STRUCTURE-BASED VIRTUAL SCREENING FOR PAR1

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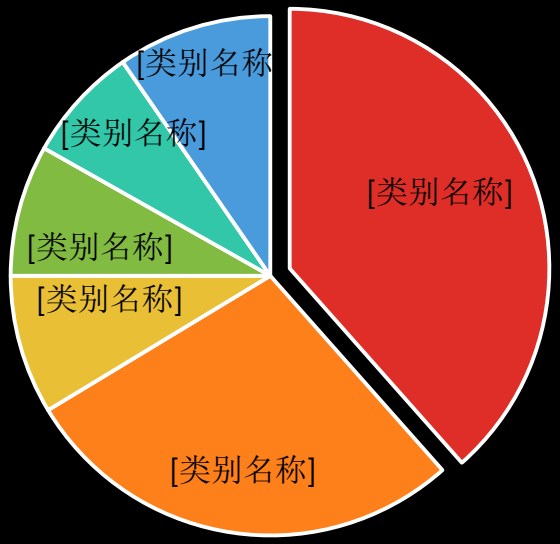
THE TARGET: PAR1

Introduction to the causes and significance of our works, and the reason we chose PAR1 as the target protein

THE TARGET: PAR1

- **Cardiovascular diseases**



An estimated 17.3 million people died from CVDs in 2008.

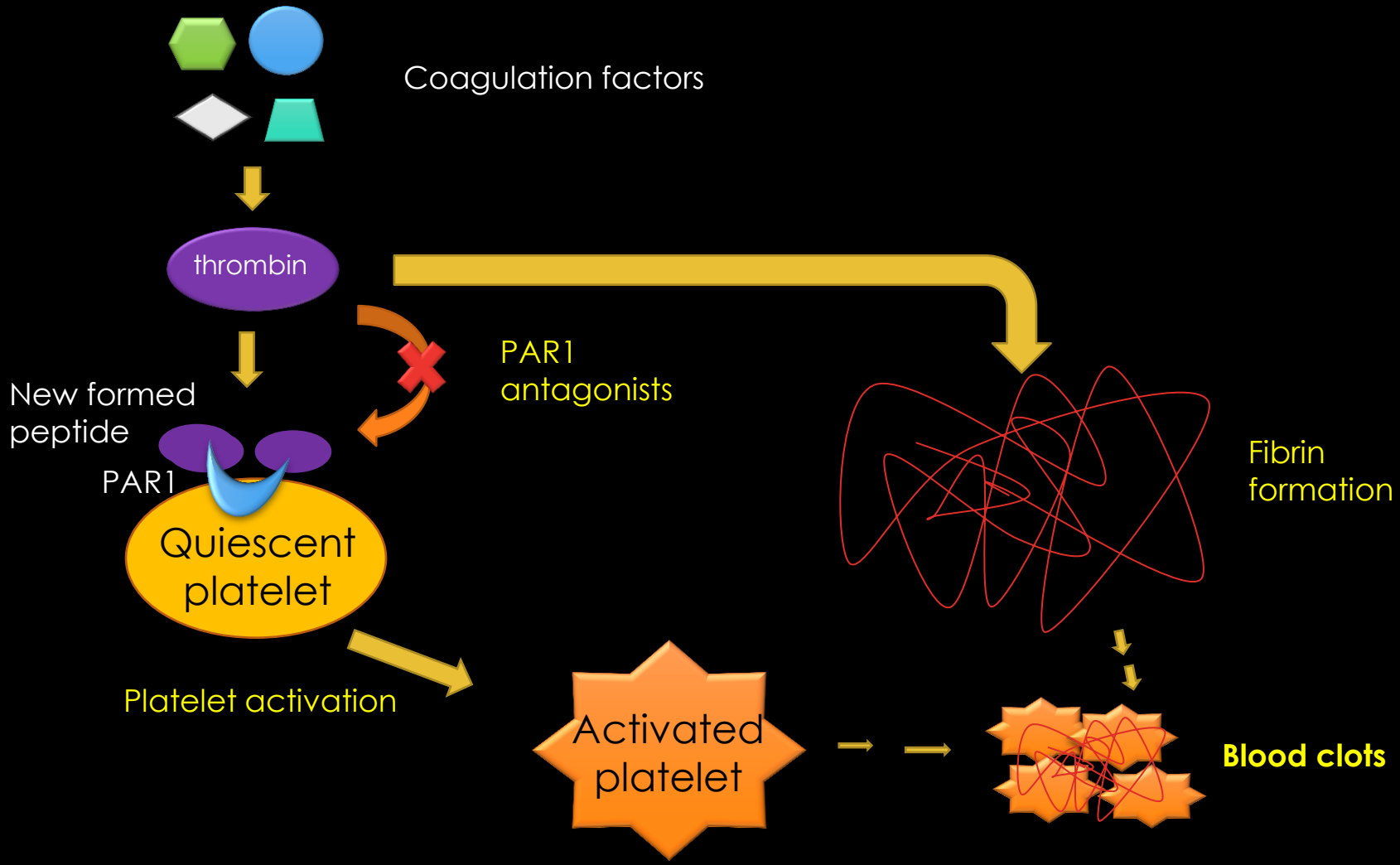
By 2030 more than 23 million people will die annually from CVDs.

