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Structural Integrity with Functional Plasticity; What Type I Interferon Receptor Polymorphisms Reveal

Nicole A. de Weerd*, Julian P. Vivian†, San S. Lim*, Stephanie U-Shane Huang*, Paul J. Hertzog*‡

* Centre for Innate Immunity and Infectious Diseases, Department of Molecular and Translational Science, Hudson Institute of Medical Research and Monash University, Clayton, Victoria 3168, Australia.

† Infection and Immunity Program, Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute and Australian Research Council Centre for Excellence for Advanced Molecular Imaging, Monash University, Clayton, Victoria 3168, Australia.

‡Corresponding author.

Summary sentence

Review of how disease associated polymorphisms that alter the structure of the type I interferon receptors reflect the importance of the receptor structure-function relationship to the maintenance of human health.

Running Title: IFNAR polymorphisms alter receptor function

Corresponding author:
Paul J. Hertzog,
27-31 Wright Street,
Clayton, Vic 3168,
Australia.
Telephone: (+61) 03 8572 2731,
email: paul.hertzog@hudson.org.au

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Abbreviations

AIDS, acquired immunodeficiency syndrome

C, carboxyl-terminal

Del, deletion mutation

ECD, extracellular domain

ENU, *N*-ethyl-*N*-nitrosourea

Ext, extension mutation

FBN, fibronectin

Fs, frameshift mutation

hCR, helical cytokine receptor

HBV, hepatitis B virus

ICD, intracellular domain

IFN, interferon

IFNAR, interferon alpha/beta receptor

IL, interleukin

LPS, lipopolysaccharide

MS, Multiple sclerosis

N, amino-terminal

PBMC, peripheral blood mononuclear cells

PDB, protein databank

SD, subdomain

SLE, systemic lupus erythematosus

SNP, single nucleotide polymorphism

STAT, signal transducer and activator of transcription

SVR, sustained virological response

TB, tuberculosis

Definitions of unfamiliar terms:

Amino acids are numbered for their position in the mature protein and designated by the three-letter amino acid code throughout.

angstrom – unit of length of interatomic distances; equal to 10^{-10} metres.

binary complex – a protein complex composed of two different proteins.

codon – three nucleotides that form the genetic unit encoding one amino acid.

exon – segment of DNA containing information encoding a protein.

extracellular domain – the region of a cell-bound receptor that is positioned on the cell surface.

frameshift mutation – induces a shift in the reading frame of a transcript during protein translation.

'hot-spot' – a residue that makes a major contribution to a binding in an interface.

intracellular domain – the region of a cell-bound receptor that is positioned inside the cell.

intron – a segment of DNA that does not encode proteins and interrupts the sequence of genes.

nonsynonymous mutation – a mutation in a codon that results in a change in the encoded amino acid.

ternary complex – a protein complex composed of three different proteins.

Abstract

The type I interferons (IFNs) activate an array of signalling pathways, which are initiated after IFNs bind their cognate receptors, interferon α/β receptor (IFNAR)1 and IFNAR2. These signals contribute to many aspects of human health including defence against pathogens, cancer immunosurveillance and regulation of inflammation. How these cytokines interact with their receptors influences the quality of these signals. As such, the integrity of receptor structure is pivotal to maintaining human health and the response to immune stimuli.

This review brings together genome wide association studies (GWAS) and clinical reports describing the association of nonsynonymous *IFNAR1* and *IFNAR2* polymorphisms with clinical disease, including altered susceptibility to viral and bacterial pathogens, autoimmune diseases, cancer and adverse reactions to live-attenuated vaccines. We describe the amino acid substitutions or truncations induced by these polymorphisms and, using the knowledge of IFNAR conformational changes, IFNAR-IFN interfaces and overall structure-function relationship of the signalling complexes, we hypothesise the effect of these polymorphisms on receptor structure. That these predicted changes to IFNAR structure are associated with clinical manifestations of human disease, highlights the importance of IFNAR structural integrity to maintaining functional quality of these receptor-mediated responses.

Type I interferons are pivotal to innate immune responses and ultimately, to human health. Understanding the consequences of altered structure on the actions of these clinically significant cell receptors provides important information on the roles of IFNARs in health and disease.

INTRODUCTION

Interferons (IFNs) are innate immune proteins first described in the 1950s (1, 2). They are central to forming an effective immune response with pivotal roles in protection from viral and bacterial infections, in cancer immunosurveillance and in regulating inflammation (3). Structurally all IFNs are α-helical proteins and are broadly classified into three types, the type I (~ 20 subtypes), type II (one member, IFNγ) and type III IFNs (four IFNλ subtypes), distinguishable by the receptors through which they function (4). The type I IFN (T1IFN) family of cytokines is the largest of the three types, including 17 IFNα subtypes, IFNβ, IFNε, IFNω, IFNκ and others, which intriguingly induce differential ligand specific responses despite sharing a heterodimeric receptor complex composed of IFNαβ receptor (IFNAR)1 and IFNAR2 (5). That the IFNAR receptors can be utilized by multiple ligands possessing as little as ~30% amino acid homology suggests a functional plasticity in ligand engagement by the IFNARs (6). Mutagenesis and biophysical interaction studies, however, provide evidence that structural integrity is also important for efficient ligand binding and functional accuracy (7-9).

The IFNARs are members of the Class II hCR and like all other hCRs fold into well-defined subdomains of ~100 amino acids in length (10). The extracellular domain (ECD) of IFNAR2 is typical of all other Class II hCRs being composed of tandem fibronectin (FBN)-III subdomains (SDs; SD1-2)(11). IFNAR2 exists in three forms; two membrane-bound forms generated by alternative splicing of the *IFNAR2* gene, IFNAR2c which possesses a long intracellular domain that binds Jak1 and STAT1/2s (12, 13) and IFNAR2b which is truncated just inside the membrane and lacks binding sites for known signalling molecules (14). The third form comprises the IFNAR2-ECD but lacks a transmembrane domain and therefore exists as a soluble form (sIFNAR2a) (15). This form of IFNAR2 is found in both

humans and mice and can be generated by either alternative splicing of the *IFNAR2* gene or by ADAM17-mediated proteolytic cleavage at the cell surface (16). In contrast to all other Class II hCRs, the ECD of IFNAR1 possesses a unique four subdomain architecture (SD1-4)(11) which perhaps, reflected by the broad range of affinities it displays for the IFNs (17), aids in the functional plasticity exhibited by the IFNAR complex. IFNAR1 is widely expressed on many different cell types and tissues throughout the body (as cited in (18) **(Fig. 1, Fig 2.)**.

The fully functional IFNAR signalling complex requires both IFNAR1 and IFNAR2 to activate the canonical Jak-STAT signalling pathway (19-21), shown to be important for an effective anti-viral response (22). However, collectively, the T1IFNs have also been shown to activate alternative signalling pathways, including the AKT, MAPK and CrkL pathways (**Fig. 1**) (23). Some evidence suggests that IFNβ and the IFNα's may selectively activate certain pathways differentially from each other. IFNβ, but not IFNα, reportedly induced the activation of JNK and IFNα, but not IFNβ, activated p38 MAPK in a mouse erythroid cell line (24). In hepatocellular carcinoma cells, IFNα2 and IFNβ both activated ERK signalling pathways, but only IFNβ showed activation of AKT in these cells (25). IFNβ has also been shown to activate AKT *in vivo* via IFNAR1, independently of IFNAR2, suggesting that individual receptors may show situational redundancy with regards to activating alternative IFN-mediated signalling pathways (21).

T1IFN subtypes have a broad range of binding affinities for their receptors (17, 26). In one study, a high relative affinity for IFNAR1 correlated with increased anti-proliferative activity, whereas high affinity for IFNAR2 correlated with greater anti-viral activity (17). In line with this observation, IFNβ, which has higher affinity for IFNAR1 than all characterised T1IFNs, was shown to induce a stronger anti-proliferative response than any other T1IFN in

fibrosarcoma cells (17). Conversely, an IFNα variant with high affinity for IFNAR2 but no measurable affinity for IFNAR1 was shown to display good anti-viral activity but no anti-proliferative activity in a range of cell lines (27). Consequently, IFNβ and IFNα exhibit differential potencies in certain situations; IFNβ is more effective at inhibiting osteoclastogenesis than IFNα2 (28) and has stronger growth inhibitory effects in some cancer cells than IFNα (29). While evidence suggests that receptor affinity contributes to the differential signalling potencies that IFNs exhibit, other factors, such as the cell type and density of receptors on the cells surface, may also have a role to play in determining cell fate upon IFN treatment (26, 30, 31).

Protein-protein interactions are critical for protein function and depend on the maintenance of the structural features that enable interaction. Factors that alter this structural integrity may influence the way the proteins communicate with binding partners and ultimately change their function. By definition, nonsynonymous mutations of amino acid residues result when a single-nucleotide polymorphism (SNP) occurs in a gene and introduces a missense mutation into the encoded protein; should this occur in a region of a protein required to permit correct protein folding for functionality, the protein may display altered functional characteristics. Monogenic disorders, where a nonsynonymous mutation has altered function of the encoded protein, have detrimental effects on human physiology and the ability to defend against pathogens or respond to an immune stimulus. Nonsynonymous polymorphisms in the ECDs of IFNAR1 and IFNAR2 have been described (see **Table 1**). These SNPs have been identified through genome wide association studies (GWAS), showing significant associations with specific or multiple diseases, or are identified upon genetic screening when patients present with adverse reactions to vaccinations. The nature and location of the residue change and any measured or hypothesized downstream effects on receptor structure and function for each of these nonsynonymous SNPs is discussed in this review. Synonymous

SNPs and those found in intergenic, promoter or intronic regions of IFNAR1 and IFNAR2 may also be associated with differential clinical outcomes, however these are discussed elsewhere (32-35).

Given the involvement of the type I IFNs in protective immune responses, polymorphisms that impact the ability of the receptors to fold correctly, alter the strength of the ligand-receptor interaction, or inhibit any necessary conformational change upon ligand engagement, are likely to have an effect on the function of the receptors and therefore the health of a host. Nonsynonymous SNPs have been identified for both *IFNAR1* and *IFNAR2* and are linked to altered health or disease susceptibilities. This review will combine studies on the disease associations of human IFNAR SNPs with current biophysical and structural information about the IFNAR proteins and their functions. We will explore the possible consequences of these polymorphisms on IFNAR protein structure and function, and reciprocally, what these disease association studies and biophysical observations infer about receptor structure and function. These considerations are important for understanding mechanism of action of the receptor system *in vivo* in humans and for the design of therapeutic agonists and antagonists in IFN-deficiency diseases.

NONSYNONYMOUS SNPs IN IFNAR1 AND THEIR DISEASE ASSOCIATIONS

SNP rs2257167 in IFNAR1 is associated with increased susceptibility to a broad spectrum of diseases

Numerous GWAS have demonstrated an association of IFNAR1 SNP rs2257167 with increased susceptibility to infection by Hepatitis B Virus (HBV) (36-38) and Malaria (39-41), progression of Human Immunodeficiency Virus (HIV) to Acquired Immune Deficiency Syndrome (AIDS) (42) and risk of Multiple sclerosis (MS) (43) and female vitiligo (44). The SNP is also associated with increased risk of death from non-small cell lung cancer (45) and

linked to severe pain in lung cancer patients (46). The clinical manifestations of this SNP appear to support a protective role for IFNAR1 in these multiple and varied diseases. IFNAR1 SNP rs2257167 is located in exon 4 of the *IFNAR1* gene (Chromosome 21:33343393) and converts G to C resulting in mutation of Val141 to Leu on β3 strand of IFNAR1-SD2, generating the mutant IFNAR1Val141Leu receptor (**Fig. 1. labelled 'A'; Fig 3A, B; Fig 5; Table 1**). While the level of mutant receptor presented on the surface of patient cells hasn't been specifically reported, the level of transcription of the *IFNAR1* gene seems to be unaffected by the SNP (43). The native Val141 altered by this SNP is conserved in most species (with the exception of mouse) but is distal to the ligand binding surface on IFNAR1 (21, 47, 48) (**Fig 3A,B**). The crystal structure of unliganded hIFNAR1 suggests that Val141 may interact with neighbouring Trp143, or with residues on adjacent strands of IFNAR1-SD2, including Glu150, Lys174 and Tyr188 (48). However, further studies are required to demonstrate whether the resultant IFNAR1Val141Leu receptor has altered cell surface expression, ligand binding characteristics or downstream signalling capacity.

Homozygous Premature stop codon mutation in *IFNAR1* gene associated with adverse vaccine responses

Following Measles-Mumps-Rubella (MMR) vaccination, a patient presented with symptoms of measles including encephalitis, fever and mild cerebral oedema; tests showed measles virus in blood and cerebral spinal fluid (49). The MMR vaccine comprises live-attenuated viruses for each disease the vaccine protects against, however, tests for rubella and mumps viruses were not reported for this patient (49). The patient was found to be homozygous for a SNP in an essential intron-exon splice site upstream of exon 6 of the *IFNAR1* gene (49). The resulting three alternatively spliced transcripts encoded frameshift (fs) error mutations introducing a premature stop codon at IFNAR1 residue 228 (~60% of transcripts; Val225fs228X) or in-frame deletions resulting in truncated IFNAR1 proteins (30-

40% of transcripts; Val225_Pro232del) **(Fig 1. labelled 'B'; Fig 3A; Table 1)** (49). This SNP introduced premature stop codons in IFNAR1-SD3 and thus any translated protein would likely lack the remainder of the ECD, including half the ligand binding interface and the entire transmembrane and intracellular domains (Fig 1). Compared to cells from control patients, fibroblasts isolated from the patient showed no detectible cellular IFNAR1 and upon stimulation with IFNα2b or IFNβ failed to activate Jak-STAT signalling molecules and to induce canonical Interferon Regulated Genes (IRGs), including *MX1* and *IFIT1* mRNA (49). Whether the transcripts resulted in production of truncated soluble forms of IFNAR1 requires further investigation.

