Cancer Drug Development : A Multidisciplinary Science

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Kick-off

Multidisciplinary Seminar Series

P20 UHCOP-DLDCCC BCM Cancer Research Alliance

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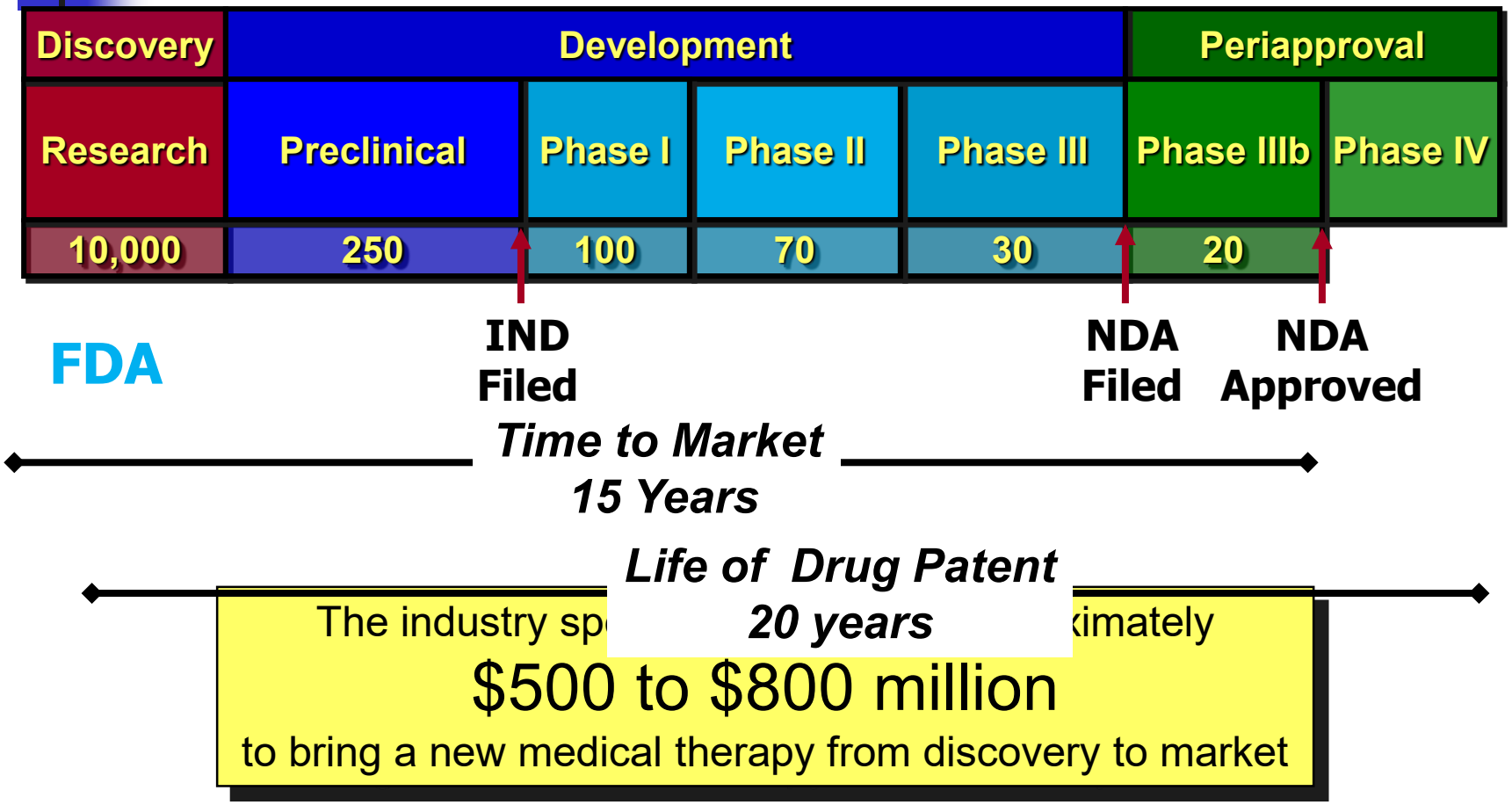
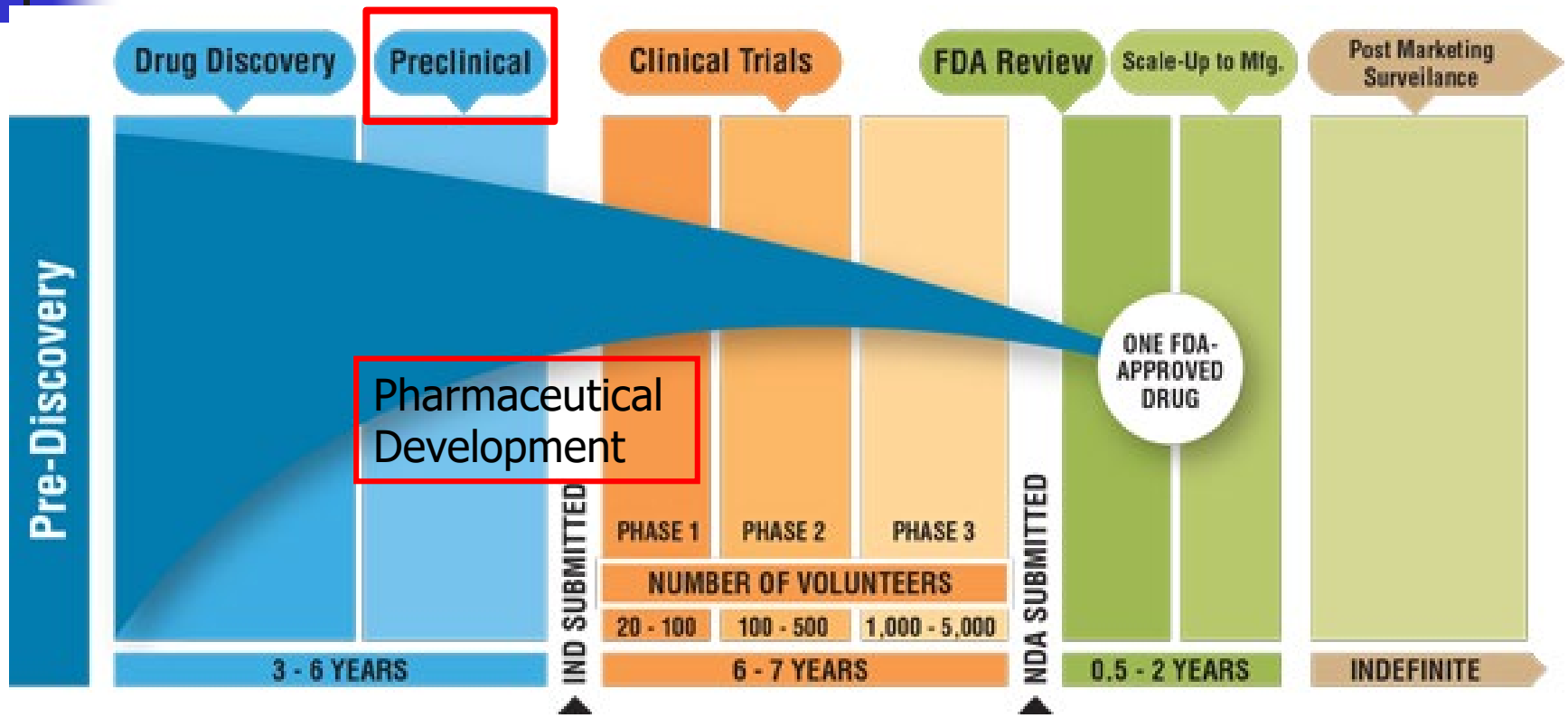
UNIVERSITY of HOUSTON
COLLEGE OF PHARMACY

Drug Development Process
from Discovery to Market



Drug Discovery and Development Timeline



NCE
NME

15 – 30 months
$5-10 MM USD

FIH

Chow, Andersson, Bhagwatwar, Giovanella*, Wu, Kim, Wang, Renbarger, Agu

Pharmaceutical Development in Preclinical Phase

(1-3 yr, $ 5-10 MM)

