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Genomic responses in mouse models poorly mimic human inflammatory diseases

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Contributed by Ronald W. Davis, January 7, 2013 (sent for review December 6, 2012)

Journal Club
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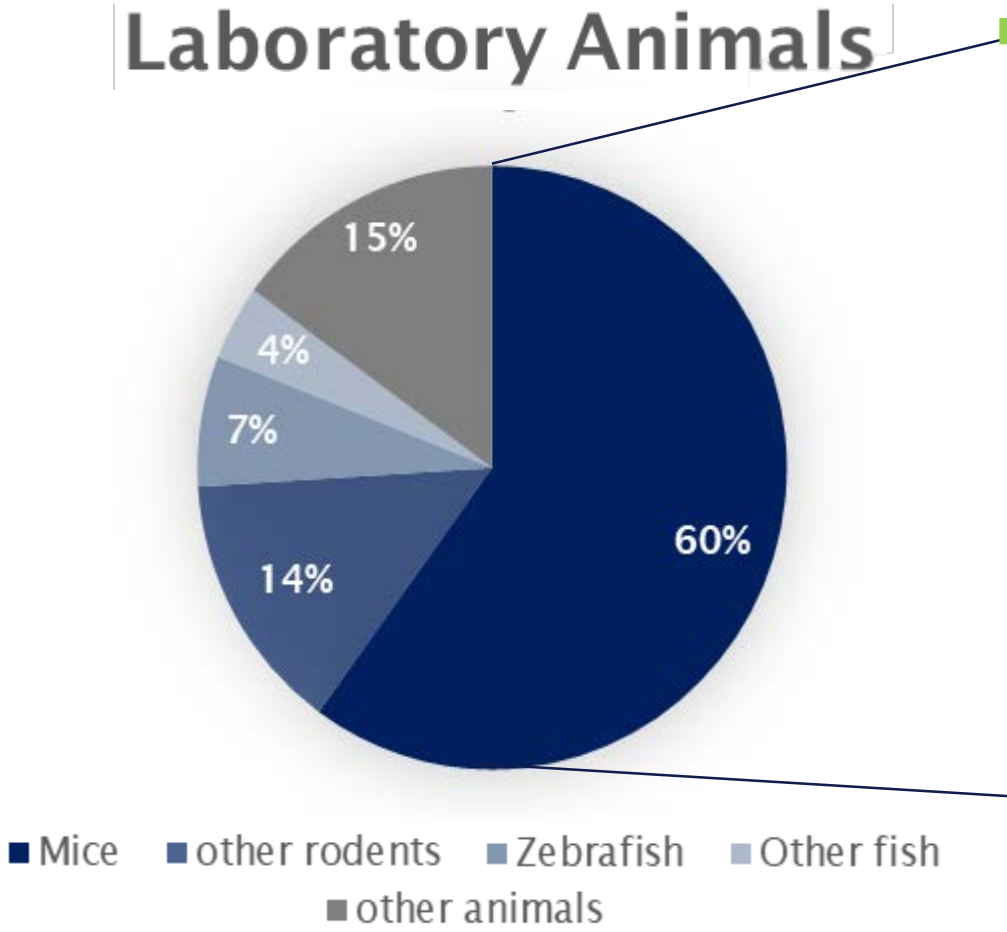
Katharina Klas, PhD Student

Animal models



Advantages	Disadvantages
• High similarity to human genome	• differing physiology
• Good genetic/molecular toolbox available	• Differing disease progression / recovery time
• Small size facilitates large scale/high throughput studies	• Generation time
• Cost-efficient model	• Artificial environment
	• (Limited genetic variation)

adapted from: aerzte-gegen-tierversuche-tierversuchsstatistiken, aerzte-gegen-tierversuchszahlen, annual-statistics-scientific-procedures-living-animals-2016

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Aim

Report a systematic comparison of the genomic response between human inflammatory diseases and mouse models

Correlations of the gene changes among human burns, trauma, and endotoxemia and the corresponding mouse model

Methods

- Human burn
- Human trauma
- Human endotoxemia
- Murine burn
- Murine trauma
- Murine endotoxemia

Methods

- Human trauma patients
  - Blunt injury associated with
    - Prehospital or emergency department systolic hypotension
    - Elevated base deficit
    - Blood transfusion requirement
    - Abbreviated injury scale score >2 for any body region (exclusive of brain)
- Human burn patients
  - Enrolled if admitted to burn centre within 96h after injury
    - Burns ≥20% of TBSA
    - Required at least one excision and grafting procedure
- All patients: treated according to SOPs

Methods

- Human Endotoxemia
  - 8 healthy male & female subjects between 18 – 40 years
    - i.v. administration of
      - either E. Coli 2ng/kg body weight
      - or 0.9% sodium chloride over a 5min period

Methods

Trauma

Blunt injury associated with:

- Prehospital or emergency department systolic hypotension
- Elevated base deficit
- Blood transfusion requirement
- Abbreviated injury scale score >2 for any body region (exclusive of brain)

Burn

- admitted to burn centre within 96h after injury
- Burns ≥20% of TBSA
- Required at least one excision and grafting procedure

Endotoxemia

- 8 healthy male & female subjects between 18 – 40 years
- i.v. administration of
  - either E. Coli 2ng/kg body weight
  - or 0.9% sodium chloride over a 5min period

Methods

Male C57BL/6J mice, 8 weeks; Jackson Laboratories

Trauma

- Trauma/haemorrhage (T/H)
- Laparotomy followed by withdrawal of sufficient blood

- Control mice underwent sham T/H

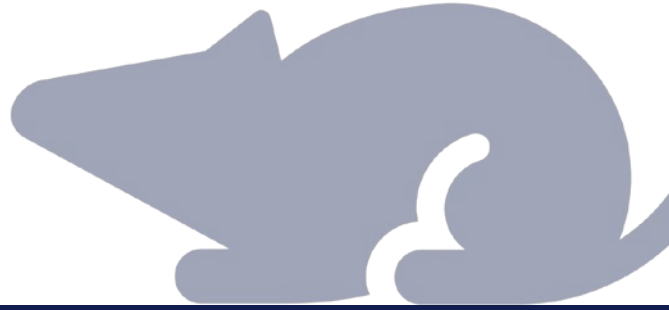
Burn

- 25% TBSA scald burn

- Control mice underwent sham burning

Endotoxemia

- 10ng i.p. injection of LPS, E. Coli

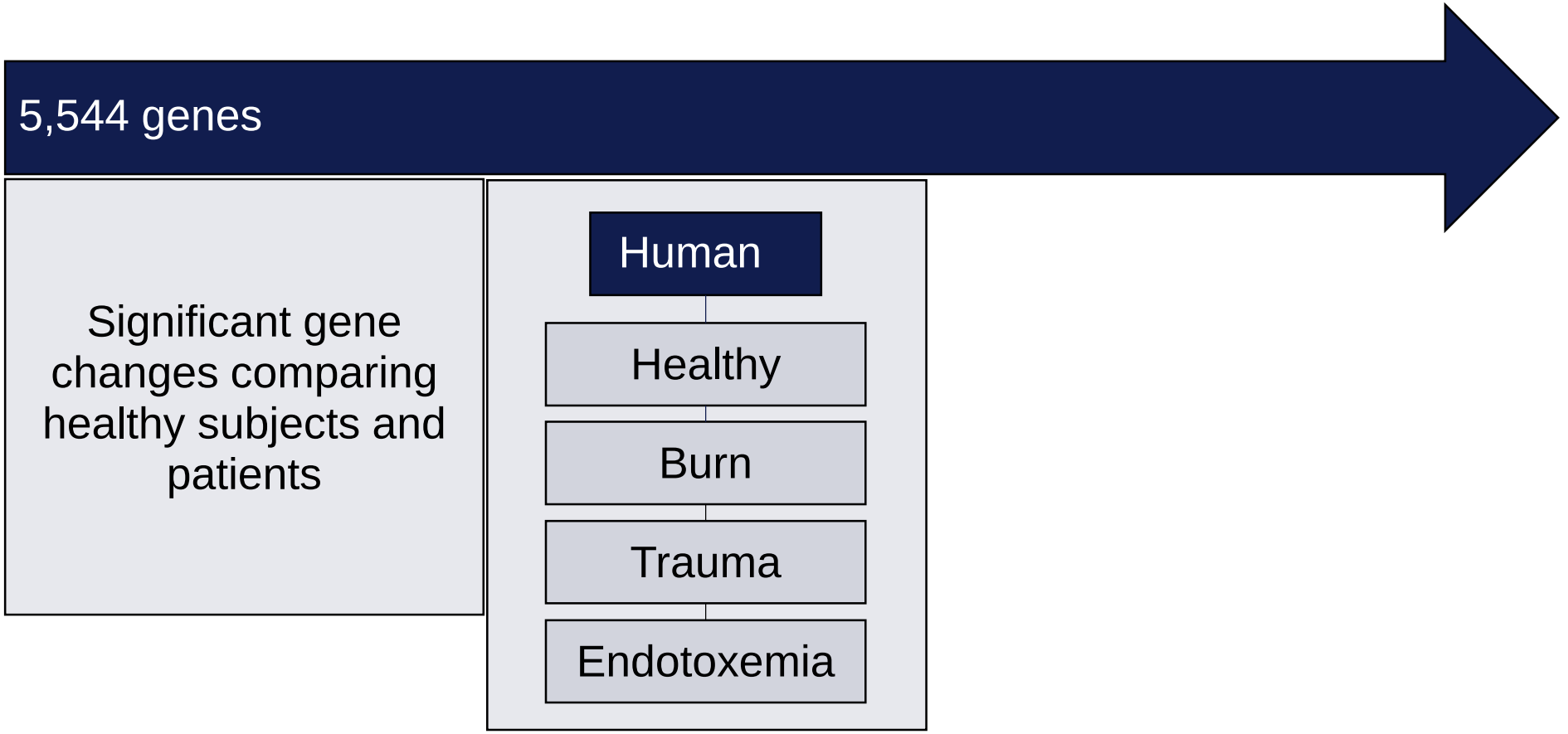


Assessment of correlation of gene changes

- Isolation of total blood leukocytes
- Extraction of total cellular RNA and subsequent hybridization onto Affymetrix HU133 Plus 2.0 GeneChip

- Max. fold changes of gene expression were measured in log scale between patients and healthy subjects

