

## Cardiorenal Function Estimation Using Near-Infrared Fluorimetry

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Society for Technology In Anesthesia  
January 7, 2016

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## Disclosures

- Support:
  - The STA/Fresenius Research Award
    - THANK YOU!
  - K08 DK 090754
- IP (published)
  - Relating to:
    - General anesthesia (20150027439)
    - Critical care patient safety (2015095408)
    - Cycling safety (20140118129)
  - None in the space we will discuss

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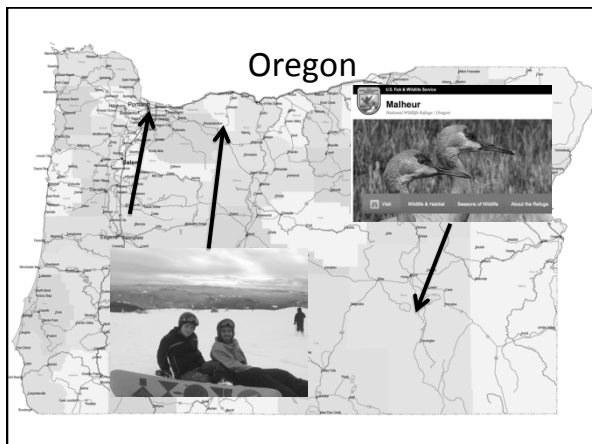
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## Perioperative AKI

- 1% major noncardiac surgery (Kheterpal 2007,2009)
  - 27m operations/y=270,000 cases of AKI/y
- 5-30% cardiac/vascular (Hou, 1983, others)
- mild AKI ↑ risk of hospital death 6-8x (KDIGO, 2012)
- Critically ill: 70% (Schreier, 2004, Xue 2006, Waikar 2006)

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## Perioperative AKI Pathophysiology

- Most common cause of AKI (all comers)
  - Hypoperfusion
- Other insults in periop environment
  - Nephrotoxins (abx, contrast)
  - Obstruction
  - Rare
- Perioperative renal monitoring should focus on physiologic indicator of renal hypoperfusion

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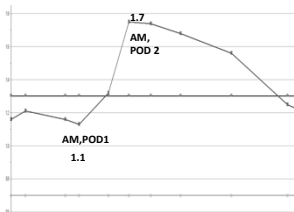
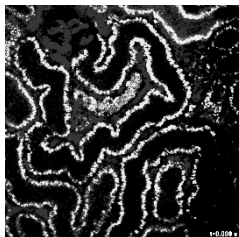
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## Diagnosis Delayed



Quantitative imaging of basic functions in renal (patho)physiology  
 Jung Suk Kang, Hideo Toma, Arnold Sapor, Fiona McCulloch, Jaron Pitt-Peterson  
 American Journal of Physiology - Renal Physiology Aug 2006;291(2):F495-F502;DOI: 10.1152/ajprenal.00521.2005

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### GFR: The Concept of Clearance

- Glomerular Filtration Rate is plasma clearance by the kidney of a filtered molecule

$$\frac{dx/dt}{\text{concentration}} = \frac{\text{mass/time}}{\text{mass/volume}} = \frac{\text{volume}}{\text{time}} = \text{flow}$$

- “The volume of plasma completely filtered per unit time”

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### GFR: The Concept of Clearance

- Availability to the nephron is assumed
- Altered by:
  - Extrarenal elimination,
  - secretion
  - resorption
- May measure plasma disappearance of applicable substance
  - Inulin, urea

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### GFR in AKI

- Greatly reduced within minutes of renal ischemia
  - Mechanism not well understood
- Physiologic indicator of extent of renal insult
- Closely correlates with outcomes including death and dialysis
- Periop renal monitoring of GFR or correlate may yield actionable data

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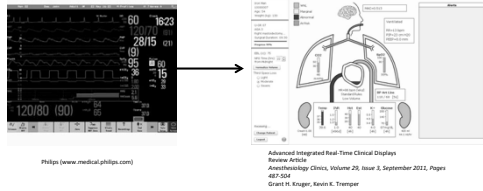
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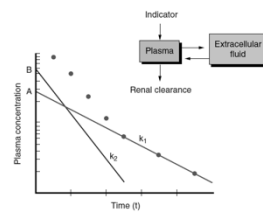
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## Need for a Perioperative Monitor



## Clearance modeling from Concentration

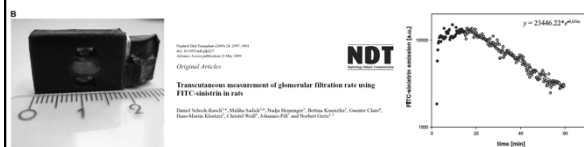
- $C = V_0 [\ln(2)/t_{1/2}]$   
– Requires  $V_0$
- 1 compartment model  
–  $GFR = (\text{dose})(k_1)/A$



From Brenner & Rector, Ch 25

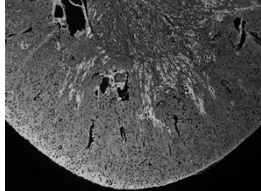
## Renal Clearance & Imaging

- Iodinated Contrast
  - Extensive literature, strong data
  - Paradoxical...
- Fluorophores and Fluorimetry
  - FITC...



