Understanding diabetes pathogenesis: the need for systems biology

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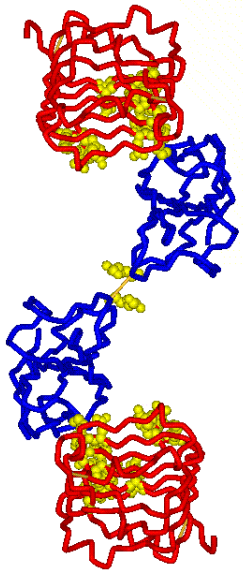
Novo Nordisk A/S



ICSB 2006

Yokohama October 8-13, 2006

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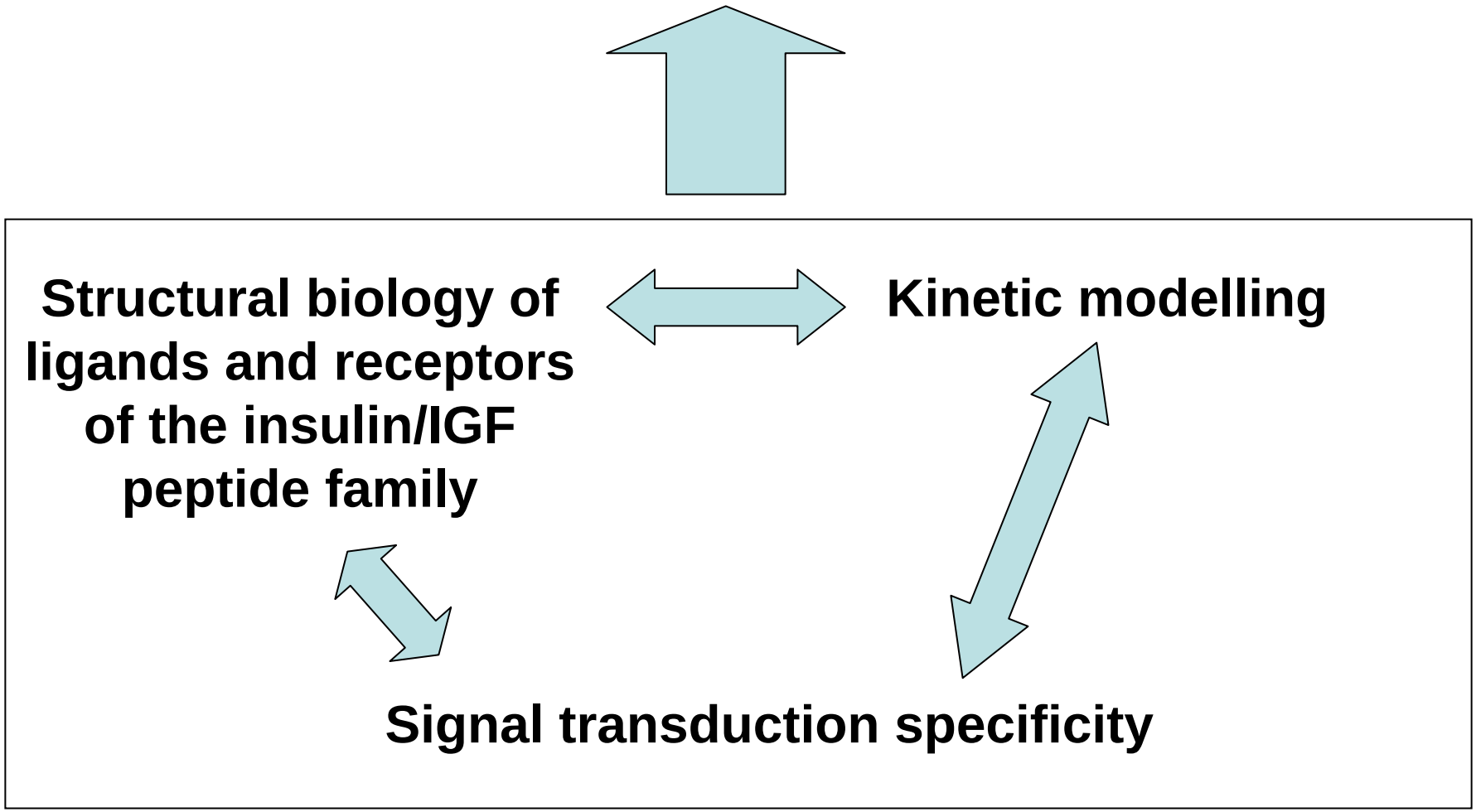
The Receptor Systems Biology Laboratory

Systems biology of diabetes



Theme of the talk:

Reductionist approaches have failed to provide an understanding of the pathogenesis of diabetes mellitus, methods to prevent it or cure it, and an adequate pipeline of drugs to treat it optimally.

A systems biology approach is warranted.

What is systems biology?

A scientific discipline that endeavours to quantify all the molecular elements of a biological system to assess their interactions and to integrate that information into models that explain and predict emergent behaviours that cannot be understood by looking at the properties of the individual components of the system.

Disease like diabetes mellitus

Candidate genes

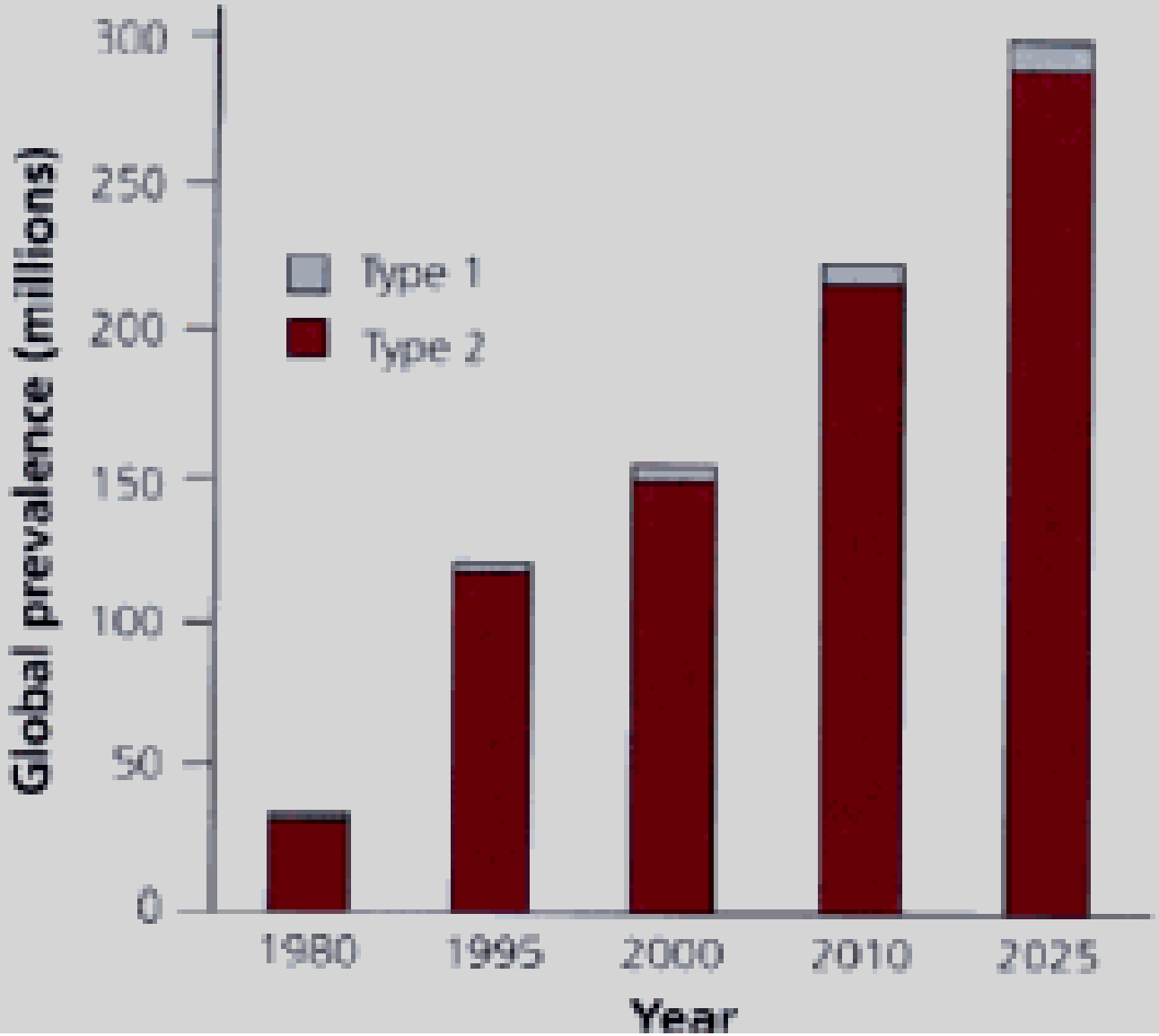
Traditional thinking about diabetes

- Find ”the” cause
- Find ”the” cure

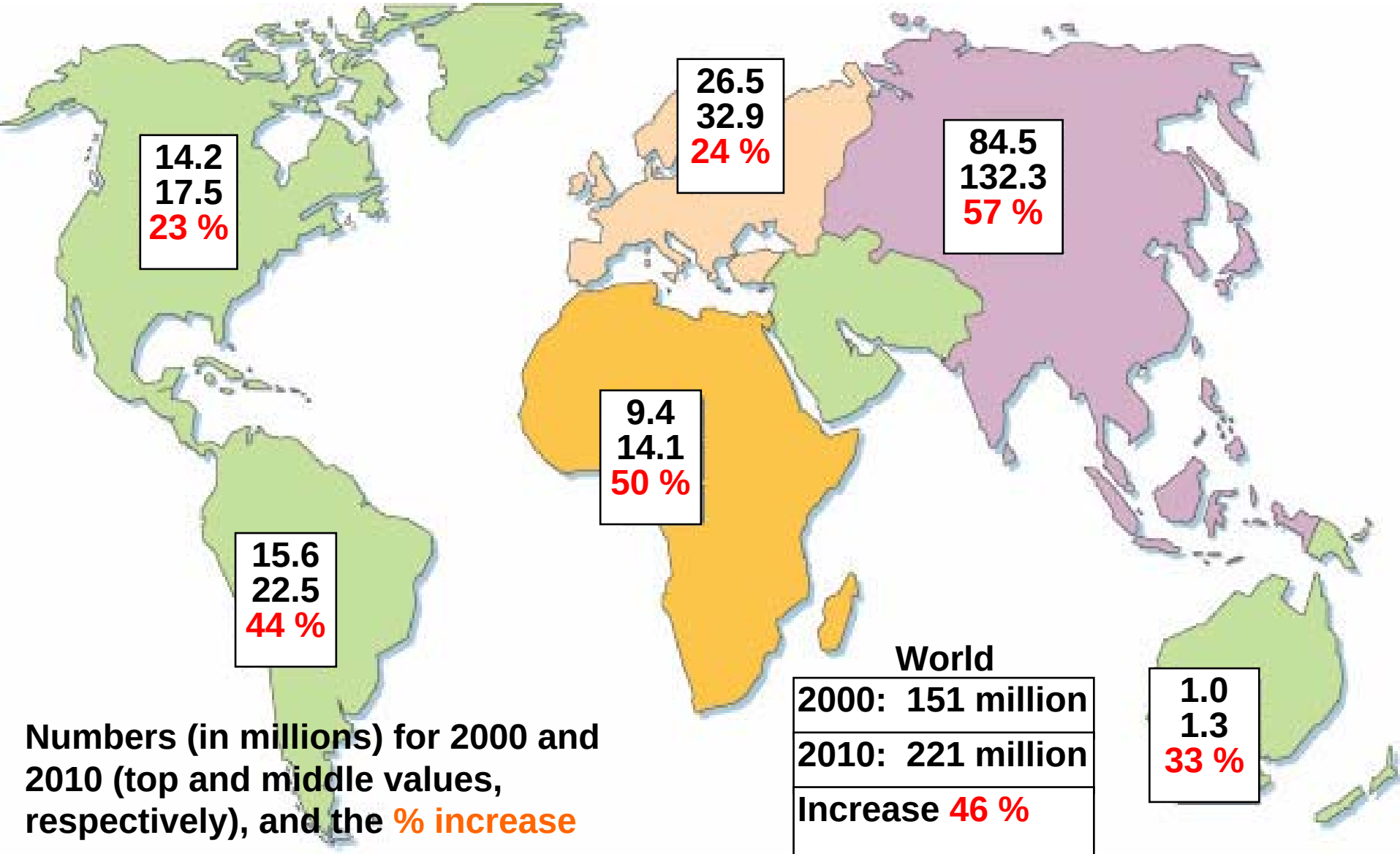
Current status

- Pathogenesis unknown
- Few drugs
- No cure
- No prediction
- No prevention
- Type 2 diabetes epidemics

Estimated global prevalence of type 1 and type 2 diabetes



Diabetes - a world epidemics



Numbers (in millions) for 2000 and 2010 (top and middle values, respectively), and the % increase

World
2000: 151 million
2010: 221 million
Increase 46 %

Zimmet P et al., *Nature* 2001;414:782-787

You don’t need to be a systems biologist to understand why…

The Lancet, 19 May 2001


Zur falschen Zeit am falschen Ort im falschen Job?

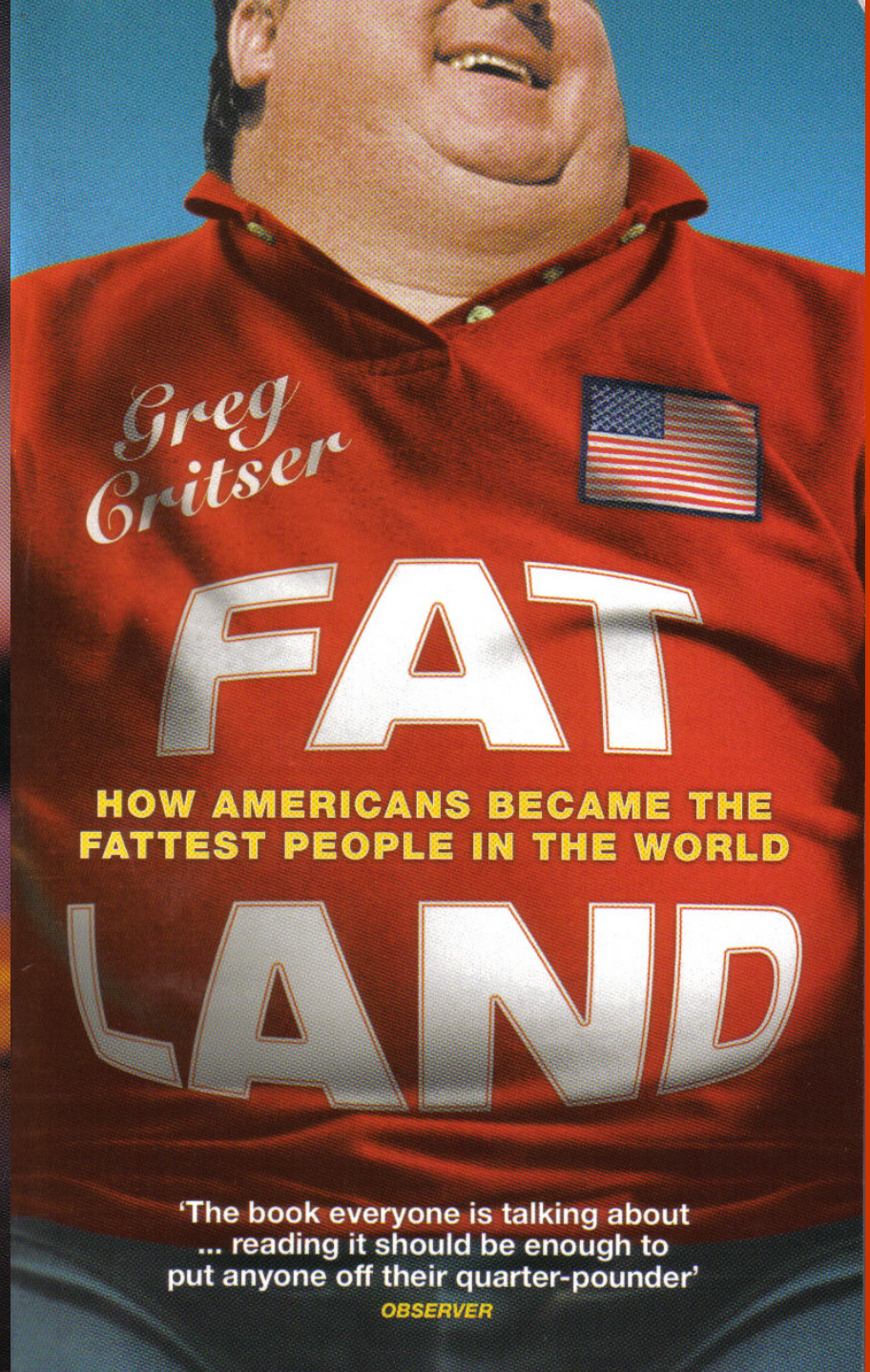

DRINK
Coca-Cola
IN BOTTLES
10 CENTS

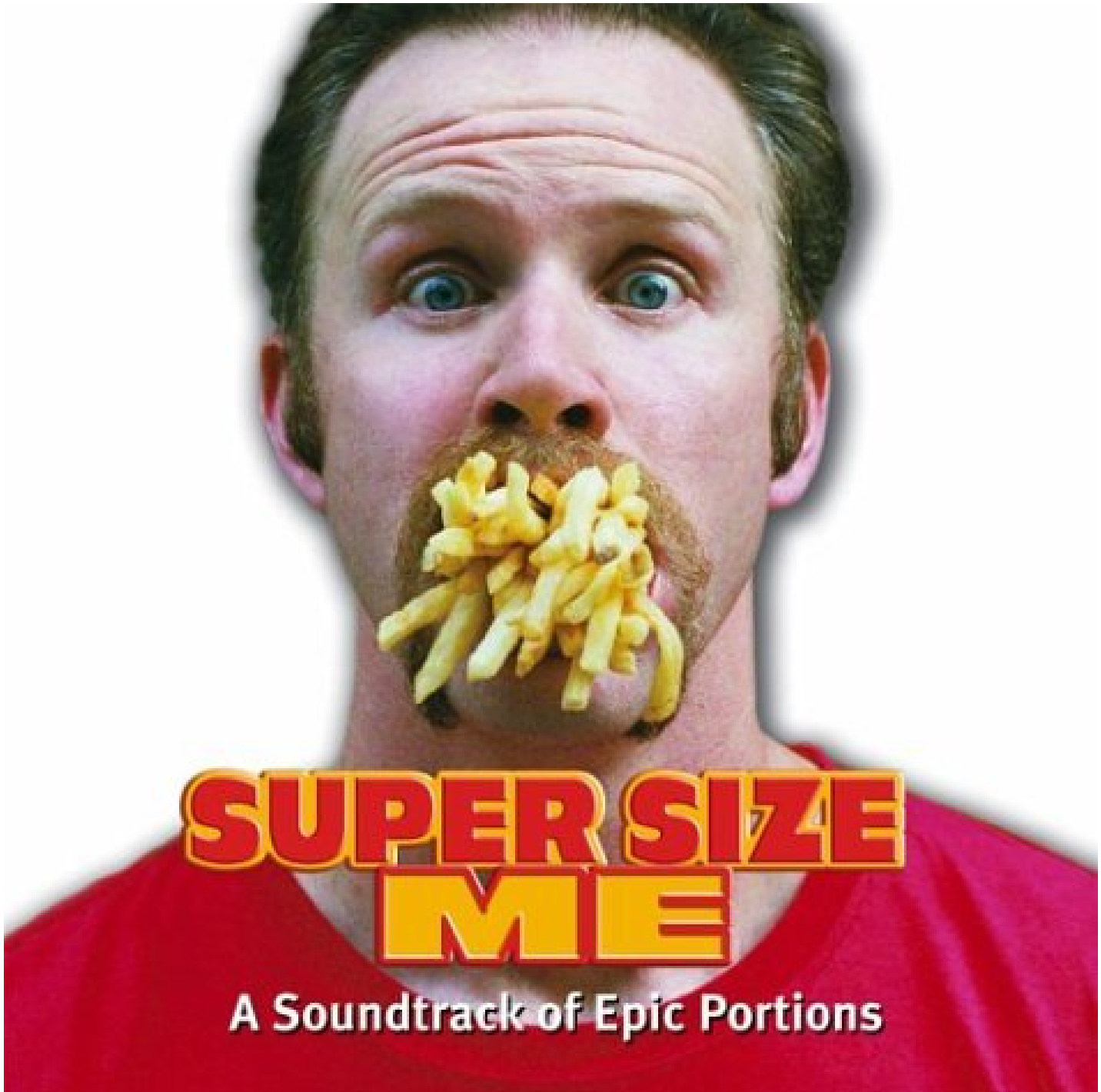
McDonald's
McDonald's 2001
Annual Meeting


