WISDOM, a grid enabled virtual screening initiative

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On behalf of the WISDOM Collaboration

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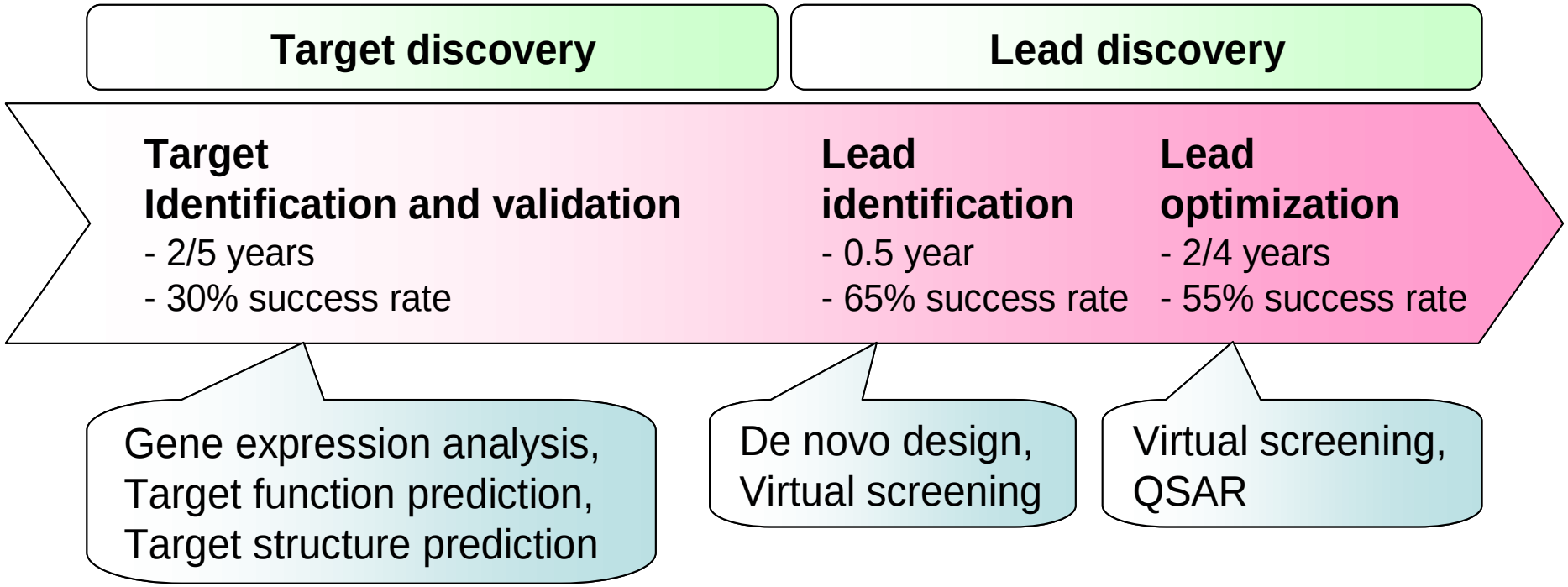
Information Society and Media

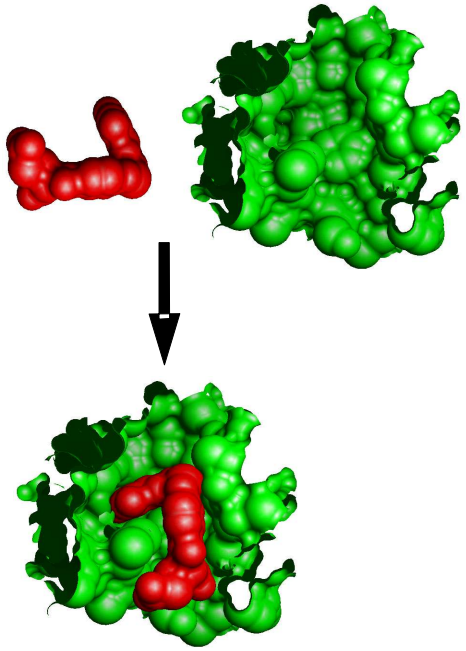
Searching for new drugs

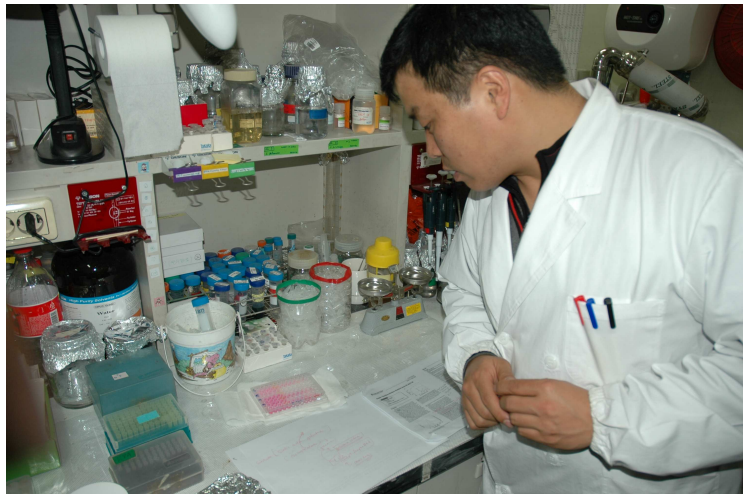
- **Drug development is a long (10-12 years) and expensive (~800 MDollars) process**
- **In silico drug discovery opens new perspectives to speed it up and reduce its cost**



