PharmaLegacy

Preclinical Specialty Pharmacology Services

CASE STUDY:

Immuno-Oncology with Humanized Mice

Doing immuno-oncology drug discovery in a large pharmaceutical company means there is almost always a desire for more and different data to drive decision-making on potential new therapeutic compounds. That was exactly the situation Dr. Michael Adams*, Senior Research Fellow at a Fortune 500 pharmaceutical company found himself in. *"Our in vivo pharmacology groups are overloaded with various projects. Having access to additional in vivo resources allows us to explore additional models that we may not have the capacity to develop ourselves. Proof-of-concept oncology agents have difficulty getting prioritized against portfolio projects – access to a top notch, outsourced group that can perform such studies can provide the data necessary to elevate these proof-of-concept ideas."* Michael looked to find such a group so his team could provide strong proof-of-concept data for an asset which was *"still in its infancy prior to Discovery portfolio entry."*

They specifically wanted to work with a CRO that could provide them with access to challenging and complex immuno-oncology models which would help them assess the activity of novel compounds, specifically using mice with humanized immune systems.

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"PharmaLegacy convinced us they had all the right pieces in place – and did the important work to validate the models that we hoped to run. They were flexible, validating new tumor models at our request without charging us for these. We have been impressed with their expertise, thoughtfulness, ability to pivot, and strong and constant communication before, during and after the models were run."

As is the nature of research, not everything went according to plan. *"The project didn't occur on the original timeline, there were unavoidable scientific delays. But PharmaLegacy worked very hard to resolve the scientific issues and get the study started. They could have pressed us to start an inadequate model, but pushed to do extra work free of charge to make sure that the study they delivered on a very reasonable budget was top notch."* While the project did not yield the results the team had expected, Michael said *"the model was executed flawlessly, suggesting there are things we perhaps don't know that may be attenuating the activity of our lead molecules and we will take the necessary steps to address this scientifically. For this reason, the data was critical for us."*

Based on the results of PharmaLegacy's studies, the study sponsor began additional studies to evaluate the target and mechanisms that may have led to the lack of robust efficacy in the model that they ran.

*Name changed due to contractual confidentiality clauses with the client company.
We would like to extend very special thanks to him for so candidly sharing his experience with PharmaLegacy.

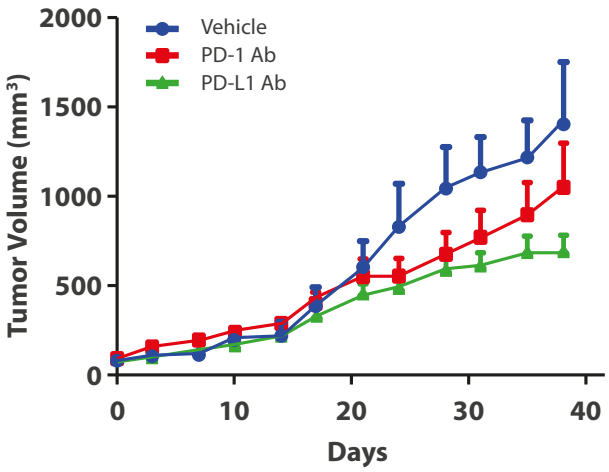
"We've been very pleased with the terrific service PharmaLegacy has provided. Some of the models were difficult to develop, but they persevered and kept us informed of the challenges – even if these led to delays. They have been so honest and conscientious as well as providing terrific expertise and services."

- Dr. Michael Adams, Senior Research Fellow

CASE STUDY:

PD-1/PD-L1 Abs

A.