KFC
Welcome

BURGER
KING
TM

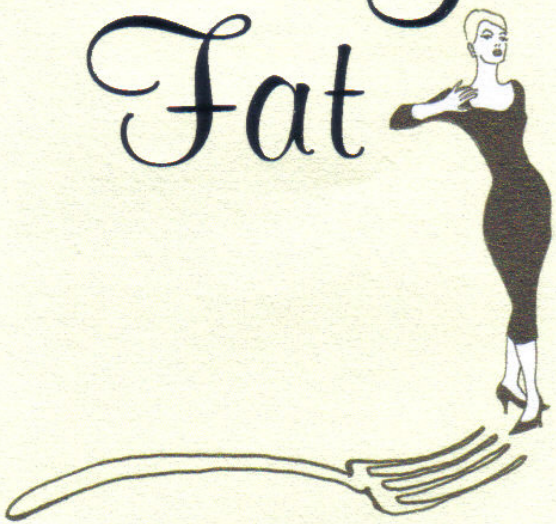

Fast Food
NATION
Eric Schlosser
The Dark Side of the All-American Meal


Greg Critser
FAT
HOW AMERICANS BECAME THE FATTEST PEOPLE IN THE WORLD
LAND
'The book everyone is talking about ... reading it should be enough to put anyone off their quarter-pounder'
OBSERVER


SUPER SIZE
ME
A Soundtrack of Epic Portions

Mireille Guiliano

French Women Don't Get Fat



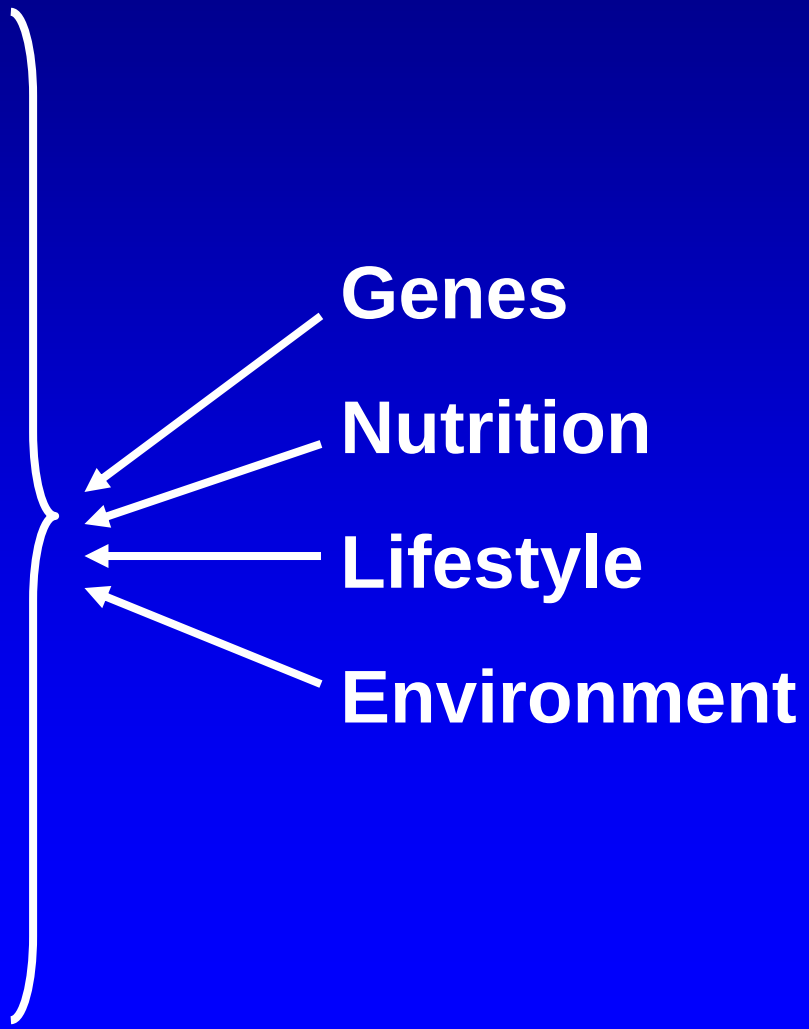
The Secret of Eating for Pleasure

Exercise!

What causes type 2 diabetes?

The beta cells do not produce enough insulin

The target cells (muscle, fat, liver) do not respond well to insulin



Conventional wisdom regarding the respective roles of insulin resistance and beta cell function in type 2 diabetes

DIABETOGENES → INSULIN RESISTANCE

DIABETOGENES → β-CELL FUNCTION

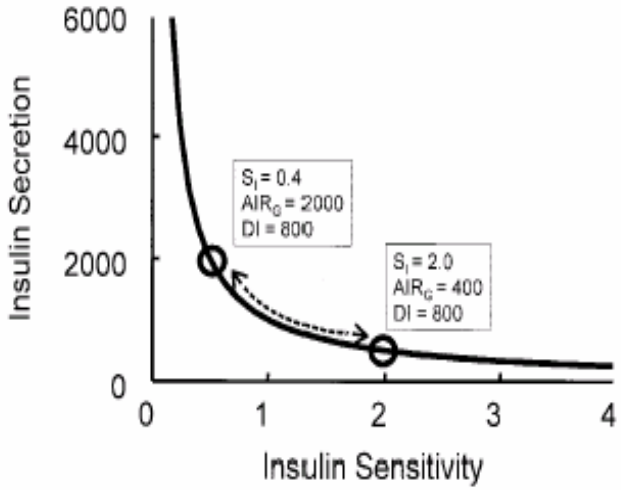


FIG. 1. The hyperbolic sensitivity/secretion curve. It is envisioned that, in the course of environmentally induced reductions in insulin sensitivity, "normal" pancreatic islets would respond by upregulation of the β-cells' sensitivity to glucose. In the example shown, individuals with an S_I of 2.0×10^{-5} min^{-1} per pmol/l and first-phase insulin response (AIR_G) of 400 pmol/l would have a disposition index [defined as the product ($S_I \times AIR_G$)] of 800. Reduction in insulin sensitivity (for example, to 0.4×10^{-5} min^{-1} per pmol/l) would result in upregulation of AIR_G to 2,000 pmol/l, with the DI remaining constant at 800. Reduction in insulin sensitivity may be due to one of several factors, including pregnancy, increased adiposity, and puberty.

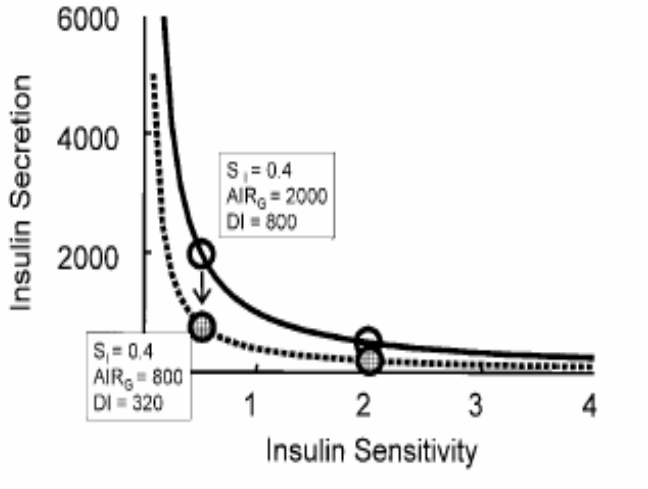
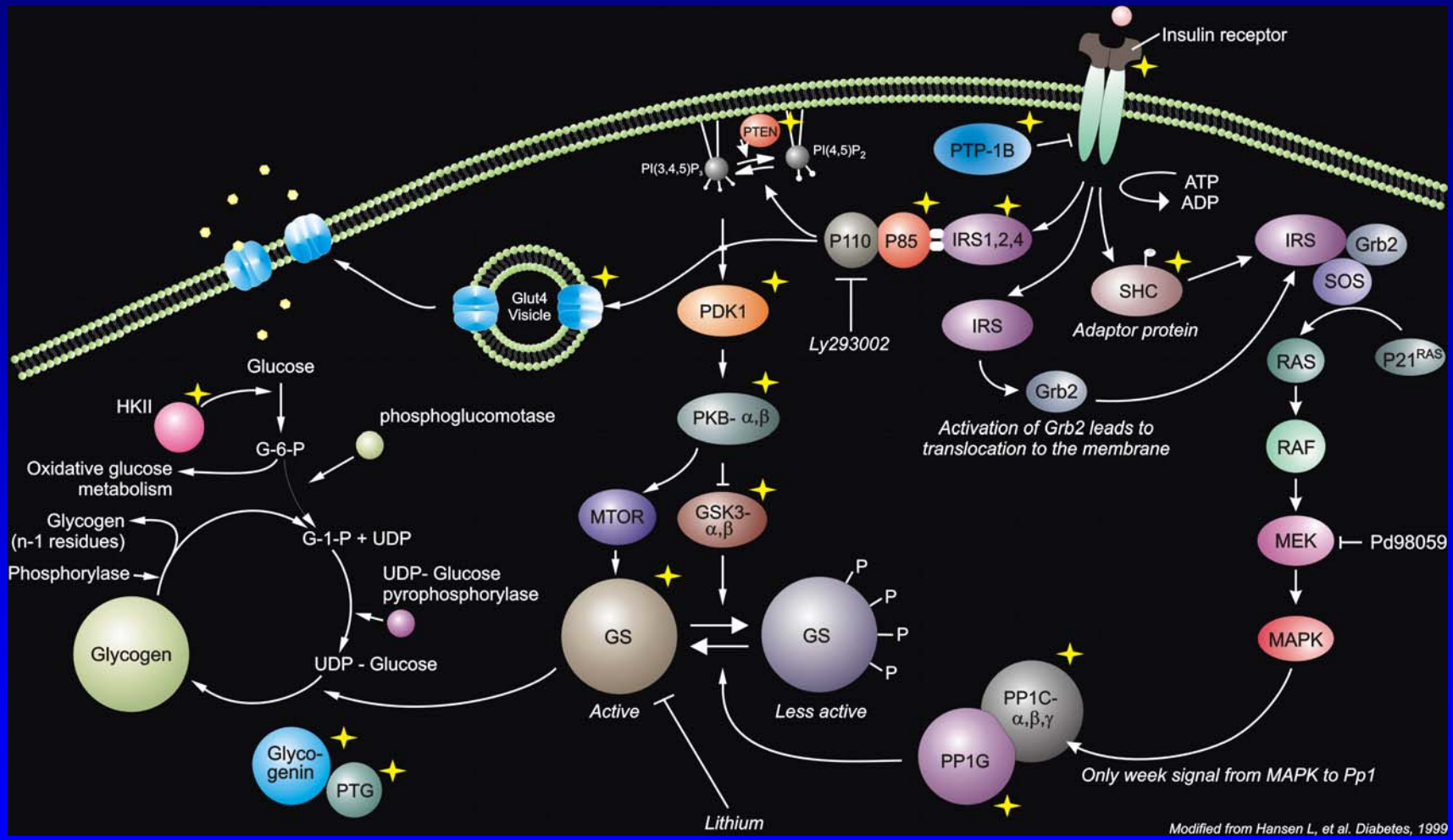


FIG. 2. Curves of "normal" individuals (○) versus individuals with a β-cell defect (⊕). Note that at elevated insulin sensitivity (S_I ~2.0×10^{-5} min^{-1} per pmol/l), it would be difficult to detect differences in insulin response, as the AIR_G is relatively low due to the minimal stress on the β-cells. When insulin resistance is present (S_I = 0.4), there is a clearer differentiation between AIR_G values, making it easier to differentiate β-cell function in individuals of similar reduced insulin resistance (14).

by insulin resistance. Under resistant conditions (e.g., S_I = 0.4×10^{-5} min^{-1} per pmol/l), the difference between

The signal transduction defect(s) in type 2 diabetes: understanding the combinatorial nature of signalling

Screening for candidate type 2 diabetogenes affecting insulin signal transduction

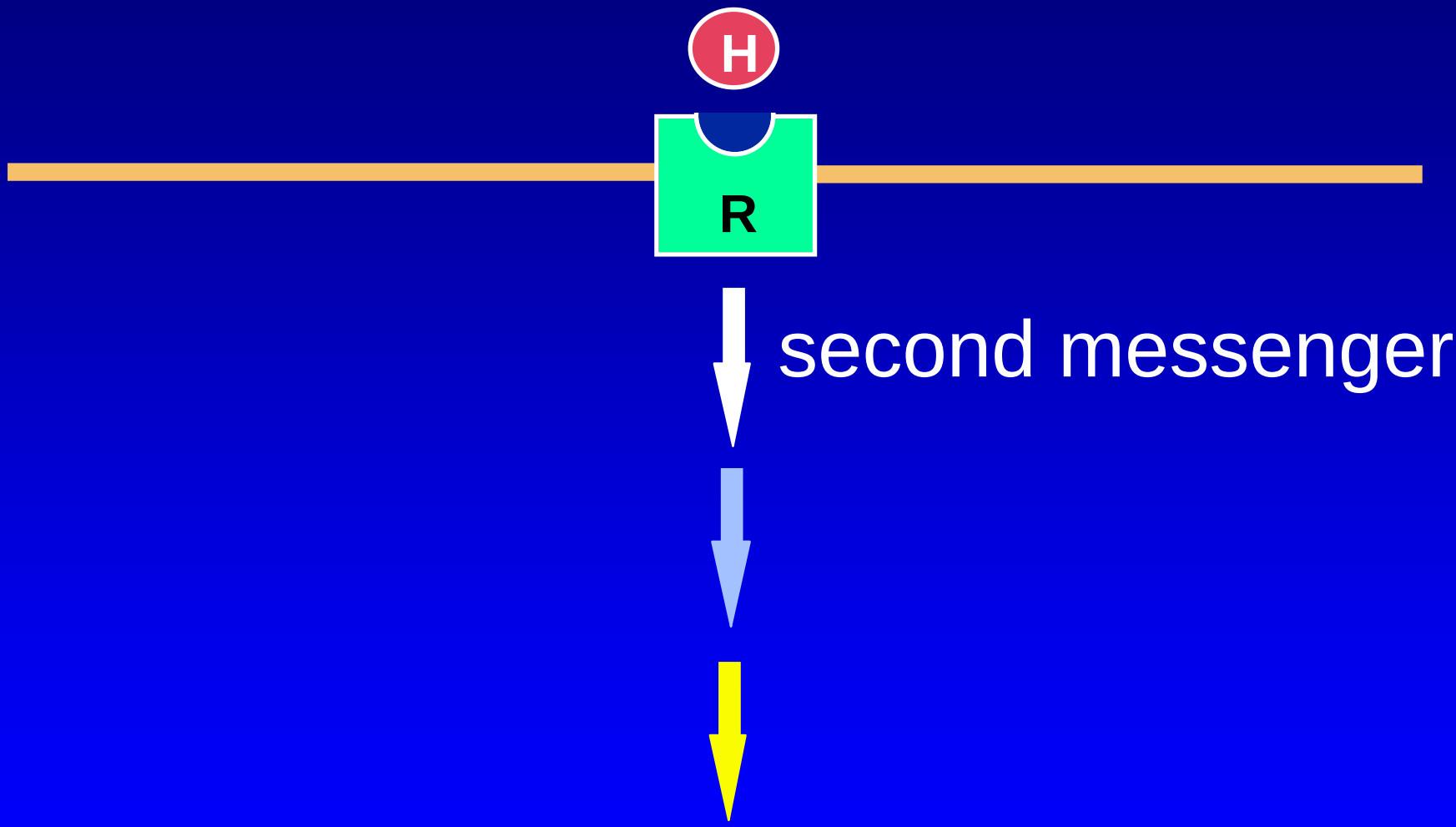


Picture from Jan Nygaard Jensen and Oluf B. Pedersen, Steno Diabetes Center, Gentofte, Denmark