Simplified principle of screening

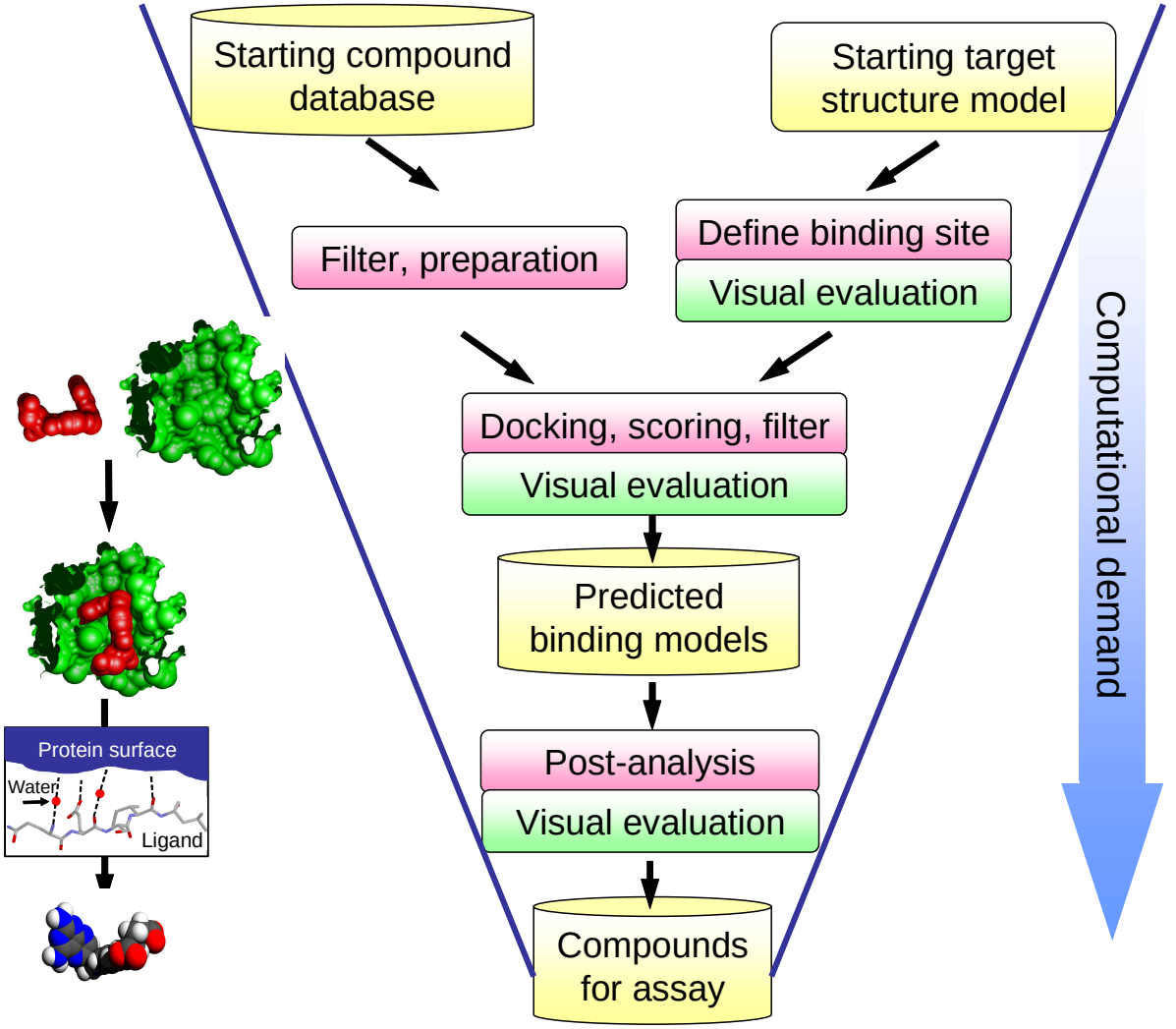
- **Biologists isolate a protein, the target, which plays an important role in the life cycle**
  - of the malaria parasite
  - of the H5N1 virus
  - of a cancer cell
  - …
- **The objective is to find other molecules which will block the action of that protein: the hits**
  - Docking of the molecule on the protein active site
- ***in silico* docking vs *in vitro docking***
  - *In silico:* calculation of the binding energy between molecules
  - *In vitro:* measurement of the chemical reaction coefficient





