We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

The Patenting of Products and Processes Used for the Treatment of Smoke Inhalation

Fernanda Oliveira de Carvalho, Érika Ramos Silva, Paula Santos Nunes, Karen Perez Pereira Ramos and Nayara Gomes Lima Santos

Abstract

Intellectual property enables the transformation of knowledge in principle and the link between knowledge and the market. The right of exclusivity guaranteed by the patent refers to the right to interfere with other products and use and sell a patented invention. On the other hand, access to the public is made available on the knowledge of the essential points and as those that characterize a novelty does not exist. Patent registries, because they are available in open access databases, are great bases of technological knowledge, which can be used in research in several areas, among them smoke inhalation treatments. Inhalation injury is the leading cause of death in burn patients and is usually caused by the uninhibited absorption of smoke, which has an extremely toxic effect on the respiratory system. The physiopathology of inhalation injury covers multiple factors, and the injured respiratory system may present deterioration in a few hours. Respiratory distress is one of the major causes of morbidity and mortality in patients affected by fire incidents. The search for suitable treatments for inhalation injury is continuing, and the treatments used for smoke inhalation are discussed.

Keywords: patents, smoke inhalation, pulmonary injury, natural products, synthetic products

1. Introduction

A patent is a public concession, granted by the State, which grants the holder the exclusive right to commercially exploit his creation. The exclusivity right secured by the patent refers to the right to prevent others from manufacturing, using, selling, offering, or importing such invention. In compensation, access is available to the public on the knowledge of key points and the claims that characterize the novelty in the invention [1].

Patent registrations, because they are available in open access databases, are a great base of technological knowledge, which can be used in researches across several areas, among them smoke inhalation treatments [1].

The pulmonary injury from smoke inhalation or combustion chemical products is the leading cause of death in burn patients, can be present in 2/3 of the population

with skin burns exceeding 70% of body surface area, and is mainly caused by inhibited smoke inhalation, which has an extremely toxic effect in the respiratory system [2].

The physiopathology of an inhalation injury encompasses multiple factors, and the injured respiratory system can present deterioration in a few hours. If combined with cutaneous burns, the inhalation injury increases even more the incidence of pulmonary complications and the mortality. On average, the mortality from burns is less than 10%, but in the presence of an inhalation injury, this increases up to 25–43%. When complications develop, such as pneumonia and multiple organ dysfunction, this can increase up to 60–80% [2].

The prevalence of burns is significantly higher in developing countries than in developed. In the USA, nearly 2 million people are burned every year. Of these, about 100,000 have moderate to severe burns, requiring hospitalization, and 70% of fire victims who die within 12 h have an inhalation injury [3, 4]. In an epidemiological study conducted by Iqbal et al. [5], which evaluated 13,295 patients, it was found that men were the majority of the victims (56.43%); the mean age of adults was 33.63 ± 10.76 years and the children's age was 6.71 ± 3.47 years, the domestic environment being the most common (68%). The mean body surface area burned was 10.64 ± 11.45% in total. Smoke inhalation injury occurred in 149 of these patients (1.12%).

Although many products and techniques have been developed to control cutaneous thermal injury, few specific therapeutical options for diagnosis were found for patients with inhalation injury. Several factors explain the slower improvement progress in the treatment of patients with inhalation injury. Inhalation injury is a more complex clinical problem. The burned cutaneous tissue can be removed and replaced by skin grafts. The injured pulmonary tissue must be protected from a secondary injury due to resuscitation, mechanical ventilation, and infection, while the host's repair mechanisms receive proper support [2].

Many consequences of smoke inhalation result from an inflammatory response involving mediators whose number and functions still remain without a complete understanding, despite enhanced tools to process clinical material. Improvements in mortality by inhalation injury are mainly due widespread improvements in intensive care, instead of interventions focused in smoke inhalation. The search for proper inhalation treatments remains, and the treatments used for smoke inhalation are discussed in this chapter.

