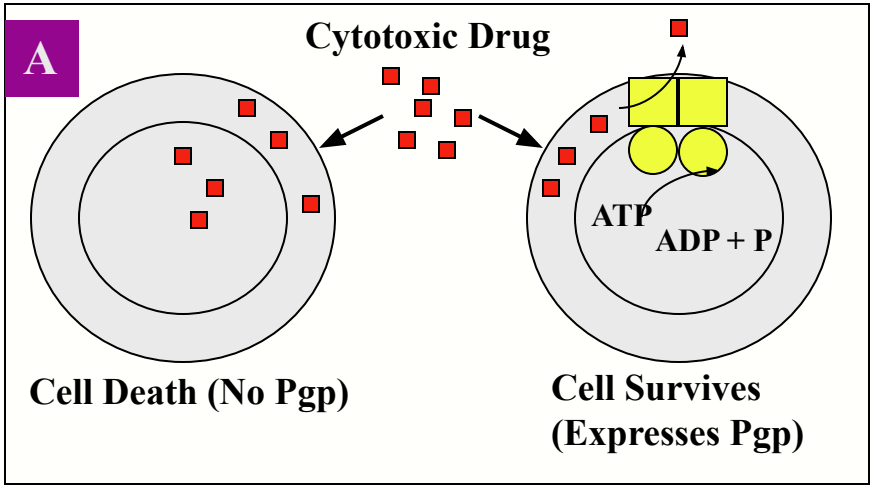
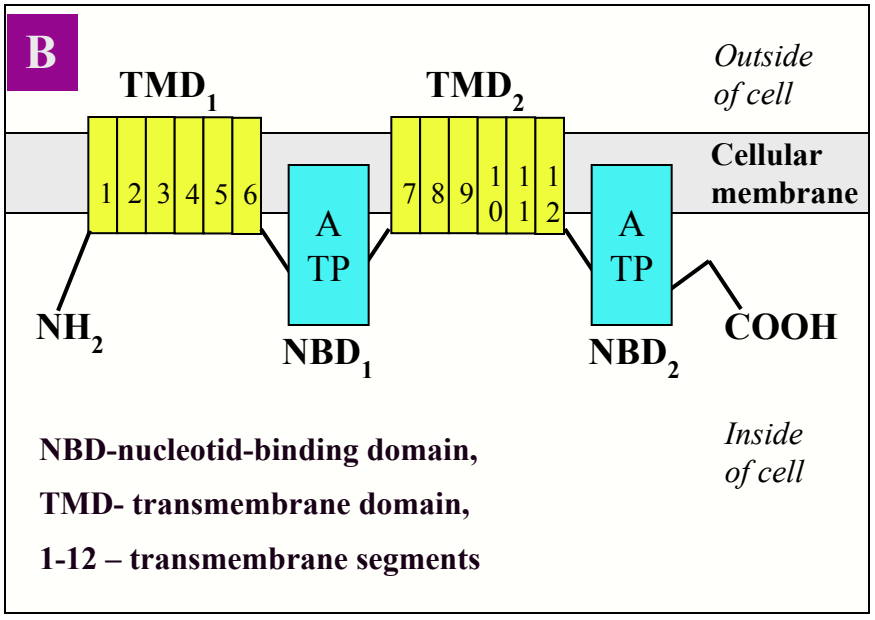
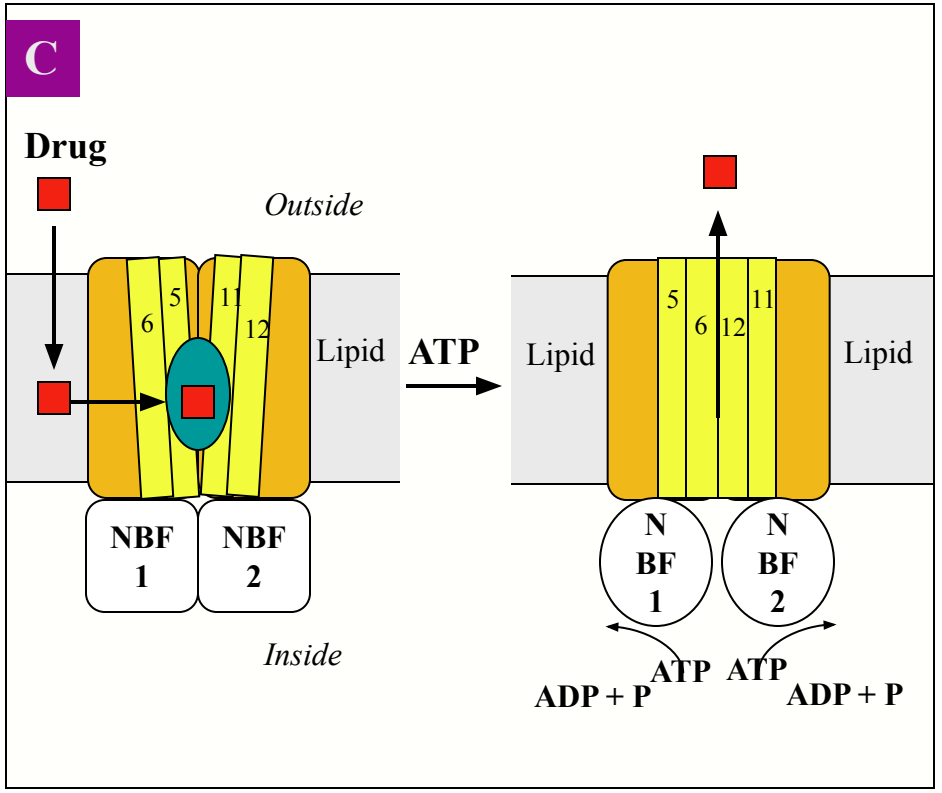
# Проблема возникающая при использовании лекарственных препаратов (преодоление резистентности, структура и функции MDR-насоса)

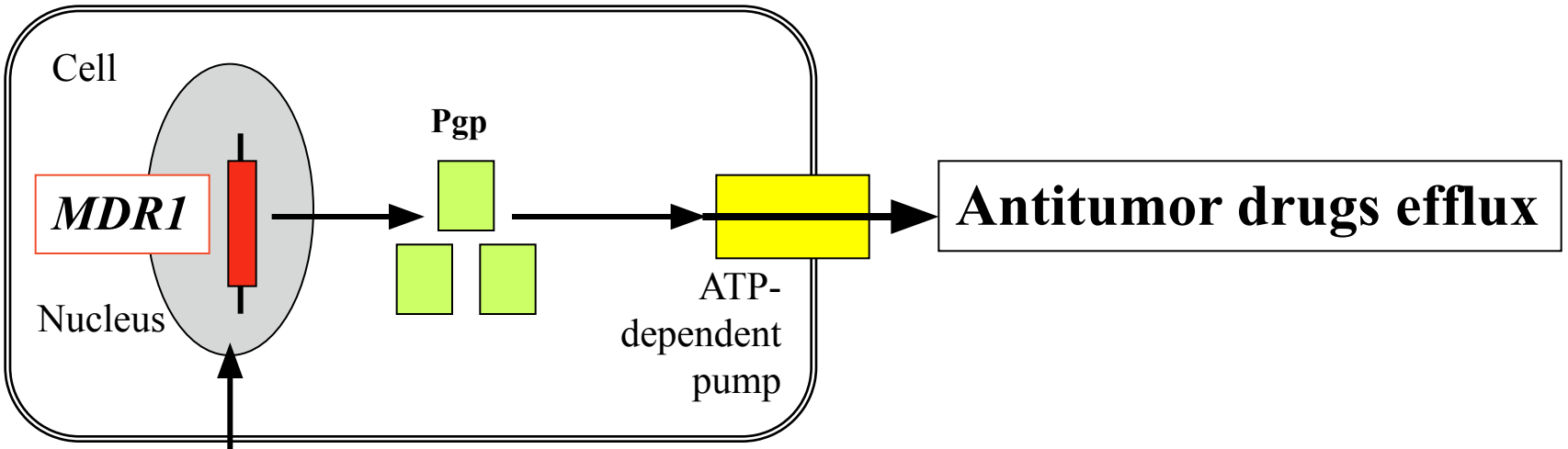
# STRUCTURE OF GLYCOPROTEIN P.



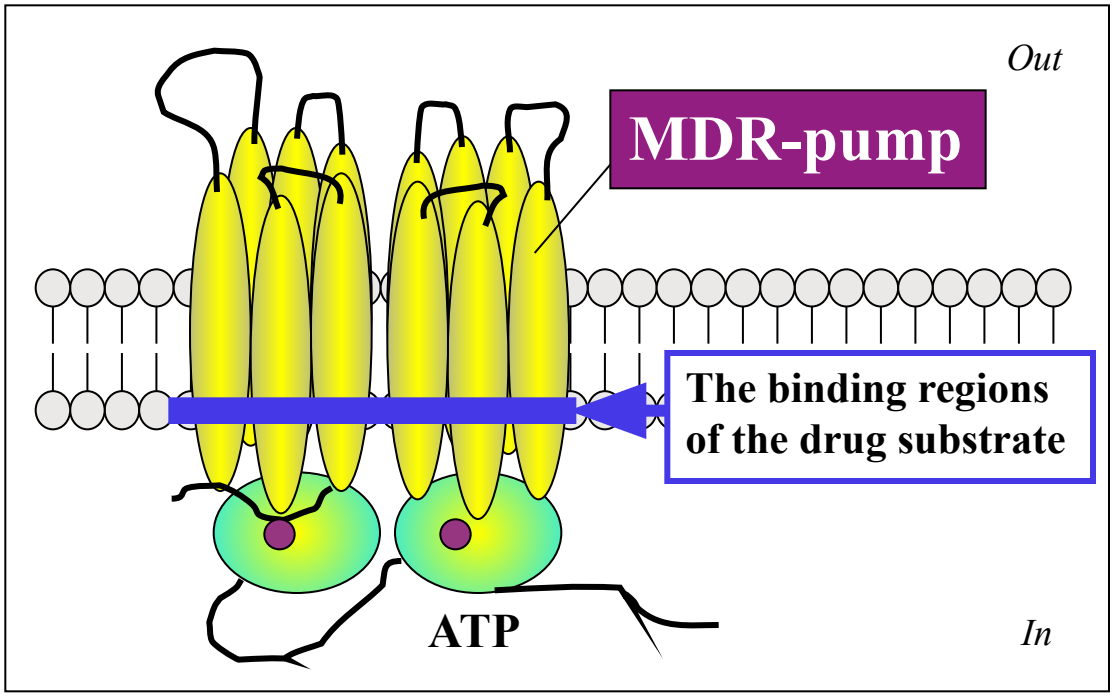
# MULTIPLE DRUG RESISTANCE OF TUMOR CELLS



