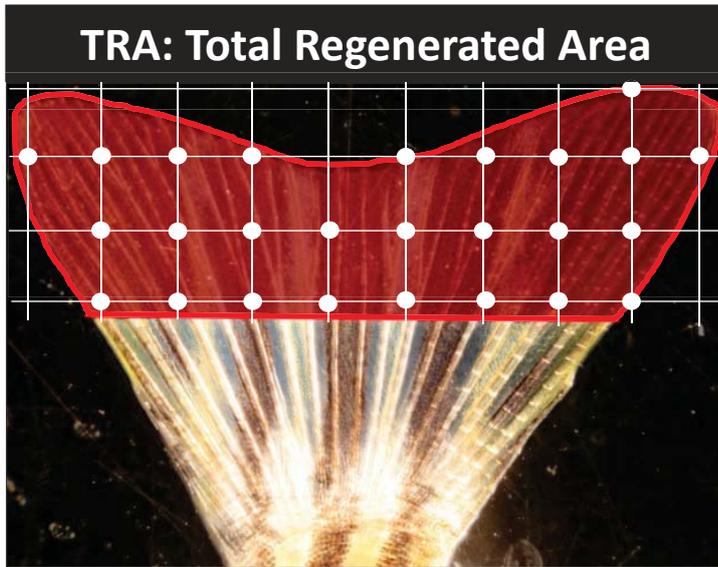


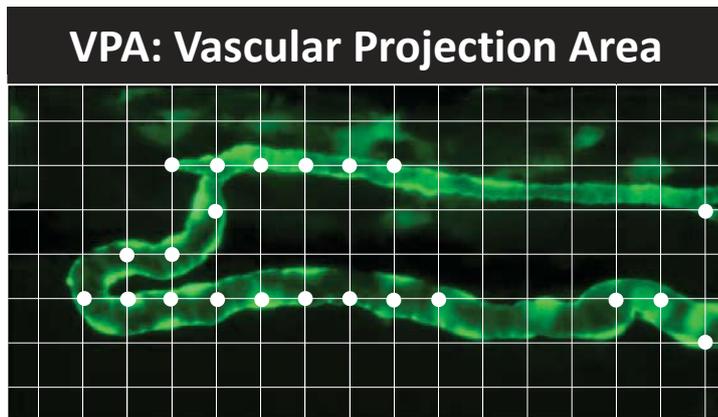
## S1 Figure. Stereology



### (TRA) Total Regenerated Area:

The amputated area is indicated in red. Test grids with known square size (point associated area) were randomly overlaid on the fin. Points falling on the area of interest were summed ( $\Sigma P$ ).

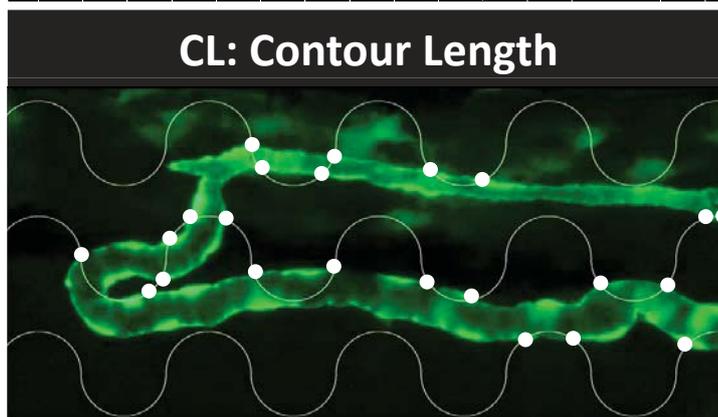
$$TRA = N_p * \left( \frac{area}{point} \right)$$



### (VPA) Vascular Projection Area:

VPA can be quantified for this simple vascular loop using the same formula as for TRA.

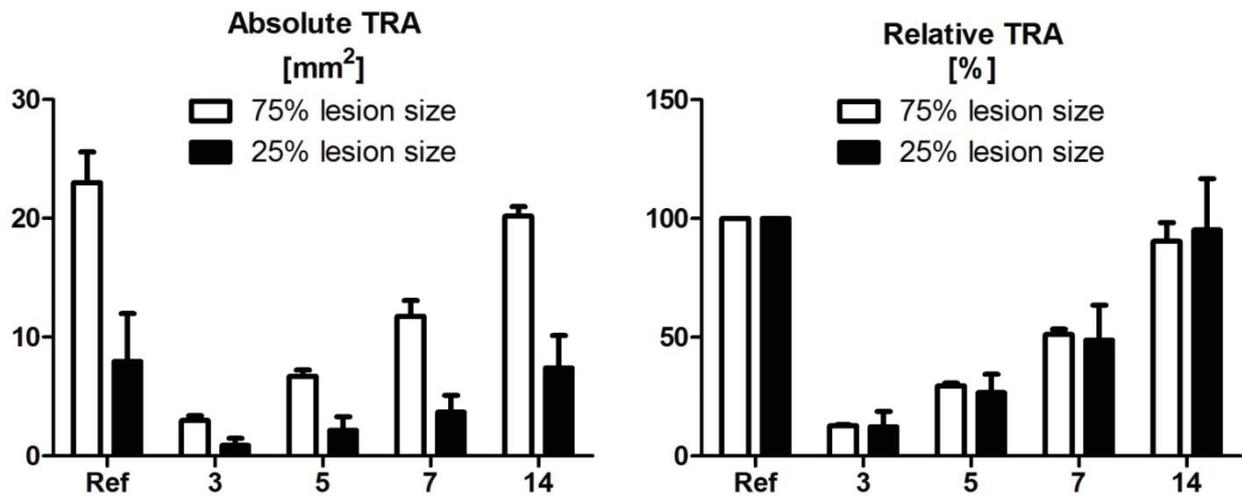
$$VPA = N_p * \left( \frac{area}{point} \right)$$



