CIVO: Drug Development in the Fast Lane

June 15, 2015

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Drug development is a slow and cumbersome process that includes assessment of new pharmaceutical compounds in countless pre-clinical studies and several phases of clinical trials. A critical stage is the transition from laboratory experiments to patient studies, whereupon the results all too often are disappointing in terms of therapeutic effect. The reason is as simple as it is challenging: cell-based experimental models are not always proper representations of human disease. Consequently, very few of the numerous tested anticancer drugs perform well enough to warrant regulatory approval, despite promising preclinical results. Huge efforts made at research centers and pharmaceutical companies are thus not only excruciatingly time consuming and expensive, but also - in most cases - futile. Meanwhile, patients in need are waiting for improved treatments.

To address this fundamental problem, Dr. Jim Olson and colleagues in Fred Hutch's Clinical Research Division developed a device that enables more accurate and efficient testing of new pharmaceutical compounds, together with automated, image-based analysis. The technology platform, called CIVO, allows simultaneous testing of multiple drugs and drug combinations directly in human tumors, thereby bypassing issues with *in vivo* distribution, metabolism, excretion etc., allowing full focus on the interaction between drugs and cancer cells in an authentic biological microenvironment. The CIVO platform is licensed to Presage Biosciences, a Seattle-based company that sprung from Dr. Olson's laboratory in 2008.

The technology and its benefits were demonstrated in the April 2015 issue of *Science Translational Medicine*. In the article, Dr. Olson and associates describe the principle of the handheld device, which enables localized administration of microliter volumes of up to eight different drugs per tumor, using an array of needles connected to drug reservoirs. The investigators showed results from several tumor models, including xenografted mice and canine patients, as well as four human lymphoma patients.

A key factor for allowing simultaneous analysis of multiple compounds is separation between the infused agents, also over time. It was demonstrated that more than 96 % of the various injectates remained within 2 mm of their respective injection sites, at least up to 24 hours, without crossover between the different regions. Besides comparing various drugs and drug combinations, CIVO explores yet another dimension: tumor depth. During injection, the needles are pushed into the in-

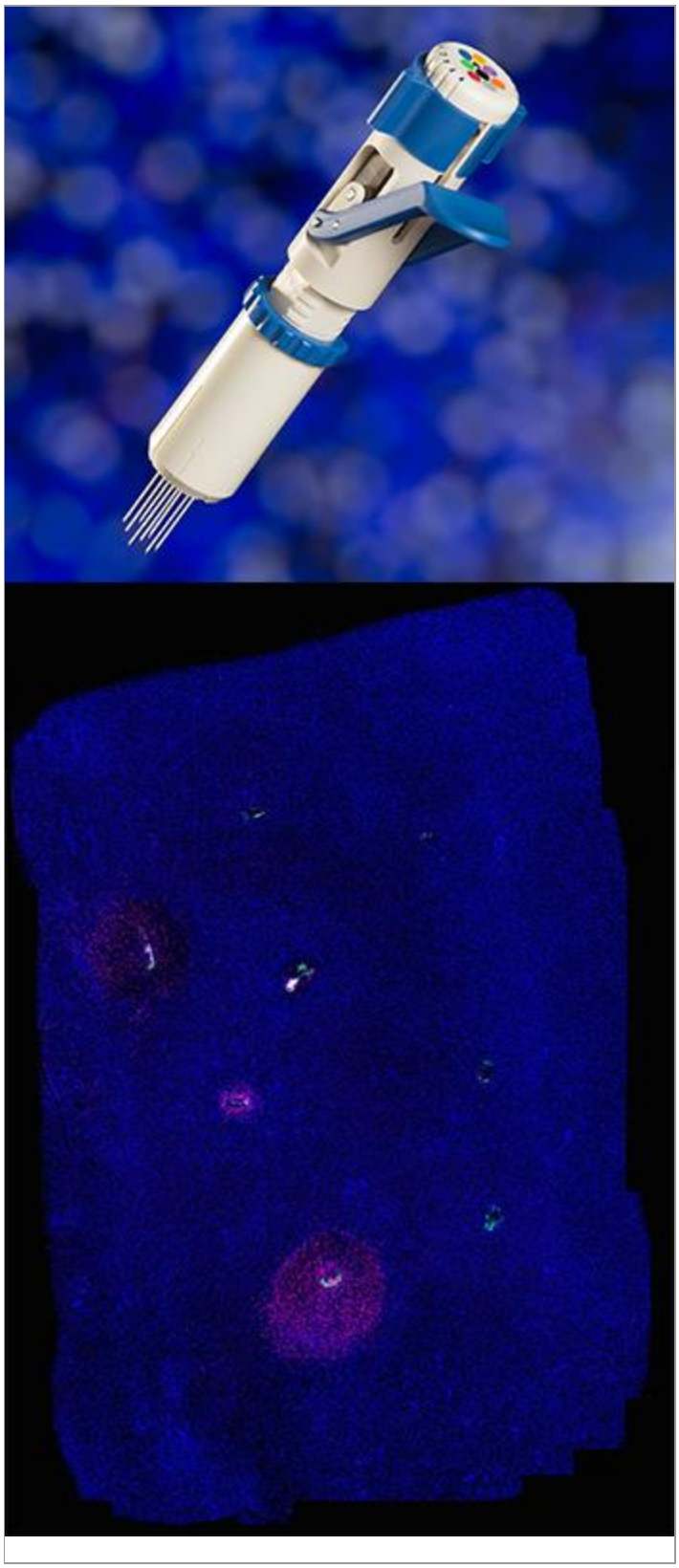
patient tumor and then slowly pulled out as the drug solution is being infused at a constant flow rate. The result is uniform tracks of drugs through the z-axis of the tumor, in a column-like fashion. After tumor resection, samples from different depths into the tissue can be used to evaluate both the uniformity of response and the effect of different microenvironments on drug efficacy. For instance, deeper-lying tumor regions may not be sufficiently vascularized and thereby contain less oxygen. Will these hypoxic regions respond differently to treatments? This is one of many questions that may be answered using the CIVO platform.

