Approcci *Structure-based* per la razionalizzazione delle interazioni proteina-ligando applicate ai recettori EGFR e VEGFR2

SAPIENZA
UNIVERSITÀ DI ROMA

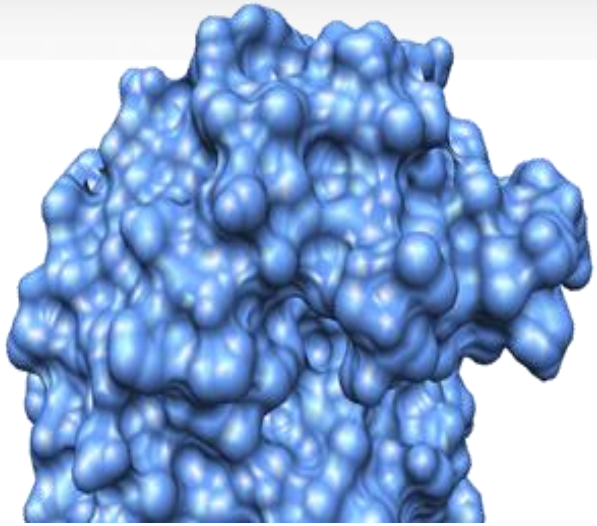
Facoltà di Farmacia e Medicina
Corso di Laurea in Farmacia
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2013/2014