A compound heterozygous mutation in *IFNAR1* gene is associated with adverse vaccine response

Another patient was identified after receiving the live-attenuated Yellow Fever (YF) vaccine and developing symptoms of the disease including fever, hypotension, lethargy and YF viral RNA in blood (49). This patient was found to be compound heterozygous for the intron-exon junction SNP above and another previously unseen mutation in exon 6 of the *IFNAR1* gene. The SNP introduced a nonsynonymous mutation that altered Trp234 to a stop codon on IFNAR1 (IFNAR1Trp234X) (**Fig 1. labelled 'B'; Fig 3A; Table 1)**. Similar to the SNP above, any translated protein would lack the remainder of the ECD, the transmembrane and intracellular domains. This patient was also shown to have no detectable cellular IFNAR1 protein and fibroblasts that failed to activate Jak-STAT signalling and IRG expression following IFN treatment (49). Interestingly, prior to this vaccination, this patient had received live-attenuated vaccinations for MMR, poliovirus and Bacillus Calmette-Guerin without adverse side-effects, suggesting that the defect caused by this SNP may be limited to certain vaccines or infectious agents, highlighting the possibility of IFNAR1-dependent and independent signalling pathways contributing to patient response to certain vaccinations. That

this patient reacted poorly to the YF vaccination may suggest an absolute requirement for fully functional IFNAR1 receptor in the response to this vaccine.

SNP rs72552343 reveals a detrimental role for IFNAR1 in *Mycobacterium tuberculosis* infection

IFNAR1 SNP rs72552343 was identified in a population of individuals susceptible to viral hepatitis who also showed increased resistance to *Mycobacterium tuberculosis* infection, an intracellular bacterial pathogen of the lung that causes tuberculosis (TB) (50). The SNP is located in exon 8 of the *IFNAR1* gene (Chromosome 21:33349399-33349404) introducing an in-frame deletion of a single codon in the *IFNAR1* gene resulting in deletion of Pro308 (IFNAR1Pro308Δ) one of the residues in the strictly conserved di-proline hinge between IFNAR1-SD3 and -SD4 (**Fig 1. labelled 'C'; Fig 3A,C**, **Table** 1). Paired proline residues located in inter-domain linkers are predicted to be crucial to maintaining local structural rigidity and to prevent unfavourable inter-domain interactions (51). The in-frame deletion of Pro308 is likely to have shortened the distance between IFNAR1-SD3 and -SD4 and therefore altered the ability of these domains to move relative to each other. Despite being distal to the ligand binding interface, the deletion was demonstrated to reduce the affinity of IFNβ for the ECD of IFNAR1Pro308Δ compared to that of normal IFNAR1 (50), confirming that the loss of Pro308 altered the strength of the IFN-IFNAR1 interaction. Furthermore, primary human peripheral blood mononuclear cells (PBMCs) from individuals heterozygous for the SNP demonstrated that the magnitude of IRG induction upon IFNβ stimulation was also significantly reduced compared to homozygous normal individuals (50). Despite the mutation being distal to the ligand-binding interface (48), that this mutation alters ligand affinity and IFNβ-mediated signalling suggests that the structural integrity of the strictly conserved SD3-SD4 hinge is important for correct functionality of IFNAR1.

This study clearly demonstrated a dichotomy in the role of IFNAR1 in human disease: on the one hand, the altered structural and functional integrity of IFNAR1 demonstrated the host protection this receptor offers from viral hepatitis yet on the other revealed the detrimental effect it has in *Mycobacterium tuberculosis* infection (50). This detrimental role for T1IFNs is in accordance with recent reports that PBMCs from TB patients show a blood IFN signature linked to detrimental clinical outcome in this disease (52) and can suppress TB-protective responses induced by other cytokines (53). Furthermore, IFNAR1 has been shown to contribute to transmission of a non-canonical, IFNβ-mediated, proinflammatory signalling pathway (21). While further research is necessary, this pathway may explain why we observe protective or detrimental effects of IFN signalling in different infection settings (54).

SNP in mouse IFNAR1-SD4 leads to susceptibility to viral infection in macrophages

An *N*-ethyl-*N*-nitrosourea (ENU)-generated mouse strain (designated *macro-1*) has been identified with a SNP in exon 9 of the *Ifnar1* gene (Chromosome 21:33349399) (55). This mouse was identified in a screen of *ex vivo* peritoneal macrophages that showed increased susceptibility to infection by a range of viruses (55). The SNP results in an A to C substitution in the *Ifnar1* gene and alters the native Thr315 to Pro in IFNAR1-SD4, (generating IFNAR1Thr315Pro; **Fig 1. labelled 'D'; Fig 3A, D3; Table 1).** That macrophages from the *macro-1* mouse are as susceptible to viral infection as those from STAT1 null mice suggests that the mutation on IFNAR1 in the *macro-1* mouse alters signalling in these mice (55) although the mechanism for the defect is yet to be fully investigated. Using the crystal structure of IFNAR1 in complex with IFNβ (21), the native Thr315 mutated in the *macro-1* mouse appears to be involved in main chain hydrogen bond formation with Leu321 and Leu322 around the β1-β2 loop of IFNAR1-SD4, likely stabilizing local protein structure (Fig 3D). Models of the structure, by contrast, predict that the substituted Pro restricts the conformation of the residue preceding it (Val314) (56-58) and

due to its ring structure and lack of hydrogen on the α-amino group, this residue is incapable of forming main chain hydrogen bonds with either Leu321 or Leu322 (59). Although the Thr315Pro mutation in the *macro-1* mouse is distal to the ligand binding region of IFNAR1, the mutation is located in a well conserved region on SD4 (**Fig 2.**). By altering the local conformation within IFNAR1-SD4, the Thr315Pro mutation has perhaps altered the way that SD4 associates with the cell membrane, with the membrane-proximal domain of IFNAR2 or permits ligand induced conformational change (60). Further research must be conducted to understand whether the SNP has altered ligand binding affinity of IFNAR1 and the mechanistic effect of the Thr315Pro mutation on IFNAR1 function in the *macro-1* mouse. This ENU-induced SNP appears to support an important role for IFNAR1 in anti-viral defence perhaps through its requirement for activation of STAT1 and the importance of regions of the receptor not directly involved in ligand interaction in transducing a signal.

SNP extends the intracellular domain of IFNAR1 and reduces IFNα-mediated signalling

A young patient presented with fever, anemia, thrombocytopenia, splenomegaly, lymphadenopathy with tests revealing positive blood culture for *Streptococcus viridans*, CMV viremia and *Mycobacterium abscessus* detected in his bone marrow (61). The patient was shown to possess SNPs in both *IFNAR1* and *IFNGR2* genes, related but distinct innate immune receptors (61). The patient had previously received the MMR vaccination with no reported side-effects (61). The SNP in *IFNAR1* gene deleted the terminal stop codon, extending the length of the encoded protein by 46 amino acids (resultant mutant protein is IFNAR1Glu557ext*46X) (**Fig 1. labelled 'E'; Table 1)**. Interestingly, while the level of IFNAR1 on the surface of fibroblasts was similar to those of control patients, these cells showed impaired IFNα-mediated STAT1 and STAT2 phosphorylation, STAT1 nuclear translocation, IRG expression and could not mount an effective IFNα-mediated response to CMV viremia (61). Collectively, these observations suggest that, although IFNAR1 was

present on the surface of the patients' cells, the function of the receptor was significantly impaired. The potential structural change that this SNP induced on IFNAR1 highlights what very little we know about the mechanism of action of the intracellular domain (ICD) of this receptor. It has previously been hypothesised that to effect STAT1/STAT2 cross-phosphorylation, the ICD of IFNAR2 may loop around the carboxyl terminal of the shorter IFNAR1-ICD enabling canonical Jak-STAT signalling (19). Although no experimental evidence has been shown to support this hypothesis, an extension of 46 amino acids on IFNAR1-ICD may reduce the likelihood of its occurrence thereby reducing signalling via the canonical Jak-STAT signalling pathway. Alternatively, to induce a reduction in IFNα-mediated signalling, the extension to IFNAR1-ICD may instead stabilise recruitment of intracellular negative regulators to the ternary signalling complex thereby reducing signal transduction. With regards to this patient however, it must be pointed out that this individual also possessed a SNP in the *IFNGR2* gene which induced a frameshift error in the receptor resulting in reduced levels of IFNGR2 and abrogated IFNγ-mediated signalling (61). Thus, interpretation of the connection of this patient to the displayed phenotype is complex due to mutation of both type I and type II IFN receptors.

NONSYNONYMOUS SNPs IN IFNAR2 AND THEIR DISEASE ASSOCIATIONS

Polymorphisms in IFNAR2 signal peptide increase disease risk associations

IFNAR2 SNP rs2229207 and IFNAR2 SNP rs1051393 are both located in exon 1 of the *IFNAR2* gene (Chromosome 21:33241945 and Chromosome 21:33241950, respectively) and both induce nonsynonymous mutations within the signal peptide of IFNAR2 pro-protein (**Fig 1. labelled 'F')**. SNP rs2229207 is associated with an increased risk of a sustained virological response (SVR) to hepatitis C (62), while SNP rs1051393 is associated with an increased risk of multiple sclerosis (43), hepatitis B infection (63), hepatitis C chronicity (64) and with severe pain in lung cancer patients (46) (**Table 1**). Both SNPs induce changes from large

hydrophobic Phe residues to smaller Ser and Val residues, respectively, in a region of the signal peptide known for being enriched in hydrophobic residues (65). Similar mutations in signal sequences of other proteins have been shown to alter nuclear export of the mRNA (66), disrupt interactions of the mRNA with translational machinery thereby targeting the mRNA for degradation (67) or alter trafficking efficacy of the pro-protein (65). In the case of the two SNPs in the *IFNAR2* signal peptide above, any of these scenarios would affect the levels of IFNAR2 that is translated and therefore secreted from the cell, either as the soluble form or for cell bound forms. Experimental evidence for the effect of these mutations on IFNAR2 protein levels is yet to be demonstrated.

SNP rs775739391 reveals the necessity of IFNAR2 in response to live-attenuated viral vaccination

Following an adverse reaction to inoculation with the live-attenuated MMR vaccine, a patient was shown to possess a novel nonsynonymous SNP in the *IFNAR2* gene (68). SNP rs775739391 leads to deletion of a single nucleotide in exon 5 of the *IFNAR2* gene (Chromosome 21:33246807) within the codon for Glu77, inducing a frameshift error and the generation of a premature stop codon **(Fig 1. labelled 'G'; Table 1)** (68). The subsequent protein would be expected to be truncated six residues after His76 and thereby lacking the rest of SD1 and half the ligand binding interface, all of SD2, the transmembrane and intracellular domains and thereby likely not be found on the cell surface (mutated protein referred to as IFNAR2Glu77fs83X, Table 1). Indeed, in fibroblasts derived from this patient IFNAR2 protein could not be detected by Western blot (68) and subsequent IFN treatment of these cells failed to induce activation of canonical downstream signalling components, such as Jak1 and STAT1 (68). The infant succumbed to encephalitis as a result of uncontrolled replication of the live-attenuated vaccine viruses, demonstrating the requirement for IFNAR2 to respond effectively to this vaccination.

A pro-inflammatory IFNAR2-independent signalling axis mediated via the high affinity IFNβ-IFNAR1 interaction has been identified that contributes to lethality in a mouse model of sepsis (21). While a high affinity interaction is also conserved in humans between IFNβ and IFNAR1 (17), no direct evidence for the existence of an IFN-mediated, IFNAR2-independent pathway has yet been specifically identified in the human system. Targeted knock out of IFNAR2 in an immortal human cancer cell line has demonstrated that if signalling can be transmitted through a single human IFNAR receptor, it is likely to show cell- or IFN-subtype specificity since these cells failed to induce any measurable IFN-mediated signalling, canonical or non-canonical (69). However, as patients deficient in functional IFNAR2 receptor are identified, it may be increasingly possible to access a suite of primary cells to investigate if such signalling defects are indeed cell-specific and result from a lack of the protective effects demonstrated by IFNAR2 or from an undetected proinflammatory pathway mediated via the remaining IFNAR1 receptor.

ROLE OF IFNARS IN HUMAN DISEASE

Due to the limitations of human clinical studies, mouse models have been critical in understanding the mechanism of action attributable to a single protein and its involvement in disease pathogenesis or suppression (22, 70-72). It is through these studies that the dichotomous nature of IFNAR-mediated functions against viral versus bacterial pathogens has been observed. These models have demonstrated that IFNAR1 is protective against most infections by viruses and extracellular bacteria (73) and suppress disease in certain non-infectious diseases such as pulmonary hypertension (74), multiple sclerosis (75) and in maintenance of intestinal health (76). In contrast, IFNAR1 has been shown to be detrimental to the host during infection by certain intracellular bacteria (54, 73) including *Listeria monocytogenes* (77), *Salmonella enterica* serovar *Typhimurium* (78) and *Mycobacterium tuberculosis* (79). A similar detrimental role for IFNAR1 during *Plasmodium* infection has

also been demonstrated whereby IFNAR1-mediated signalling impedes activation of the adaptive immune response (80). One intriguing possibility is that IFNAR1 may be selectively protective against some bacterial pathogens but detrimental against others based on whether infection is intra- or extra-cellular in nature (81). IFNAR1 also has a detrimental role during certain autoinflammatory diseases including in Sjogrens syndrome (82), in neuropathic pain (83) and systematic lupus erythematosus (SLE). Both *Ifnar1* deficiency and the use of an IFNAR1 neutralising antibody have demonstrated that IFNAR1-mediated signals are detrimental in mouse models of SLE (84, 85). Importantly, this observation has been translated into the clinic with an anti-IFNAR1 neutralising antibody showing therapeutic potential in humans for the treatment of SLE (86-89) demonstrating the translatability of mouse studies to humans in the type I IFN system in this disease.

