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(54) **Title:** SIGNATURES OF RADIATION RESPONSE

(57) **Abstract:** The present invention relates, in general, to gene expression profiles, and in particular, to a gene expression profile of an environmental exposure, ionizing radiation. The invention further relates to methods of screening patients for radiation exposure based on gene expression profiling and to kits suitable for use in such methods.



SIGNATURES OF RADIATION RESPONSE

This application claims priority from U.S. Provisional Application No. 61/704,945, filed September 24, 2012, the entire content of which is incorporated herein by reference.

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TECHNICAL FIELD

The present invention relates, in general, to gene expression profiles, and in particular, to a gene expression profile (e.g., a peripheral blood gene expression profile) of an environmental exposure, ionizing radiation. The invention further relates to methods of screening patients for radiation exposure based on gene expression profiling and to kits suitable for use in such methods.

BACKGROUND

Invasive procedures are often required for accurate screening and diagnosis of common medical conditions (Boolchand et al, Ann. Intern. Med. 145:654-659 (2006)). Examination of the peripheral blood often suffices to establish certain diagnoses, such as chronic lymphocytic leukemia (Damle et al, Blood Epub Ahead of Print (2007)), which afflicts the circulating lymphocyte directly. Measurement of total white blood cell counts and the WBC differential (e.g. neutrophils, lymphocytes, monocytes) is routinely performed in medical practice and can facilitate many diagnoses (e.g. bacterial or viral infection). Recently, it has been suggested that gene expression profiling of peripheral blood cells, particularly lymphocytes, can serve as sensitive tool to assess for the presence of certain diseases, such as systemic lupus erythematosus, rheumatoid

arthritis, neurologic disease, viral and bacterial infections, breast cancer, atherosclerosis and environmental exposures, including tobacco smoke (Mandel et al, *Lupus* 15:451-456 (2006), Heller et al, *Proc. Natl. Acad. Sci. USA* 94:2150-2155 (1997), Edwards et al, *Mol. Med.* 13:40-58 (2007), Baird, *Stroke* 38:694-698 (2007), Rubins et al, *Proc. Natl. Acad. Sci. USA* 101:15190-15195 (2004), Martin et al, *Proc. Natl. Acad. Sci. USA* 98:2646-2651 (2001), Patino et al, *Proc. Natl. Acad. Sci. USA* 102:3423-3428 (2005), Lampe et al, *Cancer Epidemiol. Biomarkers Prev.* 13:445-453 (2004), Ramilo et al, *Blood* 109:2066-2077 (2007)). Results from these studies suggest that patterns of gene expression within circulating PB cells can distinguish individuals afflicted by these conditions from those who are not (Mandel et al, *Lupus* 15:451-456 (2006), Heller et al, *Proc. Natl. Acad. Sci. USA* 94:2150-2155 (1997), Edwards et al, *Mol. Med.* 13:40-58 (2007), Baird, *Stroke* 38:694-698 (2007), Rubins et al, *Proc. Natl. Acad. Sci. USA* 101:15190-15195 (2004), Martin et al, *Proc. Natl. Acad. Sci. USA* 98:2646-2651 (2001), Patino et al, *Proc. Natl. Acad. Sci. USA* 102:3423-3428 (2005), Lampe et al, *Cancer Epidemiol. Biomarkers Prev.* 13:445-453 (2004), Ramilo et al, *Blood* 109:2066-2077 (2007)). It has, therefore, been suggested that PB gene expression profiling has potential utility in the screening for diseases and environmental exposures.

Any consideration of applying PB gene expression profiles for the detection of disease or environmental exposures requires a determination of the impact of PB cellular composition, time, gender, and genotype on PB gene expression (Lampe et al, *Cancer Epidemiol. Biomarkers Prev.* 13:445-453 (2004), Ramilo et al, *Blood* 109:2066-2077 (2007), Whitney et al, *Proc. Natl. Acad. Sci. USA* 101:1896-1901 (2003), Yan et al, *Science* 297:1143 (2002)). Additionally, it is unclear whether PB gene expression profiles that have been associated with various medical conditions are specific for that phenotype, or rather reflect a generalized response to genotoxic stress. Examination of the

specificity of PB gene expression profiles in response to different stimuli and the durability of these signatures over time is critical to the translation of this strategy into clinical practice.

Ionizing radiation represents a particularly important environmental hazard, which, at lowest dose exposures, causes little acute health effects (Kaiser, *Science* 302:378 (2003)) and, at higher dose exposures, can cause acute radiation syndrome and death (Wasalenko et al, *Ann. Int. Med.* 140:1037-1051 (2004), Mettler et al, *N. Engl. J. Med.* 346:1554-1561 (2002), Dainiak, *Exp. Hematol.* 30:513-528 (2002)). Numerous studies have been performed to attempt to understand the biologic effects of ionizing radiation in humans. Specific mutations in p53 and HPRT have been identified in somatic cells from survivors of the Hiroshima and Nagasaki atomic bombings (Iwamoto et al, *J. Natl. Canc. Inst.* 90:1167-1168 (1998), Hirai et al, *Mutant Res.* 329:183-196 (1995), Takeshima et al, *Lancet* 342:1520-1521 (1993), Neel et al, *Annu. Rev. Genet.* 24:327-362 (1990)).

Gene expression analyses have been performed on human tumor cells, cell lines, and peripheral blood from small numbers of irradiated patients in order to identify specific genes that are involved in the response to radiation injury (Jen et al, *Genome Res.* 13:2092-2100 (2003), Amundson et al, *Radiat. Res.* 154:342-346 (2000), Amundson et al, *Radiat. Res.* 156:657-661 (2001), Falt et al, *Carcinogenesis* 24:1837-1845 (2003), Amundson et al, *Cancer Res.* 64:6368-6371 (2004)). Recently, public health focus has centered on the development of capabilities to accurately screen large numbers of people for radiation exposure in light of the anticipated use of radiological or nuclear materials by terrorists to produce "dirty bombs" or "improvised nuclear devices" (Wasalenko et al, *Ann. Int. Med.* 140:1037-1051 (2004), Mettler et al, *N. Engl. J. Med.* 346:1554-1561 (2002), Dainiak, *Exp. Hematol.* 30:513-528 (2002)).

A method of screening humans for environmental exposure has been suggested. This method relies on the identification of patterns of gene expression, or metagenes in PB cells that accurately distinguish between irradiated and non-irradiated individuals (Dressman et al, PLoS Med. 4:690-701 (2007)). Metagenes can be identified in the PB that distinguish different levels of exposure with an accuracy of 96% (Dressman et al, PLoS Med. 4:690-701 (2007)).

The present invention results, at least in part, from studies designed to evaluate the specificity of PB gene expression signatures and to determine the influence of genetic variation and time on the performance of the signature. The invention also results from studies in which an examination has been made of the possibility of "training" a biodosimeter in three model systems simultaneously under the hypothesis that a biodosimeter that is functional in all three systems has a higher likelihood of performing well in the population of interest. The results of these studies indicate that this approach represents a viable strategy for identifying environmental exposures and one that can be employed for screening populations of affected individuals.

SUMMARY OF THE INVENTION

The present invention relates generally to gene expression profiles. More specifically, the invention relates to a gene expression profile of an environmental exposure, ionizing radiation. The invention further relates to a method of screening patients for radiation exposure based on gene expression profiling and to kits suitable for use in such methods.

Objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B. Peripheral blood gene expression profiles distinguish irradiated mice within a heterogeneous population (Fig. 1A) A heat map of a 25 gene profile that can predict radiation status. The figure is sorted by dosage (0 cGy, 50cGy, 200cGy, and 1000cGy). High expression is depicted as red, and low expression is depicted as blue. (Fig. 1B) A graph of the predicted capabilities of the irradiation signature across all mice (including C57Bl6 and BALB/c strains, males and females and 3 sampling time points) versus a control, non irradiated sample. All predicted probabilities for the controls are listed.

Figures 2A-2C. Impact of sex on murine irradiation profiles (Fig. 2A) Heat map images illustrating expression pattern of genes selected for classifying control, non-irradiated mice versus 50 cGy, 200 cGy, or 1000 cGy irradiated mice within female (top) and male C57Bl6 mice (bottom). (Fig. 2B) Heat map images illustrating expression pattern of genes found in the female C57Bl6 strain or male C57Bl6 strain predicting the irradiation status of the opposite sex at dosage 50 cGy, 200 cGy, 1000 cGy. High expression is depicted as red, and low expression is depicted as blue. (Fig. 2C) A leave-one-out cross-validation analysis of the classification for control (blue) versus 50 cGy (black), 200 cGy (green), and 1000 cGy (red) for the female C57Bl6 (squares) and male C57Bl6 (circles) samples is shown. The control probabilities for each prediction are shown.

Figures 3A-3C. Impact of genotype on murine irradiation profiles. (Fig. 3A) Heat map images illustrating expression pattern of genes selected for classifying control, non-irradiated samples versus 50 cGy, 200 cGy, 1000 cGy

irradiated samples between female C57Bl6 strain (top) and female BALB/c strain (bottom). (Fig. 3B) Heat map images illustrating expression pattern of genes developed in one strain as predicting the other strain (C57Bl6 or BALB/c). High expression is depicted as red and low expression is depicted as blue. (Fig. 3C) A leave-one-out cross-validation analysis of the classification for control versus 50 cGy (black), 200 cGy (green), and 1000 cGy (red) for the female BALB/c (open-circles) and female C57Bl6 (closed circles) samples is shown. The control probabilities for each prediction are shown. BK represents the application of female C57Bl6 metagenes to predict the status of female BALB/c mice, and BC represents using female BALB/c mice metagenes to predict the status of female C57Bl6 mice.

Figures 4A-4C. Impact of time on murine irradiation profiles. (Fig. 4A) Heat map images illustrating expression pattern of genes selected for classifying control, non-irradiated samples versus 50 cGy, 200 cGy, 1000 cGy irradiated samples at time points 6hr, 24hr, and 7days. (Fig. 4B) Heat map images illustrating expression pattern of genes found in the 6hr time point as applied to the dosages 50 cGy, 200 cGy, 1000 cGy at 24 hr and 7 day time points. High expression is depicted as red, and low expression is depicted as blue. (Fig. 4C) A leave-one-out cross-validation analysis of the classification for control (blue) versus 50 cGy (black), 200 cGy (green), and 1000 cGy (red) for the time points 6 hr (circles), 24 hr (squares), and 7 days (triangles) is shown. The control probabilities for each prediction are shown.

Figures 5A and 5B. Peripheral blood profiles of irradiation and LPS-treatment are highly specific. (Fig. 5A) Heat maps representing unique metagene profiles are shown which were utilized to distinguish 3 different levels

of irradiation (left) and to distinguish LPS-treatment (right) in C57Bl6 mice. (Fig. 5B) The graph at left represents the predictive capabilities of the PB irradiation signatures in the female C57Bl6 mice in predicting dosage profiles at 50 cGy (black), 200 cGy (green), and 1000 cGy (red); the middle graph represents the predictive capabilities of the irradiation signatures when validated against the LPS-treated samples (squares); at right, the LPS signature was validated against the C57Bl6 irradiated mice and the predicted probabilities for 50 cGy (black), 200 cGy (green), and 1000 cGy (red) are shown.

Figures 6A-6D. PB metagene profiles of human radiation exposure and chemotherapy treatment are accurate and specific relative to each other. (Fig. 6A) The heat map on the left depicts the expression profiles of genes (rows) selected to discriminate the human samples (columns); high expression is depicted as red, and low expression is depicted as blue. A leave-one-out cross-validation assay (Fig. 6C) demonstrated that the PB metagene of radiation was capable of distinguishing healthy donors (black), non-irradiated patients (gray), irradiated patients (red), pre-chemotherapy treatment patients (green), and post-chemotherapy patients (blue). A ROC curve analysis was used to define a cut-off for sensitivity and specificity of the predictive model of radiation. The dotted line represents this threshold of sensitivity and specificity. (Fig. 6B) The heatmap on the left depicts an expression profile of chemotherapy treatment that distinguishes chemotherapy-treated versus untreated patients. A leave-one-out cross-validation assay (Fig. 6D) demonstrated that this PB metagene of chemotherapy treatment could accurately distinguish pre-chemotherapy patients (green), chemotherapy-treated patients (blue), healthy individuals (black), pre-irradiated patients (gray) and irradiated patients (red).

Figures 7A-7C. Performance of biodosimeter. The figures are split by model system with Fig. 7A showing mouse, Fig. 7B showing human *ex vivo*, and Fig. 7C showing hospitalized patients undergoing total body irradiation (TBI) in the course of therapy. The y-axis in each shows the model-predicted dose received, and the x-axis is stratified by the time since initial radiation exposure (in hours) and by true total dose (cGy). Vertical dashed lines separate different time points. Therapeutic TBI is given in multiple doses at intervals; therefore, dose and time are perfectly confounded for this model system.

Figure 8-8. – Concurrent gene behavior. Each of the 9150 genes with mouse–human analogs were tested for correlation with radiation exposure dose. The x-axis shows that computed correlation in the human TBI patients and the y-axis shows that correlation in human *ex vivo*. Red lines indicate significant p-values after Bonferroni correction for multiple testing. The color spots indicate correlation in mice, with red indicating positive correlation and green negative. The size and brightness of the spot indicates the level of correlation for that gene in mice. The generally greener bottom left corner and redder upper right corner indicate a general agreement between mice and human data, but the presence of green spots in the upper right indicates that individual genes may behave significantly differently in different model systems.

Figures 9A-9E. Plots of the top five models and genes included in those models.

Figure 10. Gene list and expression plots.

DETAILED DESCRIPTION OF THE INVENTION

The present invention results, at least in part, from the demonstration that exposure to ionizing radiation induces a pronounced and characteristic alteration in PB gene expression. The expression profiles disclosed herein provide basis for a method of screening a heterogeneous human population, for example, in the event of a radiological or nuclear event.

Examples of gene expression profiles that can be used distinguish radiation status in humans include those set forth in Tables 7 and 9 (and Figures 9 and 10). As described in Example 1 that follows, a supervised binary regression analysis identified a metagene profile of 25 genes that can be used to distinguish irradiated from non-irradiated individuals. The PB samples used to establish the profile in Table 7 were collected 6 hours following irradiation (see Table 6 for details of exposure).

A preferred profile is set forth in Table 11 (see response genes FDXR, ASPA, RFC4, METTL8, RASL12, ASTN2, RASA4, TRIB2, BBC3, RPA1, Gna15, H2AFV, CEBPB, CDKN1A, PRIM1, NINJ1, BAX, HIST1H3D, HIST1H2BH, DDB2, BCL11B, FAM134C and LAPTM5 – details of the response genes included in Table 11 are provided in Table 7 and/or 9, with the exception of FDXR and HIST1H2BH, details for which are provided in Table 11). Subsets of the signature set forth in Table 11 (e.g., comprising at least 5 or at least 10 or at least 20 response genes) are potentially suitable for use in accordance with the present invention.

Table 11

CLPA-RET Assay V 7.0					
FAM Labeled Plex			NED Labeled Plex		
Gene	Size	Comments	Gene	Size	Comments
ANT	101	Negative Control	ANT	101	Negative Control
PRDX	105	Ligation Control	PRDX	105	Ligation Control
PCRC	110	PCR Control	PCRC	110	PCR Control
MRPS5	115	Normalizer	MRPS5	115	Normalizer
FDXR	119	Response Gene		119	Space available
ASPA	123	Response Gene	CDKN1A	123	Response Gene
RFC4	127	Response Gene	PRIM1	127	Response Gene
METTL8	131	Response Gene	NINJ1	131	Response Gene
CDR2	135	Normalizer	CDR2	135	Normalizer
RASL12	139	Response Gene	BAX	139	Response Gene
ASTN2	143	Response Gene	HIST1H3D	143	Response Gene
RASA4	147	Response Gene	HIST1H2BH	147	Response Gene
TRIB2	151	Response Gene	DDB2	151	Response Gene
BBC3	155	Response Gene	BCL11B	155	Response Gene
MRPS18	159	Normalizer	MRPS18	159	Normalizer
RPA1	163	Response Gene		163	Space available
Gna15	167	Response Gene	FAM134C	167	Response Gene
H2AFV	171	Response Gene		171	Space available
PARP1	175	Down Reg/Normalizer	PARP1	175	Down Reg/Normalizer
CEBPB	179	Response Gene	LAPTMS	179	Response Gene
CD27	183	Normalizer	CD27	183	Normalizer

FDXR [FDXR] This gene encodes a mitochondrial flavoprotein that initiates electron transport for cytochromes P450 receiving electrons from NADPH. Multiple alternatively spliced transcript variants of this gene have been described although the full-length nature of only two that encode different isoforms have been determined. [provided by RefSeq]. (Affymetrix Probe ID: 207813_s_at)

HIST2H2BH Homo sapiens H2B histone family, member J (H2BFJ), mRNA (Affymetrix Probe ID 208546_x_at)

CDR2 Homo sapiens cerebellar degeneration-related protein 2 (Affymetrix Probe ID: 209501_at)

MRPS5 Mammalian mitochondrial ribosomal proteins are encoded by nuclear genes and help in protein synthesis within the mitochondrion (Affymetrix Probe ID: 224333_s_at)

MRPS18A Mammalian mitochondrial ribosomal proteins are encoded by nuclear genes and help in protein synthesis within the mitochondrion. Has three subunits, A, B and C (Affymetrix Probe IDs: 218385_at and 221693_s_at)

PARP1 Homo sapiens PARP1 binding protein (PARPBP, mRNA (Affymetrix Probe ID: 220060_s_at)

CD27 Homo sapiens CD27 molecule, mRNA, Homo sapiens T cell activation antigen (CD27) mRNA, complete cds (cDNA clone MGC:20393 IMAGE:4575359), complete cds. (Affymetrix Probe ID: 206150_at)

In one embodiment, the invention relates to a method screening a patient for radiation exposure by collecting a sample (e.g., PB) from the patient and isolating mononuclear cells therefrom. RNA can be extracted from the mononuclear cells using standard techniques, including those described in the Examples below. The extracted RNA can be amplified and suitable probes prepared (see Examples and Dressman et al, PLoS Med. 4:690-701 (2007)). Gene expression levels can then be determined using, for example, microarray techniques (see Examples and Dressman et al, PLoS Med. 4:690-701 (2007)).

In accordance with one embodiment of the invention, a patient that displays the gene expression profile set forth in Table 7 is a patient that has been exposed to radiation (e.g., about 6 hours prior to PB collection). While the 25 genes set forth in Table 7 constitute one signature suitable for use in distinguishing radiation status, the invention also includes methods based on the use of signatures comprising the following: H200000088, H200008365, H200011577, H200014719, H200016323, H300000421, H300003103, H300010830, H300015667, H300019371, H300020858, H300021118, H300022025. Other subsets of the signature set forth in Table 7 (e.g., comprising at least 5 or at least 10 genes) are potentially suitable for use in accordance with the present invention.

In accordance with a preferred embodiment of the invention, a patient that displays the gene expression profile set forth in Table 11 is a patient that has been exposed to radiation (e.g., about 6 hours prior to PB collection). While the 23 response genes set forth in Table 11 constitute one signature suitable for use in distinguishing radiation status the invention also includes methods based on the use of signatures comprising subsets of the response gene signature set forth in Table 11 (e.g., subsets comprising at least 5, 10 or 20 response genes).

The development of a biodosimeter for the purpose of triaging patients after a major accident or attack must necessarily be conducted without samples

from otherwise healthy people who have been exposed. As described herein, model systems can be used to determine the behavior of putative biomarkers in a human population. A biodosimeter that is functional in multiple systems can be expected to perform well in the population of interest.

The studies described in Example 2 indicate that there is some gene-level concordance in the response to radiation among model systems: mouse, human *ex vivo*, and human TBI. However, that concordance is generally mild, and the generation of a biodosimeter based on just one model system for use in the other two leads to poor performance. To address this issue, a variable-selection regression model has been used that includes training data from all samples (see Example 2). This approach has resulted in a predictive model that differentiates dose in all of the model systems.

It is expected that this predictive model will perform adequately in stratifying subjects by dose in the event of an accident or attack leading to radiation exposure in an otherwise healthy human population. However, as evidenced by the existence of significant predictive genes in all three of the model systems that are not relevant in the other systems (see Example 2), it is expected that there are genes that can be used to advantage in a biodosimeter that cannot be identified with the model-systems approach. Accordingly, it is likely – given real data from such an event – that by inclusion of new genes, the accuracy of the biodosimeter can be improved upon in an exposed, otherwise healthy human population.

Finally, while the biodosimeter described performs well on microarray data, a high throughput, low cost gene expression platform may be preferred for use in the field. It is understood that at least some of the genes in the predictor may not translate well between platforms. In order to alleviate this potential problem, a relatively large set of predictors have been retained for translation. The genes set forth, for example, in Table 9 (see also Fig. 10) or the response

genes set forth in Table 11 are expected to be suitable for use in a chemical ligation dependent probe amplification- capillary electrophoresis (CLPA-CE) device (DxTerity Diagnostics).

While the expression profiles described herein are highly predictive of radiation status, sex differences can contribute to characteristically distinct molecular responses to radiation, for example at low exposure levels (e.g., about 50 cGy). Accordingly, use of gender specific assays can be advantageous, for example, at low levels of exposure.

As shown in Example 1 that follows, the time of PB collection following radiation exposure does not significantly impact the accuracy of PB signatures to predict radiation status or distinguish different levels of exposure. While time as a single variable does not lessen the accuracy in distinguishing irradiated from non-irradiated individuals, the content of the genes which comprise the PB signature can change as a function of time. Thus, while PB predictors of radiation exposure can change over time, PB signatures can continuously be identified (e.g., through 7 days) that are highly accurate at predicting radiation status and distinguishing different levels of exposure.

The invention also relates to reagents and kits suitable for use in practicing the above-described methods. Kit components can vary, however, examples of components include an array probe of nucleic acids in which the genes listed in Table 7 and/or Table 9 (see also Figs. 9 and 10), preferably, the response genes listed in Table 11, or subset(s) thereof (e.g., a subset of at least about 5, 10 or 20), are represented. A variety of different array formats or known in the art with a variety of probe structures, subset components and attachment technologies. Representative array structures include those described in USPs 5,143,854; 5,288,644; 5,342,633; 5,432,049; 5,470,710; 5,492,806; 5,503,980; 5,510,270; 5,525,464; 5,547,839; 5,580,732; 5,661,028; 5,800,992; WO 95/21265; WO 96/31622; WO 97/10365; WO 97/27317; EP 373203 and

EP 785280 (see also U.S. Published Appln. No. 20060141493). Kits of the invention can also include specific primers designed to selectively amplify the genes in Table 7, Table 9 (see also Fig. 10), the response genes in Table 11, or subset thereof. Gene specific primers and methods of using same are described in USP 5,994,076. The kits can also include additional reagents, e.g., dNTPs and/or rNTPs, buffers, enzymes, etc.

Certain aspects of the invention can be described in greater detail in the non-limiting Examples that follow. (See also Dressman et al, PLoS Med. 4:690-701 (2007) and U.S. Appln.No. 12/736,393)).

EXAMPLE 1

EXPERIMENTAL DETAILS

Murine irradiation study

Ten to 11 week old male and female C57Bl6 and female BALB/c mice (Jackson Laboratory, Bar Harbor, ME) were housed at the Duke Cancer Center Isolation Facility under regulations approved by the Duke University Animal Care and Use Committee. Between 5-10 mice/group were given total body irradiation (TBI) with a Cs137 source at an average of 660cGy/min at doses of 50, 200, or 1000cGy as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). Six hours, 24 hours, or 7 days post-TBI, approximately 500µl peripheral blood was collected by retro-orbital bleed from both irradiated and control mice. PB mononuclear cells (PB MNCs) were isolated for total RNA extractions. Total RNA was extracted with Qiagen RNAeasy Mini Kits as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). RNA quality was assayed using an Agilent Bioanalyzer 2100 (Agilent Technologies, Inc., Palo Alto, CA).

Murine LPS study

Ten C57Bl6 female mice were given intraperitoneal injections of a 100µg of lipopolysaccharide endotoxin (LPS) from *E. coli* 055:B5 (Sigma-Aldrich, St. Louis, MO) to induce sepsis syndrome as previously described (Hick et al, J. Immunol. 177:169-176 (2006)). Peripheral blood was collected 6h later from treated and control mice, and RNA was processed as described in the irradiation studies.

Human Irradiation and Chemotherapy Treatment Studies

With approval from the Duke University Institutional Review Board (IRB), between 5-12 mL of peripheral blood was collected from patients prior to and 6 hrs following total body irradiation with 150 to 200 cGy as part of their pre-transplantation conditioning (Dressman et al, PLoS Med. 4:690-701 (2007)). For additional comparison, peripheral blood was obtained from healthy volunteers and an additional cohort of patients prior to and 6 hrs following the initiation of alkylator-based chemotherapy alone (without radiotherapy). All patients and healthy volunteers who participated in this study provided written informed consent prior to enrollment, as per the Duke IRB guidelines. PB MNCs and total RNA were isolated from the blood using the identical methods as described for collection of murine cells and RNA.

DNA Microarrays

Mouse and human oligonucleotide arrays were printed at the Duke Microarray Facility using Operon's Mouse Genome Oligo sets (version 3.0 and version 4.0) and Operon's Human Genome Oligo set (version 3.0 and version 4.0). Data generated from Operon's Mouse and Human version 3 was previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). Operon's

Mouse Genome Oligo set (version 4.0)

(https://www.operon.com/arrays/oligosets_mouse.php) contains 35,852 oligonucleotide probes representing 25,000 genes and approximately 38,000 transcripts. Operon's Human Genome Oligo set (version 4.0)

(https://www.operon.com/arrays/oligosets_human.php) contains 35,035 oligonucleotide probes, representing approximately 25,100 unique genes and 39,600 transcripts. In order to compare across versions of the Operon oligo sets, Operon provided a map that matched the probes from both versions and only those oligonucleotides that overlapped between versions 3.0 and 4.0 were used in the analysis.

RNA and Microarray Probe Preparation and Hybridization

Briefly, MNCs were pelleted, and total RNA was isolated using the RNeasy mini spin column (Dressman et al, PLoS Med. 4:690-701 (2007)). Total RNA from each sample (mouse or human) and the universal reference RNA (Universal Human or Mouse Reference RNA, Stratagene, <http://www.stratagene.com>) were amplified and used in probe preparation as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). The sample (mouse or human) was labeled with Cy5 and the reference (mouse or human) was labeled with Cy3. The reference RNA allows for the signal for each gene to be normalized to its own unique factor allowing comparisons of gene expression across multiple samples. This serves as a normalization control for two-color microarrays and an internal standardization for the arrays. Amplification, probe preparation and hybridization protocols were performed as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)) and each condition examined had multiple replicates analyzed (n=3-18 per mouse condition and n=18-36 per human condition). Detailed protocols are available on

the Duke Microarray Facility web site

(<http://microarray.genome.duke.edu/services/spotted-arrays/protocols>).

Data Processing and Statistical Analysis

Genespring GX 7.3 (Agilent Technologies) was used to perform initial data filtering in which spots whose signal intensities below 70 in either the Cy3 or Cy5 channel were removed. For each analysis, only those samples in that analysis were used in the filtering process. To compare data from previously published results (Dressman et al, PLoS Med. 4:690-701 (2007)), only those probes were used that mapped to each other across the version 3.0 and version 4.0 arrays. To then account for missing values, PAM software (<http://www-stat.stanford.edu/~tibs/PAM/>) was used to impute missing values. *k*-nearest neighbor was used where missing values were imputed using a *k*-nearest neighbor average in gene space. In the analysis approach in which all samples were included, lowess normalization of the data followed by batch effect removal using 2-way mixed model ANOVA (Partek Incorporated) was performed. Gene expression profiles of dose response were used in a supervised analysis using binary regression methodologies as described previously (Dressman et al, PLoS Med. 4:690-701 (2007)). Prediction analysis of the expression data was performed using MATLAB software as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). When predicting levels of radiation exposure, gene selection and identification is based on training the data and finding those genes most highly correlated to response. Each signature summarizes its constituent genes as a single expression profile and is here derived as the first principal component of that set of genes (the factor corresponding to the largest singular value), as determined by a singular value decomposition. Given a training set of expression vectors (of values across metagenes) representing two biological states, a binary probit regression model is estimated using Bayesian

methods. Bayesian fitting of binary probit regression models to the training data then permits an assessment of the relevance of the metagene signatures in within-sample classification, and estimation and uncertainty assessments for the binary regression weights mapping metagenes to probabilities of radiation exposure. To internally validate the predictive capacity of the metagene profiles, leave-one-out cross validation studies were performed as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). A leave one out cross validation involves removing one sample from the dataset, using the remaining samples to develop the model, and then predicting the status of the held out sample. This is then repeated for each sample in the dataset. This approach was utilized as previously described (Dressman et al, PLoS Med. 4:690-701 (2007)). A ROC curve analysis was used to define a cut-off for sensitivity and specificity in the predictive models of radiation. Genes found to be predictive of radiation dose were characterized utilizing an in-house program, GATHER (<http://meddb01.duhs.duke.edu/gather/>). GATHER quantifies the evidence supporting the association between a gene group and an annotation using a Bayes factor (Pournara et al, BMC Bioinformatics 23:1-20 (2007)). All microarray data files can be found at <http://data.cgt.duke.edu/ChuteRadiation.php> and at gene expression omnibus website (GEO [<http://www.ncbi.nlm.nih.gov/geo/>], accession number GSE10640).

RESULTS

PB gene expression signatures predict ionizing radiation exposure in a heterogeneous population

In a previous study, it was demonstrated that PB collected from a single strain and gender of mice, at a single time point, contained patterns of gene expression that predicted both prior radiation exposure and distinguished different levels of radiation exposure with a high degree of accuracy (Dressman

et al, PLoS Med. 4:690-701 (2007)). In this study, a determination was made as to whether PB gene expression signatures could be identified that predict radiation exposure status within a population that was heterogeneous for genotype, gender and time of sampling. It was found that a clear pattern of gene expression could be identified within this heterogeneous population of mice that distinguished non-irradiated animals from those irradiated with 50 cGy, 200 cGy, and 1000 cGy (Figure 1A). To verify that these patterns did indeed represent genes reflecting exposure to radiation, a leave-one-out cross-validation analysis was used to assess the ability of the pattern to predict the relevant samples (Figure 1B). The results demonstrate that the pattern selected for distinguishing control animals from those irradiated at various doses has the capacity to predict the status of the samples. The accuracies of prediction of the non-irradiated samples, the 50 cGy-, 200 cGy- and 1000 cGy-irradiated samples were 92%, 78%, 91% and 100%, respectively.

Sex differences impact the accuracy of gene expression signatures of radiation

A determination was then made as to the extent to which variables within a heterogeneous population can limit the accuracy of PB gene expression profiling. In order to address the impact of sex difference, healthy adult male and female C57Bl6 mice were irradiated with 50 cGy, 200 cGy, and 1000 cGy and PB was collected at 6 hours post-irradiation, along with PB from non-irradiated control mice (n=7-10 per group). Patterns of gene expression could be identified in the PB of both male and female mice that appeared to distinguish radiation exposure status (Figure 2A). When the PB signatures from the male C57Bl6 mice were tested against the female PB samples, the heat map analysis suggested less distinction between the non-irradiated and irradiated profiles (Figure 2B). Comparable effects were observed when the female PB signatures were applied against male PB samples. A leave-one-out cross-validation

analysis demonstrated that the male and female PB signatures of radiation were 100% accurate in predicting the radiation status of PB samples from mice of the same sex (Figure 2C). The male PB signatures also were 100% accurate in predicting the status of the female mice. However, the female PB signatures were less accurate in distinguishing the non-irradiated from 50 cGy irradiated male mice, with improved accuracy in predicting non-irradiated samples from male mice irradiated with higher doses of radiation (200 cGy and 1000 cGy; Figure 2C). The basis for the observed differences in predicting the radiation status of mice across gender differences may be a function of the distinct sets of genes which are represented in the predictors of radiation exposure in males and females (Table S1). Less than 15% of the genes overlapped between the PB metagenes of males and females at each dose of radiation.

Table 1. Genes that distinguish radiation responses in male and female C57Bl6 mice. Operon Oligo ID can be queried in the OMAD database (<http://omad.operon.com>)

Operon OligoID	Gene Symbol	RefSeq	Genbank	Description
MALES				
50 Gy				
<u>M200013484</u>	<u>9030617O03Rik</u>	<u>NM_145448</u>	<u>BC021385</u>	-
<u>M200000800</u>	<u>Ccng1</u>	<u>NM_009831</u>	<u>AB005559</u>	CYCLIN G1 (CYCLIN G)
<u>M200004687</u>	<u>Dda3-pending</u>	<u>NM_019976</u>	<u>AK041835</u>	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
<u>M200003784</u>	<u>Bax</u>	<u>NM_007527</u>	<u>L22472</u>	APOPTOSIS REGULATOR BAX, MEMBRANE ISOFORM ALPHA.
<u>M200007794</u>	<u>Wig1</u>	<u>NM_009517</u>	<u>AF012923</u>	WILD-TYPE P53-INDUCED GENE 1.
<u>M200016031</u>	<u>Polk</u>	<u>NM_012048</u>	<u>AB040764</u>	POLYMERASE (DNA DIRECTED), KAPPA; DINB HOMOLOG 1 (E. COLI); DNA DAMAGE-INDUCIBLE PROTEIN B; DNA DAMAGE-INDUCIBLE PROTEIN B; POLYMERASE (DNA DIRECTED) KAPPA.
<u>M200000935</u>	<u>Gcdh</u>	<u>NM_008097</u>	<u>U18992</u>	GLUTARYL-COA DEHYDROGENASE, MITOCHONDRIAL PRECURSOR (EC 1.3.99.7) (GCD).
<u>M300010491</u>	<u>D030041N15Rik</u>	<u>NM_153416</u>	<u>BC018191</u>	ALADIN (ADRACALIN).]

<u>M200003481</u>	<u>2210412K09Rik</u>	<u>NM_029814</u>	<u>BC006947</u>	--
<u>M200006137</u>	<u>Stinp</u>	<u>NM_021897</u>	<u>AY034612</u>	STRESS INDUCED PROTEIN; THYMUS EXPRESSED ACIDIC PROTEIN.
<u>M300008376</u>	<u>Pon2</u>	<u>NM_008896</u>	<u>L48514</u>	SERUM PARAOXONASE/ARYLESTERASE 2 (EC 3.1.1.2) (EC 3.1.8.1) (PON 2) (SERUM ARYLDIARYLPHOSPHATASE 2) (A-ESTERASE 2) (AROMATIC ESTERASE 2).]
<u>M200006229</u>	<u>Dstn</u>	<u>NM_019771</u>	<u>AB025406</u>	DESTRIN (ACTIN-DEPOLYMERIZING FACTOR) (ADF).
<u>M300013831</u>	<u>Myo15</u>	<u>NM_010862</u>	<u>AB014510</u>	MYOSIN XV (UNCONVENTIONAL MYOSIN-15).
<u>M200009374</u>	<u>2310045N01Rik</u>	<u>NM_008578</u>	<u>AK009829</u>	MYOCYTE-SPECIFIC ENHANCER FACTOR 2B.
<u>M200015906</u>	<u>5530601I19Rik</u>	<u>NM_027797</u>	<u>BC022756</u>	--
<u>M200004993</u>	<u>Ifi47</u>	<u>NM_008330</u>	<u>M63630</u>	INTERFERON GAMMA INDUCIBLE PROTEIN; INTERFERON GAMMA INDUCIBLE PROTEIN, 47 KDA
<u>M200006667</u>	<u>D11Ert619e</u>	<u>NM_026538</u>	<u>AK011136</u>	PROBABLE ATP-DEPENDENT 61 KDA NUCLEOLAR RNA HELICASE.
<u>M200013613</u>	<u>Gnrpx-pending</u>	--	<u>BC005565</u>	--
<u>M300020474</u>	--	--	--	--
<u>M200004237</u>	<u>Ris2</u>	<u>NM_026014</u>	<u>AK028287</u>	RETROVIRAL INTEGRATION SITE 2; RETROVIRAL INTEGRATION SITE 1.
<u>M200005712</u>	<u>Hexb</u>	<u>NM_010422</u>	<u>U07741</u>	BETA-HEXOSAMINIDASE BETA CHAIN PRECURSOR (EC 3.2.1.52) (N-ACETYL-BETA-GLUCOSAMINIDASE) (BETA-N-ACETYLHEXOSAMINIDASE) (HEXOSAMINIDASE B).
<u>M200000599</u>	<u>Pps</u>	<u>NM_008916</u>	<u>AK054436</u>	PUTATIVE PHOSPHATASE; PI-5-PHOSPHATASE RELATED; PUTATIVE PI-5-PHOSPHATASE. [
<u>M200014192</u>	--	<u>NM_053193</u>	<u>AF322193</u>	CLEAVAGE AND POLYADENYLATION SPECIFICITY FACTOR, 160 KDA SUBUNIT (CPSF 160 KDA SUBUNIT).
<u>M200004343</u>	<u>4833412N02Rik</u>	<u>NM_029020</u>	<u>AK030624</u>	--
<u>M200002381</u>	<u>Fanca</u>	<u>NM_016925</u>	<u>AF178934</u>	FANCONI ANEMIA, COMPLEMENTATION GROUP A.

200 Gy

<u>M200013484</u>	<u>9030617O03Rik</u>	<u>NM_145448</u>	<u>BC021385</u>	--
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<u>M200000800</u>	<u>Ccng1</u>	<u>NM_009831</u>	<u>AB005559</u>	CYCLIN G1 (CYCLIN G).
<u>M200016031</u>	<u>Polk</u>	<u>NM_012048</u>	<u>AB040764</u>	POLYMERASE (DNA DIRECTED), KAPPA; DINB HOMOLOG 1 (E. COLI); DNA DAMAGE-INDUCIBLE PROTEIN B; DNA DAMAGE-INDUCIBLE PROTEIN B; POLYMERASE (DNA DIRECTED) KAPPA.
<u>M200007794</u>	<u>Wig1</u>	<u>NM_009517</u>	<u>AF012923</u>	WILD-TYPE P53-INDUCED GENE 1.
<u>M300006854</u>	<u>Sec8</u>	<u>NM_009148</u>	<u>BC034644</u>	EXOCYST COMPLEX COMPONENT SEC8. [Source:SWISSPROT;Acc:O35382]
<u>M200006137</u>	<u>Stip</u>	<u>NM_021897</u>	<u>AY034612</u>	STRESS INDUCED PROTEIN; THYMUS EXPRESSED ACIDIC PROTEIN.
<u>M200007477</u>	<u>2310047O13Rik</u>	<u>NM_024185</u>	<u>BC027202</u>	--
<u>M300020474</u>	--	--	--	--
<u>M200003982</u>	<u>Golga5</u>	<u>NM_013747</u>	<u>AF026274</u>	GOLGI AUTOANTIGEN, GOLGIN SUBFAMILY A, 5.
<u>M300020472</u>	--	--	--	--
<u>M200004045</u>	<u>AI504353</u>	<u>NM_153419</u>	<u>BC008121</u>	GLUTAMATE RICH WD REPEAT PROTEIN GRWD.]
<u>M200002527</u>	<u>Cnbp</u>	<u>NM_013493</u>	<u>U20326</u>	CELLULAR NUCLEIC ACID BINDING PROTEIN (CNBP).]
<u>M200014192</u>	--	<u>NM_053193</u>	<u>AF322193</u>	CLEAVAGE AND POLYADENYLATION SPECIFICITY FACTOR, 160 KDA SUBUNIT (CPSF 160 KDA SUBUNIT).]
<u>M300000277</u>	<u>2310004L02Rik</u>	<u>NM_025504</u>	<u>AK009150</u>	--
<u>M200012890</u>	<u>Smarca4</u>	--	<u>BC026672</u>	--
<u>M200005377</u>	<u>Itpr3</u>	<u>NM_080553</u>	<u>Z71174</u>	INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR TYPE 3 (TYPE 3 INOSITOL 1,4,5-TRISPHOSPHATE RECEPTOR) (TYPE 3 INSP3 RECEPTOR) (IP3 RECEPTOR ISOFORM 3) (INSP3R3) (FRAGMENT). [
<u>M200002473</u>	<u>Acas2l</u>	<u>NM_080575</u>	<u>AK088244</u>	ACETYL-COA SYNTHETASE 2-LIKE; ACETYL-COENZYME A SYNTHETASE 2.
<u>M300011684</u>	<u>Pold1</u>	<u>NM_011131</u>	<u>AF024570</u>	DNA POLYMERASE DELTA CATALYTIC SUBUNIT (EC 2.7.7.7).
<u>M300009152</u>	<u>Tpst1</u>	<u>NM_013837</u>	<u>AF038008</u>	PROTEIN-TYROSINE SULFOTRANSFERASE 1 (EC 2.8.2.20) (TYROSYLPROTEIN SULFOTRANSFERASE-1) (TPST-1).
<u>M200014327</u>	<u>Bcar3</u>	<u>NM_013867</u>	<u>BC023930</u>	BREAST CANCER ANTI-ESTROGEN RESISTANCE3
<u>M300013112</u>	--	--	<u>J00595</u>	IG LAMBDA-2 CHAIN C REGION.
<u>M200006566</u>	<u>Gga2</u>	--	<u>AK004632</u>	--
<u>M300007254</u>	--	<u>NM_172900</u>	--	--
<u>M200009317</u>	<u>Scd1</u>	<u>NM_009127</u>	<u>BC007474</u>	ACYL-COA DESATURASE 1 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 1) (FATTY ACID DESATURASE 1) (DELTA(9)-DESATURASE 1).

M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300020088	--	--	--	--
M300004256	Fth	NM_010239	M24509	FERRITIN HEAVY CHAIN (FERRITIN H SUBUNIT).
M300014099	Actl	NM_013798	AF195094	ACTIN-LIKE.
M300020371	--	--	--	--
M200006851	--	NM_026467	--	RIBOSOMAL PROTEIN S27-LIKE.
M300015889	--	--	--	--
M300019801	--	--	--	--
M300018553	--	--	--	--
M300021441	--	--	--	--
M300015305	--	--	--	--
M300019335	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300020777	--	--	--	--
M200003258	Cox8a	NM_007750	U37721	CYTOCHROME C OXIDASE POLYPEPTIDE VIII-LIVER, MITOCHONDRIAL PRECURSOR (EC 1.9.3.1).
M300014515	--	--	--	--
M300018314	--	--	--	--
M200001083	Hspa9a	NM_010481	AK002634	STRESS-70 PROTEIN, MITOCHONDRIAL PRECURSOR (75 KDA GLUCOSE REGULATED PROTEIN) (GRP 75) (PEPTIDE-BINDING PROTEIN 74) (PBP74) (P66 MOT) (MORTALIN).
M300018559	--	--	--	--
M300012796	Hmgn1	NM_008251	X53476	NONHISTONE CHROMOSOMAL PROTEIN HMG-14 (HIGH-MOBILITY GROUP NUCLEOSOME BINDING DOMAIN 1).
M200000777	G3bp-pending	NM_013716	AB001927	RAS-GTPASE-ACTIVATING PROTEIN BINDING PROTEIN 1 (GAP SH3-DOMAIN BINDING PROTEIN 1) (G3BP-1).
M300021668	--	--	--	--

M300002115	Xpo1	NM_134014	BC025628	EXPORTIN 1, CRM1 HOMOLOG; EXPRESSED SEQUENCE AA420417.
M300017554	4930415K17Rik	NM_133687	BC016207	--
M300004265	Ms4a1	NM_007641	AK017903	B-CELL SURFACE PROTEIN CD20 HOMOLOG (B-CELL DIFFERENTIATION ANTIGEN LY-44).
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).

1000 Gy

M200007547	Phlda3	NM_013750	BC023408	PLECKSTRIN HOMOLOG-LIKE DOMAIN, FAMILY A, MEMBER 3; TDAG/LPL HOMOLOG 1.
M200016031	Polk	NM_012048	AB040764	POLYMERASE (DNA DIRECTED), KAPPA; DINB HOMOLOG 1 (E. COLI); DNA DAMAGE-INDUCIBLE PROTEIN B; DNA DAMAGE-INDUCIBLE PROTEIN B; POLYMERASE (DNA DIRECTED) KAPPA.
M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M200007578	Cdkn1a	NM_007669	U24173	CYCLIN-DEPENDENT KINASE INHIBITOR 1 (P21) (CDK-INTERACTING PROTEIN 1) (MELANOMA DIFFERENTIATION ASSOCIATED PROTEIN).
M200007794	Wig1	NM_009517	AF012923	WILD-TYPE P53-INDUCED GENE 1.
M200015712	3300002K07Rik	NM_152809	BC033601	--
M300000277	2310004L02Rik	NM_025504	AK009150	--
M300003012	--	--	--	--
M200009576	Recc1	NM_011258	U15037	ACTIVATOR 1 140 KDA SUBUNIT (REPLICATION FACTOR C LARGE SUBUNIT) (A1 140 KDA SUBUNIT) (RF-C 140 KDA SUBUNIT) (ACTIVATOR 1 LARGE SUBUNIT) (A1-P145) (DIFFERENTIATION SPECIFIC ELEMENT BINDING PROTEIN) (ISRE-BINDING PROTEIN).
M300011684	Pold1	NM_011131	AF024570	DNA POLYMERASE DELTA CATALYTIC SUBUNIT (EC 2.7.7.7).
M300010073	--	--	--	--
M200004560	--	NM_026942	--	--
M200005905	--	--	BC022623	--
M200002473	Acas2l	NM_080575	AK088244	ACETYL-COA SYNTHETASE 2-LIKE; ACETYL-COENZYME A SYNTHETASE 2.
M200006174	0610039P13Rik	NM_028752	BC021548	--

<u>M200014932</u>	<u>Swap70</u>	<u>NM_009302</u>	<u>AF053974</u>	SWAP COMPLEX PROTEIN; SWAP COMPLEX PROTEIN, 70 KDA.
<u>M200006566</u>	<u>Gga2</u>	--	<u>AK004632</u>	--
<u>M200000662</u>	<u>Dtx1</u>	<u>NM_008052</u>	<u>AB015422</u>	DELTEX 1 HOMOLOG (DROSOPHILA); FRACTIONATED X-IRRADIATION INDUCED TRANSCRIPT 1.
<u>M300007360</u>	--	--	--	--
<u>M300013112</u>	--	--	<u>J00595</u>	IG LAMBDA-2 CHAIN C REGION.
<u>M300004265</u>	<u>Ms4a1</u>	<u>NM_007641</u>	<u>AK017903</u>	B-CELL SURFACE PROTEIN CD20 HOMOLOG (B-CELL DIFFERENTIATION ANTIGEN LY-44).
<u>M300007254</u>	--	<u>NM_172900</u>	--	--
<u>M300000491</u>	--	--	<u>AF287275</u>	IG LAMBDA-1 CHAIN V REGION PRECURSOR.
<u>M200009317</u>	<u>Scd1</u>	<u>NM_009127</u>	<u>BC007474</u>	ACYL-COA DESATURASE 1 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 1) (FATTY ACID DESATURASE 1) (DELTA(9)-DESATURASE 1).
<u>M200001144</u>	<u>Cd79b</u>	<u>NM_008339</u>	<u>AF002279</u>	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).

FEMALES				
50 Gy				
<u>M300002291</u>	--	--	--	--
<u>M200004687</u>	<u>Dda3-pending</u>	<u>NM_019976</u>	<u>AK041835</u>	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
<u>M200000800</u>	<u>Ccng1</u>	<u>NM_009831</u>	<u>AB005559</u>	CYCLIN G1 (CYCLIN G)
<u>M300016629</u>	--	--	--	--
<u>M300020491</u>	--	--	<u>U38498</u>	GUANINE NUCLEOTIDE-BINDING PROTEIN G(I)/G(S)/G(O) GAMMA-5 SUBUNIT.
<u>M300015969</u>	--	--	--	--
<u>M200006491</u>	<u>Pgls</u>	<u>NM_025396</u>	<u>BC006594</u>	6-PHOSPHOGLUCONOLACTONASE.
<u>M300010063</u>	--	--	--	--
<u>M300016018</u>	--	<u>NM_023133</u>	--	RIBOSOMAL PROTEIN S19.
<u>M200002378</u>	<u>S100a13</u>	<u>NM_009113</u>	<u>BC005687</u>	S100 CALCIUM-BINDING PROTEIN A13.

M300019659	--	--	--	--
M300019012	--	--	--	--
M300009287	--	--	--	--
M300002125	--	--	--	--
M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
M200006774	2400001E08Rik	NM_025605	BC020142	--
M300008474	D10Jhu81e	NM_138601	AB041855	--
M200000096	B3Gat3	NM_024256	BC002103	GALACTOSYLGALACTOSYLXYLOSYLPROTEIN 3-BETA-GLUCURONOSYLTRANSFERASE 3 (EC 2.4.1.135) (BETA-1,3-GLUCURONYLTRANSFERASE 3) (GLUCURONOSYLTRANSFERASE-I) (GLCAT-I) (UDP-GLCUA:GAL BETA-1,3-GAL-R GLUCURONYLTRANSFERASE) (GLCUAT-I).
M300000948	--	--	AA277150	CLATHRIN COAT ASSEMBLY PROTEIN AP17 (CLATHRIN COAT ASSOCIATED PROTEIN AP17) (PLASMA MEMBRANE ADAPTOR AP-2 17 KDA PROTEIN) (HA2 17 KDA SUBUNIT) (CLATHRIN ASSEMBLY PROTEIN 2 SMALL CHAIN).
M300001725	--	NM_175015	AA275923	ATP SYNTHASE LIPID-BINDING PROTEIN, MITOCHONDRIAL PRECURSOR (EC 3.6.3.14) (ATP SYNTHASE PROTEOLIPID P3) (ATPASE PROTEIN 9) (ATPASE SUBUNIT C).
M300006374	Psmc2	--	BC005462	26S PROTEASE REGULATORY SUBUNIT 7 (MSS1 PROTEIN).
M300005124	5730454B08Rik	NM_144530	BC005786	--
M200000777	G3bp-pending	NM_013716	AB001927	RAS-GTPASE-ACTIVATING PROTEIN BINDING PROTEIN 1 (GAP SH3-DOMAIN BINDING PROTEIN 1) (G3BP-1).
M200003749	--	--	--	--
M300018559	--	--	--	--

200 Gy

M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300020088	--	--	--	--
M300004256	Fth	NM_010239	M24509	FERRITIN HEAVY CHAIN (FERRITIN H SUBUNIT).
M300014099	Actl	NM_013798	AF195094	ACTIN-LIKE.
M300020371	--	--	--	--

M200006851	--	NM_026467	--	RIBOSOMAL PROTEIN S27-LIKE.
M300015889	--	--	--	--
M300019801	--	--	--	--
M300018553	--	--	--	--
M300021441	--	--	--	--
M300015305	--	--	--	--
M300019335	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300020777	--	--	--	--
M200003258	Cox8a	NM_007750	U37721	CYTOCHROME C OXIDASE POLYPEPTIDE VIII-LIVER, MITOCHONDRIAL PRECURSOR (EC 1.9.3.1).
M300014515	--	--	--	--
M300018314	--	--	--	--
M200001083	Hspa9a	NM_010481	AK002634	STRESS-70 PROTEIN, MITOCHONDRIAL PRECURSOR (75 KDA GLUCOSE REGULATED PROTEIN) (GRP 75) (PEPTIDE-BINDING PROTEIN 74) (PBP74) (P66 MOT) (MORTALIN).
M300018559	--	--	--	--
M300012796	Hmgn1	NM_008251	X53476	NONHISTONE CHROMOSOMAL PROTEIN HMG-14 (HIGH-MOBILITY GROUP NUCLEOSOME BINDING DOMAIN 1).
M200000777	G3bp-pending	NM_013716	AB001927	RAS-GTPASE-ACTIVATING PROTEIN BINDING PROTEIN 1 (GAP SH3-DOMAIN BINDING PROTEIN 1) (G3BP-1).
M300021668	--	--	--	--
M300002115	Xpo1	NM_134014	BC025628	EXPORTIN 1, CRM1 HOMOLOG; EXPRESSED SEQUENCE AA420417.
M300017554	4930415K17Rik	NM_133687	BC016207	--
M300004265	Ms4a1	NM_007641	AK017903	B-CELL SURFACE PROTEIN CD20 HOMOLOG (B-CELL DIFFERENTIATION ANTIGEN LY-44).
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).

1000 Gy

M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
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M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
M300011848	--	NM_173445	--	--
M300020371	--	--	--	--
M300019400	--	--	--	--
M300019801	--	--	--	--
M300014889	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300019335	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300000465	2610301D06Rik	NM_026007	AK014277	ELONGATION FACTOR 1-GAMMA (EF-1-GAMMA) (EEF-1B GAMMA).
M300019589	--	--	--	--
M300012879	--	--	AK007389	SMALL NUCLEAR RIBONUCLEOPROTEIN SM D2 (SNRNP CORE PROTEIN D2) (SM-D2).
M300002970	5730420B22Rik	NM_172597	AK017582	--
M300021668	--	--	--	--
M300011495	--	--	BG088667	SESTRIN 1 (P53-REGULATED PROTEIN PA26).
M300017752	--	--	AF516285	ANTI-VIPASE LIGHT CHAIN VARIABLE REGION (FRAGMENT).
M300007254	--	NM_172900	--	--
M200006566	Gga2	--	AK004632	--
M200006174	0610039P13Rik	NM_028752	BC021548	--
M200000312	Ly6d	NM_010742	L40419	LYMPHOCYTE ANTIGEN LY-6D PRECURSOR (THYMOCYTE B CELL ANTIGEN) (THB).
M200000320	Pou2af1	NM_011136	U43788	POU DOMAIN CLASS 2, ASSOCIATING FACTOR 1 (B-CELL-SPECIFIC COACTIVATOR OBF-1) (OCT BINDING FACTOR 1) (BOB-1) (BOB1) (OCA-B).
M200001703	Cd19	NM_009844	M84372	B-LYMPHOCYTE ANTIGEN CD19 PRECURSOR (B-LYMPHOCYTE SURFACE ANTIGEN B4) (LEU-12) (DIFFERENTIATION ANTIGEN CD19).
M200000715	BB219290	NM_145141	AF426462	FC RECEPTOR HOMOLOG EXPRESSED IN B CELLS; FC RECEPTOR RELATED PROTEIN X.
M200002822	Blnk	NM_008528	AJ298054	B-CELL LINKER; LYMPHOCYTE ANTIGEN 57.

M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
M200009317	Scd1	NM_009127	BC007474	ACYL-COA DESATURASE 1 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 1) (FATTY ACID DESATURASE 1) (DELTA(9)-DESATURASE 1).

Table 2. Genes that overlap between mouse groups. Operon Oligo ID can be queried in the OMAD database (<http://omad.operon.com>)

Operon OligoID	Gene Symbol	RefSeq	Genbank	Description
SEX				
C57Bl6 M and C57Bl6 F				
M vs F 50cGy				
M200000800	Ccng1	NM_009831	AB005559	CYCLIN G1 (CYCLIN G)
M200004687	Dda3	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M vs F 200cGy				
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
M vs F 1000cGy				
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
M200004687	Dda3	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M200009317	Scd1	NM_009127	BC007474	ACYL-COA DESATURASE 1 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 1) (FATTY ACID DESATURASE 1) (DELTA(9)-DESATURASE 1).
M200006566	Gga2	--	AK004632	--
M200006174				
M300007254				

GENOTYPE				
C57Bl6 F and BALB/c F				
BI vs BA 50cGy				
M200000800	Ccng1	NM_009831	AB005559	CYCLIN G1 (CYCLIN G)
M200004687	Dda3	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
BI vs BA 200cGy				
M200004687	Dda3	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
BI vs BA 1000cGy				
M200004687	Dda3	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
TIME				
Within C57Bl6 F				
6hr vs 24hr 50cGy				
None				
6hr vs 24hr 200cGy				
None				
6hr vs 24hr 1000cGy				
None				
6hr vs 7d 50cGy				
None				
6hr vs 7d 200cGy				
None				
24h vs 7d 50cGy				

M300000165	Lgals1	NM_008495	AK004298	GALECTIN-1 (BETA-GALACTOSIDE-BINDING LECTIN L-14-I) (LACTOSE-BINDING LECTIN 1) (S-LAC LECTIN 1)
24h vs 7d 200cGy				
None				

Impact of genotype on prediction of radiation status

Since the human population is genetically diverse, an examination was next made to determine whether gene expression signatures of radiation exposure could accurately predict the status of mice across different genotypes. PB was collected from C57Bl6 and BALB/c mice at 6 hours following 50 cGy, 200 cGy or 1000 cGy. It was possible to identify patterns of gene expression which appeared to distinguish the different levels of radiation from the non-irradiated controls within each strain (Figure 3A). However, when the PB gene expression signatures from C57Bl6 mice were tested against BALB/c mice, and vice versa, the gene expression profiles were less distinct (Figure 3B). A leave-one-out cross-validation analysis was then performed in which gene expression profiles from C57Bl6 mice were tested against PB from BALB/c mice and found that the metagene predictors of radiation from C57Bl6 mice displayed 100% accuracy in predicting the status of non-irradiated and irradiated BALB/c mice (Figure 3C). Similarly, application of the PB metagene profiles of radiation generated in BALB/c mice demonstrated 100% accuracy in distinguishing non-irradiated and irradiated C57Bl6 mice. Interestingly, less than 20% of the genes represented within the PB predictors from C57Bl6 mice and BALB/c mice overlapped (Table 3, Table 2), but both predictors were highly accurate in predicting the radiation status of the different strain of mice. Dda3, a p53-inducible gene, which

participates in suppression of cell growth (Hsieh et al, Oncogene 21:3050-3057 (2002)), was represented in both strains at all radiation doses.

Table 3. Genes that distinguish radiation responses in BALB/c mice. Operon Oligo ID can be queried in the OMAD database (<http://omad.operon.com>)

Operon OligoID	Gene Symbol	RefSeq	Genbank	Description
50 Gy				
M200013484	9030617O03Rik	NM_145448	BC021385	--
M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300000487	Bax	NM_007527	L22472	APOPTOSIS REGULATOR BAX, MEMBRANE ISOFORM ALPHA.
M300006855	Sec8	NM_009148	BC034644	EXOCYST COMPLEX COMPONENT SEC8.
M300001199	--	--	BC002257	--
M200000800	Ccng1	NM_009831	AB005559	CYCLIN G1 (CYCLIN G).
M200016031	Polk	NM_012048	AB040764	POLYMERASE (DNA DIRECTED), KAPPA; DINB HOMOLOG 1 (E. COLI); DNA DAMAGE-INDUCIBLE PROTEIN B; DNA DAMAGE-INDUCIBLE PROTEIN B; POLYMERASE (DNA DIRECTED) KAPPA.
M200003784	Bax	NM_007527	L22472	APOPTOSIS REGULATOR BAX, MEMBRANE ISOFORM ALPHA.
M200007547	Phlda3	NM_013750	BC023408	PLECKSTRIN HOMOLOG-LIKE DOMAIN, FAMILY A, MEMBER 3; TDAG/LPL HOMOLOG 1.
M300010491	D030041N15Rik	NM_153416	BC018191	ALADIN (ADRACALIN).
M200006364	Dcxr	NM_026428	AK004023	DIACETYL/L-XYLULOSE REDUCTASE.
M300007324	2700083B06Rik	NM_026531	BC022614	--
M300000486	Bax	NM_007527	L22472	APOPTOSIS REGULATOR BAX, MEMBRANE ISOFORM ALPHA.
M200007794	Wig1	NM_009517	AF012923	WILD-TYPE P53-INDUCED GENE 1.
M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
M300003395	Ly6e	NM_008529	U47737	LYMPHOCYTE ANTIGEN LY-6E PRECURSOR (THYMIC SHARED ANTIGEN-1) (TSA-1) (STEM CELL ANTIGEN 2).
M200003474	D730042P09Rik	NM_144543	AB080370	THYMOCYTE PROTEIN THY28.
M200012250	Scd2	NM_009128	M26270	ACYL-COA DESATURASE 2 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 2) (FATTY ACID DESATURASE 2) (DELTA(9)-DESATURASE 2).
M200000655	Tnfrsf6	NM_007987	S56486	TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY MEMBER 6 PRECURSOR (FAS RECEPTOR) (APOPTOSIS-MEDIATING SURFACE ANTIGEN FAS) (APO-1 ANTIGEN) (CD95).

M200008006	2410089B13Rik	--	AK010745	--
M200000279	Ly6e	NM_008529	U47737	LYMPHOCYTE ANTIGEN LY-6E PRECURSOR (THYMIC SHARED ANTIGEN-1) (TSA-1) (STEM CELL ANTIGEN 2).
M200000354	ORF21	NM_145482	BC029101	--
M300002140	D11Ert603e	NM_026023	AK004388	--
M300002232	Ppm1d	NM_016910	AF200464	PROTEIN PHOSPHATASE 2C DELTA ISOFORM (EC 3.1.3.16) (PP2C-DELTA) (P53- INDUCED PROTEIN PHOSPHATASE 1) (PROTEIN PHOSPHATASE MAGNESIUM- DEPENDENT 1 DELTA).
M300002800	Zfp369	--	BC036565	NEUROTROPHIN RECEPTOR INTERACTING FACTOR 2.
200 Gy				
M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300020088	--	--	--	--
M300004256	Fth	NM_010239	M24509	FERRITIN HEAVY CHAIN (FERRITIN H SUBUNIT).
M300014099	Actl	NM_013798	AF195094	ACTIN-LIKE.
M300020371	--	--	--	--
M200006851	--	NM_026467	--	RIBOSOMAL PROTEIN S27-LIKE.
M300015889	--	--	--	--
M300019801	--	--	--	--
M300018553	--	--	--	--
M300021441	--	--	--	--
M300015305	--	--	--	--
M300019335	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300020777	--	--	--	--
M200003258	Cox8a	NM_007750	U37721	CYTOCHROME C OXIDASE POLYPEPTIDE VIII- LIVER, MITOCHONDRIAL PRECURSOR (EC 1.9.3.1).
M300014515	--	--	--	--
M300018314	--	--	--	--
M200001083	Hspa9a	NM_010481	AK002634	STRESS-70 PROTEIN, MITOCHONDRIAL PRECURSOR (75 KDA GLUCOSE REGULATED PROTEIN) (GRP 75) (PEPTIDE-BINDING PROTEIN 74) (PBP74) (P66 MOT) (MORTALIN).
M300018559	--	--	--	--
M300012796	Hmgn1	NM_008251	X53476	NONHISTONE CHROMOSOMAL PROTEIN HMG-14 (HIGH-MOBILITY GROUP NUCLEOSOME BINDING DOMAIN 1).
M200000777	G3bp-pending	NM_013716	AB001927	RAS-GTPASE-ACTIVATING PROTEIN BINDING PROTEIN 1 (GAP SH3-DOMAIN BINDING PROTEIN 1) (G3BP-1).
M300021668	--	--	--	--

M300002115	Xpo1	NM_134014	BC025628	EXPORTIN 1, CRM1 HOMOLOG; EXPRESSED SEQUENCE AA420417.
M300017554	4930415K17Rik	NM_133687	BC016207	--
M300004265	Ms4a1	NM_007641	AK017903	B-CELL SURFACE PROTEIN CD20 HOMOLOG (B-CELL DIFFERENTIATION ANTIGEN LY-44).
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
1000 Gy				
M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
M300011848	--	NM_173445	--	--
M300020371	--	--	--	--
M300019400	--	--	--	--
M300019801	--	--	--	--
M300014889	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300019335	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300000465	2610301D06Rik	NM_026007	AK014277	ELONGATION FACTOR 1-GAMMA (EF-1-GAMMA) (EEF-1B GAMMA).
M300019589	--	--	--	--
M300012879	--	--	AK007389	SMALL NUCLEAR RIBONUCLEOPROTEIN SM D2 (SNRNP CORE PROTEIN D2) (SM-D2).
M300002970	5730420B22Rik	NM_172597	AK017582	--
M300021668	--	--	--	--
M300011495	--	--	BG088667	SESTRIN 1 (P53-REGULATED PROTEIN PA26).
M300017752	--	--	AF516285	ANTI-VIPASE LIGHT CHAIN VARIABLE REGION (FRAGMENT).
M300007254	--	NM_172900	--	--
M200006566	Gga2	--	AK004632	--
M200006174	0610039P13Rik	NM_028752	BC021548	--
M200000312	Ly6d	NM_010742	L40419	LYMPHOCYTE ANTIGEN LY-6D PRECURSOR (THYMOCYTE B CELL ANTIGEN) (THB).
M200000320	Pou2af1	NM_011136	U43788	POU DOMAIN CLASS 2, ASSOCIATING FACTOR 1 (B-CELL-SPECIFIC COACTIVATOR OBF-1) (OCT BINDING FACTOR 1) (BOB-1) (BOB1) (OCA-B).

M200001703	Cd19	NM_009844	M84372	B-LYMPHOCYTE ANTIGEN CD19 PRECURSOR (B-LYMPHOCYTE SURFACE ANTIGEN B4) (LEU-12) (DIFFERENTIATION ANTIGEN CD19).
M200000715	BB219290	NM_145141	AF426462	FC RECEPTOR HOMOLOG EXPRESSED IN B CELLS; FC RECEPTOR RELATED PROTEIN X.
M200002822	Blnk	NM_008528	AJ298054	B-CELL LINKER; LYMPHOCYTE ANTIGEN 57.
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
M200009317	Scd1	NM_009127	BC007474	ACYL-COA DESATURASE 1 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 1) (FATTY ACID DESATURASE 1) (DELTA(9)-DESATURASE 1).

The impact of time on PB gene expression signatures of irradiation

PB responses to environmental exposures may change over time as a function of changes in PB cellular composition and cellular responses themselves. Patterns of gene expression were identified in the PB of C57Bl6 female mice at 6 hrs, 24 hrs and 7 days post-irradiation which appeared to distinguish the 3 different levels of radiation versus non-irradiated mice (Figure 4A). When the PB metagene profiles of radiation exposure generated from the 6 hr time point were applied against PB samples from mice at the 24 hr and 7 day time points post-irradiation, the profiles appeared less distinct (Figure 4B). A leave-one-out cross-validation analysis demonstrated that the PB metagene profiles from each time point predicted each dose of radiation with 100% accuracy (Figure 4C). Next, a leave-one-out cross-validation analysis was performed using the metagene profiles from the 6 hr time point against each of the PB samples from mice at 24 hr and 7 day time points and the 6 hr metagene profiles demonstrated 100% accuracy in predicting the radiation status of the 24 hr and 7 day time point samples (Figure 4C). Of note, the 7 day time point following 1000 cGy exposure could not be analyzed since it was not possible to collect sufficient RNA from these PB samples to allow gene array hybridization to be performed. Although it was found that time did not impact the accuracy of PB gene expression profiles in predicting radiation status, the lists of genes which comprised these PB signatures changed significantly over 7 days (Table 4). No genes were found in common between the 6 hr predictors and the 24 hr or 7 day PB signatures of radiation in 50 cGy-, 200 cGy-, or 1000 cGy-treated mice (Table 2). A single gene, Galectin 1 (*Lgals1*), a carbohydrate binding protein that is involved in the induction of cell death (Valenzuela et al, Cancer Res. 67:6155-6162 (2007)), was found in common between the 24 hr and 7 day predictors of 50 cGy.

Table 4. Genes that distinguish the impact of time in C57Bl6 mice. Operon Oligo ID can be queried in the OMAD database (<http://omad.operon.com>)

Operon Oligo ID	Gene Symbol	RefSeq	Genbank	Description
Female C57Bl6 6hr 50 cGy				
M300002291	--	--	--	--
M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M200000800	Ccng1	NM_009831	AB005559	CYCLIN G1 (CYCLIN G).
M300016629	--	--	--	--
M300020491	--	--	U38498	GUANINE NUCLEOTIDE-BINDING PROTEIN G(I)/G(S)/G(O) GAMMA-5 SUBUNIT.
M300015969	--	--	--	--
M300010063	--	--	--	--
M300016018	--	NM_023133	--	RIBOSOMAL PROTEIN S19.
M200002378	S100a13	NM_009113	BC005687	S100 CALCIUM-BINDING PROTEIN A13.
M300019659	--	--	--	--
M300014141	V1rc22	NM_134177	AY065478	VOMERONASAL 1 RECEPTOR, C22.
M300020488	--	--	V00754	HISTONE H3.4 (EMBRYONIC).
M300019012	--	--	--	--
M300014338	--	--	--	--
M300009287	--	--	--	--
M300002125	--	--	--	--
M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
M200006774	2400001E08 Rik	NM_025605	BC020142	--
M300008474	D10Jhu81e	NM_138601	AB041855	--
M200000096	B3Gat3	NM_024256	BC002103	GALACTOSYL GALACTOSYLXYLOSYLPROTEIN 3-BETA-GLUCURONOSYLTRANSFERASE 3 (EC 2.4.1.135) (BETA-1,3-GLUCURONYLTRANSFERASE 3) (GLUCURONOSYLTRANSFERASE-I) (GLCAT-I) (UDP-GLCUA:GAL BETA-1,3-GAL-R GLUCURONYLTRANSFERASE) (GLCUAT-I).
M300006374	Psmc2	--	BC005462	26S PROTEASE REGULATORY SUBUNIT 7 (MSS1 PROTEIN).
M300005124	5730454B08 Rik	NM_144530	BC005786	--
M200000777	G3bp-pending	NM_013716	AB001927	RAS-GTPASE-ACTIVATING PROTEIN BINDING PROTEIN 1 (GAP SH3-DOMAIN BINDING PROTEIN 1) (G3BP-1).
M200003749	--	--	--	--
M300018559	--	--	--	--

Female C57Bl6 6hr 200 cGy

M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
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M300020088	--	--	--	--
M300004256	Fth	NM_010239	M24509	FERRITIN HEAVY CHAIN (FERRITIN H SUBUNIT).
M300014099	Actl	NM_013798	AF195094	ACTIN-LIKE.
M300020371	--	--	--	--
M200006851	--	NM_026467	--	RIBOSOMAL PROTEIN S27-LIKE.
M300015889	--	--	--	--
M300019801	--	--	--	--
M300018553	--	--	--	--
M300021441	--	--	--	--
M300015305	--	--	--	--
M300019335	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300020777	--	--	--	--
M200003258	Cox8a	NM_007750	U37721	CYTOCHROME C OXIDASE POLYPEPTIDE VIII-LIVER, MITOCHONDRIAL PRECURSOR (EC 1.9.3.1).
M300014515	--	--	--	--
M300018314	--	--	--	--
M200001083	Hspa9a	NM_010481	AK002634	STRESS-70 PROTEIN, MITOCHONDRIAL PRECURSOR (75 KDA GLUCOSE REGULATED PROTEIN) (GRP 75) (PEPTIDE-BINDING PROTEIN 74) (PBP74) (P66 MOT) (MORTALIN).
M300018559	--	--	--	--
M300012796	Hmgn1	NM_008251	X53476	NONHISTONE CHROMOSOMAL PROTEIN HMG-14 (HIGH-MOBILITY GROUP NUCLEOSOME BINDING DOMAIN 1).
M200000777	G3bp-pending	NM_013716	AB001927	RAS-GTPASE-ACTIVATING PROTEIN BINDING PROTEIN 1 (GAP SH3-DOMAIN BINDING PROTEIN 1) (G3BP-1).
M300021668	--	--	--	--
M300002115	Xpo1	NM_134014	BC025628	EXPORTIN 1, CRM1 HOMOLOG; EXPRESSED SEQUENCE AA420417.
M300017554	4930415K17 Rik	NM_133687	BC016207	--
M300004265	Ms4a1	NM_007641	AK017903	B-CELL SURFACE PROTEIN CD20 HOMOLOG (B-CELL DIFFERENTIATION ANTIGEN LY-44).
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).

Female C57Bl6 6hr 1000 cGy

M200004687	Dda3-pending	NM_019976	AK041835	DIFFERENTIAL DISPLAY AND ACTIVATED BY P53; P53-REGULATED DDA3.
M300008077	Ei24	NM_007915	U41751	ETOPOSIDE-INDUCED PROTEIN 2.4.
M300011848	--	NM_173445	--	--
M300020371	--	--	--	--
M300019852	--	--	--	--
M300019400	--	--	--	--

M300019801	--	--	--	--
M300014889	Gapd	NM_008084	AK002273	GLYCERALDEHYDE 3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12) (GAPDH).
M300000465	2610301D06 Rik	NM_026007	AK014277	ELONGATION FACTOR 1-GAMMA (EF-1-GAMMA) (EEF-1B GAMMA).
M300019589	--	--	--	--
M300012879	--	--	AK007389	SMALL NUCLEAR RIBONUCLEOPROTEIN SM D2 (SNRNP CORE PROTEIN D2) (SM-D2).
M300006168	--	NM_177045	--	--
M300002970	5730420B22 Rik	NM_172597	AK017582	--
M200009547	Mybbp1a	NM_016776	U63648	MYB BINDING PROTEIN (P160) 1A; NUCLEAR PROTEIN P160.
M300021668	--	--	--	--
M300011495	--	--	BG088667	SESTRIN 1 (P53-REGULATED PROTEIN PA26).
M300017752	--	--	AF516285	ANTI-VIPASE LIGHT CHAIN VARIABLE REGION (FRAGMENT).
M300007254	--	NM_172900	--	--
M200006566	Gga2	--	AK004632	--
M200006174	0610039P13 Rik	NM_028752	BC021548	--
M200000312	Ly6d	NM_010742	L40419	LYMPHOCYTE ANTIGEN LY-6D PRECURSOR (THYMOCYTE B CELL ANTIGEN) (THB).
M200000320	Pou2af1	NM_011136	U43788	POU DOMAIN CLASS 2, ASSOCIATING FACTOR 1 (B-CELL-SPECIFIC COACTIVATOR OBF-1) (OCT BINDING FACTOR 1) (BOB-1) (BOB1) (OCA-B).
M200002822	Blnk	NM_008528	AJ298054	B-CELL LINKER; LYMPHOCYTE ANTIGEN 57.
M200001144	Cd79b	NM_008339	AF002279	B-CELL ANTIGEN RECEPTOR COMPLEX ASSOCIATED PROTEIN BETA-CHAIN PRECURSOR (B-CELL-SPECIFIC GLYCOPROTEIN B29) (IMMUNOGLOBULIN-ASSOCIATED B29 PROTEIN) (IG-BETA) (CD79B).
M200009317	Scd1	NM_009127	BC007474	ACYL-COA DESATURASE 1 (EC 1.14.19.1) (STEAROYL-COA DESATURASE 1) (FATTY ACID DESATURASE 1) (DELTA(9)-DESATURASE 1).

Female C57Bl6 24hr 50 cGy

M300005062	BC027756	NM_145991	AK080861	--
M200005746	1110020J08 Rik	NM_025394	AK003864	--
M200003036	Nprl2-pending	NM_018879	BC026548	G21 PROTEIN.
M200004472	Slc25a1	NM_153150	BC037087	SOLUTE CARRIER FAMILY 25, MEMBER 1; DIGEORGE SYNDROME GENE J; SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL CARRIER; CITRATE TRANSPORTER) MEMBER 1; TRICARBOXYLATE TRANSPORT PROTEIN PRECURSOR.
M200006750	2410104I19R ik	NM_133691	BC010601	--

M200009777	Aco2	NM_080633	BC004645	ACONITASE 2, MITOCHONDRIAL.
M200007587	E130307M08 Rik	NM_026530	BC017625	--
M200002043	Mcnd6	NM_008567	D86726	DNA REPLICATION LICENSING FACTOR MCM6 (MIS5 HOMOLOG).
M200005598	Cdk9	NM_130860	AF327431	CYCLIN-DEPENDENT KINASE 9.
M200006108	Coro1b	NM_011778	AK008947	CORONIN 1B (CORONIN 2).
M300012497	Rbms2	NM_019711	AK054482	RNA BINDING MOTIF, SINGLE STRANDED INTERACTING PROTEIN 2; SCR3.
M200003074	Psmc3	NM_009439	BC003197	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 3 (26S PROTEASOME REGULATORY SUBUNIT S3) (PROTEASOME SUBUNIT P58) (TRANSPLANTATION ANTIGEN P91A) (TUM-P91A ANTIGEN).
M300013135	--	--	BC034540	--
M300019447	--	--	BC027368	--
M200009417	Mt2	--	K02236	METALLOTHIONEIN-II (MT-II).
M300021033	Lgals3	--	X16074	GALECTIN-3 (GALACTOSE-SPECIFIC LECTIN 3) (MAC-2 ANTIGEN) (IGE-BINDING PROTEIN) (35 KDA LECTIN) (CARBOHYDRATE BINDING PROTEIN 35) (CBP 35) (LAMININ-BINDING PROTEIN) (LECTIN L-29) (L-34 GALACTOSIDE-BINDING LECTIN).
M300004485	P4hb	--	J05185	PROTEIN DISULFIDE ISOMERASE PRECURSOR (PDI) (EC 5.3.4.1) (PROLYL 4-HYDROXYLASE BETA SUBUNIT) (CELLULAR THYROID HORMONE BINDING PROTEIN) (P55) (ERP59).
M200012720	--	--	BC008093	EUKARYOTIC TRANSLATION INITIATION FACTOR 5A (EIF-5A) (EIF-4D) (REV- BINDING FACTOR).
M200006860	--	NM_010312	U38505	GUANINE NUCLEOTIDE-BINDING PROTEIN G(I)/G(S)/G(T) BETA SUBUNIT 2 (TRANSDUCIN BETA CHAIN 2) (G PROTEIN BETA 2 SUBUNIT).
M300011574	--	--	--	--
M300015461	--	--	--	--
M300021713	--	--	--	--
M200009655	Cct6a	NM_009838	AB022159	T-COMPLEX PROTEIN 1, ZETA SUBUNIT (TCP-1-ZETA) (CCT-ZETA) (CCT-ZETA- 1).
M300004979	Fn1	--	BC004724	--
M200014015	Lgals1	NM_008495	AK004298	GALECTIN-1 (BETA-GALACTOSIDE-BINDING LECTIN L-14-I) (LACTOSE-BINDING LECTIN 1) (S-LAC LECTIN 1) (GALAPTIN) (14 KDA LECTIN).

Female C57Bl6 24hr 200 cGy

M300010249	Txk	NM_013698	L35268	TYROSINE-PROTEIN KINASE TXK (EC 2.7.1.112) (PTK-RL-18) (RESTING LYMPHOCYTE KINASE).
M300010028	--	--	BC026557	SIMILAR TO PTD015 PROTEIN.
M200009777	Aco2	NM_080633	BC004645	ACONITASE 2, MITOCHONDRIAL.
M200005598	Cdk9	NM_130860	AF327431	CYCLIN-DEPENDENT KINASE 9.
M200000327	Cct7	NM_007638	AB022160	T-COMPLEX PROTEIN 1, ETA SUBUNIT (TCP-1-ETA) (CCT-ETA).
M200003578	Bpnt1	NM_011794	AF125043	BISPHOSPHATE 3'-NUCLEOTIDASE 1.

M200002251	Akr1b8	NM_008012	U04204	ALDOSE REDUCTASE-RELATED PROTEIN 1 (EC 1.1.1.21) (AR) (ALDEHYDE REDUCTASE) (VAS DEFERENS ANDROGEN-DEPENDENT PROTEIN) (MVDP) (ALDO-KETO REDUCTASE FAMILY 1 MEMBER B7).
M200012683	Acat2	--	BC012496	T-COMPLEX PROTEIN (TCP-1X) (FRAGMENT).
M300002824	Hnrpk	NM_025279	BC006694	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN K (HNRNP K) (65 KDA PHOSPHOPROTEIN).
M200007603	0610009O03 Rik	NM_026660	AK089055	--
M200006373	Nars	--	AK013880	--
M200002442	Cdk4	NM_009870	X65069	CELL DIVISION PROTEIN KINASE 4 (EC 2.7.1.-) (CYCLIN-DEPENDENT KINASE 4) (PSK-J3) (CRK3).
M200006712	Shmt2	NM_028230	BC004825	--
M200002501	Lrp1	NM_008512	AF367720	LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 1; LOW DENSITY LIPOPROTEIN RECEPTOR RELATED PROTEIN; LOW DENSITY LIPOPROTEIN RECEPTOR RELATED PROTEIN 1.
M200006860	--	NM_010312	U38505	GUANINE NUCLEOTIDE-BINDING PROTEIN G(I)/G(S)/G(T) BETA SUBUNIT 2 (TRANSDUCIN BETA CHAIN 2) (G PROTEIN BETA 2 SUBUNIT).
M300004485	P4hb	--	J05185	PROTEIN DISULFIDE ISOMERASE PRECURSOR (PDI) (EC 5.3.4.1) (PROLYL 4-HYDROXYLASE BETA SUBUNIT) (CELLULAR THYROID HORMONE BINDING PROTEIN) (P55) (ERP59).
M200012927	Angptl2	NM_011923	AF125176	ANGIOPOIETIN-RELATED PROTEIN 2 PRECURSOR (ANGIOPOIETIN-LIKE 2).
M300011172	--	--	--	--
M200002468	Alad	NM_008525	X13752	DELTA-AMINOLEVULINIC ACID DEHYDRATASE (EC 4.2.1.24) (PORPHOBILINOGEN SYNTHASE) (ALADH).
M300004916	Col3a1	--	X57983	COLLAGEN ALPHA 1(III) CHAIN PRECURSOR.
M200000033	Idb3	NM_008321	M60523	DNA-BINDING PROTEIN INHIBITOR ID-3 (ID-LIKE PROTEIN INHIBITOR HLH 462).
M200003353	Anxa1	NM_010730	M24554	ANNEXIN I (LIPOCORTIN I) (CALPACTIN II) (CHROMOBINDIN 9) (P35) (PHOSPHOLIPASE A2 INHIBITORY PROTEIN).
M200014015	Lgals1	NM_008495	AK004298	GALECTIN-1 (BETA-GALACTOSIDE-BINDING LECTIN L-14-I) (LACTOSE-BINDING LECTIN 1) (S-LAC LECTIN 1) (GALAPTIN) (14 KDA LECTIN).
M200000992	Bgn	NM_007542	Y11758	BIGLYCAN PRECURSOR (BONE/CARTILAGE PROTEOGLYCAN I) (PG-S1).
M200003310	AU044919	--	BC010327	IG GAMMA-2B CHAIN C REGION, MEMBRANE-BOUND FORM.

Female C57Bl6 24hr 1000 cGy

M300000233	Capns1	NM_009795	BC018352	CALCIUM-DEPENDENT PROTEASE, SMALL SUBUNIT (CALPAIN REGULATORY SUBUNIT) (CALCIUM-ACTIVATED NEUTRAL PROTEINASE) (CANP).
M300001059	D0H8S2298E	--	BC024492	REPRODUCTION 8 (DNA SEGMENT, HUMAN S2298E).

M300013845	Atpaf2	NM_145427	BC013607	ATP SYNTHASE MITOCHONDRIAL F1 COMPLEX ASSEMBLY FACTOR 2.
M300004022	Ermelin-pending	NM_139143	AB071697	ENDOPLASMIC RETICULUM MEMBRANE PROTEIN; EXPRESSED SEQUENCE AI853222.
M200004159	Nono	NM_023144	AK013444	NON-POU-DOMAIN-CONTAINING, OCTAMER BINDING PROTEIN; NON-POU-DOMAIN-CONTAINING, OCTAMER-BINDING PROTEIN.
M200003982	Golga5	NM_013747	AF026274	GOLGI AUTOANTIGEN, GOLGIN SUBFAMILY A, 5.
M200000385	Slc1a7	NM_009201	D85044	NEUTRAL AMINO ACID TRANSPORTER B (INSULIN-ACTIVATED AMINO ACID TRANSPORTER) (ASC-LIKE NA(+)-DEPENDENT NEUTRAL AMINO ACID TRANSPORTER ASCT2).
M300006374	Psmc2	--	BC005462	26S PROTEASE REGULATORY SUBUNIT 7 (MSS1 PROTEIN).
M200004383	Cse1l	NM_023565	AF301152	IMPORTIN-ALPHA RE-EXPORTER (CHROMOSOME SEGREGATION 1-LIKE PROTEIN) (CELLULAR APOPTOSIS SUSCEPTIBILITY PROTEIN).
M200005955	1810019E15 Rik	--	AK007546	--
M200005912	Narg1	NM_053089	BC030167	NMDA RECEPTOR-REGULATED GENE 1; N-TERMINAL ACYLTRANSFERASE 1.
M200001798	Lbr	NM_133815	BC042522	LAMIN B RECEPTOR; ICHTHYOSIS.
M200015331	AV278559	NM_134152	AB071194	--
M300022323	--	--	--	--
M300021610	--	--	--	--
M300017722	--	NM_024266	X62482	40S RIBOSOMAL PROTEIN S25.
M200003662	Hprt	NM_013556	K01514	HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.8) (HGPRT) (HGPRTASE) (HPRT B).
M300004429	Blnk	NM_008528	AJ222814	B-CELL LINKER; LYMPHOCYTE ANTIGEN 57.
M300018162	--	--	--	--
M300013112	--	--	J00595	IG LAMBDA-2 CHAIN C REGION.
M300011693	--	--	--	--
M300000425	Rps11	NM_013725	AK005147	40S RIBOSOMAL PROTEIN S11.
M300017758	--	NM_027015	--	RIBOSOMAL PROTEIN S27.
M300004265	Ms4a1	NM_007641	AK017903	B-CELL SURFACE PROTEIN CD20 HOMOLOG (B-CELL DIFFERENTIATION ANTIGEN LY-44).
M300020997	--	--	--	--

Female C57Bl6 day 7 50 cGy

M300007861	Gypa	NM_010369	M73815	GLYCOPHORIN.
M200006628	W64236	NM_144805	BC019416	--
M300005566	Capn3	NM_007601	AF091998	CALPAIN 3 LARGE SUBUNIT (EC 3.4.22.17) (CALPAIN L3) (CALPAIN P94, LARGE SUBUNIT) (CALCIUM-ACTIVATED NEUTRAL PROTEINASE 3) (CANP 3) (MUSCLE-SPECIFIC CALCIUM-ACTIVATED NEUTRAL PROTEASE 3 LARGE SUBUNIT).
M200001376	Gp5	NM_008148	Z69595	PLATELET GLYCOPROTEIN V PRECURSOR (GPV) (CD42D).

M200005863	Nup210	NM_018815	AF113751	NUCLEOPORIN 210; NUCLEAR PORE MEMBRANE GLYCOPROTEIN 210; NUCLEAR PORE MEMBRANE PROTEIN 210.
M200007831	4933407D05 Rik	NM_029748	AK016715	--
M200001259	Cnih	NM_009919	AF022811	CORNICHON HOMOLOG.
M200000413	Hdgf	NM_008231	BC021654	HEPATOMA-DERIVED GROWTH FACTOR (HDGF).
M200003736	Prdx4	NM_016764	U96746	PEROXIREDOXIN 4 (EC 1.11.1.-) (PRX-IV) (THIOREDOXIN PEROXIDASE A0372) (THIOREDOXIN-DEPENDENT PEROXIDE REDUCTASE A0372) (ANTIOXIDANT ENZYME AOE372).
M300003493	--	--	BC028899	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE LIKE 2 (EC 5.2.1.8) (PPIASE) (ROTAMASE) (CYCLOPHILIN-60) (CYCLOPHILIN-LIKE PROTEIN CYP-60).
M300020830	--	--	--	--
M200004428	0610016L08 Rik	NM_029787	BC032013	DIAPHORASE 1 (NADH).
M200006257	2610312E17 Rik	NM_027432	AK050391	--
M200009010	A1840044	NM_144895	BC022921	--
M300001264	1810036I24R ik	NM_026210	AK077277	--
M300013796	Shc1	NM_011368	U15784	SHC TRANSFORMING PROTEIN.
M300021114	9130413I22R ik	NM_026242	AB041651	--
M300018312	--	--	--	--
M300003187	--	--	--	--
M300001659	Kpna2	NM_010655	BC006720	IMPORTIN ALPHA-2 SUBUNIT (KARYOPHERIN ALPHA-2 SUBUNIT) (SRP1-ALPHA) (RAG COHORT PROTEIN 1) (PENDULIN) (PORE TARGETING COMPLEX 58 KDA SUBUNIT) (PTAC58) (IMPORTIN ALPHA P1).
M300011584	--	--	--	--
M300018684	Kpna2	NM_010655	BC006720	IMPORTIN ALPHA-2 SUBUNIT (KARYOPHERIN ALPHA-2 SUBUNIT) (SRP1-ALPHA) (RAG COHORT PROTEIN 1) (PENDULIN) (PORE TARGETING COMPLEX 58 KDA SUBUNIT) (PTAC58) (IMPORTIN ALPHA P1).
M300005759	Ube2v1	--	BC019372	SIMILAR TO UBIQUITIN-CONJUGATING ENZYME E2 VARIANT 1 (EC 6.3.2.19) (UBIQUITIN-PROTEIN LIGASE) (UBIQUITIN CARRIER PROTEIN).
M200014015	Lgals1	NM_008495	AK004298	GALECTIN-1 (BETA-GALACTOSIDE-BINDING LECTIN L-14-I) (LACTOSE-BINDING LECTIN 1) (S-LAC LECTIN 1) (GALAPTIN) (14 KDA LECTIN).
M200000746	Calr	NM_007591	M92988	CALRETICULIN PRECURSOR (CRP55) (CALREGULIN) (HACBP) (ERP60).

Female C57Bl6 day 7 200 Gy

M200004758	Blvrb	NM_144923	BC027279	BILIVERDIN REDUCTASE B (FLAVIN REDUCTASE (NADPH)).
M300003852	Trem11-pending	--	AK017256	--
M300007590	--	NM_172479	--	--
M300005240	Mgst3	NM_025569	BC029669	MICROSOMAL GLUTATHIONE S-TRANSFERASE 3.
M200000621	Gpc4	NM_008150	X83577	GLYPICAN-4 PRECURSOR (K-GLYPICAN).
M300006292	1810017F10 Rik	NM_025452	AK008935	BETA-CASEIN-LIKE.
M300004473	4833406P10 Rik	--	AF404774	ACTIN-BINDING LIM PROTEIN 1 MEDIUM ISOFORM.
M300005665	2010011I20Rik	NM_025912	BC016210	--
M200015276	Pep4	NM_008820	D82983	XAA-PRO DIPEPTIDASE (EC 3.4.13.9) (X-PRO DIPEPTIDASE) (PROLINE DIPEPTIDASE) (PROLIDASE) (IMIDODIPEPTIDASE) (PEPTIDASE 4).
M300000073	Myf5	NM_008656	X56182	MYOGENIC FACTOR MYF-5.
M300002998	Nisch	NM_022656	AF315344	NISCHARIN; IMIDAZOLINE RECEPTOR I-1-LIKE PROTEIN.
M300008241	1110005A05 Rik	NM_025372	AK003451	--
M300002598	--	--	AF206023	ANTI-MYOSIN IMMUNOGLOBULIN HEAVY CHAIN VARIABLE REGION (FRAGMENT).
M200004350	--	--	BC024401	SIMILAR TO DC12 PROTEIN.
M300007147	--	--	--	--
M200009417	Mt2	--	K02236	METALLOTHIONEIN-II (MT-II).
M300022215	--	--	--	--
M200014231	Supt16h	NM_033618	AF323667	SUPPRESSOR OF TY 16 HOMOLOG; SUPPRESSOR OF TY 16 HOMOLOG (S.CEREVISIAE).
M300016699	--	--	AK011630	--
M300015461	--	--	--	--
M300006903	--	NM_007624	--	CHROMOBX HOMOLOG 3 (DROSOPHILA HP1 GAMMA); HETEROCHROMATIN PROTEIN 1 GAMMA.
M300002502	Pnn	NM_008891	Y08701	PININ; DNA SEGMENT, CHR 12, ERATO DOI 512, EXPRESSED.
M200000746	Calr	NM_007591	M92988	CALRETICULIN PRECURSOR (CRP55) (CALREGULIN) (HACBP) (ERP60).
M200009655	Cct6a	NM_009838	AB022159	T-COMPLEX PROTEIN 1, ZETA SUBUNIT (TCP-1-ZETA) (CCT-ZETA) (CCT-ZETA- 1).
M300011584	--	--	--	--

Specificity of PB signatures

In addition to inter-individual variations (Whitney et al, Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)), human populations are heterogeneous with respect to health status and medical conditions. Therefore, it is critical to determine whether PB gene expression profiles of radiation response are specific to radiation exposure itself or whether these signatures are potentially confounded by other genotoxic stresses. The choice was made to compare the PB gene expression response to ionizing radiation exposure with that of gram-negative bacterial sepsis, since this syndrome can be expected to induce similar multiorgan toxicity as is observed following radiation injury (Wasalenko et al, Ann. Int. Med. 140:1037-1051 (2004), Mettler et al, N. Engl. J. Med. 346:1554-1561 (2002), Dainiak, Exp. Hematol. 30:513-528 (2002), Inoue et al, FASEB J. 20:533-535 (2006)). A pattern of gene expression could be identified which effectively distinguished female C57Bl6 mice treated with *Escherichia coli*-derived lipopolysaccharide (LPS), experiencing sepsis syndrome, from untreated female C57Bl6 mice (Figure 5A). Applying a leave-one-out cross-validation analysis, it was found that the PB signature for 50 cGy irradiation in C57Bl6 mice correctly predicted the status of all LPS-treated C57Bl6 mice as non-irradiated, suggesting robust specificity of the signature for low level (50 cGy) irradiation and sepsis syndrome (Figure 5B). The PB signatures for 200 cGy and 1000 cGy also correctly predicted the LPS-treated mice as non-irradiated, although these probabilities were less robust than the application of the 50 cGy signature (Figure 5B). The PB signature of LPS-treatment also correctly predicted the status of all irradiated mice as "non-LPS treated" (Figure 5B, right). These data indicate that the PB gene expression profiles of radiation response and bacterial sepsis are quite specific and able to distinguish

one condition from the other with a high level of accuracy. No overlap was observed between the genes which comprised the PB signature of LPS-sepsis and the PB signatures of radiation exposure in C57Bl6 mice (Table 5).

ble 5. Genes that distinguish LPS treatment in C57Bl6 mice. Operon Oligo ID can be queried in the OMAD database <http://omad.operon.com>)

Operon Oligo ID	Gene Symbol	RefSeq	Genbank	Description
1200003295	Saa3	NM_011315	M17792	SERUM AMYLOID A-3 PROTEIN PRECURSOR.
1300009870	Ccl12	NM_011331	AF065938	SMALL INDUCIBLE CYTOKINE A12 PRECURSOR (CCL12) (MONOCYTE CHEMOTACTIC PROTEIN 5) (MCP-5) (MCP-1 RELATED CHEMOKINE).
1300005418	Il1rn	NM_031167	S64082	INTERLEUKIN-1 RECEPTOR ANTAGONIST PROTEIN PRECURSOR (IL-1RA) (IL-1RN) (IRAP).
1200001838	Upp	NM_009477	D44464	URIDINE PHOSPHORYLASE (EC 2.4.2.3) (UDRPASE).
1200000053	Fcgr1	NM_010186	BC025535	HIGH AFFINITY IMMUNOGLOBULIN GAMMA FC RECEPTOR I PRECURSOR (FC-GAMMA RI) (FCRI) (IGG FC RECEPTOR I).
1200004157	9130009C22 Rik	NM_027835	AF374384	--
1300005305	Lcn2	--	X81627	NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN PRECURSOR (NGAL) (P25) (SV-40 INDUCED 24P3 PROTEIN) (LIPOCALIN 2).
1300006479	Bst1	NM_009763	D31788	ADP-RIBOSYL CYCLASE 2 PRECURSOR (EC 3.2.2.5) (CYCLIC ADP-RIBOSE HYDROLASE 2) (CADPR HYDROLASE 2) (BONE MARROW STROMAL ANTIGEN 1) (BST- 1) (BP-3 ALLOANTIGEN) (ANTIGEN BP3).
1200004765	Gbp2	NM_010260	AF077007	GUANYLATE NUCLEOTIDE BINDING PROTEIN 2.
1300005673	Zbp1	NM_021394	BC020033	Z-DNA BINDING PROTEIN 1 (TUMOR STROMA AND ACTIVATED MACROPHAGE PROTEIN DLM-1).
1300005674	Zbp1	NM_021394	BC020033	Z-DNA BINDING PROTEIN 1 (TUMOR STROMA AND ACTIVATED MACROPHAGE PROTEIN DLM-1).
1300001891	Gp49b	NM_013532	U05264	MAST CELL SURFACE GLYCOPROTEIN GP49B PRECURSOR.
1300005166	Ifi204	NM_008329	M31419	INTERFERON-ACTIVATABLE PROTEIN 204 (IFI-204) (INTERFERON-INDUCIBLE PROTEIN P204).
1200005576	Usp18	NM_011909	AF069502	UBL CARBOXYL-TERMINAL HYDROLASE 18 (EC 3.1.2.-) (UBL THIOLESTERASE 18) (ISG15-SPECIFIC PROCESSING PROTEASE) (43 KDA ISG15-SPECIFIC PROTEASE).
1300020771	--	--	--	--
1300011591	--	NM_172893	BC024579	--

1200007439	Gtpi-pending	NM_019440	AJ007972	INTERFERON-G INDUCED GTPASE.
1300012693	--	--	--	--
1300012210	--	--	--	--
1200014281	2010008K16R ik	NM_027320	BC008158	INTERFERON-INDUCED 35 KDA PROTEIN HOMOLOG (IFP 35).
1300009340	--	NM_145481	BC021340	--
1200004564	Nte	NM_015801	AF173829	NEUROPATHY TARGET ESTERASE; SWISS CHEESE.
1300000152	Araf	NM_009703	D00024	A-RAF PROTO-ONCOGENE SERINE/THREONINE- PROTEIN KINASE (EC 2.7.1.-).
1200006264	--	NM_176831	--	--
1300000077	D15Ert417e	NM_144811	BC021398	CHROMOBX PROTEIN HOMOLOG 6.

PB signatures of radiation and chemotherapy are specific in humans

In order to extend the analysis of PB signature specificity to humans, PB was collected from a population of healthy individuals (n=18), patients who had undergone total body irradiation as conditioning prior to hematopoietic stem cell transplantation (n=47) and patients who had undergone alkylator-based chemotherapy conditioning alone (n=41). RNA of sufficient quality was available from 18 healthy donor samples, 36 pre-irradiated patients, 34 post-irradiated patients, 36 pre-chemotherapy treatment patients and 32 post-chemotherapy patients (Table 6). A supervised binary regression analysis identified a metagene profile of 25 genes that distinguished the healthy individuals and the non-irradiated patients from the irradiated patients (Figure 6A). A leave-one-out cross validation analysis demonstrated that this PB predictor of human radiation response was 100% accurate in predicting the healthy individuals and the non-irradiated patients and 91% accurate at predicting the irradiated patients (Figure 6A).

Table 6. Donor Patient Characteristics

<u>Characteristic</u>	<u>Number</u>
<i>Samples analyzed</i>	n=18 healthy donors n=36 patients pre-radiotherapy n=34 patients post-radiotherapy n=36 patients pre-chemotherapy n=32 patients post-chemotherapy
<i>Patient/Donor Age</i>	47.9 years (mean)
<i>Diagnoses</i>	MDS/AML (n=23) ALL (n=8) Multiple myeloma (n=20) Non-Hodgkin's Lymphoma (n=20) Hodgkin's Disease (n=6) Myeloproliferative disorder (n=7) Scleroderma (n=3) Sickle cell disease (n=1)
<i>Prior radiotherapy</i>	n=15
<i>Prior chemotherapy</i>	n=82
<i>Transplantation type</i>	Non-myeloablative allogeneic/200 cGy (n=24) Myeloablative allogeneic/1350 cGy (n=15) Myeloablative autologous/1200 cGy (n=8) Chemotherapy allogeneic (n=19) Chemotherapy autologous (n=22)

Patients undergoing either TBI-based or chemotherapy-based conditioning followed by allogeneic or autologous stem cell transplantation were eligible for enrollment. PB samples were collected prior to and 6 hours following either 200 cGy total body irradiation (non-myeloablative conditioning) or the first fraction (150 cGy) of total body irradiation (myeloablative conditioning). MDS=myelodysplastic syndrome, AML=acute myelogenous leukemia, ALL=acute lymphocytic leukemia

In order to test the specificity of this PB signature of human radiation response, its accuracy was next tested in predicting the status of patients who had undergone chemotherapy treatment alone. This signature correctly predicted 89% of the non-irradiated, pre-chemotherapy patients as non-irradiated and 75% of the chemotherapy-treated patients as non-irradiated (Figure 6A). Interestingly, 2 of the post-chemotherapy patients had a prior history of total lymphoid irradiation and both of these were mispredicted as "irradiated", suggesting perhaps that a durable molecular response to radiation was evident in these patients. Considering the entire population, the overall accuracy of the PB predictor of radiation was 90%. Within the chemotherapy-treated patients, a PB signature could be identified that appeared to distinguish untreated patients from chemotherapy-treated patients (Figure 6B). A leave-one-out cross-validation analysis demonstrated that this PB signature of chemotherapy treatment was 81% accurate at distinguishing the untreated patients and 78% accurate at predicting the chemotherapy-treated patients (Figure 6B). Furthermore, the chemotherapy metagene profile demonstrated 100% accuracy in predicting the status of healthy individuals, 92% accuracy in predicting the non-irradiated patients, and 62% accuracy in predicting the PB samples from irradiated patients as not having received chemotherapy (Figure 6B). The overall accuracy of the PB predictor of chemotherapy-treatment was 81%. Interestingly, no overlapping genes were identified between the PB signature of radiation and the PB signature of chemotherapy treatment (Tables 7 and 8). It is also worth noting that all 12 of the post-irradiation patients whose status was mispredicted by the PB chemotherapy signature had received prior chemotherapy in the treatment of their underlying disease.

Table 7. Genes that distinguish radiation status in humans. Operon Oligo ID can be queried in the OMAD database (<http://omad.operon.com>)

Operon Oligo_ID	Gene Symbol	RefSeq	Genbank	Description
H200000088	XPC	NM_004628	X65024	DNA-REPAIR PROTEIN COMPLEMENTING XP-C CELLS (XERODERMA PIGMENTOSUM GROUP C COMPLEMENTING PROTEIN) (P125)
H200001266	--	NM_017792	AK000380	--
H200002100	--	NM_024556	BC001340	--
H200002529	--	NM_032324	AF416713	--
H200004865	--	NM_006828	AL834463	DJ467N11.1 PROTEIN
H200006009	GTF3A	NM_002097	U14134	TRANSCRIPTION FACTOR IIIA (FACTOR A) (TFIIIA)
H200006598	PCNA	NM_002592	BC000491	PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA) (CYCLIN)
H200008365	CDKN1A	NM_000389	BC013967	CYCLIN-DEPENDENT KINASE INHIBITOR 1 (P21) (CDK-INTERACTING PROTEIN 1) (MELANOMA DIFFERENTIATION ASSOCIATED PROTEIN 6) (MDA-6)
H200011100	PPM1D	NM_003620	BC033893	PROTEIN PHOSPHATASE 2C DELTA ISOFORM (PP2C-DELTA) (P53- INDUCED PROTEIN PHOSPHATASE 1) (PROTEIN PHOSPHATASE MAGNESIUM- DEPENDENT 1 DELTA)
H200011577	--	NM_018247	AK001718	--
H200014322	--	--	BC009552	CGI-203
H200014719	ACTA2	NM_001613	X60732	ACTIN, AORTIC SMOOTH MUSCLE (ALPHA-ACTIN 2)
H200016323	--	NM_152240	BC002896	P53 TARGET ZINC FINGER PROTEIN ISOFORM 1; ZINC FINGER PROTEIN WIG1; WIG-1/PAG608 PROTEIN
H200017549	TIMM8B	NM_012459	BC000711	MITOCHONDRIAL IMPORT INNER MEMBRANE TRANSLOCASE SUBUNIT TIM8 B (DEAFNESS DYSTONIA PROTEIN 2) (DDP-LIKE PROTEIN)
H300000421	--	NM_016399	BC002638	PROTEIN 15E1.1 (PROTEIN HSPC132)

<u>H300003103</u>	--	--	--	--
<u>H300003151</u>	<u>MOAP1</u>	<u>NM_022151</u>	<u>BC015044</u>	MODULATOR OF APOPTOSIS 1; MAP-1 PROTEIN; PARANEOPLASTIC ANTIGEN LIKE 4
<u>H300010830</u>	--	<u>NM_022767</u>	<u>BC005164</u>	--
<u>H300015667</u>	--	<u>NM_022767</u>	<u>BC005164</u>	--
<u>H300018970</u>	--	<u>NM_014454</u>	<u>AK001886</u>	SESTRIN 1 (P53-REGULATED PROTEIN PA26)
<u>H300019371</u>	<u>DDB2</u>	<u>NM_000107</u>	<u>BC000093</u>	DNA DAMAGE BINDING PROTEIN 2 (DAMAGE-SPECIFIC DNA BINDING PROTEIN 2) (DDB P48 SUBUNIT) (DDBB) (UV-DAMAGED DNA-BINDING PROTEIN 2) (UV-DDB 2)
<u>H300020184</u>	<u>C19orf2</u>	<u>NM_003796</u>	<u>AB006572</u>	RNA POLYMERASE II SUBUNIT 5-MEDIATING PROTEIN (RPB5-MEDIATING PROTEIN)
<u>H300020858</u>	<u>HNRPD</u>	<u>NM_005463</u>	<u>BC011714</u>	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN D-LIKE; A+U-RICH ELEMENT RNA BINDING FACTOR
<u>H300021118</u>	<u>BBC3</u>	<u>NM_014417</u>	<u>AF354655</u>	BCL2 BINDING COMPONENT 3; BCL-2 BINDING COMPONENT 3; PUMA/JFY1 PROTEIN; BCL-2 BINDING COMPONENT 3
<u>H300022025</u>	<u>BAX</u>	<u>NM_138763</u>	<u>U19599</u>	BAX PROTEIN, CYTOPLASMIC ISOFORM DELTA

Table 8. Genes that distinguish chemotherapy treatment in humans. Operon Oligo ID can be queried in the OMAD database (<http://omad.operon.com>)

Operon Oligo ID	Gene Symbol	RefSeq	Genbank	Description
00001454	FKBP5	NM_004117	U42031	FK506-BINDING PROTEIN 5 (EC 5.2.1.8) (PEPTIDYL-PROLYL CIS-TRANS ISOMERASE) (PPIASE) (ROTAMASE) (51 KDA FK506-BINDING PROTEIN) (FKBP- 51) (54 KDA PROGESTERONE RECEPTOR-ASSOCIATED IMMUNOPHILIN) (FKBP54) (P54) (FF1 ANTIGEN) (HSP90-BINDING IMMUNOPHILIN)
00002954	SAP30	NM_003864	BC016757	SIN3 ASSOCIATED POLYPEPTIDE P30; SIN3-ASSOCIATED POLYPEPTIDE, 30KD
00004993	SOCS1	NM_003745	AB000676	SUPPRESSOR OF CYTOKINE SIGNALING 1 (SOCS-1) (JAK-BINDING PROTEIN) (JAB) (STAT INDUCED STAT INHIBITOR 1) (SSI-1) (TEC-INTERACTING PROTEIN 3) (TIP-3)
00002479	CRAMP1L	--	AB037847	--
00020334	--	NM_006372	AY034482	NS1-ASSOCIATED PROTEIN 1
00002535	--	NM_018034	BC025315	--
00002231	UVRAG	NM_003369	AB012958	UV RADIATION RESISTANCE-ASSOCIATED GENE PROTEIN (P63)
00002230	--	NM_005475	AJ012793	LYMPHOCYTE SPECIFIC ADAPTER PROTEIN LNK (SIGNAL TRANSDUCTION PROTEIN LNK) (LYMPHOCYTE ADAPTER PROTEIN)
00001588	ASGR1	NM_001671	AB070933	ASIALOGLYCOPROTEIN RECEPTOR 1 (HEPATIC LECTIN H1) (ASGPR) (ASGP-R)
00001821	BLVRA	NM_000712	AC005189	BILIVERDIN REDUCTASE A PRECURSOR (EC 1.3.1.24) (BILIVERDIN-IX ALPHA- REDUCTASE)
00001397	RAI17	--	AB033050	--
00008401	TRAF3	NM_003300	U15637	TNF RECEPTOR ASSOCIATED FACTOR 3 (CD40 RECEPTOR ASSOCIATED FACTOR 1) (CRAF1) (CD40 BINDING PROTEIN) (CD40BP) (LMP1 ASSOCIATED PROTEIN) (LAP1) (CAP-1)
00022877	LILRB1	NM_006669	AF009221	LEUKOCYTE IMMUNOGLOBULIN-LIKE RECEPTOR, SUBFAMILY B (WITH TM AND ITIM DOMAINS), MEMBER 1; LEUKOCYTE IMMUNOGLOBULIN-LIKE RECEPTOR 1; CD85 ANTIGEN
00018428	BID	NM_001196	BC022072	BH3 INTERACTING DOMAIN DEATH AGONIST (BID)

00022441	--	--	AL360143	--
00014949	HMOX1	NM_002133	X14782	HEME OXYGENASE 1 (EC 1.14.99.3) (HO-1)
00006902	TIEG	NM_005655	AF050110	TRANSFORMING GROWTH FACTOR-BETA-INDUCIBLE EARLY GROWTH RESPONSE PROTEIN 1 (TGFB- INDUCIBLE EARLY GROWTH RESPONSE PROTEIN 1) (TIEG-1) (KRUEPPEL-LIKE FACTOR 10)
00001600	NOTCH2	NM_024408	U77493	NEUROGENIC LOCUS NOTCH HOMOLOG PROTEIN 2 PRECURSOR (NOTCH 2) (HN2)
00007970	ZFP36L1	NM_004926	BC018340	BUTYRATE RESPONSE FACTOR 1 (TIS11B PROTEIN) (EGF-RESPONSE FACTOR 1) (ERF-1)
00019724	IFI30	NM_006332	AF097362	GAMMA-INTERFERON INDUCIBLE LYSOSOMAL THIOL REDUCTASE PRECURSOR (GAMMA-INTERFERON- INDUCIBLE PROTEIN IP-30)
00004653	--	--	AB033073	--
00012785	WARS	NM_004184	X67928	TRYPTOPHANYL-TRNA SYNTHETASE (EC 6.1.1.2) (TRYPTOPHAN--TRNA LIGASE) (TRPRS) (IFP53) (HWRS)
00010704	CPVL	NM_031311	BC016838	SERINE CARBOXYPEPTIDASE VITELLOGENIC-LIKE
00017278	SCO2	NM_005138	AL021683	SCO2 PROTEIN HOMOLOG, MITOCHONDRIAL PRECURSOR
00005078	--	NM_006344	D50532	MACROPHAGE LECTIN 2 (CALCIUM DEPENDENT)

Summarizing, numerous studies now highlight the power of gene expression profiling to characterize the biological phenotype of complex diseases. The potential clinical utility of gene expression profiles has been shown in cancer research, in which the identification of patterns of gene expression within tumors has led to the characterization of tumor subtypes, prognostic categories and prediction of therapeutic response (Potti et al, N. Engl. J. Med. 355:570-580 (2006), Cheng et al, J. Clin. Oncol. 24:4594-4602 (2006), Potti et al, Nat. Med. 12:1294-1300 (2006), Nevins et al, Nat. Rev. Genet. 8:601-609 (2007), Alizadeh et al, Nature 403:503-511 (2000)). Beyond analysis of tumor tissues, it has also been suggested that gene expression profiling of the peripheral blood can provide indication of infections, cancer, heart disease, allograft rejection, environmental exposures and as a means of biological threat detection (Mandel et al, Lupus 15:451-456 (2006), Heller et al, Proc. Natl. Acad. Sci. USA 94:2150-2155 (1997), Edwards et al, Mol. Med. 13:40-58 (2007), Baird, Stroke 38:694-698 (2007), Rubins et al, Proc. Natl. Acad. Sci. USA 101:15190-15195 (2004), Martin et al, Proc. Natl. Acad. Sci. USA 98:2646-2651 (2001), Patino et al, Proc. Natl. Acad. Sci. USA 102:3423-3428 (2005), Lampe et al, Cancer Epidemiol. Biomarkers Prev. 13:445-453 (2004), Ramilo et al, Blood 109:2066-2077 (2007), Horwitz et al, Circulation 110:3815-3821 (2004), Lin et al, Clin. Chem. 49:1045-1049 (2003)). While the concept of PB cells as sentinels of disease is not new, it remains unclear whether PB gene expression profiles that have been associated with various conditions are specific for those diseases or rather reflect a common molecular response to a variety of genotoxic stresses. Given the dynamic nature of the cellular composition of PB blood (Whitney et al, Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)) and the complexity of cellular responses over time (Whitney et al, Proc. Natl.

