Biomedical research has the goal of making us better
Biomedical research has the goal of making us better

To do this we need to better understand humankind biology
Animals 2013, 3 262

Figure 7. This schematic illustration (adapted with permission from an original by Professor Bert van Zupthen) attempts to describe trends in the use of animals for scientific purposes in the Western world across time. It depicts the emergence of the first vivisection studies by classical Greek physicians, the absence of animal-based research—along with most medical and scientific research—across the Middle Ages, its resurgence in the Renaissance onwards, and the rapid increase in animal studies following the rise of science-based physiology and medicine in the nineteenth century. The curves represented are nevertheless conjectural, as there are no reliable statistics on animal use for most of the period covered. Even nowadays it is hard to estimate trends in animal research, as data from several developed countries is insufficient (for instance, in the United States, rodents, fish and birds are not accounted for in the statistics). The available data, however, suggest that the number of animals used in research and testing in the Western world peaked in the 1970s, and decreased until the late 1990s, or early 2000s, to about half the number of 30 years earlier, and stabilizing in recent years. While many, if not most, researchers do not foresee an end to animal experiments in biomedicine, the European Commission has nevertheless set full replacement of animal experiments as an ultimate goal [204], and the Humane Society of the United States has the optimistic goal of full replacement by the year 2050 [192].

8. Conclusion

The historical controversy surrounding animal research is far from being settled. While the key arguments in this debate have not differed significantly since the rise of antivivisectionism in nineteenth-century England—and even before—we have since then moved a long way forward in regards to the protection of animals used in research and transparency regarding such use. While animal experiments have played a vital role in scientific and biomedical progress and are likely to continue to do so in the foreseeable future, it is nonetheless important to keep focusing on the continuous improvement of the wellbeing of laboratory animals, as well as further development of replacement alternatives for animal experiments.

Use of animal model systems has exploded in the last 100 years

![Diagram showing the use of animal model systems over time with key figures like Hippocrates, Galenus, Vesalius, and Bernard.]
Reasons for using model systems:

Identify genes that are causative mutations for birth defects

Identify genes that are causative mutations for genetic diseases (CF, Diabetes, cancer, etc)

Understand the biology of critical molecular pathways

Build genetic models of a disease to screen for novel compounds that might alleviate problem

What is the right animal model system?
These are all great model systems. Each one is uniquely useful depending on the biology being investigated.
Justifying choice of model system

Overall Benefit to Humankind

Ethical cost
  +
Monetary cost
Choosing a model system

1. is the animal’s biology appropriate for the question

2. is there a better ethical choice for a model system

3. is the question being asked valuable enough to overcome the ethical and financial obstacles.
Penicillin is good - but we could have gotten it wrong

Alexander Fleming
A. FLEMING.

The Rate of Killing of Staphylococci by Penicillin.

Some bactericidal agents like the hypochlorites are extremely rapid in their action, others like flavine or novarsenobillon are slow. Experiments were made to find into which category penicillin fell.

To 1 c.c. volumes of dilutions in broth of penicillin were added 10 c.mm. volumes of a 1 in 1000 dilution of a staphylococcus broth culture. The tubes were then incubated at 37° C. and at intervals 10 c.mm. volumes were removed and plated with the following result:

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Control</th>
<th>1/80</th>
<th>1/40</th>
<th>1/20</th>
<th>1/10</th>
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<tbody>
<tr>
<td></td>
<td>27</td>
<td>116</td>
<td>73</td>
<td>51</td>
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<td>27</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

It appears, therefore, that penicillin belongs to the group of slow acting antiseptics, and the staphylococci are only... concentration 30 or 40 times stronger than is necessary to inhibit completely the culture in broth. In the weaker concentrations it will be seen that... at first there is growth of the staphylococci and only after some hours are the cocci killed off. The same thing can be seen if a series of dilutions of penicillin in broth are heavily infected with staphylococcus and incubated. If the cultures are... clear while the control tube shows a heavy growth. This is a clear illustration of the bacteriolytic action of penicillin.

TOXICITY OF PENICILLIN.

The toxicity to animals of powerfully antibacterial mould broth filtrates appears to be very low. Twenty c.c. injected intravenously into a rabbit were not more toxic than the same quantity of broth. Half a c.c. injected intraperitoneally into a mouse weighing about 20 gm. induced no toxic symptoms. Constant irrigation of large infected surfaces in man was not accompanied by any toxic symptoms, while irrigation of the human conjunctiva every hour for a day had no irritant effect.

