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Fc fusion proteins as targeted therapeutics in oncology

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Overview

- FDA-approved mAb and Fc fusion protein products
- What is an Fc fusion protein?
  - Design
  - Structural variation of approved fusion proteins
- Fc fusion proteins in cancer
  - Aflibercept
- Summary

FDA-approved mAb products

FDA-approved mAbs and derivatives

Year							
2015	Praluent	Repatha	Cosentyx	Unituxin	Necitumumab‡	Mepolizumab‡	Idarucizumab*‡
2014	Alprolix	Entyvio	Cyramza	Sylvant	Eloctate	Keytruda	Blincyto*††
2013	Kadcyla**	Gazyva					
2012	Perjeta	Abthrax	Zaltrap	Raxibacumab†			
2011	Benlysta	Yervoy	Adcetris**	Eylea	Nulogix		
2010	Prolia/Xgeva	Actemra					
2009	Arzerra	Stelara	Ilaris	Simponi			
2008	Nplate	Arcalyst	Cimzia*				
2007	Soliris						
2006	Vectibix	Lucentis*					
2005	Orencia						
2004	Erbitux	Avastin	Tysabri				
2003	Xolair	Bexxar**	Raptiva	Amevive			
2002	Zevalin**	Humira					
2001	Campath						
2000	Mylotarg**						
1998	Simulect	Synagis	Remicade	Herceptin	Enbrel		
1997	Rituxan	Zenapax					
1994	ReoPro*						
1986	Orthoclone OKT3						

Technology

- Fc- Fusion Protein
- Human
- Humanized
- Chimeric
- Mouse

* Fab, (Fab')$_2$ or scFv antibody fragment

** Antibody-drug or radioconjugate

† First mAb approved under animal efficacy rule

†† Bispecific

‡ Pending

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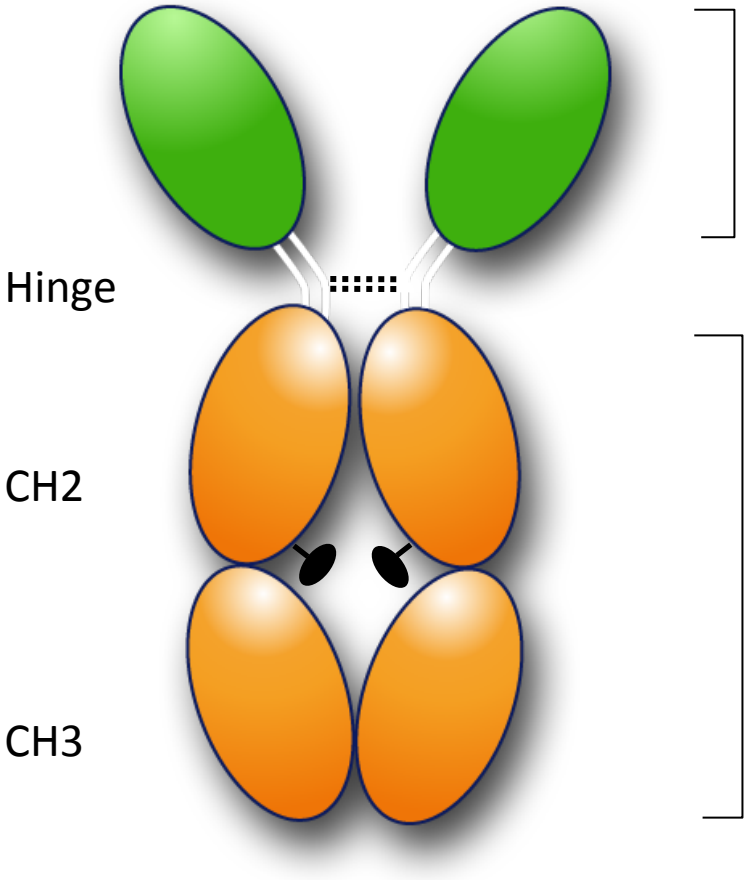
Therapeutic Fc fusion proteins
(FDA-approved 1998-2015)

