Société Médicale des Hôpitaux de Paris
Le diabète quels enjeux ?
14 janvier 2011

DIABETE DE TYPE 2

NOUVELLES PISTES THÉRAPEUTIQUES

Alain Ktorza
Institut de Recherches Servier (IdRS)

THE AIMS OF TREATMENT OF TYPE 2 DIABETES

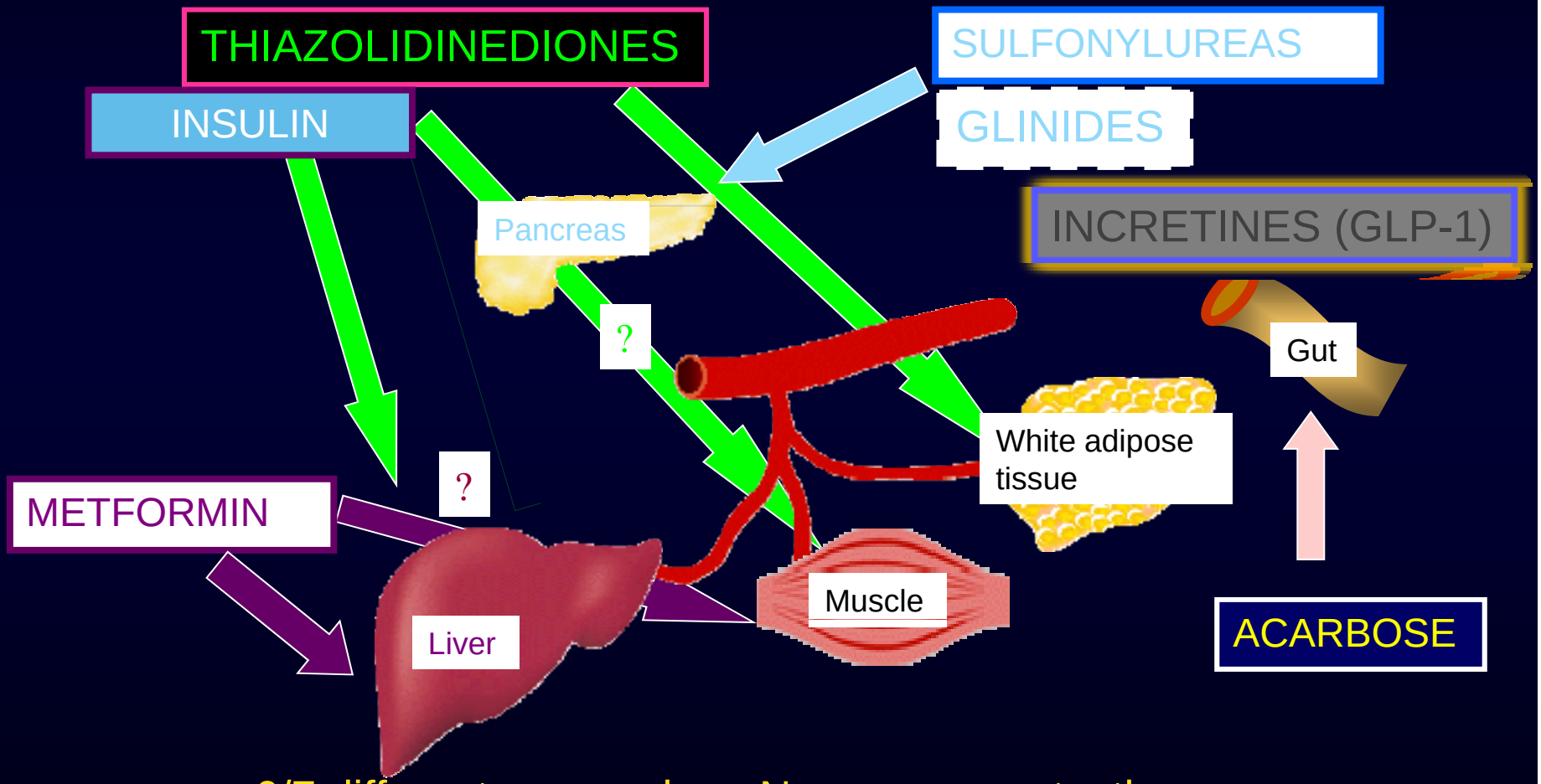
To prevent early death and improve quality of life

To prevent micro- and macro vascular complications

Optimal glycemic control

- Lipid profile
- Cardiovascular function
- Atherogenesis

CURRENT ORAL AGENTS USED IN THE TREATMENT OF TYPE 2 DIABETES



6/7 different approaches. No one prevents the progressive deterioration of glycemic control

FUNCTIONAL β CELL MASS AND TYPE 2 DIABETES

Decrease in β cell mass in type 2 diabetic patients

40-60% Reduction compared to non diabetic patients

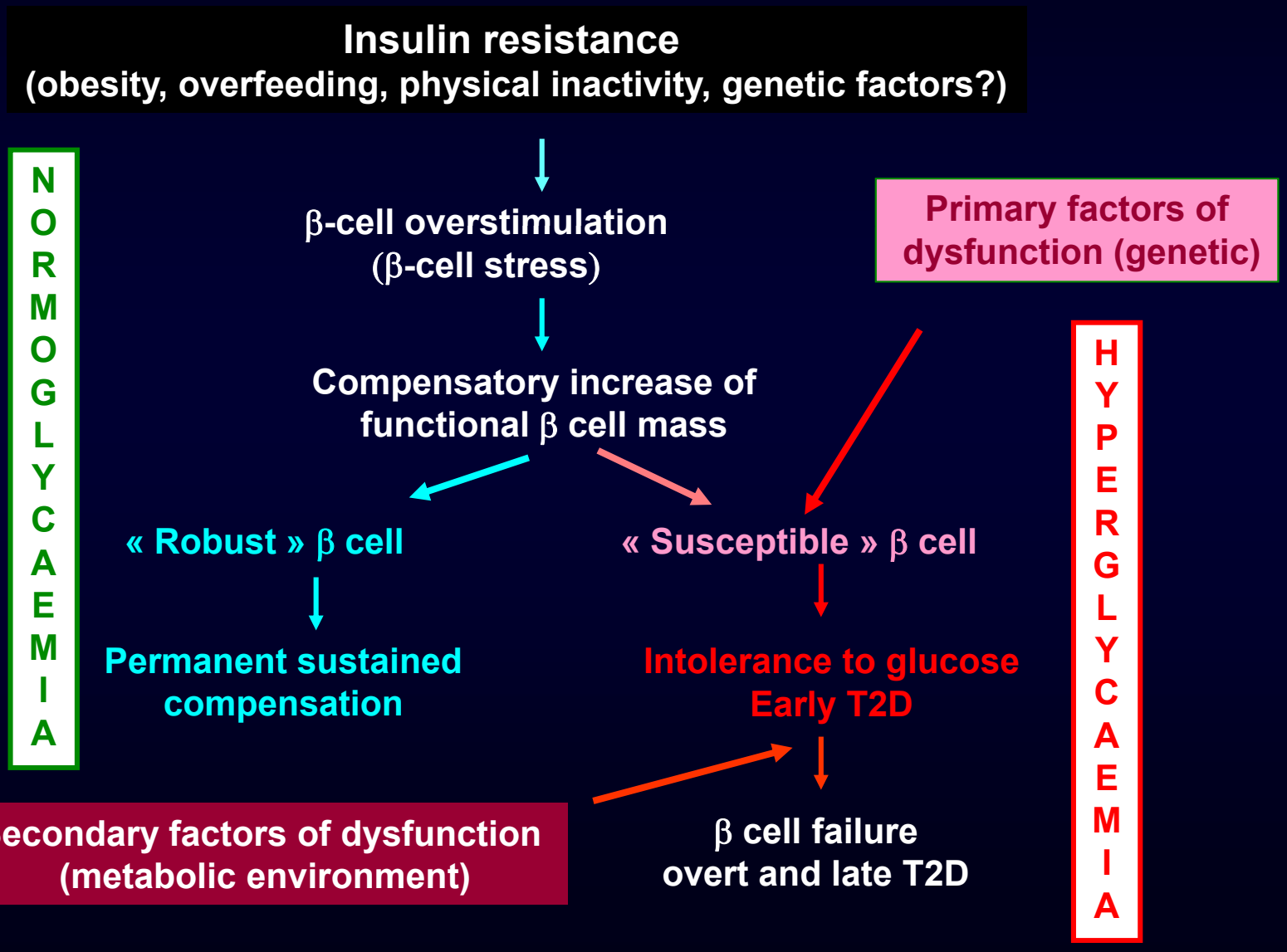
Maclean, Ogilvie – 1955, Westermark, Wilander – 1978, Saito, et al, 1978,1979, Klöppel, et al – 1985, Butler, et al – 2003, Yoon, et al – 2003, Deng et al - 2004 …

Functionnal β cell mass

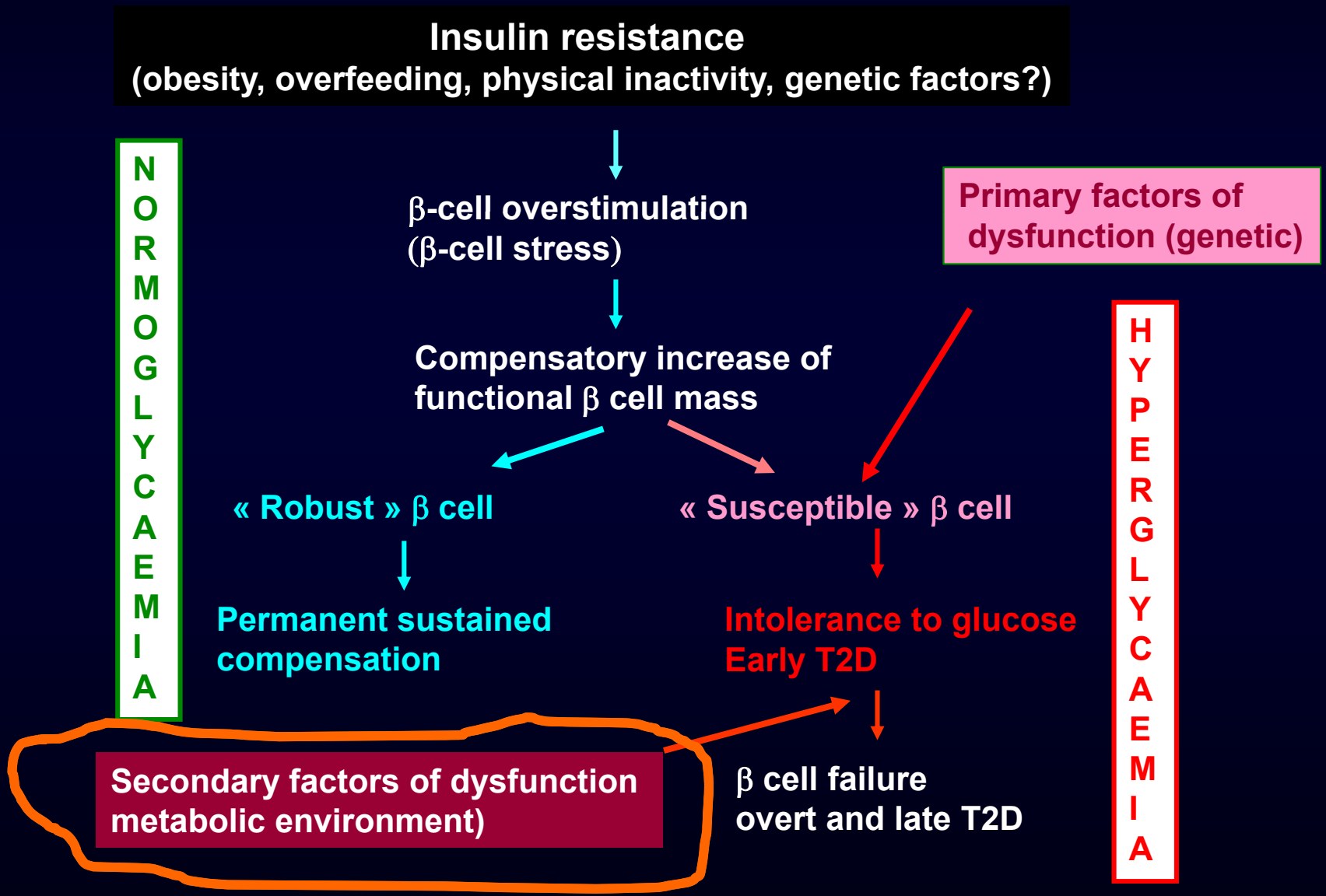
Decrease in the functional β cell mass

Progressive damage of glycemic control in type 2 diabetic patients

POSSIBLE MECANISM OF β CELL FAILURE IN TYPE 2 DIABETES



POSSIBLE MECANISM OF β CELL FAILURE IN TYPE 2 DIABETES



TOWARDS NEW TREATMENTS FOR TYPE 2 DIABETES: GENERAL STRATEGY

To meet the uncovered medical needs…

Preventing macrovascular complications of diabetes

- Lipid profile
- Vascular endothelial cells
- Cardiac function

Preventing the progressive deterioration of glycemic control

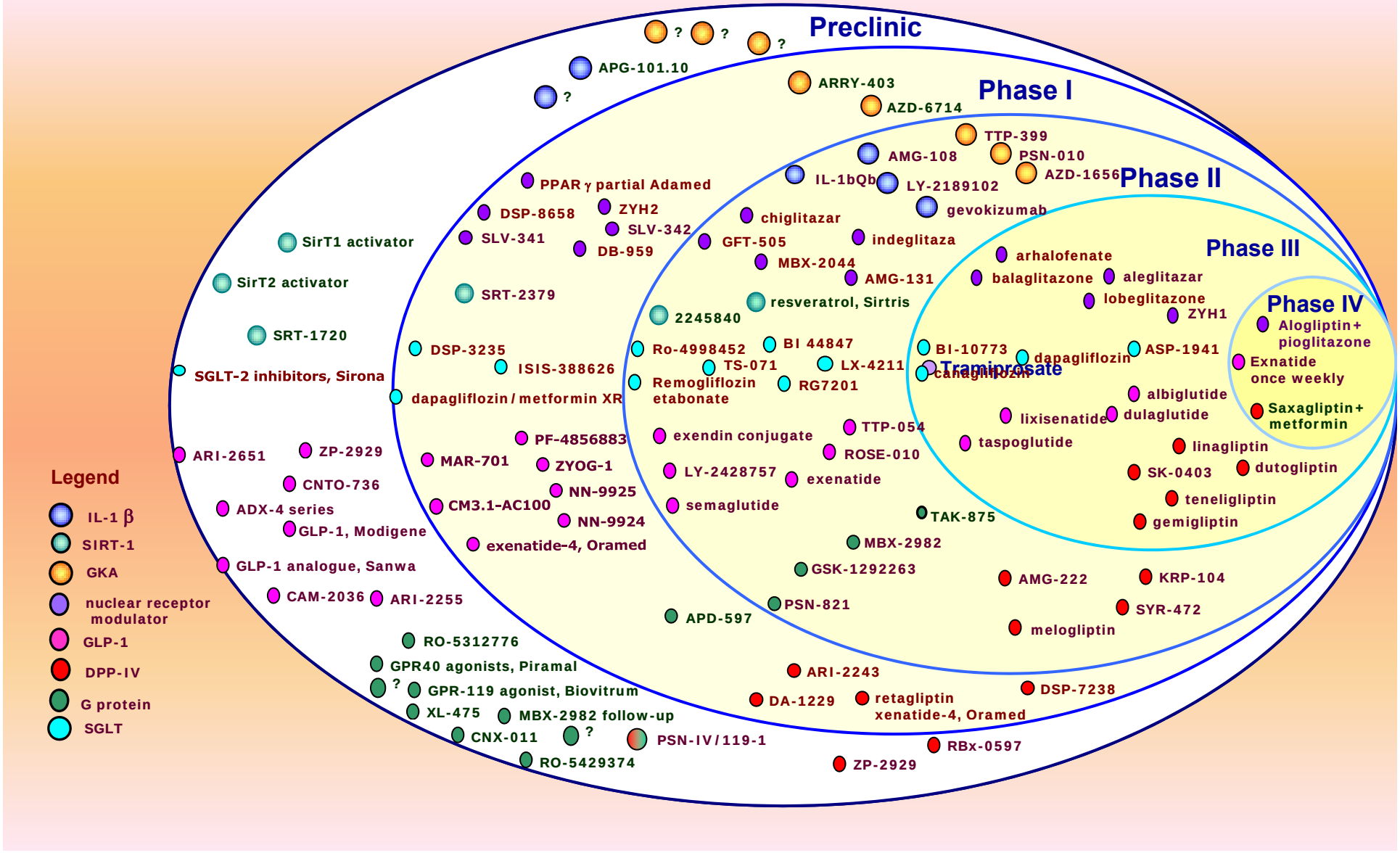
Maintining and/or restoring the functional β-cell mass

