

Insights into Pediatric Sarcomas: Biology and Patient Care

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Overview

- Background on Sarcomas
 - Genetics and Biology
- Modeling and Targeting Sarcomas
 - metastasis
- Patient Case Presentation

Cancer is the number one cause of death by disease of America's children.

In terms of person years life lost (PYLL), the average age at diagnosis of breast cancer is 61, with a calculated 16 PYLL.

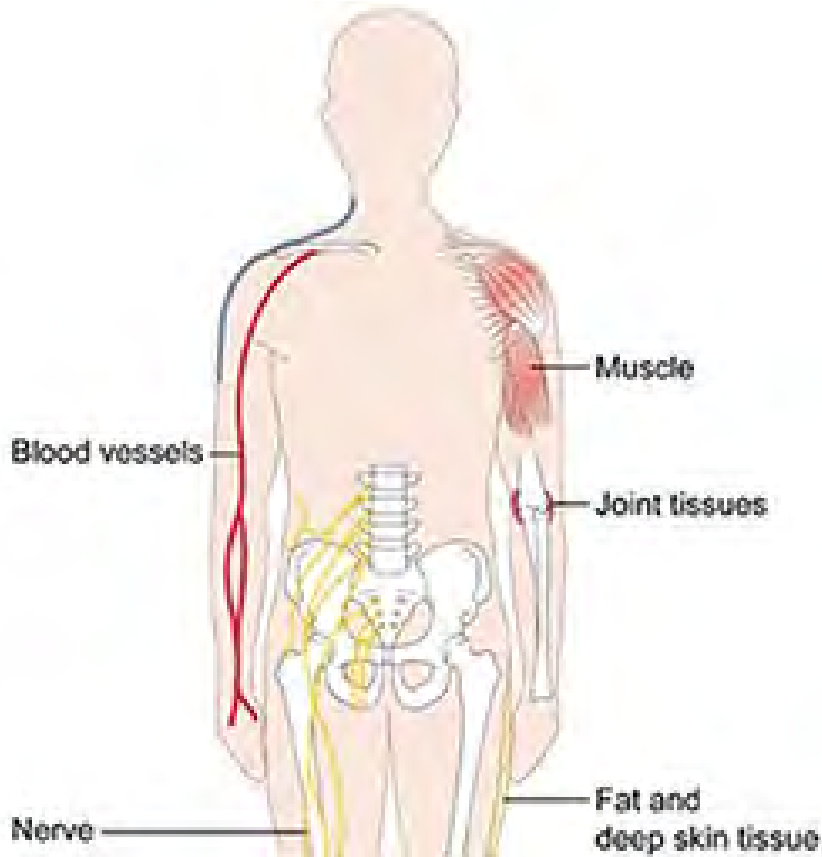
In contrast, the average age that a child is diagnosed with cancer is 10. This calculates to 67 PYLL

Pediatric Cancers are not adult cancers that reside in younger, smaller people...They are DIFFERENT Cancers!

Sarcomas: A broad group of malignancies. Dozens of subtypes have been identified.

Classified into 2 broad categories:

1. Soft tissue sarcomas (STS)
 - Tumors that have histologic resemblance to fat, muscle, nerve sheath, and blood vessels
2. Sarcomas of the bone.



Less than 1% of all new cancer diagnoses

Of 1.6-1.7 million new cases of cancer/year:

- 12,000 cases will have been STS
- 3000 cases, bone sarcomas

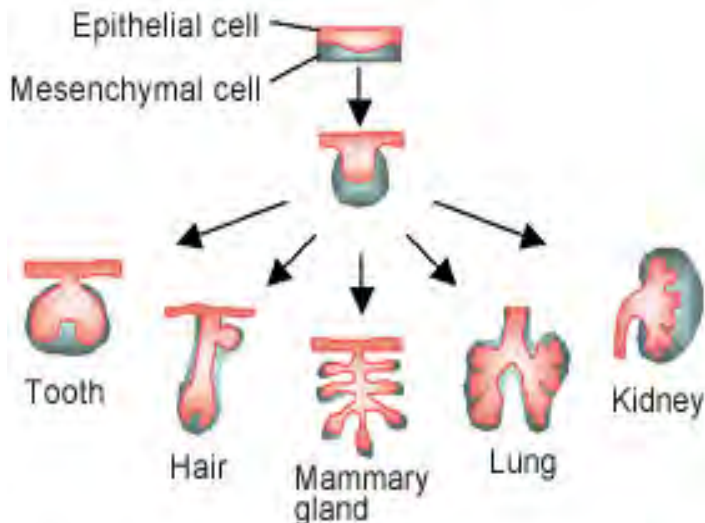
In pediatrics:

Sarcomas make up 10-15% of all malignancies

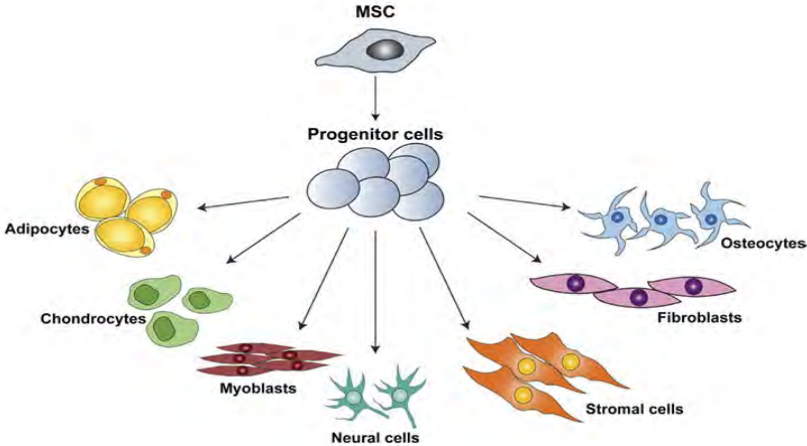
Carcinomas versus Sarcomas

<p>Carcinoma</p>	<p>Malignant tumor arising in epithelium</p> <p>The most common form of cancer</p> <p>Usually spread in lymphatic system</p>
<p>Sarcoma</p>	<p>Malignant tumor arising in connective or muscle tissue</p> <p>Usually spread by blood stream</p> <p>Frequently metastasizes to lung</p>

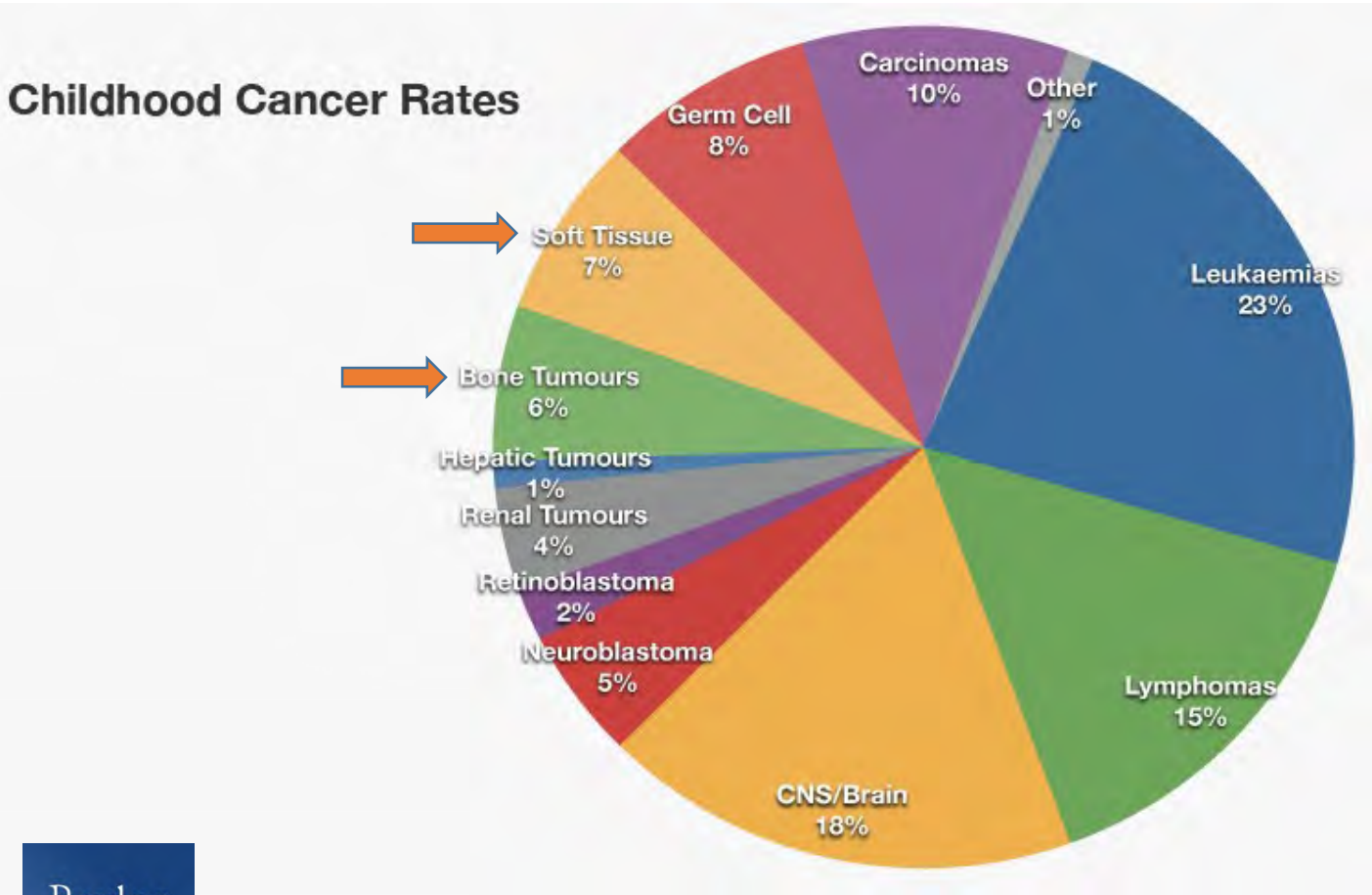
Carcinomas



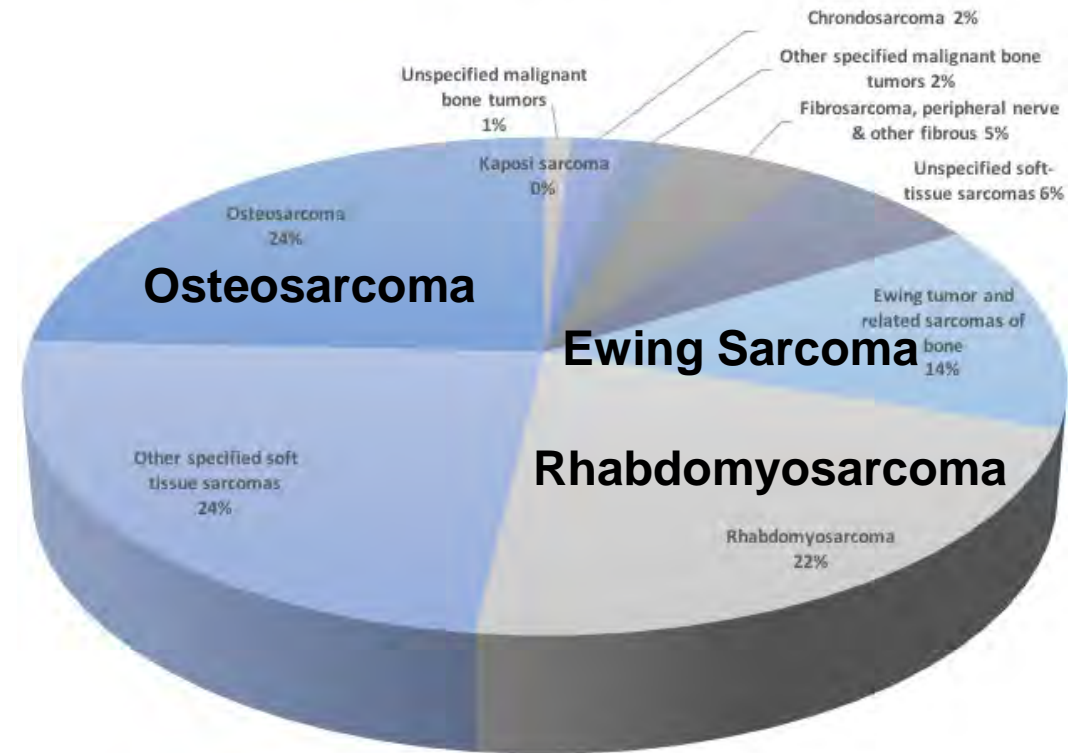
Sarcomas



Pediatric Cancer: Tumor Types



Age-Adjusted and Age-Specific SEER Cancer Incidence Rates, 2010-2014
By International Classification of Childhood Cancer (ICCC) Group and Subgroup and Age at Diagnosis Including myelodysplastic syndromes and Group III benign brain/CNS tumors
All Races, Male

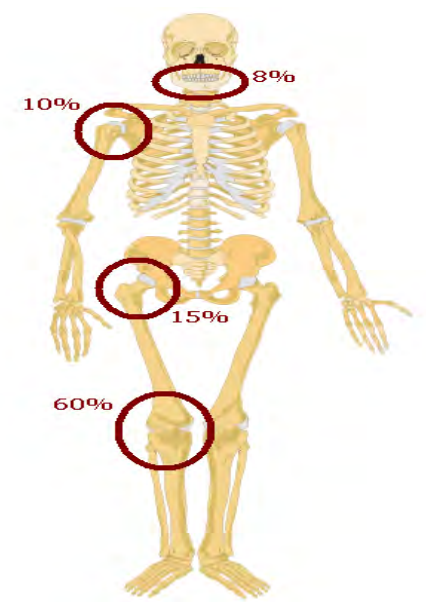
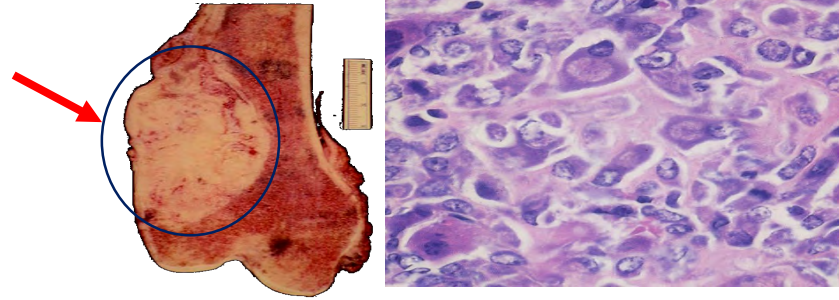


Osteosarcoma

12-18 years old; 800 new cases/year in US;
400 are kids

Treatment:

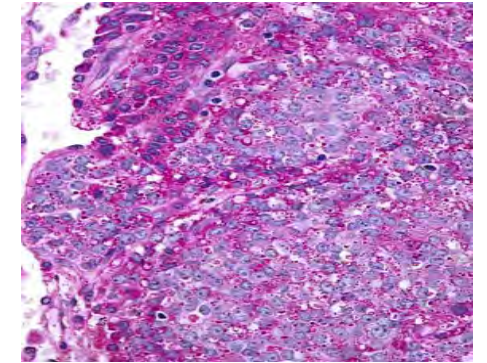
High Dose Chemotherapy
Resection of tumor



Ewing Sarcoma

10-20 year olds; 250 cases/year in the U.S.

