

# HEADT Centre Report on Research Integrity

## **Title of Article:**

**„Lysyl oxidase is essential for hypoxia-induced metastasis“**  
(Nature 440/2006)

## **Authors:**

Janine T. Erler, Kevin L. Bennewith, Monica Nicolau, Nadja Dornhöfer, Christiana Kong, Quynh-Thu Le, Jen-Tsan Ashley Chi, Stefanie S. Jeffrey, Amato J. Giaccia

## **DOI/URL:**

<https://doi.org/10.1038/nature04695>  
<https://www.nature.com/articles/nature04695>

## Background and Reasons for Inquiry:

Official HEADT Centre Research Integrity report requested by anonymous source.

Note: The HEADT Centre will remove whistleblowers names’ from a public report about possible research integrity violations if there are clear reasons why anonymization is necessary. It should be understood that names and other data may be made available to appropriate university authorities upon request.

## Specification of Analysis:

Evaluation of potential image manipulation (duplication and/or rotation/susp. data fabrication) in

Figs. 4c LOX;  
4A in supplementary materials: Intracellular LOX. Image Manipulation Detection Routine, incl. systematic context analysis and software-supported image analysis.

Figure	Routine	Aspect	Result
Fig. 4c (main article)			
	Context Analysis		
		Source/Origin	<a href="https://www.nature.com/articles/nature04695/figures/4">https://www.nature.com/articles/nature04695/figures/4</a>
		Received Via	Download, anonymous source
		File Format	Tif./jpeg.
		Image Resolution	216,244 ppi (L/B)
		Additional Information	Ausrichtung normal
		PubPeer/RW entries	<a href="https://pubpeer.com/publications">https://pubpeer.com/publications</a>
			Irregularities in Fig. 4c main, and 4 A suppl. mentioned, no RW entry.

Figure	Routine	Aspect	Result
		EXIF Data, Available/ Not Available. Irregularities, Date of Creation, Date of last edit, Camera Type, Software Tags	EXIF Data not available, RGB, no tags, Camera settings etc. unavailable. Date of Creation equals Date of last Editing; 24.2.2006
	Analysis upon Visual Inspection		
		Cropped/Rotated/ Artefacts removed/duplications, etc.	Visual similarities detectable as indicated in addendum.
	Software-supported Image Analysis		
		ORI Droplets	See addendum: Forensic Gradient Map Analysis
		Overlay	Neg.
		Feature-In-Dark	Neg.
		ImageJ/InspectJ Clone Detection/Similarity Check	Clone detection neg. at 0%/3%/5% default tolerances.
		Forensically (Error Level Analysis, Clone Detection, Level Sweep, Noise)	Pos. clone detection (settings see addendum), level sweep, Error Level Analysis, PCA neg.
Fig. 4A (suppl.)			
	Context Analysis		
		Source/Origin	<a href="https://media.nature.com/original/nature-assets/nature/journal/v440/n7088/extref/nature04695-s07.pdf">https://media.nature.com/original/nature-assets/nature/journal/v440/n7088/extref/nature04695-s07.pdf</a>
		Received Via	Download, anonymous source
		File Format	pdf, ppt

Figure	Routine	Aspect	Result
		Additional Information	no
		PubPeer/RW entries	See above link, duplication susp. in suppl. Fig. 4A
		EXIF Data, Available/ Not Available. Irregularities, Date of Creation, Date of last edit, Camera Type, Software Tags	Not available.
	Analysis upon Visual Inspection		
		Cropped/Rotated/ Artefacts removed/duplications, etc.	No positive record on visual inspection. Available image quality is very low.
	Software-supported Image Analysis		
		ORI Droplets	See addendum.
		Forensic Gradient Map	Levels of similarity can be attested.
		Feature-In-Dark	Levels of similarity can be attested.
		ImageJ/InspectJ Clone Detection/Similarity Check	Not possible due to low image quality
		Forensically (Error Level Analysis, Clone Detection, Level Sweep, Noise)	Pos. record with clone detection tool, see addendum.
			Settings: see screenshot (addendum)

## Summary of Findings

Upon closer visual and software-supported inspection of Erler et al. "Lysyl oxidase is essential for hypoxia-induced metastasis" the HEADT Centre image manipulation detection analysis routine supports the following conclusions:

### Fig 4c:

- Visual inspection of Fig 4c supports the conclusion that parts of that panel have been duplicated. Similarities are indicated in the addendum.
- Software supported analysis (ORI/Forensic Gradient Map and ForensicallyBeta Clone detection tool) support that finding.
- Note: InspectJ Clone detection revealed no positive record.

