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Anti-ART1 Monoclonal Antibody for Improved Anticancer Immunotherapy

Lead Inventors:

Brendon M. Stiles, M.D.

Professor and Chief of Thoracic Surgery & Surgical Oncology, Albert Einstein College of Medicine

Former Associate Professor of Cardiothoracic Surgery, Weill Cornell Medical College

Timothy E. McGraw, Ph.D.

Professor of Biochemistry in Cardiothoracic Surgery, Cardiothoracic Surgery, Weill Cornell Medical College

Professor of Biochemistry, Biochemistry, Weill Cornell Medical College

Business Development Contact:

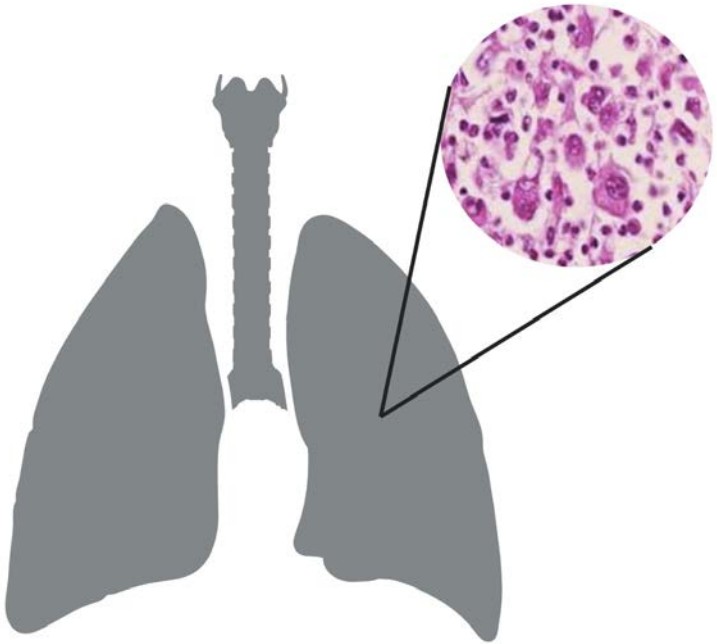
Brian Kelly

Director, Technology Licensing

(646) 962-7041

bjk44@cornell.edu

ICIs are the gold standard for NSCLC and other solid tumors, but few patients achieve a durable response



Background & Unmet Need

- In the KEYNOTE-189 trial, treatment-naïve NSCLC patients who received pembrolizumab (anti-PD-1) in addition to standard chemotherapy achieved a 48% objective response, compared to 19% in patients receiving chemotherapy alone
- However, only 0.5% of patients in the KEYNOTE-189 trial achieved a complete response, with only 34% of pembrolizumab-treated patients alive and progression-free at 12 months
- **Unmet Need:** While ICIs have improved outcomes for NSCLC, there remains a persistent unmet need for additional therapies that synergize with ICIs to prolong survival and deliver a durable response

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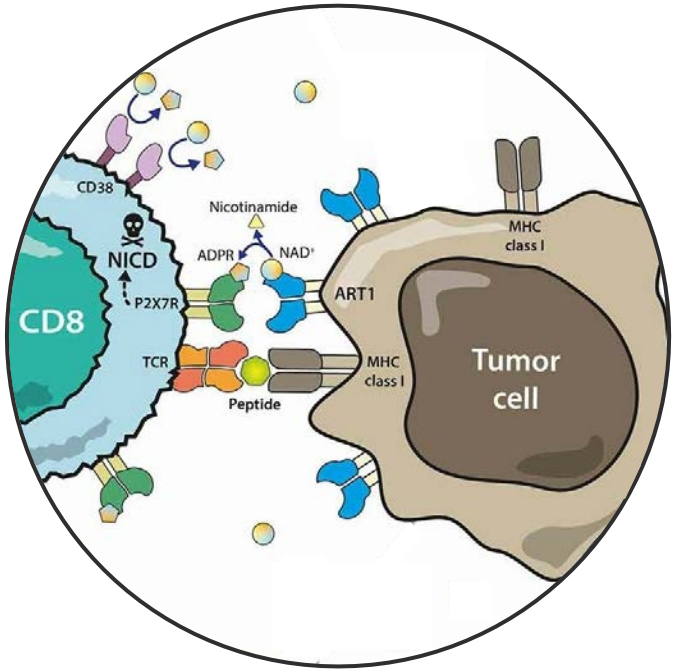
NSCLC: Non-small cell lung cancer. ICI: immune checkpoint inhibitor. Ghandi et al., *NEJM,* 2018.

