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HSTalks

Toxoplasma gondii

Prof. Geoff Hide

School of Science, Engineering & Environment

University of Salford, UK

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Overview

Toxoplasma gondii

Life cycle

Diseases

Current topics of interest

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Toxoplasma gondii

- Parasite of cats
  - Definitive host
  - Only host where *Toxoplasma gondii* can complete its life cycle
  - This includes a sexual stage in the life cycle
- But also infects other warm-blooded animals
  - Humans
    - 1 in 3 humans are infected

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Toxoplasma gondii

- Secondary hosts
- All warm-blooded animals and birds
  - Marine mammals, e.g., sea otters, dolphins
- Includes humans
- Prevalence usually high at 30–40%

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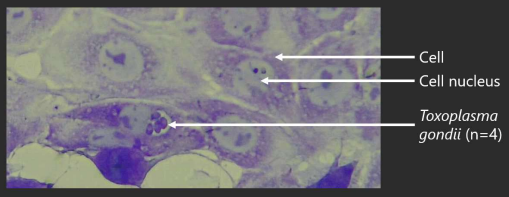
Toxoplasma gondii

- Single-celled protozoan parasite
- Intracellular life cycle



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Toxoplasma gondii – diseases

- Mostly asymptomatic
  - In humans and other mammals
- Miscarriage in humans
- Foetal abnormalities
- Retinochoroiditis
- Abortion in sheep and other animals

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Aborted lambs

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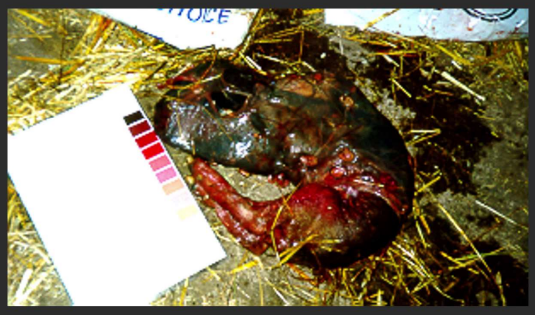

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Aborted lambs

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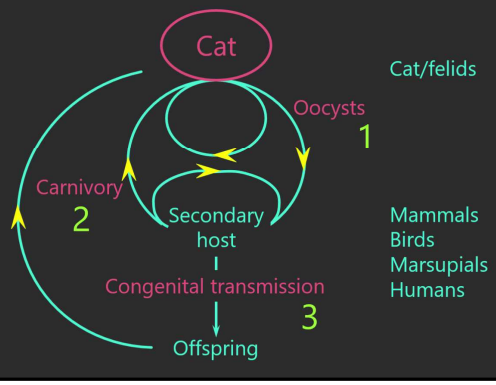
Life cycle of *Toxoplasma gondii*



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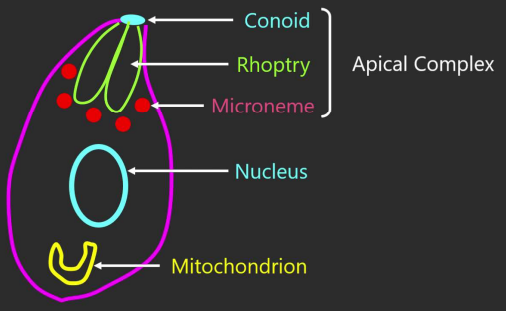
Toxoplasma gondii – cell structure



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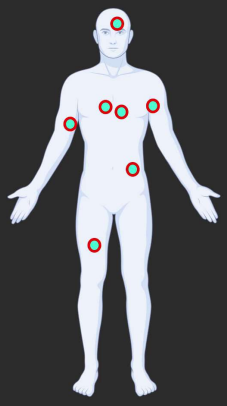

Tachyzoite stage
that circulates
and invades host cells

Immune system attacks
the infected cells

Immune system locks down
the parasite – cyst stage

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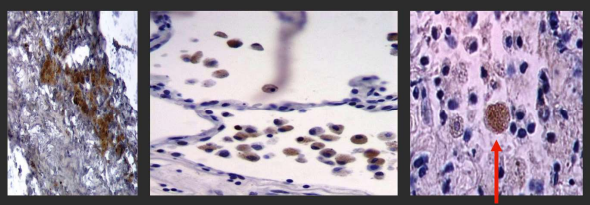
Histology



Tachyzoites
(active)

Infected
macrophages
(active)

Cyst
(dormant)

