CROWN BIOSCIENCE

Syngeneic Models

Progress immunotherapeutic development with Crown Bioscience panel of over 30 syngeneic models

A JSR Life Sciences Company

FACTSHEET

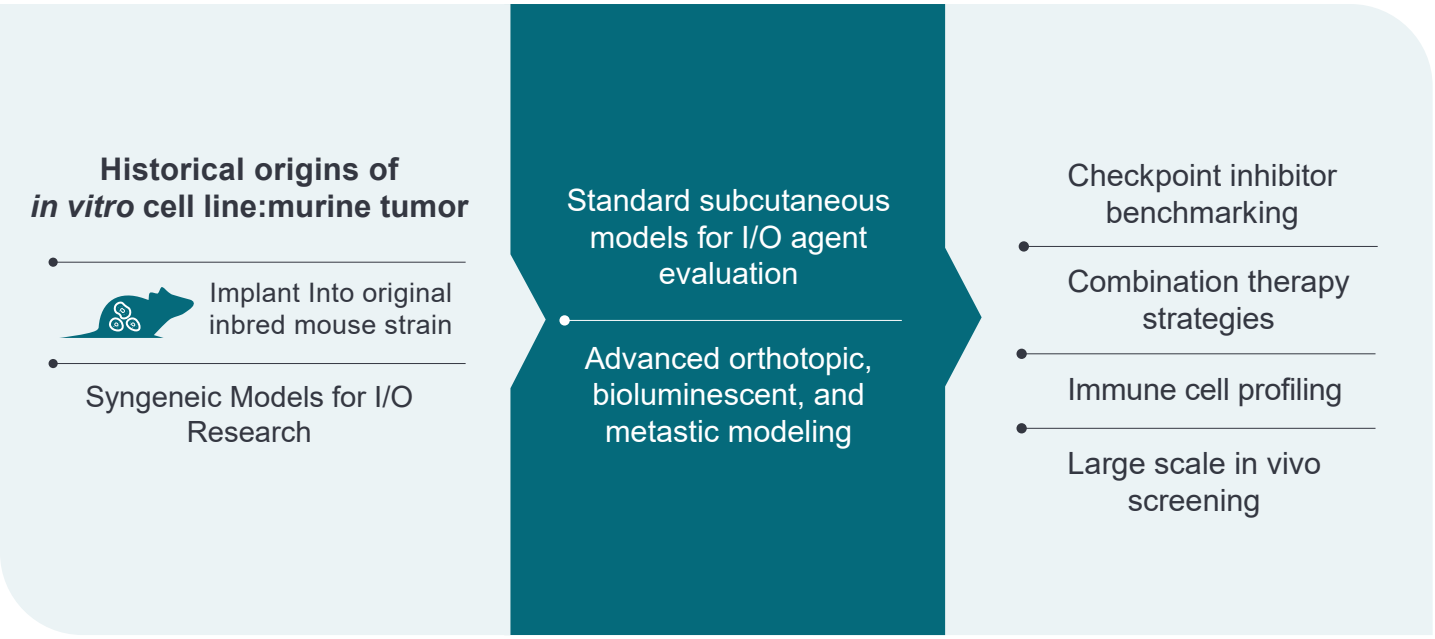
V1.0

Discover the benefits of using our fully characterized and checkpoint inhibitor benchmarked syngeneic models to accelerate your immuno-oncology drug discovery programs.

The development of novel immunotherapeutics presents many challenges, including the need for immunocompetent preclinical models. Syngeneic mouse models are undergoing a resurgence as an accessible platform to evaluate the efficacy and MOA of novel agents and combination strategies.

Crown Bioscience provides an extensive syngeneic platform of over 30 models covering more than 15 cancer types for immunotherapeutic assessment.

- Select the most appropriate models for checkpoint inhibitor novel agent/combination studies using a vast array of benchmarking data (e.g. anti-PD-1, PD-L1, CTLA-4 antibodies) complemented by immunoprofiling and NGS.
- Choose the right model for bacterial, viral, and vaccine immunotherapy research based on baseline immunophenotyping at the subcutaneous or orthotopic site.
- Evaluate efficacy quickly with standard subcutaneous models, alongside disease relevant tumor microenviroment in orthotopic and metastatic sites with bioluminescent imaging.
- Assess immunomodulatory effects through post-treatment immunoprofiling including T cell infiltration.
- Fast track new immuno-oncology agents using the first large-scale *in vivo* syngeneic screening platform.



Syngeneic Models Key Facts

Crown Bioscience provides a well characterized Syngeneic Model Panel:

- Over 30 models covering 15 cancer types, with further models undergoing validation.
- Standard subcutaneous models for efficacy evaluation, complemented by orthotopic models to better recapitulate the tumor microenvironment, and metastatic models allowing targeting of clinically relevant metastatic invasion.
- Bioluminescent metastatic models to monitor in-life disease progression, and primary to end stage disease.
- Full validation data (baseline and post-treatment immunoprofiling, immunotherapy, standard of care, and NGS data) easily searchable through **MuBase®**, Crown Bioscience's online collated immuno-oncology model database.
- Checkpoint inhibitor benchmarking data including anti-PD-1, PD-L1, and CTLA-4 antibodies to select the appropriate models for single agent and combination studies, including combination immunotherapy and immunotherapy + chemotherapy (including inducer of ICD) strategies.
- Validated immunoprofiling including treatment induced T cell infiltration assessment to characterize immunomodulatory effects of novel agents and treatment regimens.
- Microbiome analysis to correlate gut microbiomes across our syngeneic models with response to therapy.
- Crown Bioscience's large-scale, *in vivo* syngeneic screening platform **MuScreen™**, the first screening platform of its type, to fast track immunotherapy compounds.

Syngeneic Model Use in Preclinical Immuno-Oncology Research

Evaluating immunotherapeutic agents brings many challenges, including the need for preclinical models within immunocompetent hosts. Syngeneic mouse models have seen a resurgence in use as a straightforward platform enabling efficacy testing and elucidation of the mechanism of action of new immuno-oncology treatments.

