PRESS RELEASE

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AI designs drug combinations specifically for women or men to optimise heart valve disease treatment

Singapore, 11 June 2025 — Despite significant advances in medicine, most cardiovascular drugs and therapies continue to be developed and tested primarily on male patients, often overlooking important differences in how men and women respond to treatment. This gap in drug development means that women may receive less effective treatment options—highlighting the urgent need for more inclusive, sex-specific and personalised healthcare strategies.

Aortic valve stenosis (AVS), which affects nearly 1 in 8 adults over the age of 75 globally[1], is a serious heart condition that exhibits sex-specific responses to treatment. It occurs when the aortic valve—which controls blood flow from the heart to the rest of the body—becomes narrowed or stiff, making it harder for blood to flow efficiently. It can cause symptoms like chest pain, fatigue, shortness of breath, or fainting. Left untreated, severe AVS may progress to heart failure.

Harnessing the artificial intelligence (AI) driven platform, IDentif.AI, researchers from the Institute for Digital Medicine (WisDM), Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), Cancer Science Institute of Singapore, NUS and the Shu Chien-Gene Lay Department of Bioengineering at the University of California San Diego, sought to uncover sex-specific drug combinations that may slow or halt AVS progression. IDentif.AI optimised drug combinations to inhibit aortic valve myofibroblast activation—a hallmark of AVS which refers to a process causing valve cells to stiffen and scar—in female and male valve cells isolated from laboratory models. The AI platform pinpointed a list of female-biased combinations (e.g. Y-27632/SB-203580/SD-208) that were more effective in addressing AVS in female cells, while AI-optimised male-biased combinations (e.g. LY294002/Irosustat/TM5441) were notably more effective in male cells. Most of the therapeutics investigated in this study are preclinical and investigational drugs, except Losartan, a hypertension drug. Notably, IDentif.AI-pinpointed top combinations contain Losartan, and pairing Losartan with investigational drugs may help accelerate the approval of more drug candidates for AVS. Previous large-scale trials focusing on AVS drug treatments resulted in little efficacy primarily due to the failure to account for sex as a biological variable.

[1] https://pubmed.ncbi.nlm.nih.gov/16980116/

Combinatorial designs from this study may also accelerate the development of alternative treatment strategies from the standard of care—surgical or transcatheter aortic valve replacement. The findings from this study may lead to more personalised treatment strategies for AVS and beyond.

Professor Dean Ho, Director of WisDM, NUS Medicine, who co-led the study with Professor Brian Aguado at the University of California San Diego, said, "Our collaborative study demonstrates that men and women may require different medications or drug combinations to achieve the best outcomes in diseases like AVS. By optimising AI and hydrogel biomaterials, we can quickly identify and validate personalised therapies that consider these key differences. Beyond laying the groundwork for advancing AVS-specific treatment strategies, our study highlights the importance of considering sex as a biological variable and possible disparities in treatment outcomes." Prof Ho holds appointments as Director of the NUS N.1 Institute for Health and Head of Department of Biomedical Engineering (BME) at the College of Design and Engineering (CDE) at NUS. He is also Provost's Chair Professor in both the Department of BME at NUS CDE, and Department of Pharmacology at NUS Medicine.

Published in *Science Advances*, the research team selected eight drug candidates that target pathways of aortic valve myofibroblast activation. A minimum of 12 samples of male and female valvular interstitial cells (VICs)—the key cells that maintain heart valve structure and function—were isolated directly from laboratory models and cultured in hydrogel biomaterials that closely mimicked the stiffness and environment of healthy and diseased human heart valves. The team then tested 59 drug combinations in both female and male VICs cultured in hydrogel biomaterials and determined their efficacy by their respective inhibition levels of the myofibroblast activation, a process which causes valve cells to stiffen and scar. The results were then collated on the IDentif.AI platform, which ranked the combinations and pinpointed the most effective sex-specific drug cocktails for both male and female VICs.

Dr Peter Wang, co-author of the study, from Prof Ho’s research team at WisDM, NUS Medicine, added, “With the findings from our study, we aim to accelerate the development of sex-specific drug combinations for diseases like AVS and emphasise the importance of considering sex as a biological variable in treatment design." Dr Wang is also from the NUS N.1 Institute for Health and the Department of Biomedical Engineering at NUS CDE.

The study’s senior author, Professor Brian Aguado from the Shu Chien-Gene Lay Department of Bioengineering in the UC San Diego Jacobs School of Engineering, directs the Aguado iBiomaterials Laboratory focused on understanding sex differences in cardiovascular disease using biomaterials technologies. He added, “The hydrogel biomaterials developed in our laboratory enabled the discovery that male and female VICs have sex-dependent synergistic responses to drug combinations. Our observations would not have been possible using conventional tissue culture plastic materials, revealing the importance of the cell culture microenvironment to discover sex-specific biological mechanisms and paths to precision treatments. We look forward to continued work using lab-grown humanised in vitro cell culture models of valve disease as a next step to accelerate drug combination optimisation and clinical trial design.”

Armed with hydrogel biomaterials and IDentif.AI, the team also plans to expand this approach to address a wide array of other diseases that show sex-specific disease progression and treatment responses.

For media enquiries, please contact:

Gladys SIM
Senior Assistant Manager, Communications
Yong Loo Lin School of Medicine
National University of Singapore
DID: +65 9007 1322
Email: gladyssim@nus.edu.sg

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2025 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2025).

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