Discovery of Gene Signatures Through Characterization of the Osteosarcoma Genome

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Background

Osteosarcoma is the most common form of bone cancer in children and adolescents

- Tumor of the bone, characterized by formation of osteoid within the tumor[1]
- Common sites of incidence occur in shin, thigh, or upper arm
- Approximately 400 out of 800 total cases diagnosed each year in patients under 30 years of age[1] → high incidence rate attributed to rapid growth that occurs during adolescence[2]

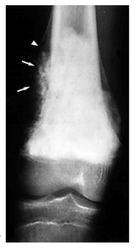

Fig 1: Osteosarcoma in right tibia.

Standard Care

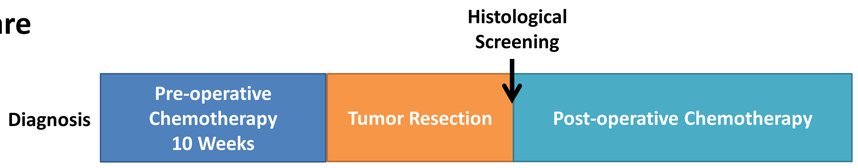

Fig 2: Standard osteosarcoma treatment regimen.

Two prognostic factors commonly used to predict patient outcome measure at diagnosis:

Chemoresistance

- Response of tumor to given pre-operative chemotherapy regimen
- Measured by histological screening in percentage of tumor necrosis or 'Huvos' grade
- High percentage of tumor necrosis (90%) reflective of good response to chemotherapy have 80% change of survival
- Patients with lower than 90% tumor necrosis have ~50% chance of survival[3]

Metastasis

- Common site of metastasis for osteosarcoma patients is lung
- Patients presenting localized disease have 80% survival rate
- Patients with evidence of metastasis at diagnosis have significantly lower survival rate of 20%[3]

Current Challenges

Current knowledge of osteosarcoma tumor biology is lacking

- Osteosarcoma incidence is linked to mutations in key pathways such as **TP53** and **retinoblastoma** (RB1)
- Lack of specific biomarkers distinguishing high risk patients at diagnosis; those with chemoresistant tumors or high risk of metastasis or relapse
  - Chemoresistant patients discovered only after 10 weeks of chemotherapy
    - No modification of post-operative chemotherapy could improve the outcome of the poor responders
  - Physicians only aware of metastasis when clinically detectable
    - Previous attempts to intensify therapy to counter clinically identified metastasis have been discouraging.[4]

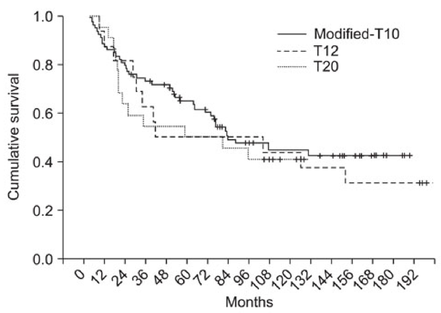

Fig 3: Survival curves comparing different treatment regimens. Dose intensity increases from Modified-T10 to T12 to T20.[5]

Previous characterization studies are restricted

- Previous gene expression studies identified a set of molecular classifiers distinguishing good versus poor responders to chemotherapy
- Confined to profiling single level of genomic control
- Use much smaller sample sizes
- Expression cannot be explained by simple copy number changes

→ more in depth characterization is needed

Proposed Solution

Identify biomarkers indicative of tumor biology

- Genomic aberrations are reflective of tumor biology and may be correlated to patient outcome and tumor subtype
- Comprehensive characterization of a large number of osteosarcoma patients may lead to a more complete understanding of tumor pathogenesis

The two aims for this project will be to:

1. Fully characterize >100 patient samples to generate candidate genes and gene signatures from several platforms (copy number, gene expression, microRNA, methylation, and next generation sequencing)
2. Integrate candidate gene lists and correlate with clinical data to identify biomarkers and construct prognostic models

