Celerion’s Symposia Series:
Bridging the Gap from Phase I to Proof-of-Concept
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Diabetes and Drug Development
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Diabetes and Drug Development

- Considerations about a complex chronic disease
  - Epidemiology
  - Physiology/Pathophysiology
  - Regulatory
## Framework for Evaluating Investments in New Drugs

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Examples of types of drugs</th>
<th>Possible influences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development cost</td>
<td>Niche drugs vs. drugs for common chronic diseases</td>
<td>Regulatory policy or new business model</td>
</tr>
<tr>
<td>Selling cost of drug</td>
<td>Specialist vs. GP</td>
<td>Regulatory policy or new business model</td>
</tr>
<tr>
<td>Differentiation from existing drugs</td>
<td>Short survival vs. chronic</td>
<td>Only influenced via investment in basic scientific research</td>
</tr>
<tr>
<td>Incidence and prevalence of treated condition</td>
<td>Rare vs. common chronic</td>
<td>Only influenced via investment in basic scientific research</td>
</tr>
</tbody>
</table>

*Drugs are most favorable for investment when they have low development and selling costs, are highly differentiated from available treatments, and target conditions with a high incidence and prevalence.*

Modified from: The Calculus of Cures Kocher R. and Roberts B.; NEJM 2014
Definition of Diabetes

- Fasting Blood Glucose $\geq 126$ mg/dL
- 2 hour post OGTT $\geq 200$ mg/dL
- Casual Blood Glucose $\geq 200$ mg/dL and Symptoms of Hyperglycemia
- HbA1c $\geq 6.5\%$
Epidemiology

**WORLD**

371 M people living with diabetes

**NORTH AMERICA AND CARIBBEAN**
- More healthcare dollars were spent on diabetes in this region than any other.
- 1 in 10 adults in this region has diabetes.

**SOUTH AND CENTRAL AMERICA**
- Only 5% of all healthcare dollars for diabetes were spent in this region.
- 1 in 11 adults in this region has diabetes.

**AFRICA**
- Over the next 20 years, the number of people with diabetes in the region will almost double.
- This region has the highest mortality rate due to diabetes.

**MIDDLE EAST AND NORTH AFRICA**
- 1 in 9 adults in this region has diabetes.
- More than half of people with diabetes in this region don’t know they have it.

**EUROPE**
- 1 out of every 3 dollars spent on diabetes healthcare was spent in this region.
- 21.2 million people in this region have diabetes and don’t know it.

**SOUTH-EAST ASIA**
- 1 in 5 of all undiagnosed cases of diabetes is in this region.
- 1 in 4 deaths due to diabetes occurred in this region.

**WESTERN PACIFIC**
- 1 in 3 adults with diabetes lives in this region.
- 6 of the top 10 countries for diabetes prevalence are Pacific Islands.

*All estimates are presented as comparative rates.*
More than 371 million people have diabetes.

TOP 10 COUNTRIES/TERRITORIES FOR PEOPLE WITH DIABETES (20-79 YEARS)

- China: 92.3 million
- India: 63.0 million
- USA: 24.1 million
- Brazil: 13.4 million
- Russian Federation: 12.7 million
- Mexico: 10.6 million
- Indonesia: 7.6 million
- Egypt: 7.5 million
- Japan: 7.1 million
- Pakistan: 6.6 million
The number of people with diabetes is **increasing** in every country.

**TOP 10 COUNTRIES/TERRITORIES FOR PREVALENCE* (%) OF DIABETES (20-79 YEARS)**

<table>
<thead>
<tr>
<th>COUNTRY /TERRITORY</th>
<th>PREVALENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Federated States of Micronesia</td>
<td>37.2</td>
</tr>
<tr>
<td>2 Nauru</td>
<td>30.1</td>
</tr>
<tr>
<td>3 Marshall Islands</td>
<td>27.1</td>
</tr>
<tr>
<td>4 Kiribati</td>
<td>25.5</td>
</tr>
<tr>
<td>5 Tuvalu</td>
<td>24.8</td>
</tr>
<tr>
<td>6 Kuwait</td>
<td>23.9</td>
</tr>
<tr>
<td>7 Saudi Arabia</td>
<td>23.4</td>
</tr>
<tr>
<td>8 Qatar</td>
<td>23.3</td>
</tr>
<tr>
<td>9 Bahrain</td>
<td>22.4</td>
</tr>
<tr>
<td>10 Vanuatu</td>
<td>22.0</td>
</tr>
</tbody>
</table>

*comparative prevalence
Half of people with diabetes don’t know they have it.

UNDIAGNOSED PERCENTAGE AND UNDIAGNOSED CASES OF DIABETES (20-79 YEARS) BY REGION
Half of people who die from diabetes are under the age of 60.

DEATHS ATTRIBUTABLE TO DIABETES BY AGE (20-79 YEARS)
4.8 million people died and 471 billion USD were spent due to diabetes in 2012.

HEALTHCARE EXPENDITURES AND DEATHS PER 1,000 DUE TO DIABETES BY INCOME GROUP
Pathophysiology

- Impact of dysglycemia on complications
- Some known contributors to diabetes
- Genes and clinical factors in diabetes prediction
Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A1c concentration and myocardial infarction, stroke, microvascular end points, cataract extraction, lower extremity amputation or fatal peripheral vascular disease, and heart failure.
UKPDS Cross-sectional and 10-year cohort data for FPG, HbA1c, weight, and fasting plasma insulin in patients on chlorpropamide, glibenclamide, or insulin, or conventional treatment.
The Ominous Octet

Insulin
Insulin sensitizer

SGLT-2
inhibitor

Metformin
AMPK?
Glucagon signaling?

Insulin sensitizer

DeFronzo R.; Diabetes 2009
Pancreatic Tissue

Pancreatic Tissue


Beta cell preservation or restoration ???
Nongenetic and Genetic Risk Factors for Type 2 Diabetes in the Malmö Study

Receiver/Operator Curves for Genetic and Clinical Factors

A Genetic Factors

B Clinical Factors

Follow-up quintile 1

Follow-up quintile 5

Follow-up quintile 1

Follow-up quintile 5
Improvement of diabetes risk score with genetic markers for genes associated with T2DM

FDA Guidance for Industry:

- Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes – 2008

- Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention - 2008
Regulatory

- Preclinical Development
  - Target identification
  - Cell studies, target engagement, signaling
  - Animal studies (efficacy and safety)
  - Toxicology studies
  - FDA consultation

- Clinical Development
  - Phase I – FIM, PK, PoC
Clinical Development

- Phase II
- Phase III
  - ~2500 exposed subjects at filing
  - 1300-1500 with 12 month data
  - 300-500 with ≥18 month data
durability, comparator

- Phase IV - Pediatric development program
  - Safety monitoring
Clinical Development
- Phase I
  - FIM, PK, Proof of Concept (PD)…
- Phase II
  - Dose finding (focusing)
- Phase III
  - Efficacy and safety
  - CV safety
Summary

- Diabetes is a complex and chronically progressive disease with increasing world-wide prevalence
- There is a need for additional diabetes drugs
- Many potential targets exist to improve glycemic control and prevent diabetic complications
- Development of new drugs is challenging and expensive
Questions?