Biomedical research has the goal of making us better.

How can we better understand humankind biology?
Animals 2013, 326

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 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.

Plot of animal usage in research over time
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)

Build genetic models of a disease to screen for novel compounds that might alleviate problem
"[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!
Justifying choice of model system

Overall Benefit to Humankind

Ethical cost + Monetary cost
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 Experimented With Dogs.
Developing rabies vaccination was a BIG deal.
Testing cosmetics on animals doesn’t really justify use of animal models.

- Developing better cosmetics
- Ethical cost
- +
- Monetary cost
Fig. 1.—Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.

Penicillium colony.

Staphylococci undergoing lysis.

Normal staphylococcal colony.

Alexander Fleming
The animal model should also be useful (reflect the biology of the problem at hand)

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.
The animal model should also be useful (reflect the biology of the problem at hand)

guinea pigs injected with penicillin die
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)

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

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

Not all of these questions even 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

This is a dangerous statement from an ignorant person!
Justifying choice of model system

Overall Benefit to Humankind

Ethical cost
+
Monetary cost
Why or how might these animals be useful for understanding Parkinson’s disease biology?
Using forward genetics to screen for novel interactors with park and pink

A - C, Ubiquitous knockdown of PD genes induces a wing position phenotype in adult flies

Molecular Brain

UAS-Pink1-RNAi

wing phenotype was heterozygosity significantly induced by park-RNAi; park-RNAi

Indeed, we found that increasing the knockdown flies was increased from ~2.1% at transgene on wing posture, male sterility

4

UAS-park

2011

have drooped

54B2;54B17

Drosophila

Molecular Brain
deficiency

42A1-2;42E6-F1

++) (P < 0.01).

94E1-2;94F1-2

on the 2 were also screened using the wing-posture phenotype (Table)

30F5;31B1

44D1-4;44F12

tub-GAL4

park RNA

+++++

deficiency

42A1-2;42E6-F1

++)

Park

+++

chromosome into the+++

knockdown flies caused lethality prior to knockdown

98B1-2;98B3-5

26D10-E1;27C1

chro-

83C1-2;84B1-2

Pink1

alone flies.

+++

Park

++++

Park

++++

 knockdown

* (Df)

Balancer

C (green) and 29°C (red). Numbers in brackets represent sample numbers. Error bars represent SEM.

Figure 1

We also examined the effect of increasing the level of dosage of genes located within the deleted cytological enhancer-containing cytological regions was deleted. Thus, crossing a

Df(2L)net-PMF

mosome, a portion of cytological regions was deleted. Prior to the screen, we examined if the deficiencies previously been shown to act in a common pathway with

Df(2L)ED611

Df(3L)BSC249

RNAi; park

Df(2L)BSC17

Df(3R)BSC56

Df(2L)BSC28

Df(3R)BSC42

Df(3R)BSC43

Df(3L)AC1

Df(2L)Mdh

50%

of wing-posture phenotype was increased from ~2.9% at

and longevity. In

loss-of-function mutants [17-19], we also tested if the

Fernandes and Rao Molecular Brain 2011, 4:17
http://www.molecularbrain.com/content/4/1/17
To identify the corresponding PD-interacting gene since they displayed strong modifiers, we found that similar enhancement was observed when a smaller deletion within this cytological region was observed. The cytological regions that showed lethal interactions with both park-RNAi and pink1-RNAi wing phenotype are indicated in bold.