ART1 is an extracellular enzyme that modifies the ion channel P2X7R, causing constitutive opening and apoptosis



Adenosine 5-diphosphate (ADP)-ribosyltransferase-1 (ART1) is an enzyme with extracellular activity which catalyzes the transfer of ADP-ribose onto proteins in the local environment

A well-known target of ART1 is the P2X7 receptor (P2X7R), an ATP-gated ion channel which is essential for inflammatory responses, anti-tumor immunity, and immune memory

In the tumor microenvironment, cytosolic nicotinamide adenine dinucleotide (NAD^+) is released extracellularly during cell stress, where it can be used by ART1 to catalyze the ribosylation of P2X7R

Mono-ADP-ribosylation of P2X7R results in constitutive activation, causing uncontrolled Ca^{2+} release and eventual apoptosis in a process termed NAD-induced cell death (NICD)

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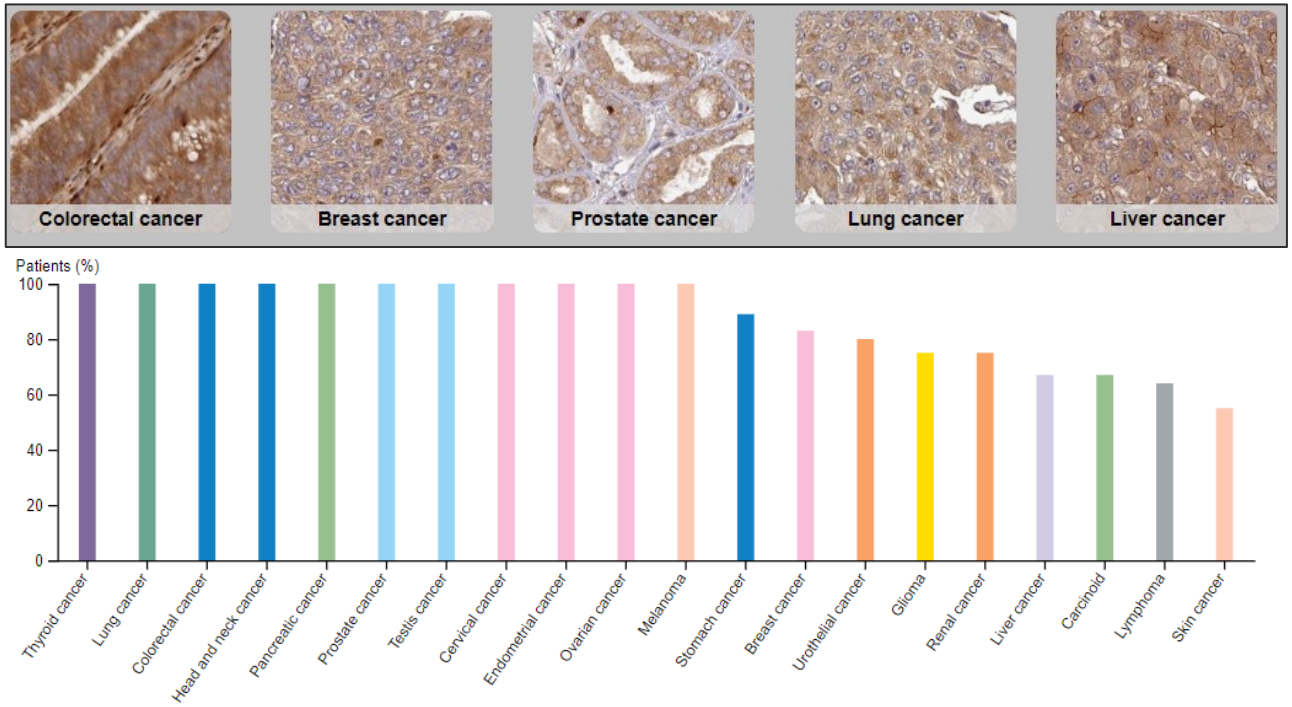
Figure adapted from Wennerberg et al. *Oncoimmunology*. 2022.

