



Role of fibrillin gene superfamily in development and differentiation of connective tissues

Margaret R Davis

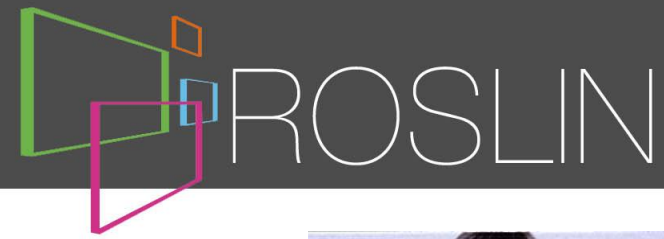
Alisa J Carlisle

Kim M Summers

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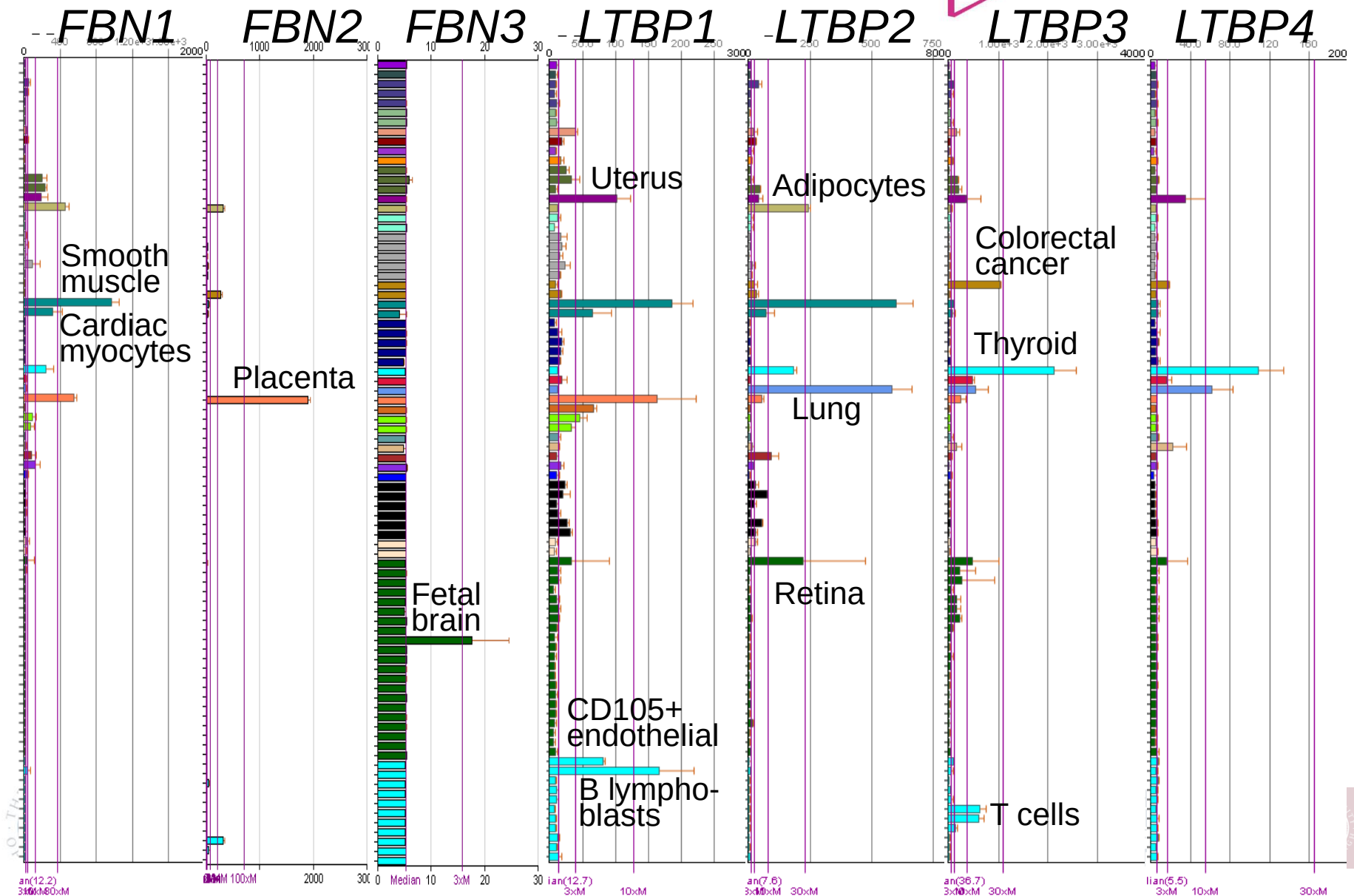
Fibrillin gene superfamily



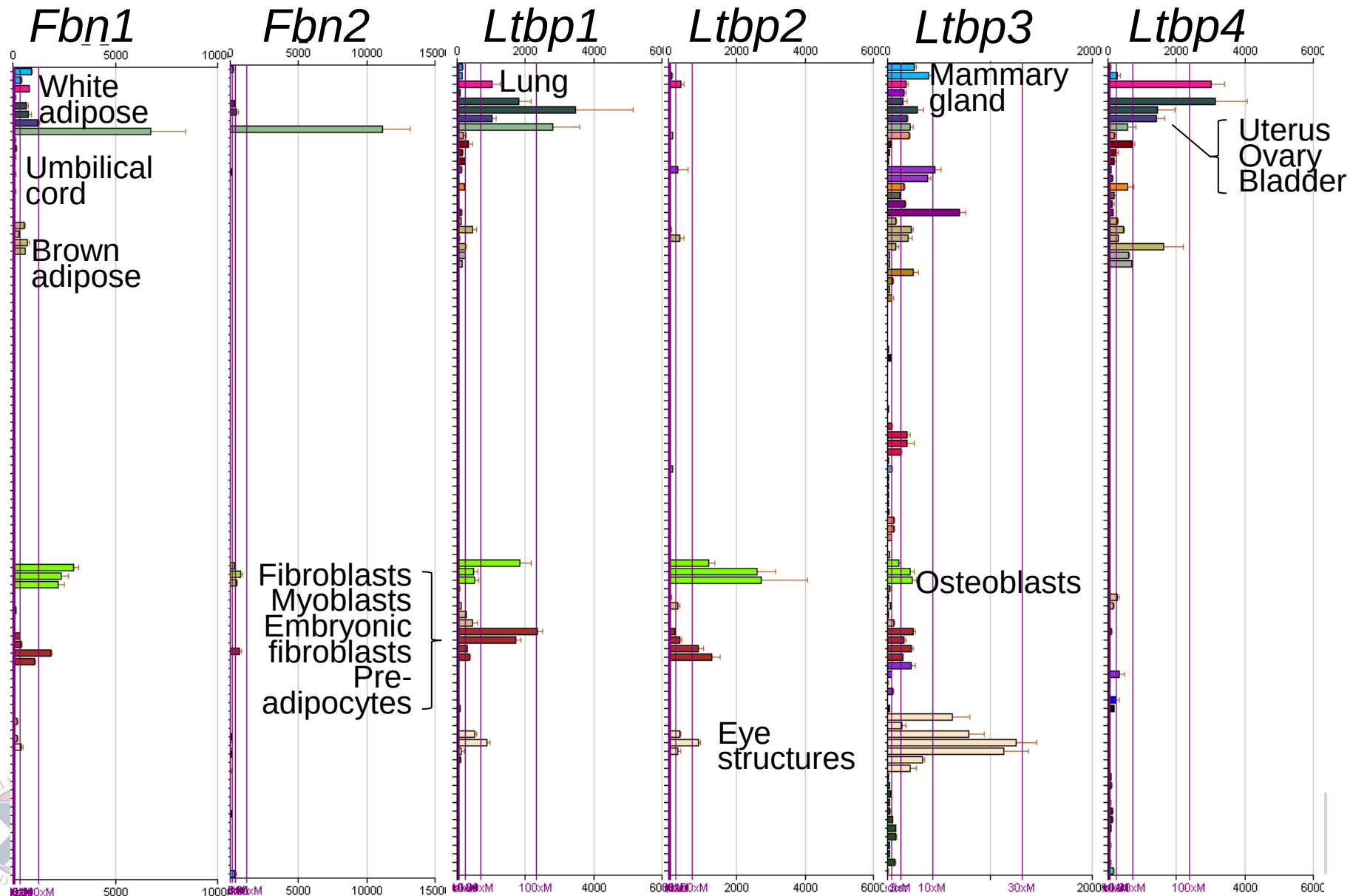
- Three fibrillins
 - *FBN1*, *FBN2*, *FBN3*
 - Some mammals (including rodents) have no functional *FBN3* gene
- Four latent transforming growth factor β binding protein genes
 - *LTBP1*, *LTBP2*, *LTBP3*, *LTBP4*
- The proteins contribute to extracellular microfibrils
- Regulate TGF β family members (TGF β s, BMPs, activins, inhibins)