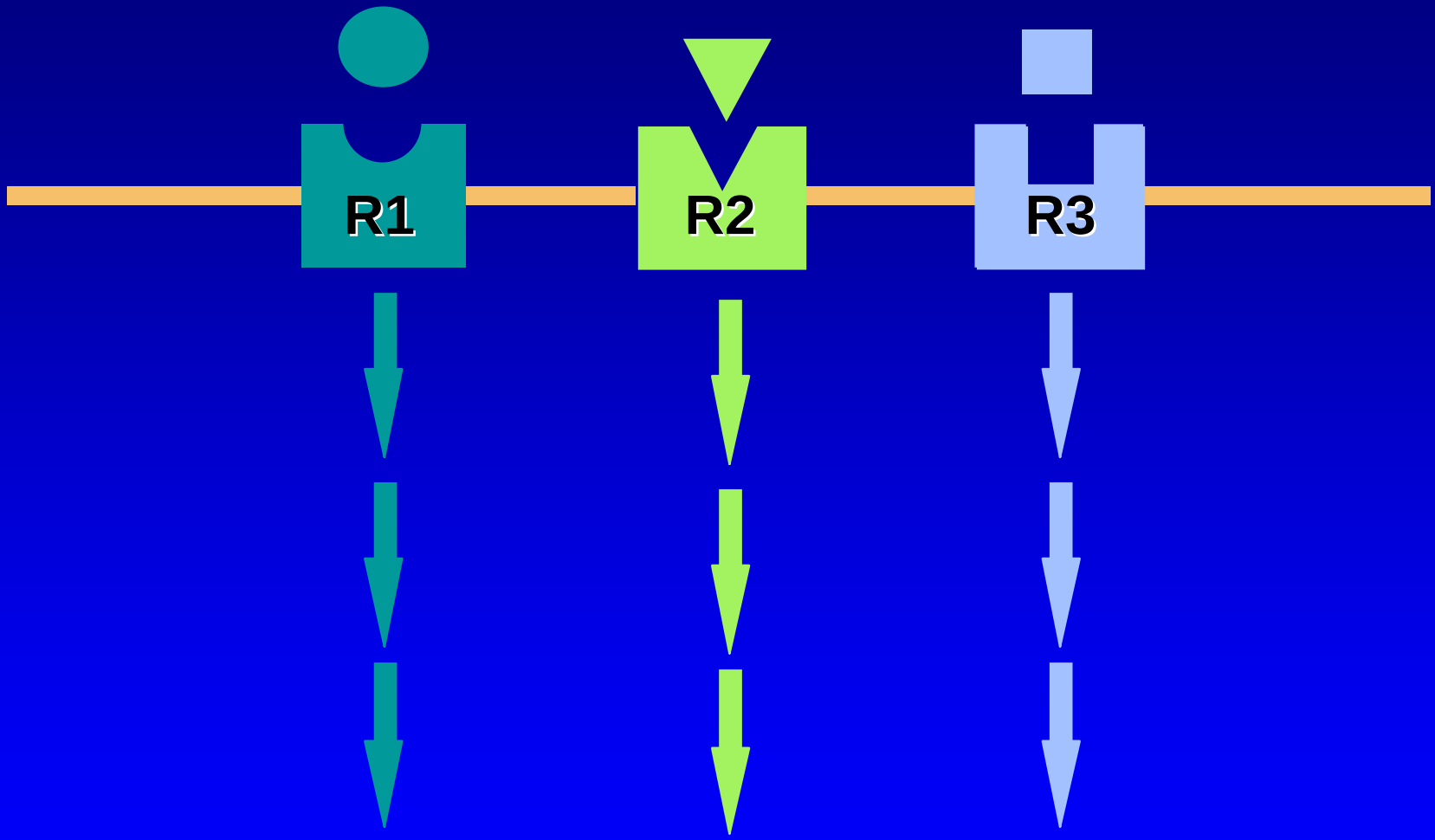
Systems biology of signal transduction:

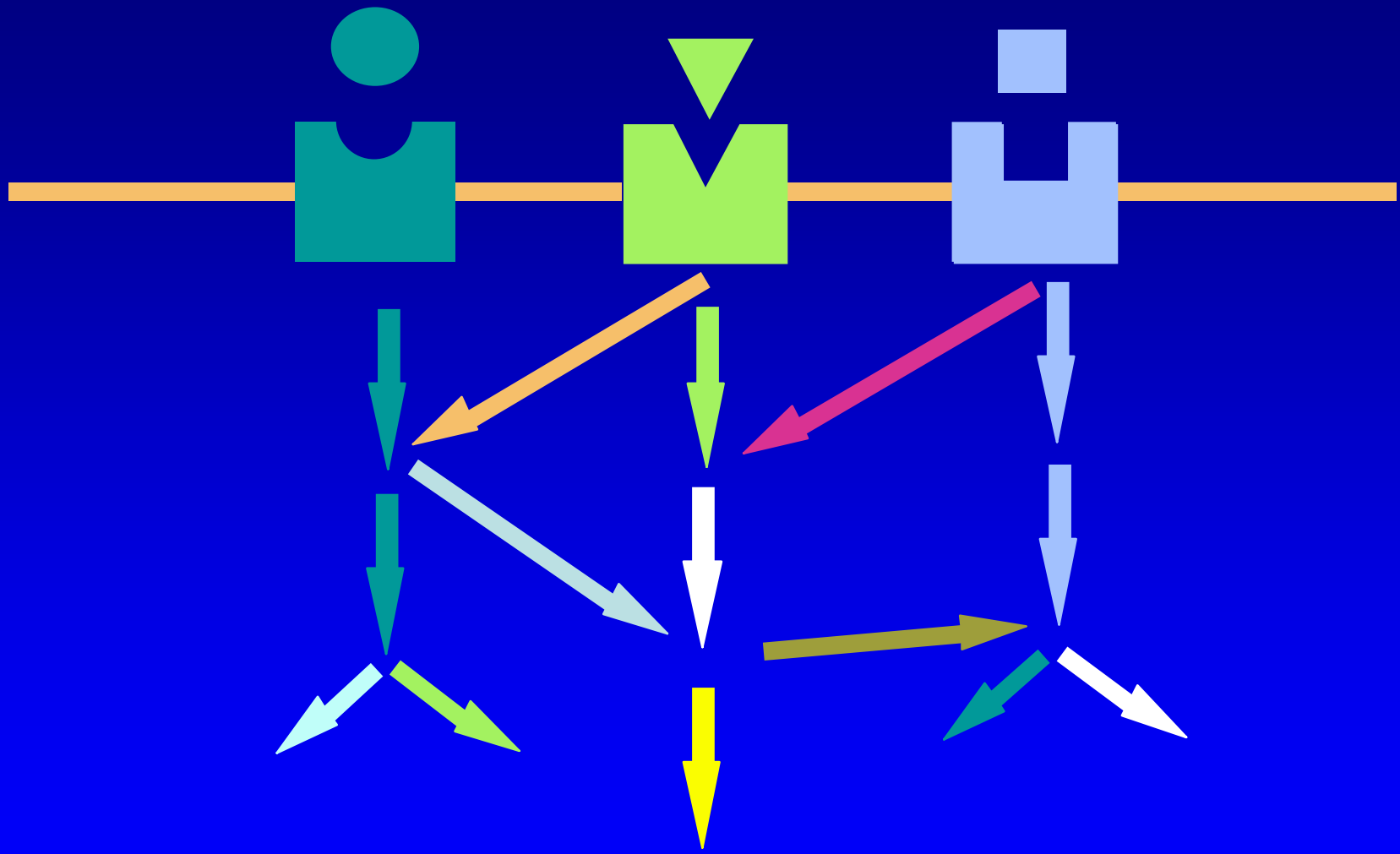
From linear thinking to four-dimensional thinking

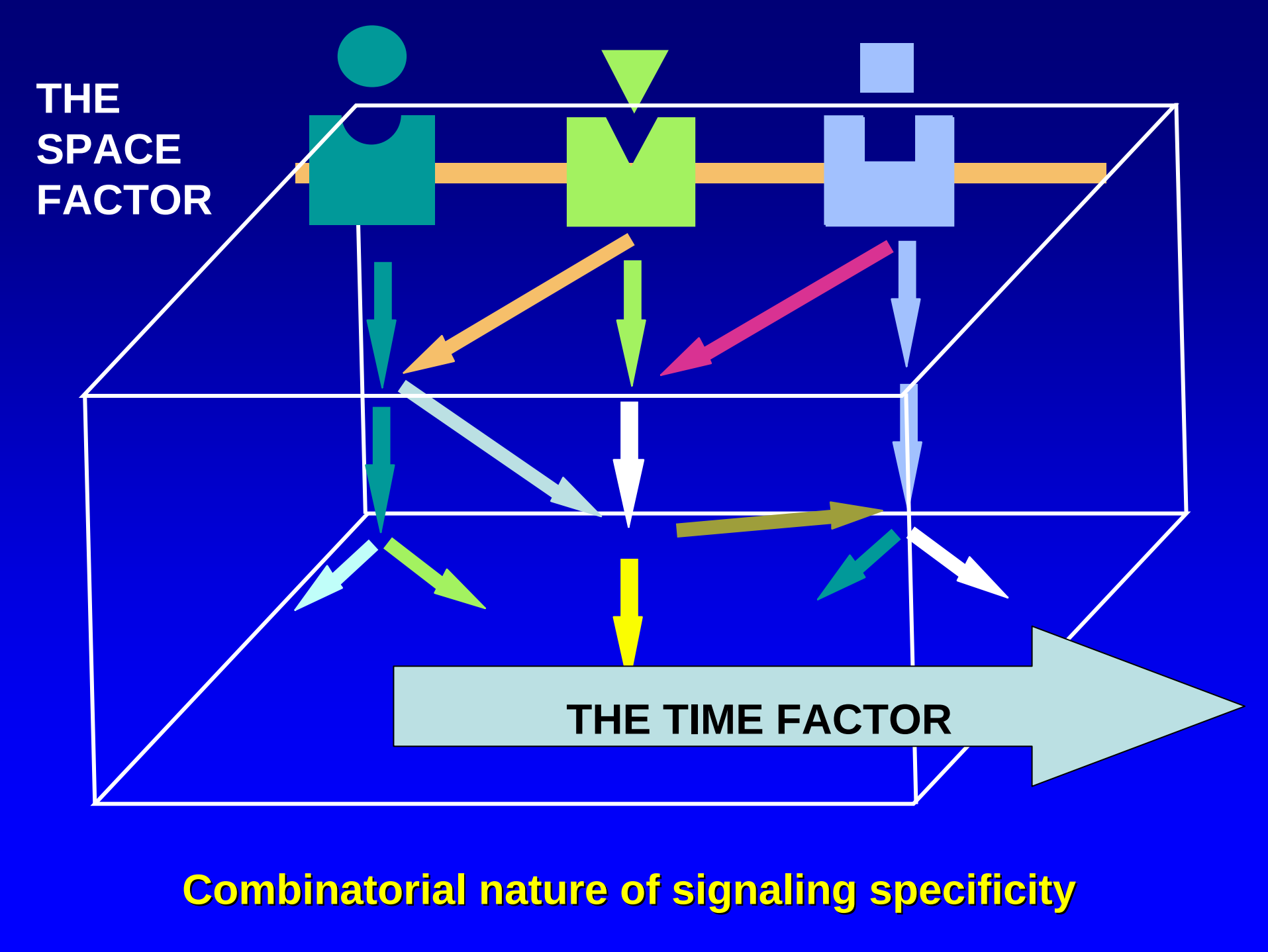
Signal transduction in the 60's



Earl Sutherland, Nobel laureate 1971

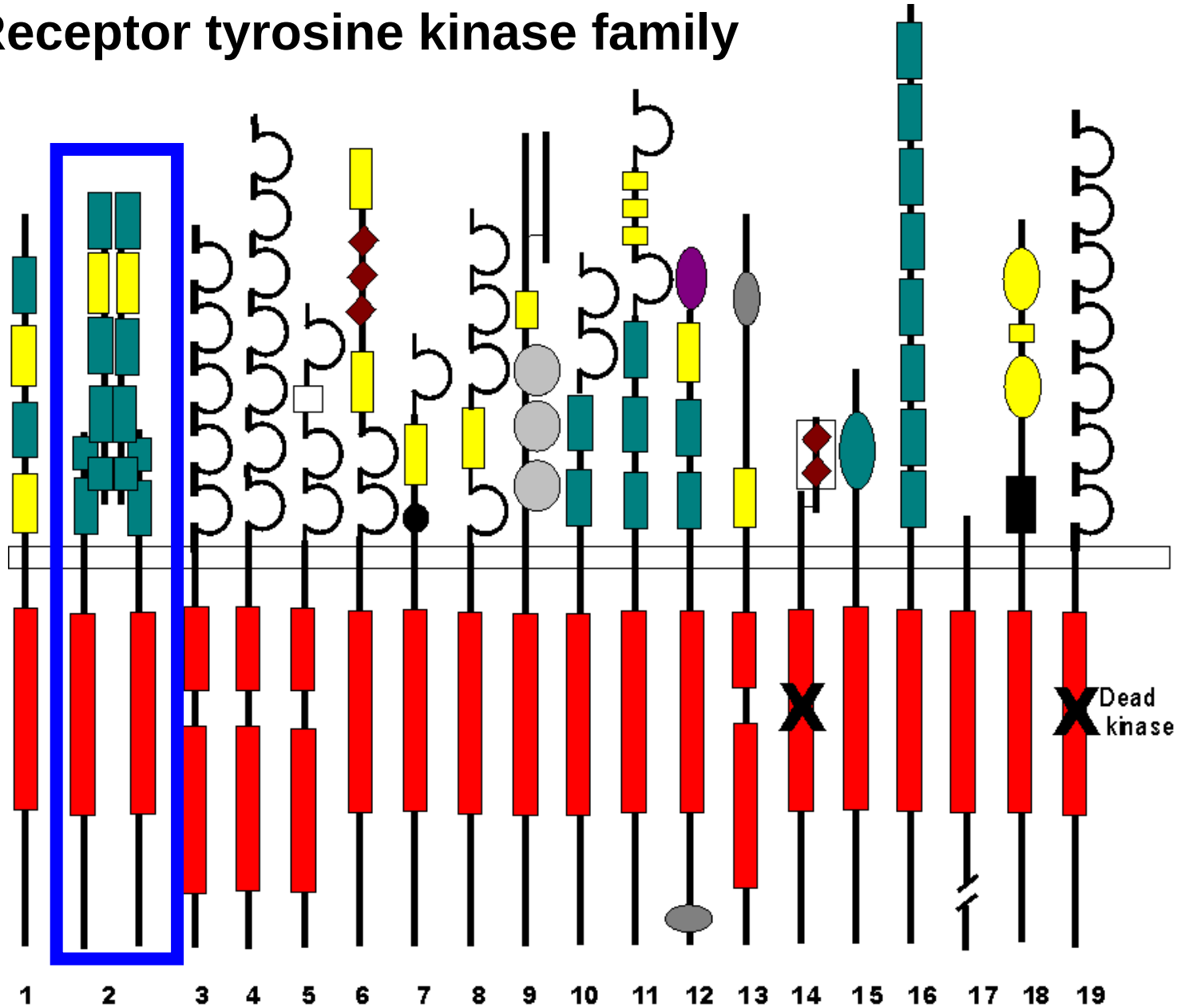

R1
R2
R3

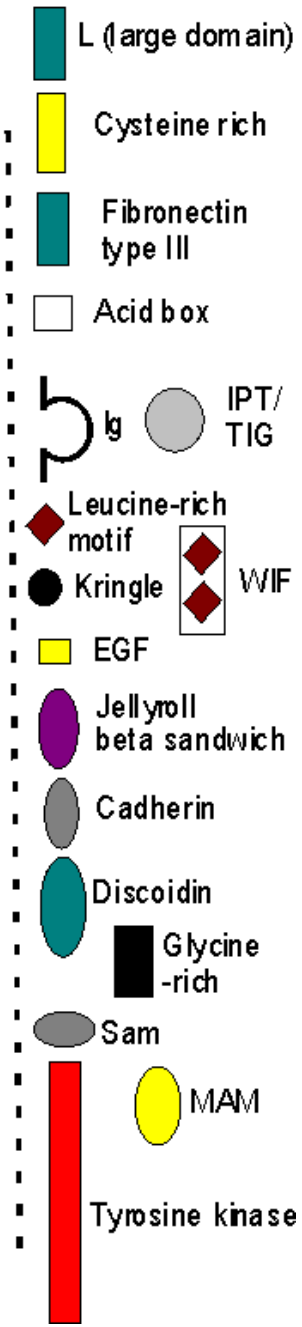




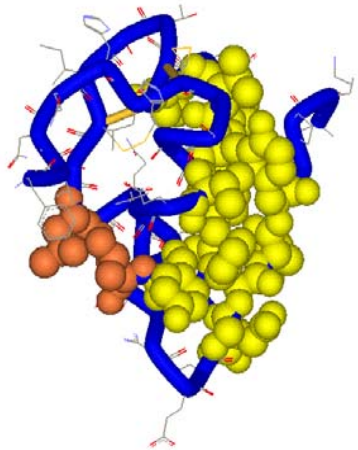
Combinatorial nature of signaling specificity

Receptor tyrosine kinase family

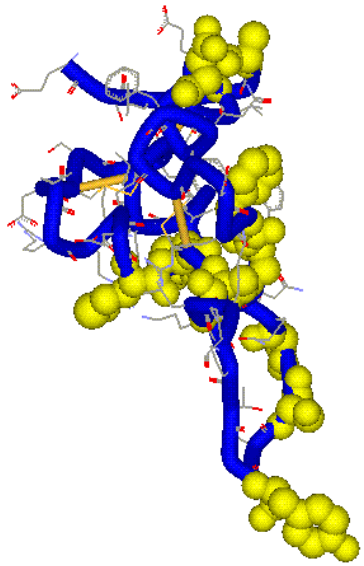




Gray SG and De Meyts P, Horm Metab Res 35:857-871 (2003)