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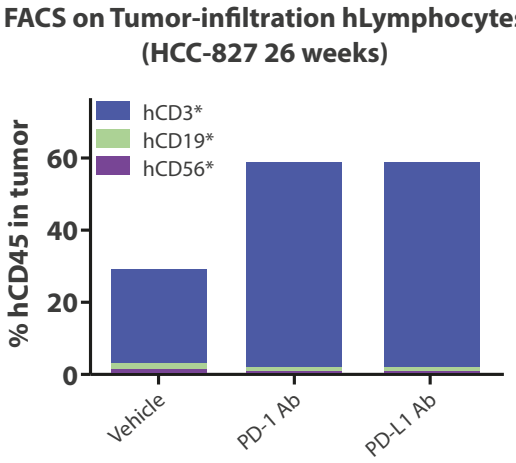

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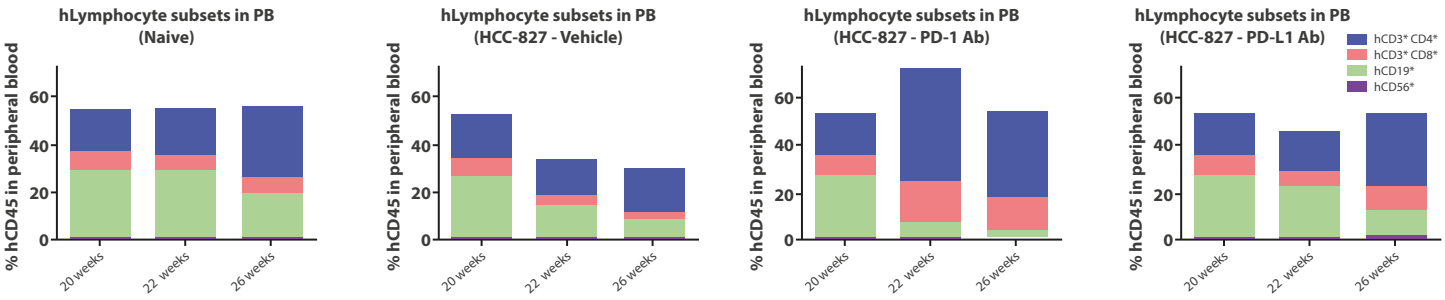


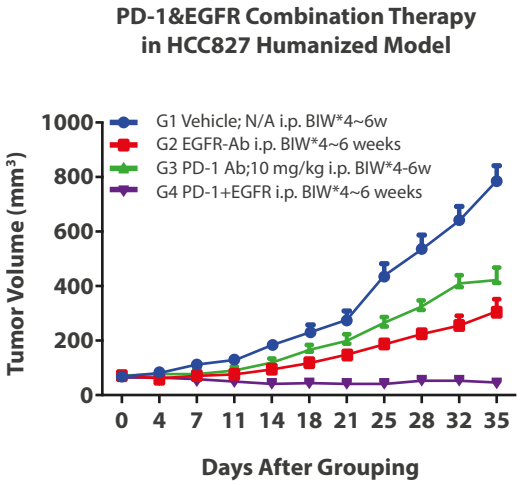
Figure 1: Evaluation of immune checkpoint inhibitor PD-1/PD-L1 Ab in HCC827 CD34⁺ humanized mouse model.

HCC827 were inoculated into CD34⁺ humanized mice and treated with either PD-1 Ab or PD-L1 Ab and compared to vehicle group. Tumor volume represents mean tumor volume ± SEM. (A)
Percentage of human T cells infiltrated into tumors (B) and proliferated in peripheral blood (C) after treatments.

PD-1/PD-L1 Combination Therapy

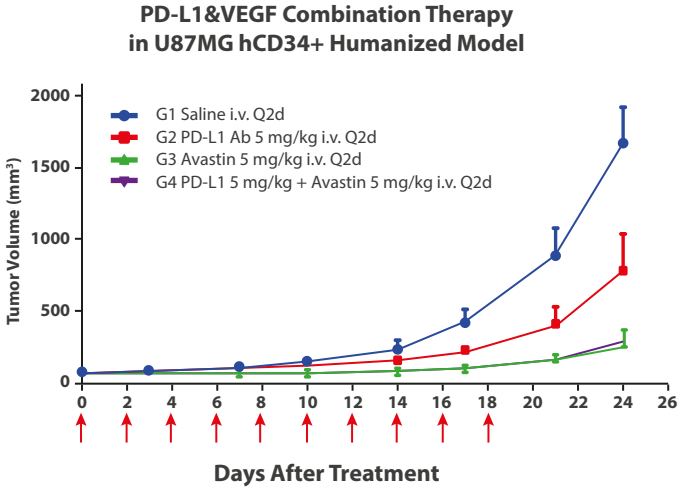
A.

