CrownBio
CONNECTING SCIENCE TO PATIENTS

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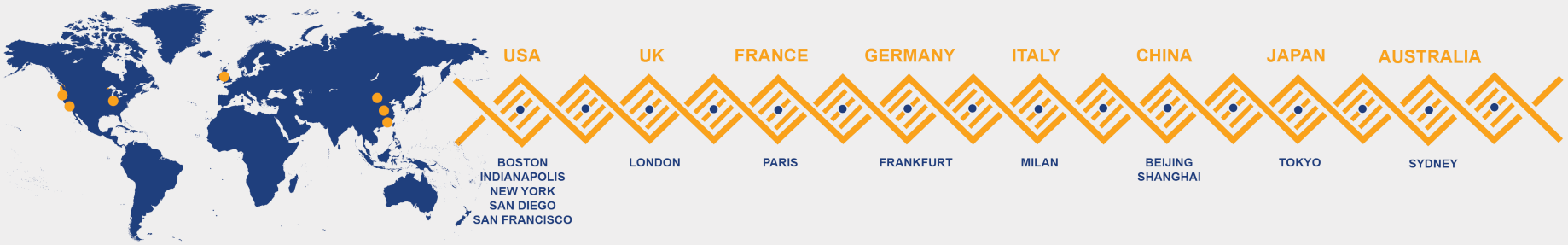
Translational Models for Cardiovascular & Metabolic Disease

CrownBio



Crown Bioscience

- A global platform technology company with expertise in **Oncology** and **Cardiovascular & Metabolic Disorders**
- Founded in 2006, headquartered in Santa Clara, California, with research centers in **China, USA,** and **UK**
- A team of **460 experts worldwide**, including highly trained PhD and MS scientists, many with overseas experience
- A **reliable partner** to provide services to the global pharmaceutical companies and many biotech companies