Improving β-cell metabolic environment (gluco-lipo toxicity)

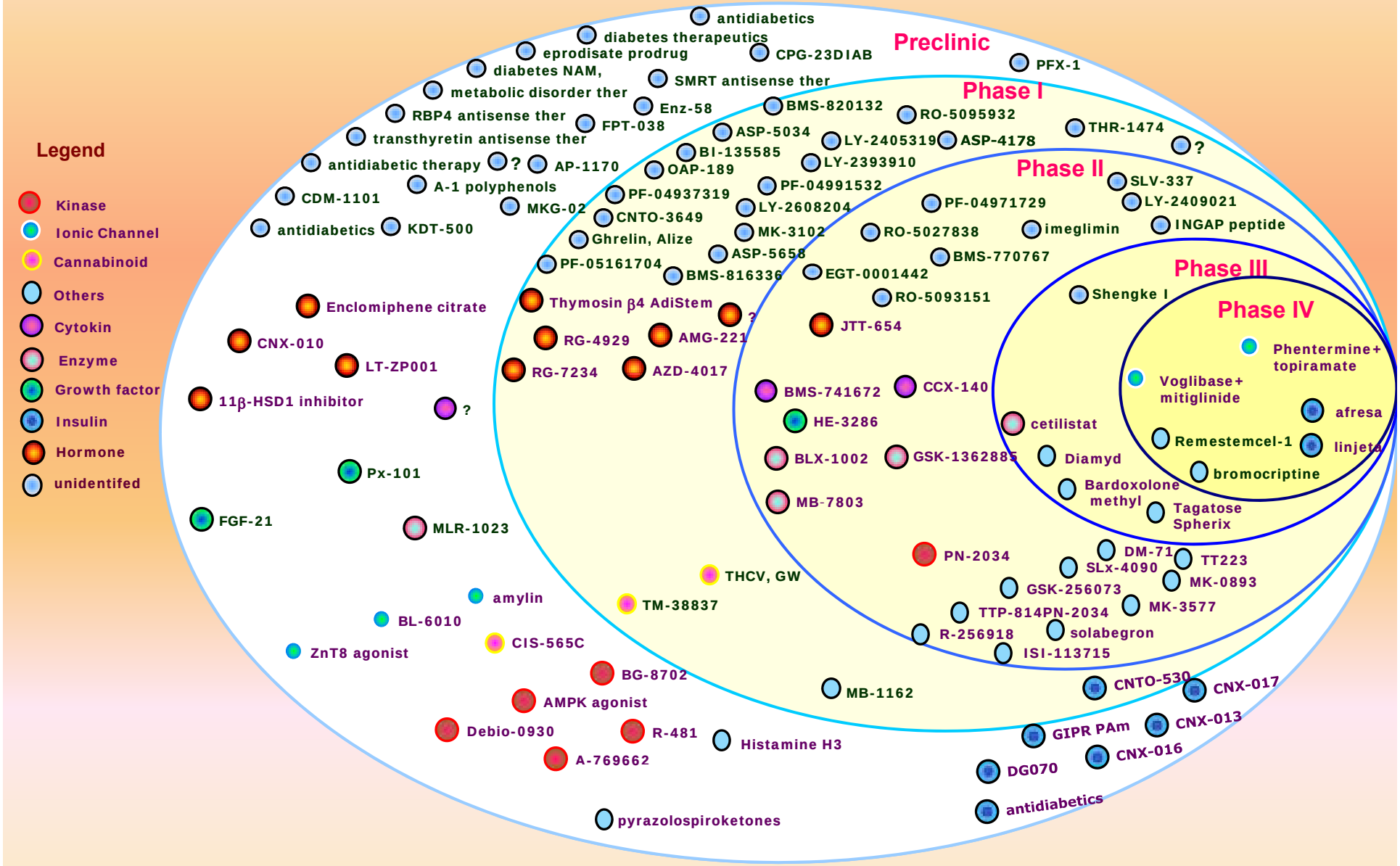
Reducing inflammation, Oxidative and ER stress

Targeting the intra-islet mechanism of β-cell function and survival

Diabetes 1/2


Preclinic
Phase I
Phase II
Phase III
Phase IV
? ? ?
APG-101.10
?
ARRY-403
AZD-6714
TTP-399
AMG-108
PSN-010
AZD-1656
IL-1bQb
LY-2189102
gevokizumab
PPAR γ partial Adamed
DSP-8658
ZYH2
SLV-341
SLV-342
DB-959
chiglitazar
GFT-505
indeglitaza
MBX-2044
AMG-131
arhalofenate
balaglitazone
aleglitazar
lobeglitazone
ZYH1
resveratrol, Sirtris
2245840
SirT1 activator
SirT2 activator
SRT-2379
SRT-1720
SGLT-2 inhibitors, Sirona
DSP-3235
ISIS-388626
dapagliflozin / metformin XR
Ro-4998452
BI 44847
TS-071
LX-4211
Remogliflozin etabonate
RG7201
BI-10773
dapagliflozin
canagliflozin
ASP-1941
Tramiprosate
Alogliptin + pioglitazone
Exnatide once weekly
albiglutide
Saxagliptin + metformin
lixisenatide
dulaglutide
taspoglutide
linagliptin
SK-0403
dutogliptin
teneligliptin
gemigliptin
ARI-2651
ZP-2929
CNTO-736
ADX-4 series
GLP-1, Modigene
GLP-1 analogue, Sanwa
CAM-2036
ARI-2255
PF-4856883
MAR-701
ZYOG-1
NN-9925
CM3.1-AC100
NN-9924
exenatide-4, Oramed
exendin conjugate
TTP-054
ROSE-010
LY-2428757
exenatide
semaglutide
TAK-875
MBX-2982
GSK-1292263
AMG-222
KRP-104
PSN-821
SYR-472
APD-597
melogliptin
RO-5312776
GPR40 agonists, Piramal
? GPR-119 agonist, Biovitrum
XL-475
MBX-2982 follow-up
CNX-011
?
PSN-IV/119-1
RO-5429374
ARI-2243
DSP-7238
DA-1229
retagliptin
xenatide-4, Oramed
RBx-0597
ZP-2929
Legend
IL-1 β
SIRT-1
GKA
nuclear receptor modulator
GLP-1
DPP-IV
G protein
SGLT

Diabetes 2/2


Legend
Kinase
Ionic Channel
Cannabinoid
Others
Cytokin
Enzyme
Growth factor
Insulin
Hormone
unidentifed
Preclinic
Phase I
Phase II
Phase III
Phase IV
antidiabetics
diabetes therapeutics
eprodisate prodrug
CPG-23DIAB
PFX-1
diabetes NAM,
SMRT antisense ther
metabolic disorder ther
Enz-58
BMS-820132
RO-5095932
RBP4 antisense ther
FPT-038
ASP-5034
LY-2405319
ASP-4178
THR-1474
transthyretin antisense ther
BI-135585
?
antidiabetic therapy
?
AP-1170
OAP-189
LY-2393910
A-1 polyphenols
PF-04991532
SLV-337
CDM-1101
PF-04937319
PF-04971729
LY-2409021
MKG-02
LY-2608204
CNTO-3649
antidiabetics
KDT-500
MK-3102
RO-5027838
imeglimin
INGAP peptide
Ghrelin, Alize
ASP-5658
BMS-770767
PF-05161704
BMS-816336
EGT-0001442
Enclomiphene citrate
Thymosin β4 AdiStem
?
RO-5093151
Shengke I
JTT-654
CNX-010
RG-4929
AMG-221
Phentermine+ topiramate
LT-ZP001
RG-7234
AZD-4017
Voglibase+ mitiglinide
BMS-741672
CCX-140
11β-HSD1 inhibitor
?
HE-3286
cetilistat
afresa
Remestemcel-1
linjeta
BLX-1002
GSK-1362885
Diamyd
bromocriptine
Px-101
Bardoxolone methyl
MB-7803
Tagatose Spherix
FGF-21
MLR-1023
PN-2034
DM-71
TT223
SLx-4090
MK-0893
THCV, GW
GSK-256073
amylin
TM-38837
TTP-814PN-2034
MK-3577
BL-6010
R-256918
solabegron
CIS-565C
ISI-113715
ZnT8 agonist
BG-8702
CNTO-530
CNX-017
MB-1162
AMPK agonist
GIPR PAm
CNX-013
Debio-0930
R-481
Histamine H3
CNX-016
A-769662
DG070
antidiabetics
pyrazolospiroketones

“SELECTIVE PPAR MODULATORS“ (SPPARM)

PPARγs AGONISTS IN TYPE 2 DIABETES THERAPY

TZD are very efficient in long-term glycemic control **but** …

Huge limitations

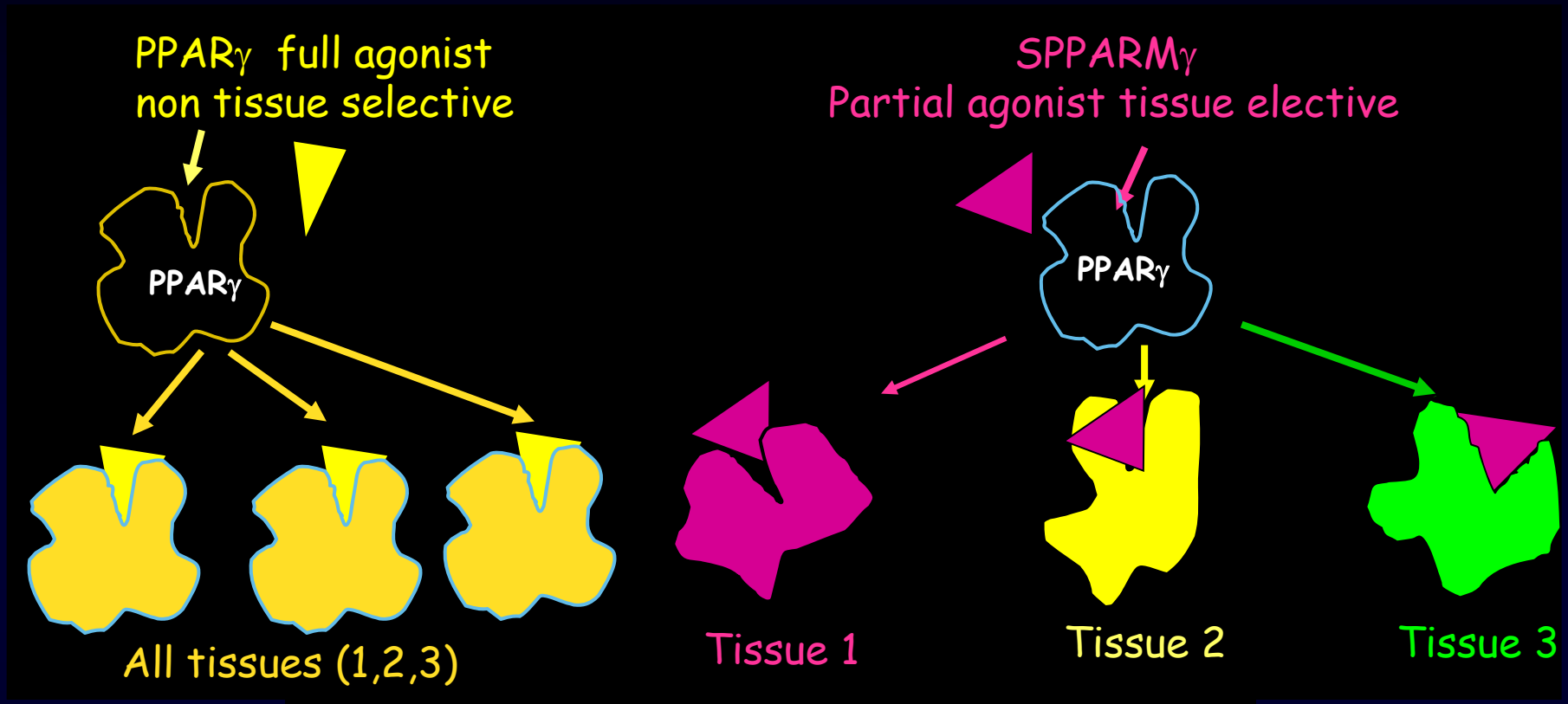
Fluid retention Oedema Adipocyte proliferation

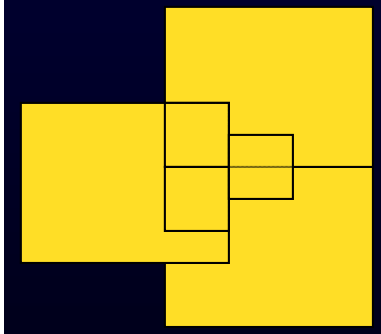
Weight gain

- Cardio vascular side effects
- Osteoporosis

"Selective PPAR Modulator" (SPPARM)

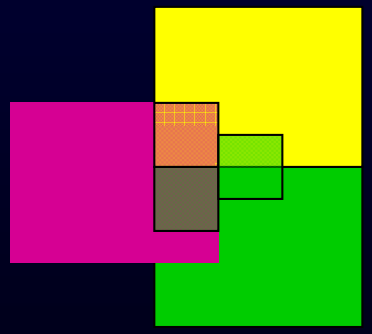
"SELECTIVE PPAR MODULATOR" (SPPARM)





