WISDOM EXPERIENCE
- CURRENT STATUS -

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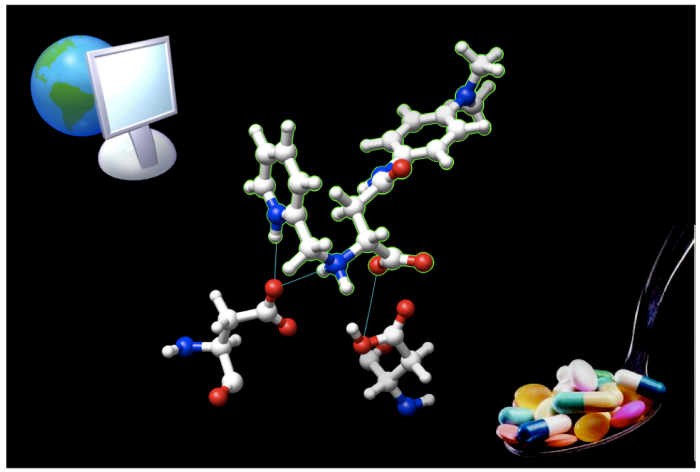


OUTLINE

1. INTRODUCTION

2. Virtual screening status
   1. Wisdom 1: Plasmepsin
   2. Wisdom 2: GST, PfDHFR

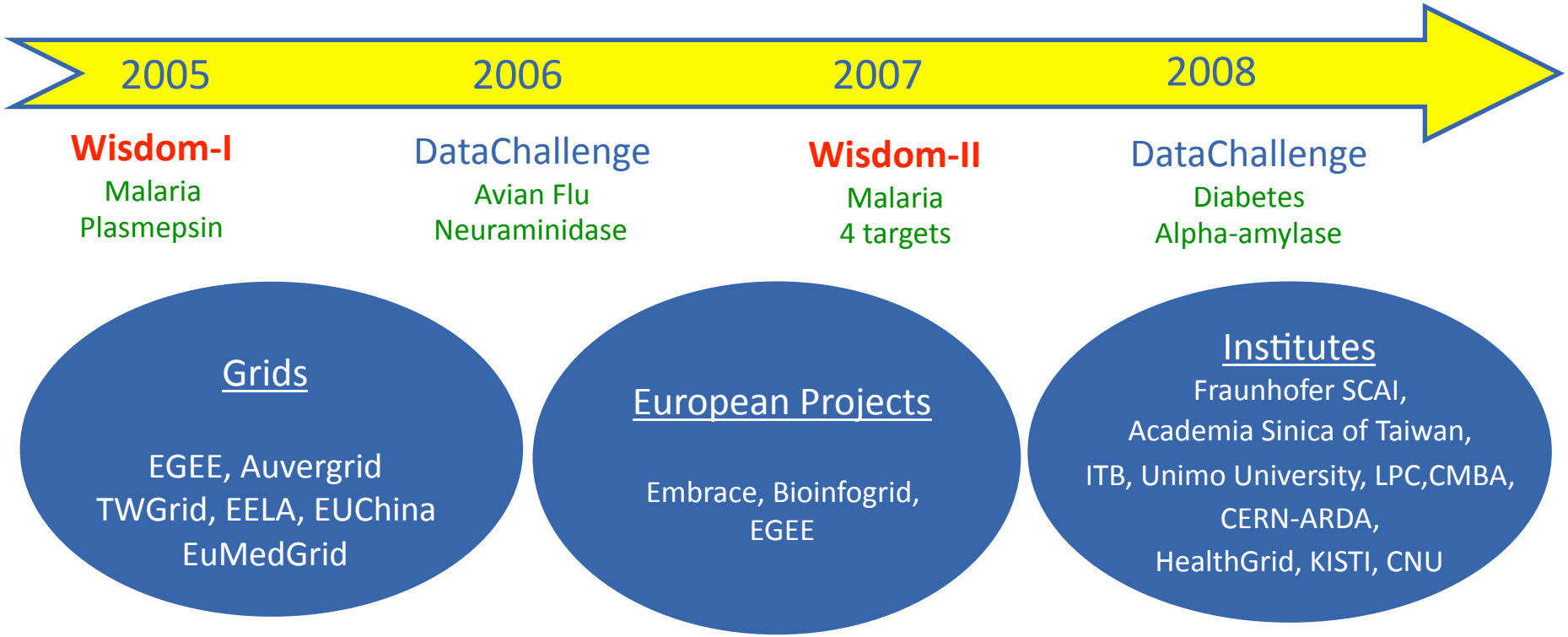
3. New project: Pancreatic Alpha Amylase

