European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

REVIEW ARTICLE OPEN

Check for updates

Clinical pharmacology insights from recent cell and gene therapy approvals relevant to pediatrics

Sahana Kunanayagam[1,2,10], Michelle C. Wang[1,2,10], Catrina M. Loucks[3,4,5], Facundo Garcia-Bournissen[6], Ruud H. J. Verstegen[1,7,8] and Tamorah Lewis[1,2,8,9]✉

The United States Food and Drug Administration has approved 44 cell and gene therapies as of May 2025, including 14 for pediatric use (excluding cord blood). This signifies an advancement in the treatment of diseases and conditions that, as of yet, cannot be effectively managed with available small-molecule drugs and therapeutic proteins. This review explores the pharmacokinetic and first-in-human dosing considerations unique to cell and gene therapies. For in vivo gene therapies, development considerations include vector shedding and biodistribution. Traditional pharmacokinetic principles do not apply to ex vivo gene therapies, given the modification of cells outside the body before re-infusion. Cellular kinetics such as expansion and persistence are relevant in cell therapies like Chimeric Antigen Receptor T cells and Tumor Infiltrating Lymphocytes. A common trend of cell and gene therapy development is the reliance on preclinical models to inform safety, efficacy, and dose selection, with first-in-human dosing further guided by data from related therapies. Rare disease and pediatric drug development present additional challenges due to small patient populations, emphasizing the importance of preclinical evidence and safety considerations. The article outlines the key considerations for cell and gene therapies that are vital for expanding their use.

Pediatric Research; https://doi.org/10.1038/s41390-026-05138-6

IMPACT:

- This article provides a synthesis of pediatric rare disease clinical pharmacology considerations for recently approved cell and gene therapies, highlighting how advanced therapeutic products compare with traditional pharmacokinetic and pharmacodynamic frameworks used for small-molecule drugs.
- The development of advanced therapeutics depends on preclinical modeling, first-in-human dosing strategies, clinical trial design, and regulatory guidance for pediatric use, emphasizing the need for a practical primer on emerging advanced therapeutic products for researchers.

INTRODUCTION

As of May 2025, the United States (U.S.) Food and Drug Administration (FDA) has approved 44 cell and gene therapies, reflecting a major shift in the treatment of diseases that are inadequately managed by traditional pharmacological agents, such as small molecules or therapeutic protein drugs.[1] Other international regulatory authorities, such as the European Medicines Agency (EMA) and Health Canada (HC), have similarly approved advanced therapies. Several approved therapies are indicated for rare diseases affecting pediatric populations, providing life-saving treatments and the potential for lifelong benefits. Specifically, 14 of the FDA approved therapies are indicated for pediatric use (excluding cord blood). In this review, the approved list of therapies is used to outline development considerations.

Small-molecule drugs are chemically synthesized, and therapeutic proteins are biologics produced by living systems.[2] In contrast, gene therapies act by delivering or editing genetic material, and cell therapies rely on the transplantation of cells.[3,4] Approved gene therapies include both in vivo and ex vivo delivery systems, and approved cell therapies include Chimeric Antigen Receptor T cells (CAR-T cells), Tumor Infiltrating Lymphocytes (TILs), and pancreatic islet cells. The approved advanced therapies are summarized with their indication and year of approval in Supplementary Table S1. Approvals of cell and gene therapies began in 2010 with a burst between 2021 and 2024 (Fig. 1), and the ongoing approvals show an upward trajectory.

Cell and gene therapies are becoming more relevant and important in the treatment of rare diseases. Rare diseases are

[1]Division of Clinical Pharmacology and Toxicology, Department of Paediatrics, The Hospital for Sick Children, Toronto, ON, Canada. [2]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada. [3]Division of Translational Therapeutics, Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. [4]Department of Anesthesiology, Pharmacology & Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. [5]BC Children's Hospital Research Institute, Vancouver, BC, Canada. [6]Division of Pediatric Clinical Pharmacology, Department of Paediatrics, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada. [7]Division of Rheumatology, Department of Paediatrics, The Hospital for Sick Children, Toronto, ON, Canada. [8]Department of Paediatrics, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [9]Division of Neonatology, Department of Paediatrics, The Hospital for Sick Children, Toronto, ON, Canada. [10]These authors contributed equally: Sahana Kunanayagam, Michelle C. Wang. ✉email: tamorah.lewis@sickkids.ca

Received: 24 October 2025 Revised: 26 March 2026 Accepted: 6 May 2026
Published online: 03 June 2026

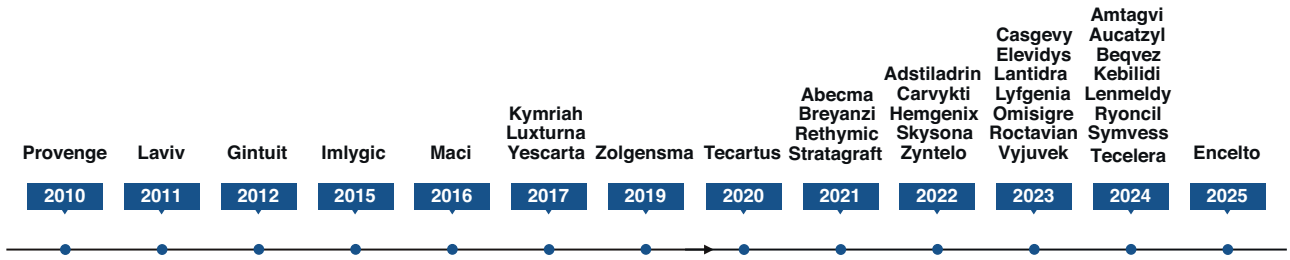

Fig. 1 Timeline of approvals. The timeline demonstrates the FDA approval dates of the listed advanced therapies through the years beginning in 2010. The timeline excludes cord blood product approvals. A large portion of approvals occurred from 2021 to 2024. Created with BioRender.com.[81]

defined as those that affect less than one in 2000 Canadians (0.05%), and in the United States as impacting less than 200,000 of the U.S. population (around 0.06%).[5] Approximately 80% of rare diseases have a genetic basis, making them potential candidates for gene therapies.[5] Several rare diseases for which gene therapies have been developed, including hemophilia B and cerebral adrenoleukodystrophy (CALD), manifest early in life, thus highlighting the importance of pediatric-focused cell and gene therapy development.[5] Therapeutic development for pediatric rare diseases introduces distinct considerations driven by physiological differences between children and adults, and ethical challenges. Cell and gene therapy clinical trials come with their own sets of unique considerations (ethical and scientific), and specific regulatory guidelines, and this complexity can be exacerbated by the enrollment of pediatric populations. The clinical development of advanced therapies is complex, and this is further intensified in pediatric populations, particularly in first-in-human (FIH) trials where higher risk profiles must be carefully managed.

In terms of clinical pharmacology, cell and gene therapies require specific pharmacological considerations. The science of clinical pharmacology encompasses both the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug in humans.[6] PK is the study of the body's effects on the drug and the changes to the drug concentration due to the body's function, while PD is the study of the mechanism of action of the drug and its effects on the body. While early-phase clinical trials traditionally emphasize dosing, PK, and safety, the risks (e.g., immune reactions) associated with cell and gene therapies require early investigation of efficacy alongside these safety risks.[6]

This review aims to inform and orient research teams of the pharmacological nuances associated with these advanced therapies, with a focus on pediatric applications. To do this, this review explores evidence from early clinical trials and regulatory requirements to identify key considerations such as the PK parameters investigated, as well as the rationale for selecting FIH dosing and the types of data (preclinical and clinical), which inform early development decisions.