Scope of work

- 1. Bioanalysis: LC-MS/MS, HPLC
- 2. Preformulation: Physicochemical properties, Stability, Compatibility; DSC
- 3. Formulation Development Strategies
- 4. In vitro Assessments and Formulation Optimization
- 5. In vivo Preclinical Evaluations in Rodent & Non-rodent Models Pharmacokinetics (PK), Bio-distribution, Efficacy, Toxicity

Chow's Lab Experiences
in Various Stages of Cancer Drug Development

- 1. Development of Busulfan® for Injection by Formulation Approach
- 2. Development of Camptothecin Lactone-Stabilized Prodrug CZ48, by Preclinical and Clinical PK Approach
- 3. Optimization of Therapy Outcomes by Clinical PK/Pharmacogenetics (PG)/Pharmacodynamic (PD) Approach

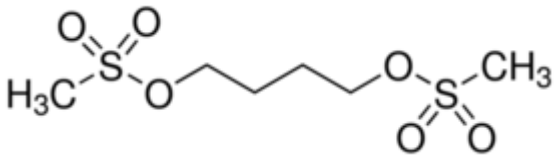
1. IV Busulfex®

Oral 2 mg Tablet

6 mg/ml, 10 ml Solution for Injection

- **Two-way Translational Research**
  - Bedside to Bench-top
  - Bench-top to Bedside

API - Busulfan



- Busulfan (BU) is a bifunctional, ablative alkylating agent (MW 246.31)
- Used for the preparative regimen before blood, bone marrow, or stem cell transplantation

Clinical Issues Prior to IV Busulfex®

- Regimen : 35 tablets q6h
  around the clock for 4 days
  (16 doses)
- Patients experienced vomiting
  resulting erratic systemic exposure (AUC)
- Grafting success related to AUC
  900 – 1500 μMol. min
- Hepatic veno-occlusive disease (HVOD)
  with AUC > 1500 μMol. min

Ample Opportunities for Translational Research at Texas Medical Center (TMC)

TMC

Largest Medical Center in the world, >1,000 acres (~ size of downtown of Dallas)
Highest densities of facilities for patient care, basic science, and translational research
50 medical-related institutes: 15 Hospitals, 2 Specialty Institutes, 3 Medical Schools,
4 Nursing Schools, Schools of Pharmacy, Dentistry and Public Health…
>100,000 employees: 20,000 physicians, researchers & advanced-degree professionals
Patients: 160,000 daily, 6 millions annually, 18,000 international, 1st air ambulance

Development Milestones (1991-1999) of Busulfan® for Injection

- 1991 A humbling start with 1-yr funding of $21,203 from MDACC for formulation development
- 1993 Patent filings (2)
- 1994 Agreements with MDACC and Orphan Medical (OM) 1-yr funding of $78,732 from OM in 1994 for preclinical PK evaluations
- 1995 & 1996 Patents granted
- 1999 FDA approval of IV Busulfex®in Feb

Impacts on UH

- Educational benefit
  - 1 M.S. and 2 Ph.D. graduates trained
- Financial benefit
  - $ 14.4 MM royalty incomes
    (June 1999 - September 2016)
  - $ 16.0 MM
    (January 2019,
    Litigation settlement)

Clinical Benefits/Impacts

- Grafting success
  - Improved patient compliance
  - Predictable systemic exposure (AUC)
  - Enhanced grafting success
- Substantial reduction of HVOD toxicity and fatal rate
  - Minimized hepatic toxicity, 20% $\rightarrow$ 3%
  - Reduced fatality,
    30-45% in 3 months $\rightarrow$ 6 – 8 % in one year

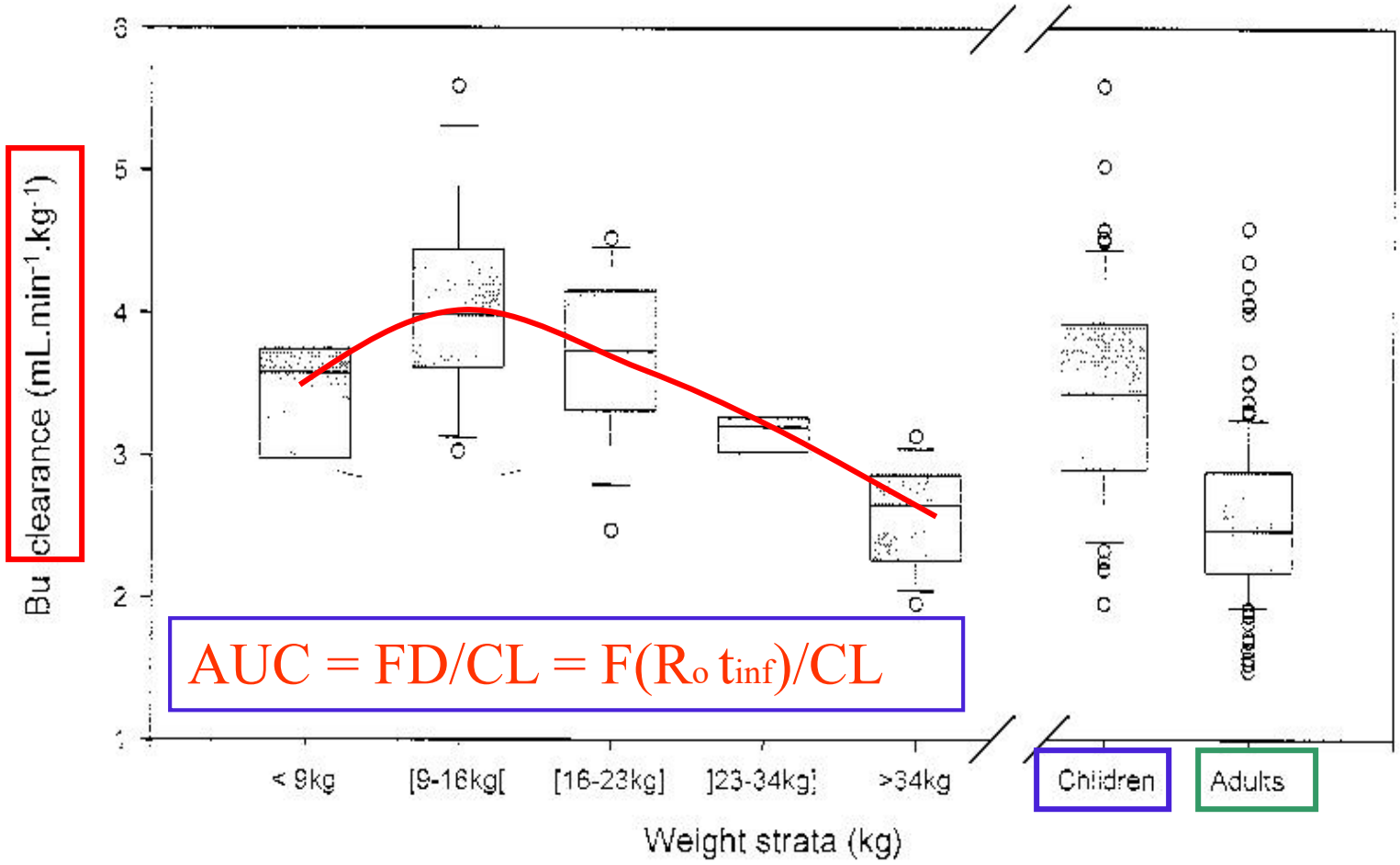
Clinical Benefits/Impacts (cont'd)

- Additional merit (not originally intended)

