Molecular Pathology of Sarcomas: Diagnostic and Therapeutic Utility

Meera Hameed MD
Role of a Pathologist

- Custodians and Curators of tumor diagnostic specimens
- Appreciation of Pathogenesis
- Determination of sub types
- Appropriate Molecular Testing for Diagnosis, Prognosis and Therapeutics
- Critical Role in Sarcoma clinical team to streamline therapeutic strategies
Conventional Pathology-Sarcomas

Sarcoma

Tumors derived from mesenchymal lineage

Tumors resemble normal counterpart
Eg., Leiomyosarcoma-Liposarcoma

No normal counterpart
Eg., Ewing Sarcoma, Synovial Sarcoma

Cell of Origin – Primitive Mesenchymal Cell?
Sarcomas-Clinical Management

Sarcomas

Low Grade
- Wide Local Excision

High Grade
- Wide or Radical Excision

Behavior: Indolent to highly invasive to metastatic
Prognosis: Age, tumor size, grade, depth, histological subtypes
Chemotherapy

Sensitive
- Gastrointestinal Stromal Tumor (GIST)
- Ewing Sarcoma
- Rhabdomyosarcoma
- Synovial Sarcoma
- Myxoid Liposarcoma
- Malignant Fibrous Histiocytoma

Intermediate
- Liposarcoma (other types)
- Myxofibrosarcoma
- MPNST
- Leiomyosarcoma

Resistant
- Chondrosarcoma
- Clear Cell Sarcoma
- Epithelioid Sarcoma
- Rhabdoid Tumor
- Alveolar Soft Part Sarcoma

Histology driven Chemotherapy- Important for targeted and non-targeted therapy
Diagnosis of Sarcomas

- Traditional Pathology
- Immunohistochemistry
- Molecular Pathology

Diagnosis and direct treatment

Diagnosis/Staging/Prognosis
Molecular Pathology of Sarcomas

- Specific Translocations or gene amplification
- Defined by Oncogenic gene mutations
- Complex karyotypes/genomic rearrangements
- Diverse tumors in each class
Molecular Pathology-Sarcomas

Translocation associated Sarcomas and relatively simple Karyotypes

- Ewing Sarcoma/PNET
- Desmoplastic Small round cell tumor
- Alveolar Rhabdomyosarcoma
- Myxoid Liposarcoma
- Extraskeletal myxoid Chondrosarcoma
- Clear cell sarcoma (soft tissue)
- Angiomatoid fibrous histiocyteoma
- Congenital/infantile Fibrosarcoma
- Low grade fibromyxoid sarcoma
- Inflammatory myofibroblastic tumor
- Alveolar Soft Part Sarcoma
- Synovial Sarcoma
- Epithelioid Hemangioendothelioma

Sarcomas with complex karyotypes and no specific translocations

- Epithelioid Sarcoma
- Leiomyosarcoma
- Myxofibrosarcoma
- Adult fibrosarcoma
- Liposarcomas other than myxoid liposarcoma
- Embryonal and pleomorphic rhabdomyosarcoma
- Osteosarcoma
- Angiosarcoma
- Undifferentiated Pleomorphic sarcoma

Mutation Driven- Gastrointestinal Stromal Tumor

Amplification associated- Liposarcoma-Angiosarcoma
### Molecular Pathology - Sarcomas

- **Ewing Sarcoma/PNET** - First discovered translocation associated sarcoma t(11;22)(q14;q22) (EWS-FLI1) New Eng J Med, 309; 496-498, 1983

