GenPro presents azacitidine efficacy study to identify epigenetic predictors of Responder vs Non-Responder AML/MDS patients.

The work will be presented in a poster session on Sunday, December 4, 2016, 6:00 PM-8:00 PM. The project is titled, "Epigenetic Profiling in High-Risk MDS and AML Patients Identifies Pretreatment Methylation Patterns That Indicate Response to Hypomethylating Agents: A Pilot Study (Abstract #2885)." It is scheduled for Session #617 - Acute Myeloid Leukemia: Biology, Cytogenetics, and Molecular Markers in Diagnosis and Prognosis, at the San Diego Convention Center, Hall GH. The lead author on the study who will be presenting is Dr. Chetasi Talati from the Department of Malignant Hematology, Moffitt Cancer Center & Research Institute, Tampa, FL. A poster summarizing this presentation is available at: ASH 2016 Poster.

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Genome Profiling, LLC
Center for Translational Cancer Research
Helen F. Graham Cancer Center and Research Institute
4701 Ogletown-
• Azacitidine is a nucleoside analog that functions as a hypomethylating agent (HMA), approved for use in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

However, the complete remission (CR) rate to HMA therapy is generally < 20%, indicating the need to more accurately identify patients most likely to respond and benefit from therapy.

The primary objective of this pilot study is to assess whether the presence of epigenetic DNA methylation markers in pre-treatment bone marrow myeloblasts can reliably differentiate azacitidine responders (R) from non-responders (NR).

A cohort of 10 patients from Moffitt Cancer Center Total Cancer Care Database and repository.

Bone marrow samples were collected within 3 weeks prior to their treatment with azacitidine.

This included 5 responders (R) and 5 non-responders (NR).

• Responders: patients who received at least 4 cycles of therapy with azacitidine and achieved CR per IWG 2009 response criteria.

• Non-responders: patients with inferior outcome to complete or partial remission per IWG 2009 response criteria.

• Institutional Review Board (IRB) approval was obtained.

• Overview of the process of Genomic DNA extraction and determination of methylation patterns among the cohort is described in Figure 1.

Total of ~2.04 million "CCGG" sites were analyzed and 88% (1.81M) were present in all samples.

Assessing methylation loads across genes and grouping genes within defined pathways (Kyoto Encyclopedia of Genes and Genomes or KEGG) revealed substantial hypermethylation in R, primarily in signaling pathways mediated by ErbB, TGFβ, and estrogen.

Comparison of the methylation signatures of individual genes reveals potentially interesting MoA targets.

These findings indicate that a targeted assay of CpG methylation sites can provide a mechanistically-based screening tool to discern potential for response azacitidine (or resistance), which warrants confirmation in a larger validation study cohort.

A clinical screening test to guide selection of HMA therapy would be of great benefit to the ~80% of MDS/AML patients receiving this standard of care with little to no improvement in outcomes.

REFERENCES
