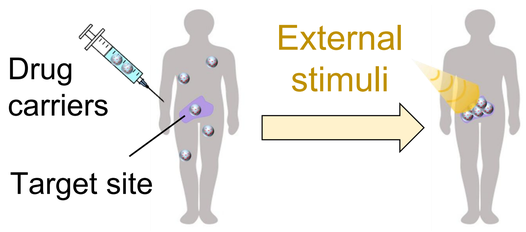
Heat-guided drug delivery via thermally induced crosslinking of polymeric micelles

Online Poster

Sota YAMADA , Kenjiro HANAOKA (Keio University, Japan)

Background

Targeted drug delivery in response to external stimuli is an attractive strategy for on-demand delivery to specific tissues. Stimulus-responsive drug carriers can undergo in situ functional changes, allowing external control of drug pharmacokinetics.



External stimuli: magnetic field, ultrasound, light, **heat**, etc.

Previous study **Magnetic targeting**

Magnetic carriers are guided to target site by external magnetic field.[1,2]

Challenge: After magnet is removed, the attractive force disappears.[3,4]

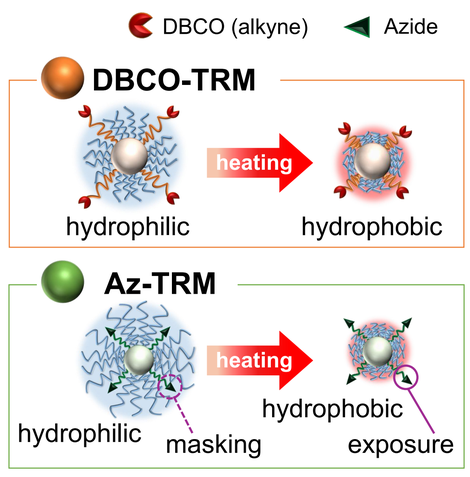
⇒ Random diffusion and off-target delivery via the systemic circulation.[5]

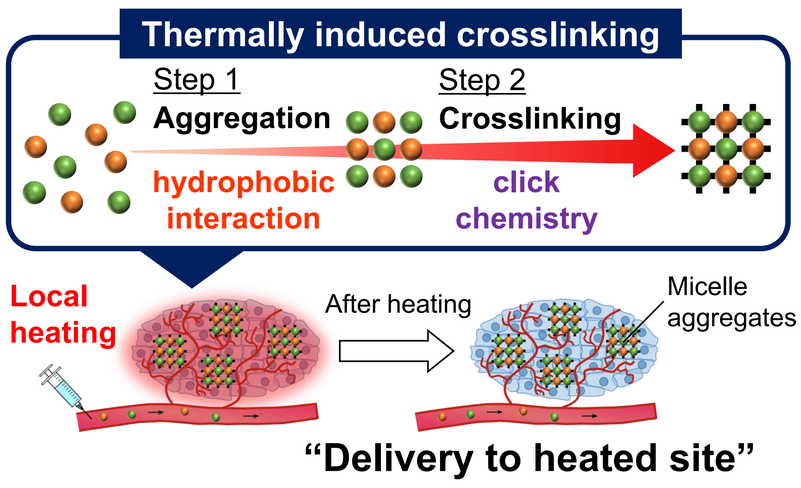
Purpose

Development of a targeted delivery strategy based on a persistent change of drug carriers by external stimulation

Strategy

Upon local heating at target tissue,
(1) thermo-responsive micelles (DBCO-TRM and Az-TRM) **aggregate via hydrophobic interaction**, and (2) the azide on Az-TRM are exposed, inducing **crosslinking by azide-alkyne click chemistry**.





⇒ **The irreversible crosslinking enables retention of the drug carriers at the heated site due to the increased size, leading to efficient targeted delivery.**

Result-1 : Crosslinkable pair of micelles

We designed a pair of thermo-responsive micelles, DBCO-TRM and Az-TRM, having dibenzocyclooctyne (DBCO) and azide, respectively.

