Novel and emerging therapies for patients with Diabetes and CKD

A/Prof Robyn Langham
St. Vincent’s Hospital
Fitzroy, Australia
Disclosures

• Past consultant for Fibrotech Therapeutics

• Speaker fees; Amgen, Shire, Janssen-Cilag

• Advisory Board; Janssen-Cilag, Orphan, MSD, GSK, Amgen.
“... diabetic nephropathy can be viewed as an inflammatory disease triggered by disordered metabolism.”
Protein Kinase Cβ Inhibition Attenuates Osteopontin Expression, Macrophage Recruitment, and Tubulointerstitial Injury in Advanced Experimental Diabetic Nephropathy

Kelly et al., JASN 2005
Disease of fibroproliferation
Probably a disease of multiple redundant pathways.

**Monocyte infiltration**
- CCR2 inhibition
- VAP-1 inhibition
- Tie2 receptors

**Stat 4 antagonists**
- PDE4 inhibitors
- MCR inhibition

**Environmental factors**
- Hypoxia
- High glucose
- Integrin interaction
- Reactive Oxygen Species

Kanasaki et al, Front Endocrinol 2013
Identification of Renox, an NAD(P)H oxidase in kidney

Miklós Geiszt*, Jeffrey B. Kopp†, Péter Várnai‡, and Thomas L. Leto*§

*Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, †Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, and ‡Endocrinology and Reproduction Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892

Edited by Irwin Fridovich, Duke University Medical Center, Durham, NC, and approved May 3, 2000 (received for review March 27, 2000)
NAPDH Oxidases – phagocytosis of microbes

The NOX Family of ROS-Generating NADPH Oxidases: Physiology and Pathophysiology
Bedard and Krause Physiological Reviews 2007
NAPDH Oxidases – non-phagocytic

McCann and Roulston, *Brain Sci.* 2013
In kidney Nox 4 is the most important, ROS is important in regulation of cell cycle, also involved in renal haemodynamics and renal ion transport

NOX 4 may be mechanosensitive
- excess of ROS - = disease.

Bedard and Krause Physiological Reviews 2007
ROS-Regulated Signaling Pathways in Diabetic Nephropathy

Lee H B et al. JASN 2003;14:S241-S245
**NAD(P)H Oxidase Mediates TGF-β1–Induced**

**Genetic Targeting or Pharmacologic Inhibition of**

Gorin et al., Am J Physiol Renal Physiol (epublished Feb 2015)
Genkyotex Completes Enrollment into Phase 2 Trial of NOX1&4 Inhibitor GKT137831 in Diabetic Nephropathy

Safety Monitoring Board Recommends Trial Continues as Planned

Top-line data expected mid-2015

Geneva, Switzerland, and Archamps, France, 13 November 2014 – Genkyotex, the leading developer of selective NOX inhibitors, today announced the completion of patient enrollment into its Phase 2 trial of GKT137831 in diabetic nephropathy. In addition, the trial’s independent Safety Monitoring Board has conducted its first scheduled safety review and recommended that the trial should continue as planned.

Safety and Efficacy of Oral GKT137831 in Patient With Type 2 Diabetes and Albuminuria NCT02010242
12 weeks, bd dose of GKT137831, 100mg bd and 200mg bd,
Endpoints UACR, delta UACR, secondary endpoints erectile dysfunction and neuropathic pain.

www.genkyotex.com
Nicotinamide Adenine Dinucleotide Phosphate Oxidase in Experimental Liver Liver Fibrosis: GKT137831 as a Novel NADPH Oxidase 4 Induces Cardiac Fibrosis and Hypertrophy Through Activating Akt/mTOR and NFκB Signaling Pathways

Running title: Zhao et al.; Nox4-Associated Signaling Pathways in Cardiac Remodeling

Qingwei David Zhao, MD, PhD; Suryavathi Viswanadhapalli, PhD; Paul Williams, BS; Qian Shi, PhD; Chunyan Tan, MD; Xiaolan Yi, MD, PhD; Basant Bhandari, PhD; Hanna E. Abboud, MD
MicroRNA-21 – a potential anti-fibrotic

