Knowledge Management in Systems Based Phenotypic Drug Discovery: *Our Experience*

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Almirall

Solutions with you in mind

Phenotypic screening approaches in Almirall

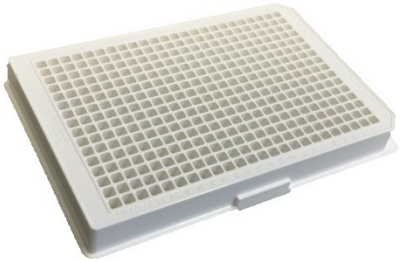
Example #1. Identification of inhibitors of the production of a pro-inflammatory cytokine.

- *Phenotypic screening.*
- *Subset of in house library.*
- *Human donor derived cell system –healthy cells-.*

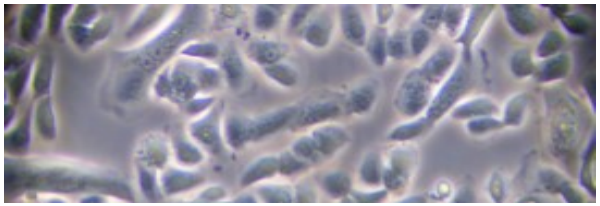
Example #2. Identification of inhibitors of a cell phenotype using a library of marketed drugs.

- *Phenotypic screening.*
- *Approved marketed drugs.*
- *Human healthy and diseased donor derived cell systems.*

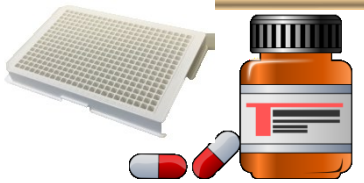
Selected subset of Almirall library



Phenotypic screening based in donor derived relevant human cells



Library of marketed drugs



Key learnings from doing phenotypic screening

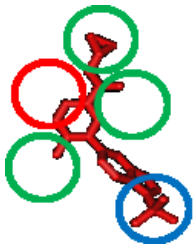
Chemical libraries: we should find ways to better exploit the biological universe of opportunities provided by phenotypic screening: *more chemically diverse libraries ?, less "conventional" chemical space ? more "bioactive" chemistry ?*

Human primary cells can be a limiting factor so that only a few thousand cpds can be screened. It is critical to select representative donors based in phenotype of interest and evaluation of protein and gene expression profiling data.

Chemical hits: access to both in house and public domain data of hits and related chemistry is required for early hit prioritization.

Current bioactivity profiling tools allow early assessment of the mechanism of action, phenotypic selectivity and potential liabilities. Some phenotype based hit optimization may be required before attempting target identification.

In the absence of a target, we should rely in **phenotype based optimization** supported by SAR of activities identified in profiling, which can provide additional criteria for prioritization.



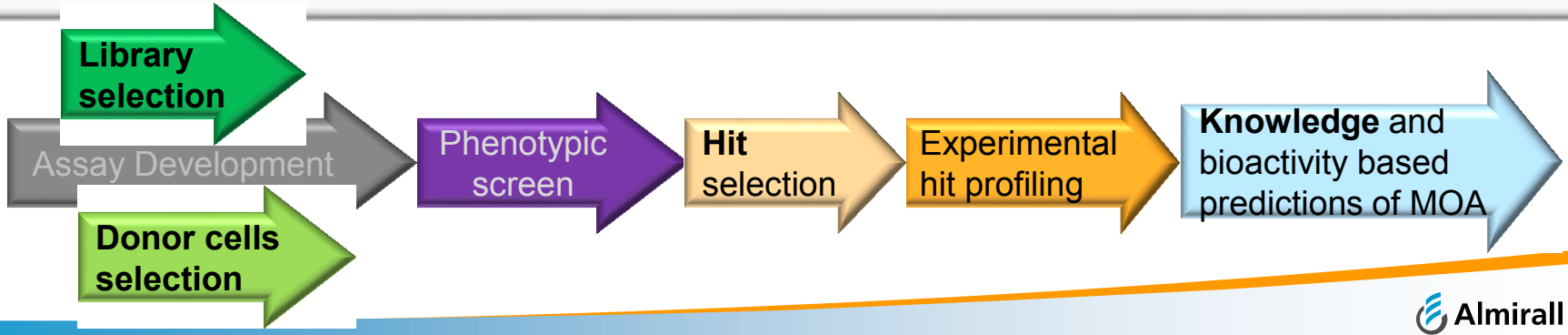
Data driven challenges in phenotypic drug discovery

More "phenotypic screening oriented" libraries: which chemical space is more likely to contain molecules active in our phenotypic system of interest ?

Donor derived human primary cells: comparison of in house gene/protein expression profiling data with verified public reference records of the same cell lineage in order to ensure that representative donors are selected.

Chemical hits: access and full integration of in house and verified public domain data obtained for hits and related molecules. Hit prioritization not only to be based in chemical structure but also in potential biological activity.

Profiling of selected hits: capability to compare the bioactivity signature of a phenotypic hit with signatures generated and integrated from public sources for reference drugs. This can be useful to identify potential liabilities and likely mechanism of action in the absence of structure similarity.



Data driven challenges in PDD: our current solutions

Library subset selected based in chemical diversity, lack of structural alerts, physicochem properties and cytotox prediction. *No additional criteria* in place.

Donor derived human primary cells: verification of phenotype of interest and a *limited number of traits*: growth properties, shape, tissue specific markers etc.

Structure based characterization of hit molecules: *non integrated* approach.

1. Prediction of pharmacological profile and potential mechanism of action based in available public information for structurally similar compounds.
2. Assessment of potential liabilities either directly, as known liabilities of structurally similar compounds, or indirectly, based in predictions of mechanism of action.

Bioactivity based profiling of selected hits: offered by service providers as *partial signatures* based in their own reference compound databases.

Current solutions are resource intensive and may be missing some of the potential offered by the powerful approaches used for hit characterization

Knowledge management in phenotypic drug discovery: Key challenges ahead

- **Chemical libraries**: tools to access to more phenotypic screening relevant chemical space
- **Human primary cells:** capability to compare with public expression profiling data to ensure that cells from representative donors are selected.
- **Chemical hits:** better integration of in house and public pharmacological data with information from structure based prediction tools.
- **Profiling of selected hits**: access to integrated bioactivity footprints based in public data would facilitate identification of likely mechanism of action and any potential liability in the absence of structure similarity.