Decrease of blood flow in the coronary arteries

Blood clots

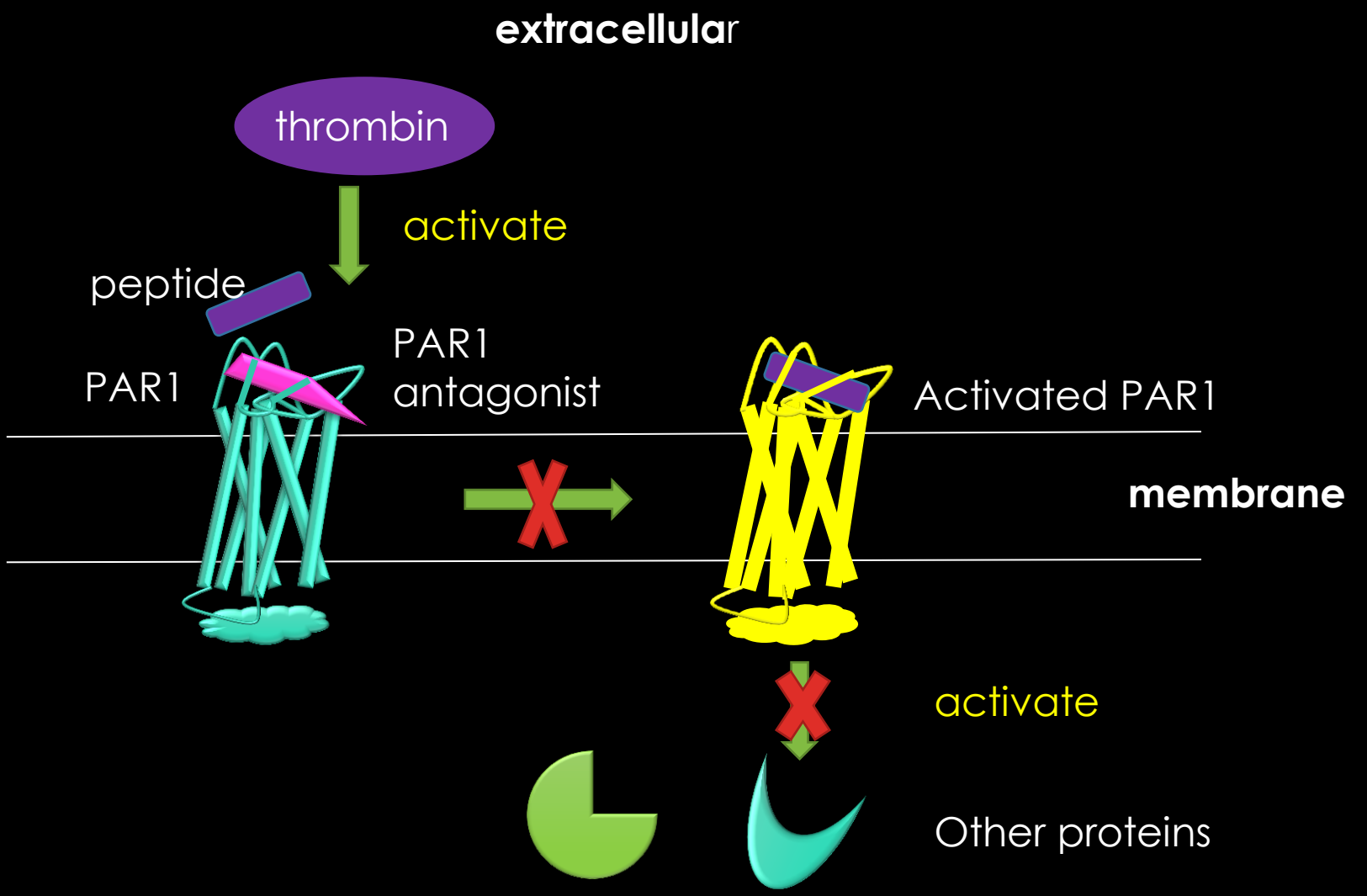
THE TARGET: PAR1

- **Coagulation process**



Journal of Medicinal Chemistry 2005, 48, 5884-5887.