t(11;22) **EWS-FLI1**: formation of novel chimeric transcription factor

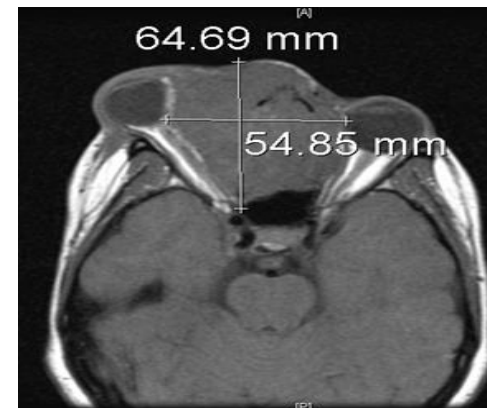


Rhabdomyosarcoma

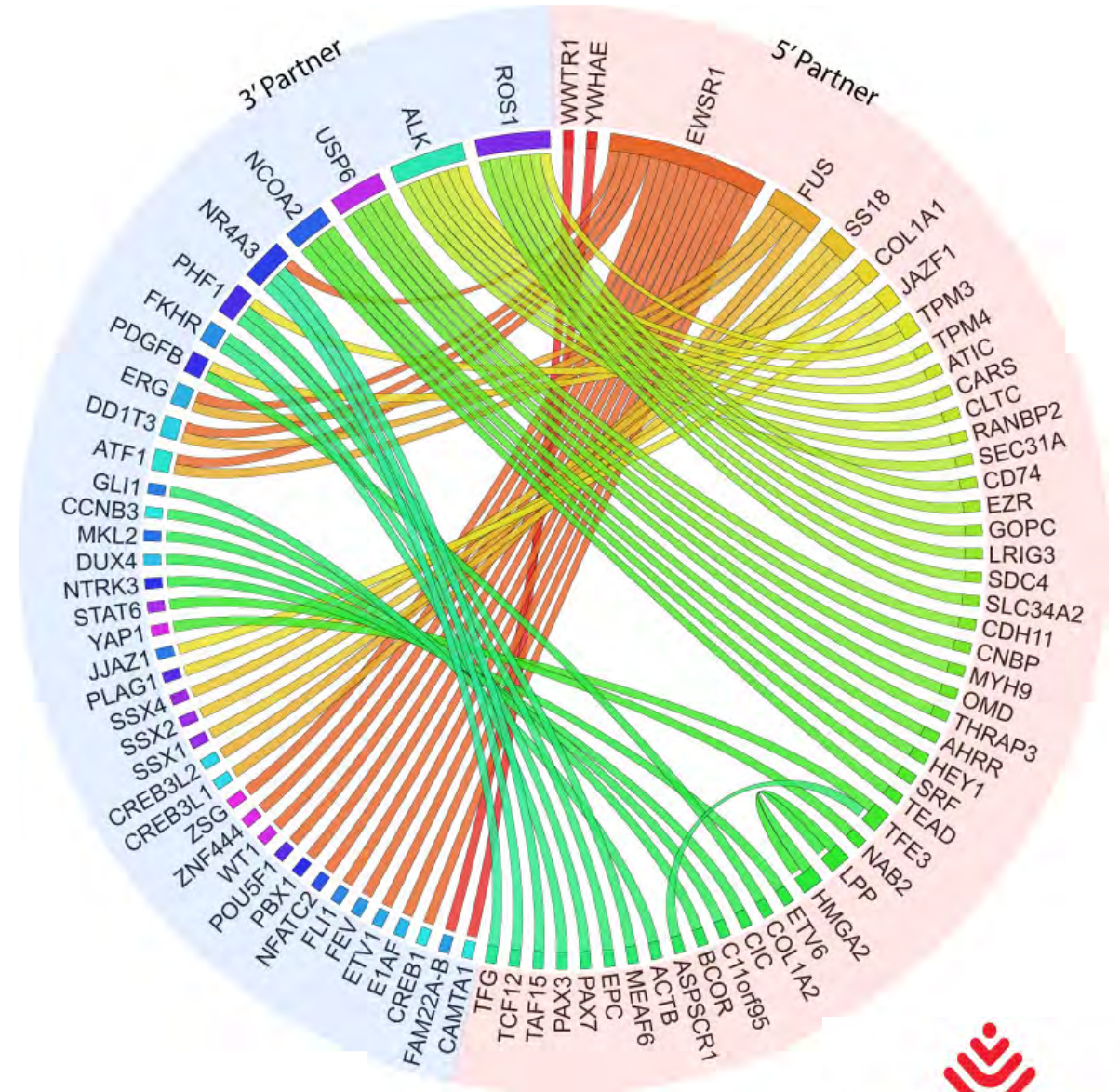
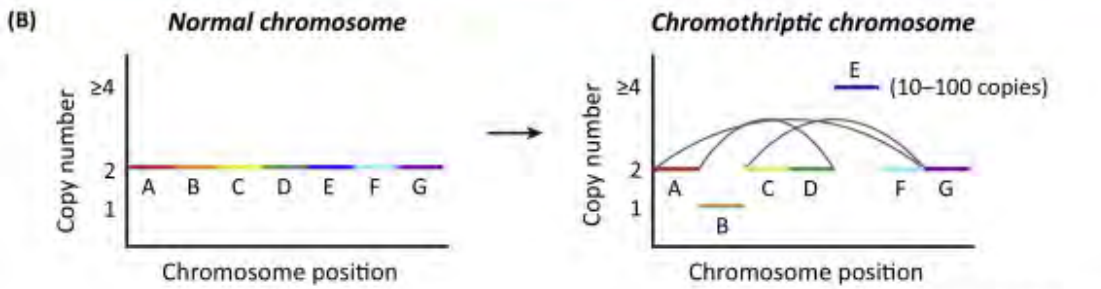
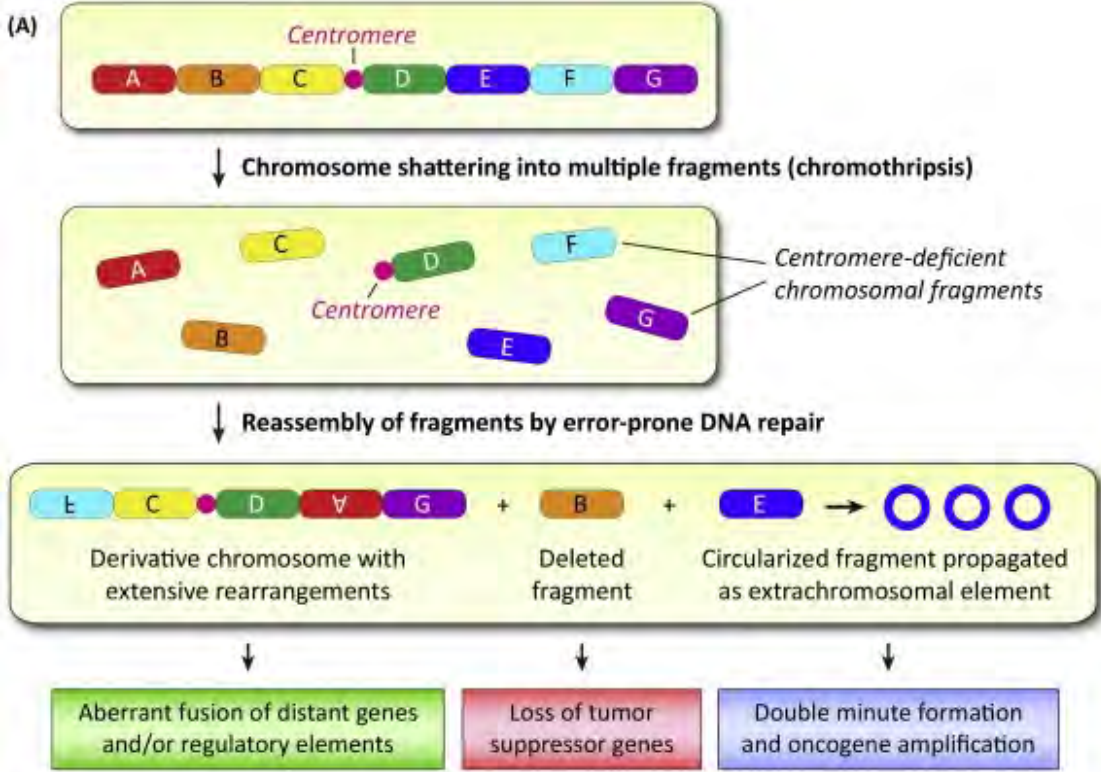
2-5 year olds; 65% before age 6
About 350-400 new cases/year in U.S.

Location:

Head and Neck (40%); GU (25%); Extremity (15%)



Genomic Catastrophes in Sarcomas: Chromothripsis

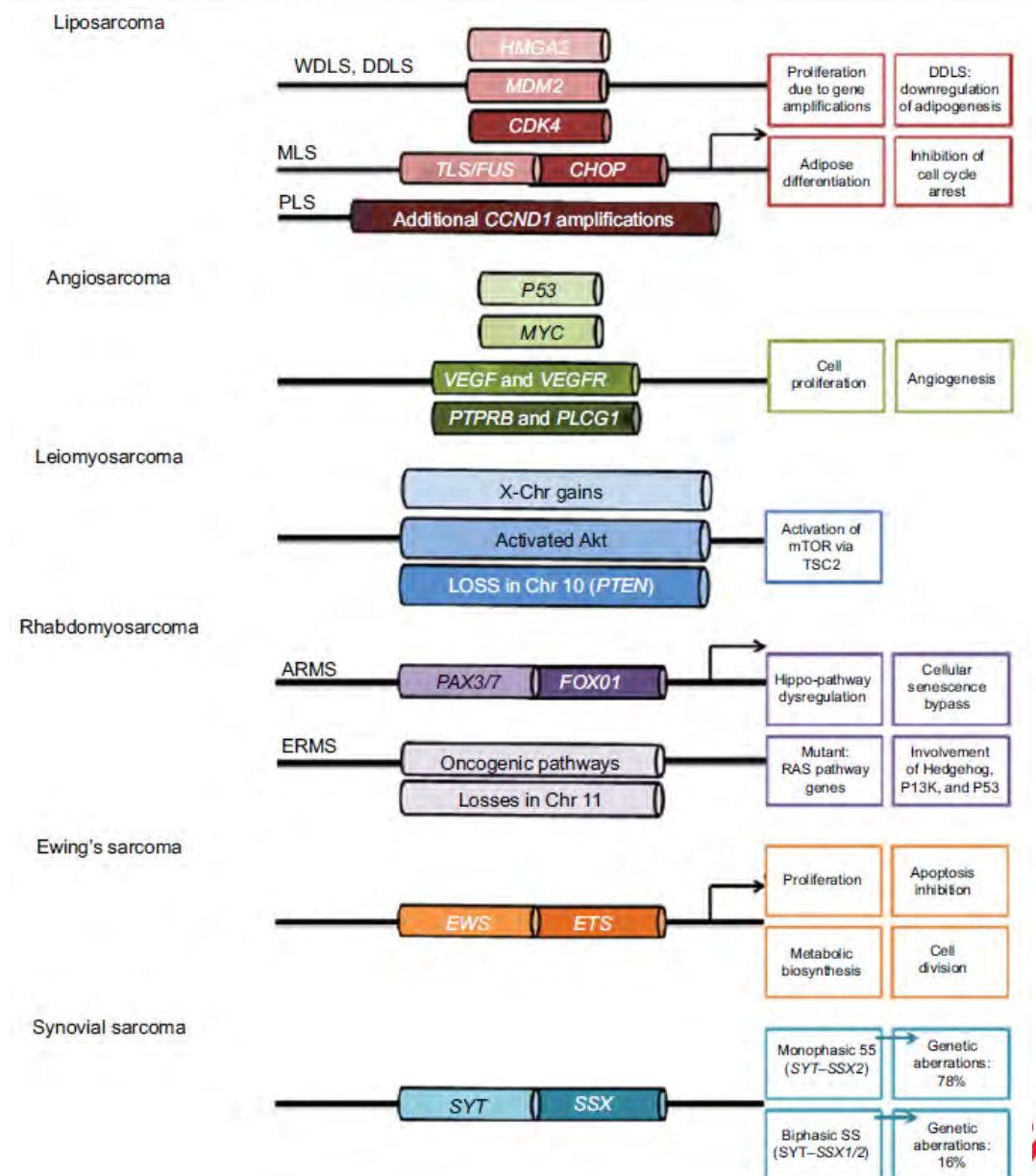


Genomic changes in sarcomas

Table 1 | **Translocations associated with sarcomas**

Translocation	Genes	Type of fusion gene
Ewing's sarcoma		
t(11;22)(q24;q12)	<i>EWSR1-FLI1</i>	Transcription factor
t(21;22)(q22;q12)	<i>EWSR1-ERG</i>	Transcription factor
t(7;22)(p22;q12)	<i>EWSR1-ETV1</i>	Transcription factor
t(17;22)(q21;q12)	<i>EWSR1-ETV4</i>	Transcription factor
t(2;22)(q33;q12)	<i>EWSR1-FEV</i>	Transcription factor
Clear-cell sarcoma		
t(12;22)(q13;q12)	<i>EWSR1-ATF1</i>	Transcription factor
Desmoplastic small round-cell tumour		
t(11;22)(p13;q12)	<i>EWSR1-WT1</i>	Transcription factor
Myxoid chondrosarcoma		
t(9;22)(q22-31;q11-12)	<i>EWSR1-NR4A3</i>	Transcription factor
Myxoid liposarcoma		
t(12;16)(q13;p11)	<i>FUS-DDIT3</i>	Transcription factor
t(12;22)(q13;q12)	<i>EWSR1-DDIT3</i>	Transcription factor
Alveolar rhabdomyosarcoma		
t(2;13)(q35;q14)	<i>PAX3-FOXO1A</i>	Transcription factor
t1:13)(p36;q14)	<i>PAX7-FOXO1A</i>	Transcription factor
Synovial sarcoma		
t(X;18)(p11;q11)	<i>SYT-SSX</i>	Transcription factor
Dermatofibrosarcoma protuberans		
t(17;22)(q22;q13)	<i>COL1A1-PDGFB</i>	Growth factor
Congenital fibrosarcoma		
t(12;15)(p13;q25)	<i>ETV6-NTRK3</i>	Transcription-factor receptor
Inflammatory myofibroblastic tumour		
2p23 rearrangements	<i>TMP3-ALK; TMP4-ALK</i>	Growth-factor receptor
Alveolar soft-part sarcoma		
t(X;17)(p11.2;q25)	<i>ASPL-TFE3</i>	Transcription factor

Note that for some tumours, notably Ewing's sarcoma, multiple variant translocations have been observed involving related genes.