High ART1 expression is observed across numerous cancer types



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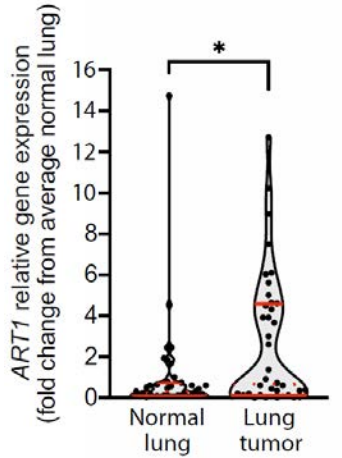
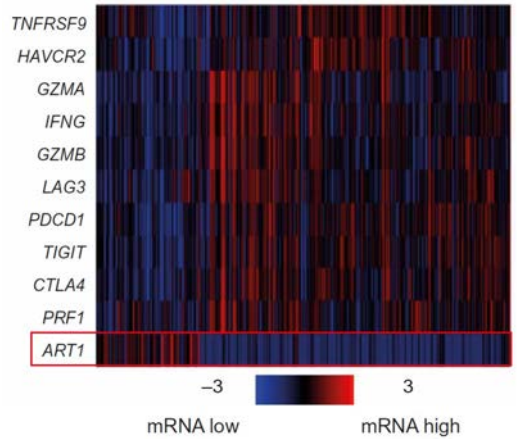
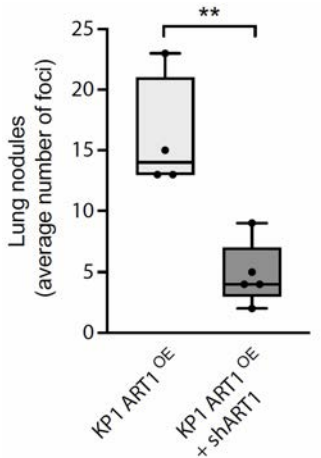
The Human Protein Atlas.
Plot shows % of patients who displayed medium to high ART1 expression.

ART1 expression is associated with a reduction in CD8+ T cells and poor prognosis

Increased ART1 Expression	Reduction in CD8+ T Cells	Poor Prognosis
		
Lung tissue from 40 patients with stage I-III NSCLC showed an increase in ART1 expression	ART1 expression in NSCLC is negatively correlated with the expression of CD8+ T cell genes	ART1 overexpression is associated with increased tumor burden in an orthotopic lung tumor model

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NSCLC: Non-Small Cell Lung Cancer. CRC: Colorectal Cancer. GBM: Glioblastoma.

[1] Wennerberg et al., *Sci Trans Med.*, 2022.

22C12 is a highly potent and specific anti-ART1 monoclonal antibody developed in collaboration with the Tri-I TDI

Development Process

Immunization
AlivaMab Mice

Binding to human ART1
ELISA (Protein)

