

# Valley of Death Translational Research & Development



Basic  
Research

Preclinical  
Development

Clinical  
Development

Regulatory Review  
Approval

Commercial  
Launch

# Layers of Complexity & Change



## Challenges in the Valley

Translate &  
Accelerate

- Diabetes
- Discovery
- Regulatory
- Development
- Business
- Economics
- Time to Market
- Education
- Implementation
- Integration

**Epidemic Reach**– Diabetes is now considered a global epidemic affecting close to 285M people (7% of the world’s population), including over 50M in India, 43M in China, 27M in the US, and over 16M in the Middle East. The incidence of Type 2 diabetes is exploding everywhere

**High Cost** – Overall cost to global healthcare systems is in excess of \$375B, 12% of global healthcare expenditures

# Partnering Strategies Translation & Acceleration


The logo for Kinexum, featuring the word "Kinexum" in a black serif font with a red swoosh underline that starts under the 'K' and ends under the 'm'.

## Strategic Services

Regulatory & Clinical Development

Established Collaboration Agreement in  
Saudi Arabia

Leverage access to assets, new  
opportunities, and business support for  
acceleration & development translation

A light blue rounded rectangular box with a dark blue border and a drop shadow. It contains the text "Diabetes, Obesity, Metabolic Disease" in bold black font. Two dark blue arrows point from the box towards the Kinexum and Exsulin sections, one pointing up and left, the other pointing down and right.

**Diabetes, Obesity,  
Metabolic  
Disease**

The logo for Exsulin, featuring a dark blue circle on the left containing the letter 'e' in white, followed by the word "xsulin" in a dark blue sans-serif font.

Exsulin Canada  
Exsulin Saudi Arabia

Leverage Expertise, Relationships,  
Opportunities, and Global Initiatives

Viable pipeline, low overhead

FDA-last option

Novel combinations & integration

# Preeminent Therapeutic Target

## Growing Evidence in Four Categories

- **Exsulin™ (INGAP Peptide) demonstrates improvement of glycemic control in multiple animal models**
- **INGAP Peptide in combination with immune modulators demonstrates full remission of T1 diabetes returning normal glycemic control in T1 animal models & shows regeneration of islets**
- **INGAP Peptide demonstrates islet regeneration in a human tissue model and a return of normal islet function including insulin, glucagon, & somatostatin**
- **INGAP Peptide demonstrates activity in human trials of both T1 and T2 diabetes**

# Exsulin Development Strategy

## A Clear Path for Development Can Be Established Based On Available Proprietary Clinical and Preclinical Data

- Focus First on established Type 1 Diabetes because of high unmet need, clear endpoint target, and less challenging regulatory path
- Improve regimen and formulation to increase efficacy and tolerability of INGAP as stand-alone treatment
- Explore efficacy and tolerability of combination treatment with immune modulators in clinical studies
- Establish a world class collaborative research effort in order to enhance the knowledge about INGAP's mode of action as a standalone and combination drug, and to characterize INGAP analogues with a different biological profile
- Dosing optimization of combination regimen with new "human islet" mouse model (Atkinson) to accelerate Phase 2 clinical trials in Canada , KSA, US to follow.
- Preclinical research using in comparable models to evaluate new Exsulin successor compound as monotherapy and combination with immune modulators  
Accelerate next research steps to prepare for future Phase 2 trials

# The List of Discovery – NOD mice

Dr. Mark Atkinson, University of Florida

AAV murine IL-10  
AAV rat proinsulin gene (vLP-1)  
Adenovirus expressing mL-4  
Aerosolinsulin  
Allogenic thymic macrophages  
Alpha Galactosylceramide  
Alpha-interferon (rIFN-alpha)  
Alpha/beta T cell receptor thymocytes  
Aminoguanidine  
Androgens  
Anesthesia  
Antioxidant MDL 29.311  
Antisense GAD mRNA  
Azathioprine  
Anti-B7-1  
Bacille Calmette Gue'rin (BCG)  
Baclofen  
Bee venom  
Biolistic-mediated IL-4  
Blocking peptide of MHC class II  
Bone marrow transplantation  
Castration  
Anti-CD3  
Anti-CD4  
CD4+CD25+regulatory T cells  
Anti-CD8  
Anti-CD28 MAb  
Cholera toxin B subunit-insulin protein  
Class I derived self-A beta(g7) (54-76) peptide  
Cold exposure  
Anti-complement receptor  
Complete Freund's adjuvant  
Anti-CTLA-4  
Cyclic nucleotide phosphodiesterases (PDEs)  
Cyclosporin  
Cyclosporin A  
DC deficient in NF-kappaB  
DC from pancreatic lymph node  
DC with IL-4  
Deflazacort  
Dexspergualin  
Dexamethasone/progesterone/growth hormone/estradiol  
Diazoxide  
1,25 dihydroxy Vitamin D3, KH1060  
1,25 dihydroxycholecalciferol  
1,25 dihydroxyl Vitamin D3  
Elevated temperature  
Emotionality  
Encephalomyocarditis virus (ECMV)  
Essential fatty acid deficient diets  
FK506  
FTY720 (myriocin)  
GAD 65 peptides in utero  
Anti-GAD monoclonal antibody  
Galactosylceramide  
Glucose (neonatal)  
Glutamic acid decarboxylase  
(intraperitoneal, intrathymic, intravenous, oral)  
Glutamic acid decarboxylase 65 Th2 cell clone  
Glutamic acid decarboxylase peptides  
(intraperitoneal, intrathymic, intravenous, oral)

