Thermal focused ultrasound ablation combined with vascular normalization drives anti-tumor immunity

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University of Virginia
CRS 2025 Annual Meeting and Exposition
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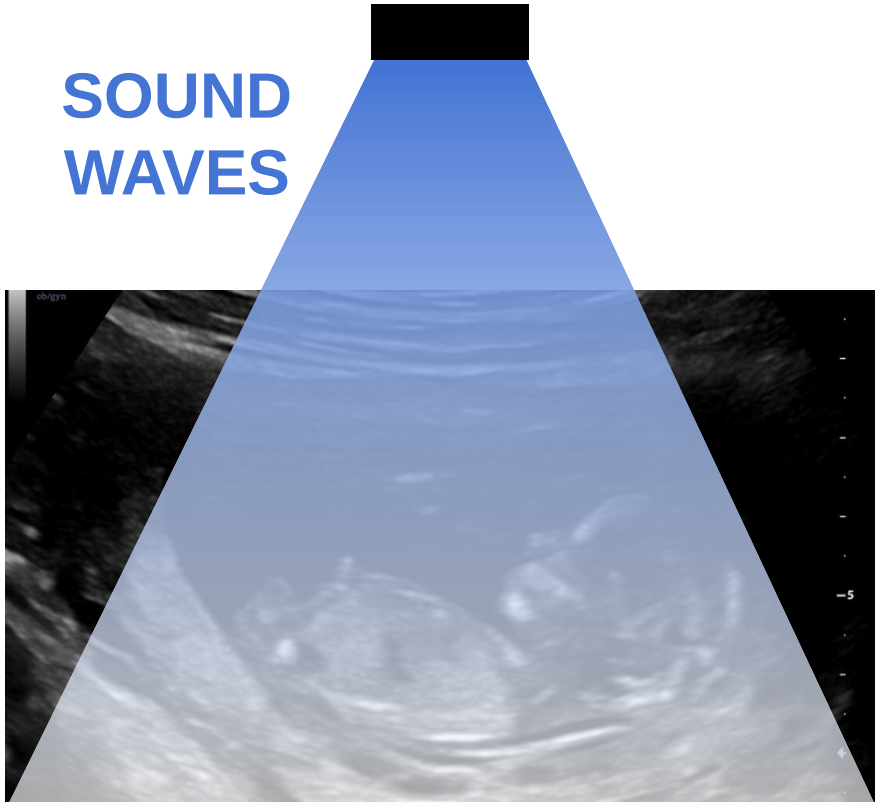
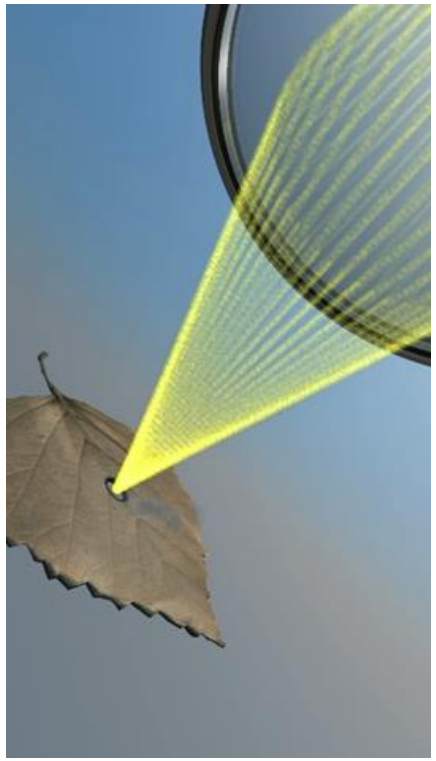
Focused Ultrasound (FUS): Concentrated Ultrasonic Energy

Diagnostic Ultrasound

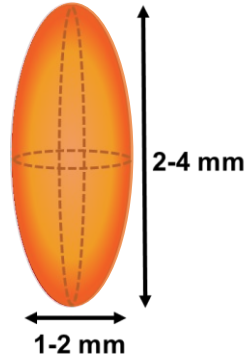


Imaging

Focusing Sound Waves



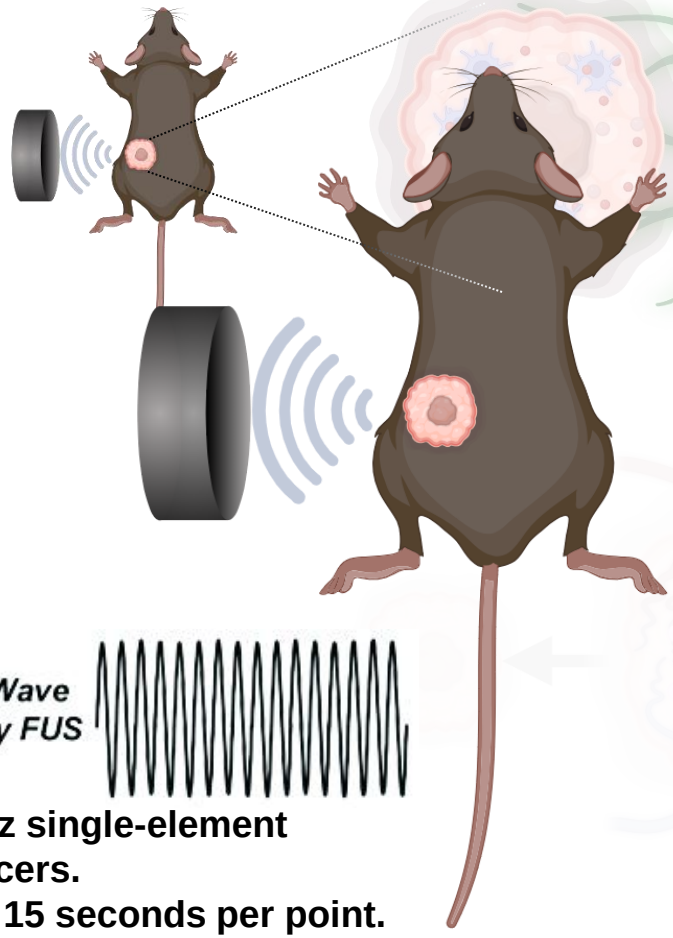
Mechanical and/or Thermal Effects



Therapy

UVA FOCUSED ULTRASOUND

Thermal FUS (tFUS) augments cancer immunity cycle



Tumor antigen

Dendritic cells

Naïve T cells

Antigen-experienced effector T cells

Continuous Wave High Intensity FUS

- 3.78 MHz single-element transducers.
- 18W for 15 seconds per point.
- Treatment points 1.5 mm apart.
- Tumors were treated in 2 or 3 planes.
- Planes 2 mm apart.

Takeaway: tFUS can destroy tumor tissue and induce local immune responses against the tumor but is often insufficient to generate long-term effects

BioRender, adapted from Rich Price

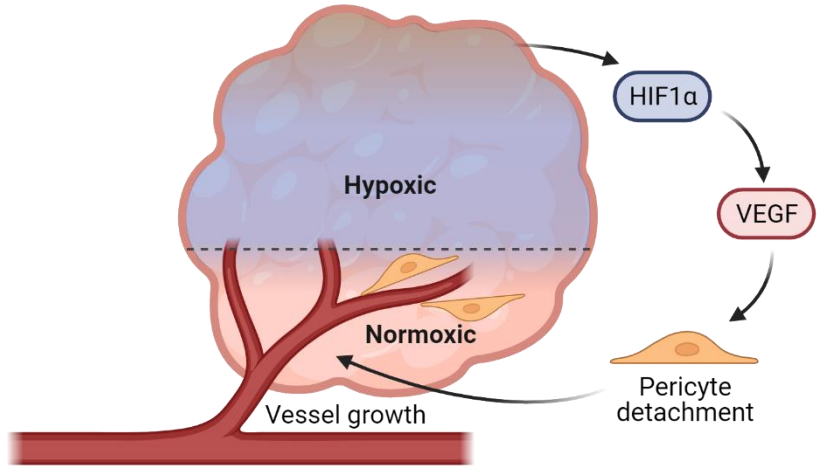
UVA FOCUSED ULTRASOUND

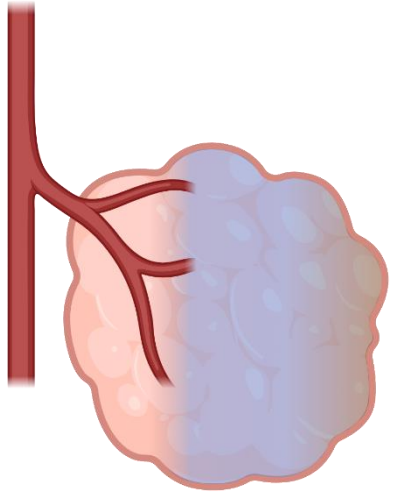
Tumor blood vessels may be standing in the way of higher FUS efficacy

Tumors grow rapidly, requiring fast vessel growth to accommodate growing tissue

Cell-cell coordination lost in neoplastic tissue, yielding disorganized, leaky network of vessels

Tumor vessels prevent maximal therapeutic efficacy





Vascular normalization – a potential solution!

Commentary | Published: 01 September 2001

Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy

Rakesh K. Jain

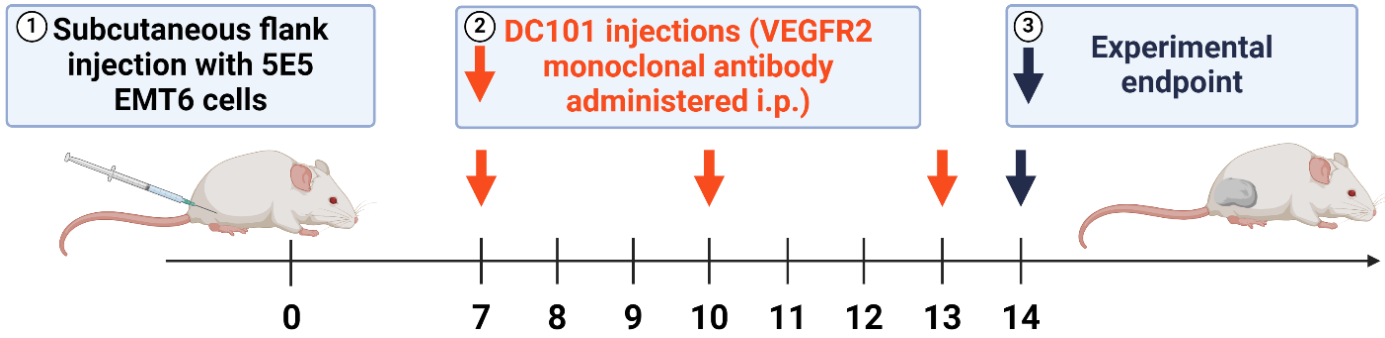
Nature Medicine **7**, 987–989 (2001)

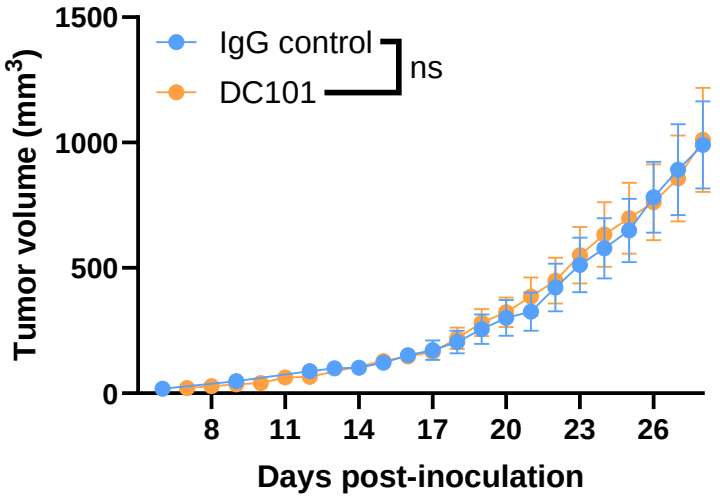
Hypothesized that partially blocking tumor vessel growth could improve tumor vessel function and therefore improve the efficacy of other therapies

Can anti-angiogenic drugs improve the efficacy of tFUS and potentiate systemic anti-tumor immune responses?