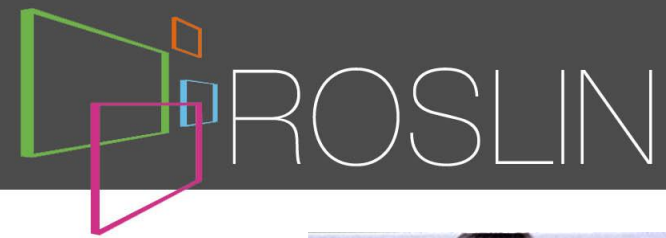
Expression of family members in humans



Expression of family members in mouse



Fibrillin superfamily disease associations



Gene	Disease/Phenotype
<i>FBN1</i>	Marfan syndrome and related conditions
<i>FBN2</i>	Congenital contractural arachnodactyly
<i>FBN3</i>	Associated with polycystic ovary syndrome (? – not replicated)
<i>LTBP1</i>	Null mice have skeletal, cardiovascular, muscle and nervous system abnormalities
<i>LTBP2</i>	Congenital glaucoma; microspherophakia
<i>LTBP3</i>	Tooth agenesis
<i>LTBP4</i>	Cutis laxa; severe pulmonary, gastrointestinal, urinary abnormalities



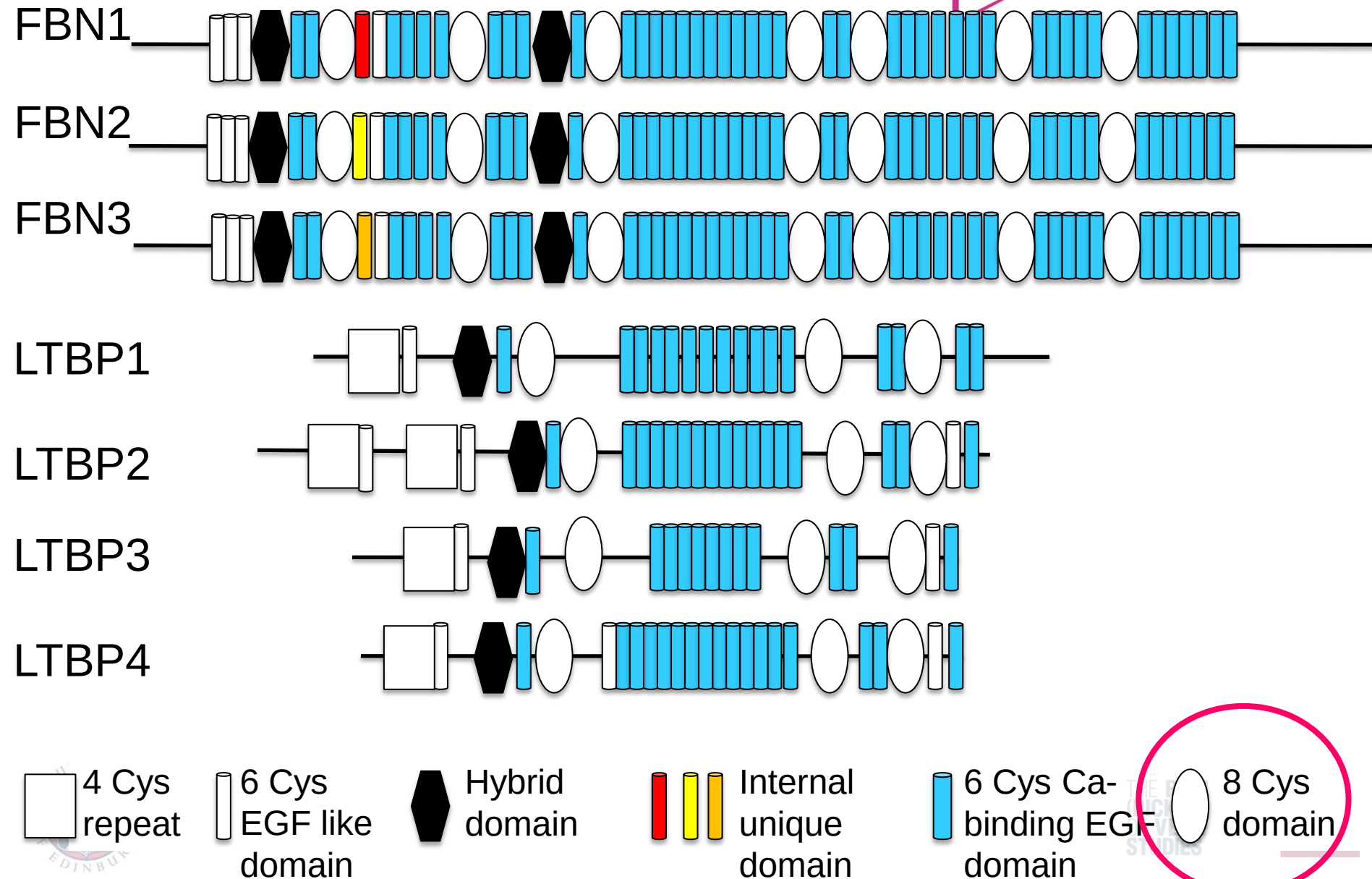
Significant role in diseases of connective tissue

