

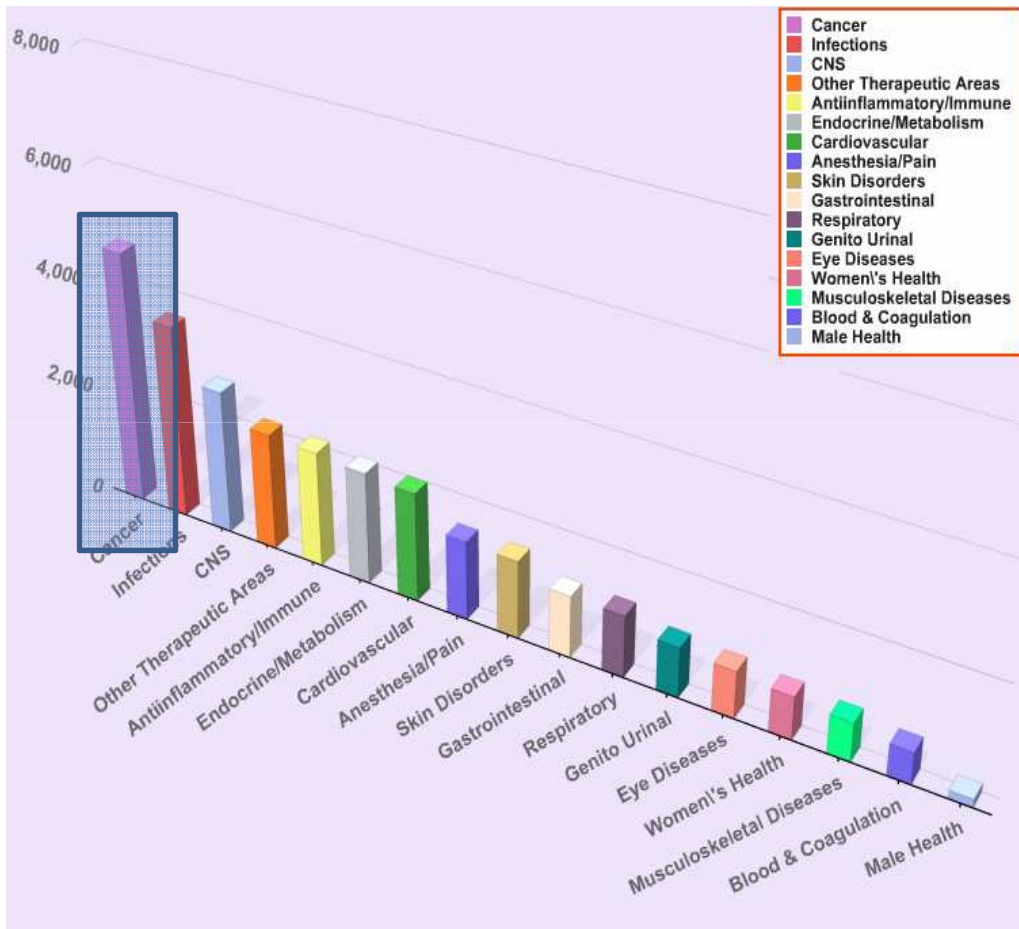
CANCER & BIOLOGICALS MARKET ANALYSIS AND OVERVIEW

Tugrul T. Kararli

PharmaCircle

www.pharmacircle.com

CANCER

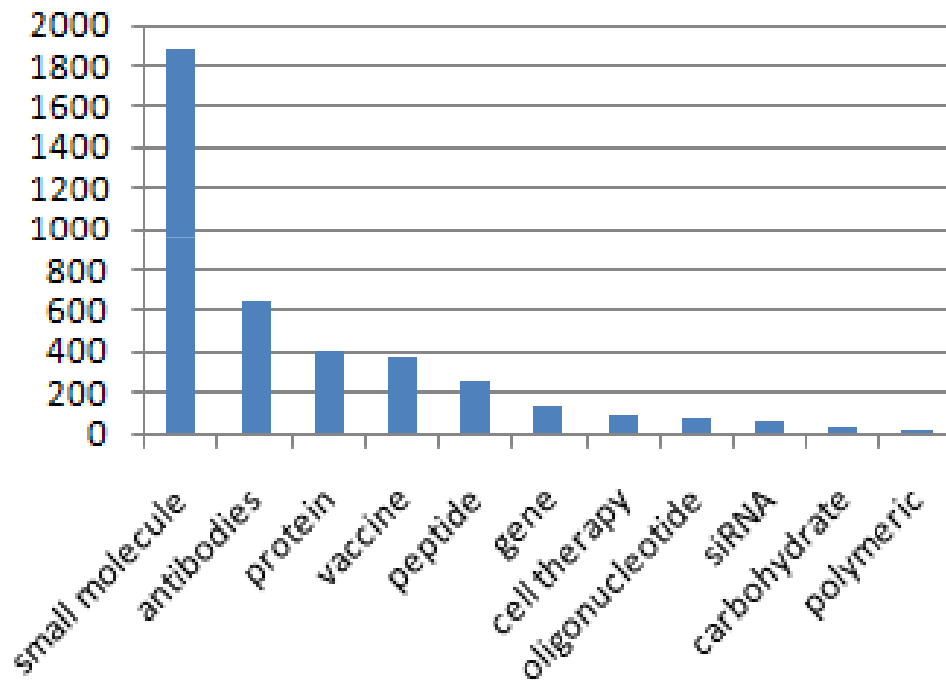


- Large segment of global products and pipeline
- **Products&Pipeline:** 16% (research to marketed phase)
- **Pipeline:** 21% (all but marketed)

MOLECULE TYPE

Biologicals; half of all cancer programs

MOLECULE TYPES & CANCER

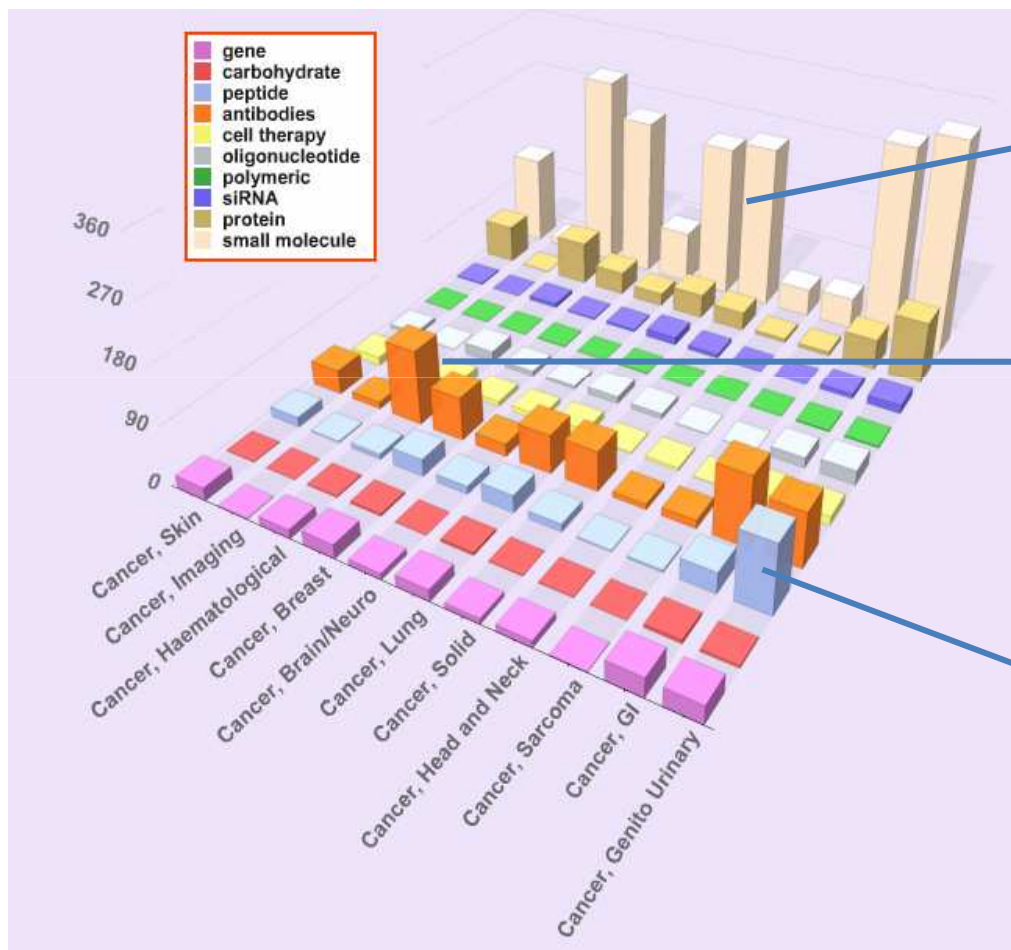


Biologicals

- 40% of all therapeutic categories
- 52% of cancer
- **Antibodies** the largest segment in cancer biologicals

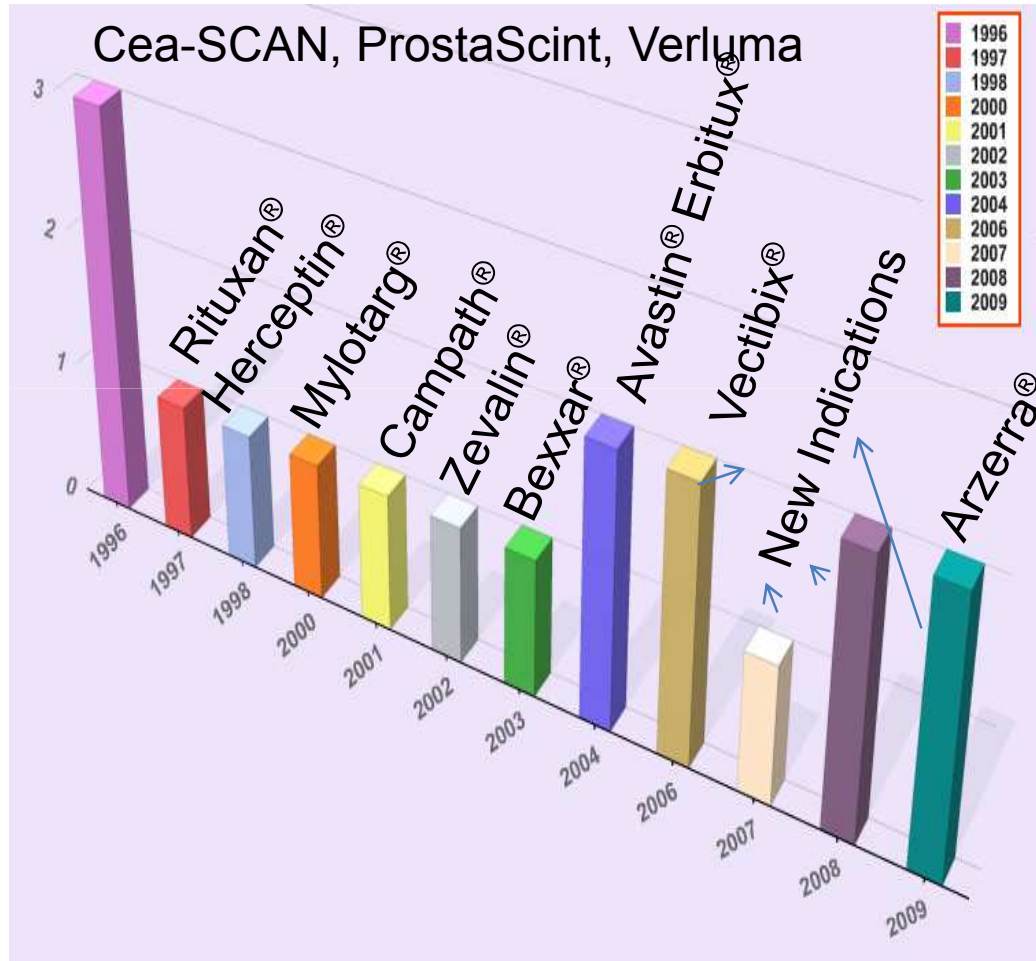
CANCER TYPES VS. MOLECULE TYPE

n=3653



- Small Mol. dominates all cancer categories
- Antibodies in haematological , GI, Genito urinary cancers
- Peptides in prostate cancer

