Chicago, Sept 9, 2017
Society of Hematopathology Workshop
Molecular Genetics of Hematopoietic Neoplasms

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Society of Hematopathology Workshop
Molecular Genetics of Hematopoietic Neoplasms
Chicago, Sept 9, 2017
Disclosure

- GENOMENON: Co-Founder
Outline

- **Background**
  - WHO classification of mature T cell lymphoma

- **Recent updates in genetics of T cell lymphoma**
  - PTCL/AITL
  - CTCL/SS
  - ALCL

- Pathobiologic and therapeutic implications

- Conclusions
Outline

- **Background**
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  - CTCL/SS
  - ALCL
  - Pathobiologic and therapeutic implications

- Conclusions
2016 World Health Organization

Mature T-cell neoplasms

Cutaneous
- Mycosis fungoides (MF)
- Sézary syndrome
- Primary cutaneous CD30+ T-cell Disorders
  - Primary cutaneous ALCL
- Primary cutaneous γδ TCL
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL
- Primary cutaneous acral CD8+ TCL
- Primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder*
- Hydroa vacciniforme-like

Extranodal
- NK/TCL nasal type
- Enteropathy-associated TCL
  - *Monomorphic epitheliotrophic intestinal T-cell lymphoma*
- Hepatosplenic TCL
- Subcutaneous Panniculitis-Like TCL
- Systemic EBV+ T-cell lymphoproliferative disorder of childhood

Nodal
- Peripheral TCL-NOS
- Anaplastic large Cell lymphoma (ALK +)
- Anaplastic Large Cell lymphoma (ALK -)
- *Breast implant-associated ALCL*
- Angioimmunoblastic TCL
  - *Follicular T cell lymphoma*
  - Nodal peripheral T cell lymphoma with TFH phenotype*

Leukemic
- Adult T-cell leukemia/lymphoma
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia

*Provisional entity.
Relative frequencies of mature T-cell lymphomas

International T-Cell Lymphoma Project

- Peripheral T-cell lymphoma: 25.9%
- Angioimmunoblastic T-cell lymphoma: 18.5%
- Natural killer/T-cell lymphoma: 12.2%
- Adult T-cell leukemia/lymphoma: 10.4%
- Systemic anaplastic large cell lymphoma, ALK+: 9.6%
- Systemic anaplastic large cell lymphoma, ALK-: 6.6%
- Enteropathy-type T-cell lymphoma: 5.5%
- Primary cutaneous ALCL: 4.7%
- Hepatosplenic T-cell lymphoma: 1.7%
- Subcutaneous panniculitis-like T-cell lymphoma: 1.4%
- Unclassifiable PTCL: 0.9%
- Other disorders: 2.5%

Subclassification of PTCL and Survival

Molecular diagnostic signatures of TCL subgroups

Iqbal J et al., Blood Rev 2016
Diagnostic and biologic gray zones in PTCL

- Morphologic, immunophenotypic and genetic overlap

PTCL-NOS

AITL

ALCL, ALK-negative

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- Conclusions
Peripheral T-cell Lymphoma/
Angioimmunoblastic T-cell Lymphoma
Mutational landscape of PTCL and AITL
Cell-type specific mutations in AITL

Nguyen and Chiba, Blood Cancer J 2017
Angioimmunoblastic T-cell Lymphoma

(a)

<table>
<thead>
<tr>
<th>Co-occurrence (n (%))</th>
<th>RHOA G17V</th>
<th>TET2</th>
<th>DNMT3A</th>
<th>IDH2 R172</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHOA G17V</td>
<td>n/a</td>
<td>72 (88)</td>
<td>30 (36.5)</td>
<td>31 (37.8)</td>
<td>82</td>
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<tr>
<td>TET2</td>
<td>72 (76.6)</td>
<td>n/a</td>
<td>29 (30.8)</td>
<td>29 (30.8)</td>
<td>94</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>30 (83)</td>
<td>29 (80.5)</td>
<td>n/a</td>
<td>15 (41.6)</td>
<td>36</td>
</tr>
<tr>
<td>IDH2 R172</td>
<td>31 (97)</td>
<td>29 (90.6)</td>
<td>15 (46.8)</td>
<td>n/a</td>
<td>32</td>
</tr>
</tbody>
</table>
Angioimmunoblastic T-cell Lymphoma

