

Scientists discover key enzyme responsible for skin blistering in the elderly

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The Granzyme B (GzmB) enzyme, which accumulates in certain tissues as we age, has been identified as a driver of itchy and sometimes life-threatening autoimmune conditions known as pemphigoid diseases

(PDs), which cause blistering and skin erosion below the skin's surface.

New research led by University of British Columbia (UBC) and Vancouver Coastal Health Research Institute (VCHRI) scientists has found that a gel containing a specific and potent inhibitor of GzmB activity, VTI-1002, resulted in significant improvements on [skin](#) affected by PDs.

"Blisters caused by these conditions can be extremely discomforting, unsightly and potentially fatal," says the study's senior author Dr. David Granville, a professor in UBC's department of pathology and laboratory medicine and executive director of VCHRI. "Given that there is currently no cure for pemphigoid diseases, the need for better treatments to care for affected individuals will continue to grow in the coming years as our population ages."

Published this week in *Nature Communications*, the study found that inhibiting GzmB reduced blistering by approximately 50 per cent in three different models.

Research results also showed that the GzmB-inhibiting gel protected the structural integrity of the skin and reduced inflammation.

"While several studies have investigated how to target and block other enzymes that may lead to PDs, our Granzyme B-blocking VTI-1002 gel reduced both the inflammation and disruption of the skin layers that contribute to blistering," says Dr. Granville.

One reason blocking GzmB is effective is because, unlike other enzymes that can break down proteins in the body, there are no inhibitors to prevent GzmB activity outside of cells, Dr. Granville explains. When GzmB accumulates over time due to chronic inflammation, the body lacks a natural defense mechanism to rein it in.

"Our study results show great promise for GzmB inhibition," says Dr. Granville. "A GzmB-blocking gel could be used as a safer, more targeted alternative for treating autoimmune blistering and other inflammatory skin diseases."

GzmB is naturally produced by [immune cells](#) in the body and plays a role in helping to eliminate unwanted cells. However, in certain conditions, GzmB escapes from these cells into the [extracellular space](#) where it accumulates and eats away at [structural proteins](#) that hold the skin together. In the case of PDs, GzmB accumulates in the blister fluid and surrounding tissues, cleaving key proteins that anchor the top layer of skin (epidermis) to the bottom layer (dermis), which leads to skin separation and blistering.

The current treatment for PDs is topical or oral corticosteroids. Often associated with [severe side effects](#) and occasionally mortality, they also contribute to skin thinning and impaired healing, both of which are already problematic among elderly individuals. Treatments are therefore needed that do not exacerbate these conditions.

More information: Sho Hiroyasu et al, Granzyme B inhibition reduces disease severity in autoimmune blistering diseases, *Nature Communications* (2021). [DOI: 10.1038/s41467-020-20604-3](https://doi.org/10.1038/s41467-020-20604-3)

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