Why translocation-related sarcomas are not necessarily targetable?

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February 19, 2014
Disclosure

- Stephen Lessnick is a member of the Scientific Advisory Board for Salarius Pharmaceuticals
  - Salarius Pharmaceuticals has licensed LSD1 inhibitors from Huntsman Cancer Institute and is developing them for clinical use
What does targetable mean?

- Specific tumors use specific molecular pathways
- Blockade (or stimulation) of these pathways inhibit tumor growth or cause cell death
- These pathways can be blocked in a pharmacologically (or biologically) delivered approach
- The drug/biologic agent has a therapeutic window
Ewing sarcoma: a paradigm for “translocation sarcoma”

Ewing sarcoma has a low mutational frequency

To date: no mutant enzymes/kinases reported at high frequency

Lawrence, et al., Nature 499, 214-8,(2013)
EWS/FLI is a driver oncogene at the top of a transcriptional hierarchy.

Direct upregulated targets: e.g., NR0B1, GSTM4, GLI1

Indirect upregulated targets: e.g., NKX2.2, KRT17

Direct downregulated targets: e.g., TGFBR2, LOX, IGFBP3

Indirect downregulated targets

No EWS/FLI transcriptional targets have been readily “targetable”
FLI DNA binding domain

- No binding pocket in FLI for drugs
- EWS thought to be disordered (and without pocket)
Transcription factors can’t be targeted because they don’t have concave drug binding pockets

(exception: steroid hormone receptors)
Unconventional wisdom: could protein-protein interactions be targeted?

Unconventional wisdom?

Yet another “unconventional” approach

Can one target enzymes that EWS/FLI binds and uses for transcriptional function?
EWS/FLI uses NuRD/LSD1 to repress target gene expression

Methylation of Histone 3

H3: ARTKQTAR KSTGGKAPRK...ARKSA

LSD1 (me2/me1)
JARID1A (me3/me2)
JARID1B (me3/me2)
JARID1C (me3/me2)
JARID1D (me3/me2)

LSD1 (me2/me1)
JARID1A (me3/me2)
JARID1B (me3/me2)
JARID1C (me3/me2)
JARID1D (me3/me2)

EZH2
JMJD3
UTX

MLL1
MLL2
MLL3
MLL4
MLL5
SET1A
SET1B
SET7/9
ASH1
Sc SET1
Sp SET1
SUV39H1
SUV39H2
SETDB1/ESET
EuHMTase/GLP
G9a
CLL8
RIZ1
Sp CLR4
Me
Me
Me
LSD1 inhibition blocks EWS/FLI function and Ewing sarcoma cell growth

LSD1 inhibition cures Ewing sarcoma xenografts
Yet another “unconventional” approach

Can one simply screen for agents that turn off EWS/FLI function?
Mithramycin turns off EWS/FLI

AraC downregulates EWS/FLI

None of the 10 response-evaluable patients demonstrated a CR or PR. These results indicate that cytarabine, given at the dose and schedule utilized, had minimal activity in the treatment of patients with relapsed or refractory Ewing sarcoma. The toxicity of this regimen prevented timely administration of the prescribed therapy and may have contributed to this observed lack of efficacy.
Targeting DNA to disrupt EWS/FLI-DNA interaction

TC71 xenografts treated with trabectedin 0.15 mg/kg q7dx3. Tumor samples were collected 24 hours after the first and 24 hours and 7 days after the third dose.

Unpublished data courtesy of Maurizio D'Incalci
Conclusions

- Translocation products are key drivers of specific sarcoma subtypes
- Translocation transcription factors aren’t “classic” drug targets
- New approaches may make translocation transcription factors targetable
- Only time will tell!