

# Developing Targeted Therapeutics



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Solutions for breakthrough targeted therapeutics exploration.



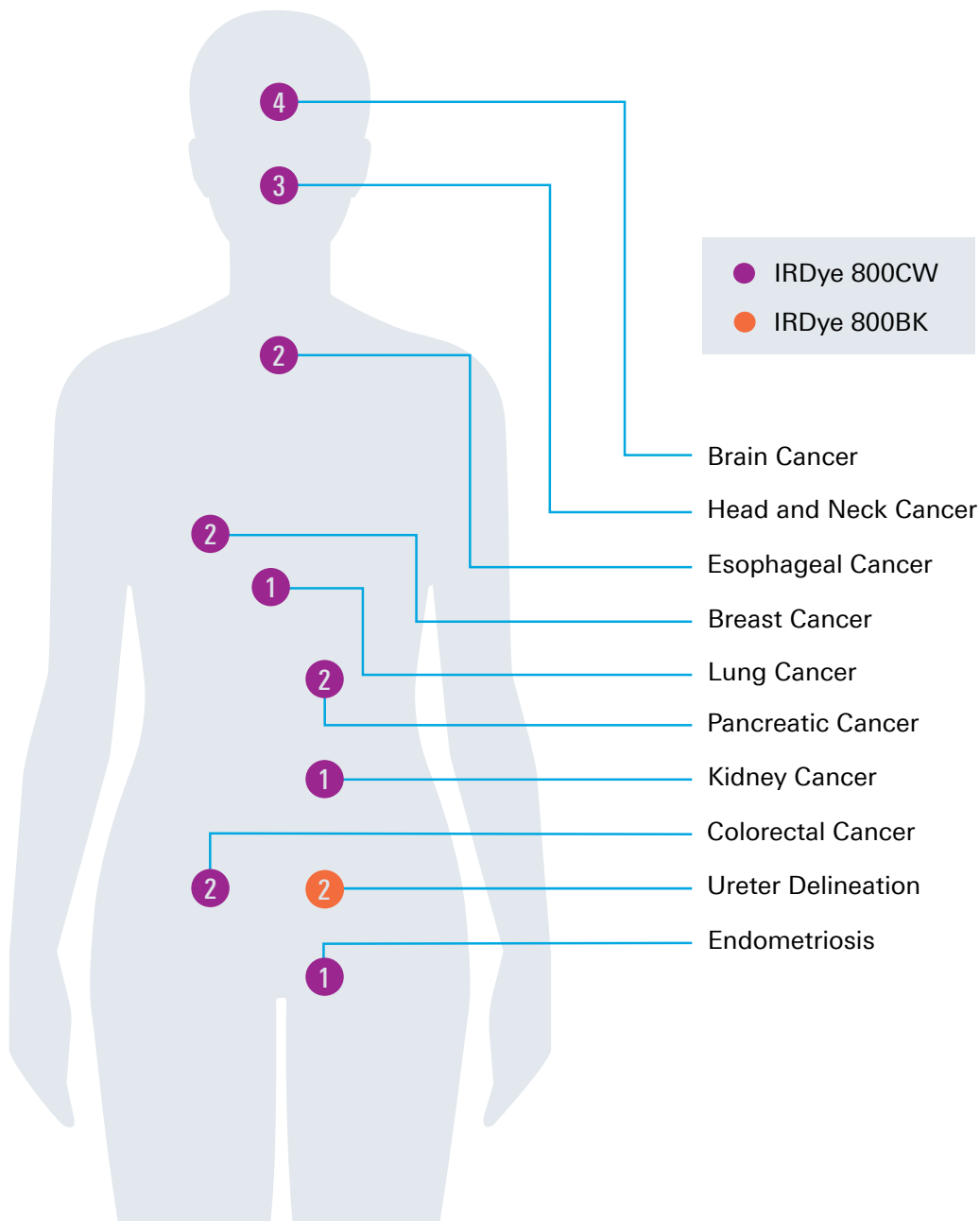
**LI-COR**<sup>®</sup>

# Why Choose LI-COR?

LI-COR pioneered near-infrared (NIR) imaging in the 1990s. More than 25 years later, researchers continue to trust LI-COR solutions to help them make critical decisions quickly and with confidence.

LI-COR solutions include imaging systems, reagents, software, and services—all supported by scientific expertise. When you choose a LI-COR solution, you prepare yourself and your targeted therapeutic for the development process.

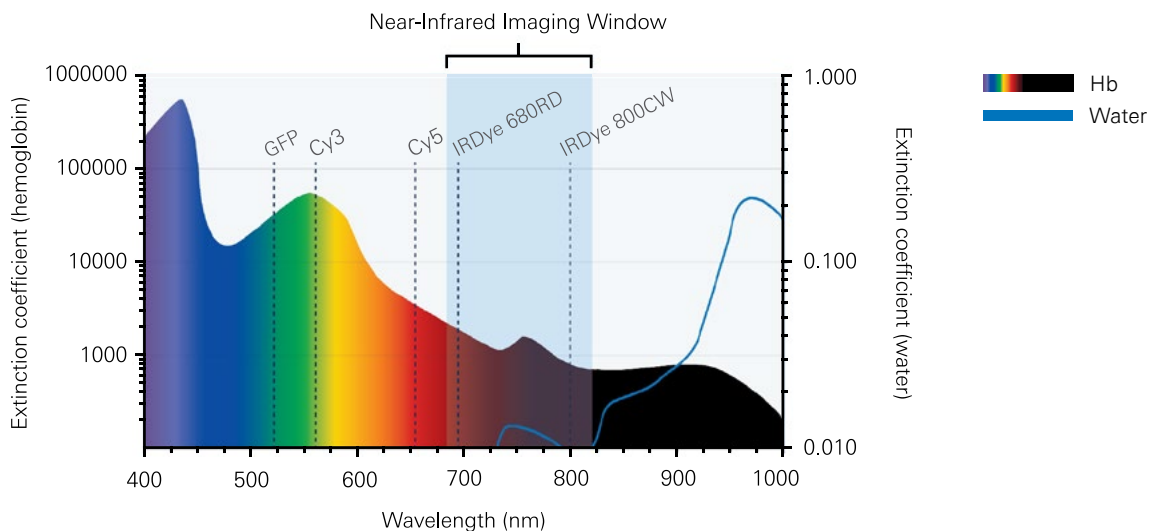
- 25k+ publications citing LI-COR imaging systems
- 20+ phase I and II clinical trials utilizing IRDye® Reagents and LI-COR imaging systems
- 50+ patents for imaging technologies worldwide
- 12+ cyanine-based dye patents on composition of matter and methods worldwide



## The LI-COR Advantage

The discovery and development of targeted therapeutics is rooted in consistent, high-quality data. Whether characterizing a ligand for pathway analysis or evaluating a therapeutic candidate, dependable data is essential for making decisions that keep you moving forward.

- High content protein profiling from DigiWest® makes efficient use of time and sample to provide comprehensive insight at the protein level.
- High sensitivity NIR imaging renders animal tissue virtually transparent reducing background autofluorescence and increasing signal-to-noise ratio.
- Multi-color detection allows you to see multiple targets or treatments on the same image from the same acquisition.
- Wide dynamic range nearly eliminates saturation to see both strong and faint signals and a range of disease states in one image.
- Stable signals are consistent over time, allowing you to reimage membranes and slides later with the same results.
- Uniform illumination over the entire imaging area means positioning during imaging won't introduce variability.












