# Diabetes mellitus

## A chronic disease

~ 200 million diabetic patients
(+ millions not yet diagnosed….)

>10% of health budget in developed countries
(~ 100 billion dollars per year in Europe)

A pandemic non-communicable disease (WHO)

# Diabetes mellitus

# =

# Several diseases which a common symptom : hyperglycemia

# Glucose

# “Dr Jekyll and Mr Hyde”

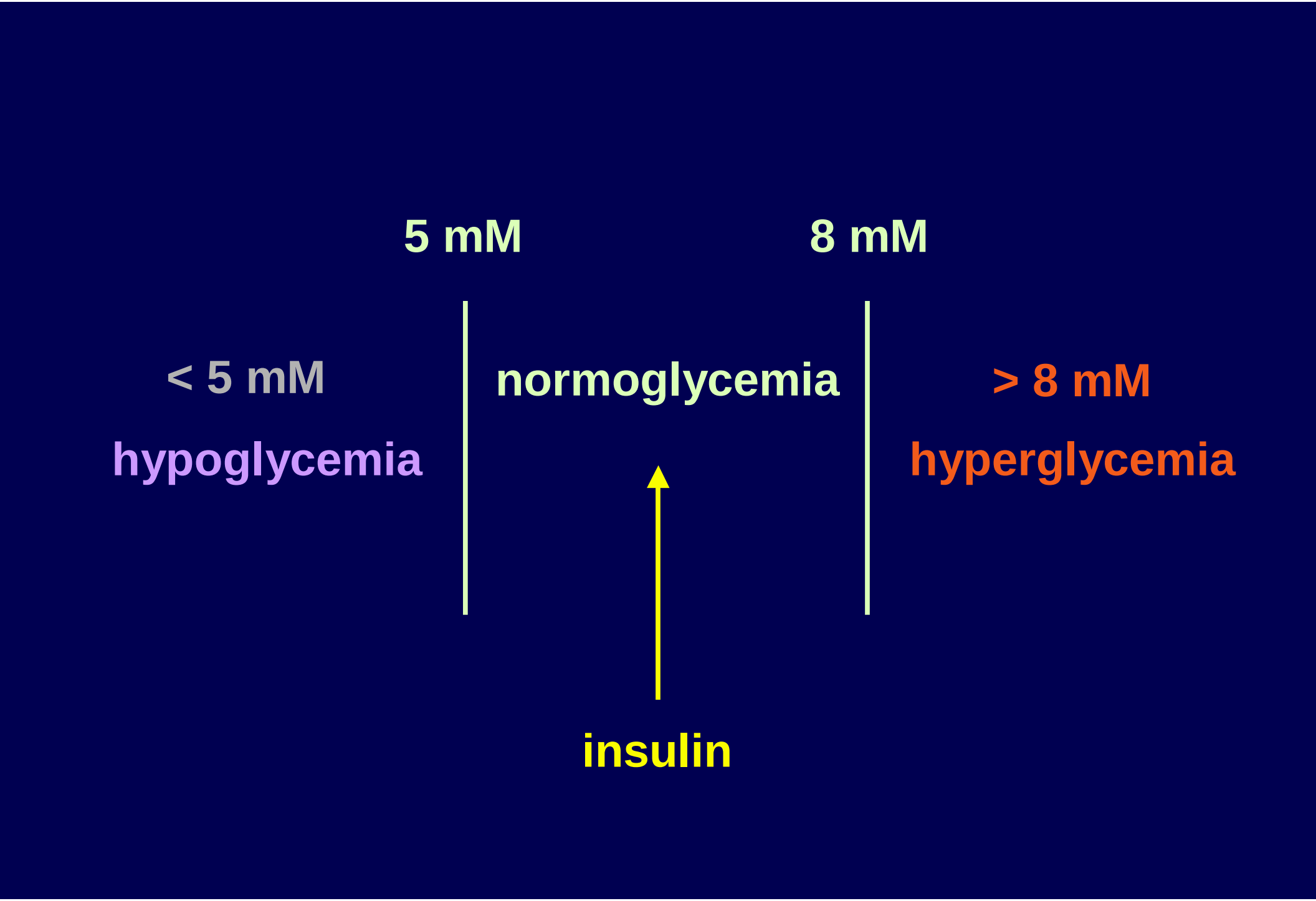
## Necessary

One of the most important source of energy of our organism

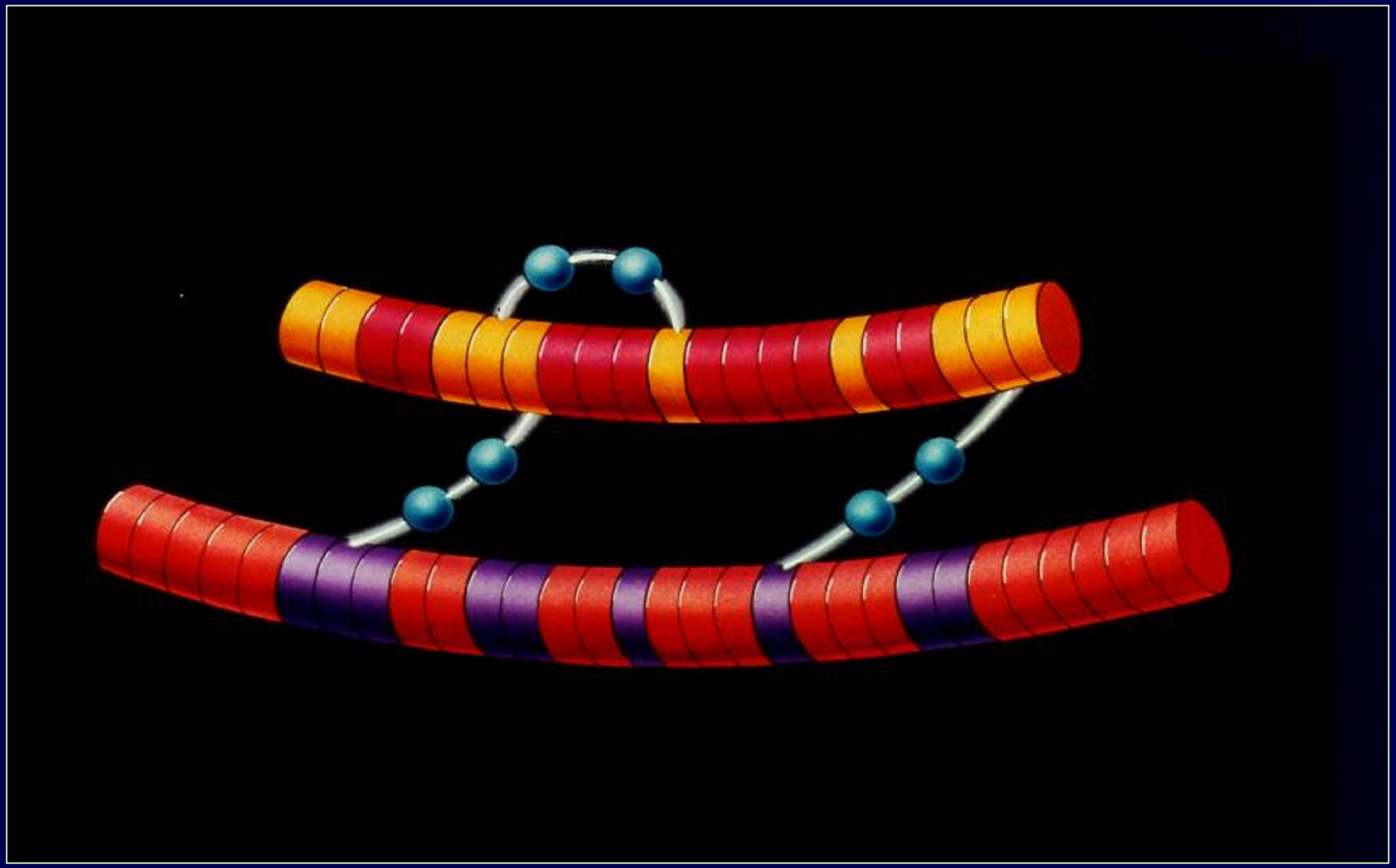
## Dangerous

if glucose blood level:

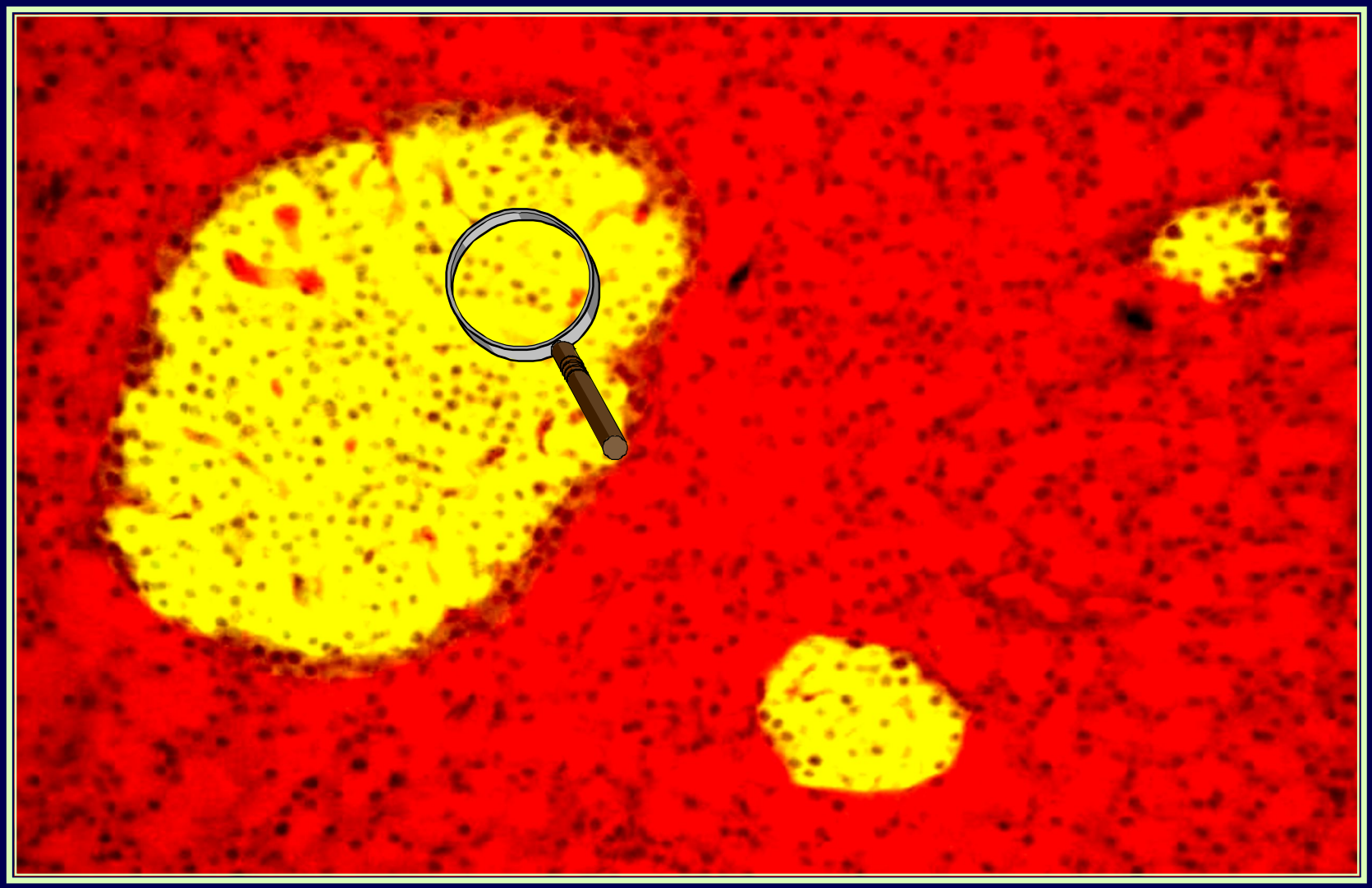
- Too low : hypoglycemia
- Too high : hyperglycemia