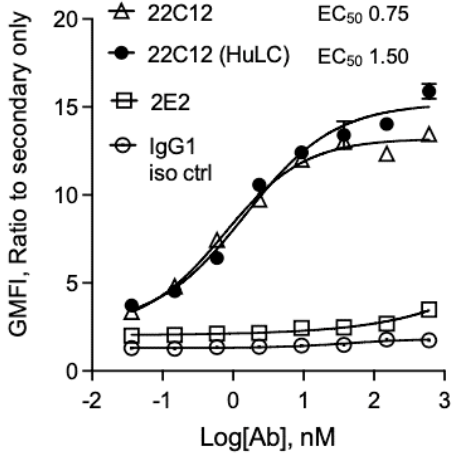
Freeze Hybridoma

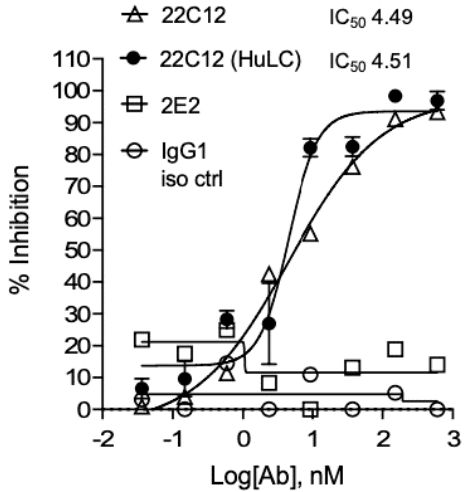
Enzymatic Assays

Mouse Crossreactivity

Animal PoC in Mice

Validation of Binding Affinity (R), ART1 Inhibition (L)





The fully humanized antibody, 22C12[1] (HuLC), has equivalent binding affinity to the murine antibody used for initial studies

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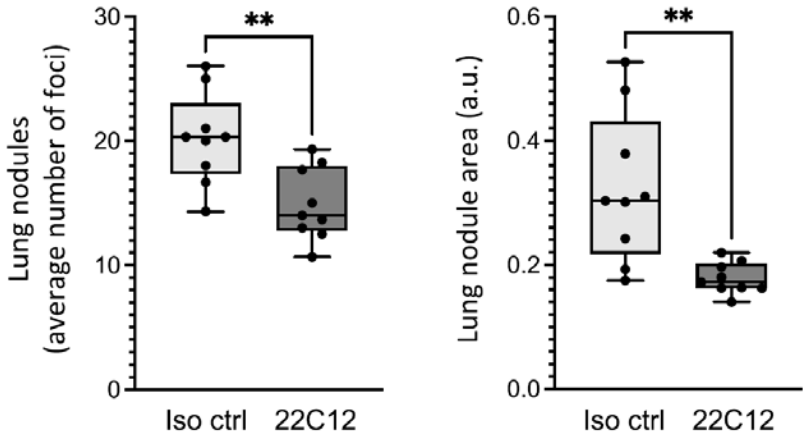
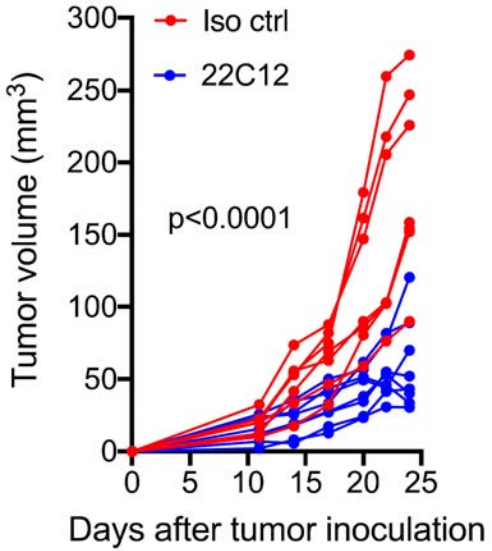
HuLC: Humanized light chain. [1] 22C12 was found to have a fully human heavy chain variable region, but a murine light chain. Engineering of the light chain generated a fully humanized antibody.
Tri-I TDI: Tri-Institutional Therapeutics Discovery Institute.

Blockade of ART1 with 22C12 reduces tumor burden in the LLC1 orthotopic lung tumor model