  Application to pediatric populations

  – individualized dose regimen

Rational Use of Busulfex®
in Pediatric Patients

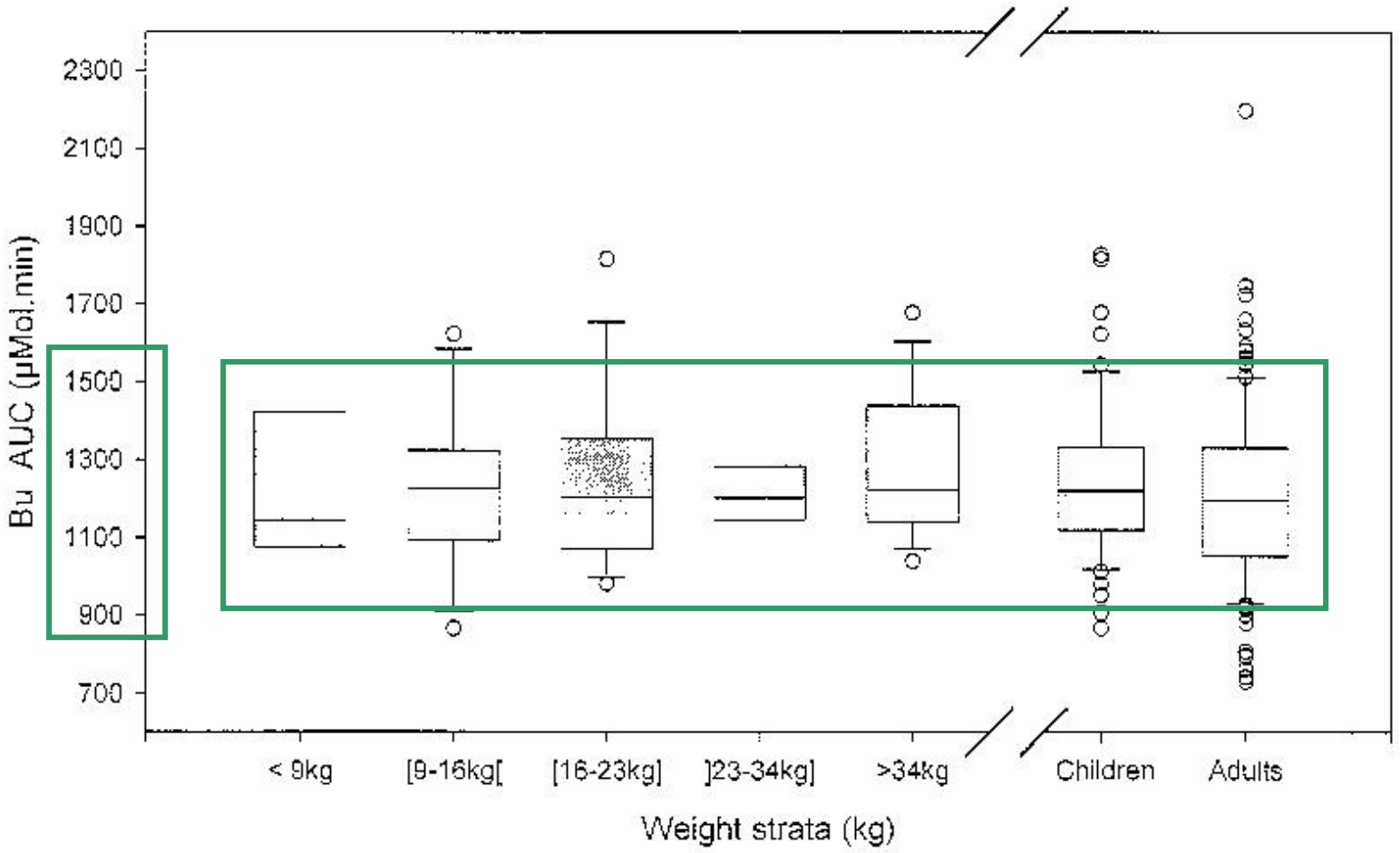


Chow, Andersson, Bhagwatwar, Giovanella*, Wu, Kim, Wang, Renbarger, Agu

Vassal et al. 2006

After Individualized Dose Adjustment

Dose′ = F(R_o t_{inf}) = CL (AUC)



Chow, Andersson, Bhagwatwar, Giovanella*, Wu, Kim, Wang, Renbarger, Agu

Clinical Benefits/Impacts (cont'd)

- Available in 46+ countries in North America, Europe, Australia, Asia
- Standard care in 65%+ transplant patients in North America

IV Busulfex®

Otsuka
Otsuka America Pharmaceutical, Inc.

Excellent Example

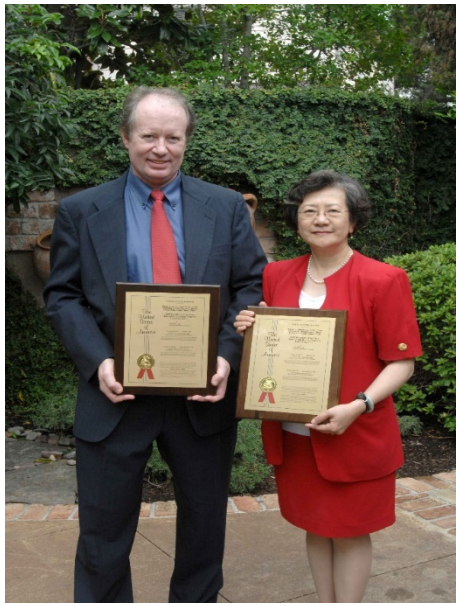
of PK-guided

Product Development
and
Clinical Usage
of Busulfan

Clinical Merits Recognized

Received "HIPLA Inventor of the Year Award", 2009 with Borji Andersson, MD. PhD.

Inducted as Fellow of National Academy of Inventors, 2016



II. CZ48
Prodrug of Camptothecin (CPT)

- Potential anticancer agent
- Topoisomerase-1 enzyme inhibitor
- Tumor suppression against 19 different human tumors (bladder, breast, colon, lung, etc.) in human tumor-xenografted nude mice (Cao et al., 2009)

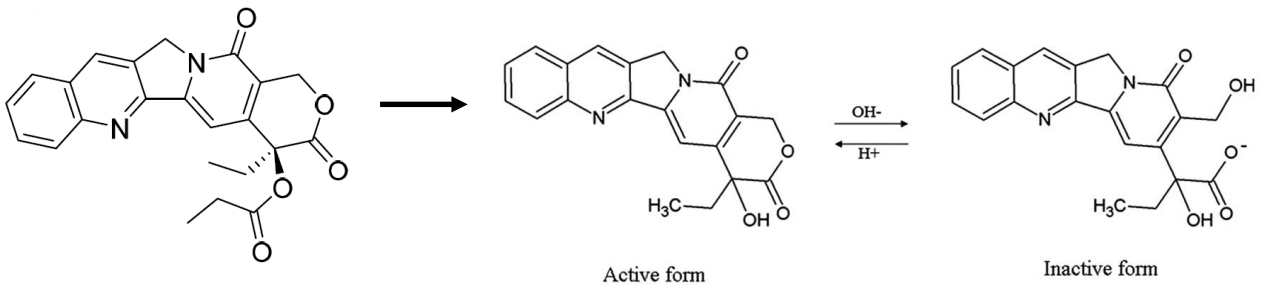
  - Biotransformation to CPT

CPT-20-O-propionate hydrate

CZ48

Advantage:

- Lactone stability



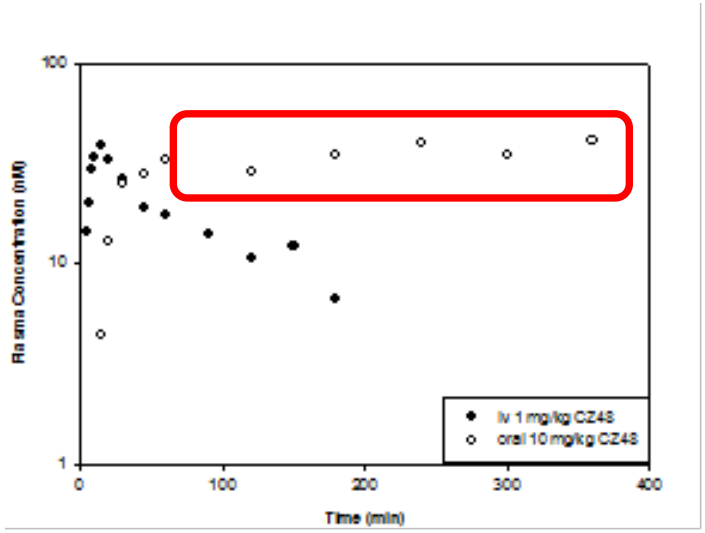
CZ48 CPT

Lactone form

Carboxylate form

at physiological pH (7.4)

