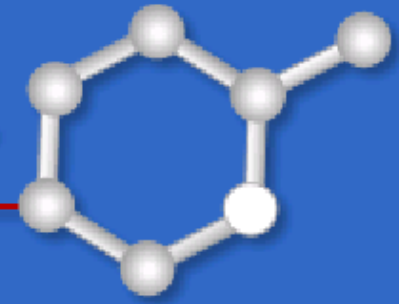




DIABETES TECHNOLOGY SOCIETY

Applying science and engineering to fight diabetes

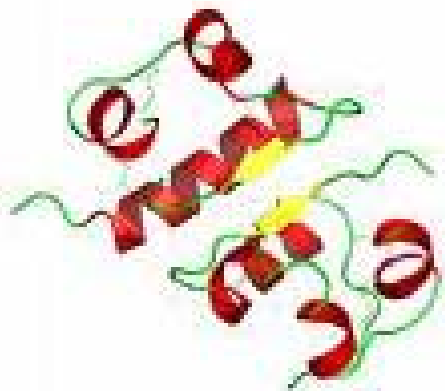


Re-Engineering Insulin: Can We Improve on Mother Nature?

November 13, 2010

Bethesda, MD

Alexander Fleming, MD



Presenter Disclosure

Alexander Fleming, M.D.

Board Member/Advisory Panel/Consultant:

Amgen, Amylin, American Type Culture Collection, Andromeda, Arisaph, Salutria, BCT, BioCon, Can-Am, Circ Pharma, Diasome, Elona, Eris, Glenmark, Helsinn, Indigene, Integrium, Institute of Pharmaceutical Discovery, Isis, Lilly Lipothrea, MannKind Corporation, N-Gene, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Orexigen, Phenomix, Plexxikon, ReceptorBio, Rhythm, Salutria, Sanofi-Aventis, Shionogi, Sirtris, Takeda Pharmaceuticals, Teva, Veroscience, Zafgen.