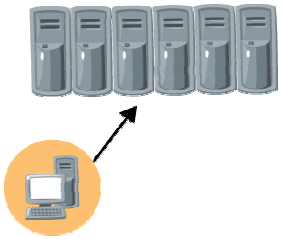
A first step towards in silico drug discovery: virtual screening

- **In silico virtual screening**
  - Starting from millions of compounds, select a handful of compounds for in vitro testing
  - Very computationally intensive but potentially much cheaper than in vitro testing
- **Where to find CPUs to make it time effective ?**

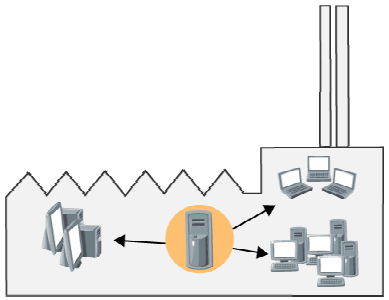


Distributed Computing in a nutshell

Cluster



Enterprise Grids

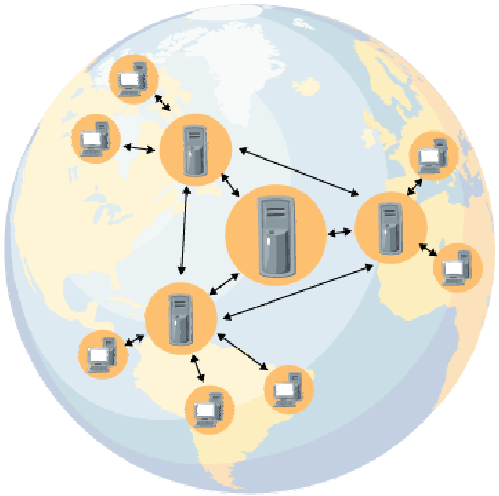


Example:
United Devices

Volunteer Computing

Example:
World Community Grid
Africa@home

‘The Grid’ (in this talk!)



