Collaborative Understanding of the Range and Evolution of Osteosarcoma Single-cells
MIB AGENTS OSTEOSARCOMA ALLIANCE

# Model Matching Matrix
## WORKING DRAFT

**Decision-Making Matrix: Cancer Drug Class vs. OS Preclinical Experimental Model**

**Overall goal**: To streamline OS drug development and increase the translatability of preclinical research findings/single-cell discoveries into clinically meaningful progress.

- Help ensure the right questions are asked using the most suitable tools.

The core idea is a grid where rows represent different **Cancer Drug Classes** and columns represent various **OS Preclinical Experimental Models**. Each cell in the matrix contains a **rating or justification** for how well that model is suited for evaluating a drug from that class, considering specific **criteria**. A **sum total rating** based on the **pre-clinical data** package generated for a particular drug/target could then be used to **establish translational relevance**/prioritization:

**Proposed Matrix Structure:**

| Cancer Drug Class | 2D Cell Lines | 3D Spheroids/Organoids | Cell line-Derived Xenografts (CDX) | Patient-Derived Xenografts (PDX) | Syngeneic Mouse Models | Genetically Engineered Mouse Models (GEMMs) | Humanized Mouse Models | Ex Vivo Tissue/Organ Slices (e.g. PUMA assay) |
|---|---|---|---|---|---|---|---|---|
| *Chemotherapy* | High | High | High | High | Medium | Medium | Medium | N/A |
| *Targeted Therapy* | High | High | High | High | Low (unless mouse target) | Medium/High (if mutation relevant) | Medium/High | High (patient-specific) |
| *Immunotherapy (ICI)* | Low/Medium | Medium | Low | Low | High | High | High | Medium/High (human-specific immune cells) |

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|---|---|---|---|---|---|---|---|---|
| *Cell Therapy (CAR-T, TIL)* | Low (screening) | Medium (co-culture) | Low/Medium | Low/Medium (humanized) | Low (unless mouse cells) | Low (unless mouse cells) | High | High (patient-specific) |
| *Oncolytic viruses, vaccines?* | High (lysis) | Medium | High | High | High | High | Medium/High | Medium |
| *Bispecific Antibodies* | Medium/High | High (co-culture) | Low/Medium (humanized) | Low/Medium (humanized) | Low (unless mouse targets) | Low (unless mouse targets) | High | Medium/High |
| *ADCs (Antibody-Drug Conjugates)* | High (screening) | High | High | High | Low (unless mouse target) | Low (unless mouse target) | Medium/High | High (patient-specific) |

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**Key considerations/criteria:**

For each cell in the matrix, we justify the rating based on the following criteria:

1. **Relevance to Mechanism of Action (MOA):**
    - Does the model adequately capture the intended MOA of the drug/drug class? (e.g. Cell surface target confirmed (heterogeneously?) expressed for adoptive cell therapy like CAR-T cells or ADC; use of WT and KO control cells).
2. **Tumor Heterogeneity & Microenvironment:** How well does the model represent the complexity of human OS tumors and their TME (primary tumor/bone vs metastatic lung TME?)

    a. **Immune Competency:**

        i. Does the model possess a functional immune system (human or mouse) that can interact with the drug?

    b. **Genetic Fidelity:**

        i. How well does the model reflect the genetic landscape of human OS tumor/tumor subtypes? (e.g. PDX models). Specifically, is the genetic lesion/pathway intended to be targeted in human patients also present in the cell and animal models used; is it demonstrated to be essential for tumor cell survival/growth in the model?)

3. **Cost & Throughput:**
    - Is the model amenable to high-throughput screening (e.g., 2D cell lines) or is it more resource-intensive or requires specific expertise (e.g., GEMMs)?
4. **Reproducibility:**
    - Is there prior data/experiences regarding reproducibility of results in this model, e.g., tumor take rate, rate of spontaneous metastasis, kinetics of orthotopic/lung metastasis growth?
5. **Translational Predictability:**
    - Are there prior data/experiences to generalize how well results from this model predict clinical outcomes in humans? In OS? In other tumor types?

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**Proposed preclinical experimental model types to be included in matrix:**

