

## **and death in the face of pathogens and vaccines The simple chicken major histocompatibility complex: life**

Jim Kaufman

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**PHILOSOPHICAL**<br>TRANSACTIONS ŏ



THE ROYAL **SOCIETY** 

PHILOSOPHICAL<br>TRANSACTIONS  $\overline{\overline{O}}$ 

# **THE ROYAL**<br> **SOCIETY**<br> **The simple chicken major histocompatibility comple chicken major histocompatibilit**<br> **complex: life and death in the face** ble chicken major histocompat<br>plex: life and death in the fac<br>of pathogens and vaccines

### **Jim Kaufman**

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Institute for Animal Health, Compton, Berkshire RG20 7NN, UK (jim.kaufman@bbsrc.ac.uk)<br>In contrast to the major histocompatibility complex (MHC) of well-studied mammals such as humans<br>and mice, the particular haplotype of In contrast to the major histocompatibility complex (MHC) of well-studied mammals such as humans<br>and mice, the particular haplotype of the B-F/B-L region of the chicken B locus determines life and<br>death in response to cer In contrast to the major histocompatibility complex  $(MHC)$  of well-studied mammals such as humans<br>and mice, the particular haplotype of the B-F/B-L region of the chicken B locus determines life and<br>death in response to cer and mice, the particular haplotype of the B-F/B-L region of the chicken B locus determines life and death in response to certain infectious pathogens as well as to certain vaccines. We found that the B-F/B-L region is muc death in response to certain infectious pathogens as well as to certain vaccines. We found that the B-F/B-L<br>region is much smaller and simpler than the typical mammalian MHC, with an important difference<br>being the expressi region is much smaller and simpler than the typical mammalian MHC, with an important difference<br>being the expression of a single class I gene at a high level of RNA and protein. The peptide-binding<br>specificity of this domi being the expression of a single class I gene at a high level of RNA and protein. The peptide-binding<br>specificity of this dominantly expressed class I molecule in different haplotypes correlates with resistance<br>to tumours specificity of this dominantly expressed class I molecule in different haplotypes correlates with resistance<br>to tumours caused by Rous sarcoma virus, while the cell-surface expression level correlates with suscept-<br>ibilit to tumours caused by Rous sarcoma virus, while the cell-surface expression level correlates with susceptibility to tumours caused by Marek's disease virus. A similar story is developing with class II  $\beta$  genes and respon ibility to tumours caused by Marek's disease virus. A similar story is developing with class II  $\beta$  genes and response to killed viral vaccines. This apparently suicidal strategy of single dominantly expressed class I an MHC.

**Keywords:** chicken; major histocompatibility complex; pathogen; vaccine

#### **1. INTRODUCTION**

It perhaps should be no surprise, given the enormous and <br>It perhaps should be no surprise, given the enormous and Second, chickens are beset concentrated enquiry into host-pathogen relationships in<br>concentrated enquiry into host-pathogen relationships in<br>human disease, that the dynamics of virus infections in It perhaps should be no surprise, given the enormous and<br>concentrated enquiry into host–pathogen relationships in<br>human disease, that the dynamics of virus infections in<br>humans and in animals that serve as biomedical model concentrated enquiry into host–pathogen relationships in<br>human disease, that the dynamics of virus infections in<br>humans and in animals that serve as biomedical models<br>can be studied with precision and elegance. There are a human disease, that the dynamics of virus infections in humans and in animals that serve as biomedical models can be studied with precision and elegance. There are at humans and in animals that serve as biomedical models<br>
can be studied with precision and elegance. There are at<br>
least three levels of such pathogen–host interactions. A<br>
great deal is known about the course of certain vir can be studied with precision and elegance. There are at least three levels of such pathogen–host interactions. A great deal is known about the course of certain viral infections in individuals with respect to both the least three levels of such pathogen-host interactions. A<br>great deal is known about the course of certain viral<br>infections in individuals, with respect to both the<br>pathogen and the bost response to the point that mathegreat deal is known about the course of certain viral<br>infections in individuals, with respect to both the<br>pathogen and the host response, to the point that mathe-<br>matical modelling has become a useful tool not just for infections in individuals, with respect to both the pathogen and the host response, to the point that mathematical modelling has become a useful tool, not just for denicting what is already known but for predicting what pathogen and the host response, to the point that mathe-<br>matical modelling has become a useful tool, not just for<br>depicting what is already known but for predicting what<br>may not be obvious as exemplified in the accompanyin matical modelling has become a useful tool, not just for<br>depicting what is already known but for predicting what<br>may not be obvious, as exemplified in the accompanying<br>reports (see other papers in this issue) A certain amo depicting what is already known but for predicting what<br>may not be obvious, as exemplified in the accompanying<br>reports (see other papers in this issue). A certain amount<br>is also known about how and why these viruses evolve may not be obvious, as exemplified in the accompanying<br>reports (see other papers in this issue). A certain amount<br>is also known about how and why these viruses evolve in<br>relation to the immune response in populations of bo reports (see other papers in this issue). A certain amount<br>is also known about how and why these viruses evolve in<br>relation to the immune response in populations of hosts.<br>Much less is clear about how and why both viruses is also known about how and why these viruses evolve in and simpler in chickens than in humans and mice, and relation to the immune response in populations of hosts. That this simplicity can have important functional Much relation to the immune response in populations of hosts. different host species are considered.

biomedical model species, why examine these questions in Given the sophistication of the analysis in well-studied<br>biomedical model species, why examine these questions in<br>any other animal? We believe that there are some real<br>advantages in using the bumble domestic chicken to stu biomedical model species, why examine these questions in<br>any other animal? We believe that there are some real<br>advantages in using the humble domestic chicken to study<br>all three levels of host–nathogen interaction any other animal? We believe that there are<br>advantages in using the humble domestic chicle<br>all three levels of host–pathogen interaction.<br>First, there are many chickens around. Some vantages in using the humble domestic chicken to study<br>three levels of host–pathogen interaction.<br>First, there are many chickens around. Some 34 billion<br>ickens are alive, however briefly, each year, and the

all three levels of host–pathogen interaction.<br>First, there are many chickens around. Some 34 billion<br>chickens are alive, however briefly, each year, and the<br>health and welfare of these animals is of serious concern First, there are many chickens around. Some 34 billion<br>chickens are alive, however briefly, each year, and the<br>health and welfare of these animals is of serious concern<br>to the poultry industry. In comparison to other popchickens are alive, however briefly, each year, and the health and welfare of these animals is of serious concern<br>to the poultry industry. In comparison to other nonhealth and welfare of these animals is of serious concern<br>to the poultry industry. In comparison to other non-<br>mammalian vertebrates, avian genetics and immunology<br>are very well studied in part because of this economic to the poultry industry. In comparison to other non-<br>mammalian vertebrates, avian genetics and immunology<br>are very well studied, in part because of this economic<br>importance. In contrast to mice, a great deal of field data mammalian vertebrates, avian genetics and immunology<br>are very well studied, in part because of this economic<br>importance. In contrast to mice, a great deal of field data<br>are continually gathered on a variety of natural infe are very well studied, in part because of this economic<br>importance. In contrast to mice, a great deal of field data<br>are continually gathered on a variety of natural infectious

diseases, and compared with humans, laboratory experidiseases, and compared with hum<br>ments can easily be performed.<br>Second chickens, are beset

Second, chickens are beset with a large variety of ments can easily be performed.<br>Second, chickens are beset with a large variety of<br>natural pathogens. Many of these pathogens are well<br>studied in the laboratory well monitored in the field and Second, chickens are beset with a large variety of<br>natural pathogens. Many of these pathogens are well<br>studied in the laboratory, well monitored in the field, and<br>known to be locked in a continuing and lethal molecular natural pathogens. Many of these pathogens are well<br>studied in the laboratory, well monitored in the field, and<br>known to be locked in a continuing and lethal molecular<br>arms race with their hosts. Indeed, the shift to inten studied in the laboratory, well monitored in the field, and<br>known to be locked in a continuing and lethal molecular<br>arms race with their hosts. Indeed, the shift to intensive<br>rearing practices may have accentuated the rise known to be locked in a continuing and lethal molecular<br>arms race with their hosts. Indeed, the shift to intensive<br>rearing practices may have accentuated the rise in<br>virulence partly through an increase in population arms race with their hosts. Indeed, the shift to intensive<br>rearing practices may have accentuated the rise in<br>virulence, partly through an increase in population<br>density but probably also through busbandry practices rearing practices may have accentuated the rise in<br>virulence, partly through an increase in population<br>density, but probably also through husbandry practices<br>and vaccination strategies virulence, partly through<br>density, but probably also<br>and vaccination strategies.<br>Third there are many in nsity, but probably also through husbandry practices<br>d vaccination strategies.<br>Third, there are many interesting differences between<br>ians, and mammals. Particularly, relevant, to this

and vaccination strategies.<br>Third, there are many interesting differences between<br>avians and mammals. Particularly relevant to this<br>discussion are the observations that the genetic loci Third, there are many interesting differences between<br>avians and mammals. Particularly relevant to this<br>discussion are the observations that the genetic loci<br>encoding certain immune system molecules are smaller avians and mammals. Particularly relevant to this<br>discussion are the observations that the genetic loci<br>encoding certain immune system molecules are smaller<br>and simpler in chickens than in humans and mice, and discussion are the observations that the genetic loci<br>encoding certain immune system molecules are smaller<br>and simpler in chickens than in humans and mice, and<br>that this simplicity can have important functional encoding certain immune system molecules are smaller<br>and simpler in chickens than in humans and mice, and<br>that this simplicity can have important functional<br>implications implications. In this simplicity can have important functional<br>implications.<br>In well-characterized mammals such as humans and

Given the sophistication of the analysis in well-studied large, complicated and redundant genetic region, with<br>omedical model species, why examine these questions in many highly expressed classical class I and class II gen implications.<br>In well-characterized mammals such as humans and<br>mice, the major histocompatibility complex (MHC) is a<br>large complicated and redundant genetic region, with In well-characterized mammals such as humans and<br>mice, the major histocompatibility complex (MHC) is a<br>large, complicated and redundant genetic region, with<br>many bighly expressed classical class I and class II genes mice, the major histocompatibility complex (MHC) is a large, complicated and redundant genetic region, with many highly expressed classical class I and class II genes (Aguado *et al.* 1999: Trowsdale 1995). Moreover, desp large, complicated and redundant genetic region, with many highly expressed classical class I and class II genes<br>(Aguado *et al.* 1999; Trowsdale 1995). Moreover, despite many highly expressed classical class I and class II genes<br>(Aguado *et al.* 1999; Trowsdale 1995). Moreover, despite<br>the fact that the high polymorphism of mammalian<br>MHC genes is thought to be driven by pathogen varia-(Aguado *et al.* 1999; Trowsdale 1995). Moreover, despite<br>the fact that the high polymorphism of mammalian<br>MHC genes is thought to be driven by pathogen varia-<br>tion different haplotynes all confer roughly equal protecthe fact that the high polymorphism of mammalian MHC genes is thought to be driven by pathogen variation, different haplotypes all confer roughly equal protection against most infectious pathogens. In fact, the strong MHC genes is thought to be driven by pathogen varia-<br>tion, different haplotypes all confer roughly equal protec-<br>tion against most infectious pathogens. In fact, the strong<br>associations with the human MHC are with autoimmu tion, different haplotypes all confer roughly equal protection against most infectious pathogens. In fact, the strong associations with the human MHC are with autoimmune diseases or biochemical defects. The best examples o tion against most infectious pathogens. In fact, the strong associations with the human MHC are with autoimmune diseases or biochemical defects. The best examples of associations with the human MHC are with autoimmune<br>diseases or biochemical defects. The best examples of<br>associations with infectious diseases are slight and the<br>level of selection on individual alleles on mammalian diseases or biochemical defects. The best examples of associations with infectious diseases are slight and the level of selection on individual alleles on mammalian MHC genes bas been calculated to be low (Hill 1998) associations with infectious diseases are slight and the level of selection on individual alleles on mammalian MHC genes has been calculated to be low (Hill 1998; Satta et al. 1994; Tiwari & Terasaki 1985) level of selection on individual alleles on mammalian MHC genes has been calculated to be low (Hill 1998; Satta *et al.* 1994; Tiwari & Terasaki 1985).