Mortality and Survival Rates for Pediatric Cancers

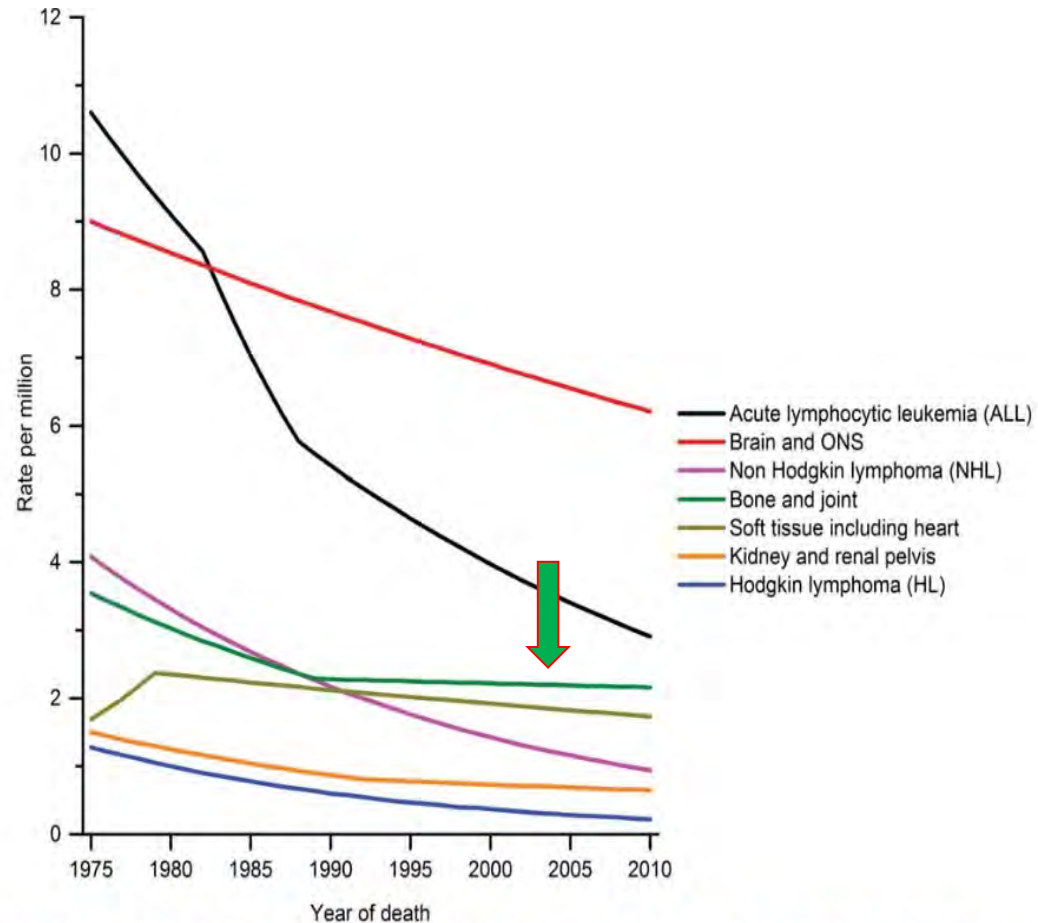
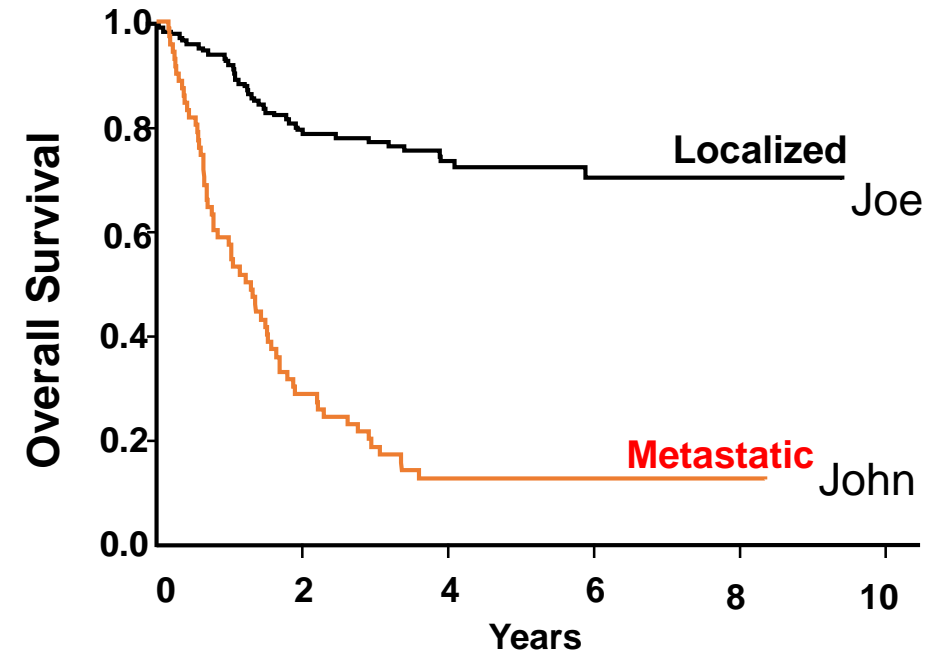
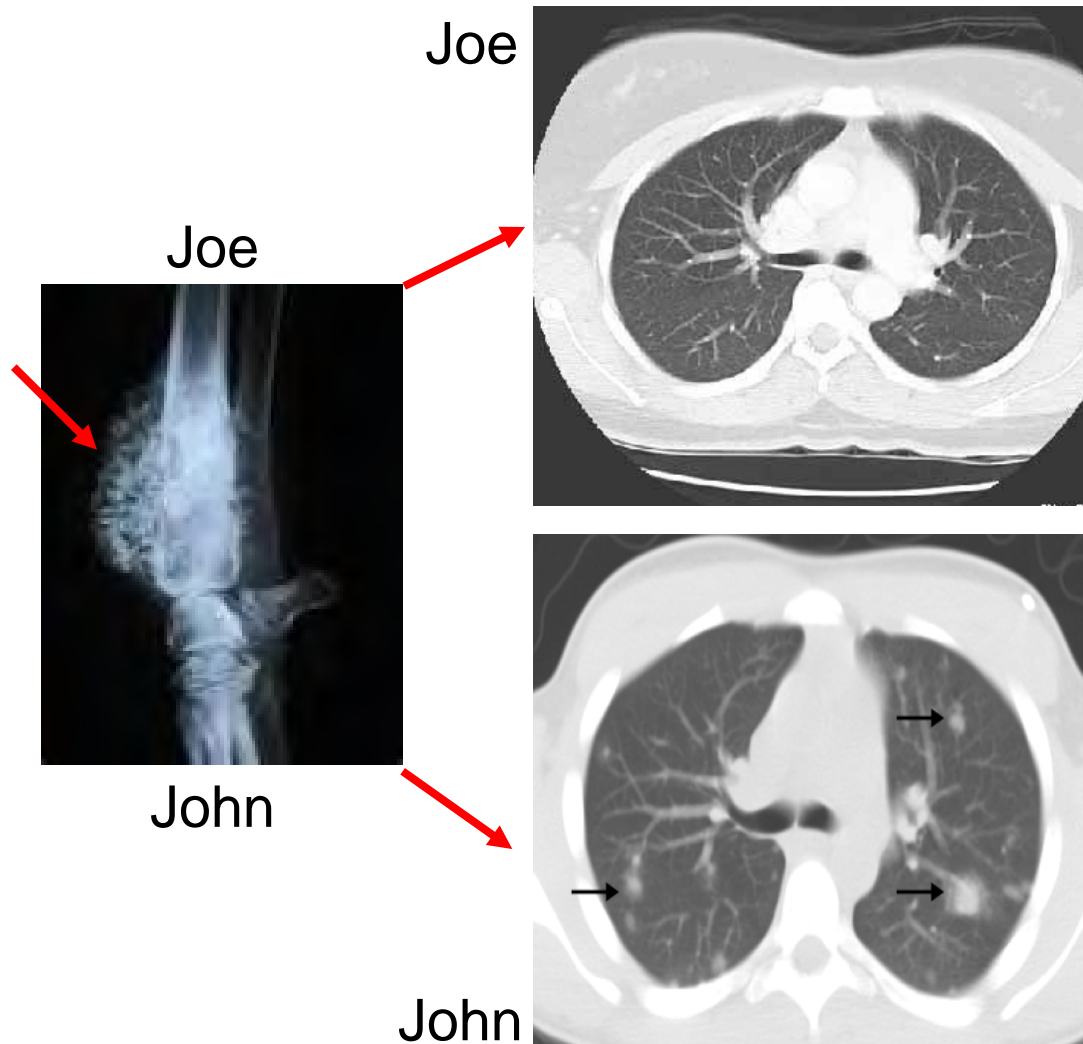


FIGURE 3. Trends in Pediatric Cancer Mortality Rates by Site, Ages Birth to 19 Years, 1975 to 2010.

TABLE 3. Pediatric Cancer 5-Year Observed Survival Rates for 2 Time Periods, Ages Birth to 19 Years

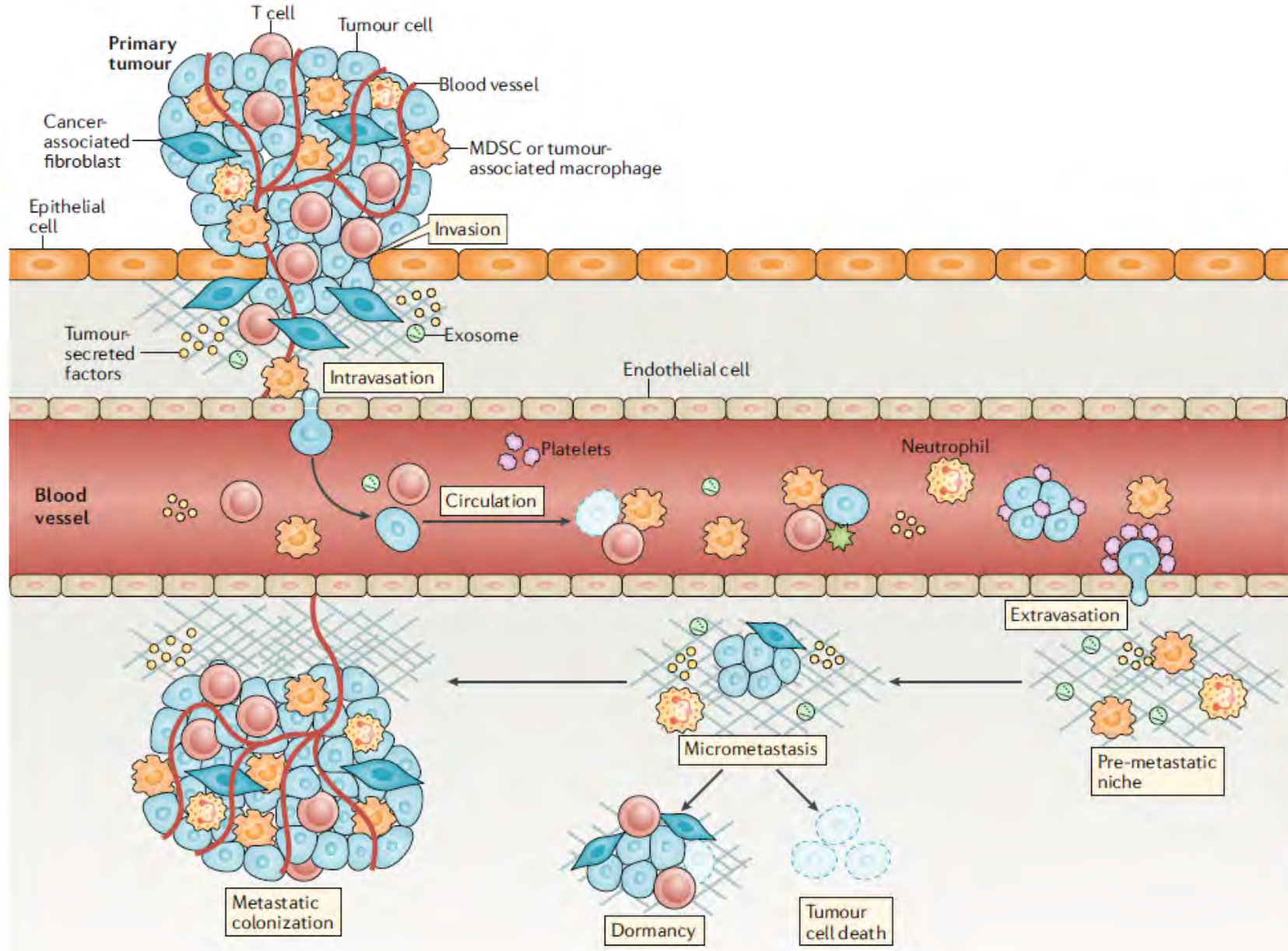
	YEAR OF DIAGNOSIS	
	1975-1979, %	2003-2009,* %
All ICCC sites	63%	83%
Leukemia	48%	84%
Acute lymphocytic leukemia	57%	90%
Acute myeloid leukemia	21%	64%
Lymphomas and reticuloendothelial neoplasms	72%	91%
Hodgkin lymphoma	87%	97%
Non-Hodgkin lymphoma	47%	85%
Brain and CNS	59%	75%
Ependymoma	37%	81%
Astrocytoma	69%	85%
Medulloblastoma	47%	70%
Neuroblastoma and ganglioneuroblastoma	54%	79%
Retinoblastoma	92%	99%
Wilms tumor	75%	90%
Hepatic tumors	25%	74%
Bone tumors	49%	73%
Osteosarcoma	45%	71%
Ewing sarcoma	42%	72%
Rhabdomyosarcoma	49%	64%
Testicular germ cell tumors	74%	96%
Ovarian germ cell tumors	75%	94%
Thyroid carcinoma	99%	98%
Melanoma	83%	95%

Why do we care about Metastatic Disease?



**90% of cancer related deaths
are due to ramifications of Metastasis**

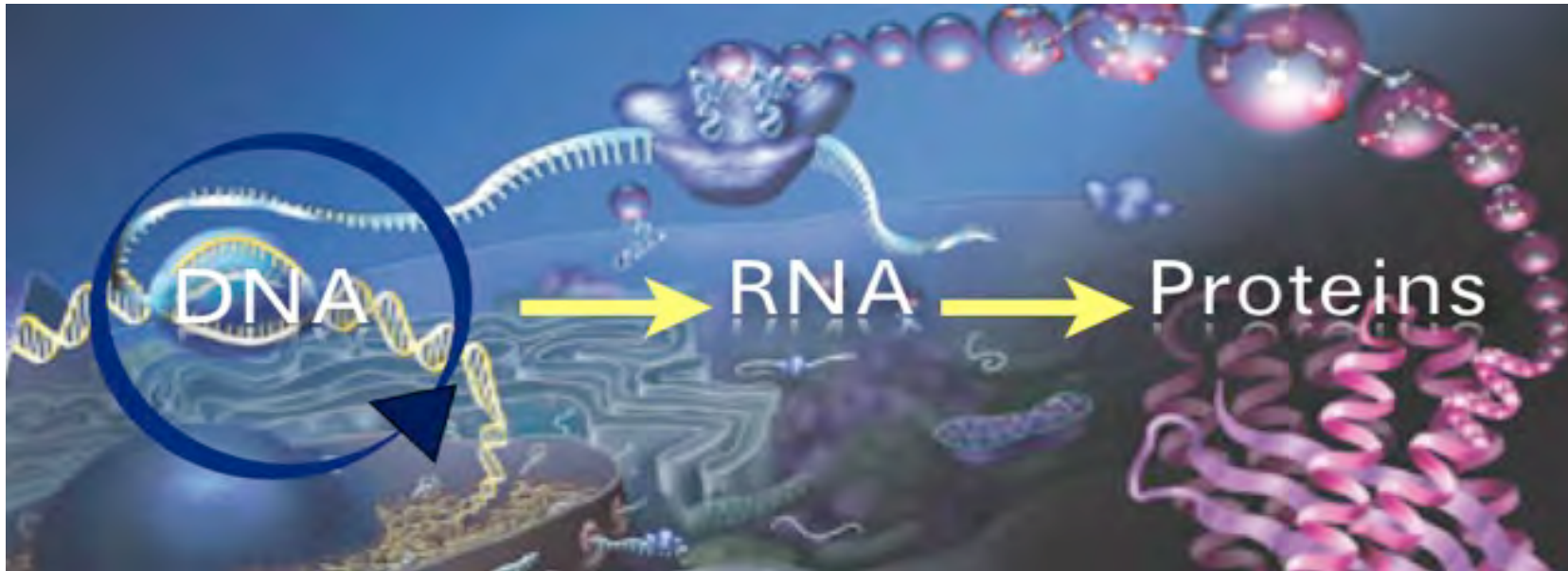
The Metastatic Cascade



Anderson, RL. et al., *Nat Rev Clin Oncol.* 2018 Dec 4.
 A framework for the development of effective anti-metastatic agents.

Mol Oncol. 2013 Apr;7(2):283-96.

What allows cancer to Develop and Metastasize?

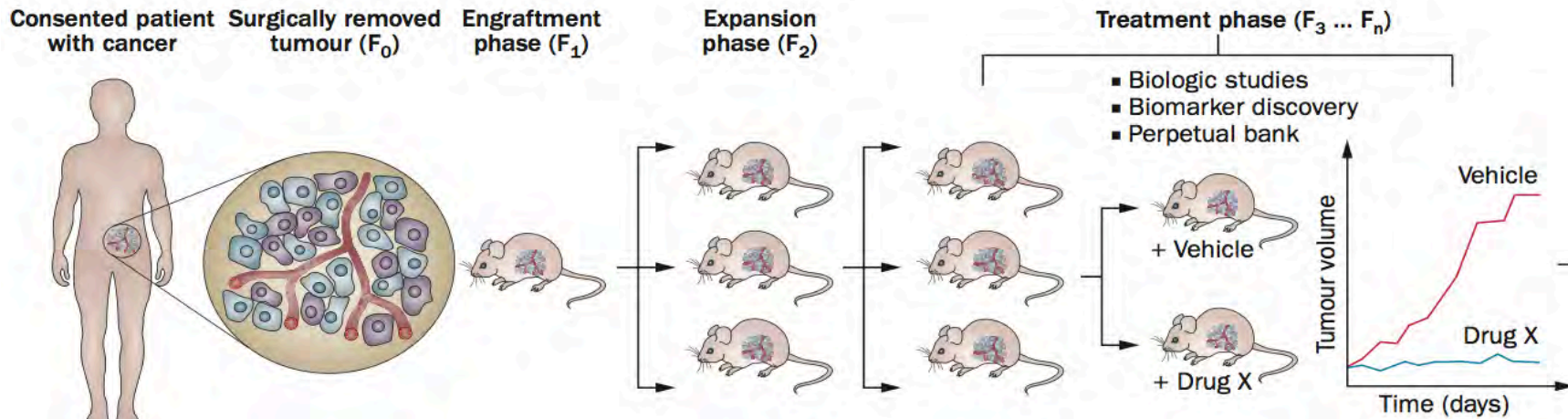


- ❑ Alterations in tumor **DNA** (mutations; amplifications; deletions)
- ❑ Alterations in tumor cell **RNA** (mRNA, microRNA) expression
- ❑ Alterations in tumor cell **Protein** expression or function

- ❑ Alterations in non-cell autonomous: **(Host ↔ Tumor)**
 - ❖ **Non-Tumor cells:** e.g., Immune cells, Stroma
 - ❖ **Surrounding conditions:** Hypoxia, metabolic alterations

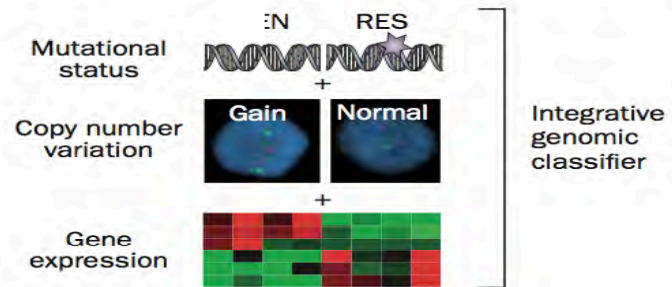
❑ ***How do we model and study these factors and mechanisms outside of the patient?***

