DBPR22998: A Potent QPCTL (IsoQC) Inhibitor Targeting the CD47-SIRPα Axis for Cancer Immunotherapy

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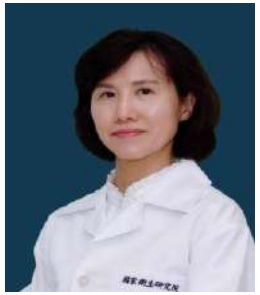
Cancer Biology



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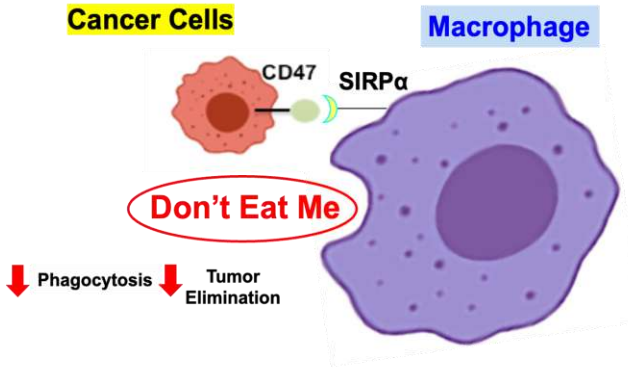
Project Summary

Category	Key Points
Key Features	• **Orally bioavailable small-molecule ISOQC (QPCTL) inhibitor** modulating CD47–SIRPα "don't-eat-me" immune checkpoint axis • **Target the post-translational modification pathway required for proper CD47 protein synthesis** • **Favorable pharmacokinetics** – strong systemic & intratumoral exposure • **Robust in vivo anti-tumor efficacy** – tumor regression & prolonged survival • Combination potential with **anti-tumor antibodies, chemotherapy, radiation, and immune checkpoint inhibitors (ICIs)** • **Limited RBC binding; lower risk of anemia**; **differentiated from CD47 antibodies**
Pharmaceutical Development	• **Crystalline form identified**; physicochemical, pre-formulation, and formulation evaluation completed • **Preclinical kilogram-scale API production completed and available** • Non-GLP 14-day repeated-dose rat toxicity study completed, providing early safety insights
Intellectual Property	• Substance patents granted: US, China, Taiwan, Japan, Korea, Canada, India, Singapore, Australia (**9 countries**) • Cancer indication patents: Taiwan granted; PTC applications under review
Business Opportunities	• Licensing or collaboration • Sponsored research for preclinical, IND, and clinical development
Targeted Indications	• Solid and hematologic cancers • Primary: **DLBCL** (combo with rituximab) • Secondary: **Radiation-resistant colon, HNSCC, HER2⁺ breast, brain tumors** (combo with SOC)
Clinical Plans	• Combination with SOC antibodies, radiation, or ICIs in refractory/resistant cancers • Patient selection based on CD47/QPCTL expression

INTRODUCTION

Role of CD47 Overexpression Cancer

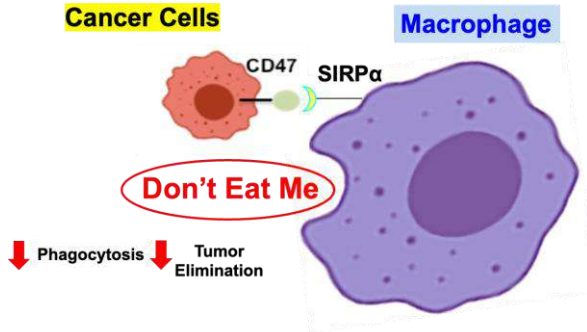


- **Immune Evasion**
  - CD47 binds SIRPα on macrophages to send a "don't eat me" signal", blocking phagocytosis
- **Tumor Progression**
  - Overexpressed in many cancers; supports tumor growth, metastasis, and therapy resistance
- **Poor Clinical Outcomes**
  - High CD47 levels correlate with shorter OS, PFS, DFS

