Convening Experts in Oncology to Address Children’s Health

Quarterly Collaboration Meetings in Pediatric Oncology

September 18, 2023 | Virtual Meeting

Reviewed Targets:

- B7H3
- PTK7
- CD22
- CD33

This meeting summary was prepared by Rose Li and Associates, Inc., under contract to The Foundation for the National Institutes of Health (FNIH). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of FNIH. Review of earlier versions of this meeting summary by the following individuals is gratefully acknowledged: Cooper Roache, Gina Castelvecchi, and Kelly E. Beazley.

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# Acronym Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ABCB1</td>
<td>ATP binding cassette subfamily B member 1</td>
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<tr>
<td>ADC</td>
<td>antibody-drug conjugate</td>
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<tr>
<td>ALL</td>
<td>acute lymphocytic leukemia</td>
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<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
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<tr>
<td>APL</td>
<td>acute promyelocytic leukemia</td>
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<tr>
<td>ASO</td>
<td>antisense oligonucleotide</td>
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<tr>
<td>ATRT</td>
<td>atypical teratoid/rhabdoid tumor</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>B-ALL</td>
<td>B-cell acute lymphocytic leukemia</td>
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<tr>
<td>B-LLy</td>
<td>B-lymphoblastic lymphoma</td>
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<tr>
<td>B7H3</td>
<td>B7 homolog 3 protein</td>
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<tr>
<td>BCL</td>
<td>B-cell lymphoma</td>
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<tr>
<td>BFM</td>
<td>Berlin-Frankfurt-Münster</td>
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<tr>
<td>BiTE</td>
<td>bispecific T-cell engager</td>
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<tr>
<td>C-CBL</td>
<td>Casitas B-lineage lymphoma</td>
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<tr>
<td>CAR</td>
<td>chimeric antigen receptor</td>
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<tr>
<td>CD22</td>
<td>cluster of differentiation 22</td>
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<tr>
<td>CD33</td>
<td>cluster of differentiation 33</td>
</tr>
<tr>
<td>CD276</td>
<td>cluster of differentiation 276</td>
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<tr>
<td>CLL1</td>
<td>C-type lectin domain family 12 member A</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CNV</td>
<td>copy number variation</td>
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<tr>
<td>COACH</td>
<td>Convening Experts in Oncology to Address Children’s Health</td>
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<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>cRIB</td>
<td>compressed rituximab in combination with InO and blinatumomab</td>
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<tr>
<td>cRIT</td>
<td>compartmental radioimmunotherapy</td>
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<tr>
<td>CRS</td>
<td>cytokine release syndrome</td>
</tr>
<tr>
<td>CTLA4</td>
<td>cytotoxic T-lymphocyte-associated protein 4</td>
</tr>
<tr>
<td>DepMap</td>
<td>Dependency Map</td>
</tr>
<tr>
<td>DIPG</td>
<td>diffuse intrinsic pontine glioma</td>
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<tr>
<td>EAE</td>
<td>autoimmune encephalomyelitis</td>
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<tr>
<td>EMT</td>
<td>epithelial-mesenchymal transition</td>
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<tr>
<td>EwS</td>
<td>Ewing sarcoma</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FLT3/ITD</td>
<td>FMS-like tyrosine kinase-3 internal tandem duplication</td>
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<tr>
<td>FNIH</td>
<td>Foundation for the National Institutes of Health</td>
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<tr>
<td>GOT</td>
<td>glutamic oxaloacetic transaminase</td>
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<tr>
<td>GVHD</td>
<td>graft-versus-host-disease</td>
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<tr>
<td>HSC</td>
<td>hematopoietic stem cell</td>
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<tr>
<td>IgH</td>
<td>immunoglobulin heavy chain</td>
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<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
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<tr>
<td>InO</td>
<td>inotuzumab ozogamicin</td>
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<tr>
<td>ITIM</td>
<td>immunoreceptor tyrosine-based inhibitory motif</td>
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</tbody>
</table>
KO | Knockout  
LAG3 | lymphocyte-activation gene 3  
LPS | lipopolysaccharide  
mAb | monoclonal antibody  
MCR | maintained complete response  
MDS | myelodysplastic syndrome  
MMAE | monomethyl auristatin E  
MRD | Minimal residual disease  
MXD3 | max dimerization protein 3  
NCI | National Cancer Institute  
nHL | non-Hodgkin’s lymphoma  
NHP | non-human primate  
NIH | National Institutes of Health  
NK | natural killer  
NSCLC | non-small cell lung cancer  
ODAC | Oncologic Drugs Advisory Committee  
OS | overall survival  
PBD | Pyrrolobenzodiazepine  
PD-1 | programmed cell death protein 1  
PD-L1 | programmed cell death ligand 1  
PDX | patient-derived xenograft  
PIVOT | Pediatric Preclinical in Vivo Testing  
PKC | protein kinase C  
PML-RARα | promyelocytic leukemia-retinoic acid receptor alpha  
PR | partial response  
PRISM | Profiling Relative Inhibition Simultaneously in Mixtures  
PTK7 | protein tyrosine kinase 7  
PXA | pleomorphic xanthoastrocytoma  
r/r | relapsed or refractory  
RMS | Rhabdomyosarcoma  
RUNX1 | runt-related transcription factor  
SHP-1 | Src homology region 2 domain-containing phosphatase 1  
SHP-2 | Src homology region 2 domain-containing phosphatase 2  
Siglec | sialic acid-binding immunoglobulin-related lectin  
SME | subject matter expert  
SNP | single nucleotide polymorphism  
SOS | Sinusoidal obstruction syndrome  
SSM | simple somatic mutation  
SV | structural variation  | triple negative breast cancer  
TriTE | trispecific T-cell engager  
VEGF | vascular endothelial growth factor  
VOD | veno-occlusive disease  
ZAP-70 | zeta chain of T-cell receptor associated protein kinase 70
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Executive Summary

Despite advances in therapeutic development for adult cancers, developing new treatment regimens for pediatric cancers poses unique challenges; effective adult treatments for cancer are not always readily translatable to the pediatric population due to differences between adults and children (e.g., cancer rates, treatment considerations, tumor characteristics), even for adults and children with the same cancer diagnosis. In addition, pediatric cancer patient populations are quite small, which complicates study design and sufficient powering for pediatric clinical trials. Convening Experts in Oncology to Address Children’s Health (COACH) assembles subject matter experts (SMEs) from diverse fields to review research landscapes for therapeutic targets of potential interest for pediatric oncology indications and offer recommendations regarding preclinical research needed to further develop existing therapeutics for use in pediatric populations. On September 18, 2023, COACH convened the Sixth Quarterly Collaboration Meeting—with SMEs from the National Cancer Institute (NCI), Food and Drug Administration (FDA), European Medicines Agency (EMA), advocacy groups, the pharmaceutical industry, Paediatric Preclinical Proof of Concept Platform (ITCC-P4), and the Pediatric Preclinical In Vivo Testing (PIVOT) consortium—to discuss and provide recommendations regarding preclinical research required to develop antibody-drug conjugates (ADCs) for the following drug targets for early phase pediatric clinical trials: B7 homolog 3 protein (B7H3), cluster of differentiation 22 (CD22), protein tyrosine kinase 7 (PTK7), and cluster of differentiation 33 (CD33).

B7H3

B7H3, encoded by the cluster of differentiation 276 (CD276) gene, is an immune checkpoint protein within the same B7 superfamily as programmed cell death ligand 1 (PD-L1). B7H3 is involved in both immune and non-immune mechanisms of cancer progression; however, B7H3’s immunoregulatory functions remain unclear. CD276 transcripts are widely expressed in pediatric solid tumors, with Wilms tumors and osteosarcomas having the highest expression, whereas acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) have low expression. Other studies have reported high B7H3 protein expression in pediatric rhabdomyosarcoma and Ewing sarcoma (EwS) tumor specimens. Although B7H3 is expressed in central nervous system (CNS) tumor-, osteosarcoma-, and rhabdomyosarcoma-derived in vitro cell lines, all adult tumor types showed moderate levels of dependency. Despite the wide range of B7H3-targeting drug modalities tested preclinically, over 50 percent of preclinical studies have used B7H3-targeting ADCs, which were effective in several in vivo models of sarcoma.

B7H3’s role in bone development could potentially impact use in pediatric therapy applications. CD276 knockout (KO) mice demonstrated lower bone mineral density, increased spleen and intraepithelial lymphocyte inflammatory cytokines, increased T cell proliferation, and earlier experimental autoimmune encephalomyelitis (EAE) development when exposed to myelin oligodendrocyte glycoprotein peptide. Monoclonal antibodies (mAbs) targeting B7H3, including omburtamab, 8H9, and enoblituzumab, MGA271, appear to have a manageable toxicity profile in pediatric patients but have demonstrated limited success in clinical trials. One Phase II study
of 131I-omburtamab in medulloblastoma and recurrent ependymoma patients under 21 years old is currently active, but not recruiting, and no results are available.

