PentaHibe® – A safe cryoprotectant for advanced cell therapies

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Peer-reviewed by Dr. Anthony E. Maida, III, Ph.D., MA, MBA, BA, BA
Clinical Research – Translational Medicine who assessed that:

"Given the referenced publications above and other source data, including over 30 years' experience in multiple laboratories, preclinical and clinical studies in cellular therapy; one of which was a 10-year study delivery cell therapy to patients with tumors to the CNS, I endorse the use of this technology as a promising substitute for DMSO or in much lower concentrations of DMSO thereby eliminating the toxicity and loss of cellular function and viability. It would be, however, appropriate to continue to monitor clinical safety and efficacy in future studies."

Introduction

Adult stem cells and CAR-T cells are increasingly used in transfusion medicine and cell-based therapies, where cells are mostly cryopreserved beforehand. It is important, therefore, that the cryoprotectant preserves cell viability and function after thawing and meets rigorous safety requirements. Today, 10% DMSO based cryopreservation formulations remain the most widely used. However, DMSO is associated with several limitations, including cytotoxic effects that can reduce post-thaw cell recovery and cause adverse reactions in patients during infusion. These challenges underscore the need for safer, less toxic cryopreservation formulations.

Pentaisomaltose, the cryoprotective agent in PentaHibe®, is a non-penetrating cryoprotective agent that eliminates DMSO or enables its significant reduction while maintaining high cell viability and function post-thaw. Chemically, pentaisomaltose is equivalent to a low-MW dextran. Since pentaisomaltose and related low MW dextrans belong to the same substance class, their safety and performance data can be assessed collectively.

This White Paper, therefore, summarises preclinical toxicology, clinical safety data, and cryopreservation performance results across pentaisomaltose and low-MW dextrans to provide an overview of the scientific knowledge relevant to PentaHibe®. The primary focus is the safety profile of pentaisomaltose as a cryoprotective agent, which is shown to be strong, and supports its use in the cryopreservation of human cells for advanced therapeutic applications.

Only high-level findings are presented here; the full toxicology and safety report, including complete datasets, are available upon request.

Key messages

1. Demonstrated safety across many animal species and humans

Extensive preclinical toxicology studies and clinical data show that pentaisomaltose is well tolerated at high single and repeated intravenous doses, with no serious safety concerns.

2. No evidence of immunological, developmental, or genetic risk

Across animal studies, pentaisomaltose shows no anaphylactic potential, no developmental toxicity, and no mutagenic effects, supporting a strong safety profile.

3. Rapid renal elimination ensuring predictable clearance

Pentaisomaltose is cleared rapidly and completely through the kidneys within 12–24 hours, consistent with the favourable pharmacokinetics of low-MW dextrans.

4. Proven cryoprotective efficacy with multiple human cell types

Pentaisomaltose yields high post-thaw viability and function in HPCs, MSCs, and T cells – matching or outperforming 10% DMSO-based formulations.

5. A safe, effective, and less toxic alternative to high-DMSO formulations

With strong safety data and high cryopreservation performance, pentaisomaltose offers a meaningful alternative to 10% DMSO-based formulations, with reduced toxicity associated with high DMSO concentrations.

Preclinical safety studies

The safety of low-MW dextrans, including pentaisomaltose, has been well-established through preclinical studies that consistently showed a favourable safety profile. These compounds were cleared from the body within hours, primarily through renal excretion, and did not accumulate in tissues, as opposed to higher-MW dextrans, whose elimination was slower; this predictable feature supports the low-risk profile of low-MW dextrans [1,2]. Across sensitisation models, low MW dextrans were not associated with anaphylactic or allergic reactions, and their smaller molecular size was linked to a lower likelihood of immunological responses [3,4]. In studies evaluating general tolerability, both single and repeated intravenous doses of low-MW dextran were well tolerated in multiple animal species, even when administered at levels many folds higher than those expected in clinical use. Only mild and transient findings were observed at the highest exposure levels [5,6]. Reproductive and genetic toxicity assessments further support this safety profile: developmental studies showed no harmful effects on pregnant animals or their offspring, and genotoxicity assays demonstrated no evidence of mutagenic or clastogenic potential [7].

