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Targeting Cancer with a Novel Antibody Drug Conjugate

PI: Lajos Pusztai, M.D., D.Phil.

Professor of Medicine, Director of Breast Cancer Translational Medicine,

Co-Director of the Genetics and Genomics Program,

Yale Cancer Center

Apeiros Team

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Lajos Pusztai, MD, DPhil. Role: PI

- Two decades of experience in laboratory and translational research
- Principal investigator of several Phase I, II and III trials and internationally recognized clinical trialist.
- Chair NCI-SWOG Breast Committee
- Inventor of several patents (http://patents.justia.com/inventor/lajos-pusztai)
- Published of over 300 manuscripts in high impact medical journals

Daryl E Klein, MD, PhD Role: Co-PI

- Leads the Fab discovery phage display program at the Yale Cancer Biology Institute
- Expert in protein production and structural biology

Jamison Langguth, MSED, MPH Role: Business Development

- 8 years of clinical trials operations experience (4 years in oncology)
- Co-founder, Aero Therapeutics
- Management degree from Harvard
- Current Blavatnik Fellow in Life Science Entrepreneurship at Yale

David Lewin, PhD Role: IP Management / Advisor

- 14 years of licensing and marketing experience in life sciences
- >20 years successfully managing scientific-based business alliances with pharmaceutical leaders in the U.S., Europe and Japan.

The continued challenge of cancer

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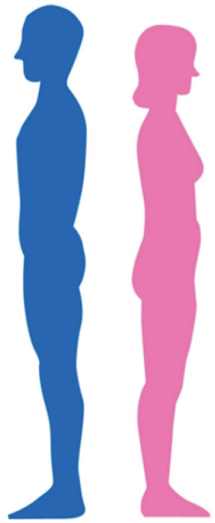
In 2019, cancer deaths overtook cardiovascular deaths in many industrialized countries. (Dagenais et. al. Lancet, Sept 03, 2019)

Our goal is to generate a novel drug, humanized anti-GABRP antibody that is conjugated to DM1 (or similar cytotoxic cargo) to treat cancers that express high levels of the GABRP receptor.

New cases per year, 2018

Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All Sites	**870,970**	**100%**	**All Sites**	**891,480**	**100%**



Antibody drug conjugates (ADC):

1. Cancer-targeting reduces adverse effects
2. Allows delivery of highly effective toxins
3. Favorable efficacy / toxicity profile
4. Several notable success stories
5. Past failures to learn from

