Atypical Neurofibroma

Courtesy of Dr. Roberto Tirabosco
H3K27me3

Å Prognostic utility
DNA methylation
Epigenetic and Biological Subgroups of Glioblastoma

**IDH1 Mutation**
- Hypermethylation (G-CIMP+)
  - Young Adults
  - Improved Outcome

**H3F3A G34 Mutation**
- Hypomethylation (G-CHOP+)
  - Adolescents
  - OLIG2+/FOXG1+

**H3F3A K27 Mutation**
- Midline Location
  - OLIG2+/FOXG1−
  - Children
  - Very Poor Outcome

- Mesenchymal Expression
  - Low Number of CNAs
  - All Ages

**PDGFRA Amplification**
- Proneural Expression
  - Children / Adults

**EGFR Amplification**
- Classical Expression
  - Adults

**Copy-Number Aberration**
- DNA Methylation

**Histone Mutation**
- Expression
MPNST

Diagnosis
NF1 Status
Localisation

Histology
- MPNST
- Epithelioid MPNST
- Low grade MPNST
- Schwannoma
- Hybrid Neurofibroma/Schwannoma

NF1 Status
- Sporadic, IHC NF1 Loss
- Sporadic, IHC NF1 Retained
- NF1 Associated
- NF1 Status Unknown, IHC NF1 Loss
- ND

Localization
- Spinal/Farvestibular
- Peripheral
- Other/NA
- CPA/CN VII
- Dermal

Methylation-based classification of benign and malignant peripheral nerve sheath tumours

[Additional text and figure details not transcribed]
How can we use sequencing data for classification?

Â Beyond single driver genes........
Tumour life history – “Armitage and Doll” model 1954
For example APC mutations are seen in ~69% of colorectal cancer but in 1% of breast cancer, and amplification ERBB2 is seen in 13% of breast cancer but only in 3% of colorectal cancer.
### Table A

<table>
<thead>
<tr>
<th>Predicted type</th>
<th>Sensitivity (%)</th>
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</thead>
<tbody>
<tr>
<td>Skin</td>
<td>88</td>
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<tr>
<td>Prostate</td>
<td>58</td>
</tr>
<tr>
<td>Pancreas</td>
<td>83</td>
</tr>
<tr>
<td>Ovary</td>
<td>71</td>
</tr>
<tr>
<td>Lung</td>
<td>93</td>
</tr>
<tr>
<td>Liver</td>
<td>71</td>
</tr>
<tr>
<td>Large intestine</td>
<td>73</td>
</tr>
<tr>
<td>Kidney</td>
<td>14</td>
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<tr>
<td>Endometrium</td>
<td>99</td>
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<tr>
<td>Breast</td>
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### Table B

<table>
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<th>Predicted type</th>
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<td>Ovary</td>
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<td>Lung</td>
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<tr>
<td>Large intestine</td>
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### Table C

<table>
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<th>Sensitivity (%)</th>
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<td>Breast</td>
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<tr>
<td>Endometrium</td>
<td>64</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Large intestine</td>
<td>94</td>
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<tr>
<td>Lung</td>
<td>99</td>
</tr>
<tr>
<td>Ovary</td>
<td>99</td>
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</tbody>
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**TumorTracer: a method to identify the tissue of origin from the somatic mutations of a tumor specimen**

Andrea Marini Marzile, Olivia Judd, Brink J, Cecilia Page, Thomas L, Francesco Zanier, Alex Kindelbach, Oliva Lattka, Charles Ford, Milan Jamal-Hanjani, Garth A. Wilson, Sienna Shaf, Charles Swanton, Fabrice Andre, Zoltan Szalay, and Aron Charles Eklund
Multiplatform Analysis of 12 Cancer Types Reveals Molecular Classification within and across Tissues of Origin

Cell 158, 929-944, August 14, 2014
Summary

Å Sequencing of tumours is worthwhile - stratification.
Å Landscape of the sarcoma research is changing and beginning to impact on diagnostics.
Å Epigenetic modifications are prevalent through multiple sarcoma subtypes - requires many more samples to improve classifiers.
Future opportunities

- Robust histological classification
- Sarcomas – recurrent fusion genes
  - Hotspot mutations in genes that control methylation and chromatin

- Technology is mature but we need mutational catalogues of increased numbers of samples
- Single cell sequencing
Acknowledgements

Adrienne Flanagan
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Roberto Tirabosco
Manu Gupta

and team
Sarcoma hotspot mutations

Long tail distribution of cancer hotspots
Balance between chromatin remodelling and histone modification has implications for sarcomas.
Epithelioid sarcoma – SMARCB1 deletion
Epithelioid MPNST – SMARCB1 deletion
Synovial Sarcoma – SYS-SSX fusion

MPNST – SUZ12, EED, EZH2 loss of function