UVA FOCUSED ULTRASOUND

α-VEGFR2 modulates tumor immune composition

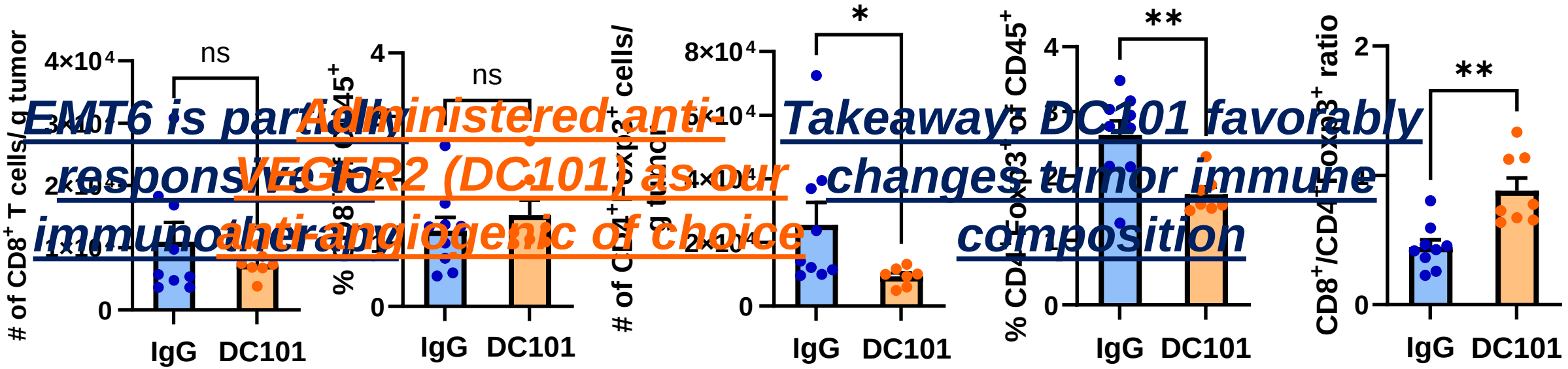




EMT6 is partially responsive to immunotherapy

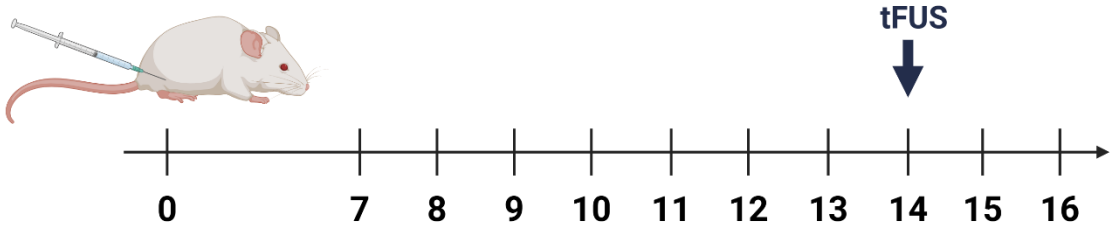
Administered anti-VEGFR2 (DC101) as our anti-angiogenic of choice

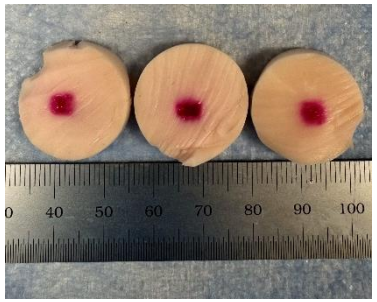
Takeaway: DC101 favorably changes tumor immune composition