PEDIATRIC RARE DISEASE CLINICAL TRIALS

Pediatric rare disease trials are subject to specific expectations and guidelines, due to safety concerns of advanced therapeutics as well as the complexity and vulnerability of pediatric patients.[7] Due to ethical considerations, novel cell and gene therapy clinical trials do not always involve a typical placebo and are often open-label.[8] Additionally, clinical trials may combine phase 1 and 2 due to the limited recruitment of participants, given the small affected population.[8] Parental health and research literacy, and the ability to understand and provide informed consent, are of paramount importance in pediatric rare disease trials with novel therapies.[7] Research teams have a responsibility to teach parents about these new therapeutics during research interactions. Additionally, research protocols must minimize risks by limiting the number and volume of blood draws.[7] The ethical justification for studying novel therapeutic studies in children can include the lack of existing treatments, the availability of supportive preclinical models, and/or existing adult data.[9]

To account for varying physiology and small participant numbers, research teams incorporate physiologically-based pharmacokinetics (PBPK) modelling to inform dosing decisions and provide greater insight before initiating FIH trials. PBPK models are used to predict the distribution of both viral vectors and the transgene products of gene therapies throughout the body to improve trial design and conduct.[10] Pediatric drug development and clinical trials also differ from adult-focused approaches due to the differences in physiology.[11] For instance, elimination pathways such as kidney function are still maturing in children, particularly in the earliest stages of life.[11] The rapid change in organ maturation affecting clearance could be important in therapies such as in vivo gene therapy, where vector components are excreted via the urine.[12] Vector materials can be filtered through the kidneys to some extent.[12] With immature renal function, the clearance of in vivo gene therapy may be impaired leading to potential vector accumulation in pediatric patients.

It is also important to account for unique disease presentation and disease progression in pediatric patients. Pediatric physiology is especially relevant when choosing validated efficacy and safety measures, and these considerations must be explained in detail during both research interactions and obtaining informed consent.[7,9] Pediatric dosing strategies for small molecules are typically extrapolated from safe and efficacious adult doses.[7,9] However, cell and gene therapies targeting pediatric patients rely on preclinical models to guide dosing. The use of preclinical models to develop FIH pediatric and adult doses are discussed in more detail in the following sections.

TRADITIONAL PHARMACOKINETIC CONSIDERATIONS – DO THEY APPLY TO CELL AND GENE THERAPIES?

In small-molecule drug development, several traditional PK concepts are routinely investigated to understand the drug exposure in the body. Important PK parameters include maximum concentration (Cmax), time to maximum concentration (Tmax), Area Under the Curve of the concentration versus time curve (AUC), and half-life ($t_{1/2}$).[6,13] These parameters reflect the absorption, distribution, metabolism, and elimination of the drug.[13] Figure 2 illustrates how these PK parameters relate to the concentration versus time curve of orally administered small molecule drugs.[6] In contrast, cell and gene therapies do not typically follow the same pharmacokinetic principles. While some terminology overlaps such as Cmax, these terms often refer to different biological processes.

Investigating drug concentrations over time, typically generated from serial blood draws, can elucidate elimination rates, clearance, and the overall drug exposure quantified by the AUC.[6] Clearance refers to the process of eliminating the drug, where reduced clearance can lead to drug accumulation and toxicity, while excessive clearance may result in reduced efficacy.[13] PK variability

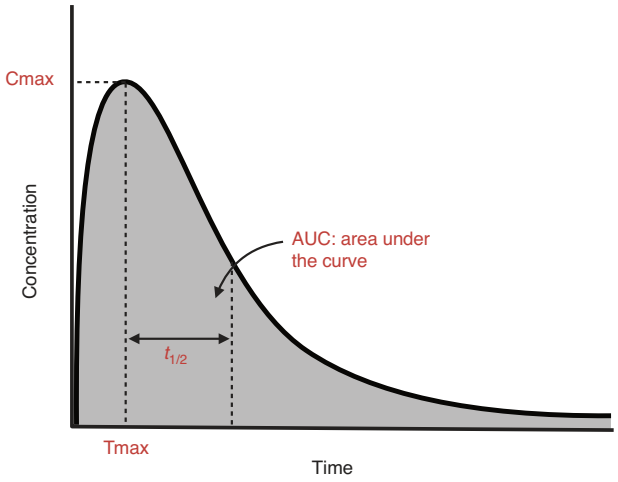

Fig. 2 Pharmacokinetic terms and concepts. Important pharmacokinetic parameters are displayed in a concentration versus time curve. The maximum concentration (Cmax) indicates the peak concentration reached following dosing. The time to maximum concentration (Tmax) indicates the time after dosing at which the peak Cmax is achieved. The Area Under the Curve (AUC) indicates the overall exposure to the therapy. The half-life ($t_{1/2}$) indicates the time it takes for a reduction of half of the plasma concentration. Created with BioRender.com.[81]

between individuals can be due to a plethora of factors such as age, co-administration of medications, comorbidities, and genetic variability.[13] Understanding PK is essential in designing clinical trials and some comparisons can be drawn between small molecule and cell and gene therapy pharmacokinetics are discussed in later sections.

GENE THERAPY

Gene therapies represent the most abundant class of advanced therapeutics approved to date (Fig. 3). Out of the 14 approved pediatric cell and gene therapies, ten are gene therapies. Such therapies are commonly indicated for rare genetic diseases that manifest early in life. For example, Zolgensma is approved for spinal muscular atrophy in patients under 2 years of age.[14] Kebilidi is indicated for aromatic L-amino acid decarboxylase (AADC) deficiency, approved in both adult and pediatric populations.[15,16] The growing number of approved gene therapies reflects their expanding role in treating pediatric genetic diseases and underscores the importance of increased understanding about these types of therapies by pediatric research teams and pediatric clinicians.

Gene therapies involve the delivery of a transgene into cells to provide a functional gene copy or repair a mutated gene.[17] Delivery methods commonly involve the use of a viral vector such as adeno-activated viruses (AAVs) and lentiviruses. Viral vectors allow the entry of a gene or components that modify a gene into the patient's cells.[17] Some gene therapies are delivered in vivo, meaning viral vectors containing the transgene or editing components are delivered to the patient, while others are delivered ex vivo, meaning patients'cells are collected and modified using viral vectors outside of the body before re-introduction.[18] Gene addition introduces a gene into cells, either by integration into the host genome or episomal expression (i.e., outside the genome).[3,18] In contrast to gene addition, gene editing introduces targeted changes to DNA sequences by causing breaks and insertions.[18]

Traditional PK considerations apply primarily to in vivo gene therapies, where a viral vector is administered to the patient. In contrast, because ex vivo gene therapy involves cell modification in the laboratory before cell infusion, traditional PK concepts are less applicable.[17] The success of gene therapies is often monitored by measuring the expression levels of the gene product.[17] The PK considerations for these two types of gene therapies are discussed in detail in the following sub-sections.

