Targeting the IGF Pathway in Pediatric Sarcomas-Lessons Learned and Questions Raised

Lee J. Helman, M.D.
Scientific Director for Clinical Research, Center for Cancer Research, NCI
Role of IGF Signaling-
Previous Studies

• IGFII is an autocrine growth and motility factor in rhabdomyosarcoma (El-Badry et al. Cell Growth and Diff 1990)

• Loss of Imprinting (LOI) of IGFII in Rhabdomyosarcomas (Zhan S, Shapiro DN, and Helman LJ JCI 1994)

• LOI of IGFII in Ewing’s Sarcoma (Zhan S, Shapiro DN, and Helman LJ Oncogene 1995)

• IGFIR is required for EWS-FLI-1 transformation of fibroblasts  (Toretsky J. et al. JBC 1997)
Previous Studies

• IGF-II overexpression in C2 myoblasts led to diminished G1 checkpoint (Zhang et al. JBC 1999)

• Resistance to apoptosis most directly correlated with phosphorylation of p70S6 kinase and 4E-BP-1. Resistance to apoptosis in IGF-II overexpressing cells was reversed by rapamycin (Wan and Helman Neoplasia 2002)
Rapalogs and IGF Signaling

• Demonstrated that rapalog treatment of RMS leads to activation of Akt *in vivo*

• Demonstrated that this activation is IGF dependent and can be blocked with IGFIR blockade (Wan et al. Oncogene 2006)

• Proteomic analysis of Dx tumor biopsies in Stage III RMS demonstrated activation of mTOR pathway proteins predicted poor DFS in both ERMS and ARMS (Petricoin EF et al. Ca Res 2007)
Nutrients
GF(insulin/IGF)

IRS-1 → PI3K → PIP2, PIP3 → PTEN → PDK1 → PKB/Akt

LKB1 → AMPK

Rapamycin, FKBP12

Rheb

TSC1, TSC2

mTOR → mLST8, Raptor, mTOR, Rictor

S6K1, 4E-BP1, rpS6, elf4B, elf4E

Top-dependent translation (e.g. IGF-II)

Cap-dependent translation (e.g. Cyclin D1, c-MYC, HIF-1α, VEGF)

Actin cytoskeleton
Preclinical Studies with human IGFIR Ab
Variable levels of IGF1R in RMS tumors and cell lines

A. Variable levels of IGF1R in RMS tumors
- Ctrl = normal skeletal muscle
- P = patients’ tumor

B. Similar degree of variation of IGF1R in RMS lines

In vivo Correlation of IGF1R and anti-IGF1R Response

IGF1R (R/cell): 13,800

IGF1R (R/cell): 2,900

Results represent largest diameter shown at Mean±SEM (n=10)
Anti-tumor Effects of h7C10 Associated with Initial Inhibition of IGF1R and p-AKT

A. Drug effects on tumor growth

B. h7C10 initially inhibits both IGF1R and p-AKT in vivo
Resistance to h7C10 is Associated with Reactivated AKT Signaling

A. Drug effects on tumor growth

B. Resistance associated with reactivated p-AKT

- IGFR (RU)
  - Ctrl: 5000
  - h7C10: 1000
  - *p = 0.02

- p-AKT (RU)
  - Ctrl: 3000
  - h7C10: 2000
  - *p = 0.40

- t-AKT (RU)
  - Ctrl: 150000
  - h7C10: 200000
  - *p = 0.36
Synergistic Inhibition between IGF1R antibody and Rapamycin

A

Rh30-Luc Tumor Growth

Tumor size (1 dimension, mm)

Time (Days)

Ctrl
Rapa
h7C10
Combo

Rx

Combination effect of h7C10 and Rapa

21 days
Conclusions

• Early evidence to suggest beneficial combination of mTOR inhibition combined with IGFIR inhibition
• Effect of IGFIR inhibition correlates with IGFIR levels
• Effect of IGFIR blockade on decrease in pAkt is lost in long-term xenografts, and this “tachphylaxis” is abrogated with mTOR inhibition
• Raises question of whether Ab should be stopped in patients who respond and then progress
Nutrients

GF(insulin/IGF)

RTK

IRS-1

PI3K

PI3K

PDK1

PKB/Akt

LKB1

AMPK

TSC1

TSC2

Rheb

mTOR

Raptor

mLST8

S6K1

4E-BP1

Rictor

mLST8

Rapamycin

FKBP12

Actin cytoskeleton

Top-dependent translation (e.g. IGF-II)

Cap-dependent translation (e.g. Cyclin D1, c-MYC, HIF-1α, VEGF)
Clinical Studies in Ewing’s and other Sarcomomas
44 year old US farmer with third systemic relapse of Ewing’s sarcoma
SARC Protocol #: SARC 011
Hoffmann-La Roche Protocol #: N021157

TITLE: SARC Global Collaboration*: A Phase II Trial of R1507, a Recombinant Human Monoclonal Antibody to the Insulin-Like Growth Factor-1 Receptor for the treatment of patients with recurrent or refractory Ewing's sarcoma, osteosarcoma, synovial sarcoma, rhabdomyosarcoma and other sarcomas

*SARC Global Collaboration represents collaboration among the Innovative Therapies for Children with Cancer (ITCC), Istituti Ortopedici Rizzoli, European Organization for Research (EORTC/STBG), Cooperative Osteosarcoma Study Group (COSS), EuroEwings, Euramos

Sponsor: F. Hoffmann-LaRoche

Coordinating Center: SARC (Sarcoma Alliance for Research through Collaboration)
17 yo boy with multiply recurrent Ewing’s sarcoma

Baseline CT Chest

Week 6 CT Chest
Refractory 25yo with EWS and Retinal Metastasis Rx with R1507

Baseline

Week 6
9/9/08 NIH MRI

9/9/08 NIH PET CT: Right orbital mass SUV 4.7
Conclusions

• IGFIRAb 1507 has good clinical activity in EWS and perhaps RMS
  – No mutations found in pathway to date
• Preclinical models did not accurately predict dramatic tumor shrinkage, but did predict activity
• Response rates less than 50%, so challenge is to identify factors that predict good response
• Must find ways to combine with other targeted Rx and or ChemoRx
IGF-1R/InR  →  IRS-1  →  PI3K  →  Akt  →  TSC1/2  →  Rheb  →  mTORC1  ↔  mTORC2  

IGF-1R Ab TK inhibitors  
PI3K/mTOR inhibitors  
LY294002  
Akt inhibitors  
Rapalogs  
mTORC1 and mTORC2 inhibition with kinase inhibitors?