The Interferons

Characterization and Application

Edited by Anthony Meager

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Preface

The Interferon field has its origins nearly 50 years ago with the discovery of an antiviral factor produced by virally infected chick cells. This factor, designated "The Interferon", provided the first evidence that antiviral defence mechanisms could be triggered by secreted cellular factors. Since interferon (IFN) was found to protect against many viruses, scientific interest was high. A research dynasty was literally founded then that has actively pursued the characterization and potential clinical applications of IFN. Initially, the field was sustained by dedicated pioneering scientists trying to understand what IFN was and how it worked. At the moment when their research was beginning to pay off with the purification of IFNs to homogeneity and increasing knowledge of their biological activities, the field was catalysed by the advent of recombinant DNA technology. The Pharmaceutical Industry too was drawn in by the "promise" of IFN's broad therapeutic activity against a range of tumours and viruses. Although the clinical success of IFNs proved to be much more limited than hoped for, the research that was generated in those heady times gave a tremendous boost to our understanding of the molecular structure of IFN' genes and proteins, their cellular receptors, their mechanism of action and their biological activities, both *in vitro* and *in vivo*. Despite the sombre assessment of the clinical worth of IFNs two decades ago, they have come back as strong market leaders for the treatment of chronic hepatitis C virus infection (IFN-alpha) and multiple sclerosis (IFN-beta). Research studies within the IFN field from then on have proved invaluable to the elucidation of IFN' induction and connected intracellular signalling pathways, cellular defence mechanisms, and the evasion mechanisms of viruses and tumour cells to IFNs.

The Interferons: Characterization and Application covers many aspects of our current knowledge of IFNs. This includes the structure and functions of all known IFN types, evolution and structure of their genes, their receptors and signalling pathways, their induction and biological activities and mechanisms whereby viruses evade their antiviral actions. In addition, coverage of the clinical applications of type I and II IFNs, together with methodologies to measure biological activities of IFNs and the antibodies that may develop against them as a consequence of IFN therapies, is provided. I believe there is a serious need for this publication, even in view of the vast amount of information available in the scientific literature and on the World Wide Web. I feel that there is no substitute to an up-to-date monograph

on the IFN field that embraces an integrated and well-selected approach to the subject. It is my hope this will provide a comprehensive foundation to the professional scientific and medicinal research community, especially newcomers to the field, and will promote further advances in the field.

I gratefully acknowledge the authors for their time, motivation and dedication in preparing their contributions, without which this book would not have been possible. I also thank Andreas Sendtko and his colleagues at Wiley-VCH for outstanding support throughout the planning and preparation of this book.