there are far fewer chances to bind a peptide to protect the individual (even in MHC heterozygotes).<br>In contrast, the chicken MHC is simple and compact, comparison to what is know Figure 1. The effect of multiple well-expressed class I genes compared to a single dominantly expressed class I gene. Pathogen<br>proteins are proteolysed in host cells and the resulting pentides are bound by MHC molecules an Figure 1. The effect of multiple well-expressed class I genes compared to a single dominantly expressed class I gene. Pathogen<br>proteins are proteolysed in host cells and the resulting peptides are bound by MHC molecules an proteins are proteolysed in host cells and the resulting peptides are bound by MHC molecules and presented to T lymphocytes of<br>the immune system. In typical mammals, a multigene family of MHC genes (each with two alleles i proteins are proteolysed in host cells and the resulting peptides are bound by MHC molecules and presented to T lymphocytes of<br>the immune system. In typical mammals, a multigene family of MHC genes (each with two alleles i the immune system. In typical mammals, a multigene family of MHC genes (each with two alleles in MHC heterozygotes)<br>encodes multiple MHC molecules on the cell surface. Each molecule has a different peptide-binding specific encodes multiple MHC molecules on the cell surface. Each molecule has a different peptide-binding sp<br>are many chances to find a peptide that binds a class I molecule. With the single dominantly expressed<br>there are far fewe

with single dominantly expressed class I and class II In contrast, the chicken MHC is simple and compact,<br>with single dominantly expressed class I and class II<br>genes in common MHC haplotypes (Kaufman *et al.* 1995,<br>1999*a b*) Moreover, the chicken MHC determines life with single dominantly expressed class I and class II<br>genes in common MHC haplotypes (Kaufman *et al.* 1995,<br>1999*a*,*b*). Moreover, the chicken MHC determines life<br>and death in response to certain infectious pathogens genes in common MHC haplotypes (Kaufman *et al.* 1995, 1999*a*,*b*). Moreover, the chicken MHC determines life and death in response to certain infectious pathogens, both relatively small and simple pathogens as well as a 1999 $a,b$ ). Moreover, the chicken MHC determines life and death in response to certain infectious pathogens, both relatively small and simple pathogens as well as at least one large and complicated virus the hernesvirus and death in response to certain infectious pathogens,<br>both relatively small and simple pathogens as well as at<br>least one large and complicated virus, the herpesvirus<br>that causes Marek's disease (Calnek 1985; Dietert et al both relatively small and simple pathogens as well as at least one large and complicated virus, the herpesvirus that causes Marek's disease (Calnek 1985; Dietert *et al.* 1990; Kaufman & Lamont 1996; Plachy *et al.* 1992; least one large and complicated virus, the herpesvirus<br>that causes Marek's disease (Calnek 1985; Dietert *et al.*<br>1990; Kaufman & Lamont 1996; Plachy *et al.* 1992; Schat<br>1987). We have developed a simple model, the 'minim that causes Marek's disease (Calnek 1985; Dietert et al. 1990; Kaufman & Lamont 1996; Plachy *et al.* 1992; Schat 1987). We have developed a simple model, the 'minimal essential MHC of the chicken', to relate the structural simplicity of the chicken MHC with the striking 1987). We have developed a simple model, the 'minimal<br>essential MHC of the chicken', to relate the structural<br>simplicity of the chicken MHC with the striking<br>functional associations in comparison with the wellessential MHC of the chicken', to relate the structural<br>simplicity of the chicken MHC with the striking<br>functional associations, in comparison with the well-<br>characterized mammalian models (Kaufman 1999simplicity of the chicken MHC with the striking<br>functional associations, in comparison with the well-<br>characterized mammalian models (Kaufman 1999; functional associations, in comparison with the well-<br>characterized mammalian models (Kaufman 1999;<br>Kaufman *et al.* 1995, 1999*a*,*b*; Kaufman & Salomonsen<br>1997: Kaufman & Venugonal 1998: Kaufman & Wallny characterized mammalian models (Kaufman 1999;<br>Kaufman *et al.* 1995, 1999*a*,*b*; Kaufman & Salomonsen<br>1997; Kaufman & Venugopal 1998; Kaufman & Wallny<br>1996) 1996). 1997; Kaufman & Venugopal 1998; Kaufman & Wallny<br>1996).<br>In this review, we would like to consider the three

1996).<br>In this review, we would like to consider the three<br>points leading to the hypothesis of the `minimal essential<br> $\text{MHC}^*$ —that in contrast to the  $\text{MHC}^s$  of humans and In this review, we would like to consider the three<br>points leading to the hypothesis of the 'minimal essential<br>MHC'—that in contrast to the MHCs of humans and<br>mice—the chicken MHC (i) determines resistance and points leading to the hypothesis of the 'minimal essential MHC'—that in contrast to the MHCs of humans and mice, the chicken MHC (i) determines resistance and susceptibility to small pathogens such as Rous sarcoma MHC'—that in contrast to the MHCs of humans and<br>mice, the chicken MHC (i) determines resistance and<br>susceptibility to small pathogens such as Rous sarcoma<br>virus (RSV): (ii) determines resistance and susceptibility mice, the chicken MHC (i) determines resistance and<br>susceptibility to small pathogens such as Rous sarcoma<br>virus (RSV); (ii) determines resistance and susceptibility<br>to a large pathogen Marek's disease virus (MDV); and susceptibility to small pathogens such as Rous sarcoma molecule in common chicken MHC haplotypes, and we<br>virus (RSV); (ii) determines resistance and susceptibility have determined the peptide-binding specificities of some<br> to a large pathogen, Marek's disease virus (MDV); and to a large pathogen, Marek's disease virus (MDV); and<br>(iii) is small and simple. For each point, we will<br>summarize a few of our published and unpublished data,<br>relate those data to our model of the 'minimal essential (iii) is small and simple. For each point, we will<br>summarize a few of our published and unpublished data,<br>relate those data to our model of the 'minimal essential<br>MHC' of the chicken and then describe a potential applisummarize a few of our published and unpublished data,<br>relate those data to our model of the 'minimal essential<br>MHC' of the chicken, and then describe a potential appli-<br>cation of mathematical modelling that could have a relate those data to our model of the 'minimal essential<br>MHC' of the chicken, and then describe a potential appli-<br>cation of mathematical modelling that could have a<br>heneficial impact on such work MHC' of the chicken, and then do<br>cation of mathematical modelli<br>beneficial impact on such work. **2. A BIRD'S EYE VIEW OF LIFE AND DEATH** 

## **IN THE FACE OF (SMALL) PATHOGENS**

The hypothesis of the `minimal essential MHC of the chicken' attempts to provide a molecular basis for the The hypothesis of the 'minimal essential MHC of the tyrosine kinase that appears to have been transduced chicken' attempts to provide a molecular basis for the from the normal chicken gene  $c$ -src. Infected chickens strik

comparison to what is known for well-characterized<br>mammalian models (figure 1). Consider a pathogen that comparison to what is known for well-characterized<br>mammalian models (figure 1). Consider a pathogen that<br>is proteclysed into pentides by the systems of antigen comparison to what is known for well-characterized<br>mammalian models (figure 1). Consider a pathogen that<br>is proteolysed into peptides by the systems of antigen<br>processing with the peptides bound by MHC molecules mammalian models (figure 1). Consider a pathogen that<br>is proteolysed into peptides by the systems of antigen<br>processing, with the peptides bound by MHC molecules is proteolysed into peptides by the systems of antigen<br>processing, with the peptides bound by MHC molecules<br>and presented to the T lymphocytes of the immune<br>system Mammals have multigene families of wellprocessing, with the peptides bound by MHC molecules<br>and presented to the T lymphocytes of the immune<br>system. Mammals have multigene families of well-<br>expressed MHC molecules for instance the human class I and presented to the T lymphocytes of the immune<br>system. Mammals have multigene families of well-<br>expressed MHC molecules, for instance the human class I<br>molecules HI A-A HI A-R and HI A-C each of which system. Mammals have multigene families of well-<br>expressed MHC molecules, for instance the human class I<br>molecules HLA-A, HLA-B and HLA-C, each of which<br>has a different pentide-binding specificity. Individual expressed MHC molecules, for instance the human class I<br>molecules HLA-A, HLA-B and HLA-C, each of which<br>has a different peptide-binding specificity. Individual<br>humans heterozygous for the MHC have six possibilities molecules HLA-A, HLA-B and HLA-C, each of which<br>has a different peptide-binding specificity. Individual<br>humans heterozygous for the MHC have six possibilities has a different peptide-binding specificity. Individual<br>humans heterozygous for the MHC have six possibilities<br>for finding an appropriate peptide to bind and present to<br>T cells in order to make an effective response. In humans heterozygous for the MHC have six possibilities<br>for finding an appropriate peptide to bind and present to<br>T cells, in order to make an effective response. In<br>contrast chickens, have single dominantly expressed for finding an appropriate peptide to bind and present to<br>T cells, in order to make an effective response. In<br>contrast, chickens have single dominantly expressed<br>MHC genes so a heterozygous individual would have just T cells, in order to make an effective response. In contrast, chickens have single dominantly expressed MHC genes, so a heterozygous individual would have just two chances to find a protective pertide. We believe that contrast, chickens have single dominantly expressed MHC genes, so a heterozygous individual would have just two chances to find a protective peptide. We believe that this may be the explanation for the strong chicken MHC MHC genes, so a heterozygous individual would have just<br>two chances to find a protective peptide. We believe that<br>this may be the explanation for the strong chicken MHC<br>associations with disease caused by certain small inf two chances to find a protective peptide. We believe that<br>this may be the explanation for the strong chicken MHC<br>associations with disease caused by certain small infecthis may be the explanation for the strong chicken MHC<br>associations with disease caused by certain small infec-<br>tious pathogens—those individuals that find a peptide<br>survive while those that do not die survive, while those that do not die.<br>As the first step in examining this hypothesis, we have hypoted in the those individuals that find a peptide<br>wive, while those that do not die.<br>As the first step in examining this hypothesis, we have<br>own that there is a single dominantly expressed class I

shown that there is a single dominantly expressed class I As the first step in examining this hypothesis, we have shown that there is a single dominantly expressed class I molecule in common chicken MHC haplotypes, and we have determined the nentide-hinding specificities of some shown that there is a single dominantly expressed class I<br>molecule in common chicken MHC haplotypes, and we<br>have determined the peptide-binding specificities of some<br>of these dominantly expressed class I molecules, the fir molecule in common chicken MHC haplotypes, and we<br>have determined the peptide-binding specificities of some<br>of these dominantly expressed class I molecules, the first,<br>to our knowledge, peptide-binding motifs identified in to our knowledge, peptide-binding motifs identified in of these dominantly expressed class  $\overline{I}$  molecules, the first to our knowledge, peptide-binding motifs identified any non-mammalian vertebrate (Kaufman *et al.* 1995). We then chose to examine a natural disease with a our knowledge, peptide-binding motifs identified in<br>y non-mammalian vertebrate (Kaufman *et al.* 1995).<br>We then chose to examine a natural disease with a very<br>cong MHC association: progression and regression of

any non-mammalian vertebrate (Kaufman *et al.* 1995).<br>We then chose to examine a natural disease with a very<br>strong MHC association: progression and regression of<br>RSV-induced tumours RSV one of the first retroviruses We then chose to examine a natural disease with a very<br>strong MHC association: progression and regression of<br>RSV-induced tumours. RSV, one of the first retroviruses<br>described is the classic replication-competent transstrong MHC association: progression and regression of<br>RSV-induced tumours. RSV, one of the first retroviruses<br>described, is the classic replication-competent trans-<br>forming retrovirus with four genes (gag env hol and gr) RSV-induced tumours. RSV, one of the first retroviruses<br>described, is the classic replication-competent trans-<br>forming retrovirus with four genes (*gag, env, pol* and *src*)<br>flanked by long terminal repeats (LTRs). The pro described, is the classic replication-competent transforming retrovirus with four genes (*gag, env, pol* and *src*) flanked by long terminal repeats (LTRs). The proteins forming retrovirus with four genes (*gag, env, pol* and *src*) flanked by long terminal repeats (LTRs). The proteins encoded by the *gag, env* and *pol* genes are involved in replication of the virus whereas the *n*-src ge flanked by long terminal repeats (LTRs). The proteins encoded by the *gag, env* and *pol* genes are involved in replication of the virus, whereas the *v*-*src* gene encodes a tyresine kingse that appears to have been tran encoded by the *gag*, env and *pol* genes are involved in replication of the virus, whereas the  $v$ -*src* gene encodes a tyrosine kinase that appears to have been transduced from the normal chicken gene  $c$ -*src*. Infecte replication of the virus, whereas the  $v$ -src gene encodes a from the normal chicken gene  $c$ -src. Infected chickens

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THE ROYAL

PHILOSOPHICAL<br>TRANSACTIONS  $\overline{0}$  which progress in some individuals and regress in others.<br>In many studies of both inbred lines and chicken populawhich progress in some individuals and regress in others.<br>In many studies of both inbred lines and chicken popula-<br>tions the chicken MHC (the B-F/B-L, region of the B which progress in some individuals and regress in others.<br>In many studies of both inbred lines and chicken populations, the chicken MHC (the B-F/B-L region of the B<br>locus) is the maior determinant of this regression and In many studies of both inbred lines and chicken populations, the chicken MHC (the B-F/B-L region of the B locus) is the major determinant of this regression and progression with regression being genetically dominant tions, the chicken MHC (the B-F/B-L region of the B locus) is the major determinant of this regression and progression, with regression being genetically dominant.<br>More detailed work in certain lines has shown that the locus) is the major determinant of this regression and<br>progression, with regression being genetically dominant.<br>More detailed work in certain lines has shown that the<br>regression depends on a functioning immune system is progression, with regression being genetically dominant.<br>More detailed work in certain lines has shown that the<br>regression depends on a functioning immune system, is More detailed work in certain lines has shown that the regression depends on a functioning immune system, is associated with CD8-bearing cells, and is targeted to the  $n$ -crc gene (Kaufman & Venugonal 1998: Plachy *et al vergression depends on a functioning immune system, is* associated with CD8-bearing cells, and is targeted to the *v*-*src* gene (Kaufman & Venugopal 1998; Plachy *et al.* 1999) All of these attributes are consistent with associated with CD8-bearing cells, and is targeted to the  $v$ -src gene (Kaufman & Venugopal 1998; Plachy *et al.* 1992). All of these attributes are consistent with the hypothesis that the regression is due to recognition *v*-*src* gene (Kaufman & Venugopal 1998; Plachy *et al.* 1992). All of these attributes are consistent with the hypothesis that the regression is due to recognition by cytolytic T lymphocytes of v-src pentides bound to c 1992). All of these attributes are consistent with the hypothesis that the regression is due to recognition by cytolytic T lymphocytes of v-src peptides bound to class I molecules located on the surface of tumour cells hypothesis that the regression is due to recognicytolytic T lymphocytes of v-src peptides bound to<br>molecules located on the surface of tumour cells.<br>We used our peptide-binding motifs to prec tolytic T lymphocytes of v-src peptides bound to class I<br>plecules located on the surface of tumour cells.<br>We used our peptide-binding motifs to predict the<br>tential binding peptides encoded by the four genes of

