

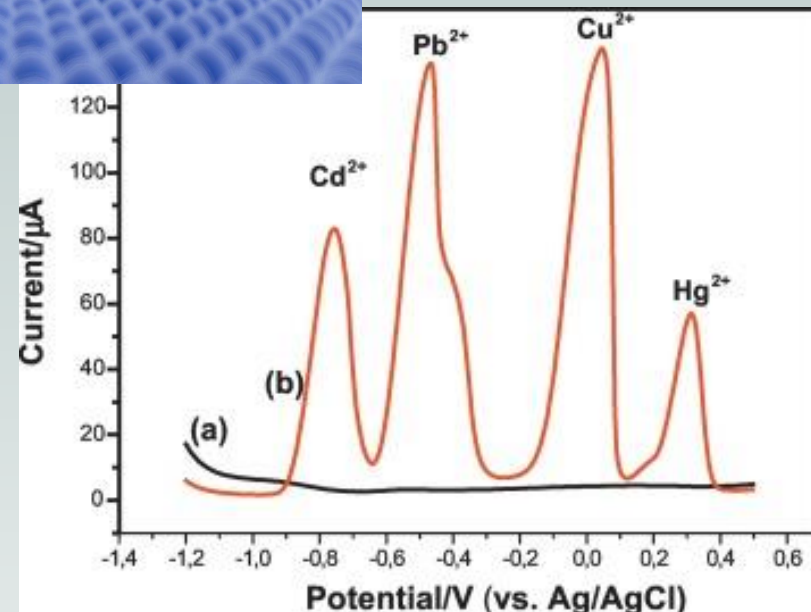
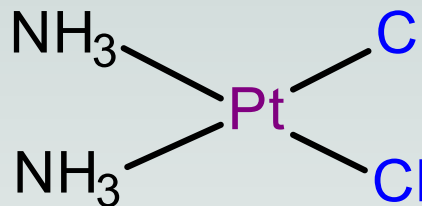
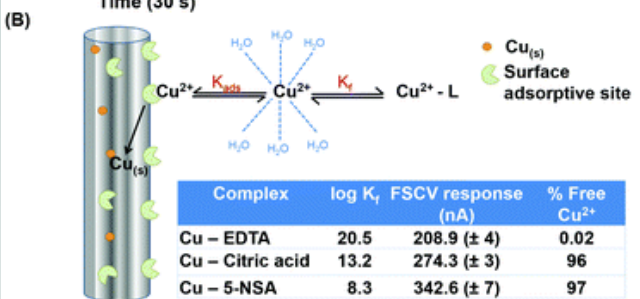
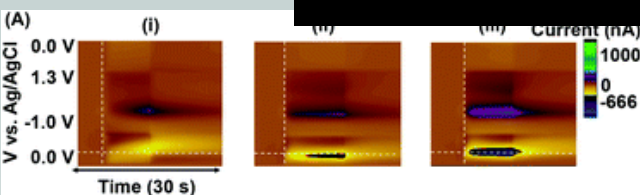
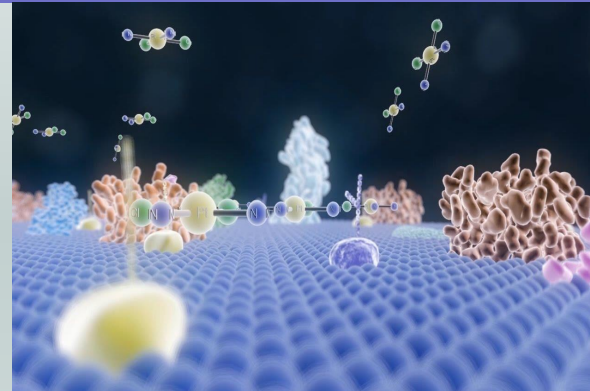
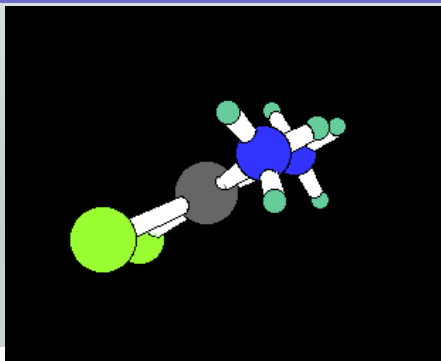
# METAL IONS IN MEDICINE AND PHYSIOLOGY

## VOLTMMETRY OF TRANSITION METALS

**RUBIN GULABOSKI**

Faculty of Medical Sciences

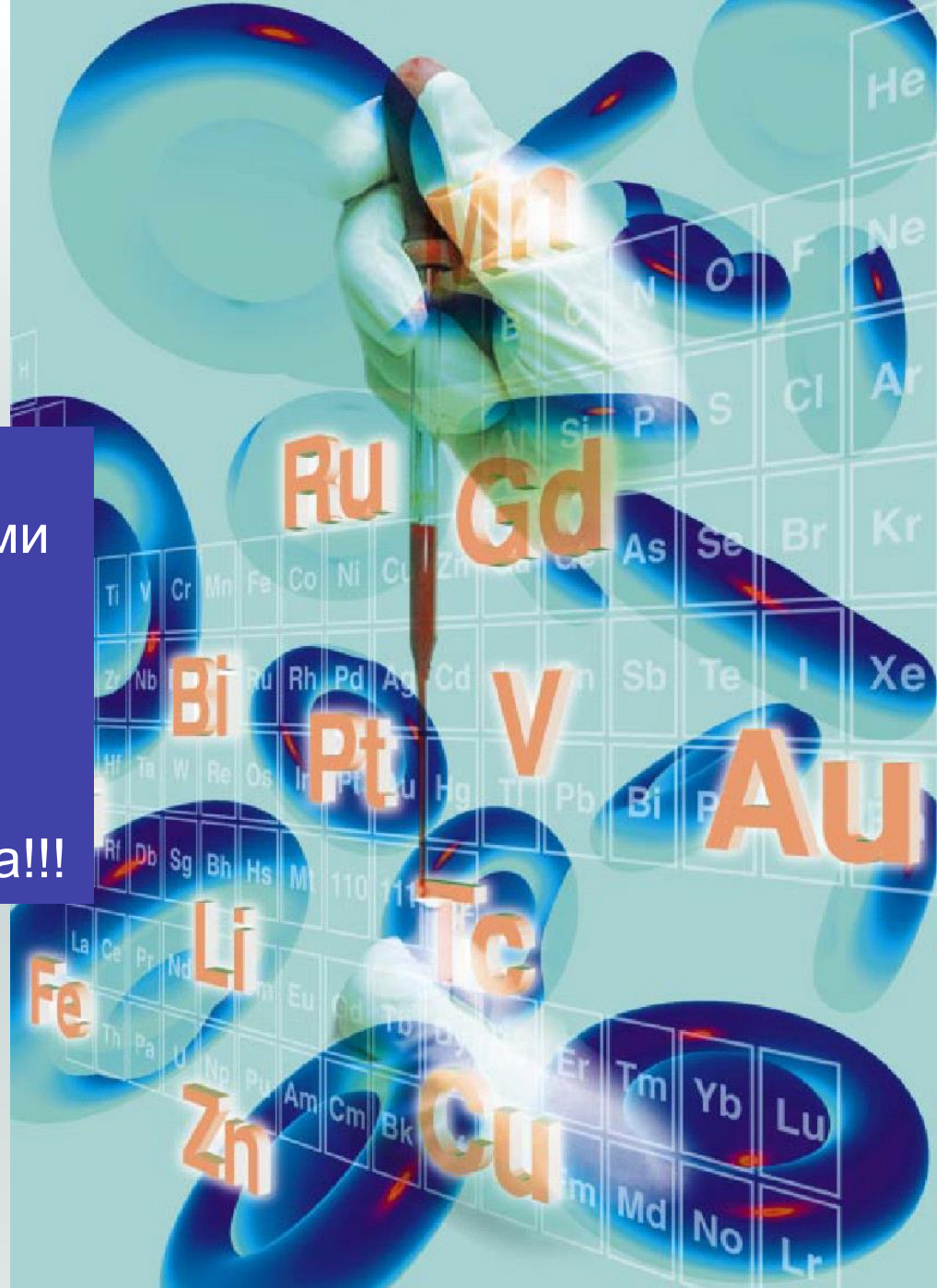
Goce Delcev University, Stip, Macedonia



# Метали во Медицината

Запамти:  
Сите метали во живите организми  
Се присутни во форма на  
ЈОНИ!!!

Никако како  
Метали во елементарна состојба!!!



	1																18	
1s	1 H 1.0079																	2 He 4.0026
2s	3 Li 6.941	4 Be 9.01218											5 B 10.81	6 C 12.011	7 N 14.0067	8 O 15.9994	9 F 18.9984	10 Ne 20.179
3s	11 Na 22.98977	12 Mg 24.305	3d, 4d, 5d	4	5	6	7	8	9	10	11	12	13 Al 26.9815	14 Si 28.0855	15 P 30.9738	16 S 32.06	17 Cl 35.453	18 Ar 39.948
4s	19 K 39.0983	20 Ca 40.08	21 Sc 44.9559	22 Ti 47.88	23 V 50.9415	24 Cr 51.996	25 Mn 54.938	26 Fe 55.847	27 Co 58.9332	28 Ni 58.69	29 Cu 63.546	30 Zn 65.38	31 Ga 69.72	32 Ge 72.59	33 As 74.9216	34 Se 78.96	35 Br 79.904	36 Kr 83.80
5s	37 Rb 85.4678	38 Sr 87.62	39 Y 88.9059	40 Zr 91.22	41 Nb 92.9064	42 Mo 95.94	43 Tc (98)	44 Ru 101.07	45 Rh 102.9055	46 Pd 106.42	47 Ag 107.868	48 Cd 112.41	49 In 114.82	50 Sn 118.69	51 Sb 121.75	52 Te 127.60	53 I 126.9045	54 Xe 131.29
6s	55 Cs 132.9054	56 Ba 137.33	57 *La 138.9055	72 Hf 178.49	73 Ta 180.9479	74 W 183.85	75 Re 186.207	76 Os 190.2	77 Ir 192.22	78 Pt 195.08	79 Au 196.9665	80 Hg 200.59	81 Tl 204.383	82 Pb 207.2	83 Bi 208.9804	84 Po (209)	85 At (210)	86 Rn (222)
7s	87 Fr (223)	88 Ra 226.0254	89 *Ac 227.0278	( ) mass numbers of most stable isotope														

# LANTHANUM SERIES

4f	58 Ce 140.12	59 Pr 140.9077	60 Nd 144.24	61 Pm (145)	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.9254	66 Dy 162.50	67 Ho 164.9304	68 Er 167.26	69 Tm 168.9342	70 Yb 173.04	71 Lu 174.967
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\* ACTINIUM SERIES

5f	90 Th 232.0381	91 Pa 231.0359	92 U 238.0289	93 Np 237.0482	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (260)
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	<b>1</b>																		<b>18</b>	
<b>1s</b>	1 <b>H</b> 1·0079	<b>2</b>																	2 <b>He</b> 4·0026	
<b>2s</b>	3 <b>Li</b> 6·941	4 <b>Be</b> 9·01218												<b>5</b> <b>B</b> 10·81	<b>6</b> <b>C</b> 12·011	<b>7</b> <b>N</b> 14·0067	<b>8</b> <b>O</b> 15·9994	<b>9</b> <b>F</b> 18·9984	<b>10</b> <b>Ne</b> 20·179	<b>2p</b>
<b>3s</b>	11 <b>Na</b> 22·98977	12 <b>Mg</b> 24·305	<b>3</b> <small>3d, 4d, 5d</small>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b> <b>Al</b> 26·9815	<b>14</b> <b>Si</b> 28·0855	<b>15</b> <b>P</b> 30·9738	<b>16</b> <b>S</b> 32·06	<b>17</b> <b>Cl</b> 35·453	<b>18</b> <b>Ar</b> 39·948	<b>3p</b>	
<b>4s</b>	19 <b>K</b> 39·0983	20 <b>Ca</b> 40·08	21 <b>Sc</b> 44·9559	22 <b>Ti</b> 47·88	23 <b>V</b> 50·9415	24 <b>Cr</b> 51·996	25 <b>Mn</b> 54·938	26 <b>Fe</b> 55·847	27 <b>Co</b> 58·9332	28 <b>Ni</b> 58·69	29 <b>Cu</b> 63·546	30 <b>Zn</b> 65·38	31 <b>Ga</b> 69·72	32 <b>Ge</b> 72·59	33 <b>As</b> 74·9216	34 <b>Se</b> 78·96	35 <b>Br</b> 79·904	36 <b>Kr</b> 83·80	<b>4p</b>	
<b>5s</b>	37 <b>Rb</b> 85·4678	38 <b>Sr</b> 87·62	39 <b>Y</b> 88·9059	40 <b>Zr</b> 91·22	41 <b>Nb</b> 92·9064	42 <b>Mo</b> 95·94	43 <b>Tc</b> (98)	44 <b>Ru</b> 101·07	45 <b>Rh</b> 102·9055	46 <b>Pd</b> 106·42	47 <b>Ag</b> 107·868	48 <b>Cd</b> 112·41	49 <b>In</b> 114·82	50 <b>Sn</b> 118·69	51 <b>Sb</b> 121·75	52 <b>Te</b> 127·60	53 <b>I</b> 126·9045	54 <b>Xe</b> 131·29	<b>5p</b>	
<b>6s</b>	55 <b>Cs</b> 132·9054	56 <b>Ba</b> 137·33	57 <b>*La</b> 138·9055	72 <b>Hf</b> 178·49	73 <b>Ta</b> 180·9479	74 <b>W</b> 183·85	75 <b>Re</b> 186·207	76 <b>Os</b> 190·2	77 <b>Ir</b> 192·22	78 <b>Pt</b> 195·08	79 <b>Au</b> 196·9665	80 <b>Hg</b> 200·59	81 <b>Tl</b> 204·383	82 <b>Pb</b> 207·2	83 <b>Bi</b> 208·9804	84 <b>Po</b> (209)	85 <b>At</b> (210)	86 <b>Rn</b> (222)	<b>6p</b>	
<b>7s</b>	87 <b>Fr</b> (223)	88 <b>Ra</b> 226·0254	89 <b>*Ac</b> 227·0278																	

( ) mass numbers of most stable isotope

# LANTHANUM SERIES

<b>4f</b>	58 <b>Ce</b> 140·12	59 <b>Pr</b> 140·9077	60 <b>Nd</b> 144·24	61 <b>Pm</b> (145)	62 <b>Sm</b> 150·36	63 <b>Eu</b> 151·96	64 <b>Gd</b> 157·25	65 <b>Tb</b> 158·9254	66 <b>Dy</b> 162·50	67 <b>Ho</b> 164·9304	68 <b>Er</b> 167·26	69 <b>Tm</b> 168·9342	70 <b>Yb</b> 173·04	71 <b>Lu</b> 174·967
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\* ACTINIUM SERIES

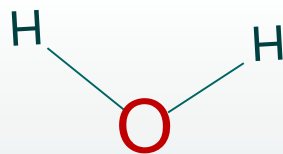
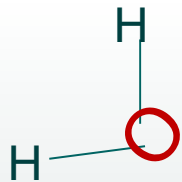
<b>5f</b>	90 <b>Th</b> 232·0381	91 <b>Pa</b> 231·0359	92 <b>U</b> 238·0389	93 <b>Np</b> 237·0482	94 <b>Pu</b> (244)	95 <b>Am</b> (243)	96 <b>Cm</b> (247)	97 <b>Bk</b> (247)	98 <b>Cf</b> (251)	99 <b>Es</b> (252)	100 <b>Fm</b> (257)	101 <b>Md</b> (258)	102 <b>No</b> (259)	103 <b>Lr</b> (260)
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Потребно е да се знае

Метали и ЛИГАНДИ.