### Fig. 4A (suppl.):

- Poor image quality in Fig. 4 (A) does not allow for an analysis upon visual inspection of the image.
- Three software-supported tools were applied: Forensic Gradient Map Analysis, Features in the Dark ORI action together with ForensicallyBeta clone detection tool all support the conclusion that two of the elements (see addendum) show a significant degree of similarity.

## Recommendations:

The HEADT Centre research integrity group strongly supports a closer investigation of the case and encourages all of the involved parties to assess and evaluate the indicated inconsistencies and to carry out a more thorough review of the case.

Berlin/March 2018



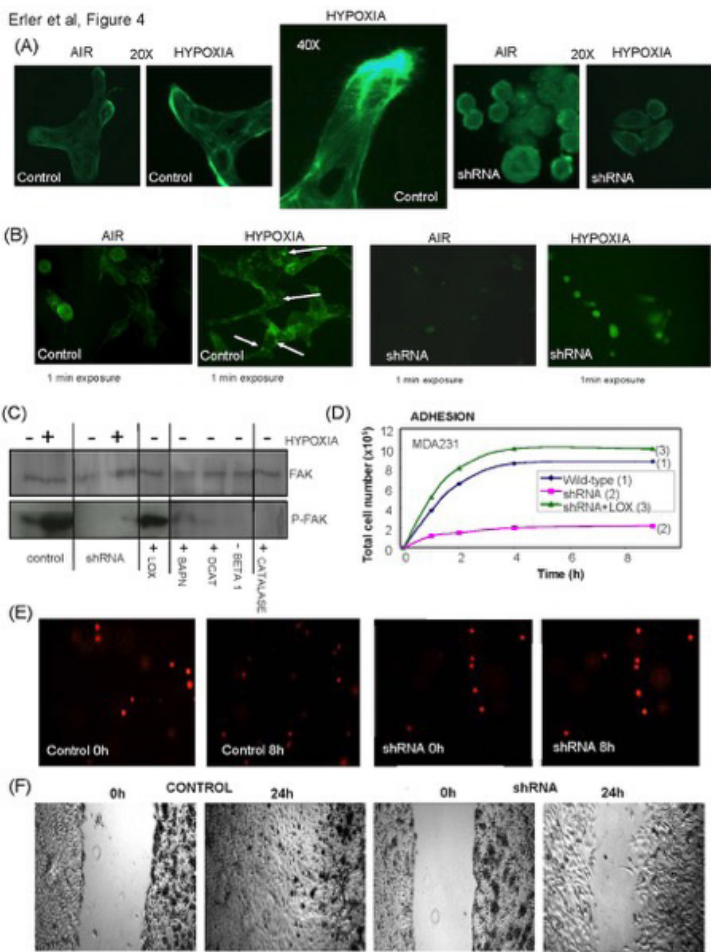
Dr. Thorsten Beck  
Researcher



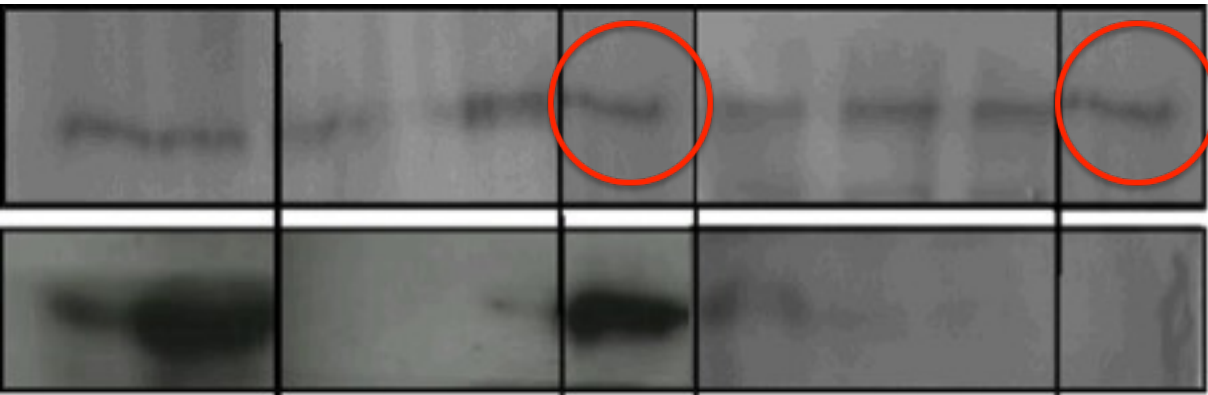
Prof. Michael Seadle, P.h.D.  
Principal Investigator