Potters Bar, October 2005 *Anthony Meager*

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Color Plates

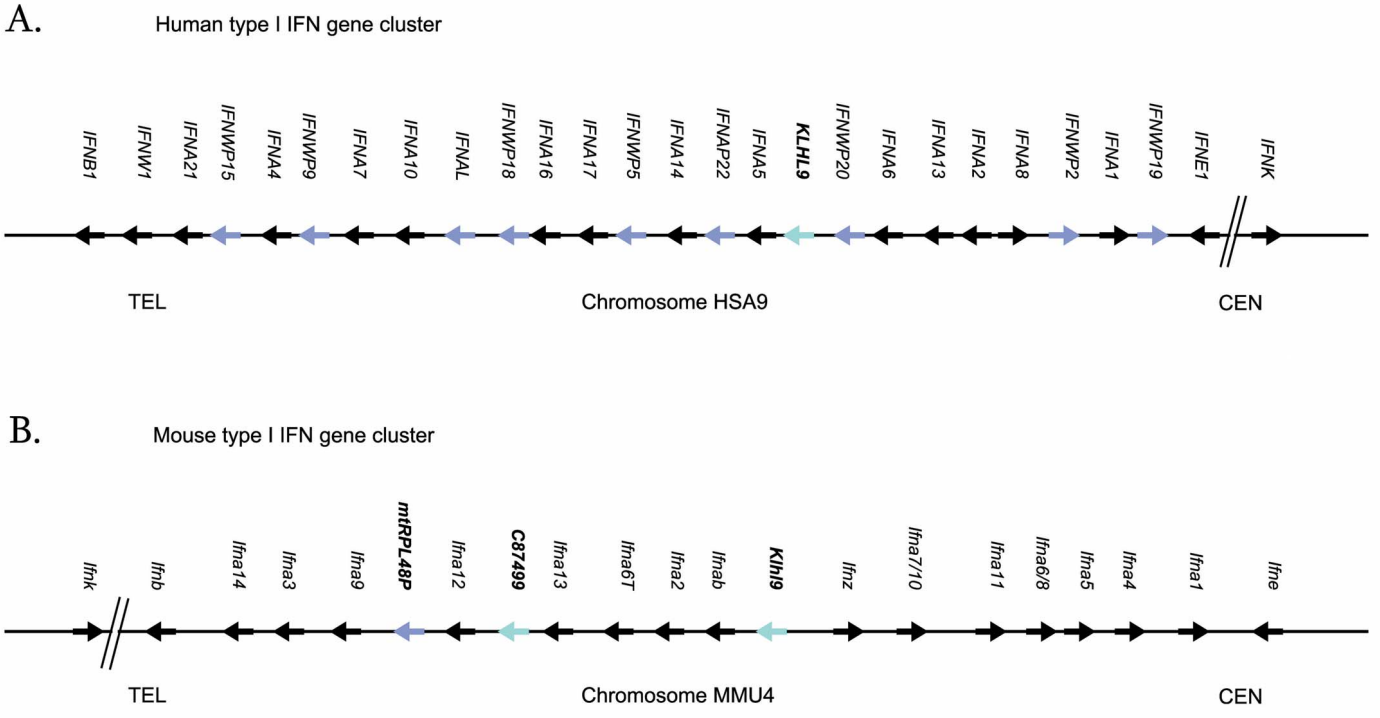


Fig. 1.1. The human and murine type I IFN gene locus. (A) Human IFN gene cluster on chromosome 9 (HSA9). (B) Murine IFN gene cluster on chromosome 4 (MMU4). The IFN gene locus was drawn using current genomic information available on NCBI human chromosome 9 (HSA9) contig (contig ID; NT_008413.16) and mouse chromosome 4 (MMU) contig (contig ID; NT_039260.4). Arrows indicate relative position and transcriptional orientation of genes. Black arrows indicate functional IFN genes, dark grey arrows pseudogenes and light grey arrows other non-IFN genes within the cluster. Orientation of the chromosome is indicated by TEL (telomeric end) and CEN (centromeric end). Nomenclature suggested by van Pesch et al. [32] is used in naming murine IFNs. (This figure also appears on page 5.)

