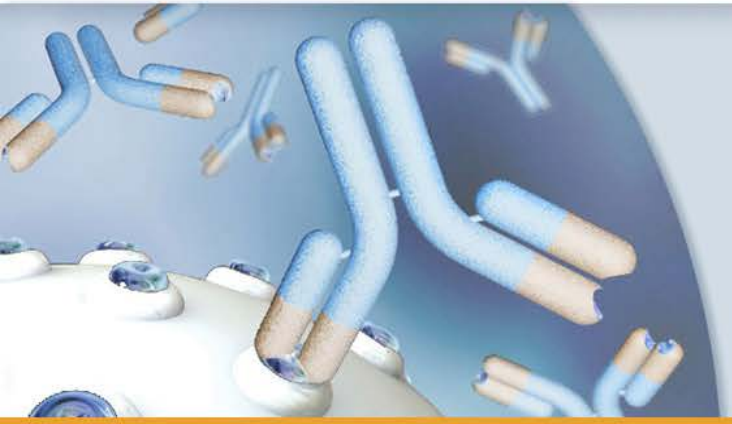
MacroGenics



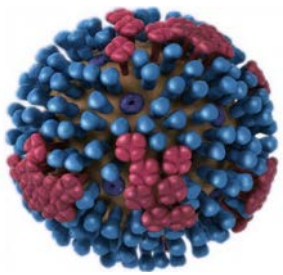
Breakthrough Biologics,
Life-Changing Medicines