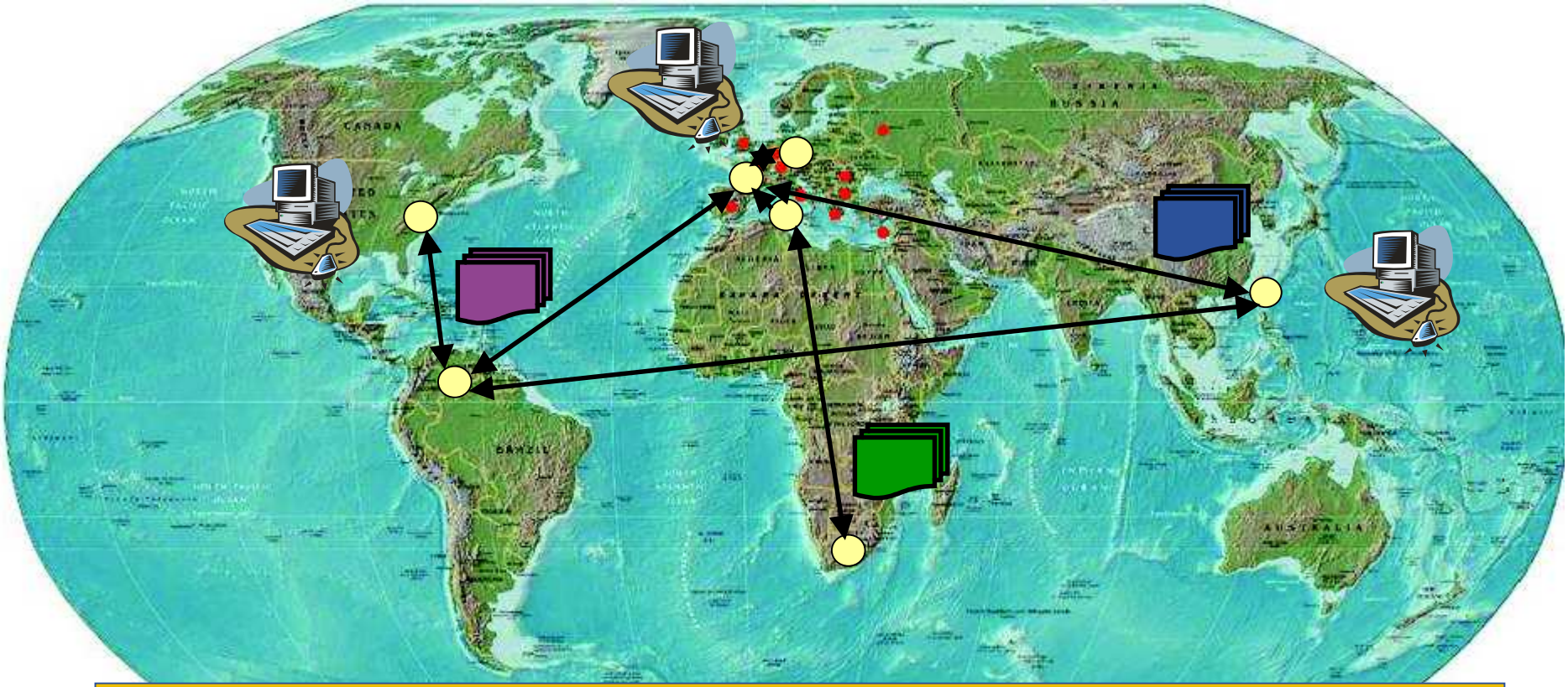
Example:
EGEE

What is the Grid?

- The World Wide Web provides seamless access to information that is stored in many millions of different geographical locations
- In contrast, the Grid is a new computing infrastructure which provides seamless access to computing power, data and other resources distributed over the globe
- The name Grid is chosen by analogy with the electric power grid: plug-in to computing power without worrying where it comes from, like a toaster

The grid added value for international collaboration

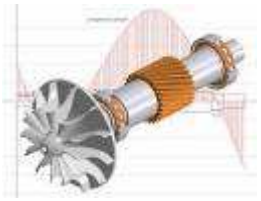
- **Grids offer unprecedented opportunities for sharing information and resources world-wide**

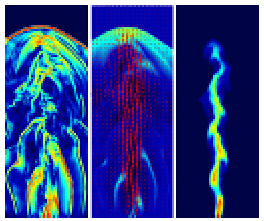


Grids are unique tools for :
-Collecting and sharing information (Epidemiology, Genomics)
-Networking experts
-Mobilizing resources routinely or in emergency (drug discovery)

The EGEE-II project

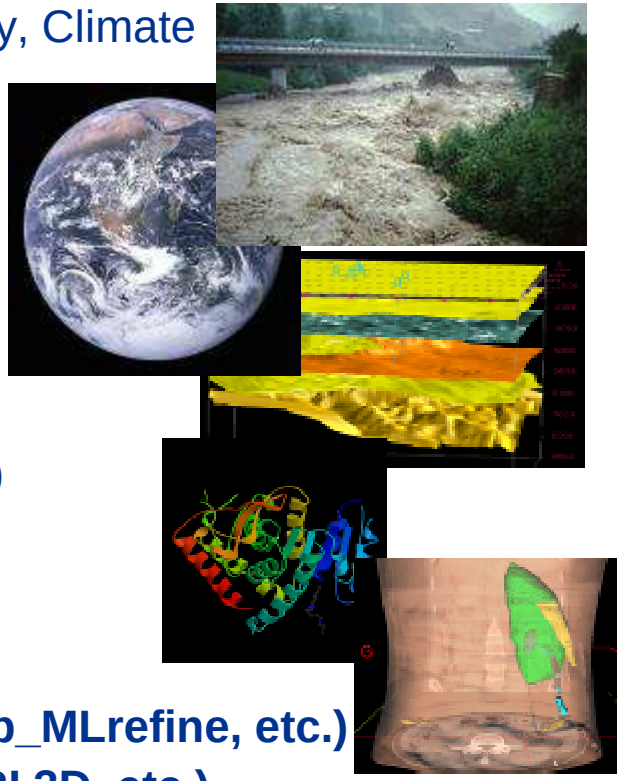
- **EGEE**
  - 1 April 2004 – 31 March 2006
  - 71 partners in 27 countries, federated in regional Grids
- **EGEE-II**
  - 1 April 2006 – 31 March 2008
  - 91 partners in 32 countries
  - 13 Federations
- **Objectives**
  - Large-scale, production-quality infrastructure for e-Science
  - Attracting new resources and users from industry as well as science
  - Maintain and further improve “gLite” Grid middleware





Applications on EGEE

- **More than 25 applications from 9 domains**
  - Astrophysics
    - MAGIC, Planck
  - Computational Chemistry
  - Earth Sciences
    - Earth Observation, Solid Earth Physics, Hydrology, Climate
  - Financial Simulation
    - E-GRID
  - Fusion
  - Geophysics
    - EGEODE
  - High Energy Physics
    - 4 LHC experiments (ALICE, ATLAS, CMS, LHCb)
    - BaBar, CDF, DØ, ZEUS
  - Multimedia
  - **Life Sciences**
    - **Bioinformatics (Drug Discovery, GPS@, Xmipp_MLrefine, etc.)**
    - **Medical imaging (GATE, CDSS, gPTM3D, SiMRI 3D, etc.)**