↓ Number and Area of Tumor Nodules



↓ Tumor Volume



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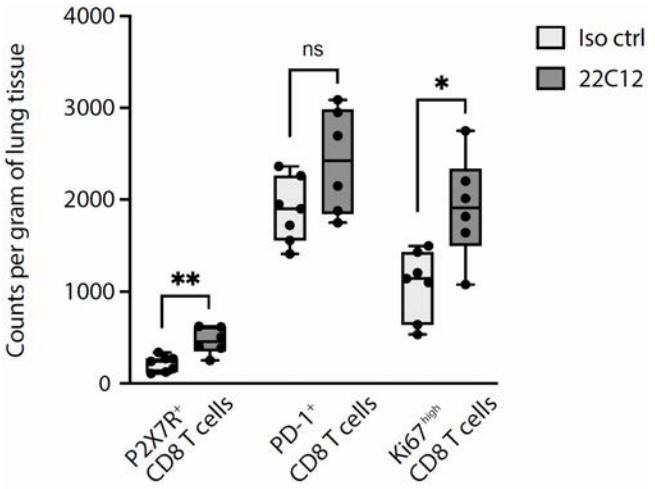
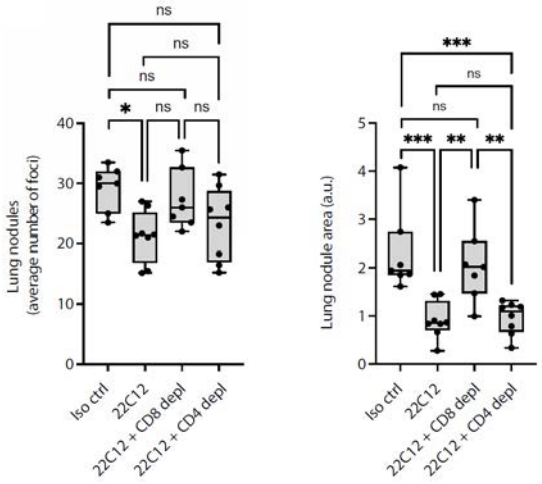
LLC1: Lewis Lung Carcinoma cell line.
Wennerberg et al., *Sci Trans Med.*, 2022.

ART1 inhibition by 22C12 reduces tumor burden by increasing tumor infiltration of CD8+ T cells

↑ Lung CD8+ T Cell Infiltration



ART1i Treatment Effect Requires CD8+ T Cells



Mechanistic data suggests that 22C12 may be an ideal combination partner for ICIs (e.g., PD-(L)1, CTLA4)

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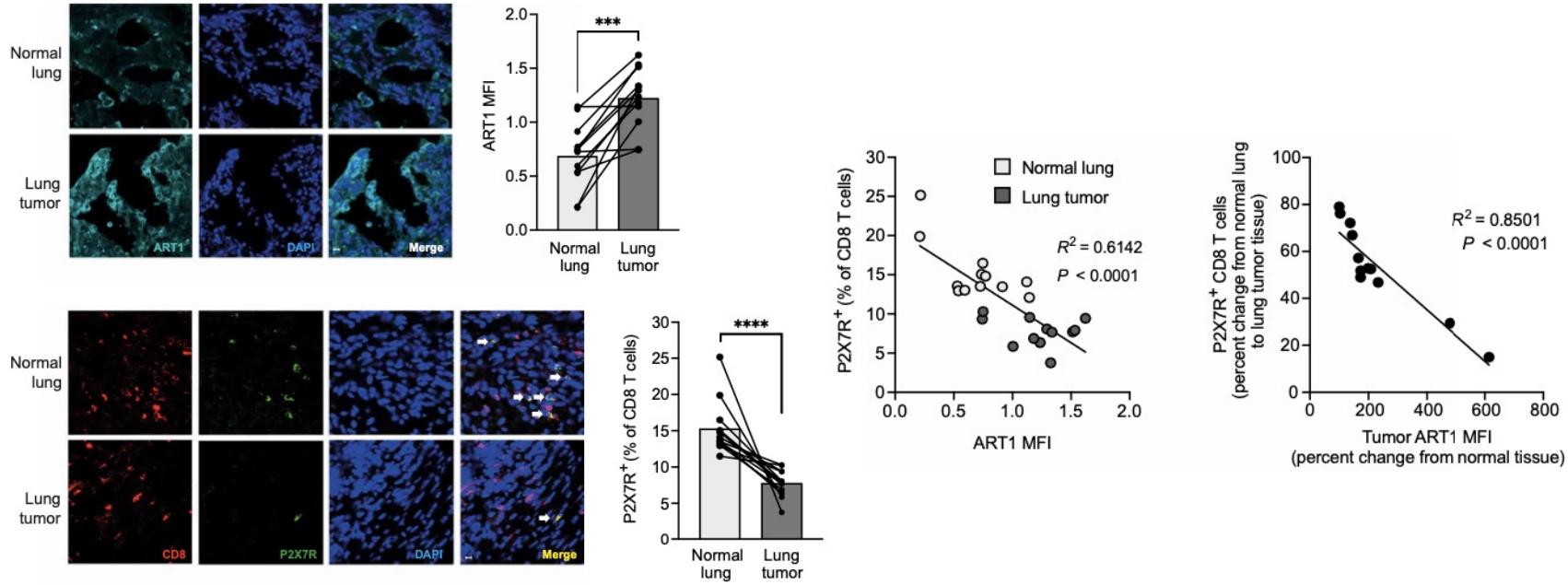
ICI: Immune Checkpoint Inhibitor. Wennerberg et al., *Sci Trans Med.,* 2022.