Antibody Therapeutics: Trends & Future Directions

June, 2015

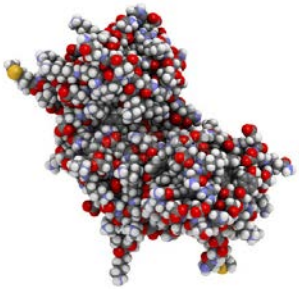
Biologic Therapeutics

Vaccines



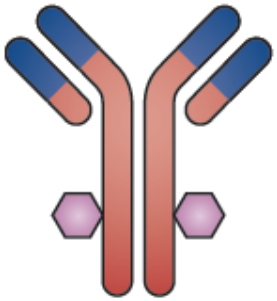
Infectious disease, cancer

Replacement therapy

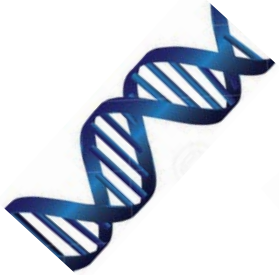


Insulin, enzymes, coagulation factors

Antibodies

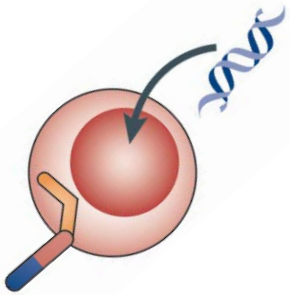


Gene therapy



Single gene defects, therapeutics

Cell therapy

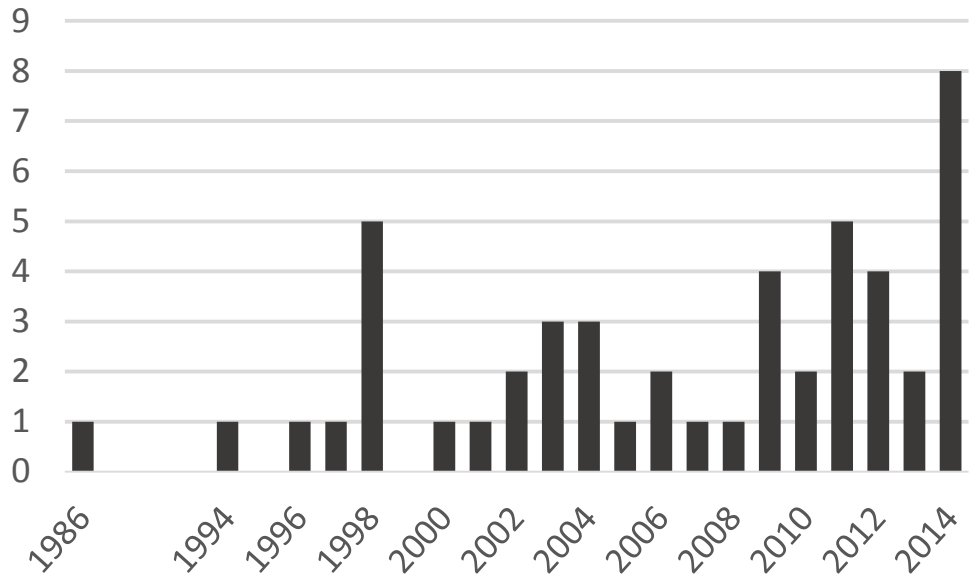


Modified lymphocytes (chimeric antigen receptors), stem cells, chondrocytes

Major industry focus and the focus of this presentation

FDA Approval of Antibodies and Antibody-Like Molecules

49 molecules approved from 1986 to December 2014



First 16 molecules:
16 years

Disease target:
Autoimmune = 38%
Cancer = 31%
Other = 31%

2nd 16 molecules:
7.5 years

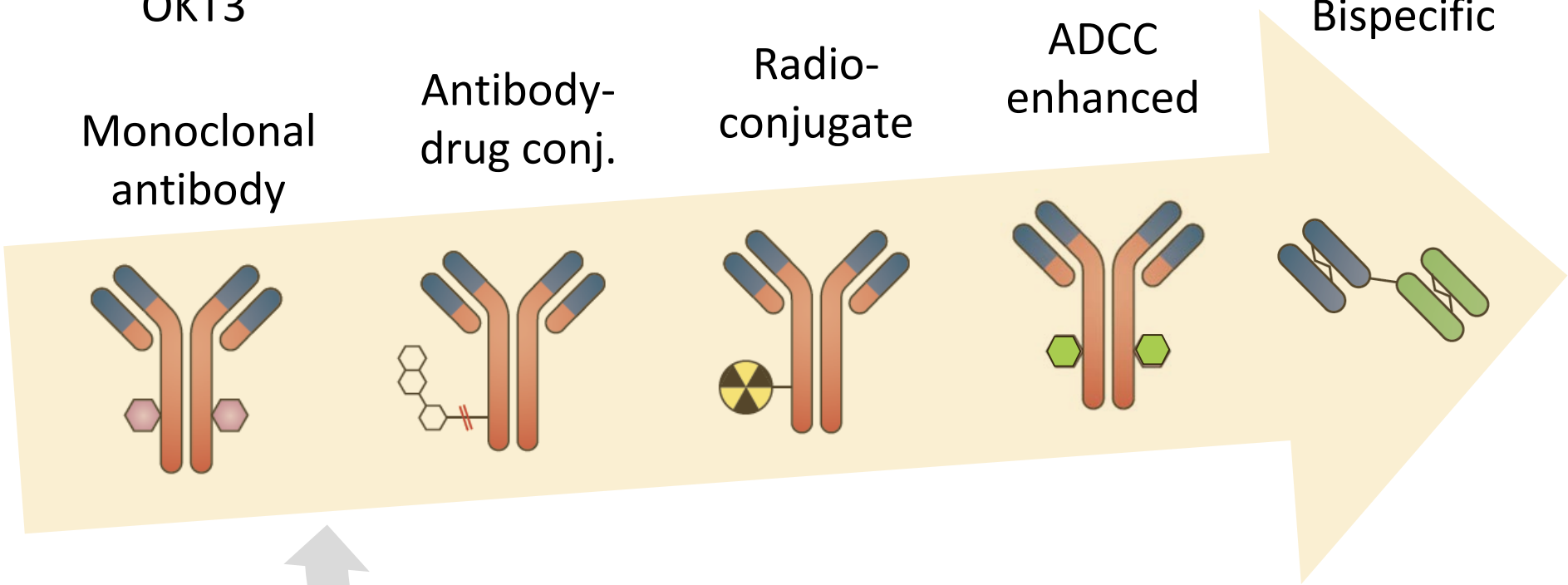
Disease target:
Autoimmune = 50%
Cancer = 31%
Other = 19%

