Validated HCC1954 Xenograft Model:

Subcutaneous, Orthotopic, And Metastatic Xenograft Tumor Model

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Understanding Breast Cancer with Xenograft Models

Breast cancer remains a leading cause of cancer-related mortality, necessitating advanced preclinical models for therapeutic development. Xenograft models, where human breast cancer cells or tumor tissues are implanted into immunodeficient mice, play a crucial role in studying tumor biology and drug response. Cell line-derived xenografts (CDXs) are established using well-characterized cancer cell lines, providing reproducible and cost-effective platforms for high-throughput drug screening. However, CDXs may not fully capture the genetic and molecular heterogeneity of patient tumors. Patient-derived xenografts (PDXs), in contrast, retain the histological and genetic profiles of the original tumor, offering more clinically relevant insights. Both models contribute to understanding tumor progression, metastasis, and resistance mechanisms. CDXs are particularly useful for early-stage drug discovery, while PDXs enable precision medicine approaches by mimicking patient-specific responses. Advancements in xenograft methodologies, including humanized mouse models, further enhance their clinical relevance, making them indispensable in breast cancer research.

HCC1954 Cell Line

The HCC1954 cell line is a widely used epithelial breast cancer model derived from a primary stage IIA, grade 3 invasive ductal carcinoma. Isolated in 1995 from a 61-year-old Asian female, this cell line represents an aggressive tumor phenotype with no lymph node metastases. HCC1954 is characterized by HER2 overexpression and a TP53 mutation, making it a valuable model for studying HER2-positive breast cancer and resistance to targeted therapies such as trastuzumab. It exhibits epithelial morphology and rapid proliferation, which facilitates *in vitro* and *in vivo* research applications, including xenograft studies. The cell line also harbors mutations in PIK3CA, contributing to dysregulated PI3K/AKT signaling, a pathway critical for cancer progression and drug resistance. Additionally, HCC1954 demonstrates anchorage-independent growth and tumorigenicity in immunodeficient mice, further supporting its use in preclinical drug testing. Its resistance to certain HER2-targeted therapies highlights the need for alternative treatment strategies, making it a crucial model for investigating novel therapeutic combinations and overcoming drug resistance in HER2-positive breast cancer.

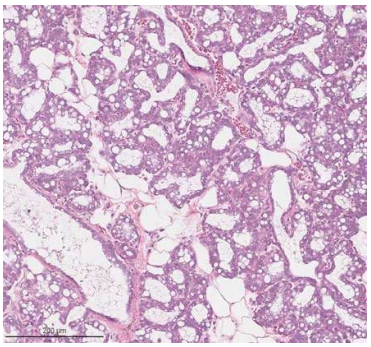

Figure 1. Tumor Histology. H&E stained section of a subcutaneously-implanted HCC1954 tumor (Altogen Labs).

Altogen Labs Validated HCC1954 Xenograft Model

The HCC1954 cell line is commonly used to generate a CDX (Cell Line-Derived Xenograft) model for studying HER2-positive breast carcinoma. This xenograft model enables researchers to evaluate the efficacy of targeted therapies, including cetuximab, JO-1, and trastuzumab, in a controlled preclinical setting. By utilizing HCC1954-derived tumors in immunodeficient mice, scientists can examine tumor growth dynamics, drug response, and potential resistance mechanisms. The model provides valuable insights into the development of novel therapeutic strategies and combination treatments for aggressive breast cancer subtypes.

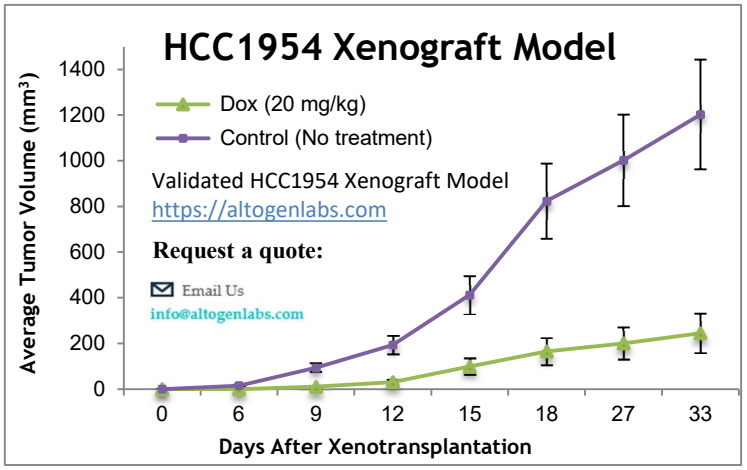

Figure 2. HCC1954 breast cancer xenografted in immunocompromised mice, mean values +/- SEM (Altogen Labs).