Summers et al Genomics 2010





ROS LIN

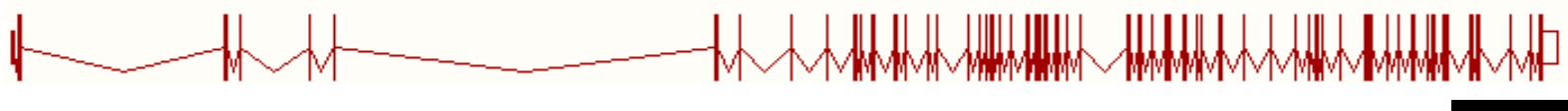


Gene structure



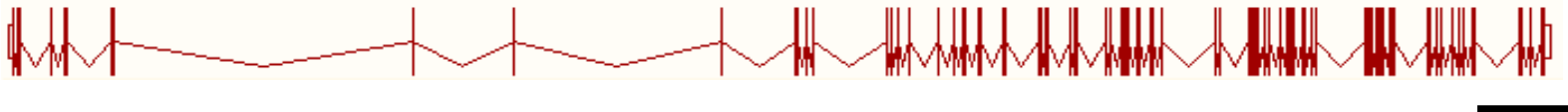
FBN1

237.41kb



FBN2

280.13kb



FBN3

82.36kb



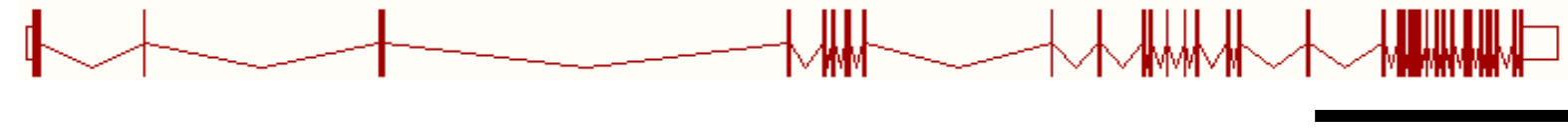
LTBP1

452.39kb



LTBP2

114.15kb



LTBP3

19.41kb



LTBP4

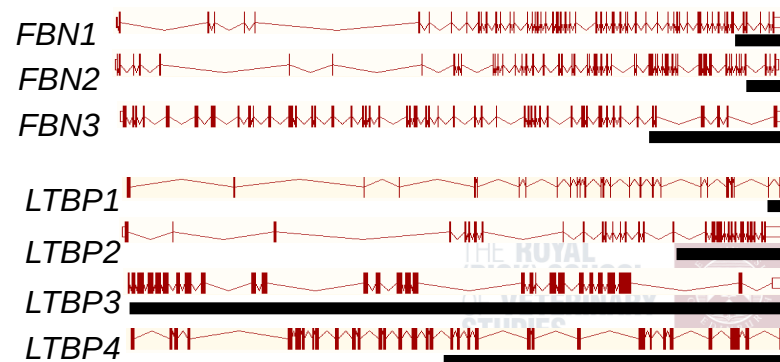
32.91kb



Properties



Gene	Chromosome	Gene size (kb)	Transcript size (kb)	Protein size (AA)	Alternative Promoters
<i>FBN1</i>	15	237	11.6	2871	Yes (5'UTR)
<i>FBN2</i>	5	280	10.7	2912	Yes (5'UTR)
<i>FBN3</i>	19	82	9.2	2809	Yes (5'UTR)
<i>LTBP1</i>	2	452	0.59-6.3	197-1721	Yes (coding)
<i>LTBP2</i>	14	114	8.6	1821	No
<i>LTBP3</i>	11	19	0.43-4.4	124-1303	Yes (coding)
<i>LTBP4</i>	19	33	0.48-4.9	160-1623	Yes (coding)

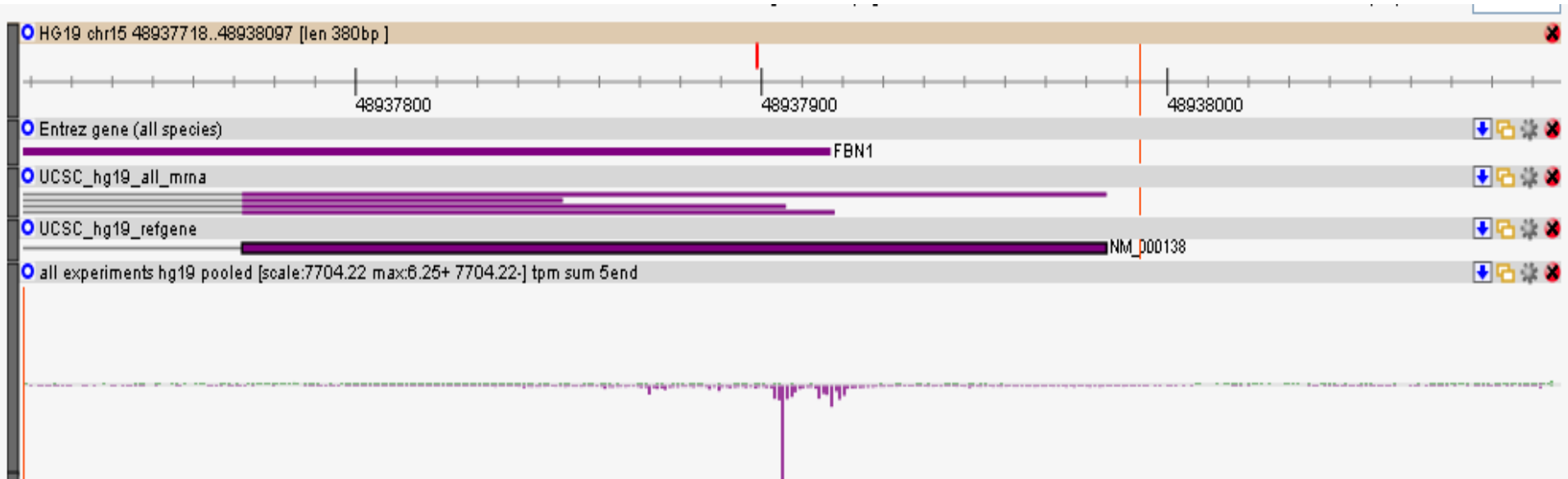
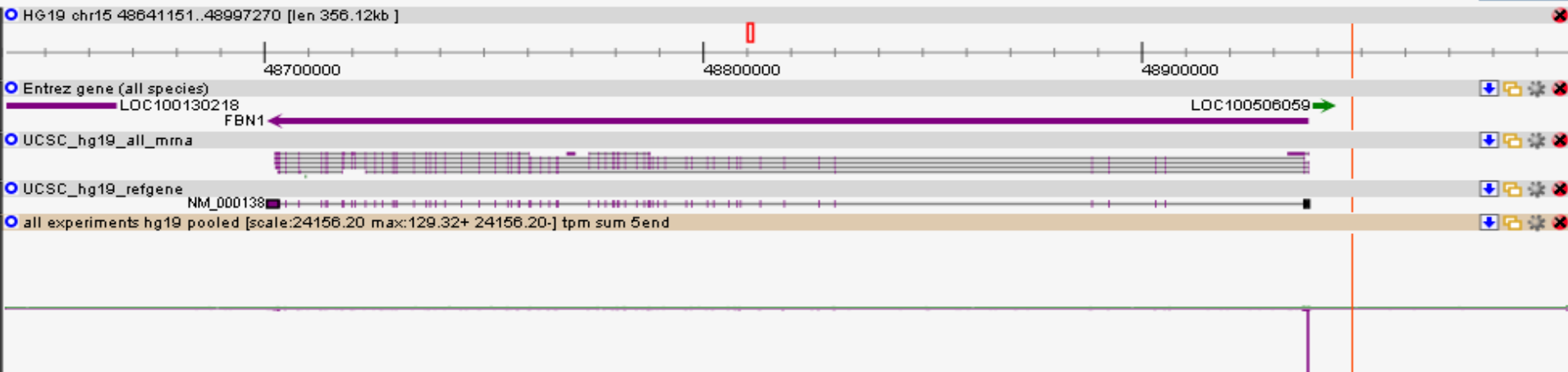


