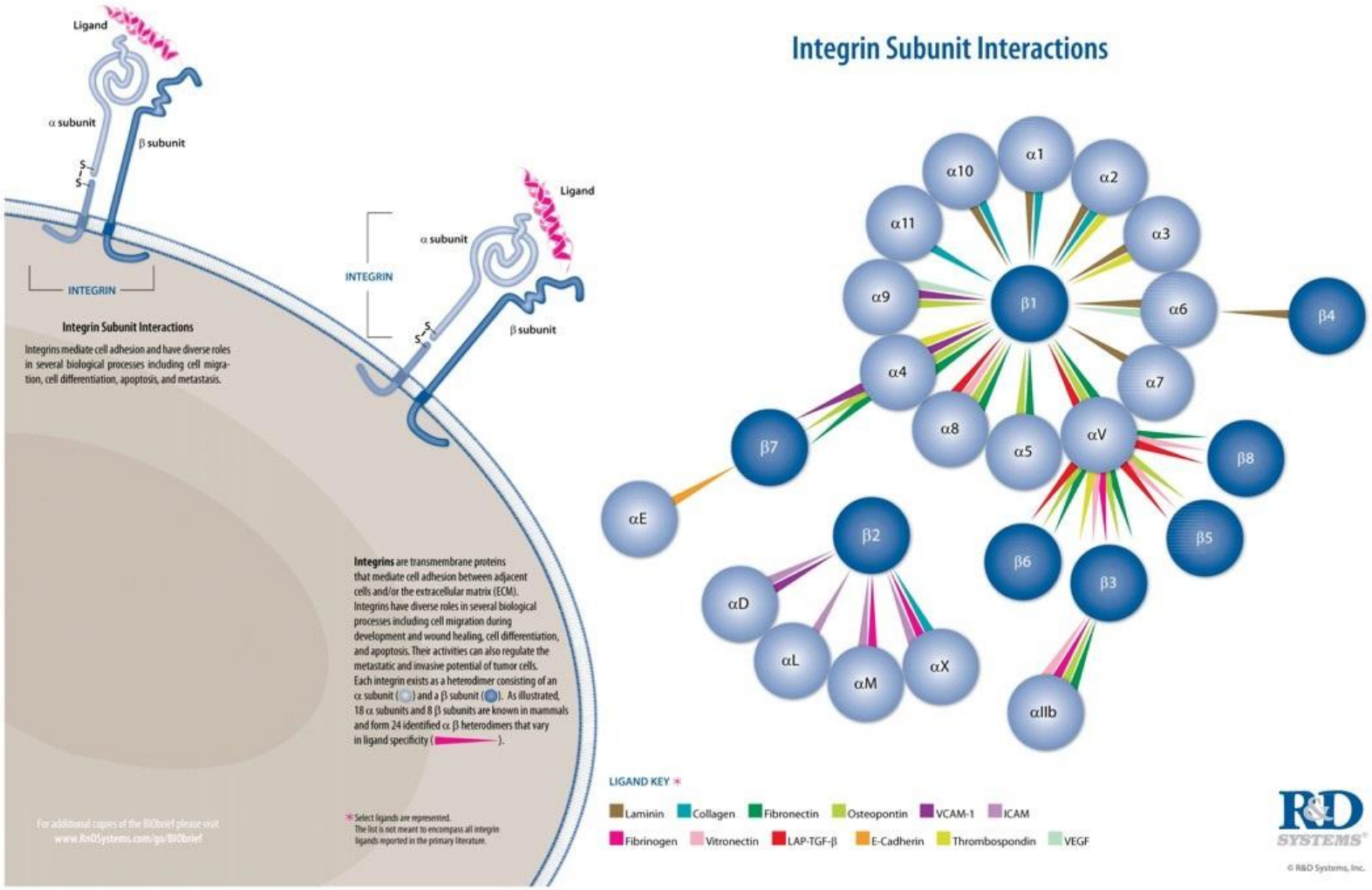
Looking for β3 integrin family selectivity: The use of snake venom disintegrin as a tool for molecular modeling approach

D.Sc Reinaldo Barros Geraldo

In the hemostasis and angiogenesis several cell adhesion molecules and transmembrane receptors are of great importance for the functioning those processes

