Bioinformatics analysis of homologies between pathogen antigens, autoantigens and the CFTR cystic fibrosis protein: A role for immunoabsorption therapy?

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Abstract

The cystic fibrosis CFTR chloride channel is involved in pathogen entry into epithelial cells, and provides the glutathione and hypochlorous acid necessary for bactericidal and viricidal actions. CFTR mutations block these effects, diminishing pathogen defence and allowing pathogen accumulation in the extracellular space, where antibody encounter is likely. The pathogen antigens observed in cystic fibrosis (including P. Aeruginosa, S. Aureus and S. Maltophilia proteins) are homologous to the autoantigens reported in cystic fibrosis and all are homologous to the CFTR protein itself. Antibodies to pathogens and autoantigens may also target the CFTR protein, acting as antagonists, further compromising its function. The tripartite relationship between pathogen antigens, autoantigens and the CFTR protein creates a feed forward cycle, diminishing the function of the CFTR protein and increasing the probability of pathogen accumulation and further antibody encounters at every turn. Kegg pathway analysis of the CFTR/autoantigen interactome indicates that the CFTR protein is also involved in pathogen entry pathways, diabetes and pancreatic and gastric acid secretion pathways, in pathways related to cardiac myopathy, and in the gonadotrophin signalling network, all which are relevant to cystic fibrosis. Interruption of this cycle by antigen and antibody adsorption, and possible by immunosuppressant therapy may perhaps be of clinical benefit in cystic fibrosis.
**Introduction.**

Cystic fibrosis is a devastating condition caused by mutations in the cystic fibrosis transmembrane conductance regulator CFTR chloride channel. The disease affects many organs resulting in general debilitation but especially targets the respiratory system leading to difficulty in breathing. There is no apparent cure or preventive strategy. The disease appears to have an immune and autoimmune component as antibodies to Saccharomyces cerevisiae and Stenotrophomonas maltophilia and to neutrophil cytoplasmic antigens and bactericidal/permeability-increasing protein (BPI) and many other proteins (the adrenoreceptor ADRB2, Calgranulin, heat shock proteins, mucins, myeloperoxidase, rheumatoid factor and 12-tumour necrosis factor, inter alia are observed in many patients Bae, Choi, et al. 2010). The disease is also influenced by infection. For example Burkholderia infection causes severe respiratory infections in cystic fibrosis patients and is often associated with this condition (LiPuma, 1998, LiPuma, 1998, Coutinho, 2007). Stenotrophomonas maltophilia infection has also been reported to worsen pulmonary symptoms while infection with S.Aureus or P.Aeruginosa are known to decrease the lifespan of cystic fibrosis patients.

Many bacteria and viruses cause problems by molecular mimicry of human proteins. When homologous to receptors, they may act as decoys, or when homologous to peptide ligands that may act as dummy ligands or decoy substrates. For example the measles virus V protein is a decoy substrate for IkappaB kinase (Pfaller & Conzelmann, 2008). They may also use the host’s cognate receptors to gain entry, as is the case with the AIDS virus and the CCR5 or CXCR4 chemokine receptors. When such mimics are antigenic and homologous to host proteins they may cause problems related to autoimmunity. Such mimicry is extensive (Elde & Malik, 2009) and has been observed between Herpes simplex, a risk factor in Alzheimer’s disease, and Alzheimer’s disease susceptibility gene products (Carter, 2010b), or between the proteins of the Epstein Barr virus or of gut bacterial flora and multiple sclerosis autoantigens (Westall, 2006, Toussirot & Roudier, 2008).

As reported below, proteins from pathogens implicated in cystic fibrosis, and many others (bacteria, fungi and viruses) are homologous to diverse CFTR mutants. Many of these homologous regions are immunogenic, suggesting an important autoimmune component to cystic fibrosis that may be amenable to therapy.

**Methods**

Mutant CFTR proteins were identified from the Cystic fibrosis mutation database [http://www.genet.sickkids.on.ca/app](http://www.genet.sickkids.on.ca/app). A “polymutant” protein was constructed (Fig 1) that included 19 point mutations, and was used for bioinformatics analysis. The sequence of this protein as well as the common DeltaF508 deletion mutation was compared with viral, bacterial and fungal proteins using the NCBI BLAST server. Heptapeptides centred on the point mutation were also screened against viral and bacterial proteomes. Pathogen antigen and autoantigens described in cystic fibrosis were aligned with the delta508 mutant using the Uniprot CLUSTAL alignment server [http://www.uniprot.org/](http://www.uniprot.org/). Antigenicity was predicted using the immune epitope database server [http://tools.immuneepitope.org/main/index.html](http://tools.immuneepitope.org/main/index.html). Antigenicity predictions from these
programmes are calculated on the basis of charge, hydrophobicity and surface localization. B cell antigenicity was determined using the BepiPred linear epitope prediction method (Larsen, Lund, et al. 2006) (See Table 1 for the predicted antigenicity of individual amino acids) and T cell antigenicity using the Average Relative Binding matrix methods that predicts IC_{50} values for the binding of epitopes to major histocompatibility complex (MHC) molecules. The B cell antigenicity of the 7 native and mutant proteins can be directly compared, as the algorithm defines antigenicity, amino acid by amino acid, along the length of the protein. In contrast, T cell epitopes are referenced as 9 amino acid strings, and each mutation generates a series of epitopes that are distinct from those in the native protein. There are 11 numerous T cell epitopes across multiple HLA-antigens and the native/mutant comparisons were restricted to HLA DRB1*0301, one of the most common alleles.

The CFTR interactome was downloaded from the Protein, Signalling, Transcriptional & Inflammation Networks Gateway (pSTIING) database and pathway analysis performed at KEGG pathways. Host proteins interacting with viruses were obtained from the VirusMint database and from the Herpes/host viral interaction database (Carter, 2010c) http://www.polygenicpathways.co.uk/herpeshost.html. The BLAST analyses return a large number of hits to multiple proteins from hundreds of bacterial, viral and fungal species. The CFTR protein is homologous to several proteins from the same species, resulting in a certain number of overall hits per species. These were semi-quantitatively analysed using a tag cloud server at http://www.tagcloud-generator.com/generator.php#anker which generates tags, sized according to the number of hits per species. The tag size was set to a font size of 4 to 25. Because of the large volume of data generated by the BLAST analyses, the original saved BLAST searches and the maps of the KEGG pathway analysis are stocked in an online database at http://www.polygenicpathways.co.uk/cysfib.htm

Results

The immunity spectrum of the CFTR mutants.

The localisation of the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) that were examined is depicted in Fig 1.

Several of these mutations are in regions of high predicted B-cell antigenicity (R171H, G480C, G551D, S895N, K1250A, N1303K) while others are less so (Fig 2).

The CFTR F508 deletion or point mutations can dramatically change the antigenicity, not only of the amino acid concerned, but also of the surrounding peptide as shown in Fig 2. For example the F508Del mutant markedly increases the predicted B-cell antigenicity over a long stretch of amino acids, not only confined to the deleted amino acid and also generates two T cell epitopes that have a higher affinity (1.5 - 3-4 fold) than those of the native protein (Fig 3). For the 19 other mutants, B cell antigenicity can be increased, decreased or little changed by the point mutation (Fig 462). The T cell epitope landscape is dramatically changed by the 19 point mutations as shown in Fig 2. All of these sequences are T cell epitopes and will bind to MHC molecules, although with different affinities. High concentrations of antigens, likely consequence of the hyper colonisation by pathogens containing these epitopes...
might be expected to saturate all MHC binding sites. 57 T cell epitopes were generated by the polymutant protein, compared to 50 for the native protein. The following epitope changes resulted in large increases in T cell epitope affinity:

LSHHGHKQLM > LSHDHKQLM (127 fold); ITLSGGQRA > ITLSGDQRA (63 fold); CVLSHGHKQ > CVLSHDHKQ (63 fold); FDDMESIPA > FDDMESIRA (6 fold); IAIYLGIGL > IAIYLCIGL (3.9 fold); DMESIPAVT > DMESIRAVT (5.2 fold). Certain epitopes in the native protein are lost due to the mutation (N=27), while others are gained (N=34), many of which were of intermediate T cell affinity (Fig 2).

The ten T cell epitopes (mutant Delta F508 protein) with the highest affinity are homologous to proteins expressed by a number of bacterial species, including S.Aureus. Other noteworthy species containing CFTR epitope homologues included Clostridial species, and Klebsiellae (Table 2, which are known to colonise CF patients (see Table 3). This type of epitope mapping may be of use in identifying novel pathogen suspects that may pose a problem in cystic fibrosis. For example, proteins from B.cereus and Brachyspira species were well represented as CFTR epitope matches (See Table 2).

F508del CFTR homology with autoantigens and pathogen proteins

The F508del mutant protein is homologous to ten autoantigens and four P.Aeruginosa and S.Maltophilia antigens reported in cystic fibrosis. The autoantigens are in turn homologous to proteins from three major pathogens implicated in cystic fibrosis (S.Aureus, P.Aeruginosa, and S.Maltophilia) (Table 4), suggesting that the autoantigens are likely to have been created by antibodies that initially targeted the pathogen proteins. The Blast results for this exercise are available at http://www.polygenicpathways.co.uk/cftrpathant.htm

Several viral or bacterial pathogens colonise cystic fibrosis patients to a much greater extent than observed with the normal population. Many of these pathogens have been reported to worsen symptomatology, for example S.Maltophilia and even S.Aureus or P.Aeruginosa. These effects are summarised in Table 3.

The heptapeptides surrounding the 19 point mutations, or the octapeptide surrounding the F508del mutation, are all homologous to proteins expressed by S.Aureus, P.Aeruginosa, and S.Maltophilia (Table 5), as well as to many other strains (not shown: see website BLASTs).

The delta508 mutant or the entire polymutant is also homologous to proteins expressed by multiple viral, bacterial and fungal strains, many of which, in particular P.Aeruginosa, S.Aureus and S.Maltophilia, are known to hypercolonise cystic fibrosis patients or to be associated with symptom exacerbation (Table 6). This survey also identified many other pathogens expressing proteins with CFTR homology, which might perhaps be considered as potential antibiotic targets. These included B.Cereus, Gordonia bronchialis and several clostridial species (Table 6).
The CFTR protein, mutated or not, contains a large number of T cell epitopes (82,376 vs. various MHC alleles) of which 1303 were of high affinity (< 100nM). The 4_5_6_number of pathogen protein homology with the 10 highest affinity epitopes is shown in Table 7. Numerous pathogen species are represented, with *P.*Aeruginosa, *S.*Aureus and *S.*Maltophilia figuring highly as pathogens expressing proteins with homology to these CFTR epitopes.

9. *P.*Aeruginosa and *S.*Aureus vatches in the mutant CFTR protein

Vatches (Viral mATCHES are short contiguous amino acid stretches covering the 2_entire human proteome that are identical in human, and viral proteins and also in the 3_proteins of other pathogens) see [http://www.polygenicpathways.co.uk/blasts.htm](http://www.polygenicpathways.co.uk/blasts.htm). They are a probable legacy of our evolutionary decent from microorganisms, and of 4_pathogen mimicry of human proteins: Despite chromosomal shuffling over millions of 5_years, the current human DNA can still encode for quite large peptide stretches that 6_are identical to those expressed by pathogen proteins (Carter, 2010d, Carter, 2010a, 7_Carter, 2010b). The *S.*Aureus and *P.*Aeruginosa vatches within the CFTR polymutant 8_are shown in Fig 4. The CFTR polymutant displays extensive homology with proteins 9_expressed by these two pathogens. The homologous regions are often within highly 10_11_immunogenic regions of the CFTR and pathogen proteins, and also cover the CFTR 12_point mutations.