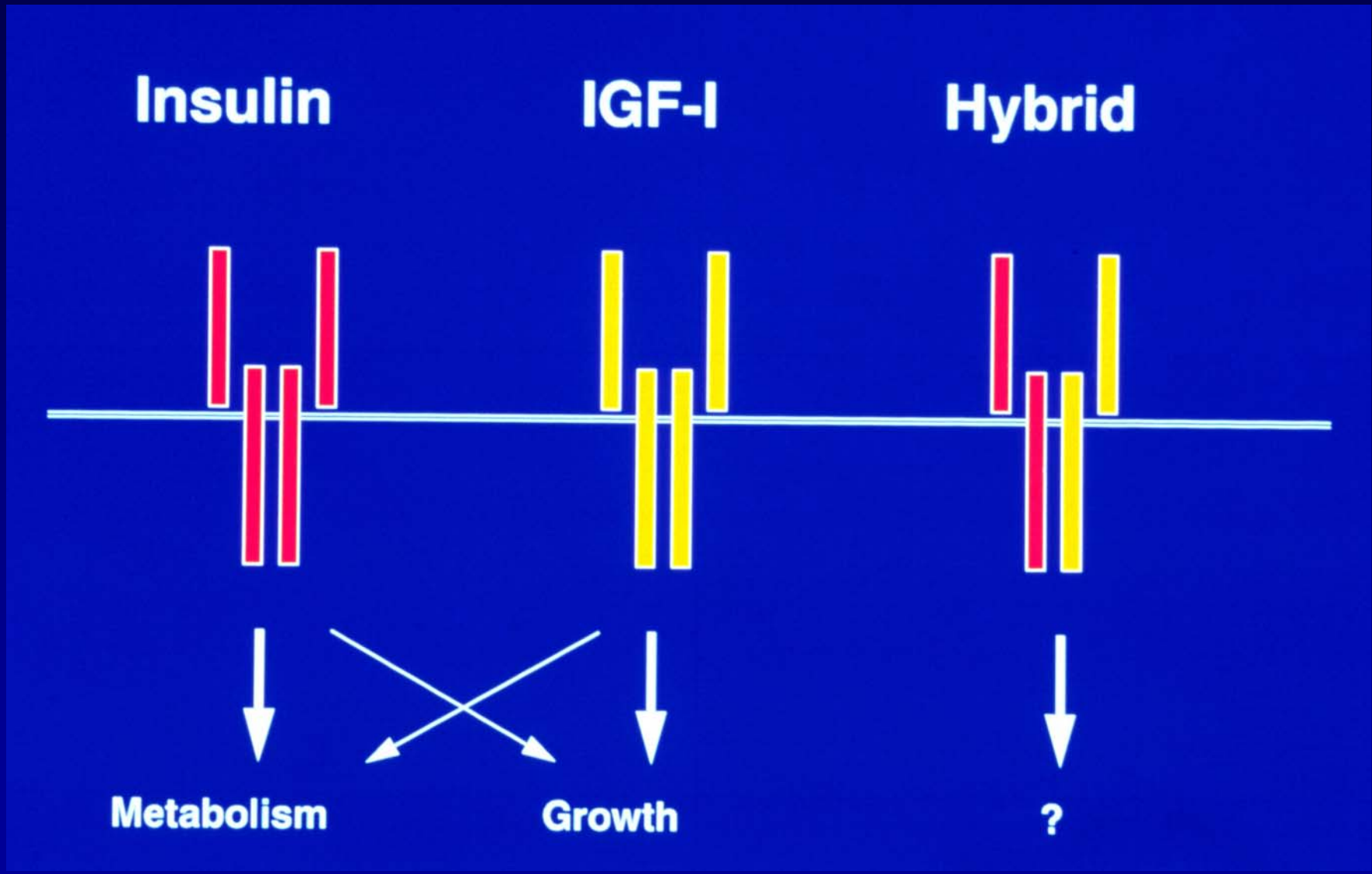


Insulin



IGF-I

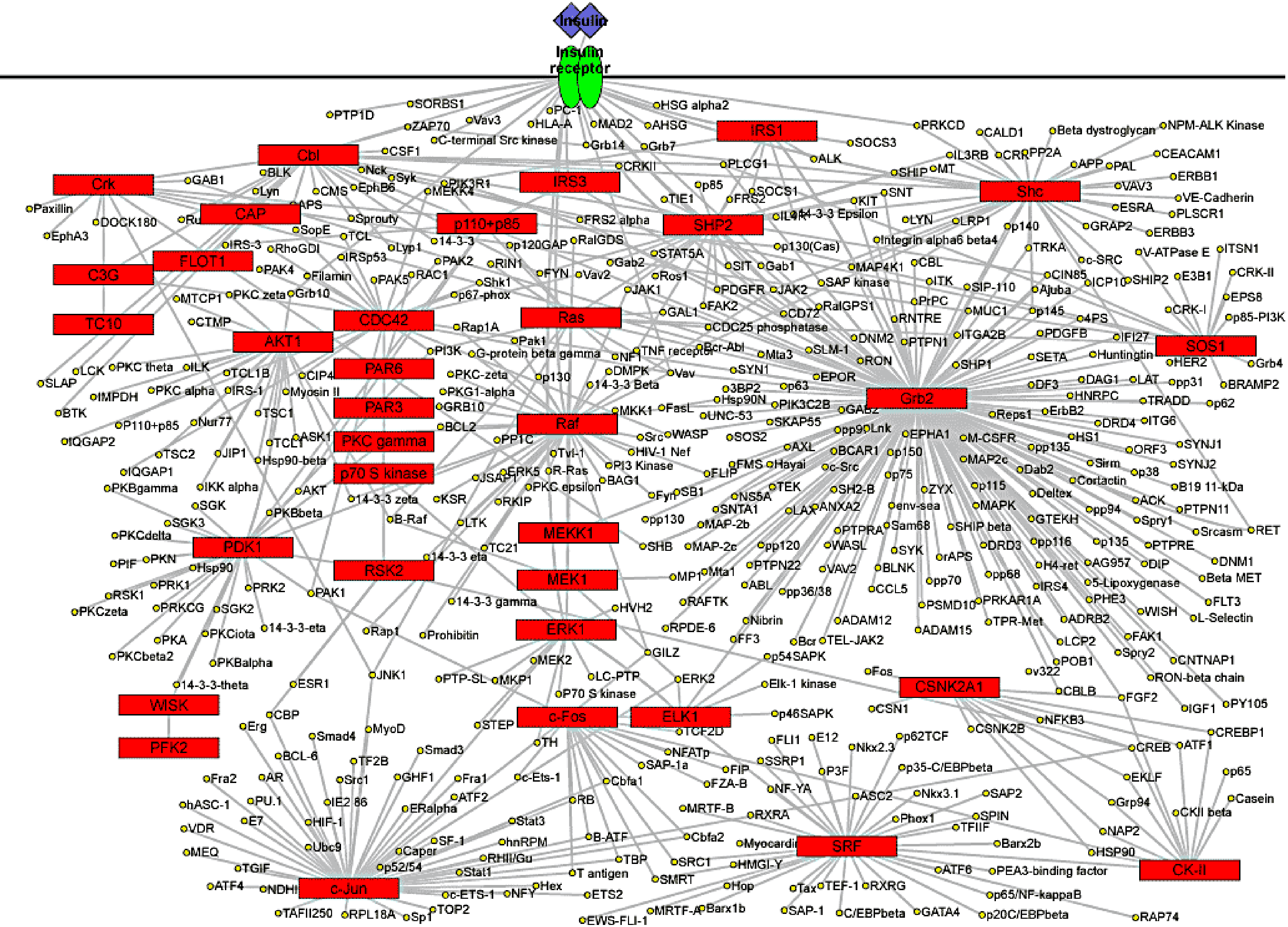
Conventional wisdom on insulin vs IGF-I actions



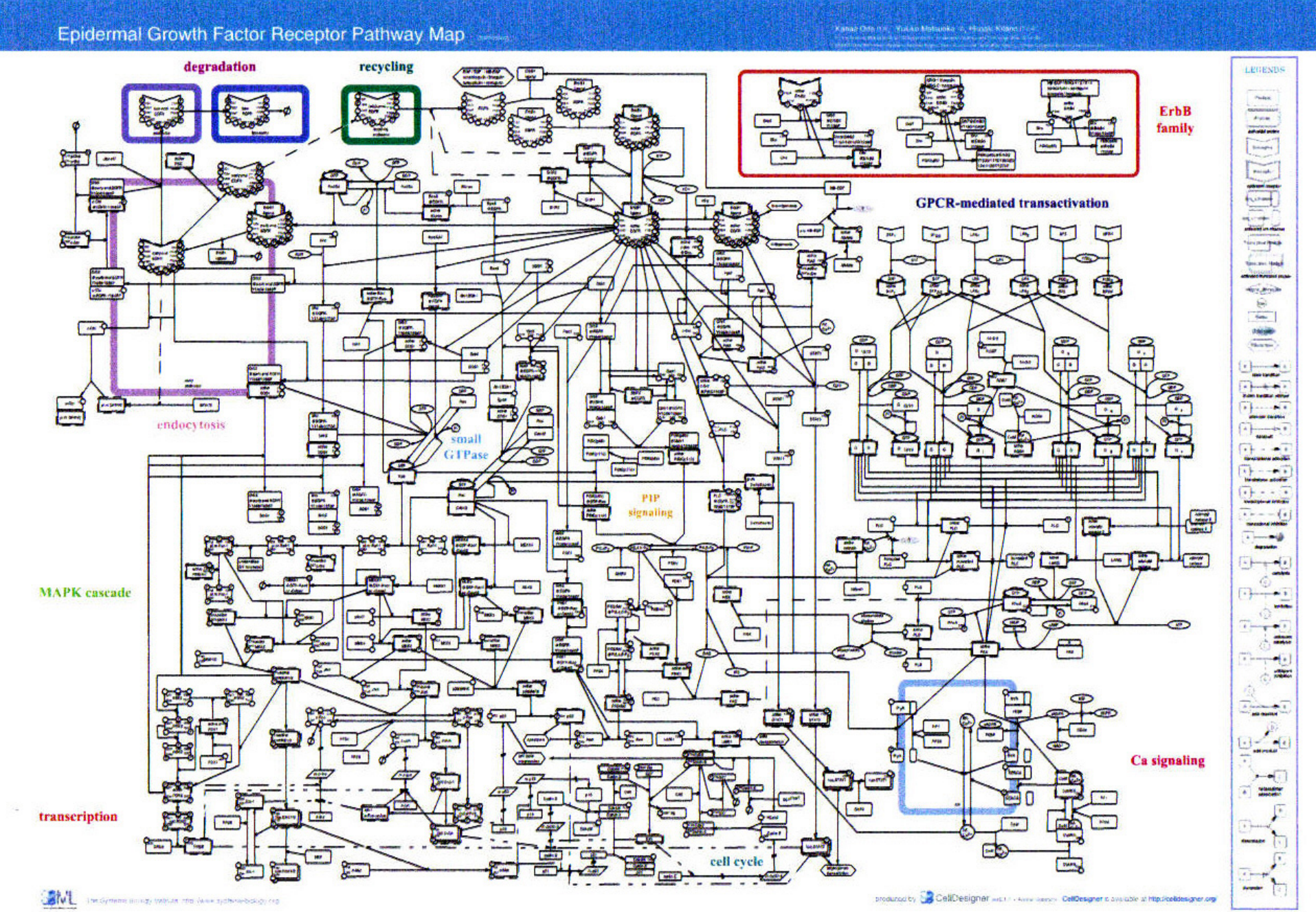
Genetic evidence for distinct roles of insulin and IGF-I receptors

- *Ir* $^{-/-}$ mice are born with almost normal size (90%) but die within a few days with severe hyperglycemia and diabetic ketoacidosis.
- *Igf1r* $^{-/-}$ are born severely growth retarded (45%) and die within minutes of respiratory failure; they have multiple abnormalities including muscular hypoplasia, delayed ossification and thin epidermis. Also mild hyperglycemia and decreased beta cell mass.

Reviewed in Kim JJ and Accili D, GH and IGF Res 12:84-90 (2002)

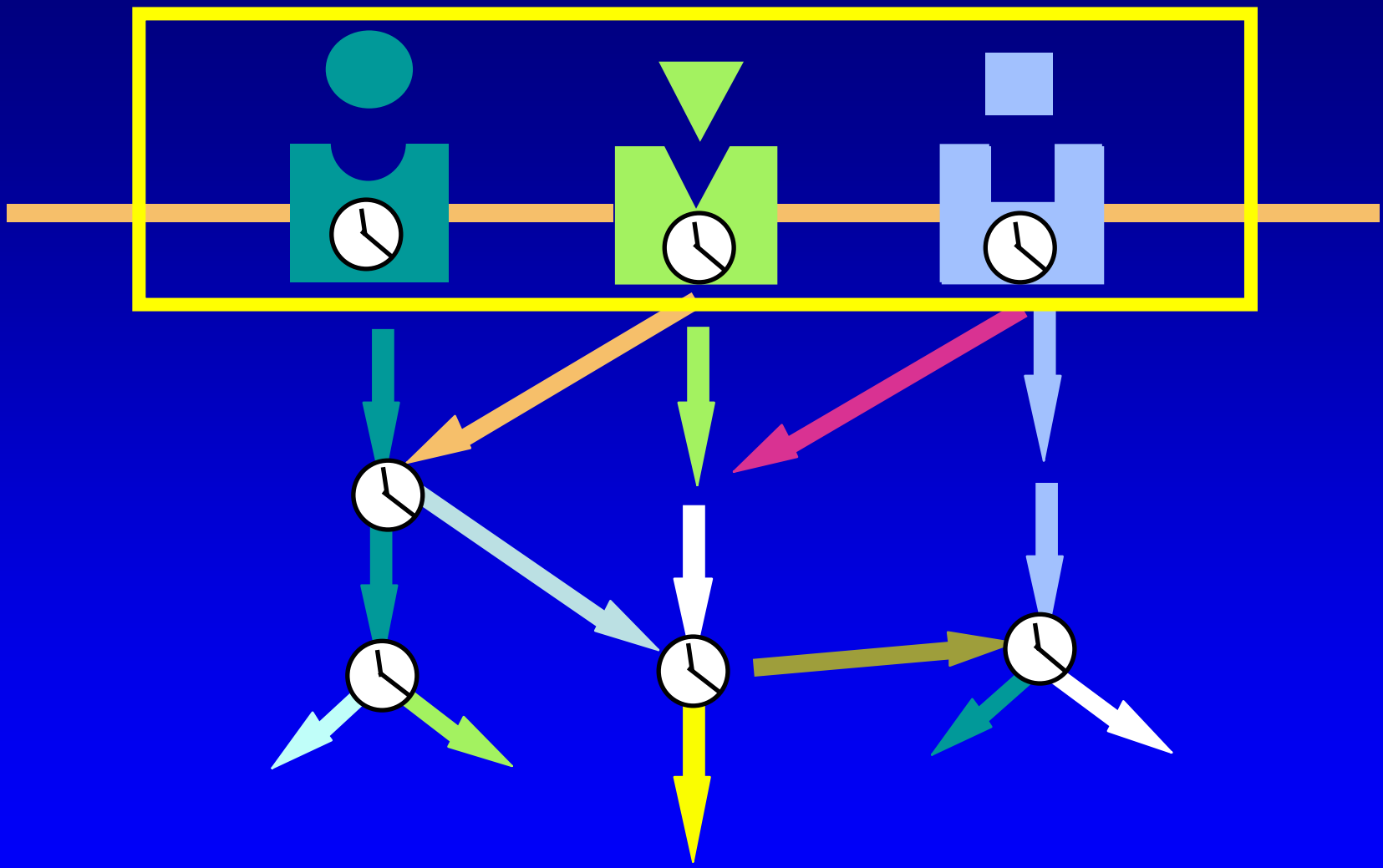

Insulin
Insulin receptor
PTP1D
SORBS1
ZAP70
Vav3
PC-1
HLA-A
MAD2
AHSG
HSG alpha2
IRS1
SOCS3
PRKCD
CALD1
Beta dystroglycan
NPM-ALK Kinase
C-terminal Src kinase
Grb14
Grb7
Cbl
CSF1
CRKII
PLCG1
ALK
IL3RB
CRR
PP2A
CEACAM1
Crk
GAB1
BLK
Nck
Syk
PIK3R1
IRS3
SHIP
MT
APP
PAL
ERBB1
Lyn
CMS
EphB6
MEKK4
p85
SOCS1
SNT
Shc
VAV3
VE-Cadherin
Paxillin
CAP
APS
TIE1
FRS2
KIT
ESRA
PLSCR1
DOCK180
Ru
Sprouty
p110+p85
FRS2 alpha
SHP2
IL4R
14-3-3 Epsilon
LYN
LRP1
p140
GRAP2
ERBB3
EphA3
SopE
TCL
IRS-3
RhoGDI
Lyp1
14-3-3
p120GAP
RalGDS
p130(Cas)
Integrin alpha6 beta4
TRKA
V-ATPase E
ITSN1
FLOT1
IRSp53
PAK2
RIN1
STAT5A
c-SRC
C3G
PAK4
Filamin
PAK5
RAC1
FYN
Vav2
Gab2
SIT
Gab1
MAP4K1
CBL
CIN85
ICP10
SHIP2
E3B1
CRK-II
MTCP1
PKC zeta
Grb10
Shk1
p67-phox
Ros1
JAK1
PDGFR
JAK2
SAP kinase
ITK
SIP-110
Ajuba
EPS8
TC10
CTMP
CDC42
Ras
GAL1
FAK2
CD72
RalGPS1
PrPC
RNTRE
MUC1
p145
4PS
CRK-I
p85-PI3K
Rap1A
CDC25 phosphatase
DNM2
PTPN1
ITGA2B
PDGFB
IFI27
SOS1
AKT1
Pak1
PI3K
G-protein beta gamma
NF1
TNF receptor
Bcr-Abl
Mta3
SLM-1
RON
SHP1
SETA
Huntingtin
HER2
Grb4
LCK
PKC theta
ILK
TCL1B
CIP4
PAR6
PKC-zeta
p130
DMPK
Vav
SYN1
EPOR
SLAP
PKC alpha
IRS-1
Myosin II
PKG1-alpha
14-3-3 Beta
3BP2
p63
DF3
DAG1
LAT
pp31
BRAMP2
IMPDH
TSC1
PAR3
GRB10
Hsp90N
PIK3C2B
Grb2
HNRPC
TRADD
p62
BTK
P110+p85
Nur77
Raf
MKK1
FasL
UNC-53
GAB2
Reps1
ErbB2
DRD4
ITG6
IQGAP2
ASK1
TCL1
PKC gamma
BCL2
PP1C
Src
WASP
SKAP55
pp90
Lnk
EPHA1
M-CSFR
HS1
TSC2
JIP1
Hsp90-beta
Tyl-1
HIV-1 Nef
SOS2
AXL
BCAR1
p150
MAP2c
pp135
ORF3
SYNJ1
IQGAP1
p70 S kinase
ERK5
R-Ras
PI3 Kinase
FMS
Hayai
c-Src
p75
Dab2
Sirm
SYNJ2
PKBgamma
IKK alpha
JSAP1
BAG1
FLIP
p38
Cortactin
B19 11-kDa
AKT
PKC epsilon
Fyn
SB1
TEK
SH2-B
ZYX
p115
Deltex
ACK
SGK
14-3-3 zeta
KSR
RKIP
NS5A
SNTA1
LAX
ANXA2
env-sea
MAPK
pp94
PTPN11
PKBbeta
B-Raf
pp130
GTEKH
Spry1
SGK3
LTK
MEKK1
MAP-2b
PTPRA
Sam68
SHIP beta
Srcasm
RET
PKCdelta
PDK1
TC21
SHB
MAP-2c
pp120
WASL
SYK
DRD3
pp116
p135
PTPRE
PIF
PKN
14-3-3 eta
rAPS
H4-ret
AG957
DIP
DNM1
Hsp90
RSK2
MEK1
MP1
Mta1
PTPN22
VAV2
BLNK
pp68
Beta MET
PRK1
PRK2
PAK1
ABL
pp70
IRS4
5-Lipoxygenase
RSK1
pp36/38
CCL5
FLT3
PKCzeta
PRKCG
SGK2
14-3-3 gamma
HVH2
RAFTK
PSMD10
PRKAR1A
PHE3
WISH
L-Selectin
Nibrin
ADAM12
ADRB2
PKA
PKCiota
14-3-3-eta
Rap1
Prohibitin
ERK1
RPDE-6
TPR-Met
ADAM15
FAK1
FF3
Bcr
TEL-JAK2
LCP2
PKCbeta2
PKBalpha
GILZ
p54SAPK
Spry2
CNTNAP1
MEK2
POB1
14-3-3-theta
ESR1
JNK1
PTP-SL
MKP1
LC-PTP
ERK2
Fos
v322
RON-beta chain
P70 S kinase
Elk-1 kinase
CSNK2A1
CBLB
FGF2
WISK
CBP
STEP
c-Fos
ELK1
p46SAPK
CSN1
IGF1
PY105
Erg
Smad4
MyoD
TCF2D
NFKB3
CSNK2B
CREBP1
PFK2
TH
FLI1
E12
p62TCF
CREB
ATF1
Smad3
NFATp
Nkx2.3
BCL-6
TF2B
SAP-1a
SSRP1
Fra2
AR
Src1
GHF1
Fra1
c-Ets-1
FIP
P3F
p35-C/EBPbeta
EKLF
p65
Cbfa1
FZA-B
NF-YA
hASC-1
PU.1
IE2 86
ATF2
RB
ASC2
Nkx3.1
SAP2
Casein
Grp94
ERalpha
MRTF-B
RXRA
CKII beta
VDR
E7
HIF-1
Stat3
Phox1
SPIN
TFIIF
NAP2
Ubc9
SF-1
hnRPM
B-ATF
Cbfa2
Myocardi
SRF
Barx2b
MEQ
Caper
HSP90
TGIF
p52/54
RHII/Gu
TBP
SRC1
HMGI-Y
ATF6
PEA3-binding factor
Stat1
T antigen
CK-II
ATF4
NDHI
c-Jun
Hex
SMRT
Hop
Tax
TEF-1
RXRG
c-ETS-1
NFY
ETS2
p65/NF-kappaB
TAFII250
RPL18A
Sp1
TOP2
MRTF-A
Barx1b
SAP-1
C/EBPbeta
GATA4
p20C/EBPbeta
RAP74
EWS-FLI-1