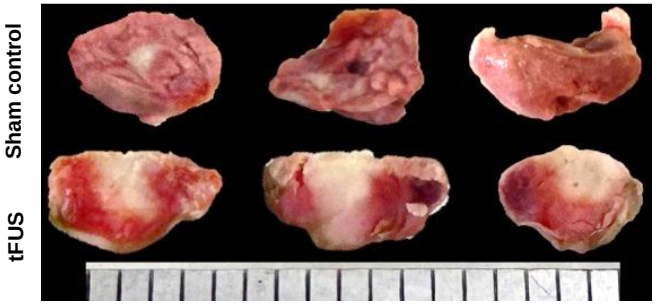


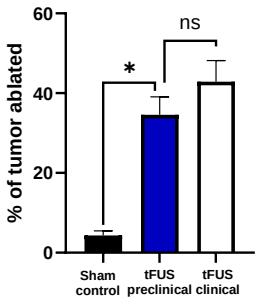
tFUS moderately controls tumor growth

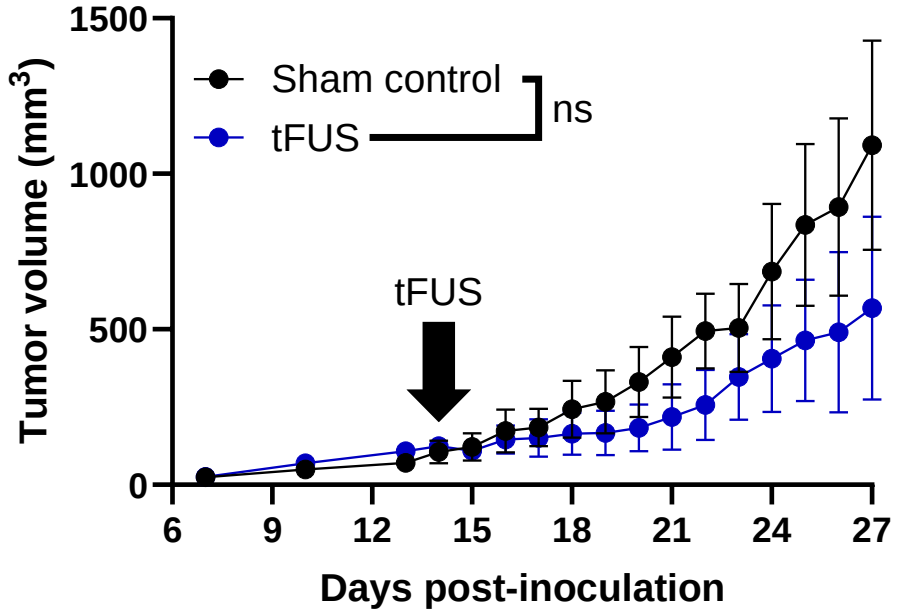
500k EMT6 cells

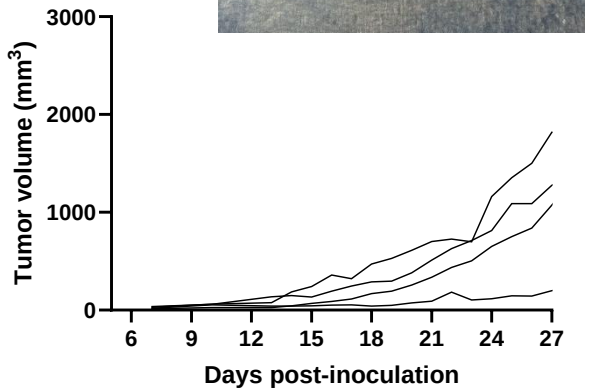


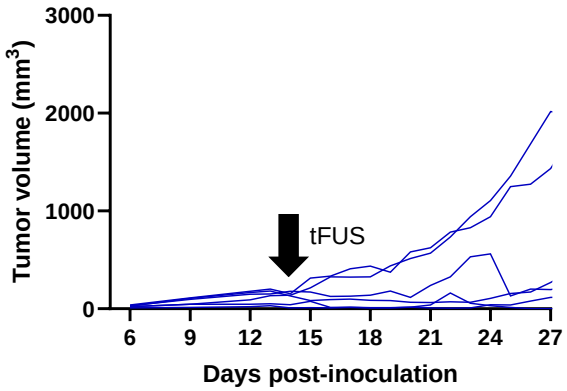






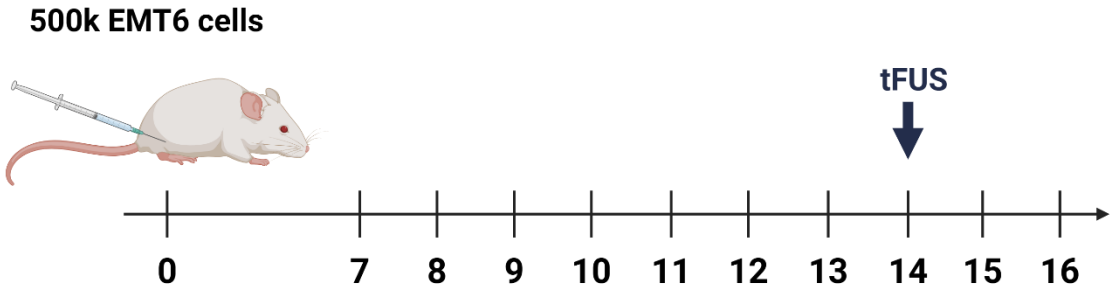




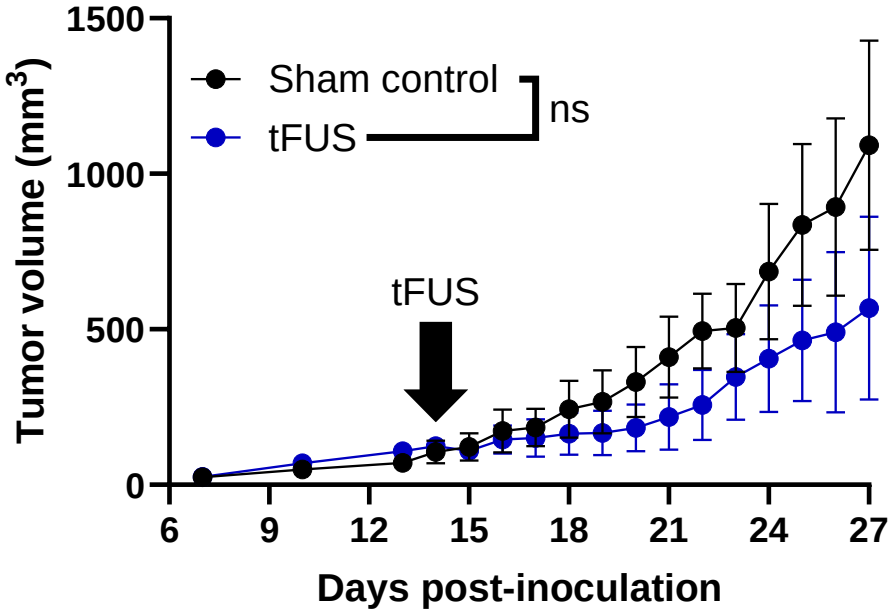


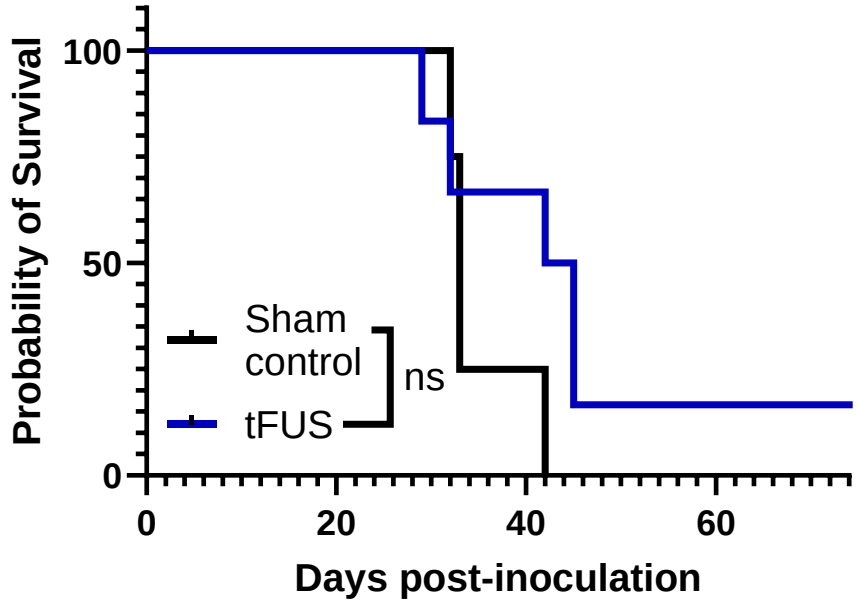
UVA FOCUSED ULTRASOUND

tFUS moderately controls tumor growth

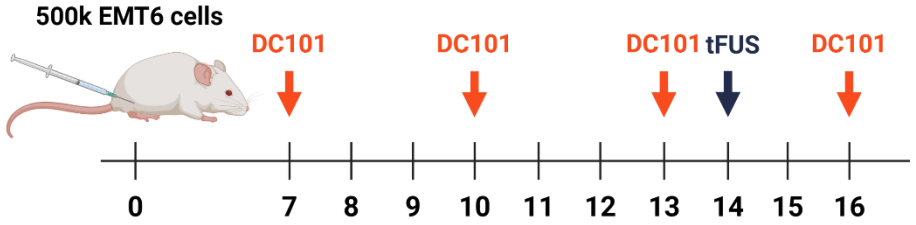


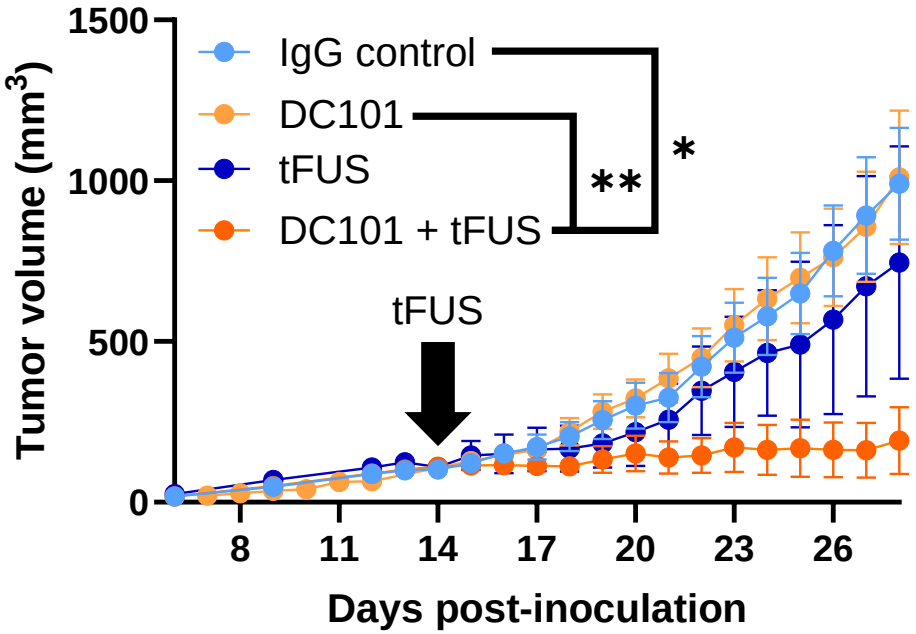
Takeaway: tFUS alone is minimally effective