The investigators found that the system offered safe and efficient drug administration, with very mild adverse effects in human patients. To assess clinical predictive ability, comparisons were made in mice between microinjection-induced local tumor responses and responses after systemic drug delivery. CIVO-injection resulted in tumor growth inhibition that was comparable to that of systemic drug delivery, and the investigators successfully predicted both resistance and increased sensitivity in tumors of different contexts using the new platform. In addition, an unexpected sensitivity to the drug mafosfamide was discovered in otherwise chemotherapy-resistant lymphoma xenografts in mice. Importantly, this effect was not revealed using standard *in vitro*cell assays, underlining their relative inadequacy compared with *in vivo* screening methods.

According to Dr. Olson, CIVO represents a major step forward towards improved cancer treatments by enabling evaluation of resistance or sensitivity to drugs in the context of a patient's own immune system. "In some cases, we can identify the specific mechanism of resistance to therapeutic agents," he added.

The long term goal is clear: "To avoid treating patients with chemotherapy that will cause harm but provide no benefit - and to find the most effective and least toxic combinations of drugs," Dr. Olson said. The immediate plan is to advance the platform and broaden its range of clinical applications. Dr. Olson's enthusiasm is contagious: "Wouldn't it be interesting if we could accurately predict which patients will fail standard of care agents so that novel therapeutics could be evaluated in first or second line regimens instead of third or fourth?" he asked. It sure would!

Klinghoffer RA, Bahrami SB, Hatton BA, Frazier JP, Moreno-Gonzalez A, Strand AD, Kerwin WS, Casalini JR, Thirstrup DJ, You S, Morris SM, Watts KL, Veiseh M, Grenley MO, Tretyak I, Dey J, Carleton M, Beirne E, Pedro KD, Ditzler SH, Girard EJ, Deckwerth TL, Bertout JA, Meleo KA, Filvaroff EH, Chopra R, Press OW, Olson JM. 2015. A technology platform to assess multiple cancer agents simultaneously within a patient's tumor. *Sci Transl Med* 7(284), 284ra58.



Images provided by Presage Biosciences

Presage Biosciences' CIVO patented arrayed microinjection drug delivery device (top) enables simultaneous assessment of multiple drugs or drug combinations directly in a single solid tumor while still in a patient's body. Presage analysis shows local response to microinjections of eight different cancer drugs within a canine patient's sarcoma tumor, as visualized by cleaved caspase staining in red for regions of apoptotic cell death due to drug response (bottom). Live tumor cells are shown in blue, the green is the injection site dye, and the red dots are dead tumor cells responding to the injected drugs.