24. Homology with the native CFTR protein

As the mutations in cystic fibrosis are point mutations, the native protein too is 25_evidently homologous to these same pathogen proteins. However, the pathogen 26_irradiance pathways are intact in these cases, and the immune system is not 27_compromised by CFTR mutations. There is no reason to suppose that high levels of 28_pathogen proteins could be attained, or that the host could not appropriately deal with 29_the pathogens. Whether the CFTR mutations increase or decrease homology to 30_pathogens is also perhaps irrelevant, as the hyper colonisation by pathogens would be 31_an expected consequence of any functional mutation (see discussion); an outcome that 32_would favour antibody production that could target any CFTR matching epitopes. As 33_antibodies are able to enter cells, such targeting could be relevant to domains in both 34_the intracellular and extracellular portions of the CFTR protein.

39. Pathway analysis of the CFTR interactome (Fig 5)

Pathway analysis of protein interaction networks is a powerful tool for 41_divining the functions of particular proteins. Those proteins shown to interact with the 42_CFR protein, from pSTIING, are shown in Table 8. Pathway analysis of the CFTR interactome (Table 9) also included the 43_autoantigens reported in cystic fibrosis, as their function is also likely to be 44_compromised by their respective autoantibodies. This pathway analysis clearly 45_demonstrates an important role for the CFTR protein in the immune system and in 46_pathogen invasion (Table 9:Fig 5 See [http://www.polygenicpathways.co.uk/cysfib.htm](http://www.polygenicpathways.co.uk/cysfib.htm) for coloured KEGG pathways). For 47_example, a number of CFTR binding partners are involved in antigen processing or
chemokine signalling and in lysosomal function, which is also related to antigen processing and pathogen destruction, as well as in chemokine signalling. While others are involved in bacterial invasion and Vibrio infection or pathogen destruction (endocytosis, junctions, phagosomes and lysosomes). These pathways are illustrated in Fig 5.

Interaction with viruses in the CFTR interactome.

The virusMINT and HSV-1 interactions showed that a number of the CFTR interacting proteins also interact with viral proteins from the adenovirus and papillomavirus as well as the Epstein-Barr, Herpes simplex, Hepatitis B and C and 12 HIV-1 viruses (Table 8), all of which also express proteins with homology to the 13 CFTR protein (Table 7). In other words, certain viral proteins with homology to CFTR may bind to the same targets as the CFTR protein and, when present, could form an integral part of the CFTR interactome. With the exception of a replete HIV-1 interaction database, viral/human protein networks are not extensively referenced in online databases, and more interactions are likely to exist.

Certain of the CFTR interactome pathways trace out a route that is used by the Herpes simplex virus, and probably other related viruses, during its life cycle. This involves entry and endocytosis, entry and exit to and from lysosomes, phagosomes and nuclei, and interference with protein processing pathways (see http://www.polygenicpathways.co.uk/herpeshost.html for a detailed view). These pathways suggest that the CFTR protein is involved in both bacterial and viral defence (Fig 5).

The pancreas, cardiac myopathy and the vas deferens in cystic fibrosis

Pancreatic insufficiency and diabetes are common features of cystic fibrosis, as are cardiac myopathy and related cardiovascular problems (Moss, 1982). Bilateral loss of the vas deferens in men, or of the uterus and vagina in women are also commonly associated with cystic fibrosis. The CFTR/autoantigen pathway analysis indicates that the CFTR protein is involved in pancreatic and gastric acid secretion pathways, in several pathways related to cardiac myopathy, and in the gonadotrophin signalling network, which latter controls the development of the sexual organs. The autoantigens implicated in cystic fibrosis are also members of a signalling network related to diabetes (Table 8; Fig 5). These pathways relate to all of the coexisting conditions described above. The involvement of the CFTR protein in these signalling networks indicates that these associated conditions are a direct result of defects in CFTR signalling.

Immune related genes that modify cystic fibrosis symptomatology or pathogen colonisation

Many genes that modify the progression or severity of the cystic fibrosis are related to immune function. These include inflammation related genes (interleukins IL1B, IL8 and IL10, transforming growth factor-beta1, tumour necrosis factor-alpha 50 and its receptor TNFR) antioxidant related genes (glutathione-S-transferase),
prostaglandin-endoperoxide synthase genes (COX1 and COX2) as well as CD95, Toll receptor TLR9, T cell receptor beta and HLA antigens. Immune activation and inflammation also play a key role in the airways in cystic fibrosis (Machen, 2006b).

There are a large number of MHC molecules, each of which has differing affinity for 5 distinct epitopes. HLA-DR2, (which recognises HLA-DRB1*15 and HLA-DRB1*16 alleles), as well as HLA-DQB1*0201, HLA-DRB1*0301, and DR7/DQA*0201 and 7HLA-B-18 have all been associated with cystic fibrosis symptomatology or pathogen colonisation.

Discussion

Nearly 2,000 mutations/polymorphisms have been described in cystic fibrosis patients. The most common is the DeltaF508 deletion which is expressed in almost 1570% of patients and the G551D, G542X, and R553X mutations are also relatively common. 20 different mutations were covered by this survey. Several mutations, particularly truncations, result in non-expression of the CFTR protein or compromised delivery to the cell surface (Davidson & Porteous, 1998). The bacterial and viral homology is of less direct relevance to these mutants, although defects in the immune and microbial related functions of the CFTR protein would also favour pathogen colonisation and immune dysfunction. These and other mutant proteins result in malfunction of the chloride channel encoded by the CFTR protein, with the resultant pulmonary pathology associated with cystic fibrosis.

In addition to its actions as a chloride channel, CFTR has a number of other properties that are highly relevant to immunity and microbiology. For example it controls the efflux of glutathione which exerts viricidal and bactericidal properties, including the S.Aureus and P.Aeruginosa targets. Glutathione levels are reduced in cystic fibrosis and glutathione aerosols have been reported to ameliorate lung epithelia oxidative stress in cystic fibrosis patients. Clinical trials with glutathione or its prodrugs are ongoing. CFTR is also important in pathogen defence, providing the chloride for the generation of hypochlorous acid by myeloperoxidase in neutrophil phagosomes. This bactericidal mechanism is defective in cystic fibrosis, likely rendered the more so by the presence of myeloperoxidase autoantibodies in cystic fibrosis.

The CFTR protein is also expressed in lymphocytes and negatively regulates the nuclear factor kappa beta (NFKB) and toll receptor (TLR4) mediated innate immune response. The delta F508 mutation has also been shown to inhibit the antigen presentation pathway (Hampton & Stanton, 2010), and autoantigens and other antigens in cystic fibrosis would therefore not be properly processed. CFTR mutations also increase immune activation in mice.

In addition to these effects, CFTR is a pattern recognition receptor that recognises P.Aeruginosa. The CFTR protein appears to be involved in P.Aeruginosa ingestion and destruction, as the delta508 mutation in infected transgenic mice increases the pulmonary P.Aeruginosa burden and decreases its clearance. This mutation-related reduced uptake of the pathogen into epithelial cells favours multiplication of P.Aeruginosa within the lungs. The CFTR protein is also an entry portal for Chlamydia Trachomatis, and Salmonella Typhi, but not the closely related murine S. typhimurium and the delta508 mutation also reduces pathogen entry into epithelial cells. C.Trachomatis binding to CFTR also reduces its chloride channel activity. Not all bacteria use the CFTR protein which may itself thus determine which bacteria are
Thus the CFTR mutations might be expected to compromise not only the chloride channel, but also the ability to kill pathogens via glutathione, or hypochlorous acid. Mutations might also be expected to alter the ability to process antigens to pathogens, or to self. CFTR mutations also activate the immune system. Many of the mutations in the CFTR protein lie within regions that are highly immunogenic, and such high immunogenicity would be shared by the viral, bacterial and fungal homologues of the protein, of which there are several thousand. The autoantigens reported in cystic fibrosis, as well as P. Aeruginosa antigens are also homologous to the Delta508 mutant protein, again within regions that are highly immunogenic. Given the vast number of pathogen proteins that show homology with various regions of the CFTR protein, and the fact that such species are more abundant in cystic fibrosis patients, cross-reactivity with the CFTR protein would seem inevitable, although to date no antibodies to CFTR have been reported or apparently assessed. Although many of the CFTR mutations are intracellular, antibodies do enter cells, and even if not mounting an intracellular immune response would be expected to bind to the immunogenic regions of the CFTR protein, in effect producing protein knockdown, equivalent to the effects of the truncated mutants that fail to reach the cell surface. It is also clear that the viral homologues of the CFTR protein are capable of binding to CFTR binding partners, potentially modifying the function of CFTR by interactome interference.

Infliximab

Infliximab is a tumour necrosis factor -alpha (TNF) monoclonal antibody used to treat autoimmune disorders. TNF antagonism prevents the activation of other inflammatory cytokines and leukocyte activation and this approach is a target in many autoimmune and inflammatory conditions (Hoffman, 2009). A recent case study has reported 2 year remission in a cystic fibrosis patient treated with infliximab. Apart from the use of immunosuppressants in cystic fibrosis lung transplant patients, and limited studies with cyclosporine, the therapeutic potential of this class of drug does not appear to have been widely studied. TNF is one of the autoantigens reported in cystic fibrosis, and shares sequence similarities with the CFTR protein (Table 2). Although certain TNF antibodies would be expected to cross-react with the CFTR protein, such effects would depend upon the epitopes targeted by the antibody, and these details are not available.

A possible scenario for cystic fibrosis (Fig 6)

Irrespective of any homology to pathogens, CFTR mutations lead to defects in chloride channel function, but also to a reduction in glutathione levels and defects in hypochlorous acid production, that would compromise viral and bacterial destruction. The channel itself is involved in bacterial entry, and impaired CFTR function reduces bacterial entry into epithelial cells, resulting in increased colonisation of the extracellular milieu. In this space, the likelihood of encountering immunocompetent cells is increased, favouring the production of anti-pathogen antibodies. Pathogen binding to the CFTR channel also impairs its function. Such mutations may also compromise the immune system, rendering it less able to process antigens, but more
susceptible to activation. Polymorphisms in immune, inflammation and glutathione related genes fine tune this network, modifying its function, for better or worse.

Upon infection, the surfeit of pathogens triggers an immune response that generates antibodies to the pathogen that also target human proteins that are homologous to the antigenic pathogen proteins, generating the autoantigens observed in cystic fibrosis. As judged by epitope homology, antibodies to pathogen proteins and to autoantigens may also tag the CFTR protein, rendering it incapable of assuming its normal functions. The constant presence of the pathogens and of the autoantigens sustains this immune response. Viral infections, in particular, would also be expected to modify CFTR function via the theft of interactome partners. Thus, antibody knockdown would have the same effect on CFTR function as the mutations that prevent CFTR expression, or its delivery to the cell surface. In these cases, the antibodies are acting as antagonists, rather than as immune activators. In extreme cases, an autoimmune response to the CFTR protein might be expected to damage, or 15 kill the cells in which the protein resides. The bioinformatics analysis suggests that antibodies to the CFTR protein should be detectable in cystic fibrosis. This does not appear to have been assessed, judging from the absence of any mention of CFTR autoantibodies in the literature. However, the high titre of pathogen antibodies, whose targets are homologous to the CFTR protein, suggests that even low affinity T cell epitope binding sites would be saturated.

