Identification and Testing of Novel, Actionable Targets to Treat Osteosarcoma and MPNST Sarcomas

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RIS Winter Gathering
Osteosarcoma Develops From Osteoblast Cells in the Bones of the Body

- Cell of origin believed to be osteoblasts, the cells that make bone
- Express osteoblast markers and form bone in the tumor
- Osteosarcoma largely develops in the long bones at areas of rapid growth
Osteosarcoma is a Rare But Deadly Cancer

- Most frequent cancer of the bone in children and adolescents
- Tumor resection and chemotherapy (M-A-C) provide best outcome
- There has been no improvement in osteosarcoma survival in the last 4 decades
- Metastatic disease substantially decreases 5-year survival rate, <29%

~20-30% of patients have macroscopic metastases at diagnosis

Malignant Peripheral Nerve Sheath Tumors Develop From Schwann Cells of Nerves

- 10% of patients with neurofibromatosis type 1 develop MPNSTs (NF1 mutation)
- Approximately 50% of cases form sporadically, in patients without NF1 syndrome
- Very poor prognosis, less than 25% if metastatic disease is present
- Treated analogous to osteosarcoma, tumor resection and non specific chemotherapy

Porter, D. E. et al., Sarcoma, 2009
The Genes Promoting Osteosarcoma and MPNST Development are Not Well Known

- Genomic instability leads to numerous chromosomal aberrations
- Bad genes get amplified and good genes are lost through this process
- Few genes have been implicated due to this complexity
The Genes Promoting Osteosarcoma and MPNST Development are Not Well Known

We set out to identify the genes driving these sarcomas 7 years ago.
With this knowledge we can develop safer and more effective treatments.
My work focuses on osteosarcoma, Dr. Largaespada and I collaborate on MPNST.

Dr. Branden Moriarity  Dr. David Largaespada  Dr. Eric Rahrmann
Method to Identify Sarcoma Genes

- Induce cancer in mice using ‘jumping’ DNA elements
- Tumor inducing insertions should occur in or near tumor causing genes
- Can activate bad genes and inactivate good genes
- Successfully used for sarcoma, leukemia, colorectal, and liver cancer

Engineered Mouse Chromosome 15

Any Chromosome

Promoter → Gene → Promoter
Jumping DNA Location Identifies Sarcoma Genes
Identified Many Known and Novel Osteosarcoma Genes

- Generated and analyzed 119 osteosarcoma tumors in mice
- We identified numerous osteosarcoma development and metastasis genes
- Some genes casually implicated previously, others completely novel
- The chromosomes are perfect, cancer completely induced by jumping DNA

Screen Results:
List of Candidate Genes

SB CIS-associated Genes

Trp53-SB CIS-associated Genes
Screen Results:
List of Candidate Genes

Bioinformatic Analysis:
Signaling Pathways, Cellular Processes, and Upstream Regulators

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PI3K-AKT-mTOR
MAPK
ErbB
Axon Guidance
ERK5
BMP
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Comparative Genomics:
Canine and Human OS Tumor Data (RNA-Seq, aCGH, methylome, WGS)

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Validation and Pre-clinical Testing:
Molecular and pharmaceutical inhibitors
**SEMA4D is a Novel, Actionable Therapeutic Target in Osteosarcoma**

1. SEMA4D activation drives the development of many osteosarcoma tumors in our model.

2. SEMA4D is expressed at high levels in Human osteosarcoma tumor samples.

3. Artificially increasing SEMA4D in human osteosarcoma cells makes them more aggressive, reducing SEMA4D makes them much less aggressive.
Antibody Therapy Blocks SEMA4D Tumor Promoting Ability

- SEMA4D antibody can block tumor promoting signals
- Soft tissue sarcomas expressing high levels of SEMA4D are associated with a poor outcome
- Antibody against SEMA4D reduced Soft tissue sarcoma tumor growth in mice
- Fully humanized SEMA4D antibody (VX15) for solid tumor treatment is in clinical trials
- Low to no toxicity compared to chemotherapy side effects

Anti-SEMA4D Therapy Has Two Modes of Action to treat osteosarcoma

- SEMA4D antibody also has potent ability to activate the immune system to kill tumors
- Thus, inhibition of SEMA4D may have a dual effect against osteosarcoma tumors by both promoting a functional immune response and inhibiting tumor progression

Potential for durable cures in pediatric osteosarcoma patients
SEMA4D is Overexpressed in Other Sarcomas and May Be a Therapeutic Option

- Analysis of other sarcoma cell lines demonstrates that SEMA4D is over expressed
  - Rhabdomyosarcoma
  - Ewing’s Sarcoma
  - Fibrosarcoma
- We plan to test anti-SEMA4D treatment on these sarcomas as well
Future Directions

1: Continue to assess the therapeutic efficacy of anti-SEMA4D antibody therapy \textit{in vitro} using human sarcoma cell lines.

2: Assess the therapeutic efficacy of anti-SEMA4D antibody therapy \textit{in vivo} using novel mouse model of sarcoma development.

3. Initiate a phase 1 clinical trial to treat pediatric sarcoma patients with anti-SEMA4D antibody.
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