5 mM
8 mM
< 5 mM
hypoglycemia
normoglycemia
> 8 mM
hyperglycemia
insulin

# Insulin

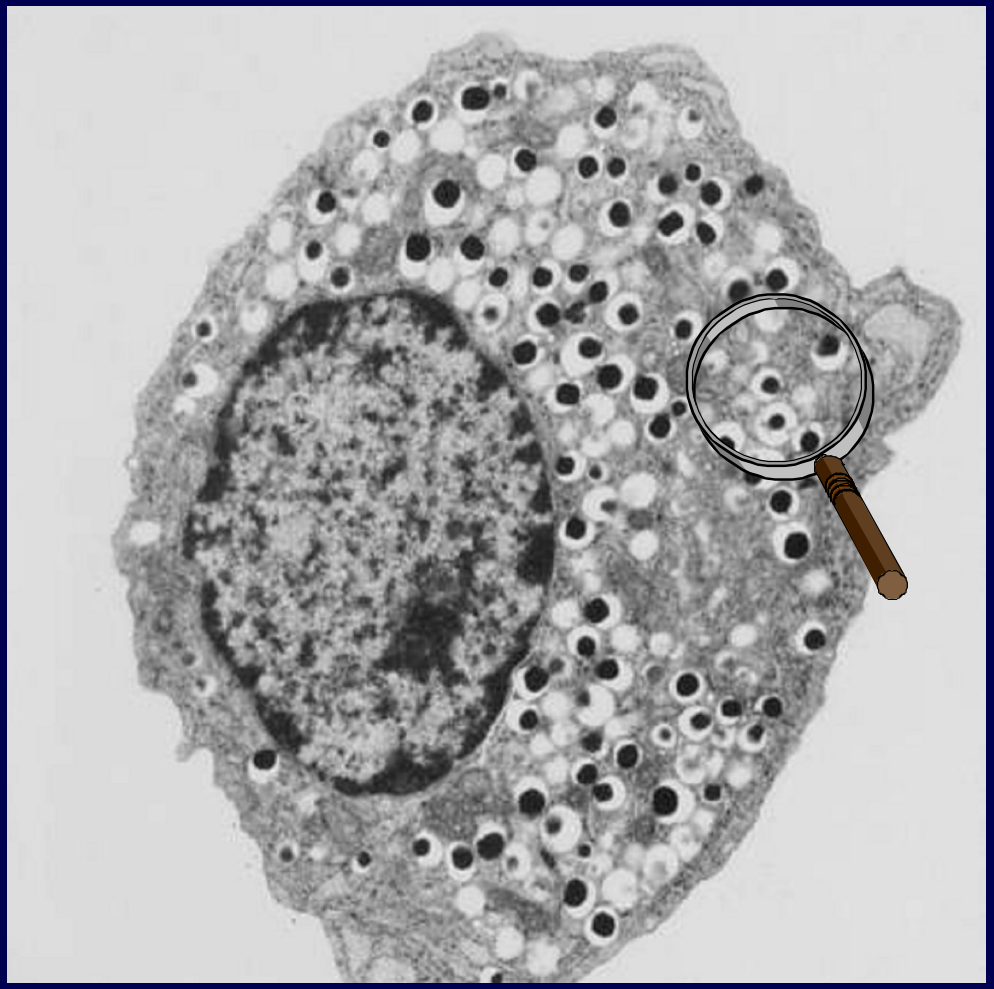


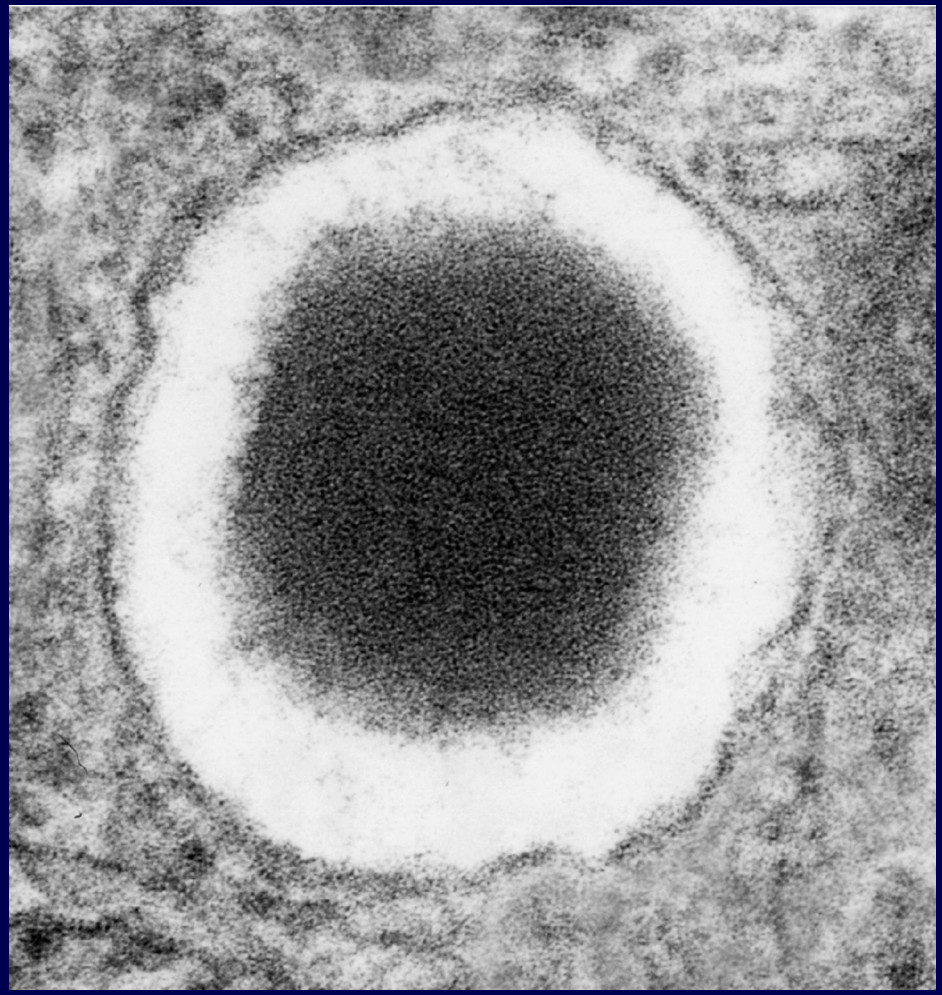
# The islet of Langerhans



L. Orci

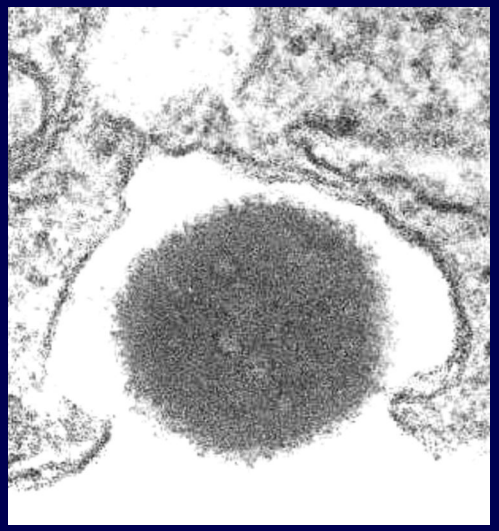
# The β cell

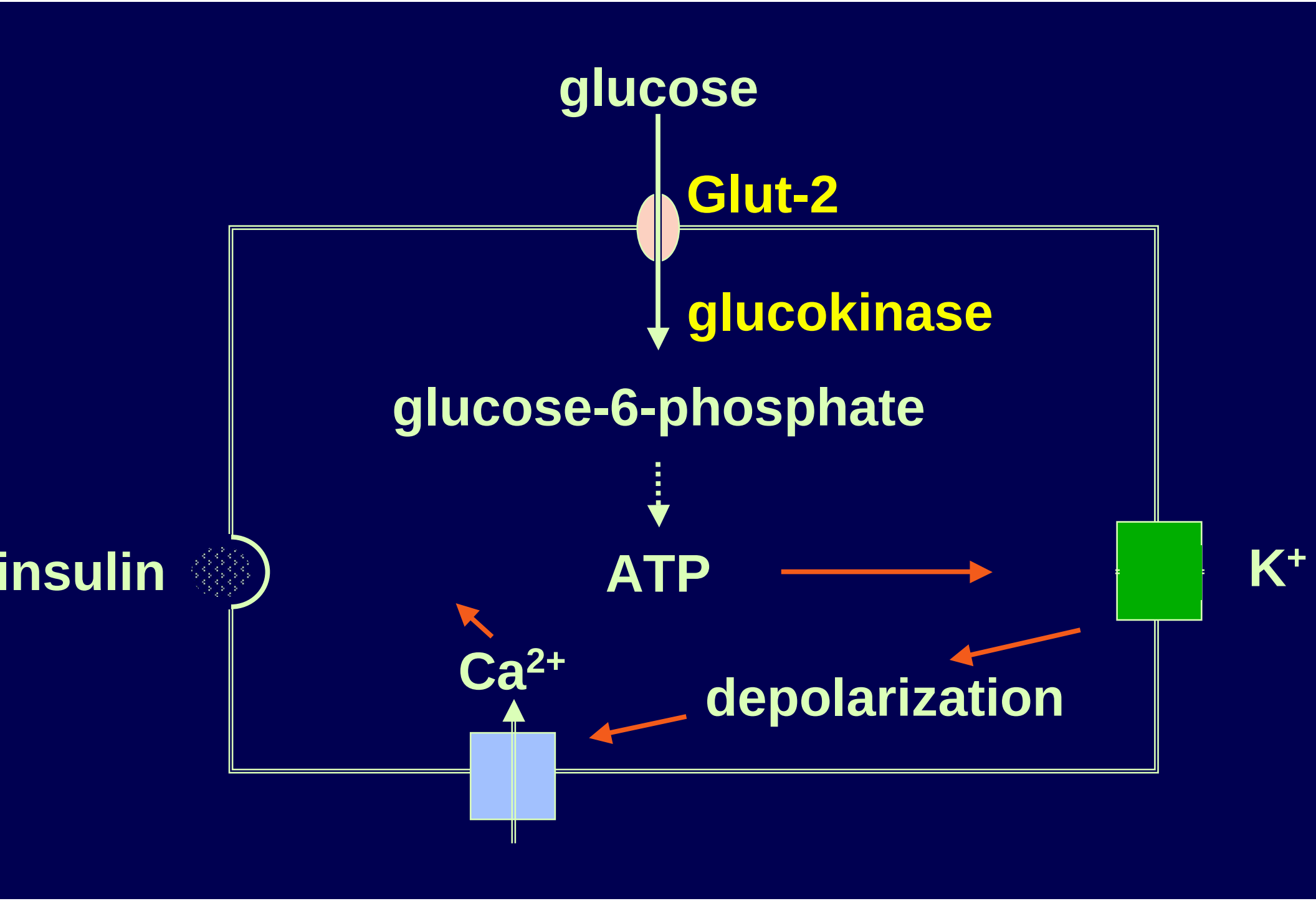


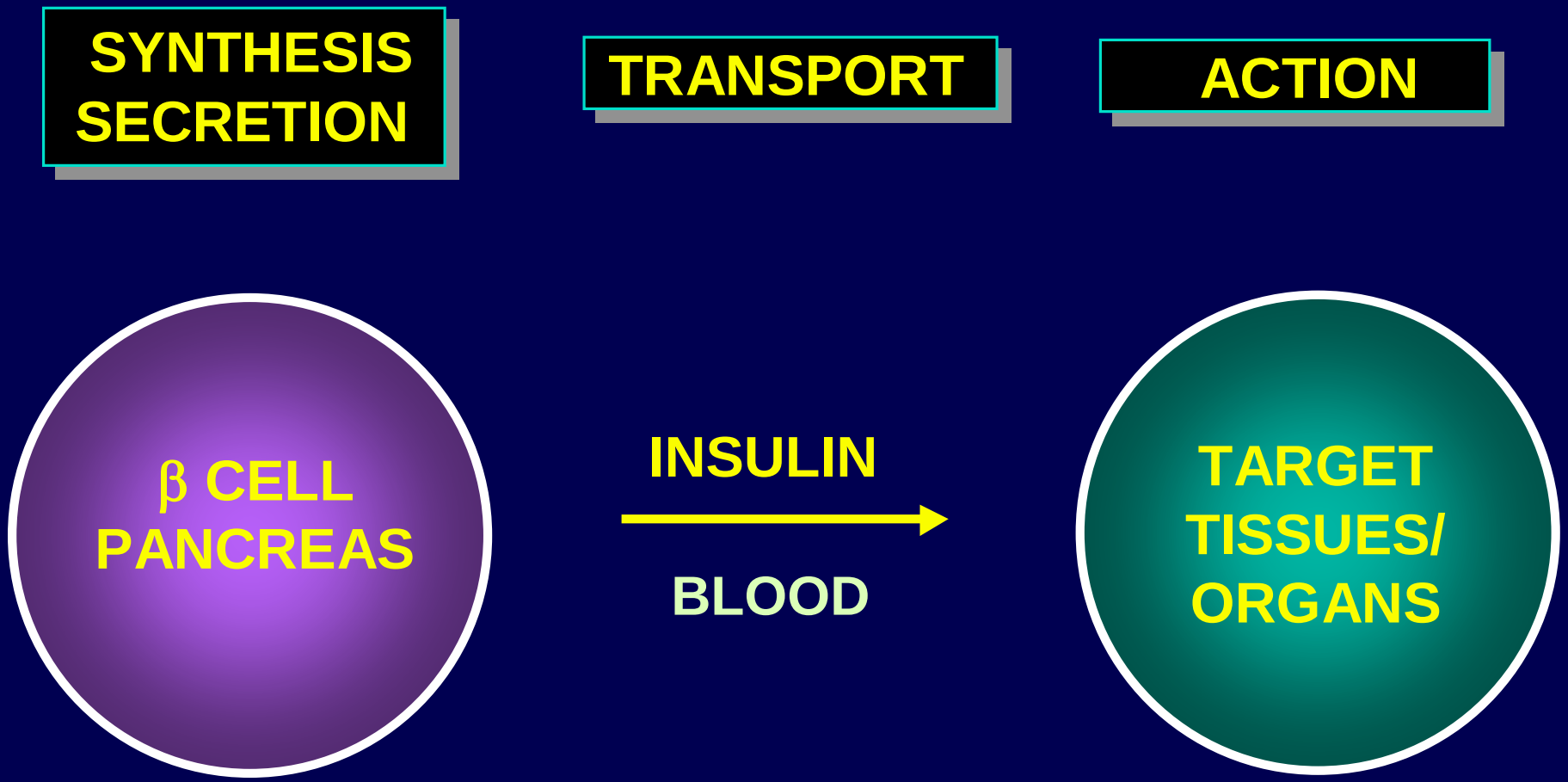


L. Orci

# Insulin secretion by exocytosis




glucose
Glut-2
glucokinase
glucose-6-phosphate
insulin
ATP
K+
Ca2+
depolarization