Cortes JR and Palomero T. Current Opinions in Hematology 2016
Summary

- Mutations in \textit{RHOA} 70\% of AITL; 20\% PTCL
- Loss of function of \textit{TET2} and \textit{DNMT3A} frequent
- \textit{IDH2} R172H is highly enriched in AITL and associates with \textit{TET2} mutations
- Mutations targeting the TCR signaling pathway (CD28, Fyn) contribute to PTCL/AITL pathogenesis
- Current model for pathogenesis of AITL suggests initial \textit{TET2/DNMT3A} mutation followed by \textit{RHOA} or \textit{IDH} mutation with lineage commitment to TFH cells
Summary

Targeted therapy for T-cell lymphoma

Cortes JR and Palomero T. Current Opinions in Hematology 2016
Cutaneous T-cell Lymphoma

Mycosis Fungoides/Sezary Syndrome
SÉZARY SYNDROME

• Malignancy of post-thymic T-cells characterized by triad of erythroderma, lymphadenopathy, pruritus

• Complex karyotypes without recurrent structural variants
Whole Genome Sequencing Confirms Complexity of Sézary Syndrome Genomes

A

B

C

D

E

F

Exome Sequencing Identifies Regions of Recurrent Aneuploidy in 74 Sézary Patients

- 1p36.11
- 3p21.31
- 9p21.3
- 10p11.22
- 10q23.31
- 10q21.2
- 13q14.2
- 17p
- 19p

TP53

RB1

PTEN

CDKN2A
Loss of Function of ARID1A in Sézary Genomes (25/62; 40%)
ARID1a inactivation detected by immunocytochemistry
Loss of Function of $TET1/2$ in Sézary Genomes (38/62; 61%)

$TET2$

P174H  L307R  R550*  Q574*  Q640*  Y867H  E1492*  P1723S  Q1828*

Splice Acceptor

Nucleic acid modifying domain

Tumor

Tumor-depleted

$TET2$
Epigenetic Modifiers are Targeted by Aneuploidy and Mutation in Sézary Genomes
ARTICLE
Received 6 Jul 2015 | Accepted 25 Aug 2015 | Published 29 Sep 2015
DOI: 10.1038/ncomms9470

Genomic analyses reveal recurrent mutations in epigenetic modifiers and the JAK–STAT pathway in Sézary syndrome

Mark J. Kiel¹,*, Anagh A. Sahasrabuddhe¹,⁎, Delphine C.M. Rolland²,⁎, Thirunavukkarasu Velusamy¹,⁎, Fuzon Chung¹, Matthew Schaller¹, Nathanael G. Bailey¹, Bryan L. Betz¹, Roberto N. Miranda³, Pierluigi Porcu⁴, John C. Byrd⁴, L. Jeffrey Medeiros³, Steven L. Kunkel¹, David W. Bahler⁵, Megan S. Lim² & Kojo S.J. Elenitoba-Johnson²,⁶

Choi J et al Nat Genet. 2015 Sep;47(9):1011-9
Ungewickell A et al Nat Genet. 2015 Sep;47(9):1056-60.
Summary

- Genomic complexity

- Somatic mutations in chromatin remodelers and epigenetic modifiers (ARID1A, TET2, DNMT3A)

- Mutations in oncogenic drivers coexist in neoplastic cells (JAK1/3, STAT3/5)

- Mutations in tumor suppressors (p53, p16, PTEN)
Anaplastic Large Cell Lymphoma
Rearrangements in ALK- ALCL

- **73 ALK- ALCL**
  - 22/73 (30%) *DUSP22* translocated
  - 6/73 (8%) *TP63* translocated
  - Mutually exclusive
  - 45 were *ALK/DUSP22/TP63* triple negative

