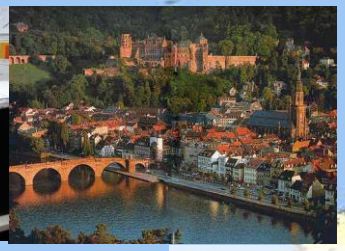
Πραγματοποιώντας Παγκόσμια Αναγωνιστική Έρευνα με τη χρήση εργαλείων της ΕΔΕΤ

Ζωή Κούρνια

Ίδρυμα Ιατροβιολογικών Ερευνών, Ακαδημία Αθηνών

Συμπόσιο Ψηφιακής Τεχνολογίας – «20 χρονια ΕΔΕΤ»

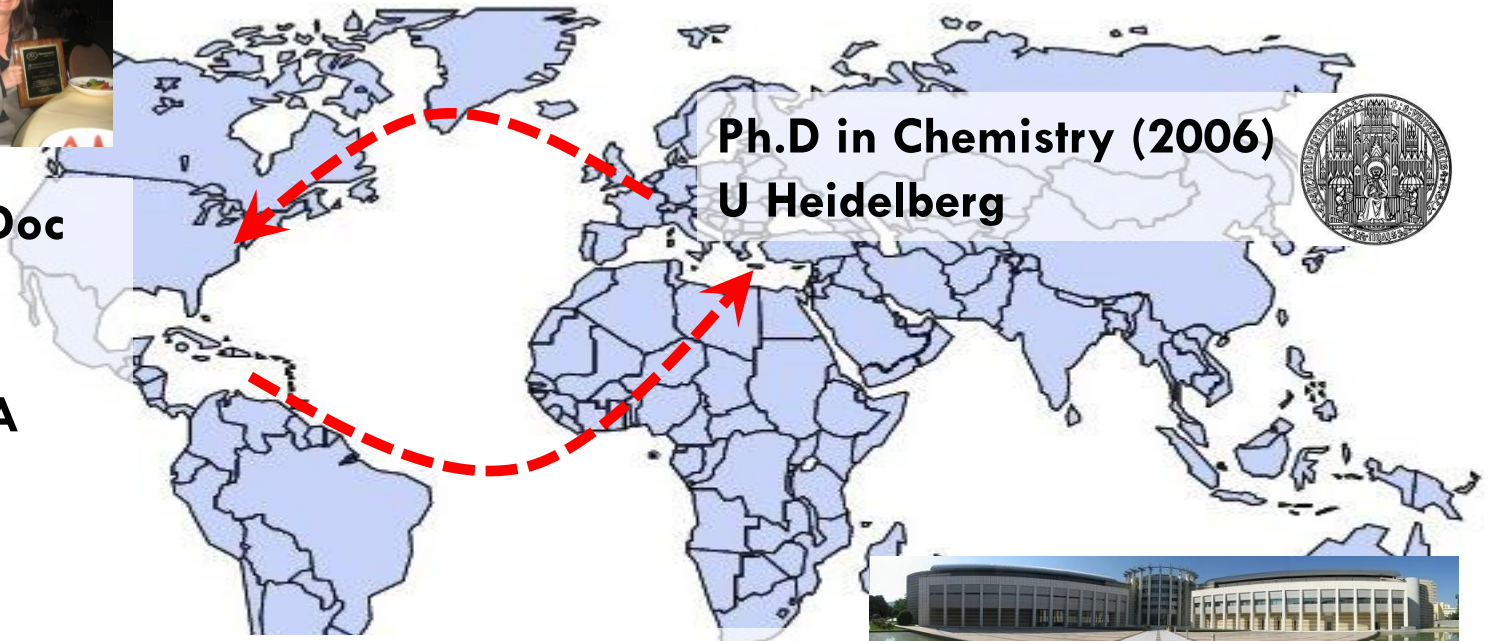
zcournia@bioacademy.gr *twitter: @zoecournia*



2001-2006
Ph.D. in Chemistry
Heidelberg University, Germany

1996-2001
Chemistry, University of Athens

2006-2009 PostDoc
Chemistry Dept,
Yale University
New Haven, USA



Ph.D in Chemistry (2006)
U Heidelberg

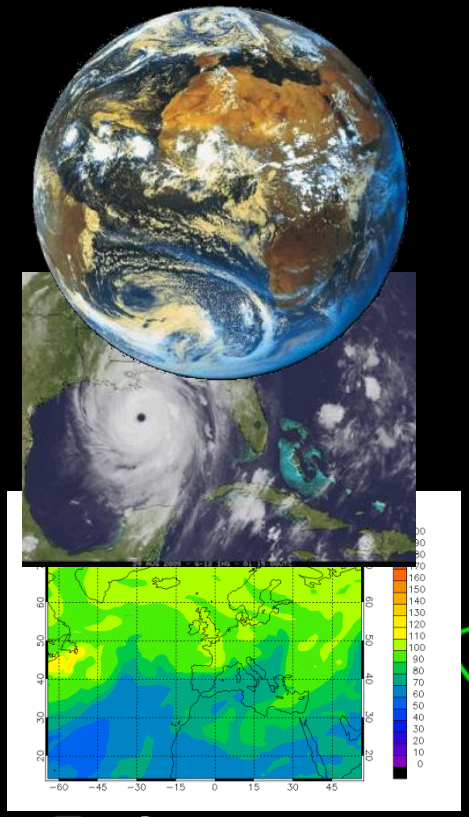
ACADEMY OF ATHENS

BRFAA

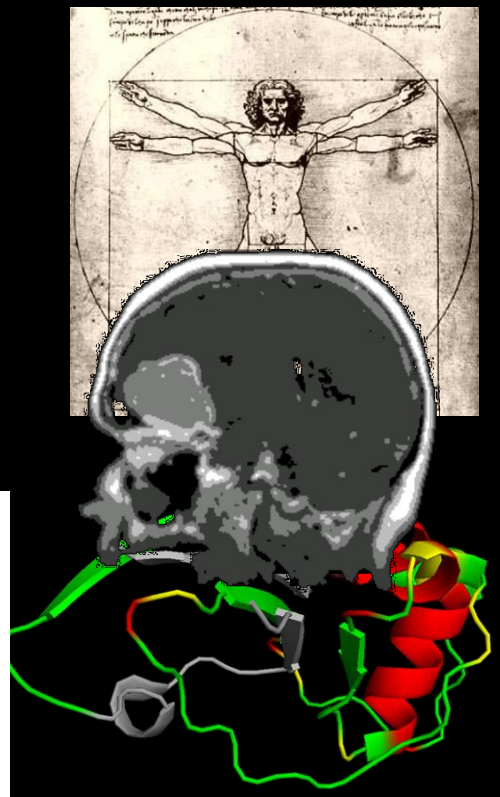
BRFAA
2010-date
Investigator

Instructor,
MSc in Data Science
& Information Technologies
University of Athens

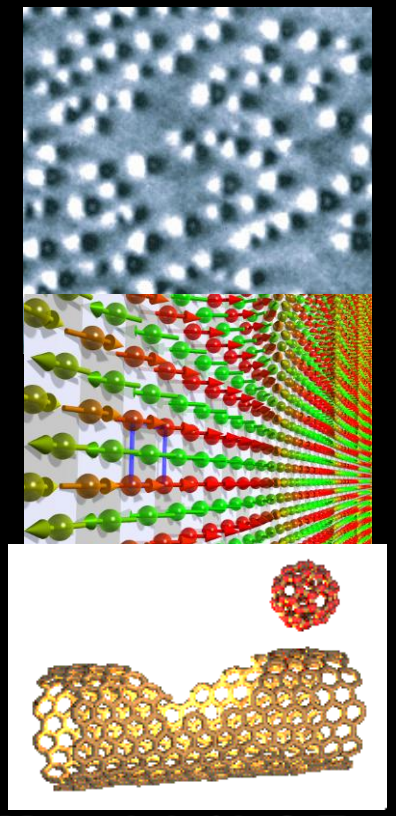
HPC Drives Science through Simulation



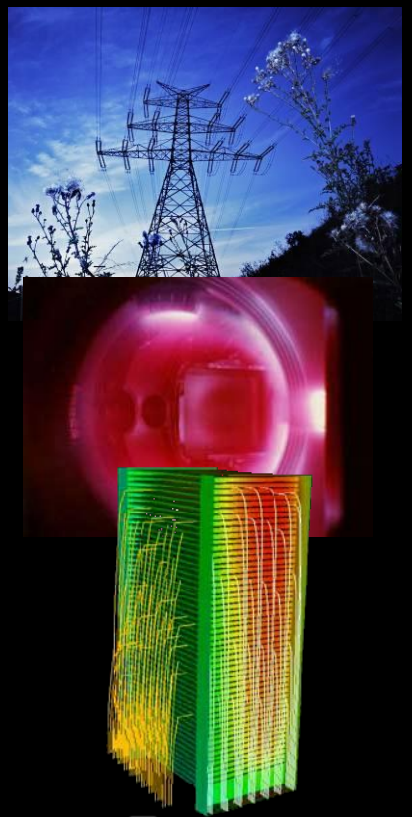
Environment
Weather/ Climatology
Pollution / Ozone Hole



Finding Cures
Medicine
Biology

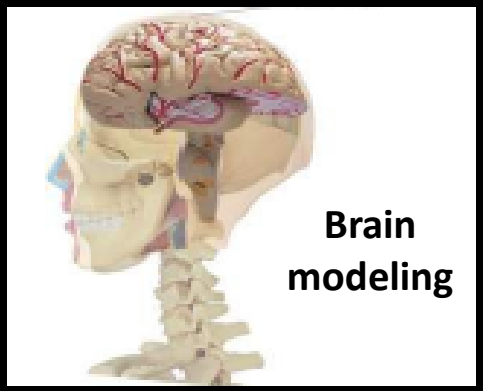


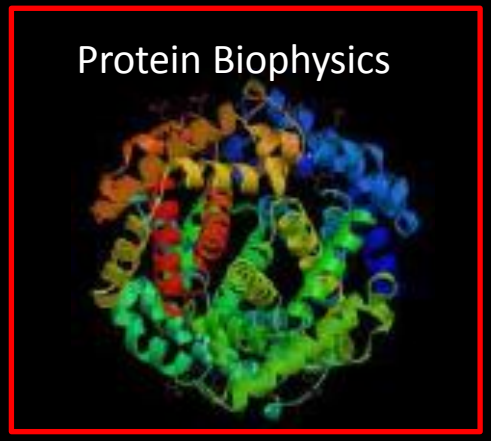
Materials/ Inf. Tech
Spintronics
Nano-science

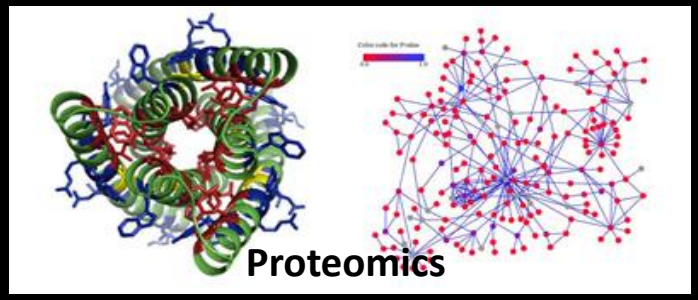


Energy
Plasma Physics
Fuel Cells

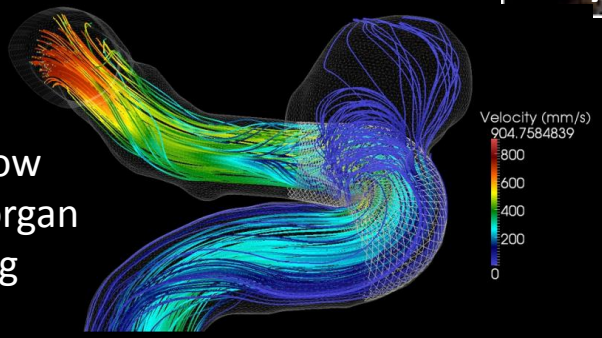
Key areas of biomedical research where HPC is key

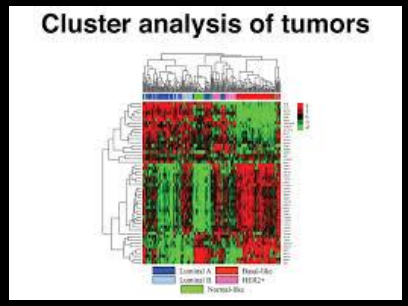






Blood flow
Whole organ modeling





Computing is transforming biomedical research

Exascale

Compute Power

time

HP 735
12 CPUs

SGI Origin
128 CPUs

LeMieux
3k CPUs

Ranger
60k CPUs

LCF
Mira 786k cores
Titan 280k cores
+ GPUs

1993
protein
10k atoms
100s ps

1997
ion
channel
100k atoms

2002
ATPase
500k
atoms

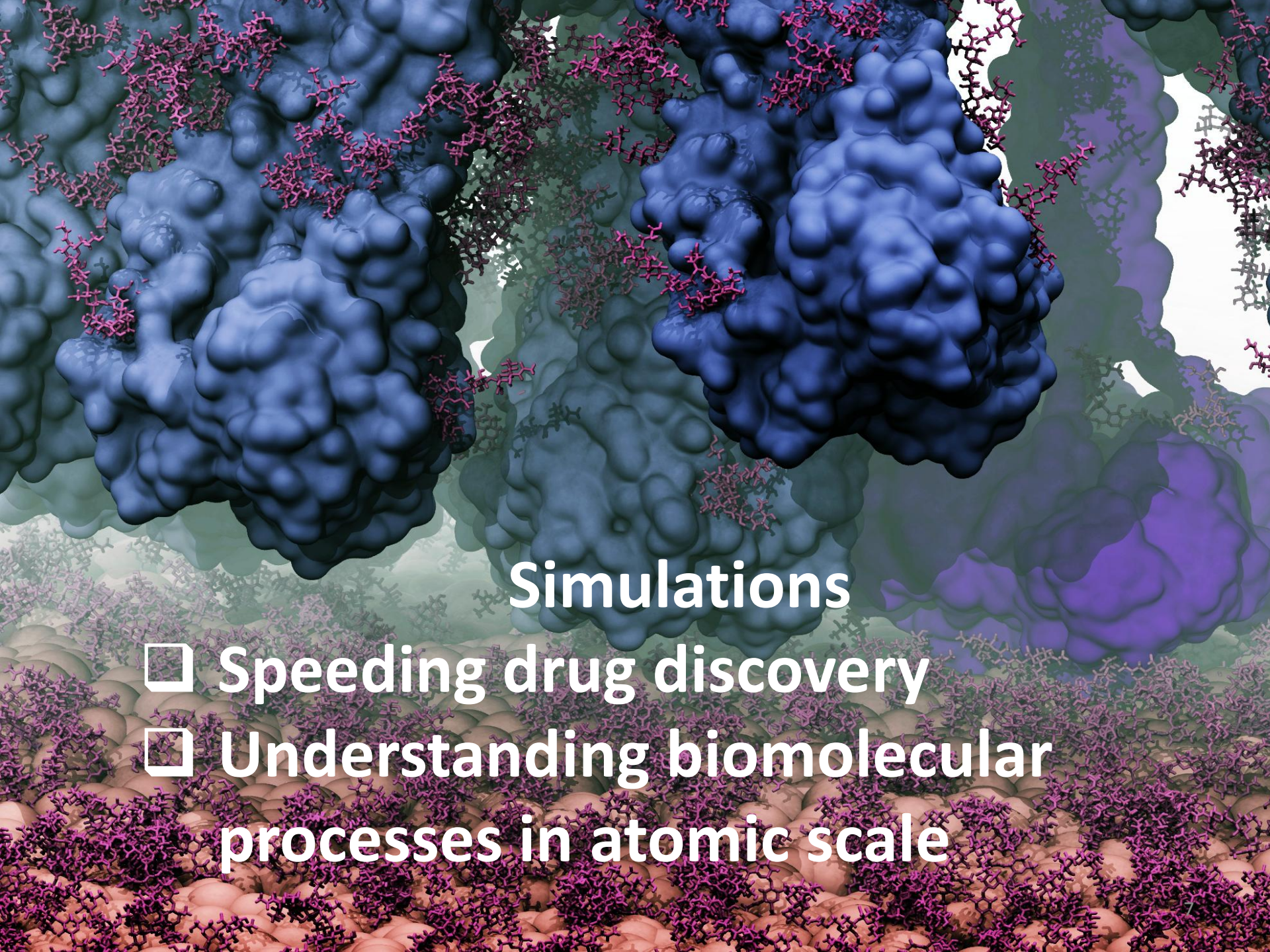
2007
ribosome
2 mil atoms
100s ns

2015
Enveloped virus
200 mil+ atoms
1-100 μs

Performance (in FLOPS):