molecules located on the surface of tumour cells.<br>We used our peptide-binding motifs to predict the<br>potential binding peptides encoded by the four genes of<br>RSV Prague strain C (the first completely sequenced We used our peptide-binding motifs to predict the potential binding peptides encoded by the four genes of RSV Prague strain C (the first completely sequenced RSV Schwartz et al. 1983; Takeya & Hanafusa 1983) The potential binding peptides encoded by the four genes of RSV Prague strain C (the first completely sequenced RSV; Schwartz *et al.* 1983; Takeya & Hanafusa 1983). The number of predicted peptides that fit the motif of the R RSV Prague strain C (the first completely sequenced<br>RSV; Schwartz *et al.* 1983; Takeya & Hanafusa 1983). The<br>number of predicted peptides that fit the motif of the B12<br>molecule from the resistant CB strain was far greater RSV; Schwartz *et al.* 1983; Takeya & Hanafusa 1983). The number of predicted peptides that fit the motif of the B12 molecule from the resistant CB strain was far greater than the number that fit the motif of the B4 molecu number of predicted peptides that fit the motif of the B12 molecule from the resistant CB strain was far greater than the number that fit the motif of the B4 molecule from the susceptible CC strain (Kaufman *et al.* 1995) molecule from the resistant CB strain was far greater<br>than the number that fit the motif of the B4 molecule<br>from the susceptible CC strain (Kaufman *et al.* 1995). We<br>then synthesized the predicted pentides for the *n*-s*x* than the number that fit the motif of the B4 molecule<br>from the susceptible CC strain (Kaufman *et al.* 1995). We<br>then synthesized the predicted peptides for the *v*-*src* gene<br>and tested their ability to bind the appropri from the susceptible CC strain (Kaufman *et al.* 1995). We then synthesized the predicted peptides for the  $v$ -*src* gene and tested their ability to bind the appropriate class I molecules A number of the peptides predict then synthesized the predicted peptides for the  $v$ -s $x$  gene<br>and tested their ability to bind the appropriate class I<br>molecules. A number of the peptides predicted to bind the<br>class I molecule from the resistant CB line and tested their ability to bind the appropriate class I molecules. A number of the peptides predicted to bind the class I molecule from the resistant CB line did in fact molecules. A number of the peptides predicted to bind the<br>class I molecule from the resistant CB line did in fact<br>bind, while none of the peptides predicted to bind the<br>class I molecule from the susceptible CC line bound class I molecule from the resistant CB line did in fact<br>bind, while none of the peptides predicted to bind the<br>class I molecule from the susceptible CC line bound<br>significantly We then used some of the peptides to vaccibind, while none of the peptides predicted to bind the<br>class I molecule from the susceptible CC line bound<br>significantly. We then used some of the peptides to vacci-<br>nate CB chickens against RSV infection, the first applic class I molecule from the susceptible CC line bound<br>significantly. We then used some of the peptides to vacci-<br>nate CB chickens against RSV infection, the first applicasignificantly. We then used some of the peptides to vaccinate CB chickens against RSV infection, the first application of such peptide vaccination to a non-mammalian vertebrate. We found that one peptide the peptide with nate CB chickens against RSV infection, the first application of such peptide vaccination to a non-mammalian vertebrate. We found that one peptide, the peptide with the strongest activity in the binding assay protected the tion of such peptide vaccination to a non-mammalian<br>vertebrate. We found that one peptide, the peptide with<br>the strongest activity in the binding assay, protected the<br>CR chickens from RSV-induced tumours (A Hofmann vertebrate. We found that one peptide, the peptide with<br>the strongest activity in the binding assay, protected the<br>CB chickens from RSV-induced tumours (A. Hofmann,<br>K. Hala and J. Kaufman, unpublished observation) an vertebrate. We found that one peptide, the peptide with<br>the strongest activity in the binding assay, protected the<br>CB chickens from RSV-induced tumours (A. Hofmann,<br>K. Hala and J. Kaufman, unpublished observation), an the CB chickens from RSV-induced tumours (A. Hofmann, K. Hala and J. Kaufman, unpublished observation), an observation consistent with our hypothesis.<br>Most interesting is the position of this protective K. Hala and J. Kaufman, unpublished observation), an

observation consistent with our hypothesis.<br>Most interesting is the position of this protective<br>peptide in the structure of the protein encoded by the<br> $v$ -src gree (figure 2). Both c-src and v-src proteins have Most interesting is the position of this protective<br>peptide in the structure of the protein encoded by the<br> $v$ -*src* gene (figure 2). Both c-src and v-src proteins have<br>three domains called src-homology regions (SH) 1-2 peptide in the structure of the protein encoded by the  $v$ -*src* gene (figure 2). Both c-src and v-src proteins have three domains called src-homology regions (SH) 1, 2 and 3 which are followed by a C-terminal tail with n  $v$ -src gene (figure 2). Both c-src and v-src proteins have three domains called src-homology regions (SH) 1, 2 and 3, which are followed by a C-terminal tail with no three domains called src-homology regions (SH) 1, 2<br>and 3, which are followed by a C-terminal tail with no<br>obvious secondary structure. A major mechanism for<br>regulating the c-src kinase involves a typosine residue in and 3, which are followed by a C-terminal tail with no<br>obvious secondary structure. A major mechanism for<br>regulating the c-src kinase involves a tyrosine residue in<br>the tail which when phosphorylated binds to the SH2 obvious secondary structure. A major mechanism for<br>regulating the c-src kinase involves a tyrosine residue in<br>the tail, which, when phosphorylated, binds to the SH2<br>domain, preventing the SH1 domain from acting as a regulating the c-src kinase involves a tyrosine residue in<br>the tail, which, when phosphorylated, binds to the SH2<br>domain, preventing the SH1 domain from acting as a the tail, which, when phosphorylated, binds to the SH2<br>domain, preventing the SH1 domain from acting as a<br>kinase. The sequences of c-src and v-src are nearly iden-<br>tical in the SH1 2 and 3 domains, but the C-terminal domain, preventing the SH1 domain from acting as a kinase. The sequences of c-src and v-src are nearly identical in the SH1, 2 and 3 domains, but the C-terminal tails are completely different. In particular, the regukinase. The sequences of c-src and v-src are nearly identical in the SHI, 2 and 3 domains, but the C-terminal<br>tails are completely different. In particular, the regu-<br>latory tyrosine is absent from the tail of y-src, so th tical in the SHI, 2 and 3 domains, but the C-terminal<br>tails are completely different. In particular, the regu-<br>latory tyrosine is absent from the tail of v-src, so the viral<br>kinase is not well regulated by the cell (leadin tails are completely different. In particular, the reguformation). The peptide, which, upon vaccination, confers kinase is not well regulated by the cell (leading to transformation). The peptide, which, upon vaccination, confers protection from tumours, is located in the C-terminal tail. This is consistent with the fact that pentides formation). The peptide, which, upon vaccination, confers<br>protection from tumours, is located in the C-terminal<br>tail. This is consistent with the fact that peptides derived<br>elsewhere in the v-src protein are likely to be t protection from tumours, is located in the C-terminal<br>tail. This is consistent with the fact that peptides derived<br>elsewhere in the v-src protein are likely to be the same as<br>the self-peptides from the c-src protein, and s tail. This is consistent with the fact that peptides derived<br>elsewhere in the v-src protein are likely to be the same as<br>the self-peptides from the c-src protein, and so will not be recognized because of T-cell tolerance. Exelf-peptides from the c-src protein, and so will not be cognized because of T-cell tolerance.<br>The observation that no peptide predicted to bind the minantly expressed class I molecule of the susceptible

recognized because of T-cell tolerance.<br>The observation that no peptide predicted to bind the<br>dominantly expressed class I molecule of the susceptible<br>CC (B4) chicken actually did bind is also consistent with The observation that no peptide predicted to bind the<br>dominantly expressed class I molecule of the susceptible<br>CC (B4) chicken actually did bind, is also consistent with<br>our prediction that the susceptible chickens do not dominantly expressed class I molecule of the susceptible CC (B4) chicken actually did bind, is also consistent with our prediction that the susceptible chickens do not present CC (B4) chicken actually did bind, is also consistent with<br>our prediction that the susceptible chickens do not present<br>any protective peptide and therefore do not elicit any<br>cytolytic T cells to regress the tumours. Such u our prediction that the susceptible chickens do not present<br>any protective peptide and therefore do not elicit any<br>cytolytic T cells to regress the tumours. Such unrespon-<br>siveness is not restricted to the B4 haplotype sin any protective peptide and therefore do not elicit any<br>cytolytic T cells to regress the tumours. Such unrespon-<br>siveness is not restricted to the B4 haplotype, since we<br>predicted that the class I motif for the B15 haplotyp cytolytic T cells to regress the tumours. Such unresponsiveness is not restricted to the B4 haplotype, since we predicted that the class I motif for the B15 haplotype fits



Figure 2. The cellular tyrosine kinase c-src and the viral<br>homologue v-src differ at the C-terminal tail, leading to<br>differences in regulation. The three src-homology domains Figure 2. The cellular tyrosine kinase c-src and the viral<br>homologue v-src differ at the C-terminal tail, leading to<br>differences in regulation. The three src-homology domains<br>(SH1\_SH2 and SH3) are depicted as circles and t homologue v-src differ at the C-terminal tail, leading to<br>differences in regulation. The three src-homology doma<br>(SH1, SH2 and SH3) are depicted as circles and the<br>C-terminal tail as a straight line (c-src) or a jagged lin differences in regulation. The three src-homology domains<br>(SH1, SH2 and SH3) are depicted as circles and the<br>C-terminal tail as a straight line (c-src) or a jagged line<br>(v-src) The C-terminal tail of c-src bears a tyrosin (SH1, SH2 and SH3) are depicted as circles and the C-terminal tail as a straight line (c-src) or a jagged line (v-src). The C-terminal tail of c-src bears a tyrosine  $(Y)$ , C-terminal tail as a straight line (c-src) or a jagged line<br>(v-src). The C-terminal tail of c-src bears a tyrosine  $(Y)$ ,<br>which, when phosphorylated  $(Y-P)$ , binds to the SH2 domain<br>inhibiting the kinase activity of the SH1 (v-src). The C-terminal tail of c-src bears a tyrosine  $(Y)$ ,<br>which, when phosphorylated  $(Y-P)$ , binds to the SH2 domain<br>inhibiting the kinase activity of the SH1 domain. In contrast,<br>the C-terminal tail of v-src bears no t inhibiting the kinase activity of the SH1 domain. In contrast, the C-terminal tail of v-src bears no tyrosine and thus is not regulated in this fashion. the C-terminal tail of v-src bears no tyrosine and thus is not

regulated in this lashion.<br>few peptides from RSV, and data in the literature show<br>that the BI5 hanlotyne confers susceptibility to a number few peptides from RSV, and data in the literature show<br>that the B15 haplotype confers susceptibility to a number<br>of strains of RSV (Brown *et al.* 1984: Cutting *et al.* 1981: few peptides from RSV, and data in the literature show<br>that the Bl5 haplotype confers susceptibility to a number<br>of strains of RSV (Brown *et al.* 1984; Cutting *et al.* 1981;<br>Kaufman *et al.* 1995) that the Bl5 haplotype confers susceptibility to a number<br>of strains of RSV (Brown *et al.* 1984; Cutting *et al.* 1981;<br>Kaufman *et al.* 1995). strains of RSV (Brown *et al.* 1984; Cutting *et al.* 1981;<br>aufman *et al.* 1995).<br>While there are other experiments to be done, we feel<br>nfident that the reason why some chickens die on infect-