In vivo gene therapies

In vivo gene therapy pharmacokinetics vs. small molecule pharmacokinetics. In vivo gene therapies do not follow traditional small molecule PK; instead, their PK is determined by viral vector behavior.[17] Three important characteristics of the vector behavior include the biodistribution, vector persistence, and shedding.[17] Biodistribution refers to the movement of the viral vector in the body, similar to the distribution of small molecule drugs (Table 1).[6,17] This is typically assessed in animal models to investigate where and to what extent the vector distributes and accumulates, where the liver and spleen are common distribution sites.[17] Small molecule distribution refers to the movement of the drug throughout the body, often quantified by the volume of distribution, describing drug presence in the plasma and/or periphery (Table 1).[6] In contrast, the biodistribution of viral vectors is described in terms of organ-specific volumes. Unlike the traditional parameter of drug elimination for small molecules, vector shedding describes the excretion of viral material into bodily fluids such as urine, saliva, and feces and is typically measured using quantitative polymerase chain reaction (qPCR). Shedding generally follows a biphasic trend, with an initial rapid excretion in the first few days post-infusion, followed by a slower decline and persistence that can continue for months.[17,19] Factors influencing vector shedding include the dose, the type of viral vector, and patient factor(s); such as age and existing immunity.[17] Monitoring vector shedding is important from a safety perspective, as it informs the risk of transmission to other people via contact with bodily fluids.[19] While small molecule elimination encompasses all processes of drug removal, vector shedding refers to the release of viral materials (Table 1).[19] Highlighting these comparisons helps to contextualize gene therapies relative to the familiar PK concepts from small molecule research, and can help research teams feel comfortable with novel therapeutics. For example, PK studies of Beqvez, an in vivo gene therapy for Hemophilia B, use non-human primates and observe AAVRh74va vector localization in the liver and spleen.[20] The clearance of the vector materials over time is also evaluated by measuring levels in the saliva and urine, with vector shedding reported for up to 1 to 4 months post-adminstration.[20] Although Beqvez is not approved for pediatric use, it exemplifies the important preclinical investigations conducted in the development of in vivo gene therapies.

In vivo gene therapy First-In-Human (FIH) dosing. Most approved gene therapies as of May 2025 are delivered in vivo (10/15).[1] Approved pediatric in vivo gene therapies include: Kebilidi (AADC deficiency), Elevidys (Duchenne Muscular Dystrophy), Luxturna (retinal pigment epithelium 65 (RPE-65)-associated inherited retinal dystrophies), Vyjuvek (Dystrophic Epidermolysis Bullosa), Zolgensma (Spinal Muscular Atrophy).[1] In vivo gene therapies involve unique FIH considerations, as physiological differences in pediatric patients influence vector biodistribution, viral vector choice, immune response, and dose selection. In vivo therapies commonly employ AAVs that are modified to reduce immunogenicity and enable tissue-specific targeting via capsid proteins.[17] AAV serotype selection depends on the capsid and impacts tissue transduction.[1,19] For example, AAV2 is used in Luxturna for efficient delivery to retinal epithelial cells.[17,21,22] In pediatric patients, immature adaptive immune systems may reduce the chance of pre-existing anti-vector antibodies and minimize the immune response.[23] In addition, organ size in younger patients will influence biodistribution and the levels at the target organ.[23]

FIH dose selection for in vivo gene therapy is informed by

preclinical models and is required by regulatory agencies.[24] The models must be selected to reflect human biology and immune responses, as they inform both safety and efficacy.[24] Preclinical models investigate the No Observed Adverse Effect Level (NOAEL), representing the highest dose where no adverse events are witnessed in the animal model, which informs starting doses through the application of safety margins.[17] In some cases, prior clinical data from similar gene therapies also contribute to dose selections.[17] Vector dosing is commonly expressed and applied as vector genomes per kilogram (vg/kg), although weight does not account for the non-linear nature of organ growth and maturation in children.[23] Therefore, it is important to consider both body weight and organ size in pediatric dosing.

Approved in vivo gene therapies have employed a combination of methods for informing FIH dosing regimens. We discuss Kebilidi, an in vivo gene therapy that delivers a functional copy of the dopa decarboxylase (DDC) gene into the putamen of the brain using a specialized SmartFlow device.[15,25] Kebilidi treats AADC deficiency, a rare pediatric disease that results in a clinical phenotype similar to Parkinson's disease.[16] The FIH dose of Kebilidi was selected based on preclinical non-human primate Parkinson's disease models, with dose escalations starting from up to 5×10^{11} vector genomes per hemisphere to assess tolerability, biodistribution, shedding in the spinal cord, and transgene expression.[25,26] Kebilidi biodistribution and shedding occur in the spinal cord, putamen, and other brain regions where the gene is most active.[15] Subsequent Parkinson's phase I adult trials identified the highest dose (3×10^{11} vector genomes) as associated with improved AADC expression, which was ultimately selected for pediatric evaluation.[27,28] Similarly, Zolgensma dosing was derived from preclinical mouse studies, where the maximum tolerated dose was identified and translated to infants with a 1.4-fold safety margin.[29]

Additional examples of approved in vivo gene therapies and their FIH doses are provided in Supplementary Table S2. These examples demonstrate how preclinical models inform starting doses in clinical trials. Figure 4a summarizes the preclinical and dose-finding evaluations and the associated go/no-go decision points used to advance in vivo therapies toward FIH studies.

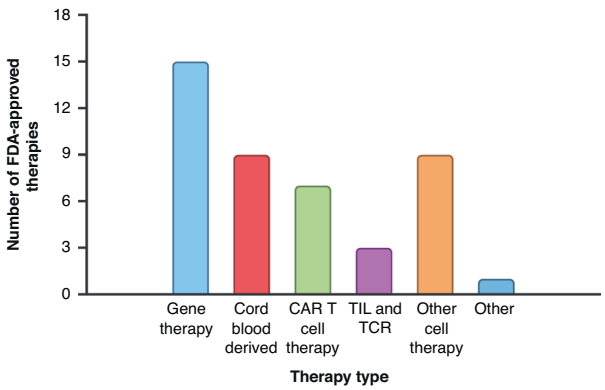

Fig. 3 Trends in the approved cell and gene therapies. The number of approved therapy types across therapeutic categories. Tumor Infiltrating Lymphocytes (TIL) and T Cell Receptors (TCR), Chimeric Antigen Receptor (CAR)-T cells. Therapies in the "Other Cell Therapy" category includes: Encelto, Gintuit, Lantidra, Laviv, Maci, Omisigre, Rethymic, Ryoncil, and Stratagraft. Therapies in the "Other" category include acellular tissue engineered vessel-tyod, which is an acellular tissue. Created with BioRender.com.[81]

Ex vivo gene therapies

Ex vivo gene therapies differ significantly from in vivo gene therapies in terms of PK, given that cells are treated with the vector "ex vivo" following cell collection.[30] The few approved ex vivo gene therapies for pediatric use include Casgevy (Sickle Cell Disease), Lenmeldy (Metachromatic Leukodystrophy), Skysona (Cerebral Adrenoleukodystrophy), Zyntelgo (Beta Thalassemia), and Lyfgenia (Sickle Cell Disease), all of which utilize lentiviral vectors for gene delivery.[1,31–33] Lentiviruses can deliver genes to dividing and non-dividing cells, an important feature in ex vivo gene therapy using hematopoietic stem cells.[34] The determination of FIH doses in approved ex vivo therapies primarily used prior established hematopoietic stem cell transplant studies to inform dosing decisions, given that these therapies often rely on CD34+ cells.