FBN1 FANTOM5



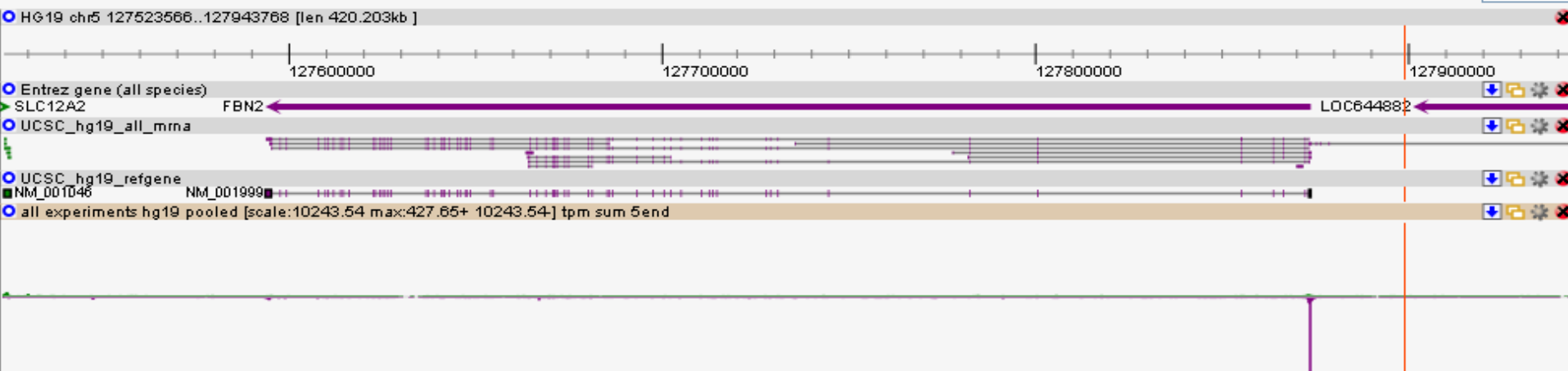
Cell type	TPM	Cell type	TPM
Sertoli cells	1667	Pulmonary SMC	568
Skin fibroblasts	945	Choroid plexus f'blasts	568
Preadipocytes	844	Brain VSMC	519
BCC cell line	826	Adipocytes	493
Preadipocytes	729	HuH cell line	491
Aortic fibroblasts	654	Gingival f'blasts	486
Carotid SMC	632	Adipocytes	476
Subclavian SMC	614	Int thoracic SMC	450
Glioblastoma A172	605	Osteoblasts	438
Myoblasts	595	BM stromal cells	425
Glioblastoma A172	589	Skeletal muscle	407
Synoviocytes	580	Preadipocyte	396

FBN1



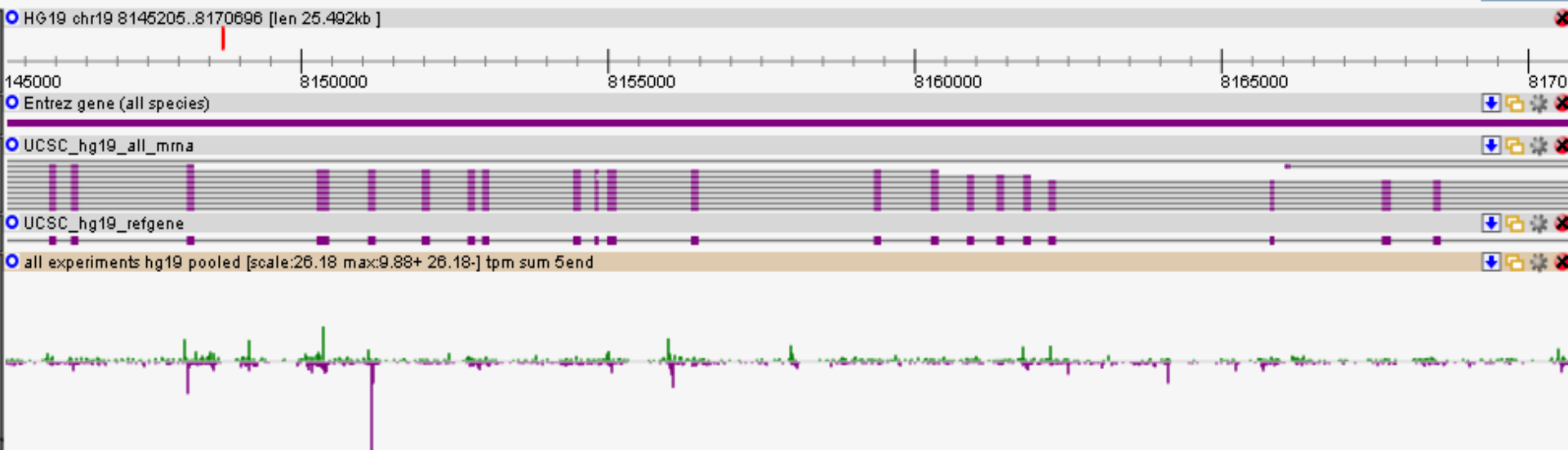
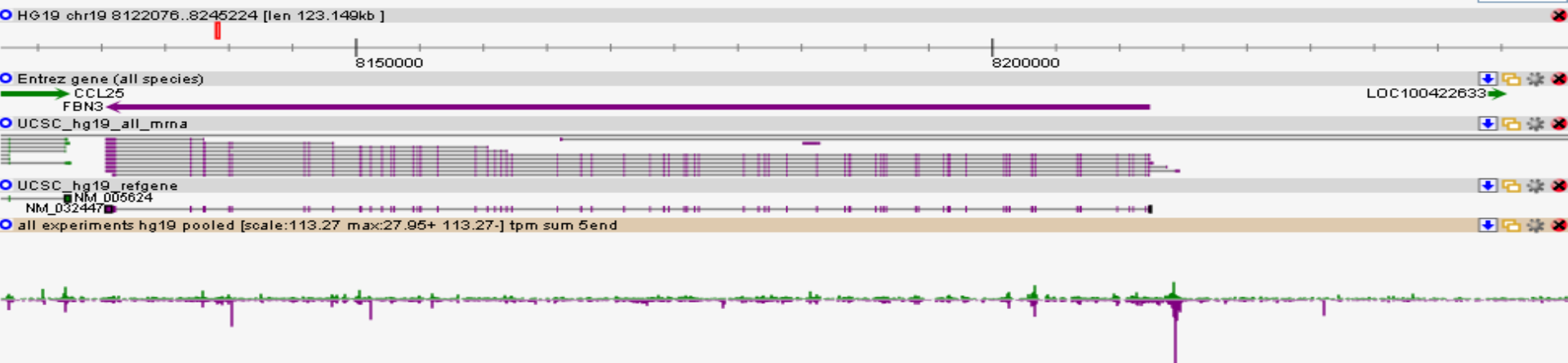
Cell type	TPM	Cell type	TPM
Extraskelatal chondrosarcoma	1276	Gastric cancer AZ521	252
Periodontal f'blast	1068	Fetal rectum	224
Placenta	717	Fetal uterus	220
Gingival f'blast	648	Osteoblasts	214
Skin fibroblast	569	Prostate cancer PC-3	207
Colonic SMC	430	SABiosciences	198
Adipocytes	424	Universal RNA	198
Gingival f'blast	394	Panc stromal cells	194
Periodontal f'blast	319	Myoblasts	193
Adipocytes	259	Prostate stromal cells	191
Fetal heart	254	Prostate SMC	190
		Skeletal muscle	174

