Modified Annexin A5 ($AnxA5_{MOD}$) Immunotherapy Delivery Platform

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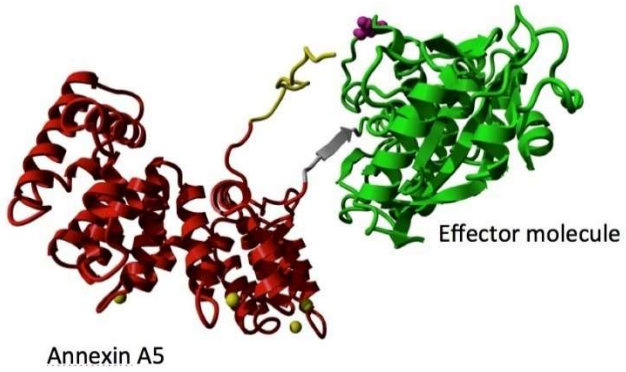
Rubicon's Modified Annexin A5 [AnxA5$_{MOD}$]

Our Modified Annexin will deliver powerful immunotherapy compounds to a common target found on the surface of tumors and tumor vasculature

Rubicon's AnxA5$_{MOD}$ (Targets the tumor and blocks immunosuppression caused by phosphatidyl serine)



Immunostimulatory Effector (Locally Reshapes the Immune System at the Tumor Site)

Important Points Upfront

Unlike other immunotherapies which inhibit the checkpoint inhibitors (e.g. PD-1/PD-L1, CTLA-4); Rubicon's $AnxA5_{MOD,}$ linked to an Immnostimulatory Effector, inhibits an inhibitor WHILE ALSO simultaneously activating the activators.

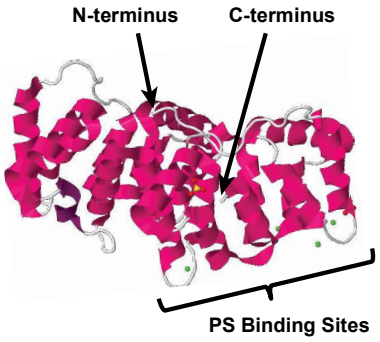
We believe enhanced targeting is critical for immunotherapies; Our $AnxA5_{MOD}$ binds to an immutable target and checkpoint inhibitor (Phosphatidylserine) that is localized on the surface of tumors and tumor vasculature.

With our technology, targeting is less disruptive to a patient's overall immune system.

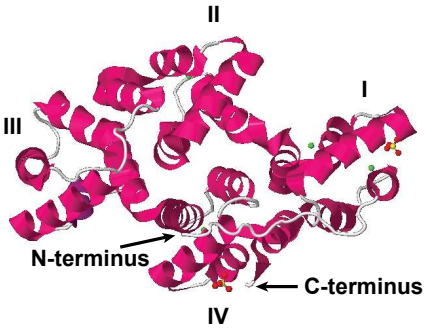
Modified Annexin [$AnxA5_{MOD}$] Platform

- Our approach uses a modified version of Annexin A5 ($AnxA5_{MOD}$), a natural high-affinity phosphatidylserine (PS) binding protein discovered by Dr. Chris Reutelingsperger at Maastricht University.
  Reutelingsperger, C.P., Hornstra, G., and Hemker, H.C. (1985) Isolation and partial purification of a novel anticoagulant from arteries of human umbilical cord. *Eur. J Biochem* **151**(3): 625-629.
- Annexin A5 (also known as **Annexin V** in the literature) is a 36 kD non-glycosylated single chain protein.
- It contains four domains, only one of which (Domain I) binds PS in a Ca^{2+} ion-dependent manner.

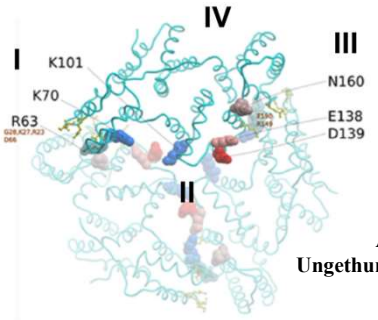
Annexin A5
Side View



Annexin A5
Top Axial View



$AnxA5_{MOD}$
Bottom Axial View

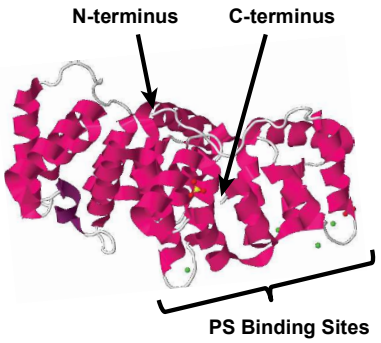


Adapted from
Ungethum et al. (2011)

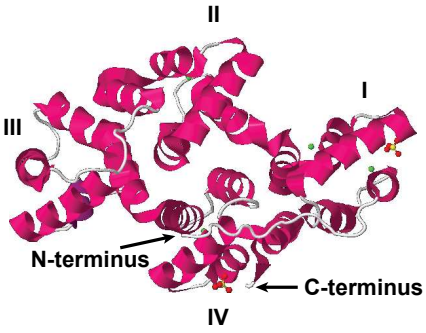
Modified Annexin [$AnxA5_{MOD}$] Platform

- Wild Type AnxA5 ($AnxA5_{WT}$) is present as a monomer when in solution, but once bound to PS on a cell membrane surface, it assembles into trimeric structures forming a 2-dimensional lattice that ultimately internalizes into the cell.
- Dr. Reutelingsperger modified the AnxA5 so that it will not internalize into the cell upon PS binding.
  Ungethum,L., Kenis,H., Nicolaes,G.A., Autin,L., Stoilova-McPhie,S., and Reutelingsperger,C.P. (2011) Engineered annexin A5 variants have impaired cell entry for molecular imaging of apoptosis using pretargeting strategies. *J Biol Chem.* **286** (3): 1903-1910.
- Rubicon has licensed this Modified Annexin ($AnxA5_{MOD}$) technology from Chris and his colleagues at MosaMedix. He works with Rubicon as a scientific advisor.