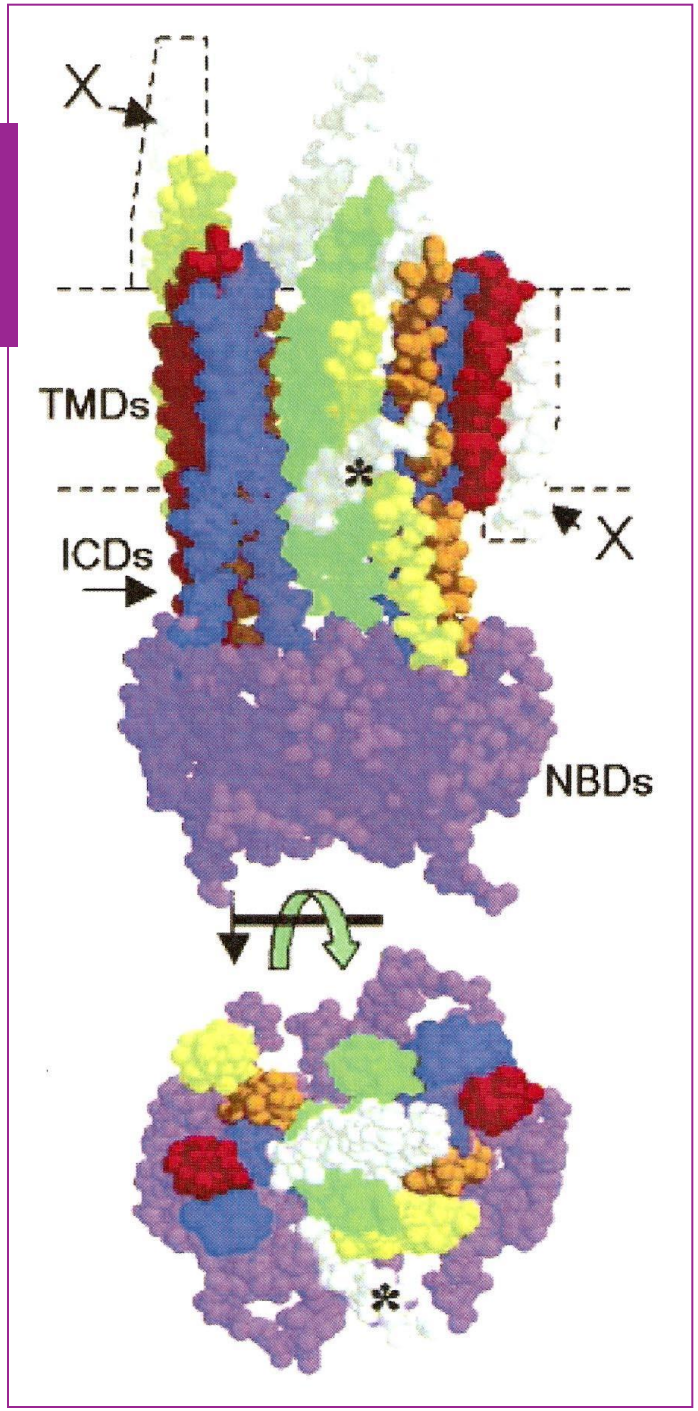

***MDR1* activation**

**Antitumor substances:**

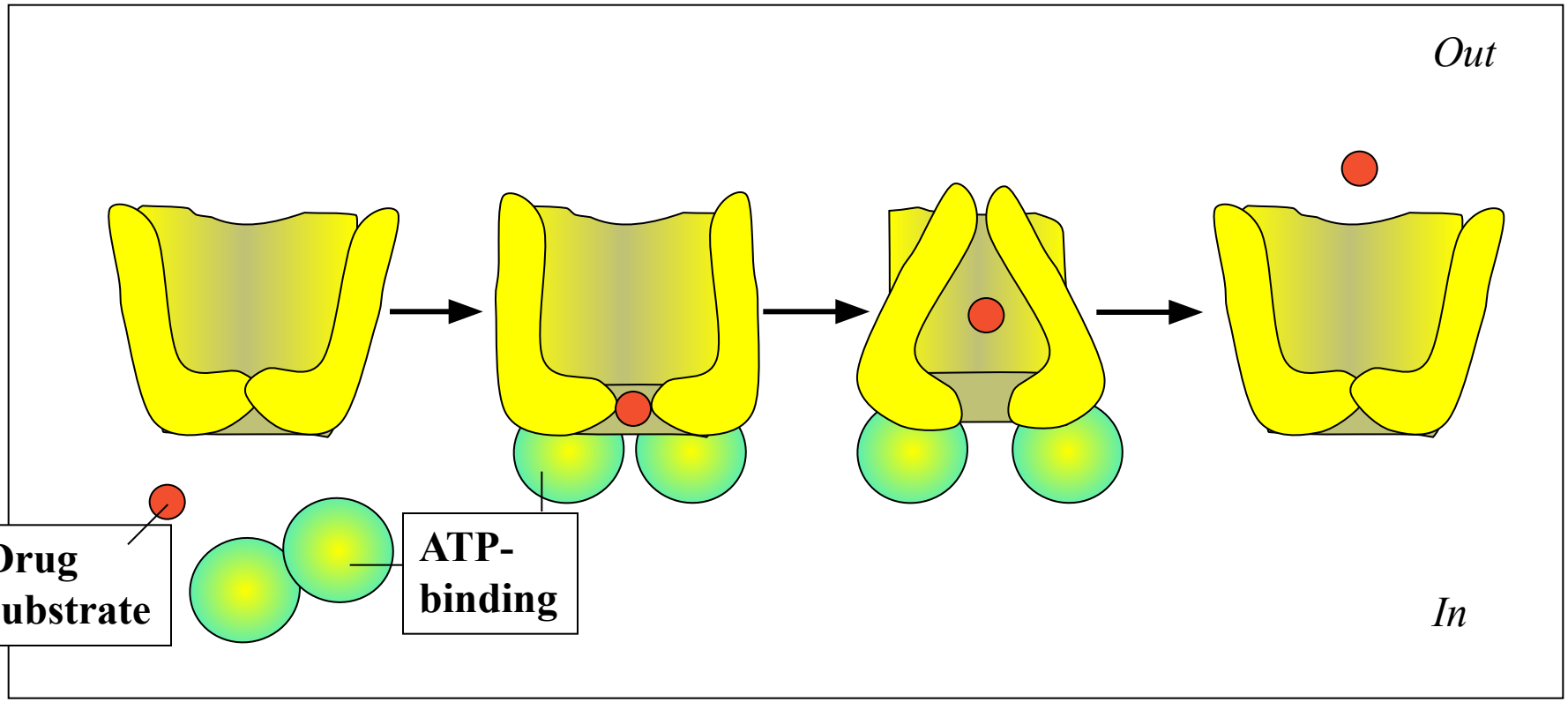
- **HSP**
- **Xenobiotics**
- **Cytostatics**
- **Steroid drugs**
- **Toxic substances**
- **Hypoxia, UV-radiation**



# STRUCTURE of MDR-PUMP

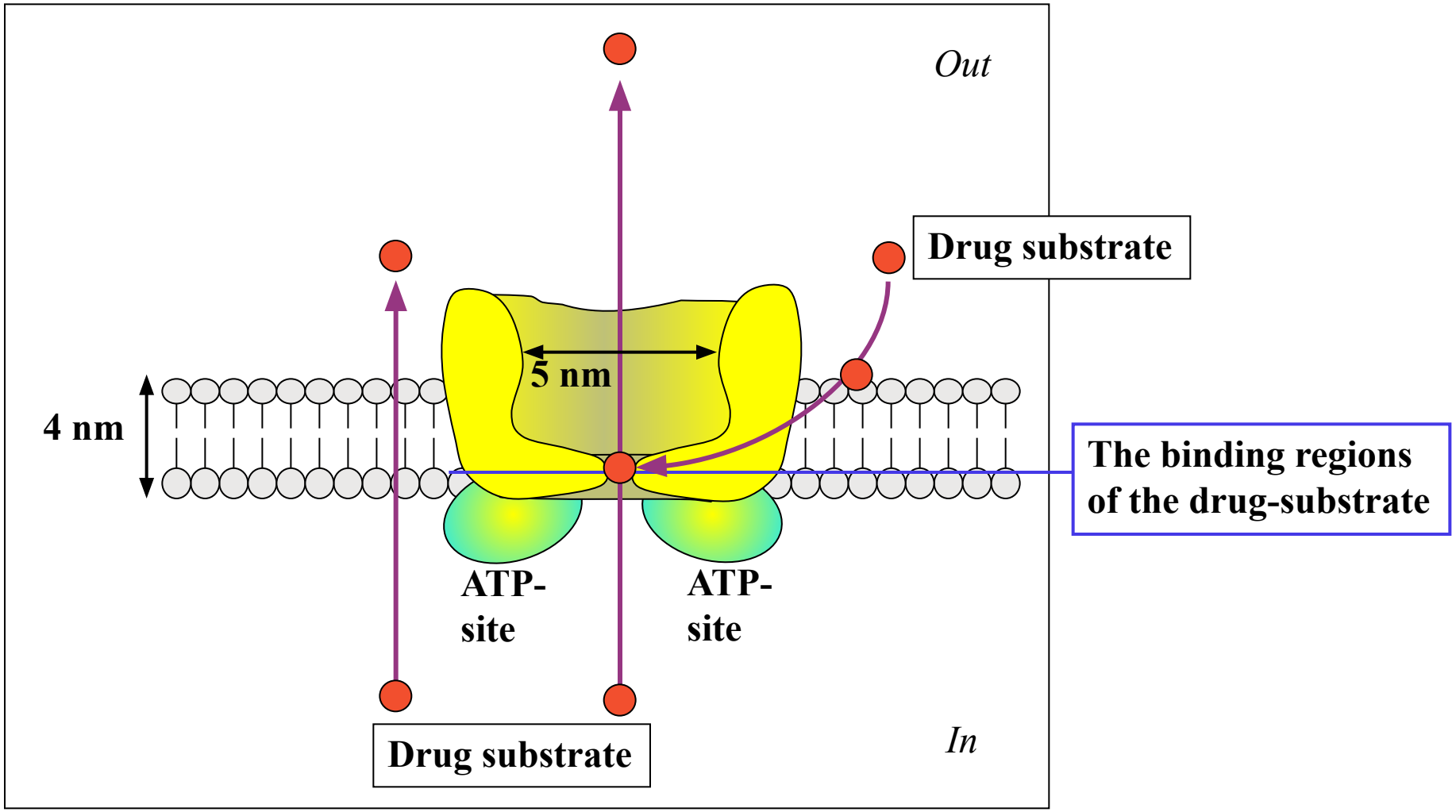


# TRANSPORT OF SUBSTRATES VIA THE MDR-PUMP

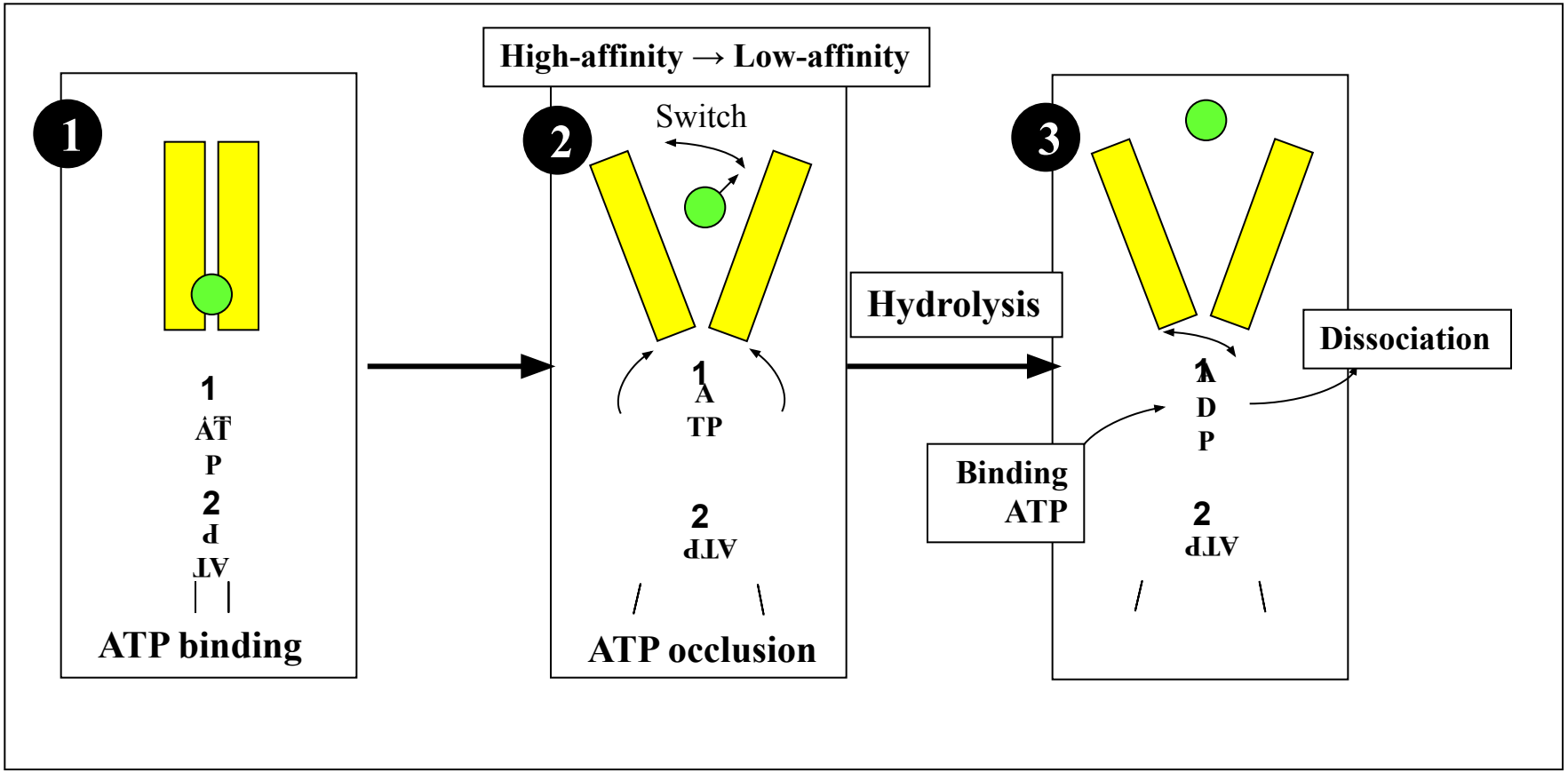



Chris van der Does and Robert Tampe
**How do ABC transporters drive transport?**
***2004, Biol. Chem., Vol. 385, pp. 927–933***

