Do animal models provide a sufficient basis for presumption of toxicity in safety testing?

Application of human cell-based assays in toxicity testing
Severe blunt trauma (n=167: up to 28 days) (4,389 gene changes ≥ 2fold)
Burn injury (n=244: up to 1 year) (2,251 gene changes ≥ 2fold)
Low dose bacterial endotoxin (n=4: 24 h) (2,251 gene changes ≥ 2fold)
Correlation of Gene Expression Changes Among Human Burn, Trauma and Endotoxin and the Corresponding Mouse Models

<table>
<thead>
<tr>
<th>Human Burn</th>
<th>0.91</th>
<th>0.47</th>
<th>0.08</th>
<th>0.05</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Human Trauma</td>
<td>0.47</td>
<td>0.08</td>
<td>0.05</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Human Endotoxemia</td>
<td>0.08</td>
<td>0.09</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse Burn</td>
<td>0.13</td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Mouse Trauma</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Mouse Endotoxemia</td>
<td></td>
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</tbody>
</table>

Seok, J. et al. PNAS 110: 3507, 2013
Genomic responses in mouse models poorly mimic human inflammatory diseases

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A cornerstone of modern biomedical research is the use of mouse models to explore basic pathophysiological mechanisms, evaluate new therapeutic approaches, and make go or no-go decisions to carry new drug candidates forward into clinical trials. Systematic studies evaluating how well murine models mimic human inflammatory diseases are nonexistent. Here, we show that, although acute inflammatory stresses from different etiologies result in highly similar genomic responses in humans, the responses in corresponding mouse models correlate poorly with the human conditions and also, one another. Among genes changed significantly in humans, the murine orthologs are close to random in matching their human counterparts (e.g., $R^2$ between 0.0 and 0.1). In addition to improvements in the current animal model systems, our study supports higher priority for translational medical research to focus on the more complex human conditions rather than relying on mouse models to study human inflammatory diseases.
Total number of mouse, rat and human orthologs differentially expressed at least at one time-point during a 24 hour time-course in response to TCDD treatment of purified primary B cells.
Mice in the ENCODE spotlight

Following on from affiliated projects in humans and model invertebrates, the Mouse ENCODE Project presents comprehensive data sets on genome regulation in this key mammalian model. See Articles p.355, p.365, p.371 & Letter p.402.

Piero Carninci

The mouse genome was sequenced in 2002 as a primary model in which to study gene function and human diseases and to develop drugs. This was followed by maps of transcribed messenger RNA molecules and of long, non-protein-coding RNAs, which facilitated such experiments and analysis. Yet although 17 mouse strains have been sequenced, genome function and regulation cannot be understood by sequence analysis alone. Now, in four papers published in this issue, the Mouse ENCODE Consortium presents data sets that dramatically enhance our understanding of the regulation of the mouse genome, and of the similarities and differences compared with the human genome.

The ENCODE project was started by the National Human Genome Research Institute in 2003, with the aim of mapping functional elements of the human genome. The project, later expanded as Mouse ENCODE and

![Diagram showing transcription-factor binding in mice and humans. Gene transcription rates are regulated by transcription factors, which bind to promoter regions close to the specific gene or to enhancer regions at distant sites. Comparisons of maps of such binding sites generated by the mouse and human ENCODE projects suggest that many differences in transcription levels between equivalent (orthologous) genes in the two organisms result from transcription-factor binding sites (labelled as TFs) occupying different locations. A further regulatory influence is the insertion of retrotransposon elements (stretches of DNA derived from reverse transcription of RNA) that may contain transcription-factor binding sites.](image-url)
“... essentially all models are wrong but some are useful.”
George E.P. Box

Animal models, especially rodents, may be poor surrogates of human biological responses to exogenous stimuli.

Path forward

• Employment of human cells and tissues, when possible, as an adjunct to animal testing

• Development of human synthetic in vitro models

• Continue to acquire new genomic information