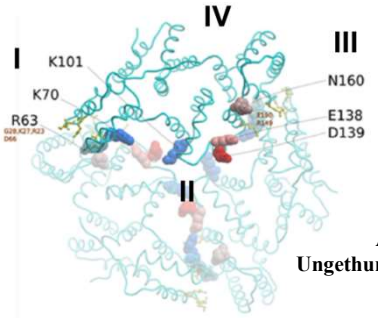
$AnxA5_{WT}$
Side View



$AnxA5_{WT}$
Top Axial View



$AnxA5_{MOD}$
Bottom Axial View



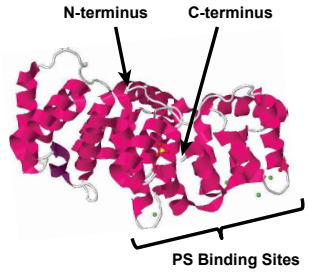
Adapted from
Ungethum et al. (2011)

Modified Annexin [$AnxA5_{MOD}$] Platform

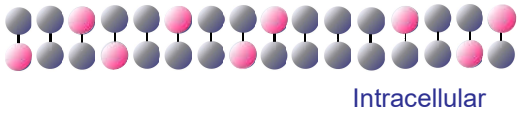
Wild Type AnxA5 ($AnxA5_{WT}$) is present as a monomer when in solution, but once bound to PS on a cell membrane surface, it assembles into trimeric structures forming a 2-dimensional lattice that ultimately internalizes into the cell. $AnxA5_{MOD}$ DOES NOT internalize into the cell upon PS binding.

AnxA5 Monomer

Side View



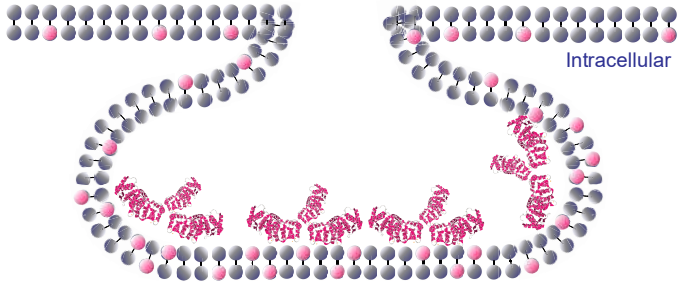
Plasma Membrane



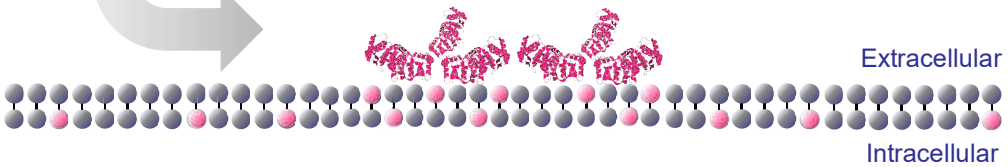
Phosphatidylserine

Two AnxA5 Trimers

$AnxA5_{WT}$

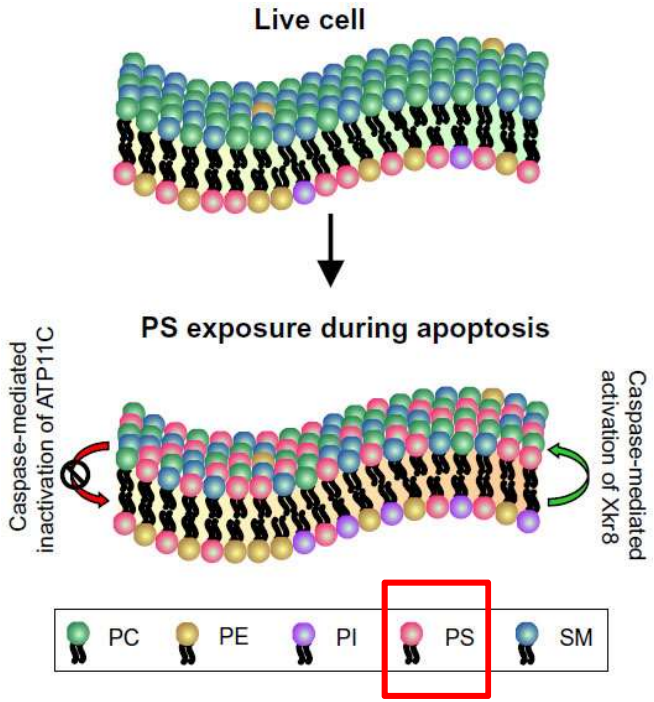


$AnxA5_{MOD}$



Since $AnxA5_{MOD}$ does not internalize, effector molecules delivered to the tumor surface are stably bound for subsequent immune signaling.

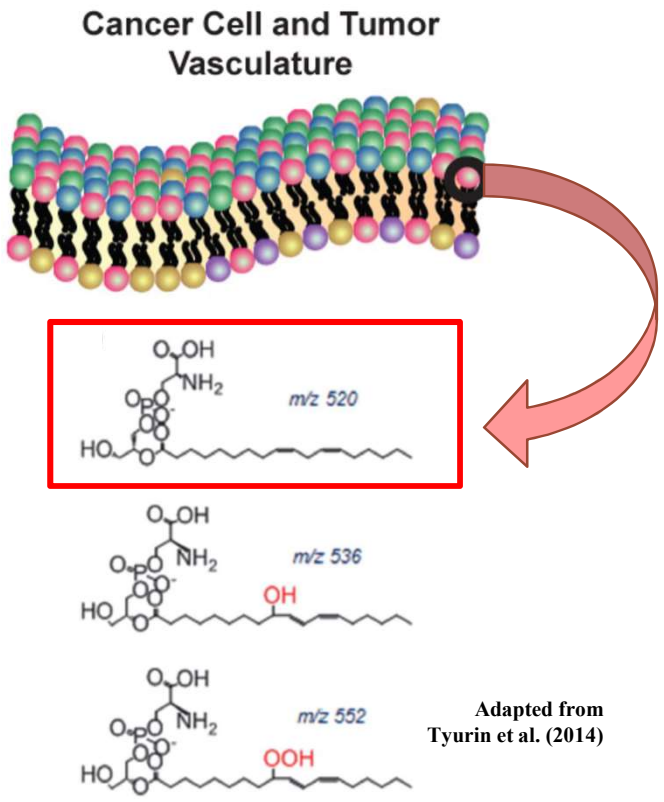
Phosphatidyl Serine



‡ Live vs Apoptotic Cell PS distribution image modified from Julian & Olson 2015 *Cell Health and Cytoskeleton* **7**:133-142

