Supplementary Materials

dendPoint: a web resource for dendrimer pharmacokinetics investigation and prediction

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Supplementary Methods

Machine learning algorithms

Random Forest is an ensemble supervised learning method that is based on the construction of a number of small/simple base predictors using decision trees (forest), outputting the average prediction in case of regression tasks or the mode in case of classification.

Supplementary Figures

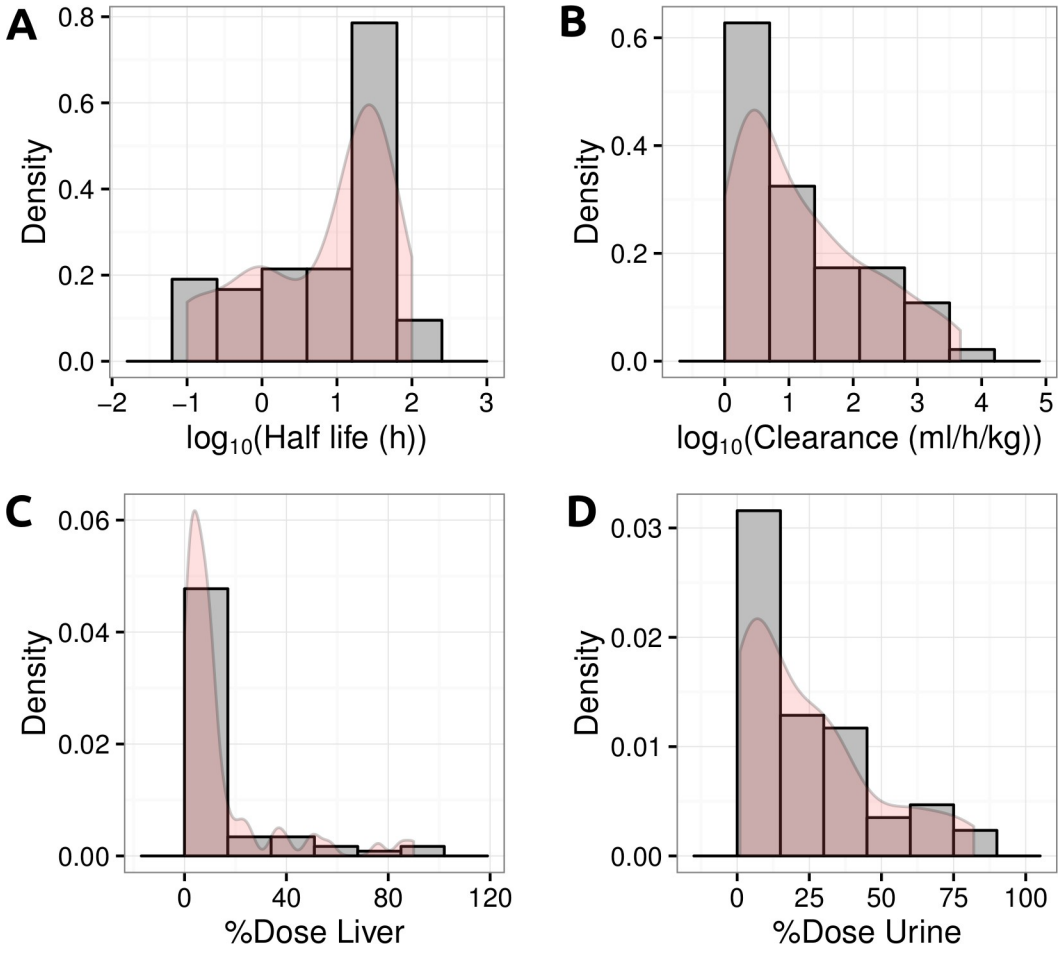

Figure S1: Distribution of experimental pharmacokinetics parameters for dendrimer constructs on the database.