Cell Line Name	HCC827
Species	Human
Cancer Type	Lung adenocarcinoma, NSCLC
Characteristic	PD-L1 high expression; EGFR high expression; VEGF median expression



B.

Cell Line Name	U87-MG
Species	Human
Cancer Type	Glioblastoma
Characteristic	PD-L1 high expression; VEGF high expression



C.

Cell Line Name	HCC1954
Species	Human
Cancer Type	Breast, Ductal carcinoma
Characteristic	PD-L1 high expression; VEGF high expression; EGFR mild expression

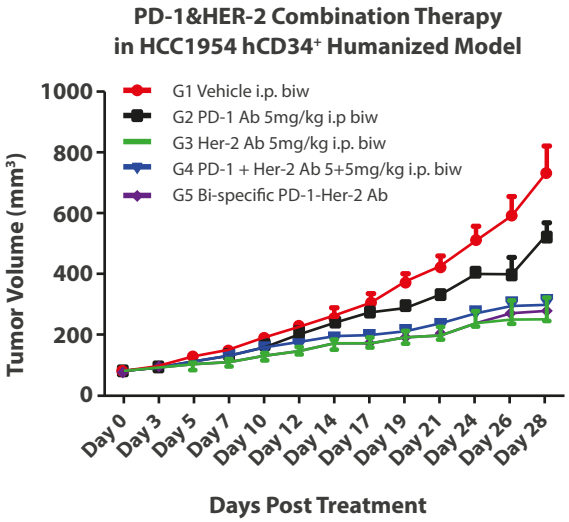
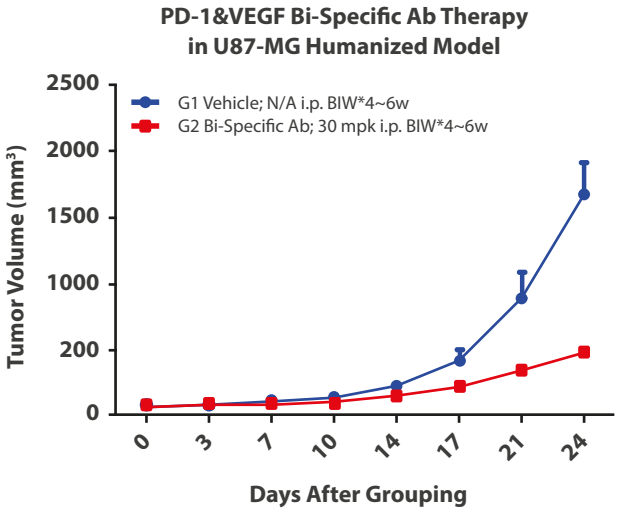


Figure 2. Evaluation of PD-1/PD-L1 combination therapy in HCC827, U87MG and HCC1954 CD34⁺ humanized mouse models. HCC827 (A), U87MG (B) and HCC1954 (C) were inoculated into CD34⁺ humanized mice and treated with either monotherapy (A: EGFR/PD-1 ab; B: PD-L1 ab/Avastin; C: PD-1/Her-2/bi-specific PD-1-Her-2 ab) or combination therapy and compared to vehicle group. Tumor volume represents mean tumor volume ± SEM. Arrow indicates time of dosing.

Bi-specific Ab

A.



