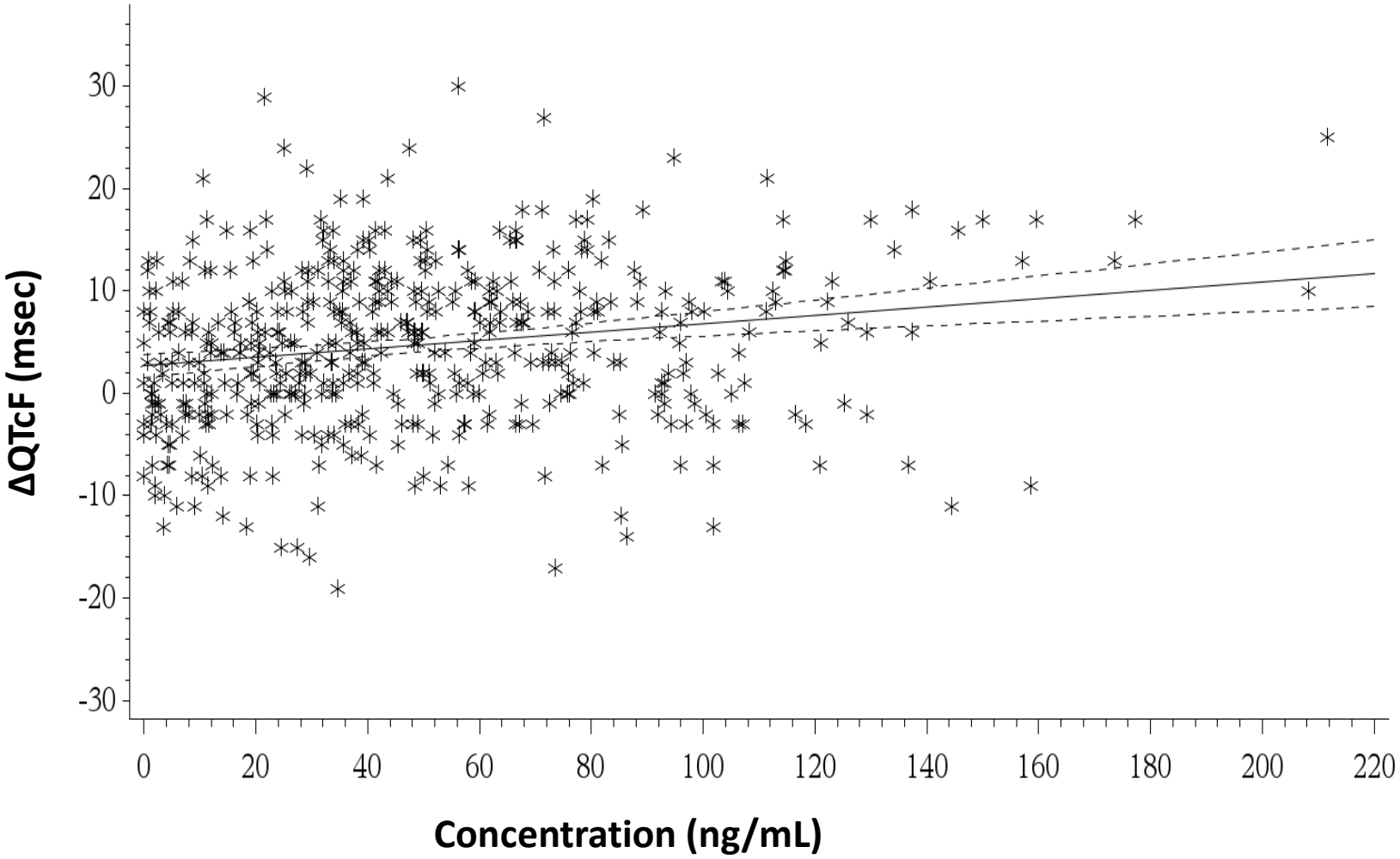
SD & MD Rifampin



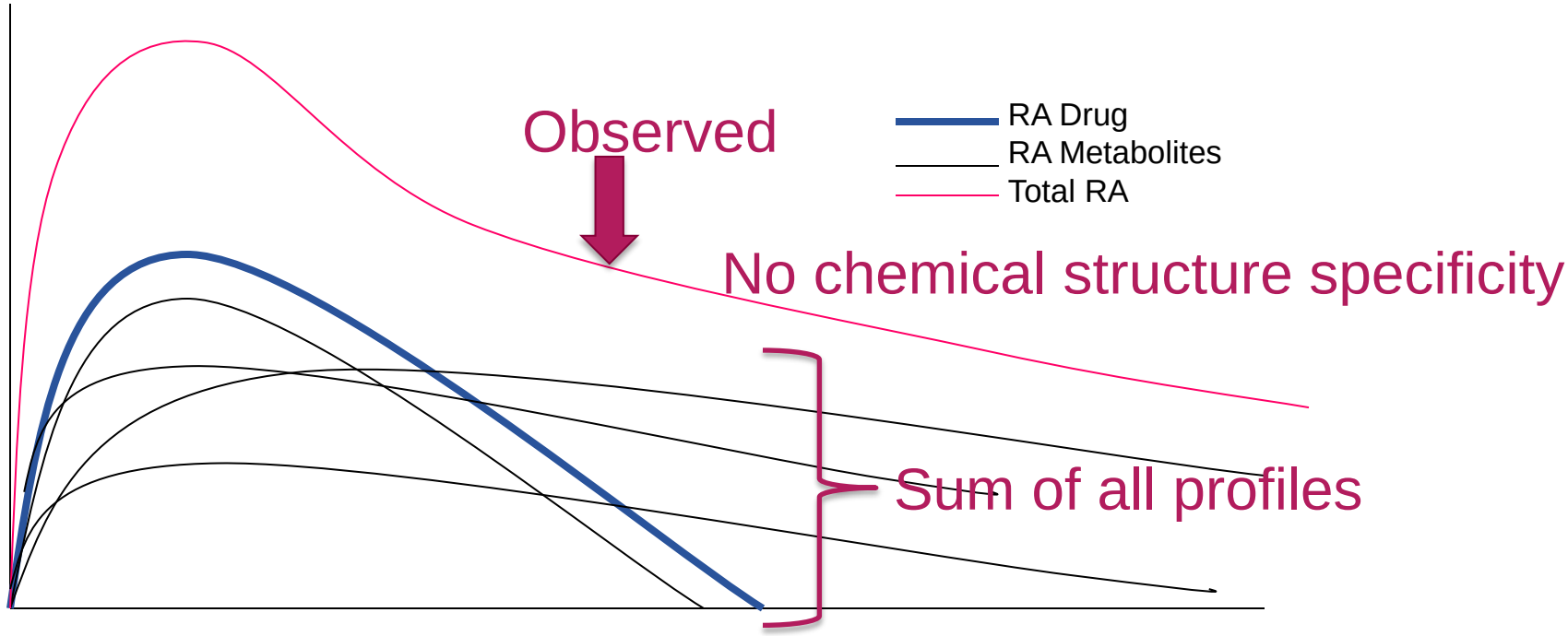
Consider cQT Early in Development

- Exposure-Response Analysis will assess cardiac liability
- Data available across a series of doses
- Could come from SAD/MAD/DDI/High Exposure studies
- Data could be collected, stored, analyzed at a later date

Data Allows for Evaluation of cQT - Change From Baseline in QTcF vs Time-Matched Concentrations