Differential activation or repression of genes

Tissue selectivity
Pharmacological profile different
from that of glitazones



Increased benefitial effects/risk ratio

Classification of products : Phase III

Origin	License	name	synonym	target(s)	Comments
Dr Reddy's	Rheoscience (Nordic Bioscience)	balaglitazone	DRF2593	SPPARM?	positive phase III results in Jan 2010
Metabolex	J&J	arhalofenate (metaglidasen)	MBX-102 JNJ-39659100	SPPARM?	in Phase II Clinical Trial for gout (Hyperuricaemia) confirmed in sept 2010; phase II/III completed in Type 2 Diabetes in 2008 and new phase II vs pioglitazone in January 2009
Chong Kun Dang	Equispharm	lobeglitazone	CKD-501 IDR-105	PPAR??	Phase III since sept 2009
Zydus Cadila		ZYH1		PPAR??	Clinical trials in India
Hoffmann-La Roche		aleglitazar	R-1439	PPAR??	Study With Aleglitazar in Patients With a Recent Acute Coronary Syndrome and Type 2 Diabetes Mellitus Since 2007 : several phase II studie evaluate renal function

Classification of products : Phase II

Origin	License	name	synonym	target(s)	Comments
Ajinomoto	Boehringer Ingelheim	BI-44847	BI 44847	SGLT2 inhibitor	web site company
Plexxikon		indeglitazar	PLX-204 PPM-204	PPAR pan agonist activity	web site company
Shenzhen Chipscreen Biosciences		chigiitazar	CS-0038 CS038	PPAR pan agonist activity	pipeline
Genfit		GFT-505	GFT505	alpha specific PPAR pan agonist	2nd phase II announced in sept 2010
Metabolex	J&J	MBX-2044 (back-up/follow on)		SPPARM?	phase II in Type 2 Diabetes completed but absent from pipeline
Amgen	InteKrin Therapeutics	AMG-131	INT-131	SPPARM?	clinical data of phase IIb presented at ADA2010

POTENTIAL INTESTINAL DRUG TARGETS LINKED TO THE BENEFICIAL EFFECTS OF BARIATRIC SURGERY

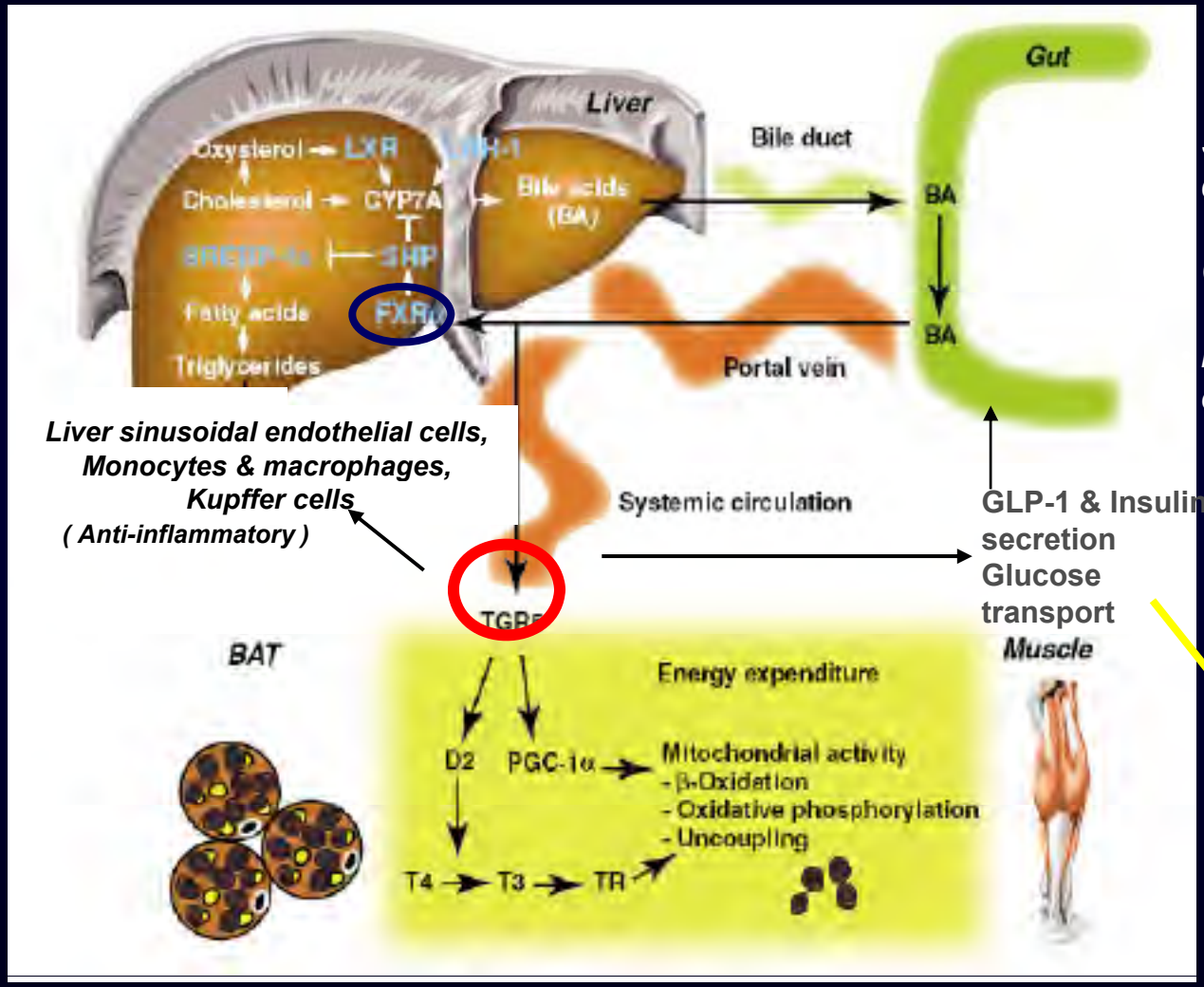
BARIATRIC SURGERY-MEDIATED EFFECTS ON SIGNALING MOLECULES

Increased delivery of food to the distal ileum and colon results in

- Increased GLP-1 (insulin secretion, beta cell survival, inhibition of gastric emptying, others)
- Increased PYY (inhibition of gastric emptying, reduced appetite)
- increased Adiponectin (glucose utilization and FFA oxidation)
- Increased Bile-acid pool size (GLP-1 and insulin secretion, energy expenditure, others)
- Decreased fasting insulin (glucose uptake, inhibition of gluconeogenesis and lipolysis)
- Decreased Ghrelin (stimulates GH secretion, hunger, gastric emptying)
- Changes intestinal microbioata composition

TGR5 ACTIVATORS

BILE ACID-TGR5 OVERVIEW



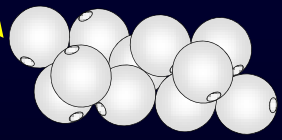
Detergent-based amphipathic properties

Solubilisation & absorption of dietary fat & lipid-soluble vitamins

Cholesterol homeostasis

Modulate gene transcription for enzymes & transport proteins

Islet



Adipocytes

- TGR5 KO mice are more glucose intolerant than wt mice after 8 weeks of HFD.
- TGR5 transgenic mice fed a high fat diet have improved glucose tolerance.

TGR5 OVERVIEW

Receptor for bile acids and natural products having triterpenoidic structure

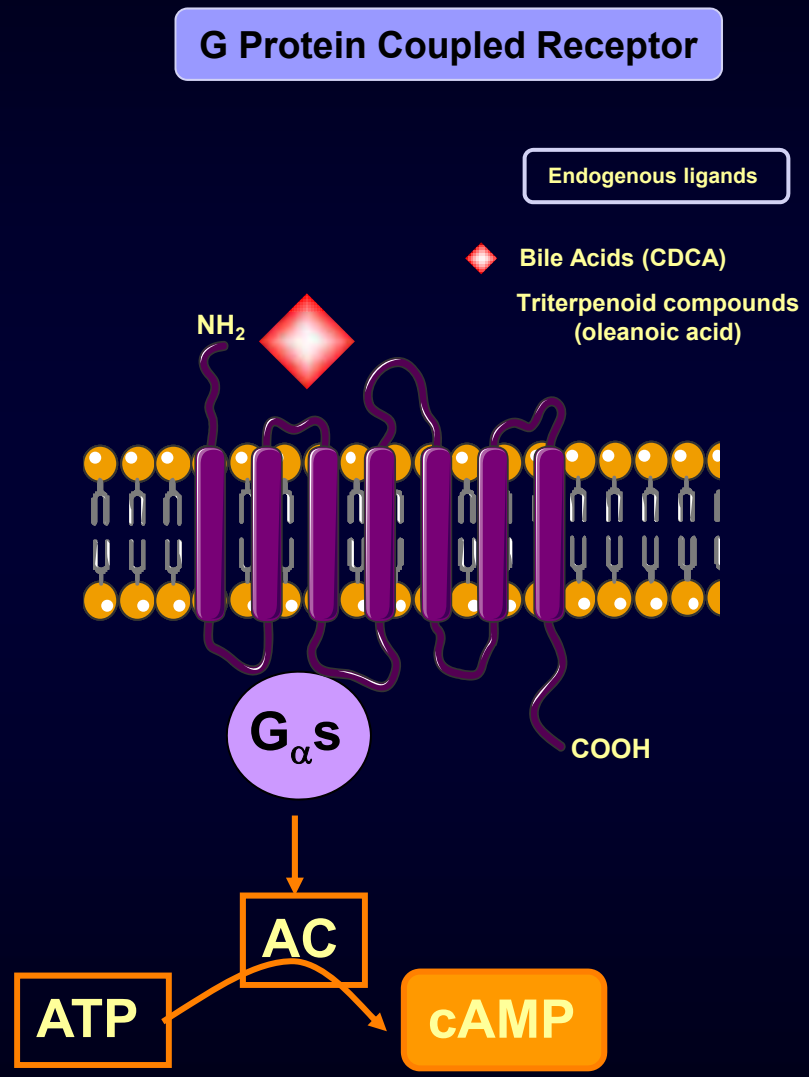
hTGR5: ~70 kD; 330 aa; no splice variants described)

7 trans-membrane protein coupled to GαS protein (cAMP induction)

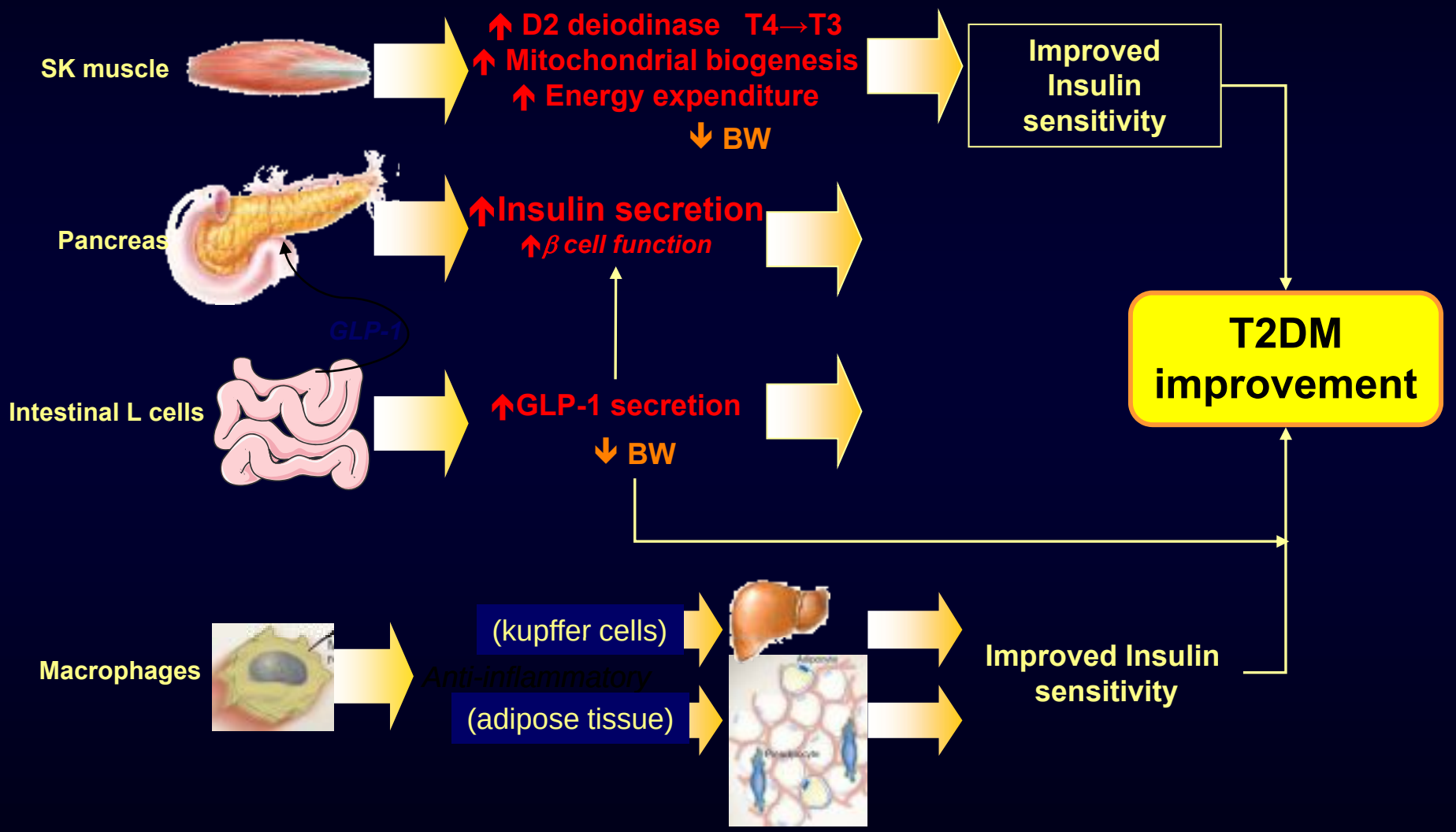
Mediates calcium influx into enteroendocrine cells