Product	Company	Year Approved	Cell Type	Type	Target	Indication
Enbrel	Amgen	1998	CHO	TNFR Fc fusion	TNF	Inflammatory disease
Amiveve	Biogen Idec	2003	CHO	Fc fusion	CD2	Inflammatory disease
Orencia	BMS	2005	CHO	CTLA4 Fc fusion	CD80, CD86	Inflammatory disease
NPlate	Amgen	2008	*E. coli*	TPO mimetic peptide Fc fusion	TPOR	Chronic immune thrombocytopenia
Arcalyst	Regeneron	2008	CHO	IL1R Fc fusion	IL1	Inflammatory disease
Eylea	Regeneron	2011	CHO	VEGFR Fc fusion	VEGF	Macular degeneration
Nulojix	BMS	2011	CHO	CTLA4 Fc fusion	CD80, CD86	Organ rejection
Zaltrap	Regeneron/ Sanofi	2012	CHO	VEGFR Fc fusion	VEGF	Metastatic colorectal cancer
Alprolix	BiogenIdec	2014	HEK	FIX Fc fusion protein	Blood clotting enzyme	Hemophilia
Eloctate	Biogen Idec	2014	HEK	FVIII Fc fusion protein	Blood clotting enzyme	Hemophilia

Fc-fusion protein design and structure

Fc-fusion format: Many proteins become "druggable"



Protein (ligand binding domain)

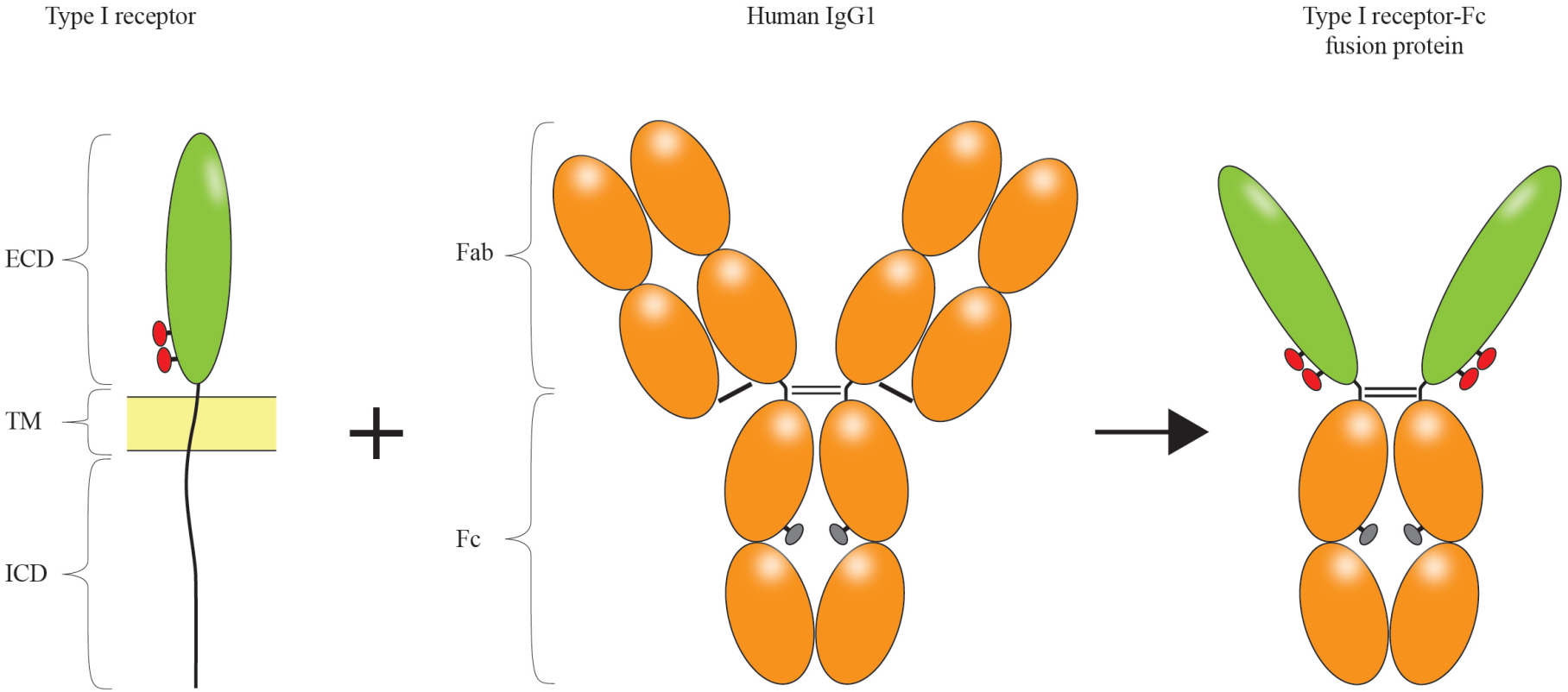
- Receptor extracellular domain
- Cytokine
- Peptide
- Enzyme

