

**Treatment of Dog/Cat hair allergy**

**: Comparison of existing and new therapies & spread strategy**

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## Abstract

: The number of companion animals such as dogs and cats (the hairy animals) is increasing in Korea. According to the companion animal registration system mandatory from 2014, 979thousands of companion animals are resisted in 2015. In addition, the companion animal market in Korea has been steadily growing since the “Pet Boom” of the 2000s. From 2015 to 2018, the average annual growth rate for the three-year period is 41.1%.<sup>1</sup> And it is expected that the total market size will reach 6 trillion won by 2020. The Ministry of Agriculture, Food and Rural Affairs has selected the companion animal industry as one of the future strategic industries.<sup>2</sup>

Thereafter companion animals market grown quantitatively but not qualitatively. A lot of adoption case in Korea. And often case that adopting with no considered as a condition for raising animals. Sometimes the dog & cat hair allergy without recognition of oneself allergy states can makes trouble.

I would like to write a review paper about treatment of dog & cat hair allergy. Through this review paper, I will examine the existing treatments for dog & cat hair allergy and compare the trends of recent treatments development. A comparison of the two treatments will introduce the treatments that dog & cat hair allergy patients can expect.

And I want to use the ecology of the companion animal industry for popularization of allergy treatment. Through the conclusion's method, I hope to offer cheap and accessible treatments to patients suffering from dog & cat allergy. I'll Also it an opportunity for the companion animal industry (especially companion animals insurance companies) to present competitive products.

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<sup>1</sup> 황원경, 정., 김도연 (2018). 2018 반려동물 보고서 : 반려동물 연관산업 현황과 양육실태. KB금융지주.

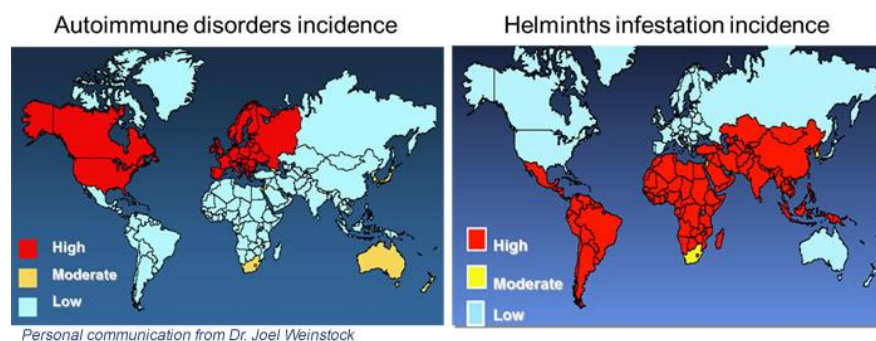
<sup>2</sup> 반려동물 시장에서의 소비자지향성 강화 방안연구. 허민영. 한국소비자원 정책연구. 18-14p 허민영 (2016). 반려동물 시장에서의 소비자지향성 강화 방안연구. 한국소비자원 정책연구.

## A. Introduction

### 1. About Dog & Cat hair allergy

: Allergy is a type 1 hyper sensitivity reaction (also immediate hyper sensitivity reaction) caused by IgE responsible for parasites in immune antibodies. Because parasites are so large that immune cells cannot engulf them, physical mechanisms are needed to remove them from the body. Thus, IgE against parasites is designed to produce rapid responses to cough, fever, runny nose, vomiting, diarrhea, itching, and mucus increase when the parasite protein is recognized.

However, with the development of industrial and hygiene ideas, the number of parasite infections has decreased and IgE has become an environment that cannot be activated properly. This situation has led to an allergy in which IgE is hypersensitive to proteins similar to parasite proteins.



**Figure1. Map of autoimmune disease and parasite infection for hygiene hypothesis**

This phenomenon has been published by David Strachan in 1989 as a **hygiene hypothesis** and has become a fact based on steady data for many years. In fact, the number of allergic patients, such as asthma and pollen allergies, has been found to be more frequent in developed countries where the environment is cleaner than in developing countries where parasite infections are frequent.<sup>3</sup>

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<sup>3</sup> Yazdanbakhsh, M., P. G. Kremsner and R. van Ree (2002). "Allergy, Parasites, and the Hygiene Hypothesis." Science **296**(5567): 490-494.

Type 1 hyper sensitivity is a violent symptom that can cause dyspnea, anaphylaxis, and suffocation to death. Is accompanied by the aforementioned weak symptoms such as runny nose, cough, sneezing.

The cause of allergic reaction is mainly protein factors. These symptoms are caused by the protein of the food protein (peach hair, shrimp, peanuts, grain etc) similar to the protein of the parasite that IgE reacted to, or the proteins of the dog & cat hair.<sup>4</sup>

Particularly, due to factors such as income increase, work-life balance, nuclear family, and change of leisure pattern, companion animals deeply come into contemporary society and frequent contact with hairy animals such as dogs and cats. Increased contact of these can increase the incidence of dog & cat hair allergy.

It is easy to think that “hair” itself is the cause of allergy because of the name of “dog & cat hair allergy”, but in fact, **the antigen is a protein factor such as dandruff, saliva and urine** attached to dog & cat hair. Many dog & cat hair allergy patients say that they “There was no allergy but now I have.” However, there is no allergy and it cannot occur.

Allergies are inherited because they are highly genetically affected. Family studies and genome analysis of autoimmune diseases such as atopy revealed genetic basis. Asthma and rhinitis are not caused by one gene but by the complex action of various genes.

In addition, environmental factors contribute to the onset of allergies, which may affect the mother’s environment in which early development occurs. Although IgE cannot pass through the placenta during pregnancy, the antigen passes through the placenta and attaches to the baby’s antigen presenting cell. Through MHC class 2, T-helper-2-cell activates B-cell to produce plasma cell and antigen-specific IgE

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<sup>4</sup> Jorgen Nedergaard Larsen, L. B. a. H. J. (2016). "Allergy immunotherapy: the future of allergy treatment." Drug Discovery Today **21**.

Production.<sup>5</sup>

In addition, since there is IgE in breast milk, IgE activity is born while being born. Although have dog & cat hair allergy, it's difficult to recognize before exposure to dog & cat hair. But dog & cat hair allergy can develop after adopt companion animals.

Patients suffering from dog & cat hair allergy are 1-20% worldwide<sup>6</sup>, and the incidence in Korea is 6~8% for dog allergies. The dog & cat hair allergy is a common cause of rhinitis and asthma.

In the case of cat hair allergy, the rate of detection of cat hair allergen was 66.7% in Korea, but there was little difference between a cat house and a non-cat house.

These figures are only a brief look at the contents of each paper. A large group survey under the same experimental conditions is necessary because the allergen disease depends on the antigen purification method and the allergen diagnosis method (SPT, Immuno CAP, etc.)

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<sup>5</sup> The immune system (ch14-14)

<sup>6</sup> Arbes, S. J., Cohn, R.D., Yin, M., Muilenberg, M.L, Friedman, W., Zeldin D,C,. (2004). "Dog allergen(CAN f 1) and cat allergen(Fel d 1) in US homes; results from the national survey of lead and allergens in housing."

