BPRQC298: A Potent QPCTL (IsoQC) Inhibitor Targeting CD47-SIRPα Axis for Cancer Immunotherapy

Institute of Biotechnology and Pharmaceutical Research
National Health Research Institutes, Taiwan
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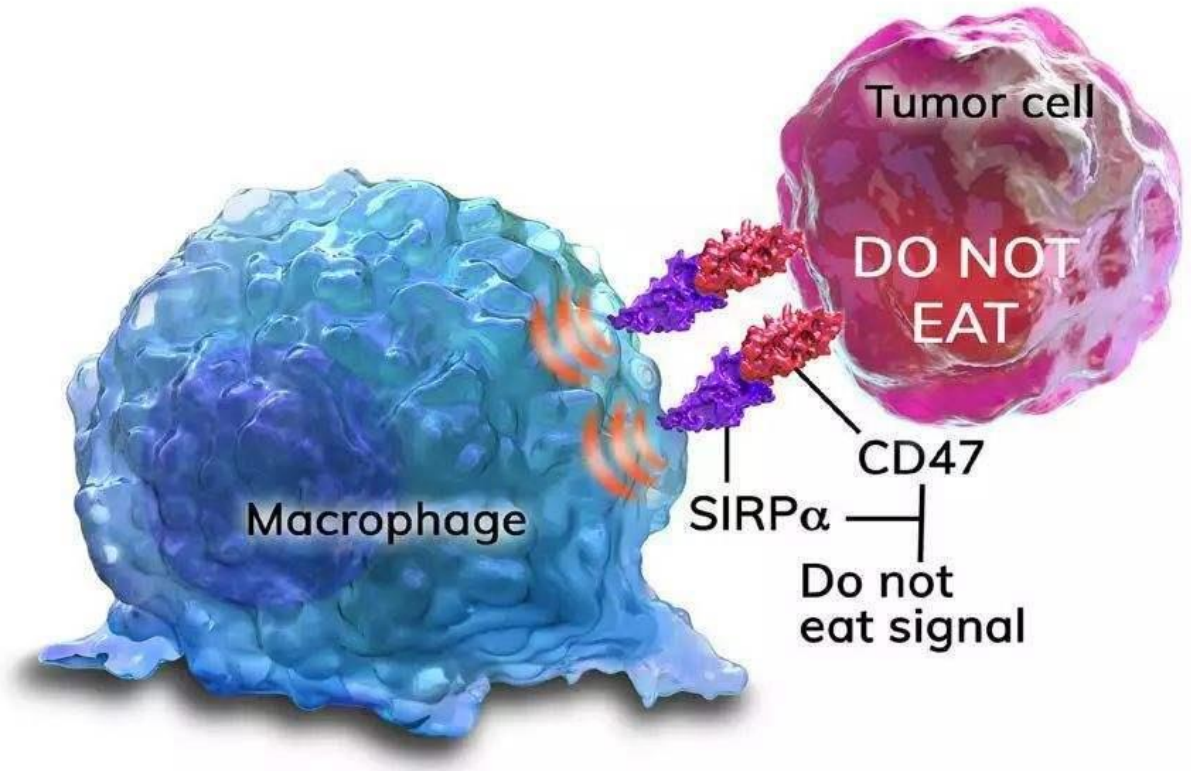
Methods of Increasing Cell Phagocytosis:

Discovery of Potent Iso-Glutaminyl Cyclase (isoQC) Inhibitors Targeting CD47-SIRPα Axis as Novel Cancer Immunotherapeutic Agents