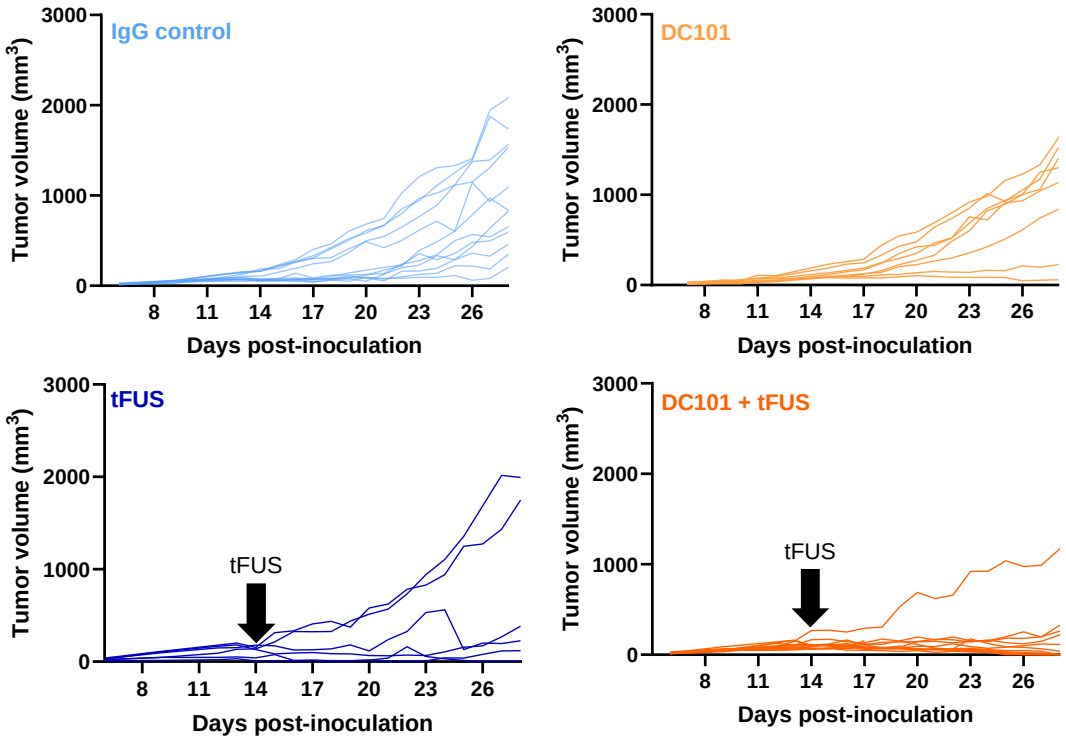




α-VEGFR2 and tFUS synergize to enhance tumor growth control and eradication







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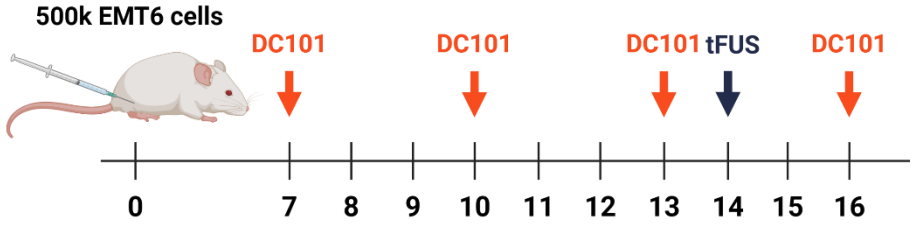
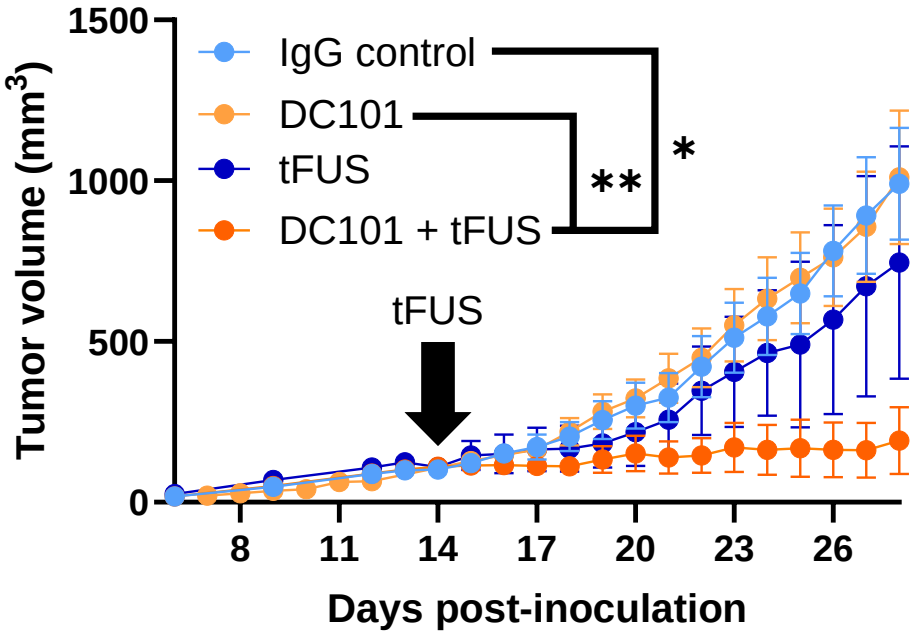
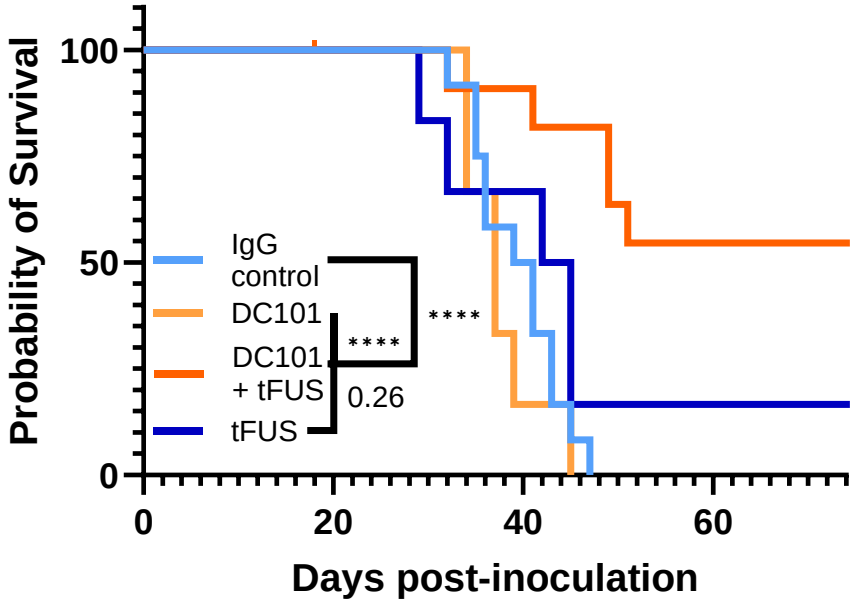
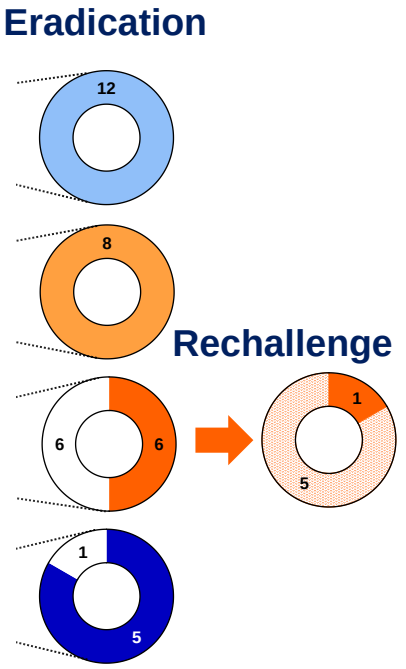


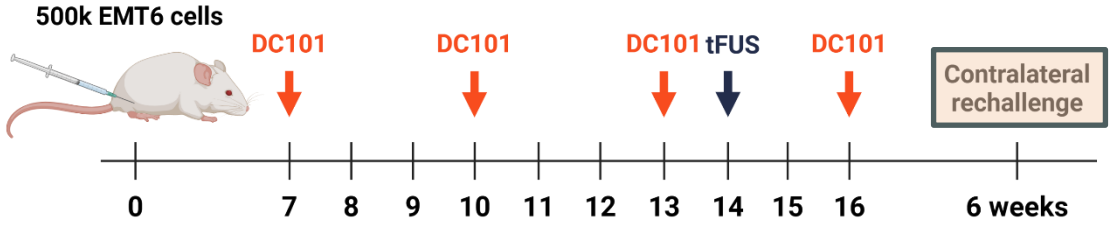
H: If we rechallenge mice, immune memory should prevent tumor growth



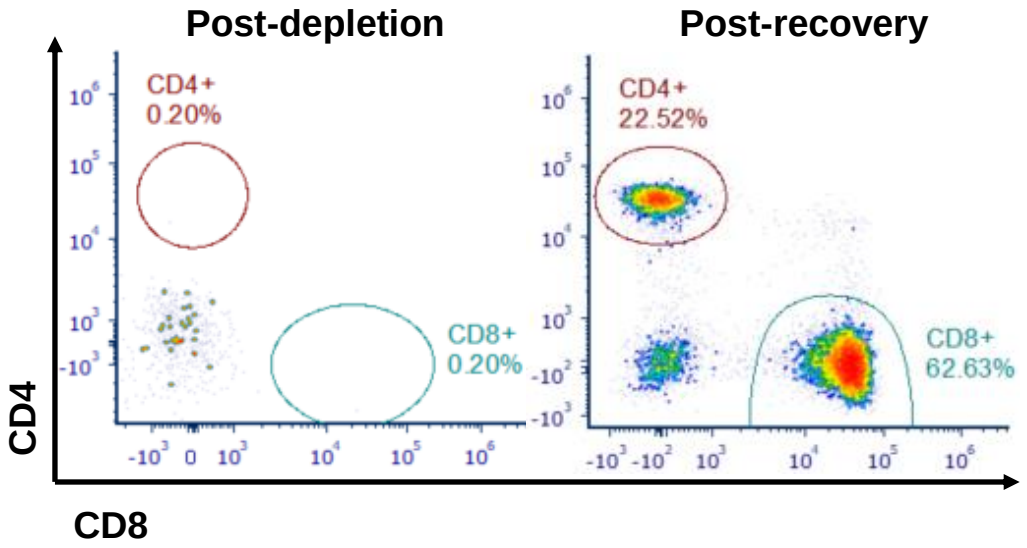


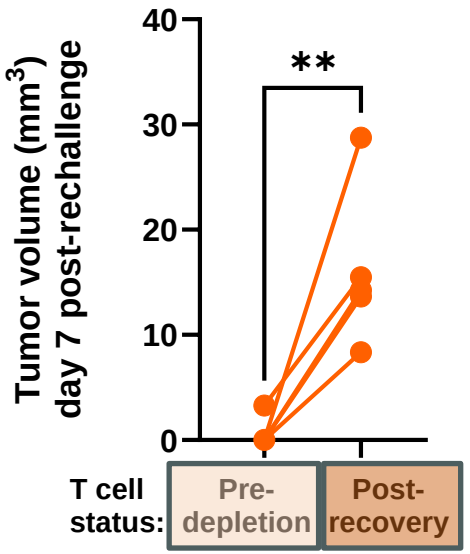


α-VEGFR2 converts tFUS into a T cell-dependent, durable immunotherapy



H: If we get rid of memory T cells, rechallenge tumors should grow

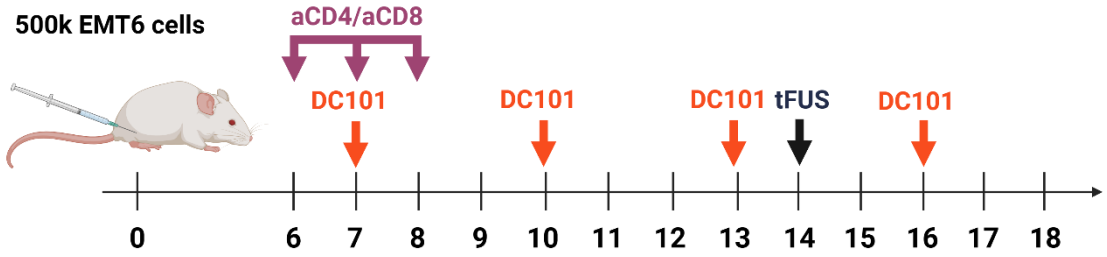




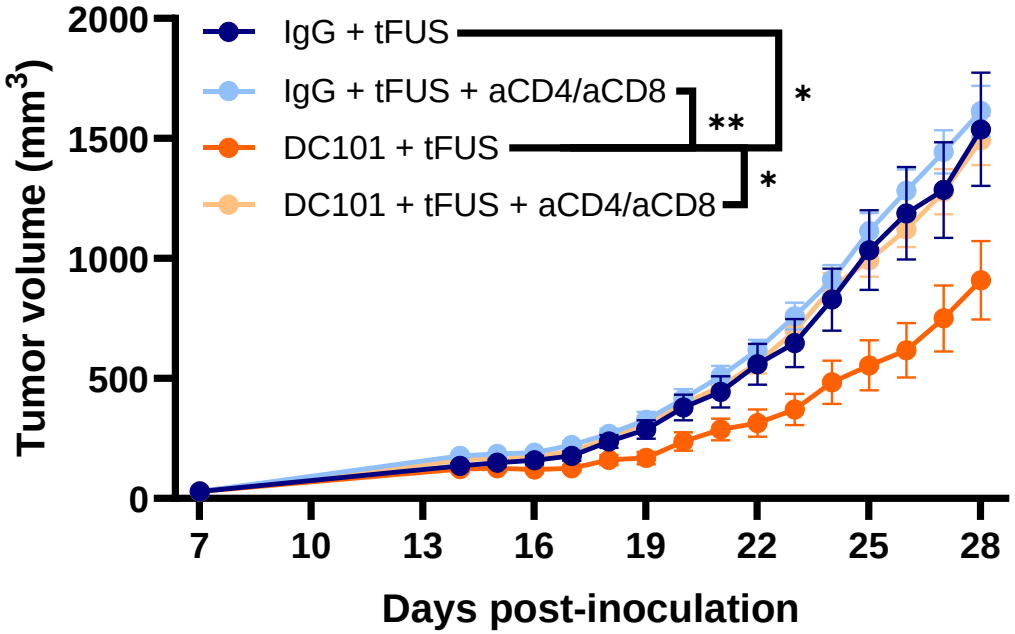
Takeaway: DC101 and tFUS synergize to control primary tumor growth and generate long-term, T cell-dependent immunity

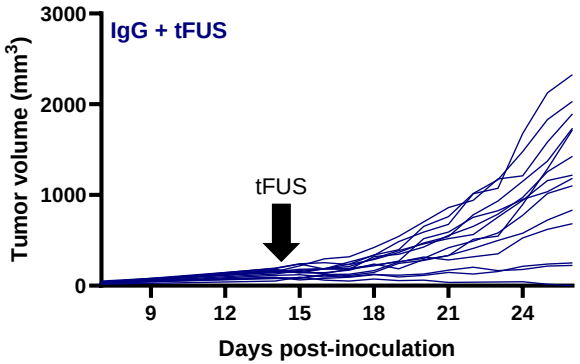
UVA FOCUSED ULTRASOUND

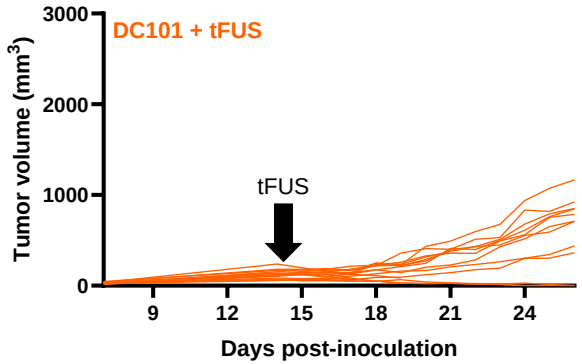
Primary tumor control from α-VEGFR2 + tFUS is T cell-dependent