## B. Allergy Mechanism

### 1. Concept of Dog & Cat hair allergy

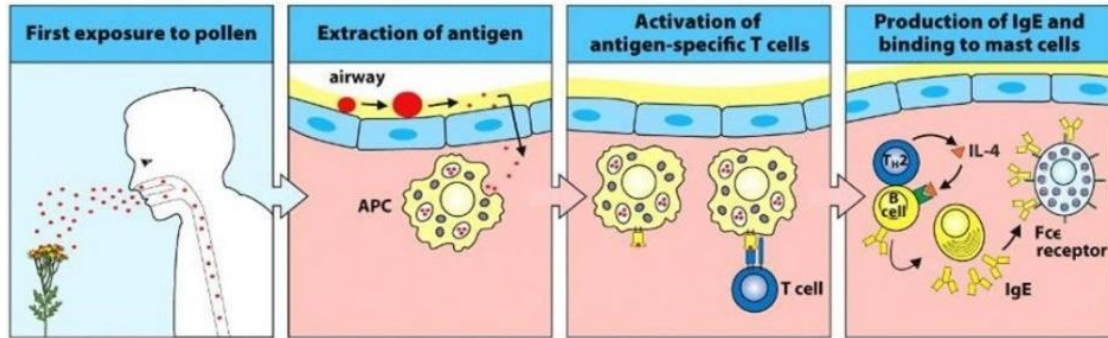


Figure2. Process of respiratory allergy (Source: Garland Science 2015, ch14-23)

: Dog & cat hair allergy is respiratory allergy. Therefore, the influx of the antigen occurs simultaneously with breathing. Inhalation of dog & cat hair antigens attached to respiratory mucosa. Antigens are getting small size through hydration. Minimized antigens can be presented by the Antigen Presenting Cell (APC) located in the mucosa. Presented APCs are processed by CD4 T-Cells to stimulate T-helper 2 Cells. These T-helper 2 Cell responses are mainly caused by basophils. When infection occurs, basophils migrate to secondary lymphoid tissues and bind to the CD40 of stimulated B- cells.<sup>7</sup>

When stimulated T-helper cells stimulate B-cells it helps IgE antibodies are secreted by CD40 legends. Secreted IgE is attached to the mast cell to induce degranulation of inflammatory substances. Inflammatory substances secreted from the mast cell can cause inflammation and cause runny nose, nausea and itching. Through these symptoms, we suffer from an allergy and discomfort with pain.

<sup>7</sup> The immune system (ch14-13)

## C. Existing Treatment of Dog & Cat hair allergy

### 1. Remove of allergen

: It is the easiest, most economical, and most basic way to treat allergies. In the case of pollen allergies or food allergies, you should avoid going out or eating the food, but removing the causative substances of dog & cat hair allergy is dissolution of adoption. Abandoned animals are goes to shelter which can cause social problems.

However, if the companion animals are accepted as a family and cannot be throw away them, several steps are taken to minimize respiratory contact with the animal's hair. Wearing mask, keep animal's hair short can help reduce the allergy. Frequent cleaning, such as frequent washing of bedding and clothing, may reduce the chance of hair getting into the respiratory tract. It is also possible to dispose the air cleaner to minimize the hair of the flying animal in the air. It can be the solution to raise a kind of hair that does not fall well (Bichon Frise, Poodle, Sphinx cat, etc.).

| Allergens                              | Number of positive home(%) |
|----------------------------------------|----------------------------|
| House dust mites                       |                            |
| <i>D. farinae</i>                      | 55(91.7)                   |
| <i>D. pteronyssinus</i>                | 27(45.0)                   |
| Fungus( <i>Aspergillus fumigatus</i> ) | 0                          |
| Pets                                   |                            |
| Dog                                    | 43(71.7)                   |
| Cat                                    | 40(66.7)                   |
| Cocroach( <i>Blatella germanica</i> )  | 7(11.7)                    |

**Table1. Detection rate of Dog & Cat hair allergen in Korean family**

However, in the case of cat hair, it is very hard to remove it completely by cleaning the house once, such as being attached to the wall for a long time. In fact, the presence of cats did not have a significant correlation with the detection of cat hair allergen, and cat hair antigen was detected in about 66.7% of the cats. This is a four times increase in the detection rate compared to the study 10 years ago, suggesting

that the companion animal allergies may become a big problem in Korea in the future. If you have a cat in house once, you can have a long-lasting antigen that causes cat hair allergy without professional cleaning.<sup>8/9</sup>

Although it is the easiest and most basic treatment method to carry out companion animal, it is hard to say that it is a good solution when you see the psychological burden of the individual not responsible for life and the social cost of organic animal increase.

However, there is a disadvantage that these measures for minimizing the contact with the fur continue to live with the companion animals and also require constant management. The purchase of air purifiers may also require burdensome monetary spending. Therefore, raising the companion animal simultaneously removing the antigens will require very demanding work, unless they breed the offspring of the hair.

## **2. Anti-Histamin uptake**

: Anti-histamine uptake is the most common method for allergy patients. It inhibits the action of Histamin, which is the major inflammatory substance in the inflammatory substance degranulated in the last stage of the allergic reaction, to suppress symptoms such as fever, runny nose, and itching.

It is easy to access at the pharmacy, so it has good accessibility and low cost. In addition, when you take your medication every time you have symptoms, you can stop allergies simply by stopping the symptoms. However, it cannot be a fundamental solution because it suppresses only the final response by allergic

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<sup>8</sup> 박창한, 권용은, 김덕인, 권혁수, 손성욱, 박흥우, 장윤석, 김선신, 성기민, 하영주 and 김윤근 (2007). "원저 : 알레르기 환자에서 한국의 대표적 흡입성 항원 16종의 특이 IgE 측정: GENEDIA-ELISA (Genedia Inhalant Allergen ELISA)법과 MAST-Immunoblot (RIDASCREEN)법 결과 비교." 천식 및 알레르기 **27**(1): 26-32.

<sup>9</sup> 박중원 (2010). 국민건강영양조사(검진조사분야) 기반의 가정 실내환경 및 알레르기질환 조사 모형 개발 보건복지부.

reactions.

It also has the disadvantage of weakening immunity throughout the body because it also blocks the inflammatory response to infections coming through other pathways aside dog & cat hair. In addition, depending on the constitution of a person, there may be a side effect of medicine and it may be a problem of overlapping with another drug. Therefore, it should be prescribed through counseling with a specialist and kept at a prescribed dose.

Depending on the type and severity of the symptoms, other medications such as bronchodilators, corticosteroids, and anti-leukotrienes may be prescribed in addition to antihistamines after consultation with a specialist.<sup>10</sup>

### **3. Allergen-specific Immunotherapy(AIT)**

: Allergen-specific Immunotherapy(AIT) was initiated by Dr.Noon in 1911 and is a fundamental immunotherapy for allergy treatment centers worldwide.

It is a treatment that aims to regression of symptoms by injecting the allergic antigen concentration into the body from a low concentration to a high concentration and making the allergic reaction insensitive. It is the method used when the allergy is severe or persistent, when the drug described above cannot be solved, when the drug has side effects, and when the antigen cannot be avoided.<sup>11</sup>

The antigens used in the treatment are obtained by refining antigens such as dandruff on dog & cat hair, and each pharmaceutical company has different purification source and refinement method. In Europe, it is made of aluminum hydroxide, which forms a complex structure with active protein and gradually

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<sup>10</sup> Jorgen Nedergaard Larsen, L. B. a. H. J. (2016). "Allergy immunotherapy: the future of allergy treatment." Drug Discovery Today **21**.