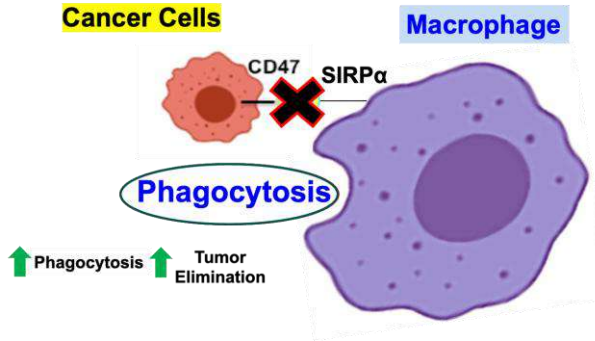
INTRODUCTION

CD47 as a Therapeutic Target

CD47 and SIRPα Signaling –
Mask Macrophage to See Cancer Cells

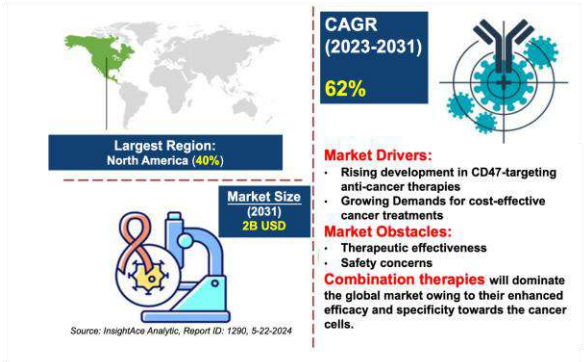


Blockade of CD47 and SIRPα Signaling –
Enhance Macrophage-Mediated Phagocytosis and Tumor Elimination

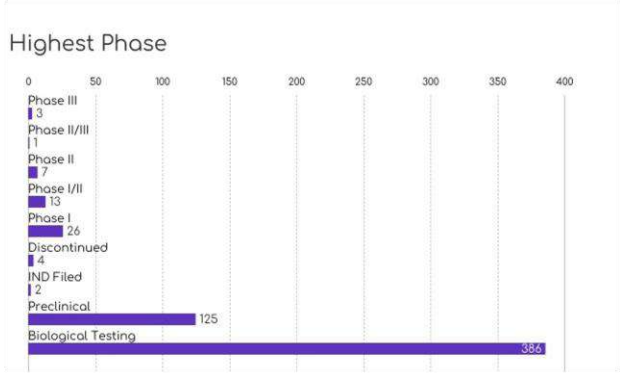


Global CD47 Inhibitors Market Analysis

Global CD47 Inhibitor Drug Market:
Market Size and Forecast from 2023 to 2031

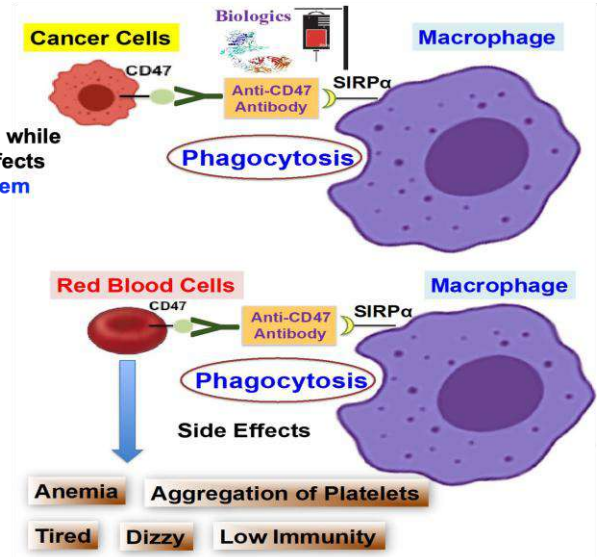


CD47-Targeting Therapeutics Landscape Analysis



Anti-CD47 Antibody Blocks CD47 and SIRPa Interaction on Both Tumor Cells and Red Blood Cells

