Novel Biodegradable NanoArtemisinin to Treat Leukemia in Blood and Brain

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Acute Myeloid Leukemia (AML) and Current Treatments

- About 22,010 cases in USA will be diagnosed with AML.
- About 11,090 patients in USA will die from AML.
- AML accounts for about 1/3 leukemias in adults , and for about 1% of all cancers.
- Low survival rate (30% for 5-year survival).
- High relapse rates and drug resistance.
- High financial burdens - $13.6B in 2020.
- AML can also occur in the central nervous system (CNS), including the brain. The drugs need to cross the blood-brain barrier (BBB) to get into the brain.

Current treatments:

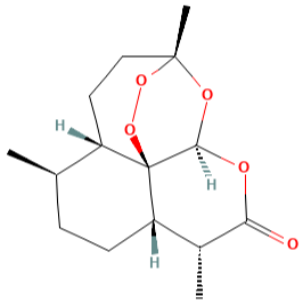
- Standard: 7&3 Cytrabine + Anthracycline
- Targeted Therapies: BCL2, FLT3, IDH Inhibitors

There is an unmet need to develop a more effective long-lasting therapy to treat AML, in the blood and brain.

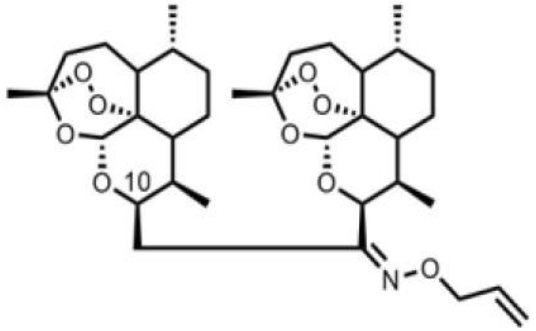
Artemisinin (ART) and AML Treatment

- Developed as an anti-malaria drug (Y. Tu, 2015 Nobel Prize).
- ARTs are also effective killing multiple human cancer cell types, including leukemia cells resistant to standard clinical antineoplastic drugs.
- 2-C ART dimers were synthesized to improve ARTs water solubility, and effectively killed 9 human leukemia cell lines.
- 2-C ART dimers still have limited water solubility (< 10 µg/mL), short half-life time , and low bioavailability.

There is an unmet need to increase the water solubility, half-life time and bioavailability of ARTs.

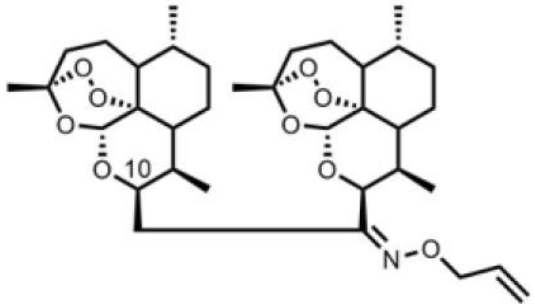


Artemisinin



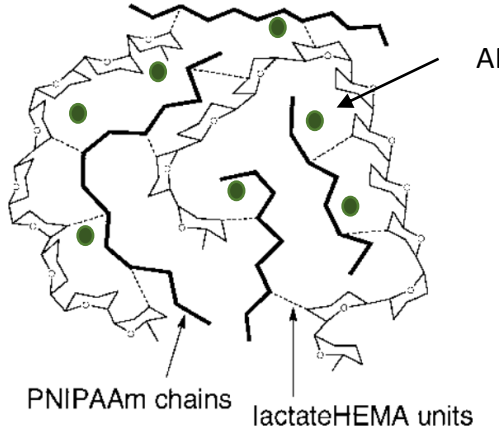
ART631

Synthesis, Loading and Physical Properties of NanoARTs



ART631

UV Emulsion Polymerization

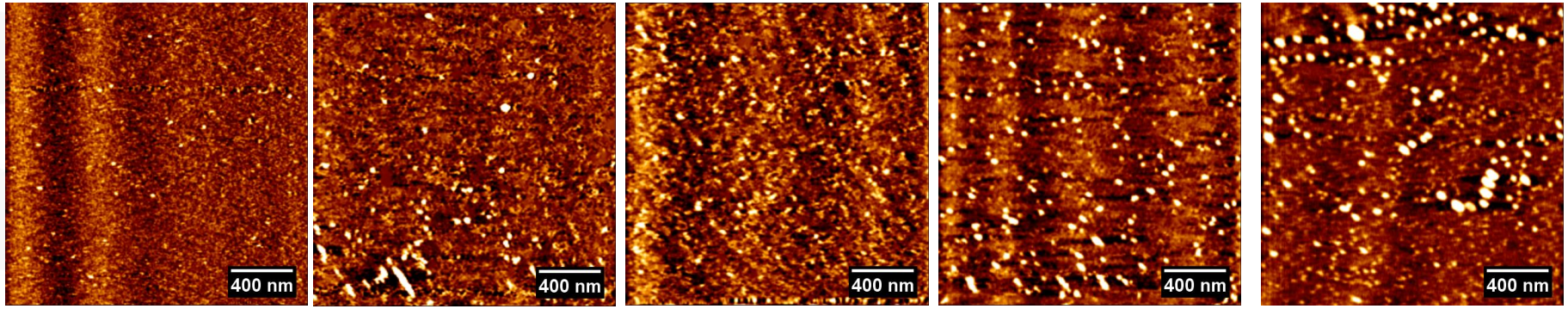


Huang X, et al. Biomacromolecules 6(4): 2131-2139, 2005.
Lowe TL, et al. U.S. Patent No. 8,545,830.
Lowe TL and Civin CI. Platform Nanoparticle Technology for Sustained Delivery of Hydrophobic Drugs. Patent Pending (PCT/US2023/019974).