MicroRNA-21 in Glomerular Injury


*Internal Medicine, University of Michigan, Ann Arbor, Michigan; †Department of Pharmaceutical Sciences, Nanfang Hospital, Southern Medical University, Guangzhou, China; ‡Department of Medicine, Albert Einstein College of Medicine, Bronx, New York; §Howard Hughes Medical Institute, The Rockefeller University, New York, New York; ‖Department of Pathology and NYU Center for Health Informatics and Bioinformatics, New York University School of Medicine, New York; and *National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona

USA

4Division of Transplantation, Lahey Clinic Medical Center, Burlington
5Tufts University, Boston, Massachusetts, USA
6Division of Nephrology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
Monocyte infiltration – CCL2
CCL2 (MCP-1)

Recruits monocytes, memory T-cells and dendritic cells to sites of inflammation produced either by tissue injury or infection.

Receptors – CCR2 and CCR4 (G-protein coupled receptors)

Role of hypomethylation of CpG sites within the CCL2 promoter region in increased CCL2 levels in serum of patients with diabetes.

Well-described role in experimental renal fibrosis, also is involved in the inflammatory milieu of diseases of neurodegeneration

Bindarit (Phase 2a) reduction in CCL2 production (NCT01109212)
CCX-140, completed and reported phase 2
- 52 week data from Ph II clinical trial – oral
- 332 patients, placebo, 5mg, 10mg.
- 5mg daily, reduction in UACR (p<0.0148)
- Attenuated annual decline eGFR (1.3 vs 2.3)
  - NCT01440257
Emapticap pegol (NOX-E36)
NOXXON Pharma
Phase 2A, presented ERA/EDTA 2014

RCT phase 2a, 72 patients with Type 2 diabetes and albuminuria

SC administration, twice a week, reduction in ACR (32% lower at 12 weeks), 50% reduction 31% v6%)

Benefits on glucose control
Spieglemer – RNA, DNA based aptemers, 3D structure, stabilised against cleavage by naturally occurring endo and exonucleases. ..
Proximagen

http://proximagen.com/

Novel GPCR ?type
-has other CCR2 antagonist for neurodegen disease
VAP-1 inhibitor

- VAP-1 is expressed in pericytes and vascular endothelium and is involved in leukocyte extravasation to inflammed tissues
- It is an enzyme (monoamine oxidase) and an adhesion molecule for lymphocytes.

ASP8232 – a novel VAP-1 inhibitor

Phase 1 clinical trial, oral drug
NCT02218099
Second messengers
Open-label, prospective RCT
n=169, PTF 82, control 87

• smaller decrease in eGFR and a greater reduction of residual albuminuria.
• Reduction in TNF alpha
cAMP preservation – PDE inhibitors

**Phosphodiesterase-5**

Blood Pressure Lowering Effects of a New Long-Acting Inhibitor of Phosphodiesterase 5 in Patients With Mild to Moderate Hypertension

Robert Wolk, William B. Smith, Joel M. Neutel, John Rubino, Dawei Xuan, James Mancuso, James Gilbert, Milton L. Pressler

– Blood vessel relaxation, improved blood flow
– Phase 2, NCT01200394

• Finished phase 2a, 16 weeks, UACR, eGFR
cAMP – PDE inhibitors

- CTP-499
  - PDE3,4 and 5
  - Concert pharma
  - Poster, Phase 1, phase 2 active in Type 2 CKD, abstract NKF spring meeting

- Roflumolast (Takeda GmbH), Daliresp
  - PDE4
  - Approved for COPD
  - Preclinical efficacy in STNX model of CKD
Intracellular steroid receptors

Perico et al., Nat Rev Drug Disc 2008
BAY 94-8862 - Finerenone

Discovery of BAY 94-8862: A Nonsteroidal Antagonist of the Mineralocorticoid Receptor for the Treatment of Cardiorenal Diseases

Dr. Lars Bärfacke1,*, Dr. Alexander Kuhl1, Prof. Dr. Alexander Hillisch1, Dr. Rolf Grosser1, Dr. Santiago Figueroa-Pérez1, Dr. Heike Heckroth1, Adam Nitsche1, Dr. Jens-Kerim Ergüden1, Dr. Heike Gielen-Haertwig1, Dr. Karl-Heinz Schlemmer2, Prof. Dr. Joachim Mittendorf1, Dr. Holger Paulsen1, Dr. Johannes Platzek3 and Dr. Peter Kolkhof4