Clinical studies

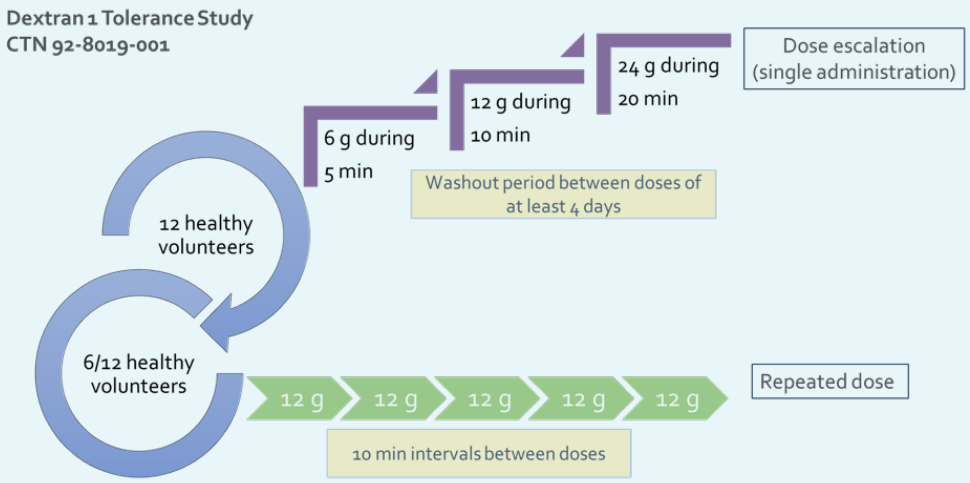
Clinical studies confirmed a favourable safety profile of low-MW dextran.

In a tolerance study (Figure 1), 12 healthy volunteers received single doses of 6 g, 12 g, or 24 g of the low-MW dextran equivalent to pentaisomaltose. The 8 adverse events reported were mostly mild and considered either unlikely or probably unrelated to treatment.

Repeated-dose administration was also well tolerated: in the same study, 6 healthy volunteers received 5 consecutive 12 g doses at 10-minute intervals, with no adverse events reported during or after dosing.

Similar findings were reported in another clinical study investigating the pharmacokinetics of the low-MW dextran (Figure 2), in which 8 healthy volunteers received single doses of 3 g, 6 g, or 12 g low-MW dextran. Again, all 7 adverse events were mild and assessed as unlikely related (3 events), not assessed (2 events), or possibly related (2 events: *menorrhagia [pain and bleeding more than usual]*).

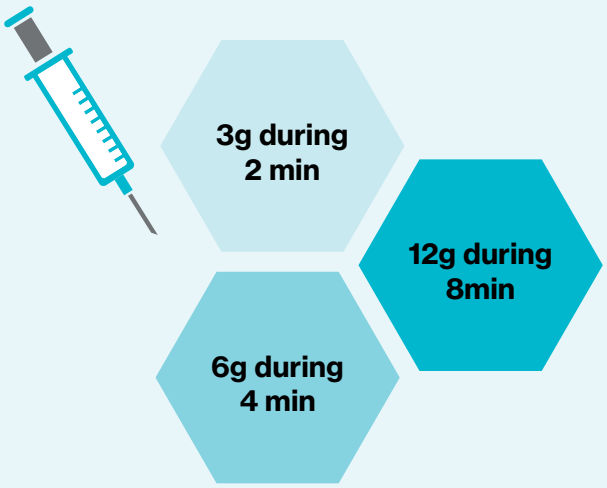
Figure 1
Clinical tolerance study design



In both studies, a mild dilution effect of some blood values e.g., haemoglobin was observed in some subjects, as well as a temporary increase in urine output, which are known and expected pharmacological responses to low-MW dextrans and were not considered clinically significant.

In conclusion, low-MW dextrans, including pentaisomaltose, were well tolerated in animals and humans and were rapidly cleared from the body, supporting a favourable safety profile. Their small size limits immunological reactions and prevents tissue accumulation. In addition, they act extracellularly without introducing intracellular toxicity. This solid safety foundation supports the suitability of low-MW dextran as a cryoprotective agent for advanced cell therapies.

Figure 2
Pharmacokinetic clinical study design



All doses administered in a randomised fashion

Washout period between doses = at least 4 days

From Safety to Performance – Preclinical Evidence for Pentaisomaltose Effectiveness as a Cryoprotective Agent

Preclinical efficacy studies

Haematopoietic stem cells

Pentaisomaltose (16%) and 10% DMSO showed comparable performance for post-thaw survival and *in vitro* function of human HPCs recovered from apheresis products, with similar recovery of viable human CD34+ progenitor cells, colony forming capacity, and haematopoietic potential to produce cells of the myeloid and erythroid lineages [8,9]. HPCs also showed similar engraftment potential in immunodeficient NSG mice, yielding comparable levels of human CD45+ cells in peripheral blood at 8 weeks and in bone marrow at 16 weeks after transplantation (Figure 3), as well as similar frequencies of myeloid and lymphoid cells within the human CD45+ population in the bone marrow [9].

