Erratum

For the article "Genomic responses in mouse models greatly mimic human inflammatory diseases" by Keizo Takao and Tsuyoshi Miyakawa, which appeared in the Early Edition of *Proc. Natl. Acad. Sci. USA* (doi: 10.1073/pnas.1401965111), the authors note the following corrections, which do not alter the over all conclusions of the published article.

1. Genes incorrectly included in analyses presented in Fig. 1

In Fig. 1, the genes that should not be included for analyses were inappropriately included for the analyses for two reasons. First, where some genes from the Human Burn and Human Trauma dataset were inappropriately included in analyses of other datasets because of data handling errors, all datasets now include only appropriate genes (see original and corrected version of Fig. 1, below). Second, the analyses originally presented in Fig. 1 included all genes with an absolute fold change (FC) greater than 1.2 for both human and mouse conditions. However, the genes with |FC| > 2.0 in human conditions and |FC| > 1.2 in mouse conditions should have been used, as was in Fig. 3, instead of the ones with |FC| > 1.2 for both human and mouse conditions. Genes that meet the same criteria are now appropriately analyzed in Fig. 1 (corrected analyses are now presented in Fig. 1). "Fold change" in the legend of the original version should have been "absolute fold change". Further corrections were made to the horizontal and vertical bars for each panel, which were inverted in the original Fig. 1, and to the Fig. 1 legend, which now includes a definition of "N".

Original version of Fig. 1:

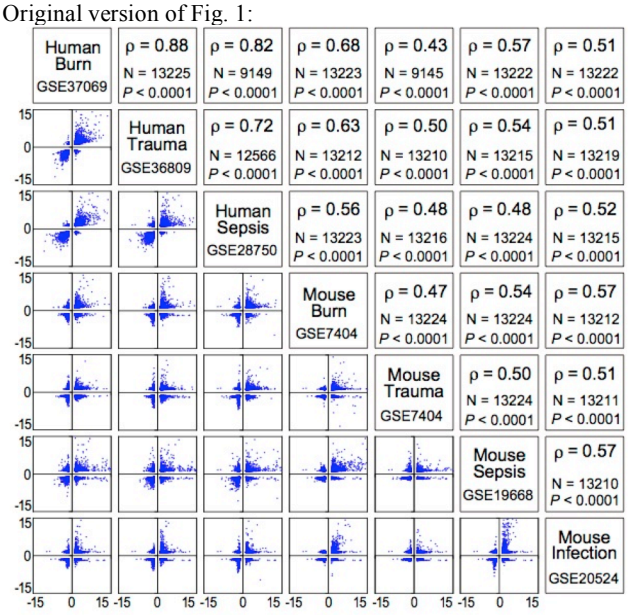


Fig. 1. Correlations of gene changes among human burns, trauma, sepsis, and the corresponding mouse models. Scatterplots and Spearman's rank correlations (ρ) of the fold changes of the genes responsive to both conditions for each pair of interest ($P < 0.05$; fold change >1.2). Vertical bar and horizontal bar for each panel represents fold change in right and upper panels, respectively. Murine models were highly significantly correlated with human conditions with Spearman's correlation coefficient (ρ = 0.43–0.68; $P < 0.0001$ for every comparison between human conditions and mouse models). The correlations between different mouse models were also significant (ρ = 0.47–0.57; $P < 0.0001$ for every comparison).

Corrected version of Fig. 1:

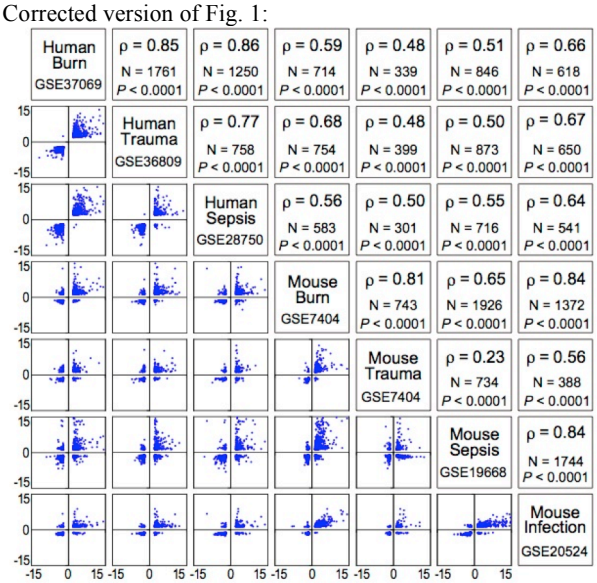


Fig. 1 Correlations of gene changes among human burns, trauma, sepsis, and the corresponding mouse models. Scatterplots and Spearman's rank correlations (ρ) of the fold changes. The criteria for gene selection were as follows: absolute fold change > 2.0 in human diseases, absolute fold change > 1.2 in mouse models, $P < 0.05$ in both conditions. Vertical bar and horizontal bar for each panel represents fold change in right and upper panels, respectively. N represents the number of probes differentially expressed in both conditions of the comparison in each panel. Murine models were highly significantly correlated with human conditions with Spearman's correlation coefficient (ρ = 0.48–0.68; $P < 0.0001$ for every comparison between human conditions and mouse models). The correlations between different mouse models were also significant (ρ = 0.23–0.84; $P < 0.0001$ for every comparison).

Along with the changes in Fig. 1, results of Spearman's rank correlation coefficient analysis for the correlation of the human and mouse gene expression levels in the abstract are corrected as follows:

Original (in the abstract, line 10-12):

Contrary to the previous findings, the gene expression levels in the mouse models showed extraordinarily significant correlations with those of the human conditions (Spearman's rank correlation coefficient: 0.43–0.68; genes changed in the same direction: 74–93%; $P = 6.5 \times 10^{-11}$ to 1.2×10^{-35}).

Corrected:

Contrary to the previous findings, the gene expression levels in the mouse models showed extraordinarily

significant correlations with those of the human conditions (Spearman's rank correlation coefficient: 0.48–0.68 in Fig. 1; significance of overlap: $P = 6.5 \times 10^{-11}$ to 1.2×10^{-35} in Fig. 2; genes changed in the same direction: 59.5–93.2% in Fig. 3).

Accordingly, the description in the Results section are corrected as follows:

Original (Page 2, 3rd paragraph, line 8-18):
The criteria for the selection of the genes of interest was fold change >1.2 and $P < 0.05$ within each condition to be compared. The correlations of the gene changes as assessed by Spearman's correlation coefficient indicated that there were highly significant similarities in gene responses between each of the human conditions and those of the mouse models (Fig. 1; $\rho = 0.43–0.68$, $P < 0.0001$ for every comparison between human conditions and the corresponding mouse models). There were also highly significant correlations among different mouse models (Fig. 1; $\rho = 0.47–0.57$, $P < 0.0001$ for every comparison between a pair of mouse models).

Corrected:
The criteria for the selection of the genes of interest was absolute fold change > 2.0 in human diseases and >1.2 in mouse conditions, and $P < 0.05$ in both conditions. The correlations of the gene changes as assessed by Spearman's correlation coefficient indicated that there were highly significant similarities in gene responses between each of the human conditions and those of the mouse models (Fig. 1; $\rho = 0.48–0.68$, $P < 0.0001$ for every comparison between human conditions and the corresponding mouse models). There were also highly significant correlations among different mouse models (Fig. 1; $\rho = 0.23–0.84$, $P < 0.0001$ for every comparison between a pair of mouse models).

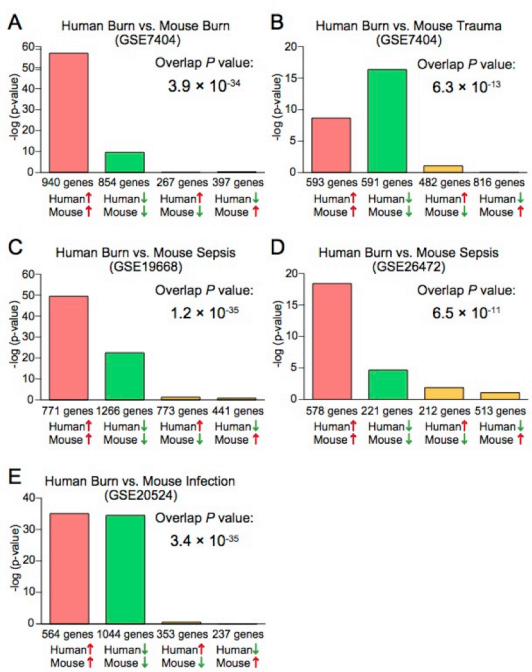
Consequently, in the Materials and Method section, the description of the criteria for the gene selections is changed as follows:

Original (Page 5, 7th paragraph, line 6):
In Fig. 1, genes meeting the criteria of $P < 0.05$ and fold change > 1.2 are plotted in the graph.

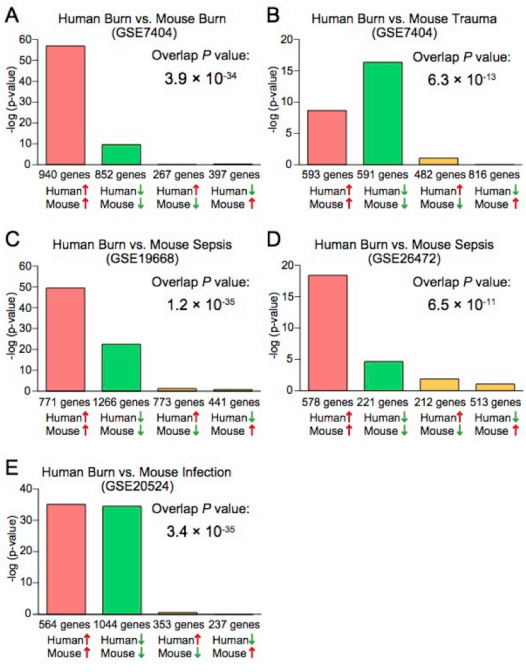
Corrected:
In Fig. 1, genes meeting the criteria of absolute fold change > 2.0 in human diseases and > 1.2 in mouse models, and $P < 0.05$ in both conditions, are plotted in the graph.

2. Correction to the number of the genes in Fig. 2*A*.
In Fig. 2*A*, where the number of genes down regulated in both Human Burn and Mice Burn is shown as "854", this should read "852". Additionally, tick marks on the Y-axis of Fig. 2*A* was duplicated, which are removed in the corrected version. The corrected Fig. 2 is given below:

Original version of Fig. 2



Corrected version of Fig. 2



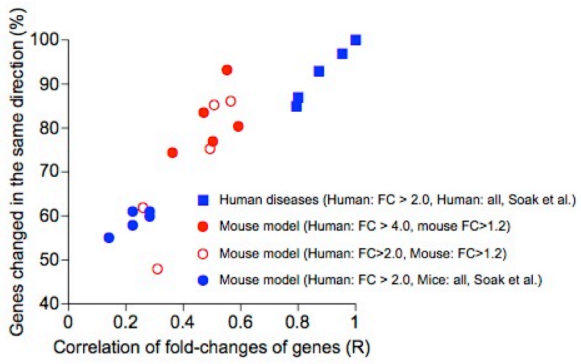
Additionally, the description of the criteria for gene selection is corrected as follows:

Original (Page 7, line 2-5):
In nonparametric ranking analysis of the gene expression signature by NextBio (Fig. 2), genes with a *P* value of 0.05 or less and an absolute fold change of 1.2 or greater were used, which is the default criterion used in analyses in NextBio.

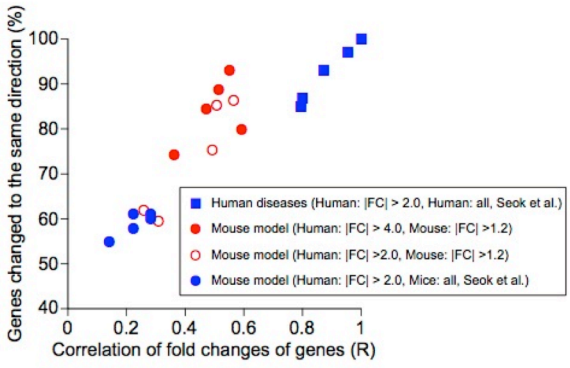
Corrected:
In nonparametric ranking analysis of the gene expression signature by NextBio (Fig. 2), genes with a *P* value < 0.05 and an absolute fold change > 1.2 were used, which is the default criterion used in analyses in NextBio.