SYNTHESIS
SECRETION
TRANSPORT
ACTION
β CELL
PANCREAS
INSULIN
BLOOD
TARGET
TISSUES/
ORGANS

# Insulin main target tissues and organs

liver

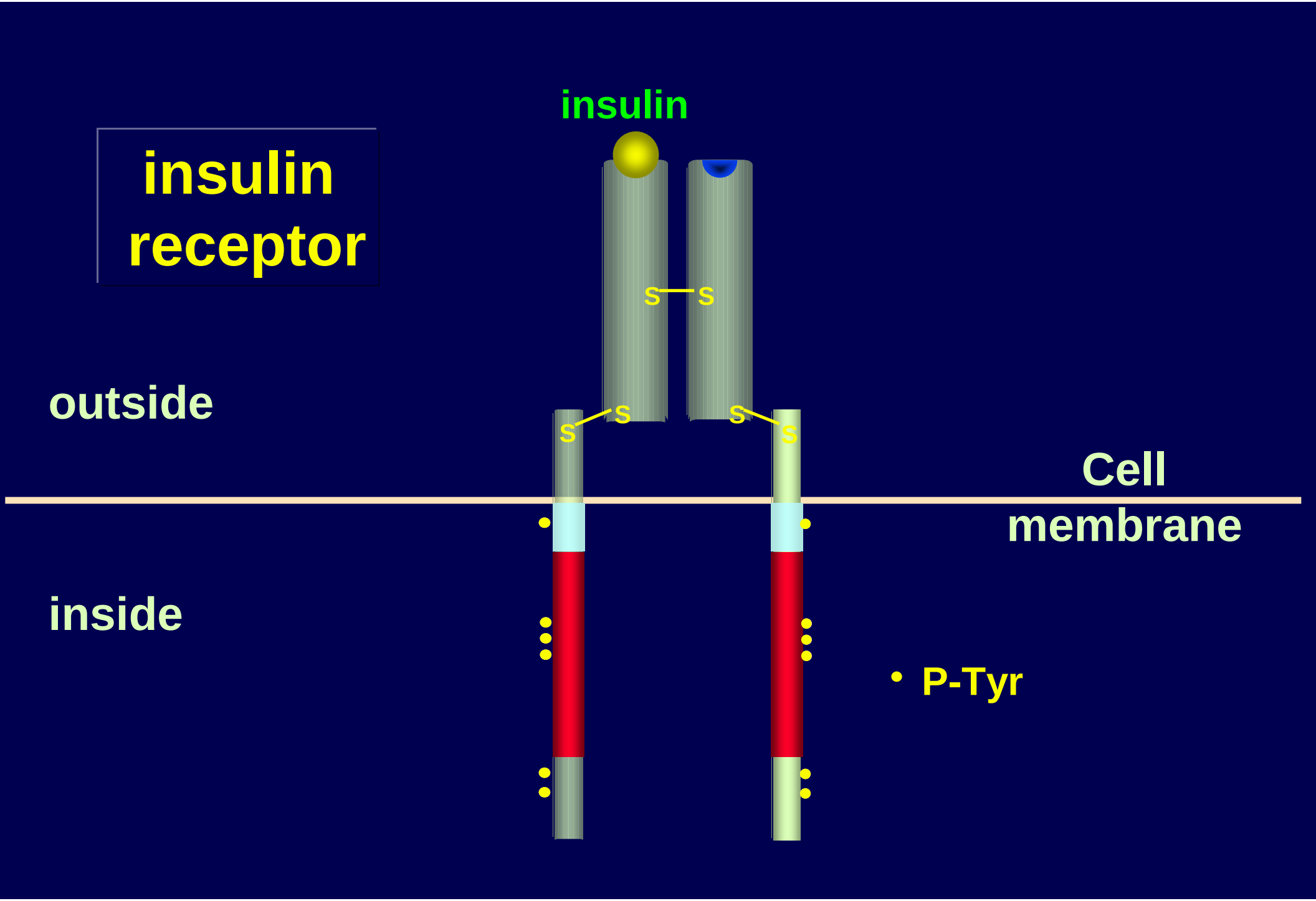
Adipose tissue

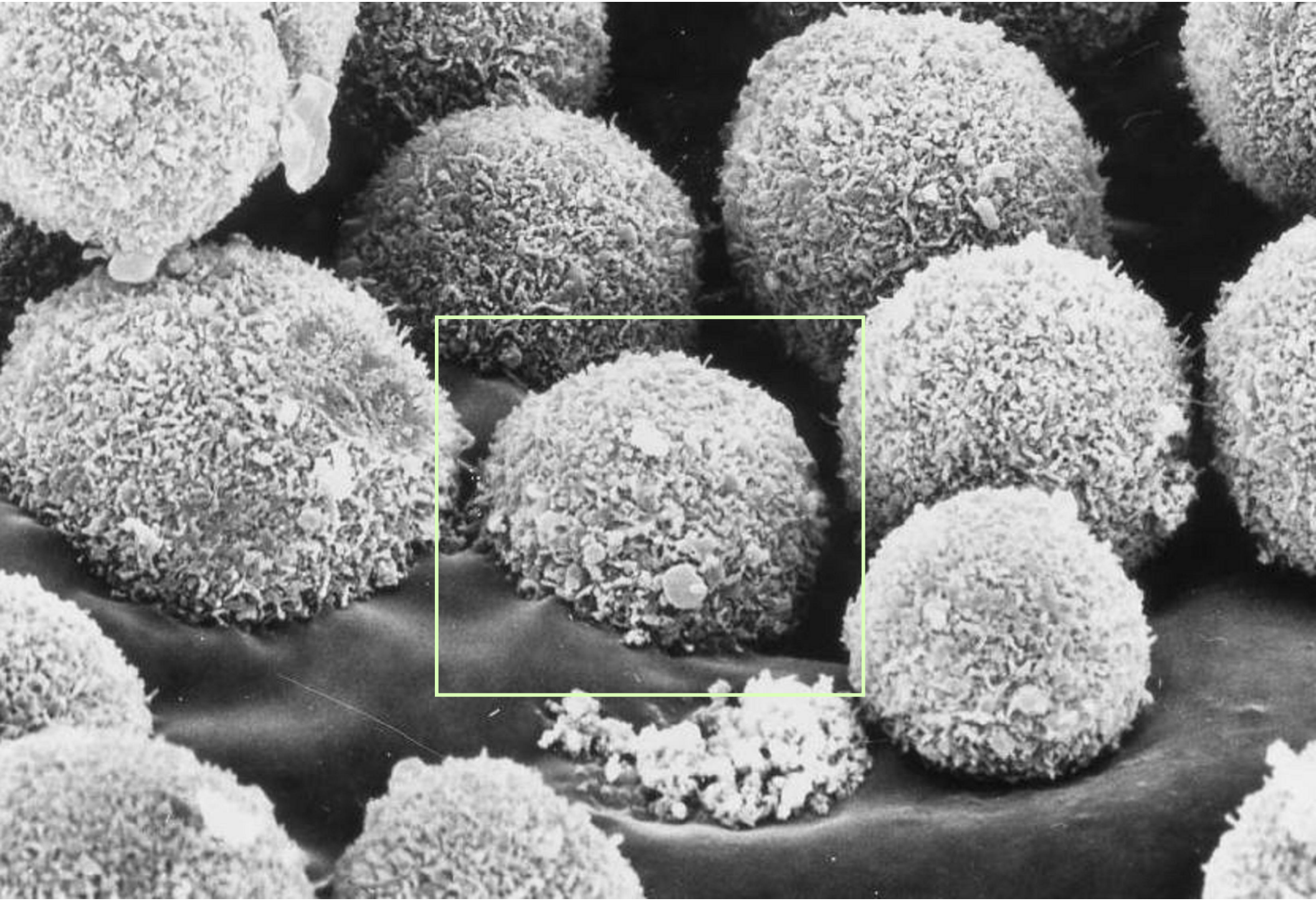
muscle

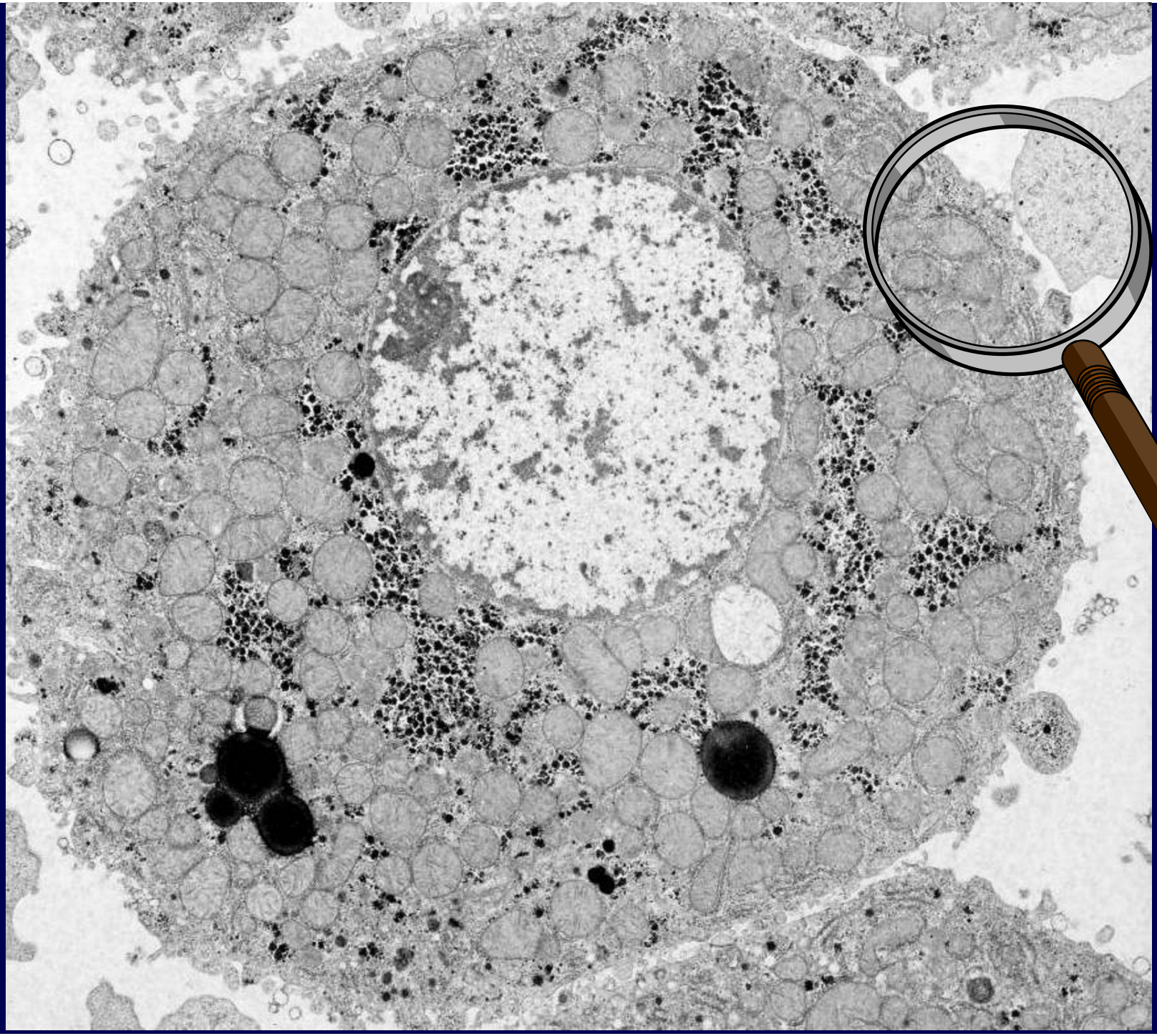
# Insulin receptor

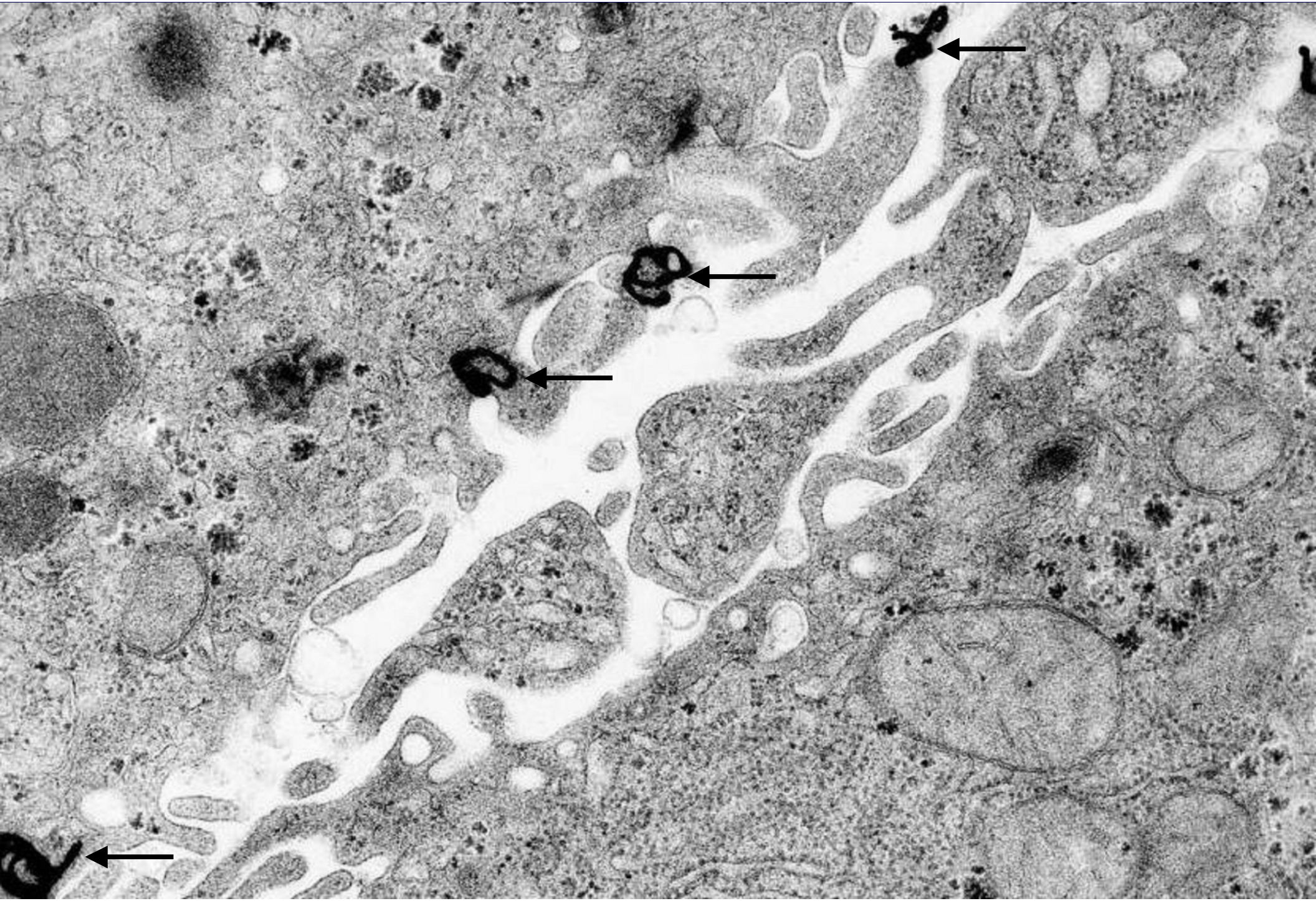
- Recognition system for insulin
- Highly specific for insulin
- Transmit the insulin biological signals to target cells

