OSU
Oregon State
UNIVERSITY

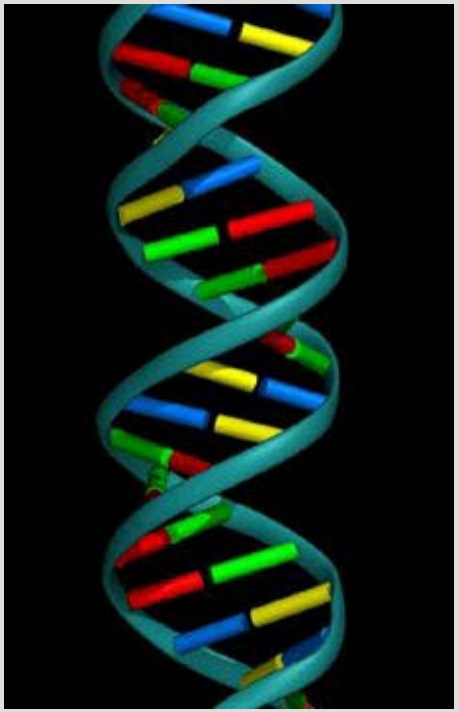
Principal Investigators Roles and Responsibilities

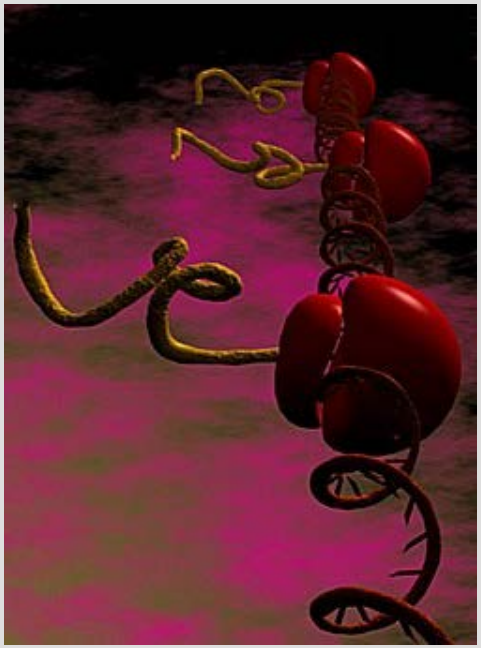
Training for Principal Investigators and Laboratory Staff on compliance with the

NIH Guidelines for Research Involving Recombinant DNA Molecules

Recombinant DNA

- ..molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or molecules that result from the replication of these constructs…





Risk Groups and Biosafety Levels

- Risk Groups (RG) rank infectious agents capable of causing disease in humans into four groups according to severity of disease, availability of interventions, and potential for community spread.
- Biosafety Levels (BSL) describe the facilities and work practices that minimize risk appropriate to the agents in use.
- RG and BSL roughly correlate.

Risk Groups (RG)

Risk Group	What it Means
RG-1	Agents that are not associated with disease in healthy adult humans; *low individual and community risk*.
RG-2	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available and the risk of spread of infection is limited; *moderate individual risk and low community risk.*
RG-3	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available; *high individual risk but low community risk.*
RG-4	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available; *high individual risk and high community risk*

Biosafety Levels (BSL)

Biosafety Level	What it Means
BSL-1	Facilities and practices for work with agents or hazards not known to cause disease in healthy adult humans; minimal hazard to personnel.
BSL-2	Facilities and practices for work with agents or hazards of moderate potential risk to personnel. May cause disease that can usually be treated. Risk of disease by contact, injection, or ingestion.
BSL-3	Facilities and practices for work with agents or hazards that ***may*** cause serious or potentially lethal disease as a result of exposure by ***inhalation***. Treatment may be available.
BSL-4	Facilities and practices for work with agents or hazards that pose a high risk of aerosol-transmitted life-threatening disease.

