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Establishment of human primary tumor xenograft models in nude mice

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Human xenograft tumor models established by transplantation of human tumor cell lines into immunodeficient mice have been routinely used for preclinical test of anticancer agents. But such tumor models have a relatively low predictive value and limited correlation with clinical findings. Recently, we developed xenograft tumor models by transplanting human fresh tumor fragments into nude mice (HuPrimeTM tumor models), and which have been used for testing clinical anticancer drugs as positive controls. A total of 272 tumor samples excised from patients have been tested for HuPrime tumor model development. The tumor take rates for the first passage were lung (15%), colon (44%), rectal (25%), liver (10%), gastric (29%), esophageal (30%), and Kidney (25%). The tumor take rates were higher for the second and third passages for various tumor types, ranging from approximately 40% to 100%. The positive control drugs tested against the HuPrime tumor models included paclitaxel, docetaxel, irinotecan, doxorubicin, 5-FU, gemcitabine and erlotinib; they produced tumor inhibition rates of 50−70%, which were consistent with their clinical findings. The HuPrime tumor tissues from all three generations presented highly similar histopathological morphology to original patient tumors. These results suggest that HuPrime xenograft tumor models provide a unique, renewable source of tumor material for testing novel anticancer agents in vivo and may give better predictive value for clinical indication and efficacy than the traditional human tumor xenografts produced by cell lines.

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Experimental therapeutic approach of human diffuse large B-cell lymphoma xenografts by doxycycline, alone or in combination with the anti-CD20 chimeric monoclonal antibody rituximab

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Background: Recent studies have reported a therapeutic efficacy of the antibiotic therapy doxycycline in Chlamydia psittaci-positive MALT ("Mucosa-Associated Lymphoid Tissue") ocular adnexal lymphoma patients. However, such an effect has also been observed in Chlamydia psittaci-negative cases, suggesting a bacterial-independent antitumor mechanism of doxycycline. We therefore investigated, in a panel of diffuse large B-cell lymphoma (DLBCL) xenografts, the therapeutic potential of doxycycline alone or in combination with the anti-CD20 monoclonal antibody rituximab.
Material and Methods: Three different DLBCL xenografts (LY3, LY8, and LY14) with a non-germinal center B-cell type (CD10 and Bcl-6 negativity, and MUM1 positivity), Bcl-2 positivity, Mib positivity, and specific rearrangement of the heavy chain of the immunoglobulins (LY3 and LY8), have been used for preclinical assays. Doxycycline was administered according to different therapeutic schedules and rituximab was injected at a dosage of 50 mg/kg per day twice a week. Therapeutic efficacy was assessed by the in vivo tumor growth inhibition (TGI).
Results: Doxycycline orally administered at a dosage ranging from 5 to 500 mg/kg/day 5 days a week for 4 weeks didn't induce TGI of the LY3 xenograft. Similarly, when doxycycline was intraperitoneally injected at a dosage of 25 mg/kg/day 5 days a week for 4 weeks, it didn't induce TGI of LY3, LY8, and LY14 xenografts. Inversely, rituximab induced a TGI ranging between 25% and 100% for the three xenografts used, without synergistic effect after doxycycline and rituximab combination.
Conclusion: In our in vivo panel of non-germinal center B-cell type DLBCL xenografts, we have not found an antitumor efficacy of doxycycline administered through different therapeutic schedules, neither an increase of the rituximab-induced TGI. These data could be explained by the use of high-grade lymphomatous models and suggest that doxycycline has currently no place in the treatment of DLBCL patients.

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Establishment, validation, and in vivo evaluation of tumor explant models of adenoid cystic carcinoma: effects of FDA-approved and candidate therapies in human ACC xenografts

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Adenoid cystic carcinoma (ACC) is an uncommon form of malignant neoplasm defined by a distinct histologic appearance which arises within secretory glands, most commonly the salivary glands of the head and neck. Standard treatment options for this malignancy include resection and local radiation therapy; however, currently no useful chemotherapy treatment exists for this cancer type. Several novel therapies have demonstrated single agent or combination activity across a range of in vivo models of human cancer; however, lack of validated ACC models has limited evaluation of these agents in treating this disease.
Recently we and others in collaboration with the Adenoid Cystic Carcinoma Research Foundation (ACCRF) have begun establishing preclinical models of ACC using tumor explants from donor patients implanted into nude mice. Once established, models are screened against a panel of drugs representing every class of approved anticancer agent as well as candidate compounds obtained from academic and pharmaceutical collaborators. The designated endpoint for these studies is a mean control tumor volume of 1−2 cm^3. In addition, tumor samples are collected from each treatment and control group and banked for molecular studies.
In one study, FDA-approved agents were evaluated alone and in combination with the VEGF-targeting monoclonal antibody bevacizumab (10 mg/kg; i.p.; q3d × 10). Class-specific activity was reported in this study as significant tumor growth inhibition (TGI=98%; $p < 0.001$) and one tumor regression was reported with single agent taxane (docetaxel) treatment (10 mg/kg; i.v.; q2dx3); co-administration with bevacizumab prevented tumor growth or produced regressions in six of seven mice. However, treatment with the protein tyrosine kinase (PTK) inhibitor dasatinib (25 mg/kg; p.o.; qdx5x2) resulted in nominal activity (TGI = 23%; $p > 0.05$) and no regressions; co-treated with bevacizumab reported significant activity (TGI = 91%; $p < 0.001$), suggesting an additive effect or a bevacizumab-mediated increase in drug delivery.
From these results, it is clear that establishment of these models offers an excellent screening tool to identify potentially useful approved and candidate agents for treatment of ACC. In addition, tissue collected from these studies provides sufficient material for molecular studies to better understand the pathology and underlying mechanisms of this disease. Development and characterization of additional ACC models is currently underway.

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Imaging the totality of cancer progression in real time

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Background: The development of GFP for imaging in the live animal has revolutionized in vivo biology, in particular, the study of metastasis (Nature Reviews Cancer 5, 796–806, 2005).
Methods: The totality of cancer progression can now be followed in real time in the live animal, with many of the steps imageable non-invasively.
Results: GFP-expressing transgenic mice transplanted with the RFP-expressing cancer cells enable the distinction of cancer and host cells. This is particularly useful for imaging the tumor microenvironment, including tumor angiogenesis. Cancer-cell trafficking through the cardiovascular and lymphatic systems is the critical means of spread of cancer. The use of fluorescent proteins to differentially label cancer calls in the nucleus and cytoplasm and high-powered imaging technology are used to visualize the nuclear-cytoplasmic dynamics of cancer-cell trafficking and extravasation in both blood vessels and lymphatic vessels in the live animal. Proliferating and dormant cancer cells are readily distinguished in the live animal.
Conclusions: This technology has furthered our understanding of the spread of cancer at the cellular and subcellular level in the live mouse. Fluorescent proteins thus enable both macro and micro imaging technology and thereby provide the basis for the new field of in vivo cell biology.