3. Data incorrectly included in Fig. 3
In Fig. 3, because of a few errors in gene selection, three data points (Human Burn (|FC| > 4.0) vs. Mouse Sepsis, Human Burn (|FC| > 4.0) vs. Mouse Infection, Human Burn (|FC| > 2.0) vs. Mouse Trauma) were derived from gene expression analysis of genes that did not meet the specified criteria. All inappropriately included genes have now been removed, and corrected analysis is presented below (corrected Fig. 3). Additionally, "FC" in the explanatory notes in the original figure should read "|FC|", "in" in the label of the vertical axis should read "to", and "Soak et al." now correctly reads "Seok et al."

Original version of Fig. 3:



Corrected version of Fig. 3:



According to changes made in Fig. 3, Table S2 is corrected as follows:

Original version of Table S2:

Table S2. Studies of human diseases and mouse models that were used in Seok et al., and are available in NextBio and GEO.

Disease/model	GEO accession	Correlation of fold changes of genes (R)			Genes changed to the same direction (%)			Overlaps p-value	Bioset Name
Human									
Burns (as reference)	GSE37069	1.00			100			–	Leukocytes of patients with severe burns on > 20% of total body surface area _vs_ healthy controls
Trauma	GSE36809	0.95			97			1.0×10^{-323}	White blood cells of severe blunt trauma patients 28d after injury _vs_ healthy subjects
Sepsis	GSE13904	0.87			93			4.4×10^{-250}	Whole blood from children with septic shock at d1 _vs_ normal
Sepsis	GSE9960	0.80			87			1.0×10^{-323}	PBMCs from patients with Gram-negative sepsis _vs_ healthy
Sepsis	GSE28750	0.79			85			1.0×10^{-323}	Whole blood of sepsis patients with community-aquired infection _vs_ healthy subjects
		Human: FC>4.0 Mouse: FC > 1.2	Human: FC>2.0 Mouse: FC > 1.2	Human: FC >2.0 Mouse: all	Human: FC>4.0 Mouse: FC> 1.2	Human: FC>2.0 Mouse: FC> 1.2	Human: FC>2.0 Mouse: all		
Mouse									
Burns	GSE7404	0.55*	0.51*	0.28	93.2	85.3	60.0	3.9×10^{-34}	WBC from blood at 7d after burn injury _vs_ burn injury sham
Trauma	GSE7404	0.59*	0.31*	0.22	80.4	48.1	61.0	6.3×10^{-13}	WBC from spleen at 3d after trauma hemorrhage _vs_ trauma hemorrhage sham
Sepsis	GSE19668	0.47*	0.49*	0.22	83.7	75.3	58.0	1.2×10^{-35}	Blood of C57BL6J mice 4hr after Staphylococcus aureus infection _vs_ uninfected
Sepsis	GSE26472	0.36†	0.26*	0.14	74.4	61.9	55.0	6.5×10^{-11}	Blood of mice 24hr after intracheal infection with S. pneumoniae serotype 2 _vs_ vehicle
Infection	GSE20524	0.50*	0.57*	0.28	77.1	86.2	61.0	3.4×10^{-35}	Blood from 8wk old BALB-c mice 1d after tail vein injection - C.albicans _vs_ saline control

*, p<0.0001; †, p=0.0162

1. Seok J, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci USA 110(9):3507-3512.

Corrected version of Table S2:

Table S2. Studies of human diseases and mouse models that were used in Seok et al., and are available in NextBio and GEO.

