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TNF/TNFR: drug target for autoimmune diseases and immune-mediated inflammatory diseases

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1. ABSTRACT

Tumor necrosis factor, a regulatory cytokine, is extremely important signaling protein in the immune system. Among TNF family, TNF-α, TNF-β are most the significant family members. Receptor of TNF namely TNFR1 and TNFR2 stimulates two different signaling pathways. TNFR1 signaling induces apoptosis pathway. Conversely, TNFR2 signaling triggers cell survival pathways. In this paper, we discuss about the TNF family with special reference to TNF-α / TNF-β, different hypothesis related to autoimmunity and role of TNF, structure of TNF-α / TNF-β, distribution and normal activity in human body of TNF, receptors and signaling pathway for drug targeting. Finally, we also discuss about the therapy for autoimmune diseases and immune-mediated inflammatory diseases (IMIDs) using small molecules or therapeutic proteins.

2. INTRODUCTION

In 1975, tumor necrosis factor was first termed and identified by a group of scientists when they were studying "hemorrhagic necrosis". Scientists found that endotoxin induced serum factor is the basis for the necrosis of tumors (1). Later, this phenomenon was described by Dr. William Coley, in New York, and he was the first to investigate the phenomenon of tumor necrosis (2). A same line of research was performed during in the early hours of 1980s which brought into the notice about the function of the function of TNF-α into spotlight. These groups of scientists described that Cachectin has an immediate role in the wasting that is characteristic of chronic diseases (3, 4). Later on, it was confirmed that these molecules were same (5, 6). Slowly, it came into view that TNF-α was a central biological mediator, associated with different immunological and inflammatory signaling processes.

TNF, a regulatory cytokine, is very crucial in signaling the protein in the immune system. This protein organizes cross-talk between immune cells and direct many of their functions (7). It has been noted that TNF-α regulates immune cell (8), as well as expression of MMP-9 and integrin *αvβ6* during tumor progression (9). This cytokine also help to release other cytokines (10). During the signaling process, the interaction of TNF-α was noted with any one of the receptors such as TNF receptor 1 (TNFR1) or TNF receptor 2 (TNFR2). TNFR1 and TNFR2 stimulate two different signaling pathways. Usually, TNFR1 signaling induces the cascade related to apoptosis (11). However, it is related to the cell type, the condition of activation of the cell as well as the cell cycle. Conversely, TNFR2 signaling trigger cell survival pathways particularly in the stimulated T cells which can cause cell proliferation (12, 13). After the attachment with the receptor, TNF- α is also related to the activation of the transcription factors NF_kB and Jun Kinase (14). It has to be noted that a protein named 'nuclear factor kappa-light-chain-enhancer of activated B cells' (NFkB) plays a significant role in regulating the immune response. This nuclear factor, NF_kB, regulates the *in vivo* production of many pro-inflammatory cytokines including TNF-α, and related proteins which are actively involved in the immune-inflammatory diseases (15). Through a common feedback loop, the expression level of TNF-α as well as expression level NF_kB is regulated (16).

Defective immune cells provoke destruction of the body's own proteins, cells and tissues within the autoimmunity and this situation can direct to the development of autoimmune diseases (17). It is also estimated that 50 distinct diseases and syndromes are related to the autoimmune diseases which affect about 5% of the population in Europe and North America and among them with two thirds of the patients being female (18). Some examples of autoimmune diseases are multiple sclerosis, rheumatoid arthritis, juvenile diabetes, lupus erythematosus, type 1 diabetes cardiomyopathy, anti phospholipid syndrome, Guillain-Barré syndrome, Crohn's disease, Graves' disease, Sjogren's syndrome, alopecia, myasthenia gravis, , and psoriasis. (19). Patients of rheumatoid arthritis and crohn's disease are treated with anti-TNF therapies along with other immune-suppressive therapies which are being regulatory approved (20, 21). Inflammatory disorders include the vast variety of human diseases and immune system and its components are regularly involved in inflammatory disorders (22). Some examples are allergic reactions and inflammatory bowel diseases (IBD). Anti-TNF therapies are also available IBD (23). Some of these inflammatory disorders are Immune-mediated inflammatory diseases (IMIDs). IMIDs are developed along with cytokine dysregulation and acute or chronic inflammation (24). As improper or unnecessary immune responses, therapy can be given through the corticosteroids, immunosuppressants, which are targeting tumor necrosis factor (TNF) (25).

