

Researchers pinpoint possible way to prevent permanent hearing loss caused by cancer drug

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University of Alberta researcher Amit Bhavsar is leading a team that has identified a receptor in cells that could be key to preventing permanent hearing loss in childhood cancer survivors who are being treated with the drug cisplatin. Credit: William Au

University of Alberta scientists have identified a receptor in cells that could be key to preventing permanent hearing loss in childhood cancer survivors who are being treated with the drug cisplatin. The researchers believe by inhibiting the receptor, they may be able to eliminate toxic side-effects from the drug that cause the hearing loss.

Cisplatin is an incredibly effective chemotherapeutic when it comes to treating solid tumors in children, contributing to an 80 per cent overall survival rate over five years, according to U of A researcher Amit Bhavsar, an assistant professor in the Department of Medical Microbiology & Immunology. The problem has always been with the [side-effects](#). Nearly 100 per cent of patients who receive higher doses of cisplatin show some degree of [permanent hearing loss](#). The ability to prevent this side-effect would dramatically improve the quality of life of childhood cancer survivors after they recover from the disease.

As Bhavsar explains, many researchers look at cisplatin's damaging side-effects from the angle of genetics, trying to determine underlying risk factors for [hearing loss](#) or examine how it works as a chemotherapeutic. A fair amount was known about the progression of [hearing](#) loss as a side-effect, but it was the initial spark—the instigating factor kicking everything off—that remained a mystery.

Bhavsar and his team thought outside the box and took things all the way

back to the [periodic table](#) with their approach, getting some clues from the chemical composition of cisplatin itself and eventually identifying a particular receptor that was getting turned on.

The receptor in question is Toll-like receptor 4 (TLR4), which is involved in the body's immune response. TLR4 works by crossing the [cell membrane](#), sticking a portion of itself outside the cell to sample the environment and to look for different signals that indicate damage or danger of some sort.

"It's a receptor that your body normally uses to detect when there's some sort of issue, like an infection. This receptor will turn on, and it'll start producing these signals that tell the cell it's under stress. Unfortunately in the case of cisplatin, those signals ultimately lead to the death of the cells responsible for hearing."

The cells affected by TLR4's signals are located within the cochlea of the ear, where they play a crucial role in hearing, translating vibrations in the ear into electrical impulses. Cisplatin also accumulates in the kidneys, but the difference is that it can be flushed out and diluted in that area of the body; in a closed system such as the ear, it accumulates and damages the cells.

"These cells don't renew. You really only get one shot and if they're gone, you're in trouble. The hearing loss is permanent," said Bhavsar.

The only way to prevent the damage is to stop the signals TLR4 produces that lead to the accumulation of cisplatin. To confirm the efficacy of inhibiting the TLR4 receptor, Bhavsar and his team looked at zebrafish models, with the help of Ted Allison, an associate professor in the Department of Biological Sciences and member of the U of A's Neuroscience and Mental Health Institute. They examined neuromasts, which are sensory cells within zebrafish that behave similarly to the

human hair cells typically damaged by cisplatin. Bhavsar was able to prove that inhibiting TLR4 led to an inhibition of the damage on the sensory [cells](#).

Bhavsar, a member of the Cancer Research Institute of Northern Alberta (CRINA), the Li Ka Shing Institute of Virology and the Women and Children's Health Research Institute (WCHRI), is collaborating with CRINA member Frederick West and Allison to refine an inhibitor that can disrupt this sampling process, removing the function that causes the toxic side-effect while still keeping the immune sensor function intact so patients don't become immunocompromised.

"It really does open the door for potential therapeutics," said Bhavsar.

The study, "Toll-like receptor 4 is activated by platinum and contributes to [cisplatin](#)-induced ototoxicity," was published in *EMBO Reports*. The work received support through operating grants from the Canadian Institutes of Health Research and the Stollery Children's Hospital Foundation through WCHRI, as well as funding from the Li Ka Shing Institute of Virology.

More information: Ghazal Babolmorad et al, Toll-like receptor 4 is activated by platinum and contributes to cisplatin-induced ototoxicity, *EMBO reports* (2021). [DOI: 10.15252/embr.202051280](https://doi.org/10.15252/embr.202051280)

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