A review by Jillela and Ustun reaffirms that a minimum of 2.5×10^6 CD34+ cells/kg is required for cell engraftment in stem cell transplants, with improved engraftment at 5×10^6 CD34+ cells/kg.[35] As a result, FIH dose selections for pediatric ex vivo gene therapies fall within this range. For example, the FIH dose of Casgevy, a CRISPR-Cas9 -based gene editing therapy that activates γ-globin expression in CD34+ hematopoietic stem cells, was informed by historical hematopoietic stem cell transplant data with a dose of approximately 3×10^6 cells/kg.[31,36] Skysona, an approved pediatric ex vivo gene therapy for cerebral adrenoleukodystrophy (CALD), also had an FIH dose informed by the 2.5×10^6 cells/kg minimum dose.[37,38] Zyntelgo, an ex vivo gene therapy for beta thalassemia, based its FIH dose on the Jillela and Ustun recommendation and uses a dose of $\geq 3.0 \times 10^6$ CD34+ cells/kg.[39] In pediatric populations, the minimum engraftment threshold serves as a baseline while higher doses are associated with improved engraftment. As a result, many pediatric trials define target doses above the minimum.[40] Figure 4b provides a stepwise diagram of key considerations and decision points in the selection of cell doses for ex vivo therapy.

CELL THERAPY

Cell therapies involve the transplantation of live cells into a patient with therapeutic intent. Cell therapy types range from T cells, stem cells, and tissue-specific cells, such as islet cells and thymus cells.[41] Among FDA-approved therapies, there are also various cord blood products that are derived from umbilical blood and are indicated for various blood-related diseases or treatments.[1] Cord-blood-derived stem cell transplantation falls outside the scope of this review due to highly variable patient-specific dosing and non-standard pharmacology (Fig. 3). The following section focuses on the PK and FIH dosing considerations in approved CAR-T cell therapies, Tumor Infiltrating Lymphocytes (TILs), T Cell Receptors (TCR), and other cell therapies (Fig. 3).[1,41] Importantly, the PK considerations and FIH dose selection are cell-type specific.[41] Additionally, the FIH trials are typically single-armed studies focused on safety due to the potential risk of immune-mediated reactions.[42] As the field of cell therapies continues to expand, understanding the unique PK and FIH strategies provides essential context for trial conduct.

Table 1. A comparison of small molecule pharmacokinetics and gene therapy pharmacokinetics terms.

Small molecule pharmacokinetic term	Gene therapy pharmacokinetic term
"elimination" (units: h^{-1})	"vector shedding" (units: vector genome/mL or vg/mg)
"volume of distribution" (units: L/kg)	"biodistribution" (units: vg/ μg gDNA or vg/mg)

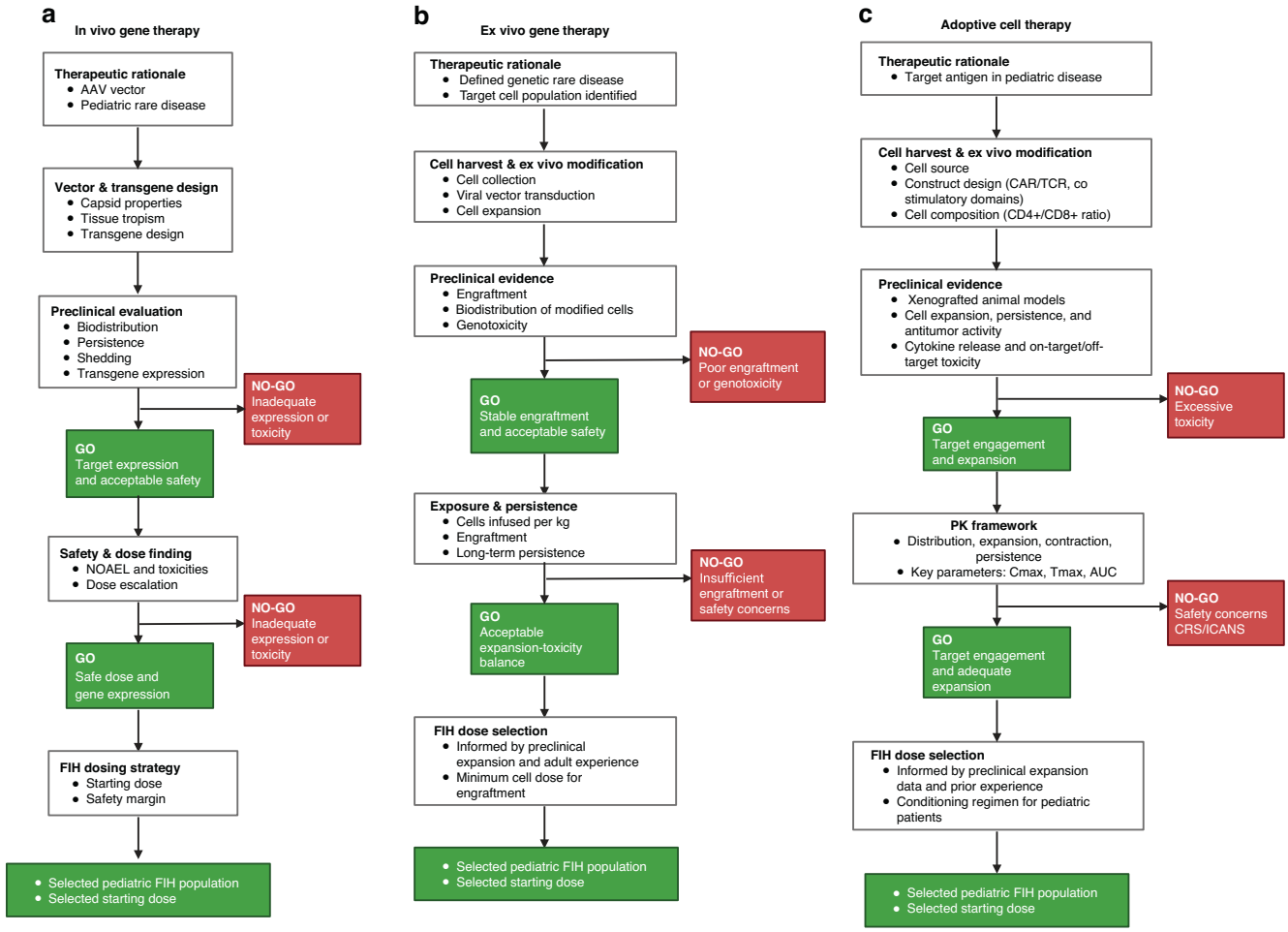

Fig. 4 Decision Flowchart for First-in-Human Cell and Gene Therapy Development. a In vivo gene therapy development with key go/no-go decisions informing FIH dosing. **b** Ex vivo gene therapy development with key go/no-go decisions guiding cell dose selection. **c** Adoptive cell therapy (CAR-T, TILs, TCR) development with key go/no-go decisions supporting FIH dosing. Created with Lucid (lucid.co) and BioRender.com.[81]