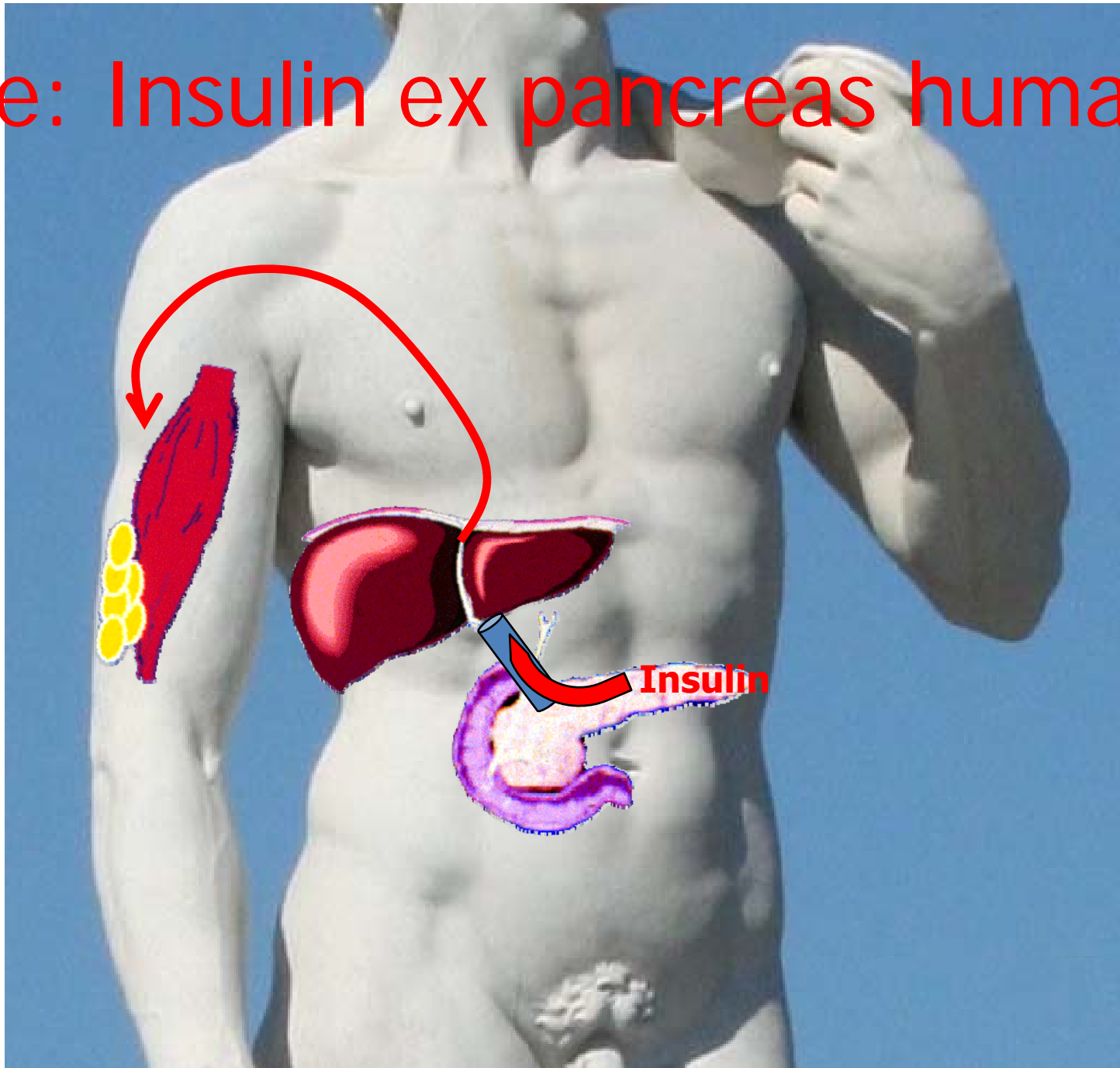
Stock/Shareholder: Exsulin Corporation

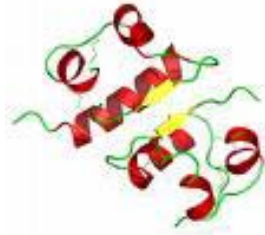
Other: Kinexum, principle

Overview

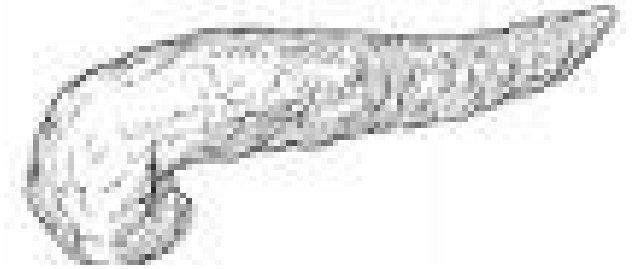
- **Addressing unmet clinical need**
- **Scientific rationale**
- **Current approaches**
- **Considerations for therapeutic development**
- **Regulatory Issues**

Ecce: Insulin ex pancreas humani



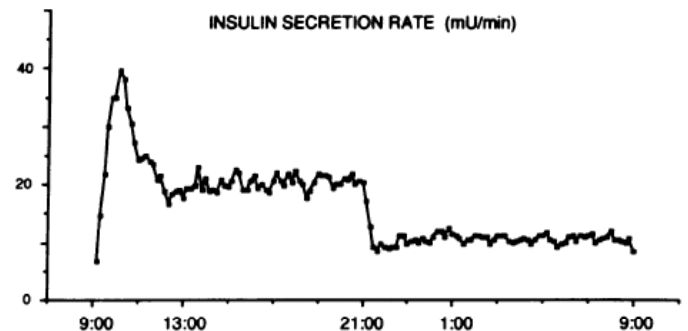


Insulin:



Hard to improve on Mother Nature

- **Because normally, insulin is secreted in—**
 - Just the right time (high and low frequency)
 - Just the right place
 - Just the right condition
 - Just the right cost and effort
- **And, insulin, the peptide has**
 - Just the right affinity for insulin and other receptors



Traditional reasons for trying to improve on human insulin:

- **Convenience**
- **Needleless administration**
- **Better metabolic control, body weight effects**
- **Less risk of hypoglycemia**
- **Less other safety concerns**
- **Affordability**



Addressing unmet clinical need for insulin delivery

- Convenience of non-injected insulin approaches becoming less important
- Injected insulin therapy very effective but safety depends on the glycemic goal
- The clear unmet clinical need is to improve the safety of insulin use—
not just hypoglycemia but
 - weight gain,
 - dyslipidemia
 - other adverse effects