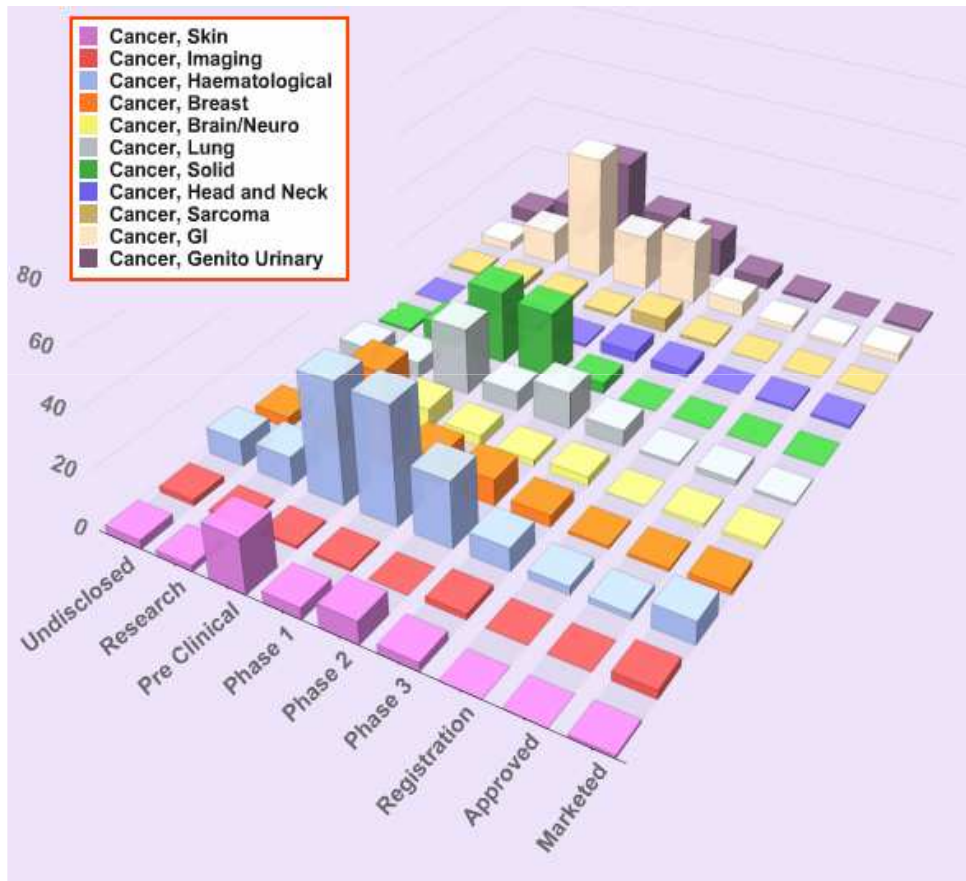
ANTIBODIES MARKETED FOR CANCER



- First diagnostic antibodies approved in 1996 for imaging; CEA SCAN, ProstaScint and Verluma
- Rituxan: First Therapeutic antibody approved in 1997 for NH-Lymphoma
- Arzerra is the latest for Cancer CLL

ANTIBODIES, CANCER

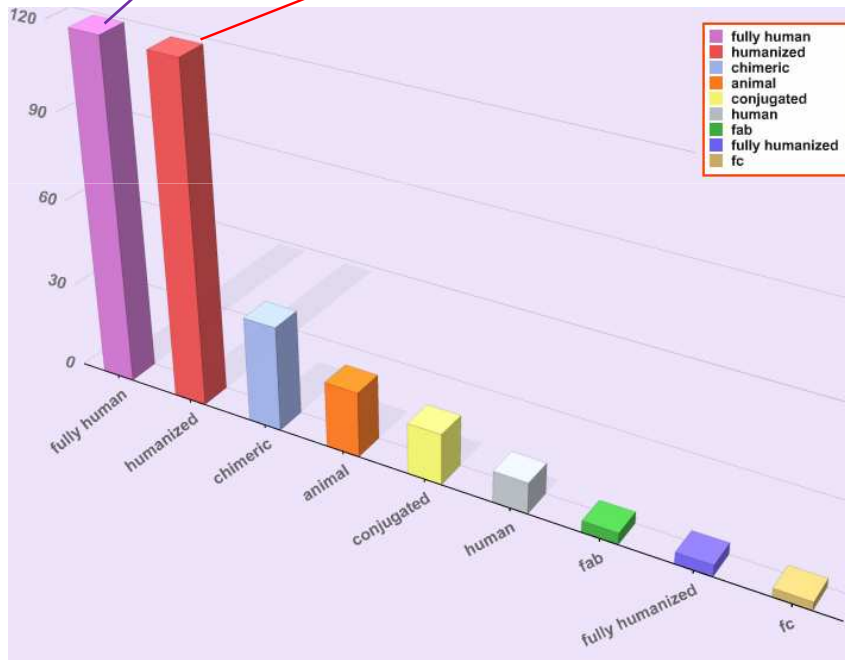
n=641



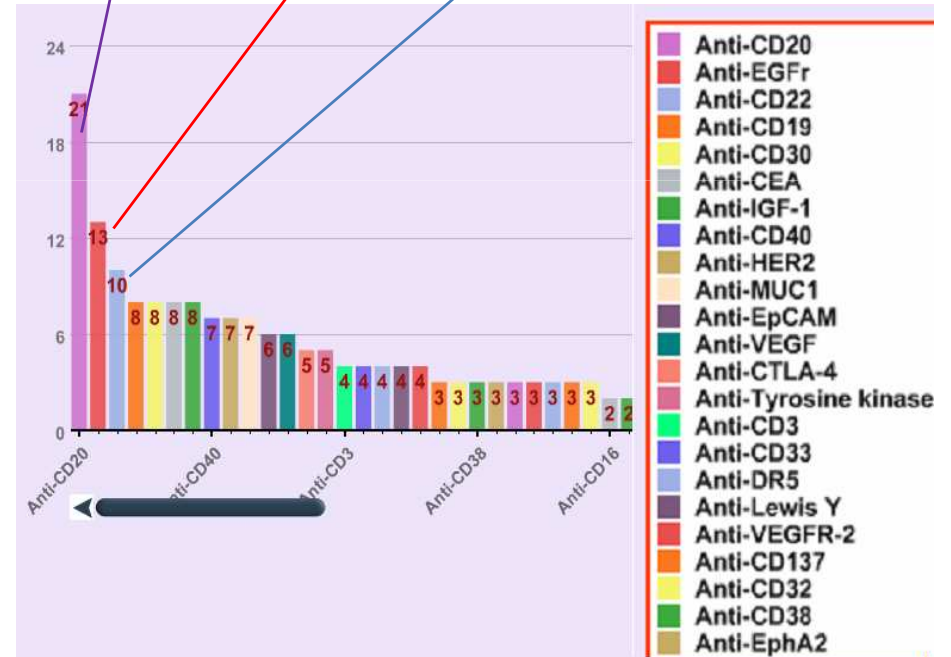
- Across all cancers; Haematological, GI, genito urinary, breast, solid, lung cancers, etc.

ANTIBODY AND CANCER

Fully Human and Humanized

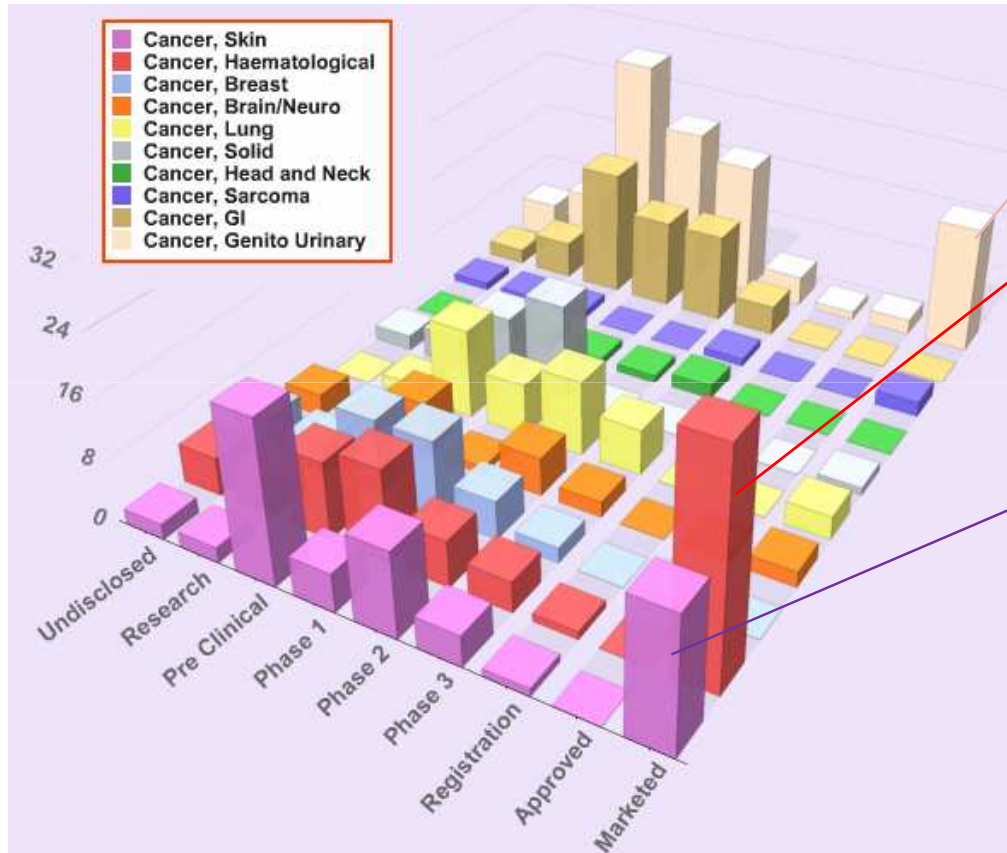


Anti-CD20/-EGFr/-CD22, etc.