CAR-T cell therapy

CAR-T cell pharmacokinetics vs. small molecule pharmacokinetics. All currently approved CAR-T therapies are autologous, meaning the cells are collected from the patient with ex vivo introduction of Chimeric Antigen Receptor (CAR) into the T cells.[42,43] This therapeutic approach combines cell therapy and ex vivo gene therapy.[42] CAR-T cell PK shares some terminology with traditional small molecule PK, such as Cmax, Tmax, and AUC (Table 2); however, the terms refer to cellular kinetics.[6,42,44] CAR-T cells undergo distribution, expansion, contraction, and persistence (Table 2).[44] CAR-T cell levels and the PK parameters are often determined by using qPCR or flow cytometry.[45] The distribution phase represents cells circulating through the body.[44,46] The expansion phase describes T cell proliferation following antigen recognition and cytokine signalling.[44,46] In CAR-T therapy, the Cmax corresponds to the peak of T cells in circulation, occurring during the expansion phase.[44] The Tmax is the time to peak expansion, often observed around 12 days post-infusion, based on CAR-T trials.[46,47] The AUC captures 0 to 28 days to observe the kinetic phases, including expansion and early persistence, while also providing a feasible assessment window.[44,47]

Expansion kinetics are key to both efficacy and safety assessments. For example, high Cmax values may be associated with improved therapeutic response, but may also increase the risk of toxicities such as cytokine release syndrome (CRS).[46,48] Following expansion, the contraction phase reflects a decline in cell levels due to apoptosis, similar to the elimination phase in small molecule PK.[42,44] The persistence phase represents a reduced population of cells that remain detectable for months to years, analogous to memory T cells.[42,46]

Emerging evidence in pediatric populations suggests that CAR-T cell expansion and persistence may be enhanced compared to adults, with higher Cmax values and prolonged persistence.[49,50] The differences in cellular kinetics are likely influenced by differences in pediatric tumor microenvironments and immune systems.[50]

In clinical development, CAR-T cell PK assessments routinely include Cmax, Tmax, and AUC values and are required by regulatory agencies. Understanding these dynamics helps in optimizing dosing and managing safety.

CAR-T cell First-in-Human (FIH) dosing. Approved CAR-T cell therapies primarily target CD19 or BCMA with differences in the co-stimulatory molecules, such as CD28 or 4-1BB .[42,44,51] For example, Kymriah and Yescarta are examples of CD19-directed therapies, while Abecma and Carvykti are BCMA-directed. .[44,52–55] All currently approved CAR-T cell therapies are indicated for hematologic malignancies (e.g., various lymphomas, leukemias, myelomas). Among these, Kymriah is the only CAR-T therapy approved for pediatric use. To understand dosing, it is important to first understand the cellular and therapeutic design of this type of cell therapy. Structurally, CAR-T receptors are composed of an

Table 2. The relevant PK parameters and phases of CAR-T Cell Therapy.

PK Parameter	Description
Cmax	The maximum concentration of CAR-T cells is, typically achieved following the expansion phase.
Tmax	The time at which the maximum concentration of CAR-T cells.
AUC $_{0–28\ days}$	The Area Under the Curve from day 0 to day 28 following infusion.
Phases	**Description**
Distribution	Initial CAR-T cell movement through the body.
Expansion	CAR-T cell proliferation following antigen recognition and cytokine signalling
Contraction	Decline in cell levels due to apoptosis.
Persistence	Sustained CAR-T cell presence at low levels for months to years.

antigen-binding segment targeted to the specific tumor antigen, the hinge and transmembrane domain responsible for transducing the signal, and co-stimulatory domains to enhance activation.[46] CAR-T cell therapy first involves the collection of both CD4+ and CD8 + T cells, ex vivo genetic modification and expansion, and chemotherapy in the recipient patient to create space for the new incoming cells and the therapeutic cell infusion.[51] The ratio of CD8+ and CD4+ T cells is an important parameter, as CD8+ cytotoxic T cells are responsible for cytotoxicity and CD4+ helper T cells facilitate the immune function.[42] Dosing for CAR-T therapies is often expressed as total cells or cells/kg. FIH dose selection integrates both preclinical studies and prior clinical experience with similar therapies. For instance, Kymriah's pediatric trials are informed by anti-leukemic activity in the xenografted mouse models and adult clinical trial data.[56,57] The selected FIH dose ranges from 1×10^7 to 1×10^9 cells per infusion.[57] Similarly, Yescarta dosing is informed by early dose-escalation studies of CD19-directed CAR-T in a small cohort of patients that evaluated cell expansion and tumor response.[58] Supplementary Table S3 summarizes FIH dosing and approved doses across several CAR-T therapies, highlighting a consistent reliance on preclinical xenografted animal models and early clinical data.[51] Figure 4c provides an outline of important steps and decision points in the development of cell therapies.

Pediatric-specific considerations are key in CAR-T dosing. Children are observed to have greater Cmax values compared to adults, which is suggested to be due to their greater proportion of naïve T cells and proliferative capacity.[59] In addition, pediatric patients have greater persistence of CAR-T cells than adult patients.[57,59] The differences in cellular kinetics can require longer follow-up and monitoring compared to adult trials.[57] A pattern emerges across CAR-T therapies where preclinical data serve as a foundation for FIH dose selections, supplemented by findings from prior trials of different CAR-T constructs.

Tumor Infiltrating Lymphocytes (TIL) and T Cell Receptor (TCR) Therapy

TIL and TCR therapies share PK characteristics with CAR-T therapies, including parameters such as cellular expansion, Cmax, contraction, and persistence. AUC is also used to quantify the duration and amount of cell presence, offering a measure of overall exposure over time by flow cytometry.[60,61] TILs are tumor-directed autologous immune cells that are collected, expanded, and reintroduced to target cancer cells.[62] In contrast, TCRs are the result of engineering patients' T cells with tumor-specific TCRs directed toward cancer antigens presented by the major histocompatibility complex (MHC).[62] This distinguishes TCRs from MHC-independent CAR-T cells.[62] Currently, no TILs and TCRs are approved for pediatric use, though future pediatric trials may expand access. Dosing strategies are expressed as cells/kg, allowing for modification based on patient size, which is relevant to pediatric patients. Similar to CAR-T therapies, TILs and TCRs may exhibit greater expansion in children due to the immaturity of the immune system.[63]

PK assessments often prioritize understanding the expansion and persistence of TILs and TCRs. For example, Amtagvi, a TIL therapy, demonstrates peak cell levels approximately 4 days post-infusion and expansion, followed by a decline and detectable persistence observed a year later.[64] Tecelra, a TCR therapy targeting MAGE-A4, reports a single Cmax value and multiple AUC values (AUC from 0 to 7 days, 0 to 28 days, 0 to 3 months, and 0 to 6 months), highlighting the importance of extended monitoring.[61] These AUC evaluations contrast the shorter time-frames often used in CAR-T cell evaluations.

FIH dosing is informed by a preclinical xenografted mouse model, where high doses were tolerable, thus guiding translational dosing in humans.[60] As highlighted, the shared features between TILs, TCRs, and CAR-T therapies facilitate a more unified approach in understanding PK and FIH dosing in these therapies (Fig. 4c).