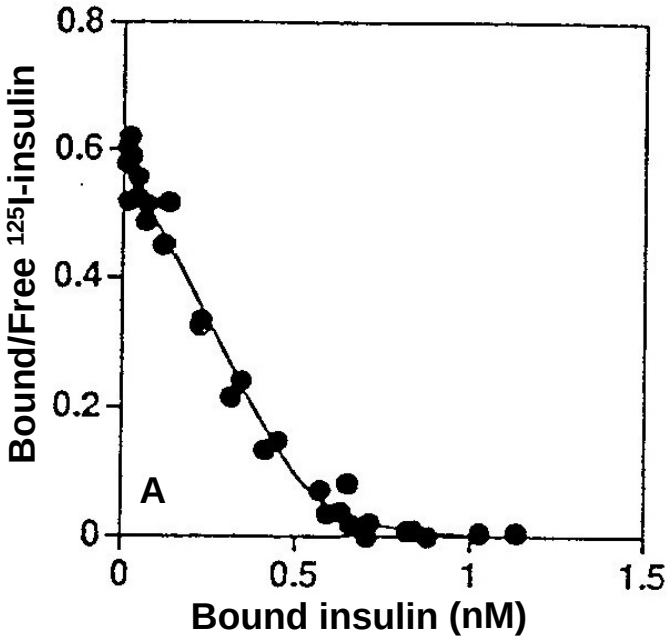
www.hprd.org



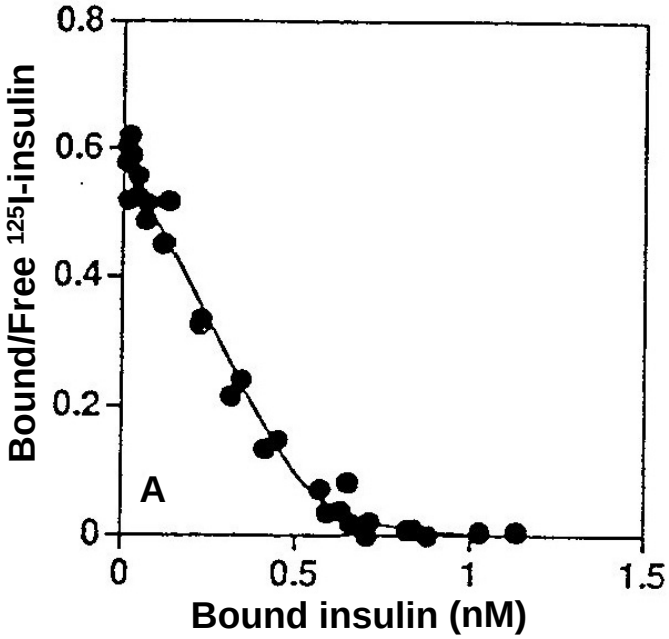
Oda K, Matsuoka Y, Funahashi A, Kitano H. Mol Sys Biol online 2005

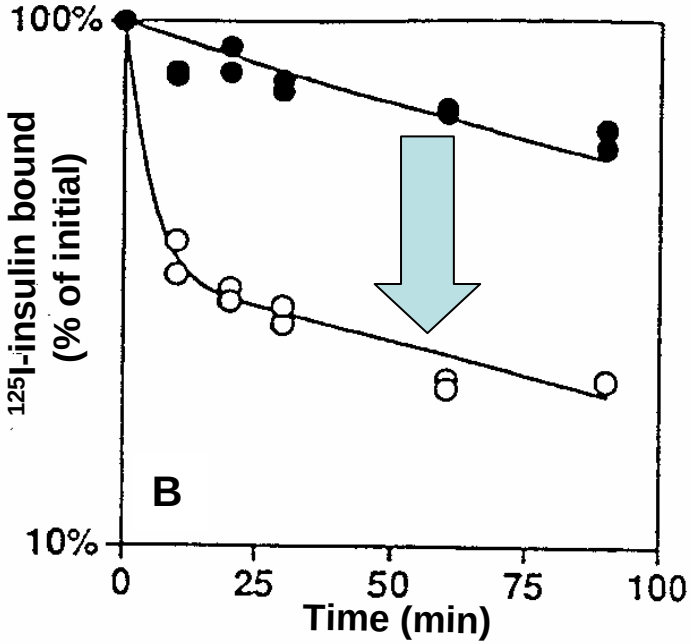
The time factor in signaling specificity

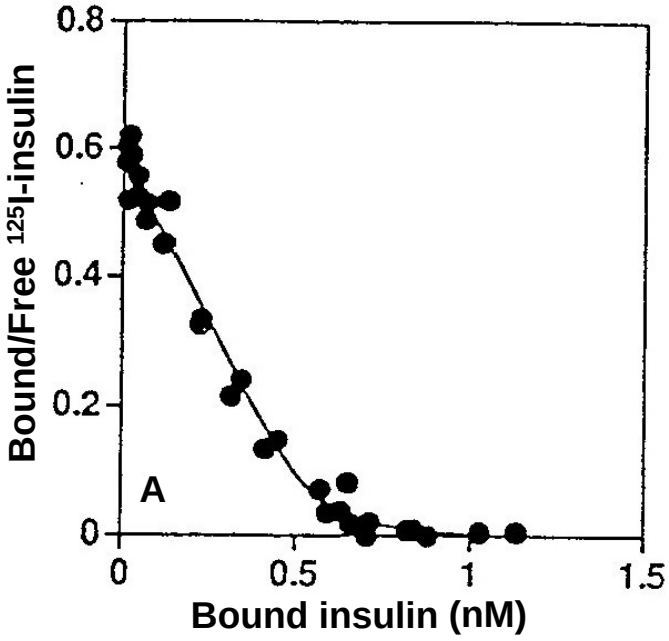


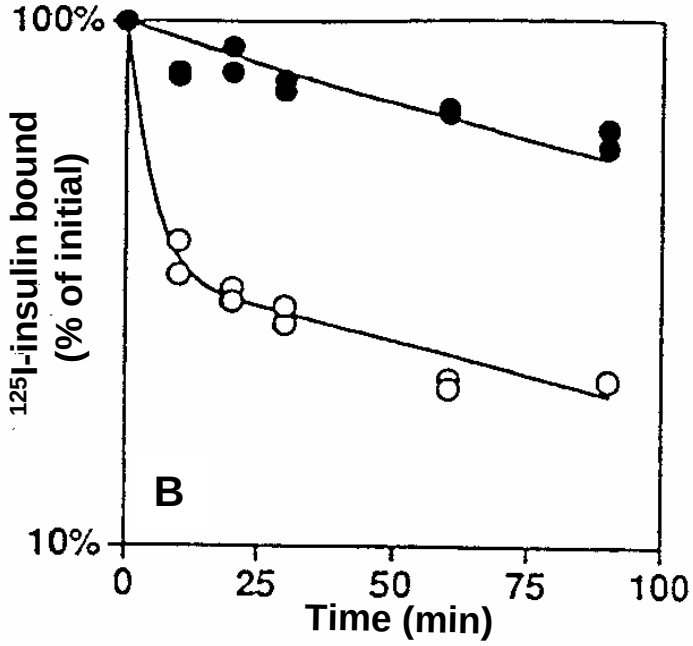


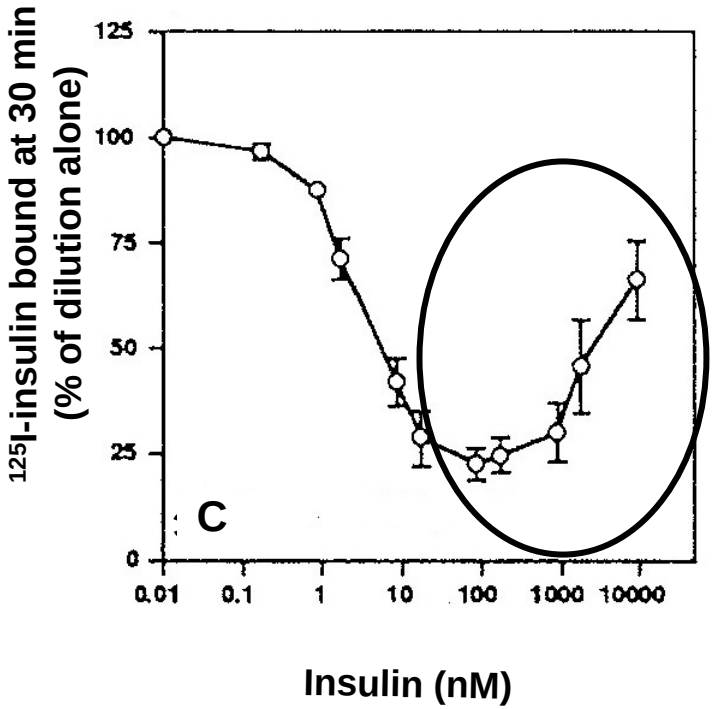
Scatchard plot of insulin binding

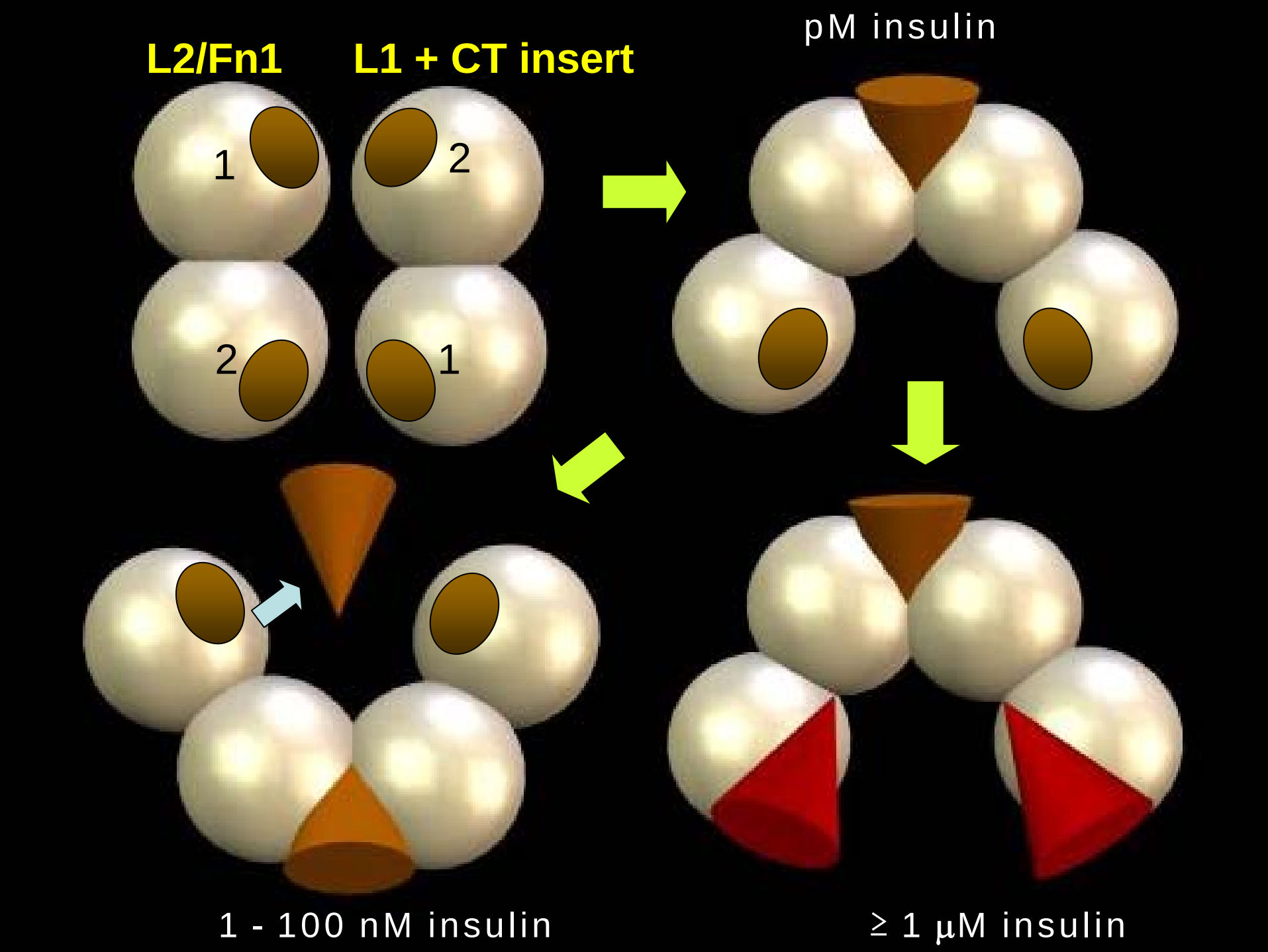

Bound/Free 125I-insulin
0.8
0.6
0.4
0.2
0
A
0
0.5
1
1.5
Bound insulin (nM)


125I-insulin bound
(% of initial)
100%
10%
B
0
25
50
75
100
Time (min)

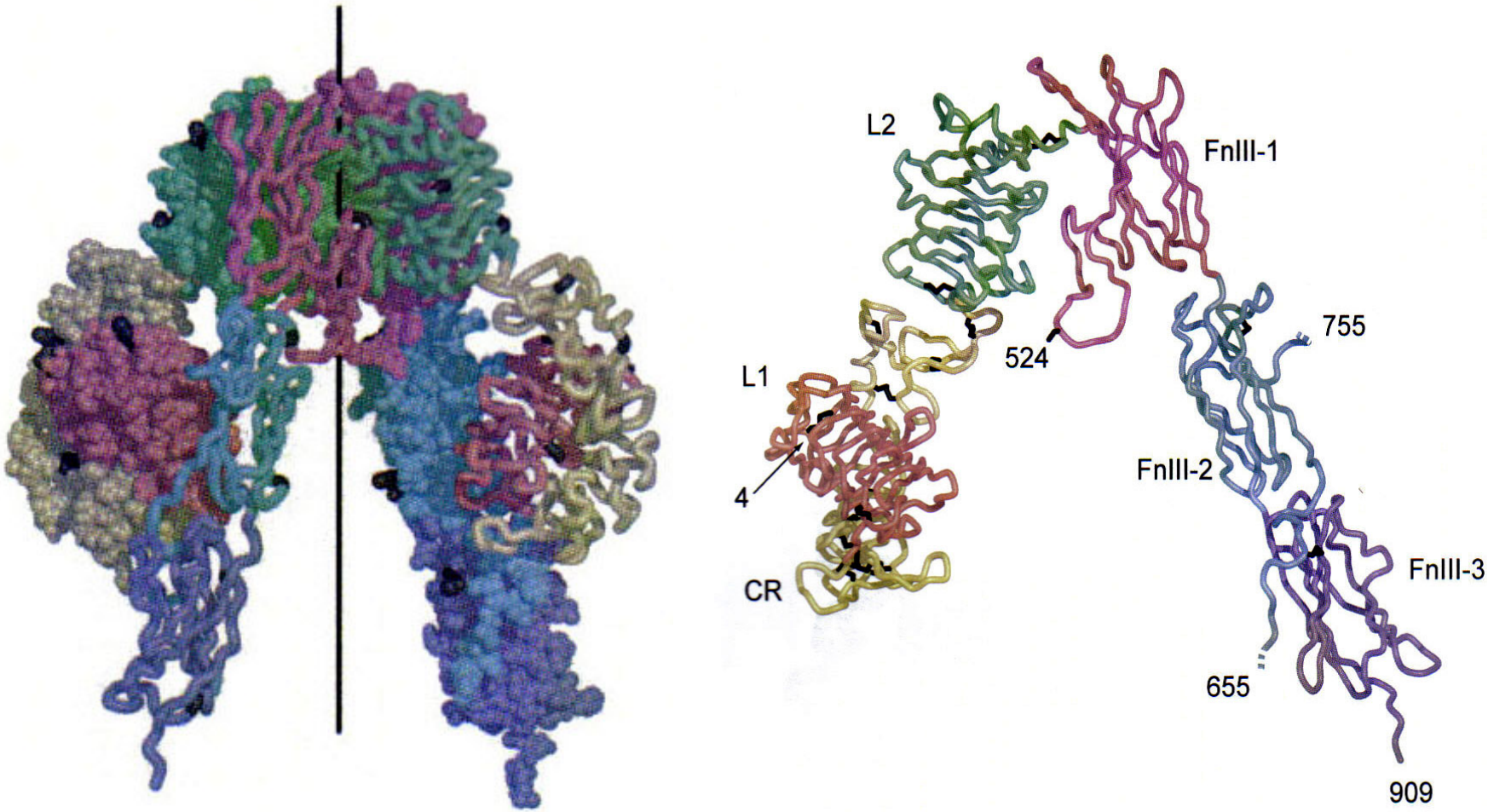

Bound/Free ^{125}I-insulin
0.8
0.6
0.4
0.2
0
A
0
0.5
1
1.5
Bound insulin (nM)


100%
10%
^{125}I-insulin bound
(% of initial)
B
0
25
50
75
100
Time (min)


^{125}I-insulin bound at 30 min
(% of dilution alone)
125
100
75
50
25
0
C
0.01
0.1
1
10
100
1000
10000
Insulin (nM)

