Discovering Impactful Drugs in Academia?

Same Successful Formula As in Industry:

Luck and Perseverance

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Foundation of Cancer Therapeutics Crash Course

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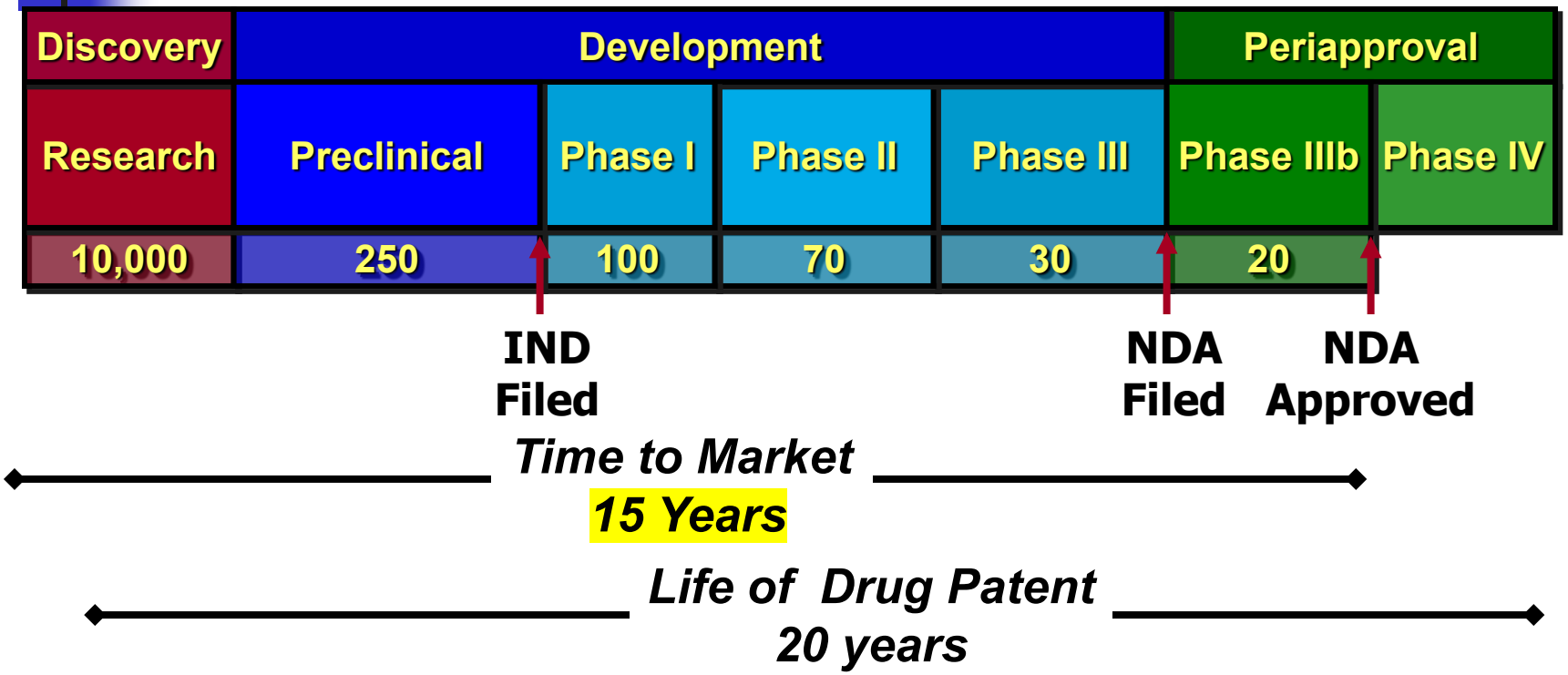
UNIVERSITY of HOUSTON
COLLEGE OF PHARMACY

Personal Experience in Developing Busulfex®

- Development Milestones of Busulfan for Injection
- Acknowledging Supports from UH and TMC
- Current inspiring climate for innovation at UH