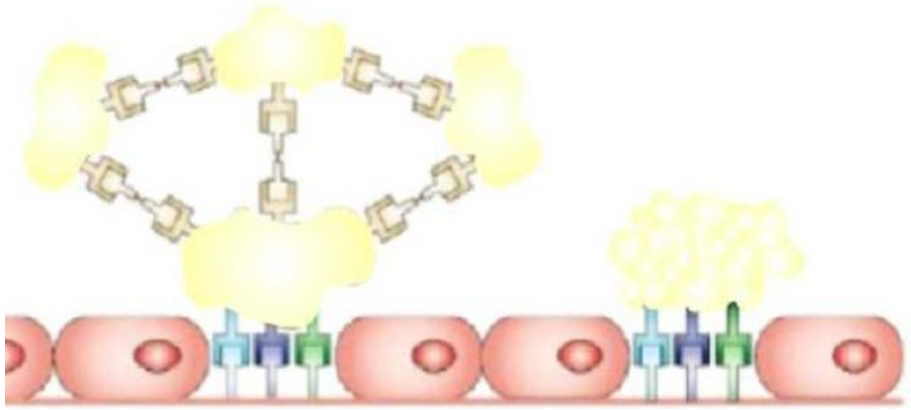


R&D System, http://http://www.rndsystems.com/BIObrief_s07.aspx

B3 Integrins family

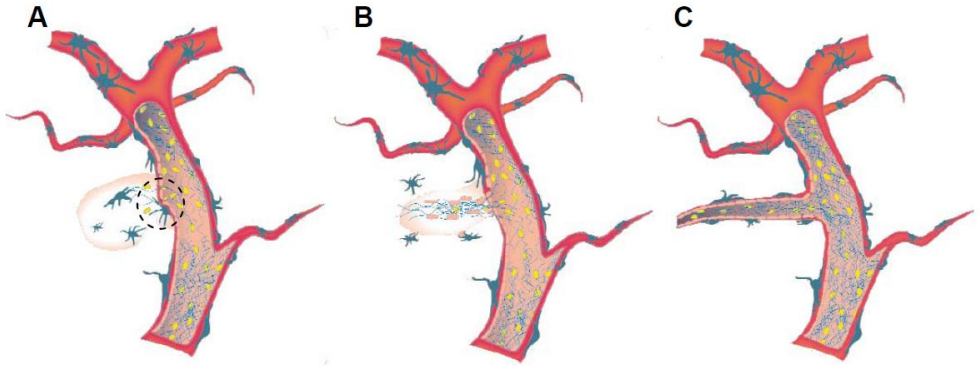
Platelets aggregation

$\alpha_{IIb}\beta_3$



Angiogenesis

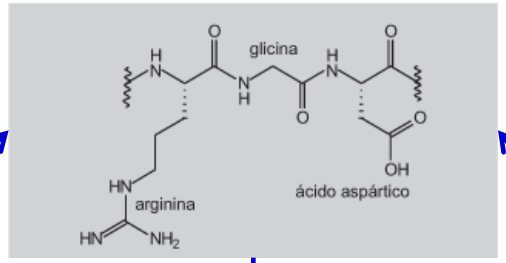
$\alpha_v\beta_3$



Disintegrins and drug design

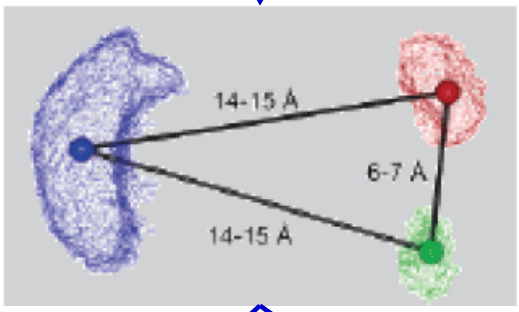
Echis carinatus

Sistrurus barbouri

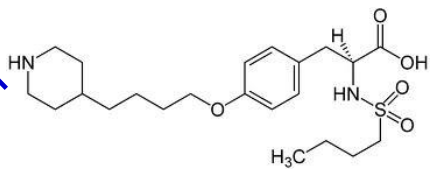


ECHISTATIN

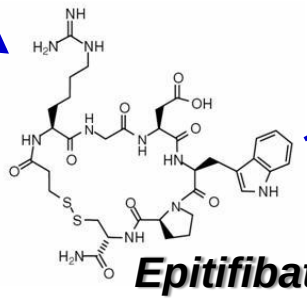
BARBURIN



Agrastat



tirofiban



Epitifibatide

Integrilin

Aims

in silico analysis

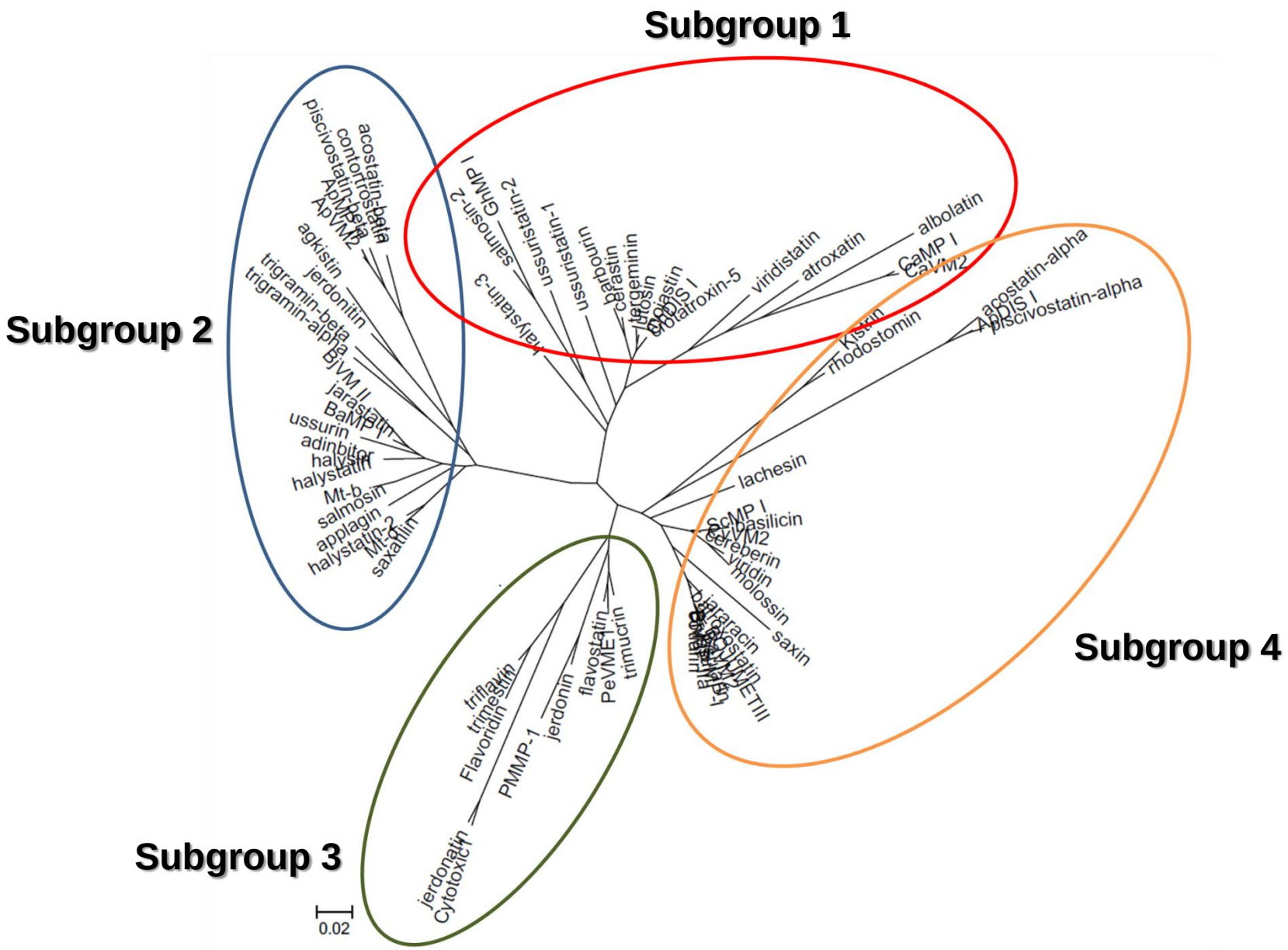
- **Structure activity relationship (SAR) of disintegrins;**