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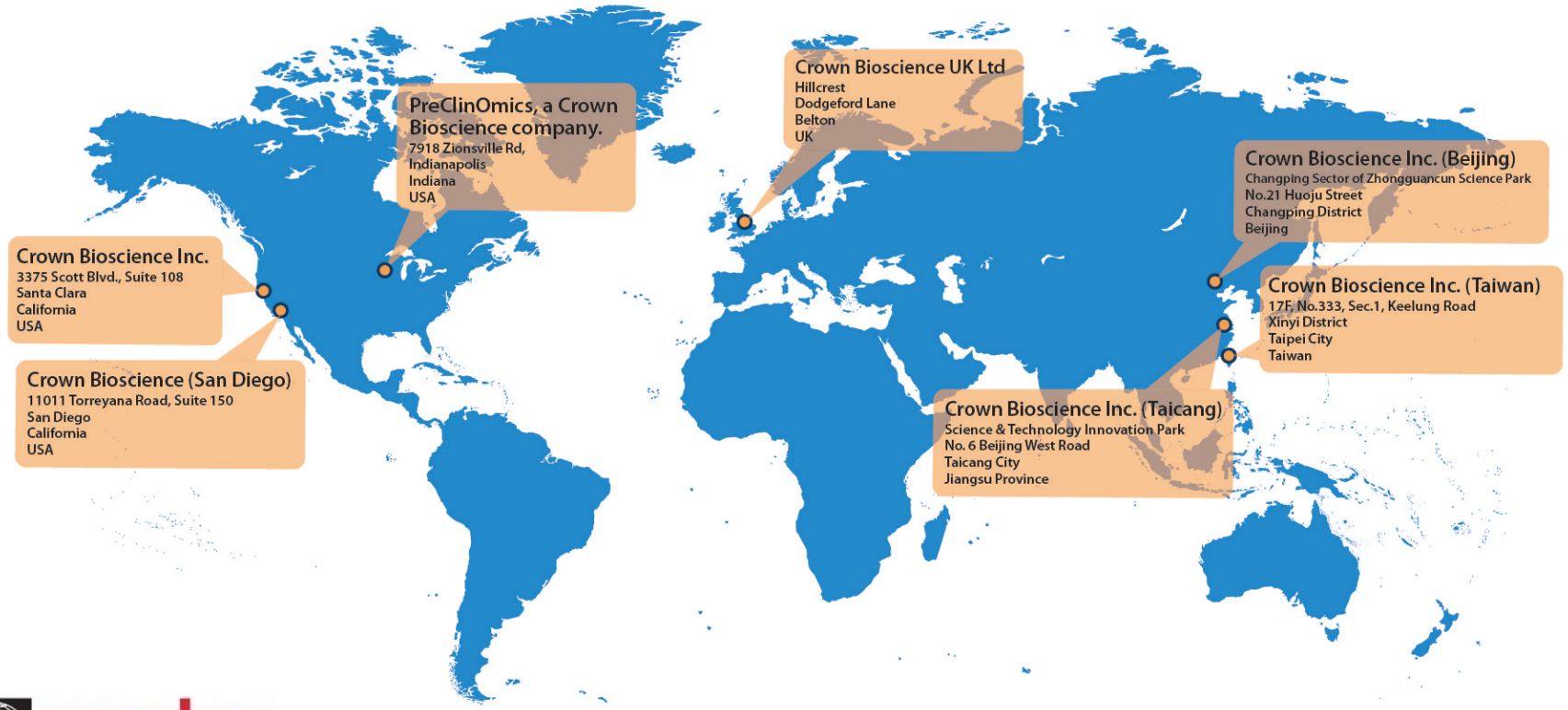
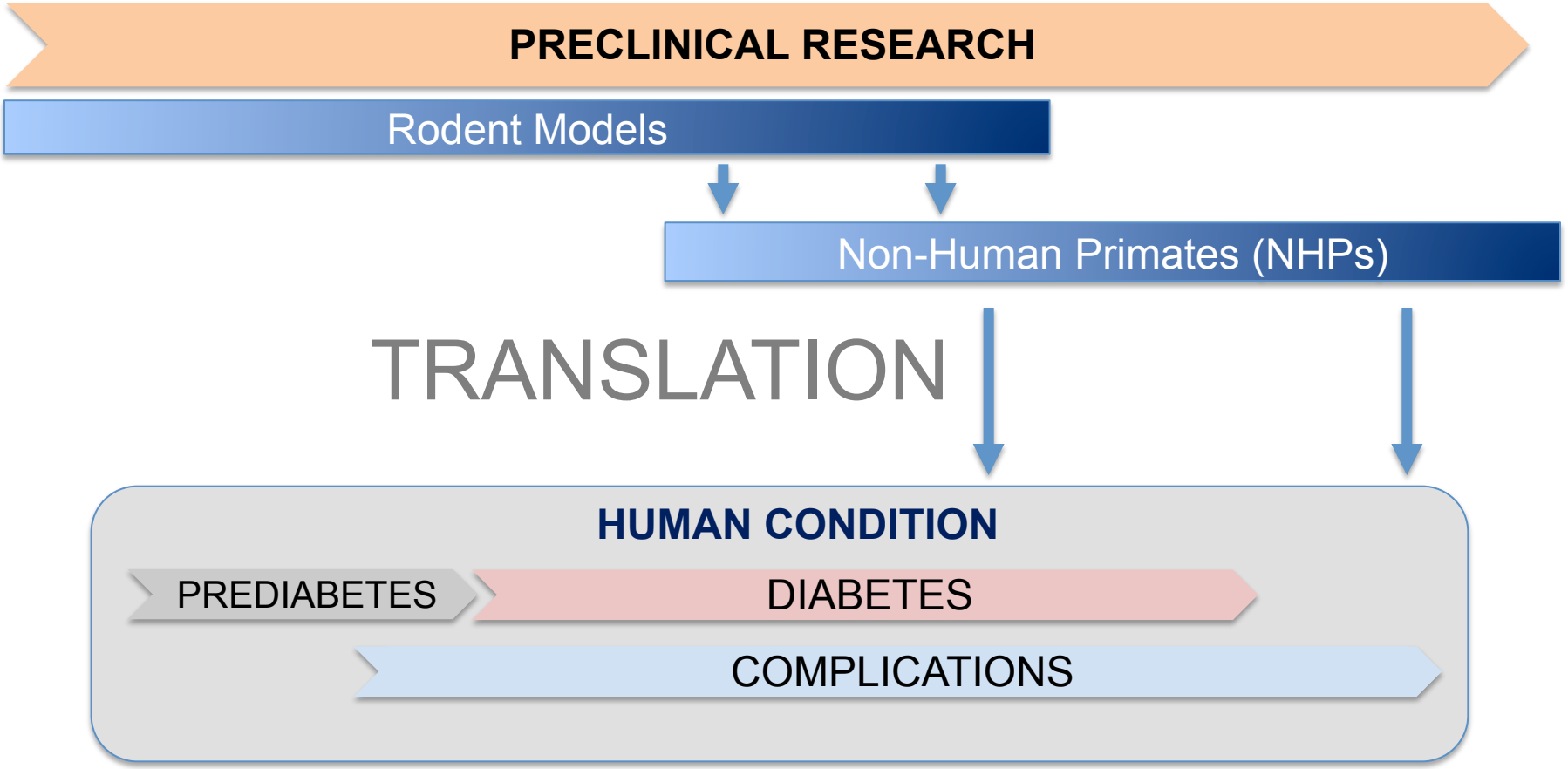
CrownBio Your Global Partner



