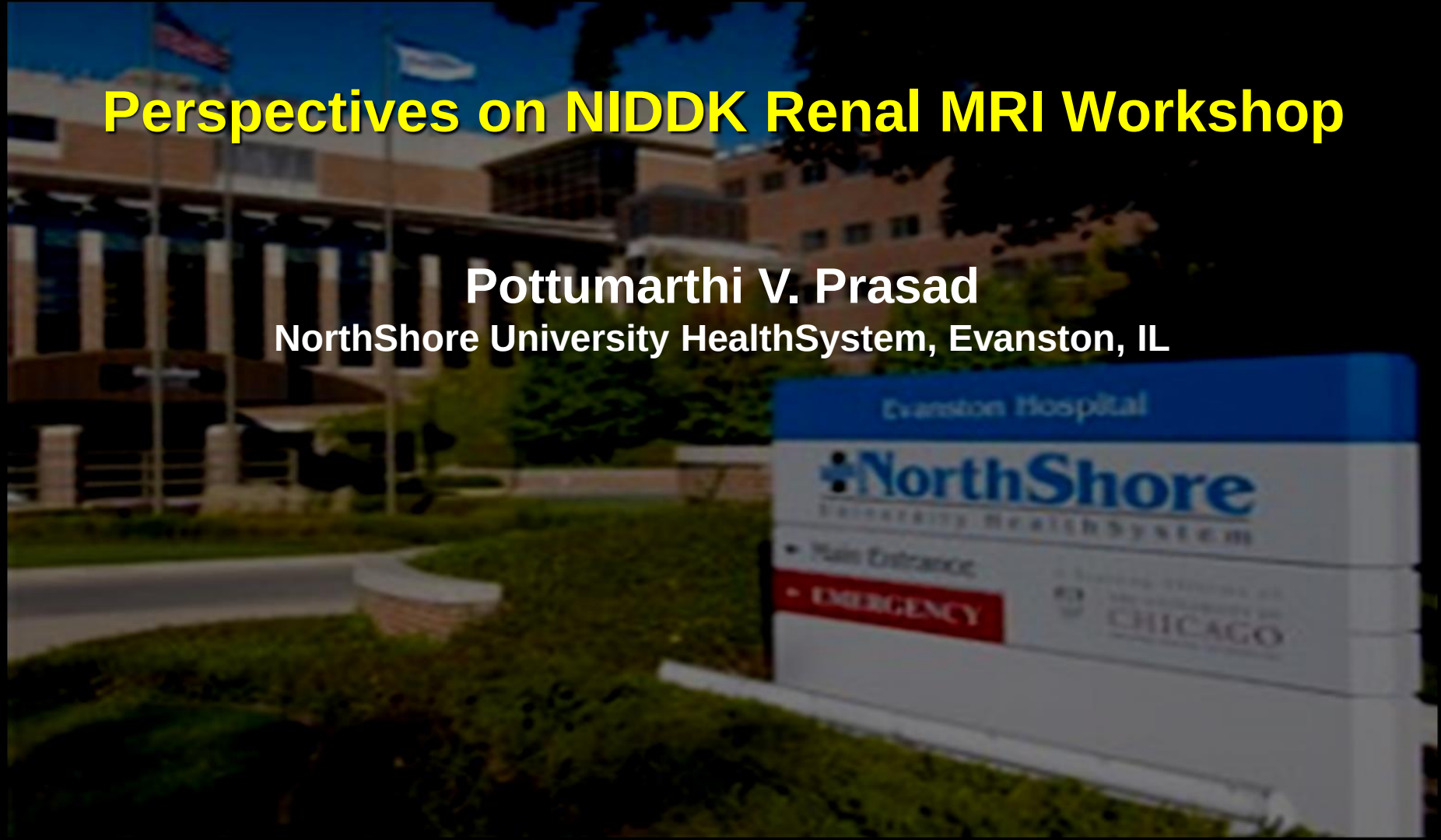
Perspectives on NIDDK Renal MRI Workshop



Pottumarthi V. Prasad
NorthShore University HealthSystem, Evanston, IL

Objective(s)

- Chart a path forward to functional renal imaging
  - cover the state of the art in renal imaging
  - learn from other fields
  - FDA qualification of imaging biomarkers
  - other translational challenges

Workshop

- https://www.niddk.nih.gov/news/meetings-workshops/renal-imaging-workshop
- 2018 July 12, 13 on NIH campus
  - Program committee included members of NIDDK (4), NIBIB (1), Investigators with varied imaging expertise as related to applications to the kidneys (5), Intramural Imaging Investigators (2)
  - Plenary sessions
    - State of the art Functional Imaging
    - Concept to Clinic – Cross-cutting issues in translation
    - Fibrosis
    - Plenary talks from outside the field
    - Where are we going? Towards single nephron function and molecular imaging
  - Poster presentations (during lunch day 1)
    - Topics not covered by oral sessions
    - Opportunity for junior investigators and trainees
  - Breakout sessions (free discussions among attendees)
    - Accelerating transition from animals to humans
    - Functional Imaging
    - Using fibrosis as a phenotype
    - Towards nephron endowment and single-nephron function
    - Molecular imaging for phenotyping and target engagement