WISDOM

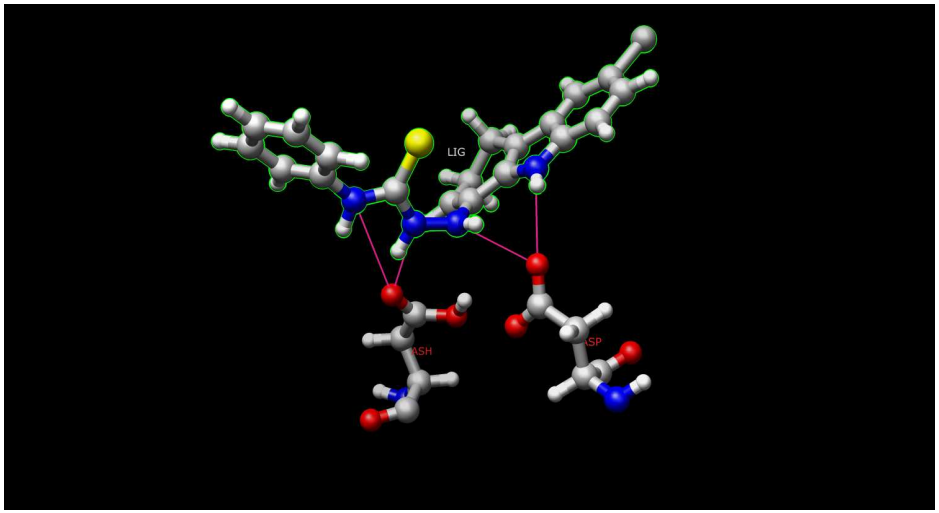
- **WISDOM stands for World-wide In Silico Docking On Malaria**

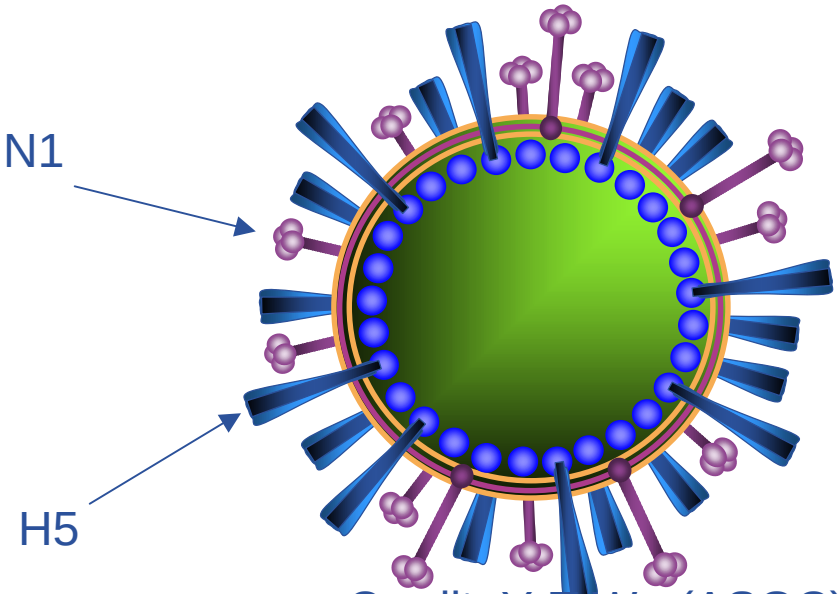
- **Goal: find new drugs for neglected and emerging diseases**
  - Neglected diseases lack R&D
  - Emerging diseases require very rapid response time

- **Method: grid-enabled virtual docking**
  - Cheaper than in vitro tests
  - Faster than in vitro tests

Biological objectives

- **Malaria: Find active molecules**
  - on a known mutated protein (DHFR)
  - on new targets:
    - Plasmepsins
    - GST
    - Tubulin
- **Avian Flu**
  - Study the impact of point mutations of the N1 enzyme
    - Tamiflu active on N1
  - Find new molecules active on N1





Credit: Y-T Wu (ASGC)

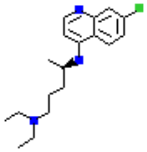
Grid-enabled virtual docking

Millions of potential drugs to test against interesting proteins!

~~High Throughput Screening ~ 10$/compound several hours~~

Too costly for neglected disease!

Compounds:

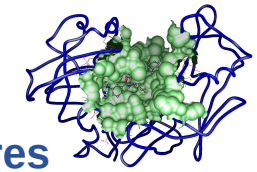


ZINC: 4.3M

Chembridge: 500 000

Molecular docking (FlexX, Autodock)
~1 to 15 minutes

Targets:

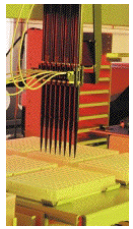


PDB: 3D structures

Data challenge on EGEE
~ 2 to 30 days on ~5000 computers

Cheap and fast!