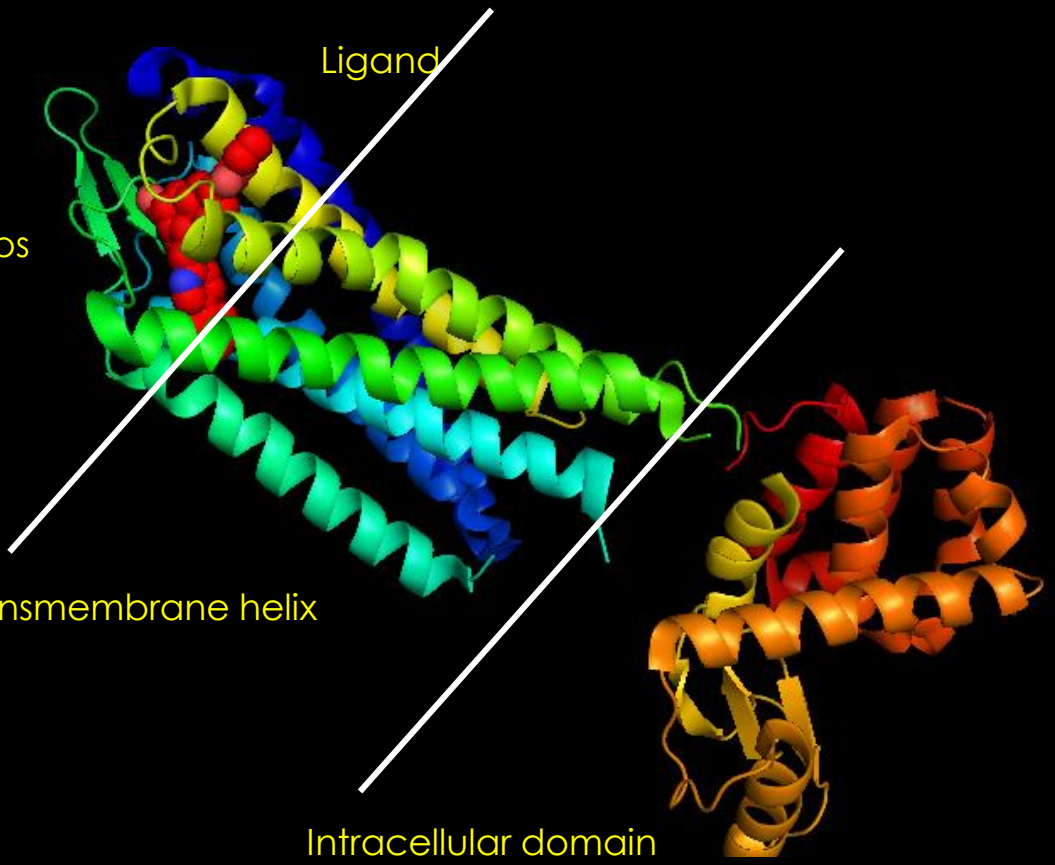
THE TARGET: PAR1



Nature, 2012,492: 387-392

THE TARGET: PAR1

- **The structure of PAR1**



PAR: Protease-activated receptors

Transmembrane protein located on the membrane of the platelets that transduce the signals, belongs to the GPCR families.