Kaufman *et al.* 1995).<br>While there are other experiments to be done, we feel<br>confident that the reason why some chickens die on infect-<br>ion with certain small pathogens is because no effective While there are other experiments to be done, we feel<br>confident that the reason why some chickens die on infect-<br>ion with certain small pathogens is because no effective<br>pentide derived from the pathogen is presented by th confident that the reason why some chickens die on infect-<br>ion with certain small pathogens is because no effective<br>peptide derived from the pathogen is presented by the<br>class I molecules to T cells. We have evidence to su ion with certain small pathogens is because no effective<br>peptide derived from the pathogen is presented by the<br>class I molecules to T cells. We have evidence to support<br>the same explanation for the response to vaccines tha peptide derived from the pathogen is presented by the<br>class I molecules to T cells. We have evidence to support<br>the same explanation for the response to vaccines that<br>elicit a class I or class II MHC-restricted response. I class I molecules to T cells. We have evidence to support the same explanation for the response to vaccines that<br>elicit a class I or class II MHC-restricted response. In<br>mammals, such phenomena have been extensively exam-<br>ined as 'immune response (Ir) gene effects' but were only elicit a class I or class II MHC-restricted response. In<br>mammals, such phenomena have been extensively exam-<br>ined as 'immune response (Ir) gene effects', but were only<br>discernible when inbred mouse and hamster strains were mammals, such phenomena have been extensively examined as 'immune response (Ir) gene effects', but were only discernible when inbred mouse and hamster strains were ined as 'immune response (Ir) gene effects', but were only<br>discernible when inbred mouse and hamster strains were<br>immunized with molecules bearing very limited epitopes<br>(for instance renetitive synthetic pentides) (Kantor discernible when inbred mouse and hamster strains were<br>immunized with molecules bearing very limited epitopes<br>(for instance, repetitive synthetic peptides) (Kantor *et al.*<br>1963: McDevitt & Chinitz 1969). In contrast, we f immunized with molecules bearing very limited epitopes (for instance, repetitive synthetic peptides) (Kantor *et al.* 1963; McDevitt & Chinitz 1969). In contrast, we find that chicken strains can show striking differences (for instance, repetitive synthetic peptides) (Kantor *et al.* 1963; McDevitt & Chinitz 1969). In contrast, we find that chicken strains can show striking differences in response to complicated commercial vaccines. From the point of view of mathematical modelling,<br>From the point of view of mathematical modelling,<br>ickens represent an opportunity to understand the

response to complicated commercial vaccines.<br>From the point of view of mathematical modelling,<br>chickens represent an opportunity to understand the<br>effects of real pathogens on populations with defined From the point of view of mathematical modelling,<br>chickens represent an opportunity to understand the<br>effects of real pathogens on populations with defined<br>genetics but on a scale almost unthinkable for hiomedical chickens represent an opportunity to understand the<br>effects of real pathogens on populations with defined<br>genetics but on a scale almost unthinkable for biomedical<br>model species both in laboratory experiments and in the effects of real pathogens on populations with defined<br>genetics but on a scale almost unthinkable for biomedical<br>model species, both in laboratory experiments and in the<br>field. One interesting challenge would be to examine genetics but on a scale almost unthinkable for biomedical<br>model species, both in laboratory experiments and in the<br>field. One interesting challenge would be to examine the<br>impact of the single dominantly expressed class I model species, both in laboratory experiments and in the field. One interesting challenge would be to examine the impact of the single dominantly expressed class I and class II loci found in chickens on the epidemiology of field. One interesting challenge would be to examine the<br>impact of the single dominantly expressed class I and<br>class II loci found in chickens on the epidemiology of<br>small infectious pathogens and simple vaccines using impact of the single dominantly expressed class I and<br>class II loci found in chickens on the epidemiology of<br>small infectious pathogens and simple vaccines, using<br>modelling to guide the understanding of the evolutionary small infectious pathogens and simple vaccines, using modelling to guide the understanding of the evolutionary small infectious pathogens and simple vaccines, using<br>modelling to guide the understanding of the evolutionary<br>dynamics of viruses and their variants in host popula-<br>tions. In this sense, the minimal essential MHC of modelling to guide the understanding of the evolutionary<br>dynamics of viruses and their variants in host popula-<br>tions. In this sense, the minimal essential MHC of<br>chickens may be useful as a simple model system for dynamics of viruses and their variants in host populations. In this sense, the minimal essential MHC of chickens may be useful as a simple model system for biomedical and evolutionary studies tions. In this sense, the minimal essential MHC of chickens may be useful as a simple model system for biomedical and evolutionary studies.

## medical and evolutionary studies.<br>**3. A LARGE PATHOGEN UNCOVERS A NOVEL**<br>MECHANISM OF PESISTANCE? RGE PATHOGEN UNCOVERS A NO<br>MECHANISM OF RESISTANCE? **MECHANISM OF RESISTANCE?**<br>As described above, small pathogens encode few

proteins, so MHC-dependent resistance and susceptibility



Figure 3. An idealized depiction of the evolution of<br>virulence in MDV field strains over the past 30 years<br>(after Witter 1996), MDV strains have been classified Figure 3. An idealized depiction of the evolution of<br>virulence in MDV field strains over the past 30 years<br>(after Witter 1996). MDV strains have been classified<br>moderate (m) virulent (y) very virulent (yy) and yery virulence in MDV field strains over the past 30 years<br>(after Witter 1996). MDV strains have been classified<br>moderate (m), virulent (v), very virulent (vv) and very<br>virulent plus (vv+), based on a variety of criteria. Vacc moderate  $(m)$ , virulent  $(v)$ , very virulent  $(vv)$  and very<br>virulent plus  $(vv+)$ , based on a variety of criteria. Vaccines used include herpesvirus of turkeys (HVT), SB and HVT (Bivalent), Rispens, and Rispens and Bivalent (also called Trivalent).

Invalent).<br>in chickens may depend simply on the peptide-binding<br>specificity of the dominantly expressed class I molecule in chickens may depend simply on the peptide-binding<br>specificity of the dominantly expressed class I molecule.<br>In larger, pathogens, that, encode, many, proteins specificity of the dominantly expressed class I molecule.<br>In larger pathogens that encode many proteins, specificity of the dominantly expressed class I molecule.<br>In larger pathogens that encode many proteins,<br>appropriate peptides will exist for even the most fastidious<br>class I molecule making differential resistance based on In larger pathogens that encode many proteins,<br>appropriate peptides will exist for even the most fastidious<br>class I molecule, making differential resistance based on<br>peptide-binding specificity of a single MHC molecule appropriate peptides will exist for even the most fastidious<br>class I molecule, making differential resistance based on<br>peptide-binding specificity of a single MHC molecule<br>unlikely However the strongest association in any class I molecule, making differential resistance based on<br>peptide-binding specificity of a single MHC molecule<br>unlikely. However, the strongest association in any species<br>(to our knowledge) between an MHC and a disease, peptide-binding specificity of a single MHC molecule<br>unlikely. However, the strongest association in any species<br>(to our knowledge) between an MHC and a disease,<br>autoimmune or infectious, is the resistance of the chicken unlikely. However, the strongest association in any species<br>
(to our knowledge) between an MHC and a disease,<br>
autoimmune or infectious, is the resistance of the chicken<br>
MHC haplotype B2I to tumours caused by classic MDV (to our knowledge) between an MHC and a disease,<br>autoimmune or infectious, is the resistance of the chicken<br>MHC haplotype B21 to tumours caused by classic MDV,<br>a hernesvirus encoding at least 80 proteins (Calnek 1985; autoimmune or infectious, is the resistance of the chicken<br>MHC haplotype B21 to tumours caused by classic MDV,<br>a herpesvirus encoding at least 80 proteins (Calnek 1985;<br>Dietert et al. 1990: Kaufman & Lamont 1996; Plachy et MHC haplotype B21 to tumours caused by classic MDV,<br>a herpesvirus encoding at least 80 proteins (Calnek 1985;<br>Dietert *et al.* 1990; Kaufman & Lamont 1996; Plachy *et al.*<br>1992 Schat 1987) a herpesvirus encoding at least 80 proteins (Calnek 1985; Dietert et al. 1990; Kaufman & Lamont 1996; Plachy et al. 1992; Schat 1987).

As with other herpesviruses, the disease course after 1992 Schat 1987).<br>
As with other herpesviruses, the disease course after<br>
classic MDV infection is long and complicated, with an<br>
initial cytolytic infection of B cells and later T cells As with other herpesviruses, the disease course after<br>classic MDV infection is long and complicated, with an<br>initial cytolytic infection of B cells and later T cells,<br>followed by a latent infection of  $CD4^+$  T cells, with classic MDV infection is long and complicated, with an<br>initial cytolytic infection of B cells and later T cells,<br>followed by a latent infection of CD4<sup>+</sup> T cells, with<br>lethal T-cell tumours arising thereafter, dependent on initial cytolytic infection of B cells and later T cells,<br>followed by a latent infection of CD4<sup>+</sup> T cells, with<br>lethal T-cell tumours arising thereafter, dependent on<br>many factors including age, sex and genetic background followed by a latent infection of CD4<sup>+</sup> T cells, with<br>lethal T-cell tumours arising thereafter, dependent on<br>many factors including age, sex and genetic background.<br>Under the pressures of intensive busbandry practices and lethal T-cell tumours arising thereafter, dependent on<br>many factors including age, sex and genetic background.<br>Under the pressures of intensive husbandry practices and<br>vaccination, the field strains of MDV have changed in many factors including age, sex and genetic background.<br>Under the pressures of intensive husbandry practices and<br>vaccination, the field strains of MDV have changed in<br>various wave including the tissue location of tumours Under the pressures of intensive husbandry practices and<br>vaccination, the field strains of MDV have changed in<br>various ways, including the tissue location of tumours,<br>the stage of disease at which animals die and the abili vaccination, the field strains of MDV have changed in various ways, including the tissue location of tumours, the stage of disease at which animals die and the ability various ways, including the tissue location of tumours,<br>the stage of disease at which animals die and the ability<br>to cause disease after vaccination (figures 3 and 4)<br>(Witter 1996) the stage of disease<br>to cause disease<br>(Witter 1996).<br>The chicken cause disease after vaccination (figures 3 and 4)<br>Vitter 1996).<br>The chicken MHC is one important resistance locus,<br>t there are others. The only other resistance locus

(Witter 1996).<br>The chicken MHC is one important resistance locus,<br>but there are others. The only other resistance locus<br>whose genetic location is known has recently been shown The chicken MHC is one important resistance locus,<br>but there are others. The only other resistance locus<br>whose genetic location is known has recently been shown<br>to be syntenic with the natural killer complex (NKC), a but there are others. The only other resistance locus<br>whose genetic location is known has recently been shown<br>to be syntenic with the natural killer complex (NKC), a<br>genetic region in mice and humans that encodes lectinwhose genetic location is known has recently been shown<br>to be syntenic with the natural killer complex (NKC), a<br>genetic region in mice and humans that encodes lectin-<br>like NK cell recentors, and determines resistance, to to be syntenic with the natural killer complex (NKC), a<br>genetic region in mice and humans that encodes lectin-<br>like NK cell receptors and determines resistance to<br>hernesviruses (Bumstead 1998: Scalzo *et al* 1995) genetic region in mice and humans that encodes lectin-<br>like NK cell receptors and determines resistance to<br>herpesviruses (Bumstead 1998; Scalzo *et al.* 1995). like NK cell receptors and determines resistance to<br>herpesviruses (Bumstead 1998; Scalzo *et al.* 1995).<br>However, there is no evidence yet for the mechanism of<br>action determined by any of the resistance loci nor is it herpesviruses (Bumstead 1998; Scalzo *et al.* 1995).<br>However, there is no evidence yet for the mechanism of action determined by any of the resistance loci, nor is it clear at which stage of the disease any of the resista However, there is no evidence yet for the mechanism of action determined by any of the resistance loci, nor is it clear at which stage of the disease any of the resistance loci act action determined by any of the resistance loci, nor is it clear at which stage of the disease any of the resistance loci act.



Figure 4. An idealized depiction of mortality after infection<br>with two MDV strains ((*a*) HPRS-16 and (*b*) C12/130) in<br>three experimental chicken lines (lines 6, 7 and N). The with two MDV strains ((a) HPRS-16 and (b)  $C12/130$ ) in differences in mortality at various stages of the disease three experimental chicken lines (lines 6, 7 and N). The<br>differences in mortality at various stages of the disease<br>between strains of MDV are presumably due to differences in<br>pathogen virulence genes, while the differences differences in mortality at various stages of the disease<br>between strains of MDV are presumably due to differences in<br>pathogen virulence genes, while the differences in mortality<br>between lines of chickens are presumably du between strains of MDV are presumably due to differences in<br>pathogen virulence genes, while the differences in mortality<br>between lines of chickens are presumably due to different host<br>resistance genes pathogen virulenc<br>between lines of ch<br>resistance genes.

An interesting feature of the MHC association is the An interesting feature of the MHC association is the<br>rank order of resistance of MHC haplotypes, which<br>annears to be roughly the same in many studies over An interesting feature of the MHC association is the rank order of resistance of MHC haplotypes, which appears to be roughly the same in many studies over many vears in which different experimental and rank order of resistance of MHC haplotypes, which<br>appears to be roughly the same in many studies over<br>many years, in which different experimental and<br>commercial chicken flocks were infected with different appears to be roughly the same in many studies over<br>many years, in which different experimental and<br>commercial chicken flocks were infected with different field and laboratory MDV strains. Classically (with backcommercial chicken flocks were infected with different<br>field and laboratory MDV strains. Classically (with back-<br>ground genes segregating freely), B21 haplotypes are the<br>most resistant to MDV the haplotypes B2\_B6\_and\_B14 field and laboratory MDV strains. Classically (with background genes segregating freely), B2l haplotypes are the most resistant to MDV, the haplotypes B2, B6 and B14 are moderately resistant and other haplotypes are much ground genes segregating freely), B2l haplotypes are the<br>most resistant to MDV, the haplotypes B2, B6 and Bl4<br>are moderately resistant, and other haplotypes are much<br>less resistant, with Bl9 being the most susceptible (Cal most resistant to MDV, the haplotypes B2, B6 and Bl4 are moderately resistant, and other haplotypes are much less resistant, with Bl9 being the most susceptible (Calnek 1985; Plachy *et al.* 1992). This pattern is difficul less resistant, with Bl9 being the most susceptible (Calnek less resistant, with Bl9 being the most susceptible (Calnek 1985; Plachy *et al.* 1992). This pattern is difficult to reconcile with a simple recognition of peptide(s) by cytolytic  $T$  cells since escape variants of MDV w 1985; Plachy *et al.* 1992). This pattern is difficult to reconcile with a simple recognition of peptide(s) by cytolytic T cells, since escape variants of MDV would be expected to have mutated precisely the peptide(s) rec cile with a simple recognition of peptide(s) by cytolytic T<br>cells, since escape variants of MDV would be expected to<br>have mutated precisely the peptide(s) recognized, so that<br>the rank order of resistance would change. The cells, since escape variants of MDV would be expected to have mutated precisely the peptide(s) recognized, so that the rank order of resistance would change. The pattern is have mutated precisely the peptide(s) recognized, so that<br>the rank order of resistance would change. The pattern is<br>also unlikely to be due to resistance unrelated to the<br>immune system (such as sickle cell baemoglobin-medi the rank order of resistance would change. The pattern is<br>also unlikely to be due to resistance unrelated to the<br>immune system (such as sickle cell haemoglobin-mediated<br>resistance to malaria) since the genes that determine also unlikely to be due to resistance unrelated to the<br>immune system (such as sickle cell haemoglobin-mediated<br>resistance to malaria), since the genes that determine such<br>resistance in mammals have few alleles immune system (such as sickle cell haemoglobin-mediated<br>resistance to malaria), since the genes that determine such<br>resistance in mammals have few alleles.