Is penicillin toxic?
Had Penicillin been injected into guinea pigs, we probably would have been delayed in finding our first antibiotic.
Had Penicillin been injected into guinea pigs, we probably would have been delayed in finding our first antibiotic.
Had Penicillin been injected into guinea pigs, we probably would have been delayed in finding our first antibiotic.
Choosing a model system

1. is the animal’s biology appropriate for the question

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Reasons for using model systems:

Identify genes that are causative mutations for birth defects

Identify genes that are causative mutations for genetic diseases (CF, Diabetes, cancer, etc)

Understand the biology of critical molecular pathways

Build genetic models of a disease to screen for novel compounds that might alleviate problem

Not all of these require the use of vertebrate animals. In some cases, the use of vertebrates isn’t justified
"[tax] dollars go to projects that have little or nothing to do with the public good — things like fruit fly research in Paris, France. I kid you not."

-Politician
"[tax] dollars go to projects that have little or nothing to do with the public good — things like fruit fly research in Paris, France. I kid you not."

-Politician

This is a dangerous statement from an ignorant person!
Invertebrates offer cost effective alternatives to vertebrates species

Overall Benefit to Humankind

Ethical cost +
Monetary cost
*Drosophila melanogaster* (fruit fly)

Thomas Hunt Morgan - Nobel Prize for Genetic Studies in *Drosophila*
Many molecular pathways associated with a particular disease are deeply conserved even when the phenotype at the end of those pathways does not resemble the disease.

Here is where use of invertebrate systems is incredibly useful!
Using forward genetics to screen for novel interacters with park and pink

park and pink1 are both genes that when mutated in us result in increased probability in developing parkinson’s disease
Using forward genetics to screen for novel interacters with park and pink
Table 7 Analysis of the interaction between a Pink1 null mutation and cytological regions that modified both park-RNAi and pink1-RNAi wing phenotype

<table>
<thead>
<tr>
<th>Deficiencies</th>
<th>Breakpoints</th>
<th>Effects of modification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pink1-RNAi</td>
</tr>
<tr>
<td>Enhancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Df(2L)net-PMF</td>
<td>21A1;21B7-8</td>
<td>++</td>
</tr>
<tr>
<td>Df(2L)BSC7</td>
<td>30C3-5;30F1</td>
<td>++</td>
</tr>
<tr>
<td>Df(2L)BSC50</td>
<td>30F5;31B1</td>
<td>+++</td>
</tr>
<tr>
<td>Df(2R)nap9</td>
<td>42A1-2;42E6-F1</td>
<td>++</td>
</tr>
<tr>
<td>Df(2R)cn9</td>
<td>42E44C</td>
<td>++</td>
</tr>
<tr>
<td>Df(2R)BSC39</td>
<td>48C5-D1;4BD5-E1</td>
<td>++</td>
</tr>
<tr>
<td>Df(3R)BSC47</td>
<td>83B7-C1;83C6-D1</td>
<td>++</td>
</tr>
<tr>
<td>Df(3R)Tpl10</td>
<td>83C1-2;84B1-2</td>
<td>++</td>
</tr>
<tr>
<td>Suppressors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Df(2L)BSC106</td>
<td>21B7;21C2</td>
<td>—</td>
</tr>
<tr>
<td>Df(2L)dp-79b</td>
<td>22A2-3;22D5-E1</td>
<td>——</td>
</tr>
<tr>
<td>Df(2L)ed1</td>
<td>24A2;24D4</td>
<td>—</td>
</tr>
<tr>
<td>Df(2L)BSC109</td>
<td>25C4;25C8</td>
<td>—</td>
</tr>
<tr>
<td>Df(2L)E110</td>
<td>25F3-26A1;26D3-11</td>
<td>——</td>
</tr>
<tr>
<td>Df(2L)BSC142</td>
<td>28C3;28BD3</td>
<td>—</td>
</tr>
<tr>
<td>Df(2L)BSC143</td>
<td>31B1;31D9</td>
<td>—</td>
</tr>
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<td>Df(2R)Exel7131</td>
<td>50E4;50F6</td>
<td>——</td>
</tr>
<tr>
<td>Df(2R)BSC550</td>
<td>53C1;53C6</td>
<td>—</td>
</tr>
<tr>
<td>Df(2R)robl-c</td>
<td>54B17-C4;54C1-4</td>
<td>—</td>
</tr>
<tr>
<td>Df(2R)P34</td>
<td>55E2-4;56C1-11</td>
<td>——</td>
</tr>
<tr>
<td>Df(3L)XD98</td>
<td>65A2;65E1</td>
<td>—</td>
</tr>
<tr>
<td>Df(3L)BSC33</td>
<td>65E10-F1;65F2-6</td>
<td>—</td>
</tr>
<tr>
<td>Df(3L)66C-G28</td>
<td>66B8-9;66C9-10</td>
<td>—</td>
</tr>
<tr>
<td>Df(3L)Scf-R6</td>
<td>66E1-6;66F1-6</td>
<td>——</td>
</tr>
<tr>
<td>Df(3L)BSC10</td>
<td>69D4-5;69F5-7</td>
<td>—</td>
</tr>
<tr>
<td>Df(3L)ME107</td>
<td>77F3;78C8-9</td>
<td>—</td>
</tr>
<tr>
<td>Df(3R)p-XT103</td>
<td>85A2;85C1-2</td>
<td>——</td>
</tr>
<tr>
<td>Df(3R)b1d104</td>
<td>89B5;89C2-7</td>
<td>—</td>
</tr>
<tr>
<td>Df(3R)p115</td>
<td>89B7-8;89E7</td>
<td>—</td>
</tr>
<tr>
<td>Df(3R)crb-F89-4</td>
<td>95D7-D11;95F15</td>
<td>—</td>
</tr>
<tr>
<td>Df(3R)Exel6202</td>
<td>96C9;96E2</td>
<td>—</td>
</tr>
<tr>
<td>Df(3R)Exel6203</td>
<td>96E2;96E6</td>
<td>——</td>
</tr>
</tbody>
</table>