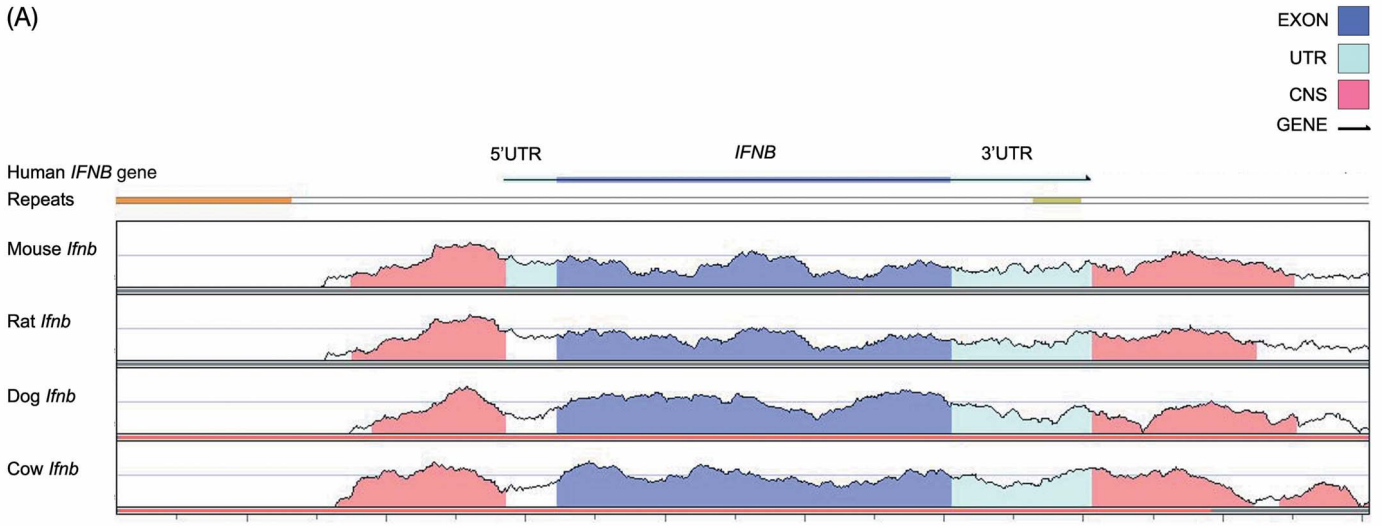


Fig. 1.2. Human type I IFN promoter sequence alignment. (A) VISTA alignment of human, mouse, rat, dog and cow IFN-β genes. The figure represents an AVID genome alignment [58] and VISTA visualization [59] of mouse, rat, dog and cow *Ifnb* genomic sequences compared to the human *IFNB* genomic sequence. At the top, the human *IFNB* gene is depicted by a dark blue line with an arrow indicating transcriptional orientation, together with 5′- and 3′-UTR regions depicted as light blue lines. The line immediately below indicates the location of repetitive elements within the genomic sequence. The graphed regions below demonstrate homology of mouse, rat, dog and cow *Ifnb* genomic regions to the human *IFNB* gene. Exon regions with more than 65% sequence identity over 100 bp are indicated by dark blue, whereas conserved noncoding sequences (CNS) and 5′- and 3′-UTRs with over 65% sequence identity are depicted in orange and light blue, respectively. (This figure also appears on page 12.)

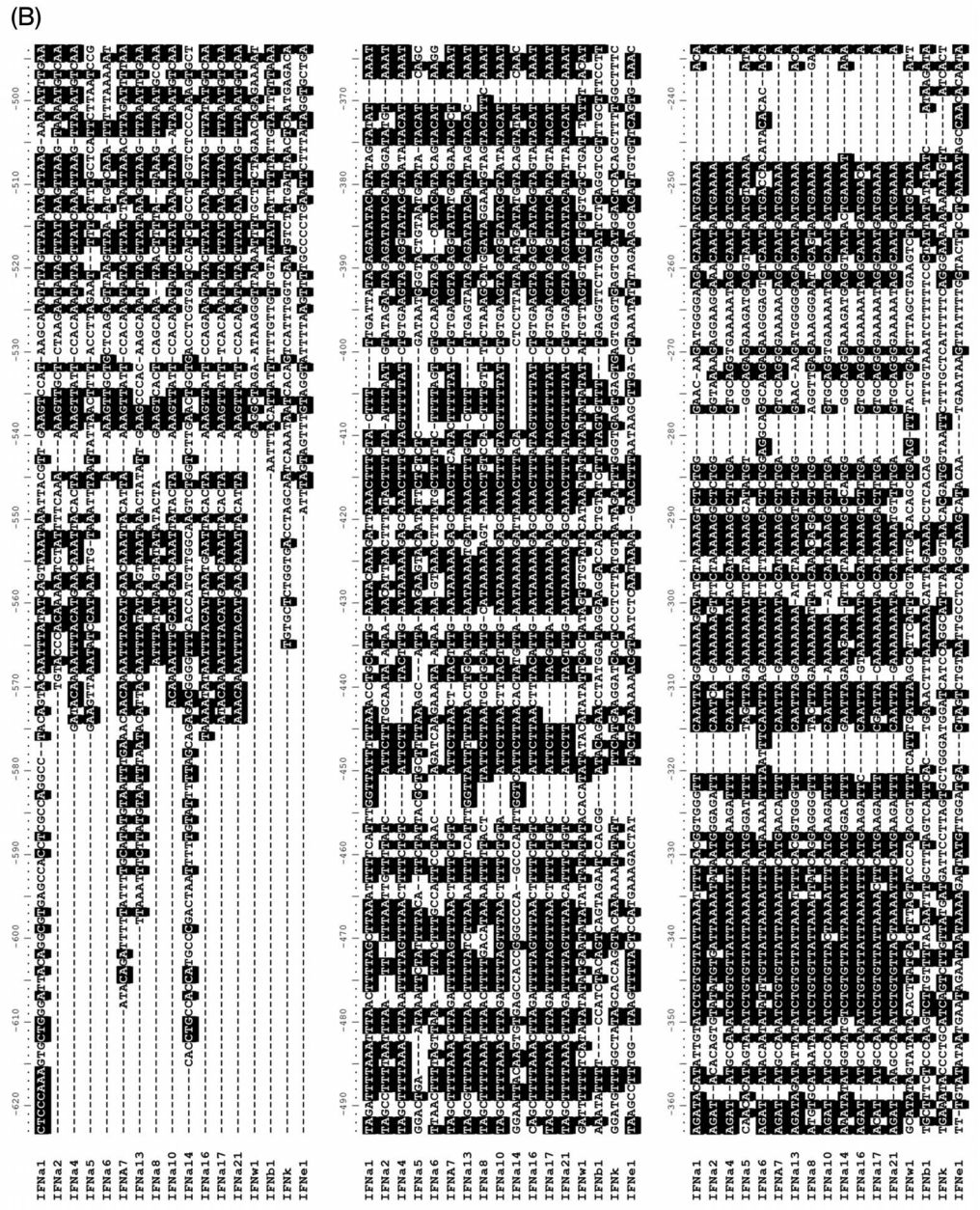


Fig. 1.2. (B) Nucleotide sequence alignment of human IFN promoter. Alignment was performed using ClustalW algorithm [79] of 500 bp 5′-flanking sequences containing the promoter elements of human IFN genes. The regulatory elements present in this region are indicated by boxed regions. (This figure also appears on pages 14–15.)