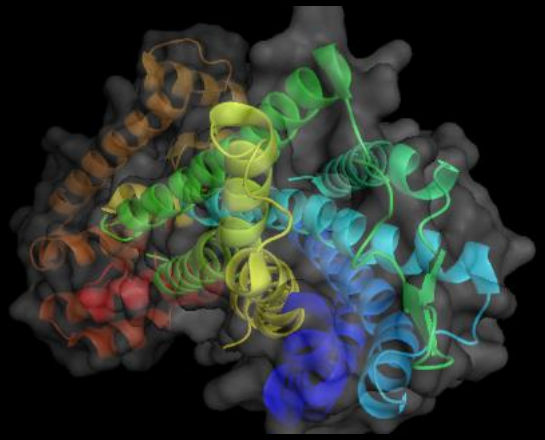
Nature, 2012,492: 387-392

METHODS

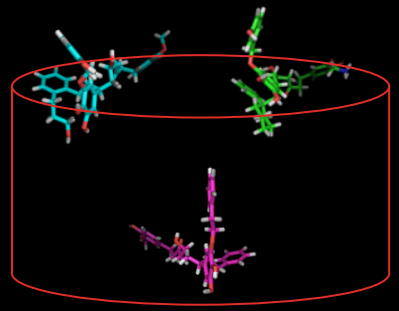
The methods to obtain possible drug candidates

METHOD

- **Structure-based virtual screening**



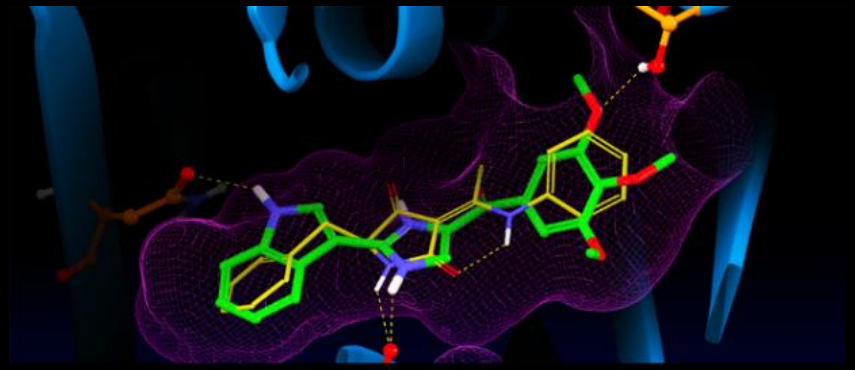
receptor



Molecule databases

$$\Delta G_{binding} = a1 \cdot \Delta G_0 + a2 \cdot \Delta G_{hbond} + a3 \cdot \Delta G_{vdw} + a4 \cdot \Delta G_{metal} + a5 \cdot \Delta G_{rot} + a5$$