2. Intellectual property aimed at the treatment of pulmonary injury by smoke inhalation

Intellectual property enables a transformation of knowledge to principle and a link between knowledge and market. It is also said that a patent is the legal document that represents the set of exclusivity rights granted by the State to an inventor. By receiving the patent rights over his product, the inventor also receives several rights and guarantees, however, with these rights also come obligations that, necessarily, must be fulfilled so the inventor can retain his rights [1].

In case of him not meeting his obligations, he is subject to a mandatory licensing of his invention or utility model. If a patent is requested and granted for technology, of a novelty product or to enhance an invention, there are several proceedings, regulations, and laws to register and grant these patents, which vary for each country, also varying the concession period. The delay in patent granting is pointed as a barrier to innovation in a country. According to the World Intellectual Property Organization (WIPO), the period for an international patent registration varies from 16 to 30 months [1].

On patents deposited with the objective of treating injuries caused by smoke inhalation, the inventors that most developed e patented products were Enkhbaatar P. et al. (6), Keith JC Jr. (5), Schmalstieg F. et al. (1), Brands (5), and Saifer et al. (1).

3. Pulmonary injury and its therapeutical challenges

The constitution and toxicity of smoke and of products generated by combustion compromise the environmental condition and health of exposed individuals, generating local or systemic affections, which may leave sequelae and even progress to death [2].

Inhalation injury by smoke can happen as a consequence of the high temperature of vapor inhaled, decrease of breathed fraction of oxygen, and presence of toxic gases such as carbon monoxide, sulfur dioxide, nitrogen, and ammonia, absorbed or not by the inhaled particulate matter [6, 7].

There are different damages to the different structures of the respiratory system [8]. In the airways, there is scaling of ciliated pseudostratified epithelium, mucosal edema, bronchorrhea, and tracheobronchial obstruction, increasing resistance and limiting air flow [9]. Sometimes, from the histological point of view, depending on the inhalation injury model, such changes can be reversible.

Regarding pulmonary parenchyma, the injuries are characterized by lung emphysema with expressive thinning of intra-alveolar septa, which burst and increase alveolar spaces. This tissue involvement can have progressive character, caused by the arrival of neutrophils in the pulmonary interstice, generating a superoxide radical, which directly harms the membrane of interstitial cells and the endothelium [10–12]. According to Ferreira and Matsubara [13], production and release of reactive oxygen species contribute to the emphysema.

About 6–7 h after initial exposure, there is an increase of IL-1β and IL-8 concentrations [14]. Besides those, other inflammatory process mediators are tumor necrosis factor-alpha (TNFα), IL-6, and nuclear factor-kappa β [2]. The actions of IL-1β, IL-6, and IL-8 stimulate adherence of leucocytes and disseminated intravascular coagulation, with IL-6 highlighted in eosinophil attraction to the injured area [15]. TNF-α is known for being a powerful inflammatory mediator in thermal lesions, inhalation injuries, and generalized infections [16].

Clinical treatment of an inhalation injury is a challenge based on the control of consequences of smoke exposure, there being no gold standard. Some immediate care assures the integrity of organs and systems of victims. It is necessary to start oxygen therapy with hyperoxia (FiO_2 = 100%) for a limited time, to discern the indication of artificial airway and invasive or noninvasive ventilatory support, patient pronation, and extracorporeal membrane oxygenation [17].

It is important to maintain airway perversity as well as alveolar stability. The administration of β2-agonist, heparin and N-acetylcysteine nebulization have a role in the management, as well as the more specific treatment of carbon monoxide or cyanide poisoning, have contributed to good therapeutic results [18, 19].

Acknowledging the systemic effects of the condition, the hydration and monitoring of micro and macro hemodynamics are extremely relevant to prevent further complications. Pharmacological treatment is based on the consequences and additional complications. Corticosteroids, antibiotics, anticoagulants, sedatives, and analgesics and, in cases of intoxication by cyanide, hydroxocobalamin, sodium nitrite, sodium thiosulfate, or sodium nitrite, by intravenous route, can be administered [3, 20].