Fig. 1A Design of polymeric micelles

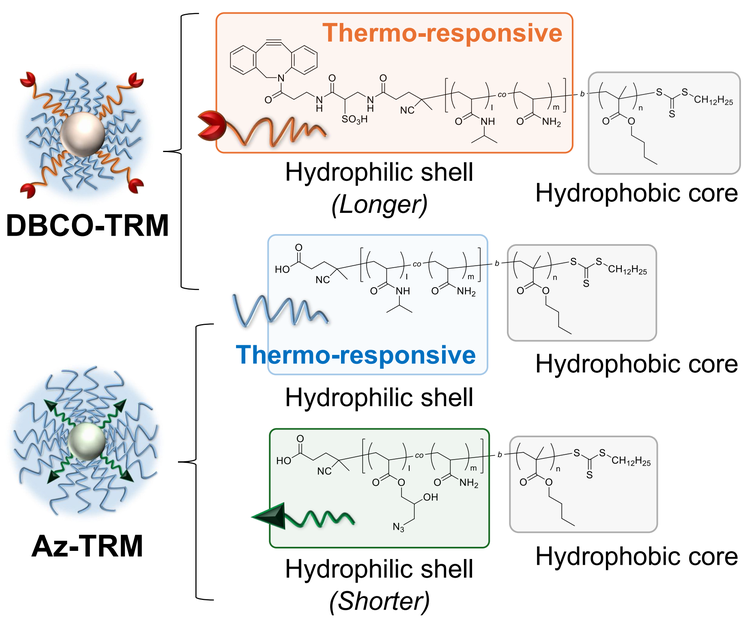


Fig. 1B Thermo-responsivity

(Micelle: 1 mg/mL in PBS)

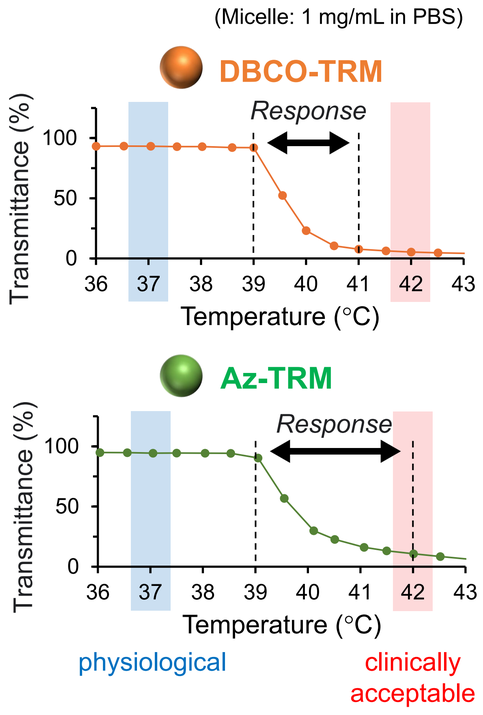
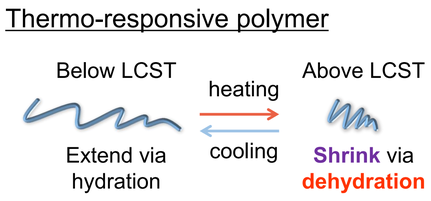


Table 1 Characterization of micelles

Micelle	Diameter (nm)	Pdi	LCST (°C)
DBCO-TRM	119 ± 1.4	0.148 ± 0.009	39.6
Az-TRM	114 ± 1.6	0.208 ± 0.017	39.7
TRM	110 ± 2.0	0.186 ± 0.019	39.4

LCST: Lower Critical Solution Temperature

Thermo-responsive polymer



Result-2 : Thermally induced crosslinking

In contrast to the behavior of the individual micelle types, the mixture was crosslinked irreversibly by heating at 42°C.