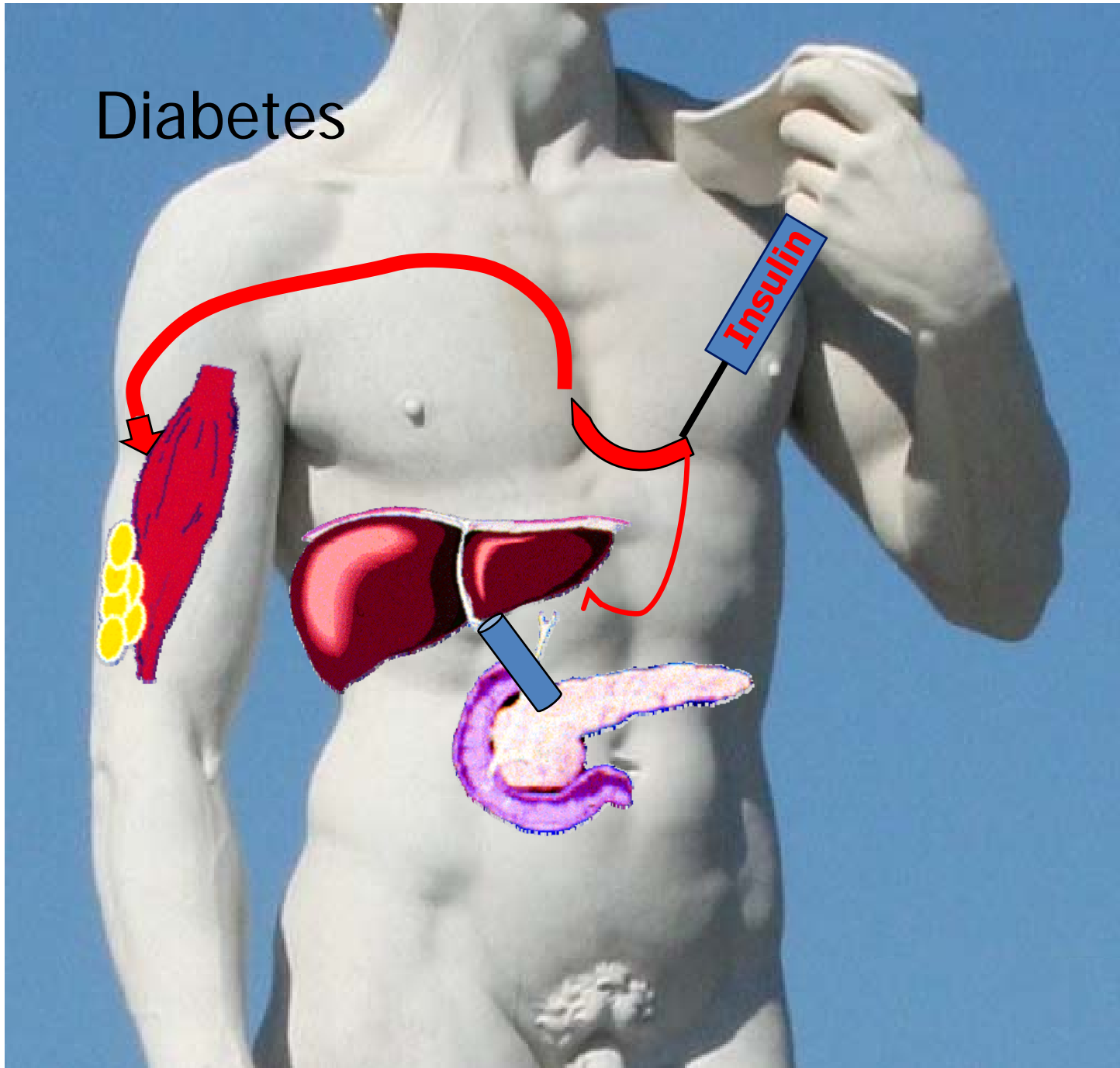