<table>
<thead>
<tr>
<th>Sarcoma Type</th>
<th>Translocation</th>
<th>Fusion gene</th>
<th>Year</th>
</tr>
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<tbody>
<tr>
<td>Ewing Sarcoma</td>
<td>t(21;22)</td>
<td>EWSR1-ERG</td>
<td>1993</td>
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<tr>
<td>Clear Cell Sarcoma</td>
<td>t(12;22)</td>
<td>EWSR1-ATF1</td>
<td>1993</td>
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<td>Myxoid/round cell Lipoarcoma</td>
<td>t(12;16)</td>
<td>FUS-DDIT3</td>
<td>1993</td>
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<td>ARMS DSRCT</td>
<td>t(2;13)&amp;(1;13)</td>
<td>PAX3&amp;PAX7-FOXO1A</td>
<td>1994</td>
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<td>Extraskelatal Myxoid Chondrosarcoma</td>
<td>t(9;22)</td>
<td>EWSR1-NR4A3</td>
<td>1995</td>
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<td>t(9;17)</td>
<td>EWSR1-TAF2N</td>
<td>1999</td>
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<tr>
<td>Synovial Sarcoma</td>
<td>t(X;11)</td>
<td>SYT-SSX1 and SSX2</td>
<td>1995</td>
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<td>DFSP</td>
<td>t(17;22)</td>
<td>COL1A1-PDGFB</td>
<td>1997</td>
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<td>Congenital fibrosarcoma</td>
<td>t(12;15)</td>
<td>ETV6-NTRK3</td>
<td>1998</td>
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<td>IMT</td>
<td>t(2p23)</td>
<td>Alk Fusions (many partners)</td>
<td>2000</td>
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<td>Alveolar Soft Part Sarcoma</td>
<td>t(X;17)</td>
<td>ASPL-TFE3</td>
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<td>Low Grade Fibromyxoid sarcoma</td>
<td>t(7;16)</td>
<td>FUS-ATF1</td>
<td>2003</td>
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<tr>
<td>Angiomatoid Fibrous Histiocytoma</td>
<td>t(12;16)</td>
<td>FUS-ATF1</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>t(12;22)</td>
<td>EWSR1-ATF1&amp;CREB1</td>
<td>2007</td>
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</tbody>
</table>
Sarcomas with simple karyotypes—Pathology Perspective

- Round Cell
- Spindle Cell
- Epithelioid Cell

Immunohistochemistry—Generally non-lineage specific (overlapping)