Laureanda: Ludovica Conforti
Matricola: 1197349

Relatore: prof. Rino Ragno

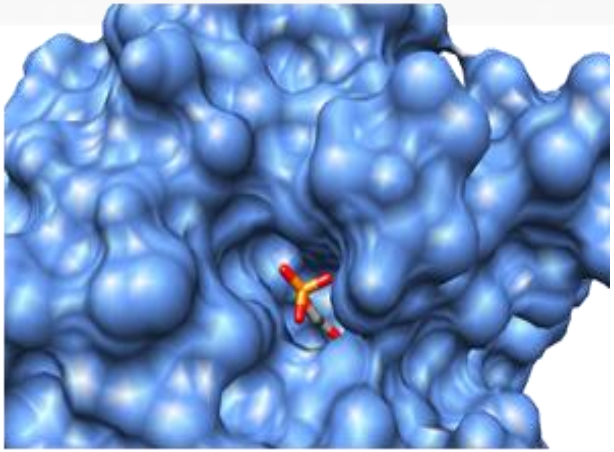
SCOPO DEL LAVORO

Target



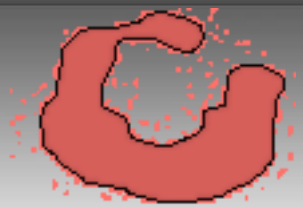
Ligand

Molecular Docking

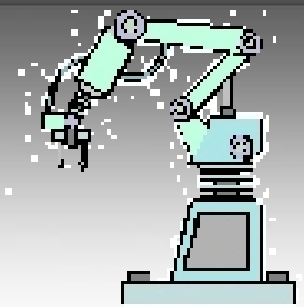


DRUG DESIGN

Drug design

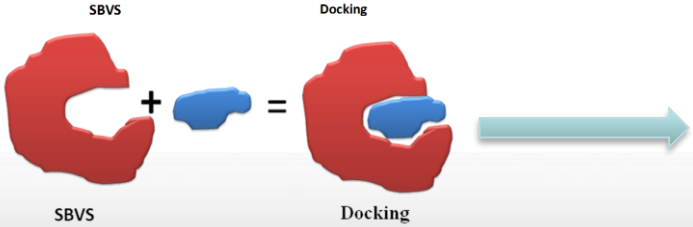


Target protein



RCSB PDB
PROTEIN DATA BANK

Dock into site

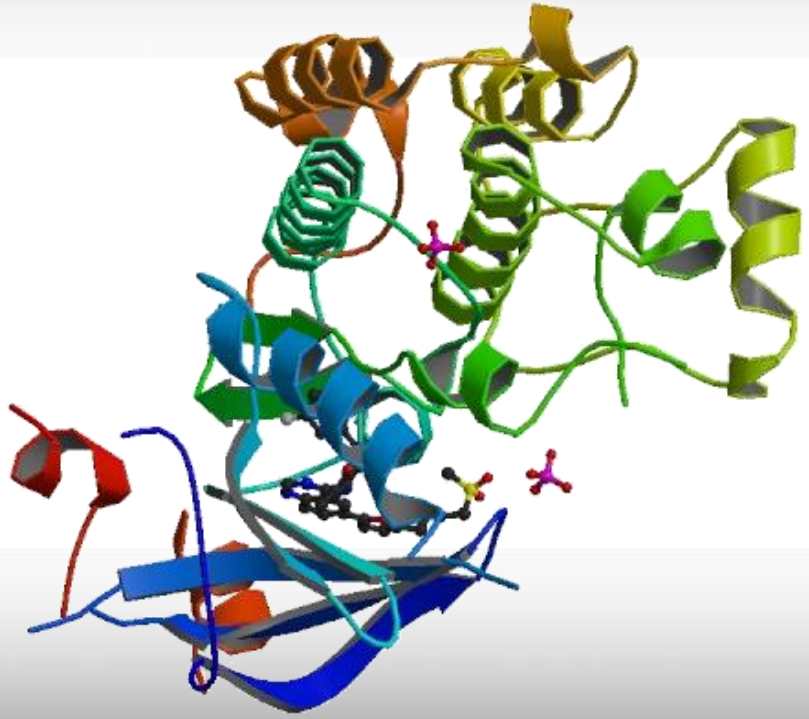


Lead compouds

Target biologico

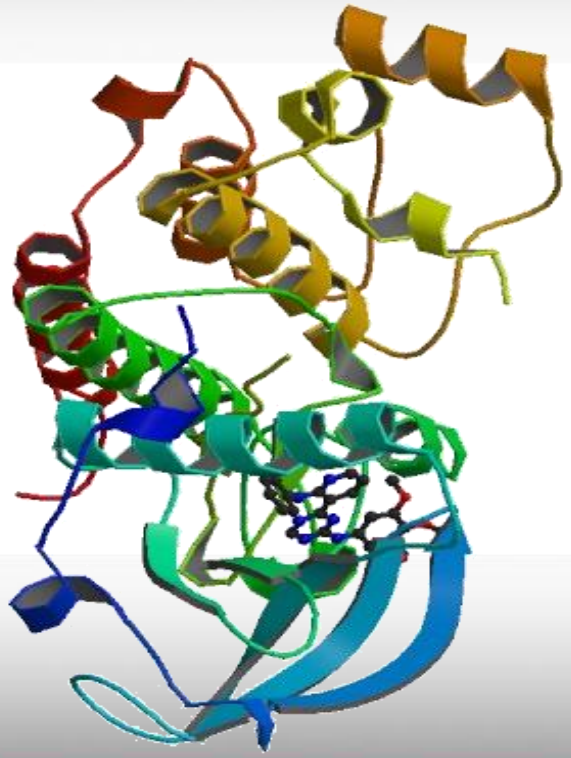
EGFR

EPIDERMAL GROWT FACTOR RECEPTOR

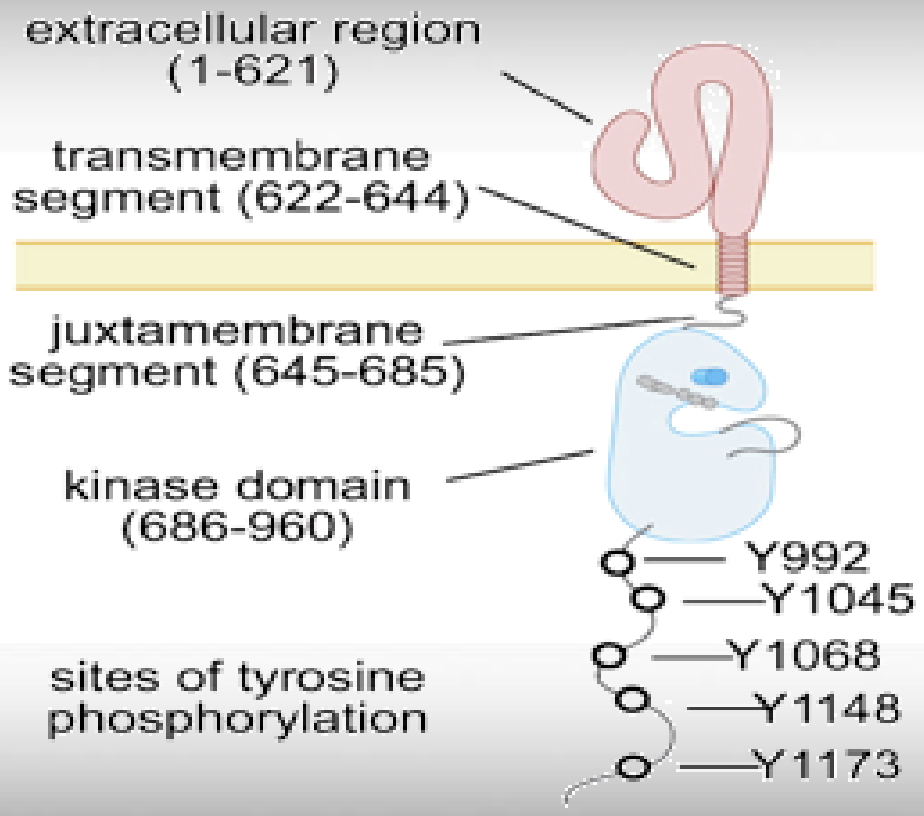


VEGFR2

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR

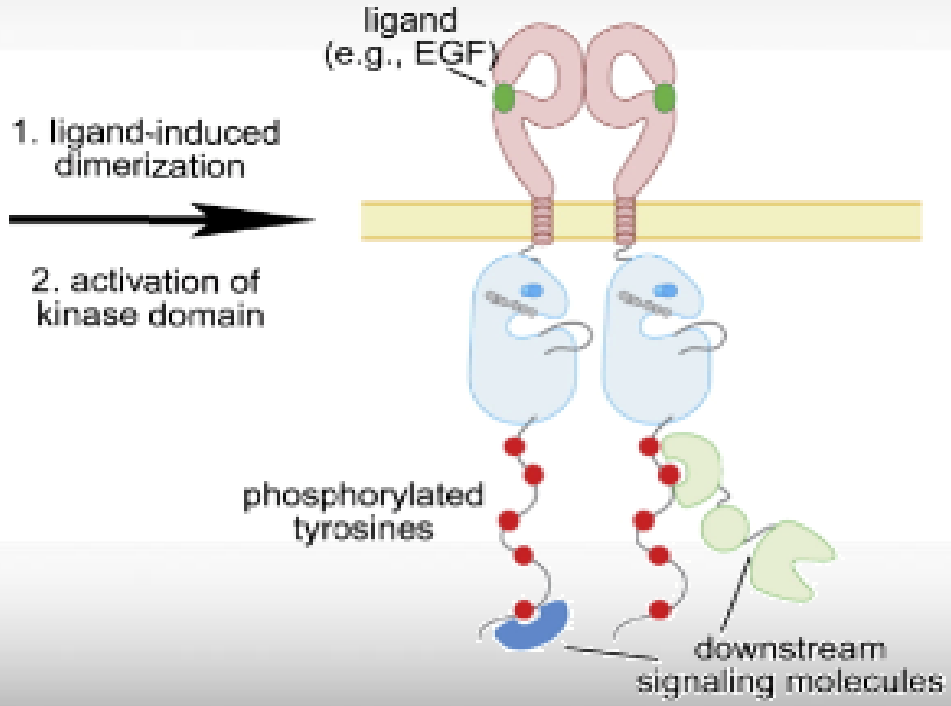


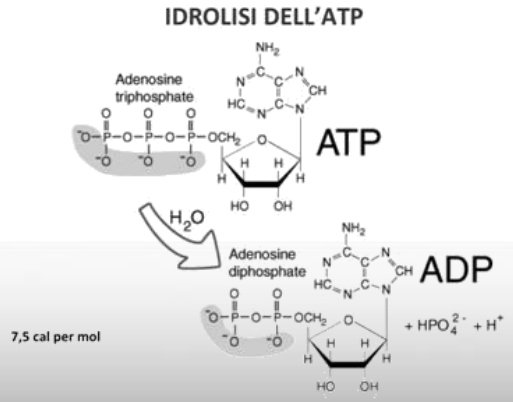
STRUTTURA


extracellular region
(1-621)
transmembrane
segment (622-644)
juxtamembrane
segment (645-685)
kinase domain
(686-960)
sites of tyrosine
phosphorylation
Y992
Y1045
Y1068
Y1148
Y1173