Megaflop	10^6
Gigaflop	10^9
Teraflop	10^{12}
Petaflop	10^{15}

Source: adapted from Prof. Rommie Amaro

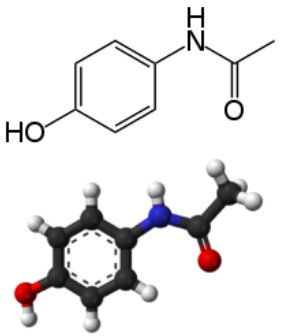

Simulations
❑ Speeding drug discovery
❑ Understanding biomolecular processes in atomic scale

Drugs block or activate diseased proteins

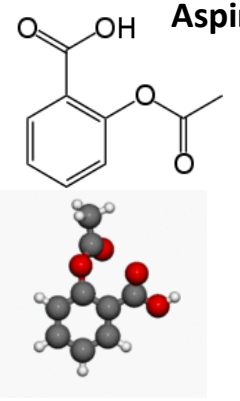
Normally they are small organic molecules

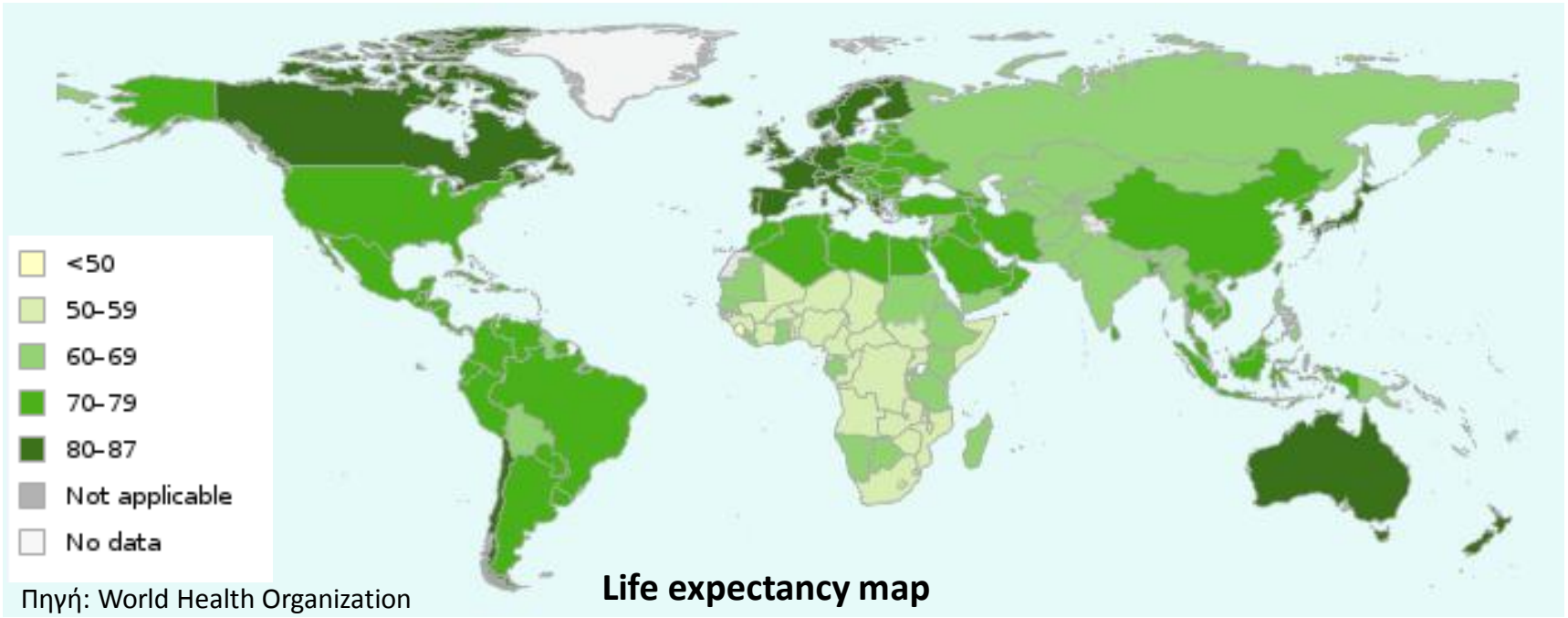
- **Therapy**
- **Relief**
- **Prevention**
- **Quality of life improvement**
- **Life expectancy prolongation**

Paracetamol (Depon)



Aspirin



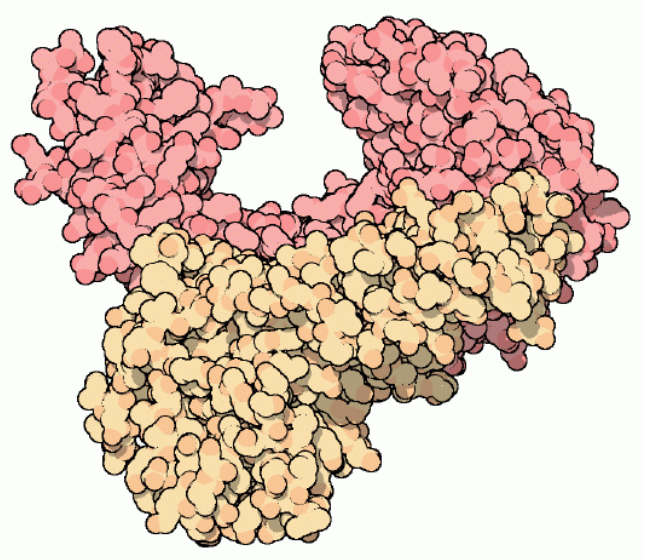


Πηγή: World Health Organization

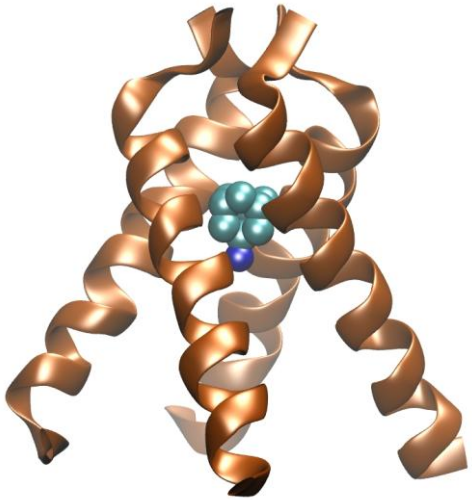
Life expectancy map

Some proteins need to be stopped

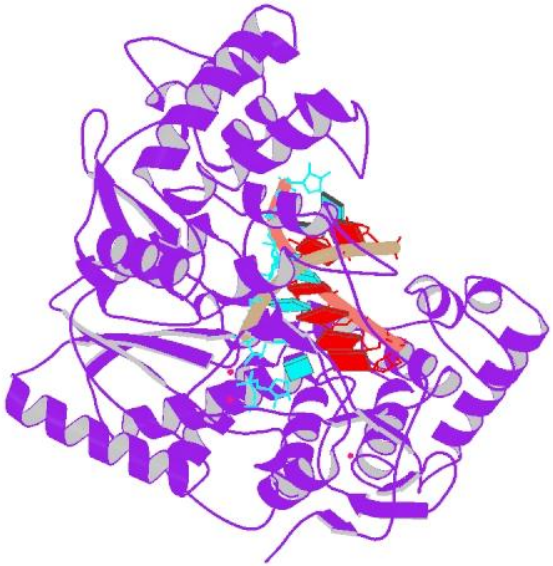
HIV-RT



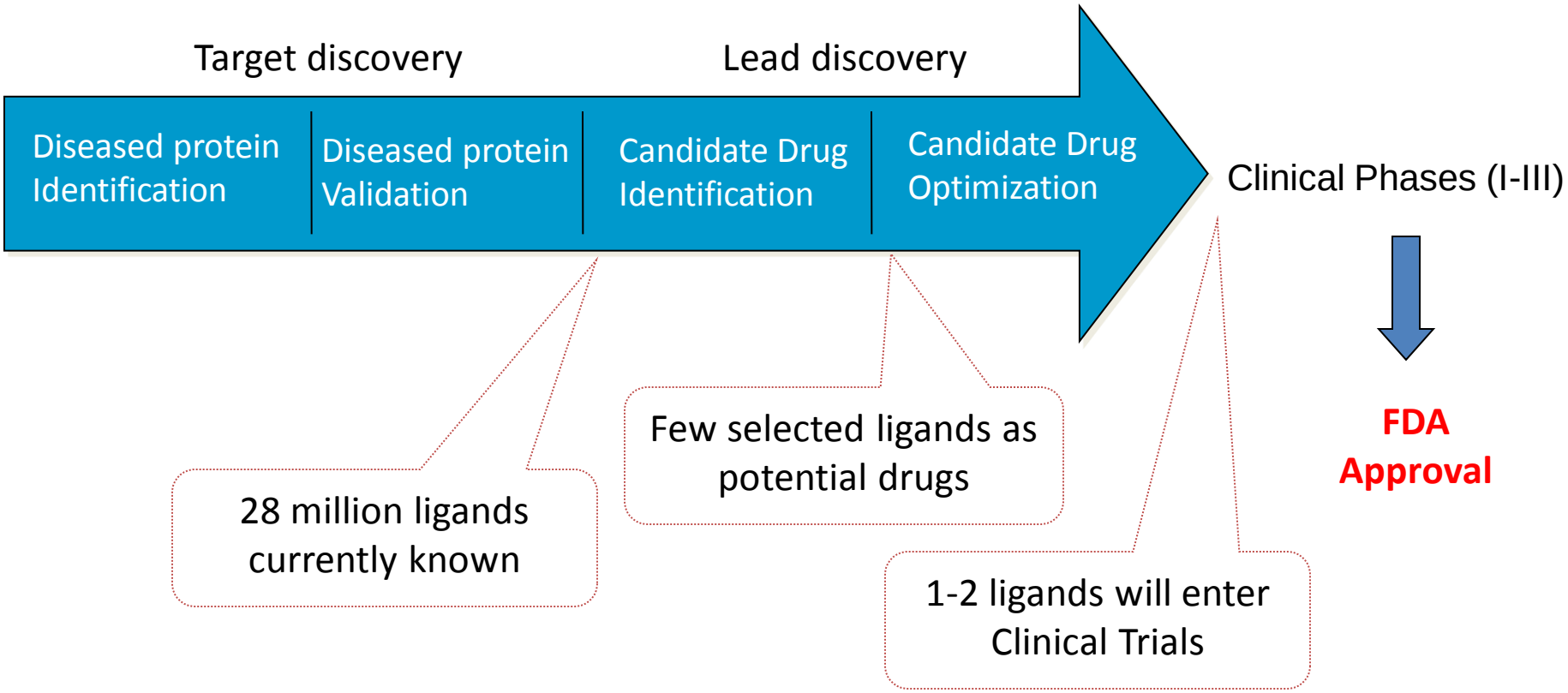
M2TM
(Influenza virus)



NS5B
(Hepatitis C)



Phases of Pharmaceutical Development



Duration: 12 – 15 years, Cost: ~ 1 billion US $

Traditional Drug Discovery

- Random screening of hundreds of thousands of molecules with High Throughput Screening (HTS) for combating the pathogen
- Random discoveries (i.e. penicillin, viagra)
- Trying out existing drugs and modifications

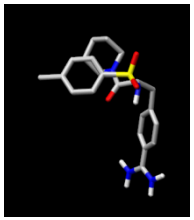
- Estimated number of small molecules that can act as drugs 10^{66}
- Estimated number of atoms in the world 10^{50}

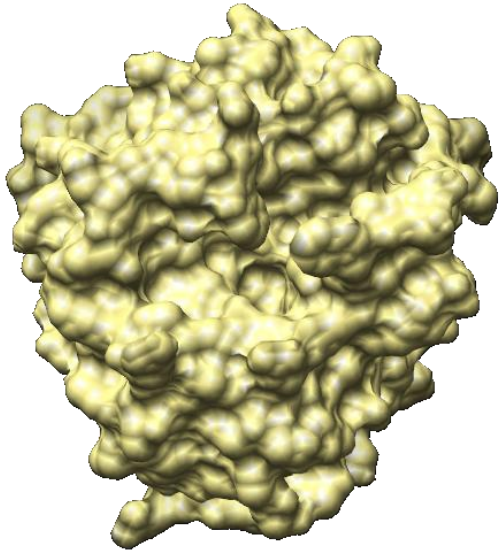
Structure-based approaches + Targeted Therapy

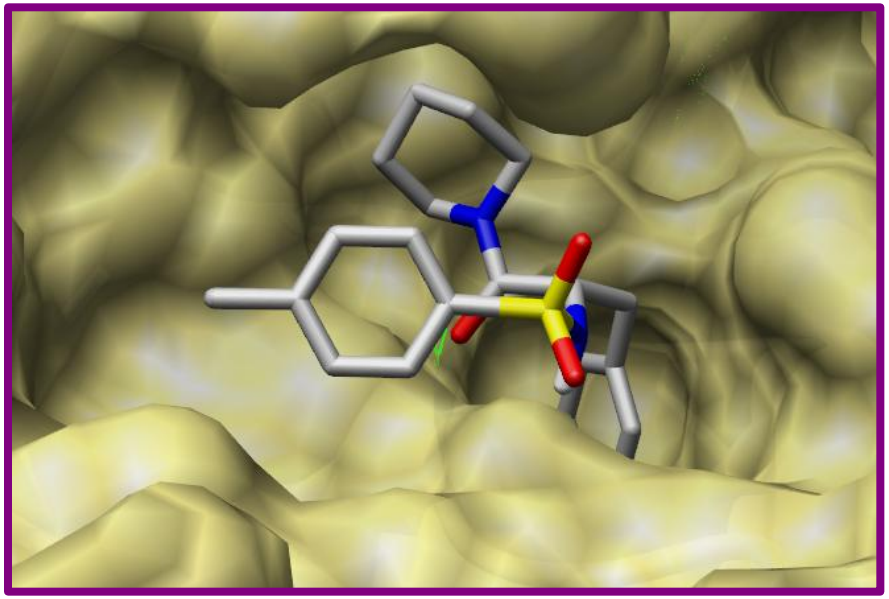
Rational Drug Discovery

- **Identify important genes for a diseases**
- **Targeting/inactivating genes (proteins) of the pathogen with small molecules = drugs**

TARGETED THERAPY!