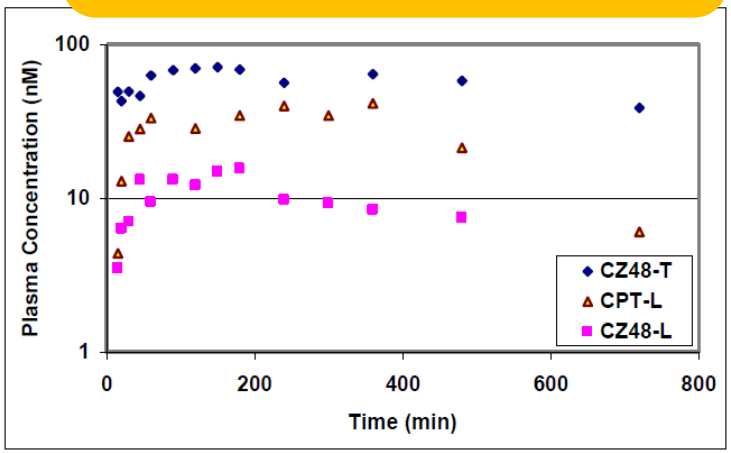
Sustained concentrations of CZ48/CPT for up to 6 hr after the oral dose of CZ48



(●): IV dose of 1 mg/kg of CZ48 in co-solvents (DMSO: PEG400: EtOH, 2:2:1, v/v/v)

(○): PO dose of 10 mg/kg of CZ48 in the same co-solvents

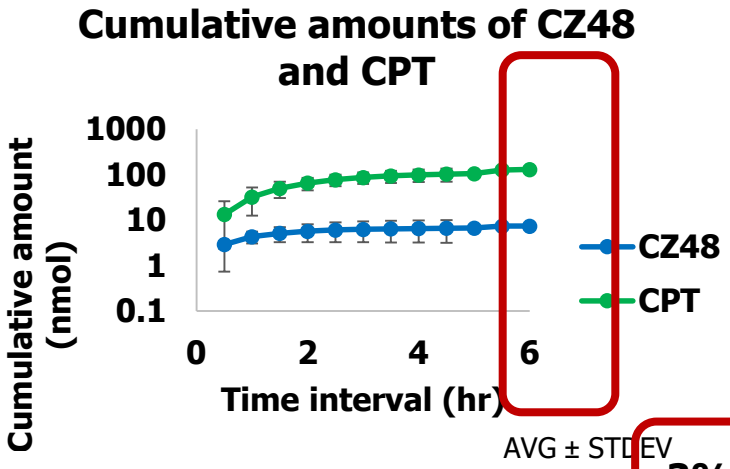
Potential enterohepatic recycling of CZ48 and CPT



(*Xaohui Li's Dissertation at UH*, 2004)

Biliary excretions of CZ48 and CPT after an IV Dose of CZ48

- IV Dose: 5 mg/kg of CZ48 in co-solvent formulation



AVG ± STDEV

Parameter	Units	CZ48	CPT
$AUC_{0\text{-}6h}$ in plasma	hr*ng/mL	3203.03 ± 1785.24	722.13 ± 397.72
CL_{total}	ml/hr	540.61 ± 236.31	2058.90 ± 888.87
CL_{bile}	ml/hr	0.87 ± 0.20	56.38 ± 15.37

AVG ± STDEV

3% of Dose

- Clearance of a drug in bile (CL_{bile}):

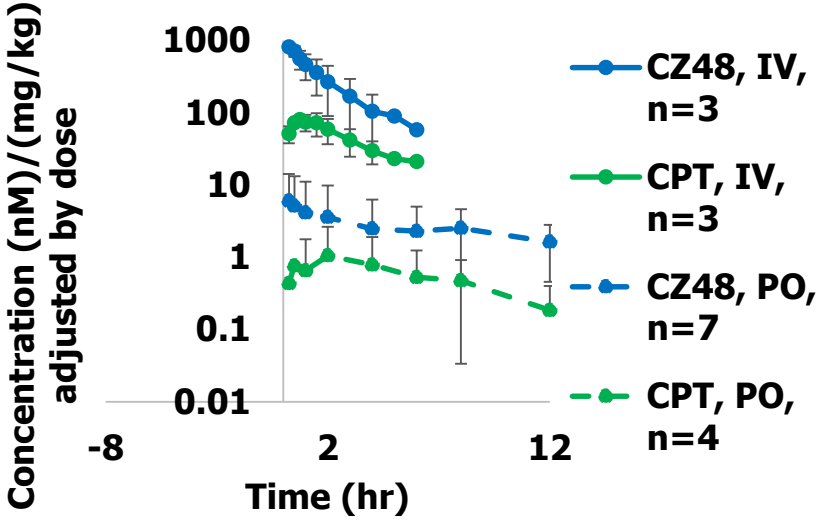
CL_{bile} = (Amount of a drug excreted into bile during a time interval)/(AUC_{plasma})

~3% of CL_{bile} in CL_{total}

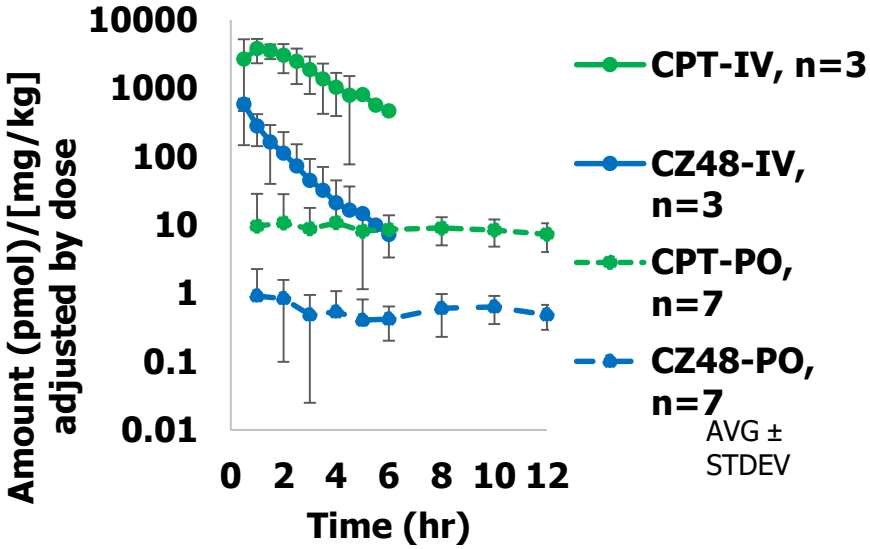
Biliary excretion: IV and PO

- Doses: 5 mg/kg of CZ48 in co-solvent formulation (IV) or 25 mg/kg of CZ48 in the same formulation (PO)

Plasma concentrations of CZ48 and CPT



Amounts of CZ48 and CPT in Bile



Biliary Excretions of CZ48 and CPT

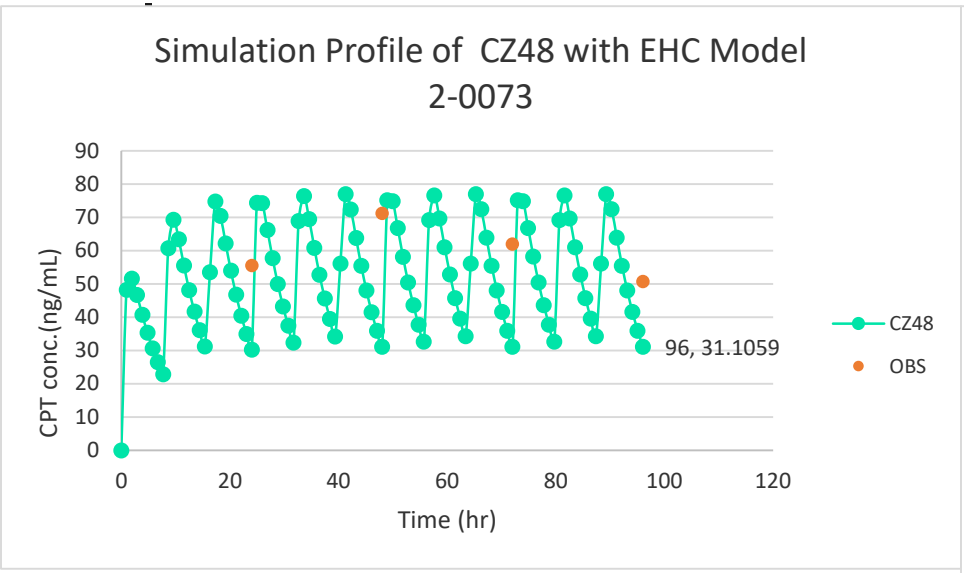
- Biliary secretions of CZ48 and CPT as their parent forms.
- Biliary clearance (CL_{bile}) of CPT (56.38 ml/hr) > CL_{bile} of CZ48 (0.87 ml/hr).
- Approximately 3 % of the dose recovered in bile as CPT.
- Increased biliary secretions of CZ48 and CPT after an oral dose, compared to those after an IV dose.
- Sustained biliary secretions of CZ48 and CPT for 12 hr post oral dose.
- **Enterohepatic recycling (EHC)** of CZ48 and CPT was minor in rats.