IFNAR2 is critical for host protective responses to influenza infection (90) and likely many more viruses due to the fact that this receptor is the primary binding partner for IFN ligands and since it recruits STAT1 and STAT2 to the receptor complex (13), molecules essential for an effective anti-viral response (71). The soluble form of IFNAR2 (sIFNAR2) is found widely in normal human body fluids (91) and has been implicated in a number of autoimmune diseases (92, 93). Reduced levels of sIFNAR2 in the serum of peripheral blood has been identified as a prognostic marker in naïve multiple sclerosis (MS) patients, with circulating levels increasing in MS patients undergoing IFNβ treatment (92). As soluble IFNAR2 can bind IFNs directly to potentiate a signal (15), that soluble IFNAR2 is depleted in naïve MS patients suggests that it may be binding circulating IFN to mediate a signalling response, thereby reducing its own levels in serum. On the other hand, active MS lesions have increased levels of ADAM17 (94), the protease shown to generate soluble IFNAR2 by proteolytic cleavage (16). Thus, during active MS and IFNβ therapy, increased ADAM17 may promote a rise in circulating soluble IFNAR2 levels and may therefore be important in a

positive response to IFNβ therapy. In a mouse model of SLE, sIFNAR2 has been found to contribute to the production of auto-antibodies (93) suggesting an important role for this receptor in the pathogenicity of this and perhaps other autoimmune diseases. Although the mechanism is yet to be fully elucidated, sIFNAR2 has been shown to function via a trans-signalling mechanism, akin to the soluble IL-6 receptor (95), whereby it can regulate IFN signalling (15, 91, 96, 97).

Structure of IFNAR1-ECD

To date, three structures of IFNAR1-IFN complexes are available; two human protein complexes and one from mouse. The human IFNAR1-IFN complexes demonstrate the binding of two different ligands – one with a hIFNα2 variant (IFNα2-YNS; PDB accession codes 3SE3) and one with IFNω (PDB accession code 3SE4 (48)). The third structure is a murine complex with IFNβ (PDB accession code 3WCY (21)). All complexes show an overall conservation of the general recognition of IFN by IFNAR1, with SD1-3 forming a continuous and extensive interface – IFNAR1-SD1 is centred on the D helix^{IFN}, SD2 on the B helix^{IFN} and SD3 on the C helix^{IFN} of the ligands. Due to the four-domain architecture of IFNAR1, this receptor forms "elbow" contacts to IFN between the IFNAR1 SD1-2 and contacts distal to the "elbow" between IFNAR1 SD2-3. IFNAR1 SD4 is extended from the primary site of IFN recognition and makes limited contacts via its β2-β3 loop (**Fig 4**). IFNAR1 SD1-3 each contribute approximately one-third of the binding interface (**Fig 4.**). By contrast, IFNAR1-SD4, which was resolved only in the murine IFNβ-IFNAR1 complex (21), is offset by ~90° from the planar arrangement of IFNAR1 SD1-3 and makes limited contact with IFNβ (**Fig 4, Fig 5**). The interface on IFNAR1-SD4 may be specific to IFNβ or specific to the murine system, since a comparable crystal structure with human IFNβ is yet to be determined. The majority contacts with IFNAR1 SD1-3 is consistent with biochemical analyses that show this region is sufficient for *in vitro* ligand binding whilst SD4 is

dispensable (21, 60, 98, 99)(**Fig 2.**). That three FBN-III domains are required to form the ligand binding region on IFNAR1 again demonstrates the unique mode in which IFNAR1 binds its ligands, a mechanism unmatched in the Class II hCR family of receptors. While IFNAR1 SD4 may not play a major role in direct ligand binding, it seems to play an important role in signal transduction (98).

Residues in the ligand-IFNAR1 interface

'Hot-spot' residues: As determined by site-directed mutagenesis of interaction interfaces, individual residues that make major contributions to the overall affinity of an interaction are referred to as 'hot spot' residues. Despite the low affinity of the IFNAR1-IFNα interaction, integrity of this interface is important for full IFNα activity, since its interruption removes IFNα-induced anti-proliferative activity (100). In this interface, only $Tyr70^{AR1}$ (IFNAR1 SD1) and $Phe238^{AR1}$ (IFNAR1 SD3) are described as 'hot-spot' residues with minor contributions from other residues (**Table 2**) (48). In contrast, the IFNAR1-IFNβ interface is much more extensive (**Fig 5.**) with major contributions found on the three membrane-distal SDs and a minor contribution from residues on IFNAR1 SD4 (Table 2) (21). On IFNAR1 SD1, Tyr70 and Tyr98 make major contributions to binding IFNβ, the former a 'hot-spot' residue conserved with IFNα and IFNω (**Fig 2.**). On SD3, two prominent residues, $Tyr240^{AR1}$ (the homologous Phe238 in human IFNAR1 is also a 'hot-spot' residue in the interface with IFNα and IFNω) and the unique $Tyr274^{AR1}$ form a 'hot-spot' of interaction in the IFNAR1-IFNβ interface; these residues are also important in determining the magnitude of the signalling response and biological activities exhibited by IFNβ (99). Residues that make minor contributions to the ligand interface are also found on other regions of $SD1\text{-}3^{AR1}$ (**Fig 2.**).

Ligand-specific residues: Comparison of the IFNAR1-IFN interfaces in the three published crystal structures (21, 48) reveals that specific residues on IFNAR1 contribute

preferentially to binding different ligands. For IFNAR1, the ability to associate with the large array of type I IFNs, often with low sequence identity, is likely achieved by the "moulding" of the receptor around a structurally conserved core or common 'anchor points' on the cytokines (48). Consistent with this hypothesis, the murine IFNAR1 orientation when bound to IFNβ deviates by 16° from the human IFNAR1 bound to IFNα2-YNS or IFNω, yet retains common sites of recognition (21) (**Fig 4, Fig 6.)**. The variation observed in the affinity of IFNAR1 for different IFN subtypes (17, 26) is possibly accounted for by differences in the docking angle and hence the interacting surface area of IFNAR1. Namely, IFNAR1 buried a surface area of 3300 $Å^2$ on IFNβ compared with 2030 $Å^2$ and 2200 $Å^2$ for IFNα-YNS and IFNω, respectively (**Fig 6.**). The extent of this interaction area correlates with the ~100-fold affinity difference between IFNβ and IFNα2 for IFNAR1. Notwithstanding these differences, common sites for recognition or potential 'anchor points' are present for IFNAR1 SD1-3 that are conserved across species (21, 48). Interestingly, $Tyr274^{AR1}$ located in the mIFNAR1-IFNβ interface on $SD3^{AR1}$ is important for formation of this high affinity interaction and mIFNβ-mediated signals (99). Since this residue is not conserved across species, and the residue with which it structurally aligns ($Gln272^{AR1}$) was not identified in the hIFNAR1-hIFN interfaces (48), $Tyr274^{AR1}$ may be an IFNβ-specific anchor point on IFNAR1 or it may contribute to the species specificity exhibited by most IFNs. Thus, whilst there is considerable scope for "sliding" of IFNAR1 to accommodate various IFN subtypes binding at different affinities, there may nonetheless be key points of ligand-specific recognition on IFNAR1 SD1-3.

The SNP identified by Hernandez et al (49) which converts Trp234 to a premature stop codon would be predicted to produce a truncated, soluble receptor comprising IFNAR1 SD1-2 and small portion of SD3 (**Fig 2.**). This protein would likely possess the ligand binding 'hot-spot' residues on SD1 (Tyr70) however it would lack the 'hot-spot' and ligand-specific

residues on SD3 that make significant contributions to the strength of the IFNAR1-ligand binding interface (including Phe238)(48, 99). This truncated form of IFNAR1 may therefore be unable to form a stable interaction with any ligand. Of the other SNPs above, none of the mutated residues have been implicated directly in the ligand binding interface. However, given that the SNPs show associations with diseases, the structural effect of these mutation on IFNAR1 is likely altering another characteristic of the receptor.

Alterations to inter-domain flexibility or mobility may alter receptor functionality

The function of cytokine receptors can also be dependent on the ability of the receptor to undertake conformational change(s) upon ligand binding to initiate secondary interactions or signal transduction (101, 102). Polymorphisms that restrict the ability of a receptor to undergo any conformational change necessary for optimal ligand binding or signal transduction could therefore alter receptor function. Helical cytokine receptors, including IFNAR1 and IFNAR2, possess highly conserved di-proline motifs in the hinge regions between subdomains, giving structural rigidity to receptors and regulating domain-domain flexibility (11, 51). Disruption of these motifs by mutation or substitution are known to lead to altered domain-domain flexibility in cytokine receptors (103, 104). For IFNAR1, SNP rs72552343 causes deletion of Pro308, one of the two highly conserved residues in the IFNAR1-SD3/SD4 di-proline hinge (50). Despite the fact that Pro308 is not directly involved in the ligand binding interface on IFNAR1, the resultant receptor showed reduced affinity for IFNβ and reduced IRG induction (50). Deletion of this residue on IFNAR1 likely alters the kinetics of the ligand-receptor interaction indirectly via a mechanism that likely affects inter-domain flexibility and therefore the stability and life-time of the ternary signalling complex (105).

Upon ligand binding, IFNAR1 undergoes a loss in mechanical stability, manifested as cooperative movements between IFNAR1-SD2 and SD3 (106, 107) and a multi-step

conformational change that is propagated along the receptor (60). Both the loss in mechanical stability and the conformational change are required for effective signal transduction (60, 106, 107). Together these observations suggest that all four subdomains of IFNAR1 are required to generate the cooperative movements necessary for effective signal transduction via this receptor. Given this hypothesis, it is likely that any force that perturbs these inter-domain movements may alter receptor functionality. Indeed, an antibody showing clinical utility for the treatment of scleroderma (108) and SLE (109) has been shown to neutralize IFNAR1 signalling by binding Arg279 on IFNAR1-SD3 (110), a residue not implicated directly in the ligand binding domain for IFNα or IFNω (48). While the antibody blocks IFN-mediated STAT activation and IRG induction (88), its mechanism of action may involve steric hinderance of ligand binding to IFNAR1 or the propagation of the conformational change essential for ligand-induced signal transduction (60). Likewise, although the mutation caused by IFNAR1 SNP rs2257167 induces a mutation distal to the ligand binding domain, given the location of the Val141Leu substitution adjacent to the SD2-SD3 hinge region, the mutation may alter the relative interdomain movements, thereby altering receptor function. Experimental evidence to these hypotheses is required.

While the relative affinity of ligands for the IFNARs has led to the hypothesis that IFNs bind initially to IFNAR2 with high affinity, followed by recruitment of IFNAR1 (the low affinity receptor)(98), we and others have hypothesized a potential third step that takes into account the mobility of IFNAR1-SD4 in relation to the three membrane distal domains (21, 111). Following IFNAR1-SD1-3 binding to ligand, we propose that there is a conformational movement of the mobile IFNAR1-SD4 that contributes to formation of a functional signalling complex (**Fig 3A**). This aligns with a study that used Förster resonance energy transfer spectroscopy and single-particle electron microscopy to demonstrate that ligand binding induces a conformational change in IFNAR1 that positions SD4 in close proximity to that of

IFNAR2 SD2 (60). Although a ligand-independent association between IFNAR1 and IFNAR2 has not been reported, this hypothesis may explain why IFNAR1 SD4 cannot be recapitulated by substitution with membrane proximal domains from homologous Class II hCRs, including those of IFNλ and IL10 (98).

Structure of IFNAR2-ECD

Protein crystallographic studies of the hIFNα2-YNS and IFNω ternary complexes and IFNAR2-IFNα2-YNS binary complex (48) provide a consensus on the IFNAR2 binding interface that is composed of primary sites on the AB-loop^{IFN} and the A and E helices^{IFN} (**Fig 6**). Together, these sites form parallel hydrophobic and hydrophilic striations involved in IFNα2 binding and indicate that there is an inherent flexibility of the IFNAR2-ECD binding surface, which allows it to accommodate various type I IFNs (112). Unlike other Class II hCRs that typically utilise both SD1 and SD2 in recognition of their ligands, IFNAR2 binds predominantly (~97 %) via SD1 (**Fig 6**). This interface is extensive (~1800 Å^2) and is comparable in size to the IFNAR1-SD1-3 interface with IFNα and IFNω (2030 Å^2 and 2200 Å^2, respectively) (48). Early mutagenesis studies indicated that IFNα2 and IFNβ bind at a similar location on IFNAR2, but with a different distribution of contributions from ligand-specific residues (**Table** 1) (9, 17, 113). Primarily for IFNα2, Met46^{AR2} is the 'hot-spot' residue in the interaction, while numerous distal and proximal residues also contribute to the interface (see **Table 1**)(48). For the IFNAR2-IFNβ interface no 'hot-spot' residue has been identified, however His76^{AR2} and Trp100^{AR2} are important for binding, residues shared by the IFNAR2-IFNα interface (see **Table 1**) (9, 48, 113, 114). Asp98^{AR2} appears to be unique to the IFNAR2-IFNβ interface in comparison with the IFNα interface (114). The SNP rs775739391 which generates IFNAR2Glu77fs83X thereby introducing a premature stop codon in IFNAR2 SD1, is predicted to encode a protein lacking numerous residues from both the IFNα and IFNβ interfaces, including Asp98^{AR2} and Trp100^{AR2} (48, 114).

