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Scientists bring to light mechanism of drug for infections

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Scientists at A*STAR's Singapore Immunology Network (SIgN) have discovered the exact mode of action by plerixafor, a drug commonly prescribed to stimulate immune responses in patients suffering from neutropenia, which causes them to become prone to oral, skin, genital infections and in worst cases, a fatal whole-body infection . A better understanding of the drug's mechanism can improve its usage to more effectively reduce risk of infections in these patients.

Scientists at SIgN employed cutting-edge imaging techniques to analyze the effects of plerixafor on the white blood cell activity in the study which was published in the *Journal of Experimental Medicine* (*JEM*).

Neutropenia is a condition characterized by the lack of a type of white blood cells, also known as neutrophils , in one's blood circulation. Plerixafor increases the concentration of these white blood cells in the blood by inhibiting a protein called CXCR4. This inhibition prevents neutrophils in the blood stream from returning to the bone marrow, which is the primary compartment where the white blood cells are stored and released. It is therefore commonly accepted that the efficacy of the drug arises only from the release of these white blood cells from the bone marrow.

However, scientists at SIgN found that the inhibition of CXCR4 by the drug actually plays a dual role – It increases the neutrophil count in the blood through their release from the lungs, while simultaneously promoting their retention in the blood stream. Discovery of this

additional mode of action not only provides a deeper understanding on the drug's mechanism, it also contributes to a more effective utilization of the drug. The ground-breaking study creates the possibility of using a combined drug treatment to maximise release of white blood cells from both the bone marrow and the lungs. The approach may be more effective in reducing the risk of bacterial infections in neutropenic patients.

The team leader, Dr Ng Lai Guan from SIgN said, "We have identified the precise mechanisms of plerixafor treatment, which has important implications on its usage. We can understand through this study the effectiveness or limitations of the drug on certain patients and thereafter craft new clinical approaches to better treat them. Our study forms a conceptual framework to establish improved therapeutic strategies for neutropenia."

Acting Executive Director of SIgN, Associate Professor Laurent Rénia, said, "Basic research as such is important for us to fully understand how drugs work, so that we can put them to best use. This is a study which can potentially be translated into clinical applications to impact the health and lives of neutropenic patients."

More information: "Neutrophil mobilization via plerixafor-mediated CXCR4 inhibition arises from lung demargination and blockade of neutrophil homing to the bone marrow" by Sapna Devi et al . www.jem.org/cgi/doi/10.1084/jem.20130056

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