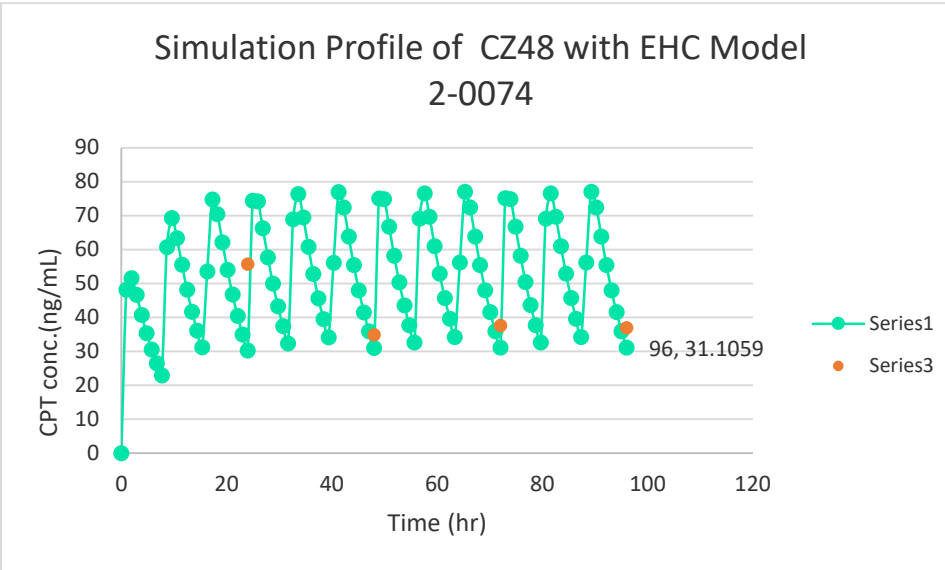
Phase I Clinical Trial Issues

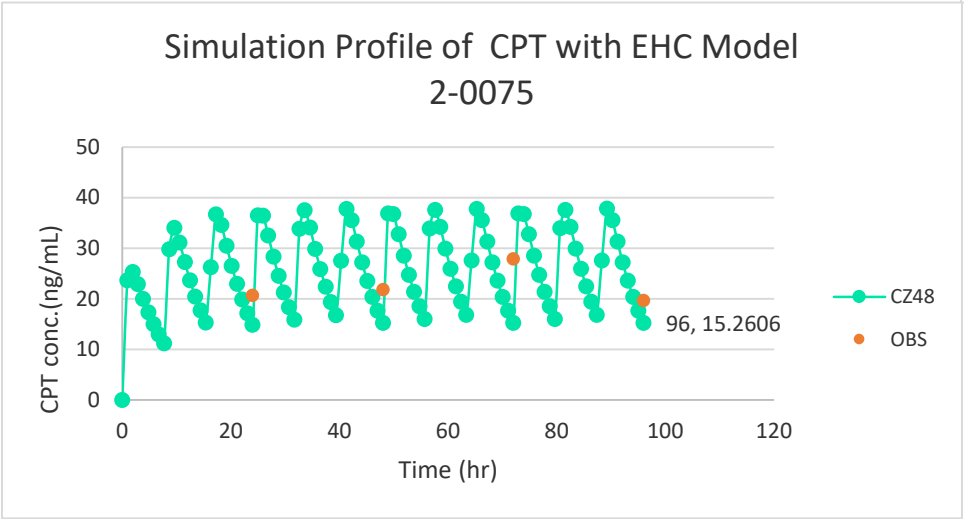
- For screening patients, blood samples were collected up to 48 h time points after

  a single oral dose.
- CZ48 reached steady state after 3 doses
- Significant accumulation of CPT levels and potential resulting toxicity in humans

