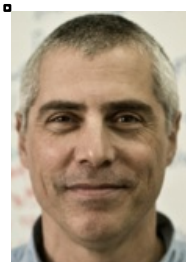
*Combinatorial Chemistry & High Throughput Screening*, 2014, *17*, 253-255 

# Personalized Drug Discovery: HCA Approach Optimized for Rare Diseases at Tel Aviv University

Leonardo J. Solmesky and Miguel Weil*

*Cell Screening Facility for Personalized Medicine, Laboratory for Neurodegenerative Diseases and Personalized Medicine, Cell Research and Immunology Department, The Sagol School of Neurosciences, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv, 69978, Israel*



Miguel Weil

**Abstract:** The Cell screening facility for personalized medicine (CSFPM) at Tel Aviv University in Israel is devoted to screening small molecules libraries for finding new drugs for rare diseases using human cell based models. The main strategy of the facility is based on smartly reducing the size of the compounds collection in similarity clusters and at the same time keeping high diversity of pharmacophores. This strategy allows parallel screening of several patient derived - cells in a personalized screening approach. The tested compounds are repositioned drugs derived from collections of phase III and FDA approved small molecules. In addition, the facility carries screenings using other chemical libraries and toxicological characterizations of nanomaterials.

**Keywords:** Drug repurposing, high content screening, nanomaterials characterization, personalized drug discovery, personalized medicine, rare diseases.

## CURRENT RESEARCH

Rare or orphan diseases are characterized by a small percentage of cases in the population that generally results in lack of knowledge about these diseases, lack of treatment and lack of research investment by pharmaceutical companies for drug discovery on such diseases [1]. Moreover, even that most rare diseases are genetically inherited and are caused by mutations in specific genes, phenotype variability between individuals suffering from the same disease exists [2]. Standard approaches towards drug development are inapplicable for rare diseases, as multi-phase clinical trials cannot be performed to evaluate efficacy. *The challenge posed by this complexity dictates the need for personalized medicine.* Today available chemical libraries of small molecules are a rich source of compounds with therapeutic potential that can serve as basis for such personalized treatment. However, a systematic methodology to evaluate the therapeutic efficacy of compounds for rare diseases is lacking. The emergence of image based high content screening/analysis (HCS/HCA) may help to solve this problem. HCA allows characterizing phenotypes of cells derived from donors with and without a disease and use it as a multi-parametrical profile or as a personal signature of the analyzed cells. Moreover, these cell or disease phenotype signatures (or biomarkers) could serve for personalization of the drug discovery process even when almost nothing is known about the disease etiology. This personalized strategy (depicted in Fig. **1**) involves developing target-based/phenotypic cell based assays and the use of libraries of small numbers of compounds. These compounds are highly diverse and representative of large collections making the personalized approach affordable. Specifically for cell based HCA assays we have adopted the use of bone marrow human mesenchymal stem cells (hMSC) (also skin fibroblasts are used) that can be maintained and expanded in culture into considerable numbers quite easily. Most importantly these cells bear the rare property to survive without serum, since they produce their own survival factors [3], allowing defined culture conditions [4, 5]. This is clearly an asset for drug screening as further discussed below. The HCA assay development is designed according to the specific disease based on a measurable disease phenotype. For example in case of Mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE), a genetic metabolic fatal disease that causes a mitochondrial dysfunction in all cells in the body, the assay is based on a differential mitochondrial activity and viability (not shown). A beneficial drug in this case would be one that could improve the energetic capacity of the MNGIE cell. Another example is to follow the recovery of IKAP protein by HCA after alternative splicing drug treatment in skin fibroblast cells of patients with Familial Dysautonomia a genetic disease caused by an exon skipping splicing mutation in the *IKBKAP* gene producing an aberrant IKAP protein [6]. In the examples mentioned above the disease etiology is clear, facilitating the choice for an HCA assay that would be most representative for patients with the disease and relevant for drug screening using generic cell-based model. In contrast, Amyotrophic lateral sclerosis (ALS) is a progressive, fatal, motor neuron degenerative

