[1]Supplementary Table S1. Effect of TG2 inhibitors on tubule formation of HUVECs in the co-culture model of *in vitro* angiogenesis.

	Area (x 10^3)	No. of junctions	No. of tubules	Total tubule length (x10^3)	Mean tubule length
Control	162 ± 1.4	**118 ± 37**	286 ± 47	14 ± 3.8	50 ± 7
Vehicle (DMSO 0.01%)	146 ± 4.7	**116 ± 27**	262 ± 31	15 ± 1.2	51 ± 4.2
R294 (50µM)	111 ± 3.2 [ab]	**79 ± 19**	164 ± 19 [a]	9 ± 1.4 [ab]	60 ± 9
R294 (100µM)	52 ± 10 [ab]	**22 ± 10 [ab]**	76 ± 19 [ab]	5.7 ± 1.1 [ab]	49 ± 7.5
Z-DON (10µM)	92 ± 2.6 [ab]	**24 ± 8 [ab]**	148 ± 28 [ab]	13 ± 1.3	54 ± 6
Z-DON (50µM)	68 ± 5.1 [ab]	**30 ± 2.6 [ab]**	96 ± 14 [ab]	8 ± 0.8 [ab]	37 ± 5
R283 (50µM)	102 ± 2.3 [ab]	**86 ± 21**	171 ± 32 [a]	8 ± 1.9 [ab]	48 ± 6.3
R283 (100µM)	46 ± 18 [ab]	**16 ± 11 [ab]**	63 ± 15 [ab]	3.8 ± 0.6 [ab]	50 ± 5.3
Suramin	22 ± 7.6 [ab]	**7.5 ± 3.1 [ab]**	48 ± 7.6 [ab]	1.2 ± 0.1 [ab]	33 ± 1.4 [ab]
Mouse IgG control	158 ± 3.9	**115 ± 32**	291 ± 36	15 ± 3.3	50 ± 5.8
TG100 antibody	149 ± 3.1	**114 ± 21**	281 ± 20	15 ± 0.9	49 ± 5.5
D11D12 antibody	78 ± 12 [ac]	**27 ± 3.4 [ac]**	92 ± 11 [ac]	7 ± 1.6 [ac]	42 ± 4.1
Cub 7402 antibody	151 ± 2.9	**115 ± 28**	276 ± 27	15 ± 1.1	48 ± 7.3
VEGF (2ng/mL)	254 ± 3.3 [ab]	**415 ± 68 [ab]**	796 ± 115 [ab]	26 ± 2.5 [ab]	33 ± 4.2 [ab]
VEGF + R294 (100µM)	207 ± 7.2 [abd]	**281 ± 32 [abd]**	563 ± 43 [abd]	20 ± 2.3 [abd]	39 ± 8.3

[1]Calibration= 1 pixel

[a] Significantly different vs Untreated control group ($p< 0.05$); [b] Significantly different vs Vehicle ($p<0.05$); [c] Significantly different vs mouse IgG ($p<0.05$); [d] Significantly different vs VEGF (2ng/ml) ($p<0.05$).

Supplementary Table S1. Effect of TG2 inhibitors on endothelial tubule formation. Tubule formation as shown in **Figure 2a, 2d** and **6d** (effects of TG2 inhibitor on VEGF stimulation) was quantified using the TCS Cellworks AngioSys Image Analysis Software (ZHA-1800). Data represent Mean values ± S.D. from 3 separate experiments.

[1]Supplementary Table S2. Early and late effect of TG2 inhibitors on tubule formation of HUVECs in the co-culture model of *in vitro* angiogenesis.

	DAY 6					DAY 12				
	Area (x 10^3)	**No. of junctions**	**No. of tubules**	**Total tubule length (x10^3)**	**Mean tubule length**	**Area (x 10^3)**	**No. of junctions**	**No. of tubules**	**Total tubule length (x10^3)**	**Mean tubule length**
Control (DMSO 0.01%)	81 ± 3	**68 ± 2.3**	162 ± 9.5	8.2 ± 0.1	51 ± 2.7	158 ± 1.7	122 ± 32	277 ± 52	14 ± 3.8	50 ± 7
R294 (Treatment A)	62 ± 4.4 [c]	**40 ± 3.9 [c]**	110 ± 8 [c]	7.4 ± 0.3 [c]	48 ± 2.4	143 ± 2.1 [c]	94 ± 24	203 ± 33 [c]	12 ± 2.5	56 ± 5
R294 (Treatment B)	84 ± 3.2 [a]	**71 ± 2.8 [a]**	157 ± 5.7 [a]	7.8 ± 0.1	50 ± 1.2	127 ± 2.3 [ac]	79 ± 19	164 ± 19 [c]	11 ± 1.4	60 ± 9
R294 (Treatment C)	58 ± 4 [bc]	**34 ± 4.8 [bc]**	107 ± 12 [bc]	7.9 ± 0.2	51 ± 1.2	46 ± 8.2 [abc]	16 ± 11 [abc]	63 ± 15 [abc]	3.8 ± 0.6 [abc]	50 ± 5.3
Suramin	29 ± 4.6 [abc]	**25 ± 5.1 [abc]**	87.5 ± 9 [abc]	2.8 ± 0.5 [abc]	35 ± 1.5 [abc]	22 ± 7.6 [abc]	7.5 ± 3 [abc]	48 ± 7.6 [abc]	1.2 ± 0.1 [abc]	33 ± 1.4 [abc]