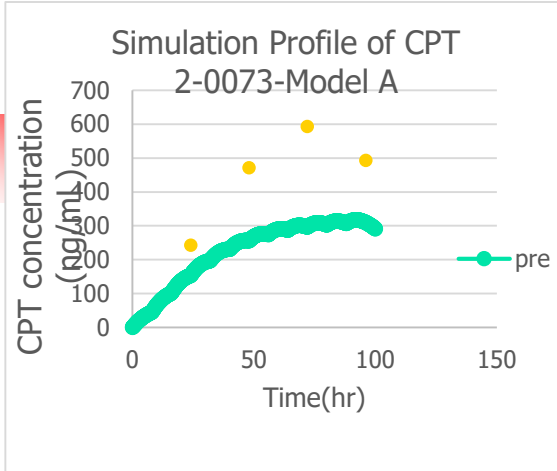
Simulation Profiles of CZ48

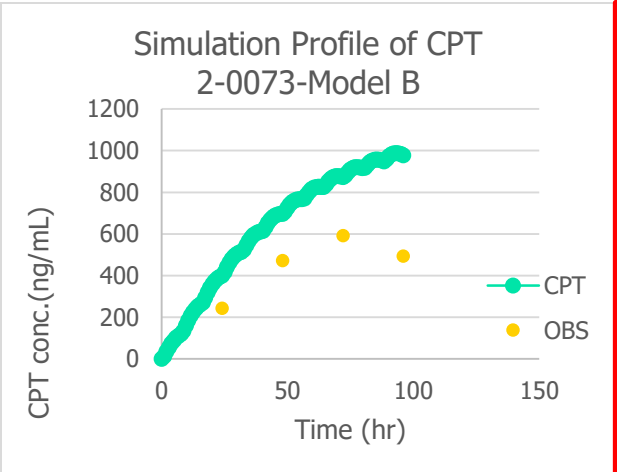


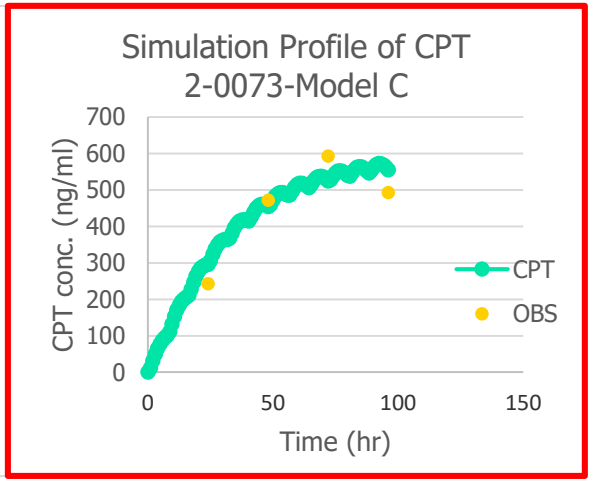


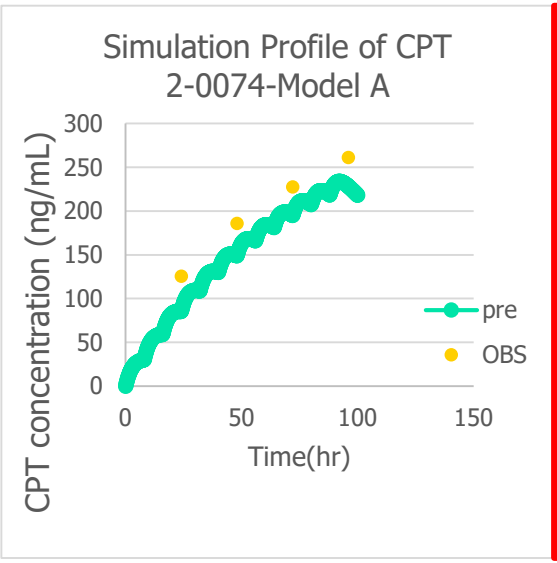


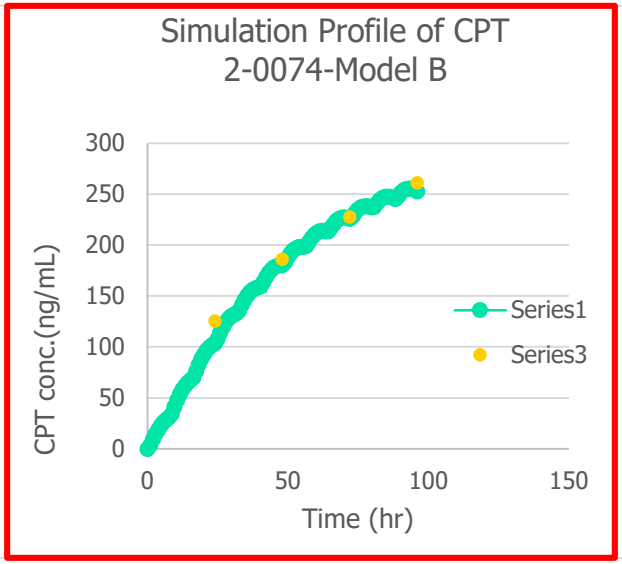
Simulation Profiles of CPT

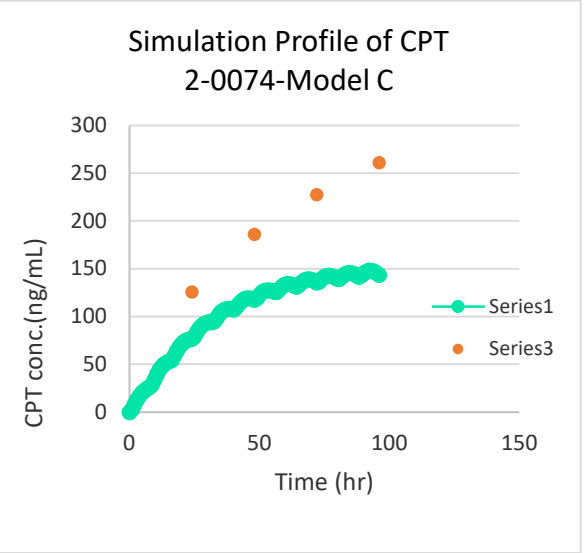






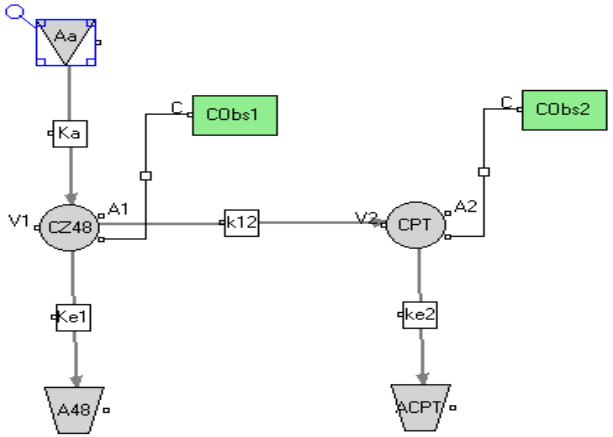




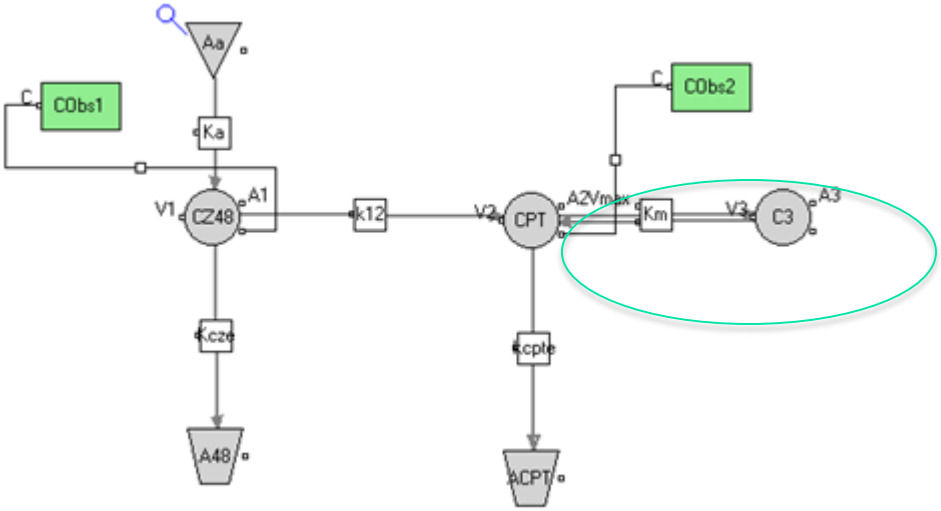


Solving Phase I Clinical Trial Issue by EHC Knowledge from Preclinical PK

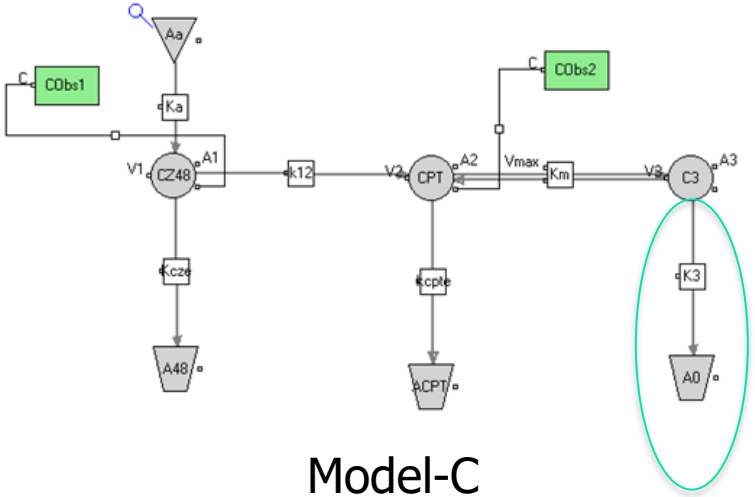
- The EHC models were developed based on knowledge gained from preclinical PK in rats
- EHC is the significant contributing factor to the accumulation of CPT levels and potential resulting toxicity in humans.



Model-A

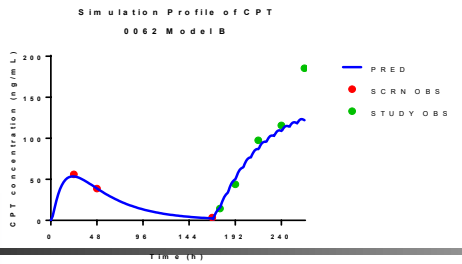


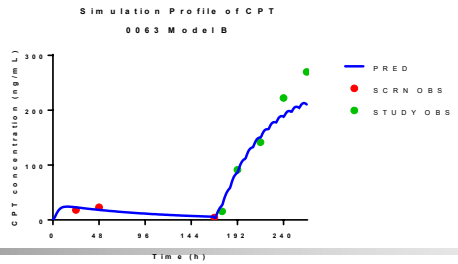
Model-B

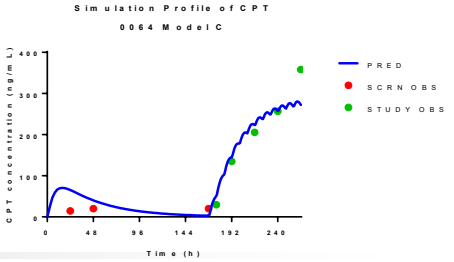


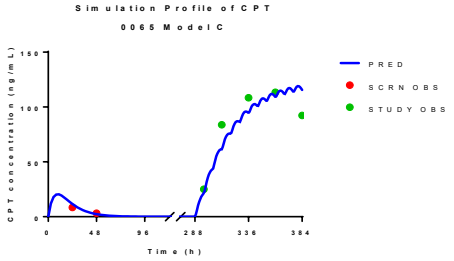
Model-C

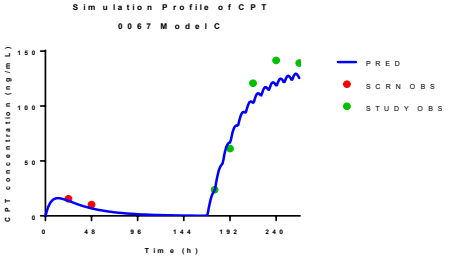
Simulation Profiles of CPT with Best Fit Model

