COMPUTE THE CURE

Accelerating the Cure: GPU-Driven Drug Discovery for Targets in Cancer

Rommie E. Amaro . UC San Diego . NVIDIA GTC 2015 . Mar 18, 2015

Game-changing advances

LCF
Mira 786k cores
Titan 280k cores
+ GPUs

2015

Enveloped virus
200 mil+ atoms
1-100 µs

Ranger
60k CPUs

2007

ribosome
2 mil atoms
100s ns

LeMieux
3k CPUs

SGI Origin
128 CPUs

HP 735
12 CPUs

2002

ATPase
500k
atoms
10s ns

1993

protein
10k atoms
100s ps

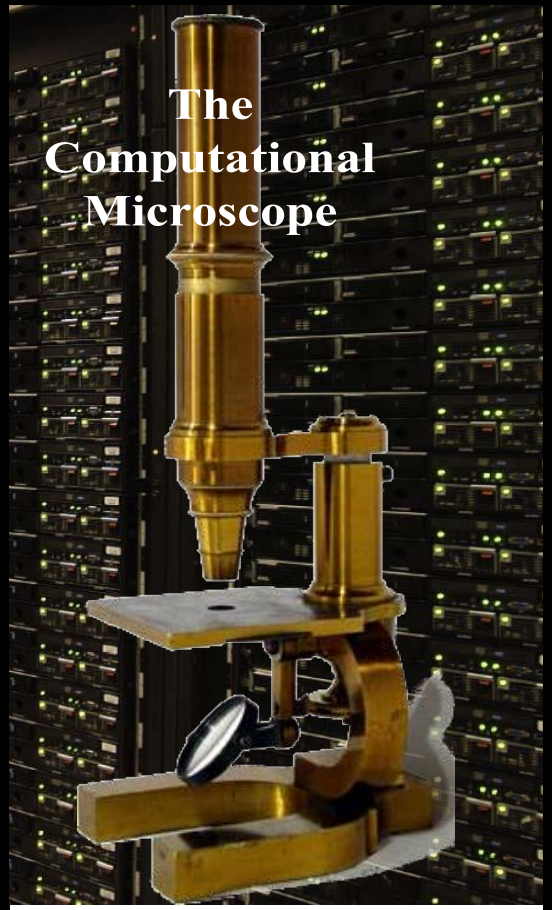
1997

ion
channel
100k atoms
1 ns

Compute Power

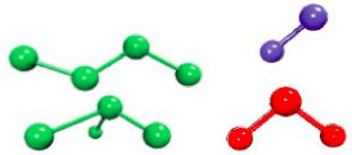
time

Enormous gains in computing power enabling new frameworks for drug discovery



100 - 1,000,000 processors

Chemistry



$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

Physics

$$m_i \frac{d^2\vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla}U(\vec{R})$$

Math

$$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i}\vec{F}_i(t)$$

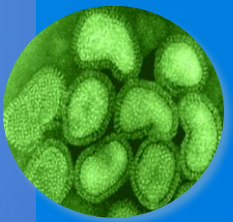
(repeat ***one billion times*** = microsecond)

Software & Tools

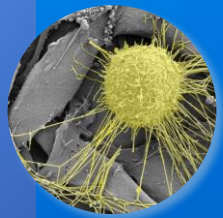
NAMD, AMBER, CADD pipeline, FTProd…

Supercomputers & GPUs

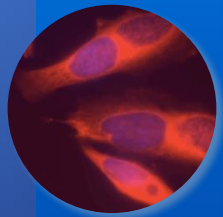
Sustained 10^{15} - 10^{18} FLOPS



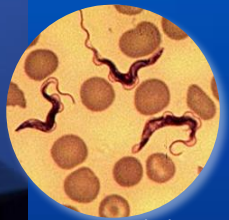
Influenza



Cancer

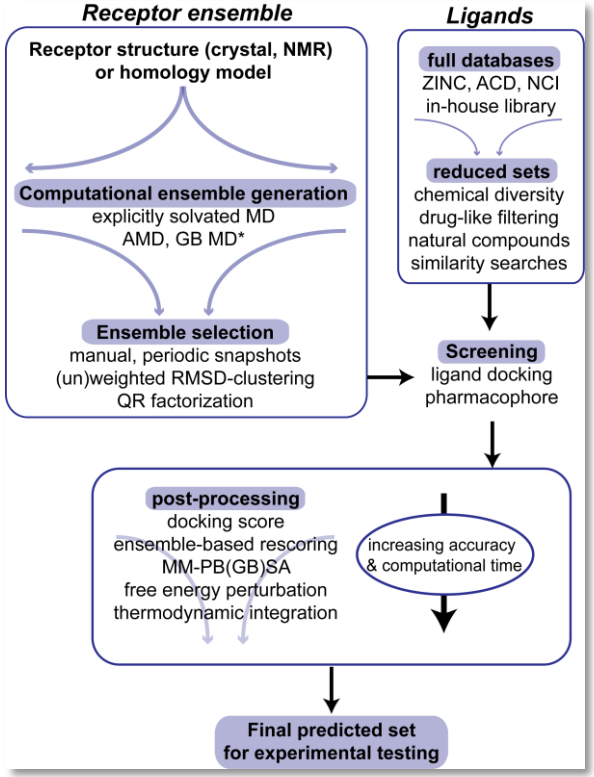


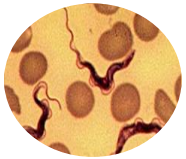
Chlamydia



Trypanosomiasis

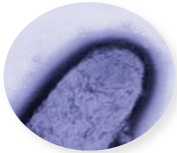
Game changing GPU advances …
life changing advances in drug discovery