aadlac INTERNATIONAL

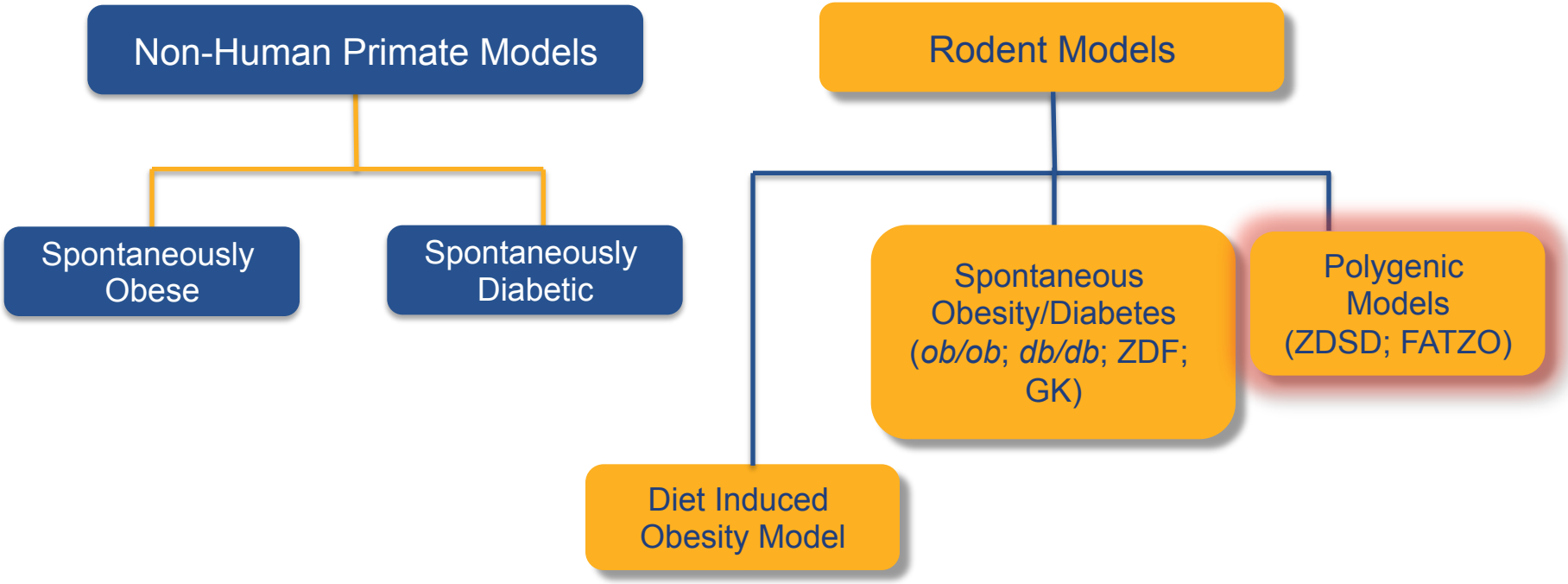
End to End Support with a Continuum of *In Vivo* Solutions



In Vivo Capabilities

- Pharmacology: efficacy, PK/PD, non-GLP tox
- Lean & fat mass (DEXA), BMI, food & liquid consumption
- Biomarker analysis
  - Glucose, HbA1c, insulin, c-peptide, lipid profile, etc.
- Tolerance tests
  - Glucose (GTT): glucose disposal rate
  - Insulin (ITT): insulin sensitivity or resistance
  - Pyruvate (PTT): hepatic glucose genesis
  - Meal (MTT): incretin response
- Graded glucose infusion (GGI): islet function
- Glucose and insulin clamps: glucose disposition and insulin sensitivity
- Organ functions: renal, cardiac, liver, etc.

