Myc inhibition as a Therapeutic Strategy in Cancer

Laura Soucek

Mouse models of Cancer Therapy Laboratory

Vall d’Hebron Institute of Oncology (VHIO)
Myc overexpression or deregulation is associated with over 50% of human cancers
The Myc network

- **Proliferation**
- **Transformation**
- **Apoptosis**
- **Differentiation**

Diagram:

- MYC (red) + MAX (green) → CACGTG
- MAX (green) + MAX (green) → CACGTG
- MAX (green) + MAD (purple) → CACGTG

Process arrows between different states.
So, what about inhibiting Myc?

TUMORIGENESIS

Reasons for skepticism:

Myc is deemed “undruggable” mainly because:
1. It does not have an active site
2. Multiple Myc proteins (c-, N- & L-)
3. Needed for normal tissue maintenance
Our model: Omomyc

Gene activation

(Soucek et al., 1998)

(Soucek et al., 2002)
Omomyc mouse model:

- TRE → Omomyc
- CMV → rtTA
- rtTA
- TRE → Omomyc

Dox + → TRANSCRIPTION
Lung Tumor mouse model: 
**LSL-KRas^{G12D}**

Hyperplasia and Adenomas by 4-6 weeks 
Carcinomas by 16-26 weeks

(Jackson et al., 2001)
Myc inhibition triggers rapid regression of Ras lung tumors

KRas only

KRas + Omomyc
Are there any side effects?

Good news:

Systemic inhibition of Myc - an efficient therapy for Ras-induced tumors – elicits only relatively mild, well tolerated and reversible side effects

Soucek et al. Nature 2008
Recurrent tumors are sensitive to a second round of treatment (no resistance has emerged)
Metronomic treatment with Omomyc can keep the animals tumor free
In summary:

- Myc is a unique, non redundant and non degenerate function in cancer cells.

- Tumors cannot evolve “around” it.

Soucek et al., Genes &Dev 2013
Important:

The therapeutic impact of Myc inhibition is not limited to KRas\textsuperscript{G12D}-induced lung tumors.
RIPT2 model (Doug Hanahan’s) of β cell tumors

Omomyc inhibits expansion of RIP-Tag2 tumors with 7 week treatment of Doxycyclin

Omomyc causes regression of RIP-Tag2 tumors with 3 week treatment of Doxycyclin

Control (no Rip-Tag2)

RIP-Tag2

TREOmo;CMVrtTA;RIP-Tag2
Omomyc expression induces death of endothelial cells in RIPT2 tumors

*TRE-Omo;CMV-rtTA;RIPT2*
Endothelial cell death precedes tumor cell death
Expression of Omomyc for 2 days affects expression profile of various chemokines and cytokines.
Angiogenic signals

Angiogenic effectors

MMP9
VEGF

Omomyc

Myc

neutrophil

mast cell

macrophage
Take home message:

There is a cross-talk between tumor and microenvironment which is dependent on endogenous Myc

Sodir et al., Genes & Dev 2011
One more challenge: brain tumors
A mouse model of glioma and Myc inhibition:

Ding H et al., Cancer Research, 2001
Guha’s Lab
In GFAP-HaRas mice there are regions with high density, GFAP-positive, pleomorphic and infiltrative astrocytes, associated with increased vascularity, all typical histopathological features of human malignant astrocytomas.
Myc inhibition on symptomatic mice

Day 1

✓ Lethargy, hunched posture and poor grooming.

Day 7

✓ Normal active behaviour
Myc inhibition reduces astrocytic density

TREOmo:CMV-rtTA; GFAP-HaRas
-Dox

TREOmo:CMV-rtTA; GFAP-HaRas
+Dox

2.5 X  5 X

GFAP IHC
Note: in the GFAP positive areas, Myc inhibition correlated with the appearance of polynucleated cells.
Some human data

(U87MG GBM human cell line)

Growth curve

Trypan Blue exclusion

Emilia Favuzzi
Omomyc causes appearance of polynucleated cells
Omomyc expression causes mitotic crisis in human U87MG GBM human cell line
Induction of mitotic crisis as a possible MOA of Omomyc in GBM
Myc inhibition in GBM tumour cells derived from patients

• pTRIPZ-Omomyc lentiviral vector in patient-derived neurospheres
Patient Derived Xenografts: Omomyc confers a significant survival advantage

\[ P \text{ value} = 0.046 \]

- Omomyc

N=6

N=7

\[ P \text{ value} = 0.046 \]
CANCER = Therapy X
= Therapy Y
= Therapy W
= Therapy Z
= Therapy XX
= Therapy XY

STOP

CANCER
From Omomyc itself to a potential drug

BREAKTHROUGH:
Omomyc can function as a Cell Penetrating Peptide (CPP)

A549 cells treated for 2 h with Omomyc-FITC peptide

Marie-Eve Beaulieu
First Biodistribution studies:

Omomyc-FITC

10 min later
Lung

- 0.25 sec
- 1 sec
- 5 sec

- ctr
- Omomyc-FITC 1 mM
Brain

5 sec

ctr

Omomyc-FITC 1 mM
Acknowledgements:

Jonathan Whitfield
Marie-Eve Beaulieu

Daniel Masso’
Toni Jauset

Erika Serrano
Thanks!

Gerard Evan
Nicole Sodir
Lamorna Swigart
Daniela Annibali

Pierre Lavigne (University of Sherbrooke, QC, Canada)

Sergio Nasi (University of Rome, La Sapienza, Italy)