Taken together, although clearly a genetic disorder, these data suggest that cystic fibrosis has a crucial autoimmune component, triggered by pathogens with homology to the mutant and related proteins.

Antibacterial agents are already used in cystic fibrosis (Wat, 2003). There are no phage or bacterial vaccines as yet, and antiviral agents and vaccination strategies could also perhaps be useful. Unfortunately, the repertoire of pathogens colonising cystic fibrosis patients is so vast that polypharmacy, with its attendant risks, might seem the only plausible option. Clearly the potential benefits of glutathione supplementation appear to be promising. Other methods of enhancing pathogen defence require further research.

It is possible that immunosuppression might be of benefit in cystic fibrosis. This is extremely counter-intuitive, given the problems of multiple infections in these patients, but a carefully controlled and supervised clinical trial may well be warranted. Indeed, the reported benefits of Infliximab (see above), although only so far reported in a case study suggest that such approaches may be of more general clinical use.

If the problems in cystic fibrosis stem even partly from autoantigens and autoantibodies, then their riddance can only be beneficial. Immunoabsorption/plasma exchange has been reported to be of benefit in the autoimmune disorder, myasthenia gravis and this type of therapy may be applicable to cystic fibrosis, using targeted antigen and antibody columns to remove the circulating antibodies and antigens. Tryptophan or phenylalanine columns have also been reported to be of use in antibody adsorption.

In summary, CFTR mutations are themselves responsible for bacterial hypercolonisation, and for reduced bactericidal and viricidal effects, creating a situation where antibody generation to a plethora of pathogens in inevitable. These antibodies target other antigens that are homologous to the pathogens’ proteins, and these include the various autoantigens that have been recorded in cystic fibrosis. The pathogen antigens and autoantigens are both homologous to the CFTR protein itself, and antibody related CFTR antagonism is a likely consequence of these effects. Interruption of this feed forward cycle may be of clinical benefit in cystic fibrosis.
Table 1: The antigenicity index (B-cell epitope) for single amino acids defined by the BepiPred server. The top 6 scoring amino acids are marked in red in other tables.

| Symbol | Amino acid   | B-epitope antigenicity |
|--------|--------------|------------------------|
| P      | Proline      | 0.145                  |
| G      | Glycine      | 0.035                  |
| D      | Aspartate    | 0.018                  |
| E      | Glutamate    | 0.003                  |
| S      | Serine       | -0.008                 |
| T      | Threonine    | -0.011                 |
| Q      | Glutamine    | -0.012                 |
| N      | Asparagine   | -0.013                 |
| A      | Alanine      | -0.024                 |
| W      | Tryptophan   | -0.025                 |
| K      | Lysine       | -0.031                 |
| R      | Arginine     | -0.062                 |
| H      | Histidine    | -0.071                 |
| V      | Valine       | -0.112                 |
| F      | Phenylalanine| -0.138                 |
| I      | Isoleucine   | -0.138                 |
| M      | Methionine   | -0.138                 |
| C      | Cysteine     | -0.175                 |
**Table 2:** T cell epitopes of the F508del mutant and their homologies in relation to bacterial and viral proteins. Genera or individual species known to colonise the airways in cystic fibrosis are highlighted in bold.

| Allele     | Epitope       | IC50 nM | Equivalent Pathogen sequence and pathogens                                      |
|------------|---------------|---------|---------------------------------------------------------------------------------|
| HLA A*0250 | TIKENIIGV     | 3.5     | • TIKENIIG: Anaerococcus prevotii; Chryseobacterium gleum; **Prevotella** copri   |
| HLA A*0211 |               | 28.4    | • TIKEFIIGV: Bacillus Cereus                                                    |
| HLA A*0203 |               | 57.9    | • TIKENIFIG: **Staphylococcus** lentus                                           |
| HLA A*0212 |               | 98.8    | • TIKENII: Bacillus copri                                                       |
| HLA A*0250 | IKENIIGVS     | 8.8     | • IKENII-VS: **Bacteroides** ovatus                                              |
|            |               |         | • IKEVNIIGV: Filifactor alocis                                                   |
|            |               |         | • KENIIGIVS: Brachyspira pilosicoli                                              |
|            |               |         | • KEQNIIGVS: Clostridium perfringens                                             |
| HLA A*0250 | IGVSYDEYRI    | 44.4    | • GISYDEYR: Brachyspira pilosicoli                                               |
| HLA A*6801 |               | 61.7    | • IGVSY-EYR: **Prevotella** marshii                                              |
|            |               |         | • IGDSEYDEYR: Acinetobacter calcoacticus                                         |
|            |               |         | • IIGVSIYDE: Coralimargarita akajimensis                                         |
|            |               |         | • IIGVSYMDE Brevibacillus brevis                                                 |
|            |               |         | • IIGVSCYDE Xanthomonas campestris                                               |
|            |               |         | • IIGVSYTDE: Burkholderia phage                                                  |
| HLA B*1503 | KENIIGVSY     | 45.9    | • KENIPVSY: Shewanella frigidimarina                                             |
|            |               |         | • KENIIGIS : Clostridium botulinum                                               |
| HLA A*3201 |               | 63.5    | • KENDIIGVS: **Clostridium difficile**                                            |
|            |               |         | • KEQNIIGVS Clostridium Perfringens                                              |
|            |               |         | • KENIIIGIVS:Brachyspira pilosicoli                                              |
|            |               |         | • NIIGVS: **Staphylococcus aureus**                                              |
|            |               |         | • KENIIIG: **Staphylococcus aureus**                                             |
| HLA A*0250 | NIIGVSYDE     | 62.6    | • IIGVSYD: Pantoea sp AND Cellulomonas flavigena and Klebsiella sp.AND Cronobacter turicensis and So
| HLA B*1503 | 76.6 |
|------------|------|
| cellulosum AND Enterobacter sakazakii AND Buchnera aphidicola AND Pelobacter propionicus |
| • NIIGVSY: Clostridium acetobutylicum |
| • GVSYDEY: Sulfurimonas autotrophica AND Eubacterium cylindroide |
| • IIGVSYD: Pantoea sp AND Cellulomonas flavigena and Klebsiella sp. AND Cronobacter turicensis and Sorangium cellulosum AND Enterobacter sakazakii AND Buchnera aphidicola AND Pelobacter propionicus |
### Table 3: A summary of some of the pathogen species isolated from cystic fibrosis patients and their effects on disease.

| Bacteria                        | Colonisation and effects on symptoms                                                                 |
|---------------------------------|------------------------------------------------------------------------------------------------------|
| Achromobacter. xylosoxidans     | Prevalent in CF patients                                                                            |
| Acinetobacter baumannii         | Isolated from Russian children with CF                                                              |
| Burkholderia Cepacia            | Associated with cystic fibrosis                                                                     |
| Chlamydia pneumoniae            | Associated with exacerbation of symptoms                                                             |
| Clostridium difficile           | Increased in CF patients                                                                            |
| Corynebacterium pseudodiphtheriticum | Isolated from CF children’s sputum                                                                    |
| Haemophilus influenzae          | Often recorded in CF sputum                                                                          |
| Helicobacter pylori             | Increased in patients with pancreatic sufficiency: Certain Mutations protect against H.Pylori infection in patients with pancreatic insufficiency |
| Klebsiella species              | Increase in CF patients                                                                             |
| Multiple strains of Mycobacteria | UK case report (Brown, 2010)                                                                        |
| Pneumocystis jirovecii          | Isolated from French children with CF                                                                |
| Prevotella species              | Isolated from the airways of CF patients                                                             |
| Pseudomonas Aeruginosa          | Infections decrease the life expectancy of CF patients                                               |
| Staphylococcus Aureus           |                                                                                                      |
| Stenotrophomonas maltophilia    | Associated with worsened clinical status                                                             |
| Streptococcus Millerii          | Isolated from CF airways                                                                            |
| Pseudomonadaceae, Xanthomonadaceae, Moraxellaceae and Enterobacteriaceae | These species are prevalent in the airways of cystic fibrosis patients                                   |
| Others                          | Over 60 bacterial genera, not typically associated with cystic fibrosis were isolated from the sputum of CF patients including species of :- Actinobacillus, Aggregatibacter, Chryseomonas, Flavimonas, Haemophilus, Pseudomonas, Stenotrophomonas, Vibrio, Acidovorax, Azonexus, Comomonas, Delftia, Eikenella, Kingella, Neisseria, Brevundimonas, Spingobium, Sphingopyxis, Xanthobacter, Abiotrophia, Enterococcus, Gemella, Granulicatella, Lactobacillus, Lactococcus, Leuconostoc, Staphylococcus, Streptococcus, Butyrovibrio, Catonella, Dialister, Megasphaera, Moryella, Oribacterium, Peptinophilus, Peptostreptococcus, Selenomonas, Veillonella, Bulleida, Fusobacterium, Leptotrichia, Actinomyces, Arthrobacter, Atopobium, Corynebacterium, Micrococcus, Propionibacterium, Rhodococcus, Rothia, Scardovia, Tessaracoccus, Bacteroides, Porphyromonas, Prevotella, Bergeyella, Capnocytophage, Mycoplasma, treponema |
| Viruses               |                                                                 |
|----------------------|-----------------------------------------------------------------|
| Epstein-Barr         | Infection can exacerbate respiratory symptoms (Winnie & Cowan, 1992) |
| Herpes simplex HSV-1 | Association has been observed but appears to be rare             |
| Cytomegalovirus      | Infection is a consistent problem in lung transplant CF patients |
| (Herpesvirus 5)      |                                                                 |
| Hepatitis B          | Occasionally observed in CF patients                             |
| Hepatitis C          | Increased in CF patients                                         |
| Influenza            | Infection worsens symptoms (Dharmaraj & Smyth, 2009)             |
| Respiratory syncytial virus | Increased in CF children                                    |
| Rhinovirus           | Rhinoviruses (common cold virus) exacerbate CF symptoms (Brownlee & Turner, 2008) |

| Fungi                |                                                                 |
|----------------------|-----------------------------------------------------------------|
| Candida and Aspergillus species; Scedosporium apiospermum and Exophiala dermatitidis | Isolated from the respiratory tract of CF patients (Muller & Seidler, 2010) |
Table 4 Clustal alignment of the autoantigens or of the antigens to P. Aeruginosa and S. Maltophilia recorded in cystic fibrosis, with the Delta505F mutant. The top 6 high scoring immunogenic amino acids (B cell epitope) are marked in red.

