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Anti-CDCP1 Antibody-Drug Conjugate for the Treatment of Solid Tumors

Lead Inventor:

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Developed in collaboration with BIDMC and Pfizer, Inc.

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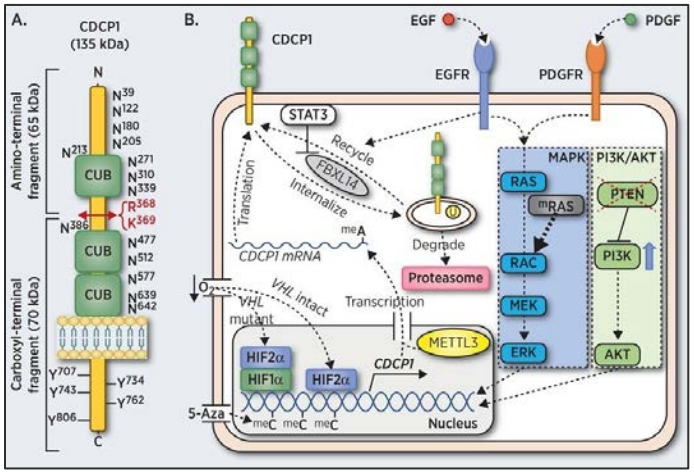
CDCP1 is an important hub of oncogenic signaling and promising therapeutic target

CDCP1 is a Promising Target for Cancer Therapy



- Over-expression of CUB domain-containing protein 1 (CDCP1) has been associated with multiple solid tumors (e.g., lung, ovary, breast, and kidney)
- CDCP1 interacts with multiple oncogenic signaling pathways, including RAS, EGFR, and Src to promote tumor growth, metastasis, and resistance
- Elevated CDCP1 expression has been correlated with poor outcomes in multiple tumor types
- CDCP1 remains a promising therapeutic target but has been largely unexplored, with only minimal preclinical development
- **Unmet Need:** Novel therapeutics for the treatment of solid tumors that complement the current standard of care (SOC) by targeting distinct mechanisms of action (MOAs) such as CDCP1

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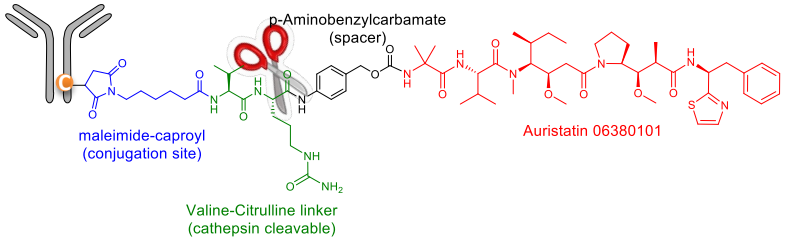
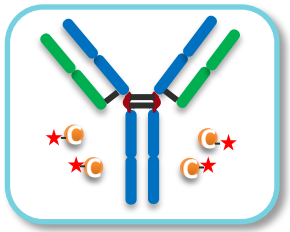
Adapted from Khan et al. Cancer Research. 2021.

The technology: anti-CDCP1 humanized ADC with preclinical efficacy against multiple solid tumor types

Technology Overview





Antibody engineered through extensive phage screening, binds human CDCP1 with 45nM affinity

4:1 Drug to antibody ratio (DAR);
<50 pM IC_{50} against PC3 cells

Payload consists of a site-specific auristatin conjugate with a cleavable linker

Demonstrated efficacy in PDX models across numerous tumor types

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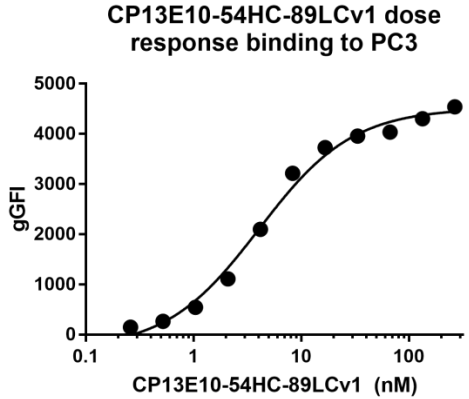
ADC: Antibody-drug conjugate. DAR: Drug to antibody ratio.
SOC: Standard of care.