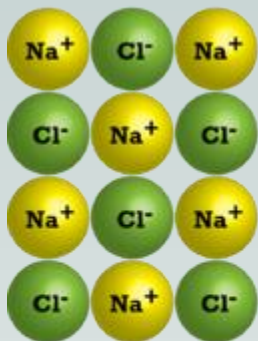
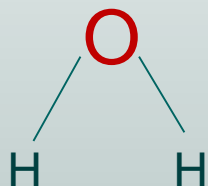
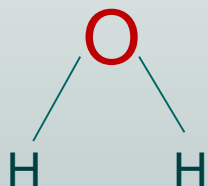
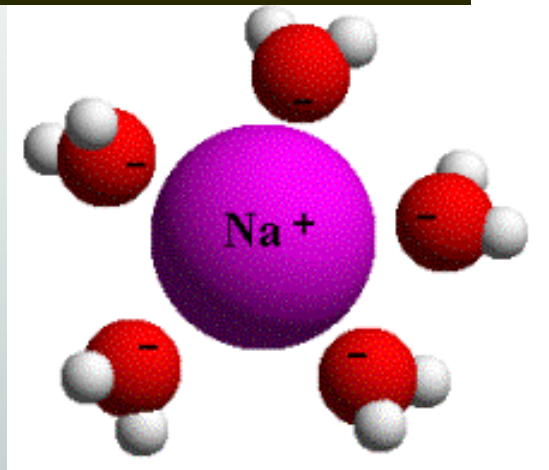
Како природата може да ги употреби металите?



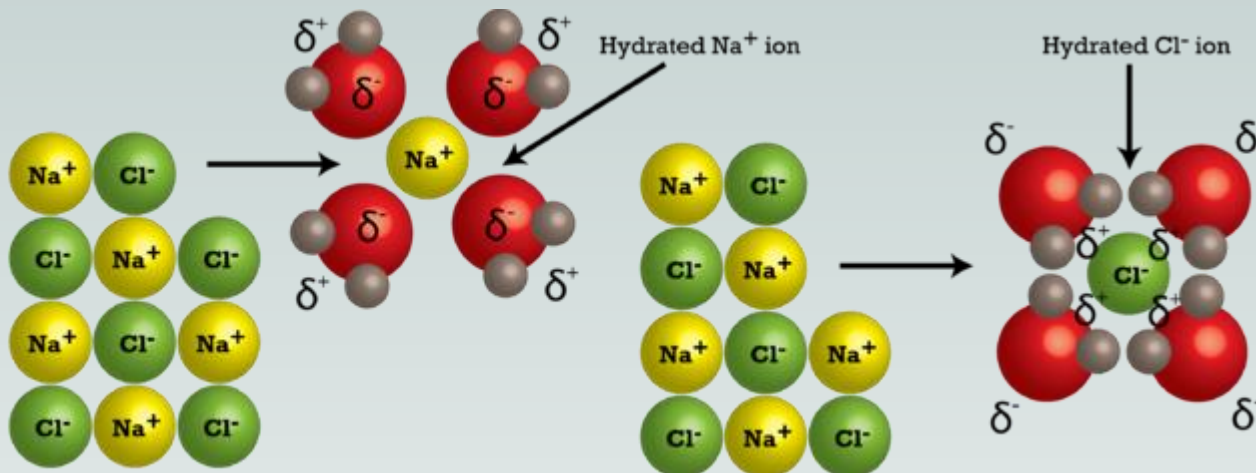


Што се случува со Катјонот на Натриум кога ќе се раствори во вода?

Na<sup>+</sup>



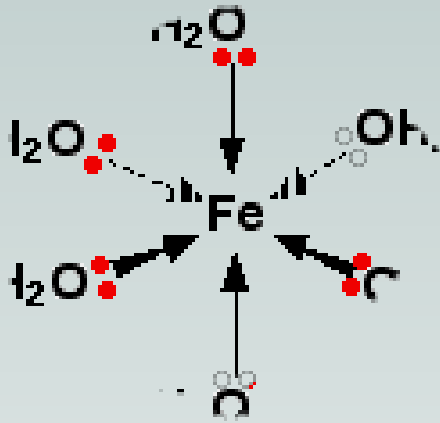
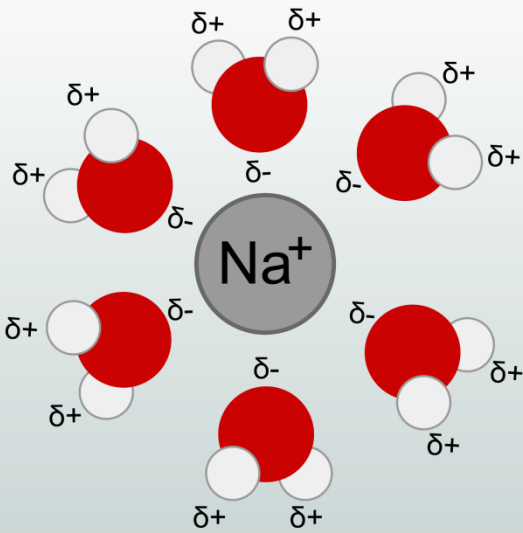
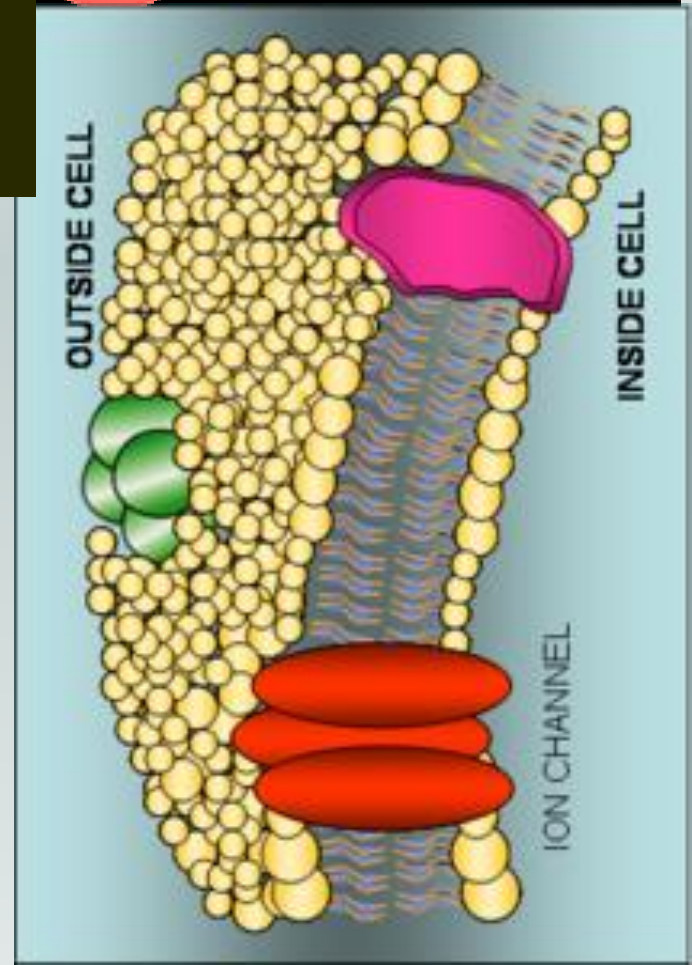
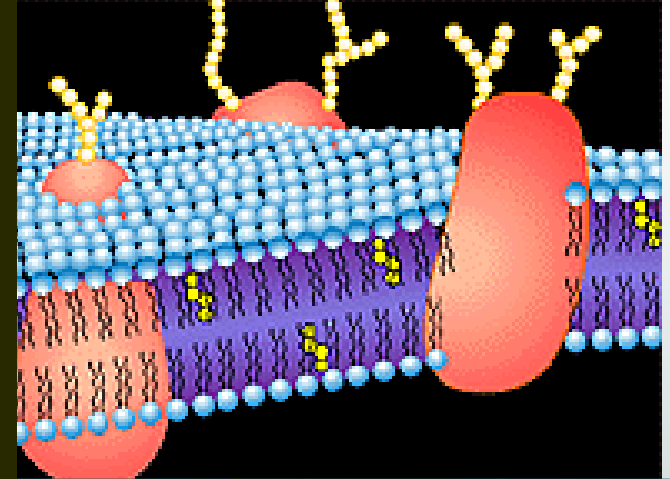
Sodium Chloride Crystal

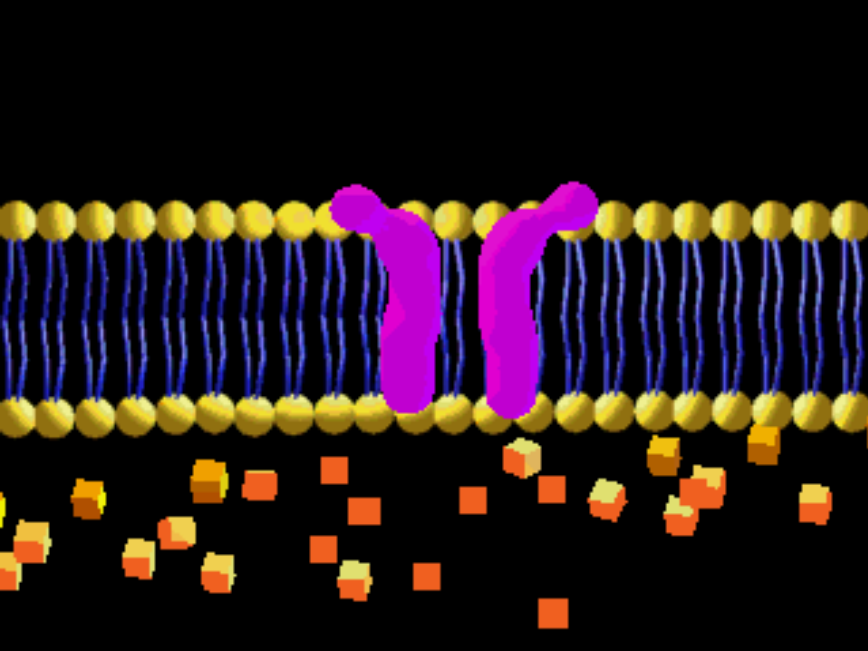




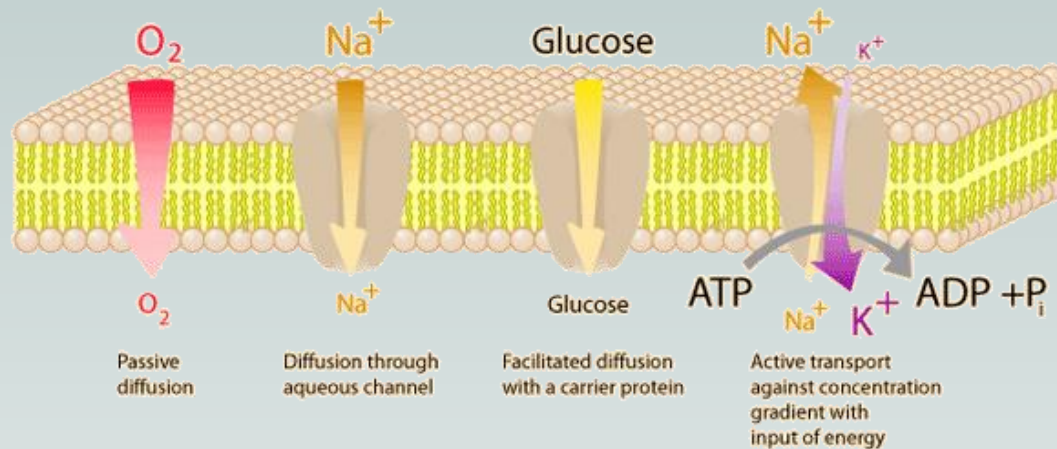
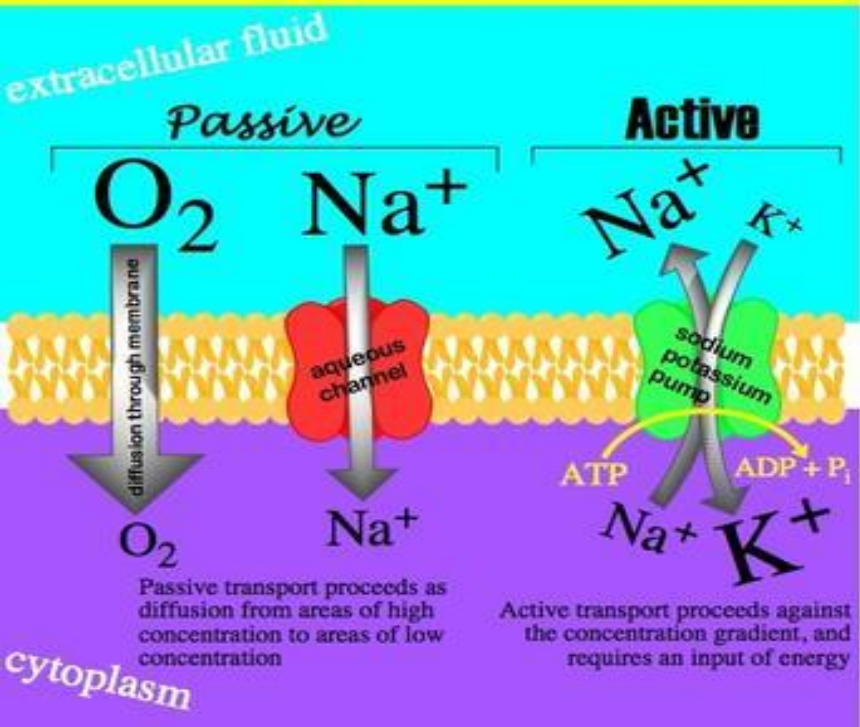
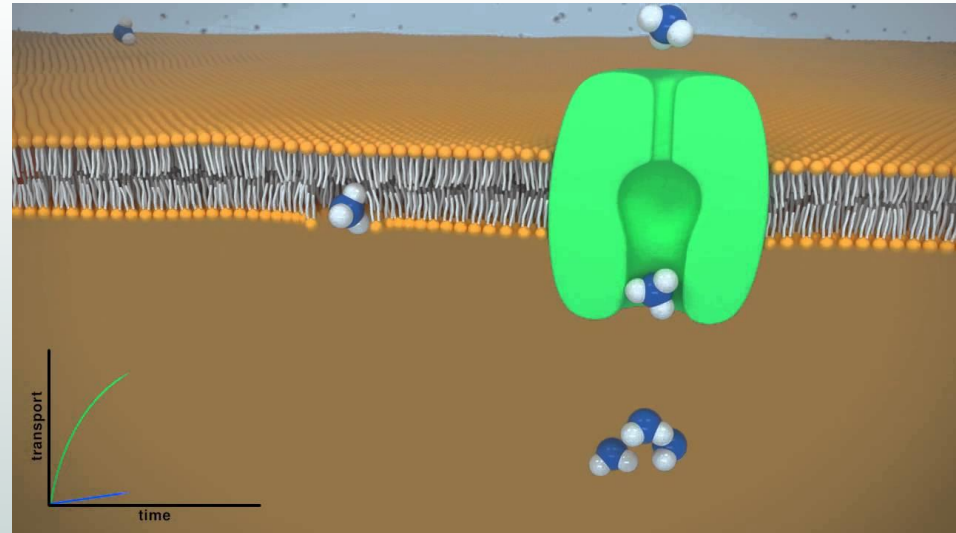
Металните катјони  
Кога се наоѓаат  
Растворени во крвта се  
СИЛНО ХИДРАТИРАНИ!!!

Стануваат силно  
**Хидрофилни јони** кои  
**НЕ МОЖЕ** (најчесто)  
Да поминат слободно  
Преку ЛИПОФИЛНАТА  
Клеточна мембрана!!!