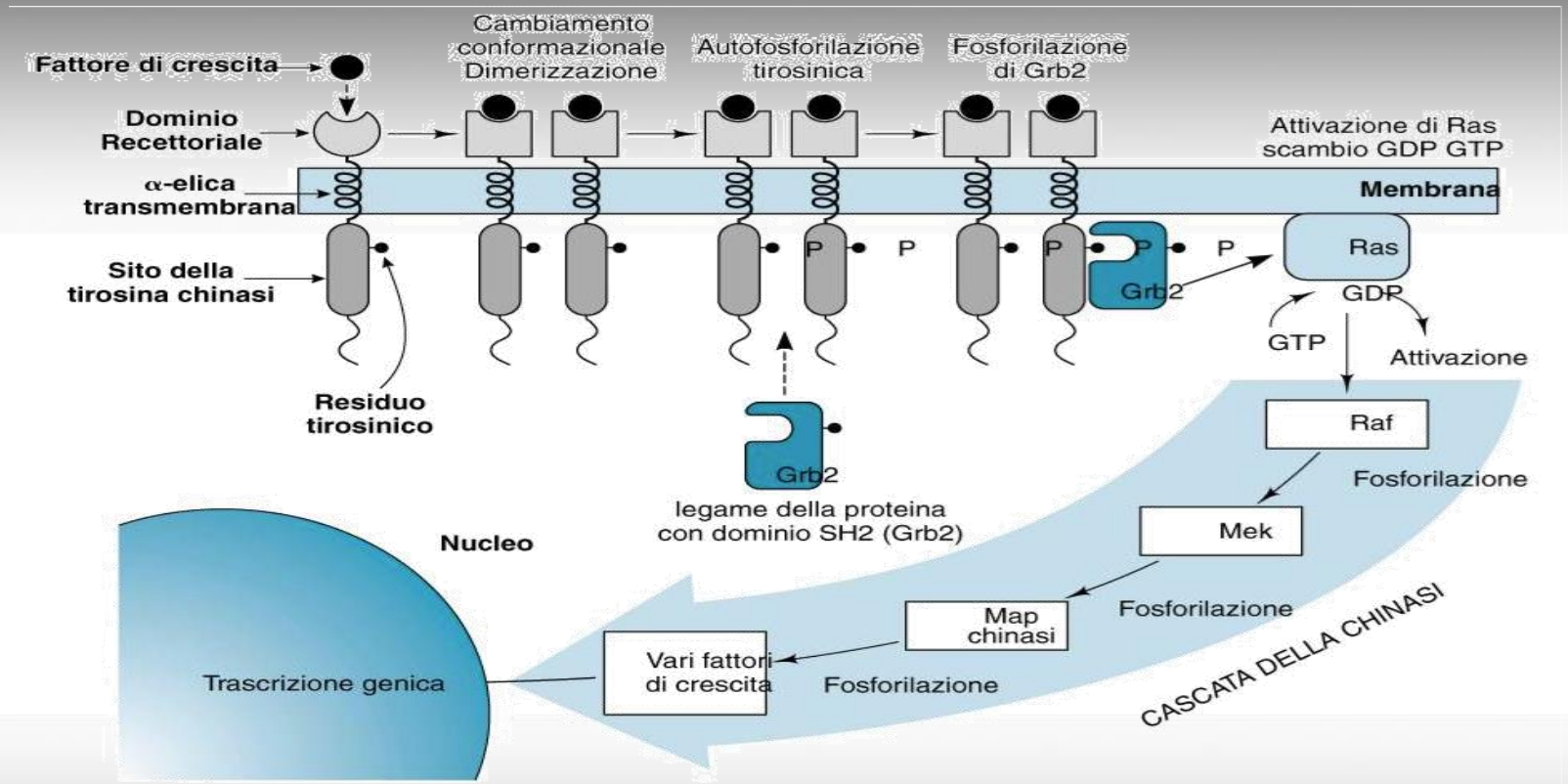
Classificazione

Tirosine chinasi

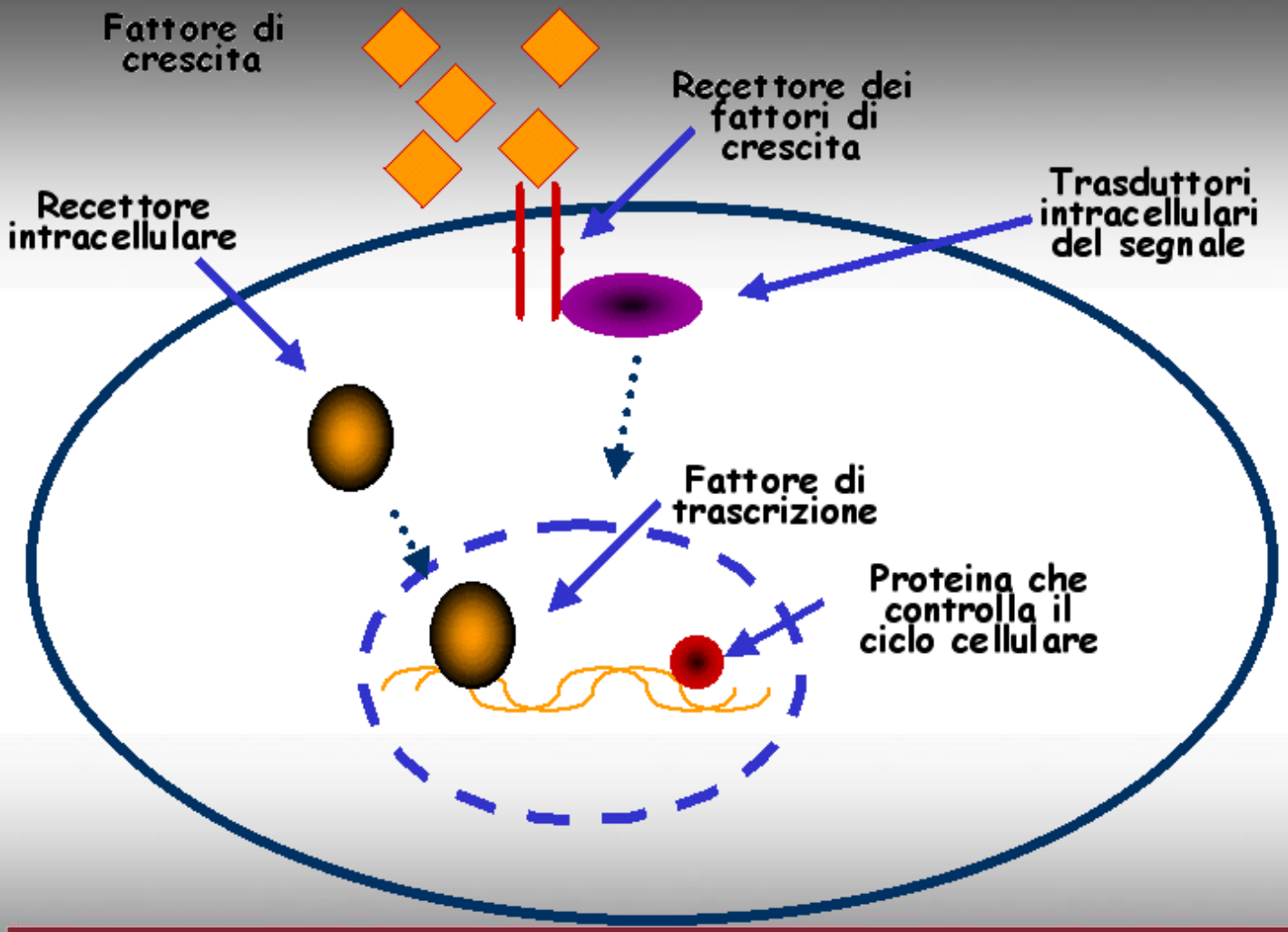




Trasduzione del segnale

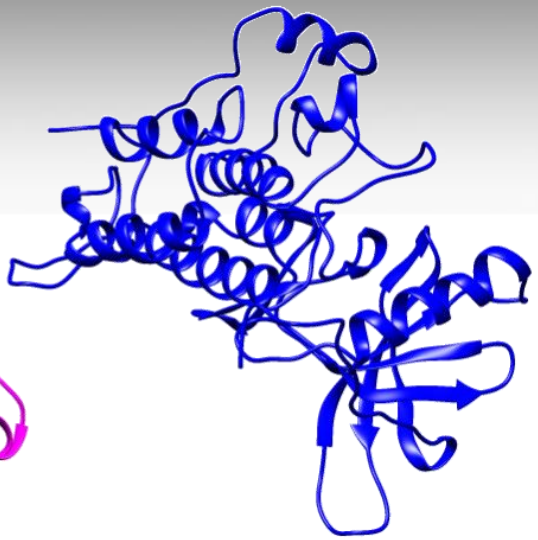


Risposta cellulare



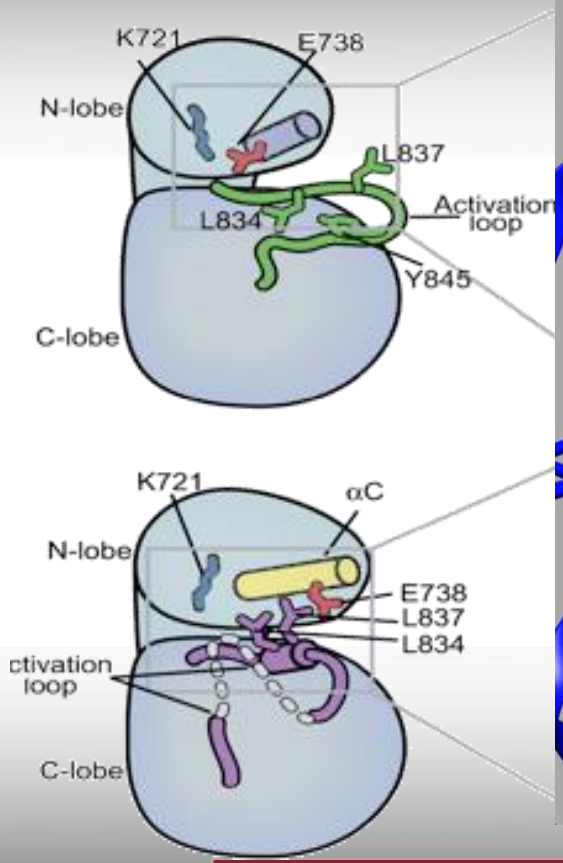
Omologia di sequenza

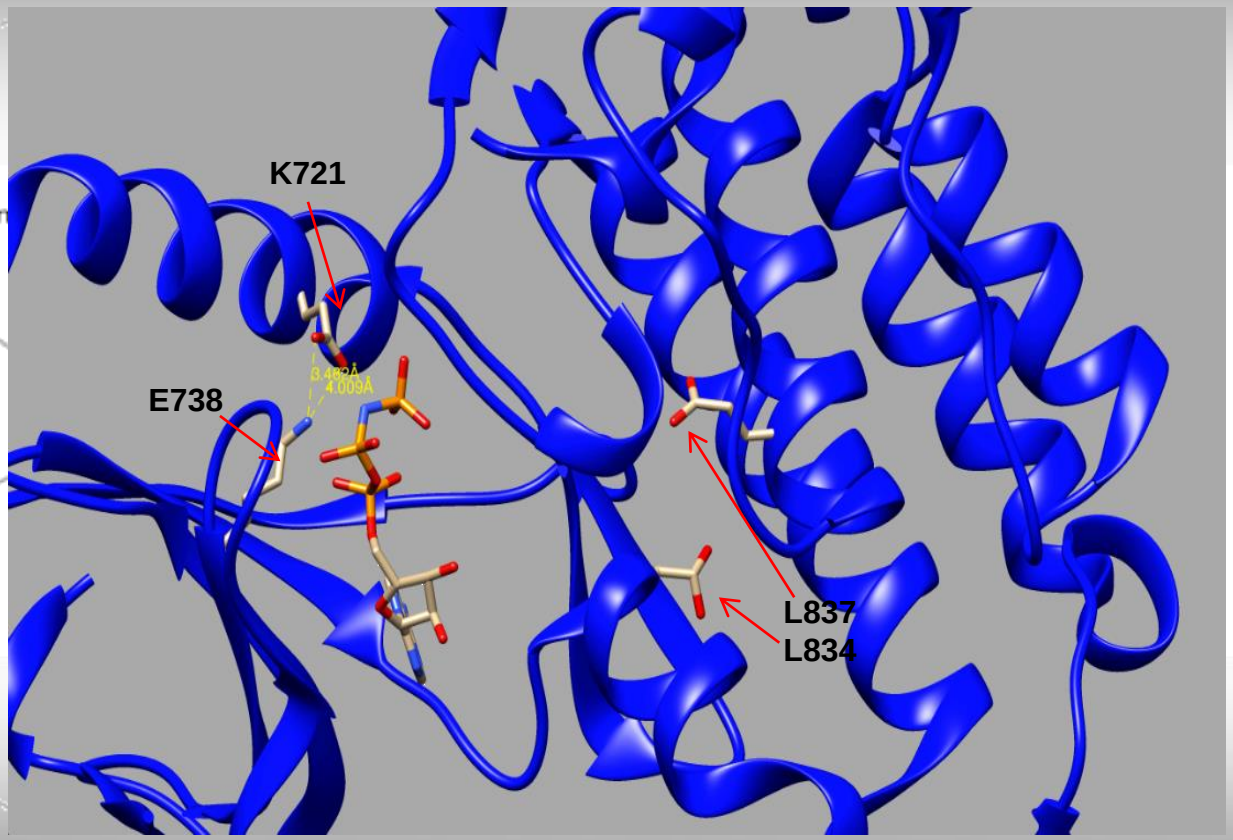
EGFR



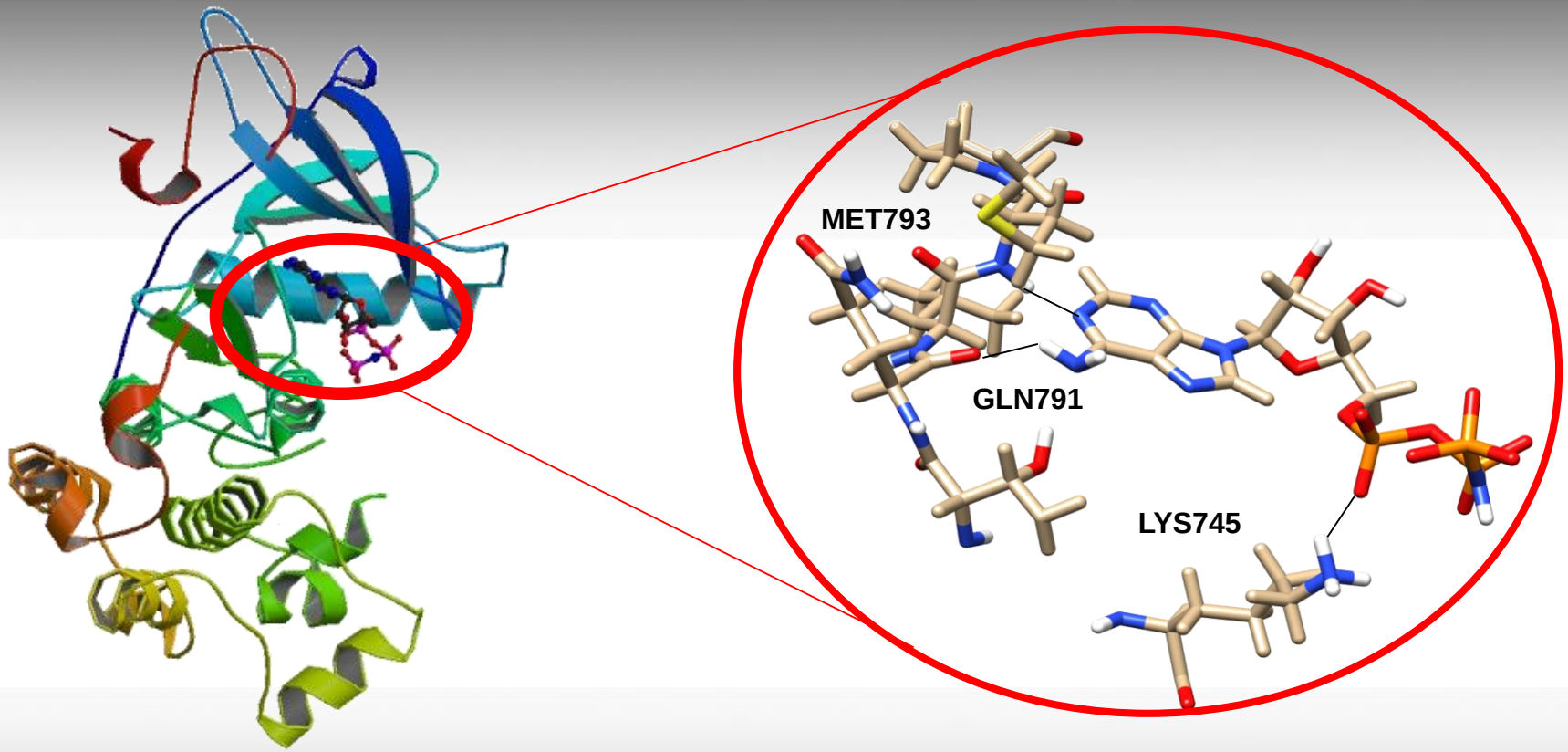
VEGFR2

Sito catalitico egfr



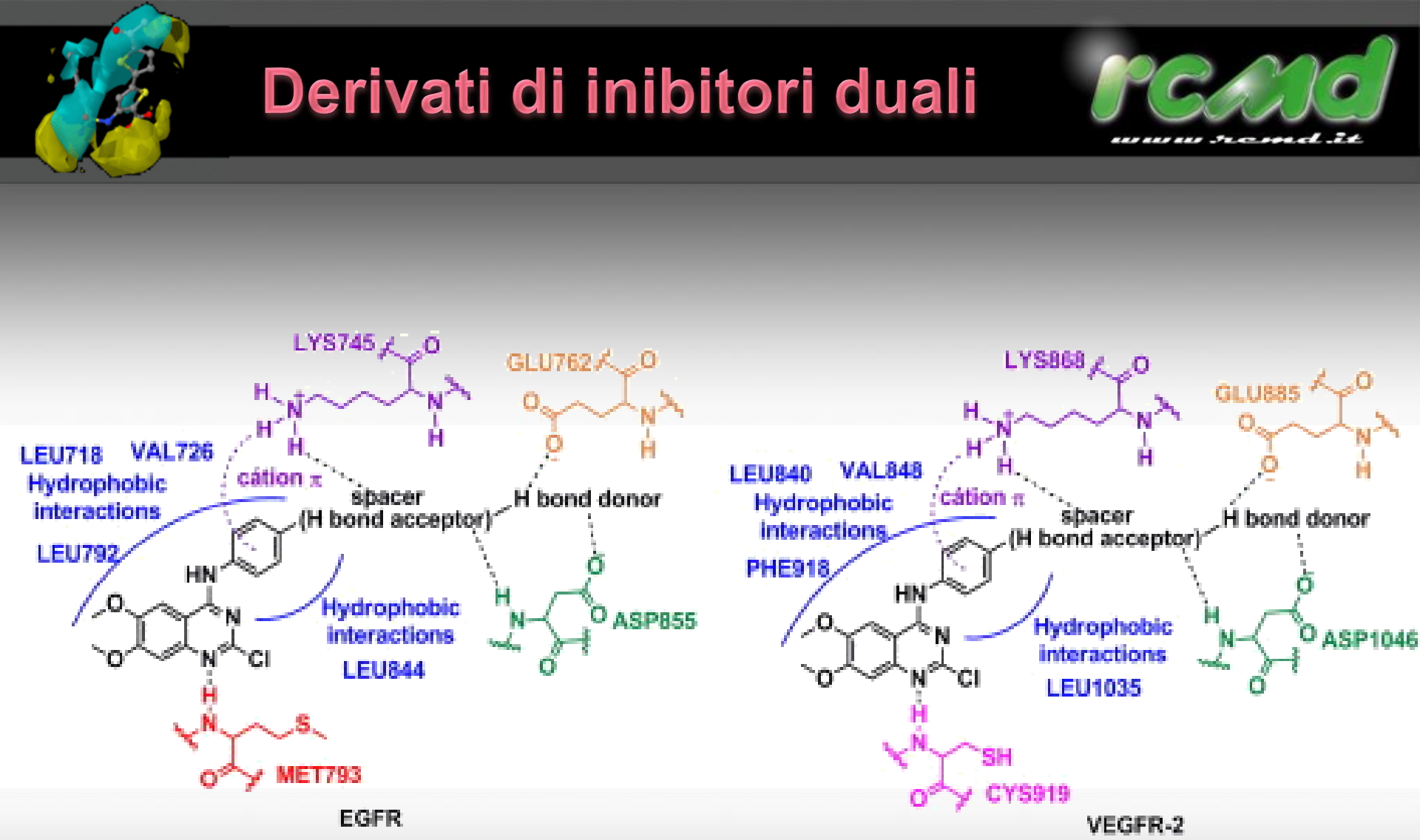


BINDING SITES



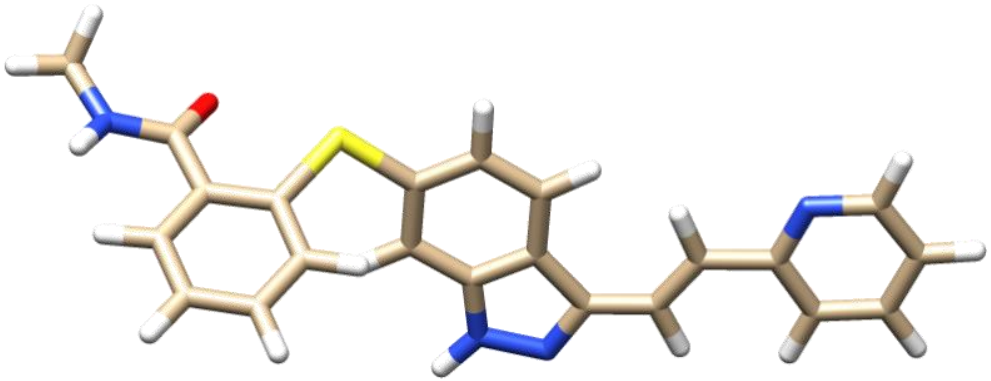
