

## **HIT and Mist: The FOG has lifted on Platelets**

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Heparin-induced thrombocytopenia (HIT) and other thrombocytopenias have been my research interests since 1979. Not surprisingly, I also became interested in the regulation of platelet production. FOG-1, GATA-1, Fli-1 and NFE2 are major transcription factors (TFs) involved in this regulation. An accident in the 1990s took my research to FOG-2 and GATA-4, key TFs in cardiac development. In this presentation I shall discuss my research in these three areas. I saw a patient with HIT in 1979 when I was a haematology registrar. He was probably the first case of HIT diagnosed in Australia. Several cases of HIT had already been reported in the USA but none in UK and continental Europe. At the time, the pathogenesis of HIT was unknown and there were no clinical diagnostic criteria, no reliable lab test and no effective treatment. Over the next 10-15 years, we made key contributions to the elucidation of the disease mechanisms, proposed clinical diagnostic criteria, established reliable laboratory tests and an effective treatment for HIT. We confirmed that HIT was caused by an IgG antibody that induced strong platelet activation via platelet Fc gamma RIIA receptors and also via its Fab domain. In the 1980's we carried out the only randomized control trial in the treatment of HIT by comparing danaparoid with dextran 70. Until then, there were many "hits and misses" in our attempts to find an effective HIT treatment. With advent of new anticoagulants in 1990's, I mistakenly thought that HIT would no longer occur after the "mist has lifted". I deliberately changed my research direction to the regulation of platelet production. We discovered a previously unrecognized negative feed-back mechanism that regulates platelet production, mediated by bone marrow stroma cell-derived thrombopoietin (TPO). In addition, platelet production is also regulated by a network of transcription factors such as FOG-1, GATA-1, Fli-1 and NFE2. We discovered these TFs interact with each other in their regulation of genes involved in megakaryopoiesis. When we over expressed GATA-1 and NFE2 in megakaryocytes, platelet production was increased; this allows us to make enough platelets *in vitro* for platelet function studies. This is a proof in concept experiment that may lead in future to large scale *in vitro* platelet production for patient treatment. In an attempt to clone human FOG-1, we accidentally cloned human FOG-2 (not yet cloned then) and this led us to study the nuclear import mechanisms and SUMOylation of GATA-4 and FOG-2 and their roles in cardiac development and cardiac hypertrophy. In conclusion, HIT, MISS and FOG are a major part of the landscape in my research journey in Australia.