# Active and Passive Transport





Inside

Outside

$K^+$   
100 mM

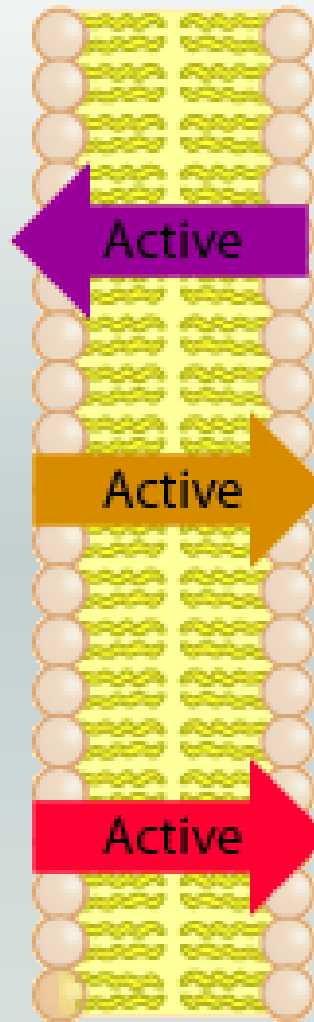
$K^+$   
5 mM

$Na^+$   
10 mM

$Na^+$   
150 mM

$Ca^{2+}$   
 $10^{-7}$  M

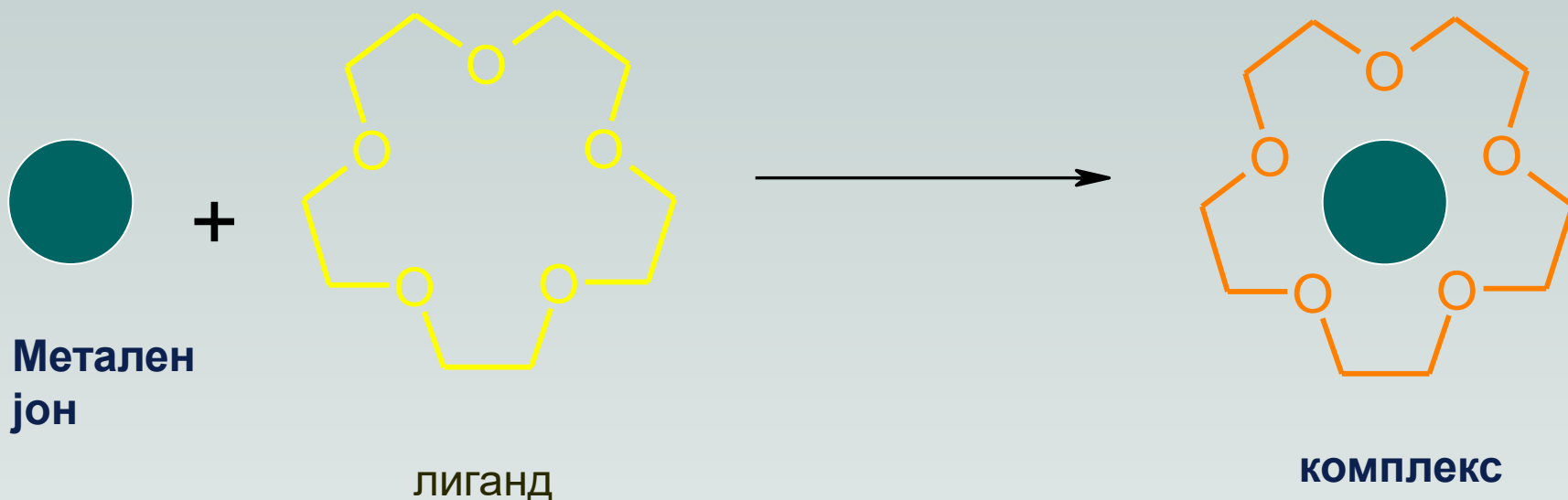
$Ca^{2+}$   
1 mM



Cell Membrane

# Метали+ Лиганди

ЛИГАНДИТЕ СЕ НАЈЧЕСТО ОРГАНСКИ МОЛЕКУЛИ КОИ МОЖЕ ДА ГО КОМПЛЕКСИРААТ (да направат хемиска врска) со даден јон, при што на тој начин ја овозможуваат неговата достапност во клетките



# Металните јони и заболувања

Голем број на заболувања може да се излекуваат со администрирање на лекарства што содржат метални јони

...но голем број на заболувања може да се иницираат поради недостаток на метални јони во организмите –

Голем број на метални јони влегуваат како кофактори во ензимите

# Каде помагаат металните јони во физиологија и медицина?

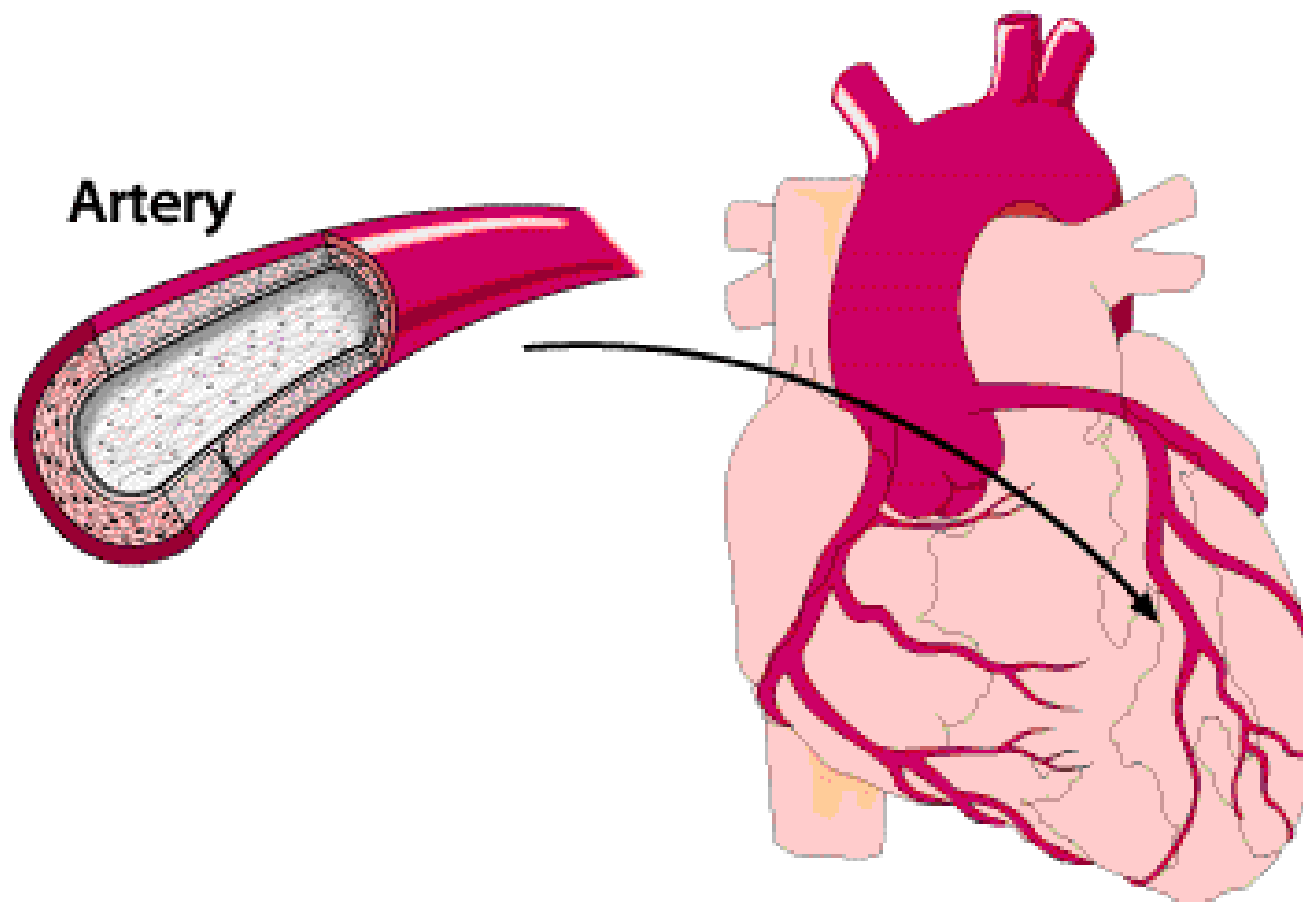
1. Спречување на заболувања на срцето
2. Скрининг на телото
3. Anti-cancer лекови
  - радиоемитери
  - Лекови што се поврзуваат на DNA
4. Anti-HIV лекови

# **1. Превенција на срцеви заболувања**



# Срцев удар

Како се оштетува срцето?

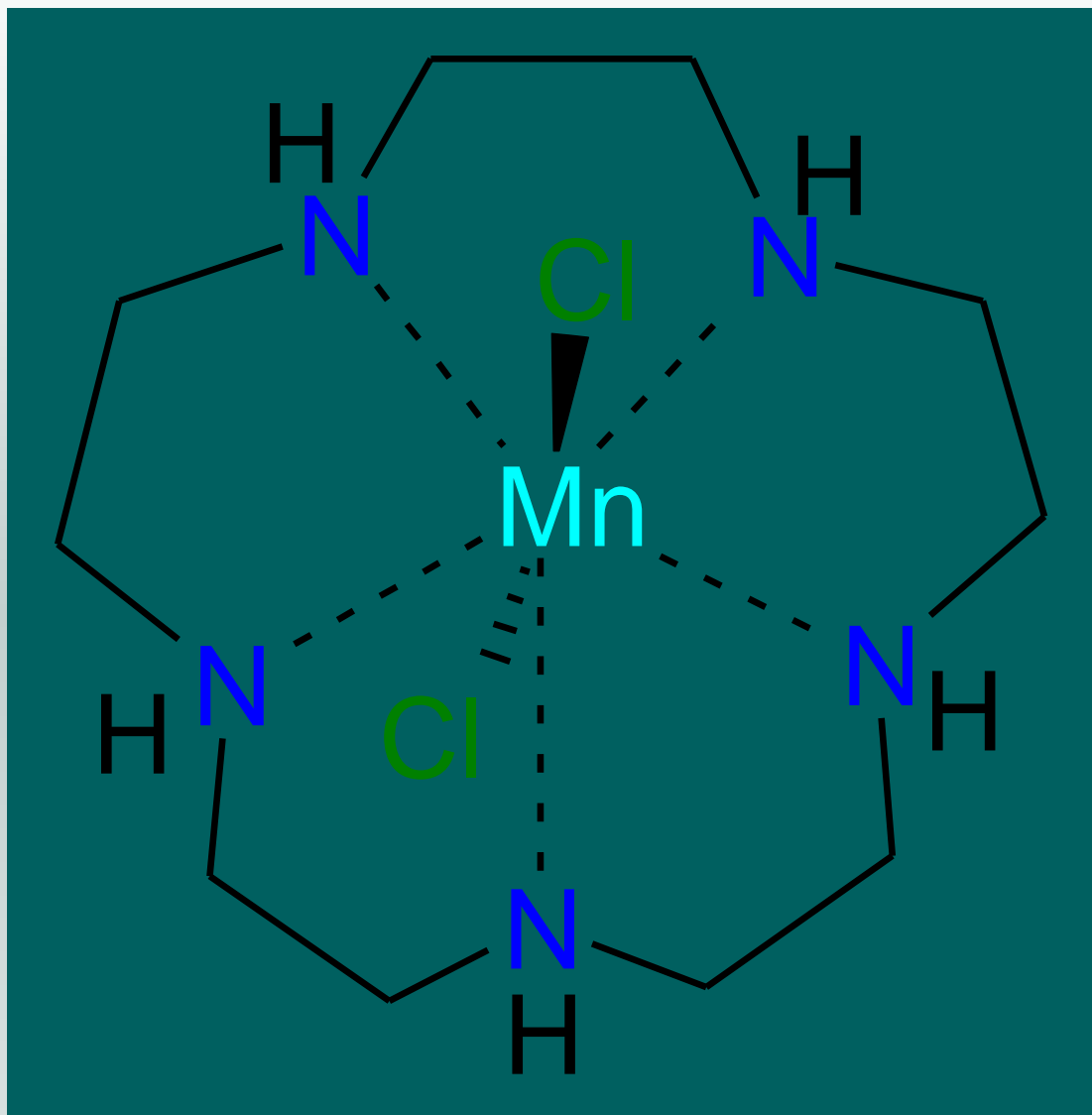


најголем дел од ткивото се  
оштетува најчесто ПОСЛЕ  
срцев удар.



Супероксидот е радикал што е екстремно штетен и реактивен –се создава ПРИ СТРЕС ПУШЕЊЕ некавалитетна исхрана

SOD ензимот го уништува супероксидниот радикал (Superoxide Dismutase)



Pentaazamacrocyclic  $Mn^{2+}$  комплексите дејствуваат како терапевтска замена  
3a SOD Riley, Nature Reviews Drug Discovery, 2002, 367-374.

## **2. Дијагнози- Скрининг на телото**



# Радиоemitери



Видови на лекараства што  
содржат метални јони:

Радиофармацевтици-0.0001 mmol

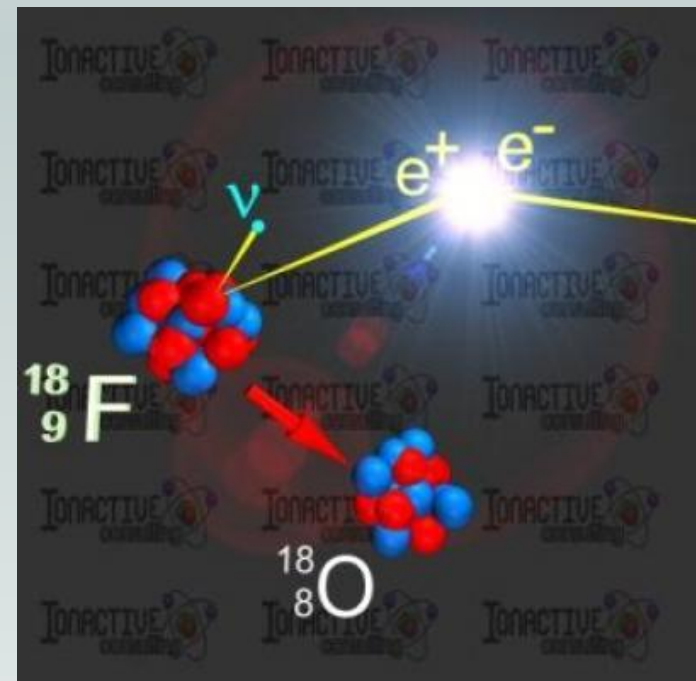
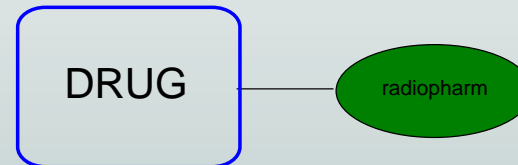
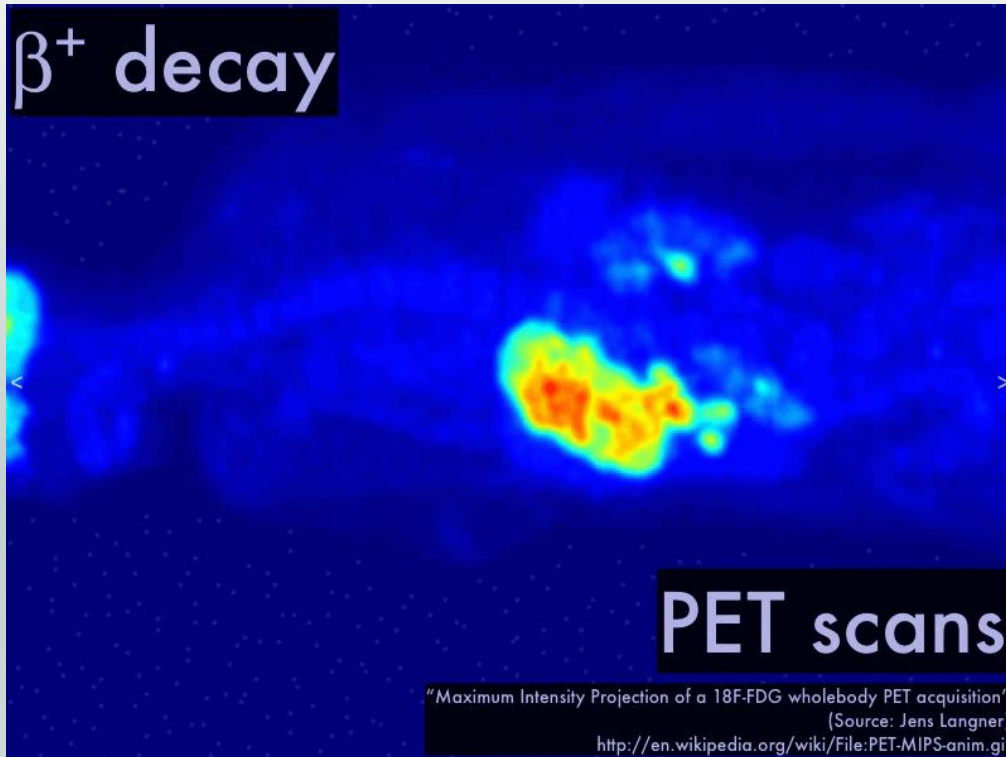
За магнетна резонанца 0.1 mmol

**Се користат** Метални изотопи што емитираат радијација (многу кратко време на полуживот!).

Треба да емитираат силно зрачење.