Assessment of correlation of gene changes



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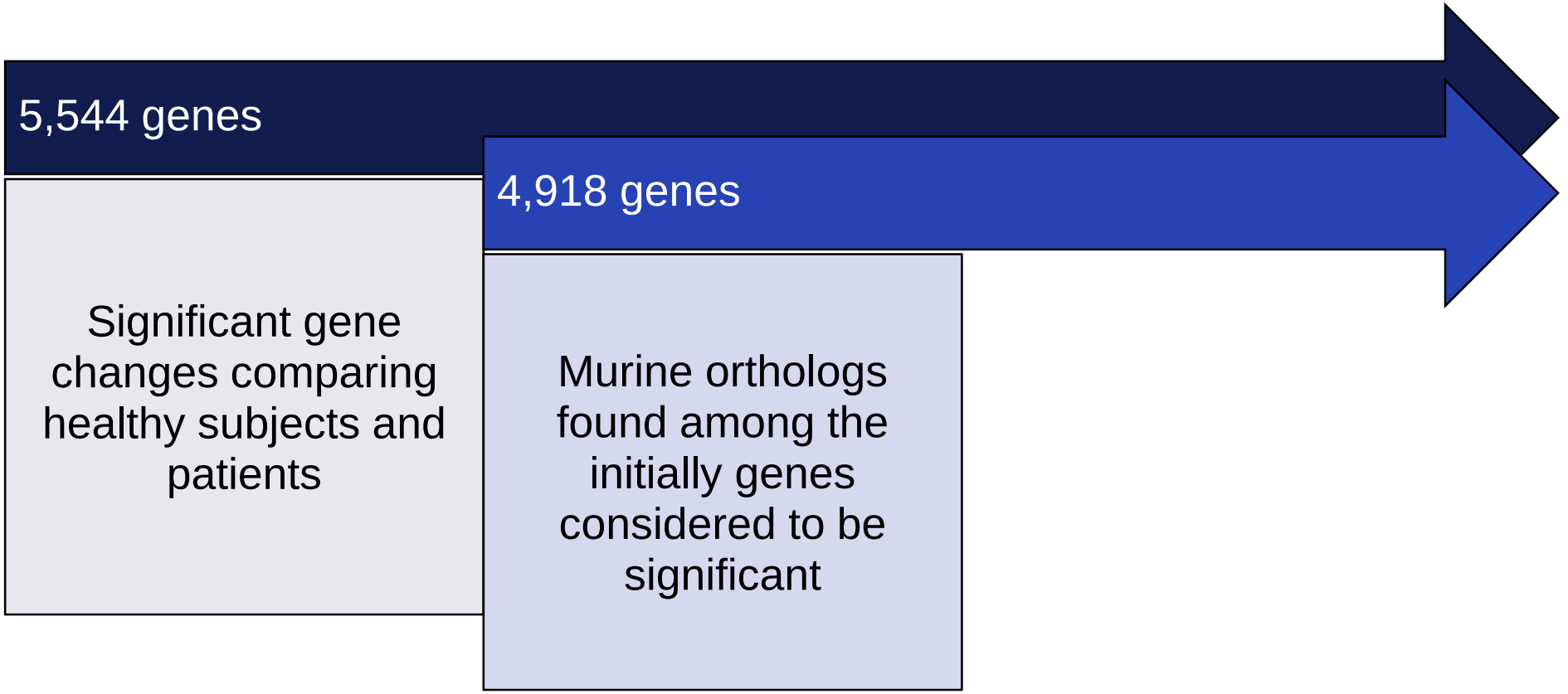

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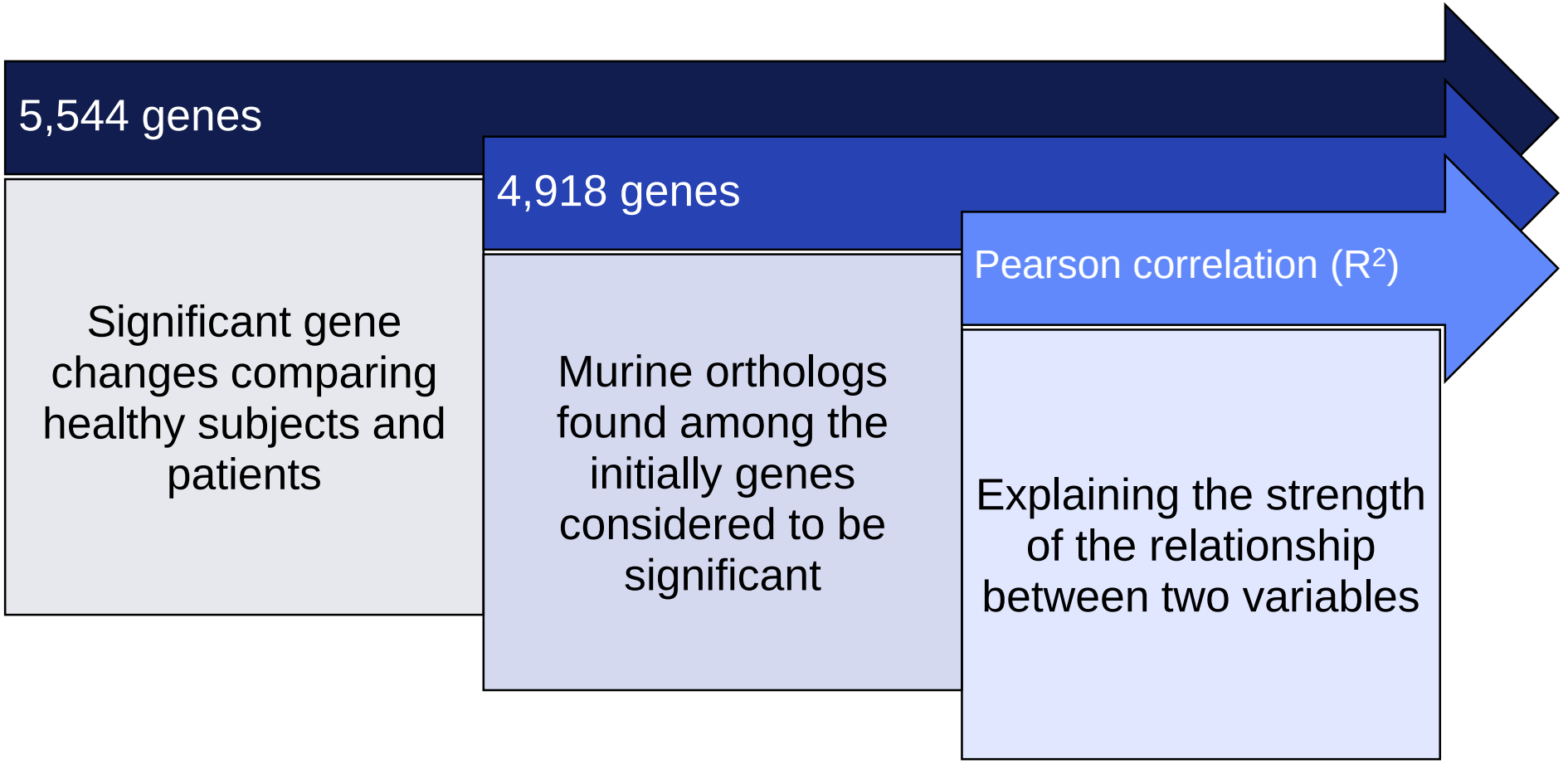


Fig. 1: Correlations of the gene changes among human burns, trauma, and endotoxemia and the corresponding mouse model

The higher (the closer to 1) the R^2 value, the higher/stronger is the correlation between two evaluated factors/models/situations.

Results in log twofold changes of 4,918 genes of human genes vs. murine orthologs

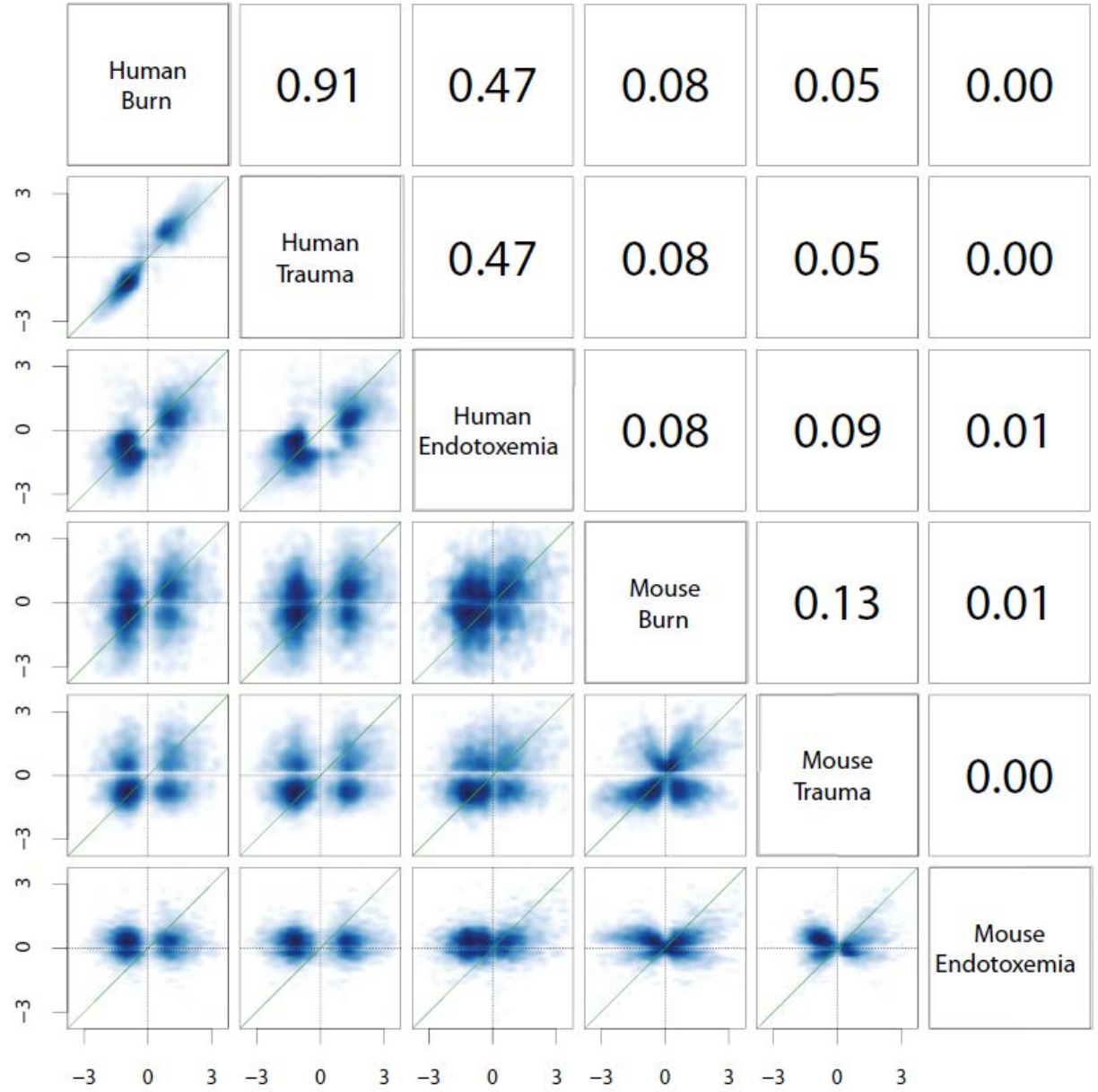


Fig. 1: Correlations of the gene changes among human burns, trauma, and endotoxemia and the corresponding mouse model