Drug Development Process
from Discovery to Market

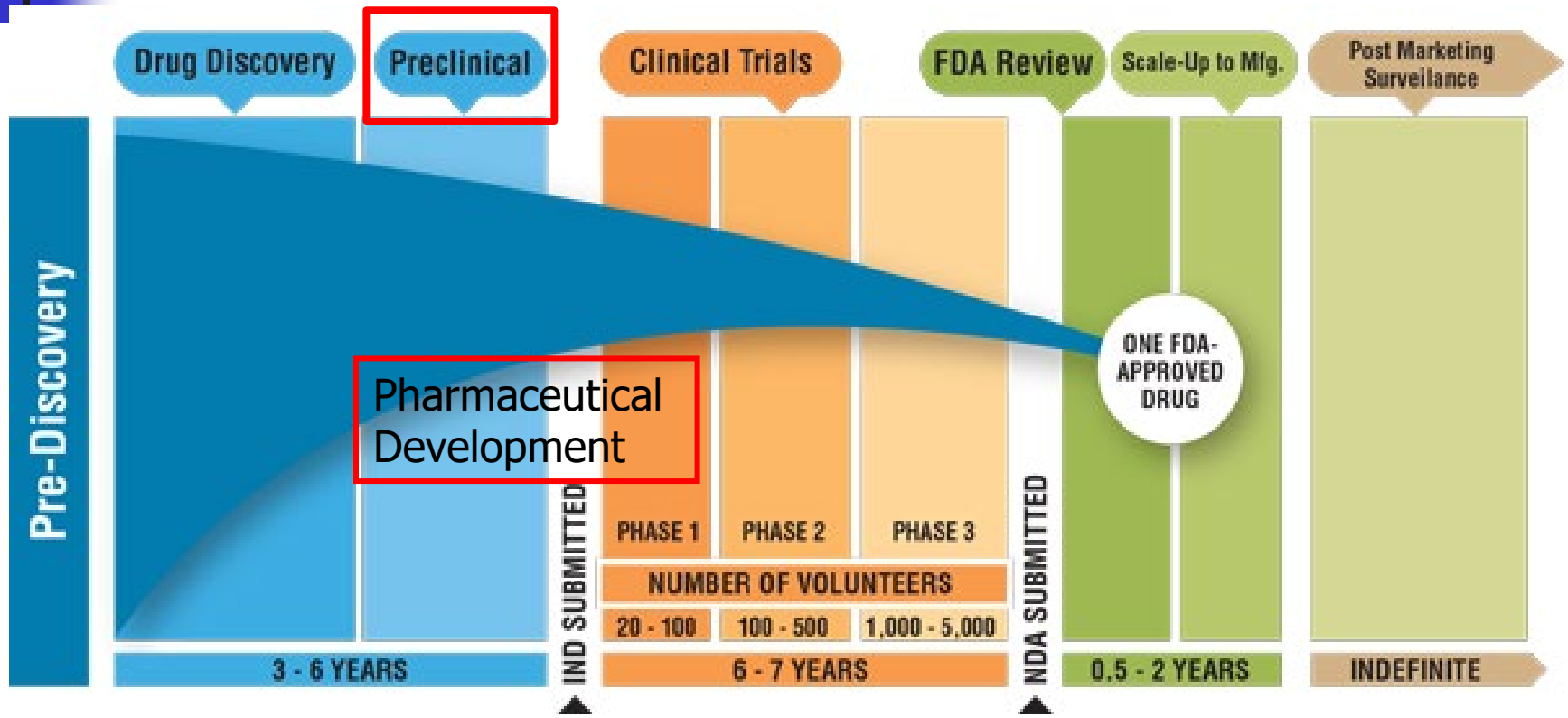


The industry spends, on average, approximately

$500 to $800+ million

to bring a new medical therapy from discovery to market

Drug Discovery and Development Timeline



NCE
NME

15 – 30 months
$4-8+ MM USD

FIH

Pharmaceutical Development in Preclinical Phase
(1-3 yr, $ 4 - 8+ 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 – Healthy and/or Diseased : for Pharmacokinetics (Pkin), Bio-distribution & Proof-of-concept Efficacy (diseased model)

IV Busulfex®

Otsuka
Otsuka America Pharmaceutical, Inc.