Syngeneic mouse tumors are allografts derived from immortalized mouse cancer cell lines which originate from the same inbred strain of mice. The recipient mice have fully competent mouse immunity and are histocompatible to the allografted tumors. Models have now been extensively profiled genomically and immunologically (both pre- and post-treatment), and for agent efficacy to allow simple and rapid model selection for preclinical studies.

Agents commonly tested using syngeneics include checkpoint inhibitors such as anti-PD-1 and PD-L1 antibodies in proof of concept studies. Syngeneics can also be utilized for evaluating a wide range of other immunotherapeutics, including bacterial, viral, and vaccine therapies, all of which have driven syngeneics to become one of the most commonly utilized immuno-oncology models in preclinical investigations.

Crown Bioscience Provides a Large and Well Profiled Panel of Syngeneic Models

Our large panel of well validated syngeneic models covers over 15 cancer types and more than 30 individual models (summarized in Table 1, availability site by site is covered within our *In Vivo* Cancer Pharmacology Model catalogs available on request). Crown Bioscience are constantly improving and expanding the syngeneic collection, and our pipeline of models currently undergoing validation includes:

- breast C127I model
- chondrogenic ATDC5 model
- colon CMT-93 model
- liver Hepa1c1c7 model
- lung LA-4 model
- kidney RAG model.

Standard Subcutaneous Models to Evaluate Novel Immunotherapies

Crown Bioscience standard syngeneic models shown in Table 1 are fully validated with growth, standard of care (SoC) and/or immunotherapy treatment data available. Complete background information, growth, and treatment data on models are included within **MuBase** our easy to use, proprietary online database. Models can be quickly searched and compared to find those appropriate for indivdual studies.

Models with baseline immune cell profiling data are also highlighted in Table 1. Crown Bioscience research has shown that baseline immune cell populations in untreated syngeneic models (T cells and the T_{eff}/T_{reg} ratio) may predict efficacy of anti-CTLA-4 and anti-PD-L1 antibodies, respectively[1]. Example FACS analysis baseline data are included within Figure 1 for T cells ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+$/FOXP3+) and ratio of $CD8^+$ T_{effect}/T_{reg} cells, with further NK, MDSC, and macrophage data available in **MuBase**.

Syngeneic Models Factsheet

Table 1: Summary of Syngeneic Immunotherapy Models

Cancer Type	Cell Line	Model Type	Anti-PD-1	Anti-PD-L1	Anti-CTLA-4	RNAseq	Immune Cell Profiling
Bladder	MBT-2*	Subcutaneous	X	X	X	X	X
Breast	4T1*	Subcutaneous, orthotopic, metastatic, bioluminescent	X (s.c., ortho)	X (s.c., ortho)	X (s.c., ortho*)	X (s.c., ortho*)	X (ortho) Ongoing (s.c.)
	EMT6*	Subcutaneous, orthotopic, bioluminescent	X (s.c.)	X (s.c.)	X (s.c.)	X (s.c.)	X (s.c.)
	JC	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	X
Colon	Colon26	Subcutaneous	X	X	X	Ongoing	X
	CT-26.WT*	Subcutaneous	X	X	X	X	X
Fibrosarcoma	WEHI-164	Subcutaneous	X	Ongoing	Ongoing	Ongoing	Ongoing
Glioma	GL261	Subcutaneous, orthotopic	Ongoing (s.c., ortho)	Ongoing (s.c., ortho)	Ongoing (s.c., ortho)	X (s.c.) Ongoing (ortho)	Ongoing (s.c., ortho)
Kidney	Renca*	Subcutaneous	X	X	X	X	X
Leukemia	C1498	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	X
	L1210	Subcutaneous	X	X	X	X	X
Liver	H22*	Subcutaneous, orthotopic, bioluminescent	X	X	X	X	X
	Hepa 1-6*	Subcutaneous, orthotopic, bioluminescent	X (s.c.)	X (s.c.)	X (s.c.)	Ongoing (s.c.)	X (s.c.)
Lung	KLN205	Subcutaneous	X	X	X	X	X
	LL/2 (LLC1)*	Subcutaneous, metastatic	X	X	X	X	X
Lymphoma	A20	Subcutaneous	X	X	X	X	X
	E.G7-OVA	Subcutaneous	X	Ongoing	Ongoing	Ongoing	Ongoing
	EL4	Subcutaneous	X	X	X	X	X
	L5178-R (LY-R)	Subcutaneous	X	X	X	Ongoing	X
	P388D1	Subcutaneous	X	X	X	X	X
Mastocytoma	P815*	Subcutaneous	Ongoing	X	Ongoing	Ongoing	Ongoing
Melanoma	B16-BL6	Subcutaneous	X	X	X	X	X
	B16-F0	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
	B16-F1	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
	B16-F10*	Subcutaneous, metastatic, bioluminescent	X	X	X	X	X
	Clone M-3 (Cloudman S91)	Subcutaneous	Ongoing	X	Ongoing	Ongoing	Ongoing
Myeloma	J558	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	X
	MPC-11	Subcutaneous	X	X	X	X	X
	P3X63Ag8U.1	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Neuroblastoma	N1E-115	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
	Neuro-2a	Subcutaneous	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Pancreatic	Pan02*	Subcutaneous, orthotopic, bioluminescent	X (s.c.)	X (s.c.)	X (s.c.)	X (s.c.)	X (s.c.)
Prostate	RM-1*	Subcutaneous	X	X	X	X	X

X = data available; *bioluminescent models established with further validation ongoing.