# FUNCTION OF THE MDR-PUMP

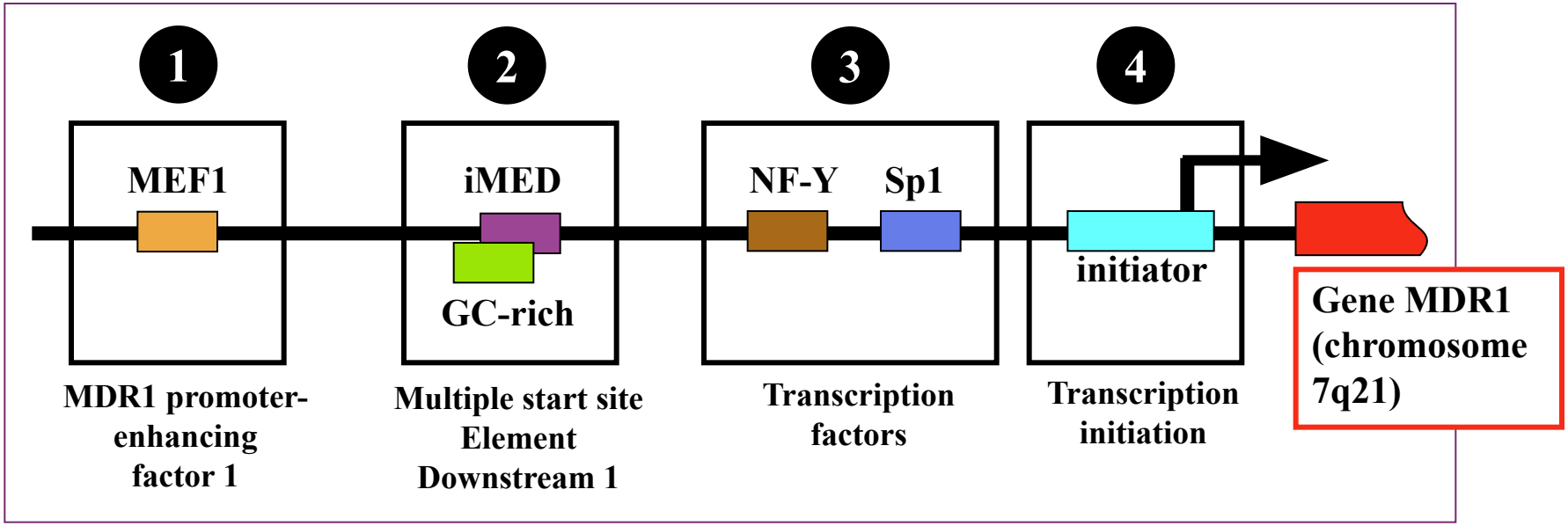


# ATP-DEPENDENT CYTOSTATIC DRUGS TRANSPORT MECHANISM




Zuben E. Sauna and Suresh V. Ambudkar
**About a switch: how P-glycoprotein (ABCB1) harnesses the energy of ATP binding and hydrolysis to do mechanical work**
*2007, Mol Cancer Ther, №6(1), pp.13-23*

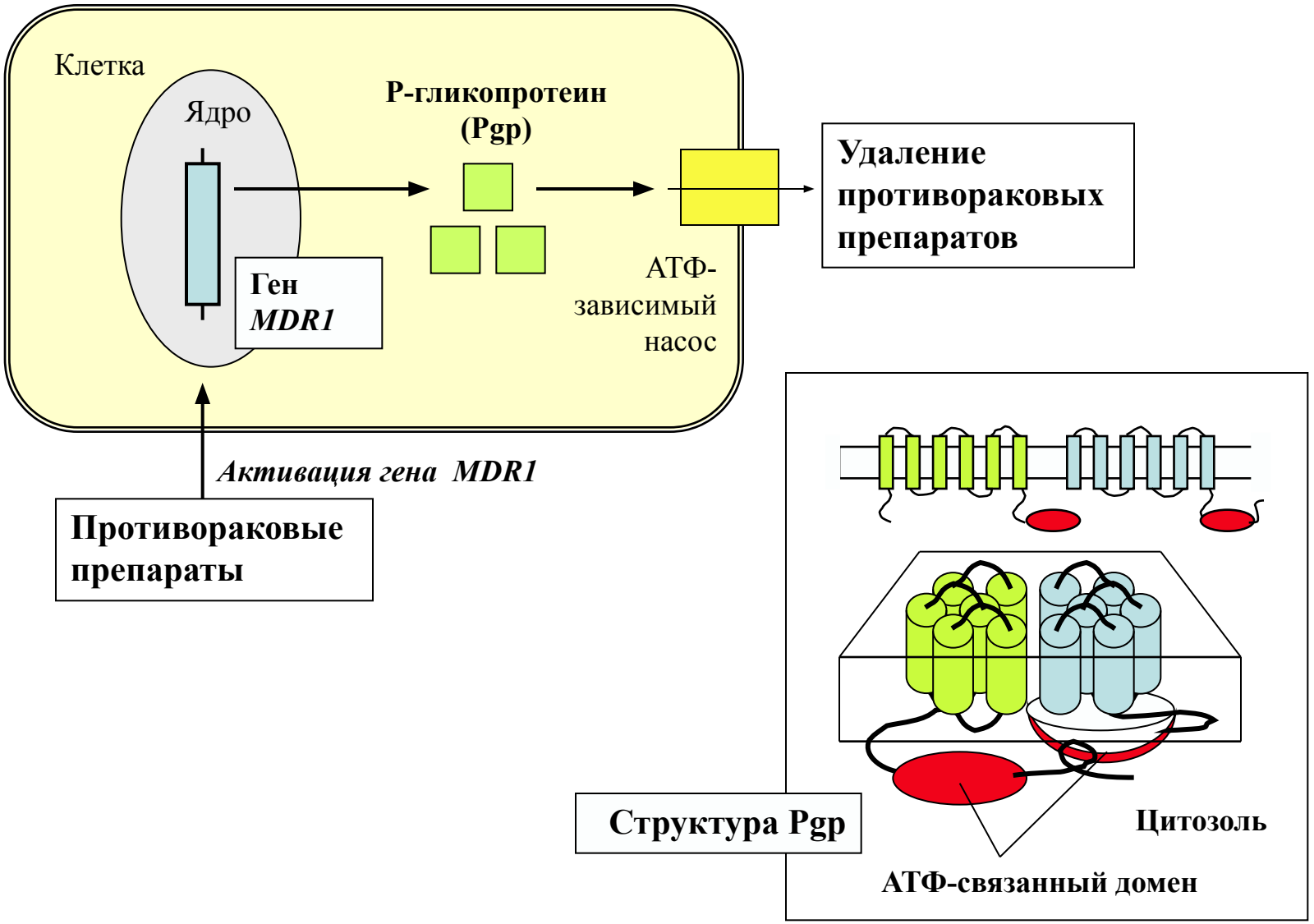
# TRANSCRIPTION OF *MDR1*




**Proteins involved in *MDR1* transcription**

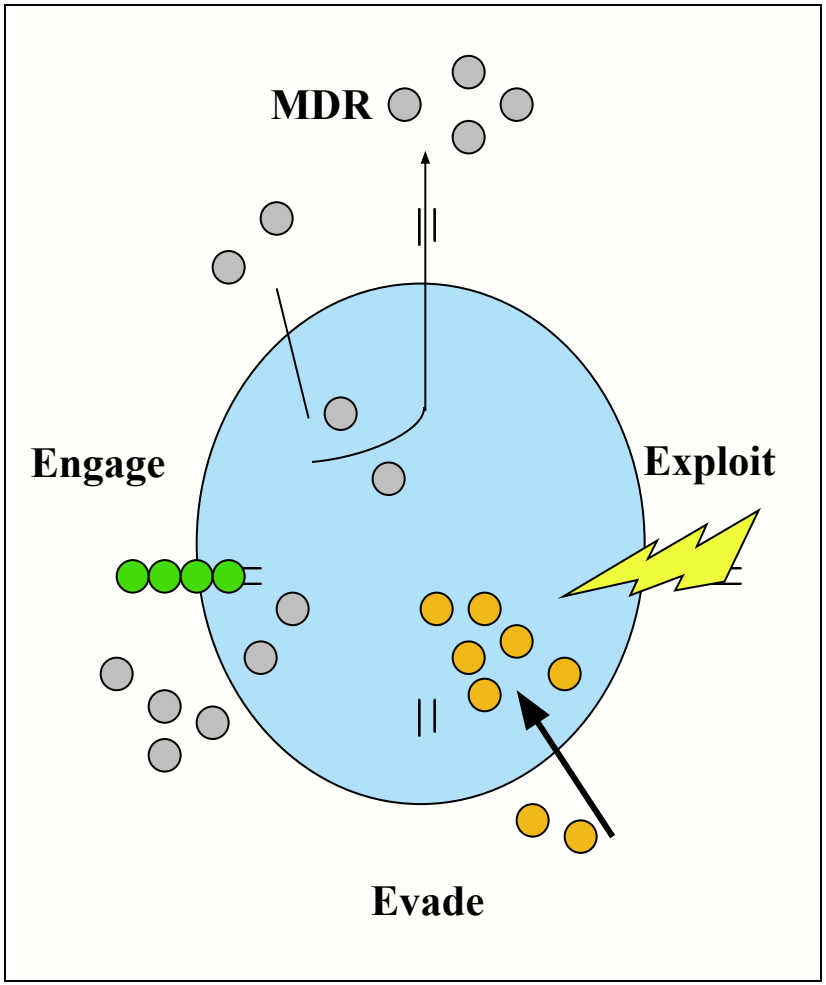
Kathleen W. Scotto and Robert A. Johnson
**Transcription of MDR1**
*Molecular Interventions, 2001, vol.1, pp.117-125*