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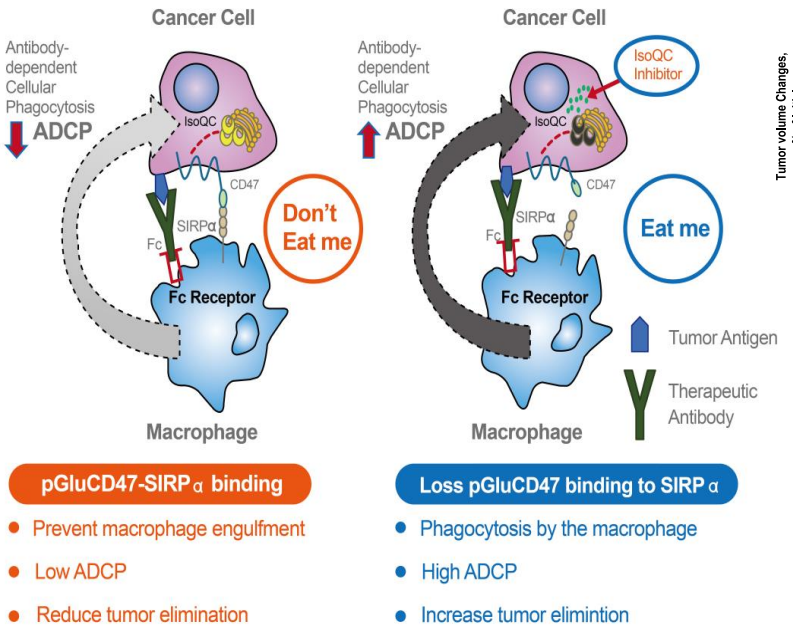
IsoQC Inhibitor DBPR22998: Product Summary

DBPR22998: A Potent QPCTL (IsoQC) Inhibitor Targeting CD47-SIRPα "Don't Eat Me" Signal

CD47 and SIRP α Signaling - Mask Macrophage to See Cancer Cell



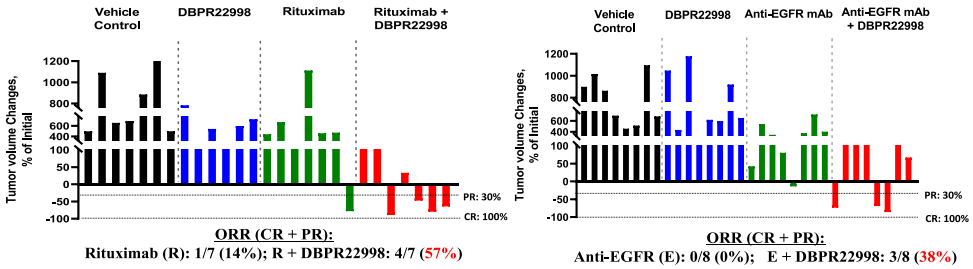
pGluCD47-SIRPα binding

- Prevent macrophage engulfment
- Low ADCP
- Reduce tumor elimination

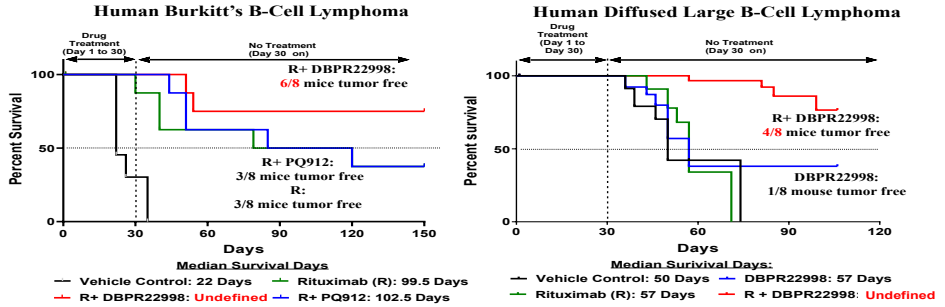
Loss pGluCD47 binding to SIRP α

- Phagocytosis by the macrophage
- High ADCP
- Increase tumor elimintion

DBPR22998 in Combination with Therapeutic Antibody Induces Tumor Regression



DBPR22998 in combination with Rituximab Prolongs Animal Survival Days



Market Position/Opportunities

- **An orally bioavailable small molecule isoQC inhibitor modulating CD47-SIRPa "Do not eat me" cancer immune checkpoint activity**
- **An innovative therapeutic approach for boosting the efficacy of cancer immunotherapy**
- **Target post translational modification process of CD47 protein synthesis**
- **Oportunity for combination with therapeutic antibodies and immune checkpoint inhibitors (ICIs)**