**Key Considerations**

- B7H3 is postnatally silent in the murine brain, and thus mouse models are unlikely to provide insightful safety data on general ADC blood-brain barrier (BBB) penetration.
- The receptor for B7H3 has not yet been conclusively identified, which limits the understanding of B7H3 biology.
- ADC developers should consider the potential for hemorrhage during trials due to B7H3 expression in tumor vasculature.
- With the inclusion of proper monitoring, the low risk of bone toxicity should not impede development of B7H3 ADCs for pediatric clinical trials.
- Exploring non-invasive biomarkers for measuring B7H3 expression could mitigate the need to collect direct tumor biopsies during clinical trials.

**Next Steps**

- B7H3 is a **moderate-to-high** priority target for COACH.
- Development of non-invasive B7H3 biomarkers and preclinical research with additional pediatric models would benefit ADC testing.
- Continued B7H3-targeting ADC clinical development requires more pediatric trials, including trial safety data collection.

**CD22**

CD22 is a transmembrane protein belonging to the sialic acid-binding immunoglobulin-related lectin (Siglec) family of lectins that primarily acts as an inhibitory co-receptor of B-cell receptor signaling. Genetic alterations of **CD22** are generally rare in pediatric cancers and not considered a major driver of carcinogenesis, although high alterations rates have been reported in osteosarcomas. **CD22** RNA is primarily expressed in B-cell ALL (B-ALL), in alignment with its primary B cell expression in healthy cells. In *vitro*, expression of CD22 in pediatric cancer cell lines is highly restricted to lymphatic cancers, including ALL, non-Hodgkin’s lymphoma (nHL), and Hodgkin’s lymphoma (HL), with most cell lines showing minimal dependency of CD22 expression for cell viability. A range of CD22-targeting ADCs have shown *in vitro* activity in lymphatic cancer cell lines. In *vivo*, CD22-targeting ADCs show efficacy in various ALL models as single agents and in combination with existing cancer drugs.

CD22-targeting ADCs—including calicheamicin-based ADCs, alpha-CD22-SN36248, CAT-02-106, HB22.7-vcMMAE, and DCDT2980S—have shown significant *in vivo* activity and dose-dependent tumor response in nHL models and minimal systemic toxicity in various xenograft models. **Cd22** KO mice exhibit normal fertility and no gross abnormalities but have reduced long-lived recirculating B cell populations and B cells with hyperresponsivity to receptor signaling. Multiple CD22-targeting ADCs have shown mild to moderate hematologic toxicities in animal models. In addition, inotuzumab ozogamicin (InO) is clastogenic in the bone marrow of male mice, and preclinical pathology has been reported in the liver. However, InO has demonstrated
efficacy in relapsed or refractory (r/r) B-ALL in adult and pediatric patients in Phase I, II, and III trials. Most CD22-targeting drugs in the development pipeline are chimeric antigen receptor (CAR) T-cell therapies, with the most advanced CAR T-cell therapies in Phase II trials.

Key Considerations

- InO still faces toxicity challenges, particularly hepatotoxicities in patients who develop sinusoidal obstruction syndrome (SOS) after bone marrow transplant.
- Testing other CD22-targeting ADCs with different linkers and payloads may help avoid hepatotoxicity in some patients and improve understanding of these toxicities.
- InO already shows high efficacy in the clinic, and the majority of CD22-targeting agents are CAR T-cell therapies, decreasing the need for CD22-targeting ADC preclinical studies.

Next Steps

- CD22 is a low-to-moderate priority target for COACH.
- Preclinical studies should focus on identifying biomarkers or genetic profiles to better understand any predisposition to hepatotoxicity.
- Preclinical studies should consider evaluating sialic acid inhibitors to prevent cis binding and thus increase CD22 expression.

PTK7

PTK7 is a highly conserved and catalytically inactive transmembrane kinase involved in Wnt and vascular endothelial growth factor (VEGF) signaling, with roles in cancer endurance and invasion, as well as tumor suppressing functions. Due to its lack of catalytic activity, direct PTK7 inhibition with a small molecule or mAb is not an effective anti-cancer strategy. PTK7 is overexpressed in several adult and pediatric cancers, including strong expression in pediatric Wilms tumors and osteosarcoma, as well as some adult non-small cell lung cancers (NSCLC), triple negative breast cancers (TNBC), and ovarian cancers. In vitro, PTK7 expression is high in pediatric osteosarcoma, neuroblastoma and rhabdomyosarcoma (RMS) cell lines, as well as EwS, but does not correlate with gene dependency. Currently, no PTK7 ADC-related preclinical literature addresses in vivo dependency or drug sensitivity.

In KO models, an initial study characterization of Ptk7 KO mice found that loss of Ptk7 leads to perinatal lethality resulting from profound developmental defects, including cranial neural tube closure defects, gastroschisis, and kidney and forelimb abnormalities. In a study characterizing a PTK7-targeting ADC in non-human primates (NHPs), major toxicities (e.g., myelosuppression) occurred due to off-target effects previously observed with other ADCs that contain microtubule inhibitors and cleavable linkers. No on-target toxicities were noted, including in tissues with PTK7 expression. The only PTK7-targeting agents are ADCs, including MTX-13 in preclinical development for solid tumors (Multitude Therapeutics) and ABBV-647 (Pfizer), which did not enter pediatric clinical trials, and development has recently been discontinued.
Key Considerations

- After treatment with standard-of-care chemotherapy, PTK7 expression remains high, making PTK7 an appealing target for subsequent lines of treatment.
- Auto activation of T cells is unlikely to occur from PTK7-targeting therapies because studies have not found expression in mature T cells and other immune cells.
- Although Pfizer cannot currently provide detailed information about the discontinuation of ABBV-647, it was not related to toxicity concerns.

Next Steps

- PTK7 is a high priority target for COACH.
- MTX-13 antibody shows high binding affinity compared to ABBV-647, which warrants further preclinical studies in pediatric cancers.
- Preclinical studies should identify PTK7 functions in pediatric tumors, such as role in Wnt signaling and effects on metastasis and angiogenesis.
- Additional studies are needed to determine appropriate ADC antibody, linker, and payload for pediatric indications.

CD33

CD33 is a single-pass transmembrane glycoprotein and a member of the Siglec family of immunoglobulin-like lectins. CD33 undergoes clathrin-mediated endocytosis, allowing ADC payloads to be internalized at a slow rate, which limits cytotoxicity and intracellular drug accumulation. CD33 alterations are infrequent across pediatric cancers and are not considered a major driver of carcinogenesis. CD33 is expressed in adult and pediatric AML malignancies as well as on mature myeloid cells and hematopoietic progenitor cells and therefore has limited relevance to solid tumor indications. In vitro, CD33 expression is highly enriched in AML cell lines, including pediatric AML cell lines MV4-11, THP1, and P31FUJ. In vivo preclinical studies have focused on AML and suggest that CD33-targeting ADCs with various payloads have strong single agent activity in multiple models. Furthermore, the combination of CD33-targeting ADCs with chemotherapy agents may be an effective strategy to overcome drug resistance.

CD33 KO mice did not show significant pathologies or overt phenotypical differences in models of acute inflammation, such as casein-induced peritonitis and lipopolysaccharide (LPS)-induced systemic response. Although product information for Mylotarg (gemtuzumab ozogamicin) in EMA and FDA documents notes several preclinical toxicities, these were seen only at concentrations significantly higher than relevant human clinical exposures. Mylotarg, which was removed from the market in 2010 due to safety concerns arising from veno-occlusive disease (VOD)-related deaths, was subsequently re-approved in 2017. As the only CD33-targeting agent on the market, Mylotarg is approved for single agent therapy in adults and pediatric patients over 2 years old with r/r AML. Currently, there are 10 active non-industry sponsored pediatric trials for gemtuzumab ozogamicin, which is the only CD33-targeting ADC actively being tested for pediatric cancers. The most common modality for CD33-targeting drug development is CAR T-cell therapy, but CD33 CAR T-cell therapies are still primarily in preclinical development.
Key Considerations

- Many aspects of the Mylotarg’s mechanism of action remain unclear; for example, subsets of adults with AML exhibiting low CD33 expression show improvement with Mylotarg treatment.
- Preclinical studies of various bispecific T-cell engagers (BiTE) and CAR T-cell therapies in pediatric models may be warranted because BiTE therapies have previously been associated with a risk of patients developing cytokine release syndrome (CRS).
- There are a lack of preclinical model systems and cell lines that appropriately reflect pediatric AML.