Selection of the best hits



Hits screening using assays performed on living cells

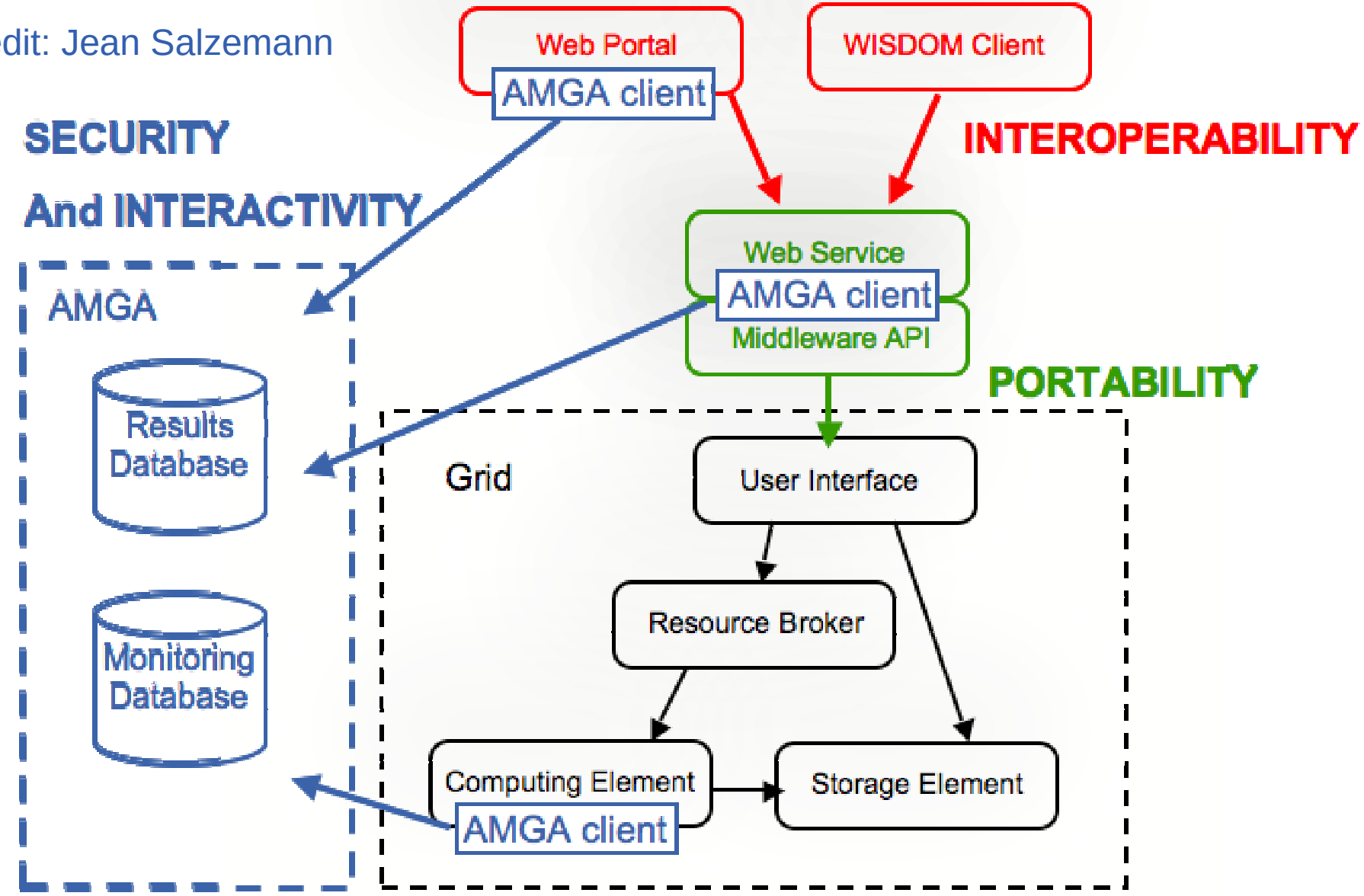
Leads

Clinical testing

Drug

Production Environment

Credit: Jean Salzemann



Statistics of deployment

- **First Data Challenge: July 1st - August 15th 2005**
  - Target: malaria
  - 80 CPU years
  - 1 TB of data produced
  - 1700 CPUs used in parallel
  - 1st large scale docking deployment world-wide on a e-infrastructure

- **Second Data Challenge: April 15th - June 30th 2006**
  - Target: avian flu
  - 100 CPU years
  - 800 GB of data produced
  - 1700 CPUs used in parallel
  - Collaboration initiated on March 1st: deployment preparation achieved in 45 days

- **Third Data Challenge: October 1st - 15th December 2006**
  - Target: malaria
  - 400 CPU years
  - 1,6 TB of data produced
  - Up to 5000 CPUs used in parallel
  - Very high docking throughput: > 100.000 compounds per hour

Post docking analysis on Avian Flu

- **Selection of the most promising molecules in a 2-step process**
  - 1st step: rejection of 85% based on docking score.
  - 2nd step: re-ranking of the remaining 15% and selection of the best 5%

- **6 known active inhibitors included in the analyse to validate the process**
  - 5 out of 6 kept in the 2250 selected compounds