Disease/model	GEO accession	Correlation of fold changes of genes (R)			Genes changed to the same direction (%)			Overlap *P* value	Bioset Name
Human									
Burns (as reference)	GSE37069	1.00			100			–	Leukocytes of patients with severe burns on > 20% of total body surface area _vs_ healthy controls
Trauma	GSE36809	0.95			97			$< 1.0 \times 10^{-323}$	White blood cells of severe blunt trauma patients 28d after injury _vs_ healthy subjects
Sepsis	GSE13904	0.87			93			4.4×10^{-250}	Whole blood from children with septic shock at d1 _vs_ normal
Sepsis	GSE9960	0.80			87			$< 1.0 \times 10^{-323}$	PBMCs from patients with Gram-negative sepsis _vs_ healthy
Sepsis	GSE28750	0.79			85			$< 1.0 \times 10^{-323}$	Whole blood of sepsis patients with community-aquired infection _vs_ healthy subjects
		Human: |FC| >4.0 Mouse: |FC| > 1.2	Human: |FC| >2.0 Mouse: |FC| > 1.2	Human: |FC| >2.0 Mouse: all	Human: |FC| >4.0 Mouse: |FC| > 1.2	Human: |FC| >2.0 Mouse: |FC| > 1.2	Human: |FC| >2.0 Mouse: all		
Mouse									
Burns	GSE7404	0.55*	0.51*	0.28	93.2	85.3	60.0	3.9×10^{-34}	WBC from blood at 7d after burn injury _vs_ burn injury sham
Trauma	GSE7404	0.59*	0.31*	0.22	80.4	59.5	61.0	6.3×10^{-13}	WBC from spleen at 3d after trauma hemorrhage _vs_ trauma hemorrhage sham
Sepsis	GSE19668	0.47*	0.49*	0.22	84.6	75.3	58.0	1.2×10^{-35}	Blood of C57BL6J mice 4hr after Staphylococcus aureus infection _vs_ uninfected
Sepsis	GSE26472	0.36*	0.26*	0.14	74.4	61.9	55.0	6.5×10^{-11}	Blood of mice 24hr after intracheal infection with S. pneumoniae serotype 2 _vs_ vehicle
Infection	GSE20524	0.51*	0.57*	0.28	88.9	86.2	61.0	3.4×10^{-35}	Blood from 8wk old BALB-c mice 1d after tail vein injection - C.albicans _vs_ saline control

*, p<0.0001; †, p=0.0162

1. Seok J, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci USA 110(9):3507–3512.

In the abstract, the number of genes that changed in the same direction among human burn and mouse models (74-93%) was originally calculated from comparisons of the genes in human burn with |FC| > 4.0 and mouse models with |FC| > 1.2. However, this has been corrected to include the number of the genes that changed in the same direction in comparisons of genes in human burn with |FC| > 4.0 or |FC| > 2.0, and mouse models with |FC| > 1.2 (59.5-93.2%). Accordingly, as shown in #1, the abstract is corrected as follows:

Original (in the abstract, line 10-12):
Contrary to the previous findings, the gene expression levels in the mouse models showed extraordinarily significant correlations with those of the human conditions (Spearman's rank correlation coefficient: 0.43–0.68; genes changed in the same direction: 74–93%; $P = 6.5 \times 10^{-11}$ to 1.2×10^{-35}).

Corrected:
Contrary to the previous findings, the gene expression levels in the mouse models showed extraordinarily significant correlations with those of the human conditions (Spearman's rank correlation coefficient: 0.48–0.68 in Fig. 1; significance of overlap: $P = 6.5 \times 10^{-11}$ to 1.2×10^{-35} in Fig. 2; genes changed in the same direction: 59.5–93.2% in Fig. 3).

Accordingly, text in the Results section is also corrected as follows:

Original (Page 2, 9th paragraph, line 6-11):
Contrary to the conclusion of Seok et al., there were significant correlations and similarities of the direction in the gene expression changes between human burn conditions and mouse models (Fig. 3; human: fold change >2.0; mouse model: fold change >1.2; $R = 0.26–0.51$; $P < 0.0001$ for all comparisons; percentage: 48.1–86.2).

Corrected:
Contrary to the conclusion of Seok et al., there were significant correlations and similarities of the direction in the gene expression changes between human burn conditions and mouse models (Fig. 3; human: absolute fold change > 2.0; mouse model: absolute fold change > 1.2; $R = 0.26–0.57$; $P < 0.0001$ for all comparisons; percentage: 59.5–86.2).