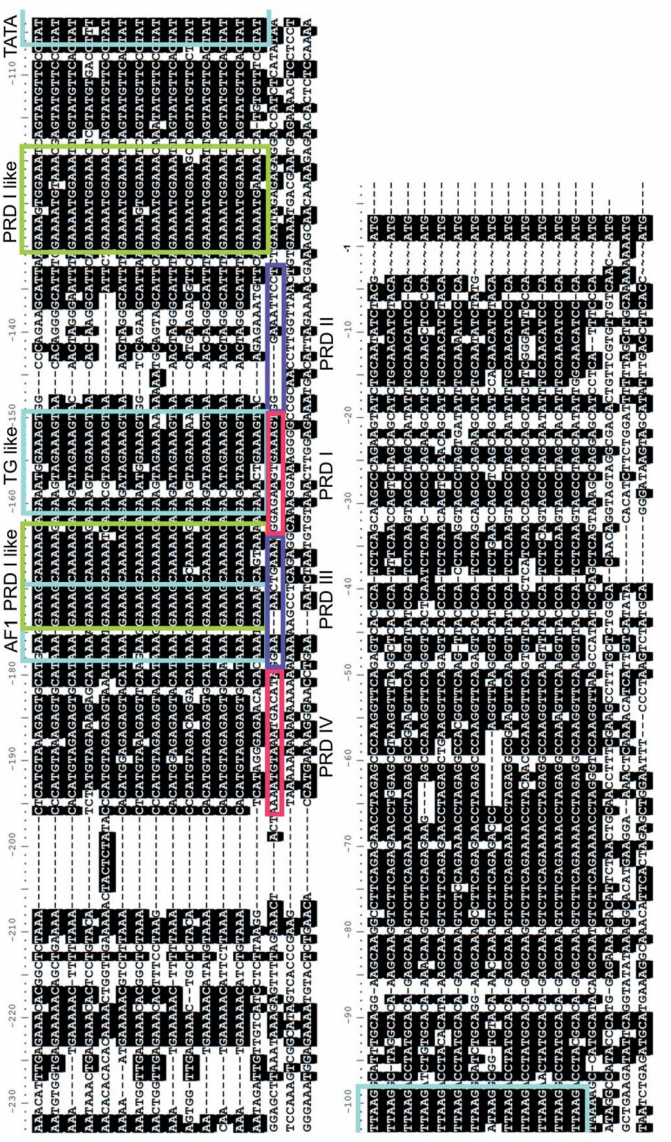


Fig. 1.2B. (*continued*)

