Developing Small Molecule, Oral Drugs to Inhibit the Enzyme Fructosamine-3-Kinase (FN3K) Induced Diabetic Complications and Other Autoimmune Diseases
History

- Fox Chase Cancer Center licensed technology.

- Fox Chase Cancer Center discovered the existence of a unique enzyme.

- A tool compound inhibitor of the enzyme, Meglumine, has been successfully tested in humans for effectiveness on psoriasis, gingivitis and mild detergent induced wounds.

- Animals studies using Meglumine demonstrate that diabetic and/or aging animals have improved kidney morphology, increased insulin sensitivity and reduced advanced glycation end products.

- Numerous cell studies support the importance of inhibiting the FN3K enzyme.
FN3K ENZYME

• A house-keeping enzyme that recovers lysine, a rare and essential amino acid, from its glycated form.
• Enzyme is unique except for a related protein that has no known human substrate.
• Fructose-3-kinase related protein does not phosphorylate fructose lysine.
• FN3K is also a unique enzyme since it phosphorylates its substrate on the 3’ position instead of 1’ or 6’.
• FN3K Knockout mouse is viable and reproduces normally, but unfortunately, the wild type does not get statistically significant numbers of kidney disease (personal comm.)
The Enzyme is Important to Inhibit Because:

- It causes
  - Formation of kidney fibrosis (glycation);
  - Inflammation;
  - Oxidative Stress.

  All three problems are factors in Diabetic Kidney Disease.

- The enzyme activity is specifically driven by too much sugar.
Importance of Stopping the Production of Toxic Sugar

- Inactivating toxic sugar results in improved kidney function in humans.

- Inducing Enzyme activity in rats causes kidney fibrosis.
3DG levels are elevated in normal rats that are fed a glycated diet, and their kidneys are similar to humans with nephropathy

- Evidence of kidney pathology are found in rat kidneys fed a glycated diet when compared with controls:

Kappler, F. et al., Diab. Tech. & Ther. 3:609 (2001)
Equal protein load. Diets fed for 8 months
Diabetic Nephropathy

Meglumine (an inhibitor of 3-DG) and our compounds derived from HTS, lower 3DG and AGE production in aging rats, resulting in a decrease in the progression of disease.

Bright green indicates the presence of AGEs in the non-treated control rats vs absence of AGEs in rats treated with inhibitor (indicating no AGEs present)
Advantages to Target FN3K Enzyme

- Cheap to make oral small molecule drug
- Easy to manufacture
- 20 years of patent life
- Probable Orphan Indication:
  - 7 years of market exclusivity
  - Shorter clinical trial
- Possibility of a companion diagnostic
Enzyme Product is a Better Biomarker for Complications than HbA1c

Increased serum 3DG levels correlate with the extent of nephropathy and retinopathy in patients, but are NOT well correlated with HbA1c

*Cohort of 110 diabetics and 57 control human subjects*

Kusunoki et al., Diabetes Care 26:1889 (2003)
Dynamis has identified drug compounds

Drug Development to Date:

- Medicinal Chemistry:
  - Developed High Through put screen.
  - Screened more than 300,000 compounds.
  - Identified 4 active core constructs.
  - Crystallized the enzyme and determined the structure of the active site.
Possible Disease Indications with Companion Diagnostic

- Certain related orphan diseases (e.g., diabetic macular edema, focal segmental glomerulosclerosis)
- Diabetic complications such as nephropathy, retinopathy, dry eye, macular degeneration and cataracts
- Scleroderma Kidney Disease
- Lupus Kidney Disease
- Ulcers and wounds
Management Team

- **Annette Tobia, Ph.D., J.D. President/CEO** Dr. Tobia is a serial entrepreneur. While a managing partner of QED Technologies, she started and administered virtual companies for venture capital firms. She was acting president of Arcturus Pharmaceutical Co., a dermatology company and a founder of Chemcore, a U of PA Atlas Ventures company, where she established and implemented the patent strategy for the company. ChemCore which was acquired by Caliper because of that strong patent portfolio. Before QED, she was Senior Vice President and General Counsel and founder of British Technology Group, USA (BTG), one of the world's leading technology transfer and licensing companies, as well as managing director of its parent company, BTG plc, a United Kingdom-based company. Prior to that she was Counsel to the President of the Bristol Myers Institute for Medical Research, where she structured strategic alliances with biotech companies and academic institutions.

- **Alice Marcy, Ph.D., Scientific Operations Officer**, is a biochemist/molecular biologist and prior to Dynamis worked for 15 years at Merck Research Labs. She has over 20 years of experience with protein expression, assay development, high throughput screening and chemical lead characterization.

- **James Devenny, Ph.D., Senior Pharmacologist** has previously worked over 18 yrs at DuPont, Merck and BMS where he was involved in the management and coordination of *in vitro*/*in vivo* research in metabolic diseases, diabetic complications, CNS biology, angiogenesis/endothelial cell biology, oncology and pharmacokinetics.

- **Erika Geimonen, Ph.D., M.S., VP Business Development**, has over 20 years of experience in business development and research. Prior to Dynamis, Erika was VP Business Development for XBiotech, a biotech company targeting inflammation by using novel native human antibodies. Prior to that she held business development positions at Schering-Plough and Luitpold Pharmaceuticals, a subsidiary of Daiichi-Sankyo group. She is also a co-chair of Philadelphia chapter of Licensing Executive Society.