Myc inhibition by an Omomyc-based therapy induces immune cell recruitment to the tumor site in a model of NSCLC

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16th ASEICA International Congress

Valencia, November 7th, 2018
Disclosures

- Postdoctoral fellow in Peptomyc S.L.
Myc is deregulated in the majority of cancers

To date, there is no direct Myc inhibitor in the clinic.
Myc is deregulated in the majority of cancers

**Therapeutic Target**

**MYC**
- Drives proliferation
- Supports microenvironment
- Blocks anti-tumor immune response

**Omomyc**: the best direct Myc inhibitor known to date
Peptomyc: Treating cancer with anti-Myc peptides

Omomyc: a Myc dominant negative

Homology model of Omomyc based on the crystal structure of the Max homodimer (Soucek et al., 1998)

TAD

B-HLH-LZ

Max

MBI MBIii MBIii MBIiv

B-HLH-LZ

c-Myc

B-HLH-LZ

Omomyc

c-Myc

QAE EQKLISEEDLRKRRERQLEQ

Omomyc

---T---I---Q---N---

MYC MAX

CACGTG

+Omomyc

MYC OMO

Omo OMO

CACGTG

Omo OMO

CACGTG

Omo MAX

CACGTG
The Omomyc transgene has shown efficacy in diverse mouse models

- **Lung cancer**
  - Soucek et al., Nature 2008; Soucek et al., Genes & Dev 2013

- **Skin Cancer**
  - Soucek et al., Cell death and diff 2004

- **Pancreatic cancer**
  - Sodir et al., Genes & Dev 2011

- **Glioblastoma**
  - Annibali et al., Nat Comm 2014

**Omomyc transgene**  
**Omomyc mini-protein**
Following intranasal administration, Omomyc co-localizes with lung tumors

KRas\textsuperscript{G12D}-driven NSCLC mouse model

microPET/CT, 24 h after i.n. admin
Omomyc significantly reduces tumor burden in KRas\textsuperscript{G12D}-driven NSCLC
Omomyc efficiently shuts down Myc transcriptional signature and changes chemokine and cytokine profiles

**On target effects**

**Immune modulation**

### Table: Gene Set Analysis

<table>
<thead>
<tr>
<th>Gene Set</th>
<th>N</th>
<th>NES</th>
<th>FDR q-val</th>
</tr>
</thead>
<tbody>
<tr>
<td>YU_MYC_TARGETS_DN</td>
<td>41</td>
<td>-2.019</td>
<td>0.003</td>
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<tr>
<td>DANG_REGULATED_BY_MYC_DN</td>
<td>236</td>
<td>-1.933</td>
<td>0.009</td>
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<tr>
<td>DANG_MYC_TARGETS_DN</td>
<td>31</td>
<td>-1.712</td>
<td>0.062</td>
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<tr>
<td>SCHUHMACHER_MYC_TARGETS_DN</td>
<td>7</td>
<td>-1.513</td>
<td>0.160</td>
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<tr>
<td>LEE_LIVER_CANCER_MYC_E2F1_UP</td>
<td>52</td>
<td>-1.478</td>
<td>0.178</td>
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<tr>
<td>WANG_NEOPlastic_TRANSFORMATION_BY_CCND1_MYC</td>
<td>20</td>
<td>-1.485</td>
<td>0.175</td>
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<tr>
<td>ACOSTA_PROLIFERATION_INDEPENDENT_MYC_TARGETS_DN</td>
<td>101</td>
<td>-1.406</td>
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</tr>
<tr>
<td>ODONNEll_TARGETS_OF_MYC_AND_TFRC_UP</td>
<td>63</td>
<td>-1.395</td>
<td>0.227</td>
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<tr>
<td>MYC_UPV1_DN</td>
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<tr>
<td>HALLMARK_KRAS_SIGNALING_UP</td>
<td>180</td>
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<td>0.035</td>
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<tr>
<td>KEGG_CHEMOKINE_SIGNALING_PATHWAY</td>
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<td>0.007</td>
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<tr>
<td>REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM</td>
<td>221</td>
<td>-1.932</td>
<td>0.013</td>
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</tbody>
</table>

Beaulieu et al., in revision
**Hypothesis**

Myc inhibition by Omomyc in KRas-driven NSCLC not only halts tumor progression but also promotes a shift from an immunosuppressive microenvironment to a more immune-stimulatory one, fostering an effective anti-tumor immune response.

Adapted from Ohaegbulam et al. 2014. Trends in Molecular Mechanisms.
Omomyc recruits T cells to the tumor site

**PRECLINICAL RESULTS – IMMUNE CELL RECRUITMENT**

Beaulieu et al., in revision

KRas\textsuperscript{G12D}-driven NSCLC mouse model

**Omomyc**

2.37mg/kg (1101100)

Vehicle Omomyc

**Intratumoral CD3\(^+\) cells / mm\(^2\)**

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Omomyc</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>500</td>
</tr>
<tr>
<td>1,000</td>
<td>1,500</td>
</tr>
</tbody>
</table>

**1 week**

**Intratumoral CD3\(^+\) cells / mm\(^2\)**

<table>
<thead>
<tr>
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<th>Omomyc</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>400</td>
<td>500</td>
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</tbody>
</table>

**4 weeks**

**Intratumoral CD3\(^+\) cells / mm\(^2\)**

<table>
<thead>
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<th>Omomyc</th>
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<tr>
<td>0</td>
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<tr>
<td>300</td>
<td>0</td>
</tr>
<tr>
<td>400</td>
<td>0</td>
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</table>
Omomyc treatment recruits activated CD4 T cells to the tumor site

**PRECLINICAL RESULTS – IMMUNE CELL RECRUITMENT**

*CD4+ T cells*

*Activated CD4+ T cells*

*CD4+PD-1+ T cells*

*CD4+PD-1+Tim-3+ T cells*
Omomyc induces the differentiation of hybrid Th1/Th17 cells

Th1/Th17 have potent anti-tumor effects (Chatterjee et al. 2017)

Conventional dendritic cells

Casacuberta-Serra et al., in preparation
Omomyc systemic administration recruits PD-1⁺Tim-3⁺ T cells to the tumor

SubQ model
Kras/p53 mutated NSCLC
(MuH-163 gift by Dr. Barbacid)

CD4⁺PD-1⁺Tim-3⁺ T cells

CD8⁺ T cells

CD8⁺PD-1⁺Tim-3⁺ T cells

Ex vivo tumor volume

Casacuberta-Serra et al., in preparation
Conclusions and future perspectives

✓ Omomyc treatment abrogates tumor progression in KRas-driven mouse models of lung adenocarcinoma, offering a new pharmacological approach to inhibit Myc in vivo.

✓ Myc inhibition by Omomyc changes the cytokine and chemokine profile in the tumors and recruits T cells to the tumor site.

❑ Study the effect of Omomyc in combination with immunotherapies (anti-PD-1, anti-CTLA-4).

❑ Validate the T cells recruitment in humanized mouse models of KRas-driven NSCLC.