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Leveraging the Old with the New:

Integration of Historic Microarray Studies with Next Gen Sequencing for Multiple Myeloma

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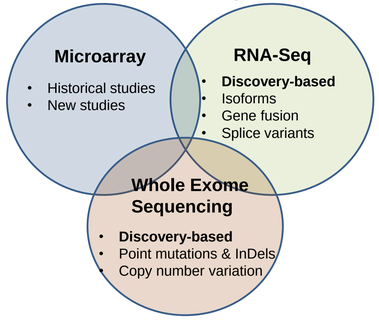
ABSTRACT

Next-Gen Sequencing (NGS) methods are rapidly providing remarkable advances in our ability to study the molecular profiles of human cancers. However, the scientific discovery offered by NGS also includes challenges concerning the interpretation of large and non-trivial experimental results. This task is potentially further complicated when a multitude of molecular profiling modalities are available, with the goal of a more integrative type of analysis of the cancer biology.

As technology advances, it is critical to leverage what has been gained from historic approaches (e.g., microarrays) with new approaches (NGS). Microarray transcriptome analyses have resulted in important advances in biomedicine. For instance, in multiple myeloma (MM) microarray approaches led to the development of a prognostic 70 gene risk score, as well as an effective disease subtyping system via cluster assignment.

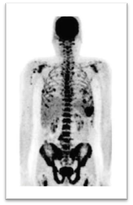
A suite of custom software tools have been developed to integrate NGS experimental data along with microarray and Affymetrix probe set-IDs, and gene annotation information from a variety of public sources. The approach employs a variety of strategies to integrate, annotate, and associate microarray and NGS datasets.

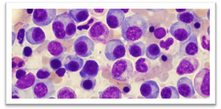
Molecular Profiling Modalities



Multiple Myeloma

Plasma Cell Malignancy



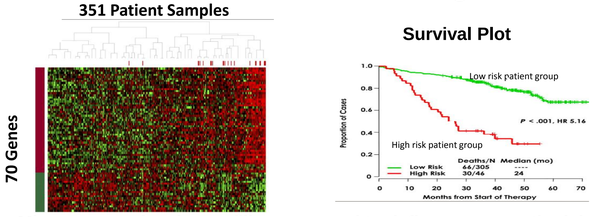


HyperCalcemia
Renal Failure
Anemia
Bone Lesions (Osteolytic)

- Epidemiology
  - ~20,000 new cases and 10,000 deaths occur in the US each year.
- MM is incurable with a clinical course characterized by remissions & relapses.
- Patient survival has improved dramatically in recent years (improved understanding of the cancer biology → New Rx)

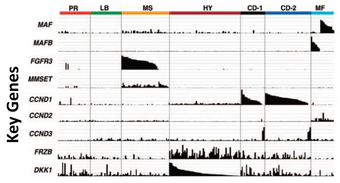
	Three year O.S.	Treatment
Past	42%	Melphalan + Prednisone
Today	>80%	1. New agents (IMiDs, Proteasome Inhibitors) 2. Autologous transplant 3. Supportive care (bisphosphonates)

Molecular Profiling



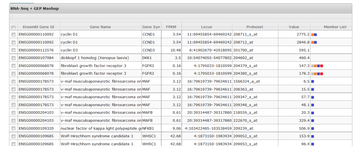
Microarray molecular profiling was used to define a prognostic risk score as well as MM disease subtypes. These items are used in clinical decision making.

Disease subtypes

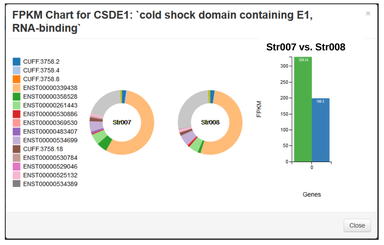


Multiple Myeloma is not a single disease/cancer entity

NGS Viewer



Integrated tabular experimental results



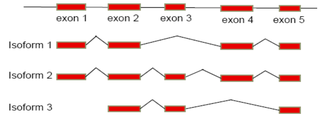
Auto-generated visualizations

Next-Gen Sequencing

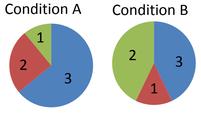
Microarray vs. NGS

	Microarray	RNA-Seq
Principle	Hybridization	Cloning & sequencing
Resolution	Several to 100 bp	Single base
Distinguish Allelic expression?	Limited	Yes
Distinguish splice forms?	Limited	Yes
Discover new genes?	No	Yes
Strandedness?	No	Yes
Dynamic range	Few hundred-fold	> 8000-fold
Cost	Medium	High (due to computation)

RNA-Seq



Isoform ratio change

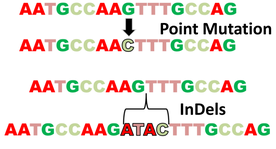


Whole Exome Sequencing

Why?
- Simpler, Cheaper, Faster
- Clinically actionable variants/mutations

Variants
- SNVs (Single Nucleotide Variant)
- InDels (Insertion/Deletion)

Types of Mutations



Conclusions

- Microarray data is compressed and is a correlative science.
- RNA-Seq is discovery based, with resolution to the base level, has a higher dynamic range, & facilitates discovery of new genes, isoforms, gene fusions, etc.
- WES provides the ability to discover clinically actionable mutations
- Integration of historical microarray studies with WES & RNA-Seq is critical, thus motivation for the NGS Association System.