

‘Naked’ liposomal delivery to heal a broken heart

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Disclosure of Financial Interest



Founder, Chief Scientific Officer, and hold equity in Bluegrass Pharmaceuticals Inc., which has an exclusive option to license patents related to the technology in this presentation.



>\$20B

Annual healthcare costs for heart attacks

1M

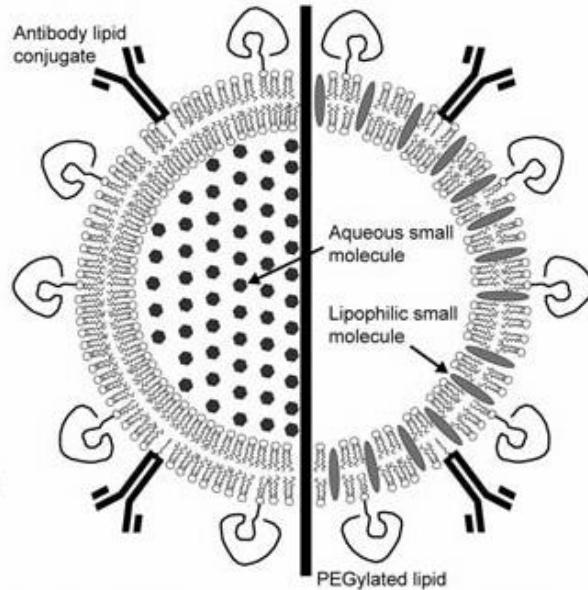
Heart attacks annually in the US

0

Therapies to treat heart attack inflammation

<https://www.cdc.gov/heart-disease/data-research/facts-stats/index.html>

Liposomal Drug Delivery



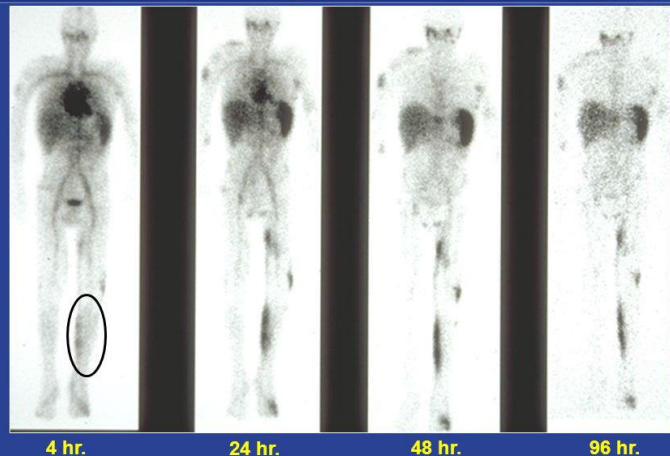
Goal:

Deliver the drug
to the tissue
in the cells
to modify a function

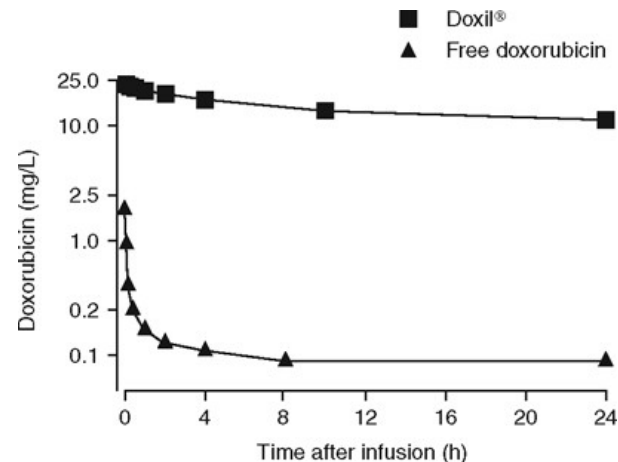
Nardo D et al. Nanomat for Clin Applic. 2020 159-211.

DOXIL – PEGylated Liposomal Delivery

Gamma Scan of Kaposi's Sarcoma Patient



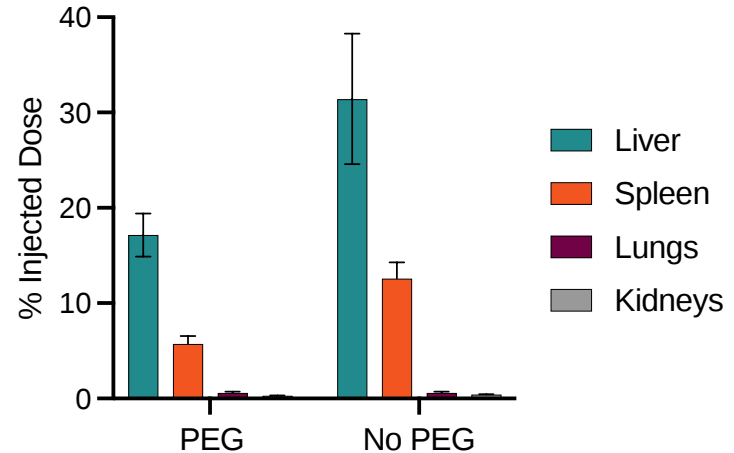
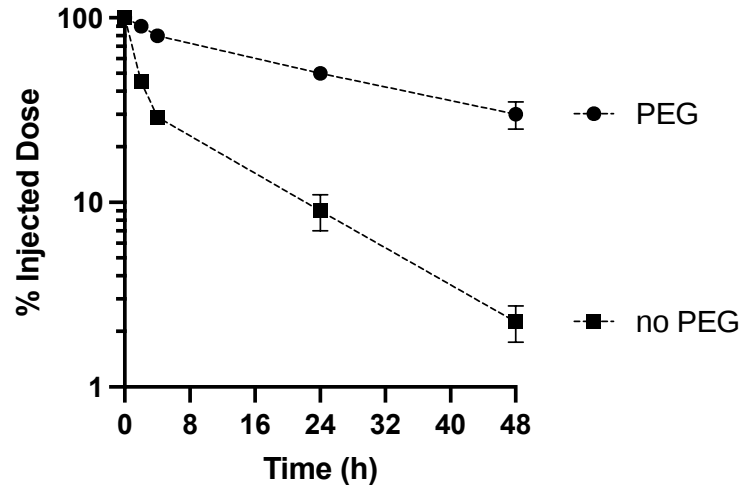
Extended circulation and accumulation in tumors