ЛИГАНДОТ го насочува металот до специфично место каде што треба да го искаже своето дејство.

# Скрининг



# Магнетна резонанца

Се анализира водата во ткивата

Човечкото тело има околу 70% вода.

Пациентот се сместува во голем суперкондуктивен магнет при што се аплицираат радиозраци, а резултантните сигнали компјутерски се обработуваат

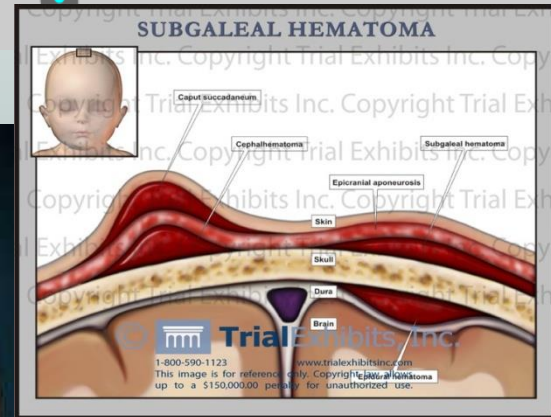
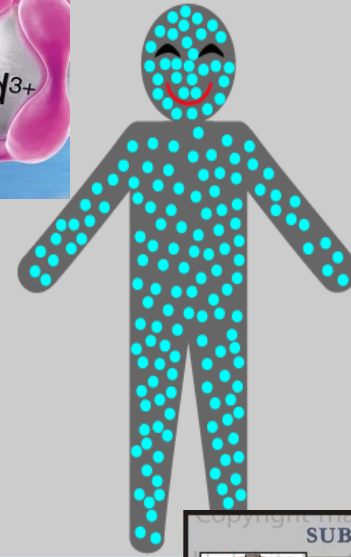
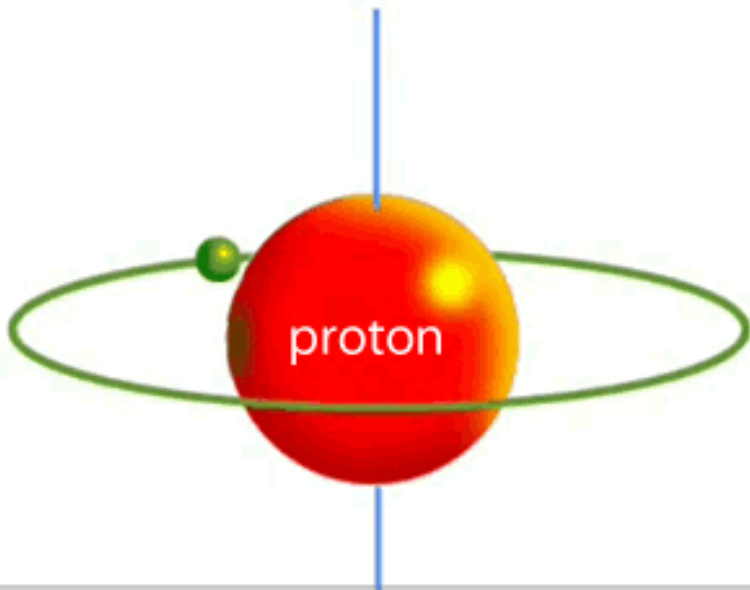














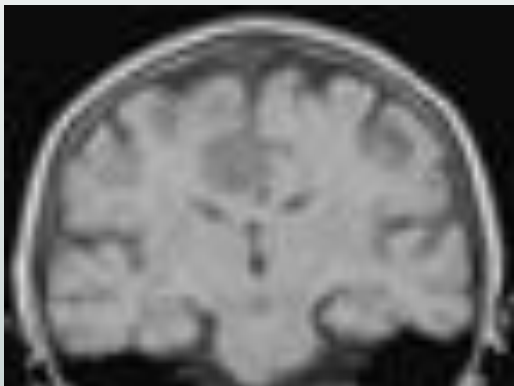
# Дали треба метален јон?

не... ама помага.

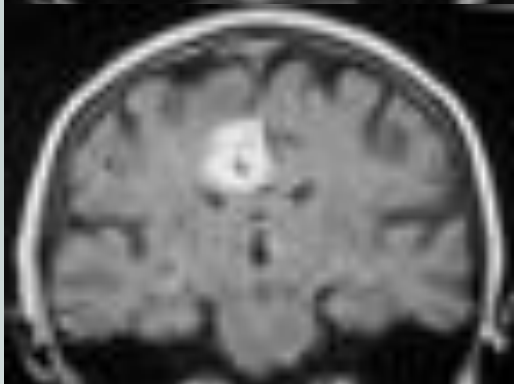
Gadolinium најчесто се употребува

внимавај **ТОКСИЧЕН!**

Магнетизмот на Gd го спречува  
сигналот од водата што доведува до  
подобрена слика

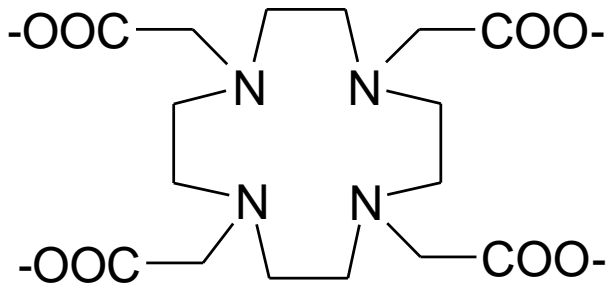


НИШТО



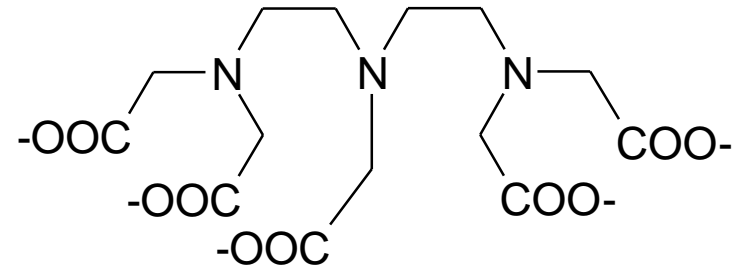
Со  
употреба  
на  
контрастна  
супстанца  
Gd





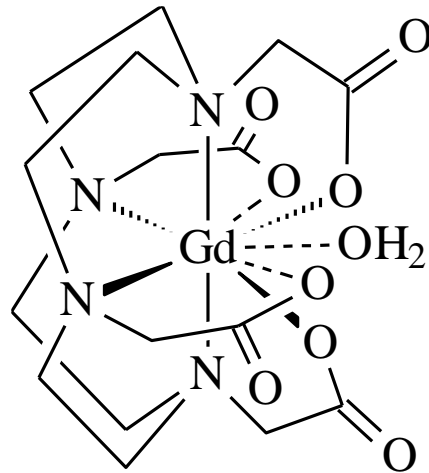
**DOTA**

1,4,7,10-tetraazacyclododecane  
-1,4,7,10-tetraacetic acid



**DTPA**

diethylene triamine pentaacetic acid



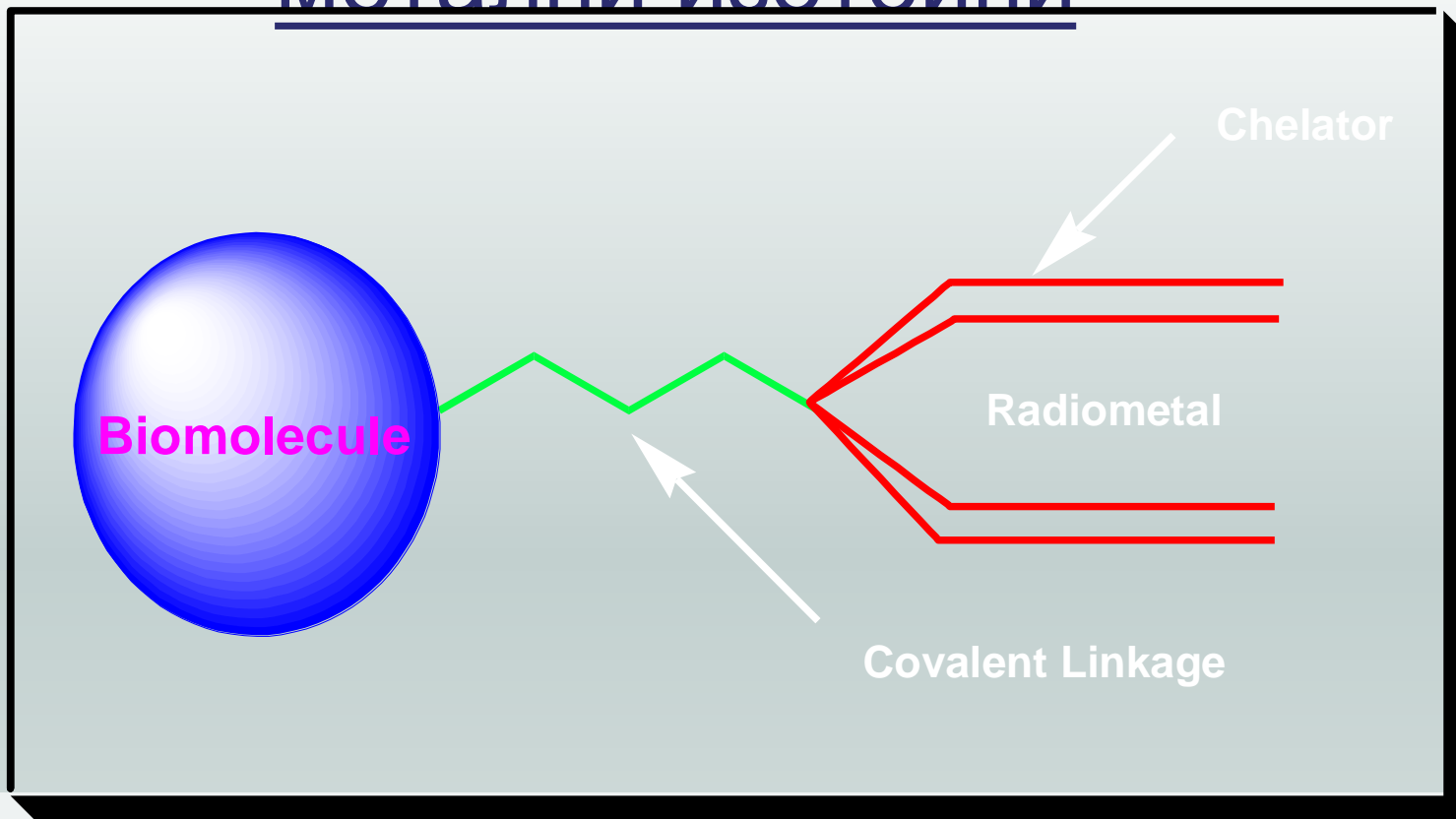
**Gd(DOTA)<sup>-</sup>**

Често користени лиганди  
Во радиофармацијата



# **3. Anti-cancer лекови**

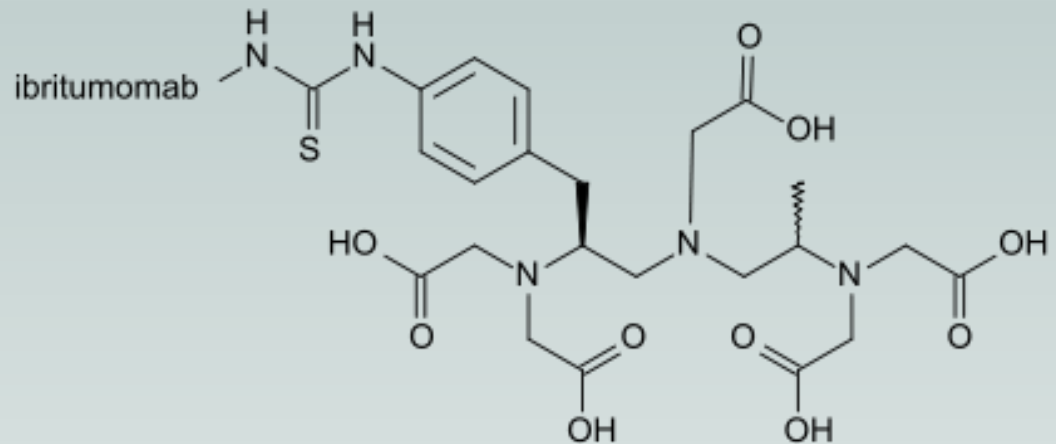
# Лекување на канцер со радиоактивни метални изотопи



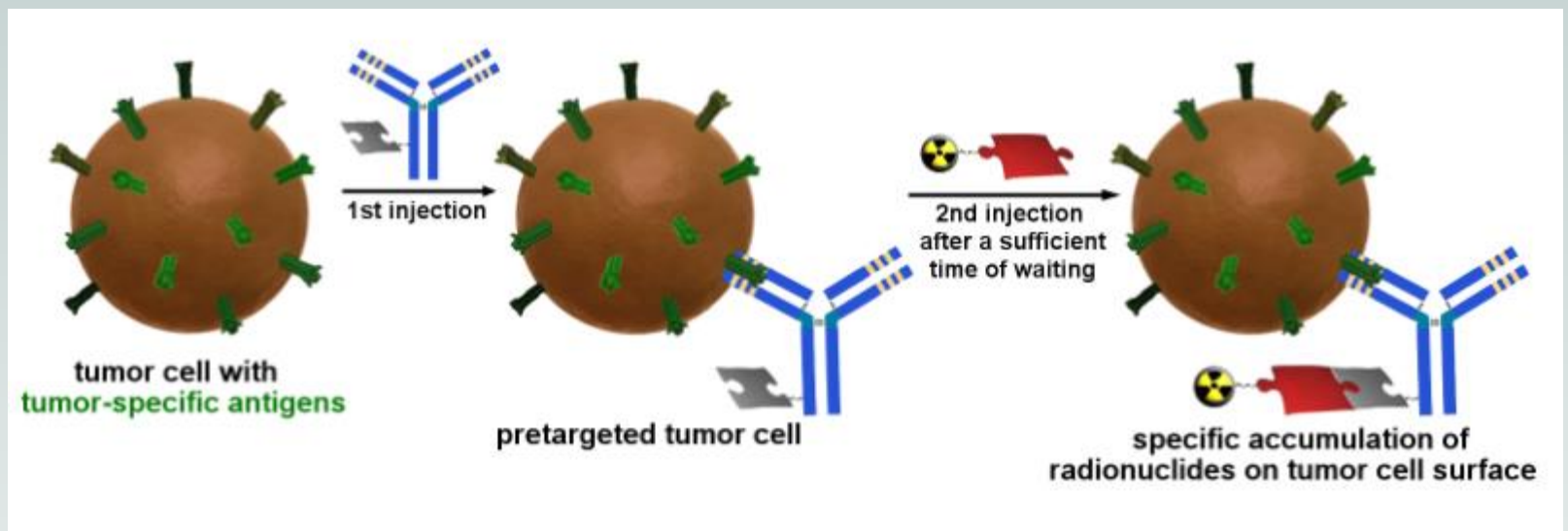
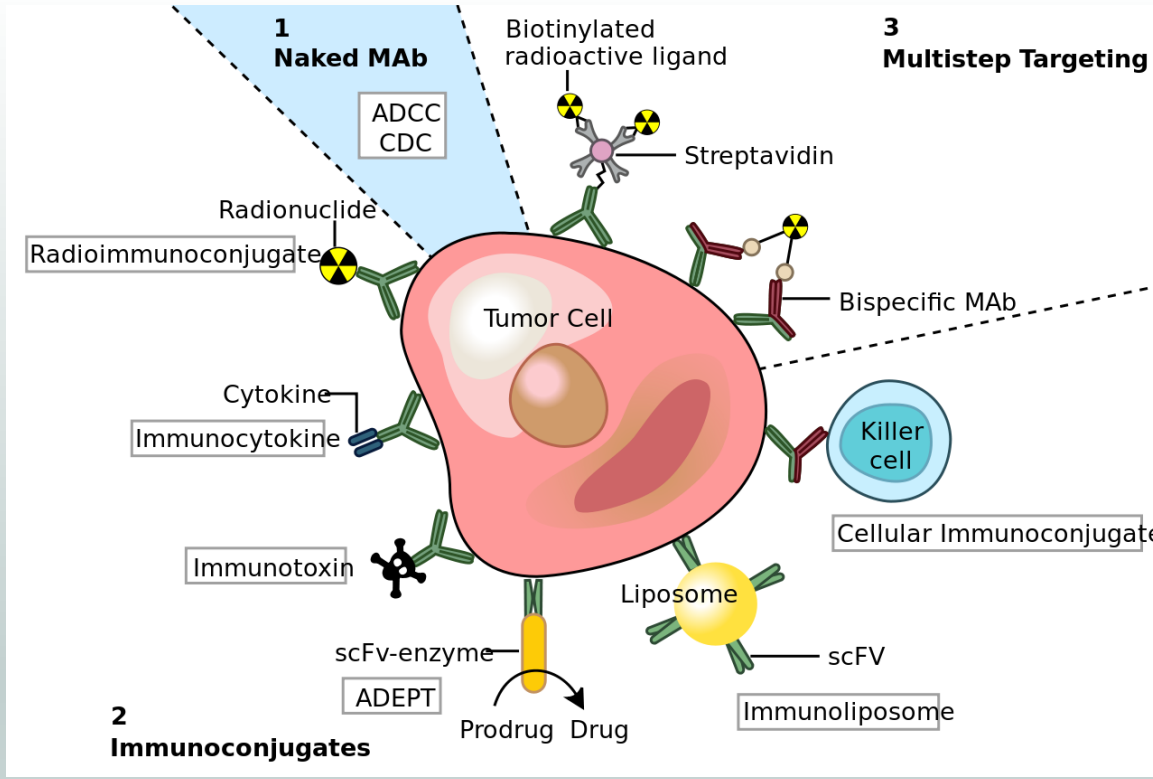
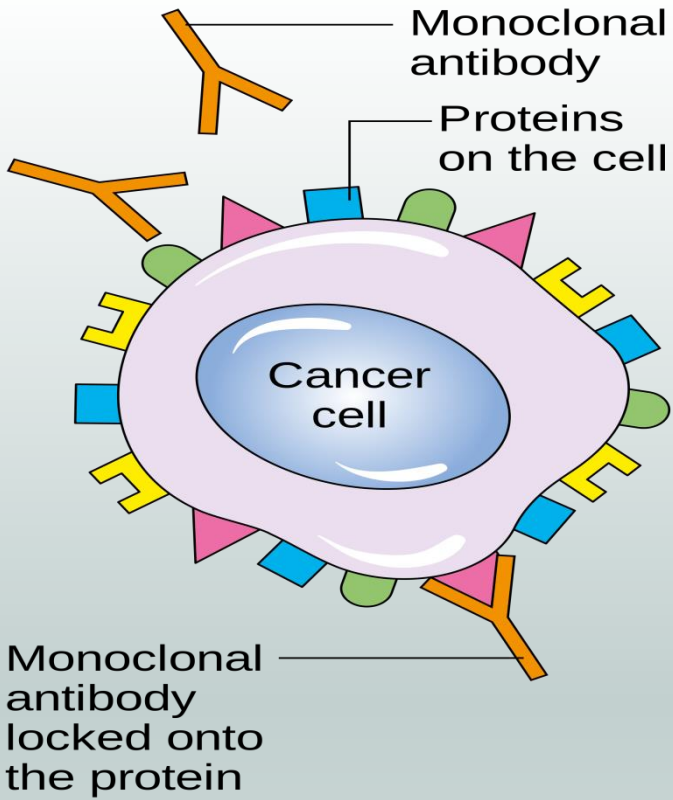
**Се употребуваат лекови за трансфер на терапевтски дози на радијација (радијацијата доаѓа од присуството на некој радиоактивен изотоп на метален јон) до специфични места во телото**