ART1 overexpression in human lung tumors correlates with lower frequencies of P2X7R$^+$ CD8$^+$ T cells



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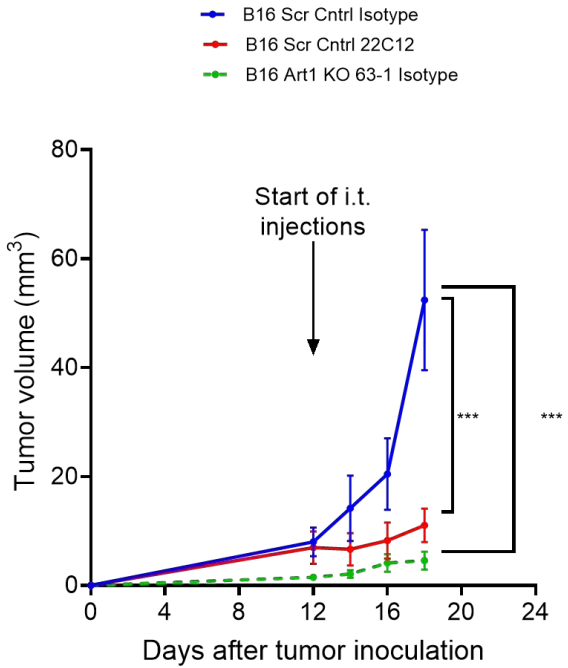
Wennerberg et al., *Sci Trans Med.*, 2022.

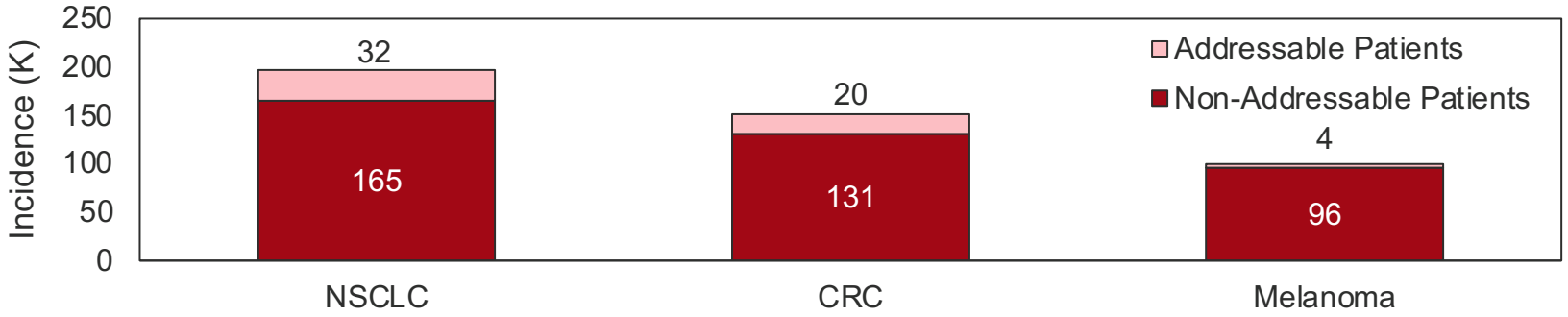
22C12 demonstrated further anti-tumor effects in a mouse model of melanoma



- In addition to NSCLC, human melanomas are shown to strongly express ART1 in the Human Protein Atlas
- Administration of mAb 22C12 **significantly reduced** the growth of subcutaneous B16 flank tumors (****P ≤ 0.0001) compared to isotype controls, similar to that seen with ART1 knock-out
- Additional cancers with high ART1 expression include **colorectal cancer and glioblastoma**, suggesting the possibility of a multiple indication anti-ART1 drug franchise