**Image in the NIR imaging window for optimal sensitivity.** Hemoglobin (Hb) and other tissue components strongly absorb visible light. In the NIR region, tissue absorbance is dramatically reduced, allowing light to easily pass through the tissue. Above 820 nm, light absorbance by water begins to increase.

# High-Content Protein Profiling with DigiWest® Technology

LI-COR and NMI TT Pharmservices have partnered to bring you the DigiWest® contract research service. With DigiWest® Protein Profiling, you can identify functional effects and therapeutic targets quickly and efficiently. Get comprehensive protein-level pathway activity profiling for lead characterization, mode-of-action studies, and biomarker discovery.

## The DigiWest® Assay Process

-  Proteins are size separated via SDS-PAGE.
-  Proteins are transferred to a blotting membrane and biotinylated.
-  Sample lanes are cut into 96 strips to generate 96 molecular weight fractions immobilized on membrane.
-  Proteins are eluted into 96-well plates.
-  Biotinylated proteins are immobilized on the surface of Neutravidin-coated Luminex beads. One distinct color-coded bead set is added to each of the 96 wells, which results in a collection of distinguishable protein-loaded bead sets from a single molecular weight fraction.
-  All bead-protein solutions are pooled together where a defined color code correlates with each molecular weight of the immobilized proteins.
-  Immunoassay: a small aliquot of the bead pool is incubated with Western blot primary antibodies overnight before Phycoerythrin-labeled secondary antibodies are added for signal generation.
-  Signal is detected on a Luminex FLEXMAP 3D® instrument.
-  DigiWest® profile of protein analytes is generated.

For more details, visit [licor.com/requestdigiwest](http://licor.com/requestdigiwest)

A DigiWest® profile provides analysis of up to 800 total and phospho proteins using a small sample of cells, tissues, or organoids. Design your DigiWest® study from a list of 1,200+ protein analytes within 50+ signaling pathway panels, including Pathway Activity Panels for cancer cell signaling. This helps you quickly narrow down your targets for further characterization and examination using an In-Cell Western™ Assay or Western blot.

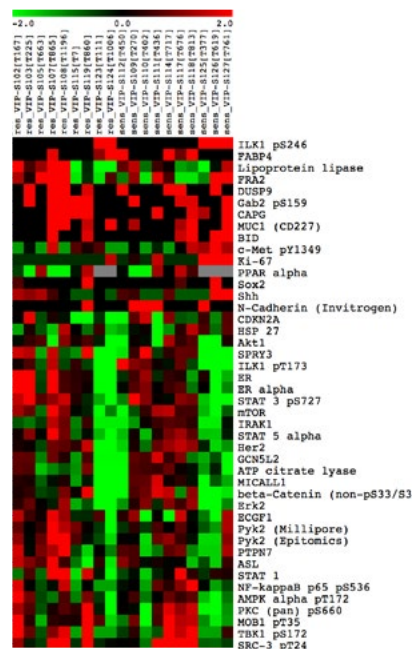
## Biomarker Discovery with DigiWest®

This study used DigiWest® for analysis of mechanisms and biomarkers of platinum resistance in ovarian cancer patients.

A set of 24 fresh frozen tumor specimens from relapsed vs cured platinum-treated ovarian cancer patients was analyzed by DigiWest®, using 466 antibodies (total and phospho proteins) covering various cell signaling pathways.

DigiWest® protein signatures distinguished platinum resistant vs sensitive patients and revealed 8 promising biomarker candidates.

This image shows a heat map of potential biomarkers (targeted with antibodies shown on the y-axis) in each tumor sample (x-axis). Red squares indicate an increase in biomarker expression compared to control, black indicates no change, and green squares indicate a decrease.



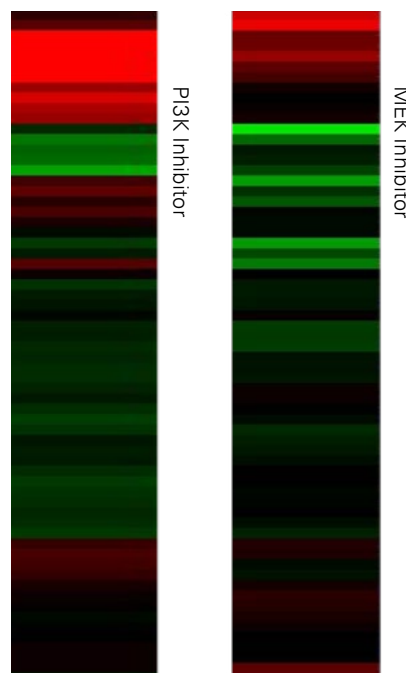
## DigiWest® for Lead Characterization

In this study, DigiWest® was used to perform a mode-of-action study of compounds in comparison to reference therapeutics.

Calu1 cells were treated with 1 MEK inhibitor vs 1 PI3K inhibitor vs 2 experimental lead compounds (data not shown) vs DMSO. Cell samples were analyzed by DigiWest®, using 156 selected antibodies (total and phospho proteins) covering different signal transduction pathways.

DigiWest® yielded distinct signatures for each compound and allowed for in-depth characterization of lead compounds as compared to reference therapeutic.

Distinct signatures for MEK vs PI3K inhibitors in Calu1 cells are shown using the heatmap. Each horizontal line indicates a different antibody. Red lines indicate an increase in biomarker expression compared to control, black indicates no change, and green lines indicate a decrease.

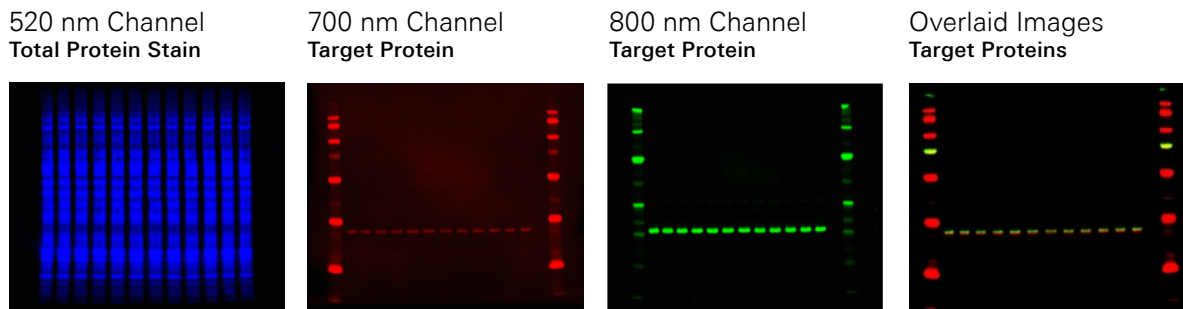


# Critical Cell Signaling Assays

Cell signaling assays performed on an Odyssey® Imager can enhance your understanding and characterization of targets, pathways, and the cellular effects of your therapeutic.

## Quantitative Western Blots

LI-COR offers the only complete solution designed to take your quantitative Western blots from validation through statistical analysis for reliable results. Accurately detect your proteins of interest using an Odyssey Imager, then perform in-depth analysis in Empiria Studio® Software.