# МЕХАНИЗМ УСТОЙЧИВОСТИ ОПУХОЛЕВЫХ КЛЕТОК К ДЕЙСТВИЮ ПРОТИВОРАКОВЫХ ПРЕПАРАТОВ

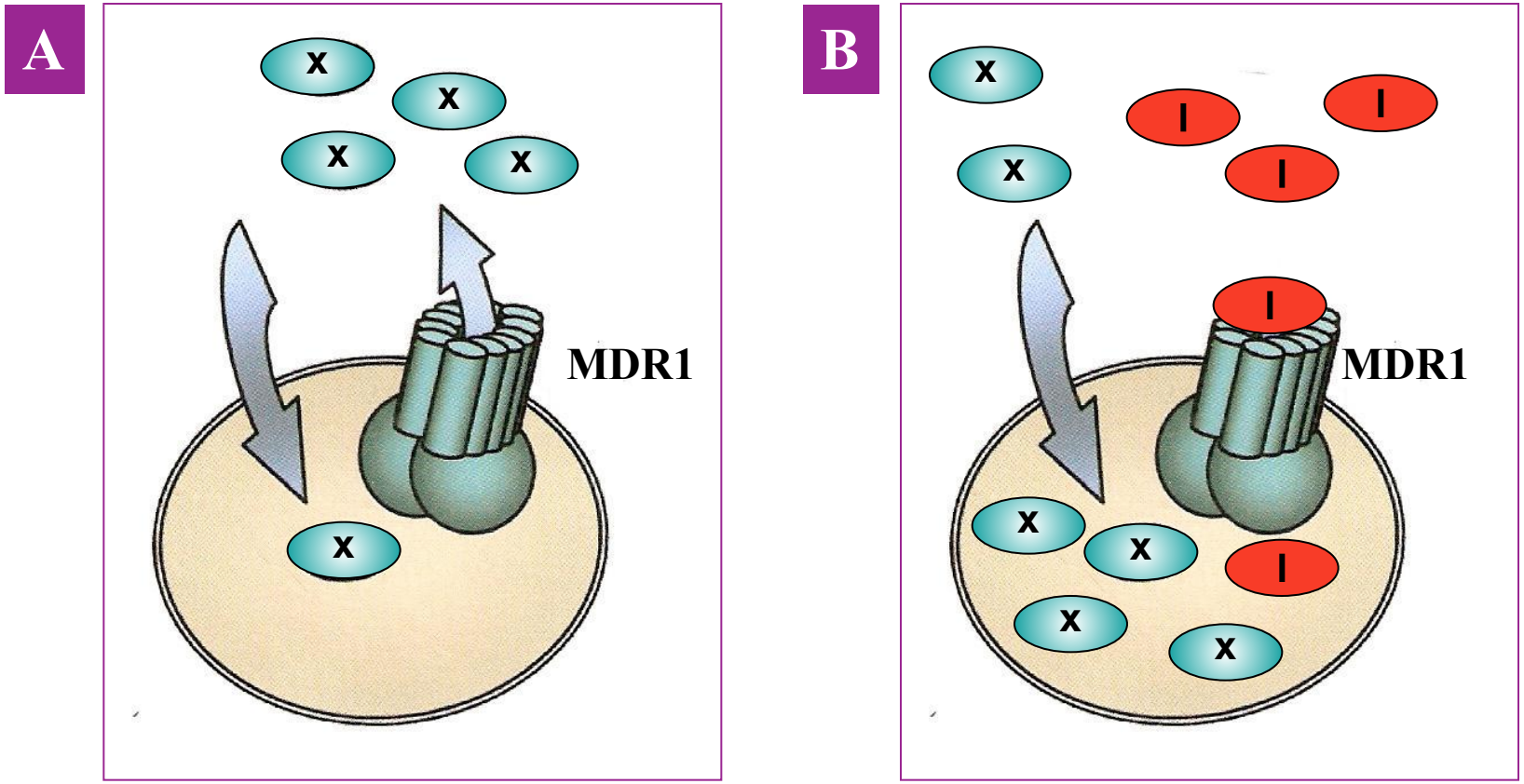


# SELECTED ANTI-CANCER DRUGS THAT ARE SUBSTRATES FOR THE FACTORS RESPONSIBLE FOR MULTIDRUG RESISTANCE

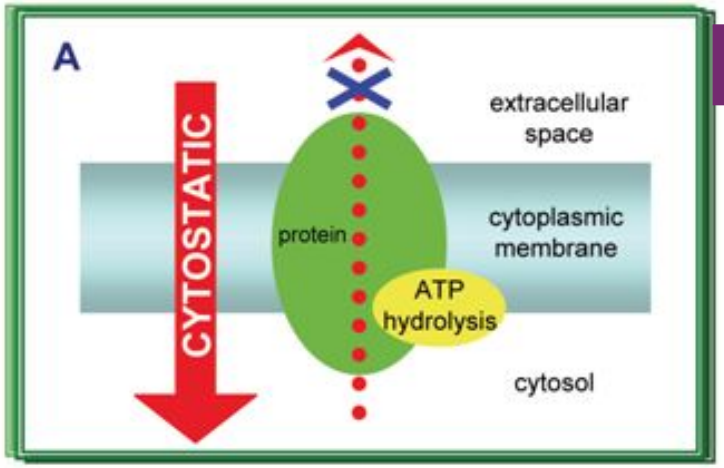
| Name | Substrates |
|---|---|
| Pgp | Doxorubicin, daunorubicin, epirubicin, etoposide, paclitaxel, docetaxel, vincristine, vinblastine, rhodamine-123, chloroquine, quinidine, aldosterone |
| MRP1 | Vincristine, daunorubicin, doxorubicin, etoposide |
| MRP2 | Methotrexate, etoposide, cisplatin, vinca alkaloids |
| MRP3 | Etoposide, teniposide, estrogen derivatives, methotrexate, vinca alkaloids |
| MRP4 | Purine analogues, estrogen derivates |
| MRP5 | Thiopurines, cyclic nucleotides |
| GSTs | Chloroethylnitrosoureas, cisplatin, anthracyclines, phosphamides |
| Topo II | Chloroethylnitrosoureas, epipodophyllotoxins, cisplatin, anthracyclines |



# ACTIVITY OF MDR-PUMP

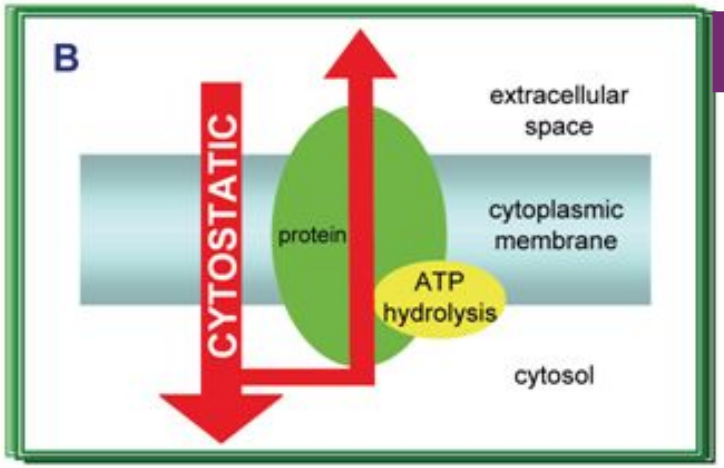


# TWO TYPES OF DRUG CELLULAR MIGRATION EVENTS IN OVERCOMING MDR :




## A. Influx of cytostatic without mediated efflux

**Транспорт цитостатика через мембрану. Отсутствует сродство к MDR-насосу**

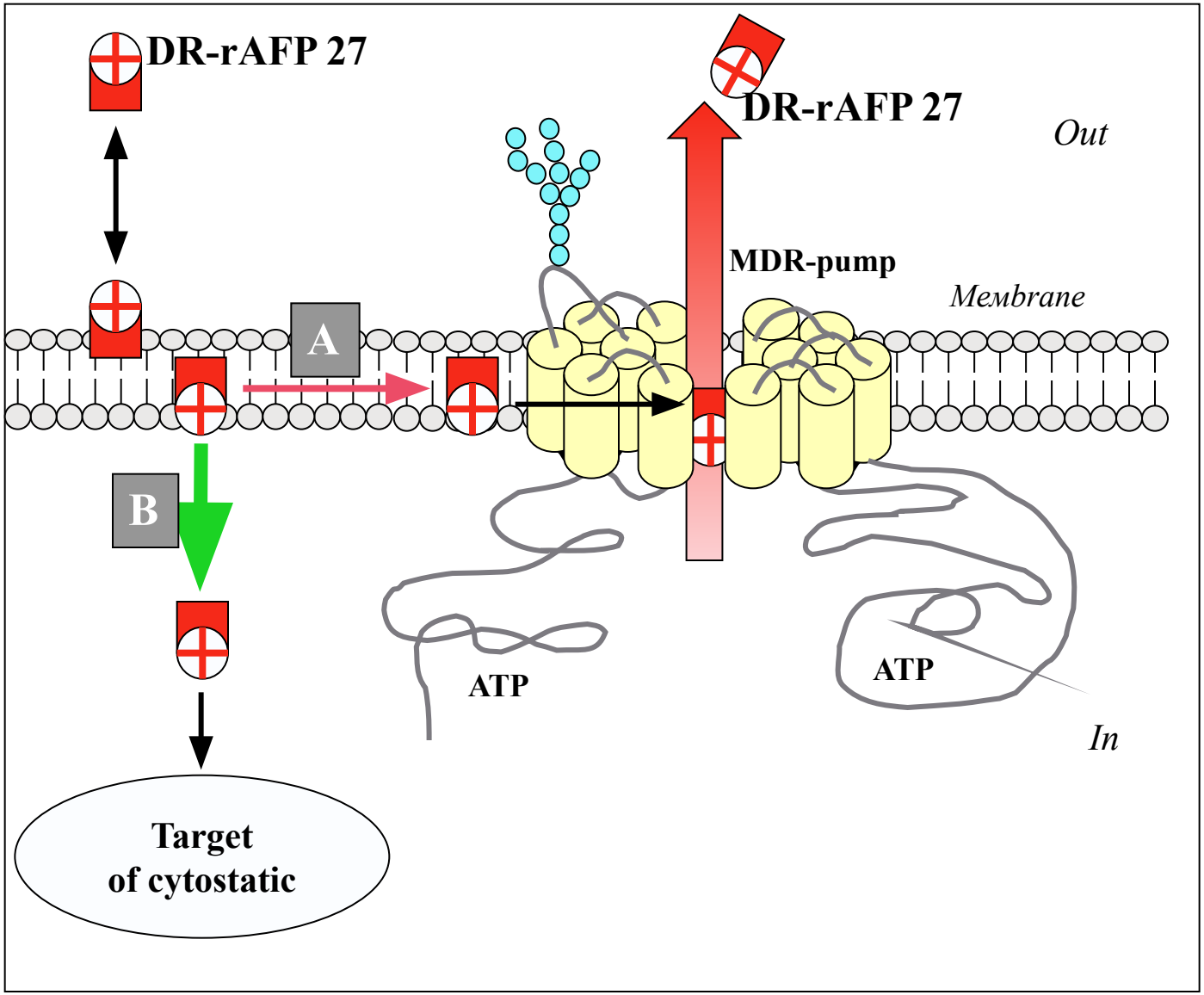



## B. Influx surpassing mediated efflux

**Транспорт цитостатика через мембрану сопровождается выходом вещества через MDR-насос**

E.Borowski, M. Bontemps-Gracz, A.Piwkowska
**Strategies for overcoming ABC-transporters-mediated multidrug resistance (MDR) of tumor cells,**
*2005, Acta Biochimica Polonika, vol.52, №3,609-627*