Competitive Advantages of DBPR22998

Parameters	DBPR22998	Competitor - PQ912
IsoQC Enzymatic assay, Ki	**0.55 nM**	6 nM
CC2C6 Binding to pGluCD47, IC_{50}	**B-Lymphoma Raji**: **1.1** uM; **Ramos**: **0.6** uM **Colon DLD-1**: **0.6** uM **Ovarian SKOV-3**: 0.2 uM **Head/Neck FaDu**: **0.7** uM	**B-Lymphoma Raji**: 6.0 uM **Colon DLD1**: 3.2 uM **Ovarian SKOV-3**: 0.2 uM **Head/Neck FaDu**: 2.1 uM
pGluCD47 and SIRPα-Fc Binding (@10 μM, % DMSO)	**B-Lymphoma Raji**: **45%** **Colon DLD-1**: **60%** **Ovarian SKOV-3**: 50%	**B-Lymphoma Raji**: 88% **Colon DLD-1**: 79% **Ovarian SKOV-3**: 50%
ADCP (% Increase vs. Antibody alone)	**B-Lymphoma Raji**: 16%	**B-Lymphoma Raji**: 9%
In Vivo Anti-tumor Efficacy (In combination with anti-tumor antibody therapeutics)	• **B-Lymphoma Raji (PK and PD)** **Median survival days:** Rutiximab = 99.5 days R + 100 mpk 22998 = **Undefined (disease-free)** • **Diffused Large B-Lymphoma SU-DHL-2** **Median survival days:** Rutiximab = 57 days R + 100 mpk 22998 = **Undefined (disease-free)** • **Head and Neck FaDu** TGI: αEGFR mAb + 22998: **85%** vs. control; **46%** vs. αEGFR mAb • **Colon DLD-1** TGI: αEGFR + 22998 **32%** vs. control; 15% vs. αEGFR mAb • **Murine colon MC38** TGI: αPDL1 mAb + 22998: **52%** vs. control; **38%** vs. αPDL1 mAb	• **B-Lymphoma Raji** **Median survival days:** Rutiximab = 99.5 days R + 100 mpk PQ912 = 120 days

DMPK, Safety Pharmacology and Toxicology

Parameters	DBPR22998	Competitor - PQ912
Pharmacokinetics (PO, mouse:30 mg/kg; rat: 5 mg/kg)	**AUC (ng/g*hr)** Mouse = 56,451; Rat: 3,117 **F (%)** Mouse = 43 ; Rat = 31	**AUC (ng/g*hr)** Mouse = 6,359; Rat: 181 **F (%)** Mouse = 82 ; Rat = 16
Metabolic Stability in Liver Microsomes	> 80% remaining in mouse, rat, dog and human	NA
CYP Inhibition Activity	1A2, 2C19, 2D6, 2E1, 3A4: > 10 µM; 2C9 = 2.8 uM	NA
Potassium Channel herG Activity	IC_{50} > 10 µM	NA
Single Dose Acute Toxicity in ICR mice	No significant toxicity @ 100, 300 and 500 mg/kg/day	NA
14-day Repeated Toxicity in ICR mice	No significant toxicity @ 100 and 300 mg/kg/day Mild toxicity @ 500 mg/kg/day	NA

Target Product Profiles

Item	DBPR22998	Competitor – PQ912
Product Description	IsoQC inhibitor targeting CD47-SIRPα axis	IsoQC inhibitor targeting CD47-SIRPα axis
Indication	Cancer	Cancer, AD
Target Patients	H/N, Colon, Breast, Ovarian, Gastric, DLBCL, AML, GBM	NA
Biomarker	CD47 over expression	CD47 over expression
Clinical PK/PD, Efficacy	NA	$T_{1/2}$ = 2-3 hours, AUC= 24, 549 ng.h/mL (800 mg, BID)
Route of Administration	Oral route	Oral route
Dose Schedule and Frequency	Once a day, 5 days a week	Once a day, 5 days a week (Cancer) BID daily (AD)
Adverse Reaction	NA	GI disorder and skin rash (800 mg BID)
Storage	Room temperature	Room temperature
Intellectual Property	US, Taiwan and TCP patents	US, TCP patents

Research Team

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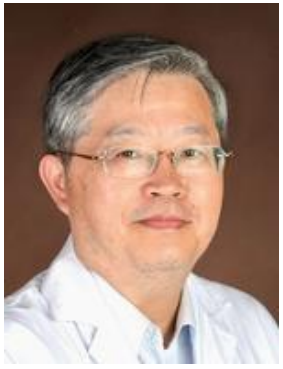

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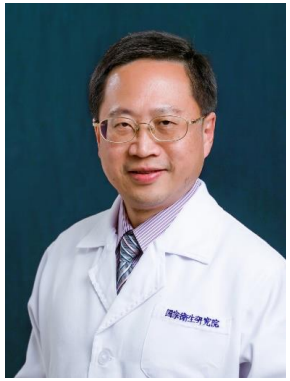

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