Broad tissue expression

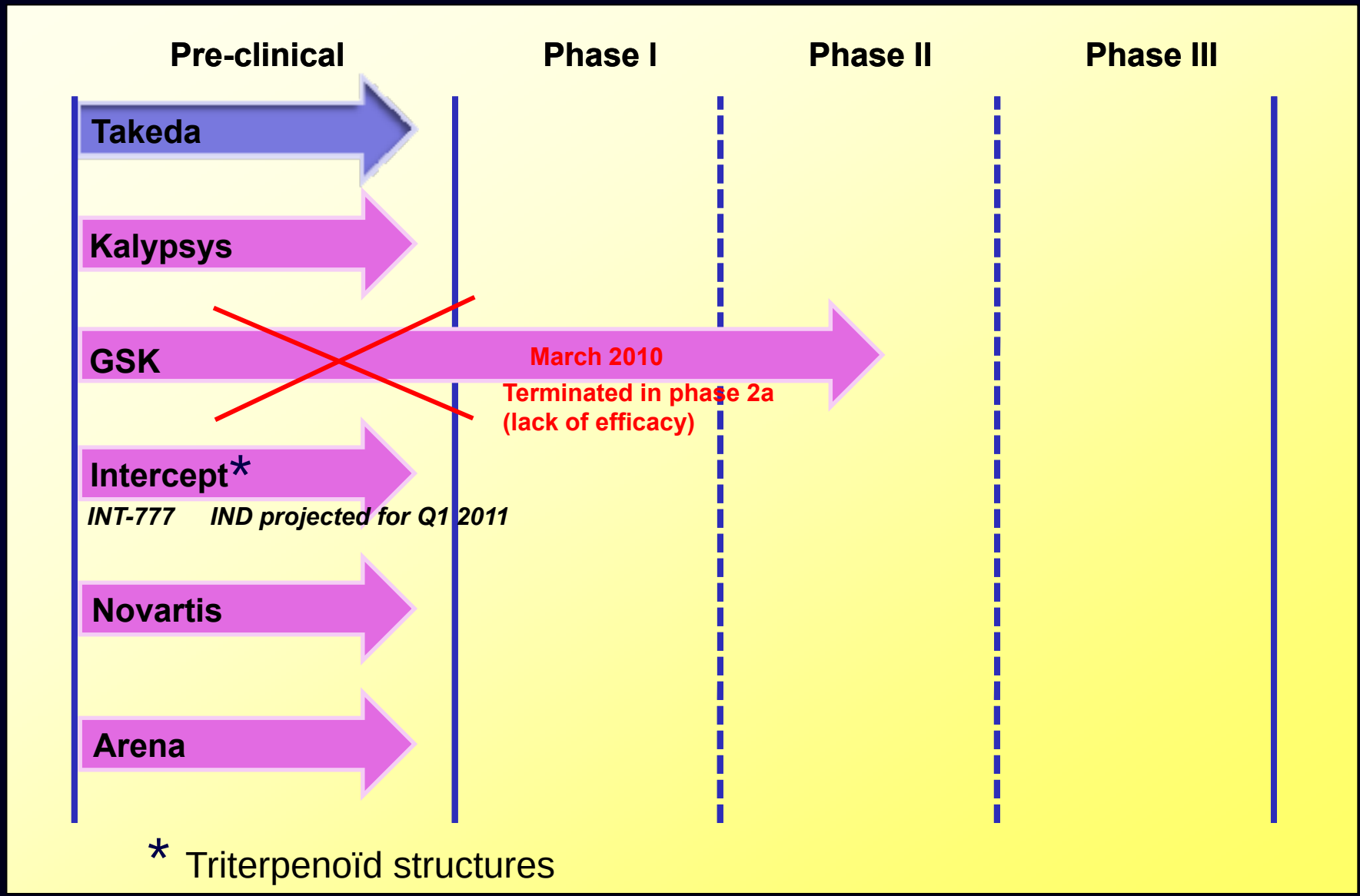
Human protein homology vs mouse and rat is 82-91%



TGR5 ACTIVATION
A THERAPEUTIC TARGET FOR TDM2 DIABETES



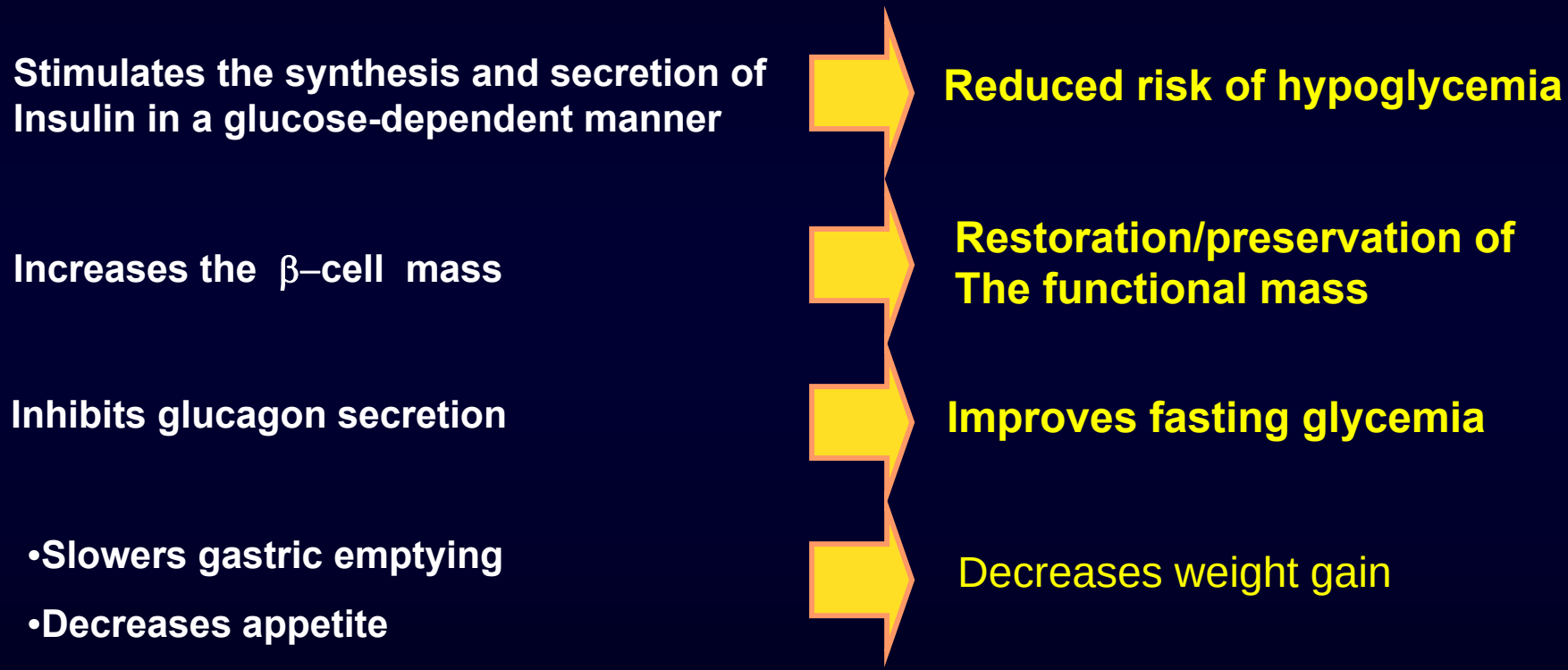
TGR 5 AGONISTS



‘INCRETIN’ AGENTS

GLP-1

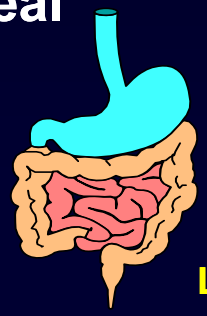
GLP-1 AND TYPE 2 DIABETES THERAPY



BIOLOGICAL EFFECTS OF GLP-1
Metabolism

GLP-1 is very rapidly inactivated by the DiPeptidyl Peptidase-IV (DPP IV)

Meal



L-cells

Half-life : 1-2 min

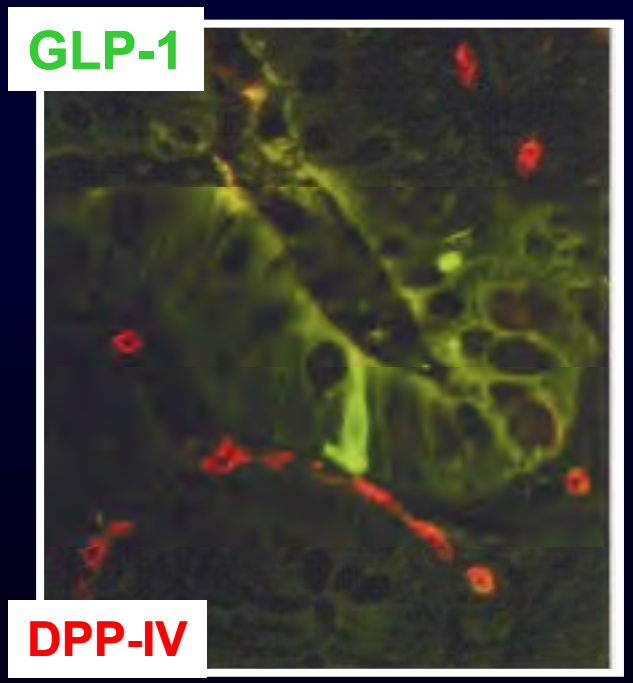
GLP1 $_{7-36}$ *active*

N C

DPPIV

GLP1 $_{9-36}$ *inactive*

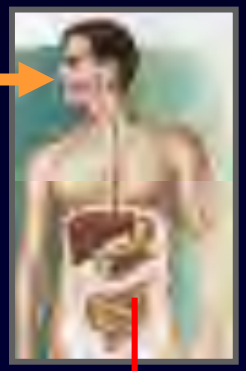
- ØSerine amino-dipeptidase
- ØPresent on cell membrane (110kDa) and in the plasma (100kDa)
- ØUbiquituous



Hansen et al (Endocrinology 1998)

GLP-1 AND TYPE 2 DIABETES : STRATEGIES

1 DPP IV Inhibition



GLP1
Endogenous

Prolonged
incretin effect

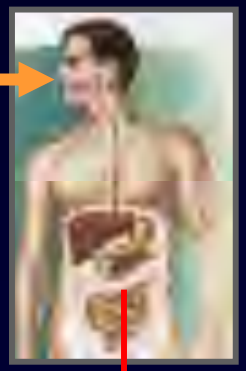
DPP-IV
inhibitor

Inactive GLP1

Vidagliptin, sitagliptin, saxagliptin, Alogliptin

GLP-1 AND TYPE 2 DIABETES : STRATEGIES

2 GLP-1R Agonistes



GLP1-R agonists

GLP1
endogenous

R-GLP1

Incretin effect

Liraglutide
Exenatide

DPP-IV

DPP-IV Inhibitor

GLP1 inactive

Classification of products : Phase III

Origin	License	name	synonym	target(s)
Zealand Pharma	Sanofi-Aventis	**lixisenatide**	AVE-00010	**GLP-1 agonist**
Ipsen	Hoffmann-La Roche Teijin	**taspoglutide IR** **taspoglutide SR**	BIM 51077 ITM-077 R-1583	**GLP-1 agonist**
Human Genome Sciences	GSK	**albiglutide**	716155 Albugon Syncria	**GLP-1 agonist**
Eli Lilly		**dulaglutide**	LY-2189265	**GLP-1 agonist**
Phenomix	Chiesi Forest Laboratories	**dutogliptin**	PHX-1149	**DPP-IV inhibitor**
Mitsubishi Tanabe Pharma		**teneligliptin**	MP-513	**DPP-IV inhibitor**
Boehringer Ingelheim		**linagliptin**	BI-1356 Ondero	**DPP-IV inhibitor**
Sanwa Kagaku Kenkyusho	Kowa Choongwae	**SK-0403**	CWP-0403	**DPP-IV inhibitor**
LG Life Sciences		**gemigliptin**	LC-15-0044	**DPP-IV inhibitor**

Classification of products : Phase II

Origin	License	name	synonym	target(s)
Eli Lilly		LY-2428757		GLP-1 agonist
Hanmi		exendin conjugate, Hanmi	HM-11260C LAPS-Exendin	GLP-1 agonist
Intarcia Therapeutics	Johnson & Johnson	exenatide	ITCA 650	GLP-1 agonist
Novo Nordisk		semaglutide	NN-9535	GLP-1 agonist
TransTech Pharma		TTP-054		GLP-1 agonist
Amgen	Servier	AMG-222		DPP-IV inhibitor
Glenmark	Merck KGaA	melogliptin	EMD 675992 GRC 8200	DPP-IV inhibitor
Kyorin		KRP-104		DPP-IV inhibitor
Takeda		SYR-472		DPP-IV inhibitor

Classification of products : Phase I

Origin	License	name	synonym	target(s)
Kissei	Dainippon Sumitomo	DSP-2235	KRP-2235	SGLT2/SGLT1 inhibitor
Marcadia Biotech	Merck & Co	**MAR-701**		**GLP-1 agonist**
Biocompatibles	AstraZeneca	**CM3.1-AC100**	GLP-1 analogue, CellMed	**GLP-1 agonist**
Novo Nordisk	Emisphere Technologies	**NN-9924**		**GLP-1 agonist**
Novo Nordisk		**NN-9925**		**GLP-1 agonist**
Pfizer		**PF-4856883**	CovX-096	**GLP-1 agonist**
Zydus Cadila		**ZYOG-1**	ZYOG1	**GLP-1 agonist**
Oramed Pharmaceuticals		**exenatide-4, Oramed**	ORMD-0901	**GLP-1 agonist**
Altea	Amylin Eli Lilly	**exenatide, transdermal**		**GLP-1 agonist**
Dong-A		**exenatide, Dong-A**	DA-3091	**GLP-1 agonist**
Marina Biotech	Amylin	**exenatide, nasal spray**		**GLP-1 agonist**
Peptron	NeoPharm	**exenatide SR, Peptron**	exenatide SR, Neopharm PT-302	**GLP-1 agonist**
Versartis		**exenatide,**	exenatide-XTEN VRS-859	**GLP-1 agonist**

Origin	License	name	synonym	target(s)
Jiangsu Hengrui Medicine		**retagliptin**	PEX-168	**DPP-IV inhibitor**
Dong-A		**DA-1229**		**DPP-IV inhibitor**
Arisaph Pharmaceuticals		**ARI-2243**		**DPP-IV inhibitor**
Dainippon Sumitomo Pharma		**DSP-7238**		**DPP-IV inhibitor**
Arena	Johnson & Johnson	APD-597	JNJ-28630355	GPR119 agonist

Classification of products : Preclinical

Origin	Name	Target
Origin	Name	Target
		SGLT2 inhibitor
Addex	ADX-4 series	GLP-1 agonist
Johnson & Johnson	CNTO-736	GLP-1 agonist
Prolor Biotech	GLP-1, Modigene	GLP-1 agonist
Sanwa Kagaku Kenkyusho	GLP-1 analogue, Sanwa	GLP-1 agonist
Arisaph Pharmaceuticals	ARI-2255	GLP-1 agonist
Arisaph Pharmaceuticals	ARI-2651	GLP-1 agonist
Camurus	CAM-2036	GLP-1 agonist
Zealand Pharmaceuticals	ZP-2929	GLP-1 agonist
Astellas	ASP-8497	DPP -IV inhibitor
Astellas	PSN-IV/119-1	DPP -IV inhibitor GPR-119 agonist
Daiichi Sankyo	RBx-0597	DPP -IV inhibitor