PROTEIN, CANCER

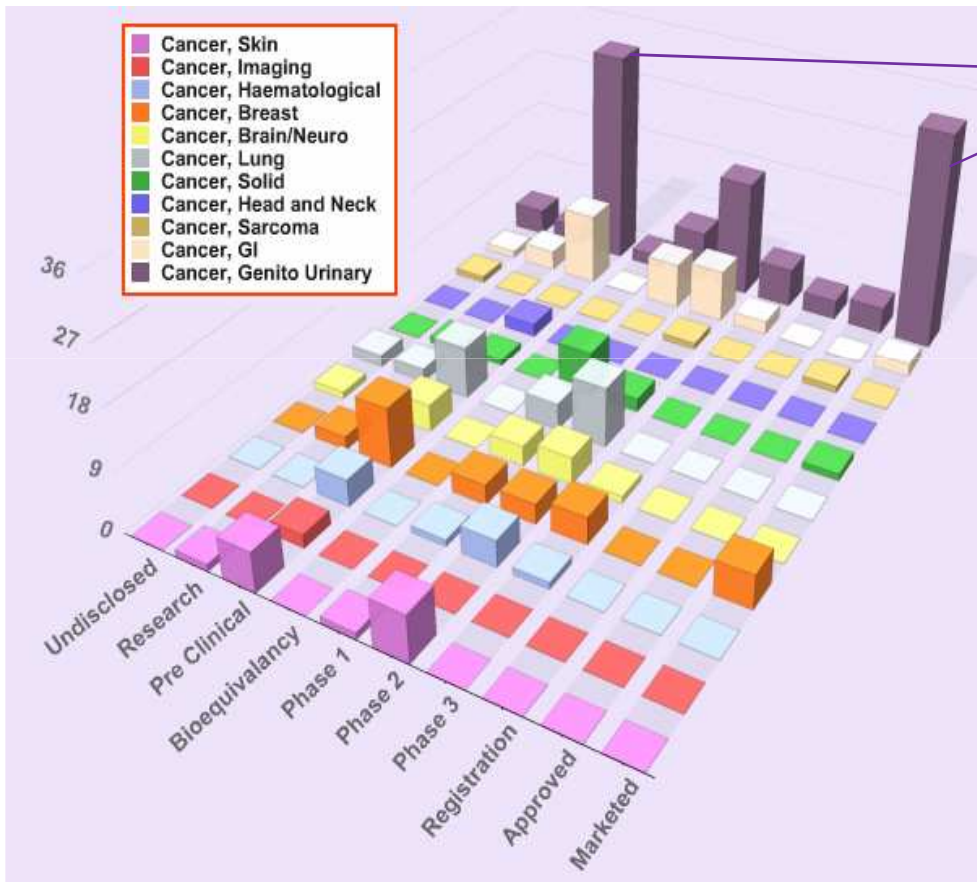
n=432



- Genito Urinary, haematological and skin cancers
- Proteins classes
Interferons > Interleukins
>TNF α > asparaginase analogs

PEPTIDE, CANCER

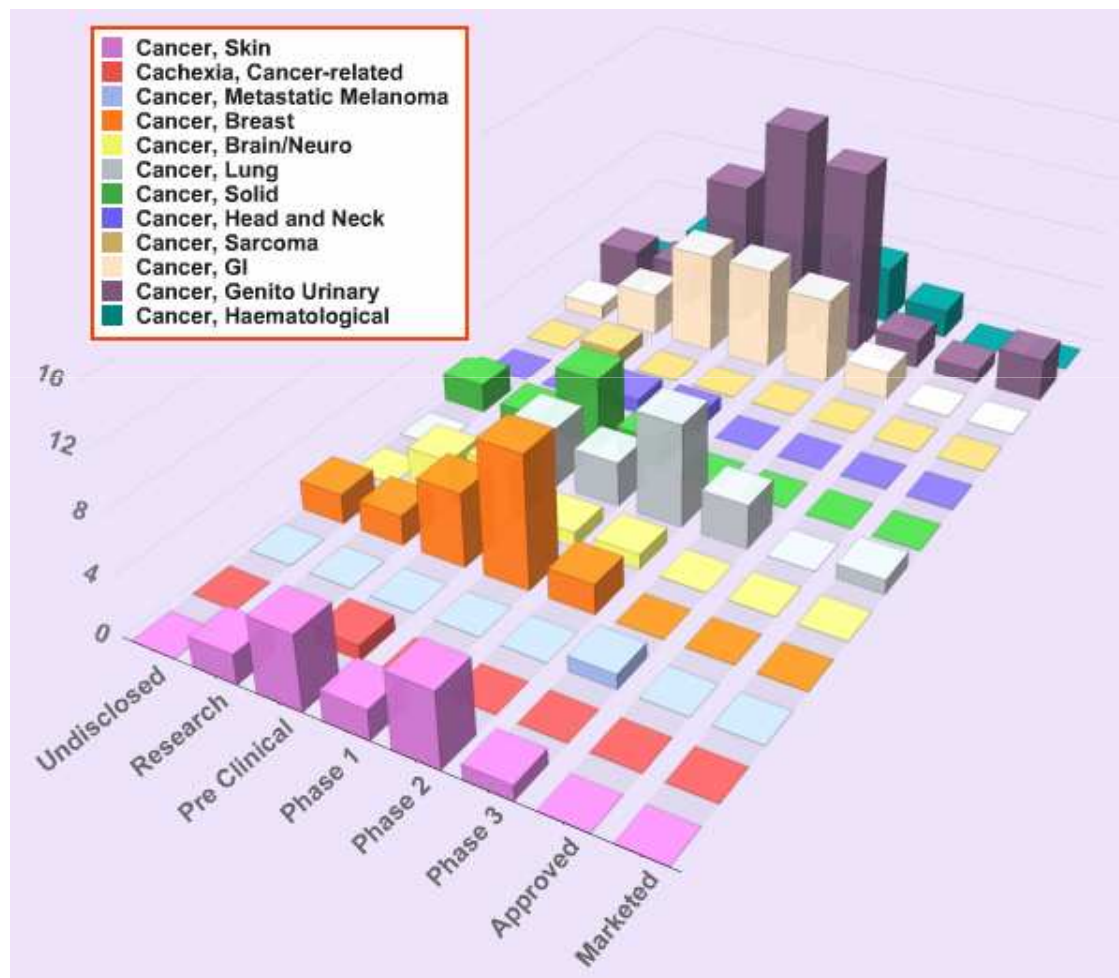
n=256



- Majority for Prostate cancer; Lupron Depot, Zoladex, etc.
- Majority of Gonadotropin Releasing Hormone Agonists

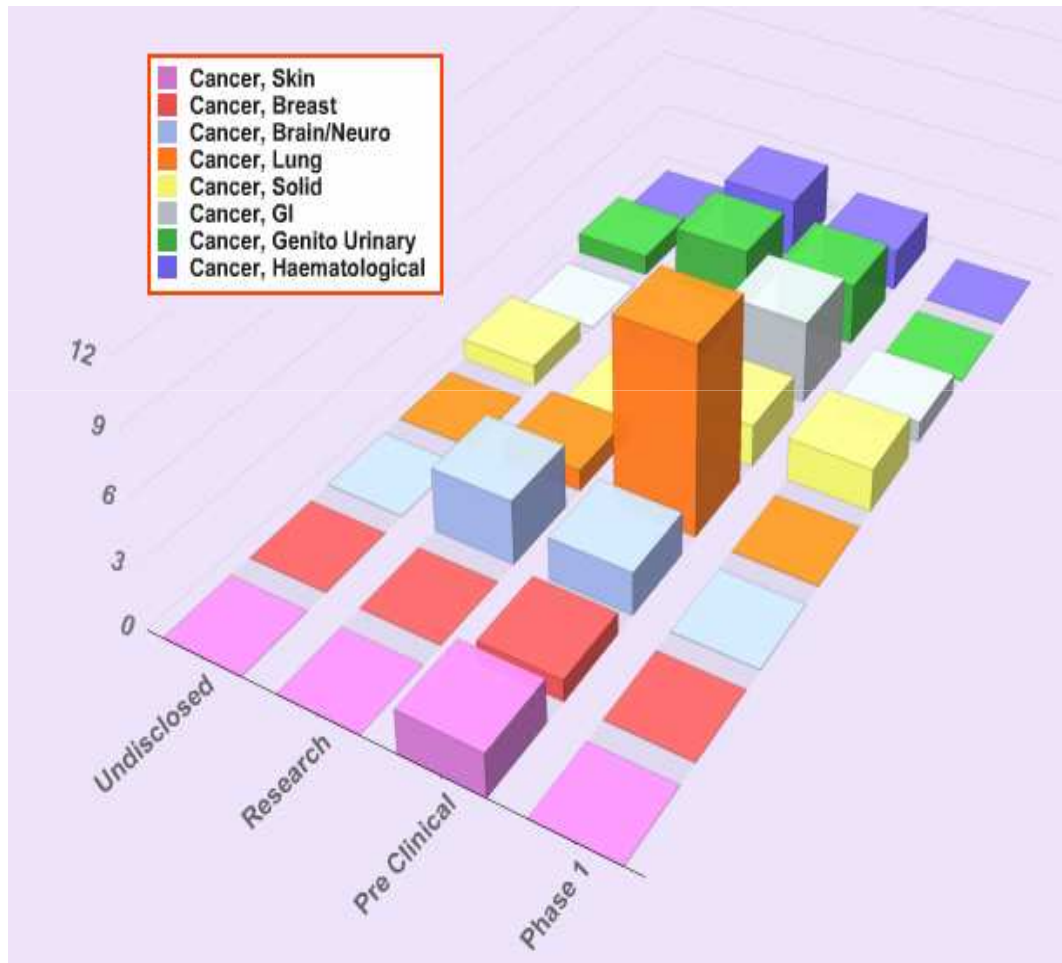
VACCINE, CANCER

N=169



- Genito urinary >GI, Breast, Skin and lung cancers
- Cell and DNA based vaccines dominate pipeline
- Cervarix (2007) and Gardasil (2006) latest approvals

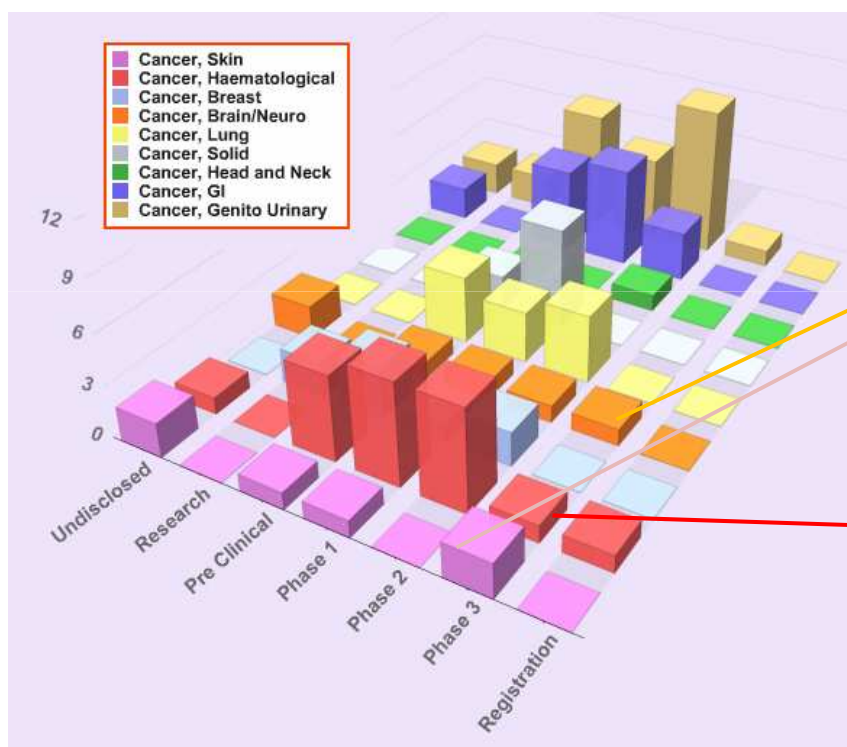
siRNA & CANCER (n=40)



- Early programs across cancer categories
- Targets; VEGF, interferon, kinases, RRM2, ApoB, etc.