- Highest correlation between human burn & human trauma

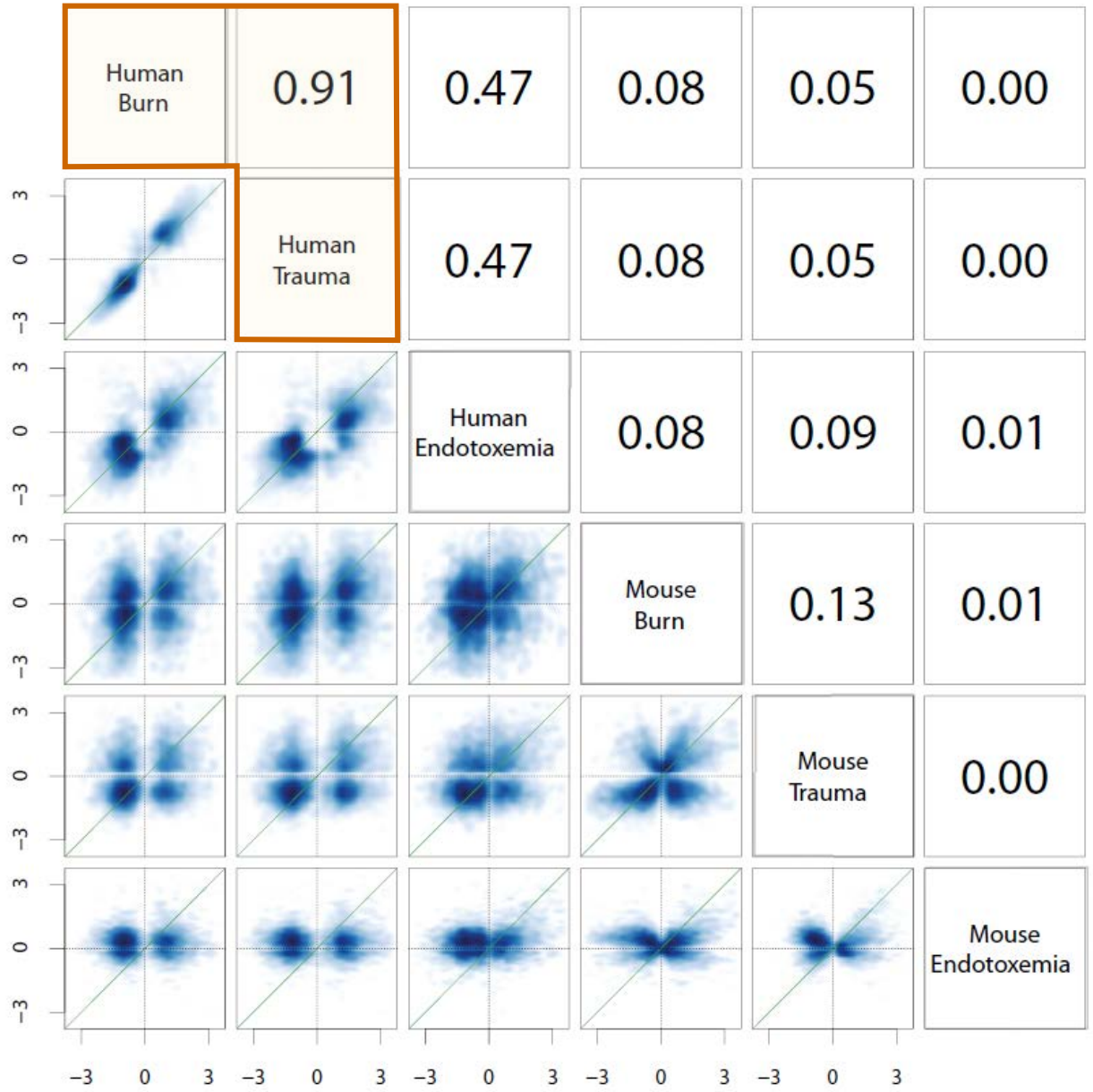


Fig. 1: Correlations of the gene changes among human burns, trauma, and endotoxemia and the corresponding mouse model

- Highest correlation between human burn & human trauma
- Moderate correlation between human injury & human endotoxemia

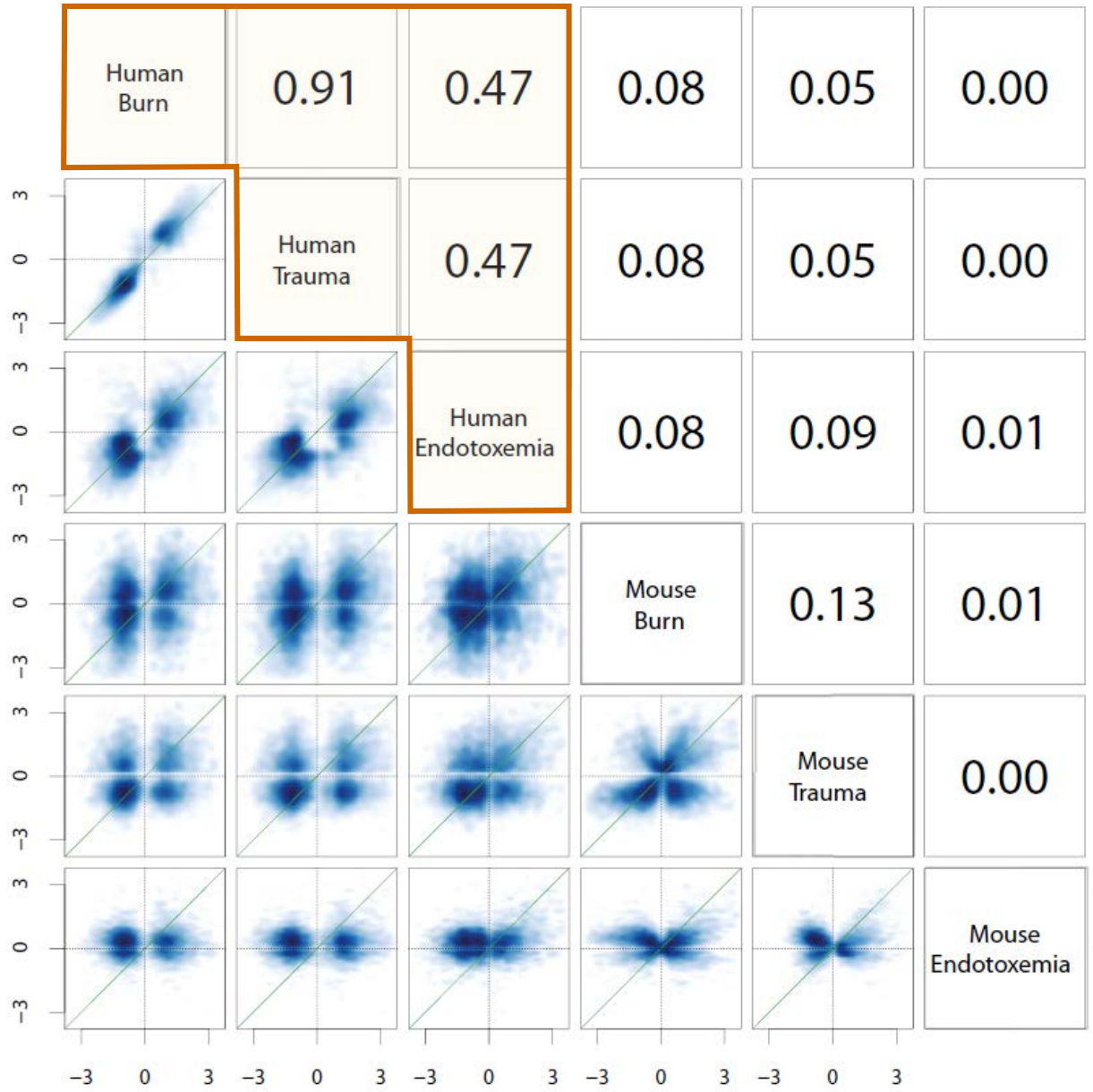


Fig. 1: Correlations of the gene changes among human burns, trauma, and endotoxemia and the corresponding mouse model

- Highest correlation between human burn & human trauma
- Moderate correlation between human injury & human endotoxemia
- Poor correlation between murine models

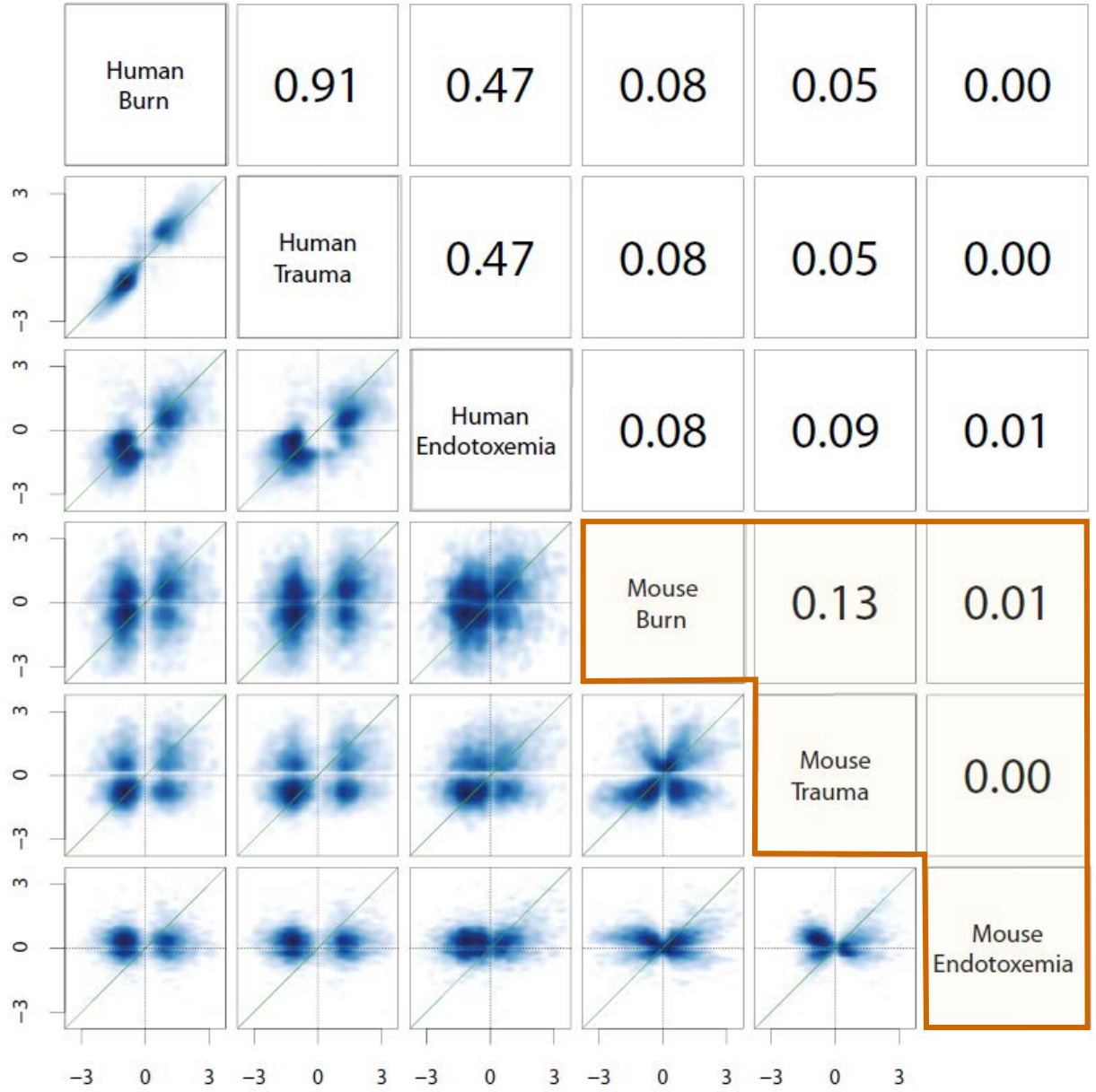
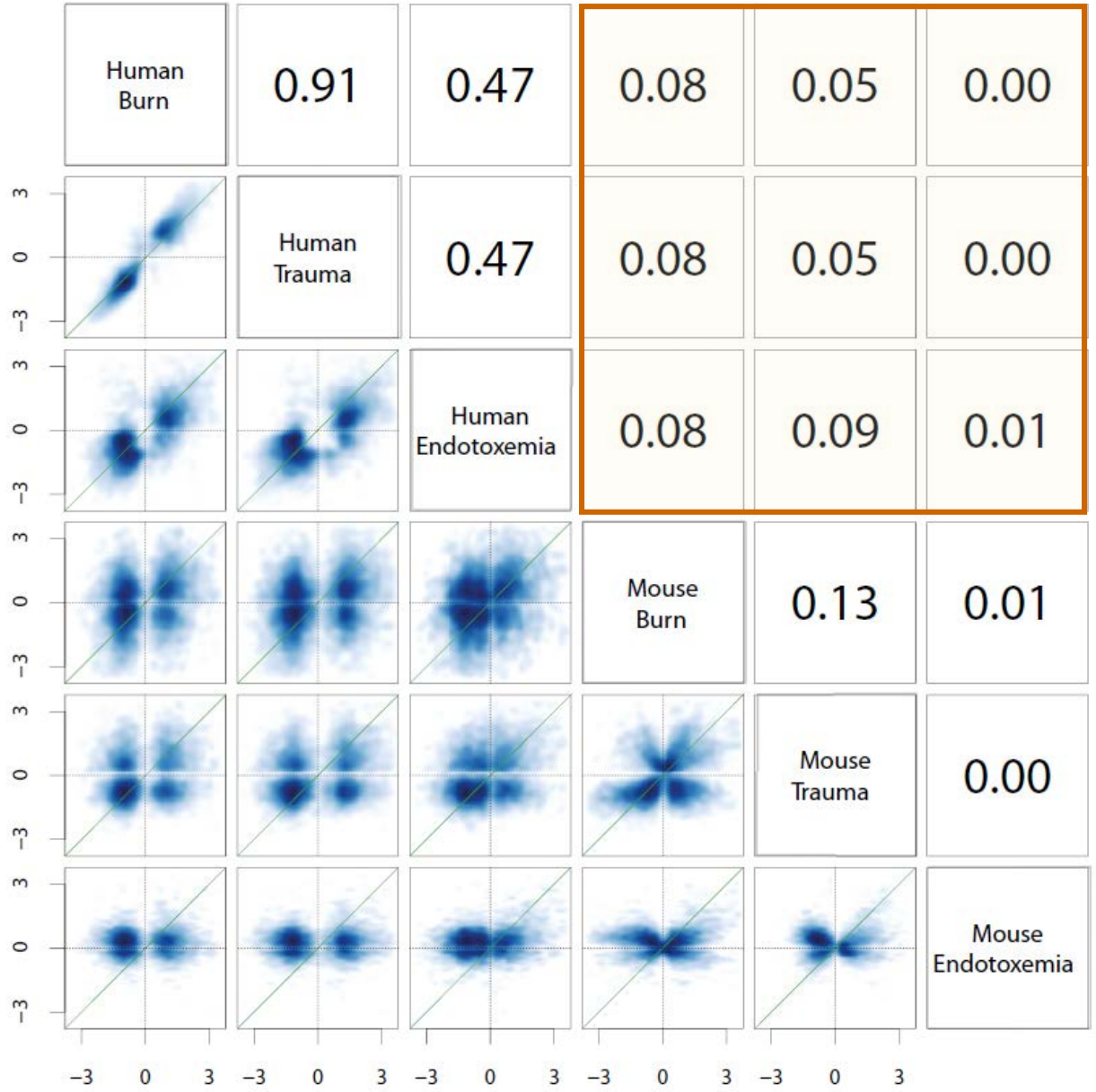