Gonadectomy  
Guanidinoethylidissulphide  
Heat shock protein 65  
Heat shock protein peptide (p277)  
Hematopoietic stem cells encoding proinsulin  
Housing alone  
Human IGF-1  
I-A beta g7(54-76) peptide  
Anti-I-A monoclonal antibodies  
Anti-ICAM-1  
IgG2a antibodies  
Immobilization  
Inomide  
Anti-integrin alpha 4  
Insulin (intraperitoneal, oral, subcutaneous, nasal)  
Insulin B chain (plasmid)  
Insulin B chain/B chain amino acids 9-23 (intraperitoneal, oral, subcutaneous, nasal)  
Insulin-like growth factor I (IGF-I)  
Anti-intercellular adhesion molecule-1 (ICAM-1)  
Interferon-alpha (oral)  
Interferon-gamma  
Anti-interferon-gamma  
Interferon-gamma receptor/IgG1 fusion protein  
Interleukin-1  
Interleukin-4  
Interleukin-4-Ig fusion protein  
Interleukin-4-plasmid  
Interleukin-10  
Interleukin-10-plasmid DNA  
Interleukin-10-viral  
Interleukin 11-human  
Interleukin-12  
Intrathymic administration of mycobacterial heat shock protein 65  
Intrathymic administration of mycobacterial heat shock peptide p277  
Islet cells-intrathymic  
L-Selectin (MEL-14)  
Lactate dehydrogenase virus (LDH)  
Large multilamellar liposome  
Lazaroid  
Anti-leukocyte function associated antigen (LFA-1)  
Anti-LFA-1  
Linomide (quinoline-3-carboxamide)  
Lipoplysaccharide-activated B cells  
Lisofylline  
Lymphocyte choriomeningitis virus (LCMV)  
Anti-lymphocyte serum  
Lymphocyte vaccination  
Lymphocytic choriomeningitis virus  
Anti-L-selectin  
Lymphotoxin  
LZ8  
MC1288 (20-epi-1,25-dihydroxyvitamin D3)  
MDL 29311  
Metabolically inactive insulin analog  
Anti-MHC class I  
Anti-MHC class II  
MHC class II derived cyclic peptide  
Mixed allogeneic chimerism  
Mixed bone marrow chimeras  
Monosodium glutamate  
Murine hepatitis virus (MHV)

Mycobacterium avium  
Mycobacterium leprae  
Natural antibodies  
Natural polyreactive autoantibodies  
Neuropeptide calcitonin gene-related peptide  
Nicotinamide  
Nicotine  
Ninjin-to (Ren-Shen-Tang), a Kampo (Japanese traditional) formulation  
NKT cells  
NY4.2 cells  
OK432  
Overcrowding  
Pancreatectomy  
Pentoxifylline  
Pertussigen  
Poly [I-C]  
Pregestil diet  
Prenatal stress  
Preproinsulin DNA  
Probucol  
Prolactin  
Rampamycin  
Recombinant vaccinia virus expressing GAD  
Reg protein  
Reg protein  
Reg protein  
Rolipram  
Saline (repeated injection)  
Schistosoma mansoni  
Semi-purified diet (e.g., AIN-76)  
Short term chronic stress  
Silica  
Sirolimus/tacrolimus  
Sodium fusidate  
Soluble interferon-gamma receptor  
Somatostatin  
Non-specific pathogen free conditions  
Streptococcal enterotoxins  
Streptozotocin  
Sulfatide (3'sulfogalactosylceramide)  
Superantigens  
Superoxide dismutase-desferrioxamine  
Anti-T cell receptor  
TGF-beta 1 somatic gene therapy  
Th1 clone specific for hsp60 peptide  
Anti-thy-1  
Thymectomy (neonatal)  
Tolbutamide  
Tolerogenic dendritic cells induced by vitamin D receptor ligands  
Top of the rack  
Treatment combined with a 10% w/v sucrose-supplemented drinking water  
Tumor necrosis factor-alpha  
TX527 (19-nor-14,20-bisepi-23-yne-1,25(OH)(2)D(3))  
Vitamin E  
Anti-VLA-4