Excellent Example

of PK-guided

Product Development
and
Clinical Usage
of Busulfan

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

TMC (1981-2017)

(2018 -)

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…
93,500+ employees: 20,000 physicians, researchers & advanced-degree professionals
Patients: 160,000 daily, 6 millions annually, 18,000 international, 1st air ambulance

IV Busulfex®

Oral 2 mg Tablet

6 mg/ml, 10 ml Solution for Injection

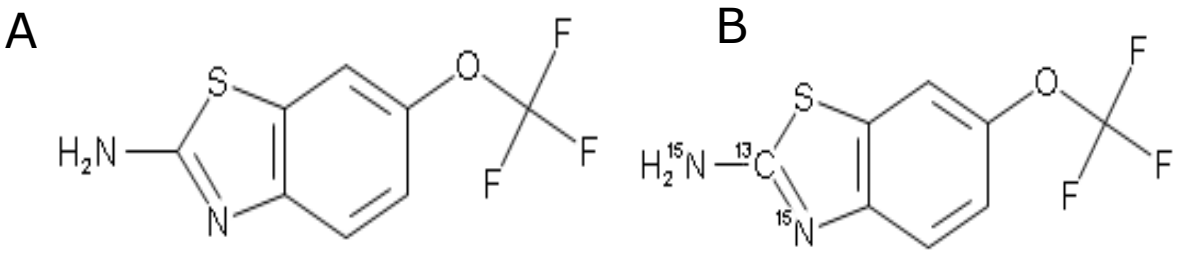
- **Two-way Translational Research**
  - Bedside to Bench-top
  - Bench-top to Bedside

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 pharmacokinetic evaluations
- 1995 & 1996 Patents granted
- 1999 FDA approval of IV Busulfex®in Feb

Central Composite Design (CCD) - other example

- Polyethylene glycol (PEG 400), propylene glycol (PG) and glycerin (GLY) to formulate a **liquid solution** containing 50 mg of riluzole in 5 ml of solvent mixture of volume



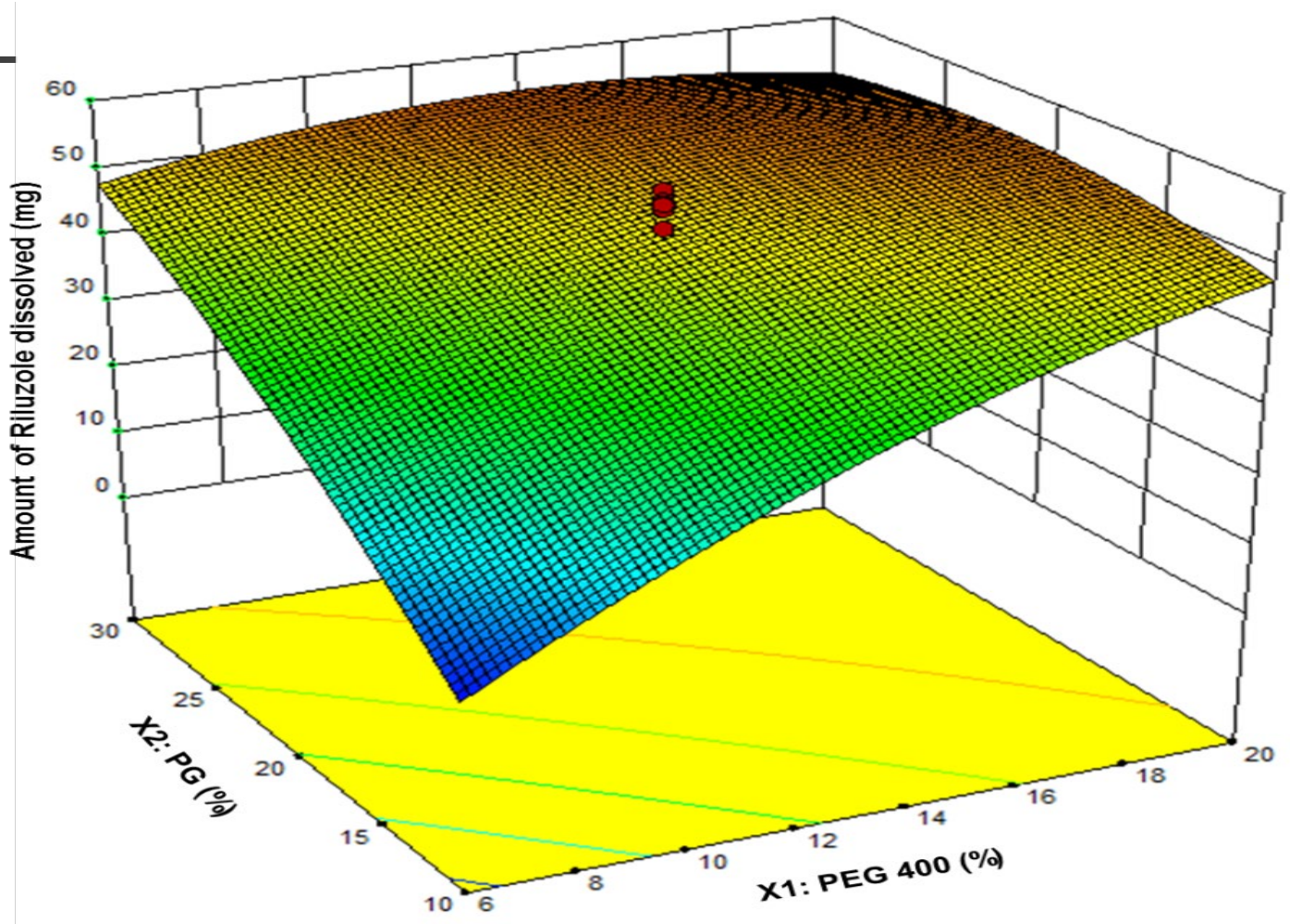
Chemical Structures of (A) **Riluzole** (MW 234.2), and (B) [^{13}C,^{15}N] Riluzole (MW 237.2) (labeled Internal Standard)