3. TNF FAMILY AND TNF-α / TNF-β

The TNF family has nearly about 15 cytokines, and most of these cytokines play an important role in inflammation and immune response (26). Few examples of the family member are CD27, CD30, CD40, CD134, CD137, Fas, TNFR1 and TNF-α-related apoptosis-inducing ligand (TRAIL). These are related to development/suppression of some autoimmune diseases or IMIDs (27,28). The cytoplasmic death domains are one of the main characteristic of TNF superfamily. They stimulate apoptosis and activate receptors (28). Among the superfamily members, no homology was identified between the cytoplasmic tails (29). Targeting TNF superfamily members are associated with various diseases, including autoimmune diseases as well as immune-mediated inflammatory diseases (IMIDs) and accomplished significant success over the therapy (30-32).

However, TNF-α (known as TNF), TNF-β (known as lymphotoxin-α), is the most significant of the family members (33). Tumor necrosis factor-β, a lymphokine cytokine, is produced by Th1 type of T-cells. It induces vascular endothelial cells for their further activity (34). TNF-β is also associated with a number of diseases such as chronic obstructive pulmonary disease (35), pathogenesis of chronic hepatitis C virus (HCV) (36), coronary artery disease and myocardial infarction (37), aortoiliac occlusive disease (one type atherosclerosis (38) and Graves' disease(39). The structure-based design of therapeutic agents is a novel approach. Presently, several scientists are routing towards structural based drug discovery (40, 41). However, understanding the structure of TNF-α / TNF-β can aid in small molecular designs that augment/suppress autoimmune diseases and IMIDs.

4. TNF AND AUTOIMMUNITY: DIFFERENT HYPOTHESIS

Throughout the life, TNF especially TNF-α / TNF-β and their receptor play a regulatory role of different immune cells by activating different genes that are responsible for inflammation, proliferation, differentiation as well as apoptosis (42, 43). TNF family members effectively take part in the communication to respond to chemical messengers in the immune system. This protein also provides security to several infectious diseases, cancer and autoimmune diseases (44). TNF first binds with the two receptors TNFR1 and TNFR2. This cytokine act on TNFR2 for any function related to T-cell survival and TNFR1 for apoptosis (45).

The progenitors T cells, as well as other different immune cells, produce and grow-up in the thymus during the development of autoimmunity. The majority of these immature immune cells will die through the process of apoptosis (46). However, it is necessary to eradicate the imperfect immune-cell progenitors. In this process, a few cells will discriminate into autoreactive T cells. Some of the T-cells are produced as autoreactive T cells. This cell pupation is also called native autoreactive T cells (47, 48). This T cell population escapes from the apoptosis during T-cell education, which enters into the blood circulatory system (49). Actually, T-cell education in the thymus engages in the process of positive and negative selection (50). However, the cell population differentiates into autoreactive T cells to encounter particular self-antigens (51). Failed T-cell education (through the process of