ATP-MET793 1.663 Å
ATP-GLN791 1.984 Å
ATP-LYS745 2.945 Å

Derivati di inibitori duali



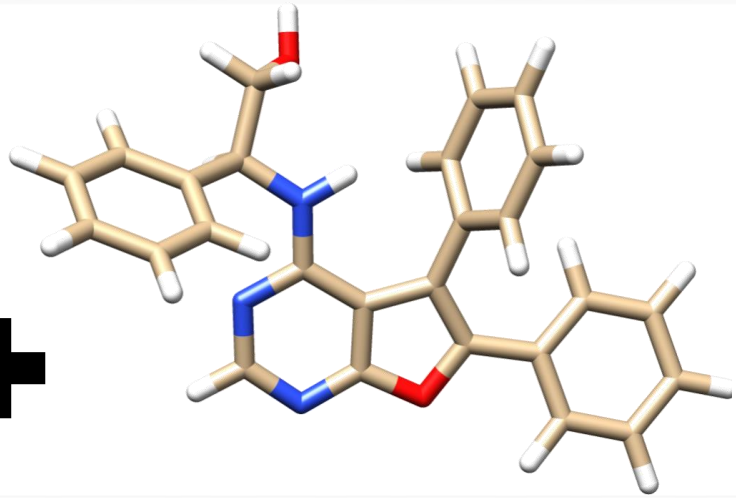
Terapia di combinazione

anti-EGFR + anti-VEGFR2



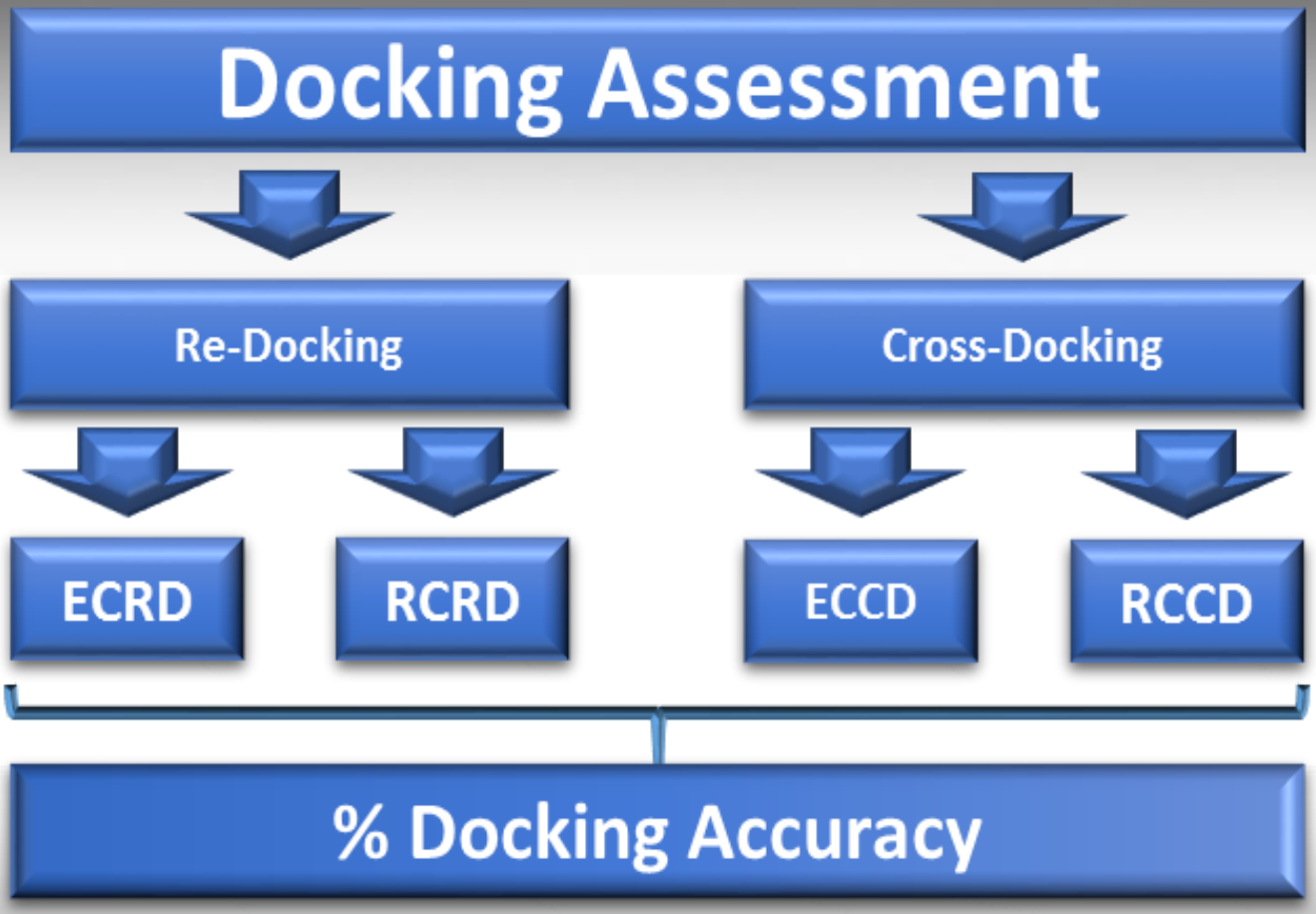
4AG8

+

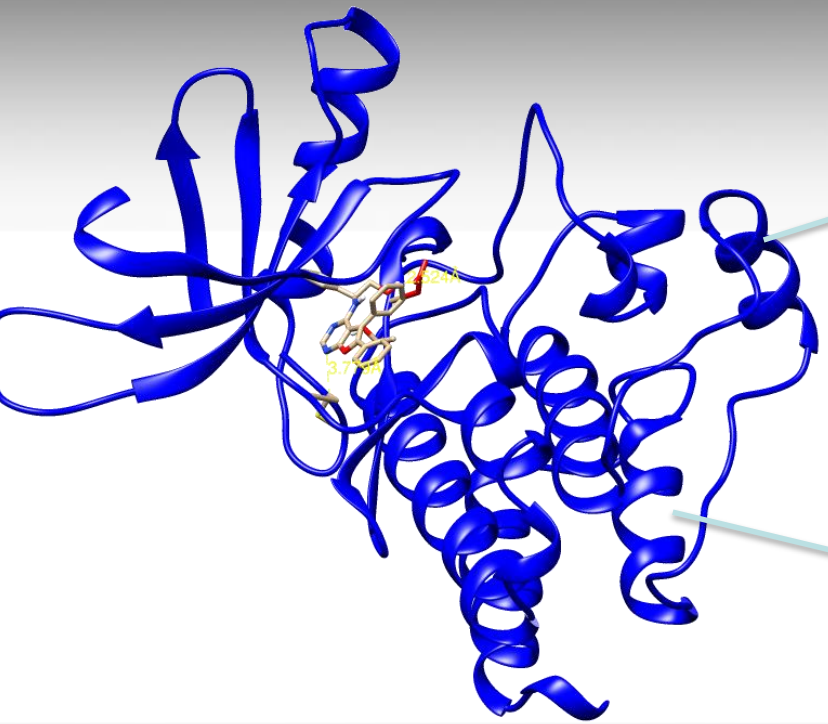


4JQ7

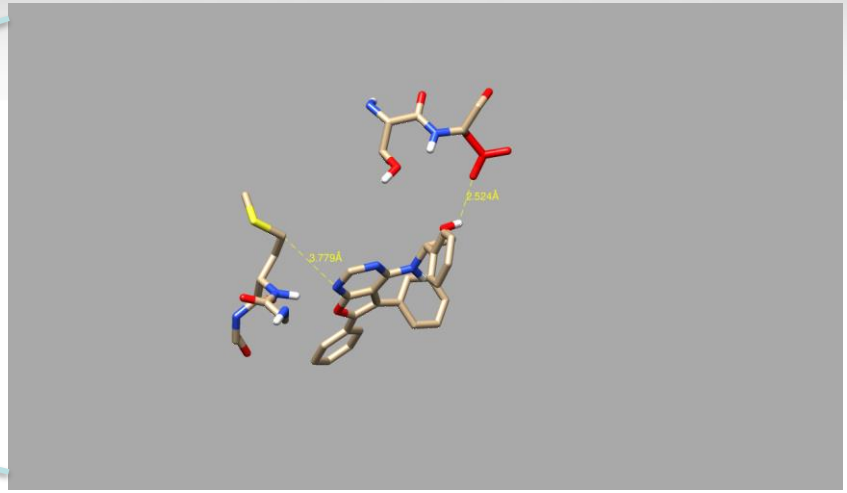
Procedura di validazione



Re-docking

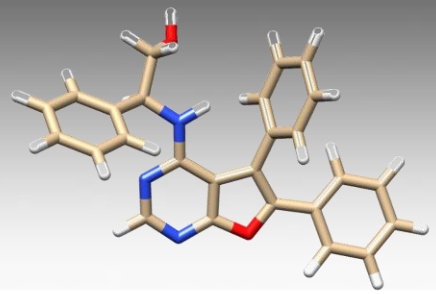


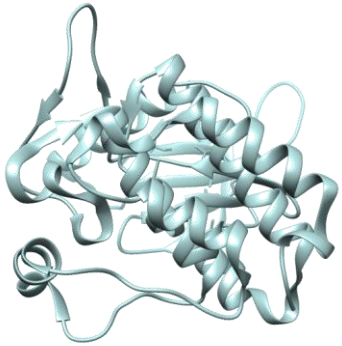
[4JQ7 + KJQ]