At the experimental level, the use of mesenchymal stem cells derived from human amnion (hAMSCs) alleviated white smoke-induced lung injury [21]. It is

likely that in the future this resource will contribute to the best clinical outcome for victims of this type of injury.

It is known, however, that the best clinical outcome for the victim of inhalation injury depends on other factors. According to Bedri et al. [22], socioeconomic and ethnic factors and the sex of the victims influence the clinical outcome. They found that Afro-descendent Americans, female and uninsured, had more complications, more surgical interventions, longer hospital stay, and higher mortality rates, even though lower body surface area burned and there is a lower proportion of inhaled lesion. These disparities further emphasize the need for further research on the underlying racial and socioeconomic factors that this review of the database could not discern.

In turn, natural products present great therapeutic potential and are the subject of study in several experimental, in vitro, and/or in vivo research. The low cost, the good availability, and the habitual use by the population, considering the regional popular knowledge, are some of the factors that contribute to this reality.

The terpene group deserves special mention, both for being part of traditional medicine for centuries and for having a low toxicity [23]. In addition to being used in the food and cosmetic industries, its effects, anti-inflammatories, antioxidants, analgesics, anticonvulsants, antidepressants, anxiolytics, anticancer, antitumor, neuroprotective, antimutagenic, antiallergic, antibiotics, and antidiabetics, are widely known.

Examples are carvacrol, linalool, borneol, limonene, myrene, and pinene. It is known, for example, that D-limonene has important immunomodulatory properties, ameliorating attacks of atopy and asthma, besides inhibiting the action of cytokines and release of substances reactive to oxygen and containing migration of eosinophils [2, 8].

4. Historical background of patents aimed to control pulmonary injury by smoke inhalation

Two years ago, our research group performed a patent review [24] in three different databases, and only 18 patents, containing the keywords "smoke inhalation" in the title, abstract, or full text, fit in the inclusion criteria for this research. There was a language bias, making it possible for many other patents to exist, regarding the use of natural and synthetic products developed for the treatment of smoke inhalation, but we believe that the results presented provide the reader a perspective on current therapeutic options and new approaches and treatments for smoke inhalation.

The oldest patent was deposited in 1977 and was on "orgotein," which is the generic name of the enzyme superoxide dismutase (SOD), which belongs to the metalloprotein group, contains copper and zinc, and was first described in 1969 by McCord and Fridovich. Those researchers found that a bovine protein (orgotein) was an enzyme that could catalyze the destruction of superoxide radicals through a disproportion in molecular oxygen and hydrogen peroxide. By destructing free superoxide radical, SOD contributes to the physiological balance between pro-oxidants and antioxidants, being known for being a potent anti-inflammatory agent [24].

Dominguéz [25] reported that orgotein is a naturally occurring protein inside a human cell and, when topically and systematically administered, produces physiological effects that do not manifest or manifest in a lower degree by the natural SOD of a patient. This exogenous manifestation decreases the amount of acute inflammatory events and influences late effects.

The most recent patent, according to the patent review mentioned previously [24], was deposited in 2013 and was about ectophosphatases. The ectophosphatases and, especially, the alkaline phosphatases are a subclass of phosphatases (hydrolases that act on ester connections). The role of ectophosphatases is not well established yet; however, it has been suggested that these enzymes perform important tasks in nutrition, proliferation, differentiation, adhesion, virulence, and infection [26]. Furthermore, it is possible to assure that there is a consistent relation between the of an organism to decay extracellular ATP by ectophosphatases activities and its capacity to acquire resistance to toxins.

Brands [27] developed a drug using ectophosphatases for prophylaxis in mammals, preferably humans, at risk of inflammatory diseases or immunocompromised conditions. Intravenous administration of alkaline phosphatase in patients subjected to myocardial revascularization resulted in a subsequent increase in plasma levels of alkaline phosphatase 4–6 h after the onset of the surgery. This endogenous alkaline phosphatase can perform an important role in the immune system, because it acts as an acute phase protein; in addition, high levels of alkaline phosphatase generate an anti-inflammatory effect in the organism.