Acad. Sci. USA 101:1896-1901 (2003)), the durability of PB signatures over time is also uncertain and could affect the diagnostic utility of this approach for public health screening.

A purpose of the studies described above was to address the capacity for PB gene expression profiles to distinguish an environmental exposure, in this case ionizing radiation, versus other medical conditions and to examine the impact of time, gender and genotype on the accuracy of these profiles. It was found that PB gene expression signatures can be identified which accurately predict irradiated from non-irradiated mice and distinguish different levels of radiation exposure, all within a heterogeneous population with respect to gender, genotype and time from exposure. These results suggest the potential for PB gene expression profiling to be applied successfully in the screening for an environmental exposure. Previous studies have indicated that inter-individual variation in gene expression occurs within healthy individuals (Whitney et al, Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)) and may therefore limit the accuracy of PB gene expression profiling to detect diseases or exposures. The results provided here demonstrate that the environmental exposure tested here, ionizing radiation, induced a pronounced and characteristic alteration in PB gene expression such that a PB expression profile was highly predictive of radiation status in a population with variable gender, genotype and time of analysis. From a practical standpoint, these data suggest the potential utility of this approach for biodosimetric screening of a heterogeneous human population in the event of a purposeful or accidental radiological or nuclear event (Wasalenko et al, Ann. Int. Med. 140:1037-1051 (2004), Mettler et al, N. Engl. J. Med. 346:1554-1561 (2002), Dainiak, Exp. Hematol. 30:513-528 (2002)).

This study revealed that sex differences can impact the accuracy of this approach, particularly in distinguishing mice exposed to lower dose irradiation from non-irradiated controls. These results imply that aspects of the PB response to ionizing radiation are specified by sex-associated genes. Whitney et al (Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)) previously showed that sex differences were associated with variation in PB autosomal gene expression in healthy individuals. The instant study suggests that sex differences may contribute to characteristically distinct PB molecular responses to environmental stress (radiation) and the accuracy of PB gene expression profiling for medical screening can be affected by sex. These sex-related differences in PB response to ionizing radiation are perhaps illustrated by the fact that only 2 genes overlapped between the male and female PB signatures of 50 cGy (Ccng1 and Dda3).

Interestingly, differences in genotype did not significantly impact the accuracy of the PB gene expression signatures to distinguish radiation response such that PB signatures from C57Bl6 mice displayed 100% accuracy in predicting the status of BALB/c mice and vice versa. This observation demonstrates that, while genotype differences can account for some variation in PB gene expression (Whitney et al, Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)), the alterations in PB gene expression induced by 3 different levels of radiation exposure are such that PB expression profiling is highly accurate in distinguishing all irradiated mice across different genotypes. Very few genes were found in common between the 2 strains of mice at each level of radiation exposure, indicating that diverse sets of genes contribute to the PB response to radiation and that unique sets of genes can be identified which are predictive of radiation response.

The time of PB collection following radiation exposure had no significant impact on the accuracy of PB signatures to predict radiation status or distinguish different levels of exposure. First, the accuracy of PB signatures to predict radiation status and distinguish different levels of radiation exposure did not decay over time. Second, when we applied a PB signature from a single time point (6 hrs) against PB samples collected from mice at other time points (24 hr and 7 days), the accuracy of the prediction remained 100% in all cases. Therefore, time as a single variable did not lessen the accuracy of this approach to distinguish irradiated from non-irradiated animals. However, the content of the genes which comprised the PB signatures changed significantly as a function of time and <20% of the genes overlapped between the PB signatures of radiation at 6 hr, 24 hr, and 7 days. Taken together, these data indicate that PB predictors of radiation response do change over time, but PB signatures can continuously be identified through 7 days that are highly accurate at predicting radiation status and distinguishing different levels of radiation exposure. From a practical perspective, these results suggest that the application of a single reference set of "radiation response" genes would be unlikely to provide the most sensitive screen for radiation exposure over time. Conversely, reference lists of PB genes that are specific for different time points could be applied in the screening for radiation exposure provided that the time of exposure was known.

A critical question to be addressed in the development of PB gene expression profiling to detect medical conditions or exposures is the specificity of PB gene expression changes in response to genotoxic stresses. The PB signatures of 3 different doses of radiation displayed 100% accuracy in identifying septic animals as non-irradiated and the PB signature of sepsis was also 100% accurate in identifying irradiated mice

as non-septic. These results demonstrate specificity in the PB responses to ionizing radiation and sepsis. These data also provide *in vivo* validation of a prior report by Boldrick et al (Proc. Natl. Acad. Sci. USA 99:972-977 (2002)) in which human PB mononuclear cells were found to have a stereotypic response to LPS exposure *in vitro* and specific alterations in gene expression were observed in response to different strains of bacteria (Boldrick et al, Proc. Natl. Acad. Sci. USA 99:972-977 (2002)). Ramilo et al. also recently reported that distinct patterns of PB gene expression can be identified among patients with different bacterial infections (Ramilo et al, Blood 109:2066-2077 (2007)). No genes were found to be in common between the PB signatures of radiation exposure and the PB signature of gram negative sepsis. Taken together, the results demonstrate that the *in vivo* PB molecular responses to ionizing radiation and bacterial sepsis are quite distinct and can be utilized to distinguish one condition from the other with a high level of accuracy.

The analyses of expression signatures in human patients demonstrated that it is possible to utilize PB gene expression profiles to distinguish individuals who have been exposed to an environmental hazard, ionizing radiation, within a heterogeneous human population with a high level of accuracy. It will be important to further test the accuracy of this PB predictor of human radiation exposure in a human population exposed to lower dose irradiation (e.g. 0.1 – 1 cGy), as might be expected via occupational exposures (e.g. radiology technicians, nuclear power plant workers) (Seierstad et al, Radiat. Prot. Dosimetry 123:246-249 (2007), Moore et al, Radiat. Res. 148:463-475 (1997), Einstein et al, Circulation 116:1290-1305 (2007)). A potential pitfall in the clinical application of PB gene expression profiling would be that variations in PB gene expression in people would be such that it might be difficult to

distinguish the effects of a given exposure or medical condition from expected background alterations in gene expression (Whitney et al, Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)). However, Whitney et al (Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)) showed that the alterations in PB gene expression observed in patients with lymphoma or bacterial infection was significantly greater than the relatively narrow variation observed in healthy individuals (Whitney et al, Proc. Natl. Acad. Sci. USA 101:1896-1901 (2003)). This study confirms that PB gene expression profiles can be successfully applied to detect a specific exposure in a heterogeneous human population and that inter-individual differences in PB gene expression do not significantly confound the utility of this approach.

It was also shown that unique PB gene expression profiles can be identified which distinguish chemotherapy-treated patients versus patients who had not received chemotherapy with an overall accuracy of 81% and 78%, respectively. Similar to the PB signature of radiation, the PB signature of chemotherapy demonstrated accuracy and specificity in distinguishing healthy individuals and pre-irradiated patients (100% and 92% accuracy, respectively). However, the accuracy of the PB signature of chemotherapy was more limited when tested against patients who received radiation conditioning (62%). This observation provides the basis for further investigation as to which families of genes may be represented in both the PB molecular response to radiation and chemotherapy. However, since all 12 of the post-irradiation patients whose status was mispredicted by the PB chemotherapy signature had received combination chemotherapy within the prior year, the true specificity of this PB signature of chemotherapy cannot be addressed via this comparison. Additional patients are currently being enrolled to this

study who have not undergone prior chemotherapy to further test the specificity of a PB metagene of chemotherapy treatment.

Peripheral blood is a readily accessible source of tissue which has the potential to provide a window to the presence of disease or exposures. Early studies applying PB gene expression analysis have demonstrated that this approach is sensitive for the detection of patterns of gene expression in association with a variety of medical conditions (Mandel et al, *Lupus* 15:451-456 (2006), Heller et al, *Proc. Natl. Acad. Sci. USA* 94:2150-2155 (1997), Edwards et al, *Mol. Med.* 13:40-58 (2007), Baird, *Stroke* 38:694-698 (2007), Rubins et al, *Proc. Natl. Acad. Sci. USA* 101:15190-15195 (2004), Martin et al, *Proc. Natl. Acad. Sci. USA* 98:2646-2651 (2001), Patino et al, *Proc. Natl. Acad. Sci. USA* 102:3423-3428 (2005), Lampe et al, *Cancer Epidemiol. Biomarkers Prev.* 13:445-453 (2004), Ramilo et al, *Blood* 109:2066-2077 (2007), Whitney et al, *Proc. Natl. Acad. Sci. USA* 101:1896-1901 (2003), Dressman et al, *PLoS Med.* 4:690-701 (2007)). It remains to be determined whether PB gene expression profiles can be successfully applied in medical practice or public health screening for the early detection of specific diseases or environmental exposures. The present results demonstrate that PB gene expression profiles can be identified in mice and humans which are specific, accurate over time, and not confounded by inter-individual differences.

EXAMPLE 2

Experimental Details:

Gene expression in peripheral blood was measured with the Affymetrix mouse 430A 2.0 microarray and Affymetrix human U133A 2.0

microarray. Because there is interest in creating predictors that are consistent for all model systems, the gene list was filtered to include only those genes with mouse–human analogs. For the results presented, analogs were mapped using Chip Comparer (Yao G. Chip comparer. 2005. <http://chipcomparer.genome.duke.edu> (accessed October 3, 2011)), though results were similar using the approach of matching gene names from the Affymetrix annotation files. Annotation mapping resulted in 9150 genes with matching analogs in both mouse and human microarrays.

In order to assess the level of concordant information among mouse, human *ex vivo*, and human TBI, correlations between each gene and known radiation exposure level (nonparametric Kendall correlation) were tested. This procedure resulted in a set of correlations and p-values for each gene in each of the three model systems. If genes are behaving consistently in response to radiation, then general agreement in these correlations is expected. There are six time points for the mouse study and two for the human *ex vivo* study. Because it is not known how closely aligned the temporal responses of mice and humans are, the level of agreement between these correlation values was examined for all possible pairings of times points. In addition, all data was tested without regard to time. The highest level of agreement is from comparing human TBI to 24-h human *ex vivo*. The highest level of agreement between mouse and human TBI is at 6 h in the mice. In general, there is much higher agreement between human TBI and human *ex vivo* data sets than there is between mouse and either human data set. It is difficult to determine whether this is caused by fundamental differences in the responses of mice and humans to radiation exposure or caused by difficulties in mapping mouse–human orthologs.

Fig. 8 shows a plot of correlation between gene expression levels and known doses. Genes showing significant positive correlation (p-value < .01 after Bonferroni correction 9150 simultaneous tests) for both human TBI and human *ex vivo* are in the top right box, and those showing significant negative correlation are in the bottom left box. There is a statistically significant level of agreement between these correlation levels (tested by comparing ranks with Kendall correlation). However, there are also a number of genes that show somewhat discordant information. For example, there are two genes in the bottom right box, which represent significant (Bonferroni corrected) positive correlation between gene expression and dose in human TBI patients but significant negative correlation between gene expression and dose in human *ex vivo*. Mouse correlation levels are indicated by the color and size of the spots, with larger spots indicating higher significance, brighter red indicating increased positive correlation, and brighter green indicating increased negative correlation. In general, if genes are reacting to radiation exposure similarly in both mouse and human, points in the upper right are expected to be red and points in the lower left to be green. Again, while there is general agreement, there are individual genes that show significantly divergent results.

Model building was restricted to the 169 genes with absolute gene-dose correlation greater than 0.2 in all three of the model systems. Because there is interest in a limited list of genes for an eventual diagnostic, use was made of a variable-selection prior distribution on the linear regression coefficients to limit the number of genes in the model. There are many resultant models that are consistent with the data. Therefore, model averaging was used to control for uncertainty in the choice of inclusion variables.

Results

A single biosignature has been built that stratifies radiation-exposed samples from three model systems by dose. The model systems used were mouse C57Bl6, human *ex vivo*, and hospitalized patients undergoing total body irradiation (TBI) in the course of therapy. The classifier uses the same genes and gene weights for samples from any of the model systems and does not include interaction effects between gene and model system. Fig. 7 shows the predictive accuracy of the classifier, using leave-one-out cross-validation, with the samples stratified by model system, dose, and time. The signature generally orders samples correctly by exposure though model estimates of exposure are low for both human data sets. This may represent differing fold changes in these genes between humans and mice, or it may be a batch effect from the use of different Affymetrix arrays.

In addition to the generation of a biosignature, it was possible to use the gene-expression measurements to test for concordant differential expression in response to radiation among three model systems. While there is some evidence of concordant regulation of genes in the presence of radiation in the three systems, individual genes that are strongly associated with radiation exposure in all three systems are the exception rather than the rule. That being the case, it is concluded that, while it is believed that a biodosimeter has been constructed that will function in an otherwise healthy human population, it is also suspected that any such biodosimeter will be underperforming when compared to one that is trained on data generated from the population for which it is designed. Because such data are impossible to obtain, it is proposed that a full solution to the challenge of biodosimetry will involve a “best guess”

biodosimeter based on available model systems together with a clear technique for incremental improvements in the field based on new training data as such data become available.

In summary, in order to obtain an exhaustive list of possible predictors of radiation dose response, three steps are iteratively repeated: 1) generate models from a candidate list of biomarkers using variable selection, 2) identify the genes in this model that account for 90% of model variability, and 3) flag these genes as important and remove them from the candidate list. This results in a collection of models, each with mildly lower accuracy than the previous. By visual inspection of each model, it is determined that accuracy falls off after model five, so all subsequent models are excluded. Plots of each of the top five models as well as the genes included in those models are included in Fig. 9.

While the models perform well in all three systems (mouse, human *ex vivo* and human TBI), all of the data used to build these models is based on Affymetrix microarrays. As such, it is expected that these models would perform well in stratifying radiation exposure in other model systems if the data for those systems was generated by Affymetrix microarray. However, because of consistency and cost, these arrays may not be optimal candidates for a field device. The genes set forth in Table 9 (see also Fig. 10) are expected to be suitable for use in a CLPA-CE device. Because of known issues with translation of genes between platforms, all of the genes in the regression models may not perform well after translation. Therefore, a selection of genes for this purpose is made based on their correlation with radiation dose in each of the model systems. Correlation in the human systems is weighed more heavily than mouse because it is assumed that these are more representative of response to radiation in an otherwise healthy human population. A list of

genes for this purpose, as well as plots showing the expression of those genes across all of the samples, is included in Fig. 10. Table 9 includes this gene list along with each of the model gene lists.

TABLE 9

mouse probe	human probe	corr TBI	corr ex vivo	corr mouse	publiCID	gene title (gene symbol)
1424638_at	202284_s_at	0.619	0.66193	0.62728	AK007630	cyclin-dependent kinase inhibitor 1A (P21) (Cdkn1a)
1449002_at	218634_at	0.541	0.67746	0.59173	NM_013750	pleckstrin homology-like domain, family A, member 3 (Phlda3)
1427005_at	201939_at	0.613	0.49072	0.45095	BM234765	polo-like kinase 2 (Drosophila) (Plk2)
1421744_at	207426_s_at	0.522	0.70652	0.28324	NM_009452	tumor necrosis factor (ligand) superfamily, member 4 (Tnfsf4)
1423315_at	211692_s_at	0.493	0.61455	0.36414	AW489168	BCL2 binding component 3 (Bbc3)
1416837_at	211833_s_at	0.467	0.54806	0.37976	BC018228	BCL2-associated X protein (Bax)
1427718_a_at	217373_x_at	0.388	0.67507	0.31838	X58876	transformed mouse 3T3 cell double minute 2 (Mdm2)
1429582_at	212993_at	0.357	0.56876	0.42769	BB360604	nucleus accumbens associated 2, BEN and BTB (POZ) domain containing (Nacc2)
1448511_at	204960_at	-0.37	-0.50824	-0.46252	NM_016933	protein tyrosine phosphatase, receptor type, C polypeptide-associated protein (Ptpca)
1452389_at	206150_at	-0.417	-0.43777	-0.45949	L24495	CD27 antigen (Cd27)
1460251_at	216252_x_at	0.367	0.59783	0.29051	NM_007987	Fas (TNF receptor superfamily member 6) (Fas)
1418751_at	205484_at	-0.403	-0.40831	-0.48322	NM_019436	suppression inducing transmembrane adaptor 1 (Sit1)
1425398_at	208579_x_at	0.388	0.5393	0.31863	BC011440	H2b histone family member /// predicted gene, OTTMUSG000000013203 (LOC665622 /// RP23-38E20.1)
1441342_at	211478_s_at	-0.432	-0.34221	-0.49455	BQ030854	dipeptidylpeptidase 4 (Dpp4)
1448861_at	204352_at	-0.317	-0.46285	-0.51973	NM_011633	TNF receptor-associated factor 5 (Traf5)
1421098_at	220059_at	-0.231	-0.48356	-0.58221	NM_019992	similar to stem cell adaptor protein STAP-1 /// signal transducing adaptor family memt (LOC10047840 /// Stap1)
1450925_a_at	218007_s_at	0.263	0.65914	0.24337	BB836796	ribosomal protein S27-like (Rps27l)
1416957_at	205267_at	-0.325	-0.43936	-0.43535	NM_011136	POU domain, class 2, associating factor 1 (Pou2af1)
1448500_a_at	219541_at	-0.369	-0.40751	-0.39013	NM_023684	Lck interacting transmembrane adaptor 1 (Lime1)
1429319_at	204951_at	-0.417	-0.21184	-0.58414	BM243660	ras homolog gene family, member H (RhoH)
1422921_at	220068_at	-0.216	-0.41069	-0.60374	NM_009514	pre-B lymphocyte gene 3 (Vpreb3)
1418472_at	206030_at	0.359	0.44159	0.26641	BC024934	Aspartoacylase (Aspa)
1417516_at	209383_at	0.475	0.22834	0.35319	NM_007837	DNA-damage inducible transcript 3 (Ddit3)
1460407_at	205861_at	-0.368	-0.28408	-0.4763	BM244106	Spi-B transcription factor (Spi-1/PU.1 related) (Spib)
1418830_at	205049_s_at	-0.356	-0.3458	-0.40654	NM_007655	CD79A antigen (immunoglobulin-associated alpha) /// similar to CD79A antigen (immunoglobulin-associated alpha) (Cd79a /// LOC100047815)
1453573_at	214472_at	0.371	0.40432	0.2737	BB088582	histone cluster 1, H3d (Hist1h3d)
1424524_at	218627_at	0.428	0.33067	0.26056	BC021433	RIKEN cDNA 1200002N14 gene (1200002N14Rik)
1460702_at	218403_at	0.228	0.63047	0.21169	AK007514	TP53 regulated inhibitor of apoptosis 1 (Triap1)
1427844_a_at	212501_at	0.43	0.21759	0.41959	AB012278	CCAAT/enhancer binding protein (C/EBP), beta (Cebpb)
1452469_a_at	209427_at	0.264	0.50848	0.3136	BF578669	Smoothelin (Smtn)

Accession	E-value	Score	Identity (%)	Description
U00096.1	0.408	204436_at	0.4151	A049040 pleckstrin homology domain containing, family O member 2 (Plekho2)
U00097.1	-0.373	201853_s_at	-0.35374	NM_023117 cell division cycle 25 homolog B (S. pombe) (Cdc25b)
U00098.1	-0.363	215967_s_at	-0.43435	NM_008534 lymphocyte antigen 9 (Ly9)
U00099.1	-0.368	204891_s_at	-0.37666	BC011474 lymphocyte protein tyrosine kinase (Lck)
U00100.1	0.425	202891_at	0.33329	BE199280 death effector domain-containing (Deed)
U00101.1	-0.207	219498_s_at	-0.40074	BB772866 B-cell CLL/lymphoma 11A (zinc finger protein) (Bcl11a)
U00102.1	0.417	215407_s_at	0.21102	NM_019514 astrotactin 2 (Astn2)
U00103.1	0.295	212864_at	0.35025	BM214378 CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 2 (Cds2)
U00104.1	0.382	219921_s_at	0.4579	BC016533 dedicator of cytokinesis 5 (Dock5)
U00105.1	-0.371	208644_at	-0.44513	AF126717 poly (ADP-ribose) polymerase family, member 1 (Parp1)
U00106.1	-0.339	201345_s_at	-0.3962	NM_019912 ubiquitin-conjugating enzyme E2D 2 (Ube2d2)
U00107.1	-0.313	219067_s_at	-0.2363	AK010349 non-SMC element 4 homolog A (S. cerevisiae) (Nsmce4a)
U00108.1	-0.387	214339_s_at	-0.28209	BB546619 mitogen-activated protein kinase kinase kinase 1 (Map4k1)
U00109.1	-0.301	34210_at	-0.44732	NM_013706 CD52 antigen (Cd52)
U00110.1	-0.31	266_s_at	-0.39079	NM_009846 CD24a antigen (Cd24a)
U00111.1	-0.274	203362_s_at	-0.30183	NM_019499 MAD2 mitotic arrest deficient-like 1 (yeast) (Mad2l1)
U00112.1	0.35	211974_x_at	0.24753	NM_009035 Recombination signal binding protein for immunoglobulin kappa J region (Rbpj)
U00113.1	0.458	209882_at	0.24657	AK018785 Ras-like without CAAX 1 (Rit1)
U00114.1	-0.254	221290_s_at	-0.31474	NM_023431 melanoma associated antigen (mutated) 1 (Mum1)
U00115.1	-0.373	202479_s_at	-0.33982	BB354684 tribbles homolog 2 (Drosophila) (Trib2)
U00116.1	0.263	201835_s_at	0.43578	AF108215 protein kinase, AMP-activated, beta 1 non-catalytic subunit (Prkab1)
U00117.1	-0.332	219528_s_at	-0.25382	NM_021399 B-cell leukemia/lymphoma 11B (Bcl11b)
U00118.1	0.264	214838_at	0.38334	BC017549 SFT2 domain containing 2 (Sft2d2)
U00119.1	-0.312	221011_s_at	-0.32929	BC026827 limb-bud and heart (Lbh)
U00120.1	0.224	203045_at	0.42673	NM_013610 ninjurin 1 (Ninj1)
U00121.1	0.263	204714_s_at	0.38486	NM_007976 coagulation factor V (F5)
U00122.1	0.349	32069_at	0.24506	NM_030563 NEDD4 binding protein 1 (N4bp1)
U00123.1	-0.276	204642_at	-0.23591	BB133079 sphingosine-1-phosphate receptor 1 (S1pr1)
U00124.1	-0.381	201529_s_at	-0.20445	BM244983 replication protein A1 (Rpa1)
U00125.1	-0.279	204023_at	-0.20604	BC003335 replication factor C (activator 1) 4 (Rfc4)
U00126.1	-0.264	205053_at	-0.26139	J04620 DNA primase, p49 subunit (Prim1)
U00127.1	0.229	219584_at	0.31401	NM_134102 phospholipase A1 member A (Pla1a)
U00128.1	0.355	208438_s_at	0.24108	NM_010208 Gardner-Rasheed feline sarcoma viral (Fgr) oncogene homolog (Fgr)
U00129.1	0.265	220075_s_at	0.28991	AF462391 mucin-like protocadherin (Mupcdh)

Protein ID	Protein Name	Accession Number	Score	E-value	Description
1433639_at	family with sequence similarity 117, member A (Fam117a)	AU0548096	-0.31355	-0.207	family with sequence similarity 117, member A (Fam117a)
1424159_at	family with sequence similarity 134, member C (Fam134c)	BC016089	-0.36451	-0.237	family with sequence similarity 134, member C (Fam134c)
1417313_at	Lsm7 homolog, U6 small nuclear RNA associated (S. cerevisiae) (Lsm7)	NM_025349	-0.23431	-0.27	LSM7 homolog, U6 small nuclear RNA associated (S. cerevisiae) (Lsm7)
1424595_at	F11 receptor (F11r)	BC021876	0.26457	0.212	F11 receptor (F11r)
1460286_at	septin 6 (septin-6)	NM_019942	-0.27134	-0.236	septin 6 (septin-6)
1416543_at	nuclear factor, erythroid derived 2, like 2 (Nfe2l2)	NM_010902	0.26059	0.292	nuclear factor, erythroid derived 2, like 2 (Nfe2l2)
1424305_at	immunoglobulin joining chain (Igj)	BC006026	-0.23869	-0.246	immunoglobulin joining chain (IgJ)
1433702_at	endoplasmic reticulum metalloproteinase 1 (Ermp1)	B1663634	-0.26059	-0.246	endoplasmic reticulum metalloproteinase 1 (Ermp1)
1449897_a_at	mature T-cell proliferation 1 (Mtcp1)	NM_010839	-0.23971	-0.24	mature T-cell proliferation 1 (Mtcp1)
1460644_at	branched chain ketoacid dehydrogenase kinase (Bckdk)	NM_009739	0.2805	0.243	branched chain ketoacid dehydrogenase kinase (Bckdk)
1428029_a_at	H2A histone family, member V (H2afv)	BC028539	-0.22078	-0.29	H2A histone family, member V (H2afv)
1427468_at	protein phosphatase 3, catalytic subunit, beta isoform (Ppp3cb)	M81483	-0.22555	-0.21	protein phosphatase 3, catalytic subunit, beta isoform (Ppp3cb)
1416772_at	carnitine palmitoyltransferase 2 (Cpt2)	NM_009949	0.21761	0.247	carnitine palmitoyltransferase 2 (Cpt2)
1451141_at	methyltransferase like 8 (Mettl8)	BC004636	-0.21441	-0.227	methyltransferase like 8 (Mettl8)
1419240_at	testis expressed gene 14 (Tex14)	NM_031386	0.28647	0.211	testis expressed gene 14 (Tex14)
1448560_at	BH3 interacting domain death agonist (Bid)	NM_007544	0.216	0.278	BH3 interacting domain death agonist (Bid)
1417333_at	RAS p21 protein activator 4 (Rasa4)	NM_133914	-0.20206	-0.249	RAS p21 protein activator 4 (Rasa4)
1419488_at	TNFAIP3 interacting protein 2 (Tnip2)	NM_139064	0.26855	0.231	TNFAIP3 interacting protein 2 (Tnip2)
1421302_a_at	guanine nucleotide binding protein, alpha 15 (Gna15)	NM_010304	0.21202	0.203	guanine nucleotide binding protein, alpha 15 (Gna15)
1449584_at	diacylglycerol kinase, gamma (Dgk)	NM_138650	0.22954	0.214	diacylglycerol kinase, gamma (Dgk)
1426025_s_at	lysosomal-associated protein transmembrane 5 (Laptm5)	U29539	0.23818	0.203	lysosomal-associated protein transmembrane 5 (Laptm5)
1433878_at	mitochondrial ribosomal protein S26 (Mrps26)	A1648866	-0.21958	-0.204	mitochondrial ribosomal protein S26 (Mrps26)
1448383_at	matrix metalloproteinase 14 (membrane-inserted) (Mimp14)	NM_008608	0.22396	0.209	matrix metalloproteinase 14 (membrane-inserted) (Mimp14)
1428067_at	RAS-like, family 12 (Rasl12)	AK014511	0.20809	0.201	RAS-like, family 12 (Rasl12)

*
*
*

All documents and other information sources cited above are hereby incorporated in their entirety by reference.

WHAT IS CLAIMED IS:

1. A method of identifying an individual exposed to irradiation comprising:

- i) obtaining a blood sample from said individual,
- ii) isolating mononuclear cells from said blood sample,
- iii) extracting RNA from said mononuclear cells,
- iv) analyzing said RNA for expression of response genes set

forth in Table 11, or a subset thereof of at least 5 genes,

wherein an individual who has an expression profile of the response genes set forth in Table 11, or said subset thereof, different from the expression profile of said response genes, or subset thereof, of a non-exposed control individual is an individual who has been exposed to radiation.

2. The method according to claim 1 wherein said individual is a human.

3. The method according to claim 1 wherein said blood sample is a peripheral blood sample.

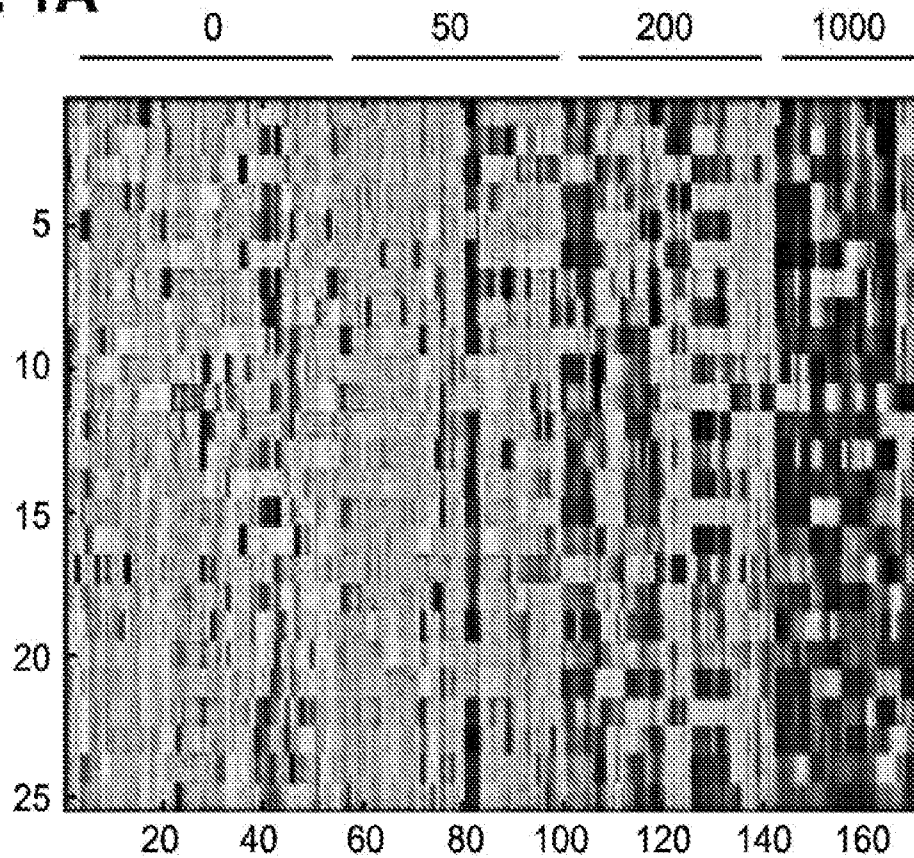
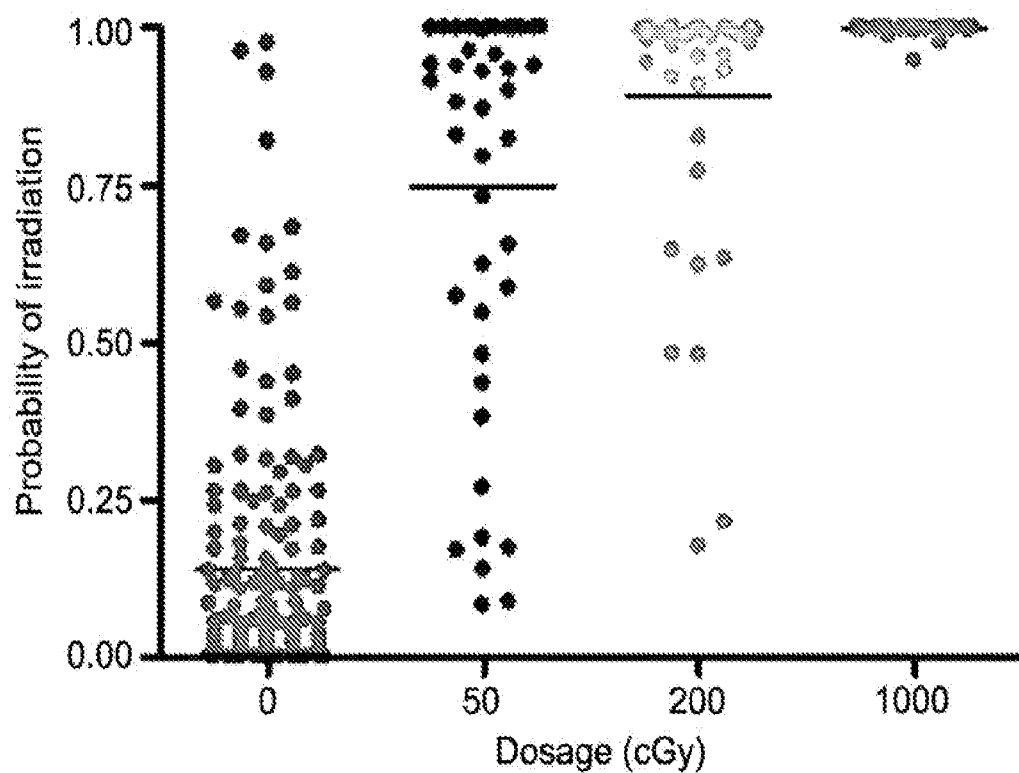
4. The method according to claim 1 wherein said blood sample is obtained within 7 days of exposure of said individual to radiation.

5. The method according to claim 1 wherein said blood sample is obtained at about 6 hours after exposure of said individual to radiation.

6. The method according to claim 1 wherein said subset comprises at least 10 of said response genes set forth in Table 11.

7. The method according to claim 1 wherein said extracted RNA resulting from step (iii) is amplified.
8. The method according to claim 1 wherein step (iv) is effected using a microarray technique.
9. A kit comprising an array probe of nucleic acids wherein the response genes set forth in Table 11, or subset thereof comprising at least 5 response genes, are represented.
10. A kit comprising primers specific for at least 5 of the response genes set forth in Table 11.
11. The kit according to claim 9 wherein said kit further comprises a NTPs or rNTPs.

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Fig. 1A**Fig. 1B**

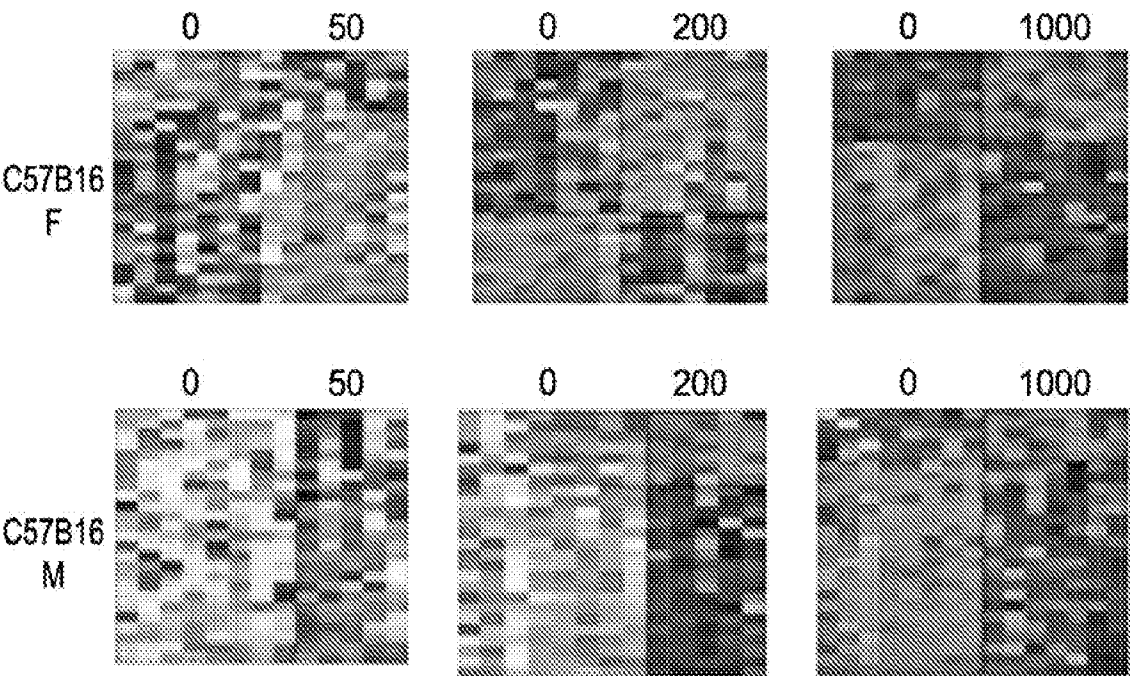


Fig. 2A

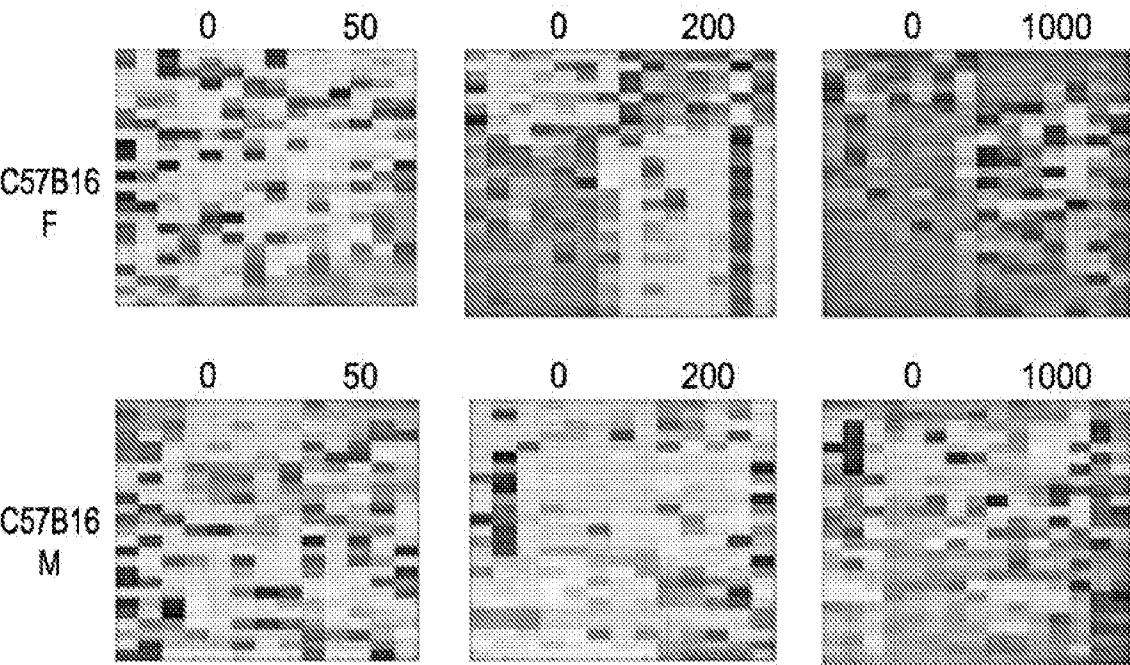


Fig. 2B

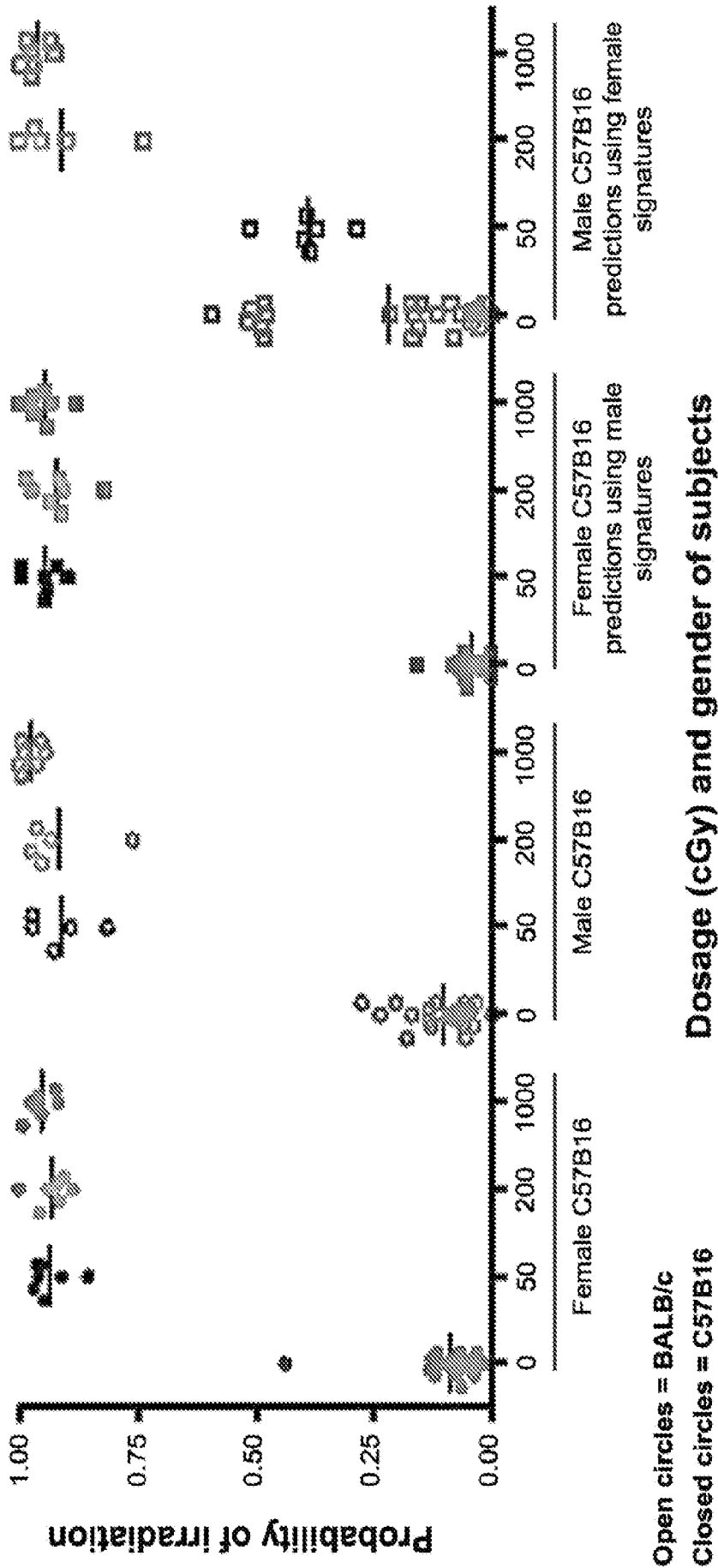


Fig. 2C

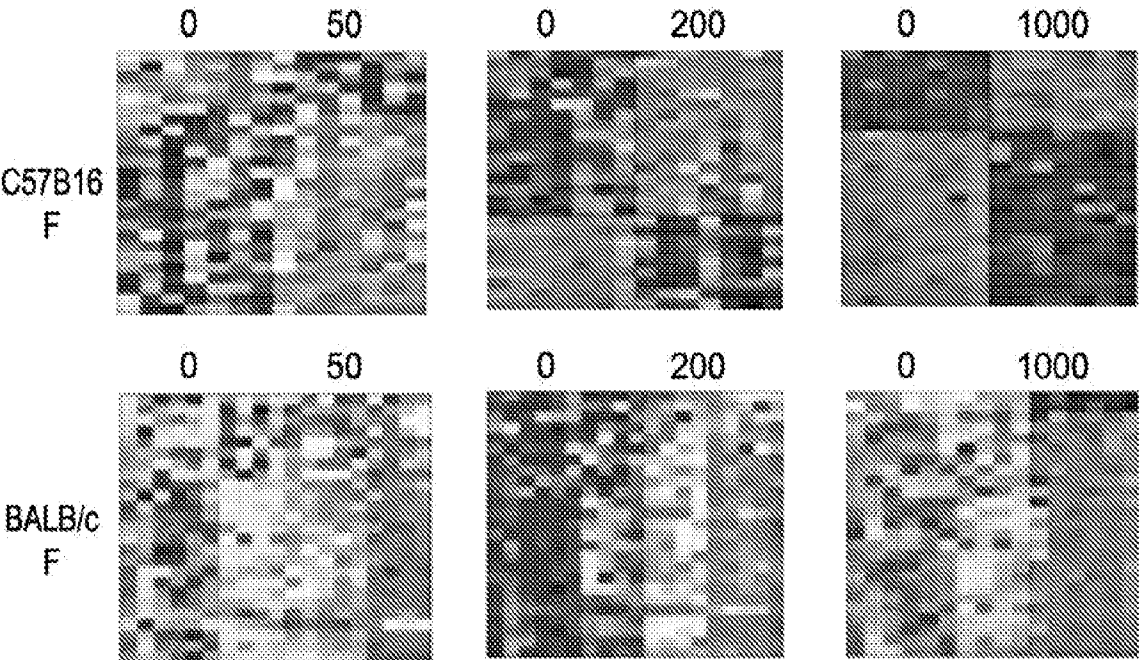


Fig. 3A

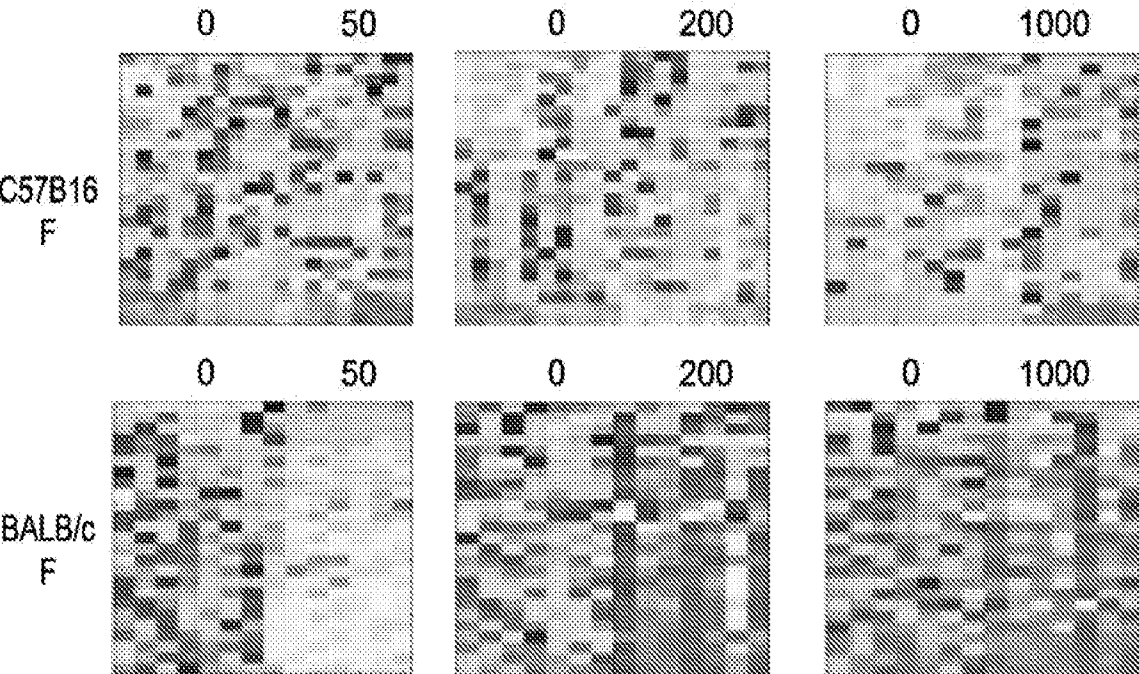


Fig. 3B

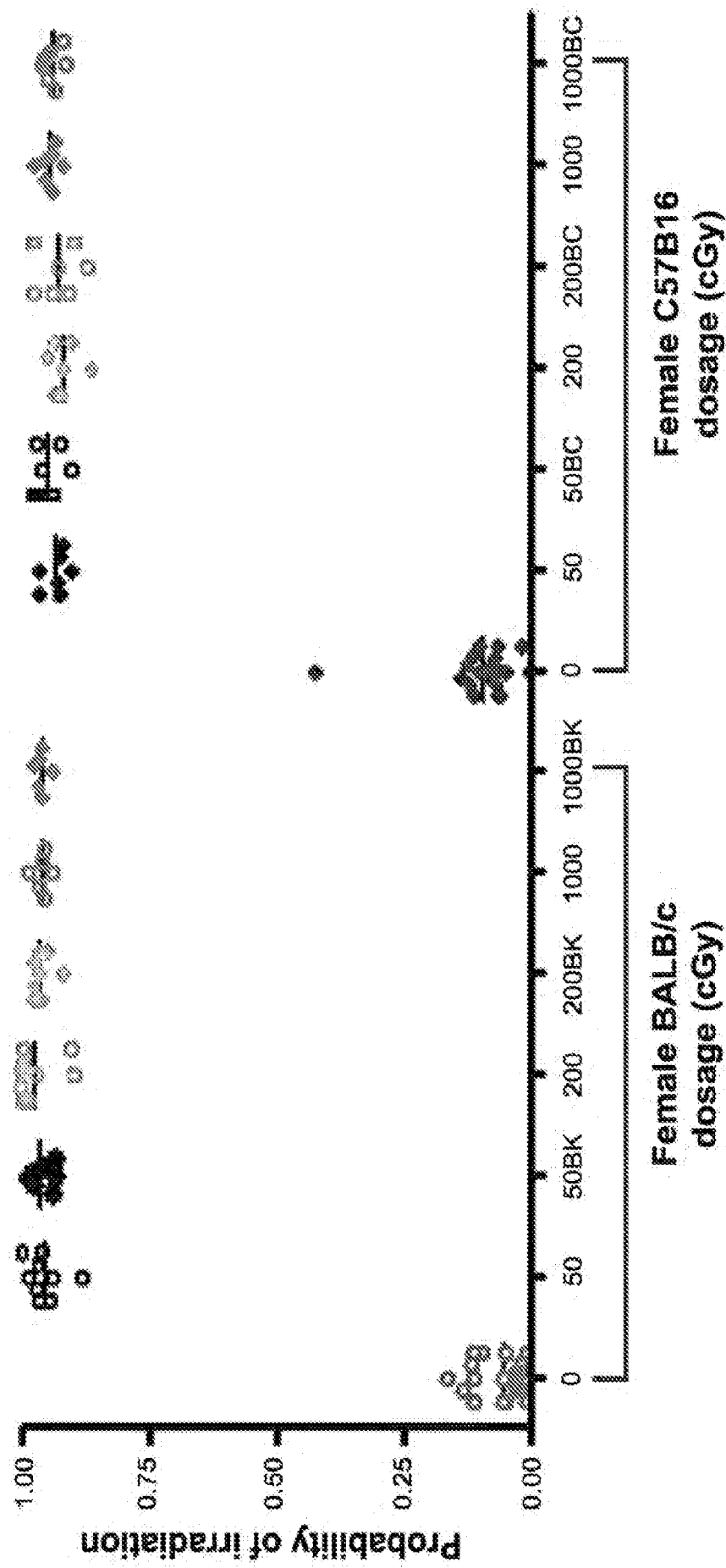


Fig. 3C

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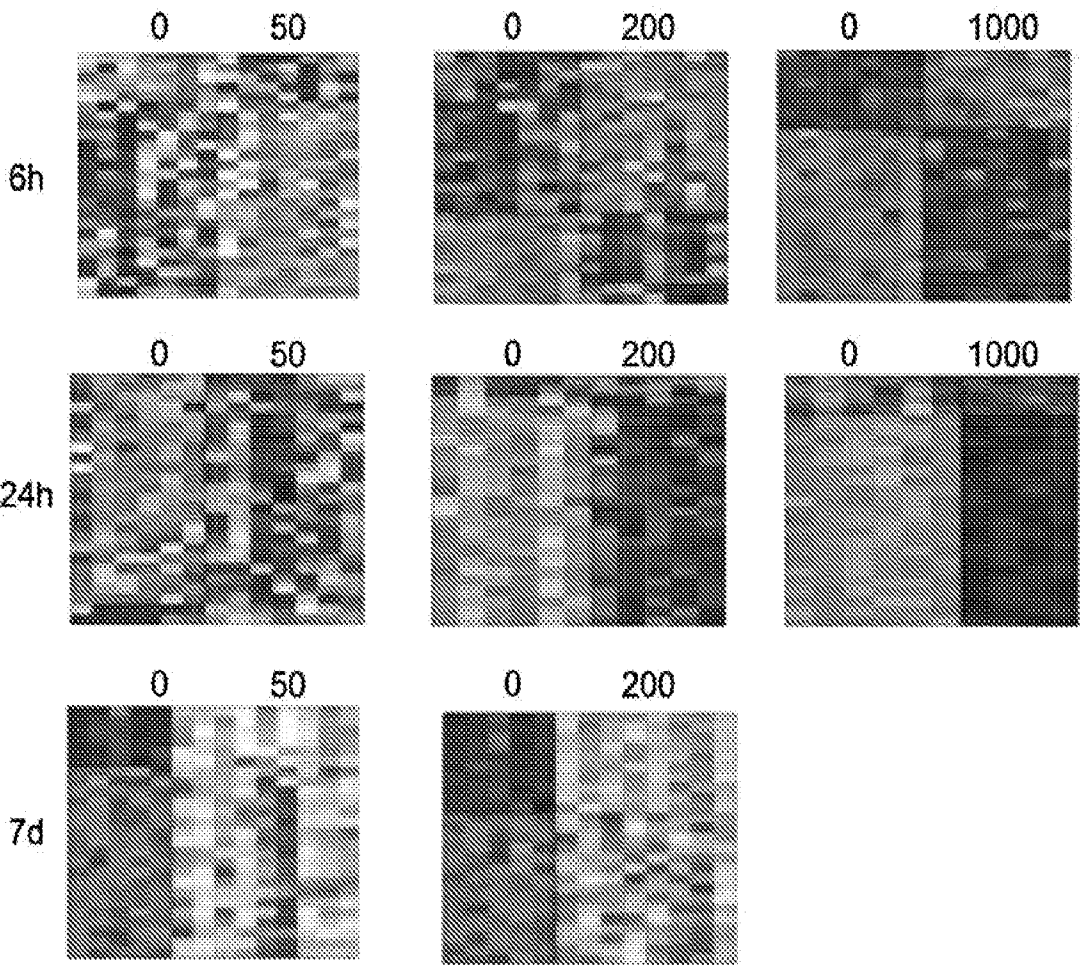


Fig. 4A

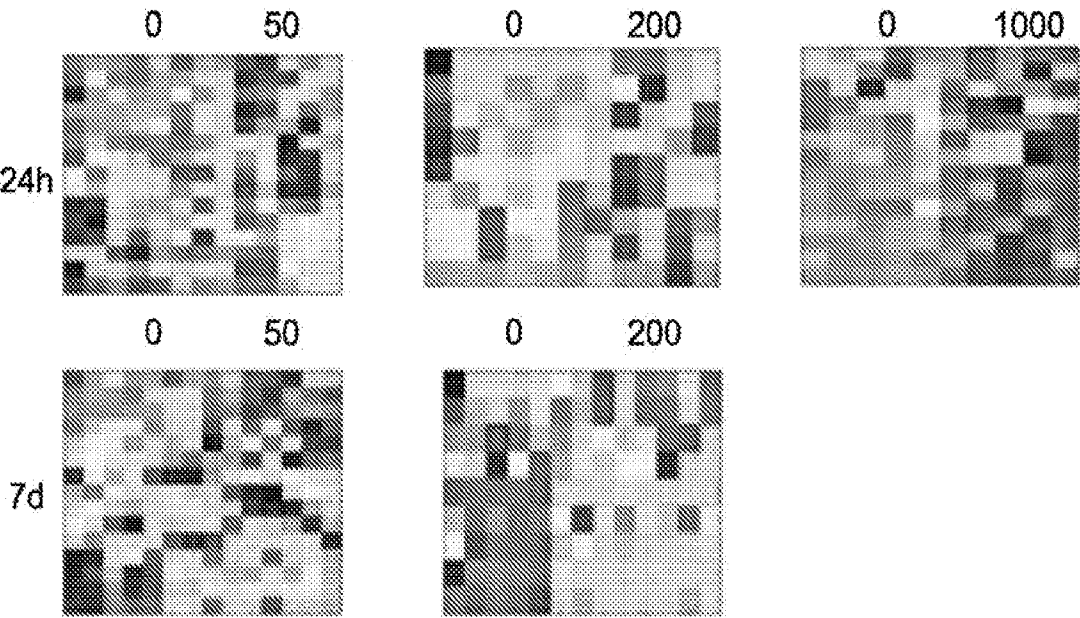


Fig. 4B

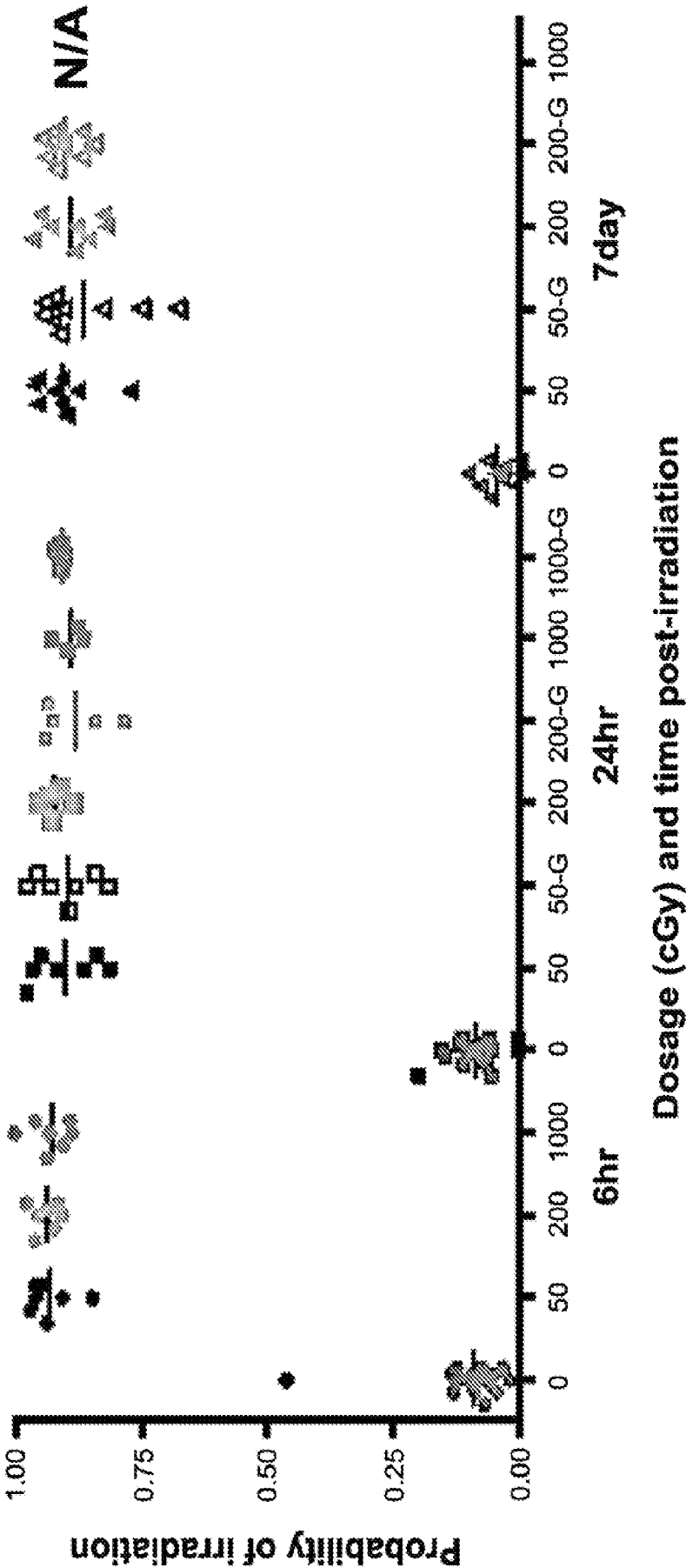


Fig. 4C

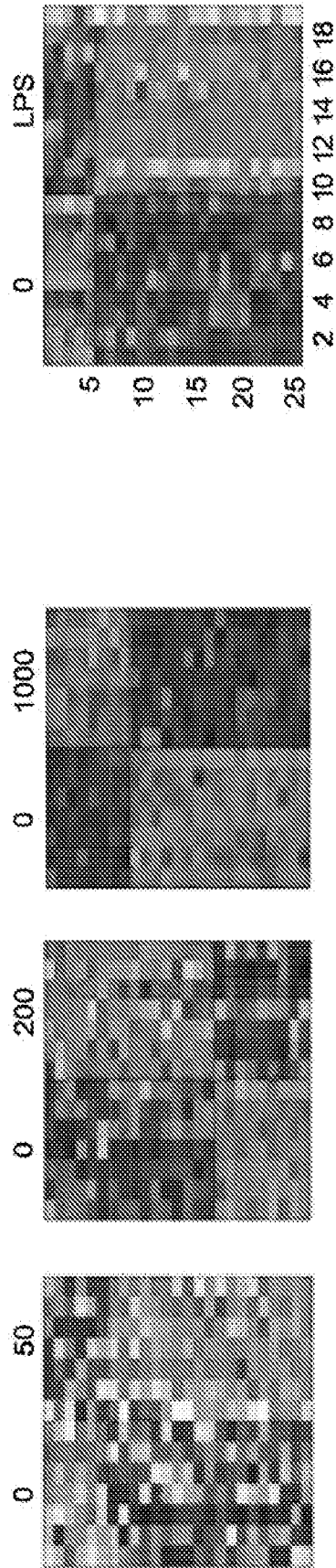


Fig. 5A

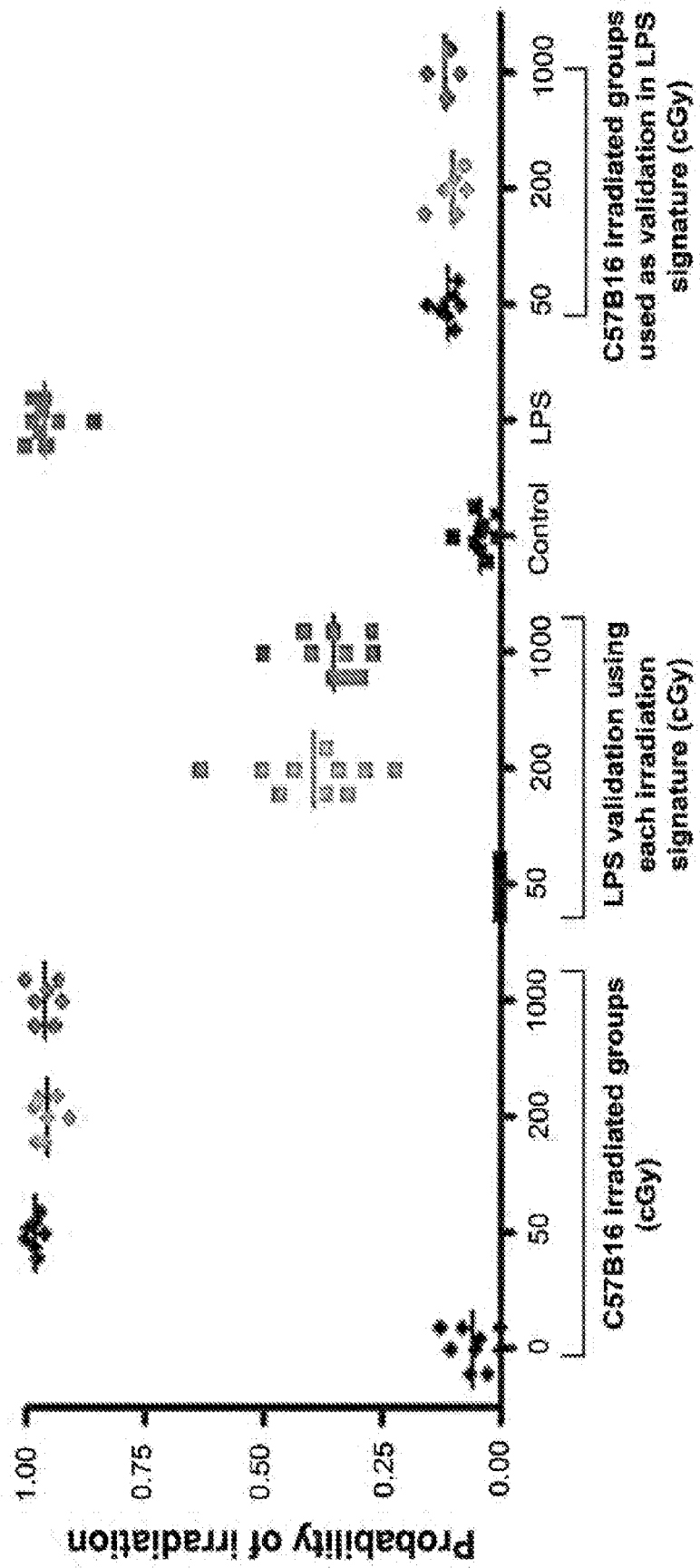


Fig. 5B

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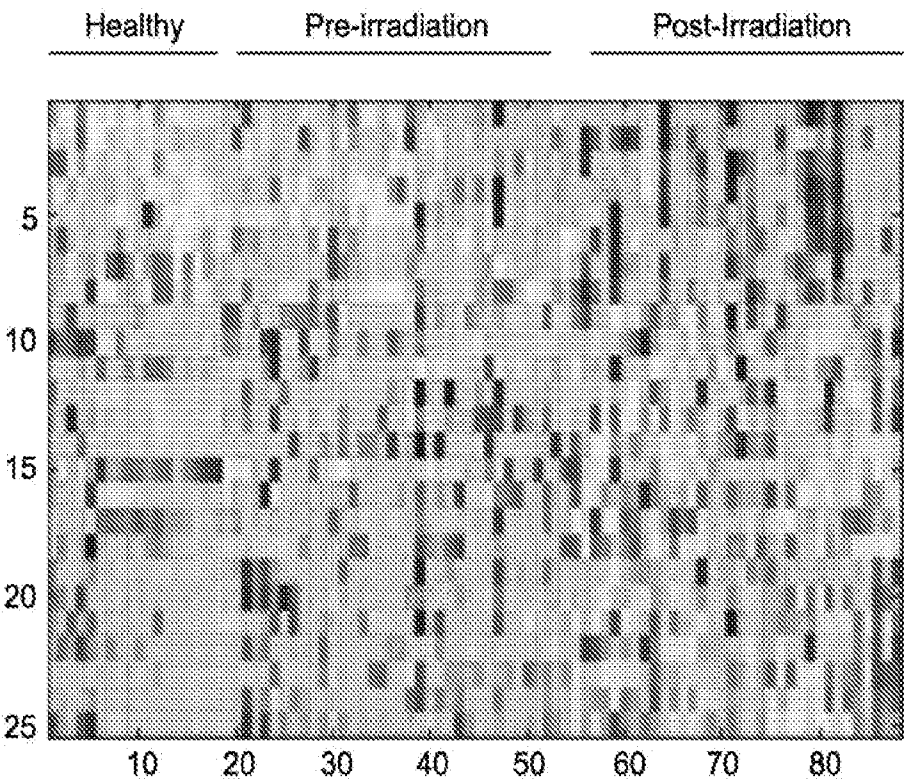


Fig. 6A

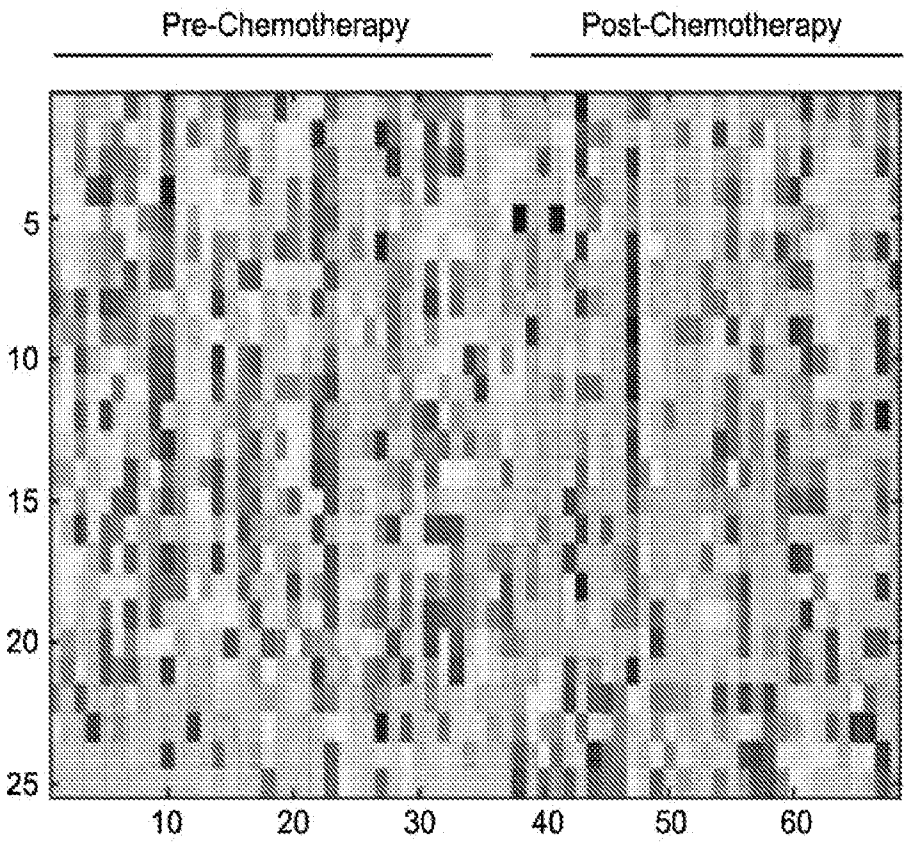


Fig. 6B

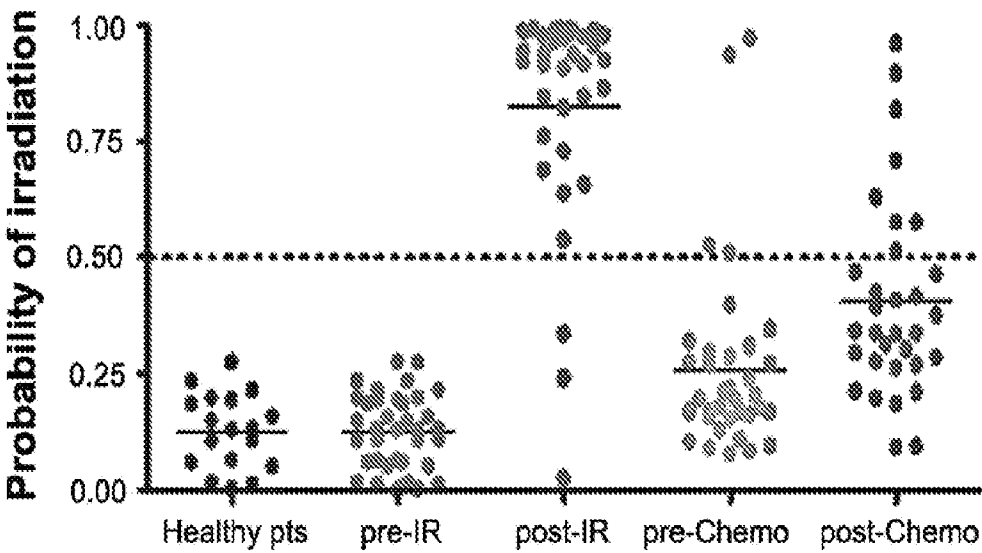


Fig. 6C

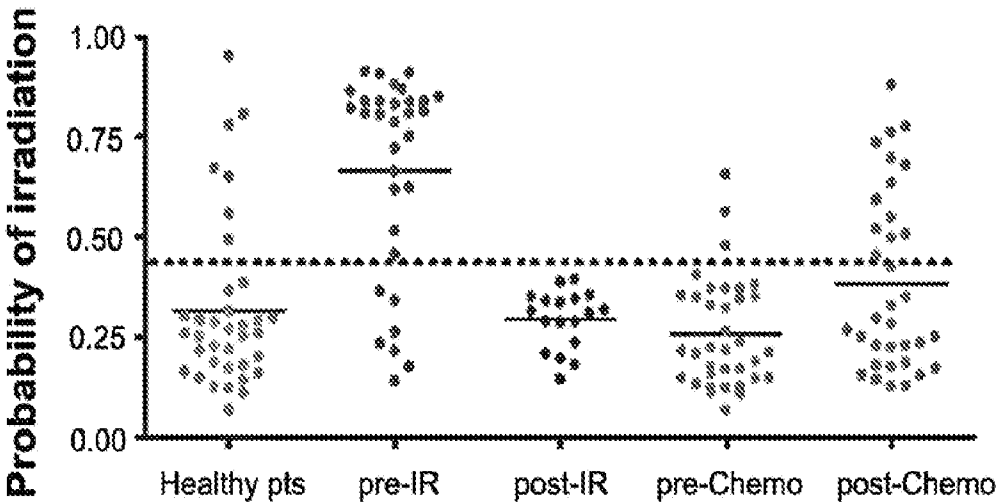


Fig. 6D

Fig. 7

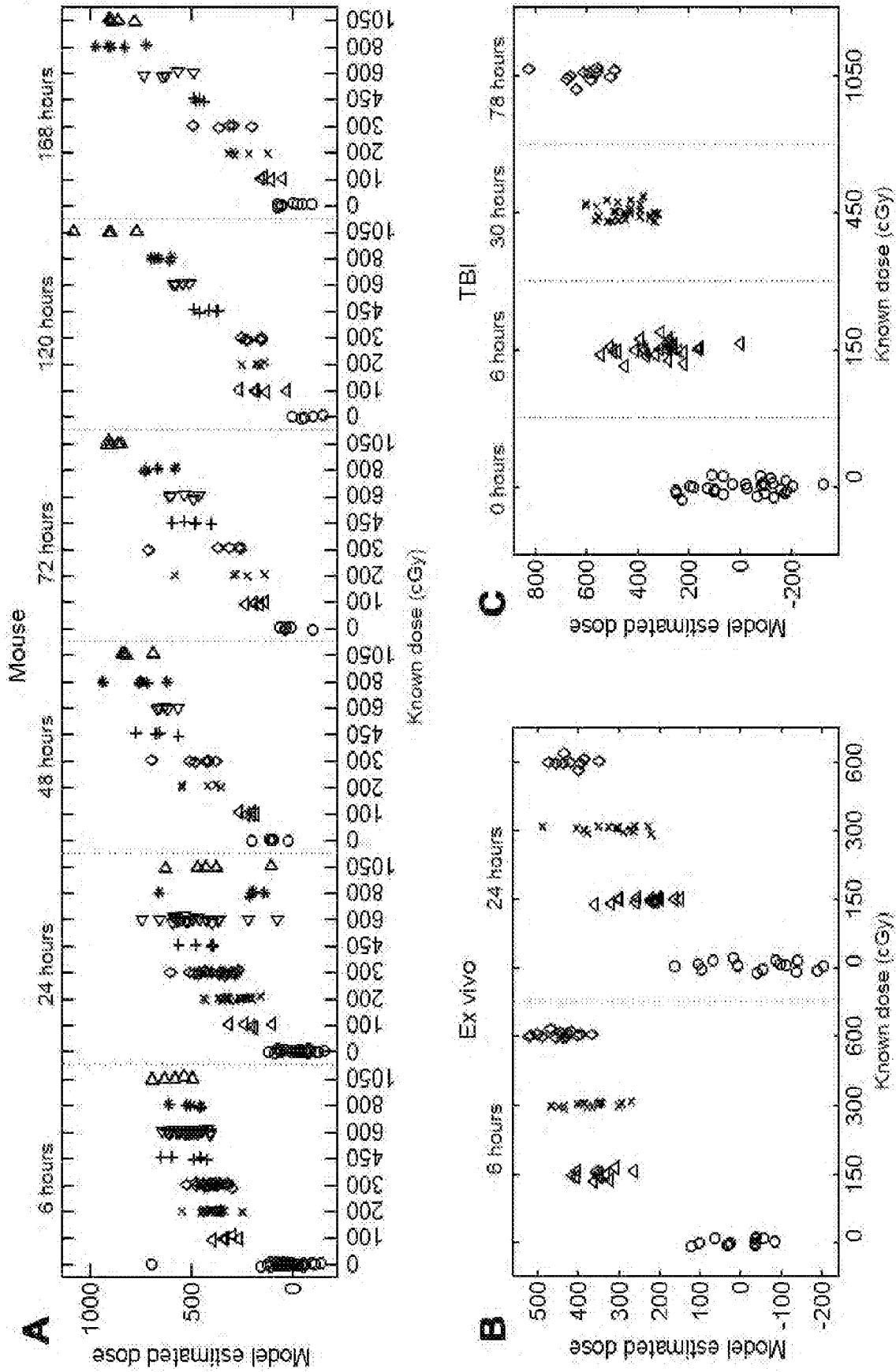


Fig. 8

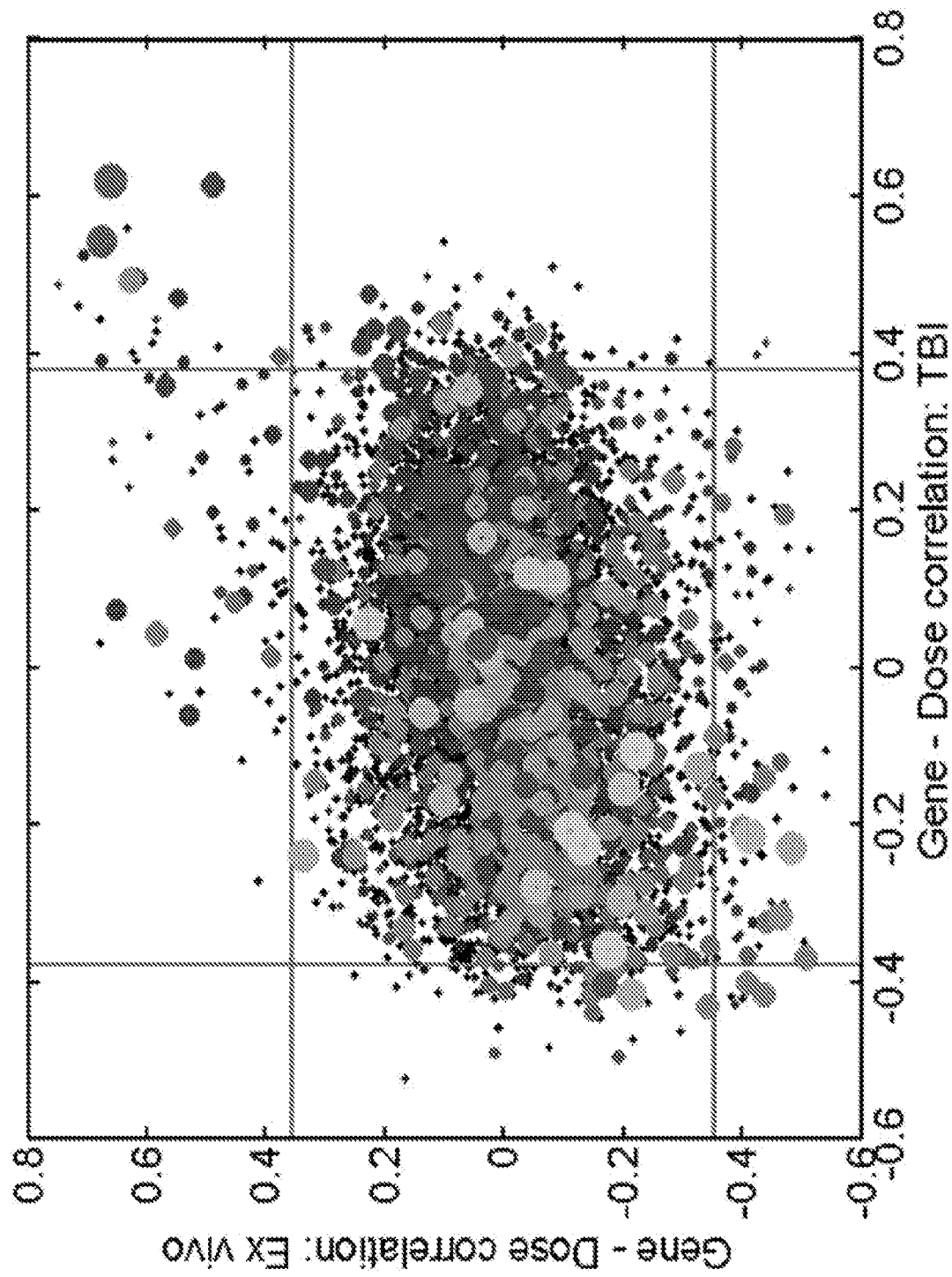


Fig. 9A

Name	Size	Packed Size	Modified
* 5pib.png	46 850	43 331	2011-10-25 10:59
* Tex14.png	50 818	47 453	2011-10-25 10:59
* Ube2d2.png	48 324	44 911	2011-10-25 10:59
* Astn2.png	48 078	44 453	2011-10-25 10:59
* Cd24a.png	46 119	42 830	2011-10-25 10:59
* Cdkn1a.png	45 449	41 862	2011-10-25 10:59
* Cds2.png	47 664	44 280	2011-10-25 10:59
* Cebpb.png	49 103	45 594	2011-10-25 10:59
* Ddit3.png	46 531	42 633	2011-10-25 10:59
* Dedd.png	48 395	44 899	2011-10-25 10:59
* Dock5.png	49 792	46 639	2011-10-25 10:59
* Igj.png	47 011	43 355	2011-10-25 10:59
* Laptm5.png	49 172	45 732	2011-10-25 10:59
* Lime1.png	48 388	45 164	2011-10-25 10:59
* LOC100047840.png	47 582	44 222	2011-10-25 10:59
* Mdm2.png	48 642	45 037	2011-10-25 10:59
* Phlda3.png	44 488	41 194	2011-10-25 10:59
* Pik2.png	45 923	42 261	2011-10-25 10:59
* Pou2af1.png	47 967	44 310	2011-10-25 10:59
* Ppp3cb.png	47 709	44 076	2011-10-25 10:59
* Qrsil.png	47 750	44 254	2011-10-25 10:59
* Rbpj.png	49 460	46 118	2011-10-25 10:59
* Rhoh.png	46 061	42 743	2011-10-25 10:59
* Rpal.png	46 923	43 282	2011-10-25 10:59
* model-1.png	45 542	42 144	2011-10-25 10:58
model-1-genes.txt	3 750	1 274	2011-10-25 10:58