<sup>11</sup> 김상하 (2010). "면역요법 update." 대한천식알레르기학회 추계학술대회 **Work Group Mini-Symposium 3 : 면역요법/알레르겐**.

releases it. In USA, it is sold as aqueous bulk-extract and used in combination with each patient.<sup>12</sup>

Although it has the advantage of fundamental treatment, it takes 3 to 5 years for the treatment, and even if it is treated, the success rate is 85 ~ 90% depending on the individual difference. The success rate is 85 to 90%, which is probably high, but when fail will be great deal because of the high cost, time and psychological burden.

In particular, allergies are not covered by health insurance if they are not insured by insurance companies, which is a huge financial burden. In Korea, health insurance does not guarantee dog & cat hair allergy as a necessary treatment for human life.

Therefore, before taking the AIT method for allergy treatment, you should consider whether you will be able to take the long-term monetary expenditure considering the case that you enter 1 ~ 20%.

This treatment consists of a build-up period to gradually increase tolerance and patient sensitivity, and maintenance therapy to reach and maintain maximum tolerable dose. There are two main types of antigen, depending on the method of injecting the antigen into the body, and there are advantages and disadvantages of each.

Anaphylaxis, a systemic allergic reaction caused by the cross-linking of basophil and IgE on the surface of the mast cell, may occur with a probability of 0.13% since the antigen is directly injected into the circulation system.<sup>13</sup>

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<sup>12</sup> Park, J.-W. (2013). "Allergen Specific Immunotherapy for Allergic Rhinitis." Korean J Med **84**(6): 798-801.

<sup>13</sup> 김상하 (2010). "면역요법 update." 대한천식알레르기학회 추계학술대회 **Work Group Mini-Symposium 3 : 면역요법/알레르겐**.

## 1) Subcutaneous Immunotherapy(SCIT)

: It is a method to dilute refined dog & cat hair allergen at a high concentration at low concentration and inject it into the body according to the fixed period. It gradually increases the antigen in the blood and gradually reduces the immune response to the dog & cat hair antigen.

This treatment is based on the susceptibility of each individual to the antigen, so you have to use your personalized drug. Therefore, the price of medication is expensive (400,000 won per month) and you should visit the hospital every time you get an injection.

Also, the dosage and date are very important treatments, so be sure to keep an eye on the dates. Therefore, the patient should take many hassles such as not traveling for a long time or traveling. During the build-up period, one or two injections per week are required, and the maintenance therapy requires one inoculation every two to four weeks.<sup>14</sup>

Because the procedure itself is an injection, there is a psychological and physical burden on the patient due to frequent injections. Occasional swelling may occur due to local late-phase responses caused by local mast cells in the injected arm. Patients with asthma should be treated under the supervision of an expert.

It is a safe method and severe side effects are reported to be 1 in 1 million. It is a treatment that cannot be started during pregnancy, but if you have done it before pregnancy, you can continue treatment even during pregnancy under doctor's diagnosis.

However, only 5% of allergy patients choose SCIT because of the hassle and burden of treatment.<sup>15</sup>

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<sup>14</sup> Park, J.-W. (2013). "Allergen Specific Immunotherapy for Allergic Rhinitis." Korean J Med **84**(6): 798-801.

<sup>15</sup> MA, C. L. C. (2010). Subcutaneous specific immunotherapy for seasonal allergic rhinitis: a review of treatment practices in the US and Europe. Curr Med.

## 2) Sublingual Immunotherapy(SLIT)

: It is a treatment using the principle that refined dog & cat hair antigens are prepared in the form of refined pills and the refined antigens are absorbed into the body by fading for 1 to 2 minutes in the mouth. It is a method of delivering to the body through blood vessels under the tongue. In addition to blood vessels, immune function in the sublingual mucosa and surrounding lymph nodes may contribute to the mechanism.

Unlike SCIT, it has the advantage that the patient can do it at home without going to the hospital. In addition, the psychological and physical burden of the patient is less than that of each injection. However, there is a disadvantage in that it is necessary to eat the medicine every day at intervals of 1-3 days. Because the price is cheaper than SCIT (about 160,000 won per month), patients who want radical allergy treatment prefer the majority of SLIT methods.

After immunotherapy, local reactions such as itching and swelling under the lips or tongue may occur in 60 to 85% of patients, but most of them disappear within 14 days. Asthma patients may be at risk, although they are reported to have few side effects, so they must be administered under the prescription of a specialist. Also, if you have mouth disease in your mouth, you should stop.<sup>16</sup>

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<sup>16</sup> 김상하 (2010). "면역요법 update." 대한천식알레르기학회 추계학술대회 **Work Group Mini-Symposium 3 : 면역요법/알레르겐**.

## D. Latest Treatment

### 1. Intralymphatic Immunotherapy

: According to a Swedish paper published in 2012, intralymphatic immunotherapy for the **treatment of cat hair allergy has been successful in inducing tolerance after only 3 injections.**<sup>17</sup> Patients participating in this study consisted of 20 men and 25 men and 20 men and women aged between 20 and 54 years.

The lymph node contains intralymphatic immunotherapy (ILIT) such as DNA, RNA, oligopeptides, adjuvants, whole cells and proteins. APC detects the antigen from these interactions and stimulates T-helper 2 cell by treating with CD4-T-cell, which stimulates B-cell to produce IgE and induce degranulation of the mast cell.

Swedish scientists injected Fel d 1, a cat hair allergen, directly into the lymph node where the B-cell was assembled, so that the antigen could be hydrated and labeled on the APC and skipped the steps leading to the lymph nodes.

Fel d 1 is the predominant cat hair allergic antigen in which more than 90% of cat hair allergic patients respond. However, in this process, the antigen that enters the antigen directly has a strong immune response in the body, which puts the burden on the body and the antigen is not transmitted properly.

To prevent such side effects, the human invariant chain and feline dandruff antigen (Fel d 1) were injected by fused form. This fuse is called the Modular Antigen Transporter (MAT) and is called MAT-Fel d 1 because it uses the cat's hair antigen. This fuse process not only regulates the immune response but also increases the expression of MHC class 2.

MHC class 2 is a part that plays a role of marking only in B cell and Mast cell's

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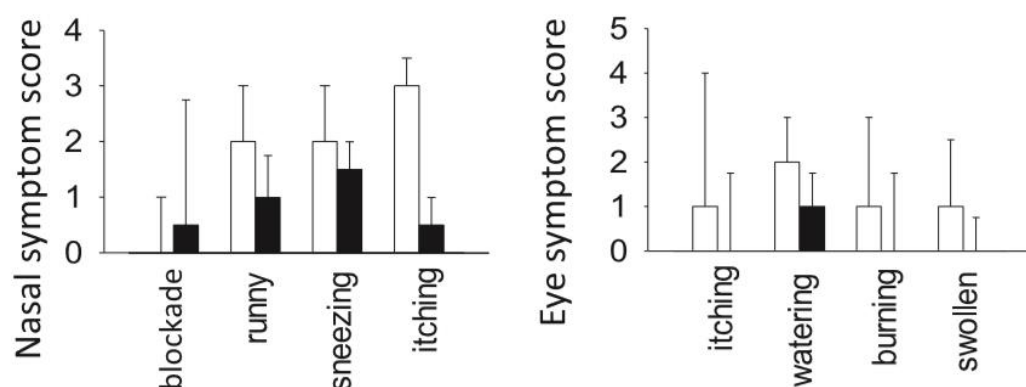
<sup>17</sup> Senti, G., R. Cramer, D. Kuster, P. Johansen, J. M. Martinez-Gomez, N. Graf, M. Steiner, L. A. Hothorn, H. Gronlund, C. Tivig, A. Zaleska, O. Soyer, M. van Hage, C. A. Akdis, M. Akdis, H. Rose and T. M. Kundig (2012). "Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections." J Allergy Clin Immunol **129**(5): 1290-1296.

surface. Increased expression of MHC class 2 by fusing the invariant chain and cat dander antigen (Fel d 1) implies targeting cat hair dandruff antigens to MHC class 2.