- **Selective profile of disintegrins against integrins receptors.**

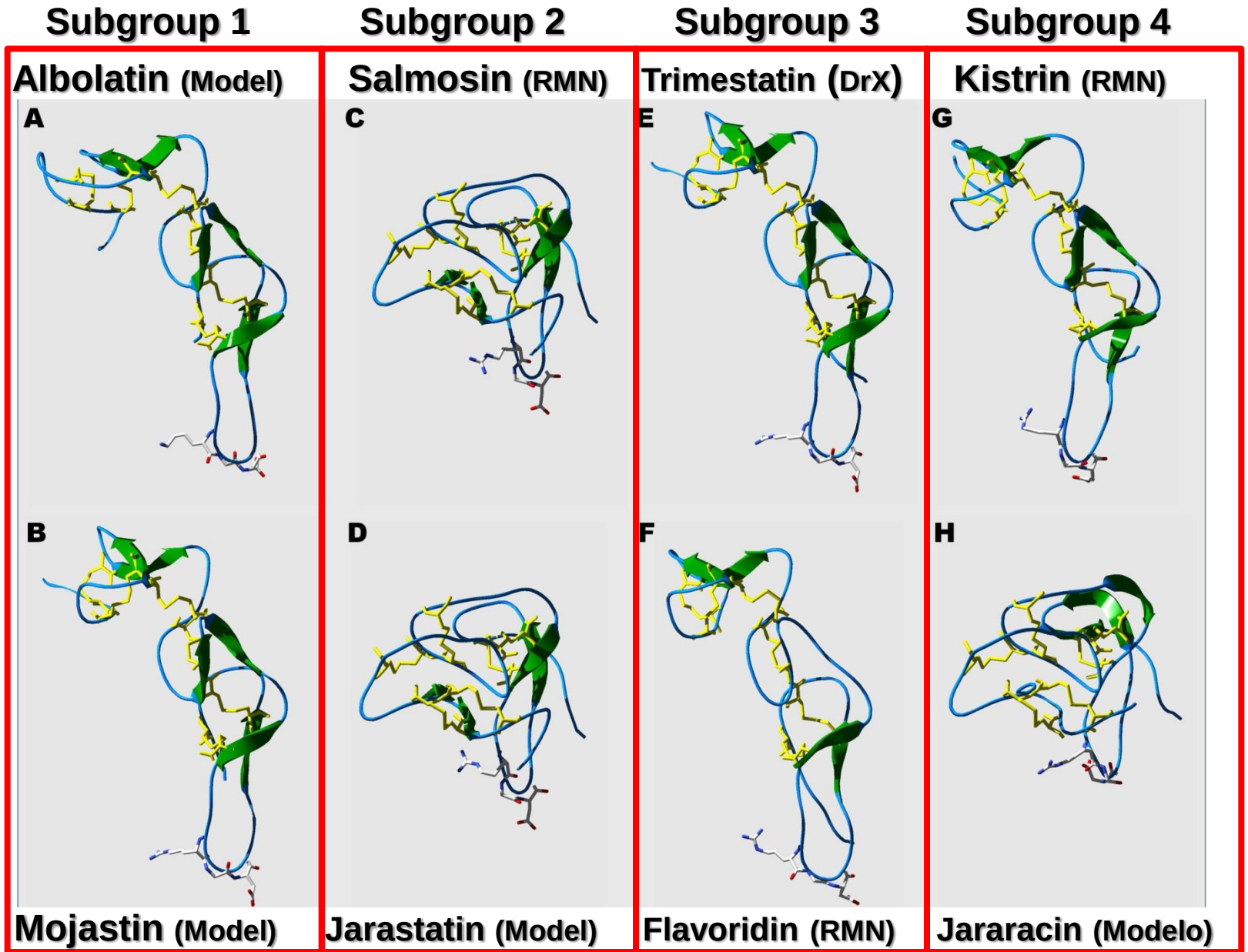
Disintegrins Alignment of …

N-terminal **C-terminal**

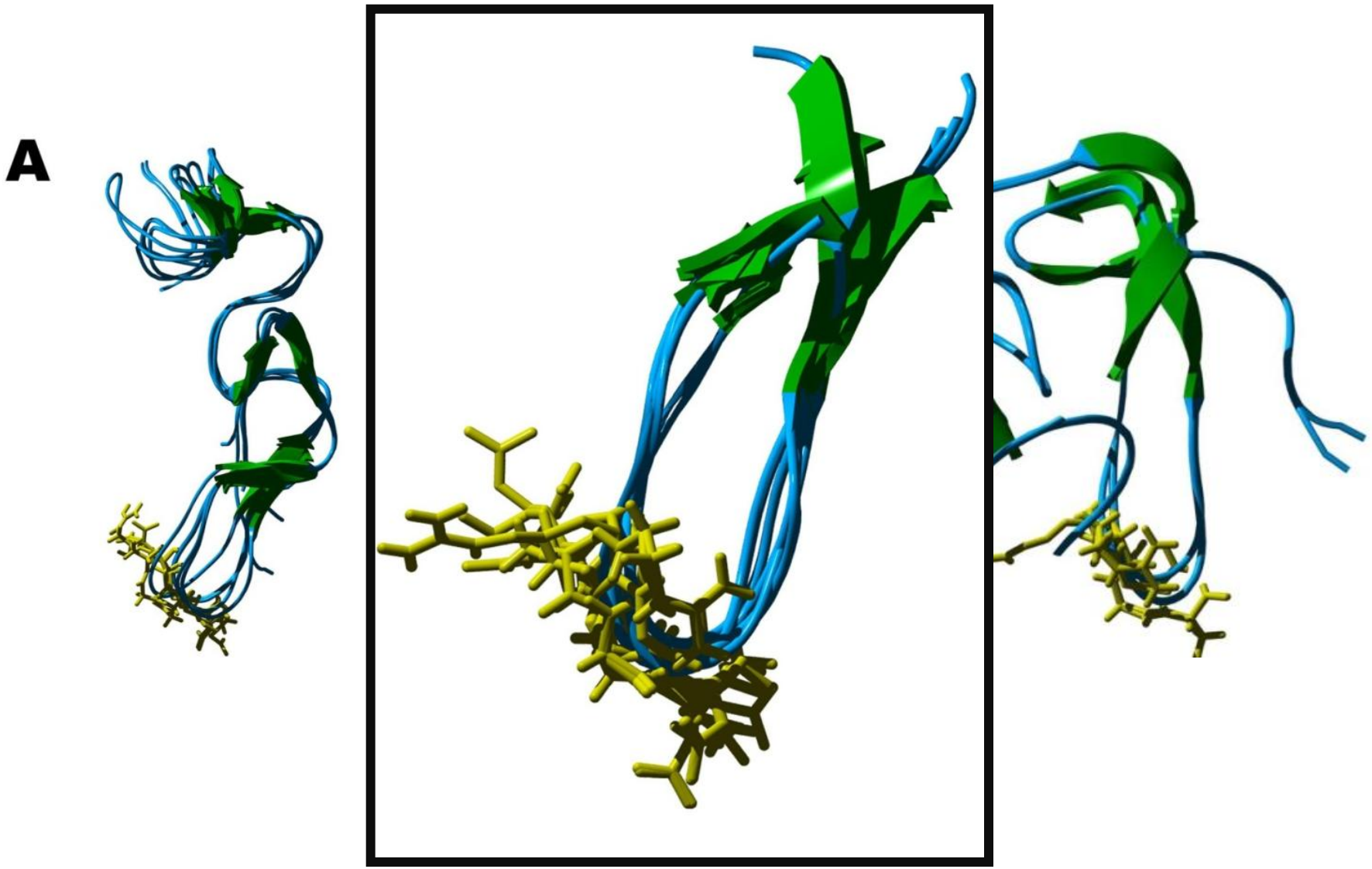
Phylogenetic tree



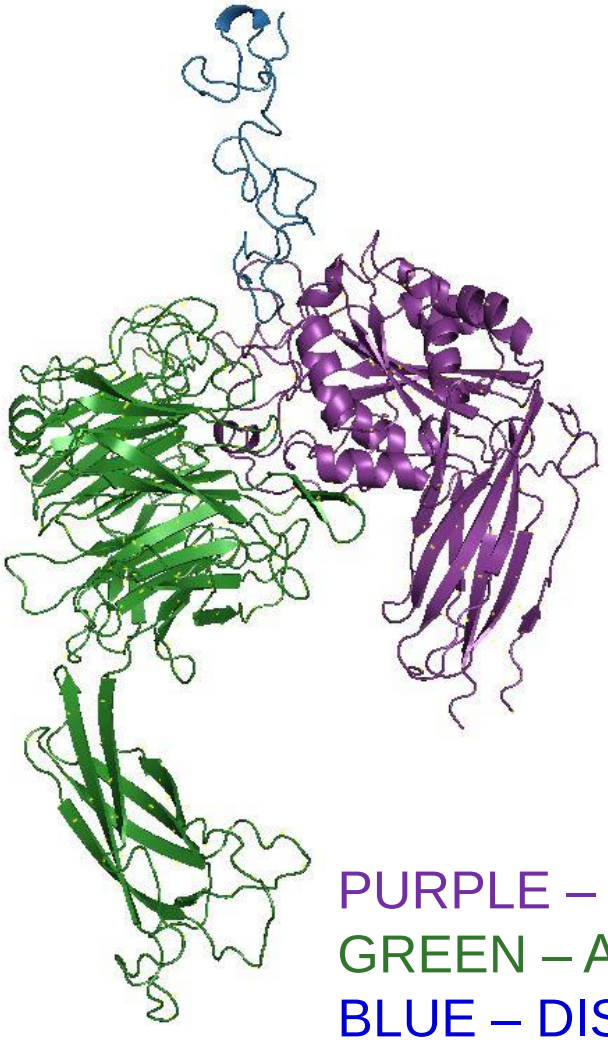
Selected disintegrins of each subgroup