[1]Calibration= 1 pixel
[a] Significantly different vs Treatment A ($p<0.05$); [b] Significantly different vs Treatment B ($p<0.05$); [c] Significantly different vs Control ($p< 0.05$).

Supplementary Table S2. Reversible effect of TG2 inhibitor R294 on tubule formation in the V2a co-culture assay. Microtubule formation as shown in **Figure 3e** was quantified using the TCS Cellworks AngioSys Image Analysis Software (ZHA-1800). Treatment A, co-culture treated with R294 (50μM) days 1-6. Treatment B, late treated with R294 (50μM) days 6-12. Treatment C, treatment with R294 (50μM) from Days 1-12. Data represent Mean values ± S.D. from 3 separate experiments.

[1]Supplementary Table S3. TG2 knock down and add back on tubule formation of HUVECs in the co-culture model of *in vitro* angiogenesis.

	Area (x10 3)	No. of junctions	No. of tubules	Total tubule length (x10 3)	Total tubule length (x10 3)	Mean tubule length
Wild type	97± 7	91.5 ± 4.9	185 ± 25	13± 2.8	49.5 ± 4.9	
Scramble vector	109.5 ± 17.6	96.5 ± 9.1	178 ± 48	11.95 ± 2.9	49 ± 1.4	
sh-TG2	69.5 ± 3.5 [ab]	28.5 ± 10.6 [ab]	59.5 ± 3.5 [ab]	4.75 ± 0.6 [ab]	34.5 ± 3.5 [ab]	
sh-TG2 + TG2 vector	90.5 ± 3.5	77.5 ± 9.1	117.5± 6.3 [ab]	9.2 ± 1.1	45 ± 4.2 [ab]	
Sh-TG2+ TG2 (W241A)	76.5 ± 3.5 [ab]	32.5 ± 4.9 [ab]	63 ± 5.7 [ab]	3.85 ± 1.3 [ab]	29.7 ± 5.1 [ab]	

[1]Calibration= 1 pixel
[a] Significantly different vs Wild type ($p<0.05$); [b] Significantly different vs Scramble vector $p<0.05$).

Supplementary Table S3. Effect of TG2 knockdown and add back on tubule formation in HUVEC co-culture model as shown in **Figure 4d**. quantified using the TCS Cellworks AngioSys Image Analysis Software (ZHA-1800). Data represent Mean values ± S.D. from 2 separate experiments.

Supplementary Table S4. List of antibodies used for IHC, IF, Western blotting and cell culture

Antigen	Species source	Company	Comments
TG2 (Clone Cub7402)	Mouse, monoclonal	Lab Vision (Thermo Fisher, UK)	
TG2 (Clone TG100)	Mouse, monoclonal	Lab Vision (Thermo Fisher, UK)	
TG2	Rabbit, polyclonal	Lab Vision (Thermo Fisher, UK)	
CD31	Rabbit, polyclonal	Abcam (Cambridge, UK)	Endothelial marker
Vinculin	Mouse, monoclonal	Sigma-Aldrich (UK)	Focal adhesion
VEGFR2, p-Tyr^{1214}	Rabbit, polyclonal	Santa Cruz (Germany)	
VEGFR	Rabbit, polyclonal	Santa Cruz (Germany)	
Akt, p-Ser^{473}	Rabbit, polyclonal	Cell Signalling (UK)	
Akt	Rabbit, polyclonal	Cell Signalling (UK)	
Phosphorylated ERK1/2	Rabbit, polyclonal	Santa Cruz (Germany)	
ERK1/2	Mouse, monoclonal	Santa Cruz (Germany)	
FN	Rabbit, polyclonal	Santa Cruz (Germany)	
VEGF	Mouse, monoclonal	BD (UK)	
von Willebrant factor	Mouse, monoclonal	Dako (Glostrup, Denmark)	A marker for angiogenesis
Rabbit IgG control		CovaLab (Lyon, France)	Control antibody
Mouse IgG control		CovaLab (Lyon, France)	Control antibody
FITC, TRITC or HRP-conjugated secondary antibodies		Dako (Glostrup, Denmark) or Sigma (UK)	