Table 1 also shows the availability of RNAseq data for our syngeneic models, which has been used to identify biomarkers to predict treatment response. Through generating detailed expression maps and mutational profiles, we have identified alternative gene splicing transcripts and gene fusions within our models. Further mutational analysis has indicated a number of our syngeneic models harbor mutations that may be useful for combination studies of targeted agents and immunotherapy, and we have identified a set of biomarkers that may be useful to predict immunotherapeutic agent response[(2)].
We also provide syngeneic tumor samples for research uses including tumor tissue histology (H&E staining), and frozen and formalin-fixed, paraffin-embedded tumor samples as required.

Advanced Orthotopic and Metastatic Disease Models, and Syngeneic Imaging Modalities

Crown Bioscience also provides advanced syngeneic modeling options (model availability detailed in Table 1):

- orthotopic models to more closely recapitulate the tumor situation and microenvironment
- clinically relevant metastatic models of disease
- bioluminescent metastatic models to study clinically relevant metastatic invasion, metastatic lesions in secondary organs, and the evaluation of agents to target this metastasis.

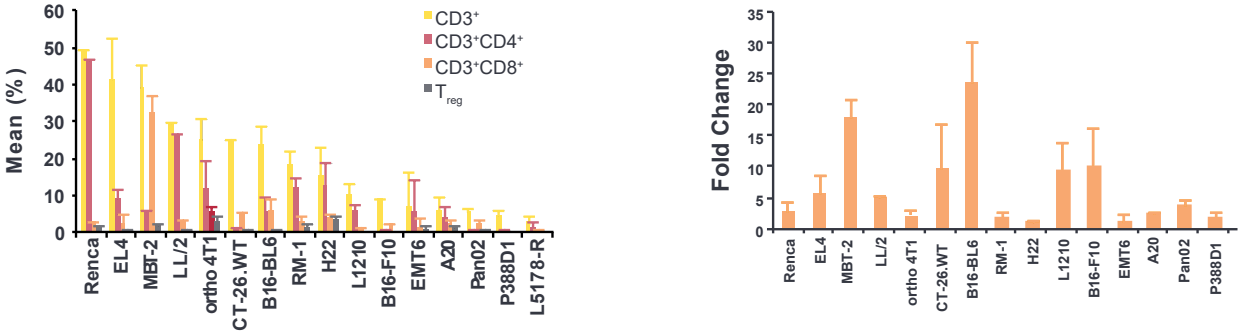
For more information on these models and our pipeline of developing bioluminescent syngeneics please request our Optical Imaging FactSheet.

Examine a Vast Array of Checkpoint Inhibitor Benchmarking Data including Anti-PD1, PD-L1, and CTLA-4 Agents

As checkpoint inhibitors continue to be approved for a variety of cancer types, preclinical evaluation via syngeneic models can be used to identify their potential indications and combination therapy strategies.
Crown Bioscience has extensively profiled our syngeneic panel *in vivo* response to a variety of checkpoint inhibitors, providing clients with the information necessary to select models and the correct doses for combination therapy (available data shown in Table 1). Waterfall plots for our models tested with anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies are shown in Figure 2 through Figure 4**.**

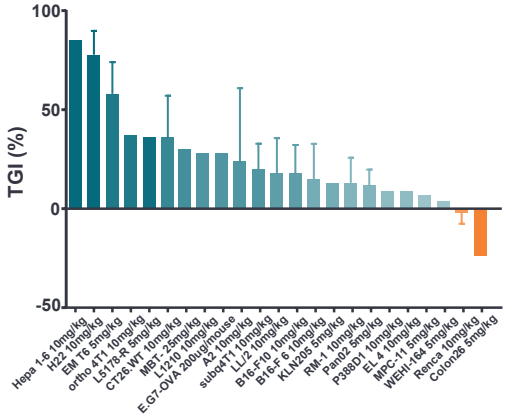
Individual control and treated spider plots are available for each model on request, to evaluate model response variability, example data for the liver syngeneic Hepa 1-6 model is included in Figure 5.

Figure 1: Basal Level of Immune Cells in Syngeneic Tumors



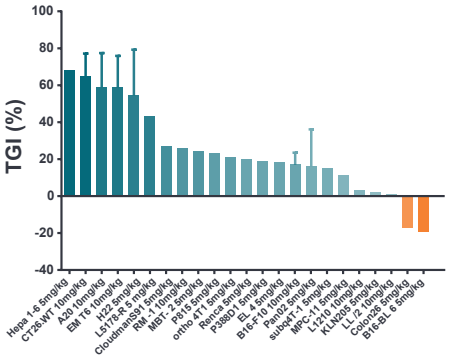
A: T cell mean % of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/FOXP3^+$ in TIL. B: Ratio of $CD8^+$ T_{effect} cells to T_{reg} cells in total cell. Data generated at Crown Bioscience Taicang site.

Figure 2: Anti-PD-1 Antibody Efficacy Benchmarking in Syngeneic Models



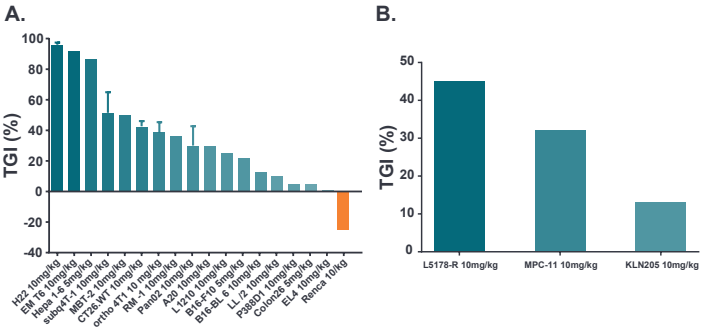
Antibody: RMP1-14. All data mean + SD. Data generated at Crown Bioscience Beijing and Taicang sites.