Fc region

FcγR binding	→	ADCC
C1q binding	→	CDC
FcRn binding	→	Half-life

Examples: Enbrel, Amiveve, Orencia, Zaltrap

Constructing an Fc fusion protein



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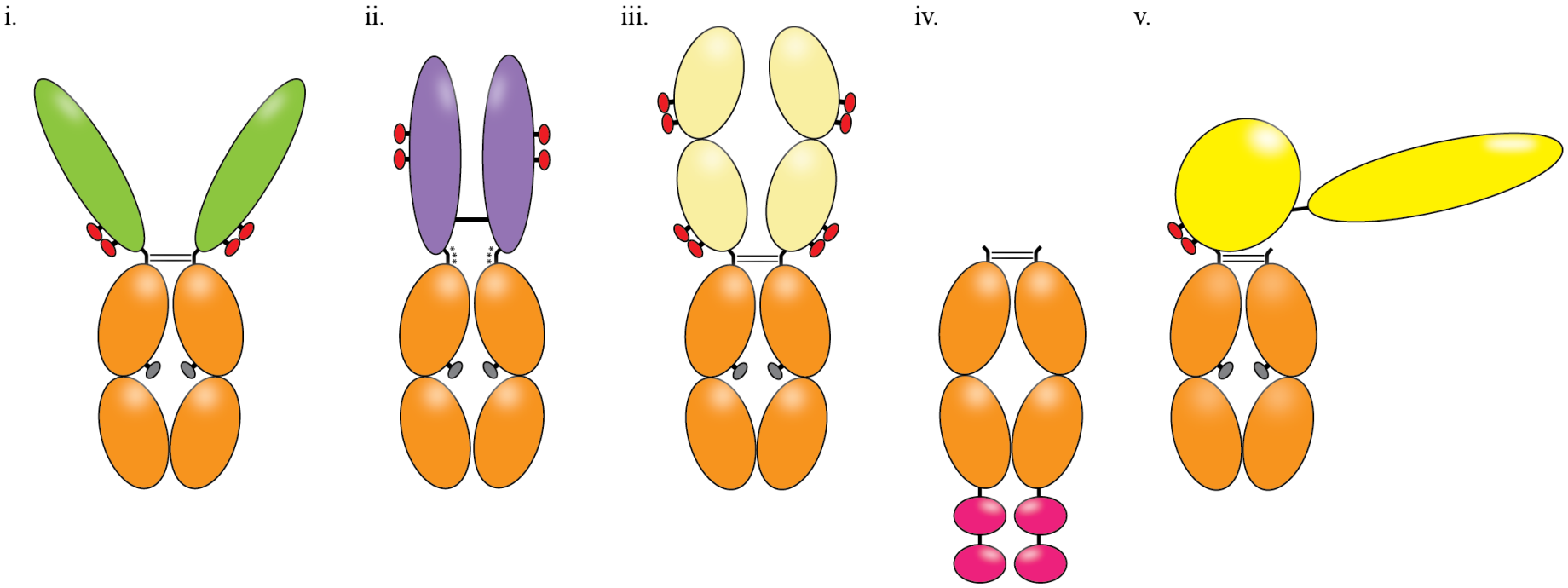
Fc fusion protein: Key structural features

- Homodimer
  - Can contain two copies of ligand binding domain
    - Receptor ECD
    - Cytokine
    - Peptide
    - Enzyme (FVIII and FXI excepted)
- Protein (ligand binding domain)
  - Replaces Fab (VL-CL, VH1-CH1)
  - High affinity for target
    - Cytokine traps (Eylea/Zaltrap Kd 0.5 pM)
  - Fused into Ig hinge
    - Hinge serves as flexible "spacer" between two parts
      - e.g., Ligand binding domain-EPKSCDKTHTCPPCP-Fc

Structural features (cont'd.)