1. **2D Cell Lines (In Vitro):**
    - **Pros:** High-throughput, low cost, easy to manipulate, good for initial screening and MOA studies demonstrating proof of target/target modulation.
    - **Cons:** Lack 3D architecture, TME, and immune system. Genetic drift in culture can be significant.
    - **Best for:** Initial screening for chemotherapy, targeted therapy (if target expressed), early MOA for ADCs/Bispecifics. Limited for immunotherapies.
2. **3D Spheroids / Organoids:**
    - **Pros:** Better recapitulate 3D architecture, cell-cell/cell-matrix interactions, and some TME aspects. Can include co-culture with cells of TME (e.g., fibroblasts, macrophages, potentially T cells). Organoids have potentialretain patient-specific heterogeneity.
    - **Cons:** Difficult to accurately recapitulate adaptive (i.e., T cell) immune components (though co-culture with immune cells is possible). More costly and labor-intensive than 2D.
    - **Best for:** Targeted therapy, chemotherapy (especially resistance studies), early immunotherapy screening (with co-culture assays), initial cell therapy screening, ADC/Bispecifics.
3. **Cell line-Derived Xenografts (CDX) (In Vivo, Immunocompromised):**
    - **Pros:** Good first step to establish *in vivo* efficacy and PK/PD studies for drugs not requiring an immune system. Great place to start for drugs with well-defined targets (e.g. CARs, ADCs)
    - **Cons:** Human cell lines grown in mice lose some human tumor characteristics. Lack human immune system and robust TME.
    - **Best for:** Chemotherapy, targeted therapy, ADCs. Poor for adaptive immunotherapies. Ok for innate immune therapies and some adoptive cell therapies.
4. **Patient-Derived Xenografts (PDX) (In Vivo, Immunocompromised):**
    - **Pros:** Maintain OS patient tumor heterogeneity, genetic mutation/pathway being targeted, also some stromal components of the original human tumor.
    - **Cons:** Lack a functional human immune system (broken record here). Costly and time-consuming to establish.
    - **Best for:** Chemotherapy, targeted therapy, ADCs. Poor for adaptive immunotherapies. Ok for innate immune therapies and some adoptive cell therapies.

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5. **Syngeneic Mouse Models (In Vivo, Immunocompetent):**
    - **Pros:** Genetically identical mouse tumor cells grown in immunocompetent mice. Have an intact and functional immune system. Typically high reproducibility in tumor take rate/metastasis kinetics, etc.
    - **Cons:** Mouse tumor cells don't fully mimic human tumors. Limited genetic diversity compared to human cancers. May not fully translate to human immune responses, especially if specific intrinsic oncogenic drivers are intricately linked to TME composition in human OS tumors
    - **Best for:** Immunotherapy (ICI, adoptive e cell therapies, oncolytic viruses, vaccines, innate immunotherapy) where the MOA relies on the host immune system. Useful for exploring immune responses, resistance mechanisms, and combination therapies. Also important to understand how drugs with well-defined molecular targets (e.g., ADCs or CARs) interact with the immune system
6. **Genetically Engineered Mouse Models (GEMMs) (In Vivo, Immunocompetent):**
    - **Pros:** Again, immunocompetency. It can also mimic key genetic drivers of human OS tumor initiation and progression more closely (e.g., MYC, p53, RB1, etc.).
    - **Cons:** Time-consuming and expensive to develop and maintain a colony. Tumors are somewhat oversimplified representations of human OS tumor genetics.
    - **Best for:** Immunotherapy (ICI, cell therapy, oncolytic viruses), targeted therapy (if genetically relevant), studying early disease progression and long-term effects (e.g., early interventional/preventative therapies?).
7. **Humanized Mouse Models...are we here yet?:**
    - **Pros:** In theory, it allows assessment of human immune cell interactions in the background of the genetic complexity of human OS PDX tumors.
    - **Cons:** Human immune system reconstitution can be incomplete or lead to Graft-versus-Host Disease (GvHD). Extremely Complex and expensive.
    - **Best for:** Immunotherapy (especially human-specific ICIs, human cell therapy (CAR-T, TIL), and bispecific antibodies.
8. **Ex Vivo Tissue/Organ Slices (e.g., PUMA assay):**
    - **Pros:** Real tumor/organ tissue with its native architecture, TME, and immune cells. Allows short-term drug testing in a more relevant context than in vitro 2D and 3D cultures.
    - **Cons:** Limited viability, short experimental window. Not suitable for long-term efficacy studies. Some specific expertise is required.
    - **Best for:** Rapid ex vivo assessment of therapies with promising in vitro (2D/3D) data.

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**Proposed Next Steps/Follow-up:**

1. **Literature Review:** Systematically review published preclinical studies for each drug class to see if it's possible to note successes and failures in clinical translation based on the utilized model type (*Related to the predictive validity study priority identified in breakout*).
2. **Establish Rating System/Justification:** Define clear criteria for scoring (e.g., 1-5 scale, or "High," "Medium," "Low," "Not Applicable" with justifications).

    a) For each cell in the matrix, concisely define *why* a particular model is suitable or not for a given drug class, referring to the criteria above.
    b) Transparency and Acceptability in Model Limitations: Explicitly state the inherent limitations of each model type

**Hope for final deliverable:** An evolving systematic tool, continuously updated by a multi-disciplinary group of experts (i.e., pediatric oncologists, cancer pharmacologists, immunologists, pathologists, etc.) as we gather new models/model data, to guide preclinical development decisions and enhance the translational success of new drugs for OS.