An Autoimmune Disease with Multiple Molecular Targets Abrogated by the Transgenic Expression of a Single Autoantigen in the Thymus

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Summary

Many autoimmune diseases are characterized by autoantibody reactivities to multiple cellular antigens. Autoantigens are commonly defined as targets of the autoimmune B cell response, but the role, if any, of these autoantigens in T cell–mediated autoimmune diseases is generally unknown. Murine experimental autoimmune gastritis is a CD4+ T cell–mediated organ-specific autoimmune disease induced by neonatal thymectomy of BALB/c mice. The murine disease is similar to human autoimmune gastritis and pernicious anemia, and is characterized by parietal and chief cell loss, submucosal mononuclear cell infiltrates, and autoantibodies to the α and β subunits of the gastric H/K ATPase. However, the specificity of T cells that cause the disease is not known.

To examine the role of the H/K ATPase in this T cell–mediated disease, transgenic mice were generated that express the β subunit of the H/K ATPase under the control of the major histocompatibility complex class II I-Eα promoter. We show that transgenic expression of the gastric H/K ATPase β subunit specifically prevents the onset of autoimmune gastritis after neonatal thymectomy. In addition, thymocyte transfer experiments suggest that tolerance of pathogenic autoreactive T cells is induced within the thymus of the transgenic mice. We conclude that the subunit of the gastric H/K ATPase is a major T cell target in autoimmune gastritis and that thymic expression of a single autoantigen can abrogate an autoimmune response to multiple autoantigens.

Many autoimmune diseases are associated with autoantibodies to specific antigens. This is true for systemic autoimmune diseases such as systemic lupus erythematosus, Sjogren's Syndrome (1), and scleroderma (2, 3), and organ-specific autoimmune diseases such as diabetes (4), primary biliary cirrhosis (5), thyroiditis (6), and pernicious anemia (7). Another feature of the autoimmune response is that multiple self-molecules are often targeted within a particular disease such that an autoantibody profile for that disease can be described (2, 8). Apart from a few examples where autoantibodies to cell surface structures have been shown to be pathogenic, the role of autoantibodies in many autoimmune diseases is unclear (9).

There is strong evidence for the involvement of T cells in the pathogenesis of autoimmune diseases such as diabetes (10), experimental autoimmune uveitis (11), experimental autoimmune encephalomyelitis (12, 13), and experimental autoimmune gastritis (14–16). To define the mechanisms associated with T cell–mediated autoimmune diseases, it is of fundamental importance to first identify the antigens targeted by the T cells. Although many autoimmune diseases have multiple autoantibody targets, it is usually not known if these molecules are also T cell targets or whether the immune response to these antigens is involved in disease induction. Furthermore, immune responses in autoimmunity are usually most clearly defined at later stages of disease when pathology is well established. The predominant specificities of lymphocytes at this phase of disease may be quite different from the specificities that initiated autoimmunity during events that may have occurred months or even years before.

Autoimmune gastritis (chronic atrophic gastritis type A) is an organ-specific autoimmune disease of humans that is the underlying basis for pernicious anemia, the most common cause of vitamin B12 deficiency in White northern Europeans (17). The autoimmune lesion, confined to the fundus and body of the stomach, is typified by gastric mucosal atrophy, submucosal lymphocytic infiltrates, and loss of parietal and chief cells from the gastric mucosa (17). Circulating autoantibodies in autoimmune gastritis and pernicious anemia target molecules associated exclusively with the parietal cell (the α and β subunits of the gastric H/K ATPase complex and intrinsic factor) (16–19).
Neonatal (day 2-4) thymectomy of BALB/c mice results in the induction of autoimmune gastritis and oophoritis with a frequency of 40-60 and 20-30%, respectively (20, 21). Murine experimental autoimmune gastritis shares many of the features displayed by human autoimmune gastritis, such as submucosal lymphocytic infiltrates, selective parietal and chief cell loss (21-23), and autoantibodies reactive with the α and β subunits of the gastric H/K ATPase (24-27). It has become a widely used model for the study of autoimmune gastritis and organ-specific autoimmune diseases (7, 16, 21, 26, 28). Murine experimental autoimmune gastritis is a T cell-mediated disease, since the transfer of CD4+ T cells, but not serum, from diseased animals to nude or SCID mice is sufficient to initiate disease (14, 15).