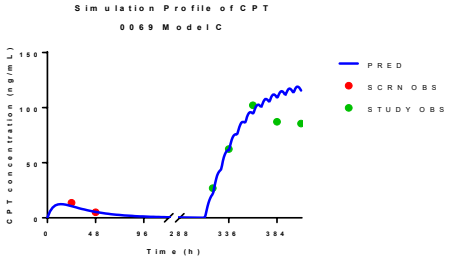


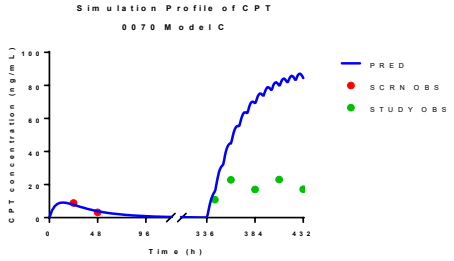


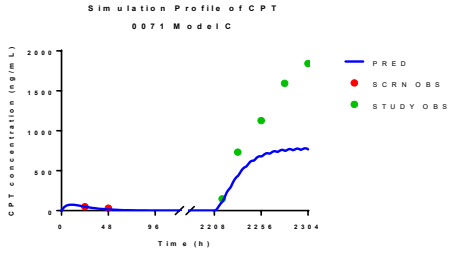


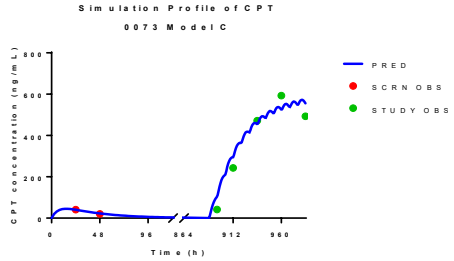


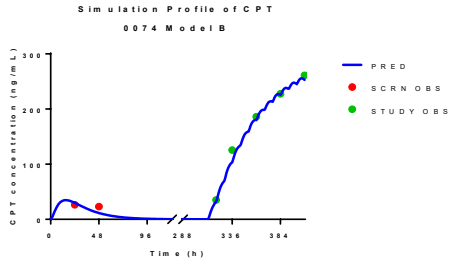


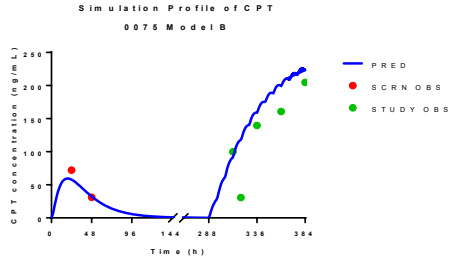












III. Optimization of Vincristine Therapy in Kenyan Pediatric Cancer Patients

- Vincristine (VCR) is metabolized by CYP 3A5 to major metabolite, M1.
- Dosing in pediatric patients are still largely empirical.
- Ethnic variations in expression of CYP 3A5
  - high expressers in

    90% Kenyan patients

    70% African Americans

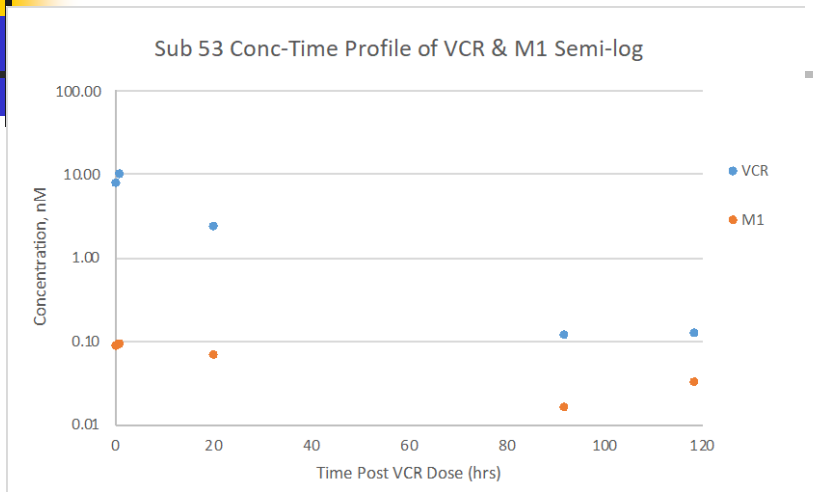
    10-15% Caucasian Americans
- Therapeutic outcomes –

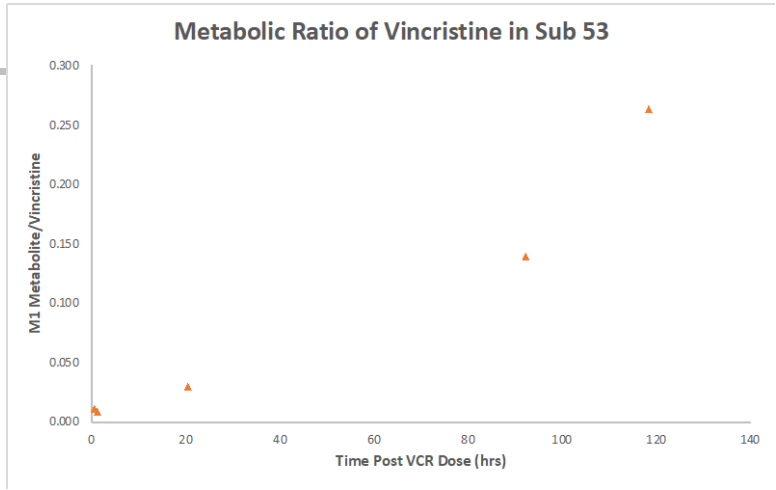
  good in Caucasian, but with significant neuropathy, poor in Kenyan patients with no or minimal neuropathy

Comparative Clinical Trial with Kenyan & Caucasian American Pediatric Patients

- Clinical trial with Kenyan (N=100) and Caucasian American (N=130) Patients, 2-16 yo
- Collaboration with Dr. Renbarger in Indiana University, School of Medicine
- Blood were collected as Dry Blood Spot (DBS) samples on Whatman paper at 6 various time points at 0.5 – 166 hr post dose
- Saliva samples were collected for pharmacogenetic typing (PG data)
- Neuropathy were evaluated through the course of therapy (Pharmacodynamic –PD data)

