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Sequencing of the *Rhodococcus equi* genome

The International *Rhodococcus equi* consortium (IREC)

Co-ordinator Prof Jose Vazquez-Boland

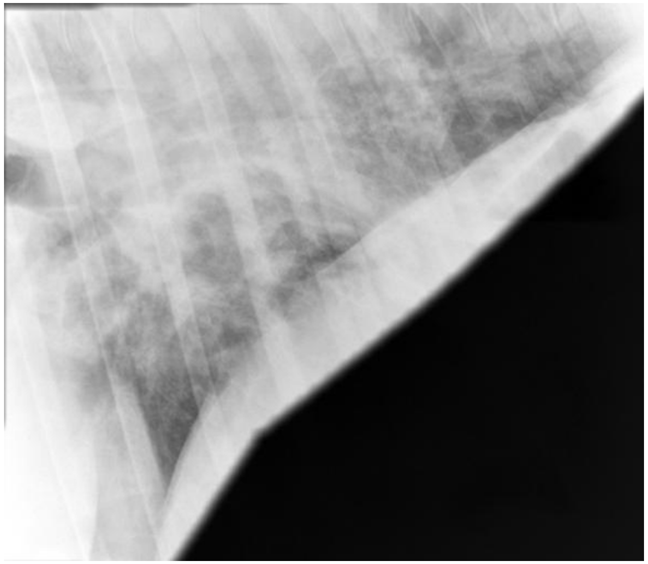
Completed Project – 1st October 2004 to 30th September 2007
HBLB VAC reporter: CM Marr

PRJ: 712

Rhodococcus equi: a soil-dwelling bacterium and…

The causative agent of “rattles”

- Severe bronchopnuemonia in foals.
- World-wide, a primary cause of mortality between 1 and 5 months of age.
- Can become endemic in stud farms.
- Prevalence is increasing.
- Ranked among the four most important infectious disease problems of the horse industry.
- Currently there is no effective vaccine.



This chest radiograph shows that much of the lung is affected: normal lung is dark, where the pneumonia has created a white, fluffy pattern

Rhodococcus equi: a soil-dwelling bacterium and…

A multi-host pathogen

- Emerging human opportunistic pathogen, particularly in immunosuppressed people.
- Pathology similar to tuberculosis.
- Also causes infections in pigs, cattle, small ruminants, dogs and cats.

A research model

- The bacterium is related to *Mycobacterium tuberculosis*.
- Able to survive within cells, in particular macrophages (one of the immune cells that kills many other bacteria).
- Good model for TB research.
- Ability to cause disease is associated with a virulence plasmid (extra DNA that is not present in all strains).

Co-sponsors:

Why study an organism’s genome?

- The genome is the genetic map.
- Every living thing has one, including bacteria.
- The genes control all aspects of an organism’s behaviour and biology.
- Mapping the genome of one bacterial species means it can be compared with others, to rapidly understand how it lives, multiplies and causes disease.
- Most importantly, this knowledge may lead to new ways to disable the organism and produce attenuated strains or identify bacterial products that can be used in novel vaccines.

Who are the International *Rhodococcus equi* consortium?

Participants

- Vazquez-Boland, University of Bristol and Edinburgh, UK
- J Parkhill, S Bentley, The Wellcome Trust Sanger Institute, UK
- W Meijer, University College Dublin, Ireland
- U Fogarty, D Leadon, T Buckley, Irish Equine Centre
- J Prescott, University of Guelph, Canada