Figure 3: Anti-PD-L1 Antibody Efficacy Benchmarking in Syngeneic Models



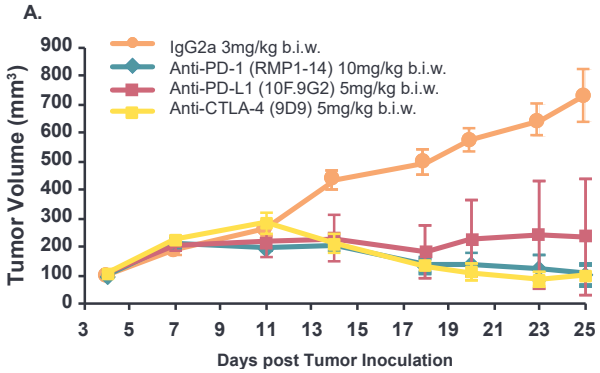
Antibody: 10F.9G2. All data mean + SD. Data generated at Crown Bioscience Beijing and Taicang sites.

Figure 4: Anti-CTLA-4 Antibody Efficacy Benchmarking in Syngeneic Models

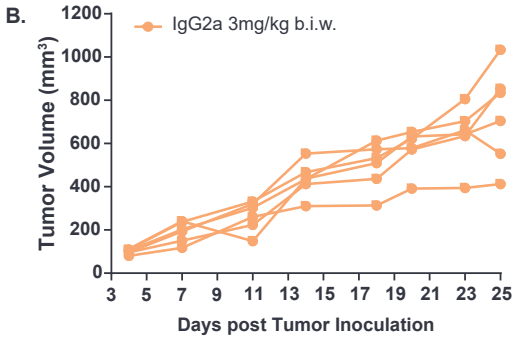


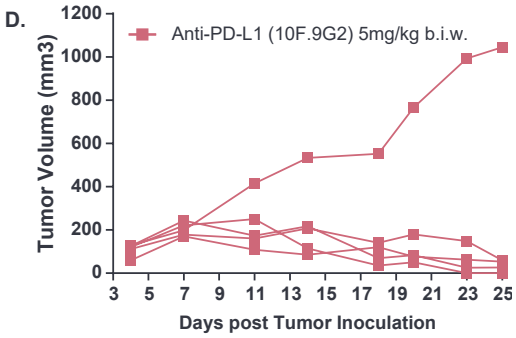
A: 9D9, data mean + SD; B: 9H10. Data generated at Crown Bioscience Beijing and Taicang sites.

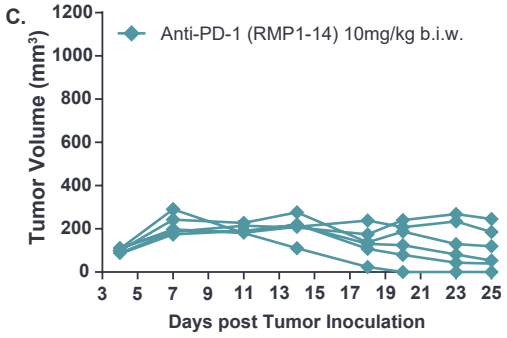
Figure 5: Variability of Hepa 1-6 Response: Control and Treatment Spider Plots

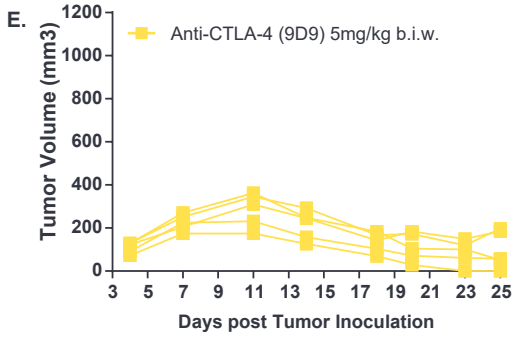


Treatment	T/C (%)	TGI (%)	p Value
Anti-PD-1 (RMP1-14)	15	85	<0.001
Anti-PD-L1 (10F.9G2)	32	68	0.042
Anti-CTLA-4 (9D9)	13	87	<0.001









A: Mean tumor volume ± SEM. B-E: Individual reponse following treatment with IgG2a or checkpoint inhibitor shown. Statistical analysis on Day 25 post inoculation. Data generated at Crown Bioscience Taicang site.

Evaluate Combination Checkpoint Inhibitor and Chemotherapy Regimens

As researchers discover that chemotherapy, radiotherapy, and targeted therapies may interact or change the tumor immune environment, suitable models are required to evaluate combinations of these agents with immunotherapy.

Crown Bioscience is utilizing our syngeneic panel to investigate combination therapy strategies. Example data treating the H22 liver cancer syngeneic model with a combination of doxorubicin and anti-PD-L1 antibody showed that combined treatment had a greater effect than either treatment alone (Figure 6).

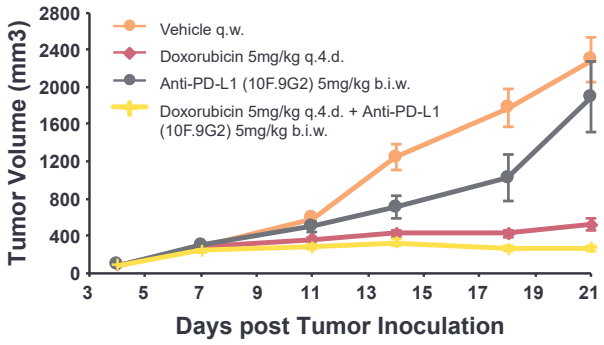
A range of checkpoint inhibitors have been trialed in combination with cyclophosphamide on the A20 B lymphoma model (Figure 7). Response to combination therapy varied, with the greatest tumor growth inhibition observed for cyclophosphamide combined with anti-GITR antibody.

Combining Inducers of Immunogenic Cell Deacth (ICD) with Immunotherapy

A number of anticancer treatment strategies such as chemotherapeutic agents (e.g. oxaliplatin, doxorubicin, bortezomib, and mitoxantrone), radiotherapy, and oncolytic viruses have been highlighted as potential inducers of ICD. These treatments are known to increase the presentation of cell-associated antigens to $CD4^+$ and $CD8^+$ T lymphocytes by dendritic cells.