Institutional Biosafety Committees

Institutional Biosafety Committees are required by the NIH:

- An IBC is required for any institution that conducts rDNA work ***and*** receives NIH funding for research.
- All non-exempt rDNA is reviewed by the IBC, regardless of the source of funding.

NIH Responsibilities of Principal Investigators

- Register all non-exempt rDNA projects with the IBC; not initiate until approved.
- Report any significant problems, violations of the NIH Guidelines, accidents or illnesses to the NIH and to the OSU Biological Safety Officer.

For additional PI responsibilities, please see Section IV-B-7 of the *NIH Guidelines*.

NIH Responsibilities of Principal Investigators

- Ensure appropriate microbiological techniques and procedures are used in the conduct of research.
- Follow IBC Spill Response Guide for remediation of spills or contamination.
- Make available to all laboratory staff information that describes the potential biohazards and precautions to be used.

Projects Needing Review

Section III of the *NIH Guidelines* describe the types of projects needing review by the IBC.

Different rDNA Projects / Different Levels of Review

- Some must be approved by combinations of IBC, RAC, NIH/OBA, IRB, IACUC or the NIH Director before initiation of work.
- Some must be approved only by IBC before initiation of work.
- Some require notification of IBC and may begin before approval.
- Some are exempt from review.

Section III-A: Major Actions

- Some types of experiments are considered as “Major Actions,” those with a high potential to have a negative impact on community / environment:
  - introduction of antibiotic / drug resistance traits into pathogens that do not naturally acquire the trait, if the potential exists for this to interfere with therapeutic use of the drugs
- Need review / approval by RAC, NIH Director, and local IBC.
- NIH sets containment requirements.

Section III-B

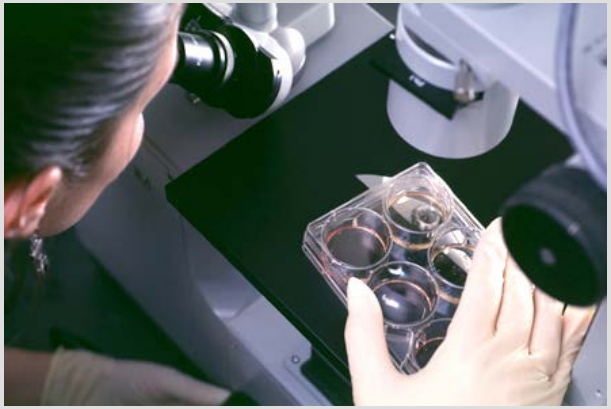
- These are also relatively high risk to personnel:
  - rDNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD_{50} of less than 100 ng / kg body weight.
    - includes botulinum toxins, tetanus toxin, diphtheria toxin, and *Shigella dysenteriae* neurotoxin
- These experiments require approval by the IBC and by NIH/OBA before initiation.

Section III-C: human gene transfer

- Sect. III-C covers deliberate transfer of rDNA, or DNA or RNA derived from rDNA, into human research participants.
  - Extensive requirements are found in Appendix M of the *NIH Guidelines*
- Requires RAC review (public), IBC review and IRB review.

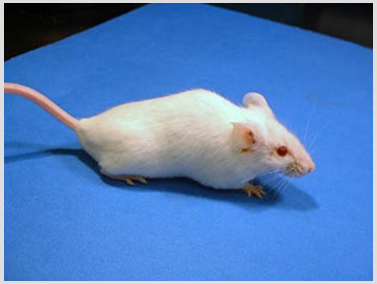
Section III-D

- All experiments in Sect. III-D require IBC review and approval before initiation:
  - experiments with RG-2, RG-3, RG-4 as host / vector systems
  - molecular cloning of rDNA from RG-2, RG-3, RG-4 into nonpathogenic prokaryotes (*E. coli* K-12, etc.) or lower eukaryotes (yeast, slime molds, etc.)