**BIOLOGICAL SCIENCES** 

THE ROYA

PHILOSOPHICAL<br>TRANSACTIONS  $\overline{\delta}$ 

THE ROYAL<br>SOCIETY

PHILOSOPHICAL<br>TRANSACTIONS

In fact, what correlates with the rank order of the<br>HC-determined resistance and susceptibility to MDV In fact, what correlates with the rank order of the MHC-determined resistance and susceptibility to MDV reported in the literature is the relative level of class I MHC-determined resistance and susceptibility to MDV reported in the literature is the relative level of class I MHC-determined resistance and susceptibility to MDV<br>reported in the literature is the relative level of class I<br>molecules found on the surface of cells (Kaufman *et al.*<br>1995: Kaufman & Salomonsen 1997) In mammals the reported in the literature is the relative level of class I<br>molecules found on the surface of cells (Kaufman *et al.*<br>1995; Kaufman & Salomonsen 1997). In mammals, the<br>level of cell-surface class I expression is remarkably molecules found on the surface of cells (Kaufman *et al.* 1995; Kaufman & Salomonsen 1997). In mammals, the level of cell-surface class I expression is remarkably consistent between MHC haplotynes (although it varies 1995; Kaufman & Salomonsen 1997). In mammals, the level of cell-surface class I expression is remarkably consistent between MHC haplotypes (although it varies considerably between cell types). In chickens, the level of level of cell-surface class I expression is remarkably<br>consistent between MHC haplotypes (although it varies<br>considerably between cell types). In chickens, the level of<br>class I molecules expressed on the surface of cells v consistent between MHC haplotypes (although it varies<br>considerably between cell types). In chickens, the level of<br>class I molecules expressed on the surface of cells varies<br>depending on the MHC haplotype of the chicken considerably between cell types). In chickens, the level of<br>class I molecules expressed on the surface of cells varies<br>depending on the MHC haplotype of the chicken,<br>differing by as much as tenfold on certain cell types class I molecules expressed on the surface of cells varies<br>depending on the MHC haplotype of the chicken,<br>differing by as much as tenfold on certain cell types.<br>Remarkably the MDV-resistant B21 haplotype has the depending on the MHC haplotype of the chicken,<br>differing by as much as tenfold on certain cell types.<br>Remarkably, the MDV-resistant B21 haplotype has the<br>fewest class I molecules on the cell surface, the MDVdiffering by as much as tenfold on certain cell types.<br>Remarkably, the MDV-resistant B21 haplotype has the<br>fewest class I molecules on the cell surface, the MDV-<br>susceptible B19 haplotype has the most and the others are Remarkably, the MDV-resistant B21 haplotype has the fewest class I molecules on the cell surface, the MDV-susceptible B19 haplotype has the most and the others are ranged in between reflecting their susceptibility to class fewest class I molecules on the cell surface, the MDV-<br>susceptible B19 haplotype has the most and the others are<br>ranged in between, reflecting their susceptibility to classic<br>MDV We have found that the difference in cell-s susceptible B19 haplotype has the most and the others are<br>ranged in between, reflecting their susceptibility to classic<br>MDV. We have found that the difference in cell-surface<br>expression is not due to transcription, transla ranged in between, reflecting their susceptibility to classic<br>MDV. We have found that the difference in cell-surface<br>expression is not due to transcription, translation, associa-<br>tion, with  $\beta$ -microglobulin, acquisition MDV. We have found that the difference in cell-surface<br>expression is not due to transcription, translation, associa-<br>tion with  $\beta_2$ -microglobulin, acquisition of peptides or<br>stability but to some aspect of transport to expression is not due to transcription, translation, association with  $\beta_2$ -microglobulin, acquisition of peptides or stability, but to some aspect of transport to the cell tion with  $\beta_2$ -microglobulin, acquisition of peptides or stability, but to some aspect of transport to the cell surface. We currently know nothing about the molecular and cellular mechanisms responsible for this disease stability, but to some aspect of transport to the cell<br>surface. We currently know nothing about the molecular<br>and cellular mechanisms responsible for this disease asso-<br>ciation in chickens, although we favour the idea that surface. We currently know nothing about the molecular H<br>and cellular mechanisms responsible for this disease asso-<br>ciation in chickens, although we favour the idea that NK<br>cell recognition of the class Leell-surface expre and cellular mechanisms responsible for this disease association in chickens, although we favour the idea that NK cell recognition of the class I cell-surface expression level<br>is an important factor (Kaufman *et al* 1995– ciation in chickens, although we favour the idea that NK cell recognition of the class I cell-surface expression level<br>is an important factor (Kaufman *et al.* 1995, 1999*a*,*b*;<br>Kaufman & Salomonsen 1997) cell recognition of the class I cell-surface expression level<br>is an important factor (Kaufman *et al.* 1995, 1999*a,b*;<br>Kaufman & Salomonsen 1997). an important factor (Kaufman *et al.* 1995, 1999*a,b*;<br>sufman & Salomonsen 1997).<br>There is no precedent among mammals for a relation-<br>in hetween cell-surface class I levels and resistance to a

Kaufman & Salomonsen 1997).<br>There is no precedent among mammals for a relation-<br>ship between cell-surface class I levels and resistance to a<br>disease Indeed variation in total class I levels on the cell There is no precedent among mammals for a relation-<br>ship between cell-surface class I levels and resistance to a<br>disease. Indeed, variation in total class I levels on the cell<br>surface between mammalian MHC banlotynes has n ship between cell-surface class I levels and resistance to a disease. Indeed, variation in total class I levels on the cell surface between mammalian MHC haplotypes has not been reported. However, there is strong evidence disease. Indeed, variation in total class I levels on the cell<br>surface between mammalian MHC haplotypes has not<br>been reported. However, there is strong evidence for<br>differences in cell-surface expression between alleles at surface between mammalian MHC haplotypes has not<br>been reported. However, there is strong evidence for<br>differences in cell-surface expression between alleles at<br>particular mammalian class I loci (Hansen *et al* 2000) been reported. However, there is strong evidence for differences in cell-surface expression between alleles at particular mammalian class I loci (Hansen *et al.* 2000; Neefies & Ploegh 1988; Neisig *et al.* 1996) Thus it m differences in cell-surface expression between alleles at particular mammalian class I loci (Hansen *et al.* 2000; Neefjes & Ploegh 1988; Neisig *et al.* 1996). Thus, it may be that the cell-surface class I expression in m particular mammalian class I loci (Hansen *et al.* 2000;<br>Neefjes & Ploegh 1988; Neisig *et al.* 1996). Thus, it may be<br>that the cell-surface class I expression in mammals<br>appears constant because it is an average of many Neefjes & Ploegh 1988; Neisig *et al.* 1996). Thus, it may be that the cell-surface class I expression in mammals appears constant because it is an average of many loci, whereas in chickens the transport of a single domina that the cell-surface class I expression in mammals appears constant because it is an average of many loci, whereas in chickens, the transport of a single dominantly appears constant because it is an average of many loci,<br>whereas in chickens, the transport of a single dominantly<br>expressed class I molecule to the cell surface determines<br>the cell-surface expression level and so differenc whereas in chickens, the transport of a single dominantly<br>expressed class I molecule to the cell surface determines<br>the cell-surface expression level and so differences are easy<br>to see. If so, it may be that the same disea expressed class I molecule to the cell surface determines<br>the cell-surface expression level and so differences are easy<br>to see. If so, it may be that the same disease-resistance<br>mechanism is operative in mammals, just wait the cell-surface expression level and so differences are easy<br>to see. If so, it may be that the same disease-resistance<br>mechanism is operative in mammals, just waiting to be to see. If so, it may be that the same disease-resistance<br>mechanism is operative in mammals, just waiting to be<br>discovered. In this case, the minimal essential MHC of<br>chickens may serve as a simple model system for the mor mechanism is operative in mammals, just waiting to be discovered. In this case, the minimal essential MHC of chickens may serve as a simple model system for the more complicated systems in humans and other mammals discovered. In this case, the minimal essential MHC<br>chickens may serve as a simple model system for the n<br>complicated systems in humans and other mammals.<br>From the point of view of mathematical modelling chickens may serve as a simple model system for the more complicated systems in humans and other mammals.<br>From the point of view of mathematical modelling, the

complicated systems in humans and other mammals.<br>From the point of view of mathematical modelling, the<br>interaction of host resistance and pathogen virulence loci<br>during the complicated course of Marek's disease presents From the point of view of mathematical modelling, the<br>interaction of host resistance and pathogen virulence loci<br>during the complicated course of Marek's disease presents<br>an interesting opportunity given the variation in b interaction of host resistance and pathogen virulence lociduring the complicated course of Marek's disease presents<br>an interesting opportunity, given the variation in both<br>host and pathogen. It seems clear that MDV is evol during the complicated course of Marek's disease presents<br>an interesting opportunity, given the variation in both<br>host and pathogen. It seems clear that MDV is evolving<br>in response to various control measures (primarily va an interesting opportunity, given the variation in both host and pathogen. It seems clear that MDV is evolving in response to various control measures (primarily vaccination), with new 'vaccine breakthrough variants' host and pathogen. It seems clear that MDV is evolving appearing sometime after the introduction of each new and class I genes. In particular, we have shown that there<br>vaccine (figure 3). Indeed, the less attenuated vaccines are two classical class I genes, but because of diff nation), with new 'vaccine breakthrough variants'<br>appearing sometime after the introduction of each new<br>vaccine (figure 3). Indeed, the less attenuated vaccines<br>used now can cause some disease in susceptible chickens appearing sometime after the introduction of each new<br>vaccine (figure 3). Indeed, the less attenuated vaccines<br>used now can cause some disease in susceptible chickens,<br>so one challenge at present is to develop a 'sustainab vaccine (figure 3). Indeed, the less attenuated vaccines used now can cause some disease in susceptible chickens, so one challenge at present is to develop a 'sustainable' disease control strategy. Also, the polymorphism i used now can cause some disease in susceptible chickens,<br>so one challenge at present is to develop a 'sustainable'<br>disease control strategy. Also, the polymorphism in the<br>important disease-resistance loci suggests, that th so one challenge at present is to develop a 'sustainable'<br>disease control strategy. Also, the polymorphism in the<br>important disease-resistance loci suggests that the<br>chickens have also been evolving in response to MDV By disease control strategy. Also, the polymorphism in the<br>important disease-resistance loci suggests that the<br>chickens have also been evolving in response to MDV. By<br>following the disease after infection of genetically defin important disease-resistance loci suggests that the chicken MHC haplotypes. (ii) Some of the genes present chickens have also been evolving in response to MDV. By in the MHC of typical mammals are found in the following t chickens have also been evolving in response to MDV. By following the disease after infection of genetically defined<br>lines of chickens with different strains of MDV, these<br>host-pathogen interactions can be examined (figure 4),<br>first at the level of immunonathology and then at t lines of chickens with different strains of MDV, these<br>host–pathogen interactions can be examined (figure 4),<br>first at the level of immunopathology, and then at the<br>levels of cells and molecules. Such studies have both host–pathogen interactions can be examined (figure 4),<br>first at the level of immunopathology, and then at the<br>levels of cells and molecules. Such studies have both<br>academic and economic interest first at the level of immunopathology, and then at the levels of cells and molecules. Such studies have both academic and economic interest.