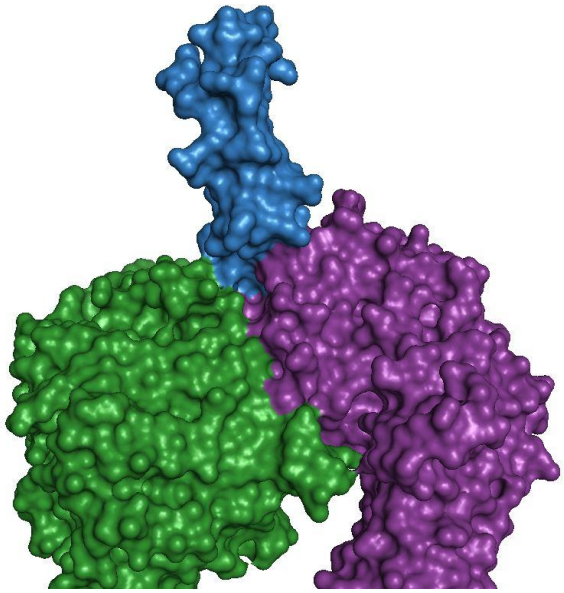


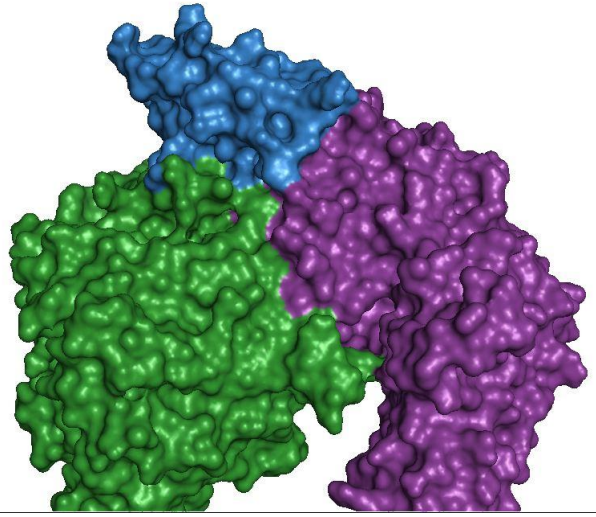
Disintegrins 3D alignment



Docking complexes



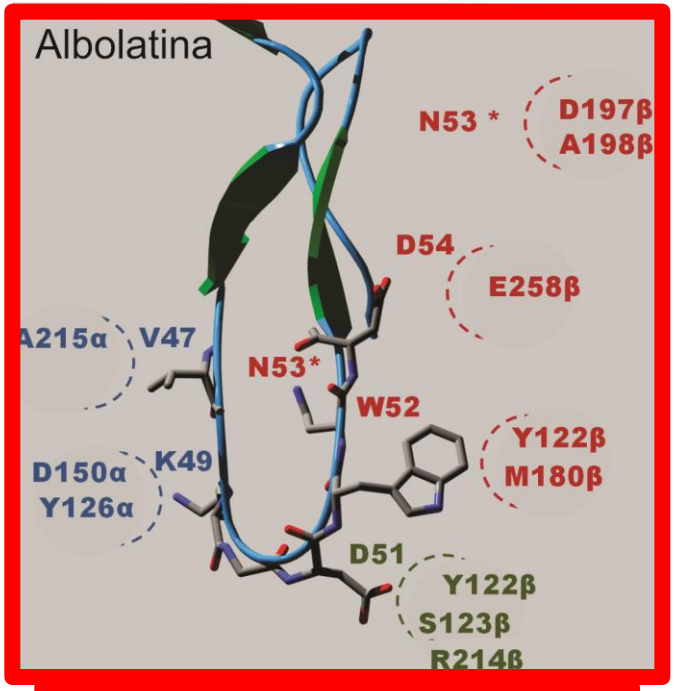




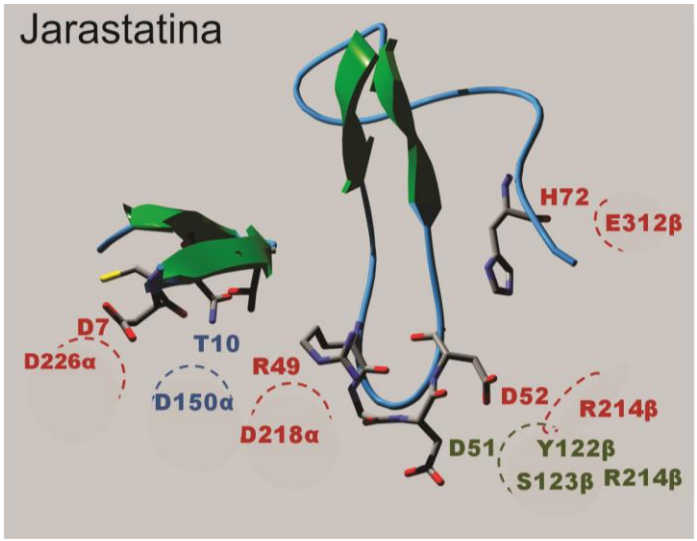
PURPLE – B SUBUNIT
GREEN – A SUBUNIT
BLUE – DISINTEGRINS

