Pharmacological evaluation of drugs & combinations in patient samples of hematological malignancies by automated flow cytometry

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ABSTRACT

The novel flow cytometry ExviTech® platform has incorporated key innovations to predict or evaluate the response of primary patient tumor cells to compounds and combinations analyzing both efficacy and hematotoxicity by dose-response curves and kinetics. We used whole sample without isolating leukocytes, which was vitally important efforts for >20 years. This approach has achieved 90% correlation with clinical patient outcome in AML 1st line treatment Cytarabine plus Idarubicin, a level of clinical correlation not achieved before with ex vivo testing. We have profiled the pharmacological activity of more than 50 drugs in more than 1,000 patient samples ofAML, MM, CLL, ALL, NHL, MF and PV. We now offer this body of knowledge to characterize the behavior of your compounds in these patient samples. Assays include depletion, apoptosis, proliferation, differentiation, autophagy, epigenetic, hypomethylating agents, etc. Optional combinations of new compounds with other drugs or drug candidates are identified by measuring synergism among combinations, and also complementarity with other individual drugs (drug active in those samples where the lead compound is resistant). In summary, we have developed an improved methodology to measure the pharmacological activity of drugs and drug combinations in hematological patient samples as well as modeling their pharmacological behavior.

METHODS

Main advantages

- Use of Flow cytometry that can identify different cell subsets or resistant cells.
- Use of whole blood instead of isolated leukocytes: maintenance of microenvironment, stromal cells, etc.
- Assays include depletion, apoptosis, proliferation, differentiation, autophagy, hypomethylating agents, etc.
- Optional combinations of new compounds with other drugs or drug candidates are identified by measuring synergism among combinations, and also complementarity with other individual drugs (drug active in those samples where the lead compound is resistant).

RESULTS

Vivia ex vivo assay clinically predictive

- Pharmacological variables EC50(CYT), Emax(CYT) and synergism CYT-IDA
- Drug sensitivity testing never achieved this high correlation
- Validates new method whole sample microenvironment etc...
- Launching interventional clinical trials relapse AML
- Enables cost-effective samples with informed consent & clinical data

CONCLUSIONS

- Since Q3 Vivia Biotech offers the PM test & KDL network to provide compound profiling & biomarker services in patients samples
- Difference is no Ficoll separation before incubation, maintenance of microenvironment and a key to measure drug-drug synergism
- Vivia’s PM test can be a companion diagnostic of your drug’s clinical trials
- Can identify synergistic drug combinations, efficient in a patient subpopulation with high unmet need
- If scalability is a concern, we can convert ex vivo biomarker into standard molecular Biomarker
- >80% prediction rate responsive patients would reduce cost and time of the drug’s clinical trial
- May rescue underperforming drugs phase II-III trials

Figure 1. The flow cytometry ExviTech® platform integrates the known advantages of flow cytometry for hematological malignancies and a sophisticated information technology that enable us to perform a more detail pharmacological evaluation of drugs and combinations.

We identify niche populations for your Me Too drug

Identifying Best Drug Combinations: Synergism vs Complementarity

Best drug combination treatment includes both synergistic & complementary drugs

Antiproliferative Effect AZA & DEC on AML BM Sample Only Detected in Cytokine Proliferation Assay

We characterize your drug in proliferation media

Pharmacologically characterized 54 protocols, drug combination treatments

Clinical Correlation Results 1st line AML CYT-IDA 90% Correct Prediction N=77

Clinical outcome

Positive predictive value %

52.1% 80.00

Negative predictive value %

40.23 89.61

Sensitivity %

86.96

Specifity %

90.74

Vivia ex vivo assay clinically predictive

- Dose response data 19 drugs in >100 MM bone marrow samples
- Represented as range of interpatient variability of their potency (EC50)
- Data on an individual patient shown by green bars, with confidence intervals (dotted)

Multiple Myeloma Pharmacological Profiles Monotherapy EC50s

Patient was resistant to all 3 treatments given, based on resistant drugs (red), while we could identify alternative sensitive drugs (green)

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