## AKI Model: CA/CPR

- 8 min KCl-induced cardiac arrest
- CPR with epinephrine
- Robust AKI measured 24h after CA/CPR
  - 10-15% cell death in PT
  - Creatinine 4-8x normal
  - GFR ~zero
  - Resolves by day 3




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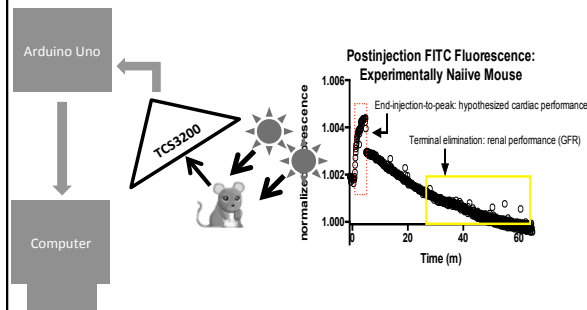
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## An Observation...




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## Imaging Cardiac Function

- Many attempts
  - Diffusion
  - Interference (Hb)
  - Fluorophore toxicity
  - Competing clearance
  - Heterogeneous methods
  - Experimental/equipment limitations

Amberidge 2010; 100:1375-80  
© 2010 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.  
**Measurement of Cardiac Output with Indocyanine Green Transcutaneous Fluorescence Dilution Technique**  
Jean-Michel L. Maunick, Dr. Eng, Daniel P. Holschneider, M.D., T. J. J. Harrold, M.S., J. Jun Yang, Ph.D., S. Oscar U. Schmitt, M.D., Ph.D., Eduardo H. Rubinstein, M.D., Ph.D.

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## Near-Infrared Fluorimetry

- Long wavelengths penetrate tissue well
- INVOS, others
- Few physiologic fluorophores but active investigation
- Frangioni Lab

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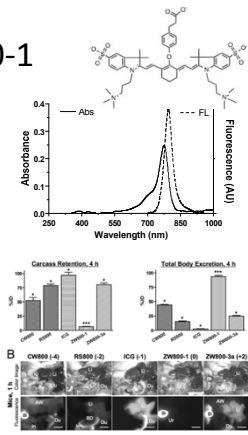
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## ZW800-1

- Zwitterionic
- MW 943 D
  - Creatinine ~100
  - Inulin ~5000
- 90% 4h recovery in urine (Choi, 2011)
- Nontoxic
- $\epsilon = 2 \times \text{ICG}$
- NEXT molecule



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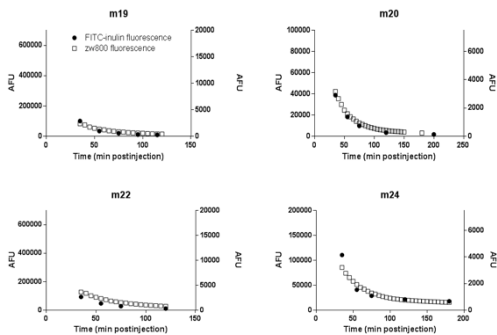
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## Early Data with ZW800-1



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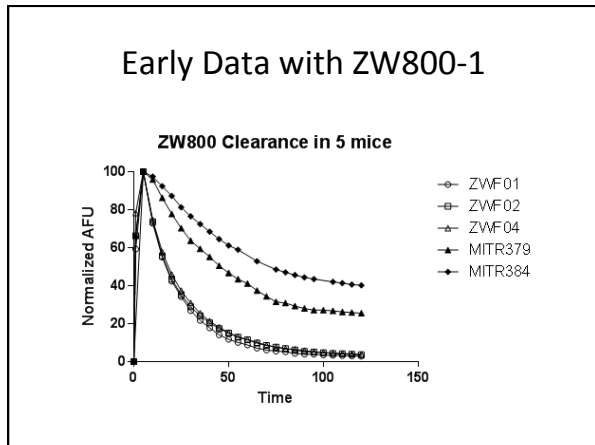
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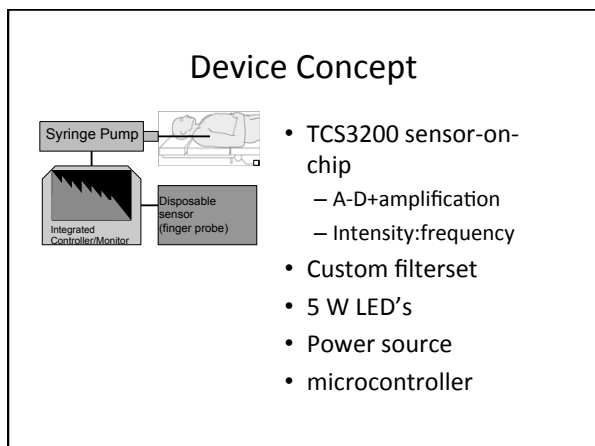
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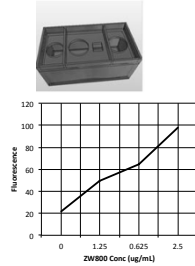
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### Device Implementation