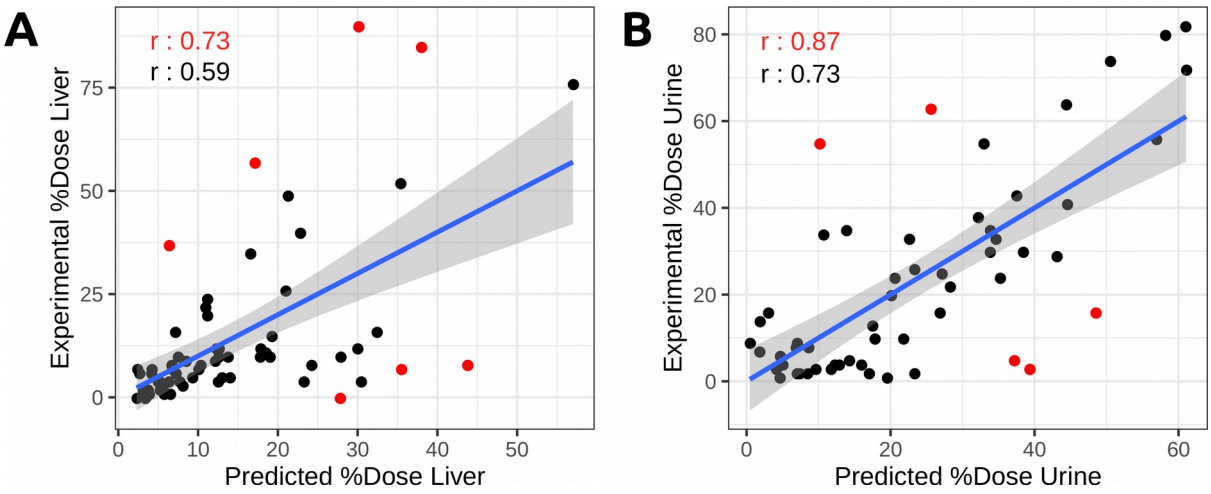

Figure S2: Predicting the percentage of dose that is recovered in the liver and urine. The graphs depict the regression plot between experimental and predicted %Doses for Liver (left-hand side graph) and Urine (right-hand side graph), which obtained of up to r=0.87 after 10% outliers were removed (shown in red).

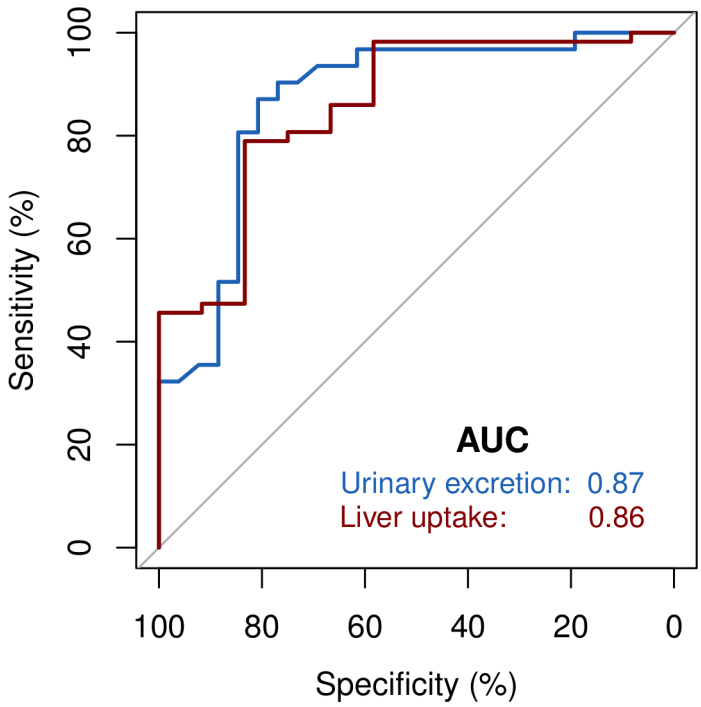

Figure S3: ROC curves dendrimer construct classification according to liver uptake and urinary excretion. Both predictions achieved an accuracy of 80% on these tasks, achieving AUCs of 0.87 and 0.86 for urinary excretion and liver uptake, respectively.