Article first published online: 12 JUL 2012
DOI: 10.1002/cmdc.201200081

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BAY 94-8862 - Finerenone

Rationale, Design, and Baseline Characteristics of ARTS-DN: A Randomized Study to Assess the Safety and Efficacy of Finerenone in Patients with Type 2 Diabetes Mellitus and a Clinical Diagnosis of Diabetic Nephropathy

Ruliope L.M.\textsuperscript{a} · Agarwal R.\textsuperscript{b} · Chan J.C.\textsuperscript{c} · Cooper M.E.\textsuperscript{d} · Gansevoort R.T.\textsuperscript{e} · Haller H.\textsuperscript{f} · Remuzzi G.\textsuperscript{k,l} · Rossing P.\textsuperscript{m} · Schmieder R.E.\textsuperscript{g} · Nowack C.\textsuperscript{h} · Ferreira A.C.\textsuperscript{n} · Pieper A.\textsuperscript{i} · Kimmeskamp-Kirschbaum N.\textsuperscript{j} · Bakris G.L.\textsuperscript{o}

ARTS-DN; NCT01874431
Mineralocorticoid receptors.. MT-3995

Safety, Tolerance and Pharmacokinetic Study of MT-3995 at a Low Dose in Subjects With Diabetic Nephropathy

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2014 by Mitsubishi Tanabe Pharma Corporation

Sponsor:
Mitsubishi Tanabe Pharma Corporation

Information provided by (Responsible Party):
Mitsubishi Tanabe Pharma Corporation

ClinicalTrials.gov Identifier:
NCT02205372

First received: July 27, 2014
Last updated: July 30, 2014
Last verified: July 2014

Purpose

The purpose of this study is to evaluate safety, tolerability and pharmacokinetics of **MT-3995** in Subjects with Diabetic Nephropathy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Nephropathy</td>
<td>Drug: <strong>MT-3995</strong></td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>
Inflammatory cytokine cascade
JAK-STAT pathway inhibitors
Stat-4 antagonist

- DiaKine – oral drug, DT 22669
- JAK Tyrosine kinases
- Acquired by Islet Sciences, interest in prevention of islet cell senescence
- Preclinical studies failed to prevent rodent diabetes

- Retinopathy/nephropathy DT 23552
JAK1/JAK2 inhibitor *baricitinib*

- Oral agent
- Phase III development as a potential treatment for rheumatoid arthritis.

**Purpose**

This is a dose ranging study to evaluate the safety and efficacy of *baricitinib* in the treatment of participants with mild to moderate diabetic kidney disease.

<table>
<thead>
<tr>
<th>Condition</th>
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<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Kidney Disease</td>
<td>Drug: <em>baricitinib</em></td>
<td>Phase 2</td>
</tr>
</tbody>
</table>
Aerpio

• Tie2Rec activator – angiopoietin receptor, tyrosine kinase inhibitor

• Ang1 and Ang4 function as agonistic or activating ligands for Tie2, whereas Ang2 and Ang3 behave as competitive antagonists.

• AKB-9778 is a small molecule, Tie-2 activating agent that effectively blocks vascular leak and pathologic angiogenesis in multiple disease conditions. It is initially being developed for the treatment of diabetic macular edema.

Targeted Glomerular Angiopoietin-1 Therapy for Early Diabetic Kidney Disease

Cecile Dessapt-Baradez,* Adrian S. Woolf,† Kathryn E. White,‡ Jiaqi Pan,* Jennifer L. Huang,§ Anthea A. Hayward,* Karen L. Price,§ Maria Kolatsi-Joannou,§ Maelle Locatelli,* Marine Dinnent,* Zoe Webster,|| Sarah J. Smillie,* Viji Nair,¶ Matthias Kretzler,¶ Clemens D. Cohen,** David A. Long,§ and Luigi Gnudi*

*Cardiovascular Division, King’s College London, London, United Kingdom; †Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester, United Kingdom; ‡Electron Microscopy Unit, University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom; §Nephro-Urology Unit, University College London, Institute of Child Health, London, United Kingdom; ||MRC CRB, ICSM Hammersmith Hospital, Imperial College London, London, United Kingdom; ¶Internal Medicine/Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan; and **Division of Nephrology, University Hospital Zurich, Zurich, Switzerland.
• Multiple pathways
• Risk of redundancy when one pathway is blocked
• IPF an epithelial-fibroblastic disease – inflammation is a secondary event
Understanding disease pathophysiology – network analysis
A Study to Evaluate ASP8232 in Reducing Central Retinal Thickness in Subjects With Diabetic Macular Edema (DME) (VIDI)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2015 by Astellas Pharma Inc

Sponsor:
Astellas Pharma Europe B.V.