Compared with rFel d 1 produced from cat dandruff in a pharmaceutical factory and MAT-Fel d 1 produced in the laboratory under the same molarity conditions, mediator release produced by basophils in allergy patients in 100 times(rFel d 1 >> MAT-Fel d 1). It can be seen that MAT-Fel d 1 reduces the production of inflammatory substances much more than rFel d 1.

In 12 experimental group and 8 control group, the skin reactivity was 23 times more resistant in the experimental group than in the control group ( $p < 0.001$ ). In the T-cell responses, there was no response in the control group, whereas the IL-10 and IgG activities in the experimental group were significantly increased. In the nasal tolerance, the experimental group and the control group showed resistance to 74 times ( $P < 0.001$ ) and 3 times ( $P < 0.008$ ) after the experiment, respectively. Finally, there was no significant change in the skin tolerance between the experimental group and the control group.

This experiment was able to induce safe tolerance by injecting the antigen directly into the lymph nodes and also showed a short-term treatment in only "4 injections". It is a much shorter treatment period than conventional treatments, which took 3 to 5 years for treatment.



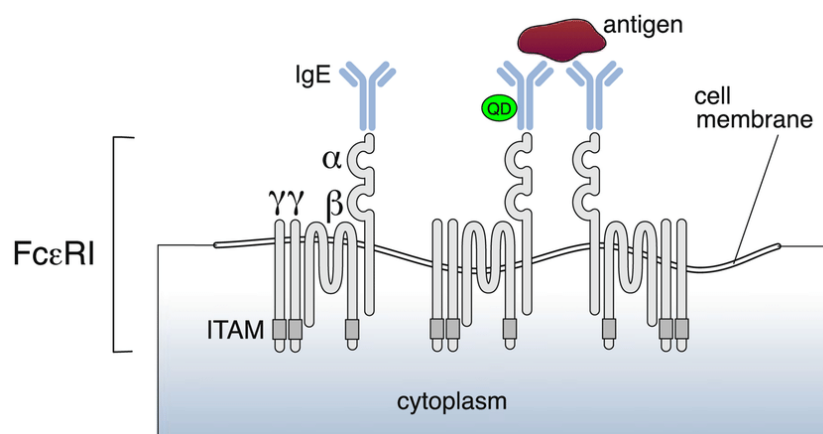
**Figure3. Symptom compares between allergen-treated and placebo-treated patient group**

In addition, this study showed that patients who underwent MAT-Fel d 1 treatment generally had significantly reduced nasal symptoms and ocular symptoms. Black bars were treated with MAT-Fel d 1, white was treated with placebo. Dog & cat hair allergy affects many mucous membranes located on the face side, so it is very uncomfortable in daily life due to the disease. As can be seen from the lesser number of white bars in the black bar, the quality of life of the person receiving the allergy treatment was increased by the above experiment.

## 2. Exon skipping treatment

: According to a paper published in the College of Veterinary Medicine and North Carolina state university in 2016, it is possible to control allergic reactions by **controlling FcεRIβ expression through 'Exon skipping technique'**.<sup>18</sup>

When IgE is attached to mast cells, degranulation occurs and inflammatory substances are secreted. In order for IgE to attach to the mast cell, a special linkage is needed. These linkages are called FcεRI and are divided into FcεRII and FcεRIβ II.



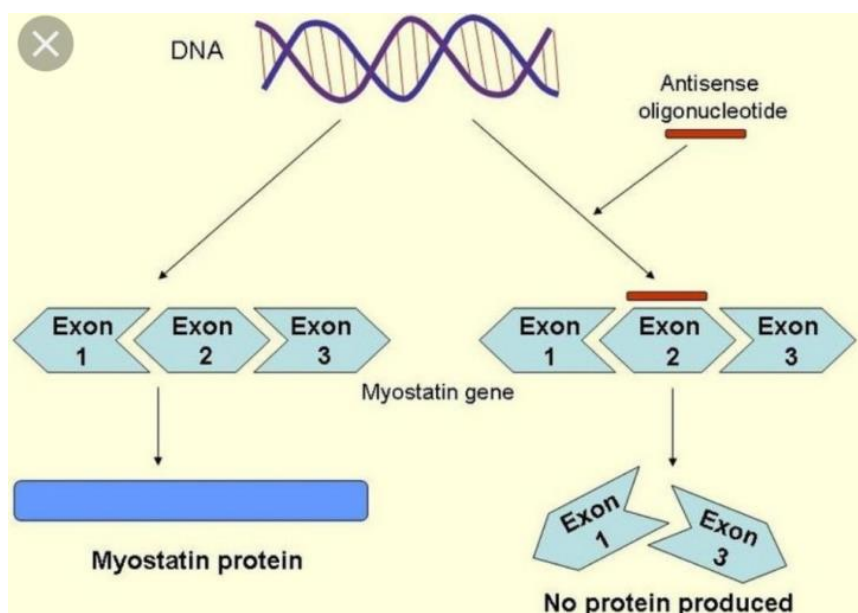
**Figure4. Sturcture of FcεRI (ResearchGate)**

<sup>18</sup> Exon skipping Cruse, G., Y. Yin, T. Fukuyama, A. Desai, G. K. Arthur, W. Baumer, M. A. Beaven and D. D. Metcalfe (2016). "Exon skipping of FcepsilonRIbeta eliminates expression of the high-affinity IgE receptor in mast cells with therapeutic potential for allergy." Proc Natl Acad Sci U S A **113**(49): 14115-14120.

FcεRII is a polypeptide with high affinity for IgE that mediates the function of IgE. Only one alpha chain is attached to IgE, while the other beta, gamma chains serve as a signal that IgE is attached to the mast cell. Therefore, there is one binding site.

Unlike FcεRII, FcεRI is a polypeptide with low affinity for IgE, which regulates IgE production and blood concentration. The structure is also different from FcεRII and there are three binding sites. This binding site has the characteristic that it binds more when attached to IgE. B cell and MHC II are also possible.