FBN2



Cell type	TPM	Cell type	TPM
Fetal parietal lobe	59	Hepatoblastoma HuH-6	10
Fetal occipital lobe	45	Fetal rectum	10
Fetal brain	43	Germ cell embryocarcin	10
Small cell GI carcinoma	33	Fetal thyroid	10
Fetal lung	20	Cord blood cell line	10
Fetal small intestine	18	Wilms tumor HFWT	10
Adult thymus	17	Maxillary sinus HSQ69	10
Neural stem cells	15	Prostate epithelial cells	10
Fetal throat	12	Rhabdomyosarcoma	9
Fetal kidney	11	Adult T-cell leukemia	8
Choriocarcinoma BeWo	11	Fetal uterus	8
Neuroectodermal tumor	11	Fetal thymus	8

FBN3

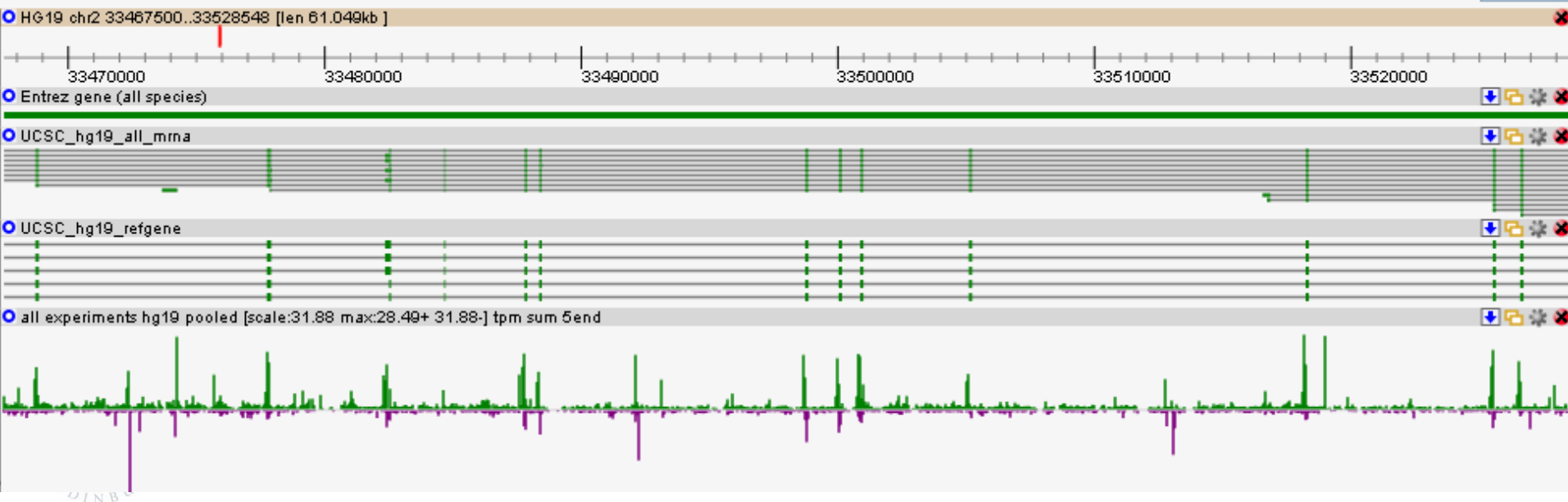
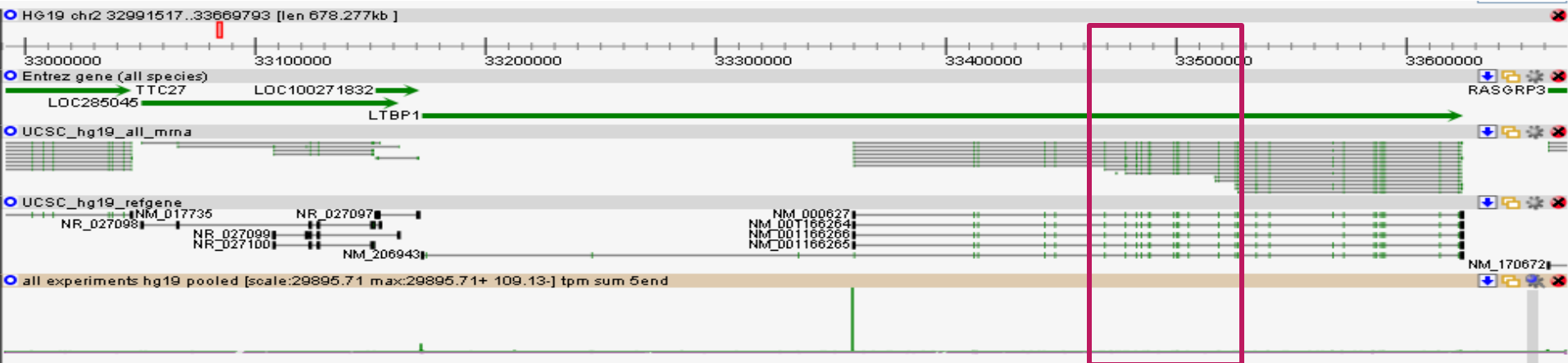