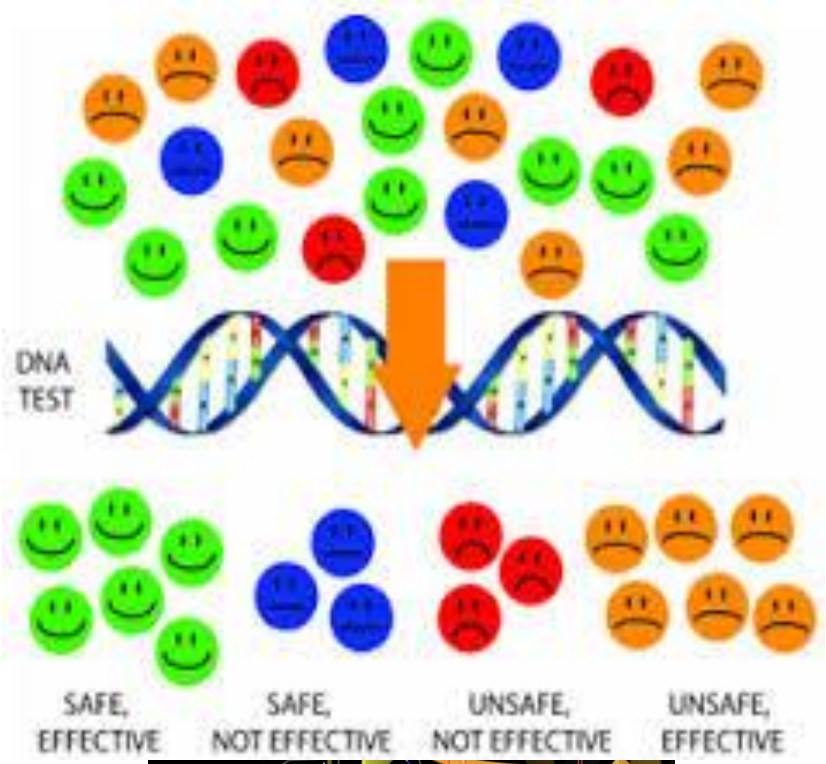






Curr Opin Drug Discov Devel. 2002 May; 5(3): 355–360

The era of Personalized Medicine



Lung Cancer

↓

genotyping

↓

4% of patients with

non-small cell lung carcinoma

Rearrangement in **ALK protein**

↓

carcinogenesis

↓

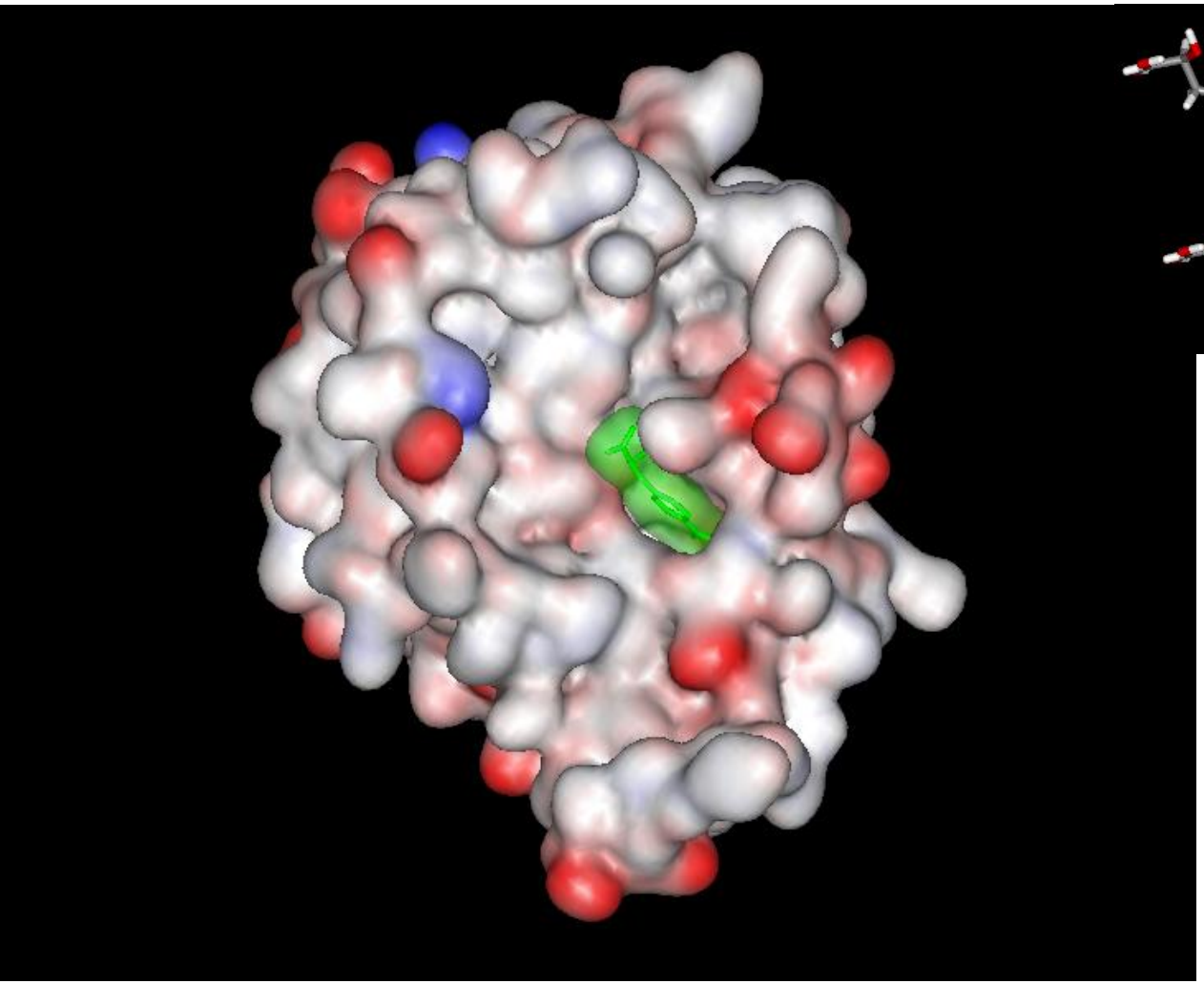
Drug design for this specific subset of patients

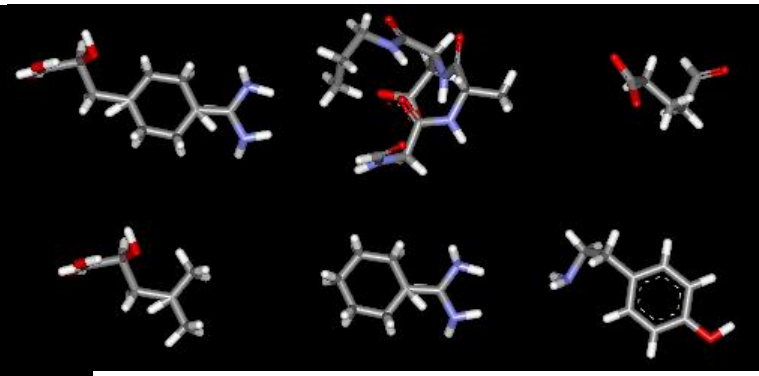
↓

Crizotinib for ALK+

lung cancer patients

Computing protein-drug structure





Virtual Screening

https://www.youtube.com/watch?v=u49k72rUdyc

My early days: HP-SEE (2010-2012)

Existing infrastructure – Blue Gene/P

HP-SEE
High-Performance Computing Infrastructure for South East Europe's Research Communities

- IBM Blue Gene/P –**two racks**, 2048 *PowerPC 450processors (32 bits, 850 MHz), a total of* ***8192 cores***
- Double-precision, dual pipe floating-point acceleration on each core;
- A total of **4 TB** random access memory;
- 16 I/O nodes currently connected via fiber optics to 10 Gb/s Ethernet switch;
- Theoretical peak performance: Rpeak= **27.85 Tflops;**
- **Energy efficiency: 371.67 MFlops/W Green top 10**

- Smaller HPC machines in **Romania**, **Bulgaria**, **Hungary**
- Upcoming purchases in **Hungary**, **Serbia** and **Greece**

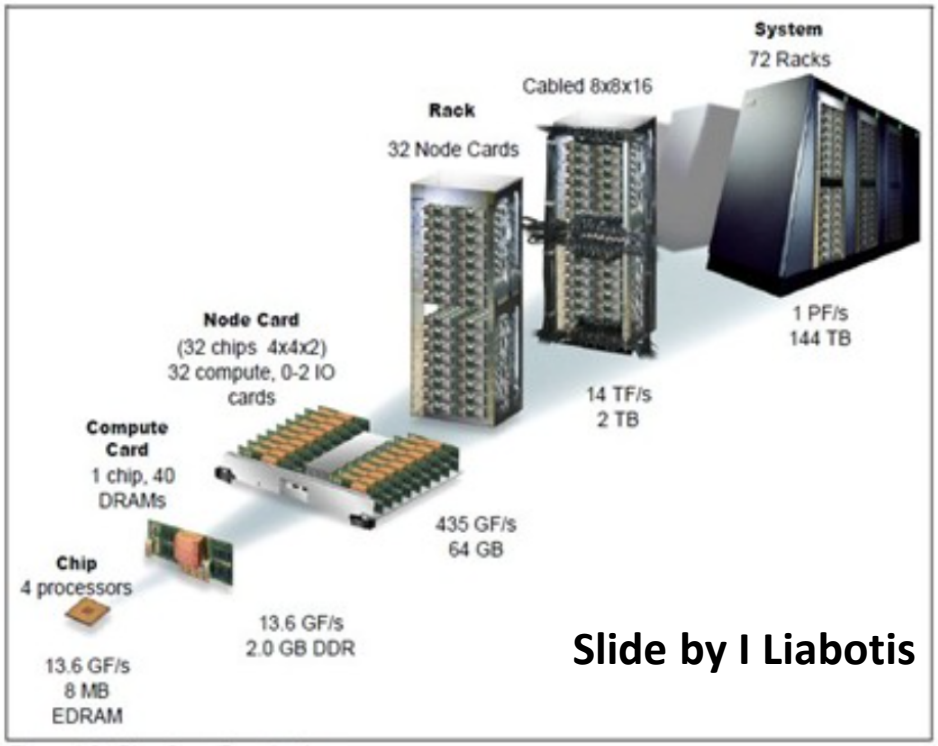
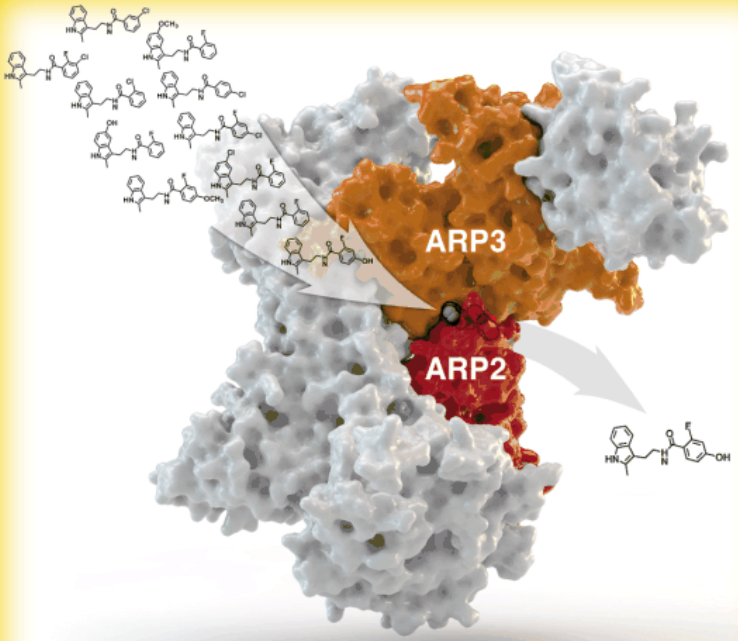


Figure 1-2 Blue Gene/P packaging

Slide by I Liabotis

CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY



7/2012

A Journal of ChemPubSoc Europe

The inside cover picture shows the optimization of a small-molecule inhibitor of Arp2/3 complex, a seven-subunit 225 kD protein that nucleates branched actin filaments. The X-ray structure of the complex bound to a known inhibitor, CK-666, was solved, and computational, synthetic, and biochemical methods were used to generate a novel inhibitor with improved potency—an important tool compound for dissecting the cellular functions of Arp2/3 complex. For more details, see the Full Paper by Brad J. Nolen et al. on p. 1286 ff.

www.chemmedchem.org

WILEY-VCH

JCTC Journal of Chemical Theory and Computation

Article

pubs.acs.org/JCTC

Free Energy Calculations Reveal the Origin of Binding Preference for Aminoadamantane Blockers of Influenza A/M2TM Pore

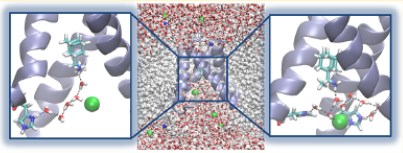
Paraskevi Gkeka,[†] Stelios Eleftheratos,[‡] Antonios Kolocouris,*[,‡] and Zoe Cournia*[,†]

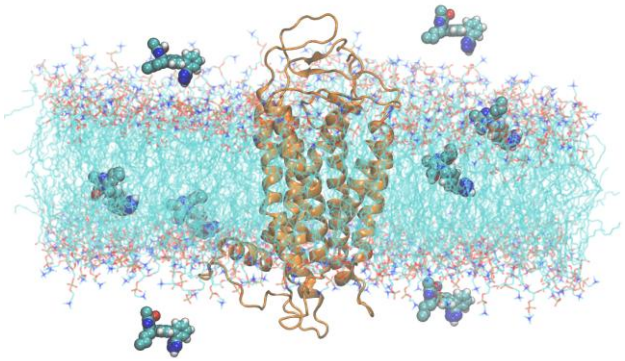
[†]Biomedical Research Foundation of the Academy of Athens, 4 Soranou Ephessiou, 11527 Athens, Greece

[‡]Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupolis-Zografou, 15771 Athens, Greece

Supporting Information

ABSTRACT: Aminoadamantane derivatives, such as amantadine and rimantadine, have been reported to block the M2 membrane protein of influenza A virus (A/M2TM), but their use has been discontinued due to reported resistance in humans. Understanding the mechanism of action of amantadine derivatives could assist the development of novel potent inhibitors that overcome A/M2TM resistance. Here, we use Free Energy Perturbation calculations coupled with





Biochimica et Biophysica Acta 1838 (2014) 1031–1046

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Insights into the molecular basis of action of the AT_1 antagonist losartan using a combined NMR spectroscopy and computational approach

Maria Zervou [a,*], Zoe Cournia [b], Constantinos Potamitis [a], George Patargias [b], Serdar Durdagi [a,1], Simona Golic Grdadolnik [c,d], Thomas Mavromoustakos [a,e]

[a] National Hellenic Research Foundation, Institute of Biology, Medicinal Chemistry & Biotechnology, Vas. Constantinou 48, 11635 Athens, Greece
[b] Biomedical Research Foundation of the Academy of Athens, 4, Soranou Efesiou, 11527 Athens, Greece
[c] Laboratory of Biomolecular Structure, National Institute of Chemistry, Hajdrihova 19, POB 30, SI-1115 Ljubljana, Slovenia
[d] EN-FIST Centre of Excellence, Dunajska 156, SI-1000 Ljubljana, Slovenia
[e] Chemistry Department of National Capodistrian University, Zographou, Athens 15784, Greece

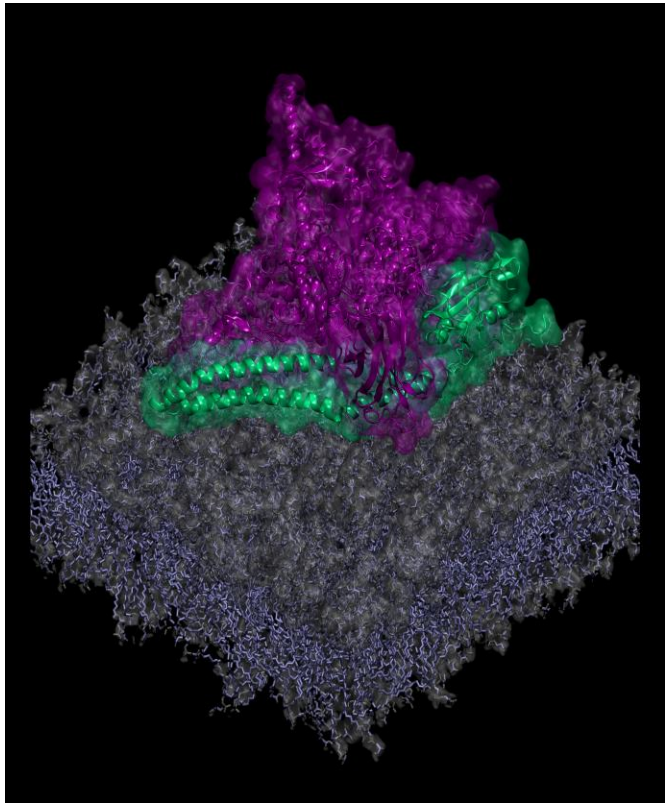
Through these publications was able to successfully apply for PRACE resources

PRACE-GR – ARIS: The Greek HPC System

Total: ~6 M core hours awarded (2014-2018)

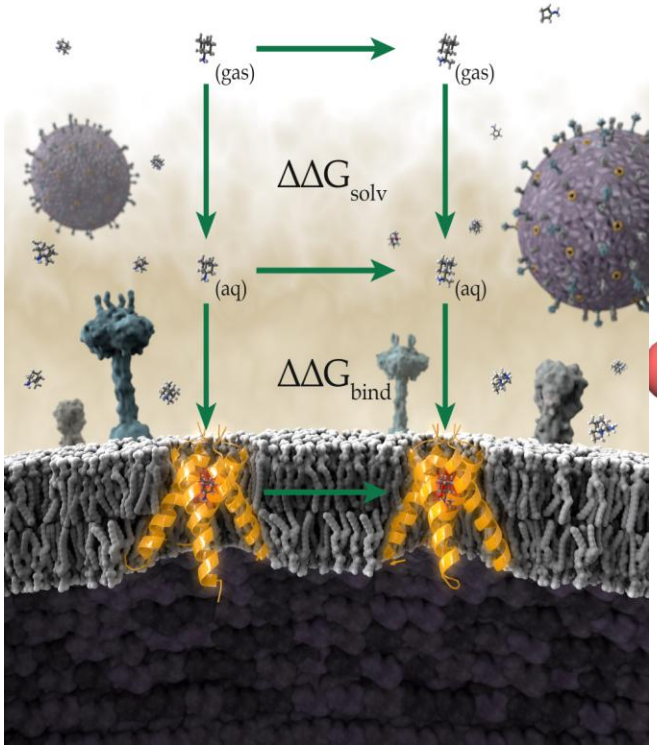
Protein-membrane interfaces in drug design