Molecular Testing
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Translocation</th>
<th>Fusion gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar Soft Part Sarcoma</td>
<td>der(17)t(x;17)</td>
<td>ASPL-TFE3</td>
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<tr>
<td>Alveolar Rhabdomyosarcoma</td>
<td>t(2;13) &amp;t(1;13)</td>
<td>PAX3-FOXO1 &amp;PAX7-FOXO1</td>
</tr>
<tr>
<td>Angiomatoid Fibrous Histiocytoma</td>
<td>t(2;22) , t(12;22) &amp;t(12;16)</td>
<td>EWSR1-CREB1, EWSR1-ATF1 &amp;FUS-ATF1</td>
</tr>
<tr>
<td>Clear Cell Sarcoma</td>
<td>t(12;22) &amp;t(12;16)</td>
<td>EWSR1-ATF1 &amp;EWSR1-CREB1</td>
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<tr>
<td>Congenital infantile fibrosarcoma</td>
<td>t(12;15)</td>
<td>ETV6-NTRK3</td>
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<tr>
<td>Dermatofibrosarcoma Protuberans</td>
<td>t(17;22)</td>
<td>COL1A1-PDGFB</td>
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<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)</td>
<td>EWSR1-WT1</td>
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<tr>
<td>Endometrial Stromal sarcoma</td>
<td>t(7;17), t(6;7) &amp;t(6;10)</td>
<td>JAZF1-SUZ12, JAZF1-PHF1 &amp;EPC1-PHF</td>
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<tr>
<td>Ewing Sarcoma/PNET</td>
<td>t(11;22), t(21;22), t(7;22), t(2;22), inv(22), t(6;21)</td>
<td>EWSR1-Fli1, EWSR1-ERG, EWSR1-ETV1, EWSR1-E1AF, EWSR1-FEV, EWSR1-ZSG &amp;FUS-ERG</td>
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<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22), t(9;17), t(9;15)</td>
<td>EWSR1-NR4A3, RBP56-NR4A3, TCF12-NR4A3, TFG-NR4A3</td>
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<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>t(3;9), t(1;2), t(2;19), t(2;17), t(2;2), t(2;17)</td>
<td>TPM3-ALK, TPM4-ALK, CLTC-ALK, RANBP2-ALK</td>
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<tr>
<td>Low grade Fibromyxoid sarcoma</td>
<td>t(7;16) &amp;t(11;16)</td>
<td>FUS-CREB3L2 &amp;FUS-CREB3L1</td>
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<tr>
<td>Myxoid-Round cell Liposarcoma</td>
<td>t(12;16) &amp;t(12;22)</td>
<td>FUS-DDIT3 &amp;EWS-DDIT3</td>
</tr>
<tr>
<td>Epithelioid Hemangioendothelioma</td>
<td>t(1;3)(p36;q25)</td>
<td>WWTR1-CAMTA1</td>
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<tr>
<td>Synovial Sarcoma</td>
<td>t(X;18) &amp;t(X;20)</td>
<td>SS18-SSX1, SS18-SSX2, SS18-SSX4 &amp;SS18L1-SSX1</td>
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</tbody>
</table>
Molecular Testing in Sarcomas - Caveats
## Infidelity in Chromosomal Translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Gene Fusion</th>
<th>Tumor Type</th>
<th>Site/Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(12;15)</td>
<td>ETV6-NTRK3</td>
<td>Infantile Fibrosarcoma, Mesoblastic Nephroma, Secretory carcinoma breast, Salivary gland carcinoma, mammary analog, AML</td>
<td>Soft Tissue, Kidney, Breast, Salivary Gland, Blood &amp; BM</td>
</tr>
<tr>
<td>t(X;17)</td>
<td>ASPL-TFE3</td>
<td>Alveolar Soft Part Sarcoma, Renal Cell Carcinoma, Subset of PECOMAs</td>
<td>Soft Tissue, Kidney, Soft tissue</td>
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<tr>
<td>t(1:2)</td>
<td>TPM3-ALK</td>
<td>Inflammatory myofibroblastic tumor (IMT), Anaplastic Large Cell Lymphoma (ALCL)</td>
<td>Soft tissue, abdomen, Skin, Lymph nodes</td>
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<tr>
<td>t(12;22)</td>
<td>EWSR1-ATF1</td>
<td>Angiomatoid Fibrous Histiocytoma &amp; Clear Cell Sarcoma</td>
<td>Soft Tissue</td>
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<tr>
<td>t(2;22)</td>
<td>EWSR1-CREB1</td>
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## Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Translocation</th>
<th>Fusion genes</th>
</tr>
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<tbody>
<tr>
<td>Ewing Sarcoma</td>
<td>t(11;22)(q24;q12)</td>
<td>EWSR1-FLI-1</td>
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<td>t(21;22)(q22;q12)</td>
<td>EWSR1-ERG</td>
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<td>t(7;22)(q22;q12)</td>
<td>EWSR1-ETV1</td>
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<td></td>
<td>t(17;22)(q12;q12)</td>
<td>EWSR1-E1AF</td>
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<td>t(2;22)(q31;q12)</td>
<td>EWSR1-SP3</td>
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<td>t(2;22)(q33;q12)</td>
<td>EWSR1-FEV1</td>
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<td>t(1;22)(p36.1;q12)</td>
<td>EWSR1-ZNF278</td>
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<td></td>
<td>t(20;22)(q13;q12)</td>
<td>EWSR1-NFATC2</td>
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<td>(inv)22</td>
<td>EWSR1-ZSG</td>
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<tr>
<td>Angiomatoid Fibrous Histiocytoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1</td>
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<tr>
<td>Clear cell Sarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1</td>
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<tr>
<td>Desmoplastic Small Round Cell Tumor</td>
<td>t(11;22)(p13;q12)</td>
<td>EWSR1-WT1</td>
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<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22)(q22;q12)</td>
<td>EWSR1-NR4A3</td>
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<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-DDIT3</td>
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<td>Myoepithelioma</td>
<td>t(19;22)(q13;q12)</td>
<td>EWSR1-ZNF44</td>
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<td>t(1;22)(q23;q12)</td>
<td>EWSR1-PBX1</td>
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<td>t(6;22)(p21;q12)</td>
<td>EWSR1-POU5F1</td>
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Sensitive but not a specific Marker
# Immunohistochecmical Profile of Round Cell Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>CD99</th>
<th>Fli1</th>
<th>LCA</th>
<th>B</th>
<th>T</th>
<th>TdT</th>
<th>CK</th>
<th>Chr</th>
<th>S-100</th>
<th>Des</th>
<th>Myogenin</th>
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<tbody>
<tr>
<td>Ewing/PNET</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/−</td>
<td>-</td>
<td>+/−</td>
<td>-</td>
<td>+/−</td>
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<tr>
<td>LBL/ALL</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/−</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
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<td>NHL-other</td>
<td>+/-</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Mesenchymal Chondrosarcoma</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>Small Cell OS</td>
<td>+/-</td>
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<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>Rhabdomyosarcoma</td>
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<td>+</td>
<td>+</td>
<td>+/-</td>
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<td>DSCRT</td>
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<td>+/−</td>
<td>+</td>
<td>+/−</td>
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</table>
Ewing Sarcoma