Trypanosomiasis

Amaro et al, PNAS 2008
Durrant et al PLOS NTD 2010

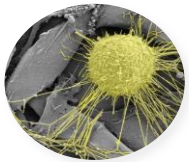


Yersinia pestis

Gabrielsen et al, PLOS One 2012

Influenza

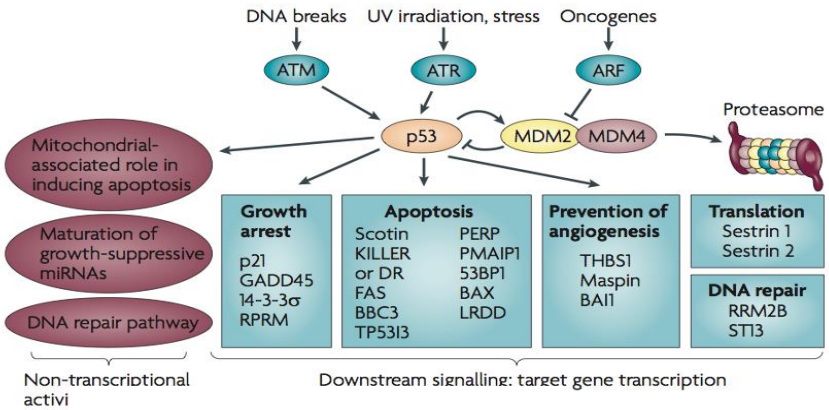
Cheng et al, J Med Chem 2007
Landon et al, CBDD, 2009
Chen et al, ACS Med Chem Lett 2013



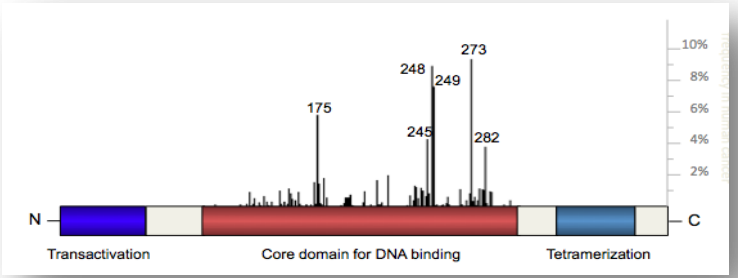
Cancer

Demir et al, PLOS Comp Biol 2011
Wassman et al, Nat Comm 2013

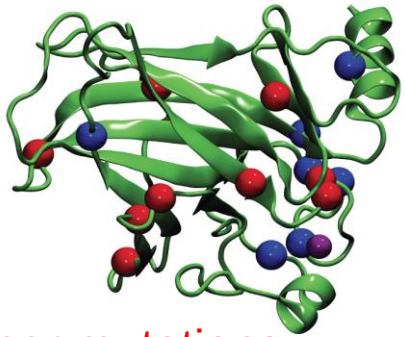
p53: Guardian of the genome



Frequency of p53 mutations in cancer



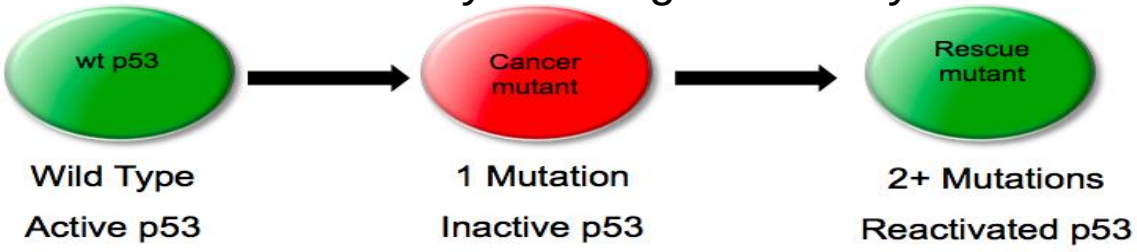
>600,000 new cancer patients annually in the US with p53 point mutations



Cancer mutations

Cancer rescue mutations

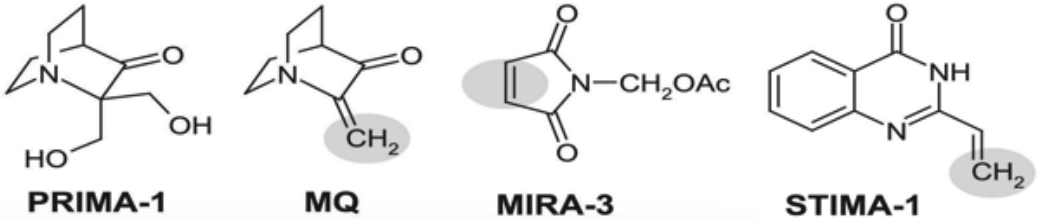
Susceptible to oncogenic mutations that inactivate by lowering its stability