Global effectiveness:

$(Hits_{sampled}/N_{sampled})/(Hits_{total}/N_{total})$

Pearlman & Charifson, JMC, 2001

Pre-sceening (AUTODOCK) over collection and sample first 15%

$EF^1 = (5/6)/15\% = 5.5$

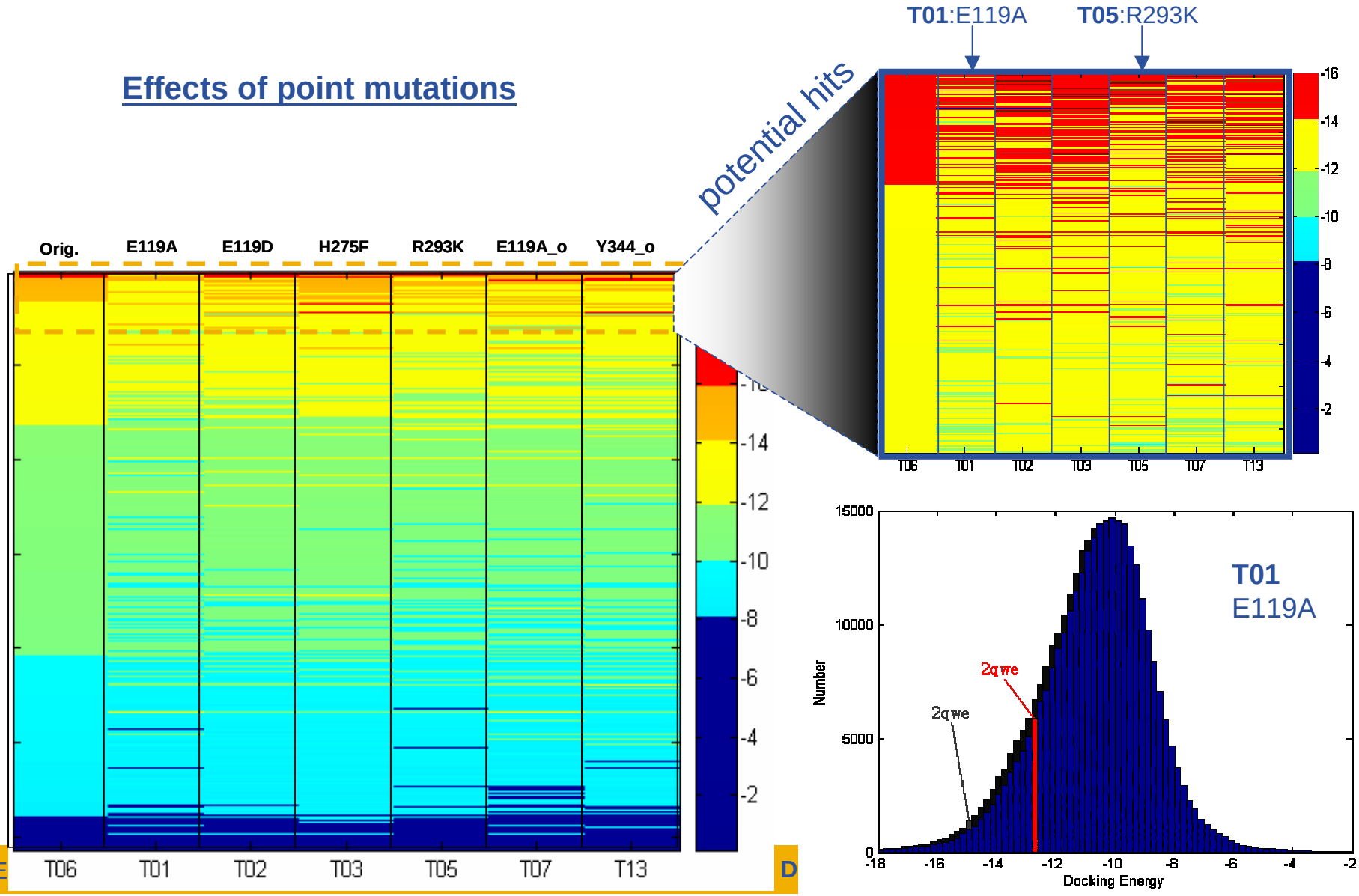
Re-ranking (SDDB) first 15% and sample first 5%

$EF^2 = (5/6)/(5\%*15\%) = 111$

Credit: Y-T Wu (ASGC)

