

# Transfer of Tetracycline Resistance to Chlamydia

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December 2, 2009



## ***NIH Guidelines: Section III-A-1***

- **Under the *NIH Guidelines* a Major Action\* is required for:**
  - Experiments involving the transfer of a drug resistance trait to a microorganism that is not known to acquire the trait naturally and the transfer could compromise the treatment of disease

**\*Major Action requires FR notice, RAC review, and NIH Director Approval**

## Review of III-A-1 Experiments

- Creation of a novel microorganism that is resistant to a therapeutic drug raises potential public health issues and requires RAC review and NIH Director approval
- Public review and RAC/NIH Director approval of this type of experiment occurred in 2007 for the transfer of tetracycline resistance to *Chlamydia trachomatis* and in 2008 for the transfer of chloramphenicol resistance to *Rickettsia conorii*

# Major Action Steps: Section III-A

- **Prior to proceeding such experiments require:**
  - Publication in the Federal Register
  - RAC Review and recommendations to NIH Director
  - NIH Director approval
  - IBC approval

# Introduction of Tetracycline Resistance (Tet<sup>R</sup>) into *C. trachomatis*

- **Obligate Intracellular Pathogen**
- **Public Health Impact**
  - Major cause of sexually transmitted disease worldwide
    - Cervicitis, urethritis, PID (infertility), epididymitis
    - Lymphogranuloma venereum (LGV) – genital ulcer-adenopathy syndrome and proctitis
  - Ocular strain is major cause of preventable blindness in developing countries

# **Introduction of Tetracycline Resistance (Tet<sup>R</sup>) into *C. trachomatis* Serovars L1, L2, L3**

- **Causal agent for Lymphogranuloma venereum (LGV)**
  - **Genital ulcer-adenopathy syndrome and proctitis**
- **Treatment Recommendations**
  - **Doxycycline or erythromycin**
    - 21 day course
  - **Azithromycin: recommended by some ID experts**

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis* (2007)

- NIH Director approved transfer of tetracycline resistance to non-ocular strains *C. trachomatis* (LGV and other genital strains) at biosafety level BL2 containment with BL3 practices (referred to as BL2+) for Drs. Rockey and Dr. Stamm only  
(72 FR 61661)

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- The *NIH Guidelines* includes requirements for BL2 laboratory facilities and equipment (App. G-II-B-3 - B-4) and BL3 practices (App. G-II-C-1 - C-2). The following BL3 practices must be followed:
  - Access must be restricted to well-trained personnel whose presence is required for the conduct of this work
  - Sealed centrifuge rotors and tubes must be used

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- In addition to BL2+ containment, the following procedures and practices must be followed:
  - Cup sonication must be used rather than probe sonication to separate the infectious form [elementary bodies (EB)] from the metabolically active [reticulate bodies (RB)] form of the bacterium.
  - If available, other techniques that do not involve the possible generation of aerosols, such as freeze-thaw, to separate EBs from RBs should be considered.

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- No work with the *C. trachomatis* serovars A, B, or C, which cause the ocular disease trachoma, may be conducted in the same laboratory in which tetracycline resistance is being introduced into *C. trachomatis* serovars that cause genital disease (L, E and G).

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- An assay for detecting the tetracycline-resistant genetic element should be developed so that in the event of a laboratory-acquired infection it will be possible to determine whether the genetically modified strain of *C. trachomatis* is the source of the infection.

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- Health surveillance steps for laboratory staff working with tetracycline resistant *C. trachomatis*:
  - In addition to being trained on proper biosafety practices, laboratory workers must be provided education on the possible clinical manifestations of laboratory-acquired *C. trachomatis* infection.

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- **Health surveillance steps for laboratory members working with tetracycline resistant *C. trachomatis*:**
  - Laboratory must have a detailed, written action plan outlining the specific steps to be taken in the case of a laboratory exposure or infection.

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- **Laboratory plan should include at a minimum:**
  - Involvement of key personnel who would provide diagnostic testing and treatment in planning responses to exposure or infection with *C. trachomatis*
  - Instructions for laboratory staff on how to respond to an exposure or infection discovered during off hours

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- **Laboratory plan should include at a minimum:**
  - Specific recommendations for managing azithromycin-allergic or sensitive lab workers; and a provision excluding individuals with known macrolide allergies from working on these experiments

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- **Laboratory plan should include at a minimum:**
  - Specific recommendations for treatment of infected laboratory staff who develop side effects while being treated with azithromycin
  - Specific precautions to be taken by infected laboratory workers with respect to protecting close contacts (e.g. family members) from further infection.

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- **Members of the laboratory should be provided with a medical card that includes at least the following information:**
  - Identification of the personnel responsible for providing diagnosis and treatment
  - A CDC telephone number for reporting the infection and obtaining treatment recommendations
  - A twenty-four hour contact number for the principal investigators.

# NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- Investigators working with this tetracycline resistant *C. trachomatis* must follow the practices and procedures set forth by the NIH Director.
- Approved investigator must ensure and document for the institution's records that an investigator to whom the resistant *C. trachomatis* is transferred has been apprised of and agrees to follow the requirements set forth by the NIH director

## NIH Requirements for work with Tet<sup>R</sup> *C. trachomatis*, cont.

- The NIH Director's 2007 approval for the creation of tetracycline resistant strains of non-ocular serovars of *C. trachomatis* was specific for Drs. Rockey and Stamm. Other investigators who wish to do similar experimental work will need to have that work reviewed by the RAC and approved by the NIH Director

## Differences Proposed by Dr. Harlan Caldwell

1. Proposed use of probe rather than cup sonication with respiratory protection
2. No requirement that laboratory staff with known allergy or sensitivity to azithromycin be excluded from this research
3. Medical cards include a 24 hour NIH OMS number but not a CDC contact phone number for reporting of exposure or infection