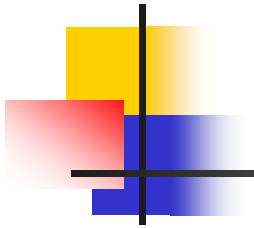
Design Space of CCD and Measured Response Values (N=3,Mean ± SD)

Design	Type	Conc. (% v/v)			Amount of Riluzole (mg) Dissolved in 5 ml
		PEG 400	PG	GLY	
(+1,-1,+1)	Edge	20	10	15	50.77 ± 1.36
(-1,-1,-1)	Edge	6	10	5	8.78 ± 1.89
(-1,+1,+1)	Edge	6	30	15	51.46 ± 2.88
(0,0,0)	Center	13	20	10	43.25 ± 4.37
(0,0,0)	Center	13	20	10	48.38 ± 4.51
(+1,+1, -1)	Edge	20	30	5	52.23 ± 2.07
(+1, -1, -1)	Edge	20	10	5	48.30 ± 1.18
(0,0,0)	Center	13	20	10	47.39 ± 1.02
(0,0,0)	Center	13	20	10	48.52 ± 5.34
(+1,+1,+1)	Edge	20	30	15	51.85 ± 3.23
(-1,-1, +1)	Edge	6	10	15	11.75 ± 0.79
(-1,+1, -1)	Edge	6	30	5	47.48 ± 1.52
(-α,0,0)	Axial	1.2	20	10	11.43 ± 3.16
(0,0,-α)	Axial	13	20	1.6	36.28 ± 7.56
(0,0, 0)	Center	13	20	10	44.32 ± 6.51
(0,+α,0)	Axial	13	36.8	10	54.18± 5.06
(0,-α,0)	Axial	13	3.2	10	14.77 ± 1.94
(+α,0,0)	Axial	24.8	20	10	50.88 ± 1.75
(0,0,+α)	Axial	13	20	18.4	53.24 ± 2.35
(0,0, 0)	Center	13	20	10	49.20 ± 3.74

3D Response Surface Plot –

Effects of Concentrations of PEG 400 and PG on mount of Riluzole Dissolved in 5 ml Volume of Solvent





Amount of riluzole dissolved (mg in 5 ml) =

$46.70 + 10.98*A + 10.96*B + 3.09*C$

$- 9.18*AB - 0.61*AC - 0.23*BC - 4.57*A^2 - 3.40*B^2$

Validation of the Selected Model

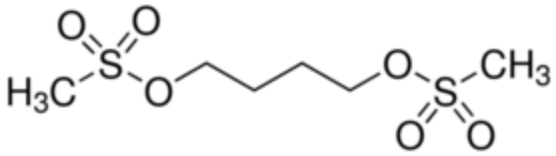
Amount of Riluzole (mg)		Intra Day (n=3)			Inter Day (n=6)		
Desired	Predicted	Observed	Accuracy (%) (Mean ±SD)	Precision (%RSD)	Observed	Accuracy (%) (Mean ±SD)	Precision (%RSD)
10	10.1	10.2 ± 0.4	101.4 ± 4.4	4.38	10.2 ± 0.4	100.8 ± 4.0	3.94
50	49.9	52.9 ± 0.3	105.8 ± 0.7	0.64	50.8 ± 1.6	101.6 ± 3.3	3.21
55	55.1	54.4 ± 1.0	98.7 ± 1.8	1.84	55.7 ± 2.4	101.3 ± 4.3	4.25

The predicted amount of dissolved riluzole was obtained from the Design Expert® software.
The observed amount of riluzole was determined experimentally using the composition defined from the software. Accuracy was calculated as the percentage of observed value over predicted value. Precision was reported as % relative standard deviation (%RSD).