LTBP1 FANTOM5



Cell type	TPM	Cell type	TPM
Gingival f'blast	1459	Aortic SMC	580
Periodontal f'blast	1384	Skeletal muscle	575
Anulus pulposus	1263	Skin fibroblasts	573
Aorta	1060	Osteoblasts	564
SMC	1014	Uterine SMC	530
Carotid SMC	955	Aortic SMC	489
Periodontal f'blasts	945	Gingival f'blast	460
Nucleus pulposus	910	Leiomyoma line 15425	431
Brain VSCM	873	Fetal trachea	429
Int thoracic SMC	777	Hepatocellular carcino	419
Pulmonary SMC	776	Aortic SMC	418
BCC TE354	640	Preadipocyte	410

LTBP1



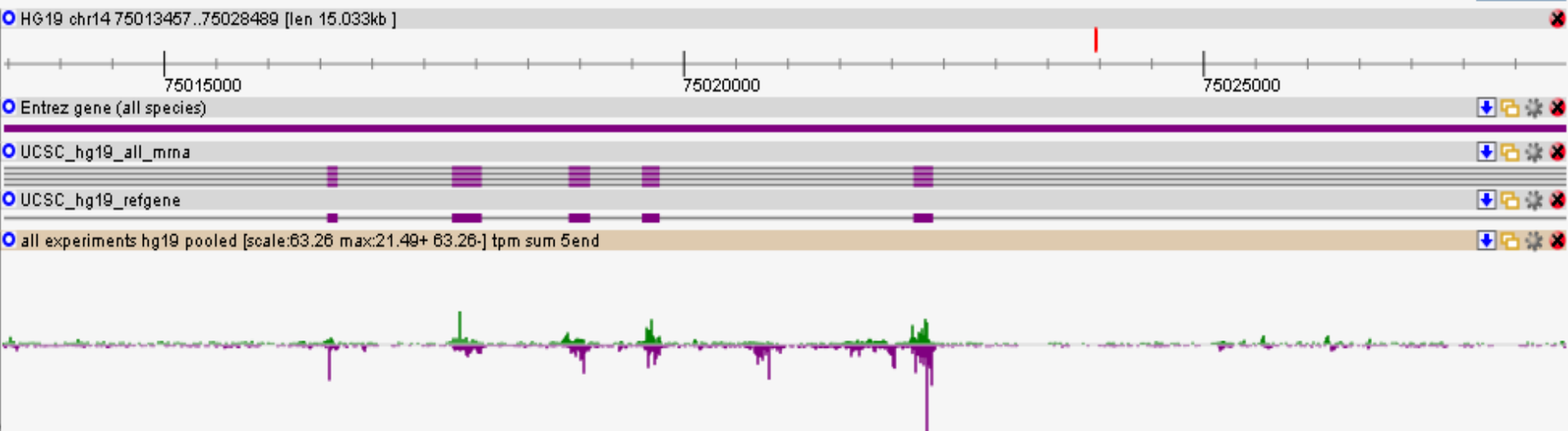
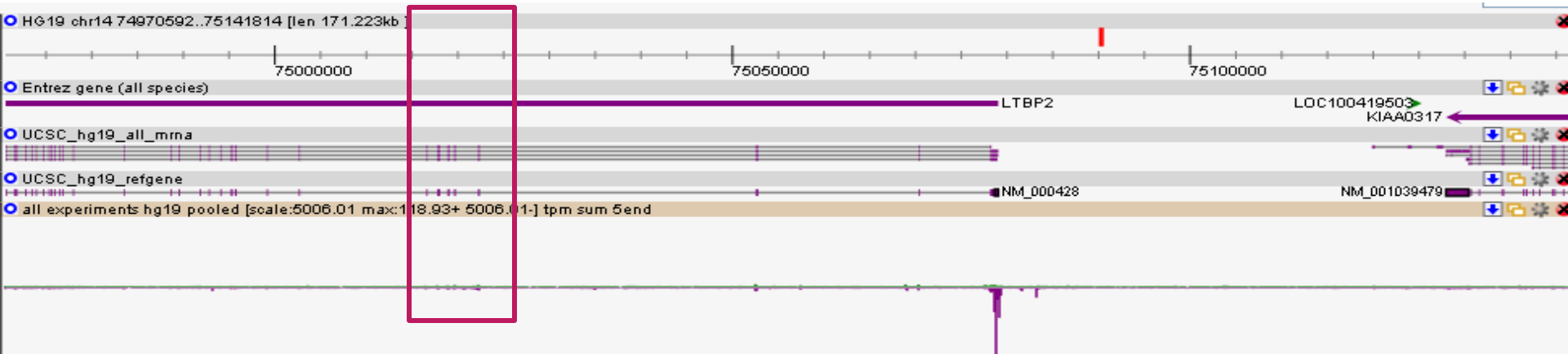
LTBP2 FANTOM5



Cell type	TPM
Aorta	443
Dura mater	409
Urothelial cells	314
Int thoracic SMC	295
Preadipocytes	293
Gingival f'blasts	280
Preadipocytes	276
Gingival epithelial cells	267
Mesenchymal stem cell	260
Preadipocytes	250
Aortic fibroblasts	238
Myoblasts	234

Cell type	TPM
Preadipocytes	232
Leiomyoma line 15425	229
Myoblasts	229
Gingival epithelial cells	227
Lymphatic endothelial	225
Pericytes	209
Skeletal muscle	189
Umbilical SMC	188
Lymphatic endothelial	180
Adipocytes	178
Aortic endothelial	175
Umbilical SMC	175