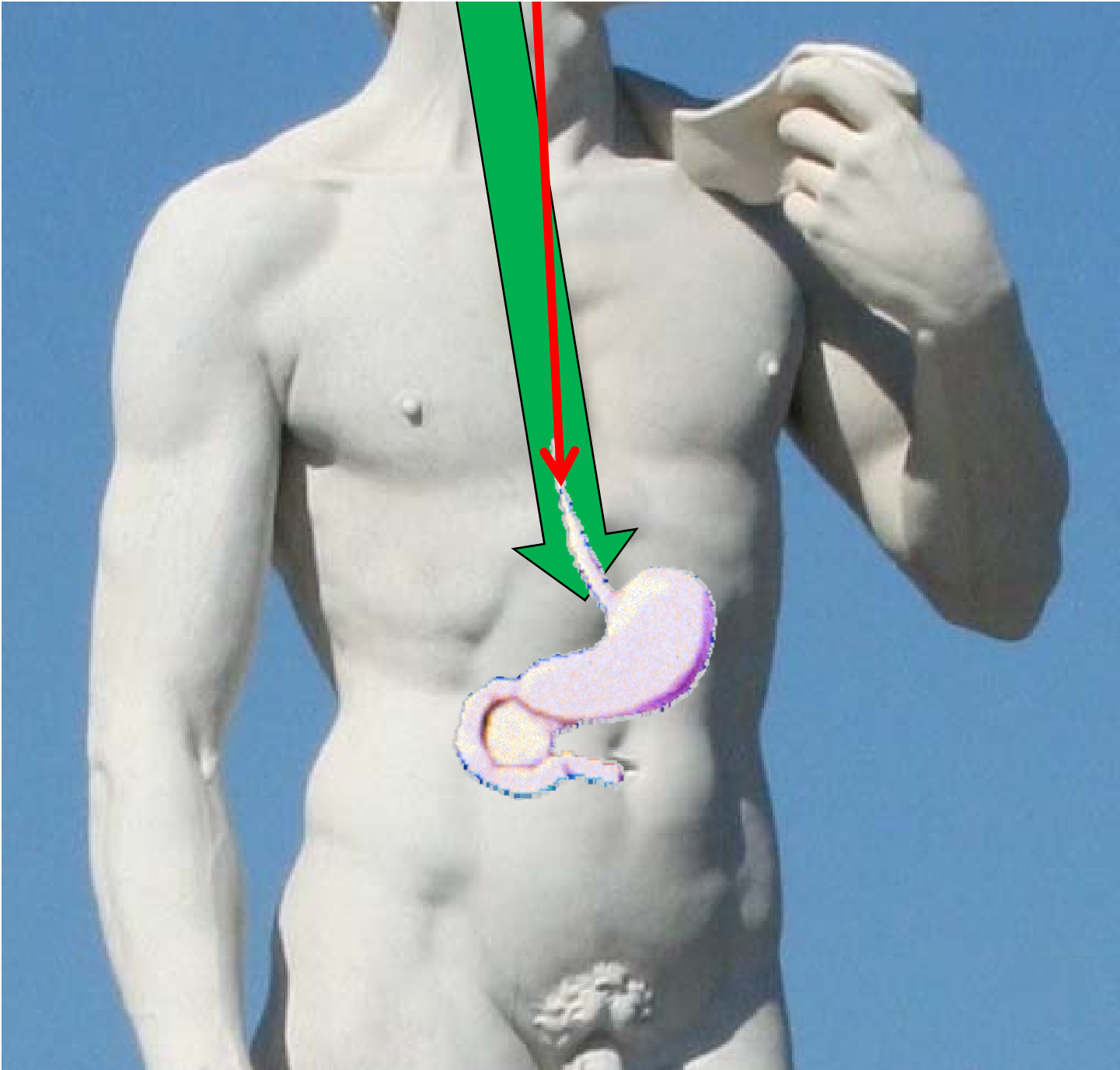
A long held hope:

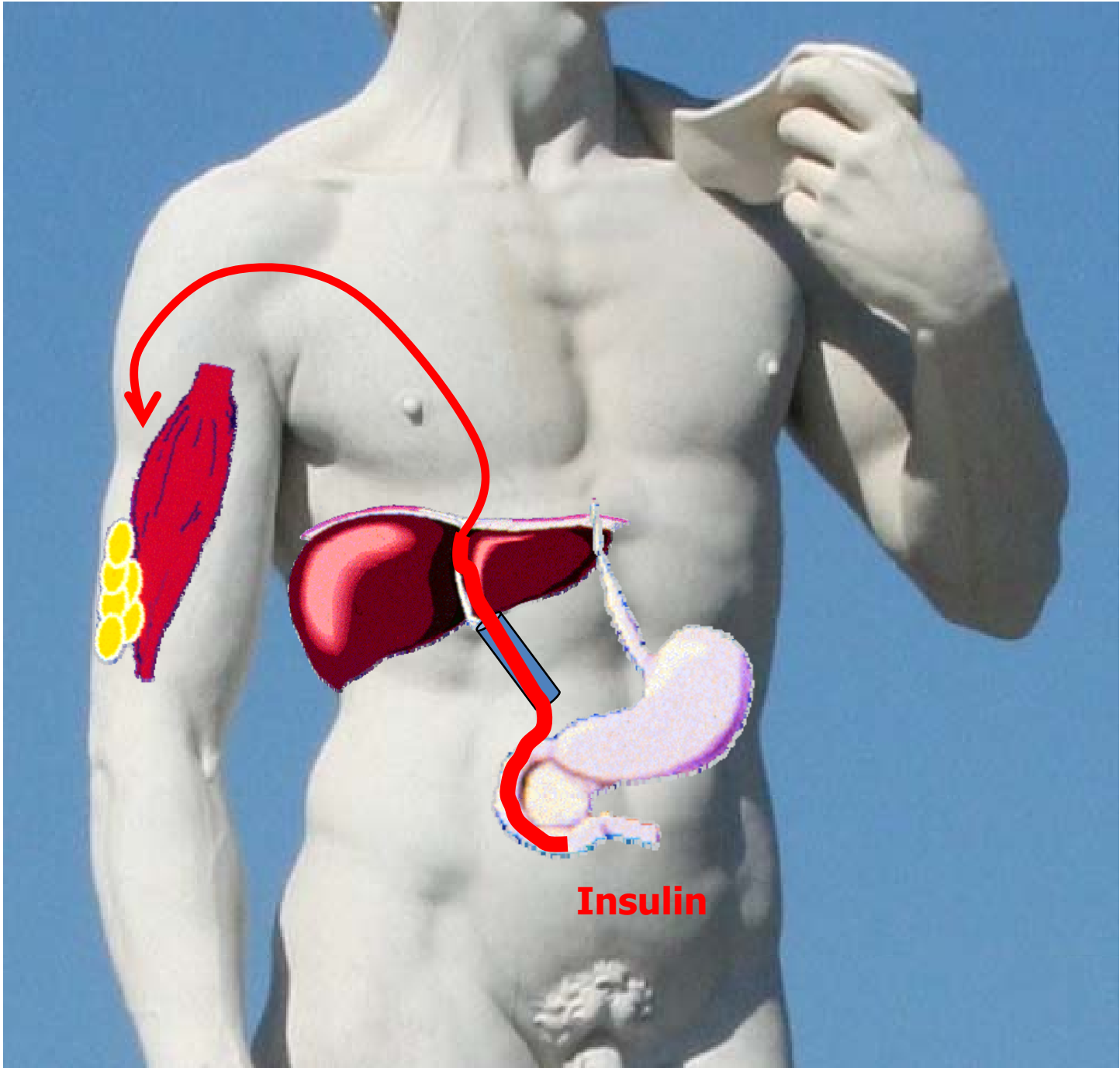
Oral delivered insulin could improved therapeutic index of insulin therapy

- **Oral insulin could correct under exposure of liver to insulin**
- **Absorption of insulin from the GI tract and transport through the portal venous system control both hepatic glucose output and peripheral glucose uptake**