- IgG Fc
  - Retains effector functions
    - ADCC
    - CDC
    - Half-life extension
    - Protein A binding
  - Amenable to molecular engineering in Fc
- Acid stabile

Structural variation: Approved Fc fusions



i. Enbrel
ii. Orencia
iii. Eylea/Zaltrap
iv. NPlate
v. Alprolix

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Fc fusion proteins in cancer

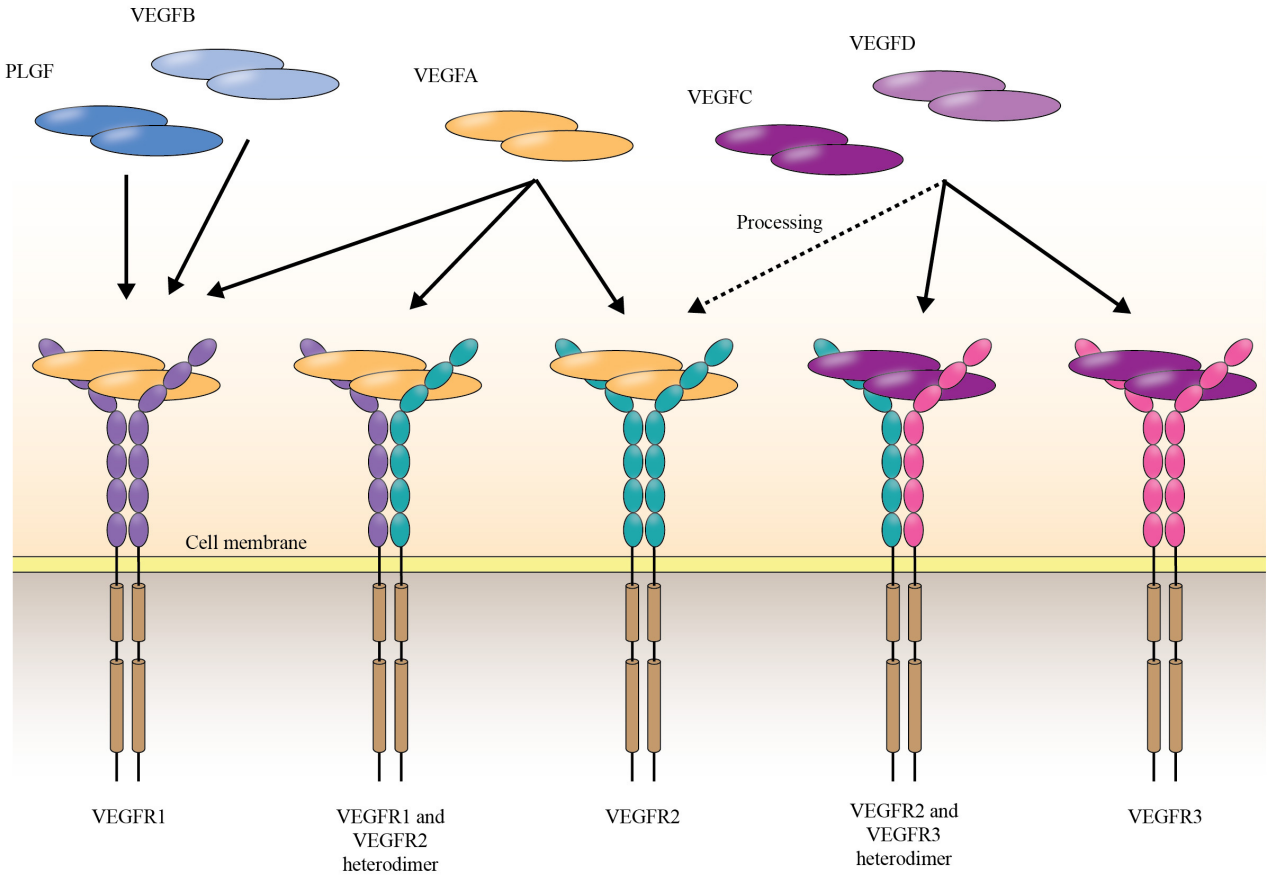
Fc fusion proteins marketed and in clinical development in cancer