Peripheral Proteins



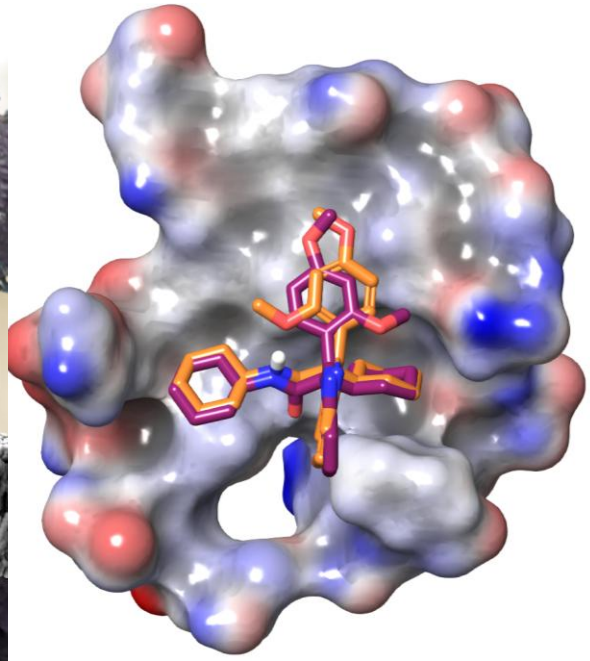
Leontiadou et al, Sci Rep, 2018
Gkeka et al, J Phys Chem B, 2015
Gkeka et al, PLOS Comp Biol, 2014

Ion Channels



Cournia et al, J Chem Inf Model, 2018
Gkeka et al, J Chem Inf Model, 2013
Ioannidis et al, J Chem Inf Model, 2016

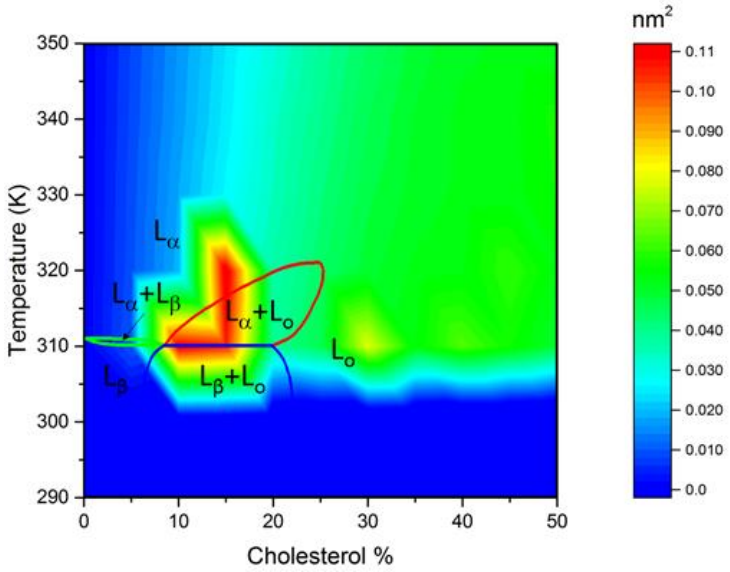
Drug Design



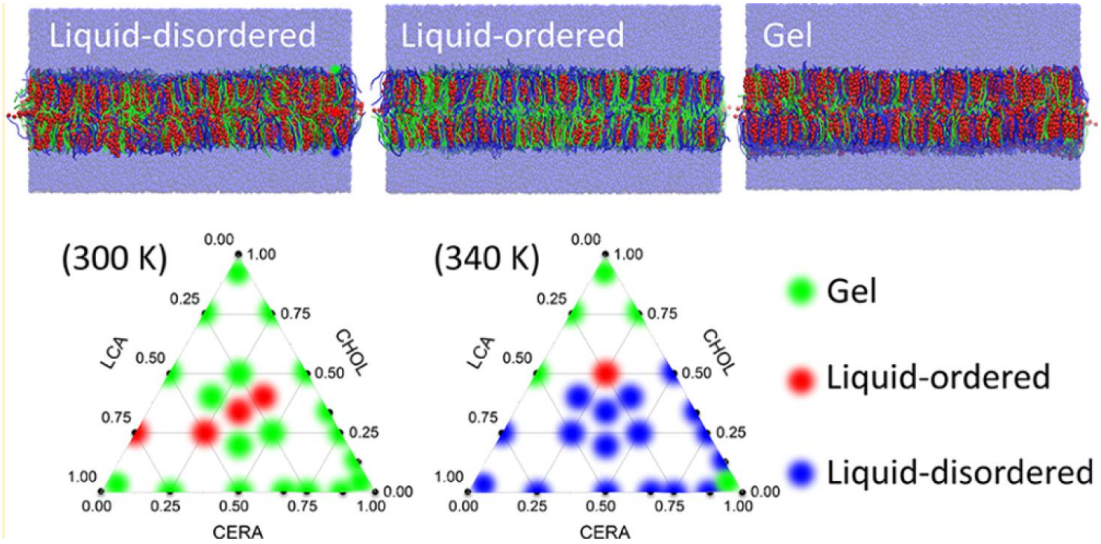
Athanasiou et al J Comput Aid Mol Des, 2018
Lionta et al, Curr Top Med Chem, 2014

Extensive studies of pure membranes

DDPC-Chol Phase Diagram

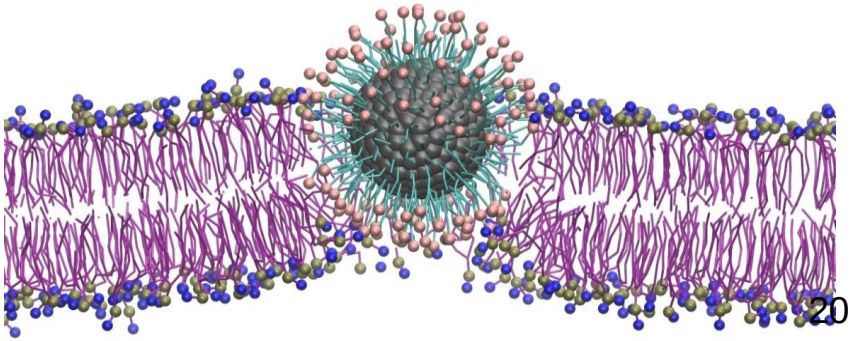


Stratum Corneum model phase diagram

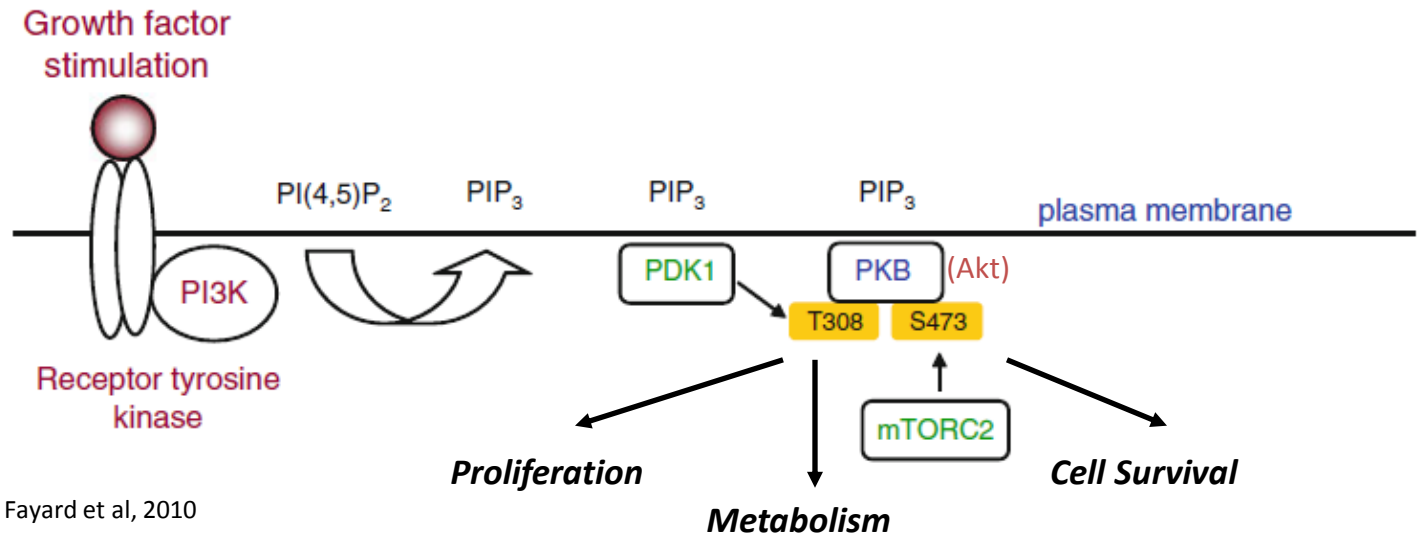


Podewitz et al, J Phys Chem B 2018
Chatzigoulas et al, J Chem Inf Model 2018
Tremi et al, J Memb Biol 2018
Wang et al, BBA Biomembranes 2016
Patitsa et al, Sci Rep 2017
Angelikopoulos et al, Nanoscale 2017
Cournia et al, J Memb Biol 2015
Gkeka et al, PLOS Comput Biol 2014

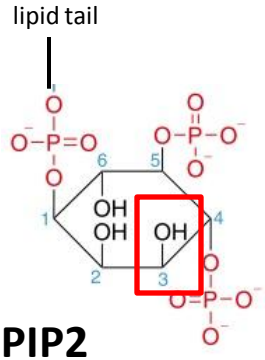
Nanocarrier – membrane interactions



PI3Kα is a lipid kinase that promotes cell survival



Fayard et al, 2010



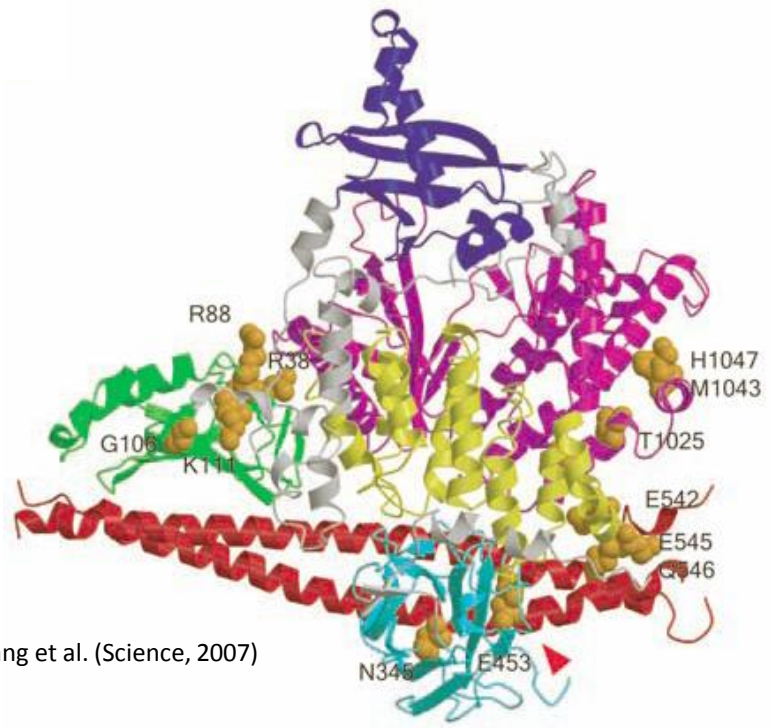
- Active PI3Ka phosphorylates PIP2 to PIP3 at the plasma membrane.

- PIP3 recruits Akt close to PDK1.

- Co-localization of these proteins leads to phosphorylation of residues, which in turn leads to proliferation, growth, survival.

Case study: mutated protein PI3Kα

- PI3Ka is a membrane-associated lipid kinase
- Involved in cell growth, proliferation, differentiation
- Most commonly mutated kinase in the human genome ⇒ cancer



Huang et al. (Science, 2007)

80% of all mutations:

Glu545Lys | His1047Arg

30% of breast cancer patients

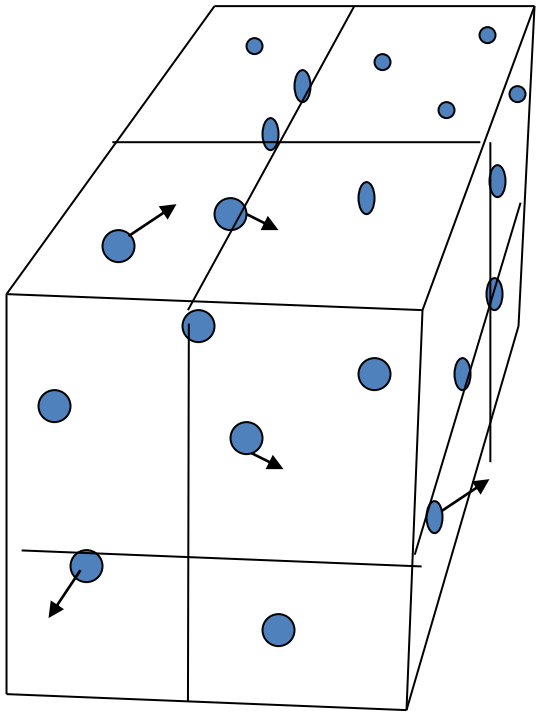
Mechanism of overactivation?

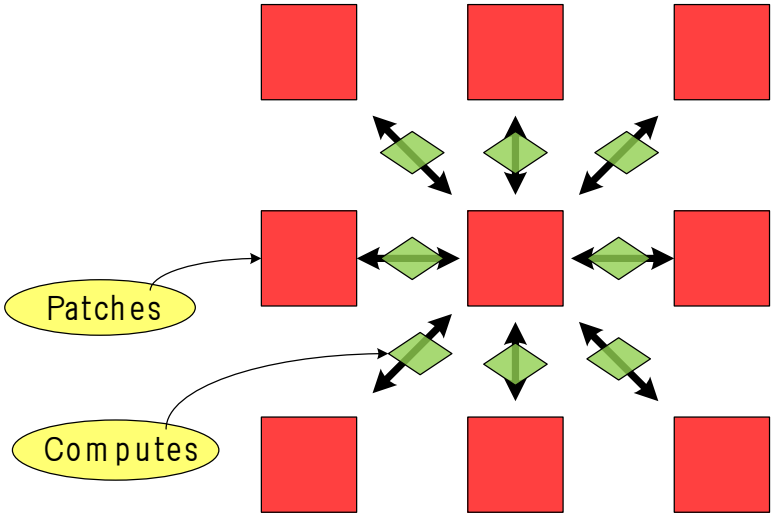
Mutant and isoform specific therapies?

MD Simulations
Virtual screening
Property prediction
***In vitro* & *In vivo* assays**
Lead Optimization

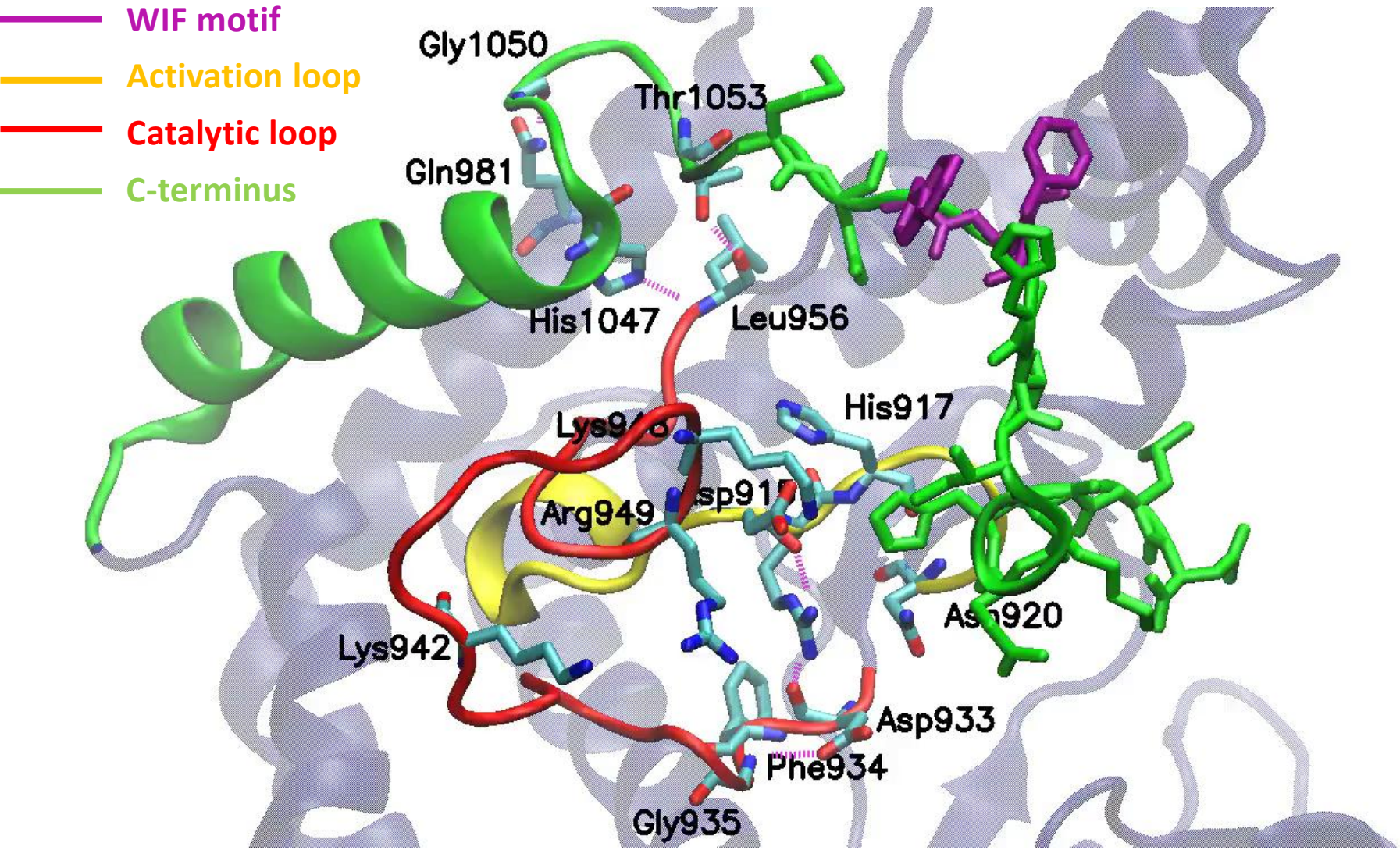
MD Simulator requirements

- **System size: ~400.000 atoms**
- Parallelization
- (getting an idea of the level of computation needed)
- Whole System is broken down into boxes (processing nodes)
- Each node handles the bonded interactions within a cutoff





Simulation of the normal protein



His-917 points away from the active site, while the C-terminus prevents the catalytic loop from reaching the ATP-binding site.