Diabetes

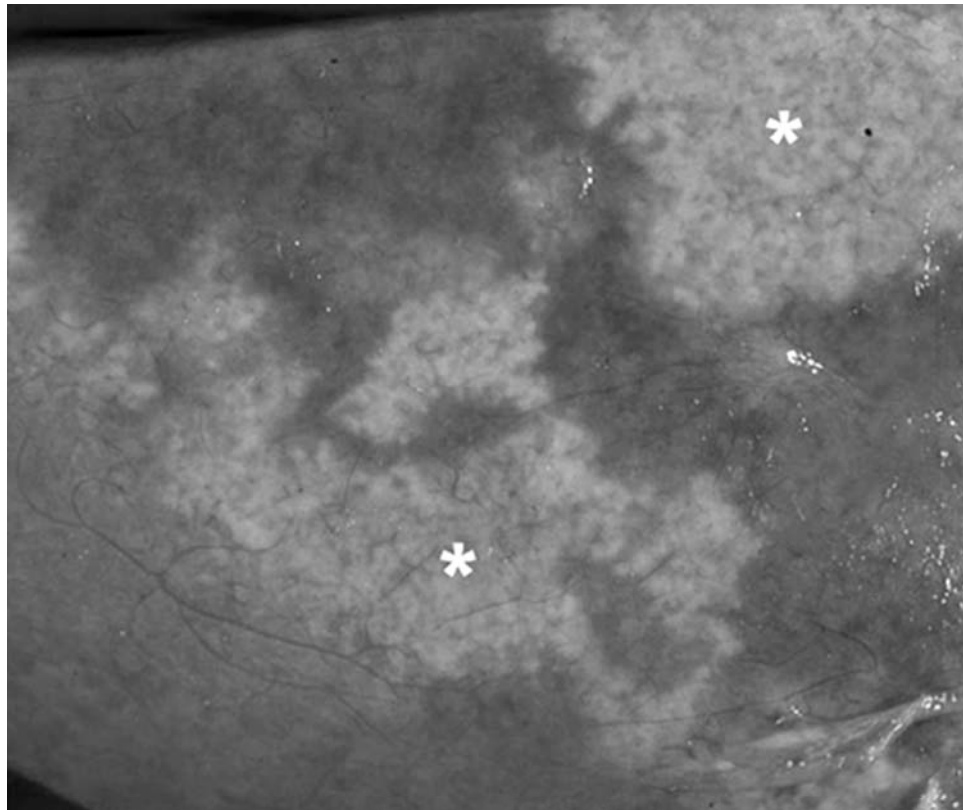






Caution: Unanticipated consequences

Subcapsular hepatic steatosis associated with intraperitoneal insulin



Khalili, K. et al. Am. J. Roentgenol. 2003;180:1601-1604

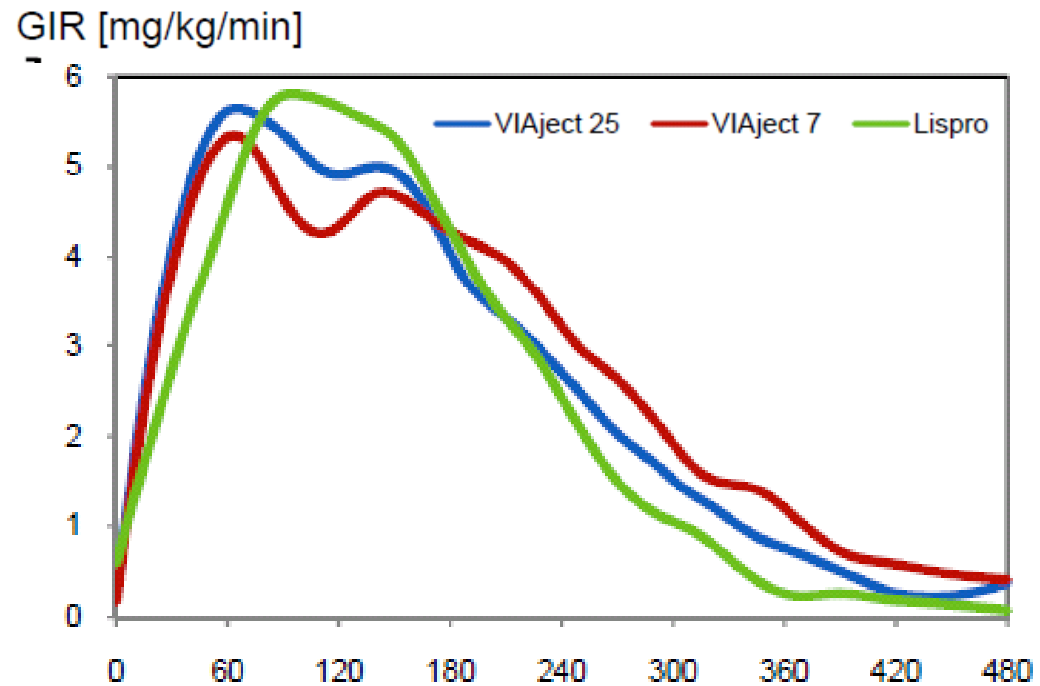
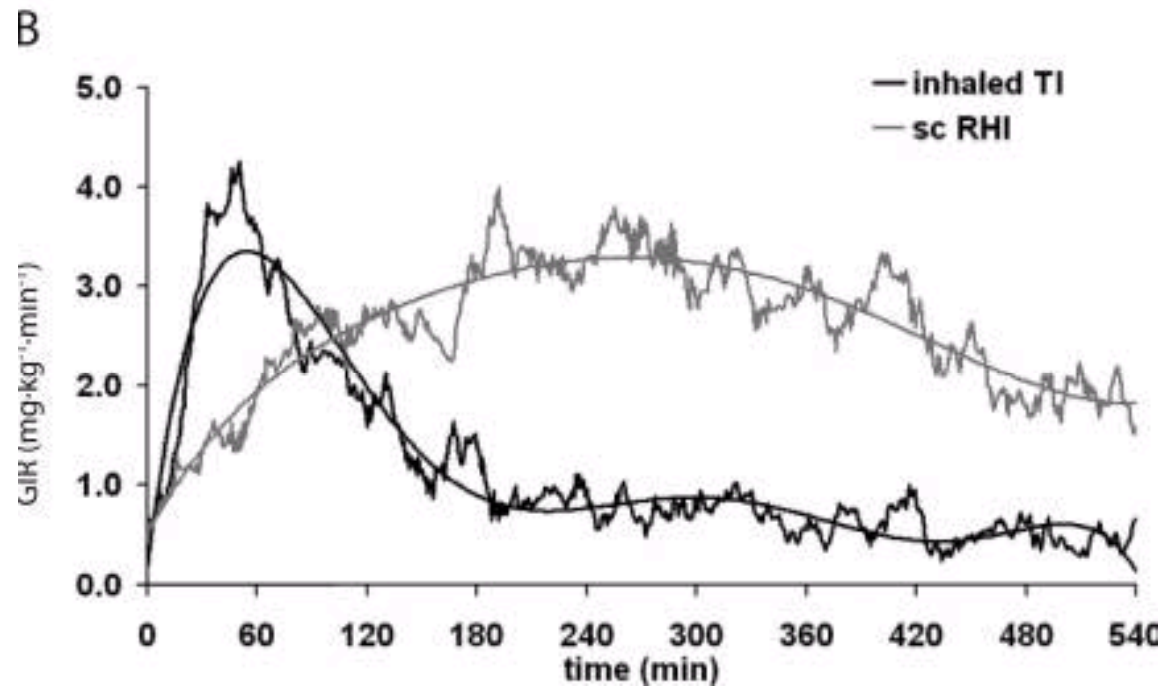
Oral Insulins Under Development