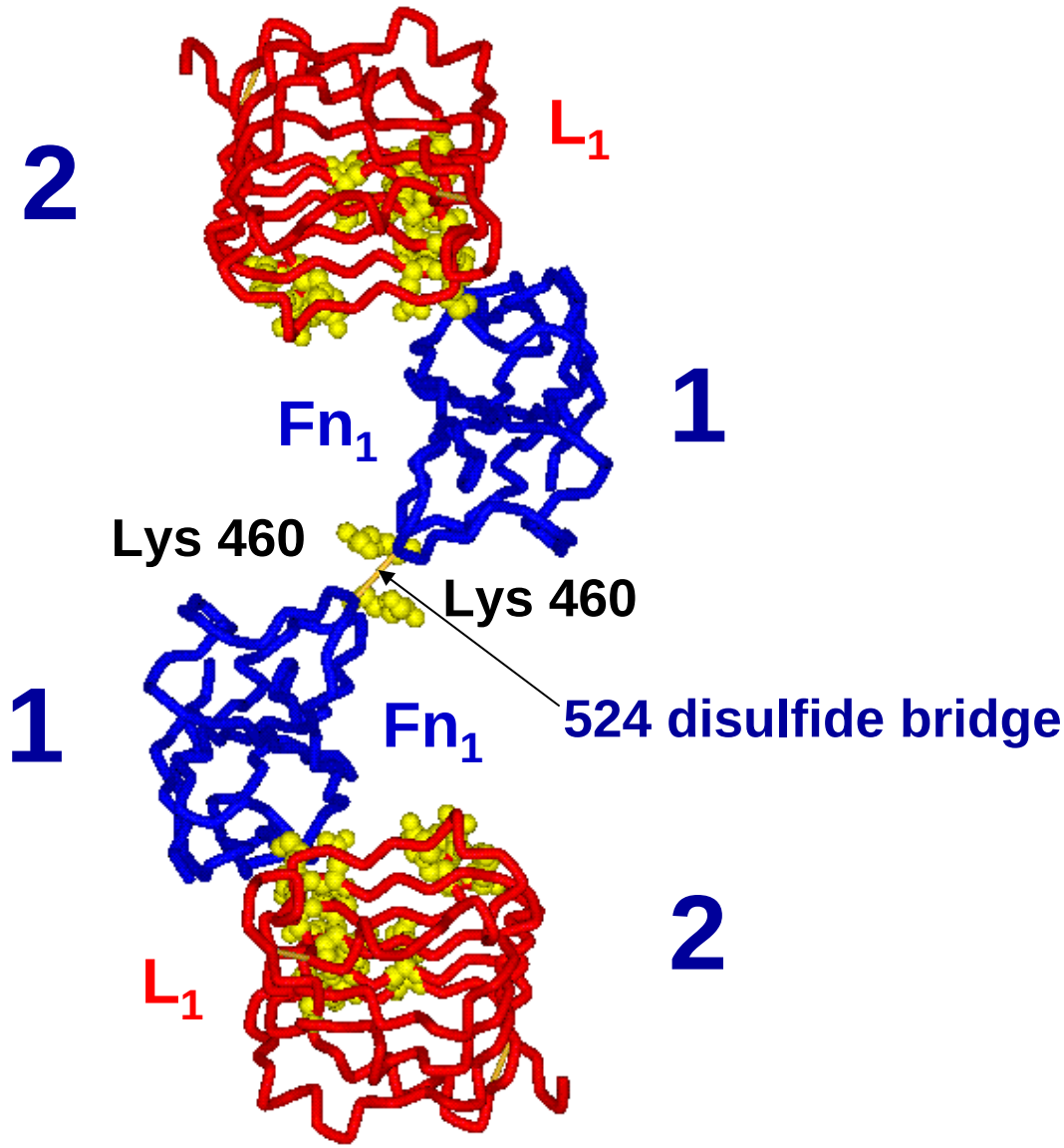

L2/Fn1
L1 + CT insert
1
2
2
1
pM insulin
1 - 100 nM insulin
≥ 1 μM insulin

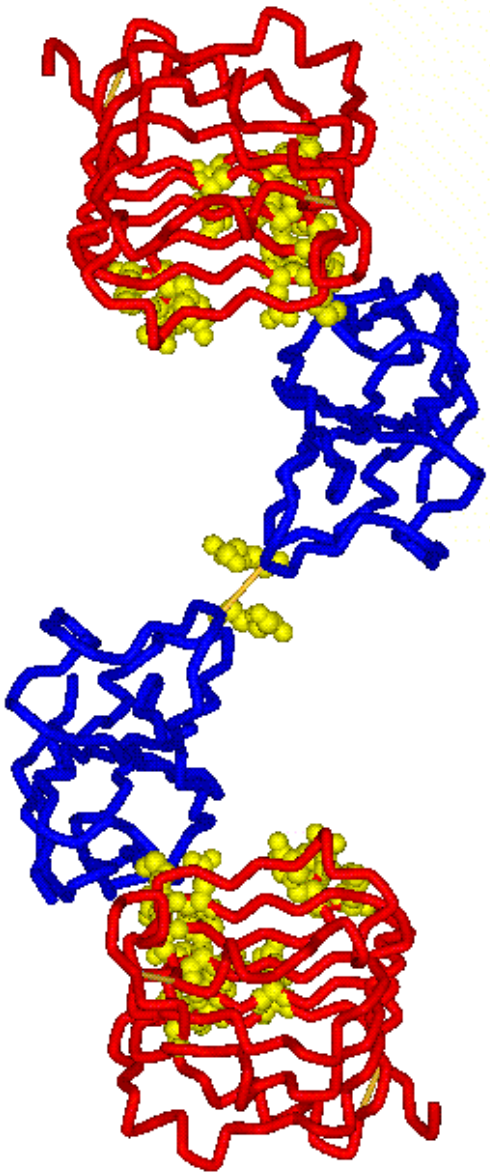
Crystal structure of the insulin receptor ectodomain



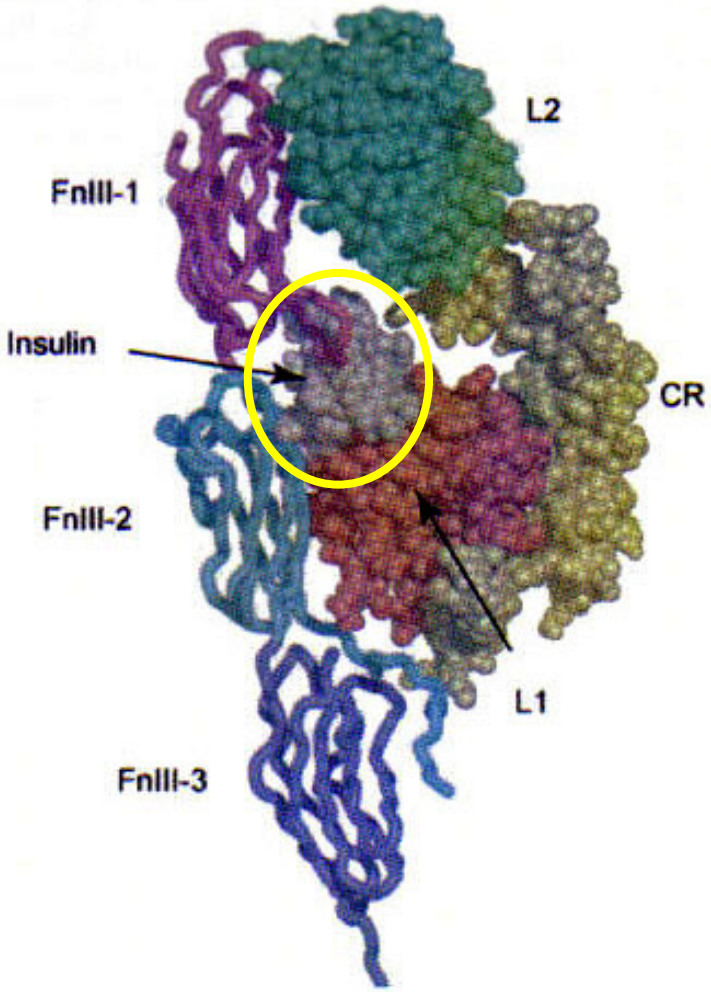
McKern NM et al, Nature 443:218-221, 2006

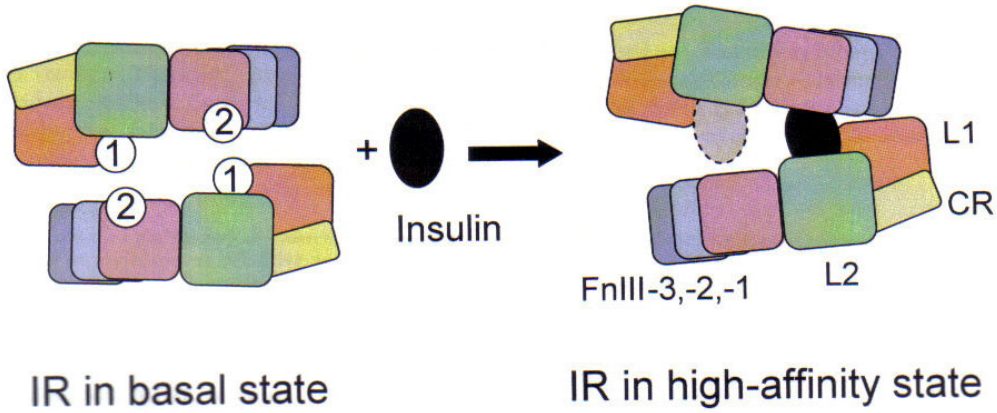
The architecture of negative cooperativity: antiparallel disposition of the four ligand binding sites





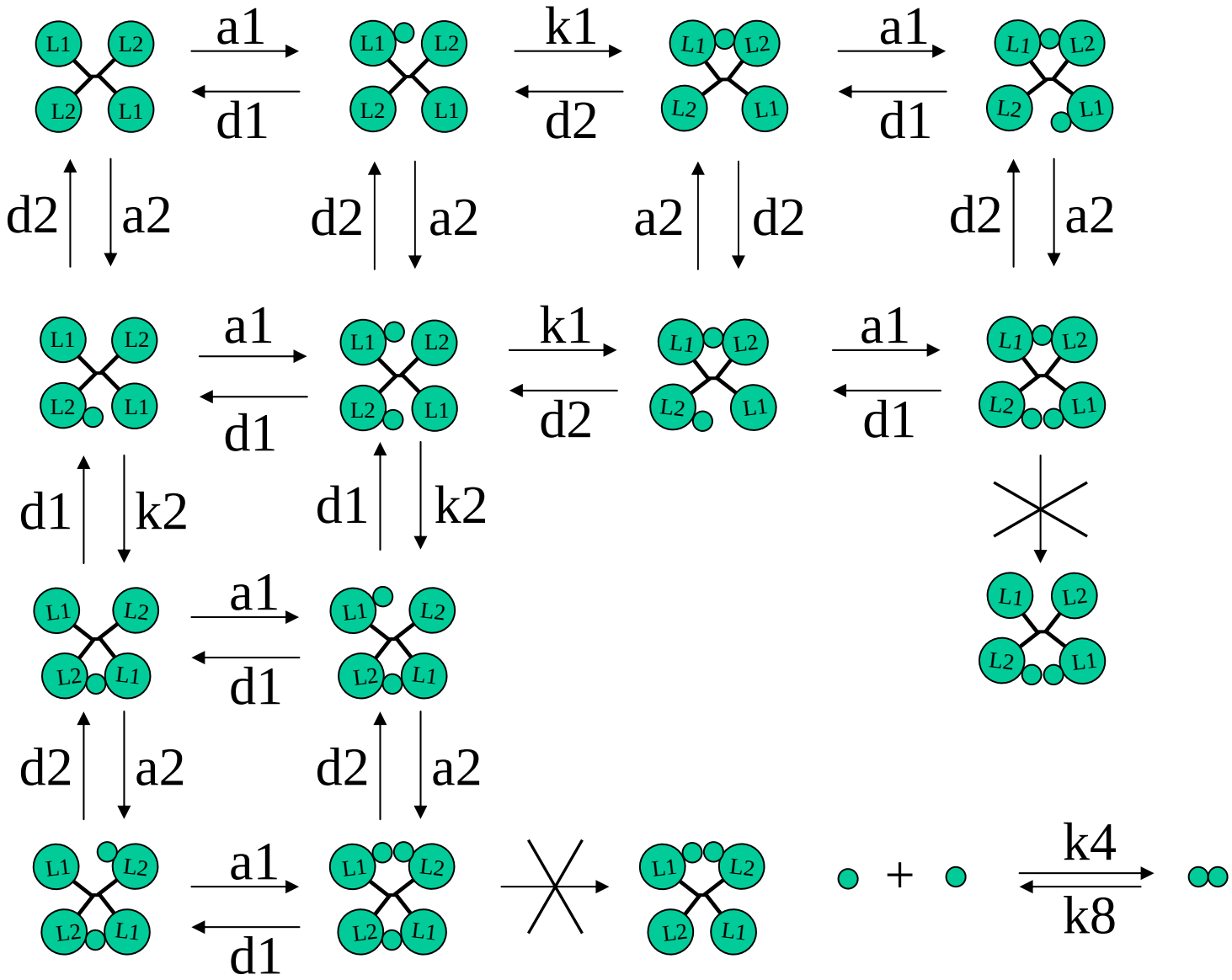
Insulin binding to the insulin receptor ectodomain





McKern NM et al, Nature 443:218-221, 2006

One-dimensional harmonic oscillator model



Modelling by Vladislav Kiselyov

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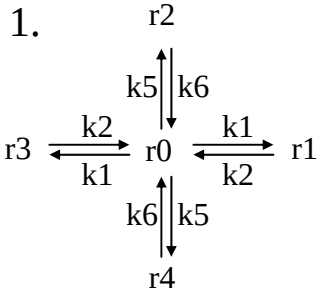

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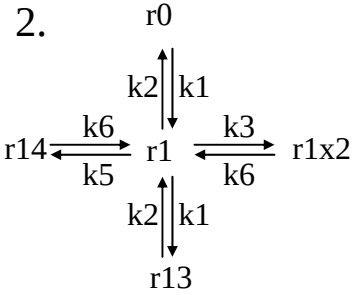

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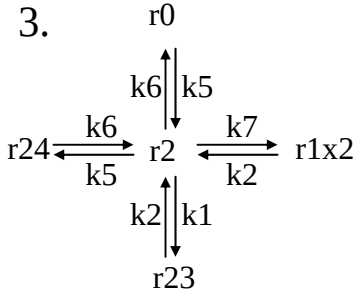

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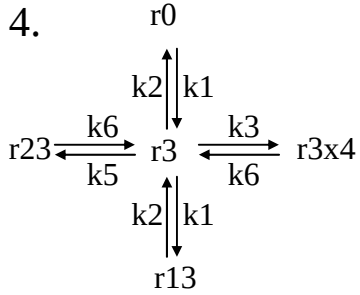

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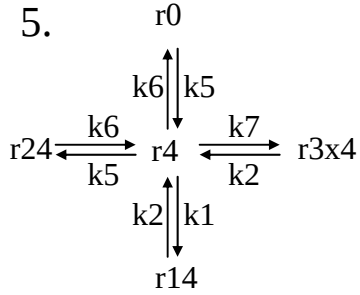

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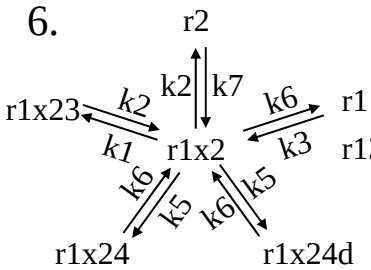

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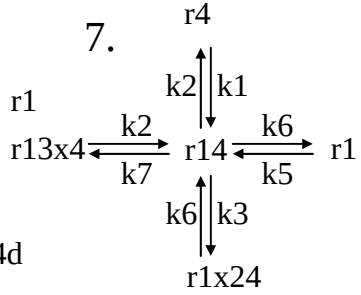

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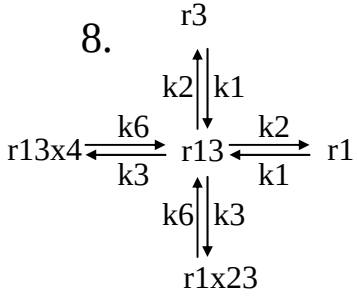

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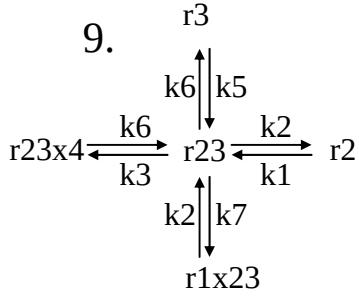

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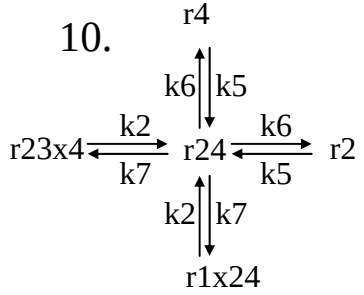

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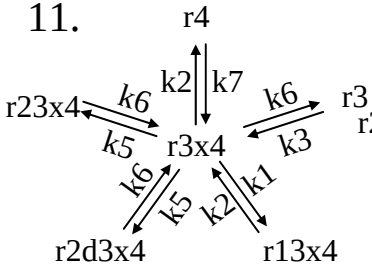

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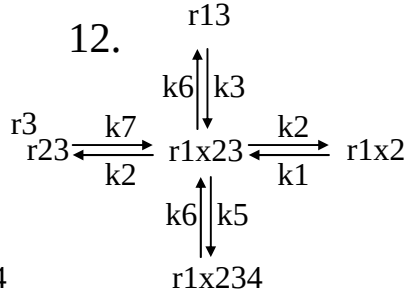

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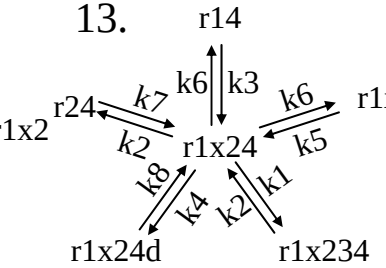

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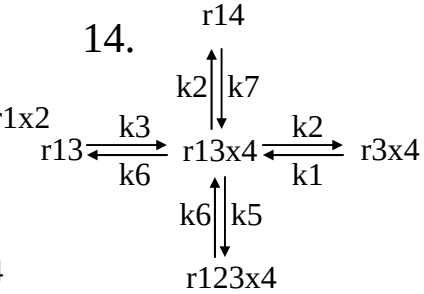

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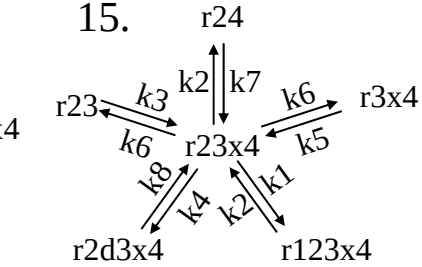

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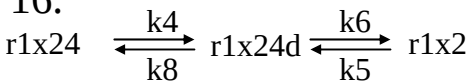