Sample	Yield %	Encapsulation Efficiency %	Loading Content %	Diameter nm	PDI	Zeta potential mV	ARTs water solubility mg/mL
Plain PLA Nanogels	86.11	-	-	108.5 ± 0.34	0.166	-9.01	-
2% NanoART	86.59	97	1.87	140.64 ± 0.32	0.173	-9.43	> 4
5% NanoART	92.69	98.4	4.62	149.58 ± 0.37	0.19	-11.67	> 4
10% NanoART	86	99.1	8.89	162.32 ± 0.44	0.193	-13.53	> 4
15% NanoART	86.59	98.58	12.7	168.36 ± 0.34	0.195	-15.6	> 4

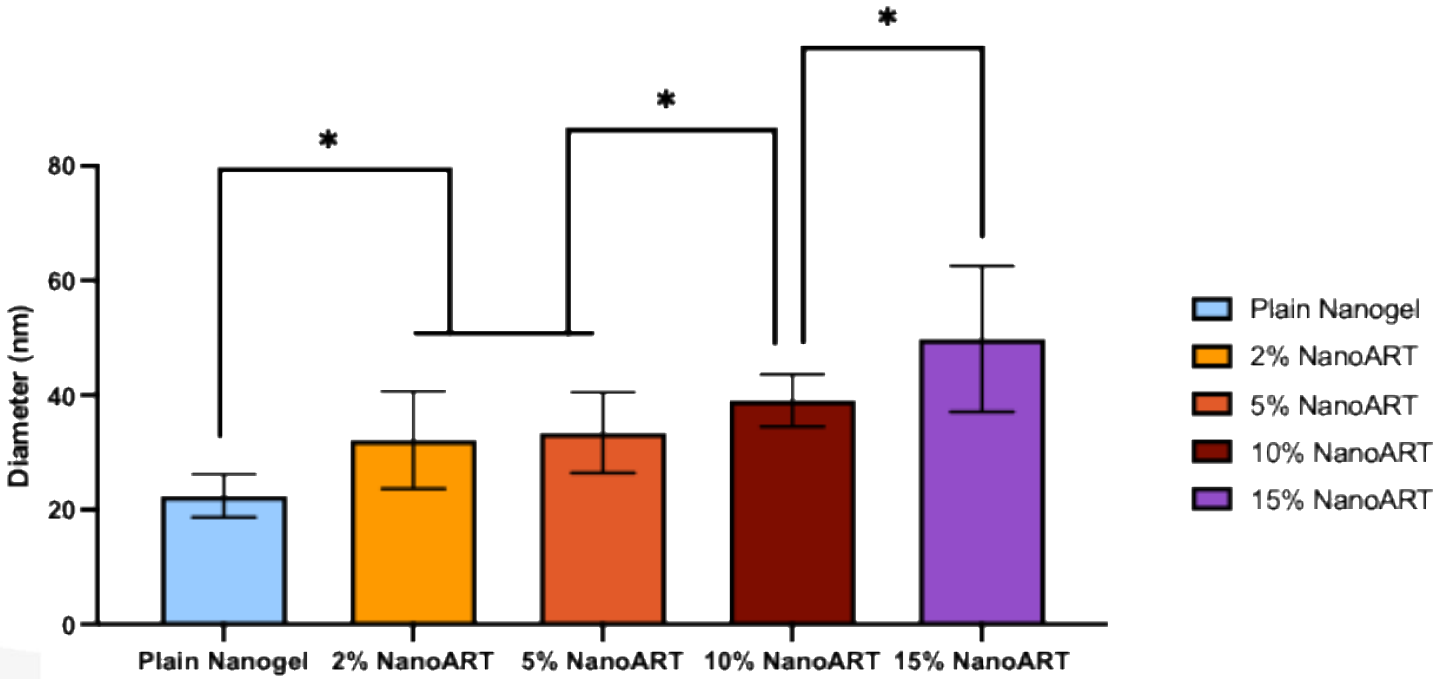
The size, PDI and zeta potential were measured at 500 µg/mL by DLS and zeta-sizer at 37 °C, respectively; the loading content and encapsulation efficiency were measured and calculated by ^{1}H NMR. n=4.

Atomic Force Microscopy (AFM) Size and Shape of NanoARTs



0 %	2 %	5 %	10 %	15 %
22.43 ± 3.76 nm	32.18 ± 8.51 nm	33.43 ± 7.02 nm	39.07 ± 4.55 nm	49.80 ± 12.72 nm