Structure of the Ternary IFNAR1-IFN-IFNAR2 Complex

The IFNAR1-SD4 and IFNAR2-SD2 are relatively untethered to the ligand and so are afforded degrees of freedom in movement (**Fig 4a. IFNAR1, Fig 5. AR2only**). This is especially the case for IFNAR1-SD4 that is displaced from the ligand-binding subdomains IFNAR1 SD1-3 by a long unstructured linker (**Fig 4**). Indeed, in electron microscopy images of a hIFNAR1-hIFNα2-hIFNAR2 ternary complex, IFNAR1-SD4 was shown to exist in variable locations in relation to IFNAR1-SD1-3 (111). This study even suggested that IFNAR1 and IFNAR2 may interact directly upon ligand binding (111). Similar structures were shown in electron microscopy images of the hIFNAR1-hIFNβ-hIFNAR2 ternary complex (60). IFNAR1-SD4 was not resolved in the crystal structures of the ternary complexes with IFNα2-YNS and IFNω but has been previously modelled in an orientation similar to the planar arrangement seen for the IFNAR1 SD1-SD2 (115). Such an arrangement is not observed in the mIFNAR1-mIFNβ binary structure in which IFNAR1-SD4 sits orthogonal to the IFNAR1-SD1-3 (**Fig 4**) (21). This orthogonal arrangement is the more likely one for IFNAR1-SD4 as it aligns with IFNAR2-SD2, which similarly sits orthogonally to the IFNAR1-SD1-3. Thus, as a ternary complex, the membrane proximal domains of IFNAR1 and IFNAR2 may be brought into close proximity with the transmembrane domains close to parallel (**Fig 3A**). Whether there is a direct interaction between IFNAR1-SD4 and IFNAR2-SD2 is a matter of debate.

Role of soluble IFNAR2 in IFNAR structure and function

In both human and murine systems, sIFNAR2 is produced through alternative splicing of the *IFNAR2* gene (116) or by ADAM17-mediated proteolytic cleavage (16). Human sIFNAR2a differs from hIFNAR2c-ECD by the substitution of the C-terminal Ser212Ala213 by Phe212Ser213 (117). In contrast, mouse sIFNAR2a differs from mIFNAR2c-ECD by an additional 11 amino acid residues at the C-terminal tail (118). Human sIFNAR2a is found in

various fluids, including serum, urine, and cerebrospinal fluid (91, 92, 119). In mouse, the transcript for sIFNAR2a is found in most tissues, and is more abundantly expressed than that encoding the full-length transmembrane form, mIFNAR2c (15). The biological importance of sIFNAR2a is implicated by findings that link elevated serum sIFNAR2a to human viral infections including hepatitis C and HIV, to chronic inflammatory disorders such as SLE and to various cancers (92, 120-125). Similarly, mice engineered to express elevated sIFNAR2a, thereby mimicking the elevated sIFNAR2a seen in human diseases, demonstrate increased susceptibility to lipopolysaccharide (LPS)-mediated septic shock (97). In contrast, the level of detectable serum sIFNAR2a was demonstrated to be significantly reduced in naïve multiple sclerosis (MS) patients and that IFNβ treatment increased the level of the soluble receptor (92, 125). A mouse model of multiple sclerosis also demonstrated that sIFNAR2a can potentiate IFNβ signalling and may have intrinsic properties that inhibit T-cell proliferation, contributing to improved clinical outcomes (126). Regardless of these studies, the mechanism of action of sIFNAR2a in health and disease remains to be fully elucidated.

Concluding remarks

Single nucleotide changes in the genetic code that alter the structure of the IFN receptors can have measurable and profound effects on the function of these proteins, influencing an individual's risk of disease and the quality of the immune responses they mount. Interferons are potent cytokines inducing highly regulated biological responses that protect from infections and cancer and maintain physiological homeostasis. GWAS studies and case reports of individuals with SNPs who display aberrant responses to otherwise safe, live-attenuated vaccinations have given us an increased understanding of the importance of IFNAR structure to maintaining health and initiating appropriate immune responses.

Using known structural information on the receptors, we have discussed the predicted structural effects of SNPs on the IFNARs and the evident or possible downstream

consequences of these changes on receptor function, providing insight into the physiological roles of the IFNARs. Increased understanding of the influence IFNAR structural features have on normal receptor function will better inform our knowledge of the roles of these receptors in maintenance of health and defence against disease.

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References

1. Fukumi H, Nishikawa F, Kitayama T. Influenza outbreaks in Japan in 1951-1953. Jpn J Med Sci Biol. 1953;6(6):649-58. Epub 1953/12/01. doi: 10.7883/yoken1952.6.649. PubMed PMID: 13162660.
2. Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci. 1957;147(927):258-67. Epub 1957/09/12. PubMed PMID: 13465720.
3. Pestka S. The interferons: 50 years after their discovery, there is much more to learn. J Biol Chem. 2007;282(28):20047-51. Epub 2007/05/16. doi: R700004200 [pii] 10.1074/jbc.R700004200. PubMed PMID: 17502369.

4. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunol Rev. 2004;202:8-32. PubMed PMID: 15546383.
5. de Weerd NA, Samarajiwa SA, Hertzog PJ. Type I interferon receptors: biochemistry and biological functions. J Biol Chem. 2007;282(28):20053-7. Epub 2007/05/16. doi: R700006200 [pii] 10.1074/jbc.R700006200. PubMed PMID: 17502368.

6. Schreiber G, Piehler J. The molecular basis for functional plasticity in type I interferon signaling. Trends Immunol. 2015;36(3):139-49. Epub 2015/02/18. doi: 10.1016/j.it.2015.01.002. PubMed PMID: 25687684.
7. Jaitin DA, Roisman LC, Jaks E, Gavutis M, Piehler J, Van der Heyden J, et al. Inquiring into the differential action of interferons (IFNs): an IFN-alpha2 mutant with enhanced affinity to IFNAR1 is functionally similar to IFN-beta. Mol Cell Biol. 2006;26(5):1888-97. PubMed PMID: 16479007.
8. Piehler J, Roisman LC, Schreiber G. New structural and functional aspects of the type I interferon-receptor interaction revealed by comprehensive mutational analysis of the binding interface. J Biol Chem. 2000;275(51):40425-33. PubMed PMID: 10984492.
9. Piehler J, Schreiber G. Mutational and structural analysis of the binding interface between type I interferons and their receptor Ifnar2. J Mol Biol. 1999;294(1):223-37. PubMed PMID: 10556041.
10. Bazan JF. Shared architecture of hormone binding domains in type I and II interferon receptors. Cell. 1990;61(5):753-4. Epub 1990/06/01. PubMed PMID: 2140527.
11. Bazan JF. Structural design and molecular evolution of a cytokine receptor superfamily. Proc Natl Acad Sci U S A. 1990;87(18):6934-8. PubMed PMID: 2169613.
12. Domanski P, Fish E, Nadeau OW, Witte M, Platanias LC, Yan H, et al. A region of the beta subunit of the interferon alpha receptor different from box 1 interacts with Jak1 and is sufficient to activate the Jak-Stat pathway and induce an antiviral state. J Biol Chem. 1997;272(42):26388-93. PubMed PMID: 9334213.
13. Zhao W, Lee C, Piganis R, Plumlee C, de Weerd N, Hertzog PJ, et al. A conserved IFN-alpha receptor tyrosine motif directs the biological response to type I IFNs. J Immunol. 2008;180(8):5483-9. Epub 2008/04/09. doi: 180/8/5483 [pii]. PubMed PMID: 18390731.
14. Cohen B, Novick D, Barak S, Rubinstein M. Ligand-induced association of the type I interferon receptor components. Mol Cell Biol. 1995;15(8):4208-14. PubMed PMID: 7623815.
15. Hardy MP, Owczarek CM, Trajanovska S, Liu X, Kola I, Hertzog PJ. The soluble murine type I interferon receptor Ifnar-2 is present in serum, is independently regulated, and has both agonistic and antagonistic properties. Blood. 2001;97(2):473-82. PubMed PMID: 11154225.
16. Pioli PD, Saleh AM, El Fiky A, Nastiuk KL, Krolewski JJ. Sequential proteolytic processing of an interferon-alpha receptor subunit by TNF-alpha converting enzyme and presenilins. J Interferon Cytokine Res. 2012;32(7):312-25. Epub 2012/03/31. doi: 10.1089/jir.2011.0116. PubMed PMID: 22458690; PubMed Central PMCID: PMCPMC3390988.
17. Jaks E, Gavutis M, Uze G, Martal J, Piehler J. Differential receptor subunit affinities of type I interferons govern differential signal activation. J Mol Biol. 2007;366(2):525-39. PubMed PMID: 17174979.

18. de Weerd NA, Nguyen T. The interferons and their receptors--distribution and regulation. Immunol Cell Biol. 2012;90(5):483-91. Epub 2012/03/14. doi: icb20129 [pii] 10.1038/icb.2012.9. PubMed PMID: 22410872.

19. Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD. How cells respond to interferons. Annu Rev Biochem. 1998;67:227-64. Epub 1998/10/06. doi: 10.1146/annurev.biochem.67.1.227. PubMed PMID: 9759489.

20. Hwang SY, Hertzog PJ, Holland KA, Sumarsono SH, Tymms MJ, Hamilton JA, et al. A null mutation in the gene encoding a type I interferon receptor component eliminates antiproliferative and antiviral responses to interferons alpha and beta and alters macrophage responses. Proc Natl Acad Sci U S A. 1995;92(24):11284-8. PubMed PMID: 7479980.

21. de Weerd NA, Vivian JP, Nguyen TK, Mangan NE, Gould JA, Braniff SJ, et al. Structural basis of a unique interferon-beta signaling axis mediated via the receptor IFNAR1. Nat Immunol. 2013;14(9):901-7. Epub 2013/07/23. doi: ni.2667 [pii] 10.1038/ni.2667. PubMed PMID: 23872679.

22. Meraz MA, White JM, Sheehan KC, Bach EA, Rodig SJ, Dighe AS, et al. Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. Cell. 1996;84(3):431-42. Epub 1996/02/09. PubMed PMID: 8608597.

23. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol. 2005;5(5):375-86. PubMed PMID: 15864272.

24. Cull VS, Tilbrook PA, Bartlett EJ, Brekalo NL, James CM. Type I interferon differential therapy for erythroleukemia: specificity of STAT activation. Blood. 2003;101(7):2727-35. Epub 2002/11/26. doi: 10.1182/blood-2002-05-1521. PubMed PMID: 12446459.

25. Matsumoto K, Okano J, Murawaki Y. Differential effects of interferon alpha-2b and beta on the signaling pathways in human liver cancer cells. J Gastroenterol. 2005;40(7):722-32. Epub 2005/08/06. doi: 10.1007/s00535-005-1616-x. PubMed PMID: 16082589.

26. Lavoie TB, Kalie E, Crisafulli-Cabatu S, Abramovich R, DiGioia G, Moolchan K, et al. Binding and activity of all human alpha interferon subtypes. Cytokine. 2011;56(2):282-9. Epub 2011/08/23. doi: 10.1016/j.cyto.2011.07.019. PubMed PMID: 21856167.

27. Levin D, Schneider WM, Hoffmann HH, Yarden G, Busetto AG, Manor O, et al. Multifaceted activities of type I interferon are revealed by a receptor antagonist. Science signaling. 2014;7(327):ra50. doi: 10.1126/scisignal.2004998. PubMed PMID: 24866020.

28. Coelho LF, Magno de Freitas Almeida G, Mennechet FJ, Blangy A, Uze G. Interferon-alpha and -beta differentially regulate osteoclastogenesis: role of differential induction of chemokine CXCL11 expression. Proc Natl Acad Sci U S A. 2005;102(33):11917-22. Epub 2005/08/06. doi: 0502188102 [pii] 10.1073/pnas.0502188102. PubMed PMID: 16081539.

29. Damdinsuren B, Nagano H, Wada H, Kondo M, Ota H, Nakamura M, et al. Stronger growth-inhibitory effect of interferon (IFN)-beta compared to IFN-alpha is mediated by IFN signaling pathway in hepatocellular carcinoma cells. Int J Oncol. 2007;30(1):201-8. Epub 2006/12/05. PubMed PMID: 17143530.

30. Levin D, Harari D, Schreiber G. Stochastic receptor expression determines cell fate upon interferon treatment. Mol Cell Biol. 2011;31(16):3252-66. Epub 2011/06/22. doi: MCB.05251-11 [pii] 10.1128/MCB.05251-11. PubMed PMID: 21690295.

31. van Boxel-Dezaire AH, Rani MR, Stark GR. Complex modulation of cell type-specific signaling in response to type I interferons. Immunity. 2006;25(3):361-72. Epub 2006/09/19. doi: 10.1016/j.immuni.2006.08.014. PubMed PMID: 16979568.

32. Hise AG, Traylor Z, Hall NB, Sutherland LJ, Dahir S, Ermler ME, et al. Association of symptoms and severity of rift valley fever with genetic polymorphisms in human innate immune pathways. PLoS Negl Trop Dis. 2015;9(3):e0003584. Epub 2015/03/11. doi: 10.1371/journal.pntd.0003584. PubMed PMID: 25756647; PubMed Central PMCID: PMCPMC4355584.