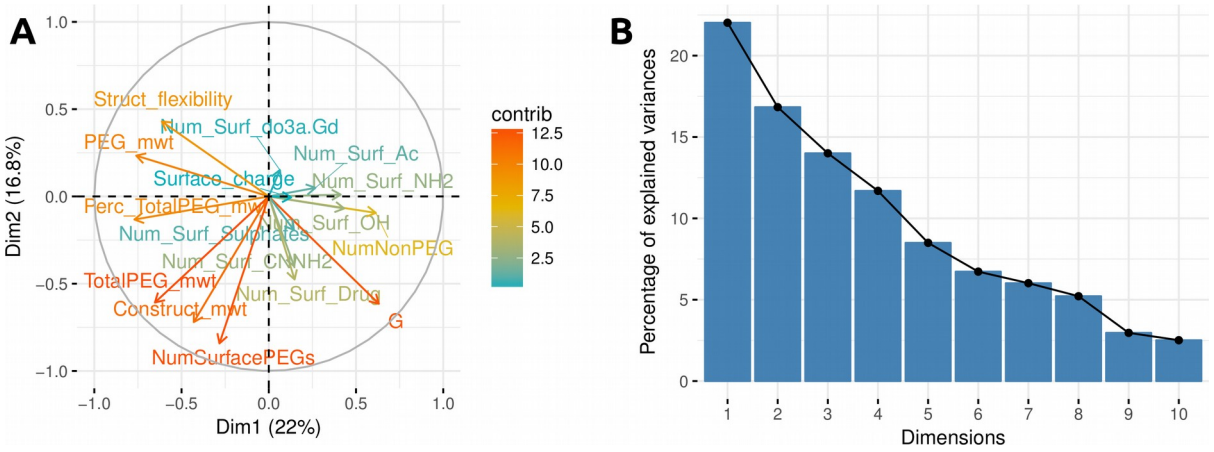

Figure S4: PCA analysis for he Half Life data set. The left-hand figure depicts the contribution of each feature to explain the variability of the data set. The right-hand figure shows a histogram of the percentage of explained variance per feature.

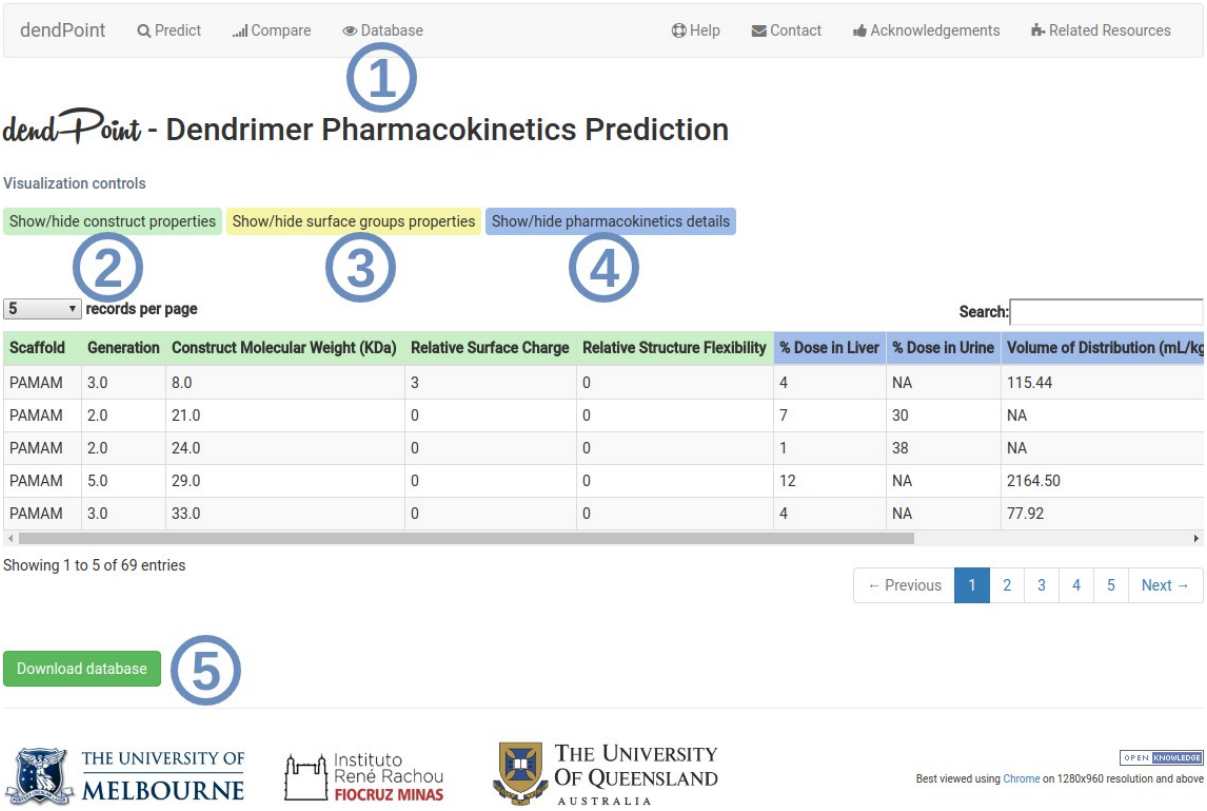

Figure S5: dendPoint database. The figure depicts the web-based interface for browsing the relational database linking dendrimer properties and pharmacokinetic behavior. By accessing the browsing option (1), users have the option to show/hide different properties (2,3,4) as well as download the full contents of the database (5).