Docking with $\alpha_{IIb}\beta_3$

SUBGROUP 1



SUBGROUP 2

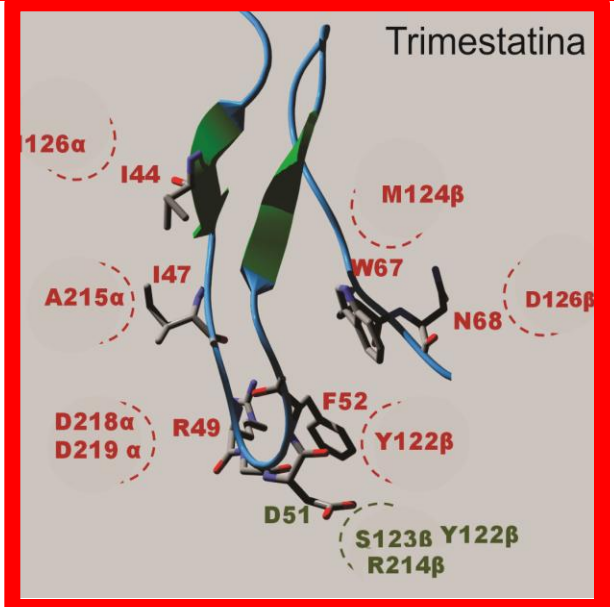


GREEN – Common to all disintegrins

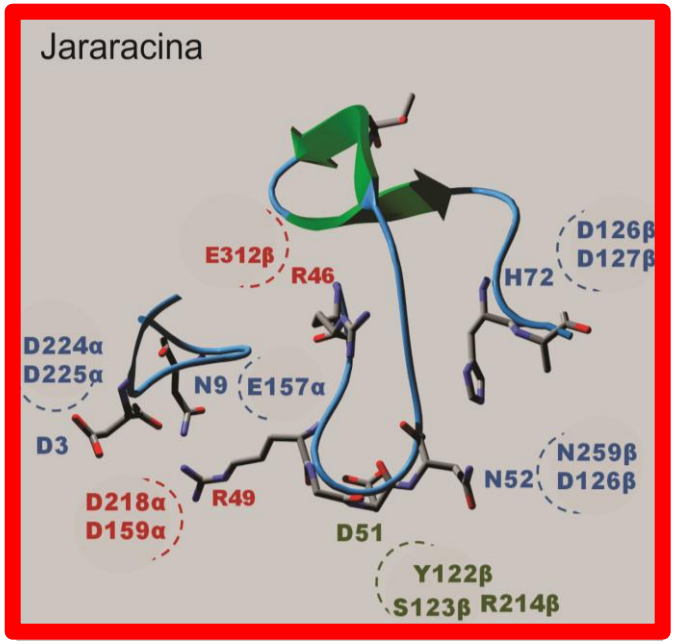
RED – Common only to subgroup

BLLUE – Only in the specific disintegrin

SUBGROUP 3



SUBGROUP 4



Docking with $\alpha_v\beta_3$

SUBGROUP 1

SUBGROUP 2

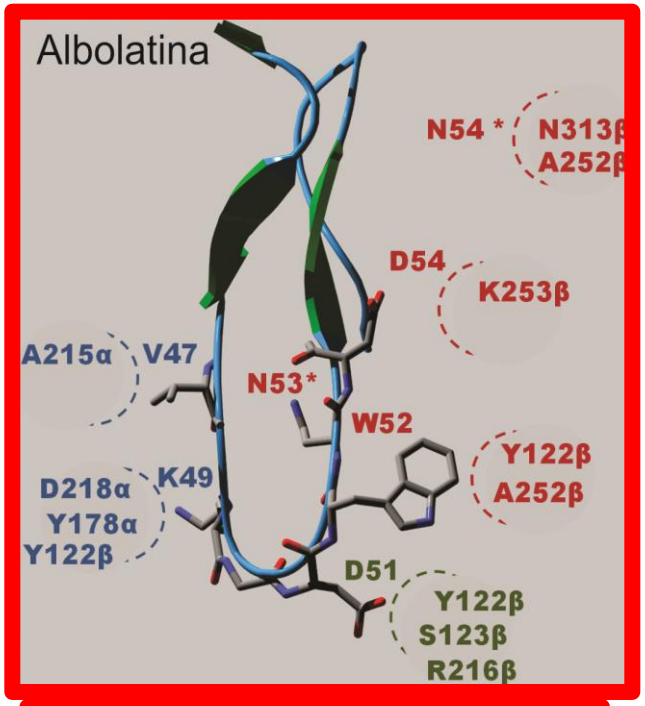
SUBGROUP 3

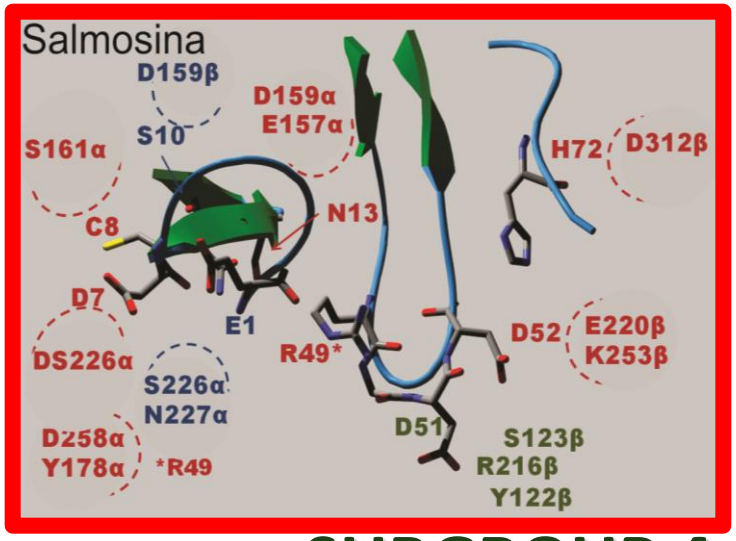
SUBGROUP 4

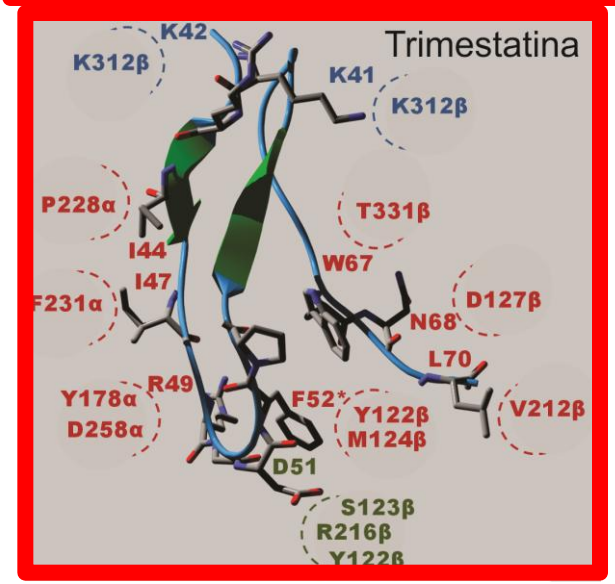
GREEN – Common to all disintegrins

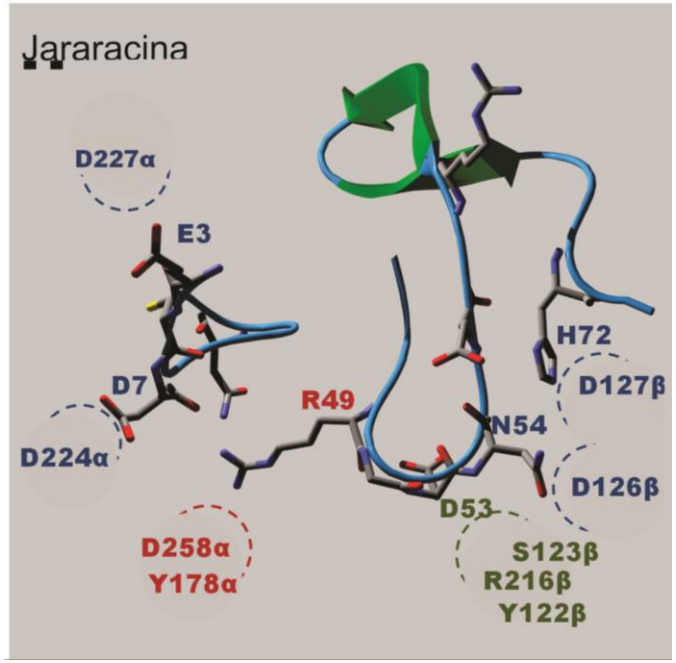