The engineered anti-CDPC1 humanized antibody and the associated hADC bind human CDCP1 with high affinity

Anti-CDCP1 Binding Dose-Response Curve



Antibody or ADC	Human CDCP1 ECD K_D [nM] pH7.4	Human CDCP1 ECD K_D [nM] pH6.8
CP13E10-54HC-89LCv1-183/290 antibody	47.38	68.88
CP13E10-54HC-89LCv1-183/290-vc0101 ADC	45.63	66.55

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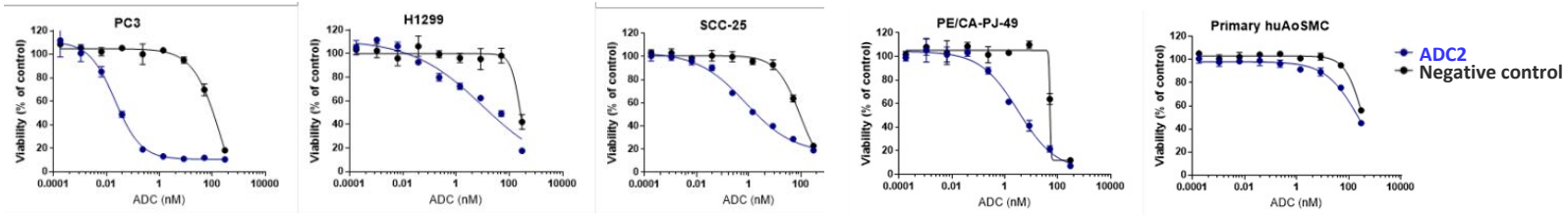
hADC: Humanized Antibody-drug conjugate.

The anti-CDCP1 hADC delivered strong in vitro cytotoxicity against multiple tumor cell lines expressing CDCP1

Anti-CDCP1 hADC Cytotoxicity in Cell Lines

Cell Category	Cell line	Cell type	Expression level	CDCP1 Receptor number	IC50 (pM)	Negative control IC50 (pM)	n
Tumor	PC3	Prostate cancer	+++	233,567	36.1 ±14.9	126,723.3 ±105006.4	3
Tumor	H1299	NSCLC	++	69,008	9,475.0 ±397.4	249,000 ±12,301.6	2
Tumor	SCC-25	Head and neck cancer	++	51,810	649.4 ±175.8	68,936.7 ±23,083.2	3
Tumor	H2009	Lung adenocarcinoma	++	48,857	754.6 ±284	148,906.7 ±85,391.1	3
Tumor	PE/CA-PJ-49	Oral squamous cell carcinoma	++	24,501	4,192.3 ±2,496.0	66,466.7 ±20,109.0	3
Healthy	HuAoSMC	Primary Aortic smooth muscle	+	12,814	269,266.7 ±37,646.3	301,166.7 ±37,409.4	3



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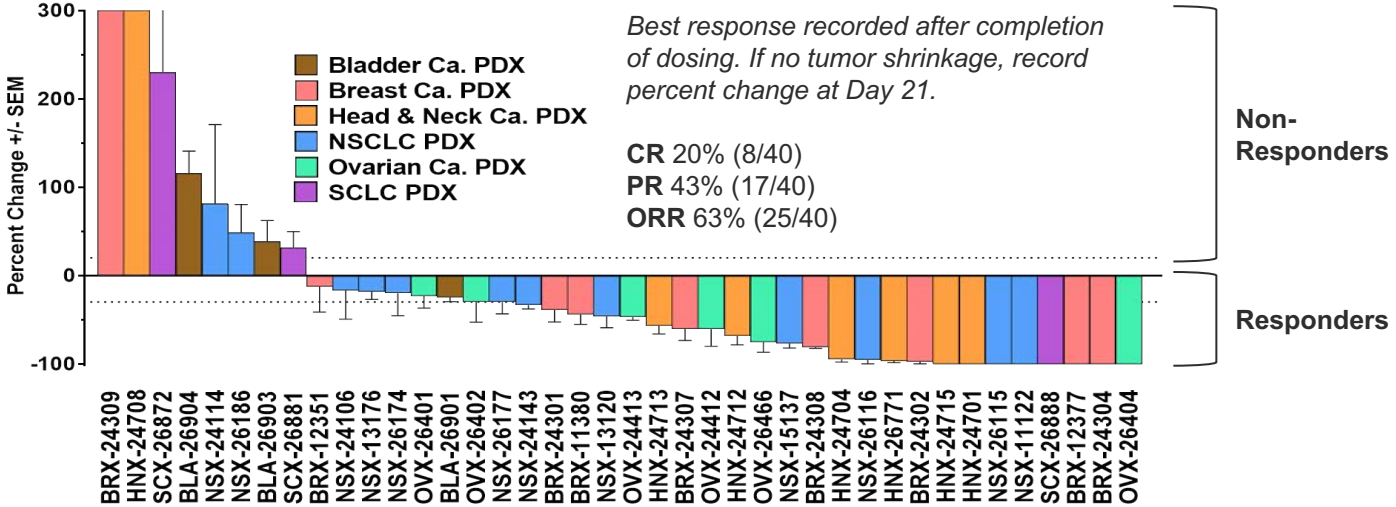
hADC: Humanized Antibody-drug conjugate. NB: The negative control is a non-targeting ADC, which was included to demonstrate induction of cytotoxicity in the absence of antibody-mediated target binding.