Combination strategies of ICDs with immunotherapies could therefore provide opportunities to harness the immune system to extend survival, even among metastatic and heavily pretreated cancer patients, and may increase the efficacy of immunotherapy in cancer types with low immunogenic status.

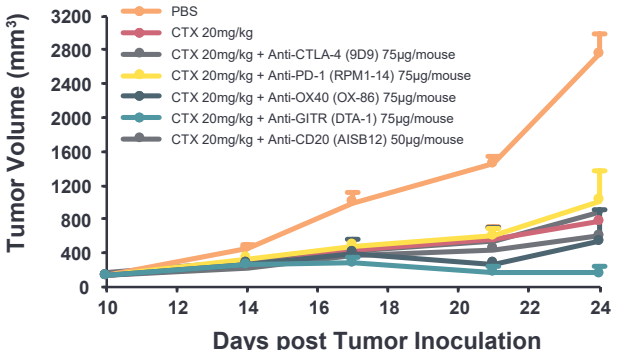
Figure 6: Combination Doxorubicin and Anti-PD-L1 Antibody Induces TGI of H22 Model Greater than Either Agent Alone



Data generated at Crown Bioscience Taicang site.

Treatment	Tumor Volume (mm3)	T/C Value (%) on Day 24	p Value
Vehicle	2291 ± 231	--	--
Anti-PD-L1 (10F.9G2)	519 ± 65	23	<0.001
Anti-CTLA-4 (9D9)	1436 ± 383	63	0.072
Anti-PD-L1 (10F.9G2)	268 ± 28	12	<0.001

Figure 7: Cyclophosphamide and Checkpoint Inhibitor Combined Treatment of A20 Model Elicits a Range of Responses



Data generated at Crown Bioscience Taicang site.

Treatment	Tumor Volume (mm3)	T/C Value (%) on Day 24	p Value
PBS	2752 ± 240	--	--
Cyclophosphamide (CTX)	776 ± 238	28	<0.001
CTX + Anti-CTLA-4 (9D9)	601 ±154	22	<0.001
CTX + Anti-PD1 (RMP1-14)	1016 ± 363	37	0.004
CTX + Anti-OX40 (OX-86)	538 ± 348	20	0.001
CTX + Anti-GITR (DTA-1)	151 ± 91	5	<0.001
CTX + Anti-CD20 (AISB12)	895 ± 110	33	<0.001

Crown Bioscience has combined the ICD oxaliplatin with anti-CTLA-4 in treating the CT26 colon cancer syngeneic model. Combination of anti-CTLA-4 immunotherapy with oxaliplatin resulted in an additive tumor growth inhibition (Figure 8), and also induced a statistically significant increase in $CD8^+$ TILs compared with oxaliplatin or anti-CTLA 4 antibody alone ($p<0.05$, Figure 9)[3]. These results effectively demonstrate the applicability for further exploring combination ICD inducer strategies
involving immunotherapy.

Microbiome Analysis of Responder vs Non-Responder Animals

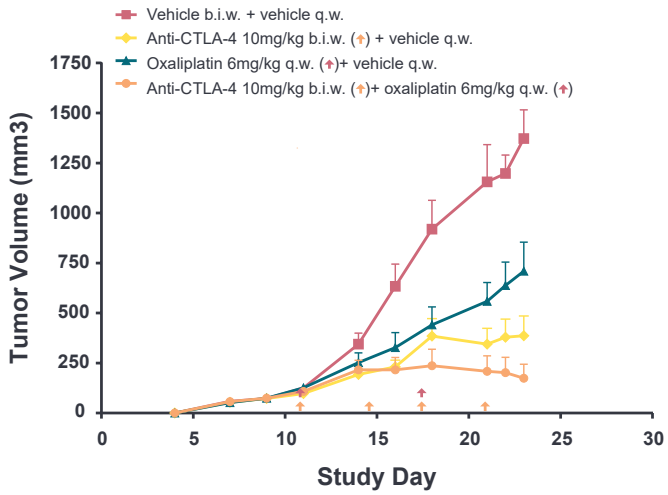
Microbiota play an important role in determining an organism's response to anticancer treatment, even in tumors far from the gastrointestinal tract, possibly because of their pro-inflammatory properties which activate the immune system.

In order to gain insights into the complex interaction between the microbiome and cancer therapy, Crown Bioscience performs fecal collection and microbiome profiling (16S rRNA sequencing) to compare gut microbiomes across our syngeneic models, which we can correlate with response to therapy.

Example data is shown in Figure 10 for animals implanted with either CT-26 or 4T1 models, and treated with anti-PD-1 antibody or isotype control. Efficacy studies revealed varying response across different tumor models and within tumor models. Gut microbiome sequencing was performed post dosing and showed that:

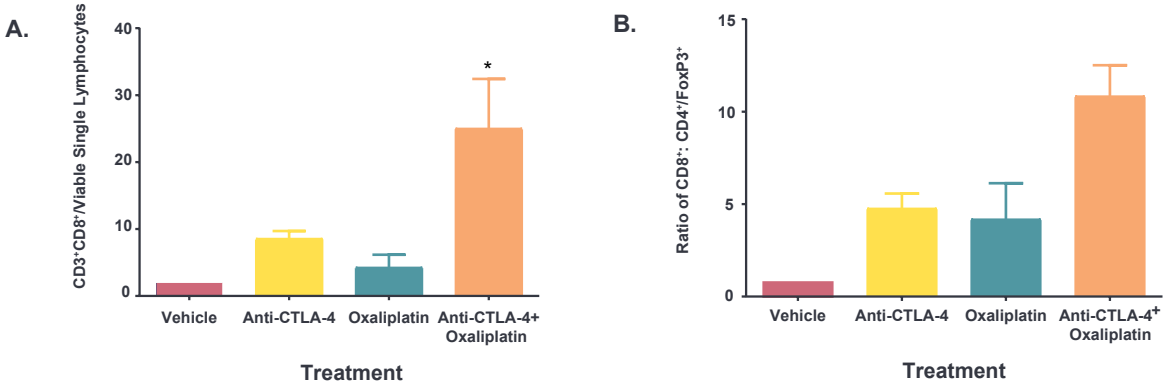
- the gut microbiome of animals that were responsive to anti-PD-1 treatment differed from animals that were treated with isotype control
- the gut microbiome of animals that were unresponsive to anti-PD-1 treatment clustered closely with animals that were treated with isotype control (Figure 10)[4].