Last 17 molecules:
3.5 years

Disease target:
Cancer = 53%
Other = 35%
Autoimmune = 12%

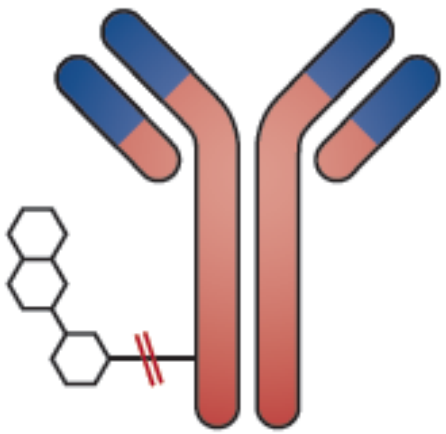
Evolution of Antibody Therapeutics

1986	2000	2002	2012	2014
OKT3	Mylotarg	Zevalin	Gazyva	Blincyto
Monoclonal antibody	Antibody-drug conj.	Radio-conjugate	ADCC enhanced	Bispecific



Murine	Chimeric	Humanized	Human
1986	1994	1997	2002

Antibody Drug Conjugates (ADCs)



Adcetris

Approved – 2011

Hodgkin Lymphoma

Kadcyla

Approved – 2013

HER2+ Breast Cancer

Industry leaders:

SeattleGenetics®

IMMUNOGEN, INC.

Next generation molecules encompass:

- Homogenous, site-specific conjugation

SUTRO BIOPHARMA

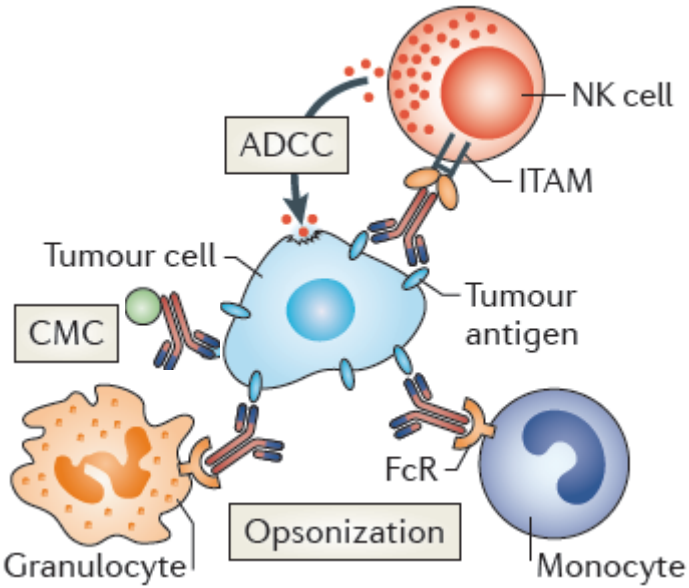
Catalent

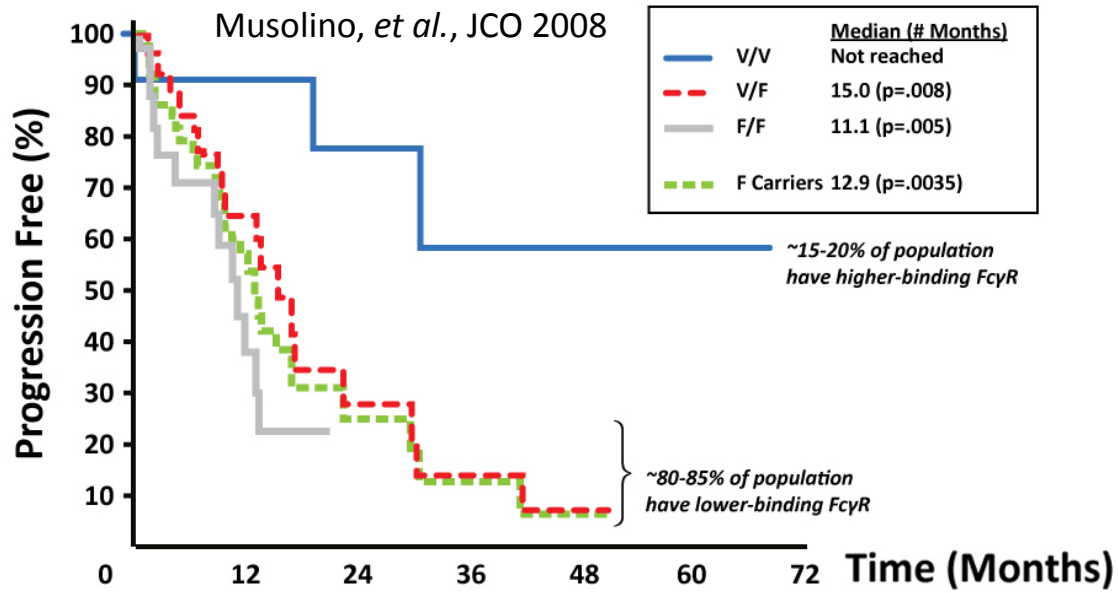
- More potent toxins; resistance to drug efflux pumps, cell-cycle independent MOA