The identified anti-CDCP1 hADC demonstrated broad in vivo activity to multiple solid tumor types

Anti-CDCP1 hADC Efficacy in PDX Models



KADCYLA® achieved ~44% ORR and TRODELVY® achieved ~33% ORR in pivotal studies
(data provided for contextual purposes only)

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CR: Complete response. Humanized ADC: Humanized Antibody-drug conjugate. ORR: Overall response rate. PDX: Patient-derived xenograft. PR: Partial response.

The anti-CDCP1 hADC was generally well tolerated in exploratory toxicology studies (ETS)

Cynomolgus Monkey ETS Results

- **Study Design:**
  - IV dose on Day 1, 22, 43
  - Necroscopy on day 46
  - 0.3 (single dose; TK), 3, 6, and 12 mg/kg

- **Study Results:**
  - No effect on body weight
  - No ophthalmology findings when examined prior to the 2nd dose
  - Clinical signs of discoloration of the skin at all doses (potentially due to epithelial CDCP1 expression)
  - **Anticipate a highest non-severely toxic dose (HNSTD) of 6 mg/kg in GLP-Tox studies**, in line with, or superior to, other assets in the class

ETS: Exploratory Toxicology Studies. Humanized ADC: Humanized Antibody-drug conjugate.

Only four ADCs are currently approved for solid tumors, leaving significant competitive headroom for novel agents

Solid Tumor ADC Market Overview

Agent	Manufacturer(s)	Type	Target	Indication
KADCYLA® (Trastuzumab emtansine)	Roche	DM1 (Tubulin inhibitor)	HER2	HER2-positive metastatic breast cancer Approved 2013 (FDA & EMA)
PADCEV® (Enfortumab vedotin-ejfv)	astellas Seagen	Monomethyl auristatin E (Tubulin inhibitor)	Nectin-4	Locally advanced or metastatic urothelial cancer Approved 2019 (FDA)
ENHERTU® (Trastuzumab deruxtecan)	Daiichi-Sankyo AstraZeneca	DXd (Topoisomerase I inhibitor)	HER2	Unresectable or metastatic HER2-positive breast cancer, after previous HER2 Tx Approved 2019 (FDA), 2021 (EMA)
TRODELVY® (Sacituzumab govitecan-hziy)	GILEAD	SN-38 (Topoisomerase inhibitor)	Trop-2	Metastatic triple-negative breast cancer (mTNBC) Approved 2020 (FDA)

Frost & Sullivan Report 2020. ADC: Antibody-drug conjugate.

The anti-CDCP1 hADC is supported by a robust international IP strategy and several peer-reviewed publications

IP Status and Publications

- **Intellectual Property:**
  - US Application and EP Application Filed: “CDCP1-targeted therapies.” (Priority Date Nov 9, 2018)
    - Additional applications filed in AU, CA, CN, JP, and MX
  - Cornell Dockets: D-8334

- **Publications:**
  - Emerling et al. “Identification of CDCP1 as a hypoxia-inducible factor 2α (HIF-2α) target gene that is associated with survival in clear cell renal cell carcinoma patients.” *PNAS.* 2013.
  - Benes et al. “The SRC-associated protein CUB Domain-Containing Protein-1 regulates adhesion and motility.” *Oncogene.* 2012.
  - Extensive preclinical data package will be made available under CDA

WCM is seeking an industry partner to perform IND-enabling studies and advance the anti-CDCP1 hADC into the clinic

Development Status & Next Steps

Development Achievements

- ☑ Anti-CDCP1 antibody screening and validation
- ☑ Generation of an anti-CDCP1 hADC lead candidate with demonstrated *in vitro* activity
- ☑ Confirmed *in vivo* activity in a broad range of solid tumor PDX models with favorable PK/PD
- ☑ Anti-CDCP1 hADC was generally well tolerated in Cynomolgus ETS studies

Next Steps

License anti-CDCP1 hADC candidate and/or naked anti-CDCP1 antibody to an industry partner with the capabilities and resources to drive preclinical and clinical development

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hADC: Humanized Antibody-drug conjugate. IND: Investigational new drug. ETS: Exploratory Toxicology Studies. PD: Pharmacodynamics. PDX: Patient-derived xenograft. PK: Pharmacokinetics.

Lead WCM Inventor: Lewis C. Cantley

Lewis C. Cantley, Ph.D.
Director of the Sandra and Edward Meyer Cancer Center, Weill Cornell Medical College
Professor of Cancer Biology in Medicine

B.S., West Virginia Wesleyan College, 1971
Ph.D., Cornell University, 1975
M.A., Harvard College, 1978

Research interests: Cancer metabolism, phosphoinositide signaling, PI-3-kinase, drug discovery.

Co-founder of numerous companies, including Petra Pharma and Agios Pharmaceuticals