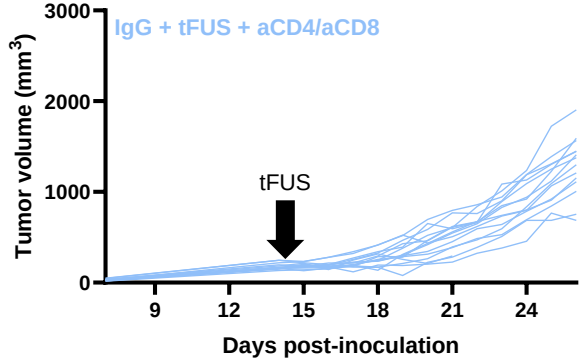


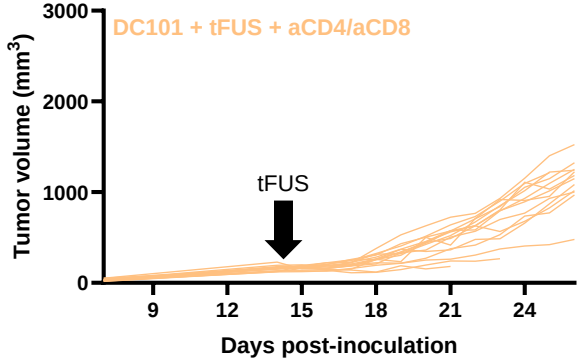
Takeaway: T cells are responsible for DC101 + tFUS primary tumor control



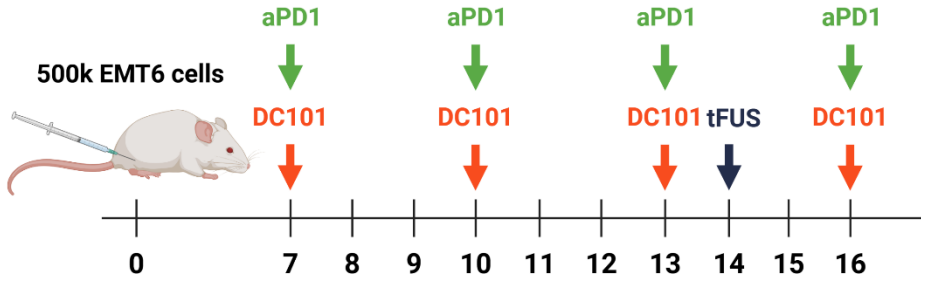






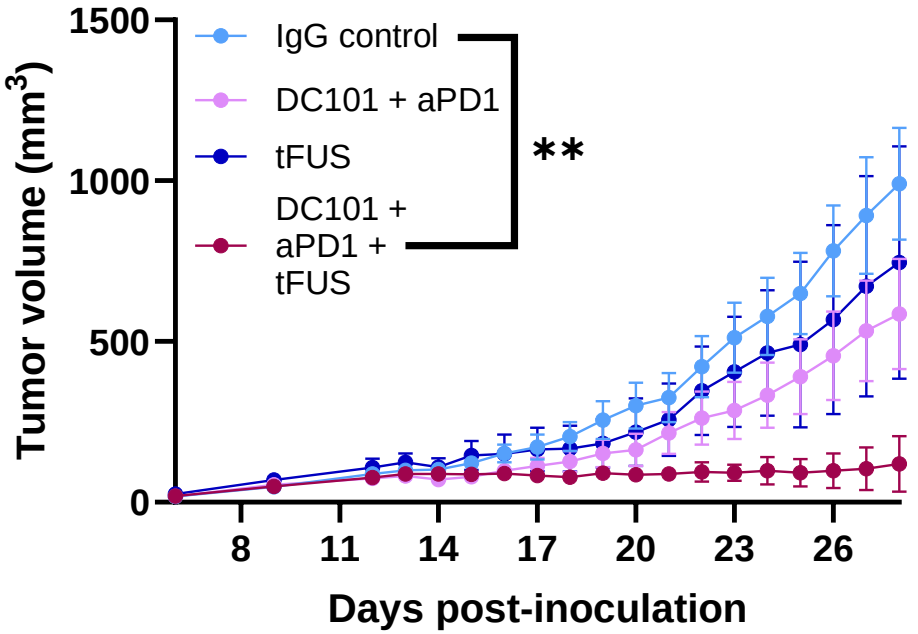


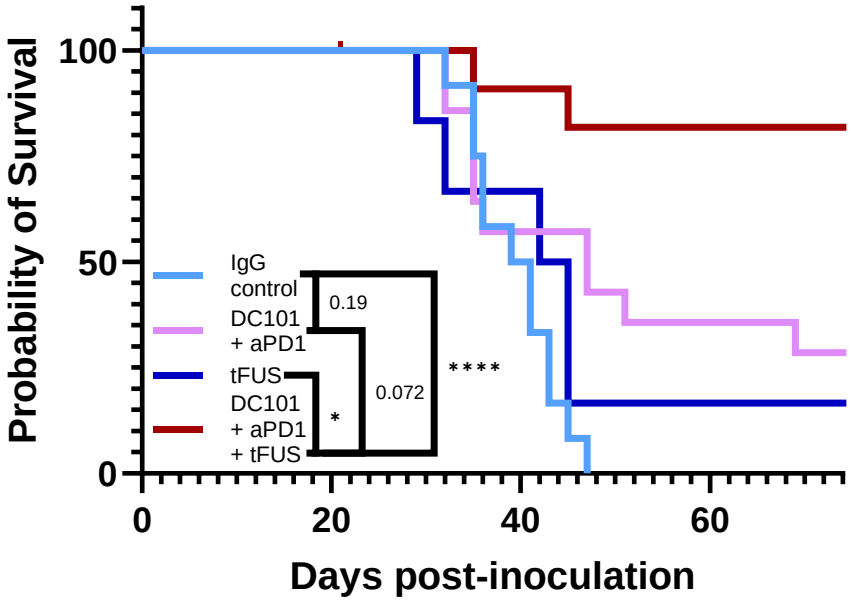
α-PD1 further boosts the efficacy of α-VEGFR2 + tFUS combination therapy

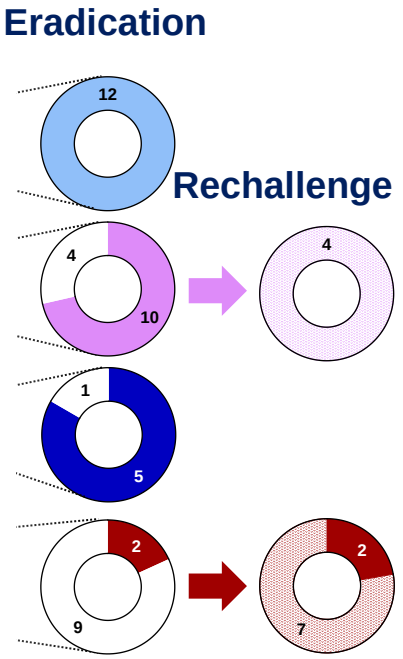


α-PD1 is a common immunotherapy that operates using separate mechanisms

Takeaway: α-PD1 improves α-VEGFR2 + tFUS primary and systemic tumor responses



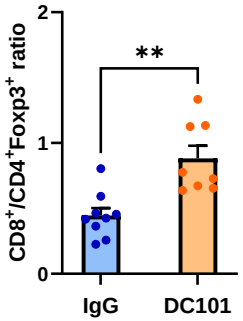


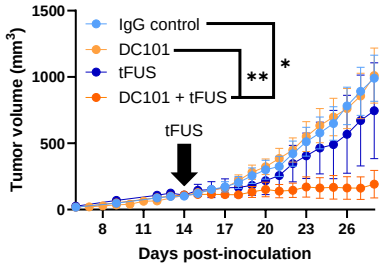


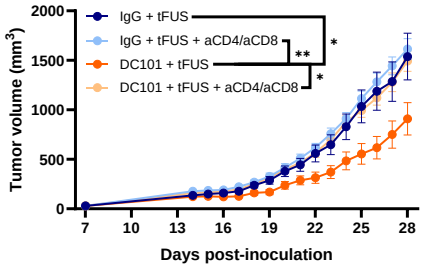
BioRender

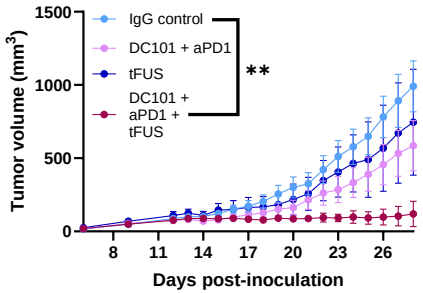
UVA FOCUSED ULTRASOUND

Conclusions and Impacts

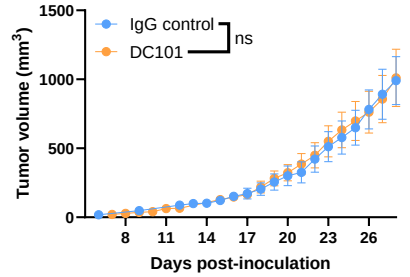




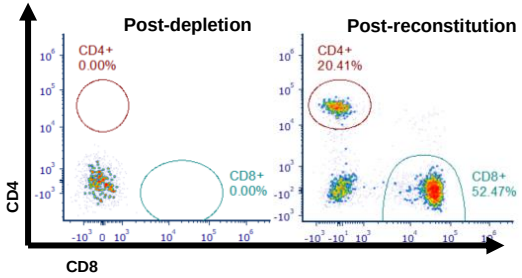




α-VEGFR2 immunologically primes EMT6 tumors to be responsive to immunotherapy

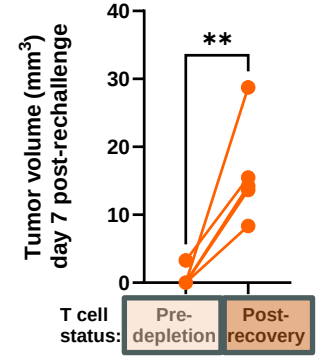


α-VEGFR2 synergistically augments tFUS-mediated tumor control



T cells are necessary for the formation of immune memory and for primary tumor control

α-PD1 further boosts α-VEGFR2 + tFUS efficacy



Given the large number of anti-angiogenic drugs on the market and uses of tFUS in the clinic, this brings us even closer to clinical trials

Acknowledgements

Supported By:

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Alliance to Cure Cavernous Malformation