Section III-D

- Other experiments in Sect. III-D - 3 / 4:
  - use of infectious viruses or defective viruses + helper viruses in tissue culture systems
    - any system capable of generating infectious virus
  - experiments involving rDNA and live animals - transgenic animals, or rDNA-modified microorganisms introduced into live animals
    - exceptions:
      - generation or breeding of transgenic rodents requiring BSL-1 containment or the purchase / transfer of transgenic rodents – these are exempt

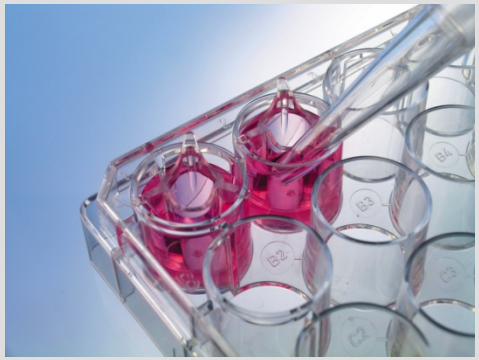


Section III-D

- Other experiments in Sect. III-D-5: **plants**
  - creation or propagation of genetically modified plants, or use of plants together with microorganisms or insects that have been genetically modified
  - containment varies according to nature of the introduced rDNA
    - rDNA from exotic or readily transmissible infectious agents or vertebrate toxins requires higher containment
    - rDNA modified insects or microorganisms require containment according to their potential to be detrimental to natural ecosystems or agriculture

Section III-E: Notifications

- Experiments needing review and approval by IBC; may begin prior to review.
  - use of not more than $^{2}/_{3}$ of genome of viruses in cell culture (no helper virus present)
  - some transgenic plants at BLP-1
  - certain transgenic plants / plant pests at BLP-2



Section III-F: Exempt

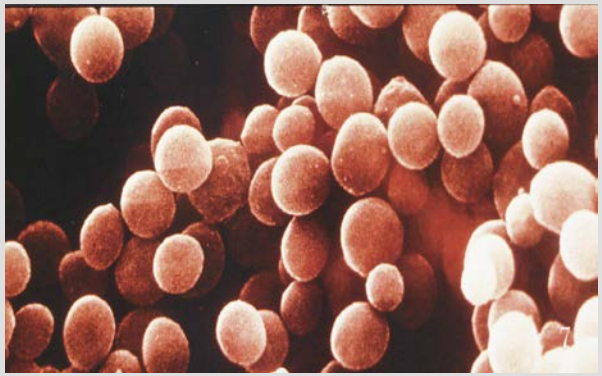
- Some experiments are exempt from review:
  - rDNA not in organisms or viruses (e.g, PCR)
  - rDNA from a single non-chromosomal or viral DNA source
  - rDNA from a single prokaryotic or eukaryotic host when propagated only in that host
  - rDNA from different species that naturally exchange DNA by known physiological processes
  - Those listed in Appendix C