Significant impact of mutations on the activity of molecules

Effects of point mutations

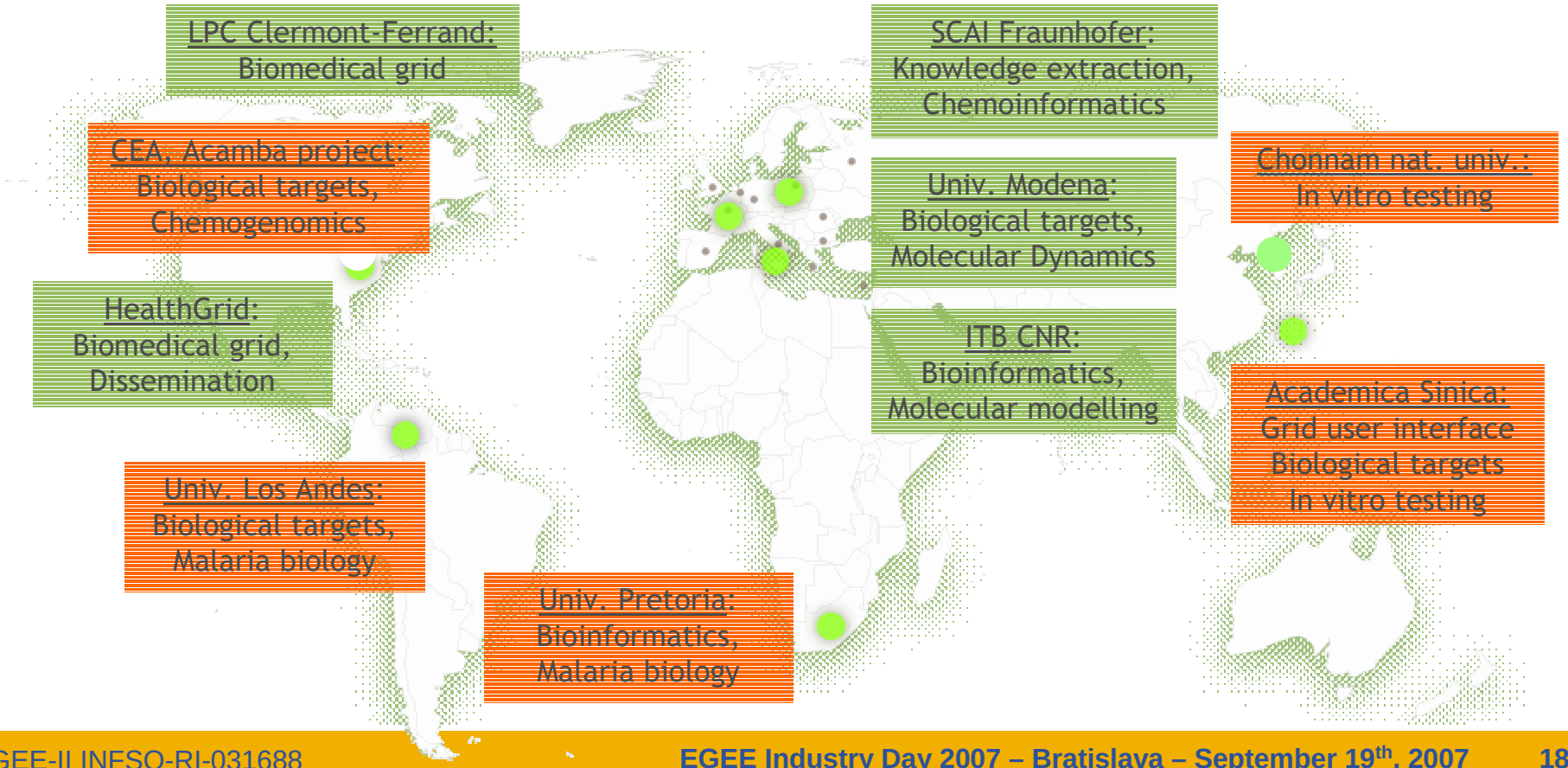


Status of in vitro tests

- **Avian Flu**
  - Initial number of compounds: 300.000
  - 123 compounds bought and tested out of the 2250 selected
    - 7 out of 123, approximately 6%, are active
  - Usual average success rate for in vitro tests: 0,1%
  - Factor 60 increase to be confirmed on more compounds
  - Tests under way at Chonnam National University (ROK)
- **Malaria**
  - Initial number of compounds: 500.000 (WISDOM-I)
  - Selection of 30 molecules in 2 steps
    - 1000 molecules selected on docking score
    - Selection of 30 molecules through molecular dynamics
  - Tests under way at Chonnam National University (ROK)
  - First results are very encouraging

Grid added value for in silico drug discovery

- The grid provides the centuries of CPU cycles required for virtual screening
- The grid provides the reliable and secure data management services to store and replicate the biochemical inputs and outputs
- The grid offers a collaborative environment for the sharing of data in the research community on Avian Flu and Malaria



Industrial perspective

- **A secure and reliable production environment was developed for Wisdom**
  - Up to 100.000 docked compounds per hour (WISDOM-II)
  - Distributed Secured Data Management
- **This environment has been used for other life sciences applications (e.g. PDB refinement within the EMBRACE project - CMBI)**
- **We are ready to address industrial requirements!**

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