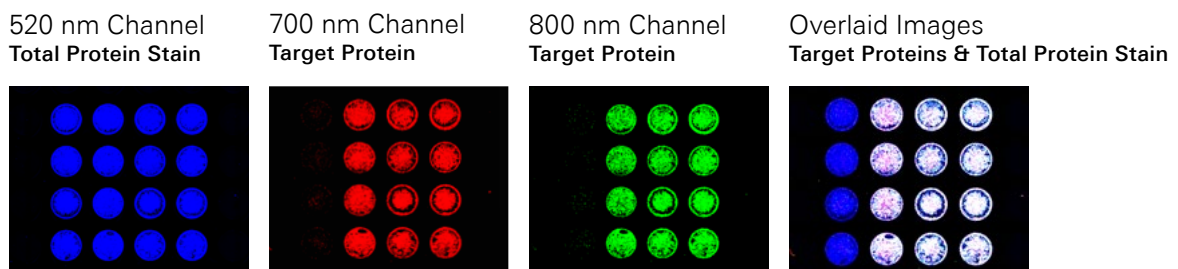


**Normalize and multiplex with ease.** See your targets and loading controls, such as Revert™ 520 Total Protein Stain, on the same blot with multiplex detection using the 520 nm, 700 nm, and 800 nm channels.

## Quantitative Cell-Based Assays

The Odyssey M and Odyssey DLx can be used to quickly characterize a broad range of cell signaling parameters using the In-Cell Western™ or On-Cell Western Assay. These assays are a higher throughput way to detect and quantify multiple targets at the same time within their cellular context, in addition to many other advantages.

- Adapt to a broad range of assays to characterize various cellular events
- Collect data from many experimental conditions or replicates in parallel
- Improve consistency with a streamlined protocol that saves time



# In-Cell Western Assay and Western Blotting Workflow Comparison

**In-Cell Western Assay:** <5 hours, 96+ Samples



Fix and permeabilize      Antibody incubations

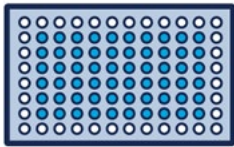
**Western Blotting:** >7 hours, 10-24 Samples



Lyse cells, transfer lysates (fractionate)      SDS-PAGE      Membrane, transfer, blocking, antibody incubations

## Typical In-Cell Western Assay Workflow

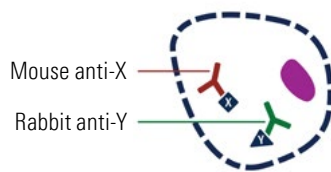
- 1 Culture cells
- 2 Stimulate or inhibit cells
- 3 Fix and permeabilize cells



- 4 Incubate with blocking buffer



- 5 Incubate with primary antibodies



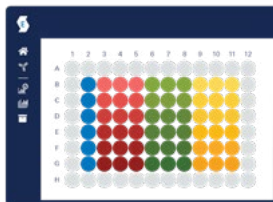
- 6 Incubate with secondary antibodies and internal control



- 7 Excite with infrared lasers



- 8 Acquire image using Odyssey Imager

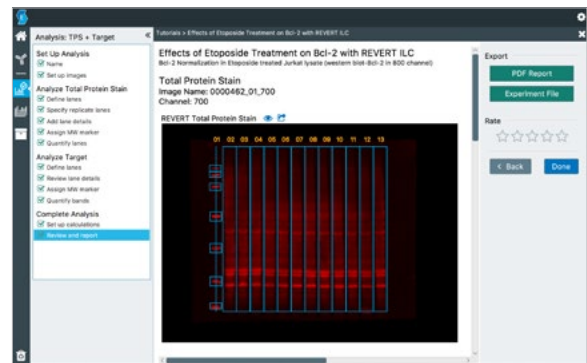
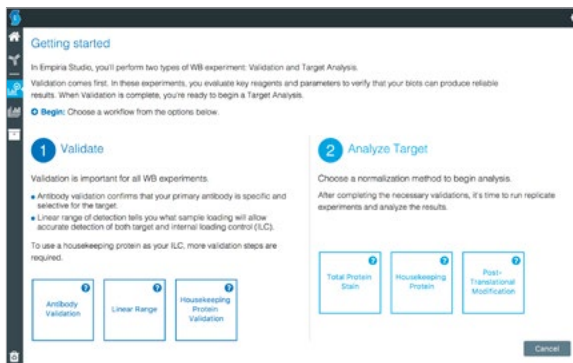




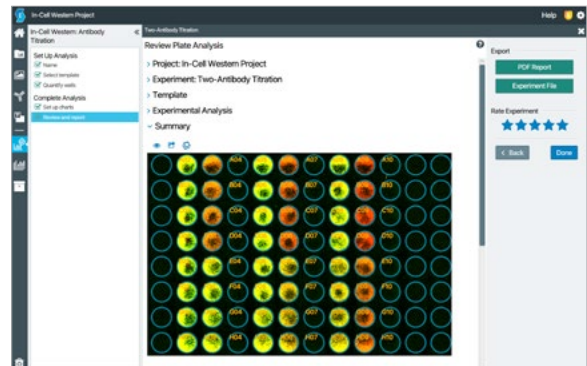
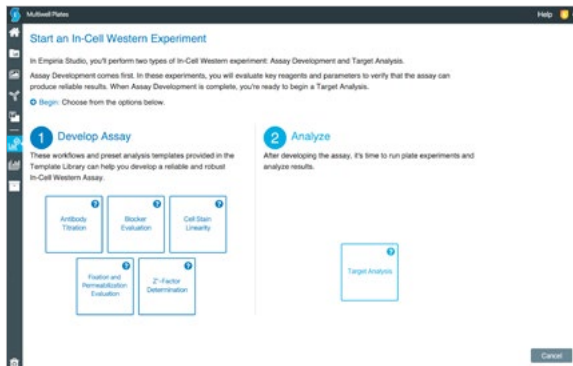


# Empiria Studio® Software

## Expert-Level Analysis Made Simple



Western Blot Analysis Workflow



Cell-Based Analysis Workflow

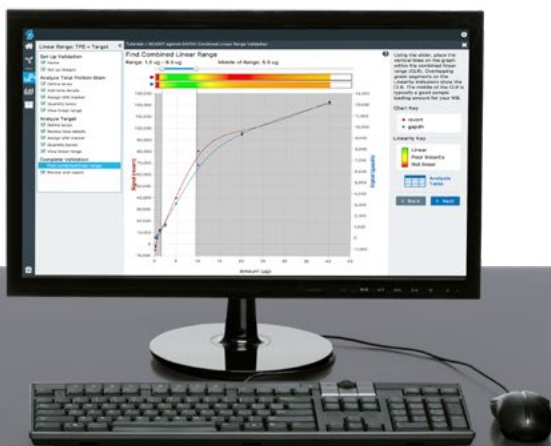


# Exceptional Results Start Here

Empiria Studio® Software helps get your therapeutics into the clinic faster with easy-to-follow workflows that guide your assay analysis and improve user-to-user consistency.

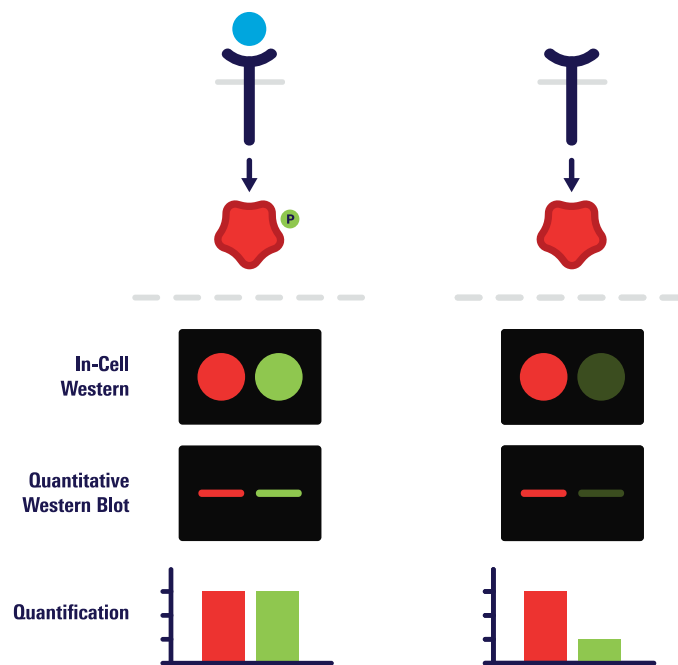
- Take the guesswork out of quantification and let Empiria Studio handle the complex math
- Manage your images and data with project-based organization
- Validate, compare replicates, and perform statistical analysis to achieve rapid, reliable results

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# Characterize Signaling Pathways with Knockdown/Knockout Assays

Knockdown/knockout assays can be performed using siRNA, shRNA, TALENs, or CRISPR/Cas9. Then the extent of knockdown/knockout can be examined using a Western blot or In-Cell Western™ Assay done on an Odyssey® Imager to characterize your pathways of interest.

