Capturing New AKI Drug Candidates From the Fires of Inflammation

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Apply basic chemical principles to the understanding of cell signaling events and the creation of new therapeutic strategies

BAF acknowledges Complexa, Inc and Nitromega, Inc
NO modifies reaction rates and expands the scope of redox signaling reactions.

NO promotes post-translational modification of proteins via formation of 2° and 3° species.

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**Chemical Structures**

- **NO$_2$-fatty acids**
  - $\text{R} \quad \text{NO}_2$ \quad \text{R}$

- **Keto-fatty acids**
  - $\text{R} \quad \text{C} = \text{O}$ \quad \text{R}$
Biological Electrophiles

Organisms have evolved a population of redox-sensing proteins containing electrophile-reactive nucleophilic amino acids that sense the metabolic and inflammatory environment and then act to regulate gene expression and metabolism.
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*transcriptional regulatory proteins*

*protein tyrosine phosphatases*

*mitochondrial ET, PTPs*
Nuclear PPAR Receptor Activation

- Ligand
- Cytoplasm
- Cell specific Response
- Proteins: Metabolism, Inflammation
- Nucleus
- mRNA
- PPAR
- RXR
- PPRE
Signaling Actions of OA-NO$_2$

- Michael addition reaction, reversible (Cys, His)
  
- Covalent PPARg ligands
  
- Induce antioxidant response via Keap1/Nrf2
  
- Adduct NF-$\kappa$B p65 subunit, inhibit DNA binding
  
- Inhibit enzyme activity – XOR, PTPs, UCP-2
  
- Stimulate HSP expression via heat shock factor
  
- Induce heme oxygenase-1 expression
  
- Inhibit AT-1 GPCR receptor function

References:

- J Biol Chem, 2006

- PNAS, 2005
- Nat St Mol Biol, 2008
- PNAS, 2007

- J Biol Chem, 2006
- Circ Res, 2009


- J Biol Chem, 2009

- PNAS, 2006
- Biochem J, 2009

- Circ Res, 2010
Ginseng → Triterpenoid → Bardoxolone

Strong in vitro and murine model data
2005-present

Phase 2 gene expression
Anti-inflammatory
Conclusions

Bardoxolone methyl was associated with improvement in the estimated GFR in patients with advanced CKD and type 2 diabetes at 24 weeks. The improvement persisted at 52 weeks, suggesting that bardoxolone methyl may have promise for the treatment of CKD. (Funded by Reata Pharmaceuticals; BEAM ClinicalTrials.gov number, NCT00811889.)

Example - natural product transitioning to pharmaceuticals for renal applications
$450+ million investment from Abbott
Renal Protective Actions of Nitro-oleic Acid

30 min ischemia
OA-NO₂ administered IP
50 min after reperfusion

10 mg/kg LPS IP, t=18 hr

T Yang, AJP:Renal 2008, 2009
Electrophilic Fatty Acids – A New Drug Class

OA-NO₂
10-nitro-octadeca-9-enoic acid
Nitro-FAs > 1 μM in healthy human urine, plasma

• Naturally occurring in humans, fish, plants, insects
• Broad activity related to regulation of metabolism, inflammation
• Develop drugs based on endogenous signaling mediators that modulate the body’s own adaptive signaling mechanisms
• Big Pharma drug development programs now include designing multi-specific therapeutics (>2 MOAs for one molecule), embracing pleitropy
Contrast-Induced Nephropathy

- Reduced nephron number, vasoconstriction, oxidative stress
- 90 million doses of contrast agent given per year
- 10-30% patients high risk (CKD, diabetes, HTN, shock) for CIN
- ~5% develop CIN = ~2.2 million cases of CIN per year
- Persistent renal dysfunction in 45% of CIN patients
- Patients with CIN have greater morbidity/mortality
- Current Rx - volume expansion, N-acetylcysteine

Iodixanol/Visipaque
iso-osmolar iodobenzene contrast agent, induces lowest incidence of CIN