- 3D printed envelope
- 2 Filtersets for correlation
  - FITC (inulin)
  - ZW800-1
- Satisfactory linear response



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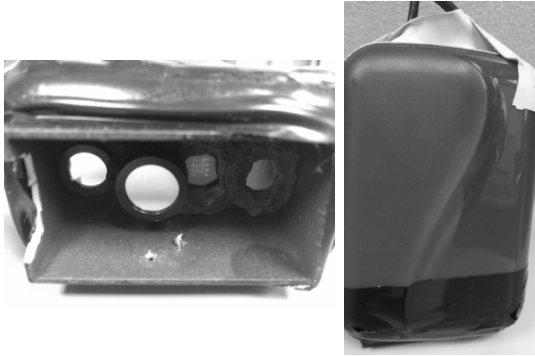
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### Device Implementation



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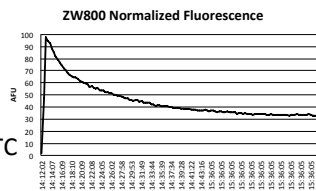
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### Device Data

- Low frequency at low brightness
- Time dependence
- Reasonable clearance signal
- Interference in FITC channel
- Opacity of 3D printed material



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## Technology Second Stage

- Biomedical Innovation Program Proposal
  - Not our molecule
  - FDA
  - Drug-device (high risk)
  - Is there any way to get around the need for exogenous fluorophore?

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## Decay without Clearance

- Noted loss of signal in nephrectomized mice
- Serum decay rate matched nephrectomy decay
- Nonrenal clearance entirely decay.
- Limitation
  - Longer clearance time results in greater decay

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## ZW800-1/FITC-Inulin Paired Clearance

- LICOR whole-animal near infrared imager
- Simultaneous injection of FITC-Inulin and ZW800-1
  - Sham and 24h after CA/CPR
  - FITC-inulin 10mg 100% lethal in CA/CPR mice
- Collect 800nm images q5m for 180 m
  - Second phase 55min-180 min
    - 1 phase model
- Collect tail blood (microcap)x4
  - 490-530nm excitation/fluorescence for FITC
    - 1 phase model

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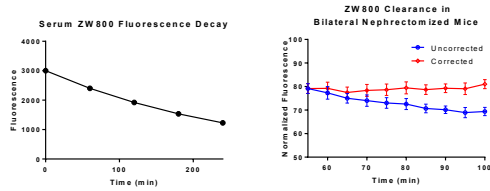
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## Imaging ZW800-1 Renal Clearance



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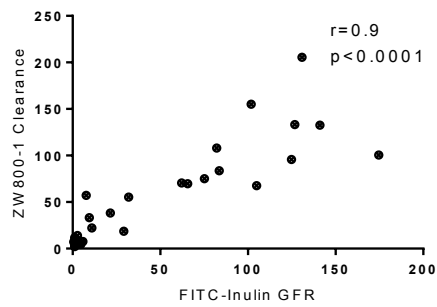
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## FITC-Inulin:ZW800 Clearance Correlation



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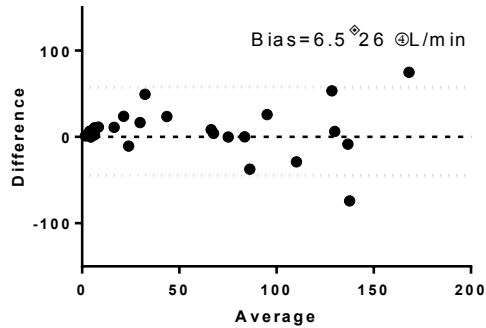
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## Bland-Altman Analysis



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## Cardiac Function and Fluorescence

- Conceptually:
  - Signal  $\sim k_1 \cdot (\text{molecules})$
  - Molecules  $\sim \text{dose} \cdot \text{time} (\text{rate delivered})$
  - Rate  $\sim \text{cardiac output} \cdot \text{diffusion restriction}$
- Hypothesis:
  - Fluorescence rate-of-rise correlates with cardiac output after rapid bolus injection