- PS is an anionic phospholipid residing on the cytosolic leaflet of the plasma membrane (96%) and largely absent from the outer leaflet in mammalian cells under normal conditions.
  Calderon, R.O., and DeVries, G.H. (1997) Lipid composition and phospholipid asymmetry of membranes from a Schwann cell line. *J Neurosci. Res* **49**(3): 372-380.
- Externalization of PS on apoptotic cells provides an "eat me" signal to macrophages for the removal of cellular debris without causing inflammation.
  Birge,R.B., Boeltz,S., Kumar,S., Carlson,J., Wanderley,J., Calianese,D., Barcinski,M., Brekken,R.A., Huang,X., Hutchins,J.T., Freimark,B., Empig,C., Mercer,J., Schroit,A.J., Schett,G., and Herrmann,M. (2016) Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease, and cancer. *Cell Death. Differ.* **23** (6): 962-978.
- It also inhibits dendritic cell (DC) maturation, further limiting inflammation.
  Chen,X., Doffek,K., Sugg,S.L., and Shilyansky,J. (2004) Phosphatidylserine regulates the maturation of human dendritic cells. *J Immunol.* **173** (5): 2985-2994.
- PS asymmetry is an ATP-hydrolysis driven process.

Phosphatidyl Serine



Adapted from Tyurin et al. (2014)

- Under certain non-apoptotic conditions, this asymmetry is disrupted:
  - Viable Tumor cells
  - Viable Tumor Vasculature
  - Aging erythrocytes
  - Activated platelets and macrophages

Schutters, K., and Reutelingsperger, C. (2010) Phosphatidylserine targeting for diagnosis and treatment of human diseases. *Apoptosis* **15**(9): 1072-1082.

- Not all externalized PS is functionally equivalent. There is growing evidence that the acyl chains of the phosphatidyl serine molecule are oxidized at one or more sites during apoptosis.
- This oxidized form of PS (PSox) is the signal that differentiates apoptotic cells destined for phagocytosis versus tumor cells and tumor vasculature that benefit from the immunosuppressive effects of PS. The non-oxidized form is boxed in red in the graphic on the left.

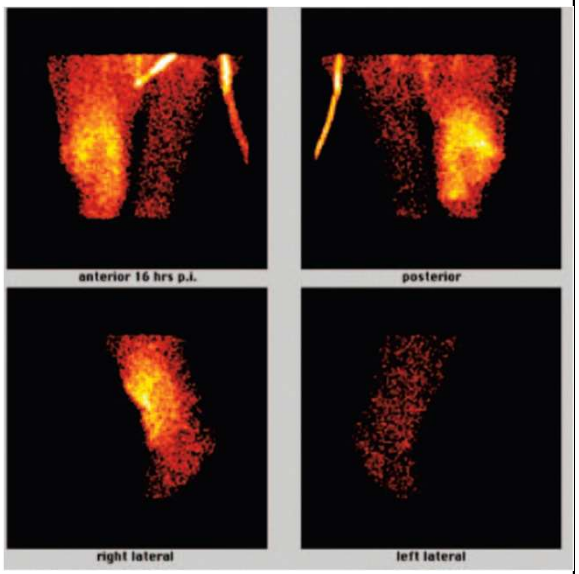
Tyurin,V.A., Balasubramanian,K., Winnica,D., Tyurina,Y.Y., Vikulina,A.S., He,R.R., Kapralov,A.A., Macphee,C.H., and Kagan,V.E. (2014) Oxidatively modified phosphatidylserines on the surface of apoptotic cells are essential phagocytic 'eat-me' signals: cleavage and inhibition of phagocytosis by Lp-PLA2. *Cell Death. Differ.* **21** (5): 825-835.

Wild Type Annexin (Anx_{WT}) Targeting of Tumors

Is there data showing Annexin A5 binding to different tumors?

- $AnxA5_{WT}$ has been used in multiple tumor imaging studies in the clinic.
- One example is the sarcoma on the right. Other examples are tabulated below:

Cancer	References
Head & Neck	van de Wiele et al. 2003 *J Clin Oncol* **21**:3483
Non-Small Cell Lung Cancer	Belhocine et al. 2002 *Clin Cancer Res* **8**:2766
Breast	Boersma et al. 2003 *Br J Radiol* **76**:553; Belhocine et al. 2002 *Clin Cancer Res* **8**:2766
Non-Hodgkin's Lymphoma	Boersma et al. 2003 *Br J Radiol* **76**:553; Belhocine et al. 2002 *Clin Cancer Res* **8**:2766
Follicular Lymphoma	Haas et al. 2004 *Int J Radiat Oncol Biol Phys* **59:**782
Leukemia	Kartachova et al. 2004 *Radiother Oncol* **72**:333
Intracardiac	Kietselaer et al. 2004 *N Engl J Med* **350**:1472; Kietselaer et al. 2002 *Netherlands Heart J* **10**:312
Sarcoma	Boersma et al. 2003 *Br J Radiol* **76**:553

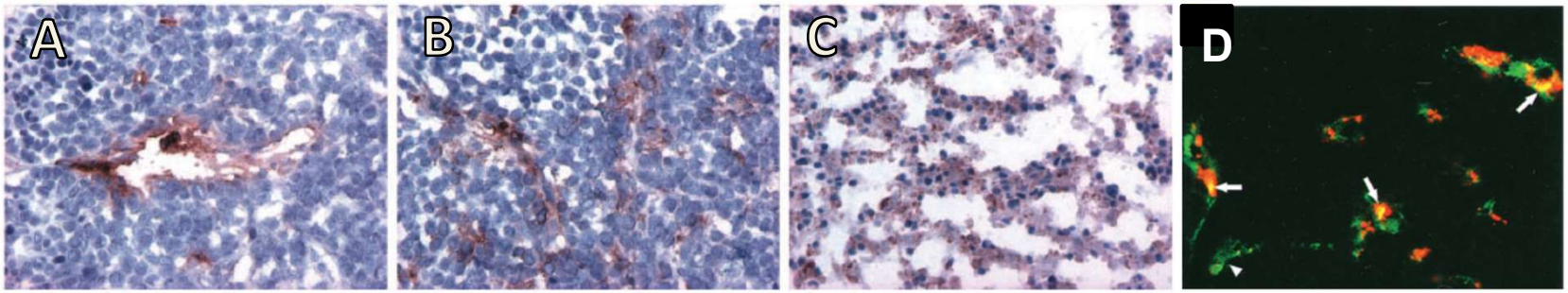


Planar images of patient with sarcoma of right leg at 16h after injection (p.i.) of BTAP-labeled AnxA5. Uptake of AnxA5 is seen in the upper right leg. Almost no uptake in the same area on the left leg.