The two patented products mentioned previously, both the oldest and the newest, were applied and studied at the clinical level, in other words, with humans. The first product was given by inhalation (nebulization) and with a therapeutic purpose of treatment and the second, through intravenous infusion but with a preventive aspect [24].

The oldest patent found was deposited in a US-based patent database, yet the latest was located in Mexico. The year with most patent deposits related to the treatment of inhalation injuries was 2009, followed by 2005 and 2008. Probably, that year had many researches and patent requests due to some disasters involving fires, such as the one in a club in Thailand, that resulted in many deceases [24].

5. Patenting of processes and products aimed at pulmonary injury by smoke inhalation: any evidences?

Besides the two products mentioned and highlighted in the previous topic, since they were the first and the last to be patented, we had three other products studied and patented, e.g., "antithrombin III (ATIII) and heparin," which refers to the exogenous administration of ATIII—a direct inhibitor of thrombin, and heparin, that inhibits coagulation proteases, decreasing fibrotic conditions and improving gas exchange in animal models of acute pulmonary injury. Since there were six patents deposited aimed at the use of this product, it was found that the inhaled administration (using a compressor nebulizer, an ultrasonic nebulizer, or a dry powder inhaler) is more efficient than intravenous injection [28]. The dose used was also mentioned in the patent, stressing that the inhalation of combined products can also be performed according to the need or symptom occurrence [29].

In five other patents, "estrogen receptor-β (ERβ)-selective ligands or compositions," with the objective of treating or preventing acute pulmonary injuries due to local inflammatory processes (smoke inhalation, prematurity with surfactant deficiency, oxygen toxicity, barotrauma by mechanical ventilation with positive pressure) or peritonitis or intravenous bacteremia, both during sepsis, were studied. Furthermore, many preclinical trials proved the anti-inflammatory properties of estrogen [29–31].

Finally, the patent on "anti-IL-8 and anti-L-selectin," which we found only one patent deposited. L-selectin's role in immunity control is as a receptor in T cells. The smoke inhalation model in sheep of Murakami and Traber [32] showed that the

anti-L-selectin antibody significantly alleviated airway obstruction. The neutrophil treatment with anti-L-selectin antibody reduces neutrophil capacity of adherence to the endothelium. It is also probable that chemokines such as IL-8 and others direct the neutrophil movement from the vasculature [33]. According to this patent, the effects on vascular permeability may point that both anti-IL-8 and anti-L-selectin decrease the lesions of endothelial cells.

These data help highlight the different means of treatment of injuries caused by smoke inhalation and the drugs being studied to control such injury. We presented the significant progress achieved in the field, demonstrating the growing interest of scholars and pharmaceutical companies in the development of products with the potential to be successful in treatment of smoke inhalation.

6. The challenges of processes and patents aimed at pulmonary injury by smoke inhalation

Intellectual property, one of the subdivisions of business law, is nothing more than the legislative norm that regulates innovations and is now gaining considerable space in the most varied academic discussions. Patent, one of the intellectual property entities, is the guarantee of ownership of the creation offered to its inventors, a fact that has been discussed since it ends up limiting its application and effectiveness [34].

The expression of intellectual property is criticized because of its ambiguity. Richard Stallman wrote an essay on this subject to enlighten this problem and fight, among other things, against other things, against the meaning of the expression, because it is a reminiscence of physical property, whose laws are very different. For him, the term unites a set of heterogeneous concepts with objectives and operation too diverging (or even opposed) to be considered as a whole, such as copyrights, related to patents and trademarks. He advocates a separate consideration of each of these areas and the abandonment of the term intellectual property (especially in the name of the World Intellectual Property Organization) [1, 34]. Actually, part of the free software community rejects this expression and follows Stallman's point of view.

