

Targeted delivery of a microRNA mimic as a novel approach to therapy for malignant pleural mesothelioma

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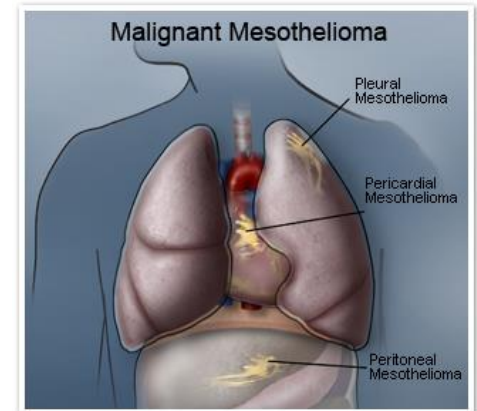
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Disclosures

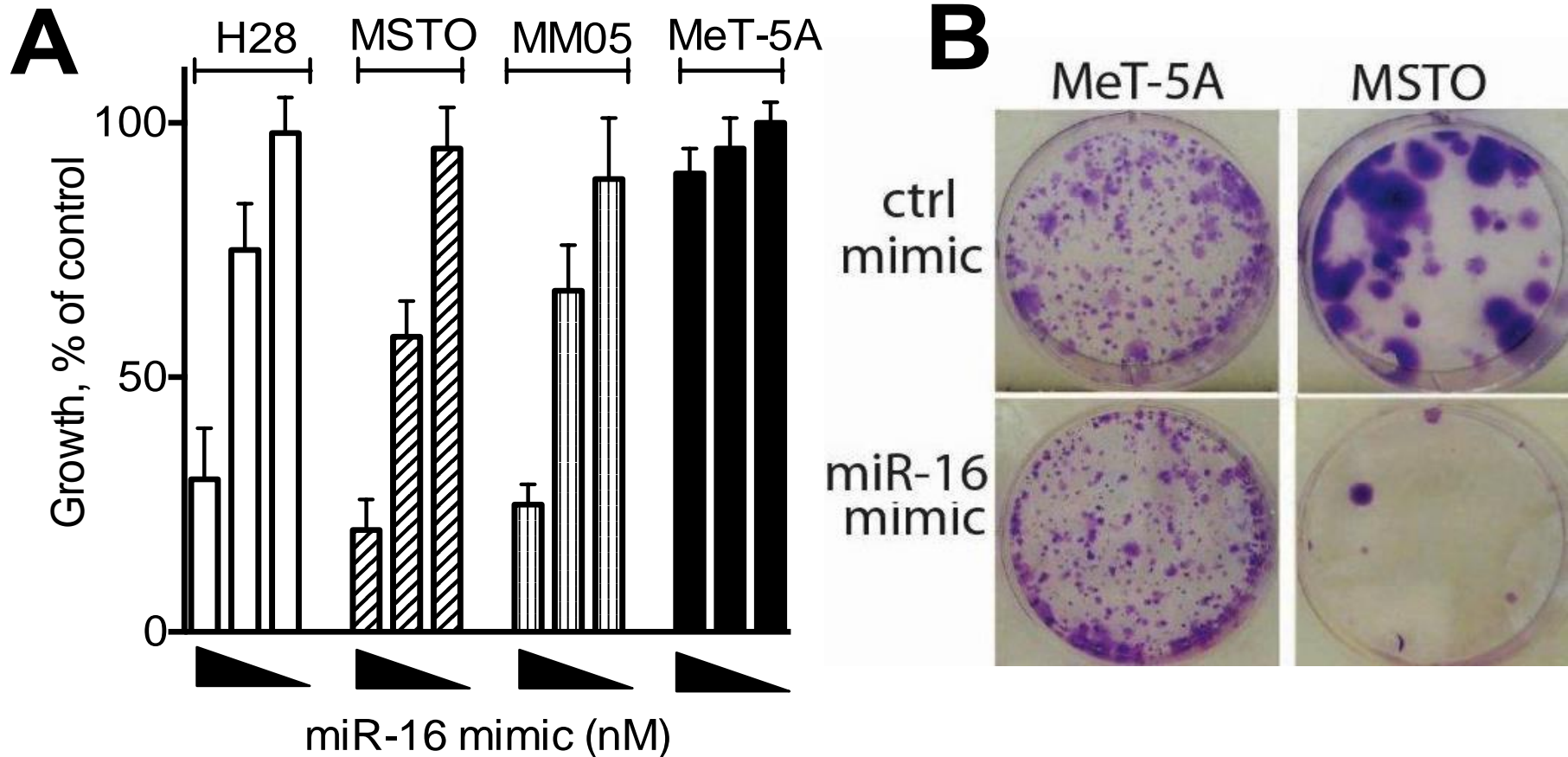
- Nothing to disclose

Malignant pleural mesothelioma (MPM): a cancer with poor prognosis & few treatments