UVA Cancer Center

Focused Ultrasound Foundation

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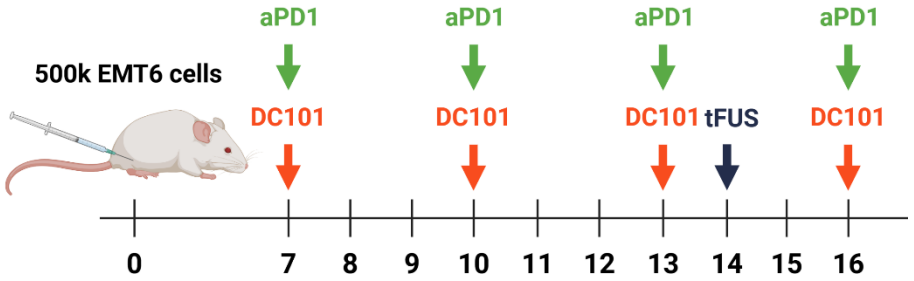
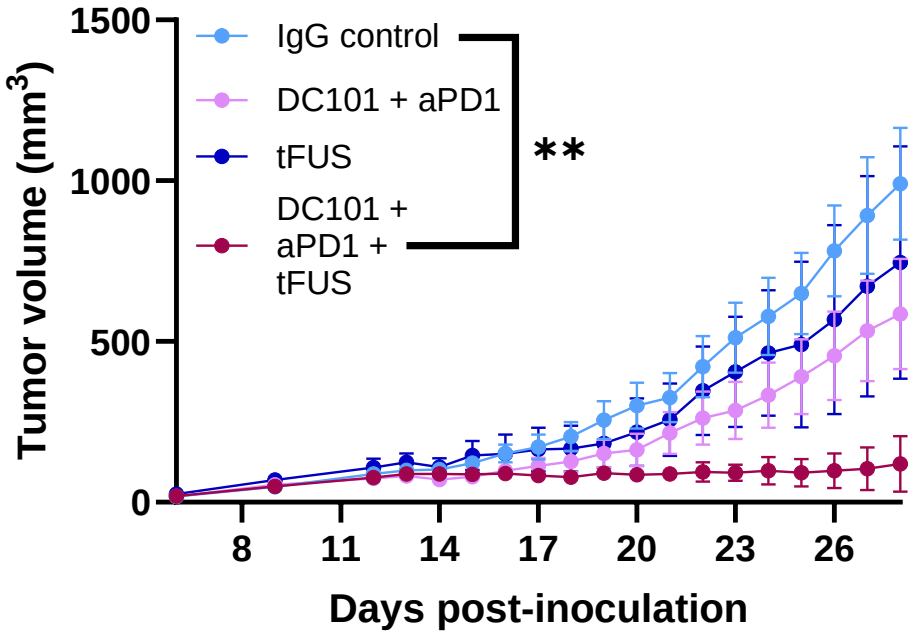
Senior Scientists

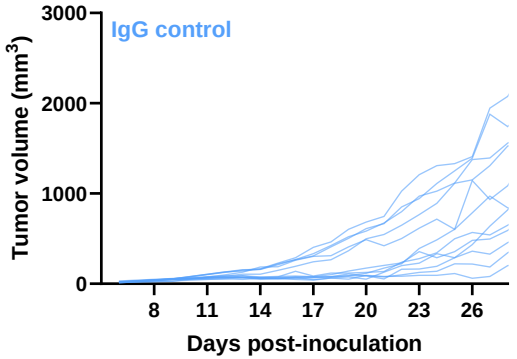
Katie Gorick
Matthew DeWitt

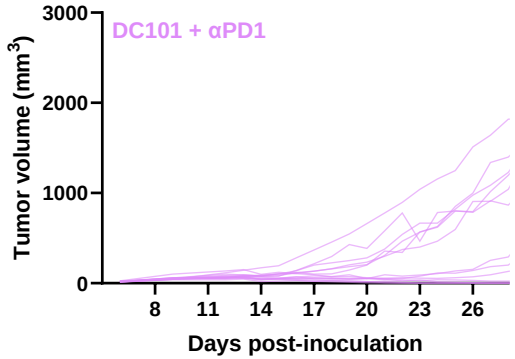
UVA FOCUSED ULTRASOUND

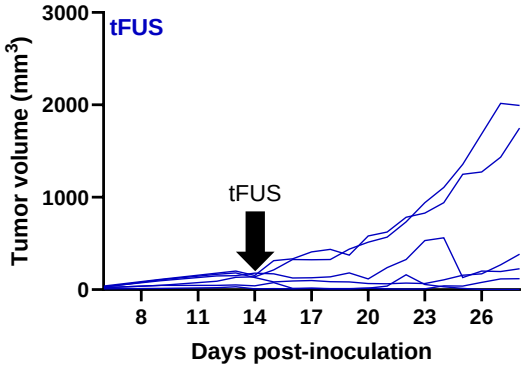
tFUS-mediated growth control is enhanced by DC101 and αPD1

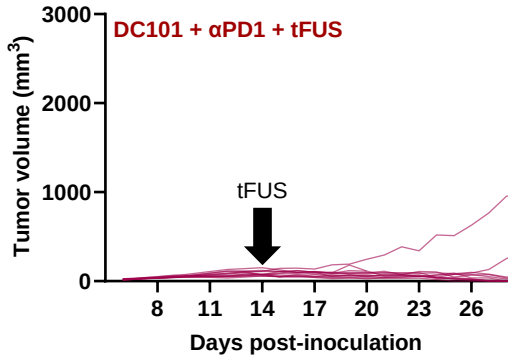












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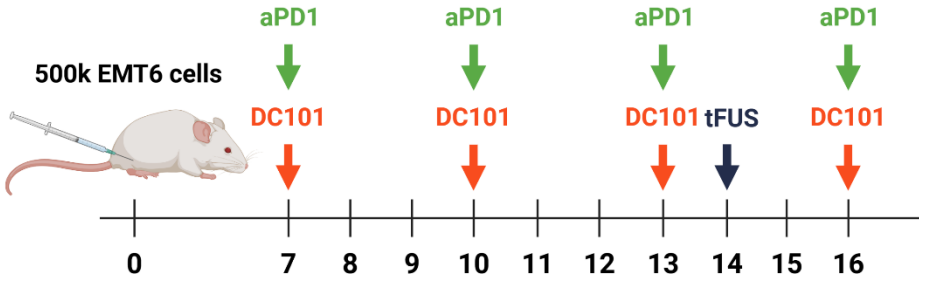
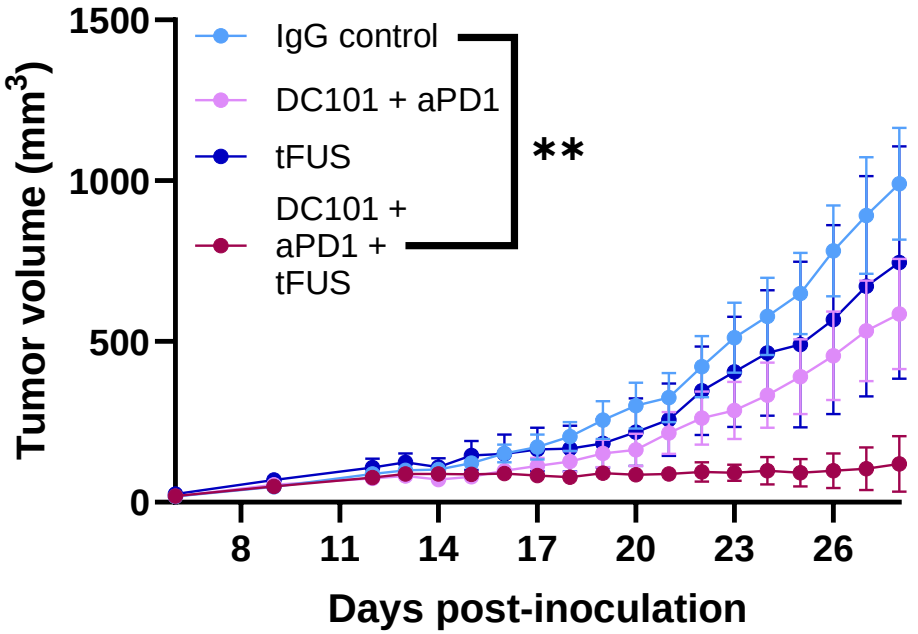
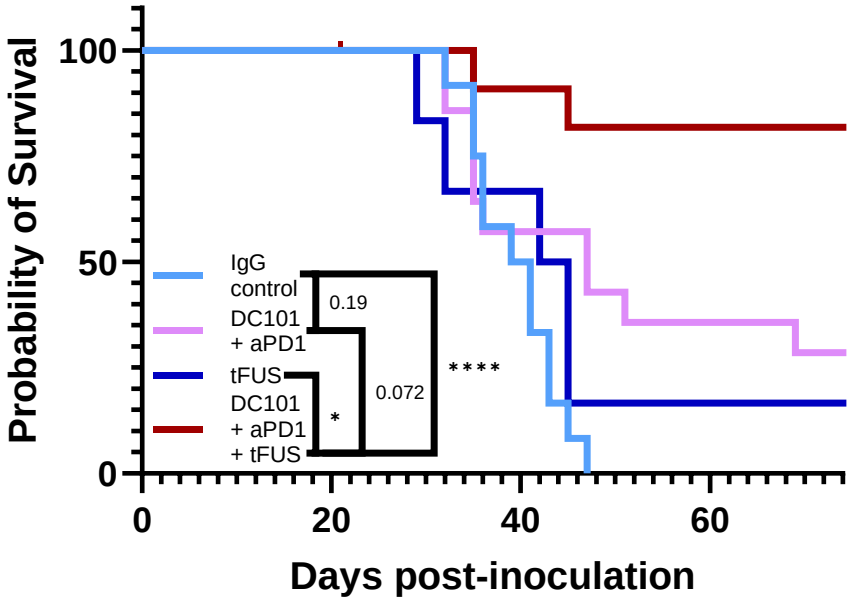
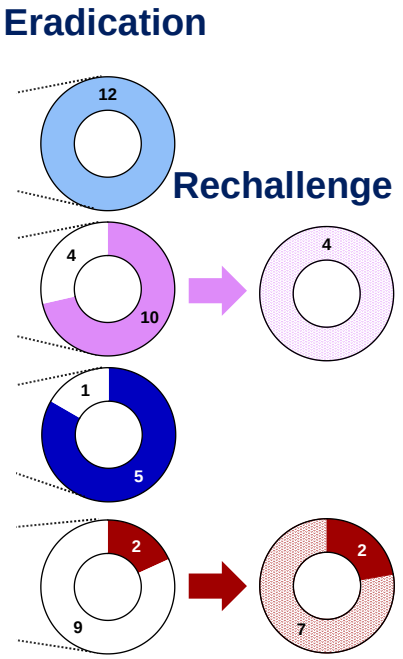
tFUS-mediated growth control is enhanced by DC101 and αPD1