- **Multiple programs still active— both human insulin and insulin analog**
- **Challenges include low bioavailability and consistent performance**
- **Most are very rapidly acting—targeted at prandial coverage only**
- **Convenience of administration probably not enough but may offer some clinical benefits**

*See Heineman et al, Journal of Diabetes science and Technology, 2008

Ultra Fast Acting Insulins

- Potential to result in less risk of hypoglycemia
- Provide better glycemic control



Fast Acting Insulins

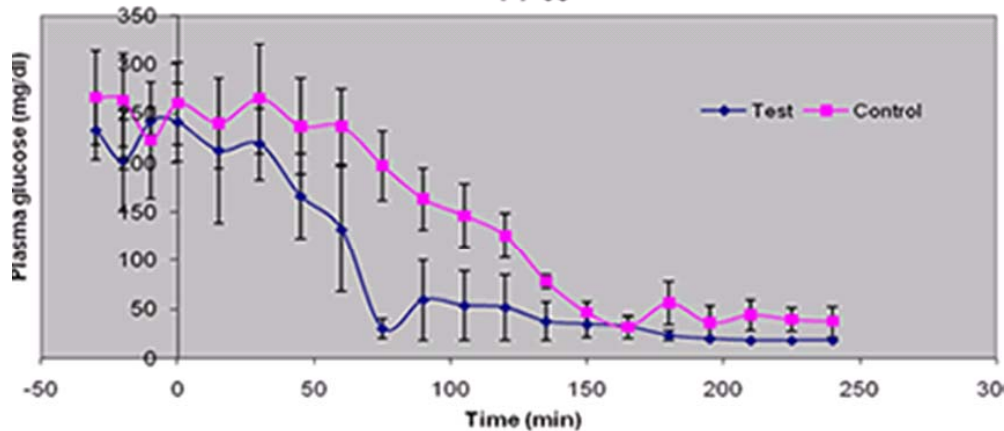
- **Multiple insulin development programs aimed at prandial coverage**
 - **Injected, monomeric Biondi**
 - **Inhaled Mannkind**
 - **Fast SQ release Halozyme**
 - **Nasal CPEX**
- **PK profile appears more physiologic than current injected insulins**
- **Will clinical benefits justify the additional costs as injected fast acting analogs become “generic”?**

Ultra Long Acting Insulins

- **Multiple insulin development programs aimed at >24 hour duration → Flamel, Novo, et al**
- **Some reports of lower day-to-day variability compared to glargine**
- **Will rates of hypoglycemia and compliance compare favorably to available long-acting insulin products?**