To establish the HCC1954 xenograft model, cells are maintained in an exponential growth phase under sterile conditions before being harvested and prepared for injection. A highly viable cell suspension (≥98% viability) is subcutaneously injected into the right flank of each mouse using a Matrigel-based medium to facilitate tumor engraftment. Tumor development is closely monitored, with measurements taken multiple times per week until the tumors reach an average size of 50–100 mm³. Once tumors are established, animals are randomized into treatment groups, and test compounds are administered according to the study protocol. Throughout the experiment, body weight and tumor size are recorded regularly to assess treatment efficacy. The study concludes when tumors reach the predetermined size limit, at which point necropsy and tissue collection are performed for downstream analyses such as histology, RNA preservation, and molecular profiling.

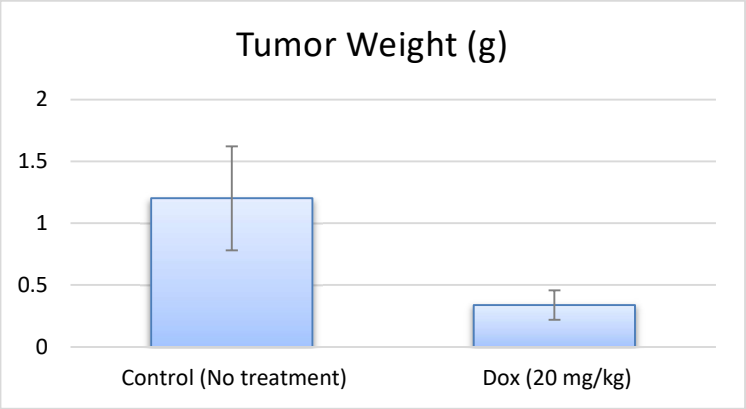

Figure 3. Tumor weight of HCC1954 cells in control, buffer only mice and doxorubicin treated mice at end of the study (Altogen Labs).

Chemotherapy: Radio-sensitization in HER2-Positive Cancers

HCC1954 is a HER2-overexpressing breast cancer cell line widely used to study targeted cancer therapies and resistance mechanisms. As a model for aggressive HER2-positive tumors, it helps researchers understand how specific treatments influence tumor behavior. Tucatinib, a HER2-directed tyrosine kinase inhibitor, has shown potential to enhance the effects of radiation therapy, leading to reduced cell proliferation and survival. However, sensitivity to tucatinib varies, particularly in cancer cells with additional mutations like PIK3CA, which can contribute to drug resistance. Combining tucatinib with a PI3K inhibitor has been shown to improve treatment response in such cases. Additionally, the sequence of treatment plays a role, with radiation followed by tucatinib producing stronger effects. These findings support the use of combination therapies to overcome resistance and improve outcomes, especially in cancers prone to metastasizing to the brain.

Chromosomal Rearrangements in HCC1954 Breast Cancer Cells

The HCC1954 breast cancer cell line exhibits a highly complex karyotype characterized by a pseudo-tetraploid genome with an average of 92 chromosomes per cell. Spectral karyotyping (SKY) reveals extensive chromosomal rearrangements, including interchromosomal and intrachromosomal translocations affecting nearly all chromosomes. Among the most notable genomic alterations are translocations involving chromosomes 4, 5, 8, 9, 11, and 18, leading to gene fusions and truncations. Key oncogenic genes such as MRE11A and NSD1 are disrupted, impacting DNA repair mechanisms and transcription regulation. Additionally, frequent rearrangements on chromosome 8, particularly in the 8q24 region, highlight a known recombination hotspot associated with cancer susceptibility. Fluorescence in situ hybridization (FISH) and long-range PCR confirm several of these genomic breaks, emphasizing the extensive genomic instability of HCC1954. This karyotypic complexity reflects the aggressive nature of HER2-positive breast cancer and provides a valuable model for studying chromosomal rearrangements in tumorigenesis.

Evaluating Therapeutics Using the HCC1954 Subcutaneous Model

The subcutaneous HCC1954 model is a widely used preclinical platform for studying HER2-positive breast cancer and evaluating novel therapeutic agents. In this model, HCC1954 cells are injected subcutaneously into immunodeficient mice, typically in the right flank, allowing for easy tumor monitoring and measurement. This approach facilitates high reproducibility in tumor growth assessment, making it ideal for testing targeted therapies such as trastuzumab and cetuximab. Tumor progression is closely tracked using digital calipers, and treatment efficacy is evaluated based on tumor volume reduction, growth inhibition, and histopathological analysis. The model provides a controlled *in vivo* environment to study drug resistance mechanisms, combination therapies, and biomarker discovery. Researchers often use it to assess pharmacokinetics, toxicity profiles, and the therapeutic potential of novel compounds.