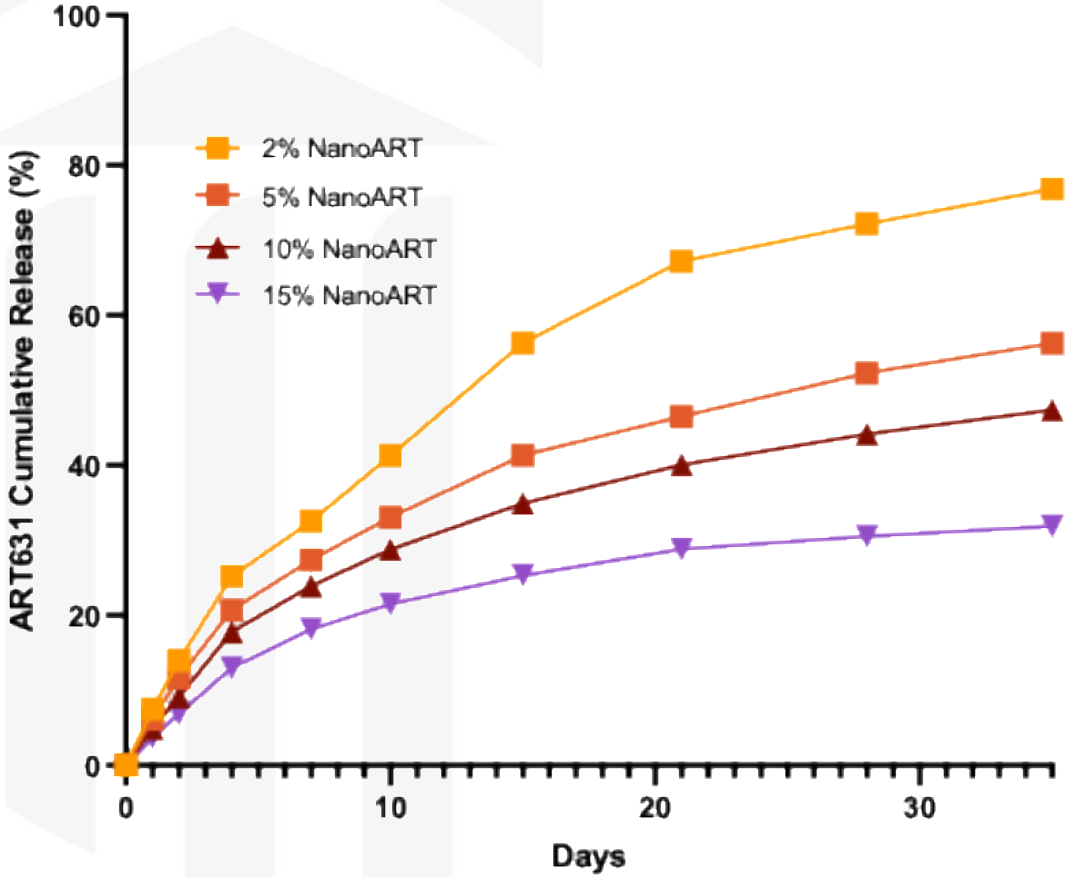
Mode: quantitative imaging (QI)-AFM; state: wet.

