Non-erythropoietic tissue-protective peptides derived from erythropoietin: WO2009094172

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Erythropoietin (EPO) is a cytokine with erythropoietic and tissue protective activities. Its action as a tissue protective agent requires, however, high dosage that results in limiting side effects associated with abnormally augmented erythropoiesis. Elimination of the erythropoietic activity of EPO while preserving its tissue protective properties was nevertheless achieved in carbamoylated EPO (CEPO), whose therapeutic activity and apparent safety were documented in experimental models of nervous, heart, kidney and other tissue damage, justifying ongoing clinical trials. Here, we review patent application WO2009094172 by Arai Pharmaceuticals, which describes novel EPO-derived peptides having tissue protective but no erythropoietic activity. The preferred peptide, UEQLERALNSS, which mimics the external 3D structure of the helix B of EPO, was shown to exhibit the same spectrum of tissue protective activity as CEPO in several in vivo models. In addition, it could reduce radiation-induced mortality when administered 24 h after irradiation in mice, suggesting its possible utility in emergency situations after mass irradiation casualties. Owing to their low manufacturing cost, high stability and low immunogenicity, such peptides might well offer a superior alternative to CEPO for therapeutic tissue protection in human pathologies and are likely to provide valuable probes to study the molecular mechanisms of EPO-mediated cytoprotection.

Keywords: erythropoietin, peptides, tissue protection, radiation injury

1. Introduction

Erythropoietin (EPO) is a 4-α-helice-bundle cytokine comprising 165 amino acids (Figure 1) that was originally described as the principal hematopoietic growth factor regulating erythropoiesis [1,2] but is now recognized to exert much broader physiological functions, including proangiogenic and tissue-protective effects in various non-hematopoietic organs [3-5]. While produced mainly by kidney cells and released as a circulating hormone, EPO can also be secreted locally by many other tissues to mediate autocrine or paracrine actions in response to physical and metabolic stress [3-5]. The hematopoietic effects of EPO, as manifested by increased proliferation and maturation as well as inhibition of apoptosis in early erythroblasts, result from binding of the cytokine to a homodimeric erythropoietin receptor (EpoR) (Figure 2) that activates several intracellular signaling events [1,2,6]. Multiple signal transduction pathways also appear to be involved in the protective mechanisms...
Non-erythropoietic tissue-protective peptides derived from erythropoietin: WO2009094172

CEPO: Carbamoylated EPO; EPO: Erythropoietin; EPOR: Erythropoietin receptor.

response [20,22]. Note that the common receptor is an EPOR/common heteromorph that binds EPO and mediates the tissue protective effect of the cytokines. This receptor has a high affinity for EPO. The second type of receptor, which exists as a preformed EPOR homodimer on the cell membrane of erythropoietic precursors, binds EPO but not CEPO and once ligated by the former initiates a signaling cascade providing cytoprotection by recruiting intracellular antioxidative mechanisms [7-9].

The erythropoietic activity of EPO has proven very valuable for the treatment of anemia associated with renal disease or cancer chemotherapy [5]. However, increased thromboembolic and hypertension complications have been associated with EPO therapy in some patients [5,10]. These adverse effects, possibly reflecting the conversion of the vasculature into a prothrombotic state and microcirculation disturbances caused by augmented erythropoiesis, thus greatly limit the utility of EPO for non-erythropoietic applications [5,11]. The potential progression of cancer has been another significant concern raised with EPO treatment [12]. Furthermore, the occurrence of anti-EPO antibodies in some hemodialysis patients on EPO has led to pure red cell anemia [13].

Nevertheless, a major advance toward the possible therapeutic exploitation of the tissue protective action of EPO came with the discovery that on carbamoylation, a modification of N-terminal and lysine residues to homocitrulline [14], the cytokine loses its erythropoietic activity but remains fully tissue protective [15]. Carbamoylated EPO (CEPO) was thus claimed to be potentially useful as a tissue protective agent in a series of patent applications assigned to the Warren Institute and Lundbeck Co. [16-18]. The therapeutic activity and apparent safety of CEPO was documented in numerous experimental studies of organ damage in rodent models (Table 1). Moreover, the tissue protective action of both EPO and CEPO was shown to be mediated via a heteromeric cell surface receptor made up of an EPOR unit in association with CD131 [19], the common β-subunit of receptors for GM-CSF, IL-3 and IL-5 (Figure 2) [20-22]. Clinical development of CEPO (Lu AA24493) is being conducted by Warren Pharmaceuticals (www.warrenpharma.com) and Lundbeck A/S (www.lundbeck.com). The compound underwent a Phase I safety trial in patients with acute ischemic stroke and a Phase IIa trial has been initiated in Friedreich’s ataxia, a degenerative disease of the nervous system, but no data have been released yet.