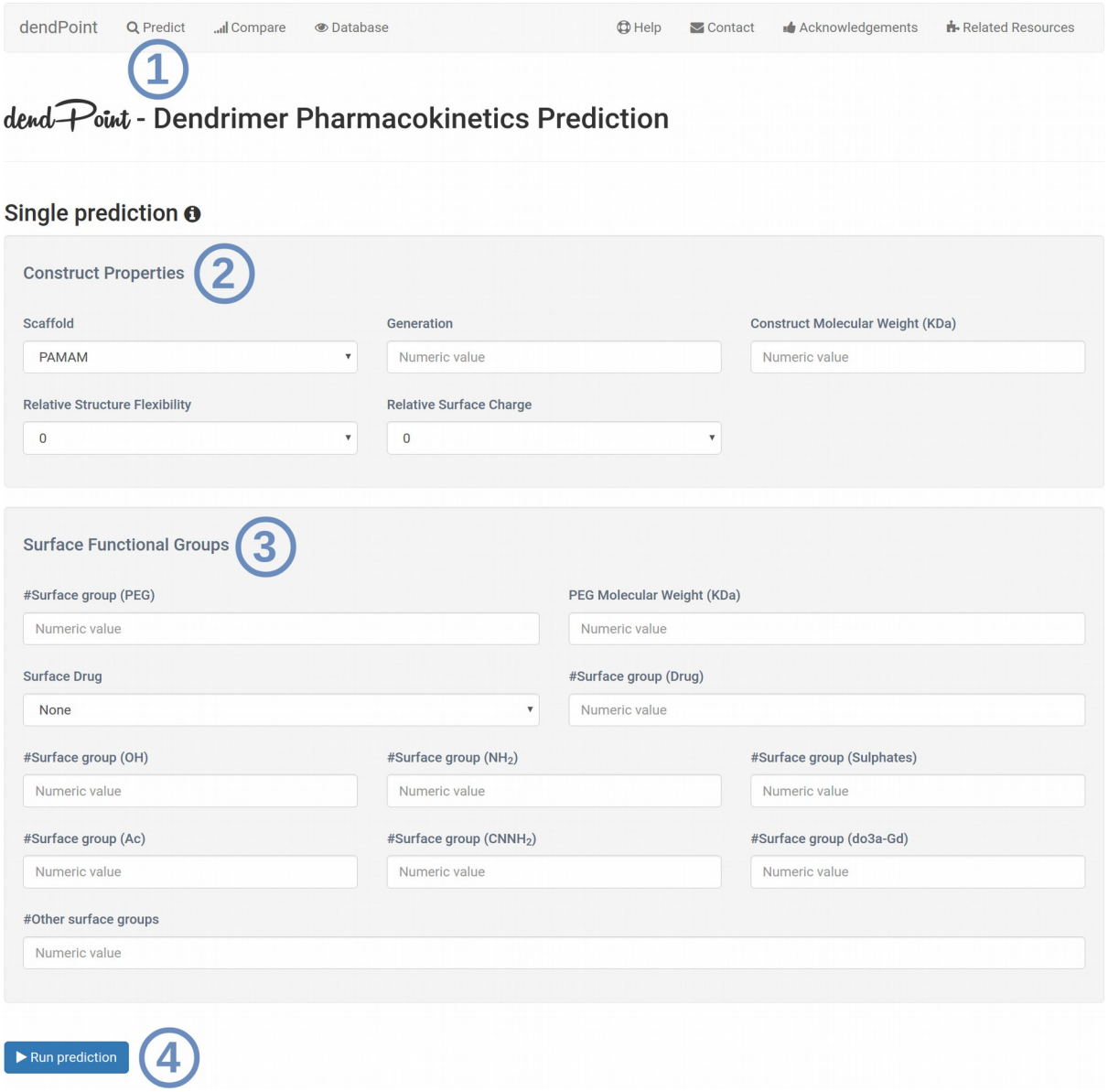

Figure S6: dendPoint submission page. The figure depicts the web-based interface for job submission. By selecting the prediction mode (1), users can specify different construct properties (2) and surface functional groups (3) prior to submission (4).