RED – Common only to subgroup

BLLUE – Only in the specific disintegrin



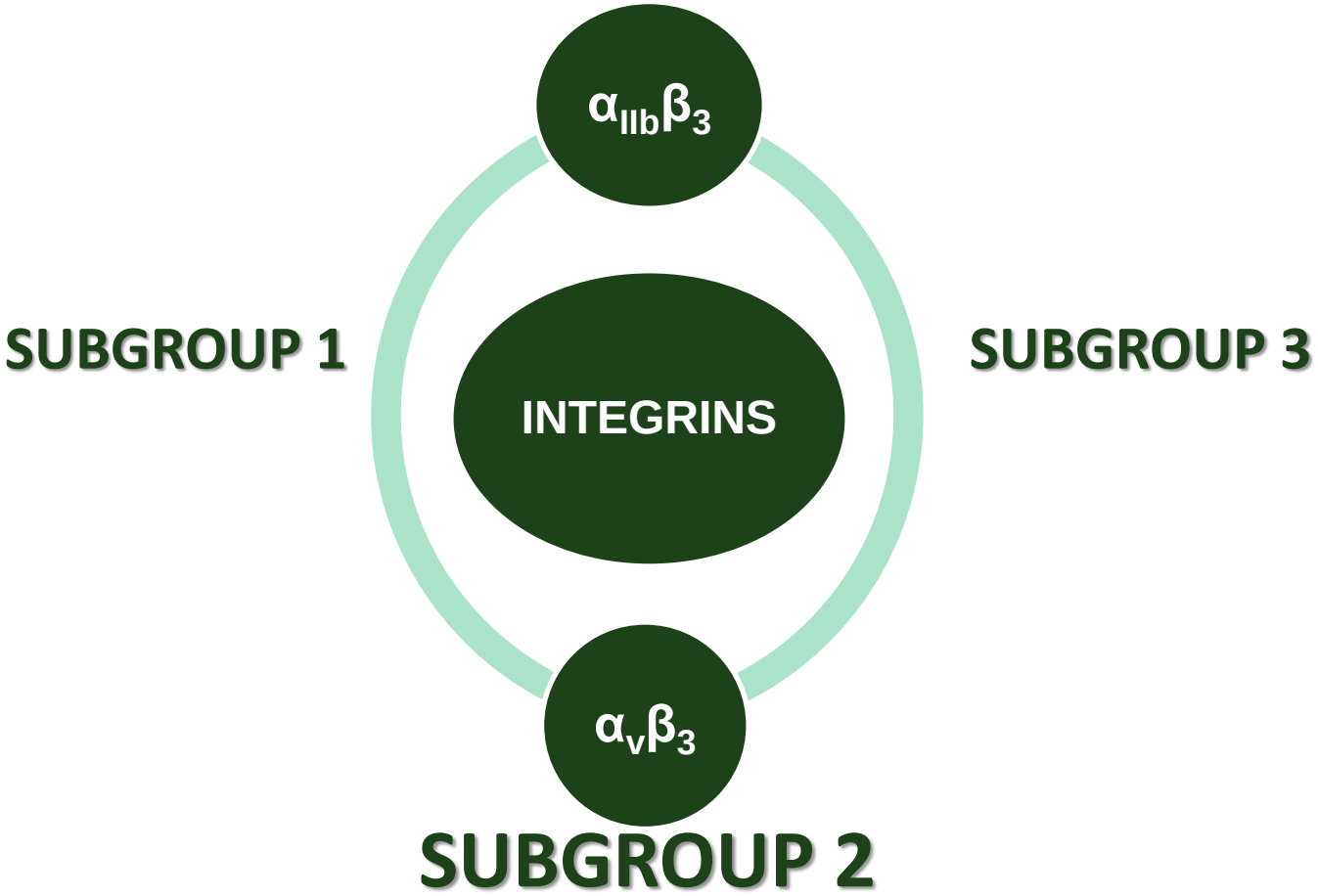






Docking complexes

PROPOSAL OF SELECTIVITY MAP



With the propose of confirming the interaction profile degree of interaction a theoretical analysis binding energy among the integrins and disintegrins was performed.

Two disintegrins studied by my group JARASTATIN (SUBGROUP2) and JARARACIN (SUBGROUP 4) for the study of molecular dynamics were selected.

Molecular Dynamics

- Strategies used in the analysis of MD simulations ::