46,XY.t(11:22)(q24:q12)
Chromosomal Translocation
Ewing Sarcoma with Type I fusion
Variant Fusions: EWSR1-ERG, EWSR1-ETV1, EWSR1-E1AF, EWSR1-FEV, EWSR1-ZSG & FUS-ERG
Fluorescence in situ hybridization detection of chromosomal translocations

Gene 1A probe
Gene 1B probe
Gene 1 probe
Gene 2 probe

Normal
Translocation

Splitting Assay
Fusion Assay
Ewing Sarcoma diagnosis by Fluorescent in-situ Hybridization
1r/1g/1y signals seen with EWSR1 probe

split signal seen with EWS breakapart probe
Molecular Testing for Sarcomas - *What can the Pathologist provide?*

- Diagnosis
- Round Cell Neoplasms: Ewing vs DSRCT vs Small Cell OS vs Poorly Differentiated Synovial Sarcoma vs. Alveolar Rhabdomyosarcoma vs. Neuroblastoma
- Spindle cell neoplasms - Confirm Synovial Sarcoma
- Benign or Malignant:
  - Low Grade Fibromyxoid Sarcoma vs Perineurioma vs low grade myxofibrosarcoma vs. fibromatosis
25 year old female with a soft tissue mass of left leg
Myxofibrosarcoma

Perineurioma

Fibromatosis

Low Grade Fibromyxoid sarcoma
Low Grade Fibromyxoid Sarcoma

Translocation associated sarcoma-t(7;16)(q33;p11)- FUS-CREB3L2

FUS break apart Probe with Split Signal

FUS break apart Probe with Split Signal
Outcome of Chromosomal rearrangements

Promoter A  Coding Sequence A

Promoter A  Coding Sequence B

Promoter B  Coding Sequence B

Promoter B  Coding Sequence B

Deregulated Gene

Fusion Gene

Adapted from Mertens et al., Sem in Oncol 36,( 4):2009.
Can Fusion genes be targeted?

Deregulated Gene ✔

- Promoter A
- Coding Sequence A
- Promoter A
- Coding Sequence B
- Promoter B
- Coding Sequence B

Fusion Gene ✗

- Promoter A
- Coding Sequence A
- Promoter A
- Coding sequence A
- Coding Sequence B
- Promoter B
- Coding Sequence B
# Targeted Therapy – Translocation-associated sarcomas

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Fusion gene- Target</th>
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</thead>
<tbody>
<tr>
<td>• Dermatofibrosarcoma Protuberans (DFSP)</td>
<td>• <strong>COL1A1-PDGFB</strong> – Imatinib</td>
</tr>
<tr>
<td>• Inflammatory Myofibroblastic Tumor (IMT)</td>
<td>• <strong>Multiple Partners-ALK</strong>- Crizotinib</td>
</tr>
<tr>
<td>• Diffuse type Tenosynovial Giant Cell Tumor (PVNS)</td>
<td>• <strong>COL6A3-CSF1</strong>- Imatinib</td>
</tr>
</tbody>
</table>
Targeted Therapy – Translocation associated sarcoma

Elusive

Fusion Gene

Promoter A
Coding Sequence A

Promoter A
Coding sequence A
Coding Sequence B

Promoter B
Coding Sequence B

Few downstream Targets

Alveolar Rhabdomyosarcoma - PAX3-FOXO1A
Ewing Sarcoma EWSR1 and FUS-IGF1R

Alveolar Soft Part Sarcoma - ASPS-TFE3
Clear Cell Sarcoma - EWSR1-ATF1 or CREB1

MET

Synovial Sarcoma – SS18-SSX1 or SSX2

FGFR - PDGFRA

FGFR - PDGFRA
Molecular Sarcomas with Driver Mutations
Gastrointestinal Stromal Tumor (GIST)