Metastatic HCC1954 Xenograft Model

The metastatic HCC1954 model is used to study the dissemination of HER2-positive breast cancer cells to distant organs preclinically. By orthotopically implanting HCC1954 cells into the mammary fat pad of immunodeficient mice, researchers can observe spontaneous metastasis, particularly to the brain. This model has been instrumental in identifying molecular features associated with brain tropism and in evaluating therapeutic strategies targeting metastatic lesions. For instance, studies have demonstrated that HCC1954 cells can develop brain metastases following primary tumor resection, mimicking clinical scenarios of metastatic progression. Additionally, the model has been used to investigate the role of natural killer (NK) cells in controlling metastatic outgrowth, revealing that NK cell depletion facilitates the expansion of HCC1954 metastatic cells in the brain.

Advancing Breast Cancer Studies with Orthotopic HCC1954 Models

The orthotopic HCC1954 model is used in nonclinical experiments to study HER2-positive breast cancer by implanting HCC1954 cells into the mammary fat pad of immunodeficient mice. This approach replicates the tumor's natural environment, providing insights into tumor behavior and treatment responses. Researchers utilize this model to evaluate therapies targeting HER2 overexpression, such as trastuzumab and cetuximab. The model has been instrumental in assessing the efficacy of various therapeutic agents, including monoclonal antibodies and small molecule inhibitors. Studies have demonstrated its utility in testing novel treatments and understanding resistance mechanisms in HER2-positive breast cancer.

Case Study: HCC1954 Cells Reveal Cholesterol-Driven ErbB2 Regulation and Therapeutic Vulnerabilities

A study comducted by Zhang J, *et* al., published by *Cell Communication and Signaling* journal investigated the role of membrane cholesterol in regulating ErbB2 levels and therapeutic responses in ErbB2-positive breast cancer. Using the HCC1954 cell line, along with SKBR3 and AU565, researchers found that cholesterol abundance stabilizes ErbB2 on the cell surface, while cholesterol depletion enhances its internalization and degradation. Compared to SKBR3 and AU565, HCC1954 cells exhibited lower cholesterol levels and increased intracellular ErbB2 localization. Treatment with the cholesterol-lowering drug lovastatin disrupted membrane rigidity and sensitized HCC1954 cells to the ErbB2 inhibitor lapatinib, leading to enhanced tumor suppression in both *in vitro* and *in vivo* models. Mechanistically, lovastatin promoted ErbB2 degradation via endocytosis, reducing its oncogenic signaling. In HCC1954 xenografts, the combination of lovastatin and lapatinib significantly inhibited tumor growth compared to lapatinib alone. These findings suggest that targeting cholesterol metabolism could enhance ErbB2-targeted therapies, providing a potential combinatorial strategy for treating ErbB2-positive breast cancer.

HCC1954 Model for Advancing HER2-Targeted Immunotherapy in Resistant Breast Cancer

Another study by Li H, *et al.*, published by *American Journal of Cancer Research*, explored strategies to overcome trastuzumab resistance in HER2-positive breast cancer using third-generation anti-HER2 chimeric antigen receptor (CAR)-T cells alone and in combination with PD1 blockade. The HCC1954 cell line, known for its intrinsic resistance to trastuzumab, was a key model in both *in vitro* and *in vivo* experiments. Anti-HER2 CAR-T cells specifically targeted HER2-positive HCC1954 and BT474 cells, leading to increased secretion of IL-2 and IFN-γ, which was further enhanced by PD1 blockade. Cytotoxicity assays revealed that anti-HER2 CAR-T cells effectively eliminated HCC1954 cells, and the addition of anti-PD1 antibody significantly boosted this effect. In xenograft models, injection of anti-HER2 CAR-T cells led to a marked reduction in HCC1954 tumor growth, which was further inhibited when combined with PD1 blockade. Mechanistically, PD1 blockade enhanced CAR-T cell persistence and function, preventing T-cell exhaustion and improving therapeutic outcomes. These results highlight the potential of combining CAR-T therapy with immune checkpoint inhibitors to treat trastuzumab-resistant HER2-positive breast cancer, with HCC1954 serving as a crucial model system for developing such targeted therapies.

