Modified receptor molecules as medicines

Nomenclature of receptor molecules or membráne ligands, native or modified, after WHO

- Common stem **-cept**
  - a preceding infix:
    - **-ba-** for B-cells factor activating receptors
    - **-ber-** for VEGF (vascular endothelial growth factor) receptors
    - **-co-** for complement receptors
    - **-far-** for the subgroup of interferone receptors
    - **-fri-** for *frizzled* receptors family
    - **-ki-** for interleukine receptors
    - **-lefa-** for CD58 receptors (lymphocyte function associated antigen 3, LFA3)
    - **-na-** for interleukin 1 receptors
    - **-ner-** for TNF (tumor necrosis factor) receptors
    - **-ta-** for CTLA4 (cytotoxic T-lymfocyte antigen 4) receptors
    - **-taci-** for transmembráne activator and calcium modulator and cyclophiline ligand interactor
    - **-ter-** for TGF (transformation growth factor) receptors
    - **-vir-** for antiviral receptors

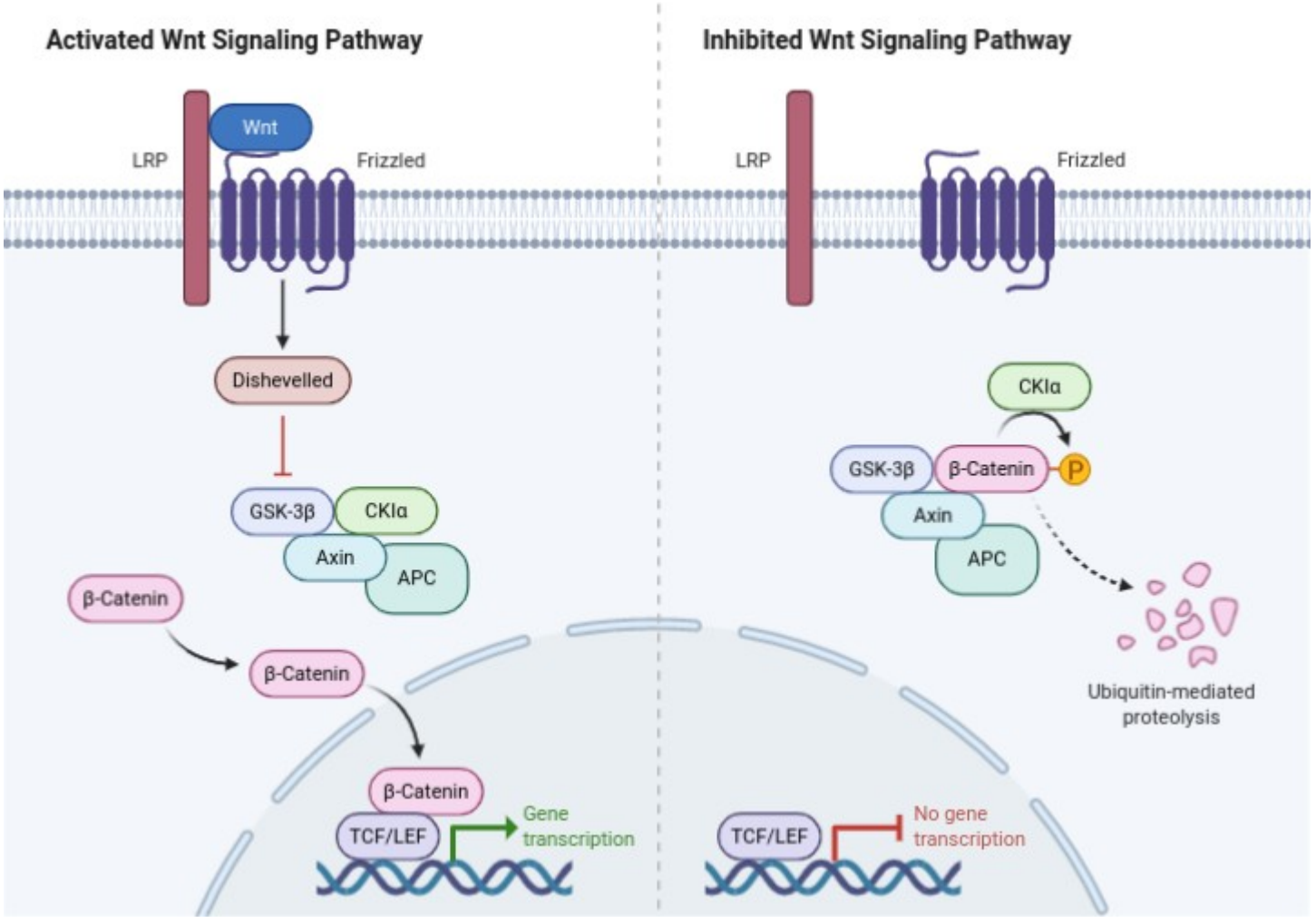
Modified *frizzled* receptors molecules

ipafricept

syn. OMP 54F28

- a fusion protein composed from the extracellular domain of human FZD8 (frizzled family receptor 8, frizzled-8), rich on Cys, and F_c fragment of human IgG_1
- M.o. A.: competes with the native FZD8 receptor for its ligands $\Rightarrow$ antagonizes WNT signaling pathway
  - Wnt [wint] signaling pathway
    - an important role in determination of the cell fate, cellular proliferaton and migration
    - an abnormal Wnt pathway signaling is linked with the development and progression of many cancers by enabling of their increased progression, angiogenesis, survival and metastasizing
    - Wnt pathway activation contributes also to tumorigenicity of cancer stem cells (CSCs)
- preclinical studies exhibited a decrease in cancer growth and occurence of CSCs
- aplication *i.v.*
- clinical studies on
  - hepatocelular carcinoma (phase 1, dose escalation)
  - reccurent platinum sensitive ovary cancer (+ carboplatin, phase 1)
  - pancreatic caner of 4th stage (+paclitaxel + gemcitabine, phase 1, dose escalation)
  - dose escalation in patients with various cancers originated in a solid tissue

Wnt signaling pathway



Wnt signaling pathway

- Wnt - abbreviation from Wingless/Int-1
- a signaling glycoprotein of Wnt family (eg. Wnt1, Wnt2) is bound to the FZD (a G-protein coupeled) receptor at the outer side of the membrane
- a mediator (eg. Dishevelled = Dsh) which then inhibits a complex of three proteins GSK3/axin/APC is activated at the inner side of the membrane
- when these proteins are inhibited β-catenin is stopped to be phosphorylated and starts to be accumulated in its non-phophorylated form