### (CL) Contour Length:

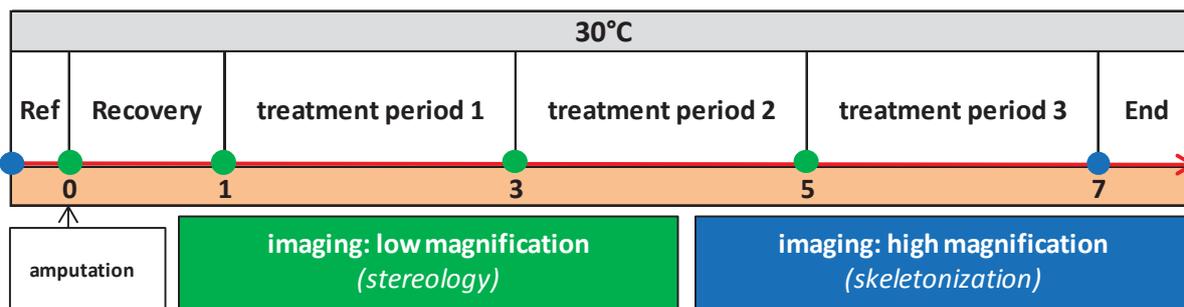
In order to determine CL, circular test lines were virtually overlaid.  $\Sigma P$  is the number of times the test line crosses the contour of the blood vessel.  $dL$  represents the distance between the test lines.

$$CL = N_p * \frac{\pi}{2} * dL$$



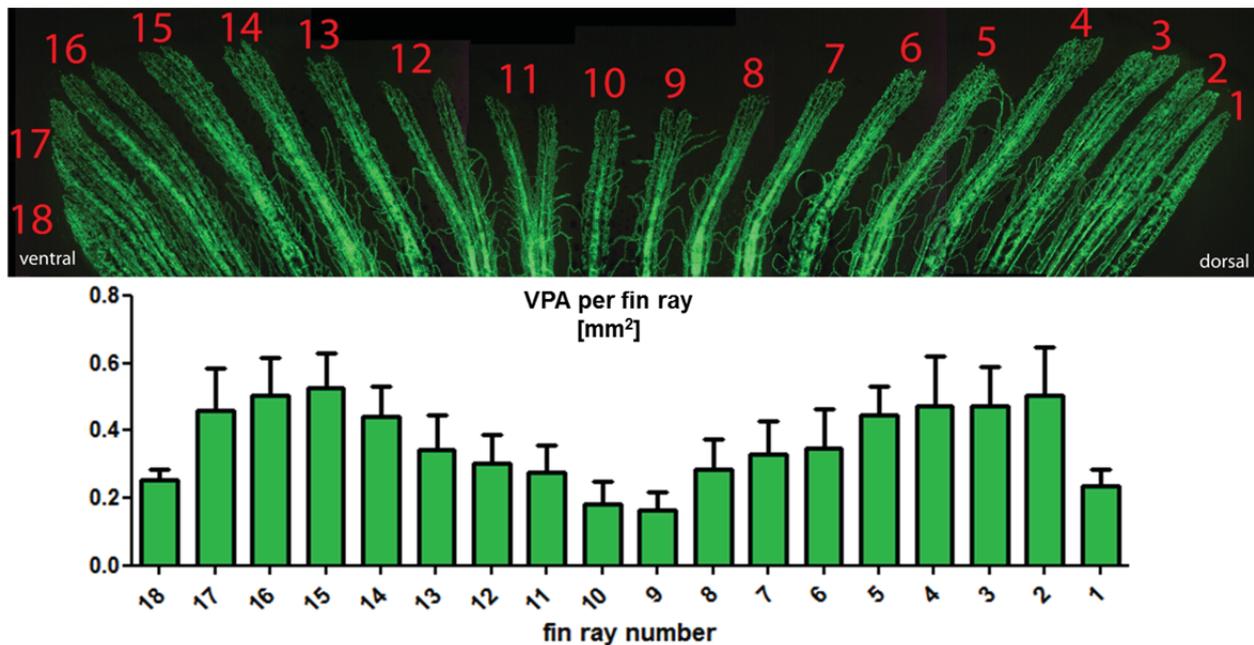
**S2 Figure.** Reference concept: Influence of lesion size ( $n = 4$ )

The caudal fin was partially amputated at either approximately 25% or 75%. This experiment revealed the importance of the reference concept. The smaller the lesion size, the smaller the regenerated area and its growth speed and vice versa (left panel). However, all results are directly comparable if expressed in relative values (right panel). Noteworthy, standard deviations were consistently smaller when bigger lesion sizes were applied.