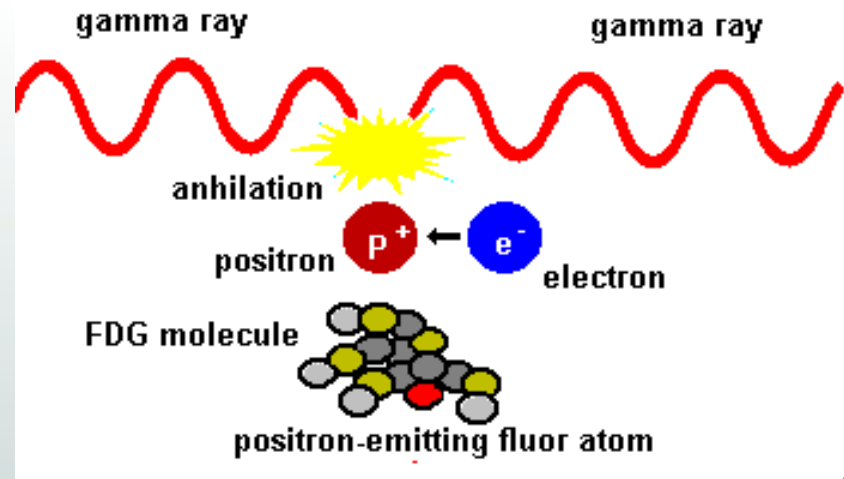
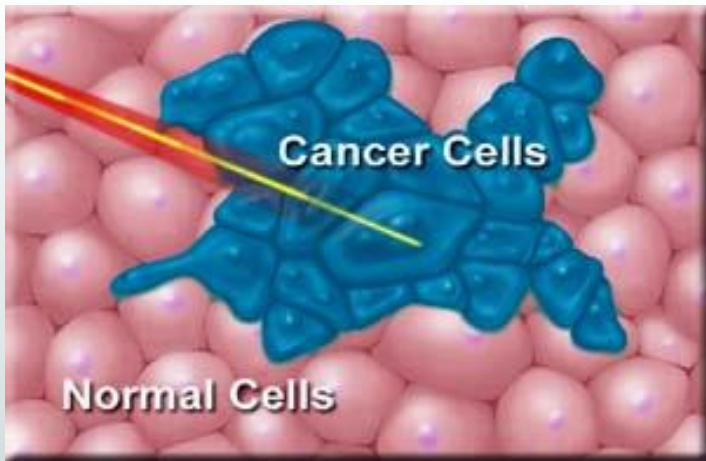
“Првата доза  $^{111}\text{In}$  (indium-111) ibritumomab се употребува за скрининг. Indium-111 емитира ГАМА зраци што може да се снимаат со специјални гама-камери. Се прави скан за да се види каква е биодистрибуцијата на лекот. Овој тест се прави за да се види дали има вишок од лекот што отишол во црниот дроб, сплинката и сл.

Ако скенот покаже дека нема вишок на биодистрибуција, тогаш се дава втора доза со употреба на  $^{90}\text{Y}$  (yttrium-90) ibritumomab за третман. Yttrium-90 емитира БЕТА РАДИЈАЦИЈА што во суштина ги убива канцерогените клетки. БЕТА ЗРАЦИТЕ СЕ ЕЛЕКТРОНИ!!! Значи, канцерогените клетки најчесто може да се третираат со супстанции ШТО ЕМИТИРААТ ЕЛЕКТРОНИ (редукциски средства!!)



**Tiuxetan chelator**





Isotope	Nuclear Reaction	$t_{1/2}$ (minutes)	Radiopharmaceuticals	Application
$^{11}\text{C}$	$^{14}\text{N}(p,\alpha)^{11}\text{C}$	20.4	Raclopride	D2 receptor density
			Methylphenidate	Dopamine transporter
$^{18}\text{F}$	$^{18}\text{O}(p,n)^{18}\text{F}$ $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$	109.8	Fluorodeoxyglucose	Glucose Utilization
			Fluorodopa	Decarboxylation and storage of dopamine
$^{15}\text{O}$	$^{15}\text{N}(p,n)^{15}\text{O}$ $^{14}\text{N}(d,n)^{15}\text{O}$	2.03	$\text{O}_2$	Oxygen Metabolism
			Water	Blood Flow
			Carbon monoxide	Blood Volume
$^{13}\text{N}$	$^{16}\text{O}(p,\alpha)^{13}\text{N}$	9.97	Ammonia	Cardiac Blood Flow

**Покрај радиоизотопи, во борбата против канцерот помагаат и Голем број неоргански соединенија како:**

NaHS;

NaHCO<sub>3</sub>-сода бикарбона!!!-ОБЕЗБЕДУВА БАЗНА СРЕДИНА

-КАНЦЕРОГЕНИ КЛЕТКИ НЕ САКААТ БАЗНА СРЕДИНА!!!  
КАНЦЕРОГЕНИТЕ КЛЕТКИ обожаваат кисела средина-ИЗБЕГНУВАЈ  
КИСЕЛИ ПИЈАЛОЦИ, ГАЗИРАНИ ПРЕД СЕ!!!!

ХИДРАЗИН-N<sub>2</sub>H<sub>4</sub>

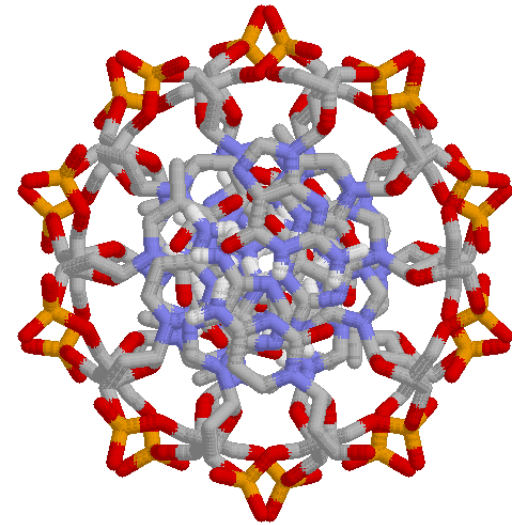
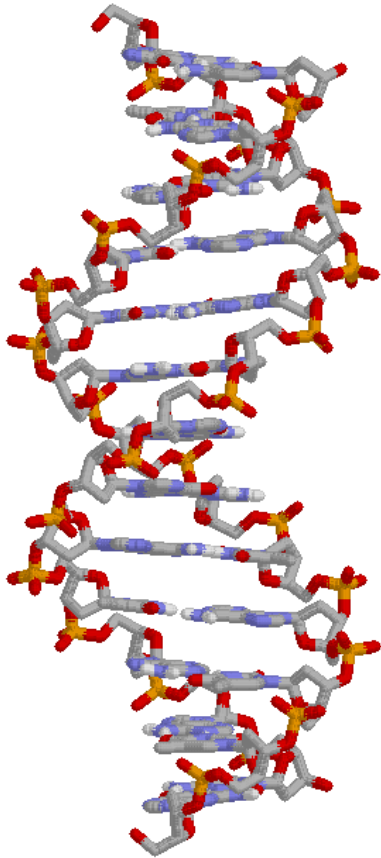
NaBH<sub>4</sub>-натриум борхидрид

Натриум тионат

ПОЛИФЕНОЛИ-присутни во овошјето и во масло добиено од  
Семки од овошје-кајсии, грозје, калинки, ...

Уништување на канцерогени  
клетки преку поврзување со DNA

# DNA двоен helix

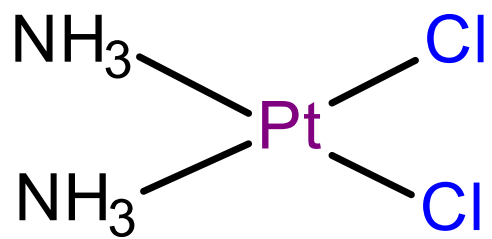




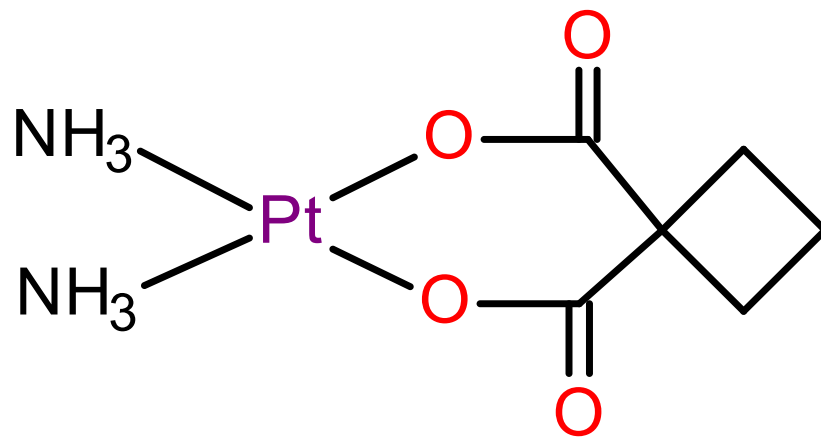
# Историја

лекови на база на платина.

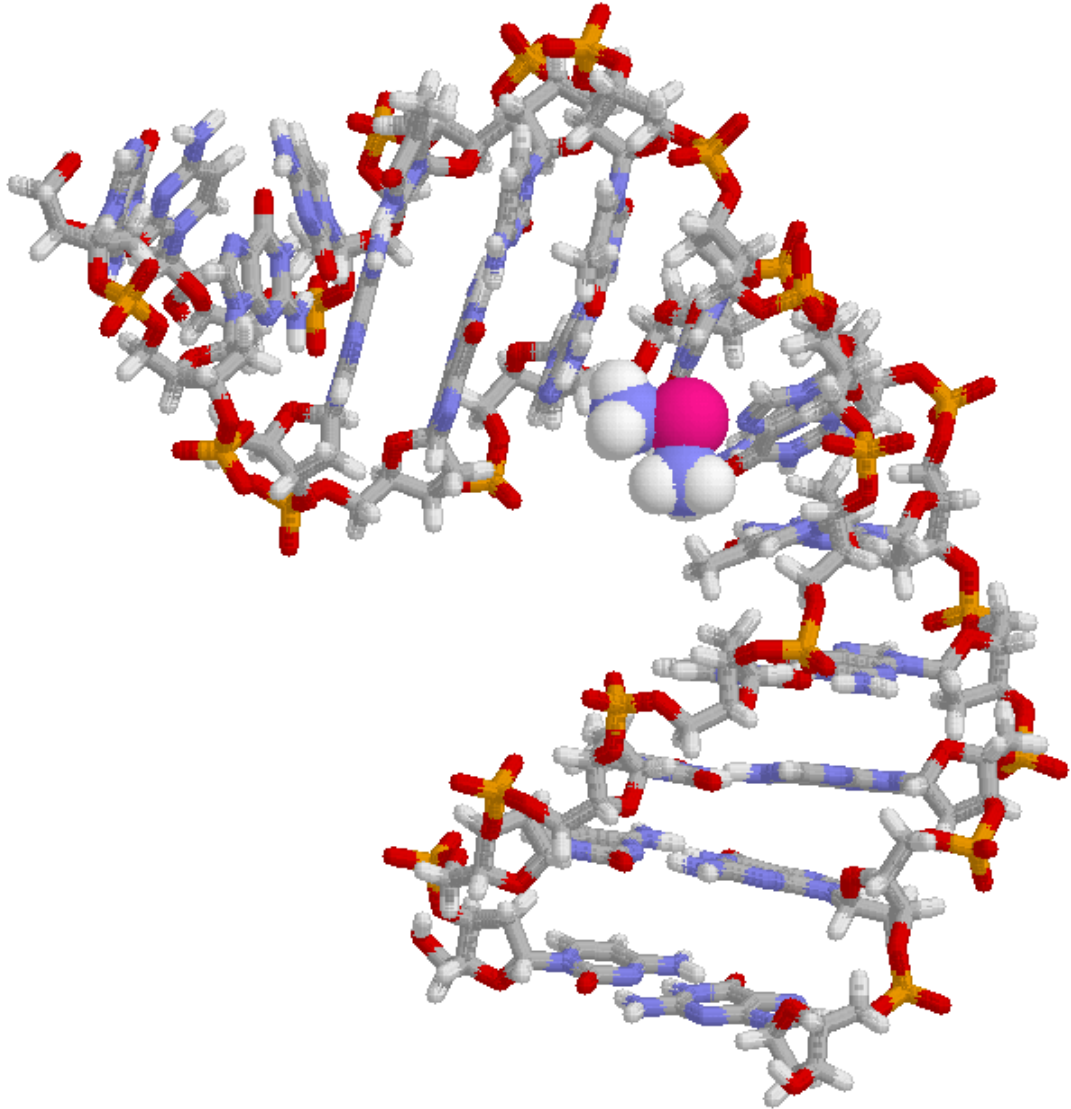
1978                      **cisplatin** е докажано дека е ефикасно при клинички третман на пациенти заболени од различни видови на канцер.