A novel ADC target

GABRP; gamma amino butyric acid receptor pi subunit

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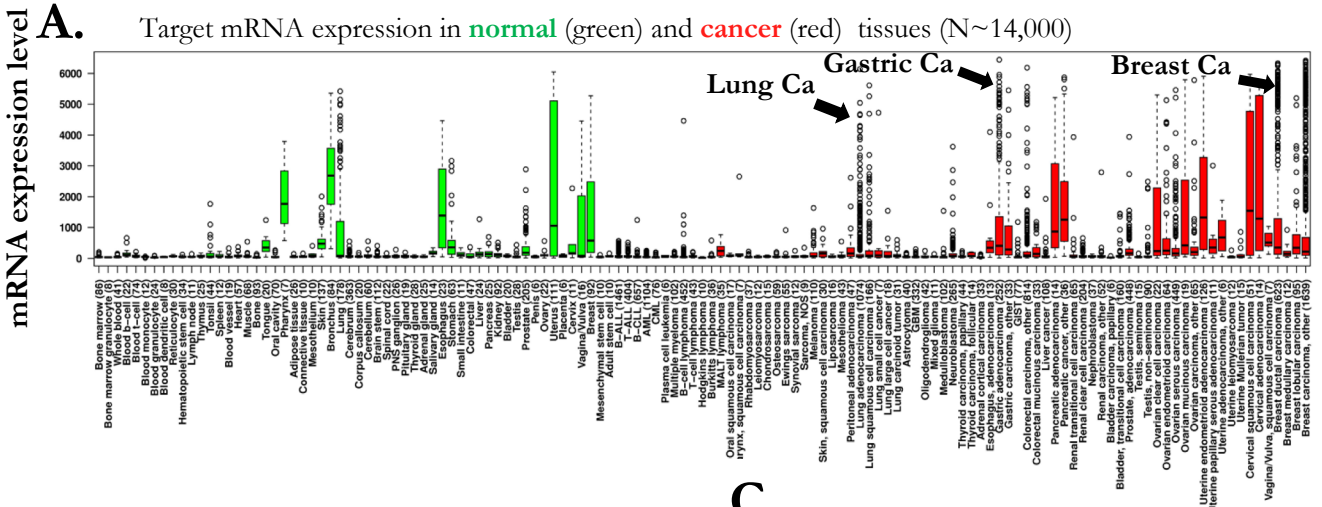
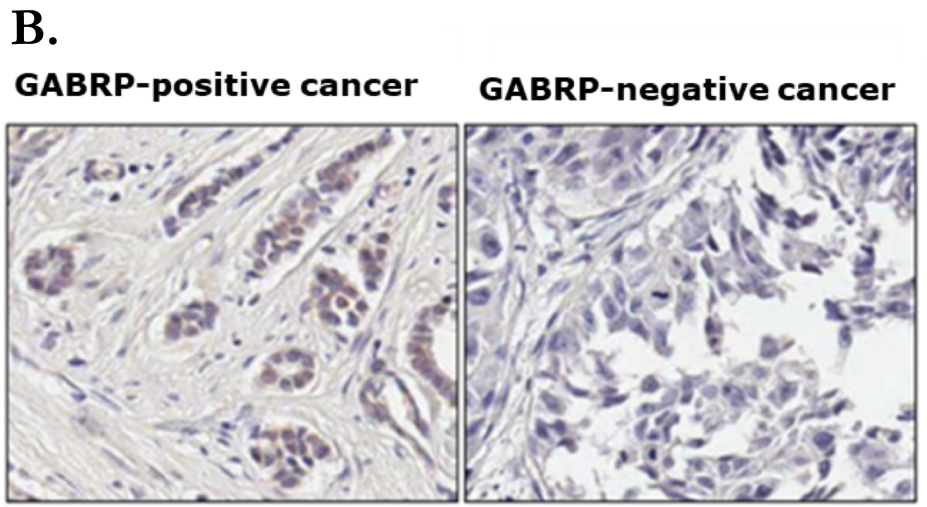
Panel A:

- GABRP mRNA is an aberrantly expressed cell surface receptor subunit, high in breast, lung, gastric, pancreatic, ovarian and colorectal cancers.
- Low in normal tissues.



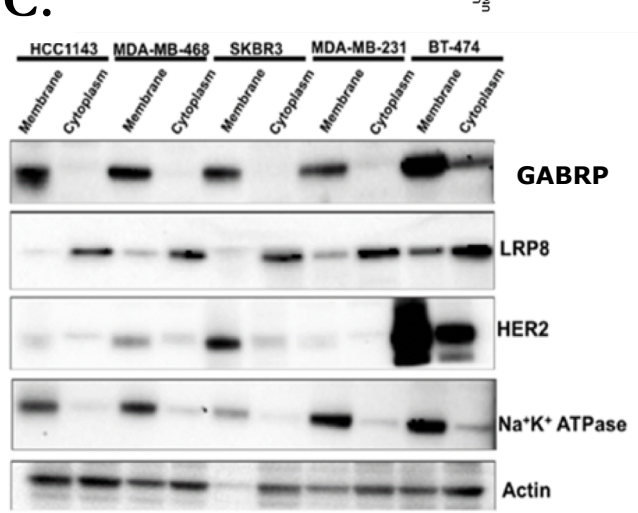
Panel B:

- GABRP protein can be detected by immunohistochemistry in subsets of breast cancer



Panel C:

- GABRP protein is expressed in the cell membrane



Wali VB, et al. Identification and Validation of a Novel Biologics Target in Triple Negative Breast Cancer. *Scientific Reports*. 2019;9(1):1-0.