Alza Oncologic Drugs Advisory Committee Meeting June 8, 1999

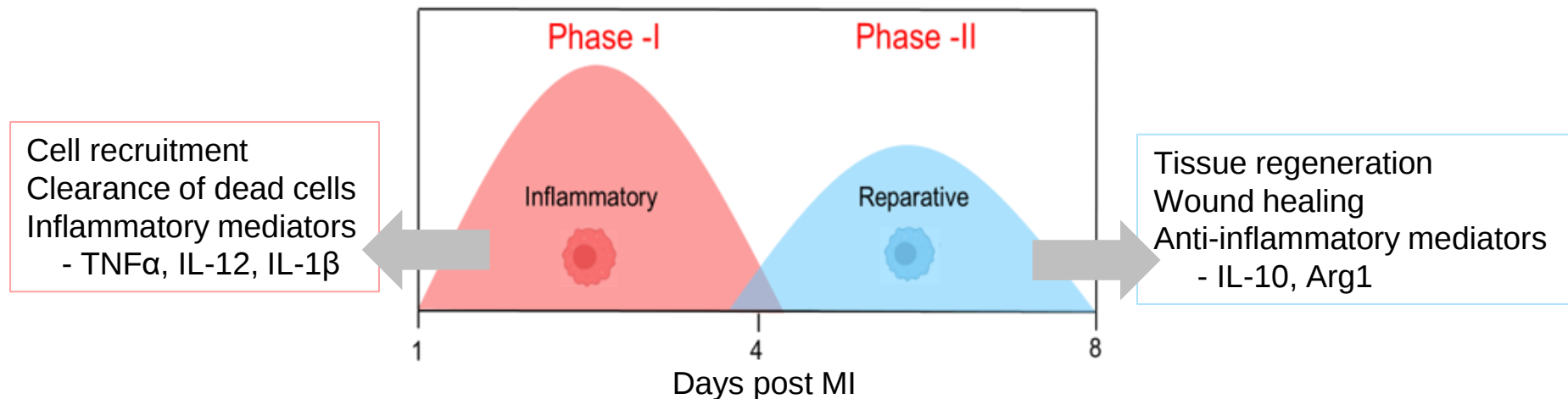
Non-PEGylated Liposomal Delivery

Immune cells remove formulations from circulation



Kierstead et al. J Control Release. 2015 1-9.

Macrophages are a target for post-MI therapy

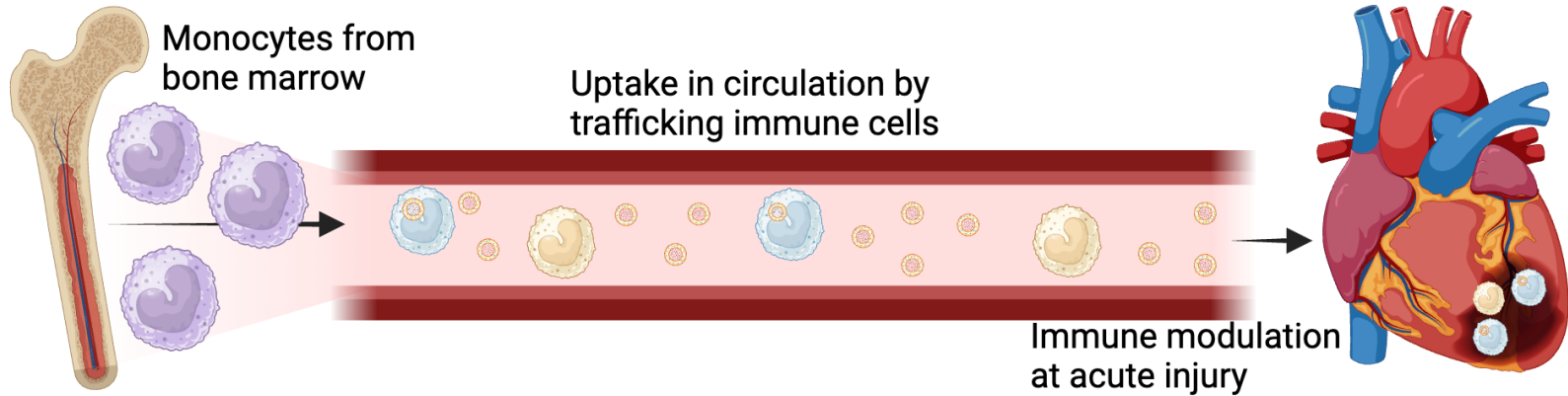


Frantz, et al. *FASEB Journal* 27, 871-881, (2013).
Heidt, et al. *Circ Res* 115, 284-295, (2014).
Dutta & Nahrendorf. *ATVB* 35, 1066-1070, (2015).

Immune suppression can be fatal

Our Premise

Non-PEGylated ('Naked') formulations administered after acute injury are rapidly taken up by trafficking immune cells to modulate inflammation at the site of injury.

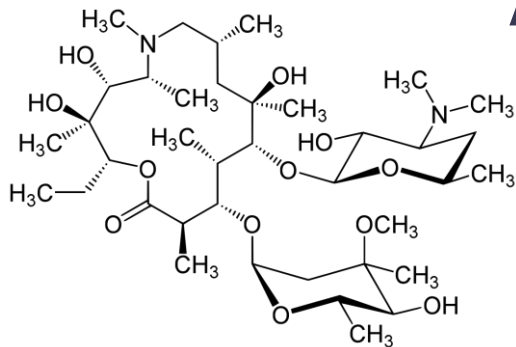


Azithromycin (AZM)

Macrolide antibiotic used by >40 million patients annually

Binds 50S subunit of bacterial ribosome

Azithromycin (AZM)

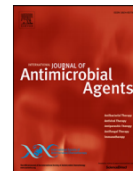


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journal homepage: www.elsevier.com/locate/ijantimicag

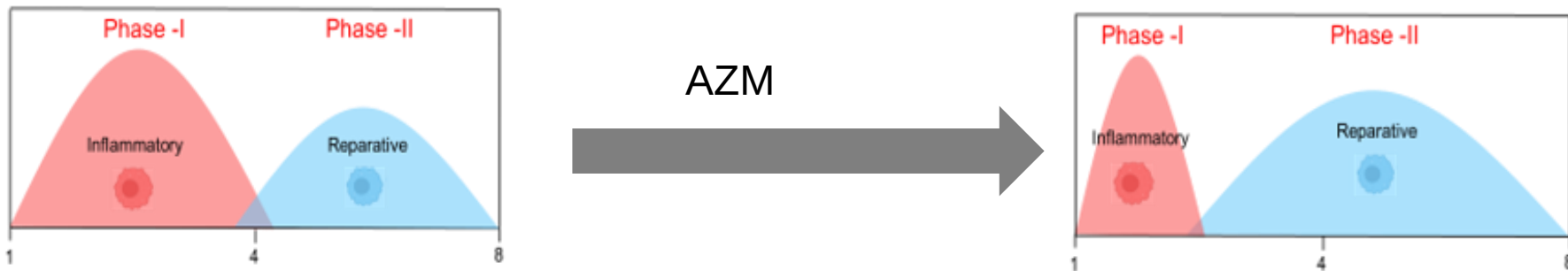


Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial[☆]