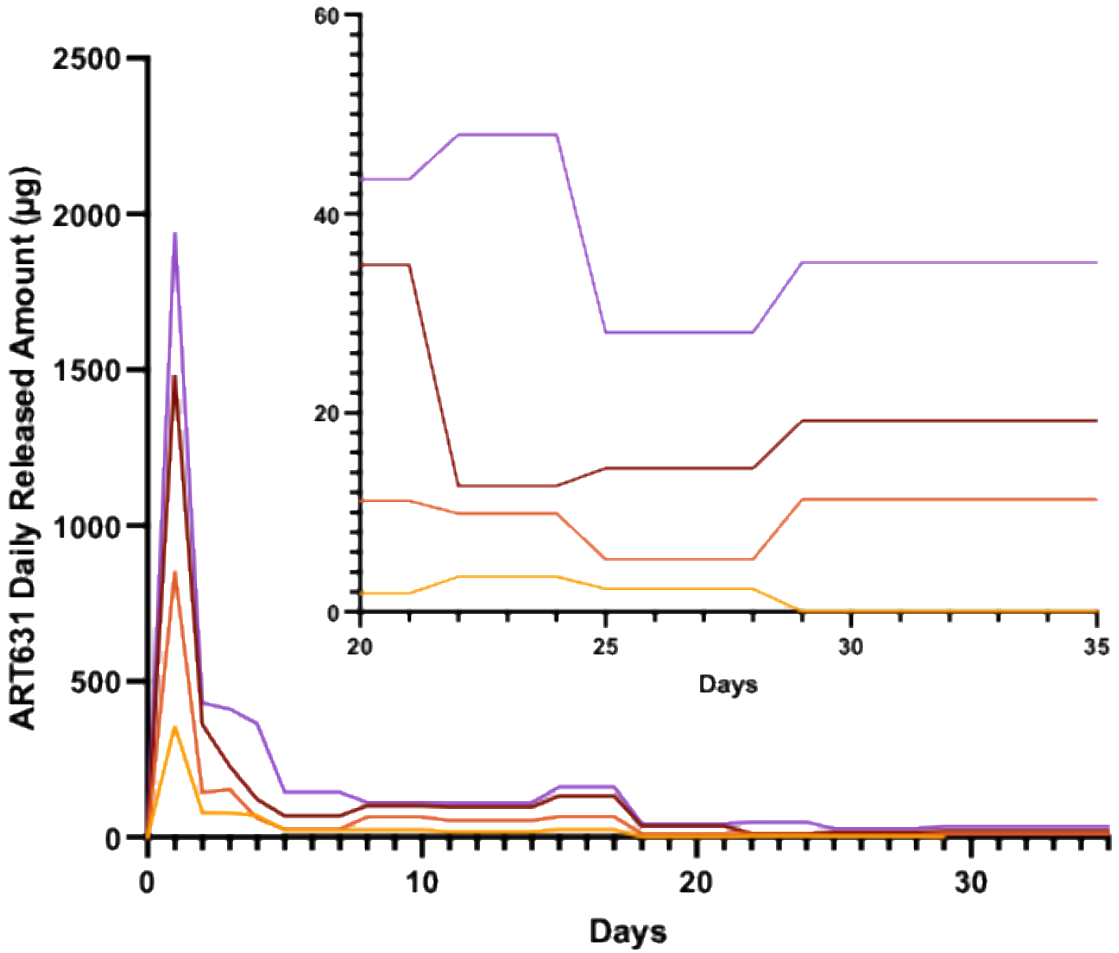


n = 100

*: $p < 0.05$

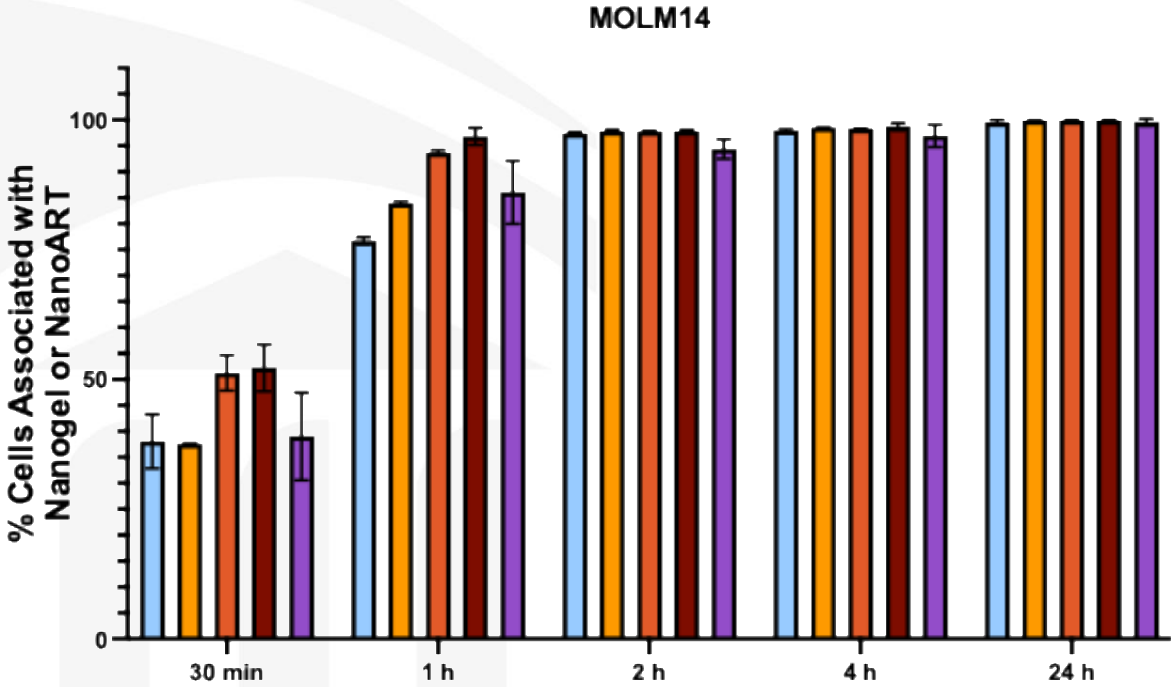
NanoARTs Sustained Release of ART631 for More than 1 Month