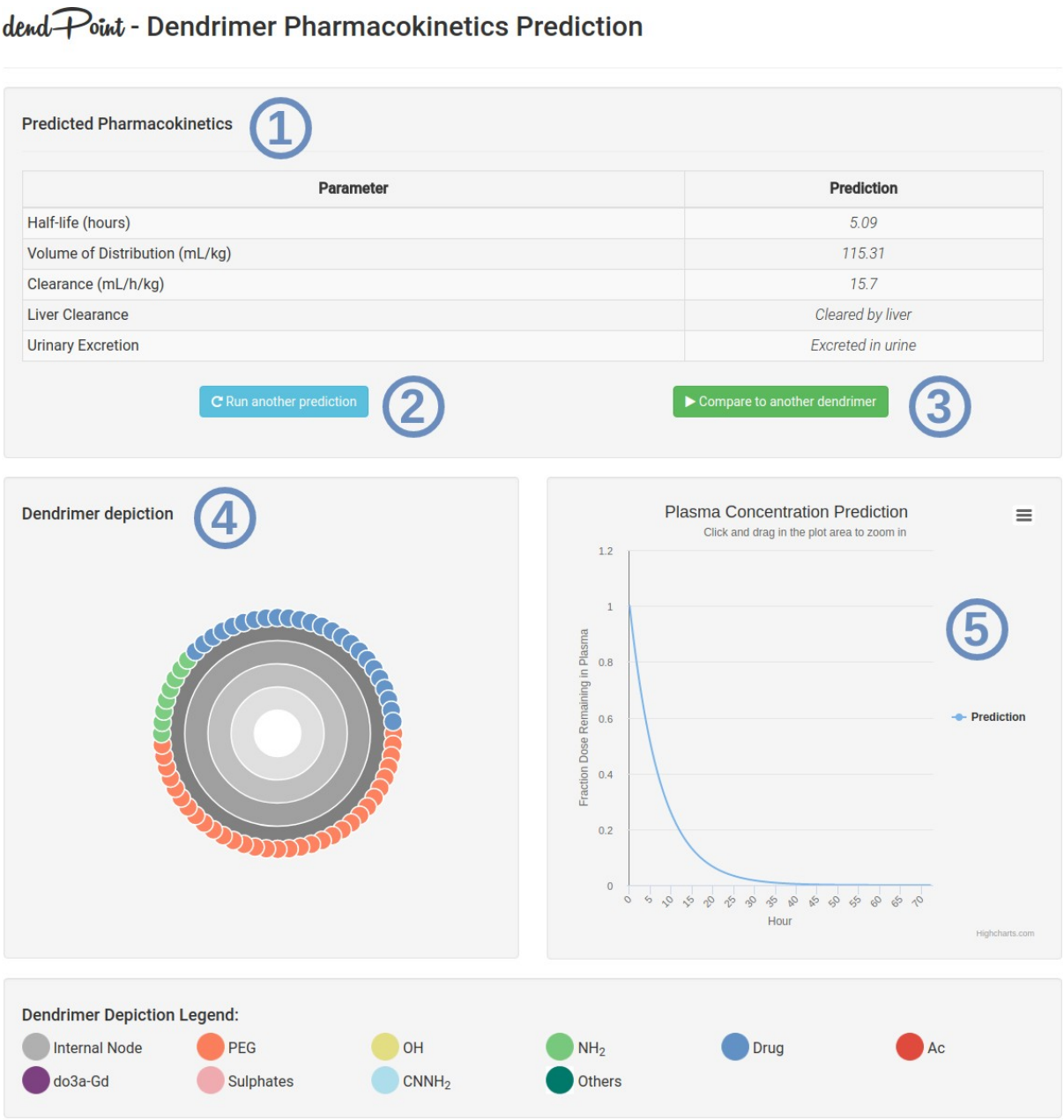

Figure S7: dendPoint result page for single dendrimer predictions. The figure depicts the prediction result page for a single dendrimer. The predicted pharmacokinetic properties for a user-defined dendrimer construct are exhibited in tabular format (1). The interface gives the user the option to either run another prediction (2) or compare the current construct with another one (3). Also a dendrimer depiction is available, showing the number of generations (as concentric grey circles) and surface groups as spheres. A plasma concentration prediction curve is also provided (5).