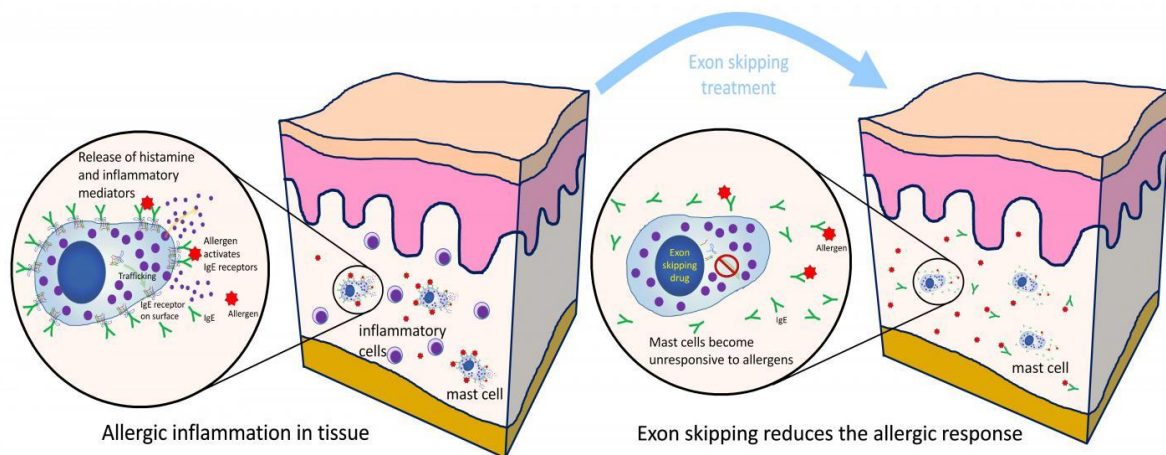
A protein enzyme called ADAM10 can cut FcεRI in 1 to 3 units, and the truncated FcεRI has the potential to attract many cells by functioning like a cytokine. These FcεRIs are made in the nucleus of the mast cell, and after they are made, they are located on the cell surface.



**Figure5. Concept of Exon skipping (Source: next Big FUTURE)**

In order for the protein to be produced, it is necessary to copy the genetic information (DNA) of the part forming the protein in the nucleus and make it as designed in the ribosome. Such a genetic information is a mRNA which is a copy of

the genome. In order to prevent the mRNA from reaching the ribosome and being designed as it is, an oligonucleotide that is complementary to the mRNA is injected, which prevents the mRNA from functioning. These oligonucleotides are called antisense oligonucleotides (AON) and the concept of silencing genetic expression with this concept is called exon skipping.

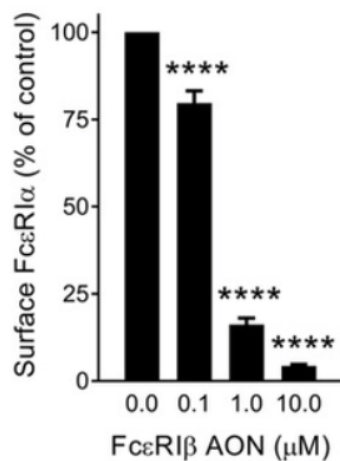


**Figure6. Concept of Exon skipping treatment of allergic response**

$Fc\epsilon RI\beta$  is a part of  $\alpha$ ,  $\beta$ , and  $\gamma$  that constitute  $Fc\epsilon RI$ , which links  $\alpha$  and  $\gamma$  structurally. When the genetic command to make  $Fc\epsilon RI\beta$  is silenced by Exon skipping technique,  $Fc\epsilon RI\beta$  to attach IgE to the surface of the mast cell disappears. Even though the dog & cat hairy allergen is inhaled, the IgE produced from B cell can not attach to the mast cell, and ultimately the inflammatory reaction substance can not be secreted.

Using this concept, the researchers analyzed the nucleotide sequence of MS4A, the exon site that expresses  $Fc\epsilon RI\beta$ , and produced  $Fc\epsilon RI\beta$ -Antisense oligonucleotides ( $Fc\epsilon RI\beta$ -AON), which are complementary to each other.

The resulting  $Fc\epsilon RI\beta$ -AON was gradually administered to (0.0, 0.1, 1.0, 10.  $\mu M$ ) rats and the results are shown in the following table..



**Figure 7. Surface activity of F according to AON concentration**

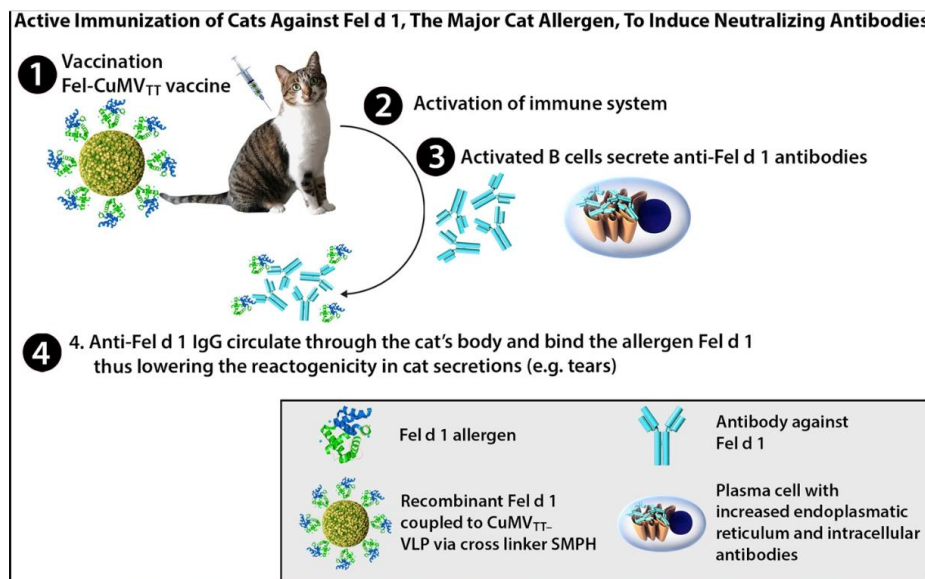
As can be seen in the table above, the expression rate of FcεRIα on the surface was remarkably decreased above 1.0 μM concentration. There was no problem with FcεRIβ-AON treatment that the cells could not degranulation or release calcium. In addition, the T-cell reaction, which plays an important role in the immune response, has not been or cannot be achieved. And the secretory function of the cytokine has not been affected. In other words, even with this treatment, there was no change in other functions of the cell and there was little side effect.

If the patient wishes, the Exon (MS4A) expression is returned to normal as soon as the treatment is stopped. So the patient can return to the original state at any time they want.

### **3. Vaccination to Cat (Cure for animal)**

In July 2019, researchers at Zurich University Hospital in Switzerland developed and released a vaccine to reduce cat hair allergen triggers. The vaccine takes a different approach from conventional therapies in that cats are treated rather than humans.

In this experiment, a cat is vaccinated by combining Fel d 1 with a cucumber mosaic virus to immunize the cat with its allergen Fel d 1.<sup>19</sup>



**Figure 8. Concept of Vaccination**

The center of the vaccine consists of Virus Like Particles (VLPs) derived from the cucumber mosaic virus. This VLP is an immunologically easily modified vegetable particle. It has the viral structure without genetic information, so it can move like a virus, but its transcription and replication do not occur.

Attach Fel d 1 allergen to the VLP using tetanus toxin-derived universal T-cell epitope tt830-843(CuMVtt) as the legend. Thanks to CuMVtt, we can get the help of T cells for the anti-Fel d 1 generation of B cells. Therefore, the vaccine is conjugated by VLP, CuMVtt and Fel d 1.