Product	Company	Status	Type	Target	Indication
Aflibercept (Zaltrap)	Regeneron/ Sanofi	Approved USA	VEGFR Fc fusion	VEGF	mCRC
FP-1039 (GSK3052230)	Five Prime/ GSK	Clinical Ph Ib	FGFRI IIIc Fc fusion	FGF	NSCLC, mesothelioma
dalantercept (ACE-041)	Acceleron	Clinical Ph II	ALK1 Fc fusion	ALK1 signaling	RCC

Zaltrap® (aflibercept)

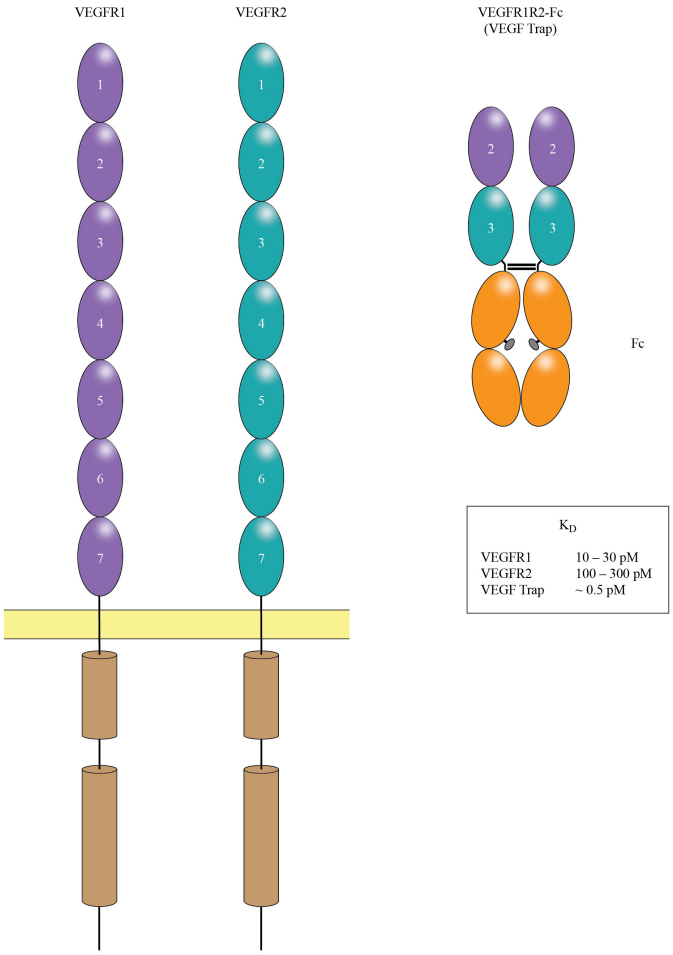
Intravenous formulation of VEGF Trap

VEGF family
Ligands and receptors



VEGF binding causes dimerization of receptors, which transduces a signal for cells to proliferate via activation of intracellular kinase domains

