Part 1

Diabetes in the USA

• We now have roughly 26 million Americans with diabetes (nearly 2 million new cases diagnosed each year) and it has been estimated that 79 million Americans have prediabetes; if so, this affects about one-third of the USA.

• Gestational diabetes, prediabetes and undiagnosed diabetes contribute dramatically to health care costs in the USA.
Of these Americans, the rate of type 2 diabetes in Chinese Americans is notably higher than the rate in Caucasian Americans, and higher than the rate in the Chinese population living in rural China.
County-level Estimates of Diagnosed Diabetes for Adults aged ≥ 20 years:

2009

From the Centers for Disease Control and Prevention: National Diabetes Surveillance System.

Michigan: more than $9 billion in annual health cost for diabetes

*Map and Data provided by the Centers for Disease Control
Table 3. Average Years of Potential Life Lost Due to Diabetes – Michigan, 2008.

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Average Years of Potential Life Lost (YPLL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12.3</td>
</tr>
</tbody>
</table>
Characteristics of Adult Diabetes Patients Cared for at the University of Michigan

<table>
<thead>
<tr>
<th></th>
<th>Total June 2011</th>
<th>Total June 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c Test</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>A1c ≤ 9%</td>
<td>83%</td>
<td>82%</td>
</tr>
<tr>
<td>A1c &lt; 8%</td>
<td>68%</td>
<td>67%</td>
</tr>
<tr>
<td>A1c &lt; 7% Limited*</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>BP &lt; 140/90</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>LDLC Test</td>
<td>82%</td>
<td>79%</td>
</tr>
<tr>
<td>LDLC &lt; 100 mg/dL</td>
<td>57%</td>
<td>55%</td>
</tr>
<tr>
<td>On Statin</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Monitor for Nephropathy</td>
<td>89%</td>
<td>88%</td>
</tr>
<tr>
<td>Eye Exam</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Foot Exam</td>
<td>76%</td>
<td>73%</td>
</tr>
<tr>
<td>Self Management Goal</td>
<td>28%</td>
<td>21%</td>
</tr>
<tr>
<td>Influenza Vaccine*</td>
<td>63%</td>
<td>62%</td>
</tr>
<tr>
<td>Pneumococcal Vaccine*</td>
<td>68%</td>
<td>66%</td>
</tr>
<tr>
<td>Tobacco Use Documented</td>
<td>81%</td>
<td>89%</td>
</tr>
<tr>
<td>Current Tobacco User</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Origins of Diabetes Research at the University of Michigan

1977

- The U-M is awarded a five-year $4.3 million grant to create the Michigan Diabetes Research and Training Center; Michigan is one of the first five institutions to receive such funding.

Stefan S. Fajans
now it’s almost 2013, and currently...
Through discovery, to promote new modalities for prevention, therapy, and education for all forms of diabetes; providing a focal point for collaboration within the University of Michigan and with partnership in the broader diabetes community.

Michigan Comprehensive Diabetes Center:
- includes information on:
  - diabetes, nutrition etc.
  - clinics
  - research
  - clinical trials
  - conferences
  - events

www.med.umich.edu/diabetes
Through discovery, to promote new modalities for prevention, therapy, and education for all forms of diabetes; providing a focal point for collaboration within the University of Michigan and with partnership in the broader diabetes community.
Diabetes Research Center
Diabetes Research Center

Center for Diabetes Translational Research

Nutrition and Obesity Research Center

Integrated Systems Biology Approach to Diabetic Microvascular Complications

Type 1 Diabetes Impact Award (DP3) Metabolic Reprogramming in Diabetic Complications
Research Strengths and Growth Areas at the Michigan Diabetes Center

Integrative Aspects of Diabetes/Metabolism
Diabetes Complications
Pancreatic Islet and Beta Cell Biology
Cellular/Molecular aspects of Diabetes/Metabolism
Clinical Research in Diabetes/Metabolism
Integrative Aspects of Diabetes/Metabolism
Diabetes Complications
Pancreatic Islet and Beta Cell Biology
Cellular/Molecular aspects of Diabetes/Metabolism
Clinical Research in Diabetes/Metabolism
Part 2
Part 2

Proinsulin Misfolding and Diabetes

Peter Arvan, M.D., Ph.D.
Metabolism, Endocrinology & Diabetes
U-M Comprehensive Diabetes Center
# Primary structure of Preproinsulin

## Signal Peptide (SP)
```
MALWMRLLPLLALLALLALWGPDPAPAA
```

## B-Chain
```
FVNYHLCCGSHLVGEALYLVCCGERGFYTTYPKTK
```

### Flanking Cleavage Site
```
RR
-2 -1
```

## C-Peptide
```
EAEDLEVEGQVELGGGPAGCSSLQPLALEGSLS
```

### Flanking Cleavage Site
```
KR
+1 +2
```

## A-Chain
```
GIVEQCCTSCISCCLYQLENYC
```

## endogenous Cys
EARLY stages of insulin synthesis:

Step #1: Translocation & Signal Cleavage

Step #2: Proinsulin Monomer Folding

Step #3: Dimerization

Step #4: Proinsulin exit from the Endoplasmic Reticulum
MIDY: Mutant INS gene-induced Diabetes of Youth

(autosomal dominant inheritance; related to MODY)
## Dominant Mutants of Preproinsulin

**MIDY sites in yellow-green; endogenous Cys**

### Signal Peptide (SP)

|   | M | A | L | W | M | R | L | L | P | L | L | A | L | A | L | W | G | P | D | P | A | A | A |   |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10| 11| 12| 13| 14| 15| 16| 17| 18| 19| 20| 21| 22| 23| 24|

### B-Chain

|   | F | V | N | Q | H | L | C | G | S | H | L | V | E | A | L | Y | L | V | C | G | E | R | G | F | F | F | Y | T | P | K | T |   |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10| 11| 12| 13| 14| 15| 16| 17| 18| 19| 20| 21| 22| 23| 24| 25| 26| 27| 28| 29| 30|

- Flanking Cleavage Site
  - -2 -1

### C-Peptide

|   | E | A | E | D | L | E | V | G | Q | V | E | L | G | G | G | G | P | G | A | C | S | L | Q | P | L | A | L | E | G | S | L | Q |   |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10| 11| 12| 13| 14| 15| 16| 17| 18| 19| 20| 21| 22| 23| 24| 25| 26| 27| 28| 29| 30| 31|

- Flanking Cleavage Site
  - +1 +2

### A-Chain

|   | G | I | V | E | Q | C | C | T | S | I | C | S | L | Y | Q | L | E | N | Y | C | N |   |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10| 11| 12| 13| 14| 15| 16| 17| 18| 19| 20| 21|
A

- hProCpepsfGFP
- ER-RFP
- merge

B

- hPro-G(B8)S-CpepsfGFP
- ER-RFP
- merge

Leena Haataja
GFP Expression in Cryosections of Different Organs From *Ins1*-hProCpepGFP Transgenic Mice

Hodish et al., JBC 2010 285: 685-694
MIDY mutants induce ER stress

Distorted Nucleus
Dilated ER
Micro-Granules
**MIDY** mutants activate ER stress response
Proposed molecular mechanisms of β-cell failure caused by misfolded proinsulin