SUMMARY
GnRH regulates a cascade of events leading to the production of sex steroid hormones and the production of gametes in both males and females. GnRH is critical for the normal functioning of the reproductive system and hence for fertility. Immunization with GnRH-carrier conjugates leads to the production of anti-GnRH antibodies and the subsequent impairment of fertility. Immunization with GnRH results in decreased testicular size, cessation of spermatogenesis and a severe reduction in testosterone levels. A marked atrophy of the prostate gland is observed following immunization of rats with the GnRH conjugate. The GnRH vaccine is currently in Phase I/II clinical trials for "immunological surgery" in patients of carcinoma of the prostate and benign prostatic hypertrophy.

GnRH is by and large an evolutionarily conserved decapeptide in mammalian species. It is a hapten and a self antigen and is therefore non-immunogenic by itself; it can be made immunogenic by linking it to non-self carriers such as TT. The carrier presumably generates a helper T cell response that "helps" GnRH-specific B cells. An important step in the development of a vaccine is the demonstration that the vaccine is sufficiently immunogenic in all individuals, irrespective of their genetic backgrounds. An important prerequisite to large scale immunization with the GnRH
vaccine is the investigation of potential genetically-influenced variations in anti-GnRH immune responses.

One of the objectives of this work was to investigate the influence of the genetic background and of the MHC in particular, on immune responses to GnRH and to ascertain whether this response can be manipulated. Most strains of mice respond to immunization with GnRH-DT by making anti-GnRH antibodies. 129 mice however, generate poor anti-GnRH antibodies when immunized with GnRH linked to DT, but the same mice make good anti-GnRH antibodies when immunized with GnRH linked to TT. Adoptive transfer experiments support the existence of suppressor cells in GnRH-DT immunized 129 mice.

Carriers are known to influence immune responses to haptens linked to them. Preimmunization with a carrier often results in an inhibitory effect on the production of antibodies to new epitopes or ligands linked to the same protein. This effect, however, is not a general one; TT-presensitization does not necessarily affect responses to all haptens. It is important therefore to study each hapten-carrier conjugate individually and this is particularly important when these conjugates are being developed as potential vaccines in humans. This thesis deals with a "self" hapten, GnRH, and an as yet untested carrier, DT. We show that preimmunization with both DT and TT separately can induce inhibitory effects
on anti-GnRH responses. Adoptive transfer experiments designed to identify the cells involved in mediating these effects suggest that T cells are responsible for both inducing suppression and for helping overcome suppression.

Since this vaccine is eventually intended for use in humans where one aims for a universal response, a phenomenon like epitopic suppression would be undesirable. One of the aims of the work described here was to devise ways of overcoming suppression due to pre-existing immunity to the carrier. One possible approach stems from the fact that carrier molecules essentially function by providing "T cell help" to hapten-specific B cells. This prompted us to ascertain whether synthetic T helper epitopes could be used as carriers as a substitute to the whole carrier molecule. Several peptides selected from DT elicited a T cell stimulatory response and one peptide spanning residues 201-222 elicited a T cell proliferative response in three strains of mice; this peptide was selected for use as a carrier and was conjugated to GnRH. Mice rendered hyporesponsive to GnRH by presensitization with DT were boosted later with the GnRH-Peptide conjugate which resulted in a "bypass" of DT-induced suppression. Furthermore, it is interesting to note that pre-existing immunity to this peptide 201-222 does not result in inhibition of the anti-GnRH response. Preimmunization
with the peptide actually results in enhancement of anti-GnRH antibody response when subsequent immunization is done with GnRH linked to DT. The GnRH vaccine is intended for use in humans where a near universal immune response is desirable, hence the use of "universal" T cell epitopes as carriers would provide a novel method of bypassing suppression induced by the carriers. Immunization of mice with GnRH-Peptide conjugates using known "universal" T cell epitopes also resulted in a good anti-GnRH antibody response.

This thesis, in conclusion, provides an insight into immunogenetic and immunoregulatory aspects of immunization with the GnRH vaccine. Besides providing useful leads in the improvement and optimization of this particular vaccine, these studies should advance the development of peptide vaccines in general.