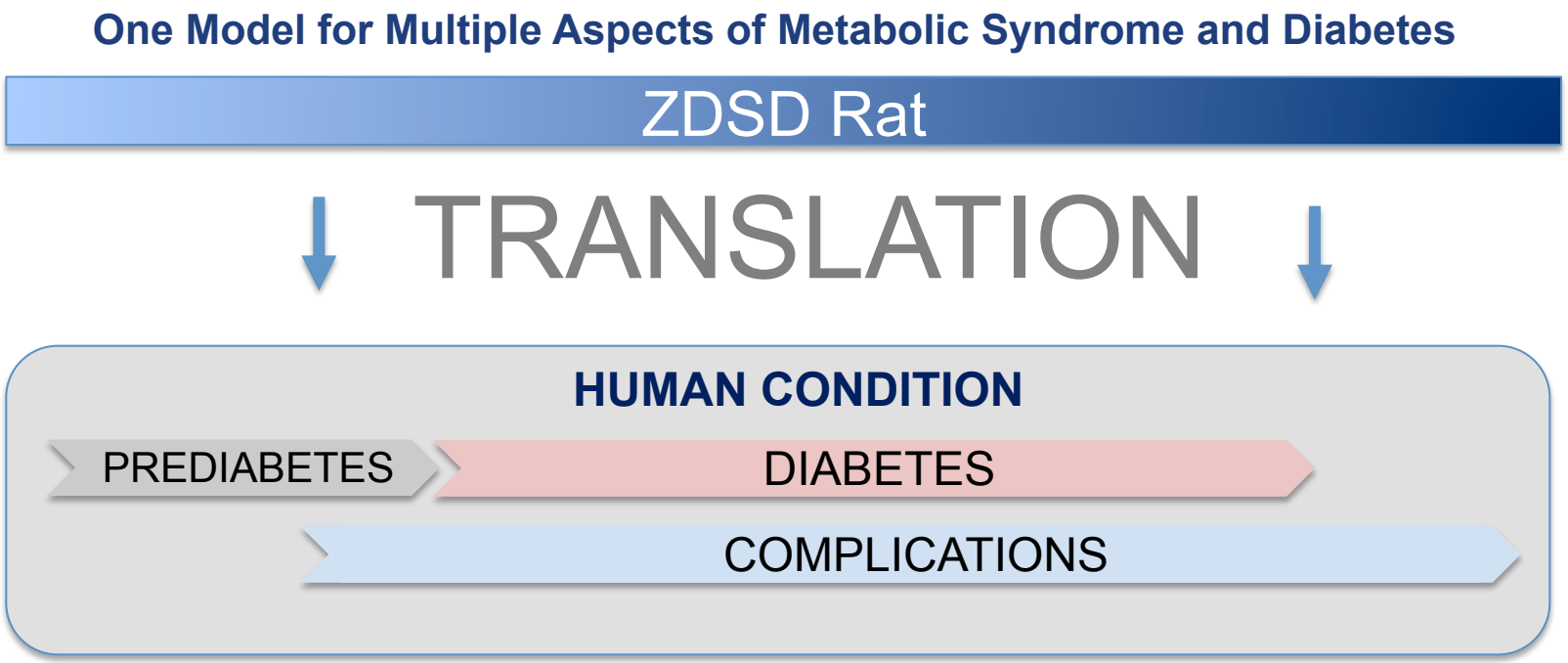
Animal Models for Cardiovascular and Metabolic Disease



- Develop various aspects of metabolic syndrome and Type 2 diabetes
- Develop diabetic complications

The ZDSD Rat

- A translational platform for modeling human disease progression & outcomes



Why is the ZDSD Rat a More Translatable Choice?

	HUMAN	ZDSD RAT	ZDF RAT
Prediabetic State	Yes	Yes	No
Intact Leptin Pathway	Yes	Yes	No
Beta Cell Failure	Late	Late	Early
Comorbidities	Many	Many	Some
Hypertension	Yes	Yes	No

The ZDSD rat most closely mimics the human condition

Development of the ZDSD Rat

- A model of diabetes and obesity with an intact leptin pathway
- Generated by crossing the lean ZDF/Crl rats to an obesity-prone Sprague-Dawley (CD) rat (polygenic obesity)

ZDF rat (Lean +/+)

Crl:CD(SD) rat

Selective breeding for obesity and diabetes

In-breeding (35+ generations)

ZDSD

Translatable Disease Progression in ZDSD Rat

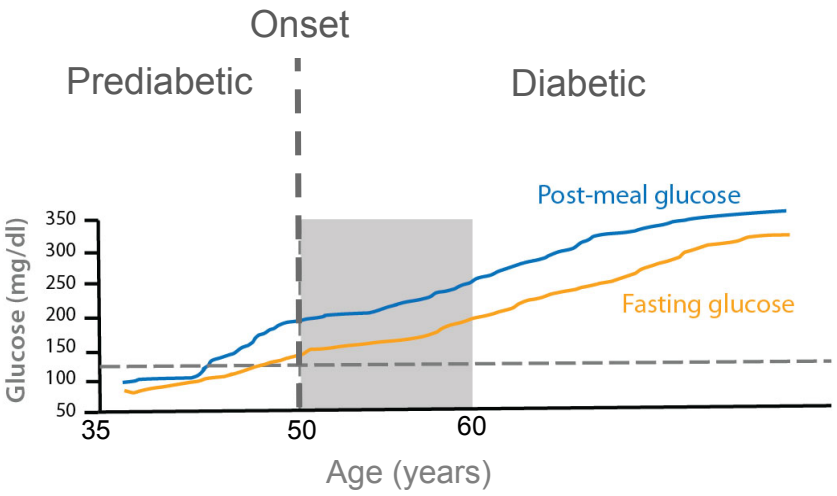
Prediabetes (8-16 weeks)	Overt Diabetes (>16 weeks)	Complications (24- weeks)
Metabolic syndrome	Hyperglycemia	Nephropathy
Insulin resistance	Polyuria, polydipsia	Neuropathy
Glucose intolerance	Glucose intolerance	Cardiovascular
Hyperlipidemia	Insulin resistance	Fatty liver
Inflammation	Beta cell failure	Osteoporosis
		Delayed wound healing