Radioactivity Plasma Profile

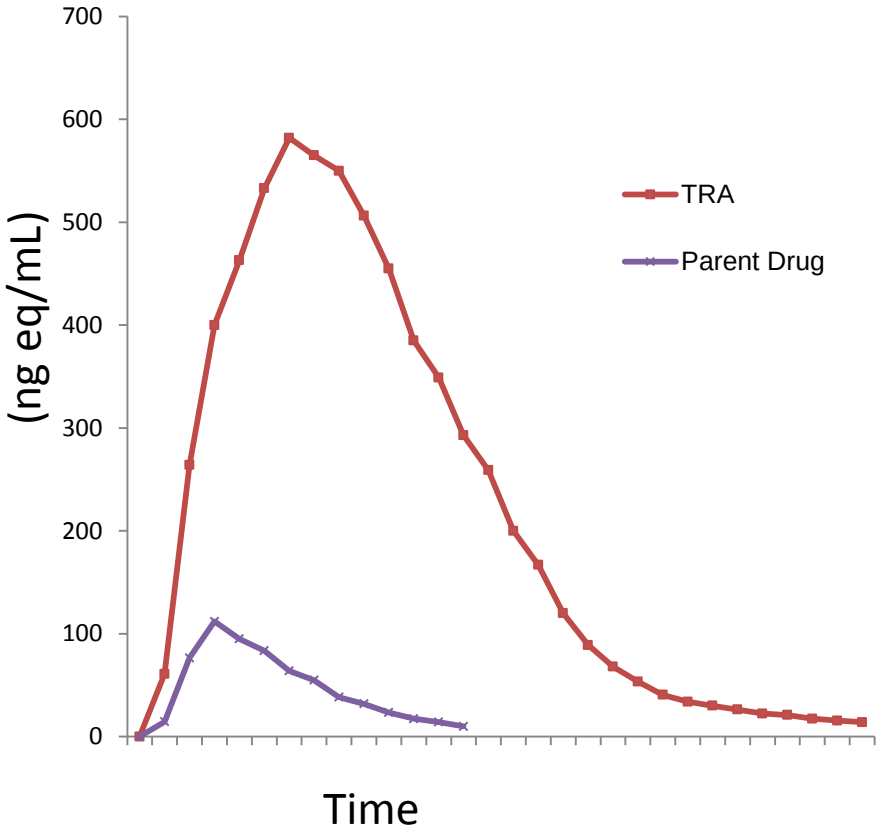


The Total Radioactivity concentration-equivalent vs time plot is a sum plot of drug + all of its RA metabolites.

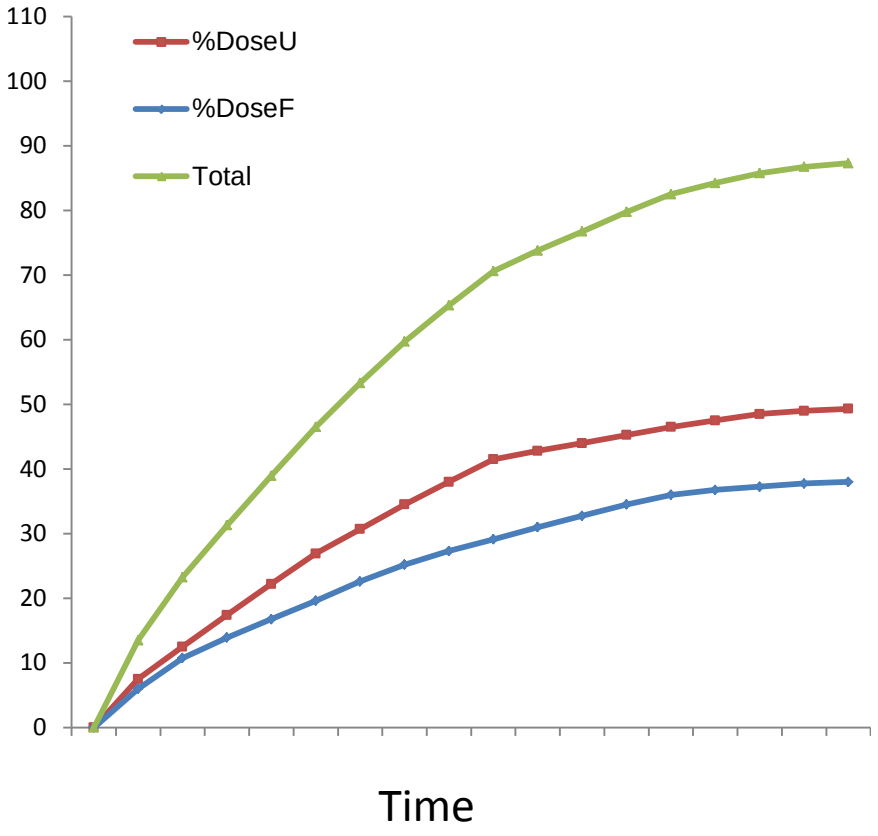
- Observed total RA Cmax ≥ Drug Cmax
- Estimated total RA AUC0-inf ≥ Drug AUC0-inf
- Estimated total RA terminal t1/2 ≥ Drug terminal t1/2