# THE CIRCUMENT OF THE MDR

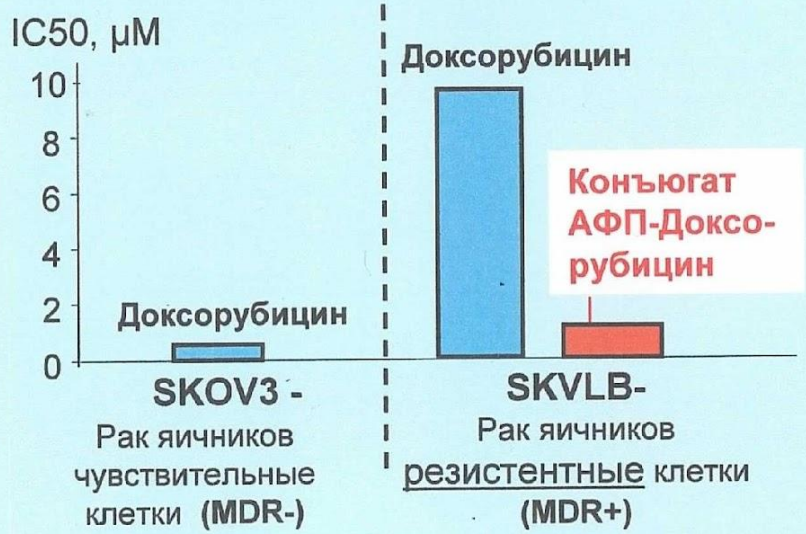


# ПРЕОДОЛЕНИЕ МНОЖЕСТВЕННОЙ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ И ПРОТИВООПУХОЛЕВАЯ АКТИВНОСТЬ КОНЪЮГАТОВ

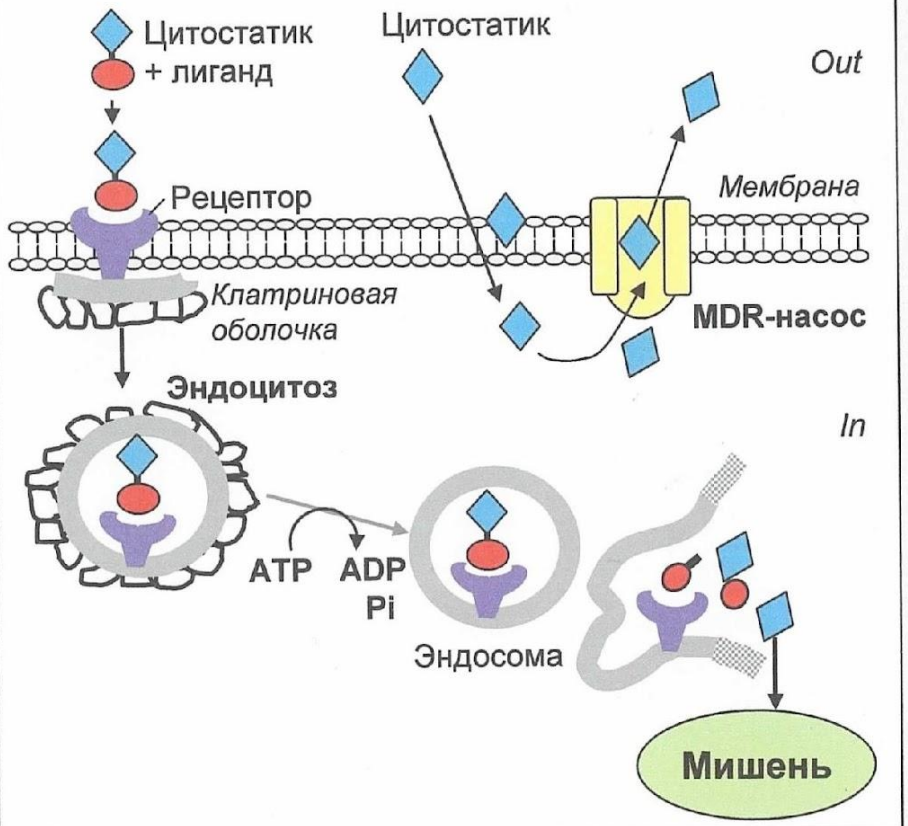
**Цитостатики:**
- Эсперамицин
- Доксорубицин
- Винбластин
- Метотрексат
- Цис-платин

**Антисенсы:**
(c-myc, bcl-2, tel)

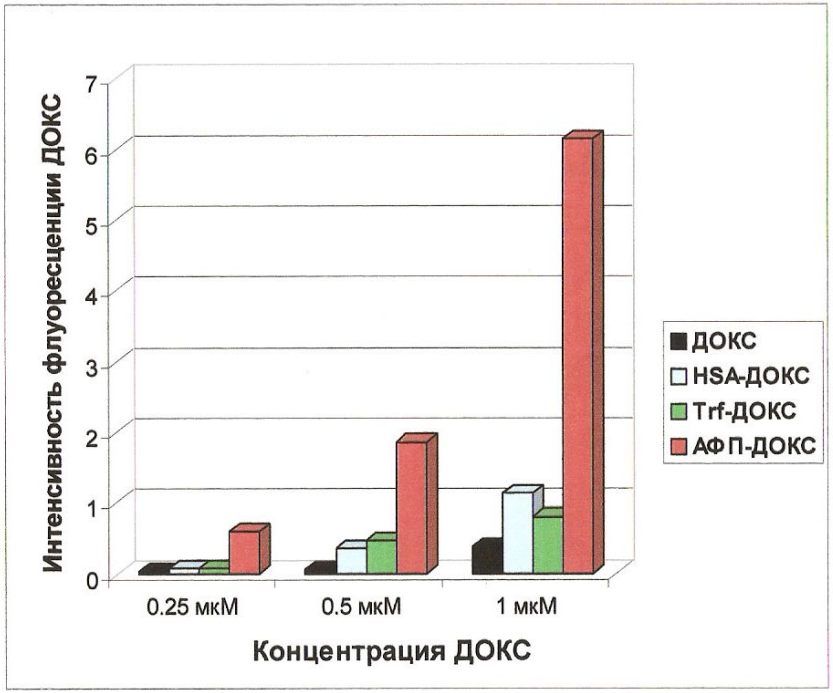

## Действие конъюгата АФП-Доксорубицин на лекарственную устойчивость опухолевых клеток человека



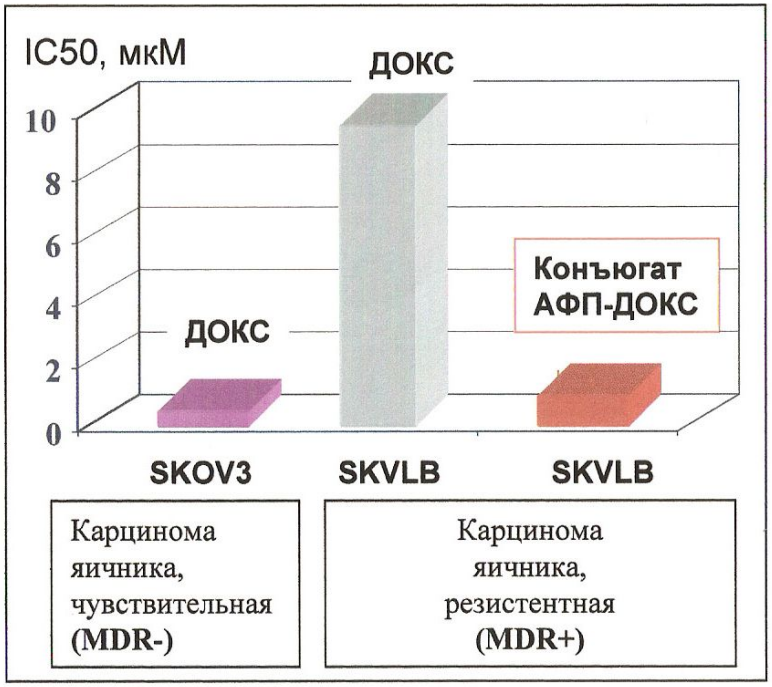

## Механизм лекарственной устойчивости



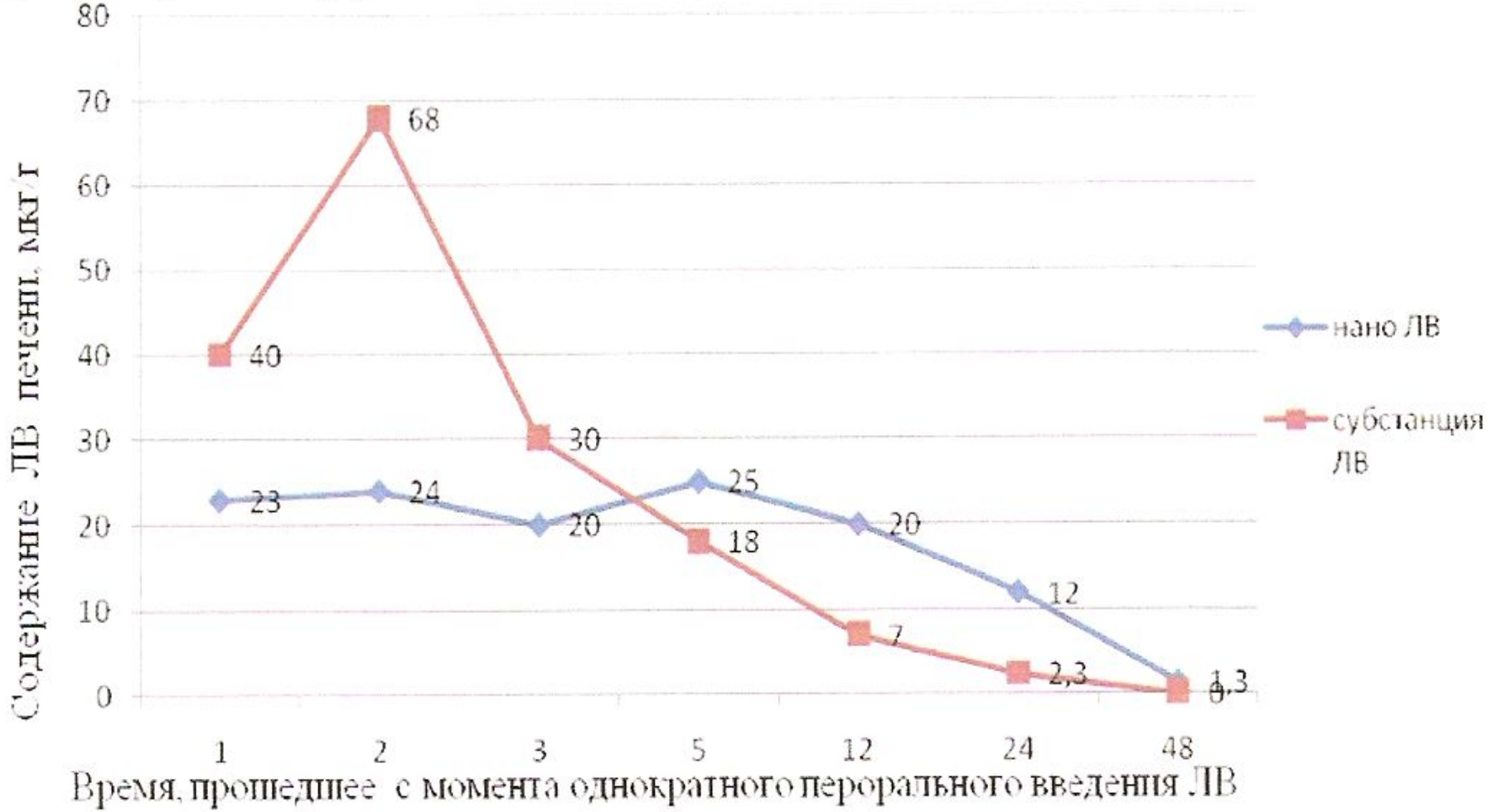
А


Интенсивность флуоресценции ДОКС
0
1
2
3
4
5
6
7
0.25 мкМ
0.5 мкМ
1 мкМ
Концентрация ДОКС
ДОКС
HSA-ДОКС
Trf-ДОКС
АФП-ДОКС