Patient-Derived Xenograft (PDX) models

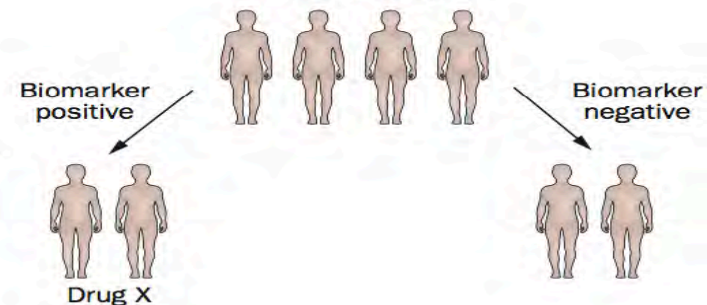


Serial blood/plasma & tumor samples

Predictive biomarker development and validation



Clinical trials



Tentler, Nature Reviews Clinical Oncology, 2012

- Excellent reflection of patient tumor biology
- Clinical relevance (better predictive value of clinical outcome)

Advantages of Genetically Engineered Mouse Models (GEMMs):

- ❑ Enables a rare disease to become common
- ❑ Immunocompetent model system: Study genetics, biology and therapeutic interventions

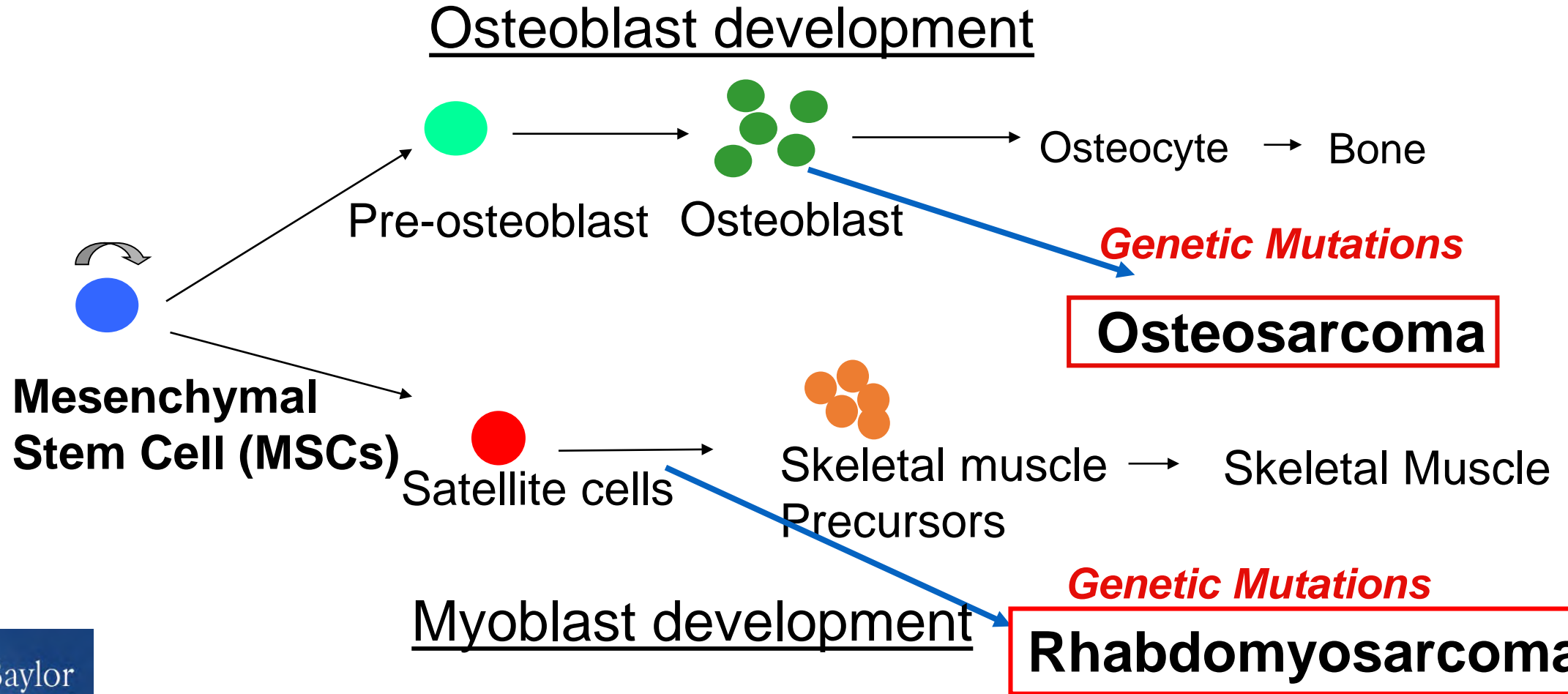


Establish own Cancer Center

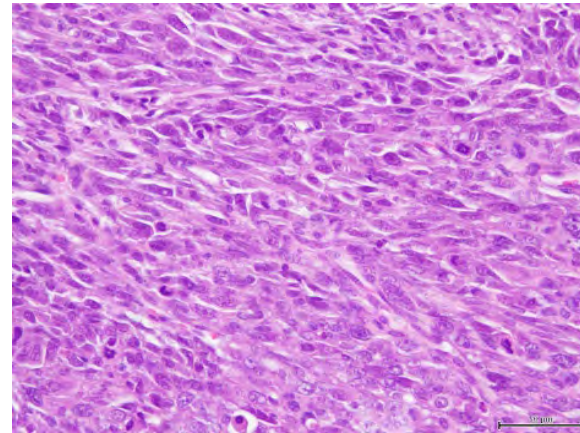
- Each **Wing** has 9 floors
- Each **floor** has 7 rooms
- 5 patients occupy/**room**

Therefore each wing of cages, can hold over 300 patients.

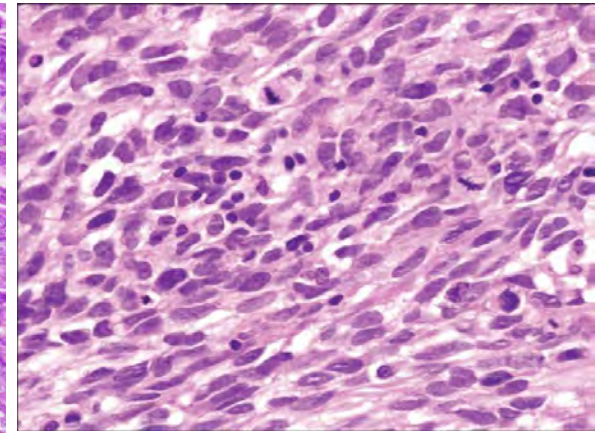
Tissue-specific alteration of p53 to induce **Localized** and **Metastatic** Sarcomas



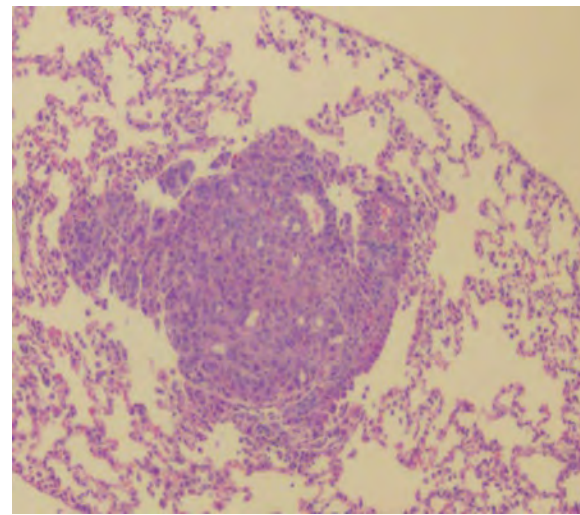
Metastatic Rhabdomyosarcoma



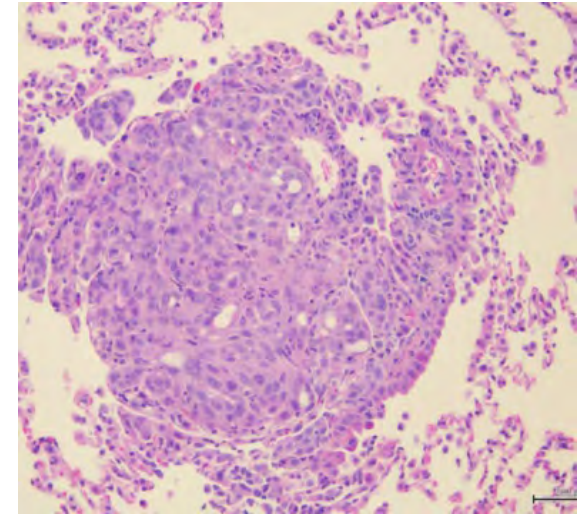
Primary



Human ERMS

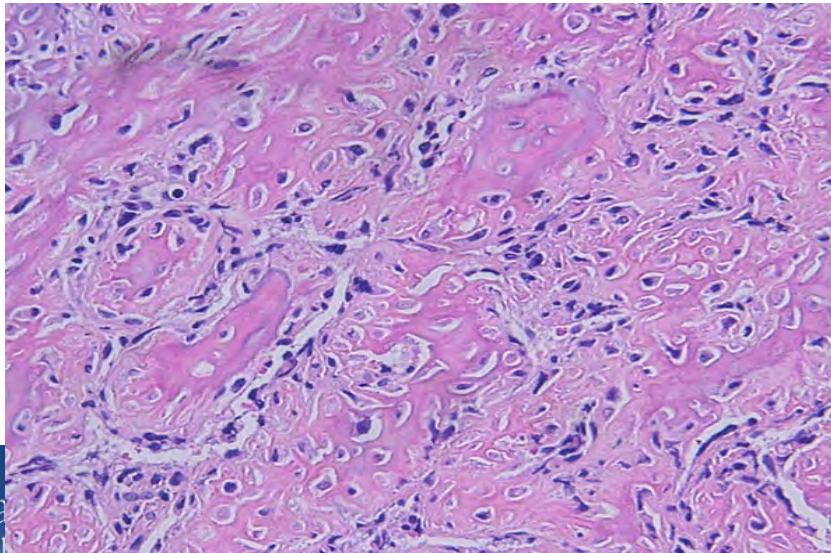
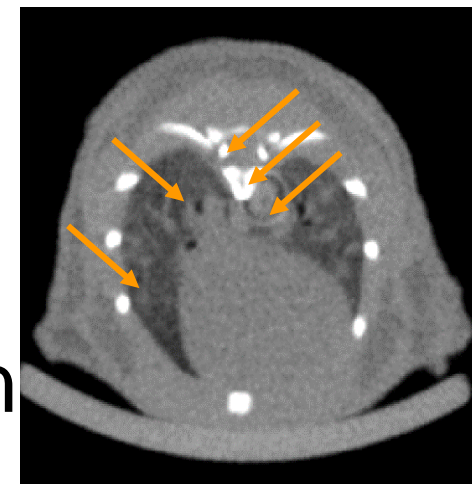


Lungs

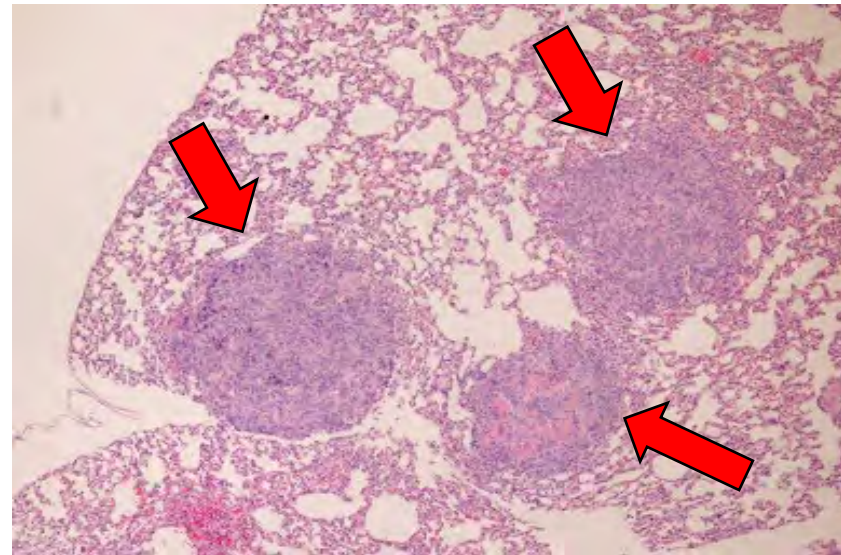


Studies Performed on Mice

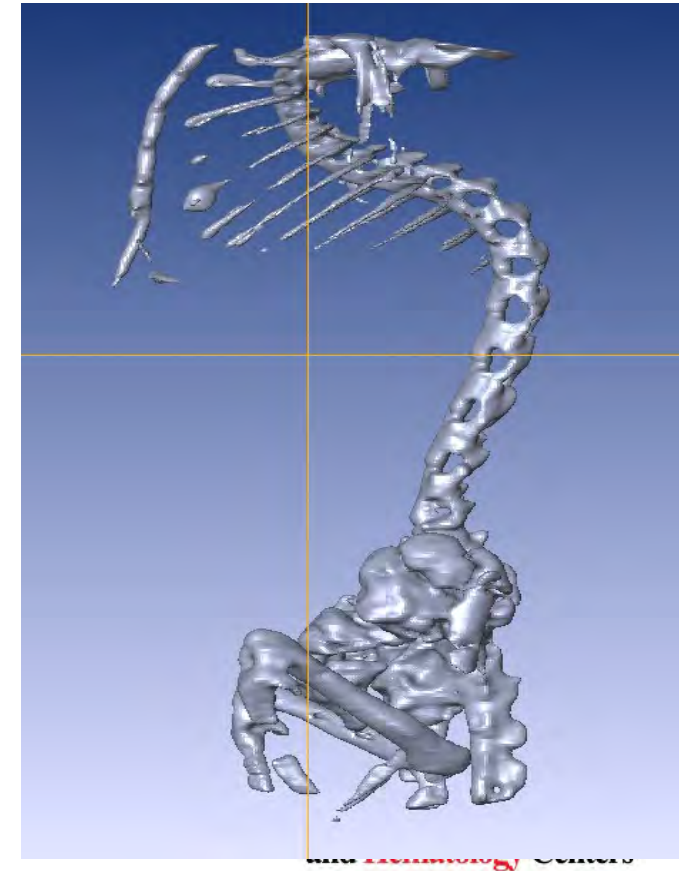
- 1) Imaging
- 2) Sample for Pathology
- 3) Isolate: Tumor DNA, RNA and Protein
- 4) Isolate Blood/Plasma: Biomarkers
- 5) Resources: Cell line models



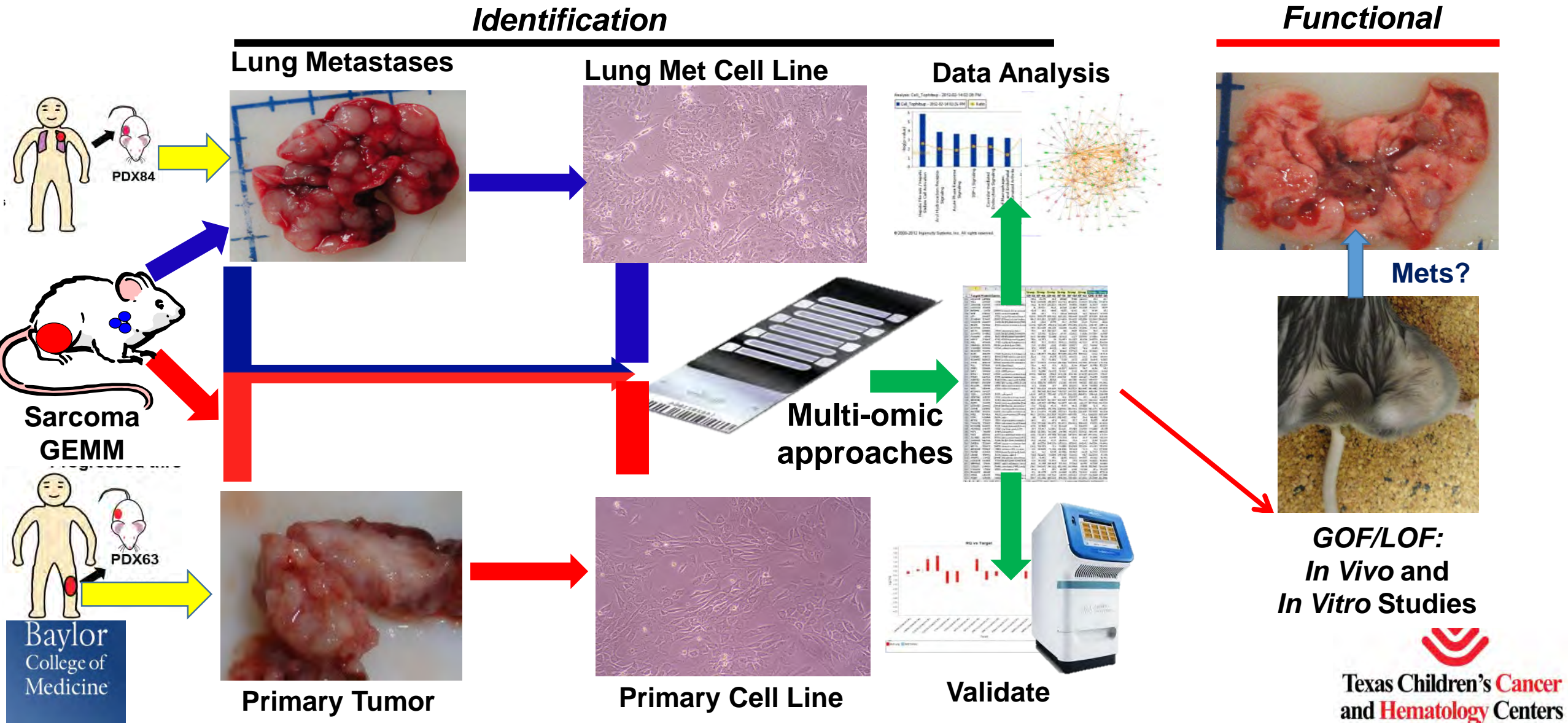
Primary (high power)