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## **4. CHICKENS HAVE A SMALL AND SIMPLE MHC IENS HAVE A SMALL AND SIMPLE<br>IN COMPARISON TO MAMMALS**

IN COMPARISON TO MAMMALS<br>As outlined above, chickens appear unable to protect THE COMPANISON TO MAINMALS<br>Themselves from certain pathogens that would never<br>hother a human and also appear unable to benefit from As outlined above, chickens appear unable to protect<br>themselves from certain pathogens that would never<br>bother a human, and also appear unable to benefit from<br>vaccines that would be adequate for a human. Our model themselves from certain pathogens that would never<br>bother a human, and also appear unable to benefit from<br>vaccines that would be adequate for a human. Our model<br>of the 'minimal essential MHC' proposes that these bother a human, and also appear unable to benefit from<br>vaccines that would be adequate for a human. Our model<br>of the 'minimal essential MHC' proposes that these<br>functional differences are due to molecular differences vaccines that would be adequate for a human. Our model<br>of the 'minimal essential MHC' proposes that these<br>functional differences are due to molecular differences<br>between the MHC of chickens and typical mammals of the 'minimal essential MHC' proposes that the<br>functional differences are due to molecular differen-<br>between the MHC of chickens and typical mammals.<br>The recently completed sequence (Aguado *et al* 199 nctional differences are due to molecular differences<br>tween the MHC of chickens and typical mammals.<br>The recently completed sequence (Aguado *et al.* 1999)<br>ows that the human MHC is at least 4 MB in size (and

between the MHC of chickens and typical mammals.<br>The recently completed sequence (Aguado *et al.* 1999)<br>shows that the human MHC is at least 4 MB in size (and<br>4 cM by recombinational distance) and contains at least The recently completed sequence (Aguado *et al.* 1999)<br>shows that the human MHC is at least  $4 \text{ MB}$  in size (and<br> $4 \text{ cM}$  by recombinational distance) and contains at least<br> $280$  genes, located in three large regions (f shows that the human MHC is at least  $4 \text{ MB}$  in size (and  $4 \text{ cM}$  by recombinational distance) and contains at least 280 genes, located in three large regions (figure 5). The class II region contains class II $\alpha$ - and  $4cM$  by recombinational distance) and contains at least 280 genes, located in three large regions (figure 5). The<br>class II region contains class  $\Pi\alpha$ - and  $\beta$ -chain genes as<br>well as some genes involved in antigen processing for the<br>class I pathway (TAPs LMPs and tapasin) an class II region contains class II $\alpha$ - and  $\beta$ -chain genes as<br>well as some genes involved in antigen processing for the<br>class I pathway (TAPs, LMPs and tapasin) and a myster-<br>ious nuclear kinase (RING3). The class I regi well as some genes involved in antigen processing for the<br>class I pathway (TAPs, LMPs and tapasin) and a myster-<br>ious nuclear kinase (RING3). The class I region contains<br>the classical class I genes for HLA-A HLA-B and class I pathway (TAPs, LMPs and tapasin) and a mysterious nuclear kinase (RING3). The class I region contains<br>the classical class I genes for HLA-A, HLA-B and<br>HLA-C molecules as well as non-classical class I genes ious nuclear kinase (RING3). The class I region contains<br>the classical class I genes for HLA-A, HLA-B and<br>HLA-C molecules, as well as non-classical class I genes<br>and certain other genes The class II and class I regions the classical class I genes for HLA-A, HLA-B and<br>HLA-C molecules, as well as non-classical class I genes<br>and certain other genes. The class II and class I regions<br>flank the class III region, which encodes many different HLA-C molecules, as well as non-classical class I genes<br>and certain other genes. The class II and class I regions<br>flank the class III region, which encodes many different<br>kinds of genes, including the complement components and certain other genes. The class II and class I regions<br>flank the class III region, which encodes many different<br>kinds of genes, including the complement components<br>C4, C2 and factor B. There are many pseudogenes, flank the class III region, which encodes many different<br>kinds of genes, including the complement components<br>C4, C2 and factor B. There are many pseudogenes,<br>repeats and repetitive elements in all three regions. The kinds of genes, including the complement components C4, C2 and factor B. There are many pseudogenes, repeats and repetitive elements in all three regions. The two most important points for the discussion that follows repeats and repetitive elements in all three regions. The two most important points for the discussion that follows repeats and repetitive elements in all three regions. The<br>two most important points for the discussion that follows<br>are (i) the fact that there are multiple classical class I<br>genes each gene locus having a large number of two most important points for the discussion that follows<br>are (i) the fact that there are multiple classical class I<br>genes, each gene locus having a large number of common<br>alleles (that is, they are highly polymorphic), an are (i) the fact that there are multiple classical class I<br>genes, each gene locus having a large number of common<br>alleles (that is, they are highly polymorphic), and each<br>allele having a different pentide-binding specifici genes, each gene locus having a large number of common alleles (that is, they are highly polymorphic), and each allele having a different peptide-binding specificity; and alleles (that is, they are highly polymorphic), and each<br>allele having a different peptide-binding specificity; and<br>(ii) that the genes (TAPs, LMPs and tapasin), the<br>products of which provide the peptides for these class I allele having a different peptide-binding specificity; and<br>
(ii) that the genes (TAPs, LMPs and tapasin), the<br>
products of which provide the peptides for these class I<br>
molecules are non-polymorphic and are located far awa (ii) that the genes (TAPs, LMPs and tapasin), the products of which provide the peptides for these class I molecules, are non-polymorphic and are located far away in the class II region products of which provide the peptides for these class I molecules, are non-polymorphic and are located far away in the class II region. becules, are non-polymorphic and are located far away<br>the class II region.<br>To lay the foundation for understanding the disease<br>sociations of the chicken MHC on a molecular level, we

in the class II region.<br>To lay the foundation for understanding the disease<br>associations of the chicken MHC on a molecular level, we<br>sequenced the  $R$ - $F/R$ - $I$  region of the  $R$  locus from the  $CR$ To lay the foundation for understanding the disease<br>associations of the chicken MHC on a molecular level, we<br>sequenced the B-F/B-L region of the B locus from the CB<br>chicken strain (B12 haplotyne) (figure 6) This region ha associations of the chicken MHC on a molecular level, we sequenced the B-F/B-L region of the B locus from the CB chicken strain (B12 haplotype) (figure 6). This region has all of the signal attributes of the MHC of well-s sequenced the B-F/B-L region of the B locus from the CB<br>chicken strain (Bl2 haplotype) (figure 6). This region has<br>all of the signal attributes of the MHC of well-studied<br>mammals: it contains the classical class I and clas chicken strain (Bl2 haplotype) (figure 6). This region has<br>all of the signal attributes of the MHC of well-studied<br>mammals: it contains the classical class I and class II<br>B-chain genes, and determines serological alloantig all of the signal attributes of the MHC of well-studied mammals: it contains the classical class I and class II  $\beta$ -chain genes, and determines serological alloantigens, mammals: it contains the classical class I and class II<br>β-chain genes, and determines serological alloantigens,<br>rapid allograft rejection, strong mixed lymphocyte reac-<br>tion and cellular cooperation in the immune response  $\beta$ -chain genes, and determines serological alloantigens,<br>rapid allograft rejection, strong mixed lymphocyte reac-<br>tion and cellular cooperation in the immune response.<br>There are many interesting differences between the rapid allograft rejection, strong mixed lymphocyte reaction and cellular cooperation in the immune response.<br>There are many interesting differences between the MHCs of typical mammals and the chicken MHCs but as tion and cellular cooperation in the immune response.<br>There are many interesting differences between the<br>MHCs of typical mammals and the chicken MHC, but as There are many interesting differences between the MHCs of typical mammals and the chicken MHC, but as this work was recently published and reviewed in detail (Kaufman *et al.* 1999*a b*: Kaufman 1999) we will simply MHCs of typical mammals and the chicken MHC, but as<br>this work was recently published and reviewed in detail<br>(Kaufman *et al.* 1999*a*,*b*; Kaufman 1999), we will simply<br>summarize the four main points (i) The B-F/B-L region this work was recently published and reviewed in detail (Kaufman *et al.* 1999*a*, $b$ ; Kaufman 1999), we will simply summarize the four main points. (i) The B-F/B-L region is simple and compact with only 11 genes identifi (Kaufman *et al.* 1999*a*,*b*; Kaufman 1999), we will simply summarize the four main points. (i) The B-F/B-L region is simple and compact, with only 11 genes identified in the 44 k B of the central region spanning the cla summarize the four main points. (i) The B-F/B-L region<br>is simple and compact, with only 11 genes identified in the<br>44 kB of the central region spanning the class II  $\beta$ -chain<br>and class I genes. In particular, we have sho is simple and compact, with only 11 genes identified in the  $44 \text{ kB}$  of the central region spanning the class II  $\beta$ -chain and class I genes. In particular, we have shown that there are two classical class I genes, but  $44 \text{ kB}$  of the central region spanning the class II  $\beta$ -chain and class I genes. In particular, we have shown that there are two classical class I genes, but because of differences in the promoters, only one is both t and class I genes. In particular, we have shown that there are two classical class I genes, but because of differences<br>in the promoters, only one is both transcribed and present<br>as RNA at a high level. Thus, there is effectively a single<br>dominantly expressed class I molecule in ma in the promoters, only one is both transcribed and present<br>as RNA at a high level. Thus, there is effectively a single<br>dominantly expressed class I molecule in many common<br>chicken MHC haplotunes (ii) Some of the genes pres as RNA at a high level. Thus, there is effectively a single<br>dominantly expressed class I molecule in many common<br>chicken MHC haplotypes. (ii) Some of the genes present<br>in the MHC of typical mammals are found in the dominantly expressed class I molecule in many common<br>chicken MHC haplotypes. (ii) Some of the genes present<br>in the MHC of typical mammals are found in the<br>sequenced region (such as class I class II B-chain TAP chicken MHC haplotypes. (ii) Some of the genes present<br>in the MHC of typical mammals are found in the<br>sequenced region (such as class I, class II  $\beta$ -chain, TAP,<br>DM, RING3 and C4 genes) but many are absent DM, RING3 and C4 genes) but many are absent sequenced region (such as class I, class II β-chain, TAP,<br>DM, RING3 and C4 genes) but many are absent<br>(including class II α-chain, LMP, DO, C2/factor B and<br>other class III region genes) (iii) There are genes present DM, RING3 and C4 genes) but many are absent (including class II  $\alpha$ -chain, LMP, DO, C2/factor B and other class III region genes). (iii) There are genes present in the sequenced region that would not be expected based (including class II  $\alpha$ -chain, LMP, DO, C2/factor B and<br>other class III region genes). (iii) There are genes present<br>in the sequenced region that would not be expected based<br>on the MHC of typical mammals including B-G ge other class III region genes). (iii) There are genes present<br>in the sequenced region that would not be expected based<br>on the MHC of typical mammals, including B-G genes



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Figure 5. Organization of human, mouse, rat and chicken MHCs, highlighting the locations and relative proximities of TAP and<br>classical class I genes (indicated with double-beaded arrow). The HLA complex of humans is divide Figure 5. Organization of human, mouse, rat and chicken MHCs, highlighting the locations and relative proximities of TAP and<br>classical class I genes (indicated with double-headed arrow). The HLA complex of humans is divide Figure 5. Organization of human, mouse, rat and chicken MHCs, highlighting the locations and relative proximities of TAP are classical class I genes (indicated with double-headed arrow). The HLA complex of humans is divide classical class I genes (indicated with double-headed arrow). The HLA complex of humans is divided into three regions, with<br>almost 4 MB (ca. 4 cM of recombinational distance) between the TAP genes and the furthest of the c A). The H-2 complex of mice has an additional region encoding a classical class I gene (the K gene in the K region), but the furthest classical class I gene (D and in some haplotypes L in the D region) is roughly 2 MB away A). The H-2 complex of mice has an additional region encoding a classical class I gene (the K gene in the K region), but the<br>furthest classical class I gene (D and in some haplotypes L in the D region) is roughly 2 MB away furthest classical class I gene (D and in some haplotypes L in the D region) is roughly 2 MB away from the TAP genes. The RT1<br>complex of rats has classical class I genes only in the A region (equivalent to the mouse K regi complex of rats has classical cl<br>from the TAP genes. The B lo<br>a distance of 30 nucleotides.



class II region class II region class III region<br>Figure 6. Cartoon of the B-F/B-L region from the B12 haplotype that was sequenced. Open boxes indicate genes; arrows indicate<br>transcriptional orientation. Solid lines undern Figure 6. Cartoon of the B-F/B-L region from the B12 haplotype that was sequenced. Open boxes indicate genes; arrows indicate<br>transcriptional orientation. Solid lines underneath indicate the regions equivalent to the class transcriptional orientation. Solid lines underneath indicate the regions equivalent to the class I, class II and class III regions of the mammalian MHC.

the mammahan MTC.<br>and C-type animal lectin genes. (iv) The chicken genes<br>are organized differently from the mammalian MHC. and C-type animal lectin genes. (iv) The chicken genes<br>are organized differently from the mammalian MHC,<br>with the TAP genes flanked by class I genes, the tapasin and C-type animal lectin genes. (iv) The chicken genes<br>are organized differently from the mammalian MHC,<br>with the TAP genes flanked by class I genes, the tapasin<br>gene flanked by class II B-chain genes, and class  $I/TAP$ are organized differently from the mammalian MHC,<br>with the TAP genes flanked by class I genes, the tapasin<br>gene flanked by class II  $\beta$ -chain genes, and class I/TAP<br>genes in between class II  $\beta$ -chain and C4 genes. The with the TAP genes flanked by class I genes, the tapasin<br>gene flanked by class II  $\beta$ -chain genes, and class I/TAP<br>genes in between class II  $\beta$ -chain and C4 genes. The two<br>most important points for the discussion that gene flanked by class II  $\beta$ -chain genes, and class I/TAP<br>genes in between class II  $\beta$ -chain and C4 genes. The two<br>most important points for the discussion that follows are<br>(i) that there is a single dominantly express genes in between class II  $\beta$ -chain and C4 genes. The two<br>most important points for the discussion that follows are<br>(i) that there is a single dominantly expressed classical class I gene, with many alleles, each of which has a (i) that there is a single dominantly expressed classical<br>class I gene, with many alleles, each of which has a<br>unique peptide-binding specificity, and (ii) that the TAP<br>and tanasin genes are polymorphic and located nearby class I gene, with many alleles, each of which has unique peptide-binding specificity, and (ii) that the TAI and tapasin genes are polymorphic and located nearby.<br>The central 44kB region is very compact, with all ique peptide-binding specificity, and (ii) that the TAP<br>d tapasin genes are polymorphic and located nearby.<br>The central  $44kB$  region is very compact, with an<br>erage gene size of  $13kB$  average intron size of  $200$ 