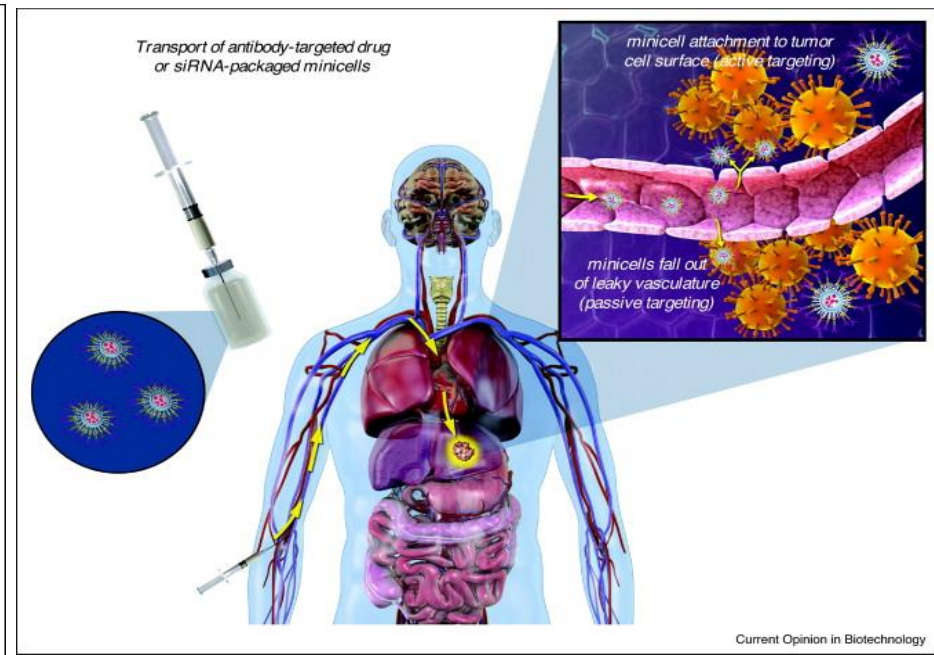
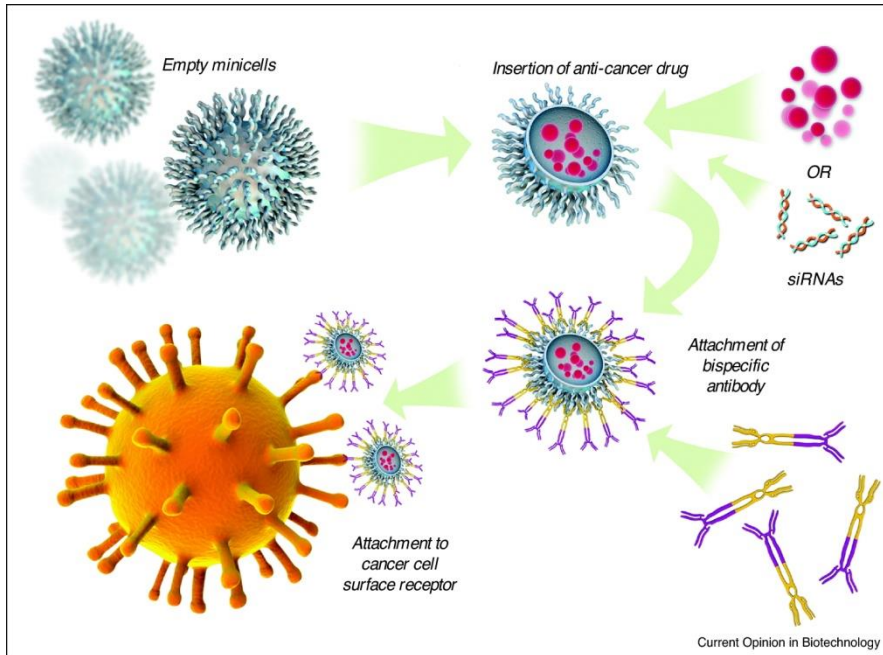
- Asbestos-related cancer arising from the mesothelium
- Resistant to Treatment: Median survival of 12 months
- 30-40 years between asbestos exposure and diagnosis
- Approximately 700 new cases/year in Australia
- **Potentially resectable disease (selected patients)**
 - Combined modality therapy: Chemotherapy followed by surgery and radiotherapy
- **Unresectable disease**
 - Chemotherapy (~50-60%)
 - Palliation, best supportive care (40-50%)
 - Experimental