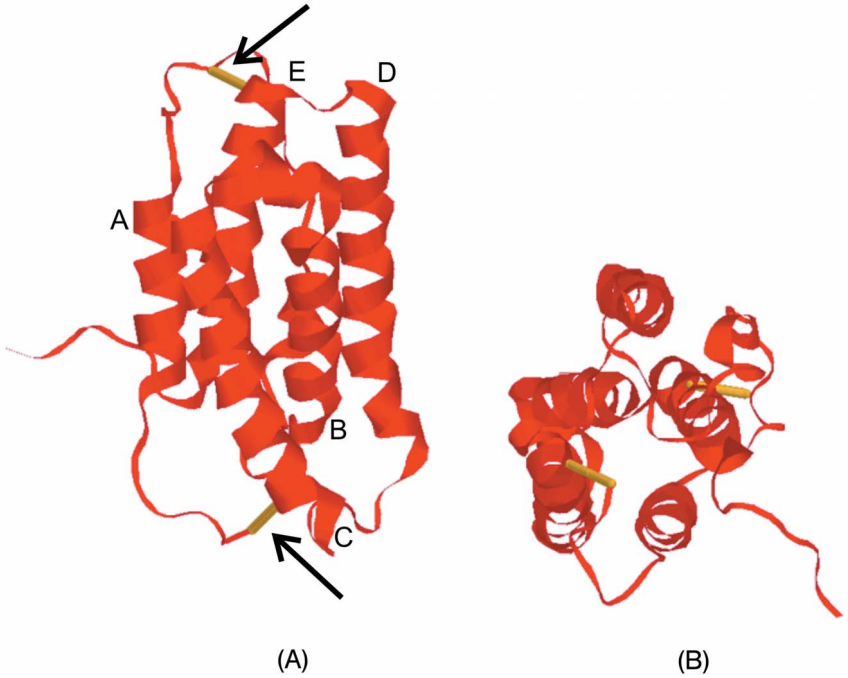
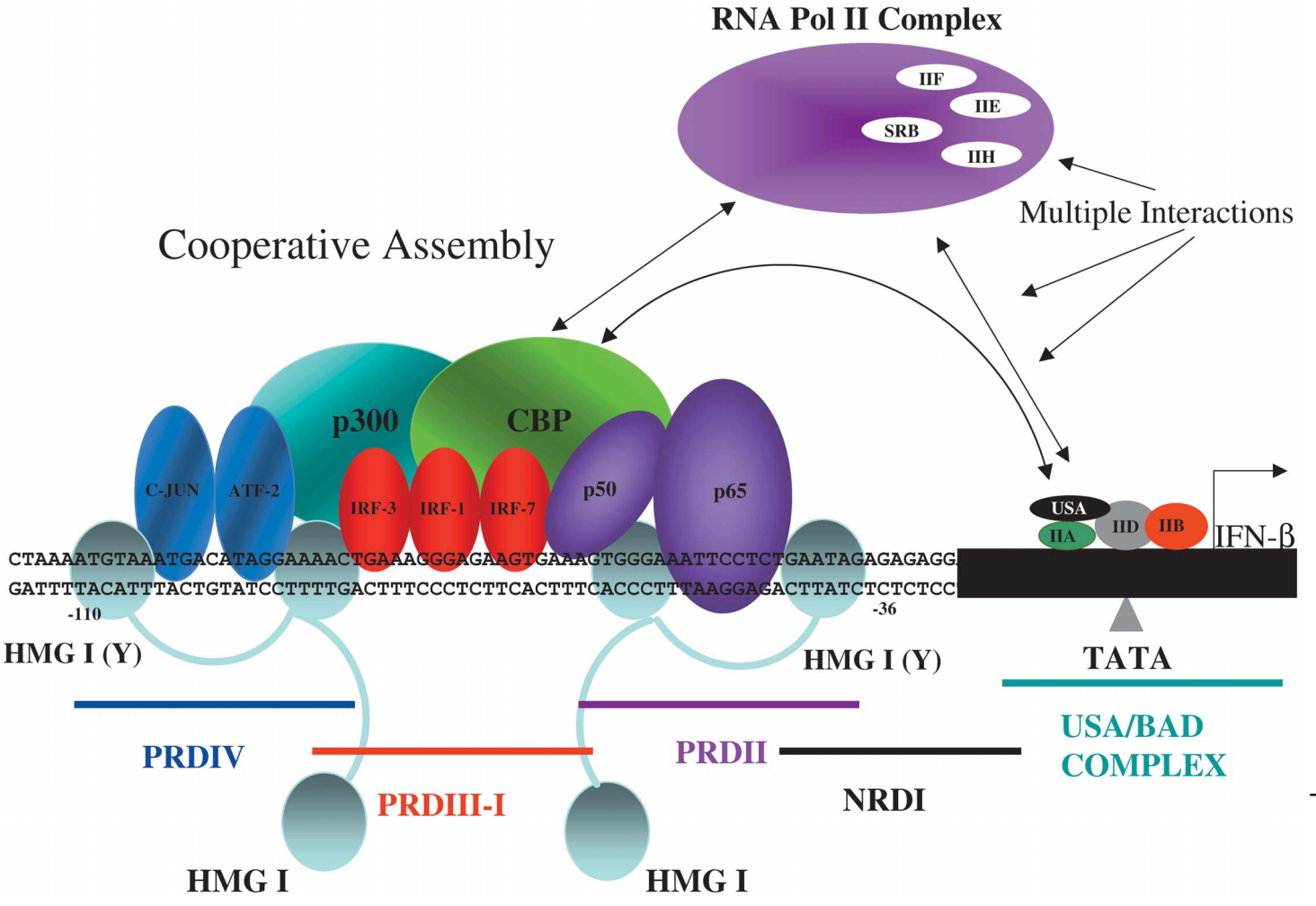


Fig. 1.4. Representative tertiary structure of human IFN-α. Tertiary structure of human IFN-α2 represented as a ribbon diagram, showing the five α-helices connected by loop regions. The disulfide bonds between cysteine residues are indicated by arrows. (A) Side view of the molecule. (B) View from above. (This figure also appears on page 25.)