A peptide corresponding to the AB loop of EPO was previously claimed to exert a neurotrophic effect without inducing erythropoiesis [23,24]. However, the mechanism of this action was not fully characterized. Furthermore, an endogenous variant of EPO lacking the AB loop was reported to be also neuroprotective and non-erythropoietic [25]. In contrast, more recent structure/activity analysis of the EPO molecule by scientists at the Warren Institute identified helix B (Figures 1 and 3), a region that does not contain lysine and, therefore, is not modified in CEPO, as a functional domain endowed with tissue protective but no erythropoietic activity (Table 2) [26,27]. Spatially adjacent amino acids exposed

Figure 1. Primary amino-acid sequence of mature human EPO. The four helical domains (A, B, C and D) of the tertiary structure are underlined. Lysine (K) residues, which are targets of carbamoylation in CEPO, are shown in larger font.

CEPO: Carbamoylated EPO; EPO: Erythropoietin.

Figure 2. Schematic representation of cell surface EPO receptors. At least two distinct types of receptor mediate, respectively, the erythropoietic and tissue protective activities of EPO. The first type of receptor, which exists as a preformed EPOR homodimer on the cell membrane of erythropoietic precursors, binds EPO but not CEPO and once ligated by the former initiates a signaling cascade that inhibits apoptosis and allows erythroid maturation of the cells. This receptor has a high affinity for EPO. The second type of receptor is an EPOR/common β-chain heteromer that binds EPO with low affinity but also binds CEPO and mediates the tissue protective effect of the cytokines. This receptor is typically expressed in tissues only after injury or metabolic stress and only elicits by EPO in non-erythropoietic tissues [4]. Besides an inhibition of programmed cell death, these mechanisms include an attenuation of the destructive potential of proinflammatory factors and trophic effects that promote accelerated healing and tissue regeneration [5-9]. EPO may also provide cytoprotection by recruiting intracellular antioxidative mechanisms [7-9].
on the aqueous face of helix B were used to design a peptide (QEQLERALNSS) which exhibited tissue protective and trophic effects in several animal models (Table 2) [20,27]. Warren Pharmaceuticals claimed the use of this peptide and several analogues and unrelated peptides for the prophylaxis or therapy of various tissue damage conditions [27]. The present application by Araiin Pharmaceuticals, a spin-off of Warren Pharmaceuticals, provides additional evidence for the potential utility of such non-erythropoietic peptides in tissue protection [28].