Adapted from Boersma et al. (2003)

Wild Type Annexin (Anx_{WT}) Targeting of Tumors

Is there data showing distribution of Annexin A5 in tumors?



Localization of Annexin A5 in A) vascular endothelial cells, **B)** tumor cells and **C)** the necrotic core of orthotopic MDA-MB-231 human breast tumors. Nu/nu mice bearing MDA-MB-231 tumors in their mammary fat pads were injected i.v. with 100 µg of biotinylated AnxA5. After 1 hour incubation, blood circulation was perfused with saline, tumors and organs removed, snap-frozen and AnxA5 detected on the frozen sections using streptavidin-HRP. Regions of brown staining localize AnxA5 to tumor vasculature, tumors cells and the necrotic core. **D)** Verification that AnxA5 binds tumor vasculature. Colocalization of AnxA5 and MECA32, a pan mouse anti-endothelial cell antibody, on the same tumor. Biotinylated AnxA5 was detected with a streptavidin-Cy3 conjugate. Sections were then stained with MECA32 antibody followed by anti-rat IgG conjugated FITC. Colocalization of MECA32 and AnxA5 is seen in yellow with the superimposition of the Cy3 and FITC images (see white arrows). Images adapted from Ran,S., Downes,A., and Thorpe,P.E. (2002) Increased exposure of anionic phospholipids on the surface of tumor blood vessels. *Cancer Res.* **62**:6132-6140.

Wild Type Annexin (Anx_{WT}) Targeting of Tumors

Other tumor models used to demonstrate biotinylated Annexin A5 localization:

- Biotinylated AnxA5 was detected on frozen tissue sections using streptavidin-peroxidase. The percentage of cells and blood vessels staining positive for AnxA5 was then determined in relation to the number of cells staining positive for the MECA-32 endothelial cell antibody.
- Positively stained cells were counted in fields of 0.317 mm^2.
- Six samples of each type were analyzed and tabulated. The table from Ran et al. (2002) has been adapted on the right.
- "Anionic phospholipid-positive vessels were present on the luminal surface of capillaries and vessels in all regions of the tumors, but were particularly prevalent in and around regions of necrosis."

Ran,S., Downes,A., and Thorpe,P.E. (2002) Increased exposure of anionic phospholipids on the surface of tumor blood vessels. *Cancer Res.* **62**:6132-6140. Table here adapted from Table 3 in that article.

Tumor	Percentage
MDA-MB-231 (Breast)	45.3 ± 5.6
B16 (Melanoma)	21.3 ± 6.6
L540cy (Hodgkin's Lymphoma)	16.7 ± 3.9
Normal	**Percentage**
Adrenal	0
Brain	0
Heart	0
Kidney	0
Intestine	0
Liver	0
Lung	0
Pancreas	0
Spleen	0
Testis	0

Wild Type Annexin (Anx_{WT}) Targeting of PS

Annexin A5 has the highest known affinity for PS

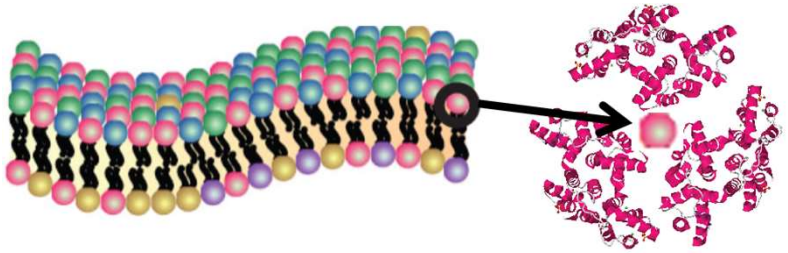
- Up to <u>three</u> AnxA5 molecules can bind a single PS in a calcium dependent manner. Indeed, a single cell with exposed PS can bind 3 x 10^6 AnxA5 molecules.

  Willems,G.M., Janssen,M.P., Comfurius,P., Galli,M., Zwaal,R.F., and Bevers,E.M. (2000) Competition of annexin V and anticardiolipin antibodies for binding to phosphatidylserine containing membranes. *Biochemistry* **39** (8): 1982-1989.

- There are other PS binding proteins, however, AnxA5's affinity for PS is unrivaled.

- *Under physiologically relevant conditions (120 mM NaCl and 3 mM $CaCl_2$) binding of β2-glycoprotein-1 is not detectable. This protein is also called Apolipoprotein H. The 80 μM dissociation constant was extrapolated and the authors consider its binding negligible *in vivo*.

  Bevers,E.M., Janssen,M.P., Comfurius,P., Balasubramanian,K., Schroit,A.J., Zwaal,R.F., and Willems,G.M. (2005) Quantitative determination of the binding of beta2-glycoprotein I and prothrombin to phosphatidylserine-exposing blood platelets. *Biochem. J* **386** (Pt 2): 271-279.



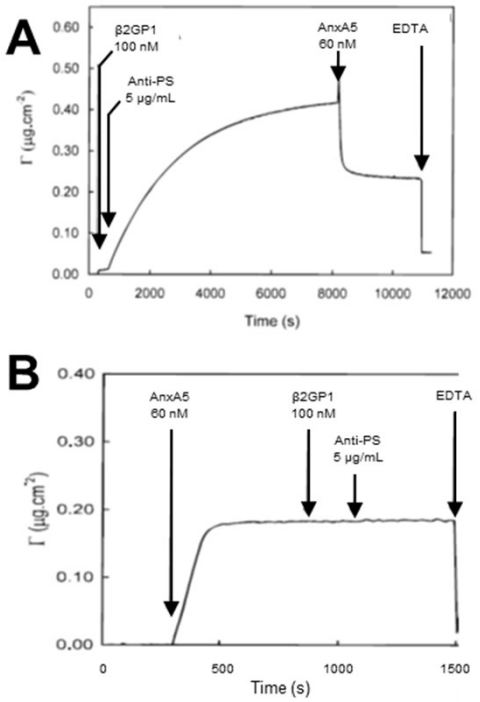
Protein	MW (kD)	Characteristics	Kd (nM)
Annexin A5	36	Ca^{2+}-dependent	**0.1**
Lactadherin	47	Glycoprotein	3-4
Synaptotagmin I	65	Ca^{2+}-dependent	15-40
Prothrombin	72	Glycoprotein	1,400
β2-Glycoprotein-1	50	Glycoprotein	80,000*

Table here adapted from Table 1 in Schutters,K., and Reutelingsperger,C. (2010) Phosphatidylserine targeting for diagnosis and treatment of human diseases. *Apoptosis* **15** (9): 1072-1082.