Figure 8: ICD Oxaliplatin and Anti-CTLA-4 Combination Results in Additive TGI



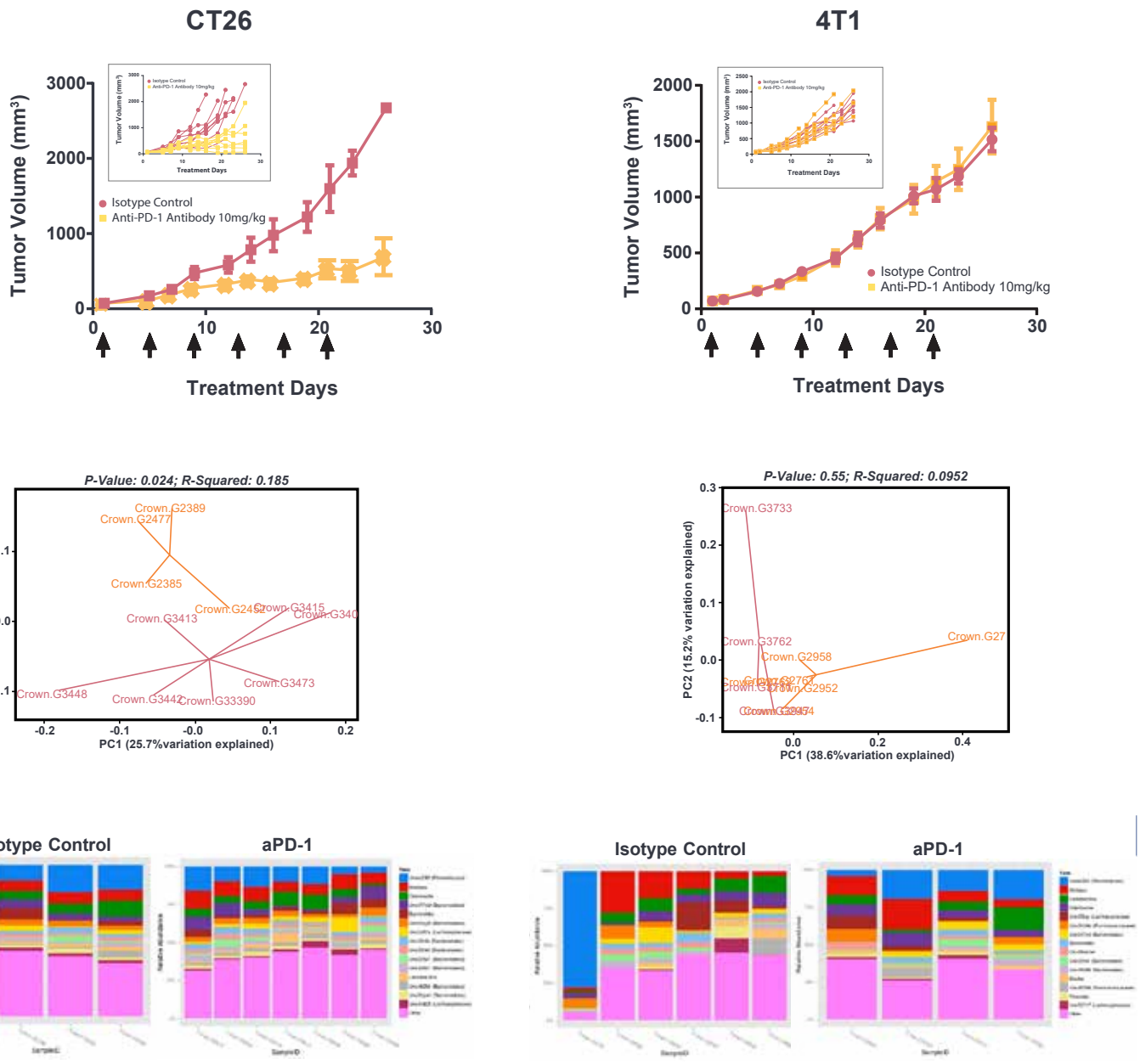
TGI reduction: Anti-CTLA-4 vs vehicle $p<0.05$. Oxaliplatin vs vehicle $p<0.01$. Combination therapy is additive over single agent therapy alone. Data generated at Crown Bioscience UK.

Figure 9: ICD Oxaliplatin and Anti-CTLA-4 Combination Results in $CD8^+$ TIL Increase



Treatment dosing and regimens as per Figure 8. A: % $CD3^+/CD8^+$ T cells, *$p<0.05$ vs single agent anti-CTLA-4 and oxaliplatin. B: Ratio T_{eff}:T_{reg}. Data generated at Crown Bioscience UK.

Figure 10: Gut Microbiome Variation between Responder vs Non-Responder Animals



Efficacy studies: n=8; mean ± SEM. Gut microbiome examined by r16S sequencing of fecal samples collected post last dose of aPD-1 or isotype control. In-between sample difference analyzed using pairwise comparisons of beta-diversity by unweighted uniFrac metric as displayed by Principal Component Analysis. Taxa abundance at the genus level is represented in stacked columns. Data generated at Crown Bioscience San Diego.

