Fusion proteins for immune applications (FPIA)

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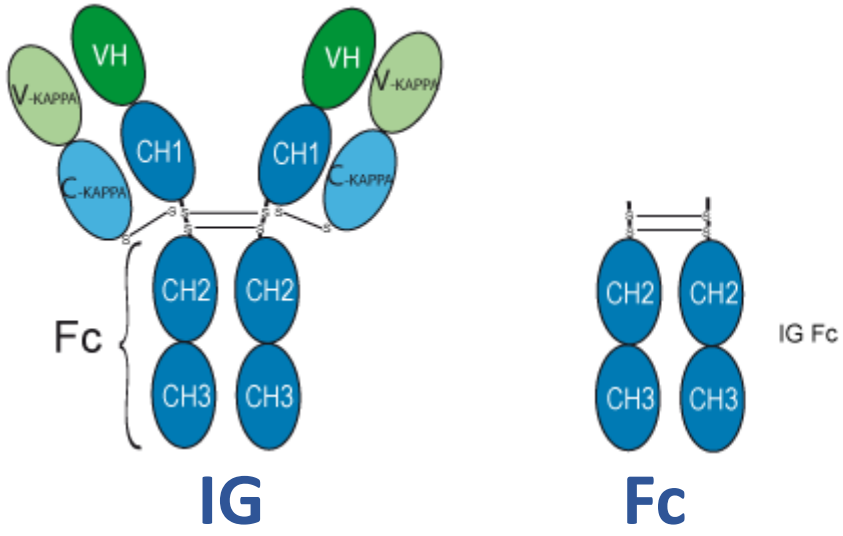
Fusion proteins for immune applications (FPIA)

Fusion proteins for immune applications (FPIA) are soluble fusion proteins, made of the extracellular region (EC) of a **receptor**, or of a **membrane ligand**, **fused to a Fc** (Fc-fusion proteins) and used as **monoclonal antibody alternatives**



A Fc corresponds to the dimeric part of an immunoglobulin (IG) or antibody (Ab) (usually IgG1), made of the CH2 and CH3 domains of the heavy chains and linked at the level of the hinge by disulfide bridges (2 for IgG1). Fc-fusion proteins are obtained by DNA recombinant technology (the fused proteins occupied the positions of the Fab arms of an IG (branches of the Y).

FPIA in clinical applications

1. In January 2016, **17 FPIA** (*next two slides*) have an **INN** (stem -**cept**) and **6** of them have been approved by the FDA: ***etanercept*** (1998), ***alefacept*** (2003), ***abatacept*** (2005), ***rilonacept*** (2008), ***belatacept*** (2011), ***aflibercept*** (2012)

2. This led to the INN stem '**-cept**' becoming widely known and 'synonyms' of FPIA, in term of structure

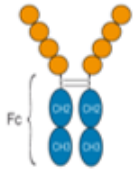
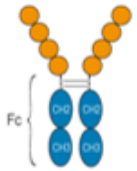
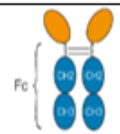
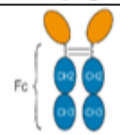
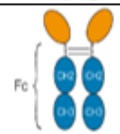
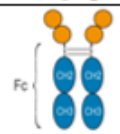
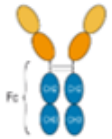
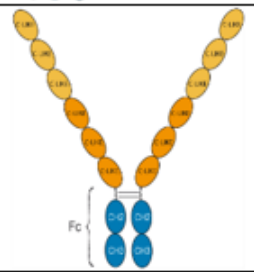
3. A FPIA can be considered as a mAb in which the two Fab arms are replaced by a binding protein. Moreover, as the MOA are similar, FPIA are antibody alternatives, in term of clinical applications

4. FPIA are intensively investigated and several ones are in clinical trials

17 FPIA have an INN (stem –cept)

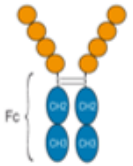
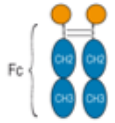
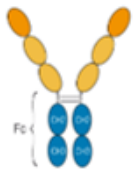
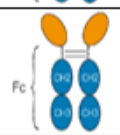
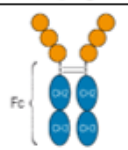
(slide 1/2)

6 have been approved by FDA

INN	Format	Identification	Target	Clinical indication	Status
lenercept ***(72)(35)***		Fusion-[TNFRSF1A]2-G1 Fc	TNF	Sepsis	
etanercept ***(81)(43)***		Fusion-[TNFRSF1B]2-G1 Fc	TNF	RA, PSA	FDA 1998 FDA 2002
alefacept ***(84)(46)***		Fusion- [CD58]2-G1 Fc	CD2	Psoriasis	FDA 2003 discontinued
abatacept ***(91)(53)***		Fusion- [CTLA4]2-G1 Fc	CD80 CD86	RA, JIA	FDA 2005 FDA 2008
belatacept ***(93)(59)***		Fusion- [CTLA4]2-G1 Fc	CD80, CD86	Prevent kidney transplant rejection	FDA 2011
atacicept ***(95)(57)***		Fusion-[TNFRSF13B]2-G1 Fc	TNFSF13, TNFSF13B	MM, NHL; RA, SLE	
aflibercept ***(95)(57)***		Fusion- [FLT1-KDR]2-G1 Fc	VEGFA	AMD, Cancers	FDA 2011 FDA 2012
rilonacept ***(95)(57)***		Fusion- [IL1RAP-IL1R1]2- G1 Fc	IL1A	CAPS	FDA 2008