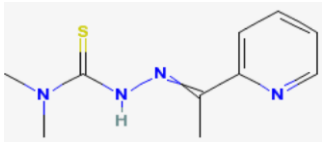
Brown *et al.* (2009) *Nature Reviews. Cancer, 9(12), 862–873*

Dream of cancer biologists: small-molecule p53 reactivation

Inactive p53 | Anti-Cancer Drug | Reactivated p53



PRIMA-1 | MQ | MIRA-3 | STIMA-1

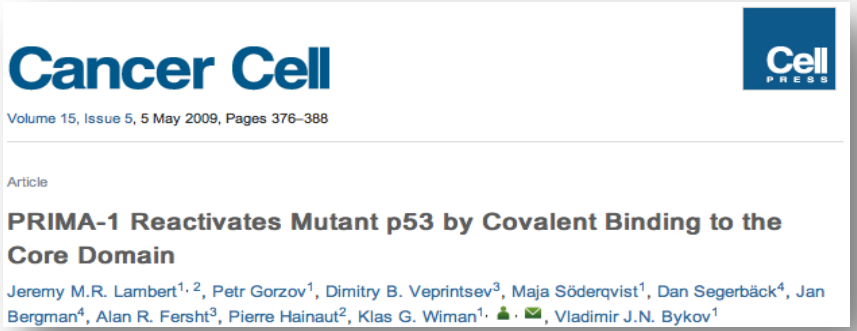


NSC319725

Martins, *et al.*, Modeling the therapeutic efficacy of p53 restoration in tumors, *Cell*, 2006.

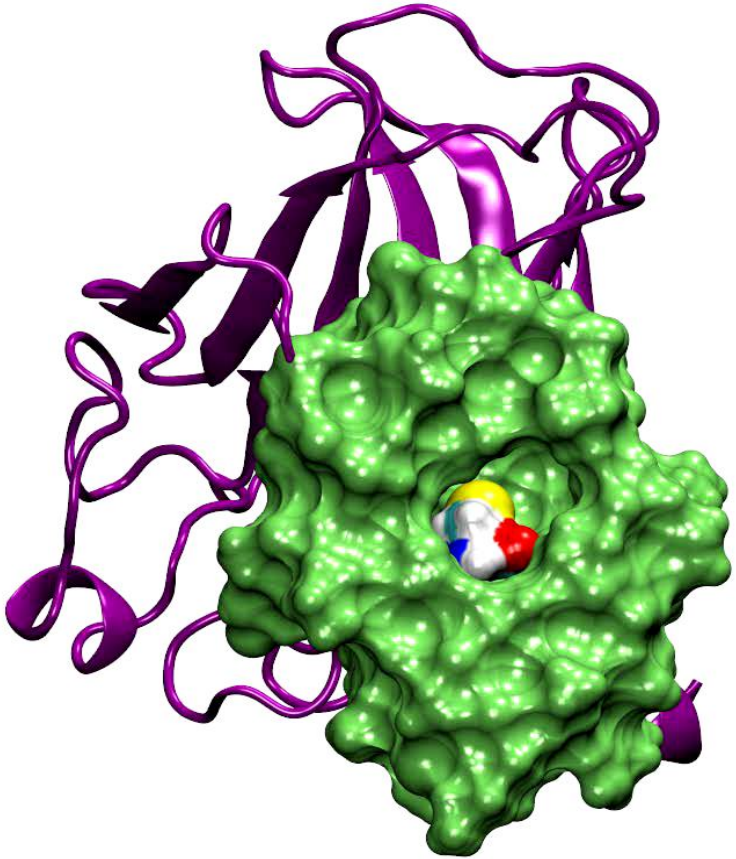
Ventura, *et al.*, Restoration of p53 function leads to tumour regression in vivo, *Nature*, 2007.

Xue, *et al.*, Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas, *Nature*, 2007.



Identified covalent attachment of products, but could not discern which of 10 cysteine residues