and tapasin genes are polymorphic and located nearby.<br>The central 44 kB region is very compact, with an<br>average gene size of 1.3 kB, average intron size of 200<br>nucleotides and intergenic distances (excluding predicted The central  $44kB$  region is very compact, with an average gene size of  $1.3 kB$ , average intron size of  $200$  nucleotides and intergenic distances (excluding predicted promoters) of as little as  $30$  nucleotides. Moreover, average gene size of 1.3 kB, average intron size of 200 nucleotides and intergenic distances (excluding predicted promoters) of as little as 30 nucleotides. Moreover, there nucleotides and intergenic distances (excluding predicted<br>promoters) of as little as 30 nucleotides. Moreover, there<br>are no obvious repetitive elements, pseudogenes or gene<br>fragments identified in the central region. In th promoters) of as little as 30 nucleotides. Moreover, there<br>are no obvious repetitive elements, pseudogenes or gene<br>fragments identified in the central region. In the absence<br>of recombinational hot spots such simplicity and are no obvious repetitive elements, pseudogenes or gene<br>fragments identified in the central region. In the absence<br>of recombinational hot spots, such simplicity and<br>compactness would be expected to result in a very low fragments identified in the central region. In the absence among outbred human populations or fixed by the of recombinational hot spots, such simplicity and founder effect in inbred strains of mice, leading to the compactn

level of recombination. This is precisely the result found<br>experimentally (Skiedt et al. 1985); not a single recombinlevel of recombination. This is precisely the result found<br>experimentally (Skjødt *et al.* 1985): not a single recombin-<br>ant was found between the genes determining the serolevel of recombination. This is precisely the result found<br>experimentally (Skjødt *et al.* 1985): not a single recombin-<br>ant was found between the genes determining the sero-<br>logically detected class  $\bf{I}$  ( $\bf{R}\text{-}F$ ) experimentally (Skjødt *et al.* 1985): not a single recombinant was found between the genes determining the sero-<br>logically detected class  $I$  (B-F) and class  $II$  (B-L) ant was found between the genes determining the sero-<br>logically detected class  $I$  (B-F) and class  $II$  (B-L)<br>molecules in over 6000 progeny, giving an upper limit of<br>0.017 cM across the chicken MHC in these experimental logically detected class I (B-F) and class II (B-L)<br>molecules in over 6000 progeny, giving an upper limit of<br>0.017 cM across the chicken MHC in these experimental<br>crosses compared with  $4 \text{ cM}$  across the human MHC a molecules in over 6000 progeny, giving an upper limit of 0.017 cM across the chicken MHC in these experimental crosses compared with  $4 \text{ cM}$  across the human MHC, a difference of at least 250-fold  $0.017$  cM across the chicken MHC in these experimental crosses compared with  $4 \text{ cM}$  across the human MHC, a difference of at least 250-fold.

The important implication from this low level of recombination is that the genes of the chicken MHC can The important implication from this low level of<br>recombination is that the genes of the chicken MHC can<br>evolve together as an allelic group, giving rise to distinct<br>hanlotynes that are relatively stable in evolution. In recombination is that the genes of the chicken MHC can<br>evolve together as an allelic group, giving rise to distinct<br>haplotypes that are relatively stable in evolution. In<br>humans and mice certain combinations of alleles of evolve together as an allelic group, giving rise to distinct<br>haplotypes that are relatively stable in evolution. In<br>humans and mice, certain combinations of alleles of<br>MHC genes ('baplotypes') are found together either haplotypes that are relatively stable in evolution. In humans and mice, certain combinations of alleles of MHC genes ('haplotypes') are found together, either humans and mice, certain combinations of alleles of MHC genes ('haplotypes') are found together, either somewhat more frequently than expected by chance among outbred buman populations or fixed by the MHC genes ('haplotypes') are found together, either<br>somewhat more frequently than expected by chance<br>among outbred human populations or fixed by the<br>founder effect in inbred strains of mice leading to the somewhat more frequently than expected by chance<br>among outbred human populations or fixed by the<br>founder effect in inbred strains of mice, leading to the<br>idea of stable haplotunes selected for differential disease among outbred human populations or fixed by the

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resistance (Bodmer 1978). However, in reality most resistance (Bodmer 1978). However, in reality most<br>mammalian MHCs in real populations are patchworks<br>because of the relatively high level of recombination and mammalian MHCs in real populations are patchworks sequence of the minor class I molecule of the B4 haplobecause of the relatively high level of recombination, and<br>in comparison, the chicken is the realization of the<br>concept of a haplotype. because of the relatively<br>in comparison, the chi<br>concept of a haplotype.<br>As mentioned above comparison, the chicken is the realization of the<br>ncept of a haplotype.<br>As mentioned above, we believe that the large, compli-<br>ted and redundant nature of the typical mammalian

concept of a haplotype.<br>As mentioned above, we believe that the large, complicated and redundant nature of the typical mammalian<br>MHC means that most haplotypes confer more or less As mentioned above, we believe that the large, complicated and redundant nature of the typical mammalian MHC means that most haplotypes confer more or less equal protection against most infectious pathogens (at cated and redundant nature of the typical mammalian<br>MHC means that most haplotypes confer more or less<br>equal protection against most infectious pathogens (at<br>least at the level of pentide presentation), whereas the MHC means that most haplotypes confer more or less<br>equal protection against most infectious pathogens (at<br>least at the level of peptide presentation), whereas the small and simple nature of the chicken MHC, particuleast at the level of peptide presentation), whereas the small and simple nature of the chicken MHC, particularly the dominant expression of a single class I gene, confers striking differences between individuals with small and simple nature of the chicken MHC, particularly the dominant expression of a single class I gene, confers striking differences between individuals with different MHC haplotypes in resistance and susceptibility confers striking differences between individuals with different MHC haplotypes in resistance and susceptibility confers striking differences between individuals with<br>different MHC haplotypes in resistance and susceptibility<br>to certain infectious pathogens. The evidence for this<br>differential resistance was discussed in 88.2 and 3. If different MHC haplotypes in resistance and susceptibility<br>to certain infectious pathogens. The evidence for this<br>differential resistance was discussed in §§ 2 and 3. If these<br>arguments are accepted, then one of the most im to certain infectious pathogens. The evidence for this differential resistance was discussed in  $\S$  2 and 3. If these arguments are accepted, then one of the most important questions is why the chicken would evolve an ann differential resistance was discussed in §§ 2 and 3. If these<br>arguments are accepted, then one of the most important<br>questions is why the chicken would evolve an apparently<br>suicidal strategy in which some MHC haplotynes le arguments are accepted, then one of the most important<br>questions is why the chicken would evolve an apparently<br>suicidal strategy, in which some MHC haplotypes lead to<br>death simply because the dominantly expressed class I questions is why the chicken would evolve an apparently<br>suicidal strategy, in which some MHC haplotypes lead to<br>death simply because the dominantly expressed class I<br>molecule fails to bind a protective pentide derived from suicidal strategy, in which some MHC haplotypes lead to<br>death simply because the dominantly expressed class I wild<br>molecule fails to bind a protective peptide derived from<br>an infectious pathogen. The problem is especially death simply because the dominantly expressed class I<br>molecule fails to bind a protective peptide derived from<br>an infectious pathogen. The problem is especially<br>perplexing in light of the fact that most chicken MHC molecule fails to bind a protective peptide derived from<br>
an infectious pathogen. The problem is especially<br>
perplexing in light of the fact that most chicken MHC<br>
haplotynes express more than one classical class I an infectious pathogen. The problem is especially<br>perplexing in light of the fact that most chicken MHC<br>haplotypes express more than one classical class I<br>molecule so that it would not seem to be such a difficult perplexing in light of the fact that most chicken MHC<br>haplotypes express more than one classical class I<br>molecule, so that it would not seem to be such a difficult haplotypes express more than one classical class I<br>molecule, so that it would not seem to be such a difficult<br>evolutionary step to upregulate expression of the poorly<br>expressed grene giving the chicken multiple wellmolecule, so that it would not seem to be such a difficult<br>evolutionary step to upregulate expression of the poorly<br>expressed gene, giving the chicken multiple well-<br>expressed class I molecules like typical mammals evolutionary step to upregulate expression of the<br>expressed gene, giving the chicken multiple<br>expressed class I molecules like typical mammals.<br>Again the answer at least at one level would and expressed gene, giving the chicken multiple well-<br>expressed class I molecules like typical mammals.<br>Again the answer, at least at one level, would appear to

expressed class I molecules like typical mammals.<br>Again the answer, at least at one level, would appear to<br>be rooted in the simple and compact nature of the<br>chicken MHC As mentioned above the low rate of Again the answer, at least at one level, would appear to<br>be rooted in the simple and compact nature of the<br>chicken MHC. As mentioned above, the low rate of<br>recombination in the chicken MHC means that alleles of be rooted in the simple and compact nature of the chicken MHC. As mentioned above, the low rate of recombination in the chicken MHC means that alleles of the MHC genes can coevolve While such coevolution chicken MHC. As mentioned above, the low rate of<br>recombination in the chicken MHC means that alleles of<br>the MHC genes can coevolve. While such coevolution<br>may apply to all the genes of the chicken MHC, thus far recombination in the chicken MHC means that alleles of<br>the MHC genes can coevolve. While such coevolution<br>may apply to all the genes of the chicken MHC, thus far<br>we have produced only the first pieces of evidence in the the MHC genes can coevolve. While such coevolution<br>may apply to all the genes of the chicken MHC, thus far<br>we have produced only the first pieces of evidence in the<br>relationship between the chicken class I and TAP genes may apply to all the genes of the chicken MHC, thus far<br>we have produced only the first pieces of evidence in the<br>relationship between the chicken class I and TAP genes,<br>as proposed in several recent reviews. In essence, w we have produced only the first pieces of evidence in the relationship between the chicken class I and TAP genes, as proposed in several recent reviews. In essence, we believe that the specificity for pentide translocation relationship between the chicken class I and TAP genes,<br>as proposed in several recent reviews. In essence, we<br>believe that the specificity for peptide translocation by<br>the TAP molecules and the specificity for peptide bind as proposed in several recent reviews. In essence, we believe that the specificity for peptide translocation by the TAP molecules and the specificity for peptide binding by the class I molecules converge in each haplotype believe that the specificity for peptide translocation by are located much nearer and are separated by recombin-<br>the TAP molecules and the specificity for peptide binding ation less frequently, so that the advantageous com the TAP molecules and the specificity for peptide binding<br>by the class I molecules converge in each haplotype, and<br>that this leads to a single dominantly expressed class I<br>molecule (or the equivalent several molecules all by the class I molecules converge in each haplotype, and<br>that this leads to a single dominantly expressed class I<br>molecule (or the equivalent, several molecules all with<br>very similar pertide-binding specificities) that this leads to a single dominantly exp<br>molecule (or the equivalent, several mole<br>very similar peptide-binding specificities).<br>In every chicken MHC haplotyne that w molecule (or the equivalent, several molecules all with<br>very similar peptide-binding specificities).<br>In every chicken MHC haplotype that we have exam-

ined (Kaufman *et al.* <sup>1999</sup>*<sup>a</sup>*), we found two classical class I genes that flank the *TAP1* and *TAP2* genes, of which one ined (Kaufman *et al.* 1999*a*), we found two classical class I<br>genes that flank the *TAP1* and *TAP2* genes, of which one<br>gene (the 'minor' gene) was transcribed very poorly<br>compared with the other (the dominantly expres genes that flank the *TAP1* and *TAP2* genes, of which one<br>gene (the 'minor' gene) was transcribed very poorly<br>compared with the other (the dominantly expressed or<br>'major' gene) Interestingly there were many more alleles gene (the 'minor' gene) was transcribed very poorly<br>compared with the other (the dominantly expressed or<br>'major' gene). Interestingly, there were many more alleles<br>of the major class I gene than the minor gene. The TAP compared with the other (the dominantly expressed or Thus, chickens (and perhaps most other non-<br>
'major' gene). Interestingly, there were many more alleles mammalian vertebrates; Kaufman 1999) may be suscep-<br>
of the major genes are also highly polymorphic, and some of the of the major class I gene than the minor gene. The TAP<br>genes are also highly polymorphic, and some of the<br>sequence variation is consistent with differences in the<br>specificity of pentide translocation. In the most obvious genes are also highly polymorphic, and some of the sequence variation is consistent with differences in the specificity of peptide translocation. In the most obvious example we found that the  $\mathcal{I}AP$  in the B4 handotype sequence variation is consistent with differences in the specificity of peptide translocation. In the most obvious example, we found that the *TAP1* in the B4 haplotype has positively charged residues in three positions wh specificity of peptide translocation. In the most obvious example, we found that the  $TAP$  in the B4 haplotype has positively charged residues in three positions where negatively charged residues are found in the other hap example, we found that the  $TAPI$  in the B4 haplotype has<br>positively charged residues in three positions where nega-<br>tively charged residues are found in the other haplotypes<br>examined. The pentides eluted from total class positively charged residues in three positions where negatively charged residues are found in the other haplotypes examined. The peptides eluted from total class I mole-cules of the B4 haplotype have three negatively charg tively charged residues are found in the other haplotypes examples of groups of genes evolving together in so-called<br>examined. The peptides eluted from total class I mole-<br>cules of the B4 haplotype have three negatively ch examined. The peptides eluted from total class I molecules of the B4 haplotype have three negatively charged<br>residues, and the dominantly expressed class I molecule of<br>the B4 haplotype has complementary positively charged<br>residues in the binding site. It seems yery likely th residues, and the dominantly expressed class I molecule of<br>the B4 haplotype has complementary positively charged<br>residues in the binding site. It seems very likely that the<br>R4 TAP only numps pertides that have three negati the B4 haplotype has complementary positively charged<br>residues in the binding site. It seems very likely that the<br>B4 TAP only pumps peptides that have three negatively<br>charged residues into the lumen of the endoplasmic residues in the binding site. It seems very likely that the B4 TAP only pumps peptides that have three negatively charged residues into the lumen of the endoplasmic