Aflibercept is a “cytokine trap” derived from two VEGF receptors



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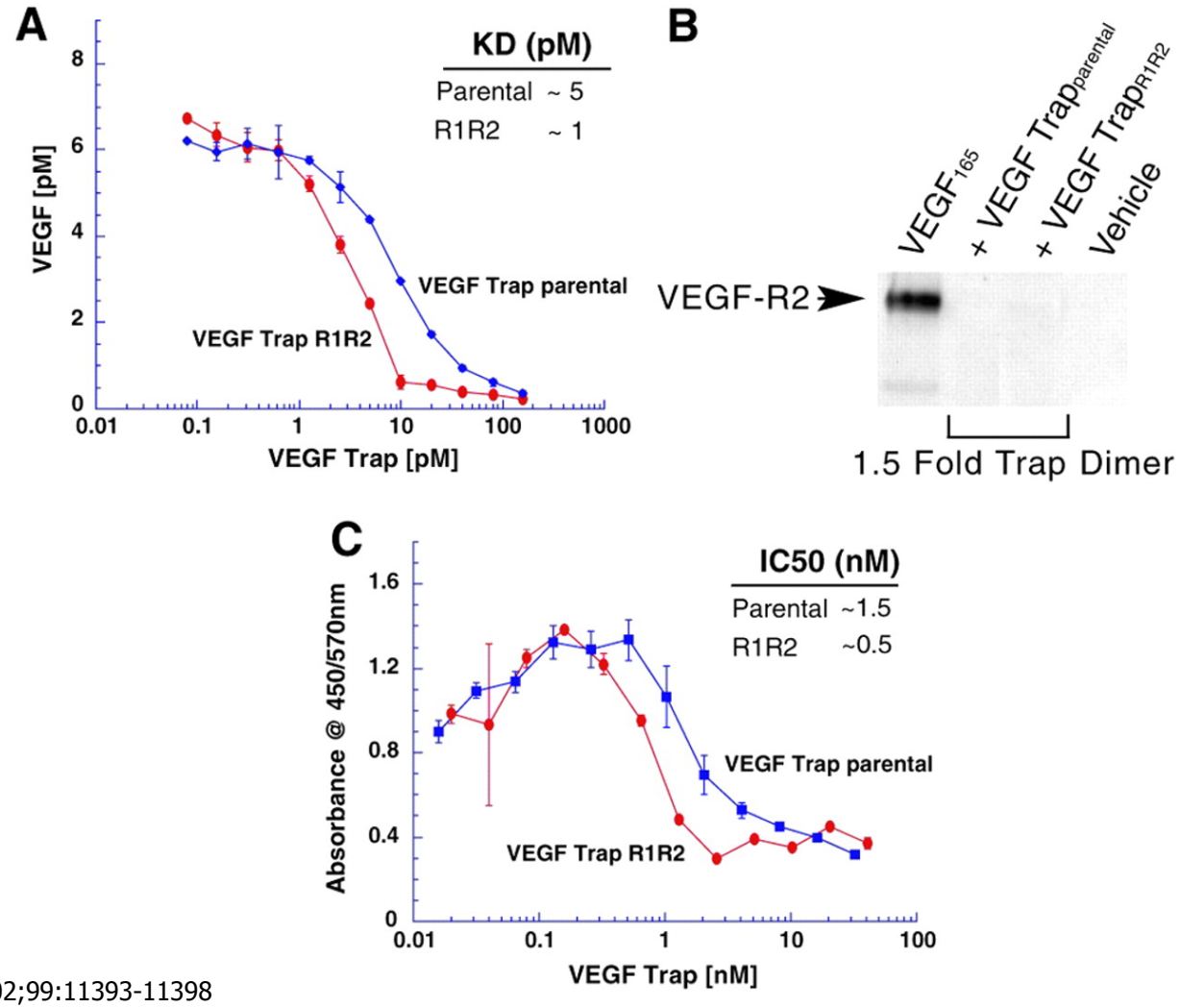
Aflibercept is engineered glycoprotein

- Each half molecule comprised of VEGFR1 domain 2 and VEGFR2 domain 3 + hinge, CH2 and CH3 regions of human IgG1 (VEGF-Trap R1R2)
- Dimer molecular weight 97 kDa; glycosylated
- Binds VEGF (VEGF-A, VEGF-B and PDGF) with higher affinity (0.5 pM) than either receptor 1 or 2 alone or bevacizumab (0.1-10 nM)
- Acts as soluble decoy receptor to block binding of VEGF to its receptor on vascular endothelial cells
- Inhibits angiogenesis