Next Steps

- CD33 is a moderate-to-high priority target for COACH.
- There is potential for preclinical studies in other CD33-targeting therapy modalities with unknown efficacy and safety profiles, such as BiTE and CAR T-cell therapies.
- Given the lack of payload variety studied in anti-CD33 ADCs, preclinical studies should explore ADCs with novel payloads that reduce toxicities.
- Preclinical studies should consider exploring novel biomarkers that have greater predictive power of VOD development and positive response to CD33-targeting agents.
- Preclinical model systems and cell lines that appropriately reflect pediatric AML should be developed for use in future testing.
Meeting Summary

Review of Meeting Objectives

Stacey Adam, PhD, Foundation for the National Institutes of Health (FNIH)

Dr. Stacey Adam welcomed meeting participants and reiterated that the goal of Convening Experts in Oncology to Address Children’s Health (COACH) is to provide expert recommendations regarding drug target prioritization and salient preclinical steps to either clarify the priority of a specific drug target, or prepare a drug target, for pediatric cancer clinical trials. The focus of this meeting is specifically on the development and effectiveness of antibody-drug conjugates (ADCs) for each of the selected targets. If meeting participants identify a target as high priority, they will identify preclinical testing needs to advance ADCs to pediatric clinical trials or clarify existing clinical challenges. If meeting participants identify a target as low priority, they will determine whether additional preclinical data could advance the target to a higher priority or declare it as not relevant for pediatric cancer indications. Participants should also consider whether preclinical testing is needed to clarify targets currently inconclusive for relevance in pediatric cancer. Dr. Adam reminded meeting participants that COACH discussions should focus on drug targets and not agents; proprietary data for reviewed agents should not be discussed within COACH, unless private sector partners choose to disclose this information.

Pediatric Cancer Drug Target Data

Stacey Adam, PhD, FNIH

Dr. Adam presented data on relevant genetic alterations, transcriptomic expression, patient survival, and in vitro and in vivo dependency for four drug targets—B7 homolog 3 protein (B7H3), cluster of differentiation 22 (CD22), protein tyrosine kinase 7 (PTK7), and cluster of differentiation 33 (CD33)—as well as data on in vitro and in vivo drug sensitivity and clinical response rates for their respective therapeutics. Within a given tumor type, the presence of alterations in a drug target does not necessarily indicate its suitability as an effective therapeutic target. Similarly, a therapeutic formulated to inhibit a differentially expressed protein in a specific tumor type may not result in a significant therapeutic effect. Although there are limitations to in vitro dependency data, they can provide scientific rationale to support further preclinical assessments. However, in vitro dependency may not always reflect in vitro drug sensitivity. To address limitations associated with each of these data types, meeting participants consider these data in combination, identifying specific pediatric indications that may be sensitive to the target therapeutics.

Data types for each drug target were compiled using different databases, as well as scientific literature. Data on relevant genetic alterations, compiled from cBioPortal and PedcBioPortal cohorts, included simple somatic mutations (SSMs), copy number variations (CNVs), and structural variations (SVs). Patient expression data were compiled from CCIDI Molecular Targets Platform and XenaBrowser. In vitro dependency data obtained from Dependency Map.
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(DepMap) were presented using Chronos scores, a normalized metric of cell viability after gene deletion, with a Chronos score of 0 indicating that a gene is non-essential, while a score of -1 indicates comparable dependency to the median of all pan-essential genes. DepMap data on in vitro sensitivity were represented with Profiling Relative Inhibition Simultaneously in Mixtures (PRISM) scores (i.e., area under the curve [AUC] derived from an 8-point dose-response curve ranging from 10µM to 610pM). A PRISM score of 1 indicates complete lack of response at all concentrations, whereas a score of 0 indicates complete loss of viability at all concentrations. In vivo dependency and drug sensitivity data were aggregated from relevant scientific literature.

Research landscape data include federal grant spending, publications, and general commercial activity relevant to each target. Federal grant data obtained from the National Institutes of Health (NIH) were further classified by subtopics and federal agency administrators. Publication data were analyzed using PubTator. Commercial activity was summarized from Citeline’s PharmaProjects and Trialtrove databases.

B7H3

Stacey Adam, PhD, FNIH

Overview

B7H3, encoded by the cluster of differentiation 276 (CD276) gene, is an immune checkpoint protein within the same B7 superfamily as programmed cell death ligand 1 (PD-L1) (Zhou et al. 2019).* B7H3 is highly expressed in some pediatric solid tumors (National Cancer Institute [NCI] Pediatric Preclinical in Vivo Testing [PIVOT] Program). In adult cancers, B7H3 is widely expressed in 60 to 90 percent in most cancer types evaluated, whereas its expression is suppressed in healthy tissues containing fully mature adult cells (Picarda et al., 2016). However, monocytes, B cells, T cells, and natural killer (NK) cells can be induced to express B7H3 after stimulation in vitro (Chapoval et al., 2001).

B7H3 is involved in both immune and non-immune mechanisms of cancer progression (Zhou & Jin, 2021). B7H3 can have co-stimulatory or co-inhibitory effects on T cells and NK cells, depending on context; however, B7H3’s immunoregulatory functions remain unclear. B7H3 also has non-immunologic protumorigenic functions in cancer cells, such as promoting epithelial-mesenchymal transition (EMT), proliferation, and metabolic reprogramming.

Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival

CD276 transcripts are widely expressed in pediatric solid tumors, with Wilms tumors and osteosarcomas having the highest expression, in agreement with preclinical model data, whereas acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) have low expression. Other studies have reported high B7H3 protein expression in pediatric rhabdomyosarcoma and Ewing sarcoma (EwS) patients tumor specimens (Lavoie et al., 2021). Some studies report a strong correlation between high CD276 RNA expression and positive

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* PD-L1 and B7H3 were previously reviewed during third COACH meeting on December 14, 2022.
survival outcomes, while other studies have shown contradicting data, leaving B7H3’s prognostic value uncertain (Wang et al., 2013).

In pediatric tumor microarrays, immunohistochemistry (IHC) showed that 84 percent of solid tumors, including those in the central nervous system (CNS), stained positive for B7H3, with 7 percent demonstrating moderate or strong staining intensity (Majzner et al., 2019). In addition, B7H3-positive staining was observed in rhabdomyosarcoma, Wilms tumor, neuroblastoma, and EwS.

Multiple pediatric patient-derived xenograft (PDX) models of solid tumors expressed high levels of CD276 RNA, with osteosarcomas and Wilms tumors demonstrating the highest expression levels (Kendsersky et al., 2021). Osteosarcomas also demonstrated the highest CD276 mRNA expression in PIVOT preclinical models, with elevated mRNA levels also measured in neuroblastoma, rhabdomyosarcoma, Wilms tumor, and embryonal brain tumor models. IHC of PDX tissue microarrays showed strong staining across all models, including osteosarcoma, neuroblastoma, Wilms tumor, Ewing sarcoma, rhabdomyosarcoma, and pleomorphic xanthoastrocytoma (PXA) models.

**Dependency and Drug Sensitivity**

**In Vitro Dependency and Sensitivity**
Although B7H3 is expressed in CNS tumor, osteosarcoma, and rhabdomyosarcoma in vitro cell lines, all adult tumor types from the DepMap dataset showed only moderate levels of dependency. Knockout (KO) of CD276 resulted in moderate reductions in cell viability across adult tumor types; however, eliminating B7H3 expression alone was not sufficient to cause entire cell lines to die.

**In Vivo Sensitivity**
Despite the wide range of B7H3-targeting drug modalities tested preclinically, over 50 percent of preclinical studies have used B7H3-targeting ADCs, and these ADCs were effective in several sarcoma in vivo models. NCI preclinical programs have tested the ADCs MGC-018 and DS-7300a, as well as a B7H3 ADC tool compound (Gorlick et al., 2022; Kurmasheva et al., 2021). Osteosarcomas have shown sensitivity to multiple B7H3-targeting ADCs, with 100 percent objective response rate in PDX models (Kurmasheva et al., 2021). In addition, DS-7300a demonstrated high efficacy (i.e., maintained complete response [MCR], complete response [CR], or partial response [PR]) in 5 of 7 osteosarcoma models (Gorlick et al., 2022). In rhabdomyosarcoma models, DS-7300a was highly effective in 17 of 21 PDX models; MGC-018 elicited response in 4 of 6 single-mouse testing models; and a pyrrolobenzodiazepine (PBD)-conjugated B7H3 ADC elicited a modified CR in 3 PDX models. In Ewing sarcoma models, CR rates were high in 3 PDX models treated with m276-SL-PBD, and DS-7300a induced a response in 6 of 15 models.

**Preclinical Safety and Toxicology**
B7H3’s role in bone development could potentially impact use in pediatric therapy applications. Cd276 KO mice demonstrated lower bone mineral density, although gross skeletal features
appeared normal despite bone density deficits (Suh et al., 2004). KO calvarial cells exhibited impaired osteogenic differentiation, suggesting B7H3 is required for late-phase osteoblast differentiation. In addition, Cd276 KO mice showed increased spleen and intraepithelial lymphocyte inflammatory cytokines, as well as increased T cell proliferation, leading to graft-versus-host-disease (GVHD) lethality (Veenstra et al., 2015). Lastly, Cd276 KO mice showed earlier experimental autoimmune encephalomyelitis (EAE) development when exposed to myelin oligodendrocyte glycoprotein peptide (Suh et al., 2003).