Wild Type Annexin (Anx_{WT}) Targeting of PS

Anx_{WT} out competes β2-glycoprotein-1 (β2GP1) when targeting PS coated lipids *in vitro*.

- Phospholipid binding proteins are evaluated by coating lipid bilayers with 20% PS on to silicon slides and then measuring changes in the degree of light polarization as the binding proteins interact with the lipid bilayer. This is known as **Ellipsometry**.
- In a study using a physiologically relevant buffer of 120 mM NaCl and 3 mM $CaCl_2$, researchers showed the bridging effect of binding a 5 µg/mL concentration of an anti-PS using 100 nM of β2GP1 was tenuous.
- The addition of only 60 nM AnxA5 partially displaced the PS antibody. Figure A.
- The addition of EDTA captures Ca^{2+} ions, hence, disrupting the AnxA5 binding to PS, which is Ca^{2+}-dependent.
- Conversely, addition of a β2GP1/anti-PS complex was unable to disrupt AnxA5 binding. Figure B.



Adapted from Willems,G.M., Janssen,M.P., Comfurius,P., Galli,M., Zwaal,R.F., and Bevers,E.M. 2000. Competition of annexin V and anticardiolipin antibodies for binding to phosphatidylserine containing membranes. *Biochemistry* **39** (8): 1982-1989.

Phosphatidyl Serine and Immunosuppression

Is there data showing Wild Type Annexin A5 binding affects PS immunosuppression?

- Chemo and radiation therapies cause tumor apoptosis, resulting in PS exposure on the cell surface.
- Ironically, this PS exposure leads to an immunosuppressive environment in the tumor!
- Evidence is mounting that PS blockade with Annexin A5 decreases non-inflammatory uptake of tumor cells in macrophages and increases inflammatory uptake by dendritic cells:

Publications from Independent Labs
Lima,L.G., Chammas,R., Monteiro,R.Q., Moreira,M.E., and Barcinski,M.A. (2009) Tumor-derived microvesicles modulate the establishment of metastatic melanoma in a phosphatidylserine-dependent manner. *Cancer Lett.* **283** (2): 168-175.
Frey,B., Schildkopf,P., Rodel,F., Weiss,E.M., Munoz,L.E., Herrmann,M., Fietkau,R., and Gaipl,U.S. (2009) AnnexinA5 renders dead tumor cells immunogenic--implications for multimodal cancer therapies. *J. Immunotoxicol.* **6** (4): 209-216.
Munoz,L.E., Franz,S., Pausch,F., Furnrohr,B., Sheriff,A., Vogt,B., Kern,P.M., Baum,W., Stach,C., von,L.D., Brachvogel,B., Poschl,E., Herrmann,M., and Gaipl,U.S. (2007) The influence on the immunomodulatory effects of dying and dead cells of Annexin V. *J. Leukoc. Biol.* **81** (1): 6-14.
Bondanza,A., Zimmermann,V.S., Rovere-Querini,P., Turnay,J., Dumitriu,I.E., Stach,C.M., Voll,R.E., Gaipl,U.S., Bertling,W., Poschl,E., Kalden,J.R., Manfredi,A.A., and Herrmann,M. (2004) Inhibition of phosphatidylserine recognition heightens the immunogenicity of irradiated lymphoma cells in vivo. *J. Exp. Med.* **200** (9): 1157-1165.
Stach,C.M., Turnay,X., Voll,R.E., Kern,P.M., Kolowos,W., Beyer,T.D., Kalden,J.R., and Herrmann,M. (2000) Treatment with annexin V increases immunogenicity of apoptotic human T-cells in Balb/c mice. *Cell Death. Differ.* **7** (10): 911-915.

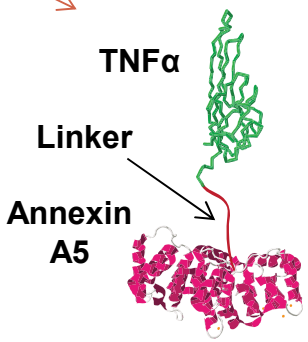
Proof of Concept Study using $AnxA5_{MOD}$

- Rubicon is creating $AnxA5_{MOD}$ derived fusion molecules that overcome tumor "editing" of the immune system by simultaneously shielding an agent of immunosuppression (phosphatidylserine) and presenting an effector signal for immunostimulation.
- As a proof-of-concept, we attached murine TNFα to our $AnxA5_{MOD}$ and tested it in a mouse triple negative breast cancer model.
- We determined that our $AnxA5_{MOD}$-TNFα construct has no toxicity at up to1 mg/kg in healthy animals, as verified in an independent commercial testing facility.
- This is well above the levels of TNFα deemed to be safe in clinical trials.