- $\Rightarrow$ β–catenin into the nucleus; after combination with transcription factors from TCF/LEF family influences genes transcripion
- „normal“ role of Wnt cascade in embryonic development: cell proliferation, gastrulation, embryonal development of the brain, limbs...

Modified molecules of interleukine receptors

inbakicept

syn. ALT-803

- fusion protein of IL-15 receptor α-chain (=fragment containing “sushi“ domain) with F_c fragment of human IgG_1, dimer
  - = sequence 1-65 of α-chain of IL-15 receptor + [232 C-terminal residues (66 - 297) + a linker (71-80) + part 81-190 of constant domain 2 of the heavy chain (CH2) + 191 of domain 3 of the heavy chain (CH3)] IgG_1, dimer
- $C_{2980}H_{4624}N_{800}O_{894}S_{28}$ (only aglycon)
- anticancer drug
- *i.v., s.c.*, *i.p.* administration
- clinical studies
  - decrease of persistence of HIV virus in lymphatic nodes (phase 2)
  - pharmocokinetics after *s.c.* administration (phase 1)
  - preparation of NK cells from a donor for usage in treatment of acute myeloid leukemia (phase 2)
  - relapsing or multiple refractory myeloma (phase 1)
  -

Modified TNF receptors

etanercept

- fusion protein of the sequence 1-235 of human p75 TNF receptor with part 236-467 of human IgG_{γ} (= F_c fragment)
- 934 AA
- M_r of aglycone 51 166.8; total cca 150 000
- preparation by a recombination technology on Chinese hamster ovary cell lines
- soluble
- MA: binds to TNF, inhibits its binding to endogenous TNF receptors $\Rightarrow$ pro-inflammatory effect supressed

Enbrel ®, Benepali ®, Erelzi ®, Nepexto ® - 25 or 50 mg, *s.c.* administration, prefilled syringes or pens

- Indicatios (combined with methothrexate, or alone):
  - rheumatoid arthritis
  - poly-articular juvenile arthritis (children over 2 years)
  - psoriatic arthritis
  - ankylosing spondylitis (Bechterev disease)
  - plaque psoriasis (PsO) in patients 4 years or older

Modified CTLA4 receptors

abatacept

Orencia ® 250 mg powder for concentrate for solution for infusion

- a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified F_c portion of human immunoglobulin G1 (IgG_1).
- produced by recombinant DNA technology in Chinese hamster ovary cells
    - MA: selectively modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, costimulatory signal. A major costimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept selectively inhibits this costimulatory pathway by specifically binding to CD80 and CD86. Studies indicate that naive T lymphocyte responses are more affected by abatacept than memory T lymphocyte responses.

