New immune analysis panel for transgenic pigs may advance cancer IR immunotherapy

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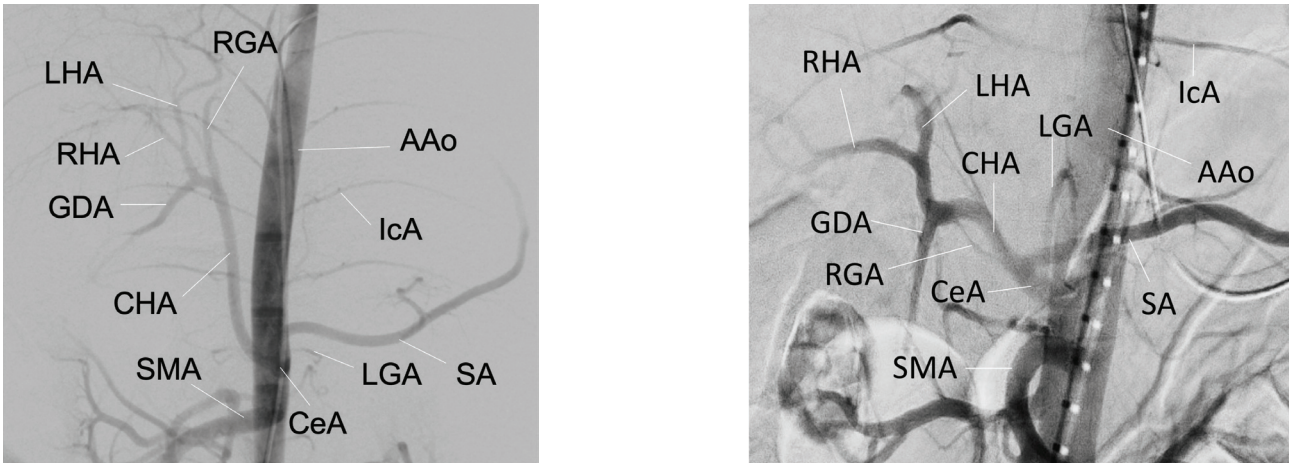
Tumors are able to grow and spread within the body to the extent that they are able to evade attack from the body's immune system. Immunotherapy seeks to enhance the body's ability to eliminate tumors on its own with a better ability to identify tumor antigens. "The concept has worked exceptionally well for some blood-borne cancers — such as leukemia and lymphomas — but apart from melanoma and certain subtypes of lung cancer, they have just started to scratch the surface of treating solid tumors," explains interventional radiologist Jason Chiang, MD, PhD, assistant professor of radiology. Dr. Chiang is conducting research to try to extend these excellent outcomes with immunotherapy to patients who suffer from solid tumors. Dr. Chiang's own research focus is on liver cancer, but much of his recent activity can apply to all solid tumors.

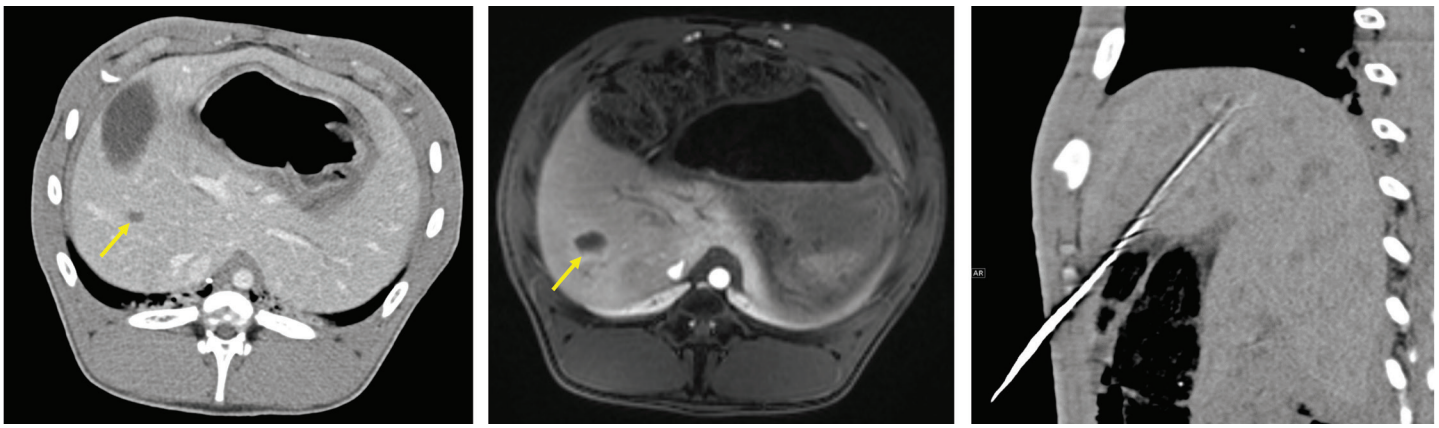


Porcine aortic angiogram (left) compared to human aortic angiogram (right).
AAo – aorta, CeA – celiac artery, CHA – common hepatic artery, GDA – gastroduodenal artery, IcA – intercostal artery, LGA – left gastric artery, LHA – left hepatic artery, RHA – right hepatic artery, RGA – right gastric artery, SA – splenic artery, SMA – superior mesenteric artery

Systemic immunotherapy has shown only limited success with solid tumors at least in part because the compact and immunosuppressive nature of these tumors prevents immunotherapy agents from reaching most of the tumor cells. Oncologists are limited in how far they can increase dosage in an effort to more deeply penetrate solid tumors. Too high a dose can spur the immune system to attack normal, healthy tissue in the manner of an autoimmune response. "This is the time for interventional radiologists and interventional oncologists to take a seat at the table and become involved in cancer immunotherapy," states Dr. Chiang. "We can help push immunotherapy to the next level in treating solid tumors using minimally invasive catheters and needles." Using these image-guided techniques, interventional radiologists are able to introduce immunotherapy agents directly into the tumor microenvironment, allowing them to deliver much higher doses than those used in systemic immunotherapy.