Lungs



Pipeline to *Identify* and *Functionally* Study Candidate Genes/Pathways in Sarcoma Development and Progression

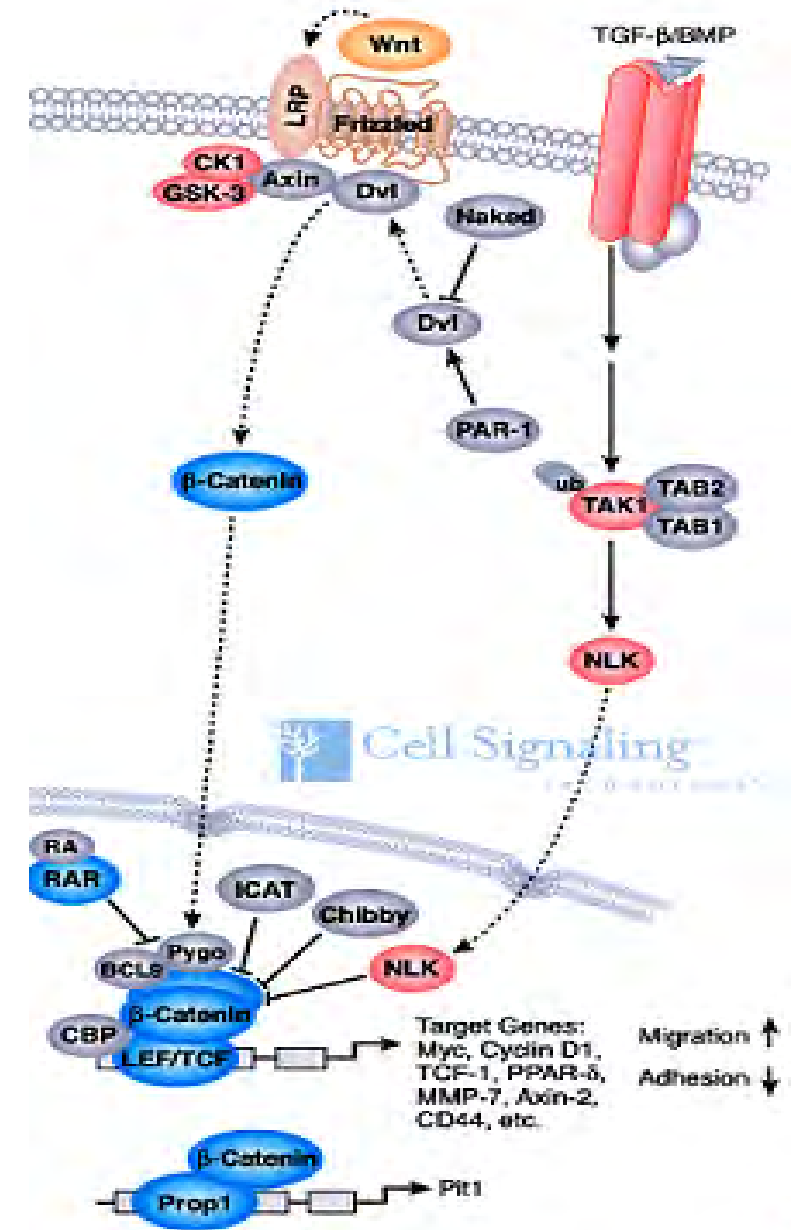
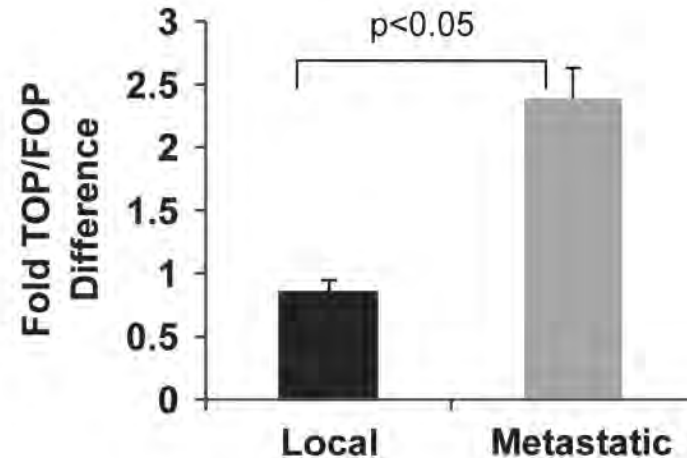


Wnt signaling pathway: Metastatic Osteosarcoma

- Highly conserved pathway
- Involved in normal embryogenesis
- Alterations in pathway implicated in Tumorigenesis.

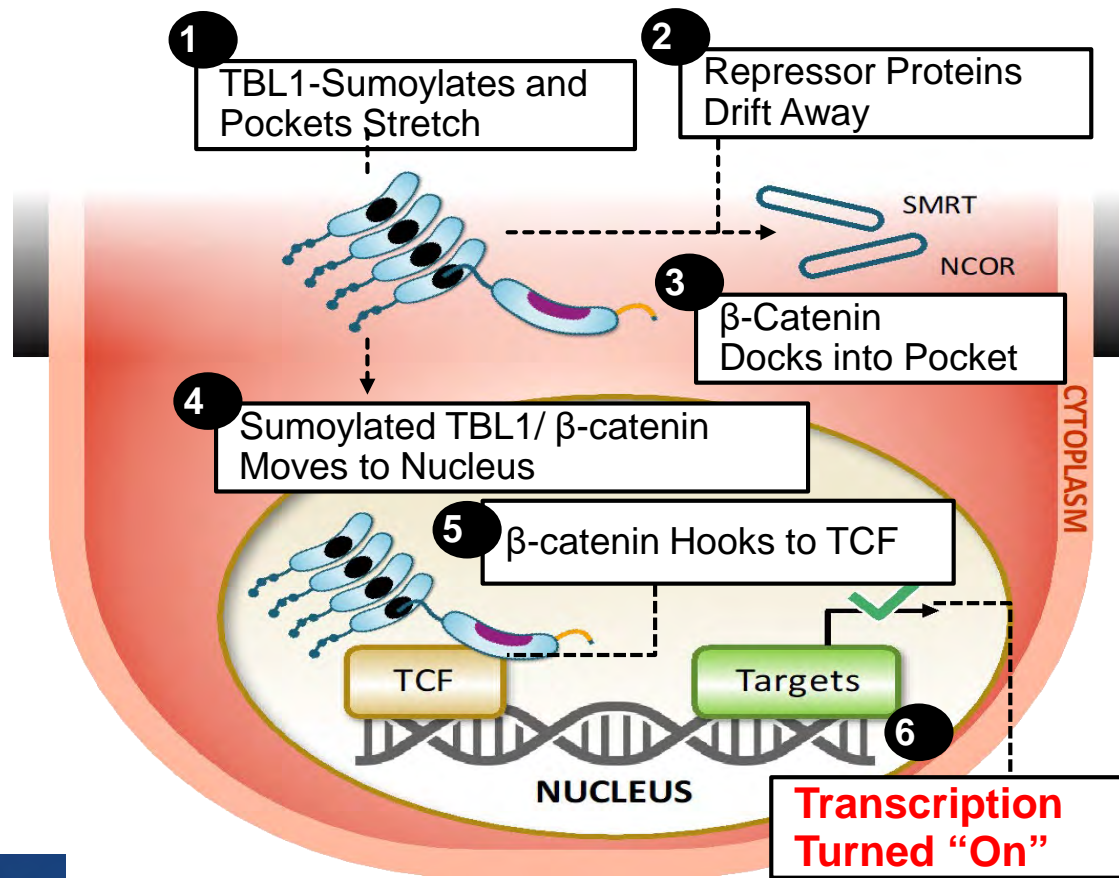
Regulation of genes:

- Cell proliferation
- Migration
- Invasion

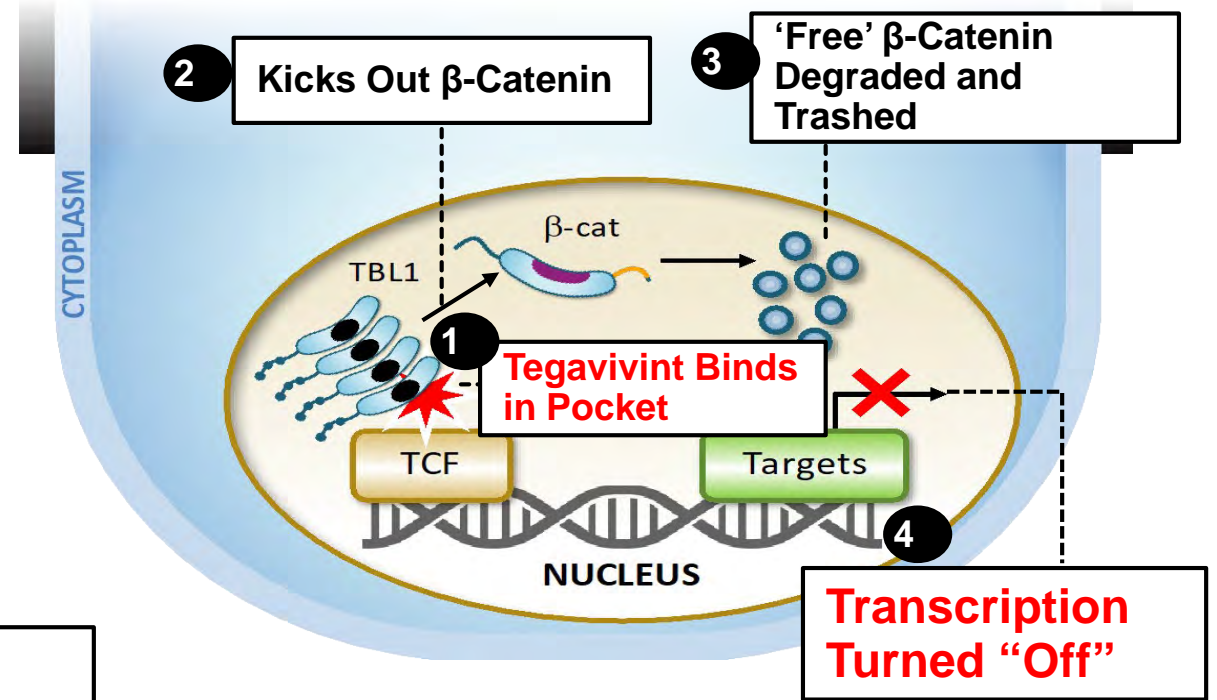


Tegavivint (BC2059): A novel Beta-Catenin Inhibitor

β -Catenin/TBL1 interaction in cancer cell



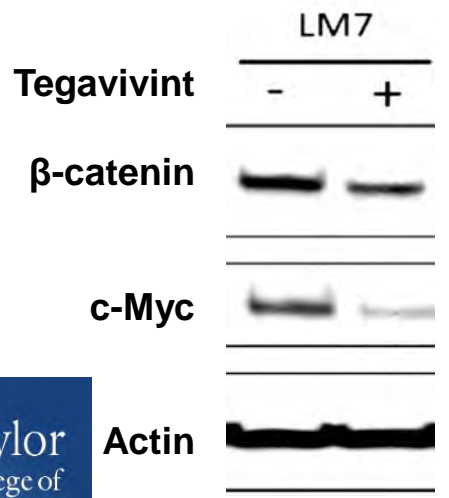
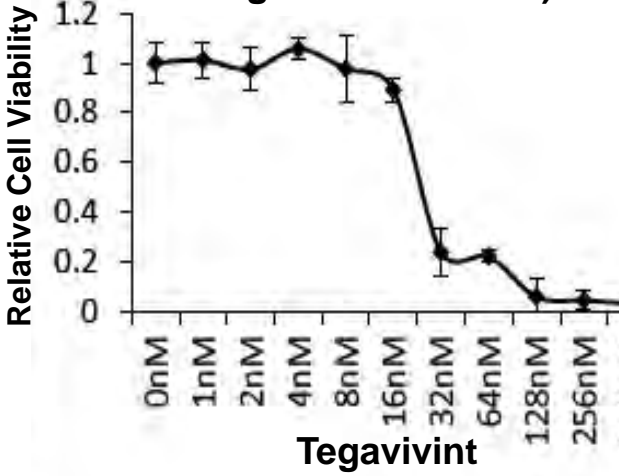
Tegavivint-treated cell



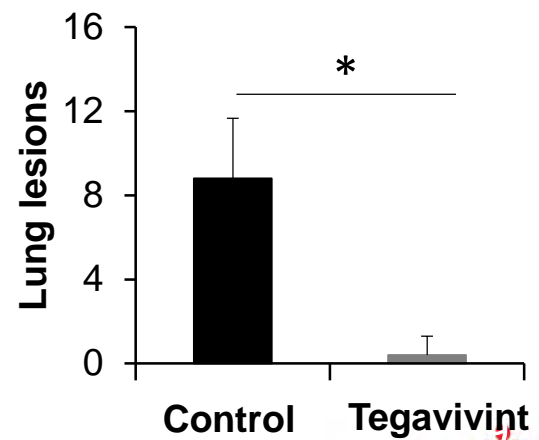
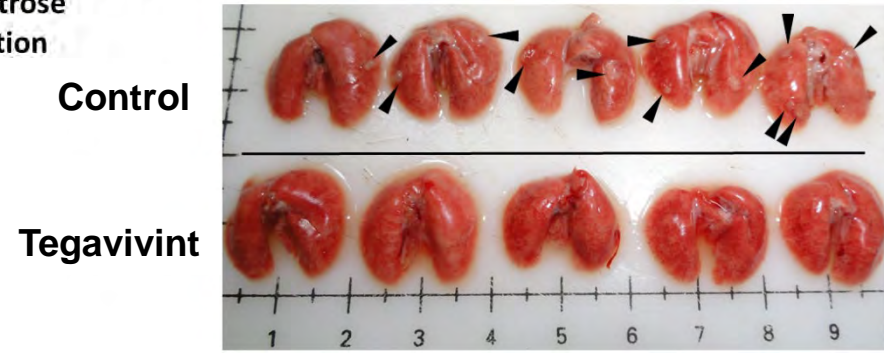
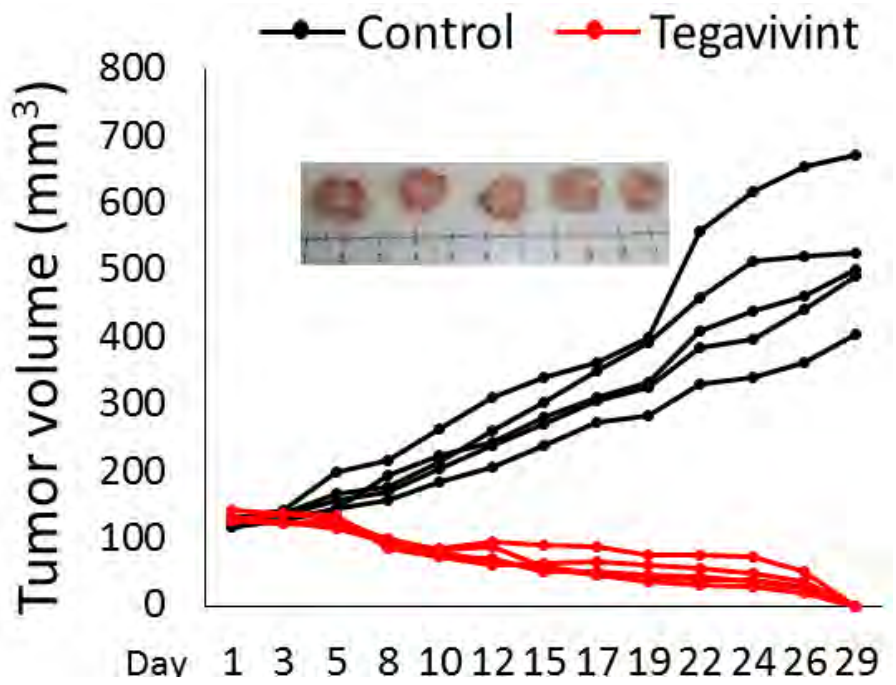
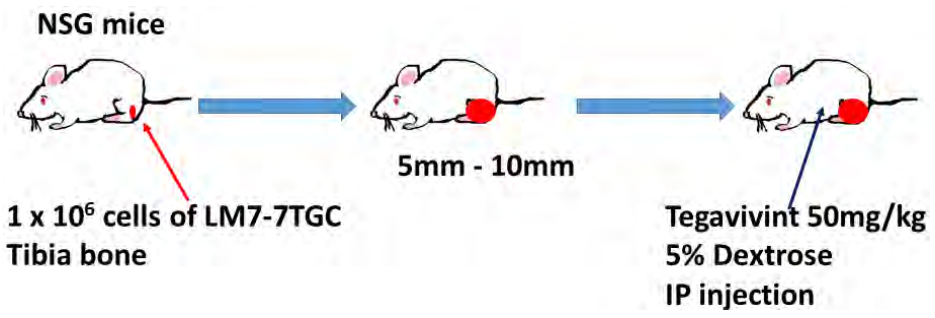
Tegavivint: Targeting metastatic OS