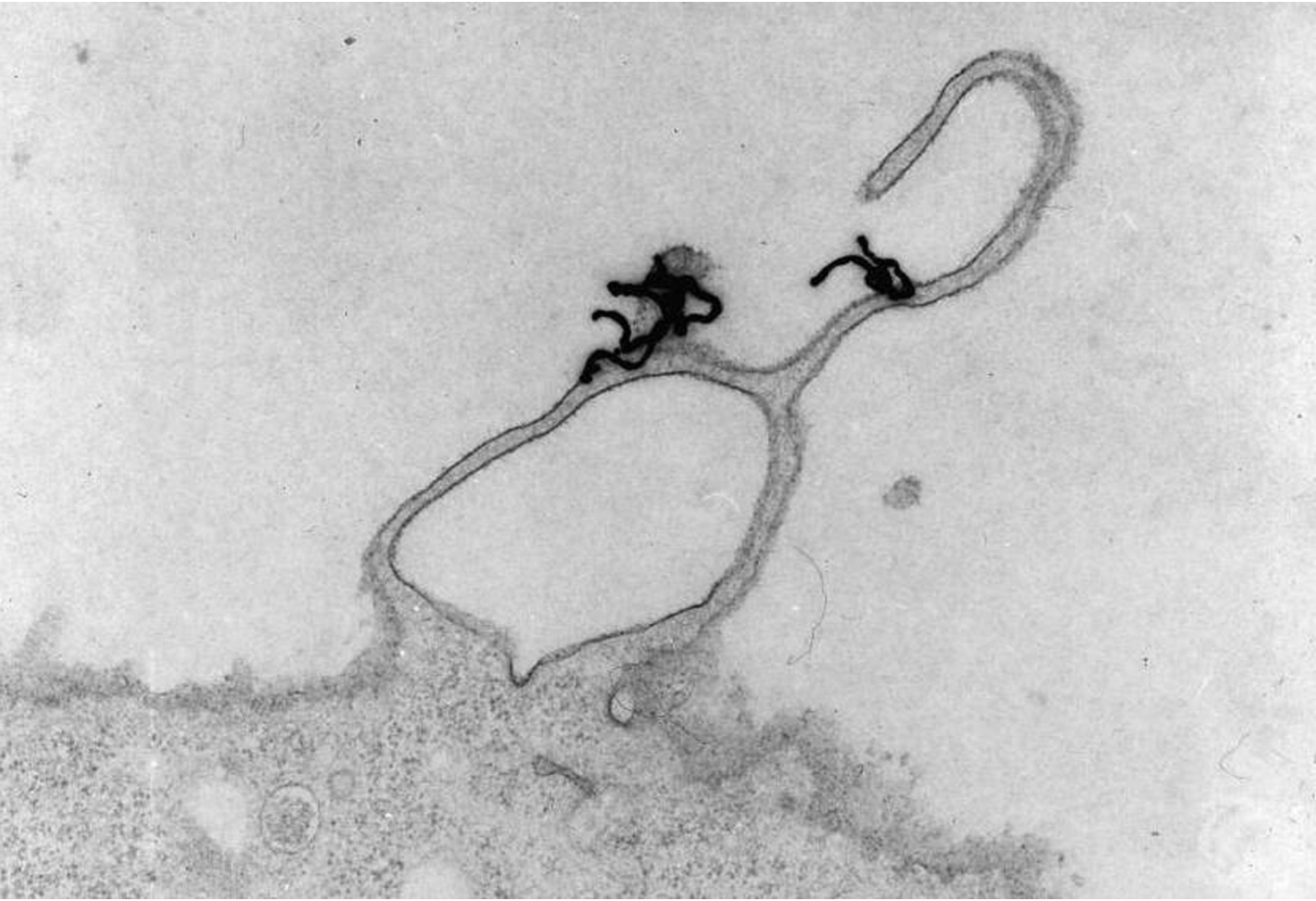
# insulin receptor

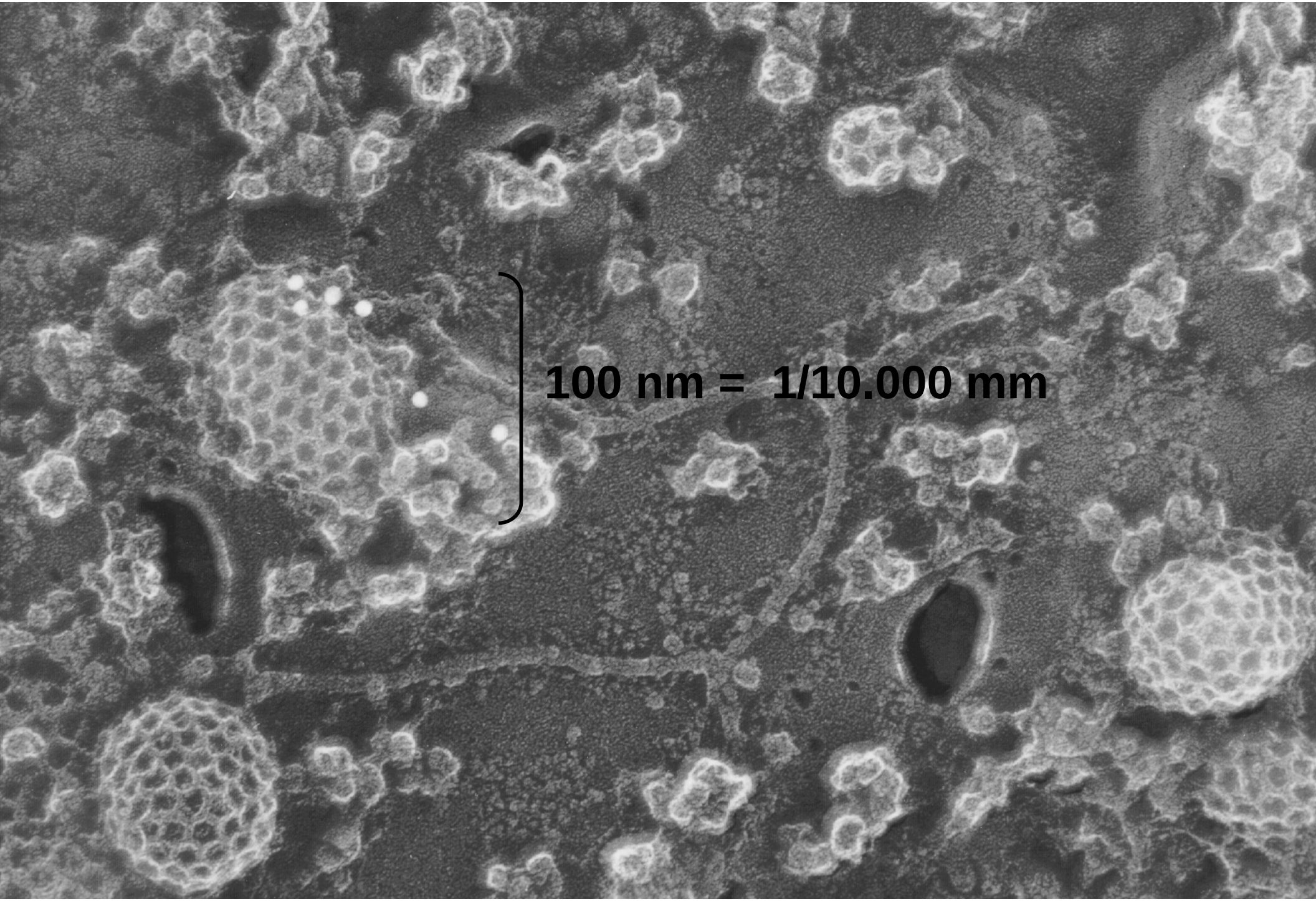


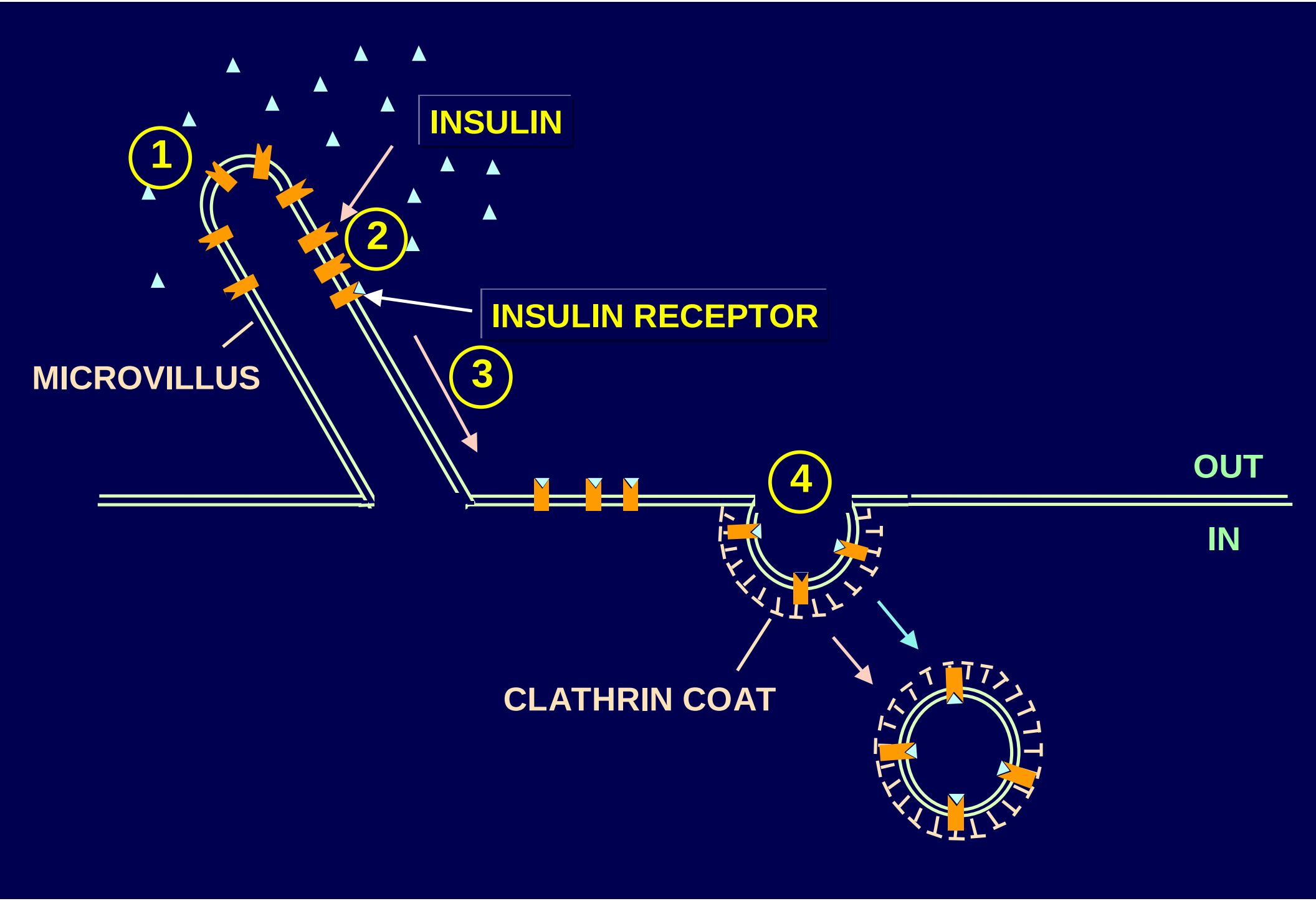


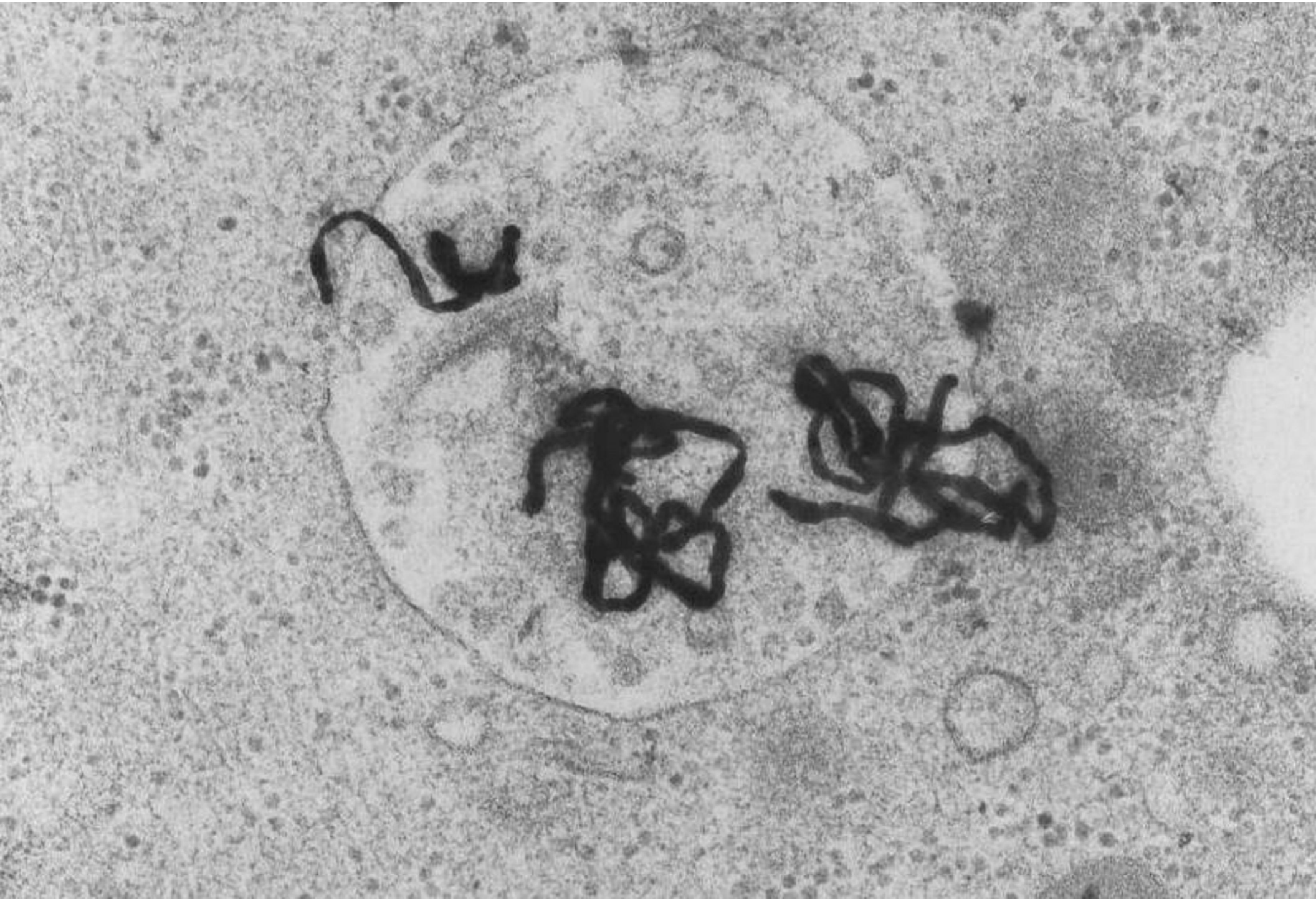




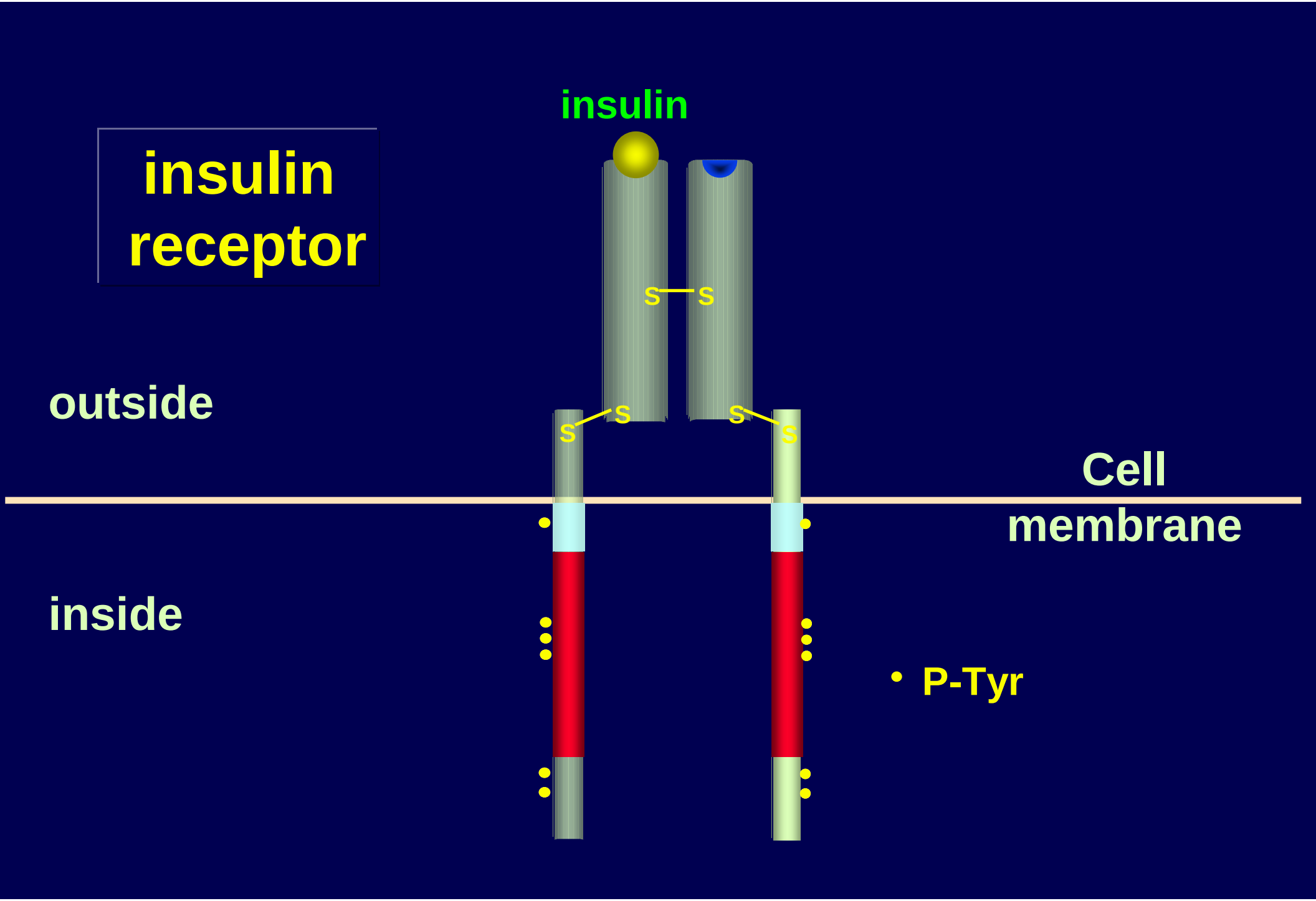



100 nm = 1/10.000 mm