References and Support

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3. Paediatr Drugs. 2008;10(5):315-27.
4. Cancer Metastasis Rev. 2009 Jun;28(1-2):247-63.
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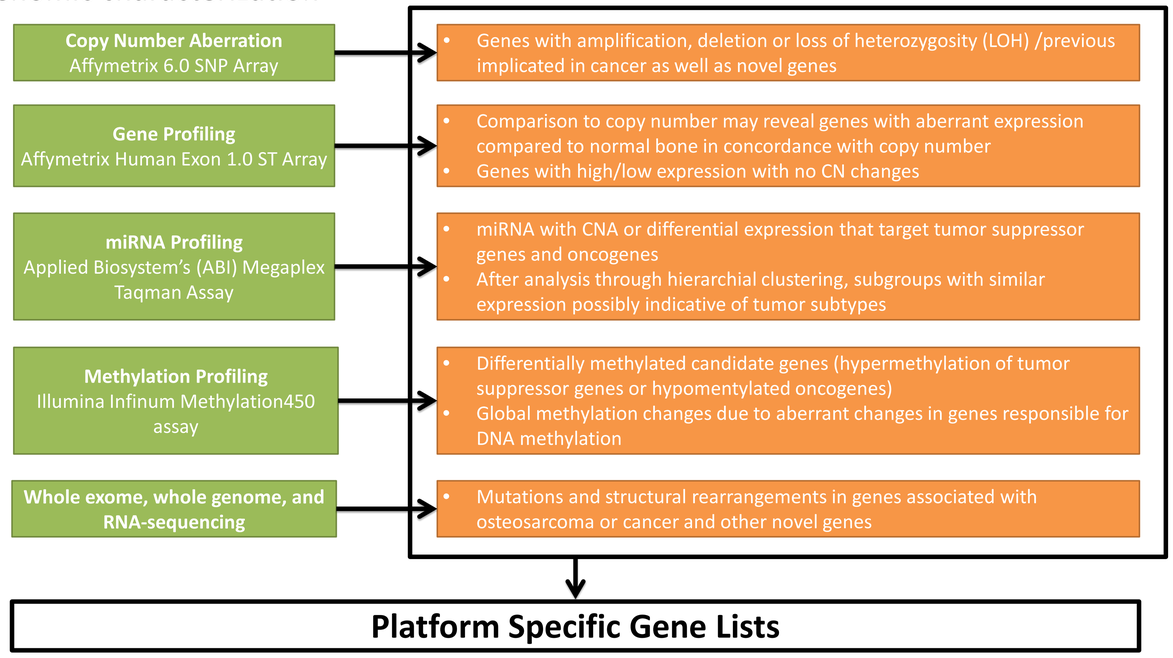
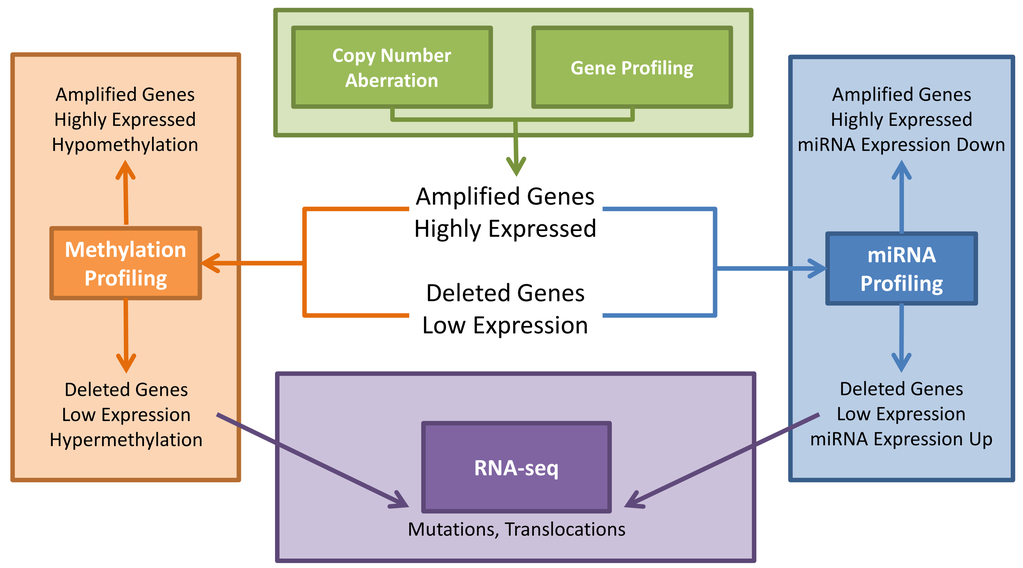
Methods and Expected Results

Genomic characterization



Gene list integration



Correlation with clinical data

- Compare algorithms and to construct molecular classifiers
- Validate with independent data set
- Construct Kaplan-Meier survival curves based on event free survival and overall survival data

Conclusion

Changing the standard of osteosarcoma treatment

- Instead of single treatment approach, results from our project will provide biomarkers which allow physicians to
  - Molecularly classify osteosarcoma patients
  - Identify high risk patients at time of diagnosis
- Traditional histopathological diagnosis might be augmented or even replaced with genomic characterization to determine tumor subtype as well as predict response to chemotherapy and metastatic potential identified through this project
- Early discovery of high risk features has important therapeutic benefits, allows physicians to customize therapy tailored to profiling results

Further studies

- Functional studies in osteosarcoma cell lines followed by animal models to identify therapeutic targets for novel drugs specific to tumor subtype
- Personalized therapy using either conventional chemotherapy or these targeted drugs, specific to each patient's tumor subtype have the potential to improve long term survival and minimize side effects