cisplatin

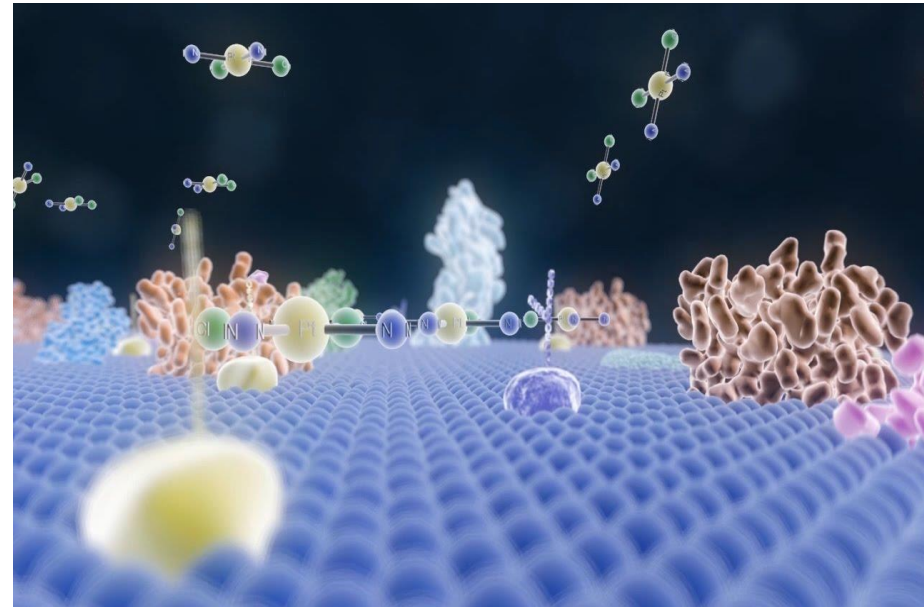
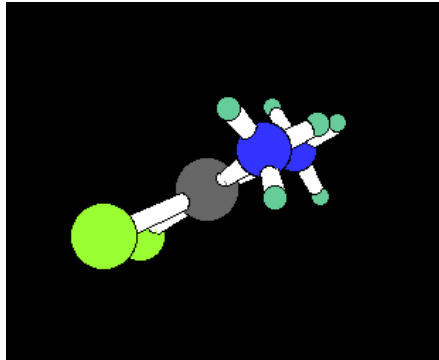
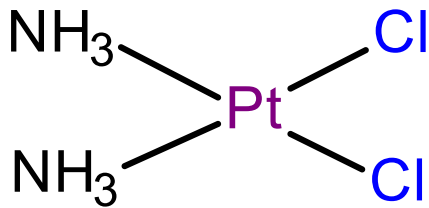


carboplatin



# Како функционира cisplatin?

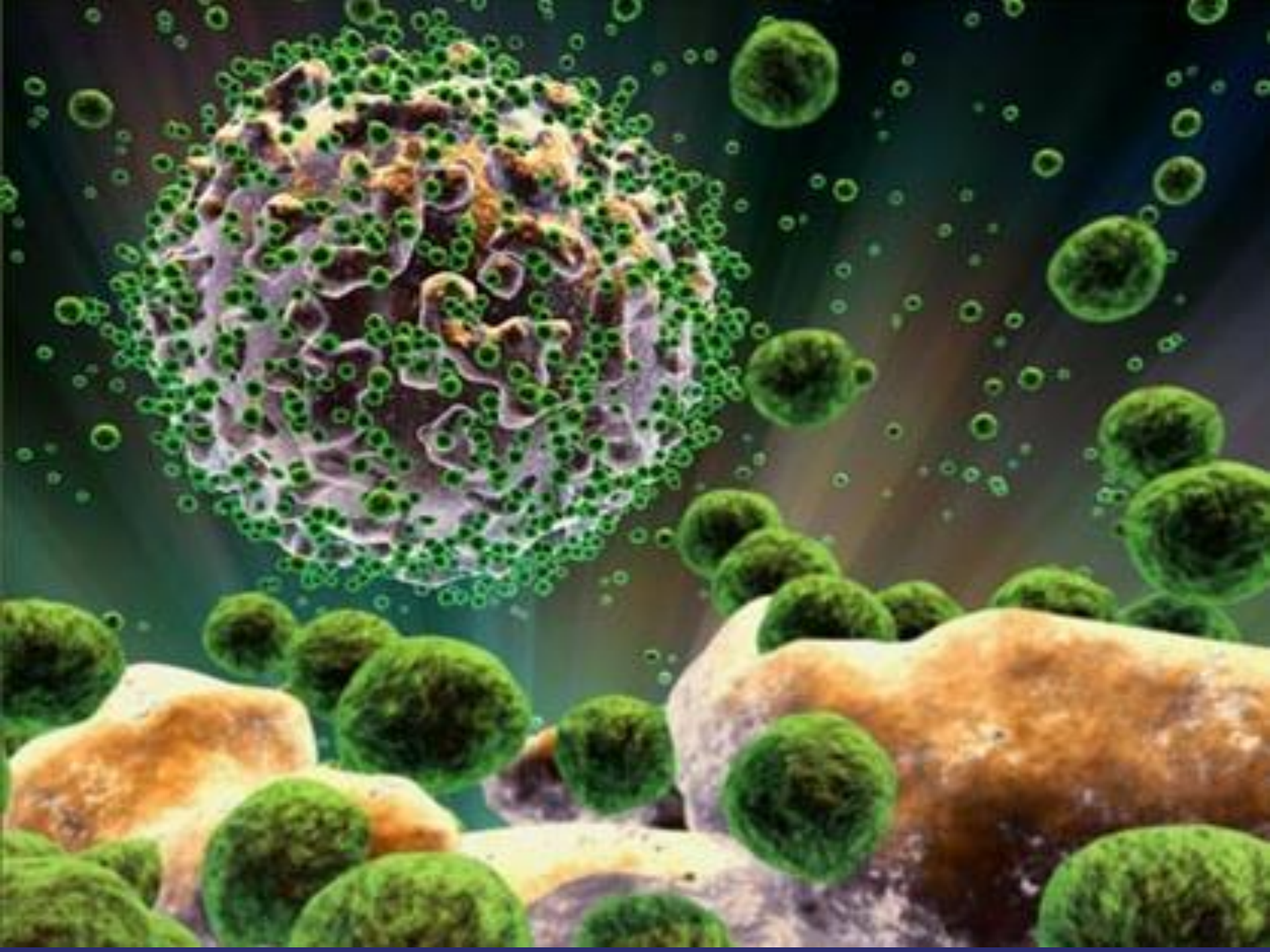
- После администратрање, еден од хлоридните лиганди се заменува со вода  $[\text{PtCl}(\text{H}_2\text{O})(\text{NH}_3)_2]^+$ . Потоа, тој лиганд на вода може да биде отстранет, при што јонот на платина може да се атачира на базите од ДНК, најчесто на гванинот. Откако ќе се формира катјонски комплекс на  $[\text{PtCl}(\text{guanine-DNA})(\text{NH}_3)_2]^+$ , Потоа со друг амолекула на гуанин може да се замени и останатиот Cl-атом. На тој начин цисплатин комплексот ја поврзува ДНК и го спречува процесот на делба на клетката и митоза.



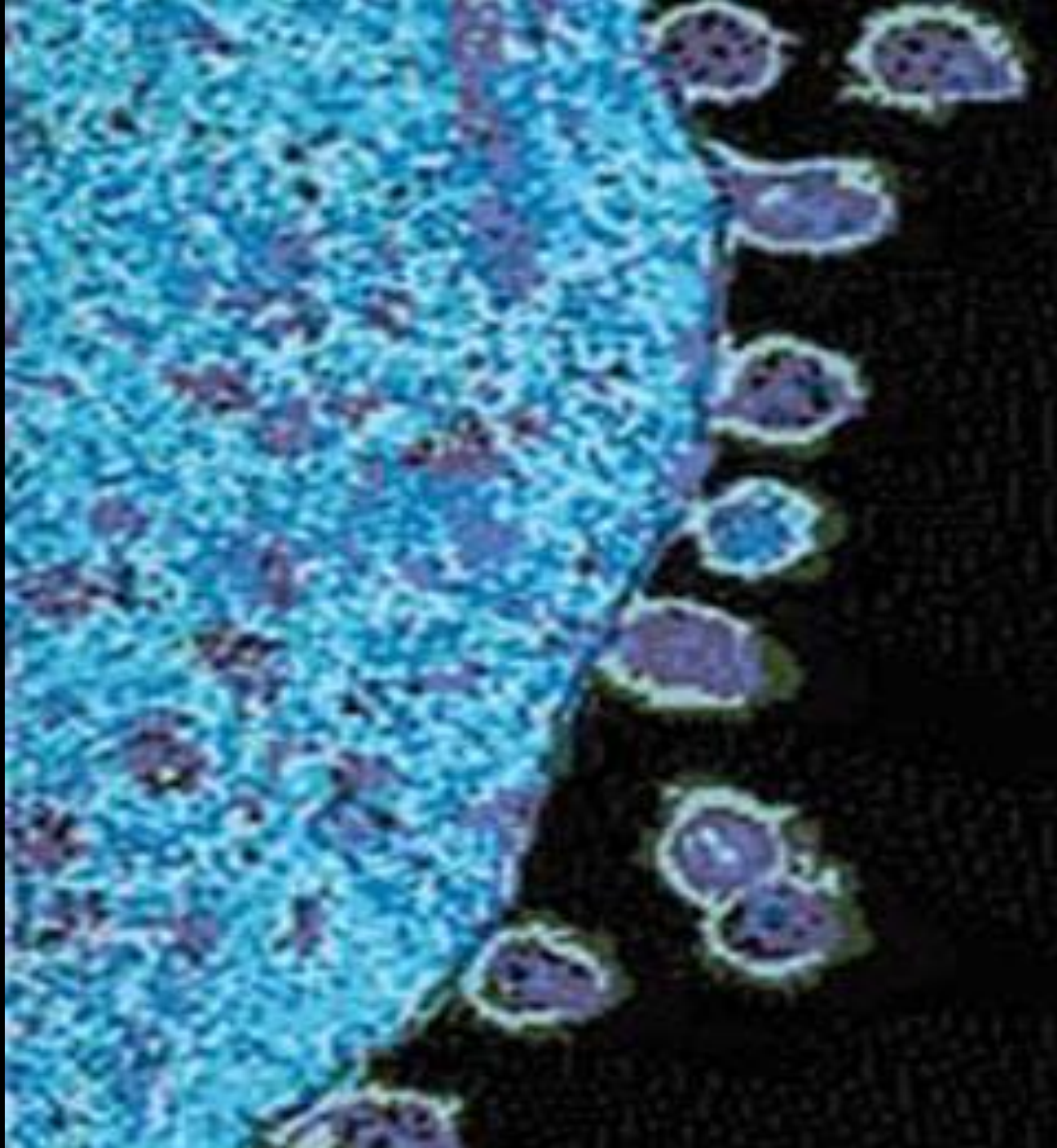


## **4. Anti-HIV лекови**



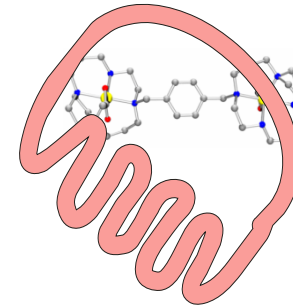
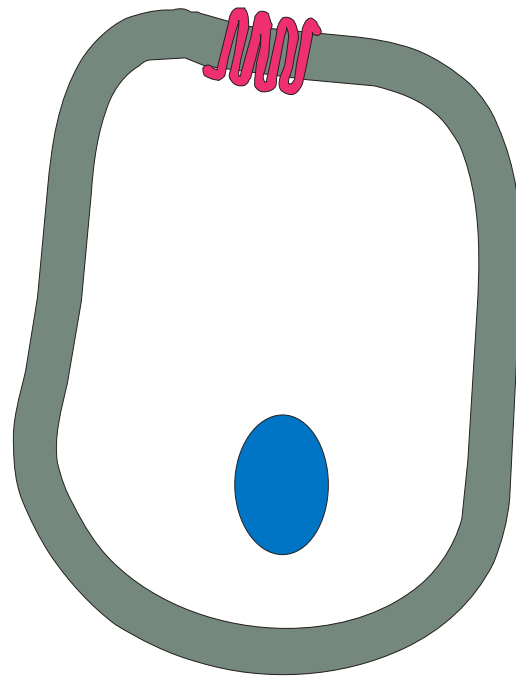