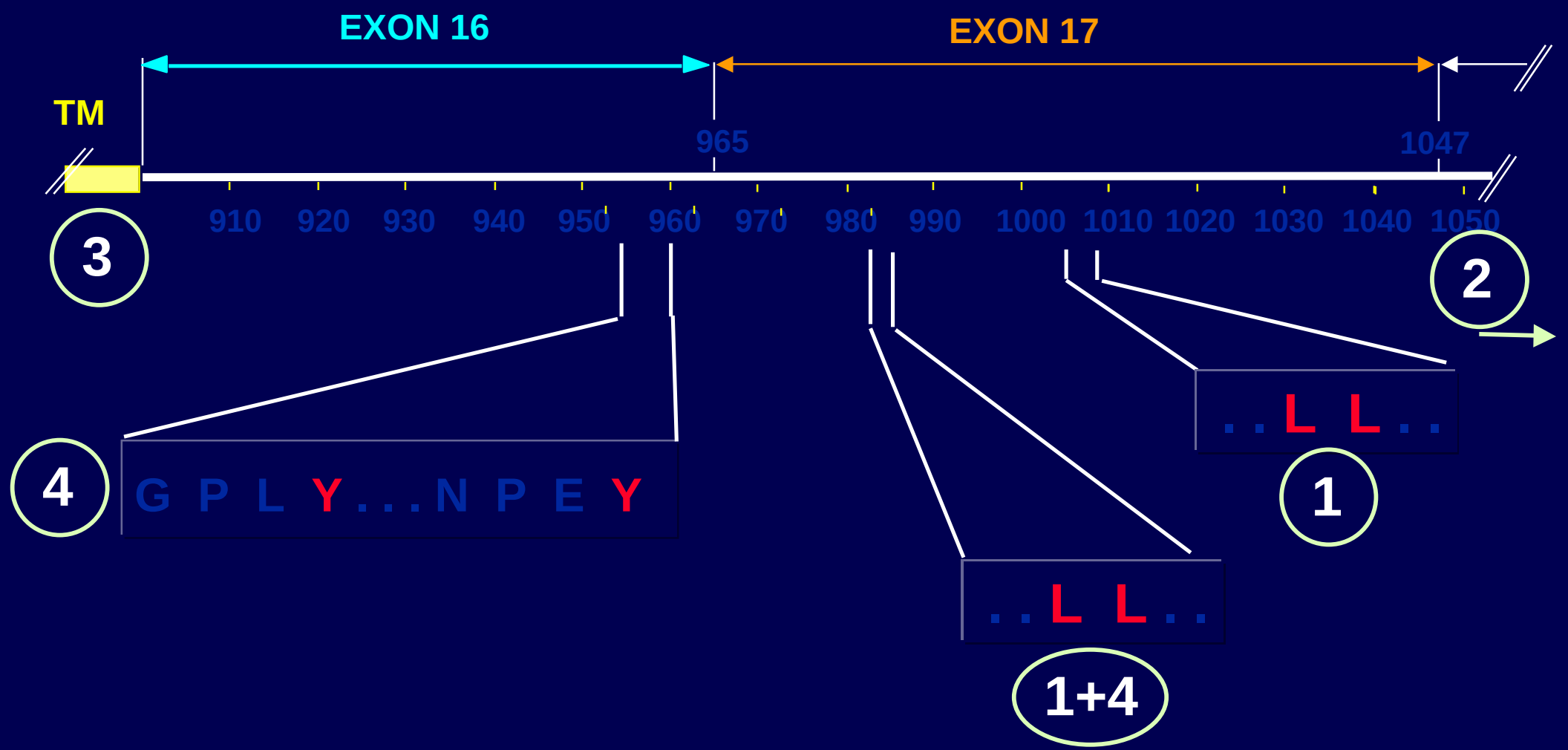

INSULIN
1
2
INSULIN RECEPTOR
MICROVILLUS
3
4
OUT
IN
CLATHRIN COAT



# insulin receptor

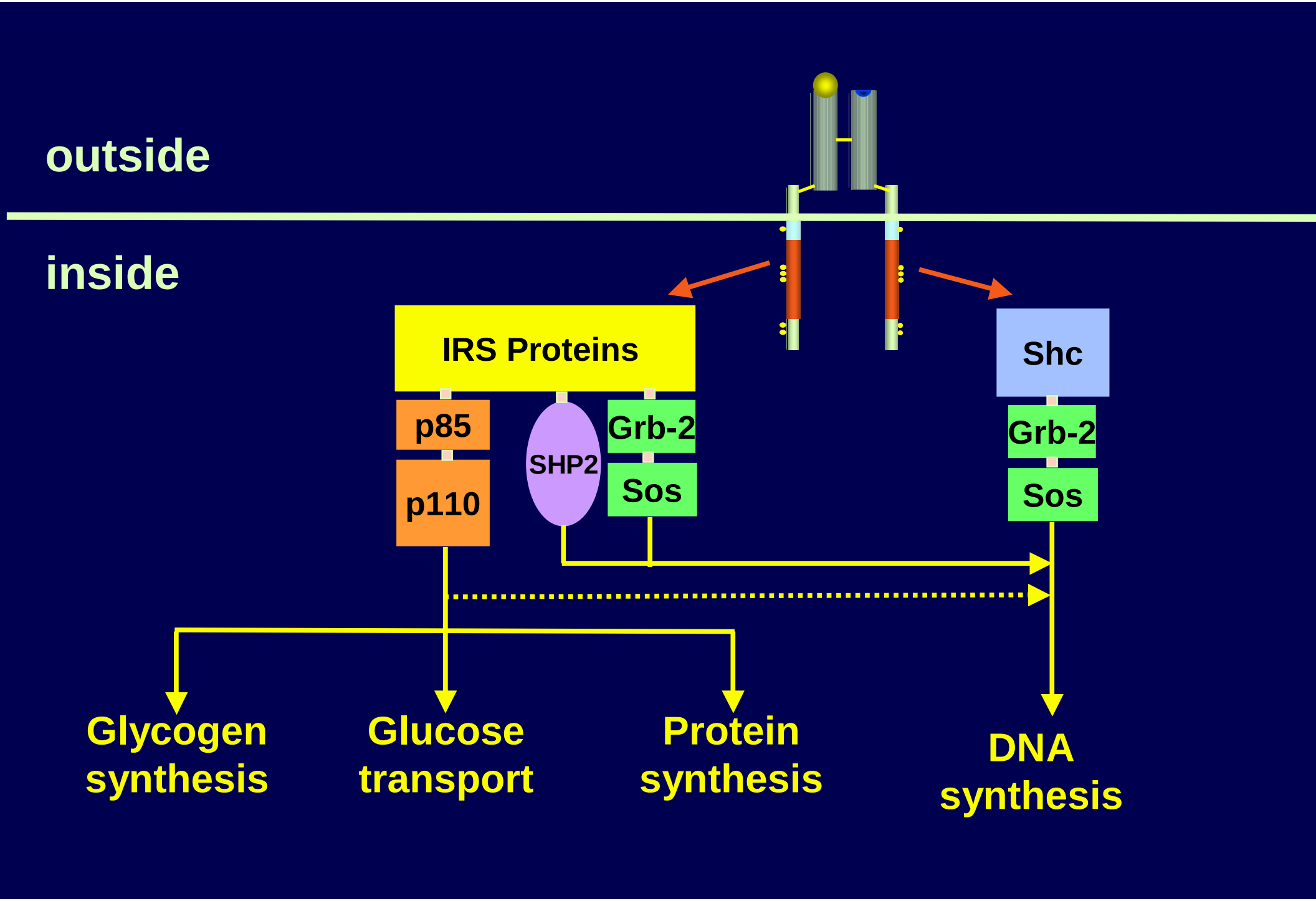


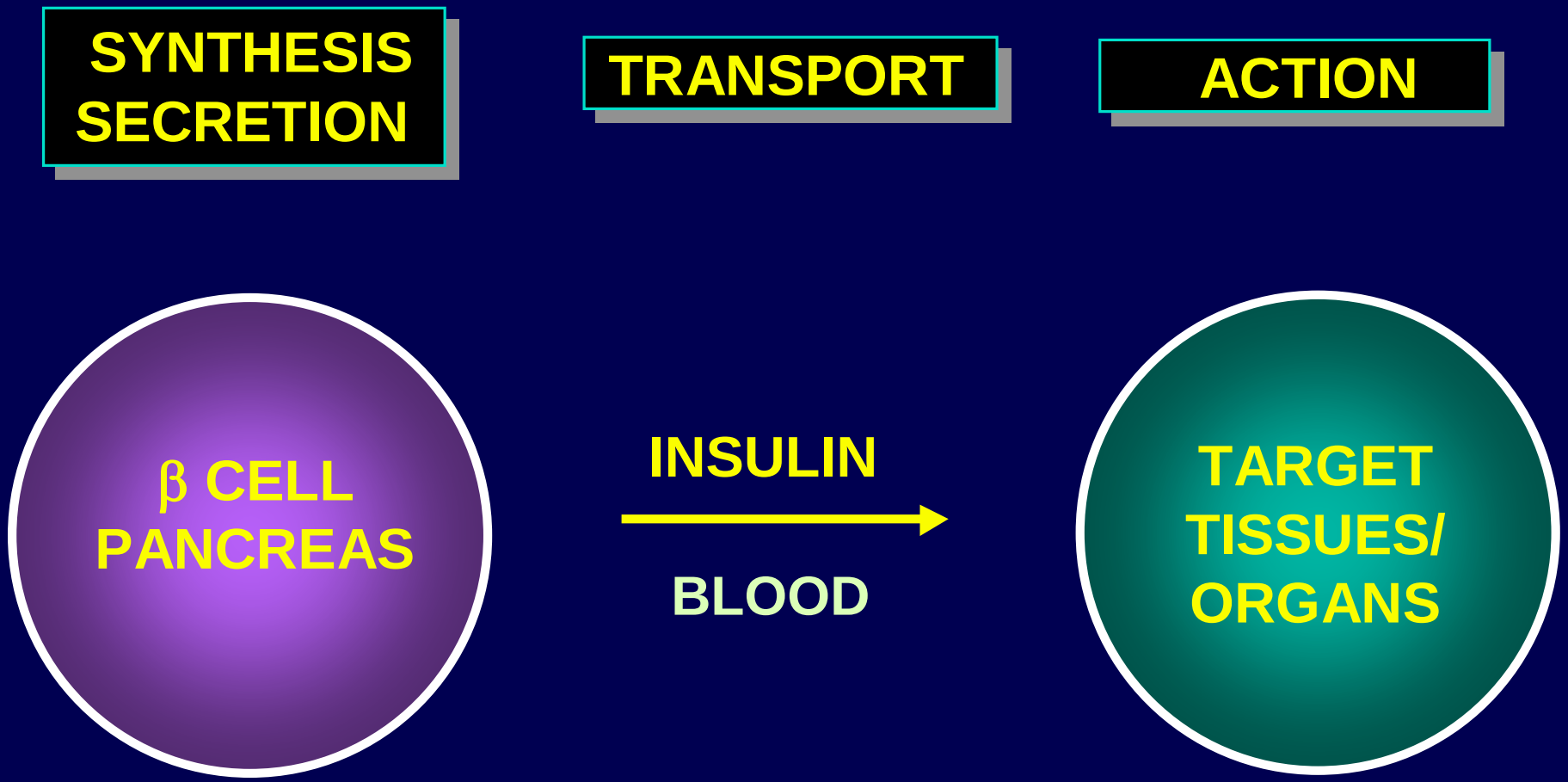