When the conjugated vaccine is inoculated to cats, B-cells produce anti-Fel d 1 antibodies against the Fel d 1 allergen via the immune system in the cat's body. The

<sup>19</sup> Thoms, F., G. T. Jennings, M. Maudrich, M. Vogel, S. Haas, A. Zeltins, R. Hofmann-Lehmann, B. Riond, J. Grossmann, P. Hunziker, A. Fettelschoss-Gabriel, G. Senti, T. M. Kündig and M. F. Bachmann (2019). "Immunization of cats to induce neutralizing antibodies against Fel d 1, the major feline allergen in human subjects." *Journal of Allergy and Clinical Immunology* **144**(1): 193-203.

anti-Fel d 1 antibodies produced are IgG type and circulate through the body. And these anti-Fel d 1 antibodies play a role in neutralizing Fel d 1. This is why cats produce less Fel d 1 allergens.

54 cats were used in the experiment. Cats were divided into groups of 5 or more and received vaccines of various concentrations ranging from 3 to 1000ug. The team tried to find the most effective vaccine concentration. Vaccines from each group were inoculated every 0, 21, 42 days, or every 3 weeks, and blood samples were drawn every 58, 71 and 85 days to produce serum samples. The collected blood samples were separated into serum and used to determine if the vaccine-induced antibody could properly neutralize Fel d 1.

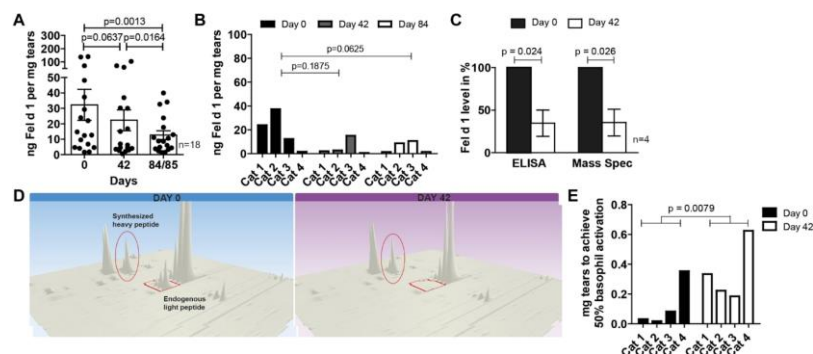


Figure 9. Anti-Fel d 1 antibodies in cat's serum

A total of 54 cats injected with different doses of the vaccine showed a significant reduction in Fel d 1. In tears, the main secretion of Fel d 1, Fel d 1 detection was much less in cats at weeks 3 and 6 of vaccine than cats at day 0 of vaccine.

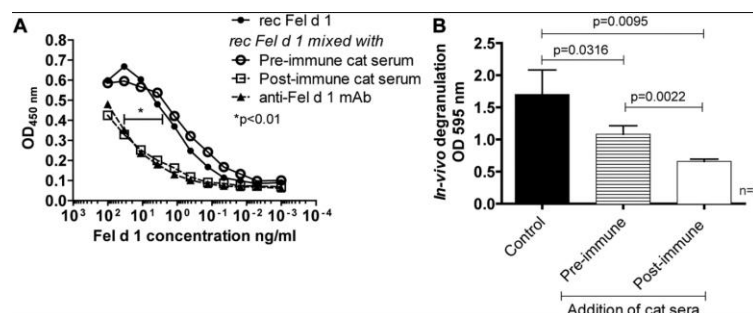


Figure 10. Reduction of Fel d 1 allergen in cat tear

40 weeks after injection, B cell stimulation through the vaccine showed a potent effect and produced persistent IgG antibodies. There were very few side effects from this vaccination. There were mild signs of mild fever, loss of appetite, and decreased activity for 1 to 3 days from the date of vaccination. In addition, there is no report that Fel d 1 plays an important role in the cat's body, and there is no toxic effect due to vaccination because vaccination does not affect the production of Fel d 1.

## E. Results

: The fundamental treatment of existing dog & cat hair allergy was focused on slowing down allergy sensitization. Therefore, the treatment process takes a long time and there is a possibility that the treatment is not successful, and the process is cumbersome and expensive. There is also a rare possibility, but there is a potentially lethal possibility of anaphylaxis. Therefore, it is very difficult to live with an allergy until a pet dies in a situation where an ordinary financial member has a dog / cat hair allergy. So, when a pet comes into the home of a patient with a dog / cat hair allergy, most people choose to send the pet out of the house rather than treat it.

On the other hand, the new therapies that we learned through the two papers mentioned above have a high probability of success, less burden on the body and less hassle. It is also a stable treatment because it can be treated with a structure that cannot be exposed to anaphylaxis. If these excellent therapies can be delivered at a low price, they can often prevent the sad situation of parting with pets due to dog / cat hair allergies.

However, there are uncertainties about the methods that have not yet been developed and are still dangerous to apply to people. This uncertainty is the same in terms of money. It is a newly studied treatment method, and in the early days, it is anticipated that there will be a considerable amount of treatment costs because the consumer will be the enemy. Therefore, pharmaceutical companies are expected to release this product as a full-fledged product through research after analyzing the demand for dog & cat hair allergy treatment market. The most recently developed cat vaccine is expected to require at least three more years for product safety testing.

The table below summarizes the time taken, cure rate, treatment burden, and cost according to the existing / latest therapies introduced above. (Do not list the vaccine to cat because it's not a cure)

|                  | Existing Treatment                                                                          |                                                                    | New Treatment                |                                                                    |
|------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------|--------------------------------------------------------------------|
|                  | SCIT                                                                                        | SLIT                                                               | Intralymphatic Immunotherapy | Exon skipping                                                      |
| Time taken       | 3-5 years                                                                                   | 3-5 years                                                          | 3 times                      | Always                                                             |
| Cure rate        | 85~90%                                                                                      | 85~90%                                                             | Unknown                      | 100%                                                               |
| Treatment Burden | <Injection><br>Follow date/<br>Must Visiting hospital/<br>Caring about sick or get medicine | <Medicine><br><br>Every time uptake/<br>Caring about mouth trouble | <Injection><br><br>Unknown   | Aerosols<br>or<br>Topical cream<br>(For delivery oligonucleotides) |
| Cost             | 400,000won<br>(339\$)/Month                                                                 | 160,000won<br>(136\$)/Month                                        | Unknown                      | Unknown                                                            |

**Table2. Compare with Existing Treatment and New Treatment**

Although new treatments have not been developed yet and have not been priced correctly, the most popular method is the Aerosol type formulation using the Exon skipping method. Immediate injection into the lymph nodes is a way to treat patients only if they are physically and psychologically burdensome and should be visited in the same context as SCIT therapy. Considering that dog & cat hair allergy is aspiration allergy, Exon skipping agent is more suitable than Aerosol type cream.

Exon skipping technology was originally a personalized medicine because it was originally developed for the treatment of specific genetic diseases. We need a lot of skills and manpower to make oligonucleotides that make complementary binding and make drugs by analyzing patients' genes to identify and silence the mutant exons in question. Therefore, the price of medicine for treatment was very expensive.

**However, mast cells that cause dog & cat hair allergy are the most common cells that all normal people have.** MS4A, an exon that produces FcεRIβ, is also a common exon of normal people. Therefore, mass production of the same AON

(Antisense oligonucleotide) can be popularized as a treatment for dog and cat hair allergy. This means that the burden of medicines for treatment can be greatly reduced. If it is well developed and sold as a drug with few side effects, it can help patients who suffer from many dog & cat hair allergies inexpensively.