4. Evolution of Wisdom Production Environment

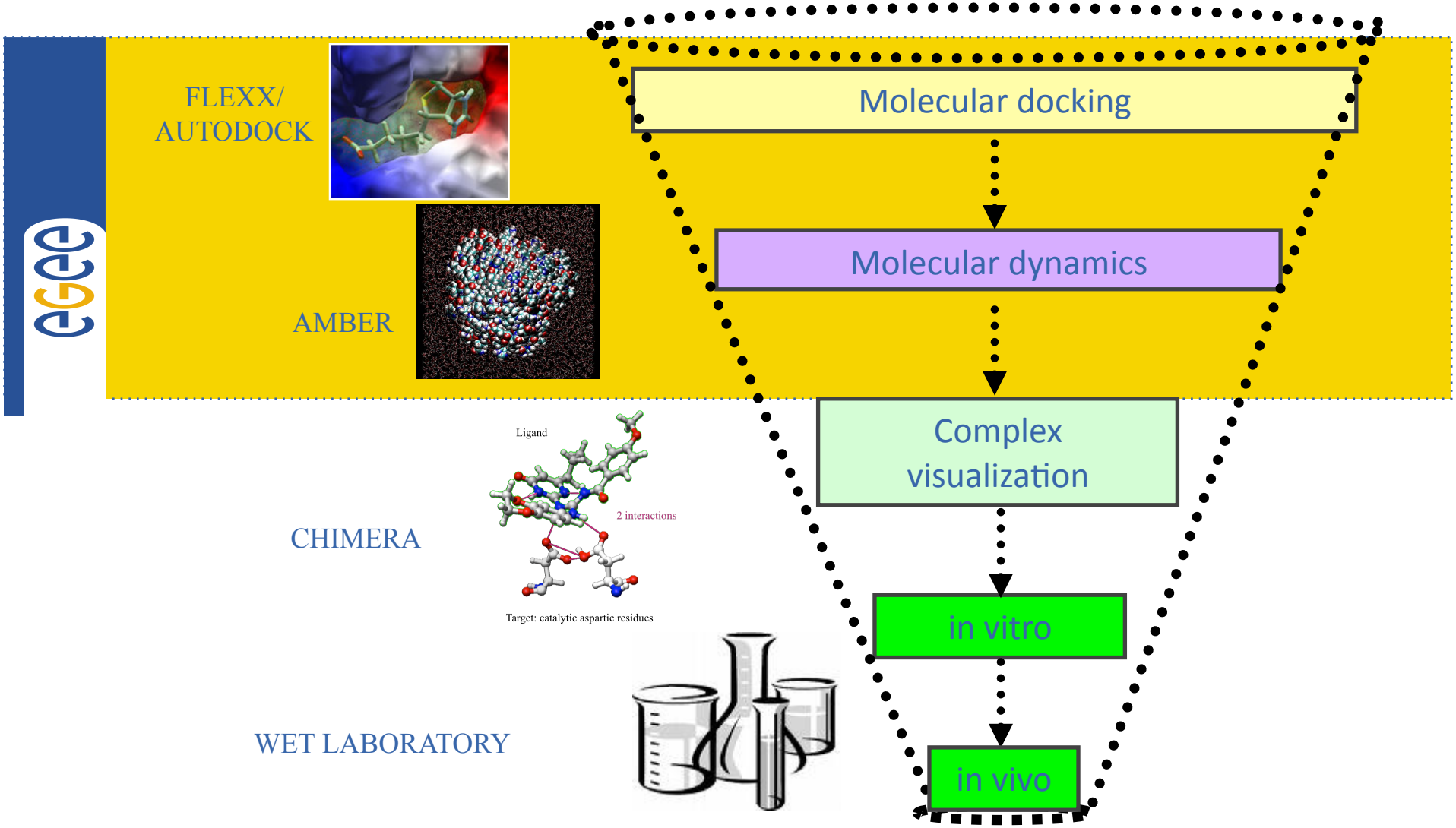
5. CONCLUSION / PERSPECTIVES

Introduction

WISDOM (World-wide In Silico Docking On Malaria) initiative aims to demonstrate the relevance and the impact of the grid approach to address drug discovery for neglected and emerging diseases.