Damage to normal cells while exerting anti-tumor effects
"Antigen sink" problem



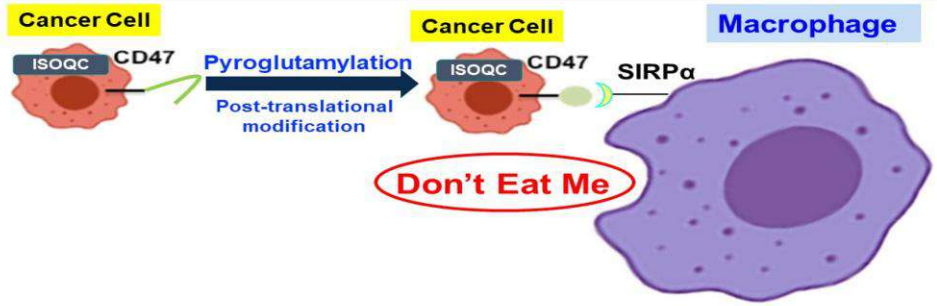
ISOQC (QPCTL)- Key Regulator of CD47 Functions

nature medicine LETTERS
https://doi.org/10.1038/s41591-019-0356-z

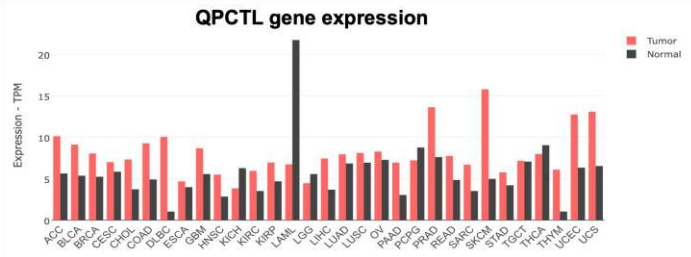
Glutaminyl cyclase is an enzymatic modifier of the CD47- SIRPα axis and a target for cancer immunotherapy

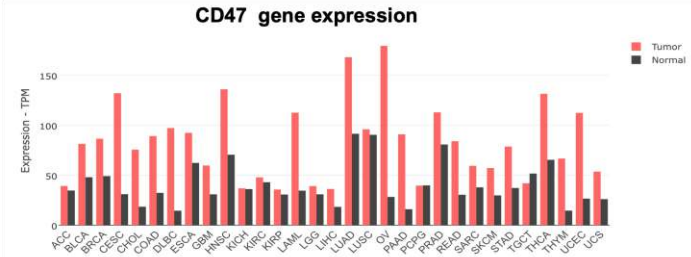
Meike E. W. Logtenberg[1], J. H. Marco Jansen[2,10], Matthijs Raaben[3,10], Mireille Toebes[1,10], Katka Franke[4], Arianne M. Brandsma[3], Hanke L. Matlung[4], Astrid Fauster[3], Raquel Gomez-Eerland[5], Noor A. M. Bakker[5], Simone van der Schot[1], Koen A. Marijt[4], Martijn Verdoes[7,8], John B. A. G. Haanen[5], Joost H. van den Berg[5], Jacques Neefjes[6,9], Timo K. van den Berg[4], Thijn R. Brummelkamp[3], Jeanette H. W. Leusen[2,11], Ferenc A. Scheeren[6,11] and Ton N. Schumacher[1,6,11]*

Logtenberg et al. Nat Med. 2019;25:612-619



ISOQC (QPCTL) Expression in Cancer





QPCTL Expression is Up-Regulated in Tumor and is Positively Correlated with CD47 Expression

IsoQC Inhibitors Competitive Landscape Analysis

Drug/Company	Target	Indication	Status
PQ912 (Vivoryon) Benchmark	QPCT/L	CDK/DKD	Phase II
858 Therapeutics*	QPCT/L	Immunology	IND Enabling
SC2882* (Scenic Biotech)	QPCTL	Hematological Cancer, Solid Tumor	IND Enabling
ISM004-1057D (ISM8207)* (InsilicoMed/Fosun Pharma)	QPCTL	Lymphoma, Solid Tumor	Phase I (China) GDC30034999 ISM8207_101 NCT06445517 CTR20240727 GDCT0513900