### 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><strong>Enhancers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Df(2L)net-PMF</td>
<td>21A1;21B7-8</td>
<td>++ ++ n/d</td>
</tr>
<tr>
<td>Df(2L)5C17</td>
<td>30C3-5;30F1</td>
<td>++ ++ n/d</td>
</tr>
<tr>
<td>Df(2L)5C50</td>
<td>30F5;31B1</td>
<td>+++ ++++++ En</td>
</tr>
<tr>
<td>Df(2R)nap9</td>
<td>42A1-2;42E6-F1</td>
<td>++ ++++++ En</td>
</tr>
<tr>
<td>Df(2R)cn9</td>
<td>42E44C</td>
<td>++ ++ En</td>
</tr>
<tr>
<td>Df(2R)8C39</td>
<td>48C5-D1;48D5-E1</td>
<td>++ +++++ En</td>
</tr>
<tr>
<td>Df(3R)8C47</td>
<td>83B7-C1;83C6-D1</td>
<td>++ ++ En</td>
</tr>
<tr>
<td>Df(3R)Tpi10</td>
<td>83C1-2;84B1-2</td>
<td>++ ++ No</td>
</tr>
<tr>
<td><strong>Suppressors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Df(2L)8C106</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)led1</td>
<td>24A2;24D4</td>
<td></td>
</tr>
<tr>
<td>Df(2L)8C109</td>
<td>25C4;25CB</td>
<td></td>
</tr>
<tr>
<td>Df(2L)E110</td>
<td>25F3-26A1;26D3-11</td>
<td></td>
</tr>
<tr>
<td>Df(2L)8C142</td>
<td>28C3;28D3</td>
<td></td>
</tr>
<tr>
<td>Df(2L)8C143</td>
<td>31B1;31D9</td>
<td></td>
</tr>
<tr>
<td>Df(2R)Exel7131</td>
<td>50E4;50F6</td>
<td></td>
</tr>
<tr>
<td>Df(2R)8C550</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)XDI98</td>
<td>65A2;65E1</td>
<td></td>
</tr>
<tr>
<td>Df(3L)8C33</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)6sFr6</td>
<td>66E1-6;66F1-6</td>
<td></td>
</tr>
<tr>
<td>Df(3L)8C10</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)Exel7131</td>
<td>85A2;85C1-2</td>
<td></td>
</tr>
<tr>
<td>Df(3R)Exel7202</td>
<td>89B5;89C2-7</td>
<td></td>
</tr>
<tr>
<td>Df(3R)Tpi115</td>
<td>89B7;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 the foundation of knowledge that allows for rapid understanding of the molecular basis of diseases once a new mutation is found that is linked to that disease.
Many of these genes are linked to Autism Spectrum Disorders.
Use of invertebrate systems can improve speed, cost, and reduce some ethical concerns.
1 in 1000 births
Identification of genes associated with human birth defects

Figure 1. Genetic scheme for identification of recessive mutations by analysis of mouse neural tube defects (NTDs).

1. Mutagenized C57BL/6 (black) males are mated with female C3H/HeJ (white) mice to establish the F1 generation. To identify F1 males that carry mutations in genes required for neural tube closure, these males were mated to wild-type females, then crossing to the resulting F1 male to generate G2 females.

2. Of interest, this disproportionate number of recessive mutations and 32 of these lines exhibit defects in neural tube closure (Table 1; also see http://mouse.ski.mskcc.org for pictures of mutant phenotypes). This relatively high number of lines with NTDs likely reflects the sensitivity of neural tube closure to a wide variety of processes including gastrulation, branching morphogenesis, patterning, apoptosis, proliferation, and cell movement. Thus, the mutant phenotype is characterized using both histological and molecular markers to systematically examine mutant embryos for defects in processes such as neural tube closure.

3. To do so, we screened based on morphological defects, including NTDs. To identify recessive point mutations in genes that result in NTDs, we used an outcrossed (C3H/HeJ or castaneous) strain of mouse to which they are mated, then crossing to the resulting F1 male to generate G2 females. From our ongoing screening, we have isolated approximately 30 loss-of-function mutations per genome. With the mouse genome containing an estimated 30,000 genes, we can screen approximately two-thirds of the mouse genome per generation.

4. Mutations in a single chromosomal region and in some cases a single gene can be identified by analyzing 1000 F1 males. F1 males that carry mutations can screen approximately two-thirds of the mouse genome and the mouse genome containing an estimated 30,000 genes, we can identify approximately 30 loss-of-function mutations per genome. With the completion of the mouse genome sequence project, this is no longer an overwhelming task. In fact, we have been able to map some of our mutations to a single locus using fewer than 250 meioses; however, typically 500–1000 meioses are needed to positionally clone a gene of interest. During this process, the phenotype can be further characterized. The most needed to positionally clone a gene of interest. During this time, the phenotype can be further characterized.