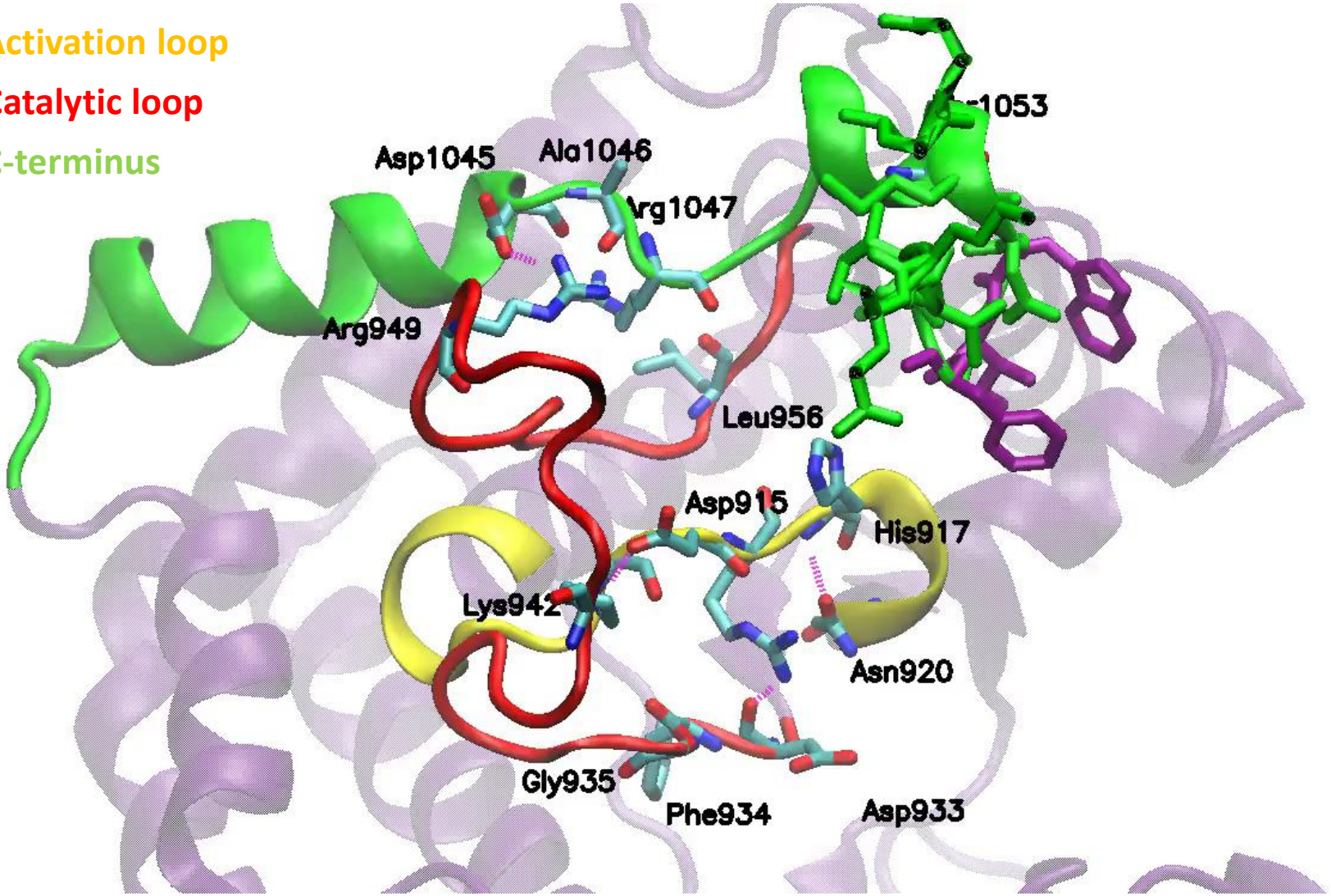
Simulation of the mutated protein

WIF motif

Activation loop

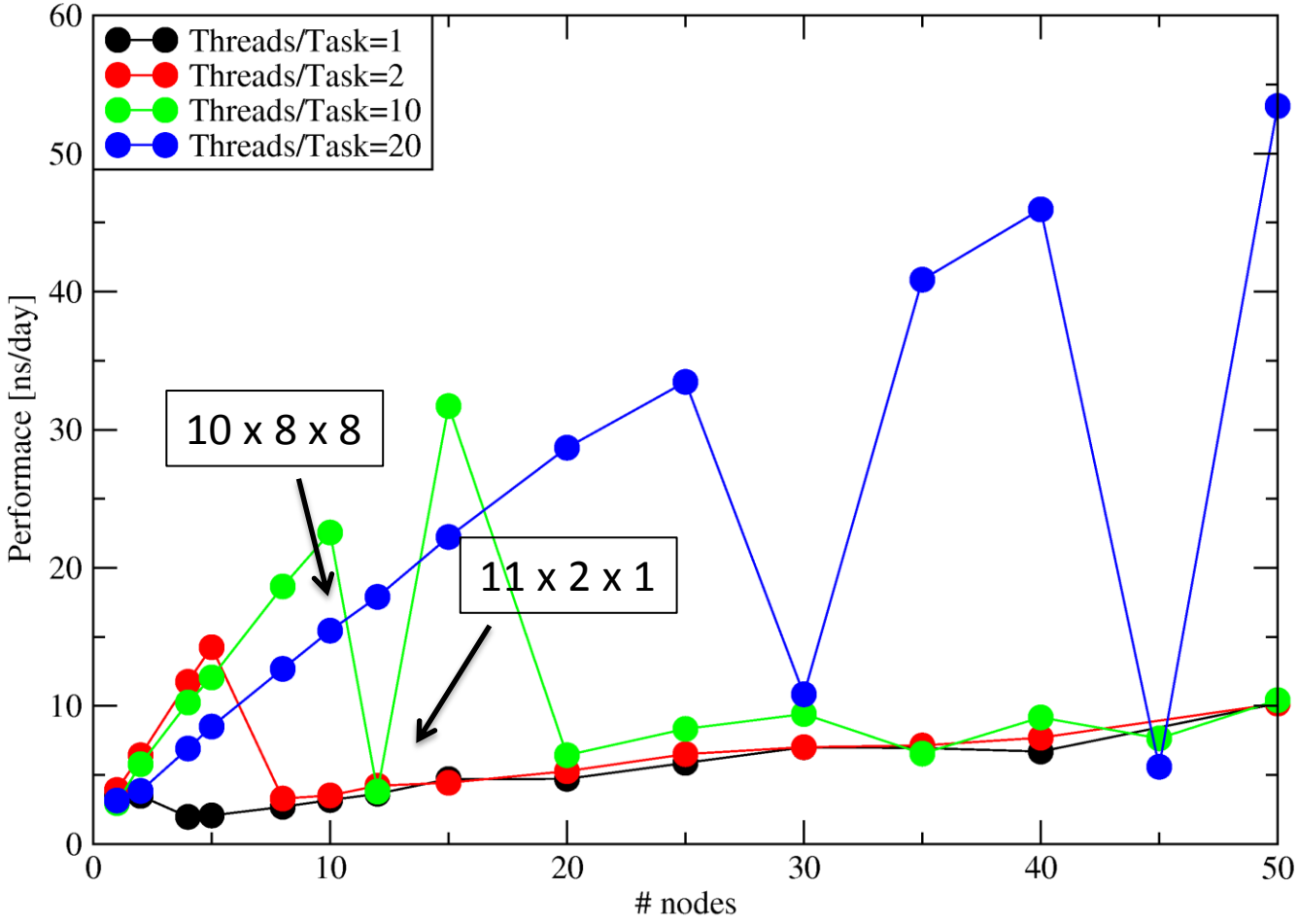
Catalytic loop

C-terminus



His-917 points towards the active site, while the C-terminus does not interfere with the access of the catalytic loop to the ATP-binding site.

GRNET HPC Support: Optimizing Performance

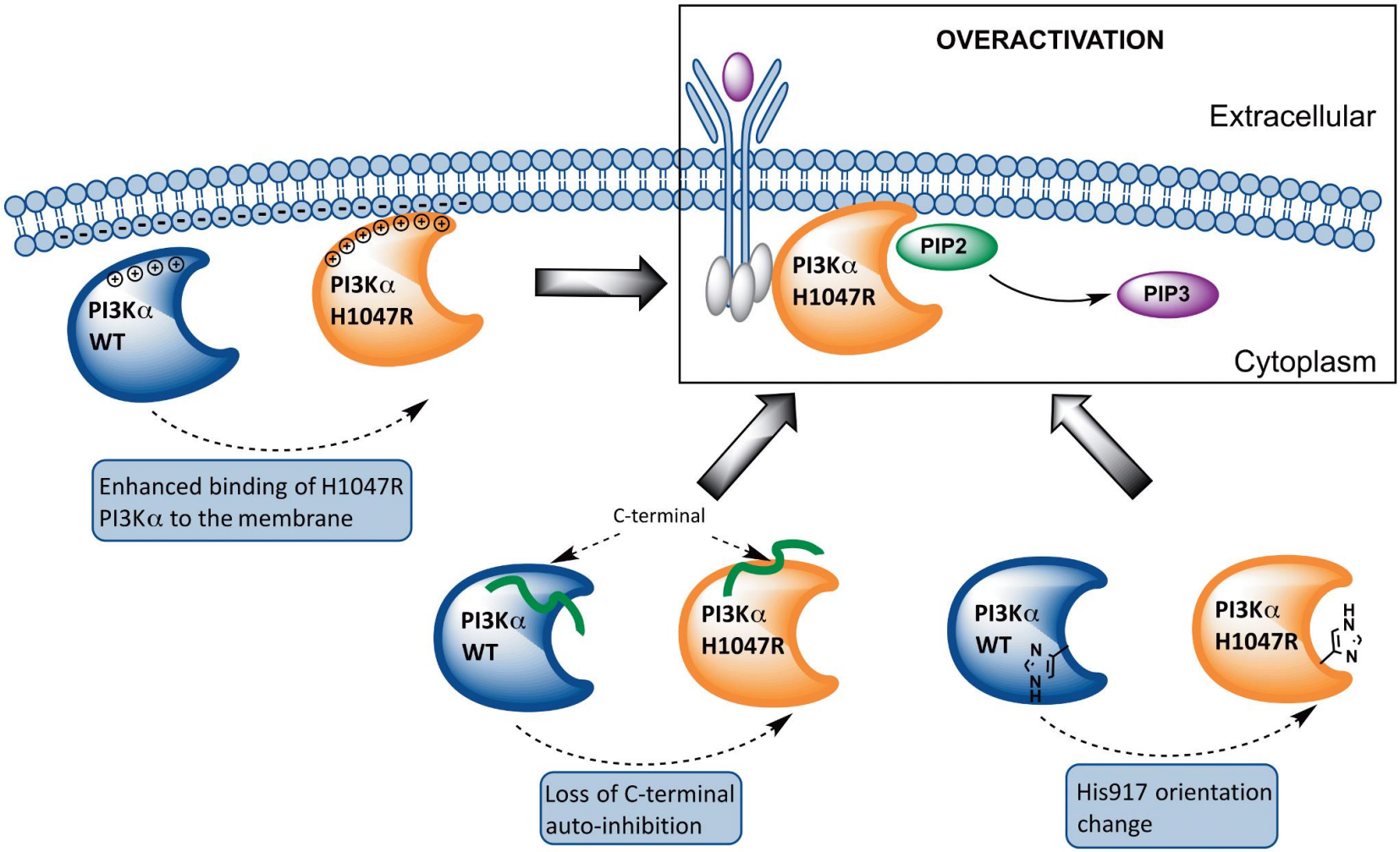


Dimitris Dellis
GRNET

PI3Kα
(400,000 atoms)

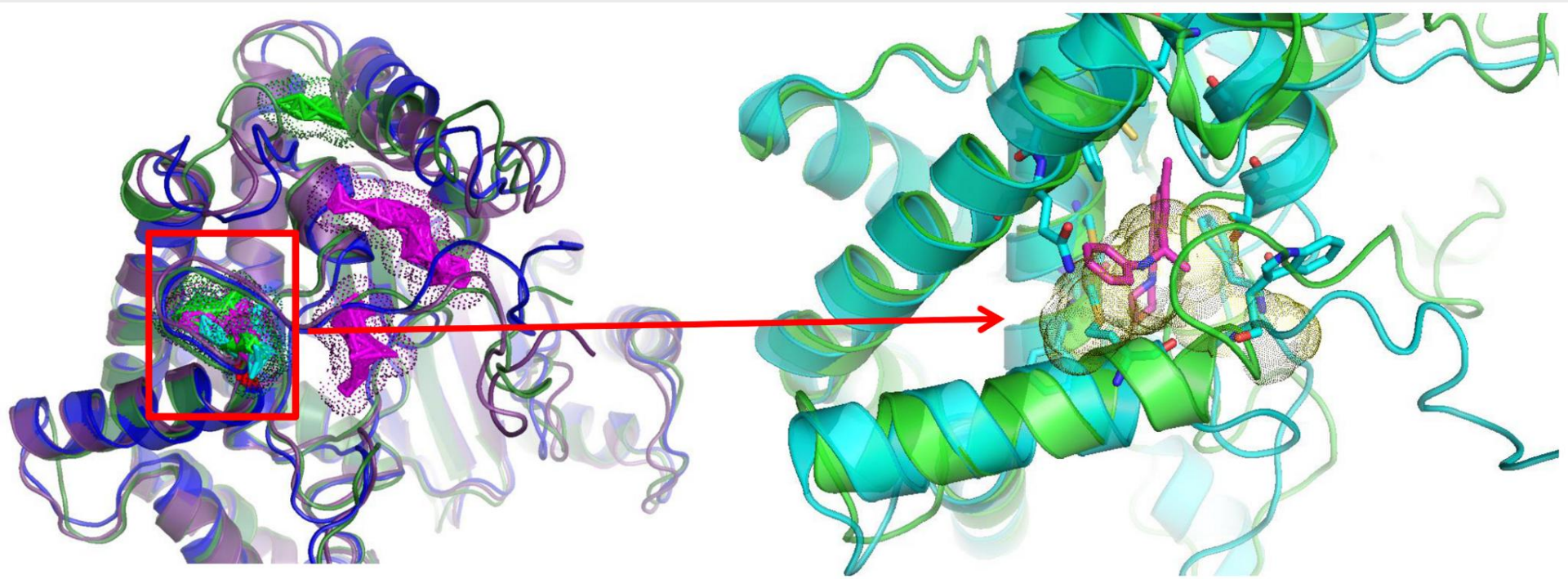
- **Both the communication and the box 3D decomposition** in cores has to be optimal in order to gain maximal performance.
- Decomposition 11 x 2 x 1 is **NOT optimal**
- Decomposition 10 x 8 x 8 is **optimal**

Proposed mechanism of H1047R overactivation



Gkeka et al, PLOS Comput Biol (2014)