### Table 1. Tissue protective activity of CEPO in experimental models in vivo.

<table>
<thead>
<tr>
<th>Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic brain injury in rats</td>
<td>CEPO administered i.p. either 6 or 24 h after injury increased brain derived neurotrophic factor expression and proliferating cells in dentate gyrus and improved spatial learning [40]</td>
</tr>
<tr>
<td>Spinal cord compression in rats</td>
<td>CEPO (10 µg/kg) injected i.v. immediately or 24 h following injury and over 6 weeks thereafter significantly improved the recovery of neurological function [15]</td>
</tr>
<tr>
<td>Spinal cord hemisection in rats</td>
<td>CEPO administered i.p. 30 min and 24 h after injury reduced the lesion size and decreased apoptosis while increasing Schwann cell infiltration into the lesion site [41]</td>
</tr>
<tr>
<td>Cisplatin-induced peripheral neurotoxicity in rats</td>
<td>CEPO (50 µg/kg) given thrice weekly significantly prevented the sensory nerve conduction velocity reduction and preserved intraepidermal nerve fiber density [42]</td>
</tr>
<tr>
<td>Wobbler mice, a model of amyotrophic lateral sclerosis</td>
<td>CEPO (32 µg/kg) given thrice weekly improved motor behavior and reduced motoneuron loss as well as astrocyte and microglia activation in the cervical spinal cord [43]</td>
</tr>
<tr>
<td>Chronic autoimmune encephalomyelitis in mice</td>
<td>CEPO (50 µg/kg) administered i.p. thrice weekly starting up to 4 weeks after disease onset reduced inflammatory cytokine expression in the spinal cord and ameliorated neurological deficit symptoms [15,44]</td>
</tr>
<tr>
<td>Radiation-induced brain injury (100 Gy to right striatum) in rats</td>
<td>CEPO (50 µg/kg) administered i.p. before and once daily for 10 days after irradiation reduced brain necrosis by 50% and improved functional outcome [31]</td>
</tr>
<tr>
<td>Embolic middle cerebral artery occlusion in rats</td>
<td>CEPO (50 µg/kg) given i.v. at 6, 24 and 48 h after artery occlusion significantly decreased the cortical infarct volume as well as the number of apoptotic cells and activated microglia in the ischemic boundary region and reduced neurologic impairment [45]</td>
</tr>
<tr>
<td>Experimental focal cerebral ischemia in rats</td>
<td>A single i.v. injection of CEPO (50 µg/ml) reduced cerebral inflammation and improved functional recovery even if administered as late as 24 h after the stroke [15,46]</td>
</tr>
<tr>
<td>Multiple infarct cerebral ischemia caused by small clot embolic stroke in rabbits</td>
<td>CEPO significantly improved clinical rating scores and motor function when administered between 5 min and 3 h after embolization but not when administered 6 h after embolization [47]</td>
</tr>
<tr>
<td>Myocardial infarction (40 min of occlusion with reperfusion) in rats</td>
<td>CEPO (50 µg/kg) administration i.v. 5 min before reperfusion followed by daily s.c. treatment for 1 week reduced cardiomyocyte loss [48]</td>
</tr>
<tr>
<td>Myocardial infarction induced by permanent ligation of a coronary artery in rats</td>
<td>A single i.v. injection of CEPO (30 µg/kg) immediately after coronary ligation reduced myocardial apoptosis by 50% at 24 h and infarction size at 4 weeks [49]</td>
</tr>
<tr>
<td>Ischemia/reperfusion cardiac injury in mice</td>
<td>A single i.v. injection of CEPO immediately before reperfusion decreased myocardial infarction by 40% [50]</td>
</tr>
<tr>
<td>Ischemia-reperfusion injury of kidney in rats</td>
<td>CEPO treatment inhibited apoptosis and α-smooth muscle actin expression in kidney tubules and promoted tubular epithelial cell proliferation and angiogenesis [51,52]</td>
</tr>
<tr>
<td>Kidney injury caused by unilateral ureteral obstruction in rats</td>
<td>CEPO decreased apoptosis and α-smooth muscle actin expression in kidney tubules [53]</td>
</tr>
<tr>
<td>Various types of wounds (non-ischemic, ischemic or infection complicated) in rats</td>
<td>CEPO administered immediately following injury limited wound size and accelerated eschar closure independent of wound type. Moreover, daily administration of CEPO significantly decreased the formation of peritonitis-induced adhesions [29]</td>
</tr>
</tbody>
</table>

CEPO: Carbamoylated erythropoietin; i.p.: Intraperitoneal; i.v.: Intravenous; s.c.: Subcutaneous.

on the aqueous face of helix B were used to design a peptide (QEQLERALNSS) which exhibited tissue protective and trophic effects in several animal models (Table 2) [20,27]. Warren Pharmaceuticals claimed the use of this peptide and several analogues and unrelated peptides for the prophylaxis or therapy of various tissue damage conditions [27]. The present application by Araiin Pharmaceuticals, a spin-off of Warren Pharmaceuticals, provides additional evidence for the potential utility of such non-erythropoietic peptides in tissue protection [28].

### 2. Chemistry

Various peptides and chimeric analogues that share consensus sequences with portions of EPO and type I cytokine receptor ligands are described, the majority of which were already presented in the Warren patent [27]. The preferred peptides include QEQLERALNSS (peptide IC) and its PEG conjugate (peptide IW) as well as its homolog comprising a pyroglutamic acid (U) instead of glutamic acid at the N terminus (peptide ID) (molecular...
Non-erythropoietic tissue-protective peptides derived from erythropoietin: WO2009094172

3. Biology

Peptide ID (also designated ARA 290 [29]) was most extensively investigated. It was shown not to stimulate erythropoiesis either in vitro or when administered intravenous (i.v.) (300 – 600 µg/kg) twice a day over a period of 28 days in mice or rabbits. As summarized in Table 3, peptide ID demonstrated tissue protective activity in several of the same in vivo models where CEPO has been found effective (Table 1). Moreover, it inhibited the growth of brain-implanted gliosarcoma cells, although less effectively than peptide IW, and suppressed the local inflammation caused by histamine challenge in rats. Remarkably, peptide ID could reduce the mortality associated with either bone marrow toxicity or gastrointestinal toxicity when administered 24 h after irradiation in models of acute radiation syndrome in mice (Table 3). Control peptides composed of the same amino acids as peptide IC but in scrambled sequence were inactive in several models.