OLIGOS/ANTISENSE, CANCER

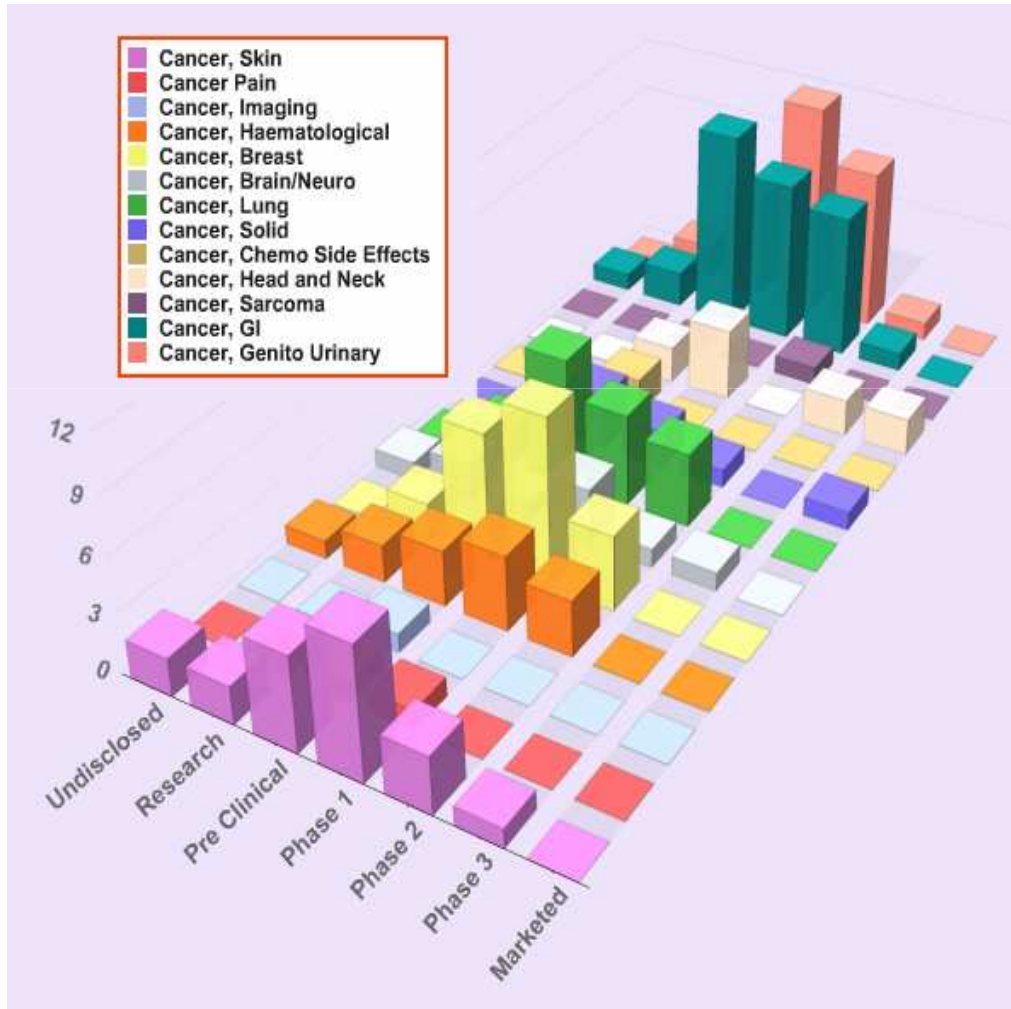
n=102



- Genasense (oligonucleotide, blocks Bcl-2 protein) / **Genta**, Cancer CLL and other cancers
- AP12009 (antisense blocks TGF-beta2), for brain cancer **Antisense Pharma GMBH**

GENE, CANCER

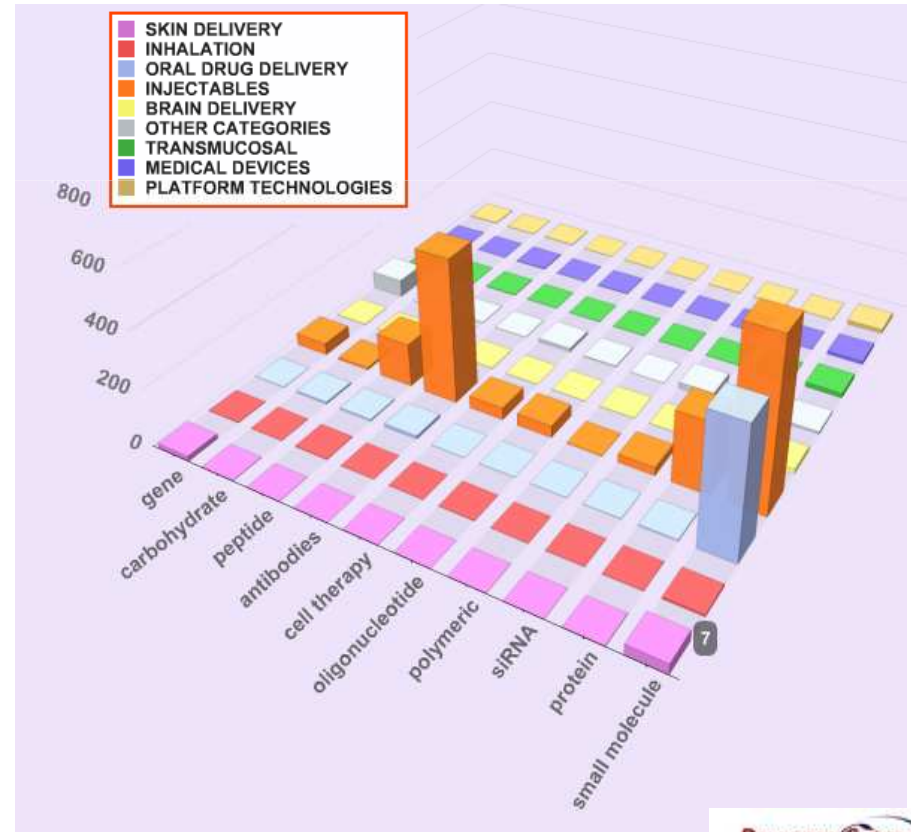
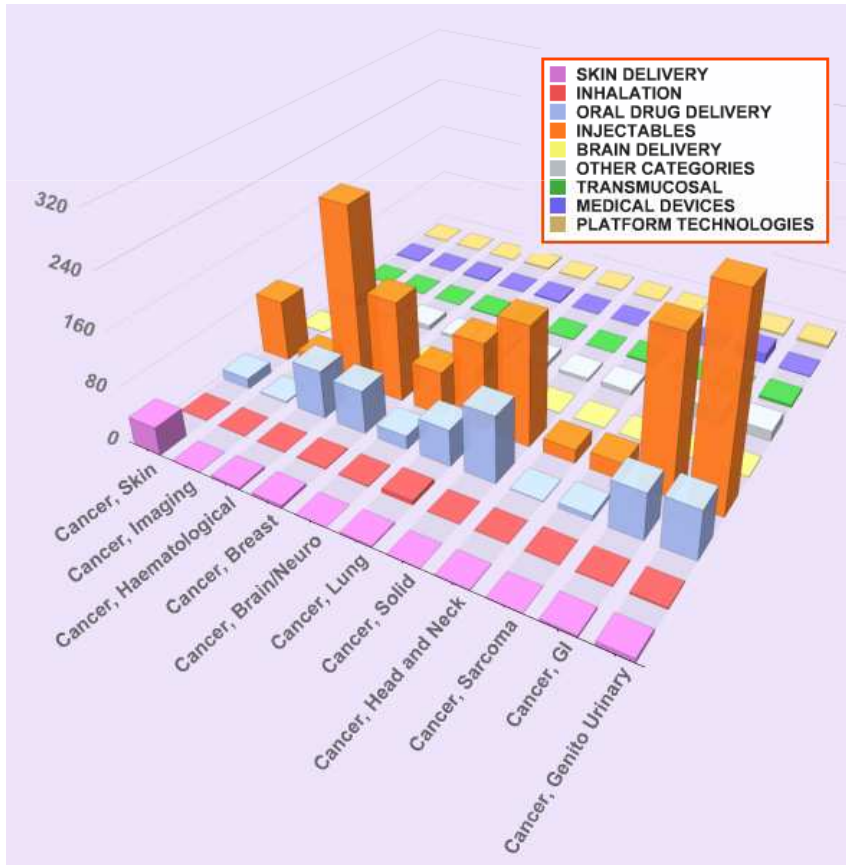
n=98



- **Gendicine** (2003) marketed for head and neck and solid cancer and **H101** (2005) for head & neck cancer in China
- GI, genito urinary, breast, skin and lung cancer programs
- Various targets, p53 etc.

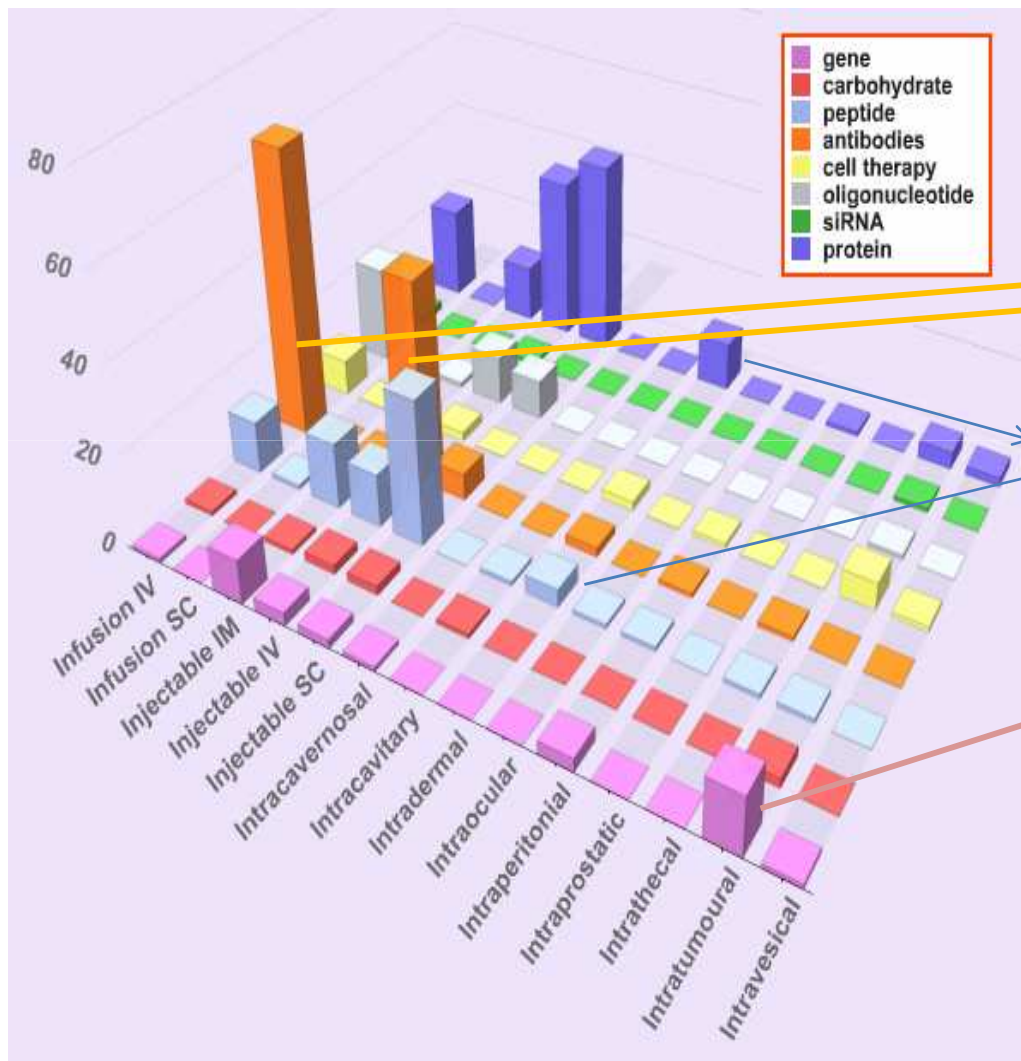
DELIVERY VS. CANCER (n=2400)

- Small molecules delivered by injectable & oral routes
- All biologicals by injectable routes
- A few inhalation and skin delivery programs for lung and skin cancers