Philippe Gautret^{a,b,§}, Jean-Christophe Lagier^{a,c,§}, Philippe Parola^{a,b}, Van Thuan Hoang^{a,b,d}, Line Meddeb^a, Morgane Mailhe^a, Barbara Doudier^a, Johan Courjon^{e,f,g}, Valérie Giordanengo^h, Vera Esteves Vieira^a, Hervé Tissot Dupont^{a,c}, Stéphane Honoré^{i,j}, Philippe Colson^{a,c}, Eric Chabrière^{a,c}, Bernard La Scola^{a,c}, Jean-Marc Rolain^{a,c}, Philippe Brouqui^{a,c}, Didier Raoult^{a,c,*}

Azithromycin-based immune modulation

Azithromycin (AZM) shifts macrophage polarization toward repair to minimize the extent secondary injury



Murphy, et al, *J Antimicrob Chemother* 2009

Feola, et al, *Antimicrob Agents Chemother* 2010

Cory, et al. *J Antimicrob Chemother* 2013

Cory, et al. *J Cyst Fibros*, 2014

Zhang, et al. *J Neuroinflamm*, 2015

Gensel, et al. *Sci Rep* 2017

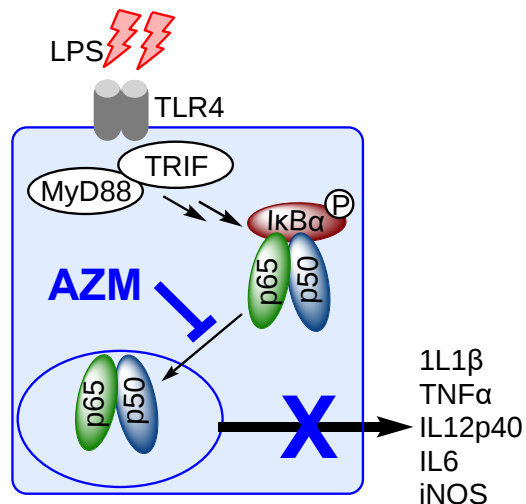
Al-Darraj, et al. *Plos One* 2018

Gensel, et al. *J Neurotrauma*, 2019

Kopper et al. *Front Cell Neurosci*, 2019

Haydar et al., *J Immunol*, 2019

Azithromycin has potential



Murphy, et al, *J Antimicrob Chemother* 2009

Feola, et al, *Antimicrob Agents Chemother* 2010

Cory, et al. *J Antimicrob Chemother* 2013

Cory, et al. *J Cyst Fibros*, 2014

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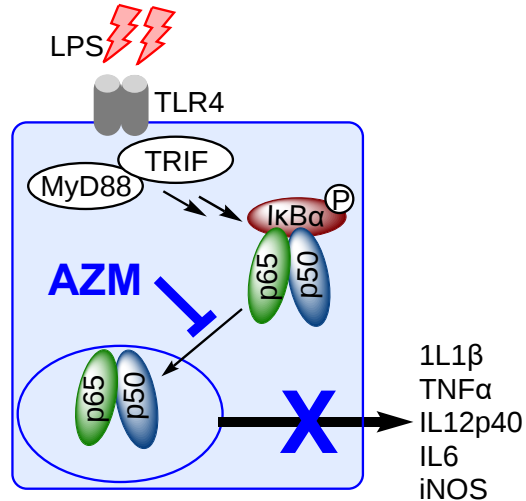
Al-Darraj, et al. *Plos One* 2018

Gensel, et al. *J Neurotrauma*, 2019

Kopper et al. *Front Cell Neurosci*, 2019

Haydar et al., *J Immunol*, 2019

Azithromycin has potential and risk



Issued warning regarding the risk of irregular heart rate

Ray et al. *NEJM*, 2019. 1881-1890.

Murphy, et al, *J Antimicrob Chemother* 2009

Feola, et al, *Antimicrob Agents Chemother* 2010

Cory, et al. *J Antimicrob Chemother* 2013

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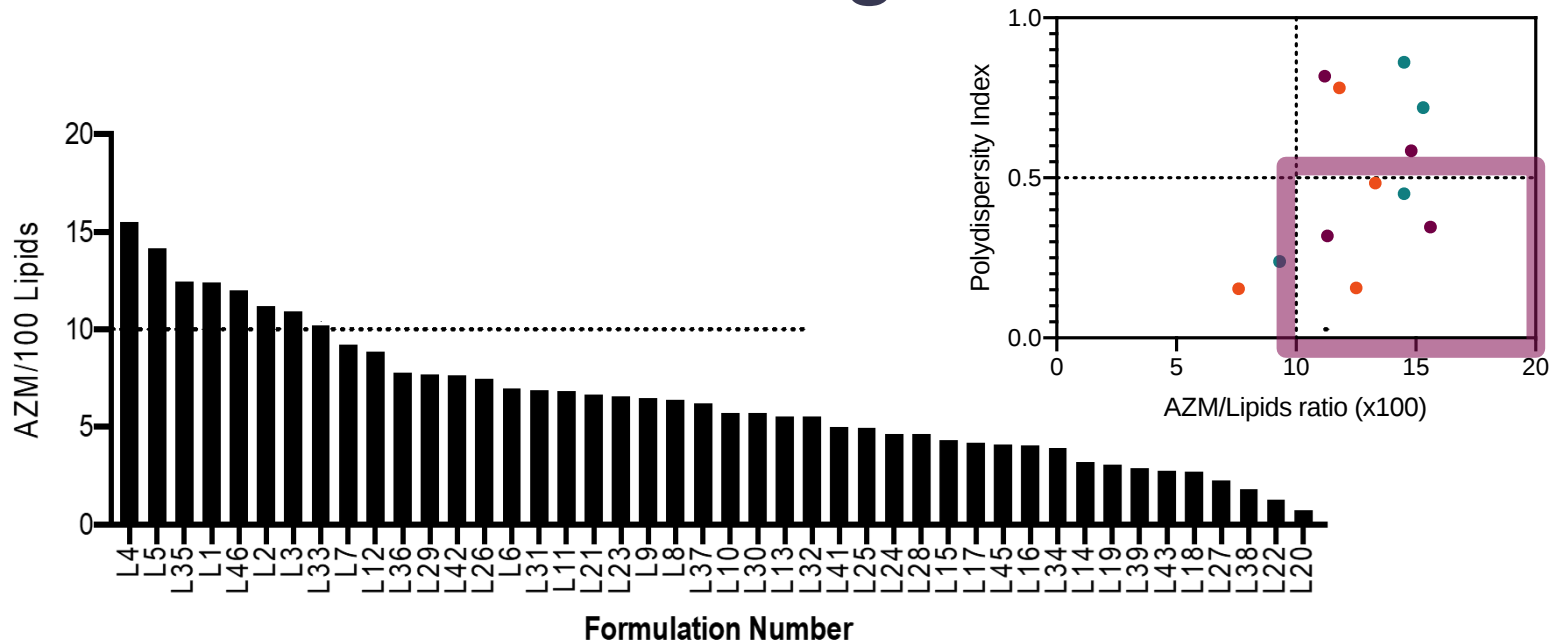
Al-Darraj, et al. *Plos One* 2018