- The ZDSD rat displays similar disease progression as human patients
- Allows the evaluation of pharmacological intervention at different disease stages

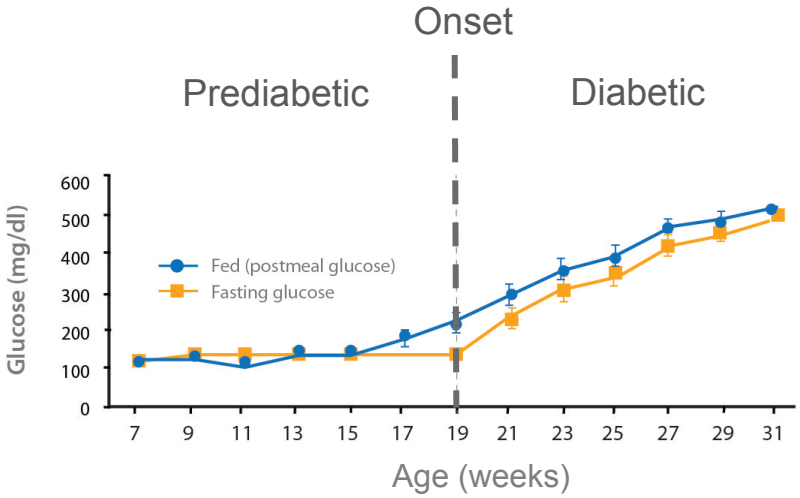
Translatable Disease Progression in ZDSD Rat

The ZDSD rat has a prediabetic state similar to human patients

Human



ZDSD Rat

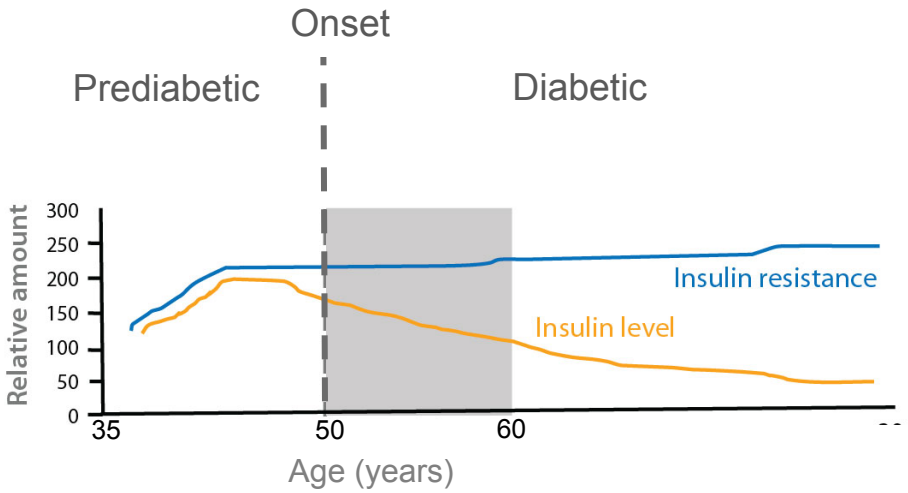


Adapted from: Peterson R. *et al*., 2015 *J Diabetes Res.* 2015 10 pages. Article ID 487816. Collaborative study with Janssen R&D

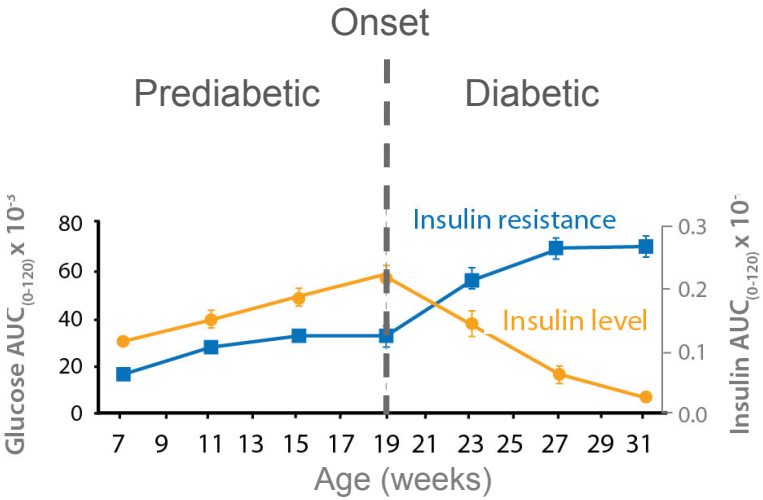
Translatable Disease Progression in ZDSD Rat