Proof of principle functional studies

GABRP gene knockdown and anti-GABRP antibody impair cell viability

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Panel A:

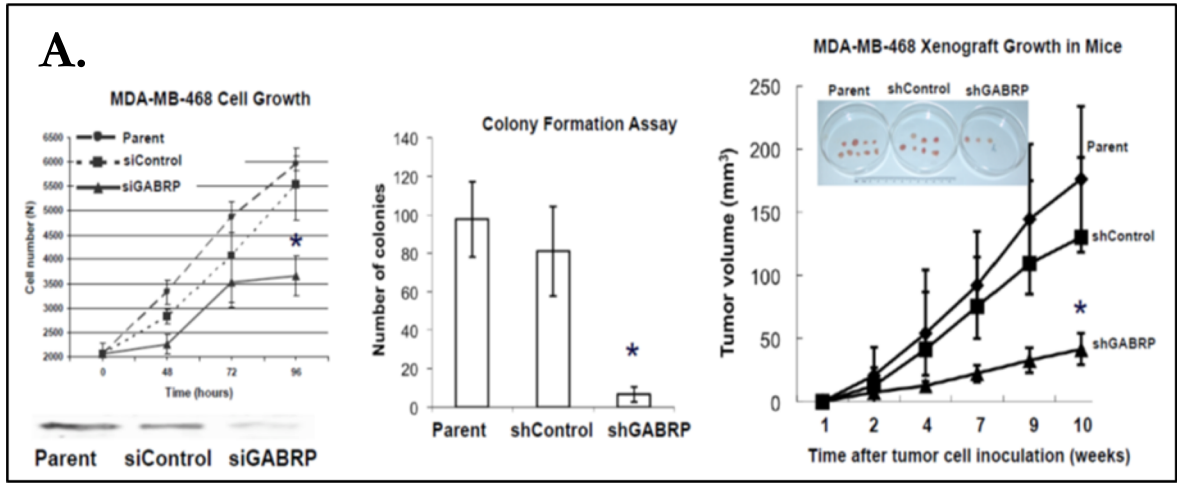
- GABRP knock-down cells show impaired growth in mice xenografts.

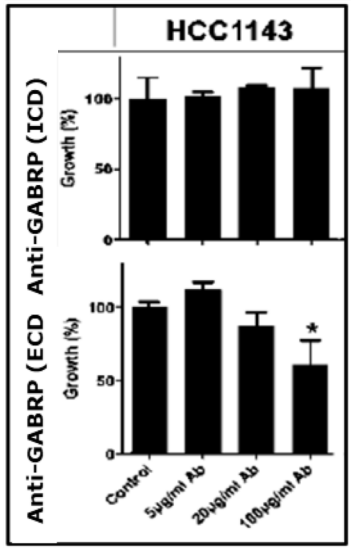
Panel B:

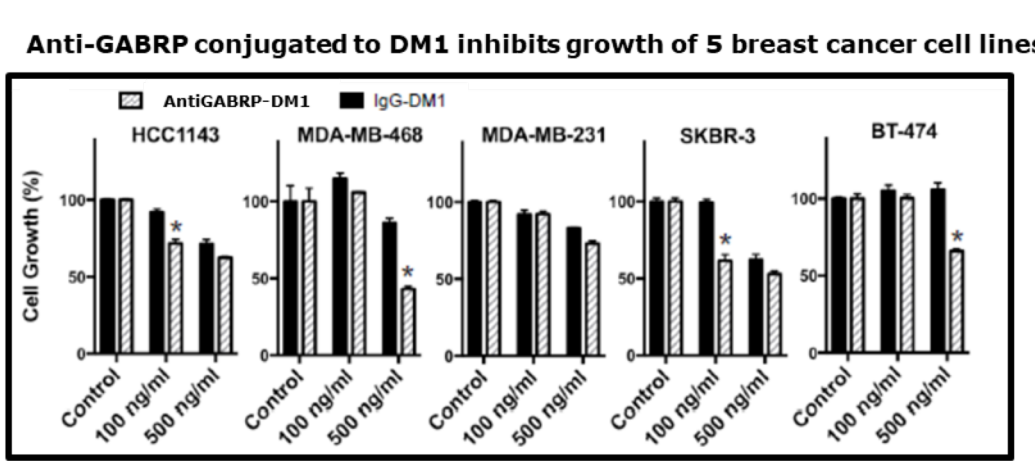
- Naked anti-GABRP extracellular domain (ECD), but not intracellular (ICD) domain, targeting antibody inhibits cell growth in vitro