Synthon

Heidelberg Pharma

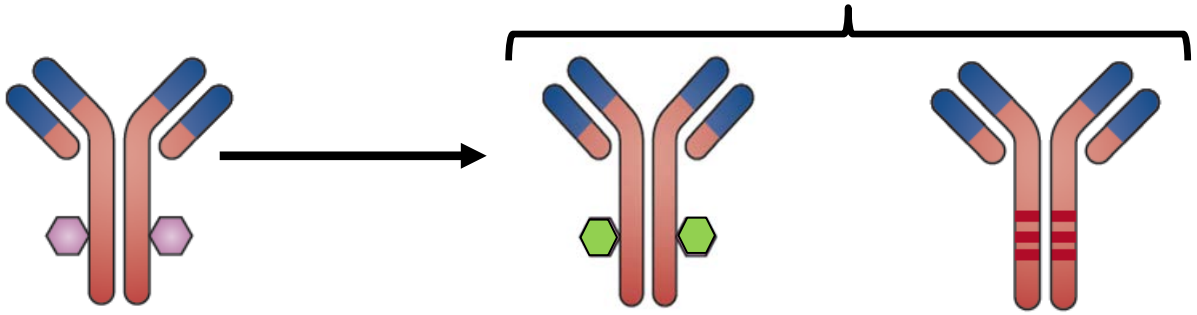
Fc-Optimized Antibodies





Weiner - *Nature Reviews*, 2015

ADCC-enhanced



KYOWA KIRIN

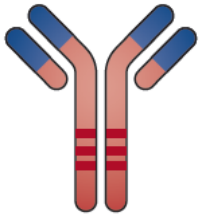
Roche GLYCART biotechnology

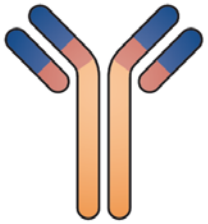
MACROGENICS

Fc-Modified Antibodies

Reduced Fc activity - several checkpoint mAbs incorporate this strategy

(1) Fc-mutation (Ala-Ala) or (2) Use of different isotype (IgG4)





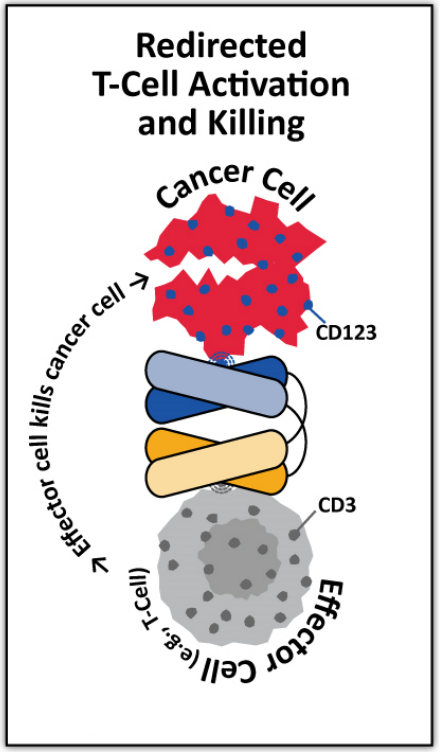
e.g. MPDL3280A (anti-PDL-1)