Dr. Chiang has been working with his UCLA colleagues to overcome one of the principal barriers to applying interventional radiology techniques to treating cancer locally with immunotherapy. Pre-clinical cancer research relies heavily on rodent animal models, but mice and rats are suboptimal models for interventional radiologists to use as their very small body size prevents interventional radiologists from performing the kinds of procedures they use in humans. Research efforts at UCLA employing interventional radiology to deliver cancer immunotherapy have focused on using transgenic pigs. These "Oncopigs" are not only similar to humans in body size — imaging and interventional tools routinely use in treating human patients are easily applied to pig research — but have other similarities that may make them superior to mice as models of human cancer. Pigs more closely resemble humans in their metabolic rate and immune system than do rodents, and their anatomy is more similar as well. In terms of liver anatomy, pigs have a celiac axis, a superior mesenteric artery, a gastroduodenal artery and a proper hepatic artery.

A further benefit of the use of pig models is that they reduce the need for the allometric scaling principles that are traditionally used to translate research findings from small animal models to humans. Allometric scaling accounts for differences in size — usually expressed in terms of the ratio of body surface areas — but does not account for differences in things like metabolic



Tumor growth in Oncopig liver over the course of two weeks, prior to microwave ablation treatment — (A) Axial contrast-enhanced CT of sub centimeter hypodense lesion corresponding to tumor growth in the right liver lobe. (B) Axial contrast-enhanced MRI showing peripheral rim enhancement and interval growth of target tumor after two weeks. (C) CT-guided placement of microwave ablation probe into the target tumor.

rate and vascular resistance. Therefore, the more similar the model animal is to humans, the less researchers have to rely on allometric scaling to translate things like drug dosage for use in human trials. "We want to improve the yield of targeted immunotherapy by using pigs as a better model of human cancer," says Dr. Chiang, pointing out that less than 7% of drugs that have been validated in rodent cancer models have been successfully translated to humans.

The transgenic Oncopig has Cre recombinase inducible mutated tumor suppressor and oncogenes TP53 and KRAS, which are found in up to one-half of all human cancers. Tumors can be induced in the Oncopig by injecting adenovirus with Cre recombinase. "The virus can enter any cell in this pig and unlock the overexpression of a gene that promotes tumorigenesis," explains Dr. Chiang.

One important area where pig models have been at a disadvantage to rodent models is in the availability of validated antibodies to allow researchers to characterize the immune response. These antibodies reveal which immune cell populations are being suppressed by tumors and which ones are activated by immunotherapy. Decades of experience in using mouse models has yielded a rich set of validated antibodies for mice, but the analogous set had not been established for pigs. Dr. Chiang and his colleagues have been working with the Flow Cytometry Core of the UCLA Jonsson Comprehensive Cancer Center to build an immune analysis panel for pigs to identify specific pathways that can be targeted with immunotherapy.

The ability to use the Oncopig model for IR immunotherapy enables researchers at UCLA to leverage the Department of Radiology's Translational Research and Imaging Center (TRIC). The TRIC lab has the same imaging and interventional tools used to treat patients available for research, specifically large-animal research subjects.

Interventional procedures can stimulate an immune response

Delivering high doses of immunotherapy drugs directly into tumor stroma is one unique advantage of using interventional procedures to treat solid tumors. But interventional procedures by their very nature can also release tumor antigens to stimulate an immune response. The immune cycle begins with recognition of a foreign antigen and sensitization of the immune system to that antigen. In the case of cancers, antigen-presenting cells pick up tumor cells and carry them to local lymph nodes, where they can activate naïve T cells to differentiate them into effector and memory T cells, priming them to identify and target the tumor. Once sensitized, the effector T cells can travel through the lymphatic system and attack cells that express that particular tumor antigen, wherever they are found.

"One thing that interventional radiology is really good at is being able to disrupt the local tumor microenvironment and release these tumor antigens," explains Dr. Chiang. This means that even ablative procedures intended to target tumors locally can simultaneously stimulate a systemic immune response that targets tumor cells at the ablation site as well as other places throughout the body. "Many interventional radiologists who treat cancer patients have seen or heard of patients with widespread metastatic disease treated with local ablation or radioembolization at one site for palliative purposes, and then seeing that not only have they treated the one tumor, but start to see all of the other non-targeted tumors melting away. This kind of 'cancer vaccine' is not really seen using traditional systemic immunotherapies," says Dr. Chiang.

Dr. Chiang is interested in further exploiting this mechanism to produce a more durable response. "We know that there is an inflammatory response to ablation and embolization, but we also know that it's temporary," explains Dr. Chiang. "Our goal is to identify these pathways and augment them. This may involve combining ablation or embolization with existing immunotherapies — including checkpoint inhibitors that are currently being used to treat blood-borne cancers and melanoma — or potentially combining them with CAR-T (chimeric antigen receptor T-cell) or NK (natural killer) cell therapy to generate a more durable anti-tumor response." R