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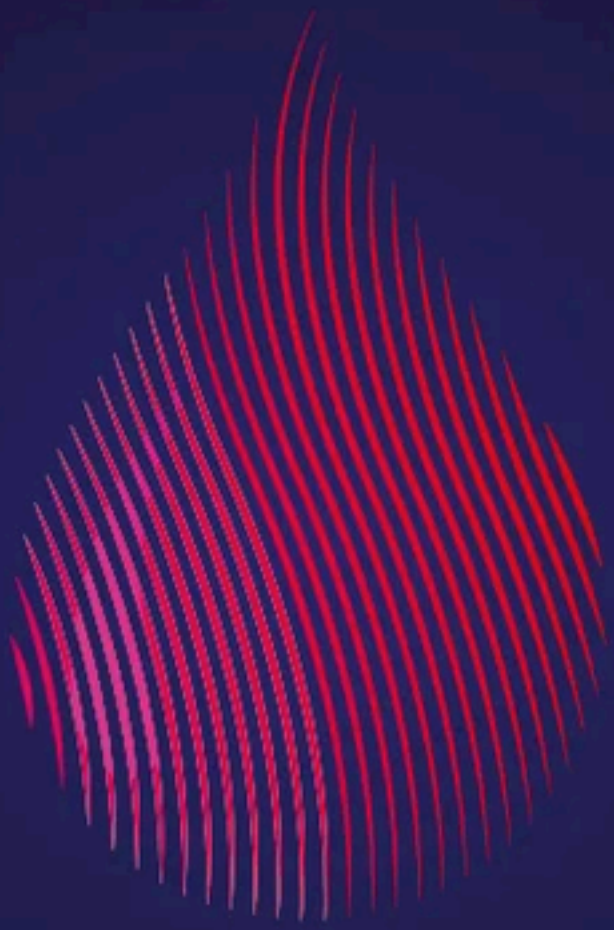

The cutting edge: Advances and challenges in blood cancer

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How DiaMedica aims to reshape treatments for ischemic diseases

DDW Editor **Reece Armstrong** speaks to **Rick Pauls**, CEO of DiaMedica, about the company's efforts in ischemic diseases and the challenges of drug discovery in this field.

RA: How did DiaMedica decide to explore ischemia?

RP: Ischemic diseases driven by restricted blood flow and endothelial dysfunction, such as preeclampsia (PE), foetal growth restriction (FGR), and acute ischemic stroke (AIS), have seen little meaningful innovation in decades and carry with them tremendous societal and economic consequences. A solution that could provide even incremental improvements may potentially relieve the burdens experienced by patients and their families and save global healthcare systems billions of dollars.

To address the needs of this underserved area, DiaMedica is advancing DM199, a novel, first-in-class, recombinant form of the naturally occurring human tissue kallikrein-1 (KLK1) protein, a therapy that if successful, would reshape the way ischemic conditions are treated.

RA: Why has there been a lack of progress in treatments for PE?

RP: The current standard of care for preeclampsia (PE) offers limited, short-term symptom management and supportive care in efforts to delay the delivery. The only cure for PE is delivery of the foetus and the placenta, often prematurely, which can lead to negative health impacts on the baby. Even though PE is the second leading cause of maternal mortality worldwide, there has been little success in the development of new therapeutics interventions often due to the risk associated with evaluating investigational therapies in pregnant women.

RA: You're focused on restoring the KLK1 protein. What's the importance behind this protein and how can its therapeutic synthesis translate to a range of ischemic conditions?

RP: DM199 is a recombinant form of the human tissue KLK1 (rhKLK1) protein, which enhances blood flow and vascular health by increasing the available levels of nitric oxide, prostacyclin and endothelium-derived hyperpolarising factor, the three key signalling molecules in promoting vasodilation and endothelial health. Other therapeutics in development often target only one of these factors, limiting impact on the disease. DM199 acts through a novel mechanism of action, activating bradykinin 2 receptors which are believed to be upregulated in ischemic conditions and therefore more prevalent in the endothelium of ischemic arteries. DM199 is the only therapy in development simultaneously targeting maternal hemodynamics and foetal outcomes.

RA: Additionally, is there any scope for its use in neurological conditions?

RP: More than 7.5 million acute ischemic strokes occur worldwide each year, and no new therapeutics have been approved for these patients beyond tPA in 1996 which only treats ~10% due to short 4.5 hour treatment window. Approximately 80% of acute ischemic stroke (AIS) patients are given supportive care only, including blood thinners and anti-platelets.

Through leveraging its unique mechanism of action, DiaMedica is evaluating the potential of DM199 to improve collateral circulation in the ischemic penumbra, the region of brain tissue that is temporarily deprived of blood flow but is not permanently damaged.

A non-recombinant form of KLK1 is already being used as a treatment option in China isolated from human urine, where it has been shown to ameliorate neurological symptoms in patients with ischemic conditions annually (up to 1 million patients treated each year) with few adverse events.

RA: What are the major drug discovery and development challenges behind therapies for ischemic conditions?