**Clinical Trial Development**

Monoclonal antibodies (mAbs) targeting B7H3, including omburtamab 8H9 and enoblituzumab MGA271, are well-tolerated by adult patients and appear to have a manageable toxicity profile, but have demonstrated limited success in clinical trials. Y-mAbs Therapeutics has discontinued the omburtamab neuroblastoma program; studies 03-133 and 03-101 are no longer recruiting patients for clinical trials, although several patients still attend study follow-up appointments (10-Q Y-mAbs Therapeutics, 2023). In the omburtamab Phase I trial (NCT00089245), the external control was deemed not fit-for-purpose due to substantial differences between the study and control populations. In Phase II and III trials (NCT03275402), the Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) determined that no patient in the trial demonstrated a response that could be unequivocally attributed to omburtamab (Basu et al., 2022).

The Phase II study of 131I-omburtamab in medulloblastoma and recurrent ependymoma patients under 21 years old is currently active, not recruiting, and no results are available; its future remains unclear due to Y-mAbs Therapeutics’ deprioritization of its omburtamab program (NCT04743661). This study is testing the efficacy of combination treatment of 131I-omburtamab with irinotecan, temozolomide, and bevacizumab in patients with recurrent medulloblastoma and 131I-omburtamab, plus compartmental radioimmunotherapy (cRIT) in patients with recurrent ependymoma.

Other key ADCs in Phase II trials, include DS-7300 (Daiichi Sankyo), HS-20093 (Jiangsu Hansah Pharmaceutical), and MGC-018 (MacroGenics). BeiGene has an ADC in preclinical development based on a linker-payload containing a topoisomerase I inhibitor, but it is still early in the clinical development pipeline (Yan, 2023).

**Research and Development Landscape**

Although B7H3 interest in general, and as an immune checkpoint, has increased over time in the scientific community, only 4 percent of B7H3 literature is focused on pediatric oncology. The majority of B7H3 publications related to pediatric oncology research are focused on gliomas, neuroblastoma, and osteoblastomas, and nearly half of FNIH pediatric cancer indications of interest are not referenced in any B7H3-related articles.
Additional Considerations for Preclinical and Clinical Development
Facilitated by Robbie Majzner, MD, Dana-Farber Cancer Institute; Marc Arca, MD, Daiichi Sankyo; Ashley Ward, MD, MacroGenics; Sri Gururangen, MD, FRCP, BeiGene

Preclinical Testing in CNS Tumors
ADCs likely do not penetrate the blood brain barrier (BBB), and thus ADC preclinical studies have not focused on targeting CNS tumors. However, PIVOT plans to measure preclinical BBB penetration in CNS models in future studies. If the BBB impedes testing ADCs systemically and these ADCs do not show a therapeutic effect, regional delivery methods, such as Ommaya reservoirs in diffuse intrinsic pontine glioma (DIPG) models, may be worth exploring. Prior B7H3-targeting ADC studies have not explored efficacy in syngeneic immunocompetent models or the potential for immune responses and antibody-dependent cellular cytotoxicity related to B7H3 engagement and inhibition; however, PIVOT is currently planning preclinical studies with immunocompetent animals. Additionally, the receptor for B7H3 has not yet been conclusively identified, which limits the current understanding of B7H3’s biology.

Translating ADCs from adults to pediatrics requires results from Phase II adult trials, and safety data from preclinical models are often required to develop strategies to avoid inducing toxicity in children. In addition, most data on BBB penetration were collected from CNS metastases in adults, highlighting the need for preclinical data on ADC efficacy in primary CNS tumors as well as direct BBB penetration capability. Because B7H3 is postnatally silent in murine and human brains, B7H3 ADC safety findings may not provide useful insights on general ADC safety and BBB penetration. However, postnatal silence of B7H3 in normal CNS tissue paired with its high expression in CNS tumors makes it an ideal ADC target, whether administered systemically or regionally (Theruvath et al., 2020). Although difficult to interpret, preclinical studies have delivered radio-labelled B7H3-targeting drugs through an Ommaya reservoir, which did not yield significant toxicity.

FDA welcomes industry ADC developers to communicate often during early stages of development to determine what additional preclinical data, if any, are necessary for regulatory submissions prior to conducting pediatric trials. Further exploration of preclinical safety, immunocompetent models, and BBB penetration should be conducted in parallel with pediatric trials and not impede their development.

Toxicity
MacroGenics has expressed interest in beginning pediatric clinical trials of B7H3-targeting ADCs but is currently awaiting safety and efficacy data from an adult Phase II clinical trial of two dose levels of MGC018 in patients with prostate cancer (NCT05551117), which was initiated in response to toxicity observed in prostate cancer patients in MacroGenics’ Phase I study of MGC018.

Because B7H3 is expressed in tumor vasculature, ADC developers should consider the potential for hemorrhage during B7H3 ADC trials, particularly in vascular sarcomas, which are potential targets for B7H3-targeting ADCs. MacroGenics’ study of Enoblituzumab (a mAb targeting B7H3)
in combination with either tebotelimab (a bispecific antibody targeting lymphocyte-activation gene 3 (LAG3) and programmed cell death protein 1 (PD-1)—another B7 family member that is highly expressed in a broad array of tumor types) or retifanlimab (a mAb targeting PD-1 closed early due to a high rate of deaths potentially linked to hemorrhagic events in patients with head and neck cancers (NCT04634825). While identifying the underlying cause of hemorrhages in cancer trials can be difficult, MacroGenics has not observed fatal hemorrhages within any other study of enoblituzumab, tebotelimab, retifanlimab, or MGC018 administered as monotherapy or combination therapy in this or other adult cancer types.

Because B7H3 plays important roles in bone development, industry partners should consider monitoring bone health in clinical trials of B7H3 ADCs. However, bone toxicities in osteosarcoma studies using agents that target proteins involved in bone development are infrequent because most osteosarcoma patients are adolescents who have completed bone development. In addition, BeiGene previously evaluated growth plate changes when testing its ADC therapy in children and did not find any significant effects on bone development. Thus, with the inclusion of proper monitoring, the low risk of bone toxicity should not impede the development of pediatric clinical trials.

**Clinical Trial Eligibility Criteria and Design**

FDA has advocated the broadening of eligibility criteria for pediatric clinical trials based on initial preclinical and clinical data, as well as the prospect of B7H3-targeting ADCs’ direct clinical benefits. The potential for bone toxicity should not solely dictate the age limit of clinical trials, especially in adolescents. Current and upcoming clinical trials should consider lowering the age requirement to include ages 12 to 18 years old, allowing studies to conduct efficacy and safety data comparisons between pediatric and adult populations. In addition, lowering the age requirement increases regulatory opportunities to recommend B7H3 targeting ADC treatment for pediatric populations.

Non-invasive biomarkers for measuring B7H3 expression are limited. Because B7H3 is robustly expressed in solid tumors, pediatric B7H3-targeting ADC trials should not mandate on-trial biopsies require biopsies, to alleviate patient hesitancy. However, because drug therapies can alter the surfaceome (i.e., the complement of cell surface proteins) of tumor cells, collecting direct tumor biopsies at multiple timepoints during ADC trials could better inform efficacy data throughout the treatment timeline.

Companies developing B7H3-targeting ADCs should consider targeted combination therapies. MacroGenics has begun an internal trial combining their B7H3-targeting ADC with a PD-1-directed mAb. In addition, MacroGenics is conducting an ongoing Phase I study for solid tumors combining their B7H3-targeting ADC with a PD-1/cytotoxic T-lymphocyte-associated protein 4 (CTLA4) bispecific drug.

**Next Steps**

In summary, B7H3 is a moderate-to-high priority target based on its high and robust expression in pediatric tumors, as well as the higher efficacy of B7H3-targeting ADCs in preclinical studies.
compared to B7H3-targeting mAbs. Although multiple trials on B7H3-targeting ADCs are ongoing, continued B7H3-targeting ADC clinical development requires more pediatric trials, clinical trial safety data collection, non-invasive B7H3 biomarkers, and preclinical research with additional models.

**CD22**

*Stacey Adam, PhD, FNIH*

**Overview**

CD22 is a transmembrane protein belonging to the sialic acid-binding immunoglobulin-related lectin (Siglec) family of lectins that acts primarily as an inhibitory co-receptor for B-cell receptor signaling. Constitutive internalization of CD22 makes it an attractive hematopoietic target for ADC development because endocytosis allows for targeted delivery of the ADC payload.

**Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival**

Genetic alterations of *CD22* are generally rare in pediatric cancers and not considered a major driver of carcinogenesis. One exception to this finding is osteosarcoma, with high alteration rates reported in multiple cBioPortal datasets, including 10 instances of gene amplifications in 104 cases with *CD22* alterations.