# HIR domains implicated in surface localization



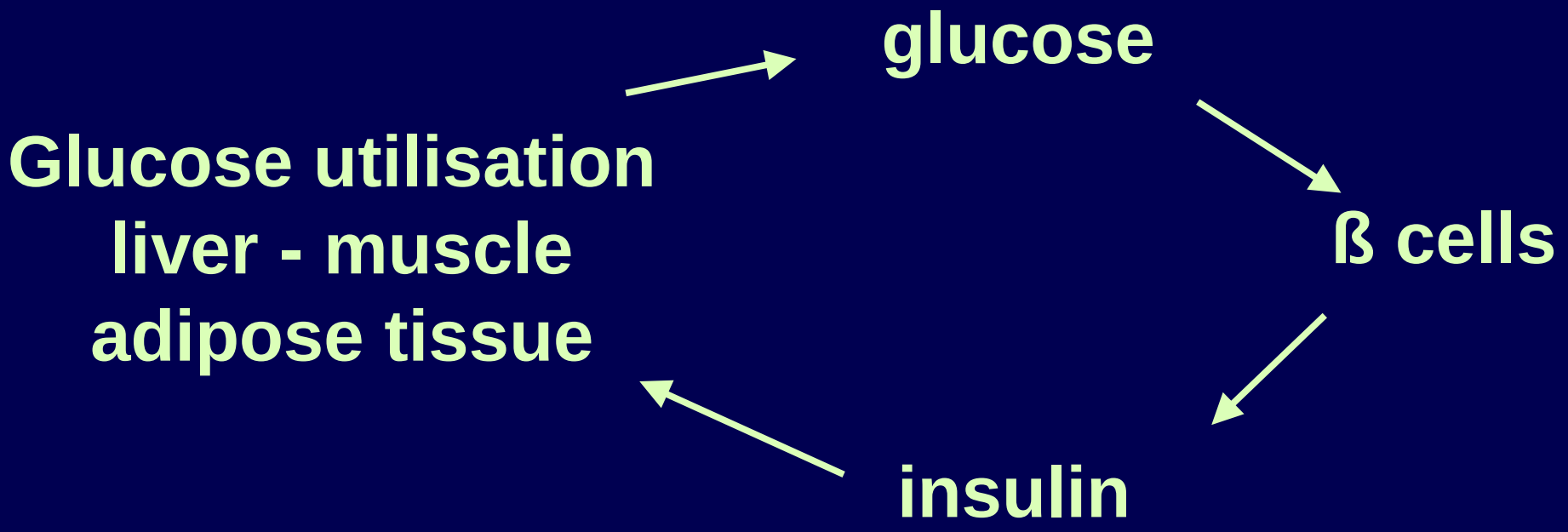
# Insulin receptor

- Recognition system for insulin
- Highly specific for insulin
- Is internalized by the target cell
- Transmit the insulin biological signals to target cells