*Address correspondence to this author at the Cell Screening Facility for Personalized Medicine, Laboratory for Neurodegenerative Diseases and Personalized Medicine, Department of Cell Research and Immunology, The Sagol School of Neurosciences, The George S. Wise Faculty for Life Sciences, Tel Aviv University, Ramat Aviv 69978, Tel Aviv, Israel; Tel: +972-3-6406981; Fax: +972-3-6422046; E-mail: miguelw@tauex.tau.ac.il

1875-5402/14 $58.00+.00 

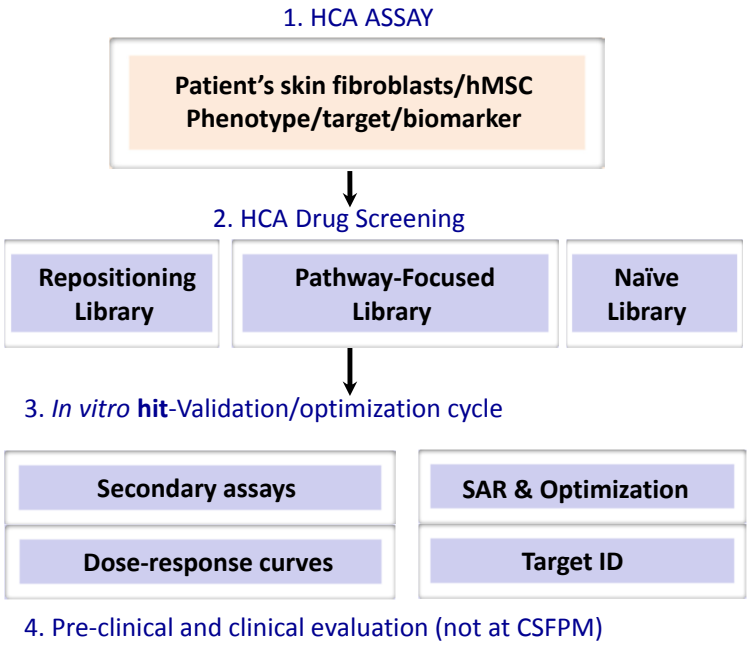



**Fig. (1).** Drug screening pipeline strategy for drug discovery at CSFPM is generally performed in 4 steps. Step1: HCA assay that involves isolation, expansion and phenotype/target/biomarker characterization of patient cells with a specific disease. Step 2: HCA drug screening of clustered libraries chosen according to patient, disease or project needs (it can be a repositioning library, a pathway-focused, or a naïve collection). Step 3: *In vitro* hit-validation/optimization cycle including secondary assay performance, dose-response curves, Structure-Activity Relationships (SAR) studies, and sometimes target identification (ID). Step 4: Pre-clinical and clinical evaluation studies of the obtained hit/lead compounds from this pipeline are performed elsewhere by interested parties.

disorder. Most cases of ALS are sporadic (sALS) and the causes of the disease are unknown [7]. The clinical course of ALS is highly variable, suggesting that multiple factors underlie the disease mechanism [8]. It is obvious that for ALS a different HCA approach needs to be developed based on novel phenotype signatures found in hMSC or skin fibroblasts of ALS patients that must be relevant for motor neurons too. In this respect we have recently found four novel ALS potential biomarkers in non-neural tissues from sporadic ALS patients in bone marrow mesenchymal stem cells (hMSC) and peripheral blood leukocytes that may have direct diagnostic and pathological implications in the disease [9, 10]. Recently these assumptions were strengthen by our findings that showed that these four potential ALS biomarkers are differentially expressed in neuronal and non-neuronal tissues of the transgenic mouse ALS model SOD-1 (G93A) as compared with wt littermates at different times within the 120 days of disease progression [10]. These results also support the relevance of using ALS-hMSC and the ALS biomarkers as basis for personalized drug screening. In this case, an HCA assay should address the existing phenotype signature differences in the ALS cells that are reflected by the molecular mechanisms and pathways responsible for the biomarkers expression differences found in cells of several ALS patients. Personalized drug screening for ALS are being performed in cells from various ALS patients in parallel in a way that hit compound assessment will be evaluated individually by testing its effects on the patient cell biomarkers profile.