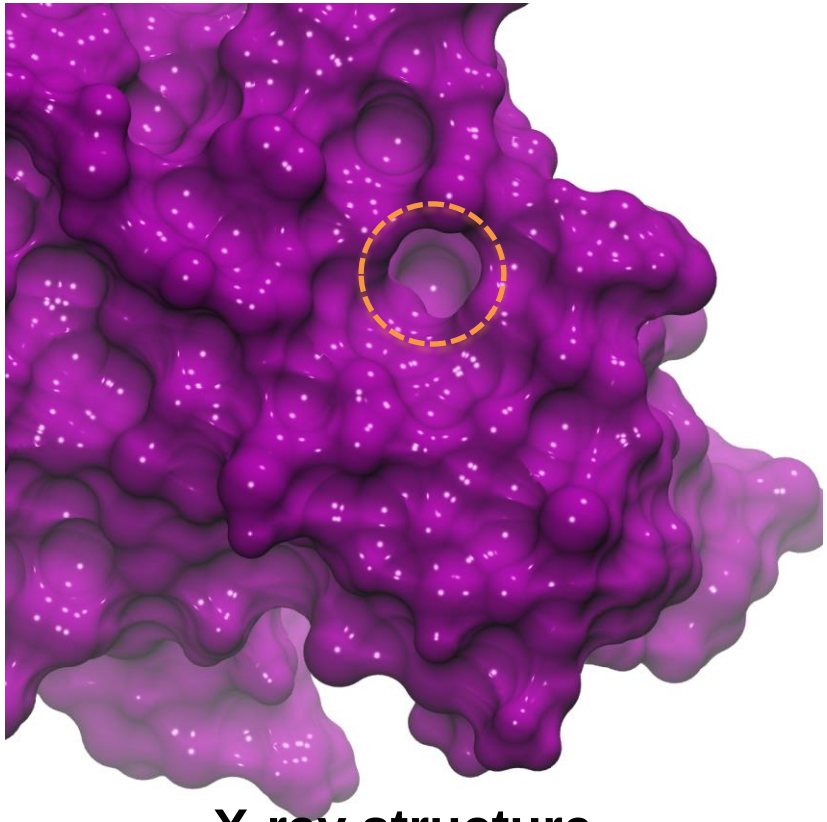
Simulations Reveal Target Flexibility



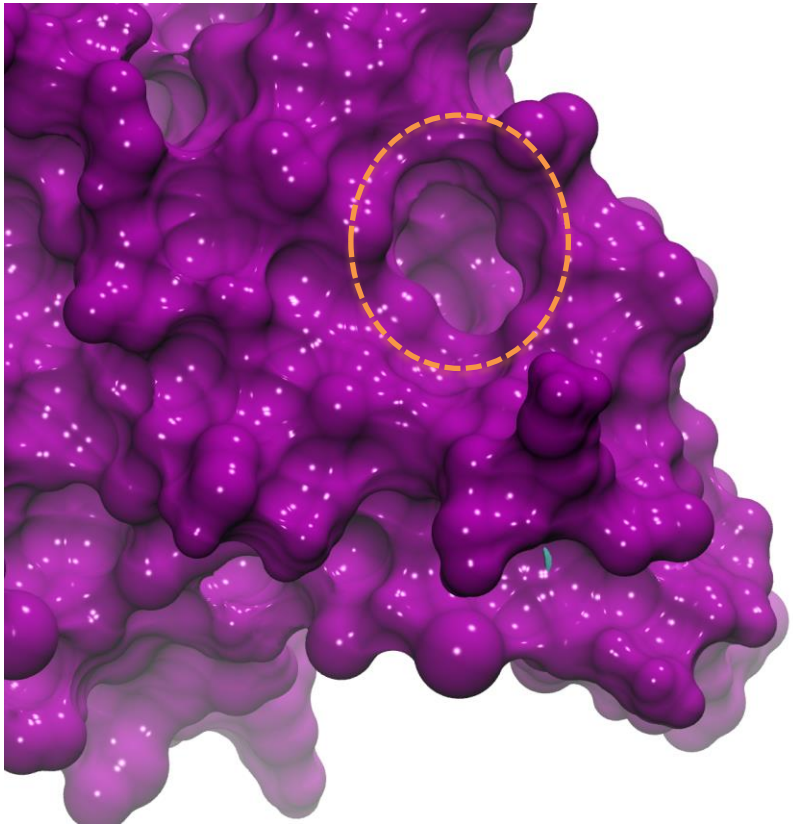
5% exposed,
matches NMR

Wassman, Baronio, Demir, et al. Nature Comm., (2013)