Gensel, et al. *J Neurotrauma*, 2019

Kopper et al. *Front Cell Neurosci*, 2019

Haydar et al., *J Immunol*, 2019

Rational iterative design of 48 formulations

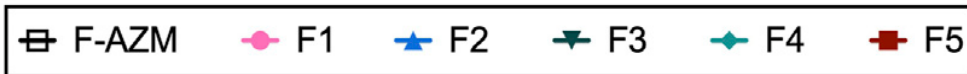
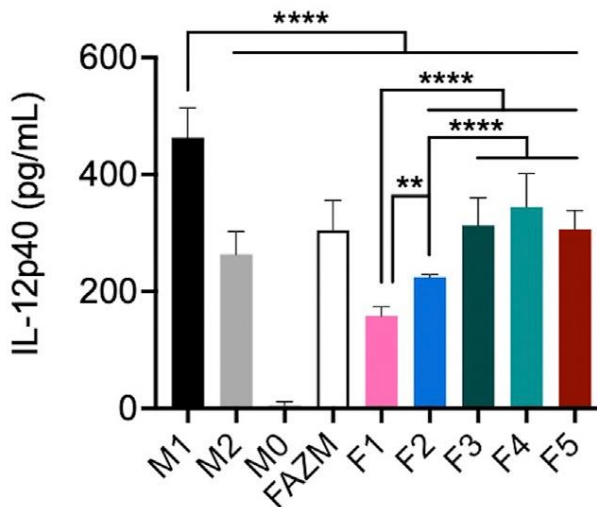
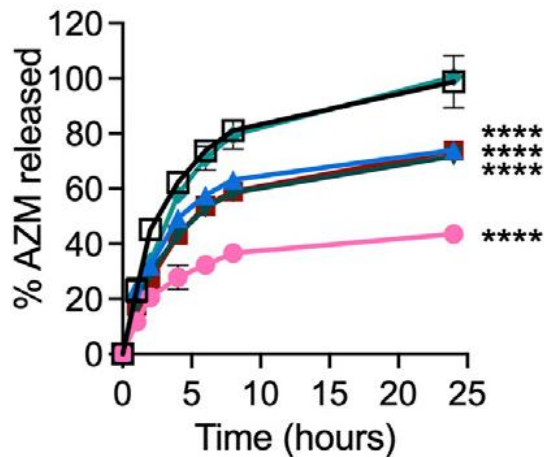


Masud et al. 2022, *Front Drug Deliv*, 2, 908709

Oh et al. 1995, *Antimicrob Agents Chemother*, 39, 2104-2111

Saturated lipids improve AZM activity

Serum stability (50% FBS)

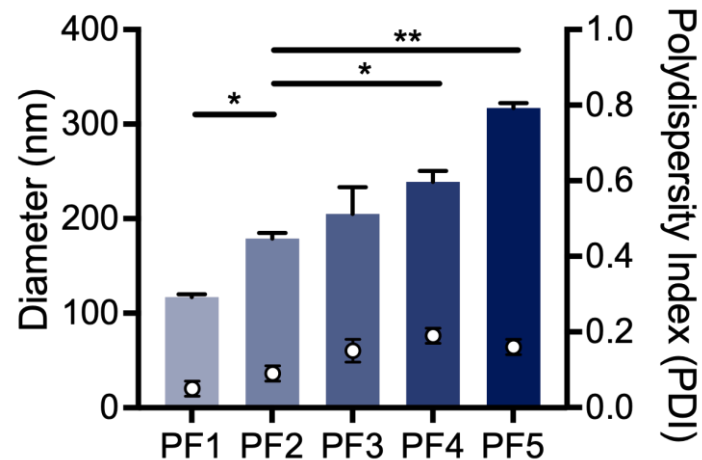


Masud et al. 2022, *Front Drug Deliv*, 2, 908709



Improved manufacturing

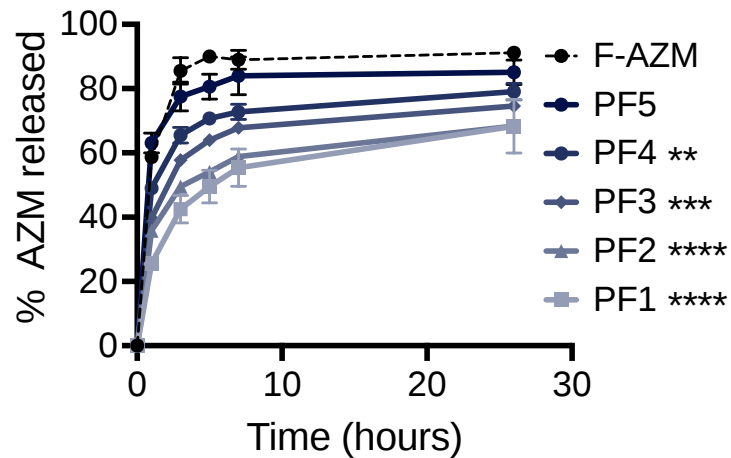
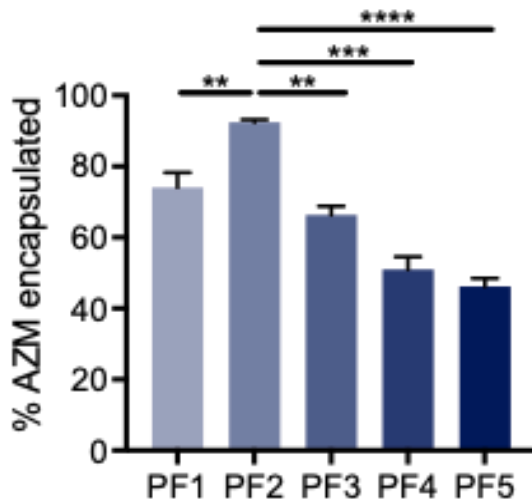
	Formulation component (<i>charge</i>)				Charge Ratio (-/+)	
	DSPC (0)	DSPG (-1)	CHOL (0)	AZM (+2)		
PF1	1	1	1	0.25	1:0.5	
PF2	1	1	1	0.50	1:1.0	
PF3	1	1	1	0.75	1:1.5	
PF4	1	1	1	1.00	1:2.0	
PF5	1	1	1	2.00	1:4.0	



Masud et al. *RSC Pharmaceut.* In Review.