We have shown that the B cell autoantigens in experimental autoimmune gastritis are also the α and β subunits of the gastric H/K ATPase complex (25). To define the T cell targets in this disease, we have produced transgenic mice that express the β subunit of the H/K ATPase under the control of the MHC class II I-Eα promoter (βH/K transgenic), resulting in widespread tissue expression of the β subunit, including the thymus. We show that transgenic expression of the β subunit alone prevents the production of autoantibodies to the α and β subunits of the H/K ATPase and the development of autoimmune gastritis manifested as gastric mononuclear cell infiltration after neonatal thymectomy. Thymocytes from βH/K-transgenic mice, in contrast to thymocytes from normal BALB/c and nontransgenic littermates, failed to transfer disease to BALB/c nude mice, suggesting tolerance induction within the thymus. We conclude that an immune response to the β subunit of the H/K ATPase complex initiates autoimmune gastritis. In addition, an autoimmune disease in which there are multiple autoantibody reactivities has been abrogated by the thymic expression of a single autoantigen.

Materials and Methods

Mice. BALB/c, C57BL/6, and Swiss mice for the production of transgenic mice were obtained from the Animal Resource Centre (Perth, Australia) or produced in the Monash University Medical School animal facility. Adult BALB/c mice for other experimental procedures were obtained from the Monash University Animal Services Centre (Melbourne, Australia). Progeny of transgenic mice were produced and housed under standard conditions at the Monash University Medical School animal facility. Transgenic mice for neonatal thymectomy were derived from lines 57 and 59 by mating the founder mouse with BALB/c mice, and from lines 25 and 50 by backcrossing the founder line twice to BALB/c mice. BALB/c nude mice used in thymocyte transfer experiments were obtained from the Animal Resource Centre. Thymocyte donors were nude mice used in thymocyte transfer experiments were obtained from the Animal Resource Centre. BALB/c, C57BL/6, and Swiss mice for the production of transgenic mice were obtained from the Animal Resource Centre (Perth, Australia) or produced in the Monash University Medical School animal facility. Adult BALB/c mice for other experimental procedures were obtained from the Monash University Animal Services Centre (Melbourne, Australia). Progeny of transgenic mice were produced and housed under standard conditions at the Monash University Medical School animal facility. Transgenic mice for neonatal thymectomy were derived from lines 57 and 59 by mating the founder mouse with BALB/c mice, and from lines 25 and 50 by backcrossing the founder line twice to BALB/c mice. BALB/c nude mice used in thymocyte transfer experiments were obtained from the Animal Resource Centre.

DNA Construction. The MHC class II I-E/H/K ATPase β subunit transgene (Fig. 1 a) was constructed as follows. A mouse H/K ATPase β subunit mini-gene was constructed by replacing a 960-bp BstEII fragment from a β subunit cDNA with a 3.97-kb BstEII fragment from a β subunit genomic clone (29). A 1.92-kb fragment encoding 5' flanking sequence nucleotides –39 to –1964 of the MHC class II I-Eα gene was blunt-end ligated to the 5' end of the β subunit mini-gene. A 350-bp fragment encoding the SV40 small t intron splice site and polyadenylation signal was ligated 3' of the mini-gene. The 5.9-kb construct was isolated from pBluescript SK- (Stratagene Inc., La Jolla, CA) by NotI and XhoI restriction enzyme digestion.

Generation of βH/K-transgenic Mice and Screening. βH/K-transgenic mice were generated using techniques previously described (30). The 5.9-kb transgene encoding the MHC class II I-E promoter and H/K ATPase β subunit mini-gene was purified on a nucleic acid chromatography system 52 column (BRL Life Technologies Inc., Gaithersburg, MD), microinjected into the pronuclei of (BALB/c × C57BL/6)F1 × BALB/c eggs, and transferred into the oviducts of pseudopregnant Swiss mice according to the method of Hogan et al. (31). βH/K-transgenic mice were identified by PCR analyses of mouse tail genomic DNA (31). PCR oligonucleotide primers designed to specifically amplify a region of 700 bp spanning the I-E promoter and β subunit mini-gene were 5'-CCC-TTGAAGACGATCTTCCC-3' and 5'-GTGCAGGTTGTGTGTGAG-3', respectively. PCR was performed in 50-μl reactions containing amplification buffer (50 mM KCl, 10 mM Tris-HCl, pH 8.3, 1.5 mM MgCl2, 0.1% gelatin), 200 μM of all four deoxyribonucleotides, 50 pmol oligonucleotide primers, and 2.5 U Tag DNA polymerase (Perkin Elmer Cetus, Branchbury, NJ). 30 cycles of 1.5 min at 95°C, 1.5 min at 65°C, and 3 min at 72°C were performed in a cycling waterbath. 10-μl samples were subjected to agarose gel electrophoresis, transferred to Nylon Hybond-N+ membrane (Amersham International, Buckinghamshire, England), incubated with prehybridization solution (6x SSC, 7% SDS, 0.1% skim milk powder) (1x SSC is 0.15 M NaCl/0.14 M tri-sodium citrate) at 65°C for 1-2 h, and hybridized overnight with 32P-labeled probes in prehybridization solution. Membranes were washed at 65°C in 0.1x SSC/0.5% SDS and fluorographed using Cronex intensifying screens (DuPont Co., Wilmington, DE) and x-ray film (Fuji) at –70°C. Four βH/K-transgenic lines (lines 25, 50, 57, and 59) were generated for analysis in this study.