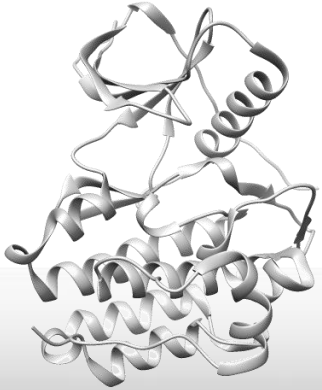


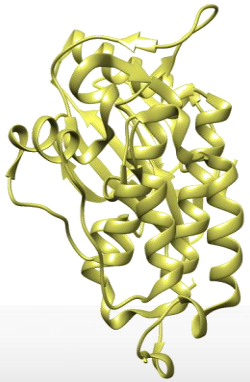
[KJQ]

Cross-docking







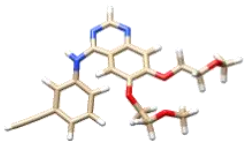


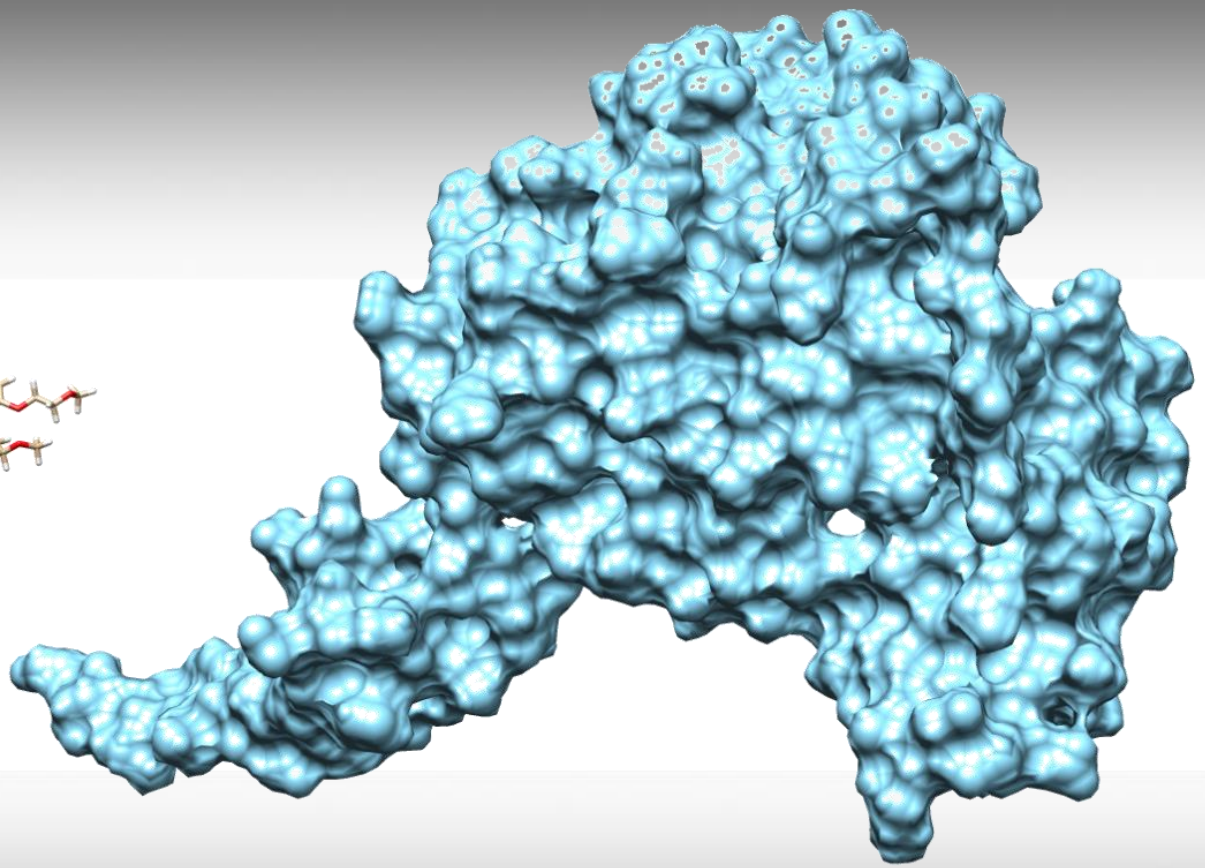
[1M17]

[2RGP]

[3W2Q]

Random





1-Selezione complessi

EGFR

LIGAND	PROTEIN
AQ4	1M17
AEE	2ITP
ITQ	2ITQ
ITQ	2ITU
HYZ	2RGP
POX	3BEL
O3P	3POZ
O3P	3W20
HKI	3W2Q
W2R	3W2R
W2R	3W2S
W19	3W33
AQ4	4HJO
KJQ	4JQ7
KJR	4JR3

RCSB PDB PROTEIN DATA BANK

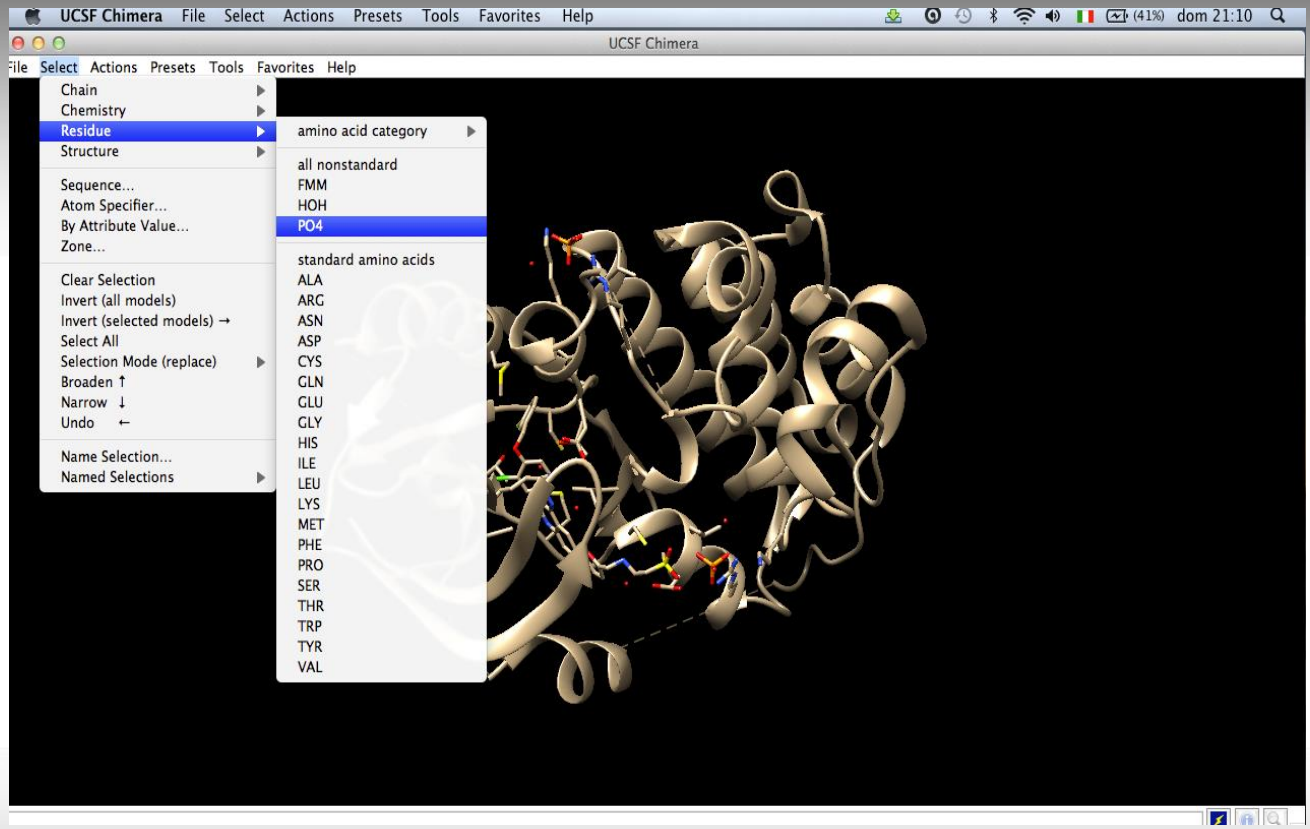
VEGFR2

LIGAND	PROTEIN
276	2QU5
2RL	2RL5
900	3B8Q
887	3B8R
C52	3CPC
A96	3DTW
706	3EFL
994	2P2H
608	2P2I
RAJ	3BE2
C19	3CP9
KII	3EWH
O3X	3U6J
OJA	3VNT
AXI	4AG8
C92	3CPB