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Bajnok J, *et al.* 2019., *ERJ Open Res.* 28; **5**(2) (Figure 2)

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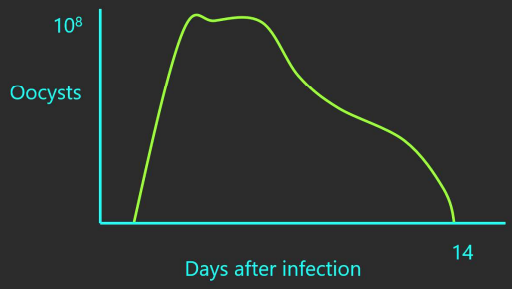
Oocyst shedding in cats



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Intermediate hosts

- Humans (UK): 10–26%
- Humans (France): up to 84%
- Sheep: 27%
- Domestic mice: 59%
- Woodmice: 40%
- Bats: 10%
- Otters: 5–97%
- Dolphins: 10–100%

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Disease

- Generally symptomless
  - People and animals typically do not show symptoms
- Immunocompromised hosts
  - AIDS, transplant, anticancer treatment
  - Opportunistic infection
- Congenital infection is serious

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Congenital transmission

- Measured by serology
- Rare in humans (1 per 1000–10000 live births)
- Infection during pregnancy: 55% transmission to foetus
- Can cause serious disease
- Asymptomatic/subclinical
- Hydrocephalus in foetus
- Retinochoroiditis
- Intracerebral calcification
- Abortion/miscarriage

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Retinochoroiditis – age 19

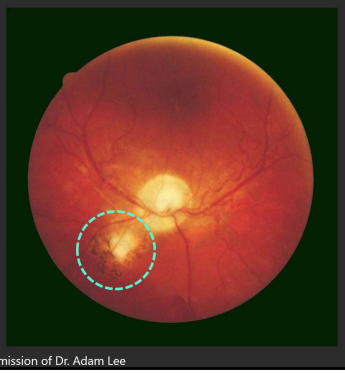

Image used with the permission of Dr. Adam Lee

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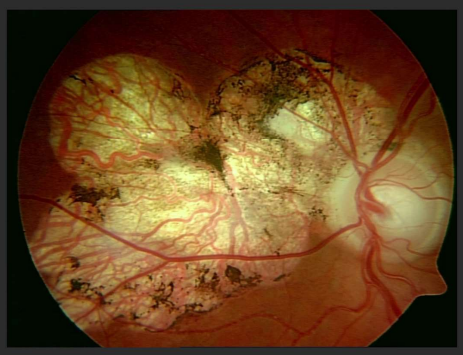
Retinochoroiditis – age 40



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Routes of transmission

What are the main routes of transmission?

Cats

- Infective oocysts
- Difficult to measure
- Difficult to advise pregnant mothers

Carnivory

- Ingestion of raw or undercooked meat
- Detect cysts in meat
- Dubey (2005) sampled the entire USA for supermarket meat; only found **seven infected samples**
- Difficult to measure

Congenital transmission

- Usually measured by serological tests
- Generally considered relatively rare
- 0.3–1.6 cases per 1000 live births

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Dubey JP, *et al.*, (2005). *J Parasitol.* **91**:1082-93.

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A dilemma

Cat is the only definitive host

But…

Parasite is ubiquitous and is often found at high prevalences

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Immune responses to *Toxoplasma gondii*

Antibody response

Cellular response

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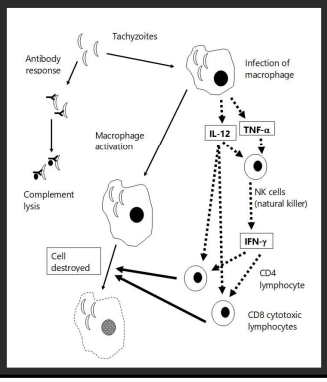
Immune responses to *Toxoplasma gondii*



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Host resistance to *Toxoplasma gondii*

- Laboratory mice are highly sensitive
- Rats are more resistant
- Humans moderately resistant
- What is the mechanism?