microRNA expression is repressed in MPM: restoration by mimics inhibits growth

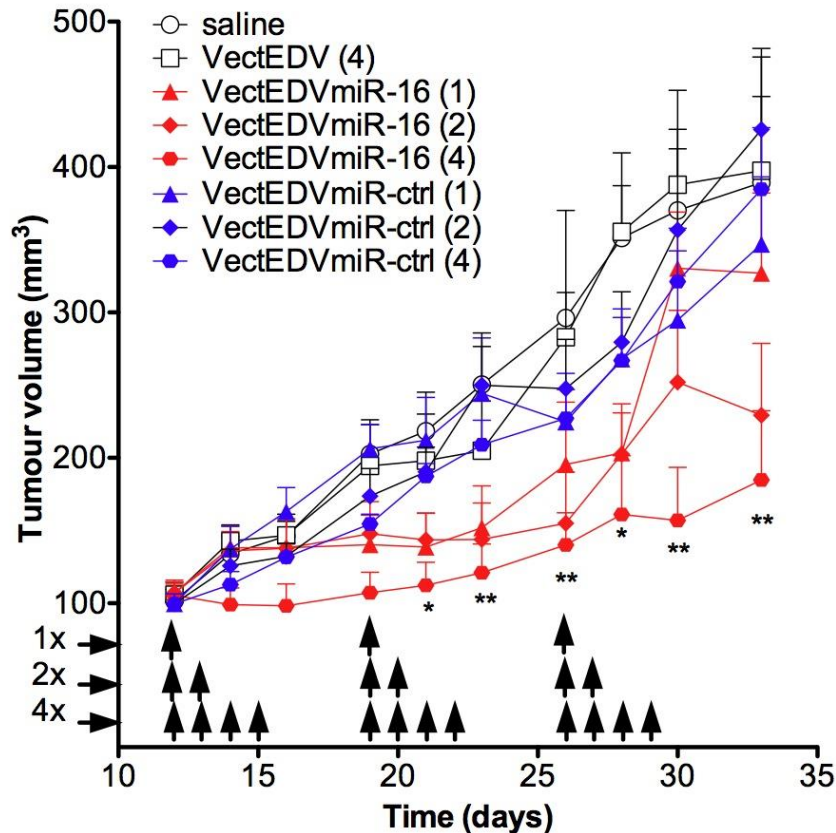


Clinical application of mimics *in vivo*: EDVs are a solution to the delivery problem



miR-16-loaded, EGFR-targeted, EDVs inhibit MPM xenograft tumour growth

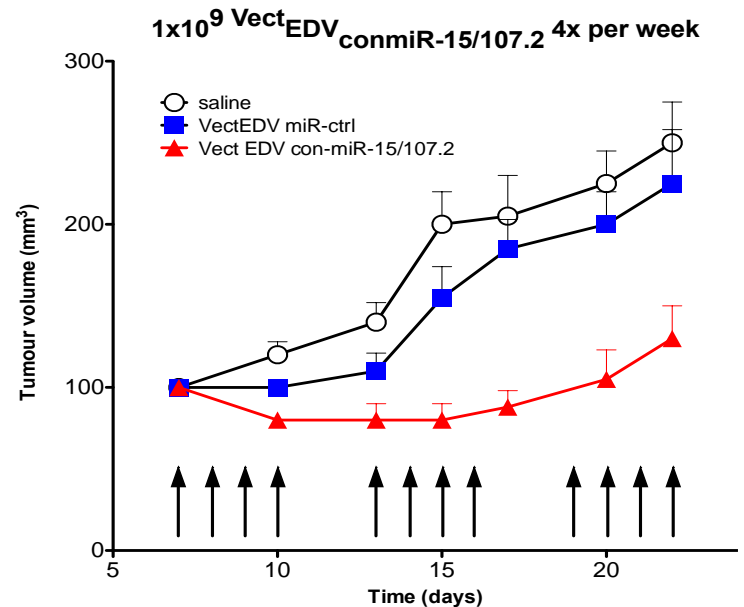
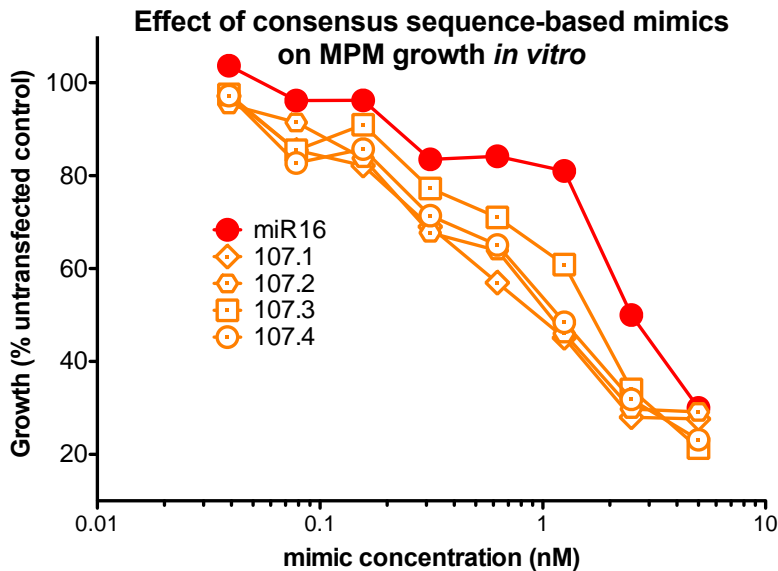
1×10^9 VectEDVmiR-16 1,2 or 4x per week