reticulum where they can bind to class I molecules. The reticulum where they can bind to class I molecules. The sequence of the minor class I molecule of the B4 haplo-<br>type is incompatible with binding pentides with three type is incompatible with binding peptides with three sequence of the minor class I molecule of the B4 haplo-<br>type is incompatible with binding peptides with three<br>negatively charged residues, so it will not assemble with<br>the numned peptides and be transported to the surface type is incompatible with binding peptides with three<br>negatively charged residues, so it will not assemble with<br>the pumped peptides and be transported to the surface.<br>Therefore, even if the minor gene was well expressed at negatively charged residues, so it will not assemble with<br>the pumped peptides and be transported to the surface.<br>Therefore, even if the minor gene was well expressed at<br>the RNA and protein levels it would not be involved i the pumped peptides and be transported to the surface.<br>Therefore, even if the minor gene was well expressed at<br>the RNA and protein levels, it would not be involved in<br>much antigen presentation. Thus, we believe that the Therefore, even if the minor gene was well expressed at<br>the RNA and protein levels, it would not be involved in<br>much antigen presentation. Thus, we believe that the<br>convergence of the specificity for pentile translocation the RNA and protein levels, it would not be involved in<br>much antigen presentation. Thus, we believe that the<br>convergence of the specificity for peptide translocation<br>and peptide binding is the reason for the single domimuch antigen presentation. Thus, we believe that the convergence of the specificity for peptide translocation and peptide binding is the reason for the single dominantly expressed class I molecule in chickens. and peptide binding is the reason for the single domid peptide binding is the reason for the single domi-<br>ntly expressed class I molecule in chickens.<br>In contrast to the proposed situation in chickens, the<br>NPs of well-studied mammals are not highly poly-

mantly expressed class I molecule in chickens.<br>In contrast to the proposed situation in chickens, the<br>TAPs of well-studied mammals are not highly poly-<br>morphic (Momberg et al. 1994: Pamer & Cresswell 1998) In contrast to the proposed situation in chickens, the TAPs of well-studied mammals are not highly poly-<br>morphic (Momberg *et al.* 1994; Pamer & Cresswell 1998).<br>Indeed there annears to be only one specificity for translo-TAPs of well-studied mammals are not highly poly-<br>morphic (Momberg *et al.* 1994; Pamer & Cresswell 1998).<br>Indeed, there appears to be only one specificity for translo-<br>cation in human TAP genes one for mouse TAP genes an morphic (Momberg *et al.* 1994; Pamer & Cresswell 1998).<br>Indeed, there appears to be only one specificity for translocation in humanTAP genes, one for mouse TAP genes and<br>two for rat TAP genes. In rats, the two specificiti Indeed, there appears to be only one specificity for translocation in human TAP genes, one for mouse TAP genes and two for rat TAP genes. In rats, the two specificities are due to differences in the  $7AP2$  gene, which dete cation in human TAP genes, one for mouse TAP genes and<br>two for rat TAP genes. In rats, the two specificities are due<br>to differences in the *TAP2* gene, which determine the speci-<br>ficity for the amino acid at the C-terminus two for rat TAP genes. In rats, the two specificities are due<br>to differences in the  $TAP2$  gene, which determine the specificity for the amino acid at the C-terminus of the peptide,<br>which is relatively unrestricted for one to differences in the *TAP2* gene, which determine the specificity for the amino acid at the C-terminus of the peptide, which is relatively unrestricted for one *TAP2* allele but must be hydrophobic for the other allele In ficity for the amino acid at the C-terminus of the peptide,<br>which is relatively unrestricted for one  $TAP2$  allele but<br>must be hydrophobic for the other allele. Interestingly, the<br>class I molecules in particular rat haplot which is relatively unrestricted for one  $TAP2$  allele but<br>must be hydrophobic for the other allele. Interestingly, the<br>class I molecules in particular rat haplotypes nearly<br>always have the same specificity for the C-termi must be hydrophobic for the other allele. Interestingly, the<br>class  $\;$  I molecules in particular rat haplotypes nearly<br>always have the same specificity for the C-terminal residue<br>as the linked  $\mathcal{T}AP2$  gene. In humans, class I molecules in particular rat haplotypes nearly<br>always have the same specificity for the C-terminal residue<br>as the linked *TAP2* gene. In humans, the TAP specificity<br>appears relatively unrestricted whereas in mice th always have the same specificity for the C-terminal residue<br>as the linked *TAP2* gene. In humans, the TAP specificity<br>appears relatively unrestricted, whereas in mice the TAP<br>specificity is for hydrophobic C-terminal resid as the linked  $TAP2$  gene. In humans, the TAP speciplears relatively unrestricted, whereas in mice the specificity is for hydrophobic C-terminal residues.<br>We believe that these data can be explained pears relatively unrestricted, whereas in mice the TAP<br>ecificity is for hydrophobic C-terminal residues.<br>We believe that these data can be explained by co-<br>olution (Joly *et al* 1998: Kaufman *et al* 1999*a h* 

specificity is for hydrophobic C-terminal residues.<br>We believe that these data can be explained by co-<br>evolution (Joly *et al.* 1998; Kaufman *et al.* 1999*a*,*b*;<br>Kaufman 1999) in terms of genetic linkage (figure 5). In We believe that these data can be explained by co-<br>evolution (Joly *et al.* 1998; Kaufman *et al.* 1999*a*,*b*;<br>Kaufman 1999), in terms of genetic linkage (figure 5). In<br>essence the less recombination that occurs between evolution (Joly *et al.* 1998; Kaufman *et al.* 1999*a*,*b*;<br>Kaufman 1999), in terms of genetic linkage (figure 5). In essence, the less recombination that occurs between two genetic loci the greater the probability of co Kaufman 1999), in terms of genetic linkage (figure 5). In essence, the less recombination that occurs between two genetic loci, the greater the probability of coevolution of the greates and the greater the specificity of i essence, the less recombination that occurs between two<br>genetic loci, the greater the probability of coevolution of<br>the genes and the greater the specificity of interaction<br>between the products they encode. For humans and genetic loci, the greater the probability of coevolution of<br>the genes and the greater the specificity of interaction<br>between the products they encode. For humans and mice,<br>class I and TAP genes are located far apart and ar the genes and the greater the specificity of interaction<br>between the products they encode. For humans and mice,<br>class I and TAP genes are located far apart and are between the products they encode. For humans and mice,<br>class I and TAP genes are located far apart and are<br>frequently separated by recombination, so that the TAPs<br>could only evolve to a 'best average fit' for all class I class I and TAP genes are located far apart and are<br>frequently separated by recombination, so that the TAPs<br>could only evolve to a 'best average fit' for all class I<br>specificities. In rats, the classical class I and TAP ge frequently separated by recombination, so that the TAPs<br>could only evolve to a 'best average fit' for all class I<br>specificities. In rats, the classical class I and TAP genes<br>are located much nearer and are separated by rec could only evolve to a 'best average fit' for all class I<br>specificities. In rats, the classical class I and TAP genes<br>are located much nearer and are separated by recombin-<br>ation less frequently so that the advantageous co specificities. In rats, the classical class I and TAP genes<br>are located much nearer and are separated by recombina-<br>ation less frequently, so that the advantageous combina-<br>tions of alleles stay together often enough to al tions of alleles stay together often enough to allow some ation less frequently, so that the advantageous combinations of alleles stay together often enough to allow some coevolution. This results in two sets of coevolving alleles, each with a particular specificity for the last tions of alleles stay together often enough to allow some<br>coevolution. This results in two sets of coevolving alleles,<br>each with a particular specificity for the last position of<br>the antigenic pentide. In chickens, the TAP coevolution. This results in two sets of coevolving alleles,<br>each with a particular specificity for the last position of<br>the antigenic peptide. In chickens, the TAPs are flanked<br>by the class I genes with only tens of nucle each with a particular specificity for the last position of the antigenic peptide. In chickens, the TAPs are flanked by the class I genes with only tens of nucleotides between the antigenic peptide. In chickens, the TAPs are flanked<br>by the class I genes with only tens of nucleotides between<br>them, and are virtually never separated by recombina-<br>tion. This result in many sets of coevolying alleles by the class I genes with only tens of nucleotides between<br>them, and are virtually never separated by recombina-<br>tion. This result in many sets of coevolving alleles, each<br>one of which affects a number of pentide positions them, and are virtually never separated by recom<br>tion. This result in many sets of coevolving alleles,<br>one of which affects a number of peptide positions.<br>Thus chickens (and perhaps most other Thus, chickens (and perhaps most other non-

one of which affects a number of peptide positions.<br>Thus, chickens (and perhaps most other non-<br>mammalian vertebrates; Kaufman 1999) may be suscep-<br>tible to certain pathogens ultimately because of the genetic Thus, chickens (and perhaps most other non-<br>mammalian vertebrates; Kaufman 1999) may be suscep-<br>tible to certain pathogens ultimately because of the genetic<br>organization of their MHC meaning that genome evoluorganization of their MHC, meaning that genome evolutible to certain pathogens ultimately because of the genetic<br>organization of their MHC, meaning that genome evolu-<br>tion plays a striking role in the life and death of<br>individuals Of course it is a mechanism of evolution th organization of their MHC, meaning that genome evolution plays a striking role in the life and death of individuals. Of course, it is a mechanism of evolution that variation at the DNA level leads to phenotypic differences tion plays a striking role in the life and death of<br>individuals. Of course, it is a mechanism of evolution that<br>variation at the DNA level leads to phenotypic differences<br>that are acted on by natural selection. There are a individuals. Of course, it is a mechanism of evolution that variation at the DNA level leads to phenotypic differences that are acted on by natural selection. There are also variation at the DNA level leads to phenotypic differences<br>that are acted on by natural selection. There are also<br>examples of groups of genes evolving together in so-called<br>'concerted evolution', although all examples that that are acted on by natural selection. There are also<br>examples of groups of genes evolving together in so-called<br>'concerted evolution', although all examples that we have<br>been able to find (some 380 papers from the Medlin examples of groups of genes evolving together in so-called<br>
'concerted evolution', although all examples that we have<br>
been able to find (some 380 papers from the Medline data-<br>
hase dating back to 1980) involve multigene 'concerted evolution', although all examples that we have been able to find (some 380 papers from the Medline data-<br>base dating back to 1980) involve multigene families or<br>repetitive elements. Indeed, 'concerted evolution' was<br>originally defined as 'the tendency of a family of re base dating back to 1980) involve multigene families or<br>repetitive elements. Indeed, 'concerted evolution' was<br>originally defined as 'the tendency of a family of repeated<br>genes to evolve in unison' (Zimmer et al. 1980) A f repetitive elements. Indeed, 'concerted evolution' was<br>originally defined as 'the tendency of a family of repeated<br>genes to evolve in unison' (Zimmer *et al.* 1980). A fasci-<br>nating aspect of the potential coevolution of g originally defined as 'the tendency of a family of repeated genes to evolve in unison' (Zimmer  $et al.$  1980). A fascinating aspect of the potential coevolution of genes within

 $\frac{1}{100}$ <br>the MHC is the fact that the genes are not related in<br>sequence or structure. Such coevolution between structuthe MHC is the fact that the genes are not related in<br>sequence or structure. Such coevolution between structu-<br>rally unrelated genes must have been an important feature the MHC is the fact that the genes are not related in<br>sequence or structure. Such coevolution between structurally unrelated genes must have been an important feature<br>of the evolution of many series of proteins involved in sequence or structure. Such coevolution between structurally unrelated genes must have been an important feature<br>of the evolution of many series of proteins involved in a<br>particular function (for instance, synthesis of a m rally unrelated genes must have been an important feature<br>of the evolution of many series of proteins involved in a<br>particular function (for instance, synthesis of a molecule<br>by a metabolic pathway). The evolution of such of the evolution of many series of proteins involved in a particular function (for instance, synthesis of a molecule by a metabolic pathway). The evolution of such ancient particular function (for instance, synthesis of a molecule<br>by a metabolic pathway). The evolution of such ancient<br>events is very difficult to study, whereas the coevolution of<br>MHC genes may still be happening. From the poi by a metabolic pathway). The evolution of such ancient<br>events is very difficult to study, whereas the coevolution of<br>MHC genes may still be happening. From the point of<br>view of molecular modelling the exploration of the events is very difficult to study, whereas the coevolution of MHC genes may still be happening. From the point of view of molecular modelling, the exploration of the relationships between the alleles of two genes and their MHC genes may still be happening. From the point of view of molecular modelling, the exploration of the relationships between the alleles of two genes and their view of molecular modelling, the exploration of the<br>relationships between the alleles of two genes and their<br>recombinational distance, the probability of coevolution<br>and the stringency of interaction will be most interesti relationships between the alleles of two genes and their<br>recombinational distance, the probability of coevolution<br>and the stringency of interaction will be most interesting. and the stringency of interaction will be most interesting.<br>Thanks to Dr Tim Powell, Dr Jansen Jacob and Dr Pete Kaiser

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PHILOSOPHICAL<br>TRANSACTIONS  $\overline{0}$ 

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**BIOLOGICAL**<br>SCIENCES