New Site Opens



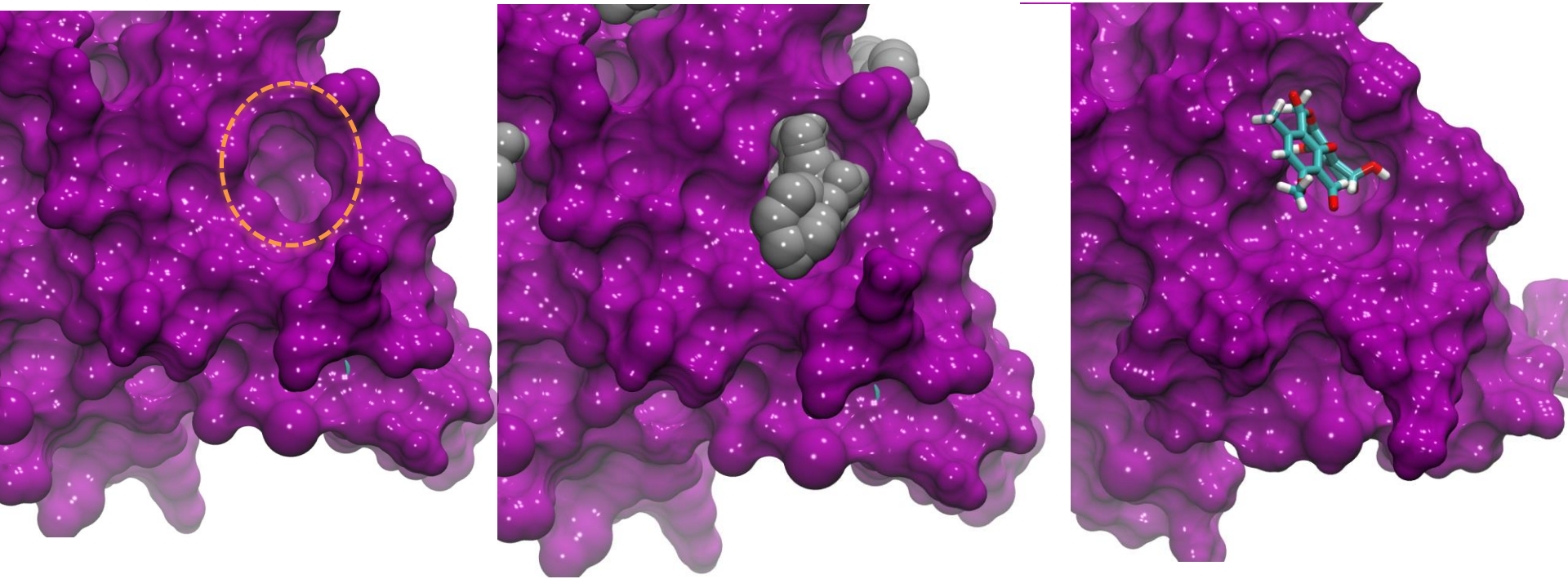
X-ray structure



“Open” MD structure

Wassman, Baronio, Demir, et al. Nature Comm., (2013)

New Site is Druggable

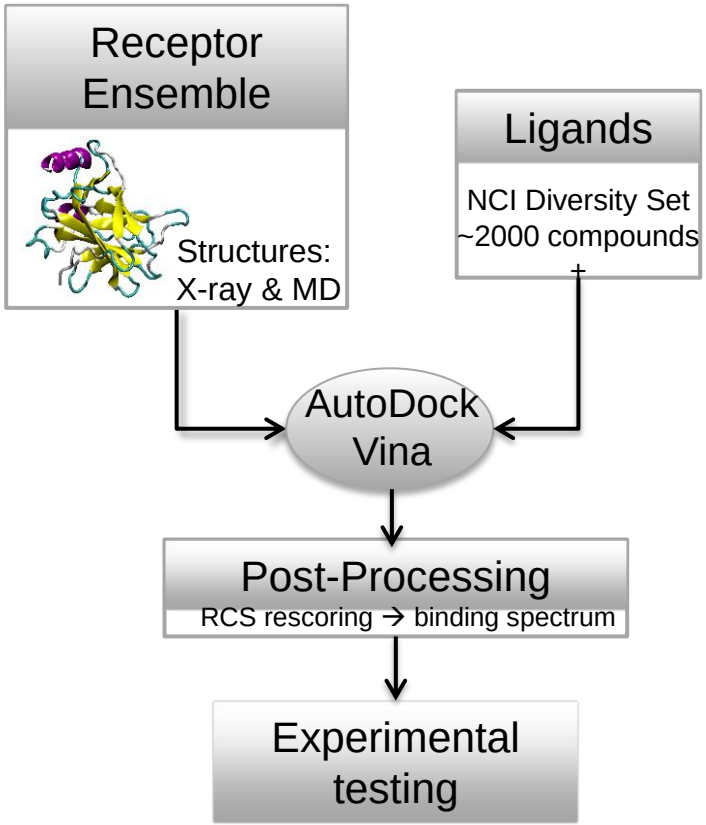


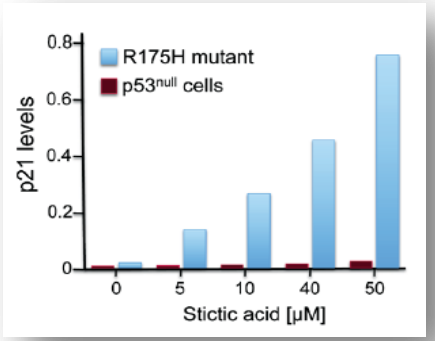
structure

Wassman, Baronio, Demir, et al. Nature Comm., (2013)

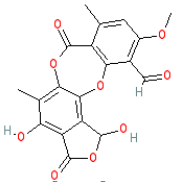
Vajda et al., Computational Solvent Mapping: http://ftmap.bu.edu/

Discovery of novel reactivation compound & rationalization of clinical trial compound