However, Exon Skipping is not a fundamental solution. Although it can block the connection between IgE and mast cells, which cause allergies, it can not overcome the constitution that reacts to dog & cat hair allergen. In this regard, antihistamine is one of the existing treatment seems to be no different from taking.

But, the Exon skipping aerosol formulation does not interfere with the intrusion of other antigens in the body, so it can differentiate from the existing methods in that it can control the allergic reaction by targeting only the respiratory tract without reducing the overall immunity of the body.

Injecting a vaccine into a cat is a major breakthrough in that it can reduce the antigenic substance in a few injections without burdening a human at all. However, the reaction of dissatisfied or worried consumers is mixed with giving cats for human convenience. A wider market, a vaccine for dog hair allergies, should also be developed.

## **F. Discussion**

### **1) Importance of the spread of Dog & Cat allergy treatment**

: Although studies on dog & cat hair allergy have been studied only as a cause of asthma and rhinitis, a variety of new therapies focusing on the allergies themselves have been researched due to the growing market needs of companion animals.

The biggest reason why the pet market was able to grow in Korea is because the companion animal is "a pleasure to be". This pleasurable companion animal was obtained from acquaintances such as relatives and friends (44.9%), from a pet shop (27.9%), from a dog sale site (7.6%), by breeding dogs (5.4%) And so on. Almost 80% of the companion animals come from the acquaintance and the pet shop.

Although it may come to mind to bring up a companion animal, it is not a matter to see that 43% (80 out of 186) of the respondents answered that they had studied basic parenting before raising a companion animal. It is found that more than half of the cases of bringing a companion animal or bringing a cute child to a pet shop and taking it impulsively. In this way, it is true that the rate of adoption by simple appeal is high in the current pet animal market, which is growing economically but is still not well cultured.

However, in a situation where dogs and cats are allergic to one in 10 people, the early adoption is not right. Therefore, it is necessary to examine the allergies of the family members who will be staying together before adopting the companion animals. However, there is very little culture in which all family members are tested and adopted in Korea.

If one or more of the family members are allergic to adoption of a companion animal, the problem can be solved by abandons the companion animal. However, 85.6% of the companion households already consider the companion animal as family<sup>20</sup>, It is very difficult to do. Recently, more and more people are trying to treat

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<sup>20</sup> 황원경, 정., 김도연 (2018). 2018 반려동물 보고서 : 반려동물 연관산업 현황과 양육실태. KB금융지주.

dog and cat hair allergy.

However, in the current situation, basic allergy treatments such as ATI are long-running, cumbersome, and costly, so many people cite it as the best way to maintain good accessibility and good antipsychotics. Fortunately, many researchers have developed an approach that minimizes the inconvenience caused by allergies by finding an easy-to-control stage for each stage based on an understanding of the allergic mechanism.

The popular spread of dog & cat hair allergy therapy is very important in that it is marketable and research is being done.

## **2) Strategy to distribute allergy treatment methods using Korean companion animal market**

: Companion animal insurance is the only thing that can grow together as the pet grows. Because companion animals are not insured in the country, the cost of treatment and treatment is so high that consumer awareness of insurance is very high.

| <b>Monthly medical bill for a 13-year-old Maltese</b> |                              |
|-------------------------------------------------------|------------------------------|
| Unit: thousand won                                    |                              |
| Insulin shots                                         | 75                           |
| Disposable syringes                                   | 20                           |
| Medication for Cushing's disease                      | 200                          |
| Diabetes checkup                                      | 300-400                      |
| <b>Total</b>                                          | <b>Approximately 600-700</b> |

**Table3. High medical cost of old dog in Korea. (Source: Korea Joongang Daily)**

Human beings invented the insurance system because they worried that it would be a disease with high treatment cost. It is insurance that you pay a small monthly

fee to the company and the company guarantees the cost of the treatment in case of a contracted disease later on. Customers before the illness can prepare for future illnesses, and the company is a great business model that allows customers to see the monetary benefits of the time and probability of getting sick.

Dog & cat fur allergy can also be covered by accident insurance. However, it is not guaranteed by the national health insurance, so it can only be processed if the private insurance of the private enterprise is enrolled.

Usually people have insurance against illnesses, but there is a companion animal insurance on the market to prepare for companion diseases. In particular, as the pet animal industry grows, pet insurance will grow in the same way. In advanced countries (Germany, UK, USA, etc.) where the animal culture is already relatively advanced, the coverage rate is about 10 ~ 20%. The same Asian country, Japan, is about 8%, but South Korea is less than 0.2%..<sup>21</sup>

The pet insurance market in Korea began in 2007, but the number of insurance contracts until 2017 is actually very low to 2,600, so the pet insurance market has not yet been activated. Since petroleum registration was implemented in Korea in 2014, pet insurance from 2007 to 2014 was an opaque market in which even the number of customers could not be identified. Since the number of customers was not known, the insurance coverage rate could not be estimated and the demand for companion households was also unpredictable. Therefore, the insurance products offered by the companies were poor.

| Type      | Company                         | Name                     | Detail                                                                                    |
|-----------|---------------------------------|--------------------------|-------------------------------------------------------------------------------------------|
| Insurance | Samsung Fire & Marine Insurance | Familiaris Dog Insurance | •Covers medical bills and property liabilities<br>•Dog-only policy                        |
|           | Lotte Non-Life Insurance        | Lotte MyPet Insurance    | •May cover surgery as well as brief visits to veterinarian<br>•Cats may subscribe as well |
|           | Hyundai Marine & Fire Insurance | Hi-Pet Insurance         | •Policy options include coverage for common pet diseases like skin and joint disease      |

**Table4. Koran Pet Insurance company status (Source: each company)**

<sup>21</sup> 황원경, 선. (2015). "국내외 반려동물보험 동향과 시사점." KB 지식 비타민.

Neutralization surgery, which should be essential for companion animals, was excluded from the guarantee and did not guarantee disease such as patellar dislocation or uterine dystrophy, which are common in dogs. In addition, since the insurance product was composed only by the contract of one year, the guarantee period was short. And when the companion animal was old, it was virtually ineffective because it was not insured. Some companies have no products for other companion species such as cats, hamsters, birds, etc.

It is very difficult for pet insurance companies to calculate insurance premiums because the cost of companion animals charged in animal hospitals is so different from hospital to hospital. They were treated the same but the cost of treatment for each veterinarian was very different.

For these reasons, the pet insurance market continued to suffer deficits, and most of the insurance companies withdrew their pet insurance in favor of consumers. However, as the pet market has increased recently, insurance companies have begun offering products that complement previous disadvantages, and they are responding to the new industry. In fact, Maritz Pet Insurance, launched in November 2018, became a hot topic with 1600 contracts in 15 days.

## G. Conclusion

: When we look at the situation of the companion animal insurance market and the trend of the latest allergy treatment. I would like to propose a way for consumer, insurance companies and animal hospitals to win-win. It is the **launch of an insurance product that adds the escape clause that guarantees care for the dog & cat hair allergy** of the caregiver who raises the companion animal.

In Korea, eight out of 100 patients suffering from allergies to dogs. And one out of every five people raises companion animals. About two out of 100 people have dog hair allergies while raising dogs. The price of medicines for the treatment of dog hair allergy is about 200,000 won per month, and a total cost of 12 million won is needed for 5 years treatment. Assuming that all of these 100 people are covered by pet insurance, a simple calculation can cover two people for 2,000 Won per person per month.