Binding site identification on PI3Kα conformers



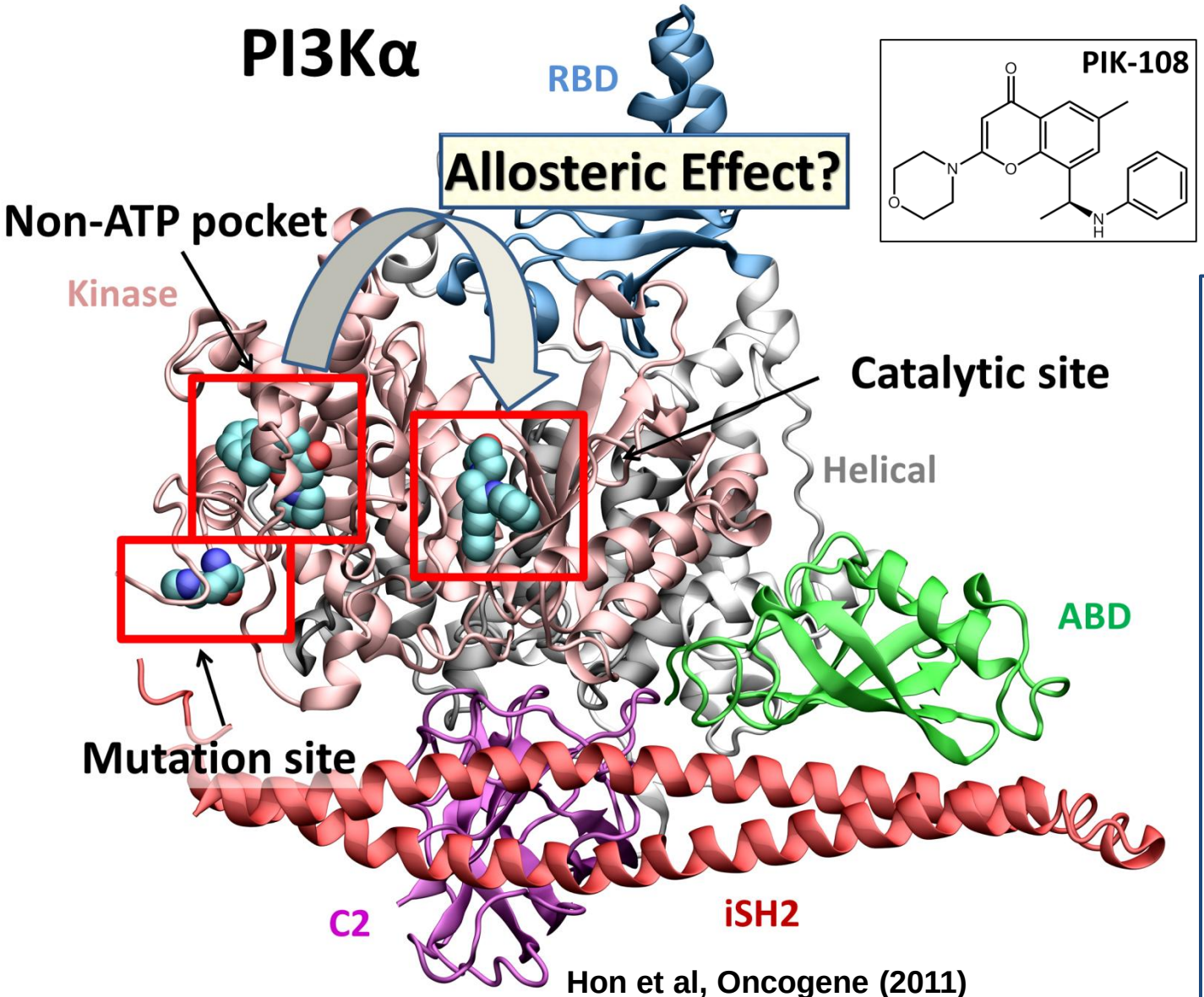
Binding site prediction on PI3Kα representative structures

Blue: WT Crystal Structure by Hon et al (2011)

Green: Cluster conformation from MD
Dots: Predicted binding site

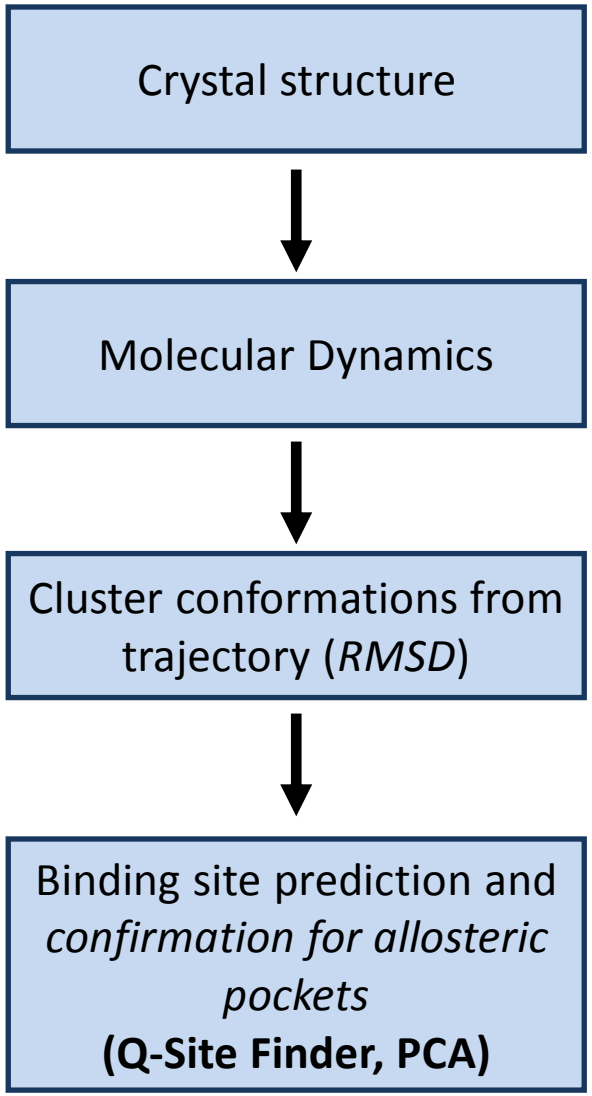
Does this binding site also exist in the mutant form and can it be exploited for selective drug design?

Mutant-specific drugs in “allosteric” pockets



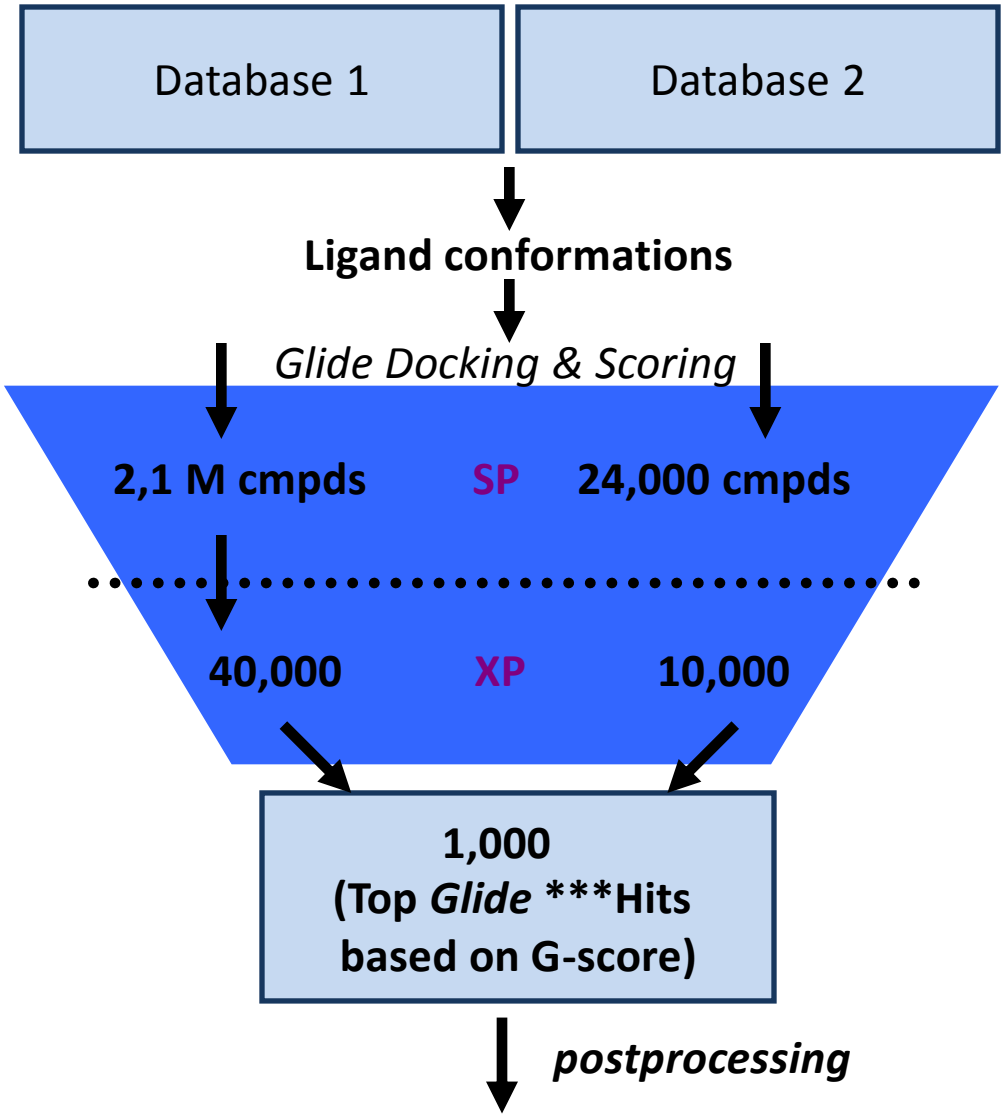
- Active site and non-ATP pocket occupied by **PIK-108**
- MD simulations of WT, H1047R apo and holo forms (100ns production run)
- Is the non-ATP pocket allosteric?
- **Can we discover allosteric pockets with simulations?**

Binding site Prediction



Lionta et al, *Curr Top Med Chem* (2014)

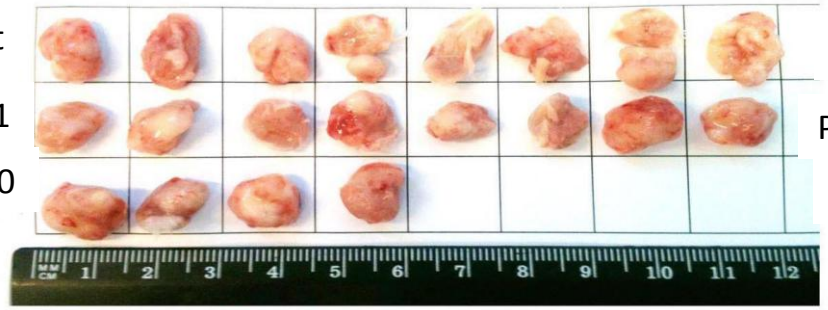
Virtual Screening



Preclinical study of PI3K-010 (xenografts)

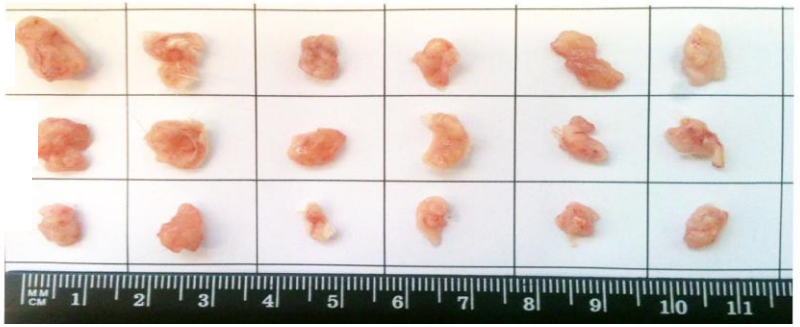
MDA-231-MB (PI3Kα WT)

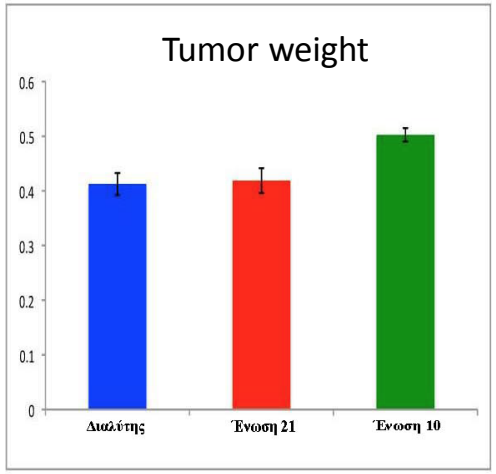
Solvent
PI3K-021
PI3K-010



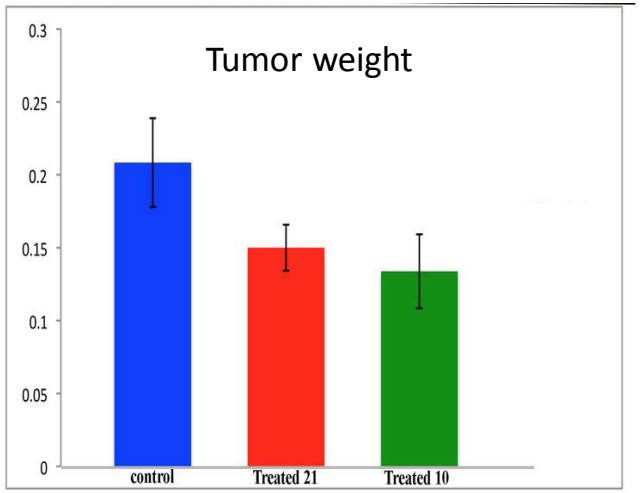
HCC1954 (H1047R PI3Kα mutant)

Solvent
PI3K-021
PI3K-010



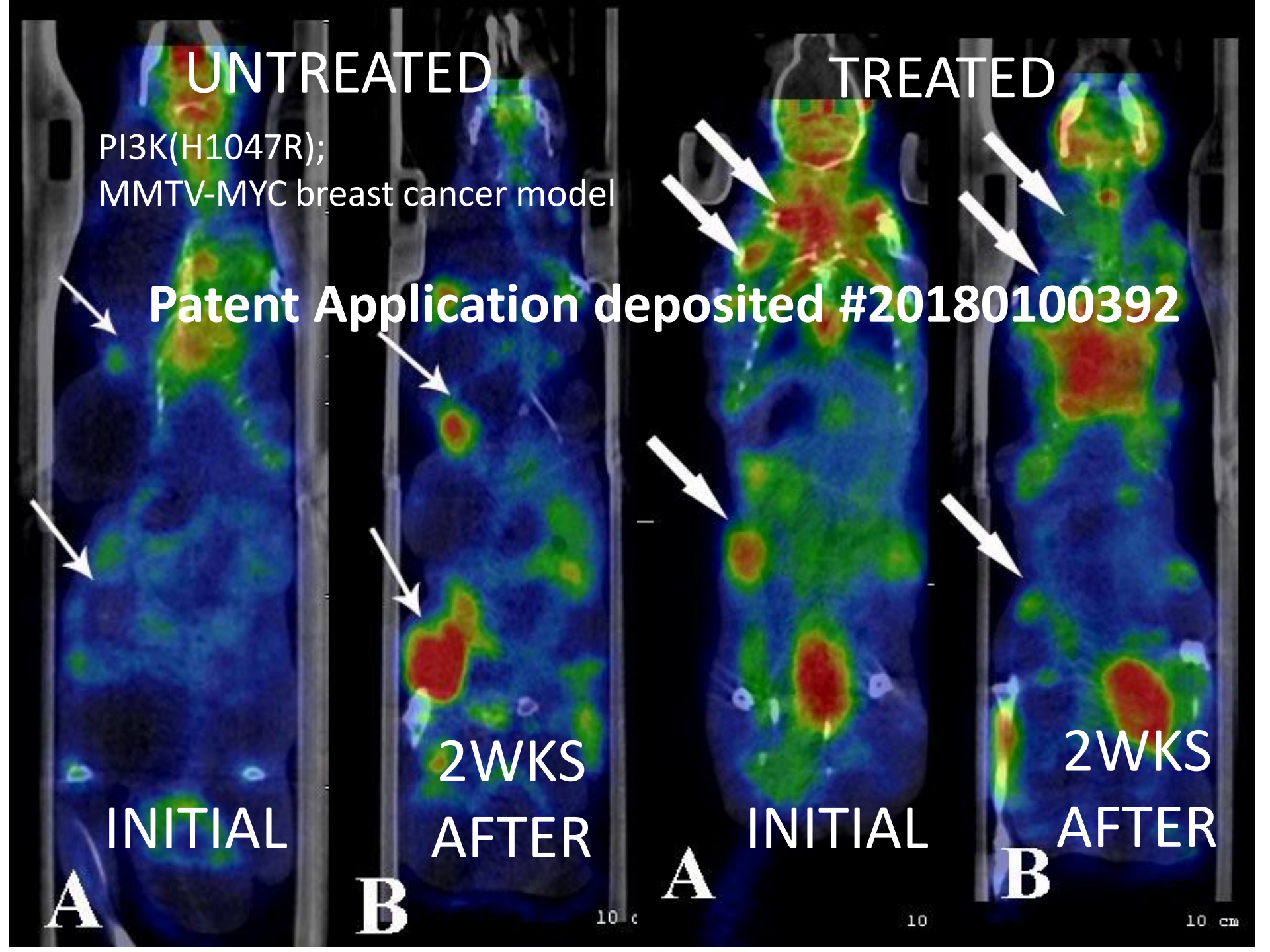


Solvent
PI3K-021
PI3K-010



(D. Stellas, Efstratiadis lab)

PI3K010 in corn oil following oral dosing in mice (100 mg/Kg).