In order to maximize the chance of success we have the ability to use the following libraries for personalized screening: A) Repurposing library: a collection of 300 drugs provided by Minoryx therapeutics, representing a universe of 9,000 Phase III and approved drugs. Repurposing is one of the most effective drug discovery strategies for rare diseases [11-13]. B) Unbiased screening of a collection of 20,000 compounds (DiverSet-CL, ChemBridge, Inc.), that could be clustered and prioritized into 600 to make screening more efficient by our computational chemist partners. Candidate drugs (hits) that are identified from the above screening are validated and optimized further as depicted in Fig. (**1**).

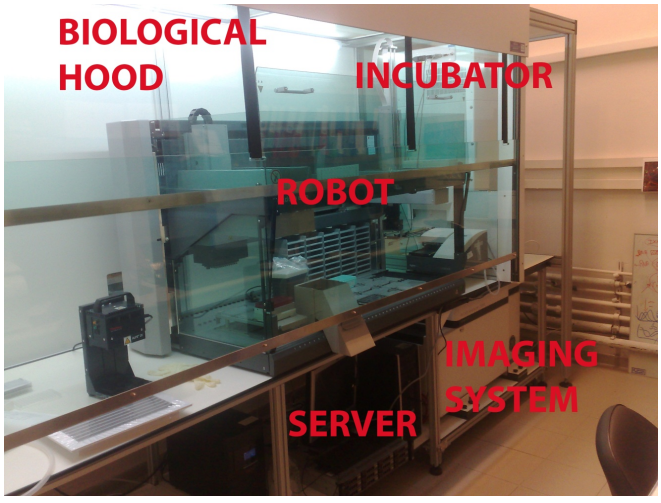



**Fig. (2).** Cell Screening Facility for Personalized Medicine at Tel Aviv University, Israel.

The CSFPM at Tel Aviv University, comprises of a fully automated integrated liquid handling robot with an IN Cell

Analyzer 2000, sterile hood and automated cell incubator with computer server for data mining and analysis (see Fig. **2**). The CSFPM has been involved in conventional phenotypic screening of small molecules libraries (using our 20,000 compounds collection) for rare neurodegenerative diseases. Such is the example of the screen we are carrying out at the present for adult polyglucosan body disease (APBD). APBD is a disorder characterized by adult-onset and progressive neuropathy with mixed upper and lower motor neuron involvement, sensory loss predominantly in the distal lower extremities, and mild cognitive difficulties [14]. In the screening we are carrying out for this disease, we evaluate the ability of compounds for reducing polyglucosans accumulation in fibroblasts derived from APBD patients based on periodic acid Schiff staining [15].

In addition, CSFPM has been recently involved in several projects for characterization of toxicity of different nanomaterials such as lipid nanoparticles [16] and hyaluronic acid conjugated carbon nanotubes [17].

## FUTURE PERSPECTIVES

CSFPM is open to collaborations both with academic labs and companies, especially in the fields of rare diseases and personalized drug discovery. CSFPM offers to biopharmaceutical industry, academic labs, medical institutions, or other potential customers outsourcing services on HCS, automated liquid handling, and drug discovery, with special emphasis on the aforementioned fields.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENTS

We thank the Mexican Friends of Tel Aviv University for their contribution in the establishment of CSFPM.

## REFERENCES

[1] Sharma, A.; Jacob, A.; Tandon, M.; Kumar, D. Orphan drug: Development trends and strategies. *J. Pharm. Bioallied Sci.,* **2010**, *2* (4), 290-299.

[2] Girirajan, S.; Eichler, E.E. Phenotypic variability and genetic susceptibility to genomic disorders. *Hum. Mol. Genet,* **2010**, *19* (R2), R176-187.

[3] Solmesky, L.J.; Abekasis, M.; Bulvik, S.; Weil, M. Bone morphogenetic protein signaling is involved in human mesenchymal stem cell survival in serum-free medium. *Stem Cells Dev.,* **2009**, *18* (9), 1283-1292.

[4] Solmesky, L.; Lefler, S.; Jacob-Hirsch, J.; Bulvik, S.; Rechavi, G.; Weil, M. Serum free cultured bone marrow mesenchymal stem cells as a platform to characterize the effects of specific molecules. *PLoS One,* **2010**, *5* (9), e12689.

