tumor, followed by lymphatic extension and specific mortality. Percutaneous injection and adjunction of mouse sarcoma proteins are associated with decreased perioperative mortality and increased hematogenous dissemination. This model will be of interest to study oncogenesis and to assess new treatments.

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New preclinical models of metastatic colon cancer: towards bridging the gap between bench and bedside therapeutic outcomes

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Background: In 2007, the small molecule receptor tyrosine kinase inhibitor sorafenib was FDA-approved for the treatment of advanced hepatocellular carcinoma (HCC). In contrast, little is known about the efficacy of adjuvant sorafenib for early stage HCC. As HCC is an intrinsically chemotherapy-resistant malignancy and as most patients suffering from HCC have reduced liver function thus not tolerating conventional chemotherapy, the impact of sorafenib-based regimens for this malignancy in earlier stages of disease progression may be important as a means to improve the clinical management of this highly lethal malignancy.
Methods: The human HCC cell line Hep3B was transfected with a hCG.pIRES vector and β-hCG expressing variants were obtained by puromycin selection. Analysis of β-hCG expression enables in vivo monitoring of relative tumor burden. Cells were orthotopically injected into the right lower lobe of the liver in a total of 50 CB17 SCID mice. Control vehicle or Sorafenib (15 or 30 mg/kg) was administered by daily gavage starting either immediately after wound healing (day 7) before circulating β-hCG was detected or after evidence of established tumors as determined by β-hCG analysis (days 14−21). Monitoring was carried out by analysis of β-hCG secretion, survival analysis and endpoint necropsy. Tissue was preserved for immunohistochemistry.
Results: All control animals needed to be sacrificed within 65 days due to primary tumor burden and ascites. No animal of this group showed local or distant metastasis. In contrast, all four dosing regimens of sorafenib significantly inhibited primary tumor growth, inhibited the formation of ascites and prolonged overall survival. However, possibly as a result of the prolonged survival, 56% (19/34) of the animals treated with sorafenib developed local, mesenteric and omental lymph node metastasis and 21% (7/34) developed secondary liver metastases. Metastatic cell lines were re-adapted to cell culture for future analysis.
Conclusions: Sorafenib prolongs survival and successfully controls primary tumor growth in an orthotopic model approximating early-stage HCC. However, it does not inhibit the development of secondary liver metastases or local and distant lymph node metastasis. The nature of these secondary growths will be addressed in follow-up experiments. Future analyses will also include adjuvant therapy of microscopic metastases following resection of the primary. Furthermore, experiments will be repeated using MHCC97-H as a second HCC cell line. Results of this ongoing study will be presented at the conference.

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Establishment and characterization of individualized patient-derived low passage human tumor models: Development, validation and evaluation for clinical correlation analysis

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The majority of patients with advanced solid tumors die from an absence of effective therapy. This is despite three decades of drug development using the current human tumor model screening platform derived from ex-vivo passaged cancer cells. While cell-derived models are useful for high throughput lead candidate identification and early stage preclinical single agent and combination optimization, these lines represent a cross section of different tumors but physically represent only a fraction of genetic and biological abnormalities which are now known to play a role in the pathogenesis and progression of human cancers. Patient-derived tumor models passaged only a few times in vivo retain physical and molecular characteristics of human cancer and may prove essential in identifying disease biomarkers and drug targets in later stage development.
To address this unmet need, we have implanted tissue from donor patients into immunocompromised mice to develop low passage models more representative of human cancer. To date one hundred seventy-four samples have been implanted over thirteen tumor types with a model development success rate of approximately sixty percent:

Tumor Type	No. of Models	%Total
Brain	8	5%
Breast	16	9%
Gastrointestinal (esophagus, colon)	(3, 18)	12%
Genitourinary (Renal, Bladder)	(5, 1)	4%
Head & Neck	16	9%
Hematopoietic	10	6%
Lung	16	9%
Neuroendocrine	3	2%
Ovary	32	18%
Prostate	2	1%
Pancreas	6	3%
Sarcoma	15	9%
Skin (melanoma, vulva)	(22, 1)	13%

Molecular and clinical outcome data was collected from donor patients and compared with data obtained from model characterization with excellent correlation. Several low passage models including colorectal, lung and ovary cancers and melanoma were screened for sensitivity to relevant standards of care with results correlating to clinical response 70% of the time. Taken together, these results demonstrate the ability to generate improved models of human cancer which retain molecular and clinical characteristics which may be used for patient drug sensitivity screening and improved oncology drug development.

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Constitutive overexpression of Id-1 in mammary glands of transgenic mice results in precocious and increased formation of terminal end buds, enhanced alveologenesis, delayed involution

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Inhibitor of differentiation-1 (Id-1) has been shown to play an essential role in cell proliferation, invasion, migration and anti-apoptosis. However, the effect of Id-1 in mammary gland development in in vivo remains unknown. Here, we analyzed the effect of Id-1 overexpression in mammary gland development of MMTV-Id-1 transgenic mice during virgin, pregnancy and involution. In virgin mice, overexpression of Id-1 led to precocious development and delayed regression of terminal end buds (TEBs) compared with wild type mice. The number of BrdUpositive cells, an indicator of cell proliferation, and the expression of Wnt signaling molecules, β-catenin and cyclin D1, which regulate ductal extension and TEB formation in virgin, were statistically higher in Id-1 transgenic mice than in wild type mice. Id-1 also had an effect on the formation and proliferation of lobuloalveolar structures during early and mid-pregnancy. The Id-1 transgenic mice had more lobulated and prominent alveolar budding than wild type mice and had significantly greater counts of lobuloalveolar structures in early pregnancy. The expression of BrdU, β-catenin and cyclin D1 was also predominantly increased in Id-1 transgenic mice. Moreover, Id-1 transgenic mice showed delayed involution in mammary gland development. Id-1 regulated the expression levels of anti-apoptotic Bcl-2 and pro-apoptotic Bax, and resulted in delay of apoptotic peak during postlactational involution. Taken together, our results suggest that Id-1 plays a pivotal role in mammary gland development through Wnt signaling-mediated acceleration of precocity and alveologenesis and Bcl-2 family members-mediated delay of involution.

Clinical methodology

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Tailored dosing of tasisulam-sodium (LY573636-sodium) to reduce hematologic toxicity and improve therapeutic index

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Background: Tasisulam (LY573636) is an acylsulfonamide with novel anti-cancer activity across a broad range of cell lines that induces apoptosis by a mitochondrial-mediated mechanism.
Material and Methods: In a phase I study and four subsequent phase 2 studies, tasisulam was administered by a 2-hour infusion using a lean