CHAPTER 1

Introduction
1.0 INTRODUCTION

Prostate is an enigmatic organ. While most other organs of the male regress with age, prostate grows and is the cause of prostatic hypertrophy in most men living for long years. A percentage of these develop carcinoma of the prostate, which has become the biggest killer of men due to cancers in USA. The same phenomenon can be expected to take place in India with longevity of life and anti-tobacco campaign gaining ground curtailing lung and buccal cancers.

The causes for prostatic hypertrophy with age are not fully understood but undoubtedly there is a role for androgens, whose conversion into active 5α dihydrotestosterone (DHT) form may be increased or the sensitivity of the organs to the hormone enhanced by modulation of the receptors.

This Thesis is aimed at blocking the action of the decapeptide Luteinising Hormone-Releasing-Hormone (LHRH) which through a cascade action promotes the secretion of androgens. Over and above this, LHRH may also have direct action on the prostate as prostate has receptors for LHRH.

LHRH is conserved through evolution and is molecularly similar if not identical in rats and in humans. Thus rat serves as a homologous model for humans for efficacy and safety studies.

Earlier work of Talwar et al (1999) has clearly indicated that a vaccine capable of inducing antibody response to LHRH is not only safe for prostatic carcinoma patients but also effective in patients in whom the antibodies of adequate titres are generated .
The vaccine used in the previous studies was a synthetic analogue of LHRH which was linked through a spacer to tetanus toxoid (TT) or diptheria toxoid (DT) as carriers (Talwar et al., 1992). This vaccine by its nature was expensive to make and could not be converted to a vaccine for large scale industrial use.

The objective of this thesis was to develop a recombinant low cost, easy to manufacture vaccine which could be used for prostatic hypertrophy and carcinoma of prostate. Two multimeric designs of the vaccines were made in which 5 repeat units of the LHRH decapeptide were interspersed with 4 to 5 promiscuous T non B peptides. The genes for these vaccines were assembled, cloned and expressed in a prokaryotic system. The expression through strong heat inducible promoters was massive but the protein aggregated in the inclusion bodies. Methods were developed to extract the recombinantly expressed multimers in good yield. It was successfully refolded into a native immunoconformation and tested as a vaccine in rats, in which with a potent adjuvant it caused the decline of testosterone levels to castration levels and leading to drastic atrophy of the prostate. The procedure was safe and the bioeffective antibodies did not have cross-reaction with extraneous tissues.