Information provided by (Responsible Party):
Astellas Pharma Inc (Astellas Pharma Europe B.V.)

ClinicalTrials.gov Identifier:
NCT02302079
First received: November 24, 2014
Last updated: January 30, 2015
Last verified: January 2015

Purpose

The purpose of this study is to evaluate efficacy and safety of ASP8232 in subjects with diabetic macular edema (DME). This study will evaluate the percent change from baseline in excess central subfield thickness (CST) in the study eye as assessed by spectral domain-optical coherence Tomography (SD-OCT) for ASP8232 monotherapy at Month 3.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>Drug: ASP8232</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Diabetic Macular Edema</td>
<td>Drug: ranibizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: Sham intravitreal (IVT) injection</td>
<td></td>
</tr>
</tbody>
</table>
Tranilast – a known but old anti-fibrotic

Tranilast halts the progression of albuminuria in diabetic Ren-2 rats

Tranilast slows the progression of diabetic nephropathy in humans (100mg/day TID)

A. Mifsud et al, Nephron Physiol 2003

B. Soma et al., Nephron 2002
Tranilast
n-(3,4-dimethoxy-cinnamoyl) anthranilic acid

• Novel, synthesized on a kilogram scale, orally bioavailable, stable and crystalline.
• CMC – AMRI, New York

Extensive preclinical studies, at 50-1000mg/kg/day with no aberrant pathology seen in any organ, normal FBE, normal renal function. FT-011 better tolerability than Tranilast.
FT011 has been studied in the Ren(2) diabetic rat, and other STZ rat models with both early and later intervention demonstrating a dose dependant reduction in urinary ACR, reduction in tubulo-interstitial fibrosis, glomerulosclerosis and abrogation of GFR decline. (*Gilbert et al, PLoS One, 2012). Efficacy has also been demonstrated in the STNx model of CKD.

In head to head studies, FT011 has been demonstrated to be more potent than tranilast.
Phase 1 clinical trial summary

- FT011 has been tested at up to 1gm as a single dose with no adverse effects.
- FT011 dosed at 500mg/day for 14 day period with no adverse events.
- FT011 has excellent PK with half life of ~10 hours.
A. ‘Omic data

- List of proteins, genes or metabolites from ‘omic data sets

B. Interactome Model

C. Network Clusters

D. Network Topology

Function and Prioritisation
A comprehensive pathway map of CKD.

Martini S et al. JASN 2013

Network graph of 97 CKD-associated pathway nodes
CKD associated pathways are shared between renal diseases.

Martini S et al. JASN 2013
Disease-specific analyses shows a close interconnection between lupus nephritis, IgA nephritis, and diabetic nephropathy.

Martini S et al. JASN 2013
Identification of Cross-Species Shared Transcriptional Networks of Diabetic Nephropathy in Human and Mouse Glomeruli

Hodgin et al., Diabetes 2013
The Molecular Phenotype of Endocapillary Proliferation: Novel Therapeutic Targets for IgA Nephropathy

Hodgin et al, PlosOne 2014

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### Canonical pathways (number of genes regulated/number of genes in the pathway)