mRNA Analysis. Transgene expression was detected by PCR analysis of cDNA generated from RNA. RNA isolation, reverse transcription, and PCR were performed essentially as previously described (32). Briefly, 3 μg of total RNA was reverse transcribed (Moloney murine leukemia virus reverse transcriptase; BRL Life Technologies Inc., Gaithersburg, MD) using oligo(dT) primer. The reaction mixture was divided in two and subjected to PCR using primers designed to amplify the H/K ATPase β subunit or actin cdna. β subunit primers: 5'-GGCTTTTGGGGATCATC-3' and 5'-GGCTTTTGGGGATCATC-3', generated a product of 617 bp, and actin primers (33), 5'-ATGATACGCTGACTCCG-3' and 5'-ATGAGGTAGCTGACTCCG-3', generated a product of 568 bp. 30 cycles of 1.5 min at 95°C, 1.5 min at 60°C, and 3 min at 72°C were performed. 15-μl samples were subjected to agarose gel electrophoresis, transferred to Nylon Hybond-N+ membrane, and hybridized with 32P-labeled probes, washed, and autoradiographed as described above.

Neonatal Thymectomy. Transgenic mice from lines 25, 50, 57, and 59 were thymectomized on day 3 (day of birth designated as day 0) under cold anesthesia. The sternum was opened at the midline and after exposing the thymus, each lobe was aspirated with a Pasteur pipette attached to a vacuum. Mice were warmed with an infra-red heat lamp and returned to their mother. Incompletely thymectomized mice (6/117) were identified when killed and not analyzed further.

H/K ATPase ELISA. Anti-H/K ATPase α and β subunit antibodies in mouse sera were detected by ELISA essentially as previously described (34).
was measured spectrophotometrically at 490 nm. Nonspecific re- 
containing 0.2 mg/ml O-phenyldiamine (Sigma Chemical Co., St. 
Louis, MO) and 0.006% H₂O₂ for 30 min in the dark. The reac-
washed three times with PBS, 0.05% Tween-20. Horseradish per-
oxidase complex (Amersham International) at a dilution 
oxidase activity was detected in each well with 100 #1 substrate 
rabbit anti-mouse Ig (Amersham International) diluted 1:500 in 
Bound antibody was detected by incubations of 100 #1 biotinylated-
examined by epifluorescence microscopy with an excitation wave-
lenghth of 440–500 nm. mAbs 1H9 and 2B6, specific for the α and 
and β subunits of the H/K ATPase, respectively, and sera from normal 
BALB/c mice were used as control antibodies (25).

Histology. Stomachs and ovaries were fixed in 10% formalin 
in phosphate buffer and embedded in paraffin. Sections (5 μm) 
were cut and stained with haematoxylin and eosin. Gastritis was assessed 
by the presence of cellular infiltrates into the gastric glands and 
muscularis mucosa (22). Oophoritis was assessed by ovarian atrophy 
and cellular infiltrates throughout the ovary and into ovarian fol-

Results

Generation of βH/K-transgenic Mice and Gene Expression. 
The aim of this study was to examine the role of autoreactive 
T cells directed against the gastric H/K ATPase in the induc-
tion of autoimmune gastritis. Antibody expression in MHC 
class II-positive cells has been shown to cause antigen-specific 
clonal deletion within the thymus (37). Therefore, to elimi-
ate potentially autoreactive H/K ATPase β subunit–specific 
T cells, we expressed the β subunit of the gastric-specific H/K 
ATPase within the thymus under the control of the MHC 
class II I-Eβ promoter. The MHC class II I-E/H/K ATPase 
β subunit transgene (Fig 1 a) was injected into (BALB/c × 
C57BL/6)F1 × BALB/c oocytes, and four lines (lines 25, 
50, 57, and 59) of transgenic mice were generated. PCR anal-
alysis of RNA demonstrated that expression of H/K ATPase