Mimics based on the miR-15/16 family consensus are active tumour suppressors

	*	#
hsa-miR-107	AGCAGC	AUUGUACAGGGCUAUCA
hsa-miR-103	AGCAGC	AUUGUACAGGGCUAUGA
hsa-miR-15a	UAGCAGC	ACAUAUUGGUUUGUG
hsa-miR-15b	UAGCAGC	ACAUCAUGGUUUACA
hsa-miR-16	UAGCAGC	ACGUAAAUAUUGGCG
hsa-miR-195	UAGCAGC	ACAGAAAUAUUGGCC
hsa-miR-497	CAGCAGC	ACACUGUGGUUUGU
hsa-miR-503	UAGCAGC	GGGAACAGUUCUGCAG
hsa-miR-424	CAGCAGC	AAUUCAUGUUUUGAA
hsa-miR-646	AAGCAGC	UGCCUCUGAGGC

CONSENSUS	U	A	G	C	A	G	C	A	C	A	u	u	A	U	G	U	U	G	C	G			
>miR-16	u	a	g	c	a	g	c	a	c	g	u	a	a	a	u	u	g	g	c	g			
>miR-15a	u	a	g	c	a	g	c	a	c	a	u	a	a	u	g	u	u	g	u	g			
>miR-15b	u	a	g	c	a	g	c	a	c	a	u	c	a	u	g	u	u	a	c	a			
>miR-195	u	a	g	c	a	g	c	a	c	a	g	a	a	a	u	u	g	g	c				
>miR-497	c	a	g	c	a	g	c	a	c	a	c	u	g	u	g	u	u	g	u				
>miR-103	a	g	c	a	g	c	a	u	u	g	u	a	c	a	g	g	g	c	u	a	u	g	a
>miR-107	a	g	c	a	g	c	a	u	u	g	u	a	c	a	g	g	g	c	u	a	u	c	a



Meso-miR-1: a phase 0/1 clinical trial of TargomiRs

- Delivery of novel sequences using EDVs – “TargomiRs”
- Phase 0/1 trial to determine biodistribution, safety and optimal dose of TargomiRs in MPM and NSCLC patients
- Involves clinicians at 3 Sydney hospitals
- Protocol for biodistribution (phase 0) and optimal dose (phase I) approved
- Trial to commence in July

Acknowledgements

ADRI

Michaela Kirschner, Yuen Yee Cheng,
Casey Wright, Marissa Williams, Anthony
Linton, Steven Kao, Nico van Zandwijk

Baird Institute

Brian McCaughan,
James Edelman, Michael Vallely

Flinders Medical Centre, Adelaide

Sonja Klebe, Doug Henderson

EnGeneIC

Jocelyn Weiss, Nancy Mugridge,
Jennifer MacDiarmid, Himanshu Brahmhatt

University of Sydney

Nicola Armstrong

Bill Walsh Cancer Centre, Sydney

Rozelle Harvie, Nick Pavlakis, Amanda
Hudson, Stephen Clarke