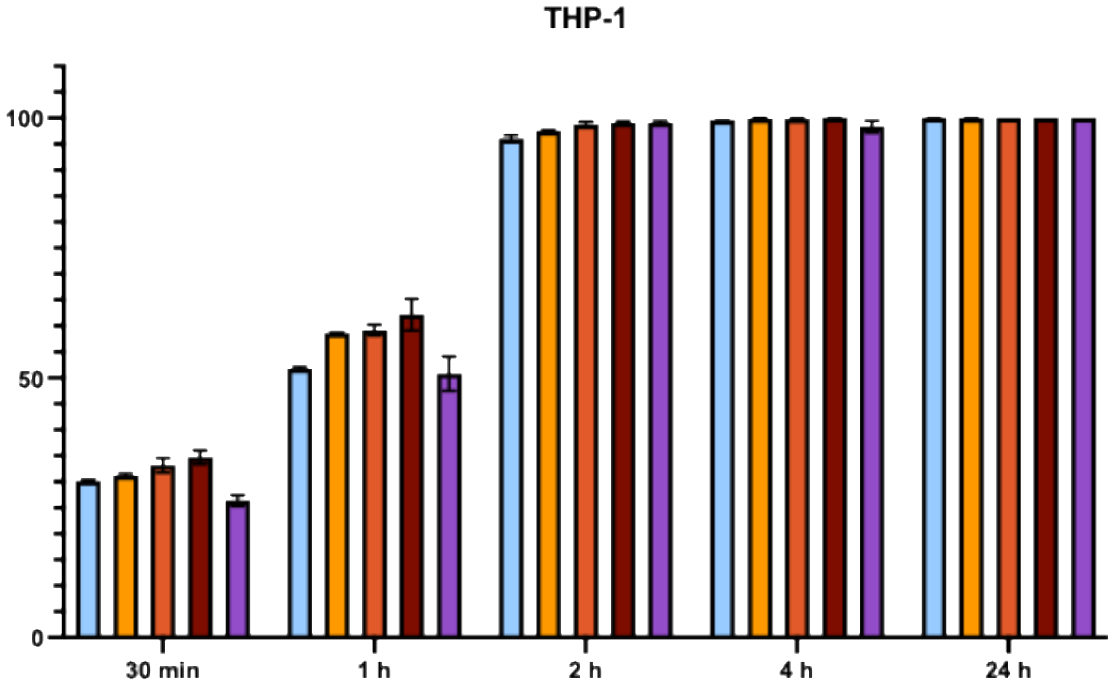


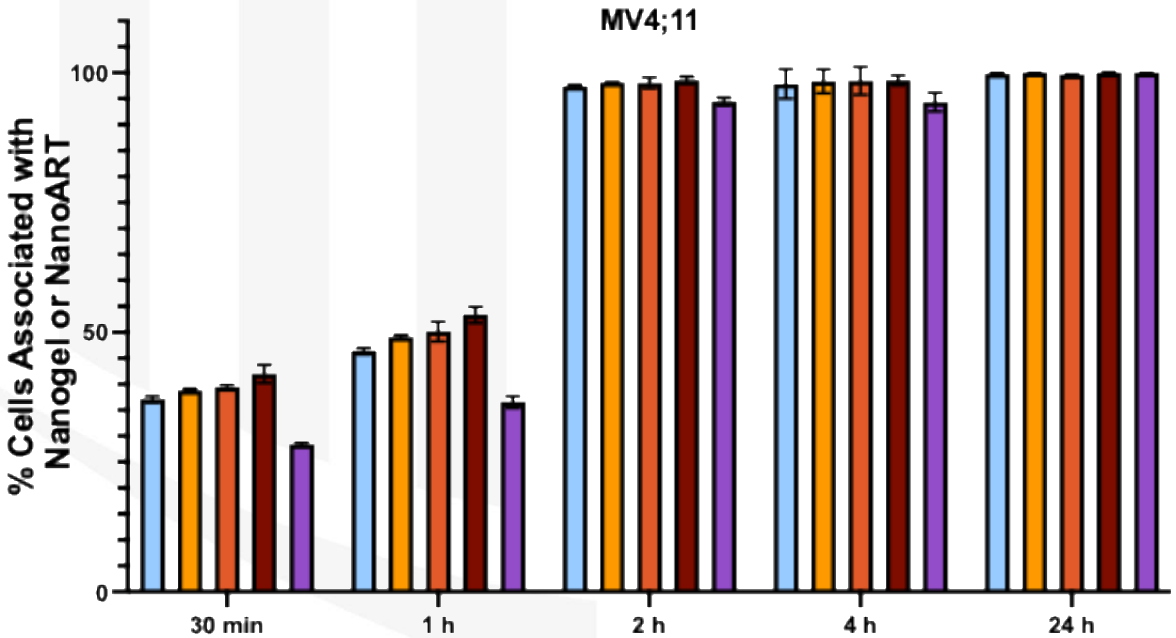


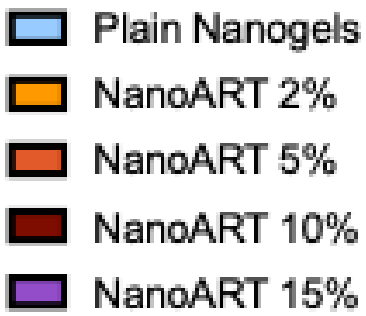
Concentration: 53.7 mg/mL; 37 °C; ART release amount was quantified by ^{1}H NMR CP800 MHz