Fig. 1: Correlations of the gene changes among human burns, trauma, and endotoxemia and the corresponding mouse model

- Highest correlation between human burn & human trauma
- Moderate correlation between human injury & human endotoxemia

- Poor correlation between murine models
- Almost random correlation between murine & human conditions



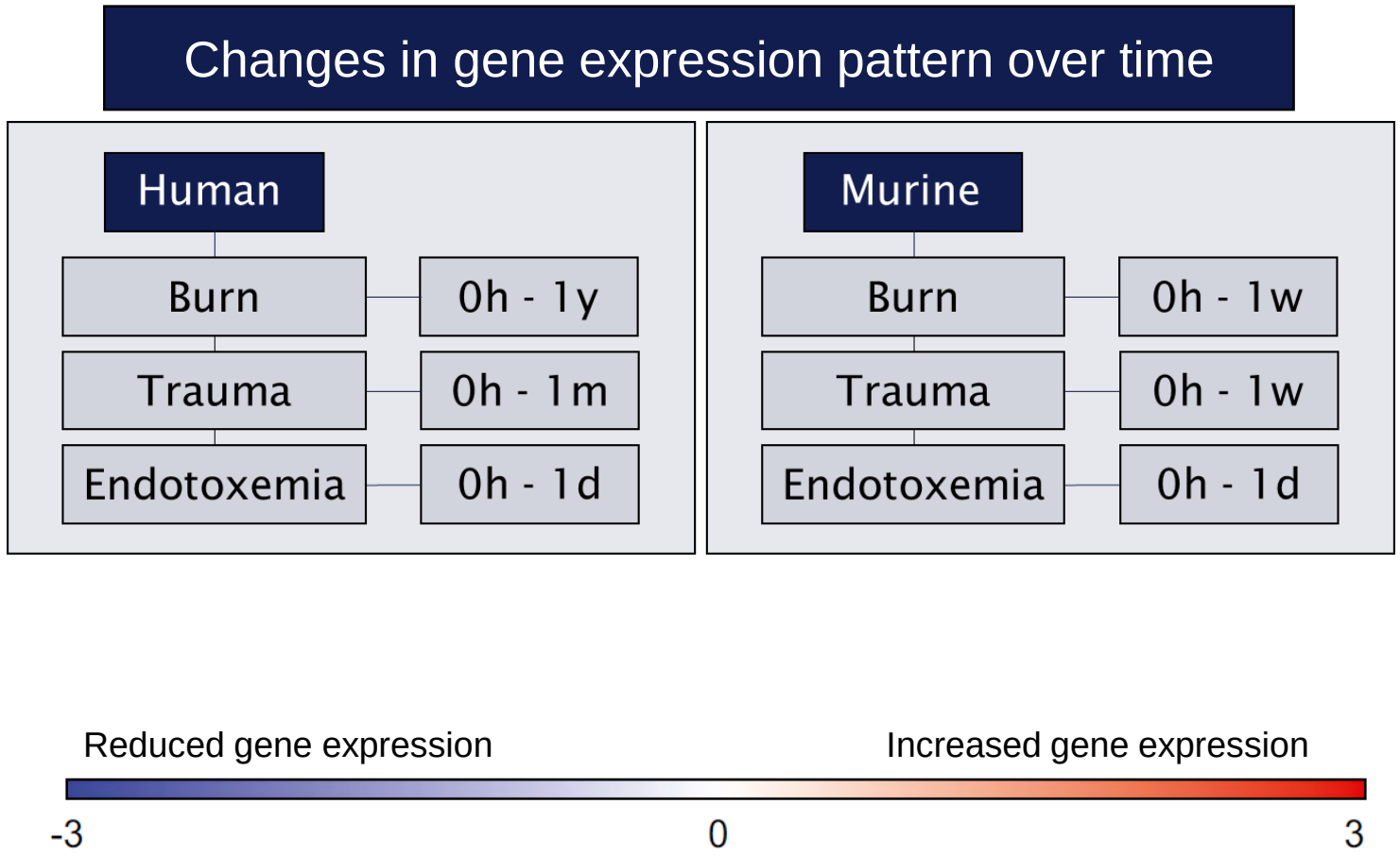
Comparison of the temporal response patterns between human and murine conditions

Assessment of temporal response patterns

Queried gene changes in human vs. murine models over time course

Analysed time-course pattern of the expression of each gene by clustering

Fig. 2A: Comparison of time-course gene changes for human burns, trauma, and endotoxemia vs. murine model



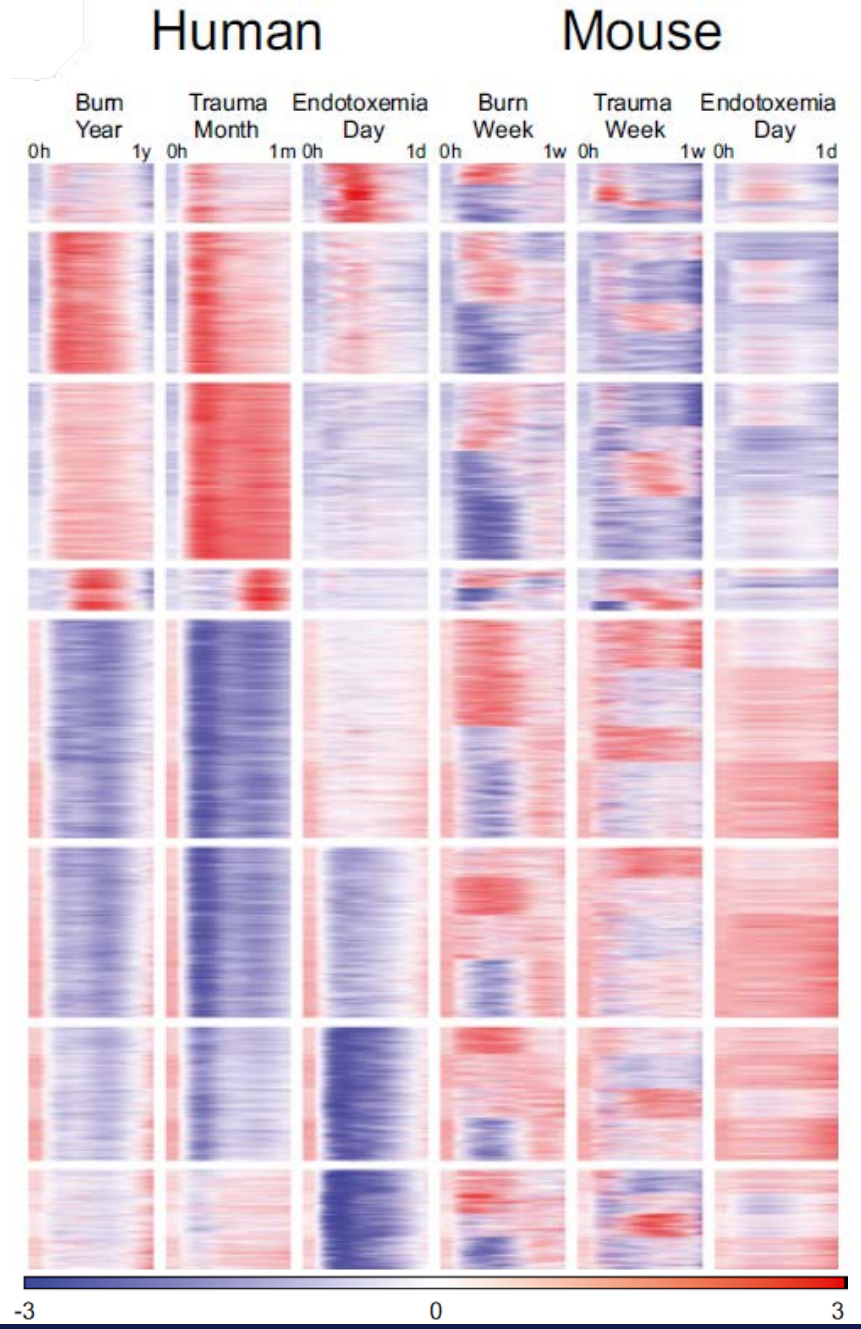


Fig. 2A: Comparison of time-course gene changes for human burns, trauma, and endotoxemia vs. murine model

- Similar changes in gene expression pattern over time within human burn vs. human trauma
  - Even though variation in time course