Other Cell Therapies

Other cell therapies encompass a diverse group of allogenic (derived from a donor rather than the patient) cell therapies with unique mechanisms of action and indications. Unlike genetically engineered therapies, these therapies often require tailored PK and FIH dosing strategies. Three cell therapies approved in pediatric populations are Omisirge, Ryoncil, and Rethymic. Ryoncil, a mesenchymal stromal cell (MSC) therapy, is indicated for steroid-refractory acute graft-versus-host disease (GVHD) in children older than 2 months of age, and demonstrates how dosing strategies are often translated from adult trials.[65] The phase 3 pediatric trial adopted a dosing regimen of 2×10^6 cells/kg twice a week based on adult trial dosing, demonstrating optimal responses.[66] This illustrates how adult dosing data can guide pediatric applications, with appropriate adaptation based on weight, immune system maturity, and clinical response.

SAFETY CONSIDERATIONS

A key consideration in cell and gene therapy development is the unique safety profiles of these therapies. These advanced therapies involve the delivery of genetic materials via viral vectors and cellular infusions, each presenting risks to patients (e.g. immune toxicity/immune reactions).[42,67] Gene therapies are often associated with immune reactions triggered by viral materials, which can cause inflammatory syndromes or reductions in maximal drug effect through inflammation-related or antibody-mediated clearance.[67] Immune-mediated reactions can cause inflammation and flu-like symptoms, and may lead to premature clearance of vectors before gene delivery.[67,68] In vivo gene therapies face additional challenges with the presence of antibodies against the viral vector materials, which can compromise treatment efficacy.[67,68] Preclinical animal models often fail to

predict the complexity of the human immune response, adding a factor of uncertainty to FIH trials.[68] As a result, close monitoring of immune-related events is important. Because of these limitations in the animal models, close monitoring of immune-related events in early-phase human trials is an important goal.[68] Another significant safety consideration is the risk of insertional mutagenesis, in which integrating vectors can alter gene expression in the host genome.[67] This raises concern about potential changes in tumor-suppressor and/or proto-oncogene expression and their contribution to the pathogenesis of cancer.[67,68] Non-integrating vectors, such as AAV vectors, are used to mitigate this risk and offer a better safety profile.

In CAR-T cell therapy, cytokine release syndrome (CRS) is a major safety concern.[42,69] CRS relates to the inflammatory immune reaction characterized by increased cytokine release.[42,69,70] The abundance of cytokines can become serious, if uncontrolled, leading to organ damage due to ongoing inflammation.[42,69] The emergence of CRS symptoms can be used in defining the therapeutic index and is often evaluated in relation to the Cmax. Immune effector cell-associated neurotoxicity syndrome (ICANS), another safety concern, can be caused by cytokines crossing the blood-brain barrier or by infused cells entering neural spaces and attacking cells in the brain.[70] ICANS presents with confusion, encephalopathy, and seizures.[42,70] While CRS typically appears shortly after treatment, ICANS can occur later in the treatment course or follow-up.[42,70] It is common for steroids to be used in the treatment of CRS and ICANS to suppress immune responses.[42] Monitoring for adverse events and symptoms related to immune responses is essential, particularly in pediatric populations. Pediatric patients are especially vulnerable to inflammation-mediated organ injury, making safety an essential part of trial design and execution.

REGULATORY GUIDANCE

Regulatory guidance from agencies such as the FDA, EMA, and HC is used when designing and conducting clinical trials for cell and gene therapies (Supplementary Table S4). These guidance documents outline key considerations for ensuring safety, efficacy, and ethical compliance. The FDA emphasizes the importance of safety monitoring, given the unique risks associated with cell and gene therapies.[71] Agencies like the FDA require supporting preclinical animal studies, though it acknowledges the limitations of animal models, such as differences in immune responses.[71] It is also recommended that maximum tolerated doses be employed in early trials to better assess efficacy.[71] Early trials in cell and gene therapies involve patients with disease, in contrast to early-phase small molecule trials that often include healthy individuals.[71] For CAR-T cell therapies, the FDA provides specific guidance on detailed PK reporting, where it is recommended that the Cmax, Tmax, the last concentration of CAR-T cells obtained (Clast), and the AUC are reported.[72] Similarly, the EMA and HC have guidelines that address cell and gene therapies.[73,74] EMA documents emphasize the importance of biodistribution studies, preclinical justification, and safety and efficacy monitoring.[74] HC also addresses the conduct of trials, including dosing considerations, ethical nuances, distinctions between FIH trials and expanded trials, and PK studies.[73] Across all three agencies, there is a consistent focus on preclinical justification, safety evaluations, and careful translation to FIH trials. In addition, the FDA, EMA, and HC have dedicated guidance documents regarding drug development with pediatric indications. These guidance documents emphasize the ethical and methodological considerations when conducting research in pediatric patients (Supplementary Table S4). These resources serve as useful tools in orienting and informing researchers navigating through cell and gene therapy development.

FUTURE DIRECTIONS

As cell and gene therapies evolve, challenges related to dosing, trial design, and cost are being met with innovative approaches, including PBPK modelling.[44] PBPK modelling is a mathematical model of the pharmacokinetics of therapies that can incorporate a wide range of time-varying physiological factors.[46] PBPK modelling can include patient or disease-specific variables, providing insight into dosing predictions.[75] This approach is emerging in rare disease research, where patient populations are smaller.[8,30,70] PBPK models can be used to inform FIH dosing in early trials.[8] For example, PBPK models are used to characterize key PK phases such as expansion and contraction.[46] In pediatric populations, PBPK models are typically adapted from adult data and incorporate age-specific physiological parameters such as organ maturation and enzyme activity.[76] The model can be used to better inform FIH dosing in this vulnerable population and guide more precise dosing. PBPK models can help predict cell distribution to organs with different doses, particularly the central nervous system, which is relevant to ICANS risk.[46] One study combined physiological data from mice and humans to create a PBPK model to predict the distribution of CAR-T cells to solid tumors.[77] The study demonstrated that xenografted mouse models showed strong target localization in comparison to human models, underscoring the potential of animal models to misinform[77] The study suggests integrating models into dosing translation to reduce the reliance on animal models.[77] The use of PBPK models can help relieve the reliance on, and ambiguity associated with, preclinical animal models to suggest the PK of cell or gene therapy.

Beyond modelling and dosing, cost remains a challenge in the use of cell and gene therapies.[5] These therapies are notoriously expensive, often hundreds of thousands or even millions of dollars per dose.[5,78] This is partly due to the costs associated with development, given that several advanced therapies are patient-specific and/or use viral vectors.[78] This is exemplified by Pfizer's discontinuation of Beqvez in early 2025 because of limited use driven by high costs and narrow eligibility criteria.[79,80] Pfizer also admitted to discontinuing viral vector-related gene therapy research, citing their cost.[80] The high cost of these advanced therapies remains an obstacle and requires attention to improve accessibility.[78]

CONCLUSION

Cell and gene therapies introduce distinct pharmacological considerations primarily driven by the vector distribution and shedding for gene therapies and cellular kinetics. Across cell and gene therapies, FIH dosing is consistently informed by a combination of preclinical models, prior clinical experience, and established practices such as transplantation-based dosing. In pediatric populations, additional considerations such as immune system maturity and physiological differences influence PK and dose selection. This review fills a gap by consolidating and highlighting essential pharmacological considerations in pediatric cell and gene therapy research. As these advanced therapies emerge as treatments for rare diseases, clinicians and researchers alike must become familiar with their unique pharmacology considerations.