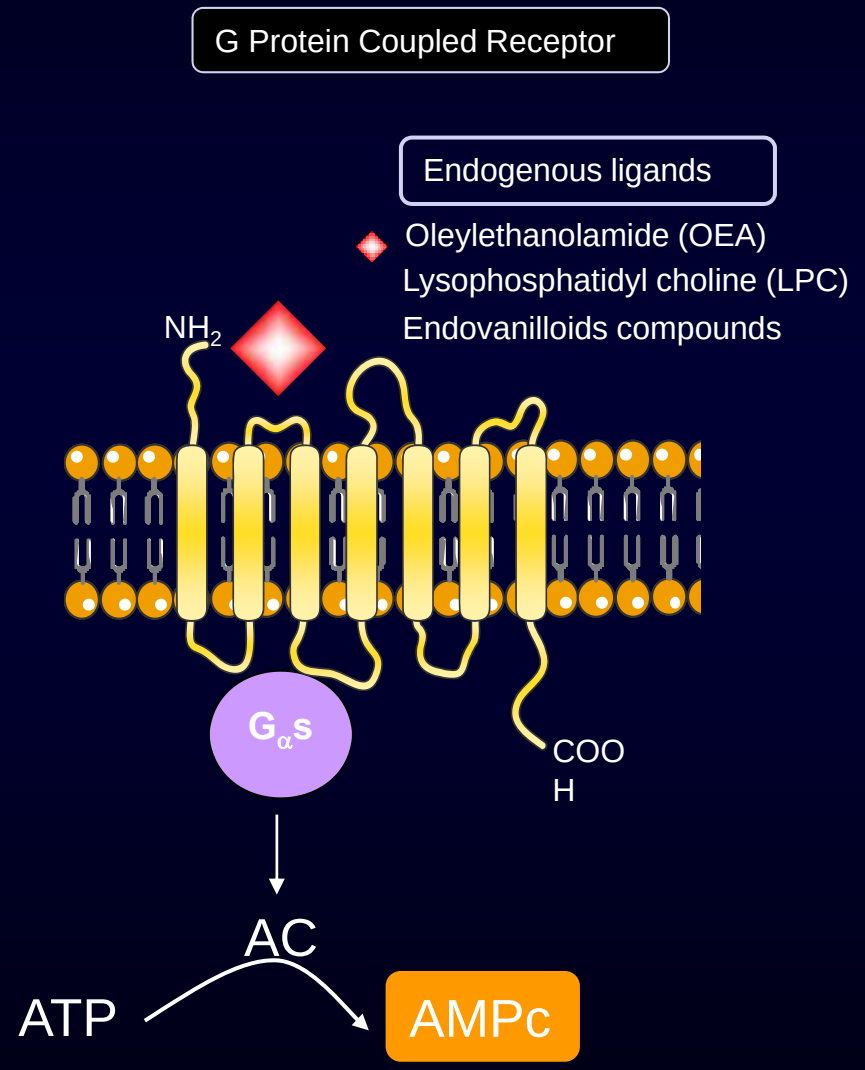
GPR 119 LIGANDS

GPR119 BIOLOGY

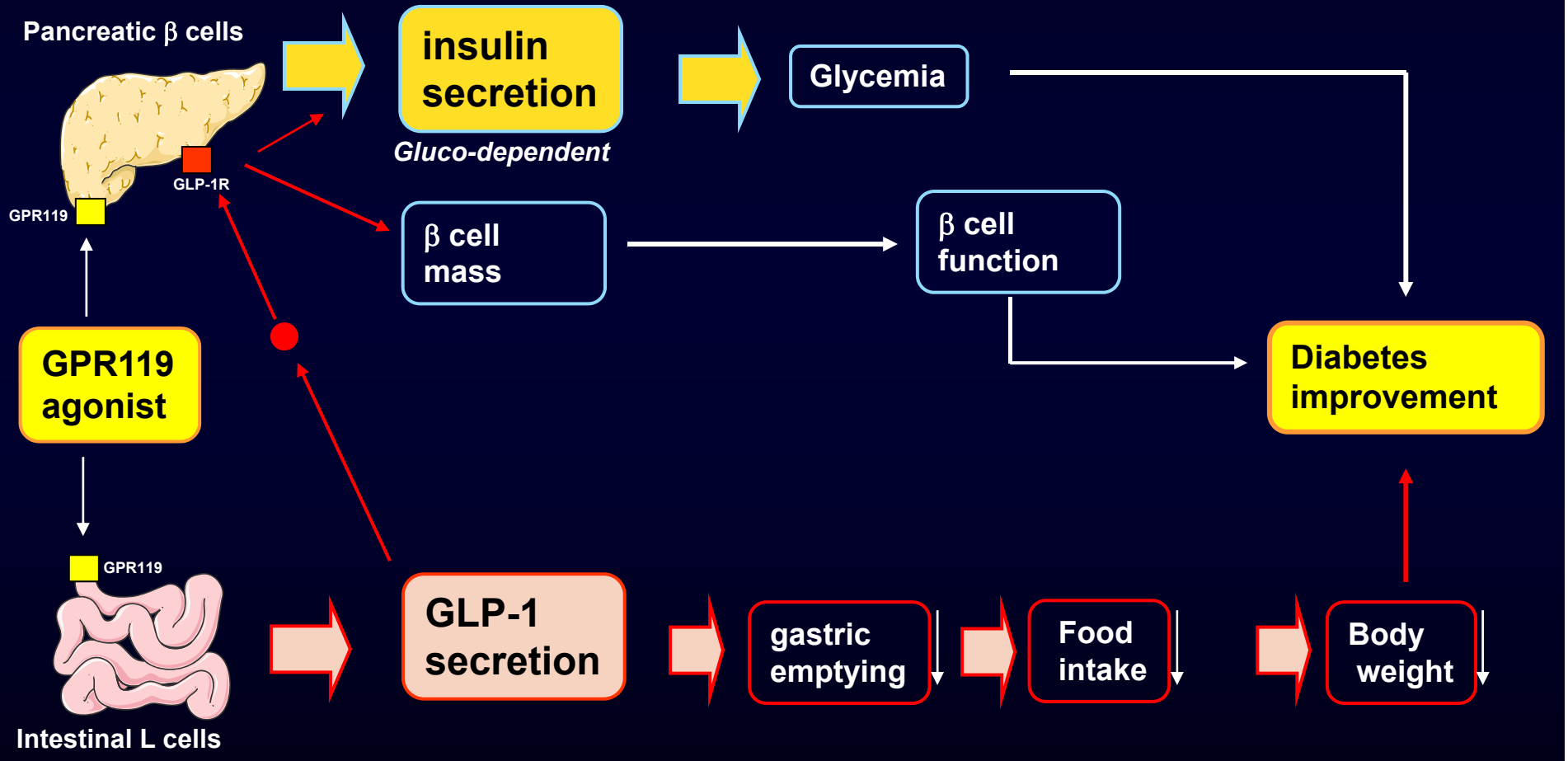
7 trans-membrane protein coupled to GαS protein (37 kD for human protein, 335 AA)

Gene localized in Xp26.1

Human protein homology vs rat and mouse is about 80%



GPR119
MECHANISMS OF ACTION
AND EXPECTED PHARMACOLOGICAL EFFECTS



HA Overton, BJP, 2008

Classification of products : Phase II

Astellas		PSN-821	GPR-119 agonist
GlaxoSmithKline		GSK-1292263	GPR-119 agonist
Metabolex	Sanofi-Aventis	MBX-2982 SAR-260093	GPR-119 agonist

GPR-119 agonist

Classification of products : Phase I

Arena	JNJ-28630355	GPR-119 agonist

GPR119 agonist

APD-597

Array BioPharm

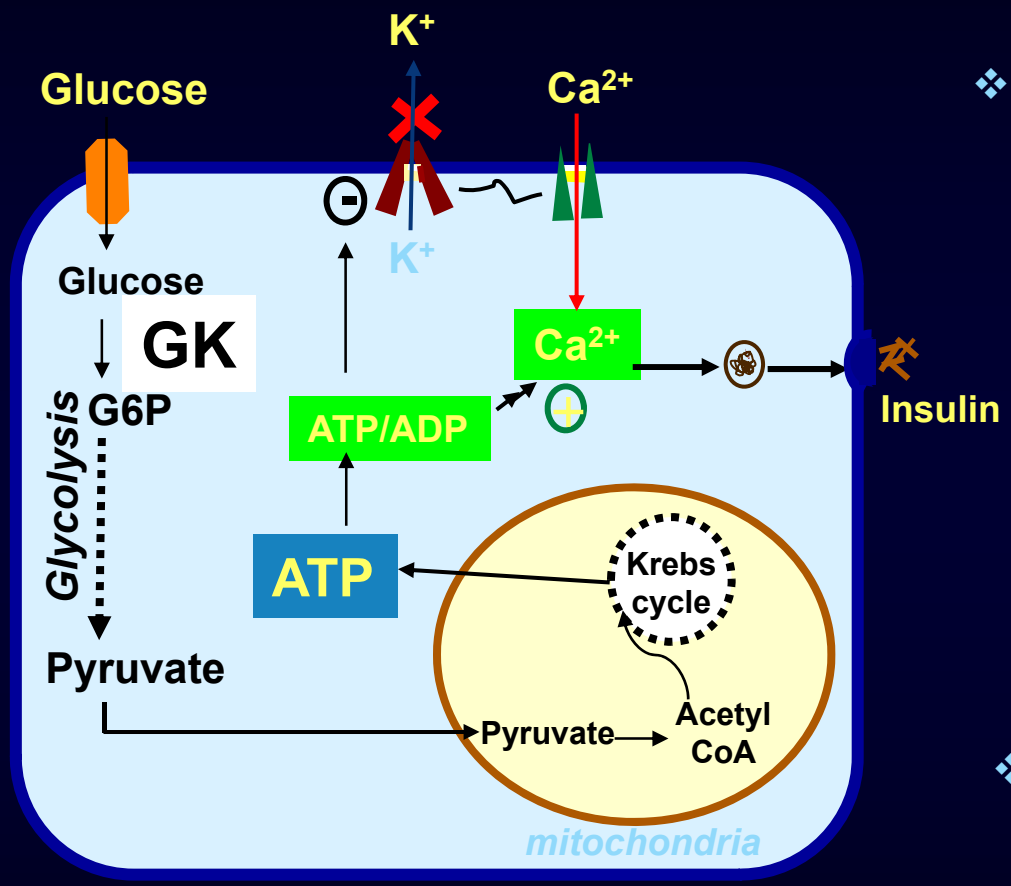
Classification of products : Preclinical

Swedish Orphan Biovitrum	GPR-119 agonist, Biovitrum	GPR119 agonist
Neurocrine Biosciences		GPR119 agonist
Hoffmann-La Roche	RO-5312776	GPR-119 agonist
Hoffmann-La Roche	RO-5429374	GPR-119 agonist
Metabolex	MBX-2982 follow-ups,	GPR-119 agonist
LG Life Sciences		GPR119 agonist

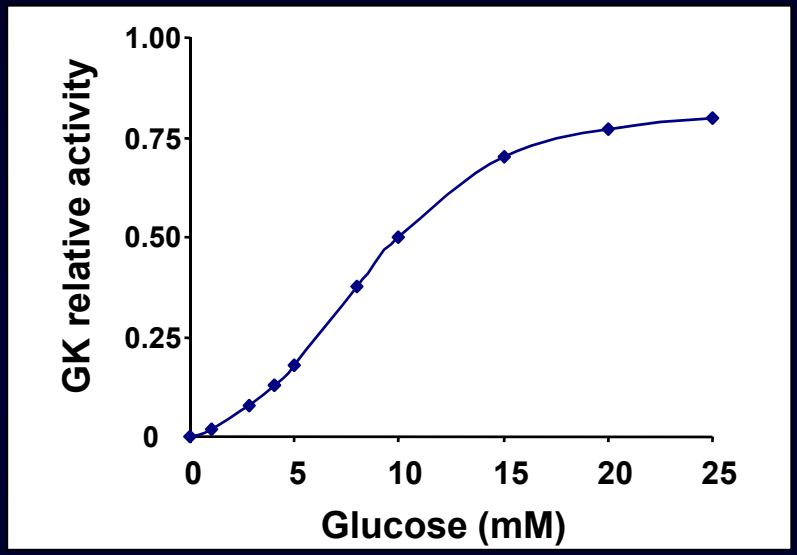
GLUCOKINASE (GK) ACTIVATORS

Role of GK in glucose-induced insulin secretion

"Glucose Sensor" of the ß-cell



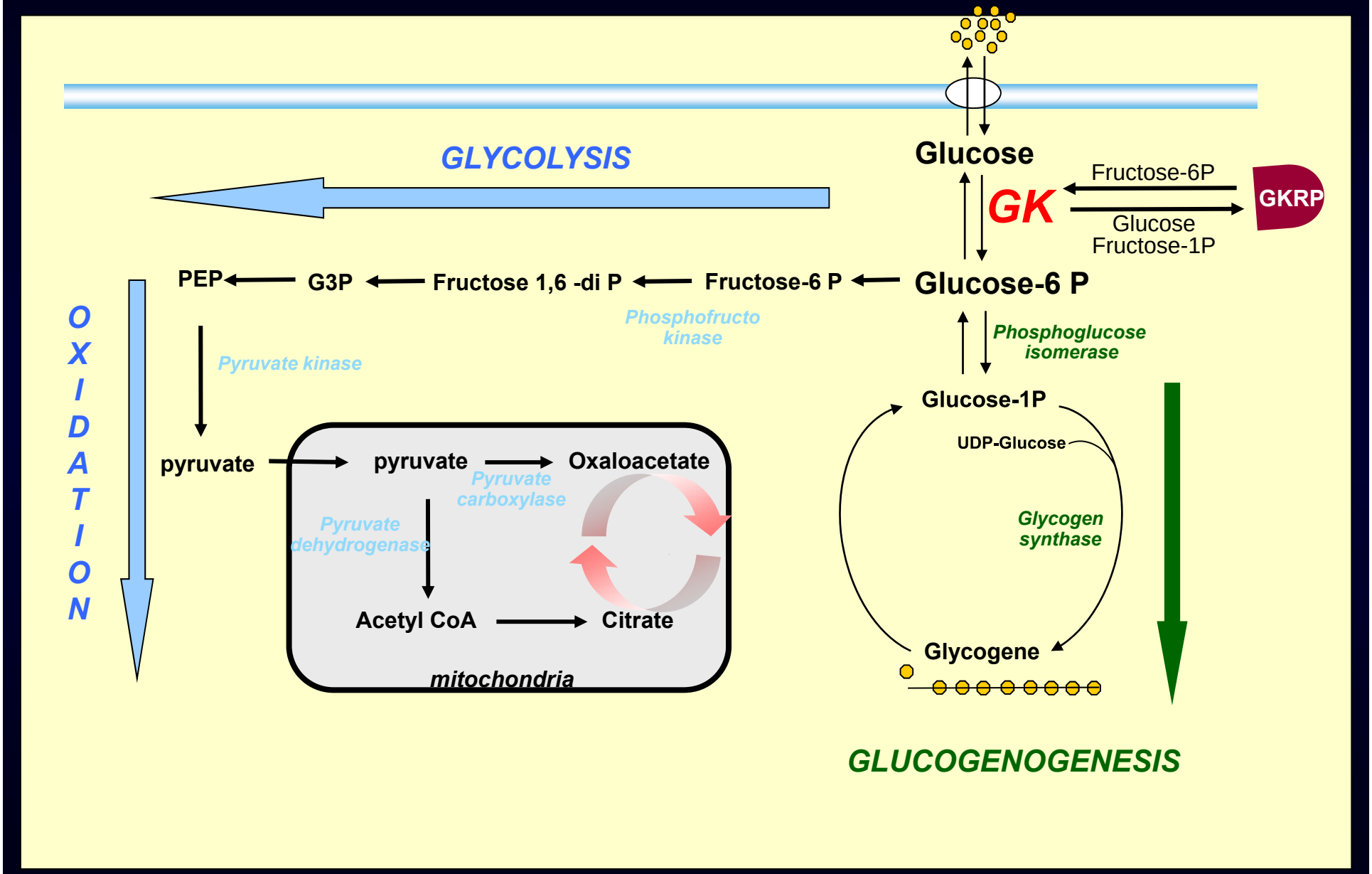
- Sigmoïdal saturation curve



- Low affinity for glucose (Km > 5mM)

