Review Article *Open Access*

Journal of Clinical Oncology & Advanced Therapy

ISSN: 3070-3786

DOI: doi.org/10.63721/26JCOAT0122

L-Tryptophan Depletion Bioreactor Integrated in the Inuspheresis System for Therapy of Cancer, Autoimmune Diseases, and Dementia

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Citation: *Rolf Bambauer, Philip Mavberg, Ralf Schiel, Richard Straube (2026) L-Tryptophan Depletion Bioreactor Integrated in the Inuspheresis System for Therapy of Cancer, Autoimmune Diseases, and Dementia. J of Clin Onco & Adv Thpy 2(2), 01-06. WMJ/JCOAT-122*

Abstract

A variant of double-membrane filtration, Inuspheresis, uses two different second-membrane filters. One of the second hollow fibers is the IN-30 lipid filter for lipid apheresis, and the other is the TKM58 filter for the therapy of autoimmune, inflammatory, environmental, and other diseases. A new bioreactor that contains immobilized tryptophan side-chain oxidase, which degrades L-tryptophan, will be integrated into the Inuspheresis system to treat all diseases with foreign tissue buildup. L-tryptophan is an essential amino acid and must be brought to the organism with the food. The human cell cannot build up L-tryptophan. L-tryptophan is one of the most important nutrients for foreign tissue growth, especially for cancer cells. The tryptophan side-chain oxidase can therefore be used as therapy for cancer forms, autoimmune diseases with antibodies, demenrtia disease with tau proteins, and others.

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Submitted: 30.05.2026 **Accepted**: 04.06.2026 **Published**: 15.06.2026

Keywords: L-tryptophan, L-Tryptophan Side-Chain Oxidase, Bioreactor, Antitumor Enzyme, Cancer, Autoimmune, Dementia

Introduction

The Inuspheresis, a further-developed variant of the cascade filtration or double-membrane filtration system, has been in use since 2015 [1]. The system consists of two hollow fiber modules connected in parallel, each with a different sieving coefficient. The first hollow fiber module completely separates blood cells from plasma. Two different second hollow fiber modules are available: IN-30-Lipidfilter for the separation of atherogenic lipoproteins and the TKM58 for the separation of inflammatory mediators, circulating immune complexes, protein- or lipid-bound

environmental toxins, and other toxic substances from the plasma. The second hollow fiber membrane modules are adapted to a special hardware system. In more than 70,000 documented treatments, the side-effect rate was only 0.7%.

For the second hollow fiber, two options are available: the IN-30 lipid filter and the TKM58 hollow fiber. The IN-30-lipid filter has optimal porosity for elimination of atherogenic lipoproteins (lipid apheresis) and is indicated for progressive atherosclerotic cardiovascular disease (ASCVD). In a multicenter study over 12 years under regular lipoprotein apheresis (LA), a 78 % reduction of severe cardiovascular events per year could be observed (from 0.27 to 0.06 events per patient per year. For every patient, reductions of 66 - 68% in LDL-cholesterol and 67 - 68% in lipoprotein (a) could be achieved [2].

The other hollow fiber TKM58 with modified porous growth for the selective removal of the following substance classes:

- Inflammatory mediators, tumor necrosis factor alpha (TNF-α), Interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen.
- Circulating immunocomplexes, autoantibodies.
- Protein- and/or lipid-bound environment toxins, such as heavy metals, microplastics, per- and polyfluorinated alkyl substances (PFAS), pesticides, and organic solution substances.

Further pathologic substances that could be reduced by double-membrane filtration include rheumatoid factor, oxidized LDL-cholesterol, alpha-2-macroglobulin, autoantibodies against connective tissue, vascular, nerve, and muscle tissues, and paraproteins.

Nutritional diseases, xenobiotics, air pollution, infections, and psychosocial stress are important for the development of chronic inflammatory diseases. Environmental chemicals, such as softening agents, pesticides, heavy metals, microplastics, and mercury, are associated with diseases [3]. To prove the presence of heavy metals and microplastics in atherosclerotic plaques, combined with a correlation to higher plaque instability, demonstrates the importance of eliminating these toxins [4]. Microplastics trigger cellular inflammation and oxidative stress and can bind to lipoproteins, PFAS, and other toxins [5]. The resulting high inflammatory parameters, such as interleukin-6, CRP, and fibrinogen, are a direct risk factor for ASCVD progression.

The Inuspheresis follows the laws of thermodynamics about the elimination and redistribution of complex substances and proteins over time [6]. The special nature of the body's nested compartments must be considered here. Each compartment is connected. The depth of the compartments is the surface area and the volume of space. The compartments are connected linearly, whereas the lymphatic system is connected in parallel, meaning that toxins move through the lymphatic system and "circulate" until they can be released through special repeated treatments. Inuspheresis must be repeated to treat complex, dysregulated metabolic processes, which is why an "initial reaction" also occurs. This is only a redistribution process between compartments, involving the dissolution of pathopeptides and other substances from their compartments [7]. To minimize this process, a further treatment must be followed as soon as 48 hours after the initial treatment, depending on the clinical situation. 24 hours must be observed between the two treatments to allow harmful substances to be released from the body cells or to pass into the next compartment through the cell membrane regeneration processes. These reactions show the effectiveness of Inuspheresis [6].