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Role of nitric oxide (NO)

- Nitric oxide inhibits intracellular pathogens
- Inducible nitric oxide synthase (iNOS) produces NO
- Arginase depletes NO
- Utilise the same substrate

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Inducible nitric oxide synthase (iNOS)

Arginase 1 (Arg1)

Rats Mice

iNOS Arg1 iNOS Arg1

Resistant Sensitive

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Virulence

- Highly virulent strains
  - Kill laboratory mice within 1 week
- Avirulent strains
  - Longer survival in mice

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Parasite strains

- 3 broad types:

Type I | Type II | Type III

Virulent | Avirulent

- Genetic markers distinguish many subtypes

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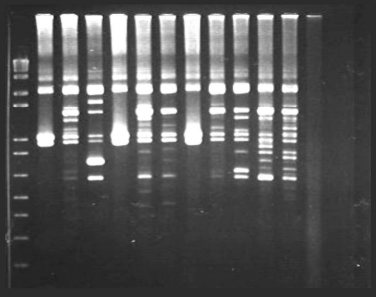
Strain typing with mobile genetic element-PCR (MGE-PCR)



Terry RS, *et al.*, (2001) *Int J Parasitol.* **31**:155-61.

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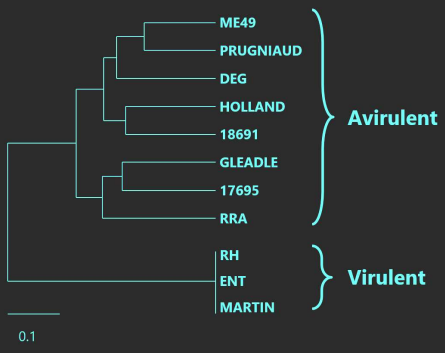
Strain typing with MGE-PCR



Terry RS, *et al.*, (2001) *Int J Parasitol.* **31**:155-61.

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Vaccines

- No human vaccines
- Sheep vaccine – Toxovax
  - Attenuated vaccine

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Treatment

- No specific treatment
- Pyrimethamine and sulphonamides are currently used
  - Reasonably effective

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Toxoplasma and behaviour

- *Toxoplasma gondii* can circulate in the entire body
- Lodges in the brain as cysts
- Does this have an effect on behaviour?

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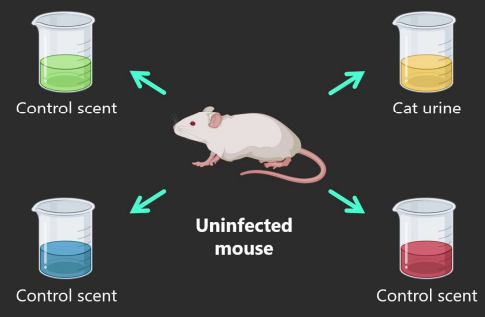
Behaviour experiments



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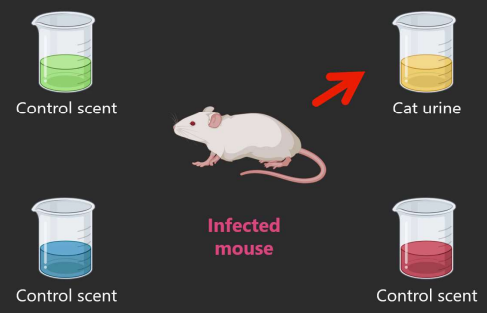
Behaviour experiments



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Behaviour and humans

- Does the presence of the parasite in the brain affect the behaviour of humans?
- Jaroslav Flegr has been trying to understand the effect of the parasite in human behaviour
- Comparisons of seropositive and seronegative people
- Association between infection and higher rate of car accidents

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Flegr J, *et al.*, (2002) *BMC Infect Dis.* **2**:11.

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Schizophrenia link?

- Study on schizophrenia
- 98 schizophrenia (57.1% toxoplasmosis)
- 96 controls (29.2% toxoplasmosis)
- Wide range of studies by many groups support this link

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Hamidinejat H, *et al.*, 2010. *Int J Infect Dis.* **14**:e978-81.

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Post-partum depression link?

- Study on post-partum depression (PPD)
- Study in China
- 106 PPD (6.6% toxoplasmosis)
- 369 controls (5.4% toxoplasmosis)
- No significant association (p=0.64)

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Gao JM, *et al.*, 2019. *J Affect Disord.* **250**:404-409.