- Not inhibited by G6P or other glucose metabolites unlike the other 3 HKs

ROLE OF GK IN HEPATIC GLUCOSE METABOLISM



GLUCOKINASE ACTIVATORS

Expectations

Several diabetic defects potentially corrected

- **Liver** — **Glucose uptake and glycogen synthesis**
- **Pancreas** — **Glucose-induced insulin secretion and ß-cell mass**
- **Gut** — **GLP-1 secretion**

Issues

- **Glucose dependent insulin secretion (hypoglycemia)**
- **Triglyceride accumulation by the liver**

COMPETITING ENVIRONMENT

PHASE II

- **R1440/Piragliatin (Roche) – *given up in 2007 (hypoglycemia)***
- **TTP-355 (Transtech Pharma) – probably discontinued 06/2009**
- **TTP-399 - *08/2009***
- **AZD 6370, AZD 1656 (Astra Zeneca) – *12/2008, 01/2009***
- **PSN-010 (Eli Lilly) - *06/2009***

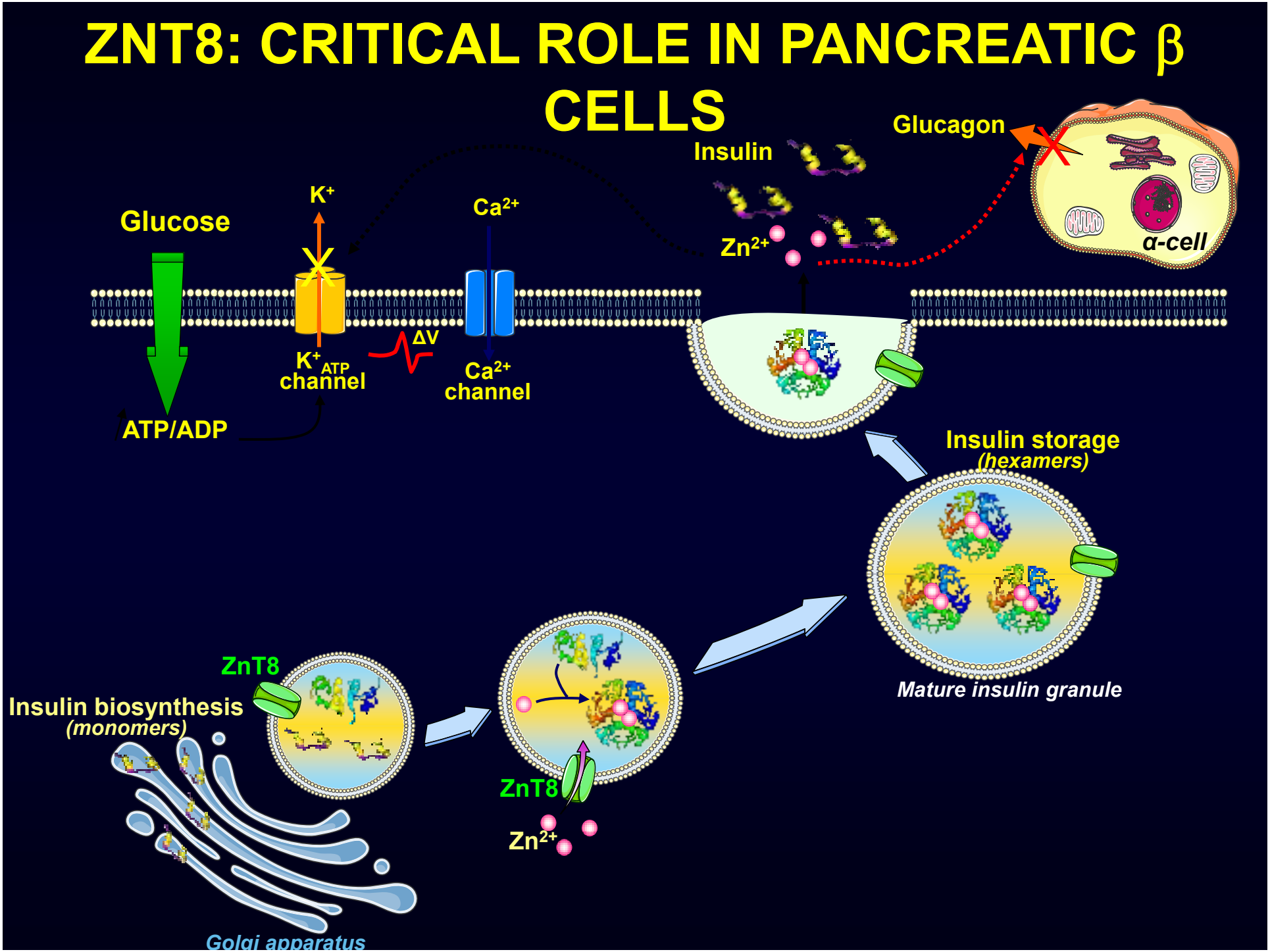
PHASE I

- **AZD6714 – *08/2009***
- **ARRY403 (AMG-151) - *04/2009***
- **TAK-329 (Takeda) - *10/2009***
- **TTP-547 - *06/2009***
- **MK-0599 - *09/2009***

Many GKAs are in preclinical development

AGONISTS OF
THE ZINC TRANSPORTER ZnT8

ZNT8: CRITICAL ROLE IN PANCREATIC β CELLS



RELATIONSHIP BETWEEN ZNT8 AND TYPE 2 DIABETES

- ***SLC30A8* variant, *rs13266634***
  - ✓ **2nd locus the most associated with type 2 diabetes in the french population**
- **World wild association of this locus with diabetes in other ethnic origins**
- **Relationship between ZnT8 and human β-cell function**

  This variant has been found to be associated with decreased
  - ✓ **insulin secretion** *(Steinthorsdottir et al, Nat genet, 2007)*
  - ✓ **Impaired proinsulin conversion** *(Kirchhoff et al., Diabetologia, 2008)*
  - ✓ **Impaired insulin secretion under IVGTT** *(Boesgaard et al., Diabetologia, 2008)*
- **ZnT-8 has been described as a major humoral antigen in type-1 diabetes**
  - ✓ ***Circulating ZnT8 autoantibodies are highly correlated both to disease duration and to the level of c-peptide*** *(Wenzlau et al., PNAS, 2007)*

IMPROVING BETA CELL FUNCTION AND SURVIVAL
GENERAL STRATEGY

Preventing the progressive deterioration of glycemic control

Maintining and/or restoring the functional β-cell mass

Improving β-cell metabolic environment (gluco-lipo toxicity)

Reducing inflammation, Oxidative and ER stress

Targeting the intra-islet mechanism of β-cell function and survival

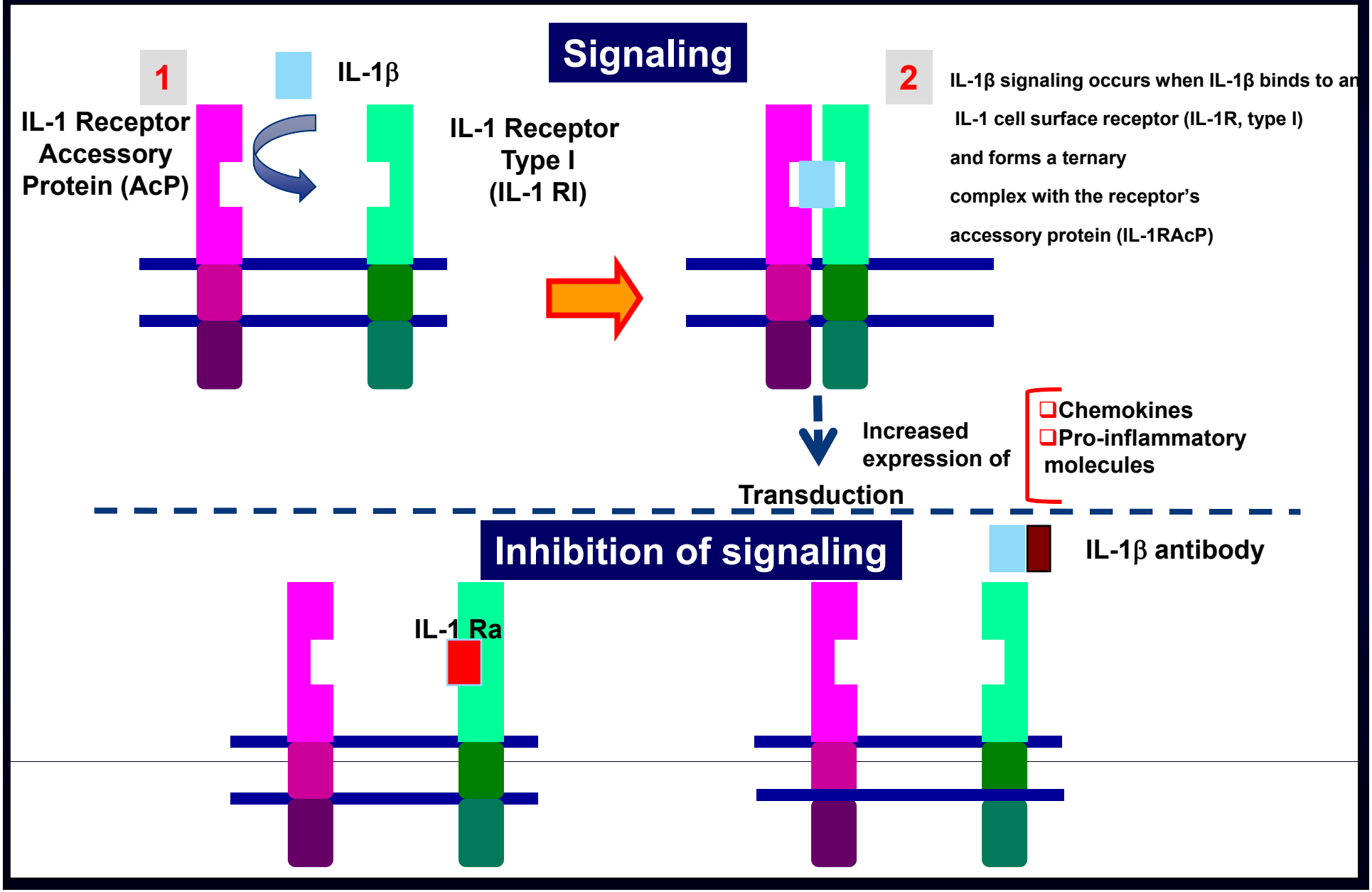
INTERLEUKIN 1-BETA (IL-1β) INHIBITORS

TYPE 2 DIABETES AND THE PRO-INFLAMMATORY CYTOKINE IL-1β

- IL-1β is the key initiator / mediator of the inflammatory cascade

- Elevated levels of IL-1β are implicated in the pathology of both insulin resistance and impaired insulin secretion
  - Adipose tissue expression of IL-1β and IL-1β mediated cytokines (IL-6, TNFα) is up-regulated in obesity
  - Pancreatic islet cell expression of IL-1β and IL-1β mediated cytokines (IL-8, MCP-1) is up-regulated in Type 2 Diabetes

IL-1β LIGAND-RECEPTOR BINDING AND SIGNALING STRATEGIES FOR INHIBITION



INHIBITION OF IL-1β : DISEASE MODIFYING POTENTIAL IN TYPE 2 DIABETES

Excess levels of IL-1β have been shown to be directly involved in beta cell dysfunction and apoptosis

Inhibition of IL-1β has shown disease modifying potential in T2D, improving:

- beta cell survival and proliferation insulin secretion (in both animal models and human trials)
- insulin resistance and lipid profile (in animal models)
- glycemic control (in both animal models and human trials)

The efficacy on long-term glycemic control and the amount of effects on HbA1c needs further investigations

Classification of products : Phase II

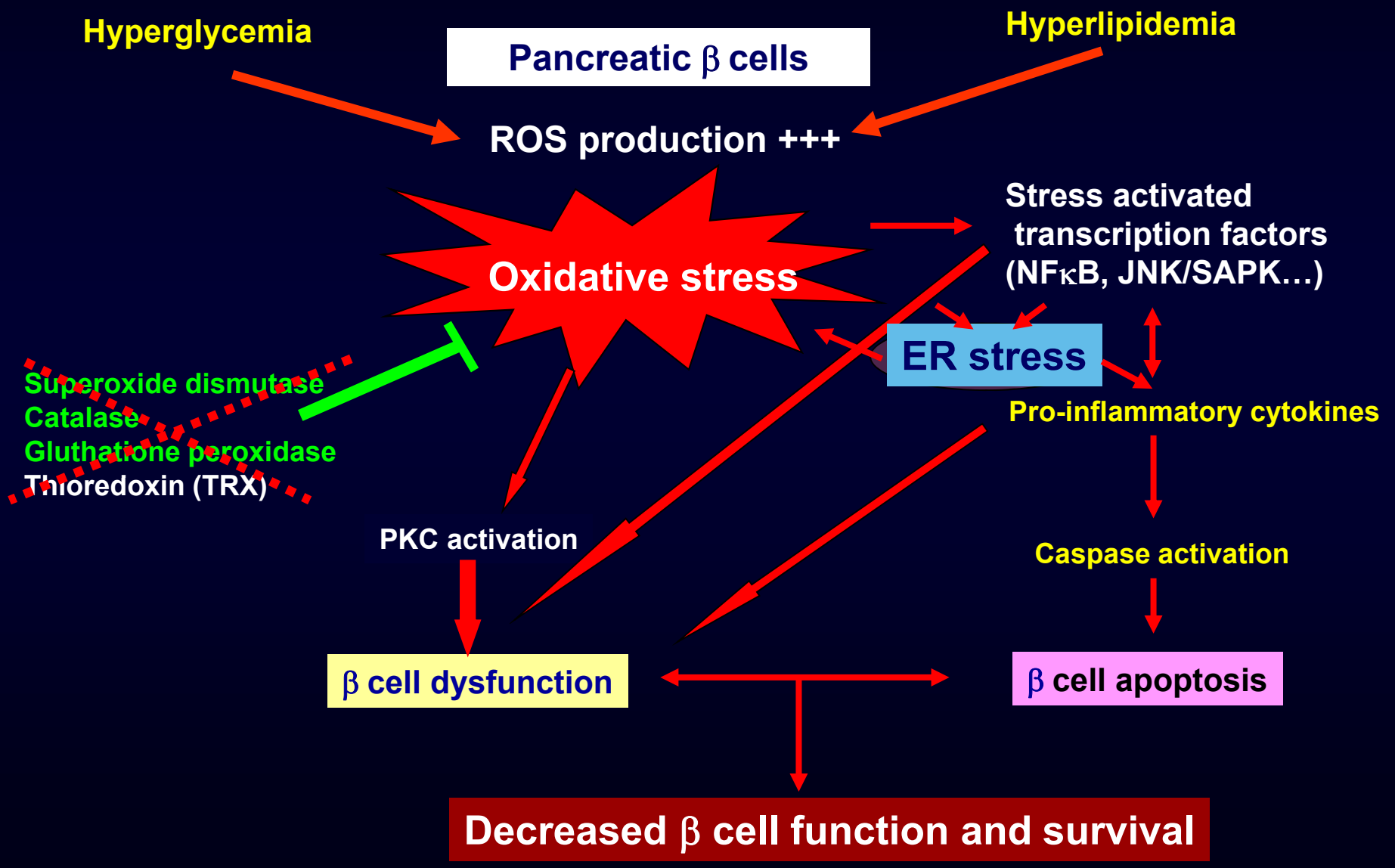
Origin	License	name	synonym	target(s)	
Eli Lilly		LY-2189102		Interleukin 1b antagonist	
Cytos Biotechnology		IL-1bQb	CYT-013-IL1bQb	Interleukin 1 Interleukin 1b antagonist	
Xoma		gevokizumab	XOMA-052	Interleukin 1b antagonist	
Amgen		AMG-108	anti-IL-1 Mab	Interleukin 1 receptor antagonist	