Assess Immunotherapy Induced T Cell Infiltration and Immunomodulatory Effects

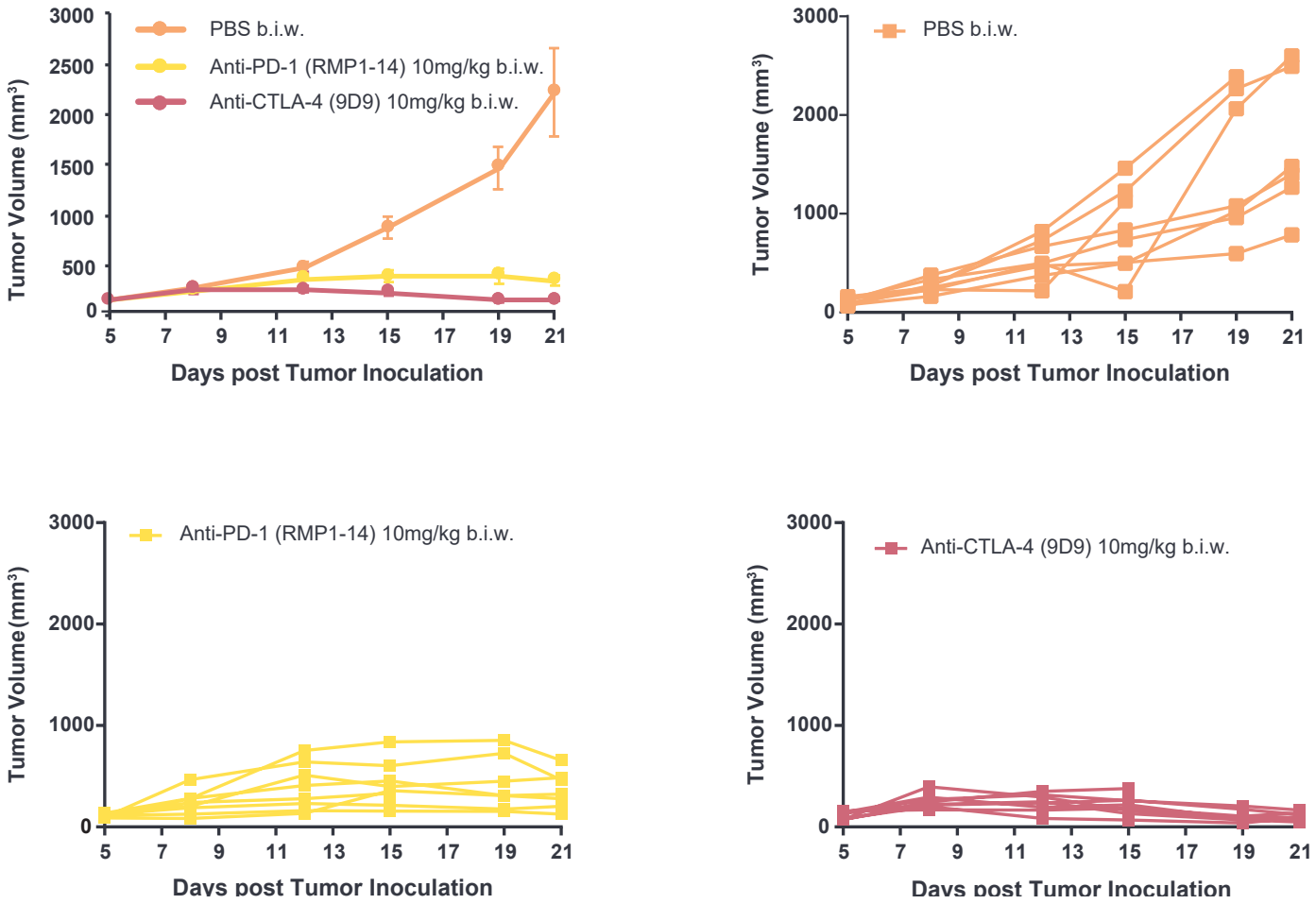
Following checkpoint inhibitor or immunotherapy evaluation, Crown Bioscience can perform immune cell profiling to evalute induced T cell infiltration and immuno-modulatory effects. Our techniques include FACS and IHC immunophenotyping, which have been validated with a range of our syngeneic models following checkpoint inhibitor treatment:

- FACS immunophenotyping: MBT-2, 4T1, EMT6, CT-26.WT, L1210, H22 ,B16-F10, and Pan02 models
- IHC immunophenotyping: A20

Example FACS immunophenotyping data for the H22 liver model, and IHC immunophenotyping for the A20 lymphoma model are detailed below.

The H22 model was treated with anti-PD-1 and anti-CTLA-4 antibodies, with response to treatment correlating with an increase in selected tumor infiltrating lymphocytes (TIL) (Figure 11 and Figure 12). T cell infiltration into A20 tumors was analyzed via IHC and immunofluorescence (Figure 13).

Figure 11: H22 Liver Syngeneic Model Responds to Checkpoint Inhibitors: Mean and Individual Response

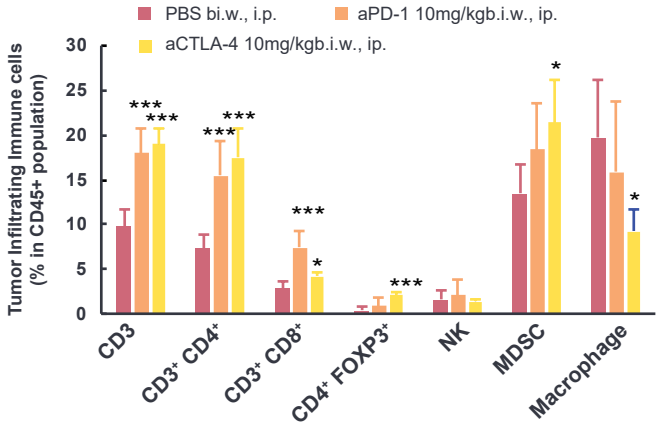


T/C values on Day 21: anti-PD-1 (RMP1-14) 16% (p=0.020); anti-CTLA-4 (9D9) 5% (p=0.012). B, C, D: Individual responses to PBS control, anti-PD-1, and anti-CTLA-4, respectively. Data generated at Crown Bioscience Taicang site.