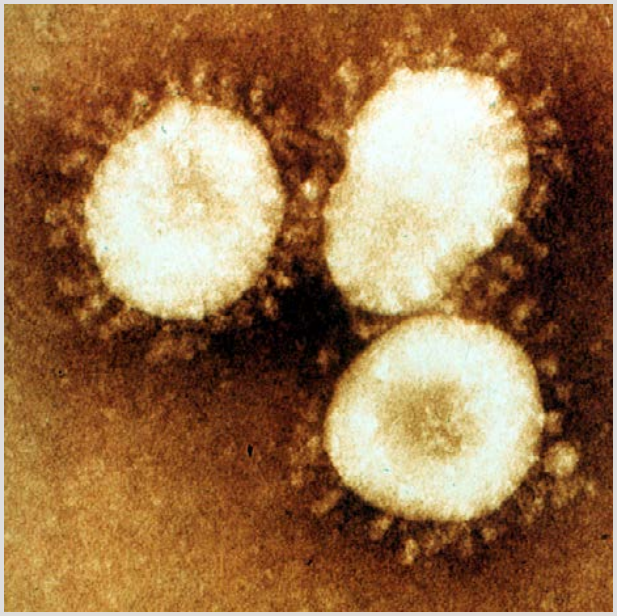
Exemptions in Appendix C

- rDNA in tissue culture with less than ½ of a viral genome
- some (not all) rDNA when *E. coli* K-12 hosts used - *NOTE*: *E. coli* BL21 is **not** exempt
- some rDNA when *Saccharomyces cerevisiae* or *S. uvarum* hosts are used
- some rDNA when *Bacillus subtilis* or *B. licheniformis* host-vector systems used
- *Kluyveromyces* host-vector systems.
- *Bacillus subtilis* or *B. licheniformis* host-vector
- some rDNA from extrachromosomal elements of gram positive bacteria propagated in those bacteria (listed in Appendix C)
- purchase or transfer of transgenic rodents; creation or breeding of many transgenic rodents requiring ABSL-1 containment.

Work with Human, Animal or Plant Pathogenic Microorganisms

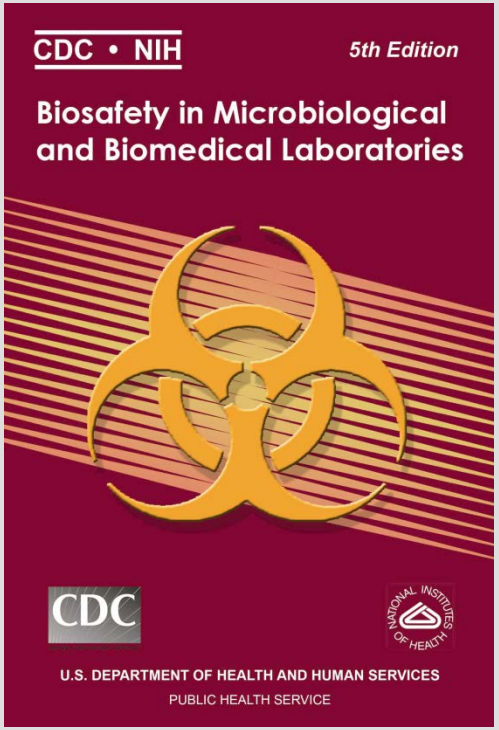
- At OSU, all work with human, animal, or plant pathogens is also reviewed by the IBC, regardless of whether involves rDNA.
- No pathogen work may begin until IBC approval has been obtained.

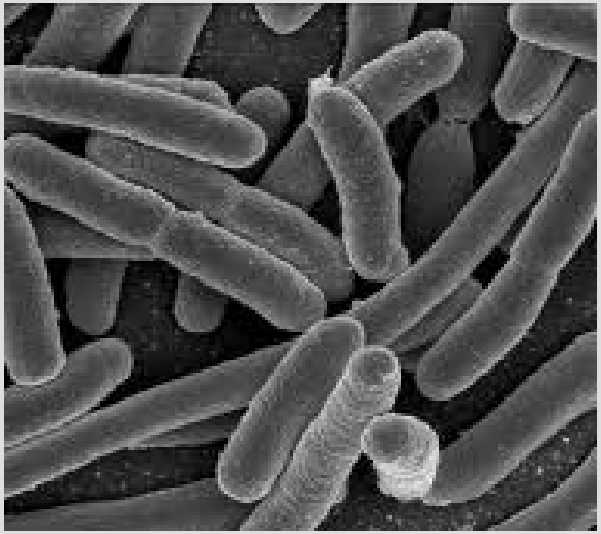




Pathogen Reviews

- For pathogen reviews and containment, use *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), currently 5th Edition.
- The BMBL has information on risk assessments, containment practices, facility requirements for safe work with all levels of pathogens.





Additional Resources

- NIH Guidelines:

http://oba.od.nih.gov/rdna/nih_guidelines_oba.html

- BMBL, 5th Edition:

http://www.cdc.gov/biosafety/publications/bmbl5/index.htm

- A Practical Guide to Containment; Greenhouse Research with Transgenic Plants and Microbes:

http://www.isb.vt.edu