Panel C:

- Anti-GABRP (ECD) conjugated to DM1 toxin inhibits cell growth in all 5 GABRP+ cell lines in vitro







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Generation of a series of proprietary antibody fragments (FAB) to target GABRP

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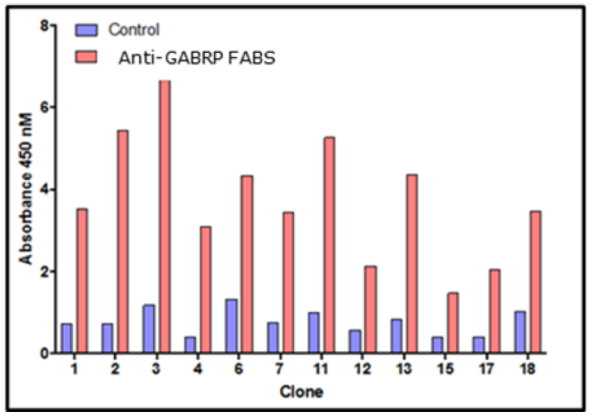
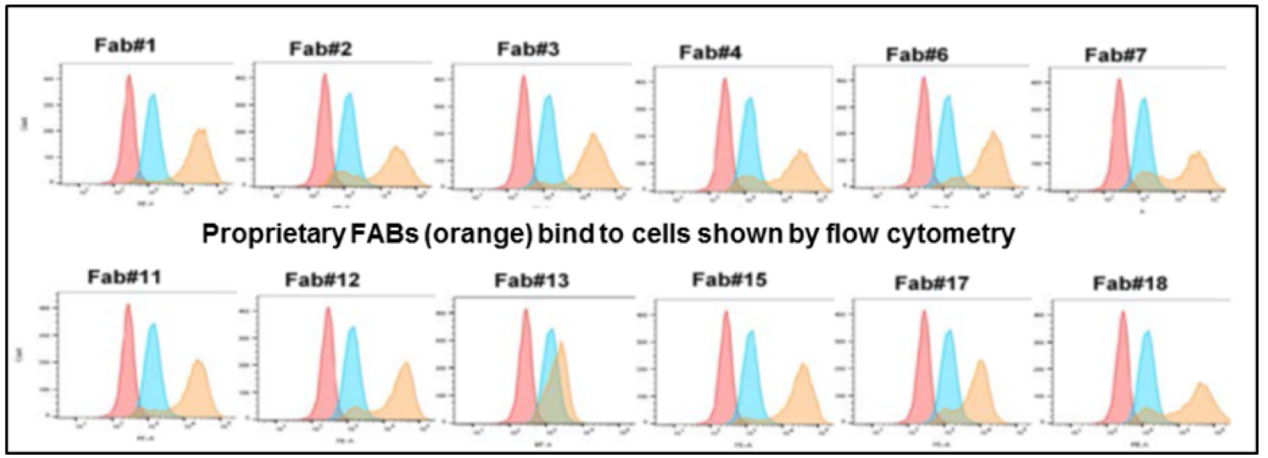
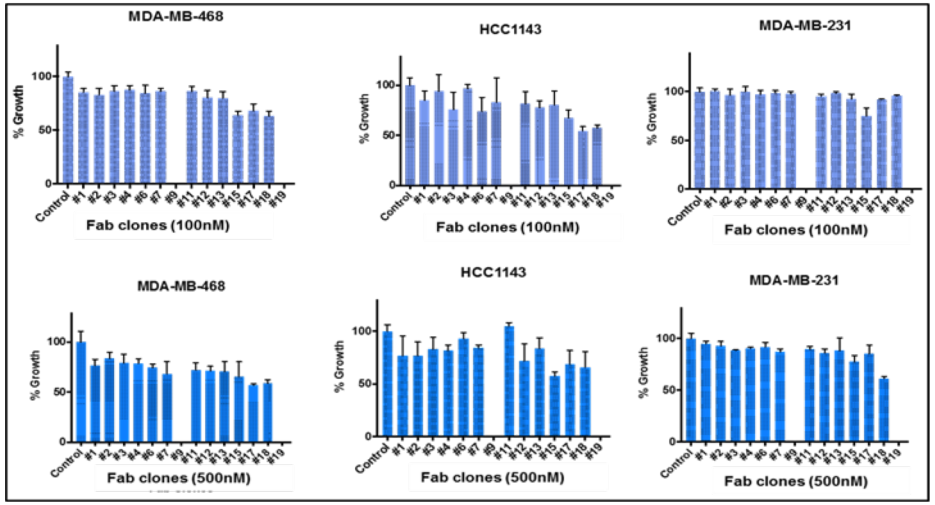
In vitro binding of FABs to GABRP using ELISA