Key Oncogenes in HCC1954: Understanding HER2, Integrins, and Cadherins

HCC1954 is a HER2-positive breast cancer cell line characterized by high invasiveness and resistance to trastuzumab therapy. The primary oncogene driving its aggressive behavior is HER2 (ErbB2), which amplifies cell proliferation and survival through the PI3K/AKT and MAPK/ERK pathways. Another critical oncogene in HCC1954 is β1 integrin (ITGB1), a key regulator of adhesion and migration that contributes to trastuzumab resistance and promotes metastasis. Studies indicate that HER2 and β1 integrin exhibit crosstalk, enhancing cancer cell motility and therapy resistance. E-Cadherin (CDH1), typically associated with epithelial integrity, is also highly expressed in HCC1954, suggesting an intermediate

epithelial–mesenchymal phenotype that supports both adhesion and migration. Additionally, CD166 (ALCAM), an immunoglobulin superfamily member, is highly expressed, reinforcing tumor invasiveness and therapy resistance.

Immuno-oncology Xenograft Models

Altogen Labs is a premier preclinical research organization specializing in the characterization and evaluation of novel pharmacological and biological therapeutics, including anticancer agents, medical compounds, vaccines, cosmetics, and natural products. Leveraging advanced laboratory technologies, the company employs a team of expert scientists dedicated to advancing oncology research and expediting drug development. Altogen Labs provides specialized immuno-oncology services utilizing humanized and immunodeficient rodent models engrafted with peripheral blood mononuclear cells (PBMC), CD34+ hematopoietic stem cells, and induced pluripotent stem cells (iPSC) to investigate immune responses, therapeutic efficacy, and toxicity. A key strength of the company is its extensive collection of over 100 in-house validated xenograft models, including cell line-derived xenografts (CDX), patient-derived xenografts (PDX), *in vitro* patient-derived cell cultures (PDC), and patient-derived organoids (PDOrg), offering clinically relevant platforms for predictive drug screening. Additionally, Altogen Labs conducts comprehensive toxicology assessments, including acute, sub-chronic, and chronic toxicity studies, to evaluate compound safety and long-term tolerability in preclinical development.

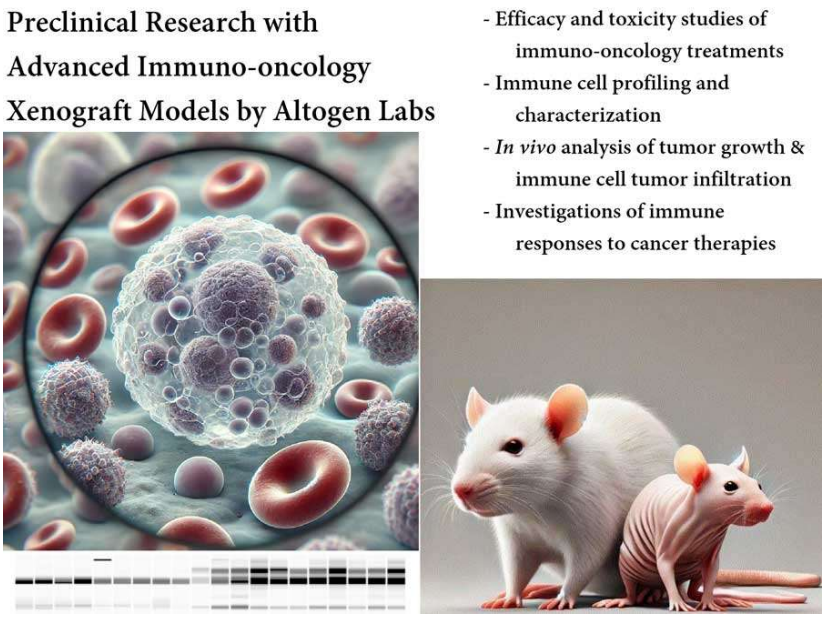

Figure 4. Advanced immune-oncology services available at Altogen Labs (Altogen Labs).

Altogen Labs offers a comprehensive range of services utilizing the HCC1954 Cell Line Derived Xenograft (CDX) model, which plays a pivotal role in advancing HER2-positive breast cancer research. The HCC1954 model is derived from a primary stage IIA, grade 3 invasive ductal carcinoma and is essential for investigating the molecular mechanisms behind tumor growth and metastasis. By using this model, researchers can explore the role of key oncogenes and tumor suppressors, including HER2 overexpression, in driving tumorigenesis and response to therapy. In addition to studying the efficacy of targeted treatments such as trastuzumab and cetuximab, the model is also employed to evaluate drug resistance, combination therapies, and the impact of specific genetic alterations. Altogen Labs provides the ability to generate genetically engineered HCC1954 cell lines with protein overexpression or RNA interference (RNAi)-mediated gene silencing, enabling precise modulation of cancer-related genes and the ability to study their functional roles in tumor progression.

