Surgeal operations are usually performed under anaesthesia – an artificially-induced insensitivity to pain. There are different types of anaesthesia such as regional and general anaesthesia. Regional anaesthesia blocks nerve impulses from painful stimulation within a certain area while the patient retains consciousness and awareness. General anaesthesia, on the other hand, induces a state where the patient loses awareness and sensation of pain all over the body.

**ANAESTHESIA IN SURGERY**

A variety of medications can be used to induce this general anaesthesia, called general anaesthetics, with most administered to patients intravenously or via inhalation. Medications that are given inhalationally are termed inhalational (volatile) anaesthetics and are a popular choice of drugs in surgery. Nonetheless, besides inducing anaesthesia, the effects of these drugs on the human body are often poorly understood. Interestingly, research is now showing evidence of interactions between anaesthetics and receptors/other proteins in the body's immune cells.

**ANAESTHETICS AND THE IMMUNE SYSTEM**

The immune system is a highly complex network of cells, organs and tissues that protects our body from foreign intruders like bacteria, viruses or fungi. Early research by Dr Yuki demonstrated that isoflurane and sevoflurane (commonly used volatile anaesthetics) can directly bind to and impair functions of a receptor (adhesion molecule) present on immune cells, called leukocyte function-associated antigen-1 (LFA-1). Isoflurane also impairs another adhesion molecule receptor macrophage-1 antigen (Mac-1).

LFA-1 is a surface protein present on all leukocytes. These are crucial cells in mediating various immune responses including leukocyte migration and immunological synapse formation. Mac-1 is present on a subclass of leukocyte, mostly innate immune cells. It mediates their recruitment and is involved in clearance of microbes and cell debris (through a process known as phagocytosis).

Dr Yuki and his team study the effect of these volatile anaesthetics on the immune system using two examples: destruction of tumour cells by immune cells, and sepsis which is a disease caused by dysregulated immune responses leading to a systemic inflammatory response upon infection.

**ANAESTHETICS WORSEN SEPSIS**

In addition to systemic inflammatory response, sepsis often causes life-threatening organ dysfunction. Severe sepsis and septic shock remains a health care burden and carries a significant high morbidity and mortality. It has a mortality rate of 20–30% and, in the US alone, around 750,000 cases of sepsis occur annually. More worrying though, these numbers are increasing worldwide. Sepsis is considered to be a time-sensitive disease and requires an urgent or emergent treatment upon diagnosis. Evaluation of
Anaesthetics are typically administered to patients regardless of the type of disease being treated during surgical operations. However, as Dr Yuki’s research proves, certain anaesthetic drugs might not be suitable for anaesthetising certain patients.

In their recent research, Dr Koutsogiannaki (Instructor in Anaesthesia, Harvard Medical School), one of Dr Yuki’s lab members, demonstrated a negative effect of the volatile anaesthetic isoflurane on sepsis outcomes. LFA-1, the receptor shown to be affected by isoflurane in vitro, is important for recruitment of neutrophils (a subclass of leukocytes), the first-defence immune cells to inflamed tissues.

Proinflammatory molecules activate LFA-1 present on neutrophils circulating in the blood stream. Activated LFA-1 then binds to intercellular adhesion molecules (ICAMs), which are present on the surface of cells on the interior of blood vessels (endothelial cells). Subsequently, neutrophils can traffic into the primary site of infection.

Dr Yuki and his team have demonstrated that, after administering isoflurane for six hours, significantly fewer neutrophils were recruited to septic tissue in their mouse model – in line with LFA-1 being hampered by the drug. However, intravenous anaesthetic propofol administration did not affect neutrophil recruitment to the primary site of infection. Similarly, Mac-1 was also hampered by isoflurane administration – isoflurane is a relatively more efficient and bacterial load higher in various tissues. The researchers also observed an increased mortality rate in septic mice exposed to isoflurane, but not to propofol.

Interestingly though, a short isoflurane administration did not affect neutrophil recruitment to the primary site of infection. Consequently, neutrophils can traffic into the primary site of infection.

Why did you first become interested in this area of research?

In our anaesthesia practice at Boston Children’s Hospital, volatile anaesthetic isoflurane is the mainstay of anaesthetic agents for paediatric cardiac surgical operations. Therefore, we use cardiopulmonary bypass. In some cardiac surgical cases, we cool the body temperature very low even down to 18°C for organ protection during cardiopulmonary bypass. Because solubility of isoflurane goes up significantly at this extreme cold temperature, I was curious what isoflurane could do to the body in this circumstance. Although the anaesthetic mechanism of volatile anaesthetics remains to be elucidated, these small molecules are proposed to be promiscuous (have multiple binding sites). One of the significant complications is perioperative infection in this population, and I wanted to see if they would affect immune cells as well by directly affecting some proteins.

Dr Yuki and his team at Boston Children’s Hospital. Dr Yuki (on the left) and his team (from left to right): Wei Wang, Matt Chamberlain, Sophia Koutsogiannaki, Hui Zha, Kazumasa Tanaya and Erika Matsunawa.

Dr Yuki’s laboratory research focuses on improving patient care.

Why are the implications of your research for the clinical usage of anaesthetics?

So far our research is based on animal model experiments. In our model, volatile anaesthetics such as isoflurane and sevoflurane, Dr Yuki and his team have investigated the effect of these anaesthetics on NK cell function. By exposing tumour cells to isoflurane and sevoflurane, Dr Yuki and his team found that the tumour cell toxicity induced by NK cells was reduced. This was theorised. More specifically, the binding of NK-cells to their targets and the localisation of the cytotoxic vesicles within the NK cells was negatively affected.

Are there indications that anaesthetics affect other processes in the human body besides immune function?

Yes, I think so. For example, some anaesthetics affect the cardiovascular system as well. A clinician who anaesthetises critically-ill children with congenital heart diseases, cardiovascular effects of anaesthetics are important issues to consider. By identifying these targets that potentially worsen cardiovascular physiology, we might be able to develop anaesthetics devoid of immunosuppressive effects as well.