Tsetse-transmitted trypanosomosis poses severe constraints to livestock productivity in sub-Saharan Africa, affecting large areas of the continent that hold the greatest potential for agricultural development. Greater exploitation of the genetic resistance to trypanosomosis (trypananotolerance) that is displayed by some breeds of indigenous West African cattle (e.g. N'Dama) is accepted as an important sustainable component for controlling the disease. It is envisaged that within-breed and crossbreeding genetic improvement of indigenous trypanotolerant breeds would be facilitated by the mapping of the chromosomal regions (quantitative trait loci, QTL) controlling trypanotolerance, followed by marker-assisted selection, or introgression of these regions, using their closely linked genetic markers. However, this prospect has been hampered by the absence of practical reliable markers for resistance due to the scarcity of genetic markers on cattle maps.

Following a genome-wide scan in an F2 cross between trypanotolerant N'Dama from The Gambia and trypanosusceptible Kenya Boran, a QTL controlling parasitaemia was mapped to a 30 cM region on bovine chromosome 7 (Bta 7). As a means of achieving higher marker density in this QTL region, and to facilitate the identification of the candidate genes mediating trypanotolerance, a combination of chromosome-microdissection, comparative, radiation hybrid (RH) and physical mapping techniques, were exploited to isolate and order new markers in the QTL region.

A high-resolution 12,000 rad Bta7 RH map consisting of 55 markers was constructed in this study. The map includes: 41 coding genes, 29 of which are novel previously unmapped genes; 4 sequence tagged sites (STS) from microdissection; and 10 microsatellites from published linkage maps. This marker density substantially exceeds that on all available published bovine maps for this region and therefore represents a significant contribution to the global bovine genome mapping effort. Additionally, 12 BAC clones representing a defined sequence-ready pool of chromosome-specific DNA resource material were isolated using STS from chromosome microdissection.

Comparative mapping analysis confirmed that the cattle Bta7 QTL is in a region of conserved synteny relative to two human chromosomes (Hsa19 and Hsa5) and five mouse chromosomes (Mmu8, Mmu9, Mmu11, Mmu17 and Mmu18). The linear order of genes within homology segments is generally conserved (particularly between cattle and humans), with few exceptions where gene order is conserved, but the conserved syntenic segments were inverted in orientation. A previously unknown small region of homology between the Bta7 trypanotolerance QTL and the murine Tir1 trypanotolerance QTL region on chromosome 17 (Mmu17) is also revealed. The size of this region is approximately 342 kb as estimated from the construction of a BAC contig. One of the BAC clones in this region of homology (RP42-102G22) defines a novel evolutionary breakpoint of conserved synteny between the bovine and the mouse genomes.

At least nine novel candidate genes, the majority of which are implicated in innate immunity, were identified within the 95% confidence interval of the Bta7 QTL region. These genes have been implicated in: relaying information about infection to transcription factors which up-regulate the transcription of genes involved in innate immune responses (ECSIT and MAP2K7); regulation of gene expression and RNA processing (ELAVL1, EIF3S4 and HNRPM4); B-cell proliferation (particularly memory B-cells) and immunoglobulin secretion (8D6 Antigen/LOC51293); leukocyte migration (SCYA25); haematopoiesis
(HSPC240); and free radical mediated destruction of phagocytosed parasites (ACP5). Amongst these genes, HNRPM4, 8D6 Antigen and HSPC240 are located in the region homology between the trypanotolerance QTL on Bta7 and the Tir1 QTL on Mmu17. In addition, a cluster of cytokine genes, plausibly involved in humoral and acquired immune responses was also mapped to the distal portion of the QTL region. The results reported in this thesis have demonstrated the vital role played by comparative genomics in accelerating gene discovery.