* = identical : = conserved . = semi-conserved: The autoantigen sequences were subsequently compared with S. Aureus (S. Aur), S. Maltophilia (S. Malt) and P. Aeruginosa (P. Aer) proteins, as shown below the Clustal alignments. These alignments are shown by the boxed regions or by double underlined regions in the autoantigen sequences. Original Lineups are at http://www.polygenicpathways.co.uk/cftrpathant.htm

| Antigen                                    | CFTR Delta508F/antigen/pathogen alignment |
|--------------------------------------------|------------------------------------------|
| Adrenergic beta receptor 2 (Fraser & Venter, 1982) |                                          |
| CFTR MP TDIKEN II GVS Y DEY RYSVIKA 25       |                                          |
| ADRB2 VTAIELCIAVDRYFAITSPFKYQSLTIN 32 P. Aer |                                          |
| ADRB2 VTAIELCIAVDRYFAITSPFKYQSLTIN 32 S. Aur |                                          |
| ADRB2 VTAIELCIAVDRYFAITSPFKYQSLTIN 32 S. Aur |                                          |
| ADRB2 VTAIELCIAVDRYFAITSPFKYQSLTIN 32 S. Aur |                                          |
| ADRB2 VTAIELCIAVDRYFAITSPFKYQSLTIN 32 S. Malt|                                          |
| Bactericidal/permeability-increasing protein BPI |                                          |
| CFTR MP TDIKEN II GVS Y DEY RYSVIKA 25       |                                          |
| BPI NPGVVRIS QKLDSQGTAALQKLKRIKIPYSDFKIE 42 S. Aur |                                          |
| BPI NPGVVRIS QKLDSQGTAALQKLKRIKIPYSDFKIE 42 S. Malt |                                          |
| BPI NPGVVRIS QKLDSQGTAALQKLKRIKIPYSDFKIE 42 P. Malt |                                          |
| BPI NPGVVRIS QKLDSQGTAALQKLKRIKIPYSDFKIE 42 P. Malt |                                          |
| BPI NPGVVRIS QKLDSQGTAALQKLKRIKIPYSDFKIE 42 S. Aur |                                          |
| BPI NPGVVRIS QKLDSQGTAALQKLKRIKIPYSDFKIE 42 S. Aur |                                          |
| Calgranulin B (S100A9)                      |                                          |
| CFTR MP GDIKEN II GVS Y DEY RYSVIKA 25      |                                          |
| S100A9 MTKMQLERNEI ITI TFQY S K LGH PD L NQ EFKELVRK 43 P. Aer |                                          |
| S100A9 MTKMQLERNEI ITI TFQY S K LGH PD L NQ EFKELVRK 43 S. Aur |                                          |
| S100A9 MTKMQLERNEI ITI TFQY S K LGH PD L NQ EFKELVRK 43 P. Aer |                                          |
| S100A9 MTKMQLERNEI ITI TFQY S K LGH PD L NQ EFKELVRK 43 S. Aur |                                          |
| S100A9 MTKMQLERNEI ITI TFQY S K LGH PD L NQ EFKELVRK 43 S. Aur |                                          |
| S100A9 MTKMQLERNEI ITI TFQY S K LGH PD L NQ EFKELVRK 43 S. Aur |                                          |
### Glutamate decarboxylase

| Protein | Sequence | Species |
|---------|----------|---------|
| GAD2 | MTCKMSQNERTIINTFHOYSVKLGPHDTLNQGEFKELVRK | S.Aur |
| GAD2 | MTCKMSQNERTIINTFHOYSVKLGPHDTLNQGEFKELVRK | S.Malt |
| GAD2 | MTCKMSQNERTIINTFHOYSVKLGPHDTLNQGEFKELVRK | P.Aer |
| SPD1 | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Aur |
| SPD1 | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Malt |
| SPD1 | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Aur |
| SPD1 | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Aur |
| SPD1 | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Malt |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.malt |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.malt |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Salm |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Malt |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Salm |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Malt |
| Bix | LACDFpterLAFQVMNILLQYVKSFDRSTKVIDFHYNELQ | S.Salm |

### Heat shock protein 60

| Protein | Sequence | Species |
|---------|----------|---------|
| CFTR | M-----G-----IKENIIGV-----SYD-----EYVRYSVIKA | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | P.Aer |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | P.Aer |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPATIAKNAVGSLIVEKIMQSSSEVGDAMAGDFVNMVEK | S.Aur |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Aur |
|-------|-----------------------------------------------------------------------------------|
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Malt |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Malt |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Malt |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Malt |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Malt |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 P.Aer |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Aur |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 P.Aer |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 P.Aer |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 P.Aer |
| HSPD1 | IPAMTIKA\textsc{NAG\textsc{E}G\textsc{V\textsc{E}}L\textsc{I}V\textsc{E}}KIMQSSSEVGYDAMAGDFVNMVEK 43 S.Aur |
| Mucin 1 (tracheal) | CFTR MPG------TIKEN11GVS------YDEY------RYRSVIKA 25 |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Malt |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Malt |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 S.Aur |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| MUC1 | RPGSVVQLTLAFREGTINHVDQFNQYKTEAASRNLTISD 44 P.Aer |
| Myeloperoxidase MPO | CFTR     | MPO                               |
|-------------------|----------|-----------------------------------|
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Aur                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 P. Aer                         |
|                   | MPO      | LPTYRSYNSVDPRIANVFTNAFYGHTLIOP   |
|                   |          | 32 S. Malt                        |
| Proteinase 3 |
|--------------|
| CFTR MP ------ GT ------ IKENII-GVS ------ ------ YDEYR ------ YRSVIKA ------ |
| 25 PRN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 VPRTN3 |
| MPO LPTYRYNDSVDPRIANVFTNAFYRGLIQ 32 S.Malt MPO LPTYRYNDSVDPRIANVFTNAFYRGLIQ 32 S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer PCRTN P.Aer |
| S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt S.Malt |
| P. Aer | S. Malt | S. Aur | P. Aer | P. Aer | S. Malt | S. Aur | P. Aer | P. Aer | S. Malt | S. Aur | P. Aer | P. Aer | S. Malt | S. Aur | P. Aer | P. Aer | S. Malt | S. Aur | P. Aer | P. Aer | S. Malt | S. Aur | P. Aer | P. Aer | S. Malt | S. Aur |
|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| PRTN3  | VPRRIGFDSGGPLICDGIQGIDSFVIWGCATRLFDFTRVALYVDDWIRSLRRV |      | PRTN3  | VPRRIGFDSGGPLICDGIQGIDSFVIWGCATRLFDFTRVALYVDDWIRSLRRV |      | PRTN3  | VPRRIGFDSGGPLICDGIQGIDSFVIWGCATRLFDFTRVALYVDDWIRSLRRV |      | PRTN3  | VPRRIGFDSGGPLICDGIQGIDSFVIWGCATRLFDFTRVALYVDDWIRSLRRV |      |
|        | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      | **     | *      |
|        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| Factor       | PRTN3 VPRRKAGICFQDSGPGICDGIQGDSTVIWGCATRLPFDFFTRVALYDWRSTLRRV | S.Aur |
|-------------|---------------------------------------------------------------|-------|
| Rheumatoid  |                                                                 |       |
| factor      |                                                                 |       |
| CFTR        | M---PG------------TIKENIIG-------VS---------------------YDEYR---Y---RSVIKA |       |
| RF          |                                                                 |       |
| KR S.Malt   |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |
| RF          |                                                                 |       |
| KR S.Aur    |                                                                 |       |

**Note:** The table contains sequences for various factors and their interactions, with specific positions highlighted for comparison.
KR P. Aer
** * : * ; * * : : :
RF
KR P. Aer
** * : * ; * * : : :
RF
KR P. Aer
** * : * ; * * : : :
RF
KR S. Malt
** * : * ; * * : : :
RF
KR S. Malt
** * : * ; * * : : :
RF
KR P. Aer
** * : * ; * * : : :
RF
KR P. Aer
** * : * ; * * : : :
RF
KR S. Malt
** * : * ; * * : : :
RF
KR P. Malt
** * : * ; * * : : :
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR S. Malt
** * : * ; * * : : 
RF
KR S. Malt
** * : * ; * * : : 
RF
KR S. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : : 
RF
KR P. Malt
** * : * ; * * : :
Table 5: Proteins from S. Aureus, P. Aeruginosa or S. Maltophilia, that contain regions homologous to the regions surrounding various CFTR mutants. The position of the mutant amino acid is shown in red within the sequences used for BLAST analysis.