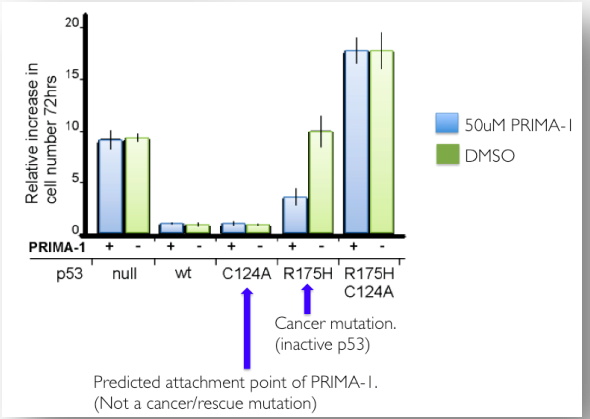




Dose-dependent rescue in mammalian cancer cells

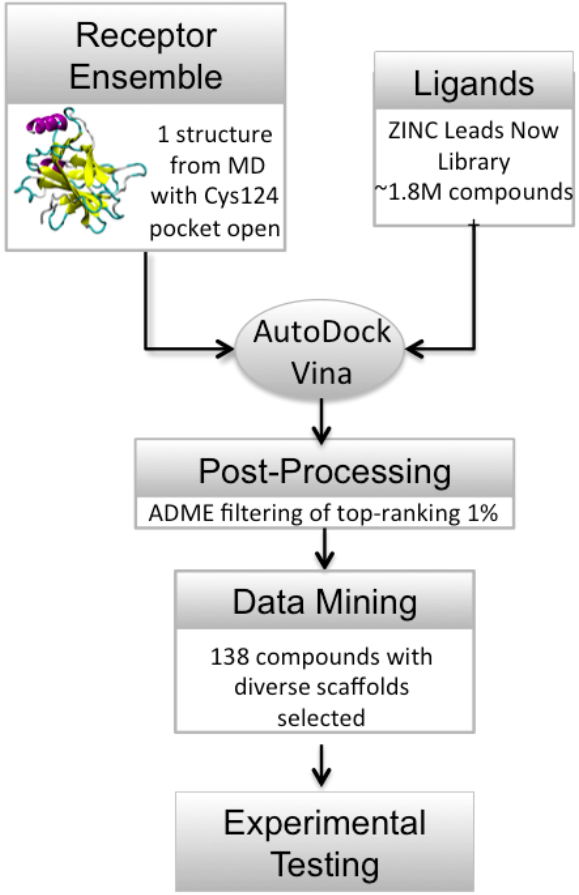


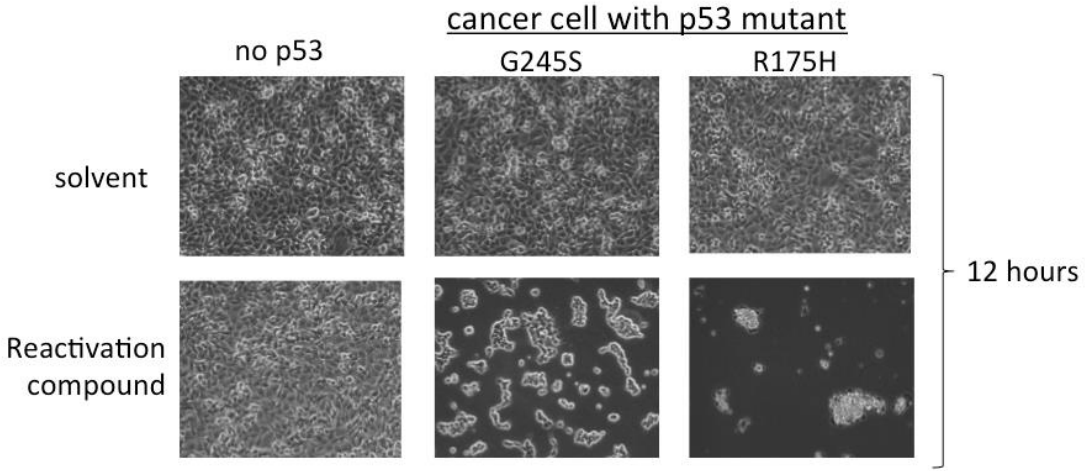
Stictic acid



Wassman, Baronio, Demir, et al. Nature Comm., (2013)

Our computational approach discovers more novel p53 reactivation compounds in 6 months than all the research efforts of the previous 20 years combined





15/138 compounds tested in mammalian cancer cell lines rescue p53 activity and kill cancer cell

aprea

NEWS, Apr 7, 2014

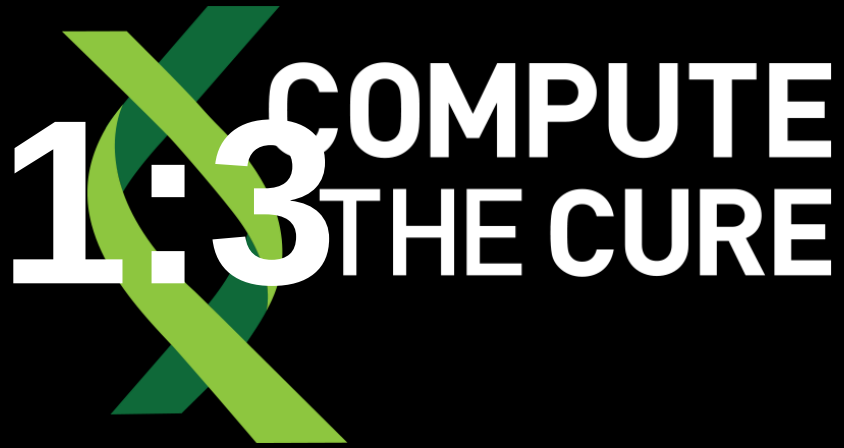
Aprea presents preclinical data at AACR – APR-246 re-sensitizes ovarian cancer cells to platinum compounds and doxorubicin

Stockholm – April 7, 2014. Aprea AB today presented preclinical data at the American Association for Cancer Research (AACR) meeting in San Diego, USA. The data reveals that Aprea's candidate drug APR-246, a compound that reactivates mutant p53, is able to resensitize ovarian cancer cells to platinum compounds and doxorubicin. A Phase Ib/II study with APR-246 in relapsed platinum sensitive ovarian cancer is currently open for recruitment. Aprea is part of the Karolinska Development portfolio.