> 40 genetic regions that interact with both pink1 and park

Potentially new places to look for mutations associated with Parkinson’s disease

Potentially new therapeutic targets
"[tax] dollars go to projects that have little or nothing to do with the public good — things like fruit fly research in Paris, France. I kid you not."

-Politician

Sometimes just general curiosity in simple systems can build foundational knowledge necessary for rapid understanding of the molecular basis of a disease.
Many of these genes are linked to Autism Spectrum Disorders.
Use of invertebrate systems can improve speed, cost, and reduce some ethical concerns.
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Figure 7. This schematic illustration (adapted with permission from an original by Professor Bert van Zupthen) attempts to describe trends in the use of animals for scientific purposes in the Western world across time. It depicts the emergence of the first vivisection studies by classical Greek physicians, the absence of animal-based research—along with most medical and scientific research—across the Middle Ages, its resurgence in the Renaissance onwards, and the rapid increase in animal studies following the rise of science-based physiology and medicine in the nineteenth century. The curves represented are nevertheless conjectural, as there are no reliable statistics on animal use for most of the period covered. Even nowadays it is hard to estimate trends in animal research, as data from several developed countries is insufficient (for instance, in the United States, rodents, fish and birds are not accounted for in the statistics). The available data, however, suggest that the number of animals used in research and testing in the Western world peaked in the 1970s, and decreased until the late 1990s, or early 2000s, to about half the number of 30 years earlier, and stabilizing in recent years. While many, if not most, researchers do not foresee an end to animal experiments in biomedicine, the European Commission has nevertheless set full replacement of animal experiments as an ultimate goal [204], and the Humane Society of the United States has the optimistic goal of full replacement by the year 2050 [192].

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Choosing a model system

1. is the animal’s biology appropriate for the question
2. is there a better ethical choice for a model system
3. is the question being asked valuable enough to overcome the ethical and financial obstacles.
Figure 4. This full-page illustration of Pasteur in his animal facility was published in Harper's Weekly in the United States, on 21 June 1884. At this time, there was moderate curiosity on Pasteur's work in the US, which would intensify after his first successful human trials of a therapeutic vaccine for rabies in 1885. In the article, the reader is reassured that the use of dogs is both humane and justified in the interest of mankind. The use of other species, however, is barely mentioned [5]. Source: Images from the History of Medicine, U.S. National Library of Science.

Robert Koch, a practicing rural physician, would follow the tradition of the great German/Prussian physiologists of his time (and indeed was a student to many of them), providing invaluable contributions to medical knowledge through animal research, mainly in the field of bacteriology and pathology. His famous "Koch postulates" would play an important role in microbiology. Along with his associates,
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Animal rights cause by Tom Regan himself [171], made researchers close themselves within their community and avoid speaking publicly about their work [172–174], which in turn left pro-research advocacy to emotion-appealing campaigns, of the likes of the Foundation for Biomedical Research's "Will I be alright, Doctor?" film [175], or the advertisement depicted in Figure 6.

Figure 6.
A large advertisement published in the 13 May 1991 edition of The Hour (p. 9), and part of a campaign in defense of animal research, sponsored by the United States Surgical Corporation. While the value of Pasteur's work is undeniable, there is, however, no scientific grounding for the claim that only by experimenting on dogs would a vaccine for rabies have been developed, or that other animal models or even non-animal methods could not have been used to achieve this in over a century. These dramatic and biased portraits of animal research are now more uncommon, as an increasing number of scientists acknowledge the need to be more candid and open to objective discussion over the possibilities and limitations of animal research, and of the scientific process altogether.