The description of the criteria for gene selection in the Material and Method is corrected as follows:

Original (Page 6, line 5-11):
Pearson correlation (R) between the human burn condition and other mouse models was calculated using genes with a *P* value of 0.05 or less and an absolute fold change greater than 4.0 (Fig. 3, solid red circles) or 2.0 (Fig. 3, open red circles) in the human burn dataset (as a reference) and genes with a *P* value of 0.05 or less and an absolute fold change greater than 1.2 in other conditions of mouse models (Fig. 3).

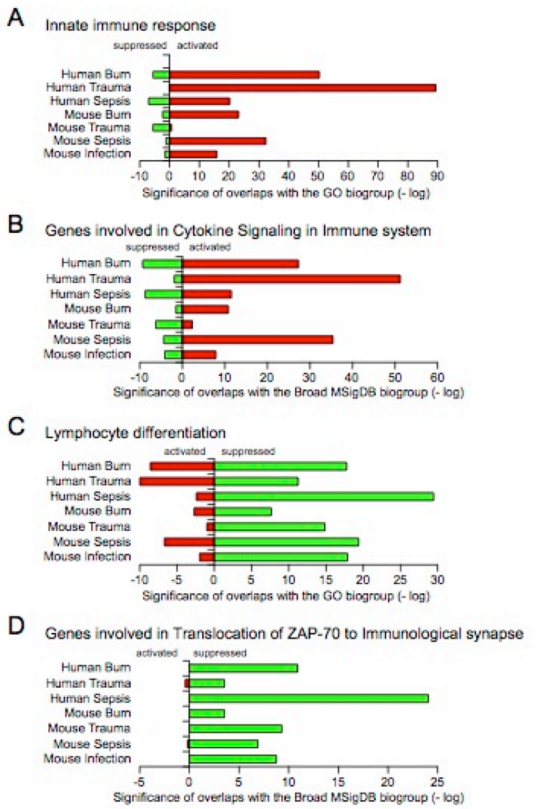
Corrected:
Pearson correlation (R) between the human burn condition and other mouse models was calculated using

genes with a P value < 0.05 and an absolute fold change greater than 4.0 (Fig. 3, solid red circles) or 2.0 (Fig. 3, open red circles) in the human burn dataset (as a reference) and genes with a P value < 0.05 and an absolute fold change greater than 1.2 in other conditions of mouse models (Fig. 3).

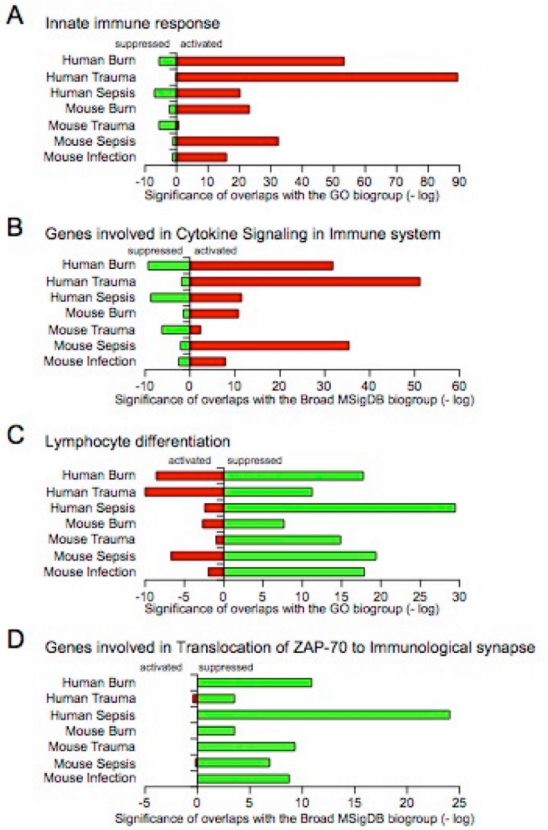
4. Corrections to errors in the size of bars shown in Fig. 4.