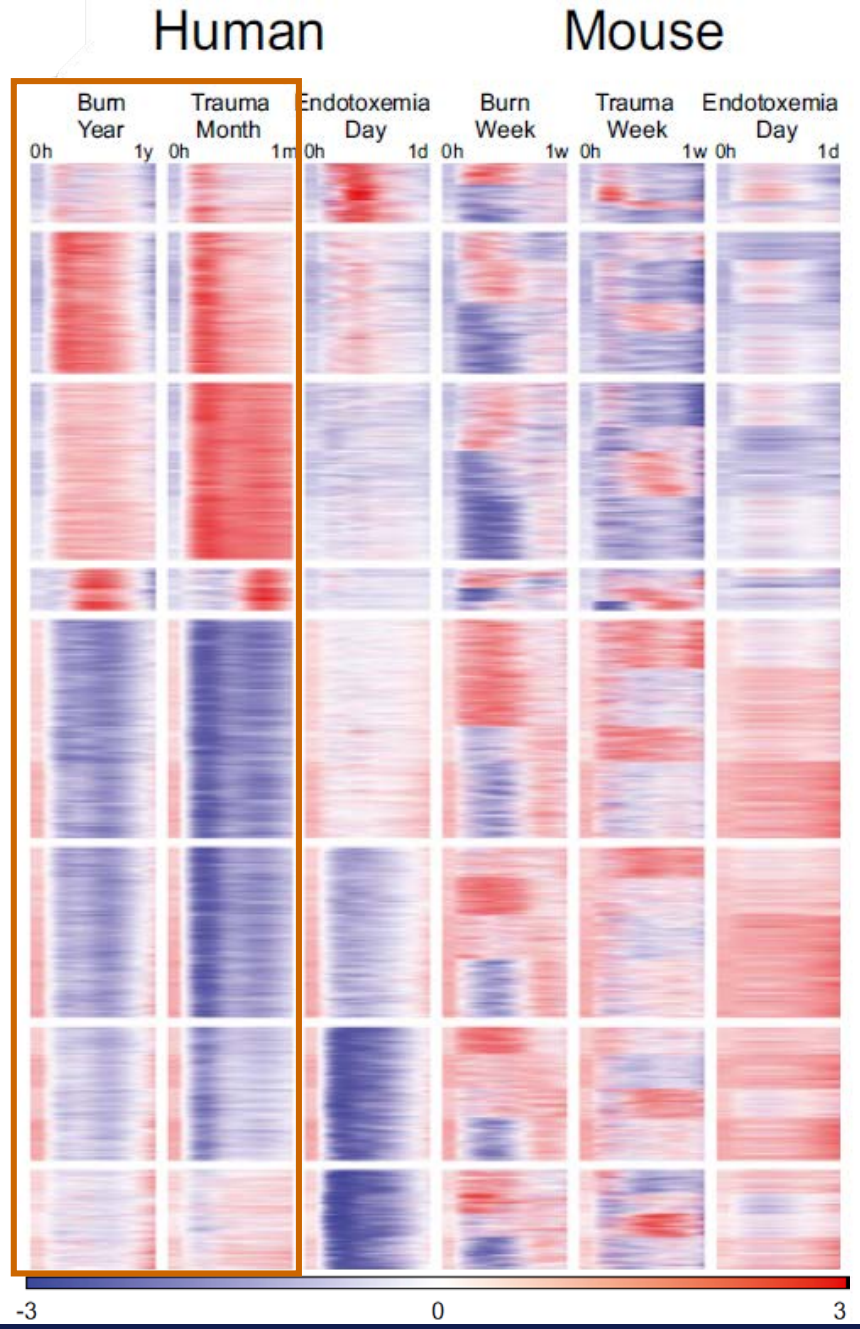


Fig. 2A: Comparison of time-course gene changes for human burns, trauma, and endotoxemia vs. murine model

- Similar changes in gene expression pattern over time within human burn vs. human trauma
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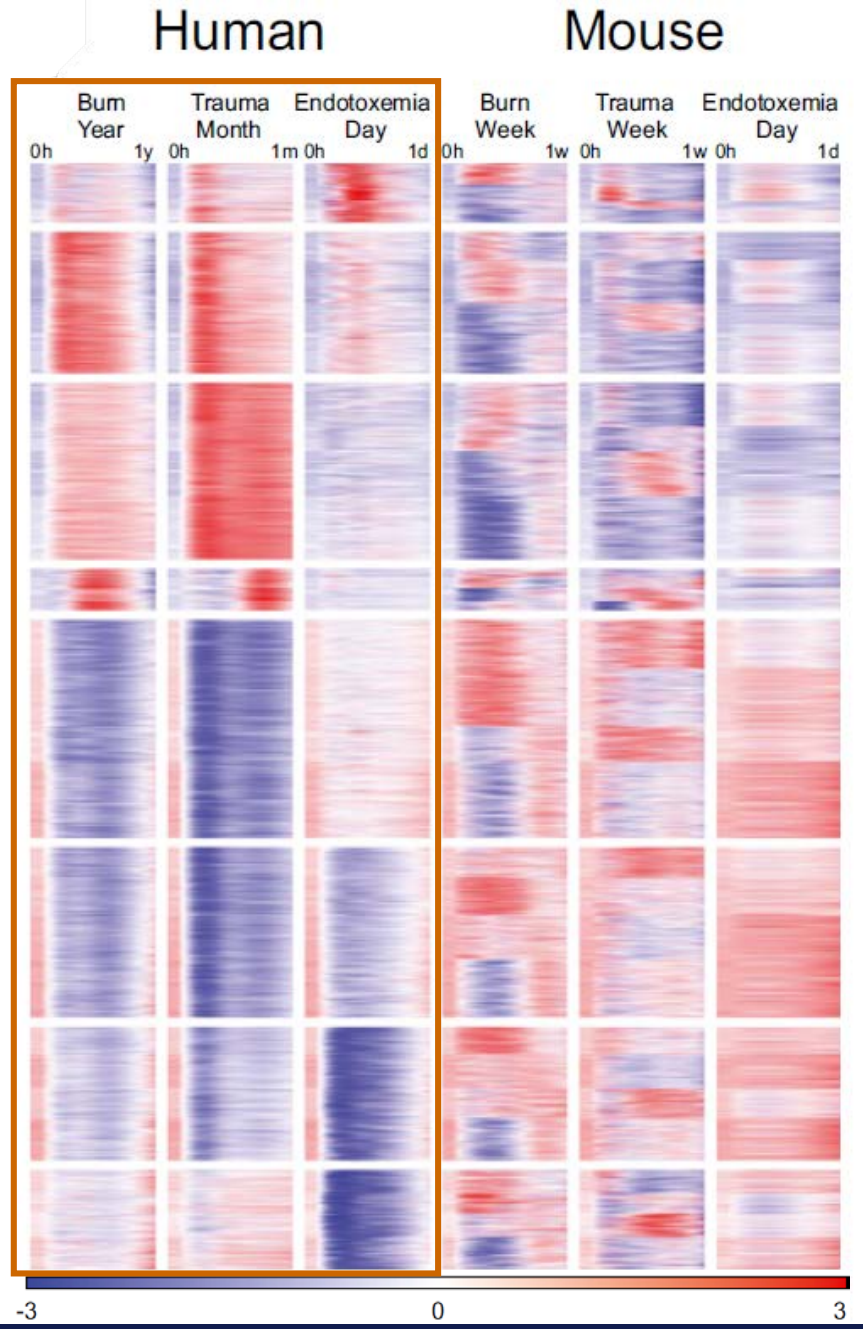
- Moderate correlation between human injury & human endotoxemia



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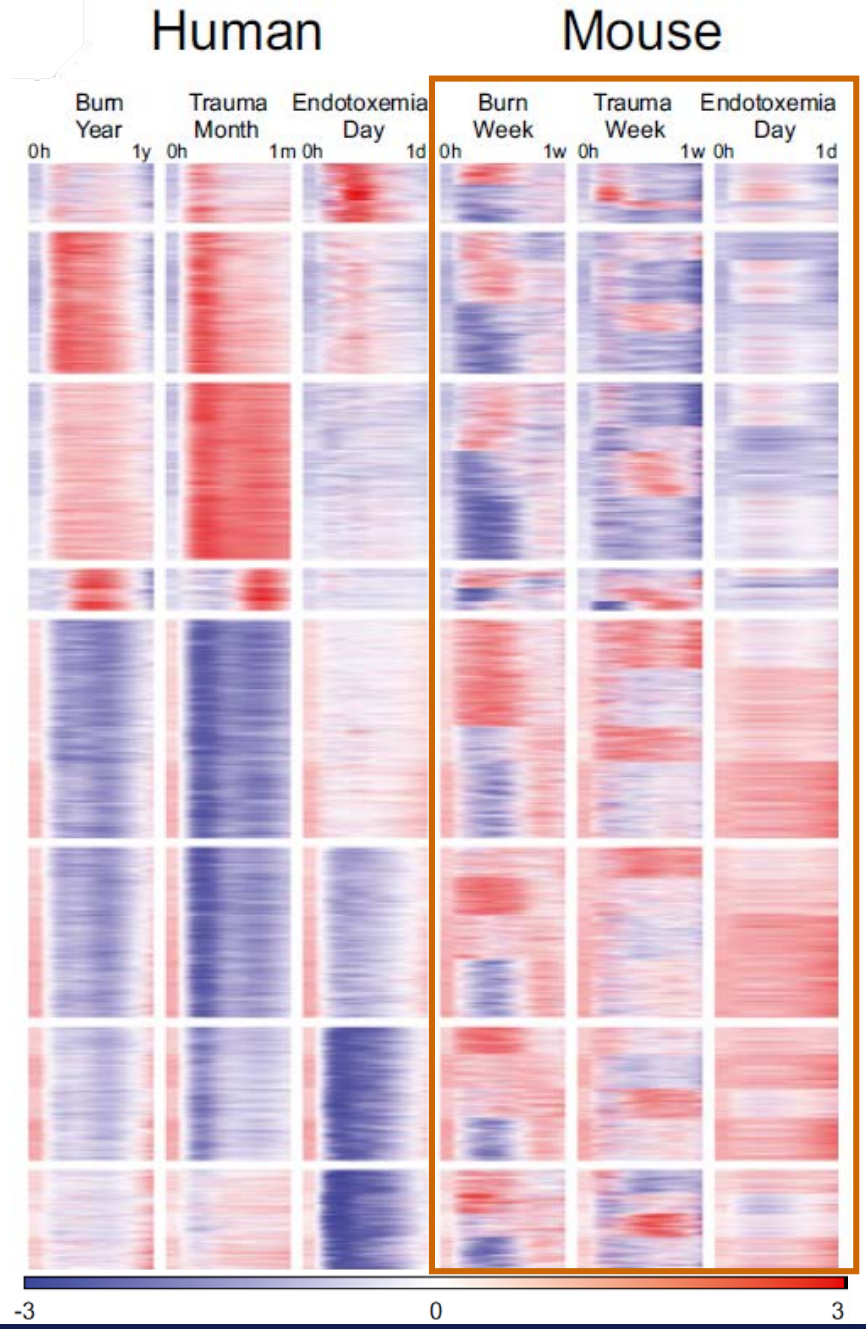
- Rather poor correlation between murine models



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- Rather poor correlation between murine models
- Almost random correlation between murine & human conditions