If you pay the additional amount of about 3 ~ 4,000 won per person and release the dog & cat hair allergy treatment product with special terms, it can bring benefits to the insurance company. It will also meet the expectation of consumers who are worried that they may have an allergic problem with their companion animals. It is not expensive at all, given that the insurance cost of a 2-year-old Maltese is between 30,000 and 40,000 won.

The reason why the pet insurance did not work well was the two reasons that the guarantee range was narrow and the consumer had fewer items to be guaranteed. And the difference of the different medical expenses for each animal hospital played a big role. However, if the caregiver can guarantee allergic treatment costs for the companion animal, it can be judged that the product has a wide range of assurance for the consumer. Simply launching a product for a person can easily market it as an insurance product that is thought of as a consumer.

Also, because it is a treatment for human diseases, it is easy to calculate the insurance fee because the medical expenses are constantly different from the animal hospital. Companion animals have different diseases and genetic diseases, so it is

troublesome to pay premiums separately. Data on human allergy can be calculated more simply than animals. This means that data on the percentage of allergic diseases in humans can be quickly applied to the already designed pet insurance structure at once.

Companion animals are not as well managed as individuals yet. There is no computer network that can verify that the company that is charged will pay the insurance fee in duplicate if each animal is charged to another insurance company for the treatment received by the animal. It may also happen that the cost of the treatment billed to another animal is taken in the name of the insured animal. According to data from the Ministry of Agriculture, Food and Rural Affairs published in 2017, it is estimated that there are about 8 million companion animals in 2016, but only 107.1, 7.5%. However, people do not have to worry about these illegal payments because they are managed by the National Health Insurance.

Because of this advantage, if the number of customers joining pet insurance increases, health checkups for companion animals will be strengthened, and veterinarians will be able to check the health of companion animals and induce continuous visitation, which is an opportunity to increase profits.

The main target group of pet insurance is those who raise young companion animals. Since Korea prefers to raise young puppies, families who raise young puppies tend not to have a long period of raising their companion animals. Therefore, the time of exposure to dog & cat fur allergy antigen is short and the condition of allergic disease is not yet clear. If they are sensitive to allergies at this time, they begin to feel anxiety about separation from companion animals. About 6% to 8% of Koreans said they had an allergic reaction to dog hair, and all of them would feel the adoption of their companion animals. The guarantee of allergic treatment fee for the guardian can function as an insurance product that can solve the uneasiness and also provide medical insurance for the companion animal.

If the existing dog and cat allergy treatment method is insured, the next generation allergy treatment such as exon skipping can be applied to the public immediately after calculating profit and loss. As a result, the public is able to treat expensive and

long-lasting allergy treatments cheaply and quickly through pet insurance.

However, there are still many issues to be considered for this proposed solution. The biggest hurdle is that do not know exactly how many people are sensitize all animals to each other. Although we know the allergic population of dogs in Korea is 6% to 8%, the allergic population of cats has not yet been formally studied or investigated. In addition, the previous studies on dog allergic patients are not reliable because they are not obtained from various sex ratios and age specimens. If the population of dog & cat hair allergy is more precisely investigated, if the insurer ultimately suffers a loss, this option will not be applicable.

In addition, treatment of dog & cat hair allergy through pet insurance is not reflected in the position of pharmaceutical companies and hospitals. Although I think it would be beneficial to increase the number of patients who want to treat allergy through this method, it is difficult to know what position to take for the increase through pet insurance. This is a problem that should be suggested after the number of allergic patients mentioned above becomes statistically counted and profitable in the insurance company's profit and loss calculation.

If researchers and insurance companies research the above problems and spread the treatment, they will be able to reduce the number of organic animals that are caused by allergies and effectively relieve patients suffering from dog & cat hair allergy.

## References

- 1.Arbes, S. J., Cohn, R.D., Yin, M., Muilenberg, M.L, Friedman, W., Zeldin D,C,. (2004). "Dog allergen(CAn f 1) and cat allergen(Fel d 1) in US homes; results from the national survey of lead and allergens in housing."
2. Cruse, G., Y. Yin, T. Fukuyama, A. Desai, G. K. Arthur, W. Baumer, M. A. Beaven and D. D. Metcalfe (2016). "Exon skipping of FcεpsilonR1β eliminates expression of the high-affinity IgE receptor in mast cells with therapeutic potential for allergy." Proc Natl Acad Sci U S A **113**(49): 14115-14120.
- Jorgen Nedergaard Larsen, L. B. a. H. J. (2016). "Allergy immunotherapy: the future of allergy treatment." Drug Discovery Today **21**.
- 3.MA, C. L. C. (2010). Subcutaneous specific immunotherapy for seasonal allergic rhinitis: a review of treatment practices in the US and Europe. Curr Med.
- Park, J.-W. (2013). "Allergen Specific Immunotherapy for Allergic Rhinitis." Korean J Med **84**(6): 798-801.
- 4.Senti, G., R. Cramer, D. Kuster, P. Johansen, J. M. Martinez-Gomez, N. Graf, M. Steiner, L. A. Hothorn, H. Gronlund, C. Tivig, A. Zaleska, O. Soyer, M. van Hage, C. A. Akdis, M. Akdis, H. Rose and T. M. Kundig (2012). "Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections." J Allergy Clin Immunol **129**(5): 1290-1296.
- 5.Thoms, F., G. T. Jennings, M. Maudrich, M. Vogel, S. Haas, A. Zeltins, R. Hofmann-Lehmann, B. Riond, J. Grossmann, P. Hunziker, A. Fettelschoss-Gabriel, G. Senti, T. M. Kundig and M. F. Bachmann (2019). "Immunization of cats to induce neutralizing antibodies against Fel d 1, the major feline allergen in human subjects." Journal of Allergy and Clinical Immunology **144**(1): 193-203.
- 6.Yazdanbakhsh, M., P. G. Kremsner and R. van Ree (2002). "Allergy, Parasites, and the Hygiene Hypothesis." Science **296**(5567): 490-494.
- 7.김상하 (2010). "면역요법 update." 대한천식알레르기학회 추계학술대회 Work Group Mini-Symposium 3 : 면역요법/알레르겐.
- 8.박중원 (2010). 국민건강영양조사(검진조사분야) 기반의 가정 실내환경 및 알레르기질환 조사 모형 개발 보건복지부.
- 9.박창한, 권용은, 김덕인, 권혁수, 손성욱, 박흥우, 장윤석, 김선신, 성기민, 하영주 and 김윤근 (2007). "원저 : 알레르기 환자에서 한국의 대표적 흡입성 항원 16종의 특이 IgE 측정: GENEDIA-ELISA (Genedia Inhalant Allergen ELISA)법과 MAST-Immunoblot (RIDASCREEN)법 결과 비교." 천식 및 알레르기 **27**(1): 26-32.
- 10.허민영 (2016). 반려동물 시장에서의 소비자지향성 강화 방안연구. 한국소비자원 정책연구.
- 황원경, 선. (2015). "국내외 반려동물보험 동향과 시사점." KB 지식 비타민.
- 11.황원경, 정., 김도연 (2018). 2018 반려동물 보고서 : 반려동물 연관산업 현황과 양육실태. KB금융지주.