Classification of products : Phase I

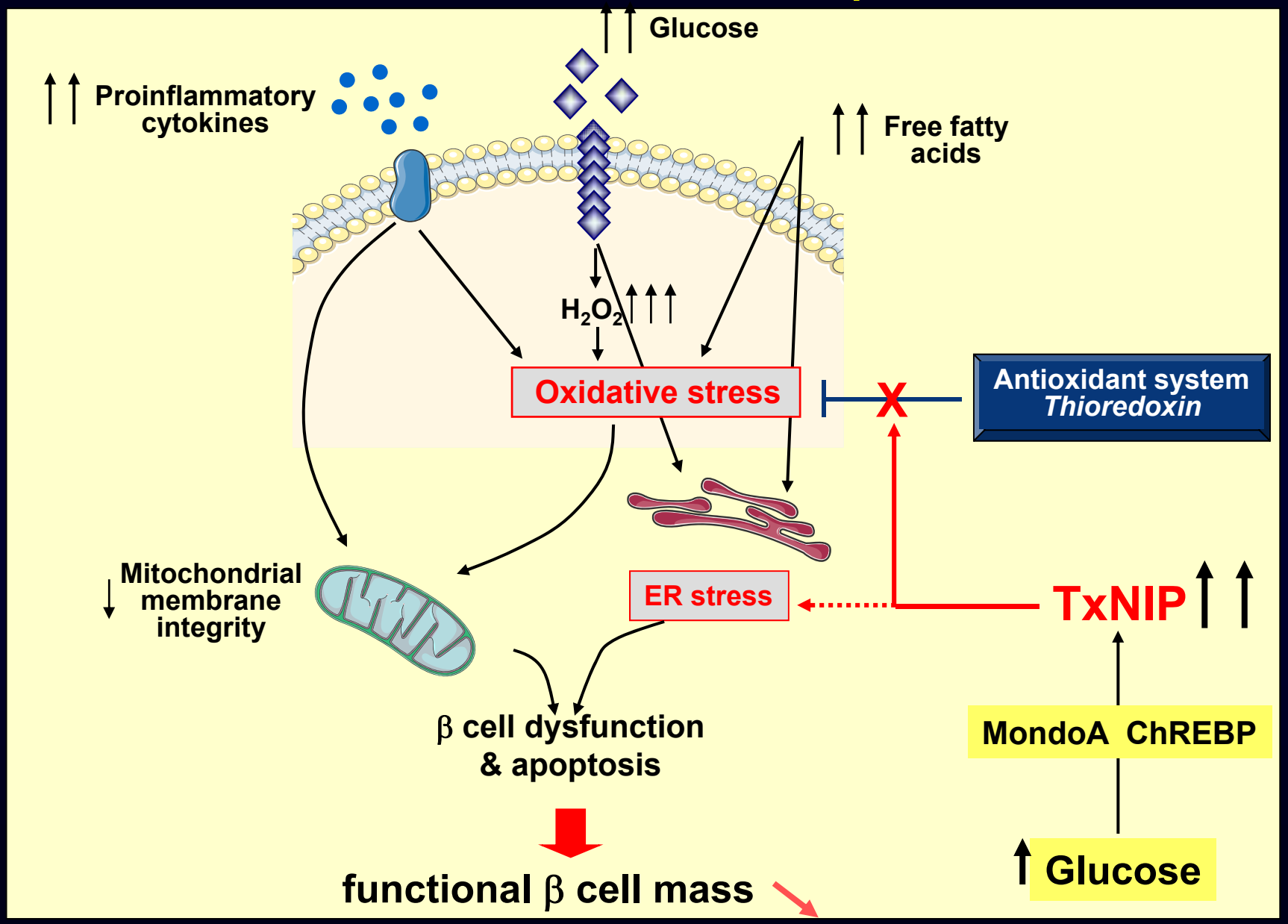
Origin	Name	Target
Merck & Co		GKA
Addex		Interleukin 1 receptor antagonist
Allostera	APG-101.10	Interleukin 1 receptor antagonist

INHIBITORS OF THIOREDOXIN-INTERACTING PROTEIN (TxNIP)

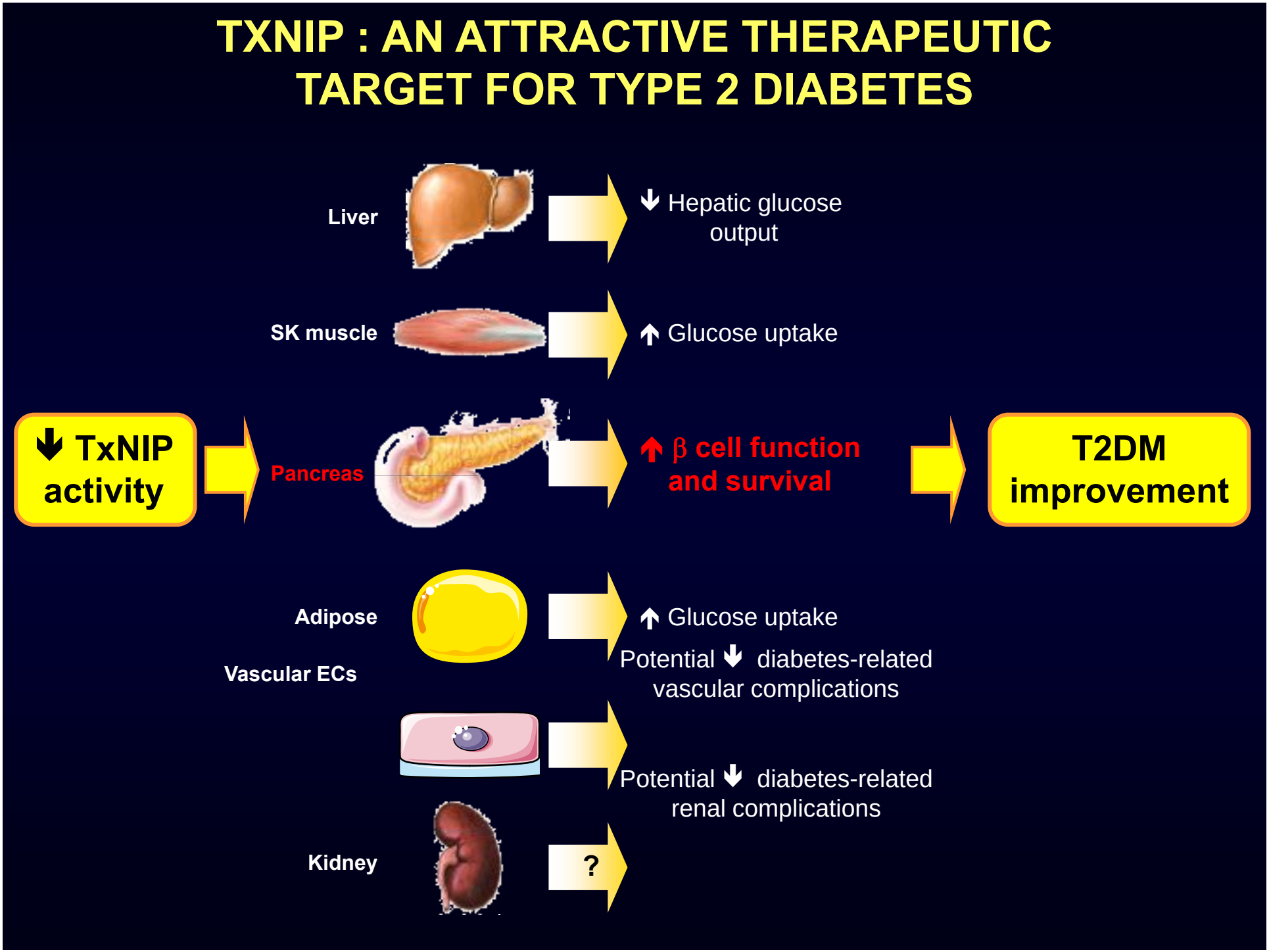
POSSIBLE MECHANISM OF DEFECTS IN CELLS SUBMITTED TO A METABOLIC STRESS



TXNIP: CRITICAL ROLE IN STRESS DISORDERS IN β CELLS



TXNIP : AN ATTRACTIVE THERAPEUTIC TARGET FOR TYPE 2 DIABETES



CONCLUSION

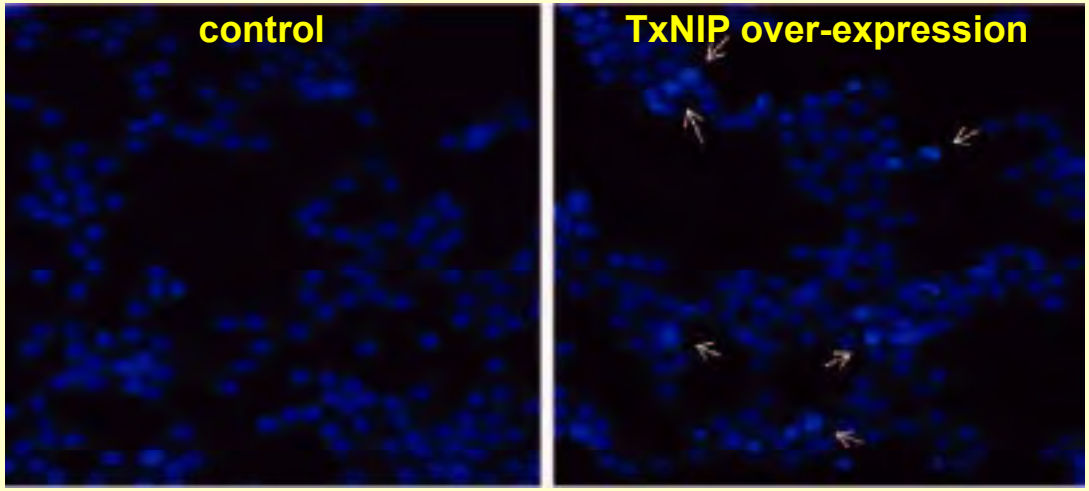
- Stopping the deterioration of glycemic control and preventing cardiovascular diseases related to type 2 diabetes are the most important challenges for new therapeutic approches for type 2 diabetes

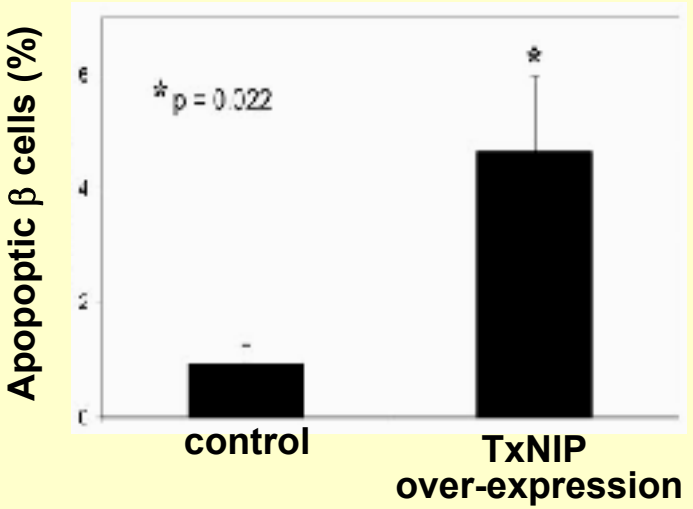
- Needs for a better understanding of the complex interplay between insulin resistance, altered lipid profile and β cell failure (alteration of the β cell micro and macro- environment)

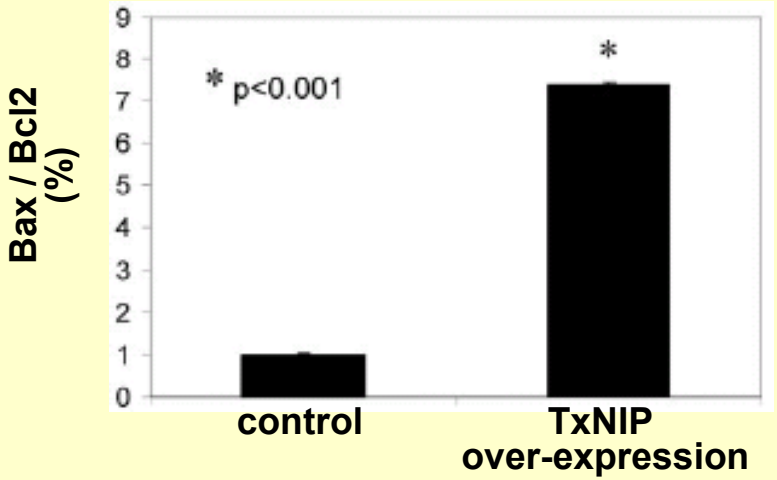
A better understanding of the pathophysiology of type 2 diabetes is needed more than ever

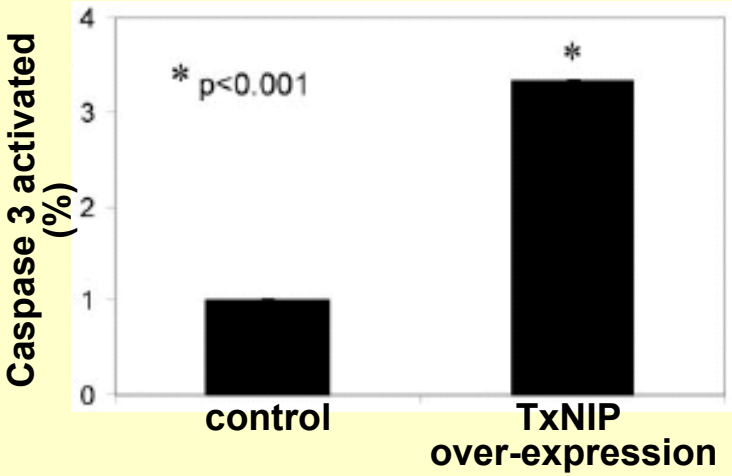
TxNIP over-expression induces β cell death by apoptosis

