“Smart” Basal Insulin Formulation That Releases Insulin in Response to Blood Glucose Concentrations of Diabetic Swine

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“the right treatment for the right person at the right time”

Diabetes Mellitus (DM) is more than one disease & is very complex and management of DM is even more complex.

The next generation of diabetes therapeutics must be flexible and responsive to the ever-changing needs of the individual patients.
Current Basal Insulin Therapy

- Most Type 2 patients, when started on insulin therapy are initially prescribed a basal only treatment regimen.

- Basal insulins are also used to treat patients with Type 1 DM.
Unmet Needs

■ Current basal Insulin cannot respond to conditions that affect glucose levels such as exercise, stress, fever etc.

■ When treating patients with Type 2 diabetes, in order to reduce Post prandial hyperglycemia, basal insulin is often administered at inappropriately high doses. Such high insulin doses result in more hypoglycemic episodes and increased weight gain that further complicate the management of DM.

■ The Dawn phenomenon (early morning increase in hepatic glucose output) is not addressed and can also lead to either inappropriately high basal doses or prolonged periods of hyperglycemia.
A self regulated basal insulin formulation that would release insulin in response to changing s.c. glucose concentrations may be more efficient and superior in controlling diabetes than a basal insulin with an unvarying release rate.

A basal insulin that modifies its release to glucose levels would be an improvement.
Outline

- What is Smart Basal Insulin
- Mechanism of Action
- *In vitro* - Proof of Concept
- *In vivo* - Proof of Concept
- Conclusions
- Acknowledgement
- Questions
Smart Basal Insulin

- Basal insulin that releases insulin proportionally to s.c. glucose levels and adjusts to changes in patient's insulin needs.

- Not a prandial substitute but instead, a glucose responsive basal insulin.

- Projected advantages:
  - Improved postprandial response (less immediate hyperglycemia and less risk of subsequent hypoglycemia)
  - Adjust to dawn phenomenon (early AM increase in hepatic glucose output)
  - Less risk of hypoglycemia and hyperglycemia due to factors such as stress, fever and exercise.
“BIOD620” injectable formulation includes insulin glargine, glucose oxidase (GOD) and peroxidase (POD) at pH ~4.

The solubility of insulin glargine is pH dependent, being more soluble at lower pH and less soluble at neutral pH.

Combination of GOD and POD responds to increased glucose concentration by producing gluconic acid, lowering the pH and thereby increasing the solubility of insulin.
Role of enzymes

Glucose $\xrightarrow{[\text{Glucose oxidase}] + [\text{Oxygen}]}$ Gluconic Acid + Hydrogen peroxide

$\xrightarrow{[\text{Peroxidase}]}$ Oxygen + Water
Mechanism Of Action

Subcutaneous Adipose Tissue

Blood Vessels

Cutis

= Glucose
= ppt. Insulin Glargine
= Glucose oxidase
Mechanism Of Action Cont...

Subcutaneous Adipose Tissue

- Glucose
- ppt. Insulin Glargine
- Glucose oxidase
- Gluconic acid

Blood Vessels

Cutis
Mechanism Of Action Cont...

Subcutaneous Adipose Tissue

- Glucose
- ppt. Insulin Glargine
- Glucose oxidase
- Gluconic acid
- Soluble Insulin Glargine
AIM: To study the glucose responsive insulin release from smart basal insulin formulation, BIOD620 under *in vitro* conditions.
**In Vitro Study- Experimental Set up**

**Set up:** Two chamber cell culture plate with a donor and receiver well was taken and fitted with 1.0 µm filter separating them.

**Test set:** Donor cell contained 1 ml of BIOD620 with 200µl of phosphate buffer saline (PBS) with glucose. Receiver well contained 1.5ml of 300mg/dl glucose PBS as the release medium.

**Control set:** Donor cell contained 1 ml of BIOD620 with 200µl of PBS without glucose. Receiver well contained 1.5ml of PBS without glucose.

**Analysis:** A 500µl aliquot sampled from receiver well and analyzed by HPLC.
In Vitro Study - Response to Glucose

AMOUNT OF INSULIN RELEASED

Formulation with and without glucose (n=3)

SET1, with glucose

SET 2, no glucose
Effect of Varying Glucose Concentration

Insulin concentration in response to different glucose concentrations

- 0 mg/dl, 6h
- 100 mg/dl, 6h
- 200 mg/dl, 6h
- 250 mg/dl, 6h
- 300 mg/dl, 6h

Amount of Insulin in mg

After 6 hours
We demonstrated that the amount of insulin released from the BIOD620 was dependent upon the glucose concentration in the environment.

Higher glucose concentration, resulted in a monotonically increasing insulin concentration.
**In Vivo Study - Proof of Concept**

**AIM:** To study the PD of diabetic pigs upon administration of a 0.25U/Kg dose of BIOD620 compared to Lantus® (Insulin glargine).
In Vivo Study - Experimental Set up

- **Animal preparation**: 6 diabetic miniature swine were fasted overnight. Morning glucose levels were high and were used as the starting point for the comparison.

- **Test Group**: 3 animals, BIOD620

- **Control Group**: 3 animals, Lantus®

- **Dose**: s.c., 0.25U/kg. Following administration of the doses, pigs were monitored and fed 500g of swine food at 360 minutes as a glucose challenge.

- **Analysis**: Plasma glucose levels were determined every 15 minutes via a commercial glucose strip method.
In Vivo Study - Post Dosing Data

Mean Plasma Glucose Levels (n=3 ±SEM), Dose 0.25U/Kg, BIOD620 vs. Lantus®

Comparison of plasma glucose levels of the group receiving smart basal formulation compared to the group received insulin glargine alone.
In Vivo Study - Post Feeding Data

Mean Plasma Glucose Levels (n=3±SEM), Dose 0.25U/Kg, BIOD620 vs. Lantus®

Comparison of plasma glucose levels of the group receiving smart basal formulation compared to the group received insulin glargine alone.
In Vivo Study - Conclusions

✓ Post injection, BIOD620 was able to reduce the abnormally high plasma glucose levels faster than the abnormally high plasma glucose levels of the Lantus® group.

✓ After feeding, post meal hyperglycemia was reduced more rapidly in BIOD620 group than in the Lantus® group.
Conclusions and Perspective

✓ The scope of this research was to develop and evaluate a smart basal insulin formulation for its glucose responsive insulin delivery potential.

✓ *In vitro* & *in vivo* studies in diabetic swine model demonstrated an increased insulin release from the BIOD620 in response to increasing glucose concentrations.

✓ BIOD620 is truly a self-regulating formulation in that it released less insulin at lower glucose concentrations, *in vitro* and *in vivo*.

✓ BIOD620 formulation is able to manage the plasma glucose levels better than the basal insulin alone.

✓ BIOD620 insulin has the potential to be a significant improvement over basal insulin and to benefit patients with diabetes mellitus.
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Questions

Thank you for your attention!!

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