Utilization of an ART1 mAb in PD-(L)1-refractory patients may represent a ~56 K addressable patient population

Epidemiology: Incidence of Advanced Cancer per Year (K)



Indication	2022 Overall Incidence[1]	Advanced Stage Rate[2]	PD-(L)1 Treatment Rate[3]	Treatment Resistance Rate[4]	Incident Addressable Patients
Non-Small Cell Lung Cancer	~197 K	~70%	~44%	~52%	**~32 K**
Colorectal Cancer	~151 K	~55%	~44%	~56%	**~20 K**
Melanoma	~100 K	~14%	~44%	~66%	**~4 K**

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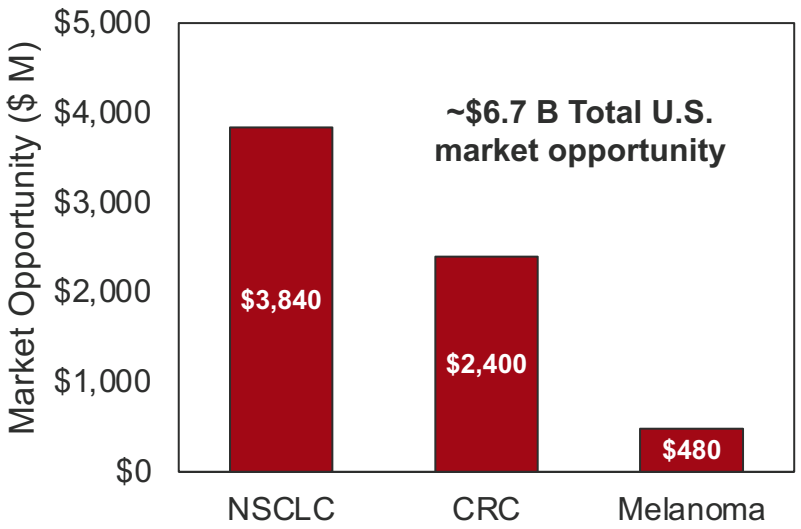
[1] ACS Cancer Facts & Figures 2022 [2] Estimations based on SEER 2000-2019 Data on Regional and Distant tumor sites. [3] Estimation based on overall cancer patients predicted to be eligible for PD-(L)1 Treatment, Haslam et al. *JAMA Netw Open.* 2019. [4] Estimation based on Overall Response Rate (ORR) reported in Keytruda Prescribing Information.

Advanced, PD-(L)1 resistant NSCLC/CRC/Melanoma patients may represent a ~$6.7 B U.S. market opportunity

Estimated Total Market Opportunity



Key Forecast Assumptions

- All patients with advanced-stage disease at diagnosis and failing PD-(L)1's are addressable
- Patients are treated with ART1i for a full year
- This analysis assumes an annual price of ~$150 K per U.S. Patient
- Price assumptions were benchmarked to the low end of currently approved PD-(L)1 inhibitors
- Assumes an 80% gross-to-net (GTN) rate
- Does not account for preference share, competition, market access, or compliance

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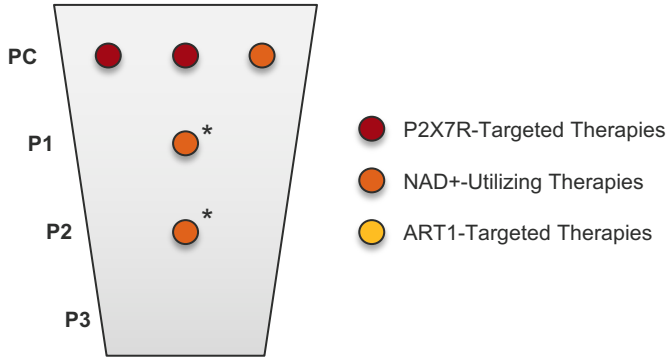
Research related to ART1 and associated pathways is limited, suggesting ART1i represents an innovative MOA