5. The most popular chemical mutagen for inducing point mutations is N-ethyl-N-nitrosourea (ENU). The advantage of gene trap strategies as opposed to the generation of point mutations is that identification of the gene trap insertions as illustrated in Figure 1 (Kasarskis et al., 1998; Anderson, 2000). Male mice are mutagenized with a dose of ENU that has been shown empirically to give approximately 50 animals and then genome scanning with simple satellite markers followed by fine-resolution mapping and sequence length polymorphisms (SSLP) markers or microsatellite markers to determine the chromosomal location typically using a backcross of outcrossed (C3H/HeJ or castaneous) strain of mouse to which they are mated, then crossing to the resulting F1 male to generate G2 females.
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>
</tr>
<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>
</tr>
<tr>
<td>Opm</td>
<td>Exencephaly and eye defect</td>
<td>12</td>
<td>Novel</td>
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<td>Z4</td>
<td>Exencephaly</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>
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<tr>
<td>1B</td>
<td>Exencephaly, spina bifida, branchial arch and cardiovascular defect</td>
<td>6</td>
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<tr>
<td>F19</td>
<td>Exencephaly</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>33C</td>
<td>Exencephaly</td>
<td>19</td>
<td>?</td>
</tr>
<tr>
<td>12</td>
<td>Exencephaly</td>
<td>1</td>
<td>?</td>
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<tr>
<td>lilR3</td>
<td>Exencephaly, neural patterning</td>
<td>16</td>
<td>?</td>
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<td>Kif3a</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
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<td>Kif3a</td>
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<tr>
<td>Opb2</td>
<td>Exencephaly, spina bifida, neural patterning, left-right patterning</td>
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<td>Rab23</td>
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<td>2A</td>
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<td>11</td>
<td>?</td>
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<td>Wimple</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
<td>5</td>
<td>IFT172</td>
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<td>Ling-ling</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
<td>9</td>
<td>Novel</td>
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<tr>
<td>10</td>
<td>Exencephaly, neural patterning, eye defect and cardiovascular defect</td>
<td>10</td>
<td>?</td>
</tr>
<tr>
<td>Flexo</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
<td>14</td>
<td>IFT88/polaris</td>
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<td>Hennin</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
<td>16</td>
<td>Novel</td>
</tr>
<tr>
<td>20D</td>
<td>Exencephaly, neural patterning, left-right patterning</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Reasons for using model systems:

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- Identify genes that are causative mutations for genetic diseases (CF, Diabetes, cancer, etc)
- Build genetic models of a disease to screen for novel compounds that might alleviate problem
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*
Neural crest cells

Diagram showing the development of neural crest cells, which contribute to various tissues such as Smooth muscle cells, Osteoblasts/Osteoclasts, Adipocytes, Chondrocytes, Melanocytes, Schwann cells, and Neurons. The process includes the formation of Neural crest, Neural tube, Notochord, and Migrating neural crest cells.
the gene *crestin* is expressed in neural crest cells

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

Enhancer elements

coding sequence

green fluorescent protein
Control experiment shows that \textit{crestin}:EGFP = \textit{crestin} mRNA and that it is expressed in Neural crest cells.
The authors next put their *crestin:EGFP* reporter into a p53 and BRAF mutant background and waited!

Normally in adult animal *crestin* is not expressed

But sometimes a cell would pop up
*crestin*+ melanomas grow
Fig. 2. Tg(crestin:EGFP) specifically marks melanoma tumors and precursor lesions.

(A) Spontaneously arising 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 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.
On a side note, transgenic animals also make adorable pets.
“mature” kidney-like organoid
organoid = Miniature organ-like structure made in cell culture

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
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.
Not discussed today

Computational approaches as models
Animal Experiments in Biomedical Research: A Historical Perspective

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