ADME/Mass Balance

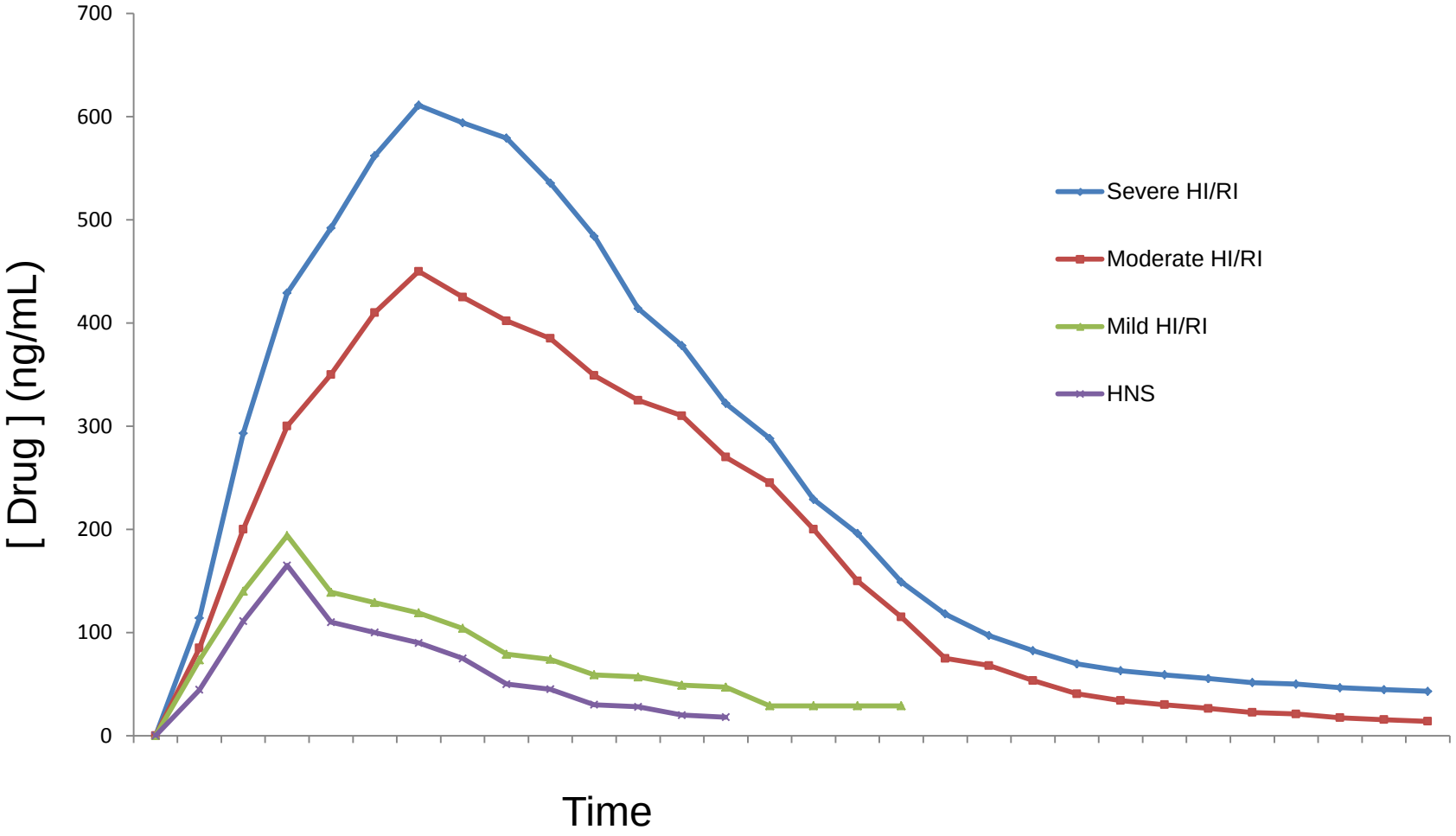
Plasma Profile



Dose Recovered



Oncology Drug Development – HI/RI



In Summary

- Development of noncytotoxic oncology therapeutics in the last decade has increased and is now the norm
  - Opportunity to test on HNS rather than patients
  - Opportunity to use classic Phase I designs
  - Shorter study timelines from start to finish
  - Robust characterization of PK
  - Lower costs per study
- Celerion has experience in all aspects of early phase development for your new oncology drug
- Together, we can beat it!

Thank you!

Questions?