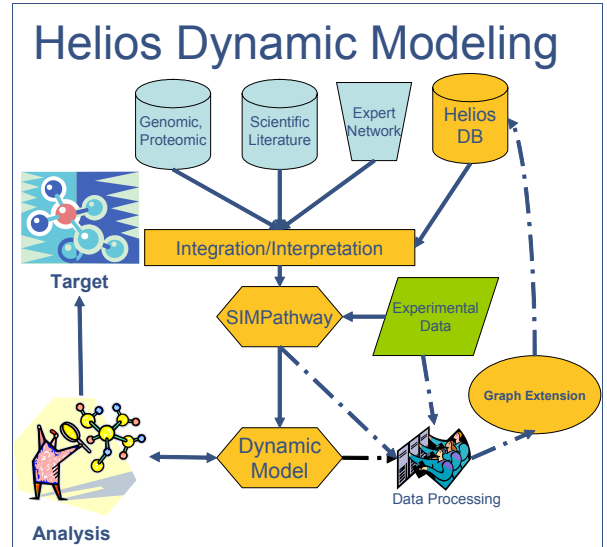




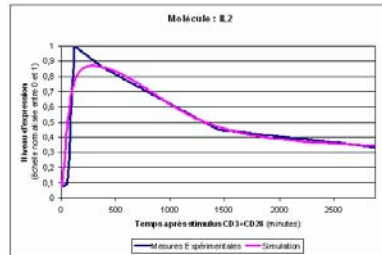
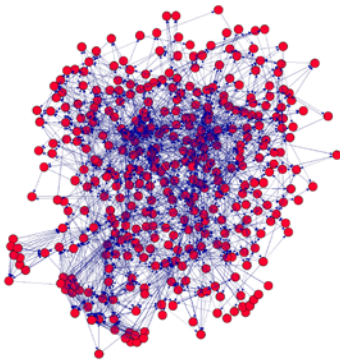
The Highway to Efficient Drug Targets

Target Designer

Helios Biosciences offers a new paradigm in systems biology : by introducing the dynamic dimension in the study of biological regulatory pathways, therapeutic targets can be characterized using fast and cost-efficient techniques. We build directed networks of intermolecular interactions and develop software to model the dynamics of these networks' responses after pathological / pharmacological stimuli.



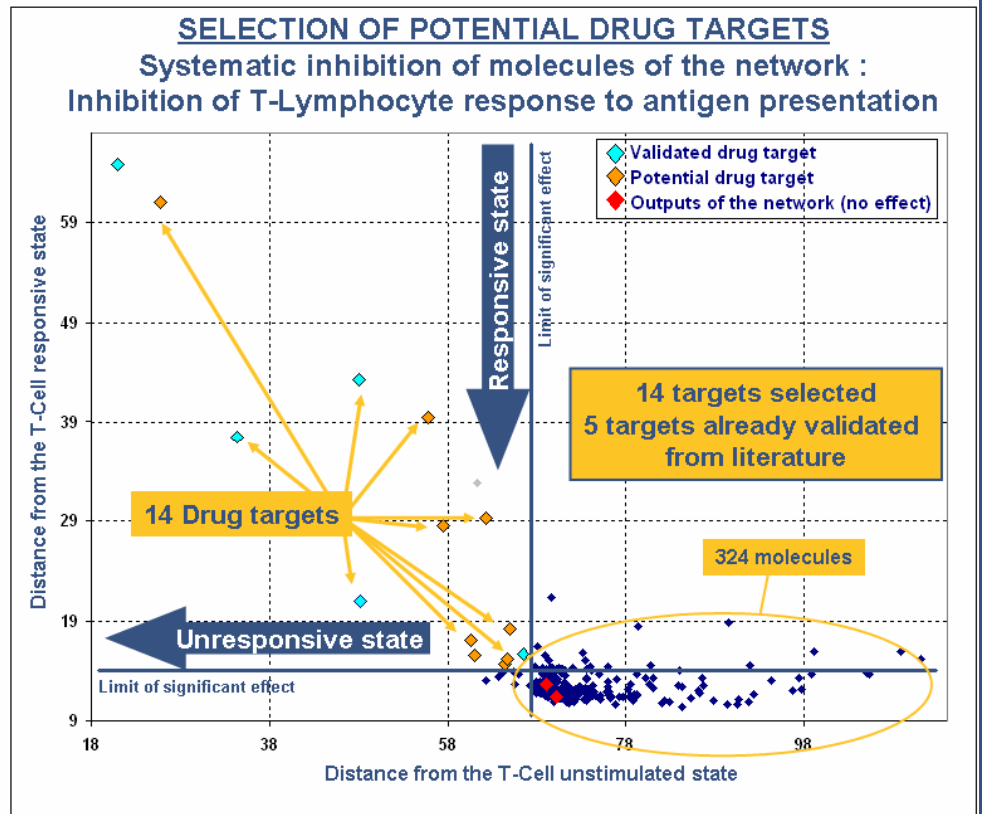
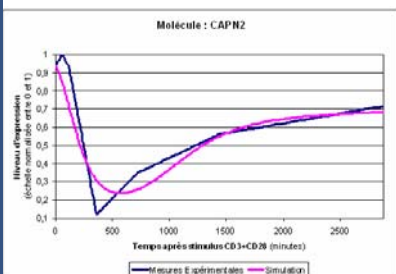
IMMUNO-DYN: Dynamic modelling of T cell Response : characterisation of targets inhibiting T cell response