The ZDSD rat displays insulin resistance and decreased insulin production similar to human patients

Human



ZDSD Rat

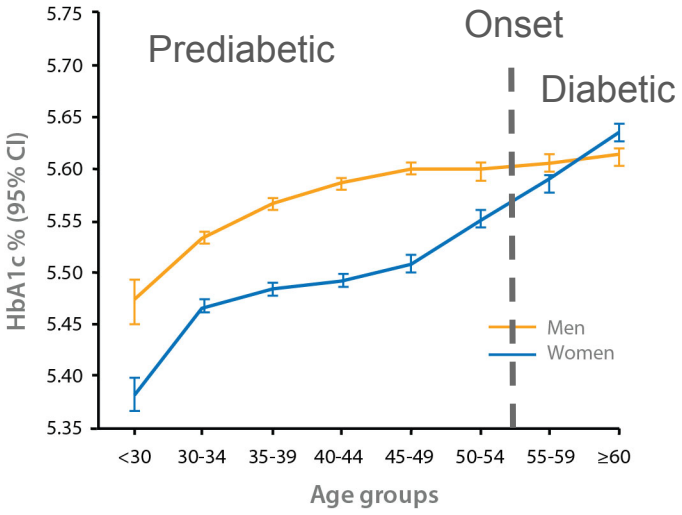


Adapted from: Peterson R. *et al*., 2015 *J Diabetes Res.* 2015 10 pages. Article ID 487816. Collaborative study with Janssen R&D

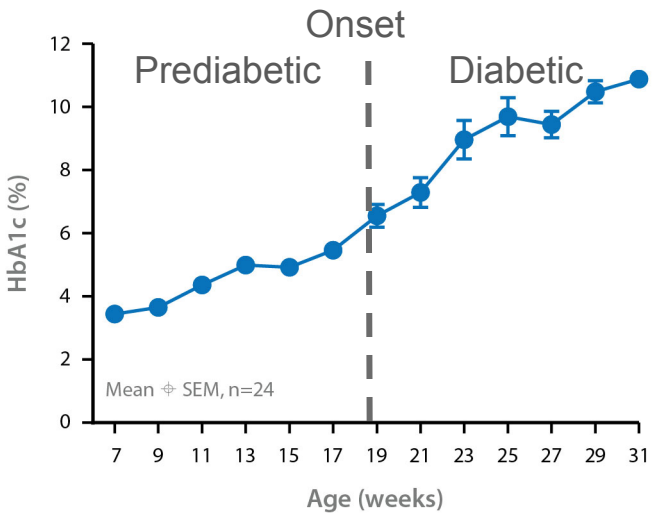
Translatable Biomarker in ZDSD Rat: Elevated HbA1c

The ZDSD rat shows a prediabetic increase in HbA1c levels similar to humans

Human



ZDSD Rat



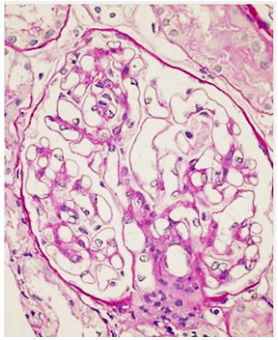
Adapted from: Bae J.C. *et al.*, 2014. *J. Diabetes Investig.* 5(1):60-65

Translatable Diabetic Comorbidities in ZDSD Rat

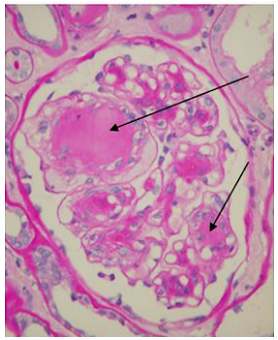
The ZDSD rat develops diabetic nephropathy similar to obese, insulin resistant patients