17 FPIA have an INN (stem –cept)

(slide 2/2)

INN	Format	Identification	Target	Clinical indication	Status
baminercept ***(98)(60)***		Fusion- [LTBR]2-G1 Fc	LTA, LTB, TNFSF14	RA	
briobacept ***(98)(60)***		Fusion-[TNFRSF13C]2-G1 Fc	TNFSF13B	RA	
sotatercept ***(102)(64)***		Fusion-[ACVR2A]2- G1 Fc	INHBA	Anemia MDS Bone loss	
dalantercept ***(105)(67)***		Fusion-[ACVRL1]2-G1 Fc	GDF2, BMP10	MM, Solid tumors	
conbercept ***(105)(67)***		Fusion- [FLT1-KDR]2-G1 Fc	VEGFA	AMD, Solid tumors	
ramatercept ***(108)(70)***		Fusion-[ACVR2B]2- G1 Fc	GDF11	Muscle wasting	
lpafricept ***(109)(71)***		Fusion- [FZD8]2-G1 Fc	Wnt ligands	Solid tumors	
luspatercept ***(110)(72)***		Fusion-[ACVR2B]2- G1 Fc	GDF11	Anemia, MDS	
asunercept ***(112)§114***		Fusion- [FAS]2-G1 Fc	FASLG	Apoptosis inhibitor GvHD prevention, GBM	

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Proteins of the FPIA

1. The proteins, which are part of the FPIA, may be **receptors** or **membrane ligands**
   - belonging to the immune system
   - or belonging to pathways (angiogenesis, adhesion, migration, differentiation, metastasis) which potentially interfere with the **immune system** (for example, at immune checkpoints)

2. At the organism level, FPIA may be potential:
   - **immunosuppressant** (in autoimmunity)
   - or **immunostimulant** (in cancers, vaccines)

Target and molecular interactions of the FPIA

1. The target is a **soluble** protein:
The FPIA binds to the soluble protein (ligand) and prevents its binding to the natural membrane receptor.
The FPIA **neutralizes the protein** (the FPIA is a 'decoy' acting as a 'trap')

2. The target is a **membrane** protein (receptor or ligand) on a cell:
The FPIA binds to the membrane protein and prevents its binding to the natural 'paired' membrane protein (ligand or receptor) on another cell.
The FPIA **blocks a cell-cell interaction** (the FPIA is 'blocking the cross-talk' between cells)

> **These MOA are identical to those of mAb.**

The FPIA interaction outcome

The interaction of a FPIA with a membrane receptor at the surface of a given cell can be:

1. **agonist** or **antagonis** for this receptor. These terms should be used in the pharmacological meaning
2. **inhibitory** or **activatory** for the cell
3. **immunosuppressant** or **immunostimulant** for the organism (final outcome of the interactions)

It is not excluded that, in the future, FPIA be used to target intracellular or nuclear proteins.

Back up slide (1/3) Receptor vs ligand for proteins

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1. The notion of **ligand** is often associated to ‘soluble’ or ‘secreted’ protein, however in the immune system many of the interactions are between membrane proteins. So a ligand can be either a soluble protein or a membrane protein at the cell surface (GPI-anchored or transmembrane). It can be also intracellular in a cell pathway.

The notion of **receptor** is often associated to ‘membrane’ protein however many receptors can become naturally soluble (by natural proteolysis or cleavage of the GPI anchor by phospholipases).

> Therefore **‘soluble’ and ‘membrane’ is not** a criteria for the distinction **between ligand and receptor**

Back up slide (2/3) # Receptor vs ligand for proteins

2. A protein **receptor** has a meaning for a given cell (it transduces the signal from the cell membrane to the nucleus). At each step of a pathway, there is a signal reception and transmission. The protein which receives the signal is the receptor. Each protein in a pathway can be successively a receptor and the ligand for the next receptor.

In **cell-cell interaction**, membrane proteins are alternative receptors. A protein is a receptor for the cell at the surface of which it is expressed, but can be a ligand for the protein expressed on the other cell. This one receiving a signal becomes itself a receptor.
> So the notion of receptor is relative and depends on **a given cell in a given status**.

Back up slide (3/3) # Receptor vs ligand for proteins

1. Both the **receptor and the ligand proteins** are defined by their ability **to interact**
2. The distinction between receptor and ligand for a protein cannot be done on ‘soluble’ or ‘membrane’
3. The distinction between receptor and ligand for a membrane protein in the immune system is **relative** and defined **for a given cell**
4. Many membrane proteins (both receptors or membrane ligands) are **inducible** (following cell activation, cell subtype, etc., in response to a previous ligand-receptor interaction).
5. Therefore, the distinction receptor versus ligand is defined by the interaction outcome, not only for a given cell, but **for a given cell in a given status**.