Aflibercept (VEGF-Trap) binds to and inhibits VEGF



From Holash *et al. PNAS* 2002;99:11393-11398

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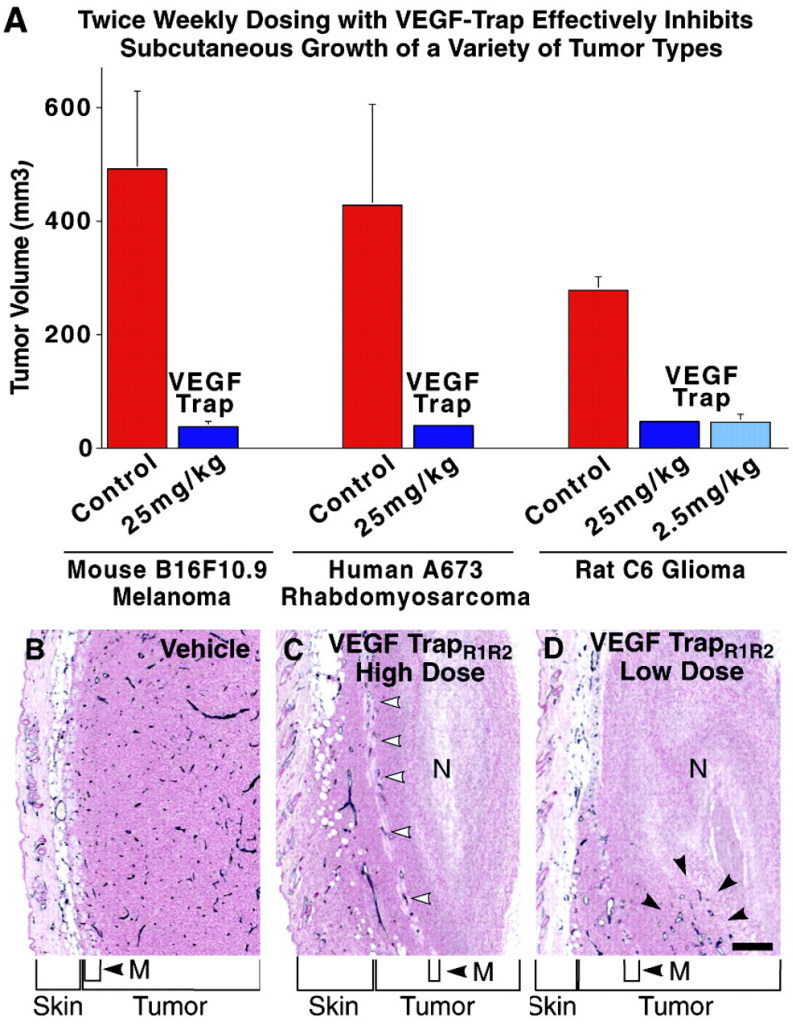
Aflibercept (VEGF-Trap) inhibits growth and vascularity of implanted tumors