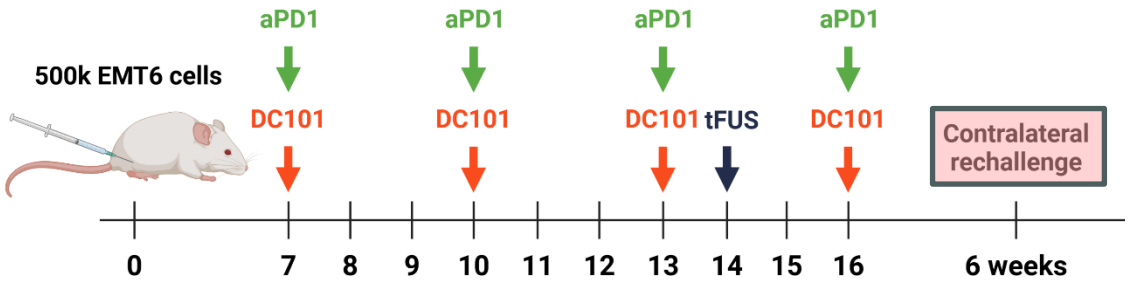


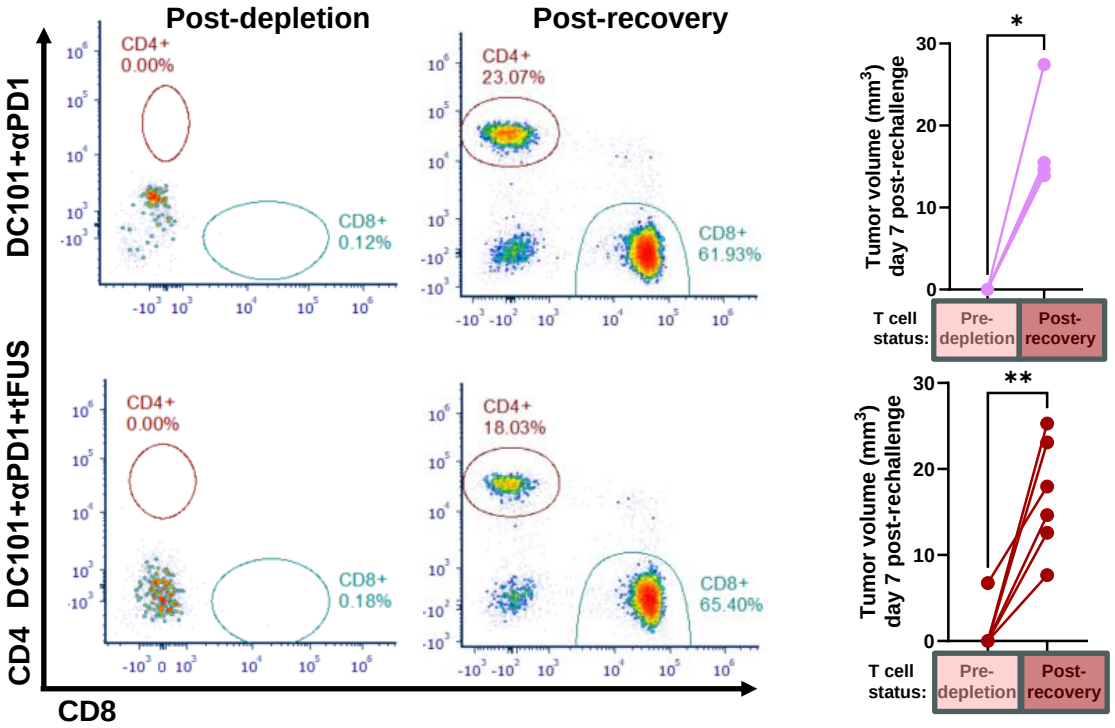






tFUS-mediated growth control is enhanced by DC101 and αPD1





Takeaway: DC101, aPD1, and tFUS maximally control primary tumor growth and generate long-term, T cell-dependent immunity

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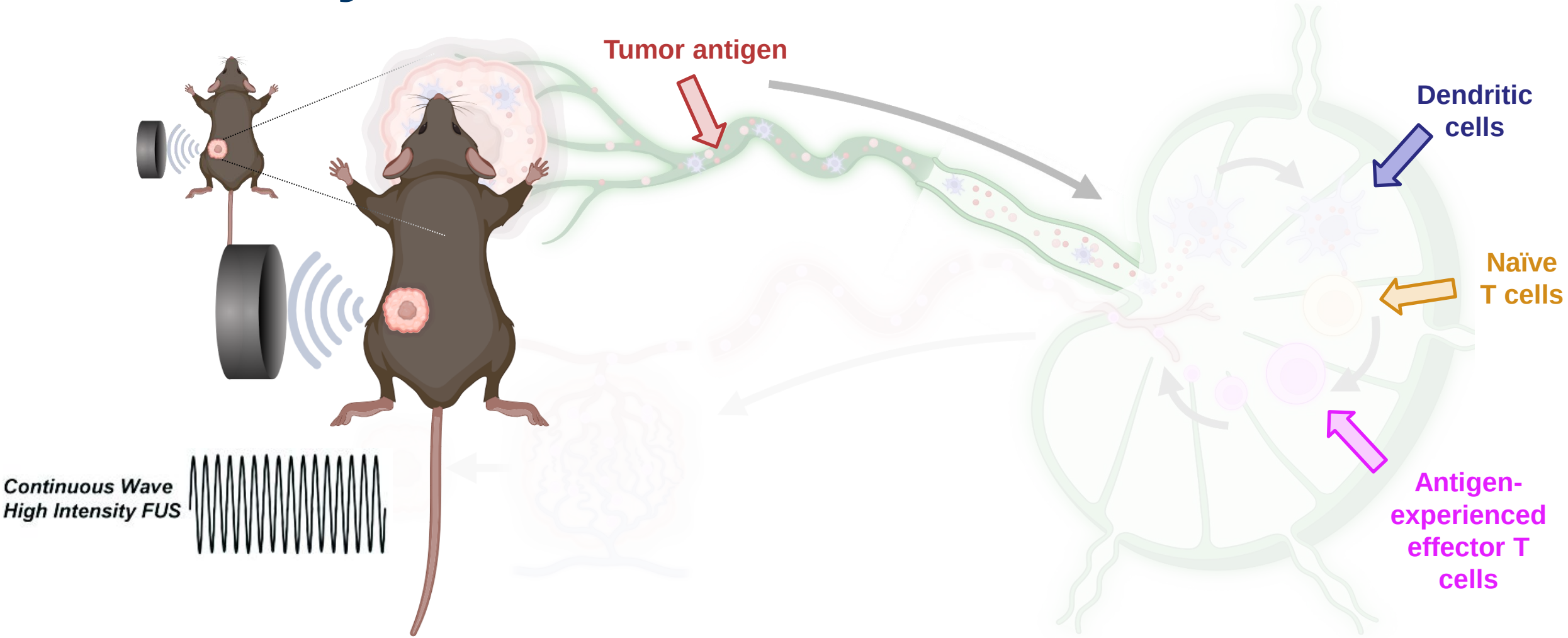
Thermally ablative focused ultrasound – tFUS



Takeaway: tFUS can destroy tumor tissue and induce immune responses against the tumor

BioRender, adapted from Rich Price

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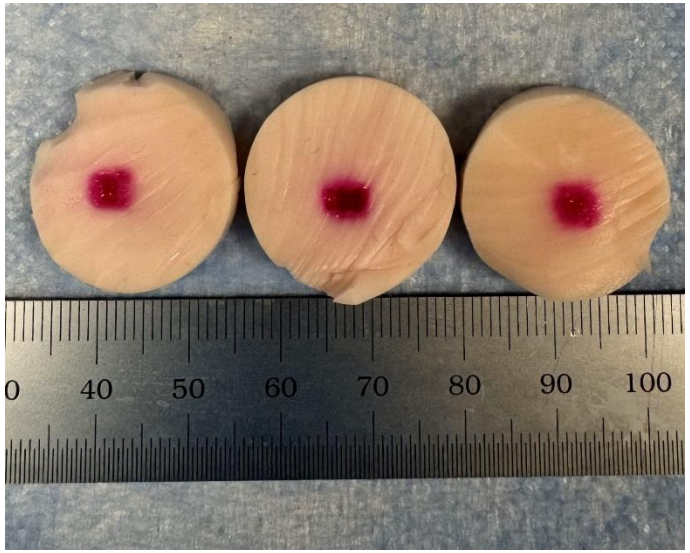
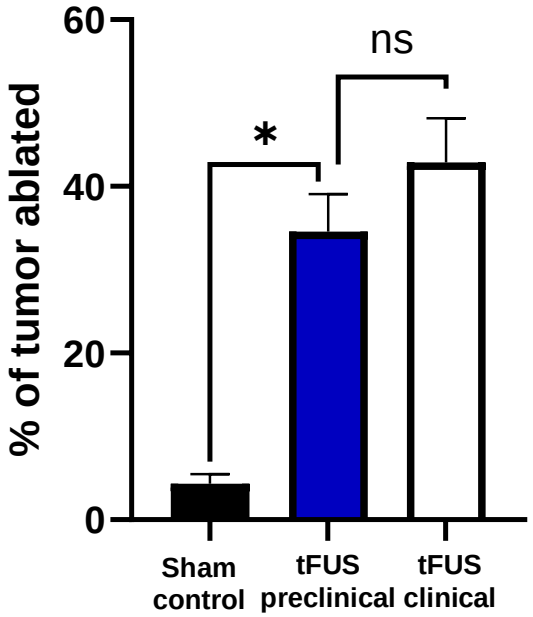
Confirming partial thermal ablation





Takeaway: tFUS achieves desired temperature, is partial, and approximates treatment in clinical trials