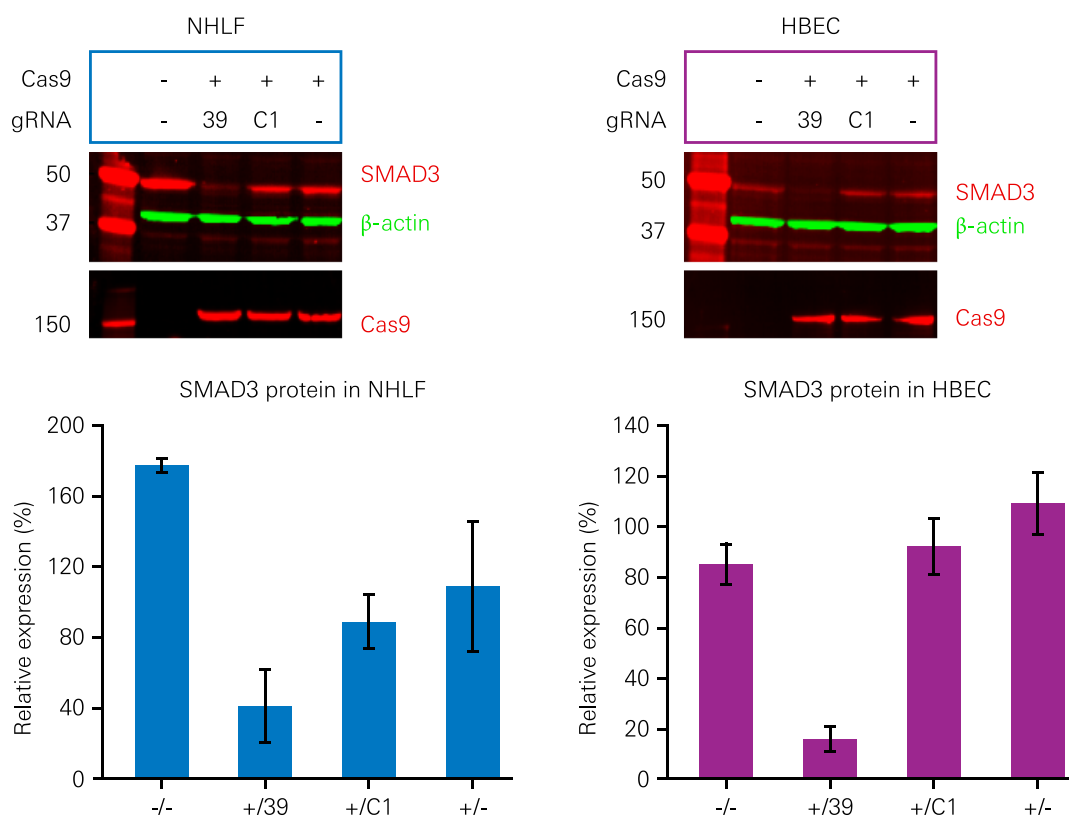


This conceptual diagram illustrates how knockdown treatment can affect protein expression. Under normal conditions, a ligand (blue) binds its cell surface receptor. This results in phosphorylation (green) of the red protein. When the ligand is knocked down, phosphorylation is reduced. For example, an Odyssey Imager can detect the phosphorylated form of the protein in the 800 nm channel (green) and total protein in the 700 nm channel (red).

# Studying Adenoviral CRISPR/Cas9 Effects on Fibrosis Development Using Near-Infrared Western Blots Imaged on an Odyssey® Imager

Example Study: "Highly efficient gene inactivation by adenoviral CRISPR/Cas9 in human primary cells."  
 Research conducted by Voets, O., et al., Galapagos BV, *PLoS One*.<sup>1</sup>

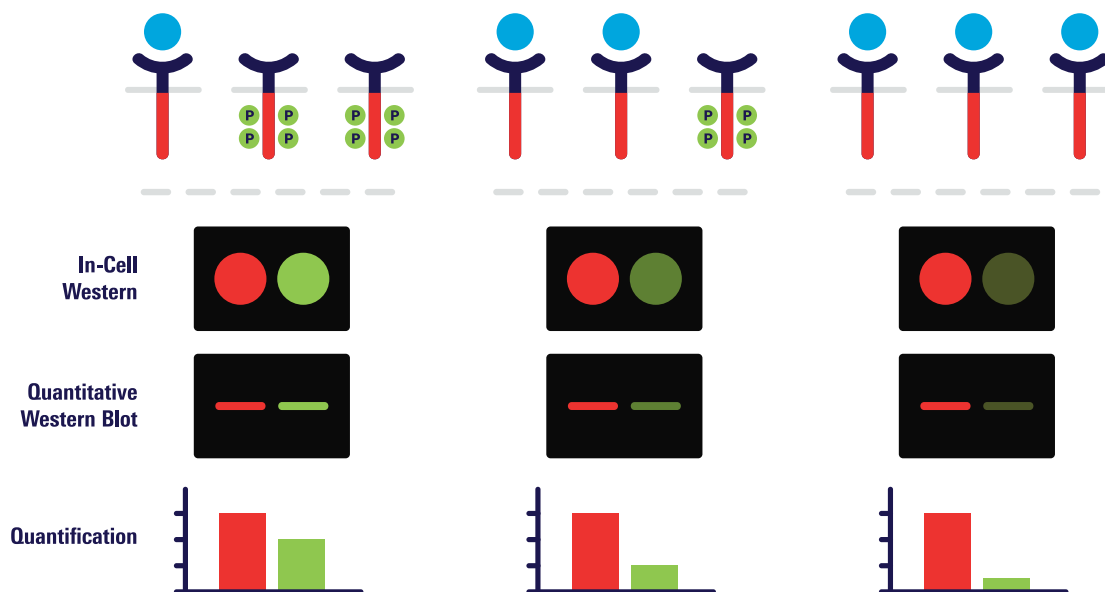
Gene knockdown techniques enable researchers to better understand disease processes and advance drug discovery by identifying and validating biological targets. This study demonstrates the use of Adenoviral (AdV) CRISPR/Cas9 to reduce the expression of SMAD3, a protein involved in triggering pulmonary fibrosis.



AdV CRISPR/Cas9 exhibited significant SMAD3 knockdown in human primary cells. SMAD3 (red) and Cas9 (red) were detected in normal human lung fibroblasts (NHLF) and human bronchial epithelial cells (HBEC) and normalized to  $\beta$ -actin (green) using IRDye® Secondary Antibodies on NIR Western blots. The presence of Cas9 and the gRNA 39 resulted in significant decrease in SMAD3 protein. Images were acquired on an Odyssey CLx Imager. Adapted from Voets, O., et al. (CC BY).