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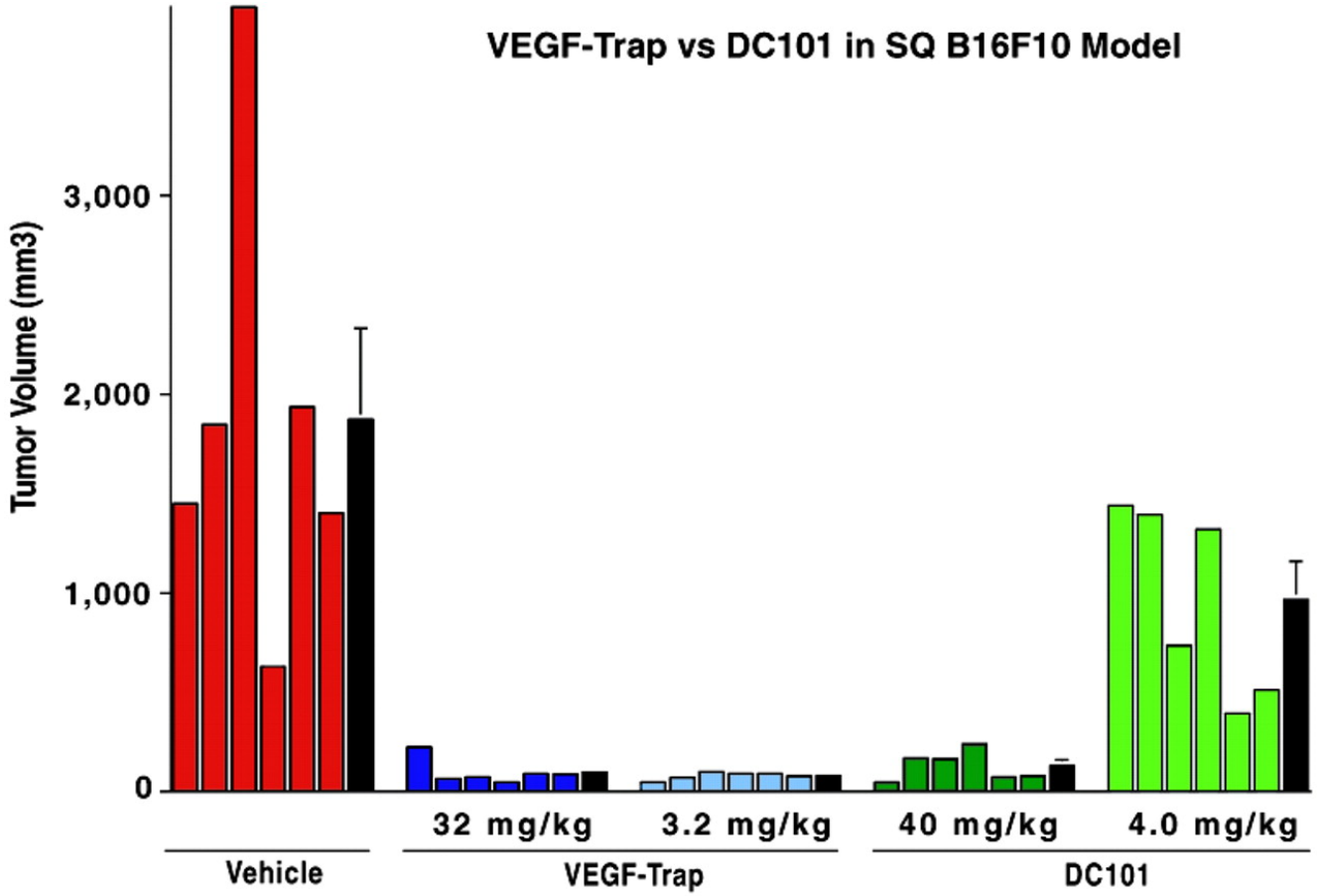
Aflibercept (VEGF-Trap) blocks tumor growth better than an anti-VEGF2 mAb



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Therapeutic development

- Initially developed by Regeneron to treat wet AMD (ophthalmic indication)
- Approved by FDA in 2011 as Eylea®
  - 2014 global sales $2.78B
- Converted to IV formulation for use in oncology

Therapeutic development (cont'd.)

- Intravenous formulation tested in mCRC
  - Zaltrap showed a 1.5 month survival advantage in the second-line VELOUR trial, with patients on Zaltrap plus standard chemotherapy having median survival of 13.5 months compared to 12 months for chemotherapy alone. Progression-free survival was 6.9 months for the Zaltrap arm versus 4.7 months for placebo.
- Partnered with Sanofi
- Approved by FDA in 2012 as Zaltrap
  - Priced at $11,000/mo—controversial

Summary

Summary

- Fc fusion proteins represent a new and promising modality in oncology
- The first Fc fusion protein in oncology was approved by FDA in 2012 for treatment of mCRC
- Zaltrap is constructed from domains of VEGFRs 1 and 2, a Type I receptor, using "cytokine trap" technology
- "Cytokine trap" technology can produce a molecule of higher affinity than the wild-type receptor and are as effective as mAbs
- Fc fusion proteins based on other binding domains (FGFR and ALK) are currently under development for use in different cancers

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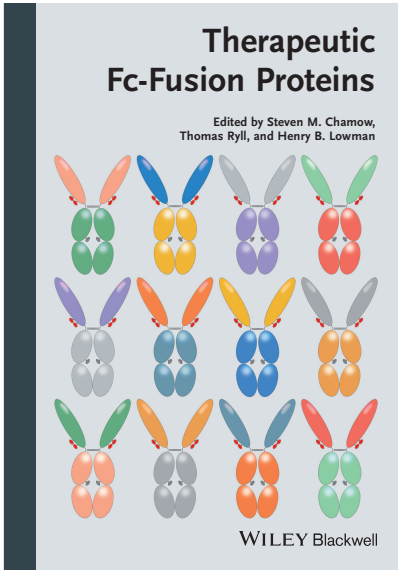

Thank you!

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For further information, see Chamow, *et al. (eds.) Therapeutic Fc Fusion Proteins* (Wiley-Blackwell) 2014.

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