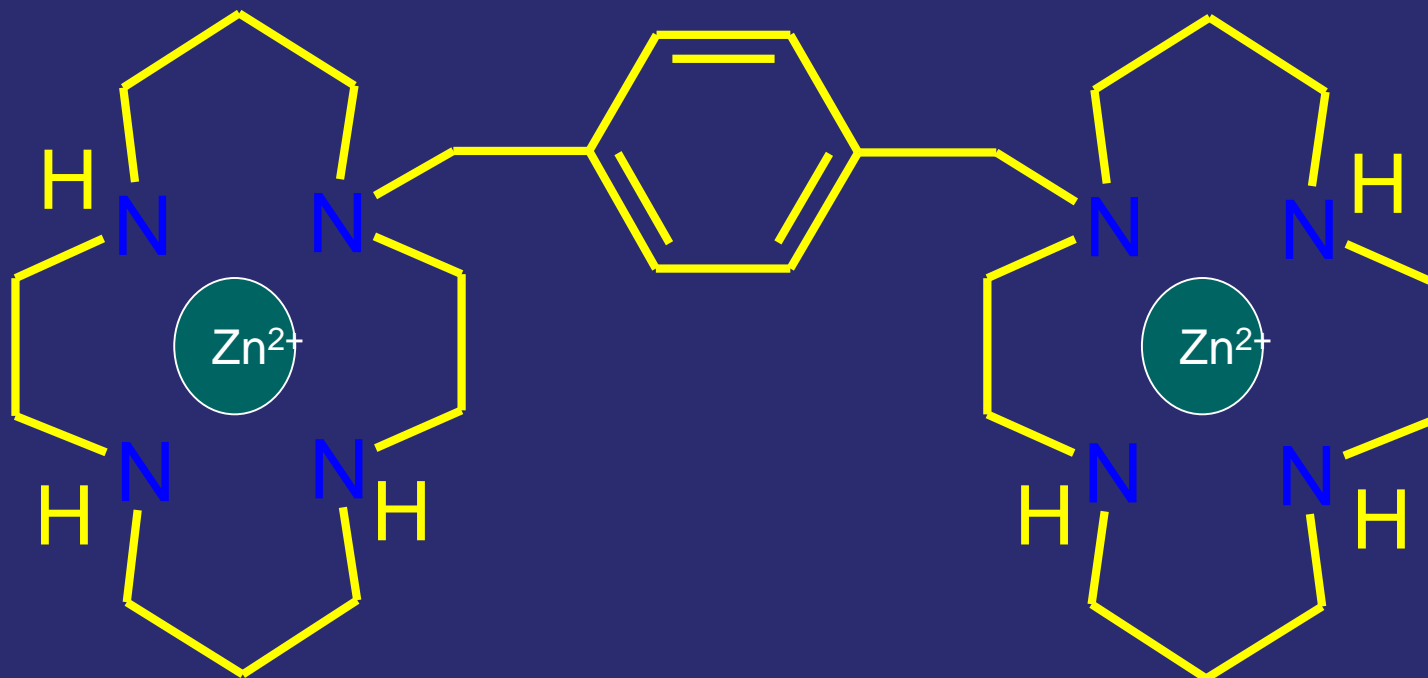


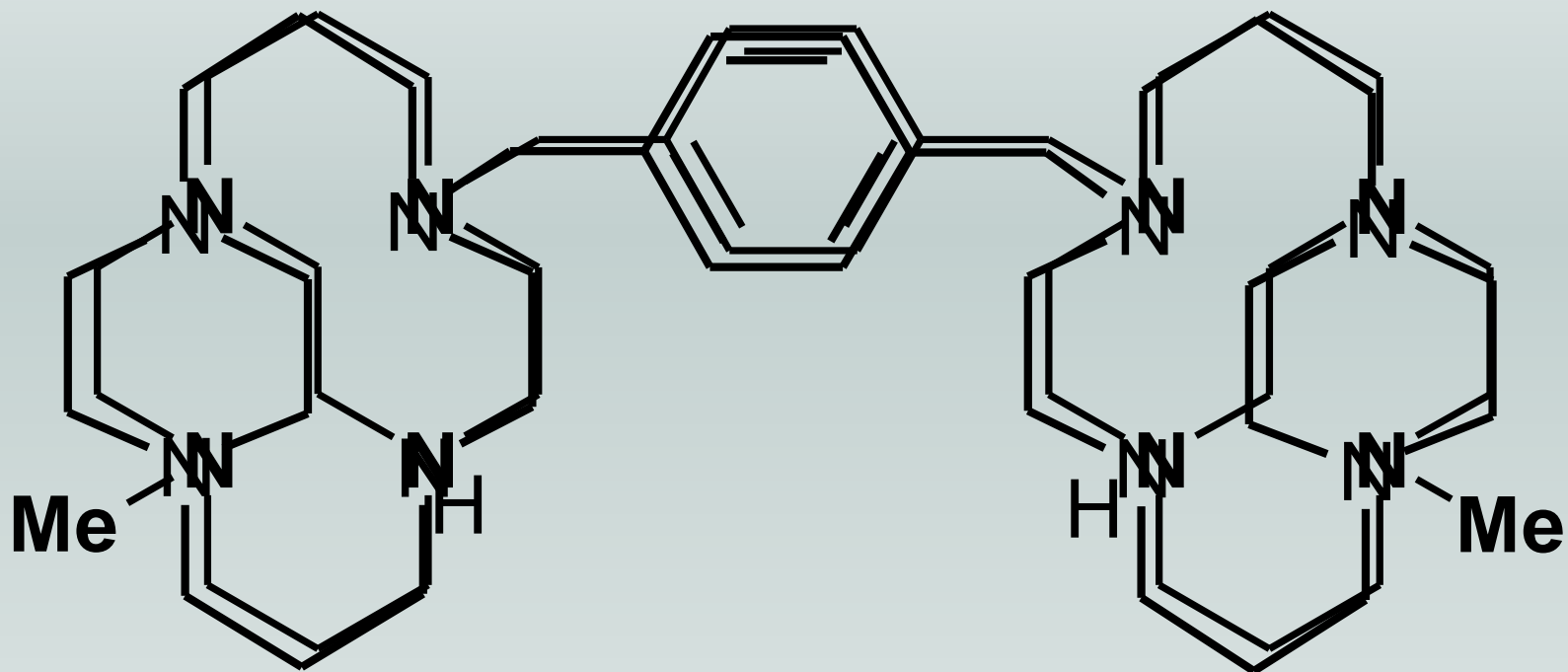




# Блокирање на нападот на вирусот







Lewis, E. A.; Hubin, T. J.; Archibald, S.J. Patent WO2005121109, 2005.

	1																			18
1s	1 H 1·0079	2																		2 He 4·0026
2s	3 Li 6·941	4 Be 9·01218												5 B 10·81	6 C 12·011	7 N 14·0067	8 O 15·9994	9 F 18·9984	10 Ne 20·179	2p
3s	11 Na 22·98977	12 Mg 24·305	3 Sc 44·9559	4 Ti 47·88	5 V 50·9415	6 Cr 51·996	7 Mn 54·938	8 Fe 55·847	9 Co 58·9332	10 Ni 58·69	11 Cu 63·546	12 Zn 65·38	13 Al 26·9815	14 Si 28·0855	15 P 30·9738	16 S 32·06	17 Cl 35·453	18 Ar 39·948	3p	
4s	19 K 39·0983	20 Ca 40·08	21 Sc 44·9559	22 Ti 47·88	23 V 50·9415	24 Cr 51·996	25 Mn 54·938	26 Fe 55·847	27 Co 58·9332	28 Ni 58·69	29 Cu 63·546	30 Zn 65·38	31 Ga 69·72	32 Ge 72·59	33 As 74·9216	34 Se 78·96	35 Br 79·904	36 Kr 83·80	4p	
5s	37 Rb 85·4678	38 Sr 87·62	39 Y 88·9059	40 Zr 91·22	41 Nb 92·9064	42 Mo 95·94	43 Tc (98)	44 Ru 101·07	45 Rh 102·9055	46 Pd 106·42	47 Ag 107·868	48 Cd 112·41	49 In 114·82	50 Sn 118·69	51 Sb 121·75	52 Te 127·60	53 I 126·9045	54 Xe 131·29	5p	
6s	55 Cs 132·9054	56 Ba 137·33	*57 La 138·9055	72 Hf 178·49	73 Ta 180·9479	74 W 183·85	75 Re 186·207	76 Os 190·2	77 Ir 192·22	78 Pt 195·08	79 Au 196·9665	80 Hg 200·59	81 Tl 204·383	82 Pb 207·2	83 Bi 208·9804	84 Po (209)	85 At (210)	86 Rn (222)	6p	
7s	87 Fr (223)	88 Ra 226·0254	*89 Ac 227·0278																	

( ) mass numbers of most stable isotope

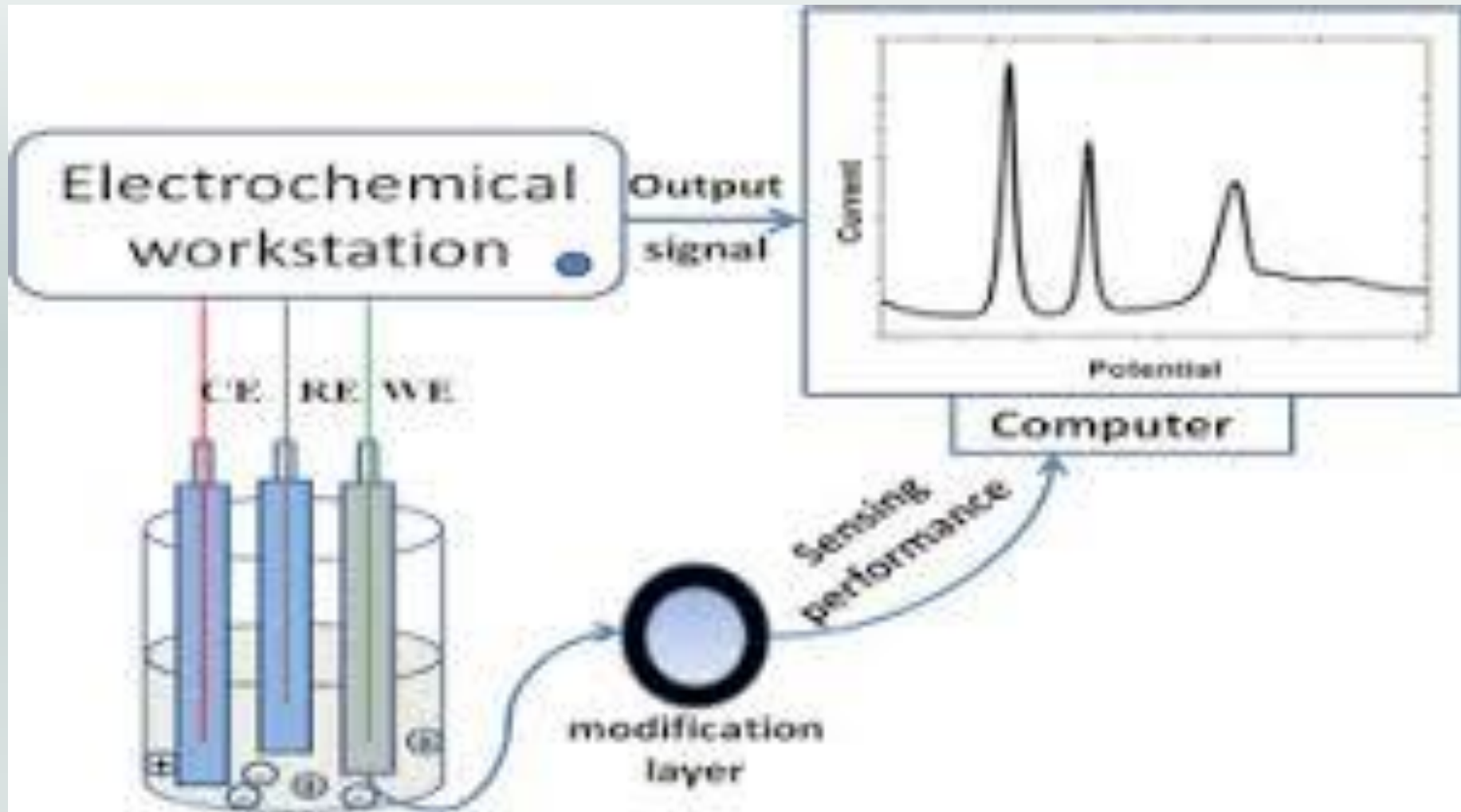
# LANTHANUM SERIES

4f	58 Ce 140·12	59 Pr 140·9077	60 Nd 144·24	61 Pm (145)	62 Sm 150·36	63 Eu 151·96	64 Gd 157·25	65 Tb 158·9254	66 Dy 162·50	67 Ho 164·9304	68 Er 167·26	69 Tm 168·9342	70 Yb 173·04	71 Lu 174·967
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\* ACTINIUM SERIES

5f	90 Th 232·0381	91 Pa 231·0359	92 U 238·0389	93 Np 237·0482	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (260)
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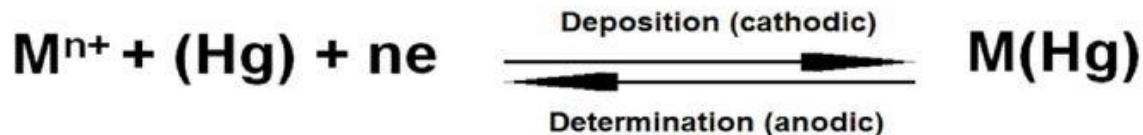
# Anodic Stripping Voltammetry of Metal Ions



# Anodic Stripping Voltammetry

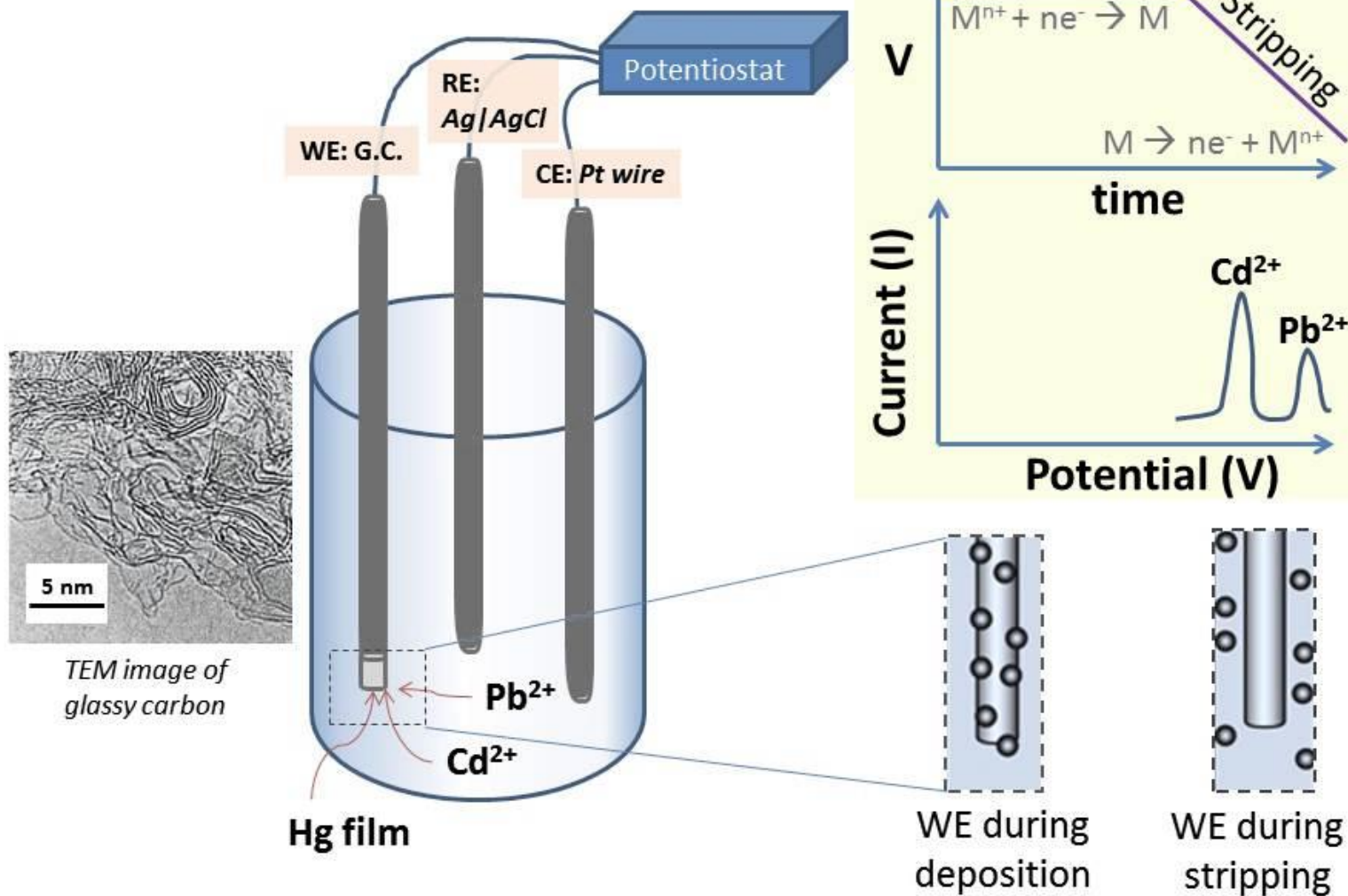
Anodic stripping voltammetry (ASV) can be used to determine all metals which are soluble in mercury with the formation of amalgams or which can be deposited electrolytically at carbon or noble metal electrodes.

The mechanism for anoding stripping voltammetry can be described using the equation:



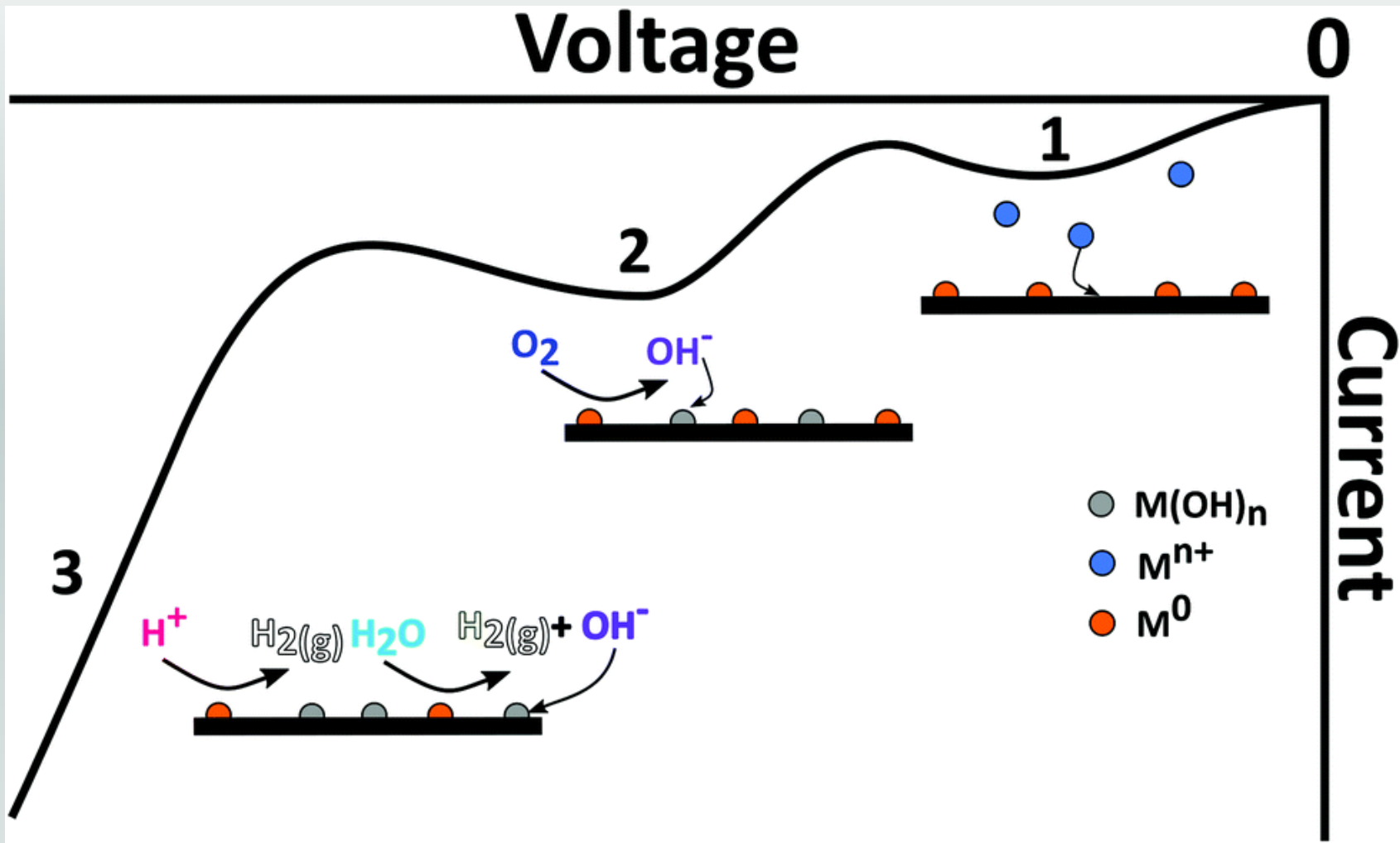
# How Anodic Stripping Voltammetry works?