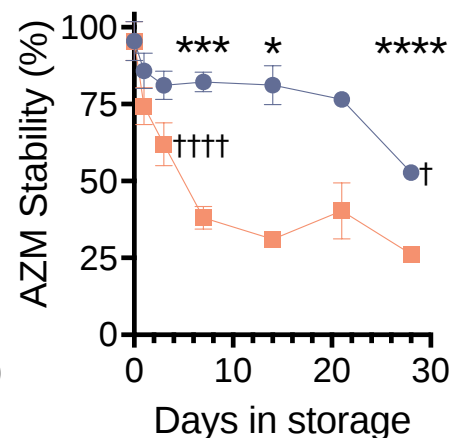
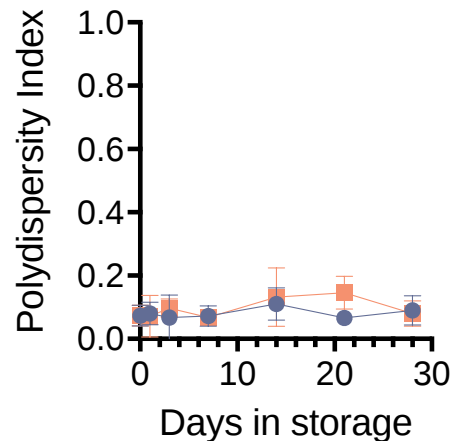
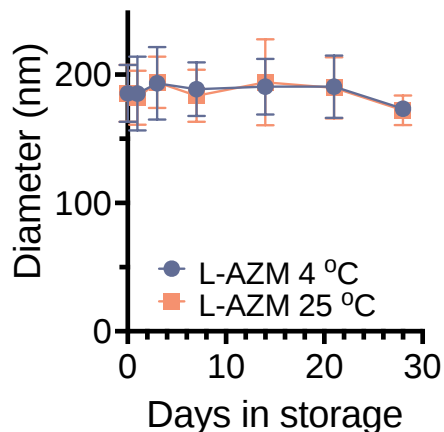
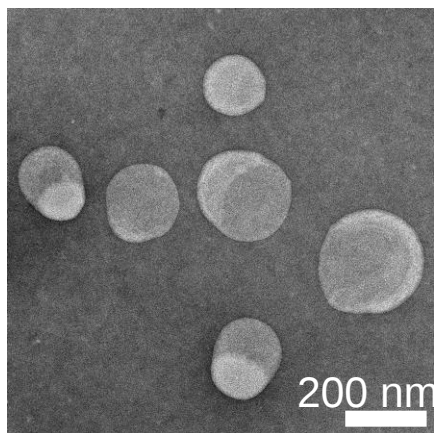


Improved manufacturing



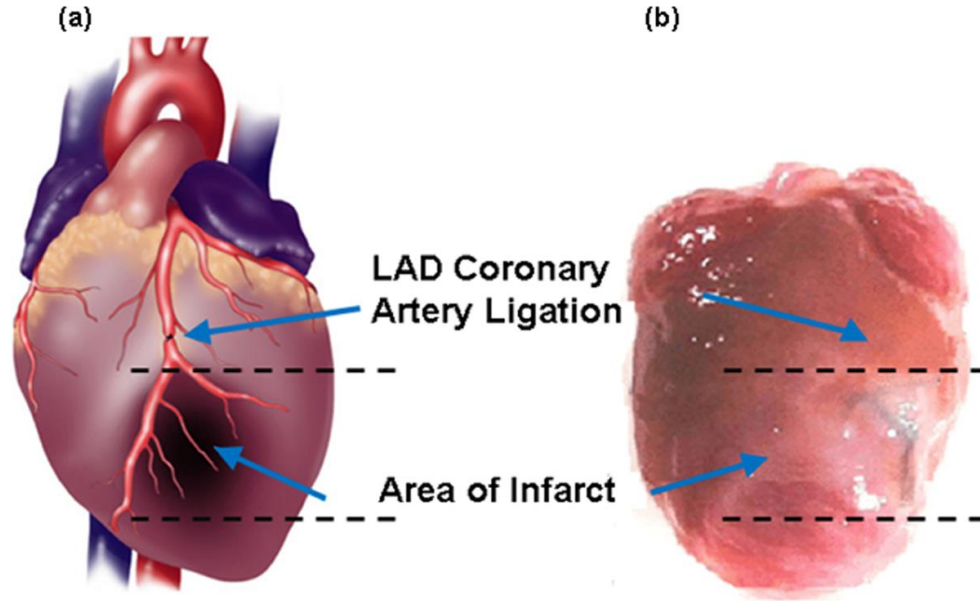
Masud et al. *RSC Pharmaceut.* In Review.

Formulations exhibit long term stability



Masud et al. *RSC Pharmaceut.* In Review.

Murine heart attack model



Liu et al. 2020, Sci Rep. 10, 5983.

Cardiotoxicity in mice

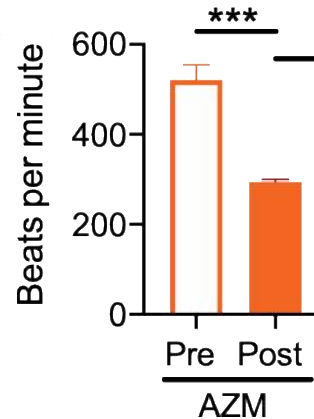
Free AZM after a heart attack:

Reduces heart rate
Associated with mortality

Mortality

1 day: 13/20

3 day: 17/20



Al-Darraj et al. 2020, Sci Rep. 10, 16596.

Cardiotoxicity in mice is reduced with L-AZM

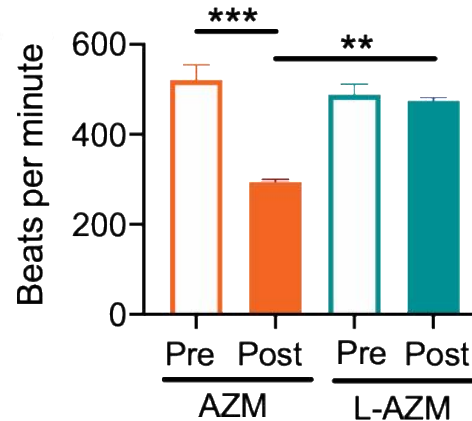
Mortality

1 day: 13/20 0/20

3 day: 17/20 2/20

Free AZM after a heart attack:

Reduces heart rate
Associated with mortality

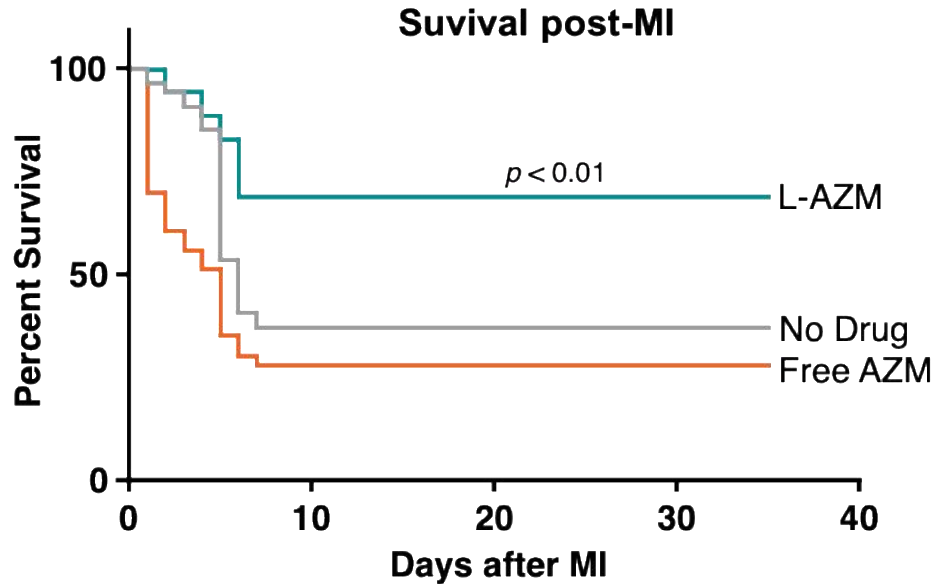


L-AZM after a heart attack:

Maintains heart rate
Reduces mortality

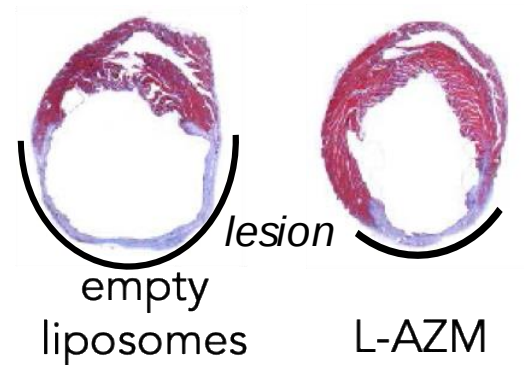
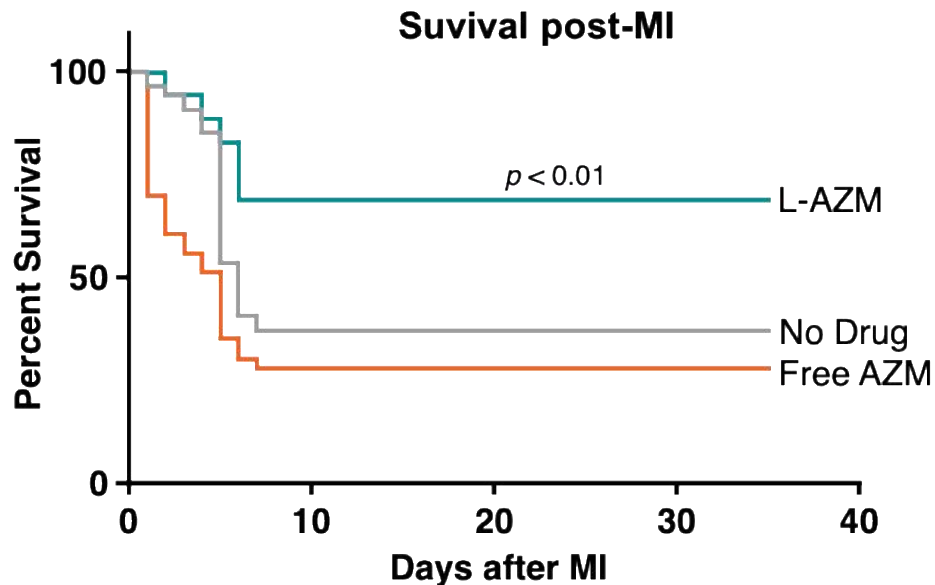
Al-Darraj et al. 2020, Sci Rep. 10, 16596.

L-AZM improves survival in mice



Al-Darraj et al. 2020, Sci Rep. 10, 16596.

L-AZM reduces scar size



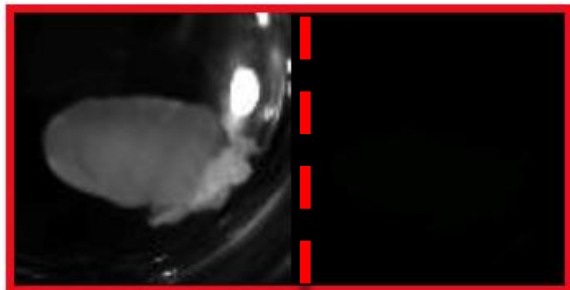
20% improved ejection fraction

Al-Darraj et al. 2020, Sci Rep. 10, 16596.

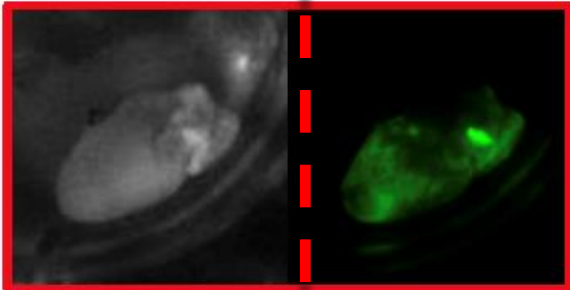
Naked formulations accumulate in the heart

bright field | fluorescent

*Sham
Surgery*



MI

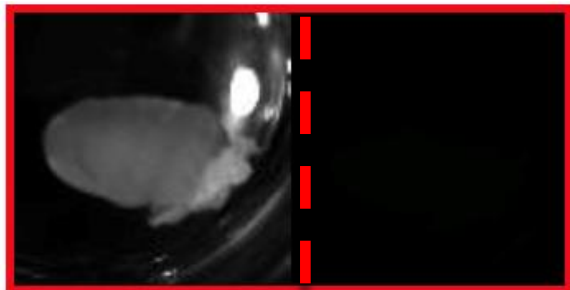


Al-Darraj et al. 2020, Sci Rep. 10, 16596.

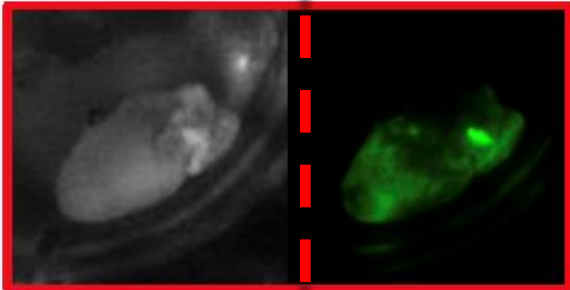
Naked formulations accumulate in the heart