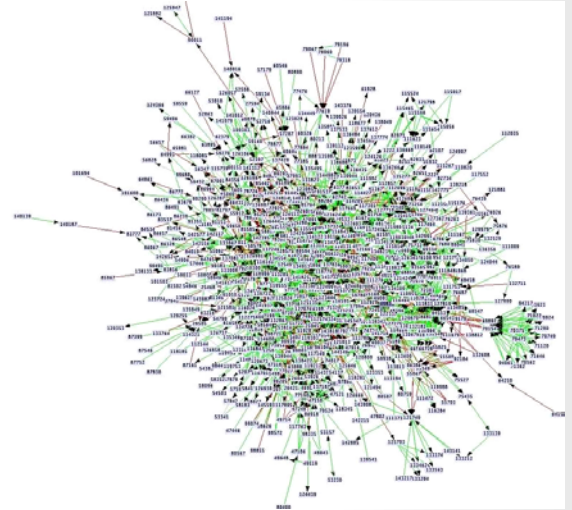
The overall relative distance between experimental data and modeled data is 16.5% which is very satisfactory given the complexity of the network (338 molecules and 1638 interactions) and the heterogeneity of the molecule expression kinetics.

The T-cell response consists of cell differentiation / activation, proliferation and apoptosis depending on stimulus and time after stimulus. The network combines cascades of general and T-cell specific signal transductions, cell cycle and apoptosis.

Red dots : molecules. Blue arrows : directed interactions.



- To overcome the shortcomings of current networks of molecular interactions - namely, that they are not accurate enough to sustain the development of large-scale dynamic models and signal propagation analyses, Helios Biosciences has developed SIMPathway : a reliable, large-scale, integrated and directed network of molecular interactions (SIMPathway = Smart Integrated Molecular Pathway).
- We have built algorithms and software to model the dynamics of the evolution of intra-cellular molecular networks during physio-pathological situations. The dynamic modeling of the human T lymphocyte transformation has been successfully performed.



Some of the Frequently Asked Questions:

- **Which molecules are in the network? How are they selected?**

We build a signal transduction network. The molecules are included based on their role in signal transduction. Most drugs used in human clinics act on signal transduction.

Any kind of molecule is included whenever it is relevant to signal transduction in the physiological function considered. Our network includes ligand/receptor couples, linkers, kinases, phosphatases, proteases, transcription factors/cofactors, enzymes synthesising second messengers and other kinds of molecules. The general organisation of the network is based on interconnected signal transduction loops. The molecules are selected based on their effect on cell phenotype/response to stimuli. See additional information on our website (database description).

- **Why use dynamic modeling instead of other drug target identification methods such as :**

a. Expression profile statistical analysis (gene clustering, expression profile mapping on molecular interaction pathways)?

Our extensive benchmark analyses within the framework of the T-lymphocyte response show that:

- *Gene clustering or variation-of-expression rates are not efficient ways to select drug targets, because the expression profiles of validated drug targets do not statistically differ from the other molecule ones within a given pathway. This may partially explain the high current attrition rate in drug targeting (selection of inefficient targets).*
- *Expression profile mapping on molecular interaction pathways only identifies the highly connected molecules ('hubs') which expression strongly changes. Acting on such molecules is a good way to produce major side effects, and as a matter of fact most drugs used in human clinics do not target such molecules. This may also partially explain the high current attrition rate in drug targeting (selection of too much toxic targets).*

The drug targets identified through our dynamic modeling integrated approach include non-hub & non-strongly modulated molecules which are experimentally validated targets.

Dynamic modeling also provides the ability to systematically assess associations of effects (co-targeting) which is not feasible through other techniques.

b. Systematic inhibition of all molecules within a given molecule interaction pathway (RNAi and other)?

Such strategies are 'systematic' only at a small scale which is a major limitation (testing of a few to a few dozens molecules). They also require the previous definition and delimitation of the pathway. Our expertise in human pathway building unambiguously shows that to be coherent, a pathway sustaining even a limited physiological function (ex.: signal transduction from a ligand / receptor couple) systematically includes more than 100 genes / proteins.

Only dynamic models provide really systematic analyses which means testing hundred of molecules.

Dynamic modeling also provides the ability to systematically assess associations of effects (co-targeting) which is not feasible through other techniques.



Primarily focused on cancer and neuronal degeneration, Helios Biosciences is your partner to streamline your Drug Discovery process

We offer several business opportunities:

- **R&D partnerships** aiming at characterizing and validating drug targets in therapeutic areas of cancer and neurodegenerative diseases. APO-KDYN is focused on the characterization of target accelerating the cell death during the androgenic deprivation treatment of prostate cancer. APO-NDYN is focusing on the characterization of therapeutic targets limiting the death of neuronal cells.

- **Access to SIMPathway**. The database of molecular interaction is a large and integrated intracellular signal transduction network. It is a curated database relying on interactions oriented in the sense of propagation of the signal.

- **Analysis of Gene Expression in Tissues and Cells**

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