REFERENCES

1. Approved Cellular and Gene Therapy Products. *Approved Cellular and Gene Therapy Products* https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products (2025).
2. Biologicals. https://www.who.int/health-topics/biologicals#tab=tab_1.
3. Sayed, N. et al. Gene therapy: Comprehensive overview and therapeutic applications. *Life Sci.* **294**, 120375 (2022).
4. Chancellor, D., Barrett, D., Nguyen-Jatkoe, L., Millington, S. & Eckhardt, F. The state of cell and gene therapy in 2023. *Mol. Ther.* **31**, 3376–3388 (2023).

5. Building a National Strategy for High-Cost Drugs for Rare Diseases: A Discussion Paper for Engaging Canadians. *Building a National Strategy for High-Cost Drugs for Rare Diseases: A Discussion Paper for Engaging Canadians* https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement/discussion-paper.html (2023).
6. Posner, J. Clinical pharmacology: the basics. *Surgery* **30**, 174–180 (2012).
7. Shakhnovich, V., Hornik, C. P., Kearns, G. L., Weigel, J. & Abdel-Rahman, S. M. How to Conduct clinical trials in children: a tutorial. *Clin. Transl. Sci.* **12**, 218–230 (2019).
8. Ahmed, M. A. et al. Unlocking the mysteries of rare disease drug development: a beginner's guide for clinical pharmacologists. *Clin. Transl. Sci.* **18**, e70215 (2025).
9. Laetsch, T. W., DuBois, S. G., Bender, J. G., Macy, M. E. & Moreno, L. Opportunities and challenges in drug development for pediatric cancers. *Cancer Discov.* **11**, 545–559 (2021).
10. Liu, S. et al. Whole-body disposition and physiologically based pharmacokinetic modeling of adeno-associated viruses and the transgene product. *J. Pharm. Sci.* **113**, 141–157 (2024).
11. Batchelor, H. K. & Marriott, J. F. Paediatric pharmacokinetics: key considerations. *Br. J. Clin. Pharm.* **79**, 395–404 (2015).
12. Agarwal, S. et al. Blood biodistribution and vector shedding of valoctocogene roxaparvovec in people with severe hemophilia A. *Blood Adv.* **8**, 4606–4615 (2024).
13. Lai, Y. et al. Recent advances in the translation of drug metabolism and pharmacokinetics science for drug discovery and development. *Acta Pharmac, Sin. B* **12**, 2751–2777 (2022).
14. Zolgensma. https://www.fda.gov/vaccines-blood-biologics/zolgensma (2025).
15. Kebilidi. https://www.fda.gov/vaccines-blood-biologics/kebilidi (2024).
16. Pearson, T. S. et al. AADC deficiency from infancy to adulthood: Symptoms and developmental outcome in an international cohort of 63 patients. *J. Inherit. Metab. Dis.* **43**, 1121–1130 (2020).
17. Sun, K. & Liao, M. Z. Clinical pharmacology considerations on recombinant adeno-associated virus–based gene therapy. *J. Clin. Pharma.* **62**, S79-S94 (2022).
18. Volodina, O. & Smirnikhina, S. The future of gene therapy: a review of in vivo and ex vivo delivery methods for genome editing-based therapies. *Mol. Biotechnol.* **67**, 425–437 (2025).
19. Ghosh, S., Brown, A. M., Jenkins, C. & Campbell, K. Viral vector systems for gene therapy: a comprehensive literature review of progress and biosafety challenges. *Appl. Biosaf.* **25**, 7–18 (2020).
20. Beqvez. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/beqvez (2024).
21. Hemgenix. https://www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix (2023).
22. Luxturna. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna (2022).
23. Simon, A. K., Hollander, G. A. & McMichael, A. Evolution of the immune system in humans from infancy to old age. *Proc. R. Soc. B.* **282**, 20143085 (2015).
24. Conlon, T. J. & Mavilio, F. The pharmacology of gene and cell therapy. *Mol. Ther. - Methods Clin. Dev.* **8**, 181–182 (2018).
25. A Study of SmartFlow Magnetic Resonance (MR) Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Participants. https://clinicaltrials.gov/study/NCT04903288 (2025).
26. Forsayeth, J. R. et al. A dose-ranging study of AAV-hAADC therapy in Parkinsonian monkeys. *Mol. Ther.* **14**, 571–577 (2006).
27. Mittermeyer, G. et al. Long-term evaluation of a phase 1 study of AADC gene therapy for Parkinson's disease. *Hum. Gene Ther.* **23**, 377–381 (2012).
28. Chien, Y.-H. et al. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. *Lancet Child Adolesc. Health* **1**, 265–273 (2017).
29. Mendell, J. R. et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. *JAMA Neurol.* **78**, 834–841 (2021).
30. Kamiya, H., Akita, H. & Harashima, H. Pharmacokinetic and pharmacodynamic considerations in gene therapy. *Drug Discov. Today* **8**, 990–996 (2003).
31. Casgevy. https://www.fda.gov/vaccines-blood-biologics/casgevy (2024).
32. Lenmeldy. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/lenmeldy (2025).
33. Lyfgenia. https://www.fda.gov/vaccines-blood-biologics/lyfgenia (2024).
34. Bulcha, J. T., Wang, Y., Ma, H., Tai, P. W. L. & Gao, G. Viral vector platforms within the gene therapy landscape. *Sig Transduct. Target Ther.* **6**, 53 (2021).
35. Jillella, A. P. & Ustun, C. What is the optimum number of $CD34^{+}$peripheral blood stem cells for an autologous transplant? *Stem Cells Dev.* **13**, 598–606 (2004).
36. Frangoul, H. et al. CRISPR-Cas9 gene editing for sickle cell disease and β-Thalassemia. *N. Engl. J. Med* **384**, 252–260 (2021).
37. Eichler, F. et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *N. Engl. J. Med* **377**, 1630–1638 (2017).
38. Skysona. https://www.fda.gov/vaccines-blood-biologics/skysona (2024).
39. Thompson, A. A. et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. *N. Engl. J. Med.* **378**, 1479–1493 (2018).
40. Ferrua, F. et al. Lentiviral haemopoietic stem/progenitor cell gene therapy for treatment of Wiskott-Aldrich syndrome: interim results of a non-randomised, open-label, phase 1/2 clinical study. *Lancet Haematol.* **6**, e239–e253 (2019).
41. El-Kadiry, A. E.-H., Rafei, M. & Shammaa, R. Cell therapy: types, regulation, and clinical benefits. *Front Med.* **8**, 756029 (2021).
42. Kast, J. et al. Recent advances and clinical pharmacology aspects of Chimeric Antigen Receptor (CAR) T-cellular therapy development. *Clin. Transl. Sci.* **15**, 2057–2074 (2022).
43. Human Gene Therapy for Rare Diseases. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-rare-diseases (2020).
44. Tegenge, M. A., Wang, X., Liu, J., Zhu, H. & Fashoyin-Aje, L. A. FDA Experience on CAR T Cell Pharmacokinetics/Pharmacodynamics and Model-Based Assessments. *Clin. Pharma. Ther.* https://doi.org/10.1002/cpt.3703 (2025).
45. Maryamchik, E., Gallagher, K. M. E., Preffer, F. I., Kadauke, S. & Maus, M. V. New directions in chimeric antigen receptor T cell [CAR-T] therapy and related flow cytometry. *Cytom. Part B Clin.* **98**, 299–327 (2020).
46. Qi, T., McGrath, K., Ranganathan, R., Dotti, G. & Cao, Y. Cellular kinetics: A clinical and computational review of CAR-T cell pharmacology. *Adv. Drug Deliv. Rev.* **188**, 114421 (2022).
47. Singh, A. P. et al. Bench-to-bedside translation of chimeric antigen receptor (CAR) T cells using a multiscale systems pharmacokinetic-pharmacodynamic model: A case study with anti-BCMA CAR-T. *CPT Pharm. Syst. Pharma* **10**, 362–376 (2021).
48. Wang, Z. & Han, W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomark Res.* **6**, 4 (2018).
49. Mueller, K. T. et al. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. *Blood* **130**, 2317–2325 (2017).
50. Ghorashian, S. et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat. Med.* **25**, 1408–1414 (2019).
51. Mc Laughlin, A. M., Milligan, P. A., Yee, C. & Bergstrand, M. Model-informed drug development of autologous CAR-T cell therapy: Strategies to optimize CAR-T cell exposure leveraging cell kinetic/dynamic modeling. *CPT Pharm. Syst. Pharma* **12**, 1577–1590 (2023).
52. Kymriah. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah (2025).
53. Yescarta. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta (2025).
54. Abecma. https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel (2025).
55. Carvykti. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/carvykti (2025).
56. Milone, M. C. et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol. Ther.* **17**, 1453–1464 (2009).
57. Maude, S. L. et al. Tisagenlecleucel in children and young adults with b-cell lymphoblastic leukemia. *N. Engl. J. Med* **378**, 439–448 (2018).
58. Porter, D. L., Levine, B. L., Kalos, M., Bagg, A. & June, C. H. Chimeric antigen receptor–modified T cells in chronic lymphoid leukemia. *N. Engl. J. Med* **365**, 725–733 (2011).
59. Martínez-Gamboa, D. A. et al. CAR T-cell therapy landscape in pediatric, adolescent and young adult oncology – A comprehensive analysis of clinical trials. *Crit. Rev. Oncol. /Hematol.* **209**, 104648 (2025).
60. Sanderson, J. P. et al. Preclinical evaluation of an affinity-enhanced MAGE-A4-specific T-cell receptor for adoptive T-cell therapy. *Oncoimmunology* **9**, 1682381 (2020).
61. Tecelra. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecelra (2024).
62. Harris, D. T. & Kranz, D. M. Adoptive T cell therapies: a comparison of t cell receptors and chimeric antigen receptors. *Trends Pharm. Sci.* **37**, 220–230 (2016).
63. Metts, J. et al. Expansion of tumor-infiltrating and marrow-infiltrating lymphocytes from pediatric malignant solid tumors. *Cytotherapy* **27**, 29–35 (2025).
64. Amtagvi. https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/amtagvi (2024).
65. Ryoncil. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/ryoncil (2025).
66. Kurtzberg, J. et al. A Phase 3, single-arm, prospective study of Remestemcel-L, ex vivo culture-expanded adult human mesenchymal stromal cells for the treatment of pediatric patients who failed to respond to steroid treatment for acute graft-versus-host disease. *Biol. Blood Marrow Transpl.* **26**, 845–854 (2020).
67. Tang, R. & Xu, Z. Gene therapy: a double-edged sword with great powers. *Mol. Cell Biochem* **474**, 73–81 (2020).