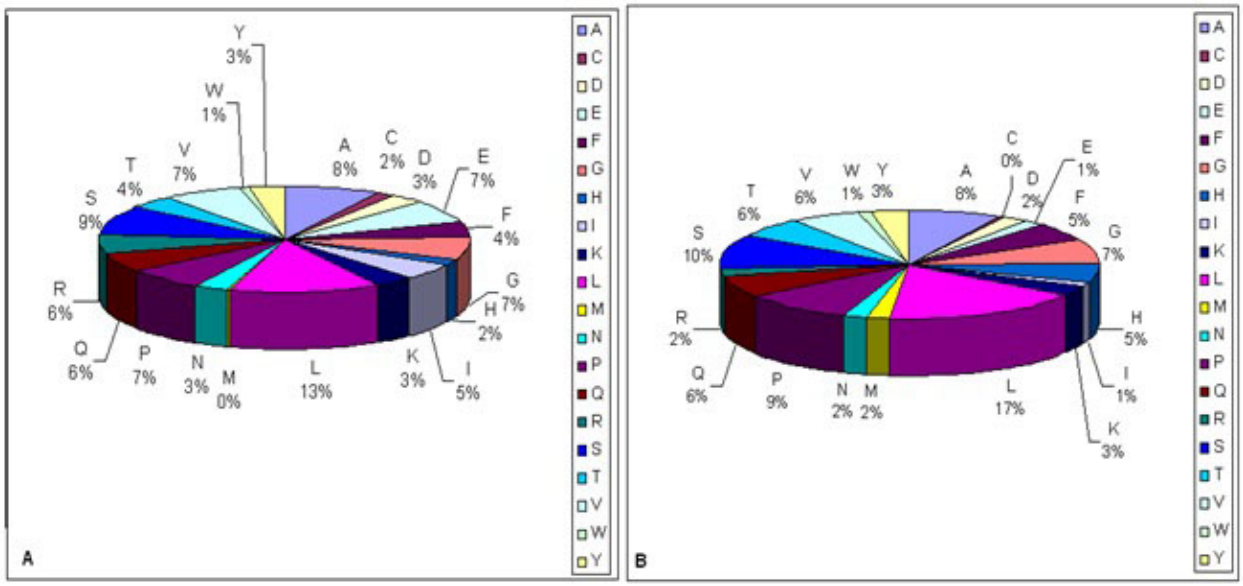

Figure 1. Amino acid composition in TNF (A) amino acids composition of TNF-α (B) amino acids composition of TNF- β.

positive and negative selection) can lead to various autoimmune diseases. In this state, TNF may have a vital role on the infection of autoimmunity and lineage in pledge of T cells (52-54). Another hypothesis by Kollias and Kontoyiannis (55) described that the deregulation of TNF production of low or high, characterizes many autoimmune diseases. Kodama *et al.* (56) proposed a hypothesis in an animal model that TNF has a possible therapeutic value, because of its ability to selectively kill autoreactive (pathogenic) T cells and leaving normal cells in animal model. They also showed that NOD mice have a deficiency in regulation of transcription factor NF-kB. In NOD mice, NF-kB dysregulation makes the pathogenic T cells selectively vulnerable to TNF-induced apoptosis (57, 58). However, low TNF gene adaptations are present during the experiment with some animal models of spontaneous autoimmunity (59). One hypothesis proposed that the TNF-induced death is total concentration dependent (60). TNF has a major role in the modulation of the autoimmune diseases and immune-mediated inflammatory diseases (IMIDs). Presently several scientist are targeting both the TNF and its soluble TNF- receptor, for the small molecular discovery. However, the efficacy of the number of small molecules associated with anti-inflammatory activity has shown a connection with the TNF concentration as well as the structure function relationship of this cytokine (61, 65).

5. STRUCTURE OF TNF-α / TNF-β

Several scientists have reported that TNFα are of two types, a membrane bound and a soluble form different function (66, 67). We presented the compositional analysis of amino acids (TNFα 232 amino acids precursor and TNF-β 205 amino acids) of TNF in Figure 1. Molecular weights of these two proteins are 25.5 kdal (TNFα) and 22.3 kdal (TNF-β). However, TNFα seems to affix the polypeptide in the membrane (68). TNFα is first formed as a type II membrane protein. Amino acids 44 to 26 of the TNFα sequence comprise the hydrophobic transmembrane region and residues 76 to 50 comprise the intracytoplasmic region. This unprocessed protein has a molecular mass of 26 kDa which is cleaved into a 17 kDa active form. This protein was synthesized as pro-TNF-α is which was expressed on the plasma membrane. Next step, this protein, is cleaved through the action of metalloproteinase's to form a mature soluble 17-kDa protein. It is interesting that both the forms are active (69). Solution form is processed in homotrimer form with total molecular mass of 52 kDa. This homotrimer form binds and cross-links the receptors (70). The TNF β has been structurally characterized (71, 72) and each monomer consists of two β -pleated sheet each of eight, anti-parallel β -strands with an N-terminal insertion. The N-terminal insertion contains three additional β -strands. It was reported that the monomer is about 60Å long and 30Å wide (73, 74). TNF β share the same fold as TNFα (Figure 2). Noatbly there exsist significant differences in the surface properties of these two molecules.