![Figure 1](image-url)

Figure 1. Structure and expression of H/K ATPase β subunit transgene. (a) Hybrid MHC class II I-Ek/H/K ATPase β subunit construct comprised the 5' flanking sequence of the MHC class II I-Ek gene (thick black line), mouse H/K ATPase β subunit mini-gene, and a SV40 small 
t intron splice site and polyadenylation signal (striped box). 
The mini-gene comprised a cDNA fragment encoding 
exons 1 and 2 and a genomic fragment encoding exons 
3–7 (exons: open boxes) and introns 3–6 (thin black lines).
(b) PCR analysis of H/K ATPase β subunit and actin 
mRNA. RNA was isolated from line 25 transgenic mice 
and nontransgenic littermates from the tissues indicated.
RNA was reverse transcribed using an oligo(dT) primer 
and amplified with oligonucleotides specific for the β 
subunit of the H/K ATPase (expected product size of 617 
bp) and actin (expected product size of 568 bp) as indicated.
PCR products were subjected to electrophoresis on 
a 1% agarose gel and then transferred to a nylon mem-
brane. Products were detected by hybridization with approp-
riate 32P-labeled probes. Bound probe was detected by 
fluorography. Analysis of actin mRNA served as an 
internal control and confirmed that similar amounts of 
RNA were used in each reaction.
β subunit mRNA in nontransgenic littermates occurred only in the stomach (Fig. 1 b). Prolonged exposure of fluorographs did not reveal expression in the thymus or any other nongastric tissue (data not shown). In contrast, βH/K-transgenic mice expressed H/K ATPase β subunit mRNA in all tissues examined, including the thymus (Fig. 1 b). Indirect immunofluorescence and immunoblotting of nontissue tissues from βH/K-transgenic mice failed to detect H/K ATPase β subunit protein (data not shown). This was likely due to the rapid degradation of the β subunit (van Driel, I., unpublished data), and is similar to the findings with the α and β subunits of the related Na/K ATPase, which show instability when expressed as individual molecules (38).

Prevention of Experimental Autoimmune Gastritis. Littermates from line 25 were thymectomized at day 3 and assessed for the development of anti-H/K ATPase antibodies, gastritis, or oophoritis over a period of 5 mo. None (0/23) of the βH/K-transgenic mice developed antibodies to the α and β subunits of the H/K ATPase, parietal cell autoantibodies, or mononuclear cell infiltrates in the gastric mucosa (Fig. 2, a and b). A delayed immune response was excluded by the absence of anti-H/K ATPase antibody reactivity up to 5 mo after thymectomy (Fig. 2 a). In our experience, maximal antibody reactivity is usually obtained by 3 mo postthymectomy (Alderuccio, F., personal observations). In contrast, thymectomized nontransgenic littermates developed anti-H/K ATPase antibodies with a frequency of 45% (9/20) (Fig. 2 a), an incidence consistent with previous reports (20). Mice were assessed for gastric mononuclear cell infiltrates by histological examination of stomachs (Fig. 3). All mice with H/K ATPase and parietal cell antibodies had cellular infiltrates in the gastric mucosa (Figs. 2 b and 3, a and b).

The occurrence of autoimmune oophoritis in neonatally thymectomized female BALB/c mice served as an internal control for our experimental system. Oophoritis was assessed by histological examination of ovaries (Fig. 3). The incidence of oophoritis in βH/K-transgenic (4/14, 28%) and nontransgenic (3/12, 25%) mice (Figs. 2 b and 3, c and d) was similar and consistent with previous reports (20). This indicated that βH/K-transgenic mice were still capable of initiating an autoimmune response to ovarian antigens, and that abrogation of autoimmune disease was gastric specific.

Anti-H/K ATPase antibodies were not found in transgenic littermates of three other independent βH/K-transgenic lines (lines 50, 57, and 59) (Fig. 4) after neonatal thymectomy. From the detailed analysis of transgenic line 25 and previously unpublished observations (Alderuccio, F., and T. Martinelli) the occurrence of anti-H/K ATPase antibodies is always accompanied by cellular infiltration of the gastric mucosa. Therefore, these data indicate that autoimmune gastritis was also prevented in these βH/K-transgenic lines. Furthermore, disease prevention was associated with transgene expression and not to chance insertion of the transgene into the mouse genome. Overall, in all four βH/K-transgenic lines, none (0/55) of the transgenic mice developed anti-H/K ATPase antibodies compared with 42% (24/56) of the nontransgenic littermates.