  - Physic-chemical properties of the system:
    - Pressure
    - Volume
    - Density

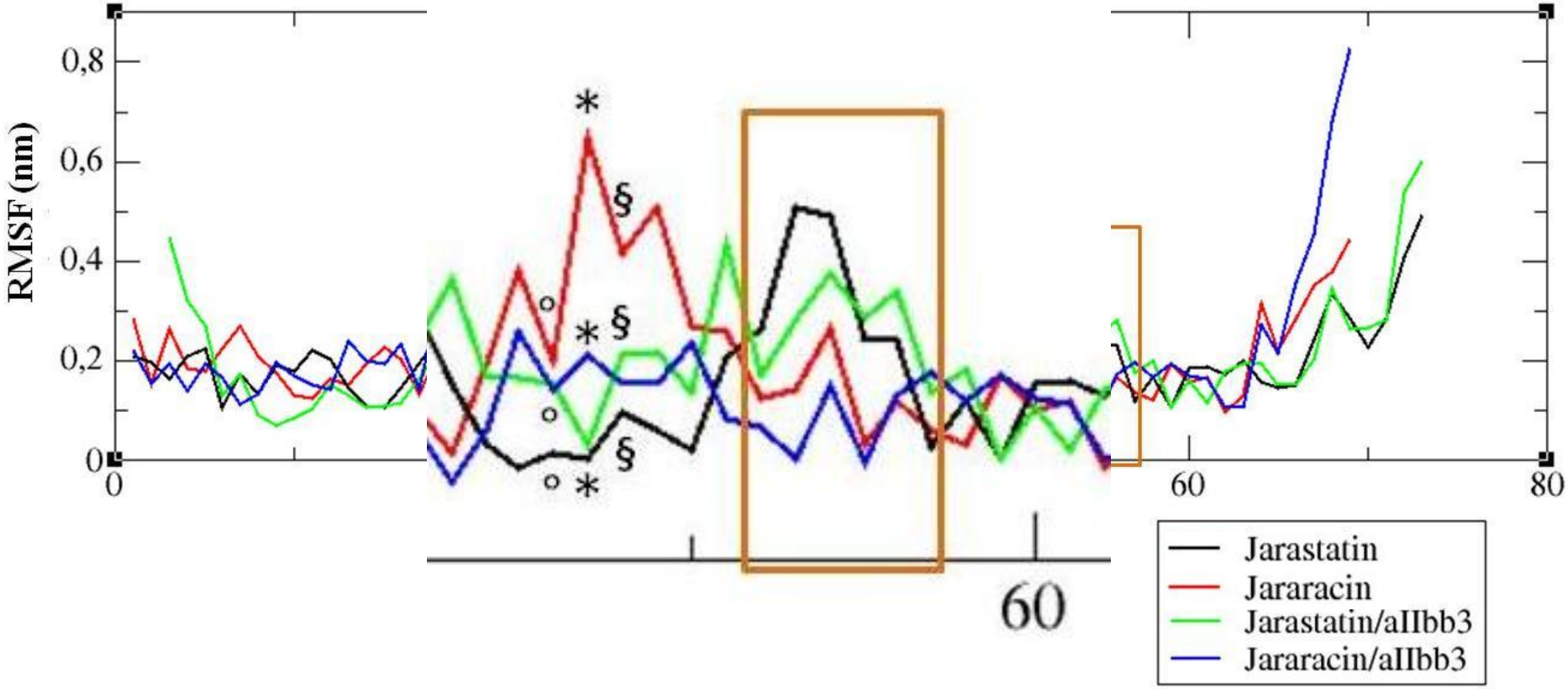
  } Indicate stability the simulation system

  - Energies
    - Total energy, Kinetic energy and Potential energy
    - Interaction Energy (amino acids, ligand, receptor, solvent, ions)

  - RMSD → Root-mean-square deviation at all amino acids in the simulation
  - RMSF → Root-mean-square fluctuation at all amino acids in the simulation
  - Radius of gyration → Refers to the distribution of the components of an object around an axis.