Parillia Castellar ER et al *Blood* 2014
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders

- 2\textsuperscript{nd} most common group of cutaneous T-cell lymphomas (CTCL): 30% of cases

- 2 different types:
  - Primary cutaneous anaplastic large cell lymphoma (c-ALCL)
  - Lymphomatoid papulosis (LyP)

- No consistent genetic abnormalities
LYMPHOID NEOPLASIA

A novel recurrent NPM1-TYK2 gene fusion in cutaneous CD30-positive lymphoproliferative disorders

• Nucleophosmin 1
• Multiple functions particularly in nucleolus associating with ribonucleolar proteins

• Non-receptor tyrosine protein kinase
• First member of JAK family
• Signal transduction by interferons and interleukins

**NPM1**

- Oligomerization
- Histone-binding
- DNA/RNA-binding

**TYK2**

- SH2
- Kinase
- FERM
- STY

**NPM1/TYK2**

- Oligomerization
- Histone-binding
- DNA/RNA-binding
- Kinase
Translocations involving TYK2 were found in clinical samples by FISH

17.2% of CD30+ cutaneous LPDs

3/15

2/14

0/151

Lymphomatoid papulosis

Primary cutaneous anaplastic large cell lymphoma

Other mature T-cell lymphoma
Tyk2 mediates multiple important inflammatory cytokine responses

Tyk2
Jak2
Jak1
STAT 1-5
IL-12
IL-23
p35 subunit
p40 subunit
p19 subunit
p40 subunit

pseudokinase
kinase

FERM
SH2

pseudokinase
kinase

N
1

C
1187
Expression of pSTAT5 in NPM1-TYK2+ lymphoma

pSTAT5

CD30+LPD
NPM1-TYK2 -

CD30+LPD
NPM1-TYK2 +
Ectopic expression of NPM1-TYK2 protein in HEK293FT cells activates STAT proteins.
In vivo modeling of NPM1-TYK2 fusion

Excised organs and skin

C57BL/6

hNPM1-TYK2

Elenitoba-Johnson Lab Unpublished

<table>
<thead>
<tr>
<th></th>
<th>C57BL/6 NPM-TYK2</th>
<th>C57BL/6</th>
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</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>0.413</td>
<td>0.112</td>
</tr>
<tr>
<td>Liver</td>
<td>1.484</td>
<td>0.985</td>
</tr>
</tbody>
</table>
Knockdown of TYK2 in MyLa cells decreases cell proliferation.

The figure shows Western blot analyses of various proteins in cells transfected with Vector, shTYK2-1, or shTYK2-2. The proteins analyzed include pSTAT1 pY701, STAT1, pSTAT3 pY705, STAT3, pSTAT5 pY694, STAT5, TYK2, and GAPDH. The graph on the right compares the proliferation rates of these different transfected cells over time (0h, 24h, 48h, 72h, 96h), with Vector as the control. The graph indicates a significant decrease in proliferation rates in cells transfected with shTYK2-1 and shTYK2-2 compared to the Vector control.
Targeting NPM1-TYK2 fusion protein in MyLa cells decreases proliferation.

IC$_{50}$ = 130 nM

Elenitoba-Johnson Lab, Unpublished
NDI-031301 inhibits downstream signaling pathways of NPM1-TYK2 and PCM1-JAK2

<table>
<thead>
<tr>
<th></th>
<th>MyLa</th>
<th>Mac-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NID-031301 (3 µM)</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td>p-NPM-TYK2 (Y1054/1055)</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>NPM-TYK2</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>p-STAT1 (Y701)</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>STAT1</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
</tr>
<tr>
<td>p-STAT4 (Y693)</td>
<td><img src="image11.png" alt="Image" /></td>
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<tr>
<td>STAT4</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
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<tr>
<td>p-STAT3 (Y705)</td>
<td><img src="image15.png" alt="Image" /></td>
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<tr>
<td>STAT3</td>
<td><img src="image17.png" alt="Image" /></td>
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<tr>
<td>p-STAT5 (Y694)</td>
<td><img src="image19.png" alt="Image" /></td>
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<tr>
<td>STAT5</td>
<td><img src="image21.png" alt="Image" /></td>
<td><img src="image22.png" alt="Image" /></td>
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<tr>
<td>β-actin</td>
<td><img src="image23.png" alt="Image" /></td>
<td><img src="image24.png" alt="Image" /></td>
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</table>