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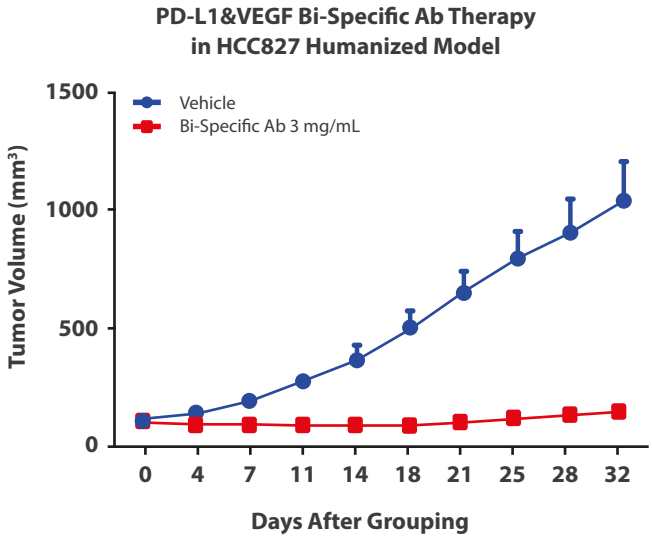
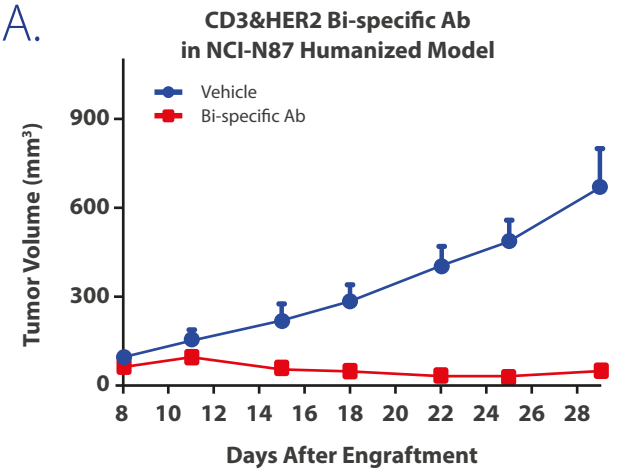


Figure 3. Evaluation of PD-1/PD-L1&VEGF bi-specific ab therapy in U87MG and HCC827 CD34⁺ humanized mouse models.

U87MG (A) and HCC827 (B) were inoculated into CD34⁺ humanized mice and treated with bi-specific ab (A: PD-1&VEGF ab; B: PD-L1&VEGF ab) and compared to vehicle group. Tumor volume represents mean tumor volume ± SEM.

A.



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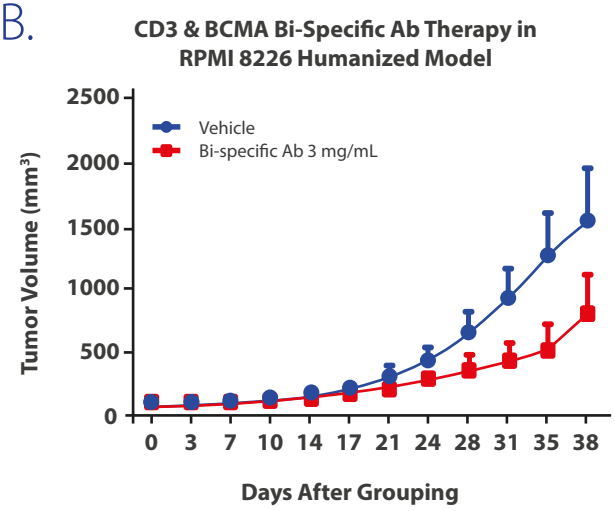


Cell Line	
NCI-N87	Gastric, HER-2 High expression
RPMI 8226	Multiple myeloma, BCMA high expression
Raji	Burkitt's Lymphoma

C.