As previously explained, patenting a product guarantees its inventor time to explore its invention safely, but there are a number of limitations in this action [35, 36]. One of the biggest challenges in the patent process in some countries is the delay in the patenting process and the low investment in this area, which does not generate incentives for research, studies, and creations of new products. The cost of a patent goes beyond the process to deposit it into a database; there is still a high investment to keep it active, which discourages some inventors who have low investment in their research.

Once a patent is deposited in a database, the entire population has access to the methodology of the invention as well as its advantages and disadvantages. Analyzing database patents, besides the analysis in the literature, is an important tool in the strategic planning of a research, because approximately 70% of the technological information is described in the patents, according to WIPO. Therefore, a thorough evaluation of patents is essential for a good development of projects and avoids potential wasted resources, in case any other researcher has already reached the expected goal.

Currently, there are several databases for patent deposits. These banks are extremely affordable and consistent, but they have some limitations. A great difficulty encountered is the duplication of patents during a search, which occurs because the same inventor ends up depositing his patent in several databases. In

the reviews of patents carried out by our group, we find a considerable number of patents in duplicity, which makes the research more laborious and time-consuming. In addition, some inventors are rather short, brief, and unspecific when carrying out the explanation of their patent. At other times, they are prolix and not objective, which end up generating difficulties in the process of searching and analyzing the most desired patents.

Another limitation is the difficulty of finding a specific patent. Due to various encodings and numberings given to patents, the search for something specific ends up taking more time. The lack of research in clinical trials is, also, another limiting factor. Most inventors carry out the patent filing process with an experimental trial, which can be justified by the interest of patenting their invention more quickly and not running the risk of another inventor developing their research. In the patent review conducted by our research group on inhalation injury 2 years ago, only three patents were found in clinical trials.

Regarding patents aimed at treatment for lung injury induced by smoke inhalation, specifically, we can observe an increasing amount of deposits in the last years. However, morbidity and mortality remain high, probably due to its extremely complicated pathophysiology. Besides the damages of the toxic and harmful gas, the oxidative stress, the interaction between cytokines and inflammatory mediators, and the activation of the NF-κB signaling pathway contribute to a greater difficulty in the treatment and control of this condition, making it difficult to standardize the research of new patents for strategies of treatment [9].

In the patent review conducted by our research group, which aimed to evaluate the development and patenting of natural and synthetic products for the treatment of smoke inhalation, a low number of patents deposited (18 in total) can be observed for this purpose. In addition, a great variety of both the mechanisms of action of the formulations and the form of administration of the formulations were observed [24]. Most new therapies are still at the stage of animal experimentation.

Early treatment remains the key to reducing mortality and improving prognosis. The inconsistent effects of certain therapies may be due to the diverse dose, mechanism of action, therapeutic duration, severity of the patients, and complementary interventions [37].

7. Conclusion

Developing better treatment strategies for this intractable disease still requires research, and the intellectual property enables the transformation of knowledge in principle and the link between knowledge and the market. However, currently, there is no particularly effective treatment for acute lung injury induced by inhalation of smoke; therefore, the search for suitable treatments for inhalation injury is continuing, and the treatments used for smoke inhalation are discussed.

Author details

Fernanda Oliveira de Carvalho*, Érika Ramos Silva, Paula Santos Nunes,
Karen Perez Pereira Ramos and Nayara Gomes Lima Santos
Post-Graduation in Health Sciences, Federal University of Sergipe, Aracaju, SE,
Brazil

*Address all correspondence to: fsoliveira.fisio@gmail.com

IntechOpen

References

[1] Barbieri JC. Uma avaliação do acordo sobre aspectos dos direitos de propriedade intelectual relacionados com o com: Cinco anos depois. RAP Rio de Janeiro. 2001;**35**(3):107-129

[2] Carvalho FO, Felipe FA, Costa ACSM, Teixeira LGB, Silva ER, Nunes PS, et al. Inflammatory mediators and oxidative stress in animals subjected to smoke inhalation: A systematic review. Lung. 2016;**194**(4):487-499