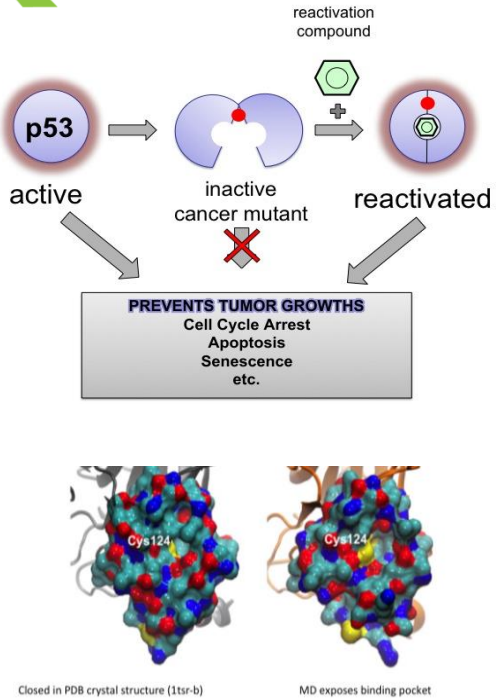
NEWS, Jan 22, 2015

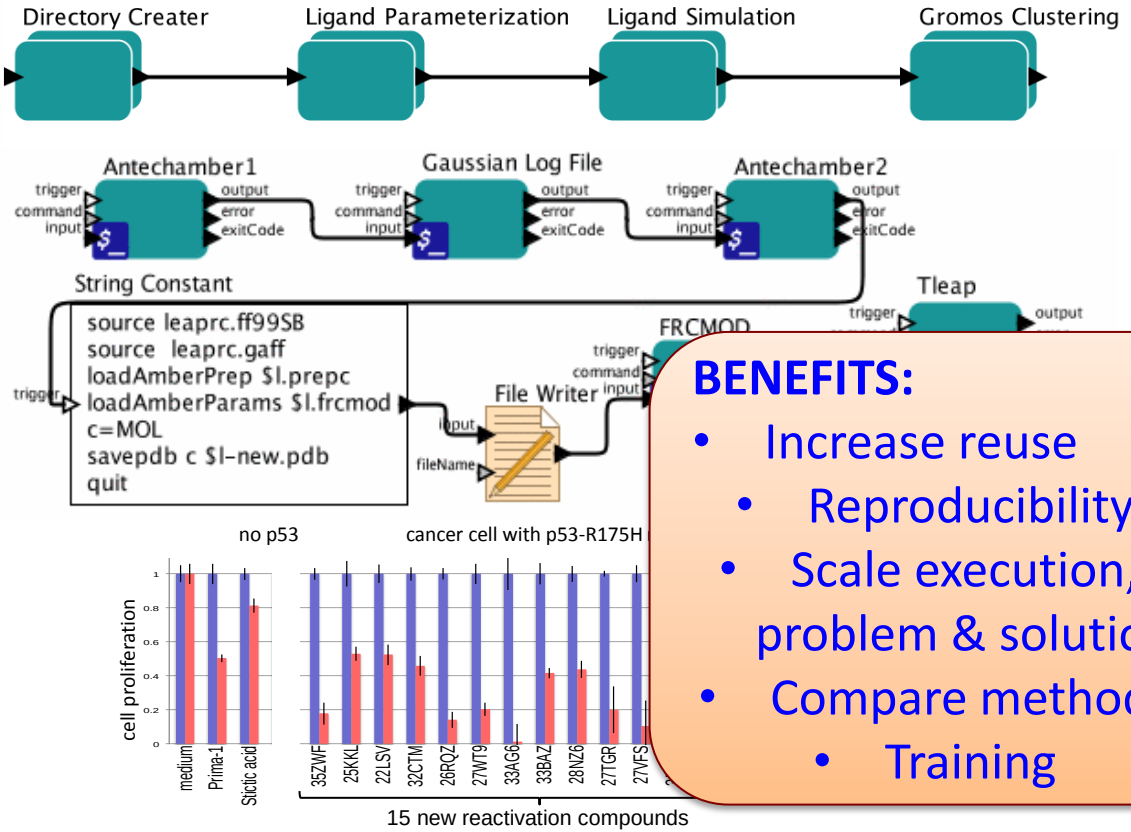
Aprea granted European orphan drug designation for APR-246 in ovarian cancer

STOCKHOLM – January 22, 2015. Aprea AB, a Karolinska Development portfolio company, today announced that the European Medicines Agency (EMA) has granted its drug candidate APR-246 orphan drug designation for the treatment of ovarian cancer. Aprea is currently conducting a Phase Ib/II trial of APR-246 in combination with standard of care chemotherapy in patients with relapsed platinum sensitive high-grade serous ovarian cancer.