LTBP2

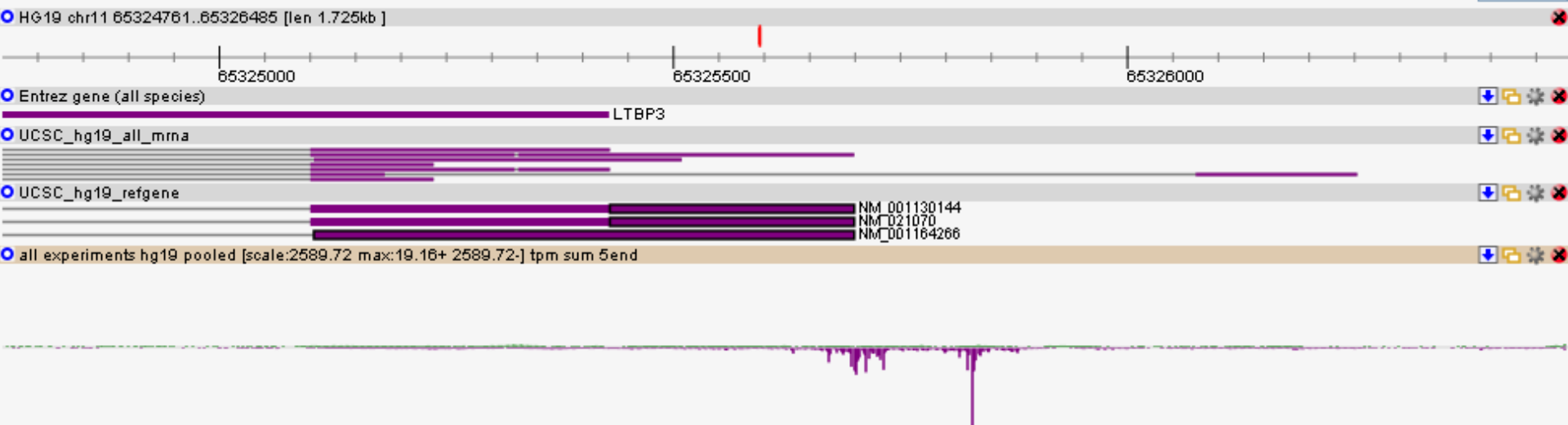
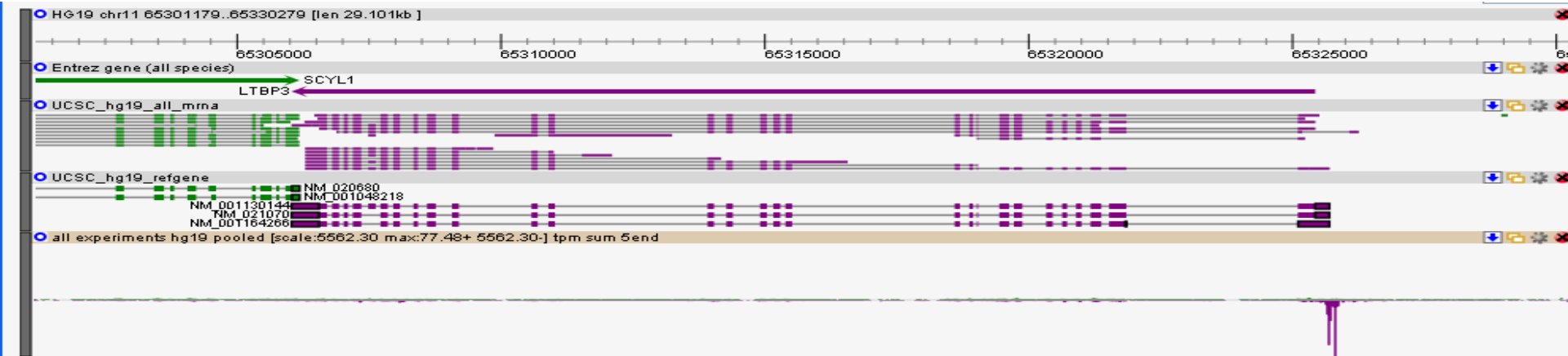


LTBP3 FANTOM5



Cell type	TPM	Cell type	TPM
Lung adenocarcinoma	456	Anaplastic carcinoma	198
Nucleus pulposus	308	Cervix	196
Aorta	293	Gastric adenocarcin	194
Astrocytes	252	Retina	191
Ovary	227	Skeletal muscle	186
Emb pancreas 1B2C6	222	Ciliary epithelial cells	179
Prostate	222	Adrenal gland	178
Int thoracic SMC	215	Fetal throat	178
Uterus	205	Ductal cell carcinoma	174
Giant cell carcinoma	202	Fetal thyroid	168
Emb pancreas 1C3IKEI	200	Dura mater	167
Thyroid	198	Astrocytes	165

LTBP3

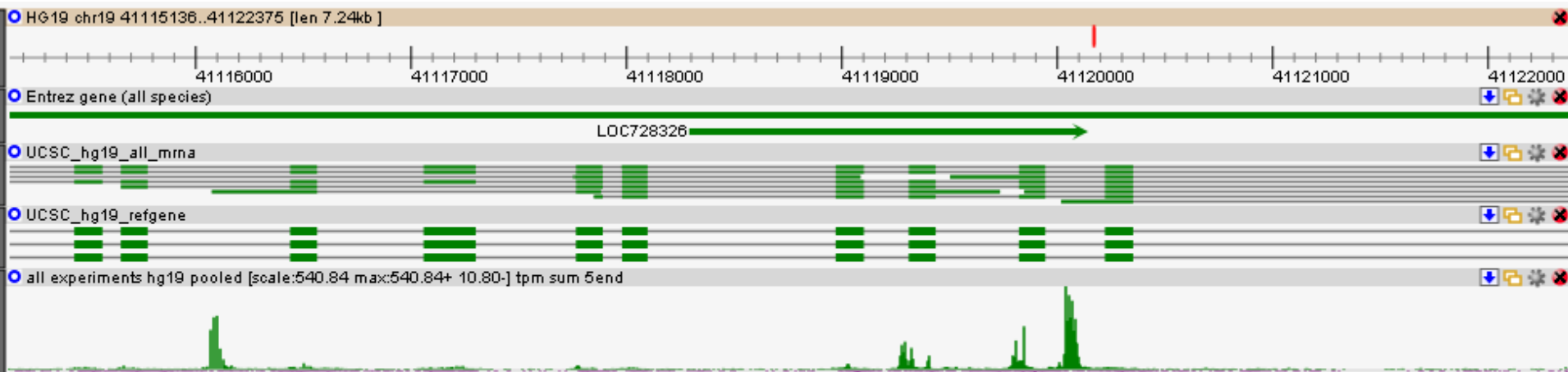


LTBP4 FANTOM5

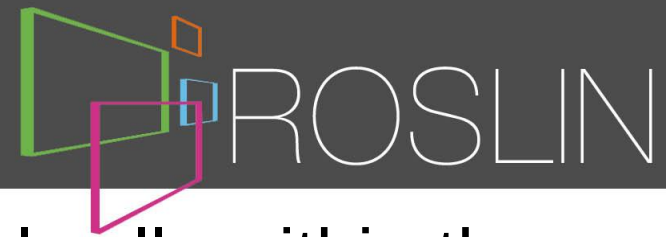


Cell type	TPM	Cell type	TPM
Prostate	436	Colon	218
Cervix	422	Neuroectodermal tumor	209
Aorta	420	Bladder	204
Uterus	315	Fetal spleen	200
Fetal rectum	271	Fetal thyroid	197
Lung	257	Fetal stomach	182
Ovary	246	Lung	180
Lens epithelial cell line	240	Fetal throat	179
Smooth muscle	233	Fetal small intestine	178
Testis	230	Anaplastic carcinoma	175
Fetal uterus	230	Fetal kidney	174
Fetal trachea	229	Oesophagus	173

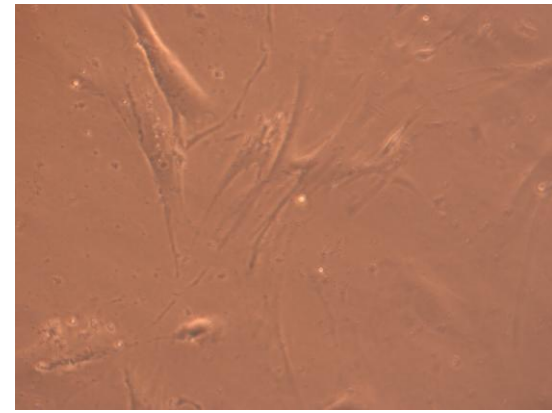
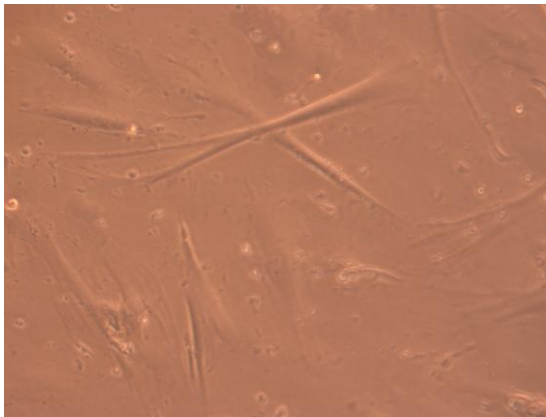
LTBP4