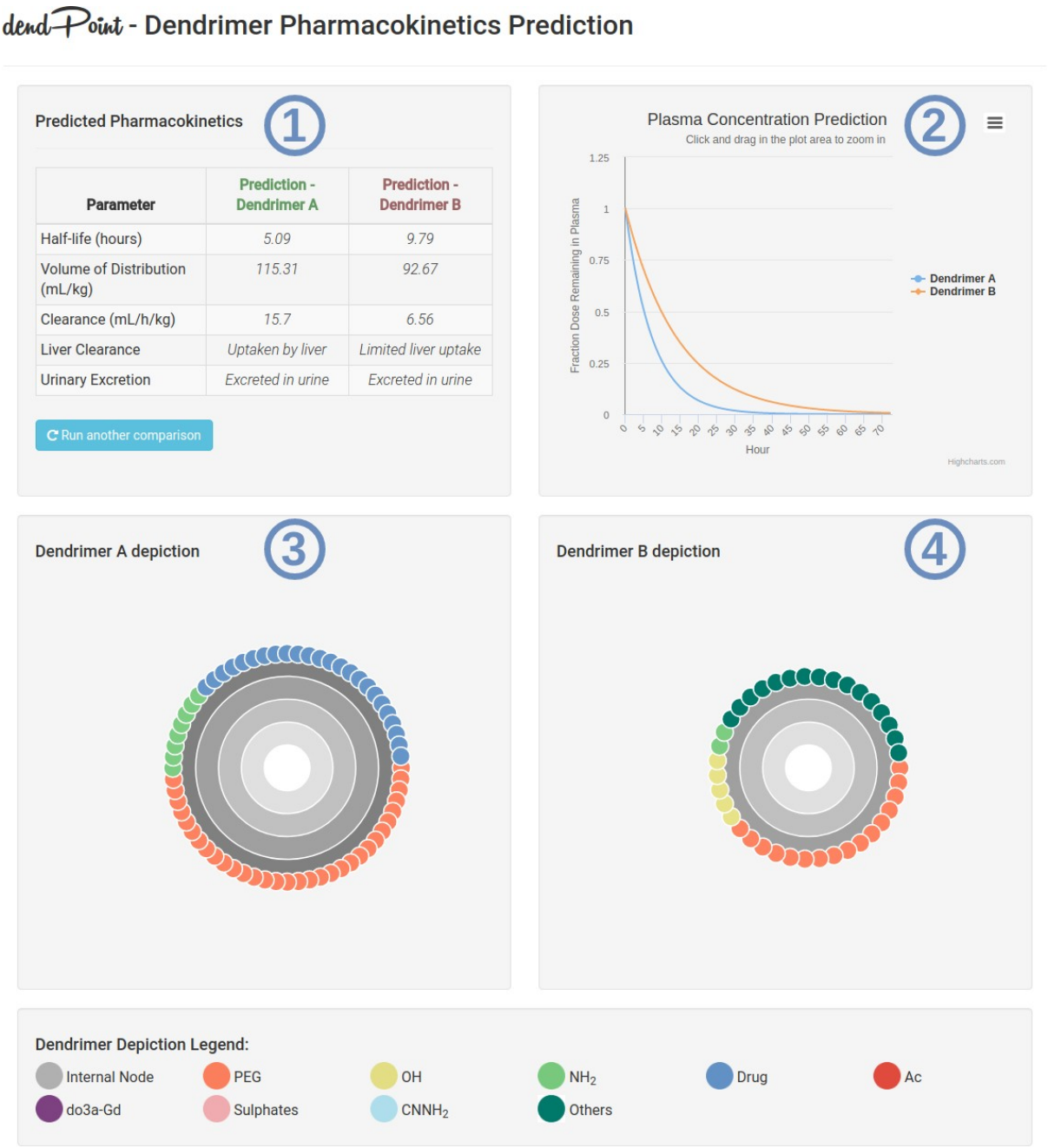

Figure S8: dendPoint result page for dendrimer comparison. The figure depicts the prediction result page for comparing pharmacokinetics of two dendrimers. The predicted pharmacokinetic properties are exhibited in tabular format for both dendrimers (1). The plasma concentration prediction curves for both constructs are also provided (2). The dendrimer depictions are plotted side-by-side, showing the number of generations (as concentric grey circles) and surface groups as spheres (3-4).

Table S1. Summary of structural characteristics and pharmacokinetic properties for dendrimers that were included in the database.