<table>
<thead>
<tr>
<th>Role of Pattern Recognition</th>
<th>p-value</th>
<th>Regulated molecules in the pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors in Recognition of Bacteria and Viruses (14/164)</td>
<td>0.0000</td>
<td>PTX3,TLR1,P1K3CA,NLRP3,MAPK1,TLR8, C1Q,A,C1Q8,BF2S1,TLR2,TLR4,NOD2, C5AR1, PRKD3</td>
</tr>
<tr>
<td>Leukocyte Extravasation Signaling (18/201)</td>
<td>0.0001</td>
<td>P1K3CA,MAPK1,ITGA2,BTKJTGGB2,WPFF1, ITGAM,TIMP1,ROA,NCF2,CD44,CYBB, MMP12,PRKDS,MMP9,JAMP1,ITGA4,ITK</td>
</tr>
<tr>
<td>TREM1 Signaling (9/71)</td>
<td>0.0001</td>
<td>TLR2,TLR4,TLR1,NOD2,MAPK1,TYROB,TLR8,LT2JTGAX</td>
</tr>
<tr>
<td>NF-kB Activation by Viruses (10/82)</td>
<td>0.0003</td>
<td>ITGB2,P1K3CA,CCR5,NRA5,MAPK1,CD4, ITGAA2,CHUK,PRKD3,ITGA4</td>
</tr>
<tr>
<td>Toll-like Receptor Signaling (8/62)</td>
<td>0.0004</td>
<td>TLR2,TLR4,TLR1,MAPK1,MAP3K3,TLR8, CD14,CHUK</td>
</tr>
<tr>
<td>Cell Cycle: G2/M DNA Damage Checkpoint Regulation (7/48)</td>
<td>0.0006</td>
<td>YWHAA,YWHAZ,TOP2A,CCNB2,CDK1, CHEK1,CCNB1</td>
</tr>
<tr>
<td>IL-8 Signaling (16/205)</td>
<td>0.0006</td>
<td>P1K3CA,NRA5,MAPK1,COGAP1,RA811IP1, ITGB2,HMOX1,ITGAM,RHOA,NCF2,CHYP, CHUK,PRKD3,GNG12,MMP9,JTGAX</td>
</tr>
<tr>
<td>Production of Nitric Oxide and Reactive Oxygen Species in Macrophages (13/210)</td>
<td>0.0089</td>
<td>P1K3CA,MAPK1,JNFR1,TLR2,APC1,TLR4, MAP3K7,RHOA,NCF2,CYBB,IRF8,CHUK, PRKD3</td>
</tr>
</tbody>
</table>

Selected canonical pathways significantly regulated (p-value<0.05) from the 424 genes regulated in E1 vs. E0 biopsies, as assessed by Ingenuity Pathway Analysis. Full pathway list in Table S3.

doi:10.1371/journal.pone.0103413.t003

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**Legend**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Kinase</th>
<th>Receptor</th>
<th>Co-factor</th>
<th>Transporter</th>
<th>Phosphatase</th>
</tr>
</thead>
</table>

- 2 genes are associated by co-citation.
- 2 genes are associated by expert curation.
- Gene A activates gene B.
- Gene A inhibits gene B.
- Gene A has a known transcription factor binding site in one of its promoters.
The Molecular Phenotype of Endocapillary Proliferation: Novel Therapeutic Targets for IgA Nephropathy

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cmap name</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydroquinine</td>
<td>0.0002</td>
</tr>
<tr>
<td>3</td>
<td>Resveratrol</td>
<td>0.0003</td>
</tr>
<tr>
<td>8</td>
<td>guaifenesin</td>
<td>0.0016</td>
</tr>
<tr>
<td>10</td>
<td>methotrexate</td>
<td>0.0025</td>
</tr>
<tr>
<td>12</td>
<td>genistein</td>
<td>0.0061</td>
</tr>
<tr>
<td>24</td>
<td>ciclosporin</td>
<td>0.0148</td>
</tr>
<tr>
<td>64</td>
<td>corticosterone</td>
<td>0.0324</td>
</tr>
<tr>
<td>72</td>
<td>methylprednisolone</td>
<td>0.0405</td>
</tr>
</tbody>
</table>

These are bioactive compounds that would be predicted to have favorable biologic activity to modulate the transcriptional responses associated with endocapillary proliferation. Full results of the analysis are available in Table S6. doi:10.1371/journal.pone.0103413.t004

- Defined distinct molecular profile of a pathologic phenotype associated with progressive renal insufficiency in IgAN.
- Identification of new therapeutic strategies for IgAN.

http://www.maayanlab.net/DPS/  
Hodgin et al, PlosOne 2014
Top 10 pathways differentially regulated by FT011 in treated and untreated diabetic animals.
Network analysis of FT011 pathway mechanisms
7 of 10 pathways common in human and animal DN is affected by FT011
New therapies - the future

- Return to the renal biopsy
  - Pharmacotranscriptomics

- Alternate dosing schedules
  - Rest periods, prevent saturation/adaptation