1:3
COMPUTE
THE CURE

Scalable Drug Discovery



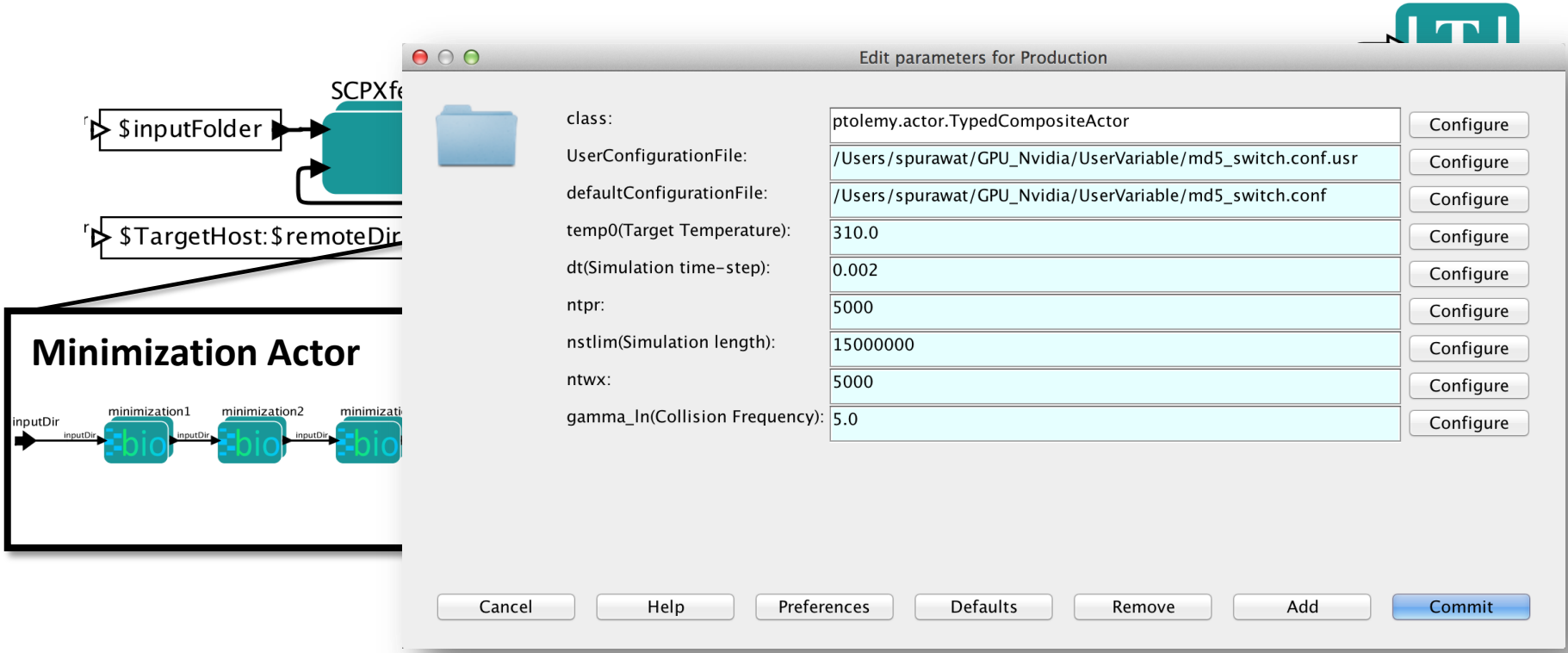


BENEFITS:

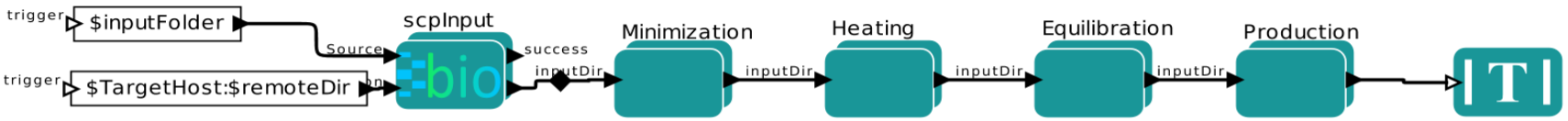
- Increase reuse
- Reproducibility
- Scale execution, problem & solution
- Compare methods
- Training

Ieong et al., 2014

AMBER GPU MD Workbench



Nimble execution on most efficient platforms



Local: Desktop or Cluster

NVIDIA TESLA

NSF/DOE: Tera/Peta Scale Resources (XSEDE)

SDSC Comet

TACC Stampede

Cloud: *Amazon Coming soon!*

amazon web services

Google Cloud Platform

CODONIS

COMPUTE THE CURE

Tool & tutorial is available for download:

http://amarolab.ucsd.edu/resources.html

Contact: ramaro@ucsd.edu

"Hands on" workshop coming soon!