Fig. 2A Individual behavior

(Micelle: 1 mg/mL in PBS containing 70% FBS)

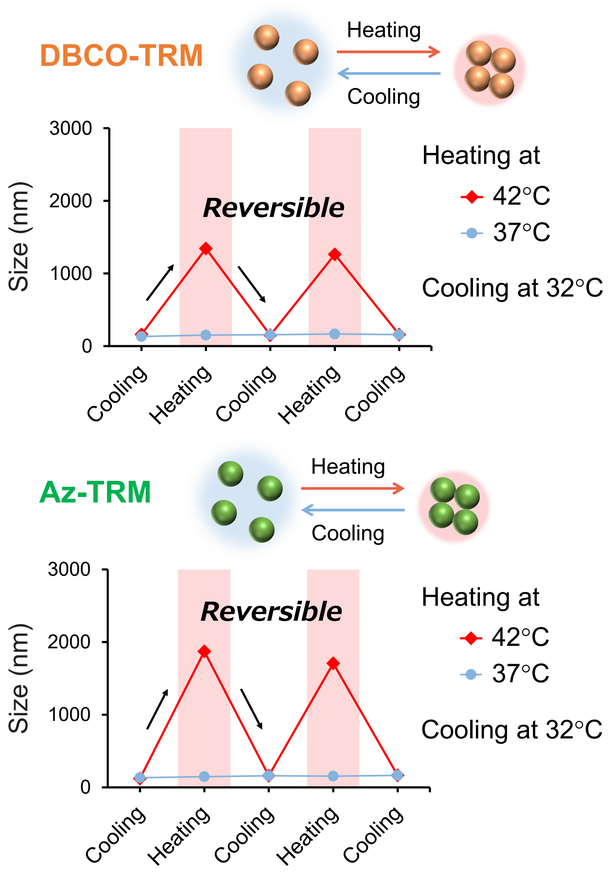


Fig. 2B Crosslinking of mixture

(Micelle: 1 mg/mL in PBS containing 70% FBS)

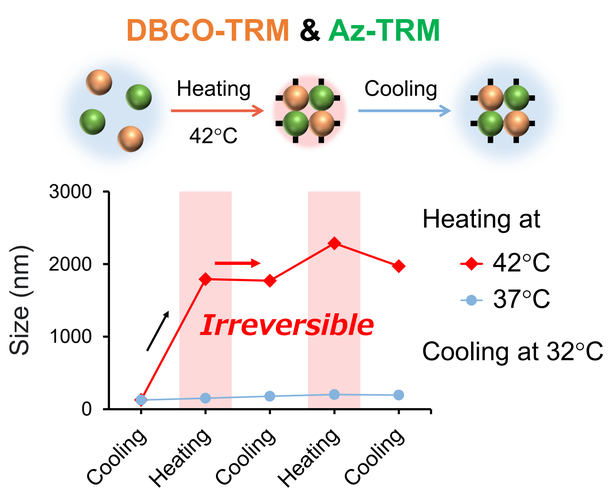
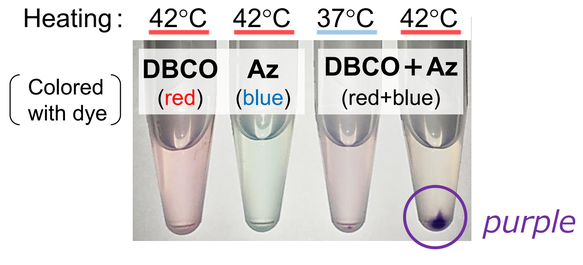


Fig. 2C Micelle aggregates

(Centrifuged after heating twice for 10 min in PBS)



Result-3 : Heat-guided drug delivery

Thermally induced crosslinking of DBCO-TRM and Az-TRM enhanced accumulation and retention at heated tumor site.

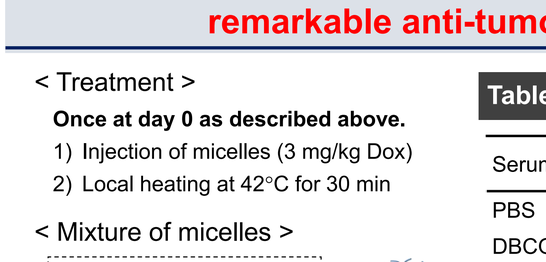


Fig. 3A Targeting to heated site

(Fluorescence: DiD in Az-TRM)