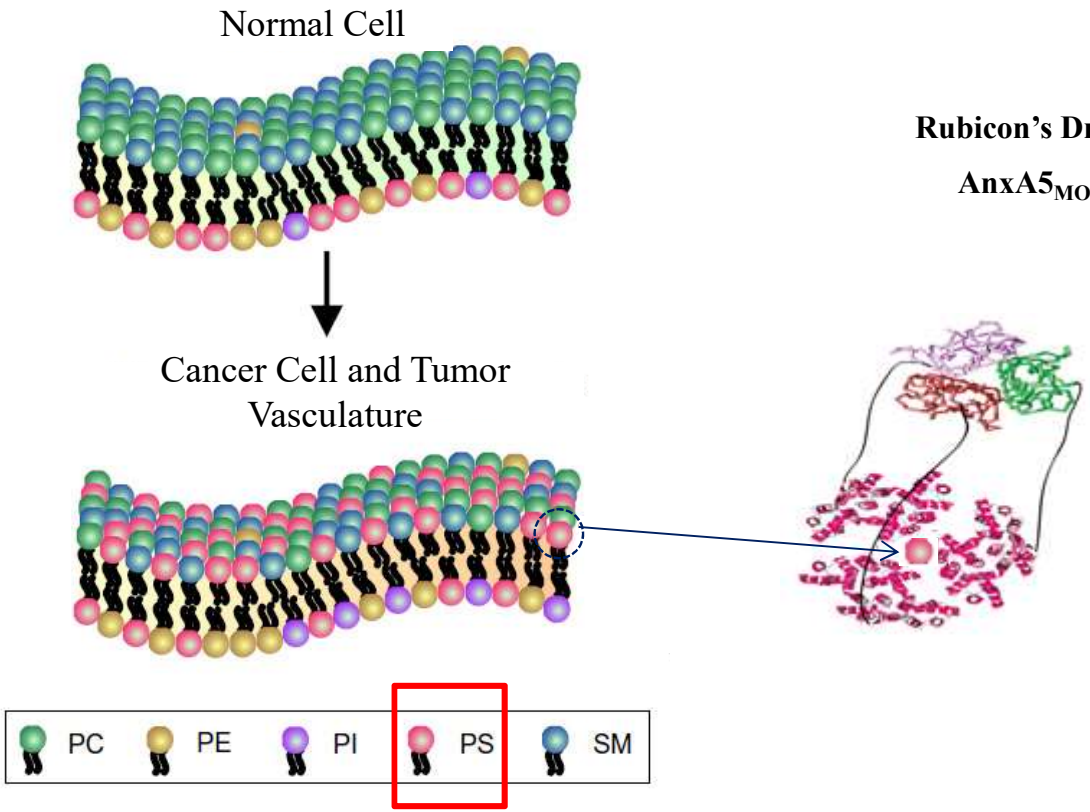
Roberts,N.J., Zhou,S., Diaz,L.A., Jr., and Holdhoff,M. (2011) Systemic use of tumor necrosis factor alpha as an anticancer agent. *Oncotarget* 2(10): 739-751.

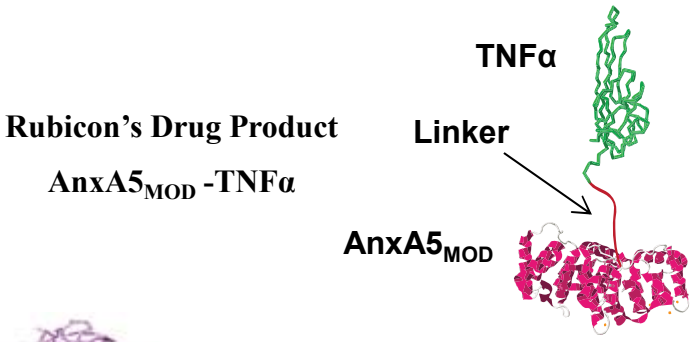
Modified Annexin A5, was designed to bind to exposed PS with the highest known affinity

Rubicon attached TNFα, a powerful anti-cancer agent, to the AnxA5



$AnxA5_{MOD}$ Mechanism of Action





Rubicon's Drug Product

$AnxA5_{MOD}$ -TNFα

Once injected, the $AnxA5_{MOD}$ will deliver the TNFα (or any other effector molecule) directly and specifically to the tumor, leaving healthy tissues alone.

Up to 3 Annexins can bind to one PS.

A trimer of TNFα is needed for activation, which can be assembled at the binding site.

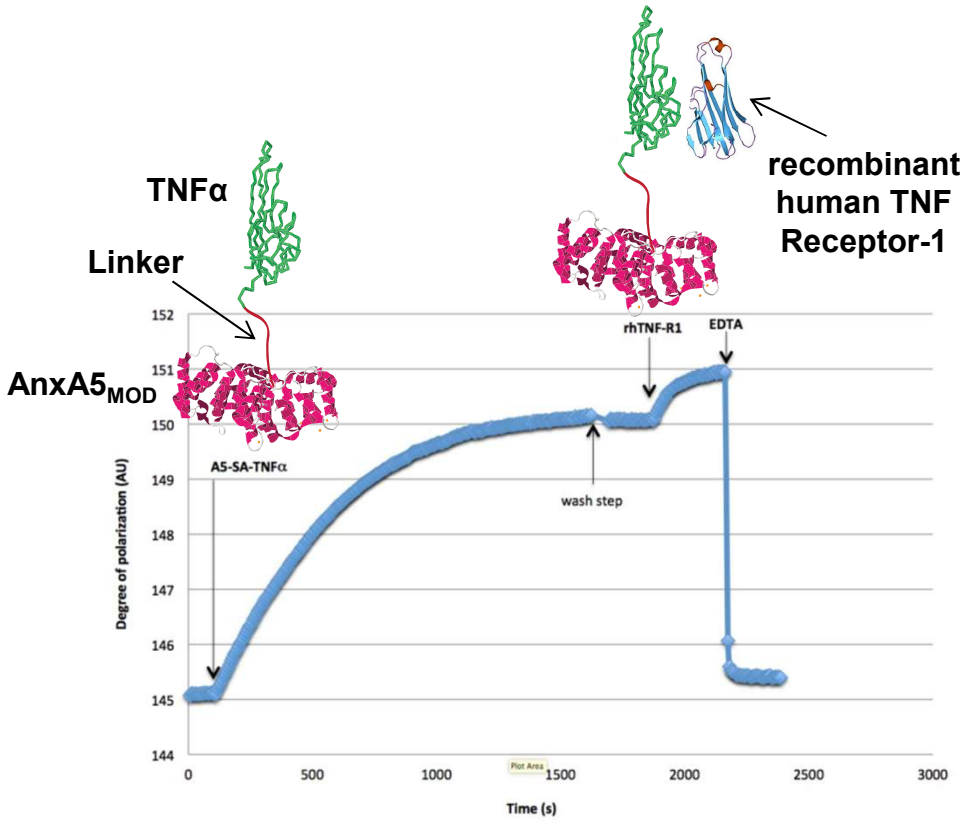
$AnxA5_{MOD}$ - TNFα Data

Triple Negative Breast Cancer Studies at Vanderbilt University

1. Well-established Triple Negative Breast Mouse Model (called 4T1) was used
2. Breast cancer tumors injected into the mice and allowed to grow for approximately 2 weeks
3. After the tumor reached a pre-determined size, $AnxA5_{MOD}$-TNFα was administered once or three times intravenously
4. After injection, the tumor size was measured by calipers and tumor viability by luminescence imaging of a citrine fluorescent protein (CFP) transfected into the tumor cells