MOLECULE TYPE VS. INJECTION SITE

n=448



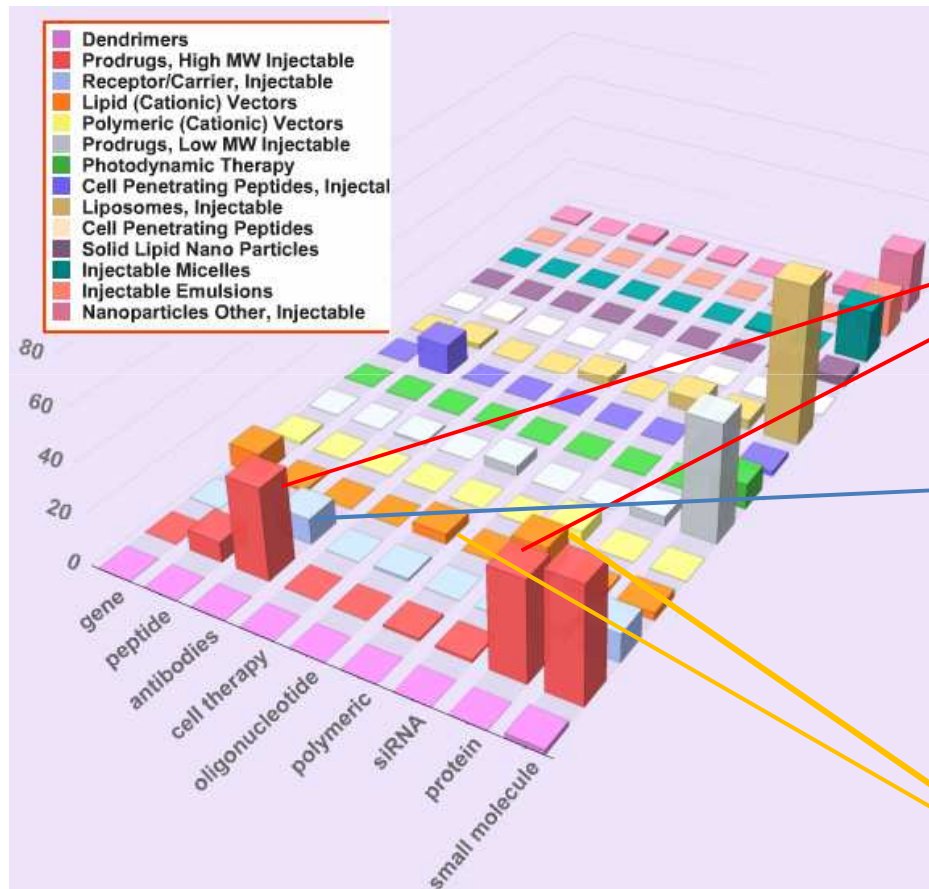
- Biologics are delivered by Injectables
- Antibodies by IV, Peptides/Proteins by SC
- A few intradermal for peptide and proteins
- Genes by intratumoural injection

PROVEN DRUG DELIVERY TECHNOLOGIES FOR CANCER DRUGS

- **Increase $t_{1/2}$ in plasma;**encapsulation (liposome) or prodrug(PEG); increases chance of uptake by cancerous tissue-
for all molecule types
- **Protect normal tissues;** target selectively through leaky vessels of cancer as bound or encapsulated; liposomes, dendrimers, nanoparticles, prodrugs, etc. - **chemo drugs/toxins**
- **Improve uptake into cancer cells;** carrier/receptor facilitated uptake by cancer cells – **all molecule types**
- **Enable escape from lysosomes;** special linking technologies for acidic environment- **all molecule types**
- **Provide long term drug release for low dose drugs;** Injectable depot, for low dose drugs

TARGETED DELIVERY VS CANCER

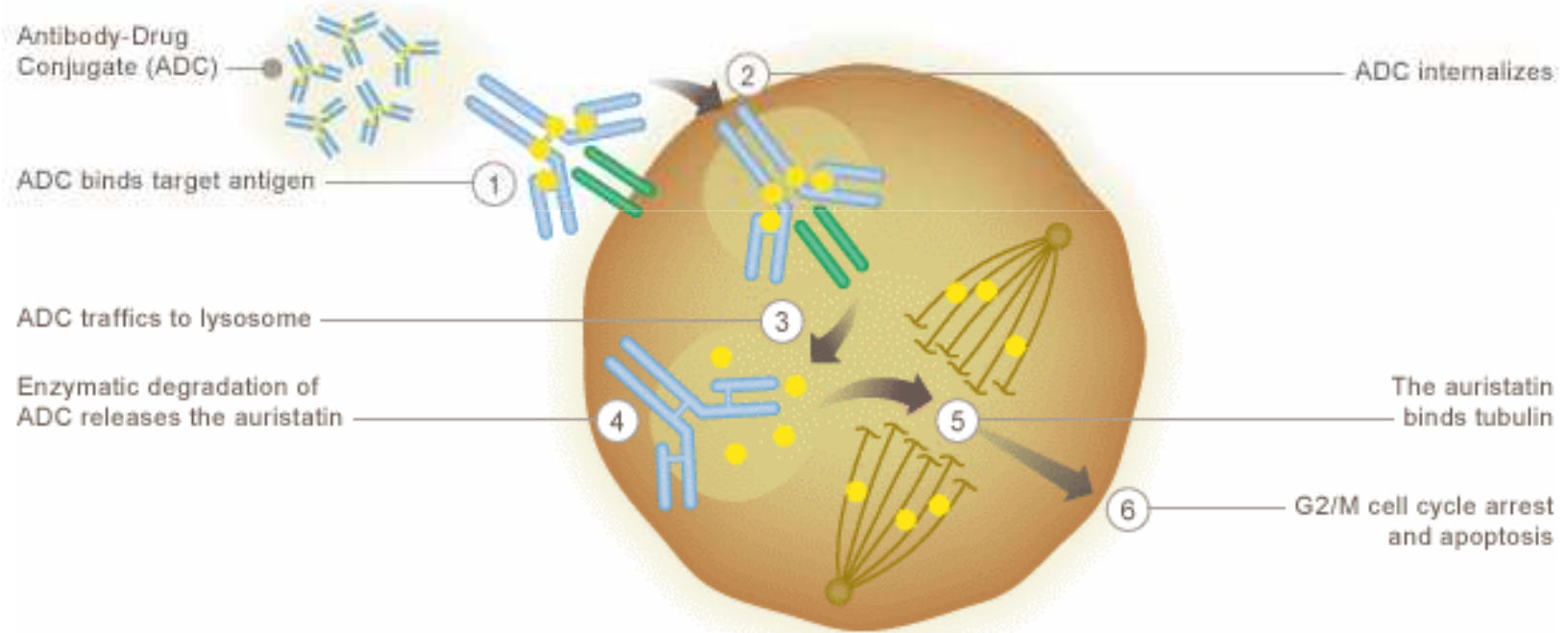
n=440



- Variety of targeted delivery techs for small molecules
- Prodrugs for protein and antibodies
- Receptor/carrier transport (antibody toxin conjugates) for – antibodies
- Cationic lipids for siRNA/Oligos

ANTIBODY DRUG CONJUGATES

ANTIBODY-DRUG CONJUGATES: EMPOWERING ANTIBODIES



From <http://www.seagen.com>

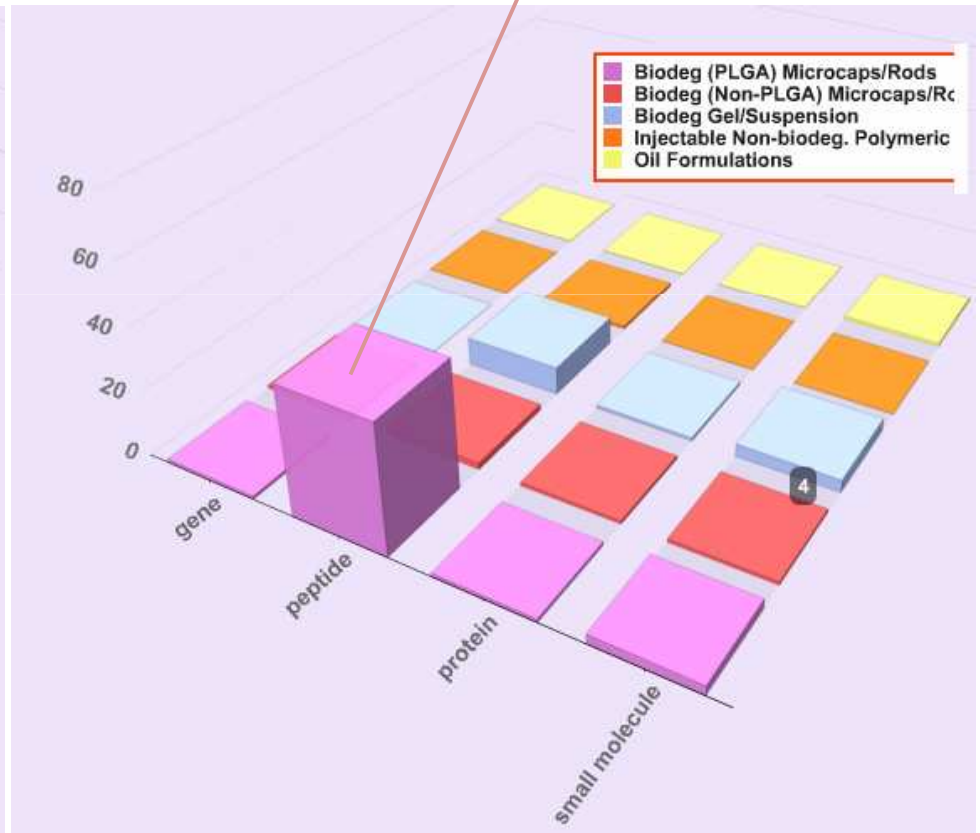
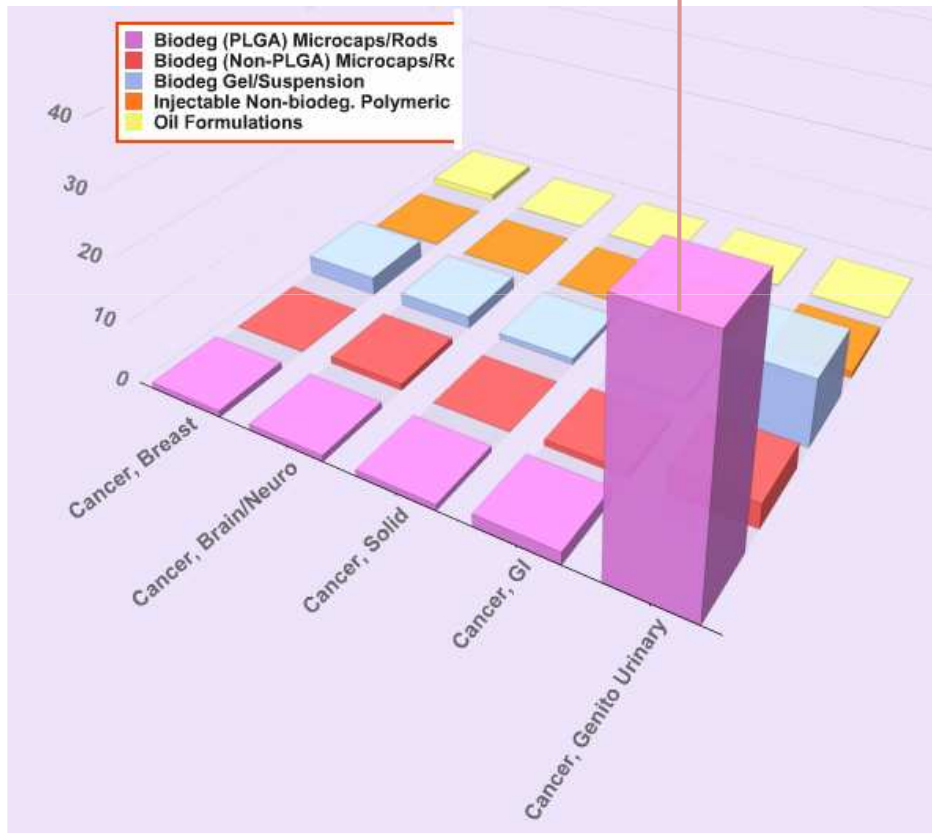
USE OF ANTIBODIES FOR TARGETING



Pipeline Name/Target	Indications/Phase	Technology/Owner
Mylotarg -gemtuzumab ozogamicin-Ant-CD33 Wyeth/PDL	Cancer AML, Marketed	anti-CD33 antibody linked to calicheamicin
Neuradiab -Anti-tenascin Bradmer Pharmaceuticals	Cancer, Glioma/Glioblastoma Multiform, Phase 3	Anti-tenascin 81C6 monoclonal antibody labeled with I-131
Trastuzumab-DM1 , Anti-Her2 Roche/Genentech	Breast cancer, Phase 3	Anti-Her2 linked to DM1, a maytansinoid. Immunogen
CR, 011-vcMMAE , Anti-GPNMB Curagen	Breast Cancer and Metastatic Melanoma, Phase 2	Fully human Anti-GPNMB conjugated to auristatin E (MMAE), Seattle Genetics
HuM195-Bi-213 PDL Biopharma	Cancer AML, Phase 2	anti-CD33 mAb (HuM195) for use with Bi-213 Actinium Pharmaceuticals
IMMU-110, Anti-hCD74 Immunomedics	Cancer NHL and Multiple Myeloma, Phase I	hCD74 doxorubicin drug conjugate, Immunomedics

