Drugs in active development, with 3 in Phase III clinical trials

Potential entities for development of life-saving drugs for pediatric indications.

Preclinical In Vivo Testing (PIVOT) consortium to assess three cancer-associated targets that could be considered high priority for future research due to clear pathways for preclinical exploration and early data to suggest a strong impact for multiple pediatric cancers.

**CD47:**
- **Key Considerations**
  - Inhibition of CD47 enables immune destruction of tumor cells.
  - CD47 is overexpressed in some tumors and enables evasion of the immune system.
  - Inhibition of CD47 allows for improved efficacy in combination with chemotherapy, immunotherapy, and/or monoclonal antibody therapy.
  - Prioritize pediatric indication preclinical research based on results from adult studies.

- **Recommendations**
  - Expand preclinical testing to relevant pediatric indications.
  - Perform preclinical research to understand the effects of CD47 inhibition on the immune system.
  - Use immunocompetent preclinical models to study CD47 inhibitor combinations, especially immunotherapies.
  - Identify biomarkers that predict CD47 inhibition sensitivity through further molecular characterization of tumors.

**EZH2:**
- **Key Considerations**
  - Inhibition of EZH2 results in increased chromatin accessibility and transcription of tumor suppressor genes.
  - EZH2 was identified as high priority for future research due to clear preclinical and early data to suggest a strong impact for multiple pediatric cancers.
  - EZH2 is an attractive target for anti-cancer therapy because it helps cancerous cells divide and proliferate by turning off tumor suppressor genes.
  - Mutations in EZH2 result in pro-cancer epigenetic changes.

- **Recommendations**
  - Use immunocompetent preclinical models to study EZH2 inhibitor combinations, especially immunotherapies.
  - Identify predictive biomarkers for sensitivity to EZH2 inhibition.

**MDM2:**
- **Key Considerations**
  - Inhibition of MCM2 results in increased P53 tumor suppressor functions (e.g., induction of apoptosis, cell cycle arrest).
  - Inhibition of MDM2 enables immune destruction of tumor cells.

- **Recommendations**
  - Test MDM2 inhibitor treatment combinations with chemotherapy or radiation.
  - Evaluate efficacy of second-generation MDM2 inhibitors in relevant preclinical models.
  - Identify predictive biomarkers for sensitivity to MDM2 inhibition.

**EZH2, MDM2, and CD47**

- **Recommendations**
  - Identify biomarkers that predict EZH2 inhibitor combinations.
  - Use immunocompetent preclinical models to study EZH2 inhibitor combinations, especially immunotherapies.
  - Perform preclinical research to understand the effects of EZH2 inhibition on the immune system.
  - Expand preclinical testing to relevant pediatric indications.
  - Use immunocompetent preclinical models to study EZH2 inhibitor combinations, especially immunotherapies.

- **Recommendations**
  - Expand preclinical testing to relevant pediatric indications.
  - Prioritize pediatric indication preclinical research based on results from adult studies.

- **Recommendations**
  - Identify predictive biomarkers for sensitivity to MDM2 inhibition.

**Clinical Development Status**
- 1 approved drug (adult and pediatric [1 indication])
- 12 drugs in active development, but 0 in Phase III clinical trials

**MDM2: Negative regulator of P53**
- **Key Considerations**
  - Inhibition of MDM2 results in evasion of apoptosis and sustained cell proliferation.
  - Inhibition of MDM2 can induce tumor suppressor genes (e.g., induction of apoptosis, cell cycle arrest).
  - Inhibition of MDM2 enables immune destruction of tumor cells.

- **Recommendations**
  - Test MDM2 inhibitor treatment combinations with chemotherapy or radiation.
  - Evaluate efficacy of second-generation MDM2 inhibitors in relevant preclinical models.
  - Identify predictive biomarkers for sensitivity to MDM2 inhibition.

- **Clinical Development Status**
  - 0 approved drugs
  - 8 drugs in active development, with 1 in Phase III clinical trials

**COACH**
- **Hallmarks of Cancer**
  - Deregulating cell proliferation
  - Sustaining proliferative signaling
  - Evading cell death
  - Enabling replicative immortality
  - Activating growth signals
  - Inducing inflammation
  - Reprogramming metabolism
  - Enabling cellular senescence

- **Target Pathways**
  - EZH2, MDM2, and CD47

- **Clinical Development Status**
  - 0 approved drugs
  - 70 drugs in active development, with 3 in Phase III clinical trials