Elenitoba-Johnson Lab, Unpublished
NDI-031301 inhibits TYK2

- Proliferation assay (72h)

<table>
<thead>
<tr>
<th>Cell line</th>
<th>IC50 (μM)</th>
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</thead>
<tbody>
<tr>
<td>HH</td>
<td>NR</td>
</tr>
<tr>
<td>MyLa (NPM1-TYK2)</td>
<td>3.407</td>
</tr>
<tr>
<td>Hut-78 (JAK1 and JAK3 mutation)</td>
<td>3.050</td>
</tr>
<tr>
<td>H9 (JAK1 and JAK3 mutation)</td>
<td>3.337</td>
</tr>
<tr>
<td>Mac1 (PCM1-JAK2)</td>
<td>3.516</td>
</tr>
<tr>
<td>MJ</td>
<td>2.824</td>
</tr>
</tbody>
</table>

NR: not reached
Summary

- Recurrent TYK2 translocations in cutaneous T-cell lymphomas

- NPM1 as one of the fusion partners

- NPM1-TYK2 translocation results in constitutive activation of TYK2 kinase

- NPM1-TYK2 fusion protein: oncogenic effects through STATs activation

- Evidence for causation and sufficiency in vivo is pending

- TYK2 may be a novel therapeutic target in a subset of CD30⁺ lymphoproliferative disorders

Velusamy et al. BLOOD 2015
Deregulated JAK/STAT signaling in ALCL, ALK -ve

Anaplastic large cell lymphoma

Subclassification of ALK- ALCL

ALK- ALCL

- DUSP22 Rearrangement
- TP63 Rearrangement
- TYK2 Rearrangement
- VAV Rearrangement
Functional Proteogenomics of ALCL
• Glycosylation is a common post translational modification

• Glycoproteins are expressed on cell surface and secreted

• Most CD markers recognize glycoproteins
Glycoproteomic Profiling By Solid Phase Extraction of Glycoproteins

PNGase F

Δ0.98406 amu

Hydrogen atom = 1.00782580
N-glycoproteomic profiles classify lymphoid neoplasia

<table>
<thead>
<tr>
<th>T/NK-cell</th>
<th>B-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL</td>
<td>NK</td>
</tr>
<tr>
<td>MM</td>
<td>MCL</td>
</tr>
<tr>
<td>BL/tFL</td>
<td>CHL</td>
</tr>
</tbody>
</table>

A distinct cytokine signature is characteristic of ALK+ ALCL

- IL2Rα (CD25)
- IL31Rβ (Oncostatin M receptor)

Potential novel biomarkers
**IL31Rβ is selectively expressed in ALK+ALCL**

- **Cell lines**

<table>
<thead>
<tr>
<th>ALCL, ALK+</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEL</td>
</tr>
<tr>
<td>Karpas 299</td>
</tr>
<tr>
<td>SR786</td>
</tr>
<tr>
<td>SU-DHL-1</td>
</tr>
<tr>
<td>SupM2</td>
</tr>
<tr>
<td>MAC2A</td>
</tr>
<tr>
<td>Jurkat</td>
</tr>
<tr>
<td>HT1080</td>
</tr>
<tr>
<td>HH</td>
</tr>
<tr>
<td>HUT78</td>
</tr>
<tr>
<td>YT</td>
</tr>
<tr>
<td>NK-92M1</td>
</tr>
<tr>
<td>RAJI</td>
</tr>
<tr>
<td>BJAB</td>
</tr>
<tr>
<td>L428</td>
</tr>
<tr>
<td>KMH2</td>
</tr>
<tr>
<td>HT1080</td>
</tr>
</tbody>
</table>