Fig. 9A Cont'd

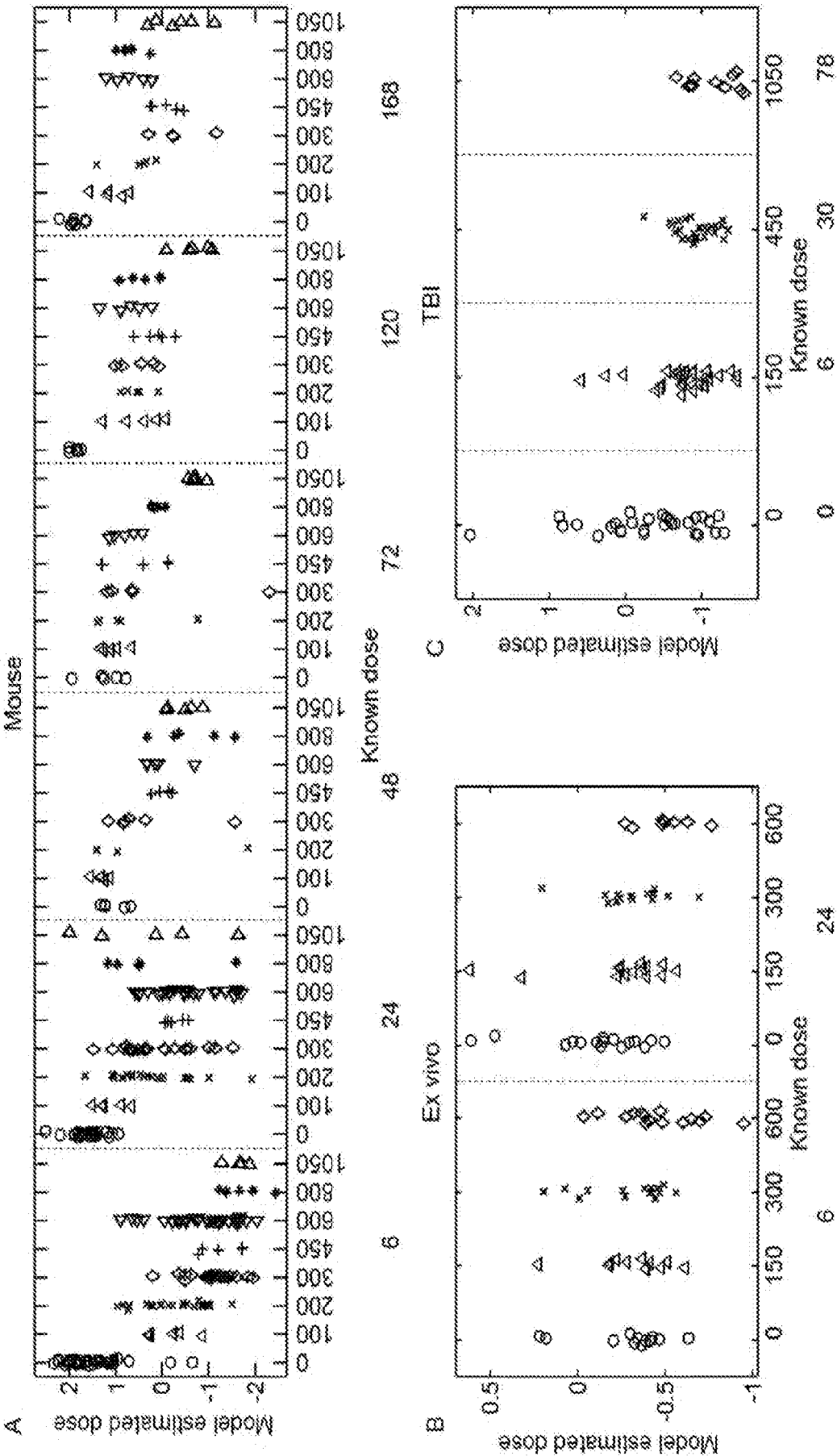


Fig. 9A Cont'd

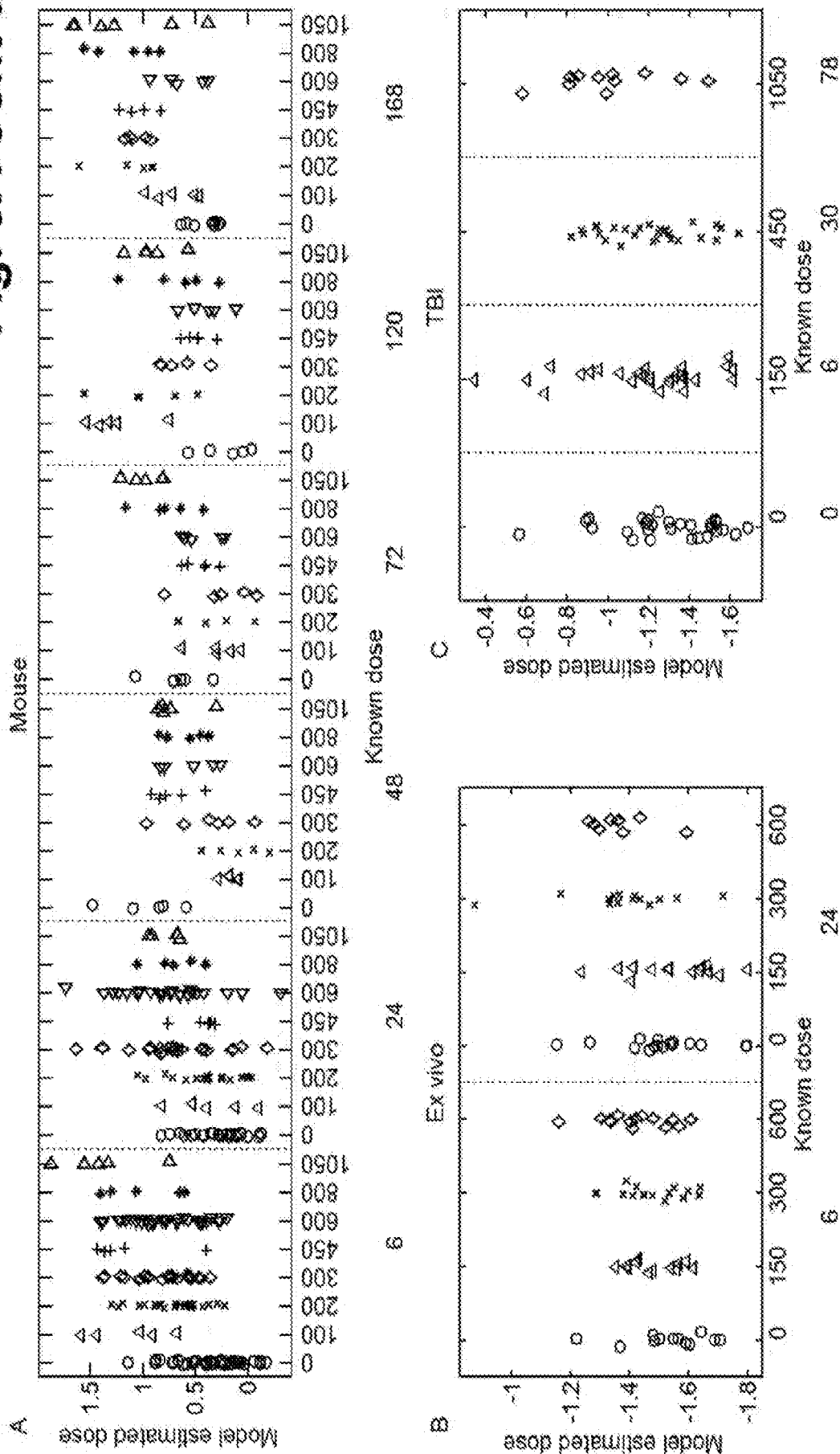


Fig. 9A Cont'd

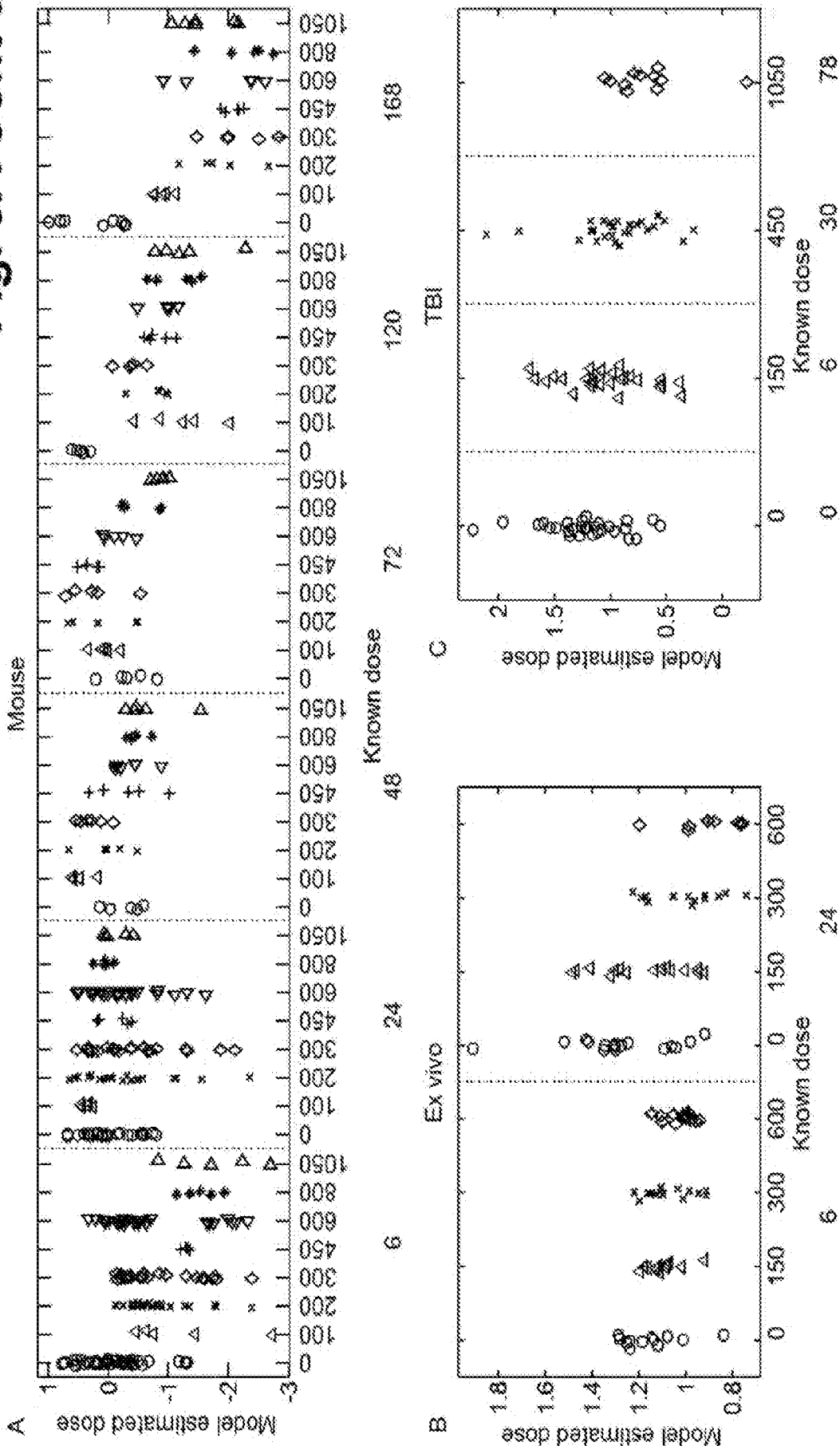


Fig. 9A Cont'd

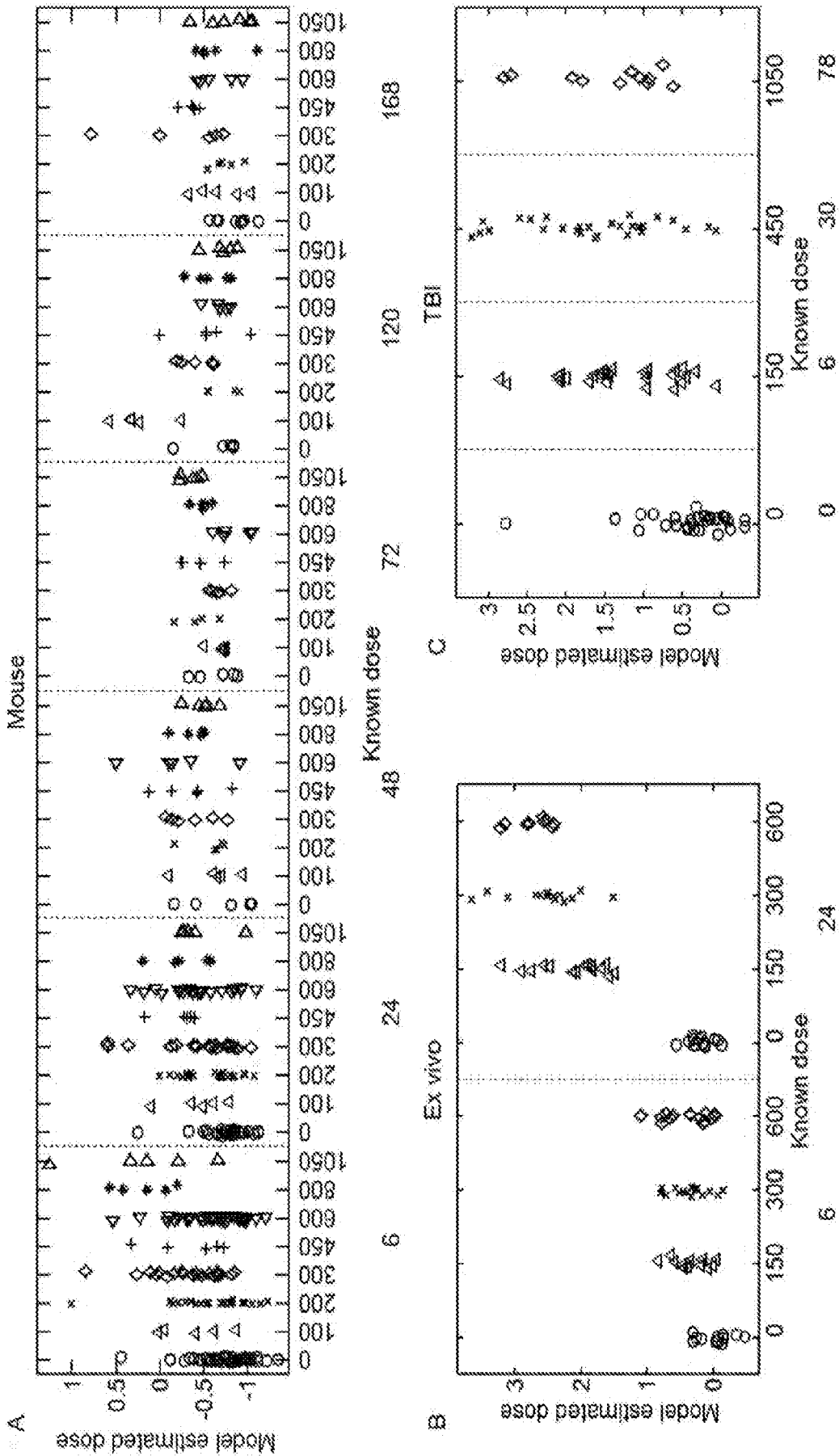


Fig. 9A Cont'd

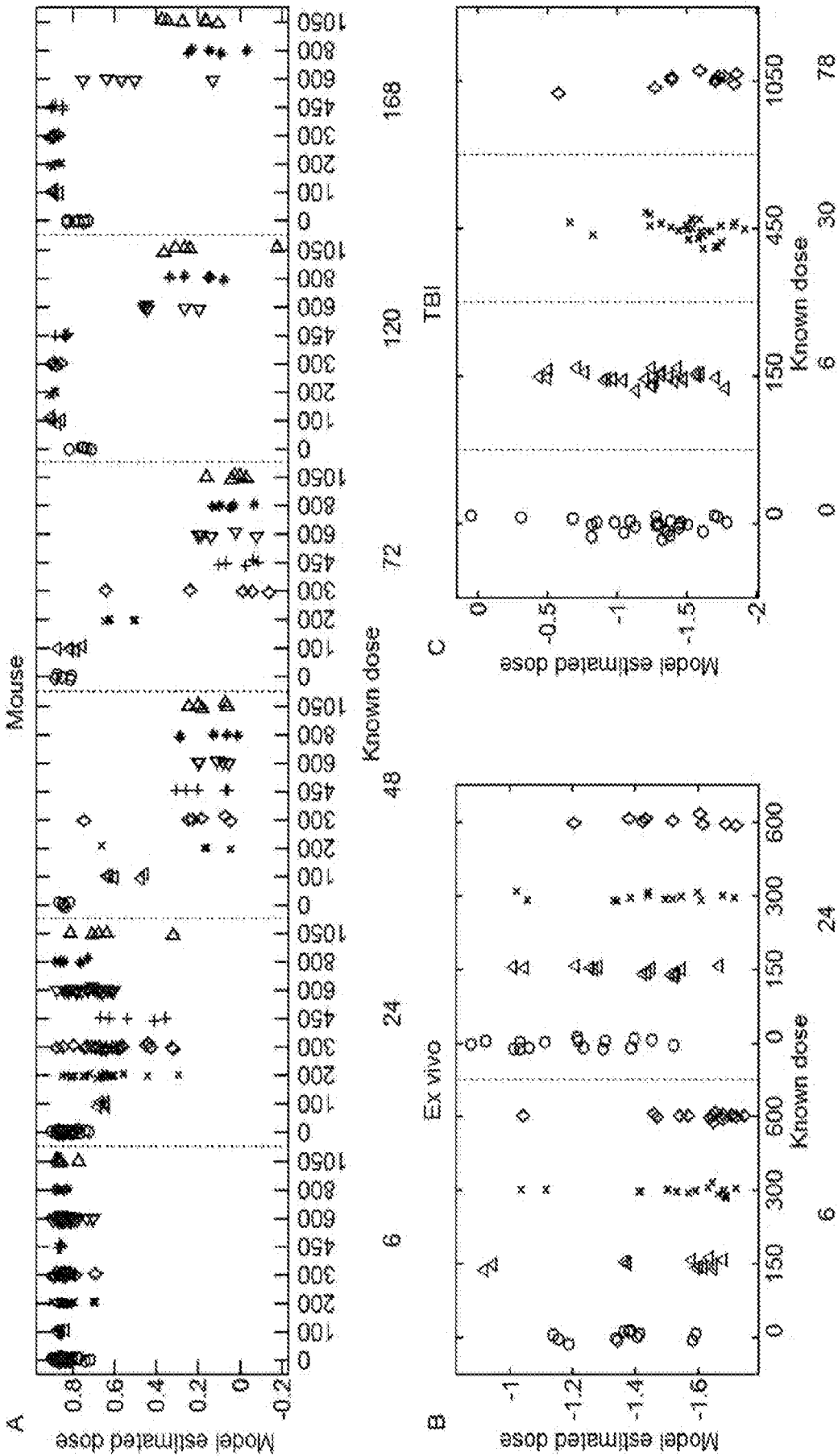


Fig. 9A Cont'd

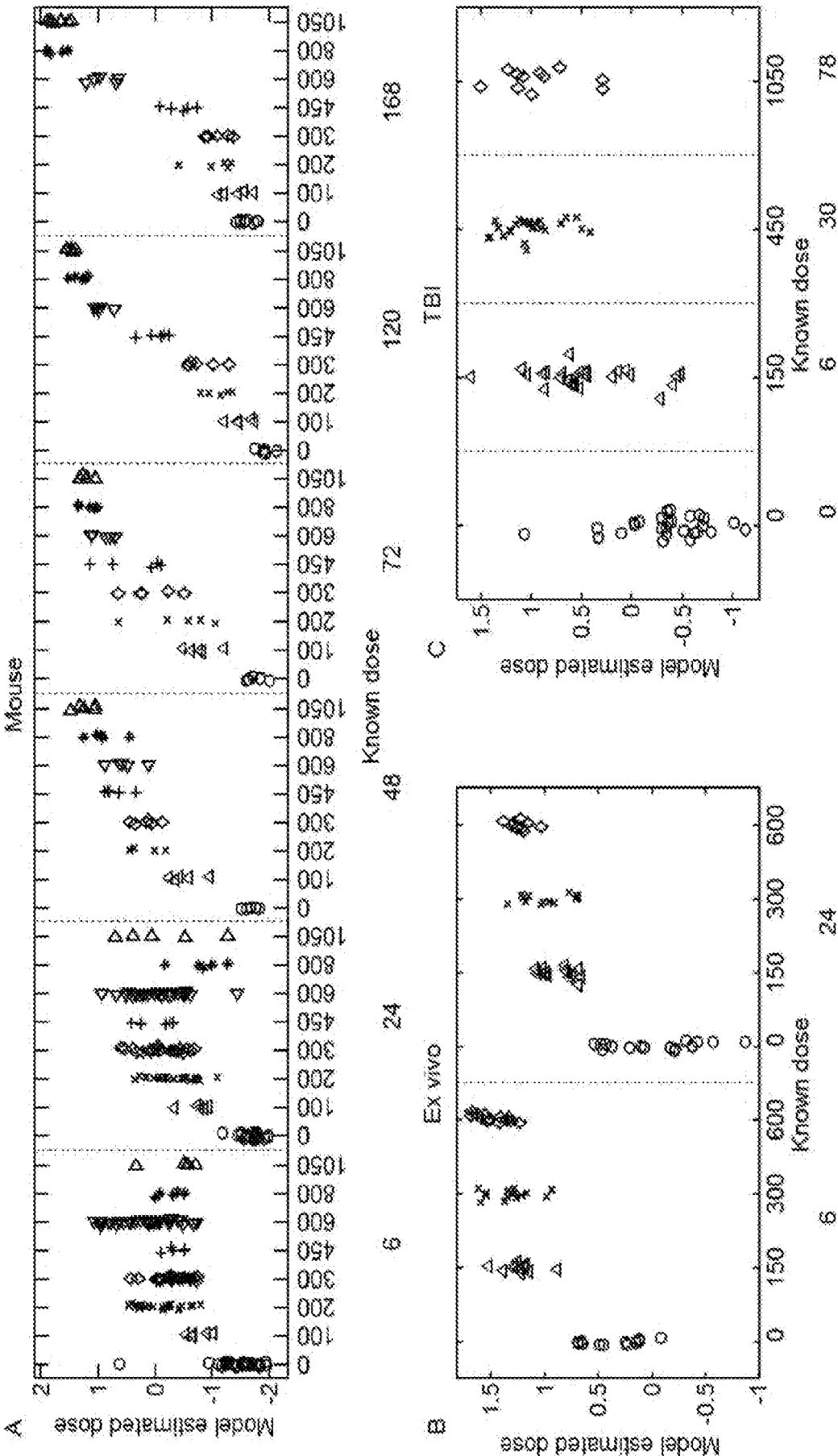


Fig. 9A Cont'd

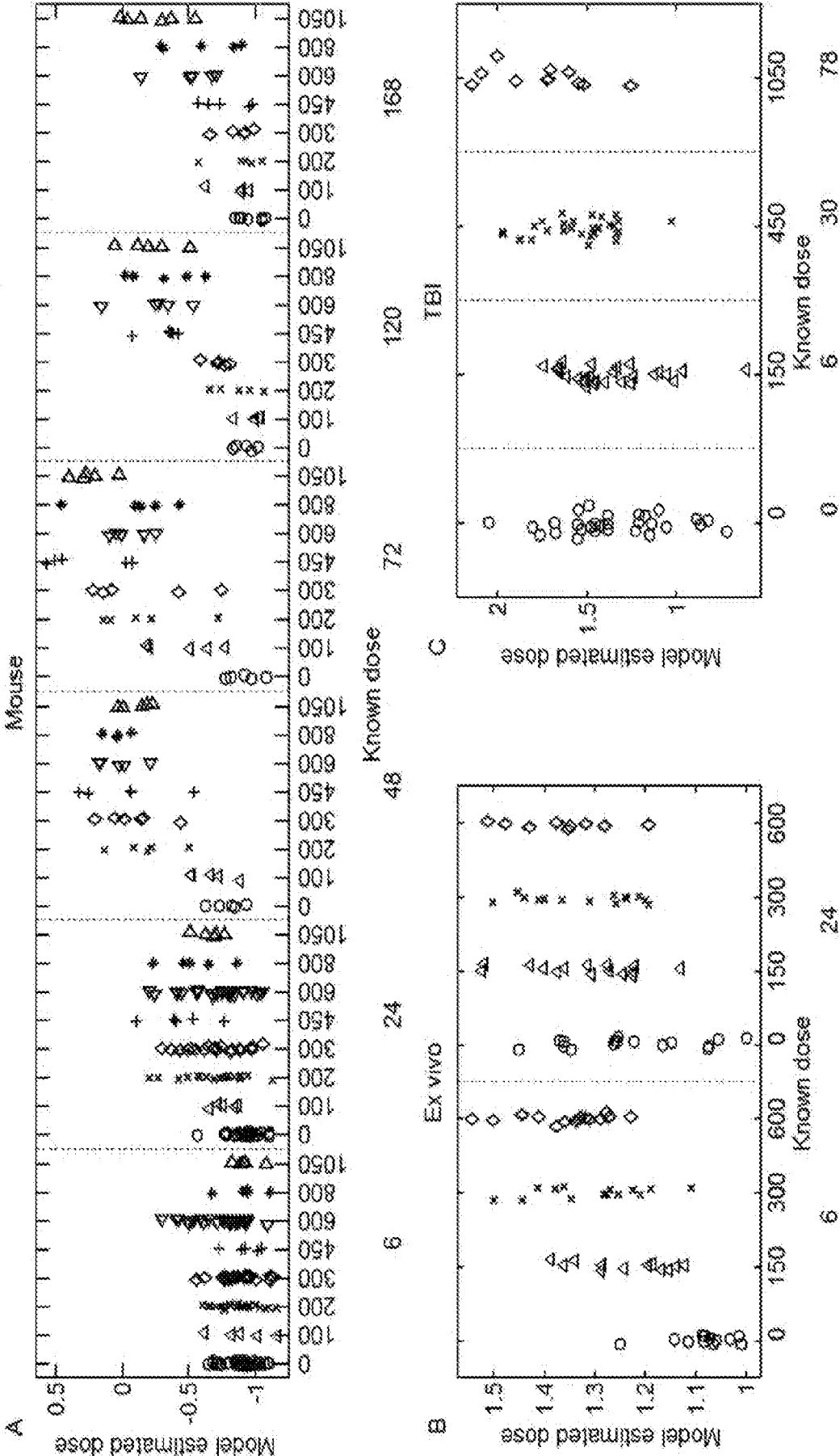


Fig. 9A Cont'd

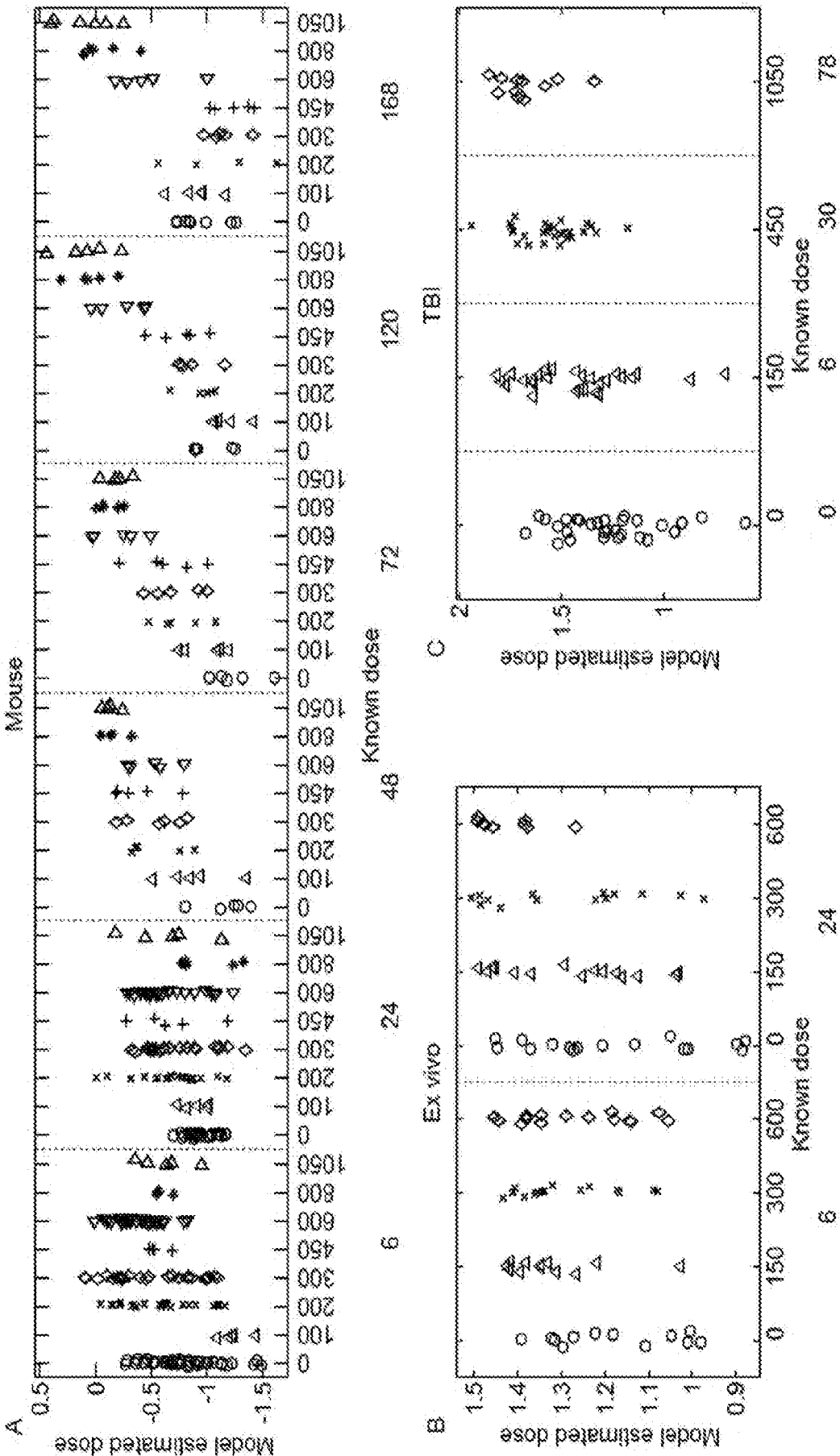


Fig. 9A Cont'd

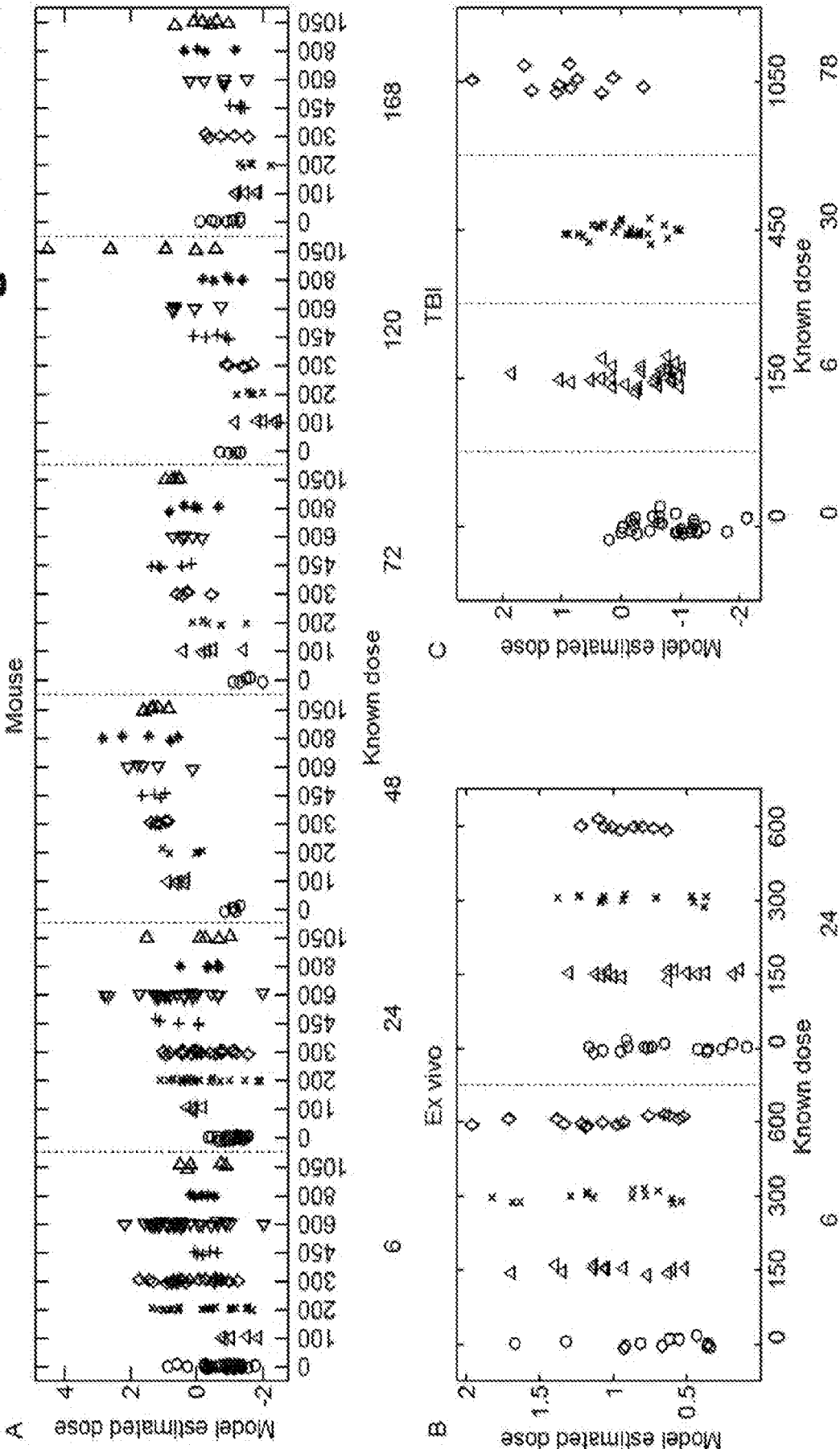


Fig. 9A Cont'd

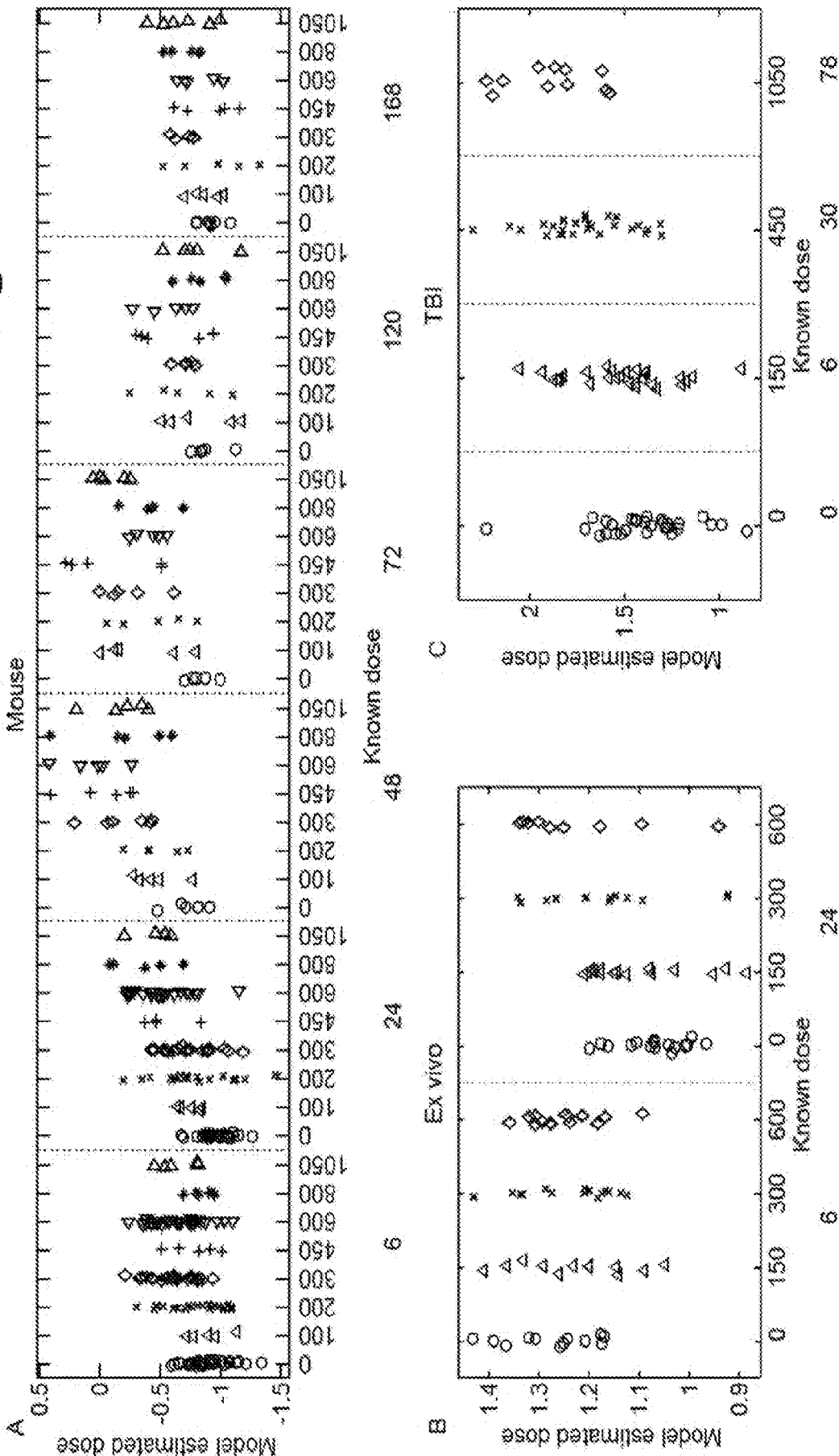


Fig. 9A Cont'd

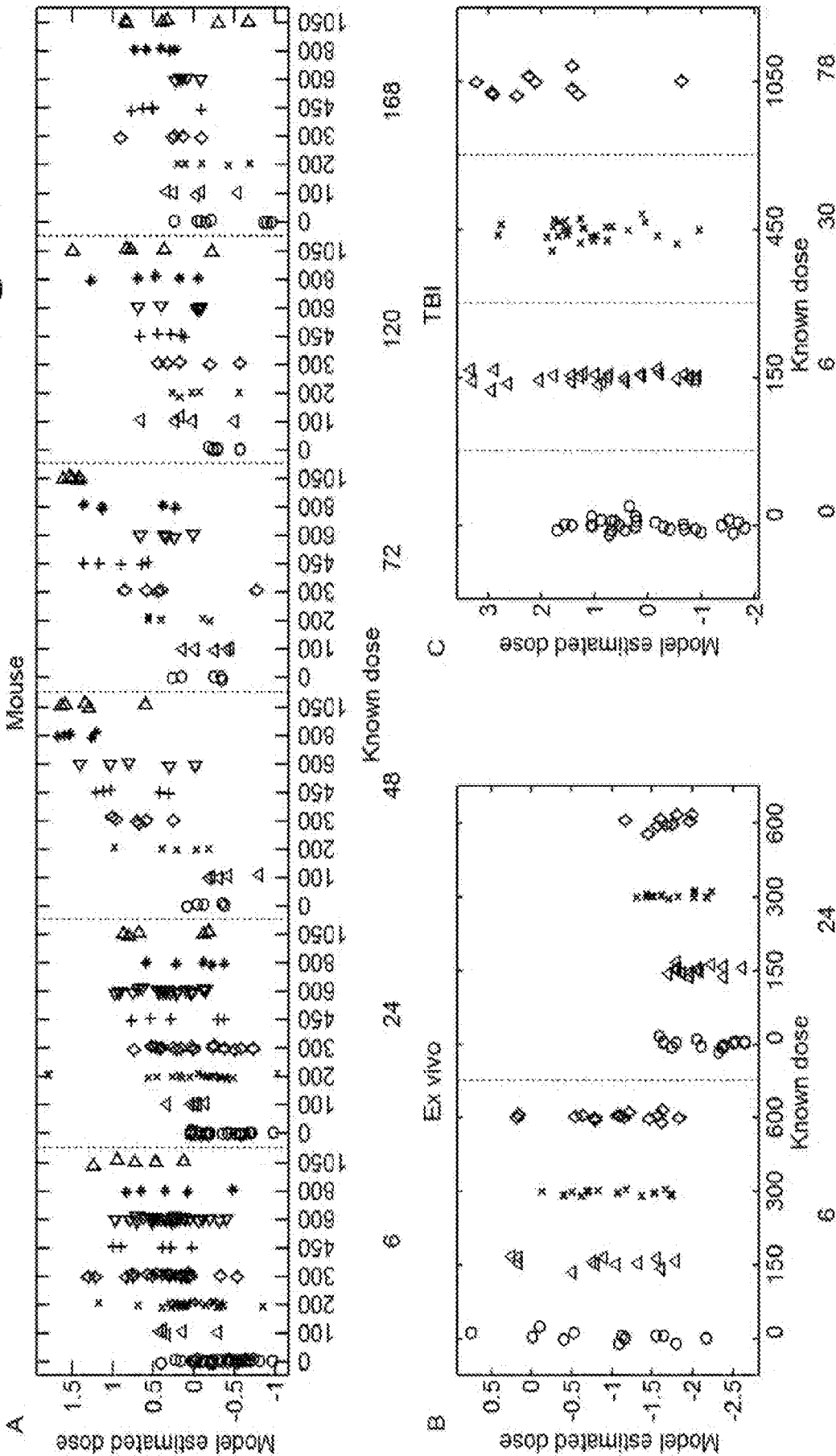


Fig. 9A Cont'd

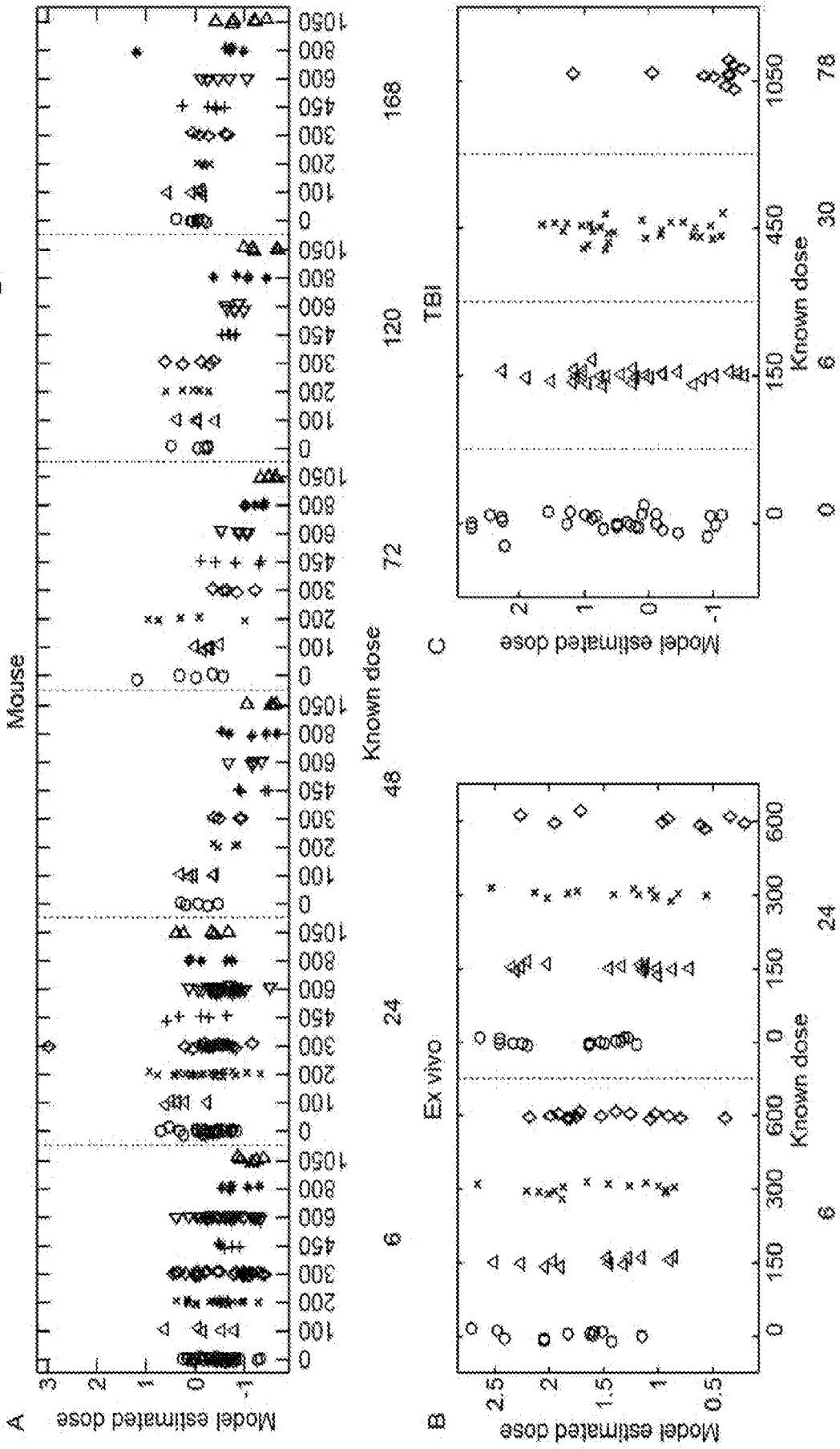


Fig. 9A Cont'd

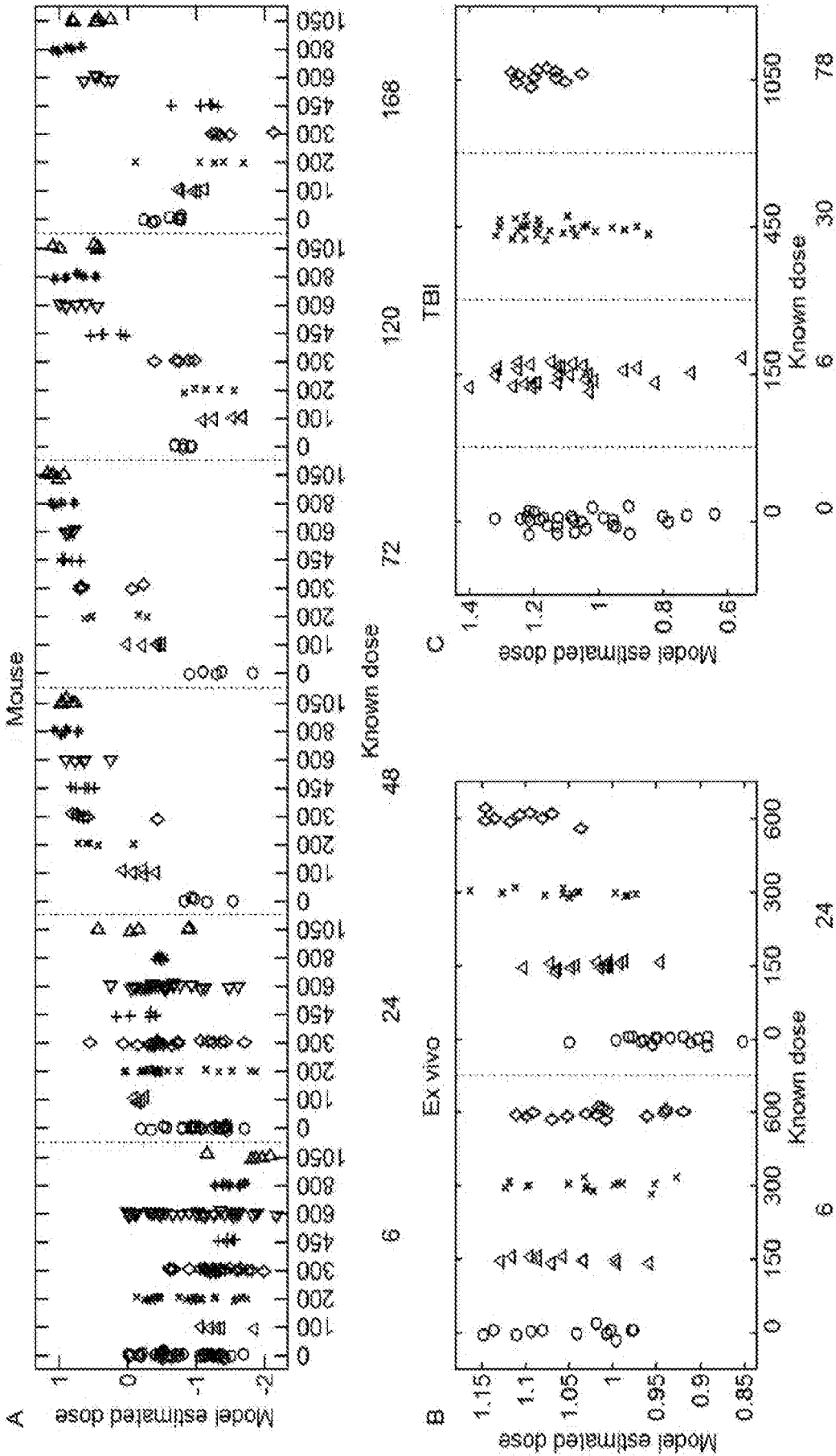


Fig. 9A Cont'd

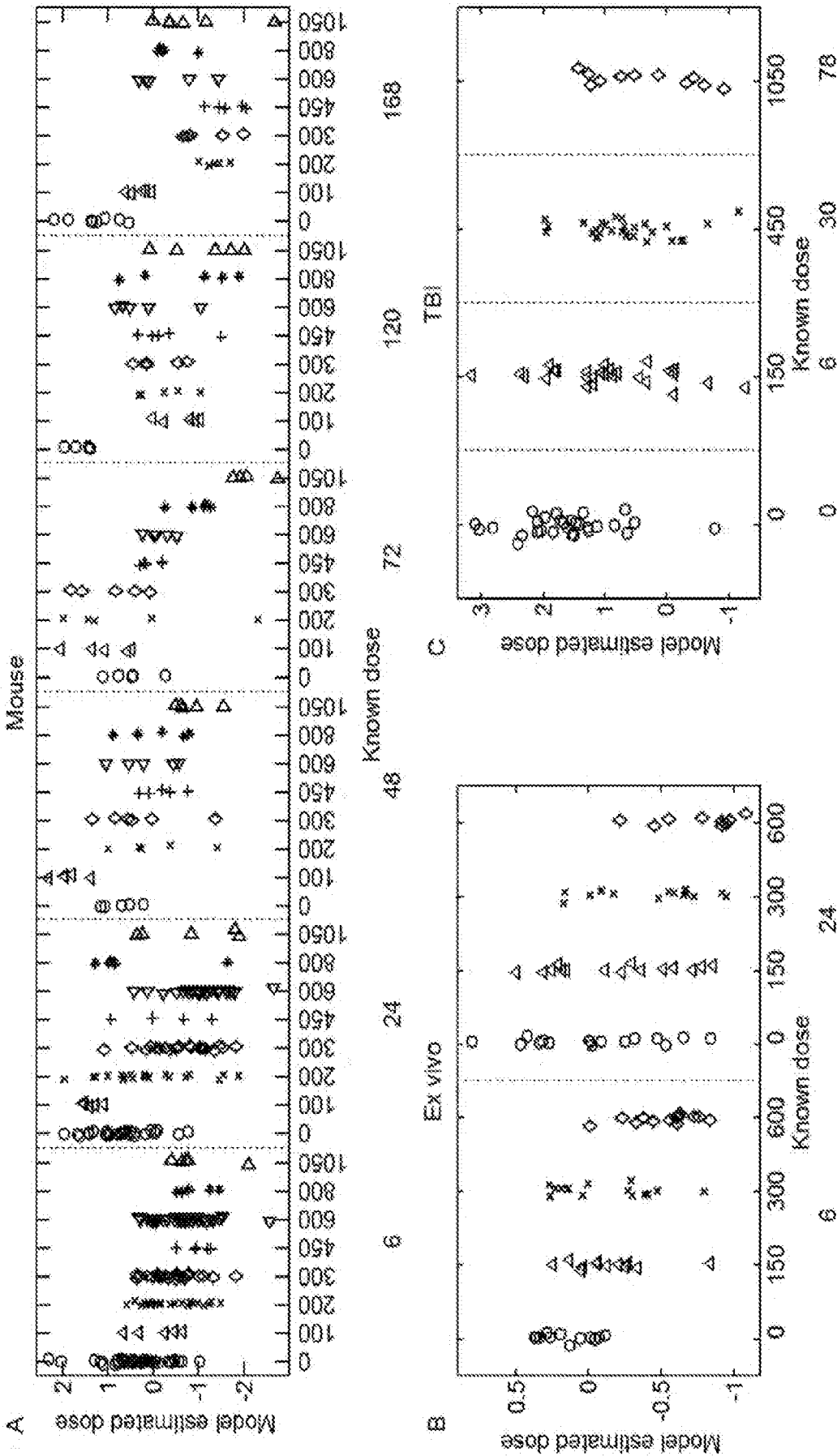


Fig. 9A Cont'd

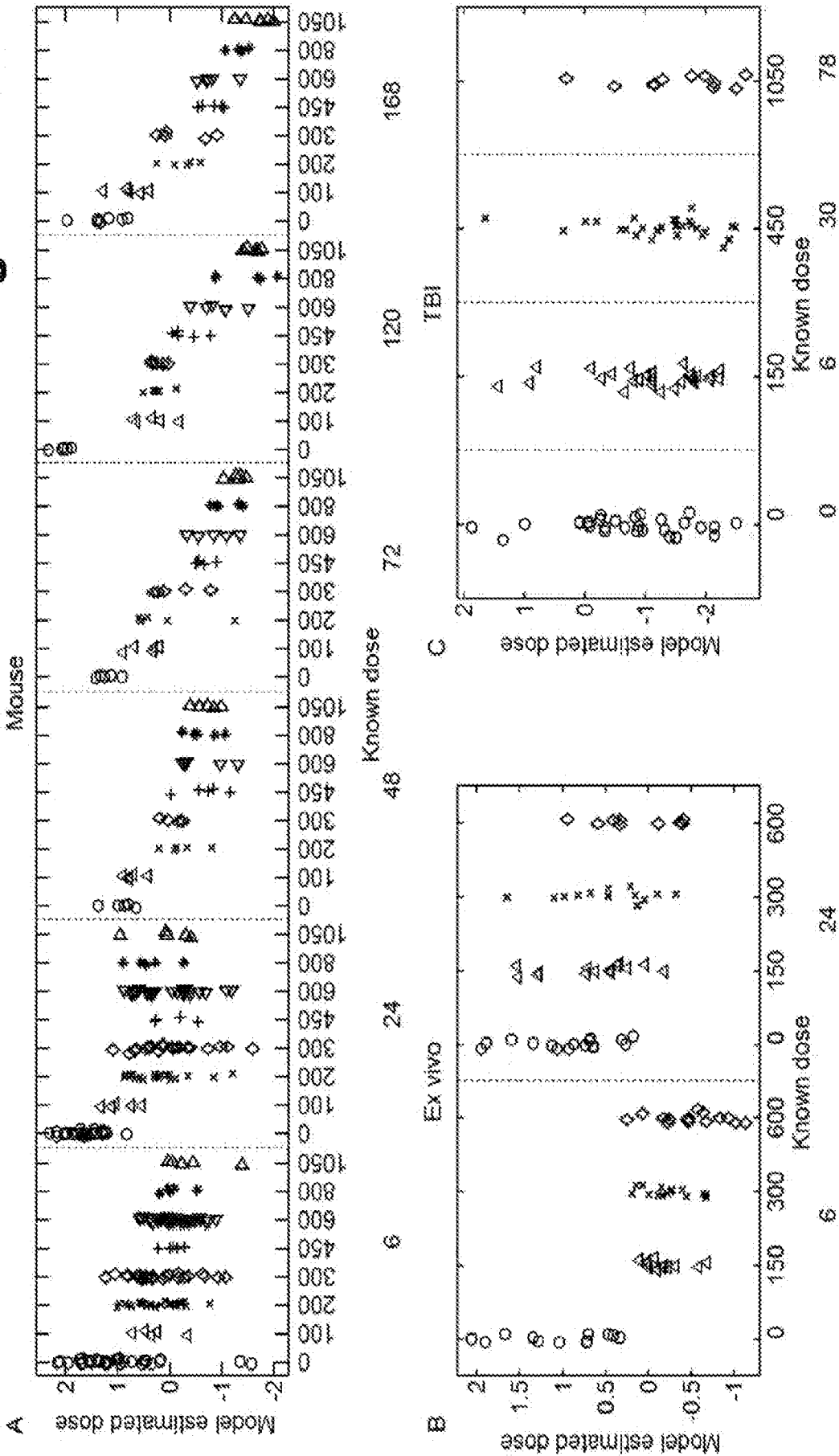


Fig. 9A Cont'd

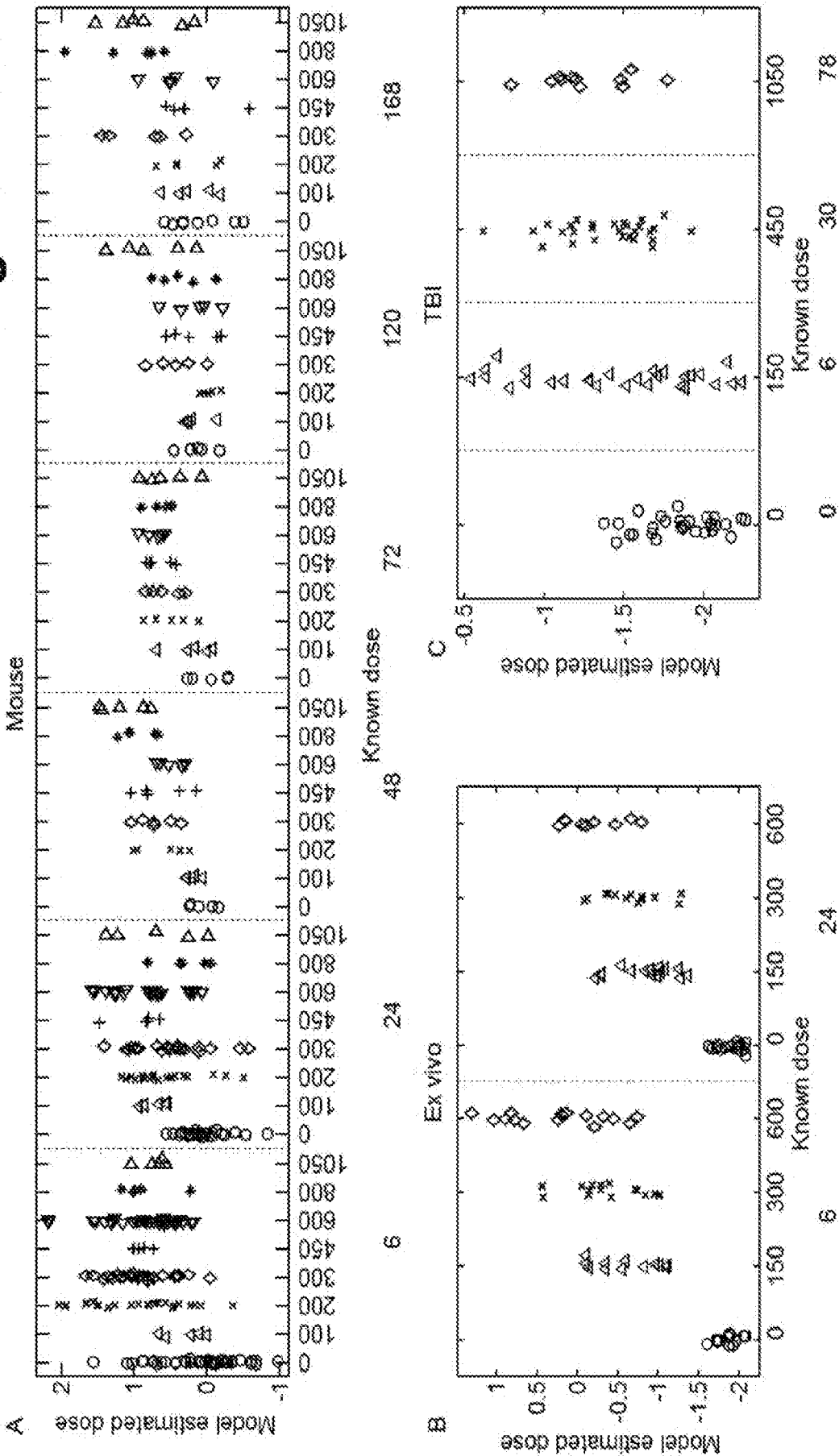


Fig. 9A Cont'd

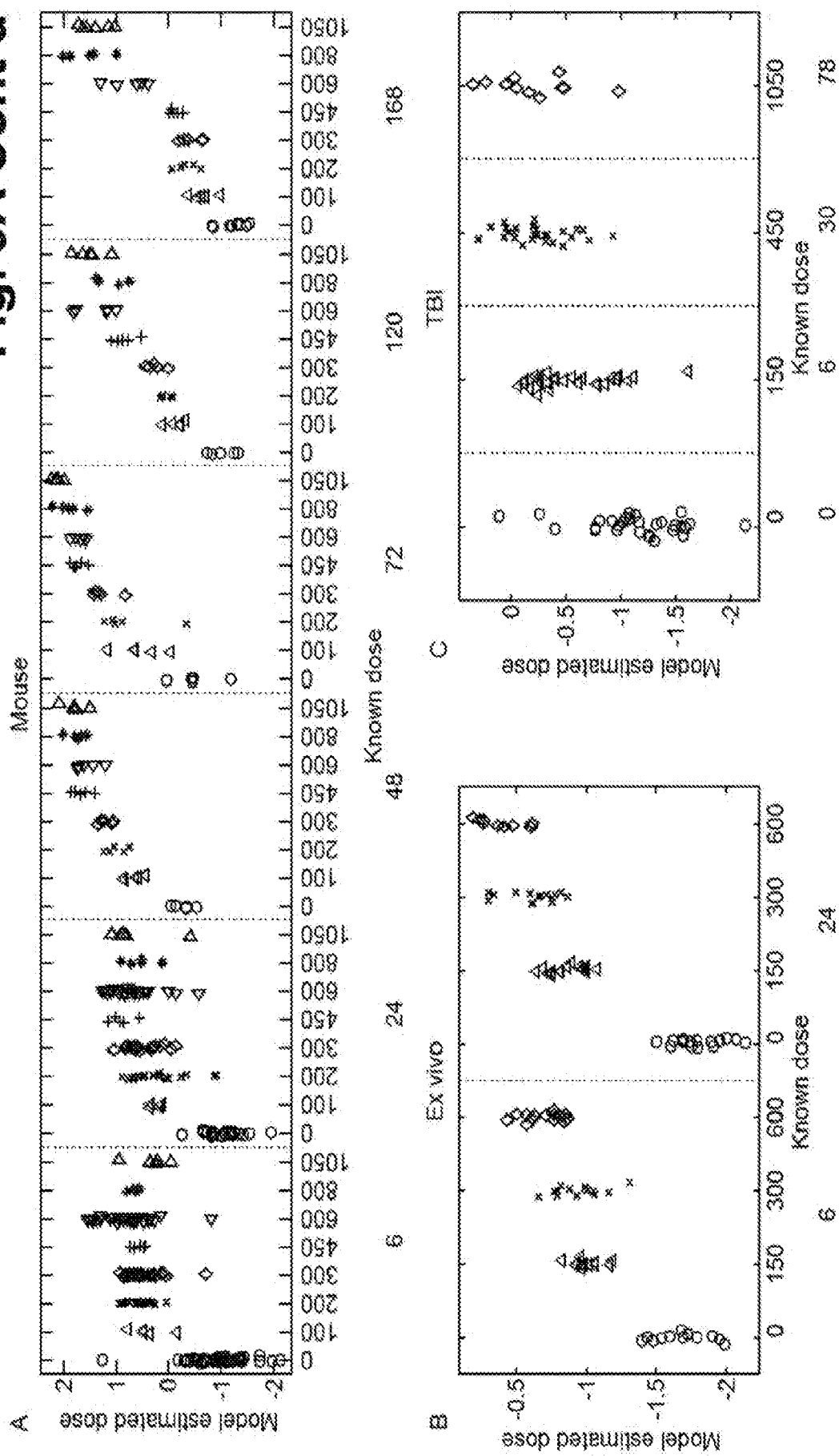


Fig. 9A Cont'd

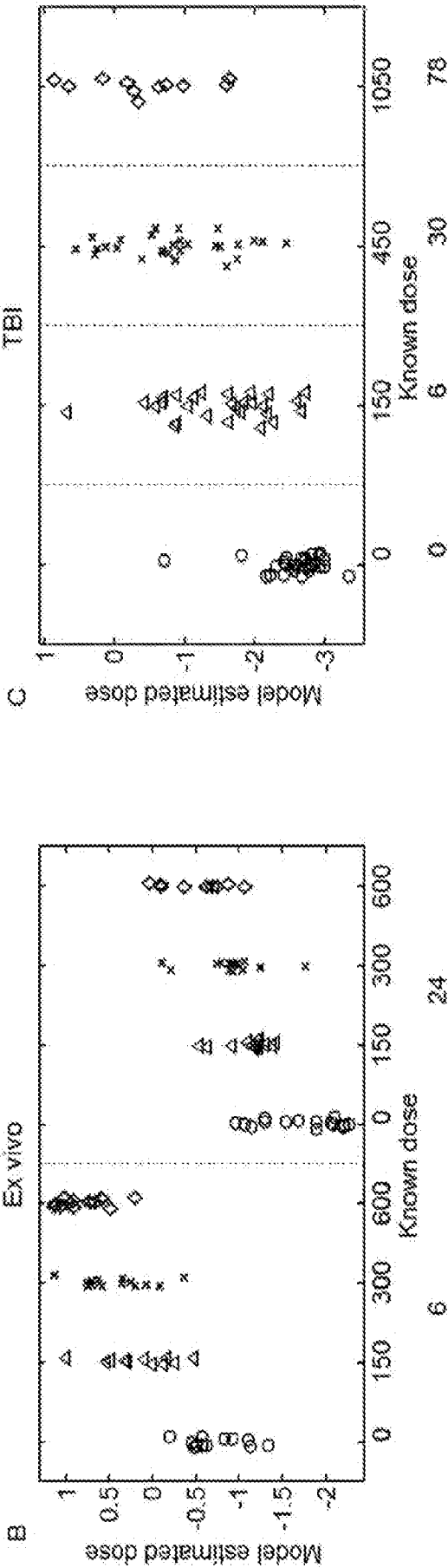
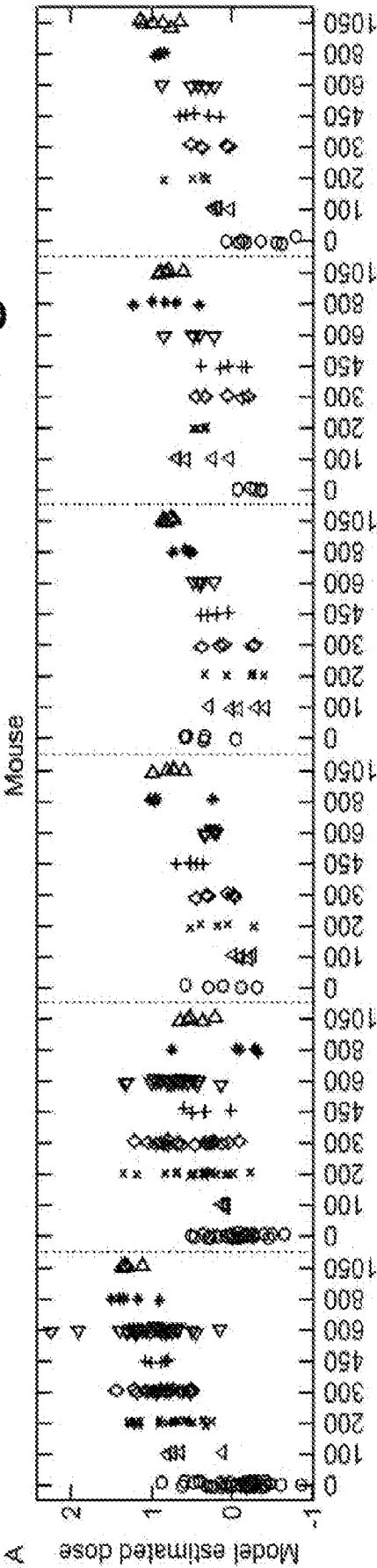


Fig. 9A Cont'd

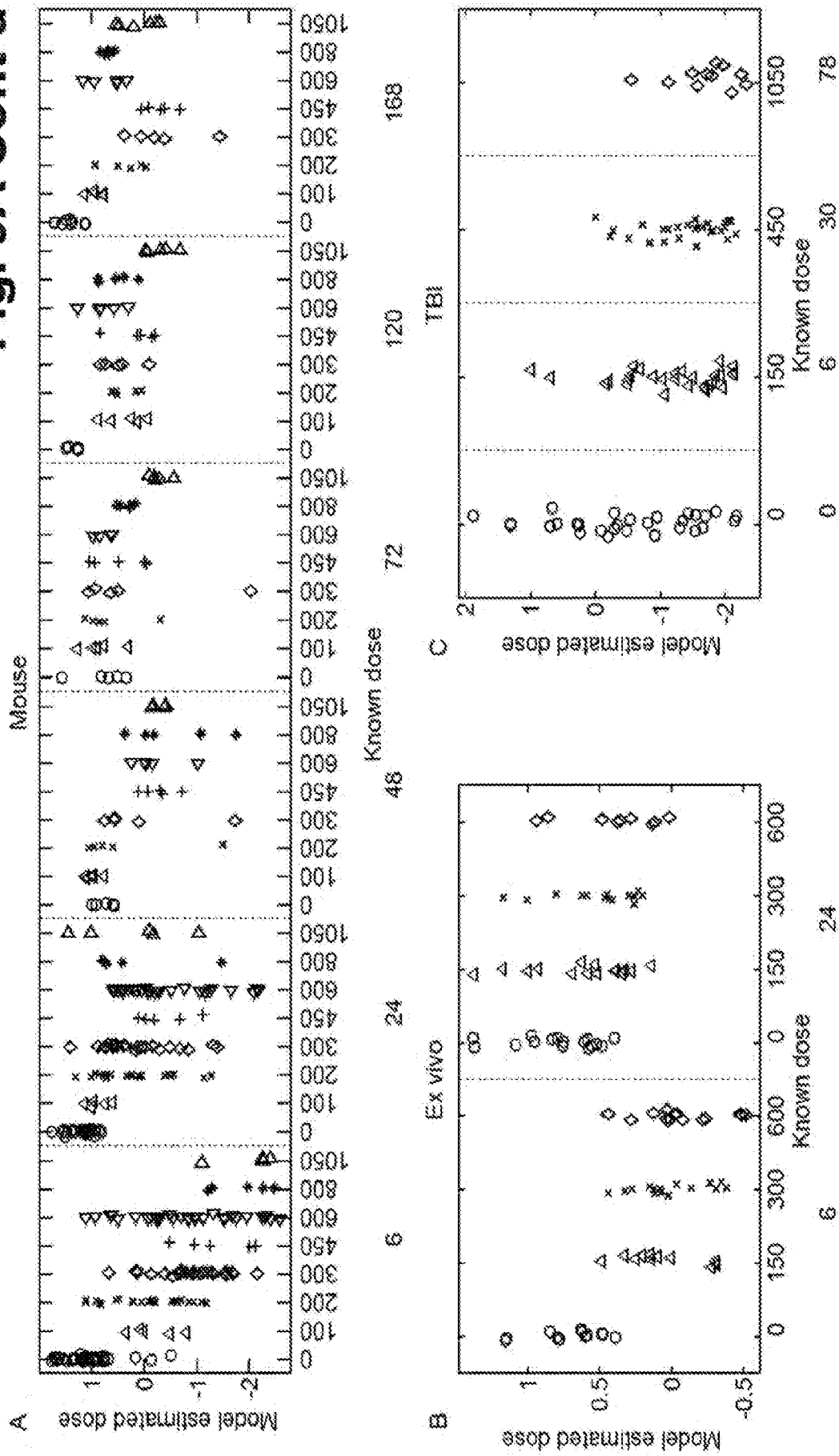


Fig. 9A Cont'd

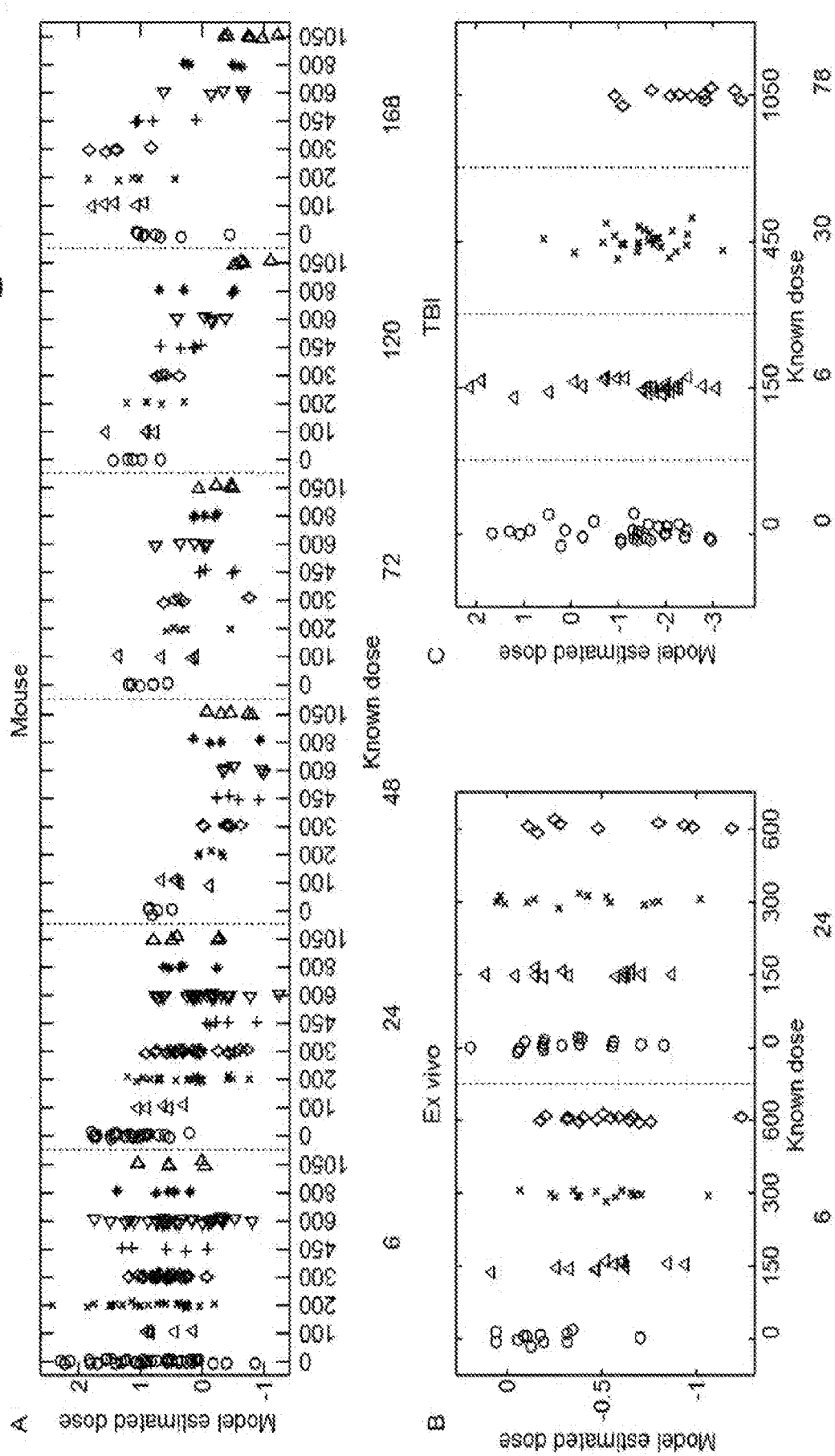


Fig. 9A Cont'd

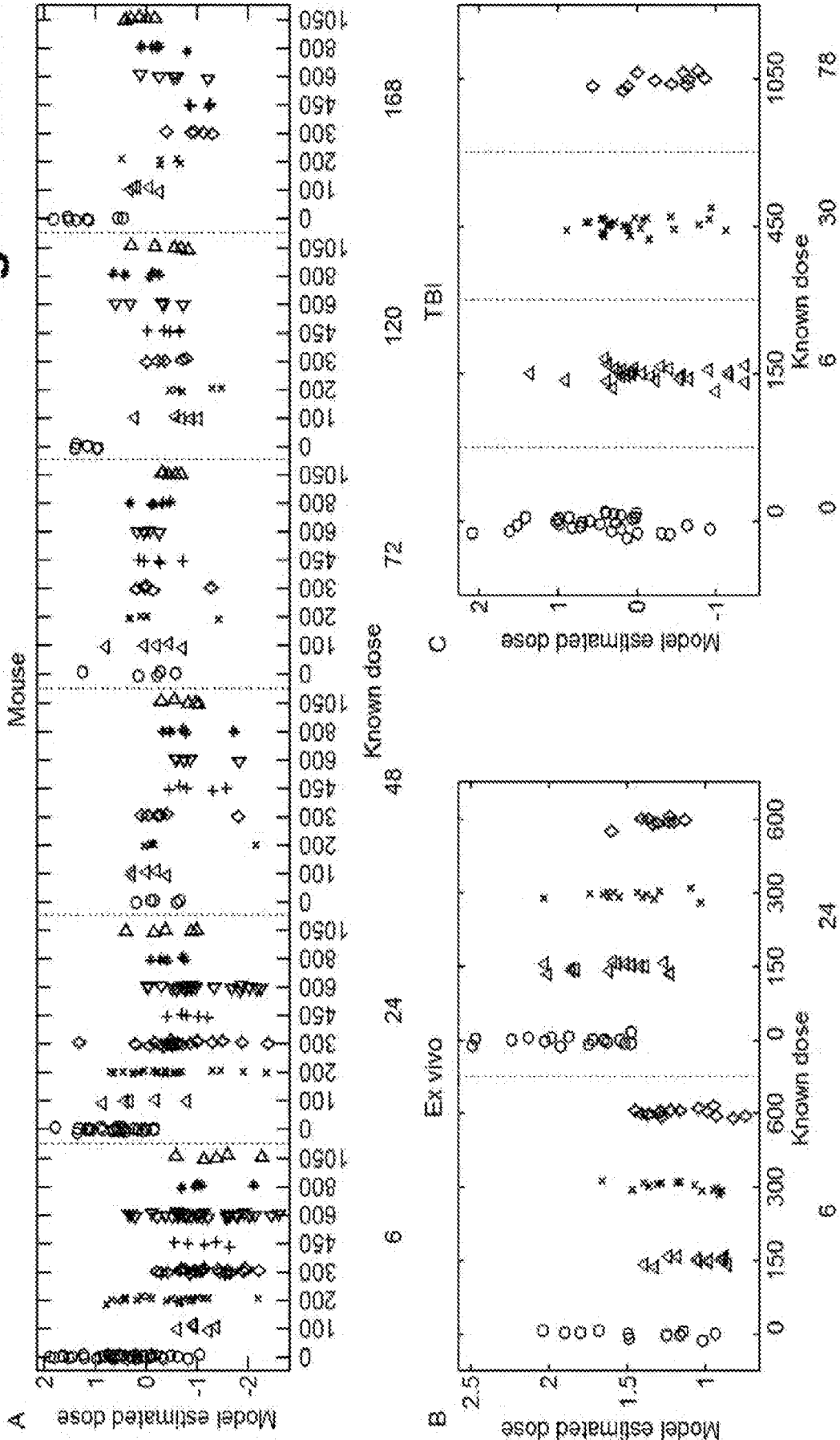


Fig. 9A Cont'd

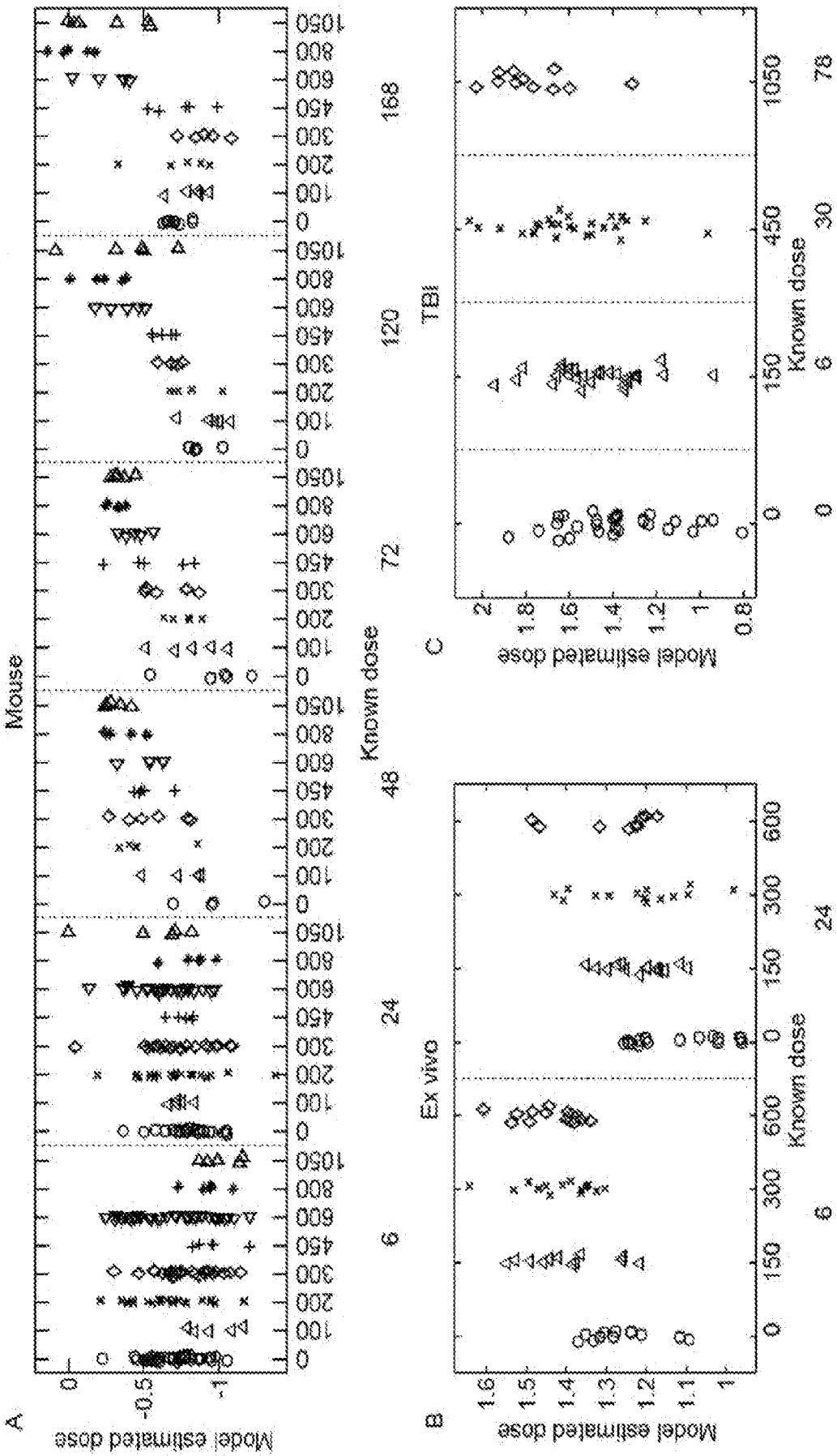


Fig. 9A Cont'd

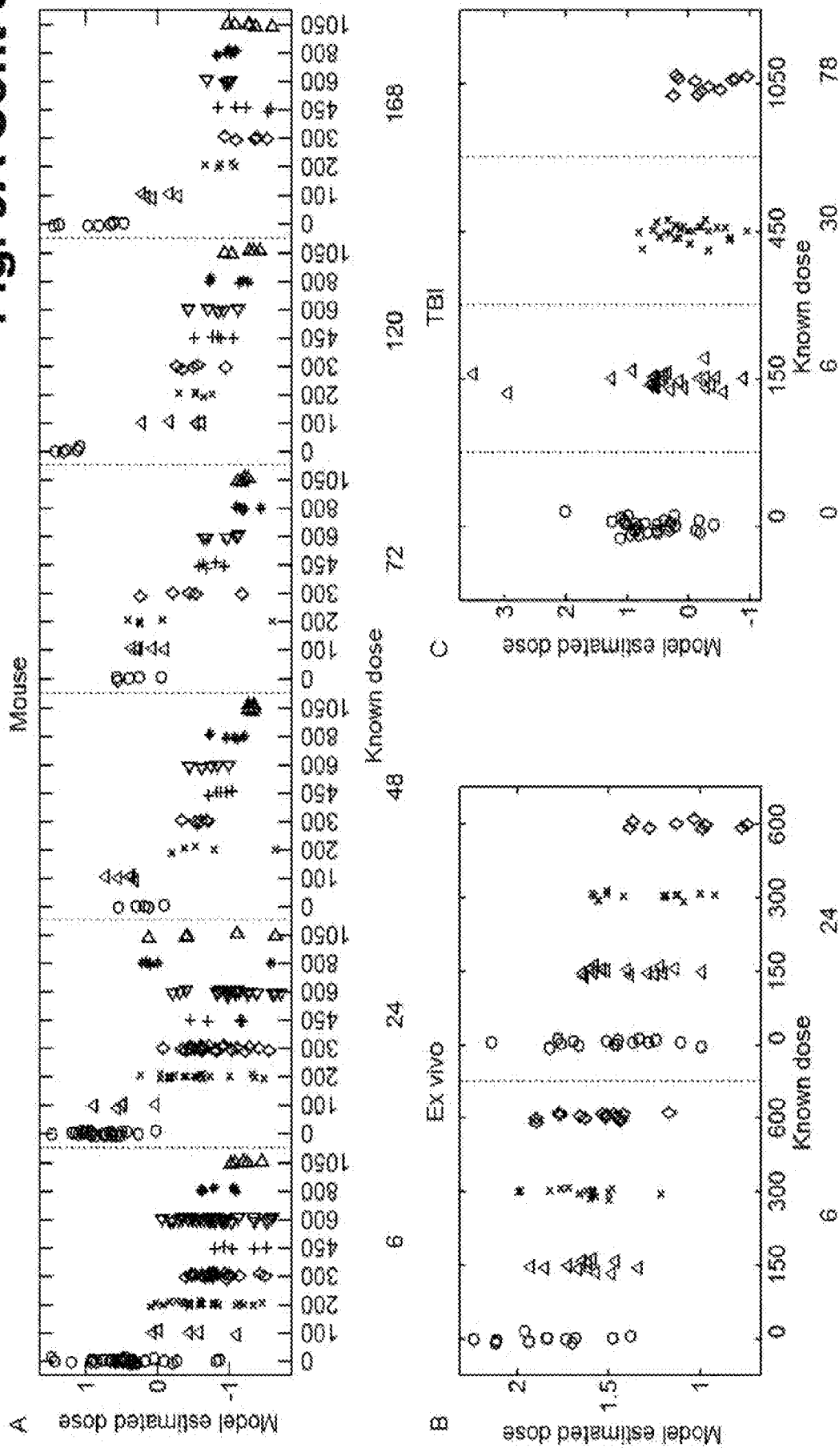


Fig. 9A Cont'd

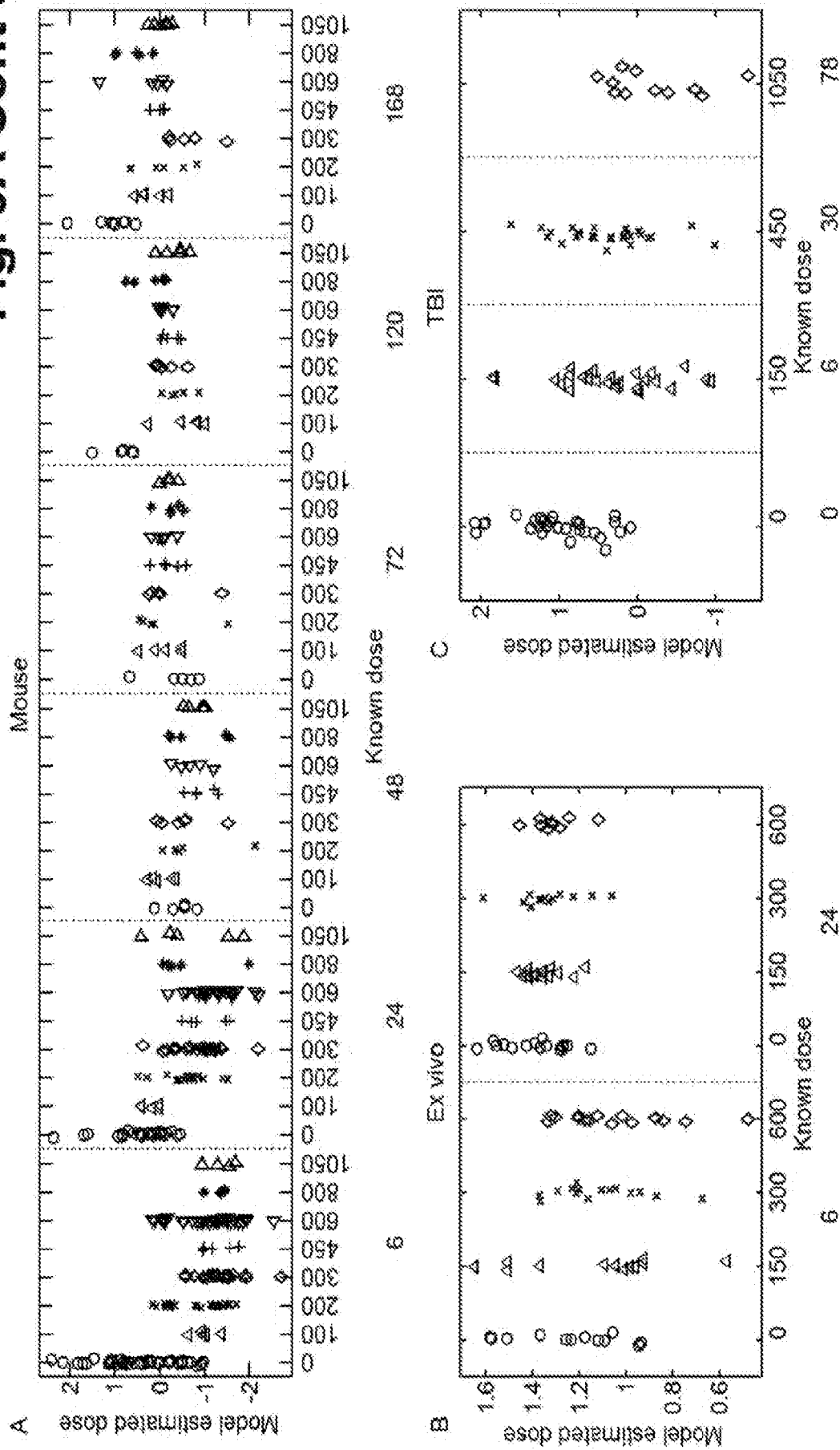


Fig. 9A Cont'd

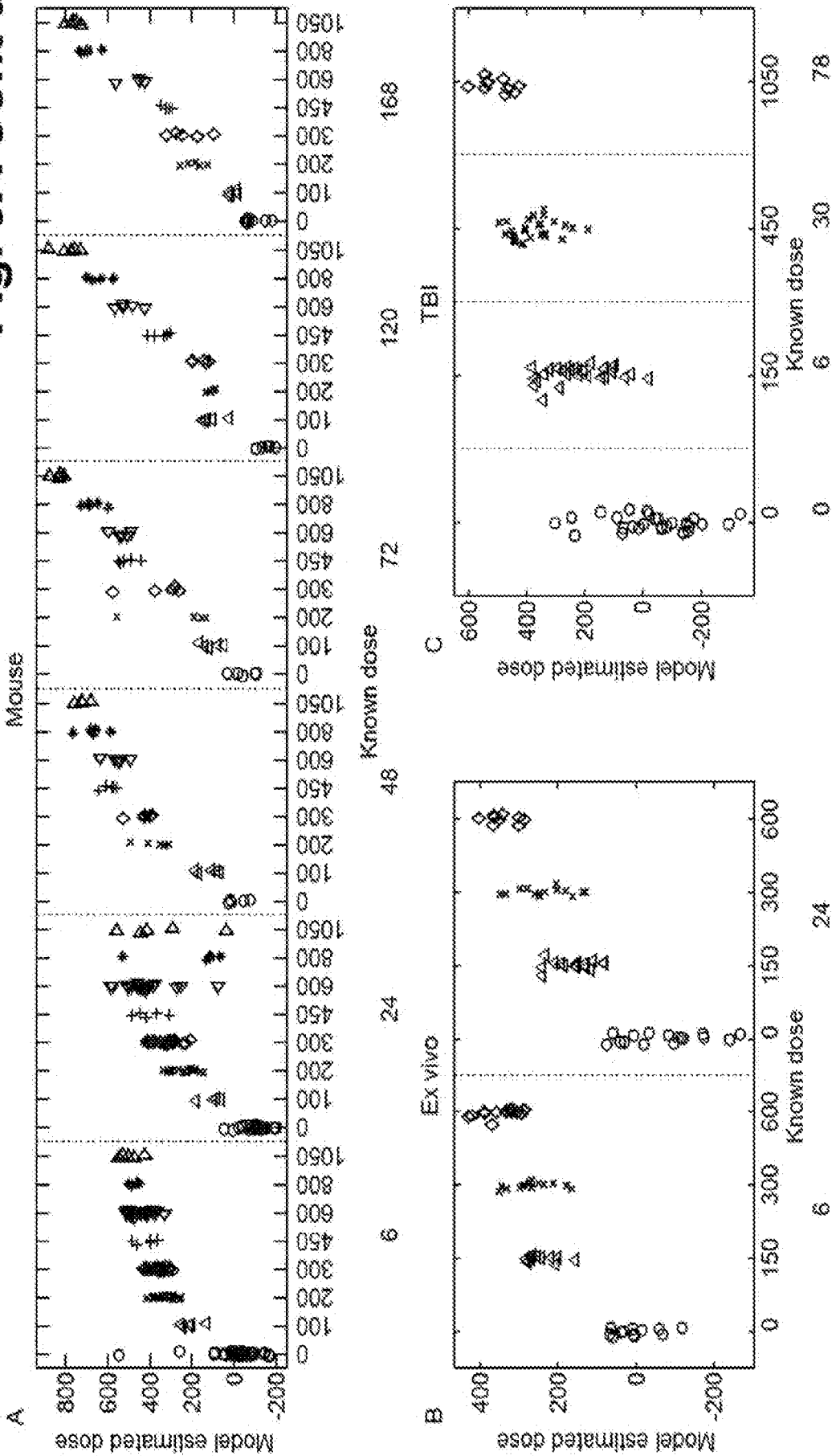


Fig. 9A Cont'd

mouse probe	human probe	publID	model-1-genes.txt gene title	gene symbol
1416957_at	205267_at	NM_0111136	"POU domain, class 2, associating factor 1"	
1417516_at	209383_at	NM_007837	DNA-damage inducible transcript 3	
1419240_at	221035_s_at	NM_031386	testis expressed gene 14	
1421098_at	220059_at	NM_019992	similar to stem cell adaptor protein STAP-1 /// signal transducing	
adaptor family	member 1 LOC100047840 /// Stap1		replication protein A1	
1423293_at	201529_s_at	BM244983		
1424305_at	Rpal		immunoglobulin joining chain	
1424638_at	212592_at	BC006026	cyclin-dependent kinase inhibitor 1A (P21)	
1425747_at	Igfj	AK007630	dedicator of cytokinesis 5	
1426025_s_at	Cdkn1a	BC016533	lysosomal-associated protein transmembrane 5	
1427005_at	Dock5	U29539	polo-like kinase 2 (Drosophila)	
1427468_at	Laptm5	BM234765	"protein phosphatase 3, catalytic subunit, beta isoform"	
1427718_a_at	Plk2	M81483	transformed mouse 3T3 cell double minute 2	
1427844_a_at	Ppp3cb	X58876	"CCAAT/enhancer binding protein (C/EBP), beta"	
1429319_at	Mdm2	AB012278	"ras homolog gene family, member H"	
1434994_at	Cebpb	BM243660	death effector domain-containing	
1448182_a_at	Rhoh	BE199280	CD24a antigen	
1448356_at	Dedd	NM_009846	ubiquitin-conjugating enzyme E2D 2	
1448500_a_at	Cd24a	NM_019912	Lck interacting transmembrane adaptor 1	
1448957_at	201345_s_at	NM_023684	recombination signal binding protein for immunoglobulin kappa 3	
region	Ube2d2		"pleckstrin homology-like domain, family A, member 3"	
1449002_at	219541_at	NM_009035	astrotactin 2	
1450309_at	211974_x_at	Rbpj		
	218634_at	NM_013750		
	Phlda3			
	215407_s_at	NM_019514		
	Astn2			

Fig. 9A Cont'd

1454891_at	212864_at	8M214378	model-1-genes.txt
1456542_s_at	Cds2	88517855	CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 2
1460407_at	218949_s_at	BM244106	glutaminyl-trNA synthase (glutamine-hydrolyzing)-like 1
	Grs11		Spi-B transcription factor (Spi-1/Pu.1 related)
	205861_at		
	SpiB		

Fig. 9B

Name	Size	Packed Size	Modified
* Mad2l1.png	46 570	42 805	2011-10-25 11:00
* Nacc2.png	45 998	42 494	2011-10-25 11:00
* Plekho2.png	47 585	44 271	2011-10-25 11:00
* Rasl12.png	49 260	45 968	2011-10-25 11:00
* Rps27l.png	48 074	44 827	2011-10-25 11:00
* Slpr1.png	46 049	42 464	2011-10-25 11:00
* Tnfsf4.png	48 103	44 373	2011-10-25 11:00
* Vpreb3.png	44 298	40 772	2011-10-25 11:00
* Aspa.png	48 920	45 324	2011-10-25 10:59
* Bax.png	46 892	43 255	2011-10-25 10:59
* Bckdk.png	47 616	43 997	2011-10-25 11:00
* Cd27.png	49 867	46 494	2011-10-25 11:00
* Cd79a.png	47 632	43 978	2011-10-25 10:59
* Cdc25b.png	46 356	43 015	2011-10-25 11:00
* Cpt2.png	48 470	45 102	2011-10-25 10:59
* Ermp1.png	49 447	46 102	2011-10-25 11:00
* Fas.png	45 362	41 575	2011-10-25 11:00
* Gna15.png	48 192	44 636	2011-10-25 11:00
* H2afv.png	47 034	43 397	2011-10-25 11:00
* Lck.png	47 410	43 819	2011-10-25 11:00
* model-2.png	46 431	42 987	2011-10-25 10:58
model-2-genes.txt	3 570	1 056	2011-10-25 10:58