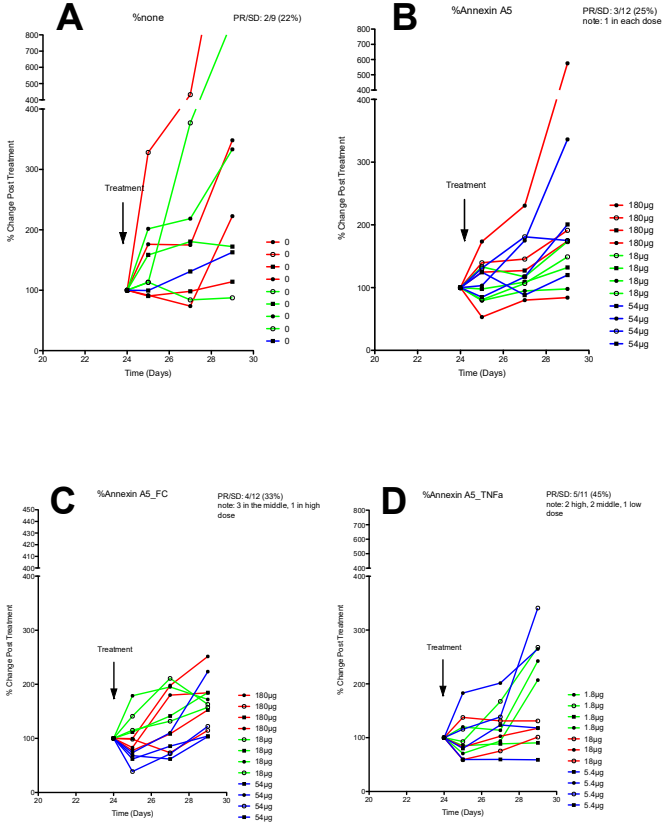
$AnxA5_{MOD}$ -TNFα Data

- Rubicon has an *in vitro* assay in place for testing new constructs, including the $AnxA5_{MOD}$ - TNFα shown here.
- We use ellipsometry to verify $AnxA5_{MOD}$ binding to PS and effector molecule binding to the relevant receptor or ligand.
- A phospholipid bilayer of 20% PS was stacked on a silicon slide for the analysis on the right.
- Successive incubations with $AnxA5_{MOD}$ - TNFα and then TNF Receptor-1 had protein binding recorded as a change in the degree of light polarization.
- The addition of EDTA captures Ca^{2+} ions, hence, disrupting the $AnxA5_{MOD}$ binding to PS, which is Ca^{2+}-dependent.

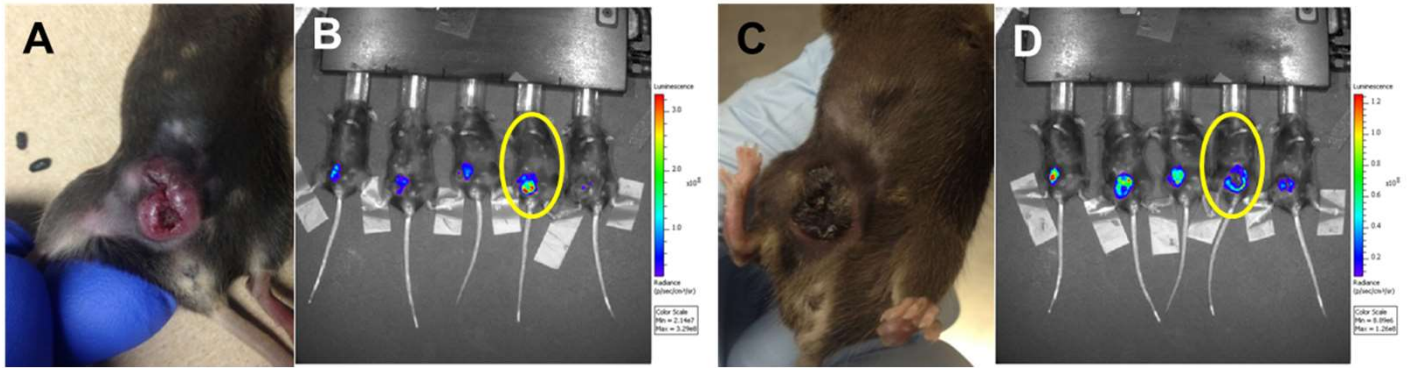


$AnxA5_{MOD}$-TNFα Single Injection Result

- 50 Balb/c mice were injected with the 4T1 tumor in the mammary fat pads and allowed to grow for 24 days before treatment with: 1) saline, 2) $AnxA5_{MOD}$ only, 3) $AnxA5_{MOD}$ bound to murine IgG2a, or 4) $AnxA5_{MOD}$ bound to TNFα.
- On day of treatment, mice received a single injection intra-retinal orbitally.
- Dosages of 18, 54 and 180 µg for the $AnxA5_{MOD}$ only and the $AnxA5_{MOD}$-IgG2a conjugate, and dosages of 1.8, 5.4 and 18 µg for the $AnxA5_{MOD}$-TNFα are shown.
- Tumor growth was tracked by caliper and the percent change in tumor volume graphed post-treatment.
- Note the lack of tumor growth inhibition when comparing the controls (Figure A) to $AnxA5_{MOD}$ only (Figure B) or $AnxA5_{MOD}$-IgG2a (Figure C).
- Tumor inhibition was seen with the 18µg dosage of $AnxA5_{MOD}$-TNFα (Figure D).