Mesenchymal stem cells

Adipose tissue-derived human MSCs cryopreserved in pentaisomaltose supplemented with a reduced level of DMSO (10% pentaisomaltose with 2% DMSO) showed comparable post thaw performance to cells cryopreserved in 10% DMSO. Viability and overall recovery remained high (~95% and 90–94%, respectively) [10]; the cells retained their phenotype and their ability to undergo adipogenic and chondrogenic differentiation. Cell functions including migration and proliferation were also similar between the two cryoprotectants, showing that pentaisomaltose-based formulations maintain similar MSC quality and function to conventional DMSO-based formulations [10].

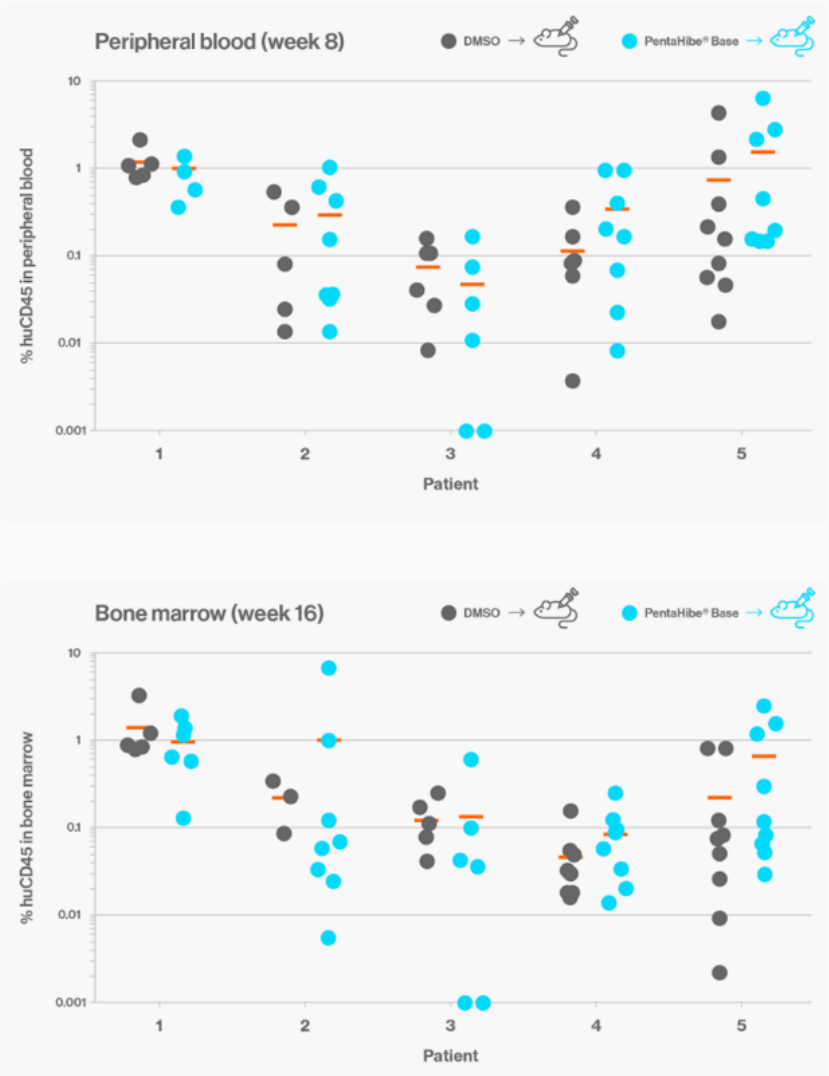
T cells

T cells cryopreserved in 10% pentaisomaltose with 2% DMSO showed improved performance compared with cells cryopreserved in 10% DMSO (Figure 4) [11]. Immediately after thawing, mean viability was higher with the pentaisomaltose-based formulation

(mean ± SD: 92.3% ± 4.3%) than with 10% DMSO (69.5% ± 17.9%), and this separation was maintained in the first 6 hours post-thawing, during which 10% DMSO had a significantly higher cell death compared to pentaisomaltose with 2% DMSO. Recovery of viable T cells was not significantly different for the two cryoprotectants: 100.7% ± 6.8% for pentaisomaltose with 2% DMSO and 70.0% ± 17.4% for 10% DMSO (Figure 4).

Functional readouts also favoured the pentaisomaltose with 2% DMSO formulation, which yielded a higher proportion of proliferating T cells (87.9% ± 7.1% versus 72.9% ± 12.5%, p=0.039) and demonstrated the strongest chemotaxis potential, outperforming 10% DMSO and other tested formulations. These findings support the use of pentaisomaltose with low DMSO concentrations as an effective alternative for T cell cryopreservation.