Fig. 2.1. Schematic representation of the IFN-β promoter enhanceosome. This diagram shows the composition and organization of the human IFN-β enhanceosome. The nucleotide sequence (−110 to −36) is situated upstream from the starting transcription site. The positive regulatory sites as well as the negative regulatory domain are named PRDs and NRD, respectively. The transcriptional proteins binding to the PRDs are also shown (c-Jun, ATF-2, IRFs and NF-κB), as well as the architectural proteins HMGI(Y) and the transcriptional coactivators proteins p300 and CBP. The multiple protein–protein interactions required for transcriptional synergy of the IFN-β promoter derived from the cooperative assembly of the enhanceosome, cooperative assembly between the enhanceosome and the USA/BAD complex, and interaction with the RNA polymerase II complex [32]. (This figure also appears on page 38.)


RNA Pol II Complex
IIF
IIE
SRB
IIH
Multiple Interactions
Cooperative Assembly
p300
CBP
C-JUN
ATF-2
IRF-3
IRF-1
IRF-7
p50
p65
USA
IIA
IID
IIB
IFN-β
CTAAAATGTAAATGACATAGGAAAACTGAAACGGGAGAAGTGAAAGTGGGAAATTCCTCTGAATAGAGAGAGG
GATTTTACATTTACTGTATCCTTTTGACTTTCCCTCTTCACTTTCACCCTTTAAGGAGACTTATCTCTCTCC
-110
-36
HMG I (Y)
HMG I (Y)
TATA
PRDIV
PRDII
USA/BAD
COMPLEX
PRDIII-I
NRDI
HMG I
HMG I

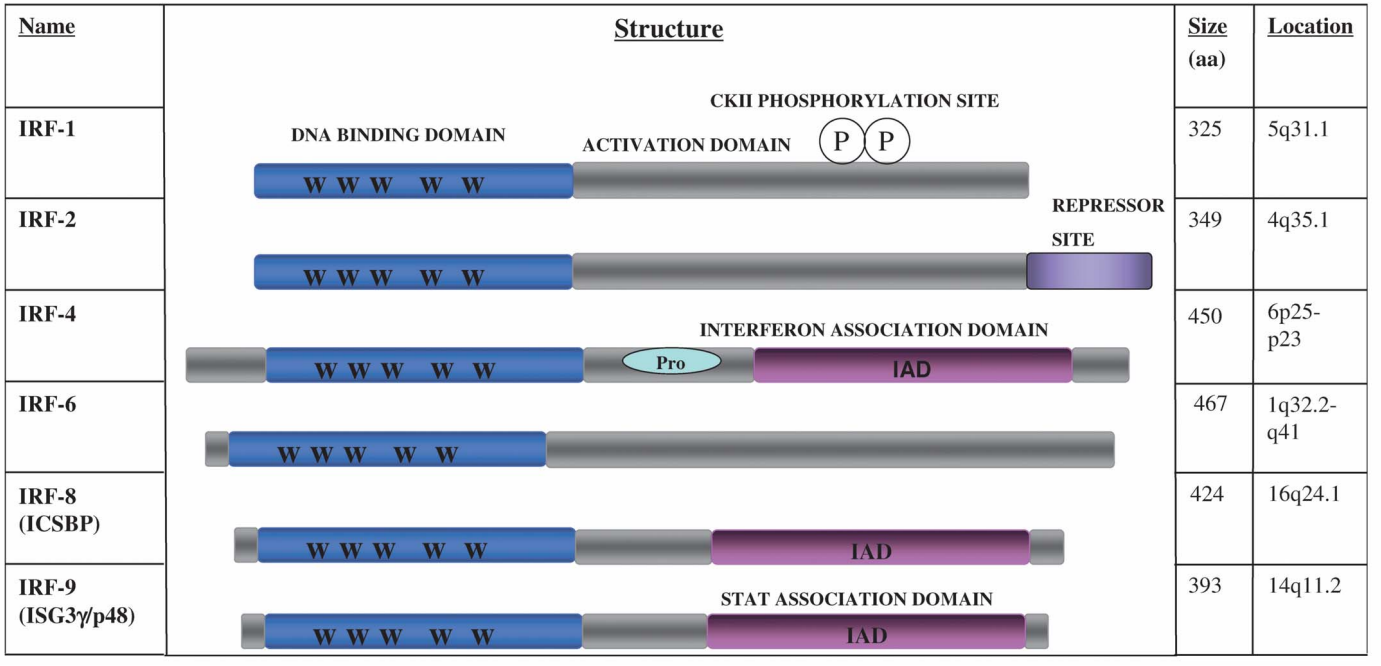


Fig. 2.2. Schematic representation of IRF-1, -2, -4, -6, -8 and -9 transcription factors. This diagram demonstrates the general structural homology amongst the IRF family. Different domains are shown: DBD, CKII phosphorylation site, repressor site and IAD. The size of each IRF as well as their chromosomal location is also described. (This figure also appears on page 44.)