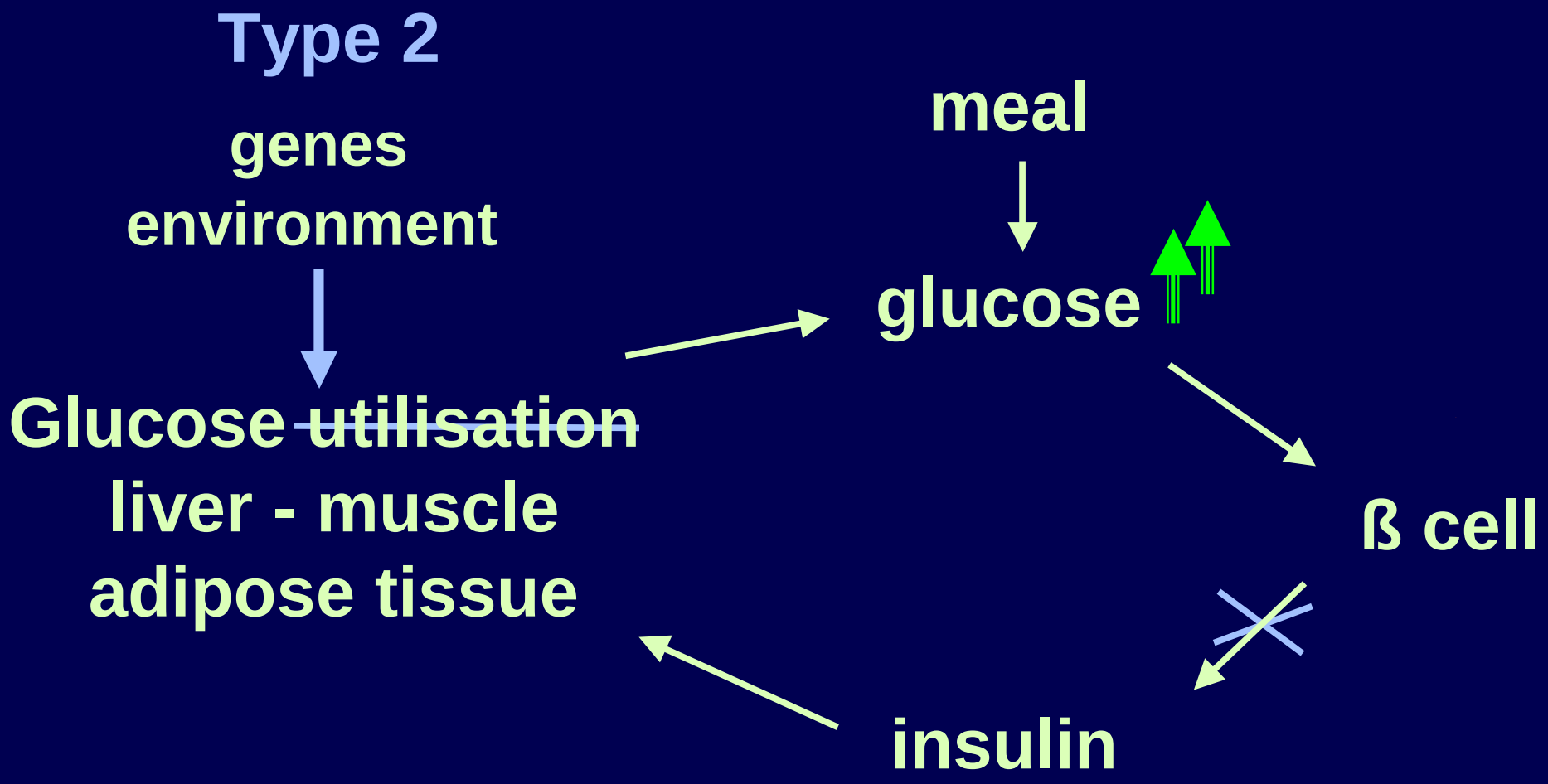

outside
inside
IRS Proteins
p85
p110
SHP2
Grb-2
Sos
Shc
Grb-2
Sos
Glycogen synthesis
Glucose transport
Protein synthesis
DNA synthesis


SYNTHESIS
SECRETION
TRANSPORT
ACTION
β CELL
PANCREAS
INSULIN
BLOOD
TARGET
TISSUES/
ORGANS

# The closed loop “glucose-insulin”



# The two types of diabetes mellitus



# The two types of diabetes mellitus

**Type 1**
**insulino-dependant**
**juvenile**

} **env. 10%**

**Type 2**
**non-insulino-dependant**
**adult**

} **env. 90%**

# Treatment of Type 2 diabetes (non-insulino-dependant)

**Today:**

- Diet + exercice
- Oral Hypoglycemic drugs
- Insulin

**Yes, but……**

- Individual variations
- Poor specificity and activity of oral hypoglycemic drugs
- Insulin……

# Treatment of Type 1 diabetes (insulino-dependant)

Mecanical administration of exogenous insulin

**Today:** Multiple insulin injections

Insulin pumps

**Yes, but……** Multiple glycemia analysis

Needles…..

**Tomorrow:** Non-invasive measurements of glycemia

“Closed loop” systems

Non-injectable insulins

# Treatment of Type 1 diabetes (insulino-dependant)

## Cell replacement therapy

**Today:** **Pancreas/islets transplantation**

**Edmonton protocol**
**12 centers**

- **34 islet transplantations carried out with success**
- **75% patients insulino-independant after 2 years**
- **1 receiver insulino-independant after 10 years**

**Yes, but……** **Immunosuppression**

**Shortage of organs**

# Treatment of Type 1 diabetes (insulino-dependant)

## Cell replacement therapy

**Tomorrow:** Gene or cell therapy involving embryonic or adult stem cells

## Some definitions:

**Gene therapy**

**Introduction of a gene(s) *in vivo* leading to ectopic insulin production or regeneration of ß-cells**

**Cell therapy**

**Generation *in vitro* of large numbers of ß-cells or surrogates followed by (re)implantation.**

# Gene therapy

**Introduction of genes in cells of a patient in order to modify their behavior**

**……for Type 1 diabetes treatment :**

***fabrication of insulin by non-ß cells***

# Gene therapy

*Fabrication of insulin by non-ß cells*

**What is possible :**

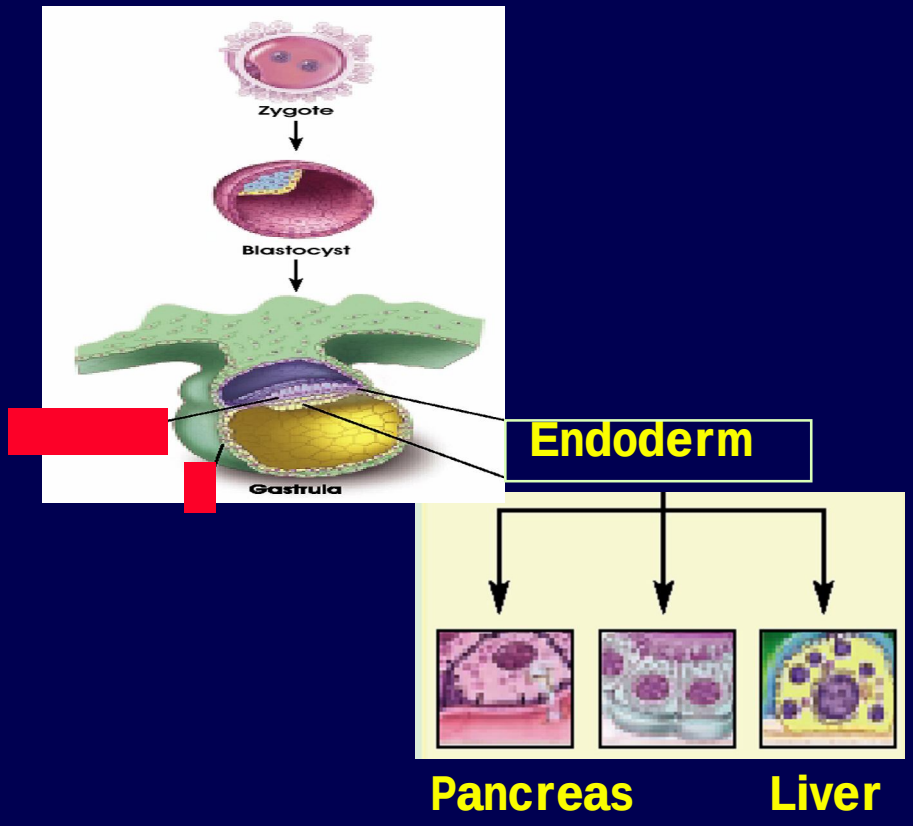
**To express insulin genes in non-ß cells**

***skin, liver, muscle…..***

**Strategy :**

**Remove cells from patient - amplify (proliferate) - induce ß-cell phenotype - implant back into patient**

# The liver and the pancreas have the same endodermal origin




- Easy access: biopsy
- No ethical problem

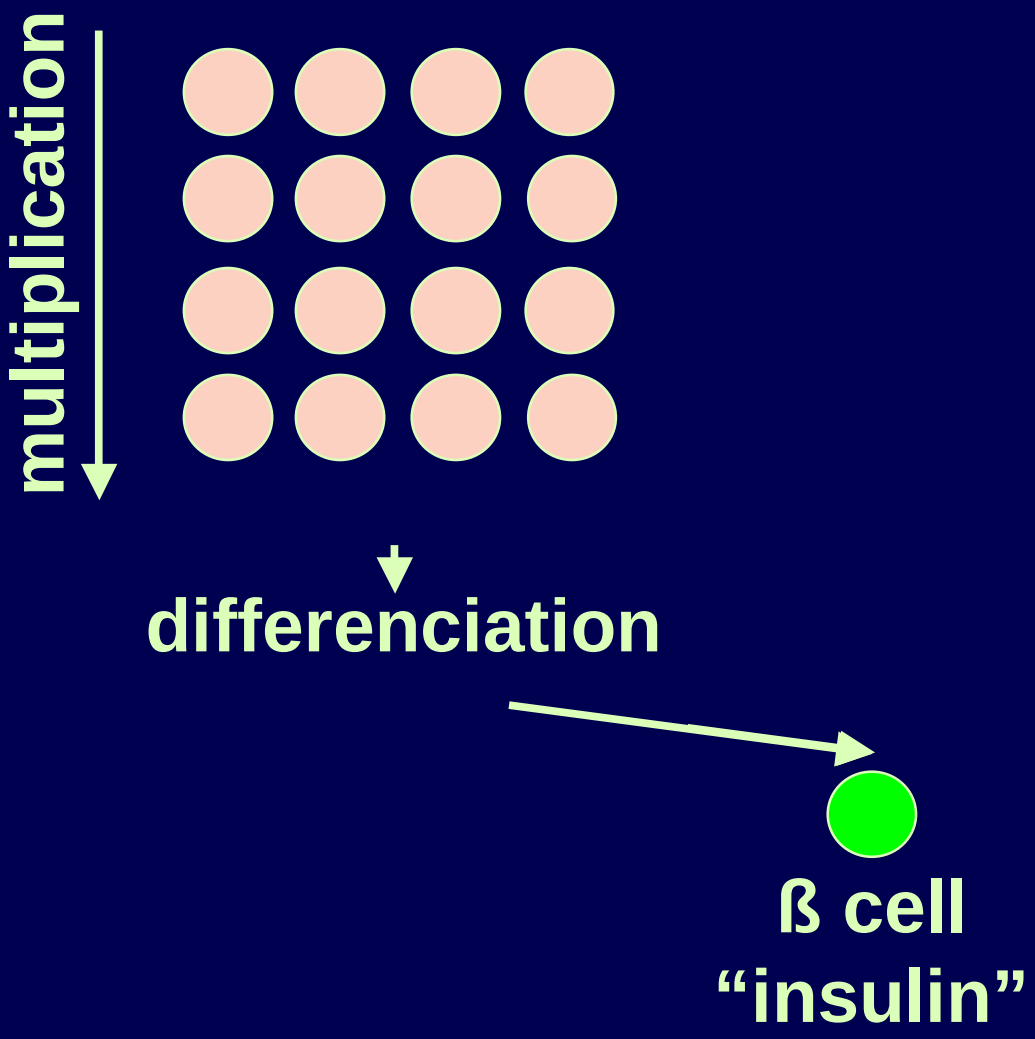
Similar genetic program → Easier production of insulin secreting cells (?)