| Mutant          | Pathogen protein homologue                                                                 |
|-----------------|---------------------------------------------------------------------------------------------|
| F508Del ENII+GVSY Del = ENII+GVSY | • >gb|ADI98793.1| probable regulatory protein DeoR family [Staphylococcus aureus subsp. aureus ED133] ENII +SY |
|                 | • GENE ID: 323774 SACOL0921 | CBS domain-containing protein [Staphylococcus aureus subsp. aureus COL] +NIIGV |
|                 | • GENE ID: 6476997 Smal_2508 | hypothetical protein Stenotrophomonas maltophilia R551-3] +IIGV Y |
|                 | • >ref|ZP_01368311.1| hypothetical protein PaerPA_01005469 [Pseudomonas aeruginosa PACS2] |
|                 |     | EN+IGV |
| R74W NALWRCF    | • >ref|ZP_06881604.1| adenylate cyclase [Pseudomonas aeruginosa PAb1] NALWR |
|                 | • GENE ID: 6477391 Smal_2892 | tRNA(Ile)-lysidine synthetase [Stenotrophomonas maltophilia R551-3] LWRC |
|                 | • GENE ID: 3793024 SAB1831c | hypothetical protein [Staphylococcus aureus RF122] NA WRC |
| R117H KEEHSIA   | • >gb|ACD39272.1| hypothetical protein PACL_0484 [Pseudomonas aeruginosa] EEH IA |
|                 | • gb|EFM07570.1| staphylococcal accessory regulator U [Staphylococcus aureus subsp. aureus ATCC BAA-39] K EHSI |
|                 | • GENE ID: 5759828 pEDINA_p19 | hypothetical protein [Staphylococcus aureus] KEEH |
|                 | • GENE ID: 6476459 Smal_3331 | threonine dehydratase [Stenotrophomonas maltophilia R551-3] EEH IA |
| Gene ID          | Description                                                                 |
|------------------|------------------------------------------------------------------------------|
| G124C IYLCLG     | 0891 | RND efflux transporter [Pseudomonas aeruginosa PA7] IYLCLG                   |
|                  | GENE ID: 5356552 PSPA7_0172 | 3-oxoacyl-(acyl carrier protein) synthase [Pseudomonas aeruginosa PA7] LCIGL |
|                  | >gb|ADI96785.1| hypothetical protein SAOV_0248 [Staphylococcus aureus subsp. aureus ED133] LCIGL |
|                  | >gb|ADI96785.1| hypothetical protein SAOV_0248 [Staphylococcus aureus subsp. aureus ED133] LCIGL |
|                  | GENE ID: 6393293 Smlt3043 | putative ISXac3 like transposase [Stenotrophomonas maltophilia K279a] YLCI |
| V201M AHFMWIA    | GENE ID: 3913891 SAUSA300_0980 | hypothetical protein [Staphylococcus aureus subsp. aureus USA300_FPR3757] HFMWIA |
|                  | >ref|ZP_06876458.1| putative acyltransferase [Pseudomonas aeruginosa PAb1] MWIA |
|                  | GENE ID: 6477949 Smal_0246 | hypothetical protein [Stenotrophomonas maltophilia R551-3] MWIA |
| N287K MIEKLRQ    | >gb|ADI98383.1| hypothetical protein SAOV_1921c [Staphylococcus aureus subsp. aureus ED133] MIEKLRQ |
|                  | GENE ID: 6477998 Smal_0813 | hypothetical protein [Stenotrophomonas maltophilia R551-3] MIEKLR |
|                  | M+EKLR |
| R344W IILWKIF    | >dbj|BAA88419.1| hydrophobic transmembrane protein [Staphylococcus aureus] IILW IF |
|                  | GENE ID: 5355417 PSPA7_0951 | hypothetical protein [Pseudomonas aeruginosa PA7] IL WKIF |
|                  | GENE ID: 6476673 Smal_2260 | hypothetical protein [Stenotrophomonas maltophilia R551-3] WKIF |
| R352E AVTEQFP    | emb|CAW29475.1| Gene info linked to CAW29475.1 probable major facilitator superfamily (MFS) transporter [Pseudomonas |
| Location | Description |
|----------|-------------|
| 38-42    | aeruginosa LESB58 AV EQFP |
| 43-53    | • gb|ADL22468.1| Ser-Asp rich fibrinogen/bone sialoprotein-binding protein SdrD [Staphylococcus aureus subsp. aureus JKD6159] VTEQF Sbjct 490 VTEQF 494 |
| 54-60    | • GENE ID: 6476745 Smal_3466 | RND efflux system, outer membrane lipoprotein, NodT family [Stenotrophomonas maltophilia R551-3] VTEQF |
| 61-67    | K464A GAGATSL |
| 68-80    | • >ref|ZP_06878929.1| fimbrial subunit CupA4 [Pseudomonas aeruginosa PAb1] Length=402 GAGATL |
| 81-91    | • GENE ID: 6395375 Smlt1512 | putative exported fimbriae-related chaperone [Stenotrophomonas maltophilia K279a] AGATSL |
| 92-102   | • gb|EFM07900.1| molybdate ABC superfamily ATP binding cassette transporter, binding protein [Staphylococcus aureus subsp. aureus ATCC BAA-39] AGATS |
| 103-113  | M469I SLLIVIM |
| 114-124  | • >gb|ADL66280.1| Sec family Type I general secretory pathway preprotein translocase SecY_1 [Staphylococcus aureus subsp. aureus str. JKD6008] SLLIVI |
| 125-135  | • GENE ID: 6478455 Smal_1028 | hypothetical protein [Stenotrophomonas maltophilia R551-3] LLIV+M |
| 136-146  | G480C PSECKIK |
| 147-157  | • gb|EES98134.1| conserved hypothetical protein [Staphylococcus aureus subsp. aureus TCH130] SECKI |
| 158-168  | • GENE ID: 6394958 sucD | succinyl-CoA synthetase subunit alpha [Stenotrophomonas maltophilia K279a] P ECKI |
| 169-179  | • >gb|AAD21623.1| succinyl-CoA synthetase alpha subunit [Pseudomonas aeruginosa PAO1] P ECKI Sbjct 130 PGECKI 135 |
| 180-185  | V510D IFGDSYD |
| 186-191  | • GENE ID: 6477620 Smal_0071 | beta-lactamase [Stenotrophomonas maltophilia R551-3] |
|  | FGDSYD | G551D SGDQRA | A561E LAR EVYK | P841R ESIRAVT | S895N KGNNTHS |
|---|---|---|---|---|---|
|  | • >gb|ADI96775.1| conserved hypothetical protein [Staphylococcus aureus subsp. aureus ED133] IF GDYS | • >gb|ADL23188.1| oligopeptide ABC superfamily ATP binding cassette transporter, membrane protein [Staphylococcus aureus subsp. aureus JKD6159] SGDQRA | • A37 thiotransferase enzyme MiaB [Staphylococcus aureus ST398] LARE YK | • GENE ID: 6391398 Smlt0713 | hypothetical protein [Stenotrophomonas maltophilia K279a] ESIRAV | • >pdb|3ITP|A Structure related to 3ITP_A Chain A, Crystal Structure Of Staphylococcal Nuclease Variant |
|  | • >ref[ZP_06881234.1] hypothetical protein PaerPAb_26559 [Pseudomonas aeruginosa PAb1] FGDSY | • >ref[ZP_06881833.1] DNA polymerase I [Pseudomonas aeruginosa PAb1] SGDQ | • GENE ID: 6474448 | AAA ATPase [Stenotrophomonas maltophilia R551-3] AREVY | • GENE ID: 5354737 | hypothetical protein [Pseudomonas aeruginosa PA7] LARE YK | • >gb|AAK50437.1| unknown [Pseudomonas aeruginosa] AREVY | • >gb|ADL23193.1| phosphate ABC superfamily ATP binding cassette transporter, membrane protein [Staphylococcus aureus subsp. aureus JKD6159] E IRAV Sbjct 180 EAIRAV 185 | • >ref[ZP_06879943.1] succinyl-diaminopimelate desuccinylase [Pseudomonas aeruginosa PAb1] SIRAVT |
| **Gene ID** | **Protein Name** | **Species** | **Gene Function** |
|------------|------------------|-------------|------------------|
| 6474583    | Smal_3703        | Stenotrophomonas maltophilia R551-3 | hypothetical protein |
| 6478446    | Smal_1019        | Stenotrophomonas maltophilia R551-3 | alpha-glucosidase |
| 7179795    | PLES_56671       | Pseudomonas aeruginosa LESB58       | hypothetical protein |
| 6477662    | Smal_0113        | Stenotrophomonas maltophilia R551-3 | filamentous haemagglutinin family outer membrane protein |
| G1349D     | LSHDH            | Stenotrophomonas maltophilia K279a | putative transmembrane protein |

**Note:** The table above lists genes and their associated proteins from various bacterial species, along with their gene IDs, hypothetical protein annotations, and protein functionality details.
Table 6: Tag clouds of the bacterial, viral and fungal species with homology to the 5CFTR polymutant or to the Delta508F CFTR mutant (an octapeptide surrounding the 6deletion point): Tag sizes range from 4 to 30 and are correlated with the number of 7CFTR homologies per pathogen species. The pathogens in red (genera or species) 8have been recorded as overpopulating cystic fibrosis patients (from Table 3). See 9http://www.polygenicpathways.co.uk/cysfib.htm for raw BLAST data.

| Polymutant vs Bacteria | Anthomonas campestris | Staphylococcus epidermidis | Clostridium sporogenes | Pseudomonas aeruginosa | Thermobacterium italicus | Clostridium sporogenes | Caldicellulosiruptor saccharolyticus | Brucella | Geobacillus thermodenitrificans | Gardnerella vaginalis | Clostridium butyricum | Mycobacterium smegmatis | Corynebacterium pseudotuberculosis | Clostridium botulinum | Clostridium kluyveri | Xanthomonas oryzae | Lysinibacillus sphaericus | Caldicellulosiruptor becscii | Geobacillus kaustophilus | Thermotoga lettingae | Lactobacillus johnsonii | Coprococcus comes | Orientia tsutsugamushi | Pneumocystis jirovecii | Clostridium caridivorans | Thermobacterium halotolerans | Bacteroides thetaiotaomicron | Clostridium scindens | Verrucomicrobiae bacterium | ButyrylVibrio proteoclasticus | Thermocrinis albus | Hemophilus influenzae | Lactobacillus jensenii | Porphromonas gingivalis | Corynebacterium efficiens | Butyribacillus extructa | Subdoligranulum variabile | Clostridium spiroforme | Shigella | Streptococcus | Sanguinis | Streptococcus | Agalactiae | Paenibacillus | Bacillus capillosus | Bacillus pantothenicus | Alkaliphilus metallicolens | Escherichia coli | Bacillus cereus | Listeria grayi | Streptococcus | Gallolyticus | Symbiobacterium thermophilum | Brevibacillus brevis | Clostridium thermocellum | Ruminococcus |
| Bacteria                                                                 | Virus                                                                 |
|------------------------------------------------------------------------|----------------------------------------------------------------------|
| *Eubacterium eligens*, *Opitutus terrae*, *Exiguobacterium sibiricum*  | *Foot-and-mouth disease virus*                                        |
| *Erwinia amylovora*, *Bifidobacterium catenulatum*                    | *West Nile virus*                                                    |
| *Nostoc sp*, *Microcystis aeruginosa*                                  | *Newcastle disease virus*                                            |
| *Bacillus pseudiofirmus*                                               | *Synechococcus phage*                                               |
| *Cytophaga hutchinsonii*, *Gemella haemolysans*                       | *S. phage*                                                          |
| *Geobacillus sp*, *Enterobacter cloacae*                              | *Human adenovirus*                                                  |
| *Lactobacillus sakei*, *Bacillus thuringiensis*                       | *CRYPTOPHLEBIA*                                                     |
| *Aeromonas hydrophila*, *Parvimonas micra*                            | *Pseudomonas phage*                                                 |
| *Bacillus anthracis*, *Aeromonas salmonicida*                         | *Acidianus rod-shaped virus*                                         |
| *Lysinibacillus fusiformis*, *Aggregatibacter aphrophilus*            | *Jordanian-type virus*                                              |
| *Bacillus mycoides*, *Lactobacillus crispatus*                        | *Clostridium phage*                                                 |
| *Dehalococcoides ethenogenes*                                          | *Norwalk-like virus*                                                |
| *Granulicatella elegans*, *Prochlorococcus marinus*                   | *Black queen cell virus*                                            |

**Polymutant Viruses**

| Virus                                                                 | Notes                                                                 |
|---------------------------------------------------------------------|----------------------------------------------------------------------|
| *Xestia c-nigrum granulovirus*                                       | Foot-and-mouth disease virus                                        |
| *Influenza A virus*, *West Nile virus*                              | *Norwalk-like virus*                                                |
| *Neodiprion sertifer NPV*                                            | *Human herpesvirus 1*                                               |
| *Lettuce mosaic virus*, *Streptococcus phage* *Leuconostoc phage*   | *Human herpesvirus 5*                                               |
| *Hyphantria cunea*                                                   |                                                                      |
| *nucleopolyhedrovirus*, *Hepatitis B virus*                         |                                                                      |
| *terrae phage*, *Dengue virus*                                       |                                                                      |
| *Human adenovirus*                                                  |                                                                      |
| *Cryptophlebia*                                                     |                                                                      |
| *leucotreta granulovirus*                                            |                                                                      |
| *Enterobacteria phage*, *Natrialba phage*                           |                                                                      |
| *Human papillomavirus*                                              |                                                                      |
| *Human herpesvirus 1*                                                |                                                                      |
| *Synechococcus phage*                                               |                                                                      |
| *Breda virus*                                                       |                                                                      |
| *Acanthocystis turfacea Chlorella virus*                             |                                                                      |
| *Acidianus rod-shaped virus*                                         |                                                                      |
| *Turkey coronavirus*                                                 |                                                                      |
| *Mamestrea configurata NPV-A*, *Staphylococcus phage*                |                                                                      |
| *Pseudomonas phage*                                                  |                                                                      |
| *Mammalian orthoreovirus*                                           |                                                                      |
| *Murid herpesvirus*                                                 |                                                                      |
| *Cereal yellow dwarf virus*                                          |                                                                      |
Border disease virus  |  Rotavirus  |  GB virus C  |  Escherichia phage  |  Bacillus phage  |  Human immunodeficiency virus 2  |  Invertebrate iridescent virus  |  Human herpesvirus 2  |  Hosta virus X  |  Human Respiratory syncytial virus  |  Human herpesvirus 8  |  Epstein-Barr  |  Stretch Lagoon orbivirus  |  Human Herpesvirus 3  |  Acinetobacter phage  |  Human bocavirus  |  Tyuleniy virus  |  Feldmannia species virus  |  Rubella  |  Human herpesvirus 7  |  Escherichia phage  |  Siberian stargazer herpesvirus  |  Maguari virus  |  Mycoplasma fermentans  |  Human calicivirus  |  Mokola virus  |  Epizootic hemorrhagic disease virus  |  Brochothrix phage  |  Hepatitis C virus  |  Lactobacillus phage  |  Human T-lymphotropic virus  |  Human enterovirus  |  Choristoneura fumiferana  |  Human endogenous retrovirus K  |  Sinorhizobium phage  |  Japanese encephalitis virus  |  Amsacta moorei entomopoxvirus  |  Burkholderia phage  |  Mumps  |  Lactate dehydrogenase-elevating virus  |  Norovirus