Time-Dependent Uptake of NanoARTs by Three AML Cell Lines

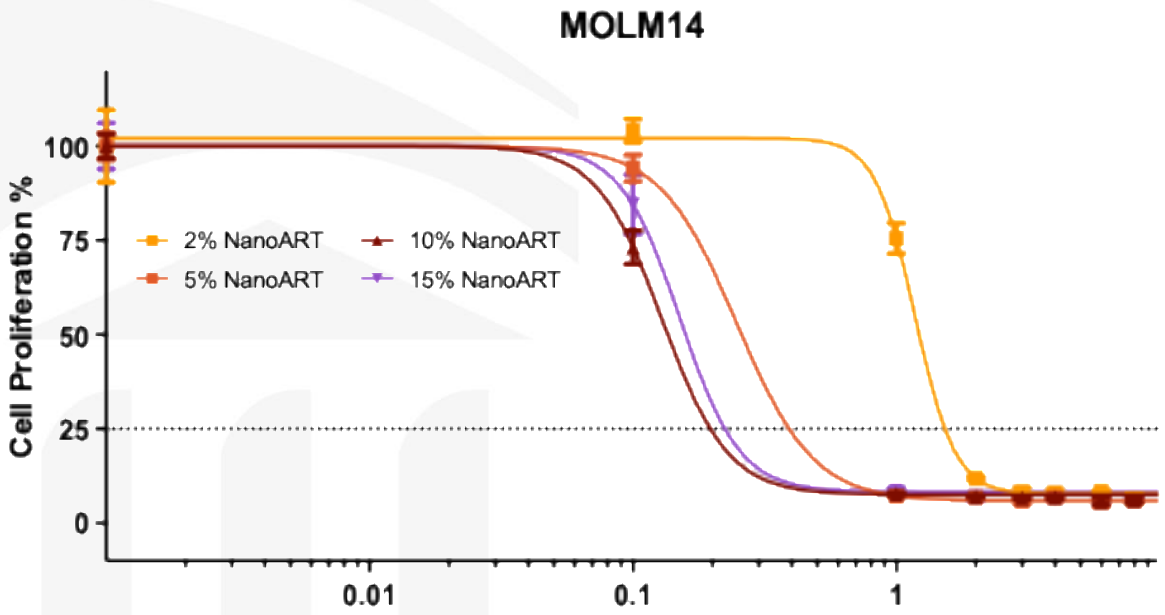


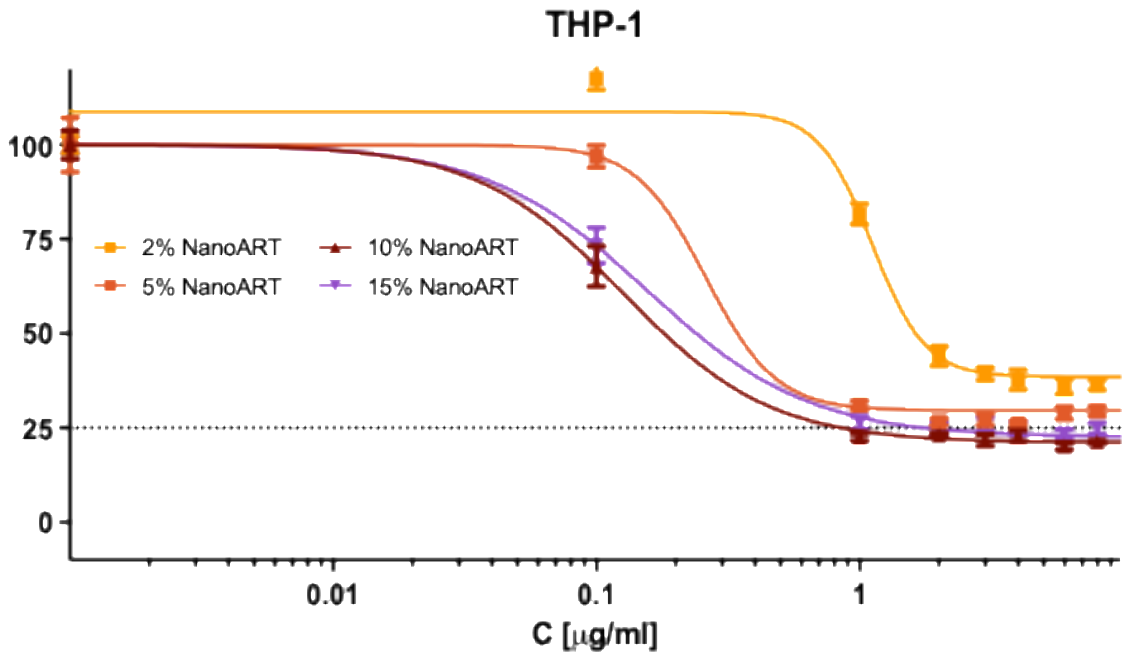


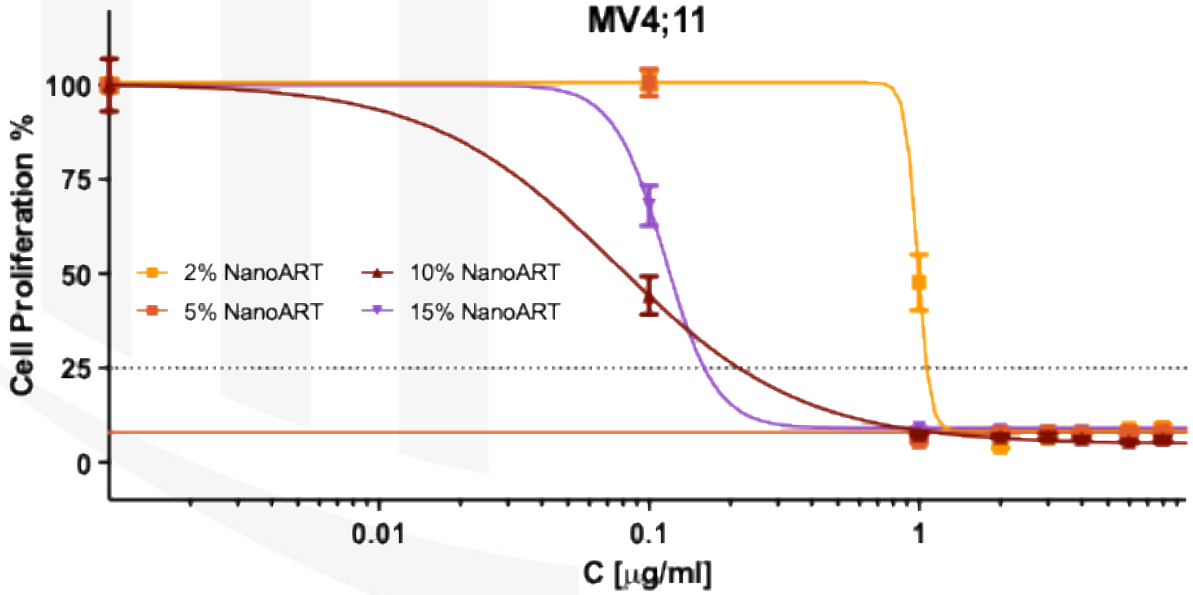