- The most common sarcoma of GI tract
- Most Common Location: Stomach, Small Bowel
- Also abdomen, mesentery and extra-GI GIST
- Annual Incidence-4000-5000 cases in United States

- Cell of Origin- Interstitial Cells of Cajal ("GI pacemaker cells")
- Mutations in C-kit gene, less commonly PDGFR-Alpha and rare BRAF mutation (7% of GIST pts)

Leading model for kinase-targeted therapy
C-kit/CD-117

• CD-117/C-Kit is a class III receptor tyrosine kinase
• Location: chromosome 4q12-13 close to PDGFRA and FLK1 receptor tyrosine kinases
• Role: normal development and function of ICC, hematopoiesis, gametogenesis and melanogenesis

• Activating kit mutations: GIST, seminomas, AML, melanomas, mastocytosis and some thymomas
Membrane Receptor Kinases
Kit and PDGFRA mutations in GIST

(adapted from Heinrich et al ASCO, 2003)
Diagnosis of GIST

- Strong C-kit immunoreactivity
- Activating mutations exons 9 and 11 - 80%
- Rare mutations – exons 13 and 17
- PDGFRA (exons 12, 14, 18) - 10-15%
- No mutation ~ 10%
- C-Kit IHC negative GIST (4%) - usually PDGFRA mut

- GIST with no known mutations
- Pediatric GIST – multifocal gastric - indolent
- GIST associated with Neurofibromatosis -1
Types of Kit Mutations

- Common Site is 5’ end of exon 11-”hot-spot”
- Point Mutations
- In-frame deletions
- Deletions Do worse
- Substitutions
- Less common site-3’end of exon 11-
- Internal tandem duplications (ITD) Indolent
- Exon 9- at EC domain-insertion of two AA, AY502-3- small bowel More Aggressive
PDGFRA mutations

- One-third of GISTS lacking in Kit mutations
- Exons 12, 14 or 18
- Gastric Location, epithelioid morphology
- Variable IHC expression for C-kit
- Indolent behavior

- Hot spot- second kinase domain (exon 18-D842V) Insensitive to Imatinib therapy
GIST-Indications for mutation Testing

- NCCN Task Force Report -2010
- High-Risk GISTs – (>5 cm and >5 mitoses/50 high power fields)
- Metastatic GISTs
- GISTs which are negative for C-kit by immunohistochemistry
- GISTs with epithelioid morphology
- Small bowel GISTs
- GISTs resistant to imatinib
Testing Algorithm for C-kit and PDGFRA

GIST TUMOR TISSUE

Fragment Analysis - C-kit Capillary Electrophoresis

Exon 11

Negative

Exon 11 Sequence Analysis

Exon 13 Sequence Analysis

Exon 9

Negative

Exon 9 Sequence Analysis

PDGFRA exons 12 and 18 Sequence Analysis
Molecular Testing for Second Site Mutation

Imatinib resistant GIST

- C-Kit Exon 13,14 Sequence Analysis
- C-Kit Exon 17 Sequence Analysis
c.1509ins6, (GCCTAT)
Kit mutation exon 17 - Resistance Mutation

G>A
GIST- Targeted Therapy

- Imatinib mesylate (STI571, Gleevec) is a selective tyrosine kinase inhibitor
- Targets Kit and PDGFRA
- Partial response or stable disease in 80% of patients with metastatic GIST
- Pathological response is necrosis and fibrosis and is heterogeneous
- Half of the patients will develop drug resistance
- Usually due to second site kit mutation
- Half of the resistant cases, no secondary mutations are identified
Sarcomas with Specific Amplifications
Retroperitoneal Liposarcoma
Sarcomas with Specific Amplifications-Well-Differentiated and Dedifferentiated Liposarcoma
Retroperitoneal Liposarcoma-WDLS

12q13-15 amplicons (MDM2, HMGA2 and CDK4 genes)
Retroperitoneal liposarcoma - Dedifferentiated