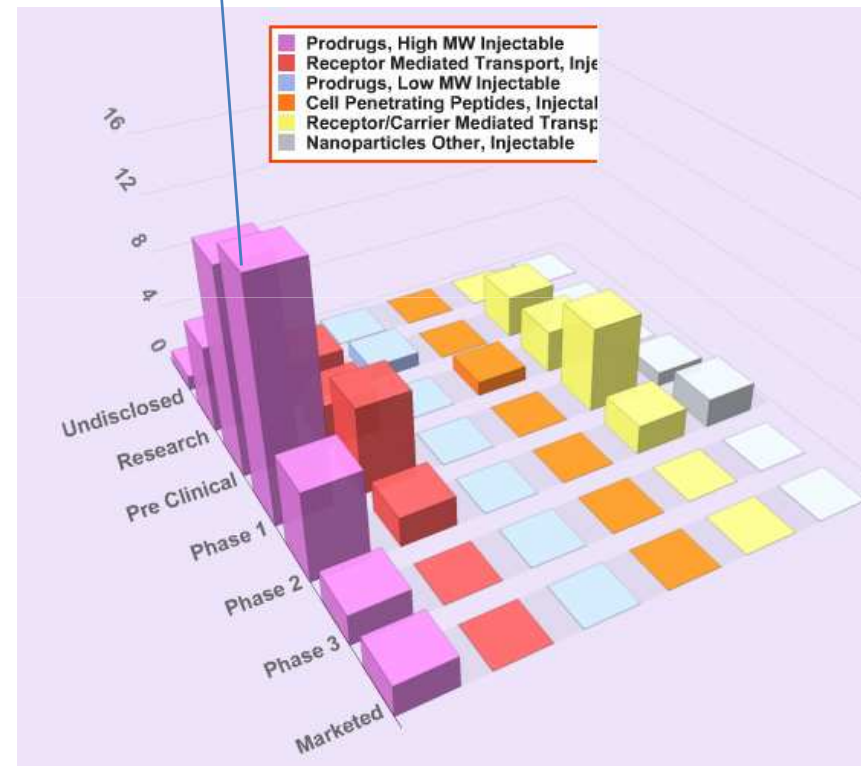
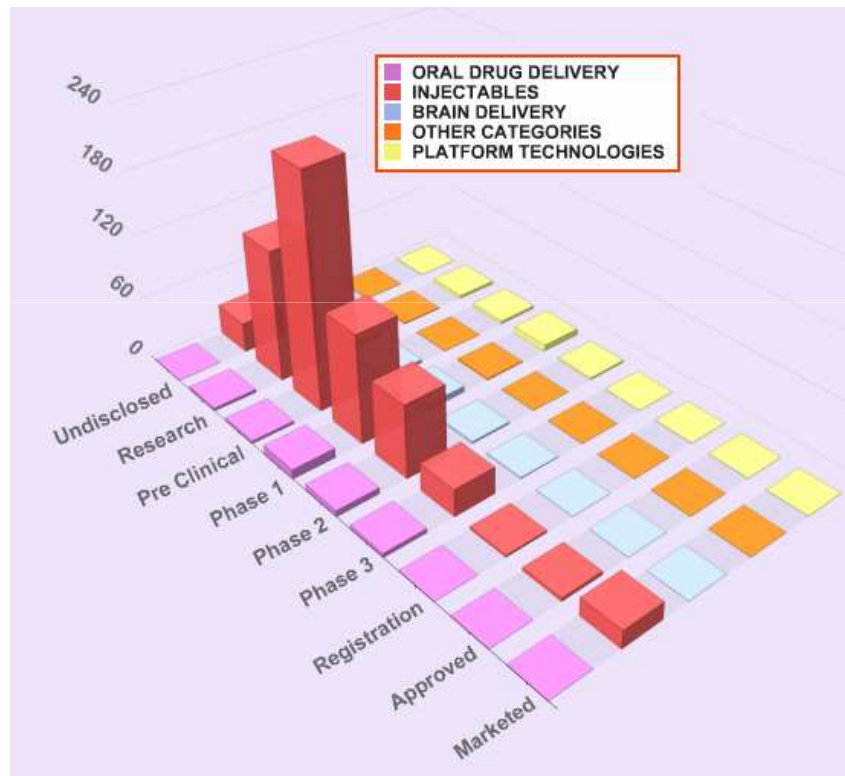
INJECTABLE DEPOT VS. CANCER (n=70)

Injectable biodegradable depot techs are used for peptides in prostate cancer to provide for up to 6 months of drug release



DELIVERY: ANTIBODY & CANCER

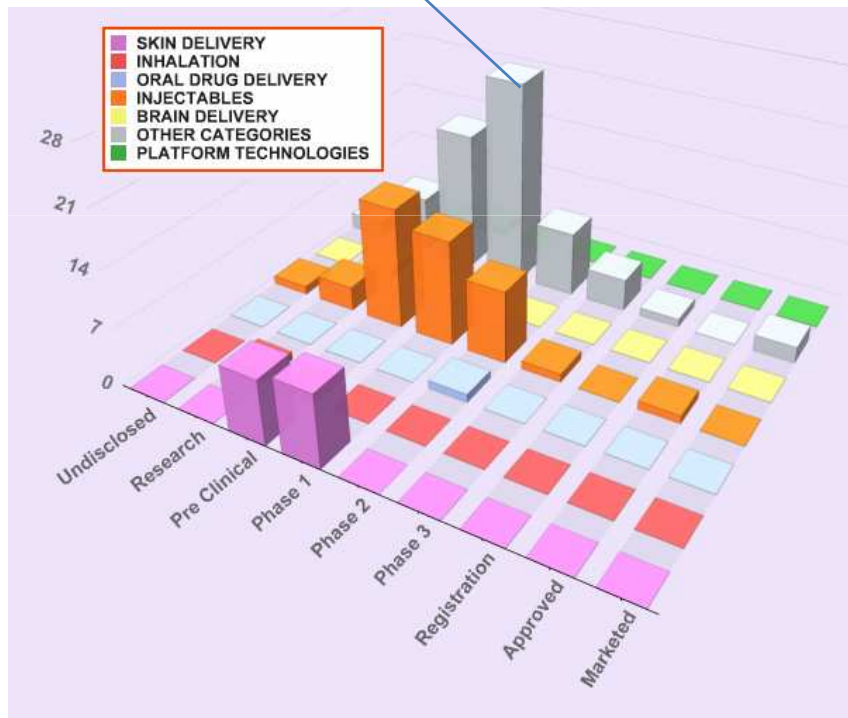
Injectables, produgs/antibody conjugates



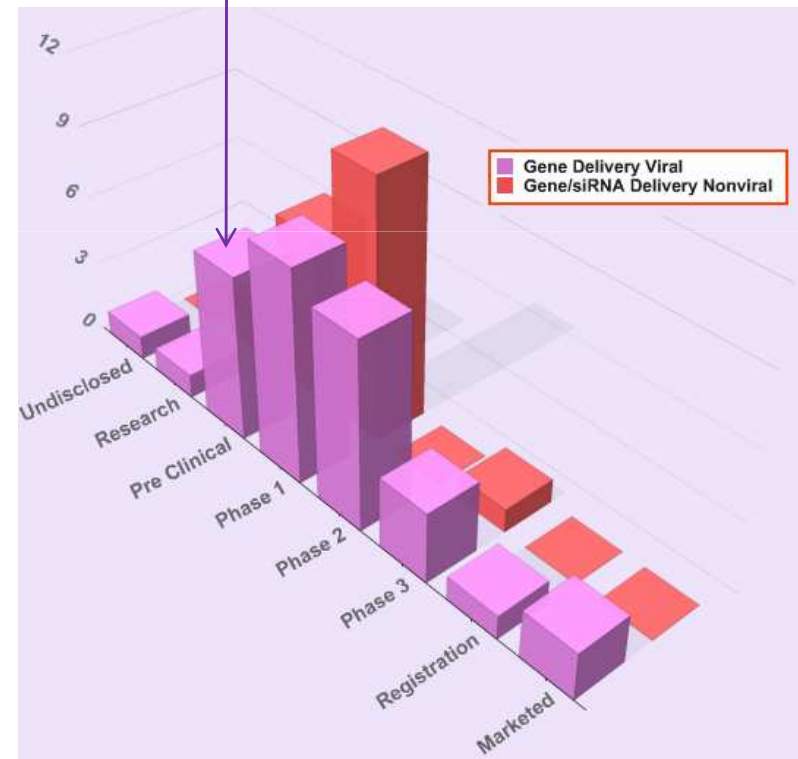
DELIVERY: GENE & CANCER

Viral vectors for gene

Viral and nonviral vectors
N=130



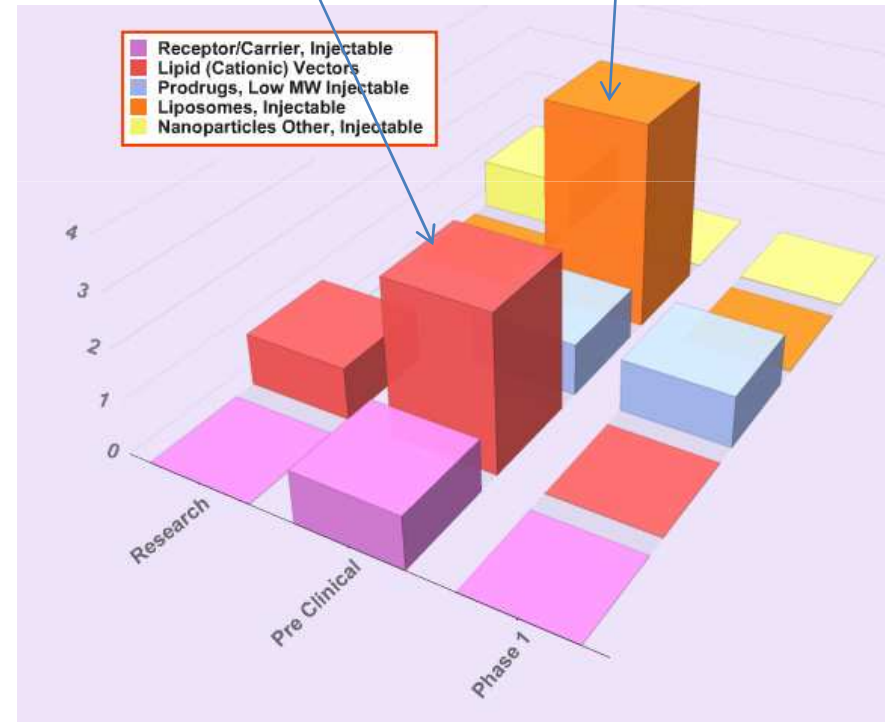
Many AAV (adeno associated viral vectors), n=53