Scaffold	G [a]	# Surface PEG (kDa)	# non-PEG sites	# non-PEG surface functionality[b]	Surface drugs[c]	Surface charge (--- to +++)[d]	Struct flexibility (0 to +++)[e]	Construct MW (kDa)	$T_{1/2}$ (h)	Cl (ml/h/kg)	% Dose in urine (day)	% Dose in liver (day)	Ref
		Surface characteristics							PK parameters				
Triazine[h]	2	10 (5)	14	6 (NH_2), 8(OH)	-	0	0	73	100	1	9 (2)	10 (2)	[1]
Triazine[h]	2	13 (2)	11	3 (NH_2), 8 (OH)	-	0	0	30	43	2.7	10 (2)	12 (2)	[1]
Triazine[h]	2	14 (0.6)	10	2 (NH_2), 8 (OH)	-	0	0	11	27	4.9	16 (2)	16 (2)	[1]
Triazine[h]	2	9 (2)	15	3 (NH_2), 12 (drug)	pac	0	0	39[f]	15	14[g]	35 (3)	11 (2)	[2]
Triazine[h]	2	8 (2)	16	4 (NH_2), 12 (drug)	pac	0	0	37	19	9[g]	55 (3)	22 (2)	[2]
Triazine[h]	2	6.5 (2)	17.5	5.5 (NH_2), 12 (drug)	pac	0	0	34	20	6[g]	41 (3)	10 (2)	[2]
Triazine[h]	2	6.5 (5)	17.5	1.5 (NH_2), 16 (drug)	pac	0	0	61	38	1.4	5 (2)	20 (2)	[3]
PAMAM	5	0	128	128 (OH)	-	0	0	29	3	500[g]	-	12 (1)	[4]
PAMAM	6	0	256	256 (OH)	-	0	0	58	4	250[g]	-	35 (1)	[4]
PAMAM	7	0	512	512 (OH)	-	0	0	117	6	50[g]	-	7 (1)	[4]
PAMAM	5	10 (2)	118	74 (Ac), 44 (NH_2)	-	+	0	52	14[g]	2[g]	2 (2)	15 (2)	[5]
PAMAM	4	0	64	7 (NH_2), 57 (do3a-Gd)	-	0	0	50	72[g]	13[g]	35 (2)	40(2)	[6]
PAMAM	5	0	128	10 (DTPA-Tc), 81 (Ac), 9 (biotin), 28 (NH_2)	-	0	0	~41	19[g]*	12[g]	-	57 (0.25)	[7]
PAMAM	3	12 (5)	12	2 (NH_2), 10 (Do3a-Gd)	-	0	0	69	20	-	-	8	[8]
PAMAM	3	9 (2)	15	15 (Do3a-Gd)	-	0	0	33	3	-	-	4	[8]
PAMAM	2	3 (5)	9	9 (Do3a-Gd)	-	0	0	24	0.6	-	38	1	[8]
PAMAM	2	7 (2)	5	5 (D03a-Gd)	-	0	0	21	6	-	30	7	[8]
PAMAM	4	60 (5)	4	4 (Ac)	-	0	0	334	78[g]	1[g]	-	6 (1)	[9]
PAMAM	5	110 (2)	5	5 (Ac)	-	0	0	284	31[g]	3[g]	-	7 (1)	[9]
PAMAM	4	63 (2)	1	1 (Ac)	-	0	0	162	41[g]	3	-	7(1)	[9]
PAMAM	4	0	64	64 (Ac)	-	0	0	36	2[g]	36[g]	-	4(1)	[9]
PAMAM	3	0	32	29 (NH_2), Cy3 (3)	-	+++	0	8	2	40[g]	-	4 (0.25)	[10]
PAMAM	3	24 (1)	8	5 (NH_2), Cy3 (3)	-	0	0	33	18	3[g]	-	4 (0.25)	[10]
polyester	3	8 (20)	8	8 (OH)	-	0	+	160	50	2	7(2)	2(0.4)	[11]
polyester	2	4 (20)	4	4 (OH)	-	0	++	87	25	3	10(2)	2(0.4)	[11]

polyester	3	8 (10)	8	8 (OH)	-	0	+	85	40	2	2(2)	6(0.4)	[11]
polyester	3	8 (5)	8	8 (OH)	-	0	+	45	31	3	3(2)	4(0.4)	[11]
polyester	1	2 (20)	2	2 (OH)	-	0	+++	44	1	152	20(2)	2(0.4)	[11]
polyester	2	4 (10)	4	4 (OH)	-	0	++	43	26	4	34(2)	6(0.4)	[11]
polyester	2	4 (5)	4	4 (OH)	-	0	++	23	11	21	22(2)	2(0.4)	[11]
polyester	1	2 (10)	2	2 (OH)	-	0	+++	22	8	103	33(2)	1(0.4)	[11]
polyglycerol	2	0	16	16 (OH)	-	0	0	6	16[g]	14[g]	55(0.04)	8(1)	[12]
polyglycerol	2	0	16	6 (SO_3), 10 (OH)	-	-	0	9	1[g]	56[g]	5(0.04)	90(1)	[12]
polyglycerol	2	0	16	13 (SO_3), 3 (OH)	-	--	0	13	1[g]	64[g]	1(0.04)	76(1)	[12]
polylysine	5	32 (1)	32	32 (COOH)	-	-	+	64	33	3	16 (5)	16(5)	[13]
polylysine	5	28 (1)	36	16 (NH_2), 15 (drug), 5 (CNNH2)	dox	+	+	53	34	2	3(5)	9(5)	[14]
polylysine	5	28 (1)	36	16 (NH_2), 20 (-$CNNH_2$)	-	+	+	45	22	3	4(5)	4(3)	[14]
polylysine	5	28 (1)	36	36 (NH_2)	-	++	+	41	29	14	4(3)	37(3)	[14]
polylysine	5	18 (1)	46	23 (NH_2), 15 (drug), 8 (-$CNNH_2$)	dox	+	+	36	35	2	13(5)	5(5)	[14]
polylysine	5	18 (1)	46	23 (NH_2), 23 ($CNNH_2$)	-	+	+	31	25	3	16(5)	3(5)	[14]
polylysine	5	18 (1)	55	55 (NH_2)	-	++	+	27	30	2	24(3)	5(3)	[14]
polylysine	5	30 (1)	34	4 (NH_2), 15 (-$CNNH_2$), 15 (drug)	dox	0	+	56	51	1	-	-	[15]
polylysine	5	32 (1)	32	6 (NH_2), 26 (drug)	MTX[otb]	0	0	64	26	2	9 (5)	8(5)	[16]
polylysine	5	32 (1)	32	6 (NH_2), 26 (drug)	MTX	-	0	64	1	24	2 (3)	52 (3)	[16]
polylysine	5	32 (1)	32	4 (NH_2), 28 (drug)	MTX[otb]	0	+	71	33	2	14 (5)	10(5)	[16]
polylysine	5	32 (1)	32	8 (NH_2), 24 (drug)	MTX	-	+	68	0.3	65	2 (3)	85(3)	[16]
polylysine	4	32 (0.57)	0	0	-	0	0	22	14	9	33 (1)	2 (1)	[17]
polylysine	4	16 (0.57)	16	16 (drug)	MTX[otb]	0	0	21	0.4	173	29 (1)	1 (1)	[17]
polylysine	5	64 (0.57)	0	0	-	0	0	48	37	1	6 (5)	8 (5)	[17]
polylysine	5	32 (0.57)	32	32 (drug)	MTX[otb]	0	0	42	24	5	2 (5)	10(5)	[17]
polylysine	3	8 (0.57)	8	8 (drug)	MTX[otb]	0	0	11	0.1	443	56 (1)	1 (1)	[17]
polylysine	3	8 (1)	8	8 (drug)	MTX[otb]	0	0	15	0.2	330	64 (1)	1(1)	[17]
polylysine	4	16 (1)	16	16 (drug)	MTX[otb]	0	0	30	21	5	24(4)	7(4)	[17]
polylysine	4	16 (2.3)	16	16 (drug)	MTX[otb]	0	0	47	34	2	8(5)	10(5)	[17]