33. Karamitros T, Papatheodoridis G, Paraskevis D, Hatzakis A, Mbisa JL, Georgopoulou U, et al. Impact of Interferon-alpha Receptor-1 Promoter Polymorphisms on the Transcriptome of the Hepatitis B Virus-Associated Hepatocellular Carcinoma. Frontiers in immunology. 2018;9:777. Epub 2018/05/02. doi: 10.3389/fimmu.2018.00777. PubMed PMID: 29713327; PubMed Central PMCID: PMCPMC5911724.
34. Zou R, Zhang G, Li S, Wang W, Yuan J, Li J, et al. A functional polymorphism in IFNAR1 gene is associated with susceptibility and severity of HFMD with EV71 infection. Scientific reports. 2015;5:18541. Epub 2015/12/19. doi: 10.1038/srep18541. PubMed PMID: 26679744; PubMed Central PMCID: PMCPMC4683517.
35. Kennedy RB, Ovsyannikova IG, Haralambieva IH, Lambert ND, Pankratz VS, Poland GA. Genetic polymorphisms associated with rubella virus-specific cellular immunity following MMR vaccination. Hum Genet. 2014;133(11):1407-17. Epub 2014/08/08. doi: 10.1007/s00439-014-1471-z. PubMed PMID: 25098560; PubMed Central PMCID: PMCPMC4249927.
36. He XX, Chang Y, Jiang HJ, Tang F, Meng FY, Xie QH, et al. Persistent effect of IFNAR-1 genetic polymorphism on the long-term pathogenesis of chronic HBV infection. Viral Immunol. 2010;23(3):251-7. Epub 2010/06/23. doi: 10.1089/vim.2009.0102. PubMed PMID: 20565290.
37. Zhou J, Smith DK, Lu L, Poon VK, Ng F, Chen DQ, et al. A non-synonymous single nucleotide polymorphism in IFNAR1 affects susceptibility to chronic hepatitis B virus infection. J Viral Hepat. 2009;16(1):45-52. Epub 2008/09/03. doi: 10.1111/j.1365-2893.2008.01040.x. PubMed PMID: 18761606.
38. Zhou J, Lu L, Yuen MF, Lam TW, Chung CP, Lam CL, et al. Polymorphisms of type I interferon receptor 1 promoter and their effects on chronic hepatitis B virus infection. J Hepatol. 2007;46(2):198-205. Epub 2006/11/28. doi: S0168-8278(06)00511-3 [pii] 10.1016/j.jhep.2006.08.017. PubMed PMID: 17125879.

39. Khor CC, Vannberg FO, Chapman SJ, Walley A, Aucan C, Loke H, et al. Positive replication and linkage disequilibrium mapping of the chromosome 21q22.1 malaria susceptibility locus. Genes Immun. 2007;8(7):570-6. Epub 2007/08/19. doi: 6364417 [pii] 10.1038/sj.gene.6364417. PubMed PMID: 17703179.

40. Aucan C, Walley AJ, Hennig BJ, Fitness J, Frodsham A, Zhang L, et al. Interferon-alpha receptor-1 (IFNAR1) variants are associated with protection against cerebral malaria in the Gambia. Genes Immun. 2003;4(4):275-82. Epub 2003/05/23. doi: 10.1038/sj.gene.6363962 6363962 [pii]. PubMed PMID: 12761564.

41. Kanchan K, Jha P, Pati SS, Mohanty S, Mishra SK, Sharma SK, et al. Interferon-gamma (IFNG) microsatellite repeat and single nucleotide polymorphism haplotypes of IFN-alpha receptor (IFNAR1) associated with enhanced malaria susceptibility in Indian populations. Infect Genet Evol. 2015;29:6-14. Epub 2014/12/03. doi: 10.1016/j.meegid.2014.10.030. PubMed PMID: 25445652.
42. Diop G, Hirtzig T, Do H, Coulonges C, Vasilescu A, Labib T, et al. Exhaustive genotyping of the interferon alpha receptor 1 (IFNAR1) gene and association of an IFNAR1 protein variant with AIDS progression or susceptibility to HIV-1 infection in a French AIDS cohort. Biomed Pharmacother. 2006;60(9):569-77. Epub 2006/10/10. doi: S0753-3322(06)00252-6 [pii] 10.1016/j.biopha.2006.08.002. PubMed PMID: 17027223.

43. Leyva L, Fernandez O, Fedetz M, Blanco E, Fernandez VE, Oliver B, et al. IFNAR1 and IFNAR2 polymorphisms confer susceptibility to multiple sclerosis but not to interferon-beta treatment response. J Neuroimmunol. 2005;163(1-2):165-71. Epub 2005/05/12. doi: S0165-5728(05)00079-2 [pii] 10.1016/j.jneuroim.2005.02.010. PubMed PMID: 15885318.

44. Traks T, Karelson M, Reimann E, Ratsep R, Silm H, Vasar E, et al. Association analysis of class II cytokine and receptor genes in vitiligo patients. Hum Immunol. 2016;77(5):375-81. Epub 2015/10/03. doi: 10.1016/j.humimm.2015.09.050. PubMed PMID: 26429320.

45. Schabath MB, Giuliano AR, Thompson ZJ, Amankwah EK, Gray JE, Fenstermacher DA, et al. TNFRSF10B polymorphisms and haplotypes associated with increased risk of death in non-small cell lung cancer. Carcinogenesis. 2013;34(11):2525-30. Epub 2013/07/11. doi: 10.1093/carcin/bgt244. PubMed PMID: 23839018; PubMed Central PMCID: PMCPMC3810840.
46. Reyes-Gibby CC, Spitz MR, Yennurajalingam S, Swartz M, Gu J, Wu X, et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. Cancer Epidemiol Biomarkers Prev. 2009;18(10):2636-42. Epub 2009/09/24. doi: 10.1158/1055-9965.EPI-09-0426. PubMed PMID: 19773451; PubMed Central PMCID: PMCPMC2759856.
47. Roisman LC, Jaitin DA, Baker DP, Schreiber G. Mutational analysis of the IFNAR1 binding site on IFNalpha2 reveals the architecture of a weak ligand-receptor binding-site. J Mol Biol. 2005;353(2):271-81. Epub 2005/09/21. doi: S0022-2836(05)00979-4 [pii] 10.1016/j.jmb.2005.08.042. PubMed PMID: 16171819.

48. Thomas C, Moraga I, Levin D, Krutzik PO, Podoplelova Y, Trejo A, et al. Structural Linkage between Ligand Discrimination and Receptor Activation by Type I Interferons. Cell. 2011;146(4):621-32. Epub 2011/08/23. doi: S0092-8674(11)00762-8 [pii] 10.1016/j.cell.2011.06.048. PubMed PMID: 21854986.

49. Hernandez N, Bucciol G, Moens L, Le Pen J, Shahrooei M, Goudouris E, et al. Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. J Exp Med. 2019. Epub 2019/07/05. doi: 10.1084/jem.20182295. PubMed PMID: 31270247.
50. Zhang G, deWeerd NA, Stifter SA, Liu L, Zhou B, Wang W, et al. A proline deletion in IFNAR1 impairs IFN-signaling and underlies increased resistance to tuberculosis in humans. Nature communications. 2018;9(1):85. Epub 2018/01/10. doi: 10.1038/s41467-017-02611-z. PubMed PMID: 29311663; PubMed Central PMCID: PMCPMC5758831.
51. George RA, Heringa J. An analysis of protein domain linkers: their classification and role in protein folding. Protein Eng. 2002;15(11):871-9. PubMed PMID: 12538906.
52. Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature. 2010;466(7309):973-7. Epub 2010/08/21. doi: 10.1038/nature09247. PubMed PMID: 20725040; PubMed Central PMCID: PMCPMC3492754.
53. Teles RM, Graeber TG, Krutzik SR, Montoya D, Schenk M, Lee DJ, et al. Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. Science. 2013;339(6126):1448-53. doi: 10.1126/science.1233665. PubMed PMID: 23449998; PubMed Central PMCID: PMC3653587.
54. Stifter SA, Feng CG. Interfering with immunity: detrimental role of type I IFNs during infection. J Immunol. 2015;194(6):2455-65. doi: 10.4049/jimmunol.1402794. PubMed PMID: 25747907.
55. Won S, Eidenschenk C, Arnold CN, Siggs OM, Sun L, Brandl K, et al. Increased susceptibility to DNA virus infection in mice with a GCN2 mutation. J Virol. 2012;86(3):1802-8. doi: 10.1128/JVI.05660-11. PubMed PMID: 22114338; PubMed Central PMCID: PMC3264364.
56. Schimmel PR, Flory PJ. Conformational energies and configurational statistics of copolypeptides containing L-proline. J Mol Biol. 1968;34(1):105-20. Epub 1968/05/28. doi: 0022-2836(68)90237-4 [pii]. PubMed PMID: 5760450.
57. MacArthur MW, Thornton JM. Influence of proline residues on protein conformation. J Mol Biol. 1991;218(2):397-412. Epub 1991/03/20. doi: 0022-2836(91)90721-H [pii]. PubMed PMID: 2010917.
58. Ho BK, Brasseur R. The Ramachandran plots of glycine and pre-proline. BMC Struct Biol. 2005;5:14. Epub 2005/08/18. doi: 1472-6807-5-14 [pii] 10.1186/1472-6807-5-14. PubMed PMID: 16105172.

59. Berg JM, Tymoczko JL, Stryer L. Section 3.6, The Amino Acid Sequence of a Protein Determines its Three-Dimensional Structure. In: Freeman WH, editor. Biochemistry 5th edition. New York2002.
60. Strunk JJ, Gregor I, Becker Y, Li Z, Gavutis M, Jaks E, et al. Ligand binding induces a conformational change in ifnar1 that is propagated to its membrane-proximal domain. J Mol Biol. 2008;377(3):725-39. Epub 2008/02/26. doi: S0022-2836(08)00035-1 [pii] 10.1016/j.jmb.2008.01.017. PubMed PMID: 18294654.

61. Hoyos-Bachiloglu R, Chou J, Sodroski CN, Beano A, Bainter W, Angelova M, et al. A digenic human immunodeficiency characterized by IFNAR1 and IFNGR2 mutations. J Clin Invest. 2017;127(12):4415-20. Epub 2017/11/07. doi: 10.1172/JCI93486. PubMed PMID: 29106381; PubMed Central PMCID: PMCPMC5707159.
62. Welzel TM, Morgan TR, Bonkovsky HL, Naishadham D, Pfeiffer RM, Wright EC, et al. Variants in interferon-alpha pathway genes and response to pegylated interferon-Alpha2a plus ribavirin for treatment of chronic hepatitis C virus infection in the hepatitis C antiviral long-term treatment against cirrhosis trial. Hepatology. 2009;49(6):1847-58. Epub 2009/05/13. doi: 10.1002/hep.22877. PubMed PMID: 19434718; PubMed Central PMCID: PMCPMC2692559.
63. Ma N, Zhang X, Yang L, Zhou J, Liu W, Gao X, et al. Role of Functional IFNL4, IFNLR1, IFNA, IFNAR2 Polymorphisms in Hepatitis B virus-related liver disease in Han Chinese population. J Viral Hepat. 2018;25(3):306-13. Epub 2017/10/29. doi: 10.1111/jvh.12817. PubMed PMID: 29080269.
64. Hennig BJ, Hall AJ. Host genetic factors in hepatitis B infection, liver cancer and vaccination response: a review with a focus on Africa. Sci Total Environ. 2012;423:202-9. Epub 2010/10/26. doi: 10.1016/j.scitotenv.2010.09.036. PubMed PMID: 20970823.
65. von Heijne G. Signal sequences. The limits of variation. J Mol Biol. 1985;184(1):99-105. Epub 1985/07/05. doi: 10.1016/0022-2836(85)90046-4. PubMed PMID: 4032478.
66. Palazzo AF, Springer M, Shibata Y, Lee CS, Dias AP, Rapoport TA. The signal sequence coding region promotes nuclear export of mRNA. PLoS Biol. 2007;5(12):e322. Epub 2007/12/07. doi: 10.1371/journal.pbio.0050322. PubMed PMID: 18052610; PubMed Central PMCID: PMCPMC2100149.
67. Pinarbasi ES, Karamyshev AL, Tikhonova EB, Wu IH, Hudson H, Thomas PJ. Pathogenic Signal Sequence Mutations in Progranulin Disrupt SRP Interactions Required for mRNA Stability. Cell Rep. 2018;23(10):2844-51. Epub 2018/06/07. doi: 10.1016/j.celrep.2018.05.003. PubMed PMID: 29874572; PubMed Central PMCID: PMCPMC6097231.
68. Duncan CJ, Mohamad SM, Young DF, Skelton AJ, Leahy TR, Munday DC, et al. Human IFNAR2 deficiency: Lessons for antiviral immunity. Sci Transl Med. 2015;7(307):307ra154. doi: 10.1126/scitranslmed.aac4227. PubMed PMID: 26424569.
69. Urin V, Shemesh M, Schreiber G. CRISPR/Cas9-based Knockout Strategy Elucidates Components Essential for Type 1 Interferon Signaling in Human HeLa Cells. J Mol Biol. 2019;431(17):3324-38. Epub 2019/06/18. doi: 10.1016/j.jmb.2019.06.007. PubMed PMID: 31207241.
70. Muller U, Steinhoff U, Reis LF, Hemmi S, Pavlovic J, Zinkernagel RM, et al. Functional role of type I and type II interferons in antiviral defense. Science. 1994;264(5167):1918-21. PubMed PMID: 8009221.
71. Durbin JE, Hackenmiller R, Simon MC, Levy DE. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. Cell. 1996;84(3):443-50. PubMed PMID: 8608598.
72. Park C, Li S, Cha E, Schindler C. Immune response in Stat2 knockout mice. Immunity. 2000;13(6):795-804. Epub 2001/02/13. PubMed PMID: 11163195.
73. Carrero JA. Confounding roles for type I interferons during bacterial and viral pathogenesis. Int Immunol. 2013;25(12):663-9. doi: 10.1093/intimm/dxt050. PubMed PMID: 24158954; PubMed Central PMCID: PMC3839063.

74. Bauer EM, Zheng H, Lotze MT, Bauer PM. Recombinant human interferon alpha 2b prevents and reverses experimental pulmonary hypertension. PLoS One. 2014;9(5):e96720. Epub 2014/05/20. doi: 10.1371/journal.pone.0096720. PubMed PMID: 24837600; PubMed Central PMCID: PMCPMC4024039.
75. Prinz M, Schmidt H, Mildner A, Knobeloch KP, Hanisch UK, Raasch J, et al. Distinct and nonredundant in vivo functions of IFNAR on myeloid cells limit autoimmunity in the central nervous system. Immunity. 2008;28(5):675-86. Epub 2008/04/22. doi: S1074-7613(08)00126-X [pii] 10.1016/j.immuni.2008.03.011. PubMed PMID: 18424188.