RNA expression data from PeCan’s database of pediatric tumor samples shows that *CD22* is primarily expressed in B-cell ALL (B-ALL), in alignment with its primary B cell culture expression in healthy cells. However, ALL RNA expression in the XenaBrowser cohort is lower than reported in other databases, whereas the Innovate study found that *CD22* was expressed in over 90 percent of adult and pediatric B-ALL, with high expression across pro-B ALL, pre-B ALL, and B-mature ALL (Macauley et al., 2014; Raponi et al. 2011).

**Dependency and Drug Sensitivity**

*In Vitro Dependency and Sensitivity*

Expression of CD22 in pediatric cancer cell lines is highly restricted to lymphatic cancers, including ALL, non-Hodgkin’s lymphoma (nHL), and Hodgkin’s lymphoma (HL), with most solid tumors showing negligible expression (Fousek et al., 2020; Yang et al., 2021). The majority of cell lines, including ALL and nHL, show minimal dependency of CD22 expression for cell viability *in vitro*, and CD22 is not essential for B cell survival.

A range of CD22-targeting ADCs have shown *in vitro* activity in lymphatic cancer cell lines. Inotuzumab ozogamicin (InO) showed effective killing of primary pediatric ALL cells *in vitro*, but efficacy was heavily dependent on calicheamicin sensitivity and the CD22 internalization capability of different cell lines (de Vries et al., 2011). Next, an anti-CD22-maytansine was broadly effective in *in vitro* killing assays on nHL B cell lines (Polson et al., 2010). Lastly, an anthracycline-based anti-CD22 ADC shows increased efficacy over monomethyl auristatin E (MMAE)-based anti-CD22 ADCs against nHL cell lines (Yu et al., 2015).
In Vivo Sensitivity
CD22-targeting ADCs show efficacy in various ALL models as single agents and in combination with existing cancer drugs. First, anti-CD22-conjugated max dimerization protein 3 (MXD3) antisense oligonucleotide (ASO)-based ADC treatment demonstrated MXD3 knockdown and apoptosis of Reh cells—an in vitro ALL model—that is accompanied with prolonged survival (Satake et al., 2016). Next, HB22.7-SAP, an anti-CD22 HB22.7 mAb-based ADC, showed significant anti-tumor activity in a xenograft mouse model of pre-B-ALL that is accompanied with prolonged survival (Kato et al., 2013). In addition, early studies of InO resulted in complete regression of Ramos and B-cell lymphoma (BCL) xenografts, providing a strong preclinical rationale for clinical development in B-ALL (DiJoseph et al., 2003). The anti-CD22 conjugated moxetumomab pasudotox-based ADC has shown strong preclinical efficacy in ALL and was FDA-approved for relapsed or refractory (r/r) hairy cell leukemia in 2018; however, this drug conjugate was removed from the market in November 2022 due to low clinical uptake (FDA PR). Lastly, the combination of InO with rituximab led to synergistic long-term survival in mice with disseminated Ramos BCL (DiJoseph et al., 2004).

Notably, CD22-targeting ADCs—including calicheamicin-based ADCs, alpha-CD22-SN36248, CAT-02-106, HB22.7-vcMMAE, and DCDT2980S—have shown significant in vivo activity and dose-dependent tumor response in nHL models and minimal systemic toxicity in various xenograft models (Vollmar et al., 2021; Yu et al., 2021, Drake et al., 2018; Abuhay et al., 2016; Li et al., 2013).

Preclinical Safety and Toxicology
Cd22 KO mice exhibit normal fertility and no gross abnormalities, but have reduced long-lived recirculating B cell populations and B cells with hyperresponsivity to receptor signaling (Otipoby et al., 1996; O’Keefe et al., 1996). However, complete loss of CD22 results in significant B cell changes (Sato et al., 1996). Multiple CD22-targeting ADCs have shown mild-to-moderate hematologic toxicities in animal models, with decreased platelet counts; dose-dependent reversible neutropenia and reticulocytopenia; and minor decreases in erythrocyte count, hemoglobin, and hematocrit (Drake et al., 2017; Li et al., 2013). In addition, InO is clastogenic in the bone marrow of male mice (Besponsa FDA PI). In the liver, preclinical pathology has been reported in InO, including altered hepatocellular foci, oval cell hyperplasia, and hepatocellular adenomas in the liver, which are reflected in liver toxicities, particularly sinusoidal obstruction syndrome (SOS) seen in patients treated with anti-CD22 ADCs (European Medicines Agency [EMA] product information for Besponsa).

Clinical Trial Development
Phase III Trials
InO has demonstrated efficacy in r/r B-ALL in adult and pediatric patients (Pennesi et al., 2022; Besponsa FDA PI). The following Phase III trials are testing InO in newly diagnosed patients and in combination with chemotherapies:
• **InO plus post-induction chemotherapy in B-ALL**: This study is evaluating 5-year disease-free survival of InO plus post-induction chemotherapy in patients between the ages of 1 and 25 years with newly diagnosed high-risk B-ALL. According to recent analysis, SOS and infections remain a concern for the chemotherapy plus InO arm, particularly during the delayed intensification phase with microbials (O’Brien et al., 2023). Additional modifications are planned for this arm to further mitigate toxicity during post-InO chemotherapy periods (NCT03959085).

• **InO in ALL**: The ALLTogether1 European study is evaluating the efficacy of InO before maintenance treatment in patients 0 to 45 years of age with newly diagnosed ALL and is currently recruiting (NCT04307576).

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**Phase II Trials**

The following are recent phase II trials:

• **InO in B-ALL**: This study is evaluating treatment response to InO (i.e., the number of patients who are minimal residual disease [MRD]-negative) at the end of cycle 1 in patients 0 to 21 years old with MRD-positive CD22-positive B-ALL and is currently recruiting (NCT03913559).

• **Compressed rituximab, InO, and blinatumomab (cRIB) plus chemotherapy and dexamethasone in B-ALL**: This study will evaluate the efficacy and safety of cRIB plus chemotherapy (mini-hyper cyclophosphamide, vincristine, methotrexate, and cytarabine) and dexamethasone in patients 1 to 25 years of age with r/r B-ALL. The study is not yet recruiting (NCT05645718).

• **InO plus blinatumomab and chemotherapy in B-ALL**: This study is evaluating the efficacy and safety of InO plus blinatumomab and chemotherapy (hyper cyclophosphamide, dexamethasone, doxorubicin, vincristine) in patients over 14 years of age with newly diagnosed B-ALL. Thus far, 53 patients have had CR (O’Brien et al., 2022). The 15-month overall survival (OS) in cohorts with and without InO were 100 percent and 87 percent, respectively. No patients have discontinued InO due to toxicity (NCT02877303).

• **InO in B-lymphoblastic lymphoma and B-ALL**: This study is evaluating the safety and efficacy of InO alone in patients 1 to 21 years of age with either r/r B-lymphoblastic lymphoma (B-Lly) or r/r CD22-positive B-ALL. InO was effective and well tolerated in heavily pretreated r/r CD22-positive B-ALL, with 19 cases of CR and 9 cases of incomplete count recovery after cycle 1 (O’Brien et al., 2022). Regarding toxicity, 6 of 21 patients developed grade 3 SOS. The study has since been amended to evaluate InO in combination with chemotherapeutic consolidation therapy (NCT02981628).

• **InO in B-cell precursor ALL**: This study is evaluating the superiority and safety of InO compared to ALLR3 chemotherapy (vincristine, mitoxantrone, dexamethasone, asparaginase) in patients 1 to 17 years of age with high-risk first bone marrow relapse CD22-positive B-cell precursor ALL and is currently recruiting (NCT05748171).

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**Phase I Trials**

The following are recent phase I non-industry sponsored trials:
• **InO in post-transplant ALL or nHL**: This is a dose-finding study of InO in post-transplant patients 16 to 75 years of age with ALL or nHL at high risk of relapse (NCT03104491). Observed toxicities include thrombocytopenia, neutropenia, nausea, and vomiting, but no veno-occlusive disease (VOD) was observed (Metheny et al., 2022).

• **InO plus Berlin-Frankfurt-Münster re-induction in B-ALL**: This study is assessing the safety and efficacy of InO with augmented Berlin-Frankfurt-Münster (BFM) re-induction in patients 16 to 60 years old with r/r B-ALL and is currently recruiting (NCT03962465).

**Research and Development Landscape**
Interest in CD22 has fluctuated greatly over time, with a recent spike of publications in 2021. There is moderate interest surrounding CD22 as a potential target in oncology, given that 21 percent of CD22 articles are oncology related, but only 5 percent of all preclinical CD22 articles focus on pediatric oncology indications. ALL and nHL are the most referenced oncology indications in CD22 literature, but the 15 FNIH pediatric cancer indications of interest are not referenced in any CD22-related articles.