One of the most important effects of Inuspheresis is the improvement of the rheology of the blood and the reduction of pro-inflammatory and rheologically active molecules such as alpha-2 macroglobulin and pro-inflammatory oxidized lipoproteins. The improvement of the hemorheology is followed by a supply of oxygen to the tissues [8,9]. After Inuspheresis treatment, an improvement in the oxygen partial pressure in damaged tissues is observed. The C-reactive protein, as an independent cardiovascular and organ-toxic risk factor, can also be reduced by at least 50 % per session [1]. Under Inusphersis therapy, the level of certain drugs could be reduced, such as protein-bound drugs and monoclonal antibodies; this must be coordinated with the therapy regimen, and the dose could be increased.

Vascular access for a venovenous procedure is used. Only in severe cases is a central venous access indicated, such as a large-bore catheter in the internal jugular or subclavian vein. In intensive care units, this procedure is also used as a life-saving treatment with low rates of side effects [1]. The treatment frequency can comprise 40–50 treatments over a period of up to two years for all

non-intensive care patients with severe and complex clinical diseases. To restore patients to a clinically stable condition, leading to regeneration and recovery, first two, then 4 – 6 treatments are given at intervals of 6 – 8 weeks. The average treatment frequency does not differ from those for rheumatoid arthritis or dilated cardiomyopathy.

For each patient, the plasma volume is calculated precisely. Blood flow and plasma flow rate are adjusted to the patient´s condition, height, body weight, and hematocrit. The decisive factor is always the patient´s clinical condition on the day the therapy is administered, according to which the necessary and patient-adapted treatment is determined daily. The side-effect rate of Inuspheresis treatments is reported to be 0.7% in more than 70,000 documented treatments. The most 90 of them are mild orthostatic dysregulations, and only some are allergic reactions [1].

In many autoimmune diseases, the removal of circulating immune complexes is necessary because circulating immune complexes accumulate in chronically deregulated production and lead to severe chronic inflammatory organ damage, especially to the nervous system and kidneys. In one or some double filtration treatments, antibodies are completely reduced, such as rheumatoid antibodies, rheumatoid factor, oxidized LDL, lipoprotein (a), fibrinogen, alpha-2-macroglobulin, autoantibodies against connective tissue, vascular, nerve, and muscle structure, mover-regulated interleukin, circulating immune complexes, paraproteins, abnormal haptens consisting of heavy metals/solvents, nanoparticles, and virus particles such as hepatitis C and HIV.

The indications of Inuspheresis are chronic central fatigue syndrome, multiple chemical sensitivity (MCS), toxic-induced immune tolerance loss syndrome, toxic-induced polyneuropathy, multiple sclerosis, chronic Lyme disease, micro/nanoparticle exposure with subsequent silent inflammation, disease of the rheumatoid spectrum, and autoimmune diseases in dermatology. Inuspheresis is the preferred indication in new chronic temporal diseases, such as chronic nervous system disease. The immune tolerance loss syndrome, a genetically based detoxification disorder associated with micro/nanoparticle exposure syndrome, is a multisystemic disease, including Alzheimer´s and Parkinson´s disease, and multiple sclerosis [10]. Table 1 shows the substances that can be eliminated with Inuspheresis systems.

Table 1: Substance Groups Eliminated by Inuspheresis with IN-30-Lipid Filter and TKM58 Filter

IN30lipid filter	TKM58 filter
LDLcholesterol	Autoantibodies
lipoprotein (a)	Circulating immune complexes
triglycerides	Proinflammatory cytokine complexes
Oxidized phospholipids	Heavy metals microplastics
CRP	Pesticides
Fibrinogen	PFAS
	TNFalpha Il6 CRP
	Fibrinogen

L-Tryptophan Depletion Bioreactor Integrated in Inuspheresis as a Possible New Therapy for All Disorders with Foreign Tissue Production

The new version is the bioreactor, which contains immobilized tryptophan side-chain oxidase III (TSO III) integrated into the Inuspheresis system, for the depletion of L-tryptophan as a new therapy for all diseases involving foreign tissue buildup in the organism. L-tryptophan, an essential amino acid, plays an important role in organism development and in the occurrence and development of foreign tissue, such as cancer and antibody development. Tumor growth can be limited by degrading certain amino acids while maintaining the body´s normal nutritional re-quirements. The L-tryptophan depletion bioreactor could be a new method for

treating diseases involving foreign tissue buildup, such as cancer and autoimmune diseases with antibody production. L-tryptophan, an essential amino acid, has been recognized as an important cancer nutrient, and its removal can lead to destruction of the tumor [11]. Normal human cells or tumor cells cannot synthesize L-tryptophan, and therefore, foreign tissue or tumor resistance is unlikely to develop. L-tryptophan is also a constituent of different biomolecules, such as serotonin and melatonin, and is needed for other synthesis processes in cell growth, and is also a very important substance, which must be supplied with food to the organism.