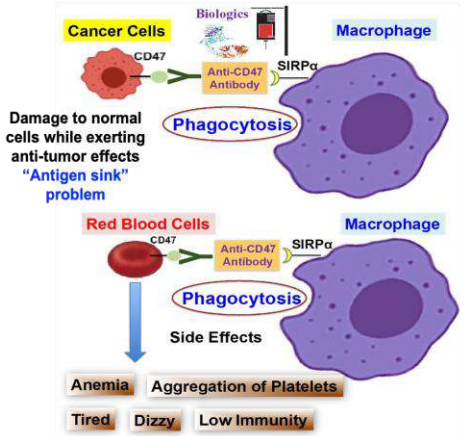
**: Structure not disclosed*

Source: Cortellis Drug Discovery Intelligence

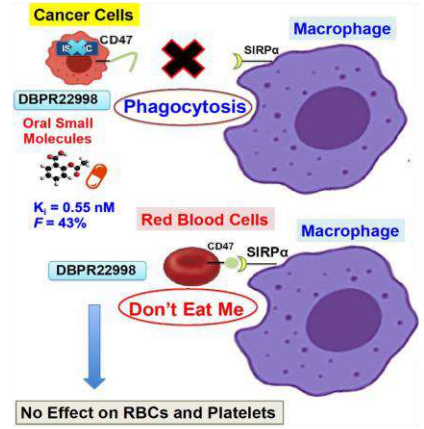
DBPR22998: A potent, orally bioavailable best-in-class small molecule isoQC inhibitor

Product Mechanism of Action and Advantages Over Current CD47 Inhibitors

Anti-CD47 Antibody Blocks CD47 and SIRPα Interaction on Both Tumor Cells and on Red Blood Cells

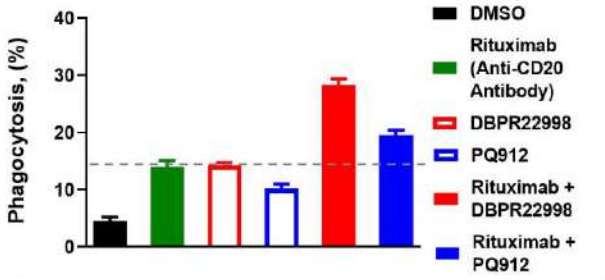


DBPR22998 –
Oral Small Molecule IsoQC (QPCTL) Inhibitor Targeting CD47 and SIRPα "Don't Eat Me" Signal



Key POC Data

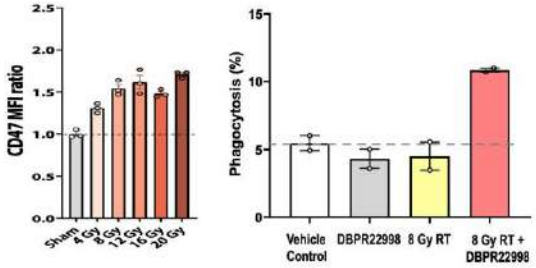
CD47-SIRPα Prevent Anti-tumor Antibody-Mediated Cellular Phagocytosis (ADCP)



DBPR22998 in Combination with Anti-Tumor Antibody Rituximab Enhances ADCP vs. Rituximab Alone and PQ912 Plus Rituximab

Tumor Cells Upregulate CD47 Expression Post Radiation for Phagocytosis Evasion

CD47 Overexpression Human Colon Cancer
HCT116 Cells

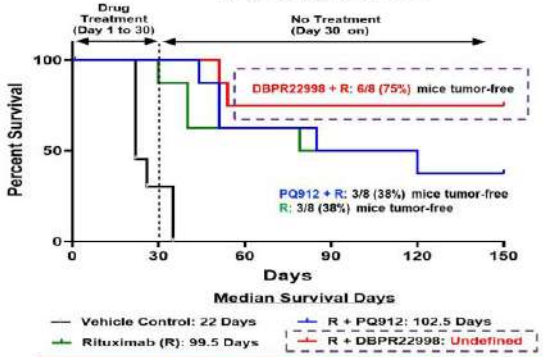


Unpublished data from collaborator Dr. CE Hsieh, CGMH

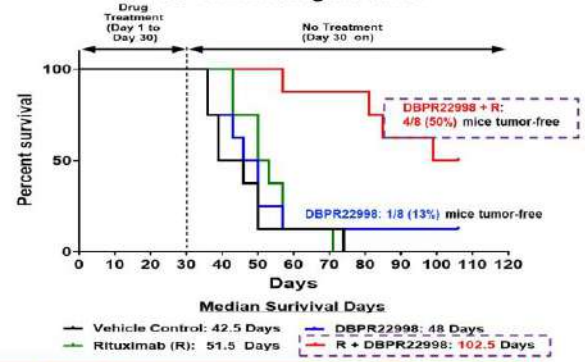
DBPR22998 in Combination with Radiation (RT) Enhances Phagocytosis vs. Either Agent Used Alone

