



BioEnergenix, through a team of experienced drug hunters, medicinal chemists, pharmacologists, and regulatory consultants, is developing first-in-class orally-active PAS kinase inhibitors for the treatment of the metabolic syndrome. BioE1115, the company's IND-stage development candidate, restores insulin sensitivity, and lowers pathological triglycerides with efficacy superior to that of marketed drugs (e.g. Lovaza), in a clinically-predictive animal model of metabolic syndrome. BioEnergenix anticipates submitting an IND for BioE1115 for an initial indication of severe hypertriglyceridemia in H2/2014, and is currently seeking a partnership for development of the molecule. Although severe hypertriglyceridemia has the most cost-effective path to proof-of-concept and registration, other potential future indications include moderate hypertriglyceridemia, type 2 diabetes and NAFLD/NASH. BioEnergenix's BioE1115 and PAS kinase inhibitor program are protected by strong intellectual property.

**BioE1115:**

BioE1115 is an orally-active nanomolar-potent and highly-selective inhibitor of PAS kinase, a cellular nutrient sensor which drives dyslipidemia (via liver SREBP1c pathway), hepatic steatosis, and insulin resistance when mis-regulated. In rodent models of metabolic disease, BioE1115 restores insulin sensitivity (comparable to glitazones in oral glucose tolerance tests) with lowering of HbA1c, and inhibits liver SREBP1c target gene expression (lipogenesis) with concomitant reduction in circulating triglycerides (far superior to Omega 3 fatty acids). Considerable oral bioavailability in humans is expected given demonstration in 3 animal species (mice, rats, and dogs).

**BioEnergenix Leadership:**

William J. Rutter, Ph.D.  
*Chairman*

Philip Needleman, Ph.D.  
*Senior Partner*

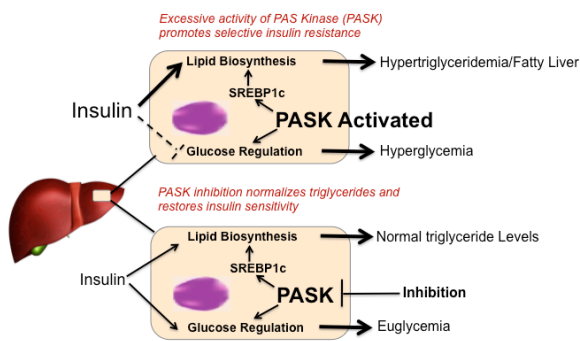
John P. McKearn, Ph.D.  
*Managing Partner*

Jeremy T. Blitzer, M.D., Ph.D.  
*Partner & VP Product Development*

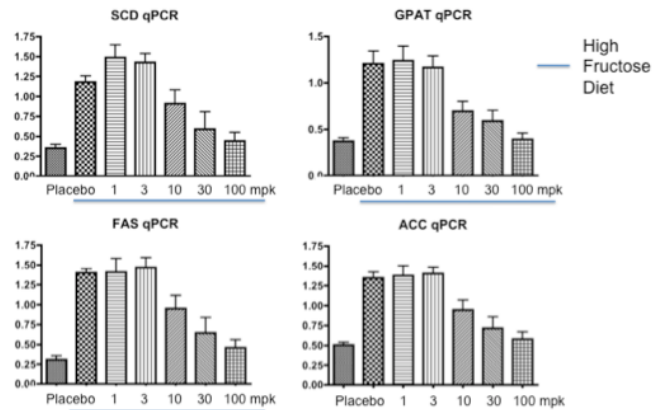
**Scientific Founder:**  
 Jared Rutter, Ph.D.

**Schematic of PAS Kinase Cellular Mechanism**

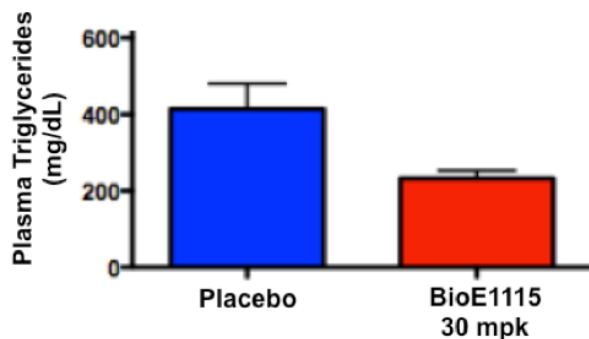
PAS kinase contributes to selective insulin resistance in the liver, which drives hypertriglyceridemia (via SREBP1c) and hyperglycemia. PAS kinase inhibition restores insulin sensitivity and lowers pathological triglycerides.