[3] Bassi E, Miranda LC, Tiermo PFGMM, Ferreira CB, Cadarmuro FM, Figueiredo VR, et al. Assistance of inhalation injury victims caused by fire in confined spaces: What we learned from the tragedy at Santa Maria. The Revista Brasileira de Terapia Intensiva. 2014;**26**(4):421-429

[4] Li H, Yao Z, Tan J, Zhou J, Li Y, Wu J, et al. Epidemiology and outcome analysis of 6325 burn patients: A five-year retrospective study in a major burn center in Southwest China. Scientific Reports. 2017;**7**:46066

[5] Iqbal T, Saaiq M, Ali Z. Epidemiology and outcome of burns: Early experience at the country's first National Burns Centre. Burns. 2013;**39**(2):358-362

[6] Peters W. Inhalation injury caused by the products of combustion. Canadian Medical Association Journal. 1981;**125**(3):249-252

[7] Souza R, Jardim C, Salge J, Carvalho C. Lesão por inalação de fumaça. Jornal Brasileiro de Pneumologia. 2004;**30**(6):557-565

[8] Zhi-Hai H, Yi J, Yun-You D, Xiao-Yang W, Yan H, Ting-Zheng F. Oxidative stress in a rat model of cotton smoke inhalation-induced pulmonary injury. African Journal of Traditional, Complementary, and Alternative Medicines. 2016;**13**(5):132-138

[9] Enkhbaatar P, Pruitt JRBA, Suman O, Mlcak R, Wolf SE, Sakurai H, et al. Pathophysiology, research challenges, and clinical management of smoke inhalation injury. Lancet. 2016;**388**:1437-1446

[10] Cox RA, Burke AS, Oliveiras G. Acute bronchial obstruction in sheep: Histopathology and gland cytokine expression. Experimental Lung Research. 2005;**31**:819-837

[11] Cox RA, Burke AS, Jacob S. Activated nuclear factor kappa B and airway inflammation after smoke inhalation and burn injury in sheep. Journal of Burn Care & Research. 2009;**30**:489-498

[12] Yamamoto Y, Sousse LE, Enkhbaatar P, Kraft ER, Deyo DJ, Wright CL, et al. γ-Tocopherol nebulization decreases oxidative stress, arginase activity and collagen deposition after burn and smoke inhalation in the ovine model. Shock. 2012;**38**:671-676

[13] Ferreira ALA, Matsubara LS. Radicais livres: Conceitos, doenças relacionadas, sistema de defesa e estresse oxidativo. Departamento de Clínica Médica da Faculdade de Medicina de Botucatu, Botucatu, SP.43. Revista da Associação Médica Brasileira. 1997;**43**(1):61-68

[14] Kurzius-Spencer M, Foster K, Littau S, Richey KJ, Clark BM, Sherrill D, et al. Tracheobronchial markers of lung injury in smoke inhalation victims. Journal of Burn Care & Research. 2008;**29**:311-318

[15] Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. The Biochemical Journal. 1990;**265**(3):621-636

[16] Tartaglia LA, Ayres TM, Wong GH. A novel domain within the 55 kd

TNF receptor signals cell death. Cell. 1993;**74**:845-853

[17] Walker PF, Buehner MF, Wood LA, Boyer NL, Driscoll IR, Lundy JB, et al. Diagnosis and management of inhalation injury: An updated review. Critical Care. 2015;**19**:351

[18] Toon MH, Maybauer MO, Greenwood JE, Maybauer DM, Fraser JF. Management of acute smoke inhalation injury. Critical Care and Resuscitation. 2010;**12**(1):53-61

[19] Sadowska AM. N-Acetylcysteine mucolysis in the management of chronic obstructive pulmonary disease. Therapeutic Advances in Respiratory Disease. 2012;**6**(3):127-135