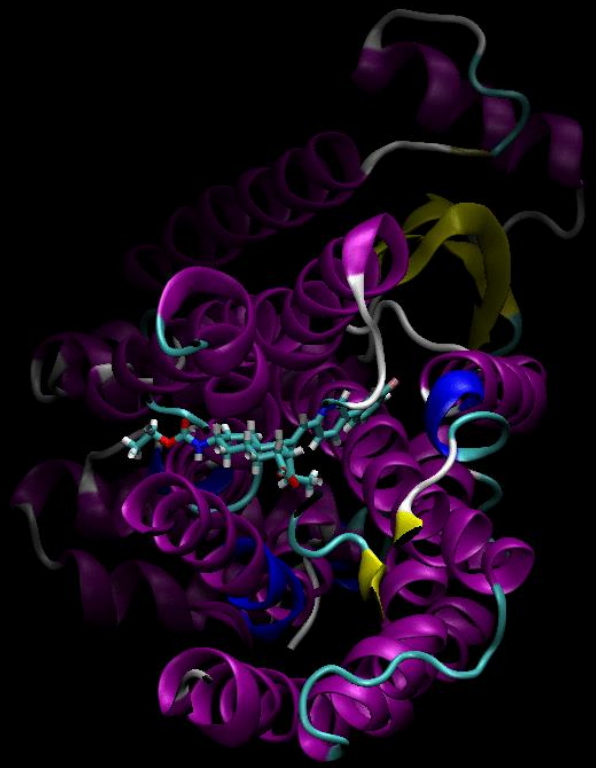
scoring



docking

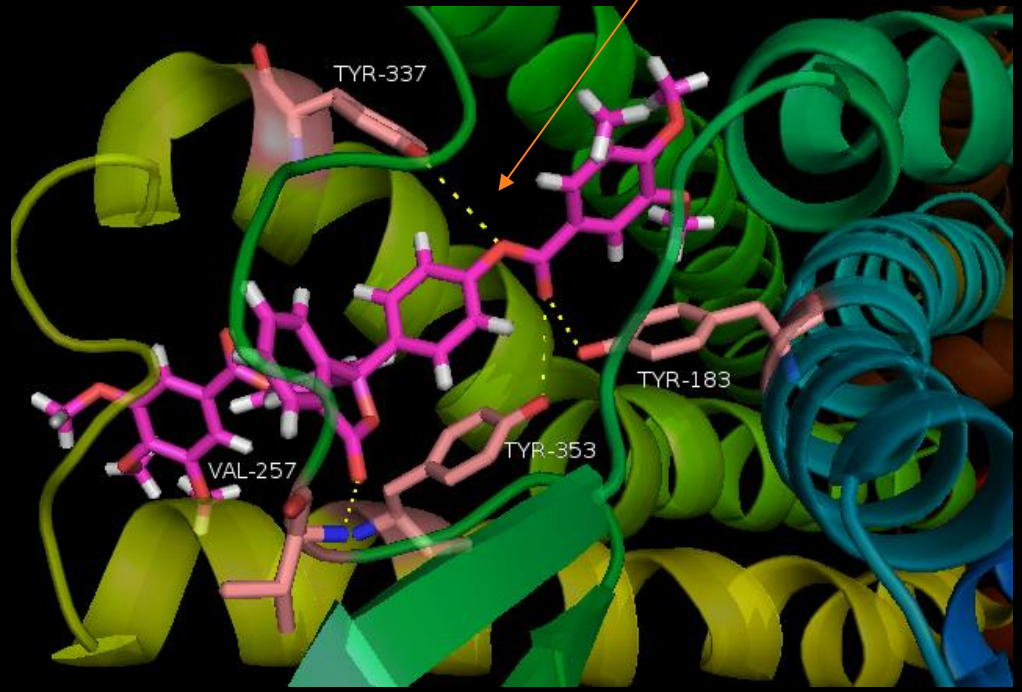
METHOD

- **Study of binding properties**



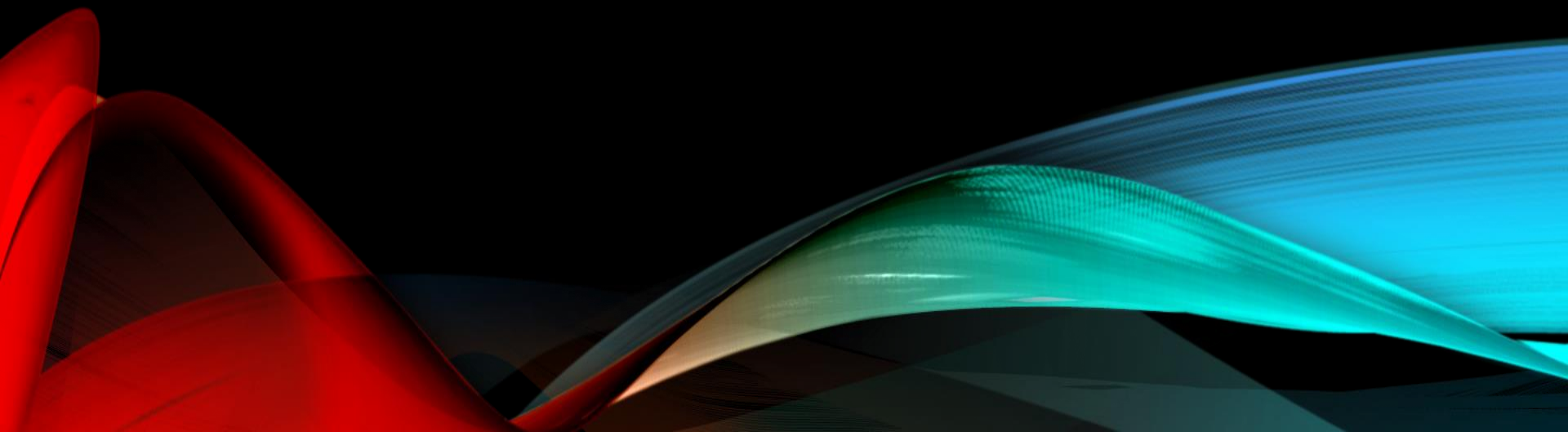
Molecular dynamics simulation

Hydrogen bond

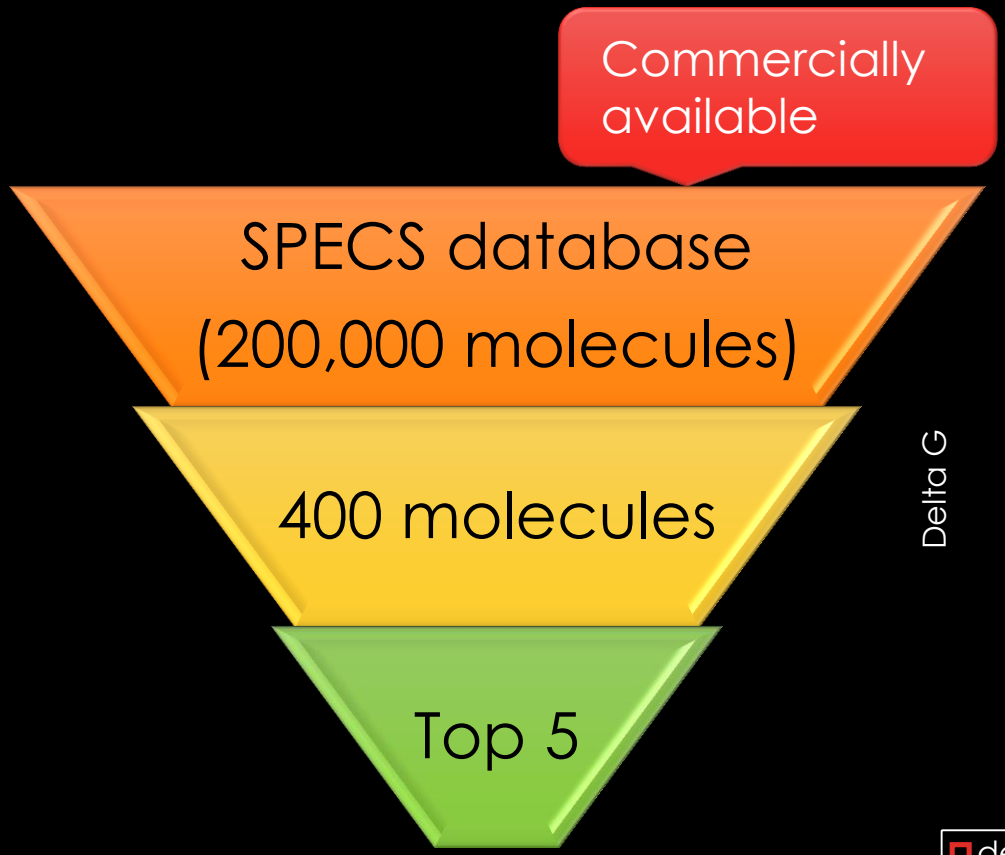


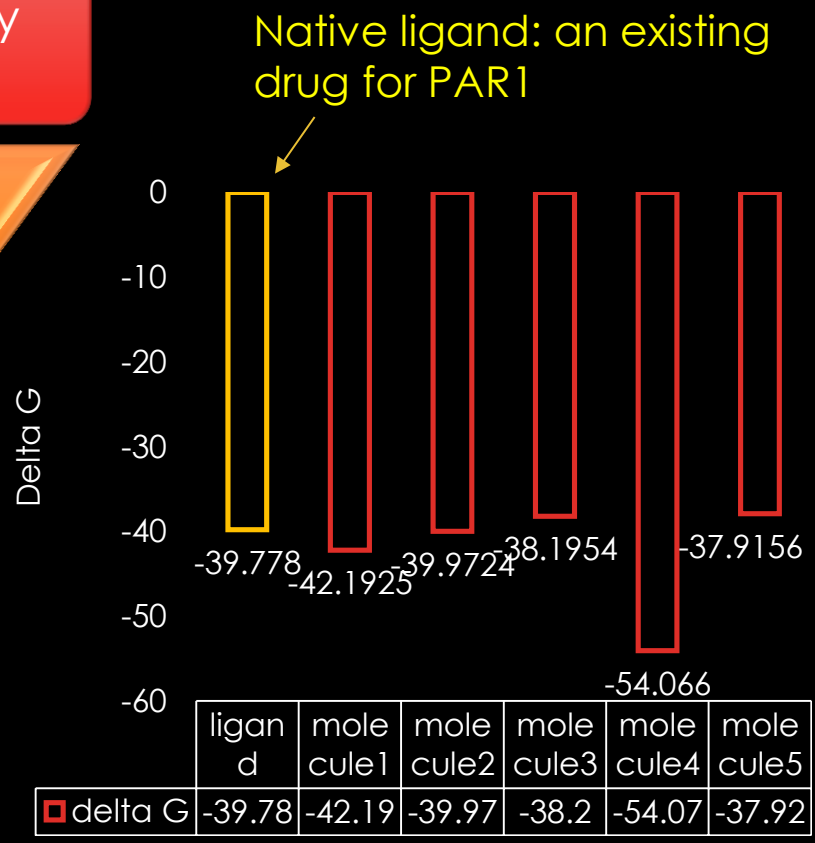