Tolerance Induction of Autoreactive T Cells within the Thymus. The prevention of experimental autoimmune gastritis in βH/K-transgenic mice after neonatal thymectomy suggests that the autoreactive T cells that cause disease in normal BALB/c or nontransgenic littermates have been tolerated. Since expression of the βH/K transgene was not confined to the thymus, it was not clear if T cell tolerance had occurred within the thymus or in the periphery. Thymocytes transferred from adult BALB/c mice to T cell-deficient BALB/c nude mice are capable of inducing autoimmune gastritis (14, 15). To assess the presence of autoreactive T cells within the thymus of βH/K-transgenic and nontransgenic littermates, thymocytes were transferred to BALB/c nude recipients. Autoimmune gastritis was induced in BALB/c nude mice by thymocyte transfer from normal BALB/c mice (5/6) and nontransgenic littermates (5/7), but not from βH/K-transgenic mice (0/7) (Fig. 5), suggesting that tolerance of pathogenic autoreactive T cells in the βH/K-transgenic mice was induced within the thymus.

Figure 2. H/K ATPase autoantibodies, gastritis, and oophoritis in neonatally thymectomized mice. (a) Mice from line 25 were thymectomized at day 3 and transgenic status was determined at weaning. At 3 mo, sera were collected from all mice and approximately half the βH/K-transgenic and nontransgenic mice were killed for histological examination. Sera were collected from the remaining mice at 5 mo of age. Anti-H/K ATPase antibodies were detected by ELISA. Filled bars, βH/K-transgenic mice at 3 mo; open bars, βH/K-transgenic mice at 5 mo; diagonal striped bars, nontransgenic mice at 3 mo; horizontal striped bars, nontransgenic mice at 5 mo. (b) Immunofluorescence (IF) to detect anti-parietal cell autoantibodies and histological examination of stomachs and ovaries of mice from a. Mice are represented in the same order as a and are shown directly below the corresponding ELISA readings. The presence of parietal cell autoantibodies, gastritis, or oophoritis is indicated by a filled box. Stripped boxes indicate male mice excluded from analysis of oophoritis.
**Discussion**