- **56 primary biopsies of ALCL**

<table>
<thead>
<tr>
<th>ALK-</th>
<th>ALK+</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL31Rβ-</td>
<td>14</td>
</tr>
<tr>
<td>IL31Rβ+</td>
<td>21</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 20.16 \]

\[ p < 0.001 \]
CRISPR-Cas9 sgRNA genome-wide vulnerability

14, 250 sgRNAs

Lentiviral Vector

- Designs: sgRNA
  - sgRNA expression: U6, U6-Tet, H1 or H1-Tet
  - Markers: GFP, RFP, PuroR
  - Promoters: UbiC, EF1a, CMV

Packaged Pooled Lentiviral sgRNA Library

Target Cell Transduction

Quantitative Identification of Enriched or Depleted sgRNA Corresponding to Gene Targets

80-90% of Sequences Within 1 Order of Magnitude

Barcoded sgRNA Amplification

Barcode Representation

Transduced Target Cells
Cytokine receptor pathways are exquisite vulnerability targets in ALK+ALCL

Markov Chain Monte Carlo Simulation

IL6-STAT3 Pathway

IL2-STAT5 Pathway
IL31Rβ contributes to oncogenesis in ALK+ALCL

IL31Rβ knockdown abrogates tumor growth in ALK+ALCL, xenotransplants

Rolland D et al., PNAS 2017
Cytokine receptor signaling is required for the survival of ALK– anaplastic large cell lymphoma, even in the presence of JAK1/STAT3 mutations

Jing Chen\textsuperscript{a}, Yong Zhang\textsuperscript{a}, Michael N. Petrus\textsuperscript{a}, Wenming Xiao\textsuperscript{b}, Alina Nicolae\textsuperscript{c,1}, Mark Raffeld\textsuperscript{c}, Stefania Pittaluga\textsuperscript{c}, Richard N. Bamford\textsuperscript{d}, Masao Nakagawa\textsuperscript{a,2}, Sunny Tianyi Ouyang\textsuperscript{a}, Alan L. Epstein\textsuperscript{e}, Marshall E. Kadin\textsuperscript{f}, Annarose Del Mistro\textsuperscript{g}, Richard Woessner\textsuperscript{h}, Elaine S. Jaffe\textsuperscript{c}, and Thomas A. Waldmann\textsuperscript{a,3}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{tumor_growth}
\caption{A: Tumor volume (mm\textsuperscript{3}) vs. Day. B: Tumor weight (g) vs. Day.}
\end{figure}
Summary

Anaplastic large cell lymphoma

- Cytokine/receptor – JAK-STAT signaling plays a prominent role in ALCL pathogenesis

- Opportunities for targeted vulnerabilities
Outline

• Background
  – WHO classification of mature T cell lymphoma

• Recent updates in genetics of T cell lymphoma
  – PTCL/AITL
  – CTCL/SS
  – ALCL

• Pathobiologic and therapeutic implications

• Conclusions
## Recurrent large structural alterations in T-cell neoplasms

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Structural Abnormality</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>ALK+ ALCL</td>
<td><em>NPM1-ALK</em></td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>Various-ALK</td>
<td>16%</td>
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<tr>
<td>T-PLL</td>
<td><em>TRA-TCL1A</em></td>
<td>70-80%</td>
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<tr>
<td></td>
<td><em>TRA-MTCP1</em></td>
<td>10%</td>
</tr>
<tr>
<td>HSTL</td>
<td>i(7q)(q10)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>EATL</td>
<td>9q gains</td>
<td>~70%</td>
</tr>
<tr>
<td></td>
<td>16q12.1 loss</td>
<td>~30%</td>
</tr>
<tr>
<td>ALK- ALCL, c-ALCL</td>
<td><em>IRF4/DUSP22</em> translocations</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td><em>TYK2/ NPM1-TYK2</em></td>
<td>17%/4%</td>
</tr>
<tr>
<td></td>
<td>VAV rearrangements</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>PCM-JAK2</td>
<td>rare</td>
</tr>
<tr>
<td>PTCL</td>
<td>P53-related genes</td>
<td>6%</td>
</tr>
<tr>
<td>F-PTCL</td>
<td><em>ITK-SYK</em></td>
<td>18-38%</td>
</tr>
<tr>
<td>AITL</td>
<td><em>ITK-SYK</em></td>
<td>rare</td>
</tr>
</tbody>
</table>
## Recurrent somatic gene mutations in T-cell neoplasms