76. Tschurtschenthaler M, Wang J, Fricke C, Fritz TM, Niederreiter L, Adolph TE, et al. Type I interferon signalling in the intestinal epithelium affects Paneth cells, microbial ecology and epithelial regeneration. Gut. 2014;63(12):1921-31. Epub 2014/02/22. doi: 10.1136/gutjnl-2013-305863. PubMed PMID: 24555997.
77. Auerbuch V, Brockstedt DG, Meyer-Morse N, O'Riordan M, Portnoy DA. Mice lacking the type I interferon receptor are resistant to Listeria monocytogenes. J Exp Med. 2004;200(4):527-33. doi: 10.1084/jem.20040976. PubMed PMID: 15302899; PubMed Central PMCID: PMC2211930.
78. Robinson N, McComb S, Mulligan R, Dudani R, Krishnan L, Sad S. Type I interferon induces necroptosis in macrophages during infection with Salmonella enterica serovar Typhimurium. Nat Immunol. 2012;13(10):954-62. Epub 2012/08/28. doi: 10.1038/ni.2397. PubMed PMID: 22922364; PubMed Central PMCID: PMCPMC4005791.
79. Dorhoi A, Yeremeev V, Nouailles G, Weiner J, 3rd, Jorg S, Heinemann E, et al. Type I IFN signaling triggers immunopathology in tuberculosis-susceptible mice by modulating lung phagocyte dynamics. Eur J Immunol. 2014;44(8):2380-93. doi: 10.1002/eji.201344219. PubMed PMID: 24782112.
80. Sebina I, James KR, Soon MS, Fogg LG, Best SE, Labastida Rivera F, et al. IFNAR1-Signalling Obstructs ICOS-mediated Humoral Immunity during Non-lethal Blood-Stage Plasmodium Infection. PLoS Pathog. 2016;12(11):e1005999. Epub 2016/11/05. doi: 10.1371/journal.ppat.1005999. PubMed PMID: 27812214; PubMed Central PMCID: PMCPMC5094753.
81. Decker T, Muller M, Stockinger S. The yin and yang of type I interferon activity in bacterial infection. Nat Rev Immunol. 2005;5(9):675-87. PubMed PMID: 16110316.
82. Szczerba BM, Rybakowska PD, Dey P, Payerhin KM, Peck AB, Bagavant H, et al. Type I interferon receptor deficiency prevents murine Sjogren's syndrome. Journal of dental research. 2013;92(5):444-9. doi: 10.1177/0022034513483315. PubMed PMID: 23533183; PubMed Central PMCID: PMC3627507.
83. Stokes JA, Cheung J, Eddinger K, Corr M, Yaksh TL. Toll-like receptor signaling adapter proteins govern spread of neuropathic pain and recovery following nerve injury in male mice. J Neuroinflammation. 2013;10:148. Epub 2013/12/11. doi: 10.1186/1742-2094-10-148. PubMed PMID: 24321498; PubMed Central PMCID: PMCPMC3896749.
84. Nacionales DC, Kelly-Scumpia KM, Lee PY, Weinstein JS, Lyons R, Sobel E, et al. Deficiency of the type I interferon receptor protects mice from experimental lupus. Arthritis Rheum. 2007;56(11):3770-83. Epub 2007/10/31. doi: 10.1002/art.23023. PubMed PMID: 17968932.
85. Baccala R, Gonzalez-Quintial R, Schreiber RD, Lawson BR, Kono DH, Theofilopoulos AN. Anti-IFN-alpha/beta receptor antibody treatment ameliorates disease in lupus-predisposed mice. J Immunol. 2012;189(12):5976-84. doi: 10.4049/jimmunol.1201477. PubMed PMID: 23175700; PubMed Central PMCID: PMC3530925.
86. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis & rheumatology. 2017;69(2):376-86. Epub 2017/01/29. doi: 10.1002/art.39962. PubMed PMID: 28130918; PubMed Central PMCID: PMCPMC5299497.
87. Casey KA, Guo X, Smith MA, Wang S, Sinibaldi D, Sanjuan MA, et al. Type I interferon receptor blockade with anifrolumab corrects innate and adaptive immune perturbations of SLE.

Lupus Sci Med. 2018;5(1):e000286. Epub 2018/12/13. doi: 10.1136/lupus-2018-000286. PubMed PMID: 30538817; PubMed Central PMCID: PMCPMC6257383.
88. Riggs JM, Hanna RN, Rajan B, Zerrouki K, Karnell JL, Sagar D, et al. Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. Lupus Sci Med. 2018;5(1):e000261. Epub 2018/04/13. doi: 10.1136/lupus-2018-000261. PubMed PMID: 29644082; PubMed Central PMCID: PMCPMC5890856.
89. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 2020;382(3):211-21. Epub 2019/12/19. doi: 10.1056/NEJMoa1912196. PubMed PMID: 31851795.
90. Shepardson KM, Larson K, Johns LL, Stanek K, Cho H, Wellham J, et al. IFNAR2 Is Required for Anti-influenza Immunity and Alters Susceptibility to Post-influenza Bacterial Superinfections. Frontiers in immunology. 2018;9:2589. Epub 2018/11/27. doi: 10.3389/fimmu.2018.02589. PubMed PMID: 30473701; PubMed Central PMCID: PMCPMC6237881.
91. Novick D, Cohen B, Rubinstein M. Soluble interferon-alpha receptor molecules are present in body fluids. FEBS Lett. 1992;314(3):445-8. Epub 1992/12/21. PubMed PMID: 1468582.
92. Orpez-Zafra T, Pavia J, Hurtado-Guerrero I, Pinto-Medel MJ, Rodriguez Bada JL, Urbaneja P, et al. Decreased soluble IFN-beta receptor (sIFNAR2) in multiple sclerosis patients: A potential serum diagnostic biomarker. Mult Scler. 2017;23(7):937-45. Epub 2016/09/11. doi: 10.1177/1352458516667564. PubMed PMID: 27613121.
93. Thibault DL, Graham KL, Lee LY, Balboni I, Hertzog PJ, Utz PJ. Type I interferon receptor controls B-cell expression of nucleic acid-sensing Toll-like receptors and autoantibody production in a murine model of lupus. Arthritis Res Ther. 2009;11(4):R112. Epub 2009/07/25. doi: 10.1186/ar2771. PubMed PMID: 19624844; PubMed Central PMCID: PMCPMC2745794.
94. Plumb J, McQuaid S, Cross AK, Surr J, Haddock G, Bunning RA, et al. Upregulation of ADAM-17 expression in active lesions in multiple sclerosis. Mult Scler. 2006;12(4):375-85. Epub 2006/08/12. doi: 10.1191/135248506ms1276oa. PubMed PMID: 16900751.
95. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci. 2012;8(9):1237-47. Epub 2012/11/09. doi: 10.7150/ijbs.4989 ijbsv08p1237 [pii]. PubMed PMID: 23136552.

96. McKenna SD, Vergilis K, Arulanandam AR, Weiser WY, Nabioullin R, Tepper MA. Formation of human IFN-beta complex with the soluble type I interferon receptor IFNAR-2 leads to enhanced IFN stability, pharmacokinetics, and antitumor activity in xenografted SCID mice. J Interferon Cytokine Res. 2004;24(2):119-29. Epub 2004/02/26. doi: 10.1089/107999004322813363. PubMed PMID: 14980076.
97. Samarajiwa SA, Mangan NE, Hardy MP, Najdovska M, Dubach D, Braniff SJ, et al. Soluble IFN receptor potentiates in vivo type I IFN signaling and exacerbates TLR4-mediated septic shock. J Immunol. 2014;192(9):4425-35. Epub 2014/04/04. doi: 10.4049/jimmunol.1302388. PubMed PMID: 24696235.
98. Lamken P, Gavutis M, Peters I, Van der Heyden J, Uze G, Piehler J. Functional cartography of the ectodomain of the type I interferon receptor subunit ifnar1. J Mol Biol. 2005;350(3):476-88. PubMed PMID: 15946680.
99. de Weerd NA, Matthews AY, Pattie PR, Bourke NM, Lim SS, Vivian JP, et al. A hot spot on interferon alpha/beta receptor subunit 1 (IFNAR1) underpins its interaction with interferon-beta and dictates signaling. J Biol Chem. 2017;292(18):7554-65. Epub 2017/03/16. doi: 10.1074/jbc.M116.773788. PubMed PMID: 28289093; PubMed Central PMCID: PMCPMC5418053.
100. Urin V, Levin D, Sharma N, Harari D, Schreiber G. Fine Tuning of a Type 1 Interferon Antagonist. PLoS One. 2015;10(7):e0130797. Epub 2015/07/15. doi: 10.1371/journal.pone.0130797. PubMed PMID: 26158644; PubMed Central PMCID: PMCPMC4497658.
101. Askari JA, Buckley PA, Mould AP, Humphries MJ. Linking integrin conformation to function. J Cell Sci. 2009;122(Pt 2):165-70. Epub 2009/01/02. doi: 10.1242/jcs.018556. PubMed PMID: 19118208; PubMed Central PMCID: PMCPMC2714414.

102. Lee B, Sharron M, Blanpain C, Doranz BJ, Vakili J, Setoh P, et al. Epitope mapping of CCR5 reveals multiple conformational states and distinct but overlapping structures involved in chemokine and coreceptor function. J Biol Chem. 1999;274(14):9617-26. Epub 1999/03/27. doi: 10.1074/jbc.274.14.9617. PubMed PMID: 10092648.
103. Walker JL, Crock PA, Behncken SN, Rowlinson SW, Nicholson LM, Boulton TJ, et al. A novel mutation affecting the interdomain link region of the growth hormone receptor in a Vietnamese girl, and response to long-term treatment with recombinant human insulin-like growth factor-I and luteinizing hormone-releasing hormone analogue. J Clin Endocrinol Metab. 1998;83(7):2554-61. Epub 1998/07/14. doi: 10.1210/jcem.83.7.4954. PubMed PMID: 9661642.
104. Bauer F, Sticht H. A proline to glycine mutation in the Lck SH3-domain affects conformational sampling and increases ligand binding affinity. FEBS Lett. 2007;581(8):1555-60. Epub 2007/03/27. doi: 10.1016/j.febslet.2007.03.012. PubMed PMID: 17382937.
105. Kalie E, Jaitin DA, Podoplelova Y, Piehler J, Schreiber G. The stability of the ternary interferon-receptor complex rather than the affinity to the individual subunits dictates differential biological activities. J Biol Chem. 2008;283(47):32925-36. Epub 2008/09/20. doi: M806019200 [pii] 10.1074/jbc.M806019200. PubMed PMID: 18801736.

106. Li H, Sharma N, General IJ, Schreiber G, Bahar I. Dynamic Modulation of Binding Affinity as a Mechanism for Regulating Interferon Signaling. J Mol Biol. 2017;429(16):2571-89. Epub 2017/06/27. doi: 10.1016/j.jmb.2017.06.011. PubMed PMID: 28648616; PubMed Central PMCID: PMCPMC5545807.
107. Chuartzman SG, Nevo R, Waichman S, Shental D, Piehler J, Levy Y, et al. Binding of interferon reduces the force of unfolding for interferon receptor 1. PLoS One. 2017;12(4):e0175413. Epub 2017/04/14. doi: 10.1371/journal.pone.0175413. PubMed PMID: 28403186; PubMed Central PMCID: PMCPMC5389645.
108. Goldberg A, Geppert T, Schiopu E, Frech T, Hsu V, Simms RW, et al. Dose-escalation of human anti-interferon-alpha receptor monoclonal antibody MEDI-546 in subjects with systemic sclerosis: a phase 1, multicenter, open label study. Arthritis Res Ther. 2014;16(1):R57. doi: 10.1186/ar4492. PubMed PMID: 24559157; PubMed Central PMCID: PMC3978926.
109. Lichtman EI, Helfgott SM, Kriegel MA. Emerging therapies for systemic lupus erythematosus--focus on targeting interferon-alpha. Clin Immunol. 2012;143(3):210-21. doi: 10.1016/j.clim.2012.03.005. PubMed PMID: 22525889; PubMed Central PMCID: PMC3358492.
110. Peng L, Oganesyan V, Wu H, Dall'Acqua WF, Damschroder MM. Molecular basis for antagonistic activity of anifrolumab, an anti-interferon-alpha receptor 1 antibody. mAbs. 2015;7(2):428-39. doi: 10.1080/19420862.2015.1007810. PubMed PMID: 25606664; PubMed Central PMCID: PMC4622752.
111. Li Z, Strunk JJ, Lamken P, Piehler J, Walz T. The EM structure of a type I interferon-receptor complex reveals a novel mechanism for cytokine signaling. J Mol Biol. 2008;377(3):715-24. doi: 10.1016/j.jmb.2007.12.005. PubMed PMID: 18252254; PubMed Central PMCID: PMC2577817.
112. Chill JH, Nivasch R, Levy R, Albeck S, Schreiber G, Anglister J. The human interferon receptor: NMR-based modeling, mapping of the IFN-alpha 2 binding site, and observed ligand-induced tightening. Biochemistry. 2002;41(11):3575-85. PubMed PMID: 11888273.
113. Chuntharapai A, Gibbs V, Lu J, Ow A, Marsters S, Ashkenazi A, et al. Determination of residues involved in ligand binding and signal transmission in the human IFN-alpha receptor 2. J Immunol. 1999;163(2):766-73. PubMed PMID: 10395669.
114. Peleg-Shulman T, Roisman LC, Zupkovitz G, Schreiber G. Optimizing the binding affinity of a carrier protein: a case study on the interaction between soluble ifnar2 and interferon beta. J Biol Chem. 2004;279(17):18046-53. doi: 10.1074/jbc.M400033200. PubMed PMID: 14960565.
115. Piehler J, Thomas C, Garcia KC, Schreiber G. Structural and dynamic determinants of type I interferon receptor assembly and their functional interpretation. Immunol Rev. 2012;250(1):317-34. Epub 2012/10/11. doi: 10.1111/imr.12001. PubMed PMID: 23046138; PubMed Central PMCID: PMCPMC3986811.