# Analyze Dose Response with IC<sub>50</sub> Assays

You can perform an IC<sub>50</sub> assay using an Odyssey® Imager to find the concentration of an inhibitor required to reduce response by half. Learn more about the dose-response characteristics of your therapeutic leads, and get the data you need to continue through discovery and development.

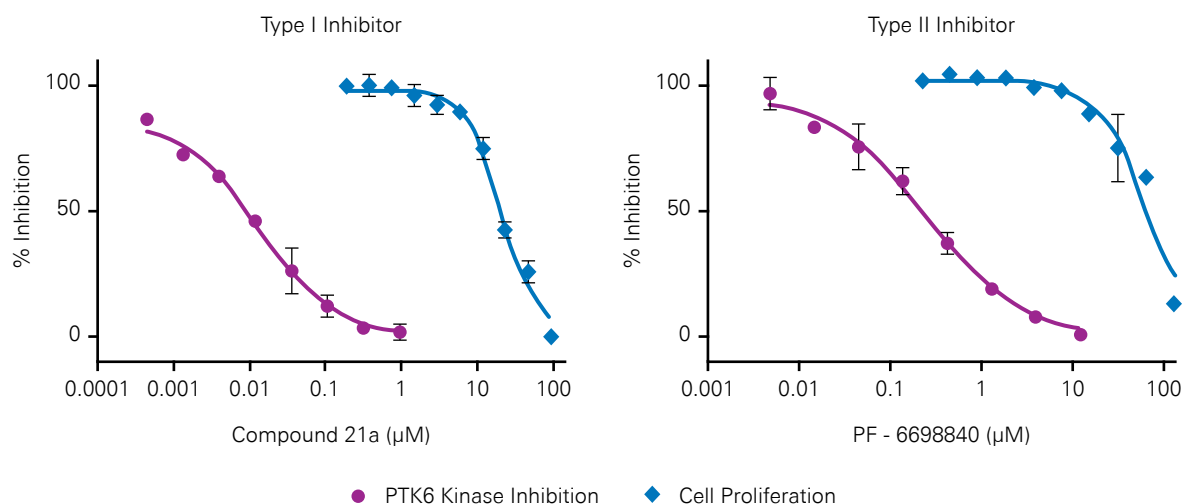


This conceptual diagram shows the concept of the IC<sub>50</sub> assay. Pan protein (red) is used for comparison. As the concentration of an inhibitor (blue circle) is increased, phosphorylation (green) is reduced. For example, an Odyssey Imager can detect the phosphorylated protein and pan protein using the 800 nm (green) and 700 nm (red) channels respectively.

## Determining IC<sub>50</sub> by In-Cell Western™ Assay Imaged on an Odyssey® Imager

Example Study: "Small molecule inhibitors reveal PTK6 kinase is not an oncogenic driver in breast cancers." Research conducted by Qiu, L., et al., Pfizer, *PLoS One*.<sup>2</sup>

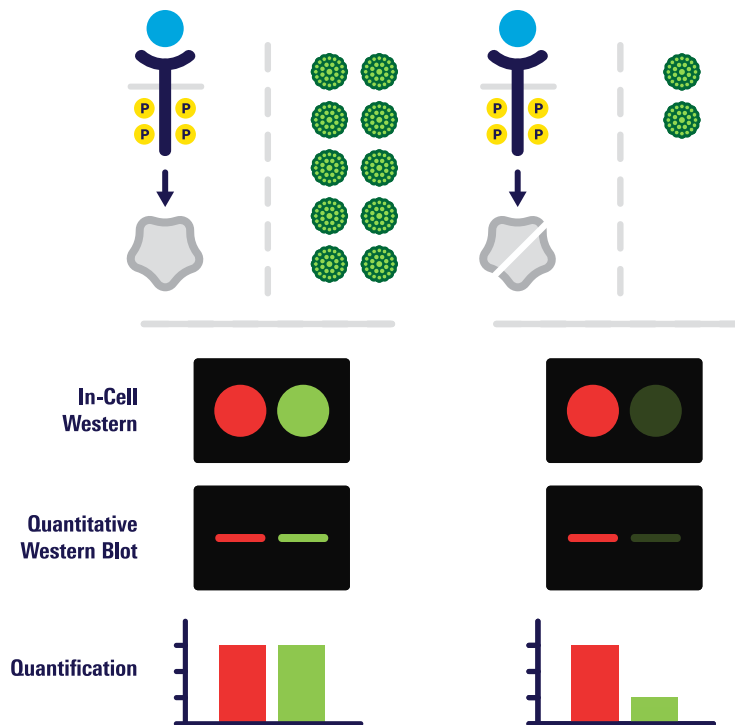
PTK6 is abnormally expressed in breast cancers, and researchers have described kinase-dependent functions of PTK6 in driving tumor growth. As with any therapeutic approach, using small molecule inhibitors to target PTK6 activity requires validation of specificity and efficacy.



Inhibition of tumor cell growth by PTK6 inhibitors is independent of PTK6 kinase activity inhibition, providing evidence against using PTK6 kinase inhibition as a therapeutic strategy for breast cancer treatment. In-Cell Western Assays imaged on an Odyssey CLx Imager were used to assess cellular levels of PTK6 autophosphorylation normalized to cell number (measured by CellTag™ 700 Stain). Adapted from Qiu, L., et al. (CC BY).

# Virus Characterization Assays

Many of the assays used for the development of targeted therapeutics, including the In-Cell Western™ Assay and NIR Western blot, can be adapted for virus characterization. When imaged on an Odyssey® Imager, these assays provide reliable, quantifiable results to characterize viral infectivity and mechanism of action for the development of antiviral therapeutics and vaccines.



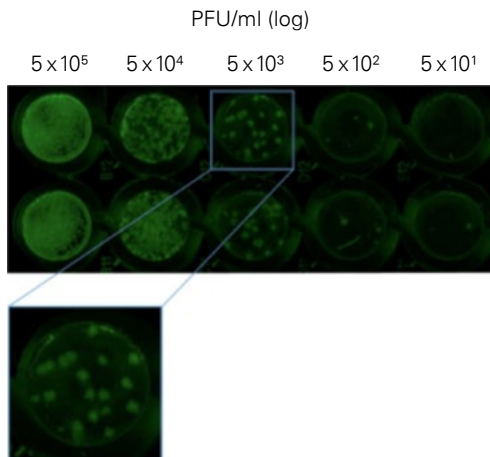
This conceptual diagram illustrates an assay to characterize viral infectivity. Virus particles (green) are detected with viral protein-specific antibodies. A protein (gray) is used as part of the host machinery for viral replication. When this protein is knocked down, the virus loses its means to replicate, resulting in a reduction of infectious virus particles. For example, an Odyssey Imager can detect virus particles in the 800 nm channel (green) and a normalizing agent in the 700 nm channel (red).

# Performing HSV-1 Titration Using the In-Cell Western™ Assay Imaged on an Odyssey® Imager

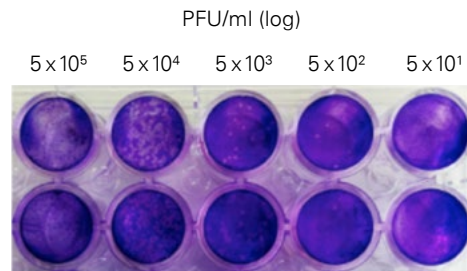
**Example Study:** "A Novel Method to Titrate Herpes Simplex Virus-1 (HSV-1) Using Laser-Based Scanning of Near-Infrared Fluorophores Conjugated Antibodies." Research conducted by Fabiani, M., et al., *Frontiers in Microbiology*.<sup>3</sup>

Quantifying viral replication using the standard plaque assay (SPA) can be labor-intensive and subjective. Using the In-Cell Western Assay to titrate Herpes simplex virus-1 (HSV-1) produced nearly superimposable results to SPA, but with many advantages. Results were detected faster (24 hours post-infection versus 48-72 hours for SPA), enabled many samples to be measured in parallel, and was found to be more suitable for titrations that produced plaques too numerous to count.