Humans And Animals Would Still Be Dying From Rabies If Pasteur Hadn’t Experimemented With Dogs.
Developing rabies vaccination was BIG deal

Cure for Rabies

Ethical cost
+ Monetary cost
Developing better cosmetics

Testing cosmetics on animals doesn’t really justify use of animal models

Ethical cost + Monetary cost
Choosing a model system

1. is the animal’s biology appropriate for the question
2. is there a better ethical choice for a model system
3. is the question being asked valuable enough to overcome the ethical and financial obstacles.
Defect in vertebrae allows spinal nerves to protrude

1 in 1000 births
Identification of genes associated with human birth defects
Table 1
Mouse Lines with NTDs That Have Been Identified in the Sloan-Kettering Mouse Mutagenesis Screen

<table>
<thead>
<tr>
<th>Line</th>
<th>Phenotype</th>
<th>Mapped to chromosome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Exencephaly, craniofacial defects and omphalocele</td>
<td>15</td>
<td>?</td>
</tr>
<tr>
<td>11A</td>
<td>Exencephaly, cardiovascular defect, polydactyly</td>
<td>7</td>
<td>?</td>
</tr>
<tr>
<td>12A</td>
<td>Exencephaly</td>
<td>4</td>
<td>?</td>
</tr>
<tr>
<td>12D</td>
<td>Exencephaly</td>
<td>16</td>
<td>?</td>
</tr>
<tr>
<td>16C</td>
<td>Exencephaly, eye defect</td>
<td>8</td>
<td>?</td>
</tr>
<tr>
<td>20</td>
<td>Exencephaly, curly tail, fused digits kidney and lung defects</td>
<td>2</td>
<td>Laminin α5</td>
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<tr>
<td>22C</td>
<td>Exencephaly, small forebrain and eye defect</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>26</td>
<td>Exencephaly</td>
<td>12</td>
<td>?</td>
</tr>
<tr>
<td>27E</td>
<td>Exencephaly</td>
<td>12</td>
<td>?</td>
</tr>
<tr>
<td>34B</td>
<td>Exencephaly</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>Dey</td>
<td>Exencephaly, spina bifida, gastrulation and eye defect</td>
<td>3</td>
<td>Novel</td>
</tr>
<tr>
<td>C2</td>
<td>Exencephaly, spina bifida</td>
<td>7</td>
<td>?</td>
</tr>
<tr>
<td>F11</td>
<td>Exencephaly and vascular defects</td>
<td>3</td>
<td>Novel</td>
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<td>Opmp</td>
<td>Exencephaly and eye defect</td>
<td>12</td>
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<tr>
<td>Z4</td>
<td>Exencephaly</td>
<td>18</td>
<td>?</td>
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<td>G2E</td>
<td>Exencephaly and eye defect</td>
<td>4</td>
<td>Novel</td>
</tr>
<tr>
<td>7A5</td>
<td>Exencephaly and small forebrain</td>
<td>5</td>
<td>?</td>
</tr>
<tr>
<td>31B</td>
<td>Exencephaly and small forebrain</td>
<td>2</td>
<td>?</td>
</tr>
<tr>
<td>1B</td>
<td>Exencephaly, spina bifida, branchial arch and cardiovascular defect</td>
<td>6</td>
<td>?</td>
</tr>
<tr>
<td>F19</td>
<td>Exencephaly</td>
<td>?</td>
<td>?</td>
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<tr>
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<td>Exencephaly</td>
<td>19</td>
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<td>12</td>
<td>Exencephaly</td>
<td>1</td>
<td>?</td>
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<td>lilR3</td>
<td>Exencephaly, neural patterning</td>
<td>16</td>
<td>?</td>
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<td>Kif3a</td>
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<td>Opb2</td>
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<td>Rab23</td>
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<td>Hennin</td>
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<td>16</td>
<td>Novel</td>
</tr>
<tr>
<td>20D</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
<td>?</td>
<td>?</td>
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</tbody>
</table>
Understanding spina bifida

Ethical cost +
Monetary cost
Testing the hypothesis that some cancers arise by reviving populations of embryonic stem cells

A zebrafish melanoma model reveals emergence of neural crest identity during melanoma initiation

