The stakeholders

Our stakeholders are top-tier research institutions and the Fundación Marcelino Botín as seed investor.
Mission-Vision-Values

![Graph showing the number of deaths and living with HIV infection over time. The graph indicates a decrease in deaths after the introduction of HAART.]
Perspective
$ of genomics
Sequenced genomes

Cumulative sequenced genomes

- Bacteria
- Eukaryotes
- Archaea

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“Omics”
Biological structures
Approvals – Expenditure- Productivity

Productivity of the pharma industry
Finding the true cost of a new drug is complex and controversial...

- New drug cost and R&D spend could be 30% higher if non-PhRMA members are included

Date: USFDA, PhRMA

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FDA Notices, withdrawals

One in Three Drugs Found to Pose Safety Risks Post-FDA Approval

Number of FDA Notices and Withdrawals of Applications for Safety or Effectiveness Reasons

- Withdrawals for S/E Reasons
- S/E Withdrawal Notices

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The explanation

Lack of knowledge of biological systems
A possible solution

We need:
1) More data
2) Put all the data to good use

Data $\rightarrow$ Information
The way forward
The way forward
The way forward
The way forward

• The first drugs devised (in part) thanks to structure-based DD and modeling were generated at the time of Cray-2
Many targets (anti-infectives, oncology) evolve mutations due to selection pressure by exposure to drug

Mutations cause a change in drug potency

Subtle changes in active site, many times in amino acid layers not in contact with drug or lead, can knock-off the activity

**In silico prediction of resistance due to mutations in target currently not straightforward**
**PELE-RP**

- An example: HIV-1 protease
- Dimer, it can easily accumulate 15-25 mutations in each monomer
- Extremely difficult system – high flexibility (two flaps on top of active site), explicit water molecule in active site
- Mutations can be idle, medium-resistance high-resistance conferring
- Classical cross-docking leads to wrong poses
PELE-RP

• IrsiCaixa AIDS Institute collaboration

• **Blind test** predictions on resistance of a group of real HIV patients

• Only sequence of protease delivered to our group

• Based on sequence, applying a PELE-RP protocol predictions called of:

  a. **No-resistance**
  b. **Medium resistance**
  c. **High resistance**.
Our computational approach detected all of the genotype changes triggering high-level resistance, even those involving a large number of mutations.
TECHNOLOGICAL SHORTCOMING

• Induced-fit docking still unresolved.

• Simultaneous exploration of ligand and receptor degrees of freedom seldom accounted for

• Simulating the whole binding event in near physiological conditions is rarely carried out. No clues on in and out migration

Reliable induced-fit docking technologies are lacking
G-Protein Coupled Receptors (GPCRs)

- Receptors, 45% (GPCRs, 25%)
- Enzyme, 28%
- Nuclear receptor, 2%
- Ion channel, 5%
- DNA, 2%
- Hormone & factors, 11%
- Unknown, 7%

Neurotransmitter

Membrane-spanning alpha helix

G-protein-coupled receptor

Extracellular side

Intracellular side

G-protein

RMSD ligand, Å
SME – HPC needs

- HPC is key for competitiveness in the Life Sciences sector
- It is especially relevant for technology-based start-ups such as NBD
- It is in part enabled by the emergence of big HPC infrastructures
- New formulas to access HPC will foster innovation of European SMEs
- Red Española de Supercomputación – RES, a success case in this direction
Thank you

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Outsourcing

The Global Drug Discovery Outsourcing Market

Pharmaceutical companies looking to save time and lower costs have turned increasingly to CROs, many of them now located in China. Over time outsourcing is expected to consume an increasingly large portion of drug discovery budgets.

Global Revenue (U.S. billions)

- 2010: $8.2
- 2012: $11.1
- 2014: $15.2
- 2016: $21.2

Source: Global Information

BIG PHARMA: Services Outsourced

- Clinical Research: 2013 - 46%, 2012 - 33%
- Analytical Testing: 2013 - 43%, 2012 - 34%
- Bioanalytical Testing: 2013 - 34%, 2012 - 26%
- Regulatory Support: 2013 - 29%, 2012 - 24%
- Chemical Synthesis: 2013 - 25%, 2012 - 20%

- Custom Manufacturing: 2013 - 24%, 2012 - 23%
- Drug Delivery: 2013 - 24%, 2012 - 22%
- Logistics & Distribution: 2013 - 23%, 2012 - 20%
- Toxicology Testing: 2013 - 23%, 2012 - 16%
- Stability, Storage & Testing: 2013 - 21%, 2012 - 18%

- Fill and Finish: 2013 - 19%, 2012 - 21%
- Blending: 2013 - 18%, 2012 - 15%
- Product Characterization: 2013 - 18%, 2012 - 10%
- Process Optimization: 2013 - 18%, 2012 - 10%
- Formulation / Pro-Formulation: 2013 - 16%, 2012 - 11%

- Sterile Compound R&D: 2013 - 16%, 2012 - 10%
- Cytotoxic: 2013 - 15%, 2012 - 8%
- High Potency Compounds: 2013 - 12%, 2012 - 11%
- Lyophilization: 2013 - 11%, 2012 - 8%

Average # of Unique Services Outsourced: 2013 - 6, 2012 - 4