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease entity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1/JAK3</td>
<td>T-PLL, NKTCL/EATL</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-35%</td>
</tr>
<tr>
<td>STAT3</td>
<td>T-LGLL, GD HSTCL/EATL, CLPD-NK</td>
<td>27-40%</td>
</tr>
<tr>
<td>STAT5B</td>
<td>T-PLL, GD HSTCL/EATL, T-LGLL</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rare</td>
</tr>
<tr>
<td>CD28</td>
<td>AITL, MF/SS</td>
<td>11%, rare</td>
</tr>
<tr>
<td>FYN</td>
<td>AITL; PTCL, NOS</td>
<td>3%, rare</td>
</tr>
<tr>
<td>PKCγ1</td>
<td>AITL, MF/SS, PTCL, NOS</td>
<td>12%, 20%, 15%</td>
</tr>
<tr>
<td>PRKCB</td>
<td>NKTCL</td>
<td>33%</td>
</tr>
<tr>
<td>CARD11</td>
<td>MF/SS, NKTCL</td>
<td>15%, 24%</td>
</tr>
<tr>
<td>TNFRSF1B</td>
<td>MF/SS, NKTCL</td>
<td>6%, rare</td>
</tr>
<tr>
<td>TET2</td>
<td>AITL, F-PTCL</td>
<td>33-47%, 58%</td>
</tr>
<tr>
<td>IDH2</td>
<td>AITL</td>
<td>~25%</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>AITL; PTCL, NOS</td>
<td>11% overall</td>
</tr>
<tr>
<td>SETD2</td>
<td>EATL I/II</td>
<td>32%</td>
</tr>
<tr>
<td>RHOA</td>
<td>AITL; PTCL, NOS</td>
<td>67%; 18%</td>
</tr>
<tr>
<td>CCR4</td>
<td>MF/SS</td>
<td>7%</td>
</tr>
</tbody>
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## Impact on therapeutic decisions

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Genetic features</th>
<th>Therapeutic relevance</th>
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<tbody>
<tr>
<td>ALCL</td>
<td>ALK</td>
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<td>cALCL</td>
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<td>ITK/SYK</td>
<td>SYK inhibitor</td>
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<td>T-PLL/ENKTCL</td>
<td>JAK3</td>
<td>JAK3 inhibitor</td>
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<td>T-PLL</td>
<td>STAT5B</td>
<td>STAT5 inhibitor</td>
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<tr>
<td>T-LGLL, NK-LPD</td>
<td>STAT3</td>
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<td>AITL</td>
<td>TET2, IDH2, DNMT3A</td>
<td>Epigenetic modulators</td>
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<tr>
<td>PTCL, NOS</td>
<td>DNMT3A</td>
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<tr>
<td>F-PTCL</td>
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Conclusions

• Genetic basis of T-cell lymphomas reveals complexity within each entity

• Profound implications for taxonomy

• Biologic subcategories and prognosis

• Targeted therapeutics
Acknowledgements

Department of Pathology, University of Pennsylvania
Megan S. Lim
Delphine Rolland
Ozlem Onder

Department of Pathology, University of Michigan
Thirunavukkarasu Velusamy
Mark J. Kiel
Anagh A. Sahasrabuddhe
Catherine A. Dixon
Nathanael G. Bailey (Univ of Pittsburgh)
Bryan L. Betz
Noah A. Brown
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QUESTIONS?