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

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 – 1,500 μMol. min
- Hepatic veno-occlusive disease (HVOD) with AUC > 1,500 μMol. min

Impacts on UH

- Educational benefit
  - 1 M.S. and 2 Ph.D. graduates trained
- Financial benefit
  - $ 30.3 MM royalty incomes
  - (June 1999 - June 2016 &
    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

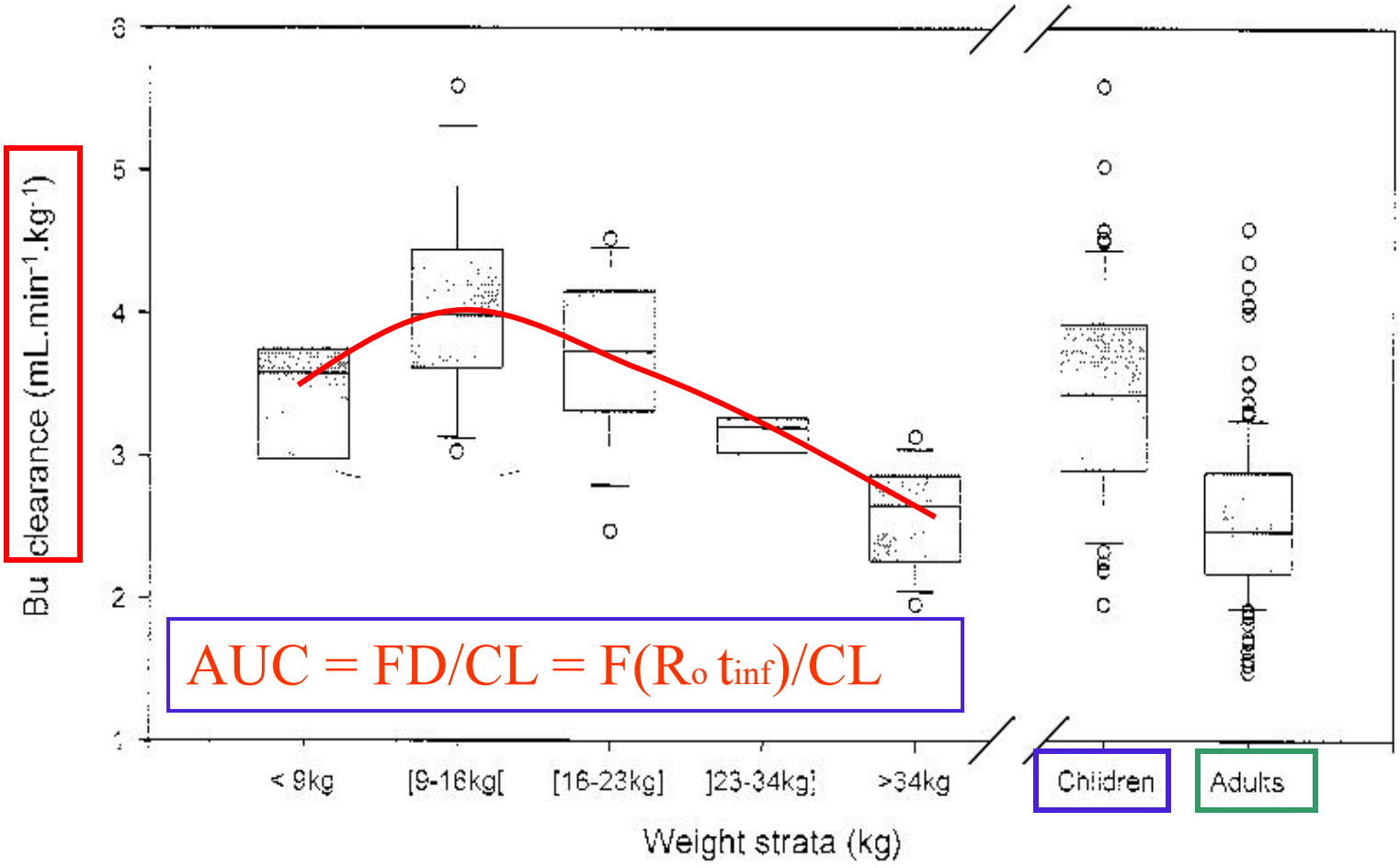
Clinical Benefits/Impacts (cont'd)