Human B-Cell Lymphoma Xenograft Tumor Models

Raji Xenograft Tumor

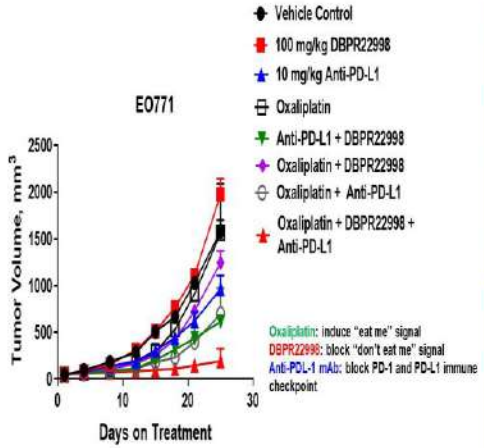


SU-DHL-2 Xenograft Tumor



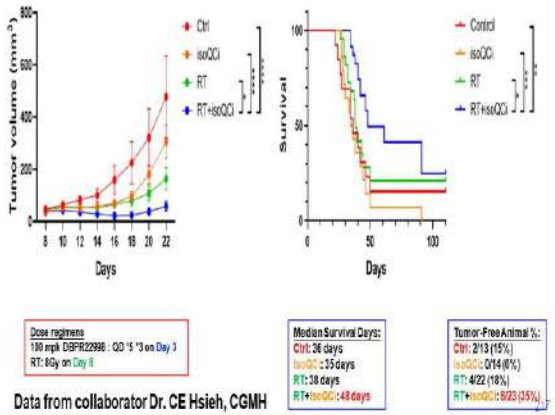
DBPR22998 in Combination with Rituximab Prolongs Post-Treatment Animal Median Survival Days and Increases Tumor-Free Animals vs. PQ912 Dual Combo and Rituximab Alone in Both Rituximab Sensitive and Rituximab Resistant Xenograft Tumor Models

CD47 and PD-L1 Overexpression TNBC Cancer
EO771 Murine Tumor



Triple Combination of DBPR22998 with ICI and Chemotherapy Enhances Anti-tumor Efficacy than Two Drug Combination

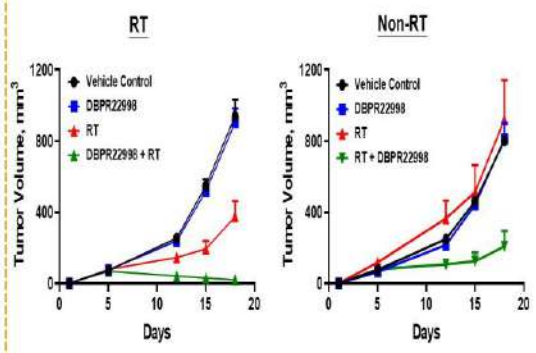
CD47 Overexpression Colon Cancer
Murine MC38 Colon Tumor



Data from collaborator Dr. CE Hsieh, CGMH

Combination of DBPR22998 with Radiation Enhances Anti-Tumor Efficacy, Extends Median Survival and Increases Tumor-Free Animals Compared with Monotherapy

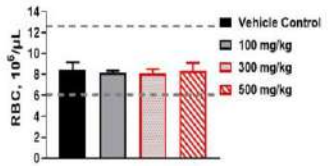
CD47 Overexpression Colon Cancer
Murine MC38 Colon Tumor



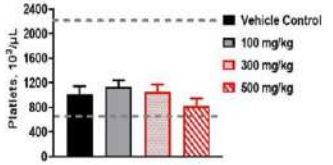
Combination of DBPR22998 with Radiation Enhances Anti-Tumor Efficacy at Both RT side and non-RT (Abscopal) Side Compared with Monotherapy