State of the art Functional Imaging

- Renal Functional MRI
  - Non-contrast methods
    - » Techniques ready for translation
      - BOLD, ASL perfusion, Diffusion MRI
    - » Techniques needing work
      - Na MRI, Elastography, MTC or T1rho

Concept to Clinic—Crosscutting Issues in Translation

- Development and Seeking Regulatory Approval for New Contrast Agents
  - Regulatory barriers different from radiopharmaceuticals
  - No venture funding to develop novel contrast agents
  - Need for changes in review process at NIH for grant reviews
- Contrast toxicity (GBCA)
- Machine Learning for Developing New Biomarkers from Imaging Data: Applications of Radiomics and Pathomics
  - Pathomics: quantifiable characterization of digital histology
- FDA Biomarker Qualification and MRI Imaging Parameters Qualified by the FDA (PKD Outcomes Consortium Measures)

Fibrosis

- Targeted contrast agents
  - Peter Caravan
    - contrast agent that targets oxidized lysine for quantifying fibrogenesis
    - Oxyamine-functionalized gadolinium chelate (Gd-OA) was used to identify fibrosis
  - Peter Boor
    - elastin-specific MR contrast agent (ESMA), to measure fibrosis
- Non-contrast methods
  - MTC
  - Elastography (US & MRI)

Plenary Talks from Outside the Field

- MR Fingerprinting
- Imaging target engagement in oncology
  - Fibroblasts in tumors different from kidney
- Cardiac PET
  - Similarity of renal and myocardial fibrosis
    - » Preliminary feasibility of ACE imaging
      - flurobenzoyl-lisinopril autoradiography

Towards single nephron function and molecular imaging

- Nephron # and function in disease
  - mean number of nephrons in normal kidneys is approximately 900,000
  - association between the total nephron number and renal pathophysiology
  - glomerular size as a marker for kidney function
- CFE MRI
  - Mostly *ex vivo* data
  - Preliminary *in vivo* data in rodents
- Single kidney GFR by DCE-MRI
- Susceptibility MR
- Molecular imaging of kidneys

Summary from Breakout Sessions: Functional Imaging

- MRI and ultrasound best suited
  - MRI affords multiple parameters of interest
  - US +: low cost, widespread availability, and access to patients in intensive care units
  - US -: inherent subjectivity or operator bias
- Confounding effects – major challenge
  - Does multi-parametric data mitigate this?
- Stress testing such as functional reserve
- Objective analysis methods
  - Mean±std. dev. too basic
  - Need to capture spatial variability (or patchiness)
  - Applications of Radiomics, AI needed to fully take advantage of spatio-temporal information
- With lack of biopsy correlations in human studies, need for pre-clinical studies exists
- Translation to clinical studies requires standardization/hybridization

Summary from Breakout Sessions: Fibrosis

- Desired ability to detect 25% cortical fibrosis
- Differentiation of glomerular, interstitial or peri-vascular is important
  - May be different processes, molecular signatures
  - Targeted contrast agents
- Challenges: complex structure including multiple compartments and cell types
- Targeting fibrogenesis may be important
- Macrophage detection with USPIO
- Need to correlate local changes with disease progression

Summary from Breakout Sessions: Translation for Animal to Patients

- Four areas of significance:
  - endogenous contrast MRI,
  - evaluation of the nephrogenic zone early in life,
    - » Nephron # at birth
  - glomerular counting by cationic ferritin,
  - 3D large volume imaging of biopsies
    - » Kidney Precision Medicine Project (KPMP)

Summary from Breakout Sessions: Molecular Imaging

- Targeted molecules to elucidate kidney biology and pathogenesis
- Challenges:
  - MI is inherently challenging to design, validate and interpret
  - Probes must be highly selective
  - Delivery of probes need to be highly predictable
  - Interference from metabolism and excretion of probe
  - Kinetic modeling to separate specific targeting from non-specific distribution
  - Safety concerns for human use
  - Multidisciplinary teams necessary

Summary from Breakout Sessions: Nephron Endowment & Single Nephron Function

- Genetic nephron endowment, loss and compensation after kidney injury, senescence – all important to identify risk of disease progression
- Nephron # is important in diabetes, hypertension, obesity, congenital anomalies, sickle cell disease, etc..
- Genetics + comorbid conditions determine nephron #
- Stereological techniques
  - Nephron endowment in humans
  - Implicated low nephron # in hypertension and CKD
- Lack of information about single nephron function *in vivo*
- CFE MRI allows for labeling individual glomeruli
  - *In vivo* imaging is challenging
    - » Ability to combine with DCE-MRI to evaluate single nephron function

Key Takeaways

- MRI and US most promising
  - Why PET has not been applied to kidneys?
- Stress testing such as functional reserve is important
- Nephron # and glomerular size are important
  - Can CFE MRI can be translated to humans?
- Targeted contrast agents for fibrosis detection
  - Only proof-of-concept data available in preclinical models
  - Regulatory approval is tough
  - Not sufficient funding mechanisms
- Analysis needs to grow beyond mean±sd.
  - Capture spatial variability (patchiness)
  - Role for AI?
- Some techniques are ready for multicenter trails
  - Thought was to find ways of adding imaging to existing trials (similar to COMBINE)
  - KPMP was thought to be an obvious choice

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