

## Shiseido Focuses on Langerhans Cells to Strengthen Skin Immunity

[TOKYO – March 19, 2014] Shiseido Co., Ltd. has long focused its research on skin immunity as an important means of maintaining skin's health, and protecting it from external and internal stressors that can lead to dermatologic problems. Through this research, Shiseido discovered that one function of skin immunity, the self-protection function that sedates the stimuli response factors of Langerhans cells,<sup>※1</sup> is important to maintaining skin homeostasis, and that this function declines with age.

Shiseido has developed a multiple component<sup>※2</sup> that effectively combines three ingredients, including  $\beta$ -glucan, to target the Langerhans cells and help recover their self-protection function. Shiseido has applied for a patent for this technology in nine countries, including Japan. Furthermore, with a prototype serum incorporating this multiple component, Shiseido proved for the first time that the skin's self-protection function can be recovered.

Shiseido is currently planning to engage in R&D for the launch of a skincare product applying these research results.

Shiseido has been researching skin immunity for more than 20 years. This includes collaborative research with the Massachusetts General Hospital/Harvard Cutaneous Biology Research Center in Boston, Massachusetts, an internationally recognized <sup>※3</sup> dermatological research institute.

※1 This is a dendritic cell that is created in the bone marrow, and exists in the prickle cell layer of the epidermis. It constitutes 2–5% of the total cell count of the epidermis and is known to be the control center for skin immunity. It was named after Paul Langerhans, the medical scientist who discovered it in 1886

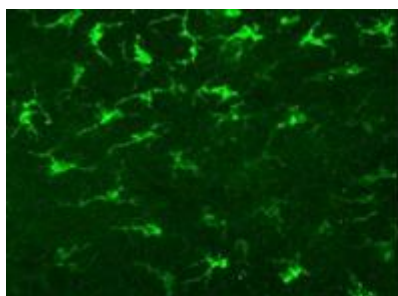


Image of Langerhans cells/cross-sectional view of epidermis showing the location of Langerhans cells

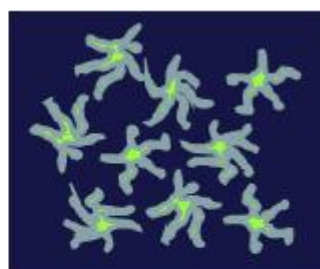


Image of Langerhans cell in epidermis

- ※2 A multiple component of  $\beta$ -glucan, aquainool (an original ingredient developed by Shiseido) and Bulgaria rose water.  $\beta$ -glucan itself is effective in enhancing the immunity of Langerhans cells, but we have discovered that the effect can be further enhanced by combining it with other elements, creating a multiple component. We have created this combination, and we have applied for patent.
- ※3 CRBC, MGH/Harvard Cutaneous Biology Research Center is a dermatological research institute which was founded with major support from Shiseido in 1989 at Massachusetts General Hospital, the largest teaching hospital of Harvard Medical School. Shiseido has sent many researchers to the CRBC to engage in collaborative research with scientists.

### Skin Immunity and Langerhans Cells

To maintain the youth and beauty of the skin, it is important to maintain its stability (homeostasis). This brings out the natural power of the skin and heightens its vitality. Shiseido has been conducting research based on the belief that the Langerhans cells, which control the immunity of skin, play an important role in maintaining this stability.

The Langerhans cell's commanding function was discovered in the 1970s, and it became the basis for the work related to dendritic cells and immunity that earned Dr. Ralph Steinman the Nobel Prize in 2011. In addition to the commanding function of Langerhans cells, the self-protection function that prevents skin troubles was recently discovered. Shiseido understands that this self-protection function also contributes to the immunity of the skin.

The commanding function is unique to Langerhans cells. Upon detecting germs, such as fungi, or foreign objects, such as chemical substances that penetrate the skin, Langerhans cells command the other immune cells (lymphoid cells) to attack and resist those foreign objects.

The self-protection function is also unique to Langerhans cells. Upon detecting a stimuli response factor that causes skin troubles, for example inflammation caused by external stimuli such as UV exposure, dryness, pollution, or emotional stress, the Langerhans cells directly attack the stimuli response factor in self defense .

In this sense, Langerhans cells are the commanders of other cells, as well as performers that take action.

### Research on skin immunity at Shiseido creates a new field of skin physiology.

In 1993, Shiseido made a landmark discovery, scientifically proving that the skin and the nervous system are closely related, mediated by the Langerhans cells, which are the commanders of the skin's immune system.<sup>※4</sup> With this discovery, Shiseido became part of creating a new field of skin physiology called Neuro-Immuno-Cutaneous-Endocrine – or the NICE theory. This finding came through a collaborative research effort with the MGH/Harvard Cutaneous Biology Research Center. It was this finding that inspired efforts to focus research on skin immunity.