## How ASV works

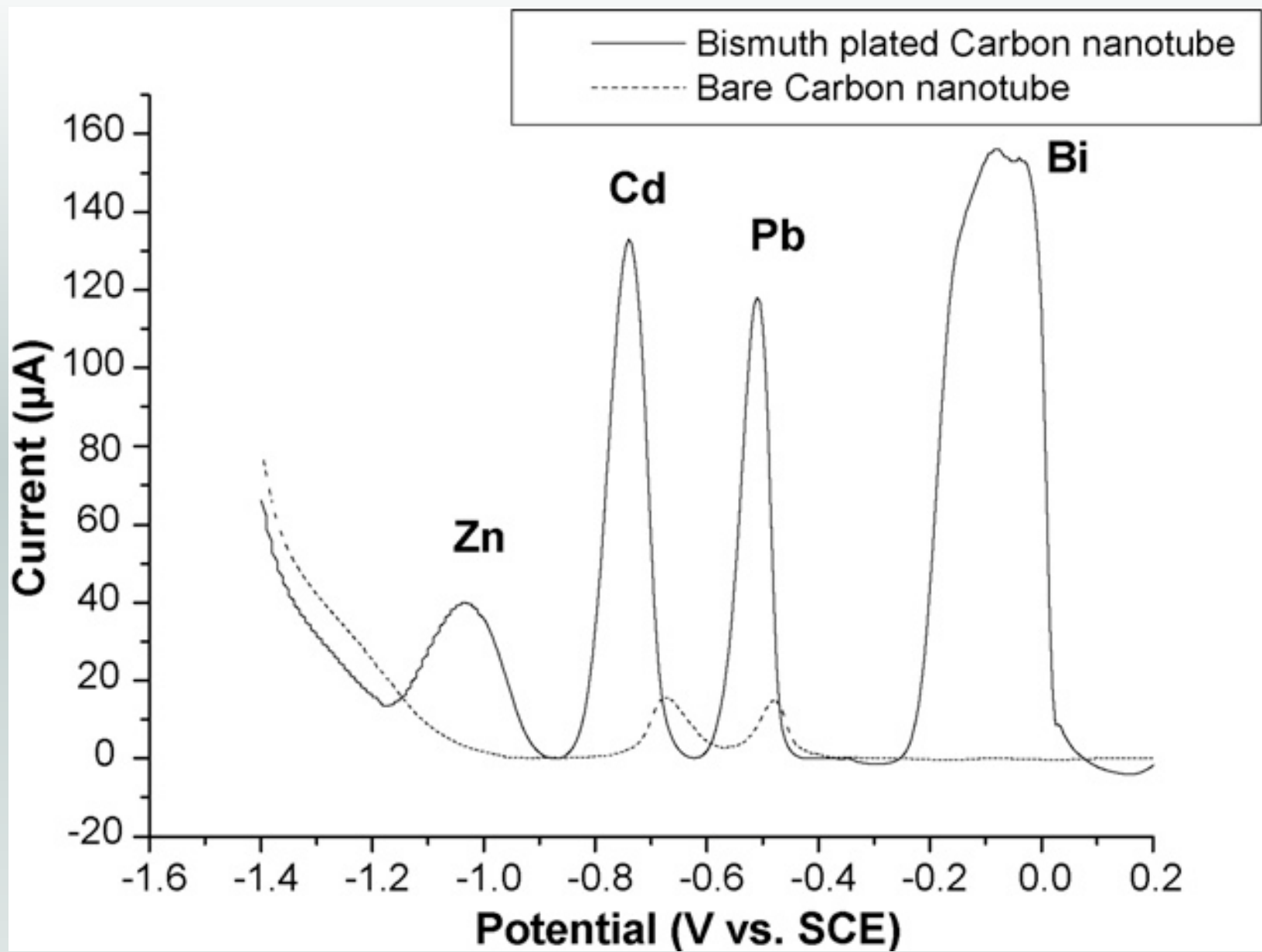


Quantitative determination of cadmium and lead by Anodic Stripping Voltammetry

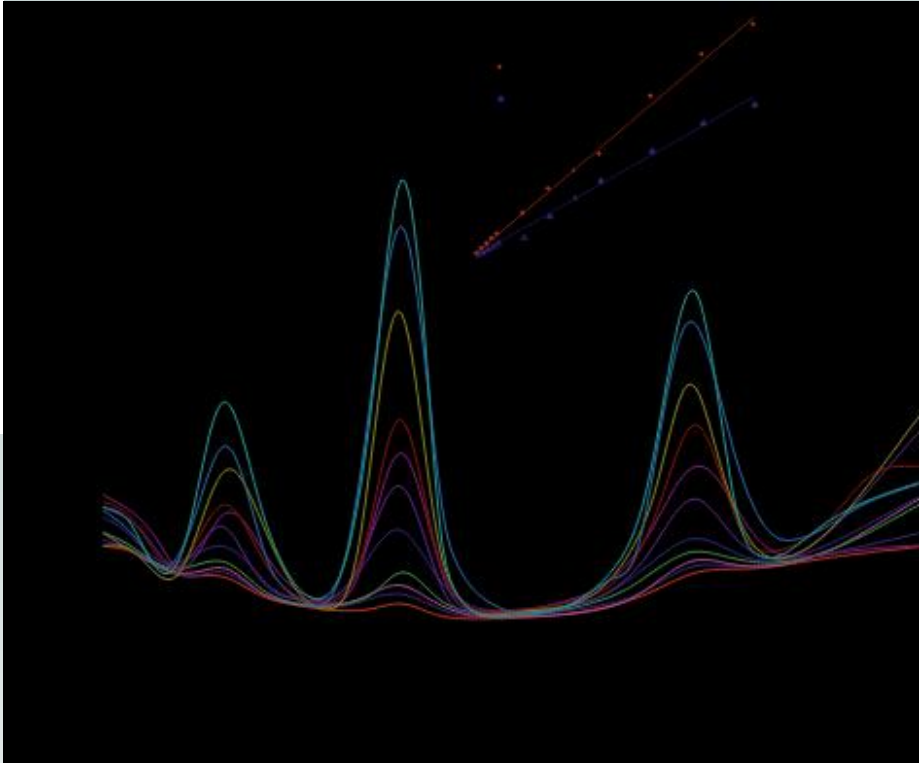
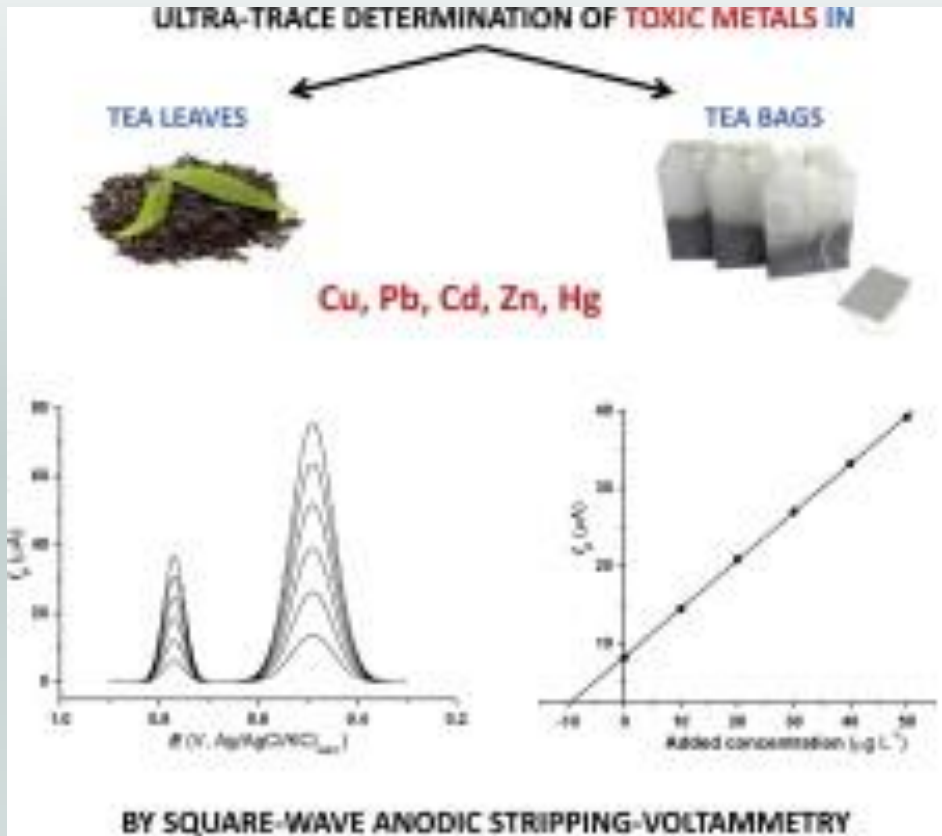
Moderator: Tami Lasseter Clare

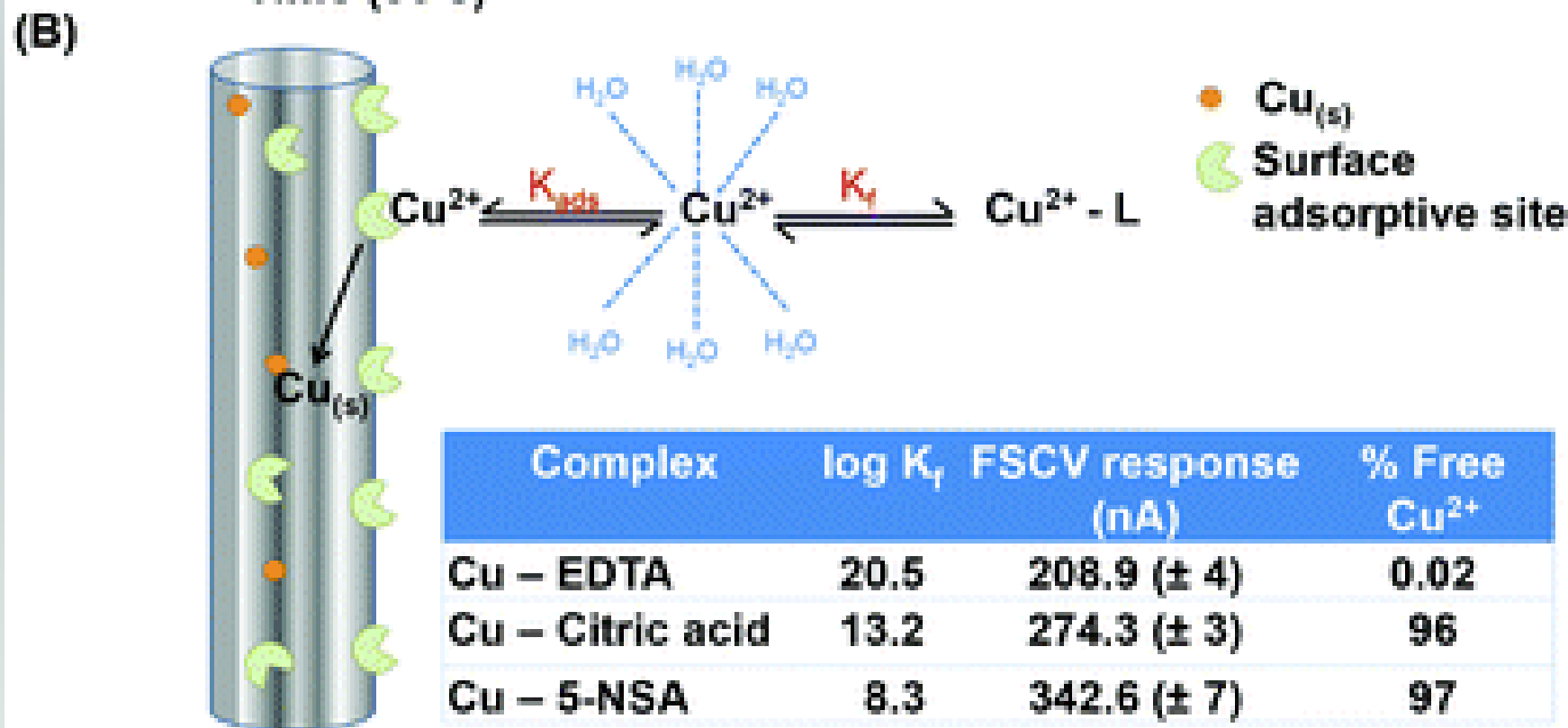
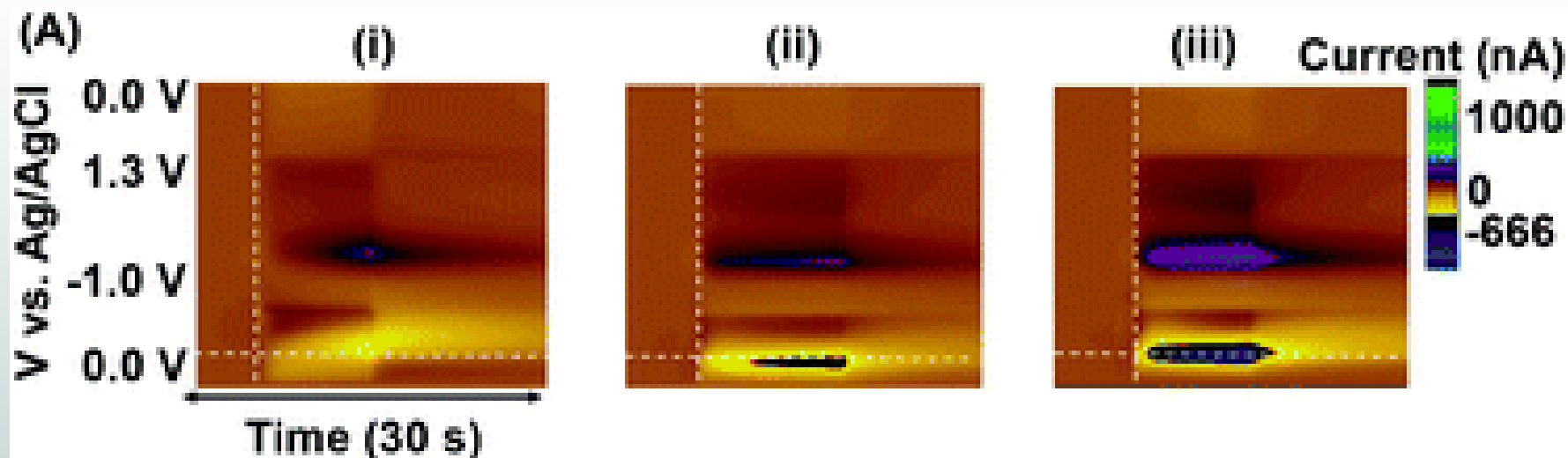






# ASV CAN BE EXPLORED FOR ULTRA-TRACE DETERMINATION OF MANY TOXIC METALLS





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