In vitro

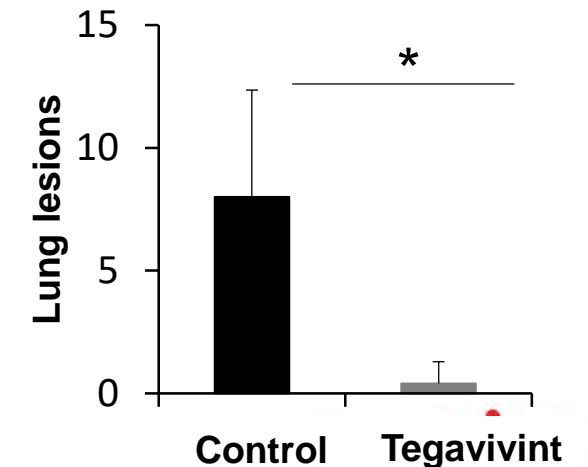
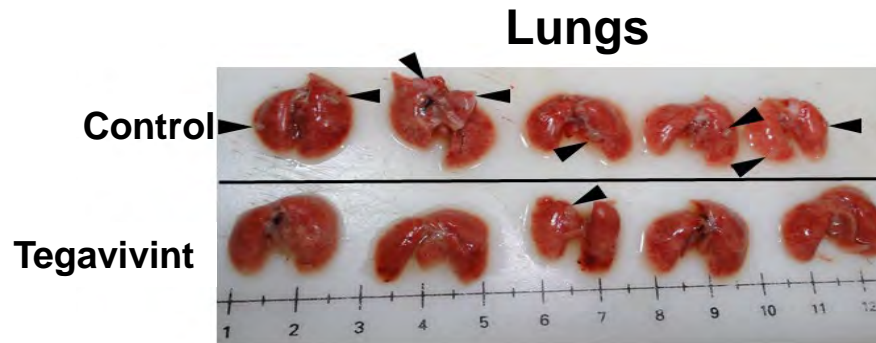
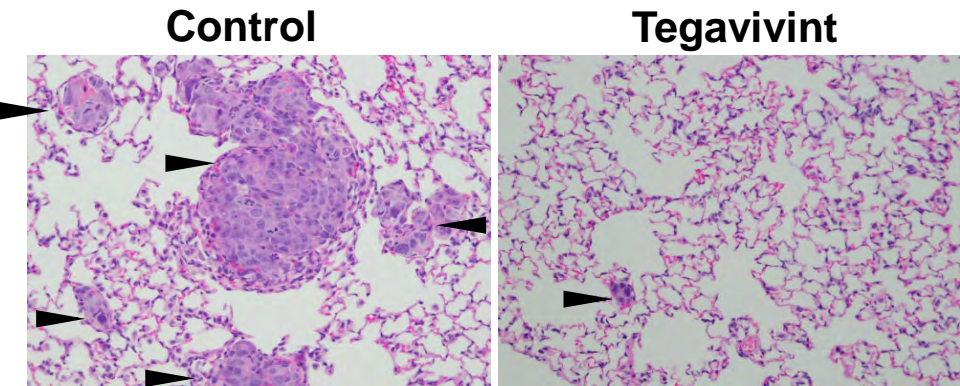
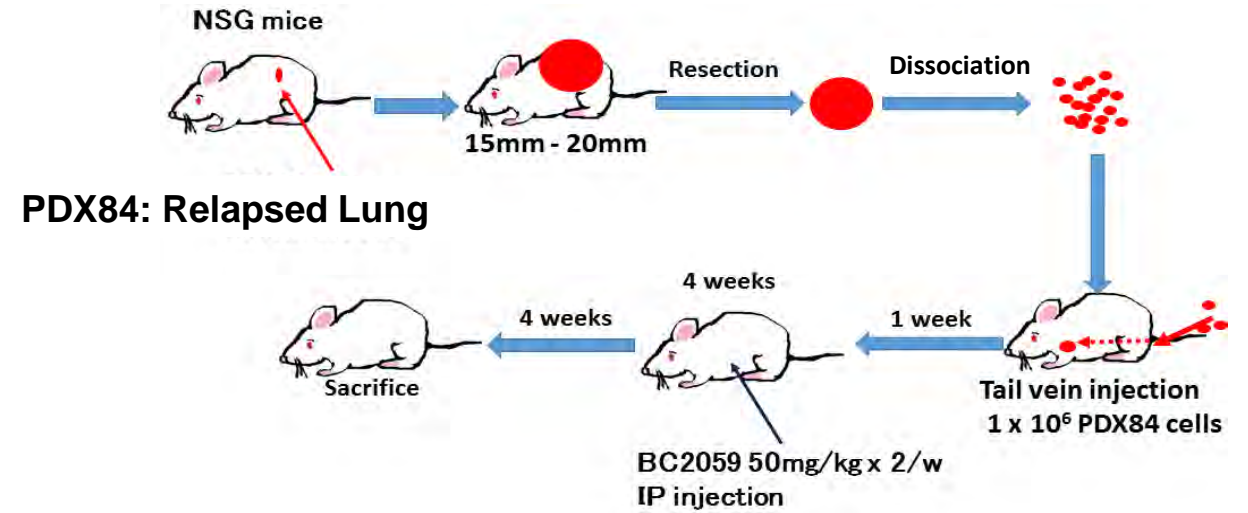
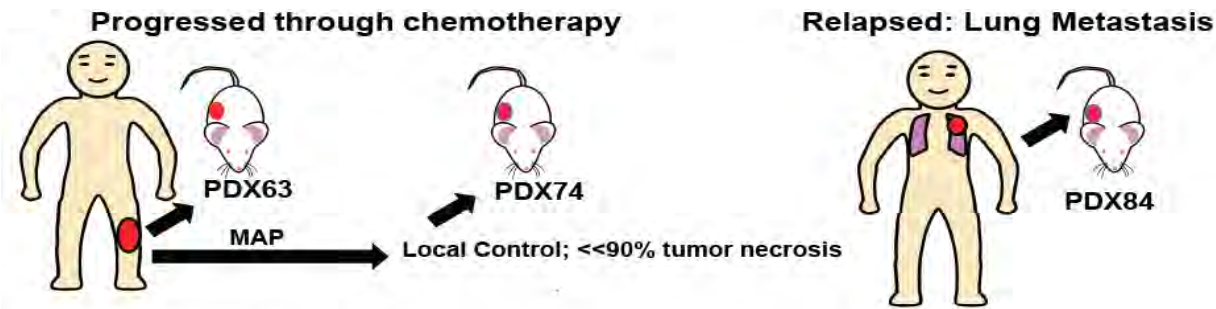
LM7 (Human metastatic lung osteosarcoma)



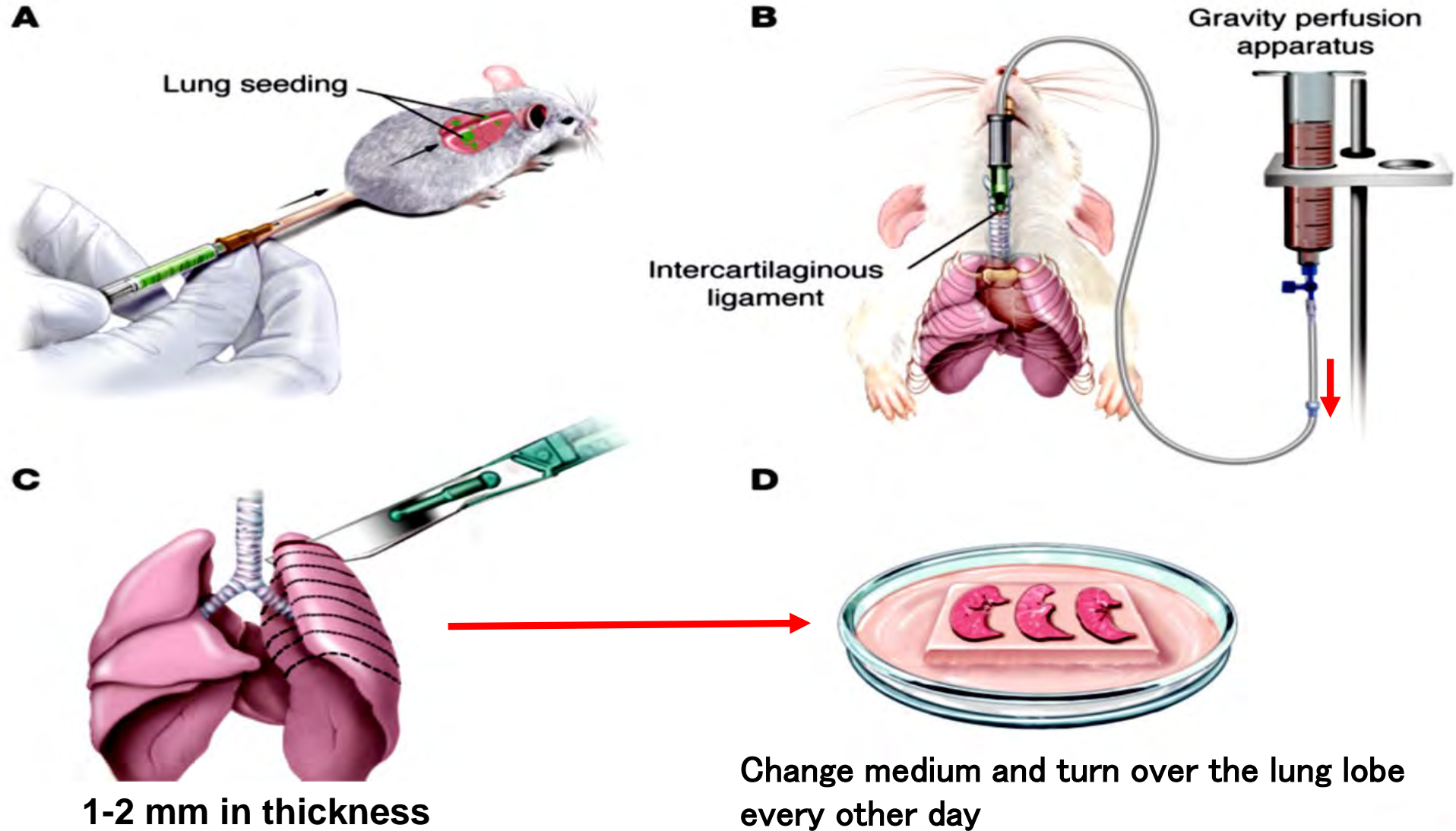
In vivo



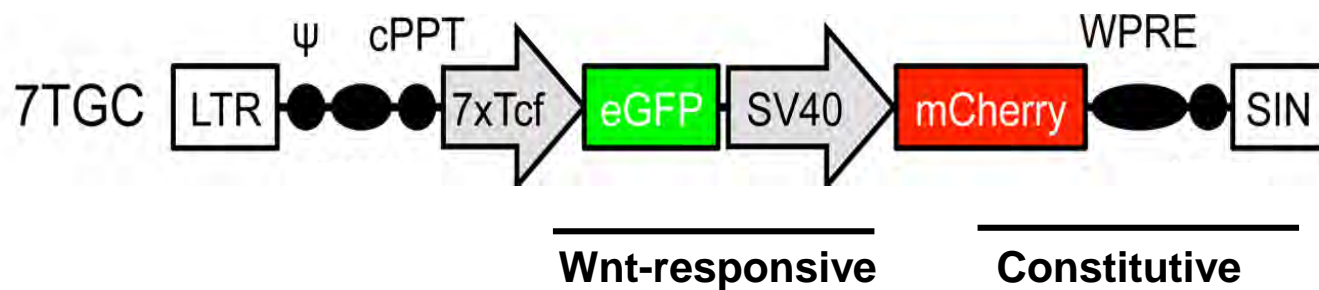
Metastatic PDX-based models: Targeting β -catenin to prevent metastatic OS



Ex vivo Pulmonary Metastasis Assay (PuMA)



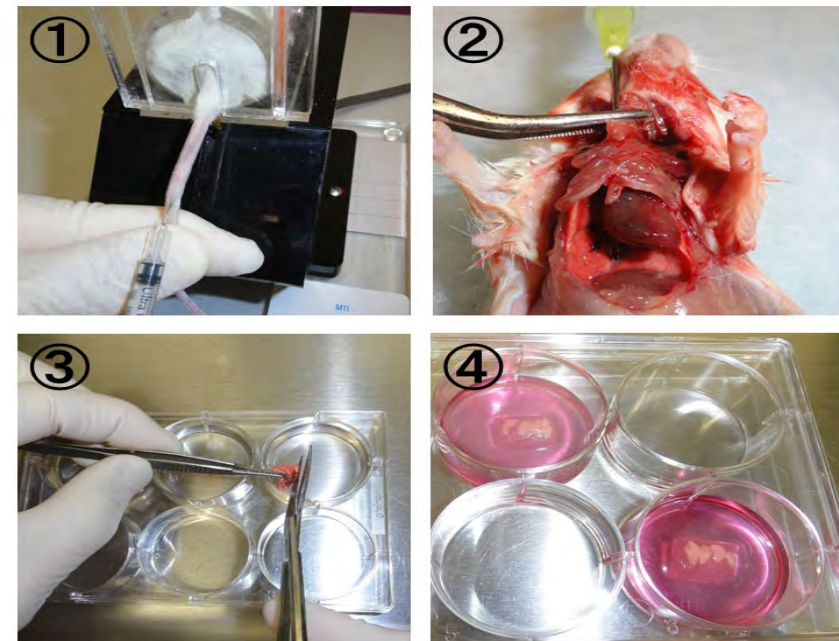
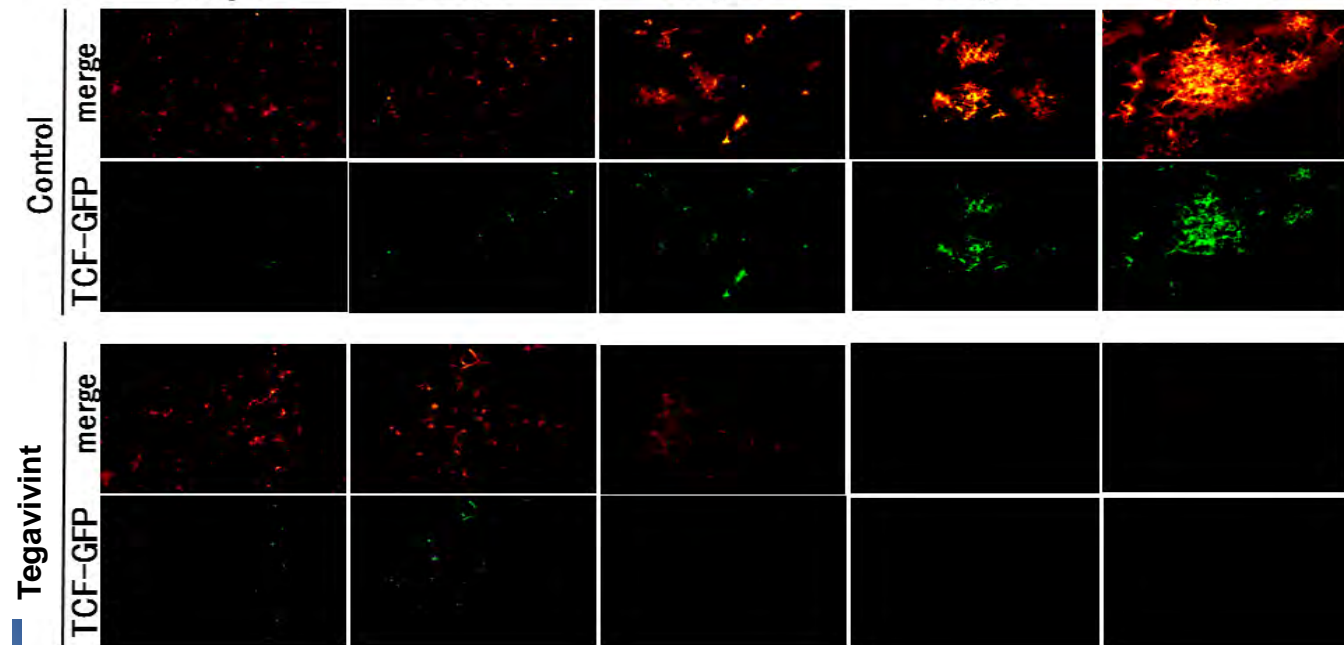
Wnt-reporter: PDX84 Lung cells