Most CD22-targeting drugs in the development pipeline are chimeric antigen receptor (CAR) T-cell therapies, with the most advanced CAR T-cell therapies in Phase II trials. Currently, Pfizer’s anti-CD22 antibody-calicheamicin conjugate (Besponsa) is the only CD22-targeting ADC on the market, approved to treat adult ALL. However, Besponsa development for indolent and aggressive nHL was discontinued due to futility. Other ADCs that are most advanced in the development pipeline include ADCT-602 (ADC Therapeutics) for ALL, which is in Phase II trials, and TRPH-222 (Redwood Bioscience).

**Additional Considerations for Preclinical and Clinical Development**
*Facilitated by Alan Wayne, MD, Children’s Hospital Los Angeles; Maureen O’Brien, MD, MS, Cincinnati Children’s Hospital*

**Preventing Hepatoxicities**
Although InO studies have demonstrated high efficacy in ALL, InO still faces toxicity challenges, particularly hepatotoxicities in patients who develop SOS after bone marrow transplant. To address hepatotoxicity with InO, clinicians should consider avoiding calicheamicin ADCs during pre-transplant conditioning and post-transplant periods. In addition, preclinical studies should focus on identifying biomarkers or genetic profiles to better understand potential predisposition to hepatotoxicity. Alternatively, testing other CD22-targeting ADCs with different linkers and payloads may help to avoid hepatotoxicity in some patients and to increase understanding of these toxicities. However, low clinical uptake, such as that observed for moxetumomab pasudotox, may complicate testing other CD22-targeting ADCs.

**Increasing CD22 Surface Expression**
CD22 surface expression in B cells is critically important for CD22-targeting ADC activity. B-ALL cancer cells with KMT2A rearrangements and potential subclones of CD22 can have reduced CD22 surface expression, which may decrease CD22-targeting ADC efficacy. Furthermore, expression of the primary CD22 ligand, α-2-6 sialic acid, on the same B cell surface as CD22 can
mask CD22 expression. Preclinical studies using in vitro ALL cell lines and in vivo PDX models should consider evaluating sialic acid inhibitors to prevent cis binding and thus increase CD22 expression. In addition, bryostatin-1, a protein kinase C (PKC) inhibitor, can potentially increase expression of CD22 by preventing its recirculation and internalization.

**Next Steps**

In summary, although preclinical studies could provide insights into increasing CD22 expression using combination therapies, CD22 is a low-to-moderate priority target because evidence indicates that InO already has high efficacy in the clinic, which decreases the competitiveness of other CD22-targeting ADCs in the development pipeline. In addition, the majority of CD22-targeting agents are CAR T-cell therapies, and thus preclinical studies likely will focus more on advancing their efficacy, rather than the efficacy of CD22-targeting ADCs.

**PTK7**

*Stacey Adam, PhD, FNIH*

**Overview**

PTK7 is a highly conserved and catalytically inactive transmembrane kinase involved in Wnt and vascular endothelial growth factor (VEGF) signaling (Damelin et al., 2017; Katoh, 2017). PTK7’s role has been linked both to cancer endurance and invasion, as well as tumor suppressing functions, and its involvement in non-canonical Wnt signaling has diverse downstream effects on cancer cells. Due to PTK7’s lack of catalytic activity, its direct inhibition with a small molecule or mAb is not likely to be an effective anti-cancer strategy; however, because PTK7 is upregulated in various adult and pediatric cancers compared to healthy tissue, it is an attractive candidate targeting antibody for ADCs.

**Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival**

*PTK7* is overexpressed in several adult and pediatric cancers, with strong expression in pediatric Wilms tumors and osteosarcoma, as well as some adult non-small cell lung cancers (NSCLC), triple negative breast cancers (TNBC), and ovarian cancers (Damelin et al., 2017; Lee et al., 2023; GTEX Portal 2023). Because mutation rates for *PTK7* are uniformly low across pediatric cancers, except in osteosarcoma, overexpression rather than gene alterations is the key *PTK7* association with oncogenesis (Smida et al., 2010).

*PTK7* RNA expression in healthy adult tissues and *PTK7* IHC staining in pediatric tissues are low, with the highest expression observed in female reproductive organs (Lee et al., 2023; GTEX Portal, 2023). RNA expression data in pediatric tumors from the PIVOT and PeCan Portal datasets indicate high *PTK7* RNA expression in Wilms tumors, osteosarcomas, and rhabdoid tumors (i.e., atypical teratoid/rhabdoid tumors [ATRTs] and extracranial rhabdoid tumors). *PTK7* expression is strongly correlated with poor survival outcomes in the XenaBrowser glioma cohorts, as well as poor outcomes with expression in glioblastomas and neuroblastomas (Lee et al., 2023; Liu et al., 2015).
Dependency and Drug Sensitivity

**In Vitro Dependency and Sensitivity**
PTK7 expression is high in pediatric osteosarcoma, neuroblastoma and rhabdomyosarcoma (RMS) cell lines, as well as EwS, but does not correlate with gene dependency (Lee et al., 2023). Most pediatric cell lines exhibit a low dependency on PTK7 that does not correlate with expression, and CRISPR KO of PTK7 in neuroblastoma cell lines does not alter their viability or sensitivity to chemotherapy.

**In Vivo Sensitivity**
Currently, no PTK7 ADC-related preclinical literature meets inclusion criteria for *in vivo* dependency or drug sensitivity. However, a PTK7-targeted CAR T-cell therapy has recently shown positive results in an IMR-5 neuroblastoma model, inducing antigen-specific cytotoxicity with limited toxicity.

**Preclinical Safety and Toxicology**
In KO models, an initial study characterizing *Ptk7* KO mice found that loss of *Ptk7* leads to perinatal lethality resulting from profound developmental defects, including cranial neural tube closure defects, gastroschisis, and kidney and forelimb abnormalities (Lu et al., 2004). Pan-mesoderm loss of *Ptk7* resulted in spina bifida in conditional KO mice, of which the majority die soon after birth (Xu et al., 2015). Although adult studies of KO mice are not possible, studies of fetal liver found changes in hematopoietic stem cell (HSC) dynamics (Lhoumeau et al., 2016). In a reconstitution experiment, *Ptk7*-deficient hematopoietic stem cells can reconstitute all mature hematopoietic lineages in lethally irradiated recipients. However, *Ptk7*-deficient cells had a very poor ability to home to the bone marrow, spleen, liver, and thymus.

In a study characterizing a PTK7-targeting ADC in non-human primates (NHPs), major toxicities (e.g., myelosuppression) occurred due to off-target effects previously observed with other ADCs that contain microtubule inhibitors and cleavable linkers (Damelin et al., 2017). No on-target toxicities were noted, including in normal tissues expressing PTK7 (e.g., kidney, bladder, and lung). Another study evaluated MTX-13, a novel PTK7-targeting ADC that consists of a PTK7 antibody conjugated to 8 molecules of the topoisomerase I inhibitor exatecan (Kong et al., 2023). Repeat-dose toxicology studies in NHPs suggested a highest non-severely toxic dose of at least 30 mg/kg, with mild-to-moderate effects observed in bone marrow, thymus, liver, gallbladder, and stomach.

**Clinical Trial Development**
PTK7-targeting ADCs have not entered pediatric clinical trials. Pfizer conducted a Phase I clinical trial for their ADC ABBV-647, but development of this ADC is now discontinued (NCT04189614).

**Research and Development Landscape**
Most PTK7 publications are unrelated to oncology, with only 8 preclinical oncology articles involving PTK7 having been published, the first in 2015. These oncology-related PTK7 articles...
reference ALL, AML, glioma, and malignant rhabdoid tumors. However, there is a significant gap associated with PTK7 in pediatric oncology based on the paucity of these articles.

The only PTK7-targeting drugs are ADCs, including MTX-13 in preclinical development for solid tumors (Multitude Therapeutics) and ABBV-647 (Pfizer). Abbvie recently announced the discontinuation of ABBV-647 development; however, because the asset is still listed in Pfizer’s development pipeline, its status is currently unknown.

**Additional Considerations for Preclinical and Clinical Development**

*Facilitated by Richard Gorlick, MD, MD Anderson Cancer Center; Kelly Goldsmith, MD, Emory University*

**Existing PTK7-Targeting ADCs**

Several screens of cell surface expression have identified PTK7 as a potential therapeutic target in neuroblastomas due to its high expression. After treatment with standard-of-care chemotherapy, PTK7 expression remains high, making PTK7 an appealing target for subsequent lines of treatment. In addition, auto activation of T cells is unlikely to occur from PTK7-targeting therapies because no studies have found PTK7 expression in mature T cells or other immune cells. Results from Pfizer’s Phase I trial of ABBV-647, including a recommended Phase II dose and toxicity data, can help inform additional preclinical studies on PTK7-targeting ADCs. Multitude Therapeutics has already conducted preclinical studies on their PTK7-targeting ADC, MTX-13, which implements a topoisomerase 1 inhibitor payload. Initial preclinical findings suggest that MTX-13 has significantly higher antibody binding affinity than ABBV-647. In addition, MTX-13’s payload allows for an increased drug-to-antibody ratio compared to ABBV-647, providing low potencies and potentially increased response.