UNTREATED
TREATED
PI3K(H1047R);
MMTV-MYC breast cancer model
Patent Application deposited #20180100392
INITIAL
2WKS AFTER
INITIAL
2WKS AFTER
A
B
A
B
10
10
10 cm

Recipient of the 1st PRACE Ada Lovelace Award

Nominated by I Liabotis (GRNET)
May 2016

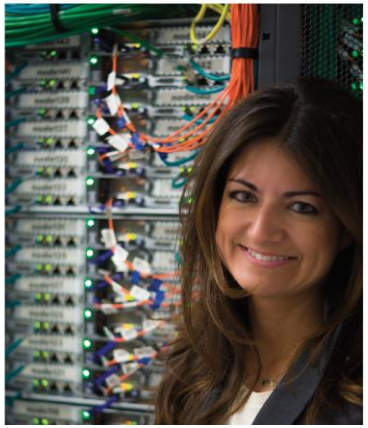
Home page » About PRACE » PRACE Awards » PRACE Ada Lovelace Award » Winner of the 1st PRACE Ada Lovelace Award for HPC

Winner of the 1st PRACE Ada Lovelace Award for HPC

Monday 2 May 2016

PRACE is proud to announce that Dr Zoe Cournia, a Computational Chemist, Investigator – Assistant Professor level at the Biomedical Research Foundation, Academy of Athens (BRFAA), Greece has been selected as the recipient of the 1st PRACE Ada Lovelace Award for HPC. The Award will be bestowed at PRACEdays16, (http://www.prace-ri.eu/pracedays16/) to be held 10-12 May 2016 in Prague. Dr Cournia was selected for her outstanding contributions and impact on HPC in Europe on a global level.

Dr Cournia was awarded core hours on PRACE resources as Principal Investigator for research on *Mechanistic studies of the Arp2/3 complex activation* and *Selective inhibition of the PI3Ka E545K mutant through MD simulations, in vitro assays and SPR experiments* in the 6th and 9th Project Access calls, she was also a collaborator on other projects in Nanotechnology and Clinical, Experimental Surgery & Translational Research.



LiFO 04.05.2016
HOME ΕΙΔΗΣΕ

Στην ερευνήτρια Ζωή Κούρνια το βραβείο «PRACE Ada Lovelace» για την ανάπτυξη αντικαρκινικών φαρμάκων

Η Ελληνίδα επιστήμονας είναι ερευνήτρια στο Ίδρυμα Ιατροβιολογικών Ερευνών της Ακαδημίας Αθηνών και ειδικεύεται στην Υπολογιστική Χημεία

4.5.2016 | 11:02

Με το πρώτο ευρωπαϊκό βραβείο «Prace Ada Lovelace», το οποίο βραβεύει γυναίκες επιστήμονες που αξιοποιούν τους υπερυπολογιστές στην έρευνά τους θα τιμηθεί η ερευνήτρια Ζωή Κούρνια για το έργο της πάνω στον σχεδιασμό αντικαρκινικών φαρμάκων και στις υπολογιστικές προσομοιώσεις βιομορίων. Η Ελληνίδα

VRE for regional Interdisciplinary communities in Southeast Europe and the Eastern Mediterranean

Vi-SEEM

Coordinator: GRNET (O. Prnjat)

Oct 2015 – Sep 2018

Life Sciences - Scientific Community

Dr. Zoe Cournia

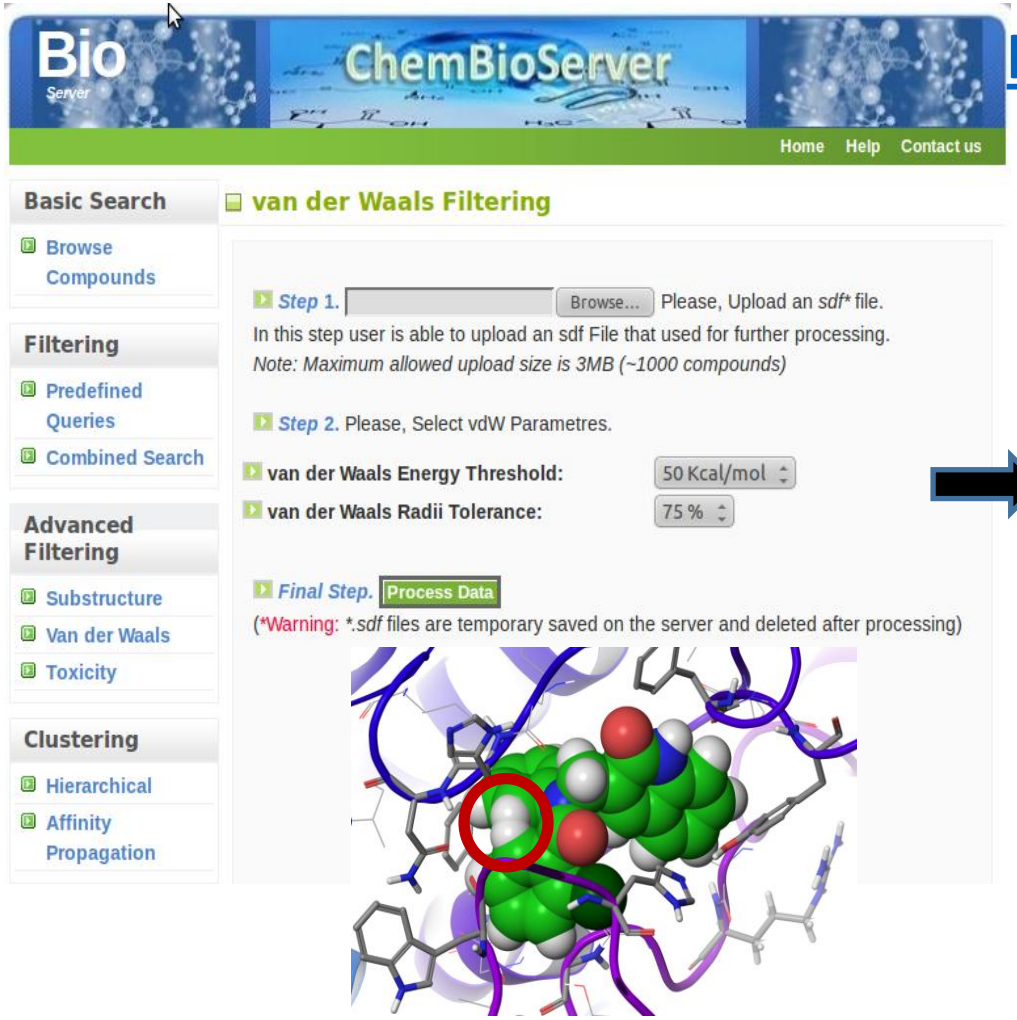
LS SC Leader

Biomedical Research Foundation, Academy of Athens

Web-server hosting of Application level services: ChemBioServer

- ChemBioServer post-processes virtual screening results for drug design

http://chembioserver.vi-seem.eu

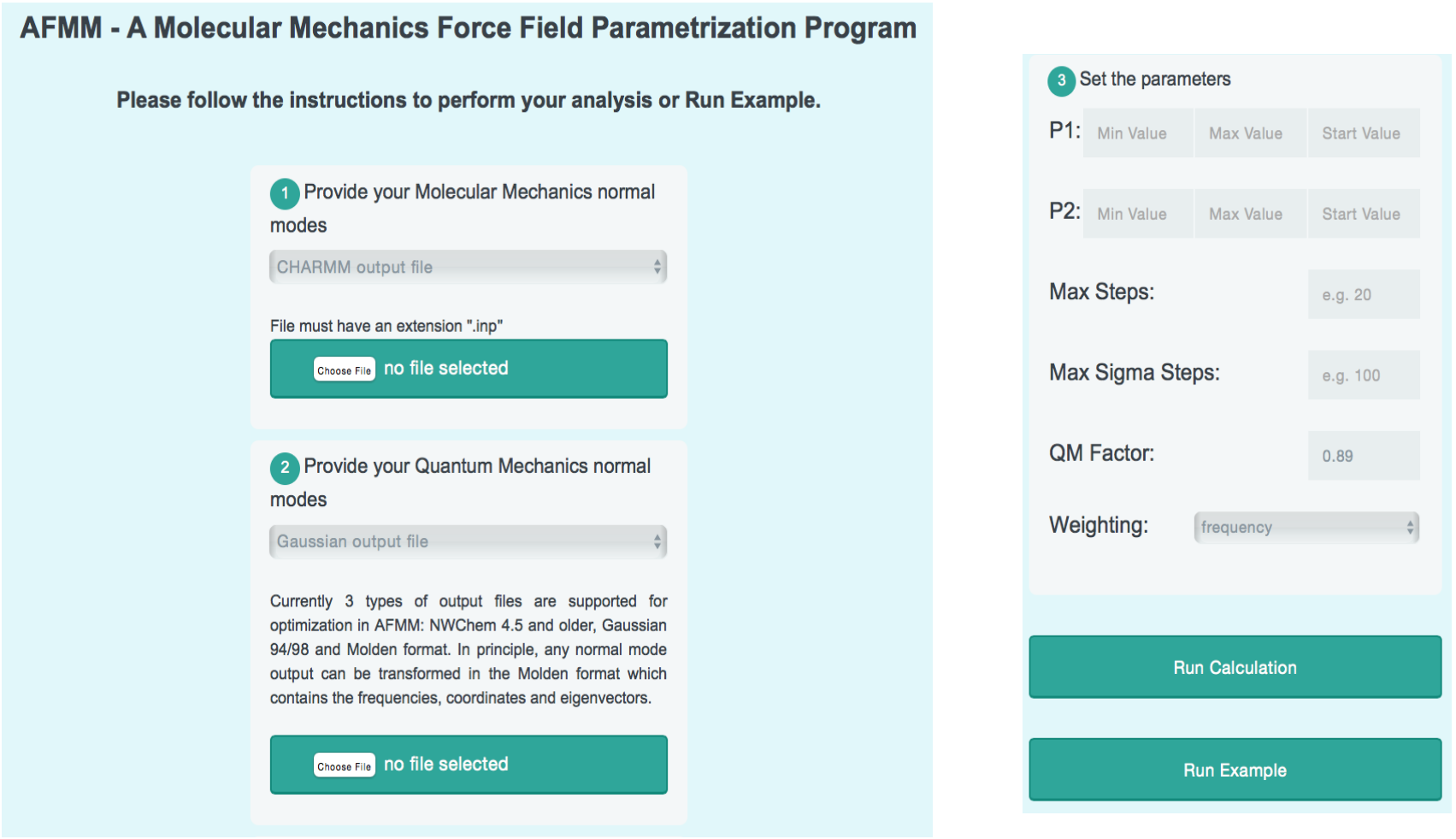


Compound ID	VDW Energy Test	VDW Distance Test
Compound: 1 AW 00785	- PASS AW 00785 - Browse List For Details...	- FAIL AW 00785 - Browse List For Details...
Compound: 2 AW 00788	- PASS AW 00788 - Browse List For Details...	- FAIL AW 00788 - Browse List For Details...
Compound: 3 AW 00785	- PASS AW 00785 - Browse List For Details...	- FAIL AW 00785 - Browse List For Details...
Compound: 4 AW 00939	- PASS AW 00939 - Browse List For Details...	- FAIL AW 00939 - Browse List For Details...
Compound: 5 AW 00694	- PASS AW 00694 - Browse List For Details...	- FAIL AW 00694 - Browse List For Details...
Compound: 6 CD 10205	- PASS CD 10205 - Browse List For Details...	- PASS CD 10205 - Browse List For Details...
Compound: 7 GK 02096	- PASS GK 02096 - Browse List For Details...	- FAIL GK 02096 - Browse List For Details...
Compound: 8 HTS 01561	- PASS HTS 01561 - Browse List For Details...	- FAIL HTS 01561 - Browse List For Details...
Compound: 9 MWP 00404	- PASS MWP 00404 - Browse List For Details...	- FAIL MWP 00404 - Browse List For Details...
Compound: 10 NRB 02577	- PASS NRB 02577 - Browse List For Details...	- FAIL NRB 02577 - Browse List For Details...

AFMM is a parameterization tool for MD simulations of small organic molecules

Vi-SEEM

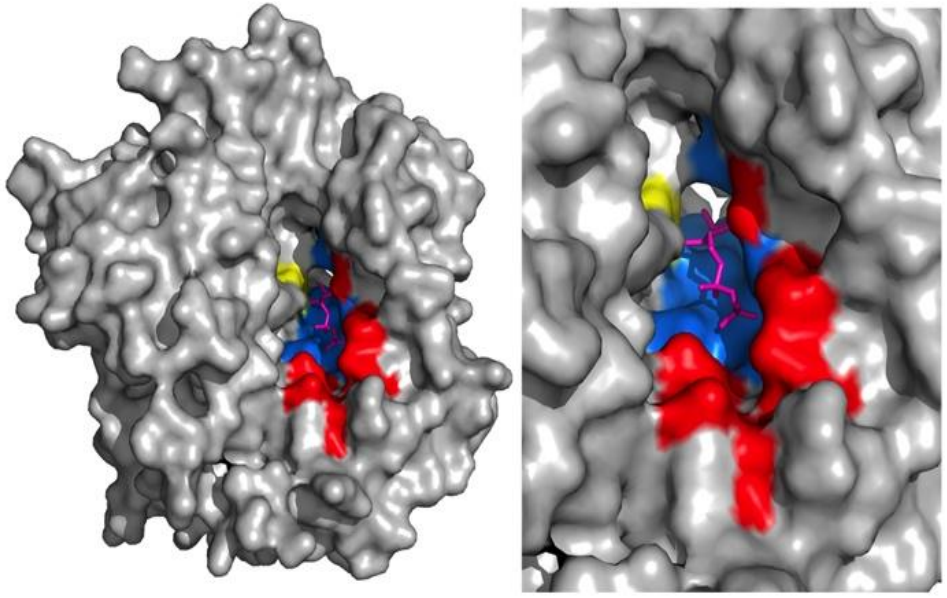
http://afmm.vi-seem.eu

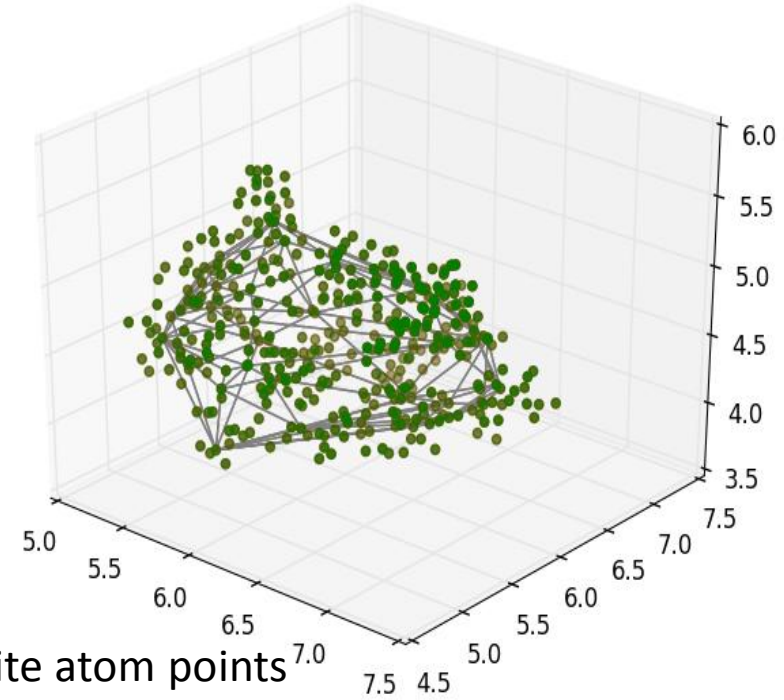


Subtract, a tool to measure the protein binding site volume

Vi-SEEM

http://subtract.vi-seem.eu





- Computes the 3D convex hull of protein binding site atom points
- Computes the volume of the convex hull and the volume of the atoms included in the solid based on their van der Waals radii.
- Subtraction of those two volumes yields the volume of the cavity.