Figure 3
Engraftment of CD34+ cells cryopreserved in pentaisomaltose or DMSO in mice (Svalgaard J.D. 2018)



CD = cluster of differentiation; DMSO = dimethyl sulfoxide; PentaHibe® Base = 16% pentaisomaltose.

Conclusions

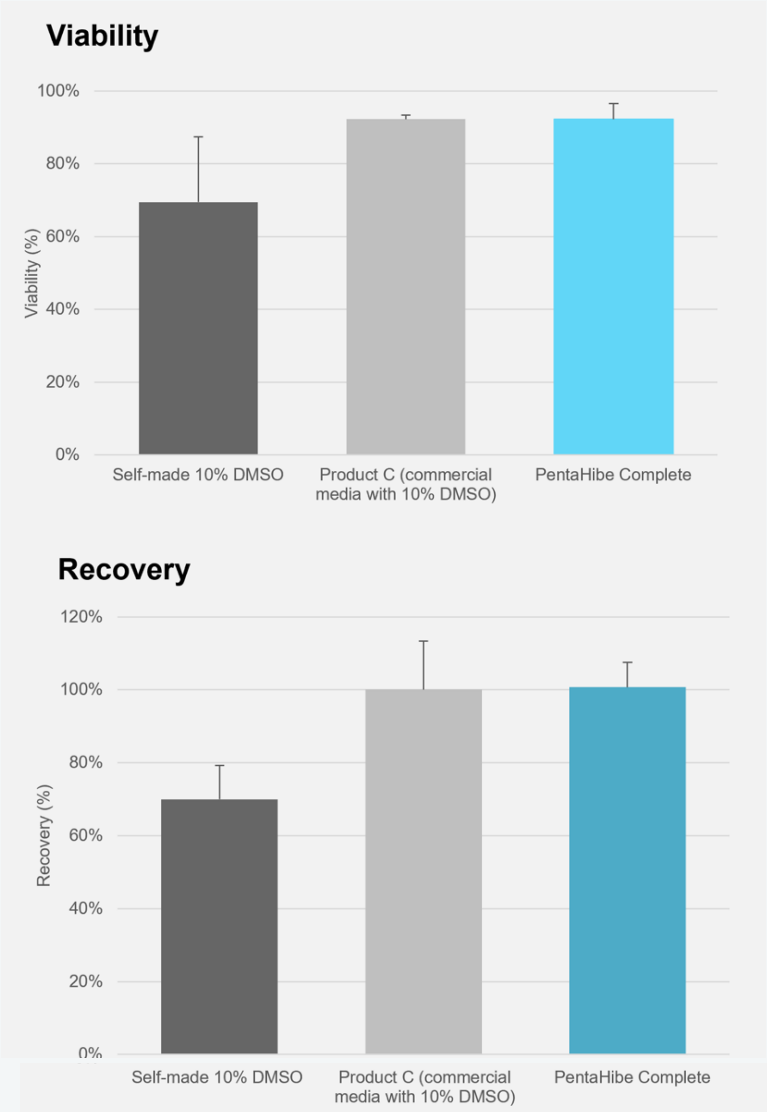
Low-MW dextran (equivalent to pentaisomaltose) was well tolerated by healthy volunteers following both single and repeated dosing. Potential side effects – such as reduced haemostasis, dilution of some blood values e.g., haemoglobin, and increase in urine volumes and creatinine clearance – were mild and not a safety concern. Importantly, low-MW dextran was rapidly and completely cleared from serum within 12–24 hours via renal elimination.

Across animal studies, low-MW dextran demonstrated a strong safety profile, with no evidence of anaphylactic, teratogenic, or mutagenic potential under either single or repeated dosing conditions.

Pentaisomaltose also showed high cryoprotective performance, with comparable or superior results to 10% DMSO in the cryopreservation of human HPCs, adipose-derived MSCs, and T cells, as measured in post-thaw viability and recovery, phenotype preservation and cell differentiation capacity, and cell functions such as proliferation and chemotaxis.

Collectively, these findings highlight pentaisomaltose as a safe, effective, and less toxic alternative to conventional DMSO-based cryopreservation approaches and strongly support its use for the cryopreservation of human cells intended for cell-based therapies.

Figure 4
Viability and recovery of T cells after cryopreservation in pentaisomaltose or DMSO (Haastrup E.K. 2021)



DMSO = dimethyl sulfoxide; PentaHibe® Complete = 10% pentaisomaltose with 2% DMSO.

Abbreviations

CAR = chimeric antigen receptor; CD = cluster of differentiation; DMSO = dimethyl sulfoxide; HPC = haematopoietic progenitor cells; MSC = mesenchymal stem cells; MW = molecular weight; NSG = NOD scid gamma; SD = standard deviation.

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