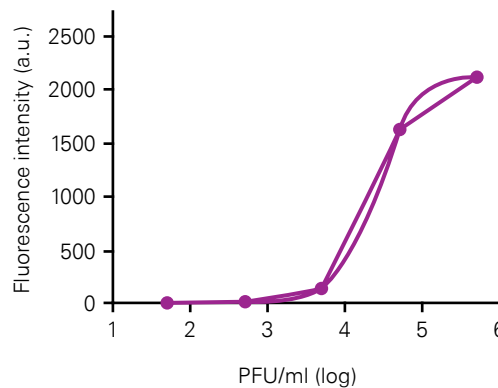
## A. In-Cell Western Assay



## B. Standard Plaque Assay



## C.



The In-Cell Western Assay is a suitable technique to detect HSV-1 infection in cells. Vero cells were seeded in 96-well plates and infected with HSV-1 in 10-fold serial dilutions. (A) Cells were fixed and immunostained 24 hours post-infection with anti-gB antibody followed by IRDye® 800CW Goat anti-Mouse Secondary Antibody. Plates were imaged using an Odyssey Imager with a representative image shown. (B) A representative image of SPA performed using the same HSV-1 dilutions used for the In-Cell Western Assay. (C) Standard curve for the mean value of fluorescence intensity was detected for each point. Adapted from Fabiani, M., et al. (CC BY).

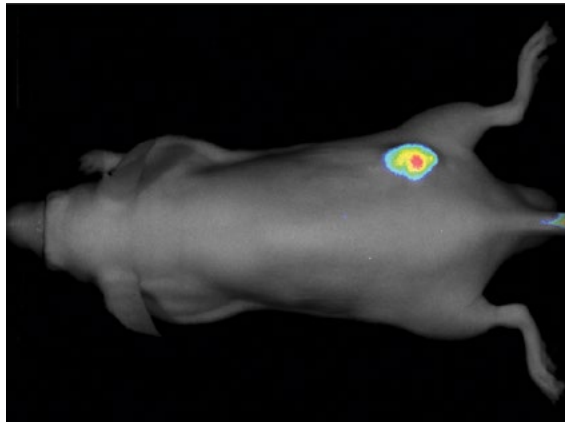


# Examine Therapeutic Activity in Live Animals

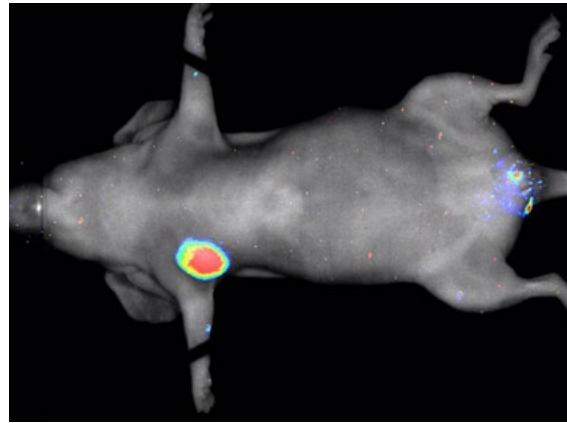
The Pearl® Trilogy Small Animal Imaging System lets you take your studies *in vivo* to capture a detailed representation of therapeutic activity in live animals. The wide dynamic range of the Pearl Trilogy captures signal from various disease states in one image. Uniform illumination and consistent camera settings allow you to accurately track your therapeutic or therapeutic response over time.

The Pearl Trilogy offers several detection methods, including NIR, infrared fluorescent protein (iRFP), and bioluminescence. Two-color imaging on the Pearl Trilogy allows you to simultaneously view two targets labeled with spectrally distinct dyes to assess biodistribution and clearance, colocalization, efficacy, and other key factors for therapeutic development.

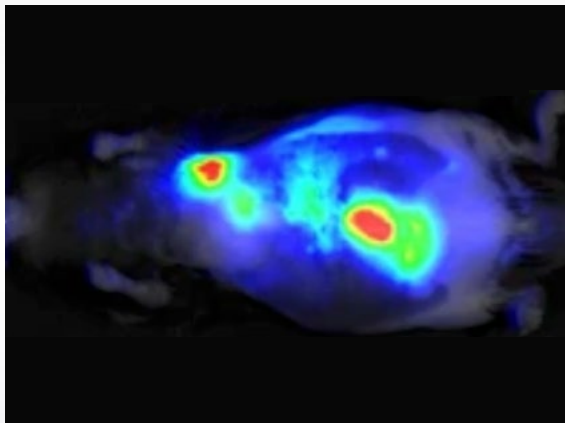




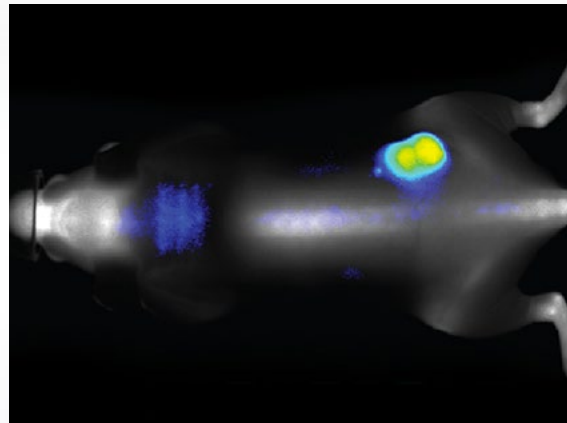
Specificity of a subcutaneous tumor derived from a prostate cancer cell line captured using a Pearl Imager.



A human breast cancer tumor was implanted, then imaged on a Pearl Imager to visualize ATX activity.



iRFP713 and a Pearl Trilogy Imager were used to track Pdx1-Cre activity and monitor *in vivo* tumor progression.<sup>4</sup>

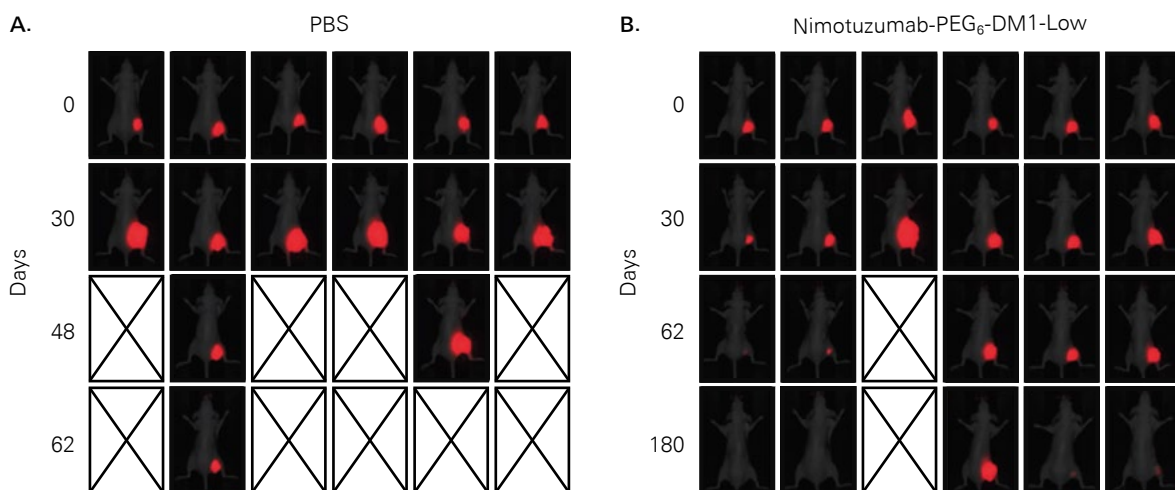


Overlaid images of multiple targets from a Pearl Imager show an A431 tumor on the right hip and skeletal features.