Drug discovery workflow



Biological results: targets

MALARIA TARGETS	IMPLICATED IN	PARTNERS INVOLVED IN	
			
Plasmepsin from *Plasmodium falciparum*	Hemoglobin degradation	SCAI, Germany, CNRS, France	CNU, Sth Korea
GST from *Plasmodium falciparum*	Parasite detoxification	Univ. of Pretoria, South-Africa	Univ. of Pretoria, South-Africa
DHFR from Plasmodium falciparum	Parasite DNA synthesis	Univ. of Modena, Italia	Univ. of Mahidol, Thailand

WISDOM-I -> Plasmepsin

- ***In vitro* results : 30 Compounds tested**

- > New experiments performed decreasing reaction time

  - 3 compounds with IC_{50}< Pepstatin A (reference inhibitor)
    - 2 thiourea compounds (known scaffold)
    - 1 guanidino compound (new scaffold)
  - 4 compounds have good IC_{50} values < 10 nM
  - 4 compounds with no inhibition activity
  - Others > 10 nM

- ***In vivo* results : 10 Compounds tested**
  - 5 compounds IC_{50} > 8.3 µM
  - 4 compounds IC_{50} > 25 µM
  - 1 Thiourea compound with lowest IC_{50}= 5,2 µM

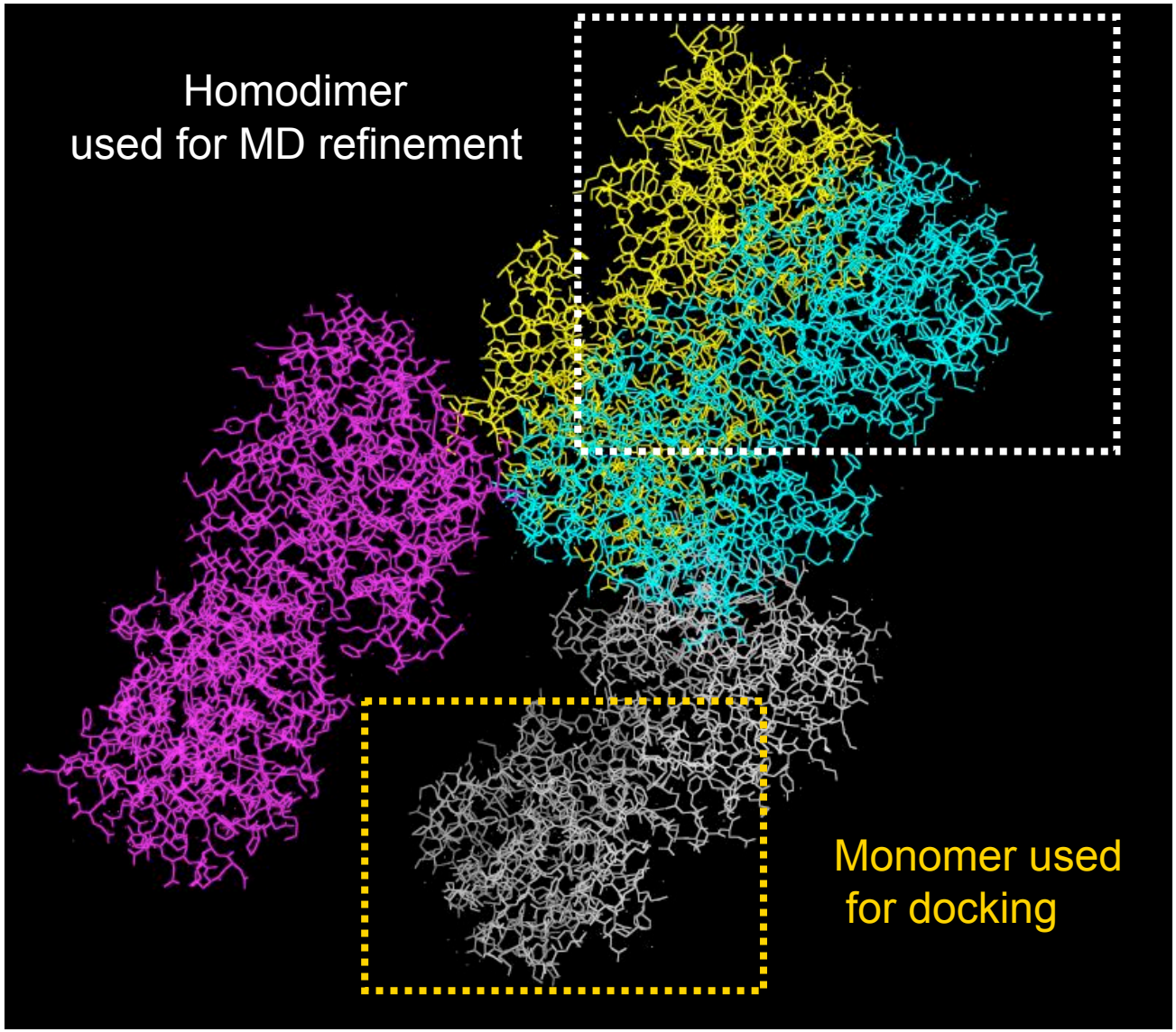
Low selectivity between red blood cells and parasite cells