4. Expert opinion

The preferred peptides of the present application, along with those of the earlier Warren patent [27], display a spectrum of tissue protective activity similar to that of CEPO and may offer the advantage of being relatively easier and cheaper to manufacture, more stable on storage and less immunogenic than the latter. Although peptide ID exhibits a half-life of only ~2 min after i.v. dosing in rats and rabbits [26], the PEG conjugate (peptide IW) is likely to possess more favorable pharmacokinetics. Overall, these peptides appear thus very promising and might well provide a pharmaceutically superior alternative to CEPO for tissue protection in a wide range of medically important indications (Table 4). Nevertheless, much work remains to be done to fully evaluate their prospects for clinical development.

One most innovative aspect of this application concerns the possible utility of peptide ID for the mitigation of radiation-induced pathologies, an indication for which active agents are sorely needed [30]. Its efficacy on subcutaneous injection would make it a suitable candidate for use in emergency situations after mass irradiation casualties. However, the preliminary data presented in the application must be substantiated by more extensive studies of the restorative action of the peptide on the bone marrow and gut mucosa following radiation damage. In addition, the mitigating activity of the peptide should be documented toward the radiation-induced injury of other organ systems, such as the brain where CEPO was previously found effective [31]. It is also important to note that in the context of radioprotection, the lack of erythropoietic activity of the peptide may actually be less than optimal for full reconstitution of hematopoietic lineages. Whether the erythropoietic EPO-mimetic peptide, hematide, currently developed by Affymax [32-34] would synergize with peptide ID in mitigating radiation-induced hematopoietic injury might thus be worth examining.

While peptide ID was shown to inhibit the growth of glioblastoma cells, further studies should determine its possible effects on tumor cells whose growth is known to be stimulated by EPO, such as prostate or breast cancer.
Figure 4. Design of the preferred peptides of the present application. Surface exposed residues of helix B are shown in bold underlined. These were used to construct peptide IC that mimics the 3D structure of the external surface of helix B but whose linear sequence is unrelated to EPO. Peptide IC was pegylated at the N terminus to yield peptide IW. Alternatively, the N-terminal glutamic acid residue of peptide IC was replaced by a pyroglutamic acid (U) residue, yielding peptide ID.

EPO: Erythropoietin.

Table 3. Biological activity of peptide ID (ARA 290) in models of tissue protection in vivo.