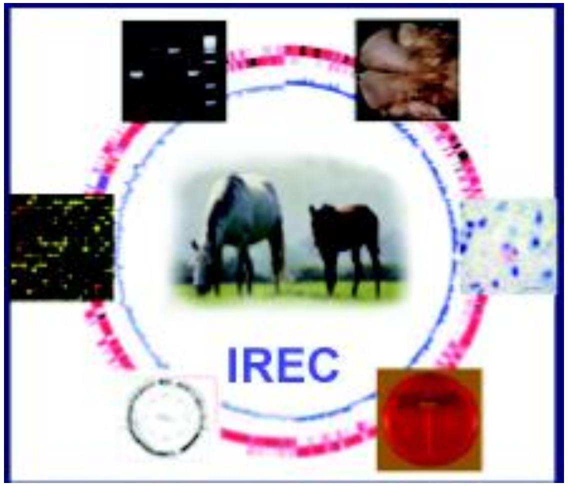
Collaborators & friends

- S Takai, University of Kitasato, Japan,
- I Sutcliffe, University of Sunderland, UK
- J Navas, Universidad de Cantabria, Spain,
- S Ricketts, Beaufort Cottage Laboratories, Newmarket, UK
- Many laboratories worldwide that contributed strains for the population genetics/molecular epidemiology study

Co-sponsors:

Objectives of the *Rhodococcus equi* genome initiative

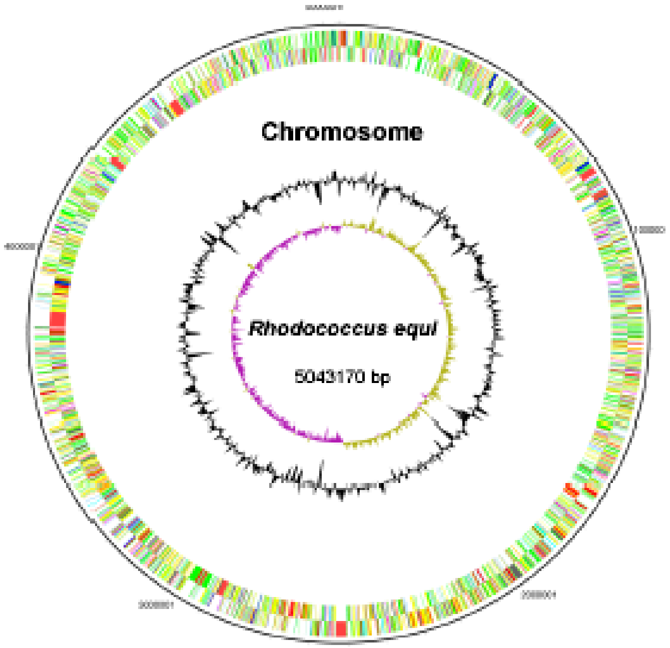
- An international collaboration
- to understand and gain insight into
- the biology, pathogenesis, population genetics, epidemiology and evolution of *R equi*
- through genomics research,
- with a view to develop novel vaccines and control measures for rhodococcal pneumonia with a rational basis



Co-sponsors:

Features of the *Rhodococcus equi* genome

- Circular chromosome of 4,525 predicted genes
- Separate virulence plasmid with 73 coding sequences
- 29% of the products encoded by the *R equi* genome are of unknown function
- Large number of surface-associated proteins and transporters, larger secretome and many regulatory genes
  - This is consistent with its dual life-style as it can both live in soil and within animals, causing disease
- Many genes controlling antimicrobial resistance
  - This is one reason it is a very difficult disease to treat



Virulence plasmid*
(80,609 bp)

M. Letek et al 2010 PLoS Genetics 6: e1001145

Co-sponsors:

Gene markers can be used to study how the organism interacts with animals

- *R equi* virulence plasmid can be classified into categories based on gene markers.

- Each plasmid type is associated with infection of specific species and there is a specific "horse-type" which differs from plasmids affecting cattle and pigs.

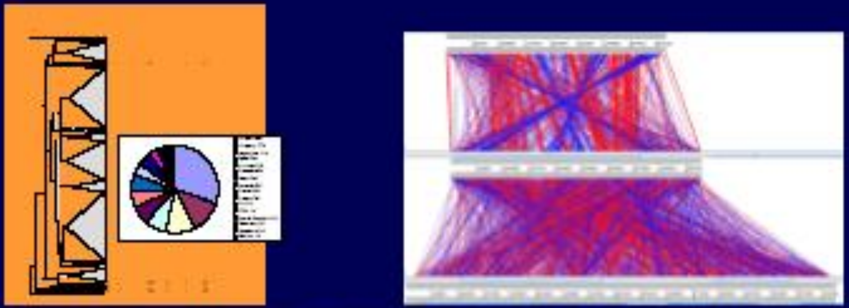
- Humans can be affected by strains carrying any of the three animal species-specific virulence plasmids, but this may be because humans who become infected usually have major underlying illnesses that are compromising their immune system.