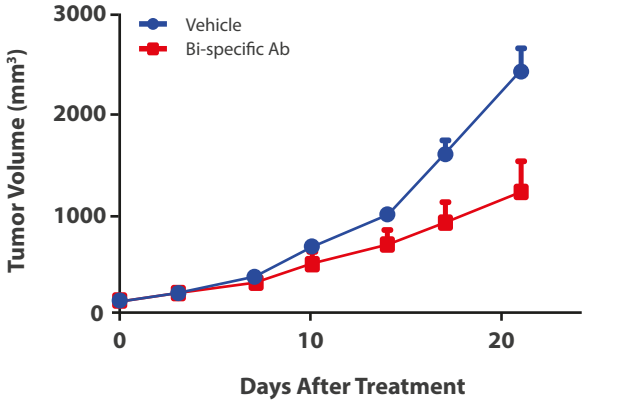
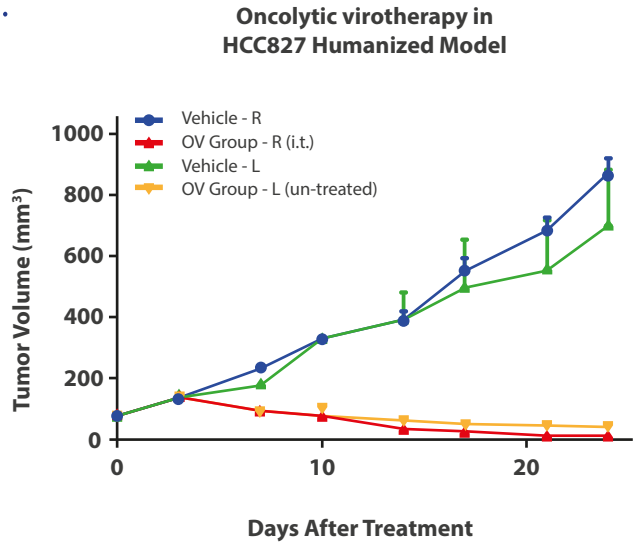


Figure 4. Evaluation of CD3 bi-specific ab therapy in NC1-N87, RPMI8226 and Raji CD34⁺ humanized mouse models.

NC1-N87 (A), RPMI8226 (B) and Raji (C) were inoculated into CD34⁺ humanized mice and treated with bi-specific ab (A: CD3&HER2 ab; B: CD3&BCMA ab; C:CD3&CD20) and compared to vehicle group. Tumor volume represents mean tumor volume ± SEM.

Oncolytic Virotherapy

A.



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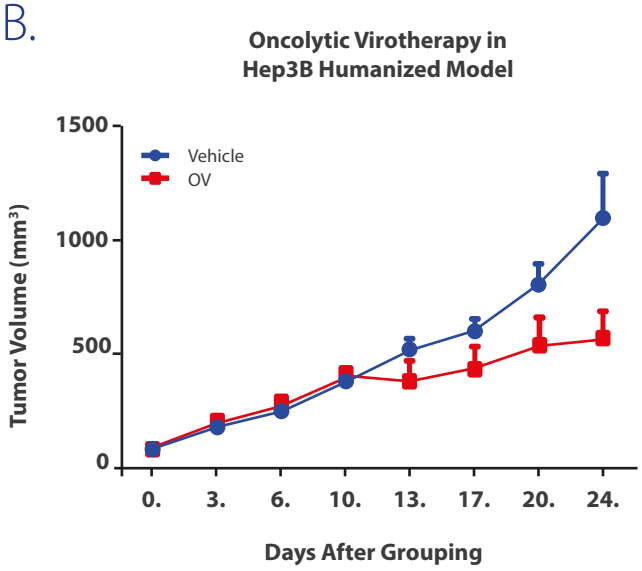

Figure 5. Evaluation of oncolytic virotherapy in HCC827 and Hep3B CD34⁺ humanized mouse models. HCC827 were inoculated into both flanks of CD34⁺ humanized mice, tumor on the right flank was treated with oncolytic virotherapy and left flank was left untreated and compared to vehicle groups (A), Hep3B were inoculated into CD34⁺ humanized mice and treated with oncolytic virotherapy and compared to vehicle group (B). Tumor volume represents mean tumor volume ± SEM.