WISDOM-2-> PfDHFR

- Re-ranking of compounds according to their free energy of binding calculated using MM-PBSA and MM-GBSA
- Analysis of interaction focusing on H-Bond between ligands and Asp54, Ile14 and Ile164 (key residues in wr9 interactions)
- Visualization of best scoring compounds (~200)
  - Evaluation of mobility after MD
  - Evaluation of binding orientation, comparison with WR99210
- Selection of the 16 best scored compounds for in vitro testing based on:
  - Good interactions with the target
  - Reasonable chemical structure

Credit Gianluca Degliesposti

WISDOM-2-> GST



1q4j - Crystallographic unit cell

WISDOM-2-> GST

METHOD 1:

- Checking clashes with second subunit of the functional biological dimer minimized for 5000 best scored compounds.
- These 5000 compounds were refined by MD procedure and checked afterwards.
- Post MD analysis will include the following:
  - Check of clashes of compounds using Chimera
  - Do an interaction analysis, focussing on the key amino-acids, looking for the H-bonding with the ligand.
- Compile a list of 100 top performing ligands

WISDOM-2-> GST

METHOD 2:

- Extract the best 15000 molecules based on their docking score (FlexX) as well as their binding modes.
- Try to extract scaffold structures that can be linked to inhibition / activity using libMCS from Chemaxon.
- Clustering these molecules based on their molecular fingerprints.
- Extracting the centroids from these clusters
- Selection of the 25 best compounds for in vitro testing based on:
  - Good interactions with the target
  - Leadlike and druglike structures

WISDOM-2-> GST

- 32 compounds under testing + compounds all other the virtual screening workflow to validate - > Total : 60 cpds
- Reference: S-hexyl glutathione is a known inhibitor inhibiting GST about 40% at 500 uM -> bench mark for testing the compounds.
- A primary screen was done on the 60 compounds:
  - 1mM of the glutathione substrate
  - 500 uM, 250uM and 100 uM compound concentrations.
- 6 compounds were currently highlighted

-> Further kinetic studies

- Problems with solubility were encountered.

New project –> α-Amylase

TARGET	IMPLICATED IN	PARTNERS INVOLVED IN	
			
Human Pancreatic Alpha-amylase	Break down Dietary starch	KISTI, Sth Korea CNRS, France	CNU, Sth Korea