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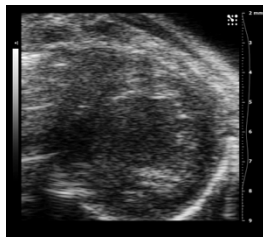
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## Measurement of Cardiac Function

- 2D echocardiography
- Well characterized in mouse
- LF function:
  - FS
  - EF




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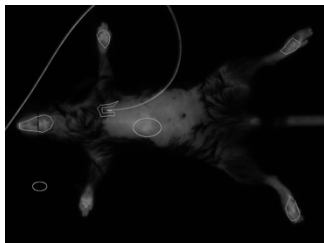
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## Fluorescence Distribution Protocol

- CA/CPR
  - 2h
  - 24h
- Inject ZW800-1
  - Rapid NIR imaging
  - 1 image/s\*10m
- Analysis
  - 7 ROI
  - Correlate with TTE




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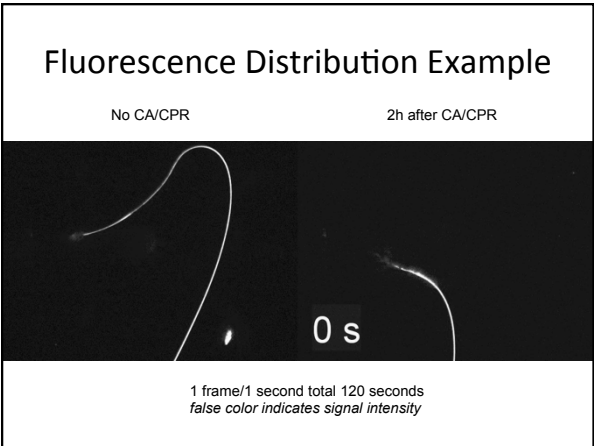
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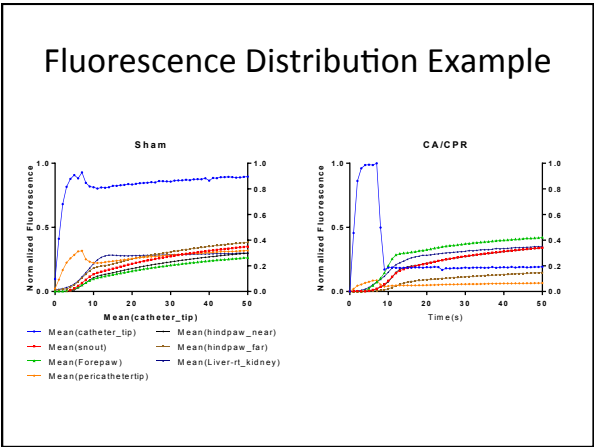
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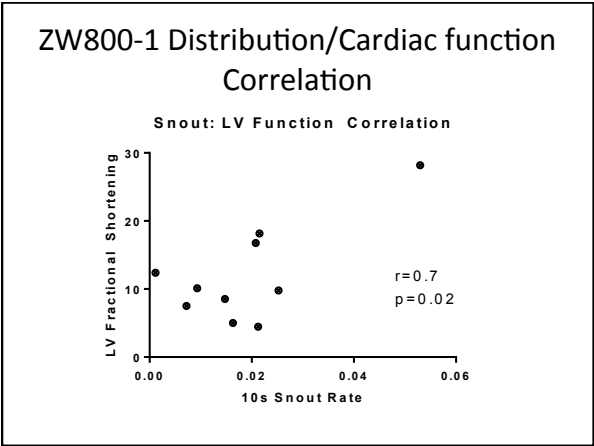
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### Summary

- ZW800-1 is renally cleared, with plasma quenching
- Compensation for plasma quenching yields replicable measurement of GFR
- Well tolerated in critically ill animals
- ZW800-1 clearance compares favorably with Inulin GFR

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### Summary

- ZW800-1 fluorescence uptake correlates with FS
- Additional data analysis underway
- Promising minimally invasive technique in rodents
- Regulatory, IP challenges for this technology

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### Future Directions

- Scientific
  - Complete current data analysis and publish
  - Continue collaboration with Choi lab
- Technology
  - Identified need and desire for realtime monitors of renal function
  - Significant interest in perioperative community
  - 2 additional, derivative technologies in very early stages

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## Acknowledgements



- Society for Technology In Anesthesia
  - Fresenius Research Award
- NIDDK
  - K08
- Jeffrey Kirsch, Nabil Alkayed, Sharon Anderson
  - Chair and Mentors
- Mizuko Ikeda and Rumie Wakasaki
- Sumio Hoka

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