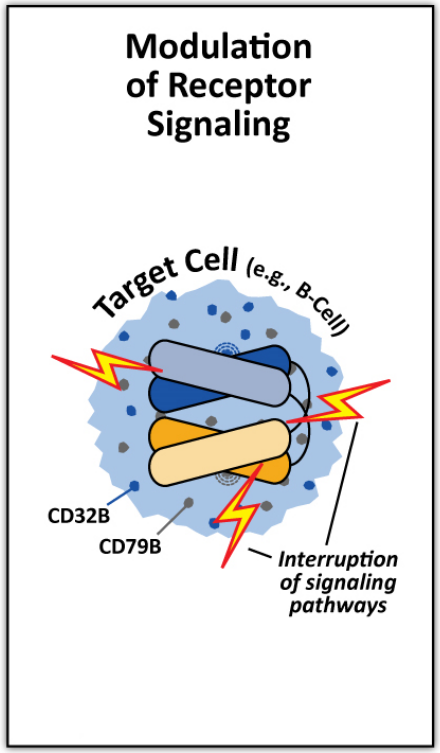
e.g. nivolumab (anti-PD-1)

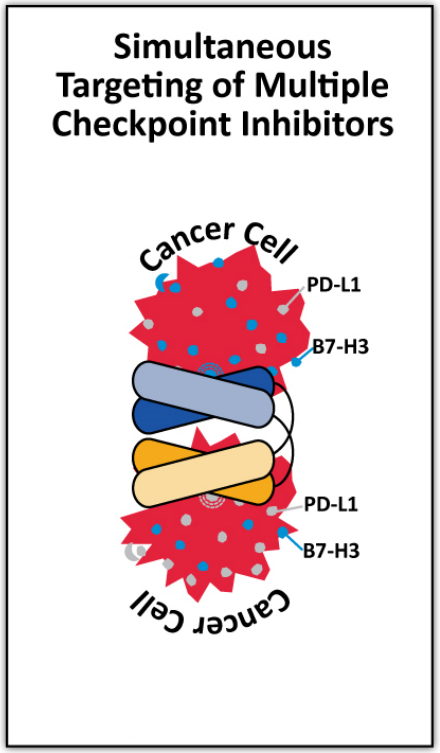
Huge investment in this drug class:

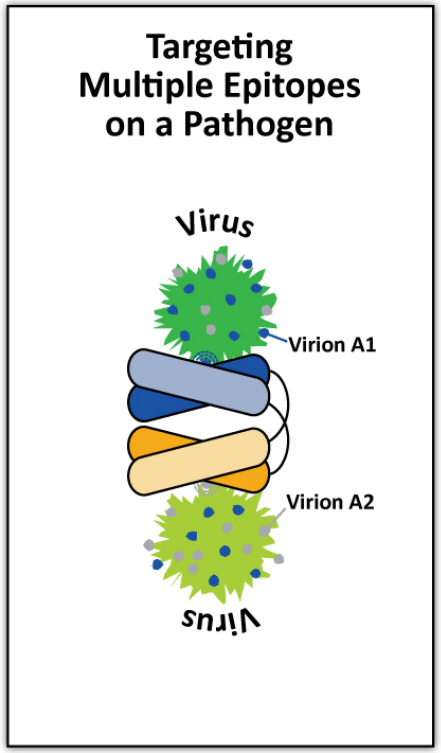
			Total Trials (inc. PI-led)	Active Industry Sponsored Trials						
				Phase 3	Phase 2	Phase 1	Total	Single agent	Combo studies	% Combo
PD-1	BMS	Nivolumab	64	13	16	7	36	16	20	56%
	Merck	Keytruda	61	6	12	8	26	15	11	42%
PD-L1	MedImmune	MEDI4736	26	1	10	10	21	6	15	71%
	Genentech	MPDL3280A	19	2	6	10	18	7	11	61%
	Pfizer/Merck Kgaa	MSB0010718C	3	0	2	1	3	3	0	0%
	Total		173	22	46	36	104	47	57	55%