RP: The major challenges in therapeutic development for ischemic conditions span both scientific and translational domains. Ischemic diseases are complex and multifactorial, involving impaired blood flow, inflammation, and endothelial dysfunction, each varying across tissues and patient populations. Identifying drug candidates that can restore perfusion without triggering adverse effects remains a major hurdle.

Translationally, existing animal models often fail to replicate the chronic and heterogeneous nature of human ischemia, making predictive validation difficult. Moreover, demonstrating clear functional improvement in clinical settings beyond surrogate biomarkers like blood flow or eGFR requires innovative trial designs and robust patient stratification. Success ultimately depends on integrating mechanistic insight with targeted delivery and biomarker-driven development to translate promising biology into durable clinical benefit.

RA: You recently posted positive Phase II results for DM199. How pleased were you with the data and how important is it that the therapy did not cross placental barrier?

RP: We were very happy with the interim data from Part 1a of the ongoing Phase II investigator-sponsored trial evaluating DM199 in preeclampsia (PE). DM199 was generally safe and well tolerated, with no serious adverse events reported in response to any dose, no discontinuation of treatment, and no induction of early labour. The interim data showed a statistically significant and sustained blood pressure reduction in mothers treated with DM199 at the highest therapeutic dose, and an enhanced dilation of the uterine spiral arteries, suggesting improved blood flow to the foetus. Notably, the interim data also showed that DM199 was not detected in any cord blood samples, supporting the expectation that DM199 will not cross the placental barrier to expose the developing foetus – a potentially important safety benefit. The two first-line hypertensives, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are small molecules which cross the placenta, are contraindicated in pregnancy. Taken together, these findings demonstrate the potential for DM199 to be a safe, disease-modifying treatment for both preeclampsia and foetal growth restriction.

RA: You're examining how DM199 could treat stroke? What's the approach and how large is the unmet need for this therapeutic area?

RP: The unmet need in acute ischemic strokes (AIS) is significant. More than 7.5 million people experience AIS worldwide each year, with the majority occurring in women. Currently approved therapies are only available to approximately 20% of AIS patients and are limited by treatment window and availability of specialised care. Unfortunately, there have been no new therapeutics approved for AIS in over 25 years. The current treatments target removal of the clot via thrombolytic therapy (tPA) or mechanical thrombectomy. Approximately 80% of AIS patients are given supportive care only, including blood thinners and anti-platelets.

In AIS, DM199 aims to improve collateral circulation in the ischemic penumbra, the region of brain tissue that is temporarily deprived of blood flow but is not permanently damaged. In response to ischemic conditions, production of the bradykinin 2 receptor, a key regulator of blood pressure, is significantly upregulated in affected arteries in the brain. Through the increase of bradykinin 2 receptor activation, however, the body needs the ligand bradykinin which DM199 releases, resulting in vasodilation in the ischemic penumbra area, may increase blood flow and oxygenation to improve patient outcomes.

> **The major challenges in therapeutic development for ischemic conditions span both scientific and translational domains.**

DM199 has compelling clinical evidence supporting its potential to lower blood pressure, enhance blood flow, and improve endothelial health. A Phase II trial evaluating DM199 in AIS demonstrated improved outcomes in patients with small and medium vessel occlusions. In a subgroup of patients that did not receive mechanical thrombectomy (MT), DM199 improved physical recoveries (excellent outcomes) when compared to placebo. Notably, DM199's treatment window represents a five-fold increase from the 4.5 hours required for tPA to 24 hours, offering the potential for absolute improvement outcomes.

RA: What are your plans heading into 2026?

RP: Following the announcement of the positive interim data from the Phase II investigator-sponsored trial of DM199 in preeclampsia, we raised $30 million in a private placement. We are using these proceeds to file an investigational new drug (IND) application to initiate a Phase II trial to evaluate DM199 in people experiencing preeclampsia and foetal growth restriction in the US. We hope to initiate this study in 2026.

We are also proceeding with the enrollment of the dose expansion cohort (Part 1b) for the investigator-sponsored Phase II trial of DM199 in preeclampsia as well as initiate Parts 2 and 3 of the study evaluating DM199 in expectant management and foetal growth restriction. This Phase II investigator-sponsored trial is an open-label, single-centre, single-arm, safety and pharmacodynamic, proof-of-concept study.

In addition, the pivotal Phase II/III3 ReMEDy2 study evaluating DM199 in AIS is enrolling as planned with interim data anticipated in 2026. ReMEDy2 is an adaptive design, randomised, double-blind, placebo-controlled trial studying the use of DM199 to treat AIS. The base case of 300 patients should result in completion of trial in 2027 to potentially support registration.

Biography:

Rick Pauls has served as DiaMedica's President and CEO since 2009 and as a board member since 2005, including Chairman of the Board from 2008 to 2014. He previously served as Managing Director and Co-Founder of CentreStone Ventures, where DiaMedica was the fund's first investment, and worked in venture capital and structured finance for GMAC.