Fig. 9B Cont'd

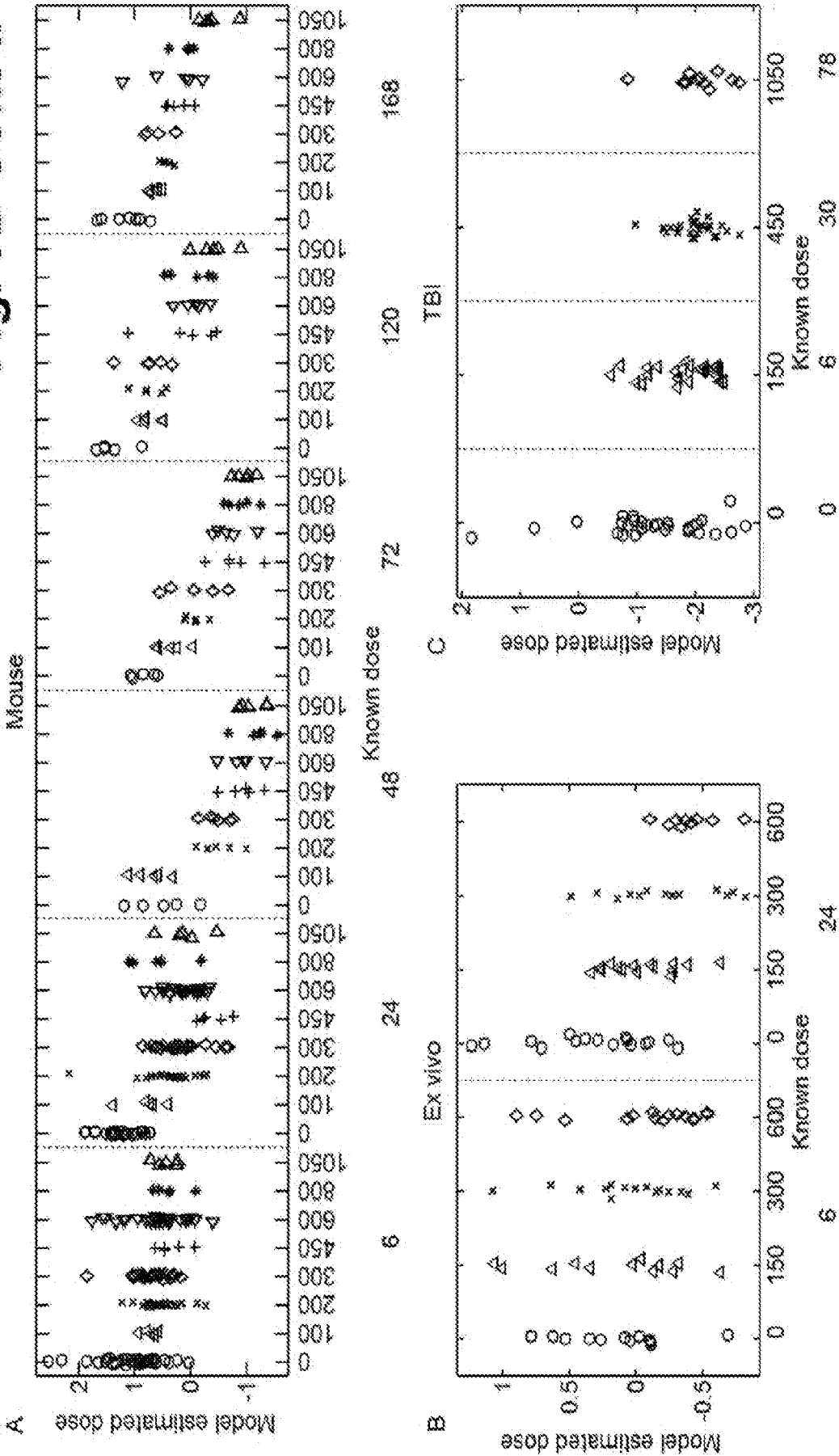


Fig. 9B Cont'd

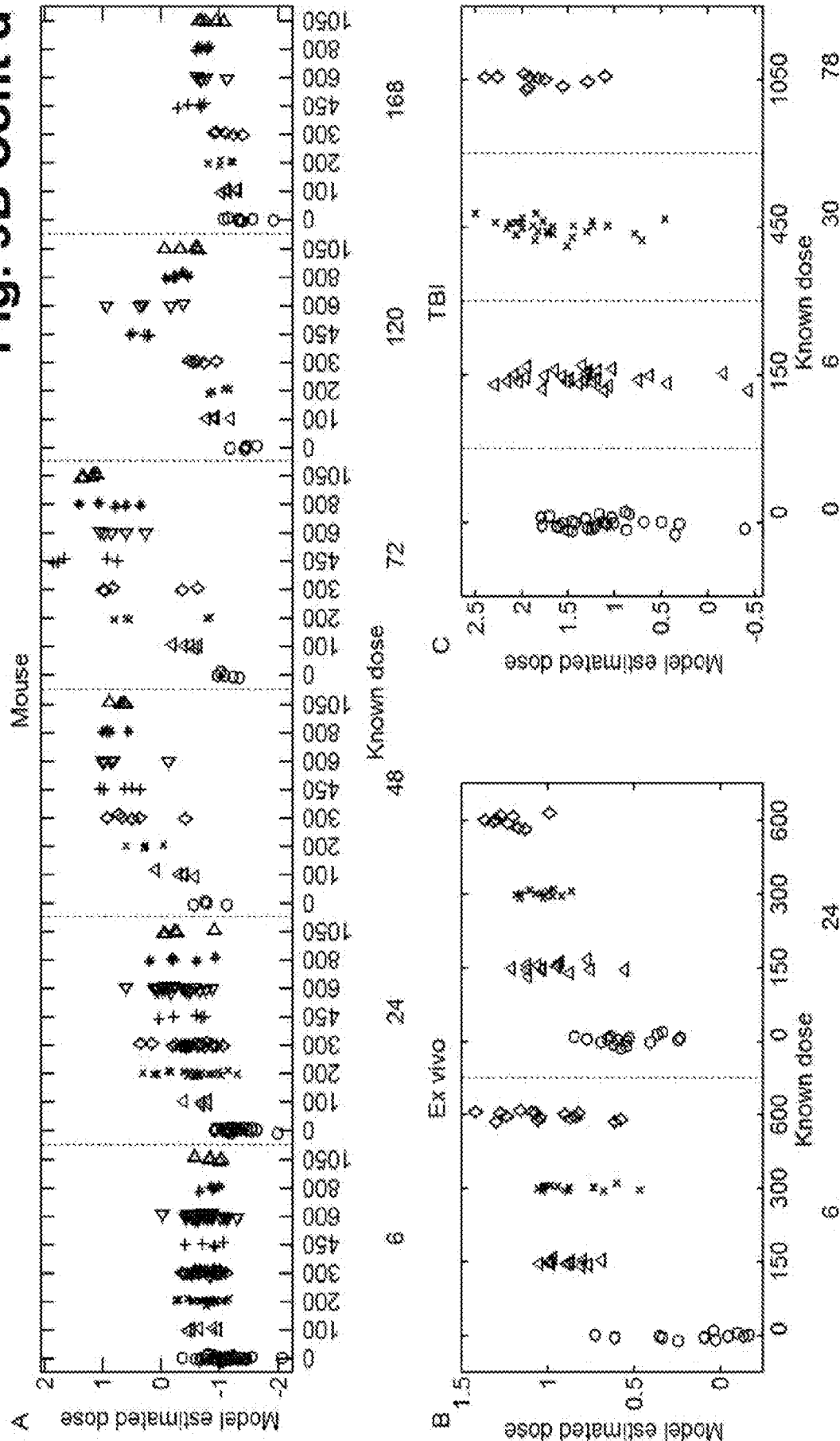


Fig. 9B Cont'd

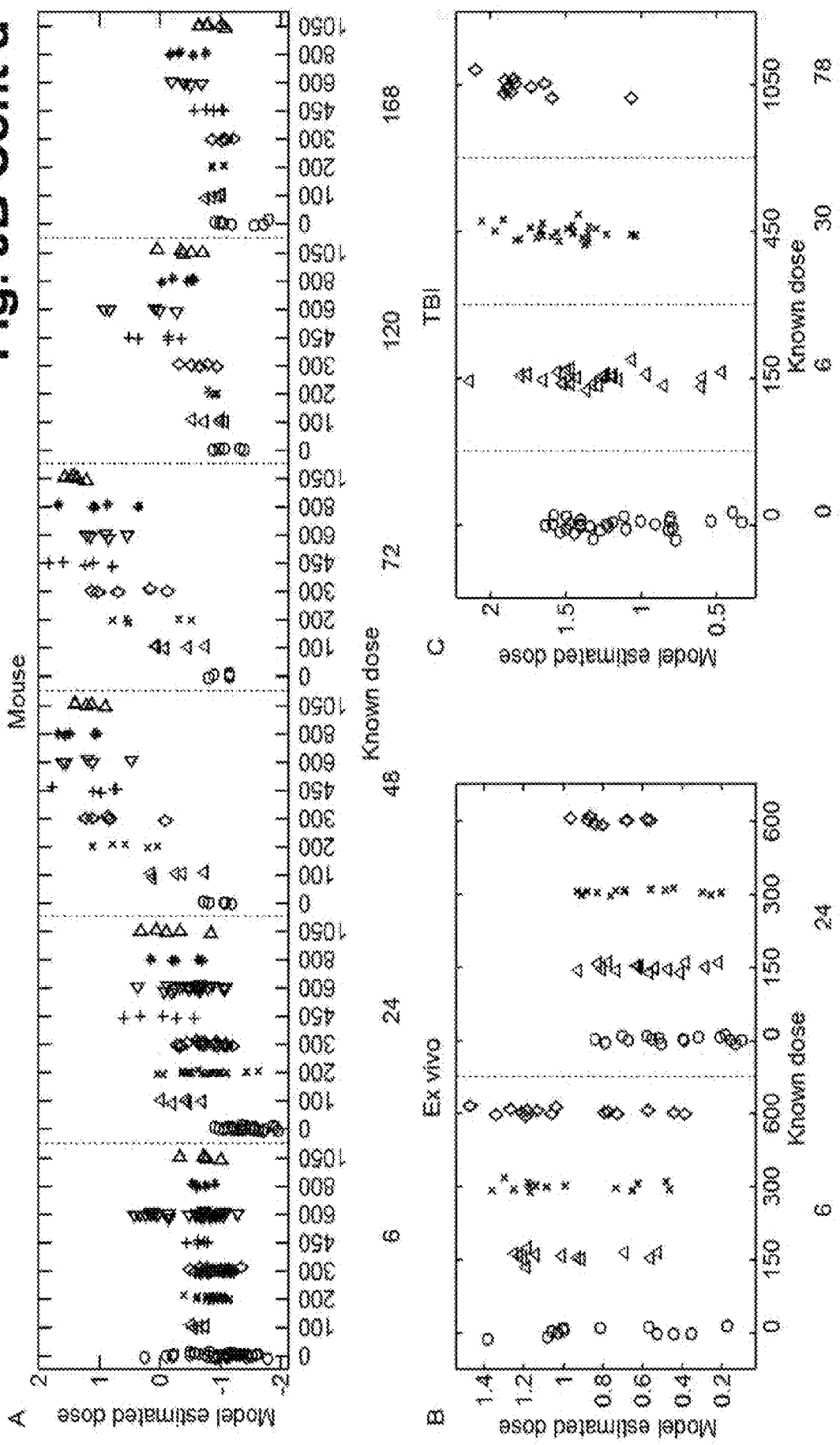


Fig. 9B Cont'd

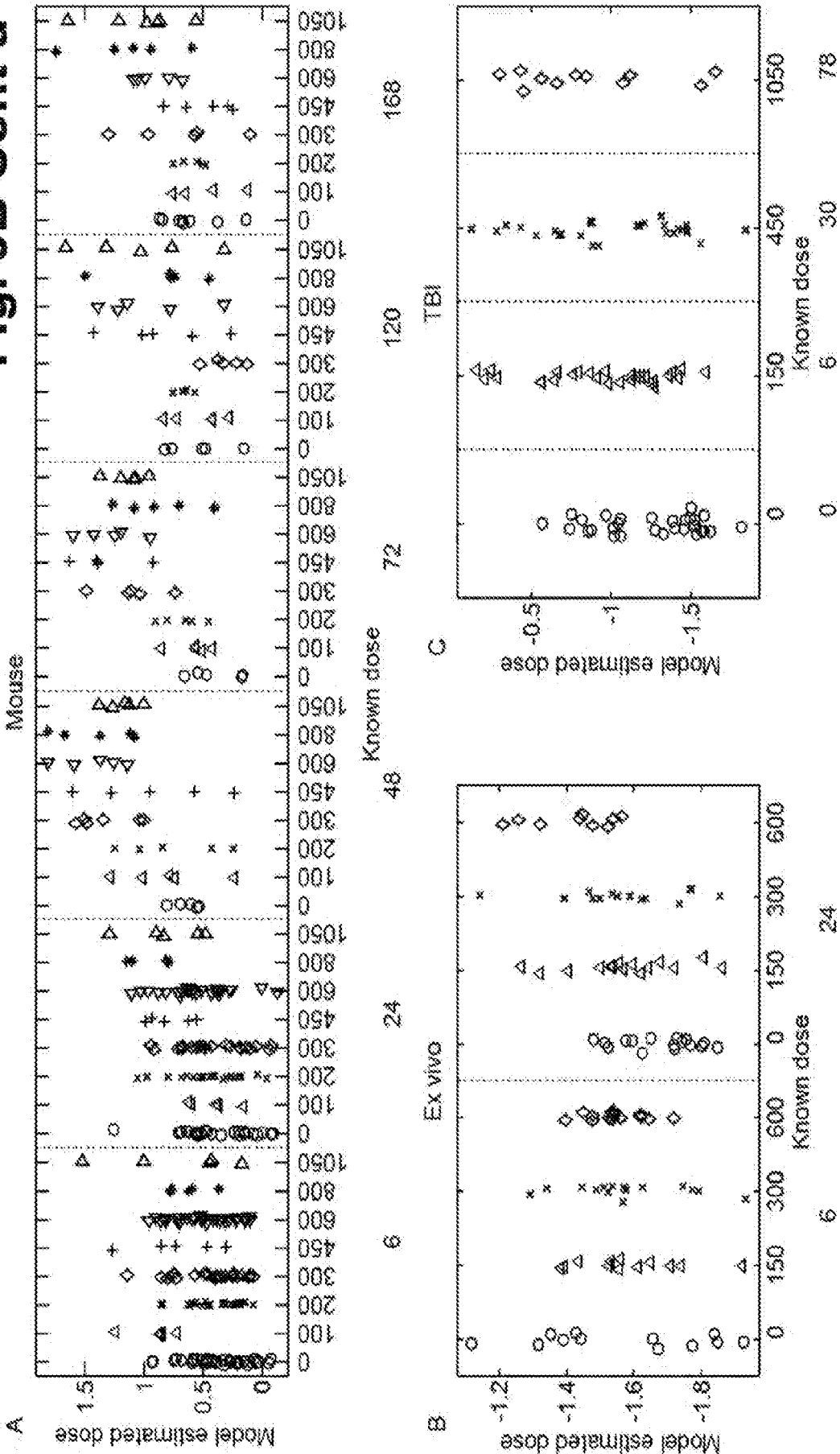


Fig. 9B Cont'd

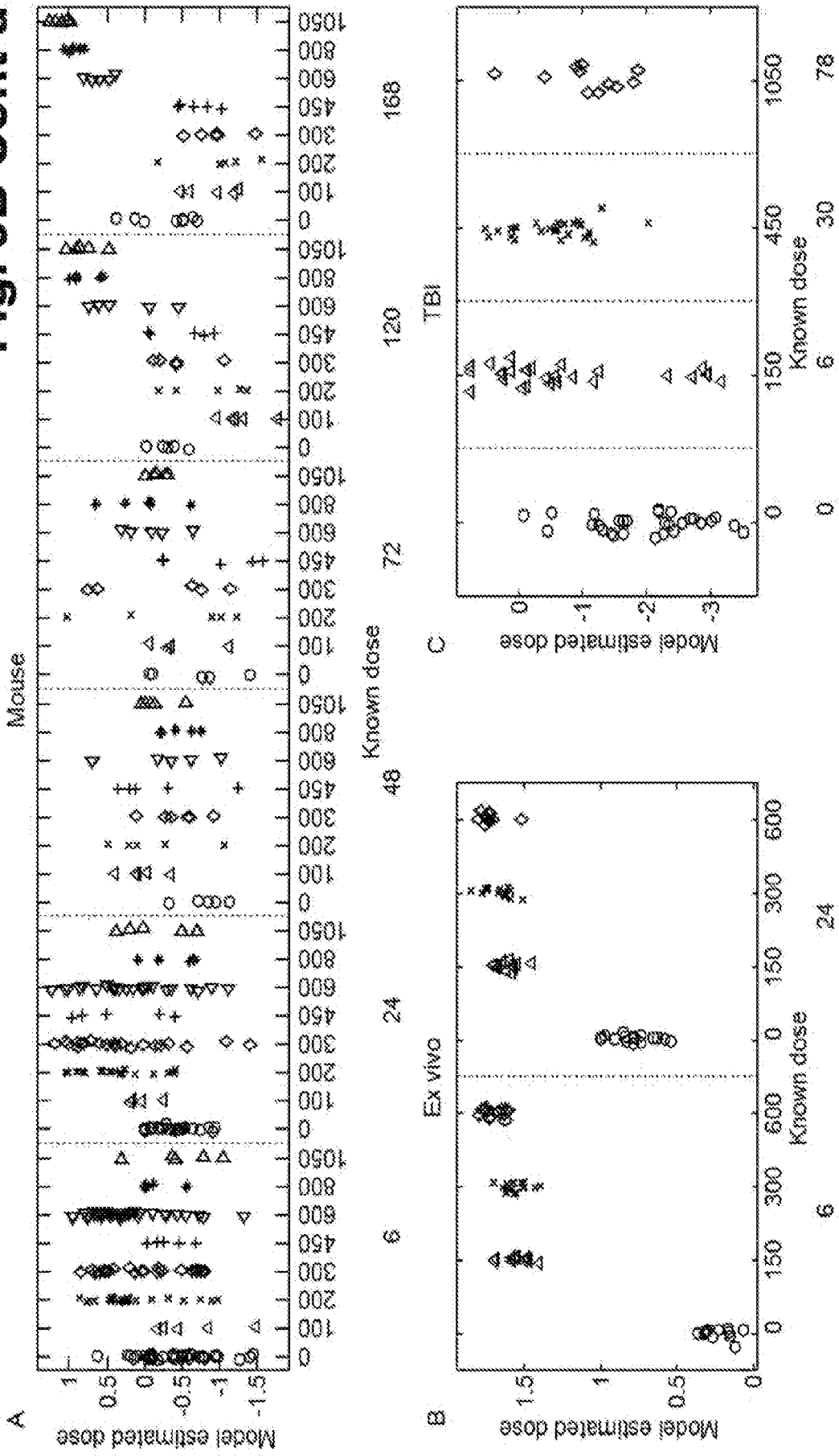


Fig. 9B Cont'd

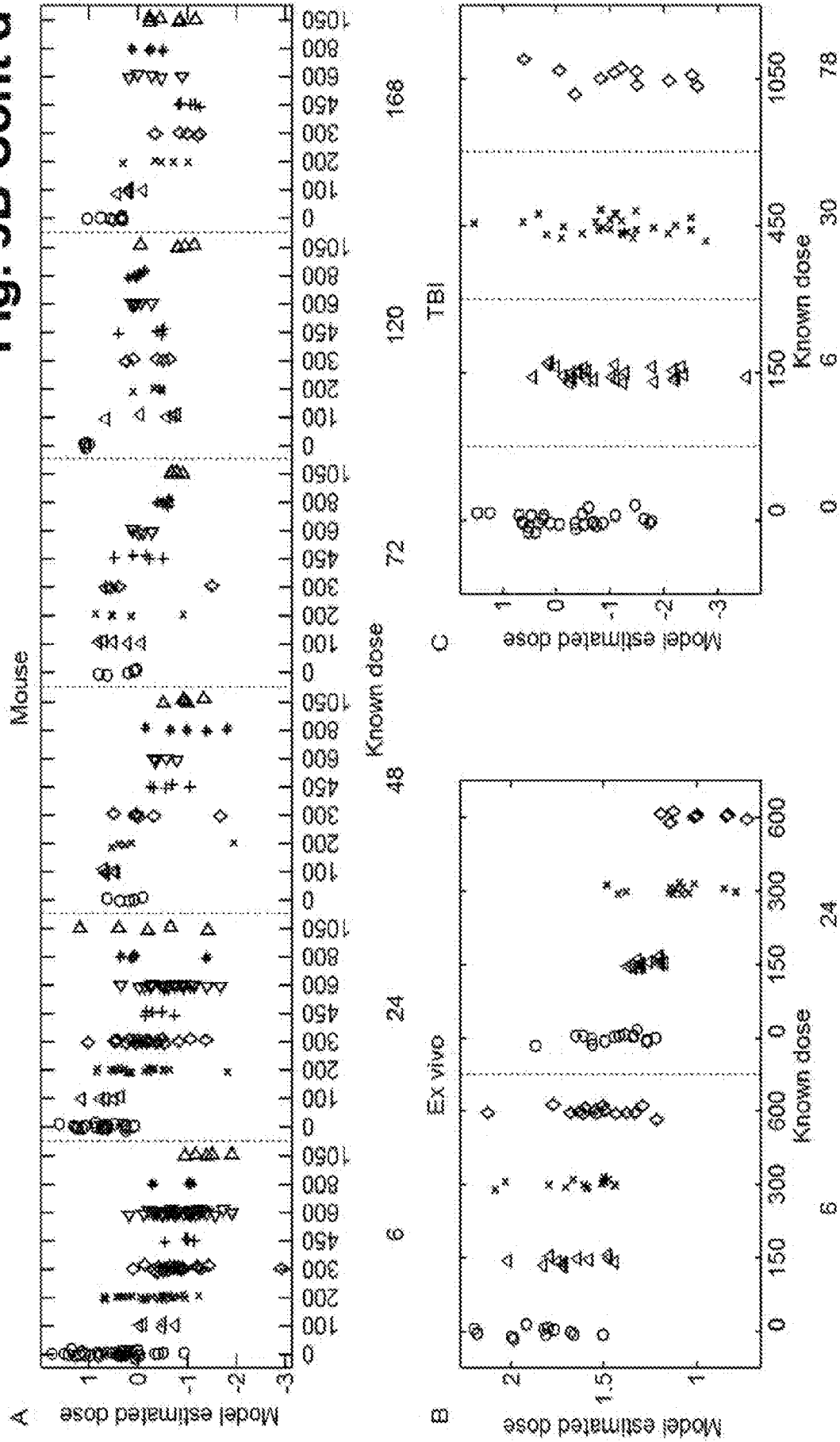


Fig. 9B Cont'd

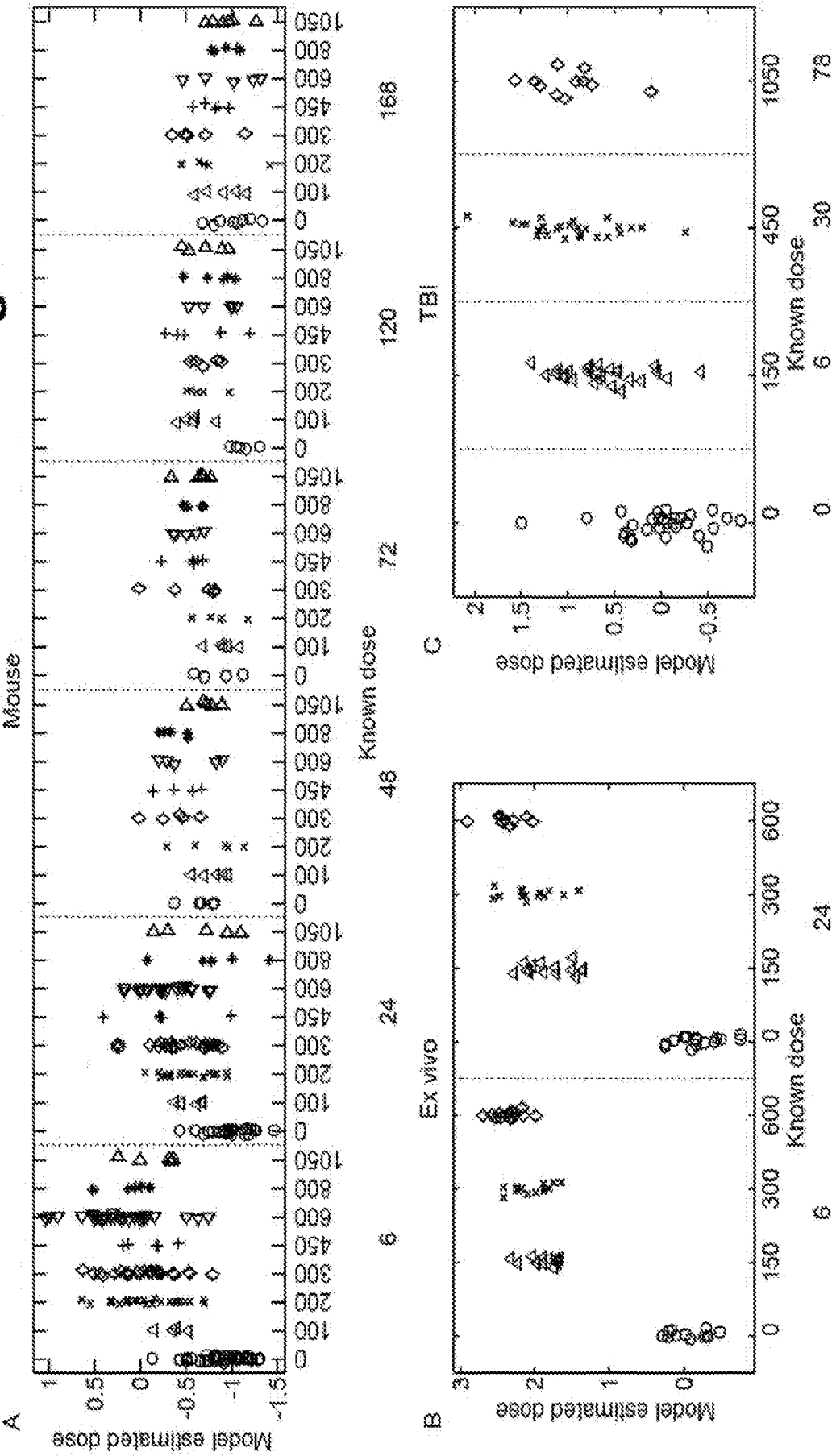


Fig. 9B Cont'd

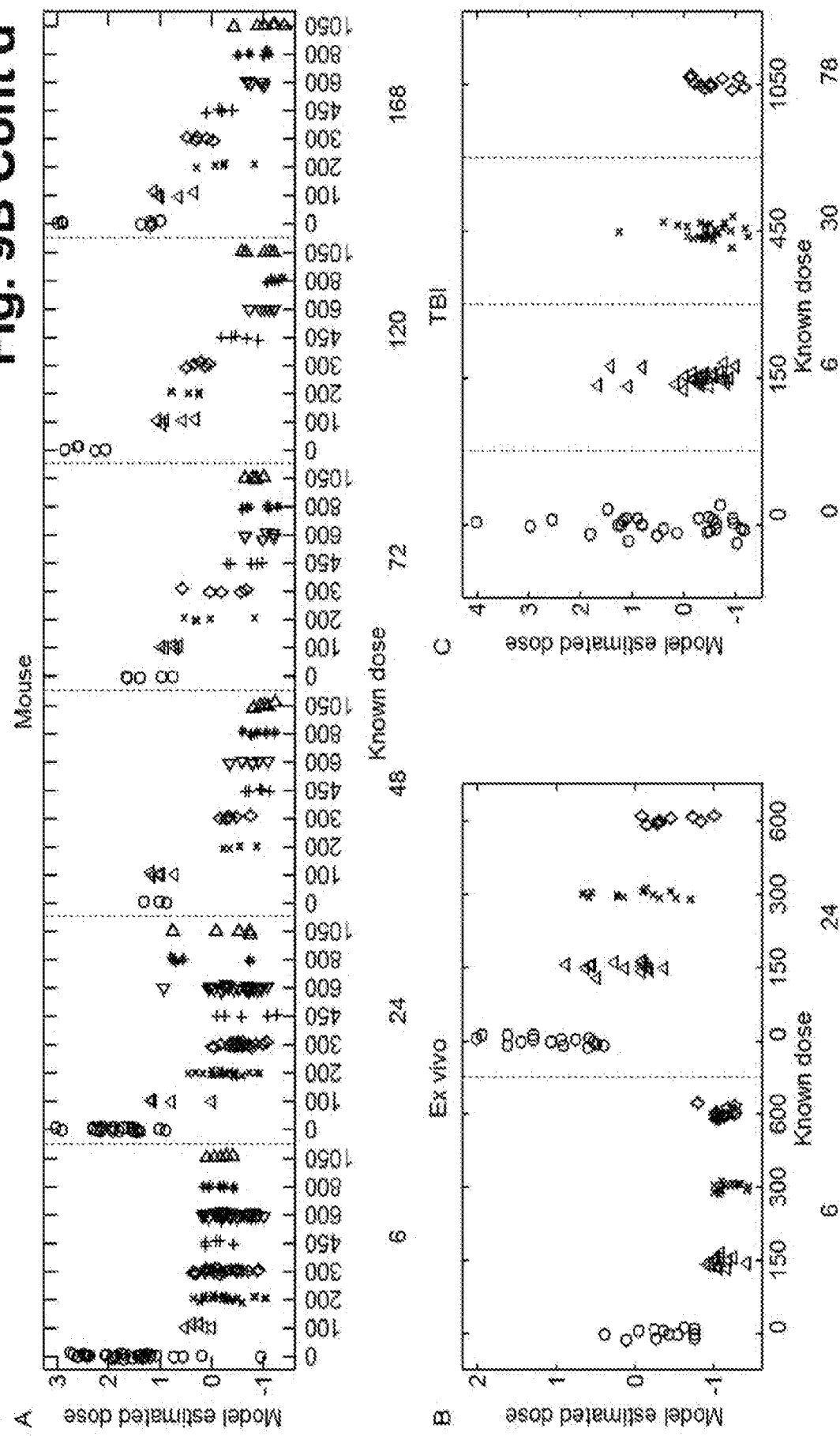


Fig. 9B Cont'd

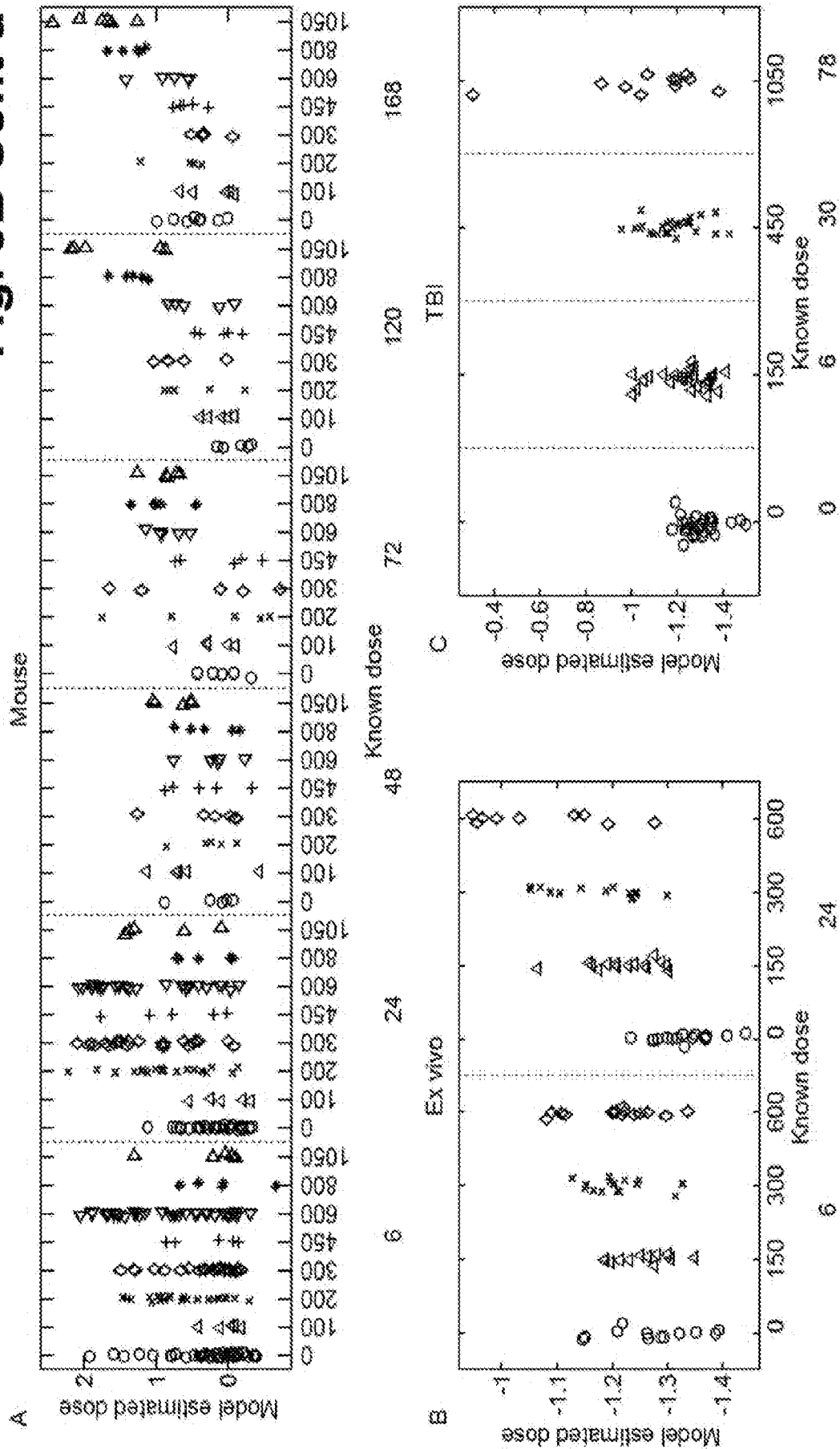


Fig. 9B Cont'd

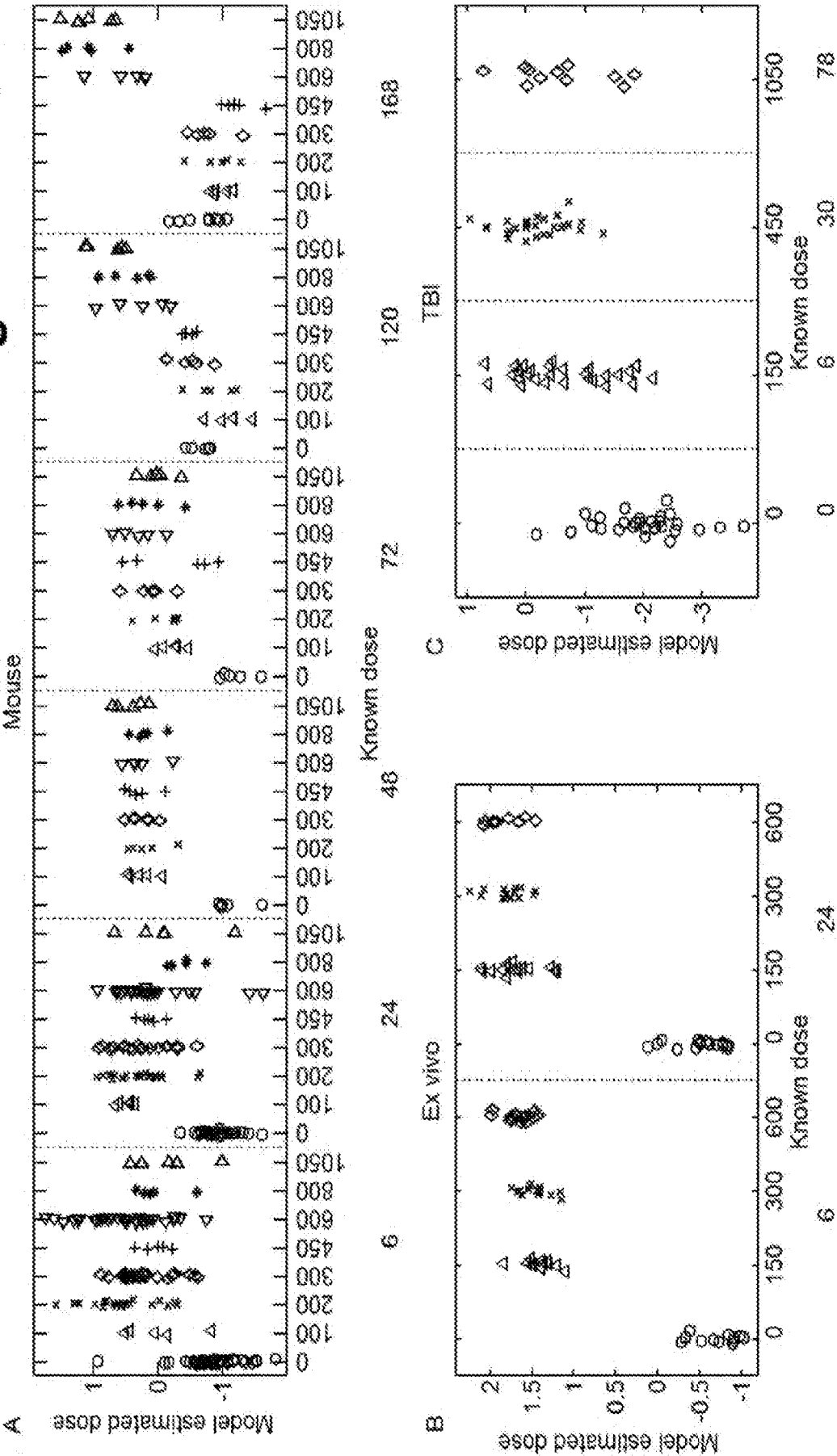


Fig. 9B Cont'd

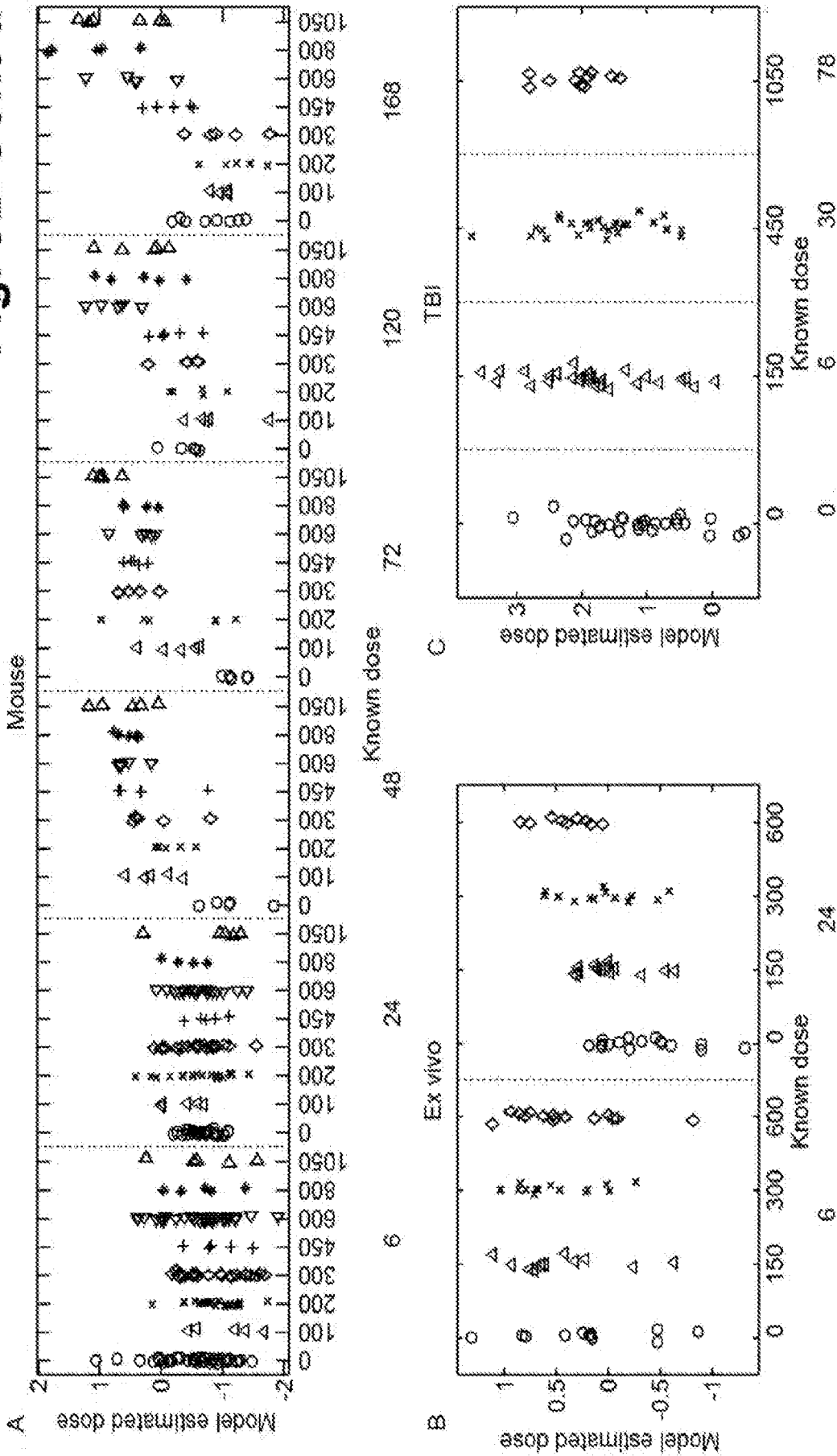


Fig. 9B Cont'd

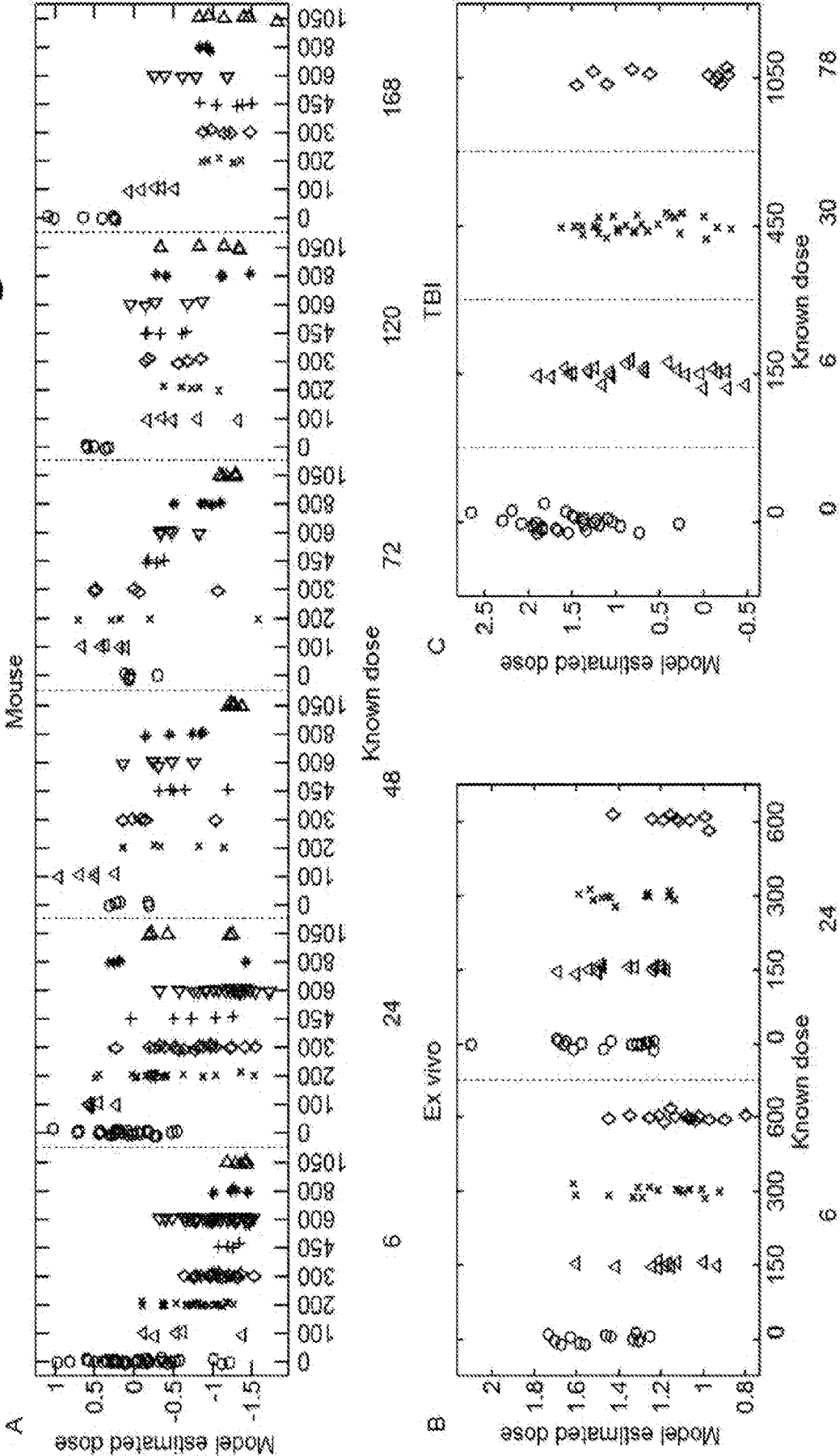


Fig. 9B Cont'd

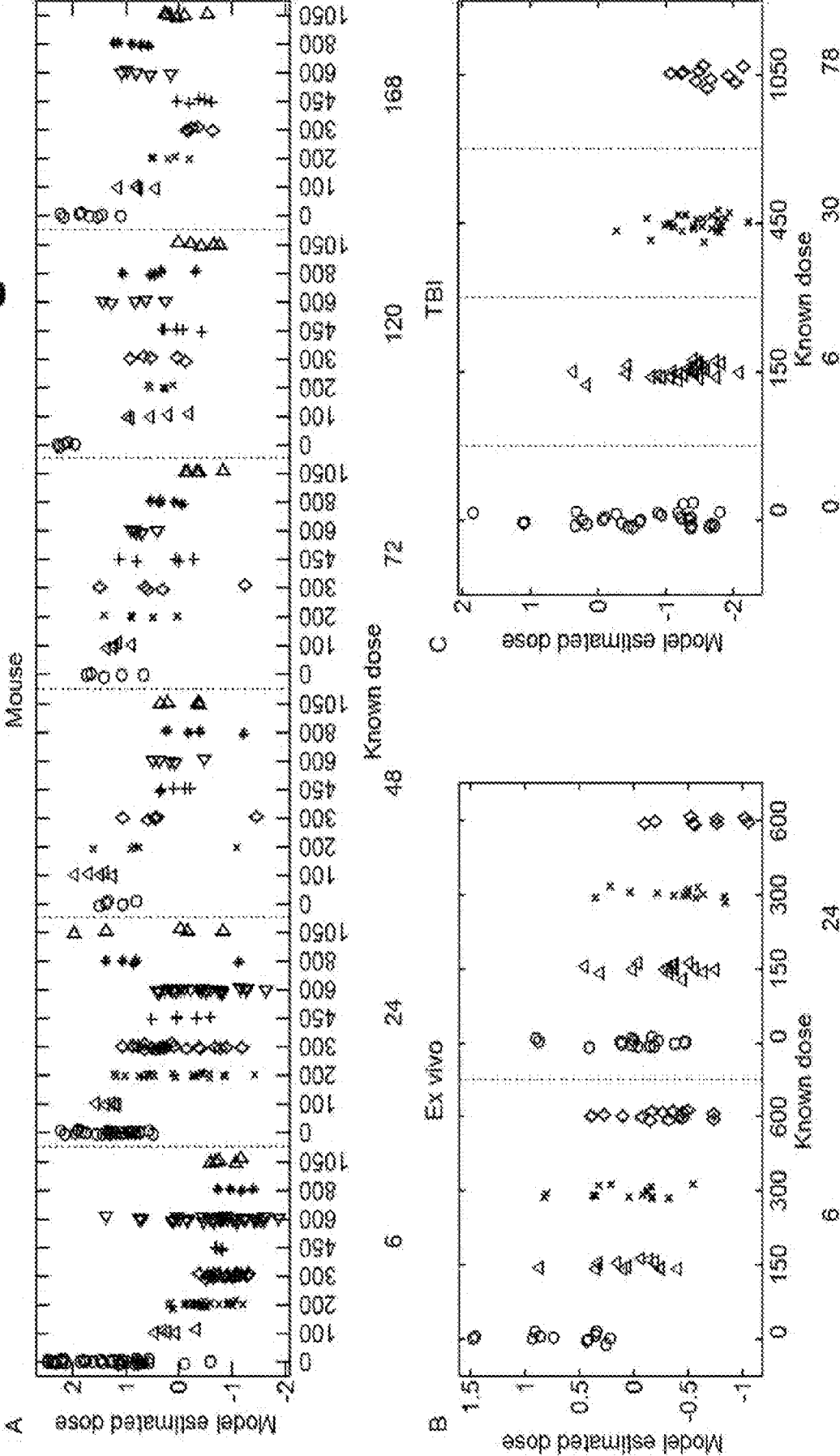


Fig. 9B Cont'd

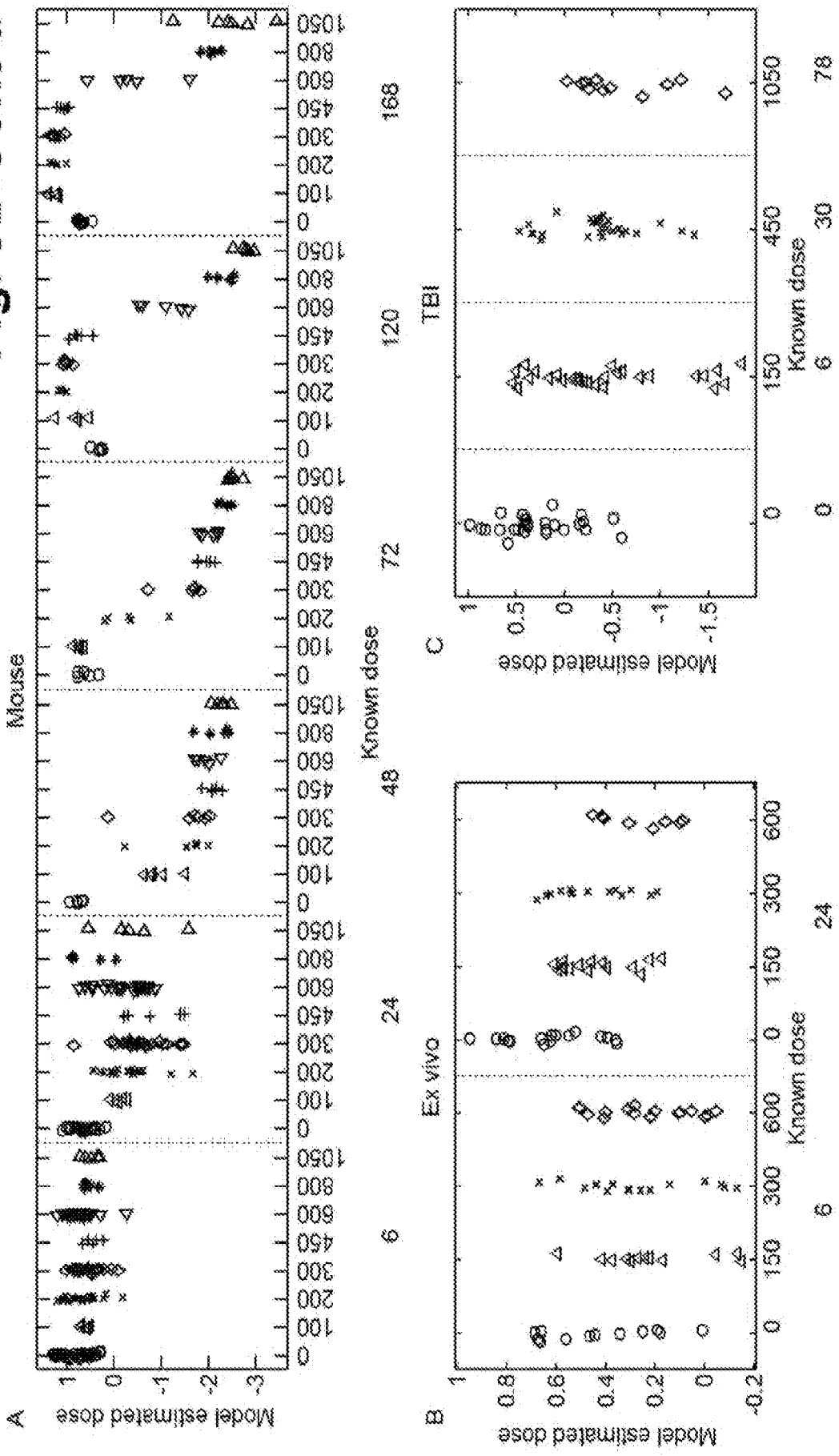


Fig. 9B Cont'd

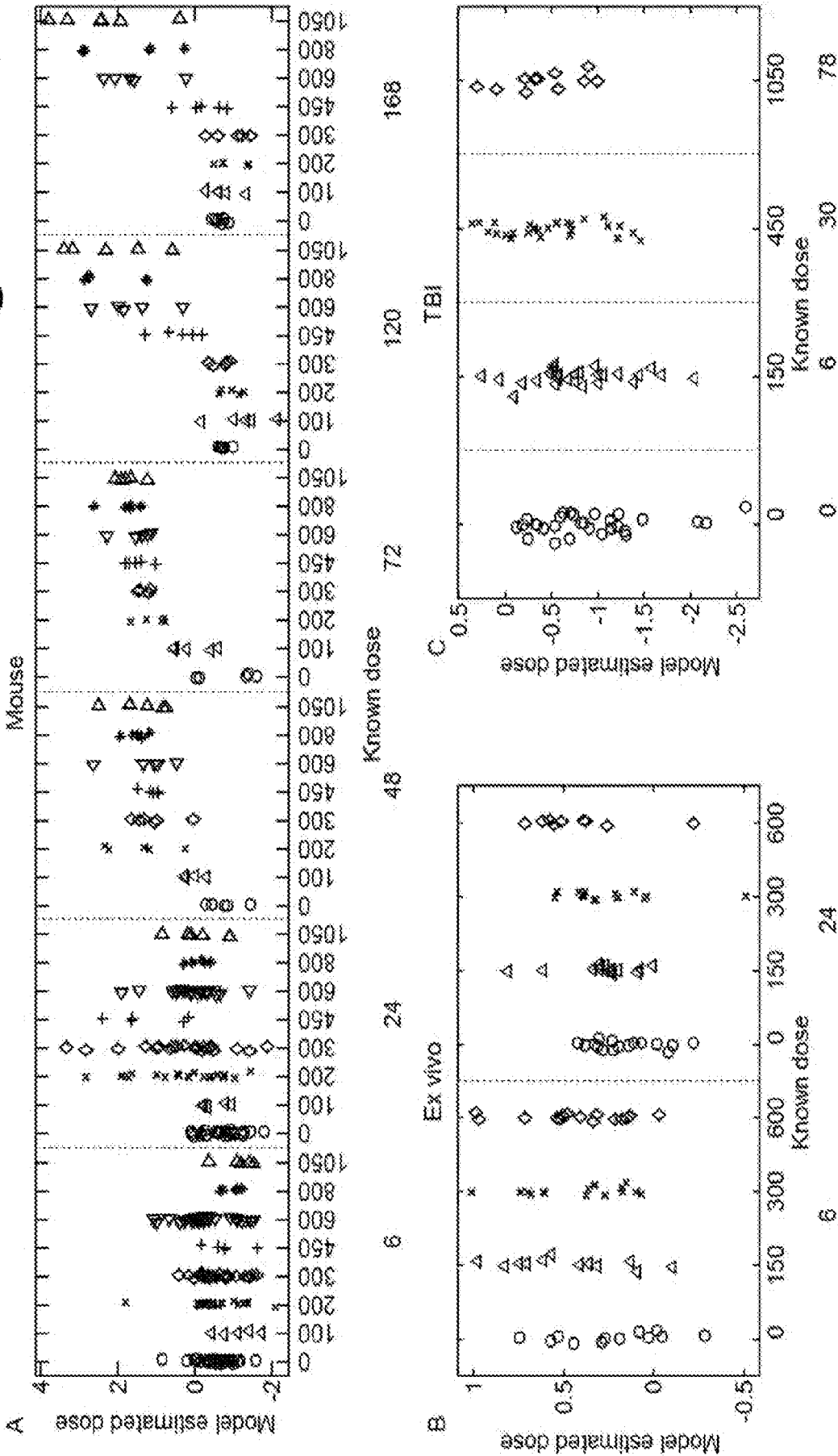


Fig. 9B Cont'd

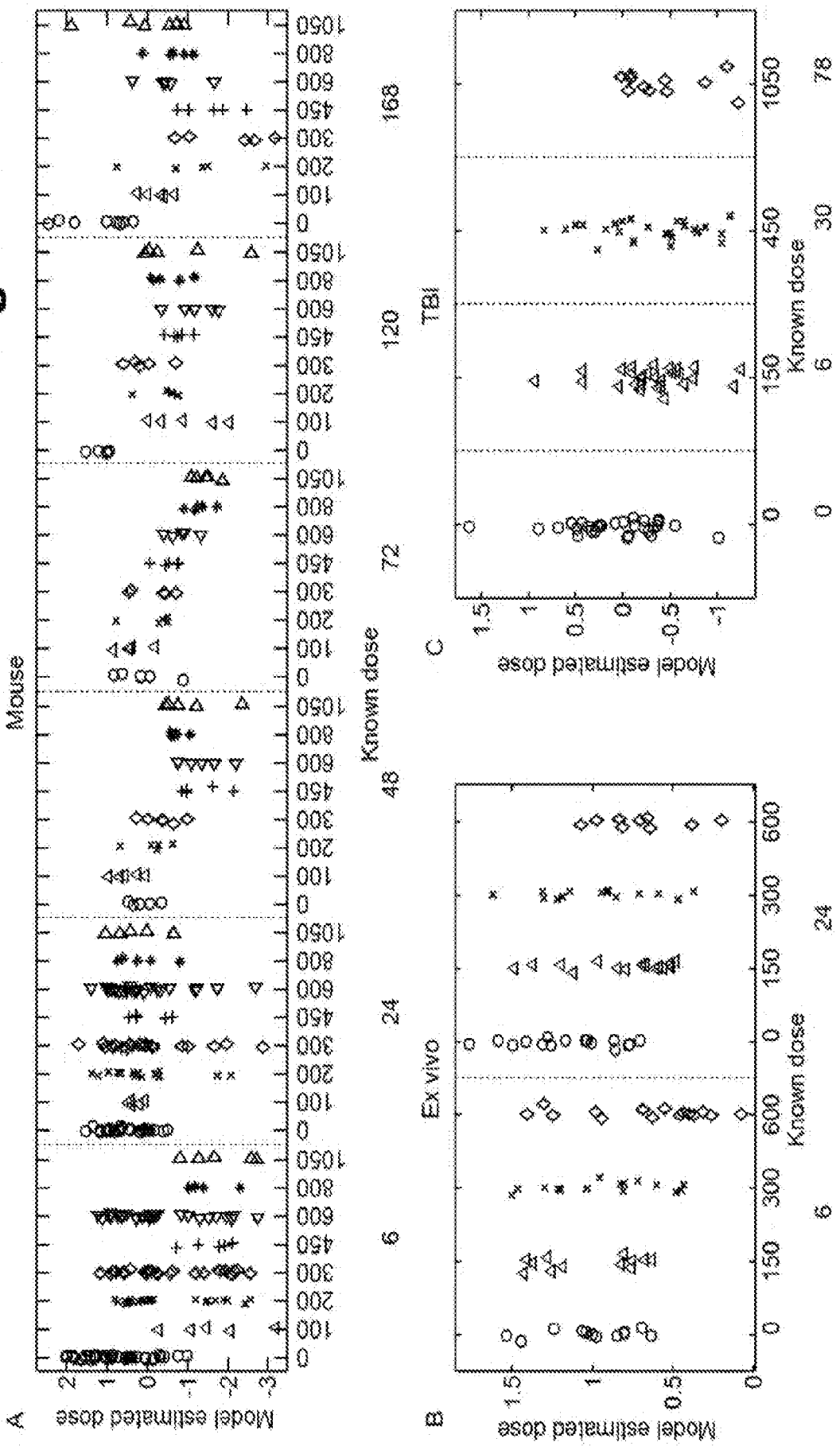


Fig. 9B Cont'd

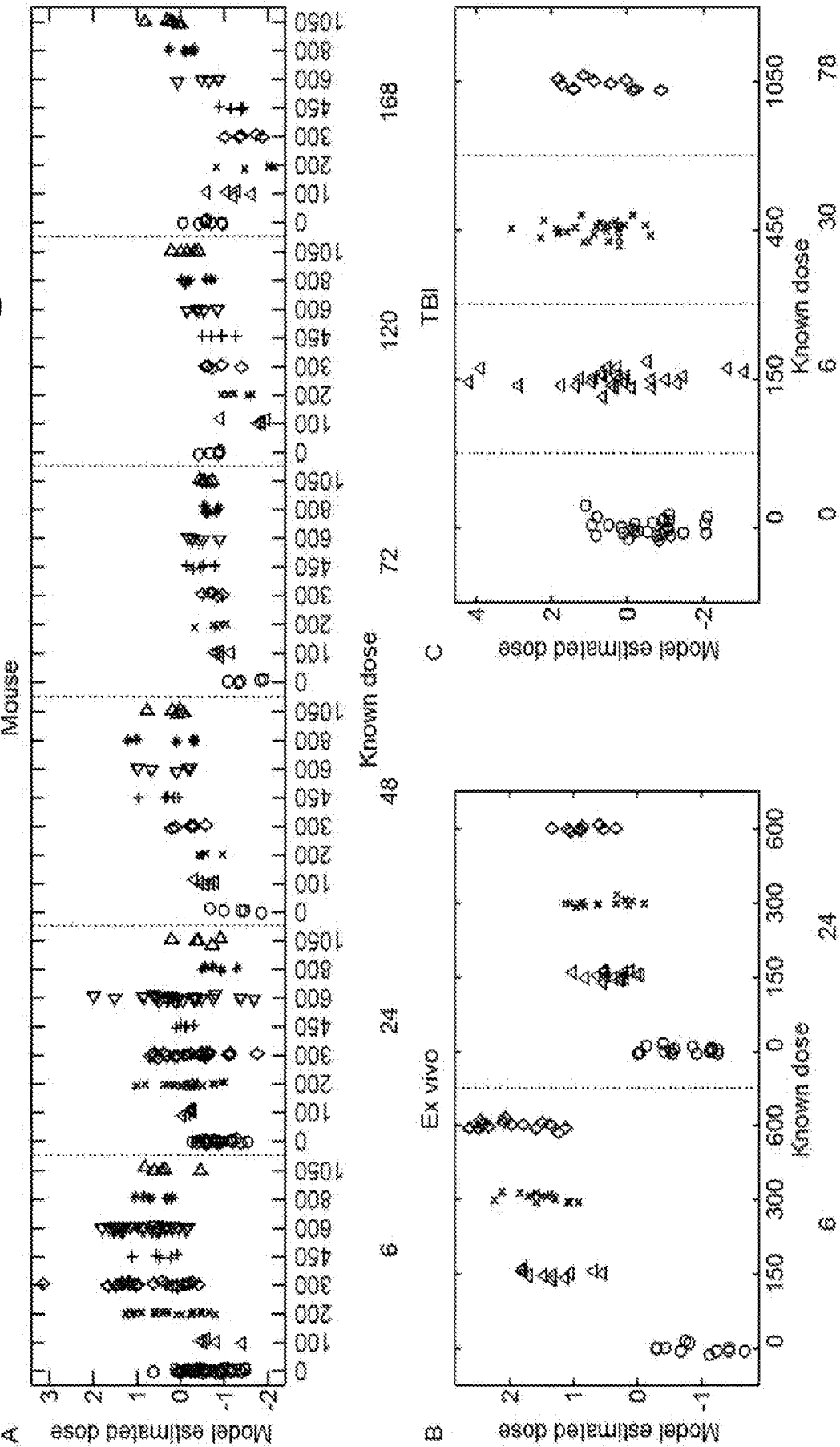


Fig. 9B Cont'd

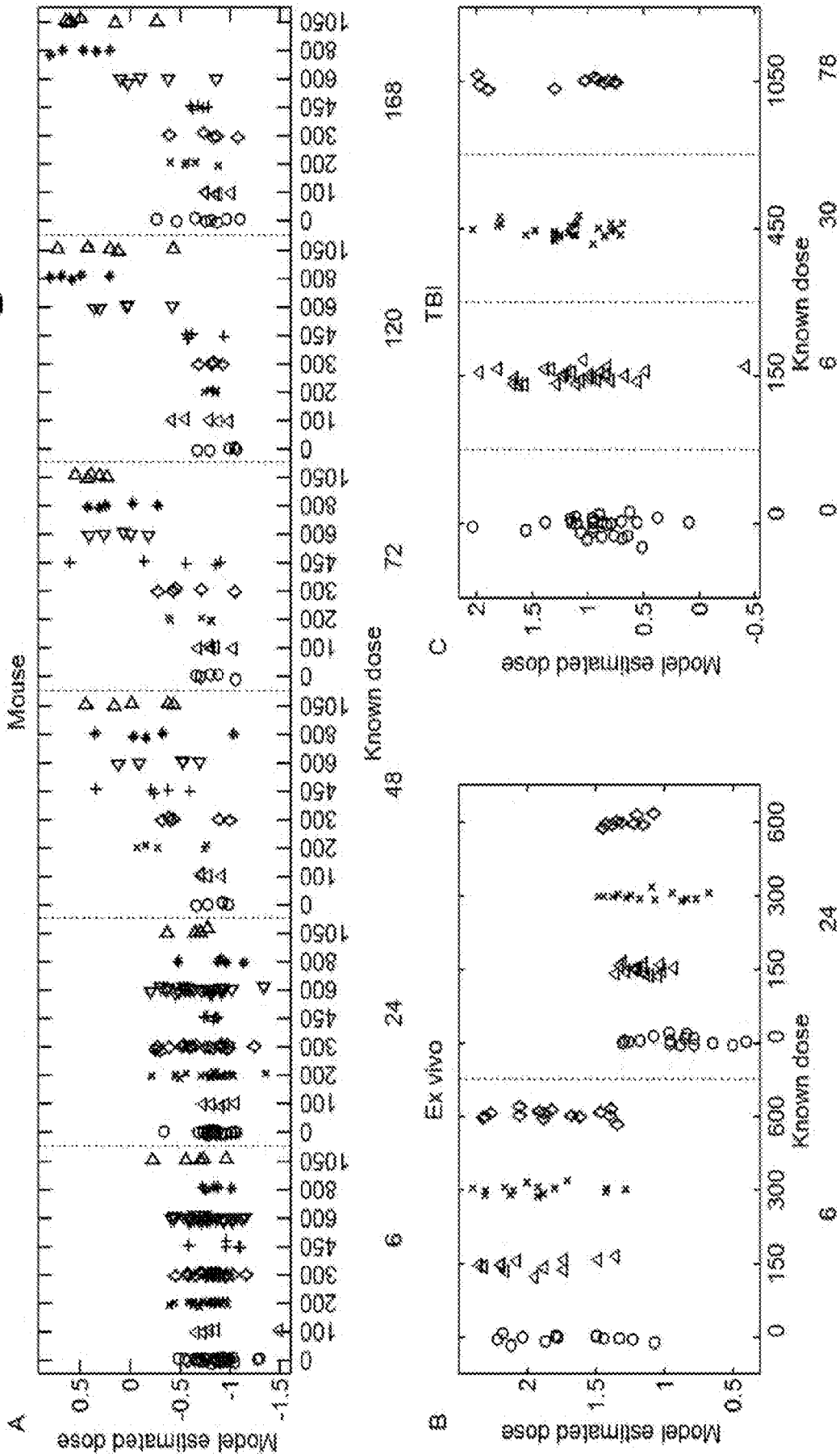


Fig. 9B Cont'd

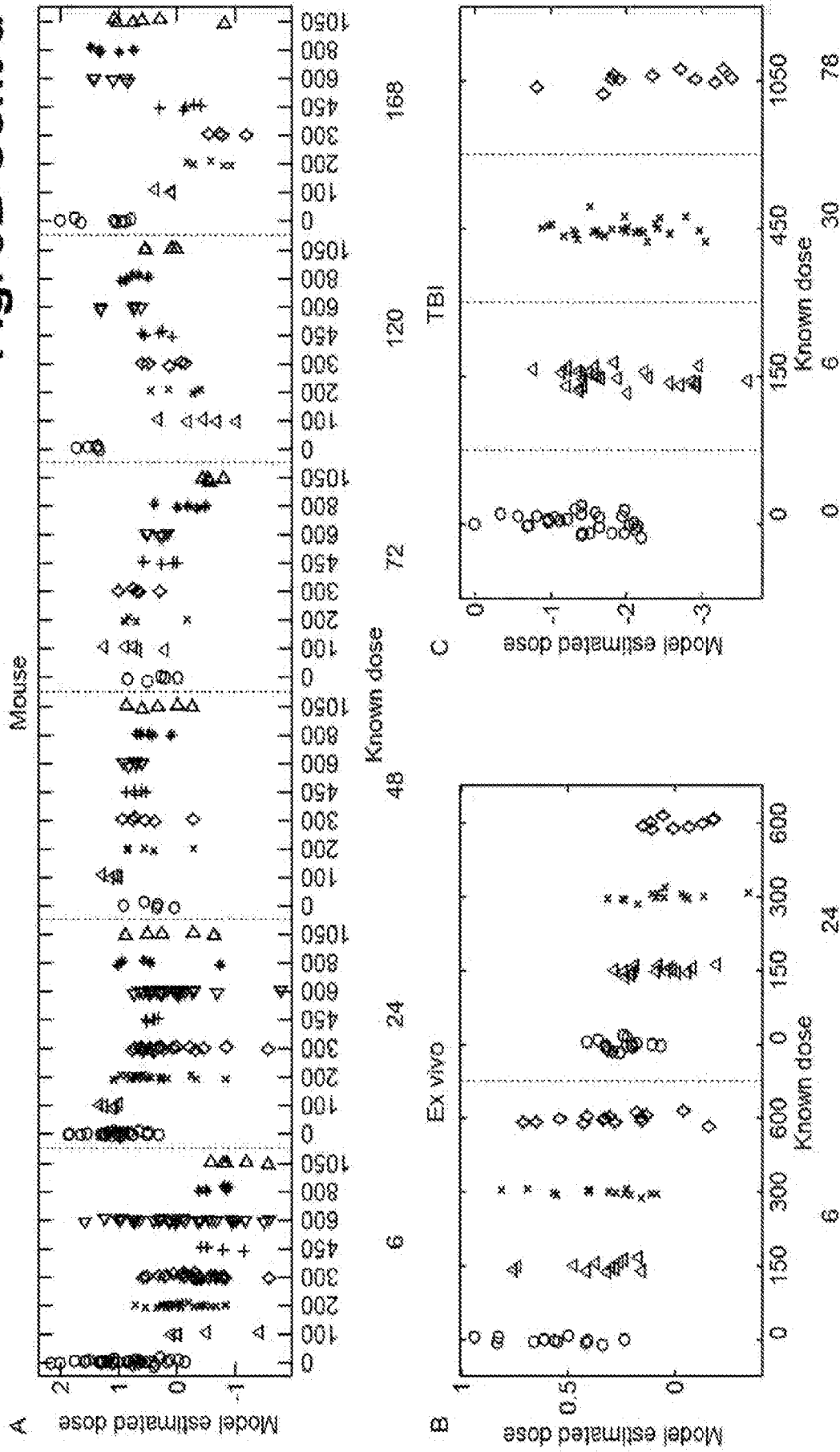


Fig. 9B Cont'd

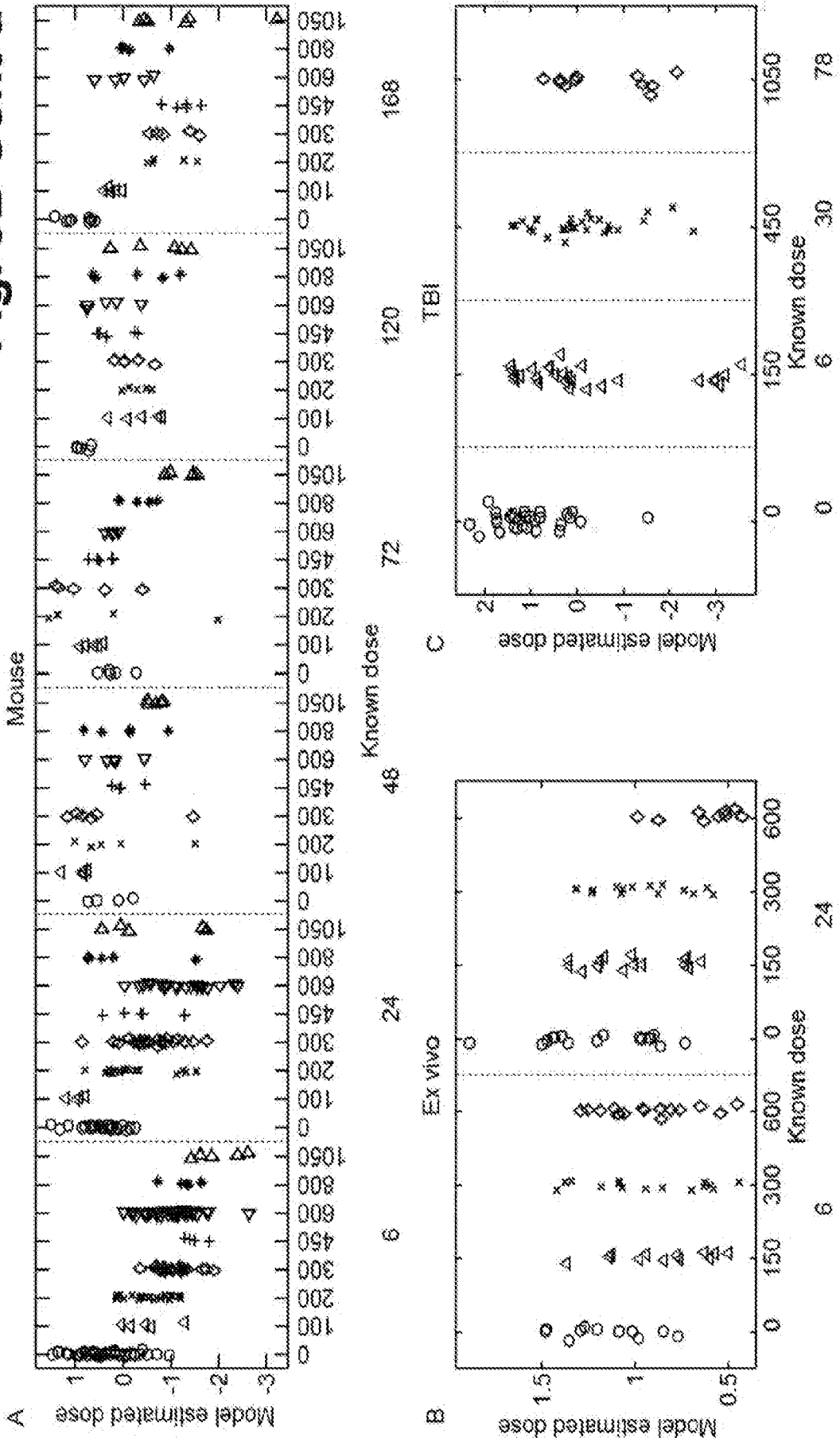


Fig. 9B Cont'd

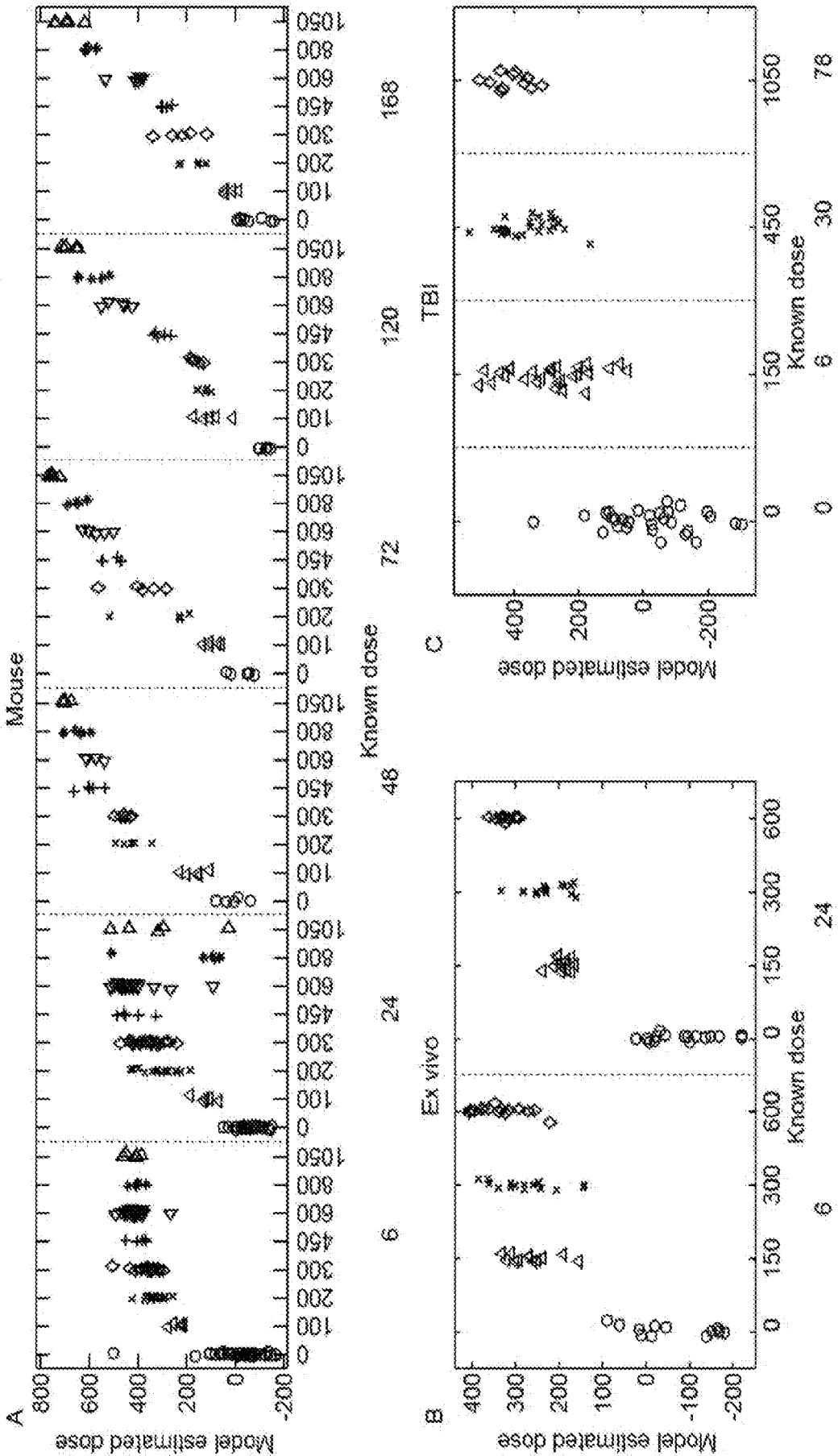


Fig. 9B Cont'd

mouse probe	human probe	model-2-genes.txt publiCID	gene title	gene symbol
1416772_at	204264_at	NM_009949	carnitine palmitoyltransferase 2	Cpt2
1416837_at	211833_s_at	BC018228	BCL2-associated X protein	Bax
1418472_at	206030_at	BC024934	aspartoacylase	Aspa
1418830_at	205049_s_at	NM_007655	CD79A antigen	
(immunoglobulin-associated alpha)	207426_s_at	NM_009452	"tumor necrosis factor (ligand)	
(immunoglobulin-associated alpha)	201853_s_at	NM_023117	cell division cycle 25 homolog B (S.	
1421302_a_at	205349_at	NM_010304	guanine nucleotide binding protein,	
alpha 15				
Gna15				
1421744_at	207426_s_at	NM_009452	"tumor necrosis factor (ligand)	
superfamily, member 4"				
Inf4				
1421963_a_at	201853_s_at	NM_023117	cell division cycle 25 homolog B (S.	
pombe)				
Cdc25b				
1422460_at	203362_s_at	NM_019499	MAD2 mitotic arrest deficient-like 1	
(yeast)				
Mad211				
1422921_at	220068_at	NM_009514	pre-B lymphocyte gene 3	
Vpreb3				
1423571_at	204642_at	BB133079	sphingosine-1-phosphate receptor 1	
Slpr1				
1425396_a_at	204891_s_at	BC011474	lymphocyte protein tyrosine kinase	Lck

Fig. 9B Cont'd

model-2-genes.txt			
1427103_at containing, family O member 2" plekho2	204436_at	AA049040	"pleckstrin homology domain
1428029_a_at	212206_s_at	BC028539	"H2A histone family, member V"
H2afv			
1428067_at	219167_at	AK014511	"RAS-like, family 12"
Ras112			
1429582_at and BTB (POZ) domain containing"	212993_at	BB360604	"nucleus accumbens associated 2, BEN
Nacc2			
1433702_at metallopeptidase 1	218342_s_at	BI663634	endoplasmic reticulum
Ermp1			
1450925_a_at	218007_s_at	BB836796	ribosomal protein S27-like
Rps271			
1452389_at	206150_at	L24495	CD27 antigen
			cd27
1460251_at 6)	216252_x_at	NM_007987	Fas (TNF receptor superfamily member Fas
1460644_at dehydrogenase kinase Bckdk	202030_at	NM_009739	branched chain ketoacid

Fig. 9C

Name	Size	Packed Size	Modified
 Ptprcap.png	46 352	42 958	2011-10-25 11:00
 Sft2d2.png	48 206	44 582	2011-10-25 11:00
 Sit1.png	47 772	44 472	2011-10-25 11:00
 Tnip2.png	49 964	46 588	2011-10-25 11:00
 Triap1.png	48 391	45 100	2011-10-25 11:00
 6-Sep.png	50 742	47 217	2011-10-25 11:00
 1200002N14Rik.png	48 367	44 711	2011-10-25 11:00
 8bc3.png	45 267	41 826	2011-10-25 11:00
 Dpp4.png	45 895	42 180	2011-10-25 11:00
 F5.png	47 771	44 441	2011-10-25 11:00
 Fam117a.png	48 141	44 811	2011-10-25 11:00
 Mmp14.png	46 968	43 340	2011-10-25 11:00
 Mum1.png	48 323	44 867	2011-10-25 11:00
 Nsmce4a.png	47 588	44 361	2011-10-25 11:00
 Plal1a.png	48 094	44 744	2011-10-25 11:00
 model-3.png	46 186	42 772	2011-10-25 10:58
 model-3-genes.txt	2 080	785	2011-10-25 10:58

Fig. 9C Cont'd

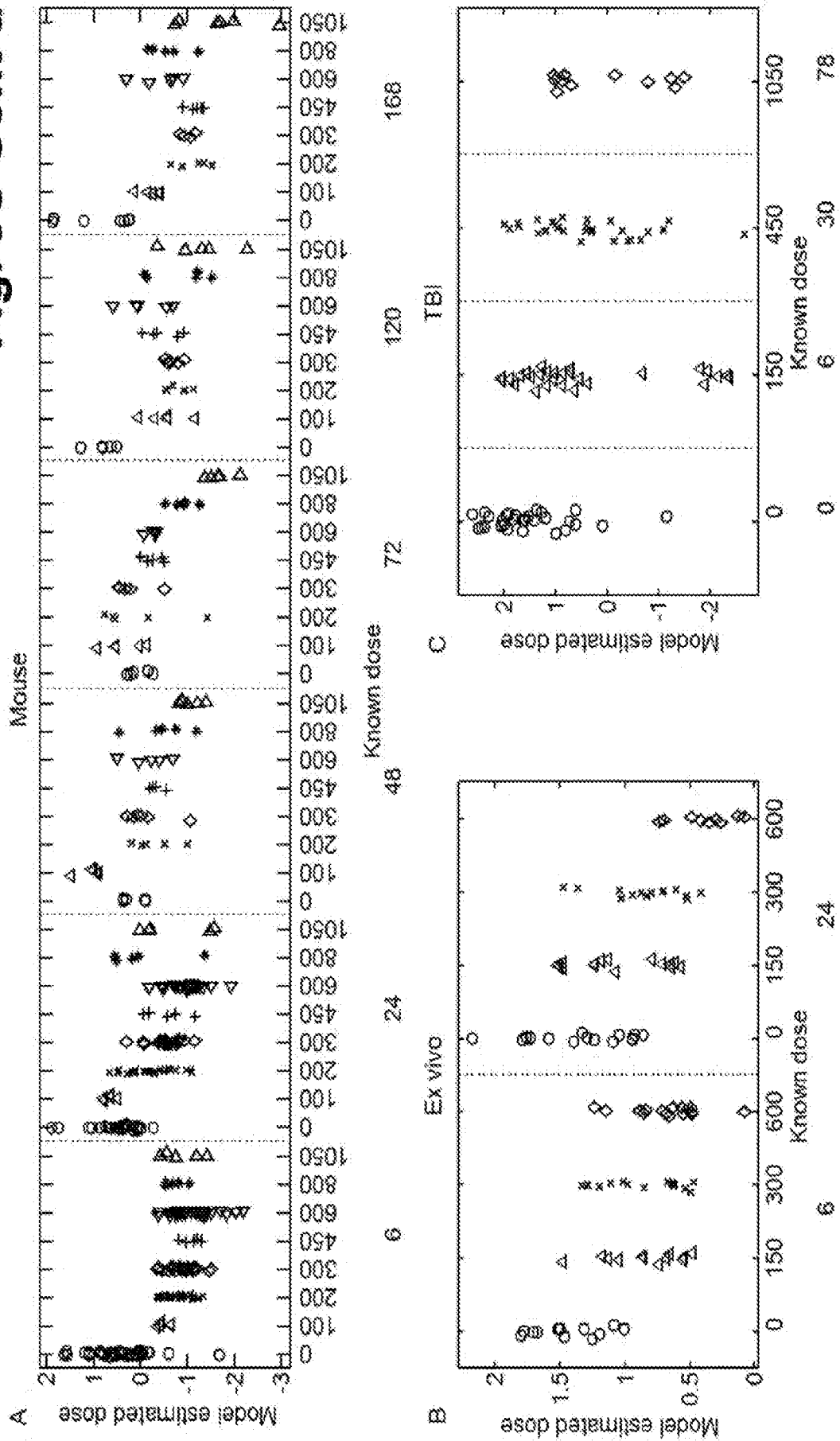


Fig. 9C Cont'd

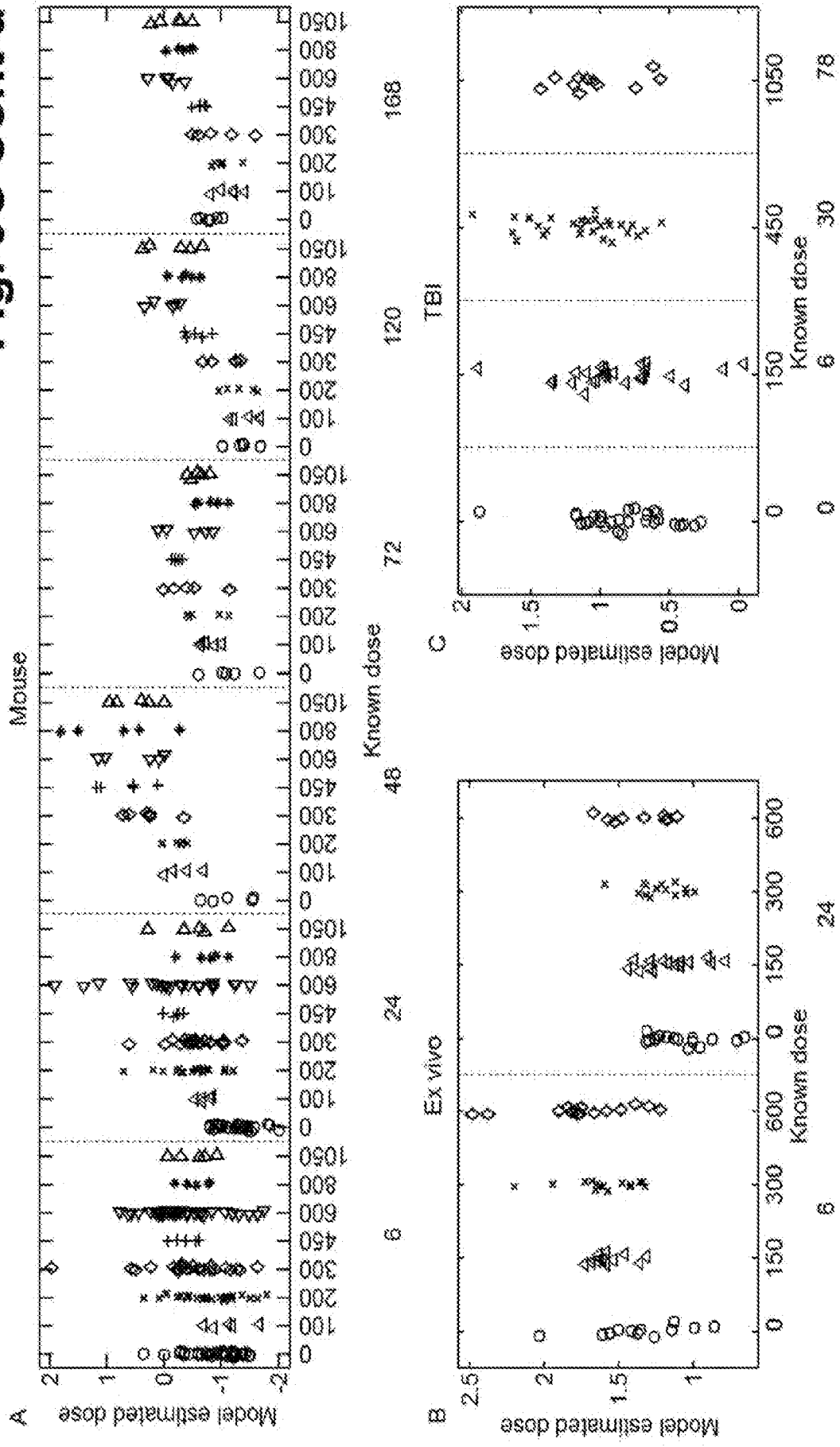


Fig. 9C Cont'd

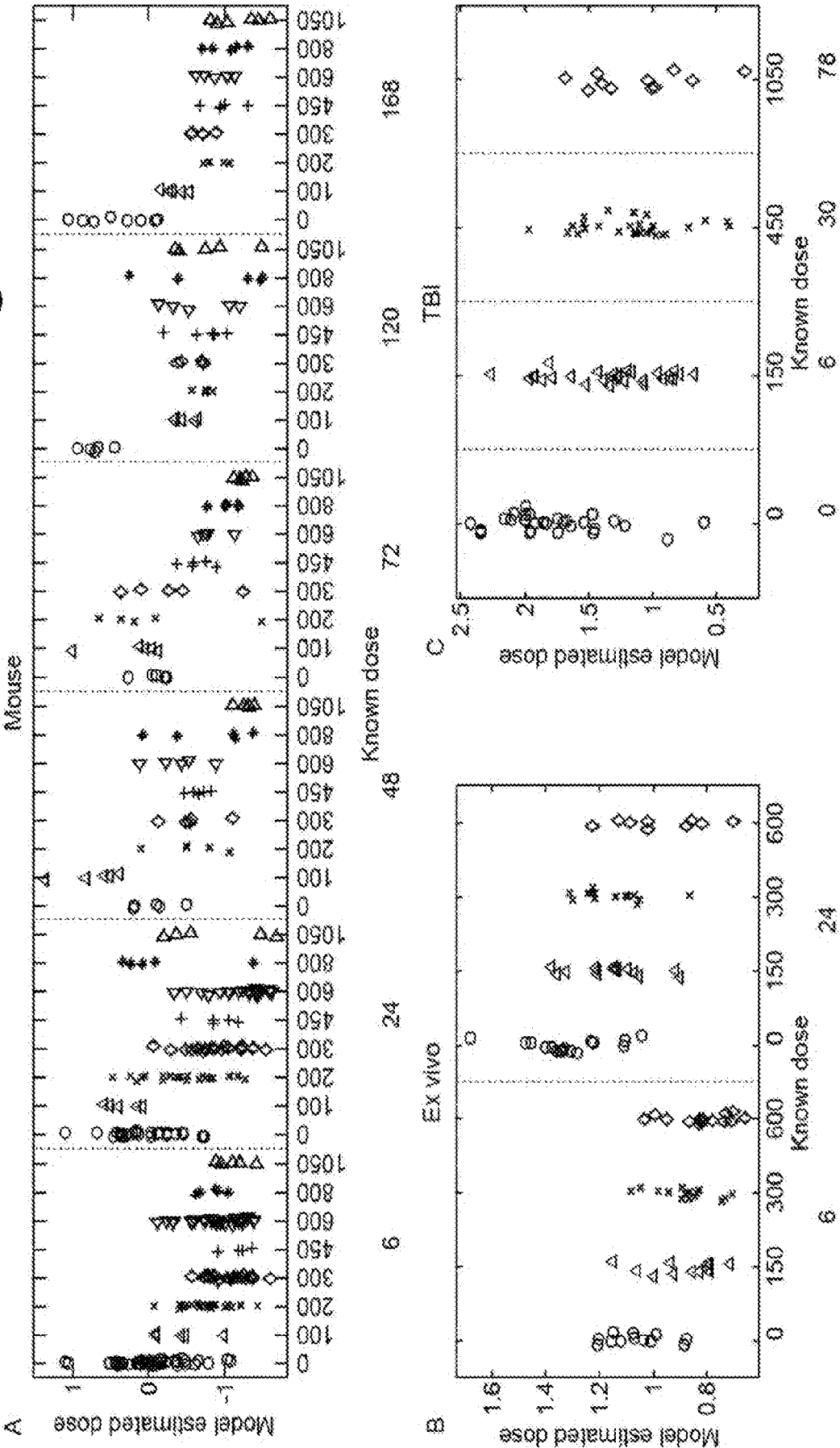


Fig. 9C Cont'd

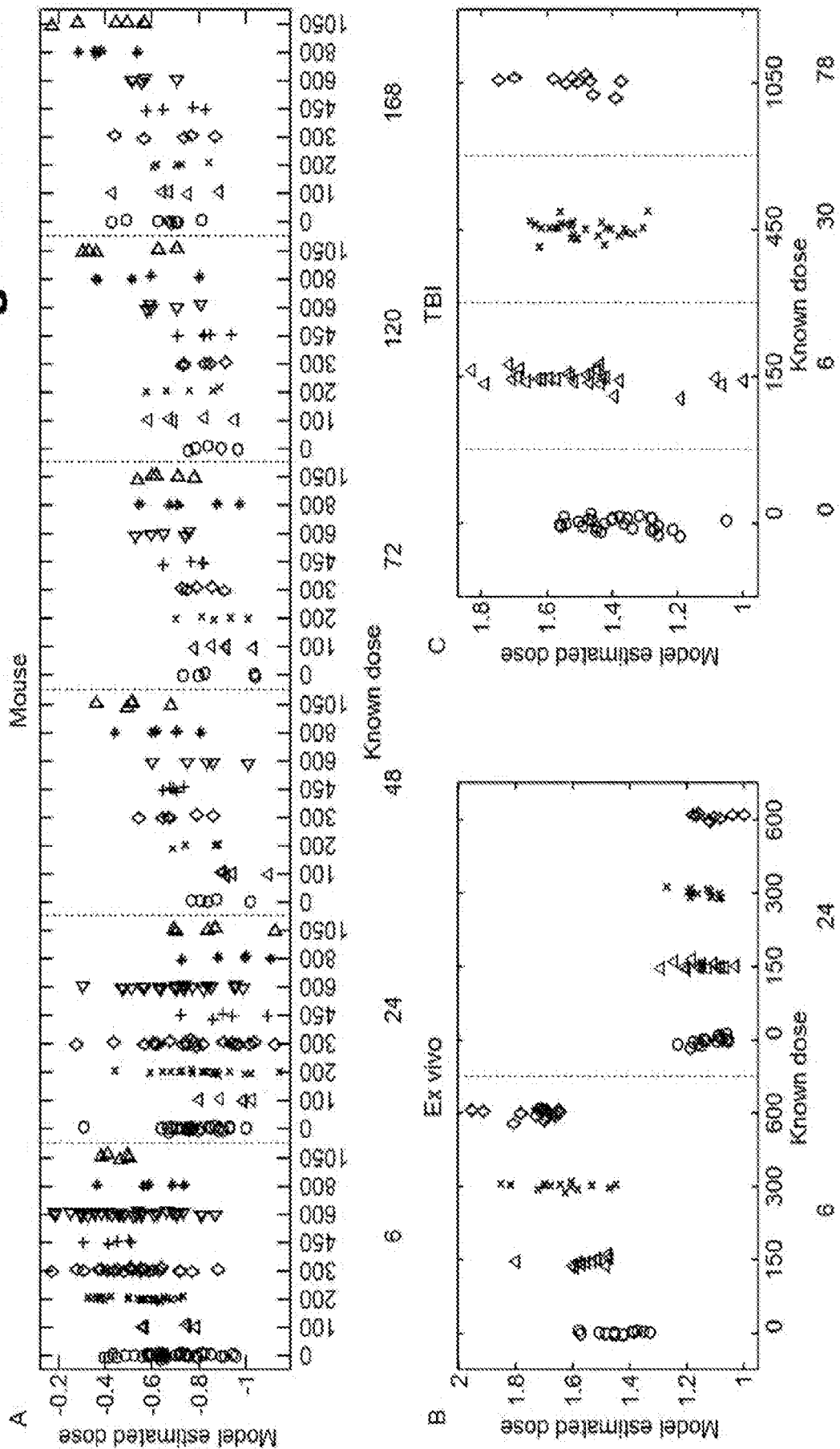


Fig. 9C Cont'd

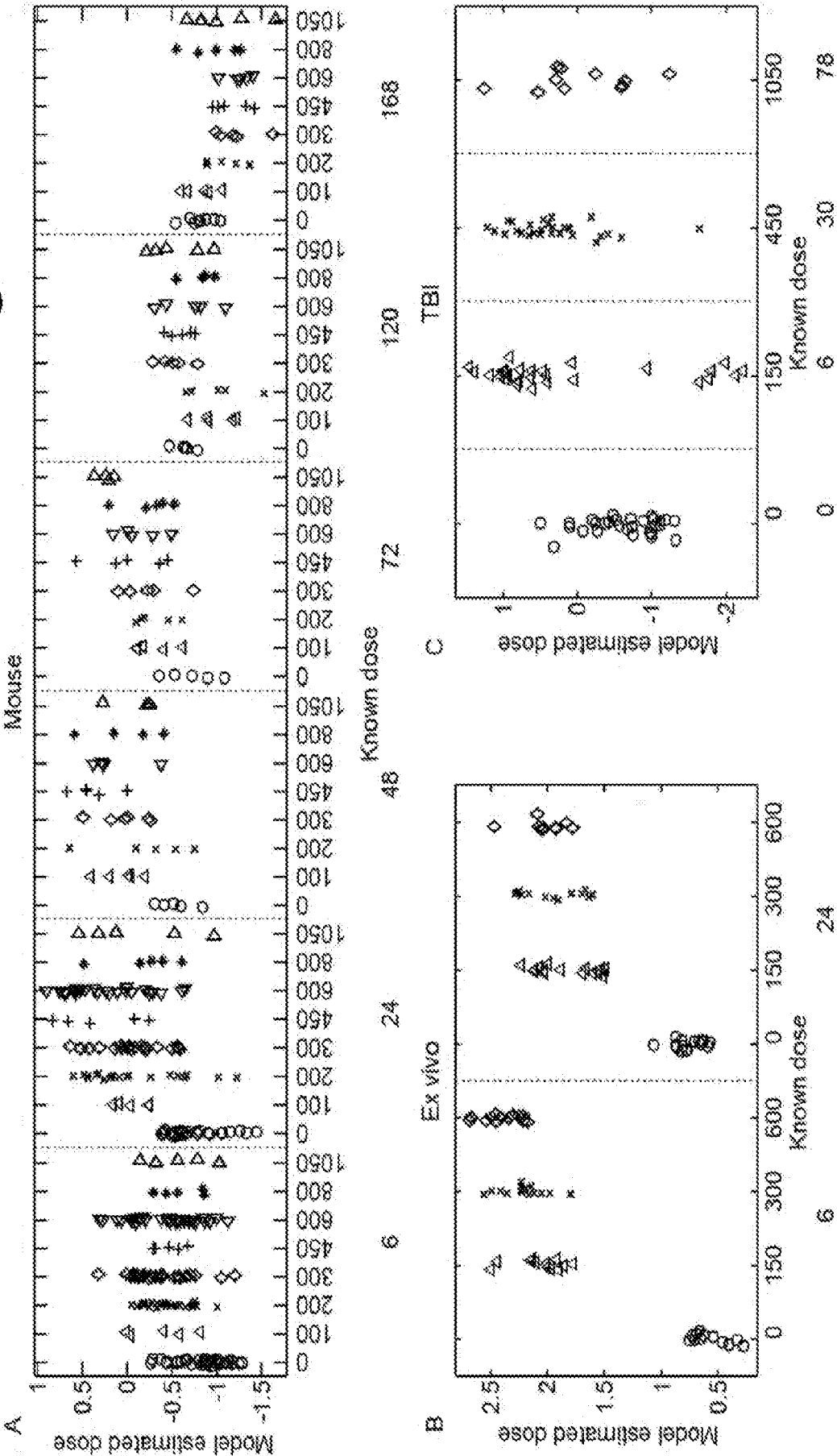


Fig. 9C Cont'd

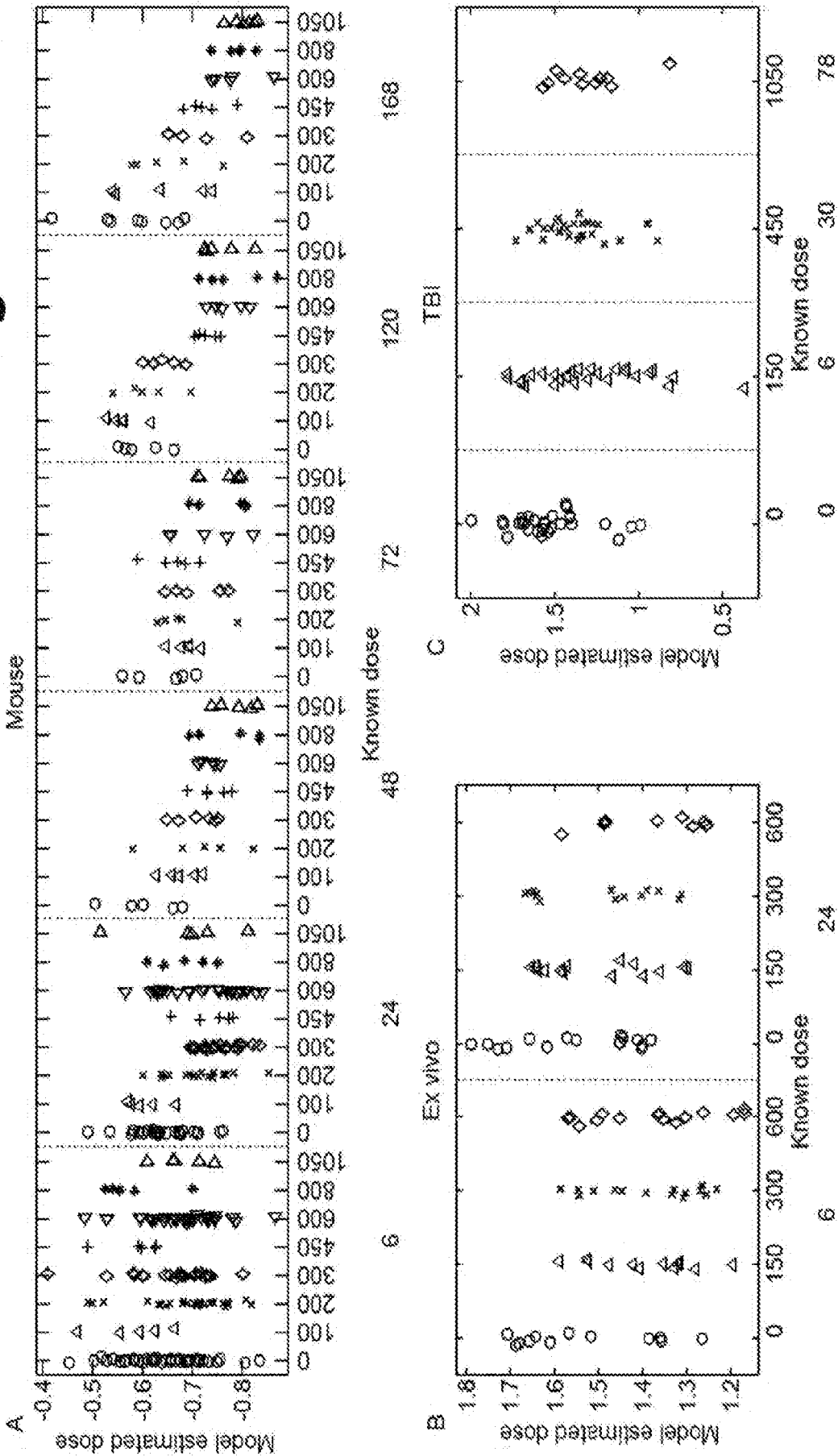


Fig. 9C Cont'd

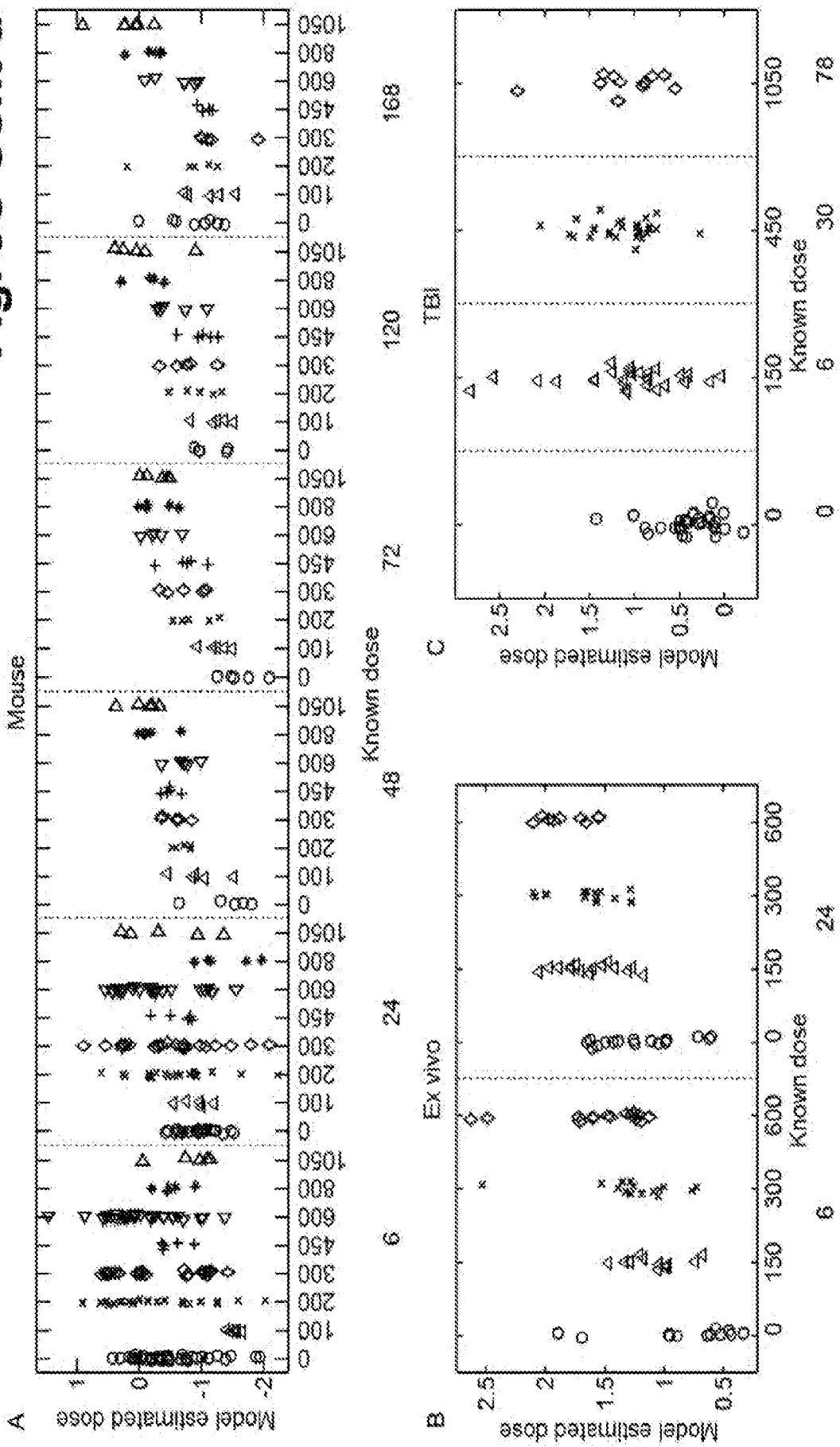


Fig. 9C Cont'd

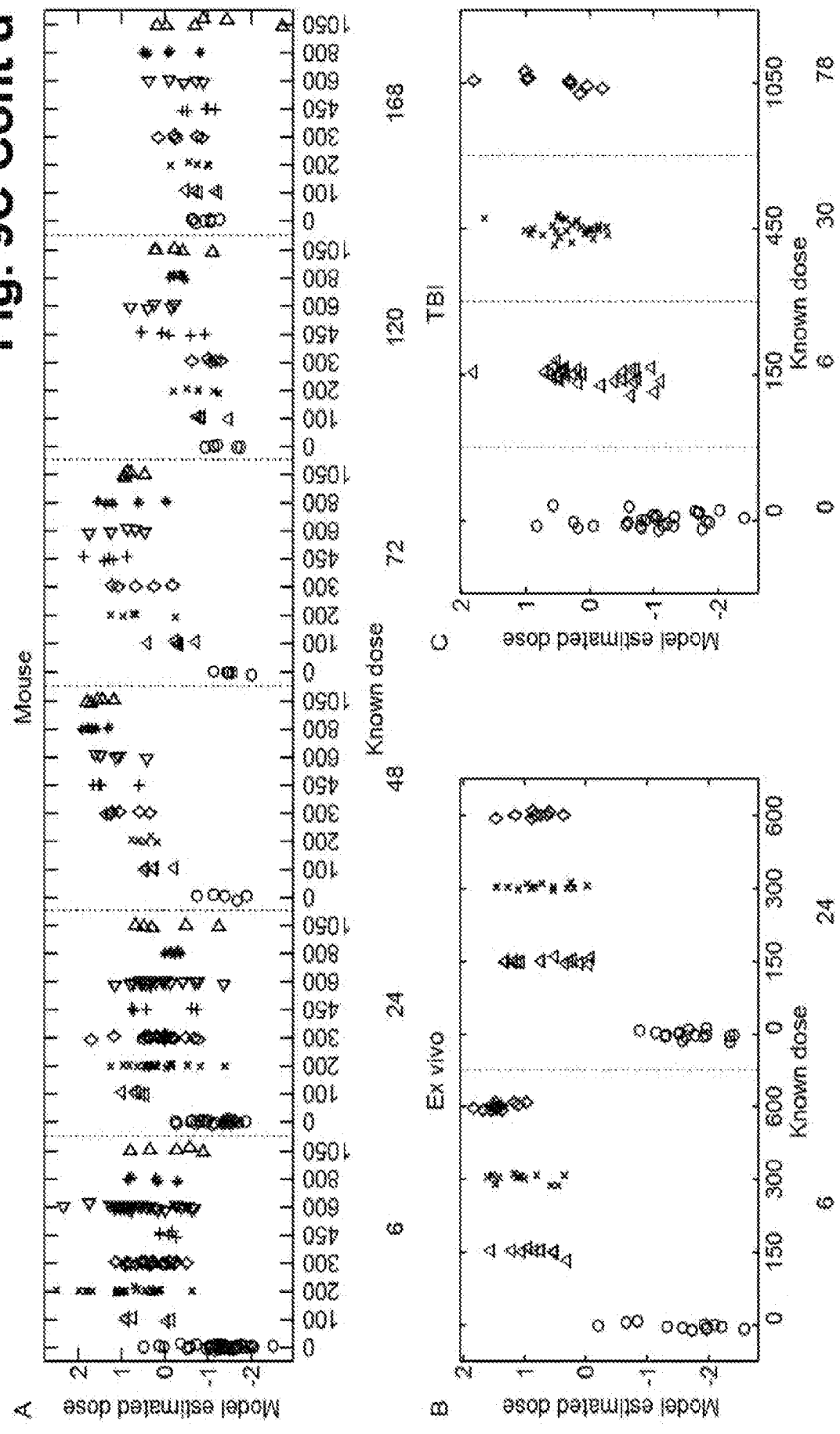


Fig. 9C Cont'd

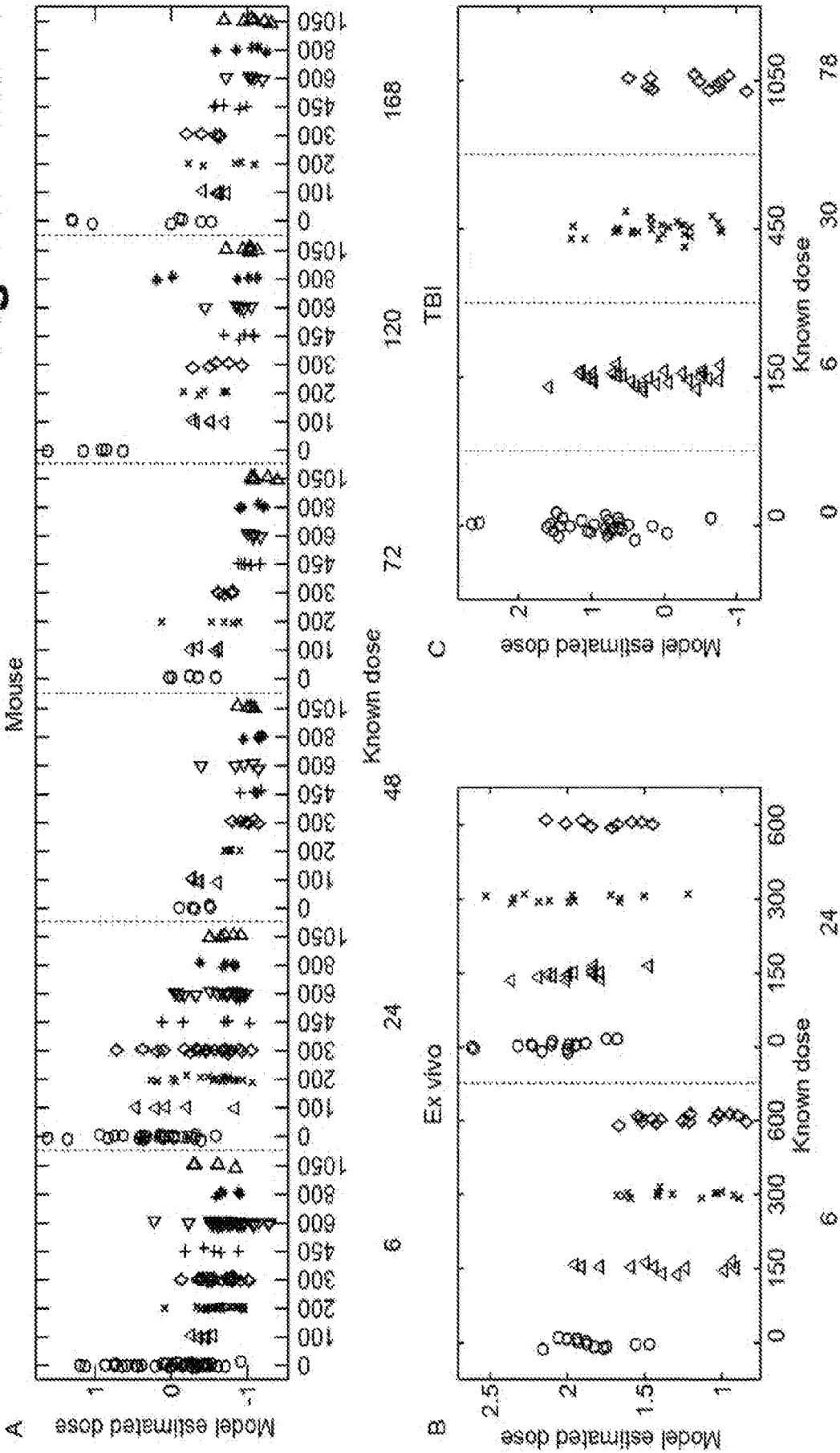


Fig. 9C Cont'd

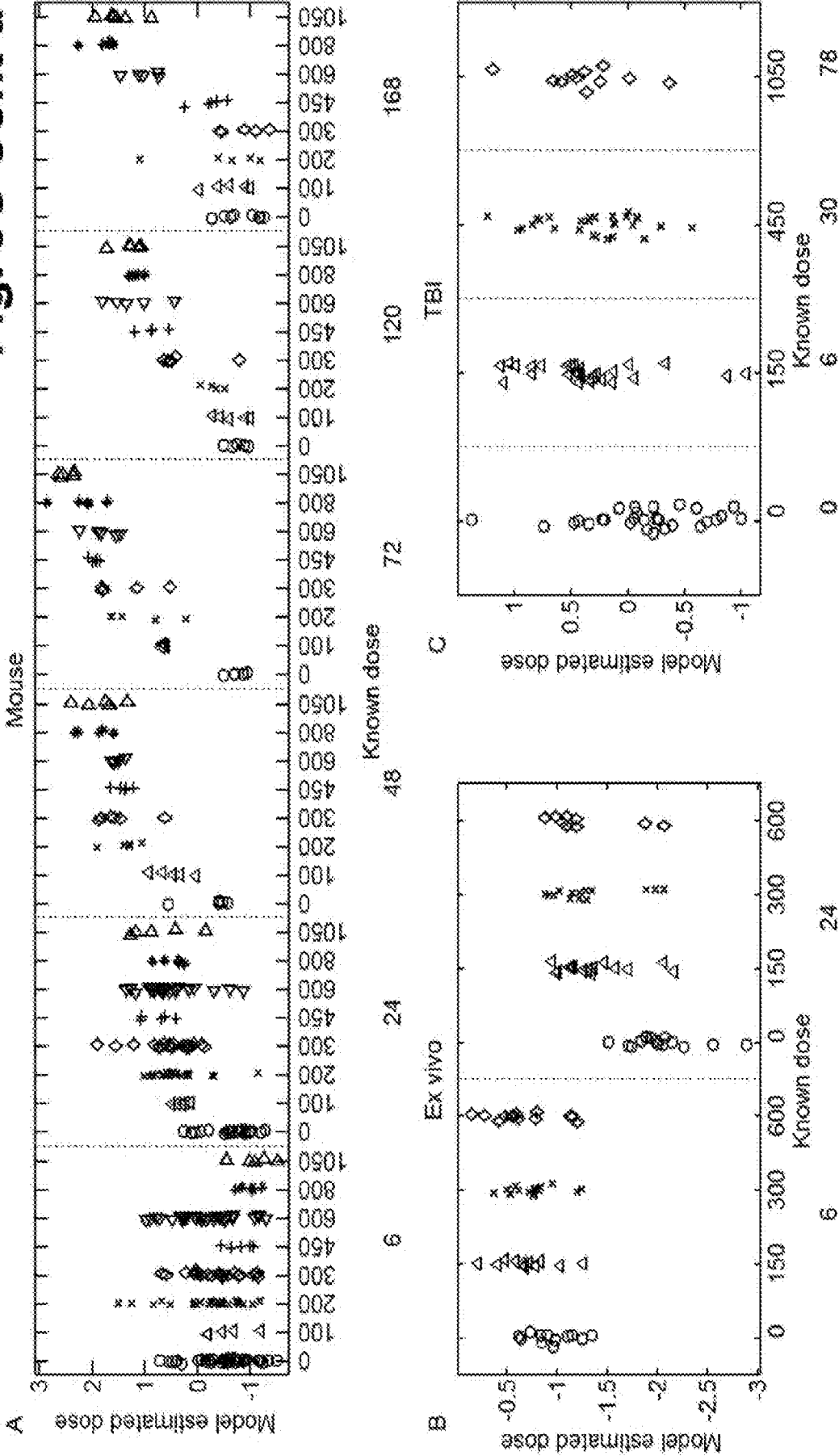


Fig. 9C Cont'd

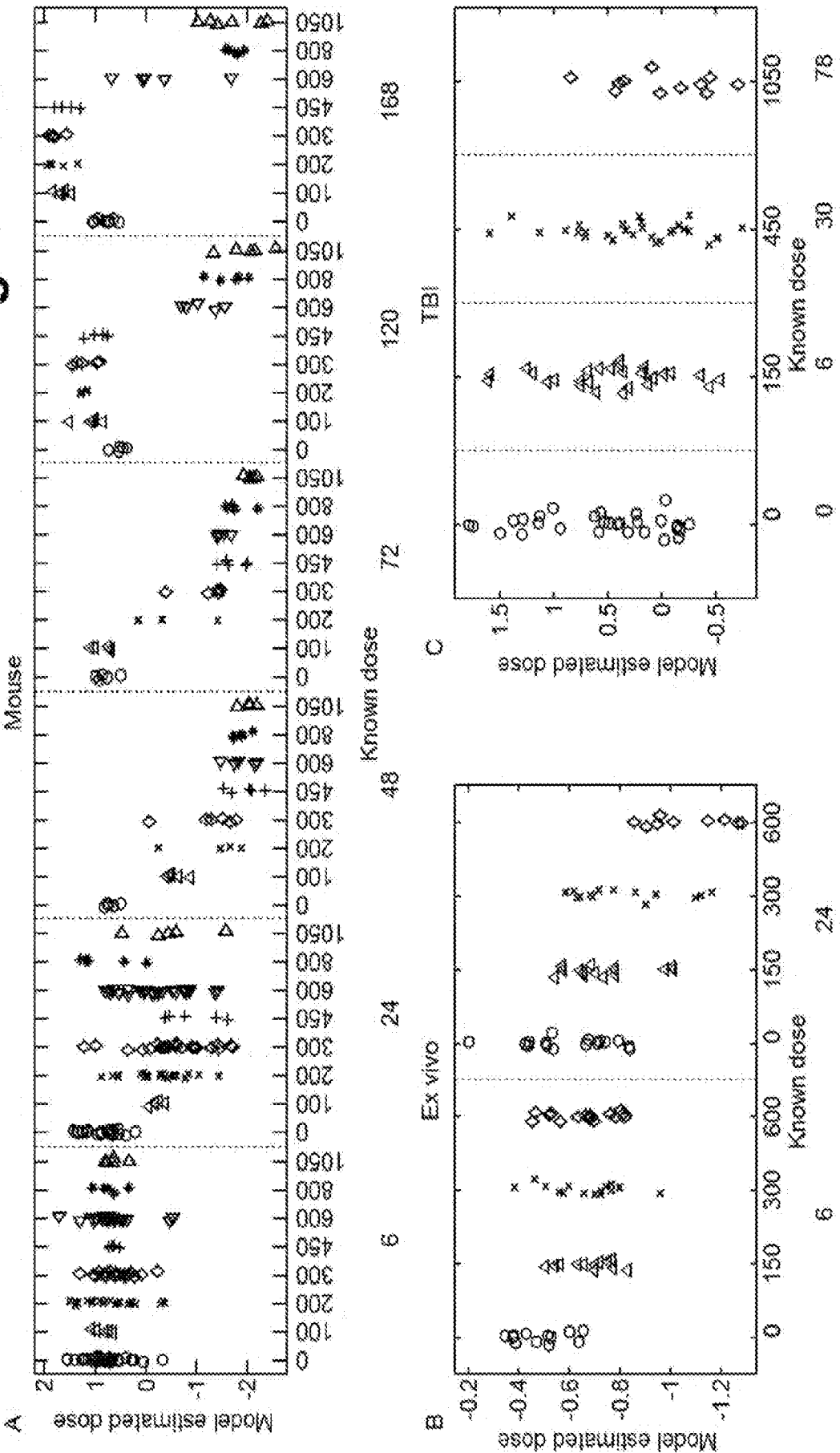


Fig. 9C Cont'd

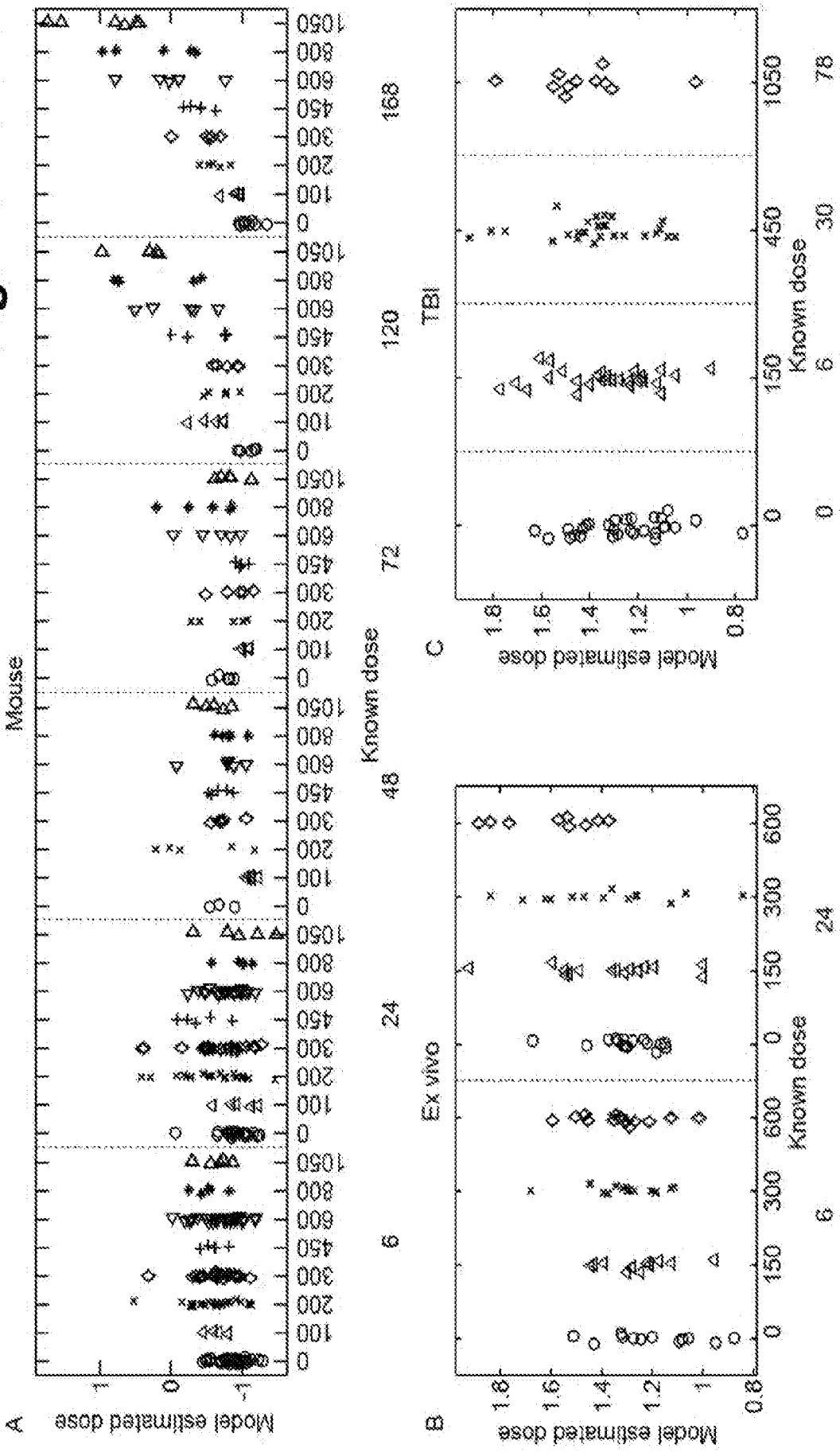
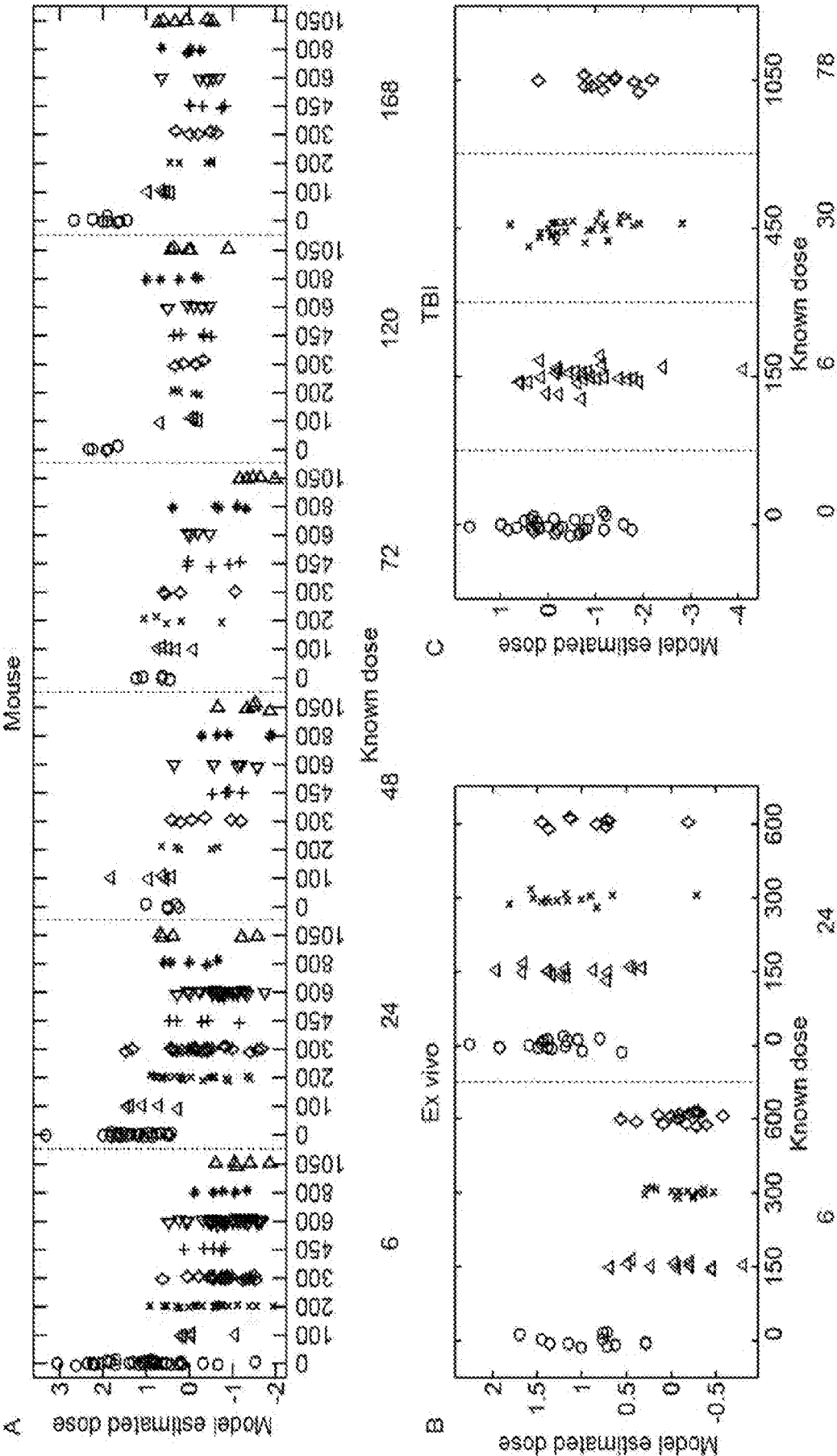


Fig. 9C Cont'd



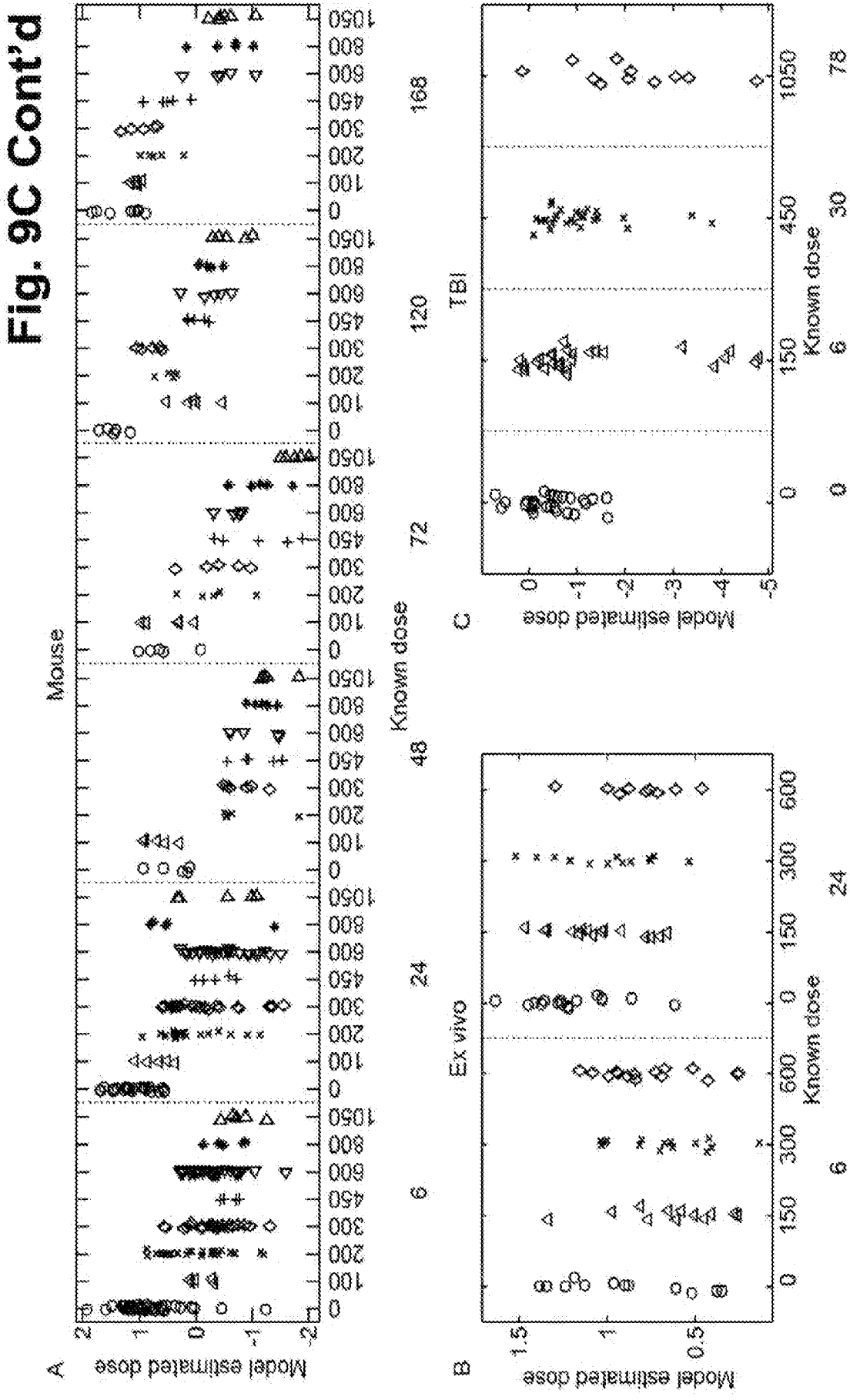


Fig. 9C Cont'd

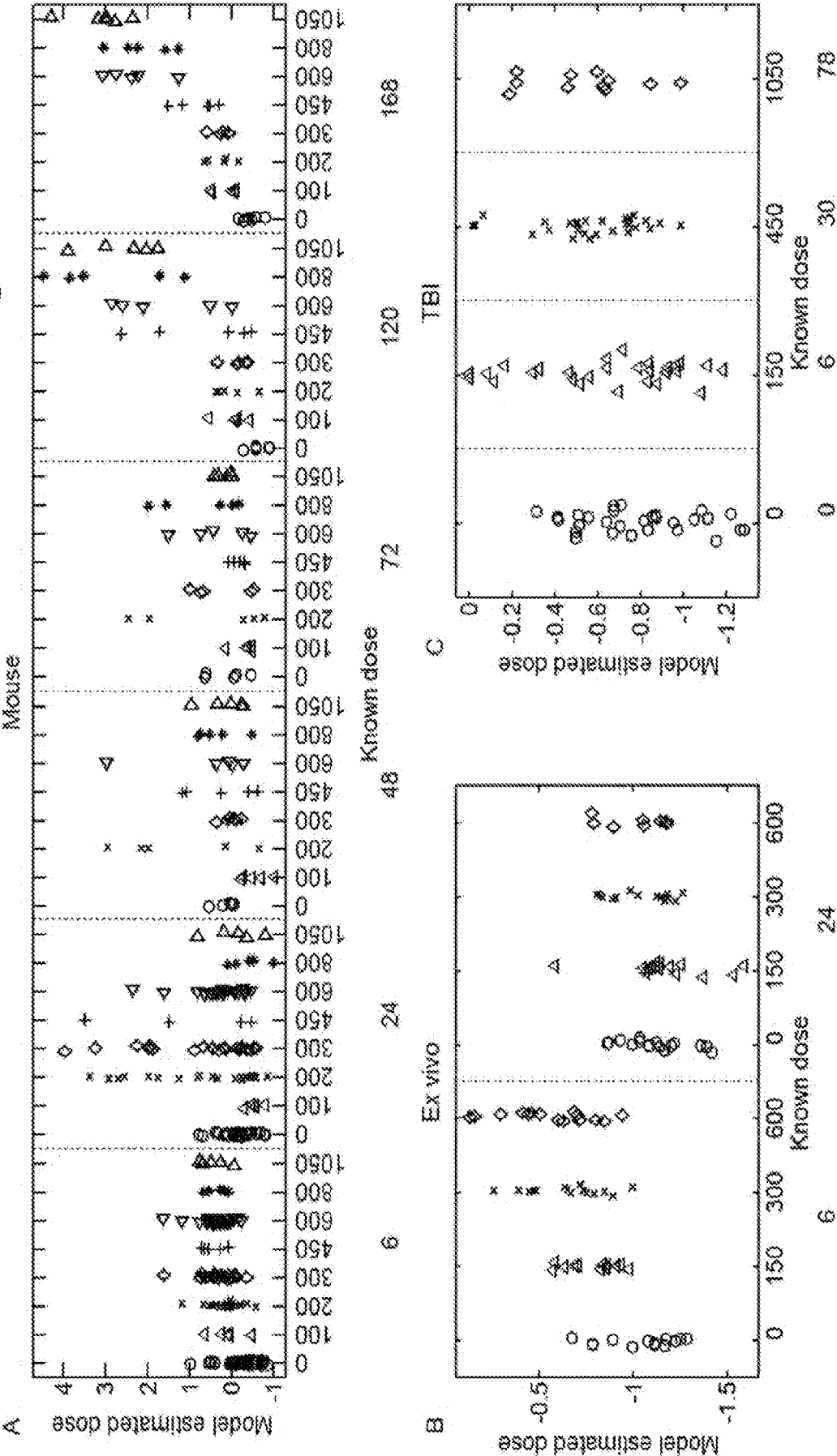


Fig. 9C Cont'd

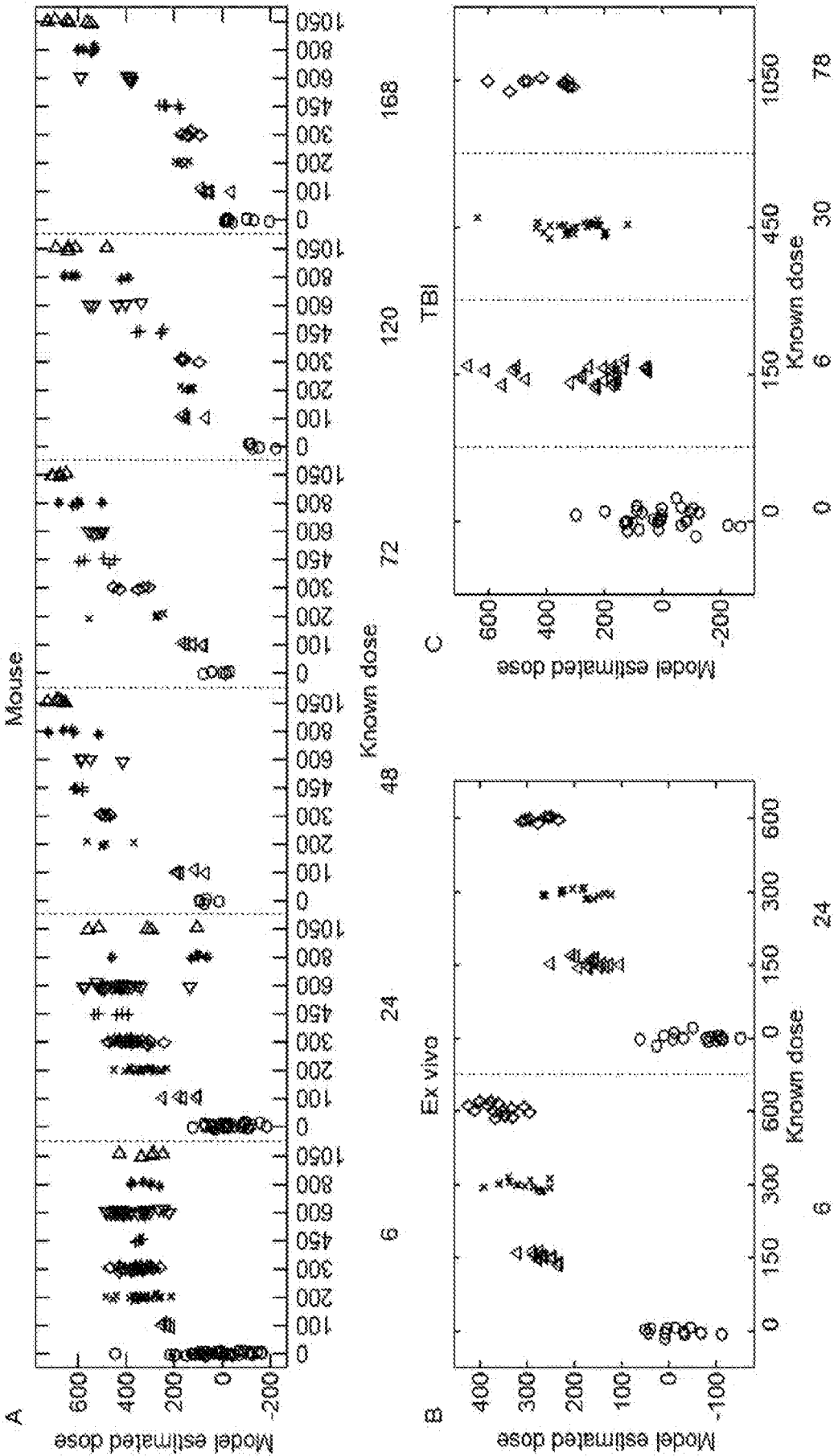


Fig. 9C Cont'd

mouse probe	human probe	model-3-genes.txt publciD	gene title	gene symbol
1416536_at (mutated) 1	221290_s_at	NM_023431	melanoma associated antigen Mum1	
1417785_at	219584_at	NM_134102	phospholipase A1 member A Plala	
1418751_at	205484_at	NM_019436	suppression inducing transmembrane Sitr1	
adaptor 1	48531_at	NM_139064	TNFAIP3 interacting protein 2 Tnfr2	
1419488_at	211692_s_at	AW489168	BCL2 binding component 3 Bbc3	
1423315_at	218627_at	BC021433	RIKEN CDNA 1200002N14 gene 1200002N14rik	
1424524_at	214838_at	BC017549	SFT2 domain containing 2 Sft2d2	
1425027_s_at	219067_s_at	AK010349	non-SMC element 4 homolog A (S. Nsmce4a	
1428213_at cerevisiae)	221249_s_at	AW548096	"family with sequence similarity Fam117a	
1433639_at 117, memberA"	211478_s_at	BQ030854	dipeptidylpeptidase 4 Dpp4	
1441342_at	217279_x_at	NM_008608	matrix metalloproteinase 14 Mmp14	
1448383_at (membrane-inserted)	204960_at	NM_016933	"protein tyrosine phosphatase, ptprcap	
1448511_at	receptor type, C polypeptide-associated protein"	NM_007976	coagulation factor V F5	
1449269_at	204714_s_at	NM_019942	septin 6 6-Sep	
1460286_at	214298_x_at	AK007514	TP53 regulated inhibitor of Triap1	
1460702_at	218403_at			
apoptosis 1				

Fig. 9D

Name	Size	Packed Size	Modified
 Ninj1.png	46 800	43 358	2011-10-25 11:00
 Parp1.png	49 539	46 047	2011-10-25 11:00
 Prkab1.png	48 055	44 622	2011-10-25 11:01
 Retsat.png	47 380	43 919	2011-10-25 11:00
 Smtn.png	48 248	44 653	2011-10-25 11:01
 Cd52.png	47 538	44 159	2011-10-25 11:01
 Fgr.png	49 422	45 647	2011-10-25 11:00
 Hist1h3d.png	46 482	42 915	2011-10-25 11:01
 Ly9.png	46 693	43 300	2011-10-25 11:00
 Map4k1.png	47 737	44 411	2011-10-25 11:00
 Mrps26.png	47 347	43 794	2011-10-25 11:00
 Mtcp1.png	46 289	42 612	2011-10-25 11:00
 Mupcdh.png	48 931	45 421	2011-10-25 11:00
 Nfe2l2.png	48 120	44 520	2011-10-25 11:00
 model-4.png	48 721	45 337	2011-10-25 10:58
 model-4-genes.txt	1 605	705	2011-10-25 10:58