$AnxA5_{MOD}$-TNFα Single Injection Result



A. *PyMT tumor bearing mouse prior to $AnxA5_{MOD}$-TNFα injection*

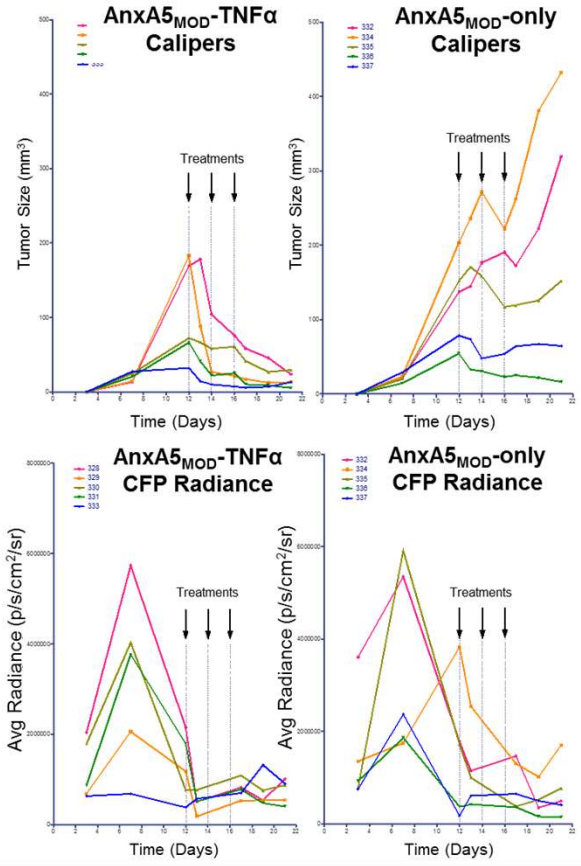
B. *The PyMT model could be imaged by bioluminescence since it expressed a citrine fluorescent protein (CFP). Note the mouse in A had the largest tumor in its group (circled in yellow) and was treated while the others had tumors too small for treatment.*

C. *The same tumor show signs of gross necrosis 35 hours post-injection.*

D. *Cell death is more than skin deep as the pattern of CFP luminescence is greatly diminished.*

Note: PyMT tumors are a second breast tumor model in which we were able to evaluate our research molecule.

$AnxA5_{MOD}$-TNFα Multiple Injection Result

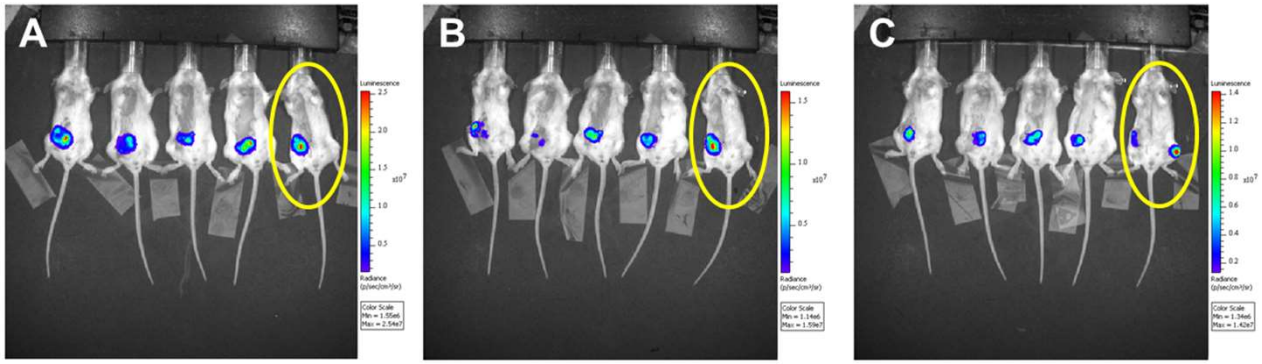


Results of the 4T1 (murine Triple Negative Breast Cancer) model:

- **$AnxA5_{MOD}$**-TNFα (18 µg) or **$AnxA5_{MOD}$**-only (180 µg) was administered on days 12, 14 and 16 (black arrows)
- Tumor growth was tracked both by caliper (Figures A,B) and by CFP luminescence (C,D)
- While caliper measurements indicated no change in the tumor volume for those mice treated with **$AnxA5_{MOD}$**-only (Figure B), the CFP radiance detected by imaging indicates an early response to this treatment (Figure D), supporting the observations of others regarding **$AnxA5_{MOD}$**'s ability to overcome PS immunosuppression; however, continued monitoring revealed a relapse of the tumors.
- **Treatment with $AnxA5_{MOD}$-TNFα revealed a more consistent tumor reduction both by caliper (Figure A) and CFP bioluminescence (Figure C).**

$AnxA5_{MOD}$-TNFα Multiple Injection Result

Imaging of the CFP radiance for four 4T1-bearing mice treated with Modified AnxA5-TNFα and one receiving Modified AnxA5 only (circled yellow).



A) Image of tumor on Day 12 (prior to treatment)

B) Day 13 (1 day post-treatment)

C) Day 19 (7 days post-treatment from 1st injection on Day 12)

Injection of mice occurred on Days 12, 14 and 16.

Note the presence of a 4T1 metastasis on the $AnxA5_{MOD}$ Only treated mouse and the stagnant state of the tumors in the four mice treated with $AnxA5_{MOD}$-TNFα.

$AnxA5_{MOD}$ Program: Study Conclusions

- The key to specific PS targeting in the tumor microenvironment is to create a **targeting agent** that binds specifically and **directly to PS.** Rubicon's Modified Annexin A5, a protein with the highest known affinity to PS, is that key.
- In our Phase I SBIR grant, an AnxA5 conjugate with tumor necrosis factor α (**$AnxA5_{MOD}$-TNFα**) provided evidence that this approach offers a uniquely effective strategy to direct the patient's immune system to 4T1 tumors, a murine version of **triple negative breast cancer (TNBC)**.
- Over 200,000 women per year are diagnosed with breast cancer in the US, representing 29% of all new cancer diagnoses in women.
- Of these, 10-20% are diagnosed as TNBC [tumors not expressing estrogen receptor (ER), progesterone receptor (PR), or HER-2 genes] and have exceptionally poor prognoses.
- Future studies include other effector proteins.

Important Points

We bind an immutable target and checkpoint inhibitor that is localized to the tumor so targeting should be less disruptive to a patient's overall immune system.

- We target Phosphatidylserine (PS), a phospholipid found on the inner leaflet of normal cells but on the outer surface of tumors and their vasculature. All solid tumors!
- Phosphatidylserine is immutable. It is an integral part of the cell's membrane. Its expression cannot be mutated nor effected by acquired drug resistance.
- PS causes immunosuppression.
- We use PS as a target for binding, which disrupts its immunosuppression and we deliver other immunoactivators simultaneously.
- Our proof-of-principle contruct, $AnxA5_{MOD}$-TNFα, was safe up to 1 mg/kg in toxicity studies.

Remember This

Unlike other immunotherapies which inhibit the checkpoint inhibitors (e.g. PD-1/PD-L1, CTLA-4); Rubicon inhibits an inhibitor while simultaneously activating the activators.

Platform Technology Overview

Thank You

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