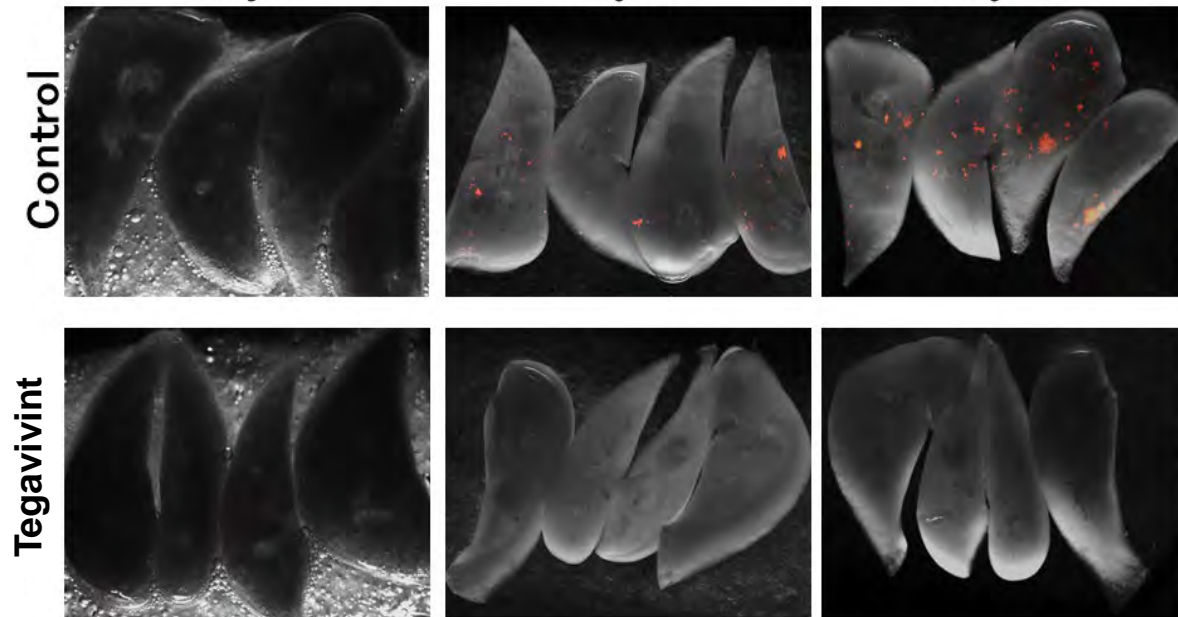
Initiated
Tegavivint



Day0 Day7 Day14 Day21 Day28



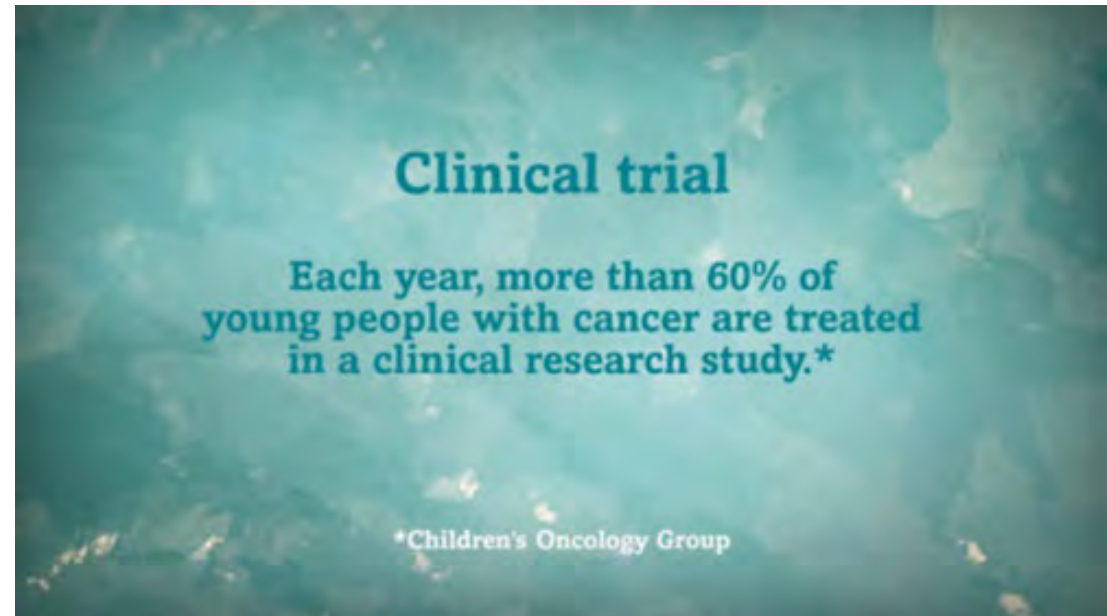
Day0 Day21 Day28



Clinical Trial: Tegavivint for Advanced Pediatric Cancers



The world's childhood cancer experts



Impact: Develop clinical trial for Tegavivint in advanced pediatric cancers

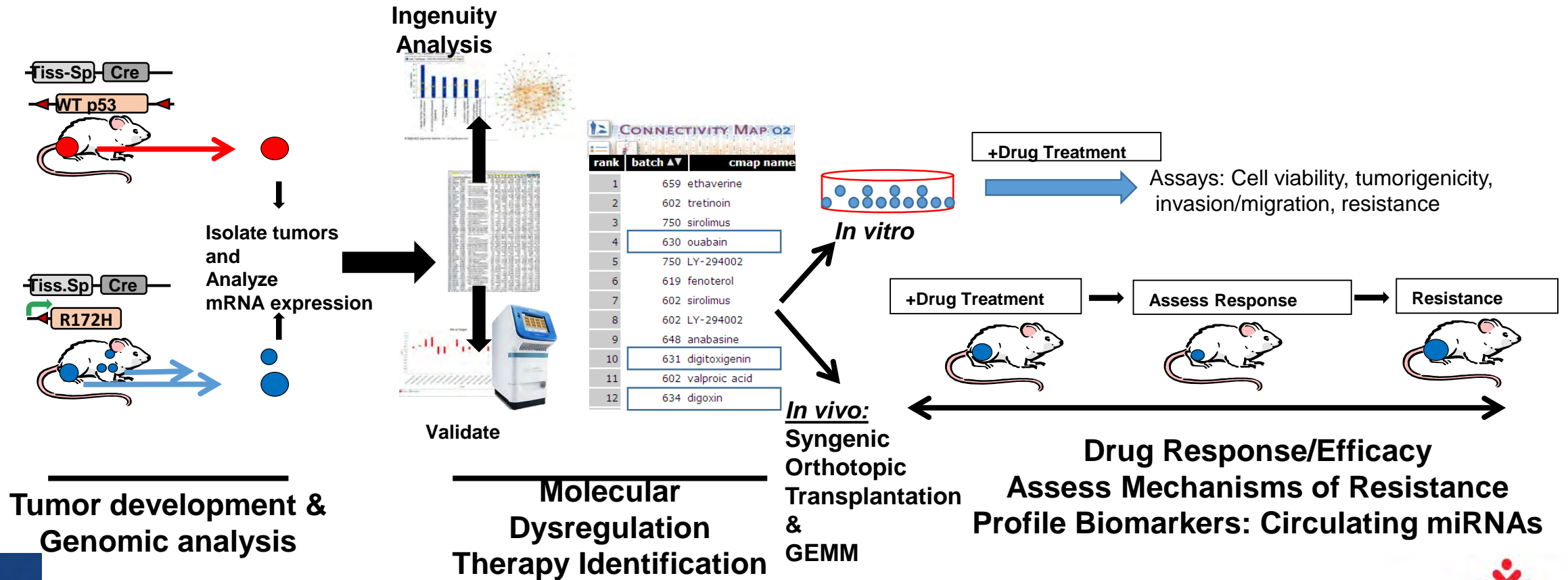


Muscal



Wulff

Schema: Functional genomic platform for target identification, drug discovery/efficacy, and biomarker establishment



Patient Story

Case presentation:

History of Present Illness (HPI):

- J.R., a 13 year old male presented to his primary pediatrician in 5/00 with a few day history of right knee pain and swelling with mild effusion. States that swelling became more severe after playing softball in school. Intermittent pain persisted throughout the remained of the year. Pain worse with walking or running and would awaken him at night. Pain alleviated with NSAIDs.



Past Medical History: No illnesses, No Hospitalizations

Immunizations : UTD

Developmental History: Appropriate for Age

Social History: Lives with parents and two older siblings (sisters)—healthy

Family Hx: No h/o Cancer

Allergies: NKDA

Meds: NSAIDs

Review of Systems: As above, plus no fevers, night sweats or weight loss.

Exam: Vital Signs: Afebrile. RR 18 BP: 127/69 wt 63.6kg ht: 175cm

HEENT: PERRLA, EOMI, No oral lesions

Neck: No masses, enlarged lymph nodes

Lungs: CTA b/l

CV: RRR, no murmurs

Abd: No masses or organomegaly

Extr: Swelling below right knee, greater along medial aspects

Neuro: CN II-XII intact, Deep Tendon Reflexes intact

Skin: No rashes, lesions, bruising

Labs: WBC: 5.9 (nml) Hgb: 14.5g/dL (nml) Plts: 307,000/mm³ (nml)

Electrolytes: Creatinine: 0.8, Normal

Referred for further evaluation.

11/00: X-Ray of Right lower extremity concerning for tibial lesion

12/00: MRI revealed a right proximal tibia lesion.



- Mixed lytic (destructive)/blastic (new bone)
- Cortical breakthrough “Codman’s triangle”
- Radial ossification: “sunburst”

Differential Diagnosis:

Leg lesion:

Malignant
vs non-Malignant

What do we do now??

Biopsy: 12/00: Positive for Osteosarcoma

Infectious?

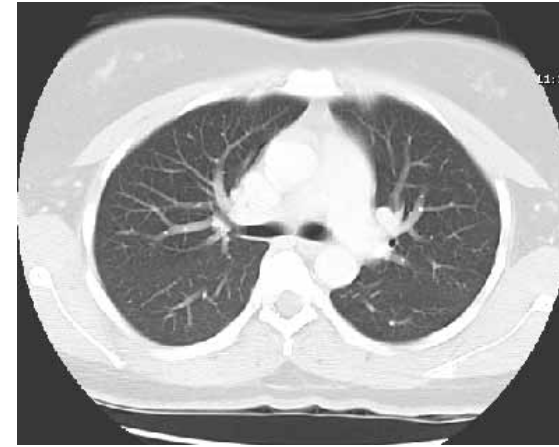
Post-traumatic event/sequelae?

Osteosarcoma Work-Up:

Disseminates to:

- 1) Lung
- 2) Bone
- 3) Lymph node

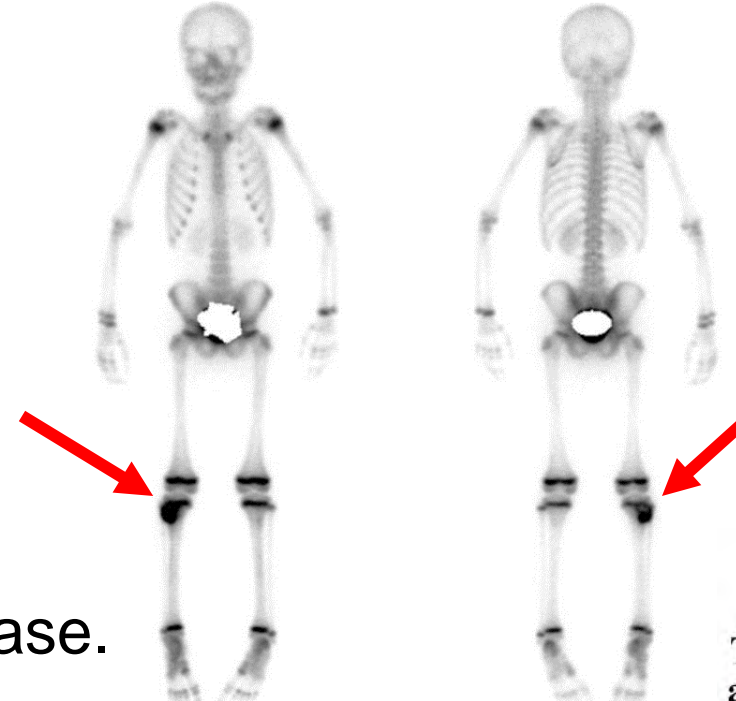
Chest CT scan



Anterior Posterior

Bone Scan

- Injection of 20mCi Of ^{99m}Tc Osteolite
- Measures new bone growth or breakdown



J.R., both bone scan and Chest CT were **Negative** for evidence of metastatic disease.

Treatment Modalities:

Neoadjuvant chemotherapy

Surgery

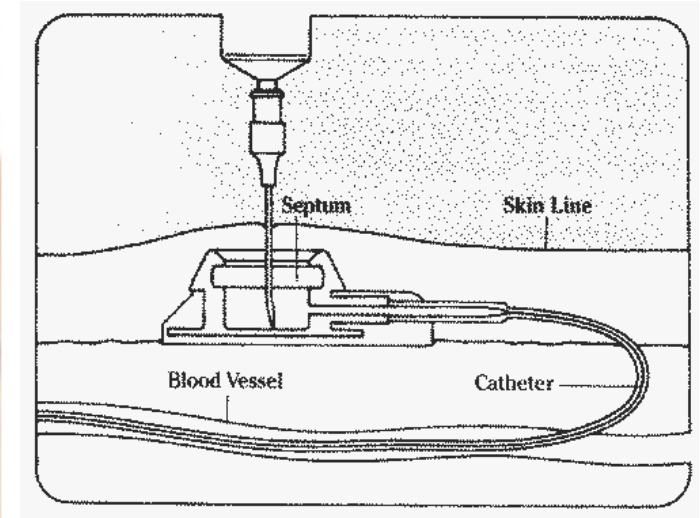
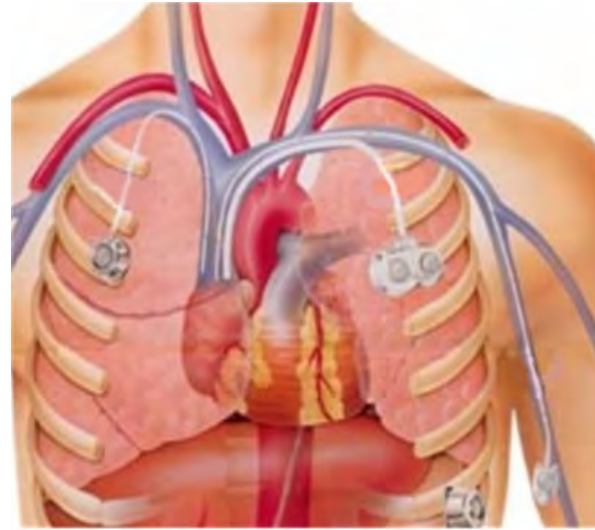
Assessment of Response

MORE Chemo

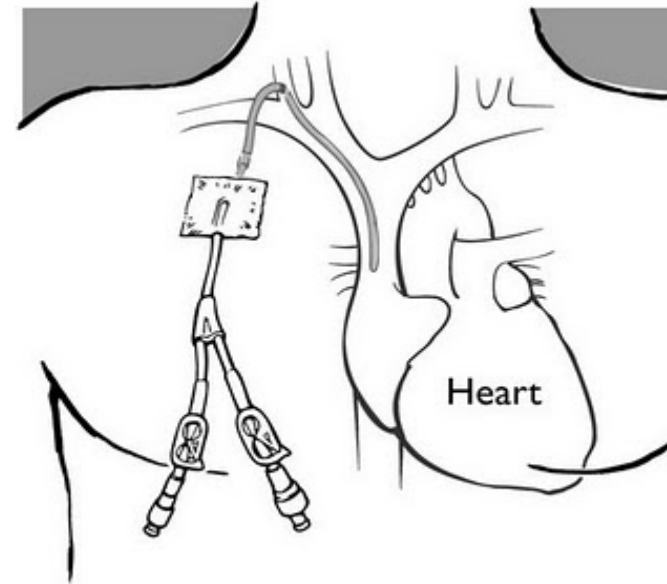
Continuous follow-up evaluations

Means to Give Chemotherapy:

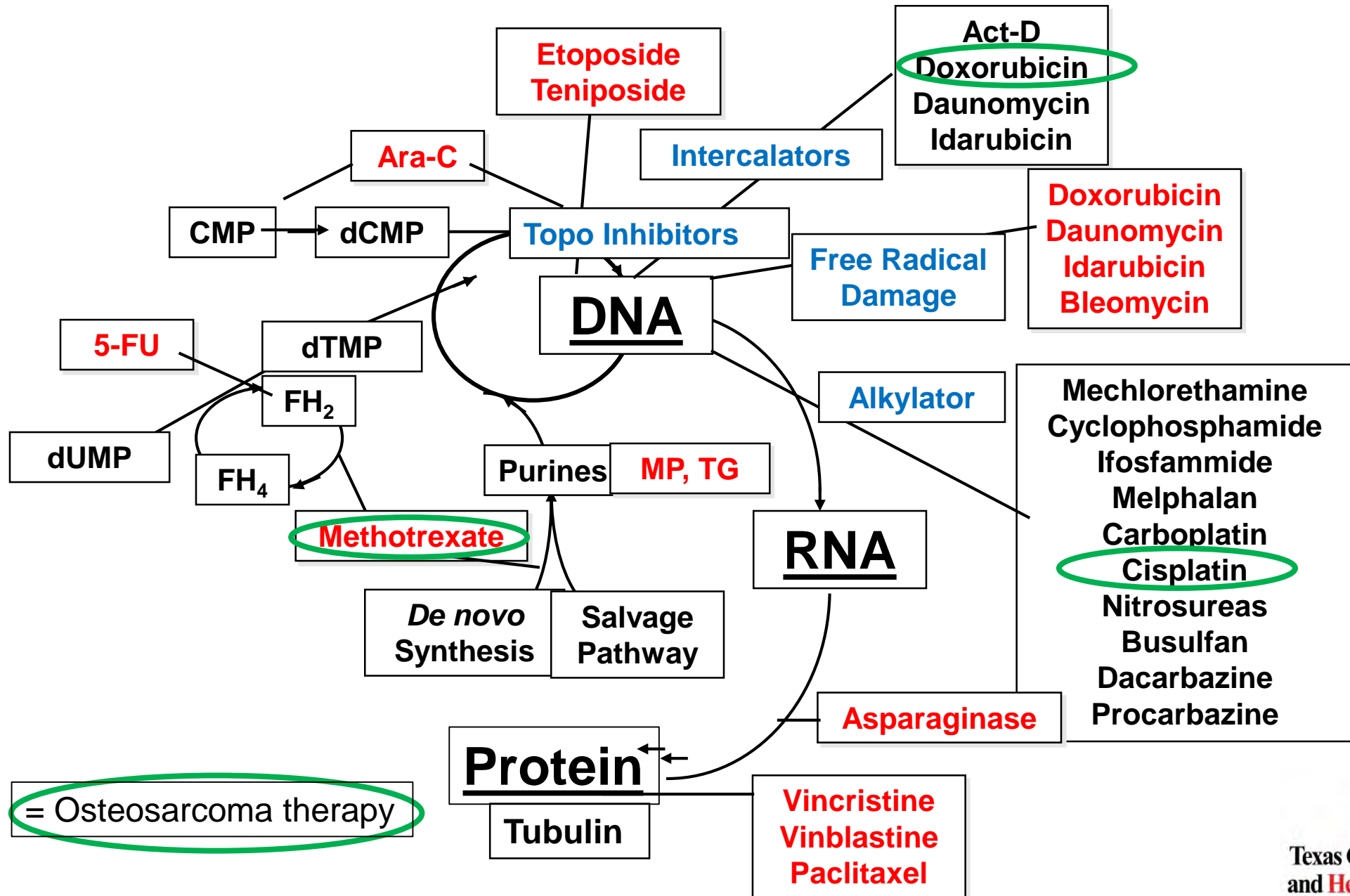
1) Port-A-Cath (PAC)



2) Double Lumen Hickman



Mechanism of Action



Purpose of Chemotherapy: Cause destruction of (rapidly) dividing cells—
Hopefully the cancer cells will be preferentially affected

Typical Side Effects:

- Nausea, Vomiting, Constipation, Diarrhea
- Rash
- Electrolyte changes—Na⁺, K⁺, etc..
- **Decrease in Blood counts/Myelosuppression**
Makes patients very susceptible to infection, bleeding, fatigue
- **HAIR LOSS**
- Peripheral neuropathy (VCR)
- Hearing Loss (Cisplatin)
- Nephrotoxicity/Kidney damage
- Liver Damage
- Lung damage
- Cardiac Toxicity
- Infertility
- Development of secondary malignancies (usually leukemias)

Goal: More Directed Therapy

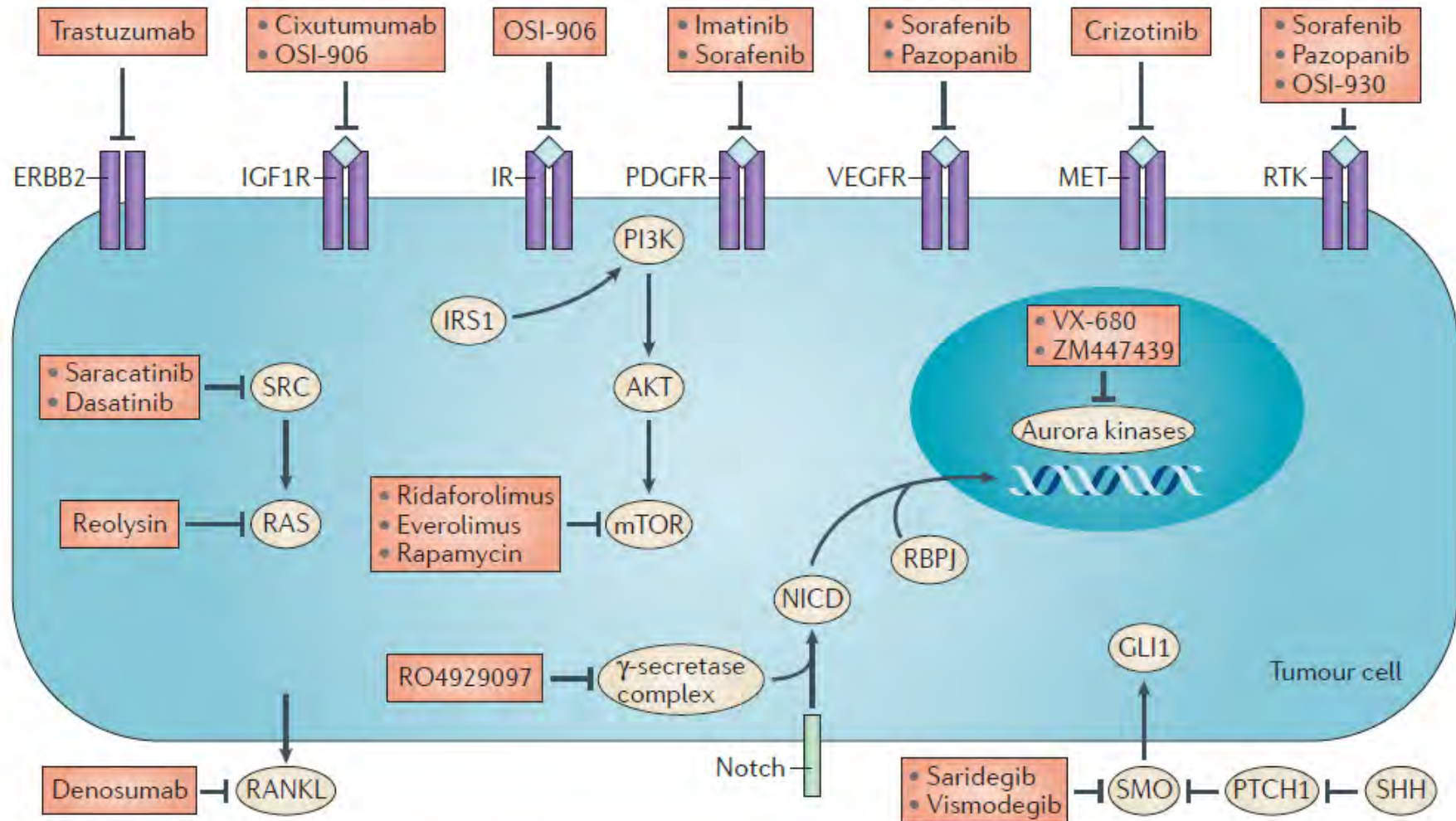


Figure 2 | **Pathways for targeted therapies in osteosarcoma.** This figure schematically shows molecular targets and associated drugs identified for therapeutic intervention in osteosarcoma. Therapeutic targets include specific cell

Limb Salvage: Osteoarticular Reconstruction



Cadaveric
prosthesis



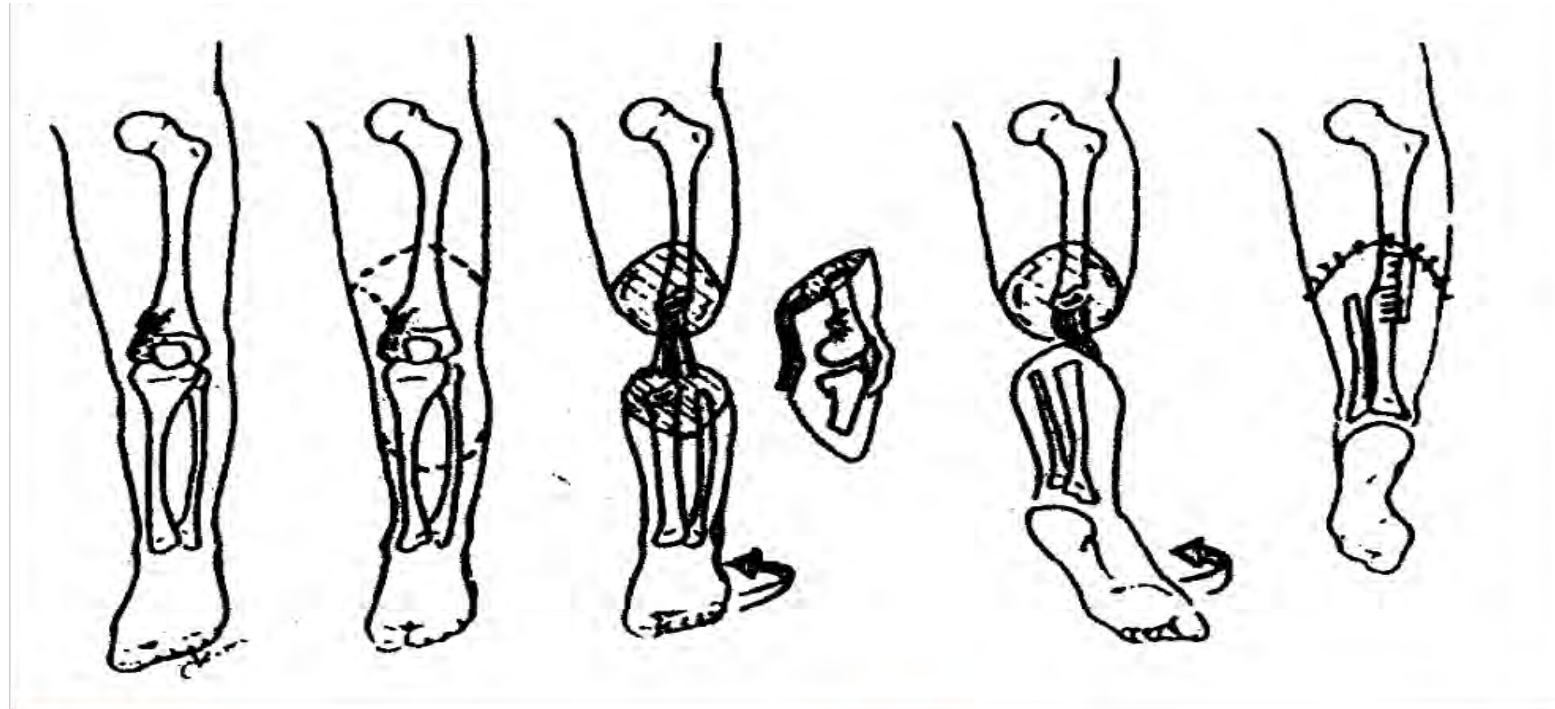
Non-expandable



Expandable



Van Ness Rotationplasty



Type of [autograft](#) wherein a portion of a [limb](#) is removed. The remaining limb below the involved portion is rotated and reattached.

Ankle joint becomes the knee joint. Limb rotated because the ankle flexes in the opposite direction compared to the knee.

Benefit: functioning knee joint and can run and jump.

Van Ness Rotationplasty

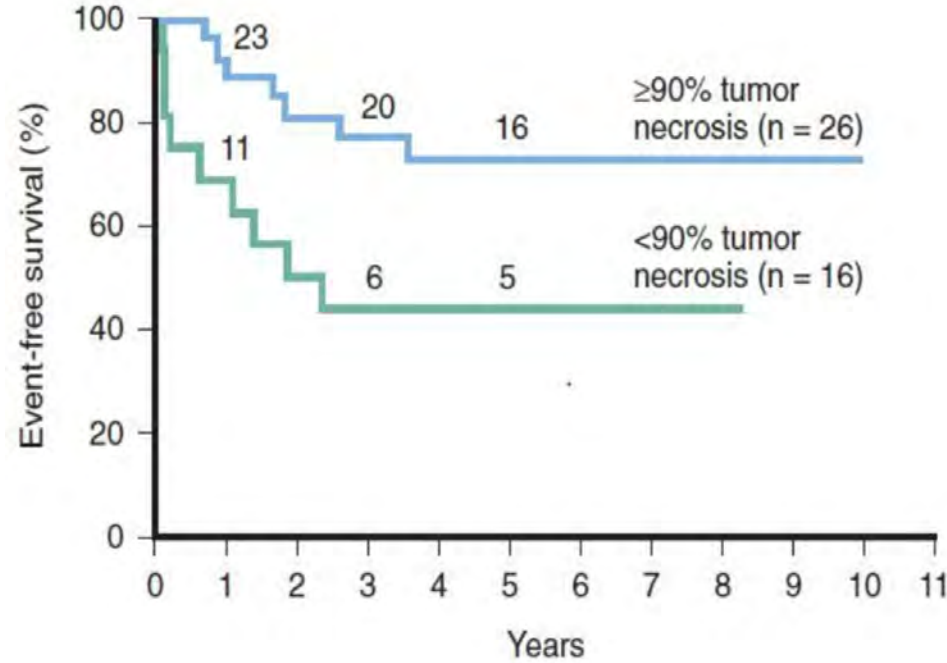


Assess Response:

Need pathologist to evaluate excised tumor for **% necrosis** (tumor death)

Desire:
Greater than 90% necrosis is evidence that tumor is responding to chemotherapy
Continue on with current therapeutic regimen

Less than 90% concerning for inappropriate response and consider change in chemotherapy/treatment regimen



J.R. was noted to have >90% necrosis on his pathology

Follow-Up Evaluations:

- Monitored every 6 months post-therapy for 2 additional years:
- J.R. remained in **REMISSION** until 10/03 when chest CT
Noted 3 right sided lung nodules.
- Surgery (open thoracotomy) for excision of nodules—12/2/03.
Removal of 4 subpleural nodules (lymph nodes)
and one large calcified nodule from right lower lobe:

Hospitalized x 1 week

RLL 2 Nodules: + Metastatic Osteosarcoma

6/14/04. Underwent right lower lobectomy. +Right hilar lymph node with evidence of disease.

Importance: No evidence of disease elsewhere.

Presently No evidence of disease

Patient went onto obtain his PhD from BCM and now is a post-doc....

Summary:

- ❑ Sarcomas—Heterogenous group of mesenchymal tumors; no driver point mutations, more chromosomal aberrations

- ❑ Treatment: Standard of care consists of toxic chemotherapy targeting DNA synthesis/replication and very morbid surgery

- ❑ Development and implementation of models
 - Gain insights into disease biology
 - Test novel therapeutic agents and regimens

- ❑ Need for new therapies and translation to clinical trials

Thank you

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