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## Study finds that microinjection platform enables assessment of multiple cancer drugs directly in tumors, predicts systemic response

- Data published in *Science Translational Medicine* show positive findings using patented new technology with multiple cancer drugs tested in xenografted mouse models and canine patients –
- Results from first-in-human study in lymphoma patients confirm feasibility for toxicity-sparing assessment of drug efficacy in cancer patients –

SEATTLE – April 22, 2015 – A newly developed technology for simultaneously comparing response to multiple cancer drugs or combinations while a tumor is still in a patient’s body has been shown to accurately predict systemic response to the drugs, according to researchers at Fred Hutchinson Cancer Research Center and Presage Biosciences. The patented technology, called CIVO™, consists of an arrayed microinjection drug delivery device and quantitative analysis methodology.

The findings by Jim Olson, M.D., Ph.D., and colleagues at Fred Hutch and Richard Klinghoffer, Ph.D., and colleagues at Presage Biosciences with collaborators at Celgene are published online April 22 ahead of the May 2015 issue of *Science Translational Medicine*, a publication of the American Association for the Advancement of Science.

“Currently, only 7 percent of new oncology drug candidates that demonstrated anti-cancer activity in preclinical studies subsequently demonstrate sufficient efficacy in clinical trials to warrant FDA approvals,” said Olson, Member of the Clinical Research Division at Fred Hutch, a pediatric oncologist at Seattle Children’s Hospital and Founder of Presage. “As a practicing pediatric oncologist, I deal every day with the limitations of current cancer therapies, and I’ve made it my life’s work to help find solutions to this challenge. We developed CIVO because patients desperately need better approaches to identify treatments that will provide benefit and improve patient survival.”

## **CIVO Technology**

CIVO enables the placement of multiple columns of drugs for analysis directly into the tumor along the needle axis, spanning the full depth of the tumor. This makes it possible to assess drug effects with multiple biomarkers and in multiple regions along the injection axis to capture the heterogeneity of response within the tumor. Later, (typically 24-72 hours after injection), the tumor is resected for subsequent analysis, and responses are measured with multiple immunohistochemistry-based assays and high-resolution scanning.

The CIVO technology intentionally bypasses bioavailability, biodistribution, metabolism, and excretion issues associated with systemic dosing, making it possible to focus on whether a drug engages its target, how cancer cells respond to target engagement, and whether the ultimate fate of the exposed cells indicates potential for patient therapeutic response – all in the context of an actual tumor microenvironment.

Presage holds six U.S. patents on its proprietary CIVO technology, including method claims covering the evaluation of drug response directly in a tumor.

CIVO™ has been deployed with more than 100 approved and investigational drugs, and dozens of canine cancer patients have been dosed with the CIVO™ system. Additionally, enrollment is open and the first human patients have been dosed with CIVO in an ongoing first-in-human study.

“We have employed CIVO to investigate drug response earlier in the development process as it enables evaluation of multiple drugs and combinations efficiently and directly in the native tumor microenvironment,” said Rajesh Chopra, Corporate Vice President of Translational Research at Celgene. “Presage’s approach is entirely novel and has demonstrated the ability to characterize tumor heterogeneity and drug resistance and has shown the potential to address these challenges through novel drug combinations.”

## **Testing Methods and Results**

In the publication, entitled “**A technology platform to assess multiple cancer agents simultaneously within a patient’s tumor**,” researchers summarize the findings from multiple tests of CIVO in human xenografted mouse models, canine patients and human patients. The results show:

### Human Xenografted Mouse Models

- In xenograft lymphoma models CIVO microinjection of well-characterized anti-cancer agents (vincristine, doxorubicin, mafosfamide, prednisolone) induced

spatially defined cellular changes around sites of drug exposure, specific to the known mechanisms of action of each drug, and the observed localized responses predicted responses to the same drugs systemically delivered in animals.

- In pair-matched drug resistant and drug sensitive lymphoma models, CIVO™ correctly demonstrated tumor resistance to doxorubicin and vincristine.
  - This cohort also identified an unexpected enhanced sensitivity to the active form of cyclophosphamide in multi-drug-resistant lymphomas compared with chemotherapy-naïve lymphomas.
- A CIVO-enabled in vivo screen of oncology agents led to the finding that a novel mTOR pathway inhibitor exhibits significantly increased tumor-killing activity in the drug-resistant setting compared with chemotherapy-naïve tumors.

### Canine Patients

- Feasibility studies to assess the utility of CIVO in canine patients demonstrated that microinjection of drugs is toxicity-sparing while inducing robust, easily tracked, drug-specific responses in naturally occurring tumors.

### Human Patients

- Early data show that in lymphoma patients who had microdoses of vincristine injected using CIVO into the tumors in their lymph nodes, clear cell death was observed in cells surrounding the injections. Patients reported only mild discomfort and no serious adverse events.
- The feasibility study to assess the utility of CIVO in human patients demonstrated that microinjection of drugs is toxicity-sparing while inducing robust, easily tracked, drug-specific responses in naturally occurring tumors.
- Presage is evaluating CIVO in humans in collaboration with Seattle Cancer Care Alliance (SCCA) and Fred Hutch, with funding support from the National Cancer Institute (NCI)<sup>1</sup>.

“This analysis creates a comprehensive portrait of drug response that has never been seen before this early in the drug development process,” said Klinghoffer, Chief Scientific Officer of Presage Biosciences. “Using this technology, we can assess how drugs, both as single agents and in combinations, impact the biology of tumor cells in the context of the native tumor microenvironment. In addition to solely focusing on cancer cells, translation of CIVO to the clinical setting has enabled assessment on all aspects of tumor biology, including drug effects on tumor-infiltrating immune cells. This sets the stage for a new type of pre-Phase 1 clinical study in which multiple drugs or drug combinations can be tested

simultaneously, directly in a patient's own tumor, without toxicity associated with systemic drug delivery."

### **About Fred Hutchinson Cancer Research Center**

At [Fred Hutchinson Cancer Research Center](#), home to three Nobel laureates, interdisciplinary teams of world-renowned scientists seek new and innovative ways to prevent, diagnose and treat cancer, HIV/AIDS and other life-threatening diseases. Fred Hutch's pioneering work in bone marrow transplantation led to the development of immunotherapy, which harnesses the power of the immune system to treat cancer with minimal side effects. An independent, nonprofit research institute based in Seattle, Fred Hutch houses the nation's first and largest cancer prevention research program, as well as the clinical coordinating center of the Women's Health Initiative and the international headquarters of the HIV Vaccine Trials Network. [Private contributions are essential](#) for enabling Fred Hutch scientists to explore novel research opportunities that lead to important medical breakthroughs. For more information visit [www.fredhutch.org](http://www.fredhutch.org) or follow Fred Hutch on [Facebook](#), [Twitter](#) or [YouTube](#).

### **About Presage Biosciences**

Presage Biosciences is an oncology company pioneering the incorporation of human efficacy data much earlier in the drug development and clinical trial processes with its patented CIVO arrayed microinjection platform. The CIVO platform allows for simultaneous assessment of multiple drugs or drug combinations directly in a single solid tumor while still in a patient's body to assess efficacy, resistance and drug synergies in the tumor's native microenvironment. Presage partners with oncology-focused pharmaceutical companies through strategic alliances to provide in vivo data to validate novel targets, promote drug candidates to the right indications and discover effective drug combinations. Presage also is actively building an internal portfolio of cancer compounds and using CIVO to advance these to the clinic. Presage is privately held and based in Seattle. For more information, visit [www.presagebio.com](http://www.presagebio.com).

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