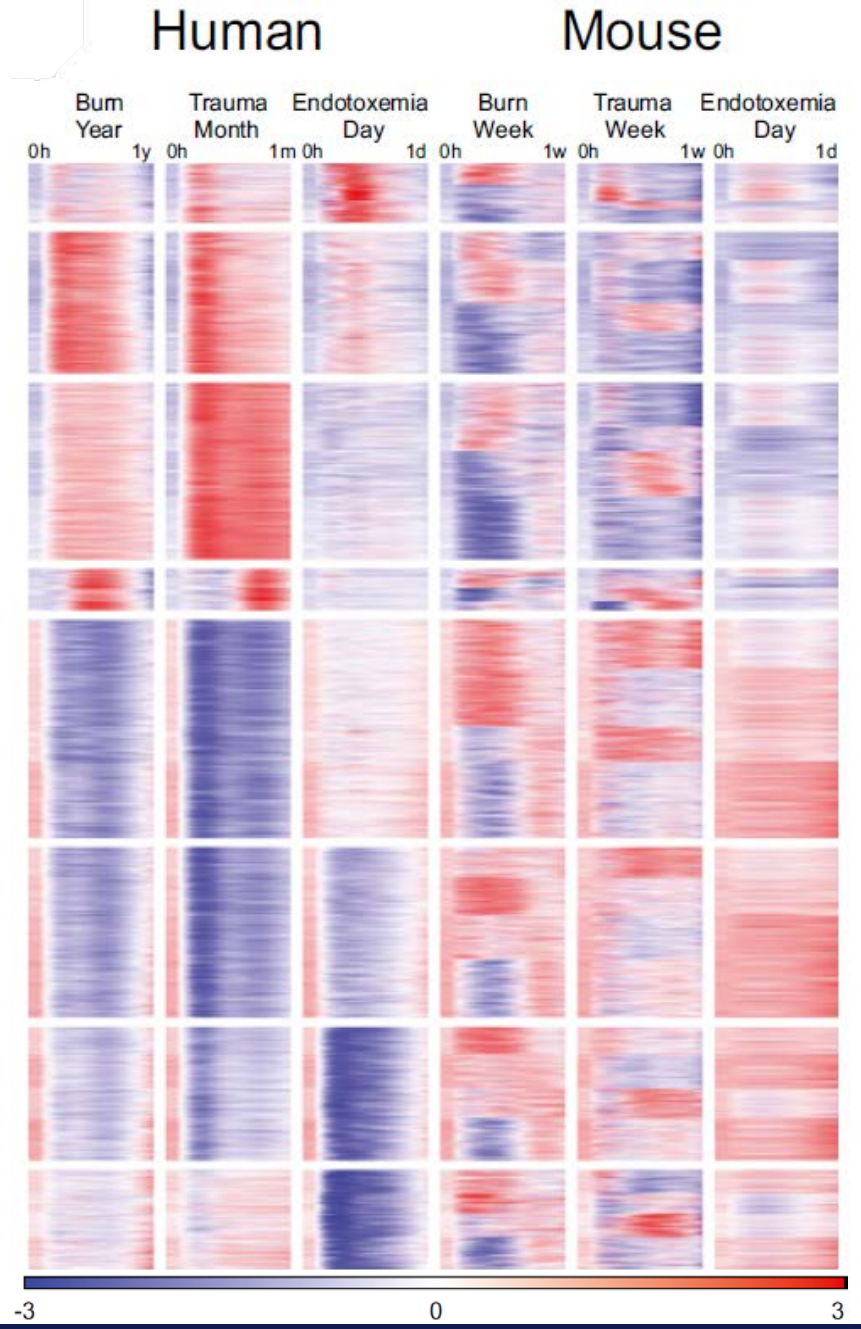


Fig. 2B: Comparison of recovery times of gene changes in human burns, trauma, and endotoxemia vs. murine model

Recovery Time:
time for the gene to decrease to one-half of its maximum value

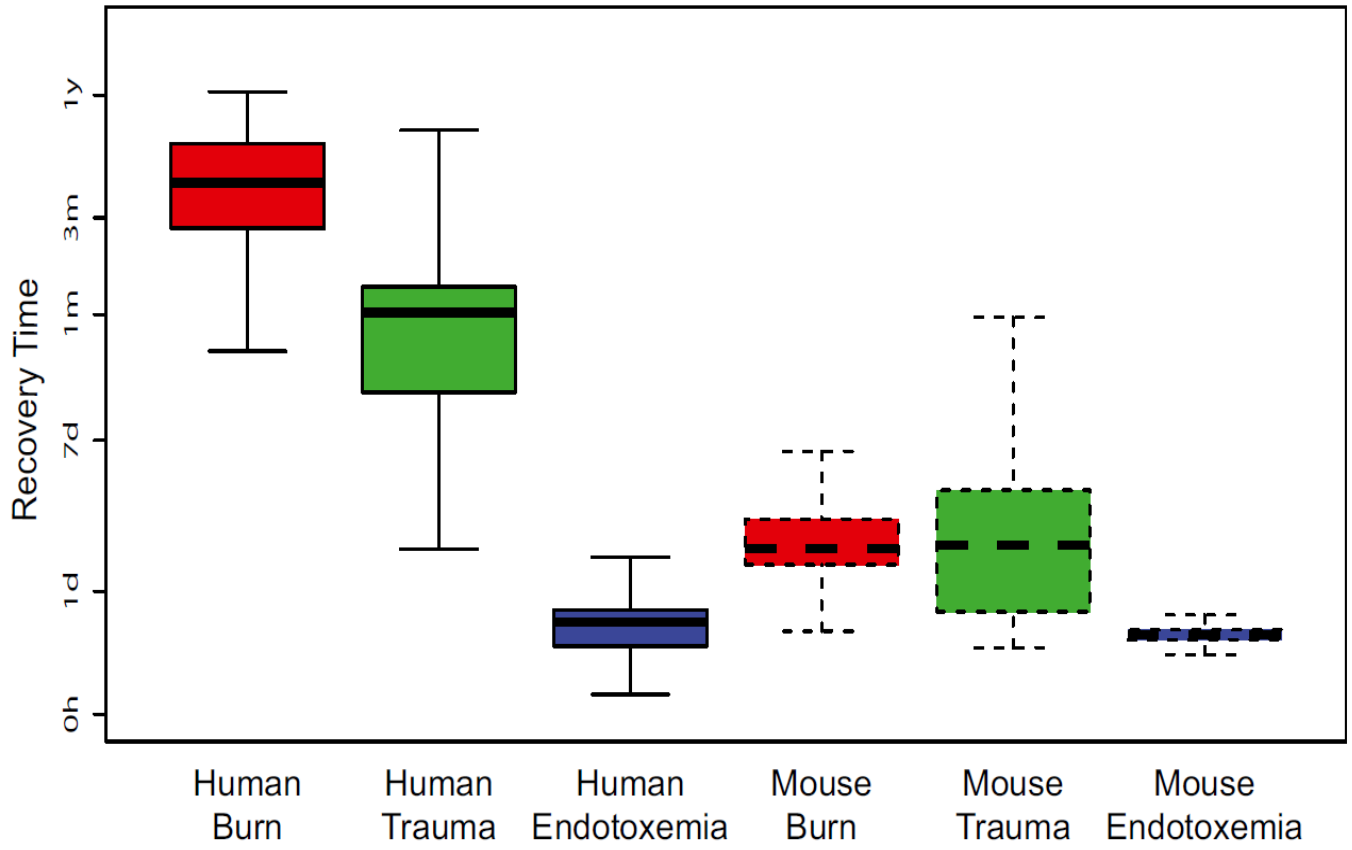


Fig. 2B: Comparison of recovery times of gene changes in human burns, trauma, and endotoxemia vs. murine model

Genomic recovery	
Human	**Mouse**
up to 1 year	within 4 days
great variability	little variability

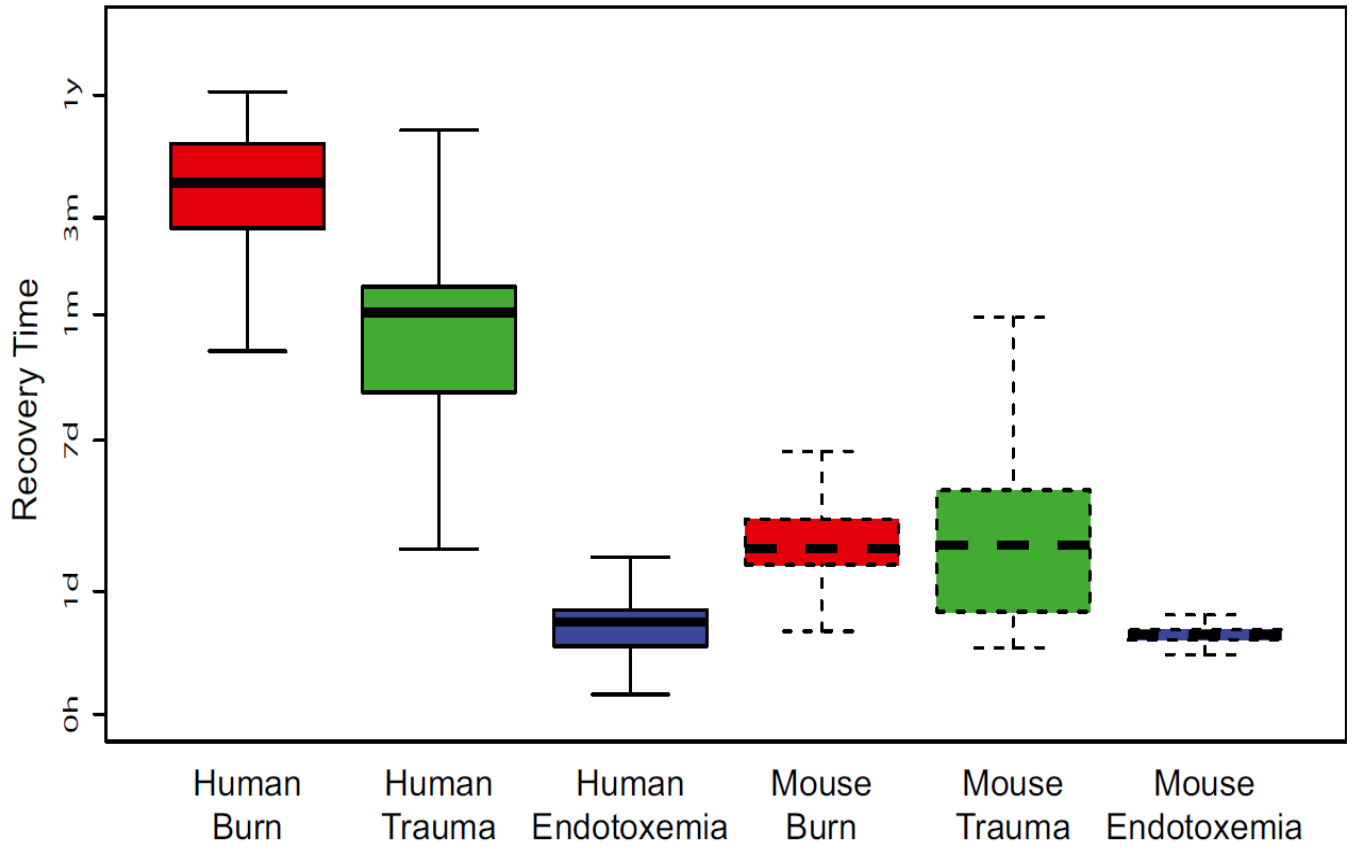


Fig. 2C: Comparison of gene expression changes in human burns, trauma, and endotoxemia vs. murine model in the context of HLA-DRA