polylysine	5	32 (1)	32	32 (drug)	MTX^{otb}	0	0	59	51	2	1(7)	12(7)	[17]
polylysine	4	16 (0.57)	16	16 (NH_2)	-	++	+	13	0.1	213	74 (1)	3(1)	[18]
polylysine	4	16 (0.57)	16	16 (Ac)	-	0	+	14	0.1	1433	72(1)	0.3(1)	[18]
polylysine	4	32 (2)	0	0	-	0	+	68	75	1	3(7)	9(7)	[19]
polylysine	3	16 (2)	0	0	-	0	+	34	24	3	26 (5)	4(5)	[19]
polylysine	4	32 (0.57)	0	0	-	0	+	22	10	17	43(1)	2(1)	[19]
polylysine	4	32 (0.2)	0	0	-	0	+	11	0.7	383	80(1)	0(1)	[19]
polylysine	3	16 (0.2)	0	0	-	0	+	6	0.6	647	82(1)	0(1)	[19]
polylysine	4	0	32	32 (COOH)	-	--	+	5	0.9	71	25(1)	12(1)	[20]
polylysine	4	0	16	16 (SO_4)	-	---	+	10	0.9	21	30 (1)	26(1)	[20]
polylysine	4	0	32	32 (SO_4)	-	---	+	14	1	24	3(1)	49(1)	[20]
polylysine	4	0	32	32 ($[SO_4]_2$)	-	---	+	7	0.2	1736	63(1)	0(1)	[20]
polylysine	3	0	16	16 (NH_2)	-	+++	+	2	0.1	1942	8(1)	5(1)	[21]
polylysine	4	0	32	32 (NH_2)	-	+++	+	4	0.1	4630	4(1)	10(1)	[21]
polylysine	4	0	32	32 (NH_2)	-	+++	+	4	0.1	2880	4(1)	24(1)	[21]

[a]Dendrimer generation

[b]Functionality or identity of chemical groups conjugated to non-PEGylated surface reactive sites

[c]Surface conjugated drugs representing paclitaxel (pac), doxorubicin (dox), α-carboxyl OtButylated methotrexate (MTX^{otb}) and methotrexate bearing unmodified α-carboxyl functionality (MTX).

[d]Strength of surface charge (from highly anionic [---] to highly cationic [+++]). Assigned based on discussion in the respective manuscripts or based on the number and type of surface charge as well as surface PEG loading.

[e]Structural flexibility of the dendrimer (from relatively rigid [0] to highly flexible [+++]). Relative structural flexibility of each dendrimer construct was assigned based on discussion in the respective manuscripts.

[f]Exists as a 400 kDa aggregate in solution.

[g]Pharmacokinetic parameters calculated based on data that was extrapolated from plasma concentration vs time curves shown in the manuscript.

[h]Surface treatment of the published triazine dendrimers has resulted in 24 available surface groups rather than the standard 16.

*Represents a recalculated value since the value reported in the manuscript was not the correct terminal Half-life.

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