## Measuring Efficacy of an Antibody-Drug Conjugate Using iRFP Imaged on a Pearl® Imager

**Example Study:** "Therapeutic potential of nimotuzumab PEGylated-maytansine antibody drug conjugates against EGFR positive xenograft." Research conducted by Hartimath, S.V., et al., *Oncotarget*.<sup>5</sup>

Epithelial cancers commonly overexpress epidermal growth factor receptor (EGFR). Nimotuzumab is tolerated better by patients than other anti-EGFR antibodies used to treat epithelial cancers and does not exhibit high cutaneous toxicity. However, like other anti-EGFR antibodies, acquired resistance often reduces its efficacy. Conjugating nimotuzumab to PEGylated-maytansine (PEG<sub>6</sub>-DM1) can improve its efficacy and shows promise as a treatment for cancers of epithelial origin.

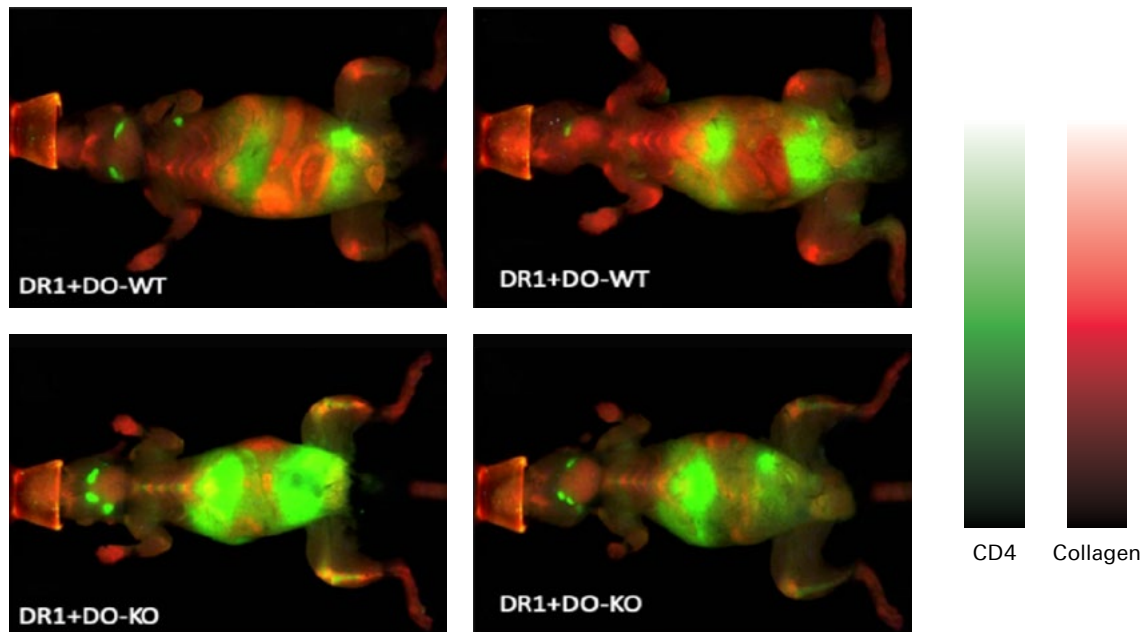


Nimotuzumab conjugated to PEG<sub>6</sub>-DM1 was shown to reduce tumor volume in mouse xenografts bearing iRFP-702 tumors. (A) Of the mice treated with PBS, only one mouse reached the study endpoint on day 62. (B) Of the mice treated with nimotuzumab-PEG<sub>6</sub>-DM1-Low, the study found two were cured by day 62 with no tumor regrowth and two others were cured by day 180. In one mouse tumor growth was slowed, and one mouse did not respond to the therapy. Images were acquired using a Pearl Imager. Adapted from Hartimath, S.V., et al. (CC BY).

## Observing Colocalization of CD4 T Cells and Denatured Collagen with a Pearl® Imager

Example Study: "Lack of the MHC class II chaperone H2-O causes susceptibility to autoimmune diseases." Research conducted by Welsh, R.A., et al., *PLoS Biology*.<sup>6</sup>

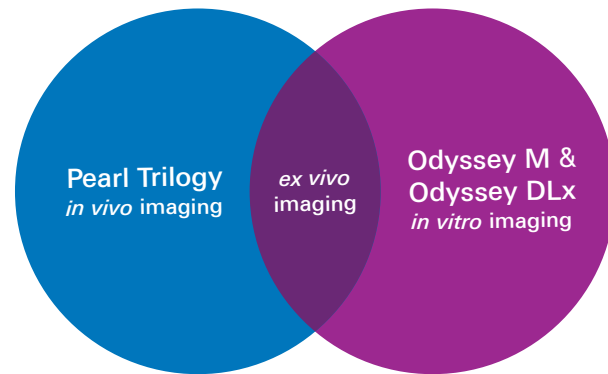
Millions are affected by autoimmune disease. A better understanding of the contributing risk factors may help in early identification and intervention for improved outcomes. This study examines an apparent link between DO, an accessory molecule found in the Major Histocompatibility Complex class II pathway, and susceptibility to various autoimmune diseases.



Colocalization of CD4 T cells and denatured collagen was observed only in the diseased joints of DR1+DO-KO mice. 48 hours before imaging, DR1+DO-KO and DR1+DO-WT mice with collagen-induced arthritis were injected intravenously with a collagen mimetic peptide probe labeled with IRDye® 680RD (red) and intraperitoneally with a CD4 probe labeled with IRDye 800CW (green). Colocalization (orange) of CD4 T cells and denatured collagen was found only in affected joints of DR1+DO-KO mice, suggesting increased susceptibility to rheumatoid arthritis in these mice. Images were acquired using a Pearl Imager. *Adapted from Welsh, R.A., et al. (CC BY).*

# Measure Uptake and Localization with Tissue and Organ Imaging

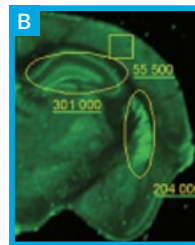
An Odyssey® M Imager or Odyssey DLx Imager and a Pearl® Trilogy Small Animal Imager are an ideal combination to assess the performance of your targeted therapeutic throughout development. After your *in vitro* and *in vivo* studies, take the next step with *ex vivo* imaging. With whole organ and tissue section imaging, you can evaluate which organs are absorbing your therapeutic and where it accumulates in the tissue.



The Odyssey M, Odyssey DLx and Pearl Trilogy are capable of high-sensitivity *ex vivo* imaging. Image whole organs using either the Odyssey M, Odyssey DLx, or the Pearl Trilogy to visualize uptake, then perform in-depth analysis using tissue section imaging on the Odyssey M or Odyssey DLx to determine exact tissue localization.