Fig. 9D Cont'd

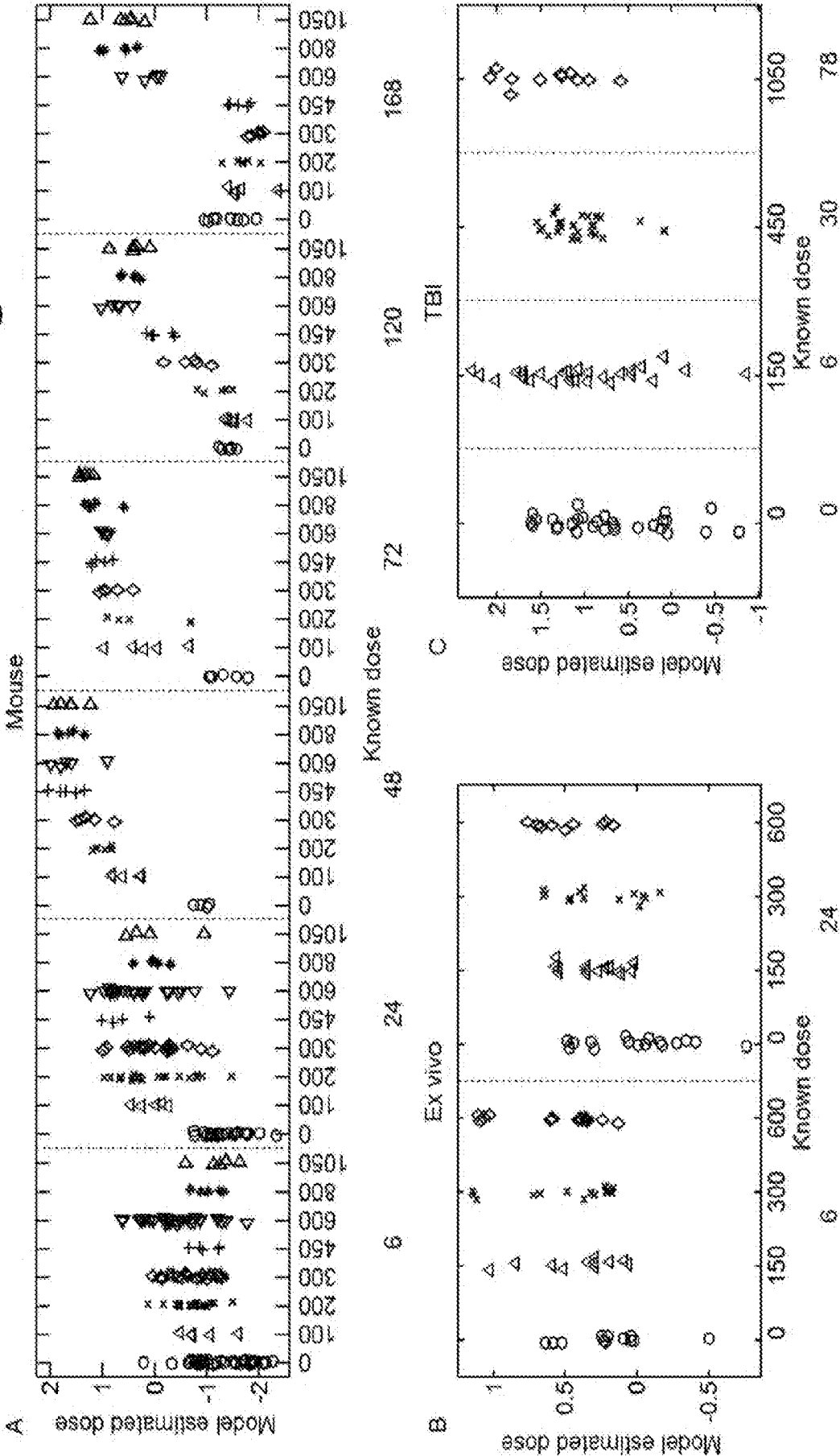


Fig. 9D Cont'd

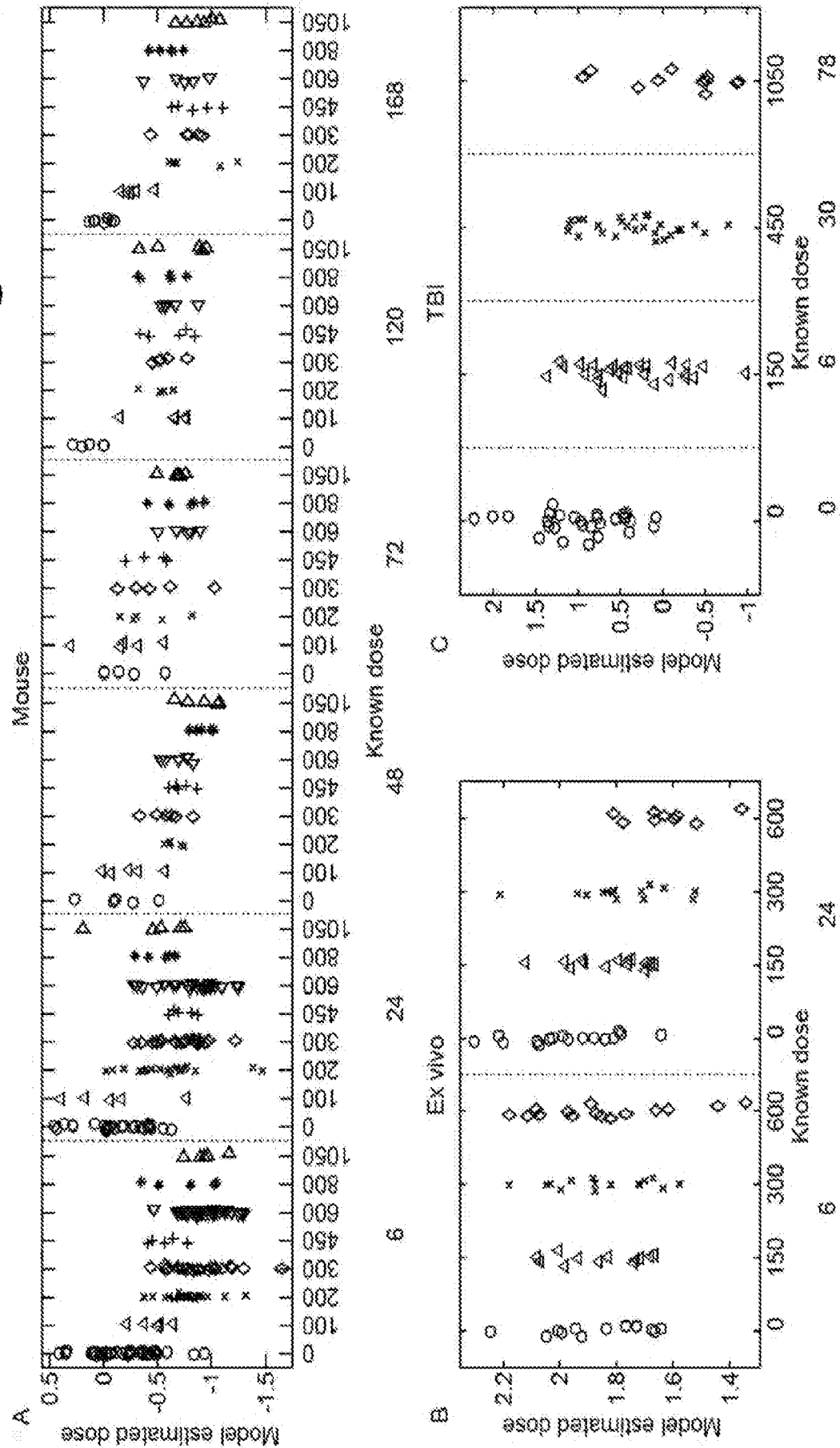


Fig. 9D Cont'd

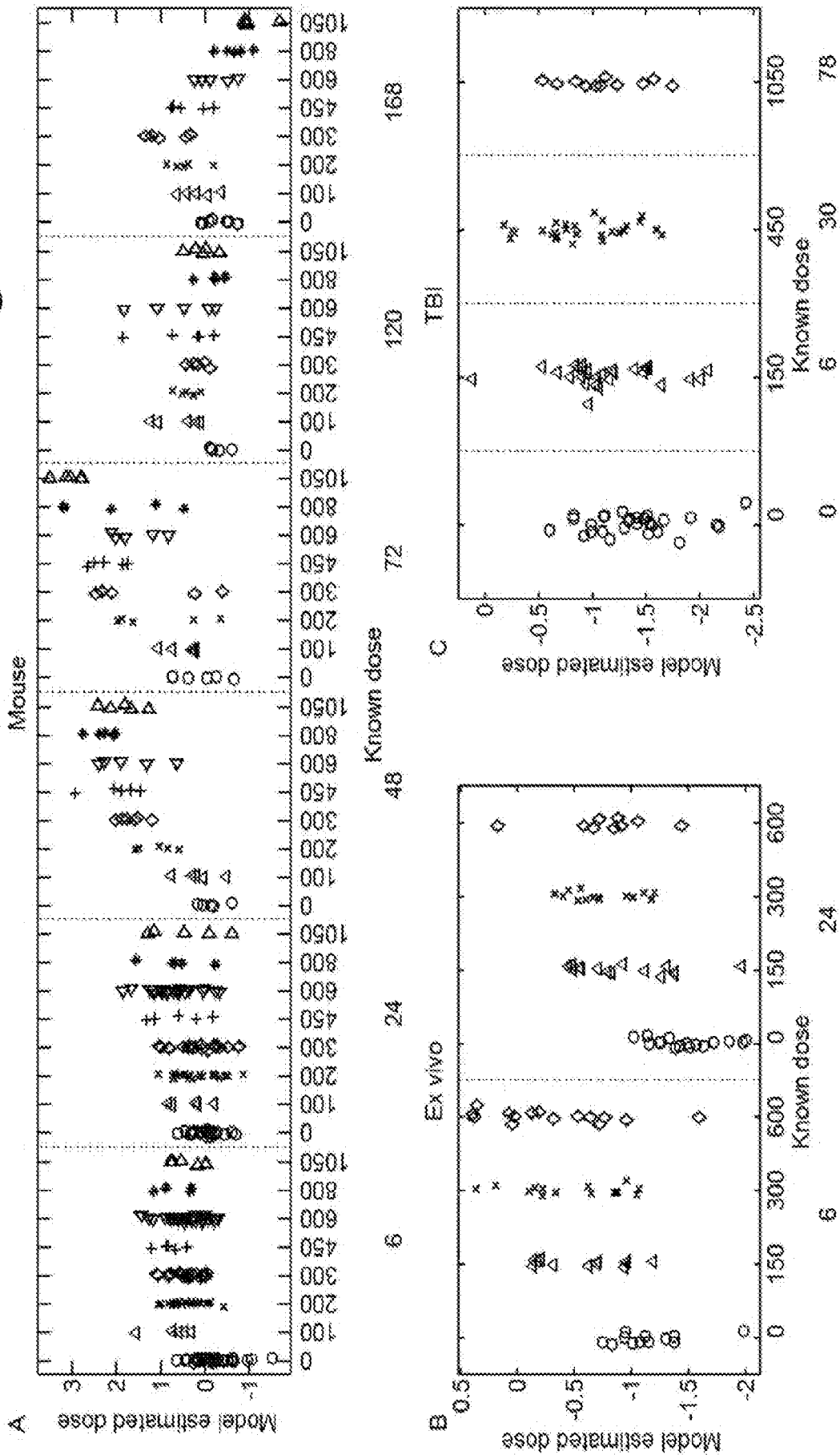


Fig. 9D Cont'd

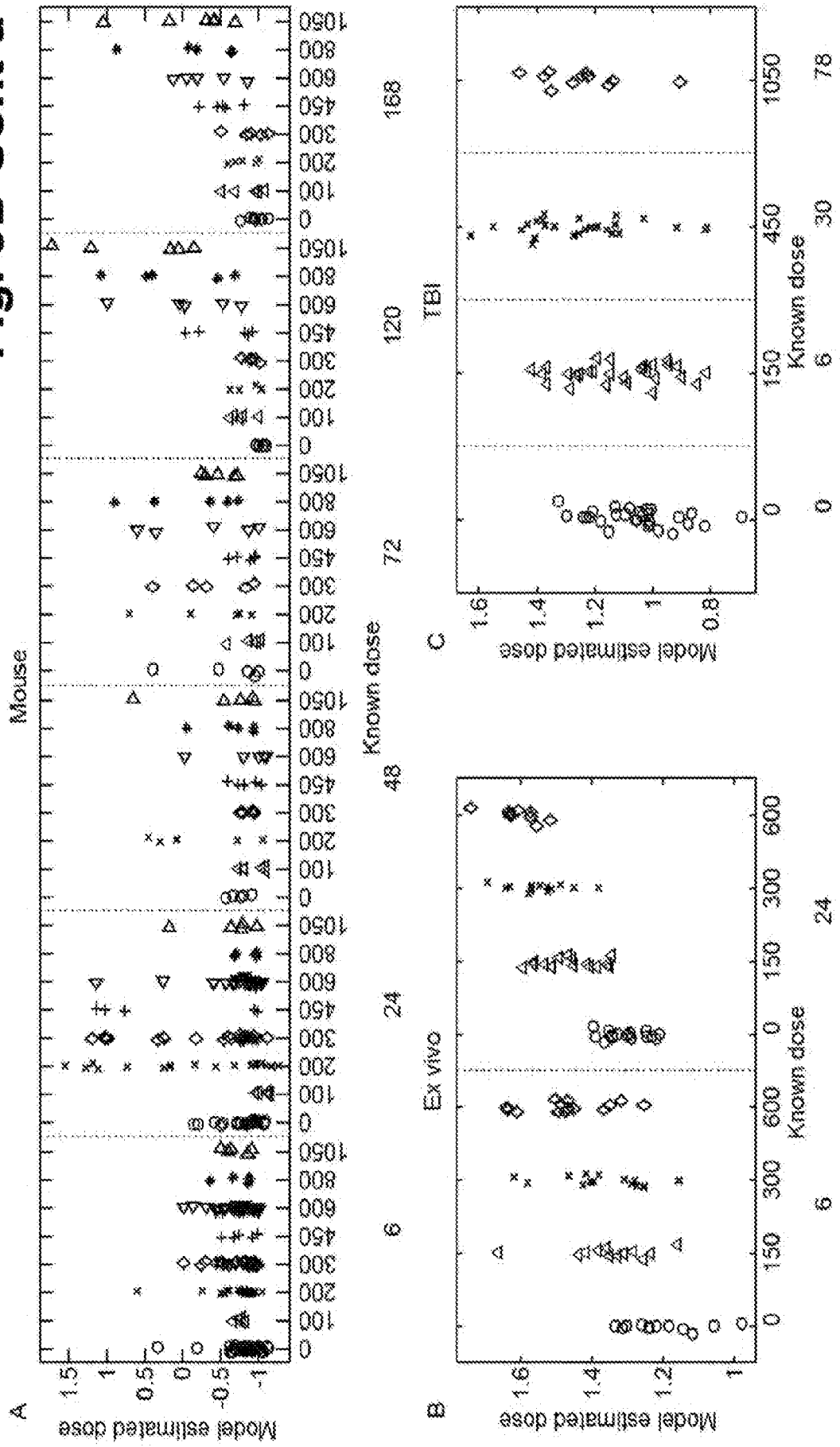


Fig. 9D Cont'd

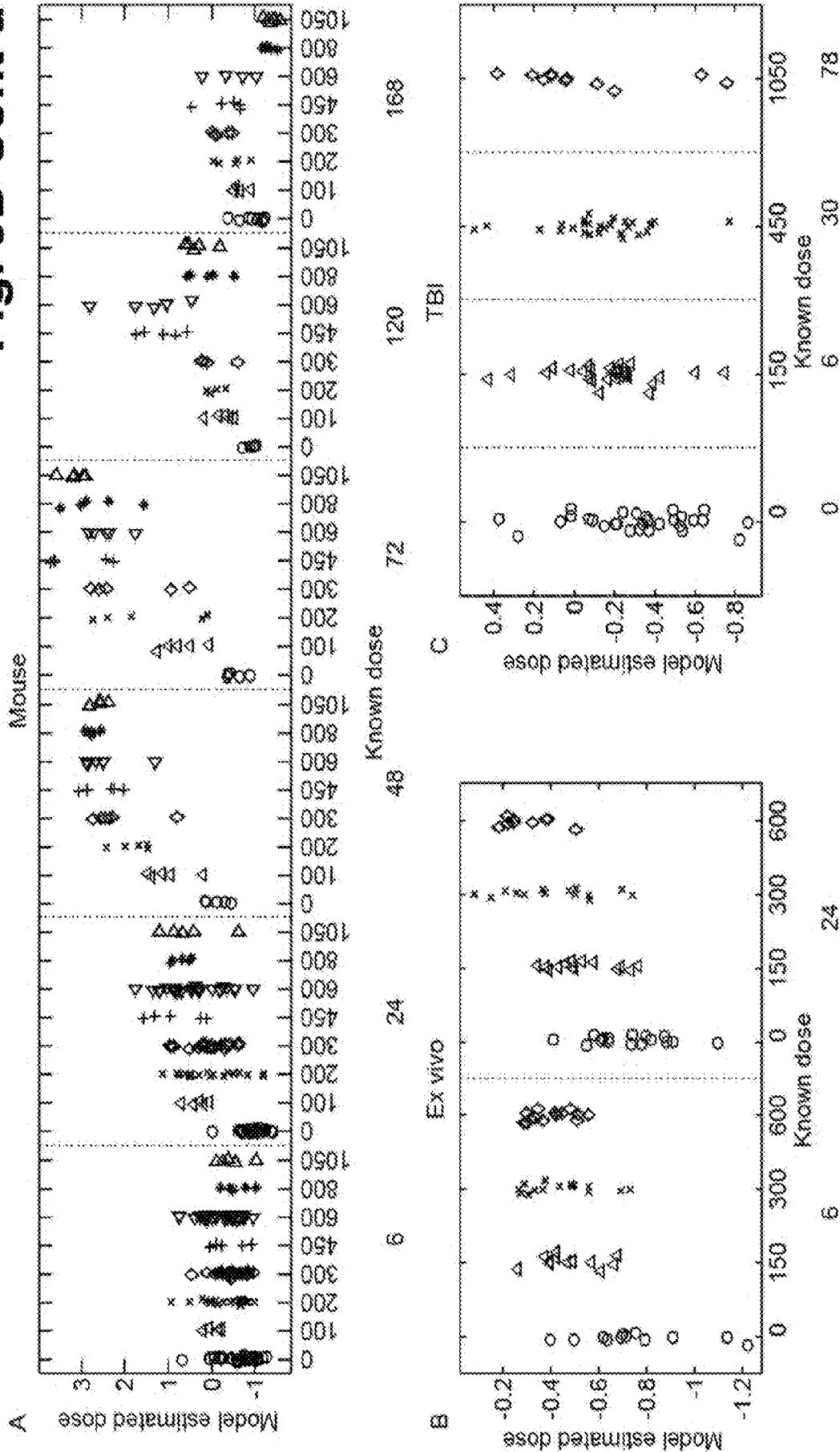


Fig. 9D Cont'd

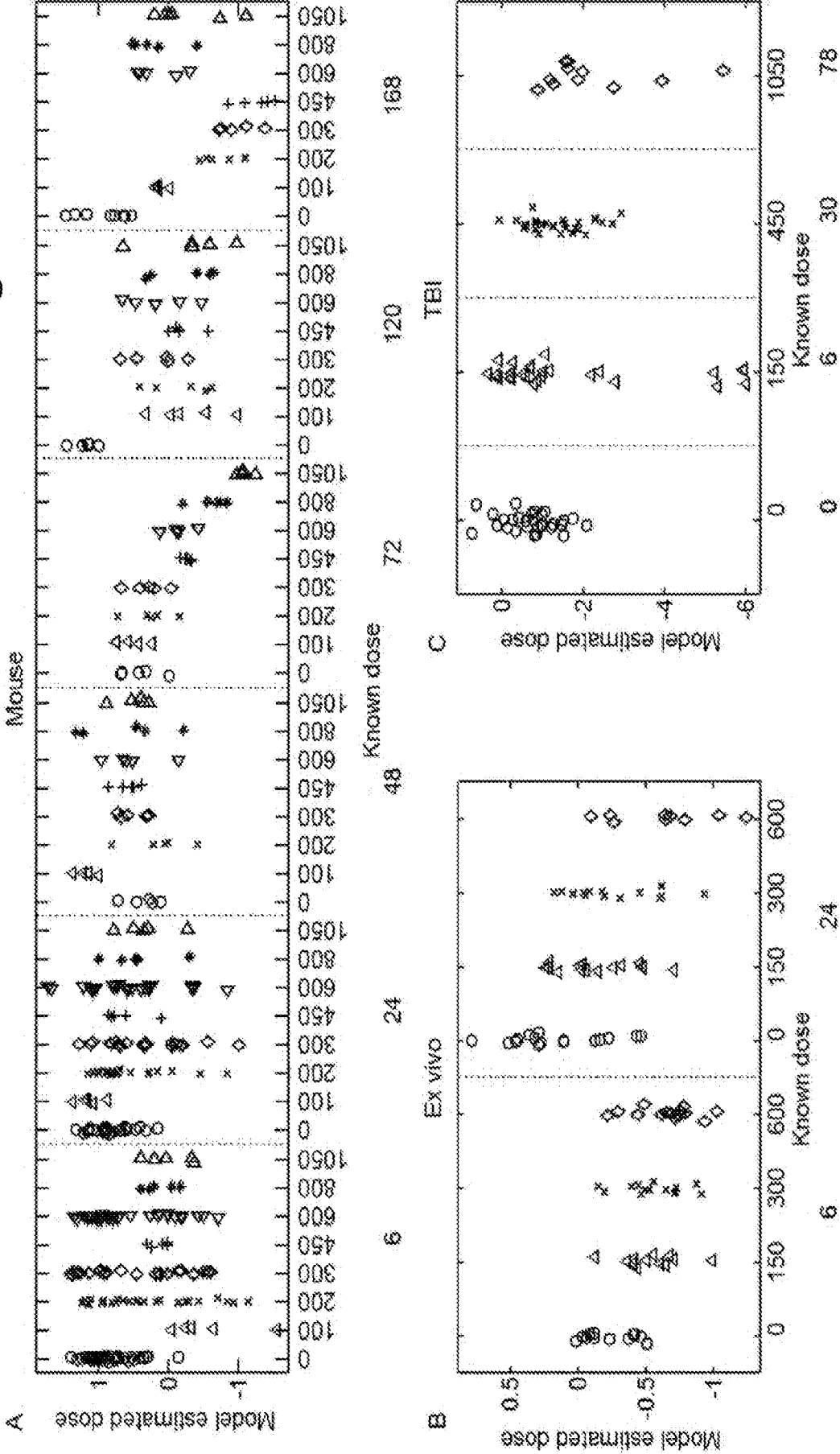


Fig. 9D Cont'd

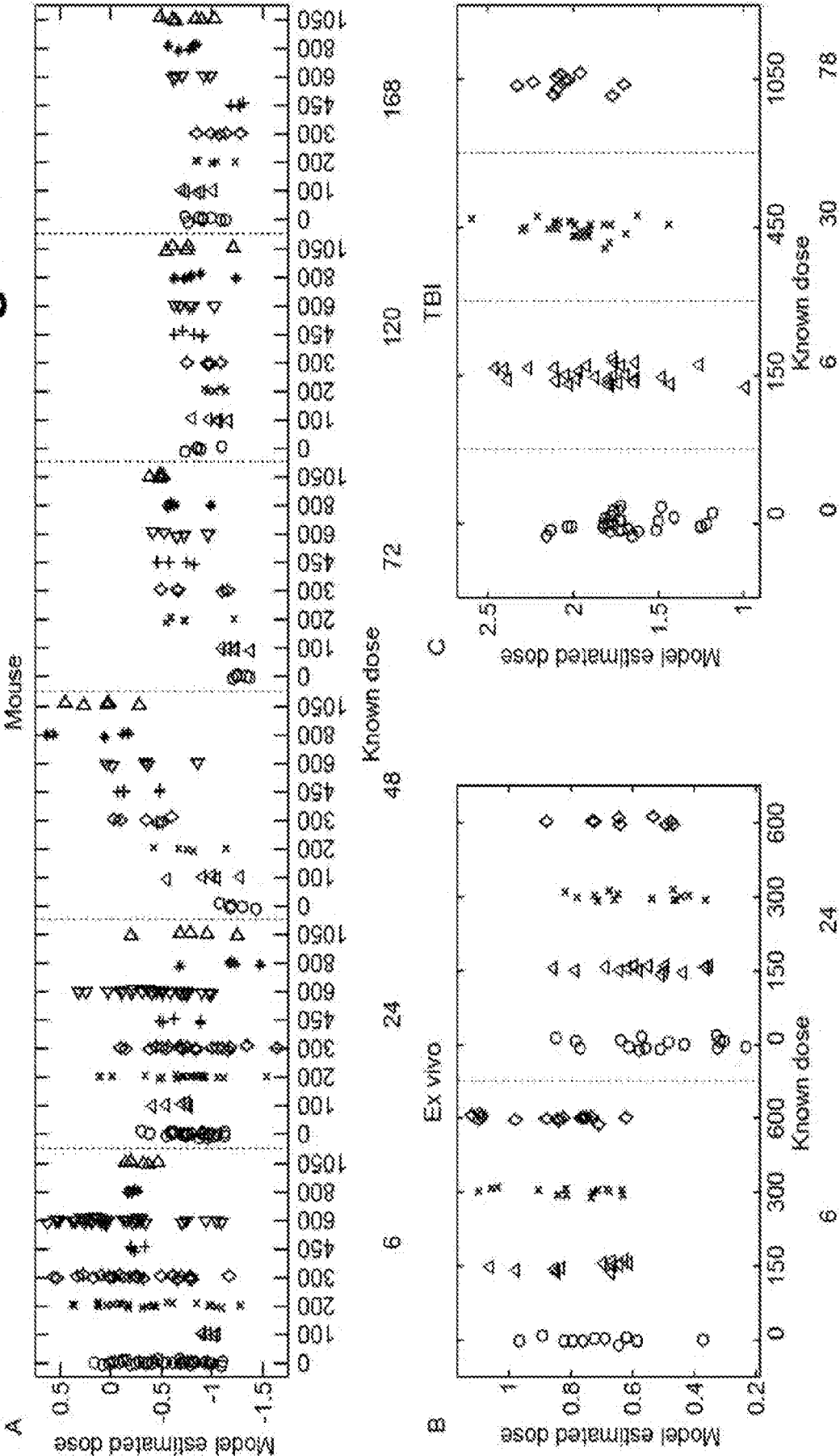


Fig. 9D Cont'd

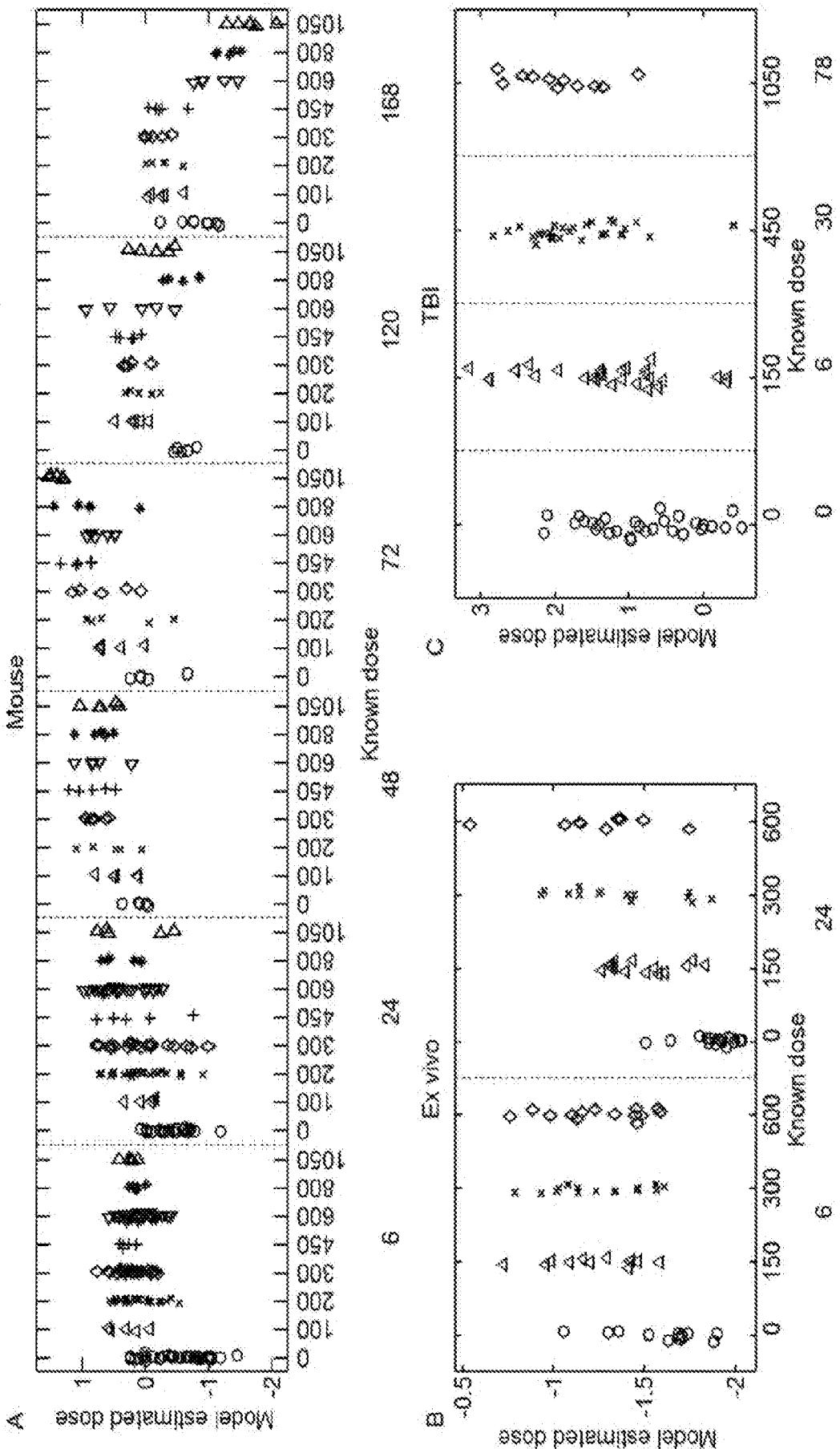


Fig. 9D Cont'd

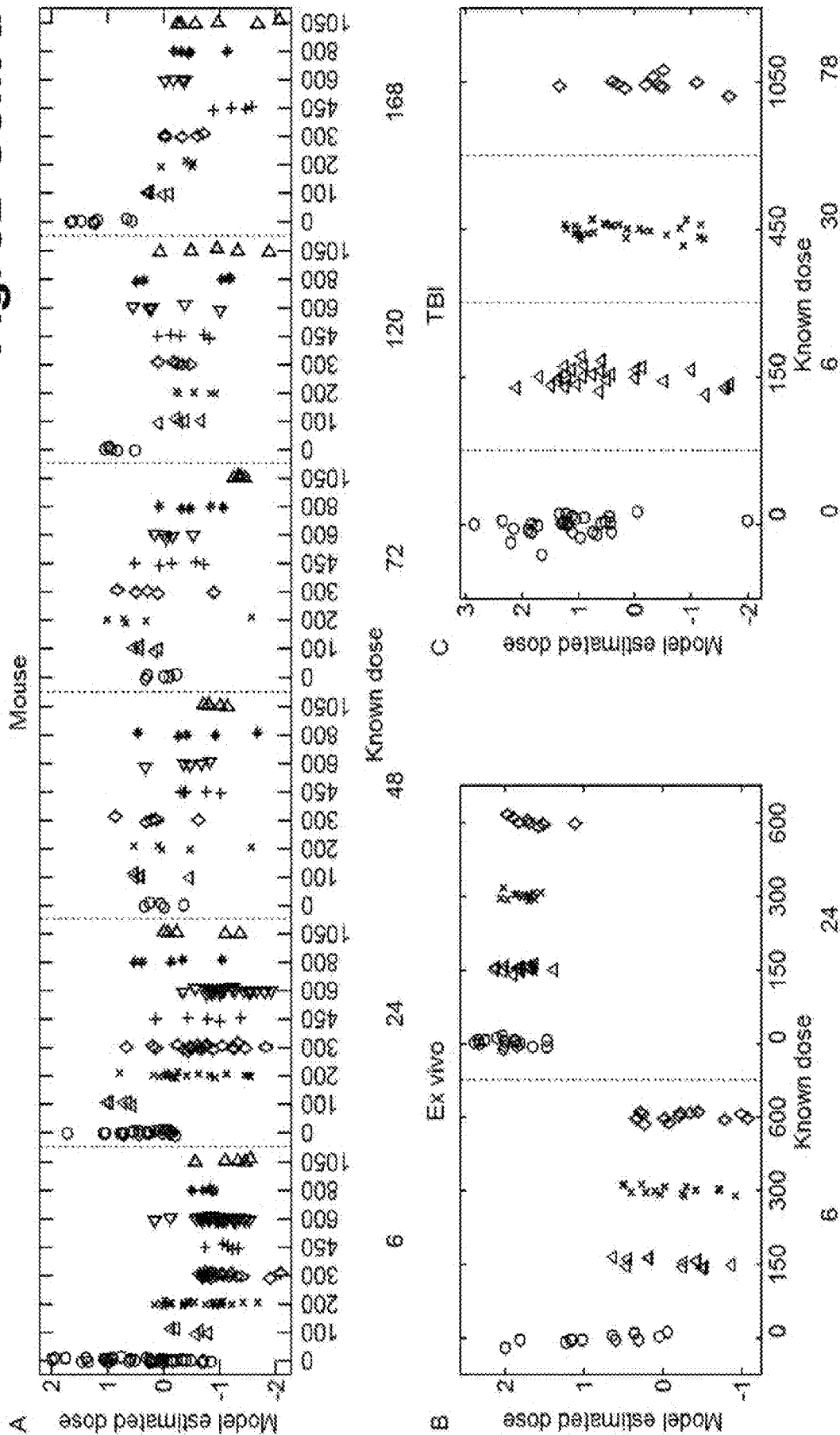


Fig. 9D Cont'd

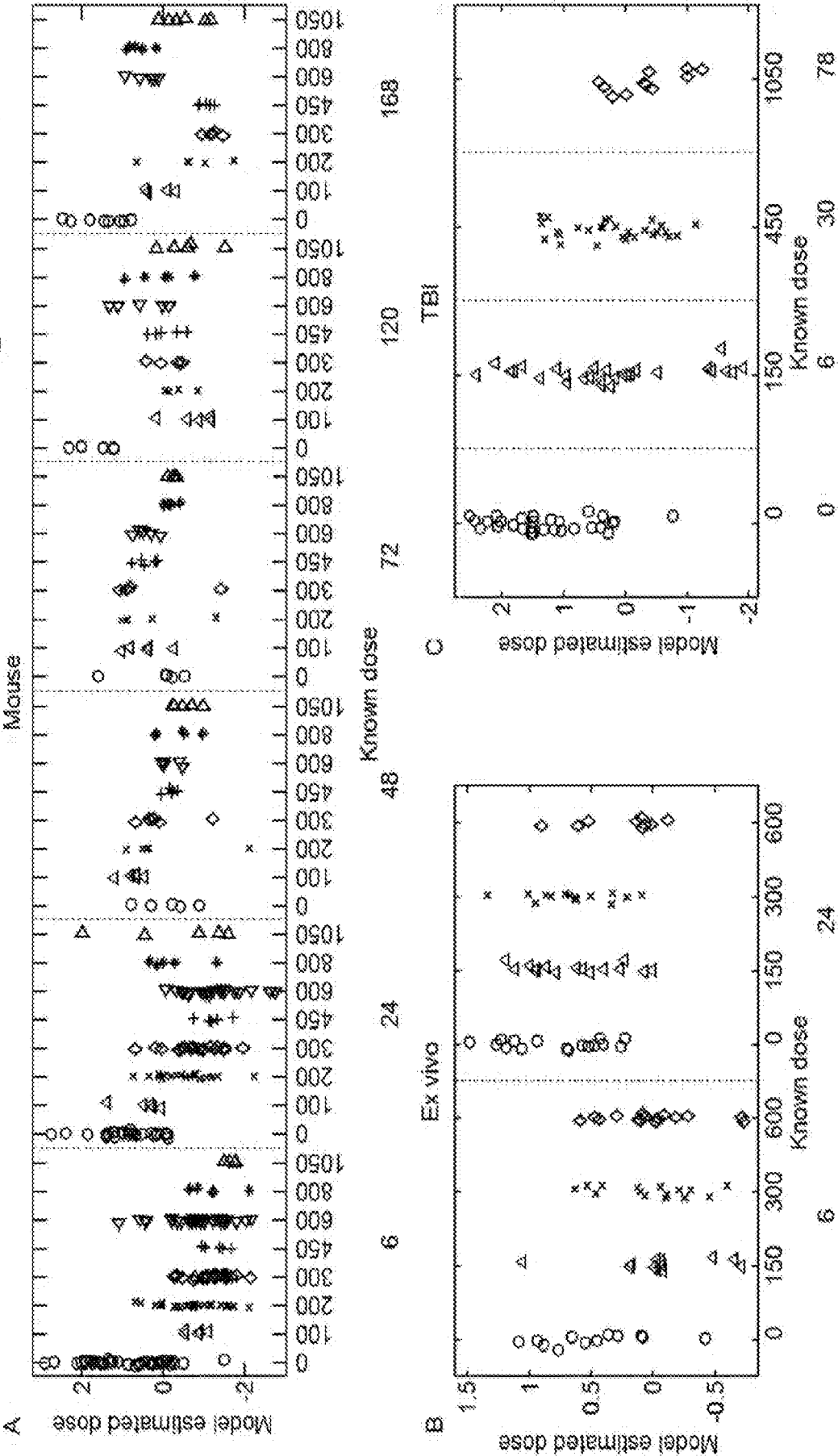


Fig. 9D Cont'd

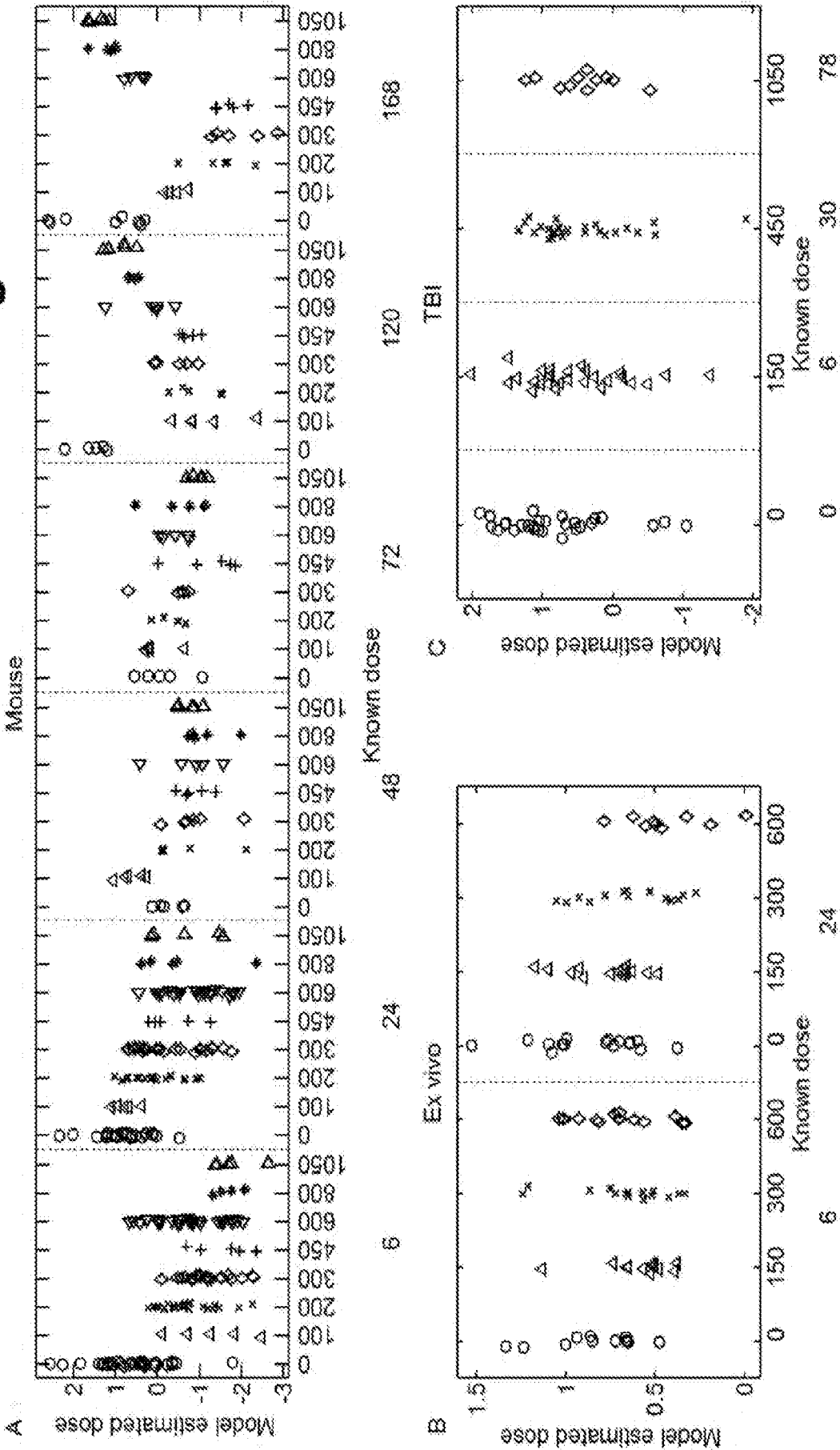


Fig. 9D Cont'd

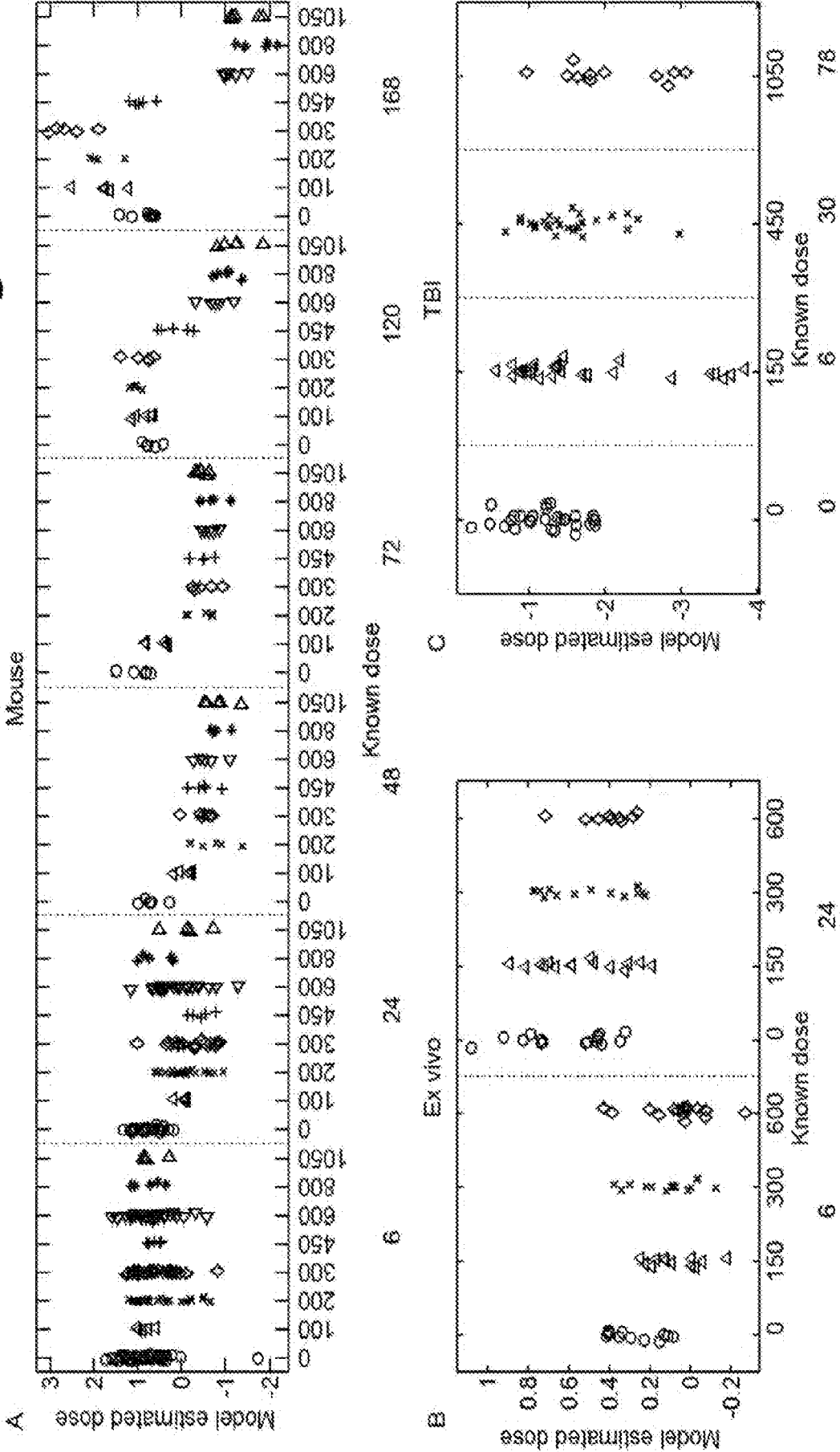


Fig. 9D Cont'd

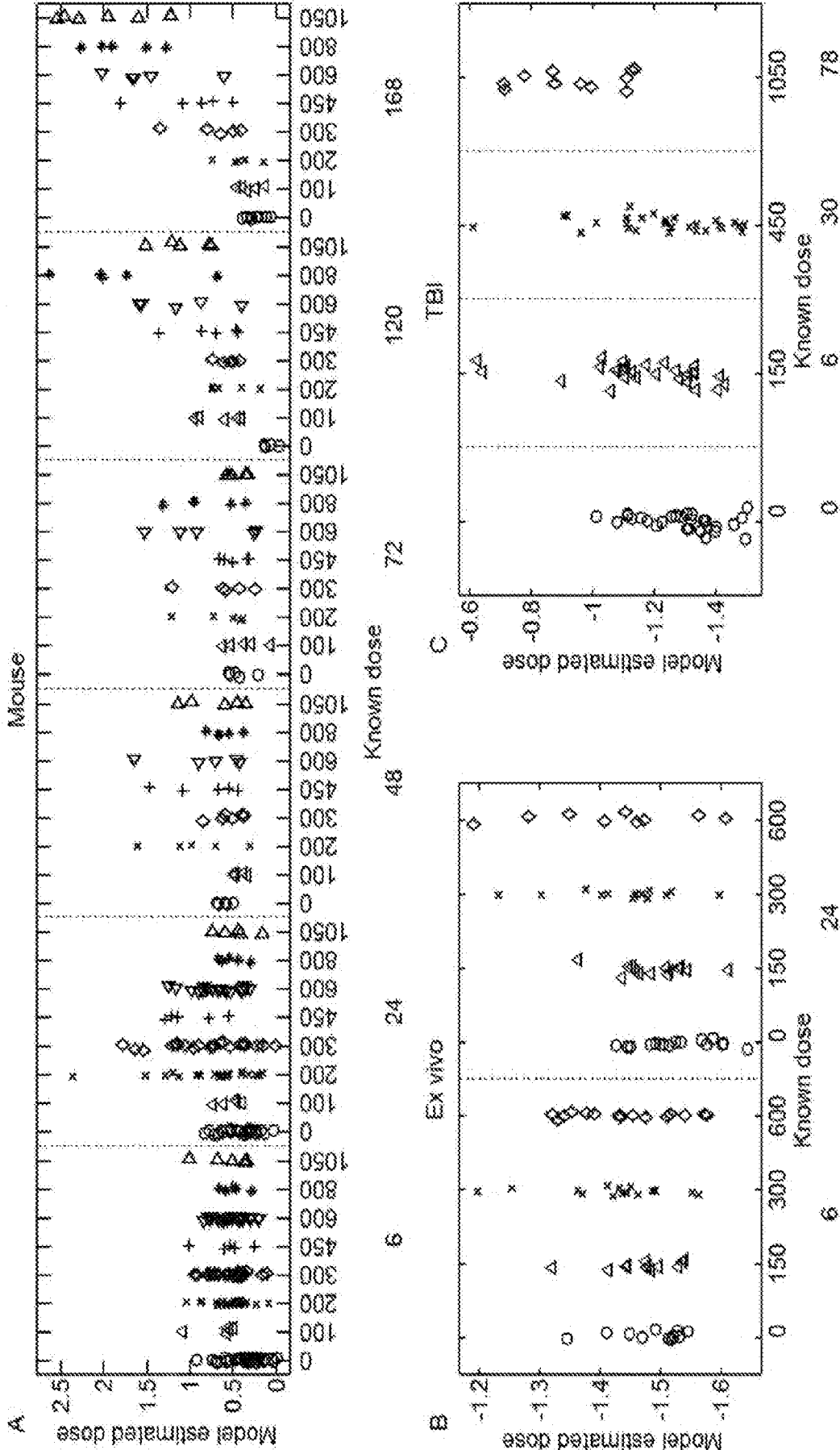


Fig. 9D Cont'd

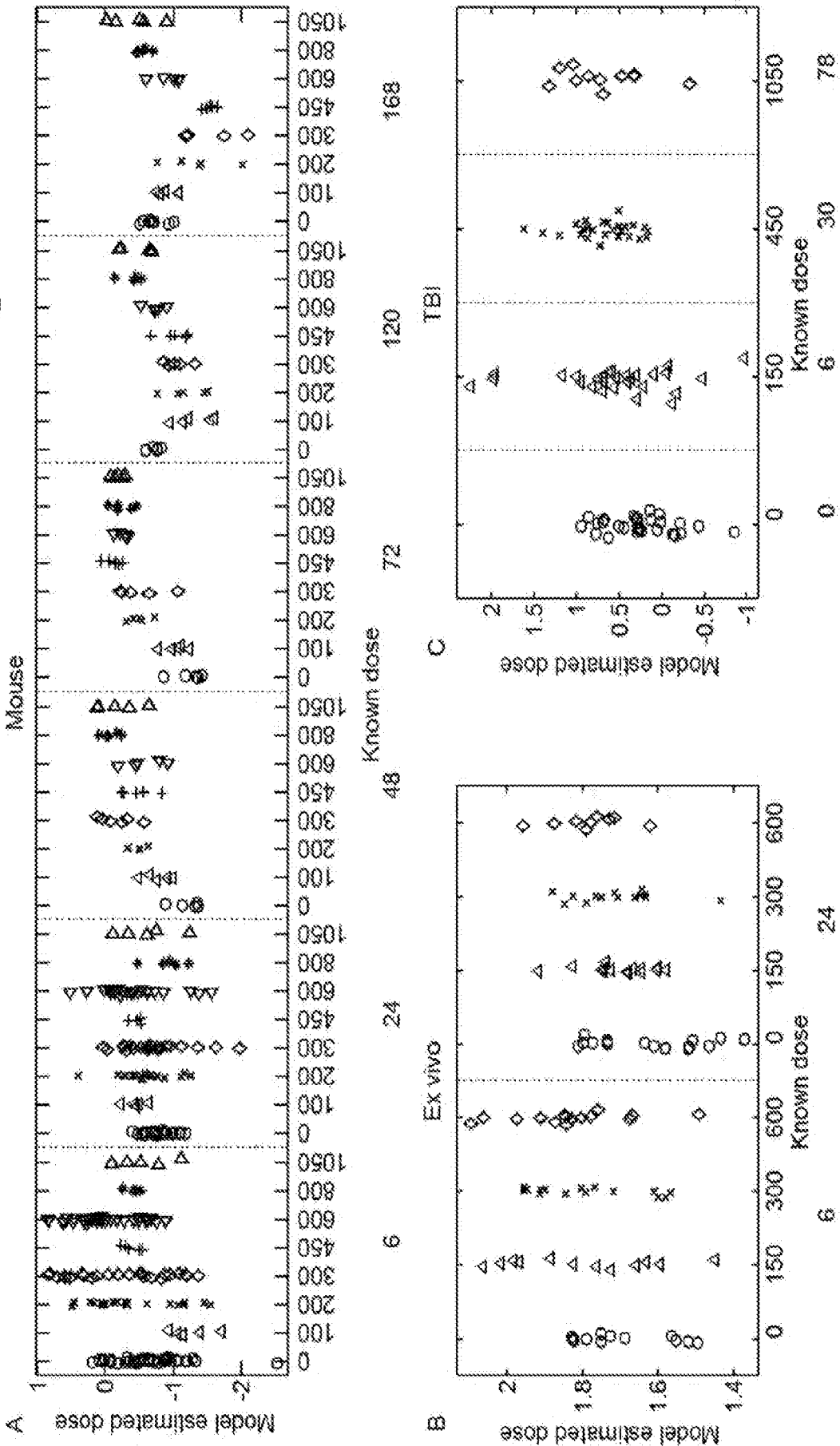


Fig. 9D Cont'd

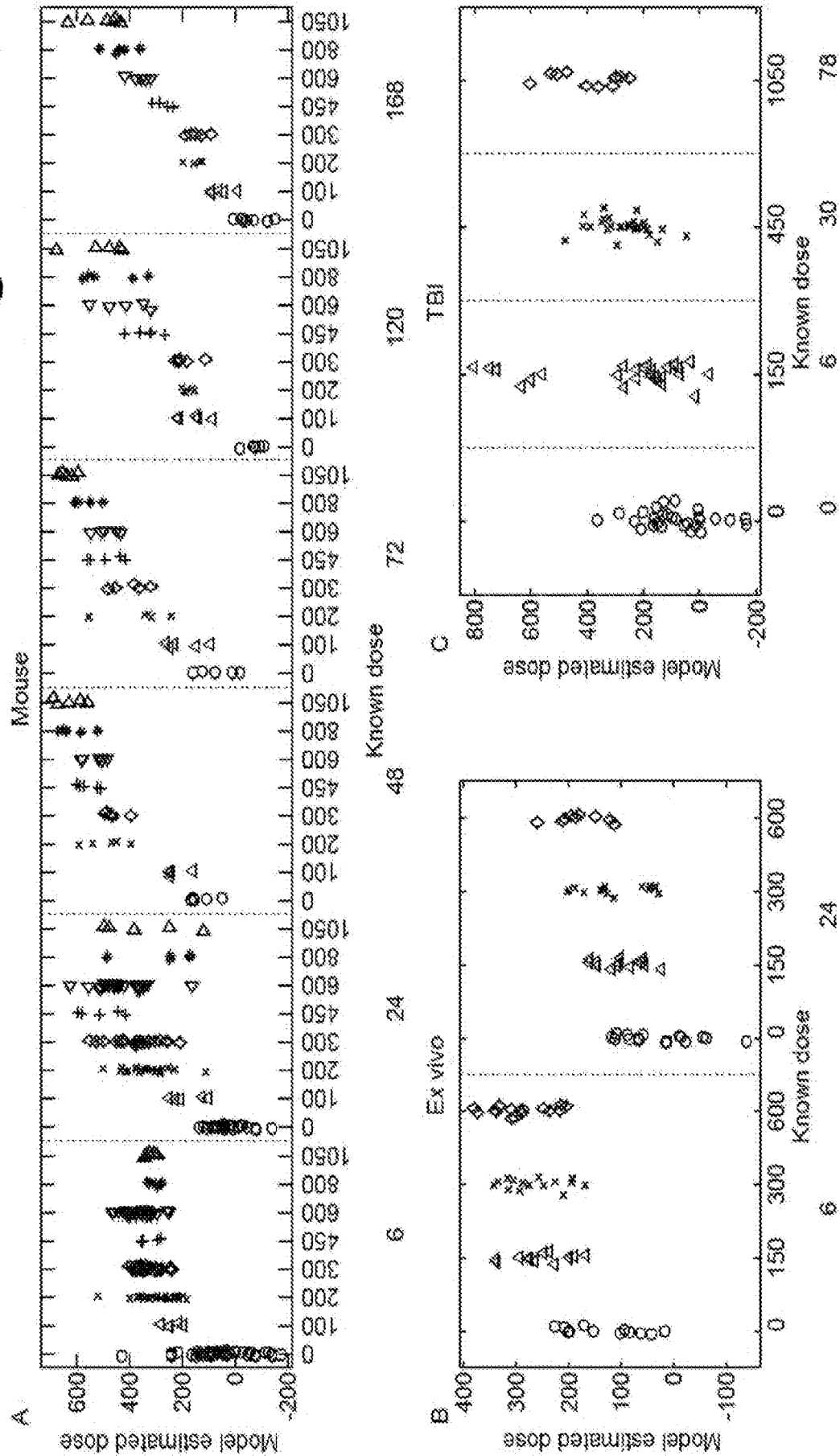


Fig. 9D Cont'd

mouse probe	human probe	model-4-genes.txt publciD	gene title	gene symbol
1416543_at	201146_at	NM_010902	"nuclear factor, erythroid derived	
2, like 2"		Nfe2l2		
1419526_at	208438_s_at	NM_010208	Gardner-Rasheed feline sarcoma viral	
(Fgr) oncogene homolog		Fgr		
1422503_s_at	208644_at	AF126717	"poly (ADP-ribose) polymerase	
family, member 1"		Parp1		
1424716_at	218124_at	BB775176	"retinol saturase (all trans retinol	
13,14 reductase)"		Retsat		
1426014_a_at	220075_s_at	AF462391	mucin-like protocadherin	
		Mupcdh		
1433878_at	213795_s_at	AI648866	mitochondrial ribosomal protein S26	
		Mrps26		
1439323_a_at	214339_s_at	BB546619	mitogen-activated protein kinase	
kinase kinase kinase 1		Map4k1		
1448417_at	203045_at	NM_013610	ninjurin 1	
		Ninj1		
1449156_at	215967_s_at	NM_008534	lymphocyte antigen 9	
		Ly9		
1449897_a_at	216862_s_at	NM_010839	mature T-cell proliferation 1	
		Mtcp1		
1452457_a_at	201835_s_at	AF108215	"protein kinase, AMP-activated, beta	
1, non-catalytic subunit"		Prkab1		
1452469_a_at	209427_at	BF578669	smoothenin	
		Smtn		
1453573_at	214472_at	BB088582	"histone cluster 1, H3d"	
		Hist1h3d		
1460218_at	34210_at	NM_013706	CD52 antigen	
		Cd52		

Fig. 9E

Name	Size	Packed Size	Modified
* F11r.png	46 849	43 597	2011-10-25 11:01
* Mettl8.png	47 023	43 488	2011-10-25 11:01
* N4bp1.png	47 508	43 749	2011-10-25 11:01
* Rit1.png	48 035	44 526	2011-10-25 11:01
* Traf5.png	47 007	43 548	2011-10-25 11:01
* Bcl11a.png	48 384	44 866	2011-10-25 11:01
* Bcl11b.png	48 434	44 982	2011-10-25 11:01
* Dgkg.png	48 144	44 811	2011-10-25 11:01
* model-5.png	48 012	44 548	2011-10-25 10:58
model-5-genes.txt	801	416	2011-10-25 10:58

Fig. 9E Cont'd

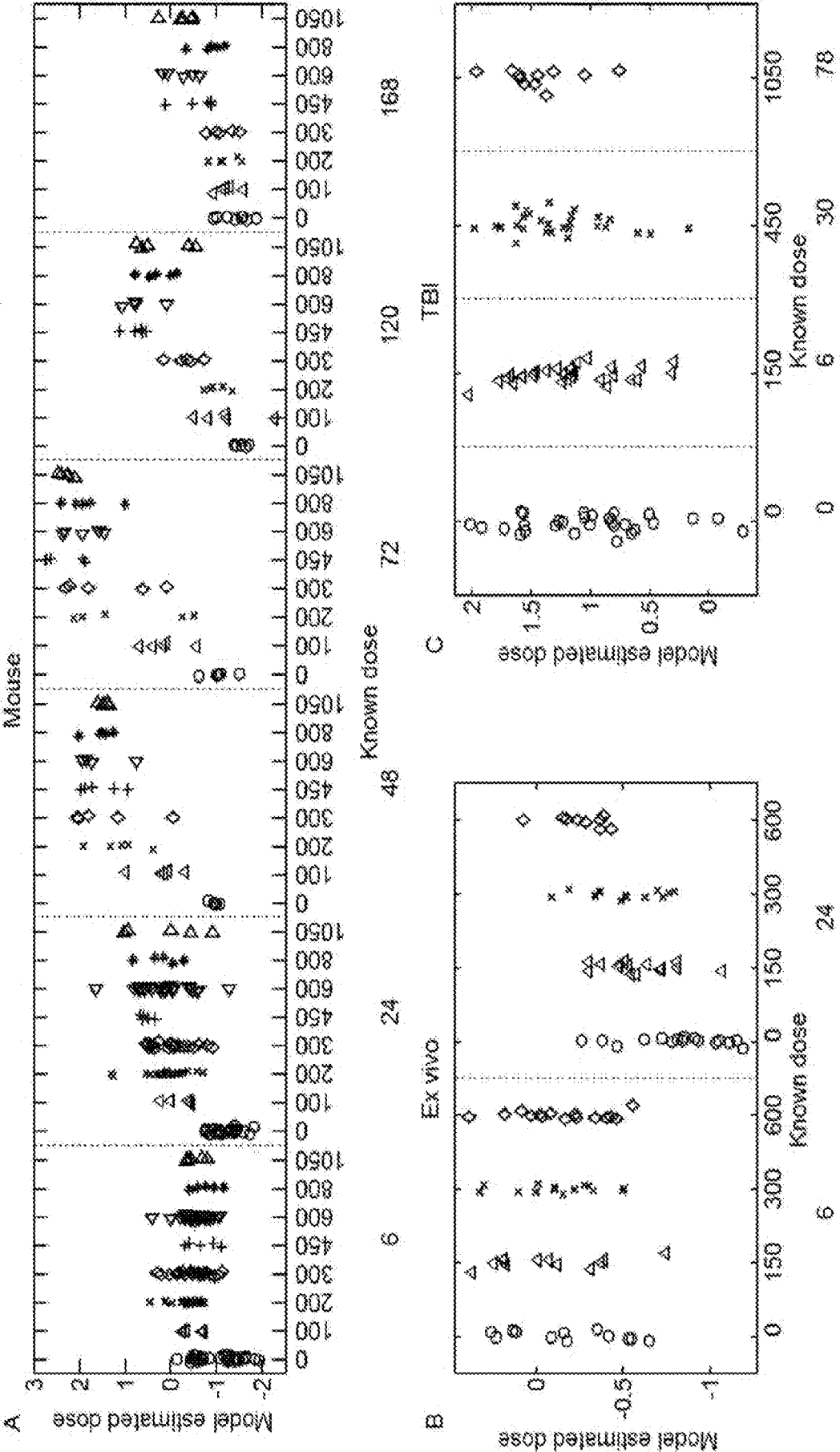


Fig. 9E Cont'd

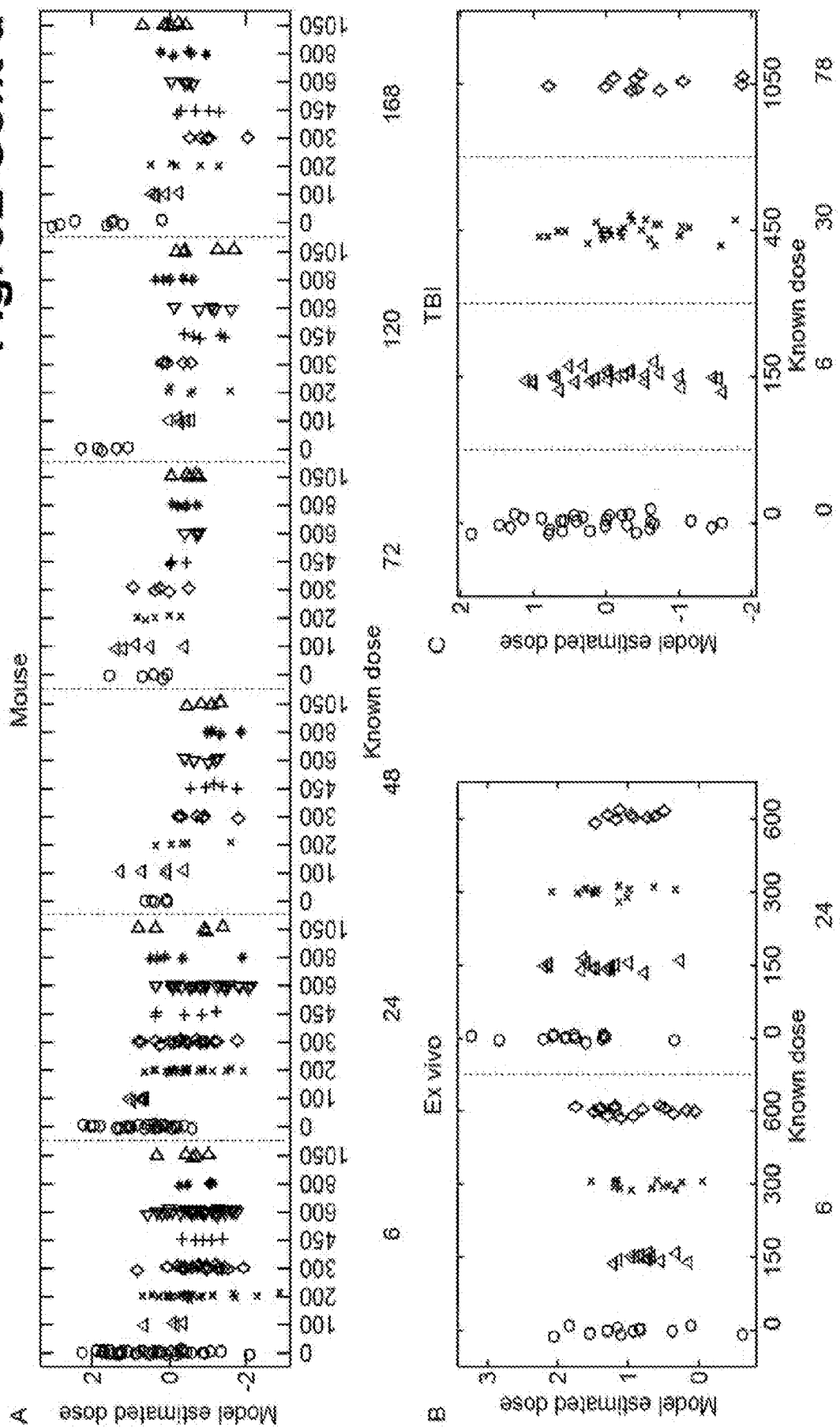


Fig. 9E Cont'd

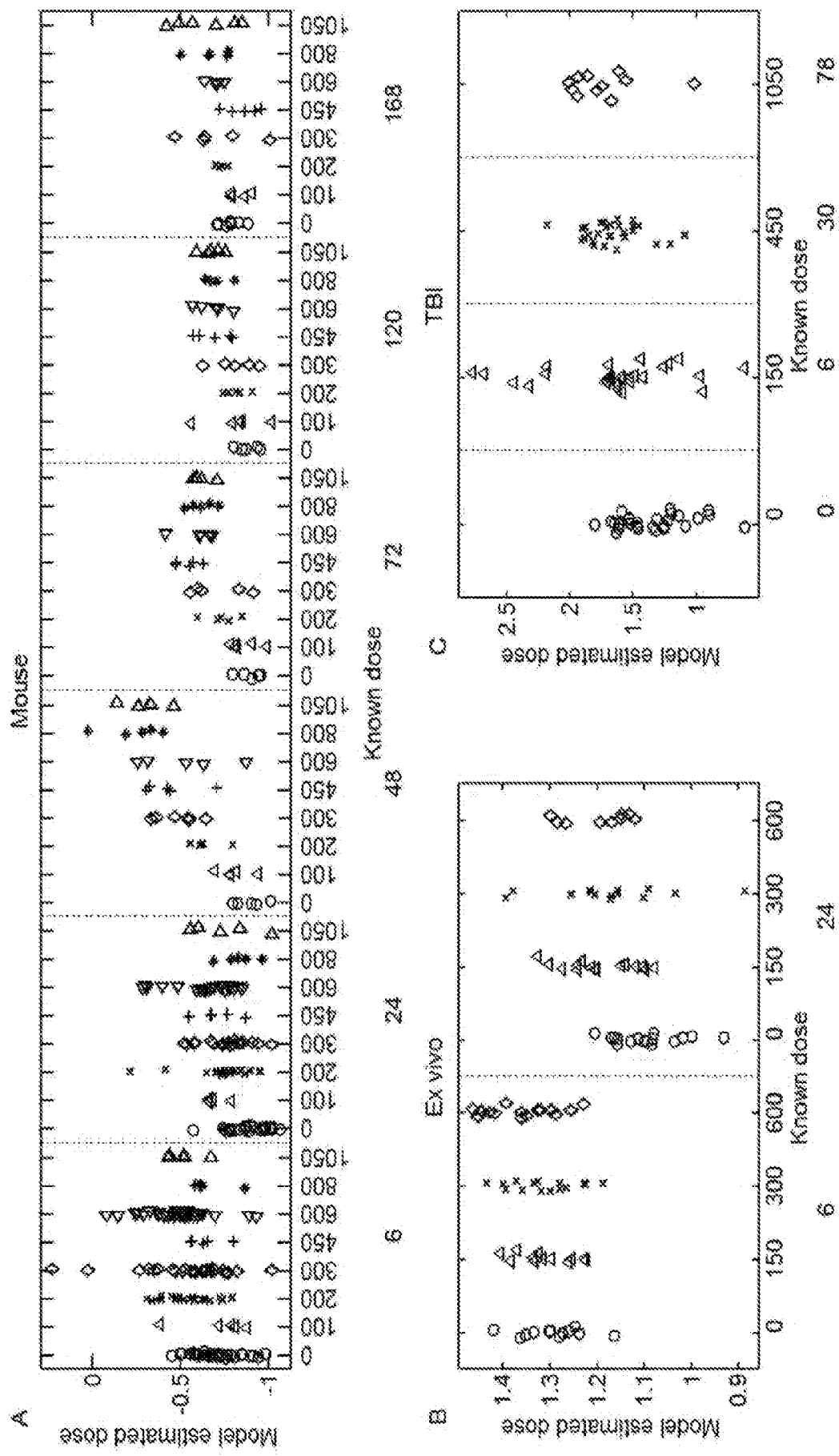


Fig. 9E Cont'd

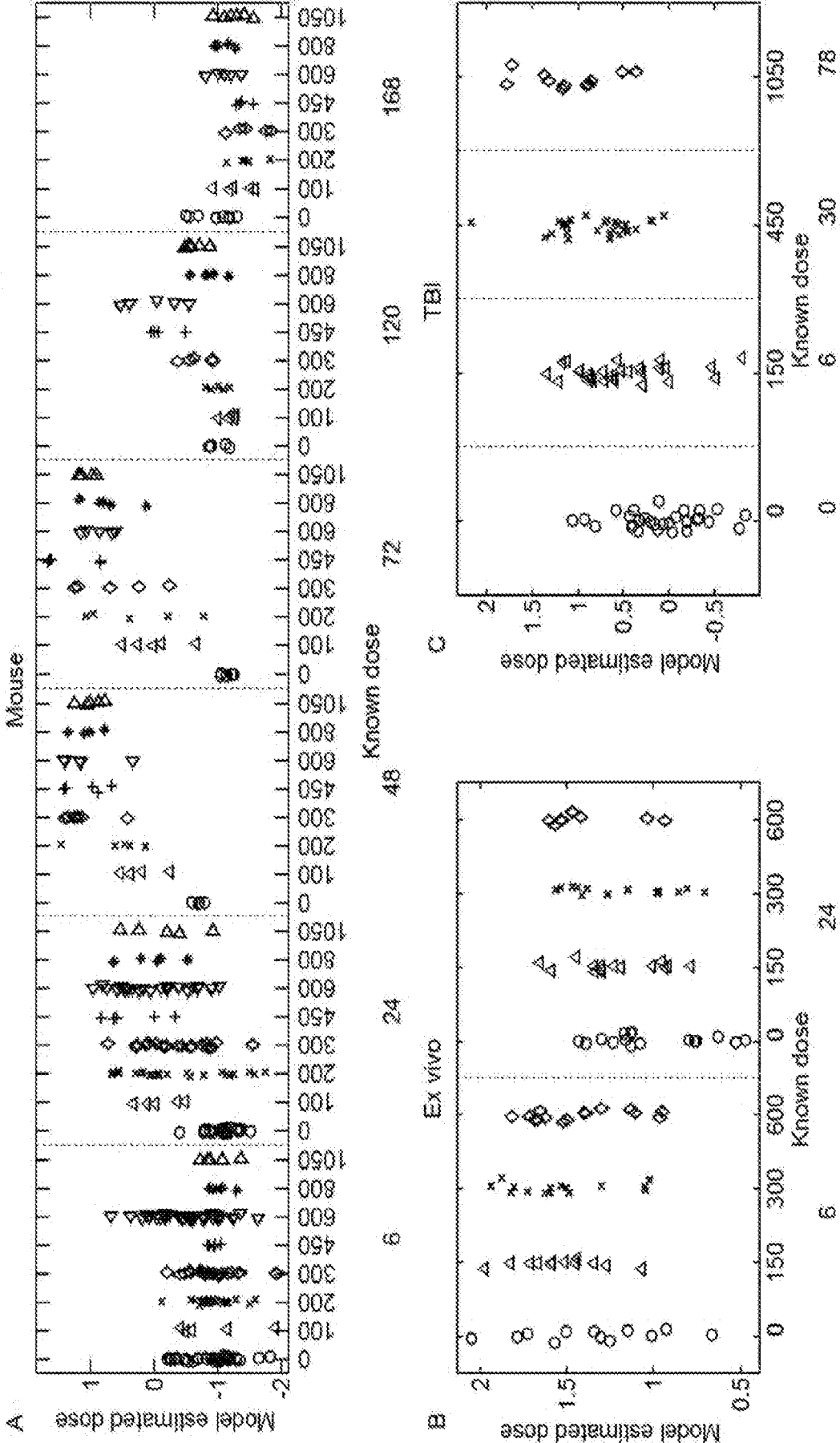


Fig. 9E Cont'd

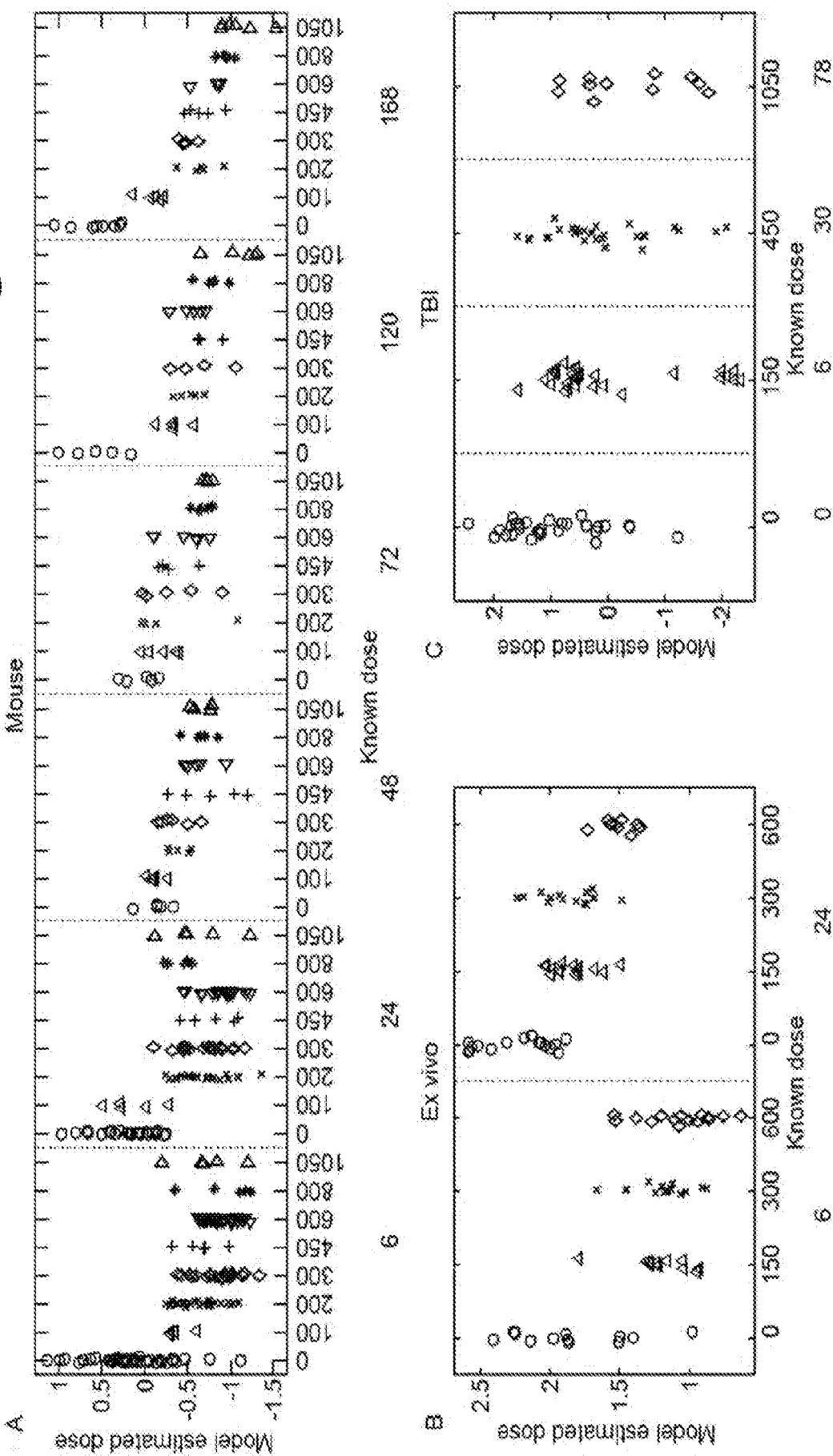


Fig. 9E Cont'd

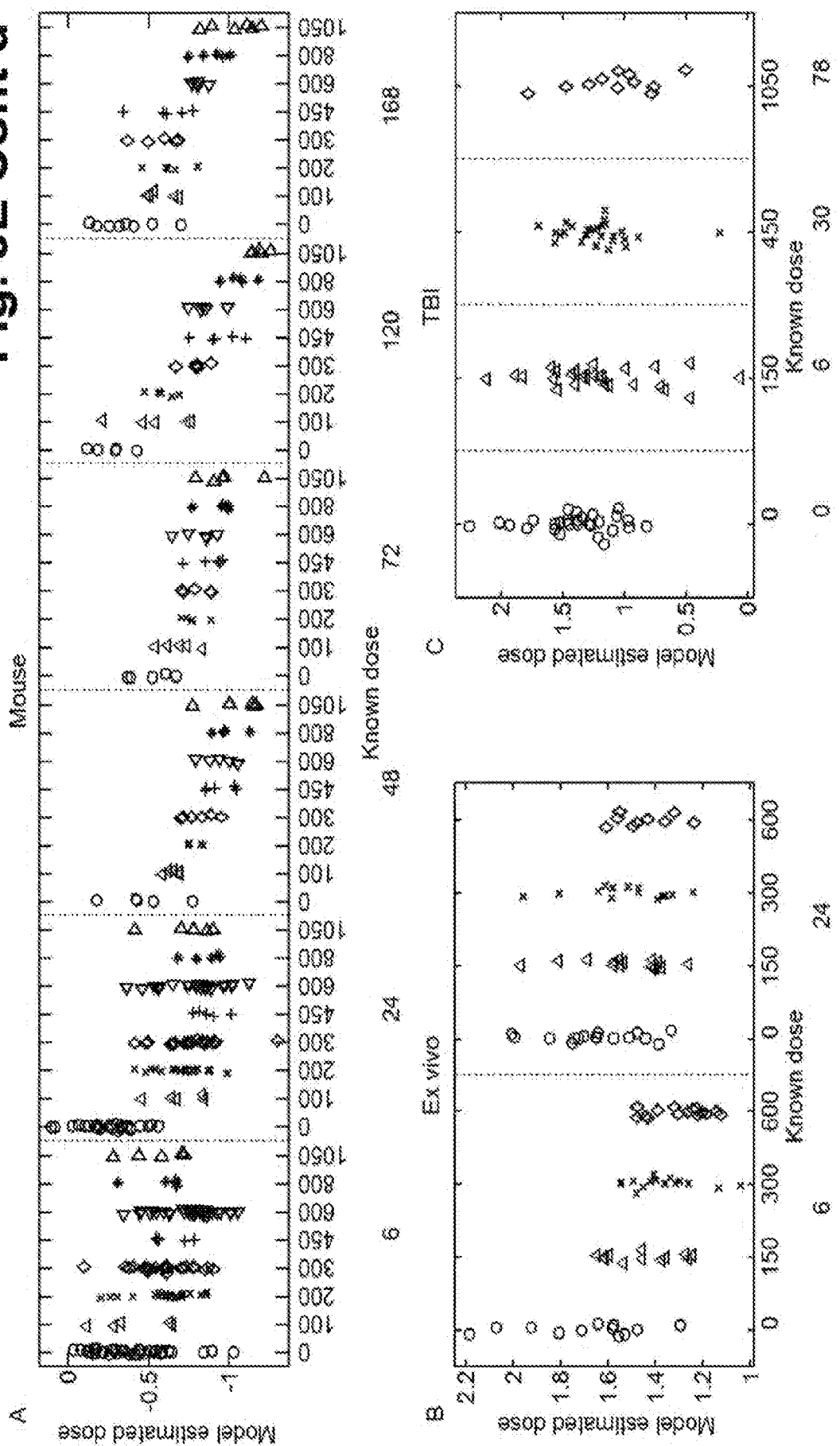


Fig. 9E Cont'd

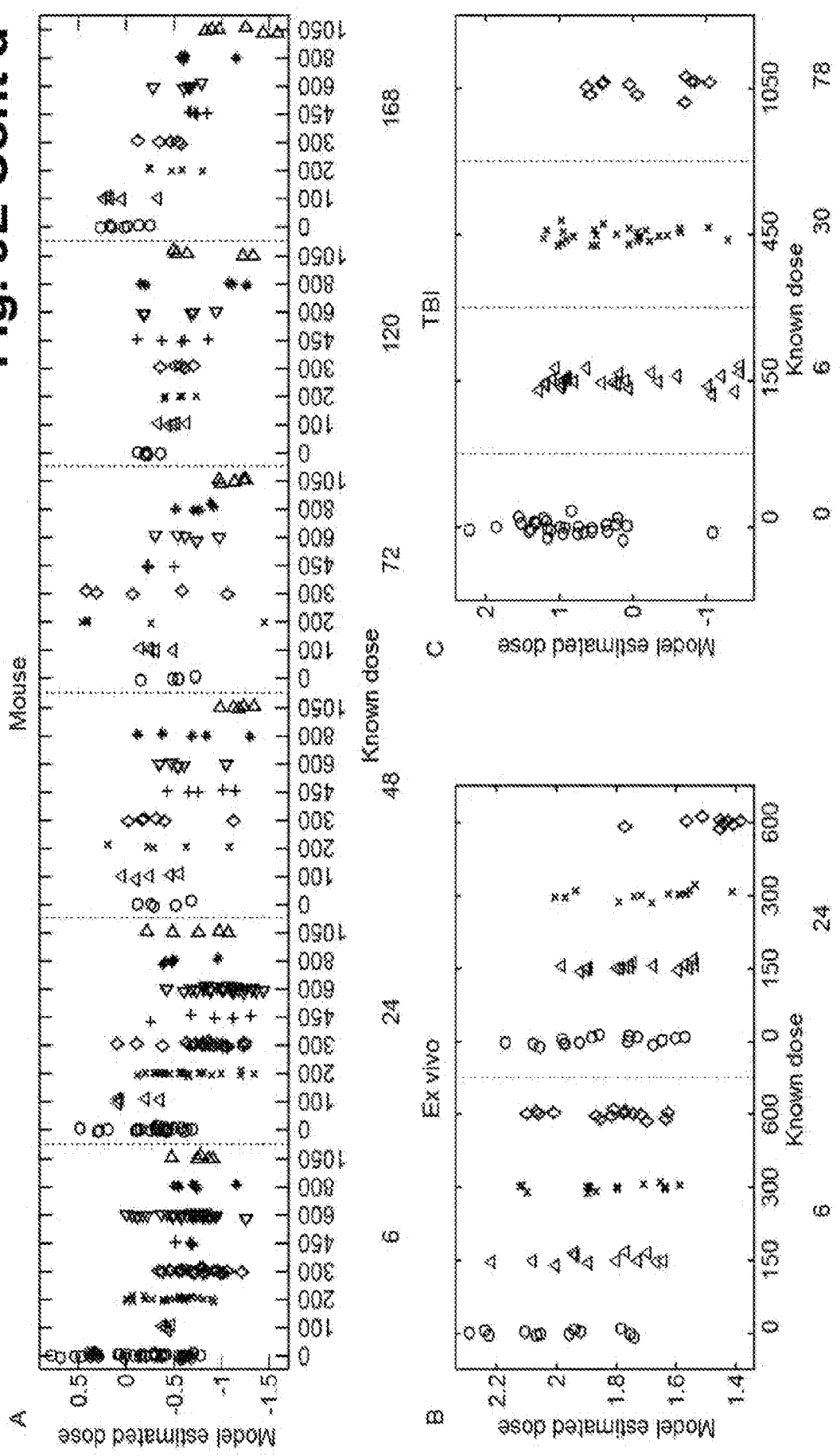


Fig. 9E Cont'd

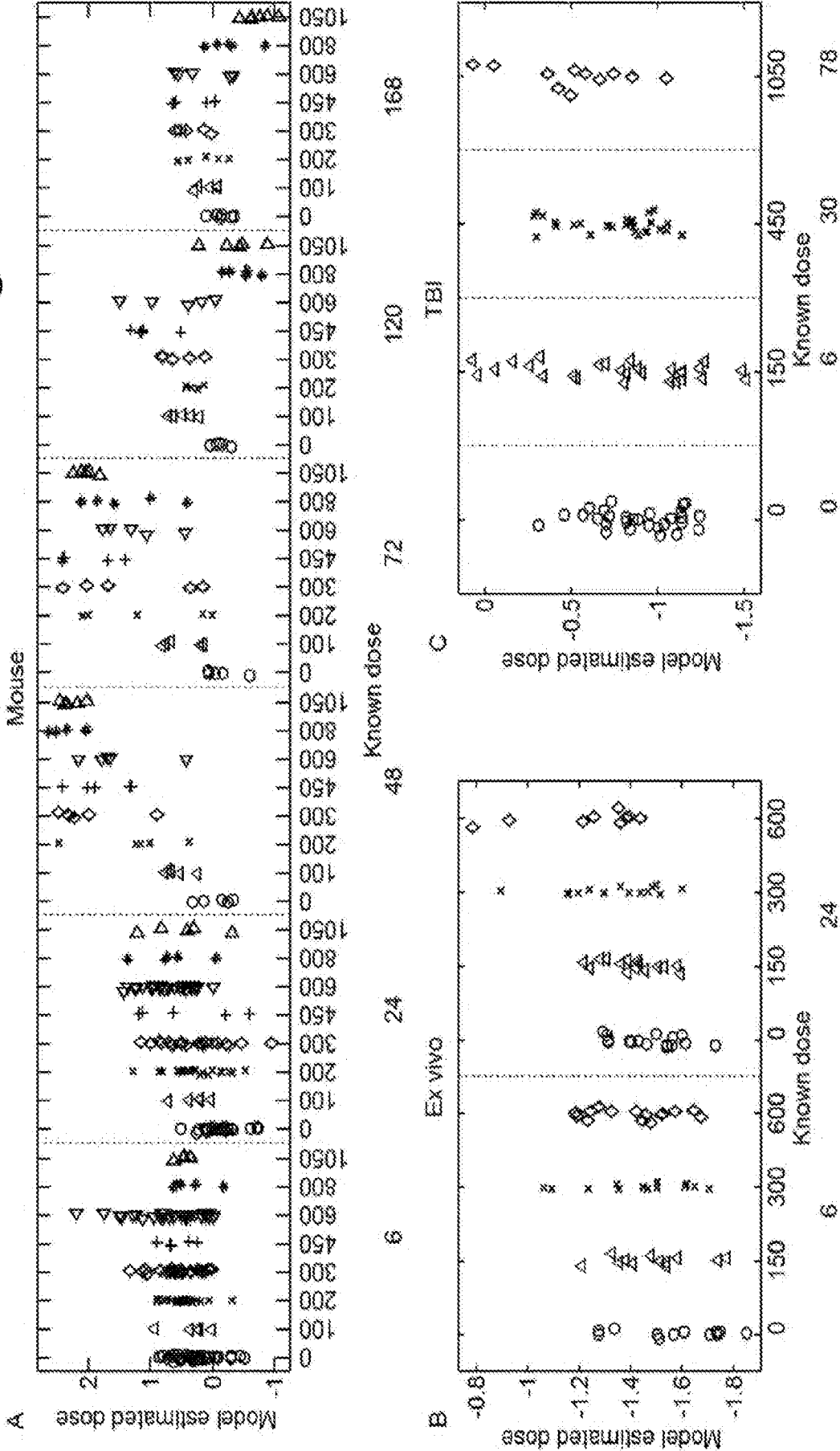


Fig. 9E Cont'd

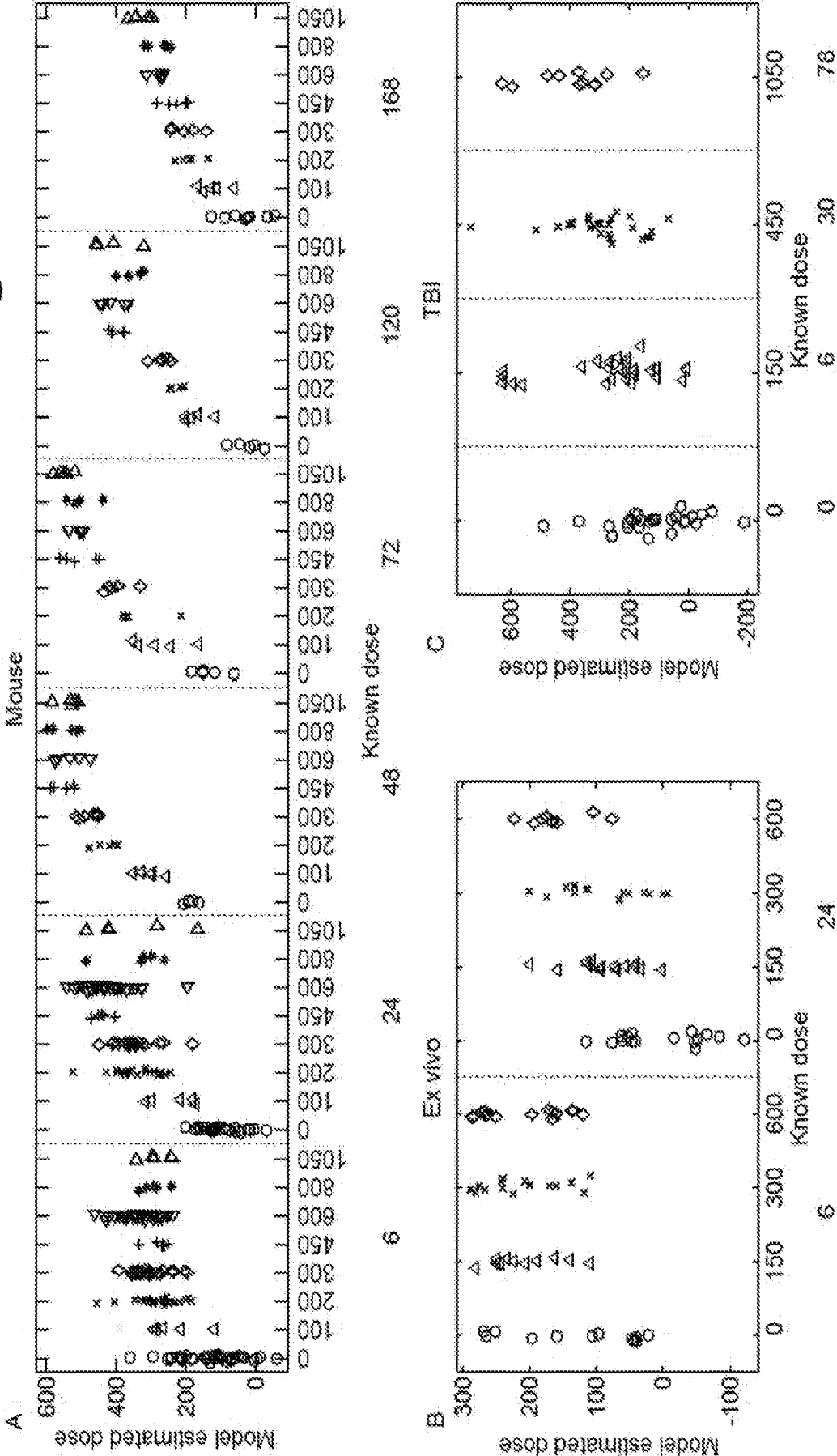


Fig. 9E Cont'd

mouse probe	human probe	model-5-genes.txt publicID	gene title	gene symbol
1418154_at	32069_at	NM_030563	NEDD4 binding protein 1	
1424595_at	N4bp1 221664_s_at	BC021876	F11 receptor	
1426552_a_at	F11r			
protein) 1428710_at	219498_s_at	BB772866	B-cell CLL/lymphoma 11A (zinc finger	
	BC111a			
	209882_at	AK018785	Ras-like without CAAAX 1	
	Rit1			
1448861_at	204352_at	NM_011633	TNF receptor-associated factor 5	
	Traf5			
1449584_at	206395_at	NM_138650	"diacylglycerol kinase, gamma"	
	Dgkg			
1450339_a_at	219528_s_at	NM_021399	B-cell leukemia/lymphoma 11B	
	BC111b			
1451141_at	220007_at	BC004636	methyltransferase like 8	
	Mett18			

Fig. 10

Name	Size	Packed Size	Modified
✱ 82-Bld.png	46 923	43 270	2011-10-25 11:13
✱ 83-Rasa4.png	50 761	47 523	2011-10-25 11:13
✱ 84-Tnip2.png	48 799	45 453	2011-10-25 11:13
✱ 85-Gna15.png	47 930	44 426	2011-10-25 11:13
✱ 86-Dgkg.png	49 394	46 074	2011-10-25 11:13
✱ 87-Laptn5.png	50 323	47 105	2011-10-25 11:13
✱ 88-Mrps26.png	49 111	45 725	2011-10-25 11:13
✱ 89-Mmp14.png	48 514	44 879	2011-10-25 11:13
✱ 90-Ras12.png	50 537	47 280	2011-10-25 11:13
✱ 1-Cdkn1a.png	45 178	41 626	2011-10-25 11:11
✱ 2-Phlda3.png	45 717	42 227	2011-10-25 11:11
✱ 3-Pik2.png	46 320	42 666	2011-10-25 11:11
✱ 4-Tnfsf4.png	47 538	43 699	2011-10-25 11:11
✱ 5-Bbc3.png	46 441	42 796	2011-10-25 11:11
✱ 6-Bax.png	47 935	44 303	2011-10-25 11:11
✱ 7-Mdm2.png	50 196	46 636	2011-10-25 11:11
✱ 8-Nacc2.png	47 266	43 749	2011-10-25 11:11
✱ 9-Ptprcap.png	46 888	43 588	2011-10-25 11:11
✱ 10-Cd27.png	48 782	45 651	2011-10-25 11:11
✱ 11-Fas.png	46 426	42 800	2011-10-25 11:11
✱ 12-Sit1.png	49 371	46 135	2011-10-25 11:11
✱ 13-LOC665622.png	47 875	44 514	2011-10-25 11:12
✱ 14-Dpp4.png	48 855	45 460	2011-10-25 11:12
✱ 15-Traf5.png	47 944	44 539	2011-10-25 11:12
✱ 16-LOC100047840.png	48 418	45 098	2011-10-25 11:12
✱ 17-Rps27l.png	48 613	45 317	2011-10-25 11:12
✱ 18-Pou2af1.png	49 199	45 758	2011-10-25 11:12
✱ 19-Lime1.png	50 292	47 213	2011-10-25 11:12
✱ 20-Rhoh.png	47 931	44 642	2011-10-25 11:12
✱ 21-Vpreb3.png	45 308	41 720	2011-10-25 11:12

Fig. 10 Cont'd

Name	Size	Packed Size	Modified
✱ 22-Aspa.png	49 208	45 622	2011-10-25 11:12
✱ 23-Ddit3.png	48 358	44 628	2011-10-25 11:12
✱ 24-Spib.png	48 014	44 262	2011-10-25 11:12
✱ 25-Cd79a.png	47 895	44 332	2011-10-25 11:12
✱ 26-Hist1h3d.png	47 739	44 360	2011-10-25 11:12
✱ 27-1200002N14Rik.png	49 211	45 630	2011-10-25 11:12
✱ 28-Triap1.png	49 709	46 310	2011-10-25 11:12
✱ 29-Cebpb.png	50 040	46 870	2011-10-25 11:12
✱ 30-Smtn.png	48 992	45 583	2011-10-25 11:12
✱ 31-Retsat.png	47 864	44 429	2011-10-25 11:12
✱ 32-Plekho2.png	47 739	44 462	2011-10-25 11:12
✱ 33-Cdc25b.png	45 493	42 046	2011-10-25 11:12
✱ 34-Ly9.png	48 545	45 170	2011-10-25 11:12
✱ 35-Lck.png	49 138	45 747	2011-10-25 11:12
✱ 36-Dedd.png	50 441	47 101	2011-10-25 11:12
✱ 37-Bcl11a.png	48 478	44 976	2011-10-25 11:12
✱ 38-Astn2.png	48 377	44 779	2011-10-25 11:12
✱ 39-Cds2.png	49 764	46 564	2011-10-25 11:12
✱ 40-Dock5.png	49 402	46 252	2011-10-25 11:12
✱ 41-Parp1.png	49 837	46 491	2011-10-25 11:12
✱ 42-Ube2d2.png	50 150	46 807	2011-10-25 11:12
✱ 43-Nsmce4a.png	48 922	45 619	2011-10-25 11:12
✱ 44-Map4k1.png	48 246	44 895	2011-10-25 11:12
✱ 45-Cd52.png	48 545	45 201	2011-10-25 11:12
✱ 46-Cd24a.png	46 050	42 746	2011-10-25 11:12
✱ 47-Mad2l1.png	46 611	42 847	2011-10-25 11:12
✱ 48-Rbpj.png	51 070	47 661	2011-10-25 11:12
✱ 49-Rit1.png	49 038	45 596	2011-10-25 11:12
✱ 50-Mum1.png	47 141	43 455	2011-10-25 11:12
✱ 51-Trib2.png	49 703	46 218	2011-10-25 11:12

Fig. 10 Cont'd

Name	Size	Packed Size	Modified
✱ 52-Prkab1.png	47 152	43 549	2011-10-25 11:12
✱ 53-Bcl11b.png	48 787	45 377	2011-10-25 11:13
✱ 54-Sft2d2.png	47 581	43 843	2011-10-25 11:13
✱ 55-Lbh.png	48 605	45 239	2011-10-25 11:13
✱ 56-Ninj1.png	47 744	44 425	2011-10-25 11:13
✱ 57-F5.png	48 074	44 755	2011-10-25 11:13
✱ 58-N4bp1.png	49 627	46 188	2011-10-25 11:13
✱ 59-Slpr1.png	47 338	43 782	2011-10-25 11:13
✱ 60-Rpal.png	48 613	44 997	2011-10-25 11:13
✱ 61-Rfc4.png	47 234	43 691	2011-10-25 11:13
✱ 62-Prim1.png	50 984	47 649	2011-10-25 11:13
✱ 63-Piala.png	49 211	46 090	2011-10-25 11:13
✱ 64-Fgr.png	49 357	45 711	2011-10-25 11:13
✱ 65-Mupcdh.png	49 925	46 331	2011-10-25 11:13
✱ 66-Qrs1.png	49 568	46 031	2011-10-25 11:13
✱ 67-Fam117a.png	47 000	43 873	2011-10-25 11:13
✱ 68-Fam134c.png	49 556	46 063	2011-10-25 11:13
✱ 69-Lsm7.png	48 855	45 356	2011-10-25 11:13
✱ 70-F11r.png	47 609	44 379	2011-10-25 11:13
✱ 71-6-Sep.png	48 787	45 186	2011-10-25 11:13
✱ 72-Nfe2i2.png	48 151	44 404	2011-10-25 11:13
✱ 73-Igj.png	47 151	43 374	2011-10-25 11:13
✱ 74-Ermp1.png	50 558	47 194	2011-10-25 11:13
✱ 75-Mtcp1.png	47 437	44 011	2011-10-25 11:13
✱ 76-Bckdk.png	49 661	46 214	2011-10-25 11:13
✱ 77-H2afv.png	50 192	46 858	2011-10-25 11:13
✱ 78-Ppp3cb.png	50 637	47 360	2011-10-25 11:13
✱ 79-Cpt2.png	48 324	44 971	2011-10-25 11:13
✱ 80-Mettl8.png	48 702	45 171	2011-10-25 11:13
✱ 81-TeX14.png	51 327	47 911	2011-10-25 11:13
□ allCorr-genes.txt	17 925	4 947	2011-10-25 11:38

Fig. 10 Cont'd

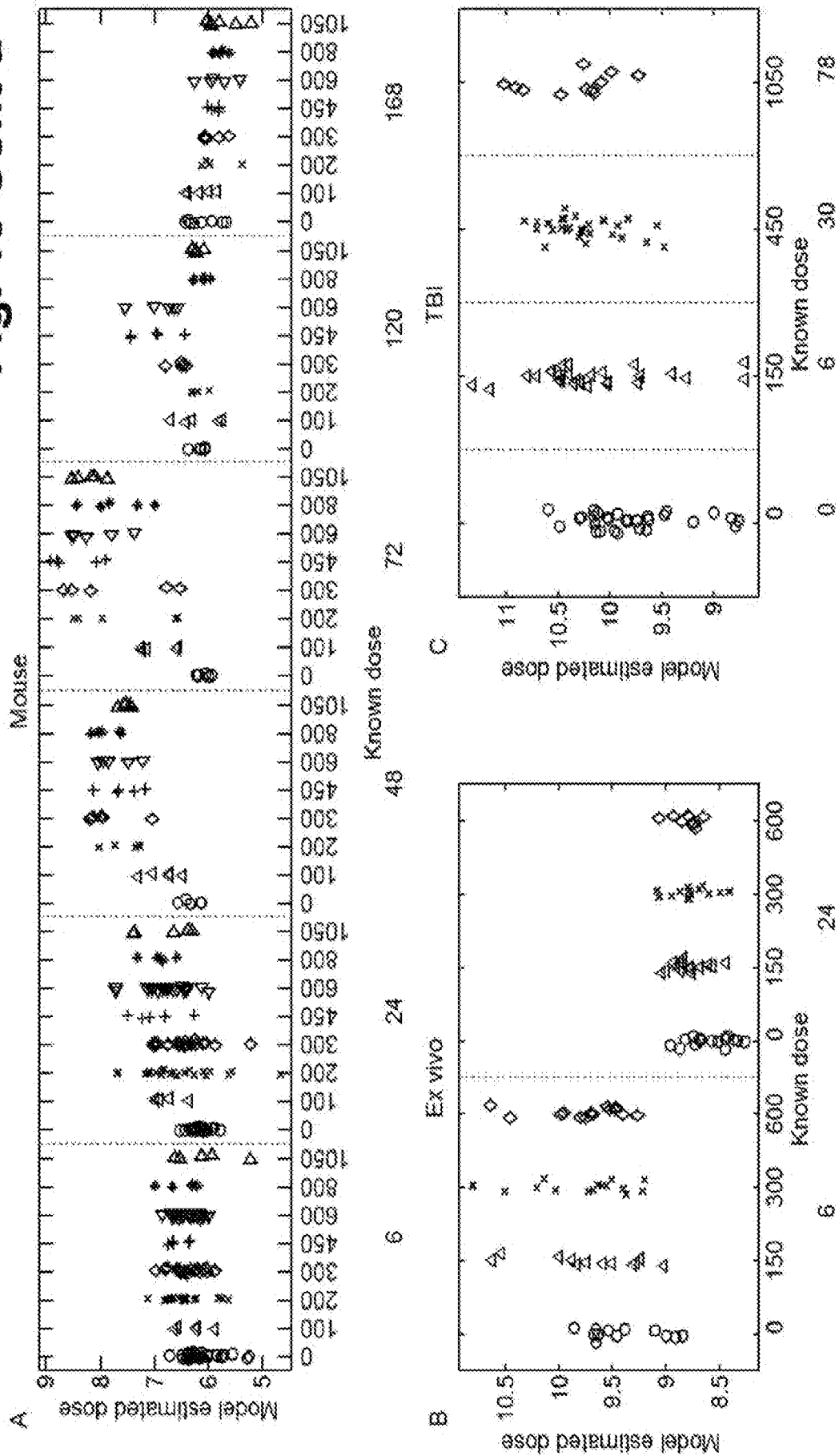


Fig. 10 Cont'd

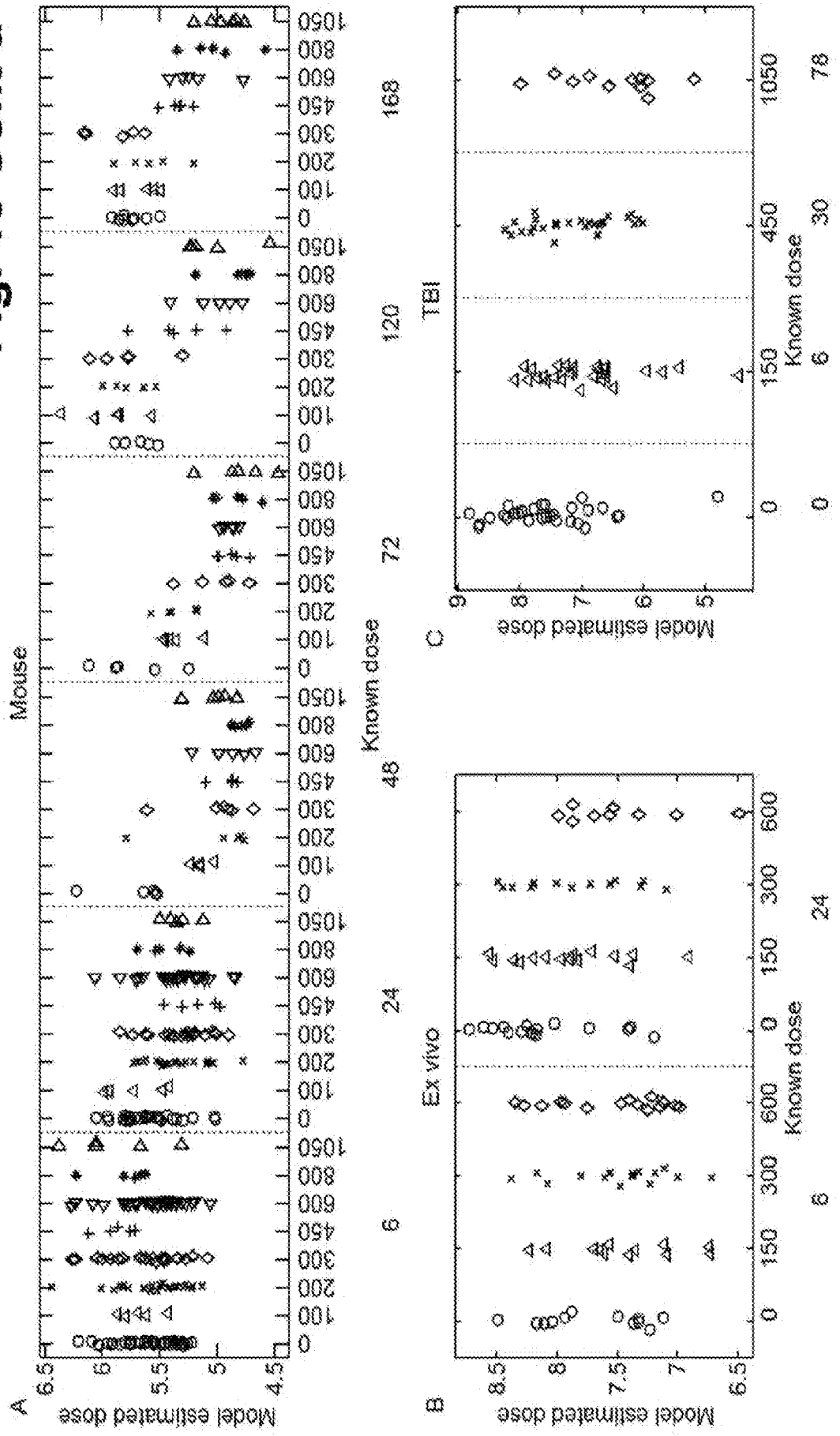


Fig. 10 Cont'd

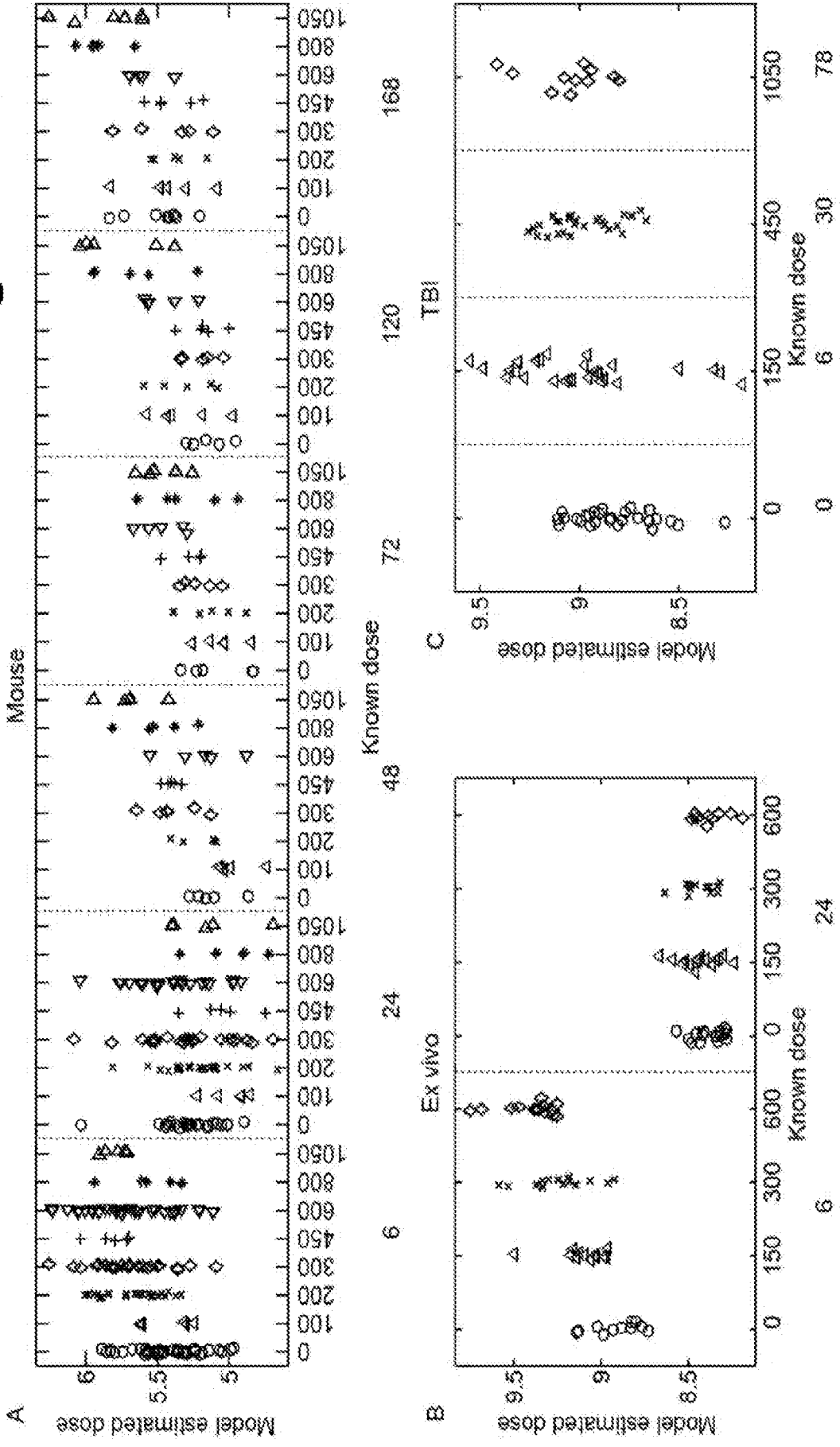


Fig. 10 Cont'd

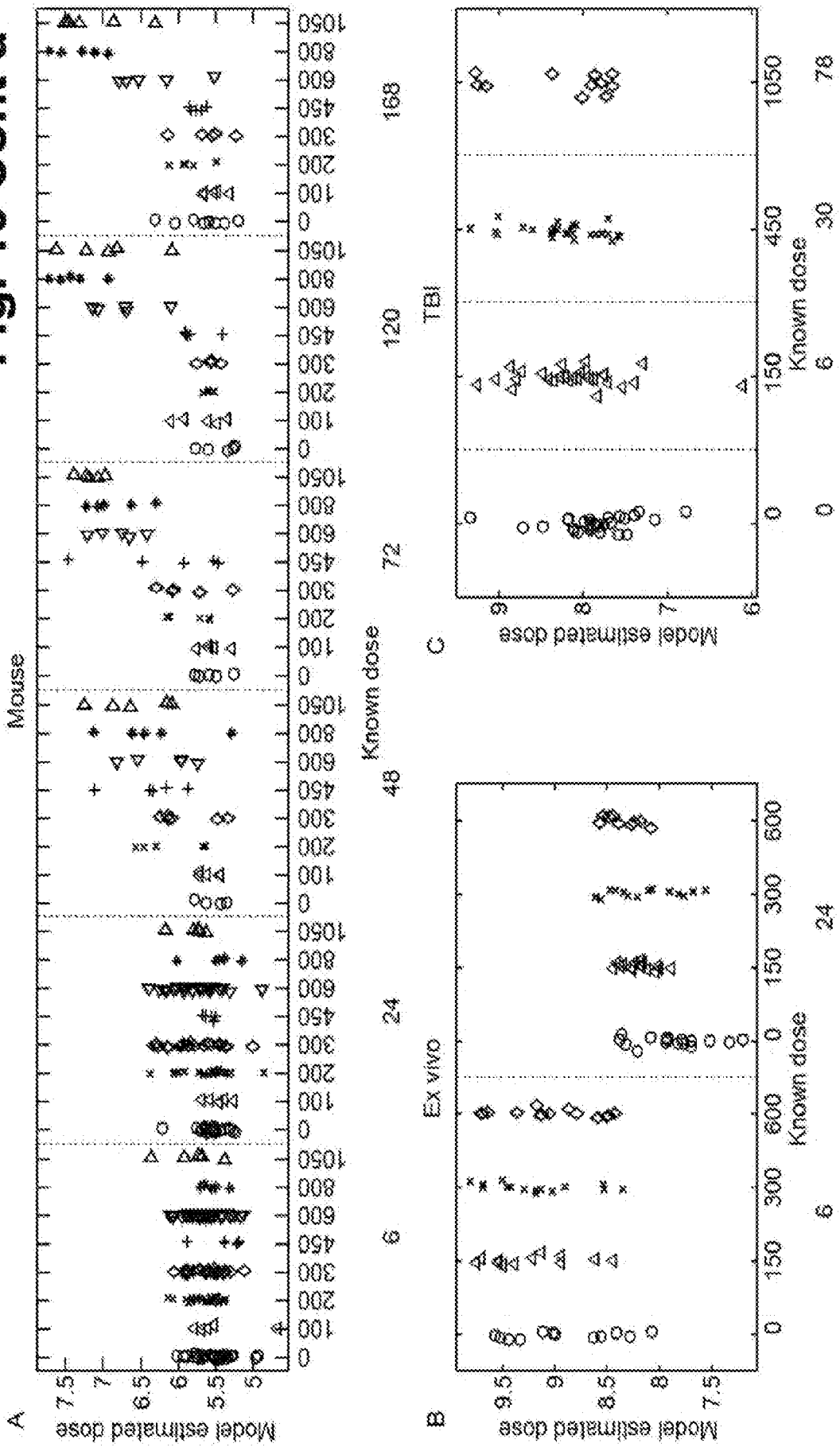
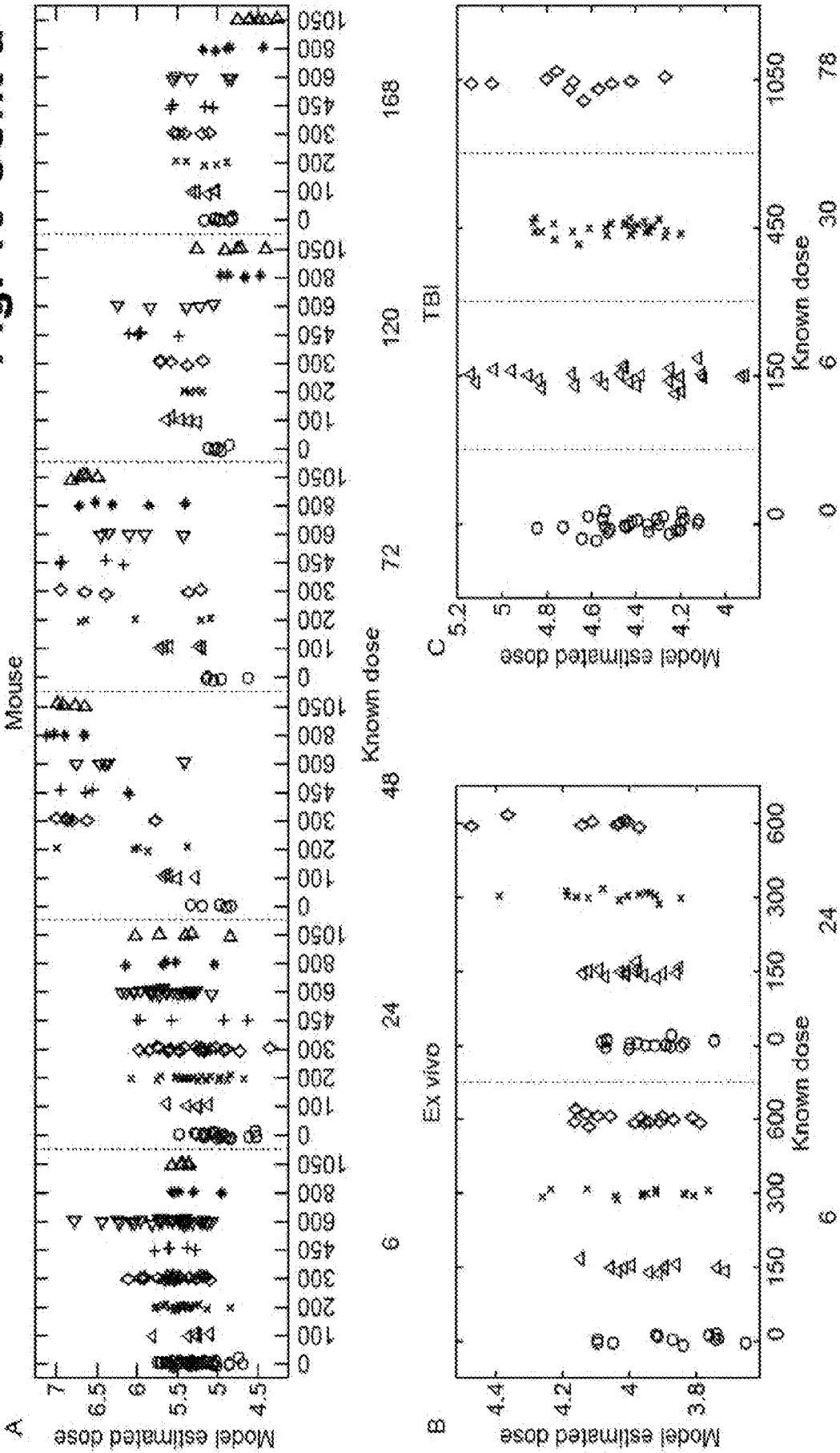