Log^2 expression changes of HLA-DRA over time

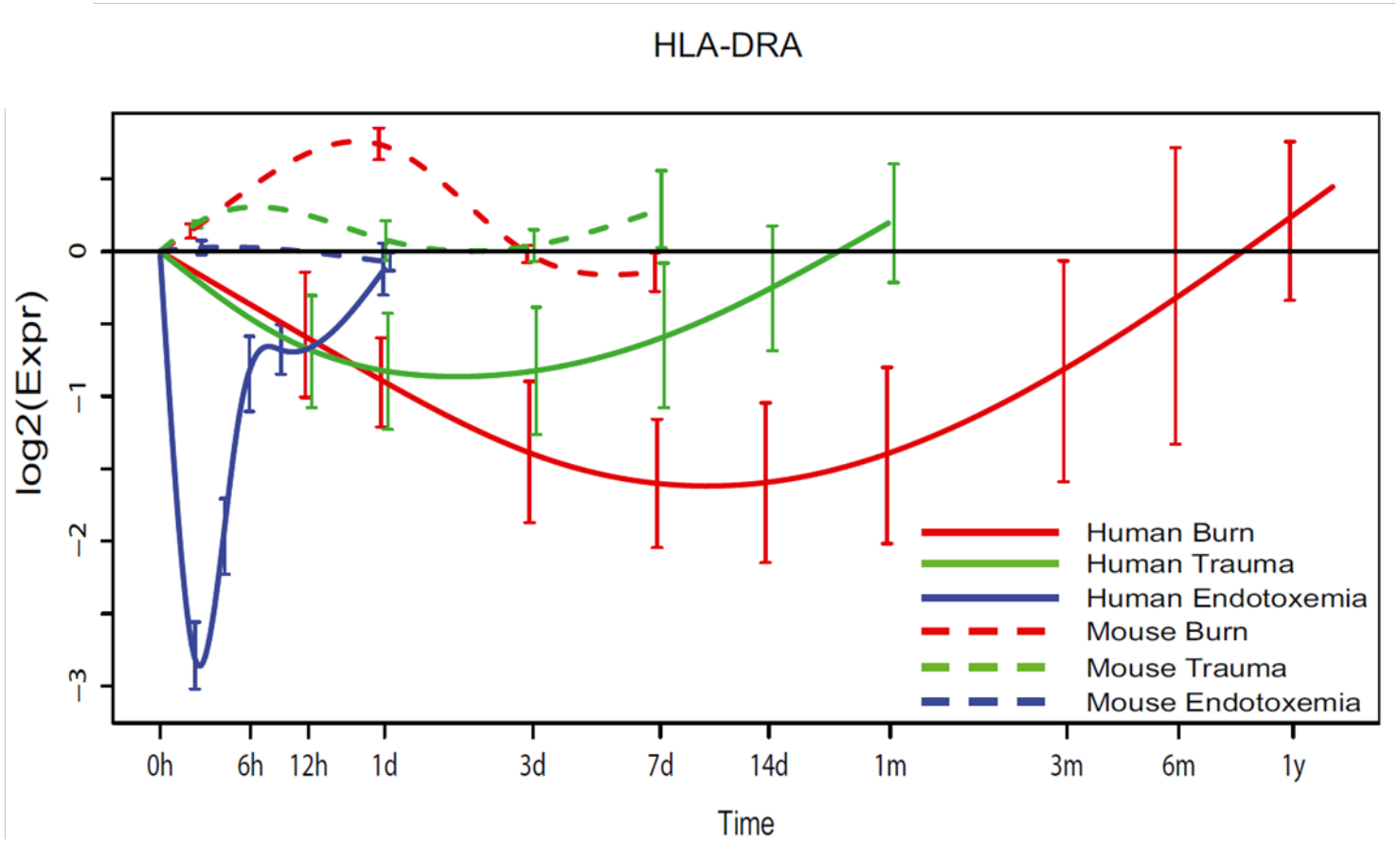
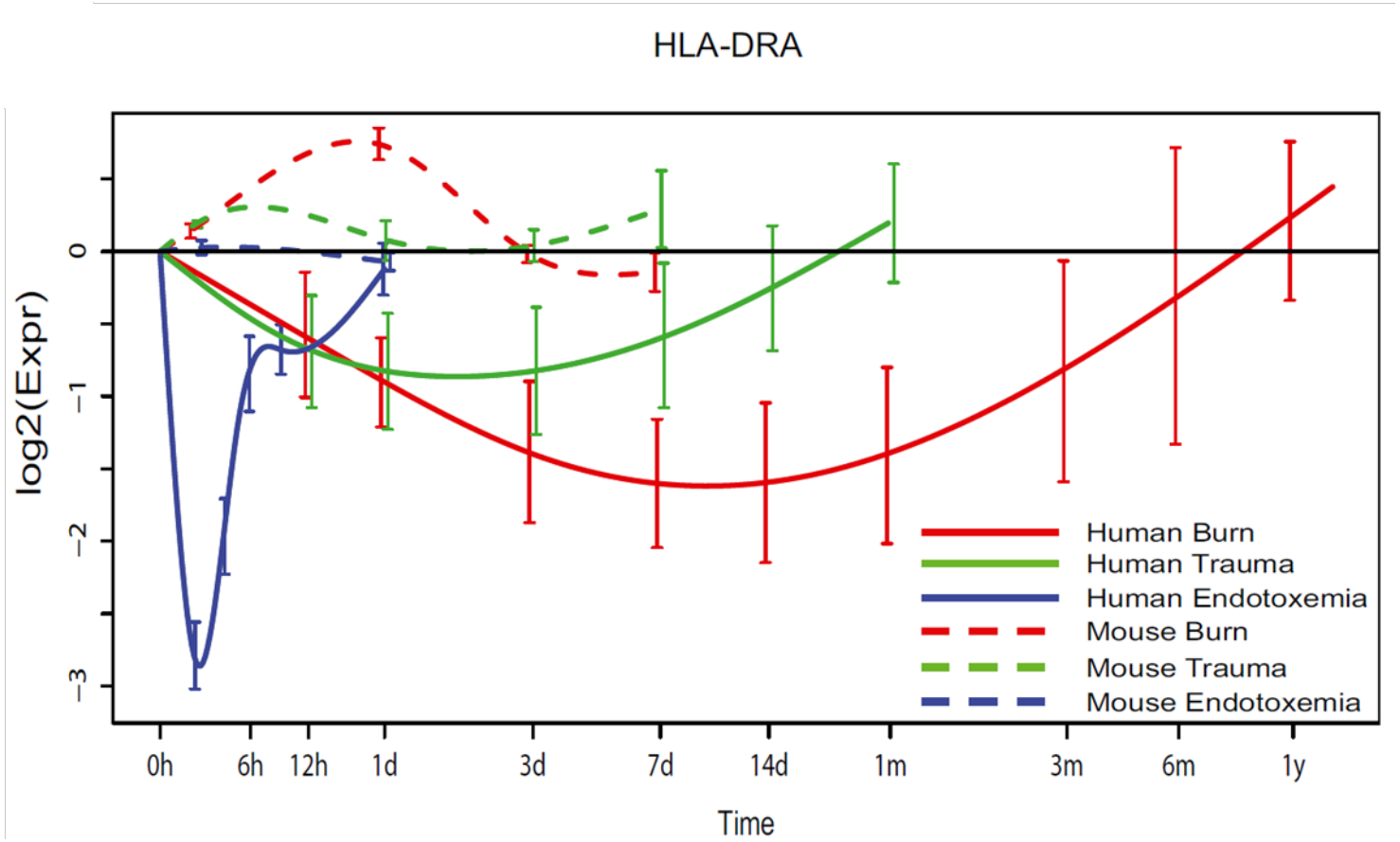


Fig. 2C: Comparison of gene expression changes in human burns, trauma, and endotoxemia vs. murine model in the context of HLA-DRA

- Gene response time occured within first 6-12 hours

Human: HLA-DRA changed over long time period

Mouse: HLA-DRA changed only minimally



Comparison of significantly regulated pathways between human and murine conditions

Assessment of pathway changes

Identification of major signalling pathways in human injury

Comparison to human endotoxemia and murine models

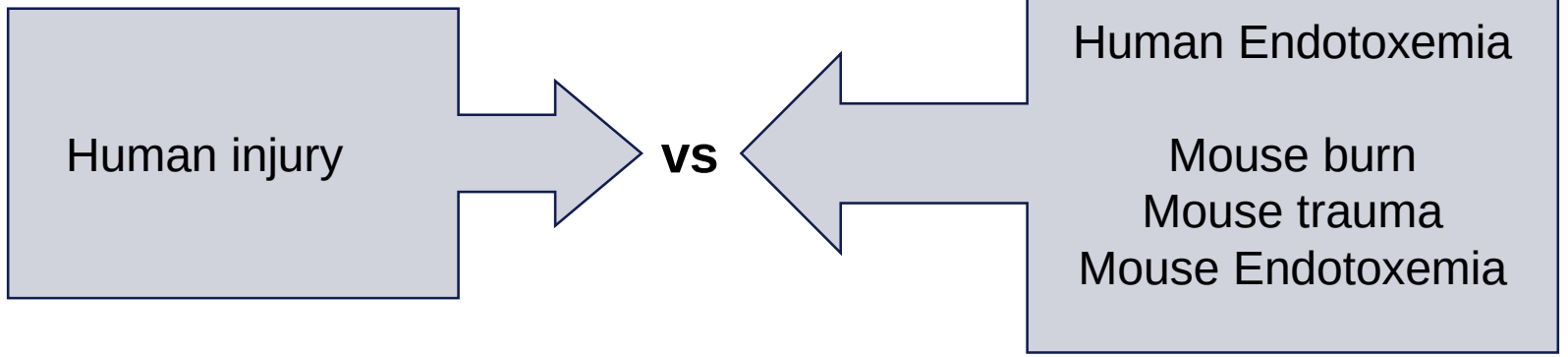


Fig. 3: Pathway comparison in human burns, trauma, and endotoxemia vs. murine model