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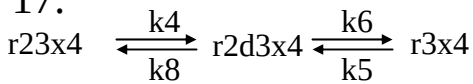

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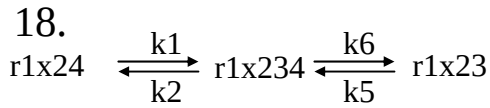

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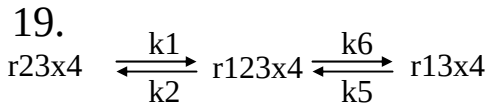
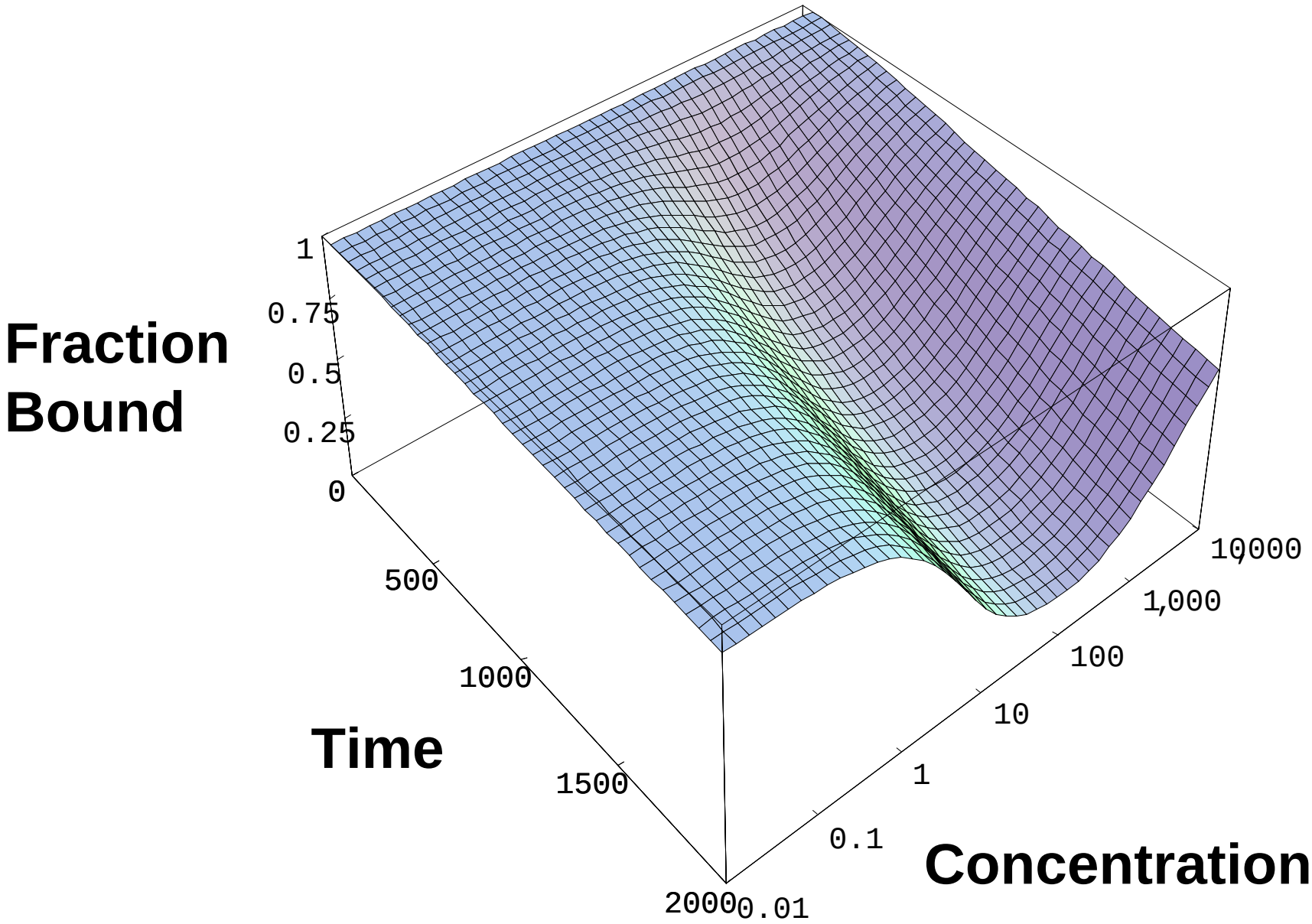


Mathematical modelling by Vladislav Kiselyov

Modelling of insulin receptor dissociation kinetics

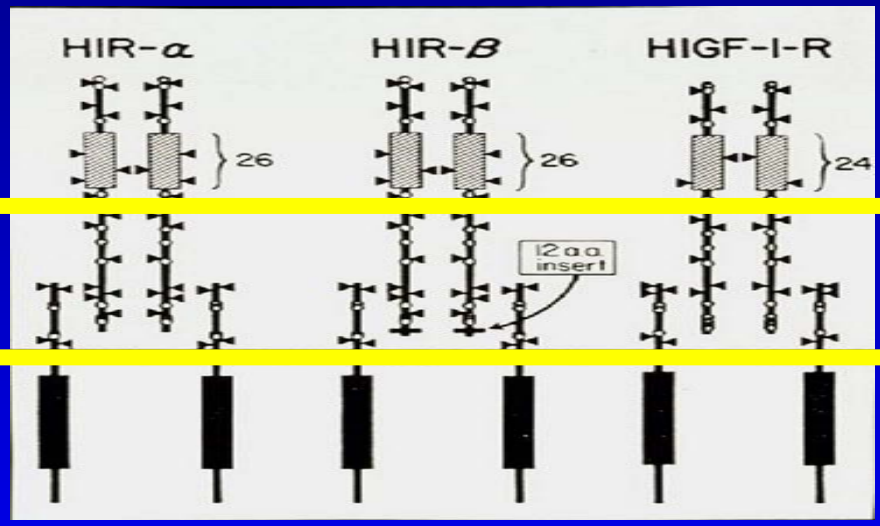


Insulin

Insulin analogues

IGF-II

IGF-I



Ligand binding kinetics

Beta cells

Adipocytes

Muscle

FRET /BRET analysis

IRS-1 IRS-2 IRS… SHC

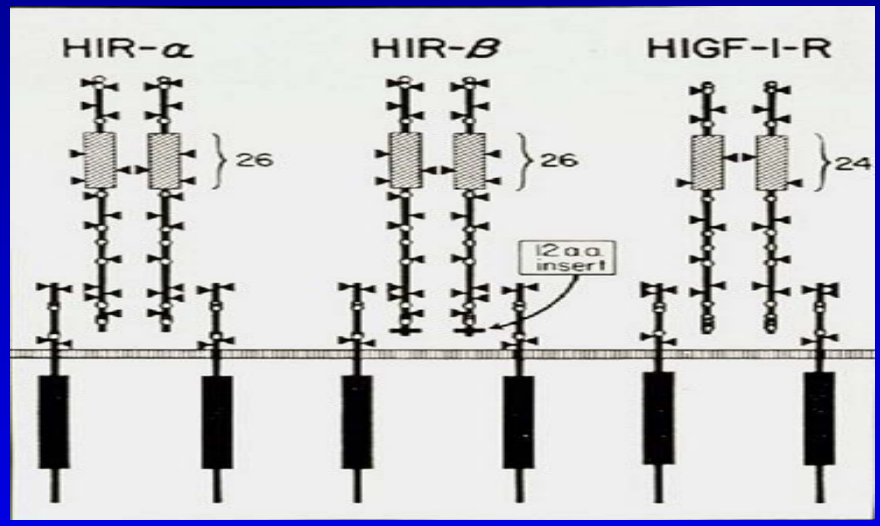
Modelling of signalling pathways

Insulin

Insulin analogues

IGF-II

IGF-I



Beta cells

Adipocytes

Muscle

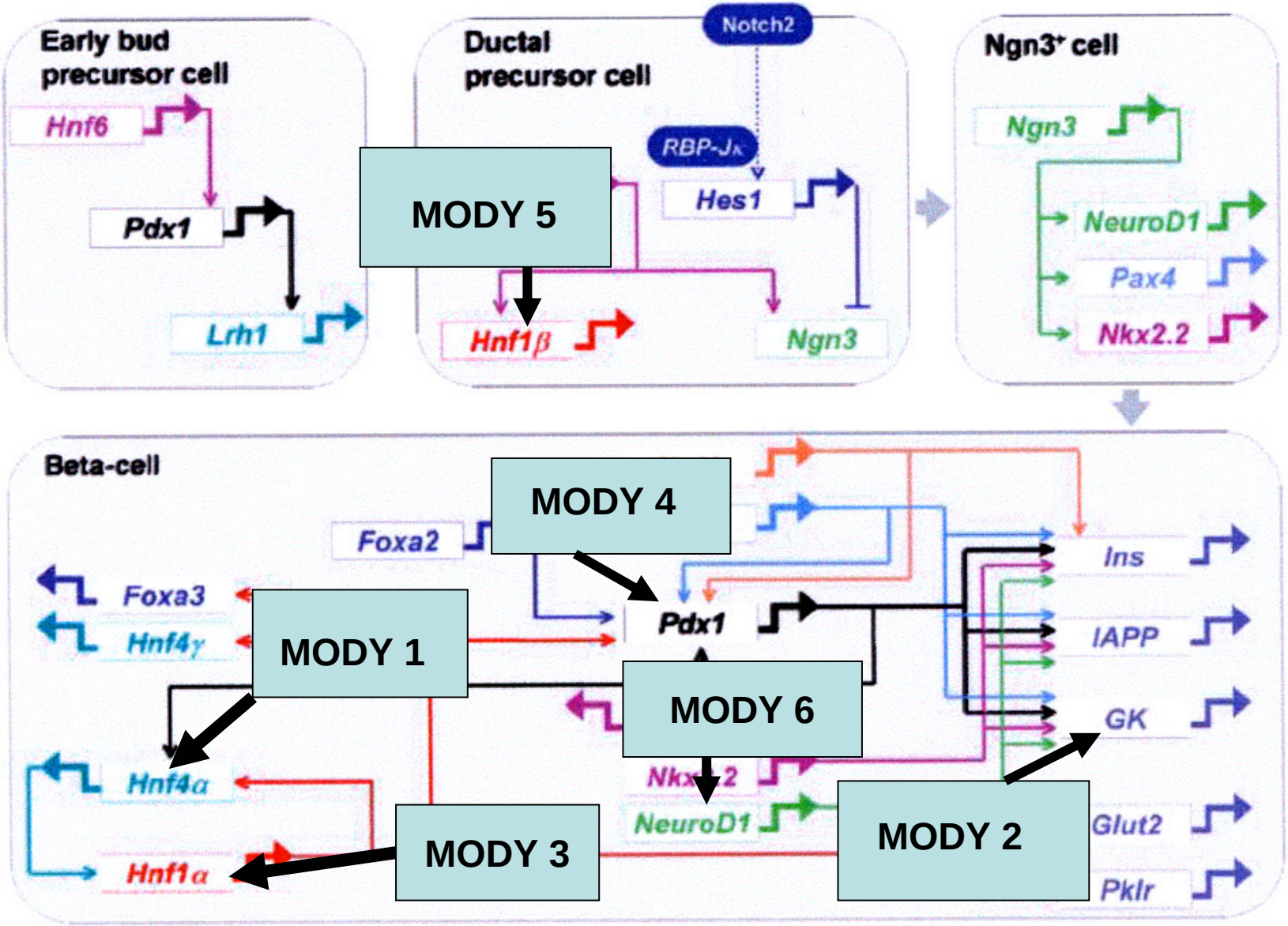
siRNAs

Phosphoproteomics (SELDI-TOF)

cDNA Microarray Gene Analysis

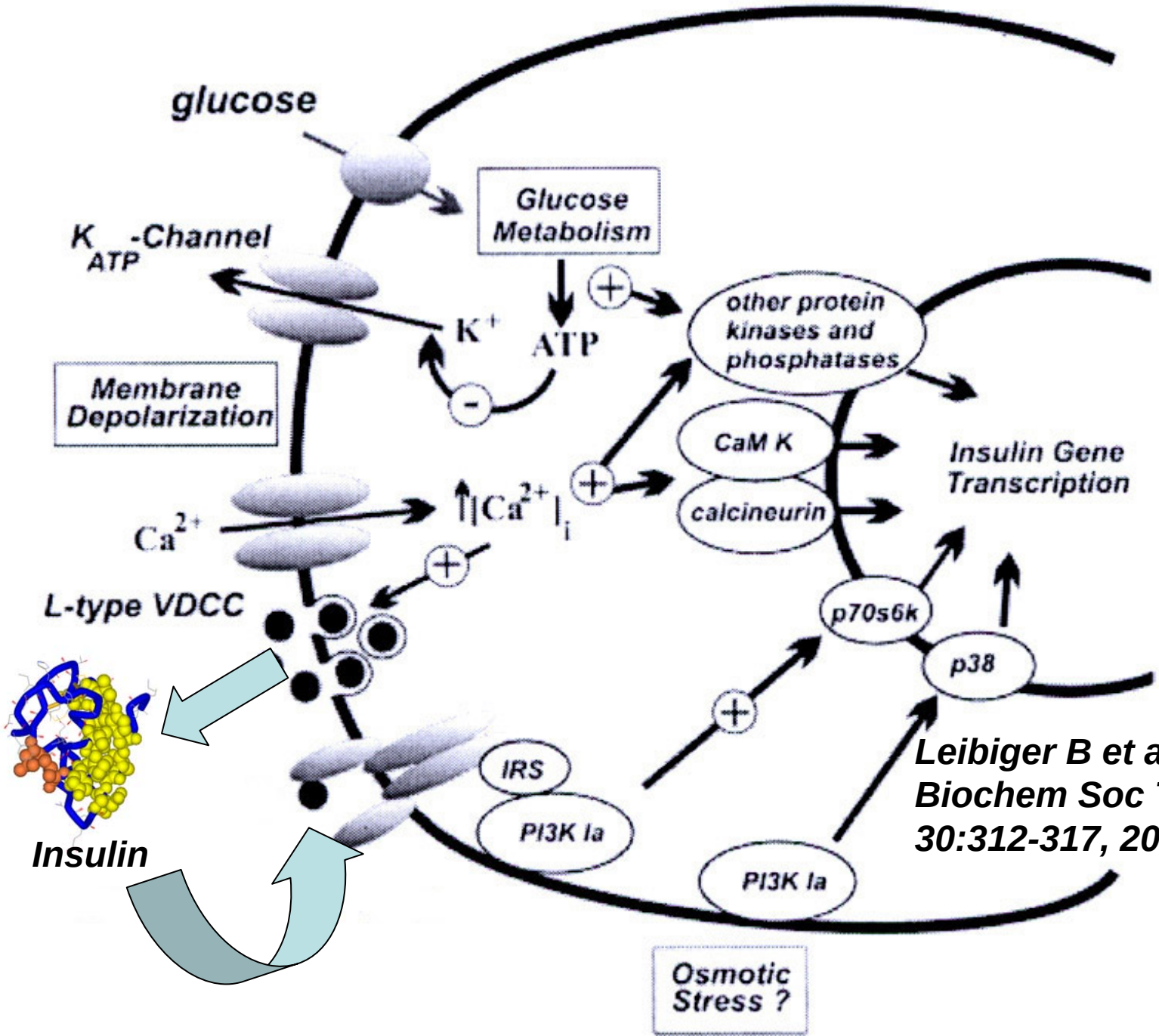
The beta cell defect in type 2 diabetes: transcriptional, functional and systemic aspects

Transcriptional networks controlling beta cell development and function



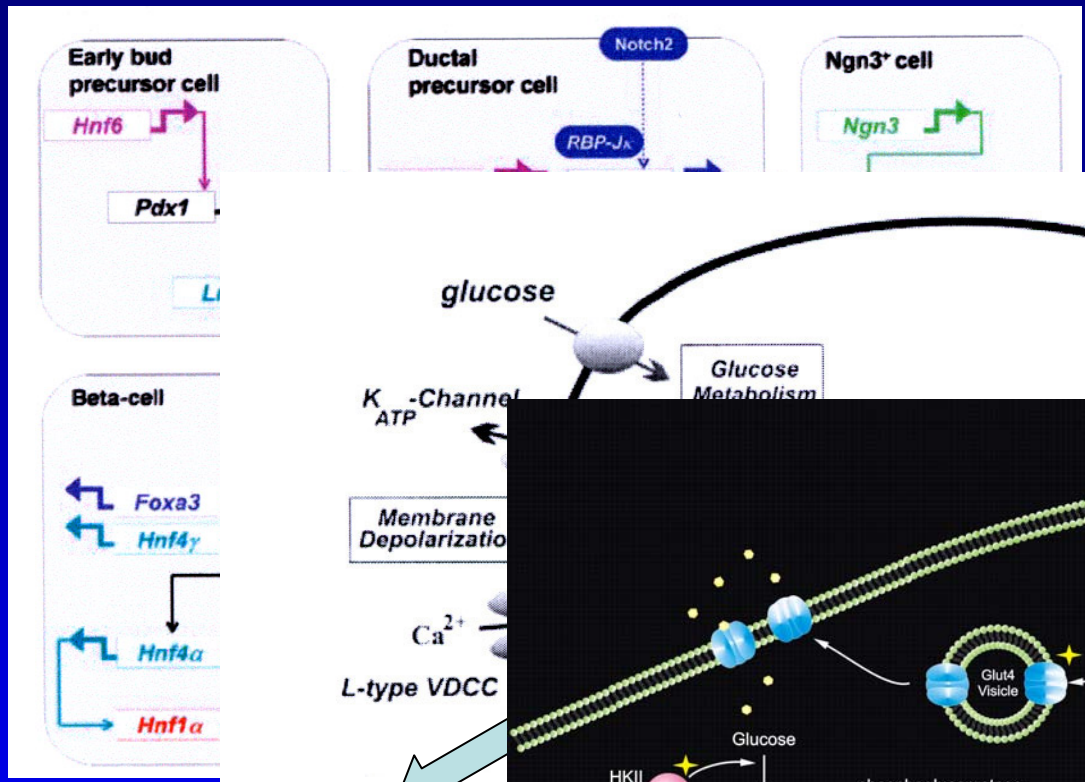
Servitja JM and Ferrer J , Diabetologia 47:597-613 (2004)