Fig. 10 Cont'd



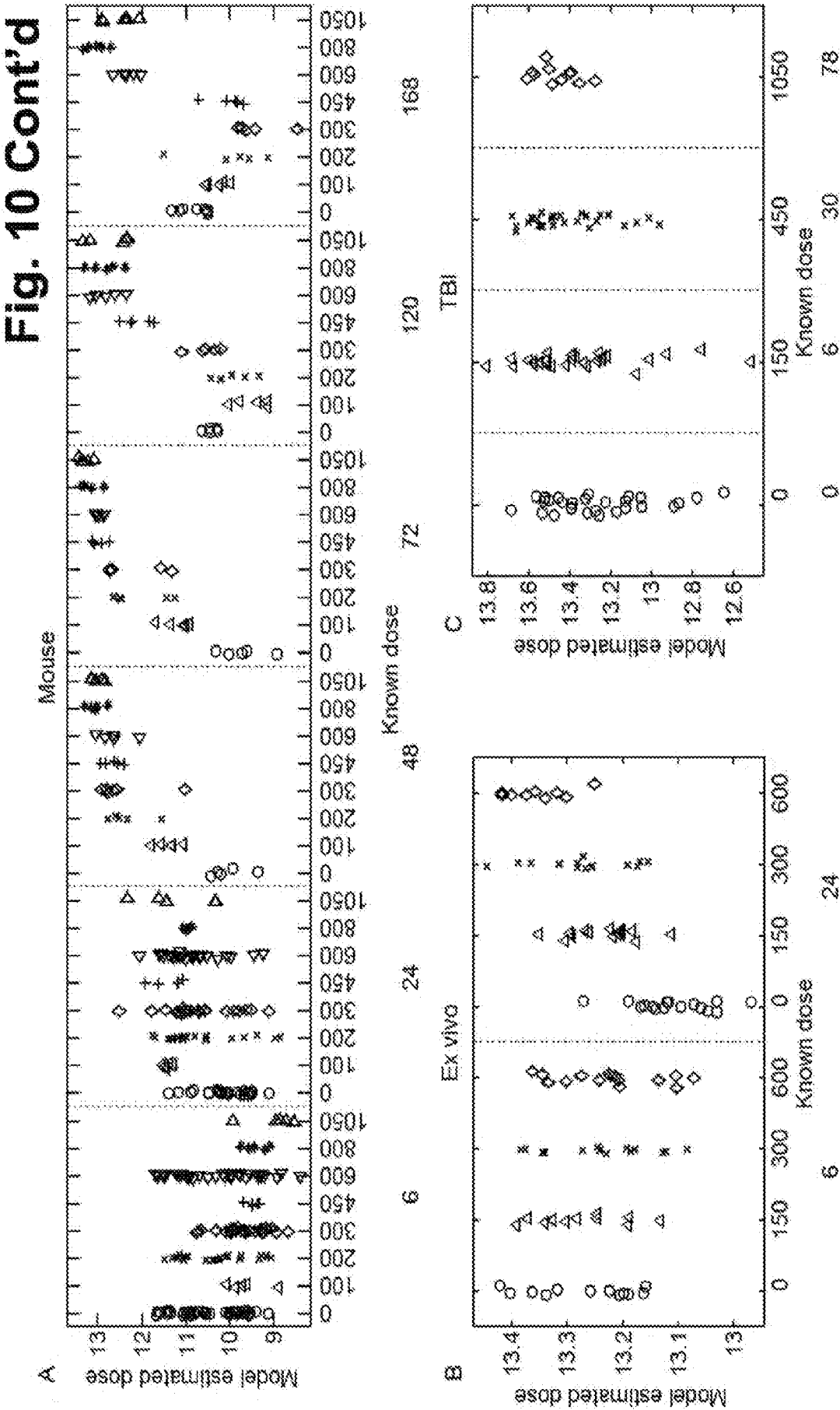
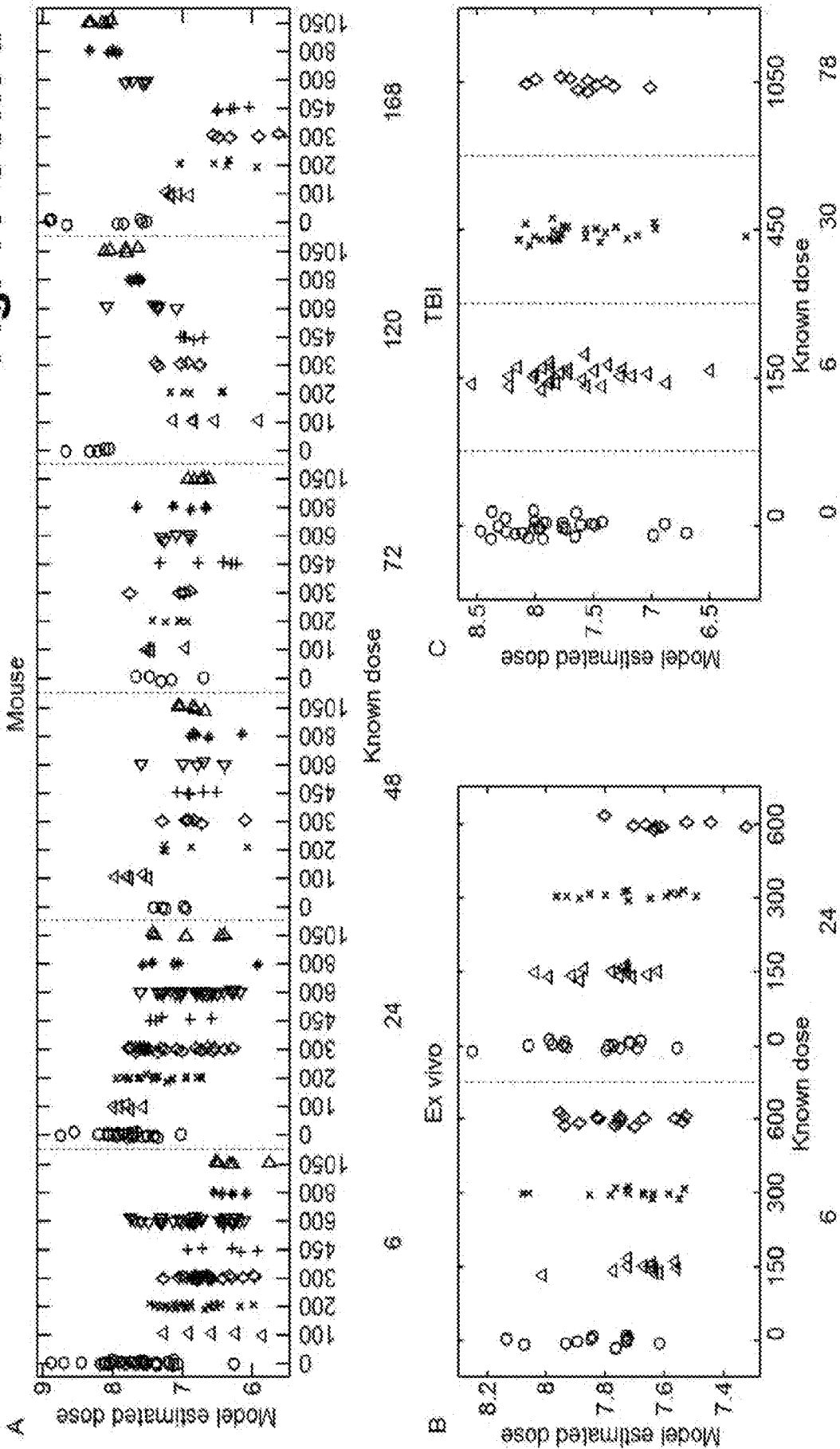


Fig. 10 Cont'd



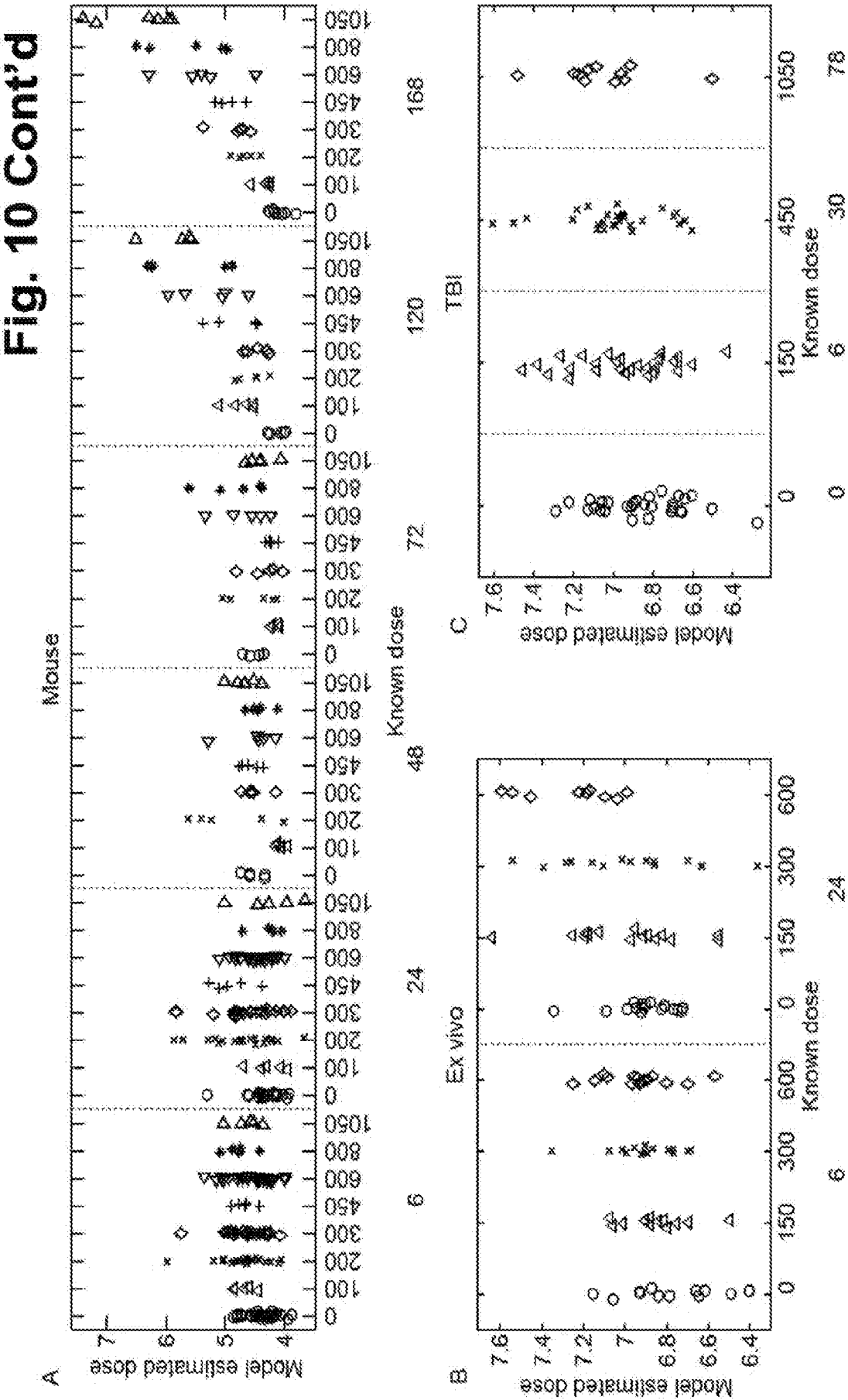


Fig. 10 Cont'd

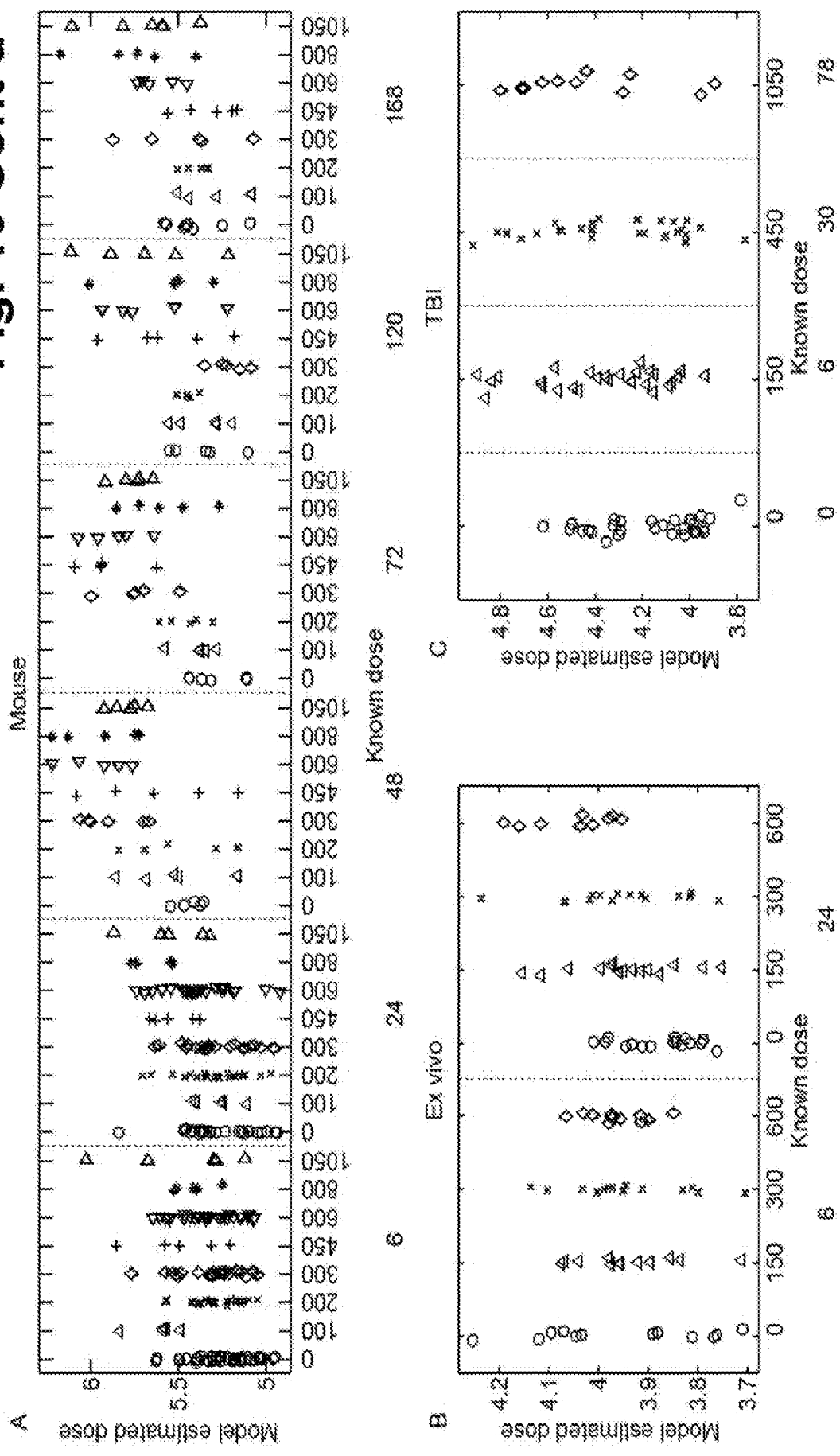


Fig. 10 Cont'd

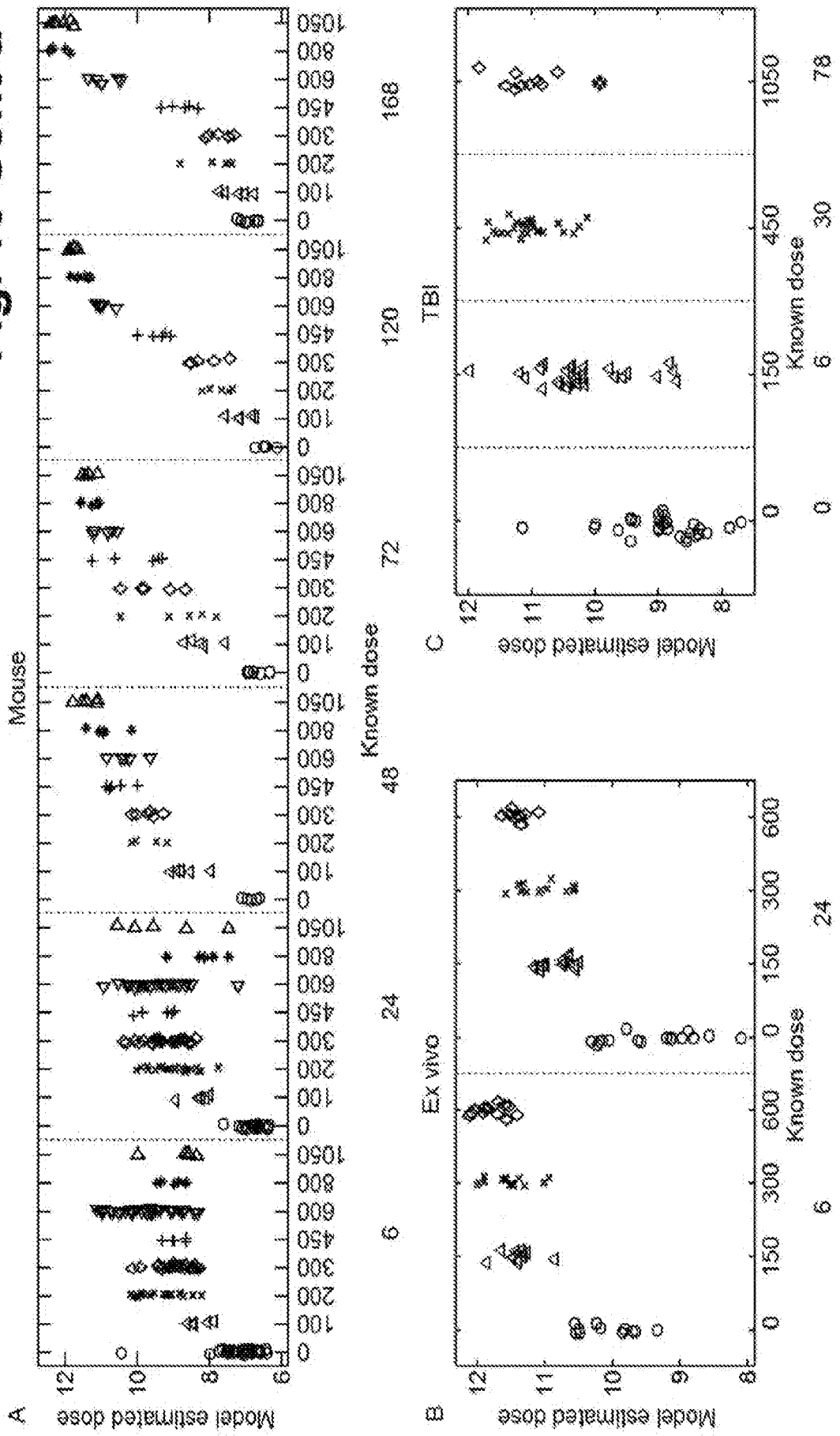


Fig. 10 Cont'd

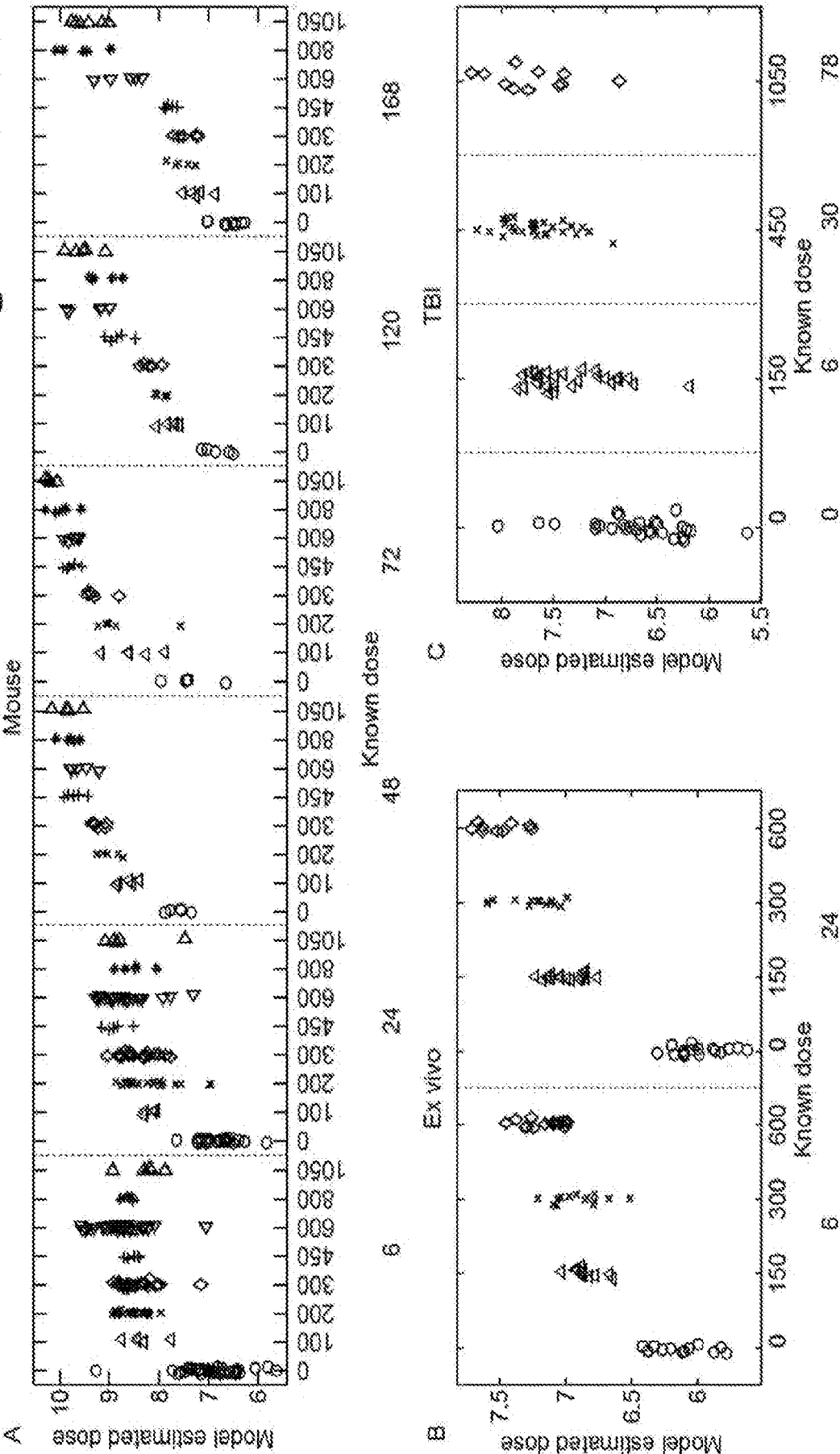


Fig. 10 Cont'd

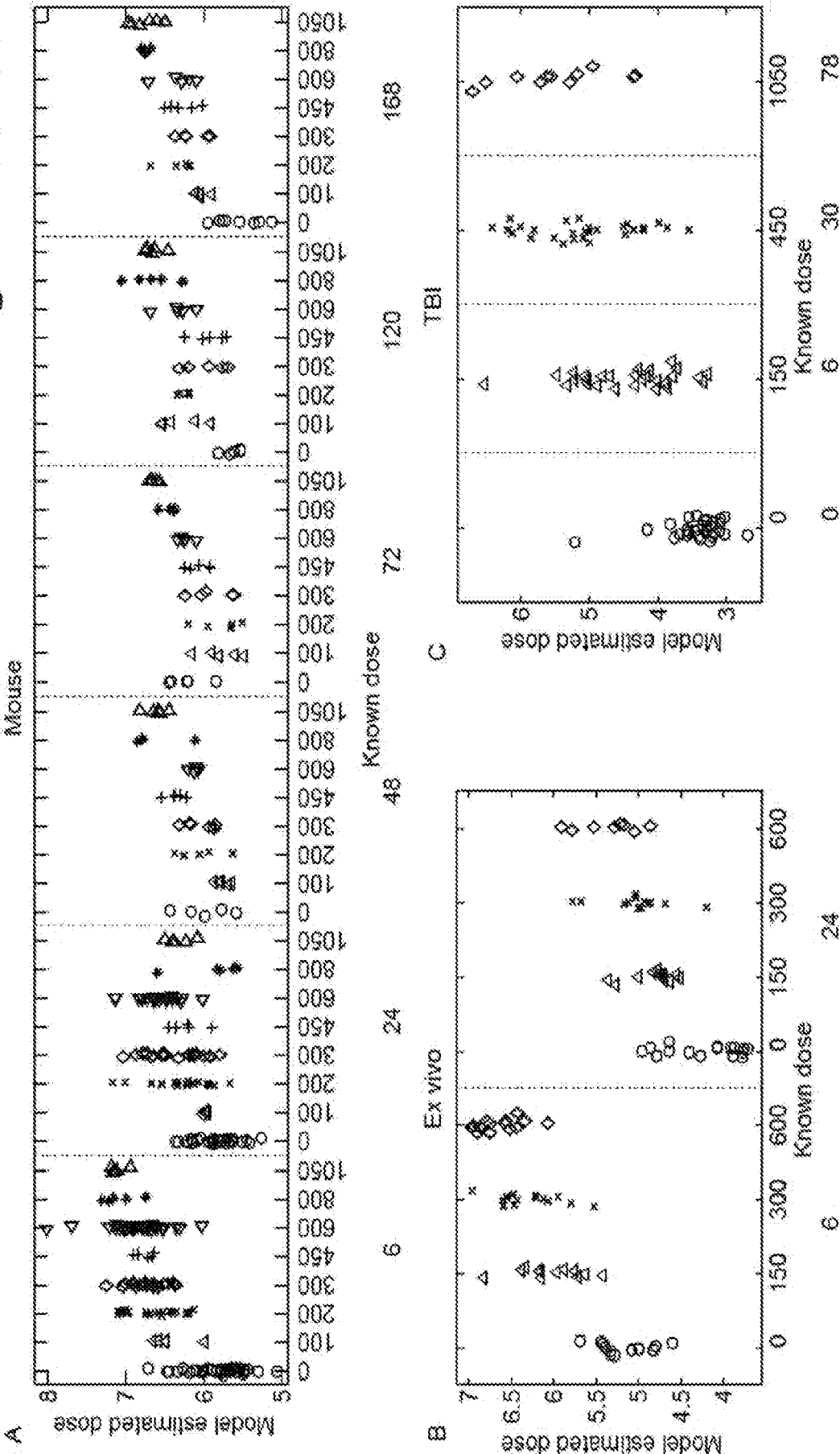


Fig. 10 Cont'd

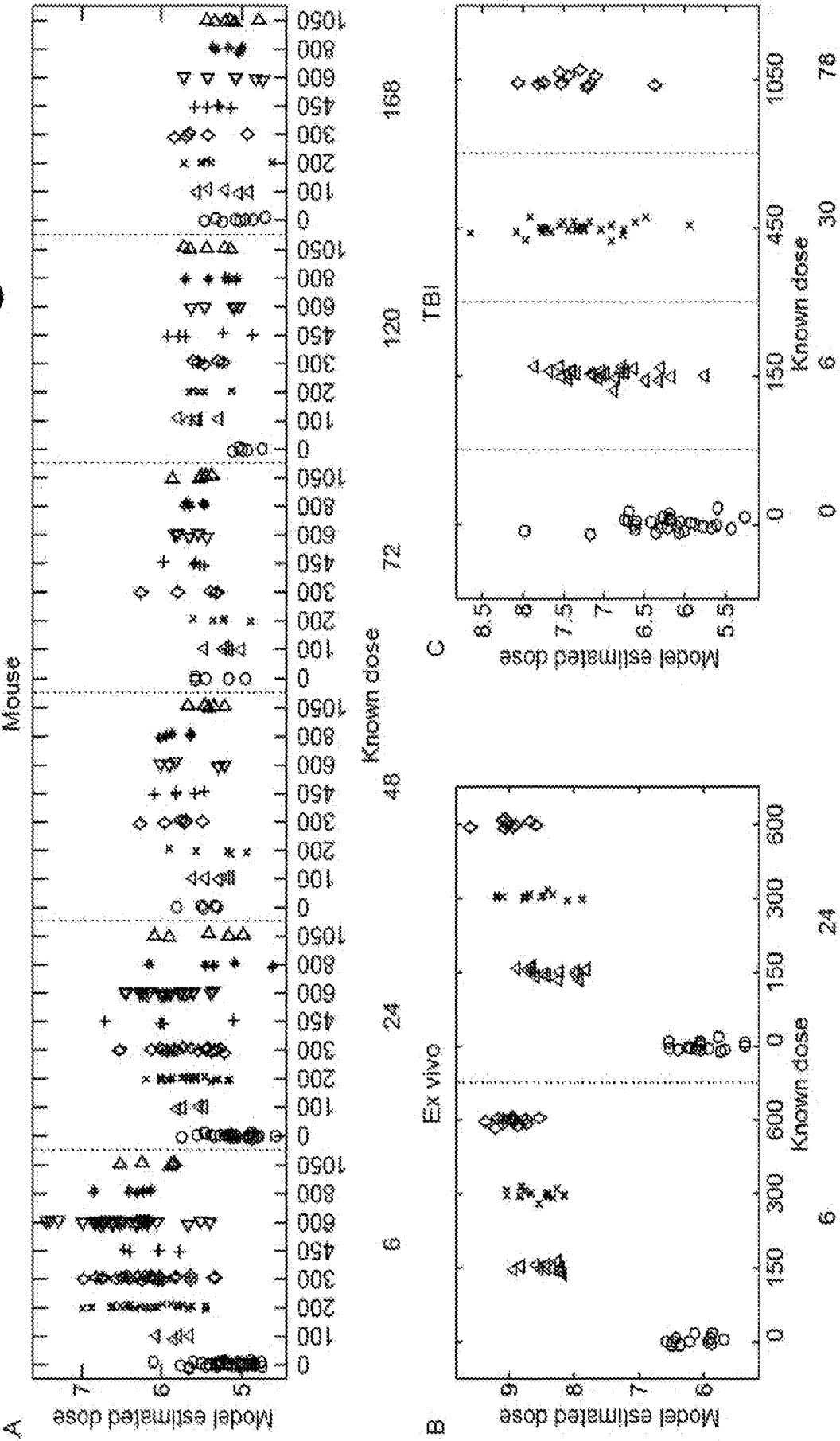


Fig. 10 Cont'd

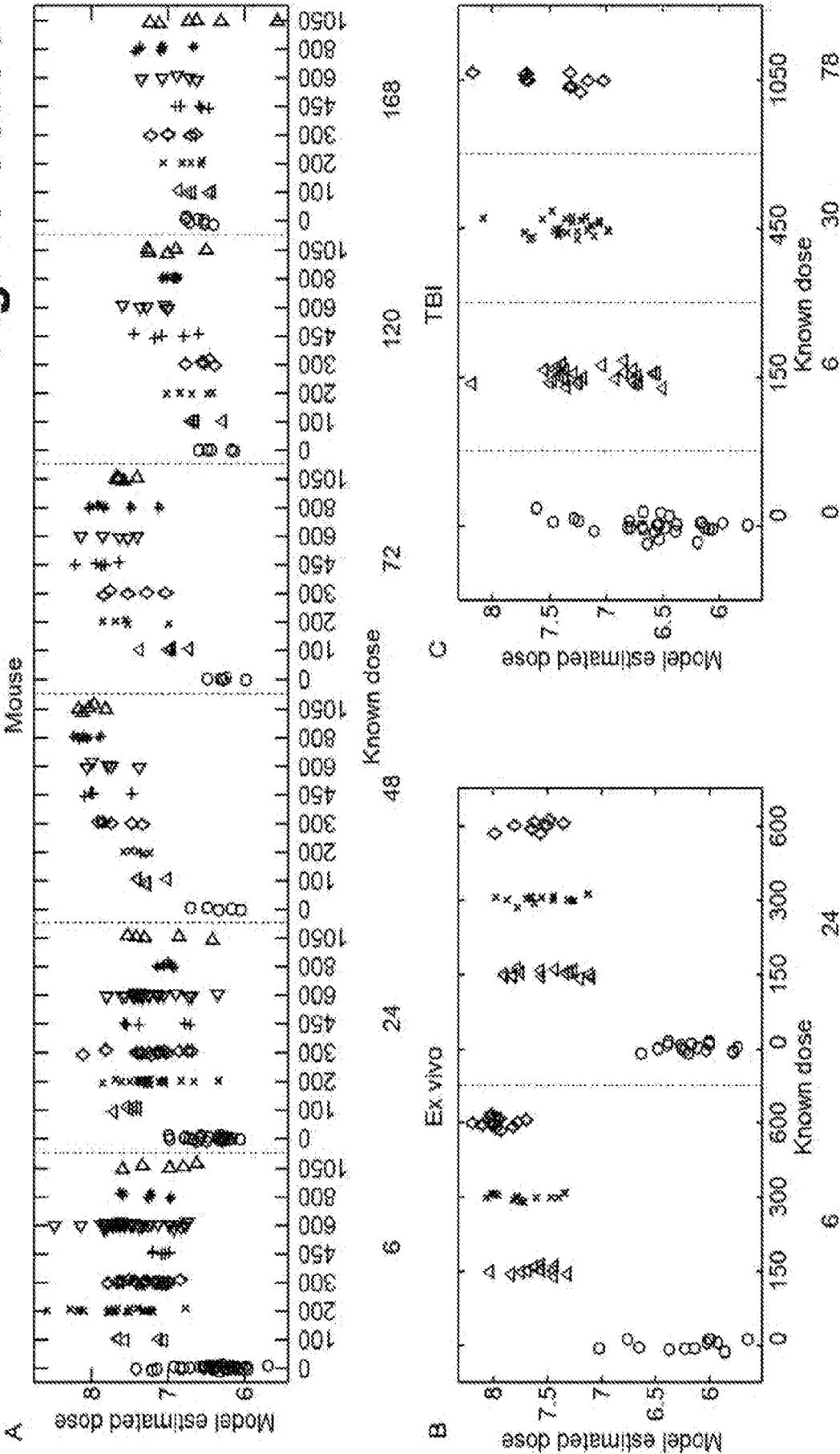


Fig. 10 Cont'd

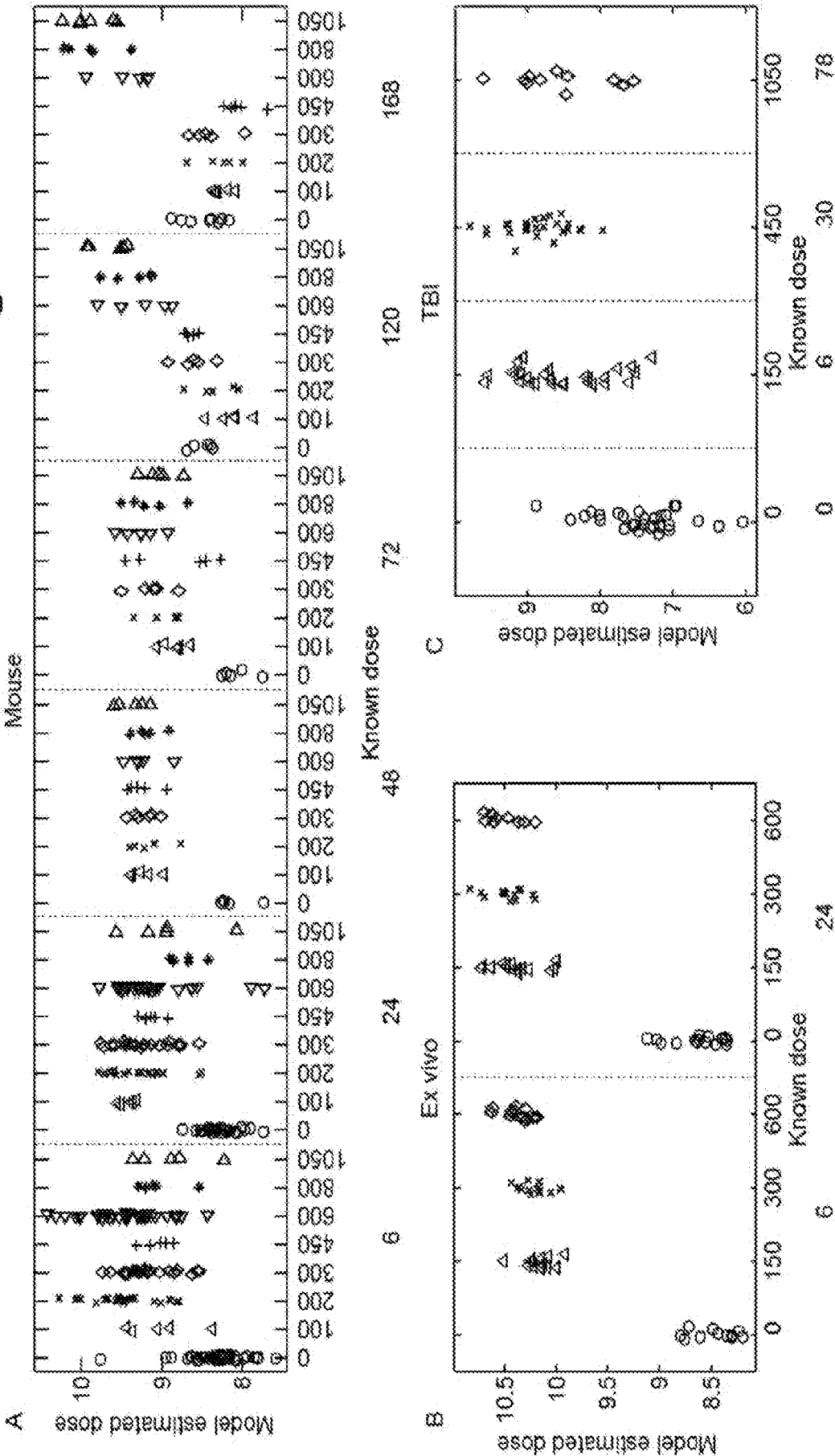


Fig. 10 Cont'd

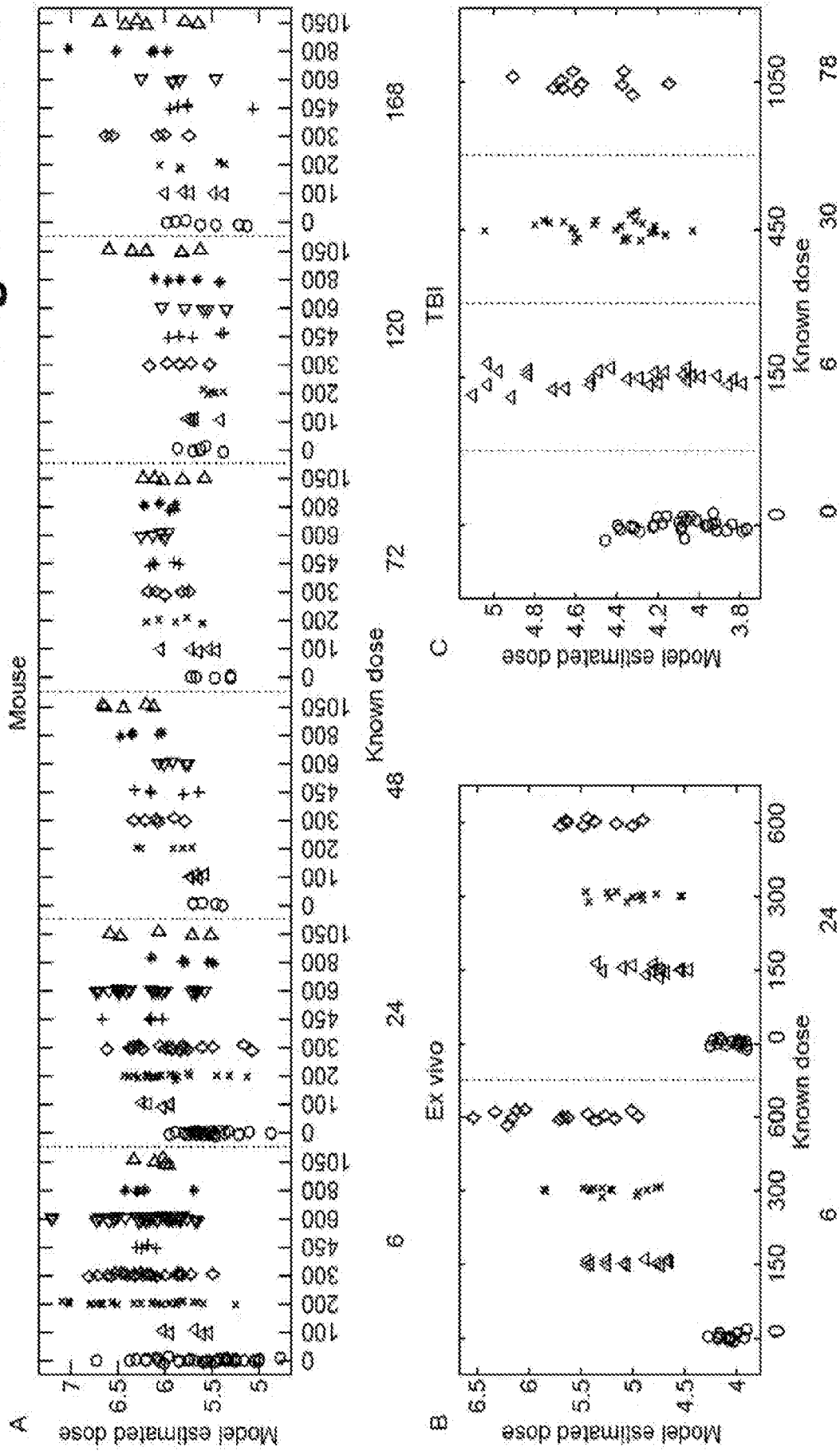


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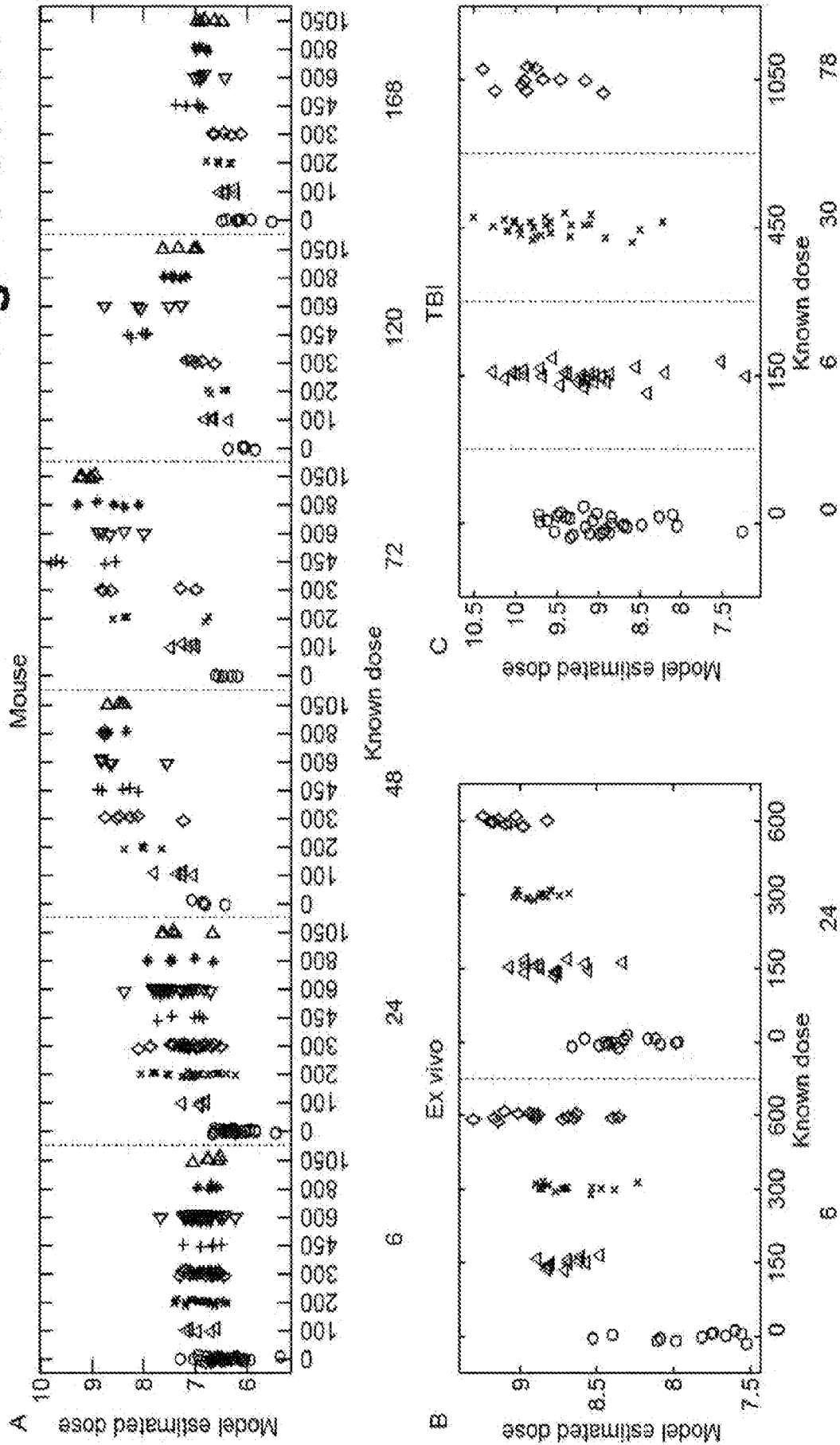


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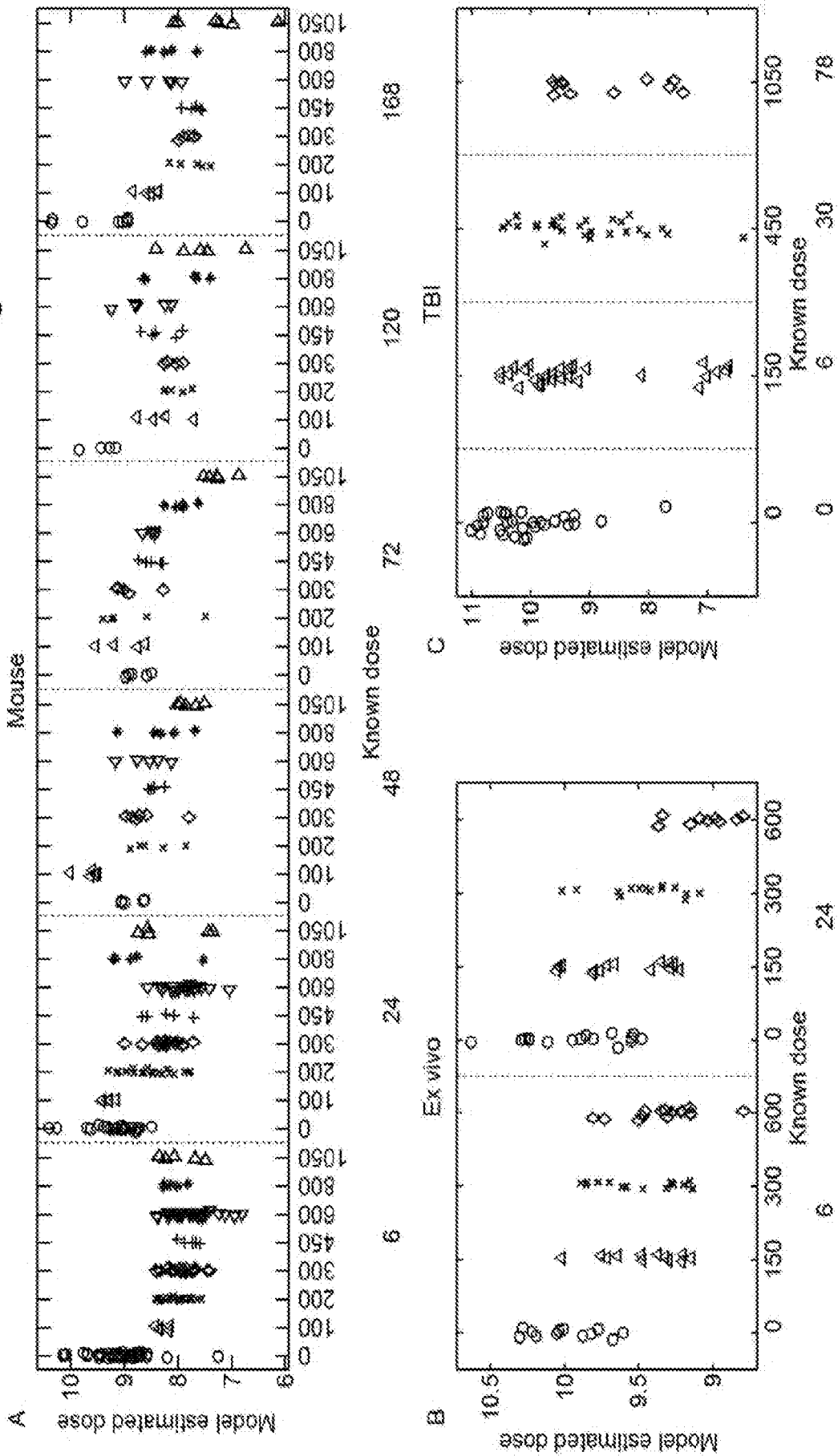


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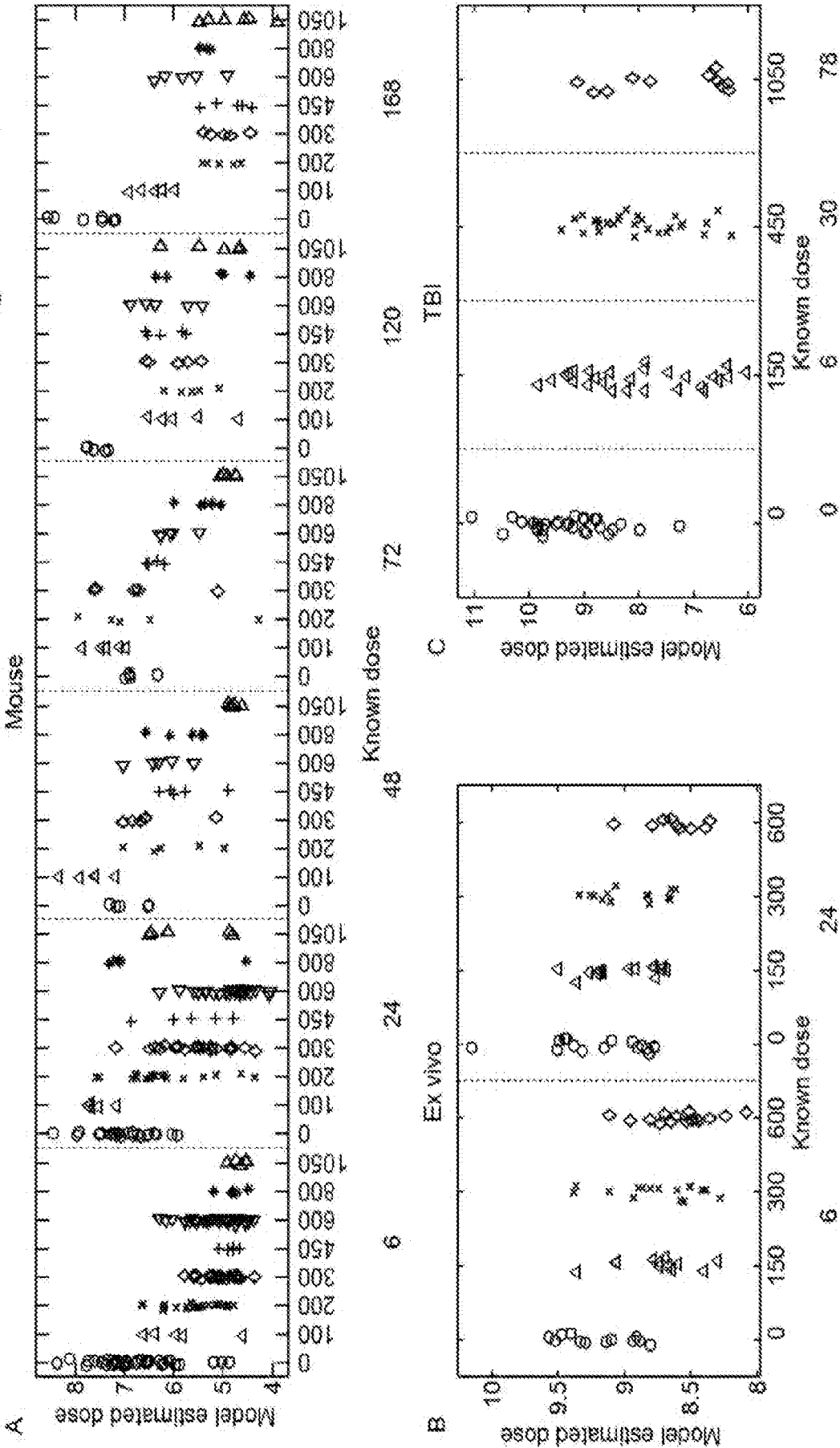


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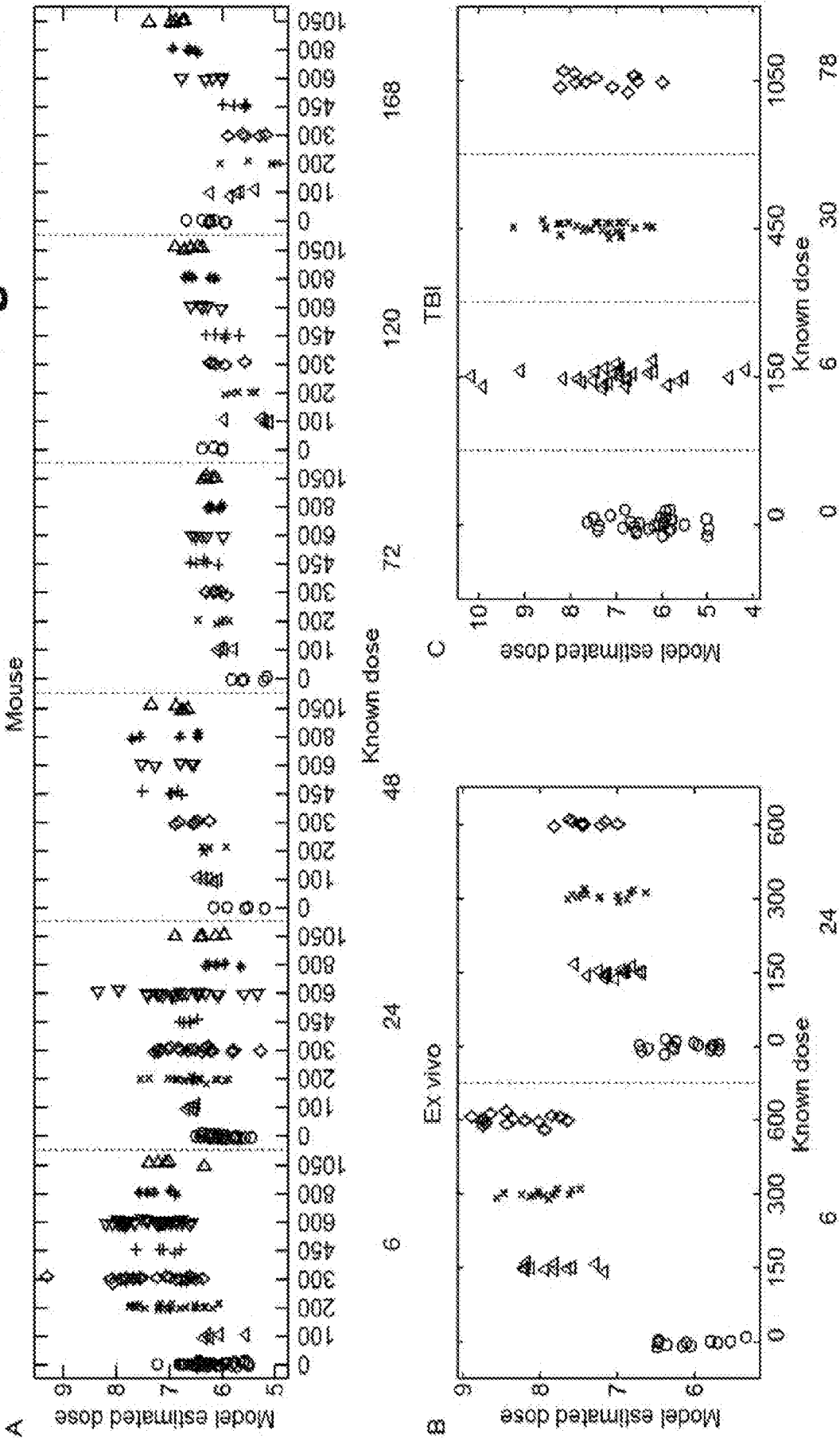


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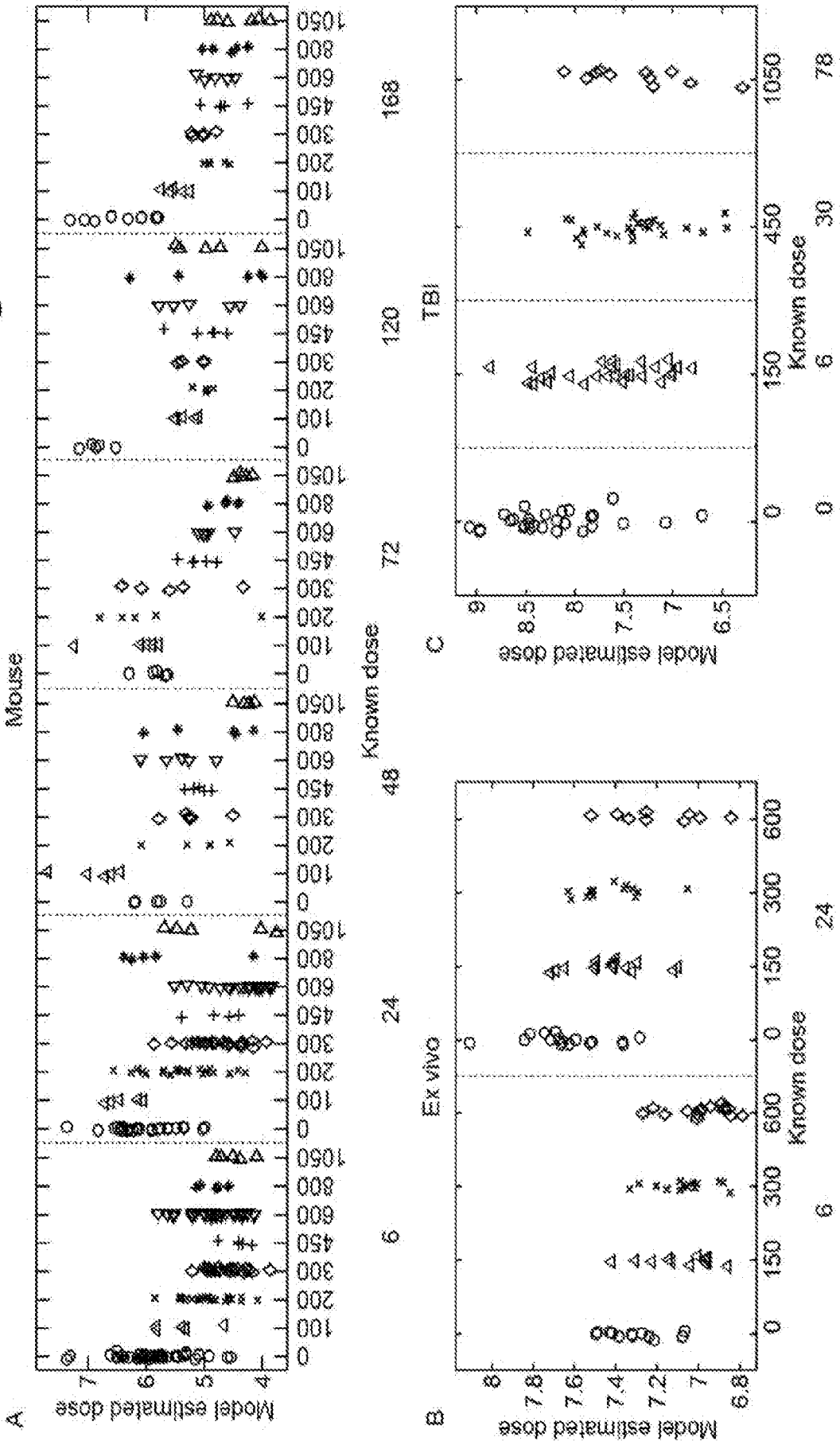


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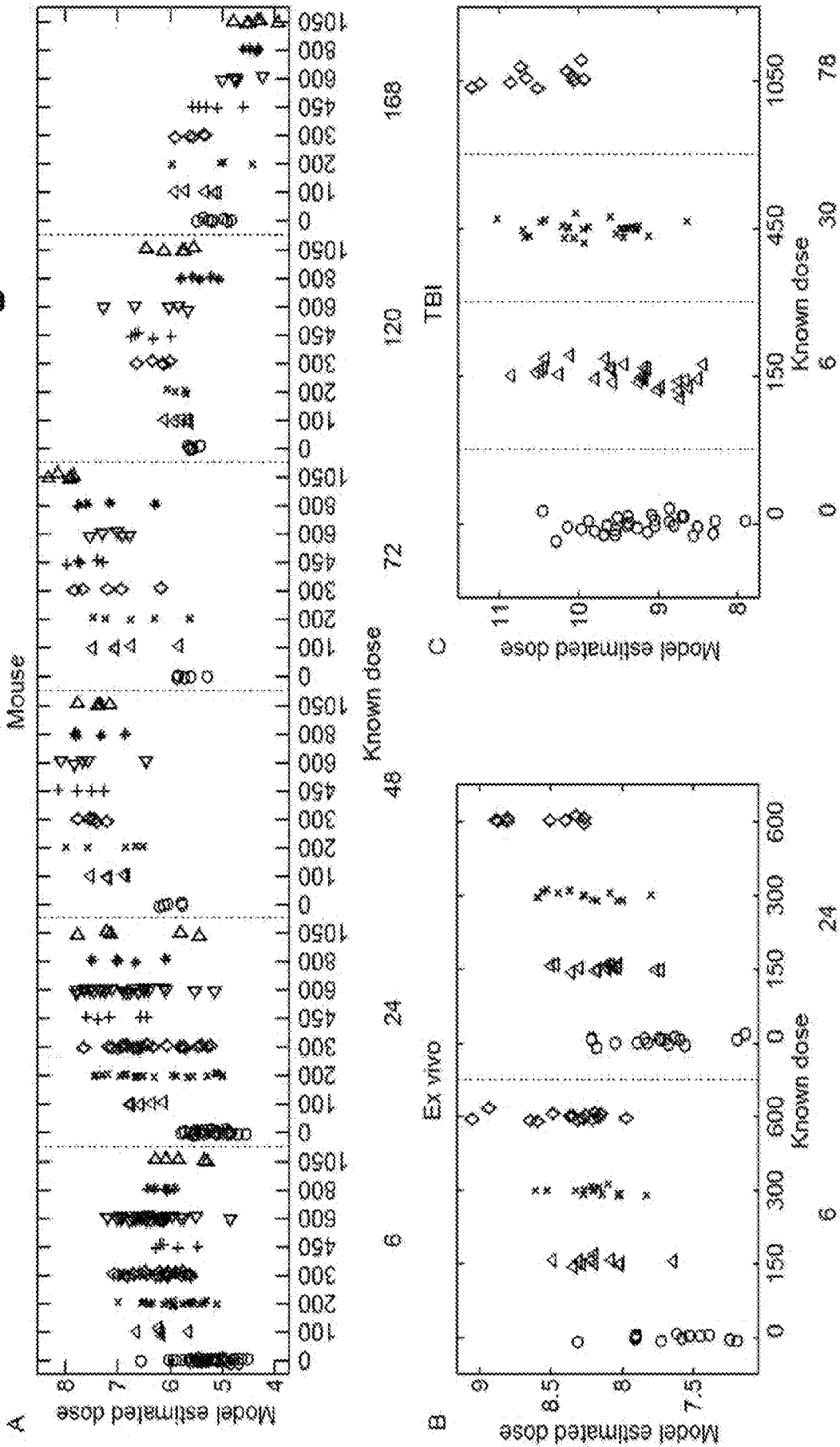


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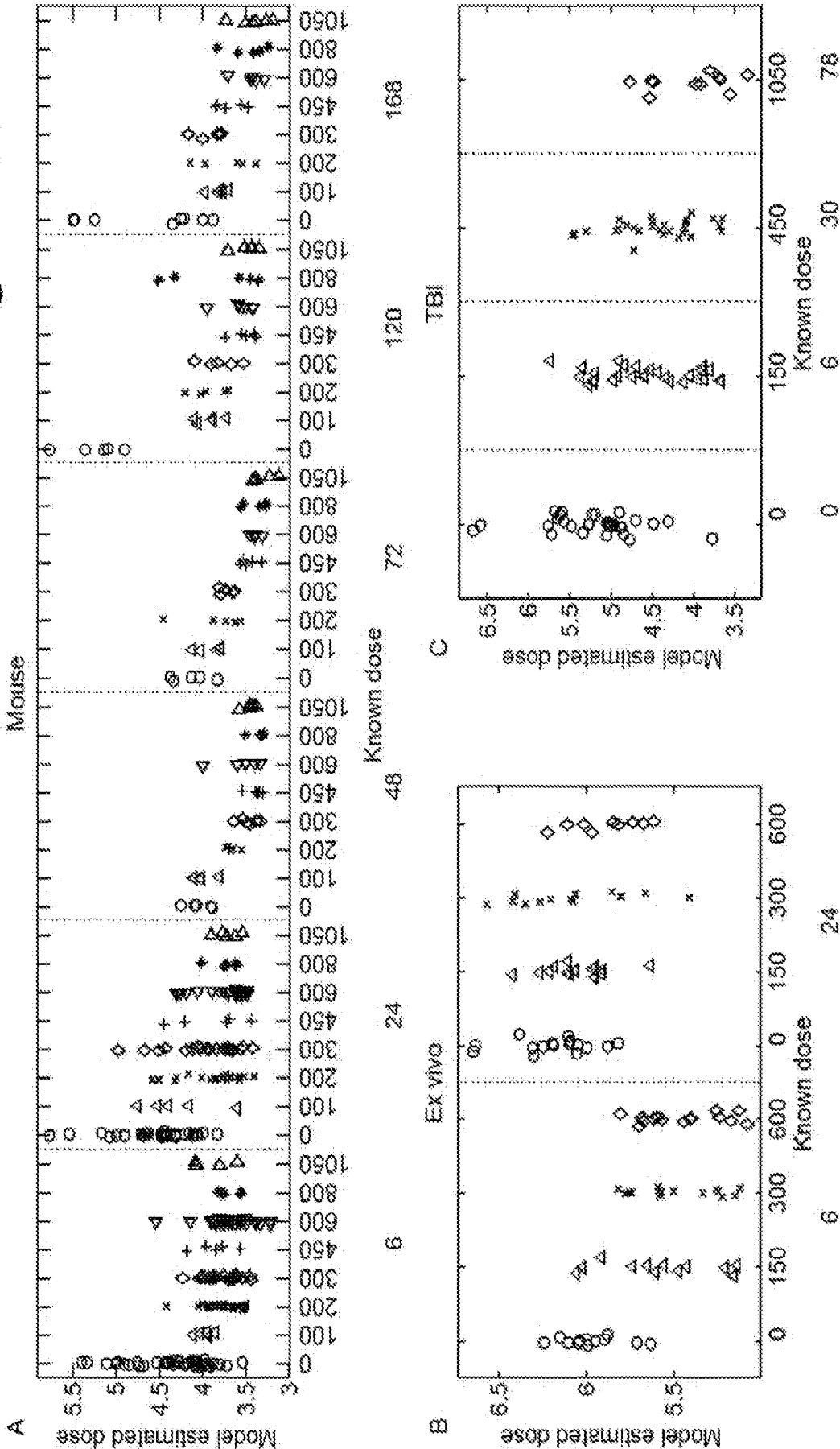


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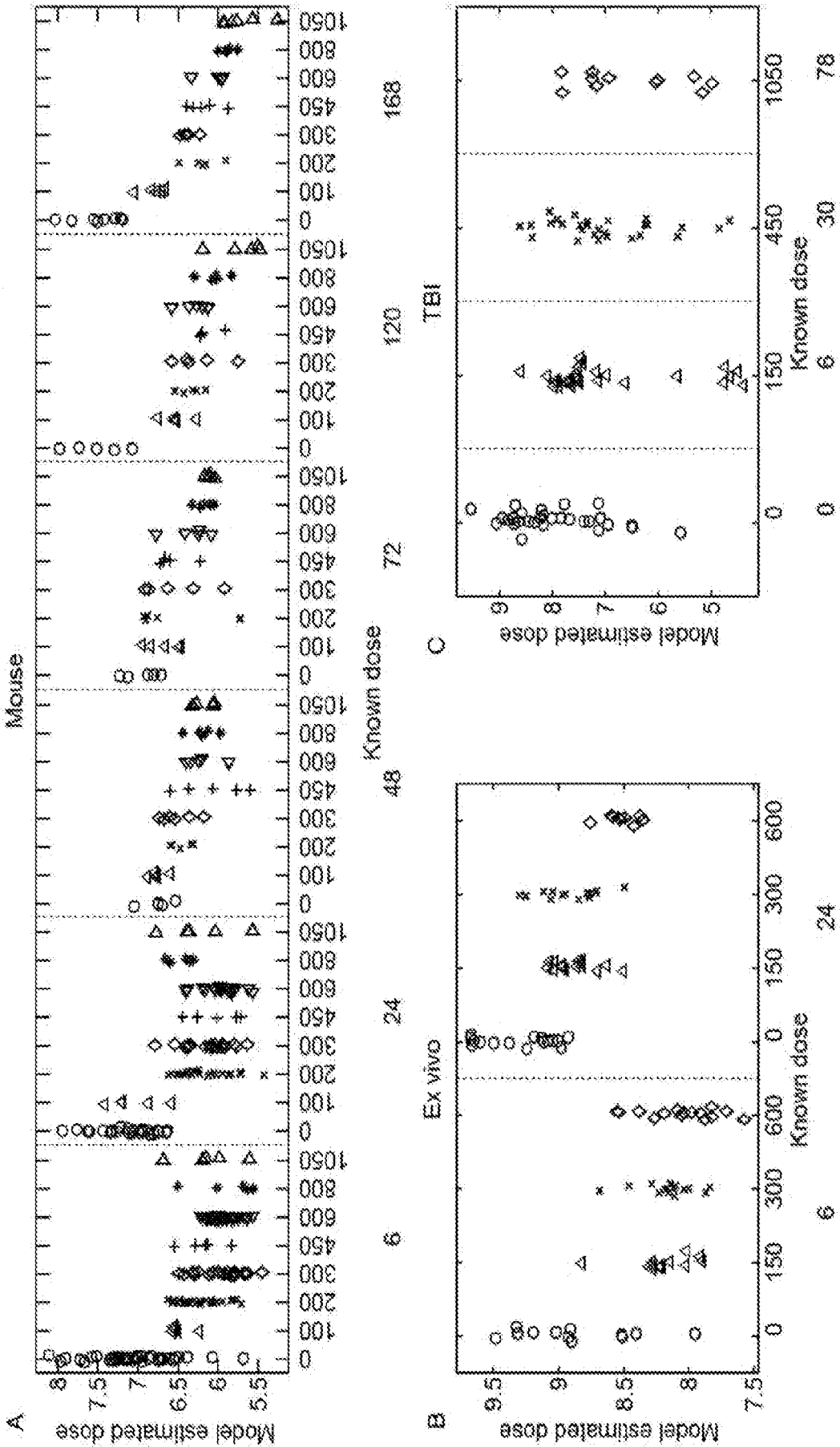


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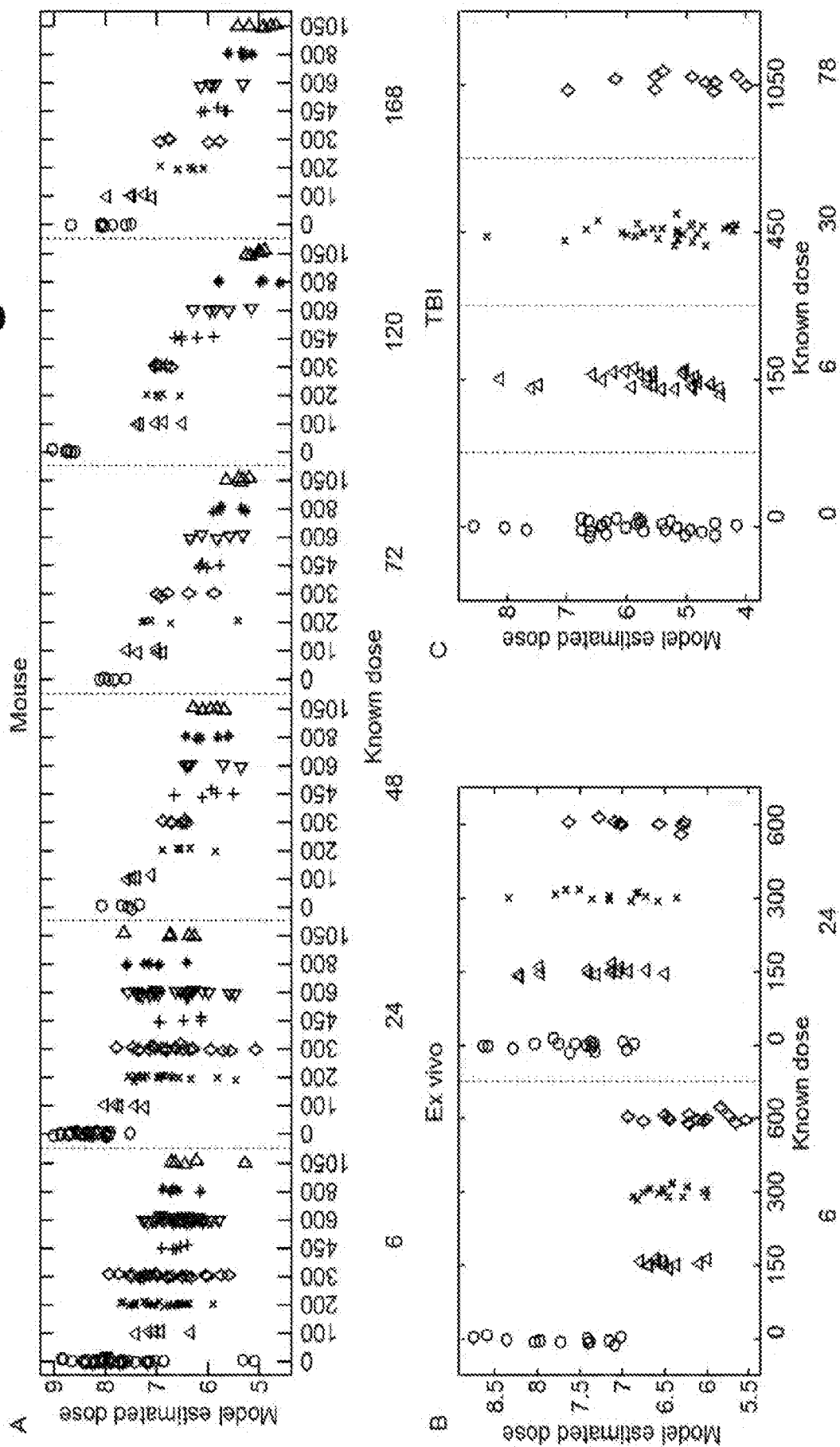


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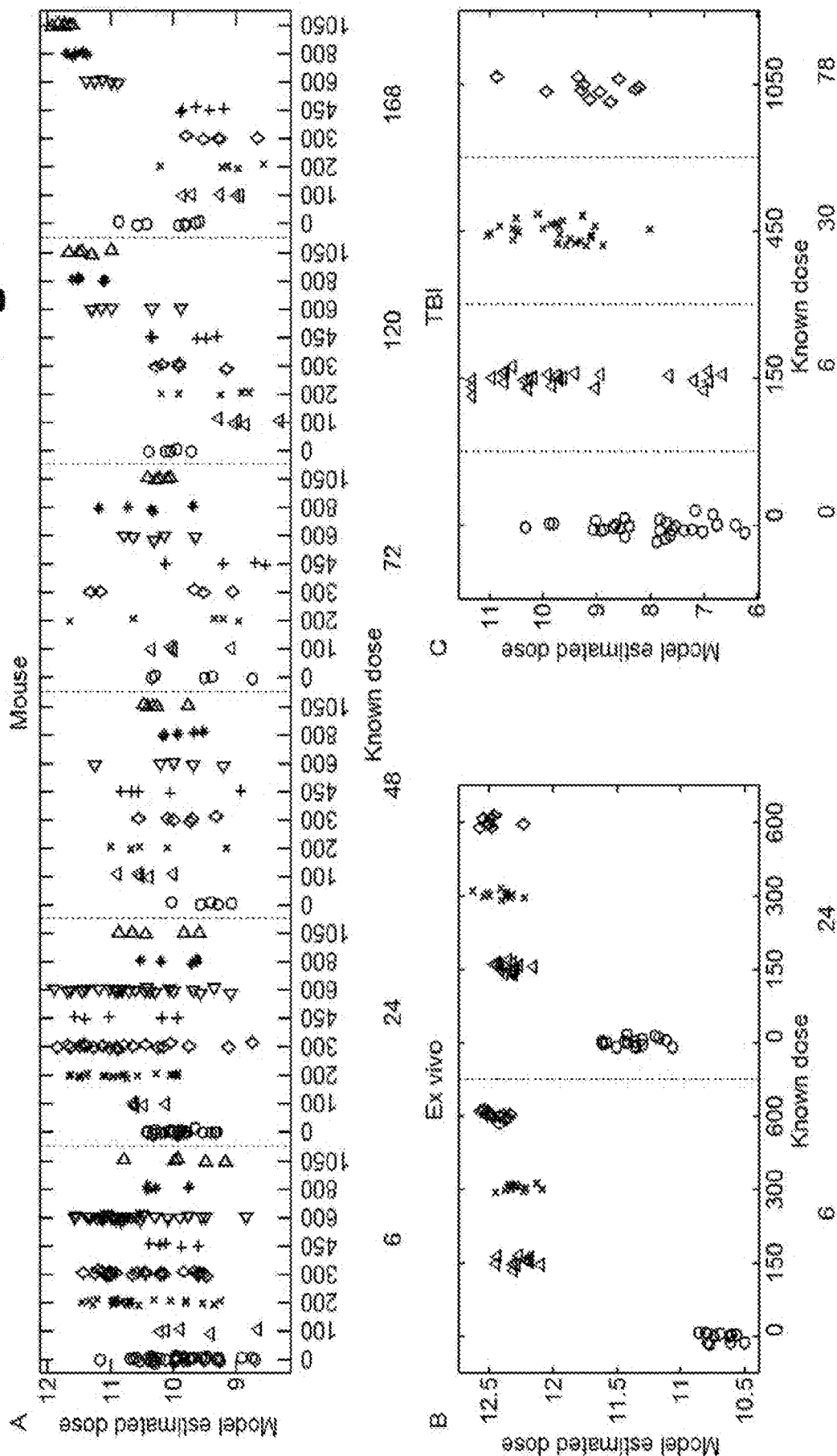


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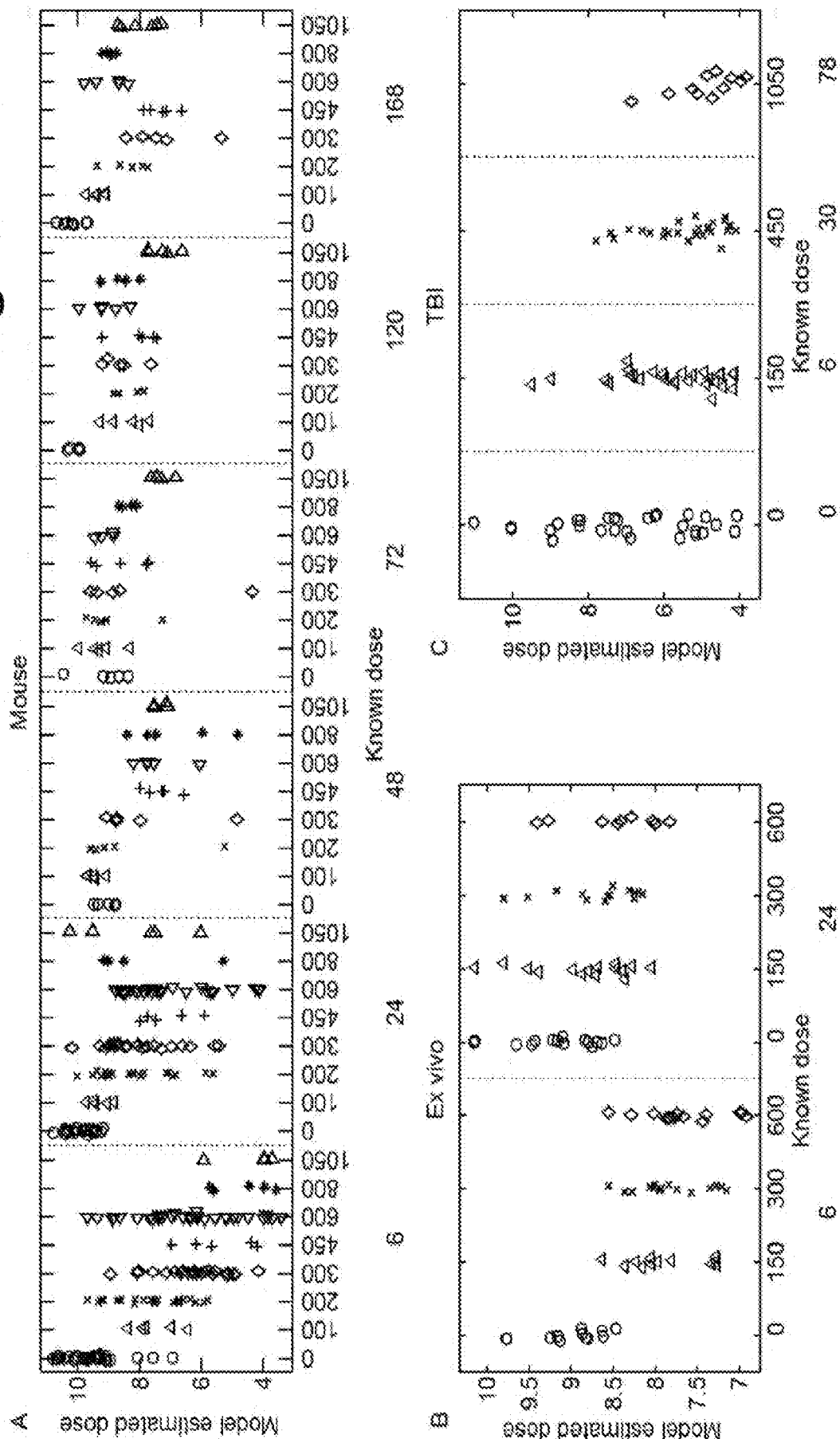


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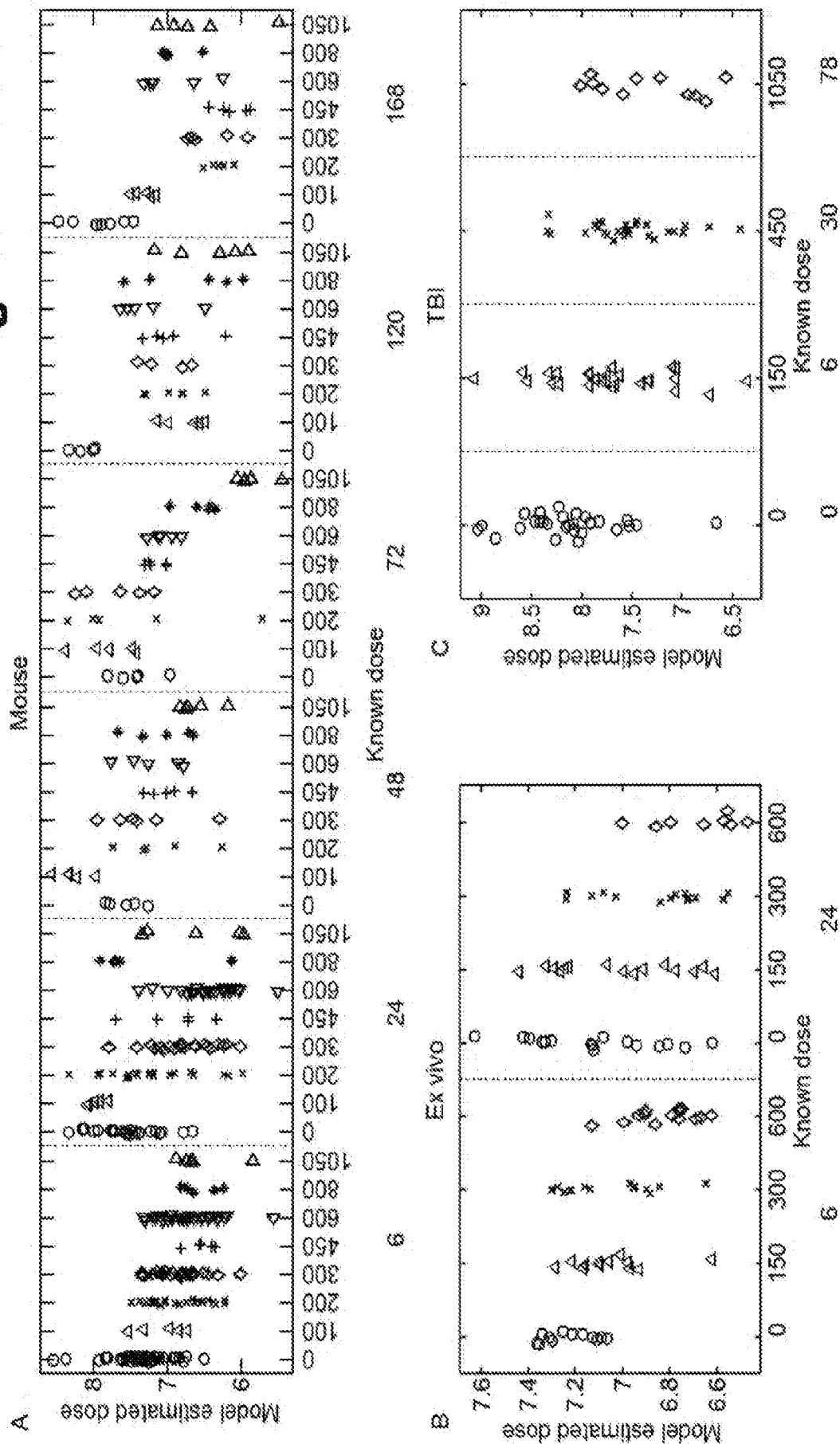


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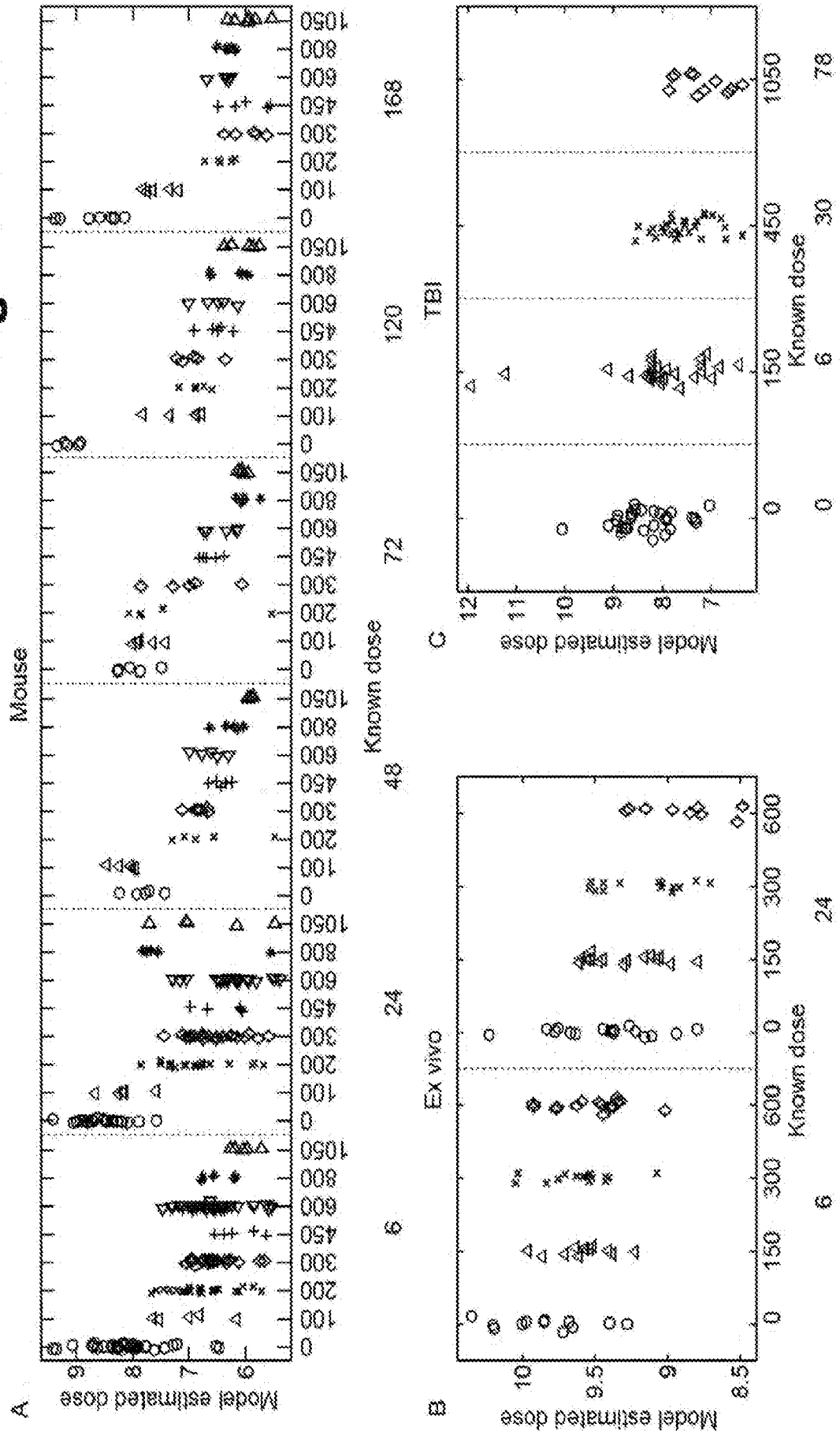


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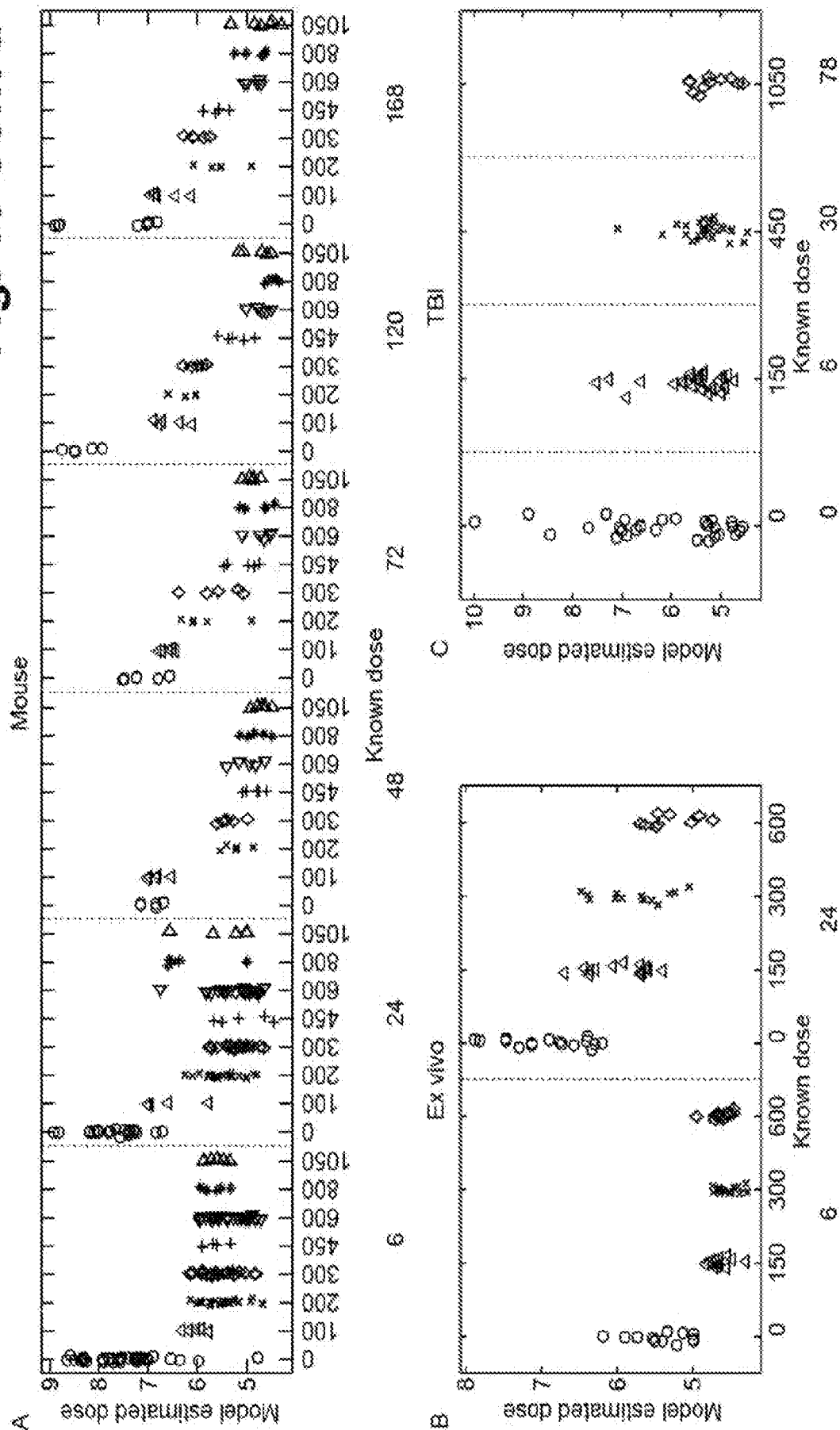


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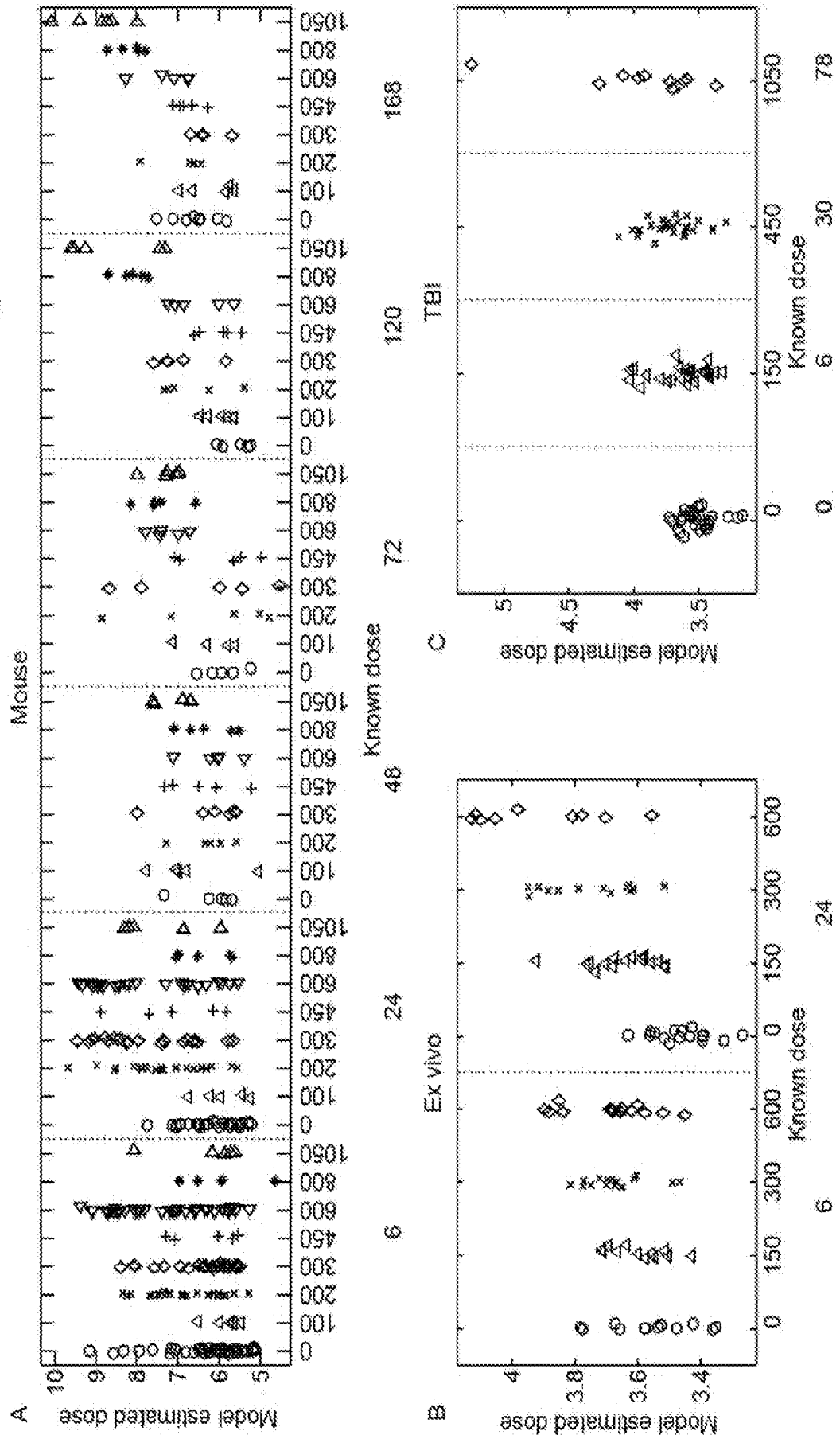


Fig. 10 Cont'd

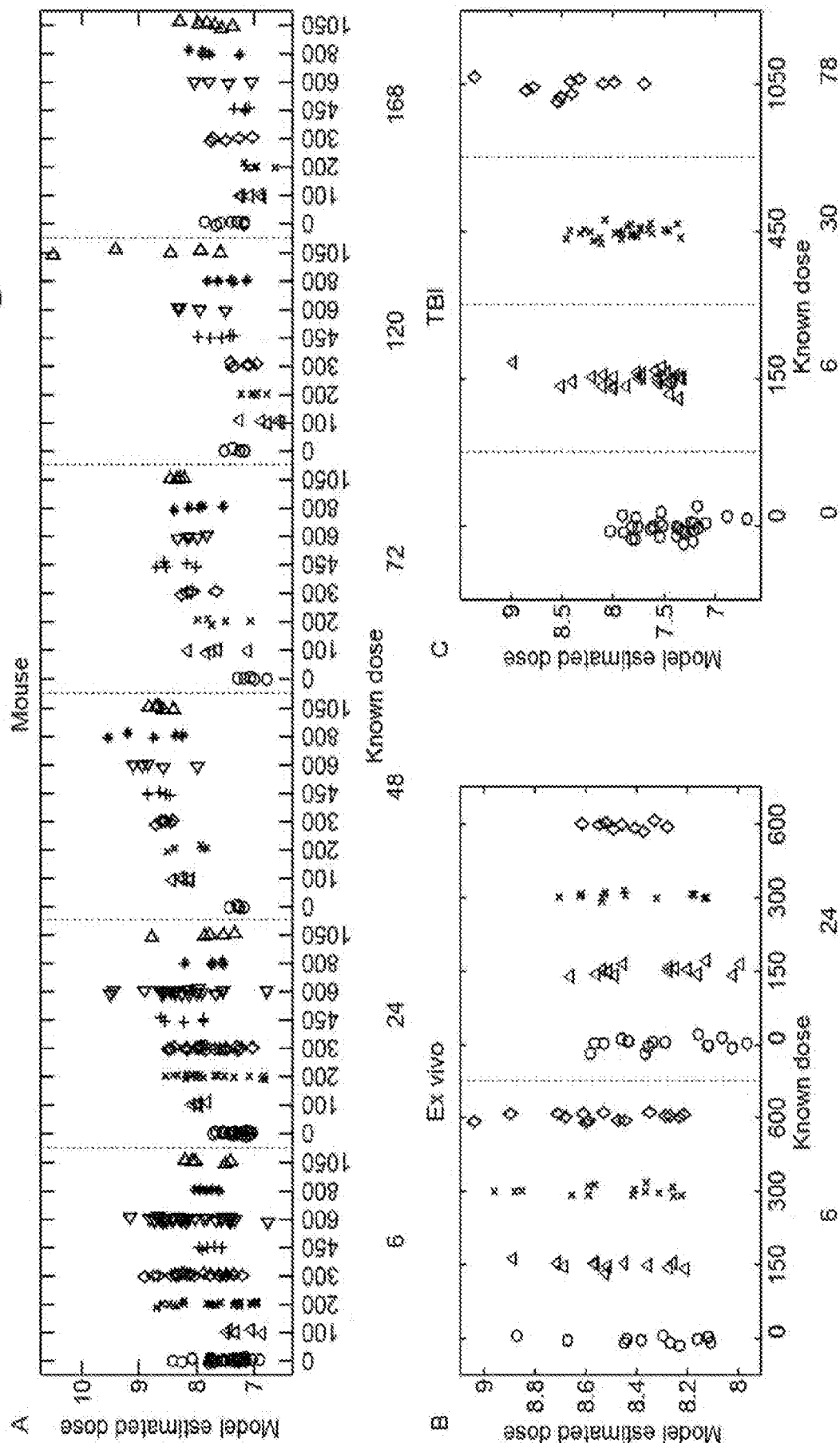


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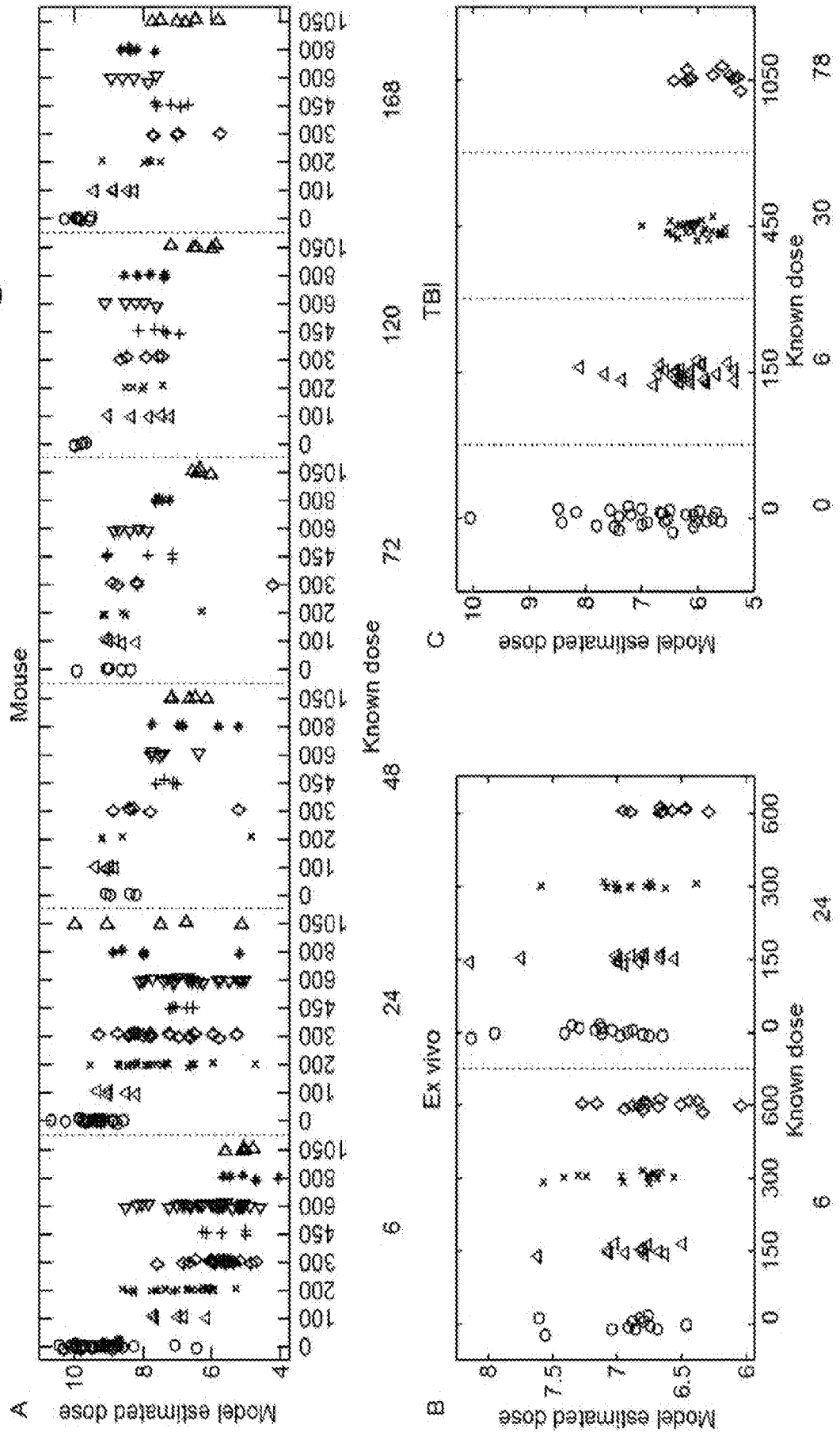


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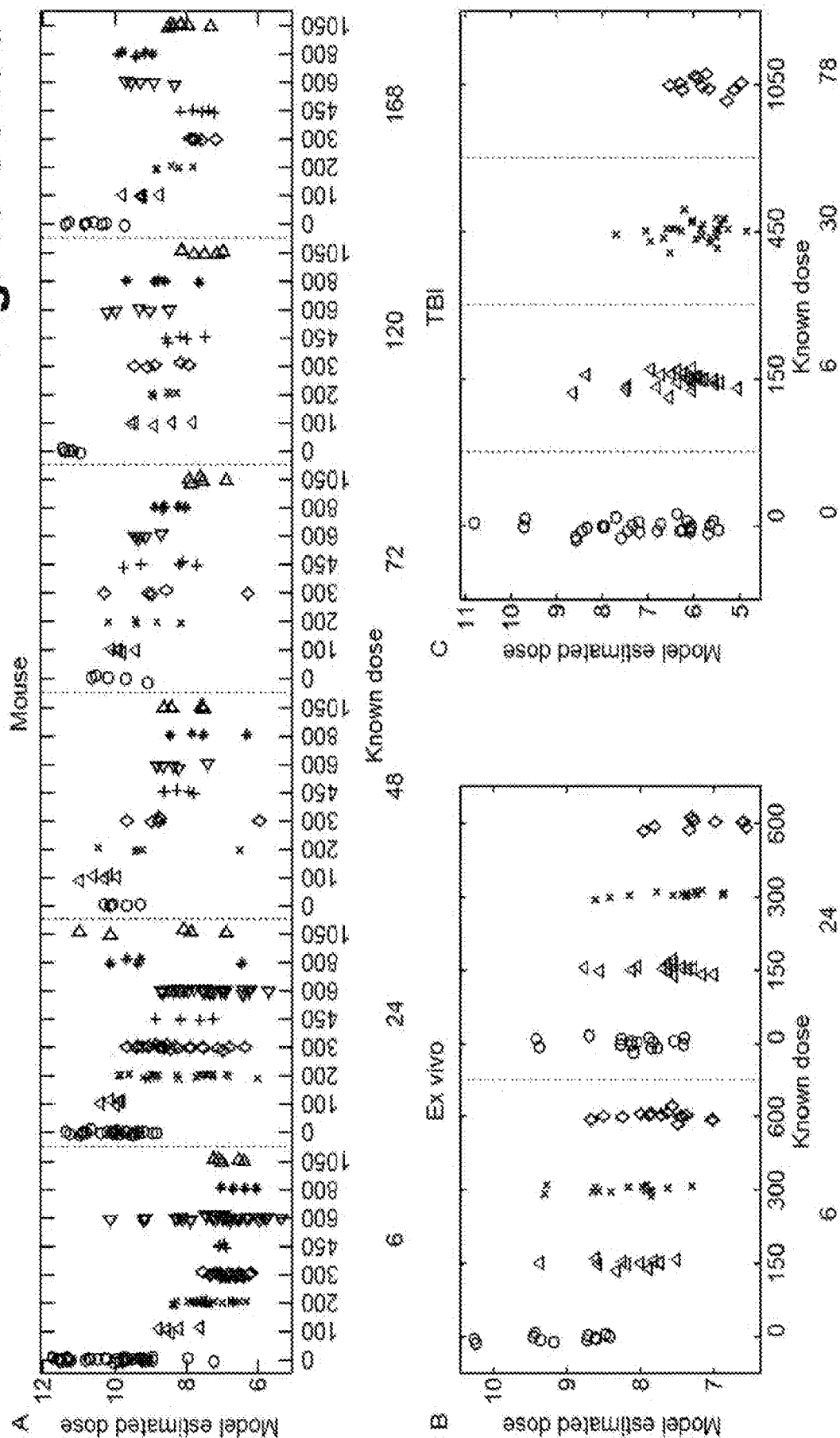


