

ASX Release

Anagrelide Paper by Professor Steve Watson SUDA Scientific Board Member

PERTH, AUSTRALIA – 12 November 2018: SUDA Pharmaceuticals Ltd (ASX: SUD), a leader in oro-mucosal drug delivery, has attached a paper co-authored by Professor Steve Watson, a member of SUDA’s Scientific Board for the Anagrelide project.

The paper, titled *“Anagrelide is an anti-megakaryocytic and not an anti-platelet agent”*, was published on 7th November 2018 in the online journal “Platelets” by Steve P. Watson & Amanda Dalby (2018).

The paper is an important step in the re-classification of anagrelide into a new therapeutic class as an anti-megakaryocytic agent. There is significant evidence of platelets playing an important role in cancer growth, invasion and metastasis. Anagrelide is currently the only clinically available small molecule that has the ability to lower the platelet count without an effect on red or white cell production, and is therefore a unique agent.

SUDA welcomes this move to recognise the true therapeutic activity of anagrelide and supports Professor Watson’s belief that this change will assist in furthering the research into the use of anagrelide in cancer.



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NOTES TO EDITORS:

About SUDA Pharmaceuticals Ltd

SUDA Pharmaceuticals Ltd (ASX: SUD) is a drug delivery company focused on oro-mucosal administration, headquartered in Perth, Western Australia. The Company is developing low-risk oral sprays using its OroMist® technology to reformulate existing pharmaceuticals. The many potential benefits of administering drugs through the oral mucosa (i.e.: cheeks, tongue, gums and palate) include ease of use, lower dosage, reduced side effects and faster response time. SUDA's product pipeline includes ZolpiMist™, a first-in-class oral spray of zolpidem for insomnia. ZolpiMist is marketed in the USA and SUDA has rights to the product outside of the US and Canada. SUDA has submitted a Marketing Authorisation Application to the Australian Therapeutic Goods Administration for ArTiMist®, its novel sublingual malaria treatment for children. In a Phase III trial, ArTiMist was shown to be superior to intravenous quinine. Other products in development include oral sprays for the treatment of: migraine headache; chemotherapy-induced nausea and vomiting; erectile dysfunction; PAH; epileptic seizures and pre-procedural anxiety; and cancer. For more information, visit www.sudapharma.com

About blood platelets in cancer

Cancer survival across all solid tumour types has been shown to be related to the number of blood platelets a patient has, cells which are more usually associated with the clotting process. However, platelets are now known to provide essential growth factors that nourish cancer cells and enable them to take hold and develop into tumours. Hence, those patients with the highest platelet numbers are least likely to survive. This has been shown across a wide range of solid tumours including cancer of the brain, oral cavity, the head and neck, thyroid carcinoma, gastrointestinal cancers, pancreatic, hepatocellular cancer, colorectal cancer, cancer of the lungs and bronchus, cancer of the ovaries, endometrium, cervix, breast, prostate, kidneys, skin mesothelioma, melanoma and gallbladder.

About Anagrelide

The pharmacology of anagrelide enables the selective lowering of platelet numbers without significantly affecting clotting or the formation of other blood cell lines and, in this respect, is unique. Currently anagrelide is only available as a solid oral formulation and is used exclusively as an anti-thrombotic agent. The drug's fundamental limitation which precludes its use in the treatment of cancer is its cardio-stimulatory side-effect profile. These effects are known to be due to a highly potent cardio-excitatory metabolite of the drug, formed in large quantities during its initial passage through the liver after oral administration. The use of proprietary non-enteral formulation such as an oro-mucosal spray would minimise this first pass effect in the liver.



Anagrelide is an anti-megakaryocytic and not an anti-platelet agent

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History

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The term ‘anti-platelet’ is widely used to describe small molecules that cause a reduction in platelet function, leading to reduced aggregation and thrombus formation. Drugs such as P2Y₁₂ receptor antagonists (e.g. clopidogrel, prasugrel, ticagrelor) and aspirin target the feedback pathways of activation and are used prophylactically in patients at risk of arterial thrombosis. However this term is sometimes mistakenly used to describe molecules that cause a reduction in platelet count, causing unnecessary confusion given the distinct actions and applications of platelet-inhibitory and platelet-lowering drugs.

‘Grel’ is the official INN naming stem for drugs with anti-platelet activity. However, it is also part of the name of the platelet-lowering agent, anagrelide [1,2], which reflects its originally intended development as an anti-platelet agent [3], an action mediated by inhibition of phosphodiesterase (PDE) III. The official classification of anagrelide by the World Health Organisation is as an anti-platelet agent [4]. However, in clinical trials involving multiple dosing, anagrelide was found to produce a profound-lowering of platelet count at doses well below those needed for its anti-aggregatory effects [5]. Numerous studies have since shown that anagrelide reduces the platelet count in human at concentrations that have no significant effect on platelet activation [1,6]. Anagrelide was therefore only developed as a platelet-lowering agent.

Anagrelide is orally active and has been used in the clinic for over 20 years for treatment of myeloproliferative disorders, such as essential thrombocythaemia which is associated with an over-production of platelets and increased risk of thrombosis [7]. Anagrelide remains the only clinically available small molecule that lowers platelets counts without an effect on red or white cell production, and is therefore a unique agent [8]. Anagrelide is well tolerated and does not prolong bleeding or increase bruising, consistent with only a fraction of circulating platelets being required for normal haemostasis [5,9].

Anagrelide has been shown to cause disruption of megakaryocyte maturation at the post-mitotic stage, leading to a reduction

in cell size and ploidy, and a decrease in platelet production [2,10]. Gene expression studies link signalling through the eIF2 α /ATF4 pathway to the anti-megakaryocytic properties of anagrelide [11], leading to changes in expression of numerous genes involved in megakaryopoiesis, including the transcription factors GATA-1 and FOG-1 [12]. This action is independent and separate from anagrelide’s PDE III inhibitory action which is only seen at higher concentrations and accounts for the anti-aggregatory action that was first seen in development.

Despite the above, anagrelide continues to be referred to as an anti-platelet agent [4,13–15]. This causes unnecessary confusion for researchers, healthcare workers and their patients, as well as patent offices, and may hold back research and evaluation of anagrelide in additional diseases that could benefit from the drug’s unique selective platelet-lowering activity such as cancer metastasis, chronic obstructive airways disease, diabetes, systemic lupus erythematosus and various autoimmune diseases [16–20].

It is time to correct the misuse of ‘anti-platelet’ for platelet-lowering agents, such as anagrelide and rafigrelide [21], and propose that this group be termed ‘anti-megakaryocytic’. We predict that this will reinvigorate interest in such drugs for new therapeutic uses that could benefit from a reduction in platelet count, including cancer.

Declaration of interest

SPW is on the Scientific Advisory Board of Suda Pharmaceuticals Limited.

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