6. TNF: DISTRIBUTION AND NORMAL ACTIVITY IN HUMAN BODY

TNFα exists in different cell types whereas TNF-β is available in very few cells. TNFα is created by extensive group of cells such as macrophages, CD41, CD81, T-lymphocytes, B-lymphocytes, LAK cells, NK cells, neutrophils, astrocytes, endothelial cells, smooth muscle cells, and a number of non-hematopoietic tumour cell lines (75). It has been noted that some cells can be induced to produce both of the two types of TNF. Several activities of TNFα are related to species-specific (76). Banner *et al.* (77) described the structure activity relationship and function by crystallization of X-ray structure of TNF-β in complex with TNFR-1. As a regulatory cytokine, TNF plays a vital role for communication between immune cells and controls many

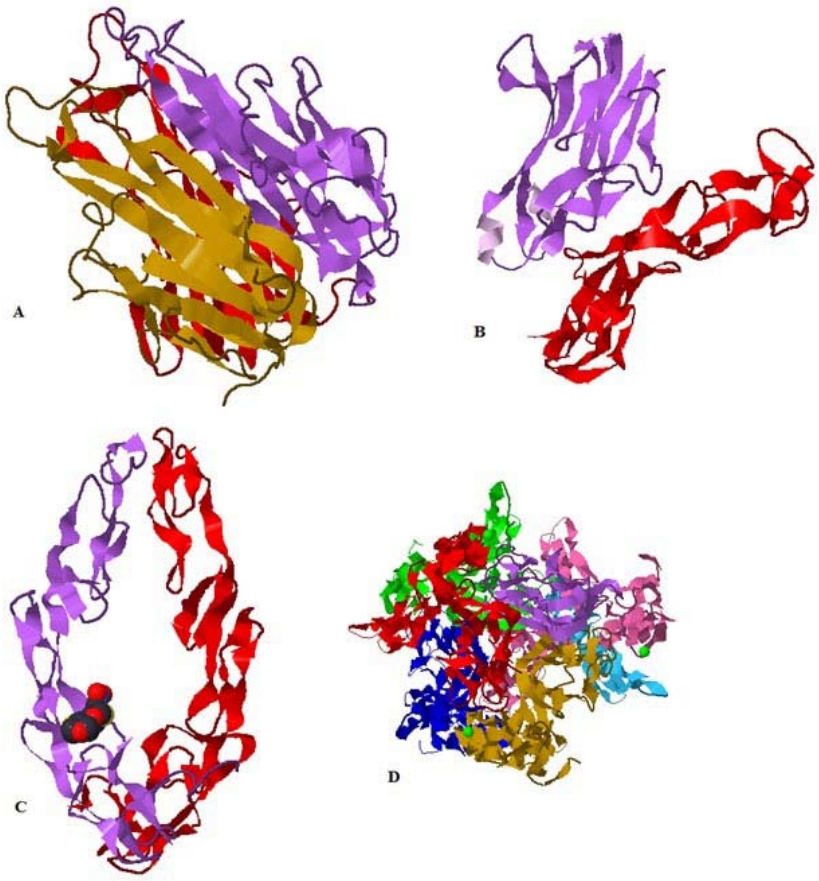

Figure 2. The secondary structure of TNF-α ,TNF-β, TNFR1,TNFR2 (A)tumor necrosis factor alpha (PDB ID: 1a8m) (B)tumor necrosis factor beta (PDB ID: 1tnr) (C) tumor necrosis factor receptor 1 (PDB ID: 1ft4)(C) tumor necrosis factor receptor 2/TNF-tnfr2 complex (PDB ID: 3alq)

of their functions (78). TNFα play variable important functions such as immunostimulation (79), resistance to infection agents (79, 80), resistance to tumors (79, 80), sleep regulation (81-83) and embryonic development (84, 85). It has been noted that TNFα mRNA is produced during the diurnal rhythm in the brain with highest levels during peak sleep periods (86). Conversely, lack of the TNFR-1 receptors resulted in reduced sleep in animal models (87). However, IL-1 plays a similar kind of role (88). During normal embryonic development, TNF mediated apoptosis also plays a normal role. However, a number of receptor such as Fas, TNFR involved in this process (89, 90).