[20] Gupta K, Mehrotra M, Kumar P, Gogia AR, Prasad A, Fisher JA. Smoke inhalation injury: Etiopathogenesis, diagnosis, and management. Indian Journal of Critical Care Medicine. 2018;**22**(3):180-188

[21] Cui P, Xin H, Yao Y. Human amnion-derived mesenchymal stem cells alleviate lung injury induced by white smoke inhalation in rats. Stem Cell Research & Therapy. 2018;**9**:101

[22] Bedri H, Romanowski KS, Liao J, Al-Ramahi G, Heard J, Granchi T, et al. A National Study of the effect of race, socioeconomic status, and gender on burn outcomes. Journal of Burn Care & Research. 2017;**38**:161-168

[23] Nuutinen T. Medicinal properties of terpenes found in *Cannabis sativa* and *Humulus lupulus*. European Journal of Medicinal Chemistry. 2018;**157**:198-228

[24] De Carvalho FO, Silva ÉR, Felipe FA, Teixeira LGB, Zago LBS, Nunes PS, et al. Natural and synthetic products used for the treatment of smoke inhalation: A patent review. Expert Opinion on Therapeutic Patents. 2017;**27**(8):877-886

[25] Domínguez A. Modificación de la superóxido dismutasa para mejorar sus propriedades biofarmacéuticas. Biotecnologia Aplicada. 2006;**23**:11-16

[26] Freitas-Mesquita AL, Meyer-Fernandes JR. Biochemical properties and possible roles of ectophosphatase activities in fungi. International Journal of Molecular Sciences. 2014;**15**(2):2289-2304

[27] Brands R. Method for increasing the activity of the immune system of a mammal at risk of inflammatory diseases. WO2009106368. 2009

[28] Murakami K, Bjertnaes LJ, Schmalstieg FC, McGuire R, Cox RA, Hawkins HK, et al. A novel animal model of sepsis after acute lung injury in sheep. Critical Care Medicine. 2002;**30**(9):2083-2090

[29] Enkhbaatar P, Murakami K, Traber DL. Method of preventing fibrin clots in pulmonar tissue through the use of aerosolized anticoagulants. EP2322189. 2011

[30] Enkhbaatar P, Murakami K, Traber DL. Method of preventing fibrin clots in pulmonary tissue through the use of aerosolized anticoagulants. EP1725244. 2006

[31] Enkhbaatar P, Esechie A, Wang J, Cox RA, Nakano Y, Hamahata A, et al. Combined anticoagulants ameliorate acute lung injury in sheep after burn and smoke inhalation. Clinical Science. 2008;**114**:321-329

[32] Murakami K, Traber D. Pathophysiological basis of smoke inhalation injury. News in Physiological Sciences. 2003;**18**:125-129

[33] Smith WB, Gamble JR, Clark-Lewis I, Vadas MA. Chemotactic desensitization of neutrophils demonstrates interleukin-8 (IL-8)-dependent and IL-8-independent

mechanisms of transmigration through cytokine-activated endothelium. Immunology. 1993;**78**(3):491-497

[34] Barbosa DB. Tratado da propriedade intelectual. In: Dois Estudos sobre os Aspectos Jurídicos do Patenteamento da Tecnologia Round up Ready no Brasil—A Questão da Soja Transgênica. Rio de Janeiro: Lumen Juris; 2013

[35] Cockburn I, Long G. The importance of patents to innovation: Updated crossindustry comparisons with biopharmaceuticals. Expert Opinion on Therapeutic Patents. 2015;**25**(7):739-742

[36] Jones BW. Broadening the scope of inherent anticipation and its impact on the patentability of chemical structures, comment, Smith Kline v. Apotex. 5. The John Marshall Review of Intellectual Property Law. 2006;**456**:455-476

[37] Guo B, Bai Y, Ma Y, Liu C, Wang S, Zhao R, et al. Preclinical and clinical studies of smoke-inhalation-induced acute lung injury: Update on both pathogenesis and innovative therapy. Therapeutic Advances in Respiratory Disease. 2019;**13**:1-11