Clinical History

- **H/o stage IV mantle cell lymphoma (MCL) initially diagnosed in the right groin and treated in 2002 with 8 cycles of R-HCVAD with CR**
- **Relapse of MCL in 2004 during the 4th cycle of R maintenance; pt achieved PR, consolidated by XRT**
- **Relapse of MCL in 2008 at the base of tongue; treated with 7 cycles of R/Velcade. Biopsy showed no disease but PET uptake suggested otherwise**
- **In 11/2012 patient was diagnosed with relapsed MCL in leukemic phase and achieved CR, however in 11/2013 her MCL relapsed and she was started on BTK inhibitor ibrutinib that she took until 2/2015 when the bone marrow showed 15% involvement by MCL**
- **Patient was treated with EPOCH+Velcade in 2/2015 and in 3/2015 by hyperfractionated Cytoxan followed by CART19 cells**

- **In 5/2015, the patient reported progressive enlargement of left supraclavicular lymph node**
Tumor morphology (05/2015)
Diagnosis

Poorly differentiated tumor of mesodermal origin with evidence of rhabdomyoblastic and possible neuroblastic differentiation:

poorly differentiated sarcoma (PD-Sc) with striated muscle and (?) limited neural differentiation
Clonal relationship of the PD-Sc and MCL

- Molecular studies performed on sarcoma tissue and cell line: both positive for the immunoglobulin (IgH) gene rearrangement matching the IgH rearrangement of the MCL
- FISH for IgH-Cyclin D1 (CND1) gene fusion: positive in sarcoma cells (as also seen in MCL; not shown)
The key questions:

1. What are the mechanisms of the trans-differentiation?

2. Can we provide any therapeutic guidance?
Trans-differentiation of lymphoma (including MCL) has been described in the past but:

- it has been limited to histiocytic/dendritic sarcoma, hence to malignancies of other immune cells (M Hure et al. 2012)
- causes, let alone mechanisms, remained unknown

Potential causes of trans-differentiation: spontaneous or therapy-induced (history of multiple therapies favors the latter).

In CART19-treated patients tumor conversions have been seen to:

- CD19- plasmablastic lymphoma in CLL pt (A. Evans et al. 2015)
- AML in ALL pts (E. Jacoby et al. 2016)

both these “trans-differentiations” are also fairly limited: one is a form of large-cell transformation, the other “dedifferentiation” to a common progenitor cell
In-depth analysis of patient’s MCL and PD-Sc

- Analysis (RNA-Seq) of MCL and primary and cultured PD-RMSc cells for gene expression
- Analysis (WES) of MCL and PD-Sc cells for gene mutations
- Analysis of MCL and PD-RMSc cells for genome-scale DNA methylation
Comparative genome-scale gene expression analysis in MCL and PD-Sc cells

Similar results were obtained using Hoffman and Biocarta data sets as reference
ENTPD8 (G165R): novel mutation with unknown oncogenic potential

p53 (G266V): pathogenic, seen in carcinomas of lung, colon, pancreas, and liver

Mutation distribution in p53 gene
Gene promoter DNA methylation in MCL vs. PD-Sc

Number of gene promoters evaluated: 24,770

Number of gene promoters differentially methylated between MCL and PD-Sc: **12,054** including 547 promoters of miR genes
## Promoter de-methylation in PD-Sc of genes associated with muscle and neuronal differentiation

<table>
<thead>
<tr>
<th>Gene #</th>
<th>GO: contractile fiber</th>
<th>GO: muscle contraction</th>
<th>GO: transmission of nerve impulse</th>
<th>GO: neurotransmitter binding</th>
<th>GO: neuron differentiation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CAV3, OBSCN, ABLIM2, MYL4, TNNC2, MYH3, MYL1, ANKRD2, MYLPF, MYLK2, CSRP3, CACNA1S, TNNT3, MYO18B, TRIM54, ANK2, SORBS2, SVIL, ATP2A1, RYR1, MYOM1, PLEC</td>
<td>FXYD1, MYL4, TNNC2, TRPV1, DRD2, MYH3, MYL1, DAG1, ANKRD2, MYLK2, CACNG1, CACNA1S, TNNT3, RYR1, SMPX, CHRND, MYOM1, MB</td>
<td>PRX, KCNMB3, SCN2B, DRD2, GABRA6, SLC12A5, ASZ1, MYLK2, KCNIP1, DMPK, SLC17A7, PDE7B, MUSK, GABRR1, GRM2, P2RX1, RAPSN, NMUR2, SLC1A6, GHRL, CACNA1A, HTR2A</td>
<td>HTR3E, SSTR5, MCHR1, GABRR1, GABRA1, SLC6A11, NMUR2, GABRA6, MC2R, SORCS1, BRS3, CHRND</td>
<td>NRTN, NDN, DRD2, RXRA, BRSK2, CABP4, RPGRI1, CDH4, TP73, LINGO1, HOXC8, DLX1, BDNF, LAMB2, GBX2, GHRL, BMPR1B, PITX3, LHX8, DCLK1, CACNA1A, NGF, CDH23</td>
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</tbody>
</table>
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H.Y. Wang

RNA expression analysis
E. Orlando
H. Bitter

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Qun-bin Xiong

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S.F. Lacey
J. Melenhorst

Clinical
S. Schuster

Panel Dx: Mantle cell lymphoma transdifferentiated to sarcoma