OUR WORKS

The process and results of our works



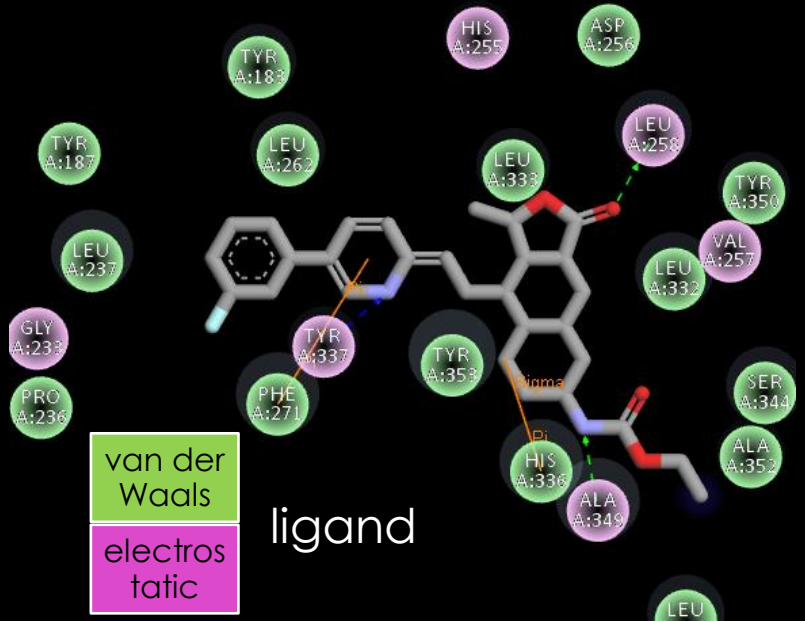
OUR WORKS


Commercially available
SPECS database (200,000 molecules)
400 molecules
Top 5


Native ligand: an existing drug for PAR1
Delta G
0
-10
-20
-30
-40
-50
-60
-39.778
-42.1925
-39.9724
-38.1954
-54.066
-37.9156
ligand
molecule1