NanoART631 Effectively Killed Three AML Cell Lines



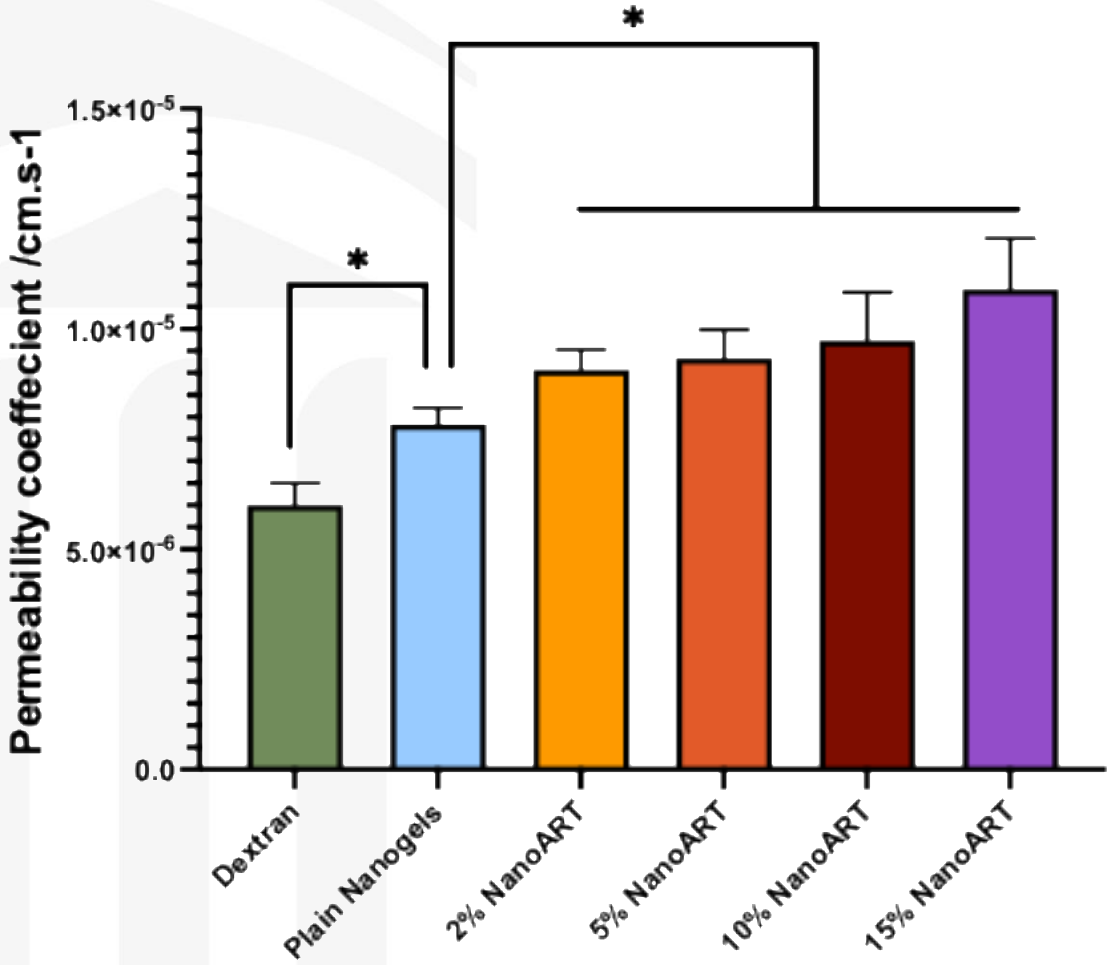


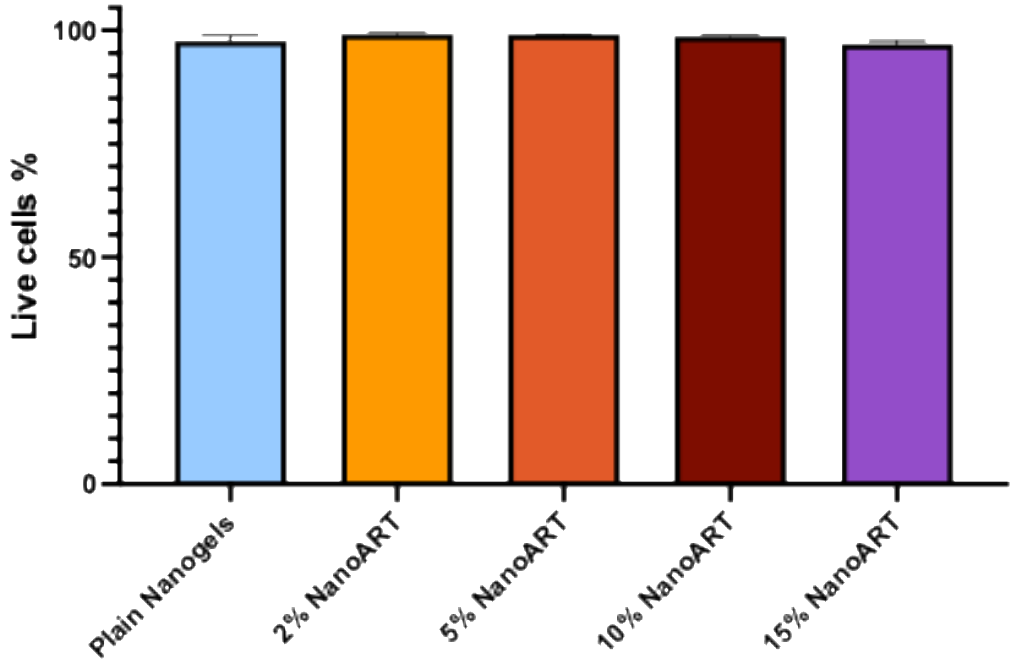


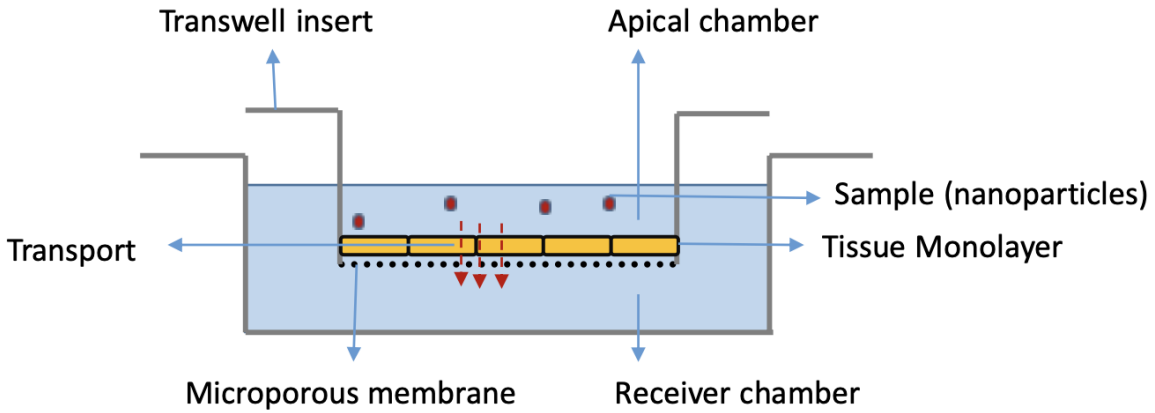
IC_{50} (nM)