Cell Lines Validated in the hCD34⁺ Humanized Model

Cell Line	Cancer Type	PD-L1 Expression (MFI)	Growth Curve in huCD34⁺ humanized mice	Efficacy (TGI%)
Hep3B	Liver, HCC	0.58% (1950.9)	Validated	Oncolytic virus (40%)
A549	Lung, NSCLC	10.44% (5918.2)	Validated	PD-1 (14.4%), PD-1+TIM3 (14.1)
HCC827	Lung, NSCLC	97.21% (127814.1)	Validated	PD-1 (46%), PD-L1 (63%), PD-1+EGFR, PD-L1+VEGF (Bi-specific), Oncolytic virus (73%); 4-1BB (25%)
NCI-H1975	Lung, NSCLC	92.51 (53768.4)	Validated	Unknown
MDA-MB-231	Brest, Adenocarcinoma	94.56% (55430.0)	Validated	IFN-γ (54%), PD-1/PD-L1+ INF-γ (ongoing), IFN-γ + radiotherapy (ongoing), TGF-β+PD-1 (ongoing)
JIMT-1	Breast, Ductal carcinoma	TBD	Validated	PD-1 (50%)
HCC1954	Breast, Ductal carcinoma	93.01% (246785.6)	Validated	PD-1 (15.5%), HER2
NCI-N87	Gastric	23.29% (7694.8)	Validated	Bi-specific (CD3+HER2)
MKN-45	Gastric	0.10% (630.9)	Validated	Unknown
Raji	Burkiit`s Lymphoma	TBD	Validated	Bi-specific (CD3+CD19)
A-375	Melanoma	TBD	Validated	/
SK-MEL-5	Melanoma	0.60% (1712.3)	Validated	PD-1 (13%)
RPMI8226	Multiple myeloma	2.43% (5918.1)	Validated	Bi-specific (CD3+; CD3+CD20)
U87MG	Gioma	84.58% (31043.4)	Validated	PD-1 (54%), PD-1+VEGF, PD-1+VEGF (Bi-specific), LAG3
ECA-109	Esophageal squamous carcinoma	14.39% (6531.9)	Validated	Oncolytic virus (ongoing)

Being Correct is Everything

To advance a compound from discovery to clinical, or to halt its development, is a huge and costly decision. For the benefit of you and your company, and for the well-being of patients in need of treatment, that decision needs to be based on correct information.

PharmaLegacy has more capability to provide rich, correct answers to pharmacological questions due to our huge repository of in vivo models, the rich experience of our company and scientists, our intense focus on pharmacology, and our proprietary technological platforms.

There's a lot on the line. Let PharmaLegacy get the correct answers.

Quick Facts:

- Over 300 validated animal models of disease spanning over 40 different diseases
- Scientific staff average over 15 years of pharmacology experience
- FDA Part 11 compliant
- 45,000 ft2 facility with 22,000 ft2 of SPF and conventional vivarium to house 10,000 rodents and large animals
- On-site capacity for up to 350 non-human primates
- Partnerships with three premium non-human primate centers having capacity for 30,000 monkeys (Cynomolgus and Rhesus)
- Capacity to run 200 animal studies concurrently while strictly following AAALAC and ILAC guidelines
- Research data is electronically managed by BioBook (IDBS, UK)
- Web-based live video streaming allows remote monitoring of operations from any location worldwide
- Operations structured for maximum protection of clients' work and intellectual property
- 24/7 access to PharmaLegacy representatives

Expect More from Pharmacology

No animal study can predict with certainty how a therapy will perform in human subjects, yet that is what you need them to do. You need to get as much information from them as possible. Due to study design, the models and technologies available, or lack of proper expertise, most preclinical, in-vivo pharmacological studies are not providing as much information as they could be. These missing insights can derail a pipeline. Missed opportunities are not what you should expect from pharmacology CROs. You should expect more.

Now you can

You can expect more from PharmaLegacy because PharmaLegacy has more: more models, more experience, and more focus. We have over 300 validated animal models, including non-human primate models and many humanized rodent models, spanning over 40 different diseases in the fields of cancer, auto-immunity, inflammation and bone. Our staff has an average of 15 – 20 years of pharmacology experience, and most of them have been with PharmaLegacy for more than 5 years.

When you search for a pharmacology CRO, set your expectations high.
Contact PharmaLegacy and let's discuss how we can exceed them.

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