**S3 Figure.** *Experimental setup of detailed angiogenic assay (DAA).*

Zebrafish were first imaged right before amputation of the caudal fin (Ref). For pro- and anti-angiogenic drug solutions, one day of recovery for the fish is advisable to let anastomoses between arteries and veins at the regeneration front to be properly formed. For PTK787, water and drug solution were exchanged at 1, 3, and 5 dpa, thus leading to three treatment periods of equivalent concentrations. In order to reduce damage following excessive fluorescent exposure, the dynamic follow-up was performed using imaging at low magnification (50x). These images were analyzed using stereological approach. High magnification images (200x and more) were acquired only at the reference time point (before amputation) and at 7 dpa. These images were used for skeletonization and advanced analysis.



**S4 Figure.** Identification and quantification of individual fin rays ( $n = 7$ )

Stereology allowed quantification of absolute values for various parameters from individual fin rays. This can be very important to reduce the area of interest to specific sites. In this example, the fin rays were numbered from dorsal to the ventral aspect.

**S1 Table. Formulary**

Full name	Abbrev.	Unit	Formula	Explanation
Area (stereology)	TRA, VPA	[mm <sup>2</sup> ]	$Area = N_p * \left(\frac{area}{point}\right)$	Where $N_p$ is the number of points obtained by counting, area/point= the applied size of the grid (point associated area) dL= distance between grid lines.
Length (stereology)	CL	[m]	$Length = N_p * \frac{\pi}{2} * dL$	
Vessel Area Density	VAD	[%]	$VAD = \frac{VPA}{TRA} * 100$	
Average Vessel Diameter	D	[μm]	$d = \frac{2 * VPA}{CL}$	Assumptions that vessels are round structures and the diameter of a vessel is smaller than its length.
Vascular Exchange Surface	VES	[μm <sup>2</sup> ]	$VES = \pi * VPA$	We assessed the vascular exchange surface, as the area of the outer surface of the vasculature. Assumption that vessels are cylindric structures.

## S Text. Info on the graph energy

From the skeleton-derived graph (branching points=nodes), the adjacency matrix  $A$  can be constructed. It consists in a double array  $A = [a_{ij}]$ , whose entries  $a_{ij}$  are the number of edges connecting node  $i$  to node  $j$ . There are several properties related with enumerating walks and connectivity for the adjacency matrix that have received an increased attention in the context of urban transport problems, social networks analysis (i.e. the study of human interactions with graph theoretical tools)<sup>1</sup> etc. The spectrum of a graph, defined as the set of eigenvalues derived from the adjacency matrix also shed light about the structure of the graph (subject of Spectral Graph Theory). The energy of the graph, defined to be the sum of the absolute values of the eigenvalues of the adjacency matrix of that graph, rose from theoretical chemistry where eigenvalues were associated with the stability of molecules<sup>2</sup>. To mention some properties of the eigenvalues of the graph, the eigenvalues are arranged in a decreasing sequence. The Perron–Frobenius Theorem implies immediately that if the graph is connected, then the largest eigenvalue has multiplicity 1 and this eigenvalue is an *average* degree (i.e. number of incident edges to a node) for the graph<sup>3</sup>. Non-connected nodes or components translate in zero entries in the adjacency matrix providing zero-valued eigenvalues. Due to the non-negative nature of the absolute value function, any added node will either have any impact on the energy of the graph (i.e. the associated eigenvalue will be zero in case of isolated nodes) or a magnitude proportional to its degree (i.e. eigenvalue will have a non-negative contribution to the graph energy being larger if the node is more connected). Therefore, the larger the graph energy, the more connected is the graph and consequently this quantity expresses the connectivity between the nodes.

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1) Skillicorn, D. B. (2005) Social Network Analysis via Matrix Decompositions, in Emergent Information Technologies and Enabling Policies for Counter-Terrorism (eds R. L. Popp and J. Yen), John Wiley & Sons, Inc., Hoboken, NJ, USA. Chapter 19.

2) Gutman, Ivan (1978), "The energy of a graph", 10. Steiermärkisches Mathematisches Symposium (Stift Rein, Graz, 1978), Ber. Math.-Statist. Sect. Forsch. Graz 103, pp. 1–2

3) Kay Buttler, Steven (2008) Eigenvalues and Structures of Graphs. PhD dissertation, University of California, San Diego.