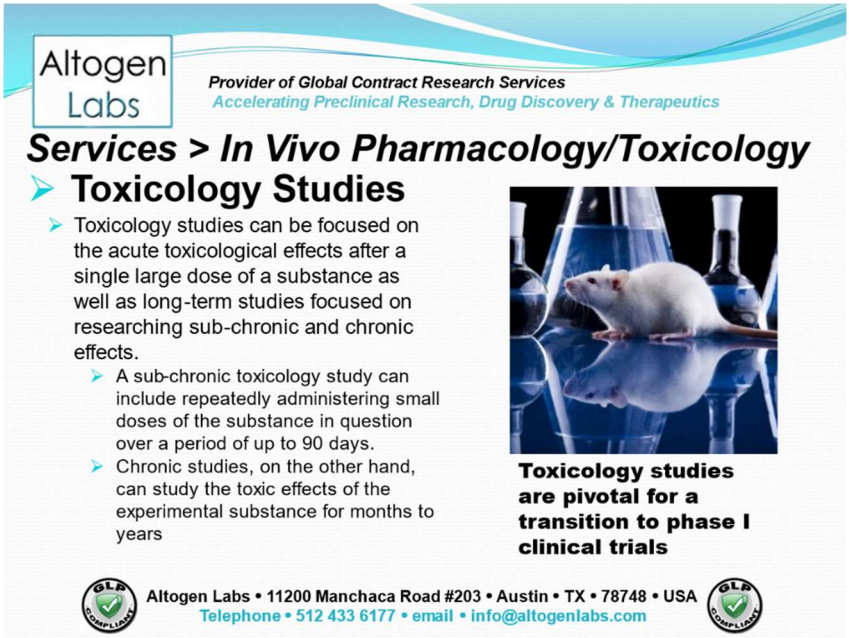

Figure 5. *In vivo* toxicology studies available at Altogen Labs for HCC1954 (Altogen Labs).

Xenograft studies using the HCC1954 model at Altogen Labs are conducted following a structured, rigorous protocol to ensure reproducibility and high-quality data. Once tumors reach a mean volume of 90-100 mm^3 in staged studies or are fully engrafted in unstaged studies, compound dosing is initiated, with treatment regimens tailored to the specific research objectives. Test compounds are administered through various routes, including intravenous, intraperitoneal, oral gavage, or intratumoral injections, at specified doses once or twice daily over a 28-day period, or for a customized study duration as required. Throughout the study, tumor growth is closely monitored and measured, and the animals are observed for any signs of adverse effects. Altogen Labs strictly adheres to IACUC regulations and maintains GLP compliance, ensuring ethical animal care and the highest standards of scientific integrity. Additional services include detailed histological analysis, gene expression profiling through RT-PCR, blood chemistry assessments, toxicity evaluations, survival studies, and advanced fluorescence-based imaging techniques. This comprehensive approach allows for in-depth analysis of tumor progression, therapeutic responses, and the molecular underpinnings of HER2-positive breast cancer.

References:

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Keywords: HCC1954, breast cancer, xenograft, breast, *in vivo*, cancer, preclinical, nonclinical, research, *in vivo* pharmacology, CDX, PDX, orthotopic, metastatic

Other Available Altogen Labs Validated Xenograft Models:

BT474 Xenograft Model: https://altogenlabs.com/xenograft-models/breast-cancer-xenograft/bt474-xenograft-model/

Hs578T Xenograft Model: https://altogenlabs.com/xenograft-models/breast-cancer-xenograft/hs578t-xenograft-model/

MCF7 Xenograft Model: https://altogenlabs.com/xenograft-models/breast-cancer-xenograft/mcf7-xenograft-model/

HCC1954 Xenograft Model: https://altogenlabs.com/xenograft-models/breast-cancer-xenograft/hcc1954-xenograft-model/

T-47D Xenograft Model: https://altogenlabs.com/xenograft-models/breast-cancer-xenograft/t-47d-xenograft-model/

ZR-75-1 Xenograft Model: https://altogenlabs.com/xenograft-models/breast-cancer-xenograft/zr-75-1-xenograft-model/