FAB binding to GABRP expressing MD-MB468 cells using flow cytometry



Naked anti-GABRP FABs inhibit cell growth in vitro



Patent Pending

"Anti-GABRP Antibodies and Fragments Thereof, Conjugates Comprising Same, and Methods of Use"

ADC Market Size in TNBC alone by 2024

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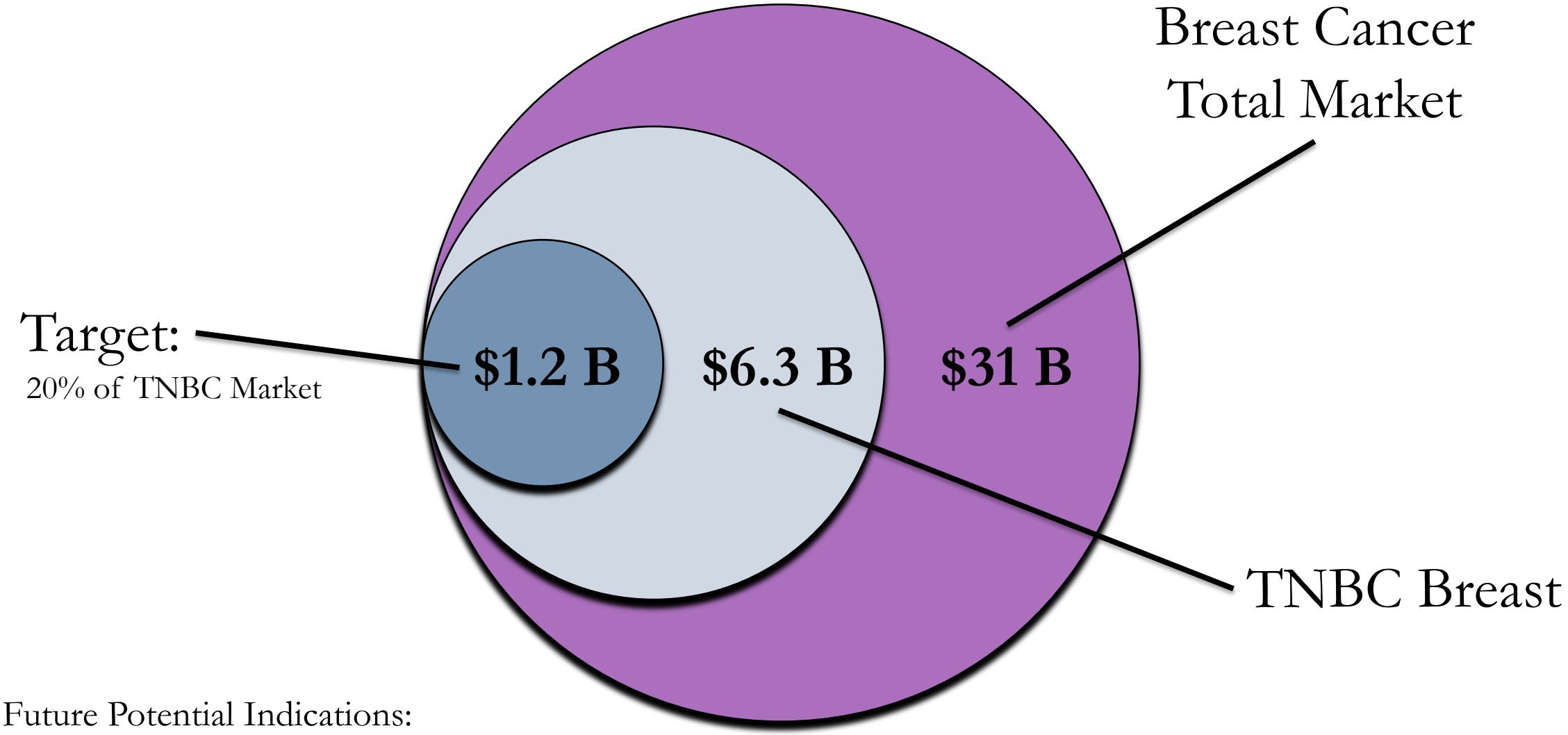

