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From FKBP12 to IMPDH: Ten Years of Immunology Targets at *Vertex*

Mark Murcko, *Vertex* Pharmaceuticals Inc., Cambridge, Massachusetts, USA

The evolution of research on some different autoimmune and inflammatory targets (like psoriasis, rheumatoid arthritis, asthma, hepatitis C, or organ-transplant rejection) has been described. The used approach for the design of new inhibitors was based on FLBP12, thte target for FK506. NMR and crystal structures were solved in 1991 opening the way for designing more potent compounds. This led to the discovery of a ternary complex formed by calcineurin, FKBP12, and FK506, where calcineurin, a Ca^{2+}- and calmodulin-dependent phosphatase, is involved in the immunosuppressive action of FK506. Calcineurin is a potential component of TCR and IgE receptor signaling pathways involved in transcription and exocytosis. In 1994, the research team abandoned this project, as FK506 seemed to induce nephro- and neurotoxicities, and as clinical studies were suggesting that the properties were not dramatically improved compared to cyclosporin.

Another project focused on p38 mitogen-activated protein (MAP) kinase inhibitors. Blocking p38 has been shown to reduce levels of the proinflammatory cytokines IL-1β and TNFα, acting as a cytokine suppression factor. It may therefore have applications in the treatment of inflammatory diseases, such as asthma, *Crohn*'s disease and rheumatoid arthritis. A phase-I clinical trial for the VX-745 inhibitor has already started.

A new potent inhibitor (VX-740) has also been developed for IL-1β-converting enzyme (ICE) as a treatment for rheumatoid arthritis (RA) and other inflammatory diseases. It is now being tested in phase-I clinical trials. VX-740 has been shown to block the production of IL-1β and IFNγ, and to reduce experimentally induced joint inflammation in animals without significant toxicity.

Another project deals with inosine-5'-monoposphate dehydrogenase (IMPDH). IMPDH catalyses the NAD-dependent oxidation of IMP to XMP which is the rate-limiting reaction of guanosine nucleotide (GMP) *de novo* biosynthesis. As proliferating B- and T-lymphocytes are dependent on this pathway, and not on the salvage pathway, the inhibition of IMPDH is of great therapeutic potential.

Solving the three-dimensional structure in 1996 [1][2] in complex with mycophenolic acid (MPA, from the first generation of inhibitors developed by *Hoffmann-La Roche*) allowed advanced structure-based drug design of new inhibitors for IMPDH with high potency and tolerability. This research led to the development of VX-497, which seems to be very promising for immunosuppressive therapy. This inhibitor shows potential for treatment of psoriasis, an autoimmune disease of the skin, rheumatoid arthritis, inflammatory bowel disease (IBD), atopic dermatitis, steroid-dependent asthma, organ transplantation, systemic lupus erythematosis (SLE) or hepatitis-C virus (HCV). VX-497 has a good tolerability when compared to other IMPDH inhibitors like MPA, mizoribine, or ribavirin showing significant side-effects. VX-497 shows IC_{50} values at about 100 nM and is suitable for oral administration. It is active *in vivo* against collagen-induced arthritis in mouse, plaque-forming cell assay in mouse, heterotopic heart transplant in rat, skin transplant in mouse or graft *vs.* host disease in mouse. Preclinical pharmacology establishes antiviral and immunosuppressive potential whereas toxicology testing demonstrates good safety and tolerability. VX-497 has been tested in a single-dose escalation study in healthy volunteers and is now being investigated in phase-II clinical trials for HCV and psoriasis.

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Regulation of Intracellular Signalling and Transcription by Induced Proximity Using Synthetic Ligands

Isabella Graef, Stanford University, Medical School, Stanford, CA, USA

In signal transduction, molecular interaction results in the transfer of information along specific pathways. Strategies to control signalling pathways came from the insight that ligand-induced protein dimerization (or induced proximity) can initiate or regulate the information transfer. There are several examples where induced proximity is involved in signalling of mammalian cells, such as the augmerization of membrane receptors (receptors for growth factors and cytokines), phosphorylation-induced association of proteins (ZAP70, JAK, STATS) and the nuclear translocation of proteins. The strategy for regulating protein interactions by induced proximity can be simplified in a restricted diffusion model. The chemical inducer of dimerization is a small dimeric lipophilic ligand that permeates the cell membrane. In the cytoplasm, the ligand brings togeth-