[5] Solmesky, L.J. *Characterization of Human Mesenchymal Stem Cells from Bone Marrow*, 1st ed.; Lambert Academic Publishing: Saarbruken, Germany, **2012**.

[6] Slaugenhaupt, S.A.; Blumenfeld, A.; Gill, S.P.; Leyne, M.; Mull, J.; Cuajungco, M.P.; Liebert, C.B.; Chadwick, B.; Idelson, M.; Reznik, L.; Robbins, C.; Makalowska, I.; Brownstein, M.; Krappmann, D.; Scheidereit, C.; Maayan, C.; Axelrod, F.B.; Gusella, J.F. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. *Am. J. Hum. Genet.,* **2001**, *68* (3), 598-605.

[7] Rothstein, J.D. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. *Ann. Neurol.,* **2009**, *65* (Suppl 1), S3-9.

[8] Piaceri, I.; Del Mastio, M.; Tedde, A.; Bagnoli, S.; Latorraca, S.; Massaro, F.; Paganini, M.; Corrado, A.; Sorbi, S.; Nacmias, B. Clinical heterogeneity in Italian patients with amyotrophic lateral sclerosis. *Clin. Genet.,* **2012**, *82* (1), 83-87.

[9] Nachmany, H.; Wald, S.; Abekasis, M.; Bulvik, S.; Weil, M. Two potential biomarkers identified in mesenchymal stem cells and leukocytes of patients with sporadic amyotrophic lateral sclerosis. *Dis Markers,* **2012**, *32* (4), 211-220.

[10] Lilo, E.; Wald-Altman, S.; Solmesky, L.J.; Ben Yaakov, K.; Gershoni-Emek, N.; Bulvik, S.; Kassis, I.; Karussis, D.; Perlson, E.; Weil, M. Characterization of human sporadic ALS biomarkers in the familial ALS transgenic mSOD1G93A mouse model. *Hum Mol Genet,* **2013**, *2*(23), 4720-4725.

[11] Palomino, J.C.; Martin, A. Is repositioning of drugs a viable alternative in the treatment of tuberculosis? *J. Antimicrob. Chemother.,* **2013**, *68* (2), 275-283.

[12] Sardana, D.; Zhu, C.; Zhang, M.; Gudivada, R.C.; Yang, L.; Jegga, A.G. Drug repositioning for orphan diseases. *Brief Bioinform.,* **2011**, *12* (4), 346-356.

[13] Tobinick, E.L. The value of drug repositioning in the current pharmaceutical market. *Drug News Perspect.,* **2009**, *22* (2), 119-125.

[14] Roe, C.R.; Bottiglieri, T.; Wallace, M.; Arning, E.; Martin, A. Adult Polyglucosan Body Disease (APBD): Anaplerotic diet therapy (Triheptanoin) and demonstration of defective methylation pathways. *Mol. Genet. Metab.,* **2010**, *101* (2-3), 246-252.

[15] Kakhlon, O.; Glickstein, H.; Feinstein, N.; Akman, H.; DiMauro, S.; Minassian, B.; Michaeli, A.; Rayan, A.; Grossman, T.; Solmesky, L.; Weil, M.; Kozakov, D.; Lossos, A. Searching for Efficient Therapeutic Avenues To Treat Adult Polyglucosan Body Disease (APBD) and Lafora Disease (LD) Using a High-Throughput Screening Platform. *Neurology,* **2013**, *80* (Meeting abstracts I), P03.053.

[16] Solmesky, L.J.; Shuman, M.; Goldsmith, M.; Weil, M.; Peer, D. Assessing cellular toxicities in fibroblasts upon exposure to lipid-based nanoparticles: a high content analysis approach. *Nanotechnology,* **2011**, *22* (49), 494016.

[17] Dvash, R.; Khatchatouriants, A.; Solmesky, L.J.; Wibroe, P.P.; Weil, M.; Moghimi, S.M.; Peer, D. Structural profiling and biological performance of phospholipid-hyaluronan functionalized single-walled carbon nanotubes. *J. Control Release,* **2013**, *170* (2), 295-305.

**Received: September 19, 2013** **Revised: November 5, 2013** **Accepted: November 6, 2013**