**Toxicity and Future Preclinical Studies**

Although Pfizer cannot provide detailed information about the discontinuation of ABBV-647 until its official presentation of Phase I trial data in October 2023, ABBV-647’s discontinuation was not related to toxicity concerns. The ABBV-647 payload is an auristatin microtubules inhibitor that has potential off-target effects, whereas MTX-13’s topoisomerase 1 inhibitor payload may have fewer off-target effects. Although PKT7-targeting CAR T-cell therapies in adults have shown in vivo efficacy, and off-target effects may be mitigated upon payload internalization, additional preclinical studies are needed to determine an appropriate ADC antibody, linker, and payload for pediatric indications. In addition, preclinical studies should consider identifying functions of PTK7 in pediatric tumors, such as PTK7’s role in Wnt signaling and its effects on metastasis and angiogenesis.

**Next Steps**

In summary, PTK7 is a high priority target because of its high cell surface expression in neuroblastomas, positive in vivo efficacy of PTK7 CAR T-cell therapy in neuroblastoma models, and low likelihood of T cell auto activation. In addition, the MTX-13 antibody shows high binding affinity, which warrants further preclinical studies in pediatric cancers.
**CD33**  
*Stacey Adam, PhD, FNIH*

**Overview**
CD33 is a single-pass transmembrane glycoprotein and a member of the Siglec family of immunoglobulin-like lectins (Hammood et al., 2021; Molica et al., 2021; Walter, 2014). When phosphorylated on its immunoreceptor tyrosine-based inhibitory motif (ITIM), CD33 recruits Src homology region 2 domain-containing phosphatases 1 and 2 (SHP-1 and SHP-2) to inhibit myeloid cellular activation and proliferation, including cytokine production and phagocytosis. Downstream pathways in CD33 signaling, including Sky, Casitas B-lineage lymphoma (C-CBL), VAV, and zeta chain of T-cell receptor associated protein kinase 70 (ZAP-70), are poorly understood. However, CD33 undergoes clathrin-mediated endocytosis, allowing ADC payloads to be internalized. Moreover, slow internalization rates limit cytotoxicity and intracellular drug accumulation.

**Relevant Genetic Alterations, Transcriptomic Expression, and Patient Survival**
*CD33* alterations are infrequent across pediatric cancers and are not considered a major driver of carcinogenesis; more common genetic alterations in pediatric AML affect runt-related transcription factor 1 (RUNX1) and RAS pathways (Cheng et al., 2023). However, *CD33* expression was associated with high-risk FMS-like tyrosine kinase-3 internal tandem duplications (FLT3/ITDs) and inversely associated with low-risk disease in two pediatric AML trials (Pollard et al., 2012, 2016).

*CD33* is expressed in adult and pediatric AML malignancies, as well as on mature myeloid cells and hematopoietic progenitor cells, and therefore has limited relevance to solid tumor indications (Willier et al., 2021). *CD33* expression has been associated with both side effects and prognosis. *CD33* expression on hematopoietic precursors in brain metastases of healthy children is associated with on-target side effects. Glioma and neuroblastoma cohorts show correlations between high *CD33* expression and negative survival outcomes; however, limited literature is available to support these associations. Clinical studies have found high *CD33* expression is also associated with poor outcomes in pediatric AML (Pollard et al., 2012).

**Dependency and Drug Sensitivity**

**In Vitro Dependency and Sensitivity**
CD33 expression is highly enriched in AML cell lines, including in the pediatric AML cell lines MV4-11, THP1, and P31FUJ (Wijnen et al., 2023). MOLM13 and MOLM14—popular models of CD33-positive AML—have been used extensively *in vitro* and *in vivo* but are of adult origin. Furthermore, AML cell lines are difficult to generate and undergo significant changes *in vitro* that may limit their relevance to the study of human disease (Milan et al., 2019).

**In Vivo Sensitivity**
Preclinical studies have focused on AML and suggest that CD33-targeting ADCs with various payloads have strong activity as single agents in multiple models, shown below:
1. **IMGN779** has a DNA-alkylating payload and shows significant tumor reduction and prolonged survival in EOL-1 and MV4-11 models (Kovtun et al., 2018).

2. **CD33-targeted thorium-227 ADC** significantly reduced tumor volume in HL-60 xenograft model and demonstrated dose-dependent survival improvements (Hagemann et al., 2016).

3. **Single dose SGN-CD33A** displayed antitumor activity in MDR-negative and MDR-positive murine models of AML (Kung Sutherland et al., 2013).

4. **Anti-CD33 carrying a DNMT3A RNA interference (RNAi) payload** led to significant tumor reduction in OCI-AML2 and KG1 AML xenograft models (Bäumer et al., 2022).

The combination of CD33-targeting ADCs with chemotherapy agents may be an effective strategy to overcome drug resistance. Combination $^{225}$Ac-lintuzumab (anti-CD33) and venetoclax is an effective strategy in AML models, particularly for overcoming venetoclax resistance (Garg et al., 2020). In addition, combination treatment with gemtuzumab ozogamicin (a CD33-targeting ADC) and daunorubicin/cytarabine chemotherapy eliminates nearly all AML burden and extends OS (Zhang et al., 2017).

Anti-C-type lectin domain family 12 member A (CLL1)-based ADC has been tested as an alternative to CD33-targeting ADCs to limit toxicities in acute promyelocytic leukemia (APL) xenograft models using HL-60 cells (Jiang et al., 2018). Expression of CLL1 was consistent across different types of AML. Compared with CD33-targeting ADCs, an anti-CLL1-based ADC demonstrated a reduced effect on the differentiation of healthy normal human CD34-positive cells to various lineages, in both an *in vitro* colony formation assay and an *in vivo* xenotransplantation model.

**Preclinical Safety and Toxicology**

*CD33* KO mice did not show significant pathologies or overt phenotypical differences in models of acute inflammation, such as casein-induced peritonitis and lipopolysaccharide (LPS)-induced systemic response (Brinkman-Van der Linden et al., 2003). These data also suggest that there is no major nonredundant role of CD33 in development and distribution of hematopoietic cells. *CD33*-deficient mice also showed no gross morphological or histological abnormalities but showed a slight reduction in erythrocyte count and hematocrit, as well as an increase in the mean concentration of serum glutamic oxaloacetic transaminase (GOT).

In EMA and FDA documents, product information for Mylotarg (gemtuzumab ozogamicin)—an ADC with a broadly cytotoxic calicheamicin payload—notes several preclinical toxicities; however, these toxicities were only observed at ADC concentrations significantly higher than relevant human clinical exposures (*EMA PI; FDA PI*). Commonly observed toxicities—including those in the liver, bone marrow, and lymphoid organs, as well as hematological toxicities (i.e., decreased red blood cell mass and white blood cell counts)—were observed in rats and monkeys at 18- and 36-times the human clinical exposure, respectively. Rats also developed preneoplastic lesions in the liver at 54-times the human clinical exposure, but these toxicities were not observed in monkeys. Nervous system effects were not observed in animals, unlike other antibody-calicheamicin conjugates.
Clinical trials for Mylotarg have also reported liver and hematologic toxicities, including thrombocytopenia, neutropenia, hyperbilirubinemia, and rare cases of VOD (EMA PI). Patients receiving hematopoietic stem cell transplantation prior to Mylotarg were more likely to develop VOD. Although Mylotarg was removed from the market in 2010 due to safety concerns arising from VOD-related deaths, it was subsequently re-approved in 2017.

Clinical Trial Development
There are 10 active non-industry sponsored pediatric trials for gemtuzumab ozogamicin, which is the only CD33-targeting ADC actively being tested for pediatric cancers. While results are not yet available for any trial, trial data has identified single nucleotide polymorphisms (SNPs) that alter CD33 surface expression in ATP binding cassette subfamily B member 1 (ABCB1) expressing-cells, which acts as a predictor of gemtuzumab ozogamicin response in pediatric AML (Chauhan et al., 2019; Lamba et al., 2017; Rafiee et al., 2019).

Phase III Trials
The following are recent phase III trials:

- **MyeChild01 in Children With Acute Myeloid Leukemia**: This study will establish dose tolerances and compare multiple combination therapies, including the combination of gemtuzumab ozogamicin, daunorubicin, and cytarabine, in patients up to 17 years old with AML. (NCT02724163).
- **CPX-351 and/or Gilteritinib in Newly Diagnosed AML**: This study compares standard chemotherapy to therapy with liposome-encapsulated daunorubicin-cytarabine (CPX-351) and/or gilteritinib for patients up to 21 years old with newly diagnosed acute myeloid leukemia with or without FLT3 mutations (NCT04293562).
- **Venetoclax in Children With Relapsed AML**: This study evaluates if the randomized addition of venetoclax to a chemotherapy backbone (fludarabine/cytarabine/gemtuzumab ozogamicin) improves survival of patients up to 21 years old with AML in first relapse who are unable to receive additional anthracyclines, or in second relapse (NCT05183035).