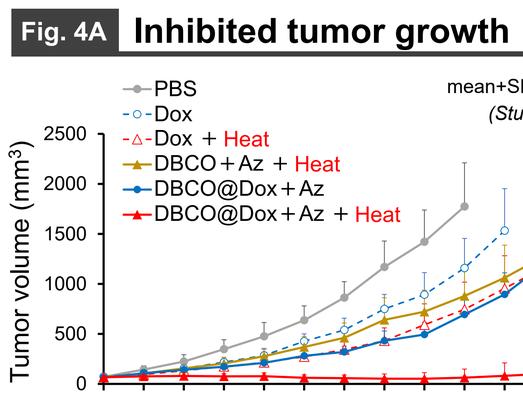
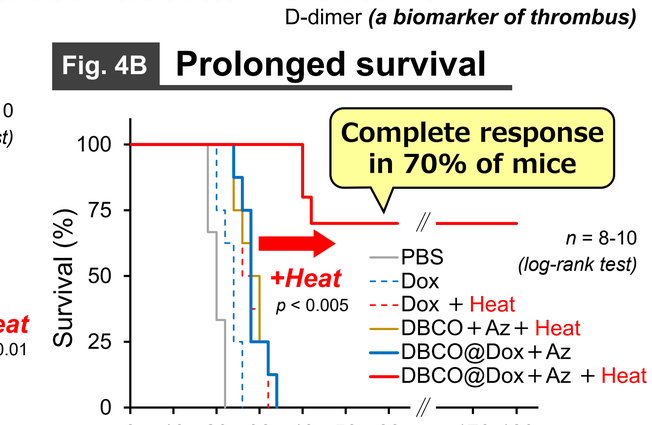


Fig. 3B Sustained retention

mean±SD, *n* = 5
(Student t-test, n.s.; p > 0.05)



Result-4 : Crosslinking-enhanced therapy

Heat-guided delivery of doxorubicin achieved remarkable anti-tumor efficacy after a single treatment.

< Treatment >

Once at day 0 as described above.

1) Injection of micelles (3 mg/kg Dox)
2) Local heating at 42°C for 30 min

< Mixture of micelles >

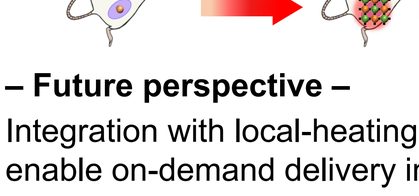


Table 2 No acute toxicity

(Tumor bearing mice after 48 h i.v.)

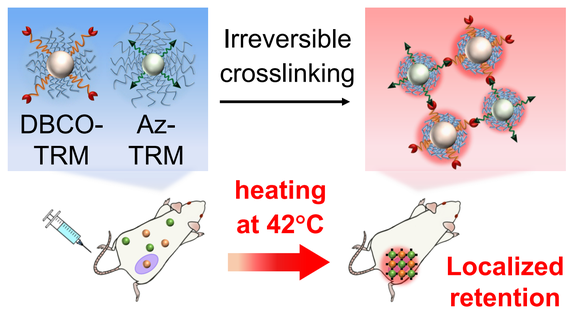
Serum biomarkers	ALT (U/L)	AST (U/L)	BUN (mg/L)	CRE (mg/L)	D-dimer (mg/L)
PBS	98±20	45±4.5	182±11	1.30±0.14	1.96±0.44
DBCO-TRM@Dox + Az-TRM	111±15	45±4.8	164±17	1.32±0.13	1.95±0.46
DBCO-TRM@Dox + Az-TRM + Heat	99±16	44±11	180±19	1.24±0.17	1.89±0.35

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BUN: blood urea nitrogen
CRE: creatinine
D-dimer ***(a biomarker of thrombus)***

Fig. 4A Inhibited tumor growth

Fig. 4B Prolonged survival

Conclusion



1. **Developed a mild local heating-guided drug delivery system based on thermally crosslinkable micelles.**
2. **Achieved sustained retention at heated site and improved anti-tumor efficacy.**

– Future perspective –

Integration with local-heating devices may enable on-demand delivery in deep tissues.

Publication

Sota Yamada *et al.* *Commun. Chem.* **2024**, 7, 287.

Reference [1] *Front Chem* **2018**, 6, 619. [2] *Materials Today* **2019**, 31, 86–99. [3] *Appl Nanosci* **2014**, 4, 385–392. [4] *J Supercond Nov Magn* **2021**, 34, 1709–1735. [5] *Pharmaceutics* **2021**, 13, 1157.