7. TNF AND ITS RECEPTORS

After binding with the receptor, the biological activity of the TNF starts. Trans-membrane glycoproteins TNFR1 and TNFR2 receptors are involved in the binding process have multiple cysteine-rich repeats in the N-terminal domains (91). The molecular weight of TNFR-1 is 55 kDa, and TNFR-2 is 75 kDa (92). Naismith *et al.* (93) proposed the complex structure of TNFR-1. TNFR-1 comprises 434 amino acids and TNFR-2 comprises 439 amino acids. It has been reported that these receptors share very limited similarity in the extracellular region (94). It has been reported that human TNFα binds with the TNF receptors compactly. The disassociation constant, K_d during binding is 0.5 nM for TNFR-1 and 0.1 nM for TNFR-2. It has been described that after binding with the TNFR-1 receptor, the toxic effects of TNFα has become intercede (95, 96).

Conversely, during binding of TNF-β with the receptor, properties of 'TNF-β' have been described by Banner *et al* (72). At this time, LT-β can be able to form heterotrimer with TNF-β. This heterotrimer binds with the TNF receptors. Banner *et al.* (72) developed the Van der Waals surface of the TNF-β trimer structure with its receptor through Rasmol. There some differences between the primary characteristic of TNFR1 and TNFR2 (Table 1). A death domain is found in the TNFR1; were as the domain is not present in TNFR2 (97). The death domain of TNFR1 contains 80 amino-acid which rapidly engages the apoptotic signaling pathway of the cells (98, 99). It was observed in mice model that TNFR1 are resistant to endotoxin-induced lethality; whereas TNFR2 remain sensitive, (100, 101). Fiers (96) reported that TNFR-1 and TNFR-2 are both N-glycosylated; conversely, TNFR-2 is only O-glycosylated.

Table 1. Differences between the primary characteristic of TNFR1 and TNFR2

Sl. No.	TNFR1	TNFR1
1	Death domain is found in the TNFR1	No death domain is found in the TNFR1
2	It is N-glycosylated	This is both N-glycosylated and O-glycosylated
3.	It activates the pathway of apoptosis through cross talking with the adapter protein such as Fas-associated death domain (FADD) or TNFR1-associated death domain(TRADD)	It tigers the T-cell survival pathway. It also cross talk with protein the transcription factor nuclear factor-κB(NF-κB) ultimately cleave NF-κB from its inhibitor Molecule, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor(IκBα)
4.	It may performs some pro-survival functions which is based on the crosstalk with TNFR2	It may performs some pro-apoptotic functions which is related to immune response and some other pro-apoptotic functions which is based on the crosstalk with TNFR1

Table 2. TNF signaling pathway and its role in different disease

Sl. No.	Disease	Defect/function in signaling pathway	References
1	Diabetes mellitus type 1	Pathogenic T cells and related defects in TNF signalling	125
2	Multiple sclerosis	Death of oligodendrocytes	126
3	Cardial infarction	Greater role in protecting from ischaemia specially to the females	127
4	Rheumatoid arthritis	Major differences in the role of p38 MAPK in inflammatory signaling and TNF-alpha regulation by p38 MAPK	128
5	Psoriasis	Decreases in T cell-inflammatory gene expression (IFN-gamma, STAT-1, granzyme B) and T cell numbers may be due to a reduction in DC-mediated T cell activation	129
6	Crohn's disease	Alteration of the sequence of tumor necrosis factor receptor-2	130
7	Ulcerative colitis	TNFR polymorphisms	131
8	Systemic lupus erythematosus	Altered expression of TNF-alpha signaling pathway proteins	132
9	Ankylosing spondylitis	single-nucleotide polymorphisms (SNPs)	133
10	Sepsis	TNF gene polymorphism	134