- ※4 Nature; 13 May, 1993

### **Discovery: a new mechanism of skin trouble**

In 2007, Shiseido identified a mechanism of skin disorders, distinct from the known mechanism triggered by skin stress factors such as UV exposure and dryness. The new mechanism engages when the skin responds to stress or external stimuli, generating factors within the cornified cells (keratinocytes) that make up the epidermis. Excessive skin damage factors are produced, which can lead to various skin troubles<sup>※5</sup>.

Another research facility reported that Langerhans cells respond to stimuli response factors by attacking and sedating them, using their self-protection function to minimize skin troubles.

Shiseido then conducted research to determine whether a relationship exists between aging and the self-protection function of the Langerhans cells, and if so, to develop a skin care solution to address this mechanism.

※5 J Invest Dermatol 2007; 162:362

### **Developing a multiple solution that acts directly on Langerhans cells and enhances skin immunity.**

In 2014, Shiseido discovered that the self-protection function that sedates stimuli response factors of Langerhans cells declines with age. When the skin's self-protection function declines, it upsets skin's homeostasis, resulting in roughness or decreased firmness caused by the degenerated barrier function of the horny cell layer, and degradation of collagen fibrosis in the dermis. To recover this self-protection function and heighten the immunity of the skin, Shiseido developed a multiple component that effectively combines three ingredients, including  $\beta$ -glucan, which directly influences the Langerhans cells.

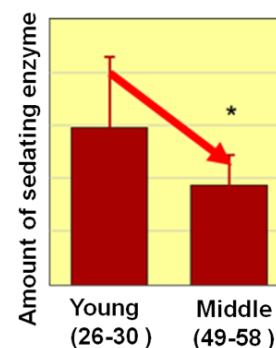
When scientists used the prototype serum incorporating this multiple component, they were able to prove that the self-protection function of the Langerhans cells can be heightened.

The new finding, development of relevant ingredients, and effects

#### **(1) Age-related decline of the self-protection function in Langerhans cells**

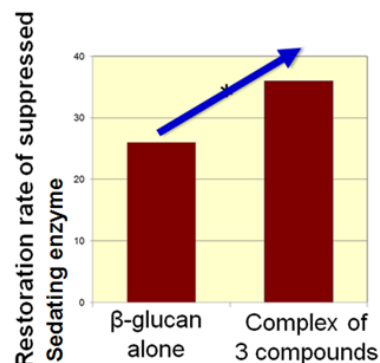
The surface of Langerhans cells are covered with CD39 enzyme (elimination factor). As this enzyme sedates the stimuli response factor, Langerhans cells exert the self-protection function.

To investigate the transition with age, Shiseido scientists conducted tests using samples from both younger (26~30/N=10) as well as more mature skin (49~58/N=12), and analyzed the level of elimination factors in the Langerhans cells. The function of the mature group substantially decreased compared with the younger group, suggesting that the self-protection function, which sedates stimuli response factors, declines with age.



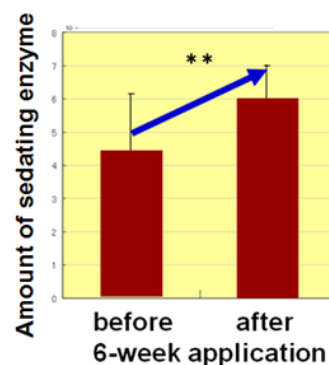
## (2) Development of ingredients to directly affect Langerhans cells and heighten immunity of skin

Shiseido then began to develop ingredients that would influence Langerhans cells and restore their self-protection function, to heighten the immunity of the skin. Researchers found that the multiple component combining three ingredients, including  $\beta$ -glucan, (which is abundant in yeast and fungi such as agaricus and is known to have a high immunity-activating function) was more effective in heightening the self-protection function of the Langerhans cells than  $\beta$ -glucan alone.



## (3) Prototype product confirms effectiveness on humans.

When Shiseido researchers asked test subjects to use a prototype serum incorporating this multiple component for six weeks, they were able to confirm that the declined self-protection function of the Langerhans cells was strengthened, and that skin immunity had been boosted. Particularly among the mature group, the function recovered to a level comparable to that of the younger group before usage.



### Future direction

Shiseido will work on R&D to launch a skincare product that is based on this research. Shiseido will also report the results of the basic research that constituted the foundation of this new technological development at the annual meeting of the Society for Investigative Dermatology (SID), to be held in Albuquerque, New Mexico, this May.

Shiseido will continue to conduct basic research to develop new solutions for maintaining skin stability.