116. Hertzog PJ, Williams BR. Fine tuning type I interferon responses. Cytokine Growth Factor Rev. 2013;24(3):217-25. doi: 10.1016/j.cytogfr.2013.04.002. PubMed PMID: 23711406.
117. Novick D, Cohen B, Rubinstein M. The human interferon alpha/beta receptor: characterization and molecular cloning. Cell. 1994;77(3):391-400. Epub 1994/05/06. doi: 0092-8674(94)90154-6 [pii]. PubMed PMID: 8181059.
118. Owczarek CM, Hwang SY, Holland KA, Gulluyan LM, Tavaria M, Weaver B, et al. Cloning and characterization of soluble and transmembrane isoforms of a novel component of the murine type I interferon receptor, IFNAR 2. J Biol Chem. 1997;272(38):23865-70. PubMed PMID: 9295335.
119. Novick D, Cohen B, Tal N, Rubinstein M. Soluble and membrane-anchored forms of the human IFN-alpha/beta receptor. Journal of leukocyte biology. 1995;57(5):712-8. Epub 1995/05/01. PubMed PMID: 7759950.
120. Ambrus JL, Ambrus JL, Jr., Chadha S, Novick D, Rubinstein M, Gopalakrishnan B, et al. Mechanism(S) of interferon inhibitory activity in blood from patients with AIDS and patients with lupus erythematosus with vasculitis. Res Commun Mol Pathol Pharmacol. 1997;96(3):255-65. Epub 1997/06/01. PubMed PMID: 9261885.
121. Mizukoshi E, Kaneko S, Kaji K, Terasaki S, Matsushita E, Muraguchi M, et al. Serum levels of soluble interferon Alfa/Beta receptor as an inhibitory factor of interferon in the patients with chronic hepatitis C. Hepatology. 1999;30(5):1325-31. Epub 1999/10/26. doi: 10.1002/hep.510300516. PubMed PMID: 10534358.
122. Iseda T, Yokoyama M, Kanayana H, Oomoto Y, Kagawa S. [An investigation of serum soluble interferon receptor levels in patients with renal cell carcinoma]. Nihon Hinyokika Gakkai Zasshi. 2000;91(5):514-9. Epub 2000/06/15. PubMed PMID: 10853333.
123. Kanayama H, Takahashi M, Nishitani M, Kagawa S. [Analysis of serum soluble interferon alpha/beta receptor levels in patients with urological diseases]. Nihon Hinyokika Gakkai Zasshi. 2000;91(9):630-6. Epub 2000/11/09. PubMed PMID: 11068427.
124. Ambrus JL, Sr., Dembinski W, Ambrus JL, Jr., Sykes DE, Akhter S, Kulaylat MN, et al. Free interferon-alpha/beta receptors in the circulation of patients with adenocarcinoma. Cancer. 2003;98(12):2730-3. Epub 2003/12/12. doi: 10.1002/cncr.11843. PubMed PMID: 14669296.
125. Orpez-Zafra T, Pavia J, Pinto-Medel MJ, Hurtado-Guerrero I, Rodriguez-Bada JL, Martin Montanez E, et al. Development and validation of an ELISA for quantification of soluble IFN-beta receptor: assessment in multiple sclerosis. Bioanalysis. 2015;7(22):2869-80. Epub 2015/11/17. doi: 10.4155/bio.15.208. PubMed PMID: 26571364.
126. Suardiaz M, Clemente D, Marin-Banasco C, Orpez T, Hurtado-Guerrero I, Pavia J, et al. Recombinant soluble IFN receptor (sIFNAR2) exhibits intrinsic therapeutic efficacy in a murine model of Multiple Sclerosis. Neuropharmacology. 2016;110(Pt A):480-92. Epub 2016/07/28. doi: 10.1016/j.neuropharm.2016.07.026. PubMed PMID: 27452720.
127. Song le H, Xuan NT, Toan NL, Binh VQ, Boldt AB, Kremsner PG, et al. Association of two variants of the interferon-alpha receptor-1 gene with the presentation of hepatitis B virus infection. Eur Cytokine Netw. 2008;19(4):204-10. Epub 2008/12/24. doi: ecn.2008.0137 [pii] 10.1684/ecn.2008.0137. PubMed PMID: 19103527.
128. Cajean-Feroldi C, Nosal F, Nardeux PC, Gallet X, Guymarho J, Baychelier F, et al. Identification of residues of the IFNAR1 chain of the type I human interferon receptor critical for ligand binding and biological activity. Biochemistry. 2004;43(39):12498-512. PubMed PMID: 15449939.

Figure Legends

Figure 1A

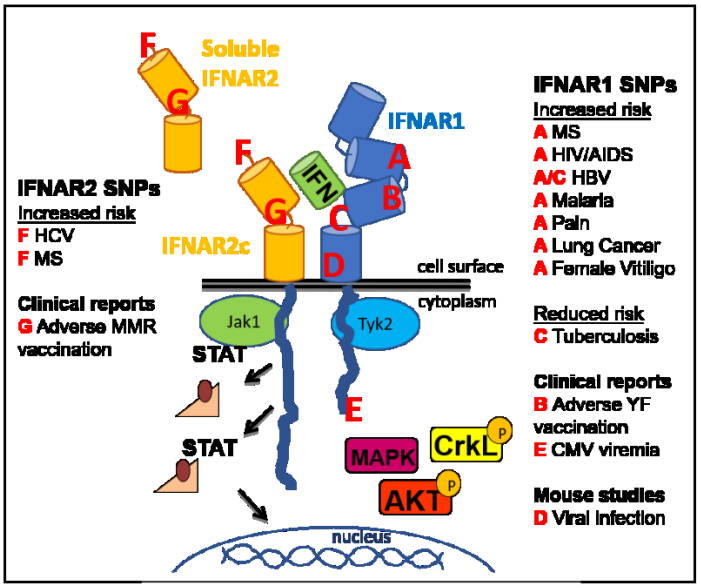


Figure 1B

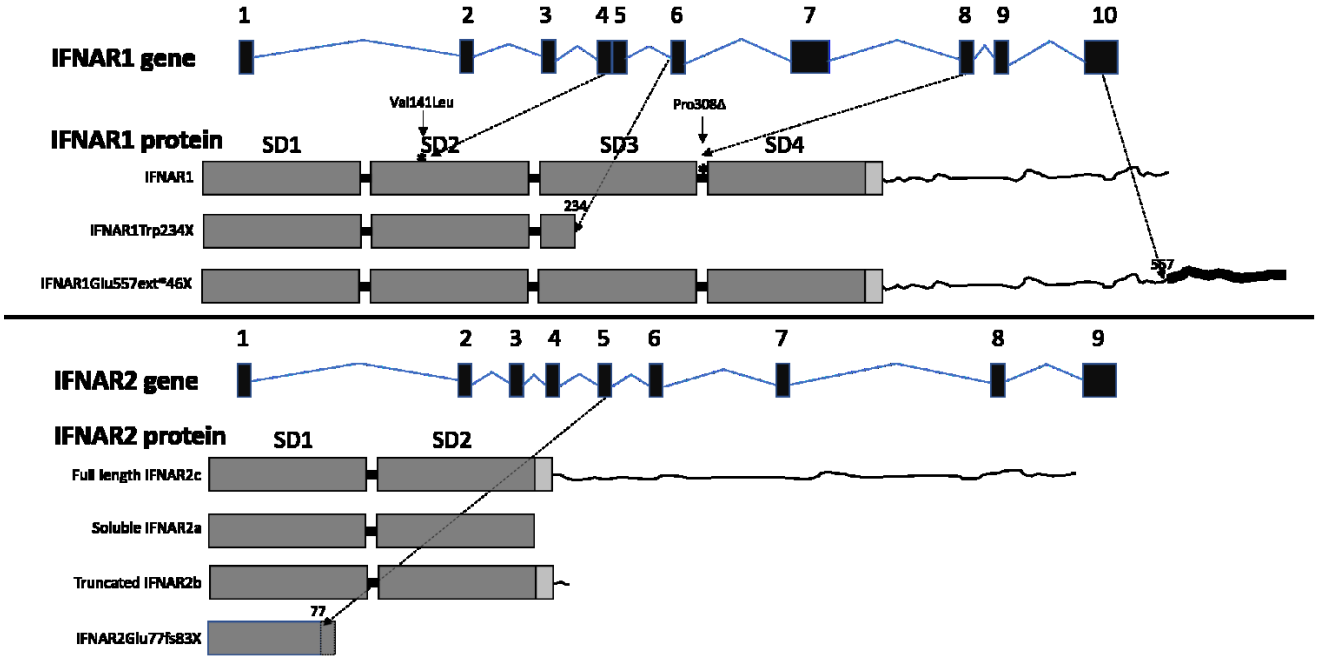


Fig 1. SNPs in IFNAR1 and IFNAR2 with clinical associations. (A) Nonsynonymous SNPs identified in IFNAR1 (blue) and IFNAR2 (orange) and their clinical associations. Indicated on IFNAR1 and IFNAR2 are the approximate locations of SNPs discussed: **A**, SNP

rs2257167, IFNAR1Val141Leu; **B**, SNP inducing IFNAR1Val225fs228X and IFNAR1Trp234X; **C**, SNP rs72552343, IFNAR1Pro308Δ; **D**, ENU SNP *macro-1*, IFNAR1Thr315Pro; **E**, SNP inducing IFNAR1Glu557ext*46X; **F**, SNP rs2229201, IFNAR2Phe8Ser and SNP rs1051393, IFNAR2Phe10Val; **G,** SNP rs775739391, IFNAR2Glu77fs83X. Clinical associations include: MS, Multiple Sclerosis; HIV/AIDS, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; HBV, Hepatitis B Virus; YF, Yellow Fever; HCV, Hepatitis C Virus; MMR, Measles Mumps Rubella. Approximate locations of mutated residues are shown on the receptors in red, labelled A-G. **(B)** Diagrammatic representation of the genes encoding IFNAR1 (top section) and IFNAR2 (bottom section) showing (top row) approximate exon (boxes)-intron (lines) boundaries of the genes, (second row) the domain structure of the normal encoded proteins, the exon location of SNPs discussed throughout this review (arrows) and a comparison of the mutated receptor structure compared to the normal receptor (comparisons of rows 2, 3 and 4). Asterisks denote the approximate locations of nonsynonymous SNPs in IFNAR1 that produce proteins of similar length to the normal IFNAR1 receptor. Subdomains (SD) of receptors are shown as black rectangles and identified as SD1-4. The transmembrane domains are shown as grey rectangles. Intracellular domains are shown as unstructured lines. Information on exon-intron boundaries and exon numbers was gained from http://asia.ensembl.org/index.html.

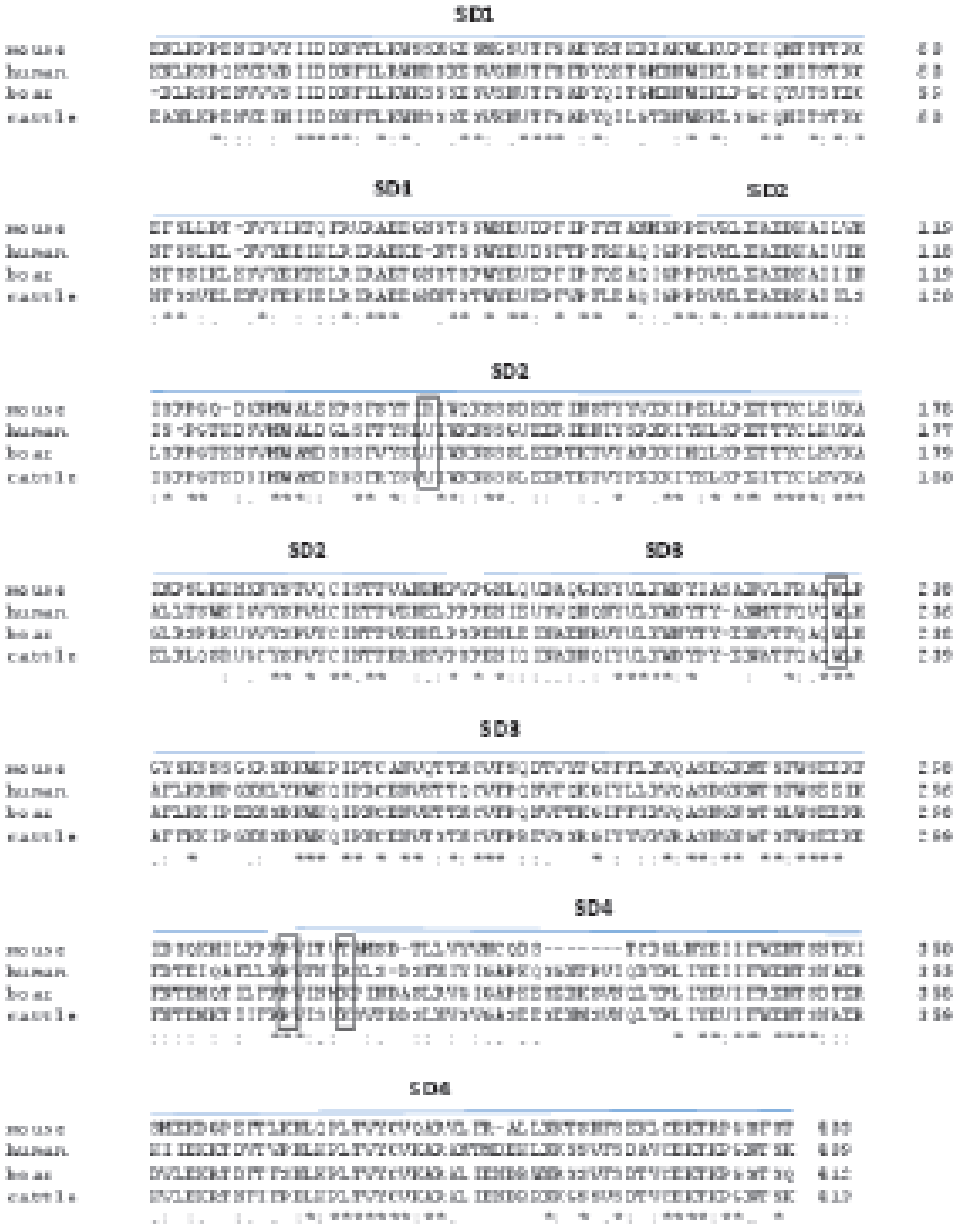


Fig. 2. **Locations of SNPs on IFNAR sequences.** (A) genome map of in exon-intron boundaries and the translated normal and mutated proteins for IFNAR1 and IFNAR2. (B) Alignment of sequences of mouse, human, boar and cattle IFNAR1-ECD (generated using Clustal Omega). Subdomains (SD) are indicated. Bold boxes indicate the location of disease-associated non-synonymous SNP mutations (see text). GenBank accession numbers: mouse AAH43935.1; human NP_000620.2; boar NP_998937.1; cattle NP_776977.1. (C) Alignment

of IFNAR2-ECDs (generated using Clustal Omega) from mouse and human. Subdomains (SD) are indicated. Bold boxes indicate the location of disease-associated non-synonymous SNP mutations (see text). GenBank accession numbers: mouse AAC53351.1; human AAH02793.1; boar NP_001191704.2; sheep NP_001009342.1.