bright field | fluorescent

Sham
Surgery

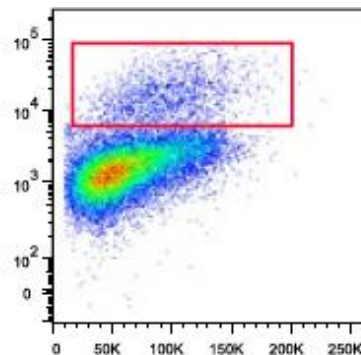


MI

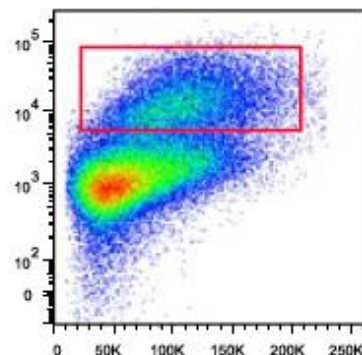


Liposome
DiD

In macrophages



Sham



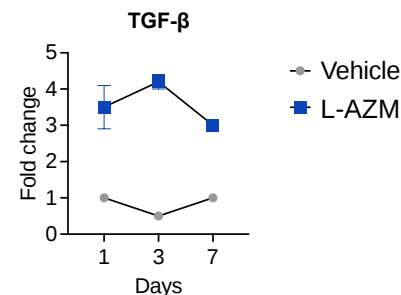
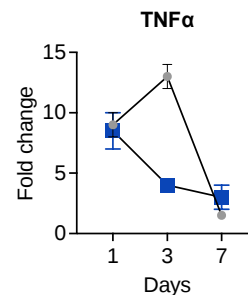
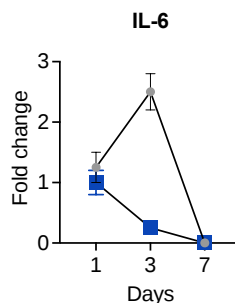
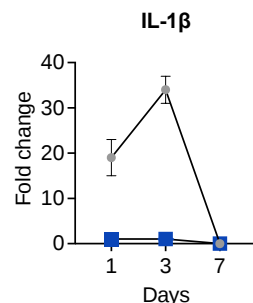
MI

Gating: CD45+ Ly6G- F4/80+

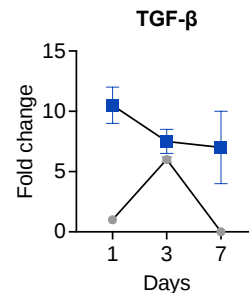
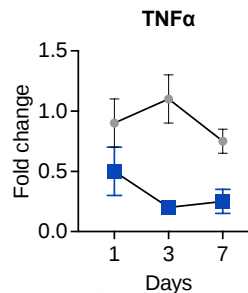
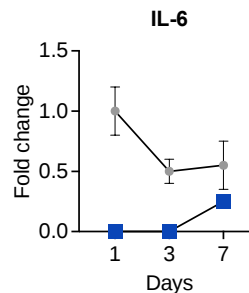
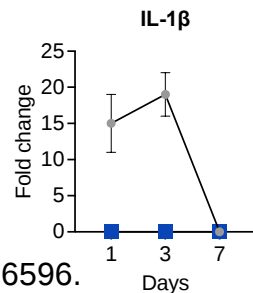
Al-Darraj et al. 2020, Sci Rep. 10, 16596.