**Polymutant Fungi**

- **Candida glabrata**  |  Debaryomyces hansenii  |  Ustilago maydis  |  Vanderwaltozyma polyspora  |  Ashbya gossypii  |  Moniliophthora perniciosa  |  Penicillium marneffei  |  Lachancea thermotolerans  |  Kluveromyces lactis  |  Sordaria macrospora  |  Aspergillus fumigatus  |  Coprinopsis cinerea  |  Emericella nidulans  |  Podospora amera  |  Scheffersomyces stipitis  |  Nectria haematococca  |  Schizosaccharomyces pombe  |  Aspergillus flavus  |  Saccharomyces cerevisiae  |  Cryptococcus neoformans  |  Phaeosphaeria nodorum  |  Schizosaccharomyces pombe  |  Aspergillus clavatus  |  Ajellomyces capsulatus  |  Aspergillus niger  |  Pichia pastoris  |  Schizopyllium commune  |  Yarrowia lipolytica  |  Gibberella moniliformis  |  Trichophyton verrucosum  |  Alternaria brassicicola  |  Schizosaccharomyces japonicus  |  Aspergillus oryzae  |  Talaromyces
| **stipitatus** Neurospora crassa | **Debaryomyces hansenii** Nectria haematococca Gibberella zeae |
|---------------------------------|---------------------------------------------------------------|
| **Verticillium albo-atrum** Kluveromyces lactis **Candida** dublinskiensis **Aspergillus** nidulans **Sclerotinia** | |
| **sclerotiorum Arthrodema benhamiae** Schizosaccharomyces japonicus Magnaporthe oryzae **Coccidioides posadasii Candida** tropicalis | |
| **Uncinocarpus reesii** Neosartorya fischeri **Pachia guilliermondii** Funarium oxysporum **Coccidioides immitis Meyerozyma guilliermondii** Botryotinia fuckeliana **Pyrenophora tritici-repentis** | |
| **Pichia guilliermondii** Magnaporthe oryzae **Clavispora lusitaniae Paracoccidioides brasiliensis Lodderomyces elongisporus** | |
| **Vanderwaltozyma polyspora** | |

| **DeltaF508** | **Gordonia bronchialis Catenibacterium mitsuokai Lactobacillus ultunensis** |
|--------------|-----------------------------------------------------------------------|
| **Bacteria** | **Aggregatibacter** actinomycetemcomitans **Neisseria gonorrhoeae Orientia tsutsugamushi Pseudomonas syringae Clostridium nové** |
| **Waddlia chondrophila Fusobacterium varium** | |
| **Streptomyces scabies Bacillus thuringiensis Vibrio harveyi Anaerococcus vaginalis** | |
| **Pedobacter Selenomonas Bacteroides vulgatus** | |
| **Streptococcus Millerii Bacillus cereus Sebaldella termitidis** | |
| **Idiomarina loihensis DesulfoVibrio Clostridium spiroforme Treponema denticola Francisella tularensis** | |
| **Catenulispora acidiphila** | |
| **Bacteroides thetaiotaomicron Clostridium cellulolyticum Clostridium perfringens Frankia Photobacterium damselae Bacteroides pectinophilus Rhodococcus Helicobacter pylori Clostridium papyrosolvens Peptoniphilus** | |
| Bacteroides | Enterococcus faecalis |
|------------|----------------------|
| Burkholderia cenocepacia | Burkholderia glumae |
| Francisella philomiragia | Rickettsia |
| Pediococcus acidilactici | Oribacterium |
| Lactobacillus casei | Enterococcus faecalis |

**Viruses**

| Virus | Description |
|-------|-------------|
| DeltaF508 | Equine infectious anemia virus |
| Trichoplusia ni | Hepatitis C virus |
| Human immunodeficiency virus | Escherichia phage |
| Mycobacterium phage | Tamiami virus Mushroom bacilliform virus |
| Staphylococcus phage | Geobacillus virus Molluscum |
| contagiosum virus | Lumpy skin disease virus | Feline coronavirus |
|------------------|--------------------------|-------------------|
| Dengue virus | Human herpesvirus 3 | Lactobacillus phage |
| Human herpesvirus 7 | Influenza A virus | Human papillomavirus |
| Human cytomegalovirus | Antheraea mylitta cypovirus | Enterobacteria phage |
| cyanophages | Marseillevirus | Human Herpesvirus 1 |
| Lumpy skin disease virus | Mycobacterium phage | Main Drain virus |
| Feline coronavirus | Measles | Acanthamoeba polyphaga mimivirus |
| Dengue virus | Human papillomavirus | Chronic bee paralysis virus |
| Human herpesvirus 3 | Capsicum chlorosis virus | Japanese encephalitis virus |
| Norovirus | Lactobacillus phage | Broad bean true mosaic virus |
| Lactobacillus phage | Human | Enterobacteria phage |
| Marseillevirus | Human | Synechococcus phage |
| Human | Herpesvirus 1 | Synechococcus phage |
| Human | Measles | Haemorrhagic kidney syndrome virus |
| Amsacta moorei entomopoxvirus | Northway virus | Aedes aegypti virus |
| Highlands J virus | Western equine encephalomyelitis virus | Bacillus phage |
| Western equine encephalomyelitis virus | Campylobacter phage | Human poliovirus |
| Haemorrhagic kidney syndrome virus | Food mosaic Marseillevirus | Sclerosporpha macrospora virus |
| Pseudomonas phage | Musca domestica salivary gland hypertrophy virus | Deerpox virus |
| Murine cytomegalovirus | Toscana virus | Listeria monocytogenes |
| Epstein-Barr virus | Toscana virus | Gloxinia tospovirus |
| Human herpesvirus 6 | Maromegalovirus | Human enterovirus 71 |
| Human enterovirus 71 | SARS coronavirus | Emiliana nervosa |
| Haemorrhagic kidney syndrome virus | Adoxophyes honmai NPV | Klebsiella phage |
| Infectious bronchitis virus | Human | Canna streak virus |
| Bovine papillomavirus | Human | Influenza A virus |
| Foot-and-mouth disease virus | Acidianus filamentous virus | Burkholderia cepacia |
| Plasmids | Leptospira biflexa temperate bacteriophage | Paramecium bursaria |
| Chlorella virus | Simian-Human immunodeficiency virus | Erwinia phage |
| Bacteriophage | Mumps | African swine fever virus |
| Bidens mottle virus | Peanut mottle virus | Streptococcus phage |
| Peanut | Human herpesvirus 8 | Streptococcus phage |
| Brochothrix phage | Human endogenous retrovirus K | Vaccinia virus |
| Aeromonas phage | Human Respiratory syncytial virus | Neisseria meningitidis |
| Clostridium phage | Human endogenous retrovirus | Wheat yellow mosaic virus |
| Human herpesvirus 8 | Human | Elephant endotheliotropic herpesvirus 2 |
| Pea | Human endogenous retrovirus | Massilia virus |

| DeltaF508 Fungi | Ashbya gossypii | Lachancea thermotolerans |
|------------------|----------------------|--------------------------|
| Puccinia sorghi | Hypocreanecorina | Moniliophthora perniciosa |
| Trichoderma hamatum | Aspergillus |
oryzae Aspergillus terreus Nectria haematococca
Lentinula edodes Sclerotinia sclerotiorum Puccinia graminis Vanderwaltozyma polypora Fusarium oxysporum Puccinia recondita Paracoccidioides brasiliensis
Debaryomyces hansenii Zygosaccharomyces rouxii
Cadophora gregata Schizosaccharomyces japonicus
Enterocytozoon bieneusi Dekkera bruxellensis
Emericella nidulans Ajellomyces capsulatus
Coccidioides immitis Verticillium albo-atrum Clavispora lusitaniae
Botryotinia fuckeliana Ajellomyces dermatitidis Uncinocarpus reesii Chaetomium globosum Debaryomyces hansenii
Puccinia placenta Trichoderma asperillum Aspergillus niger Brettanomyces custersianus Coprinopsis cinerea
Sordaria macrospora Gibberella zeae
Saccharomyces cerevisiae Candida tropicalis Neurospora crassa
Penicillium chrysogenum Phaeosphaeria nodorum Neosartorya fischeri Aspergillus fumigatus Scheffersomyces stipitis Laccaria bicolor
Lodderomyces elongisporus Pichia guillermondii Puccinia striiformis Tubereulasterum Candida albicans Trichophyton mentagrophytes Pichia stipitis Arthrodema benhamiae Podospora anserina Aspergillus nidulans Yarrowia lipolytica
Ajellomyces dermatitidis Aspergillus flavus Chaetomium globosum Arthrodema otae
Lodderomyces elongisporus Pichia pastoris Arthrodema benhamiae Aspergillus nigere Magnaporthe oryzae Candida dubliniensis Kluyveromyces lactis
Cryptococcus neoformans Penicillium marneffei Schizosaccharomyces pombe
Malassezia globosa Coprinopsis cinerea Opegrapha varia Pyrenophora tritici-repentis Encephalitozoon intestinalis Candida glabrata Clavispora lusitaniae
Blastocladiella emersonii
Table 7: Bacterial and viral homologues of the ten highest affinity CFTR T cell epitopes; Genera or species known to colonise CF patients are shown in bold.

| Allele       | CFTR Position | Epitope       | Ic50 nM | Pathogen homologue                                    |
|--------------|---------------|---------------|---------|-------------------------------------------------------|
| HLA A*0211   | 1:263-271     | EMIENIQSV     | 2.1     | EMIENIQ \ Flavobacterium johnsoniae; Paenibacillus curdianolyticus Xanthomonas fuscans: Xanthomonas oryzae IENIQSV Vibrio fischeri EMIENTQ Klebsiella pneumoniae |
| HLA A*0250   | 1:263-271     | EMIENIQSV     | 2.3     |                                                       |
| HLA A*0211   | 1:869-877     | FLAEVAASL     | 1.9     | LAEVAASL                                              |
| HLA A*0250   | 1:869-877     | FLAEVAASL     | 2.1     | Slackia heliotrinireducens: Actinosynnema mirum: Brevibacillus brevis; Dinoroseobacter shibae FLAEVADSL Pseudomonas fluorescens FLAQEVAASL Burkholderia cenocepacia FLAEVA Stenotrophomonas maltophilia FLAEVAA Ruminococcus sp: Pseudomonas mendocina |
| HLA A*0202   | 1:869-877     | FLAEVAASL     | 2.3     |                                                       |
| HLA A*0211   | 1:199-207     | FMWIAPLQV     | 1.6     | MWIAPL \ Lactobacillus delbrueckii WIAPLQ Comamonas testosterone: Ferrimonas balearica: Starkeya novella: Rhodobacter capsulatus Vibrio parahaemolyticus: Xanthomonas campestris WIAPLTV Staphylococcus aureus WIRPLQV Pseudomonas aeruginosa FMWGAPL Stenotrophomonas maltophilia WLAPLQV Borrelia recurrentis FMWIA Prevotella oris: Clostridium carboxidivorans |
| HLA A*0250   | 1:199-207     | FMWIAPLQV     | 2.2     | V201M                                                  |
| HLA A*0211   | 1:1138-1146   | IMSTLQWAV     | 2.4     | MSTSAIQWAV \ Streptomyces lividans IMGTLQW           |
| HLA A*0250   | 1:1138-1146   | IMSTLQWAV     | 2.4     |                                                       |
| HLA A*0250 | 1:136-144 | LLHPAIFGL | 2.1 |
|------------|----------|-----------|-----|
|            |          | LHPAIFGL  |     |
|            |          | Gluconobacter oxydans |
|            |          | LHPAIFG   |     |
|            |          | Cytophaga hutchinsonii |
|            |          | LLQPAIFG  |     |
|            |          | Photorhabdus asymbiotica |
|            |          | LNPAIFGL  |     |
|            |          | Brachyspira pilosicoli |
|            |          | LHPALFGL  |     |
|            |          | Brevundimonas sp |
|            |          | LLHPDIFG  |     |
|            |          | Sinorhizobium medicae |
|            |          | LLHP-VFGL |     |
| **Stenotrophomonas maltophilia** | | | |
|            |          | LLHIPAIF |
|            |          | **Pseudomonas aeruginosa** |