Nanocrystal webserver: Creation of nanoparticles

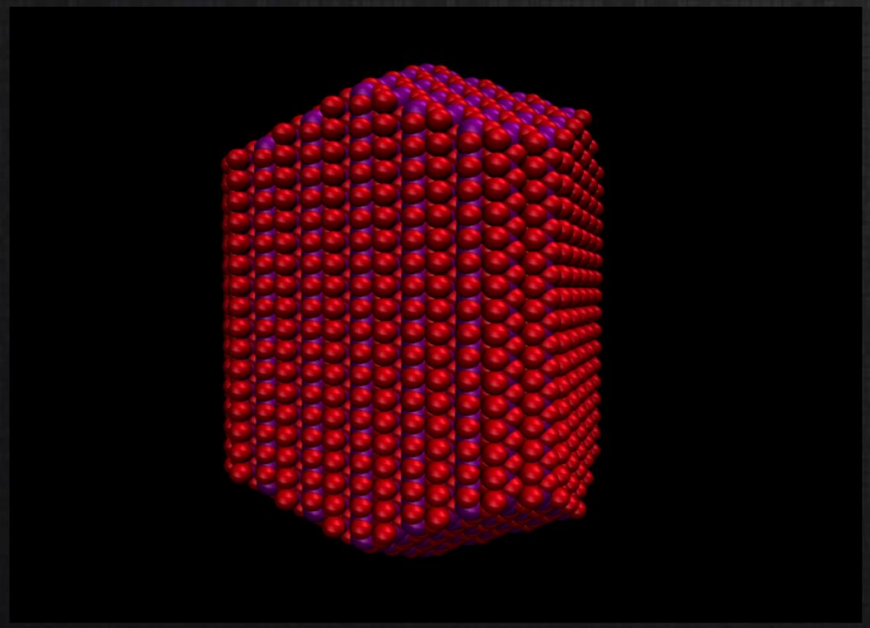
http://nanocrystal.vi-seem.eu

nanocrystal.vi-seem.eu

Meetings a... | In the News... | Exploring G... | Insights | Nanoparticl...

A crystallographic tool for the construction of nanoparticles

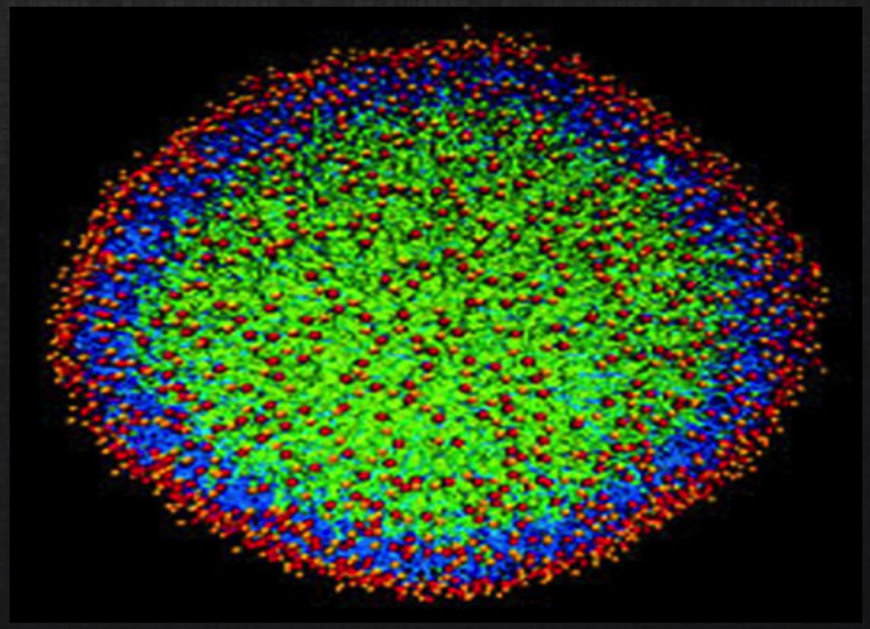
This tool constructs nanoparticles for simulation of any material and size.



Continue

A tool for the construction of spherical nanoparticles

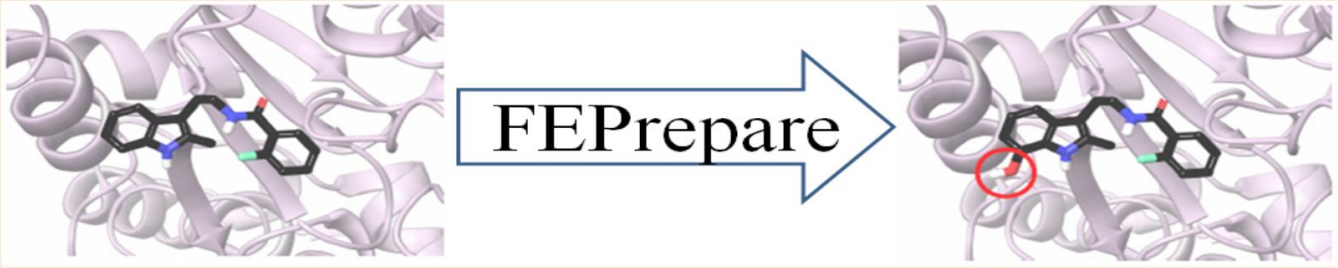
This tool constructs spherical nanoparticles of a given radius.

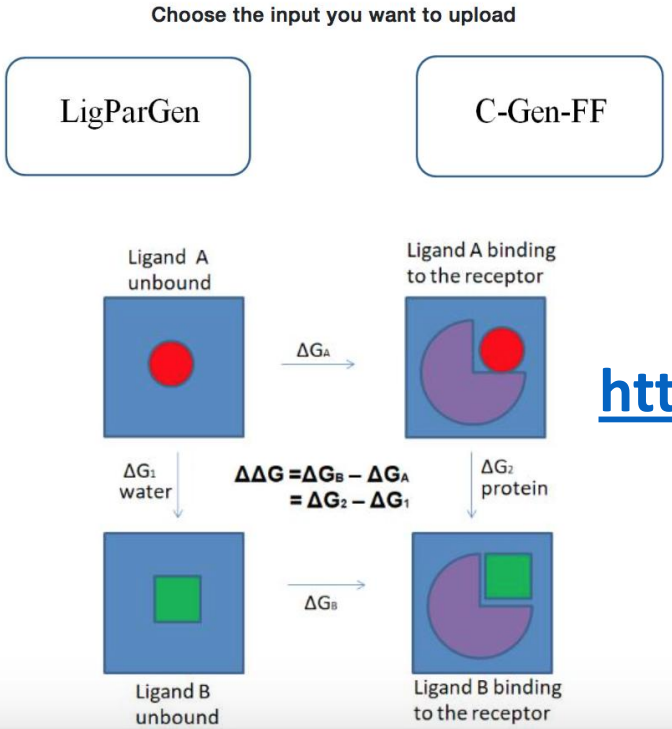


Continue

FEPrepare: Automating Free Energy Perturbation calcuations for Drug Design

Vi-SEEM





http://feprepare.vi-seem.eu

VI-SEEM Virtual Research Environment Portal

Vi-SEEM

SCIENTIFIC REPORTS

OPEN

Insights into the mechanism of the *PIK3CA* E545K activating mutation using MD simulations

Hari Leontiadou, Ioannis Galdadas, Christina Athanasiou & Zoe Cournia

Received: 13 June 2016
Accepted: 4 May 2018
Published online: 19 October 2018

Phosphoinositide 3-kinase alpha (PI3Kα) is involved in fundamental cellular processes including cell proliferation and differentiation and is frequently mutated in human malignancies. One of the most

Available

1. Investi

2. Investi

3. PSOMI

Data Availability

All data (input files, output files, trajectories) have been deposited and can be freely accessed at https://repo.vi-seem.eu/handle/21.15102/VISEEM-254.

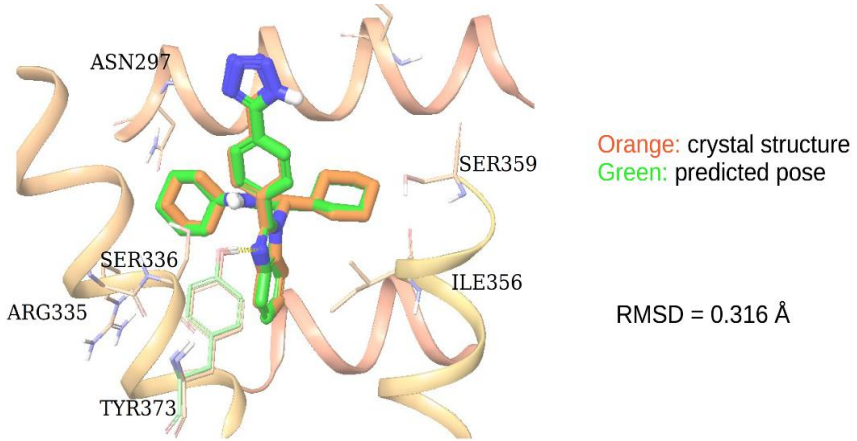
7. Insights into the mechanism of the PIK3CA E545K activating mutation using MD simulations - E545K oncogenic mutant of PI3Ka

8. Insights into the mechanism of the PIK3CA E545K activating mutation using MD simulations - Wild-Type (normal) PI3Ka

VI-SEEM Success Story: The D3R Project

Farnesoid X Receptor (FXR) – Computer-Aided Drug Design competition:
D3R challenge Grand Challenge 2 (Oct 2017 – Feb 2018)

- **Worldwide drug design competition organized by University California, San Diego & Roche Pharmaceuticals**
- Goal: Predict blinded experimental data courtesy of Roche
- **D3R project was allocated 5,000 GPU card hours of VI-SEEM resources**



- C. Athanasiou, S. Vasilakaki, Z. Cournia (Biomedical Research Foundation Academy of Athens)
- D. Dellis (Greek Network of Research and Technology)
- W. Sherman (Silicon Therapeutics)

e:Presence

Πρόσβαση Υποστήριξη Επικοινωνία Ημερολόγιο Είσοδος EL

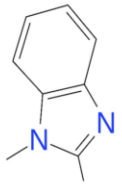
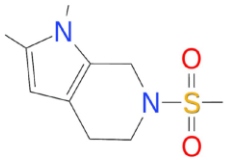
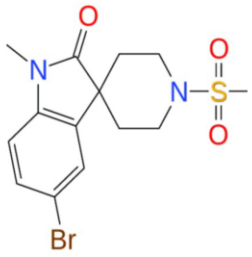
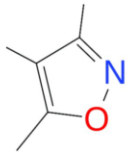
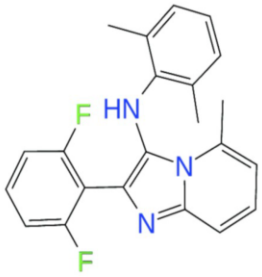
Εύκολη Πρόσβαση

Άμεση σύνδεση των μελών στις διαδραστικές τηλεδιασκέψεις

Χρήση της Υπηρεσίας			
Συνολικά:	46885	10902	483
Σήμερα:	0	0	0
Τώρα:	0	0	0

VI-SEEM Success Story: The D3R Project

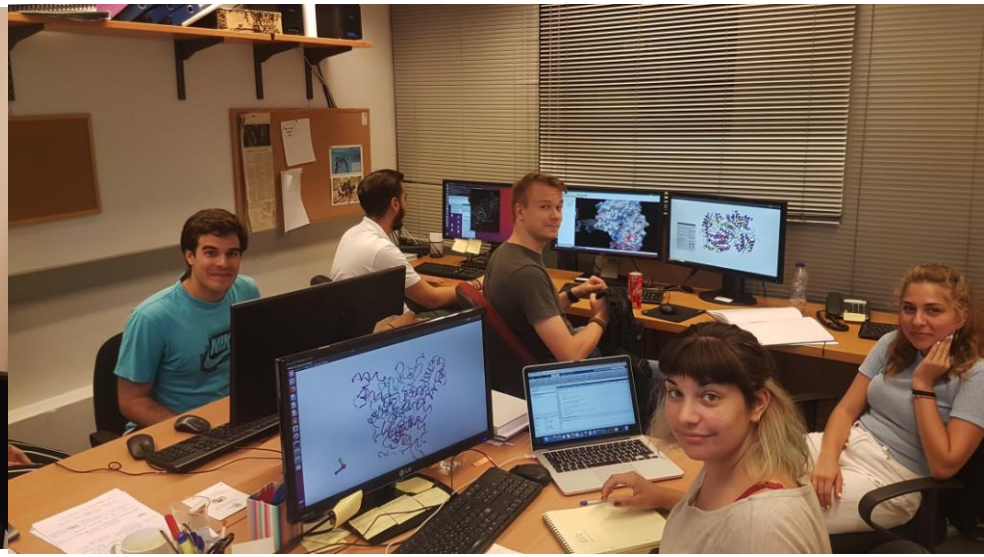
- Ranked #1 out of 46 teams in this worldwide drug design competition

	Benzimidazoles	Sulfonamides	Spiros	Isoxazoles	Miscellaneous
					
	6-9, 13-14, 19-22, 24-32, 35-36	15-17	10-12	4, 23, 33	1-3, 5, 18, 34
Mean RMSD:	**0.84 Å**	**2.95 Å**	**3.45 Å**	**4.94 Å**	**5.57 Å**
Mean Rank:	**8**	**6**	**9**	**43**	**24**
	✔ Known chemotype in crystal structures ✔ Docking, alignment, minimization worked really well	✔ Cross docking predicted unknown binding mode	✔ Cross docking predicted unknown binding mode	✔ Diversity in binding modes did not allow for accurate prediction	✔ Cross docking did not work

Athanasiou et al, JCAMD 2018

Σύστημα Κεντρικής Υποστήριξης της Πρακτικής Άσκησης Φοιτητών ΑΕΙ

ΑΤΛΑΣ
Κόμβος Πρακτικής Άσκησης



Πέτρος Δημητρόπουλος
Βασίλης Γεωργακόπουλος
Έλενα Ροδίτη
Δήμητρα Γερογιαννοπούλου
Πέτρος Κοντραζής
Γιώργος Γαλανόπουλος
Αναστασία Θεοδωροπούλου
Δημήτρης Ντεκουμές
Γιούλη Βαρδάκα
Αργυρώ Ντάλιανη

Coordinator GRNET 2016: I Liabotis
Coordinator GRNET 2018: A Sotiropoulos
Supervisors: D Dellis (GRNET), Z Cournia (BRFAA)

2016:
Juan Zamora (Imperial Coll., UK)
Samanta Makurat (Gdansk U, PL)

2018:
Pedro Santos (Coimbra U, PT)
Petteri Vannika (Turku U, FL)

Infrastructure on High Performance Computing

HPC Europa

Pan-European Research

Coordinator GRNET : E Athanasaki

Supervisors: Z Cournia (BRFAA) / D Dellis (GRNET)

Leandro Battini
University of Buenos Aires
Argentina

15.11.2018 – 28.2.2019

Optimization of antivirals against Chikungunya virus using Free Energy Perturbation method

Phaedon Brotzakis
ETH Zurich
Switzerland

8.1.2019 – 20.3.2019

Conformational studies of wild-type and mutated K-Ras binding to a membrane

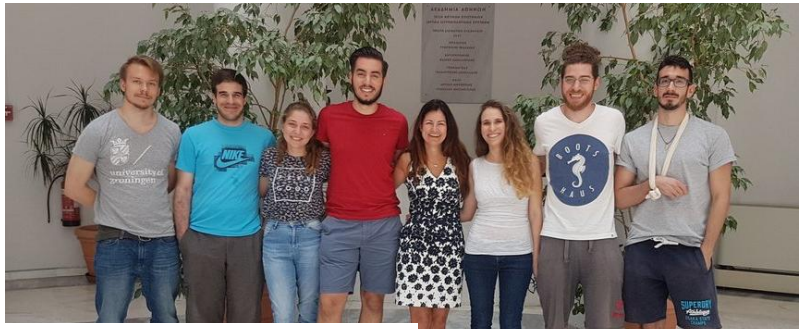
Michail Paparoudakis
University of Ediburgh
UK

1.2.2019 – 20.4.2019

Investigating predictive models for the discovery of new c-Myc inhibitors

Project Team & Thank you!

BRFAA
Cournia lab (MD, drug design, cells)
Dr. Evi Gkeka
Dr. Hari Leontiadou
Ioannis Galdadas, Christina Athanasiou



Efstratia
Dr. Ersi
Dr. Dimi

NCSR D
Coulado
Anna Ka
Maria Ou

Universi
Agianiar
Dr. Maria

University of Ioannina
Christoforidis lab (cell-free assays)
Alexandra Papafotika
Dr. Vasiliki Lazani

American Association for Cancer Research