molecule2
molecule3
molecule4
molecule5
delta G
-39.78
-42.19
-39.97
-38.2
-54.07
-37.92

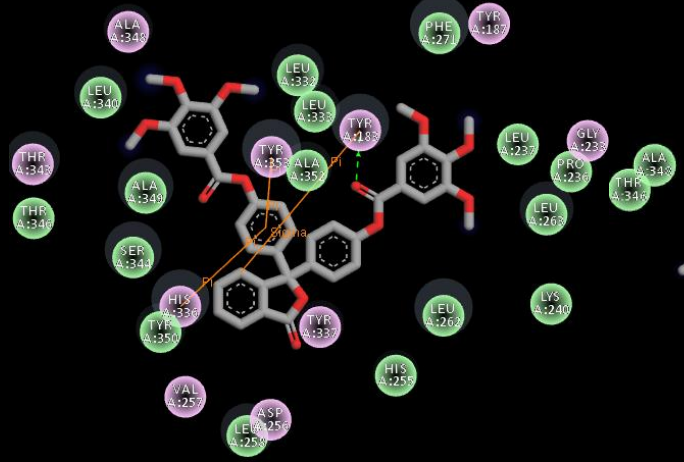
RESULTS

- **Binding properties**

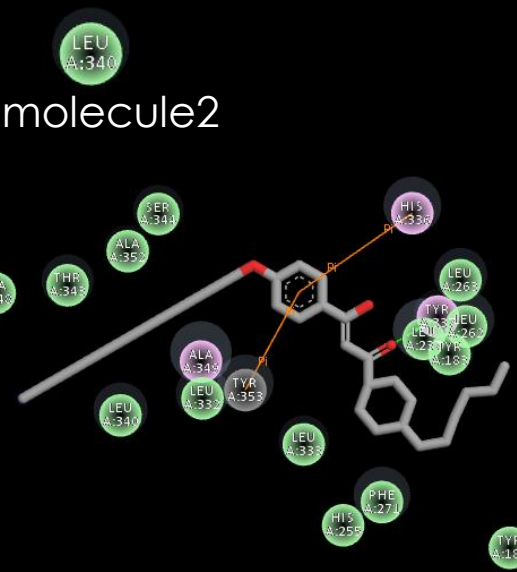


- Y-shaped or V-shaped
- Van der Waals interaction as the main
- Several hydrogen bonds or pi-pi interactions