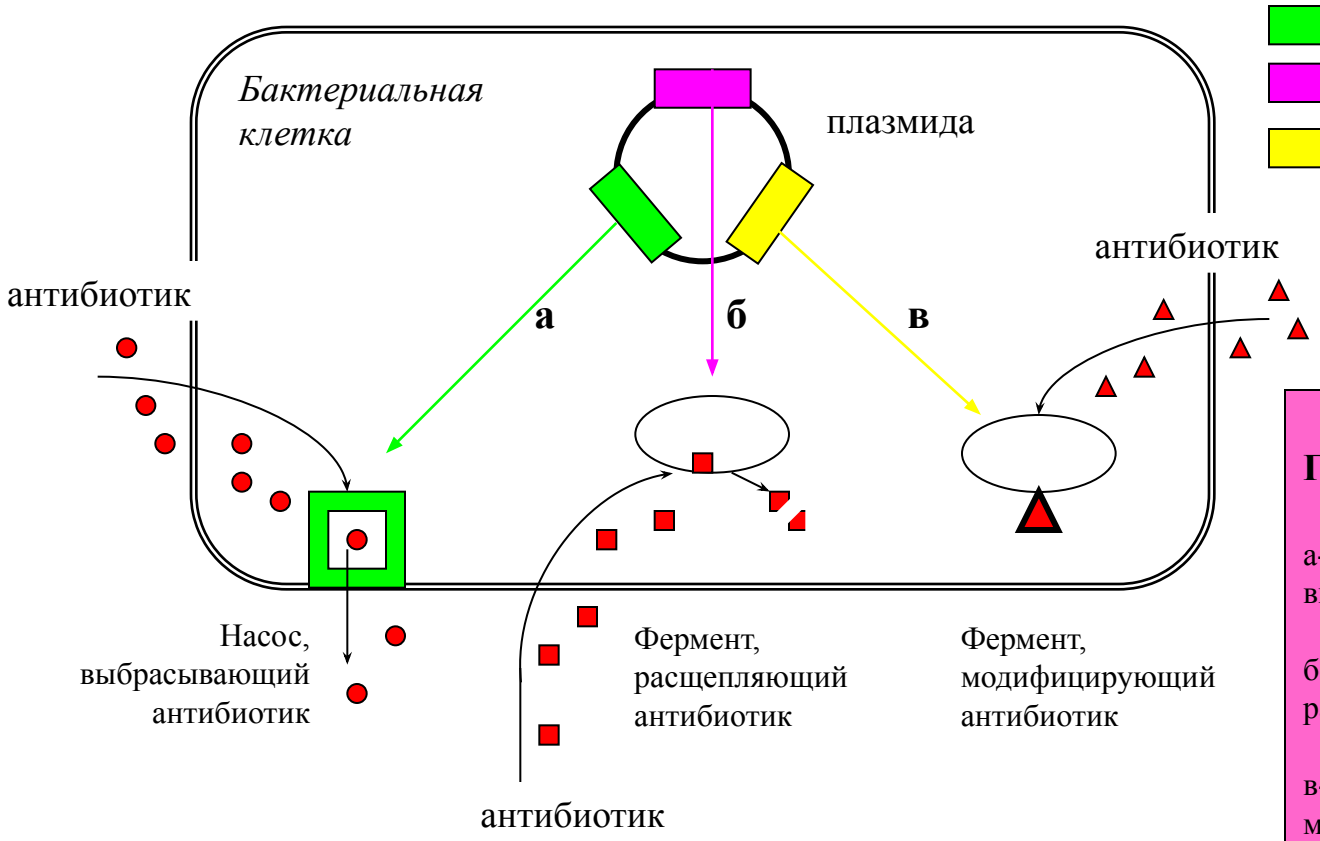
Б


IC50, мкМ
0
2
4
6
8
10
ДОКС
ДОКС
Конъюгат
АФП-ДОКС
SKOV3
SKVLB
SKVLB
Карцинома
яичника,
чувствительная
(MDR-)
Карцинома
яичника,
резистентная
(MDR+)

Изменение концентрации ломефлоксацина в печени с течением времени при однократном пероральном введении субстанции ЛВ и ЛВ, включенного в состав НЧ



# «ГЕНЫ УСТОЙЧИВОСТИ»

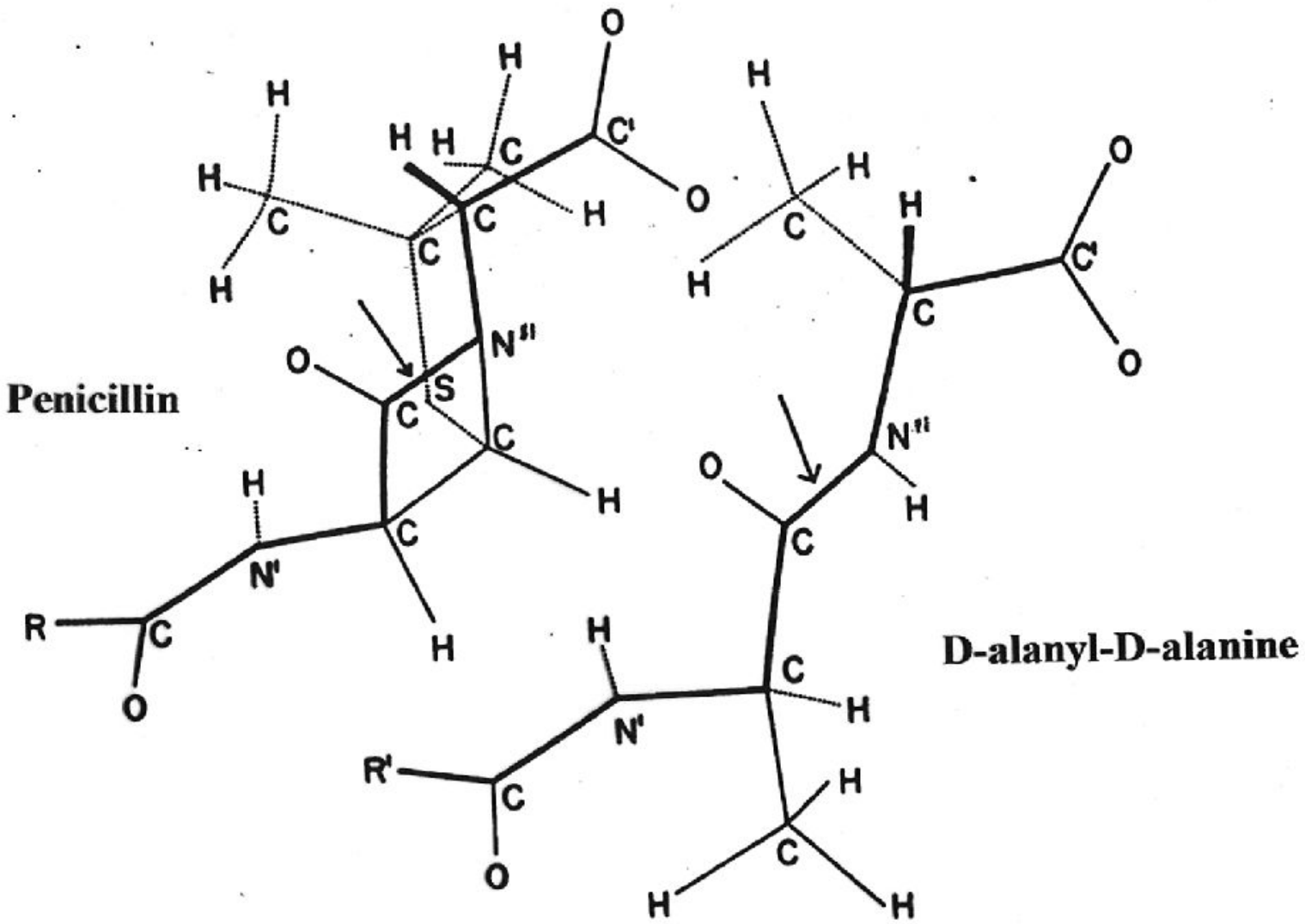



**Гены устойчивости:**

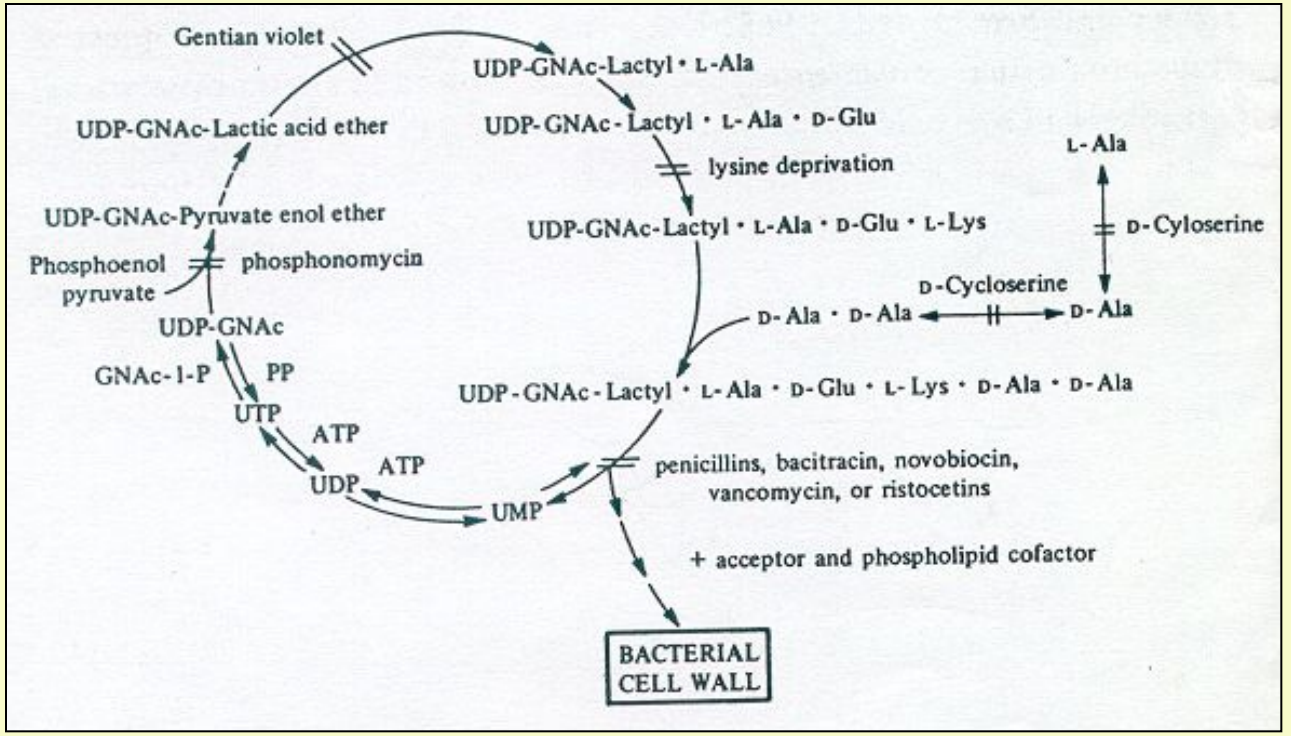
а- кодируют мембранные насосы, выбрасывающие антибиотики

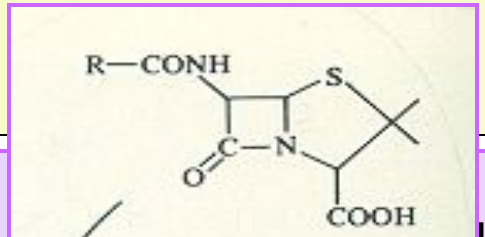
б- кодируют ферменты, расщепляющие антибиотики

в-кодируют ферменты, модифицирующие антибиотики

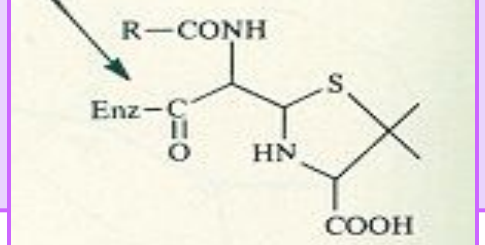

Penicillin
D-alanyl-D-alanine

**Biosynthesis of the uridine nucleotide precursors of the peptidoglycan. The points of inhibition by various substances are indicated.**



