Chemical profiling for theranostics applications

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Technology Overview:

Non-targeted chemical profiling can reveal valuable information about metabolic flux of a biological specimen. In contrast to focusing on specific biomolecules it works by generating an overall biochemical profile associated with disease or therapeutic interventions. Harnessing the ability of Raman spectroscopy to provide quantitative biochemical analyses in real time and in a label-free manner, we plan to build a catalogue of spectral and biochemical markers associated with diseases and therapy.

Biomedical application potential:

Recently we reported that biochemical profiling of newly generated isogenic metastatic breast cancer cell lines can provide information about molecular biomarkers that constitute the metastatic site. Subtle differences in the vibrational signatures of these markers are reflective of the multiple and complex interactions between metastatic cells and host homeostatic mechanisms. These parameters can be utilized to develop decision algorithms with high diagnostic accuracy.

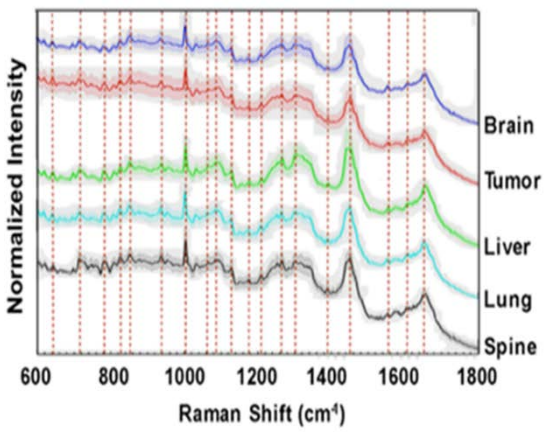
Using the same technology we demonstrated that time dependent therapeutic efficacy of proteasome inhibitors on multiple myeloma cells could also be evaluated in a label-free manner. Information revealed by chemical profiling of single cell can be used to design patient specific treatment strategies.

Tissue heterogeneity and variation in tumor microenvironment are important parameters in accurately determining the pharmacokinetics or therapeutic efficacy of a drug. Novel methods with the ability to measure real-time tumor drug response using a minimally invasive procedure has potentially high clinical utility. Our current efforts are directed towards translating this technique as platform for assessing the biochemical differences at tissue level in a label-free and objective manner.

Ongoing project:

1. Analytical determination of biomarkers for diagnosis of breast cancer metastatic progression.
2. Labe-free approaches to identify UV induced damage in skin fibroblasts.
3. Assessment of effects of proteasome inhibitors on multiple myeloma cell lines.
4. Identification non-alcoholic steatohepatitis (NASH) associated changes in mouse models.
5. Monitoring i*n vivo* drug-induced apoptosis in tumors using Raman spectroscopy.

A



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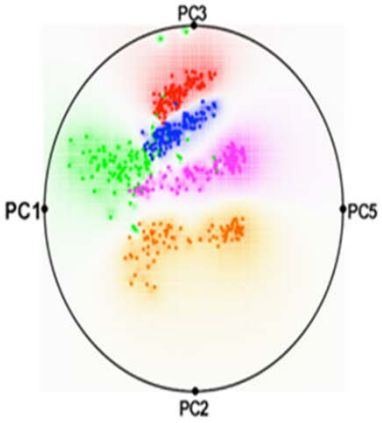
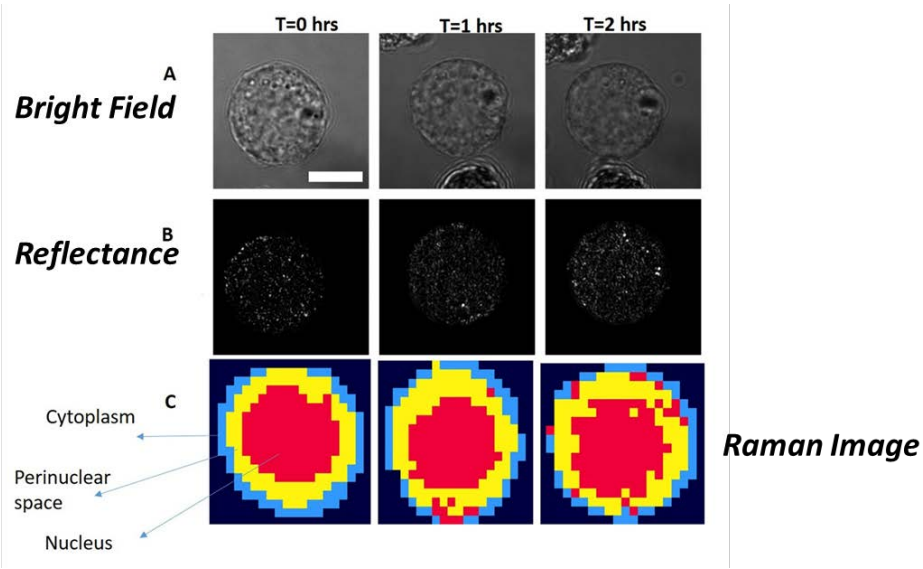


A. Raman spectra along with standard deviation acquired from brain, primary tumor (1° Tumor), liver, lung, and spine cell lines.
B. Principal component scores plot shows the clustering of the spectral data corresponding to each organ-specific cell line, red: primary tumor, blue: brain, green: liver, orange: lung, and purple: spine.