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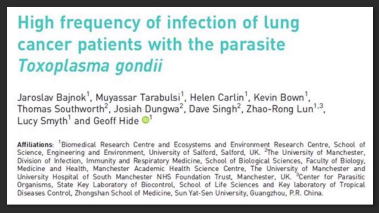
High frequency of *Toxoplasma gondii* infections in lung cancer patients



High frequency of infection of lung cancer patients with the parasite *Toxoplasma gondii*

Jaroslav Bajnok[1], Muyassar Tarabulsi[1], Helen Carlin[1], Kevin Bown[1], Thomas Southworth[2], Josiah Dungwa[2], Dave Singh[2], Zhao-Rong Lun[1,3], Lucy Smyth[1] and Geoff Hide[1]

Affiliations: [1]Biomedical Research Centre and Ecosystems and Environment Research Centre, School of Science, Engineering and Environment, University of Salford, Salford, UK. [2]The University of Manchester, Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester NHS Foundation Trust, Manchester, UK. [3]Center for Parasitic Organisms, State Key Laboratory of Biocontrol, School of Life Sciences and Key laboratory of Tropical Diseases Control, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, P.R. China.

72/72 (100%) infected

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Approach

- PCR detection using 5 genetic markers
- Antibodies to *Toxoplasma gondii*, iNOS and arginase
- Immunohistochemistry
- Immunofluorescence

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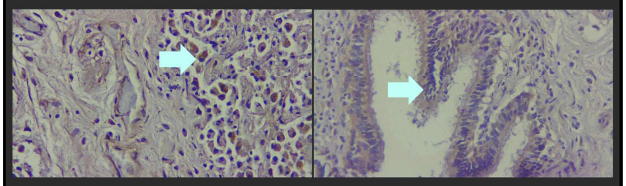
Immunohistochemistry



Toxoplasma gondii localisation

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Immunofluorescence – cyst

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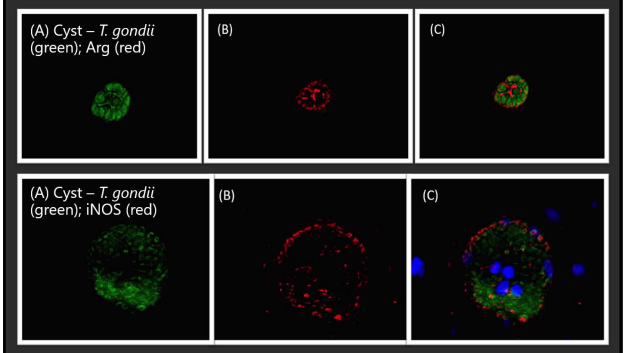

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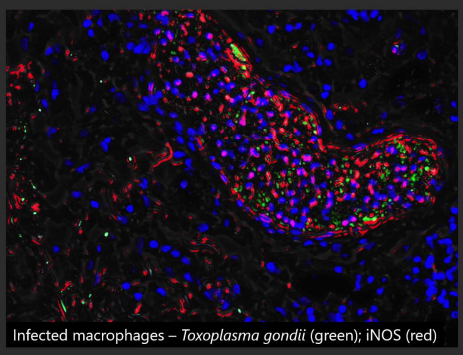
Immunofluorescence – macrophages



Infected macrophages – *Toxoplasma gondii* (green); iNOS (red)

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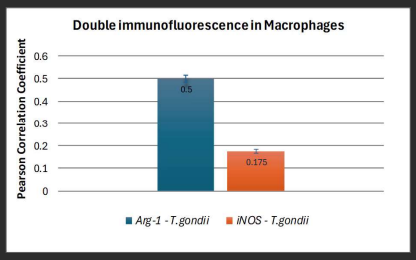
Arg-1 and iNOS in macrophages



Infected macrophages (active phase)

High association with arginase

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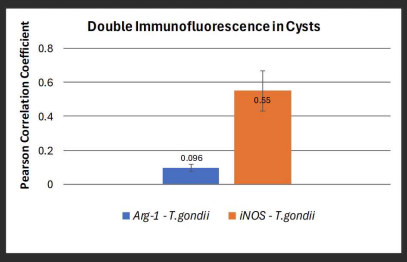
Arg-1 and iNOS in cysts



Cysts (dormant phase)

High association with iNOS

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Immunology of infection

- iNOS and arginase-1 involved in infection evolution
- Wider role of immunological molecules in pathology
- Cancers?
- Pregnancy?

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Future perspectives

- What are the important routes of transmission?
  - 1 in 3 humans are infected, how do we become infected?
- What is the true spectrum of disease in humans and animals?
  - Infected but largely asymptomatic
  - But behaviour experiments show otherwise
- What is the true global impact of *Toxoplasma* infection?

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Summary

Toxoplasma gondii

Life cycle

Diseases

Current topics of interest

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Acknowledgements

- I would like to thank many collaborators and my PhD students for enabling me to enjoy the scientific challenges of working with *Toxoplasma*
- I declare that I have no conflicts of interest

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