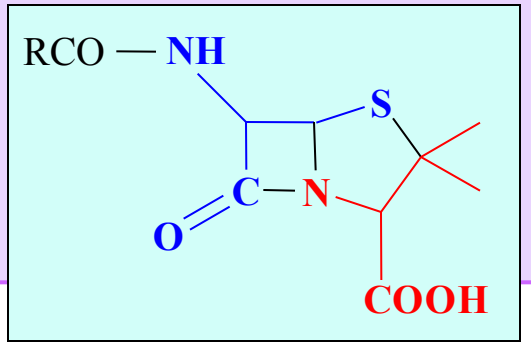

**пенициллин**




**транспептидаза**

**l mechanism of inhibition of transpeptidation by penicillins**

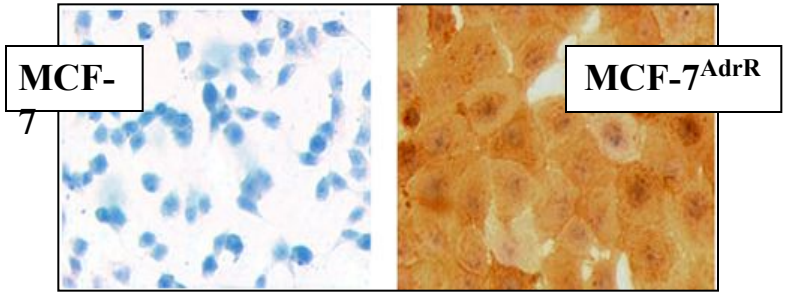
Пенициллин – циклический дипептид двух аминокислот: L-цистеина и D-валина (L-Cys-D-Val):



# ОБРАЩЕНИЕ МНОЖЕСТВЕННОЙ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ КОНЪЮГАТОМ АФП С ДОКСОРУБИЦИНОМ

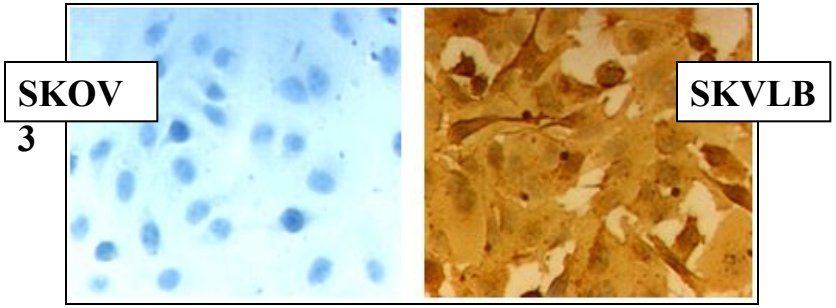
## Выявление белка MDR1 в опухолевых клетках (коричневое окрашивание)

**Рак молочной железы человека**



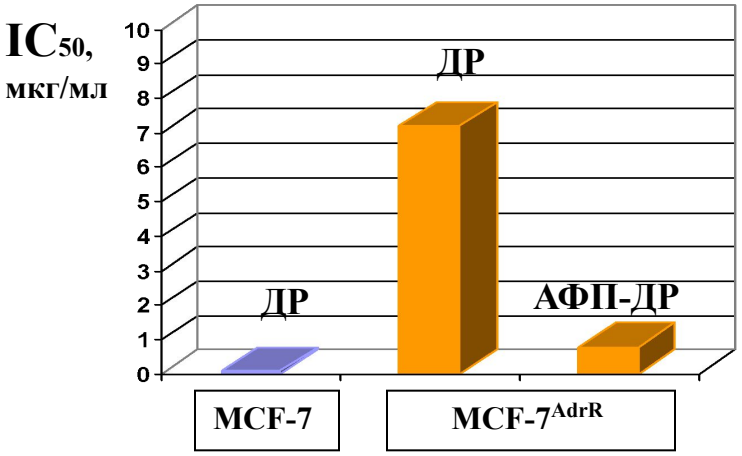

Резистентны к ДР

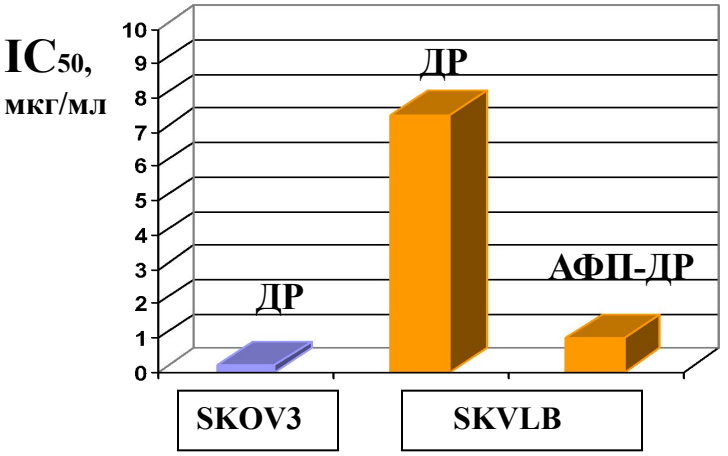
**Рак яичника человека**



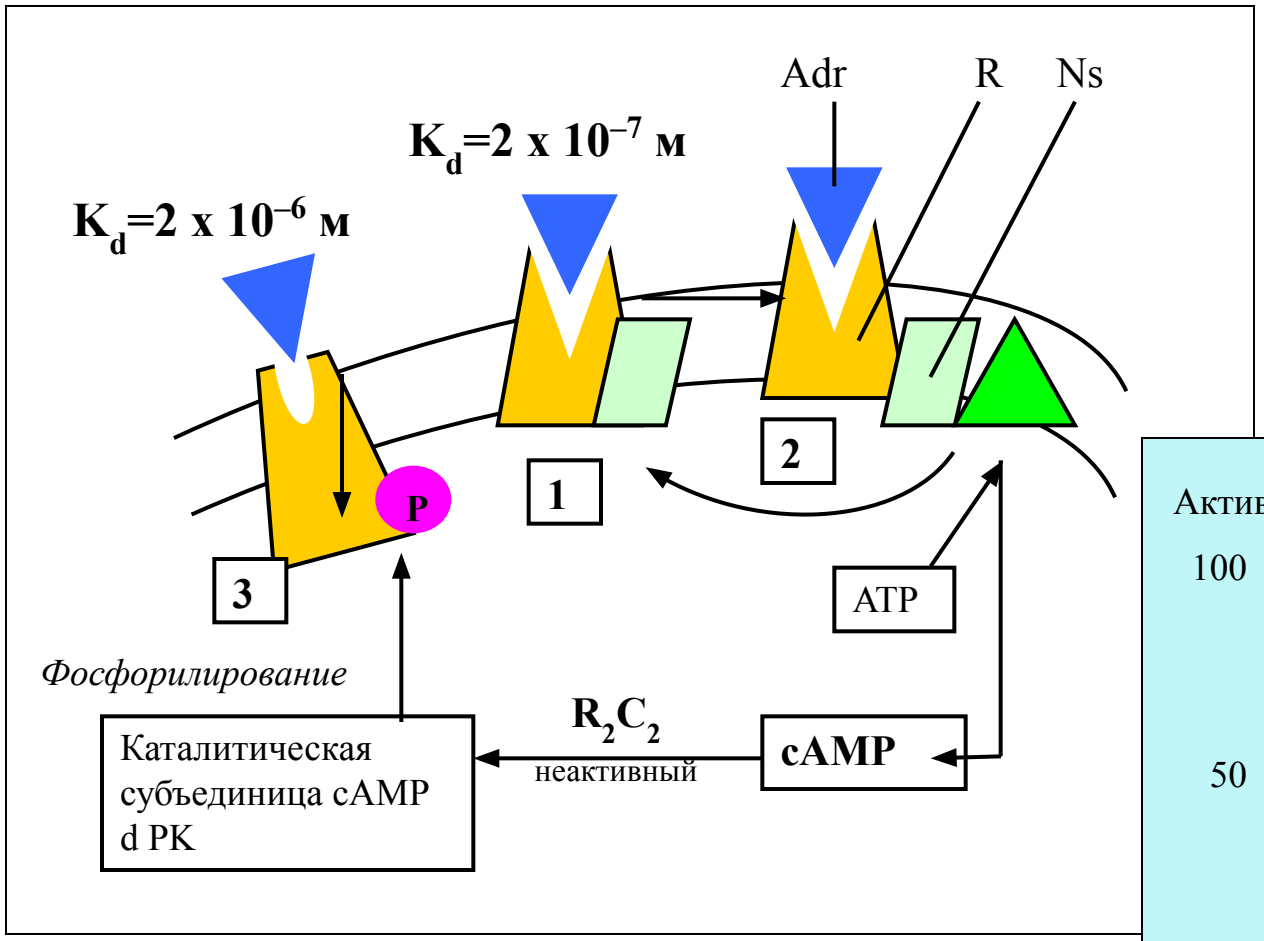

Резистентны к ДР

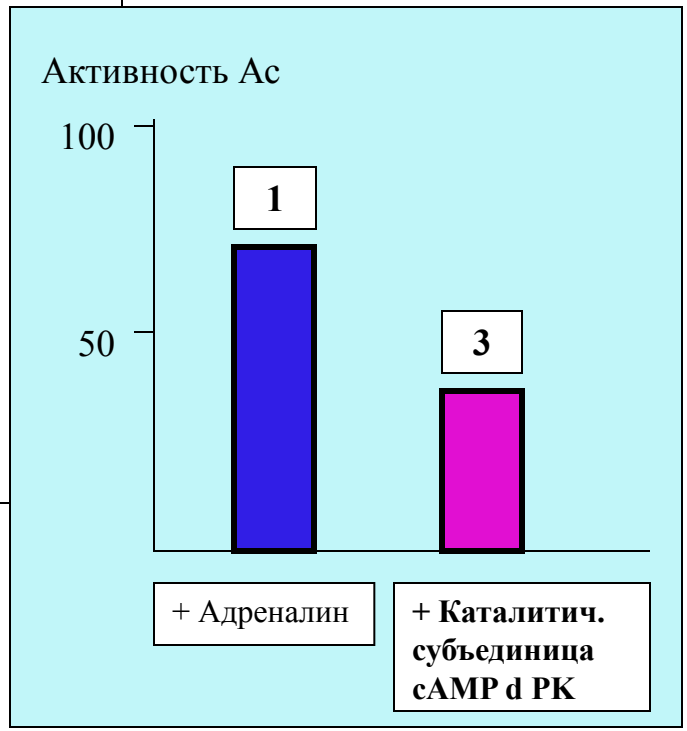
## Резистентность MDR1$^{+}$ клеток к доксорубицину и высокая чувствительность к конъюгату АФП с доксорубицином

