Optimizing Early Phase Antidiabetic Drug Development

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The Ominous Octet: Pathologies, Therapies and Targets

Hyperglycemia in Type 2 Diabetes

- Neurotransmitter dysfunction
  - GLP-1 receptor agonists
  - Amylin
  - Bromocriptine
- Increased lipolysis and reduced glucose uptake
  - Thiazolidinediones
- Impaired insulin secretion
  - Sulfonylurea
  - Meglitinide
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
- Increased glucagon secretion
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - Amylin
- Increased hepatic glucose production
  - Metformin
  - Insulin
  - Thiazolidinediones
- Decreased glucose uptake
  - Metformin
  - Insulin
  - Thiazolidinediones
- Decreased incretin effect
  - Metformin
  - α-Glucosidase inhibitors
  - Colesevelam

DeFronzo RA, [20]
Tahrani AA, et al. [25]
An Uphill Battle Imagine leading an expedition where every step is more difficult than the last...

The long journey begins in the lab, where scientists spend years testing thousands of ideas. Next, crossing the so-called "Funding Valley of Death" requires the resources and time needed to complete clinical trials, testing safety and effectiveness among what could end up being thousands of volunteers. At the end of this steep financial and scientific climb: Food and Drug Administration approval for a new treatment. Ultimately, it may have taken up to 15 years and more than $1 billion to bring this treatment to the market.

3 to 6 years
Basic Research/Drug Discovery
5,000-10,000 Potential Treatments

Pre-Clinical/Translational
250 Potential Treatments

6 to 7 years
Clinical Trials
5 Potential Treatments

Phase 1

Phase 2

Phase 3

0.5 to 2 years
FDA Review

One Approved Treatment!

By the end of the expedition, you may have spent up to 15 years and more than $1 billion to bring one product to the market.

For more information, visit: brightfocus.org/clinicaltrials

1 Although we are using the word "treatment," clinical trials also involve medical research studies in which people participate as volunteers to test new methods of prevention, screening, and diagnosis of disease.

2 After approval, the product is manufactured for sale on the market, and the process enters Phase 4 (Post-Marketing Monitoring/Clinical Trials). At this point, the FDA monitors for public safety and adverse events, and the sponsor company may begin Phase 4 Clinical Trials to obtain information about long-term effects or to test the product in special patient populations.

3 The "Funding Valley of Death" is the financial challenge many promising treatments face in having the opportunity to be scientifically tested in a clinical trial. In many cases, further financial support or partnerships are necessary to proceed.

* The cost of bringing a drug to market depends on a number of variables, but could be more than $1 billion, including approximately $50-840 million for Basic Research/Drug Development and Pre-Clinical/Translational research, and approximately $50-970 million to complete all three Phases of the Clinical Trials.
Cardiovascular Risk Assessment

In order to satisfy the initial approvability hazard ratio requirements of 1.8 to 1.3, drug development programs should target between approximately 120 to 700 CV events respectively. This will require studying between 4,500 and 15,000 T2DM patients.

Adds at least a year to the drug development process and an estimated $250$ to $500$ million US Dollars to the cost of developing a new diabetes medication.


Figure 1—FDA CV safety: CI bars. The FDA guidelines provide statistical hurdles for approval. Five hypothetical examples of possible hazard ratios and the upper limit of the 95% CI of a development plan are shown as well as the regulatory consequences of each outcome.
FMD as an Early Signal of CV Risk

Non-Invasive, ultrasonographic measure of nitric oxide cascade mediated vascular dilation of the diameter of the brachial artery in response to hyperemia induced by short-term occlusion of the forearm.

The FMD response is sensitive to even short term interventions and is highly correlated to cardiovascular outcomes.

FMD as an Early Signal of CV Risk

Figure 2. Power curves for estimating subjects required for flow-mediated dilatation studies in crossover and parallel studies. Relation between effect on maximum percent change in flow-mediated dilation (%) and number of subjects required in crossover and parallel study designs at 80% power and 5% significance, 4–6 h and 3 months apart with three monitoring strategies: 1, 2, or 4 measures pre- and post-treatment.

Repeatability of the Hyperinsulinemic-Euglycemic Glucose Clamp

Period 1 and Period 2 Mean Plasma Glucose and Glucose Infusion Rate (GIR) vs. Time

- **P1 Plasma Glucose (mg/dL)**
- **P2 Plasma Glucose (mg/dL)**
- **P1 GIR (mg/kg/min)**
- **P2 GIR (mg/kg/min)**
Repeatability of the Hyperinsulinemic-Euglycemic Glucose Clamp

All Period Mean Plasma Glucose and Glucose Infusion Rate (GIR) vs. Time

- **Blood Glucose (mg/dL)**
- **GIR (mg/kg/min)**

**Timepoint (minutes):**

- 0
- 20
- 40
- 60
- 80
- 100
- 120
- 140
- 160
- 180
- 200
- 220
- 240
- 260
- 280
- 300
- 320
- 340
- 360

**Graph Description:**
- The graph shows the mean plasma glucose and glucose infusion rate (GIR) over time.
- **Plasma Glucose (mg/dL):** The black line represents the plasma glucose levels, which are maintained near the target level throughout the timepoints.
- **GIR (mg/kg/min):** The red line represents the GIR, which increases significantly over time, indicating an effective glucose clamp.

**Key Points:**
- The study demonstrates the repeatability of the hyperinsulinemic-euglycemic glucose clamp protocol.
- The consistent maintenance of plasma glucose levels suggests good control and repeatability of the experimental conditions.
- The increasing GIR indicates efficient glucose disposal and insulin sensitivity over time.
Additional Testing Methods

- **Glycemic Control or Metabolic Regulation**
  - 24hr glucose
  - Continuous Glucose Monitoring
  - Oral Glucose Tolerance Tests (OGTT)
  - Meal Tolerance Tests (MTT)
  - Intravenous Glucose Tolerance Tests (IVGTT)
  - Pancreatic Maximum Stimulation Tests
  - Graded Glucose Infusions (GGI)
  - Glucose Clamping
  - Isotope Dilution Methods
    - Stable and radioactive isotopes

- **Satiety**
  - Visual Analog Scales (VAS)
  - Food intake models

- **Cardiometabolic Endothelial Function Testing**
  - Flow Mediated Dilation (FMD)

- **Substrate Utilization and Energy Expenditure**
  - Indirect Calorimetry

- **Metabolically Relevant Medical Imaging**
  (DEXA, MRI)

- **Metabolically Relevant Biopsies**
  (Adipose, Muscle)
Risks Deferred are Risks Accepted
Questions?