Human Breast Adenocarcinoma Model

Introduction

Noble Life Sciences has optimized a xenograft model of the triple negative MDA-MB-231-luciferase human breast adenocarcinoma in the NCG mouse. The triple immunodeficient NCG mouse has a very high take rate for MDA-MB-231 and is thus an ideal host for the *in vivo* propagation for these human tumor cells.

Methods

Female NCG mice aged 6 - 7 weeks old were divided into three groups:

1) Subcutaneous model (6 mice)
2) Orthotopic mammary fat pad model (6 mice)
3) Intravenous metastatic model (5 mice)

All mice from each group were injected with $2x10^6$ MDA-MB-231-luciferase cells. Cells injected subcutaneously or in the mammary fat pad were suspended in 50% Matrigel.

- For groups (1) and (2), tumor growth at the primary site was tracked by measuring the palpable tumor with calipers 2 - 3 times per week beginning two days after transfer. Tumor volume was calculated using the following formula: MIN (L:W)2 x MAX(L:W)/2 .

  Whole body luminescent imaging was performed once per week beginning two days after tumor cell transfer to track growth of the primary tumor and any metastatic lesions.

- For group (3), metastatic tumor growth was tracked by whole body luminescent imaging once per week beginning two days after tumor cell transfer.

The general health of all mice was monitored by measuring body weight 2 - 3 times per week beginning the day of cell transfer.

At the conclusion of the study, select mice from each group were sacrificed and organs were harvested and imaged to reveal further information about metastatic lesions.

Model Applications

- Development of new treatments for triple-negative breast cancer
- Assessment of cancer treatment regimens using human immune cell components
- Determination of optimal drug dosing, treatment schedule and route of administration to maximize therapeutic window

Model Read-Outs

- Palpable tumor size
- Body weight
- Whole body luminescent imaging
- Presence of metastatic lesions
- Organ dissection and luminescent imaging endpoint

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Results

Tumor Growth and Body Weight: The figures below depict the change in tumor volume (**Figure 1**) and body weight (**Figure 2**) in mice inoculated with MDA-MB-231 cells.

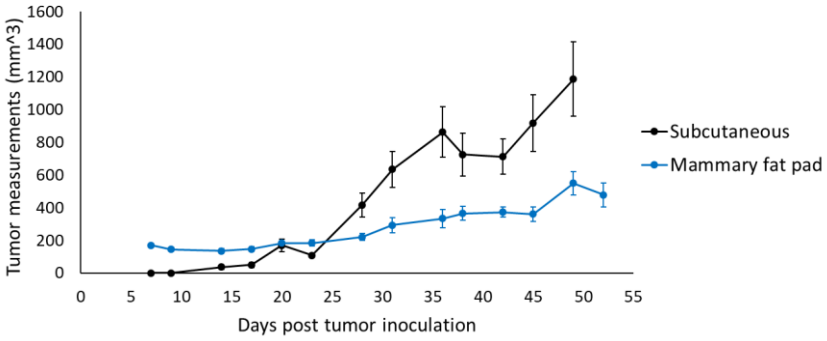

Figure 1. Tumor growth of MDA-MB-231 human breast adenocarcinoma xenograft. Tumor size was tracked 2-3 times per week. Mean +/- standard error is shown of 6 mice per group.

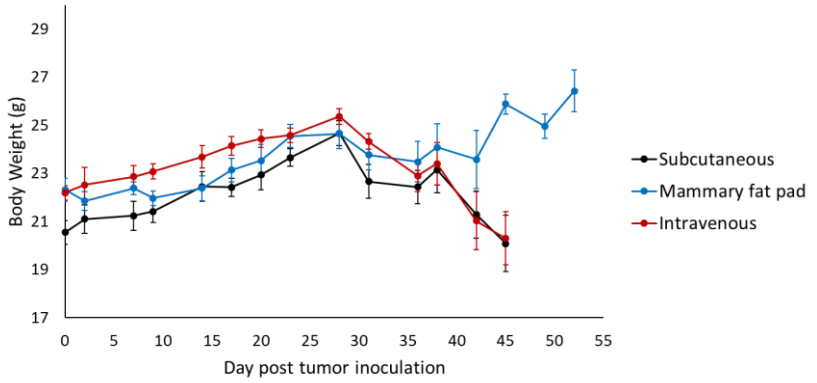

Figure 2. Body weight of mice inoculated with MDA-MB-231 cells. Body weight was measured 2-3 times per week. Mean +/- standard error is shown.

Bioluminescent Imaging: The total luminescent flux increases with time for all injection methods, with the greatest signal seen in the subcutaneous model, consistent with the palpable tumor size (Figure 3).