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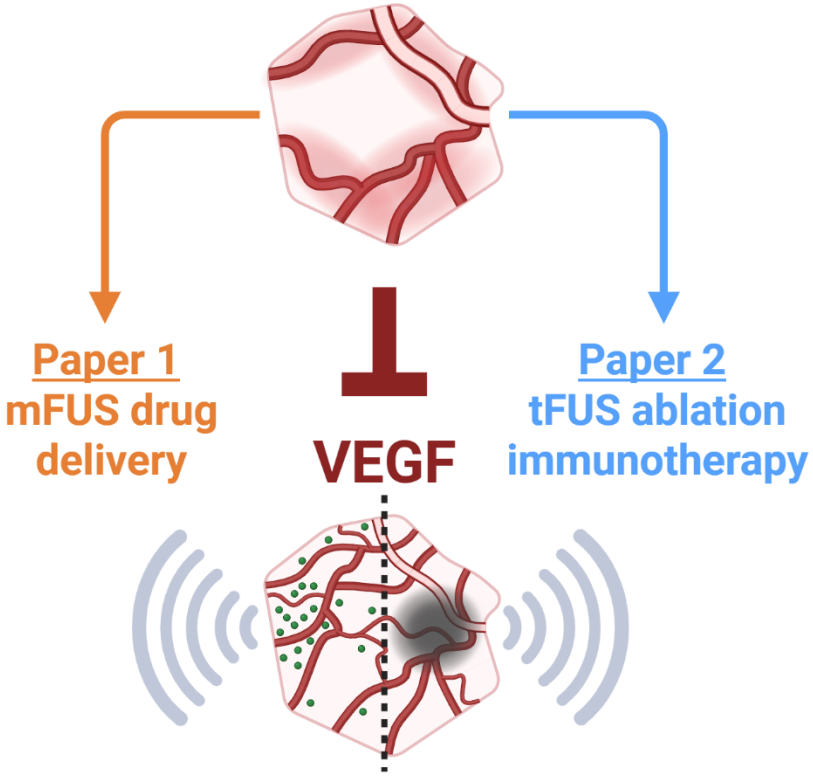
Goal: Improve Focused Ultrasound Efficacy with VEGFR2 Blockade in Solid Tumors

Paper 1: VEGFR2 blockade augments focused ultrasound-mediated model drug delivery to solid tumors

Paper 2: VEGFR2 blockade converts thermally ablative focused ultrasound into a potent driver of T cell-dependent anti-tumor immunity



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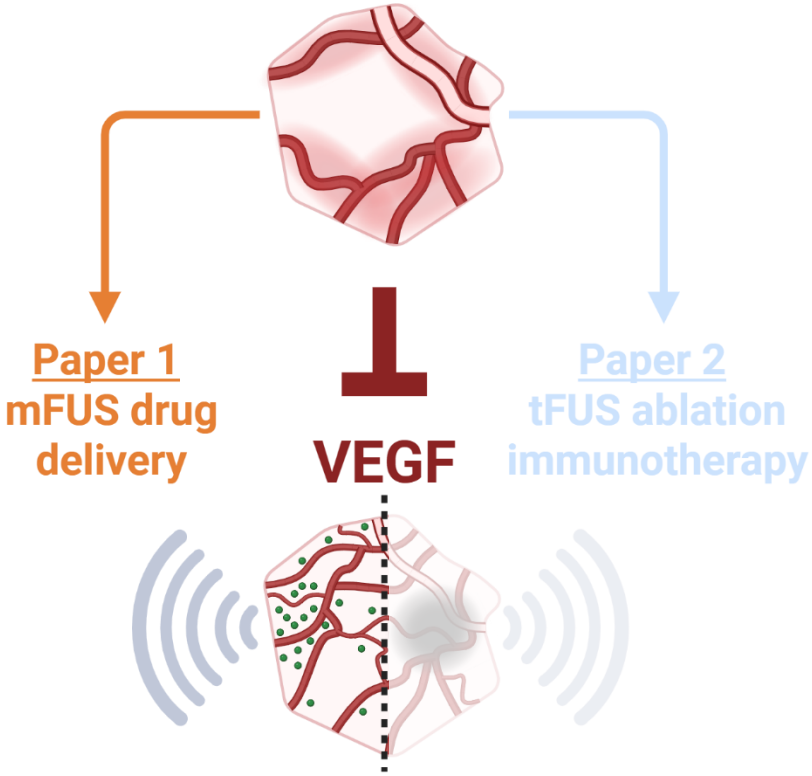
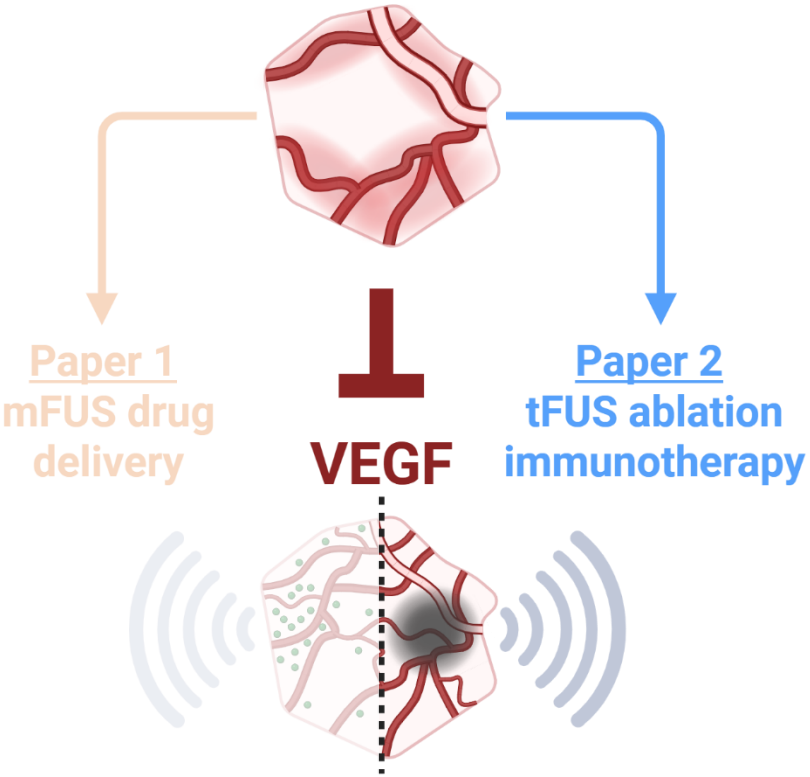
Future Directions:

- Employing even larger model drugs closer to the size of monoclonal antibodies or large nanoparticles
- Track tumor growth effect of antibody delivery following DC101 + mFUS
- Quantify antibody delivery with immunoPET and correlate intratumoral concentration with growth control



Future Directions:

- Examine T cell dependency of primary tumor eradication with tFUS combination therapy
- Exploring antigen acquisition and trafficking post-tFUS therapy
- Interrogate whether tFUS combination therapy generates distal tumor control
- Clinical translation given clinical stages of anti-angiogenics, anti-PD1, and tFUS



Publications

Akerlof, K.L., Schenck, T., Bankston, A., Mitchell, K., Syl, A., Eddy, L., Hall, S.H., Lad, N., Lake, S.J., Ostrom, R.B.J., Rosenberg, J.L., **Schwartz, M.R.**, Sisti, A.R., Smith, C.T., Solomon, L., & Velez, A.K. (2025). Training researchers to engage in policy in the U.S.: Mapping the growth and diversity of program models. Evidence & Policy, 24, 00081.

Schwartz, M., & Balkrishnan, R. (2023). Impacts of religious liberty court case outcomes on pre-exposure prophylaxis accessibility for Medicaid beneficiaries. AIDS, 37(9), 1493–1494. https://doi.org/10.1097/qad.0000000000003586

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Gorick, C. M.*, Breza, V. R.*, Nowak, K. M., Cheng, V. W. T., Fisher, D. G., Debski, A. C., Hoch, M. R., Demir, Z. E. F., Tran, N. M., **Schwartz, M. R.**, Sheybani, N. D., & Price, R. J. (2022). Applications of focused ultrasound-mediated blood-brain barrier opening. Advanced Drug Delivery Reviews, 191, 114583. https://doi.org/10.1016/j.addr.2022.114583

Nowak, K.M., **Schwartz, M.R.**, V.R. Breza, and R.J. Price (2022) Sonodynamic Therapy: Rapid Progress and New Opportunities for Non-Invasive Tumor Cell Killing with Sound. Cancer Letters. https://doi.org/10.1016/j.canlet.2022.215592

Schwartz M.*, Debski A.*, Price, R.J. (2021). Ultrasound-Targeted Nucleic Acid Delivery for Solid Tumor Therapy, Journal of Controlled Release. https://doi.org/10.1016/j.jconrel.2021.10.010

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Pending Publications

Schwartz, M.R., Anwar, N.Z., Kitelinger, L.E., Thim, E.A., Bullock, T.N.J, DeWitt, M.R., Price, R.J. (2025). VEGFR2 blockade converts thermally ablative focused ultrasound into a potent driver of T cell-dependent anti-tumor immunity. *In preparation.*

Schwartz, M.R.*, Hoch. M.R.*, Miller, G.W., Gorick, C.M., Price, R.J. (2025). VEGFR2 blockade augments focused ultrasound-mediated model drug delivery to solid tumors. *In preparation.*

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Kathy Nowak
Matt Hoch
Lydia Kitelinger
Josh Samuels
Nareen Anwar
Tanya Cruz
Eden Gordon
Ryan Gladwell

Lab Manager

Ji Song

Committee Members

Richard Price
Mete Civelek
Timothy Bullock
Andrew Dudley
Sepideh Dolatshahi

Recent Grads/ Postdocs

Delaney Fisher
Andrew Thim
Alex Mathew
Aly Witter
Colleen Curley
Kelsie Timbie
Brian Mead
Josh Heuslein

Senior Scientists

Katie Gorick
Matthew DeWitt

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DOBRODOŠLI

BUGGS
TEMPLE
1918

Lake Zurich
Lake Zurich

PITT
CHICAGO
BASKETBALL


THE SANDLOT
UNDESIRABLE
№1


FOOD
SPIRITS
MUSIC
















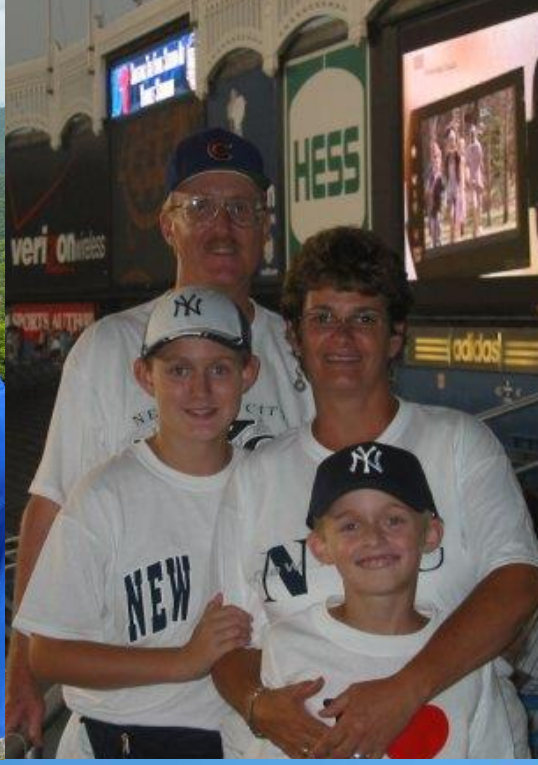
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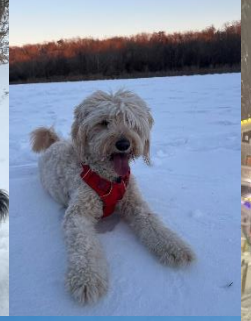










Thank you for listening!