12q13-15 amplicons (MDM2, HMGA2 and CDK4 genes)
**Retroperitoneal Liposarcoma**

- **Cell Invasion**: Laminin 5 γ2 chain, p16\textsuperscript{Ink4a}, α\textsubscript{v}β\textsubscript{3} Integrin
- **Cytoplasmic Sequestration**: p16\textsuperscript{Ink4a}, CDK4
- **DNA damage, mitogenic stimulation, oxidative stress etc.**

**Angiogenesis Inhibition**: VEGF

**Apoptosis**: E7, p53

**Nucleus**
- **P16 Ink4a**: INK4a/ARF, p14ARF, MDM2
- **DNA damage, mitogenic stimulation, oxidative stress etc.**

**Cytoplasm**
- **Rb**: E6, p21\textsuperscript{Cip1}, p53
- **Cyclin D1**, CDK4

**Cytoplasmic Sequestration**: p16\textsuperscript{Ink4a}, AE1
Retroperitoneal Liposarcoma

Outcome depends on completeness of surgical resection and histology
Poor outcomes in patients with rapidly growing or incompletely resected tumors

Poor response to Radiation and chemotherapy

Clinical Trials based on genomic targets

- Nutlin-Competitive Inhibitor of MDM2-p53 interaction
- CDK4 Inhibitor-Phase 1 and Phase II
- Aurora Kinase inhibitors
## Subtype Specific genomic Alterations

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Gene Mutation</th>
</tr>
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<tbody>
<tr>
<td>Pleomorphic Liposarcoma</td>
<td>TP53 (17%) and NF1 (8%)</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>NF1 (10.5%)</td>
</tr>
<tr>
<td>Myxoid /round cell Liposarcoma</td>
<td>PIK3CA (18%)</td>
</tr>
</tbody>
</table>

Amplification Associated Sarcomas

• Angiosarcoma
• Biologically heterogeneous-Anatomical Site based
• Multifocal, local recurrence and early hematogeneous spread
• 30%- 5 year survival
• 40% of radiation induced sarcomas are angiosarcoma developing after RT therapy for breast cancer
KDR Activating Mutations in Angiosarcomas are sensitive to specific kinase inhibitors. Antonescu et al., Cancer Res 2009;69:7175-7179

Up-regulation of vascular specific receptor tyrosine kinases (TIE1, KDR/VEGFR2, SNRK, TEK, FLT1/VEGFR1) in AS in breast/chest wall AS both primary and secondary. 10% showed KDR mutations – sensitive to Sorafenib and Sunitinib.
Consistent MYC and FLT4 gene amplifications in Radiation induced angiosarcoma but not in other radiation associated atypical vascular lesions. Guo et al., Genes, Chromosomes, Cancer 50:25-33, 2010

Radiation associated Angiosarcoma

Patients with MYC and FLT4 amplifications showed complete or partial response to Sorafenib

Primary Angiosarcoma

RT-induced Sarcoma- not AS
Targeted therapy driven molecular testing

- Drug and Mutation Test
- Imatinib Mesylate-kit/PDGFRA
- Imatinib mesylate- COL1A-PDGFB - t(17;22)
- Imatinib mesylate-CSF1-COL6A3 fusion
- PIK3CA inhibitors –PIK3CA mutation
- Crizotinib- Alk translocation
- Sorafinib-VEGFR2/KDR mutations
- Ridaforolimus- mTOR inhibitor-TSC1 and 2 loss and increased level of p70S6K
- Tumor Type
- Gastrointestinal stromal Tumor (GIST)
- Dermatofibrosarcoma Protuberans (DFSP)
- Giant cell tumor of tendon sheath
- Myxoid/round cell liposarcoma
- Inflammatory myofibroblastic tumor
- Angiosarcoma
- PEComa and related tumors
Molecular Pathology of Sarcomas: Diagnostic and Therapeutic Utility

Is Molecular Testing useful?

Pediatric Round Cell and Spindle Cell Tumors: Diagnostic Utility

Benign vs Malignant Tumors

Targeted Therapy: GIST, DFSP, Angiosarcoma

Clinical Trials

A meaningful outcome of these trials require accurate histopathological and appropriate molecular studies of these tumors by an experienced pathologist
It’s all becoming clear 
now that I can 
get it into focus
Thank You