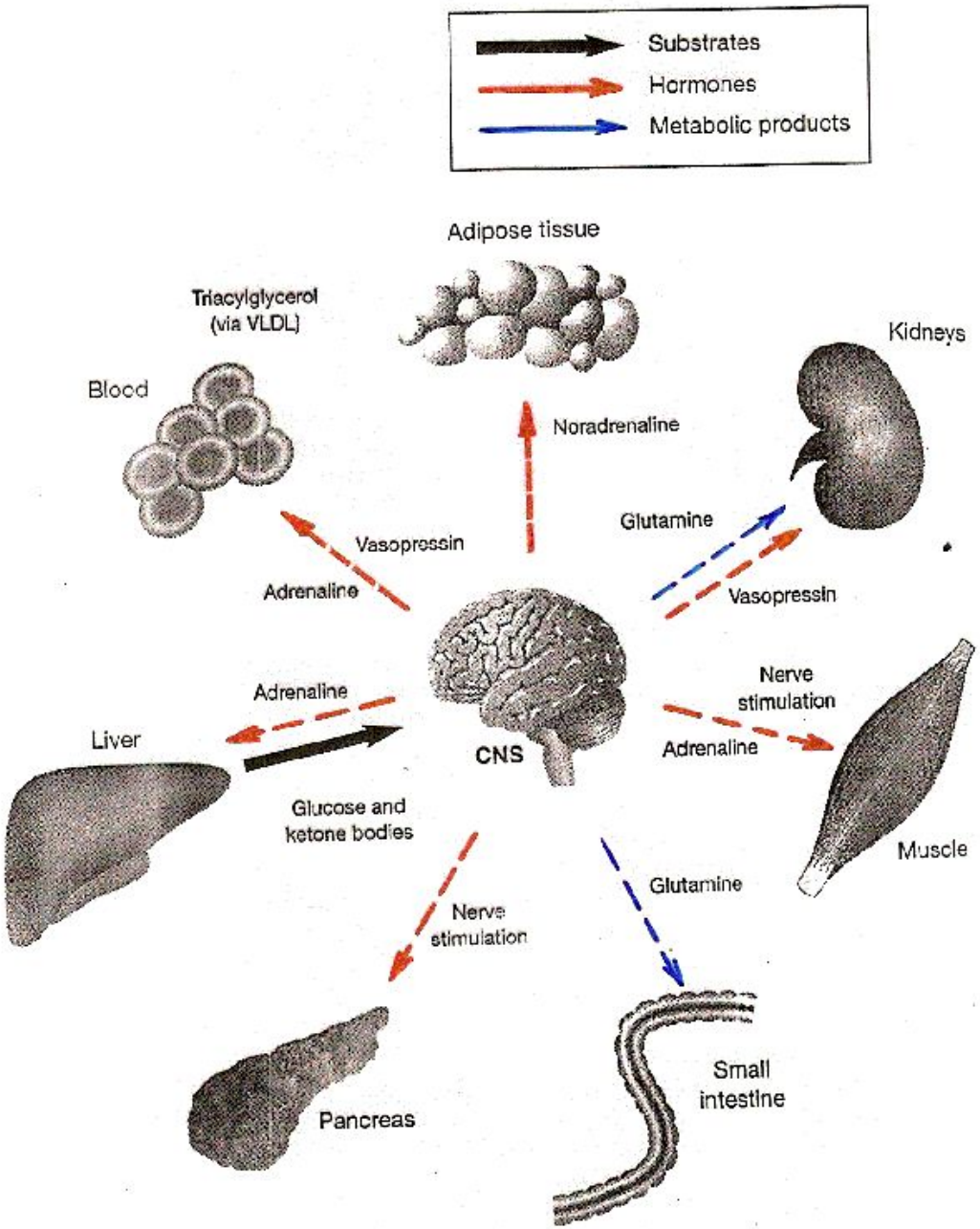


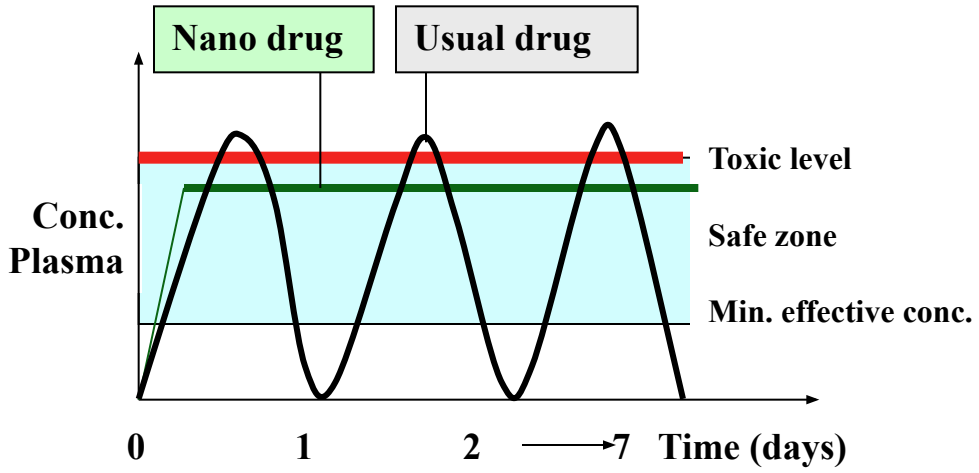
# Десенситизация аденилатциклазы при воздействии адреналина, дибутирил-cAMP и протеинкиназы



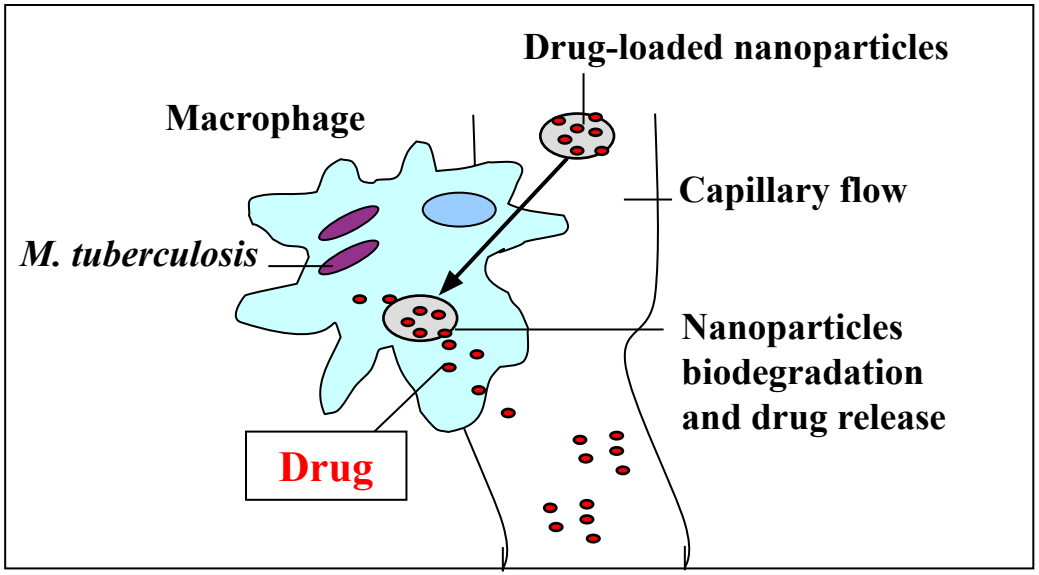

Substrates
Hormones
Metabolic products
Adipose tissue
Triacylglycerol
(via VLDL)
Blood
Kidneys
Noradrenaline
Vasopressin
Adrenaline
Glutamine
Vasopressin
Adrenaline
Liver
CNS
Nerve
stimulation
Adrenaline
Glucose and
ketone bodies
Muscle
Glutamine
Nerve
stimulation
Pancreas
Small
intestine

# ADVANTAGES OF NANO DRUG DELIVERY FOR TREATMENT OF TUBERCULOSIS



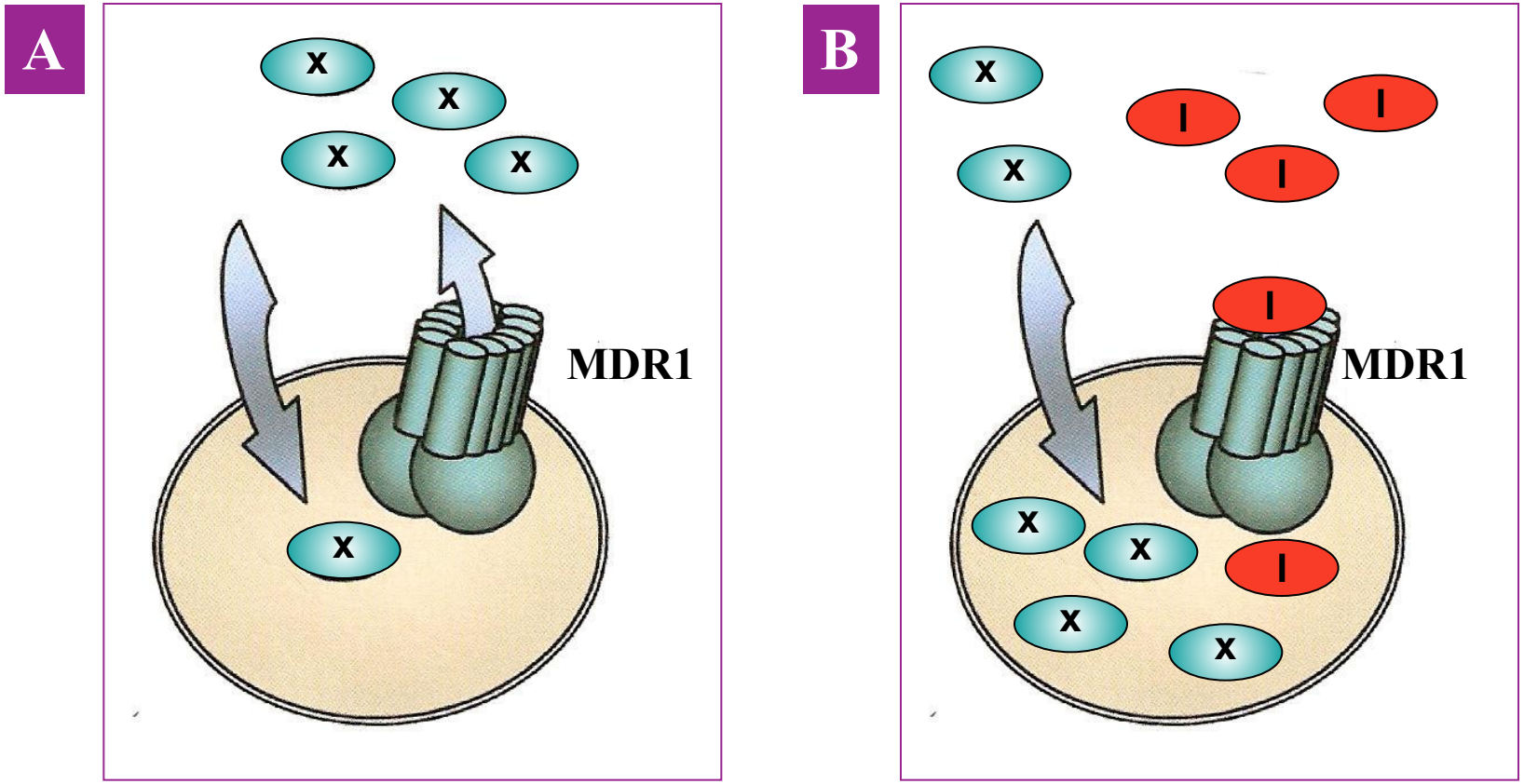

**Reduce the dosage of antituberculosis drugs**

- Reduce dosage frequency
- Minimise the toxicity of drugs
- Reduce the cost of TB treatment
- Improve patient compliance




**Targeting antituberculosis drugs in infected Macrophages**

# ACTIVITY OF MDR-PUMP



# SELECTED ANTI-CANCER DRUGS THAT ARE SUBSTRATES FOR THE FACTORS RESPONSIBLE FOR MULTIDRUG RESISTANCE

| Name | Substrates |
|---|---|
| **Pgp** | Doxorubicin, daunorubicin, epirubicin, etoposide, paclitaxel, docetaxel, vincristine, vinblastine, rhodamine-123, chloroquine, quinidine, aldosterone |
| **MRP1** | Vincristine, daunorubicin, doxorubicin, etoposide |
| **MRP2** | Methotrexate, etoposide, cisplatin, vinca alkaloids |
| **MRP3** | Etoposide, teniposide, estrogen derivatives, methotrexate, vinca alkaloids |
| **MRP4** | Purine analogues, estrogen derivates |
| **MRP5** | Thiopurines, cyclic nucleotides |
| **GSTs** | Chloroethylnitrosoureas, cisplatin, anthracyclines, phosphamides |
| **Topo II** | Chloroethylnitrosoureas, epipodophyllotoxins, cisplatin, anthracyclines |