Human

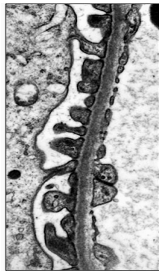
Normal glomerulus



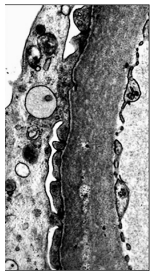
Diabetic glomerulus



Normal

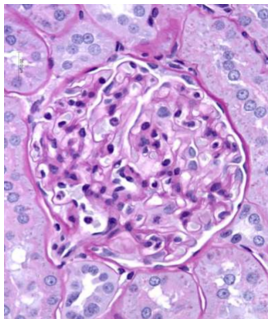


Diabetic

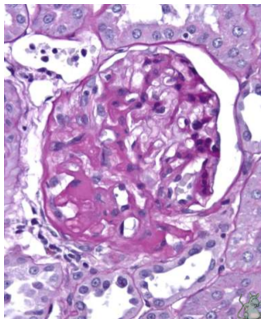


ZDSD Rat

Normal glomerulus



Diabetic glomerulus



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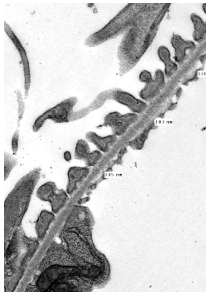
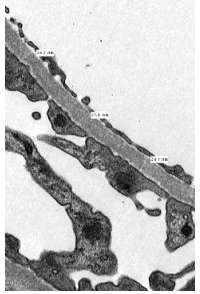


Diabetic



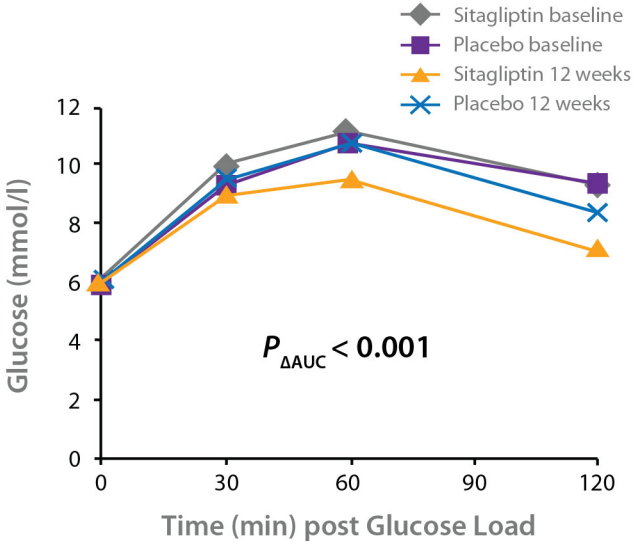
Thickening of basement membrane

Adapted from: Hale L.J. and Coward J.M., 2013. *Clinical Science* 124(6):351-370

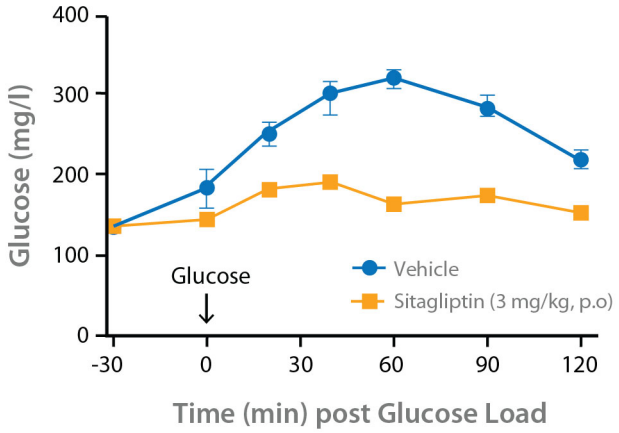
Translatable Therapeutic Efficacy in ZDSD Rat

The ZDSD rat responds to standard of care sitagliptin similarly to human patients in oral glucose tolerance tests

Human



ZDSD Rat



Adapted from: Hage C. *et al.*, 2013. *J Intern Med.* 273(4):410-421

Summary of ZDSD Rat Features

- Highly translatable model compared to conventionally used rodents
- Spontaneously develops metabolic syndrome
- Distinct prediabetic state with elevated biomarkers
- Type 2 diabetes progression similar to the human disease
- The ZDSD rat becomes obese on a normal diet and in the presence of functional leptin signaling
- The model responds to antidiabetic compounds similarly to human patients

The ZDSD Rat

- One translational model for multiple aspects of diabetes

Validation of one model can support multiple arms of an antidiabetic drug development program