In Fig. 4, because of a data input error, some values were incorrectly presented (Fig. 4*A*, Human Burn; Fig. 4*B*, Human Burn, Mouse Sepsis, and Mouse Infection; Fig. 4*C*, Human Sepsis). The corrected Fig. 4 is given below.

Original version of Fig. 4



Corrected version of Fig. 4



Accordingly, text in the Results section is changed as follows:

Original (Page 3, in the third paragraph, line 4 – page 6 line 14):

There was significant overlap between genes annotated in GO as "innate immune response" and the genes up-regulated in the mouse models of burn (Fig. 4*A*, $P = 6.3 \times 10^{-24}$), sepsis ($P = 4.6 \times 10^{-33}$), and infection ($P = 1.3 \times 10^{-16}$), as well as in human burn ($P = 5.0 \times 10^{-51}$), trauma ($P = 4.1 \times 10^{-90}$), and sepsis conditions ($P = 6.3 \times 10^{-21}$). Significant overlap was also detected between "genes involved in cytokine signaling in immune system (canonical pathways, Broad MSigDB)" and genes up-regulated in the mouse models of sepsis (Fig. 4*B*, $P = 4.0 \times 10^{-36}$), burn ($P = 1.6 \times 10^{-11}$), and infection ($P = 1.3 \times 10^{-8}$), as well as in human burn ($P = 5.5 \times 10^{-28}$), trauma ($P = 6.5 \times 10^{-52}$), and sepsis conditions ($P = 3.2 \times 10^{-12}$). With regard to down-regulated pathways/biogroups, genes annotated "lymphocyte differentiation (GO)" significantly overlapped with genes down-regulated in the mouse models of burn (Fig. 4*C*, $P = 2.2 \times 10^{-8}$), trauma ($P = 1.4 \times 10^{-15}$), sepsis ($P = 4.2 \times 10^{-20}$), and infection ($P = 1.3 \times 10^{-18}$), as well as in human burn ($P = 1.7 \times 10^{-18}$), trauma ($P = 5.6 \times 10^{-12}$), and sepsis conditions ($P = 3.3 \times 10^{-30}$). There was also significant overlap between "genes involved in Translocation of ZAP-70 to immunological synapse (canonical pathways, Broad MSigDB)" and genes down-regulated in all of the human disease conditions and mouse models of these conditions (Fig. 4*D*, human burn, $P = 1.3 \times 10^{-11}$; human trauma, $P = 0.0003$; human sepsis, 8.7×10^{-25}; mouse burn, $P = 0.0003$; mouse trauma, $P = 5.1 \times 10^{-10}$; mouse sepsis, $P = 1.3 \times 10^{-7}$; and mouse infection, $P = 1.8 \times 10^{-9}$).

Corrected:

There was significant overlap between genes annotated in GO as "innate immune response" and the genes

up-regulated in the mouse models of burn (Fig. 4*A*, $P = 6.7 \times 10^{-24}$), sepsis ($P = 4.6 \times 10^{-33}$), and infection ($P = 1.3 \times 10^{-16}$), as well as in human burn ($P = 4.8 \times 10^{-54}$), trauma ($P = 4.1 \times 10^{-90}$), and sepsis conditions ($P = 6.3 \times 10^{-21}$). Significant overlap was also detected between "genes involved in cytokine signaling in immune system (canonical pathways, Broad MSigDB)" and genes up-regulated in the mouse models of sepsis (Fig. 4*B*, $P = 4.0 \times 10^{-36}$), burn ($P = 1.6 \times 10^{-11}$), and infection ($P = 1.3 \times 10^{-8}$), as well as in human burn ($P = 1.6 \times 10^{-32}$), trauma ($P = 6.5 \times 10^{-52}$), and sepsis conditions ($P = 3.2 \times 10^{-12}$). With regard to down-regulated pathways/biogroups, genes annotated "lymphocyte differentiation (GO)" significantly overlapped with genes down-regulated in the mouse models of burn (Fig. 4*C*, $P = 2.2 \times 10^{-8}$), trauma ($P = 1.4 \times 10^{-15}$), sepsis ($P = 4.2 \times 10^{-20}$), and infection ($P = 1.3 \times 10^{-18}$), as well as in human burn ($P = 1.7 \times 10^{-18}$), trauma ($P = 5.6 \times 10^{-12}$), and sepsis conditions ($P = 3.5 \times 10^{-30}$). There was also significant overlap between "genes involved in Translocation of ZAP-70 to immunological synapse (canonical pathways, Broad MSigDB)" and genes down-regulated in all of the human disease conditions and mouse models of these conditions (Fig. 4*D*, human burn, $P = 1.3 \times 10^{-11}$; human trauma, $P = 0.0003$; human sepsis, $P = 8.7 \times 10^{-25}$; mouse burn, $P = 0.0003$; mouse trauma, $P = 5.1 \times 10^{-10}$; mouse sepsis, $P = 1.3 \times 10^{-7}$; and mouse infection, $P = 1.8 \times 10^{-9}$).