2-Pulizia dei cristalli

UCSF CHIMERA

an Extensible Molecular Modeling System



3-Rimodallamento

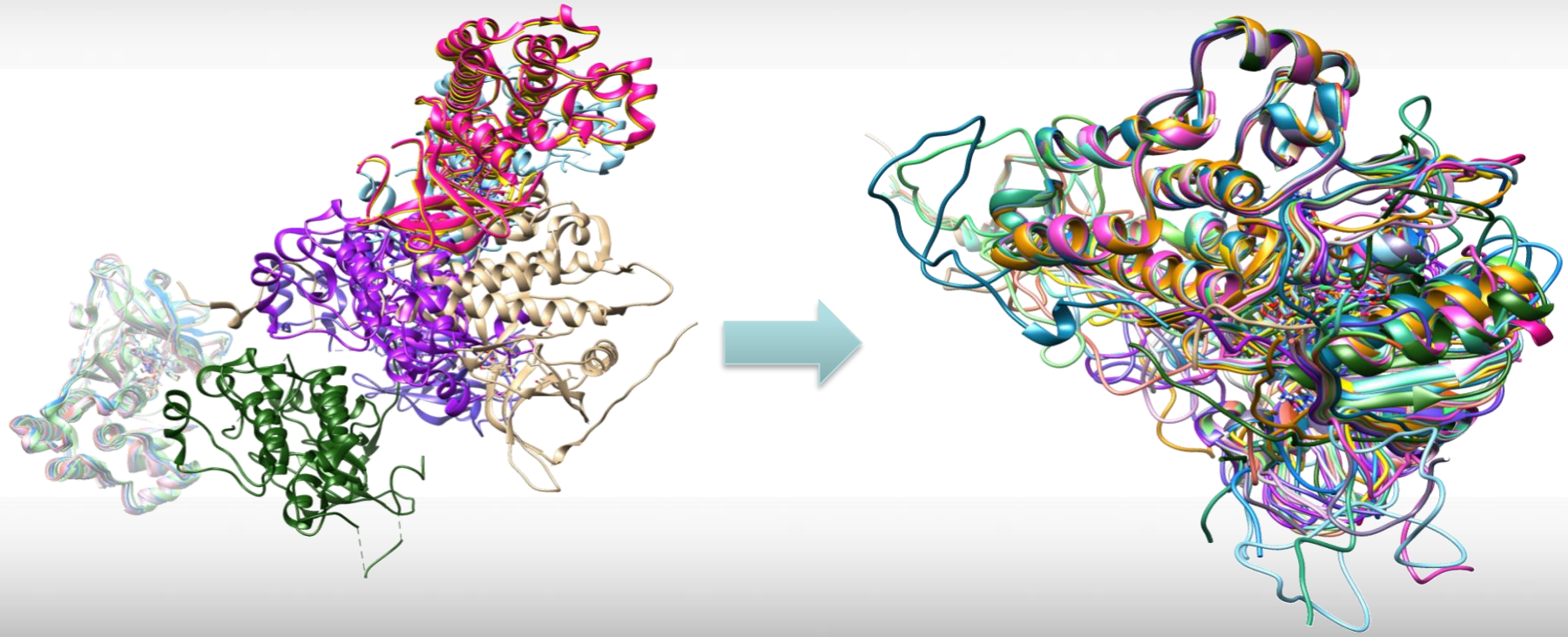
UCSF CHIMERA

an Extensible Molecular Modeling System

MODELLER

4-Allineamento e minimizzazione

ALLINEAMENTO AL COMPLESSO A RISOLUZIONE MIGLIORE



PROGRAMMI DI DOCKING

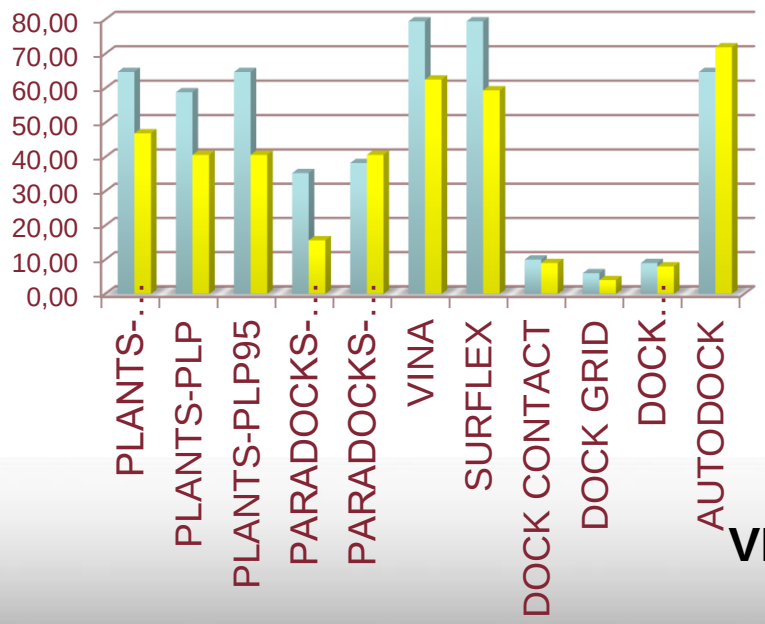
- PLANTS
- SURFLEX
- AUTODOCK
- AUTODOCK-VINA
- PARADOCKS
- DOCK

RMSD

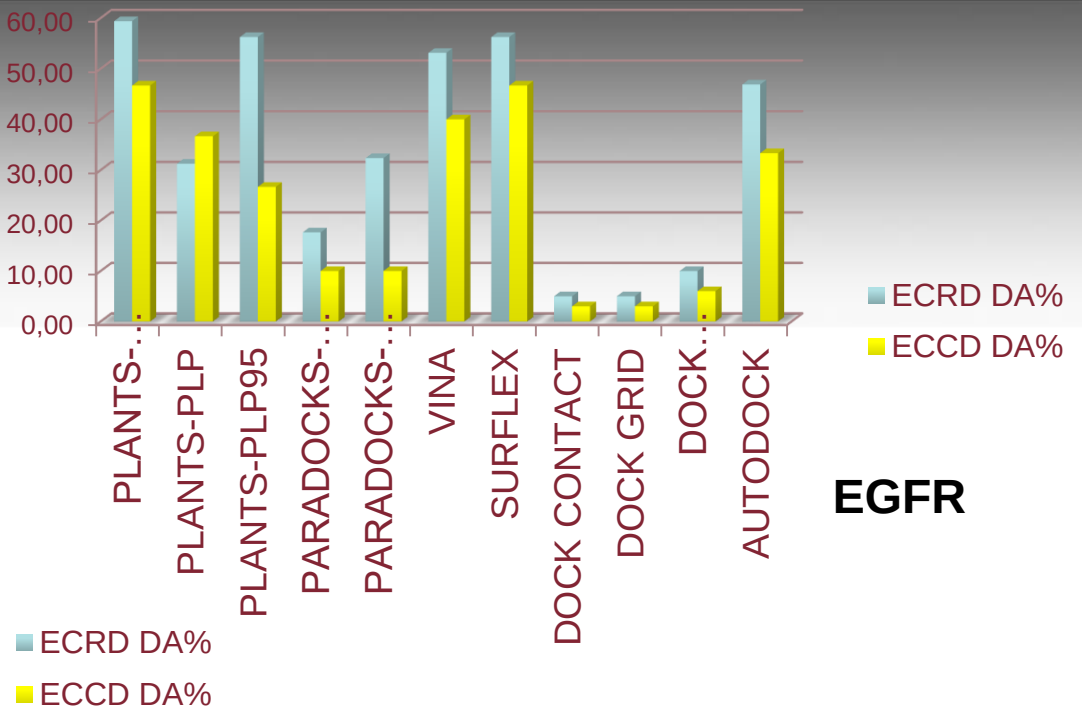
ROOT-MEAN-SQUARE-DEVIATION

$$DA = frmsd \leq a + 0.5\,(frmsd \leq b - frmsd \leq a)$$

DA% ECRD-ECCD

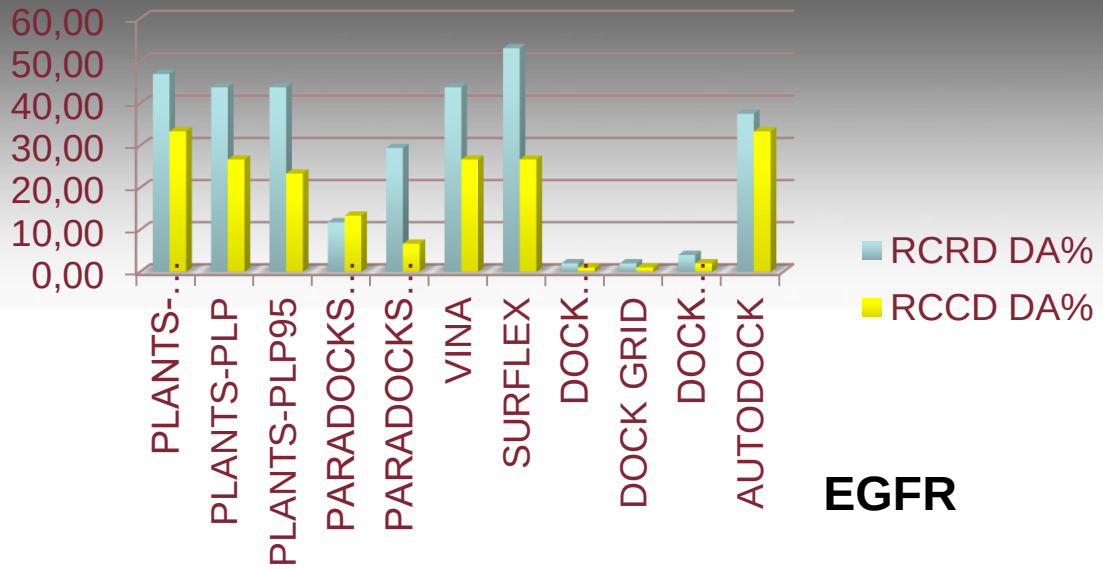


VEGFR2

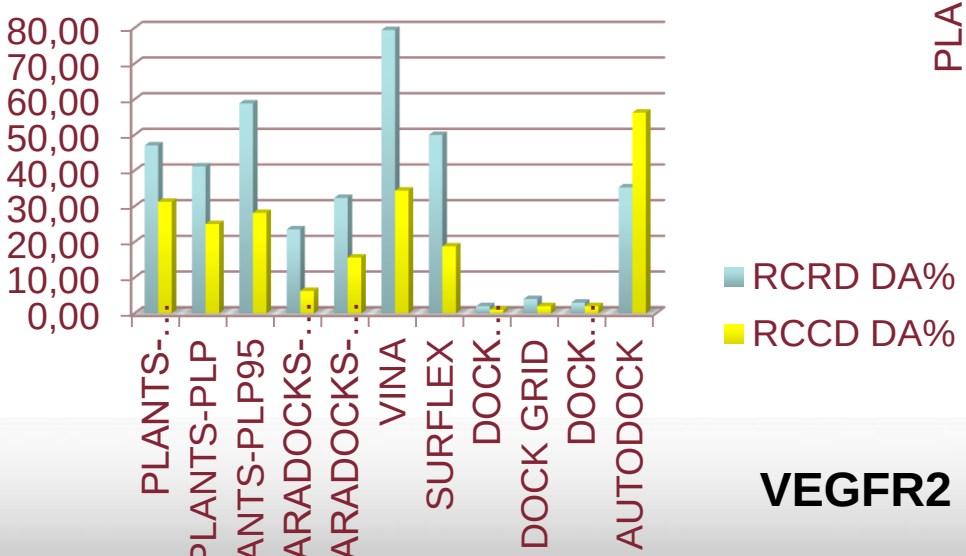