Indications

- in combination with methotrexate, abatacept is indicated for:
- the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor.
- the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate

belatacept

Nulojix ® 250 mg powder for concentrate for solution for infusion

- a selective costimulation blocker
- a soluble fusion protein consisting of a modified extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fused to a portion (hinge-CH2-CH3 domains) of the F_c domain of a human immunoglobulin G1 antibody.
- produced by recombinant DNA technology in a mammalian cell expression system (chinese hamster ovary cells)
- two amino acid substitutions (Leu104 to Glu; Ala29 to Tyr) were made in the ligand binding region of CTLA-4.

- M.A.: belatacept binds to CD80 and CD86 on antigen presenting cells. As a result, belatacept blocks CD28 mediated co-stimulation of T cells inhibiting their activation. Activated T cells are the predominant mediators of immunologic response to the transplanted kidney. Belatacept, a modified form of CTLA4-Ig, binds CD80 and CD86 more avidly than the parent CTLA4-Ig molecule from which it is derived. This increased avidity provides a level of immunosuppression that is necessary for preventing immune-mediated allograft failure and dysfunction.

Indications

- in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adults receiving a renal transplant. It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.

Modified interleukine-1 receptors

rilonacept

Rilonacept Regeneron 80 ® (formerly Arcalyst ®) powder for *s.c.* injections)

- a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human type I interleukin-1 receptor (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG_1.
- summary formula of aglycone $C_{9030}H_{13932}N_{2400}O_{2670}S_{74}$
- M_r cca 251 000
- produced by a recombinant technology on Chinese hamster ovary cells
- M.A.: rilonacept binds to and blocks the activity of the cytokine IL-1 and binds both IL-1β and IL-1α, which are the primary pro-inflammatory cytokines implicated in many inflammatory diseases.
- also binds the endogenous IL-1 receptor antagonist (IL-1ra) but with a lower affinity than IL-1β or IL-1α.

- Indications: treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells
- Syndrome (MWS), in adults and children aged 12 years and older.
  - CAPS is a genetic disease generally caused by mutations of NLRP-3 gene (=[*Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3* gene)
  - an orphan drug

Modified receptors of VEGF

aflibercept

Eylea ® *intravitreal injection; pre-filled syringe*

- antiangiogenic activity
- a heterodimeric fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the F_c portion of human IgG_1
- produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology
- originally proposed as an anti-neoplastic
- acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

- Indications:
  - neovascular (wet) age-related macular degeneration (AMD)
  - visual impairment
    - due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
    - due to diabetic macular oedema (DME)
    - due to myopic choroidal neovascularisation (myopic CNV)

Modified TGF receptors

sotatercept

syn. ACE-011

CAS 1001080-50-7

- a dimeric fusion protein consisting of the extracellular domain of the human ActRIIA linked to the F_c portion of human IgG1 and may be an effective therapy in a variety of diseases involving bone loss.
- Red Cell Maturation Agent for the Treatment of Anemia, and Bone Anabolic Agent for the Treatment of Cancer-Related Bone Loss
- M.A.:
  - „ligand trap“ inhibiting „negative regulators“ of the late stage of erythropoesis
  - neutralizes ligands of superfamily TGF-β, eg. activins A and B, and grow differentiation factors (GDFs) including GDF11
- clinical studies for
  - anemia in kidney failure (phase 2)
  - pulmonary arterial hypertension (phases 2 and 3)
  - myelodysplastic syndrome and chronical myelomonocytic leukemia (phase 2)
  - Diamond-Blackfan anemia (phase 2)
  - β-thalasemia (phase 2)
  - anemia caused by a chemotherapy in treatment of non-small cell lung carcinoma (phase 2)
  - ...

luspatercept
syn. ACE-536
CAS 1373715-00-4
Reblozyl ® *powder for injection solution (s.c.)*

- a soluble, recombinant fusion protein composed of a modified form of the extracellular domain of human activin receptor type IIb (ActRIIb) and linked to the human IgG1 F_c domain, with red blood cell stimulating activity.
- inhibits several ligands in the transforming growth factor (TGF)-beta superfamily.
- summary formula of aglycone $C_{3350}H_{5070}N_{906}O_{1044}S_{38}$
- total 332 AA residues
- produced by a recombinant technology in Chinese hamster ovary cells
- M.A.:
  - neutralizes ligands of superfamily TGF-β, eg. activins A a B
- inhibits Smad2/3 signaling, that results into erythroid cells maturation by means of differentiation of erythroid precursors in a late stage (normoblasts) in bone marrow.
- Smad2/3 signaling is abnormally increased in models of diseases characterized by an non-efficient erythropoesis, i.e. MDS and β-thalasemia, and in bone marrow of patients with MDS
- administered *s.c.*

- indications:
  - anemia caused by β-thalasemia
  - anemia dependent on transfusions, formed as the result of myelodysplastic syndrome, with circular sideroblasts, if there is unsatisfactory response on epoetin treatment