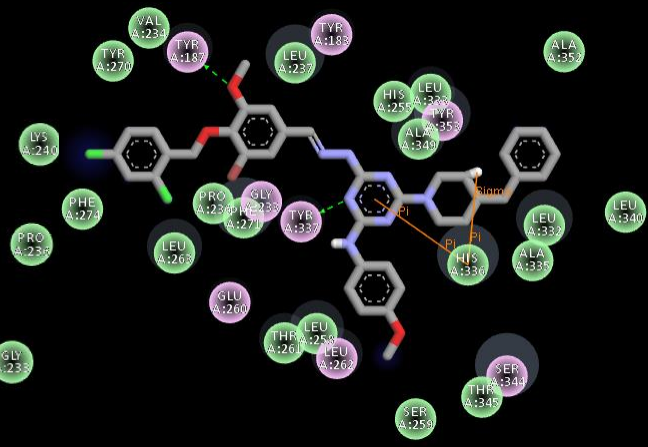
molecule1



molecule2

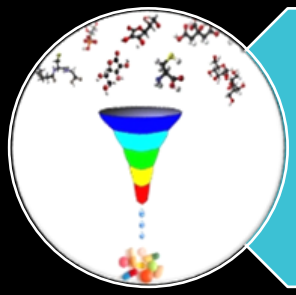


molecule4

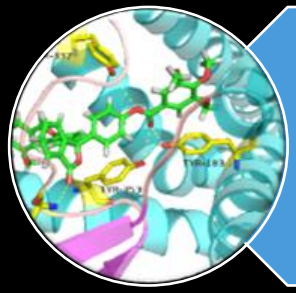


CONCLUSION

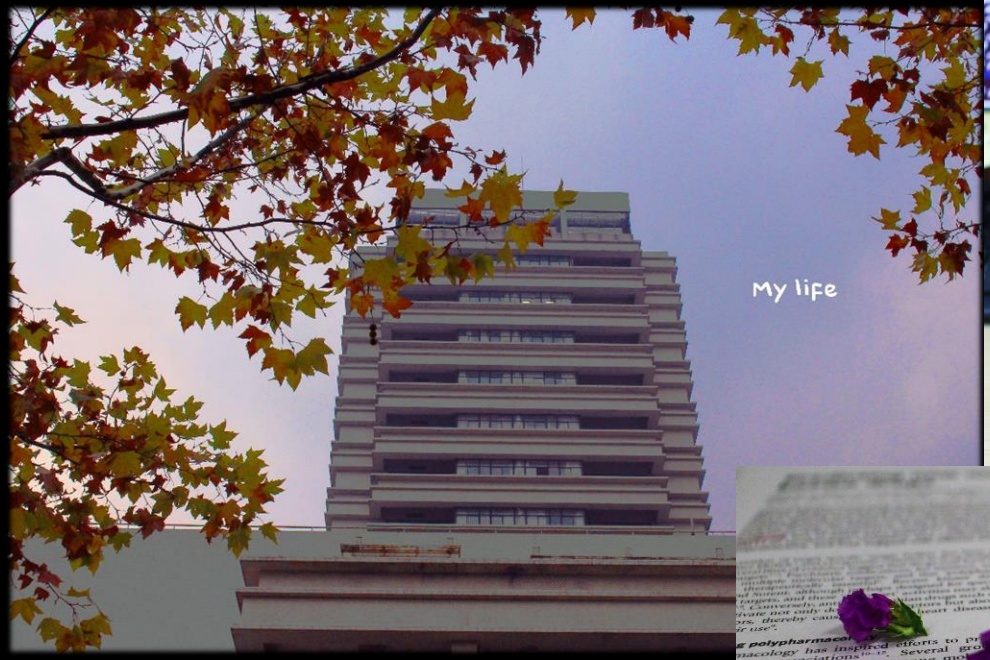
We chose PAR1 as our target protein which plays an important role in the coagulation process and can activate the platelets. Our goal is to inhibit this activation.



Structure-based virtual screening method has been adopted to find the potential PAR1 antagonists.



Three molecules forms strong interaction with the target protein, and the binding properties are similar to the native ligand. So they were considered to be the potential drug leads.



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THANK YOU !