Co-sponsors:

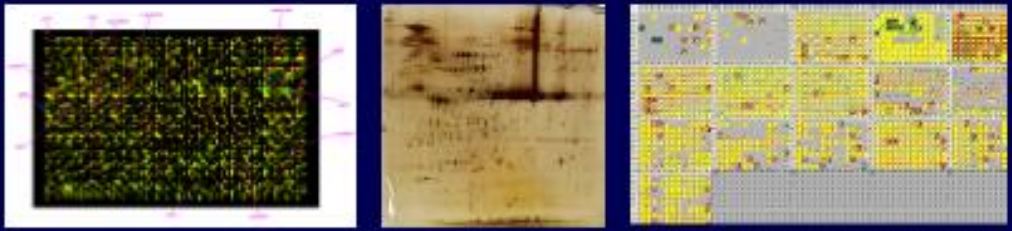
Rhodococcus equi genome initiative - future developments

The availability of the genome sequence opens the postgenomic era of *R. equi* research, offering a unique and unprecedented opportunity to make rapid progress in our understanding of the biology and pathogenesis of this major equine pathogen

R. equi genome sequencing programme



Molecular epidemiology, population genetics & comparative genomics



Functional genomics at the host-pathogen-environment interface

Fundamental:
Integrative
and
systems biology

Translational:
novel vaccines,
chemotherapeutics,
rapid diagnostics,
control measures

The fundamental knowledge on *R. equi* and its interaction mechanisms with the host and the environment, derived from the genome sequence and its downstream functional analysis, provides a rational framework for the identification of novel strategies to control rhodococcal infection in foals and on stud farms.

Commentary on these conclusions

This was a very exciting project, which allowed UK scientists to join others from Canada and Ireland to make important advances, which should pave the way towards future vaccines to prevent this devastating disease.

Scientist’s summary

- The bacterium *R. equi* is the etiological agent of “rattles”, a severe respiratory condition of foals associated with a high case-fatality rate if antimicrobial treatment is not administered at an early stage of the disease.

- *R. equi* infection is a major cause of mortality in horses between 1 and 5 months of age, and has been ranked among the four most important disease problems of the horse industry.

- The organism is endemic on many stud farms throughout the world and represents a real challenge because there is no effective vaccine available.

Scientist’s summary

- The problem is aggravated by the lack of rapid diagnostic tests capable of identifying the early stages of infection in foals and the extent of *R. equi* subclinical carriage and endemicity in the Thoroughbred studs.

- Modern research into vaccine development and drug discovery requires a profound knowledge of the complex mechanisms used by microbes to cause infection.

- Understanding these mechanisms can lead to the identification of microbial “Achilles heels” that can be specifically targeted by vaccines and drugs, resulting in the neutralisation of the infectivity of the microbe.

Scientist’s summary

- Today, the most straightforward and cost-effective approach to achieve rapid progress in our understanding of the biology of an organism is to sequence and functionally analyze its genome (the collection of genes that define a living being).

- With this in mind, in 2004 we started this project with the aim of determining the complete genome sequence of a clinical isolate of *R. equi*.

- The project has been successfully completed and the genome sequence of *R. equi* and corresponding catalogue of encoded products is now available to the international scientific community for study.

- The *R. equi* genome and preliminary functional analysis has been published in a mainstream genetics journal (Letek et al. 2010, PLoS Genet. 6:e100145.

Scientist's summary

- Besides the significant advancement of knowledge that the outcome of the project represents, the benefits of this research should flow to the horse breeding industry in the form of potential new drugs, vaccines and rapid diagnostic tests to treat, prevent and control rhodococcal pneumonia in foals.