ZDSD Rat

TRANSLATION

HUMAN CONDITION

PREDIABETES

DIABETES

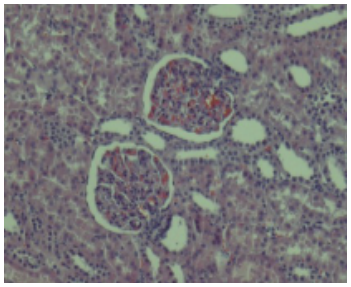
COMPLICATIONS

Non-Human Primate Models of Diabetes

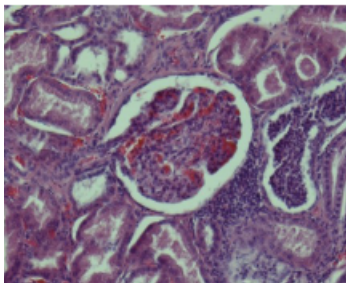
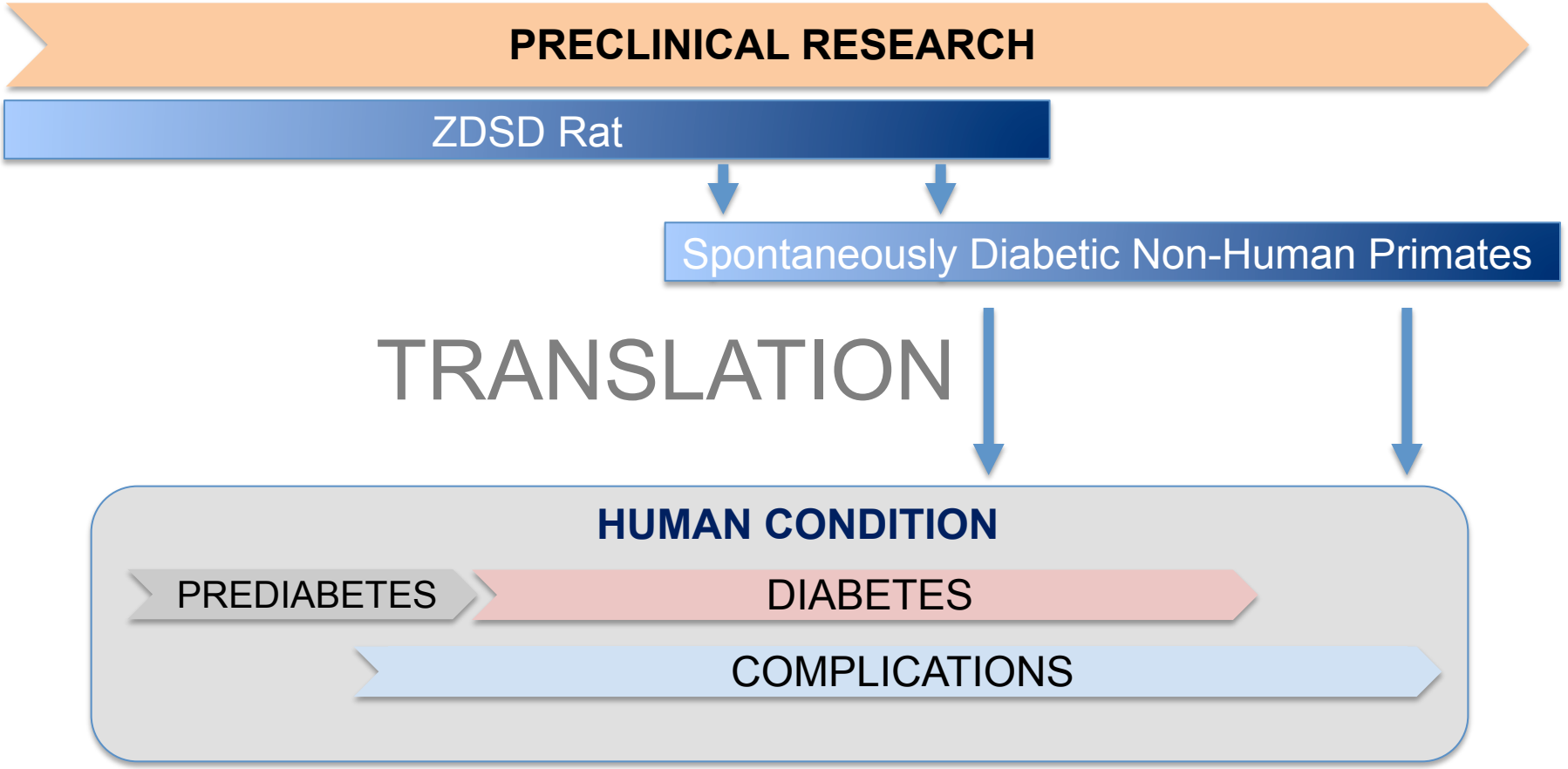
Non-human primate models of spontaneous diabetes show prediabetic and diabetic states and associated comorbidities

	Normal	Prediabetic	Diabetic
Subjects (n)	11	19	20
Age (years)	5.7 ± 0.2	15.1 ± 0.6*	17.3 ± 0.7*#
Body Weight (kg)	5.5 ± 0.5	8.6 ± 0.6*	7.5 ± 0.7
Fasting Blood Glucose (mg/dl)	87 ± 4.7	91 ± 2.8	185 ± 13.7*#
HbA1c (%)	4.6 ± 0.1	5.1 ± 0.4	9.3 ± 0.9*#
Glucose Clearance Rate (g/l/min)	2.9 ± 0.26	1.8 ± 0.13*	1.2 ± 0.15*#

Normal



Diabetic Nephropathy



End to End Continuum of *In Vivo* Solutions