Phase II Trials
The following are recent phase II trials:

- **Stem Cell Transplantation Plus Gemtuzumab Ozogamicin Therapy in Average Risk AML/MDS**: This study will evaluate efficacy and toxicity gemtuzumab ozogamicin in patients up to 25 years old with average risk of AML or myelodysplastic syndrome (MDS) following allogeneic stem cell transplantation (NCT02117297).
- **Immunchemotherapy and Stem Cell Transplantation in High-Risk AML/MDS**: This study will evaluate gemtuzumab ozogamicin in combination with chemotherapy followed by allogeneic stem cell transplantation in patients up to 25 years old with high risk of AML or MDS (NCT02221310).
- **Tretinoin and Arsenic Trioxide With or Without Gemtuzumab Ozogamicin in APL**: This study will evaluate the efficacy of tretinoin and arsenic trioxide with or without...
gemtuzumab ozogamicin in treating patients 10 years or older with previously untreated acute promyelocytic leukemia (APL) (NCT01409161).

- **Treatment Study for Children and Adolescents With APL:** This study will evaluate the efficacy of tretinoin and arsenic trioxide with or without gemtuzumab ozogamicin in treating patients less than 18 years old with promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) transcript-positive APL (NCT04793919).

**Phase I Trials**
The following are recent phase I trials:

- **Fractionated Gemtuzumab Ozogamicin in AML:** This study is evaluating the efficacy of gemtuzumab ozogamicin monotherapy in pediatric AML patients 2 years or older who have undergone standard induction chemotherapy (NCT03737955).

- **Liposomal Cytarabine, Daunorubicin, and Gemtuzumab Ozogamicin in Relapsed Refractory Pediatric Patients with AML:** This study will determine dosing and side effects of liposomal cytarabine, daunorubicin, and gemtuzumab ozogamicin in treating patients up to 21 years old with r/r AML (NCT04915612).

- **Tagraxofusp-erzs in Combination With Gemtuzumab Ozogamicin in Relapsed/Refractory AML:** This study will determine the recommended phase II dose of tagraxofusp-erzs in combination with gemtuzumab ozogamicin in patients 12 years or older with r/r AML (NCT05716009).

**Research and Development Landscape**
Focus on CD33 in the literature peaked during 2013 and has decreased over the last 3 years. There is a strong interest in CD33 as a potential target in oncology, with 65 percent of CD33 articles being related to oncology. Although the number of preclinical investigations into CD33 as an oncology target have fluctuated since 2015, the proportion of preclinical oncology articles has generally increased. However, a moderate gap still exists in the pediatric oncology space based on the paucity of CD33-related pediatric oncology articles. AML is mentioned in four times as many CD33 articles than ALL, which is the second most referenced indication. nHL, glioma, HL, and Wilms tumors are referenced in less than 10 articles each.

First approved in the United States in 2017 for AML, Pfizer’s anti-CD33 antibody-calichaemicin conjugate (Mylotarg) is the only CD33-targeting ADC on the market (Mylotarg PI). Pfizer’s ADC is approved for single agent therapy in adults and pediatric patients over 2 years old with r/r AML. Pediatric approval for single agent therapy is based on an open label study in patients 1 to 16 years old, reporting CR in 8 of 29 patients. In addition, Pfizer’s ADC is approved for combination therapy with daunorubicin and cytarabine in adults and pediatric patients with newly diagnosed de novo CD33-positive AML (except APL). Pediatric approval is based on AAML0531, which found significant improvement in progression-free survival, despite no difference in OS.

The CD33-targeting ADCs BVX-001 and ORM-6151 are in preclinical testing for hematological cancers. ADCs discontinued from clinical development, potentially due to potential toxicity or
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market saturation, include SGNCD33A (vadastuximab talirine, pyrrolobenzodiazepine dimer payload), IMGN779 (DGN462 payload), and AVE9633 (DM4 payload). The most common modality for CD33-targeting drug development is CAR T-cell therapy, with CD33 CAR T-cell therapies are still primarily in preclinical development. Notably, there are also 8 trispecific T-cell engagers (TriTEs) and 5 bispecific T-cell engagers (BiTEs) in the pipeline. AMG330 is a BiTE that previously entered clinical trials but was discontinued due to an unfavorable risk-benefit profile and a change in company priorities (Ravandi et al., 2018).

Additional Considerations for Preclinical and Clinical Development

Facilitated by Andy Kolb, MD, the Leukemia and Lymphoma Society; Jessica Pollard, MD, Dana-Farber Cancer Institute

Improvement of CD33-targeting ADCs

Although clinical studies have provided extensive data on the efficacy and toxicities of Mylotarg, many aspects of the agent’s mechanism of action remain unclear. For example, adults with core-binding factor AML show improvement with Mylotarg treatment, despite this subset of AML showing low CD33 expression. In addition, other disease characteristics can affect the efficacy of CD33-targeting agents, such as splice site SNPs in CD33 that affect antibody binding. Preclinical studies should consider testing antibodies that target different CD33 binding sites to improve efficacy in AMLs containing CD33 alterations that prevent antibody binding. Preclinical studies should consider testing antibodies that target different CD33 binding sites to improve efficacy in AMLs containing CD33 alterations that prevent antibody binding for current ADCs. In addition, given the lack of payload variety studied in anti-CD33 ADCs, preclinical studies should explore ADCs with novel payloads that reduce toxicities.

Biomarkers for Predicting Toxicity

High expression of CD33 does not positively correlate with the risk of developing VOD, which is already difficult to quantify due to changes in VOD diagnostic criteria. In addition, preclinical studies that explore a CD33 expression threshold for the use of CD33-targeting agents could fail to identify patients with low CD33 expression who may still respond to Mylotarg. Thus, preclinical studies should consider exploring novel biomarkers that have greater predictive power for VOD development and positive response to CD33-targeting agents. When screening for CD33 expression levels, clinics should also consider using commercial flow antibodies that target the same binding site as the agent’s antibody; using a standard immunoglobulin heavy chain (IgH) antibody may underrepresent patients that could potentially be responsive to CD33-targeting agents.

Other Modalities of CD33-Targeting Agents

Unlike Mylotarg, the efficacy of many CD33 BiTE therapies is unclear, and many BiTE therapies have an associated risk of patients developing cytokine release syndrome (CRS). Like BiTE therapies, CD33-targeting CAR T-cell therapies have not provided clear efficacy signals. Thus, preclinical studies of BiTE and CAR T-cell therapies may be warranted, as well as discussions with companies about reevaluating CD33-targeting agents that have been discontinued from development. However, there is currently a lack of preclinical model systems and cell lines that appropriately reflect pediatric AML. These preclinical models would require development and validation before testing CD33-targeting agents in pediatric indications.
**Next Steps**

In summary, although CD33-targeting ADCs show a range of effectiveness in patients with differing levels of CD33 expression, CD33 is a moderate-to-high priority target because of the potential for preclinical studies in other therapy modalities, such as BiTE and CAR T-cell therapies. In addition, targeting CD33 has shown efficacy in many adult cases of AML, which has historically been difficult to treat.
Appendix A: Feedback and Next Steps

The next COACH meeting will occur on December 1, 2023, from 9:00 am to 1:00 pm ET. Meeting participants will discuss three targets: human epidermal growth factor receptor 2 (HER2), chemokine receptor 8 (CCR8), and TEA domain transcription factor 1 (TEAD1). For the final COACH meeting in March 2024, Ms. Murza and Dr. Adam will contact participants to determine whether discussions will be about the next top 3 targets or a different set of targets.

Next, Ms. Murza reviewed the COACH program to facilitate a discussion about whether the program should be renewed and potentially modified after the final meeting in March 2024. Meeting participants agreed that the consolidation of information for each target has been informative, especially for industry partners and FDA determining preclinical studies and data that may be needed to develop an initial pediatric study plan. However, multiple participants suggested that future iterations of COACH focus on novel targets that lack clinical and preclinical data, which may better guide the development of preclinical studies. Dr. Adams encouraged meeting participants to discuss the value of COACH with their teams and will send a formal survey to collect feedback on the future direction of COACH.

Lastly, Dr. Adam provided an overview of the previously planned ACT4PEDS program, which aimed to form public-private partnerships that would unify efforts in pediatric preclinical testing. ACT4PEDS planned 8 essential tasks:

- Developing a unified catalogue of existing preclinical pediatric models
- Harmonizing data standards
- Enhancing data commons
- Analyzing target feasibility
- Developing new murine models with similar goal as PIVOT
- Forming a strategic advisory committee with similar goals as COACH
- Establishing a high-throughput in vitro testing platform
- Testing specific agents at established partnership sites

Dr. Adams requested that meeting participants consider whether pediatric preclinical testing and therapeutic development would benefit from a program similar to ACT4PEDS. To better assess interest in the program, meeting participants recommended contacting new stakeholders, rather than those who were previously uninterested.
Appendix B: Bibliography


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