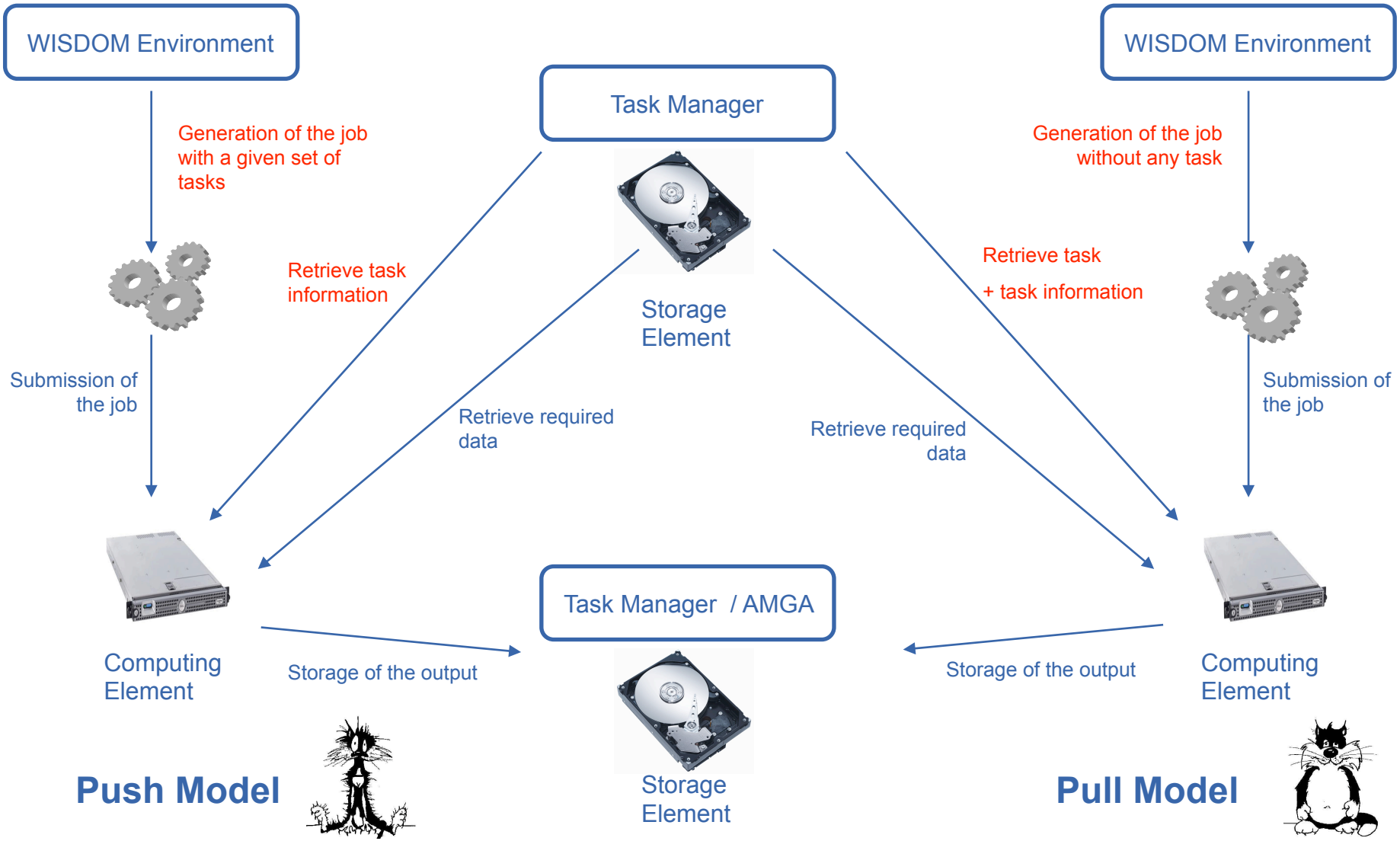
- **Drug Target**
  - Control of HPA activity can be used as a means of controlling blood glucose levels
  - Inhibitors of alpha-amylase : treatment of diabetes or obesity
- **Improvement in database preparation:**
  - Use of Chembridge Database to ease the commercial availability in comparison with ZINC
  - A.D.M.E.T filtering of database (FAF drugs tool with 200 rules)

Evolution of Wisdom Prod. E

After 3 years of development, the WISDOM environment has reached its final stage. A new environment is designed to improve its:

- **Flexibility**: Environment is suitable for short deadline jobs submissions and large-scale computing-intensive deployments.
- **Efficiency**: As soon as a task is submitted idle agents can pick it up and start running it almost instantly.
- **Versatility**: Environment can be used in multiple area like bioinformatics, physics…

Evolution of Wisdom Prod. E



Evolution of Wisdom Prod. E

Statistics of the last large-scale deployment (credits to Kisti):

Number of tasks submitted	Corresponding CPU time	Real processing time on the Grid	Agents running concurrently	Average task retrieval time
300,000	40 years	2,5 days	7,000	2 seconds

- > Crunching factor of 6000 that shows a distribution efficiency of 85%.

Credit J. Salzemann

CONCLUSION

- **Biochemical aspect: successful results validated the combination of EGEE Grid and *in silico* drug discovery**
  - > suggesting that the overall WISDOM approach used to select the candidates is able to discover potential inhibitors.

- **Grid aspect: new WISDOM production environnent allowed good grid performances**
  - > performances similar to those obtained on clusters with grid scalability
  - > grid workload management overhead is reduced.

Perspectives

- **Current WISDOM developments target non-grid experts:**
  - "**Bioinformatics platform**" for simple an transparent use of grid services through the WISDOM environment.

  = >> DEMO 10
  - " **DrugScreener-G**": integrated environment for grid-based virtual screening under the WISDOM environment (Kisti)

  = >> POSTER 10

- **Future WISDOM deployments on:**
  - DEISA (MD)
  - OSG (docking)
  - ALABAMA SUPERCOMPUTER CENTER (docking)

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