Follicular dendritic cells



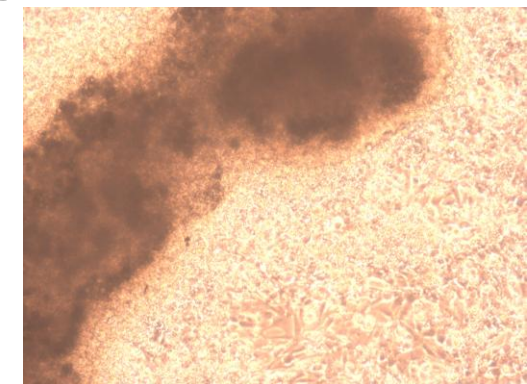
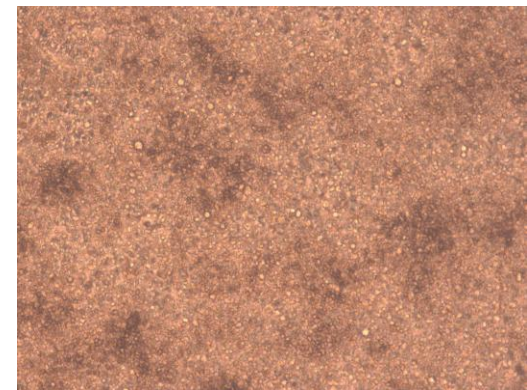
- Follicular dendritic cells are stromal cells within the germinal centres of lymphoid tissues
- Trap and retain immune complexes
- Promote B cell maturation
- Gene expression pattern consistent with mesenchymal origin in mouse (Mabbott et al in revision)
- HK cells originate from tonsil germinal centres and behave as follicular dendritic cells



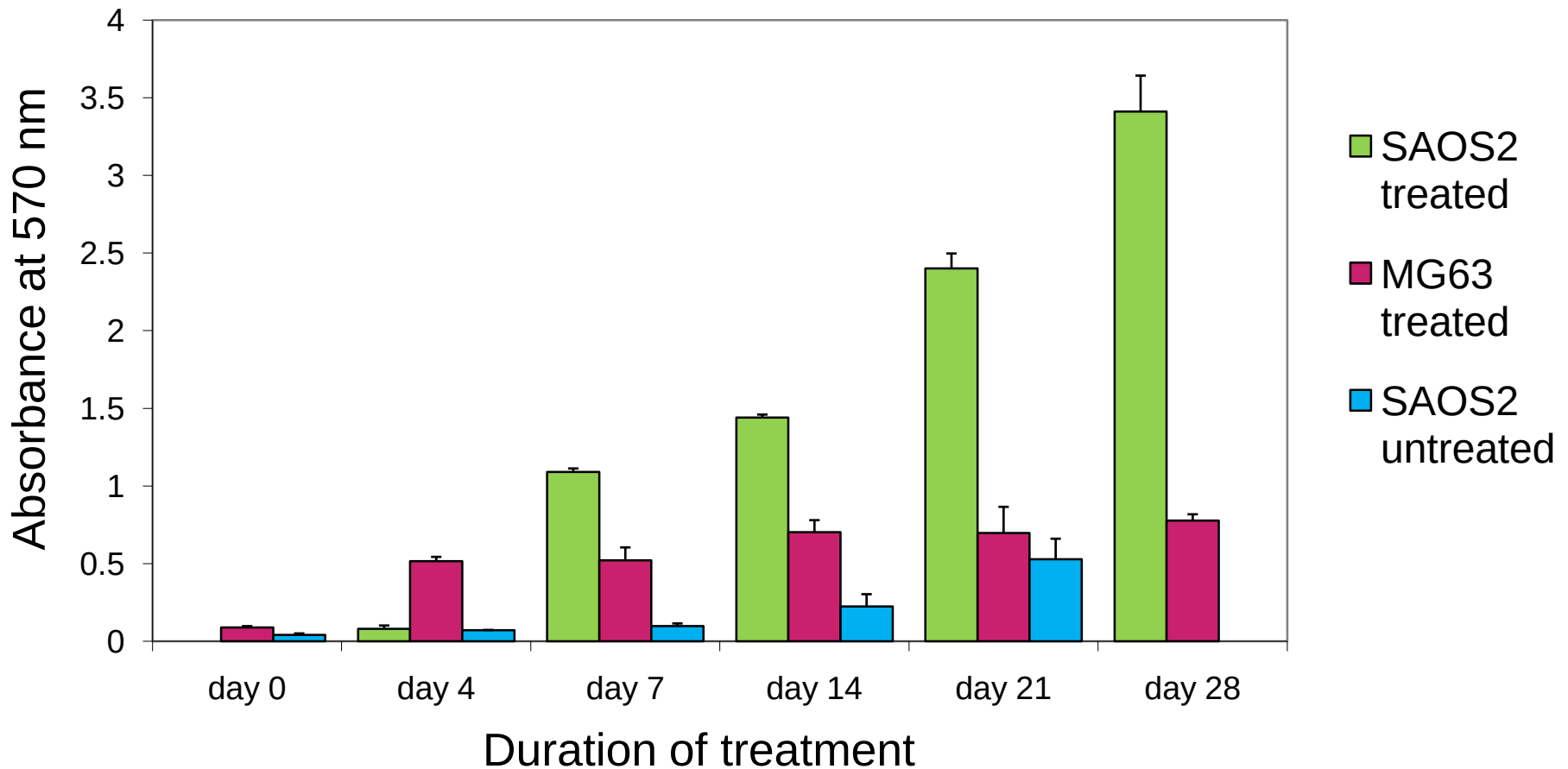
Saos-2 human osteosarcoma cell line



- Saos-2 (“sarcoma osteogenic”)
 - Primary osteosarcoma from 11 year old Caucasian girl in 1973
 - Heteroploid line
 - Osteoblastic features
 - Deposit a mineralisation-competent extracellular matrix similar to osteoblasts
 - High level of alkaline phosphatase, increasing with time in culture
 - Osteonectin positive
 - Time course of mineralisation
 - 0, 15, 30, 45, 60, 80, 100, 120, 150, 180, 240 minutes, 4, 8, 24 hr, 4, 7, 14, 21, 28 days of treatment
 - Early time points have not been published



Calcification of different cell lines



Other data sets

- Smooth muscle cell study
- MSC differentiation
- All mesenchymal cell types

Thank you for giving us the
opportunity to be part of Fantom5