Bispecific Molecules: Easily Configured for Range of Modalities





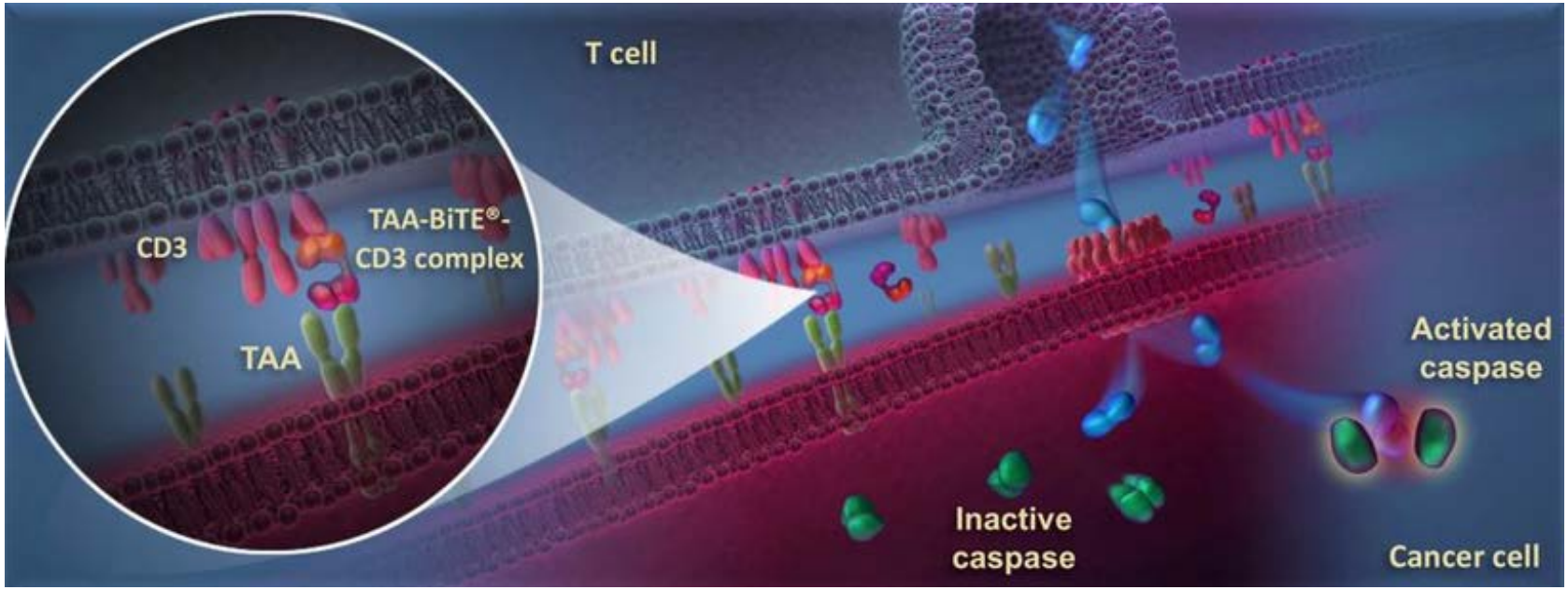




Bispecific Molecules: Redirected T Cell Killing

Blincyto – first FDA-approved bispecific (December 2014)