The pathogenesis of many autoimmune diseases relies upon autoreactive T cells (10, 11, 16, 39), however, specificities of the T cells that induce autoimmune diseases are not known. Many investigations into autoimmunity have concentrated on the autoantibody response apparent in the later stages of disease when the immune system is recognizing several target molecules. However, it is unclear whether these end-stage responses are of relevance to the initiation of the disease process. An initial immune response with accompanying tissue destruction and inflammation will result in the influx of lymphocytes with multiple antigen specificities. The release of
The same pattern of disease prevention was found in all the
by the presence of cellular infiltrates in the gastric mucosa.
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failed to develop anti-parietal cell autoantibodies and mono-
dent ~H/K transgenic mouse lines. Transgenic littermates
transgenic littermates was at the expected frequency, as defined
nuclear cell infiltrates in the gastric mucosa. In contrast, the
autoimmune gastritis would be prevented if T cells of this
within the thymuses of ~H/K-transgenic mice. Thus, au-
soned that during T cell development, autoreactive T cells
subunit mRNA expression was found in all tissues examined
gastric H/K ATPase/β subunit was driven by the 5' flanking
of transgenic mice were produced in which expression of the
ment of autoimmune gastritis.
specificity are required for the onset of disease.
Clonal deletion of developing T cells within the thymus
can be directed by MHC class II-positive cells (37). Four lines
of transgenic mice were produced in which expression of the
gastric H/K ATPase/β subunit was driven by the 5' flanking
region of the MHC class II I-Ek gene (40). H/K ATPase β
subunit mRNA expression was found in all tissues examined
from βH/K-transgenic mice, including the thymus. We rea-
soned that during T cell development, autoreactive T cells
specific for the H/K ATPase β subunit would be tolerant
within the thymuses of βH/K-transgenic mice. Thus, au-
toimmune gastritis would be prevented if T cells of this
specificity are required for the onset of disease.
We neonatally thymectomized mice from four indepen-
dent βH/K transgenic mouse lines. Transgenic littermates
failed to develop anti-parietal cell autoantibodies and mono-
nuclear cell infiltrates in the gastric mucosa. In contrast, the
incidence of autoimmune gastritis in thymectomized non-
transgenic littermates was at the expected frequency, as defined
by the presence of cellular infiltrates in the gastric mucosa.
The same pattern of disease prevention was found in all the
four independent βH/K-transgenic lines, indicating that the
phenomenon observed was reproducible and not associated
with the insertion of the βH/K transgene within a partic-
ular genetic locus. Neonatally thymectomized BALB/c mice
also develop oophoritis (20). The incidences of oophoritis
in both βH/K-transgenic mice and nontransgenic littermates
were identical. This finding indicated that the immune system
of transgenic mice was still capable of initiating an autoim-
mune response to ovarian antigens. Thus the prevention of
thymectomy-induced autoimmune disease in β-H/K-trans-
genetic mice was gastric specific. From these data we conclude
that a T cell response to the H/K ATPase β subunit is an
absolute requirement for the development of autoimmune
gastritis. Furthermore, it appears that the immune response
to the other molecular target in this disease, the H/K AT-
pase α subunit, is either insufficient to cause disease, or is
a secondary event to an anti-β subunit response.
In contrast to thymocytes from normal animals, thymo-
cytes from βH/K-transgenic mice were unable to induce au-
toimmune gastritis when transferred to nude mice. This sug-
gests that in βH/K transgenic mice disease-causing T cells
are being silenced within the thymus. This finding has general
implications for tolerance to peripheral self-antigens. It sug-
gests that tolerance to the H/K ATPase β subunit in normal
animals must be occurring at an extra-thymic location. How-
ever, our data do not directly address whether the mecha-
nism of tolerance in the periphery is deletion, anergy, or sup-
pression (41–43). It has been proposed that tolerance to
extra-thymic antigens may involve transport of antigen to
the thymus by recirculating macrophages (44). An implica-
tion of our findings is that the gastric antigen either does
not reach the thymus, or does not accumulate at a concentra-
tion sufficient to cause thymic tolerance.
The prevention of autoimmune gastritis in βH/K-
require an initial immune response to the \( \beta \) subunit resulting in tissue damage and inflammation. The \( \alpha \) subunit-specific autoantigens in subcellular particles, it may explain the cellular organelles or subcellular particles, such as the nucleosome in systemic lupus erythematosus and the nucleolus in scleroderma (2, 8). Thus, if monospecific T cells can drive multiple B cell responses to closely associated molecules such as autoantigens in subcellular particles, it may explain the autoantibody profiles seen in many autoimmune diseases.

Alternatively, an immune response to the \( \alpha \) subunit may require an initial immune response to the \( \beta \) subunit resulting in tissue damage and inflammation. The \( \alpha \) subunit–specific T and B cell immune responses associated with autoimmune gastritis may be secondary phenomena not associated with initiation of disease. This possibility is similar to the model of "determinant spreading" described recently by Lehmann et al. (46). The \( \alpha \) subunit may carry "cryptic" determinants (46) that become immunogenic after the initial immune response to the \( \beta \) subunit. Thus the role of the \( \alpha \) subunit in the induction of autoimmune gastritis is still to be resolved.

We will elucidate the role of the H/K ATPase \( \alpha \) subunit in experimental autoimmune gastritis by the generation of \( \alpha \) subunit transgenic mice in which the H/K ATPase \( \alpha \) subunit will be expressed within the thymus.

Our findings here argue that an immune response to the \( \beta \) subunit of the gastric H/K ATPase is essential for the development of autoimmune gastritis. The ability to identify the causative antigens in autoimmune diseases has obvious ramifications in developing successful immunotherapeutic strategies. This approach, directed towards the identification of T cell targets in autoimmune gastritis, is applicable to other autoimmune diseases and will help to expand our understanding of the mechanisms and molecular basis of autoimmune diseases.

This study was supported by grants from the National Health and Medical Research Council of Australia, the William Buckland Foundation, and the Alfred Group of Hospitals.

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Received for publication 25 February 1993.

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Title:
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Date:
1993-08-01

Citation:
ALDERUCCIO, F., TOH, B. H., TAN, S. S., GLEESON, P. A. & VANDRIEL, I. R. (1993). AN AUTOIMMUNE-DISEASE WITH MULTIPLE MOLECULAR TARGETS ABROGATED BY THE TRANSGENIC EXPRESSION OF A SINGLE AUTOANTIGEN IN THE THYMUS. JOURNAL OF EXPERIMENTAL MEDICINE, 178 (2), pp.419-426. https://doi.org/10.1084/jem.178.2.419.

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