14-day Repeated Dose Toxicity Study in Mice

Red Blood Cells

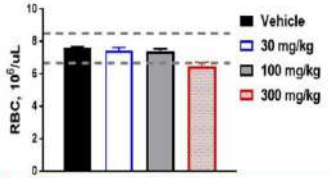


Platelets

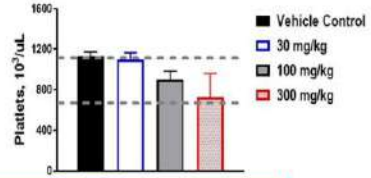


14-day Repeated Dose Toxicity Study in Rats

Red Blood Cells



Platelets



DBPR22998 Does not Cause Decrease in RBC and Platelets Numbers at All Dose Levels in 14-Day Repeated Dose Toxicity Test in Mice; Mild Decline at 300 mg/kg/day in Rats

Target Product Profiles

Parameters	DBPR22998	PQ912 (Benchmark)
IsoQC Enzymatic assay, K_i	**0.55 nM**	**6 nM**
CC2C6 Binding to pGluCD47, IC_{50}	**B-Cell Lymphoma Raji**: **1.1** μM; **B-Cell Lymphoma Ramos**: **0.6** μM **Colon DLD-1**: **0.6** μM **Colon HCT-116**: **0.4** μM	**B-Cell Lymphoma Raji**: 6.0 μM; **B-Cell Lymphoma Ramos**: 2.4 μM **Colon DLD1**: 3.2 μM **Colon HCT-116**: 1.1 μM
pGluCD47 and SIRPα-Fc Binding, IC_{50}	**B-Cell Lymphoma Raji**: **0.5** μM **Colon DLD-1**: **0.6** μM	**B-Lymphoma Raji**: 2.9 μM **Colon DLD-1**: 1.3 μM
Phagocytosis, %	**B-Cell Lymphoma Raji**: Rituximab (R): 14% R+ DBPR22998: **28.5%** **Colon HCT116:** Radiation (RT): 5% RT+ DBPR22998 : **10.5%**	**B-Lymphoma Raji**: Rituximab (R) : 15% R+ DBPR22998: 19.5%
In Vivo Anti-tumor Efficacy **(In combination with anti-tumor antibody therapeutics, radiation, chemotherapy, ICIs)**	**Combination with Antibody Therapeutics:** • **B-Cell Lymphoma Raji** TGI, % of Control: Rituximab + 22998: **93% (4/7 mice tumor regression)** TGI, % of Rituximab: **78% (1/7 mice tumor regression)** Median survival days: Rituximab (R): 99.5 days (3/8 mice tumor-free) R + 22998 = **Undefined (disease-free, 6/8 tumor-free)** • **B-Cell Lymphoma SU-DHL-2** Median survival days: Rituximab: 51.5 days R + 100 mpk 22998: **102.5 days (4/8 mice tumor-free)** • **Head and Neck FaDu** TGI, % of Control: Anti-EGFR mAb + 22998: **85%** TGI, % of Anti-EGFR mAb: **46% (3/8 mice tumor regression)** **Combination with Radiation:** • **Murine colon MC38** Median survival days: Radiation: 38 days (4/22 mice tumor-free) Radiation + 22998: **48 days (8/23 mice tumor-free)** **Combination with Chemotherapy and ICI:** • **Murine breast EO771** TGI, % of Control: Anti-PD-L1 mAb + 22998 + oxaliplatin: **88%** TGI, % of Anti-PD-L1 mAb + 22998: Anti-PD-L1 mAb + 22998 + oxaliplatin: **69%**	• **B-Lymphoma Raji** Median survival days: Rituximab = 99.5 days R + 100 mpk PQ912 = 102.5 days
Pharmacokinetics **(PO, mouse:30 mg/kg; rat: 5 mg/kg)**	**Plasma AUC (ng/mL*hr)** Mouse = **56,451** Rat: **3,117** **F (%)** Mouse = 43 Rat = 31	**Plasma AUC (ng/mL*hr)** Mouse = 6,359; Rat: 181 **F (%)** Mouse = 82 Rat = 16
14-Day Repeated Dose Toxicity in Rodents	**ICR mice** No significant toxicity @ 100 and 300 mg/kg/day Mild toxicity in organ weight change and mild liver enzymes increase @ 500 mg/kg/day No decline in RBC and platelet numbers at all doses tested **SD Rats** No significant toxicity @ 30 and 100 mg/kg/day Mild toxicity in organ weight change and mild liver enzymes increase @ 300 mg/kg/day Mild decline in RBC and platelet numbers @ 300 mg/kg/day	NA