| HLA A*0211 | 1:209-217 | LLMGLIWE | 1.9 |
| HLA A*0250 | 1:209-217 | LLMGLIWE | 1.9 |
| HLA A*0219 | 1:209-217 | LLMGLIWE | 2.3 |
| HLA A*0202 | 1:209-217 | LLMGLIWE | 2.4 |
|            |          | LLMGLIWE |
| **Stenotrophomonas maltophilia** | | | |
|            |          | **Pseudomonas aeruginosa** |

| HLA A*254-1162 | 1.9 |
|                | SLMRSVSRV | **Pseudomonas aeruginosa** | **Stenotrophomonas maltophilia** |
| HLA A*0211 | 1:1154-1162 | SLMRSVSRV | 2.3 |
|-------------|-------------|------------|-----|
| Citromicrobium bathyomarinum |
| LMRVSRR |
| Pseudocowpox virus |
| LMRNVSRV |
| Clostridium asparagiforme |
| MRSVSRV |
| Erythrobacter litoralis |
| SLMR-VSR |
| **Stenotrophomonas maltophilia** |
| **LMRQARSVSR** |
| **Pseudomonas aeruginosa** |

| HLA A*0250 | 1:768-776 | VLNLMTHSV | 2.1 |
|-------------|-------------|------------|-----|
| VLNLMTH |
| Ralstonia sp: Leptothrix cholodnii: |
| Rhodoferax ferrireducens |
| LNLMTTH |
| **Lactobacillus** jenensis |
| +LMTHSV |
| Streptomyces clavuligerus |
| LNLMT S |
| **Human herpesvirus 5** |
| (cytomegalovirus) |
| NLMTH |
| **Staphylococcus aureus** |

| HLA A*0250 | 1:121-129 | YLCIGLCLL |
|-------------|-------------|------------|
| G124C | |
| 2.2 | |
| LCIGLCL |
| **Bacteroides** sp: Bacillus cereus: |
| Bacillus thuringiensis: |
| Chlorobaculum parvum |
| IGLCLL |
| **Stenotrophomonas maltophilia** |

| HLA A*0211 | 1:88-96 | YLGEVTKAV | 1.7 |
|-------------|-------------|------------|-----|
| YLGEVTKAV |
| **Streptococcus** oralis |
| **Streptococcus** pneumoniae and other strep species: |
| Eubacterium cylindroide: |
| Lysinibacillus fusiformis |

| HLA A*0250 | 1:88-96 | YLGEVTKAV | 2.1 |
|-------------|-------------|------------|-----|
| YLGEVTKAV |
| **Streptococcus** oralis |
| **Streptococcus** pneumoniae and other strep species: |
| Eubacterium cylindroide: |
| Lysinibacillus fusiformis |
Table 8: The binding partners of the CFTR protein as defined by pSTIING. The viral binding partners of these proteins are also noted.