EGFR

DA% RCRD-RCCD

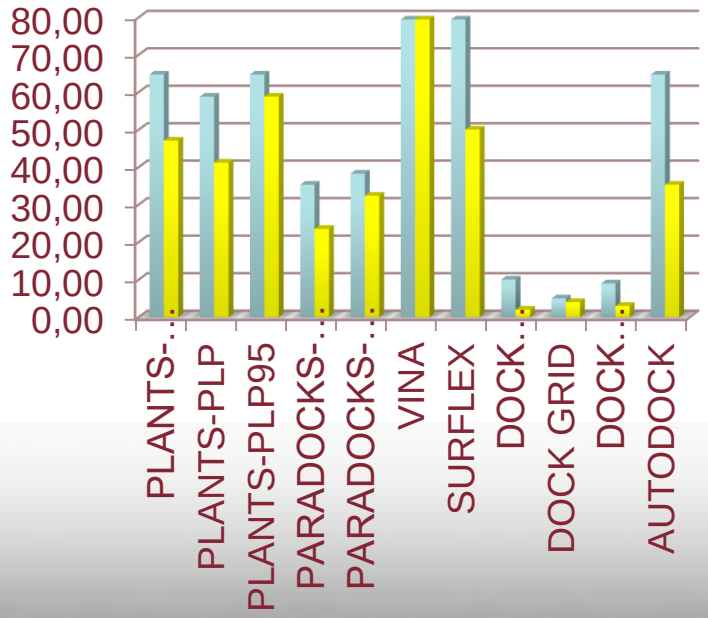


EGFR



VEGFR2

DA%: ECRD-RCRD



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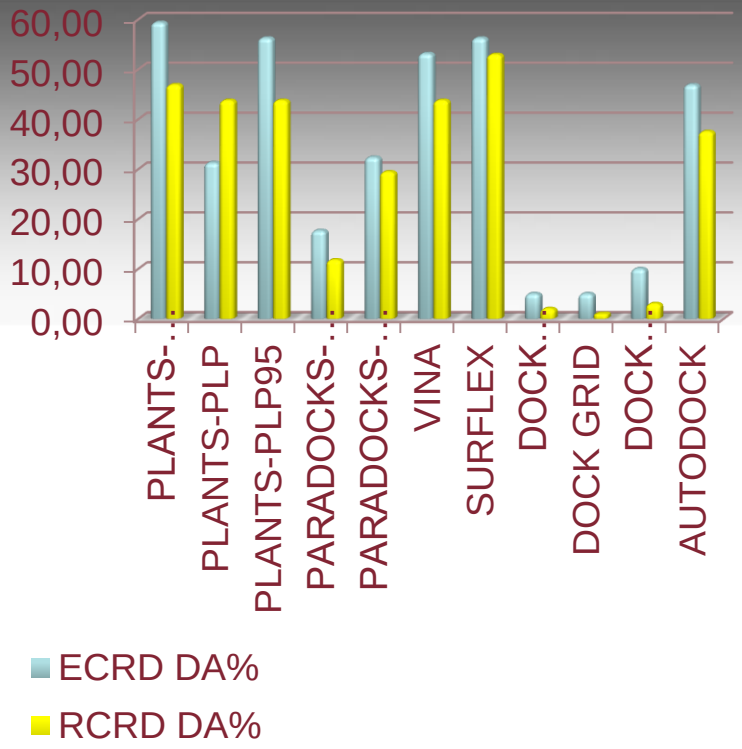
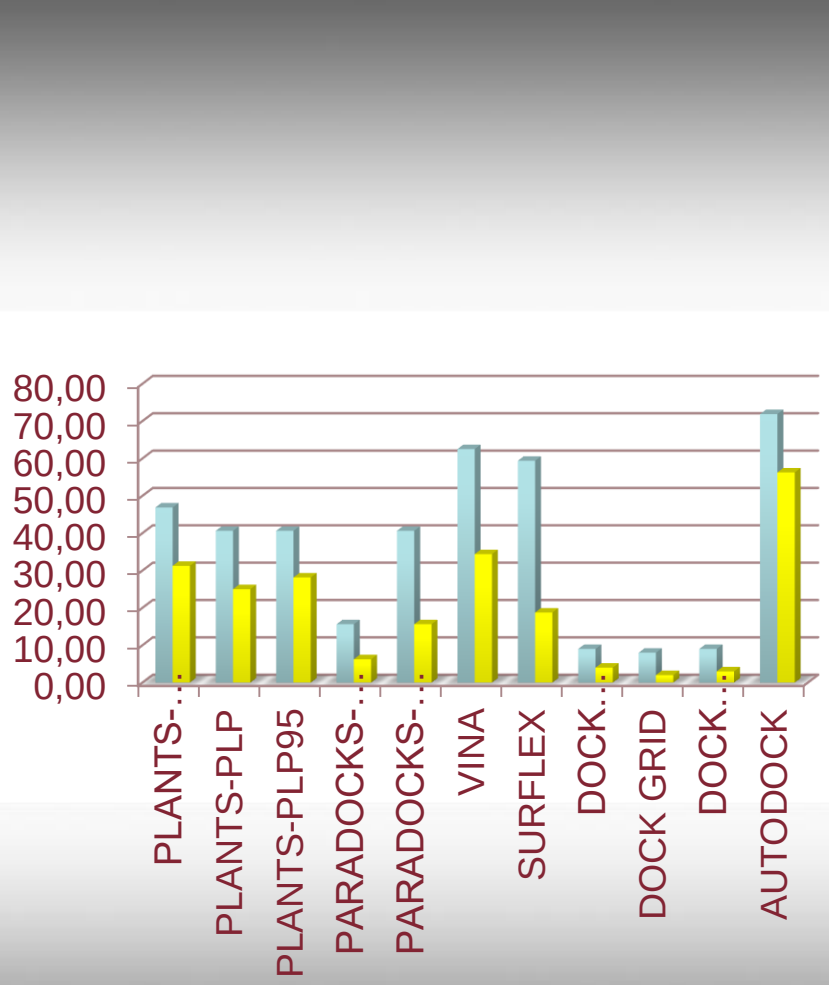
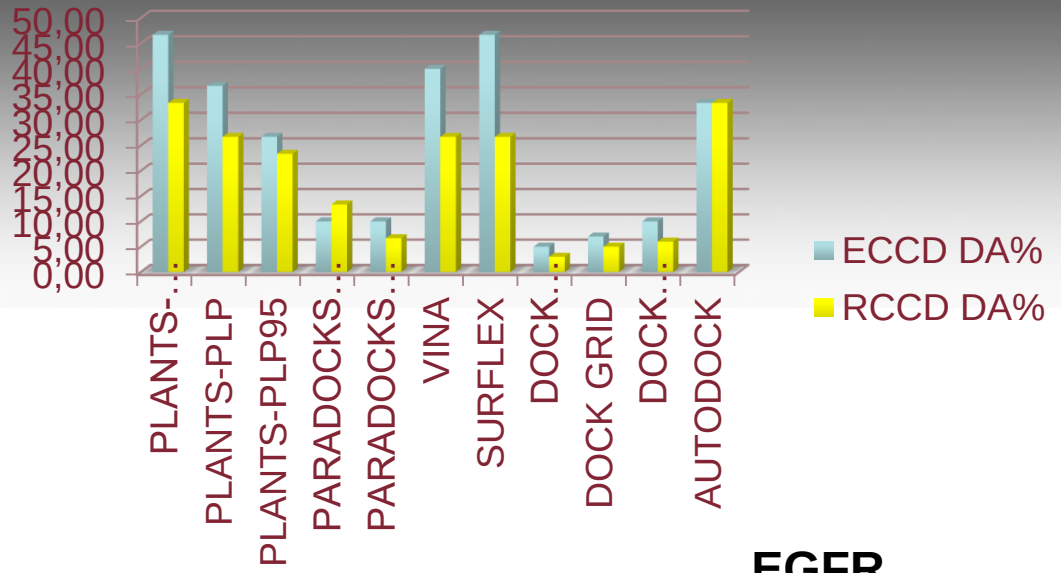


EGFR

DA%: ECCD-RCCD



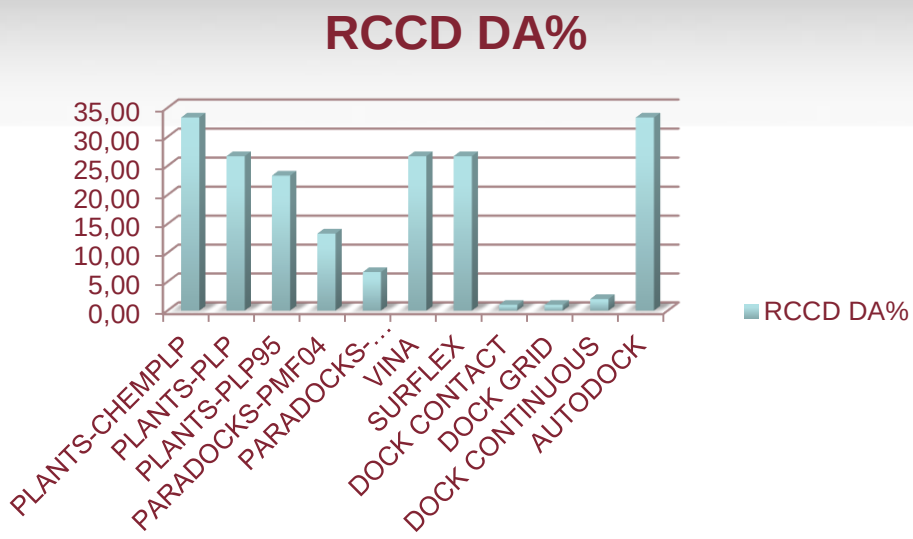
VEGFR2



EGFR

IL PROGRAMMA MIGLIORE

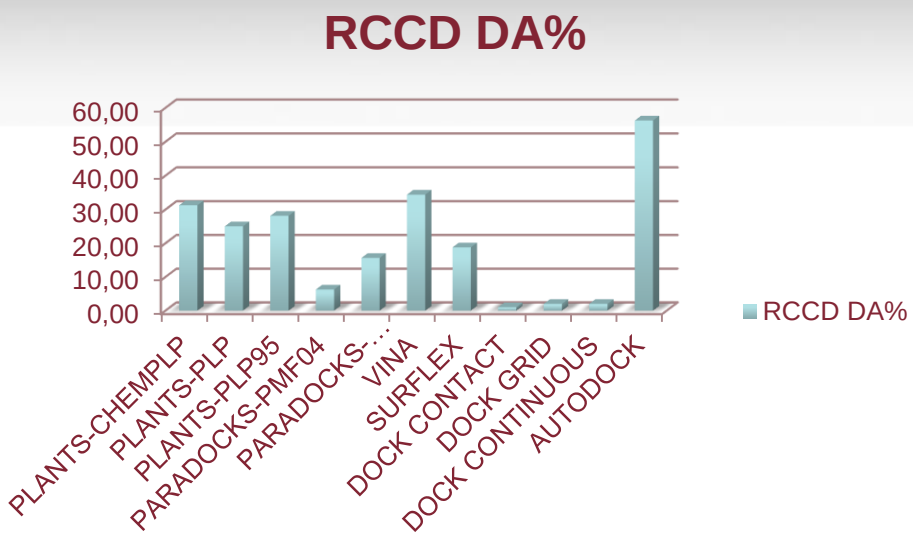
EGFR



CHEMPLP/AUTODOCK

DA: 33,33%

VEGFR2



AUTODOCK

DA: 56,25%

MODELLO 3-D QSAR

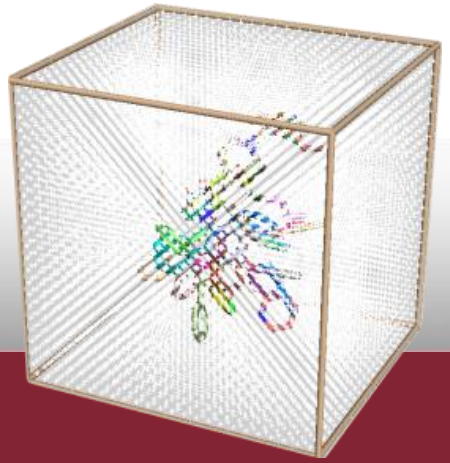
Scelta del training set

Allineamento delle molecole

Calcolo del campo di interazione molecolare (MIF)