Positive feedback of insulin secretion on beta cell function



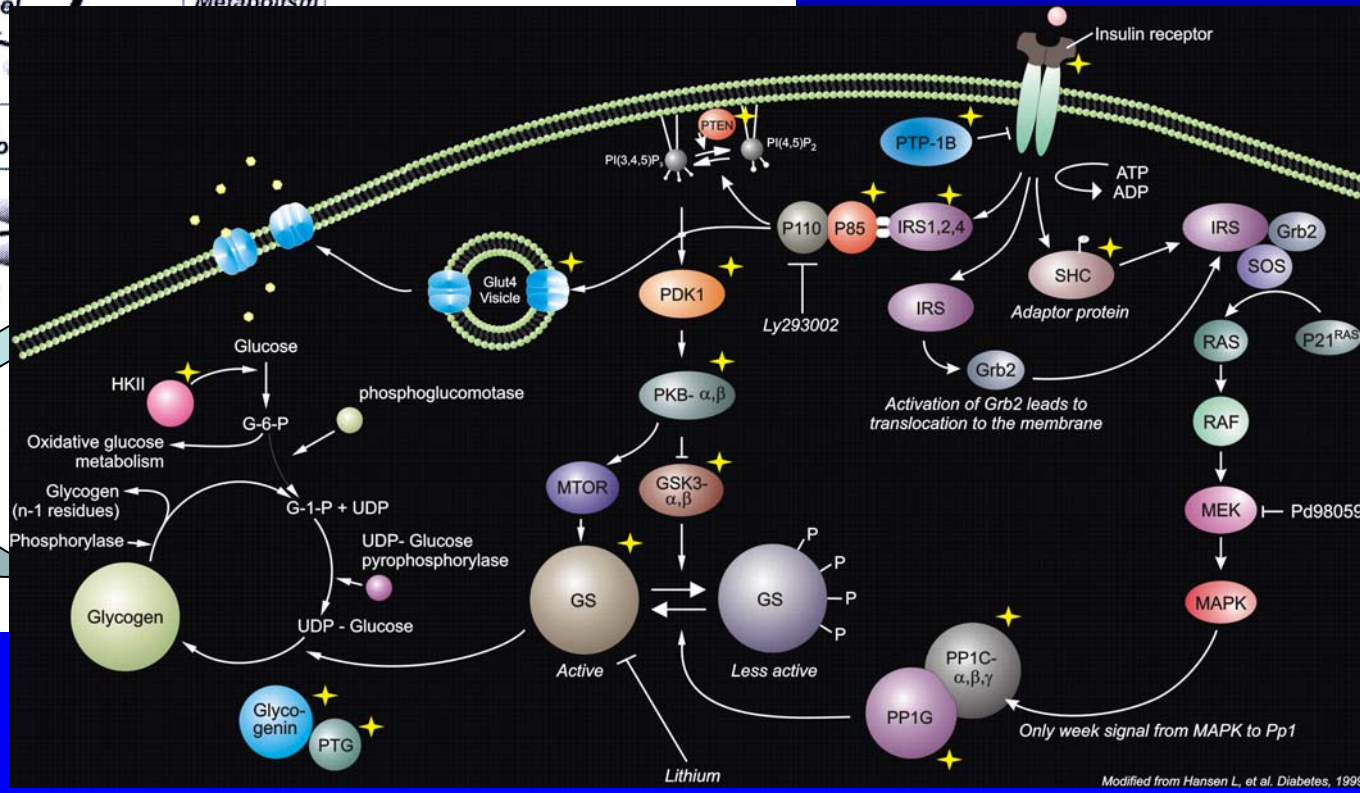
Leibiger B et al, Biochem Soc Trans 30:312-317, 2002

Multi-layered complexity in pathogenesis of type 2 diabetes



Beta cell differentiation

Beta cell secretion and function



Peripheral insulin action

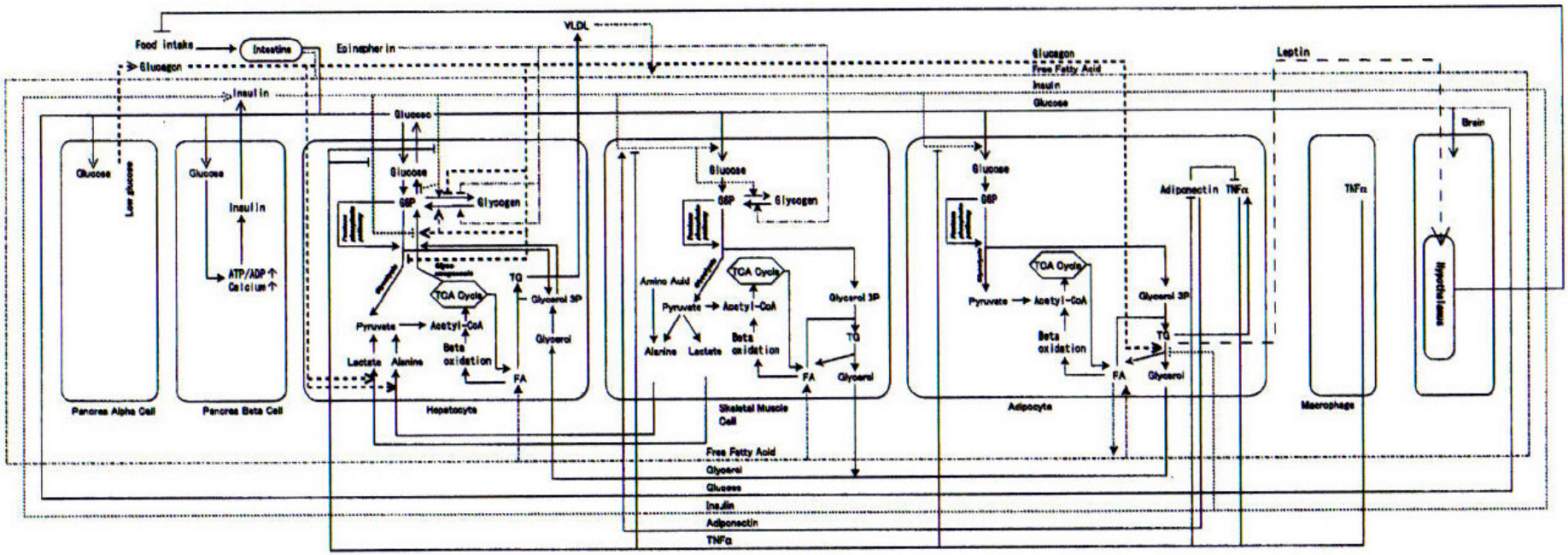


FIG. 1. Schematic illustration of energy control system regulation relevant to diabetes and the metabolic syndrome.

Metabolic Syndrome and Robustness Tradeoffs

Hiroaki Kitano,[1,2,3] Kanae Oda,[4] Tomomi Kimura,[2,4] Yukiko Matsuoka,[5] Marie Csete,[6] John Doyle,[7] and Masaaki Muramatsu[4]

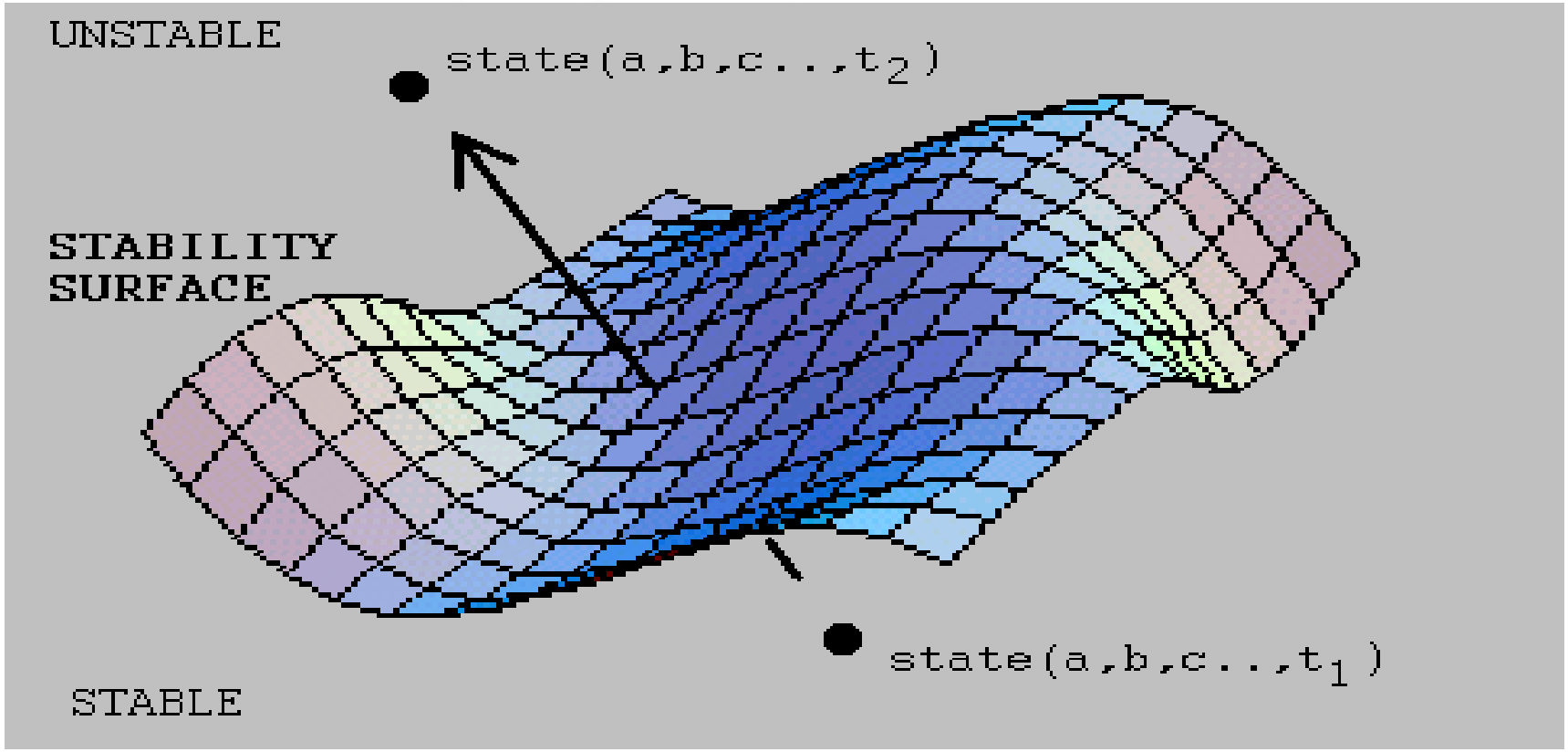
Diabetes, 53 suppl.3: S6-S15, 2004

Perspectives in Diabetes

Onset of Type 1 Diabetes

A Dynamical Instability

Birgitte Freiesleben De Blasio, Per Bak, Flemming Pociot, Allan E. Karlsen, and Jørn Nerup



Diabetes, 48:1677-1685, 1999

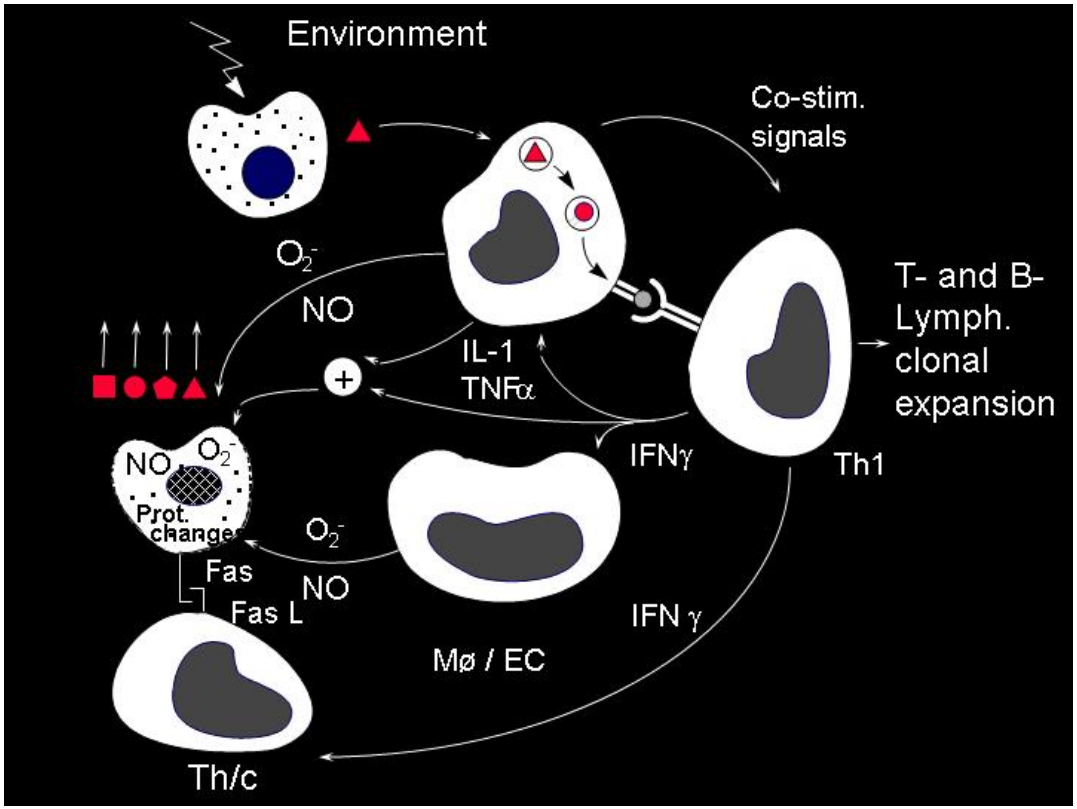


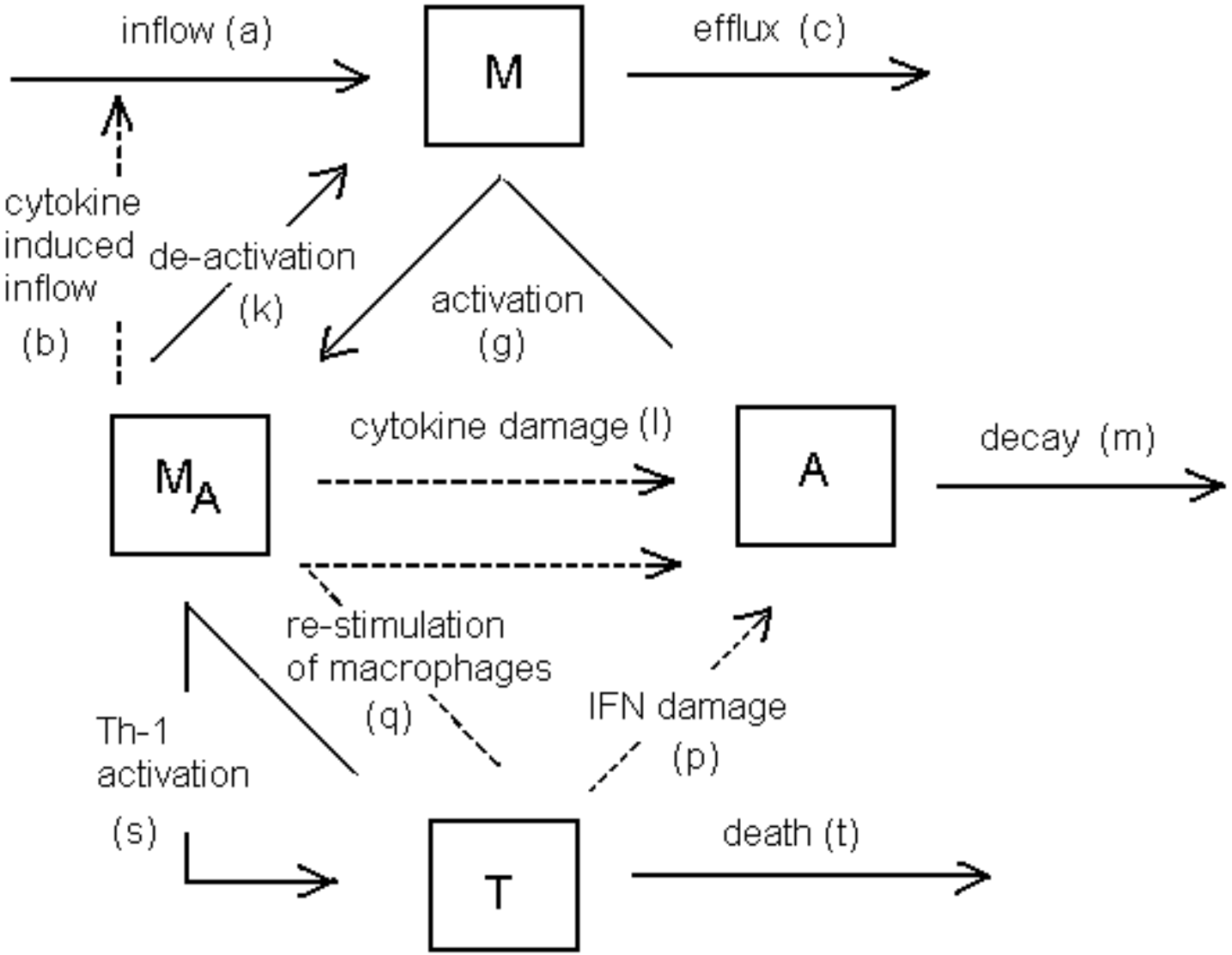
TABLE 1
List of symbols

A, amount of β-cell antigenic proteins in volume.
M, numbers of macrophages in volume.
M_A, numbers of antigen-expressing macrophages in volume.
T, numbers of activated Th-lymphocytes in volume.
$\dot{A}$, the derivative of A with respect to time, i.e. $\frac{dA}{dt}$.
$\dot{M}$, the derivative of M with respect to time.
$\dot{M}_A$, the derivative of M_A with respect to time.
$\dot{T}$, the derivative of T with respect to time.

a, recruitment rate of macrophages to volume.
b, IL-1 -, TNF-α–induced recruitment rate of macrophages.
c, efflux rate of macrophages from volume.
g, uptake rate of β-cell antigens in macrophages.
k, decay rate of activated macrophages.
l, effective rate of IL-1–, TNF-α–induced β-cell damage.
m, clearance rate of free β-cell proteins.
p, effective rate of IFN-γ–induced β-cell damage.
q, effective rate of β-cell damage caused by effector-macrophages.
s, proliferation rate of Th-lymphocytes.
t, death rate of activated Th-lymphocytes.

The Copenhagen model of type 1 diabetes

Diabetes, 48:1677-1685, 1999



Extended mathematical model of type 1 diabetes onset

Diabetes, 48:1677-1685, 1999

VIEWPOINT

Systems Biology and New Technologies Enable Predictive and Preventative Medicine

Leroy Hood,[1*] James R. Heath,[2,3] Michael E. Phelps,[3] Biaoyang Lin[1]

Systems approaches to disease are grounded in the idea that disease-perturbed protein and gene regulatory networks differ from their normal counterparts; we have been pursuing the possibility that these differences may be reflected by multiparameter measurements of the blood. Such concepts are transforming current diagnostic and therapeutic approaches to medicine and, together with new technologies, will enable a predictive and preventive medicine that will lead to personalized medicine.

Science, 306:640-643 (2004)

INNOVATION

Can cell systems biology rescue drug discovery?

Eugene C. Butcher

Nat Rev Drug Disc 4:461-467 (2005)

What is simple is wrong, and what is complicated cannot be understood.

Paul Valery (1871 – 1945)

RS BL
Receptor Systems Biology Laboratory
HAGEDORN RESEARCH INSTITUTE

Thank you!

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