Future Potential Indications:

Lung, Gastric, Pancreatic, Ovarian and Colorectal.

Competitive Landscape

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	Immunomedics	Seattle Genetics	Celldex	Sanofi	Pfizer	Pfizer
Other name	Sacituzumab Govetican / IMMU-132	Ladiratuzumab vedotin / SGN-LIV1A	Glembatumumab vedotin / CDX-011	SAR566658	cofetuzumab / PF6647020	PF6647263
Target	Trop-2	LIV-1	gpNMB	CA6	PTK7	EphA4
Tumor expression	88%	71%	40%	UNK	29%	UNK
Cytotoxin	SN-38	MMAE	MMAE	maytansinoid DM4	auristatin-0101	Enediyne/DNA
Single-agent activity (ORR)	35%	27%	18%	13%	20%	0%
Registrational trials	ASCENT ≥3rd line	Active arm in ISPY-2; Phase II trial 2018	METRIC; 1st-3rd line; Same as Capecitabine	Phase II	Phase II	Phase I

FDA approved ADCs (2019):

1. Ado-trastuzumab emtansine (TDM1) for HER2 positive Breast Cancer
2. Brentuximab vedotin for CD30 positive Hodgkin's lymphoma
3. Gemtuzumab ozogamicin for CD33 positive Acute Myeloid Leukemia

Kadcyla™ worldwide sales 914 million USD in 2018.

Where we are, and where we want to be

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1. We have:
   - Identified a novel target that is high in cancers low in normal tissues and developed a detection assay
   - Demonstrated proof-of-principle functional importance and inhibitory effect by naked antibody and ADC
   - Generated proprietary FABs and secured initial IP

2. Next steps to IND
   - Affinity maturation and generation of a full length humanized anti-GABRB antibody.
   - Custom conjugation to cytotoxic cargo (i.e. DM1, exatican, SN38) and characterization of cytotoxic effect in vitro and in vivo.
   - GMP production, pre-clinical PK and toxicity studies

3. Phase I/II clinical testing
   - Intimal focus on TNBC in the neoadjuvant and first/second line metastatic space

Timeline to the clinic

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