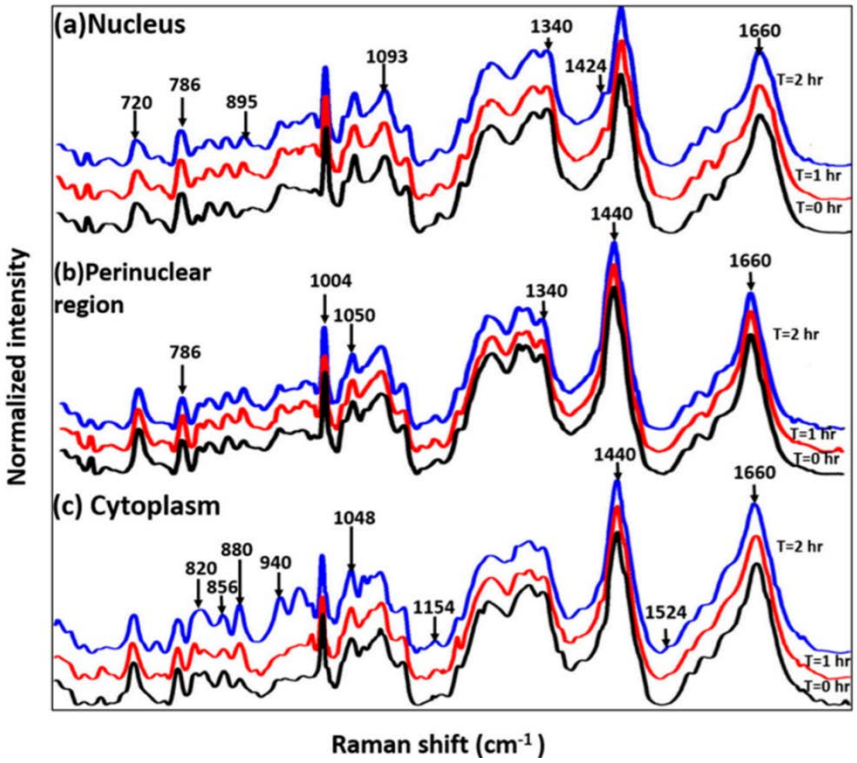
Table: Summary of diagnostic accuracy of different decision algorithms for classification of isogenic metastatic breast cancer cell lines

	PLSDA[1] algorithm	SVM[2] algorithm	PLSDA[1] feature-specific algorithm
Reference Identification	**Correct Classification (%)**	**Correct Classification (%)**	**Correct Classification (%)**
1° Tumor[3]	99.3 (0.7)4	98.9 (1.1)	97.2 (2.8)
Brain	98.0 (2.0)	99.6 (0.4)	91.7 (8.3)
Liver	97.4 (2.6)	94.3 (5.7)	91.1 (8.9)
Lung	93.3 (6.7)	97.3 (2.7)	85.8 (14.2)
Spine	96.1 (3.9)	98.2 (1.9)	90.6 (9.4)

[1]Partial Least Squares Discriminant Analysis.
[2] Support Vector Machines.
[3]Primary Tumor cell line.
[4]Values in parenthesis = percentage misclassifications



Temporal monitoring of the RPMI8226 cell treated with Bortezomib A. Bright field image B. confocal reflectance C. Four cluster Raman images.



Spectra extracted from individual clusters of single myeloma cell annotated to an intracellular region in cluster Raman image A. Nucleus, B. Perinuclear Region, C. Cytoplasm.

Background Publications

1. Winnard, P.T., Jr.; Kluth, J.B.; Raman, V. Noninvasive optical tracking of red fluorescent protein-expressing cancer cells in a model of metastatic breast cancer. Neoplasia, 2006, 8, 796-806.
2. Hideshima, T.; Richardson, P.; Chauhan, D.; Palombella, V.J.; Elliott, P.J.; Adams, J.; Anderson, K.C. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res. 2001, 61, 3071–3076.
3. Uckermann, O.; Galli, R.; Anger, M.; Herold-Mende, C.; Koch, E.; Schackert, G.; Steiner, G.; Kirsch, M. Label-free identification of the glioma stem-like cell fraction using Fourier-transform infrared spectroscopy. International journal of radiation biology 2014, 90, 710-717.
4. Krafft, C.; Popp, J. The many facets of Raman spectroscopy for biomedical analysis. Analytical and bioanalytical chemistry 2015, 407, 699-717.
5. Austin, L.A.; Osseiran, S.; Evans, C.L. Raman technologies in cancer diagnostics. The Analyst 2016, 141, 476-503.
6. Pully, V.V.; Lenferink, A.T.M.; Otto, C. Time-lapse Raman imaging of single live lymphocytes. Journal of Raman Spectroscopy 2011, 42, 167-173.

Center Publications

1. Kang, J.W.; Lue, N.; Kong, C.R.; Barman, I.; Dingari, N.C.; Goldfless, S.J.; Niles, J.C.; Dasari, R.R.; Feld, M.S. Combined confocal raman and quantitative phase microscopy system for biomedical diagnosis. Biomedical optics express 2011, 2, 2484-2492.
2. Kang, J.W.; Singh, S.P.; Nguyen, F.T.; Lue, N.; Sung, Y.; So, P.T.; Dasari, R.R. Investigating effects of proteasome inhibitor on multiple myeloma cells using confocal Raman microscopy. Sensors, 2016, 16-27.
3. Winnard, P.T., Jr.; Zhang, C.; Vesuna, F.; Kang, J.W.; Garry, J.; Dasari, R.R.; Barman, I.; Raman, V. Organ-specific isogenic metastatic breast cancer cell lines exhibit distinct raman spectral signatures and metabolomes. Oncotarget 2017.