DELIVERY: OLIGOS & CANCER

Most Injectable, 1 inhalation, 1 nasal and 1 rectal, n=66

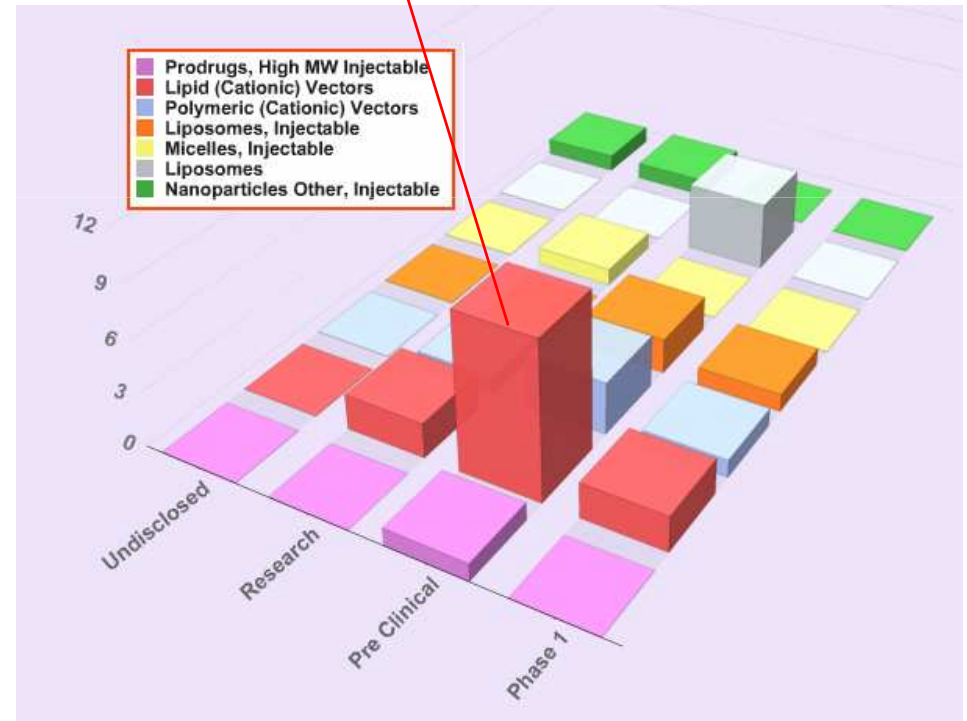
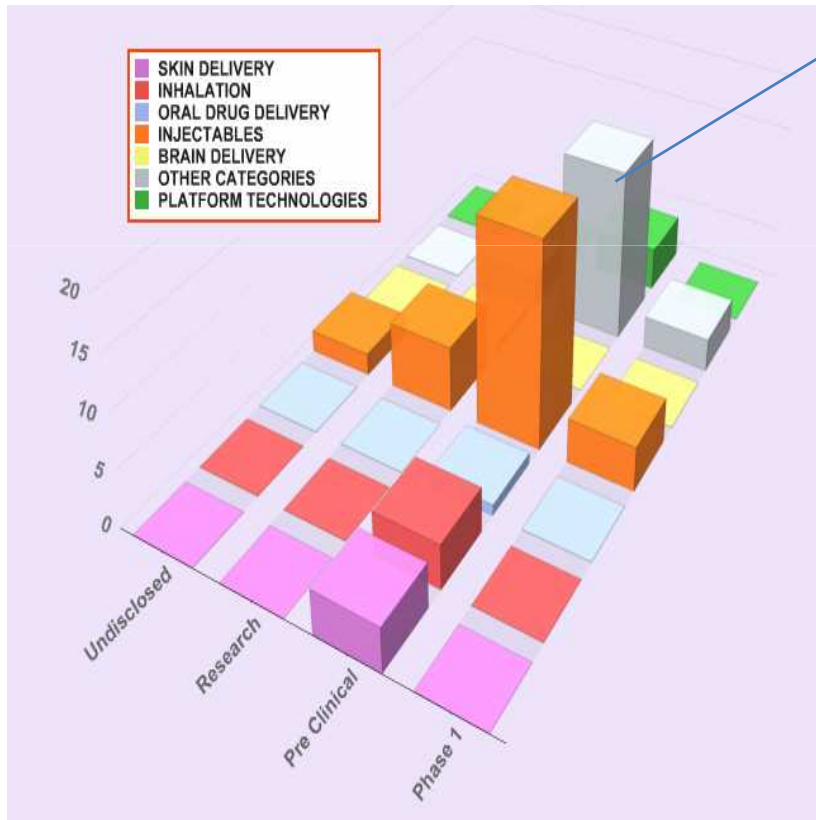
Liposomes and Cationic lipids, n=12



DELIVERY: siRNA & CANCER

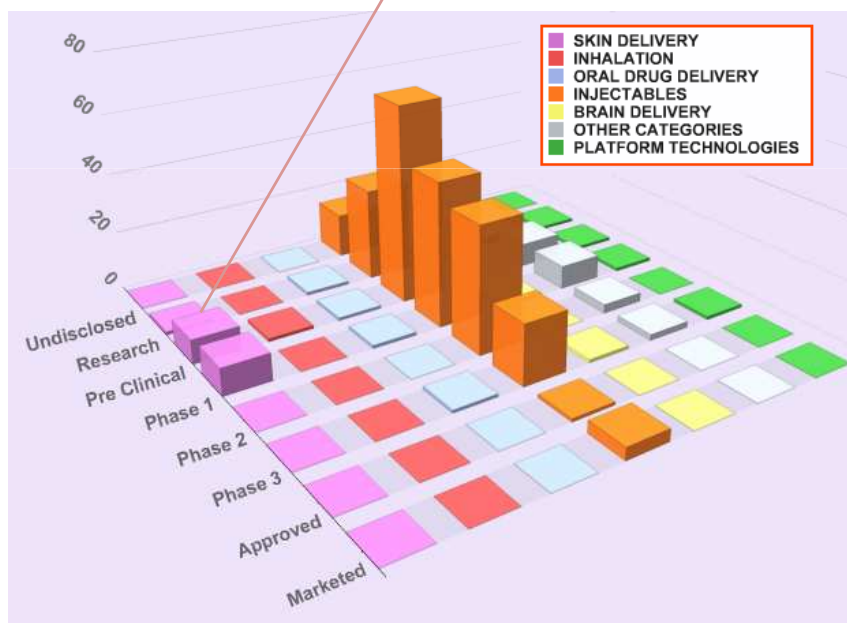
n=53

Cationic lipid/liposomes, n=28

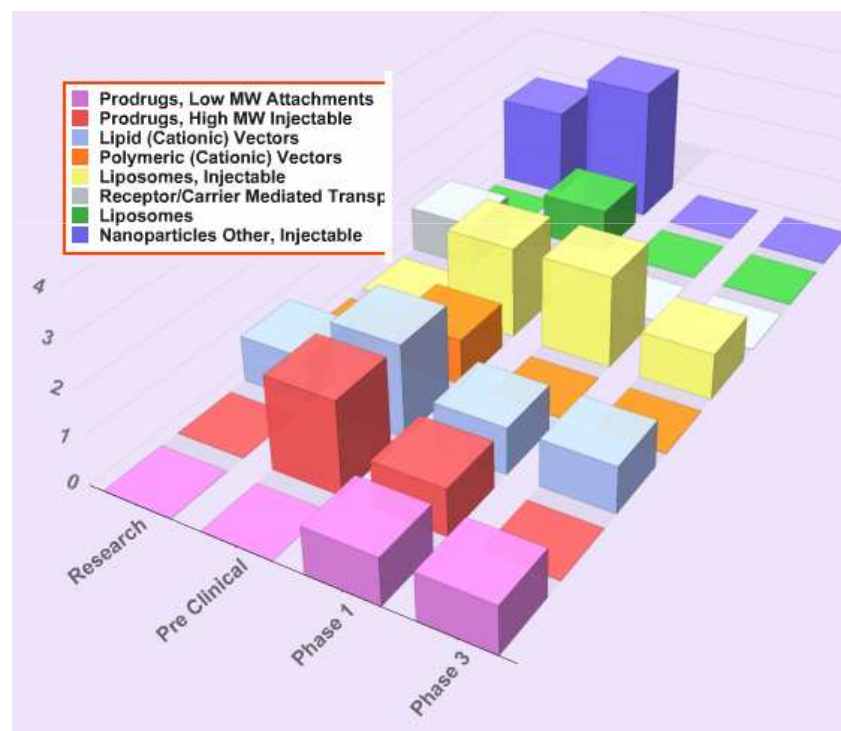


DELIVERY: VACCINE & CANCER

Injectables and a few skin delivery

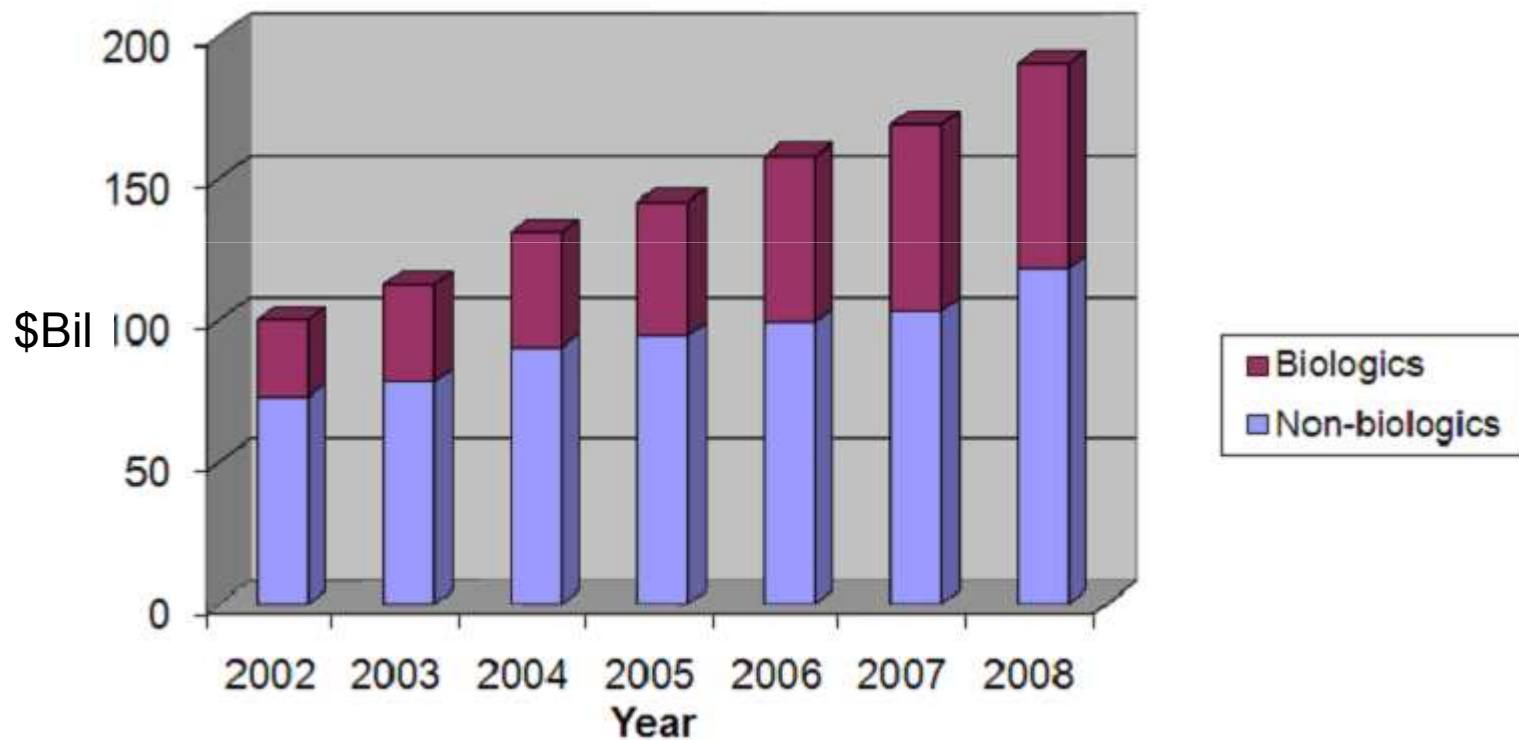


Across targeted delivery platforms



WORLD SALES OF TOP 25 DRUGS

Biologicals rapidly growing in sales

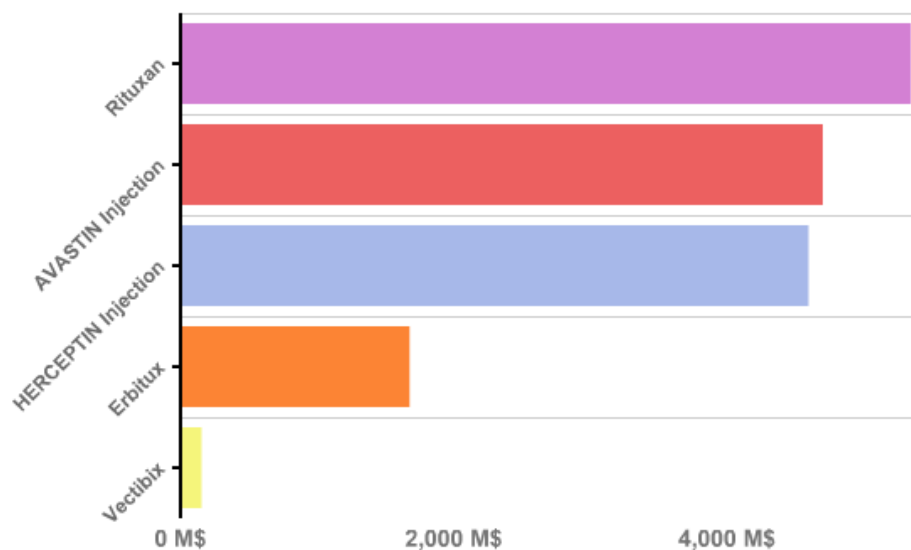


ANTIBODY BASED SALES-WORLD-2008

TOTALS (25 Products)	World	31110	100
	Ex_us	15195	48.84
	Japan	1235	3.97
	Europe	5008	16.1
	Usa	15430	49.6