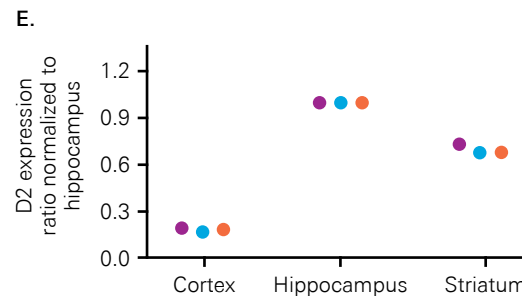
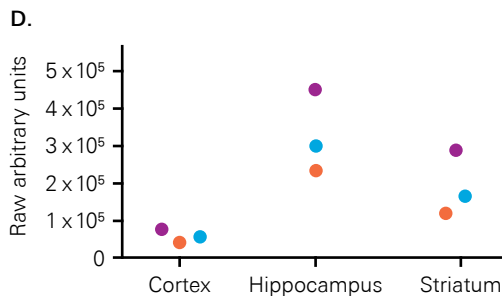
Colorimetric



NIR fluorescence



Reimaged section

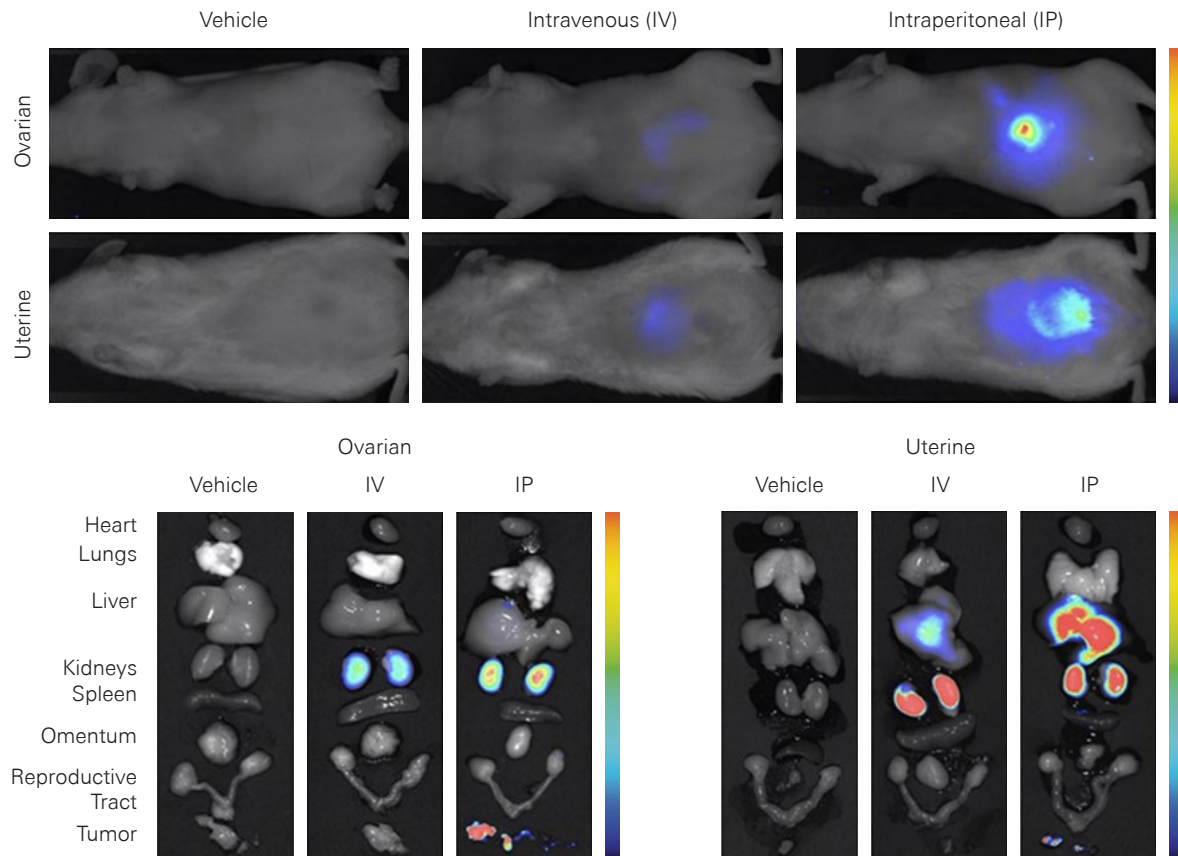


Traditional colorimetric microscopy compared with fluorescently labeled tissue sections for quantification of D2 protein expression. (A) Traditional colorimetric imaging compared with (B) NIR fluorescence tissue imaging. (C) The same tissue section from (B) was reimaged one year later, with the proportionality of signals staying the same. (D) The same trends are seen in the raw data, showing the reliability of fluorescence. (E) Raw data normalized to the hippocampus data. Adapted from Eaton, S.L., et al. (CC BY).<sup>7</sup>

# Assessing Biodistribution of an siRNA Delivery System for a Promising Cancer Treatment Using the Pearl® Trilogy Imager

Example Study: "p5RHH nanoparticle-mediated delivery of AXL siRNA inhibits metastasis of ovarian and uterine cancer cells in mouse xenografts." Research conducted by Mills, K.A., et al., Washington University School of Medicine, *Scientific Reports*.<sup>8</sup>

Ovarian and uterine cancers are often diagnosed at advanced stages, underscoring the need to identify therapeutic targets and means of delivering therapies to tumors. One promising therapeutic target is the AXL protein, which is involved in ovarian and uterine cancer metastasis. One potential treatment option is to silence AXL expression with siRNA, but a mechanism is needed to deliver the siRNA to the tumor.



p5RHH-siRNA nanoparticles were found to localize to tumor cells *in vivo*. To determine localization of p5RHH nanoparticles and to identify the best delivery method, mice bearing either uterine or ovarian cancer tumors were injected either intraperitoneally (IP) or intravenously (IV) with p5RHH-siControl nanoparticles labeled with a fluorescent probe. Excised tumors from IP-injected mice showed more probe localization than those from IV-injected mice. Live mouse and whole organ images were acquired on a Pearl Trilogy Imager. *Adapted from Mills, K.A., et al. (CC BY).*

# Regulatory Products and Services

LI-COR offers an extensive range of regulatory products, tools, and services designed to help your lab align with regulatory compliance guidelines.

## 21 CFR Part 11-Ready Software

Image Studio™ 21 CFR Part 11-Ready Software is a secure, database-driven software designed to help your lab comply with the Food and Drug Administration's (FDA) 21 CFR Part 11 regulations. Regulated labs with a controlled workflow can ensure traceability for access control, data acquisition, and analysis.

- Image archive
- Time and date stamped change logs
- Electronic signature and approval
- Version control

## Installation and Operational Qualification

An Installation Qualification and Operational Qualification are recommended for labs that are audited externally. During these qualification services, a certified LI-COR technician will confirm that all instruments and software are installed and performing according to LI-COR standards with documentation provided that establishes qualification.



# Consistency and Speed Without Compromise

From academic discovery to preclinical validation, LI-COR has the products, tools, and services to let you make critical decisions about your targeted therapeutics with confidence. LI-COR solutions support a wide range of cell signaling and preclinical validation assays to provide you with the high-quality, consistent data you depend on.

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## References

1. Voets, O., Tielen, F., Elstak, E., Benschop, J., Grimbergen, M., Stallen, J., et al. (2017). Highly efficient gene inactivation by adenoviral CRISPR/Cas9 in human primary cells. *PLoS ONE*, 12(8). e0182974. <https://doi.org/10.1371/journal.pone.0182974>
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