In vitro







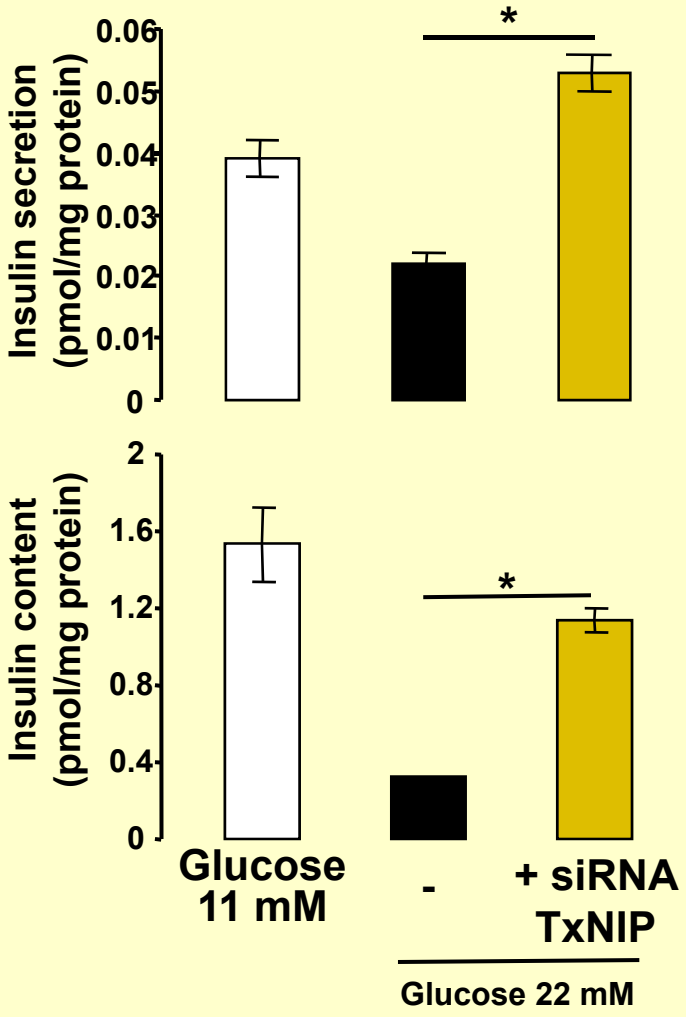


Minn et coll., Endocrinol., 2005

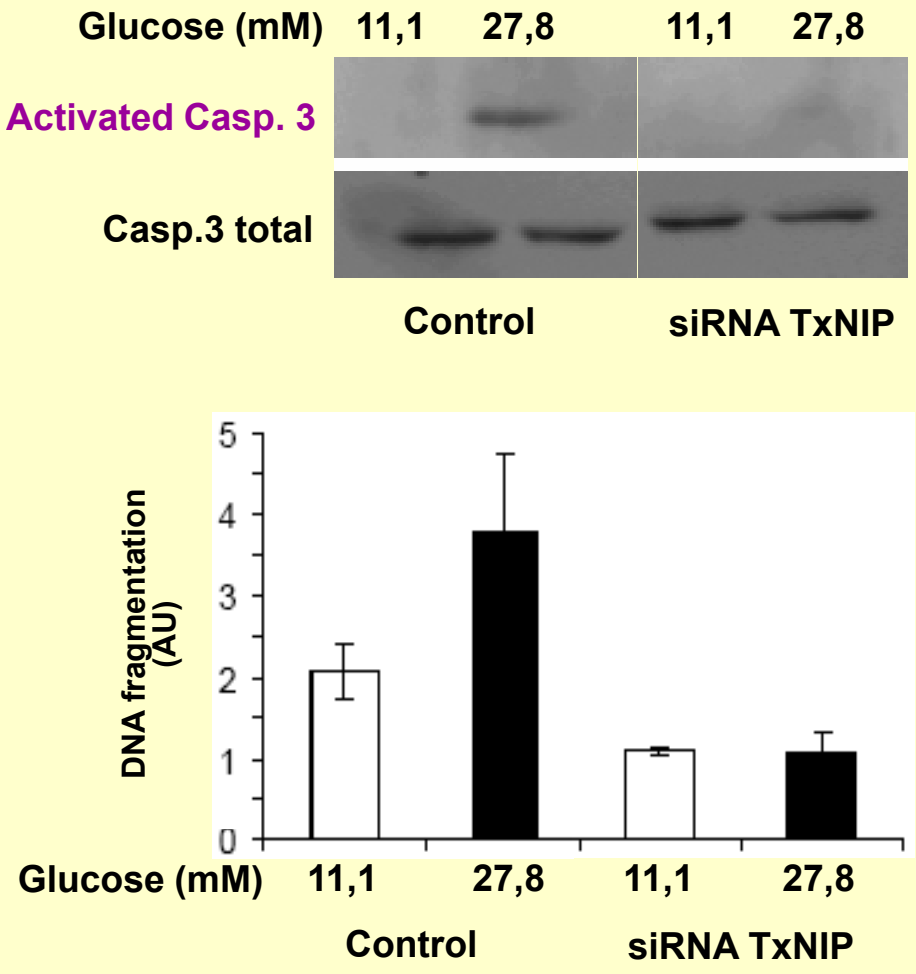
TxNIP down-regulation increases functional β cell mass

In vitro

Improvement of β cell function



Protection against apoptosis



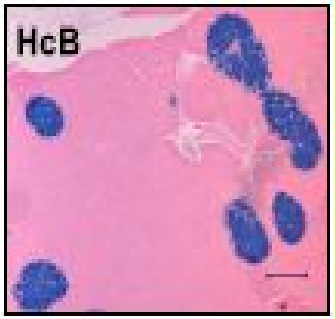
TxNIP deficiency induces an increase in β cell mass

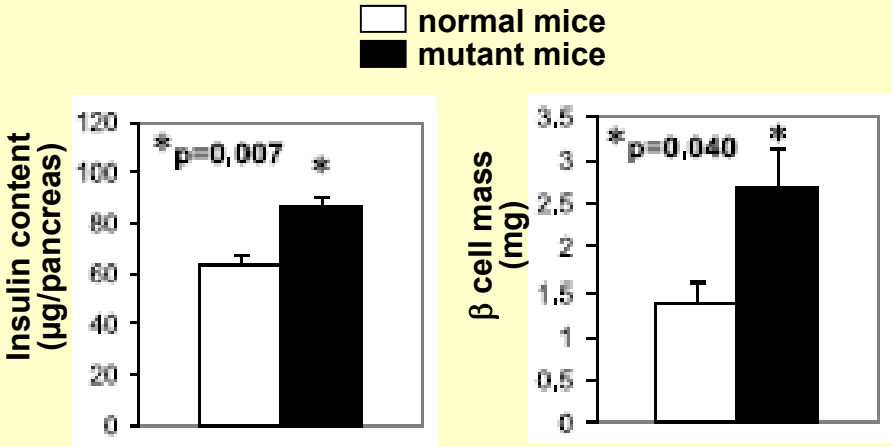
In vivo

Increase of β cell mass

Normal mice

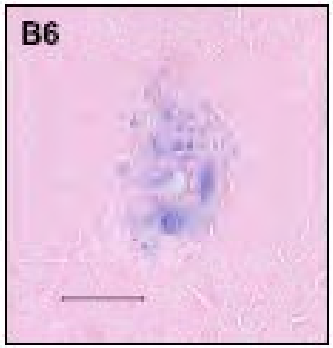
Mutant mice



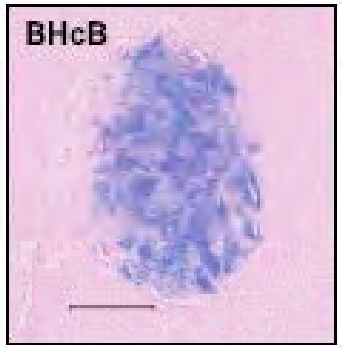


Protection *versus* a streptozotocin-induced diabetes

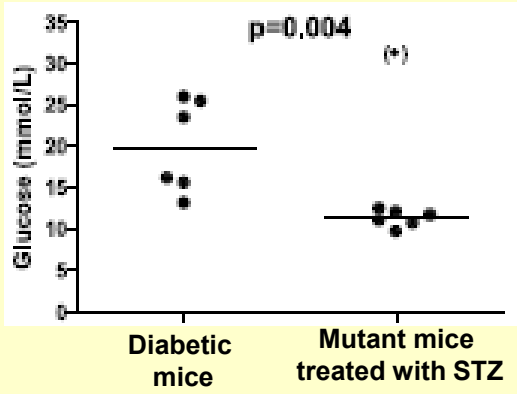
Diabetic mice



Mutant mice treated with STZ



Glycemia 18 days post-STZ



Hyperglycemia induces TxNIP up-regulation in pancreatic islets

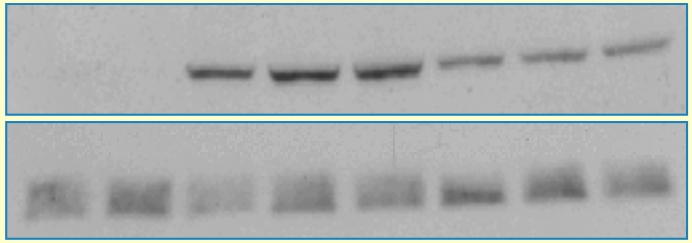
In vivo / in vitro

Psammomys obesus

in vivo

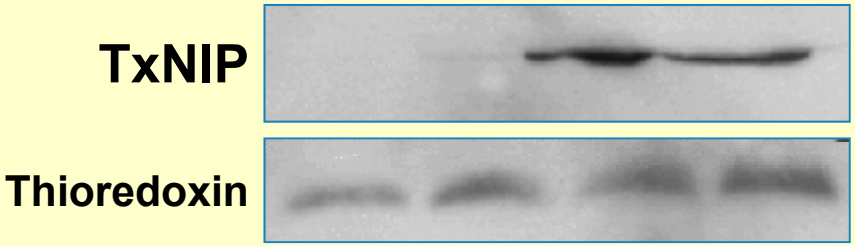
Non diabetic | T2DM

4 days | 2 weeks | 3 weeks



in vitro

Glucose 3,3 mM | Glucose 22,2 mM

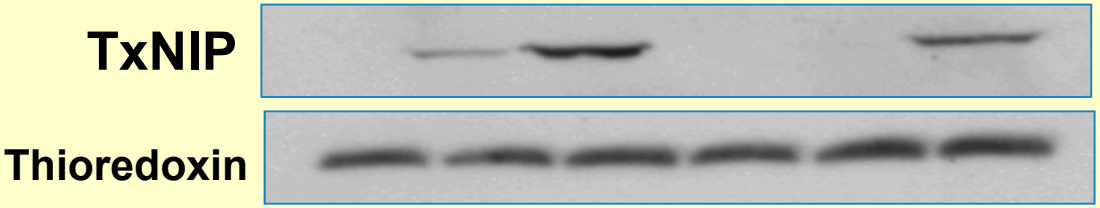


INS-1E cell line

2 days | 5 days

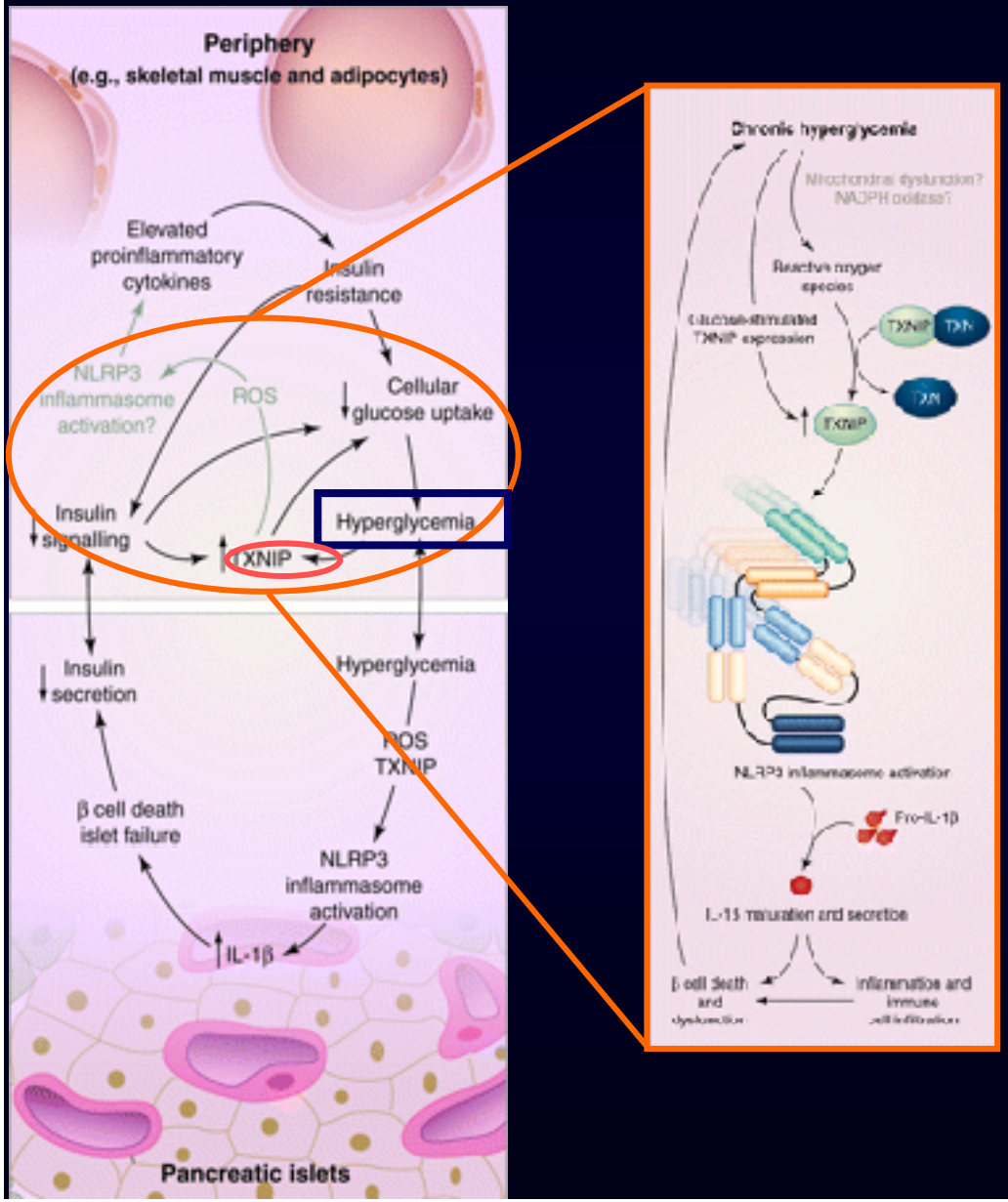
Glucose concentration

2,7 mM | 11,1 mM | 22,2 mM | 2,7 mM | 11,1 mM | 22,2 mM



TXNIP LINKS OXIDATIVE STRESS TO INFLAMMASOME ACTIVATION AND PANCREATIC β-CELL FAILURE IN T2D

ZHOU ET AL., NAT. IMMUNOL., FEVR 2010



- **Prolonged hyperglycemia increases ROS, which triggers TXNIP-dependent activation of the NLRP3 inflammasome and secretion of IL-1β.**
- **Elevated IL-1β causes β-cell death and dysfunction, exacerbating chronic hyperglycemia.**