**High Fructose-Dieted Rats – SREBP1c Target Genes**  
 BioE1115 (7 days of dosing) inhibits liver SREBP1c target gene expression (lipogenesis) with ED35 and ED50 < 30 mpk.



**High Fructose/High Fat-Dieted Rats – Circulating Triglycerides**  
 BioE1115 (7 days of dosing) lowers circulating triglycerides (ED35 < 30 mpk).



**BioE1115 In Comparison to Marketed Therapeutics**  
 Pre-clinical studies predict a broad BioE1115 product profile with considerable reduction in triglycerides (greater than standard of care) and beneficial effects on insulin sensitivity. (Data is from BioE1115 animal studies, product labels, literature, and input from KOLs).

	Triglycerides	HbA1c (A1c pts)	Fasting Blood Glucose	Insulin
BioE1115	70-80% reduction	>1 pt reduction	60% reduction	65% reduction
Lovaza	33-51.6% reduction	No effect	No effect	No effect
Vascepa	33% reduction	No effect	No effect	No effect
Tricor	33-54.5% reduction	No effect	No effect	No effect
Lipitor	51.8% reduction	No effect	No effect	No effect
Glucophage	16% reduction	1.4 pt reduction	22% reduction	Decreased
Januvia	+/-	0.5-0.6 pt reduction	7% reduction	Increased

**Toxicology/Safety:**

- IND-enabling GLP toxicology/safety program underway
- No effects on cardiovascular safety pharmacology (e.g. QT interval)
- Non-mutagenic (Ames assay)
- Non-clastogenic (chromosome aberration assay)
- Clean in vitro pharmacology panel (137/137 receptors, transporters, ion channels, and enzymes)
- Highly-selective for PAS kinase vs. 49/49 other kinases

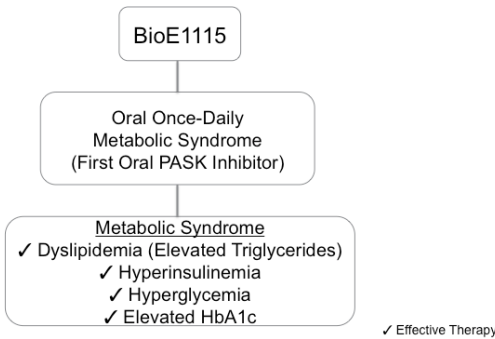
**BioE1115 Chemistry, Manufacturing, and Controls:**

- Efficient chemical synthesis defined at kg scale
- GMP campaign in near-term

**BioE1115 Regulatory/Clinical Strategy:**

- Potent insulin resensitization and triglyceride-lowering activities suggest a **broad** therapeutic/product profile compared to marketed drugs
- Severe hypertriglyceridemia will be initial indication (no outcomes studies likely required for FDA approval)
- Initial IND filing anticipated for H2/2014
- Other future indications could include type 2 diabetes and NAFLD/NASH
- Team has extensive clinical/regulatory experience in these areas

**Platform Opportunities:**



**Comprehensive BioEnergenix Intellectual Property:**

- Global rights owned by BioEnergenix
- BioE1115 is a novel chemical entity with full composition of matter coverage (20 years plus Hatch-Waxman extensions)
- Composition coverage of BioE1115 analogs, prodrugs, and related genera
- Composition coverage of several other PAS kinase inhibitor chemical scaffolds
- Claims on methods of treating dyslipidemia and other facets of the metabolic syndrome with BioE1115 and other chemical series
- Multiple layers of defensive filings including PAS kinase target and associated assays

**Next Steps:**

- GMP BioE1115 campaign
- Completion of remaining IND-enabling GLP animal toxicology/safety studies
- IND filing for initial indication of severe hypertriglyceridemia (H2/2014)

Synergenics Pipeline	Dosage Form	Leads	Pre-clinical Candidate	IND Candidate	Phase I Clinical
Pain/Inflammation (Pathologica)					
PA300 (Polyamine Pathway)	Oral	→			
	Oral (Enteric-Coated)	→			
Multiple Sclerosis (Pathologica)					
PA300 (Polyamine Pathway)	Oral	→			
	Oral (Enteric-Coated)	→			
Dyslipidemia & Metabolic Disease (BioEnergenix)					
BioE1115 (PAS Kinase)	Oral	→			

BioEnergenix is actively seeking strategic partners for BioE1115 development. Please contact Jeremy T. Blitzer, M.D, Ph.D. (email: [jblitzer@synergenics.net](mailto:jblitzer@synergenics.net); tel: 415-554-8170) for further information.