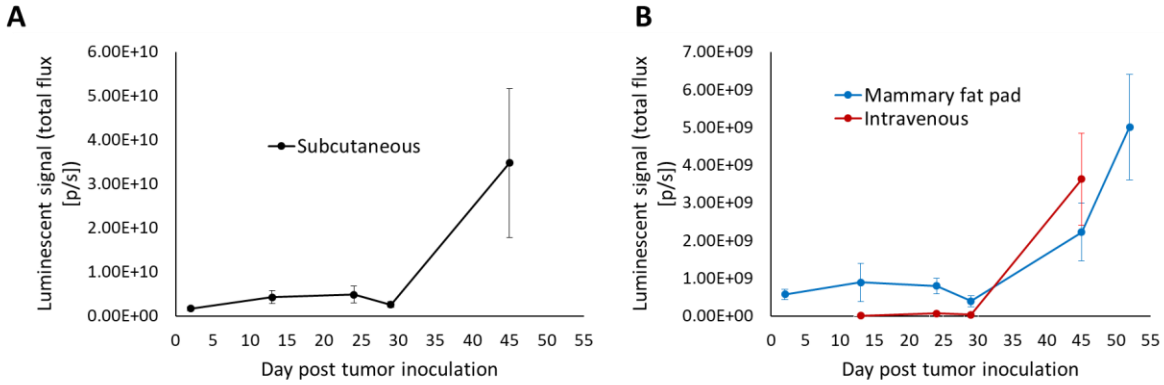

Figure 3. Whole body luminescence of mice inoculated with MDA-MB-231 cells. Mean +/- standard error is shown.

Tumor growth kinetics determined using whole body luminescent imaging were similar to those obtained by tumor volume measurement demonstrating the usefulness of whole body luminescent imaging to track growth of both palpable and non-palpable tumors.

Tumor Metastasis: Luminescent imaging enables non-invasive tracking of metastatic lesions over time. As shown in **Figure 4**, metastases were observed by day 29 regardless of administration route.

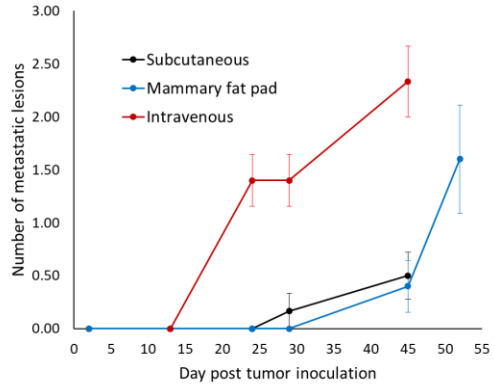

Figure 4. Average number of metastatic lesions of mice inoculated with MDA-MB-231 cells on day 0. Metastatic lesions were approximated from whole body luminescent imaging. Mean +/- standard error is shown.

The average number of metastases (>2 lesion locations per mouse) was greatest when cells were injected intravenously, followed by injection into the mammary fat pad and subcutaneous inoculation. Metastatic lesions were found in the liver, lung, kidney, and femur of several mice. Representative whole body and organ dissection luminescent images are shown in **Figure 5 and 6**.

Figure 5 A - C. Representative whole body luminescent images of mice inoculated with MDA-MB-231 cells A) subcutaneous, B) orthotopic mammary fat pad, or C) intravenous day 24 post cell transfer.

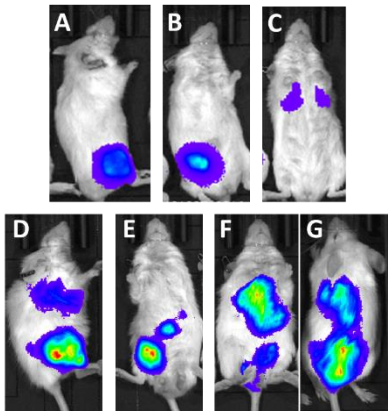

Figure 5 D – F. Representative images showing metastatic lesions for mice inoculated via D) subcutaneous, E) orthotopic mammary fat pad, or F,G) intravenous route (supine and dorsal view) on day 45 post cell transfer.

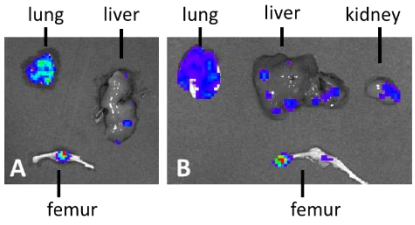

Figure 6. Representative images of organs from mice inoculated via A) subcutaneous, or B) orthotopic mammary fat pad route on day 55 post cell transfer.

Summary

Breast cancers are defined as different subtypes based on the presence or absence of three receptors that can fuel their growth: estrogen, progesterone, and HER2 receptors. Many of the most effective therapies for breast cancer target these receptors and are thus ineffective for triple-negative breast cancer which lacks expression of all three.

Therefore, the availability of xenograft models of human triple-negative breast cancer is imperative to the development of effective treatments. Xenograft models using human cancer cells allow for high throughput animal studies while capturing many of the characteristics of the human-derived cancer cells that are not possible with animal-originated disease.

The results presented herein demonstrate the growth of the MDA-MD-231 human breast adenocarcinoma model as a xenograft in the NCG mouse. Regardless of the route of administration, cells injected into NCG mice formed tumors thereby demonstrating the utility of the model for the preclinical study of new therapies to treat triple-negative breast cancer. We also demonstrate that all models lead to the growth of metastatic lesions at different time points and can thus be used to study metastatic disease.

About Noble Life Sciences

Noble Life Sciences provides integrated GLP and non-GLP preclinical services designed to accelerate the development of promising new therapies for the treatment of cancer. Services include pharmacology, disease models, early safety assessments, toxicology, GLP custom polyclonal antibodies, cell line development and analytical testing.

Noble Life Sciences offers murine models for the development of potential new oncology vaccines, drugs and immunotherapies including:

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- Xenograft Models
- Orthotopic & Ectopic Models
- Metastasis Models
- Leukemia Models

Contact us to learn more about our services for the development of new oncology drugs and cancer immunotherapies.
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