<table>
<thead>
<tr>
<th>Model</th>
<th>Treatment protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle cerebral artery occlusion in rats</td>
<td>Peptide (2 µg/kg) administered i.v. on reperfusion and as three additional doses at 2 h intervals thereafter</td>
<td>Significant reduction in infarct volume at 24 h and improved cognitive performance in foot fault assay</td>
</tr>
<tr>
<td>Recognition of novel objects in rats</td>
<td>Peptide (24 nmol/kg) given i.p. 3 h after the first exposure to the novel objects or twice daily for 5 days before and immediately after training</td>
<td>Improved recognition of the novel objects suggesting that the peptide may influence the consolidation phase of memory acquisition</td>
</tr>
<tr>
<td>Bilateral renal ischemia/reperfusion injury in mice</td>
<td>Peptide (1 or 10 µg/kg) injected i.p. at 6 h after reperfusion</td>
<td>Reduction in biochemical markers of renal dysfunction</td>
</tr>
<tr>
<td>Brain implant of gliosarcoma cells in rats</td>
<td>Peptide (30 µg/kg) injected i.p. daily for a period of 25 days</td>
<td>Inhibition of cortical tumor growth</td>
</tr>
<tr>
<td>Brain implant of gliosarcoma cells in rats</td>
<td>Peptide (25 nmol/kg) injected i.p. daily for 3 weeks starting either immediately or 2 weeks after gliosarcoma implantation</td>
<td>Significant reduction in tumor size when the treatment was started at implantation but not when it was started 2 weeks later</td>
</tr>
<tr>
<td>Histamine-induced ear inflammation in rats</td>
<td>Peptide (30 µg/kg) injected i.v. 30 sec after histamine challenge in ear</td>
<td>Reduction of the amount of edema associated with the histamine challenge</td>
</tr>
<tr>
<td>Histamine-induced wheal formation in rats</td>
<td>Peptide (30 µg/kg) administered i.v. before or at the time of histamine challenge</td>
<td>Suppression of wheal formation lasting up to 24 h following a single dose of peptide</td>
</tr>
<tr>
<td>Full-thickness punch biopsy wound in rats</td>
<td>Peptide (24 nmol/kg) administered s.c. daily for 10 days</td>
<td>Faster healing of open wound</td>
</tr>
<tr>
<td>Pressure ulcer induced by skin compression and ischemia in rats</td>
<td>Peptide (30 µg/kg) administered s.c. at the beginning of ischemia and daily for a period of 12 days</td>
<td>Significant reduction of wound size</td>
</tr>
<tr>
<td>Hematopoietic toxicity induced by total body irradiation (796 or 831 cGy) in mice</td>
<td>Peptide (30 µg/kg) injected s.c. at 24 h after irradiation and then daily for 29 days</td>
<td>Increased 30-day survival of mice treated with the peptide compared to vehicle control (at 796 cGy: 45 vs 10%; at 831 cGy: 20 vs 5%)</td>
</tr>
<tr>
<td>Gastrointestinal toxicity induced by partial body irradiation (15 Gy) in mice</td>
<td>Peptide (30 µg/kg) injected s.c. at 24 h after irradiation and then daily for the duration of the study</td>
<td>Increased 20-day survival of mice treated with the peptide compared to vehicle control (40 vs 7%)</td>
</tr>
</tbody>
</table>

i.p.: Intraperitoneal; i.v.: Intravenous; s.c.: Subcutaneous.
In this respect, it is interesting that a recent patent application [36] claimed that EPO may promote tumor cell growth through a new receptor type that involves the ephrin signaling network members, ephrinAl and EPH-B4 [37]. This suggests that multiple receptor systems may be implicated in the non-hematopoietic effects of EPO-derived peptides, a notion consistent with the observation that the AB loop peptide has neurotrophic activity (Table 2) [23,24]. The possibility that the peptides of the present application may be able to activate this novel receptor deserves to be carefully investigated as it might impact on their safety profile.

Irrespective of the contribution of other receptors, there is strong evidence that the common-β chain in association with EPOR plays a predominant role in tissue protection [20,22]. Analysis of the mechanism of action of peptide ID should, therefore, benefit from recent structural studies that elucidated the interaction of GM-CSF and IL-3 with their receptors [38,39]. This may help to identify putative sites of contact of the peptide with the common β-chain and clarify its mode of signaling. Moreover, a thorough dissection of the intracellular components of this signaling in various cell types may uncover novel biochemical targets for tissue protection and perhaps shared and unique pathways. It is indeed quite puzzling that a single type of agents could alleviate such a variety of pathologies (Table 3).

In conclusion, besides their potential as future therapeutic candidates, the peptides claimed in this application are likely to serve as valuable probes for unraveling the molecular mechanisms of EPO-mediated tissue protection.

Table 4. Pathologies in which EPO-mimic tissue protective peptides may prove useful.