R^2 of the five most activated/suppressed pathways

Negative correlations are shown in - R^2

Reference: Human injury

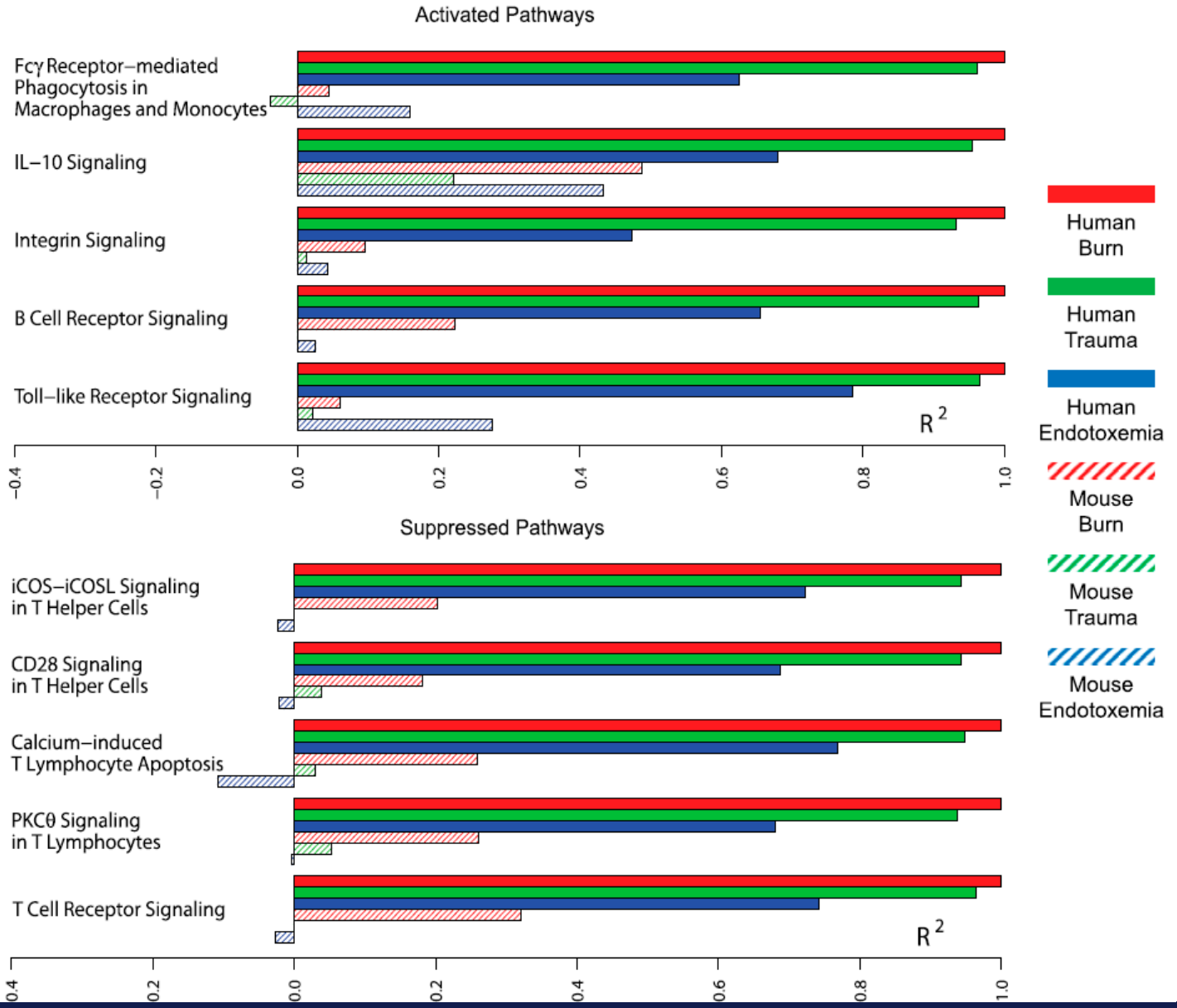
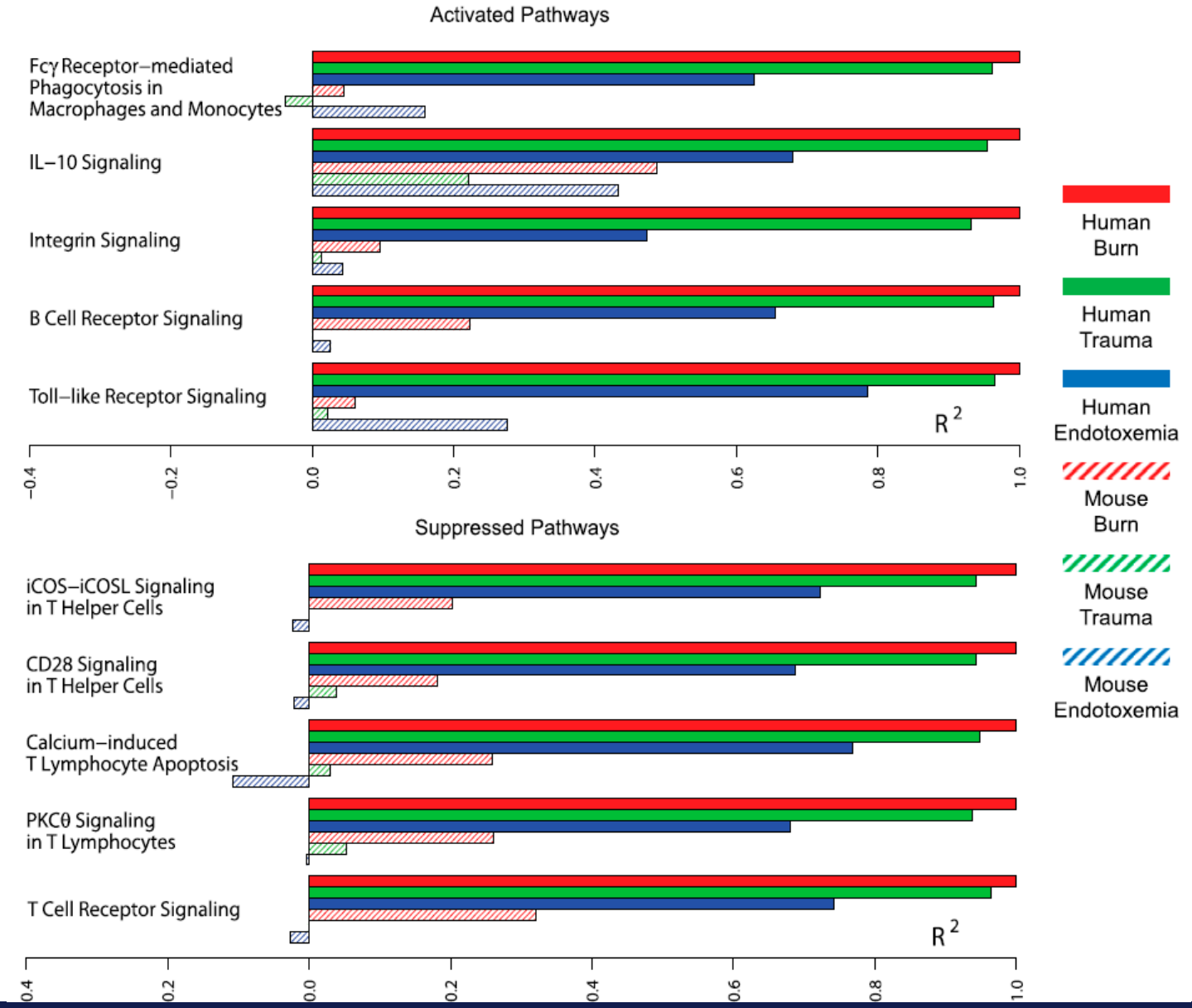


Fig. 3: Pathway comparison in human burns, trauma, and endotoxemia vs. murine model

Human	
innate immunity	up-regulated
adaptive immunity	down-regulated

Pathway comparison between human vs. murine model			
	Human Trauma		
	Correlation in %		
	median	min.	max.
Human Endotoxemia	95%	82%	100%
Mouse Burn	65%	48%	79%
Mouse Trauma	51%	35%	71%
Mouse Endotoxemia	61%	43%	80%



Comparison of additional acute inflammatory diseases and mouse models

Fig. 4: Comparison of the genomic response to severe acute inflammation

Human: genomic responses correlate well with each other

Mouse: human genomic responses are poorly mimicked by mouse model

Disease	GEO accession	R^2	Percent
Human			
Burns (as reference)	GSE37069	1.00	100
Trauma	GSE36809	0.91	97
Endotoxemia (test)	GSE3284	0.47	88
Endotoxemia (verification)	GSE3284	0.59	90
ARDS	GSE10474	0.55	84
Sepsis	GSE13904	0.76	93
Sepsis	GSE9960	0.64	87
Sepsis	GSE13015	0.61	86
Sepsis	GSE28750	0.63	85
Acute Infection	GSE6269	0.50	83
Mouse			
Burns	GSE7404	0.08	60
Trauma	GSE7404	0.05	61
Endotoxemia	GSE7404	0.00	47
Endotoxemia	GSE5663	0.00	50
ARDS	GSE19030	−0.01	48
Sepsis (CLP)	GSE5663	0.03	53
Sepsis (CLP-Mild)	GSE5663	0.02	52
Sepsis	GSE19668	0.05	58
Sepsis	GSE26472	0.02	55
Infection	GSE20524	0.08	61

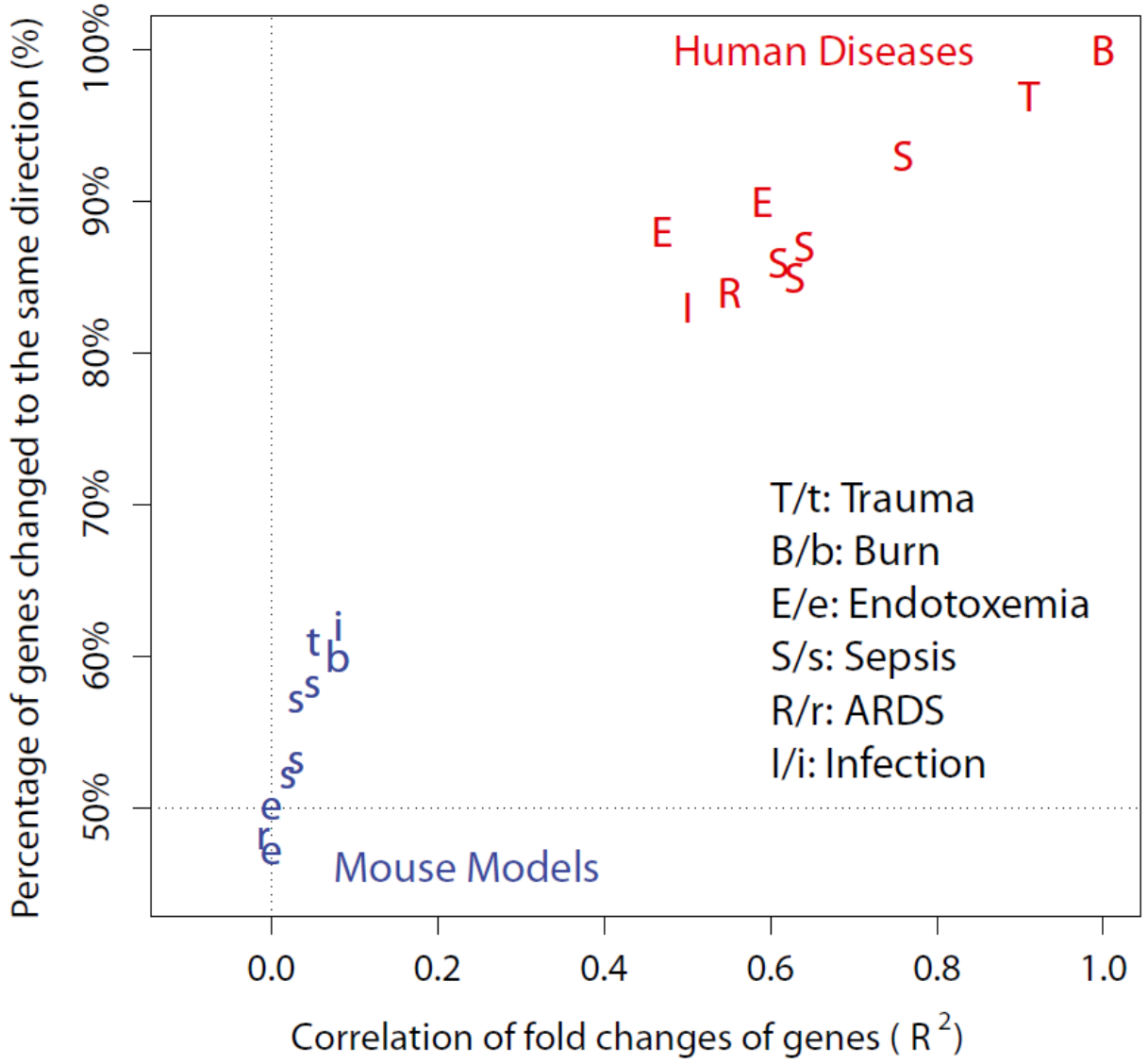
R^2 represents Pearson correlation. Negative correlations are shown as $-R^2$. Percent represents the percentages of genes changed to the same direction between the two datasets. CLP, cecal ligation and puncture.

Fig. 4: Comparison of the genomic response to severe acute inflammation

Correlation (R^2) vs. directionality (%)

Human: genomic responses correlate well with each other

Mouse: human genomic responses are poorly mimicked by mouse model



Conclusion

Conclusion

Genomic changes in Human Burn & Human Trauma correlate strongly while there is a moderate correlation to Human Endotoxemia.

Genomic changes in Murine Burn, Murine Trauma & Murine Endotoxemia correlate rather poorly.

Genomic changes in Human vs. Murine models correlate more or less randomly.

Genomic responses in murine models poorly mimic human inflammatory diseases.

Discussion

Discussion

- Patients received drugs that may affect their pathophysiologic and genomic responses

- despite large heterogeneities in human patients → highly consistent genomic response in patients

Discussion

Why do mouse models mimic human diseases so poorly?

- Evolutionary distance
- Complexity of human disease
- Inbred nature of the mouse
- Differences in cellular composition
- Different temporal spans in recovers