L-AZM promotes a reparative phenotype

Cardiac
Tissue

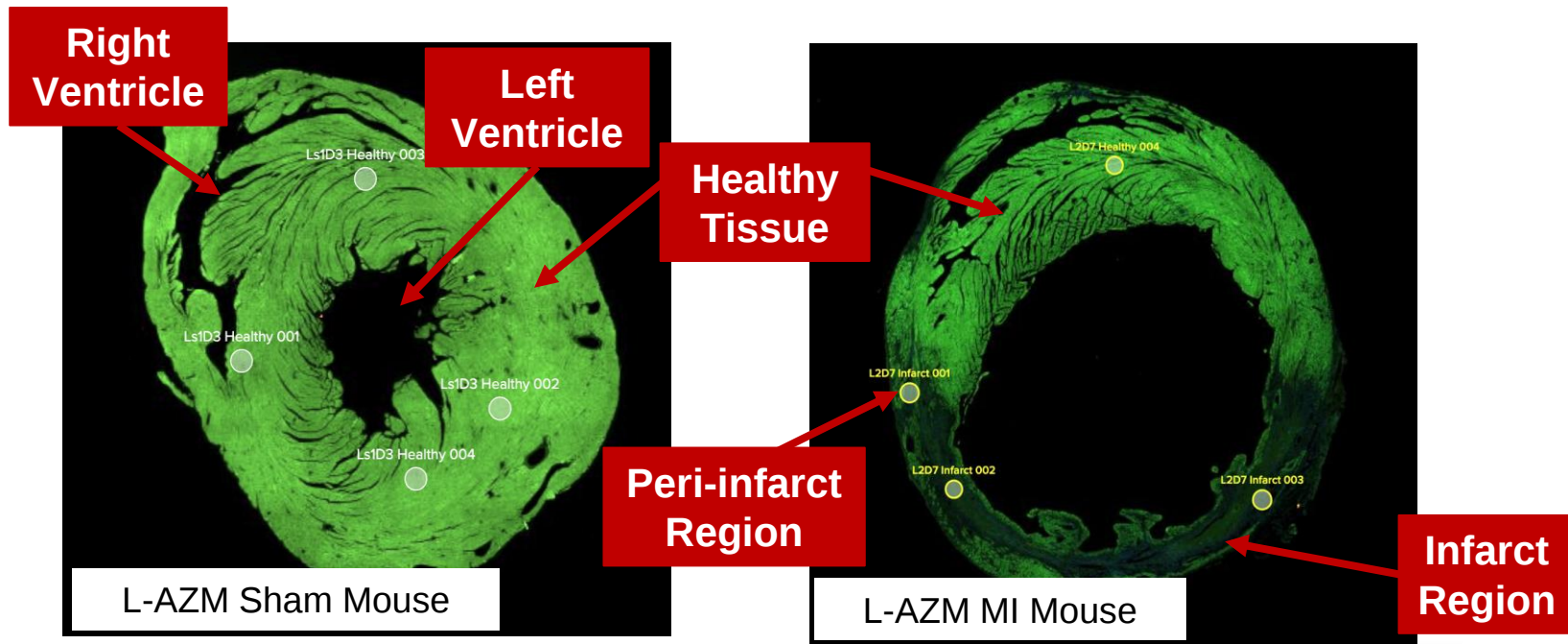


Peripheral
Blood



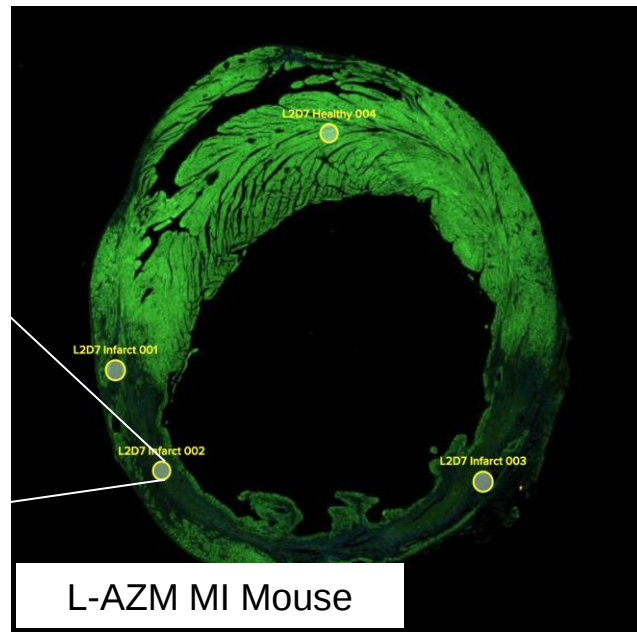
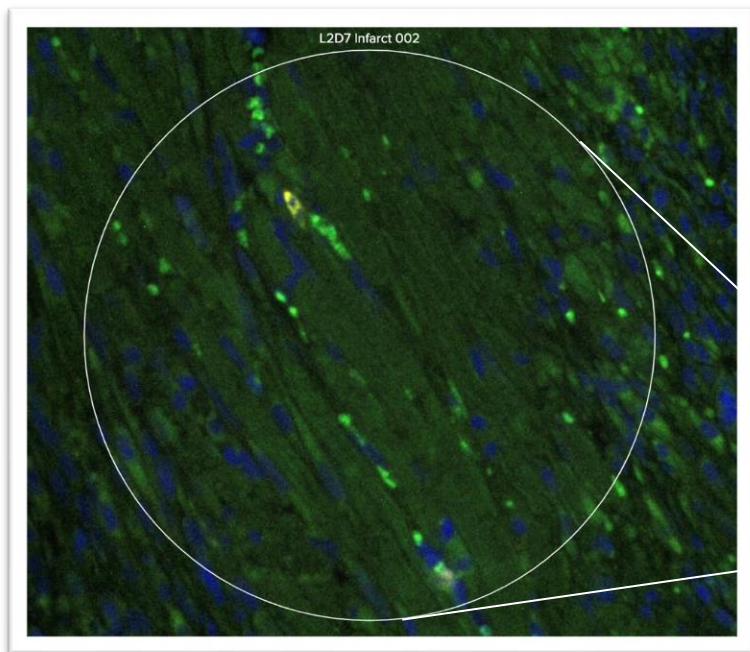
Al-Darraj et al. 2020, Sci Rep. 10, 16596.

Digital spatial profiling of treated mice



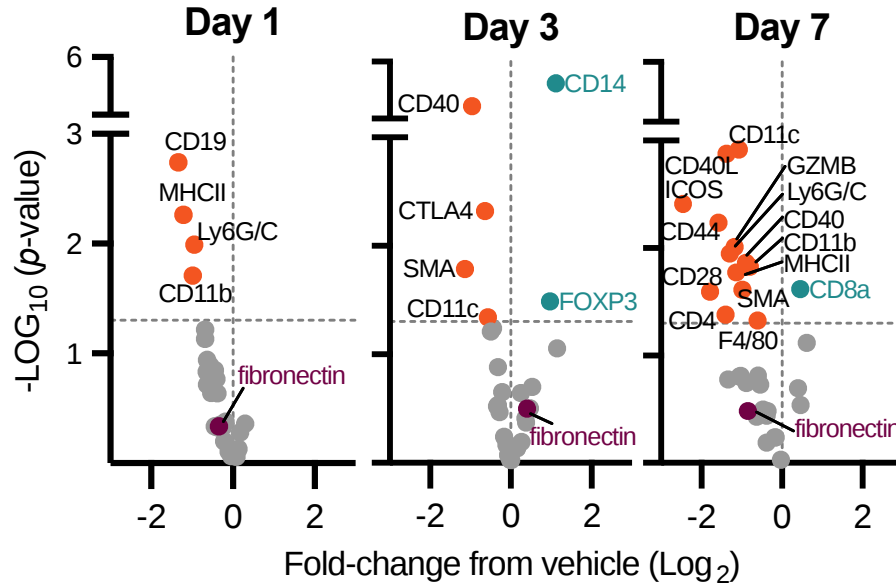
Unpublished

Digital spatial profiling of treated mice



Unpublished

Naked L-AZM reduces inflammation

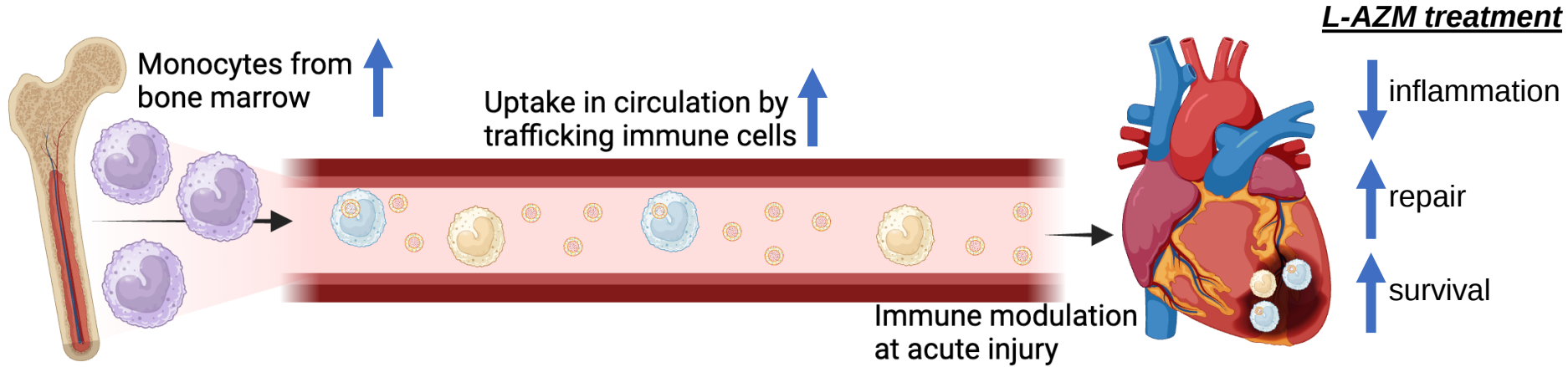


Immune markers are reduced with L-AZM

Fibronectin levels are unchanged with L-AZM

Unpublished

Summary



Conclusions

Natural phagocyte activity helps deliver nanoparticles to acute injury.

L-AZM reduces inflammation, promotes repair, and improves survival.

‘Naked’ delivery offers a unique approach to treat sterile inflammation.

Ongoing studies focus on elucidating the mechanism of delivery, biodistribution and pharmacokinetics, and large animal efficacy studies.

Thank you!

Venditto Lab

Priyanka Tripathi, PhD

Nabilah Ibnat, PhD → **Poster 364**

Kaysi Lee

Julian Mory → **Poster 131**

Diariis Baez Maldonado

Areli Medina Hernandez

Hannah Herrmann

Justin Hornaday

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KSCHIRT

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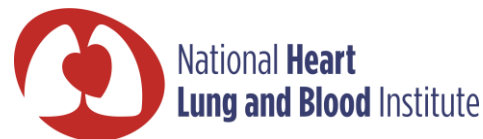
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PHILADELPHIA, PA
JULY 13-18, 2025

**NEXT-GENERATION
DELIVERY INNOVATIONS**

Thank you!



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