Charles K. Kaufman,1,2,3,4 Christian Mosimann,5 Zi Peng Fan,6,7 Song Yang,1,2 Andrew J. Thomas,1 Julien Ablain,1,2,4 Justin L. Tan,1 Rachel D. Fogley,1 Ellen van Rooijen,1,2,4 Elliott J. Hagedorn,1,2,4 Christie Ciarlo,1,4 Richard M. White,8 Dominick A. Matos,9 Ann-Christin Puller,10 Cristina Santoriello,1,11 Eric C. Liao,2,4,12 Richard A. Young,6,13 Leonard I. Zon1,2,3,4,11*

Science Jan 29th 2016
Neural crest cells

Mesoderm
- Smooth muscle cells
- Osteoblasts
- Adipocytes
- Chondrocytes
- Melanocytes
- Schwann cells

Ectoderm
- Neural crest
- Ectoderm
- Migrating neural crest cells
- Neural tube
- Notochord

Neurons
the gene *crestin* is expressed in neural crest cells

The authors make a transgenic line that will report *crestin* expression by driving EGFP

neural crest cells are stem cells
Transgenes and transgenics

- Transgene
  - Enhancer elements
  - Coding sequence
- Crestin
- Green fluorescent protein

Transgenic
Control experiment shows that *crestin*:EGFP transgene expressed where *crestin* mRNA is

Crestin Not expressed in adults
The authors next put their *crestin:*EGFP reporter into a p53 and BRAF mutant background and waited!
p53/BRAF/crestin:EGFP

Fig. 2. Tg(crestin:EGFP) specifically marks melanoma tumors and precursor lesions. (A) Spontaneous tumors (outlined) in p53/BRAF/crestin:EGFP zebrafish express EGFP (brackets), whereas the remainder of the animal is negative. (B) crestin:EGFP expression is also visible in precursor, nonraised lesions. (C) Example of a single crestin:EGFP+ cell in p53/BRAF background. (D) Scale expressing crestin:EGFP from precursor, nonraised regions [(B), bottom, arrow] were plucked, photographed [(D), left and middle], and subjected to ISH for crestin transcript [(D), right]. There is a concordance of EGFP (green) and crestin transcript (purple, dotted outlines, scales curl during ISH procedure, indicated by the curved arrow, observed in 5 of 5 scales). (Bottom right) crestin:EGFP–scales are negative for crestin ISH staining (observed in 7 of 7 tested scales). (E) Cohort of p53/BRAF/crestin:EGFP zebrafish were tracked over time for the appearance of crestin:EGFP+ patches and tumors, with crestin:EGFP+ cells/patches (green line) identifiable before raised melanoma tumors (black line). (F) Example of an EGFP+ preclinical patch tracked over time (6, 9, 11.5, and 17 weeks) as it expands into a clinically apparent melanoma tumor. (G) Scale autotransplant and expansion of crestin:EGFP+ patch of cells. At day 0, the recipient site is free of crestin:EGFP+ cells (pre–scale transplant), but immediately after transplant of a single scale (post–scale transplant), the patch of EGFP+ cells is apparent (white circle). This patch expands outward, and even upon removal of the original transplanted scale after the day 33 photograph, EGFP+ cells remain in place and continue to expand. The magnification and size of white circle is the same in each image.
Melanomas are derived in part from a reactivation of developmental programs in adults.
On a side note transgenic animals also make adorable pets.
Choosing a model system

1. is the animal’s biology appropriate for the question

2. is there a better ethical choice for a model system

3. is the question being asked valuable enough to overcome the ethical and financial obstacles.

Organoids are providing alternative approaches for designing genetic model systems.

organoid = Miniature organ-like structure made in cell culture
Organoids can be derived from adult somatic cells of individual patients
"mature" kidney-like organoid

organoid = Miniature organ-like structure made in cell culture

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<table>
<thead>
<tr>
<th>ECAD</th>
<th>LTL</th>
<th>PODXL</th>
<th>Merge/DNA</th>
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capsule = PODXL+ Podocytes wrapping and filtering blood

proximal tube = LTL+ epithelium

Distal tube = E-Cad+ epithelium

Glomerulus
Organoids can be used for drug screens

WT

Polycystic kidney

1 in 500 to 1 in 1000 people worldwide
No cure - fatal
Organoids can be used for drug screens

WT

Polycystic kidney

1 in 500 to 1 in 1000 people worldwide
No cure - fatal
Not discussed today
Computational approaches as models

Take home
Model systems are necessary to understand humankind biology

Choosing the right model system requires weighing the benefit vs the ethical and financial costs

The answer isn’t always going to be easy
Review

Animal Experiments in Biomedical Research: A Historical Perspective

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Received: 15 February 2013; in revised form: 11 March 2013 / Accepted: 11 March 2013 / Published: 19 March 2013