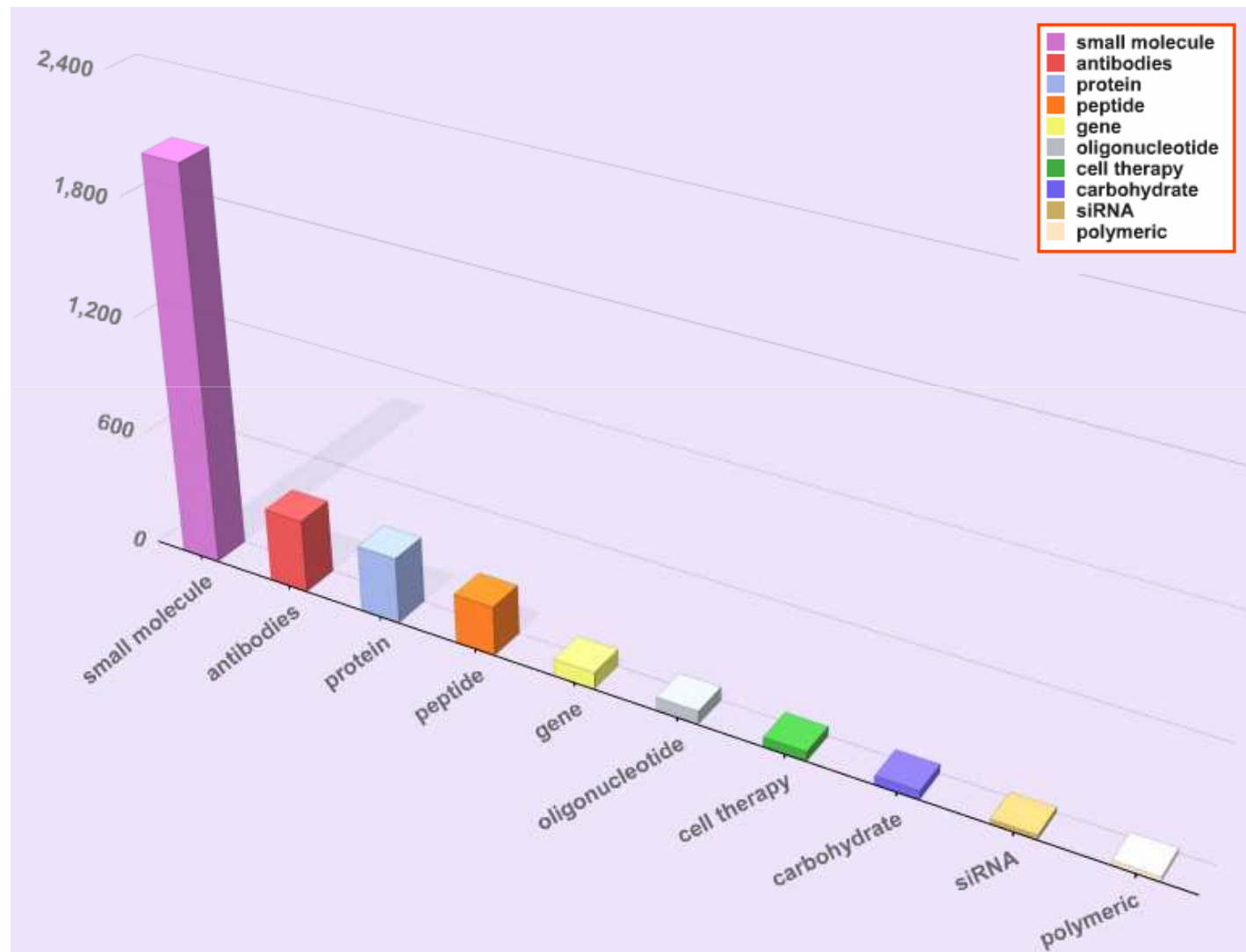
6 CANCER & ANTIBODY (Bottom); 50% OF TOTAL ANTIBODY (Top) PRODUCT SALES

TOTALS (6 Products)	World	16474	100
	Ex_us	8468	51.4
	Japan	608	3.69
	Europe	4683	28.43
	Usa	7520	45.65



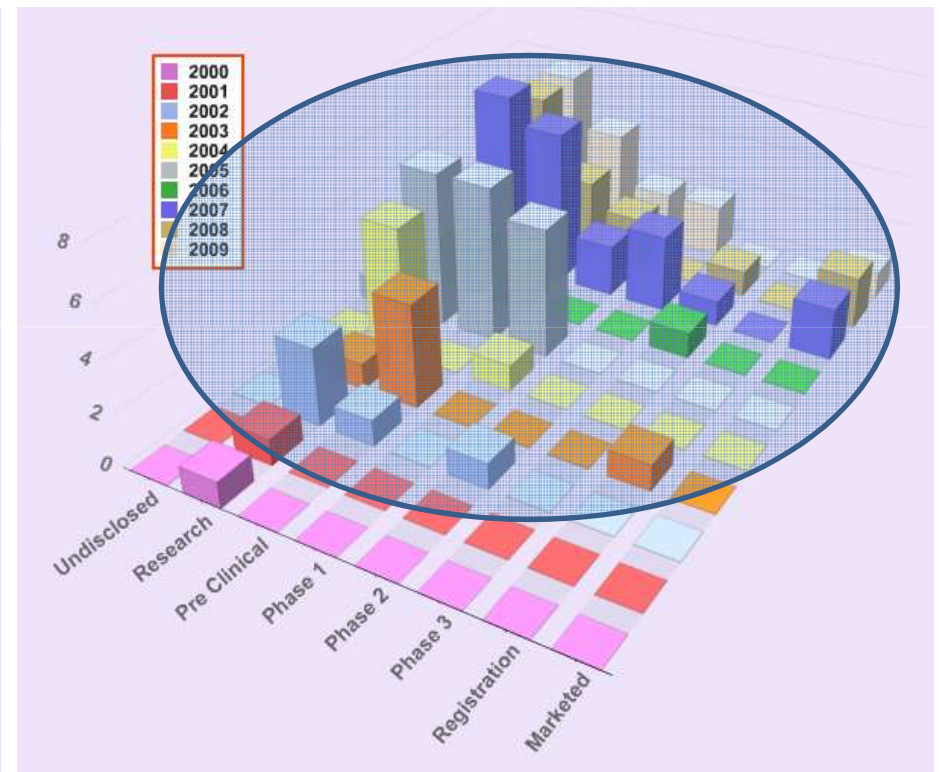
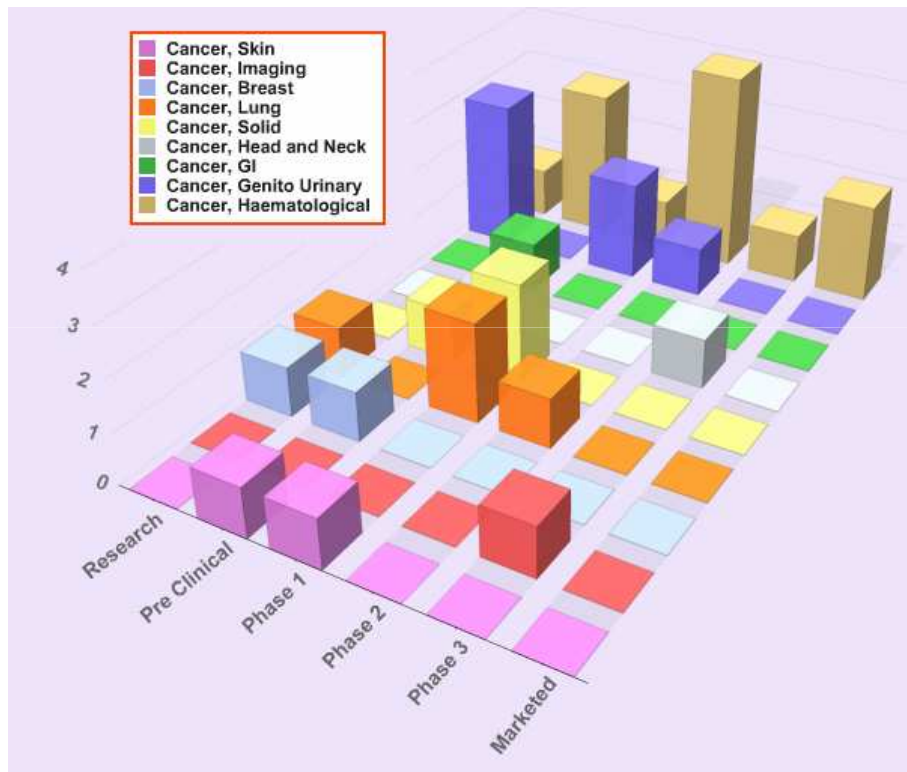
PRODUCT DEALS SINCE 2000

n=3338



ANTIBODY PRODUCT DEALS-SINCE 2000

More Product Deals since 2002 across all cancer categories (n=201)



SAMPLE OF ANTIBODY DEALS

Licensors	Licensee	Product	Phase	Current Phase	Total Deal/ Territories
Medarex Dec 2006	GSK	Arzerra	Phase 3	Marketed/US (Cancer CLL), Phase 2/3 Various cancers and others	\$1600M (\$102/\$357/1200mil) , USA, EU, Japan
Amgen Feb 08	Takeda	Vectibix	Marketed	Marketed, Various Cancers	\$902 (\$200/\$702) Japan
PDL Pharma Aug 08	BMS	HuLuc63	Phase I	Phase I, Cancer MM	\$860 (\$60/\$800) World
Seattle Genetic Dec 09	Takeda/ Millenium	SGN-35	Phase 2	Phase 2/3 Haemotological cancers	\$260 (60/230), ex- US
Merrimack Oct. 09	Sanofi Aventis	MM-121	Phase I	Solid Cancers	\$530 (60/470)- World
Oxford Biother May 09	GSK	New Antibodi es	Research	Cancer	\$370 (?/370)- Exclusive option to license/World

CONCLUSIONS

- Cancer has been the largest therapeutic target
- Biologics nearly half of all cancer programs and antibodies is the most rapidly growing segment of the biologics
- Dual role of antibodies; as a killer for cancer cells and delivery vehicle in drug conjugates
- Applications of prodrugs (PEG, etc.) for proteins & antibodies, depot techs for peptides, cationic lipids for siRNA and oligos, viral vectors for gene molecules