Thymoglobulin  
Anti-CD3  
ALS + Exendin-4  
LSF + Exendin-4  
EGF + Gastrin  
Regulatory T Cells  
Islet Transplantation  
Microspheres  
FTY720  
siCAM-Ig (Adenovirus Vector)

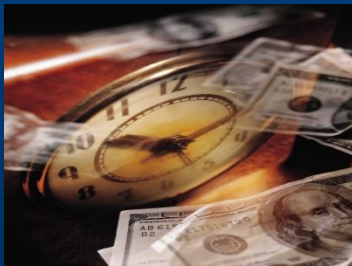
**N=193 as of 2004**

**Early 2011 est. - ~400**

**Conventional Wisdom  
Overturned**

**How many discoveries can navigate the valley of death in the  
old paradigm ?**

# Balancing Act & Risk



- Time from Discovery to Commercialization 10-20 years
- Average Exit for VCs = 5 years
- Average Exit for Angel Investors = 14 years

# Challenges in the Valley

- Time, cost, and risk of translating discoveries to commercial development have undergone significant change in the past 5 years.
- Big pharma is outsourcing discovery and early stage development in an effort to mitigate risk.
- New sources of partnerships and funding are necessary.
- Shift of risk promises great returns to innovators able to cost effectively achieve milestones.
- Reducing timelines and costs to achieve milestones requires know-how.



# **Translational Strategy & Acceleration to POC Is Within Reach**

- **Driven by translating science into a product strategy, which reflects clinical context, regulatory pathway, and competing approaches**
- **Focus on the Shortest Path to Proof of Concept Study – Regulatory, Preclinical, CMC, clinical**
- **Base on understanding value inflection and risks during the drug development process**
- **Maximize the reach of resource-constrained innovator companies**
- **Business structure that allocates resources for milestones & value creation**

# Kinexum Catalyzes Development Regulatory & Clinical Support for Innovation

Small companies can successfully  
innovate and create value by—

- Sourcing and directing funds for execution and achievement of milestones
- Starting with a solid plan and rapidly building it out  
– business-regulatory-clinical development
- Utilizing necessary and sufficient animal models
- Striking the right balance in advancing the manufacturing process
- Targeting proof of concept clinical studies
- Executing efficiently on the critical path