Subject 53 (5 yo M): VCR & M1 PROFILES

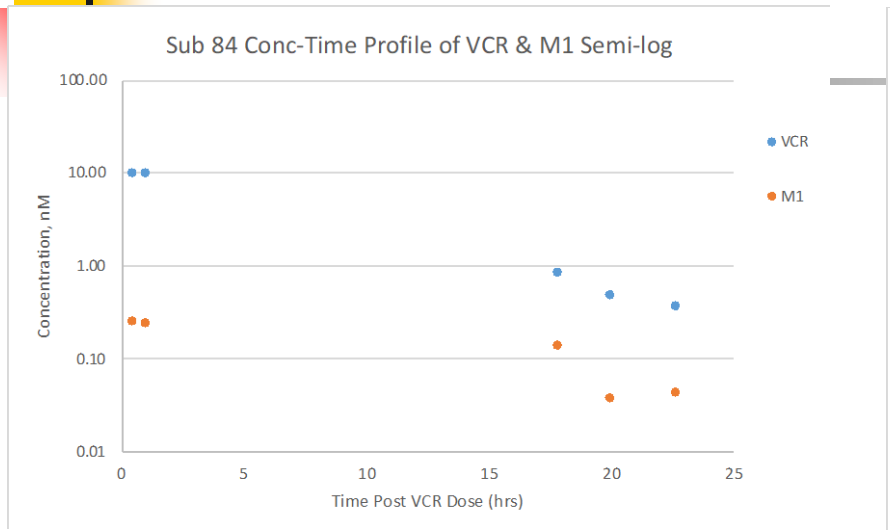


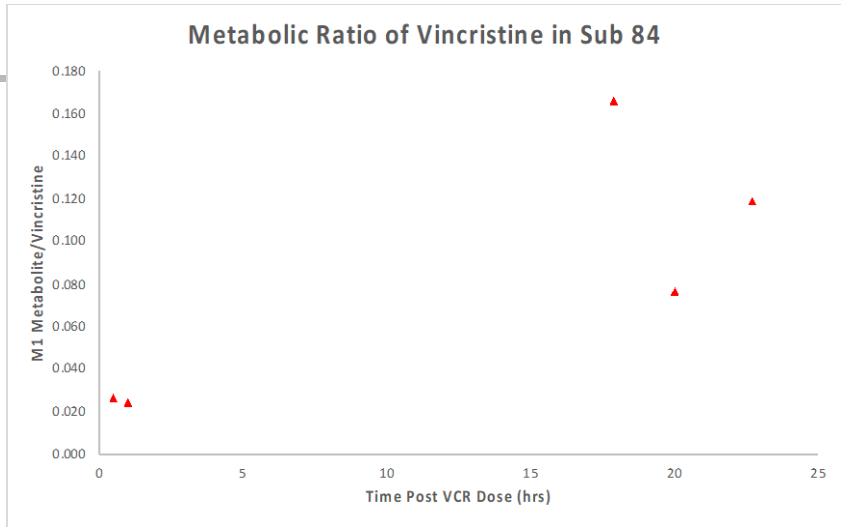


Subject 53					
Age (yrs.)	5	**Time post dose**	**VCR Conc.**	**M1 Conc.**	**M1 metabolite/Vincristine**
Body weight (kg)	15.5	**hrs.**	**nM**	**nM**	
Sex	Male	0.52	7.66	0.09	0.011
Dose delivered (mg)	1.4	1.05	9.95	0.09	0.009
		20.33	2.24	0.07	0.03
Calculated actual dose delivered (mg/m2)	2.04	92.17	0.11	0.02	0.14
		118.48	0.12	0.03	0.264

Chow, Andersson, Bhagwatwar, Giovanella*,
Wu, Kim, Wang, Renbarger, Agu

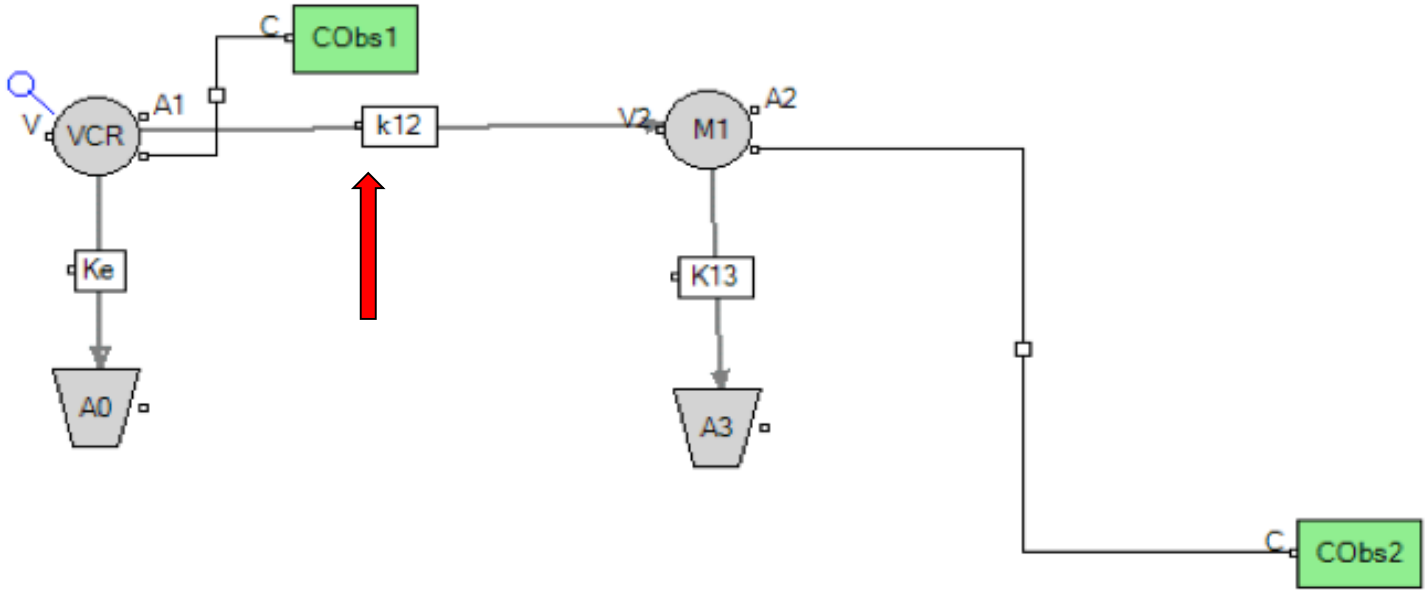
Subject 84 (3 yo F): VCR & M1 PROFILES





Subject 84					
Age (yrs.)	3	**Time post dose**	**VCR Conc.**	**M1 Conc**	**M1 metabolite/Vincristine**
Body weight (kg)	13.1	**hrs.**	**nM**	**nM**	
Sex	Female	0.5	9.47	0.25	0.026
Dose delivered (mg)	1.2	1	9.57	0.23	0.024
		17.87	0.83	0.14	0.166
Calculated actual dose delivered (mg/m2)	2	20	0.48	0.04	0.077
		22.7	0.36	0.04	0.119

Co-Modeling of VCR and M1



PK/PG/PD analysis and correlation will be established for future dosing modification, optimization or personalization in Kenyan, African American and Caucasian American pediatric cancer patients.

Welcome to Gain Research Experiences for Cancer Research

- P20 Mission in Education
  - UR students
  - UR and non-UR students
    - Research on Health Disparity in Cancer Research

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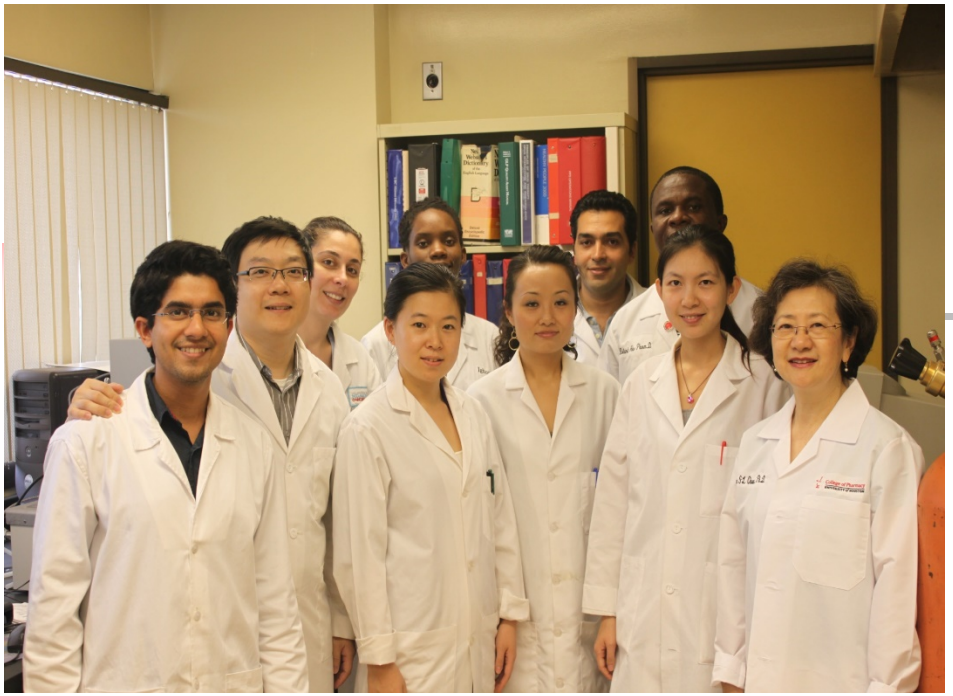
  - Dr. Beppino Giovanella* (SFCR)
  - Dr. Jamie Renbarger (Univ of Indiana, Medicine
- Lab members
  - Drs. Wu, Bhagwatwar, Phadungpojna, Li, Dong, Kim, Zhang, Sarkar, Wang
  - Agu, El-Zailik, Lincha, Nguyen, Eure



Thank You!!!

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