8. RECEPTOR (TNFR1 AND TNFR2) RELATED SIGNALING PATHWAY FOR DRUG TARGETING

There are two structurally distinct membrane receptors which are TNFR1 and TNFR2 (Figure 2). TNF can bind any of the two receptors (102,103). Afterwards, the downstream signaling events begin. Normally, when TNF binds with TNFR1; it activates the pathway of apoptosis. Conversely, when its bind with TNFR2; it tigers the T-cell survival pathway. At the time of the interaction, these pathways depend on several other factors such as the activation state of the cell, host specificity, and the other factors (104). It has been recorded that shortcoming TNF signaling may modify the balance between TNF's pro-survival and apoptotic effects (105). Conversely, from the several literature, it has been well understood that several diseases can be treated through the targeting TNF signaling pathway specially autoimmune diseases such as type 1 diabetes (106,107), Sjogren's syndrome (108), Crohn's disease(109-110), multiple sclerosis(111,112), systemic lupus erythematosus (113) and ankylosing spondylitis (114) (Table 2). Exogenous TNF effectively kills autoreactive T cells to treat and reverse type-1 diabetes in animal models (115-117). Surprisingly, it was also noted that TNF restore insulin production even in end-stage diabetes (118). TNFR signaling pathways play a vital function in the pathogenesis of several diseases. Among these two pathways related to two receptors (TNFR1 and TNFR2), several scientists were tried to demolish the autoreactive immune cells through the specific activation of TNFR2 and observed on autoreactive and normal T lymphocytes. This has a high potential of avoiding or reducing the toxicity (119). Therefore, TNFR2 pathway is now one of the therapeutic targets for several diseases especially autoimmune diseases. TNFR1 is expressed all over the body. Conversely, TNFR2 has a more limited expression and agonists specifically targeting the TNFR2 pathway are having enormous promises as safer and more effective treatment than TNF or current therapies for various autoimmune diseases (120).

9. IN THE CLINIC: THERAPY USING SMALL MOLECULES OR THERAPEUTIC PROTEINS

Presently, small molecules or therapeutic proteins (such as monoclonal antibody) can be used for anti-TNF therapy and it is well established as an effective target to control certain human diseases especially autoimmune diseases. Several scientists have developed molecules for targeting the TNF specific signaling and synthesis pathways to develop the drugs (121,122). Several molecules were in the clinical or preclinical trial which can inhibit TNF (122-124). Here, we have listed some of the molecules which are in the clinical or preclinical trial (Table 3). These molecules may be a better drug for anti-TNF- therapies in the near future and could either replace the existing therapies.

10. CONCLUDING REMARKS

Presently, several works have been performed on structure based drug design. The knowledge based onprotein structure can help in optimize specific inhibitors with the design. Nevertheless, our proteomics's analysis in this paper clearly illustrates the structure of TNF proteins. We have presented information such as - its distribution, normal activity in human body and receptors. We have also presented TNF signaling pathway which can be used for drug targeting for diseases and its inhibitors which will be used in the clinic. Our proteomics data and information will guide the future researchers in safer and more effective lead discovery as well as provide more understanding about the pharmacological properties of these two proteins.

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Table 3. Some list of the small-molecules/therapeutic proteins for TNF inhibitor (TNF-A / TNF-B) for the therapeutic purpose

Sl. No.	Small-molecules/Therapeutic Proteins	Target	Indication for Treatment	Reference
1	Adalimumab (Human monoclonal antibody)	TNF-alpha inhibitor	For the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease	135, 136
2	Golimumab (Human monoclonal antibody)	TNF-alpha inhibitor	For the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis	137, 138
3	Certolizumab pegol (Human monoclonal antibody)	TNF-alpha inhibitor	For the treatment of Crohn's disease and rheumatoid arthritis	139,140
4.	Etanercept (fusion protein produced through DNA Technology)	TNF-alpha inhibitor	Used to treat rheumatoid, juvenile rheumatoid and psoriatic arthritis, plaque psoriasis and ankylosing spondylitis	141,142
5.	Infliximab (Human monoclonal antibody)	TNF-alpha inhibitor	for the treatment of psoriasis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis and ulcerative colitis	143,144
6	Pegsunercept	TNF-alpha inhibitor	for the treatment of rheumatoid arthritis	145,146
8	Xanthine	TNF-alpha inhibitor	reduce inflammation	147,148
9	Bupropion	TNF-alpha inhibitor	Crohn's disease and psoriasis.	149-152
10	PEG-sTNFR1	TNF-alpha inhibitor	Obstruction-induced renal injury, arthritis	153-156
11	PEG-TRAIL	TNF-alphainhibitor	rheumatoid arthritis.	157-161
12	CDP-870	TNF-alpha inhibitor	airway inflammation, skin lesions	162-164

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