Development Pipeline Overview



* RBN-2497 is in clinical development for both a monotherapy and in combination with pembrolizumab

Key Pipeline Agents

Candidate	Company	Indication	Stage	Current Status
RBN-2397 (PARP7 Inhibitor)	ribon therapeutics	SCCL	Phase 1	Est. Primary Completion 12/2022
		Solid Tumors	Phase 1b/II	Est. Primary Completion 5/2023
RBN-012759 (PARP14 Inhibitor)	ribon therapeutics	Cancer (Unspecified)	Preclinical	Unspecified
nfP2X7 mAb (Non-functional P2X7R)	BIOSCEPTRE	Cancer (Unspecified)	Preclinical	Lead Optimization
nfP2X7 CAR-T (Non-functional P2X7R)	BIOSCEPTRE	Cancer (Unspecified)	Preclinical	Lead Optimization

Competitive Landscape Summary

- **ART1 is a novel target** – there are currently no known candidates in development targeting ART1 or its associated pathway
- Mono-PARPS (e.g., PARP7i / PARP14i) also target NAD+-utilizing enzymes but do not act directly on the ART1 pathway
- Candidates targeting P2X7R (the ligand-gated channel downstream of ART1) target a non-functional form and act via a separate MOA from ART1

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Corporate Websites; Clinicaltrials.gov; Biomedtracker.

The ART1 program is supported by a robust IP strategy and several peer-reviewed publications

IP Status & Publications

- **Intellectual Property:**
  - PCT Patent Application (PCT/US23/62151): “Targeting ART1 for Cancer Immunotherapy”. Priority date: Feb 7, 2022.
  - Cornell Docket: D-9386
- **Publications:**
  - Wennerberg et al. “The ART of tumor immune escape.” *Oncoimmunology.* 2022.
  - Wennerberg et al. “Expression of the mono-ADP-ribosyltransferase ART1 by tumor cells mediates immune resistance in non–small cell lung cancer.” *Science Translational Medicine*. 2022.
  - Chen et al. “ART1, an extracellular ADP-ribosyltransferase, is over-expressed in non-small cell lung cancer and facilitates cancer cell survival by immune-mediated mechanisms” *Journal of Thoracic Oncology.* 2016.
  - ***The Tri-I TDI has produced an extensive preclinical data package that is available under CDA***
- **Press Releases:**
  - “A Potential New Target for Cancer Immunotherapies” *Weill Cornell Medicine Newsroom.* Published Mar 16, 2022.
  - “Enzyme Could be New Target for Immunotherapies” *Cornell Chronical.* Published Mar 17, 2022.

WCM is seeking partners to perform additional IND-enabling studies and advance 22C12 into the clinic

Development Status & Next Steps

Development Achievements

- ☑ Development of 22C12 using the AlivaMab mouse
- ☑ *In vitro* validation of 22C12 affinity for ART1 and blockade of ART1 activity
- ☑ Demonstration of activity against lung cancer and melanoma models *in vivo* in mice
- ☑ Confirmation of P2X7R downregulation, ART1 upregulation in human NSCLC

Next Steps

License anti-ART1 mAbs to an established company with the capabilities and resources to drive clinical development

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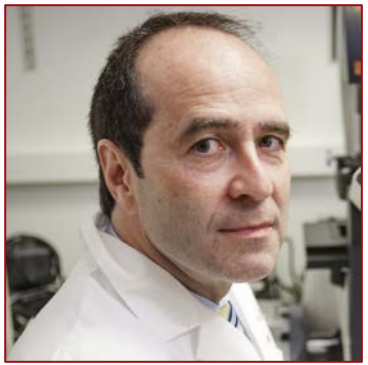
Summary of Inventors

Brendon M. Stiles, M.D.
Professor and Chief of Thoracic Surgery & Surgical Oncology, Albert Einstein College of Medicine

Former Associate Professor of Cardiothoracic Surgery, Weill Cornell Medical College



Timothy E. McGraw, Ph.D.
Professor of Biochemistry in Cardiothoracic Surgery, Cardiothoracic Surgery, Weill Cornell Medical College

Professor of Biochemistry, Biochemistry, Weill Cornell Medical College

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