5. Incorrect description of datasets in the Materials and Methods,

In the Materials and Methods subsection "Datasets for Human Diseases and Mouse Models," there were errors in some of the dataset names used for analyses. Datasets listed in the subsection were used in Fig. 1. Datasets used in Fig. 2, Fig. 3, and Fig. 4 were specified in Table S1, Table S2, and in the Materials and Methods subsection "Comparison of Pathways/Biogroups Altered in the Human Diseases and Mouse Models", respectively. Text is corrected as follows:

Original (Page 5, 6th paragraph, line 1 - 19):

The datasets that we analyzed in the present study were the same as those used in the study by Seok et al. (1) and are registered in NextBio. In the present study, the following datasets were used for gene expression pattern analyses: "leukocytes of patients with severe burns on >20% of total body surface area vs. healthy controls" from GSE37069 is referred as "Human Burn"; "white blood cells of severe blunt trauma patients 14 d after injury vs. healthy subjects" from GSE36809 is referred as "Human Trauma"; "whole blood of sepsis patients with community-acquired infection vs. healthy subjects" from GSE28750 is referred as "Human Sepsis"; "WBC from blood at 7 d after burn injury vs. burn injury sham" from GSE7404 is referred to as "Mouse Burn"; "WBC from spleen at 3 d after trauma hemorrhage vs. trauma hemorrhage sham" from GSE7404 is referred to as "Mouse Trauma"; "Blood of C57BL6J mice 4 h after Staphylococcus aureus infection vs. uninfected" from GSE19668 is referred to as "Mouse Sepsis"; "Blood from 8-wk-old BALB-c mice 1 d after tail vein injection - Candida albicans vs. saline control" from GSE20524 is referred to as "Mouse Infection." Only genes with a *P* value of 0.05 or less and an absolute fold change of 1.2 or greater were considered to be differentially expressed.

Corrected:

The datasets that we analyzed in the present study were the same as those used in the study by Seok et al. (1) and are registered in NextBio. In Fig. 1, the following datasets were used for gene expression pattern analyses: "leukocytes of patients with severe burns on >20% of total body surface area vs. healthy controls" from GSE37069 is referred as "Human Burn"; "white blood cells of severe blunt trauma patients 28 d after injury vs. healthy subjects" from GSE36809 is referred as "Human Trauma"; "whole blood of sepsis patients with community-acquired infection vs. healthy subjects" from GSE28750 is referred as "Human Sepsis"; "WBC from blood at 7 d after burn injury vs. burn injury sham" from GSE7404 is referred to as "Mouse Burn"; "WBC from blood at 3 d after trauma hemorrhage vs. trauma hemorrhage sham" from GSE7404 is referred to as "Mouse Trauma"; "Blood of C57BL6J mice 4 h after Staphylococcus aureus infection vs. uninfected" from GSE19668 is referred to as "Mouse Sepsis"; "Blood from 8-wk-old BALB-c mice 1 d after tail vein injection - Candida albicans vs. saline control" from GSE20524 is referred to as "Mouse Infection." Datasets used in Fig. 2, Fig. 3, and Fig. 4 were specified in Table S1, Table S2, and in the Materials and Methods subsection "Comparison of Pathways/Biogroups Altered in the Human Diseases and Mouse Models", respectively. Only genes with a *P* value < 0.05 and an absolute fold change > 1.2 were considered to be differentially expressed.