Creazione del modello statistico

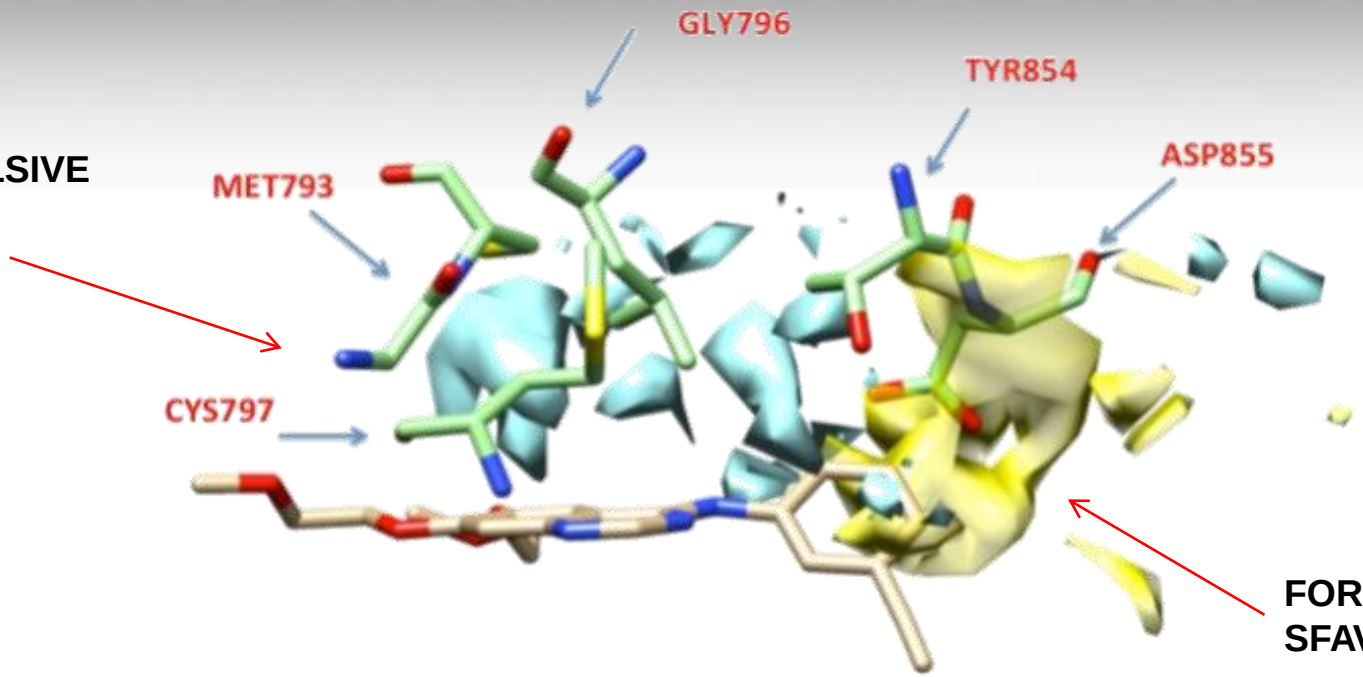
Interpretazione mappe di correlazione



EGFR: Modello 3-D QSAR

PROBE C

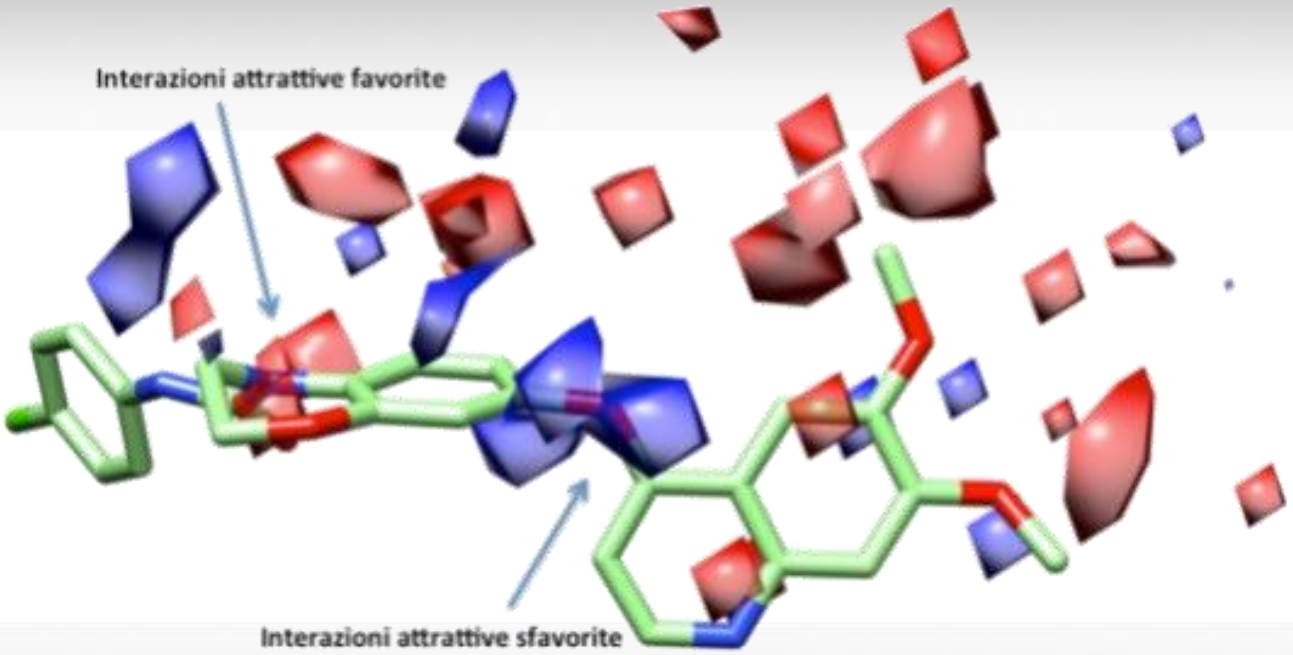
FORZE REPULSIVE FAVORITE



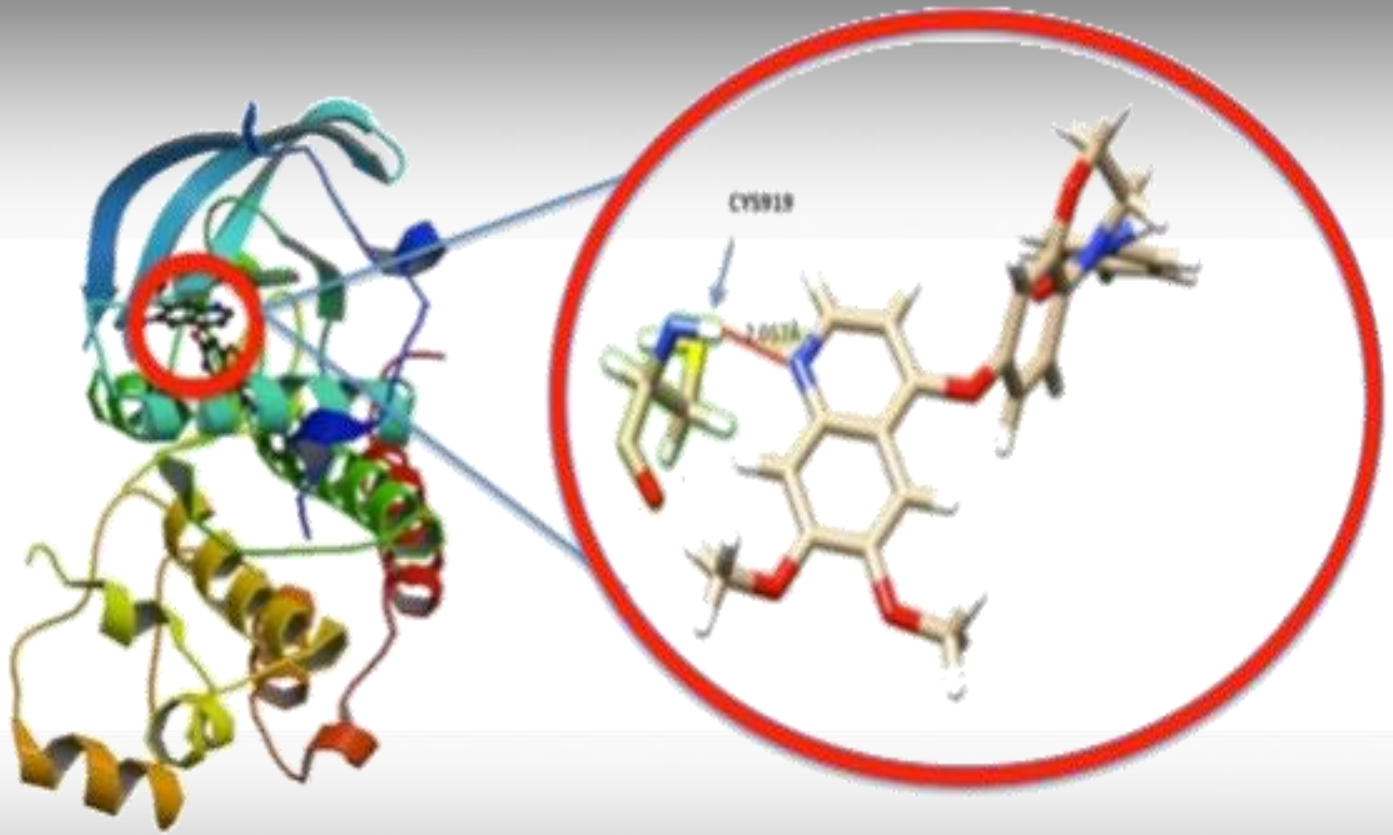
FORZE REPULSIVE SFAVORITE

VEGFR2: Modello 3-D QSAR

PROBE HD



VEGFR2: Modello 3-D QSAR



Conclusioni

- SONO STATI DETERMINATI I PROGRAMMI DI DOCKING Più AFFIDABILI PER PROSEGUIRE STUDI SULLA PROGETTAZIONE DI NUOVI LIGANDI E QUINDI DI FARMACI ANTITUMORALI
  CON MAGGIOR POTENZA.

- SI è CRETO UN MODELLO 3-D QSAR PER POTER PREDIRE L'ATTIVTà BIOLOGICA DI NUOVI LIGANDI

GRAZIE PER L'ATTENZIONE