Standard of Care and Experimental Treatment Data also Available

A range of SoC agents, experimental treatments, and combination chemotherapies have been trialed with our syngeneic models (results shown in Table 2).

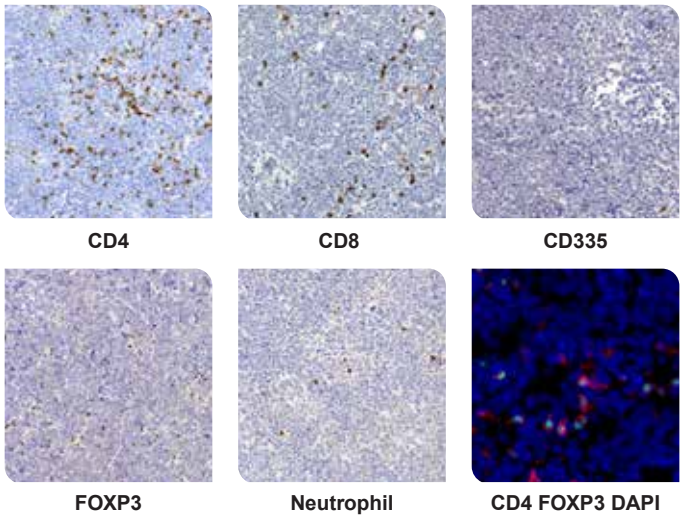
Figure 12: H22 Liver Syngeneic Model: Response to Checkpoint Abs Correlates with an Increase in Selected TILs



FACS result on Day 21: 2 days post the 5th dose. Data generated at Crown Bioscience Taicang site. *p<0.05, **p<0.01, ***p<0.001.

p Value vs Control	CD45+	CD3+	CD3+ CD4+	CD3+ CD8+	CD4+ FOXP3+	NK	MDSC	Macro-phage
Anti-PD-1 10mg/kg	0.082	<0.001	<0.001	<0.001	0.145	0.506	0.056	0.343
Anti-CTLA-4 10mg/kg	0.179	<0.001	<0.001	0.046	<0.001	0.758	0.017	0.028-

Figure 13: A20 Tumor T-Cell Infiltration



IHC (images 20x) of CD4, CD8, CD335, FOXP3, and neutrophils (Ly6G/C) was used to label helper T-cells, cytotoxic T cells, NK, T_{reg}, and neutrophil cells. All IHC assays were run with BondRX Autostainer (Leica) and stained on 4µm FFPE sections of A20 without treatment. IF (image 40x) of CD4 (red) and FOXP3 (green) was stained on frozen sections of the A20 model to label T_{reg} cells (run on Bond RX). DAPI (blue) is used to label the nucleus.

Table 2: Syngeneic Model Standard of Care and Experimental Treatment Data

Cancer Type	Syngeneic Model	Treatment	T/C (%)	p Value
Breast	4T1	Paclitaxel	Day 27: 75	0.042
Colon	CT-26	VEGF-TRAP	Day 15: 50	0.007
		Cisplatin	Day 20: 52	0.002
		Oxaliplatin	Day 23: 50	<0.01
Liver	H22	Doxorubicin	Day 21: 23	<0.001
		Sorafenib	Day 28: 52	0.047
Lymphoma	A20	Cyclophosphamide	Day 20: 6.4	<0.001
Melanoma	B16-BL6	Cisplatin	Day 35: 43	0.016
Melanoma	B16-F10	Cisplatin	Day 28: 30	0.006
Pancreatic	Pan02	Gemcitabine	Day 21: 58	<0.001
		Gemcitabine + cisplatin	Day 21: 40	<0.001
		Gemcitabine + paclitaxel	Day 45: 33	<0.001

Day: days post-tumor inoculation.

Fast-Track the *In Vivo* Screening of Immunotherapy Compounds

For immunotherapeutic agents, *in vitro* screening is not the optimum approach for evaluating PD effect and/or efficacy across multiple cancer types. However, as an alternative, large-scale, parallel, *in vivo* screening of syngeneic models can provide a cost effective approach.

Crown Bioscience are therefore utilizing our syngeneic platform to offer a unique large scale **MuScreen** to fast track immunotherapy treatment strategies, the first platform of its type. **MuScreen** can be used for both single agent and combination studies, reducing variability and improving screening efficiency. We provide a syngeneic efficacy screening panel and tumor microarrays to fit your research needs. For further information please consult the **MuScreen** FactSheet available from the Crown Bioscience website: **www.crownbio.com/publications/factsheets/.**

Conclusions

Immunotherapy research and agents such as anti-PD-1 antibodies are showing considerable success in oncology; providing both patient benefits and commercial success for the pharmaceutical industry. However, progress in the field is hindered through a lack of experimental immunotherapy models featuring a fully competent immune system.

Syngeneic models (allografts derived from immortalized mouse cancer cell lines, which originated from the same inbred strain of mice) are a simple way to evaluate novel immunotherapy treatments through eliciting an immune response, in fully immunocompetent mice.

Crown Bioscience has validated a large panel of syngeneic models, covering a variety of cancer types, with a commitment to further extend this model selection. Alongside subcutaneous models, bioluminescent imaging of orthotopic and metastatic tumous allows more clinically relevant stromal interactions to be modeled and investigated.

Full characterization including immunoprofiling, NGS, and checkpoint inhibitor benchmarking allows rapid selection of appropriate models for client studies. Immunomodulatory effects of novel agents can be evaluated through assessment of immunotherapy induced T cell infiltration, validated for a range of models. Our models are also available for a wide variety of agent assessment from checkpoint inhibitors to other immnunotherapeutics including bacterial, viral, and vaccination research.

As immunotherapies are combined with chemotherapy and targeted agents, in an effort to extend patient survival, Crown Bioscience is also utilizing its wide ranging Syngeneic Panel to interrogate different combinations including with inducers of ICD and can offer a large scale **MuScreen** to fast-track strategies.

References

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