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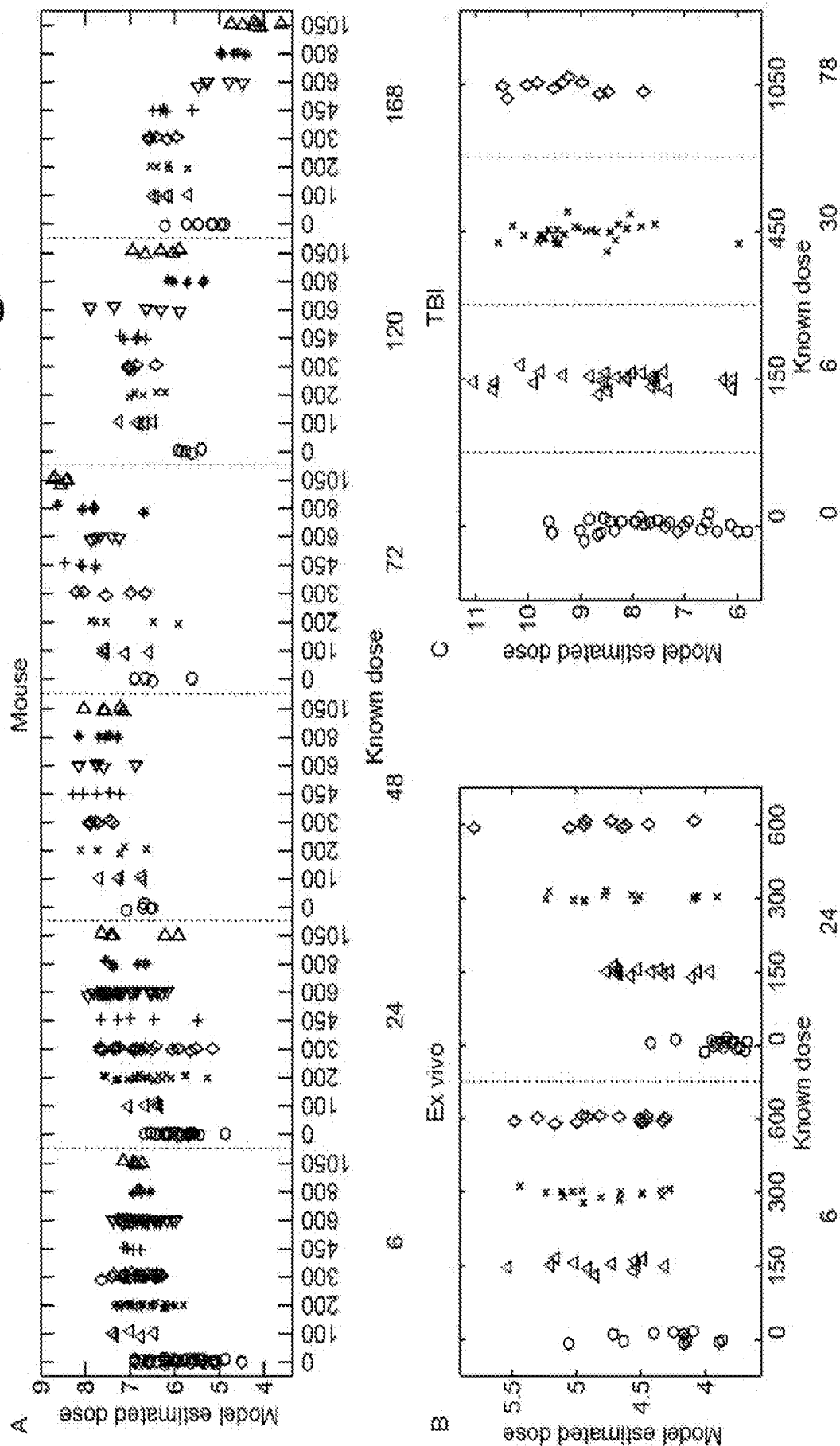


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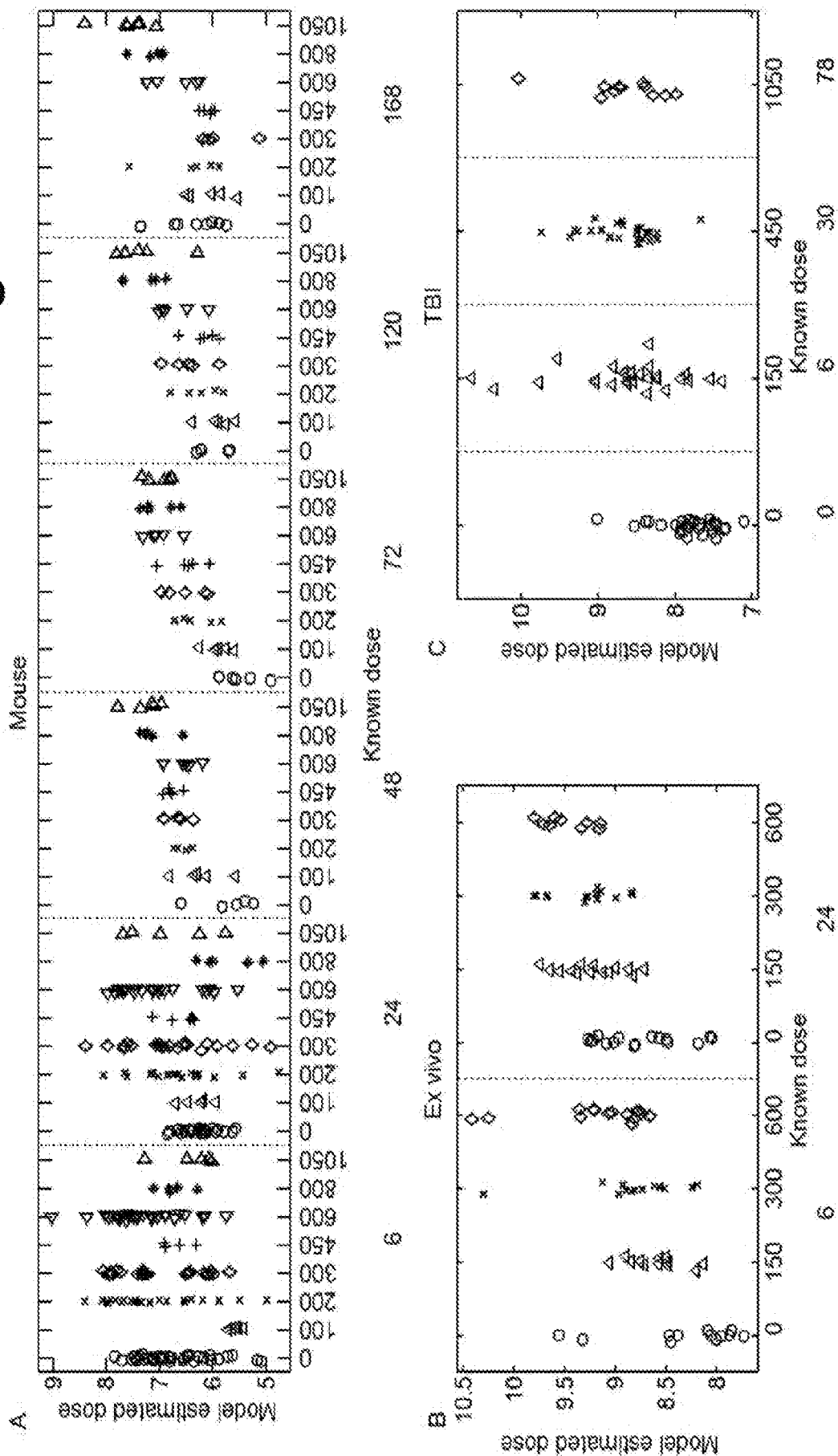


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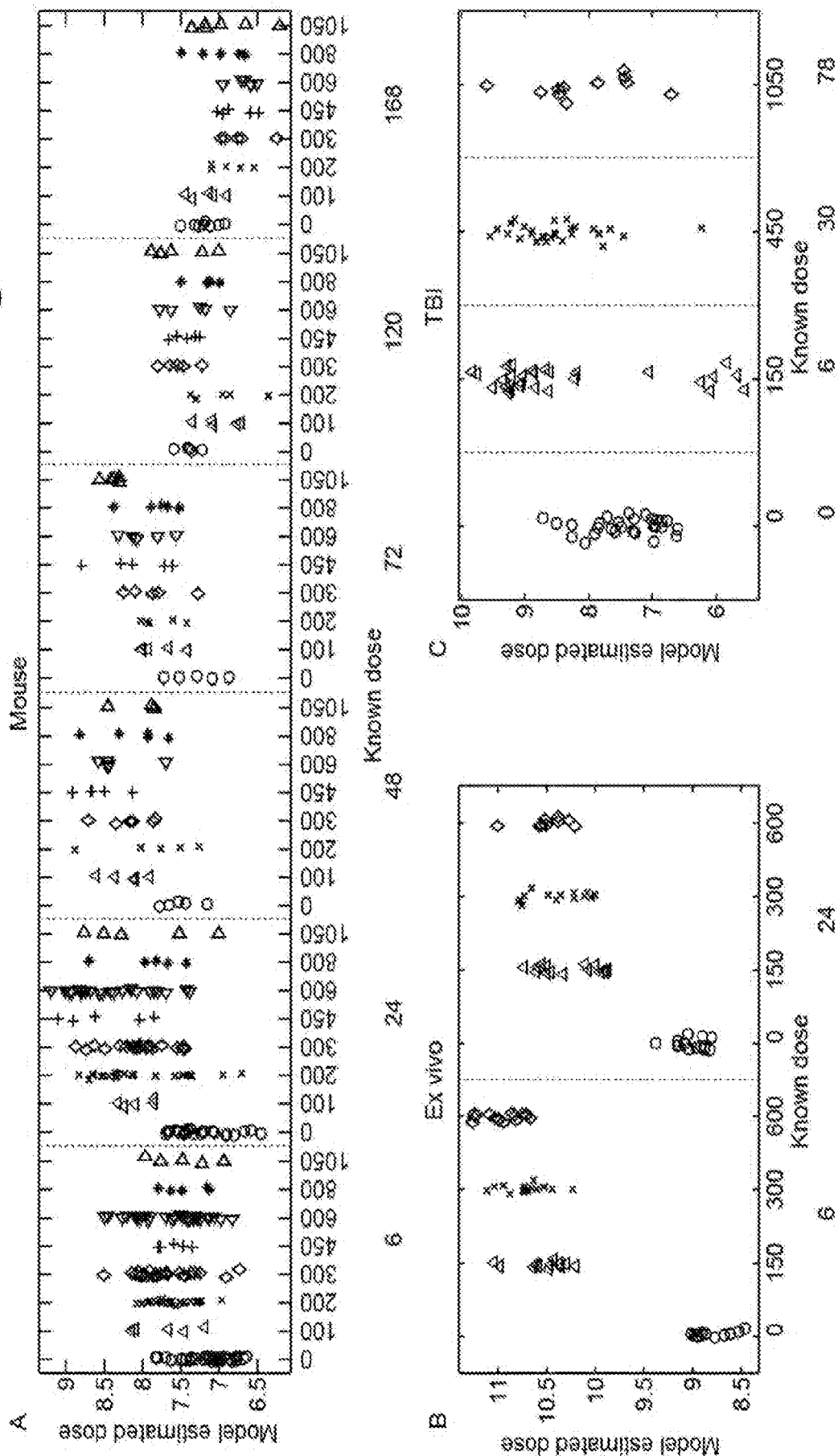


Fig. 10 Cont'd

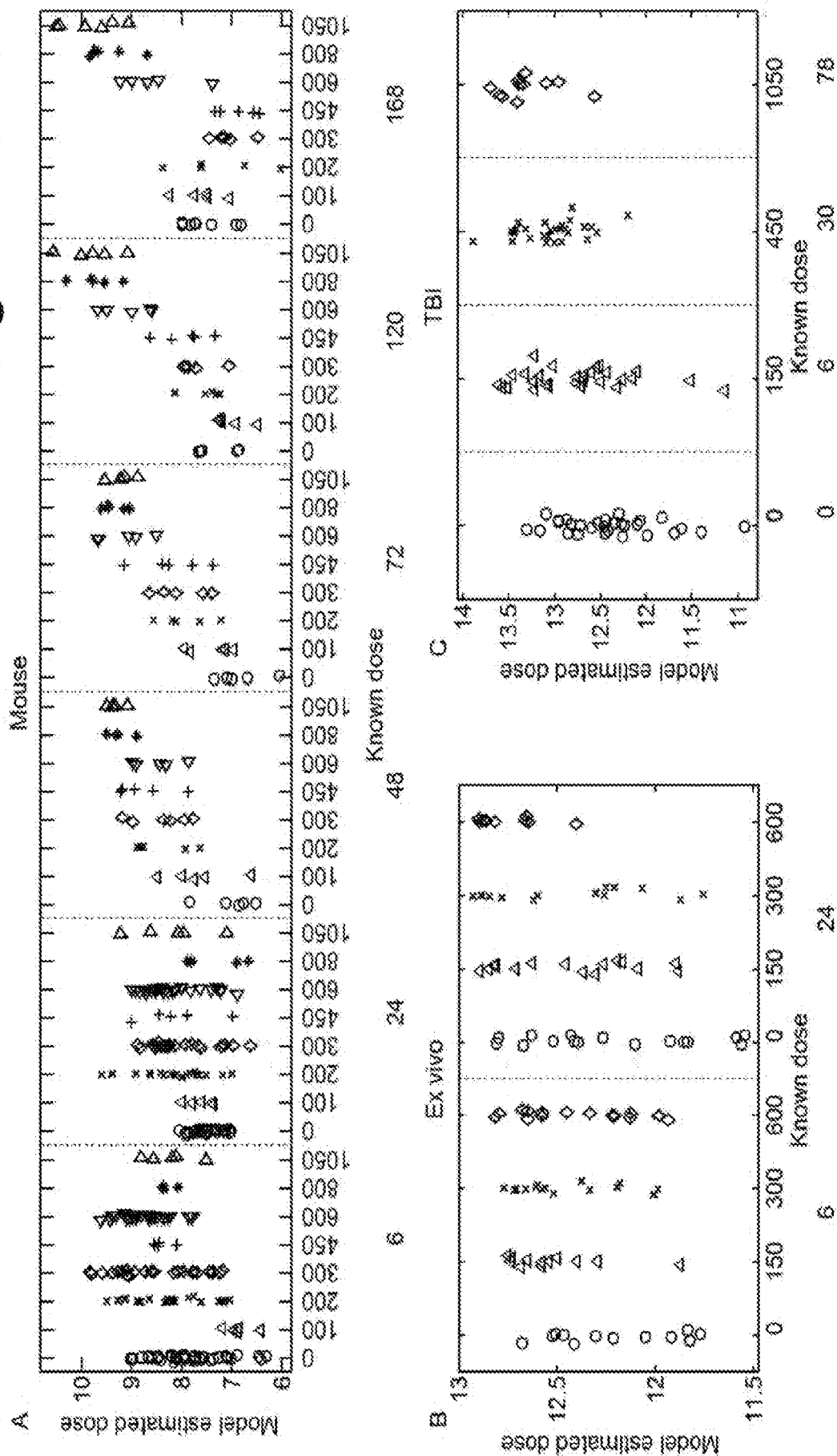


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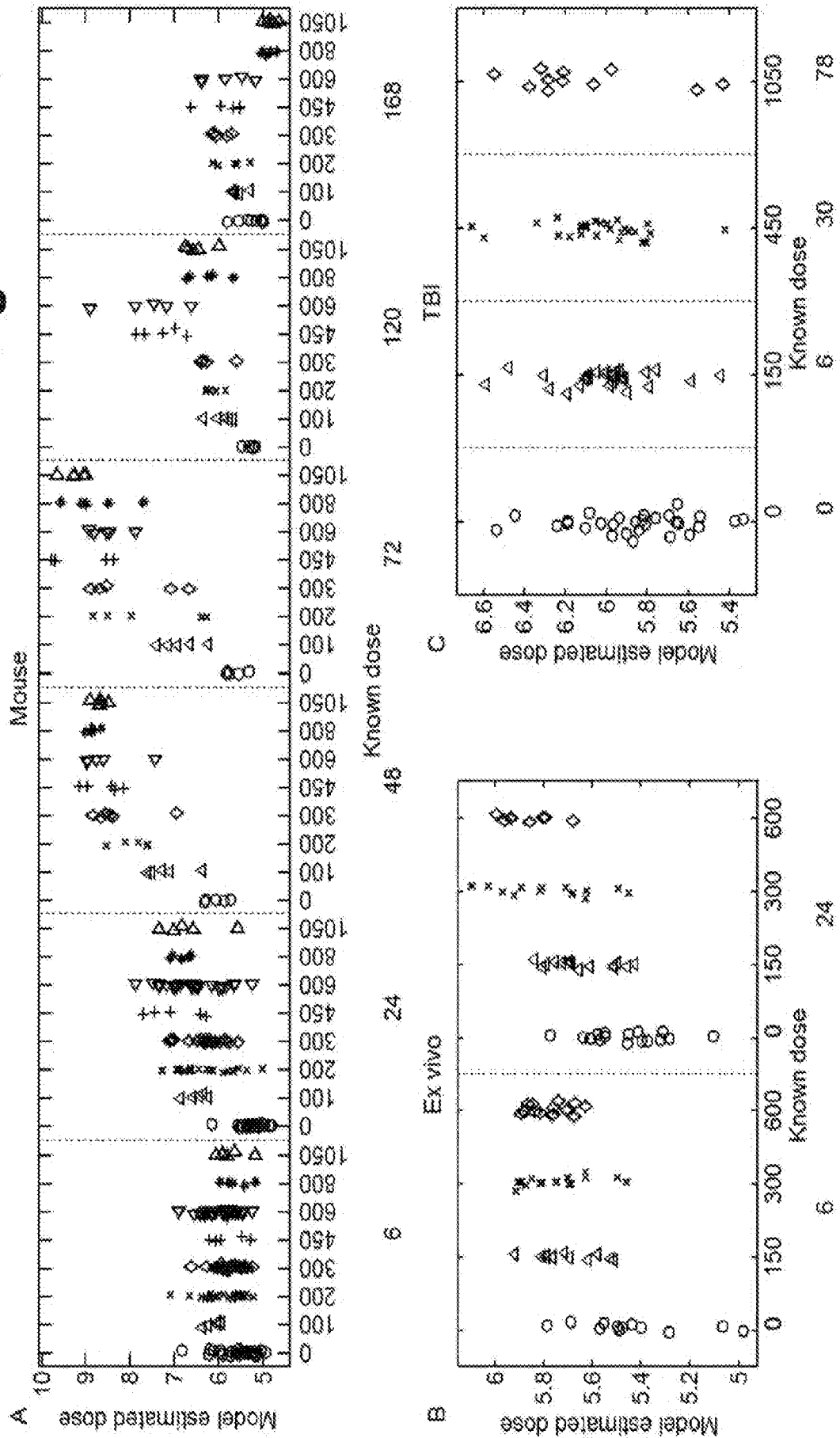
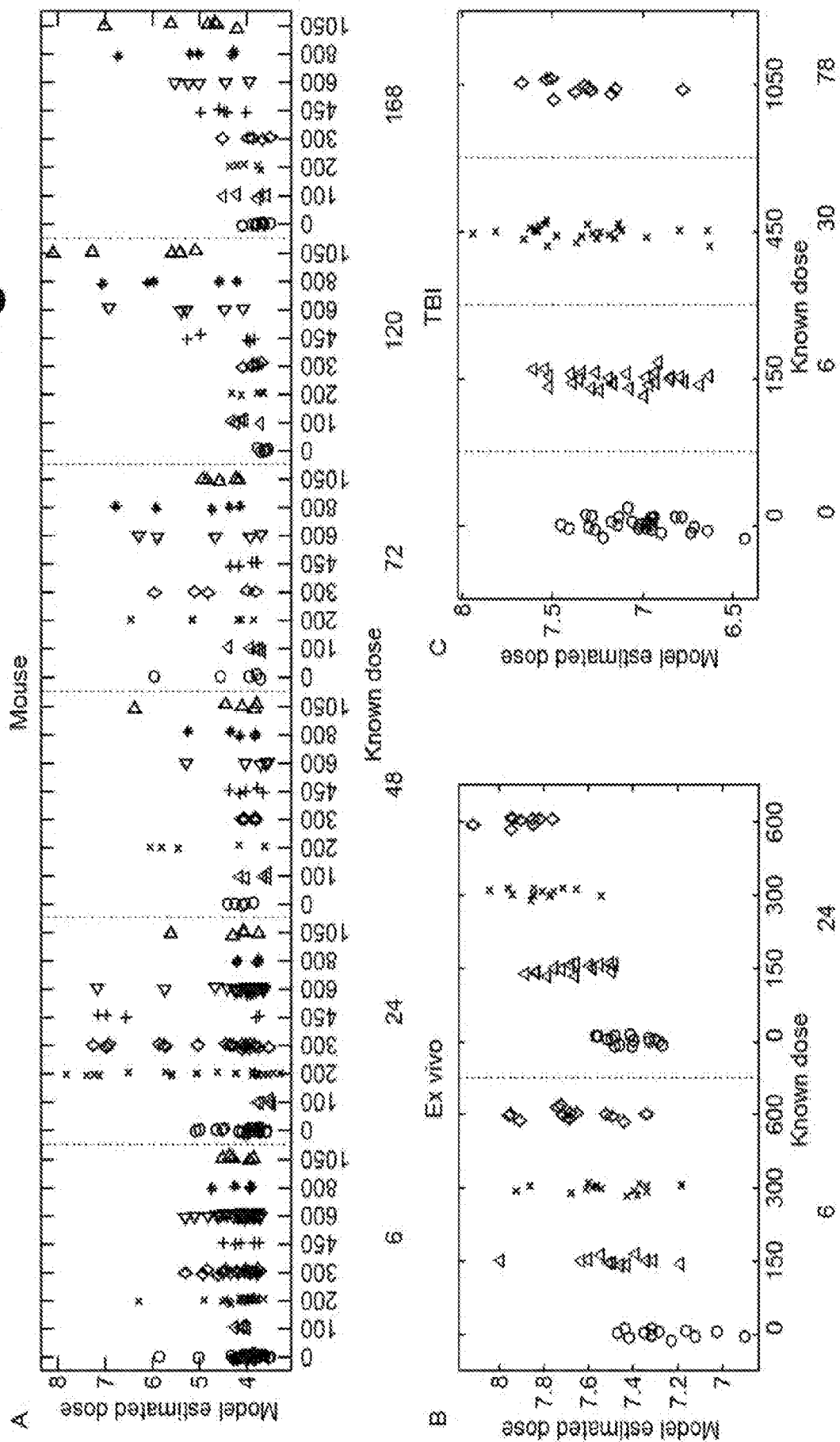


Fig. 10 Cont'd



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Fig. 10 Cont'd

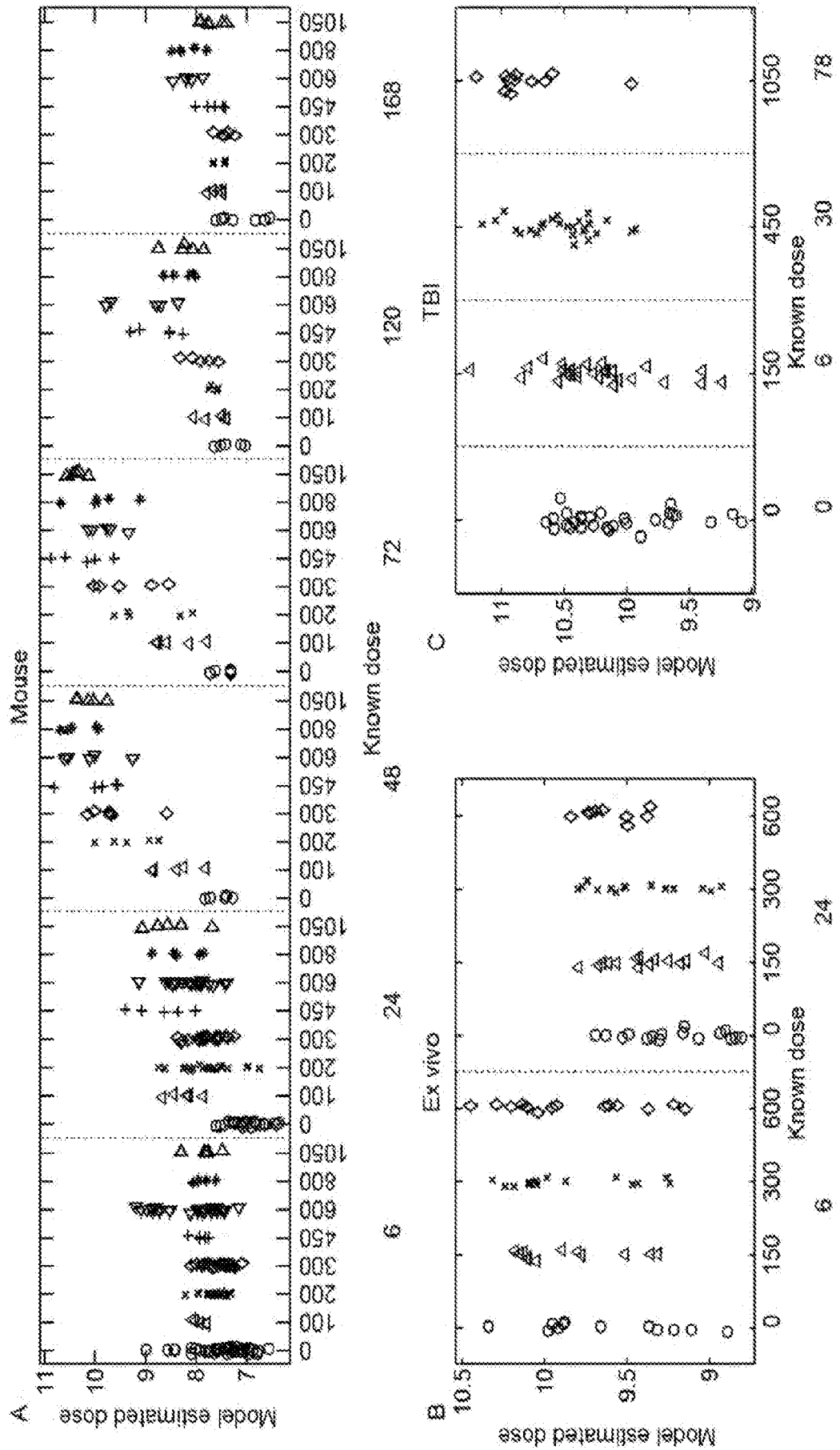


Fig. 10 Cont'd

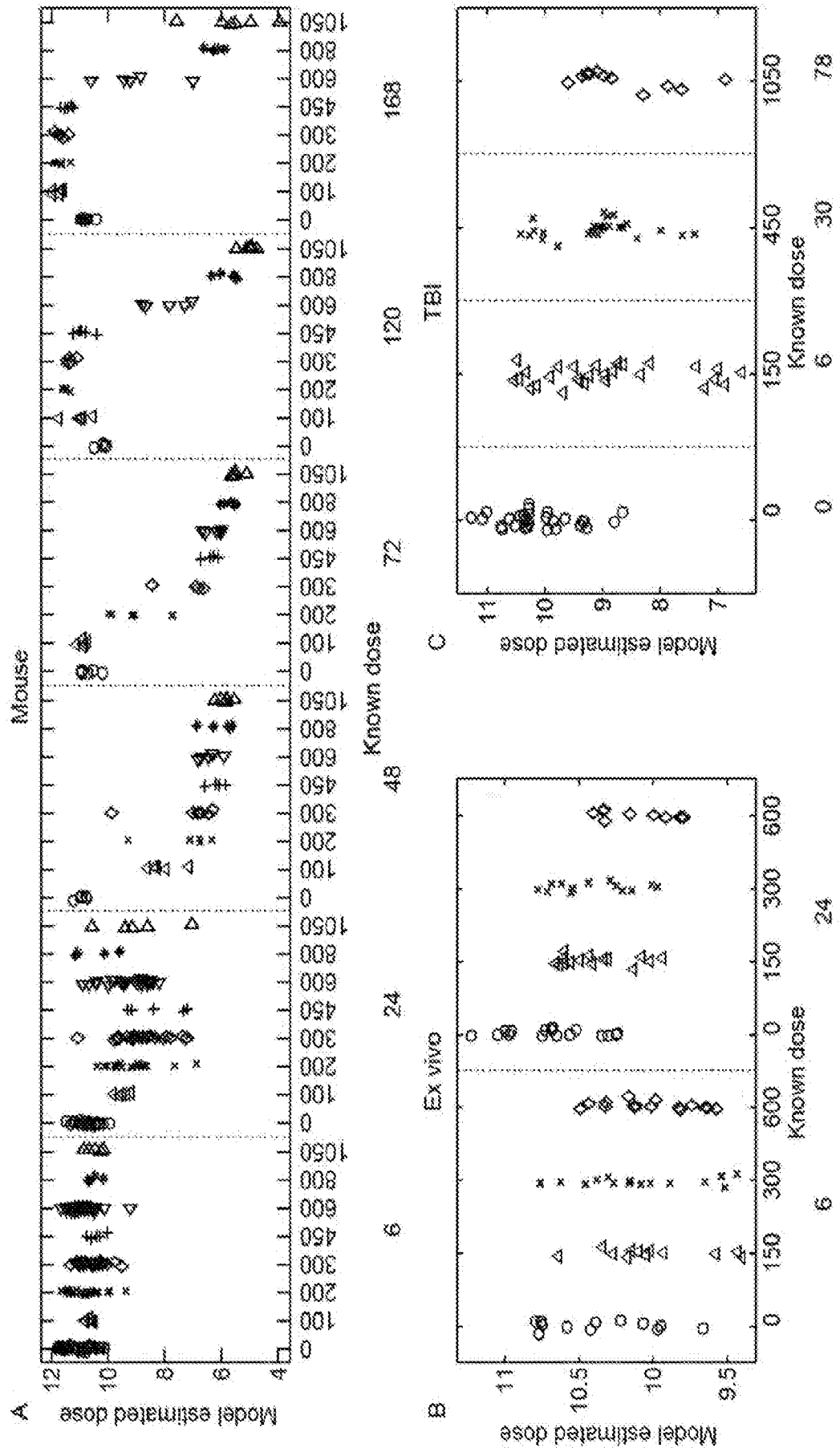


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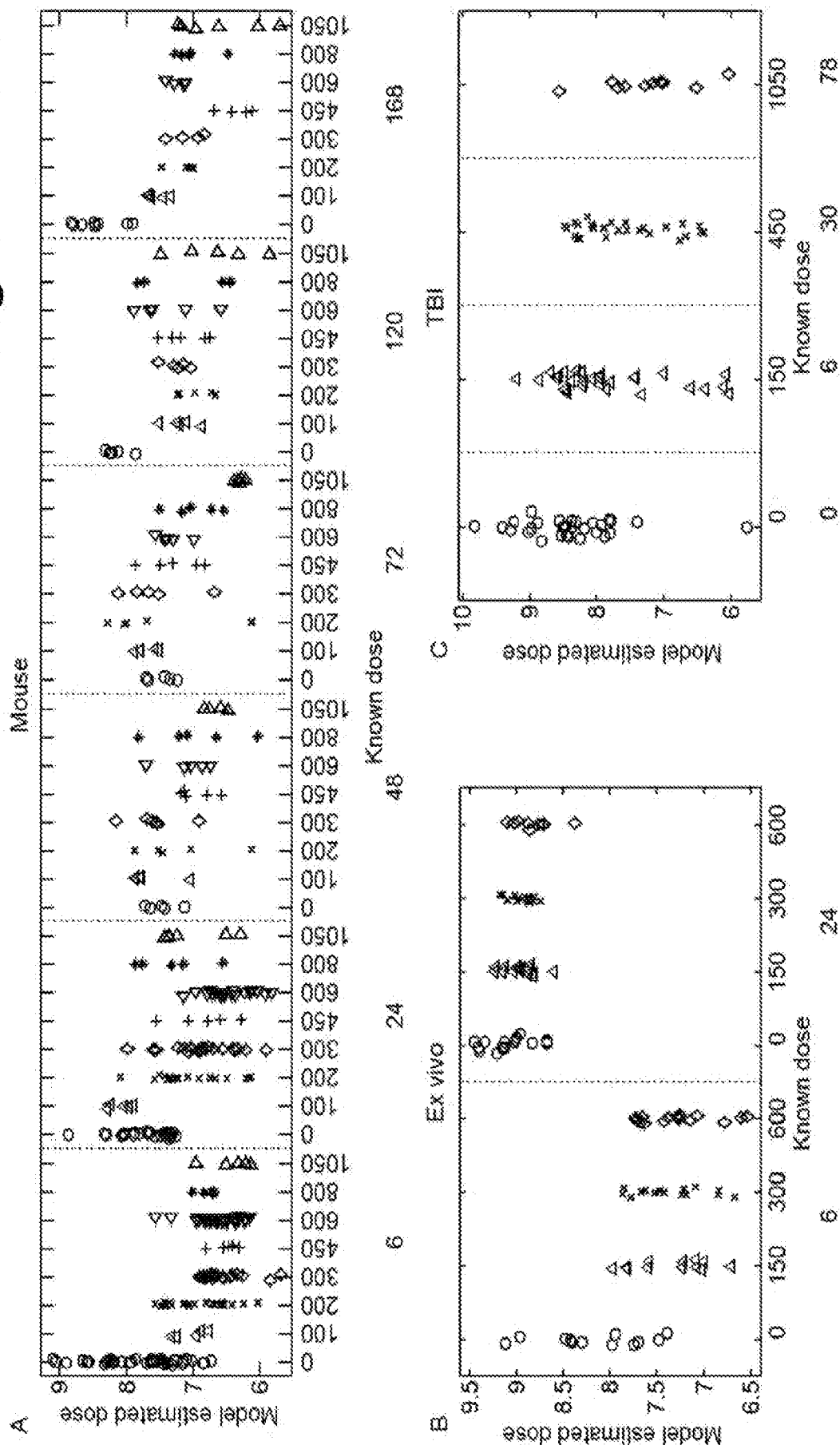


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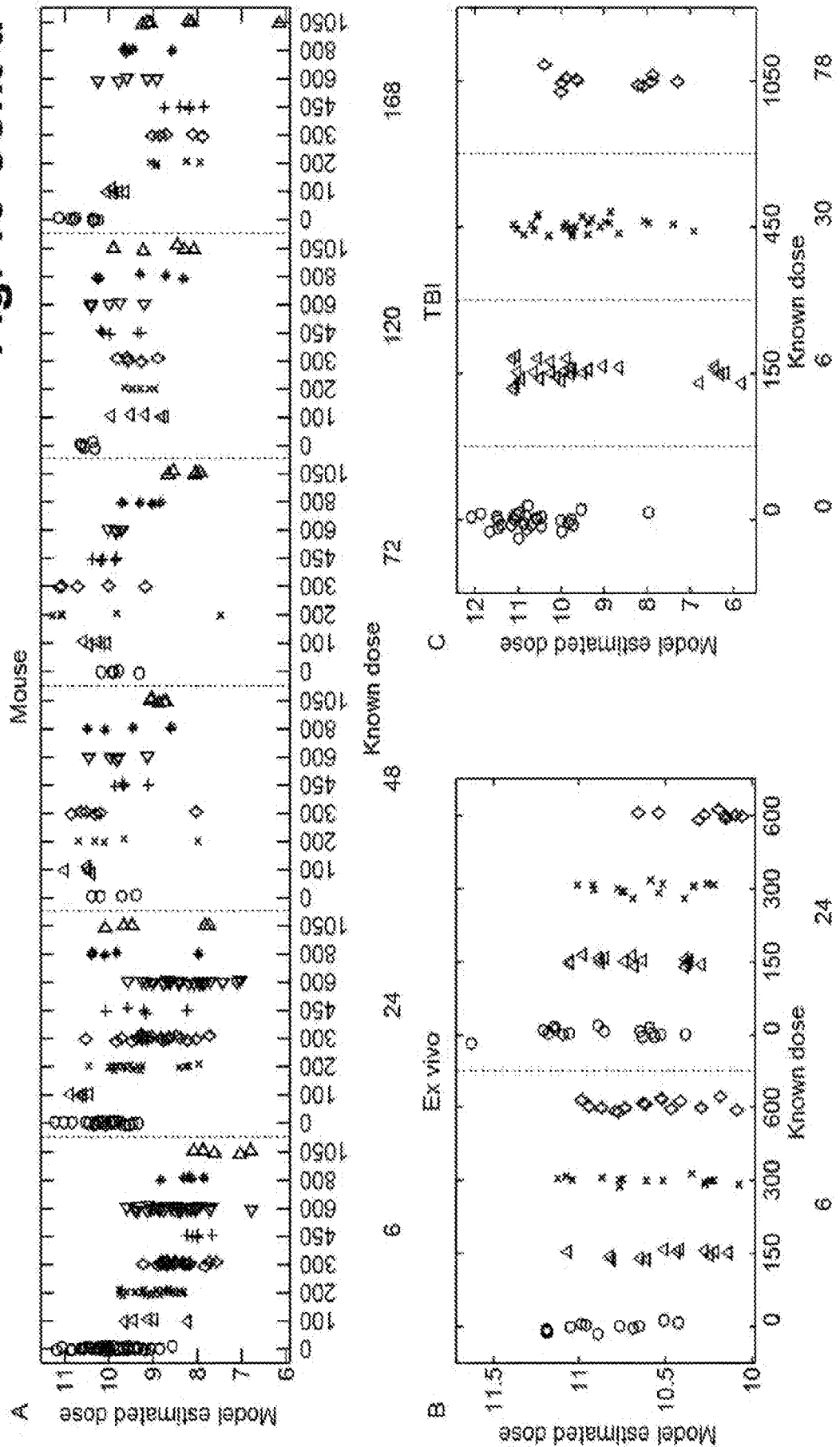


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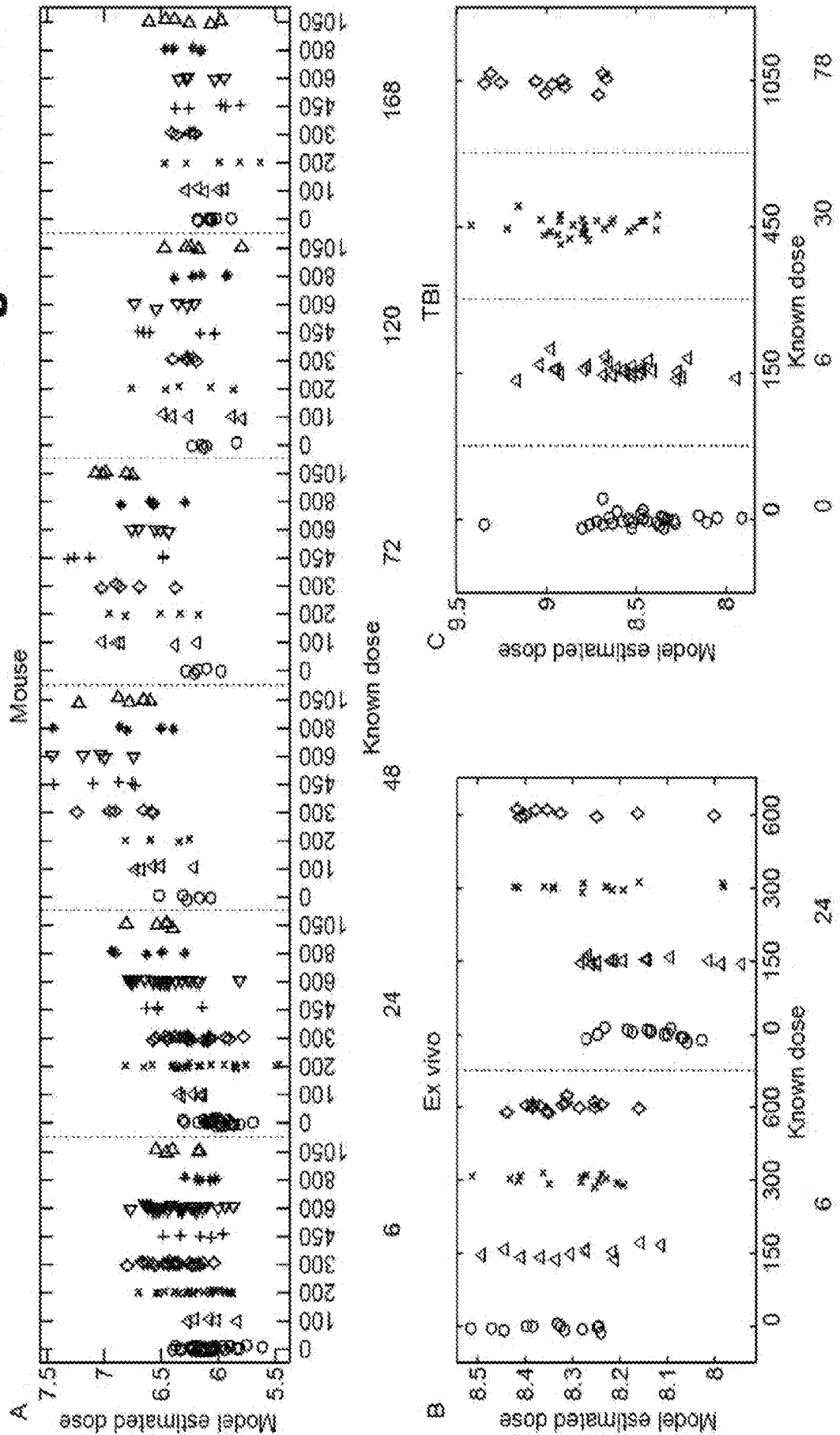


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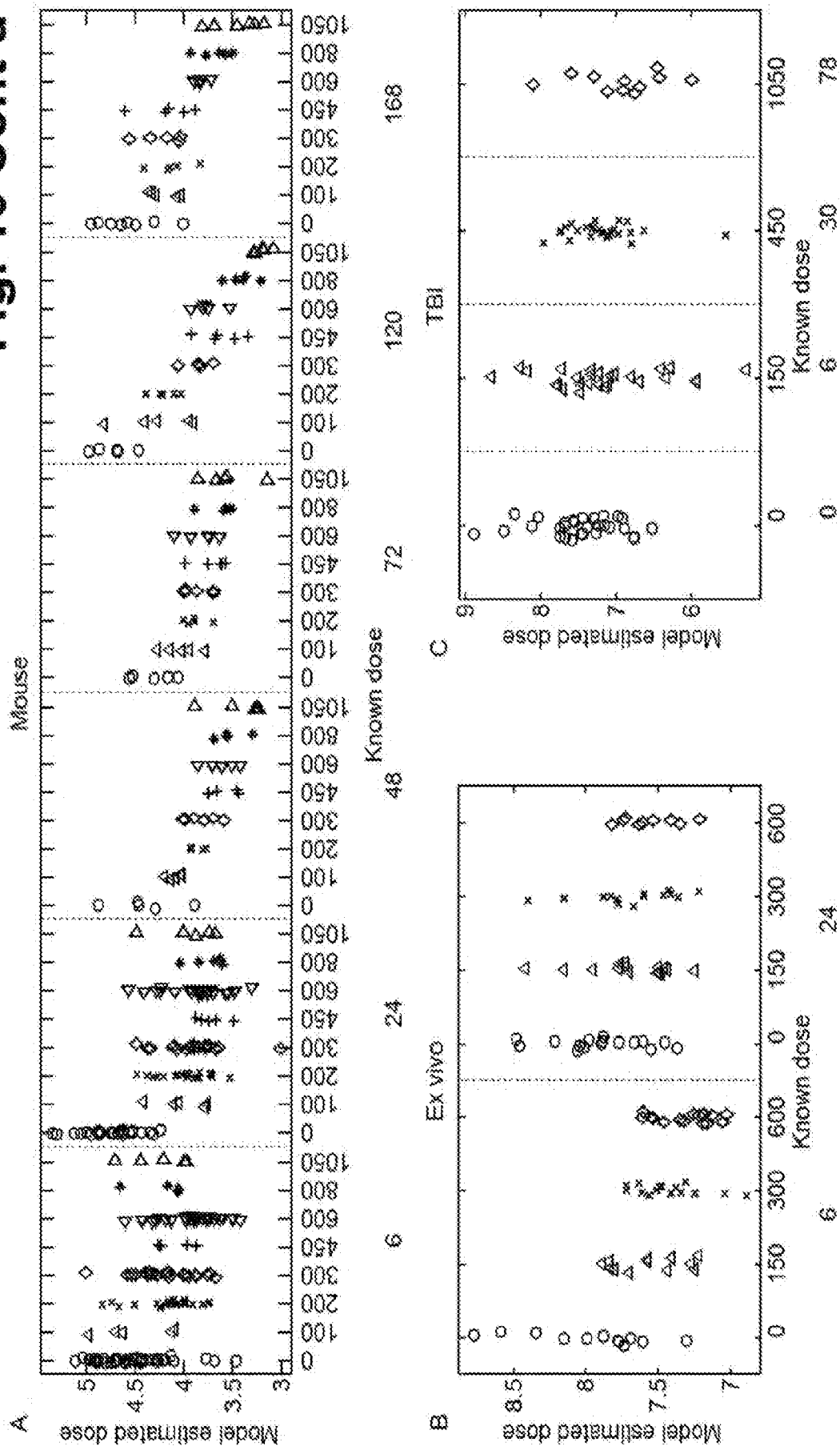


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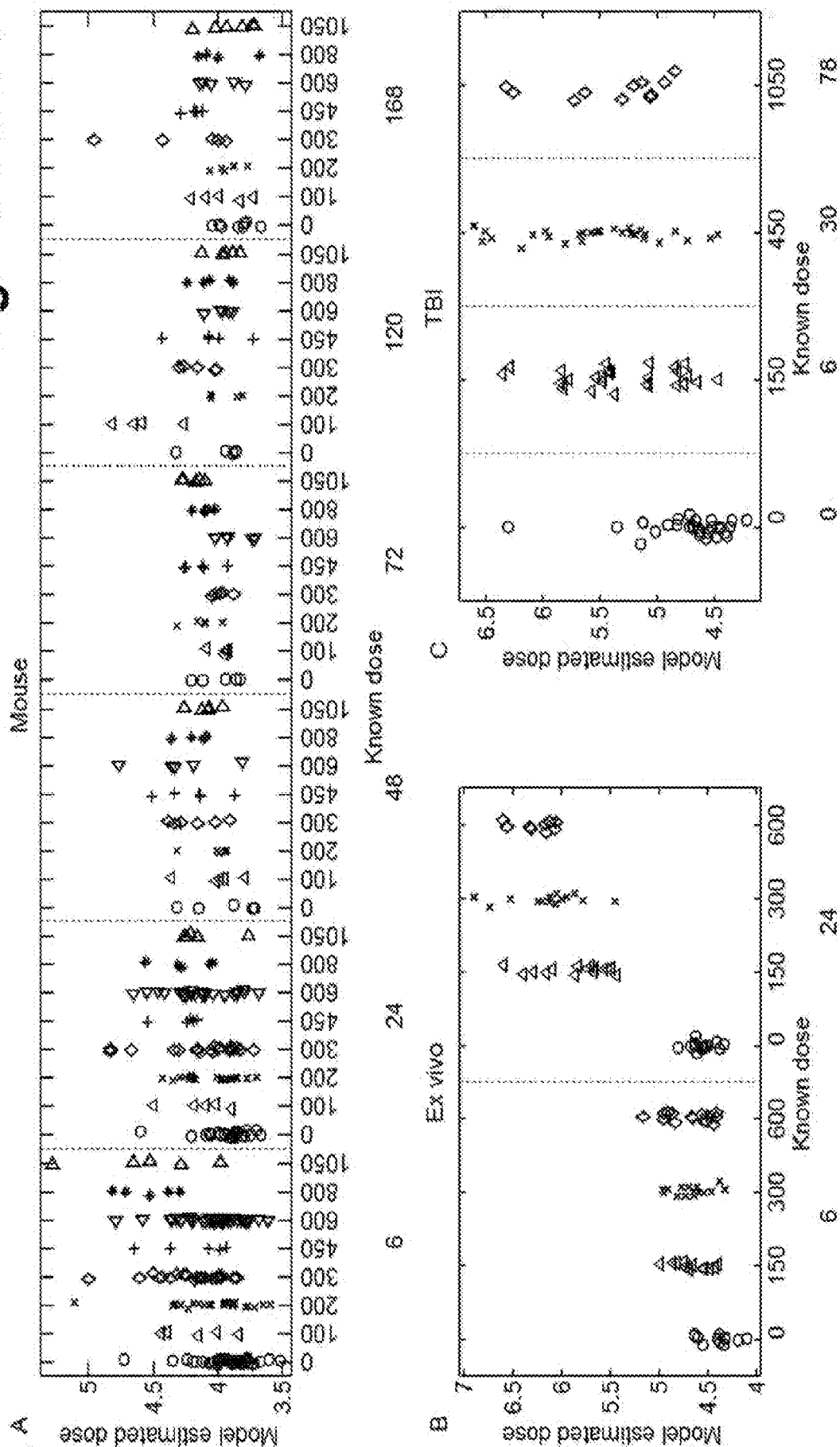


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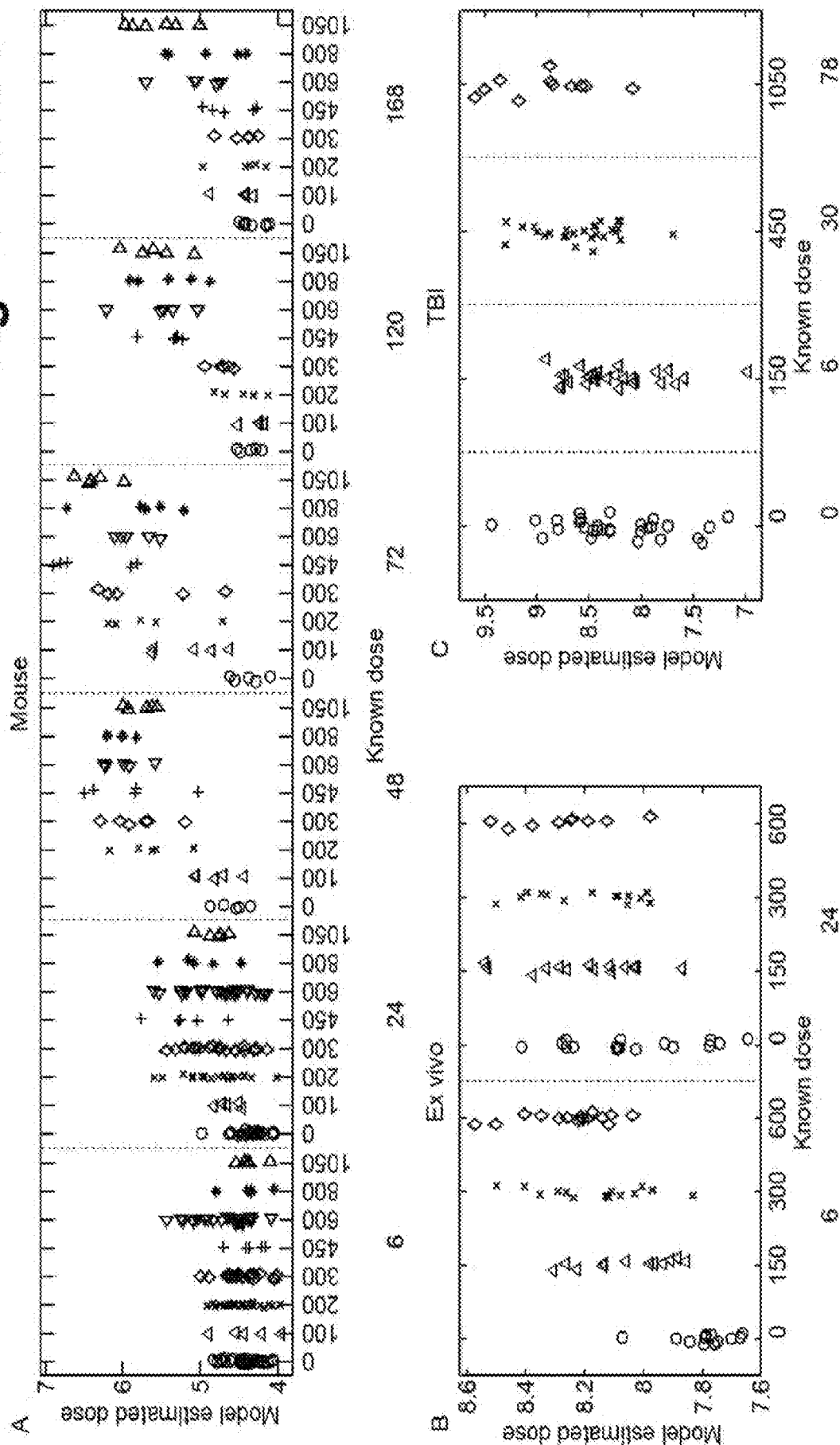


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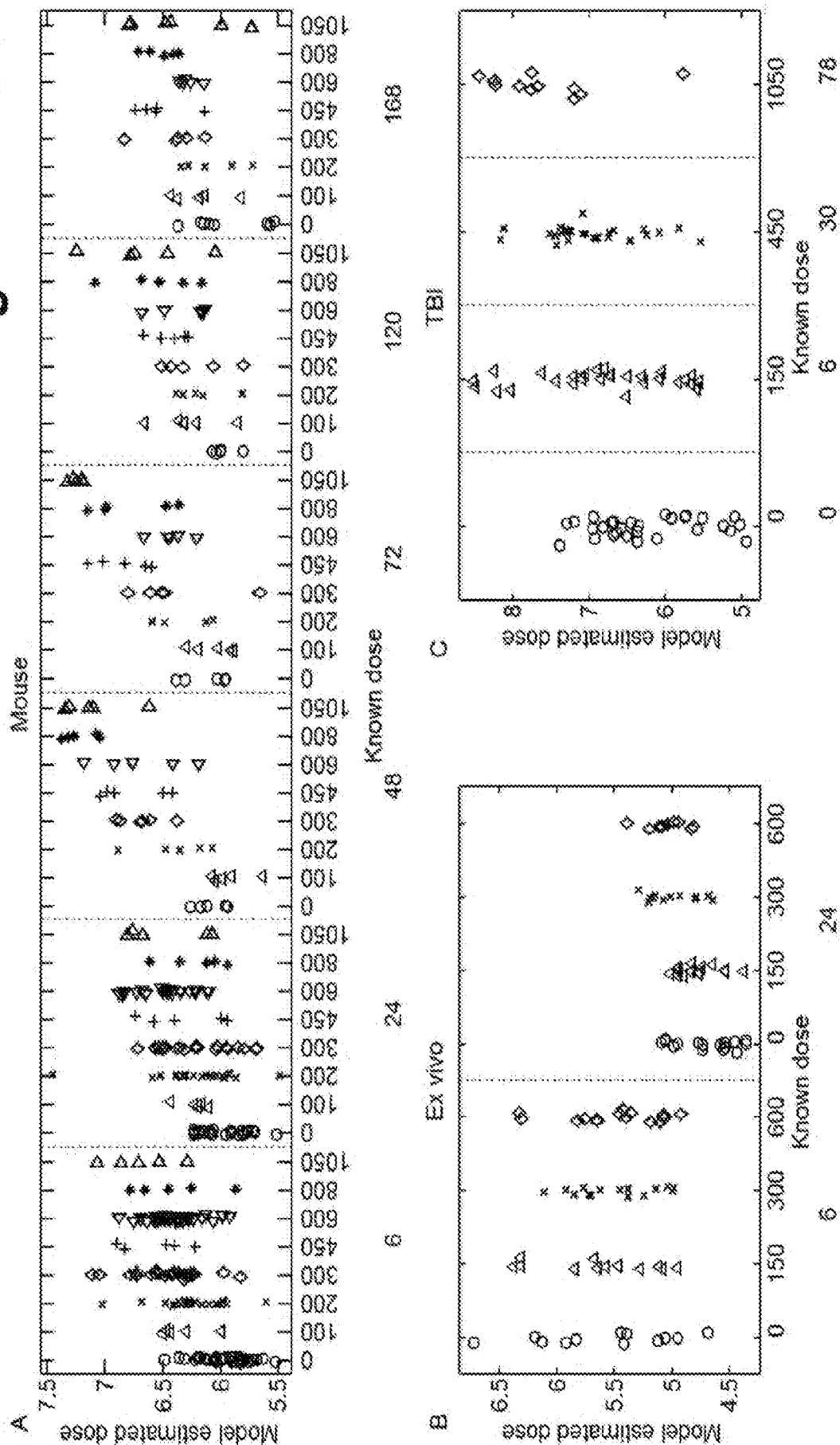


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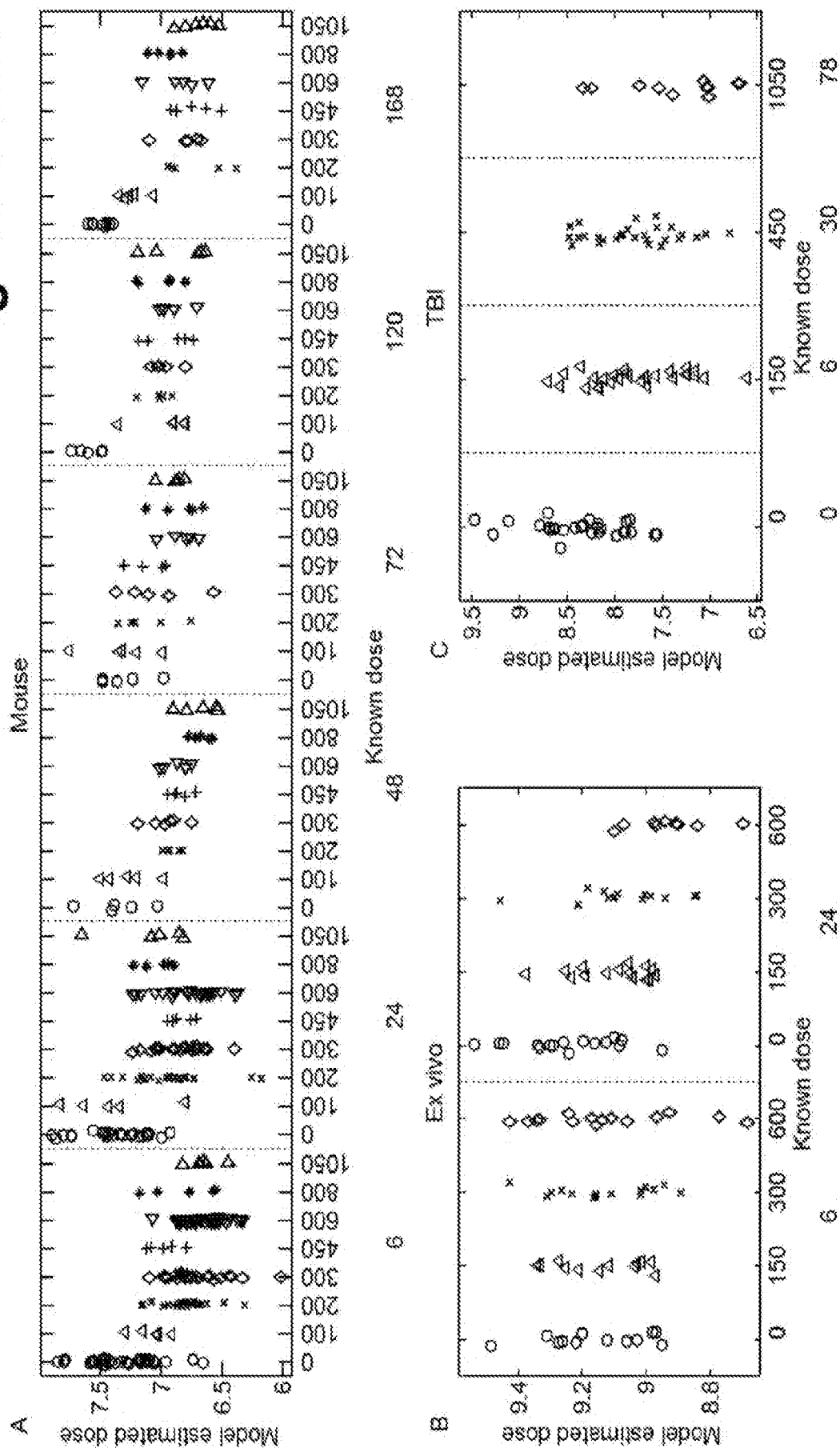


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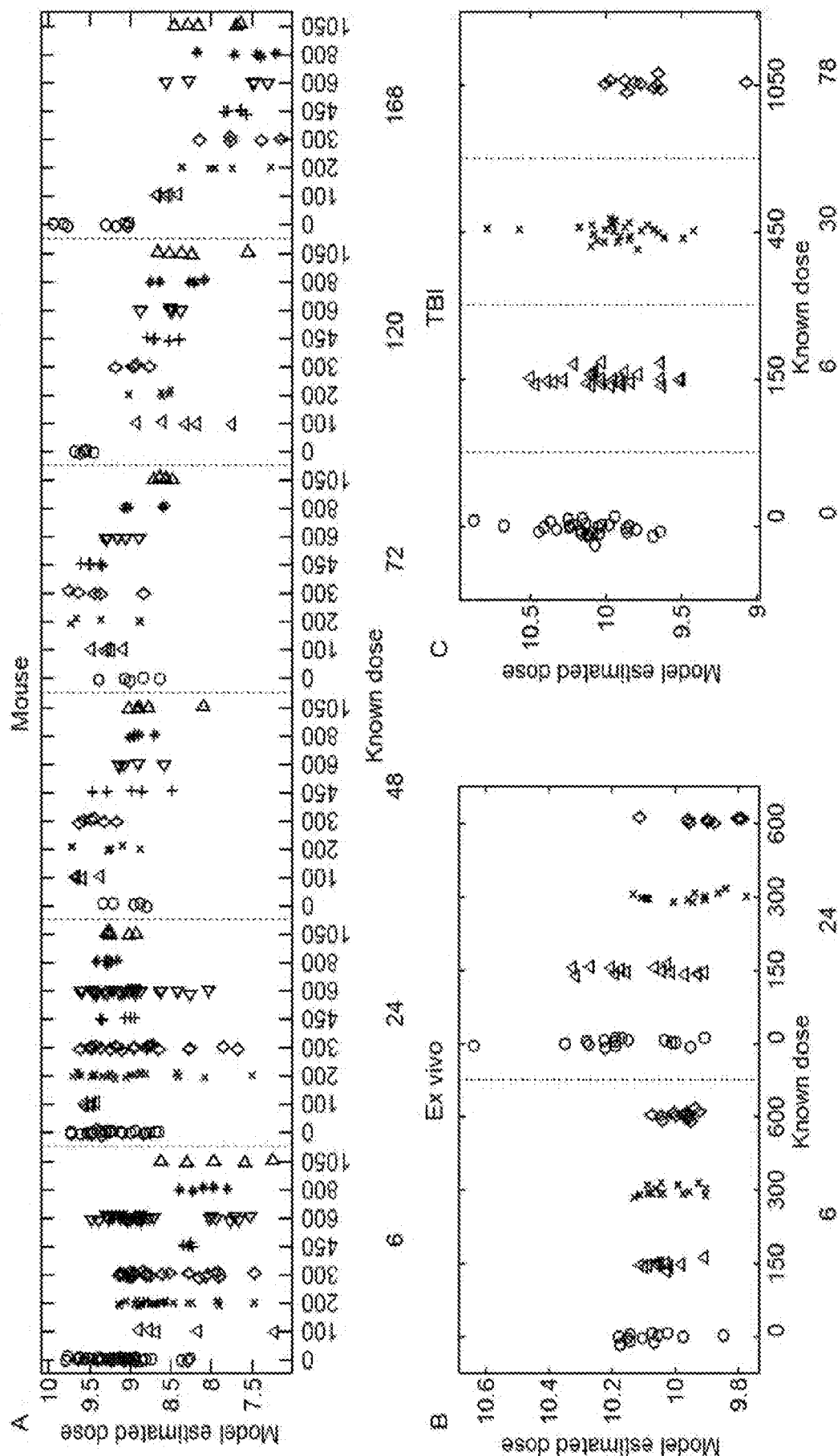


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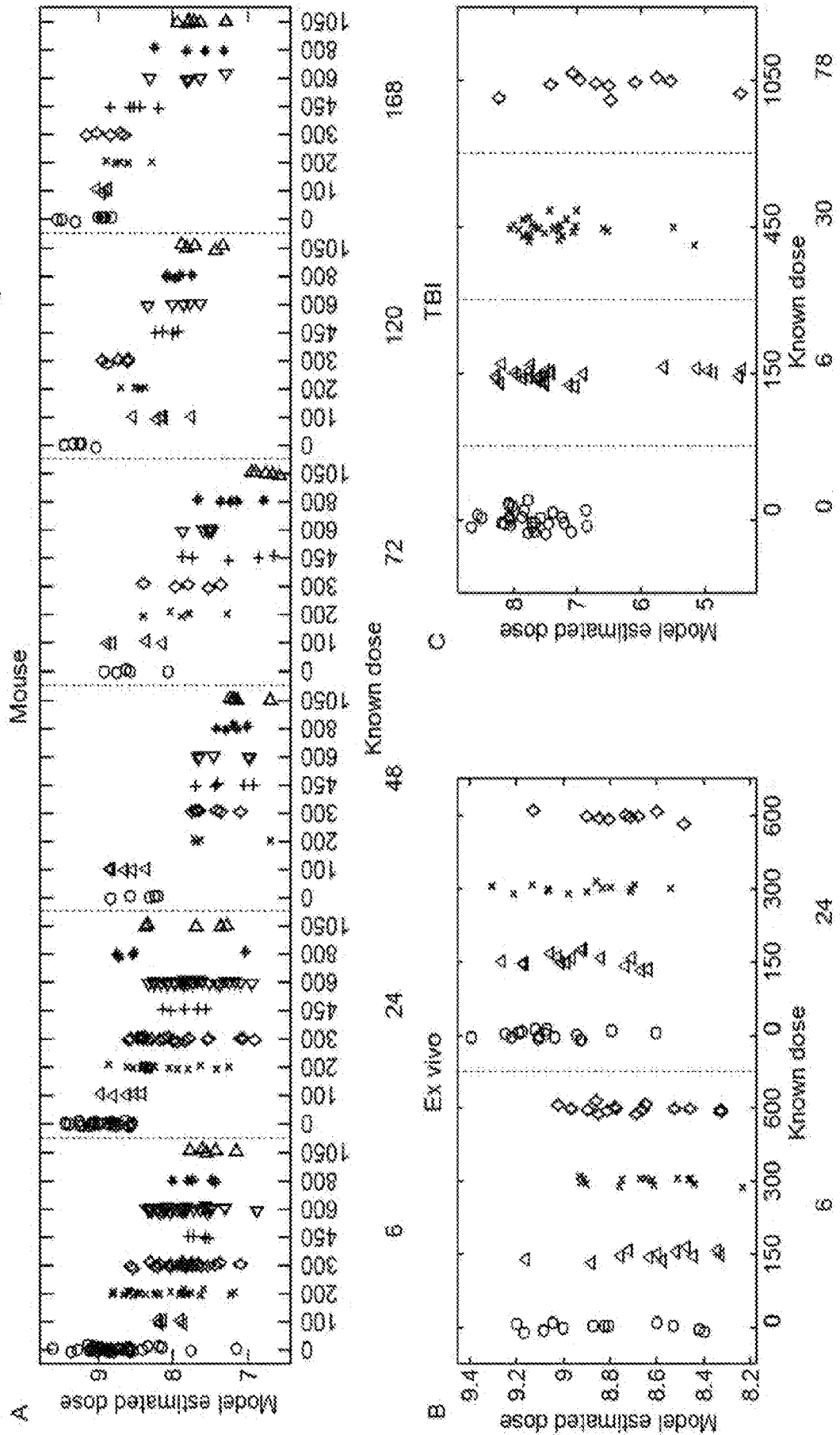


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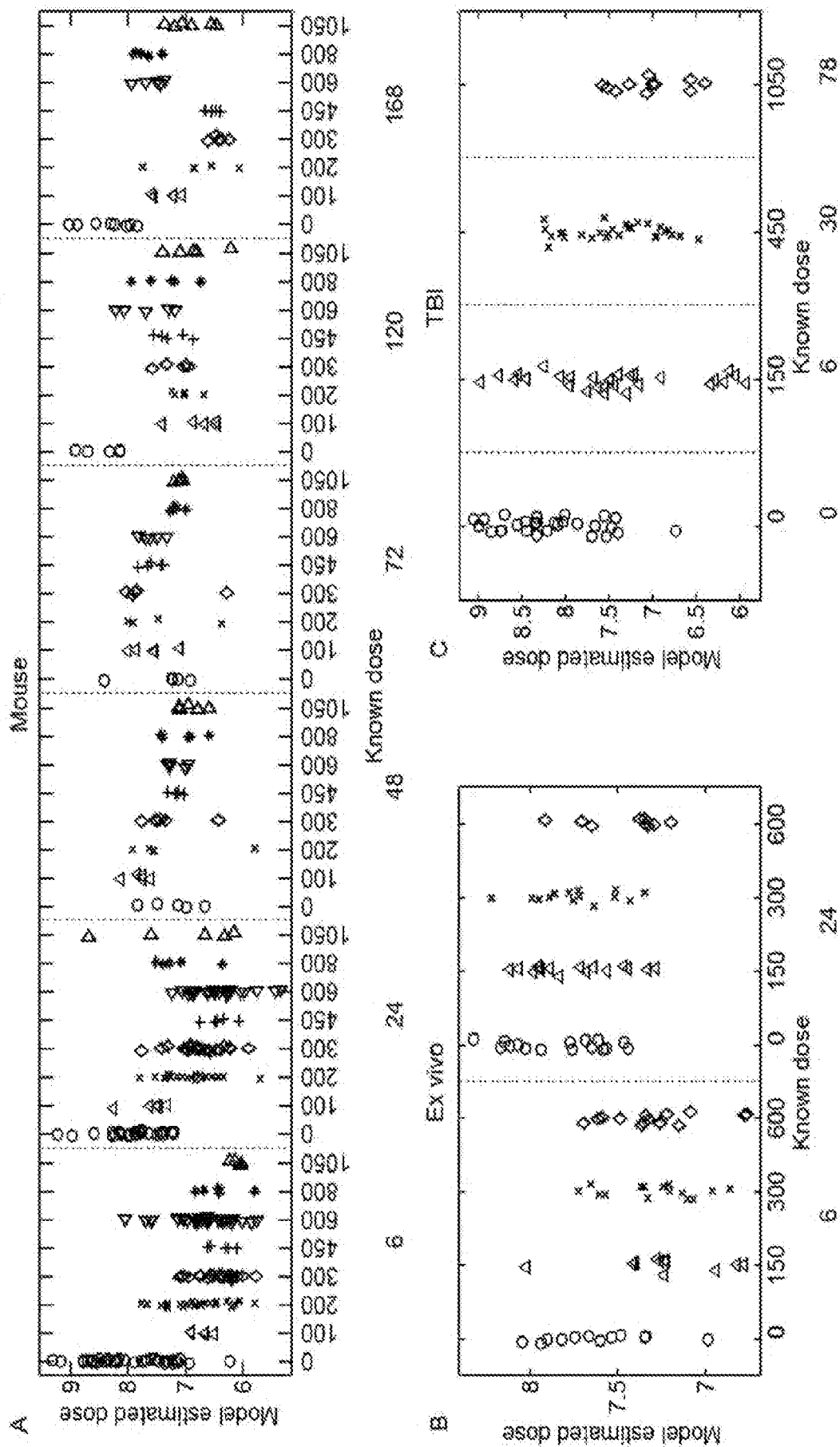


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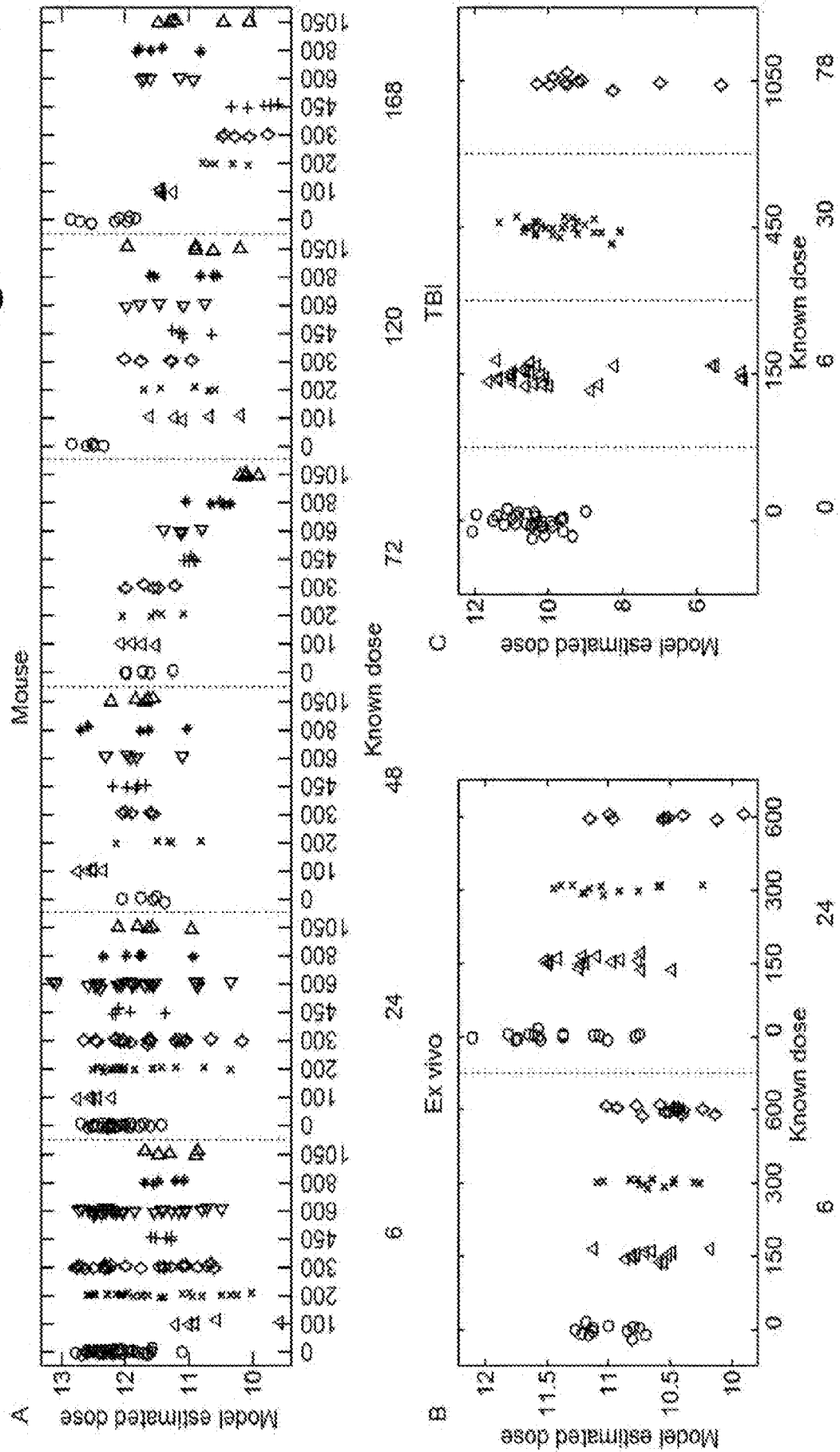


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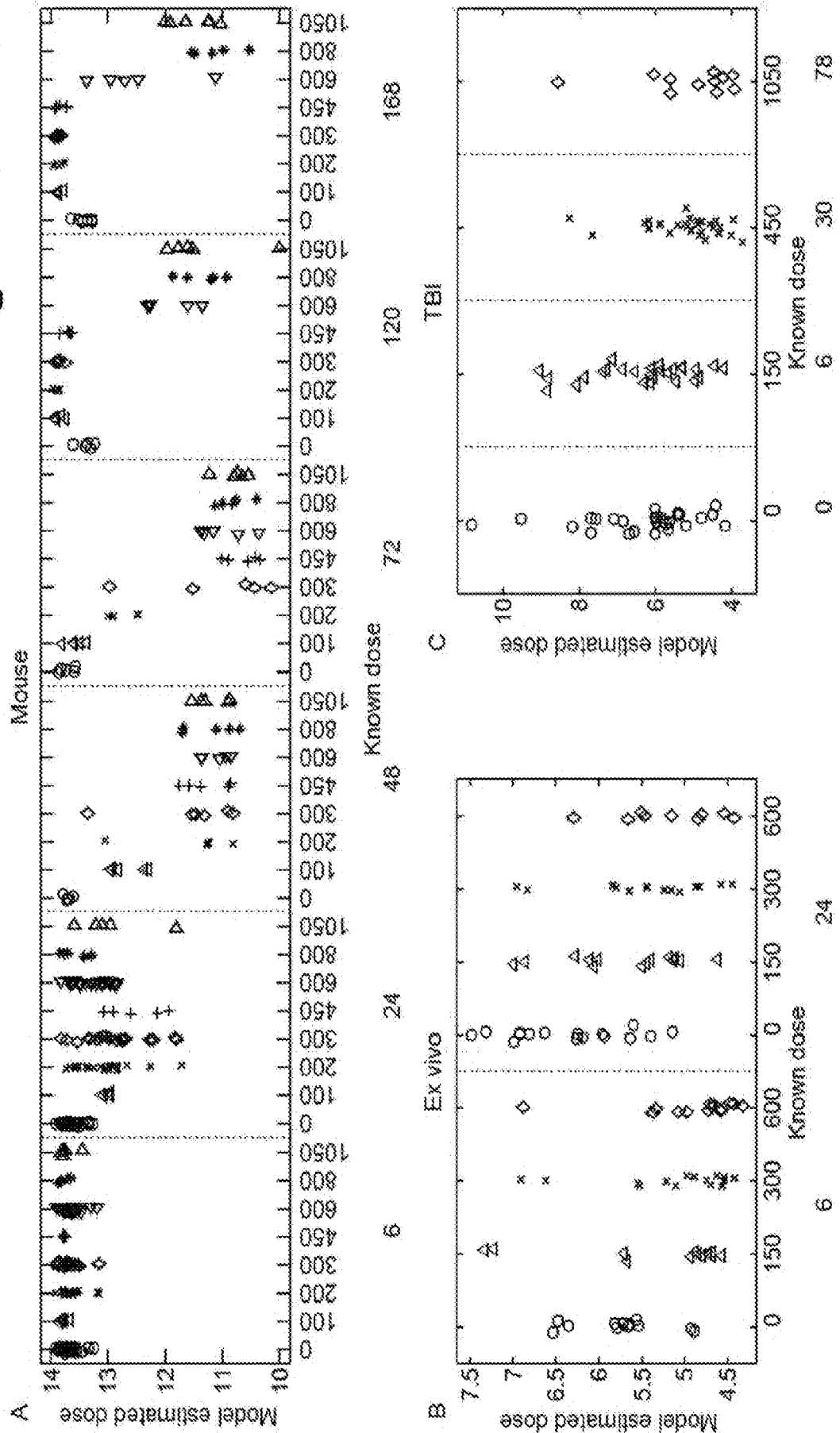


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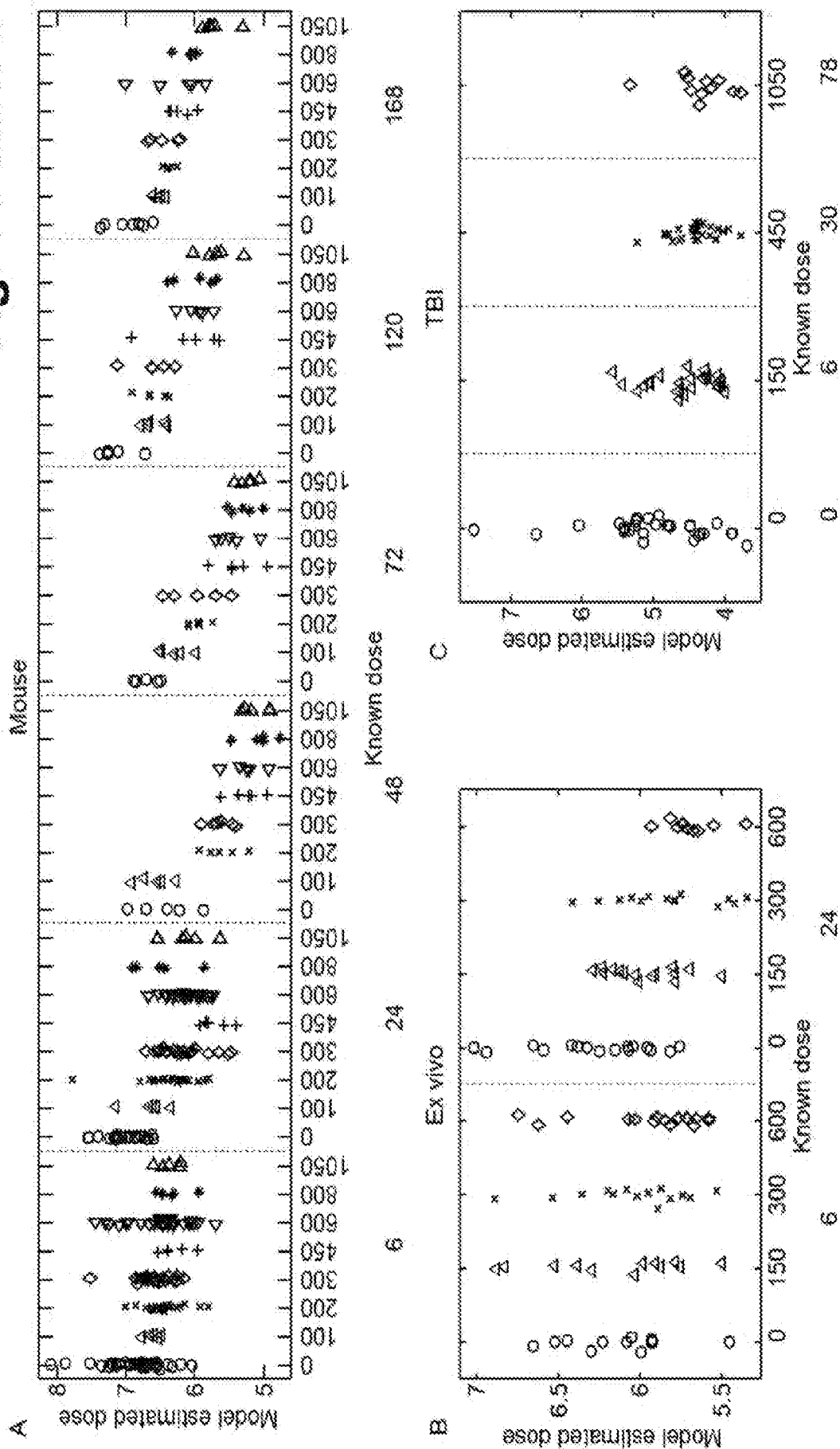


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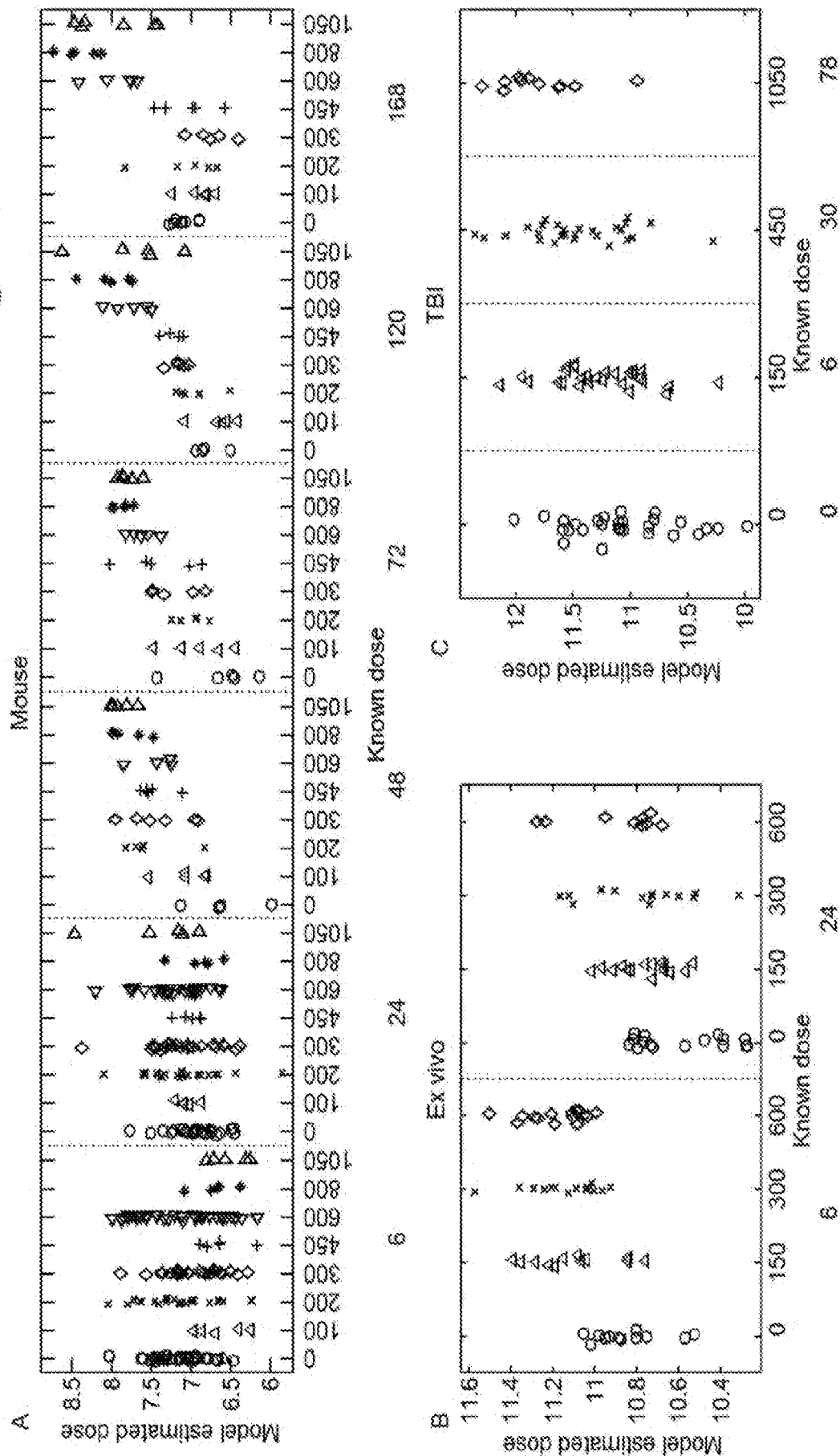


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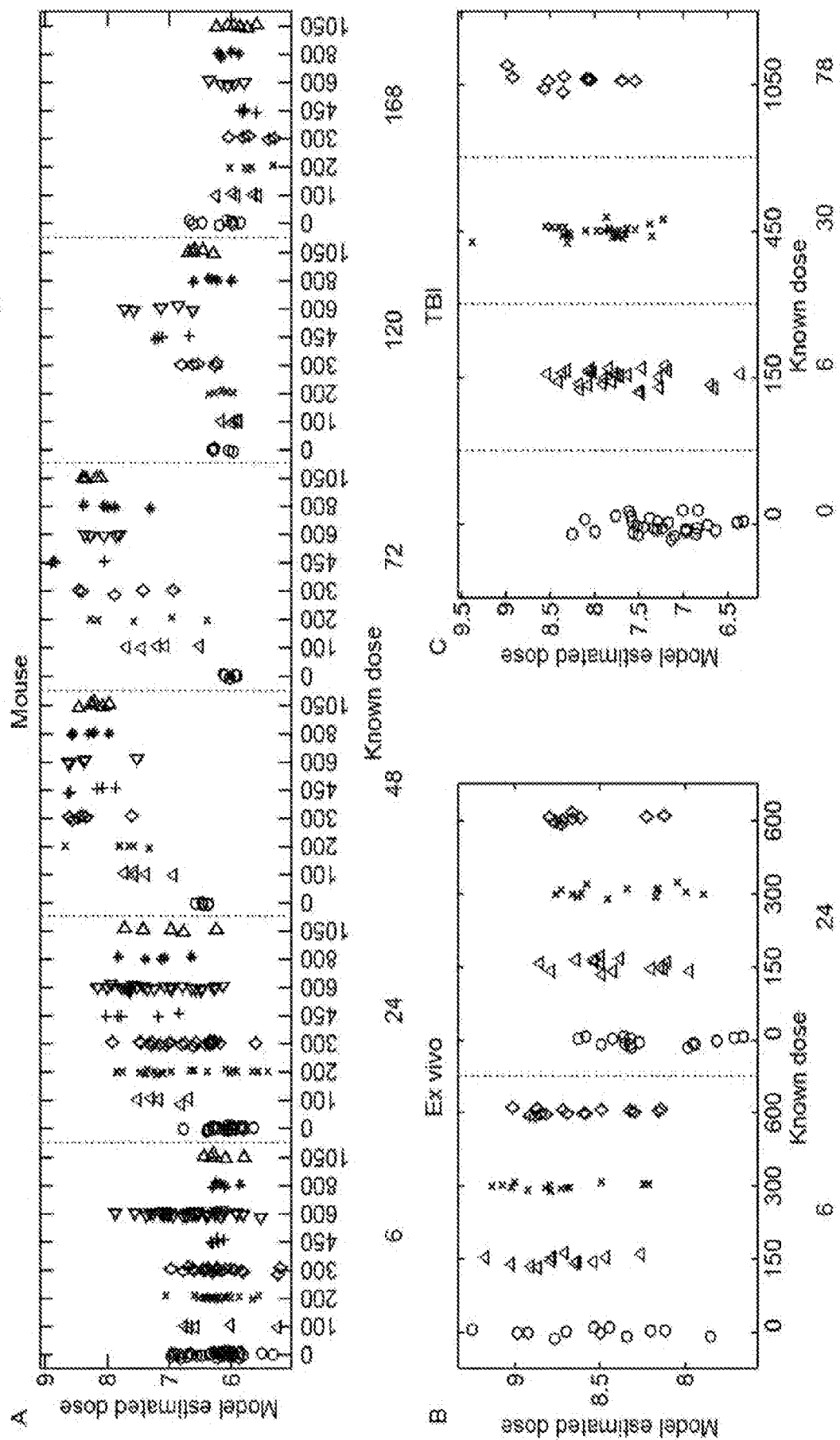


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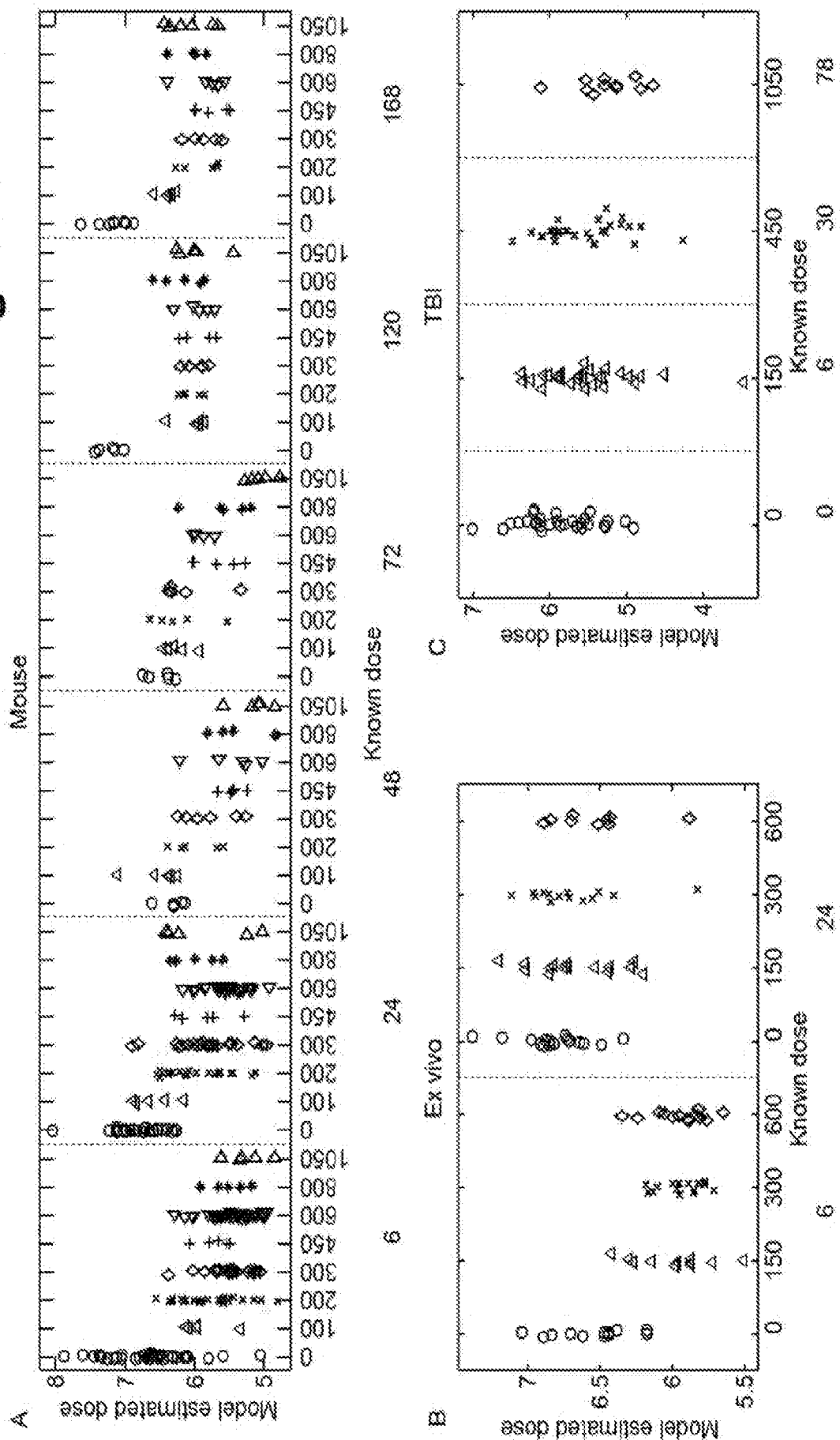
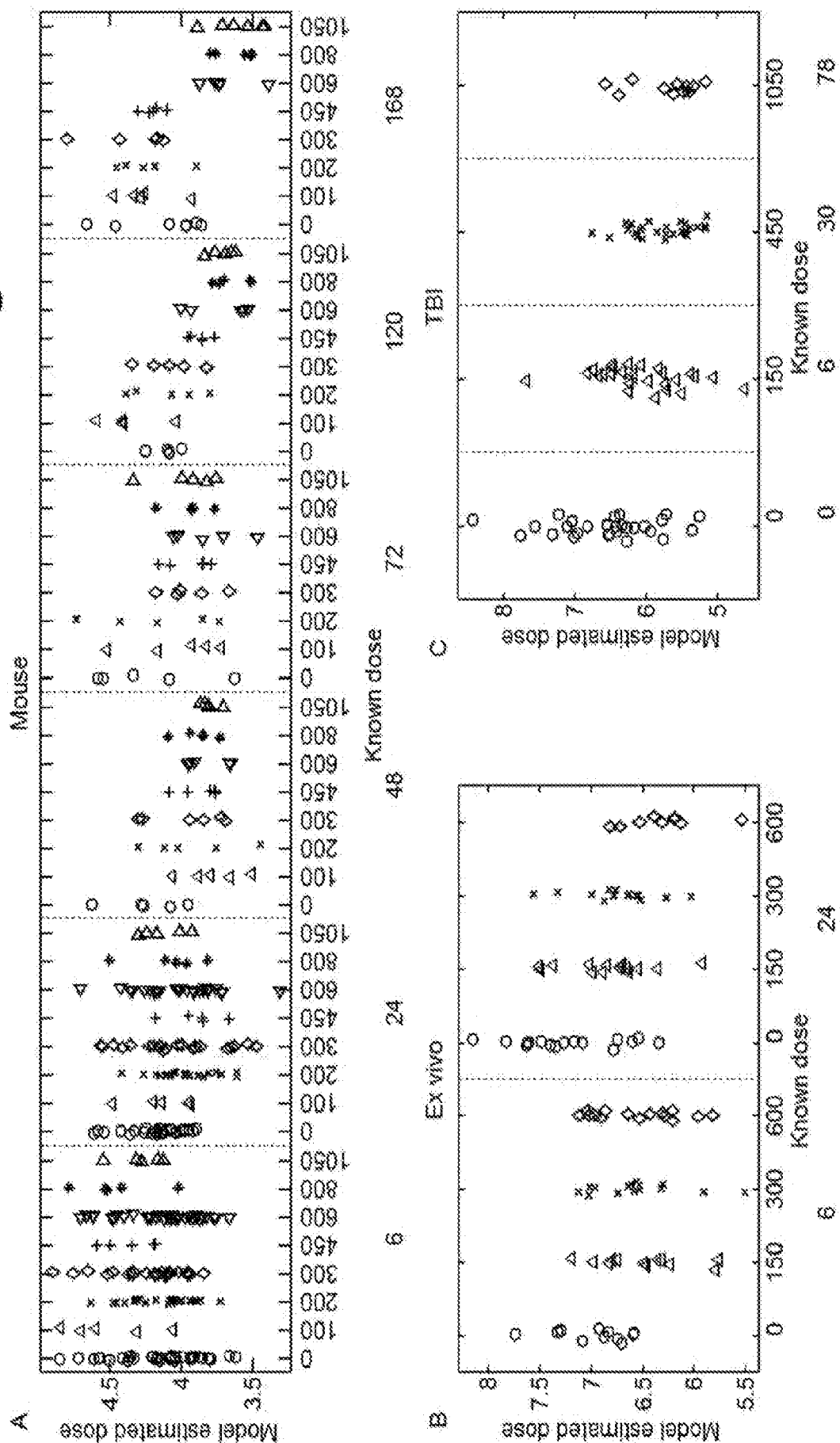
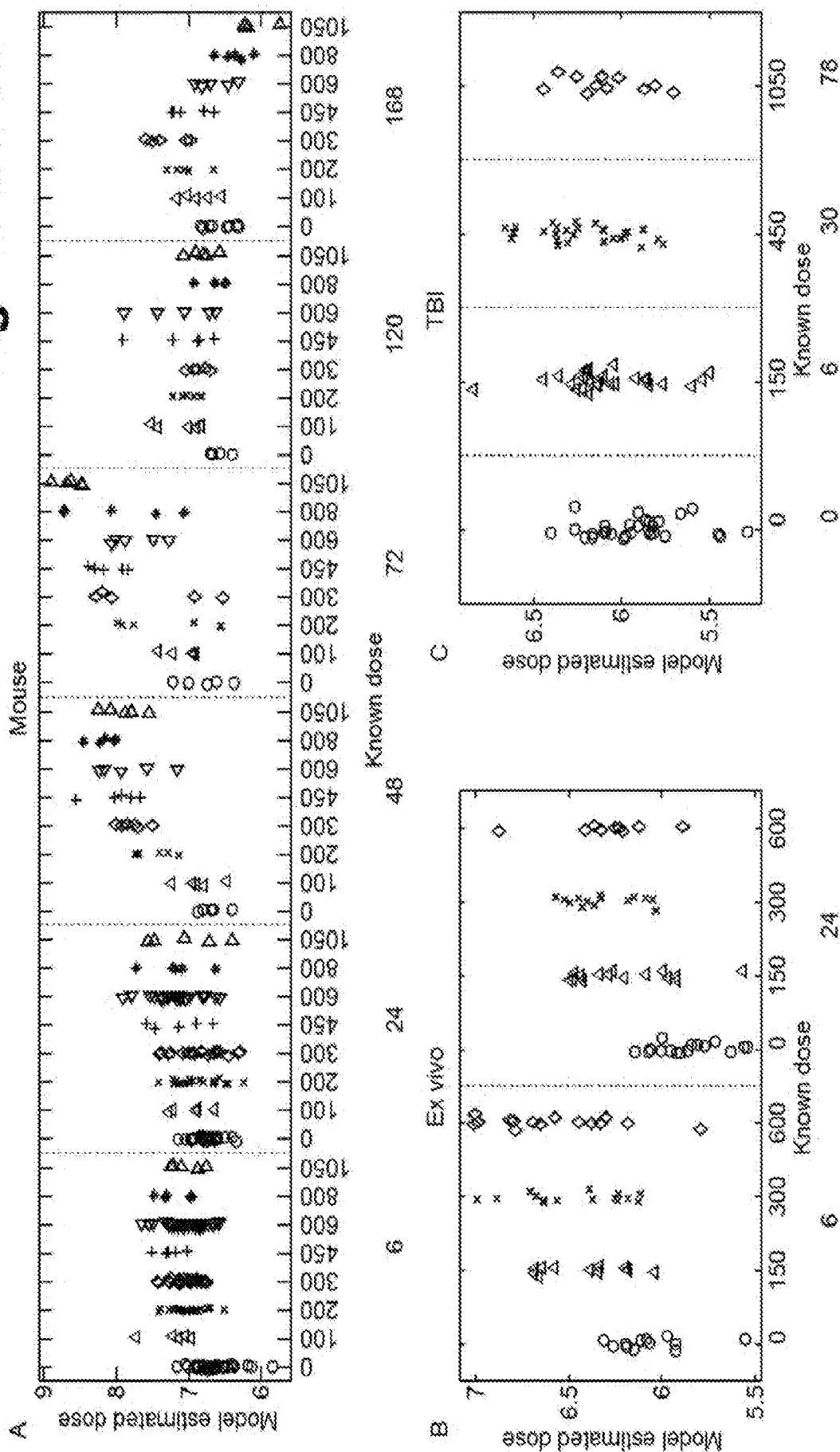


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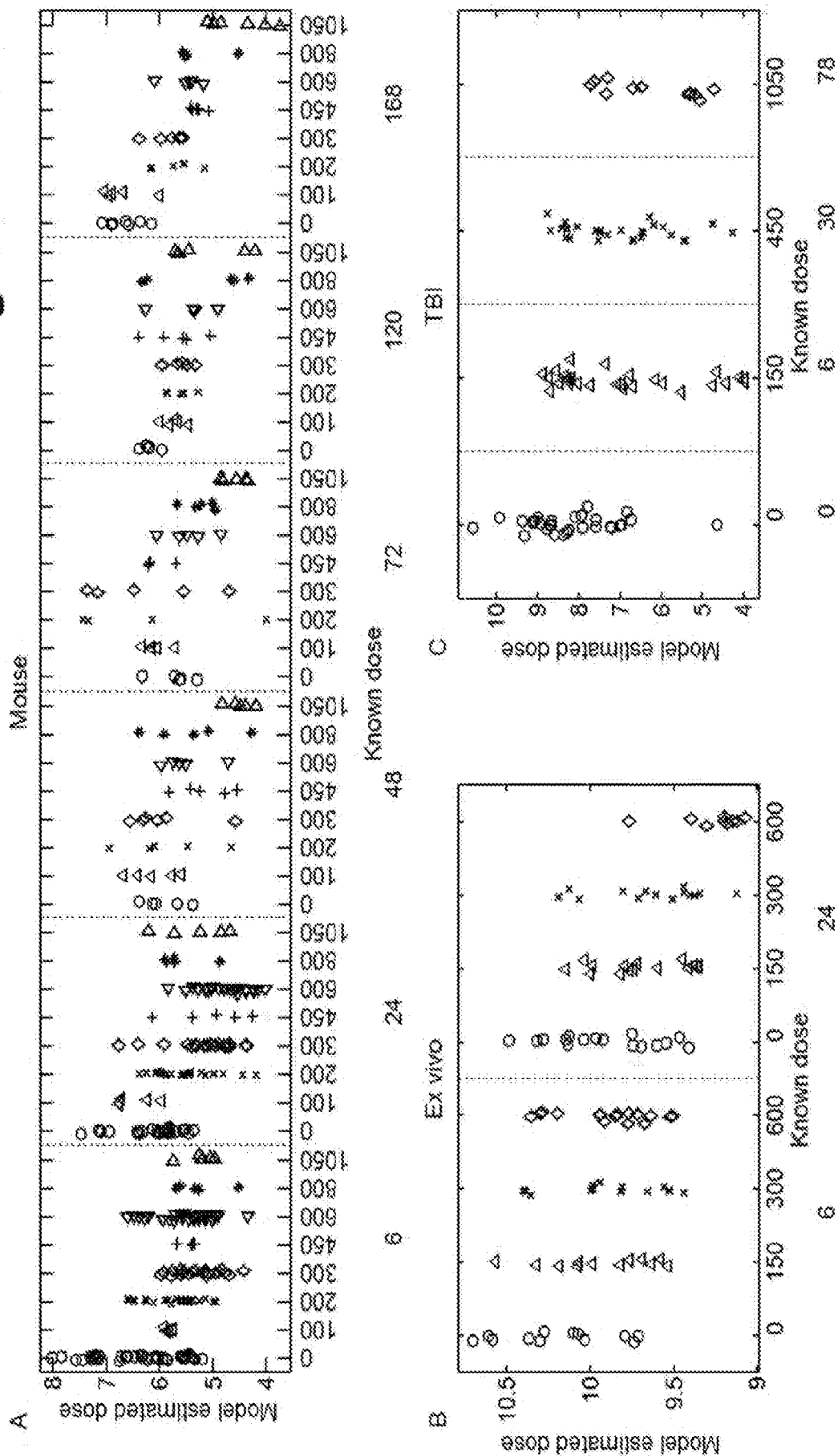
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Fig. 10 Cont'd



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Fig. 10 Cont'd



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Fig. 10 Cont'd

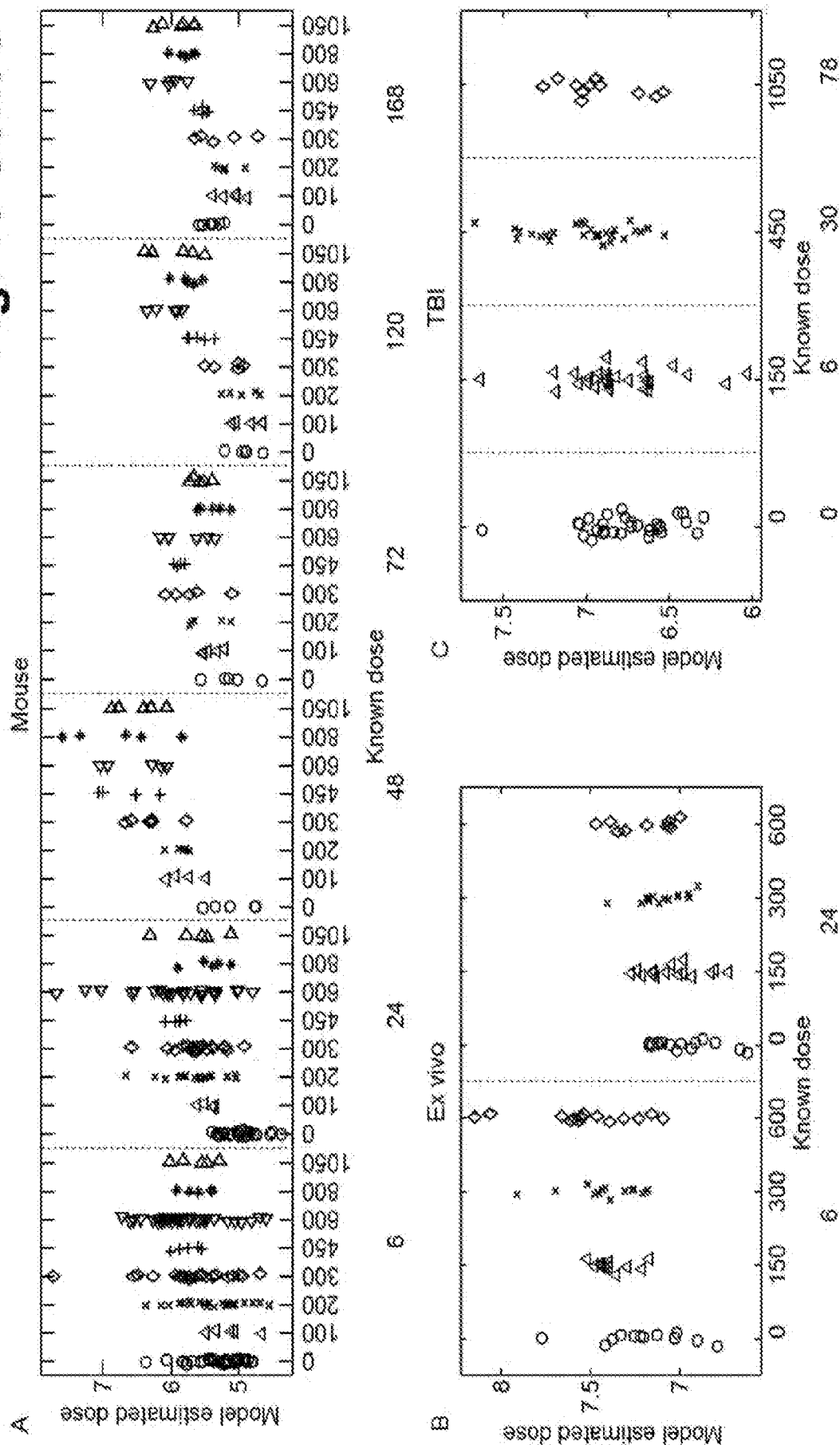


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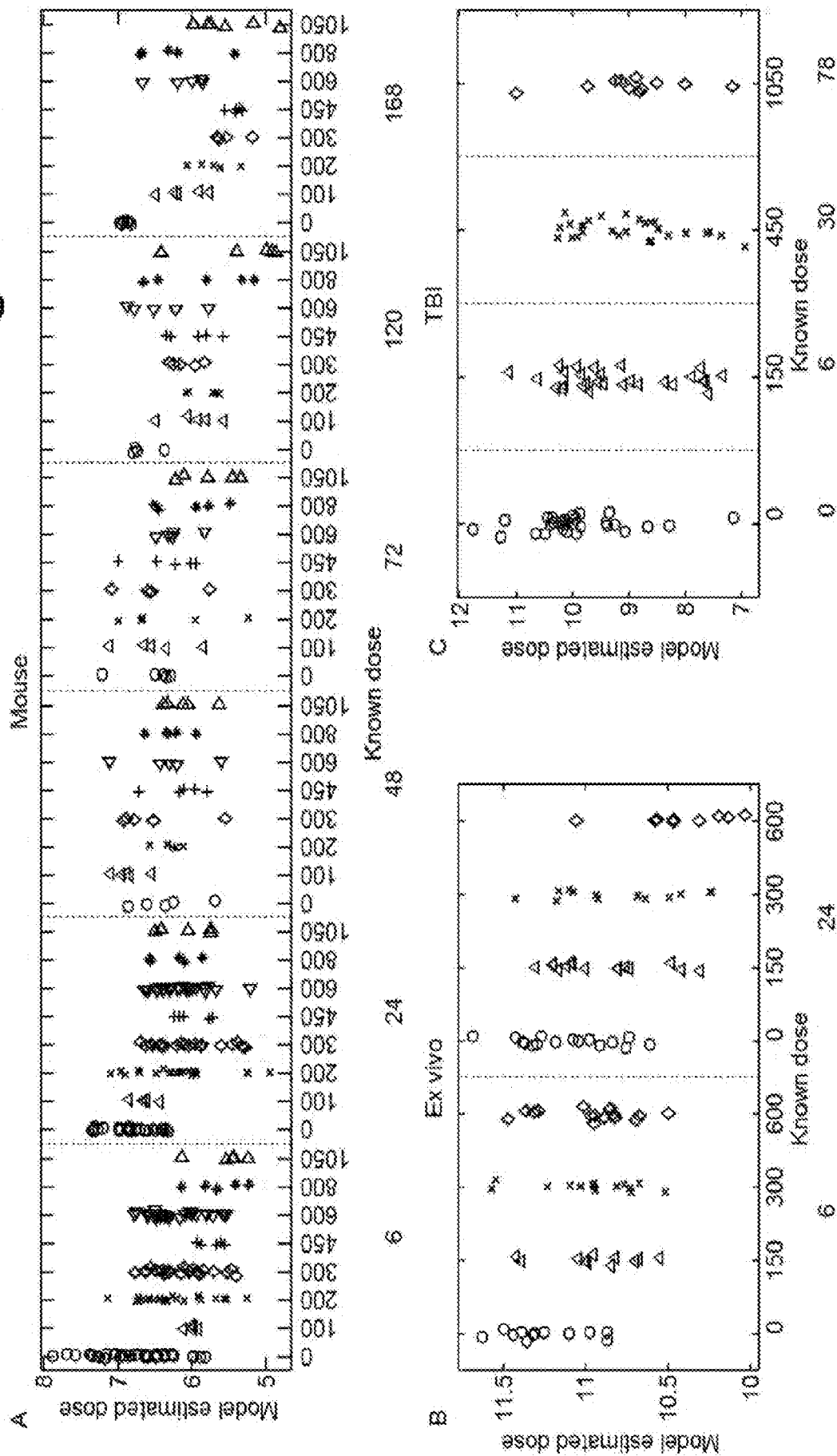