Smart Insulins

Mean plasma glucose level of Swine with 0.25U/Kg(4x) higher dose
1-7-08

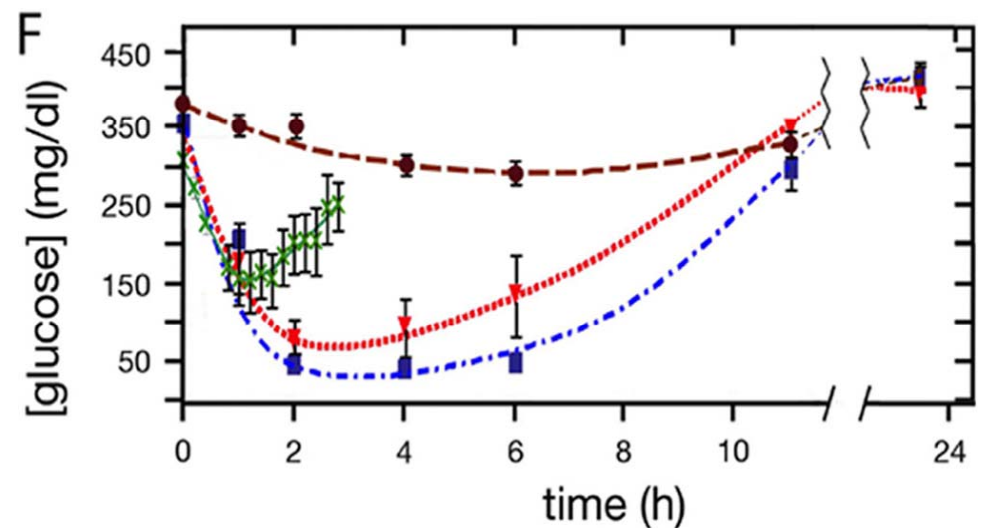
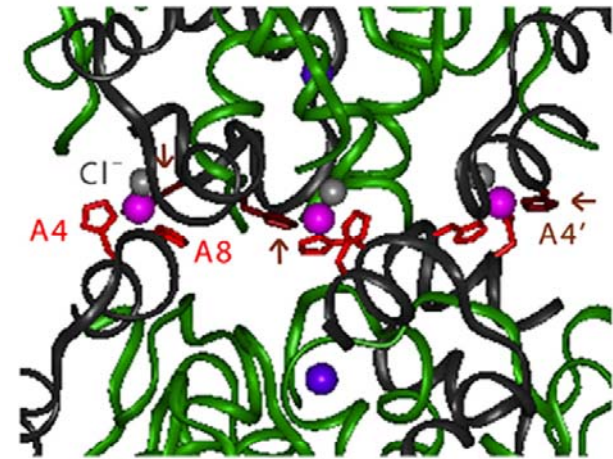


Comparison of plasma glucose levels of test and control groups before feeding.
Test group received smart basal formulation, while control group received insulin glargine alone.



DESIGN OF ZINC-STAPLED INSULIN HEXAMERS AS A LONG ACTING DEPOT*

JBC Papers in Press, 2010,
Nelson B. Phillips^{‡1}, Zhu-li Wan^{‡1}, Linda Whittaker[‡],
Shi-Quan Hu[‡], Kun Huang[‡], Qing-xin Hua[‡], Jonathan
Whittaker[‡],
Faramarz Ismail-Beigi[§], and Michael A. Weiss^{‡§2}



Pump insulins

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press release

JDRF Launches Research Program to Accelerate Delivery of Faster Acting Insulin; Key Step on Road to an Artificial Pancreas

Media Contact:

Joana Casas, (212) 479-7560, mcasas@jdrf.org

William Ahearn, (212) 479-7531, wahearn@jdrf.org

NEW YORK, August 16, 2010 - JDRF announced today another important step on the road to the development of an artificial pancreas - an automated system to better manage the blood sugar of people with type 1 diabetes - with the establishment of a research program to speed the development of faster-acting insulin.

**Challenge: Clinical Design
and Regulatory Evaluation**

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Additional copies are available from:

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<http://www.fda.gov/cder/guidance/index.htm>*

Challenge: Clinical Design and Regulatory Evaluation

- **Conventional insulin paradigm**
 - Open label
 - Non-inferiority comparison to another insulin product
 - Aimed at T1 and T2DM
- **Oral agent paradigm**
 - Double blind
 - Add on to background therapy
 - Comparison to placebo
 - Aimed at T2DM

Safety concerns/opportunities for insulin products

- **Hypoglycemia...hypoglycemia...hypoglycemia...**
- **Weight gain and dyslipidemia**
- **Risk of increased cancer risk**
- **Antigenicity**

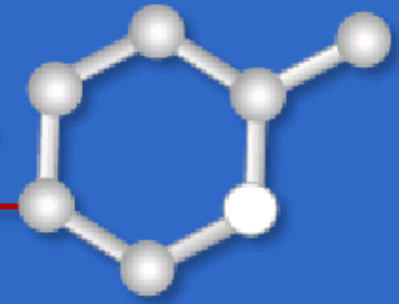
Summary

- **Currently available insulin products still allow room for improvement of new insulin products**
- **New insulin products will need to show substantial advantages to be successful**
- **Progress is likely to be incremental**



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Re-Engineering Insulin: Can We Improve on Mother Nature?

We need to try.