# **New Opportunities to Maximize Impact Diabetes, Obesity, & Metabolic Disease**

**Integrating Regulatory, Clinical  
Development, and Business**

**Drug, Device, Nutrition, Lifestyle  
Integration & Combinations**

**New Strategic Collaborations**

# Integrate Complementary Assets & Approaches To Restore Health

Common Patient Database

## Diabetes

Current approach to diabetes

Immune & Inflammatory Modifiers

Medicinal Food/Diet

Exsulin Regeneration Platform

Diagnostics & Monitoring

Exercise/Stress Transformation

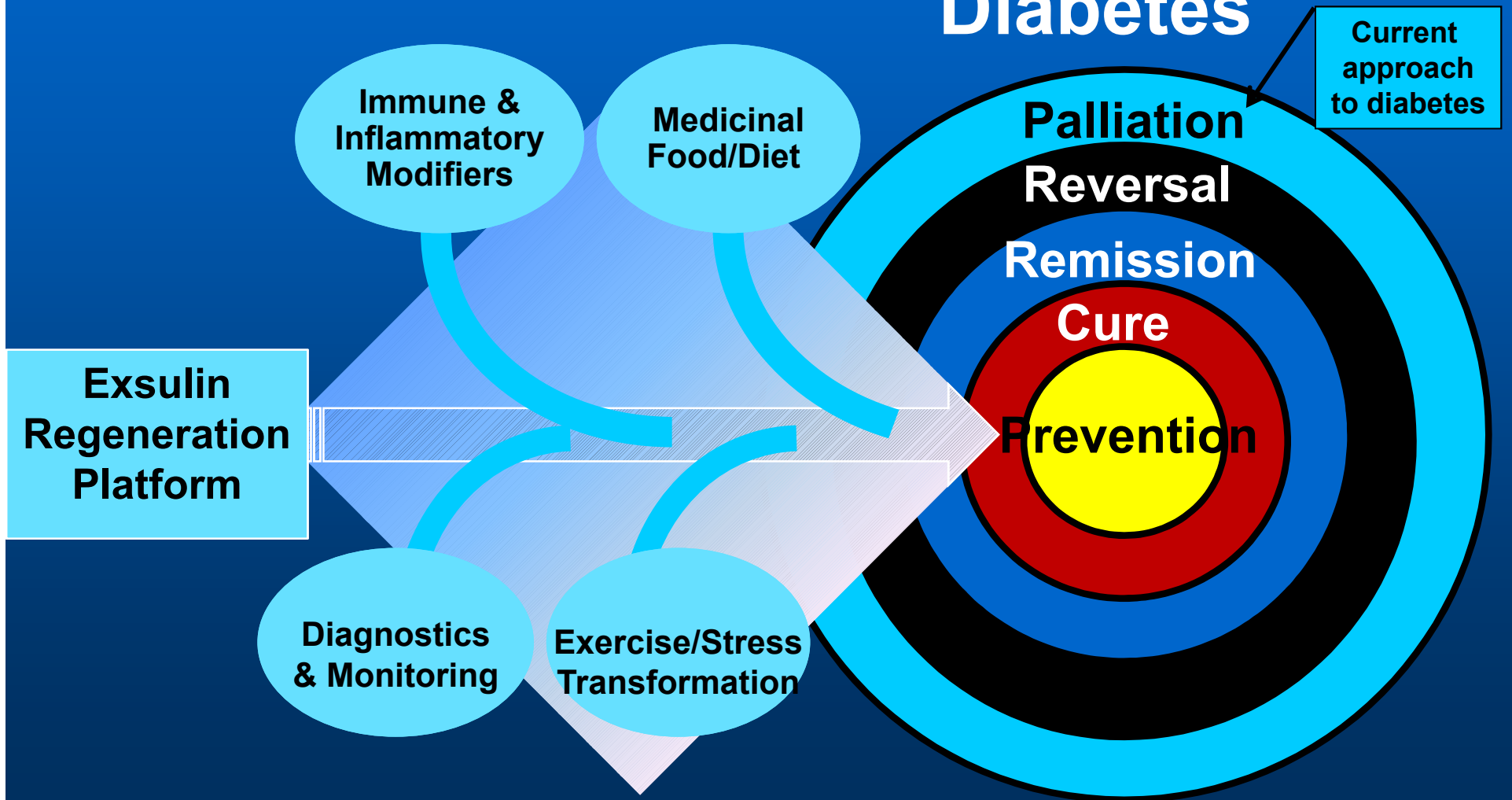
Palliation

Reversal

Remission

Cure

Prevention



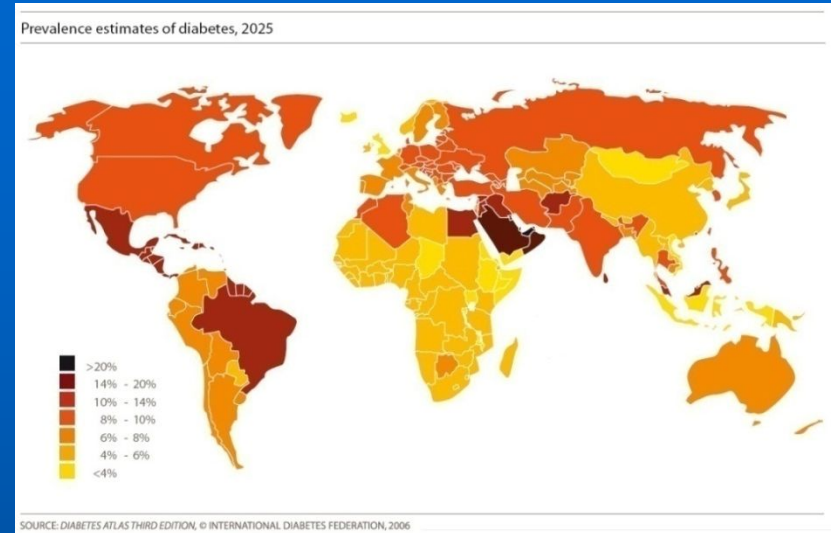
# Leverage for Growth

- **Expand services to strategic business and partnering advisory services**
- **Fully leverage Kinexum relationships, leadership, and reputation in diabetes, obesity, metabolism**
- **Partnering advisory services for companies focused on solutions for metabolic disease**
- **Leverage virtual pipeline of assets**
- **Lead and attract investment**
- **Expand enterprise value**
- **Integrate translational strategy for commercialization**
- **Drug, Device, Nutritional Supplements, Lifestyle Integration & Combinations**

# Experience

## Funding Progress & Milestones

- Build relationships and good will around important initiatives
- Leverage relationships to support science, business operations, PR, investments
- Seek out environments where your product is especially important



## Business

- Angel
- Grants
- Tax Credits
- Venture Capital
- Partnering

## Collaboration

- Resources
- Philanthropy
- Saudi Arabia
- Economic Development
- Wide Net of Industry Stakeholders