- Additional merit (not originally intended)

  Application to pediatric populations

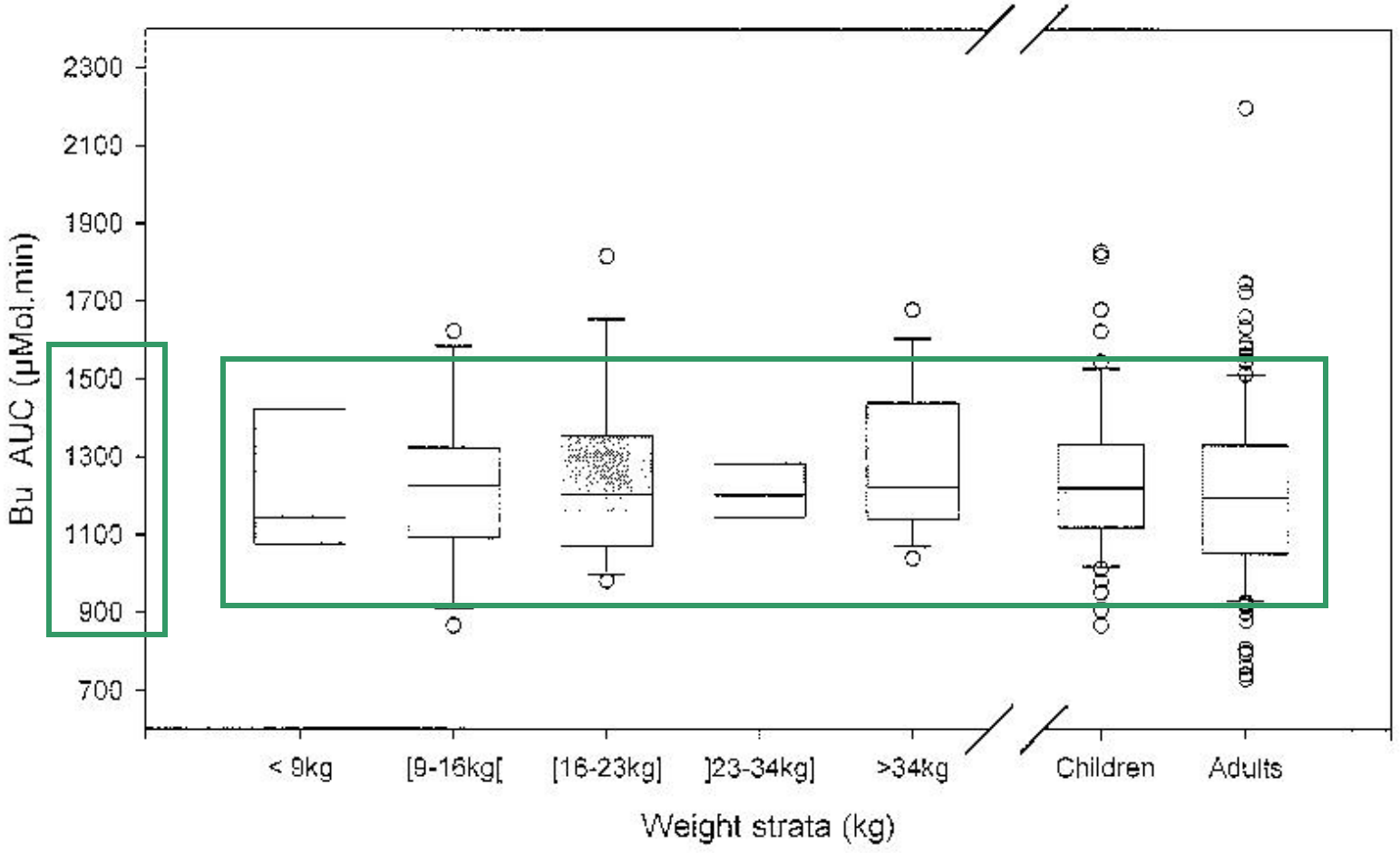
  – individualized dose regimen

Rational Use of Busulfex in Pediatric Patients



Vassal et al. 2006

After Individualized Dose Adjustment



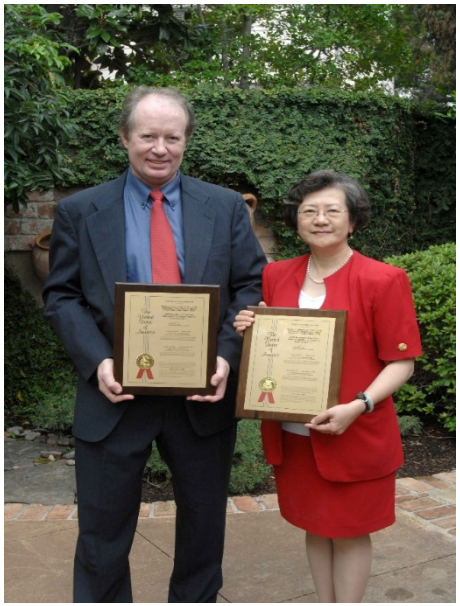
Clinical Benefits/Impacts (cont'd)

- Available in 46+ countries in all continents, North America, Europe, Australia, Asia & Africa
- Standard care in >65% transplant patients in North America

Clinical Merits Recognized

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

Inducted as Fellow of National Academy of Inventors, 2016



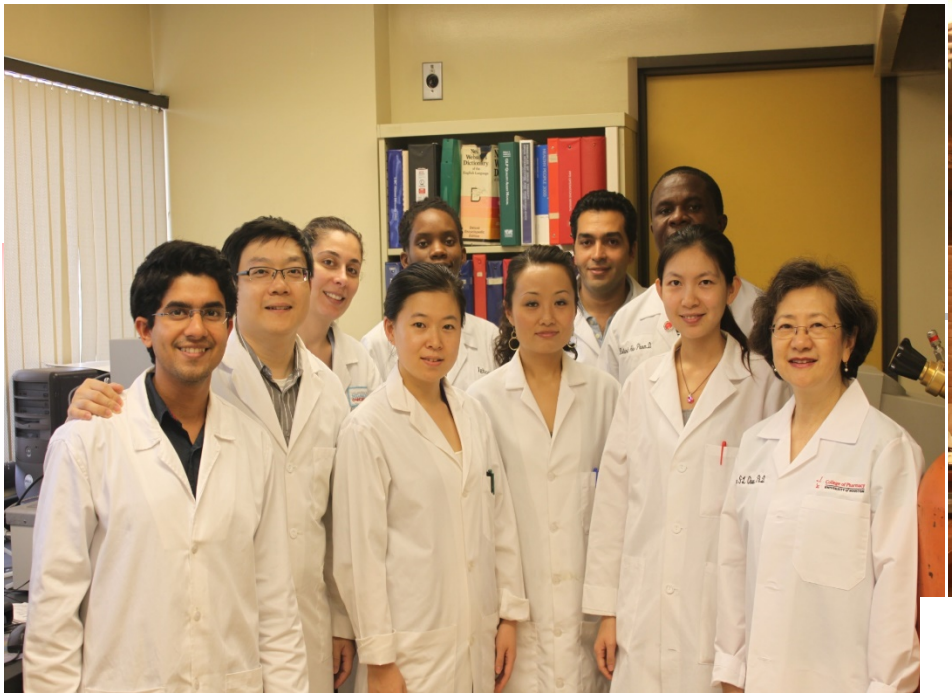
Acknowledgements

TMC Location

- Late Julie Norris –(1973-90, ORP Director; 1991-4 Assist VP for Res)
  - Agreement in 1994 with MDACC
    without requiring UH to pay patent filing expenses,
    but sharing incomes equally
- Art Valis – (1998-2006, VP for Res and IPM)
  - establishing policy in 2005
    returning significant incomes to inventors and
    institution unit nurturing the innovation research
    on campus
- COP & PPS – Collegial and supportive environment

Current Inspiring Climate for Innovation at UH

- Income return to continue nurturing innovation
- UH filing provisional patent application immediately after receiving disclosure
- Technology Gap Funding
- Partnering with *Wolff Center for Entrepreneurship* for commercialization




Our Happy Family
Tanay's Graduation, May 2014

Thank You!!!


2019 aaps PharmSci 360