L-tryptophan-degrading enzymes have three isoenzymes, which are called tryptophan side-chain oxidase I, II, and III. These three isoenzymes can be differentiated by tryptic digestion and have different molecular weights and different efficiencies. All the TSO enzymes have heme that can catalyze essentially similar reactions involving L-tryptophan as substrate. The most effective TSO is type III. A column that contains TSO III, immobilized on silica beads as a bioreactor in the Inuspheresis system is shown. The bioreactor in a plasmapheresis system was tested in different animals. In sheep and rabbits, L-tryptophan depletion in plasma was at 95 % and 100 % rates, respectively, by a single pass through the bioreactor [12]. The results in immune supprimized rats with tumors, and in 20 different tumor cell lines, were impressive, too. The greatest efficacy of L-tryptophan was observed in breast cancer and medulloblastoma. Gene technology of TSO from Pseudomonas is associated with the formation of endotoxin; therefore, the gene technology must use a fungal source for TSO production. Blood tryptophan depletion by TSO results in a significant antineoplastic activity. A combination of L-tryptophan depletion with all other available cancer therapies is possible [13].

Indoleamine 2,3-dioxygenase 1 (IDO 1) is the key enzyme in the catabolism of L-tryptophan through the kynurenine pathway (KP), and this enzyme is found in advanced-stage cancer and is associated with poor disease prognosis and immune suppression [14]. IDO 1 activity during malignant tumor diseases seems to be a part of the tumoricidal immune defense strategy, when L-tryptophan deprivation and production of pro-apoptotic tryptophan catabolism counteract T cell responsiveness [15]. Schmer et al. isolated, in 1978, the L-tryptophan-depleting enzyme indolyl-3-alkane-α-hydrolase from blood, which was named TSO III [12,16]. Schmer found that the treatment of certain tumors by deprivation of the essential amino acid L-tryptophan has the advantage over non-essential amino acid deprivation, because tumor cells cannot synthesize L-tryptophan, but need it for their growth. Ai, Yefu, et al. extracted and purified TSO from Pseudomonas, and they showed that TSO suppresses hepatocellular carcinoma through degradation of tryptophan [17].

The bioreactor from Schmer et al. is based on silica. The amino groups containing silica beads were activated with 25 % glutaraldehyde [12,13]. The activated amino-silane beads can be stored in the buffer of 0.2 M sodium acetate, pH 5.5, at 4° C and remain fully active for more than 6 weeks. After different washing procedures, the pre-activated microreactors, consisting of a polyacrylic-cellulose copolymer, were equilibrated with 0.2 M sodium acetate at pH 5.5 and filled with 1 % TSO solution in the same buffer. The reaction conditions, wash procedures, and sterilization were identical to the procedure described for the silica beads-derived bioreactor. The silica-based enzyme reactor was filled in columns, washed, and sterilized [12].

The sterilized bioreactor, which contains immobilized TSO III, is integrated in the Inuspheresis system. After different tests, this system can be used as treatment for all diseases with foreign tissue buildup. Especially the cancer treatment will be daily for 4 – 5 hours and 5 days a week over 1 to a maximum of 4 - 5 weeks (1 cycle), until a remission is reached. If no remission is reached, a second cycle can be repeated 2 to 3 months later [13]. Important is that the tryptophan depletion can be used in all cancer diseases, especially in breast cancer and medulloblastoma. Resistance development is not possible; therefore, this therapy can be used by the same patient again [18].

The second indication group will be autoimmune diseases with antibodies, such as multiple sclerosis [19]. The production of antibodies is foreign tissue and needs tryptophan; therefore, the therapy must be tryptophan depletion. Alterations in the activity of TSO cause imbalances in the levels of serotonin and other neuroactive metabolites, which can contribute to motor, psychiatric, gastrointestinal, and other dysfunction often seen in Parkinson´s disease [20]. Another indication for tryptophan depletion could be Alzheimer disease,

in which the tau proteins are found.

A great advantage of the bioreactor integrated in the Inuspheresis is the improvement of the hemorheological properties and reduction of alpha-2 macroglobulin, pro-inflammatory oxidized lipoproteins, and other toxic substances. A further important advantage is that no resistance against the tryptophan depletion is possible because L-tryptophan is one of the most important nutrients for all metabolism and cell growth; without L-tryptophan no foreign tissue growth is possible. Therefore, tryptophan depletion therapy is indicated for diseases with foreign tissue building, especially all cancer forms, autoimmune diseases with antibodies, Parkinson´s, Alzheimer´s diseases, etc.

Conclusion

The double filtration version, Inuspheresis, with two different second filters for lipid apheresis and autoimmune and environmental diseases is shown. A further development, the bioreactor, which contains the immobilized tryptophan side-chain oxidase for the depletion of L-tryptophan for the therapy of all diseases with foreign tissue buildup is discussed. L-tryptophan as an essential amino acid must be supplied to the organism and is one of the most important nutrients for cell growth. The bioreactor with immobilized TSO enzyme depletes all foreign tissue buildup and can be used as therapy in all cancers, autoimmune diseases with antibodies, Alzheimer´s, and Parkinson´s diseases.

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