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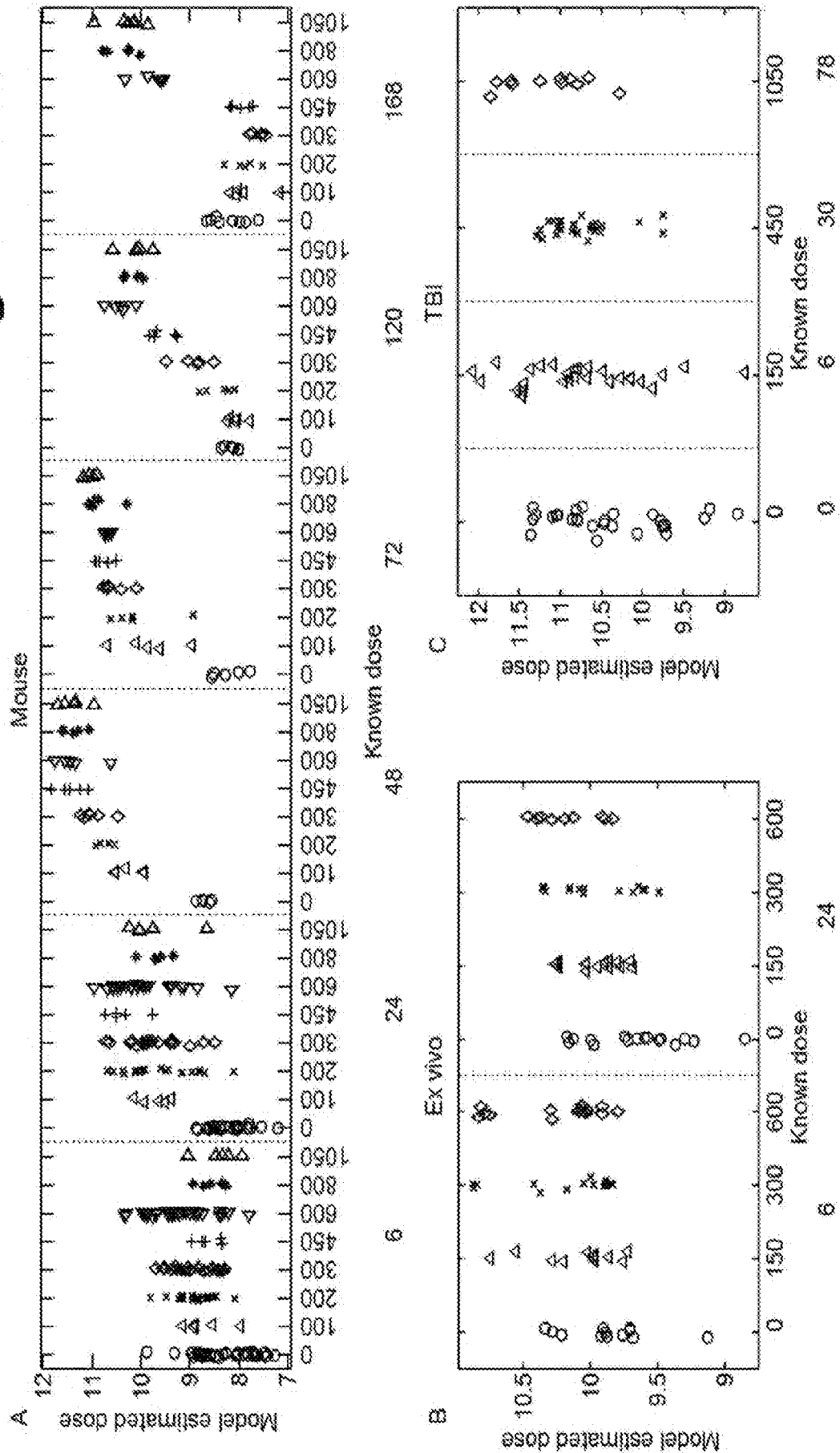


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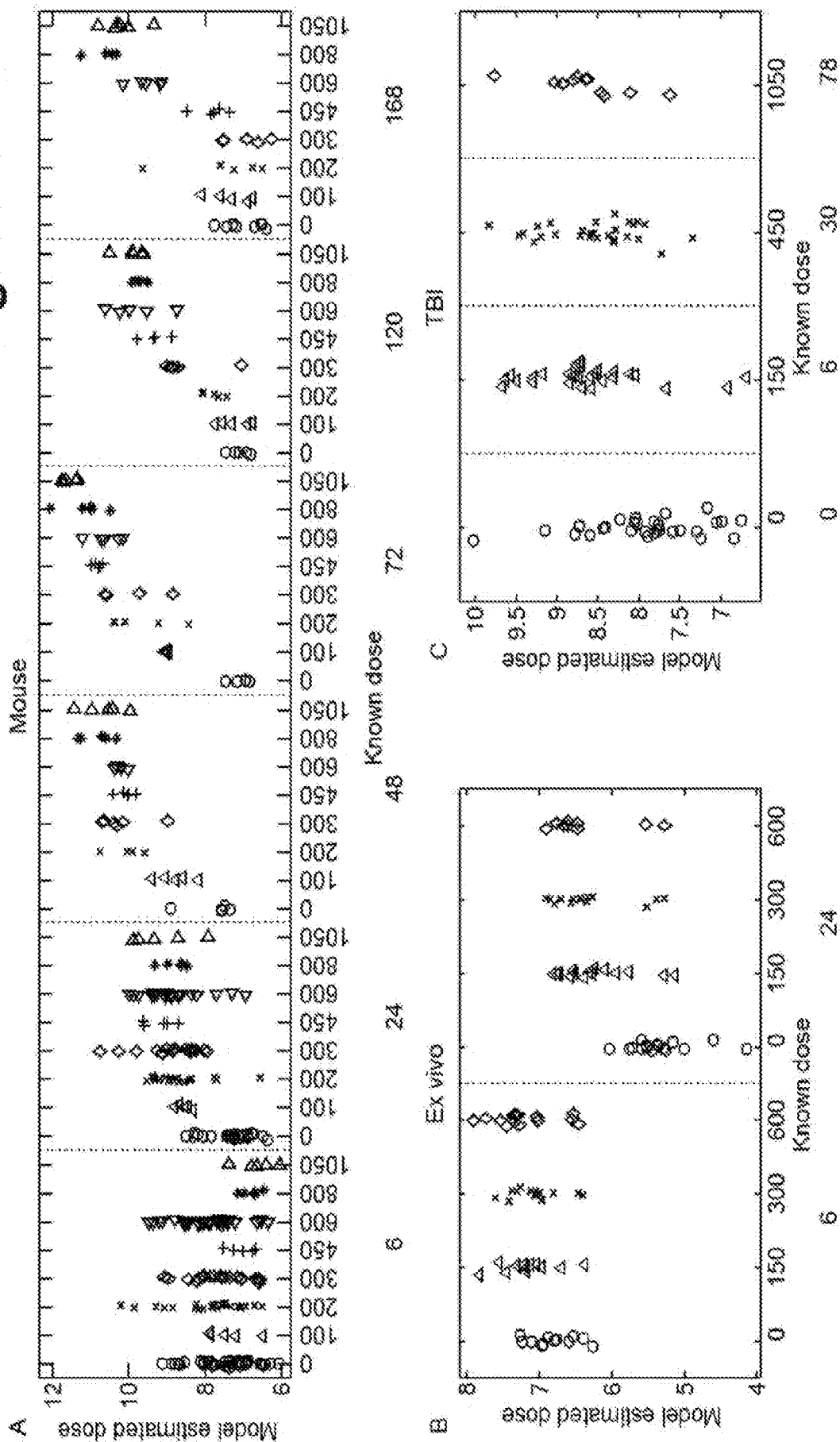


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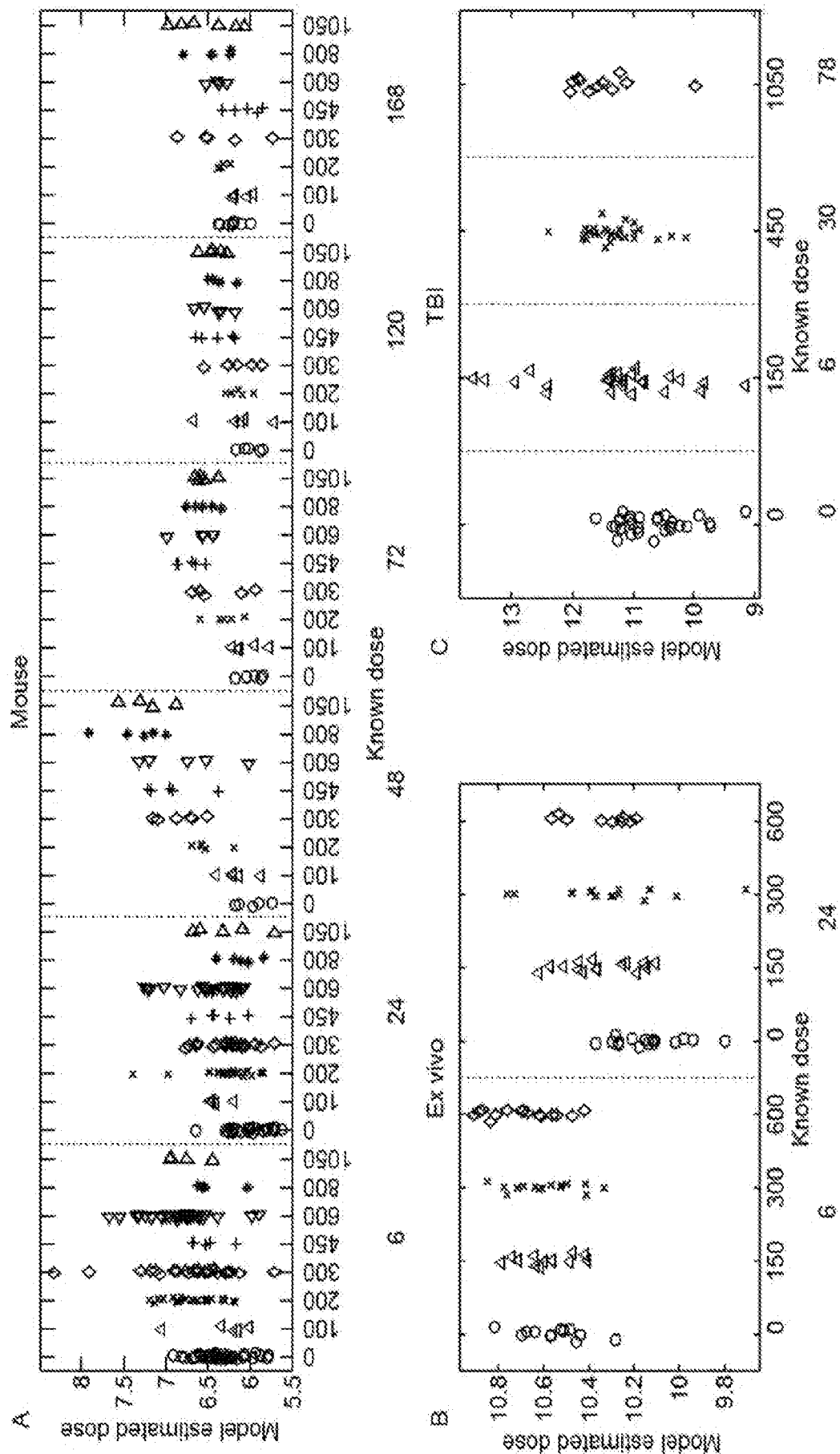


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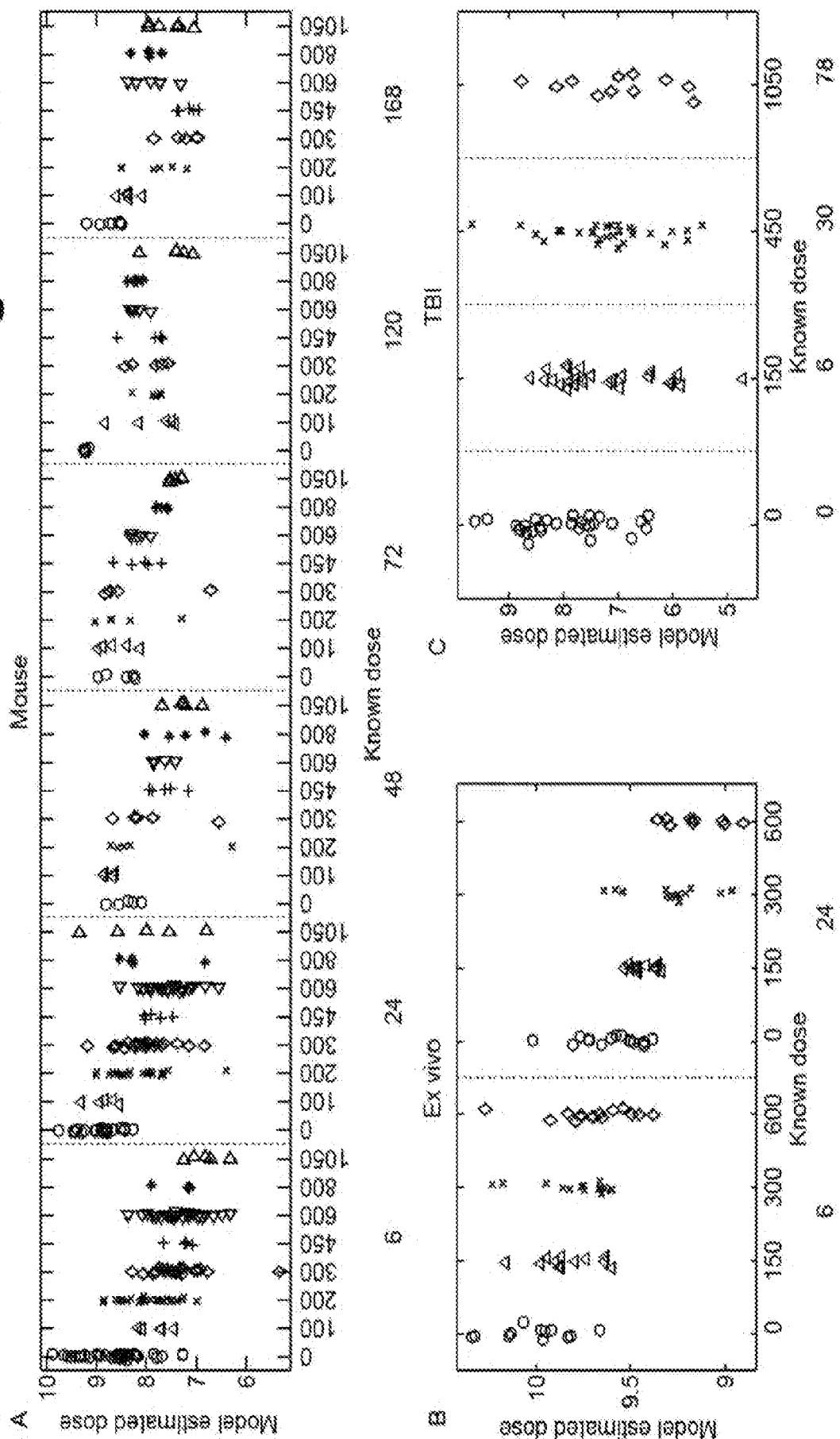


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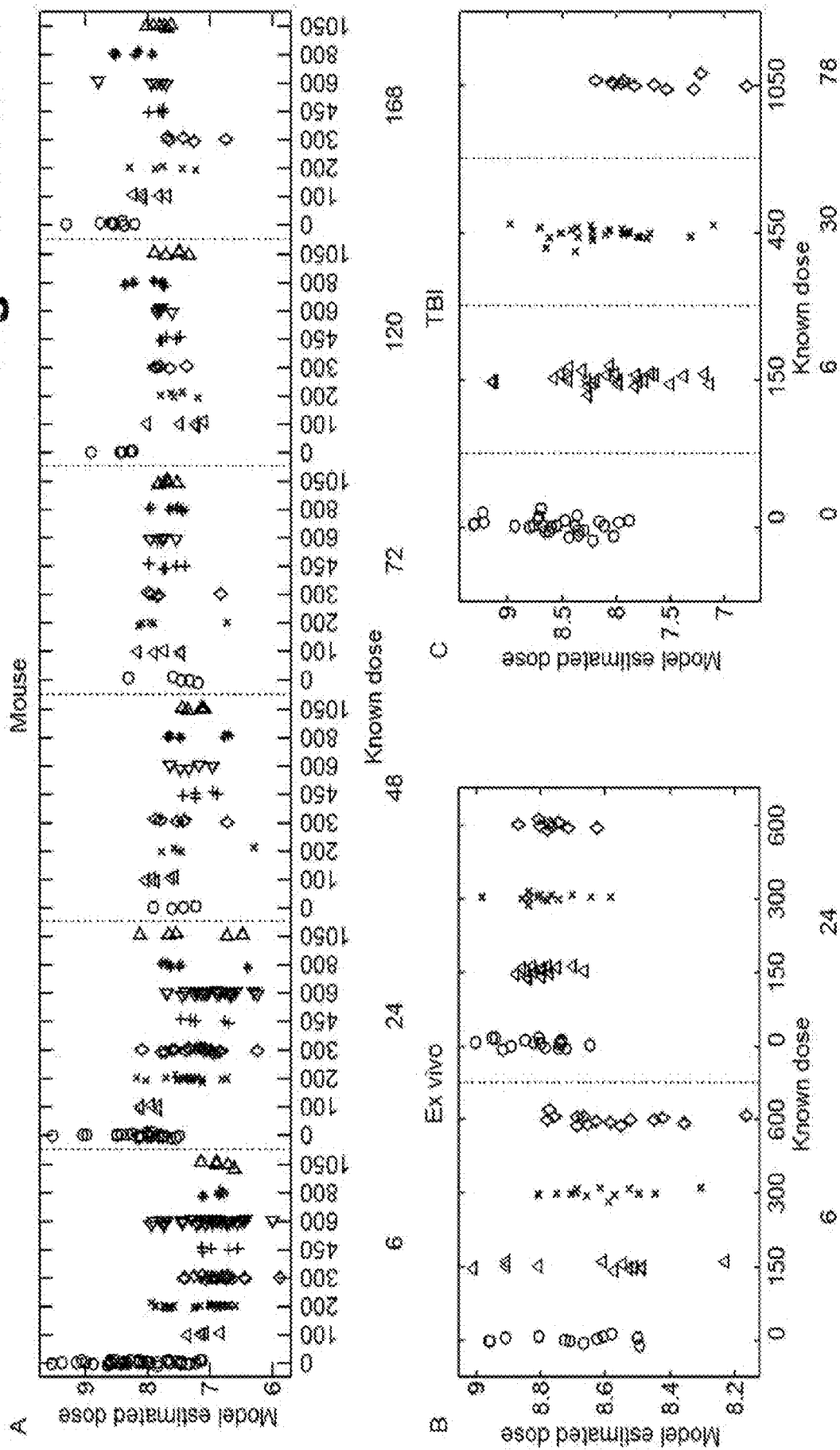
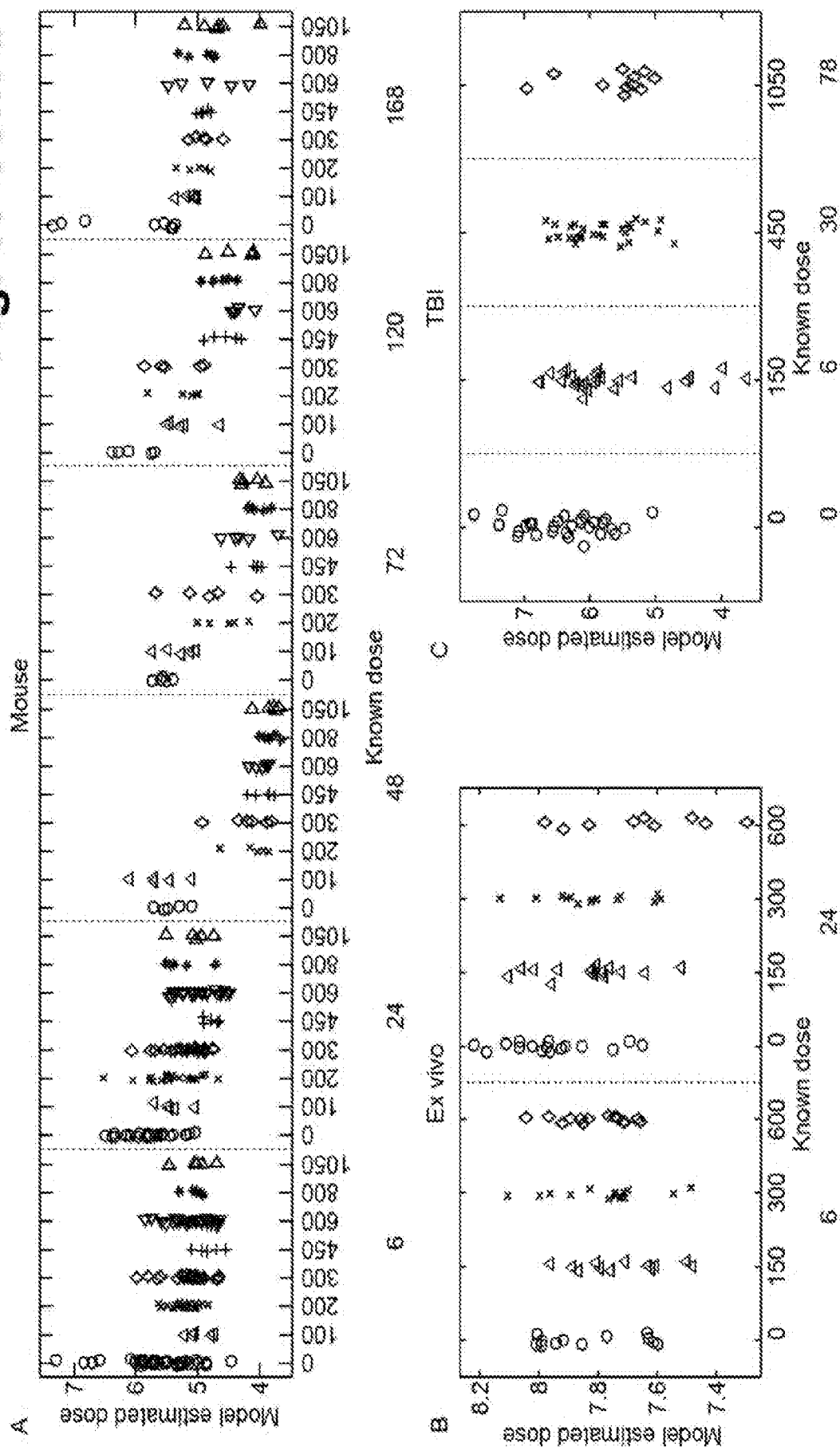
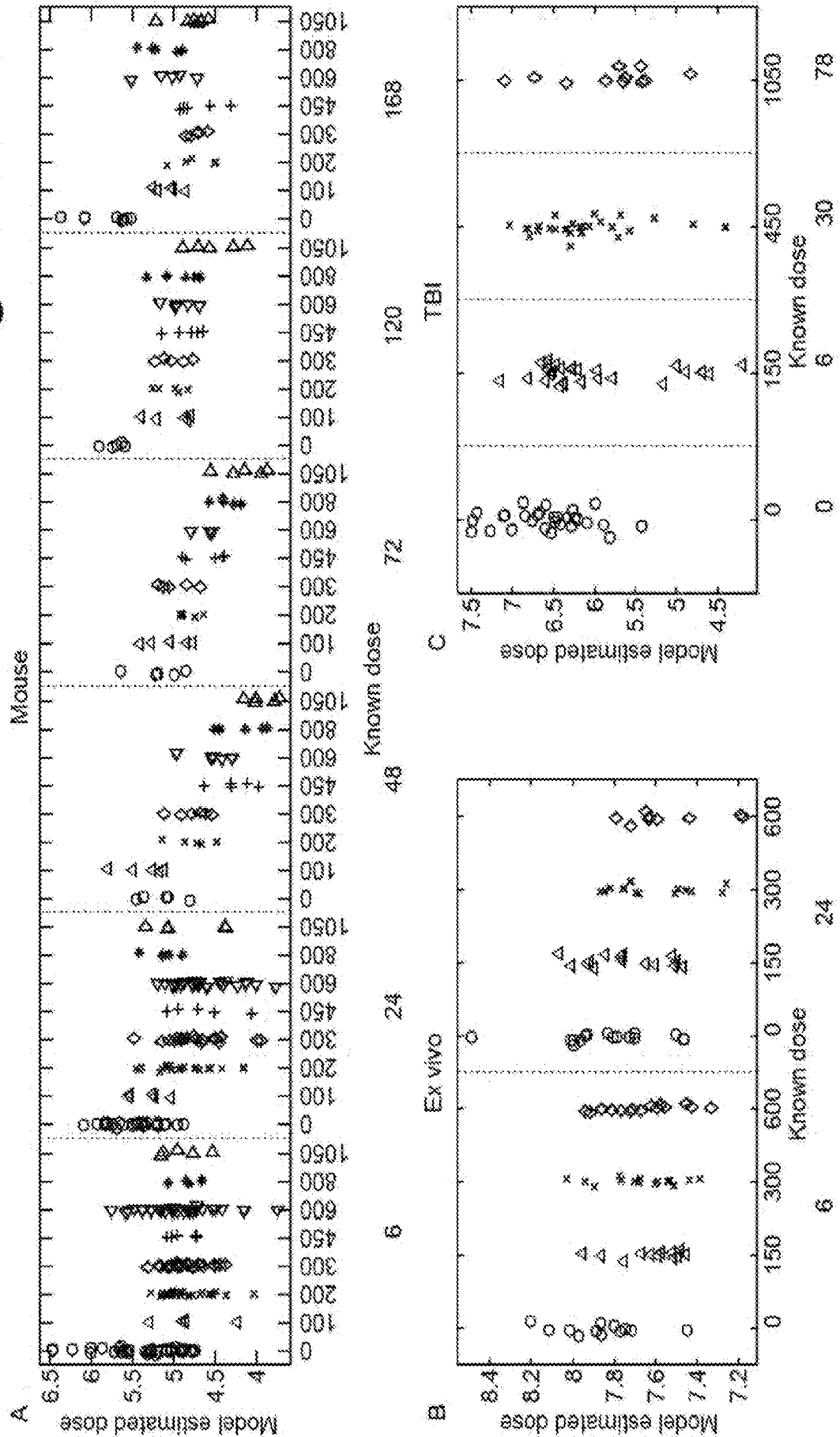


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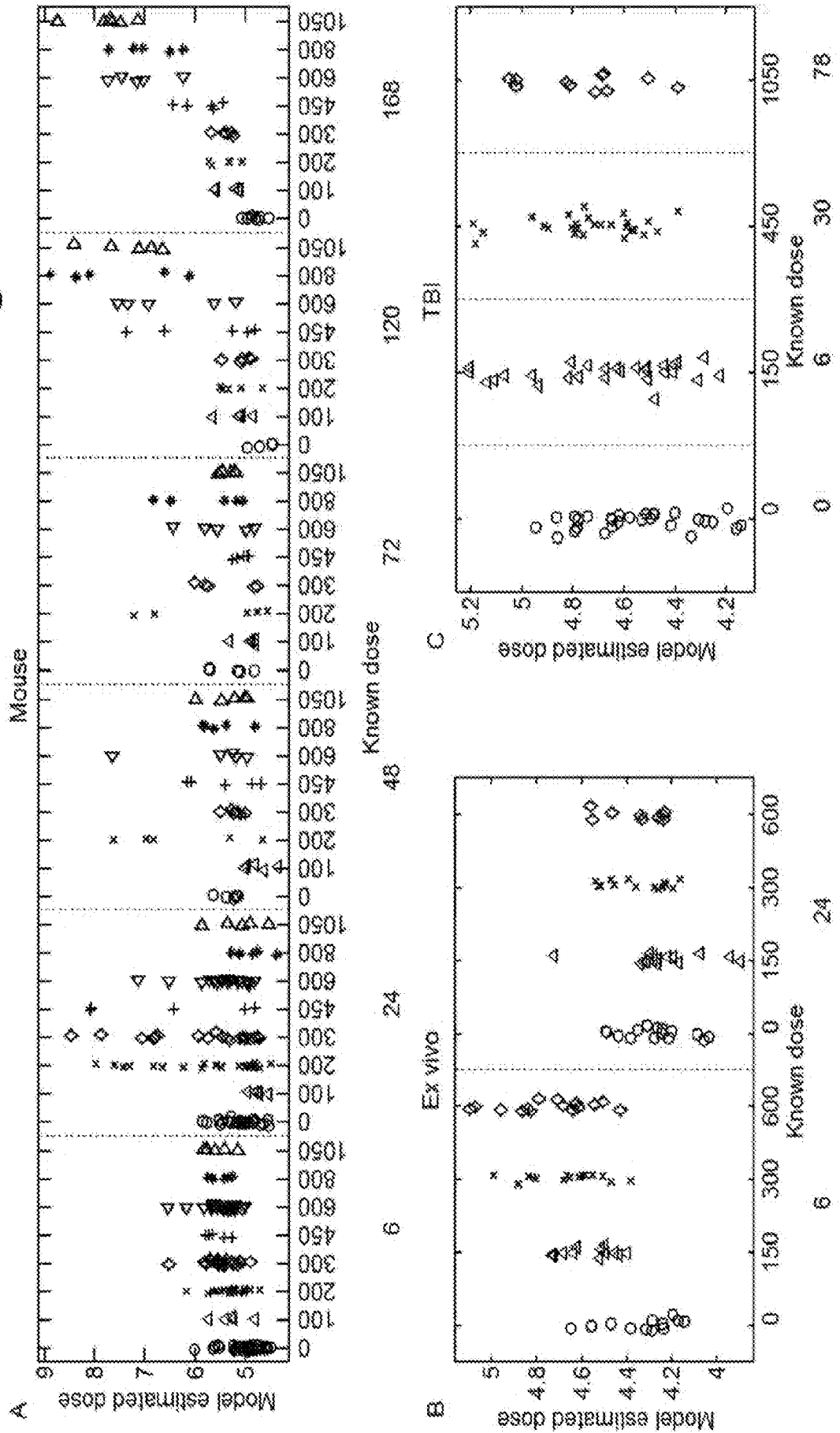
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Fig. 10 Cont'd



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Fig. 10 Cont'd



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Fig. 10 Cont'd

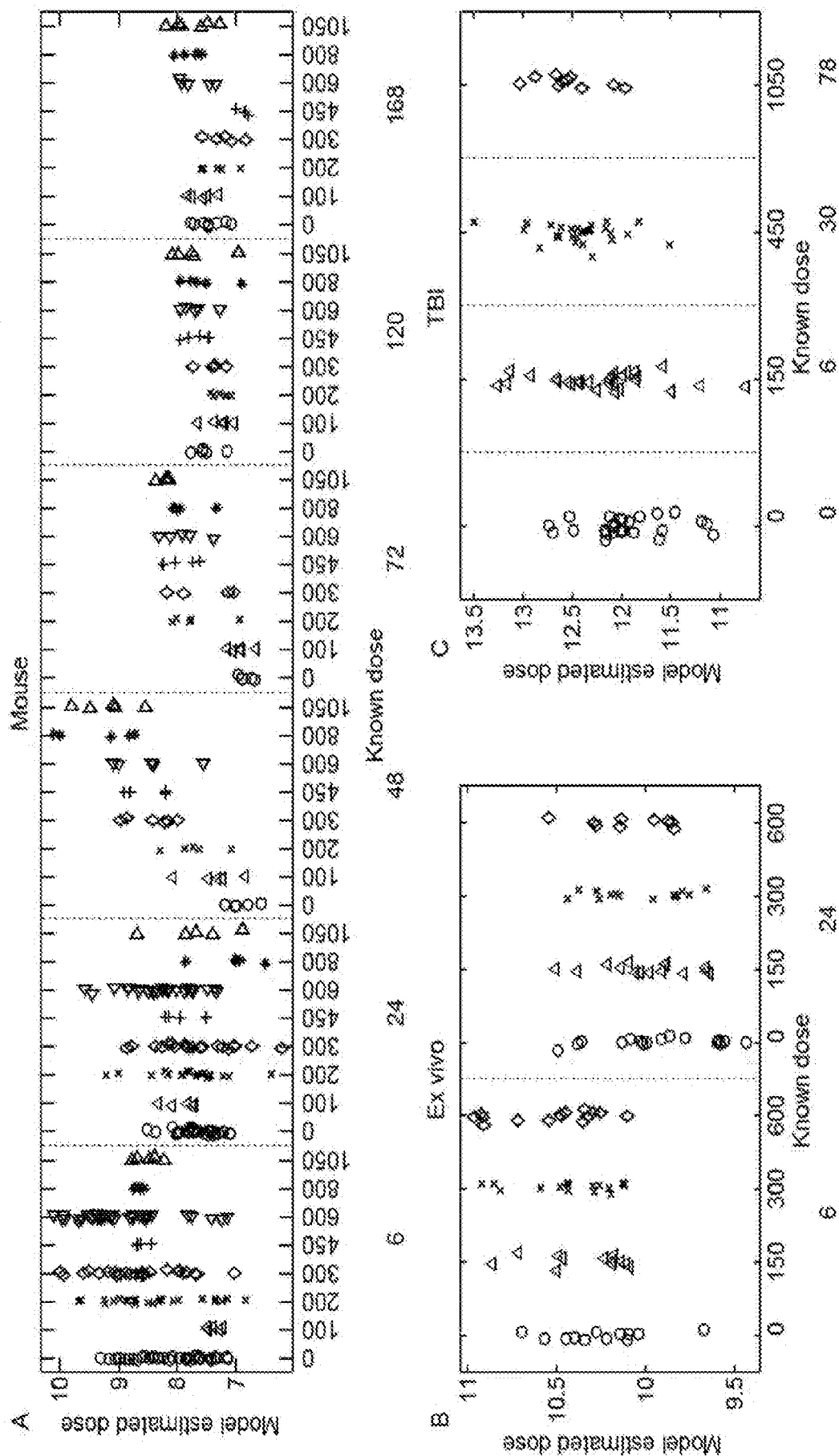


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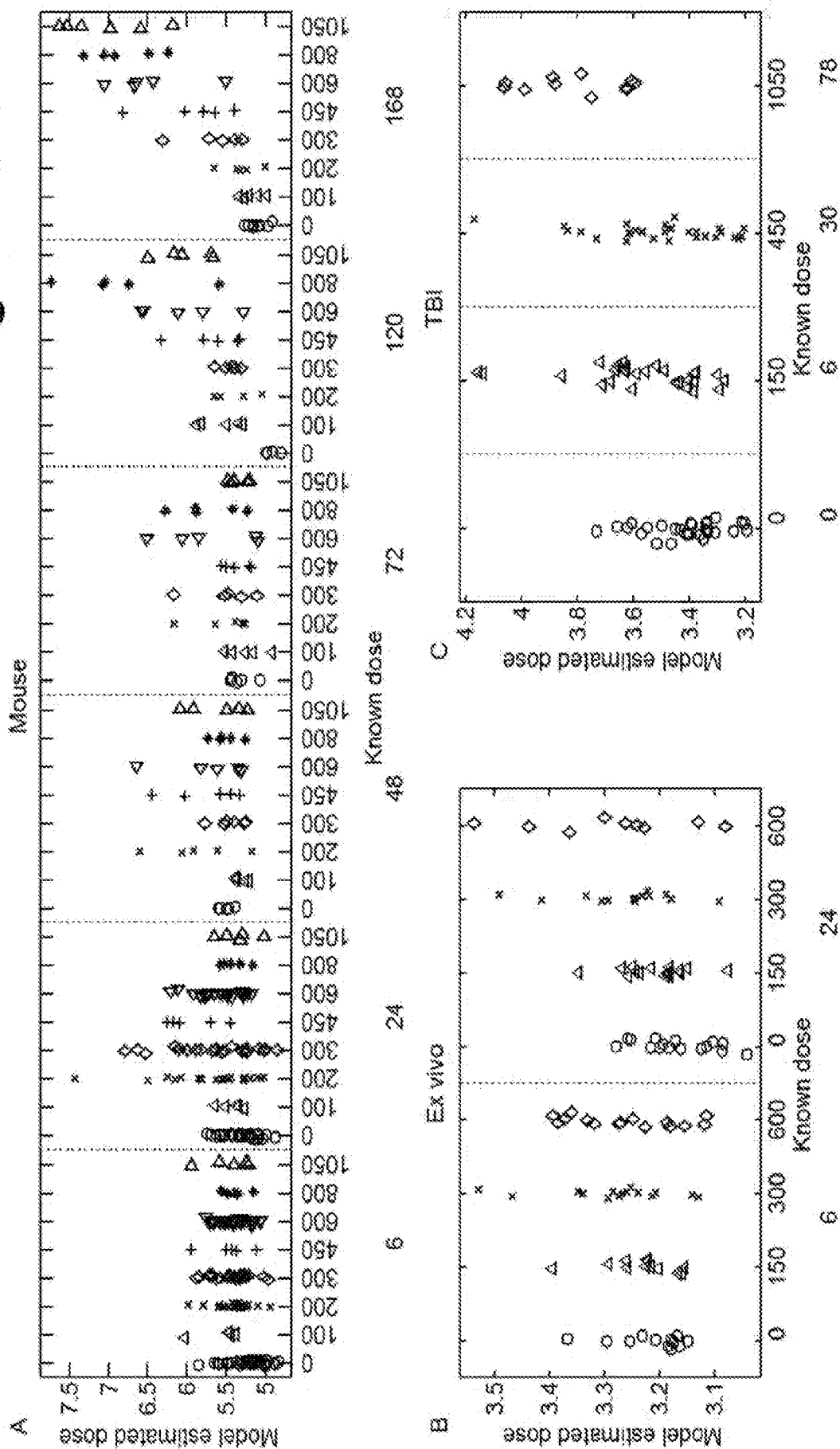


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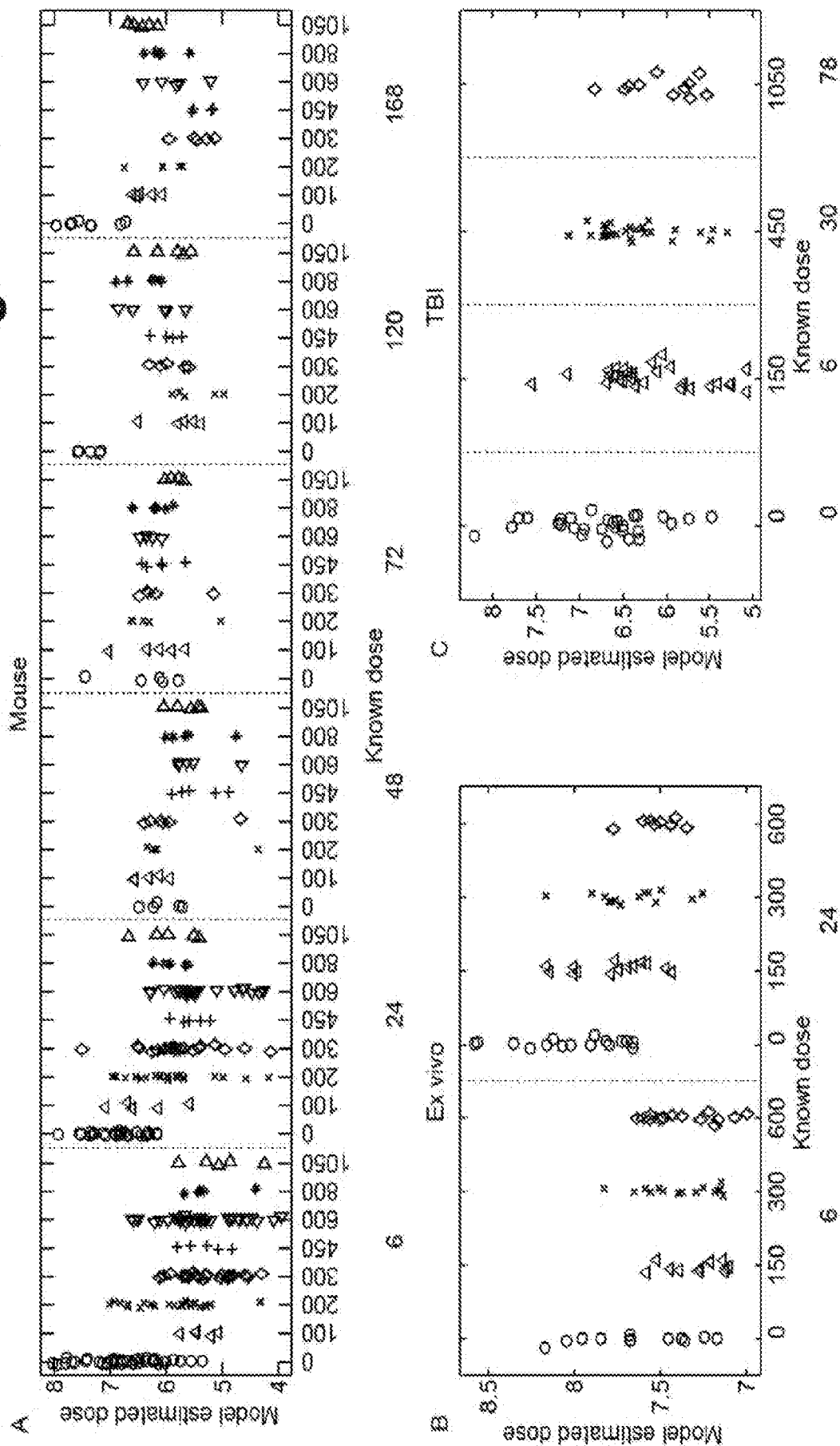


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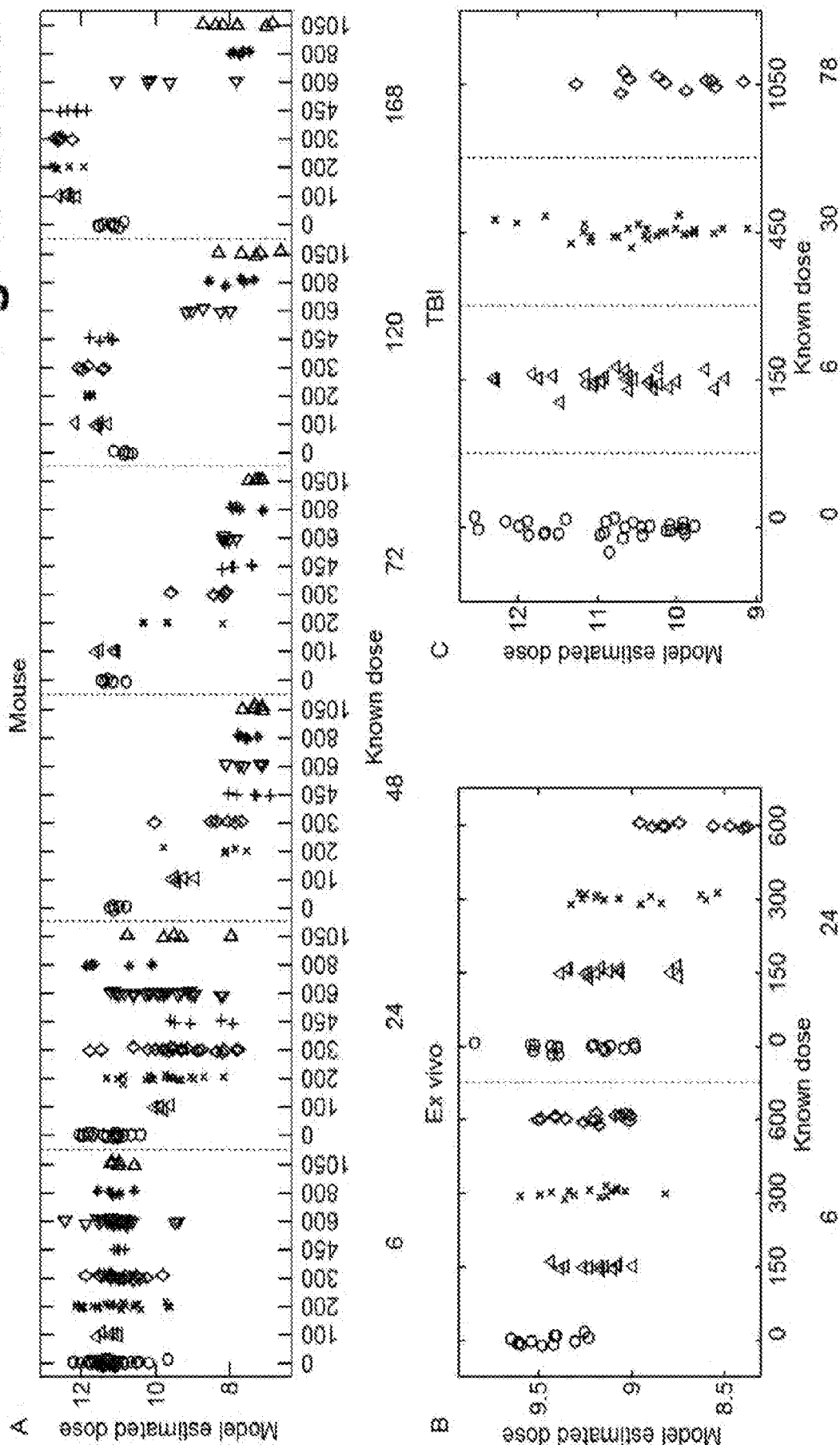


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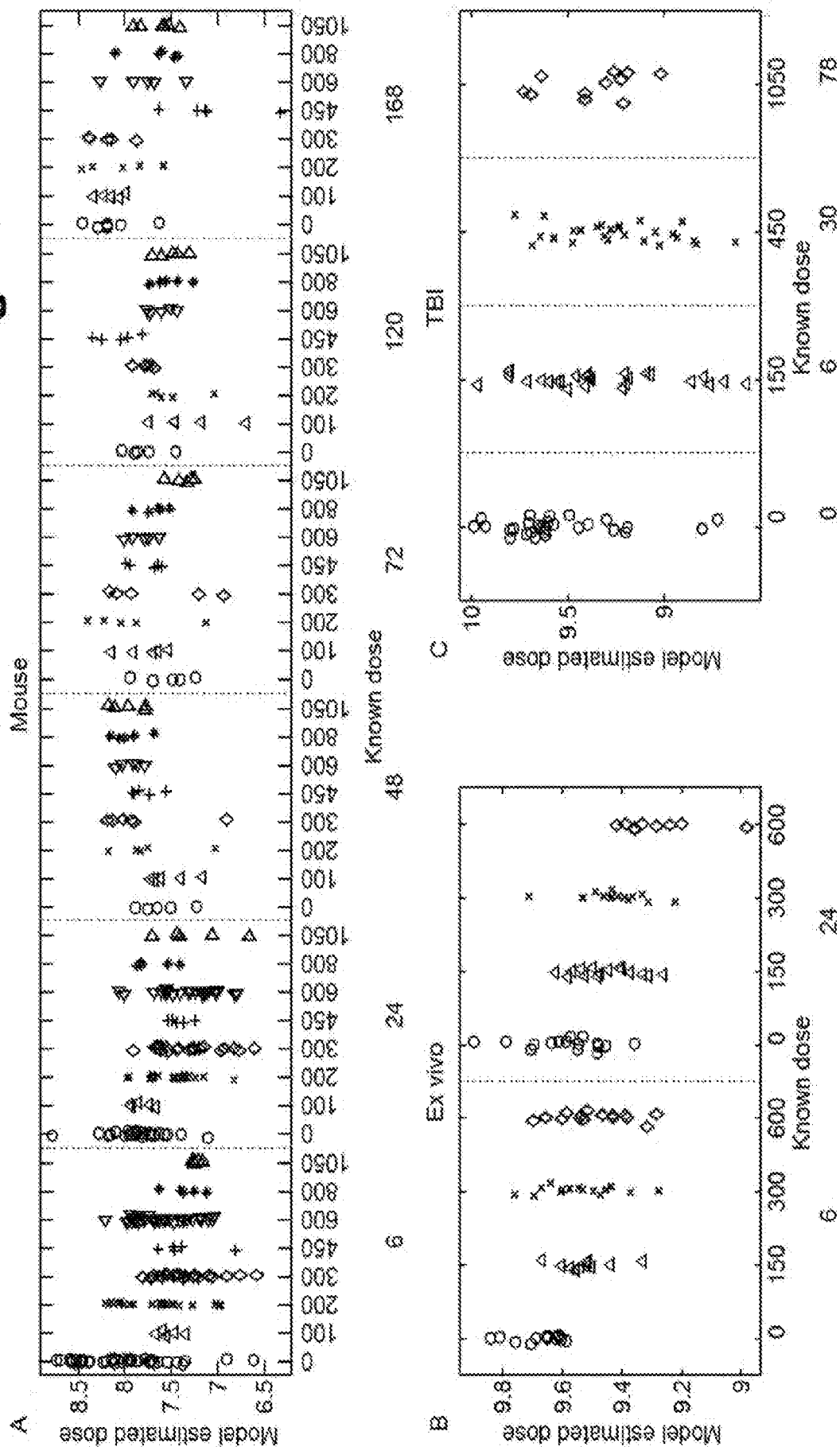


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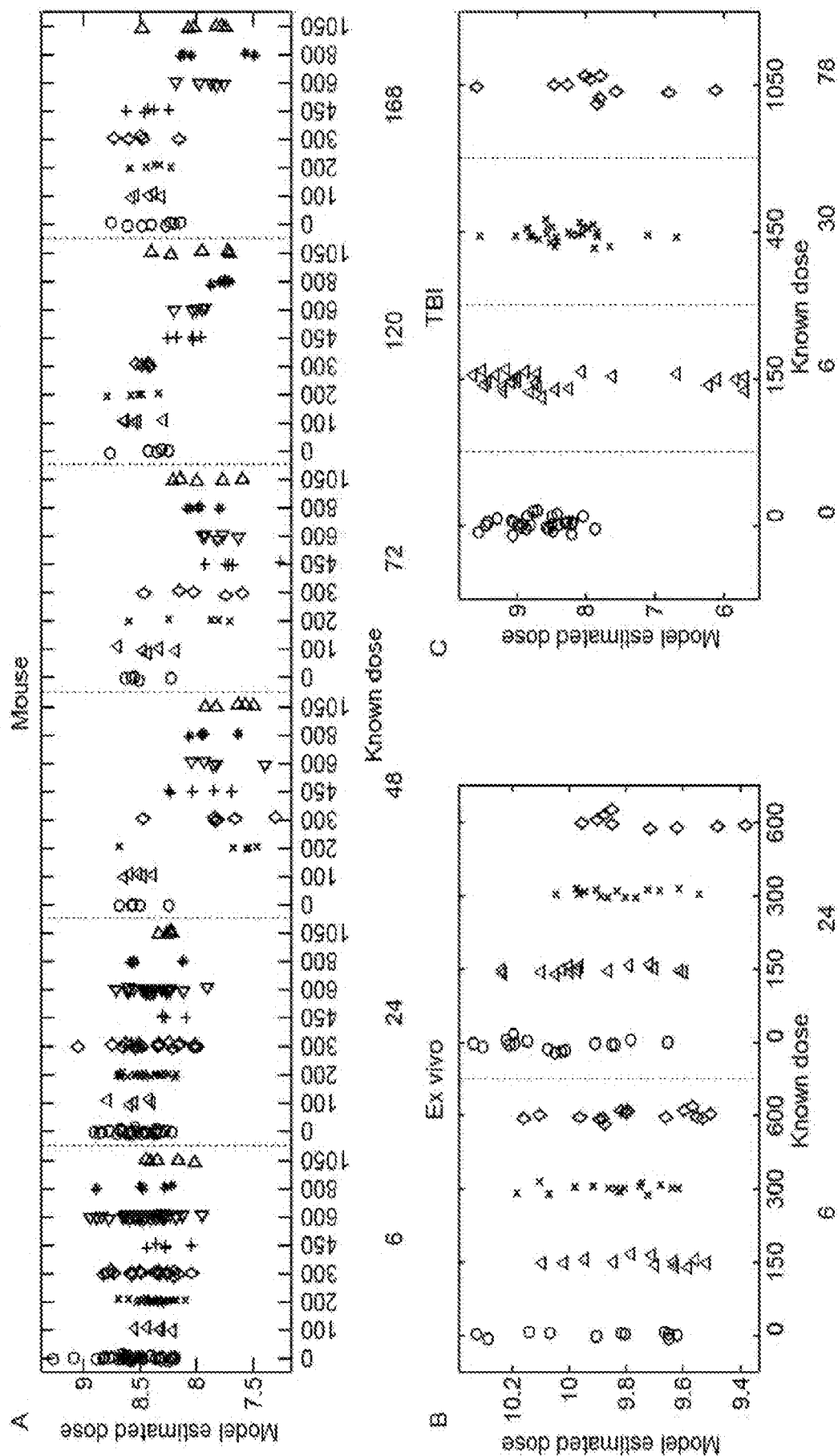


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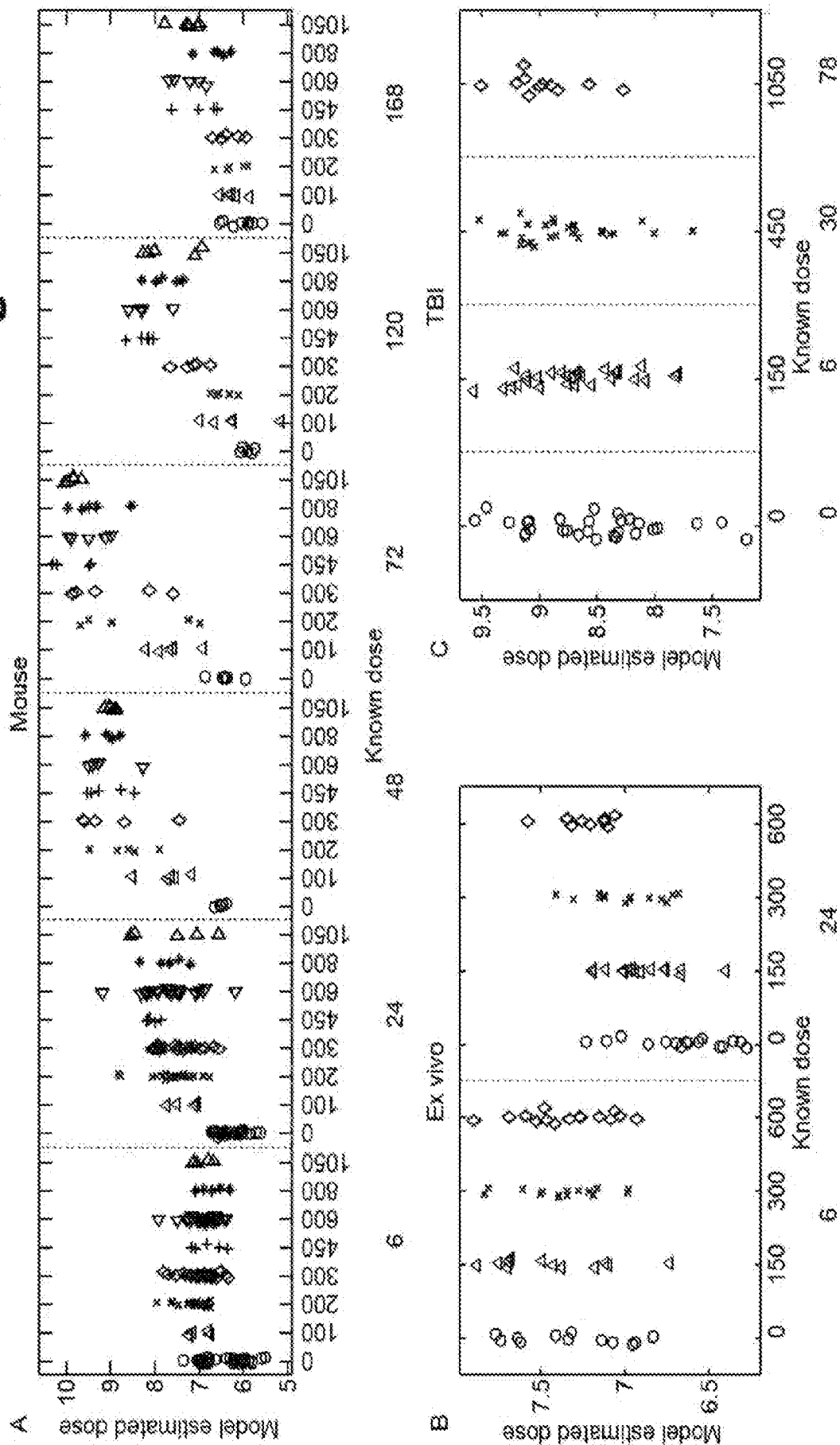


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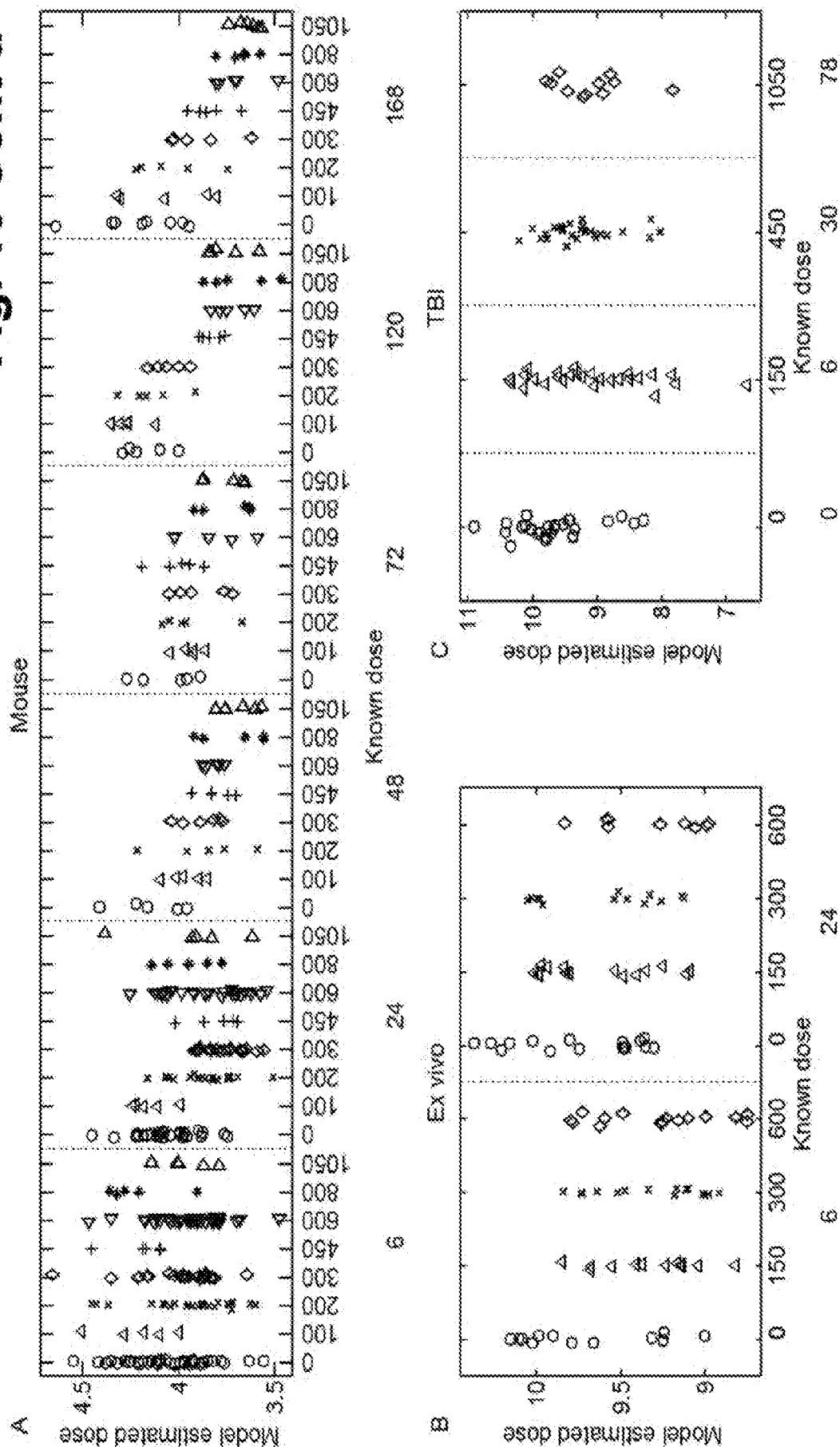


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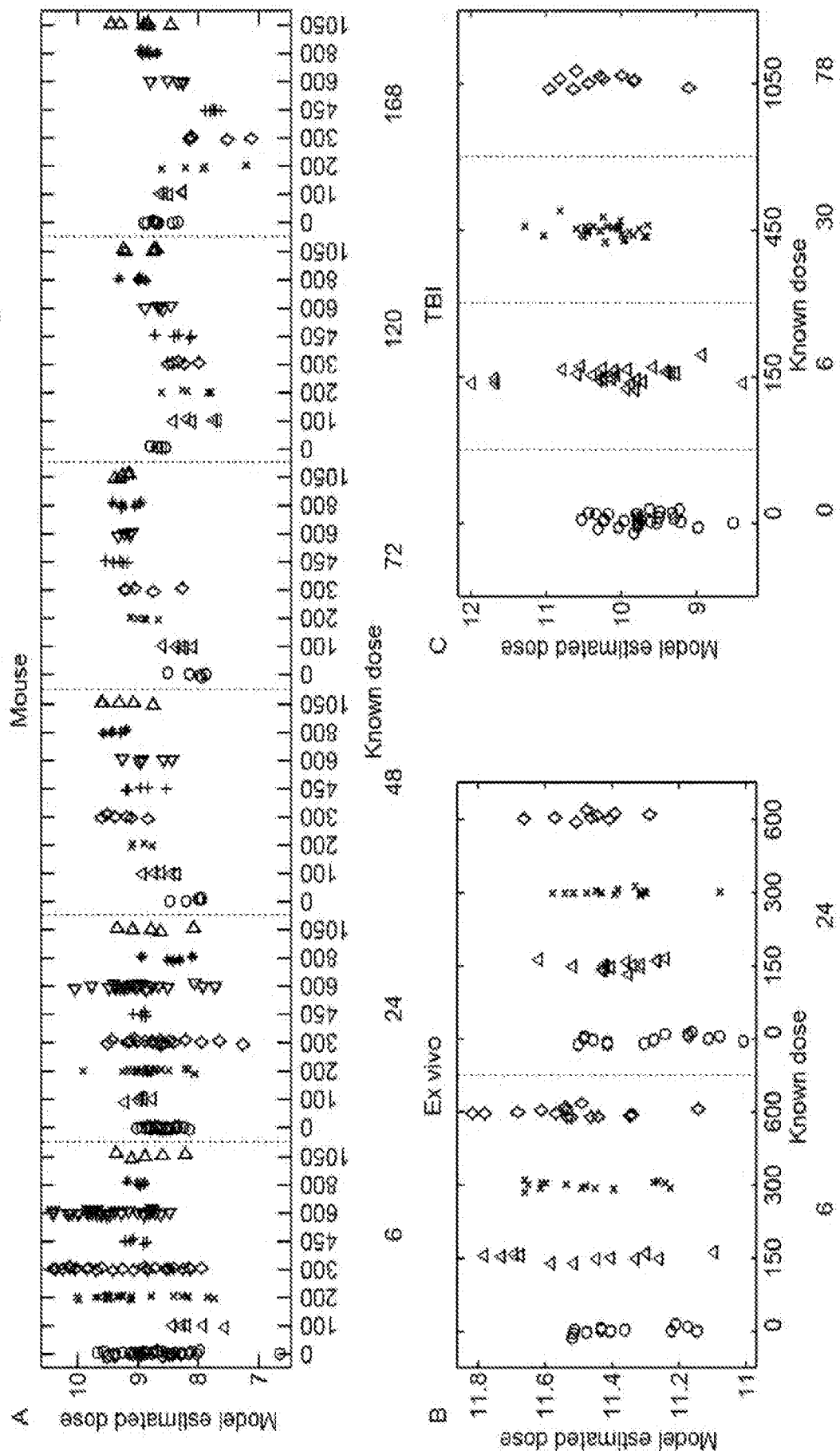


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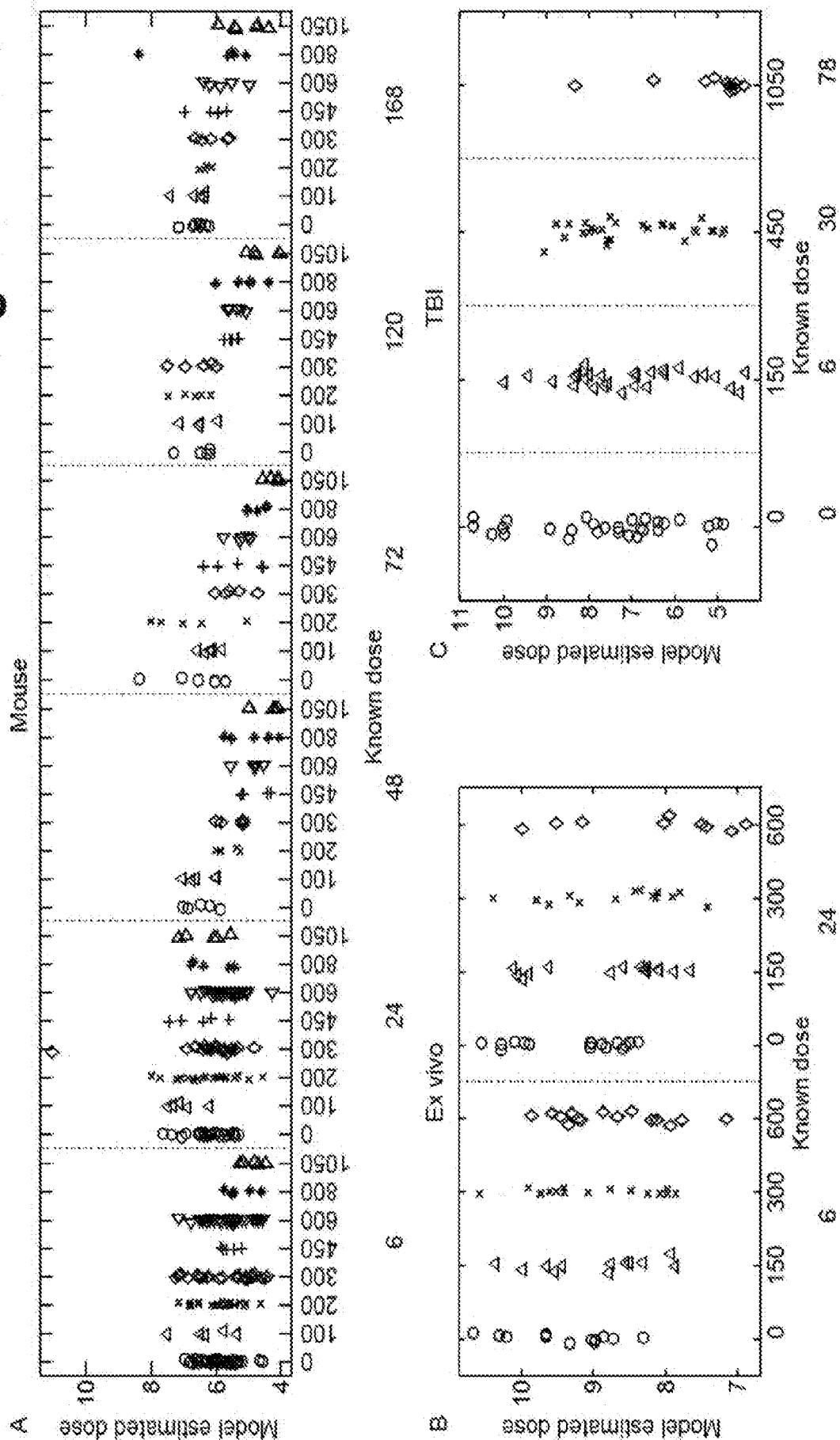


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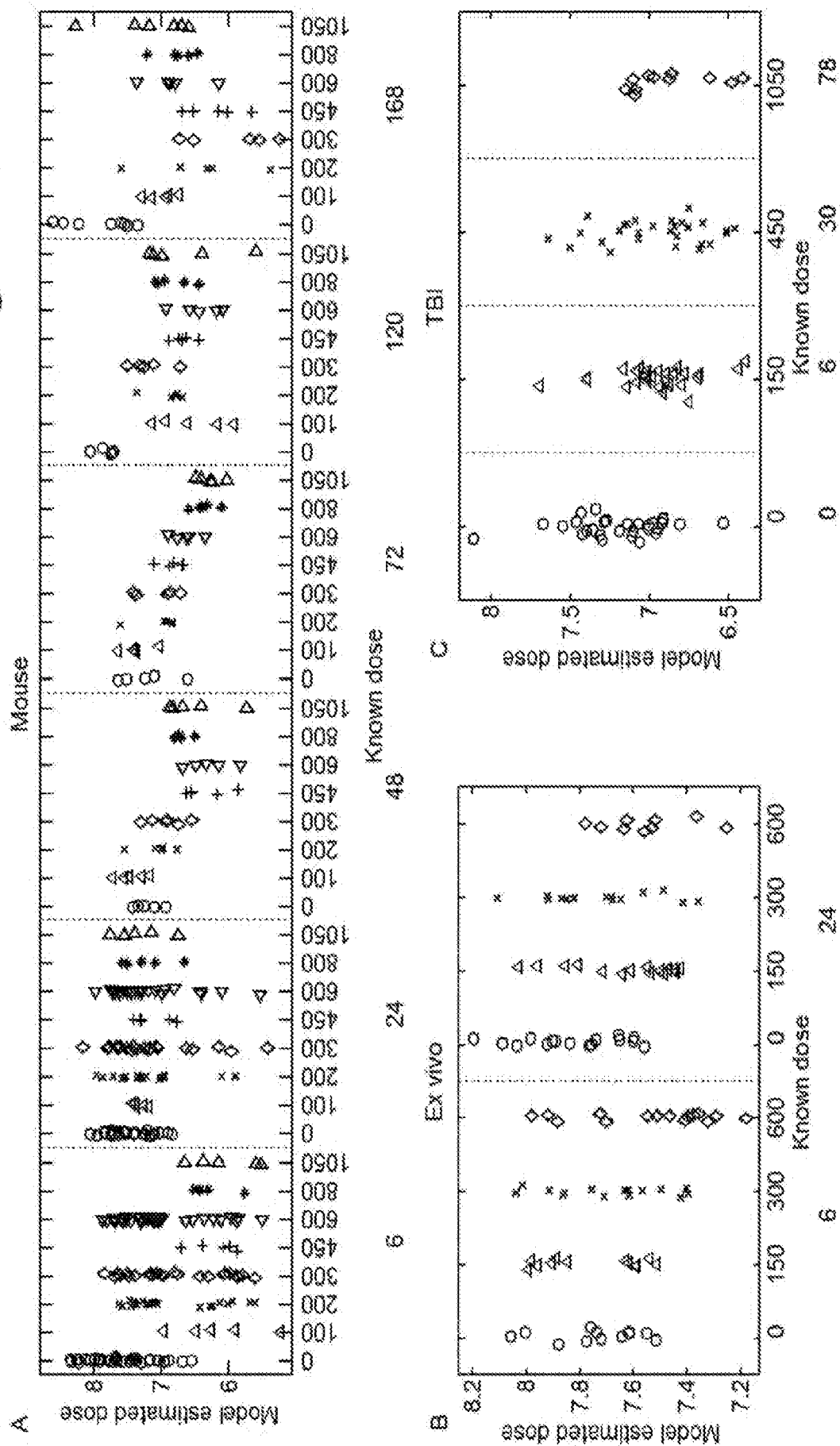


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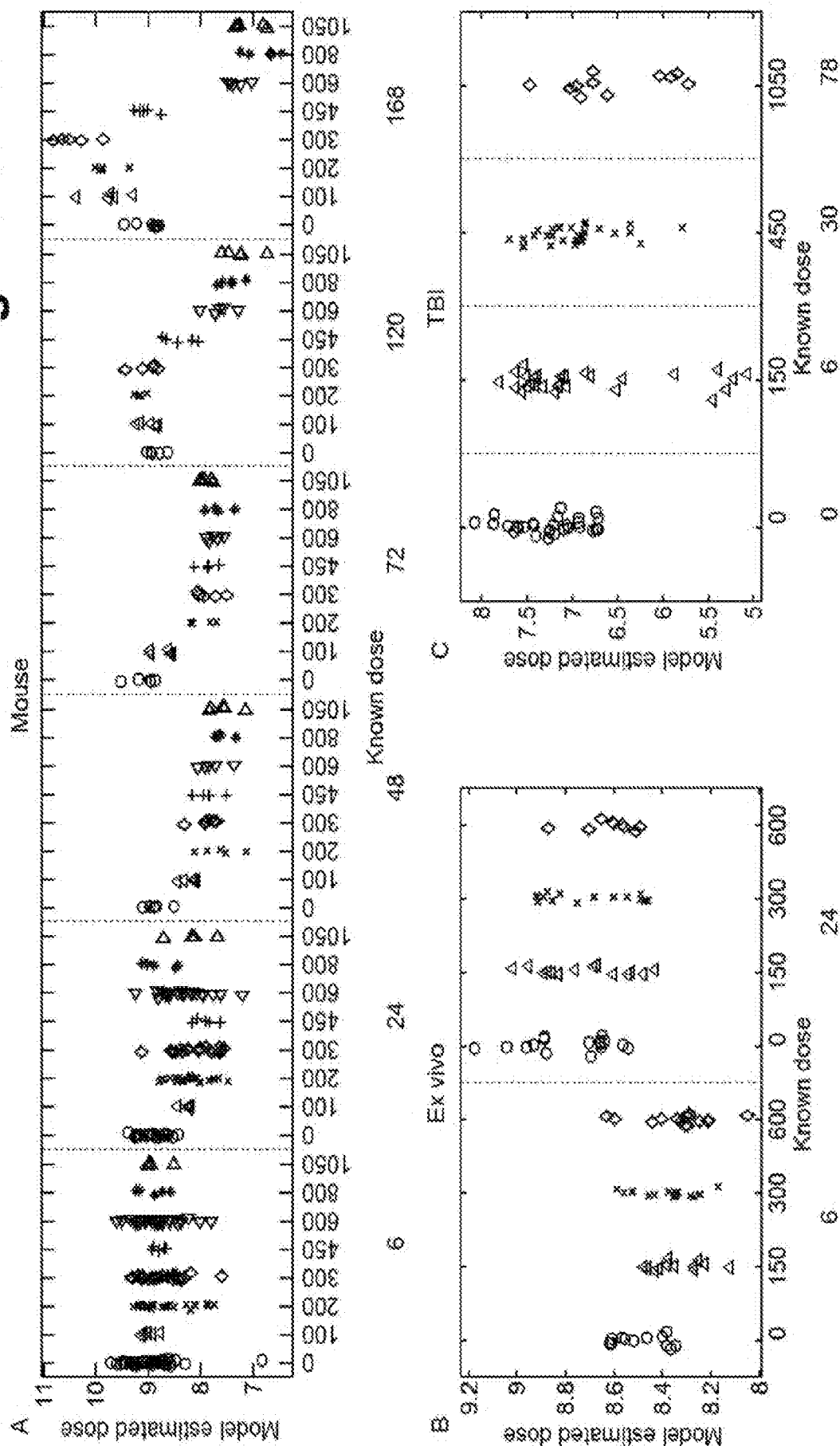


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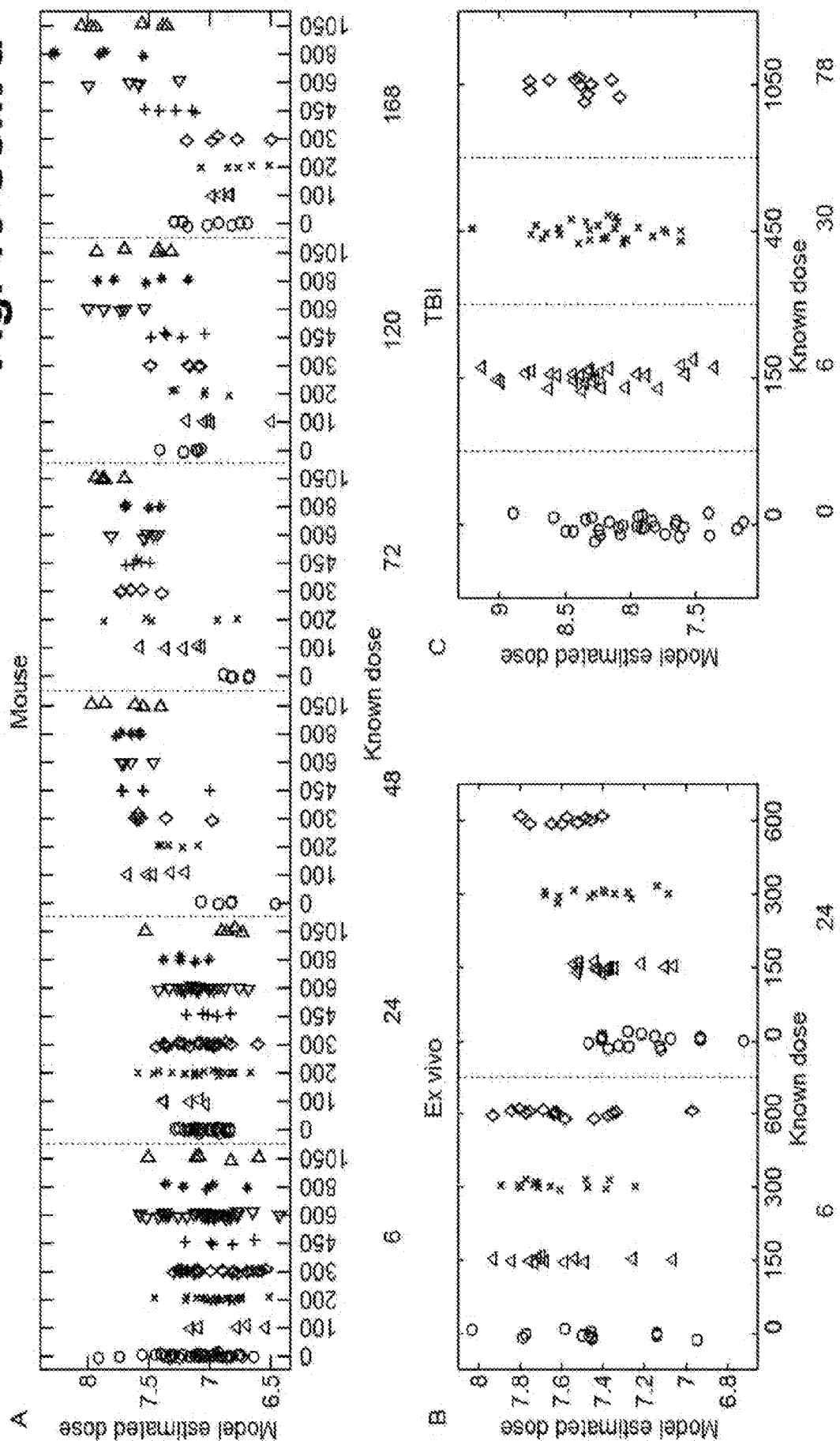


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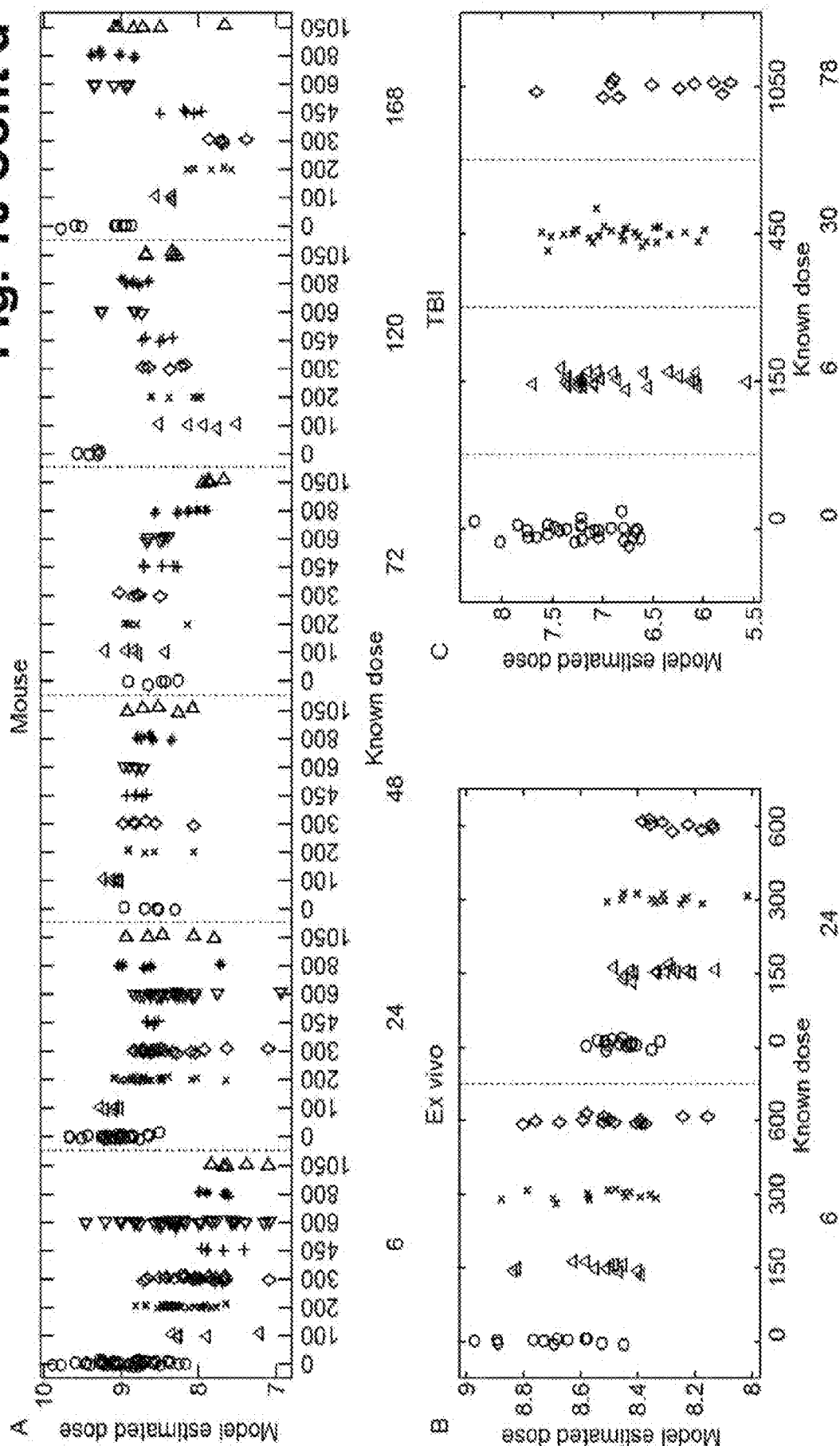


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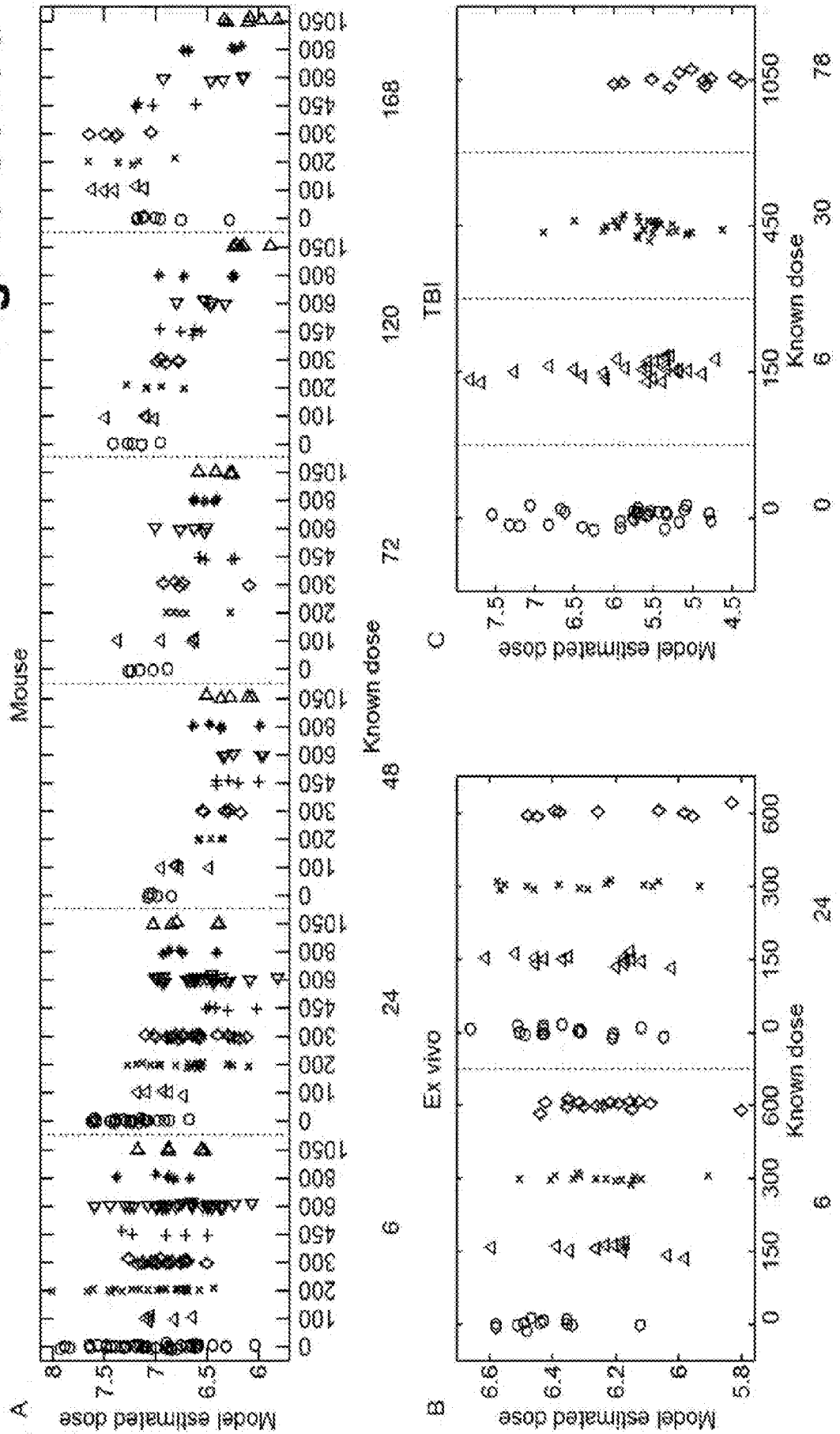


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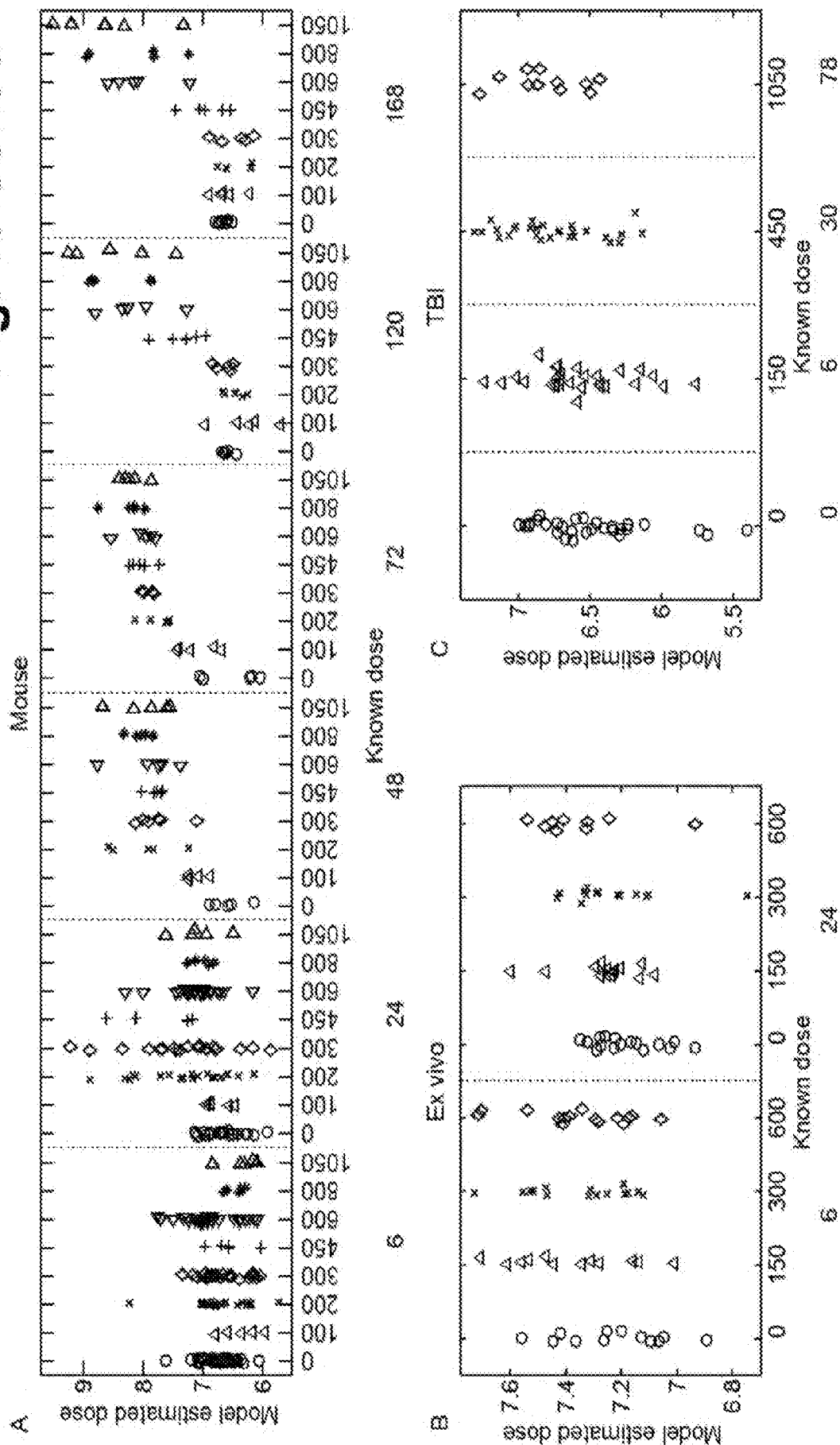


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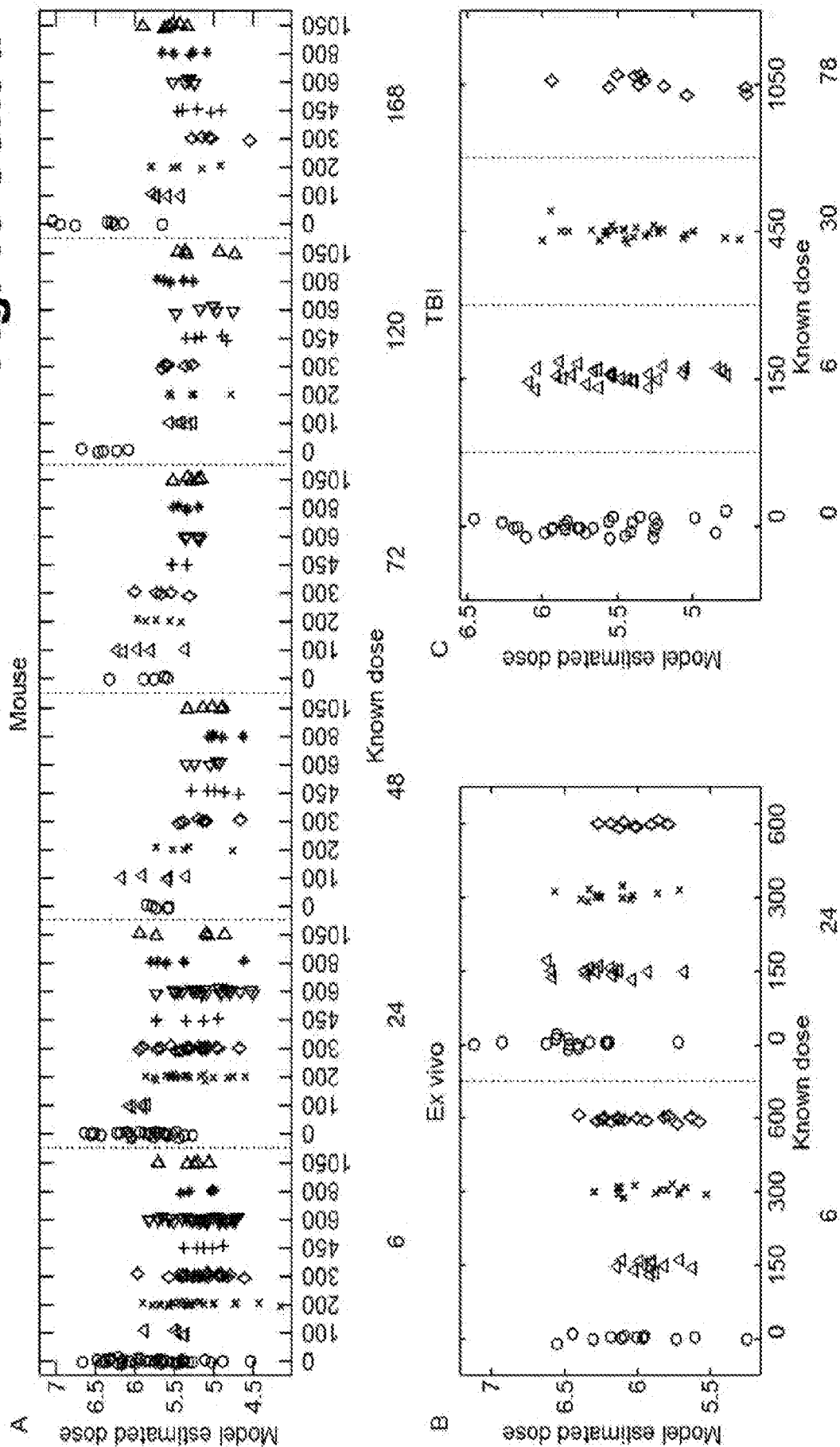
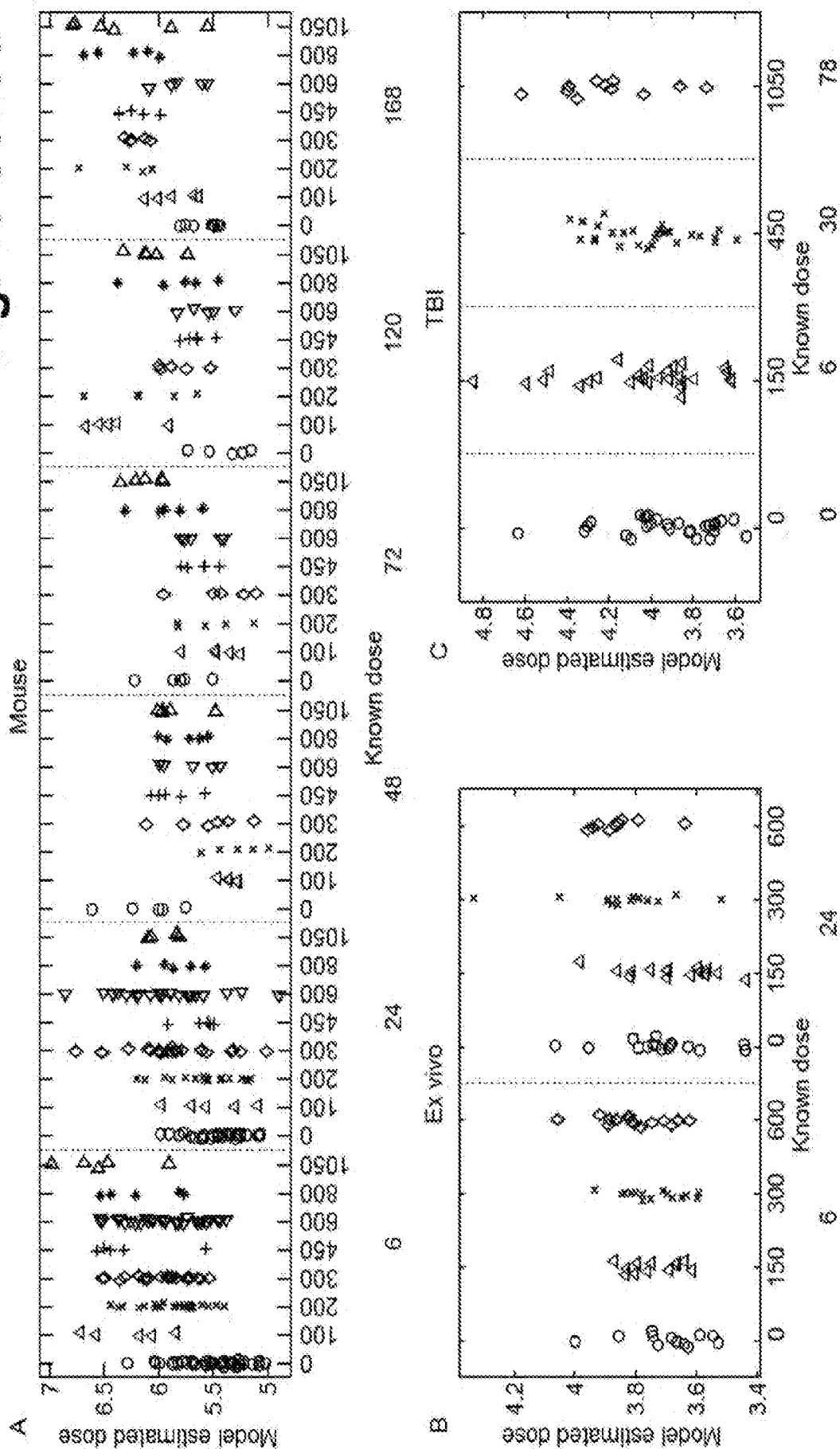


Fig. 10 Cont'd



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Fig. 10 Cont'd

mouse probe publciD	human probe gene title	allcorr-genes.txt corr TBI gene symbol	corr ex vivo	corr mouse
1424638_at	202284_s_at	0.619 0.66193 0.62728 AK007630		
	cyclin-dependent kinase inhibitor 1A (P2L)			
1449002_at	218634_at	Cdkn1a 0.541 0.67746 0.59173 NM_013750		"pleckstrin
	homology-like domain, family A, member 3			
1427005_at	Phlda3			polo-like
	201939_at	0.613 0.49072 0.45095 BM234765		
	kinase 2 (Drosophila)			
1421744_at	Plk2			"tumor
	207426_s_at	0.522 0.70652 0.28324 NM_009452		
	necrosis factor (ligand) superfamily, member 4			
1423315_at	Tnfsf4			BCL2 binding
	211692_s_at	0.493 0.61455 0.36414 AW489168		
	component 3			
1416837_at	Bbc3			
	211833_s_at	0.467 0.54806 0.37976 BC018228		
	BCL2-associated X protein			
1427718_a_at	217373_x_at	Bax		transformed
	mouse 3T3 cell double minute 2	0.388 0.67507 0.31838 X58876		
	Mdm2			
1429582_at	212993_at	0.357 0.56876 0.42769 BB360604		"nucleus
	accumens associated 2, BEN and BTB (POZ) domain containing			
1448511_at	Nacc2			
	204960_at	-0.37 -0.50824 -0.46252 NM_016933		
	"protein tyrosine phosphatase, receptor type, C polypeptide-associated protein			
1452389_at	Ptpnrcap			
	CD27 antigen	-0.417 -0.43777 -0.45949 L24495		
	206150_at			
1460251_at	Cd27			
	216252_x_at	0.367 0.59783 0.29051 NM_007987		Fas (TNF
	receptor superfamily member 6)			
	Fas			

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Fig. 10 Cont'd

1418751_at	205484_at	-0.403	-0.40831	-0.48322	NM_019436
suppression inducing transmembrane adaptor 1					
1425398_at	208579_x_at	0.388	0.5393	0.31663	BC011440
family member	/// predicted gene, OTTMUSG000000013203				"H2b histone
1441342_at	LOC665622 /// RP23-38E20.1	-0.432	-0.34221	-0.49455	BQ030854
dipeptidyl peptidase 4					
1448861_at	204352_at	-0.317	-0.46285	-0.51973	NM_011633
TNF receptor-associated factor 5					
1421098_at	220059_at	-0.231	-0.48356	-0.58221	NM_019992
similar to stem cell adaptor protein STAP-1	/// signal transducing adaptor family member 1				
1450925_a_at	218007_s_at	0.263	0.65914	0.24337	BB836796
protein S27-like					ribosomal
1416957_at	205267_at	-0.325	-0.43936	-0.43535	NM_011136
"POU domain, class 2, associating factor 1					
1448500_a_at	219541_at	-0.369	-0.40751	-0.39013	NM_023684
Lck interacting transmembrane adaptor 1					
1429319_at	204951_at	-0.417	-0.21184	-0.58414	BM243660
"ras homolog gene family, member H					
	RhoH				

allCorr-genes.txt

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Fig. 10 Cont'd

1422921_at	220068_at	allCorr-genes.txt			
pre-B lymphocyte gene 3		-0.216	-0.41069	-0.60374	NM_009514
1418472_at	206030_at	Vpreb3			
aspartoacylase		0.359	0.44159	0.26641	BC024934
1417516_at	209383_at	Aspa			
inducible transcript 3		0.475	0.22834	0.35319	NM_007837
	Ddit3				
1460407_at	205861_at				
Spi-B transcription factor (Spi-1/pu.1 related)		-0.368	-0.28408	-0.4763	BM244106
1418830_at	205049_s_at	SpiB			
CD79A antigen (immunoglobulin-associated alpha)		-0.356	-0.3458	-0.40654	NM_007655
(immunoglobulin-associated alpha)					similar to CD79A antigen
1453573_at	214472_at				
cluster 1, H3d "		0.371	0.40432	0.2737	BB088582
	Hist1h3d				"histone
1424524_at	218627_at				
1200002N14 gene		0.428	0.33067	0.26056	BC021433
	1200002N14Rik				
1460702_at	218403_at				
regulated inhibitor of apoptosis 1		0.228	0.63047	0.21169	AK007514
	Triap1				
1427844_a_at	212501_at				
"CCAAT/enhancer binding protein		0.43	0.21759	0.41959	AB012278
	(C/EBP), beta				
	Cebpb				
1452469_a_at	209427_at				
		0.264	0.50848	0.3136	BF578669
	Smtm				smoothelin
1424716_at	218124_at				
saturase (all trans retinol 13,14 reductase)		0.328	0.48316	0.21699	BB775176
	Retsat				"retinol

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Fig. 10 Cont'd

allCorr-genes.txt				
1427103_at	204436_at	0.408	0.23909	0.4151 AA049040
homology domain containing, family O member 2	plekho2			"pleckstrin
1421963_a_at	201853_s_at	-0.373	-0.31872	NM_023117
cell division cycle 25 homolog B (S. pombe)				
1449156_at	215967_s_at	-0.363	-0.27731	NM_008534
lymphocyte antigen 9				
1425396_a_at	204891_s_at	Ly9	-0.30439	BC011474
lymphocyte protein tyrosine kinase				
1434994_at	202891_at	Lck	0.2367	0.33329 BE199280
effector domain-containing	Dedd			death
1426552_a_at	219498_s_at	-0.207	-0.40074	-0.5177 BB772866
B-cell CLL/lymphoma 11A (zinc finger protein)				
1450309_at	215407_s_at	BC111a	0.32549	0.21102 NM_019514
				astrotactin
1454891_at	212864_at	Astn2	0.295	0.38999 0.35025 BM214378
CDP-diacylglycerol synthase (phosphatidate cytidyltransferase) 2				
1425747_at	219921_s_at	Cds2	0.382	0.20148 0.4579 BC016533
cytokinesis 5				dedicator of
1422503_s_at	208644_at	Dock5	-0.371	-0.21958
"poly (ADP-ribose) polymerase family, member 1				AF126717
		parp1		

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Fig. 10 Cont'd

1448356_at	201345_s_at	allCorr-genes.txt	NM_019912
ubiquitin-conjugating enzyme E2D 2	-0.339	-0.3962	-0.24294
1428213_at	219067_s_at	Ube2d2	AK010349
non-SMC element 4 homolog A (S. cerevisiae)	-0.313	-0.2363	-0.53325
1439323_a.at	214339_s_at	Nsmce4a	88546619
mitogen-activated protein kinase kinase kinase 1	-0.387	-0.28209	-0.31461
1460218_at	34210_at	Map4k1	NM_013706
CD52 antigen	-0.301	-0.44732	-0.23463
1448182_a.at	266_s_at	Cd52	NM_009846
CD24a antigen	-0.31	-0.39079	-0.27628
1422460_at	203362_s_at	Cd24a	NM_019499
MAD2 mitotic arrest deficient-like 1 (yeast)	-0.274	-0.30183	-0.47179
1448957_at	211974_x_at	Mad211	NM_009035
recombination signal binding protein for immunoglobulin kappa J region	0.35	0.34858	0.24753
1428710_at	209882_at	Rbpj	Ras-like
without CAAX 1	0.458	0.20127	0.24657
1416536_at	221290_s_at	Rit1	NM_023431
melanoma associated antigen (mutated) 1	-0.254	-0.31474	-0.47849
1426641_at	202479_s_at	Mum1	BB354684
tribbles homolog 2 (Drosophila)	-0.373	-0.33982	-0.20071
1452457_a.at	201835_s_at	Trib2	"protein
kinase, AMP-activated, beta 1 non-catalytic subunit	0.263	0.43578	0.27368
prkab1			AF108215

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Fig. 10 Cont'd

	allCorr-genes.txt				
1450339_a_at	219528_s_at	-0.332	-0.25382	-0.40917	NM_021399
B-cell leukemia/lymphoma 11B					
1425027_s_at	214838_at	0.264	0.32868	0.38334	BC017549
containing 2					SFT2 domain
1451629_at	Sft2d2	-0.312	-0.29563	-0.32929	BC026827
limb-bud and heart	221011_s_at				
1448417_at	203045_at	Lbh	0.32868	0.42673	NM_013610
		0.224			ninjurin 1
1449269_at	Ninj1	0.263	0.30359	0.38486	NM_007976
factor V	204714_s_at				coagulation
1418154_at	F5	0.349	0.24506	0.29962	NM_030563
binding protein 1	32069_at				NEDD4
1423571_at	N4bp1	-0.276	-0.23591	-0.45768	BB133079
sphingosine-1-phosphate receptor 1	204642_at				
1423293_at	201529_s_at	Slpr1	-0.381	-0.29003	BM244983
replication protein A1					
1424321_at	204023_at	Rpal	-0.279	-0.20604	BC003335
replication factor C (activator 1)					
1449061_a_at	205053_at	Rfc4	-0.264	-0.26139	
primase, p49 subunit					"DNA
	prim1				

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Fig. 10 Cont'd

1417785_at	219584_at	allCorr-genes.txt	
phospholipase A1 member A	0.229	0.34463	0.31401 NM_134102
1419526_at	208438_s_at	Pla1a	
Gardner-Rasheed feline sarcoma viral (Fgr) oncogene homolog	0.355	0.24108	0.20653 NM_010208
1426014_a_at	220075_s_at	Fgr	
protocadherin	0.265	0.29008	0.28991 AF462391
			mucin-like
1456542_s_at	218949_s_at	Mupcdh	
glutaminyl-tRNA synthase (glutamine-hydrolyzing)-like 1	-0.219	-0.31394	-0.3352 BB517855
1433639_at	221249_s_at	Qrs11	
"family with sequence similarity 117, member A	-0.207	-0.31355	-0.34594
1424159_at	212697_at	Fam117a	AW548096
"family with sequence similarity 134, member C	-0.237	-0.36451	BC016089
1417313_at	204559_s_at	Fam134c	
"LSM7 homolog, u6 small nuclear RNA associated (S. cerevisiae)	-0.27	-0.23431	NM_025349
1424595_at	221664_s_at	Lsm7	
		0.212	0.26457 0.39171 BC021876
			F11 receptor
1460286_at	F11r		
septin 6	214298_x_at	-0.236	-0.27134
			-0.32698
1416543_at	201146_at	septin-6	
factor, erythroid derived 2, like 2	0.292	0.26059	0.22969 NM_010902
1424305_at	212592_at	Nfe212	
immunoglobulin joining chain	-0.246	-0.23869	-0.34685
1433702_at	218342_s_at	IgJ	
endoplasmic reticulum metalloproteinase 1	-0.246	-0.26059	-0.31119
		Ermp1	BI663634

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Fig. 10 Cont'd

allCorr-genes.txt				
1449897_a_at	216862_s_at	-0.24	-0.23971	-0.34503
mature T-cell proliferation 1				NM_010839
1460644_at	202030_at	Mtcp1	0.2805	0.26367
chain ketoacid dehydrogenase kinase				NM_009739
1428029_a_at	212206_s_at	Bckdk	-0.29	-0.22078
"H2A histone family, member V				-0.25844
1427468_at	209817_at	H2afv	-0.22555	-0.40766
"protein phosphatase 3, catalytic subunit, beta isoform				M81483
1416772_at	204264_at	Ppp3cb	0.247	0.21761
palmitoyltransferase 2				0.34419
1451141_at	220007_at	Cpt2	-0.227	-0.21441
methyltransferase like 8				-0.37742
1419240_at	221035_s_at	Mettl8	0.28647	0.2828
expressed gene 14				NM_031386
1448560_at	211725_s_at	Tex14	0.278	0.216
interacting domain death agonist				0.23144
1417333_at	212706_at	Bid	-0.249	-0.20206
RAS p21 protein activator 4				-0.29435
		Rasa4		NM_133914

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Fig. 10 Cont'd

1419488_at interacting protein 2	48531_at	allCorr-genes.txt 0.231	0.26855	0.21262	NM_139064	TNFAIP3
1421302_a_at nucleotide binding protein, alpha 15	205349_at	tnip2 0.203	0.21202	0.32868	NM_010304	"guanine
1449584_at "diacylglycerol kinase, gamma	206395_at	Gna15 0.214	0.22954	0.25658	NM_138650	
1426025_s_at lysosomal-associated protein transmembrane 5	201721_s_at	Dgkg 0.203	0.23818	0.26071	U29539	
1433878_at mitochondrial ribosomal protein S26	213795_s_at	Laptm5 -0.204	-0.21958	-0.27873	AI648866	
1448383_at metallopeptidase 14 (membrane-inserted)	217279_x_at	Mrps26 0.209	0.22396	0.2449	NM_008608	matrix
1428067_at family 12	219167_at	Mmp14 0.201	0.20809	0.2713	AK014511	"RAS-like,
	" ras112					

A. CLASSIFICATION OF SUBJECT MATTER**C12Q 1/68(2006.01)i, C12N 15/11(2006.01)i, G01N 33/48(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12Q 1/68; C40B 30/00; A61P 35/00; C40B 60/12; A61K 38/17; C12N 15/11; G01N 33/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: irradiation, identifying, RNA, CLPA-RET Assay, gene expression profile

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 10-2009-0034011 A (KOREA INSTITUTE OF SCIENCE AND TECHNOLOGY) 7 April 2009 See abstract, claims 1, 4, 12, 14 and paragraph [53].	9-11
X	US 2009-0023149 A1 (KNUDSEN) 22 January 2009 See abstract and claims 1-18, 30, 34.	9-11
X	WO 2008-082712 A2 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK et al.) 10 July 2008 See abstract and claims 1, 36, 57.	9-11
A	KR 10-2009-0121842 A (KOREA INSTITUTE OF SCIENCE AND TECHNOLOGY) 26 November 2009 See abstract and claim 1.	9-11
A	US 2009-0062196 A1 (D'ANDREA et al.) 5 March 2009 See abstract and claims 28-34, 43.	9-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

11 December 2013 (11.12.2013)

Date of mailing of the international search report

11 December 2013 (11.12.2013)

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2013/000218**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-8
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-8 pertain to diagnostic methods for the human body, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2013/000218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 2009-325900 A8	02/07/2009
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