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Disease/condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain/nervous system</td>
<td>Stroke</td>
<td>Peptides may stimulate neurogenesis, neuronal differentiation, and activate brain neurotrophic, anti-apoptotic, anti-oxidant and anti-inflammatory signaling to help recovery [54]</td>
</tr>
<tr>
<td></td>
<td>Traumatic brain injury</td>
<td>Current trials in neuroprotection have failed to show any consistent improvement in outcome. Peptides may be part of novel treatment strategies [54,55]</td>
</tr>
<tr>
<td></td>
<td>Spinal cord injury</td>
<td>Devastating condition that is costly for healthcare systems and for which there exists no effective treatment. Peptides may offer novel regenerative and neuroprotective strategies [56,57]</td>
</tr>
<tr>
<td></td>
<td>Diabetic neuropathy and retinopathy</td>
<td>These conditions characterized by progressive nerve fiber loss and retinal damage are the most common complications of diabetes [58]. Peptides may provide neuroprotection and prevent apoptosis in the retina [59]</td>
</tr>
<tr>
<td>Heart/vascular system</td>
<td>Myocardial infarction</td>
<td>Cardiovascular diseases are the leading cause of death in industrialized countries [60]. Peptides may help limit infarct size and post-infarct remodeling and improve clinical outcomes [61]</td>
</tr>
<tr>
<td></td>
<td>Chronic heart failure</td>
<td>Peptides may improve perfusion and reduced apoptosis in cardiac tissue [62]</td>
</tr>
<tr>
<td>Kidney</td>
<td>Acute renal failure</td>
<td>Peptides may alleviate ischemia-induced tissue damage in the kidney [63]</td>
</tr>
<tr>
<td></td>
<td>Ischemia/reperfusion injury</td>
<td>Peptides may alleviate ischemia-induced tissue damage of graft in kidney transplantation [64]</td>
</tr>
<tr>
<td>Skin/conjunctive tissues</td>
<td>Acute and chronic wounds</td>
<td>Effective management of acute and chronic wounds remains a challenging clinical problem. Peptides may accelerate wound healing [29,65]</td>
</tr>
<tr>
<td>Multiple organ systems</td>
<td>Radiation injury, without or with other traumas</td>
<td>There is a pressing need for effective and safe treatments to mitigate radiation-induced tissue injury and multi-organ failure in case of mass irradiation casualties resulting from a nuclear accident or radiological terrorism [66,30]. Small peptides that are effective on s.c. administration, are inexpensive to manufacture and have long shelf-life would be ideally suited for this application [30]</td>
</tr>
</tbody>
</table>

EPO: Erythropoietin.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
Bibliography


- An excellent overview of the role of locally produced EPO in limiting the destructive potential of pro-inflammatory cytokines in the brain, heart, kidney and other tissues.


- This review summarizes the evidence that EPO contributes to wound healing responses, physiological and pathological angiogenesis, and the body’s innate response to injury in the brain and heart.


- This review demonstrates that despite its beneficial effect in recruiting multiple cytoprotective pathways in various organs, EPO may also contribute to vascular stenosis with intima hyperplasia, increase the incidence of thrombotic vascular effects and significantly elevate mean arterial pressure.


- This seminal study provides the first evidence that the erythropoietic and tissue protective activities of EPO can be dissociated, as exemplified by the ability of CEPO to exert cytoprotection and neuroprotection in vivo without inducing erythropoiesis.


19. Murphy JM, Young IG. IL-3, IL-5, and GM-CSF signaling: crystal structure of the human beta-common receptor. Vitam Horm 2006;74:1-30


- This important paper demonstrates that the common beta-subunit in combination with EPOR expressed in non-hematopoietic cells constitute a tissue protective receptor targeted by EPO and CEPO. Neither EPO nor CEPO were tissue protective in mice lacking the common beta-subunit.


- This excellent article reviews the role of EPO in preventing the programmed cell death as well as reducing the development of secondary, pro-inflammatory cytokine-induced injury in tissues and in providing subsequent trophic support to enable tissue regeneration and healing. The putative therapeutic potential of non-erythropoietic tissue protective CEPO and EPO-derived peptides is also discussed.


- Shows that a 17-mer peptide sequence of the AB loop of EPO can induce the differentiation and prevent cell death in neuronal cells while being unable to promote erythropoiesis. This suggests the existence of mechanisms of tissue protection that are independent of the helix B of EPO.


- This article is highly relevant to the present application. It presents the original evidence that a peptide composed of adjacent amino acids forming the aqueous face of helix B is tissue protective but not erythropoietic.
Non-erythropoietic tissue-protective peptides derived from erythropoietin: WO2009094172

28. Arais Pharmaceuticals, Inc. Tissue protective peptides and peptide analogs for preventing and treating diseases and disorders associated with tissue damage. WO2009094172; 2009

These studies show that, similar to CEPO, peptide ID of the present application was immediately after injury in several wound models.

32. Affymax, Inc. Peptides that bind to the erythropoietin receptor. WO2004101611; 2004
33. Affymax, Inc. Erythropoietin receptor peptide formulations and uses. WO2009025958; 2009
36. Alepor GMBH & Co KG. Novel tissue protective erythropoietin receptor (NEPOR) and methods of use. WO2009068677; 2009

This application claims that the ephrin family members, ephrinA1 and EPH-B4, together with EPOR, are components of a novel type of receptor that allows EPO to promote the survival and growth of tumor cells.


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