# Stem cell therapy

**Implantation of insulin secreting cells obtained from:**

**Stem cells**

# From one stem cell to billions of specialized cells



# Stem cells

**Totipotent or pluripotent, they divide and multiply in culture and can differentiate in several types of specialized cells**

***One can distinguish embryonic and adult stem cells***

# Use of stem cells to create ß-cells

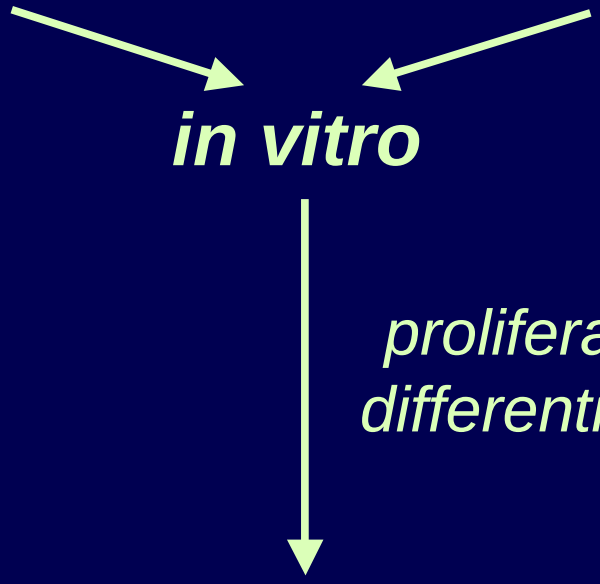
**Embryonic stem cells**

**totipotent**

**Adult stem cells**

liver, pancreas, brain,
muscle,bone marrow,skin….

**pluripotent**



***in vitro***

*proliferation*
*differentiation*

**ß-cell**

# Gene and cell therapy

## *The risks and the ethic problems*

**Insulin is a very potent hormone : in excess it causes death**

**The B cell is very complex: it will be difficult to develop a substituting cell**

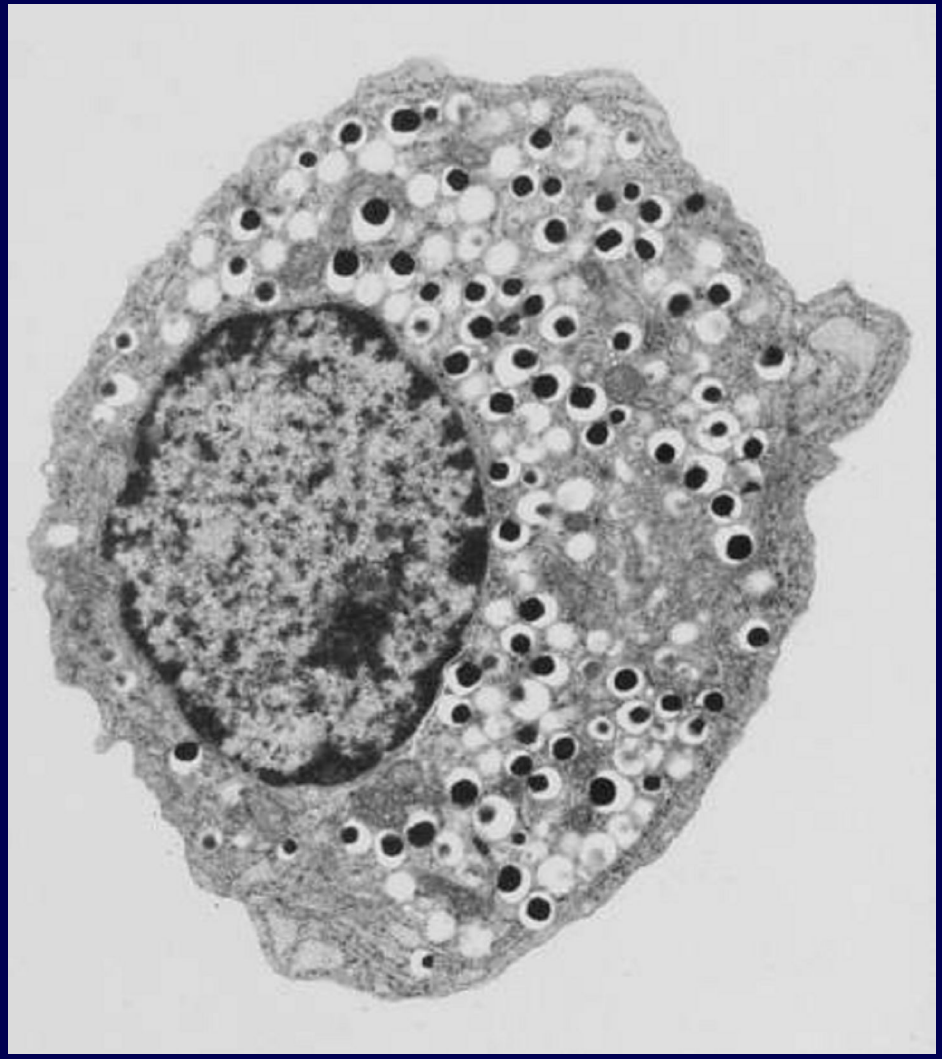
**Gene therapy is experimental: first people died already of this treatment…**

**Embryonic stem cells : the ethic problem….**

# The Beta Cell

Insulin regulated secretory pathway

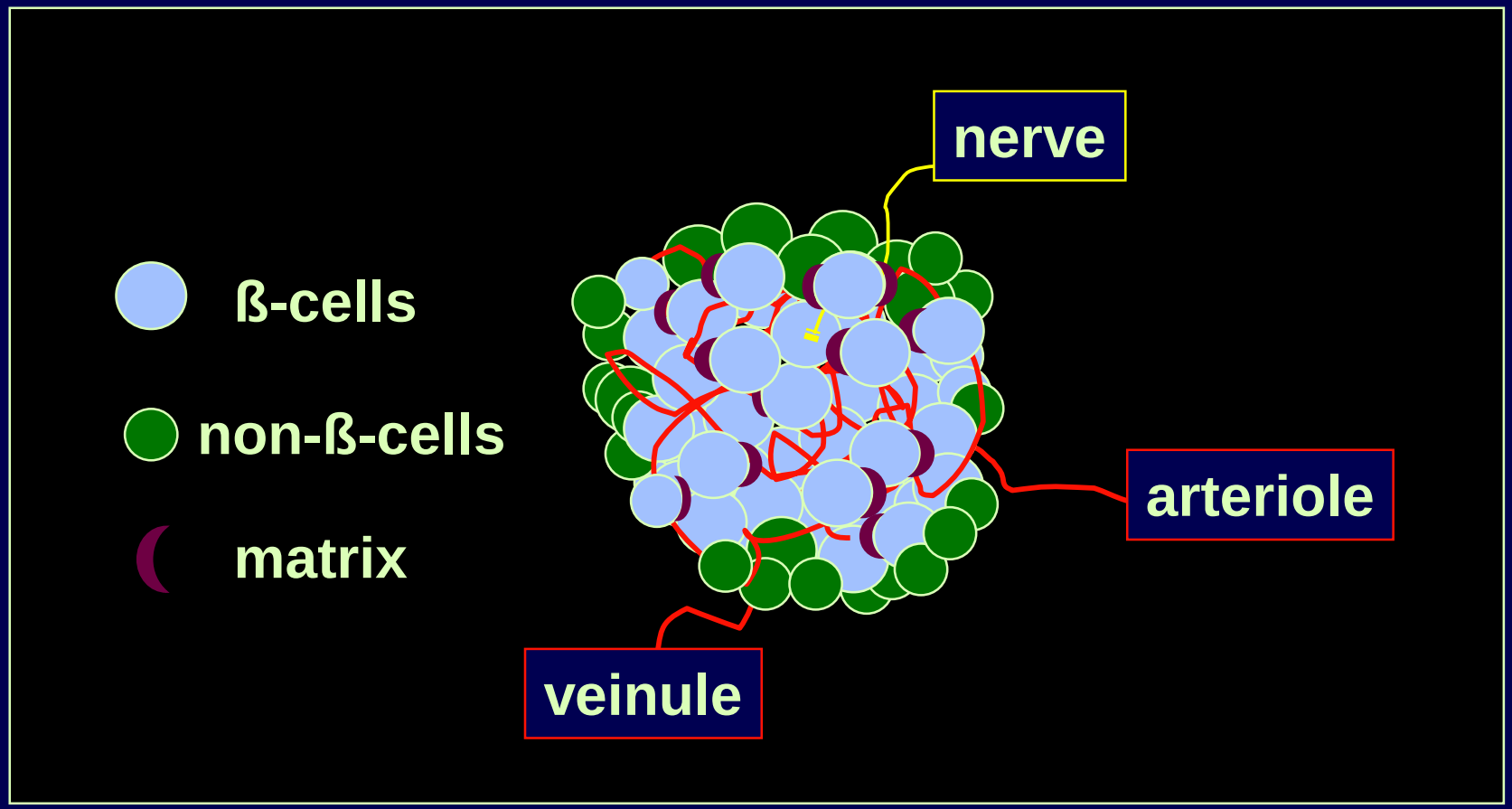
Stimulus secretion coupling



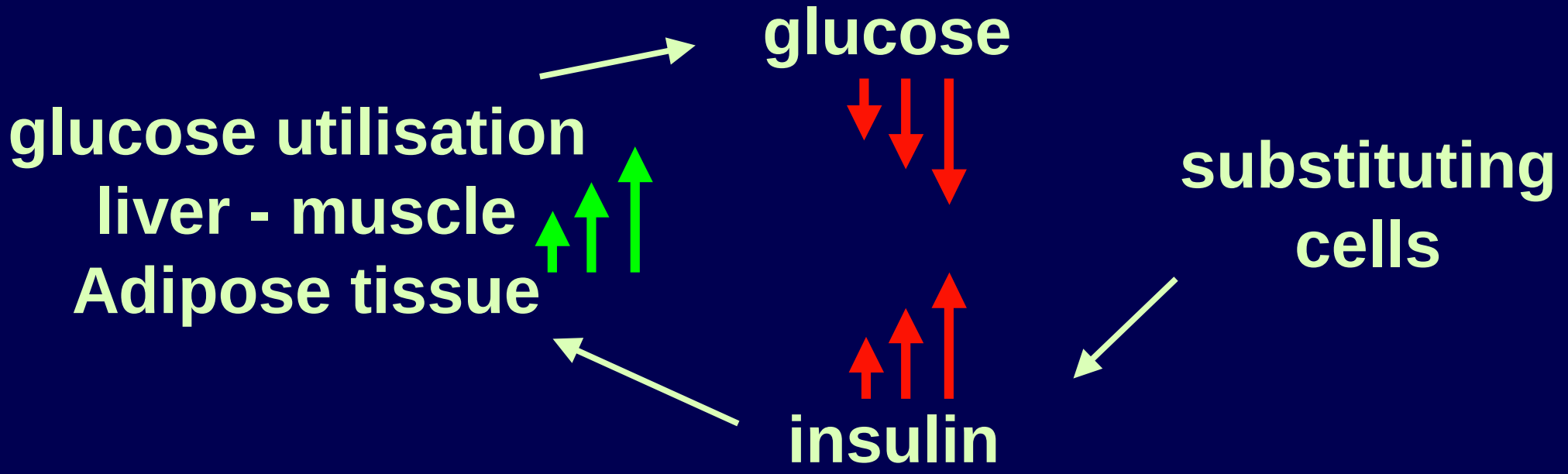
Communication (cells and matrix)

Micrograph: Lelio Orci, Geneva

# The role of cellular environment on ß-cell function



# Consequences of the opening of the closed loop “glucose-insulin”



# Conclusions

**Preliminary studies with mouse and human stem cells are encouraging**

**But…..**

**We are still far from developing highly differentiated human ß-cells in sufficient numbers to cure diabetes**

**Using stem cells will require us to overcome both technical and ethical obstacles**

**Still a long way to go…..**

**Be careful and always remember the complexity of the β cell and the dangers of insulin itself!!!**

# La Faculté de médecine de l'Université de Genève

## Sa Localisation


HUG

CMU

# La Faculté de médecine de l’Université de Genève

## CMU 5/6

# La Faculté de médecine de l'Université de Genève

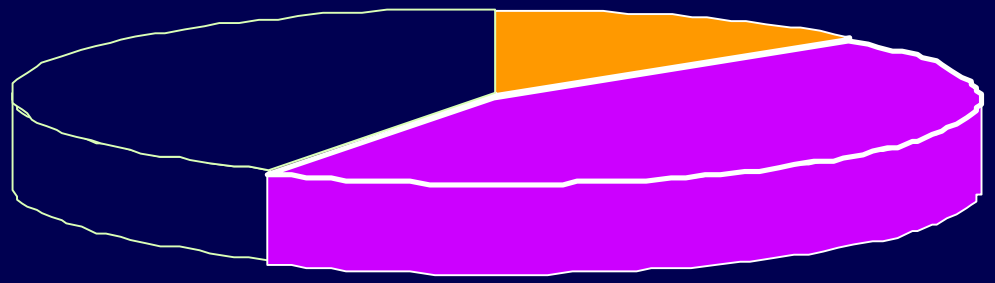
1'300 étudiants : 944 étudiants en médecine humaine
101 étudiants en médecine dentaire
255 étudiants postgradués

100 diplômés en médecine en moyenne/an

1'700 employé(e)s

Corps administratif et technique (720)

Corps professoral (220)



Corps enseignants et de chercheurs (760)

250 groupes de recherche

Budget 100 Millions ▪ €

Thank you for your attention!