- Complete response rate > 40% in R/R ALL

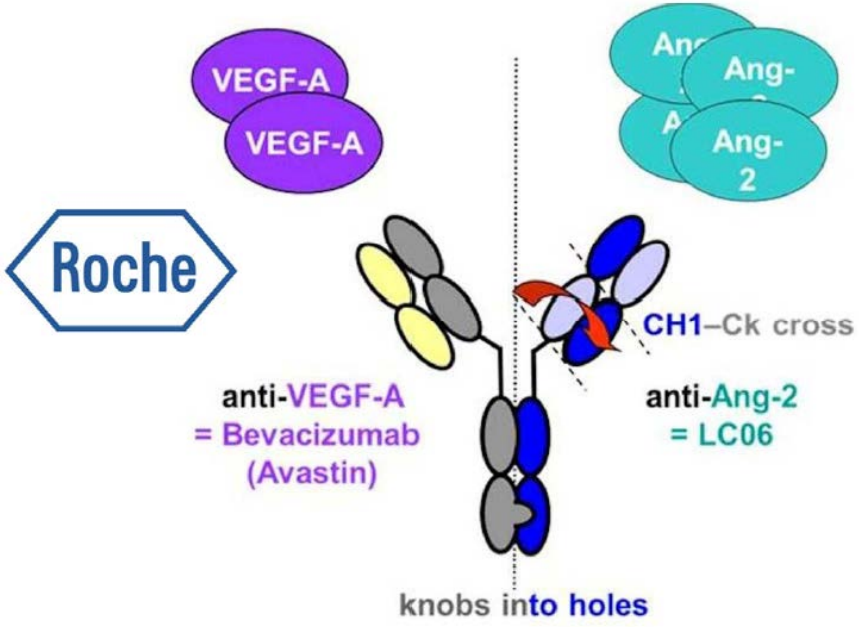


Next generation molecules are under clinical investigation

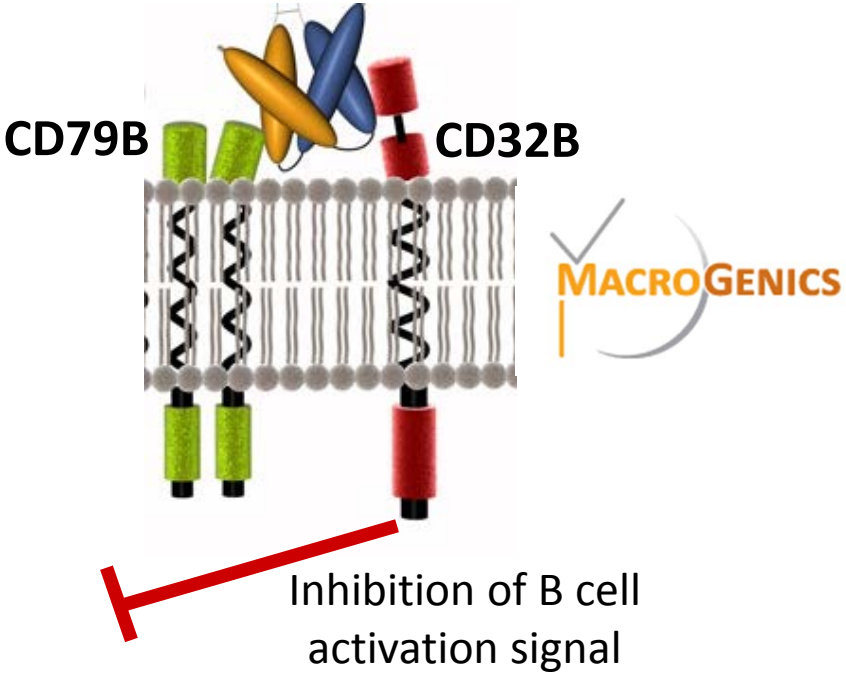
- Increased potency and improved patient convenience
- Redirected NK cell killing is also being investigated
- Both solid tumors and hematological malignancies targeted

Examples of Bispecific Molecules in Clinical Trials

Targeting 2 soluble ligands
e.g. VEGF-A x ANG-2 (Phase 3)



Dual-targeting a single cell
e.g. CD79B x CD32B (Phase 1)



Emerging industry effort to dual-target checkpoint inhibitors

MacroGenics

Trends and Future Directions: Next 5-10 Years

- Increased effort to more specifically target tumors, particularly in the context of potent empowered antibodies
  - Dual targeting of tumor antigens e.g. bispecific ADCs
  - Novel strategies e.g. masked antibodies
- Increased focus on combination therapy
  - Antibody-antibody combinations
  - Combinations across different modalities e.g. vaccines or chimeric antigen receptors (CARs) with checkpoint inhibitor antibodies
  - Novel-novel combinations will need to overcome economic hurdles
- Technological breakthroughs generated by cancer-focused research should start to filter through to other disease areas
  - Infectious disease; redirected T cell killing and cell therapy