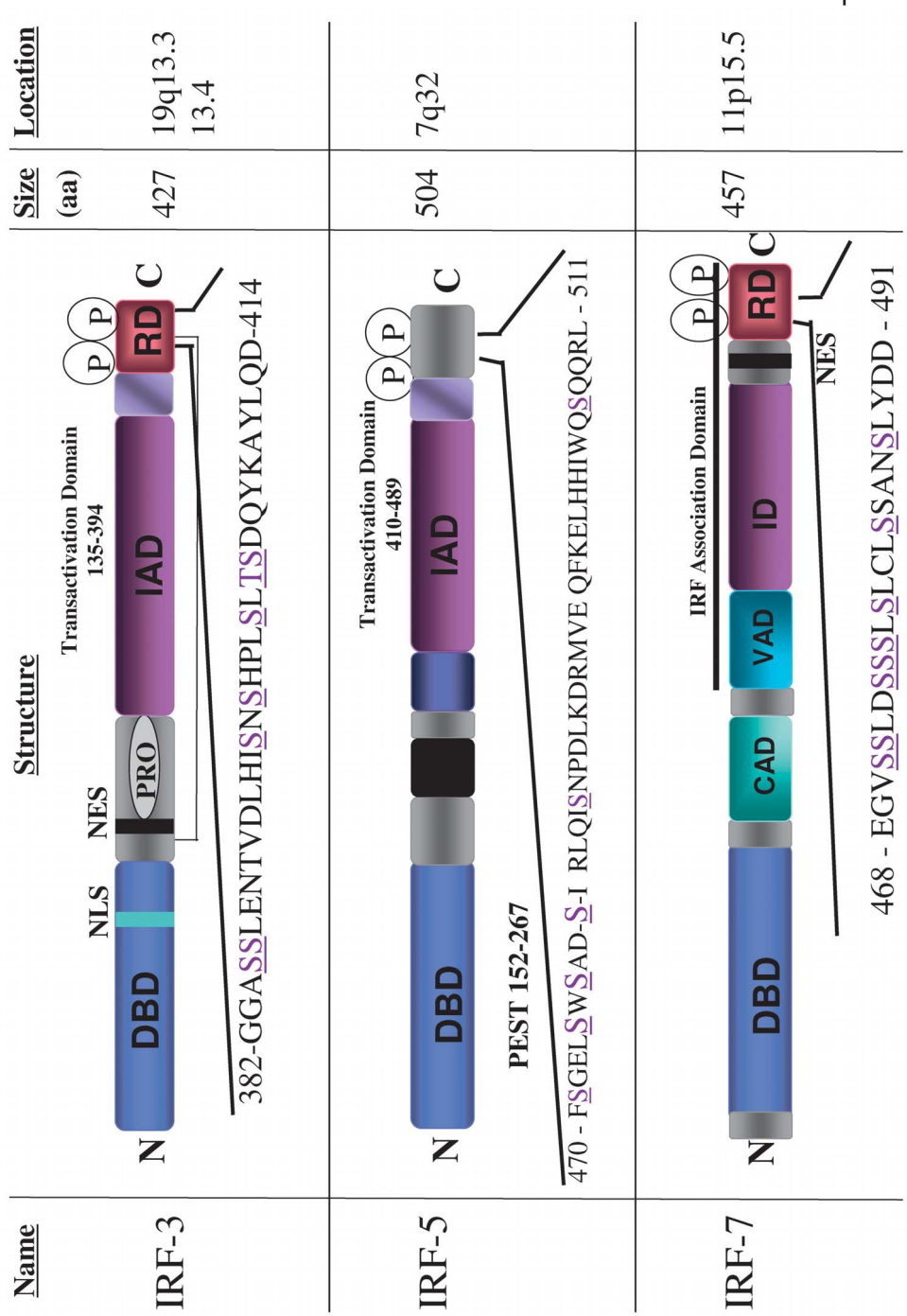
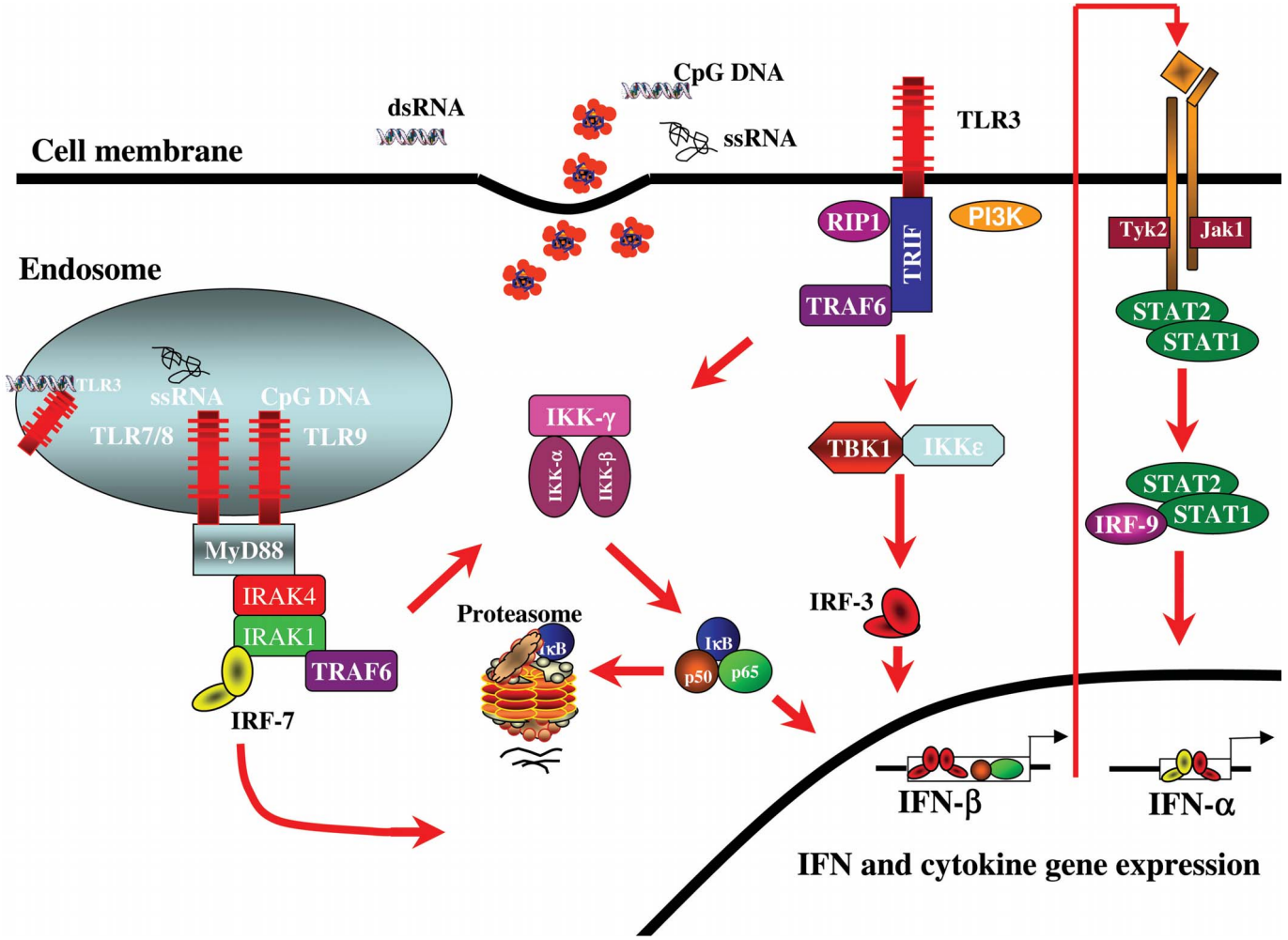


Fig. 2.3. Schematic representation of IRF-3, -5 and -7 transcription factors. Different domains are shown: NLS, NES, DBD, CAD, VAD, IAD and the signal response domain (RD). The sequence of amino acids 382–414 (IRF-3) and the sequence of amino acids 468–491 (IRF-7) are amplified below the schematic. Important amino acids are shown in larger letters with the respective position number. (This figure also appears on page 48.)


Cell membrane
dsRNA
CpG DNA
ssRNA
TLR3
RIP1
TRIF
PI3K
TRAF6
Tyk2
Jak1
STAT2
STAT1
Endosome
TLR3
ssRNA
CpG DNA
TLR7/8
TLR9
IKK-γ
IKK-α
IKK-β
TBK1
IKKε
STAT2
IRF-9
STAT1
MyD88
IRAK4
IRAK1
TRAF6
IRF-7
Proteasome
IκB
p50
p65
IRF-3
IFN-β
IFN-α
IFN and cytokine gene expression