Samples	MOLM14	MV4;11	THP-1
ART631	32	27	42
2% NanoART	19	21	23
5% NanoART	23	21	30
10% NanoART	16	8	14
15% NanoART	38	8	26

NanoARTs Penetrated through *In Vitro* Blood Brain Barrier



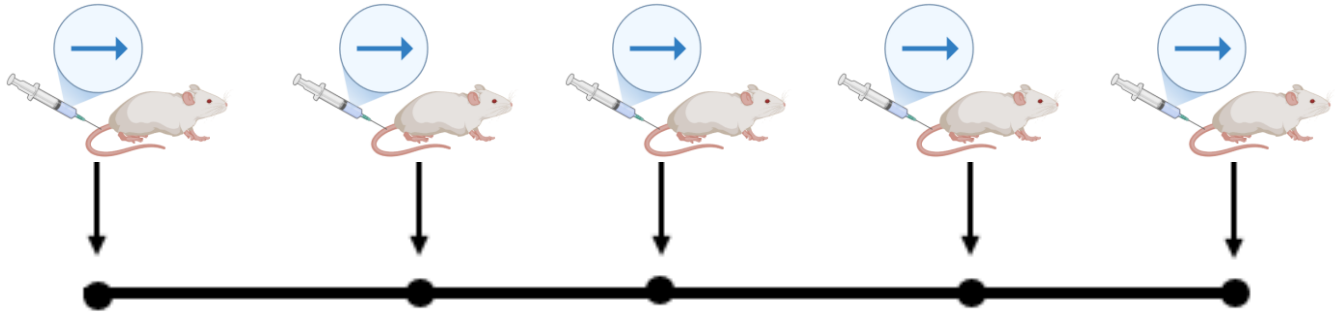




Permeability coefficient of NanoART631s, plain nanogel or dextran (4000 Da) crossing *in vitro* blood-brain barrier (human cortical microvessel endothelial cell monolayer).
*: $p < 0.05$.

Mice Maximum Tolerated Dose (MTD) Study

Method: Intravenous (IV) injection.
Animal model: Female NRG immunodeficient mice, 6 per group.



	Day 0	Day 7	Day 14	Day 21	Day 28
NanoART631 5% Dose	100 mg/kg	200 mg/kg	300 mg/kg	400 mg/kg	500 mg/kg
ART631 Dose	5 mg/kg	10 mg/kg	15 mg/kg	20 mg/kg	25 mg/kg

ALL mice were tolerated with the highest dose (500 mg/kg) of 5% NanoART injection.

The MTD of NanoART is calculated as equivalent to 4.26 mM ART631, which is ~100,000 times more than the in vitro-assessed IC_{50}.

Conclusion

- NanoARTs increased ART631's water solubility >400-fold and sustained its release for at least 35 days.
- NanoARTs were very potent in killing three type of AML cells (MOLM14, THP-1 and MV4;11) with IC_{50}<40 nM.
- NanoARTs were 1.5 times more permeable than 4k Da dextran control across the hCME cell membrane (*in vitro* BBB model).
- NanoARTs were tolerated by NRG mice at a dose of 500mg/kg IV (25mg/kg ART631).

Acknowledgements

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Thank you!

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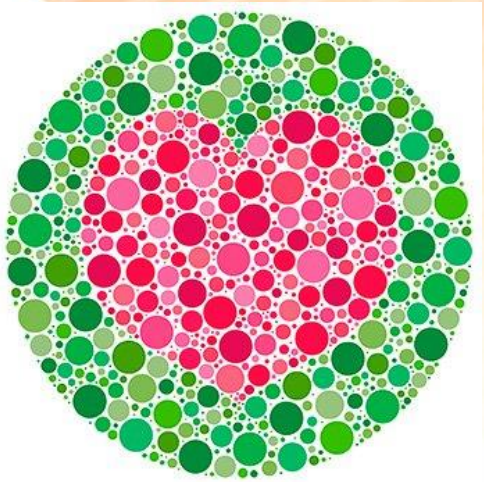

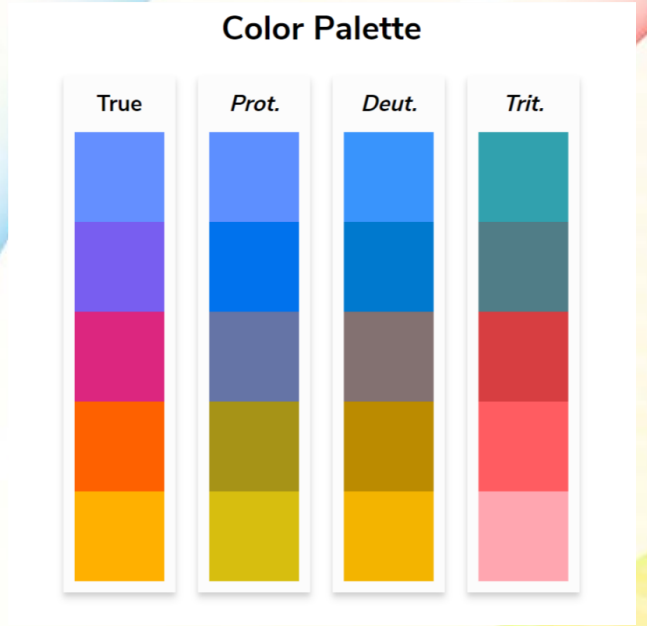

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