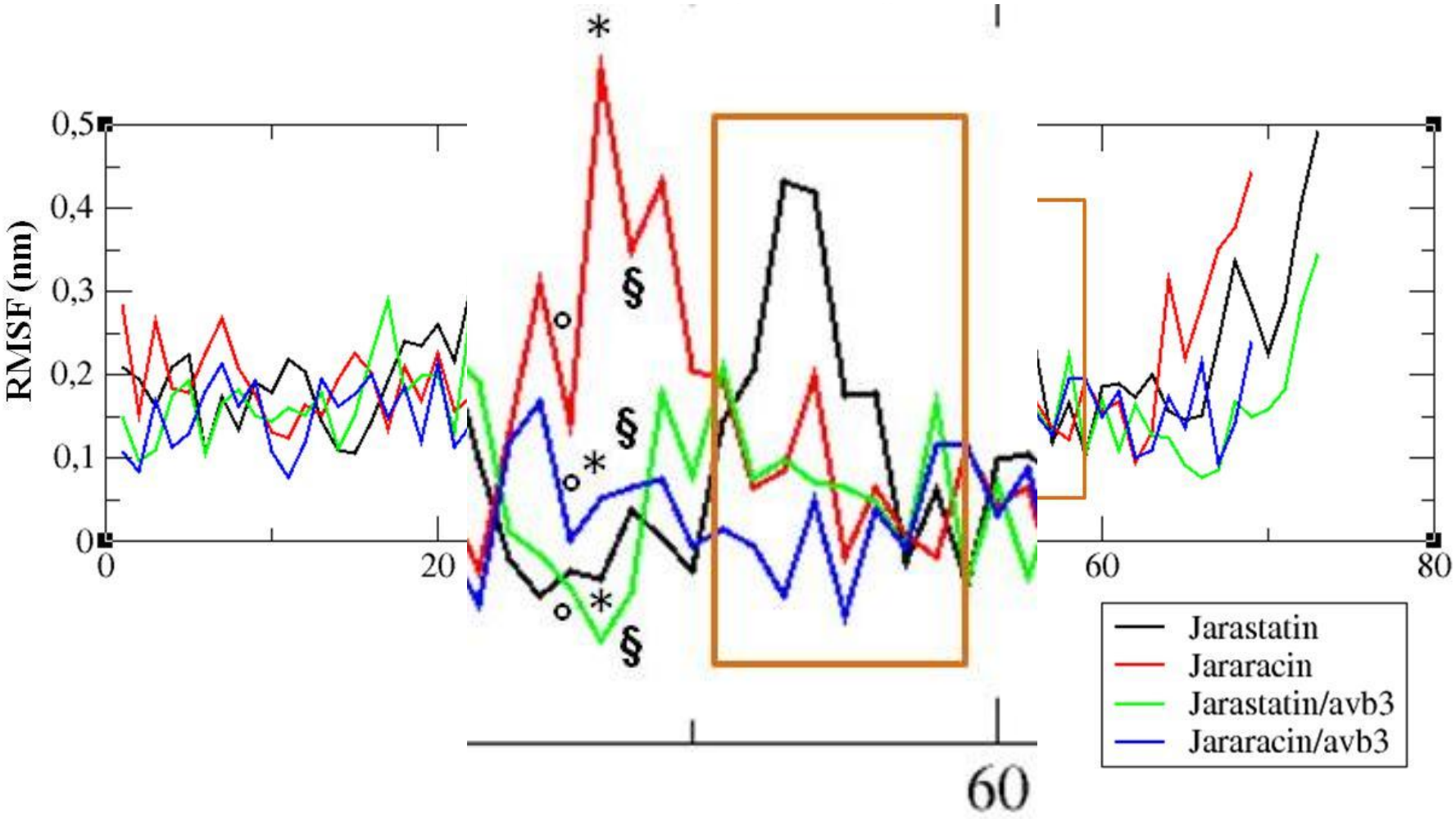
Molecular Dynamics

RMSF with disintegrins binding with $\alpha_{IIb}\beta_3$ during the 10ns.



Molecular Dynamics

RMSF with disintegrins binding with $\alpha_v\beta_3$ during the 10ns.



Molecular Dynamics

Energy Studies

	Energia total	Energia de Lennard-Jones	Energia de Coulomb	Energia de Interação
Jararacina isolada	$-1,28_x10^5$	$-1,87_x10^3$	$-1,76_x10^5$	-
Jararacina/$\alpha_{IIb}\beta_3$	$-1,6_x10^6$	$-2,04_x10^6$	$-2,23_x10^6$	$-4,27_x10^6$
Jararacina/$\alpha_v\beta_3$	$-1,38_x10^6$	$-1,77_x10^6$	$-1,89_x10^6$	$-3,66_x10^6$
Jarastatina isolada	$-1,27_x10^5$	$-2,04_x10^3$	$-1,73_x10^5$	-
Jarastatina/$\alpha_{IIb}\beta_3$	$-1,39_x10^6$	$-1,96_x10^6$	$-2,11_x10^6$	$-4,07_x10^6$
Jarastatina/$\alpha_v\beta_3$	$-1,5_x10^6$	$-1,91_x10^6$	$-2,04_x10^6$	$-3,95_x10^6$

Differences of interaction energy between the disintegrins

Jararacina/$\alpha_{IIb}\beta_3$ — Jarastatina/$\alpha_{IIb}\beta_3$ = **-2,0 x 10^5 kJ/mol**

Jarastatina/$\alpha_v\beta_3$ — Jararacina/$\alpha_v\beta_3$ = **-2,9 x 10^5 kJ/mol**

Conclusões (*in silico*)

Within the group of PII - medium size disintegrins, we can subdivide on some distinct subgroups. That being Subgroup 4 (jararacin and kistrin) still could be more divided.

Subgroups 1 and 3 that are in the transition of the phylogenetic tree exhibit high affinity for αIIbβ3 and αvβ3 integrins; while one subgroup shows more affinity for αvβ3 and subgroup 4 (jararacina) more affinity for αIIbβ3.

Molecular Dynamics corroborated the data showing that the rigid docking jararacin (subgroup 4) has a higher affinity for αIIbβ3, in contrast to jarastatina (subgroup 2) showed higher affinity for αvβ3 .

Greetings

To my collaborators:

Profª. Lina B. Zingali (UFRJ) e Profª. Helena C. Castro (UFF)

Prof. Rodolpho Albano (UERJ)

Prof. Hugo Verli (UFRGS)

Drª. Ana Moura (Butantã Institut – SP)

Prof. Carlos R. Rodrigues (UFRJ)

To the technical support Aninha, Dione and Augusto

To all of my group in UEMP lab., LabHemoVen e LaBioMol.

Financial supports:

FAPERJ

CAPES

CNPq