Figure 3A

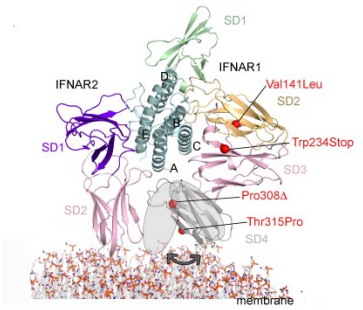


Figure 3C

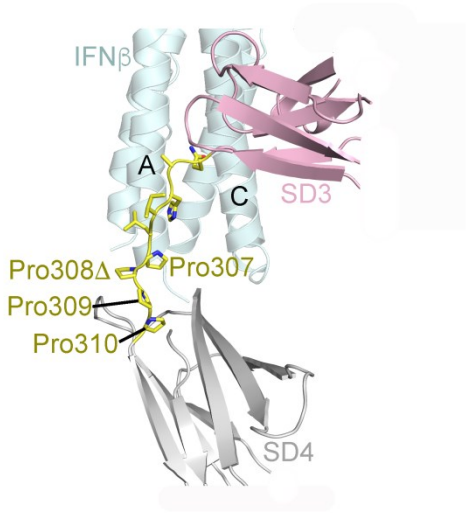
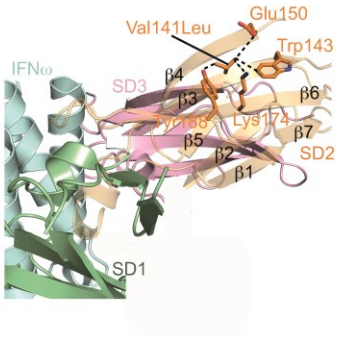


Figure 3B



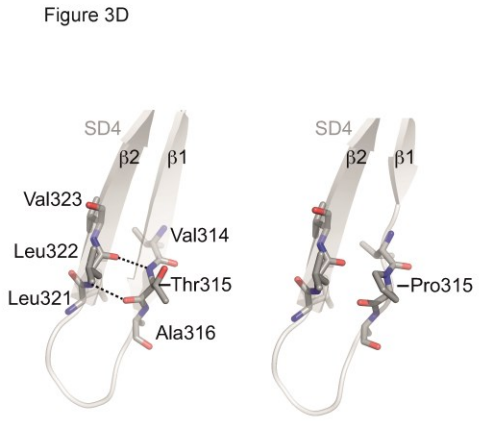
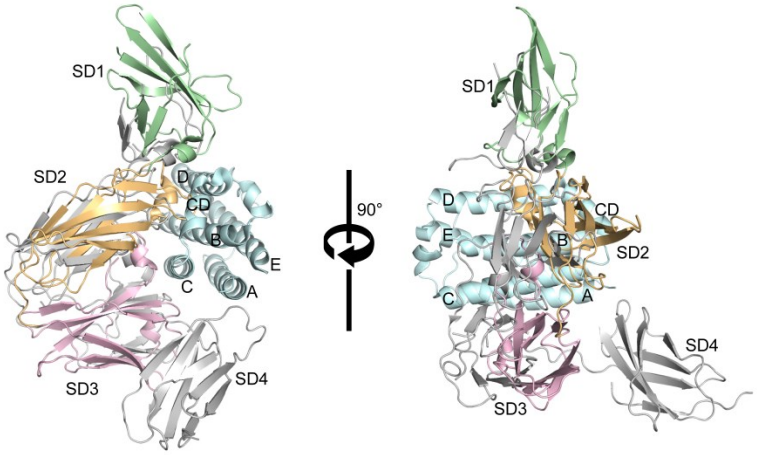


Fig. 3. Model of the functional IFNAR1/IFNAR2/IFN complex on the cell surface showing locations of SNPs on the receptors. (A) The complex was modelled as a hybrid of the human IFNAR1-SD1-3/IFNAR2/IFNω with the murine IFNAR1-SD4 (coloured by subdomain (SD)). Murine IFNAR1-SD4 is coloured grey and is rotated by ~16° relative to the human IFNAR1, shown by the grey ovals superimposed on SD4. The orthogonal displacement of the IFNAR1-SD4 from SD1-3 aligns this domain with IFNAR2-SD2 and increases the proximity of their transmembrane domains (membrane is depicted as sticks). The highly flexible linker between IFNAR1-SD3 and SD4 and the paucity of contacts between SD4 and IFN enables a high degree of movement for SD4 that we propose is necessary for functional signalling (the arrow indicates a hypothetical movement of IFNAR1-SD4 upon ternary complex formation). The labels for SDs of IFNAR1 (SD1-4) and IFNAR2 (SD1-2) are colour coded as per the SD on these receptors. The helical IFN is positioned

between IFNAR2 (left of the IFN) and IFNAR1 (right of the IFN) is shown in cyan with helices labelled as A-E. The approximate locations of SNPs on IFNAR1 and IFNAR2 are indicated by red spheres and labelled according to the nomenclature given in the text – on IFNAR1 are Val141Leu (B), ProΔ308 (C), Thr315Pro (D).

Figure 4A



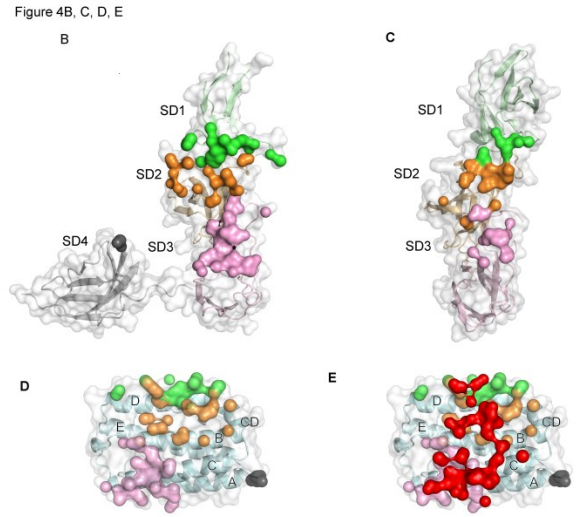


Fig. 4 Overall structure and footprints of IFNAR1 bound to IFN. (A) Two orthogonal views of the complexes between IFNAR1 and IFN are shown. Human IFNAR1 is coloured by subdomain (SD1=green, SD2=orange, SD3=pink). Murine IFNAR1 (overlaid on human IFNAR1) is coloured grey and rotated by ~16° relative to the human IFNAR1. Differences between the human and murine receptors are most noticeable on IFNAR1SD2-4. The orthogonal displacement of IFNAR1-SD4 from IFNAR1SD1-3 is most noticeable in the view on the right. **(B)** Contact atoms of IFNβ on murine IFNAR1 mapped to the surface of the receptor. Atoms are coloured according to the subdomain of IFNAR1 to which they bind (SD1=green, SD2=orange, SD3=pink, SD4=grey). **(C)** Contact atoms of IFNω on human IFNAR1 mapped to the surface of the receptor. Atoms are coloured by subdomain of IFNAR1 to which they bind (SD1=green, SD2=orange, SD3=pink). (D) Contacted atoms mapped to the surface of murine IFNβ (coloured by IFNAR1 subdomain as in (B)). (E) Contacted atoms mapped to the surface of human IFNω (red) overlaid on the footprint of

murine IFNAR1 on IFNβ (coloured by IFNAR1 subdomain as in (B)). The comparison of footprints of IFNAR1 on IFNω and IFNβ shown in (E) highlights regions of overlap or "anchor points" for SD1-3 as well as regions where recognition diverges.

Figure 5A, B

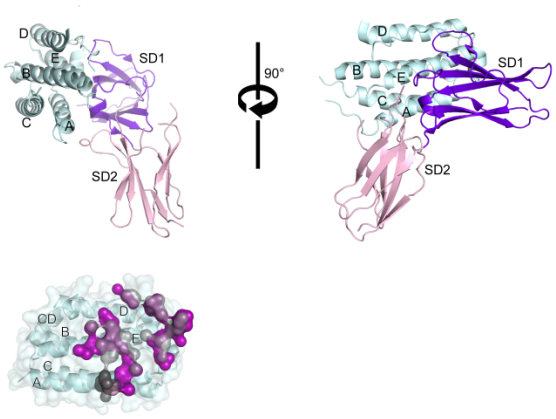


Fig 5. Structural overview of IFNAR2 in complex with IFN. (A) Two orthogonal views of the complexes between IFNAR2 and IFN. Human IFNAR2 is coloured by subdomain (SD1=purple, SD2=pink). (C) Footprint of IFNAR2 on IFNα and IFNω. The footprint on IFNα is coloured by IFNAR2 subdomain as in (A). **(B)** The footprint on IFNω is coloured by IFNAR2 subdomain (SD1=light grey, SD2=dark grey). The overlay of the footprints highlights "hotspots" of conservation on the AB loop and E helix as well points of divergence on the A and E helices. Notably, SD1 dominates the binding interface with SD2 contributing very little surface area.

Table 1: Disease-associated SNPs that result in substitution or deletion of amino acids on the human IFNARs; these SNPs are associated with altered disease susceptibility or resistance.

Recepto	SNP ID	AA change[1]	Condition[2]	Phenotype[3]	Ref
IFNAR1	rs2257167	Val141Leu	Multiple sclerosis	Increased risk	(43)
			Cerebral malaria	Increased risk	(40)
			HIV/AIDS	Increased risk of progression	(42)
			HBV	Increased risk chronic nfection	(37)
			HBV & HCV	HBV-ACLF risk	(36)
			Lung Cancer	Increased risk/pain	(45, 46)
			Female Vitiligo	Increased risk	(44)
	Unassigned	Val225fs228X	Measles/YEL-AVD	Adverse reaction to /accination	(49)
	Unassigned	Trp234X	Yellow Fever	Adverse reaction to /accination	(49, 50)
	rs72552343	Pro308Δ	HBV	Increased susceptibility	(50, 127)
			Tuberculosis	Reduced risk	(50)
	Unassigned	Glu557ext*46	HLH, CMV	Increased risk	(61)

		X	viremia		
IFNAR2	rs1051393	Phe10Val	HCV	Increased risk	(49, 63)
			Persistent HCV	Increased risk	(63, 64)
			Multiple sclerosis	Increased risk	(43, 64)
	rs2229201	Phe8Ser	HCV	More likely to have had an SVR	(43, 62)
	rs775739391	Glu77fs83X	Measles	Adverse reaction to vaccination	(68)

[1] All amino acid residues are numbered according to its position in the mature IFNAR protein. fs, frameshift; stop, stop codon; del, deletion; X, premature stop codon; ext*, extension of protein by number of residues indicated.

[2] HIV/AIDS, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; HBV, Hepatitis B Virus; HCV, Hepatitis C virus; YEL-AVD, Yellow fever vaccine-associated viscerotropic disease; MMR, Measles- Mumps-Rubella; HLH, hemophagocytic lymphohistiocytosis; CMV, cytomegalovirus.

[3] HBV-ACLF, Acute-on-Chronic Liver Failure in HBV; SVR, Sustained virologic response,

Table 2: Residues identified in the IFNAR-IFN interface by mutational studies and protein crystallography.

Receptor	Ligand	'Hot-spot' residues	Minor ligand binding residues	Ref
IFNAR1	hIFNα2-YNS	Tyr70, Phe238	Phe96, Leu132, Glu133, Leu134, Ser136, Tyr157, Asn242	(48, 128)
	mIFNβ	Tyr70, Tyr98, Tyr240, Tyr274	Asp66, Thr67, Asn68, Phe97, Asn128, Leu132, Glu133, Lys134, Ser182, Leu183, Lys184, Pro238, Gly239, Ser243, Ser244, Ser245, Thr275, Thr277, Asp300, Gln302, Leu335	(21)
	hIFNω	Tyr70, Phe238	Asn68, Fhe96, Leu131, Asp132, Leu134, Thr181, Ser182, His236, Phe238, Asn242	(48)
IFNAR2	hIFNα2-YNS	Met46	Thr44, Ile45, Ser47, Glu50, Leu52, His76, Glu77, Val80, Trp100, Ile103	(48)
	hIFNβ		His76, Asn98, Trp100	(114)
	hIFNω		Thr44, Ile45, Met46, Glu50, Val80, Trp100, Ile103	(48)