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## Turbocharged Artificial Intelligence: A Powerful New Digital Health Technology Can Optimize Combination Therapy in Pediatric Leukemia

**CHICAGO** – A new report published ahead-of-print in *SLAS Technology* introduces a landmark advance in personalized and precision medicine from the University of California, Los Angeles – a powerful digital health platform named Phenotypic Personalized Medicine that can overcome the complex challenges of efficacy and toxicity in optimizing drug ratios in combination therapies for pediatric leukemia.

Acute lymphoblastic leukemia, also known as ALL, is the most common pediatric cancer. While ALL has a five-year survival rate of approximately 85 percent, nearly one in five children will relapse and have a dismal prognosis, often requiring bone marrow transplantation. The conventional treatment approach for ALL is to use combination therapy, or the simultaneous administration of multiple drugs. During the maintenance phase of treatment, patients receive a combination of steroids, vincristine, methotrexate, and 6-mercaptopurine (6-MP). Dosing of methotrexate and 6-MP are adjusted to balance efficacy with side effects, including reduced levels of a subset of white blood cells, known as neutrophils, which can lead to life-threatening infections.

High drug dosages in combination therapy are often the cause of these side effects, and they are typically determined using dose escalation, where the drug concentrations given to patients are slowly increased to the point where toxicity is observed. The patients are subsequently given dosages of these drugs at the highest levels that don't cause unacceptable side effects. This is called the maximum tolerated dose, or MTD, commonly employed standard of care in cancer treatment. This approach, while effective, has resulted in substantial toxicity and has also been associated with drug resistance, or even the onset of other cancers. Furthermore, when the drugs used for treatment and their respective doses are critical parameters that determine treatment efficacy and toxicity, the number of possible drug-dose combinations becomes prohibitively large. The conventional dose escalation approach can sample only a small set of these possible dosage combinations, making it virtually impossible to pinpoint the optimized drug ratios to use in combination therapy.

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**To address this pervasive challenge in cancer treatment, a team of bioengineers led by Dean Ho, Ph.D., and Chih-Ming Ho, Ph.D., at the University of California, Los Angeles (UCLA) has developed a powerful digital health platform named Phenotypic Personalized Medicine, or PPM. Using PPM, a patient's physical response to drug treatment, such as a change in tumor size or toxicity, can be represented by a parabola or U-shaped map. This is a revolutionary discovery because it can pinpoint the exact drug doses in combination therapy to result in optimal treatment outcomes.**

Implementation doesn't require any complex knowledge of the patient's genome or biological processes that control the disease. While this information may be important for selecting drugs to use on a patient, it isn't capable of determining the right dosages during the progression of treatment, which can have a profound impact on efficacy and safety. What's more, it can be applied to every disease indication and all patients and optimizes combination therapy for the entire duration of care. These stunning attributes represent a landmark advance in personalized and precision medicine.

In this study, patient drug dosing records are obtained and multiple instances of deviations outside of normal neutrophil levels are noted. PPM retrospective optimization is conducted to determine dose combinations that would have avoided these deviations. In some cases, PPM identifies drug dosages as much as 40 percent lower than those that were given in the clinic. The PPM maps that identify the optimal dose combinations that would have eliminated the deviations from normal neutrophil levels are shown to be patient-specific. These findings demonstrate the importance of individualizing treatment for ALL.

The PPM technology platform is akin to artificial intelligence, or AI that is operating at a remarkable level of efficiency. More specifically, PPM rapidly identifies optimal parameters, in this case the best drug-dose ratios for multi-drug therapy, among a prohibitively large set of possible combinations, and without complex algorithms or modeling. Of note, PPM isn't only applicable to personalizing care in that Dean Ho and Chih-Ming Ho's teams have harnessed the core technology at the foundation of PPM to optimize novel drug combinations to completely transform the drug development landscape. In fact, their new therapies have also been clinically validated, dramatically outcompeting current clinical standards.

"Personalizing combination therapy in a sustained fashion is a game-changer for the optimization of cancer treatment," says Dean Ho, professor of oral medicine and biology, and bioengineering at UCLA. "PPM is like turbocharged AI, operating at peak efficiency, and it doesn't fail. This means truly personalized medicine and optimized drug development are now a reality," adds Ho, who is also co-director of the Weintraub Center for Reconstructive Biotechnology at UCLA.

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Recently, Dean Ho and Chih-Ming Ho co-led a prospective clinical study that used PPM to optimize and personalize immunosuppression following liver transplant to prevent organ rejection. Using PPM, the efficiency of managing the prevention of organ rejection was substantially improved over the patients in the control arm.

“Pinpointing globally optimal drug doses is virtually impossible using dose escalation,” says Chih-Ming Ho, distinguished research professor of mechanical and aerospace engineering at UCLA. “The clinical validation of PPM shows that we no longer have to rely on maximum tolerated dosing to treat patients,” adds Chih-Ming Ho, who is also a professor of bioengineering.

Given that PPM is clinically validated and a scalable technology, the research team is preparing to recruit patients to prospectively optimize combination therapy for pediatric leukemia within the next year. “Actionably optimizing combination therapy provides clinicians with a powerful weapon to improve patient outcomes,” says Vivian Y. Chang, Ph.D., assistant professor of pediatrics and hematology and oncology at UCLA. “This is an exciting technology that could markedly improve our ability to individualize care, and also develop new drug combinations for a broad spectrum of cancers,” adds Chang, who is also the co-director of the Pediatric Cancer Predisposition Clinic at UCLA.

Other authors of the study include co-first authors Dong-Keun Lee, Ph.D., and Theodore Kee, Ph.D., both from UCLA. Co-corresponding authors Dean Ho, Chih-Ming Ho, and Vivian Y. Chang are also members of the Jonsson Comprehensive Cancer Center.

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Access to “**Optimizing Combination Therapy for Acute Lymphoblastic Leukemia Using a Phenotypic Personalized Medicine Digital Health Platform: Retrospective Optimization Individualizes Patient Regimens to Maximize Efficacy and Safety,**” is limited to SLAS members and *SLAS Technology* subscribers until on or about May 20, 2017, when it will be published in the June issue of *SLAS Technology* at http://jla.sagepub.com/content/22/3.toc. In the meantime, to read the abstract, visit *SLAS Technology* OnlineFirst at http://jla.sagepub.com/content/early/recent.

In addition, Dean Ho will make a related presentation entitled “Optimizing Clinical Combination Therapy Using a Phenotypic Personalized Medicine Technology Platform” on Monday, Feb. 6, at 3:00 p.m. at SLAS2017, the 2017 SLAS International Conference and Exhibition, Feb. 4-8, 2017, in Washington, DC. For more information, visit www.SLAS2017.org.

*SLAS Technology* is one of two MEDLINE-indexed scientific journals published by SLAS and was previously published (1996-2016) as the *Journal of Laboratory Automation* (JALA). For more information about SLAS and its journals, visit www.slas.org/publications/scientific-journals.

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***SLAS Technology:*** *2015 Impact Factor 1.297. Editor-in-Chief Edward Kai-Hua Chow, Ph.D., National University of Singapore (Singapore). SLAS Technology (**Translating Life Sciences Innovation**) was previously published (1996-2016) as the Journal of Laboratory Automation (JALA).*