| Gene symbol | Name                                                | Viral binding                                      |
|-------------|------------------------------------------------------|---------------------------------------------------|
| ADCY8       | Adenylate cyclase type 8 activated adenylyl cyclase) | -                                                 |
| AHSA1       | Activator of 90 kDa heat shock protein ATPase homolog 1 | -                                                 |
| AIFM1       | Apoptosis-inducing factor 1, mitochondrial precursor | -                                                 |
| APIB1       | AP-1 complex subunit beta-1                         | HIV-1                                             |
| APOA2       | Apolipoprotein A-II precursor                        | Hepatitis C, HSV-1 (Carter, 2010c)                |
| ATAD3A      | ATPase family AAA domain-containing protein 3A       | -                                                 |
| ATP2A2      | Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 2) ATPase) | -                                                 |
| ATP2A3      | Sarcoplasmic/endoplasmic reticulum calcium ATPase 3 3) | -                                                 |
| ATXN2L      | Ataxin-2-like protein                                | -                                                 |
| BCR         | Breakpoint cluster region protein                    | -                                                 |
| C6orf48     | Protein G8                                          | -                                                 |
| C8orf55     | C8orf55 protein                                      | -                                                 |
| CALU        | Calumenin precursor                                  | -                                                 |
| CANX        | Calnexin precursor                                   | HIV1, HSV-1                                       |
| CAPNS1      | Calpain small subunit 1                              | -                                                 |
| CD59        | CD59 glycoprotein precursor                          | HIV-1, HSV-1 (Carter, 2010c)                      |
| CDH1        | Epithelial-cadherin precursor                        | -                                                 |
| CLCA1       | Chloride channel, calcium activated, family member 1 | -                                                 |
| CLINT1      | Clathrin interactor 1                                | -                                                 |
| CLTA        | Clathrin light chain A                               | -                                                 |
| CLTCL1      | Clathrin heavy chain 2                               | -                                                 |
| COPB1       | Coatamer subunit beta                                | HIV-1                                             |
| CSE1L       | Exportin-2                                           | Epstein-Barr,                                    |
| CSTB        | Cystatin-B                                           | -                                                 |
| DAB2        | Disabled homolog 2                                   | -                                                 |
| DERL1       | Derlin-1                                             | -                                                 |
| DNAJA1      | DnaJ homolog subfamily A member 1                    | Moloney murine leukemia virus                     |
| DNAJA2      | DnaJ homolog subfamily A member 2                    | -                                                 |
| DNAJB1      | DnaJ homolog subfamily B member 1                    | HSV-1 (Carter, 2010c)                             |
| DNAJC5      | DnaJ homolog subfamily C member 5                    | -                                                 |
| EDG4        | Lysoosphosphatidic acid receptor Edg-4               | -                                                 |
| EMD         | Emerin                                               | HSV-1 (Carter, 2010c)                             |
| EPS8        | Epidermal growth factor kinase substrate 8           | -                                                 |
| EXO1        | Exonuclease 1                                        | -                                                 |
| Protein   | Description                                                        | References                        |
|-----------|-------------------------------------------------------------------|-----------------------------------|
| FAM120A  | UPF0318 protein FAM120A                                          | -                                 |
| FAT       | Cadherin-related tumor suppressor homolog precursor               | -                                 |
| FLOT2     | Flotillin-2                                                       | -                                 |
| GNA11     | Guanine nucleotide-binding protein subunit alpha-11 subunit alpha | -                                 |
| GNA12     | Guanine nucleotide-binding protein G(i), alpha-2 subunit          | -                                 |
| GNB2L1    | Guanine nucleotide-binding protein subunit beta 2-like 1          | Epstein-Barr, Human adenovirus 2 and 5, HIV-1, |
| GOPC      | Golgi-associated PDZ and coiled-coil motif-containing protein     | Human papillomavirus type 18      |
| GPIAP1    | GPI-anchored membrane protein 1                                  | Vaccinia Virus                    |
| GRN       | Granulins precursor                                              | HIV-1                             |
| HAX1      | HS1-associating protein X-1                                       | Epstein-Barr, HIV-1               |
| HCLS1     | Hematopoietic lineage cell-specific protein                       | -                                 |
| HSP90AB1  | Heat shock protein HSP 90-beta                                   | HSV-1 (Carter, 2010c)            |
| HSPA1A    | Heat shock 70 kDa protein 1                                       | Epstein-Barr HSV-1 (Carter, 2010c) |
| HSPA1L    | Heat shock 70 kDa protein 1L                                      | Simian virus 40                   |
| HSPA2     | Heat shock-related 70 kDa protein 2                              | -                                 |
| HSPA5     | 78 kDa glucose-regulated protein precursor protein grp78         | Epstein-Barr HSV-1 (Carter, 2010c) |
| HSPA7     | Heat shock 70 kDa protein 7                                       | -                                 |
| HSPA9B    | Stress-70 protein, mitochondrial precursor                        | -                                 |
| HSPB1     | Heat shock protein beta-1                                         | Epstein-Barr                      |
| HSPD1     | 60 kDa heat shock protein, mitochondrial precursor                | Epstein-Barr, HIV-1              |
| IL1RAPL1  | X-linked interleukin-1 receptor accessory protein-like 1 precursor | -                                 |
| IPO7      | Importin-7                                                       | -                                 |
| Kab       | KARP-1-binding protein 1                                          | -                                 |
| KPNB1     | Importin beta-1 subunit                                           | HIV-1, HSV-1, Simian virus 40, Papillomavirus, HSV-1 (Carter, 2010c) |
| LGALS3    | Galectin-3                                                        | -                                 |
| LGALS4    | Galectin-4                                                        | -                                 |
| LIMA1     | LIM domain and actin-binding protein 1                           | -                                 |
| LIN7C     | Lin-7 homolog C                                                  | -                                 |
| LMNA      | Lamin-A/C                                                        | Adenovirus, HIV-1, HSV-1, Papillomavirus, HSV-1 (Carter, 2010c) |
| LMO7      | LIM domain only protein 7                                         | -                                 |
| LRRFIP2   | Leucine-rich repeat flightless-interacting protein 2              | -                                 |
| MLP       | Mucin-like protein                                                | -                                 |
| Protein Code | Description                                                                 | References |
|-------------|-----------------------------------------------------------------------------|------------|
| MS4A5       | Membrane-spanning 4-domains subfamily A member 5                           |            |
| MUC13       | Mucin-13 precursor                                                          |            |
| PCMT1       | Protein-L-isoaspartate(D-aspartate) O-methyltransferase                     |            |
| PDCD6       | Programmed cell death protein 6                                            | HSV-1 (Carter, 2010c) |
| PDZK1       | PDZ domain-containing protein 1 exchanger regulatory factor 3)             |            |
| PLD2        | Phospholipase D2                                                            |            |
| PLEKHA6     | Pleckstrin homology domain-containing family A member 6                     |            |
| PPP2R1A     | Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform | HIV-1, Papillomavirus, Simian virus 40 |
| PRKAR2A     | cAMP-dependent protein kinase type II-alpha regulatory subunit              | Adenovirus, Hepatitis B, HIV-1 |
| PRKDC       | DNA-dependent protein kinase catalytic subunit                              | Adenovirus, HIV-1, HSV-1, |
| PSAP        | Proactivator polypeptide precursor                                          |            |
| PSMD2       | 26S proteasome non-ATPase regulatory subunit 2                              | Epstein-Barr |
| PSME2       | Proteasome activator complex subunit 2                                      |            |
| RCN1        | Reticulocalbin-1 precursor                                                  | Epstein-Barr |
| RCN2        | Reticulocalbin-2 precursor                                                  | Epstein-Barr, Papillomavirus, |
| REPS1       | RalBP1-associated Eps domain-containing protein 1                           |            |
| RNF5        | E3 ubiquitin-protein ligase RNF5                                            |            |
| RPS27A      | Ubiquitin                                                                   | HIV-1      |
| RYK         | Tyrosine-protein kinase RYK precursor                                        |            |
| RYR2        | Ryanodine receptor 2                                                        |            |
| S100A7      | Protein S100-A7                                                             |            |
| S100A9      | Protein S100-A9                                                             |            |
| SEC61A1     | Protein transport protein Sec61 subunit alpha isoform 1                     |            |
| SEC61A2     | Protein transport protein Sec61 subunit alpha isoform 2                     |            |
| SFXN3       | Sideroflexin-3                                                              |            |
| SH3BGRL2    | SH3 domain-binding glutamic acid-rich-like protein 2                        |            |
| SLC9A2      | Sodium/hydrogen exchanger 2 exchanger 2)                                    |            |
| SLC9A3R1    | Ezrin-radixin-moesin-binding phosphoprotein 50 exchange regulatory cofactor NHE-RF) exchanger |            |
| SLC9A3R2    | Na(+)/H(+) exchange regulatory cofactor NHE-RF2                              |            |
| SNX4        | Sorting nexin-4                                                             |            |
| SNX9        | Sorting nexin-9                                                             |            |
| SORL1     | Sortilin-related receptor precursor | - |
|----------|-------------------------------------|---|
| SPTLC1   | Serine palmitoyltransferase 1       | - |
| SQRDL    | Sulfide:quinone oxidoreductase, mitochondrial precursor | - |
| STX1A    | Syntaxin-1A                         | - |
| SVIL     | Supervillin                         | - |
| TACSTD1  | Tumor-associated calcium signal transducer 1 precursor | - |
| TCEB1    | Transcription elongation factor B polypeptide 1 | HIV-1 |
| TCEB2    | Transcription elongation factor B polypeptide 2 | HIV-1 |
| TFG      | Protein TFG                         | - |
| TIAM1    | T-lymphoma invasion and metastasis-inducing protein 1 | - |
| TJP1     | Tight junction protein ZO-1         | - |
| TJP3     | Tight junction protein ZO-3         | - |
| TMEM43   | Transmembrane protein 43            | - |
| TMOD3    | Tropomodulin-3                      | - |
| TPM3     | Tropomyosin alpha-3 chain           | Ectromelia virus strain Moscow |
| TRIP12   | Thyroid receptor-interacting protein 12 | - |
| UBE2J1   | Ubiquitin-conjugating enzyme E2 J1 | - |
| UBE3A    | Ubiquitin-protein ligase E3A        | Papillomavirus |
| UNQ1922  | Galactosyltransferase               | - |
| VCP      | Transitional endoplasmic reticulum ATPase ATPase p97 subunit) | - |
| VPS4A    | Vacuolar protein sorting-associating protein 4A | - |
| WFS1     | Wolframin                           | - |
| WSB1     | WD repeat and SOCS-containing protein 1 | - |
| XPNPEP3  | Putative Xaa-Pro aminopeptidase 3   | - |
| XPO1     | Exportin-1                          | HIV-1 |
| Pathway and number of proteins | Gene symbols | Comments |
|-------------------------------|-------------|---------|
| Protein processing in endoplasmic reticulum (18) | CANX, DERL1, DNAJA1, DNAJB1, DNAJC5, HSP90AB1, HSPA1A, HSPA1L, HSPA2, HSPA5, BIP, RNF5, SEC61A1, SEC61A2, UBE2J1, VCP, WFS1+, CALU | Endoplasmic reticulum stress is a feature of cystic fibrosis |
| Ubiquitin mediated proteolysis (5) | TCEB1, TCEB2, TRIP12, UBE2J1, UBE3A | Protein degradation via this pathway is impaired in CF patients (Paul, 2008) |
| Protein export (3) | HSPA5, SEC61A1, SEC61A2 | |
| Antigen processing and presentation (8) | CANX, HSPA1A, HSPA1L, HSPA2, HSPA5, HSP90AB1, PSME2 + Autoantigen TNF | The delta F508 mutation has also been shown to inhibit the antigen presentation pathway (Hampton & Stanton, 2010), |
| Chemokine signalling pathway (5) | ADCY8, GNAI2, TIAM1 + IL1RAPL1, + autoantigen TNF | CFTR controls the NFkB mediated chemokine inflammatory response |
| Endocytosis (10) | CLTA, CLTLC1, DAB2, HSPA1A, HSPA1L, HSPA2, PLD2, VPS4A + CLINT1, COPB1, | CFTR is a pattern recognition receptor that allows entry of P.Aeruginosa by endocytosis |
| Vibrio cholerae infection (4) | CFTR, SEC61A1, SEC61A2, TJP1 | Inflammation of airway epithelial cells due to bacterial colonisation is a characteristic feature of cystic fibrosis (Machen, 2006a) |
| Bacterial invasion of epithelial cells (4) | CDH1, CLTA, CLTCL1, HCLS1. | |
| Chagas disease (3) | GNA11, GNAI2, PPP2R1A | |
| Toxoplasmosis (5) | GNAI2, HSPA1A, HSPA1L, HSPA2 + autoantigen TNF | - |
| Lysosome (5) | AP1B1, CLTA, CLTCL1, PSAP + CSTB | The CFTR protein is involved in lysosomal acidification in alveolar macrophages and these cells are less able to kill bacteria in CFTR knockout mice |
| Phagosome (2) | CANX, SEC61A1, SEC61A2 | CFTR provides the |
Dilated cardiomyopathy (7)  | ADCY8, RYR2, TPM3, ATP2A2, EMD, LMNA + Autoantigen TNF  | Cardiomyopathy is a complication of cystic fibrosis
Hypertrophic cardiomyopathy (HCM) (6)  | ATP2A2, EMD, LMNA, RYR2, TPM3 + Autoantigen TNF  |
Arrhythmogenic right ventricular cardiomyopathy (ARVC) (4)  | ATP2A2, EMD, LMNA, RYR2 + TMEM43  |
Cardiac muscle contraction (3)  | ATP2A2, RYR2, TPM3  |
Pathways in cancer (9)  | BCR, CDH1, FAT, HSP90AB1, TCEB1, TCEB2, TFG, TPM3 + WSB1  |
Thyroid cancer (3)  | CDH1, TFG, TPM3  |
Spliceosome (3)  | HSPA1A, HSPA1L, HSPA2  |
Pancreatic secretion (6)  | ADCY8, ATP2A2, ATP2A3, CFTR, CLCA1, RYR2  |
Type 1 Diabetes  | GAD2, HSPD1 and and TNF autoantigens  |
Tight junction (5)  | GNAI2, HCLS1, PPP2R1A, TJP1, TJP3  |
Gap junction (4)  | ADCY8, GNA11, GNAI2, TJP1, CDH1, LMO7, TJP1  |
Adherens junction (3)  | CDH1, LMO7, TJP1  |
Apoptosis (6)  | AIFM1, CAPNS1, LGALS3, PRKAR2A, PDCD6, TNF  |
Calcium signalling pathway (5)  | ADCY8, ATP2A2, ATP2A3, GNA11, RYR2. Added RCN1, RCN2  |
MAPK signalling pathway (4)  | HSPA1A, HSPA1L, HSPA2, HSPB1 + autoantigen TNF  |

chloride for the generation of hypochlorous acid by myeloperoxidase in neutrophil phagosomes. This bactericidal mechanism is defective in cystic fibrosis.
| Pathway Description                                    | Genes Involved                                      | Description                                                                 |
|-------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------|
| Gonadotrophin releasing hormone signalling pathway (3) | ADCY8, GNA11, PLD2;                                 | CFTR is expressed in the hypothalamus, in GnRH containing cells, and controls the reproductive endocrine axis |
| Progesterone-mediated oocyte maturation (3)            | ADCY8, GNAI2, HSP90AB1                              | Respiratory epithelial ion transport is regulated by progesterone and oestrogen |
| Gastric acid secretion (3)                            | ADCY8, CFTR, GNAI2                                  | The CFTR chloride channel modulates gastric acid secretion (Schubert, 2010)   |
| Long-term depression (3)                              | GNA11, GNAI2, PPP2R1A                               | -                                                                           |
The position and nature of the CFTR mutations studied (highlighted in red). Del = deletion; X = stop codon termination.

A polymutant protein containing all of the point mutations was constructed for bioinformatics analysis.

```
MQRSPLEKASVVSKLFFSWTRPILKRGYQRQRLSELDIYQPSVDSDNLSEKLERWDELASKNNPLIN
NATIVE
MQRSPLEKASVVSKLFFSWTRPILKRGYQRQRLSELDIYQPSVDSDNLSEKLERWDELASKNNPLIN
```

Polymutant

```
MQRSPLEKASVVSKLFFSWTRPILKRGYQRQRLSELDIYQPSVDSDNLSEKLERWDELASKNNPLIN
```

Fig 1

```
```
Fig 2 The B-cell and T-cell immunogenic profile of the CFTR mutations. The antigenicity is based on a scan of the whole protein and not simply of the amino acid concerned.
Fig 3

The effects of CFTR mutations on B-cell and T-cell immunogenicity. The plots are based on scans of the entire CFTR protein. All mutants were used to constitute a polymutant protein. The epitope prediction servers generate a table of antigenicity values for each amino acid along the entire length of the protein. The delta values reflect subtraction of the native from the CFTR values.

As a rough guideline, peptides with IC₅₀ values <50 nM are considered high affinity, <500 nM intermediate affinity and <5000 nM low affinity.
Fig 4: Examples of P. Aeruginosa or S. Aureus vatches within the polymutant CFTR protein. Highly predictive threshold at 0.35) The alignment regions are boxed and the identical amino acids shaded in grey.

Red amino acids are the point mutations within the CFTR protein.
Fig 5 Results of the Kegg pathway analysis of the CFTR interactome, including the autoantigens observed in cystic fibrosis. The spokes radiating from the CFTR protein contact with proteins within the CFTR interacome. Proteins known to bind to viral proteins are highlighted in white. The pathways on the right (entry/endocytosis/intercellular spread/protein removal) are those used by Herpes simplex and many other viruses during their sojourn in the host cell. The pathways relating to diseases are shown on the left.
Fig 6. A pathogenic feed forward cycle in cystic fibrosis

1: CFTR mutations result in chloride channel deficiency with associated problems in fluid homoeostasis. They also favour pathogen accumulation in the extracellular milieu. 2: CFTR mutations also compromise glutathione and hypochlorous acid availability, reducing bactericidal and viricidal effects. 3: Hypercolonisation by diverse pathogens results in antibody production. 4: Because of pathogen mimicry, these antibodies also target autoantigens, and possibly the CFTR protein itself. Epitope sharing between pathogen/autoantigen and the CFTR protein favours the maintenance of antibody production. 5: Reductions in CFTR and autoantigen function compromises CFTR related pathways, which include those related to the associated pathologies of cystic fibrosis. Repeated reductions in CFTR function continue the cycle, resulting in further pathogen colonisation etc.
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