68. McNally, E. M. Improving the safety of systemic viral gene therapy. *J. Clin. Invest* **134**, e177078 (2024).
69. Shimabukuro-Vornhagen, A. et al. Cytokine release syndrome. *J. Immunother. Cancer* **6**, 56 (2018).
70. Kirouac, D. C., Zmurchok, C. & Morris, D. Making drugs from T cells: The quantitative pharmacology of engineered T cell therapeutics. *npj Syst. Biol. Appl.* **10**, 31 (2024).
71. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal (2020).
72. Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products (2024).
73. Guidance documents: Biologics, radiopharmaceuticals, cell and gene therapies. *Guidance documents: Biologics, radiopharmaceuticals, cell and gene therapies* https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents.html.
74. Guidelines relevant for advanced therapy medicinal products. https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview/guidelines-relevant-advanced-therapy-medicinal-products.
75. Johnson, T. N., Small, B. G. & Rowland Yeo, K. Increasing application of pediatric physiologically based pharmacokinetic models across academic and industry organizations. *CPT Pharmacomet. Syst. Pharm.* **11**, 373–383 (2022).
76. Verscheijden, L. F. M., Koenderink, J. B., Johnson, T. N., De Wildt, S. N. & Russel, F. G. M. Physiologically-based pharmacokinetic models for children: Starting to reach maturation? *Pharmacol. Ther.* **211**, 107541 (2020).
77. Brown, L. V., Gaffney, E. A., Ager, A., Wagg, J. & Coles, M. C. Quantifying the limits of CAR T-cell delivery in mice and men. *J. R. Soc. Interface* **18**, 20201013 (2021).
78. Rouce, R. H. & Porteus, M. H. Cell and gene therapy accessibility. *Science* **385**, 475–475 (2024).
79. Pfizer halts Hemophilia B gene therapy. https://www.bleeding.org/news/pfizer-discontinues-beqvez-hemophilia-b-gene-therapy (2025).
80. Opportunities lie with Beqvez Discontinutation. https://blogs.bmj.com/medical-ethics/2025/04/03/opportunities-lie-within-beqvezs-discontinuation/ (2025).
81. Biorender. https://BioRender.com.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of the RareKids-CAN Network Clinical Trial Operations and Coordinating Hub (CTOCH). In particular, we thank Breanne Stewart and Yunna Bystrova at RareKids-CAN and the Maternal Infant Child and Youth Research Network (MICYRN) for their guidance and support of this project. We also extend our sincere thanks to the broader RareKids-CAN community for their ongoing contributions to advancing pediatric rare disease research.

AUTHOR CONTRIBUTIONS

S.K.: Conceptualization and design, wrote the manuscript, assisted in revising the manuscript, and approved the final version of the manuscript. M.C.W: Conceptualization and design, wrote the manuscript, assisted in revising the manuscript, and approved the final version of the manuscript. C.M.L.: Assisted in revising the manuscript and approval of the final version of the manuscript version. F.G.B.: Assisted in revising the manuscript and approval of the final version of the manuscript version. R.H.J.V.: Assisted in revising the manuscript and approval of the final version of the manuscript version. T.L.: Conceptualization and design, wrote the manuscript, assisted in revising the manuscript, and approved the final version of the manuscript.

FUNDING

This work was supported by the RareKids-CAN: Pediatric Rare Disease Clinical Trials and Treatment Network, funded by the Canadian Institutes of Health Research (CIHR) Institute of Genetics (192262). CML receives salary support from the Michael Smith Health Research BC Scholar program.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-026-05138-6.

Correspondence and requests for materials should be addressed to Tamorah Lewis.