Addendum:

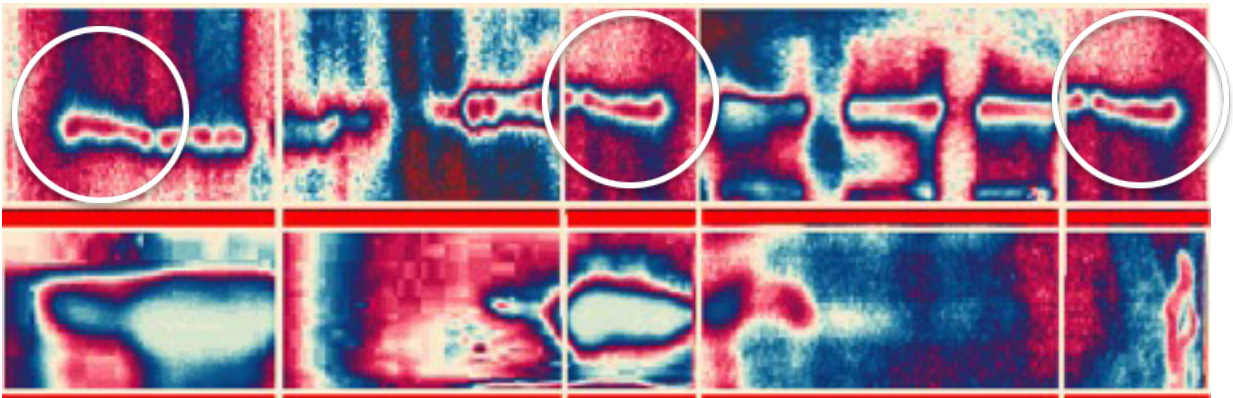
Fig. 4 (C)  
Main article:



Regions of Interest (ROIs) in Fig. 4 (C)  
Main Article:

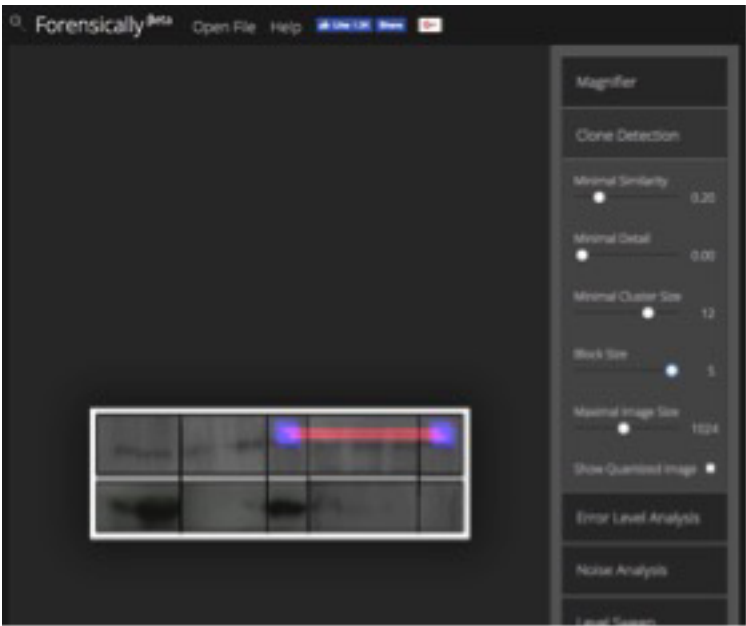


Forensic Gradient Map-Analysis of ROIs in Fig. 4 (C)  
Main article:



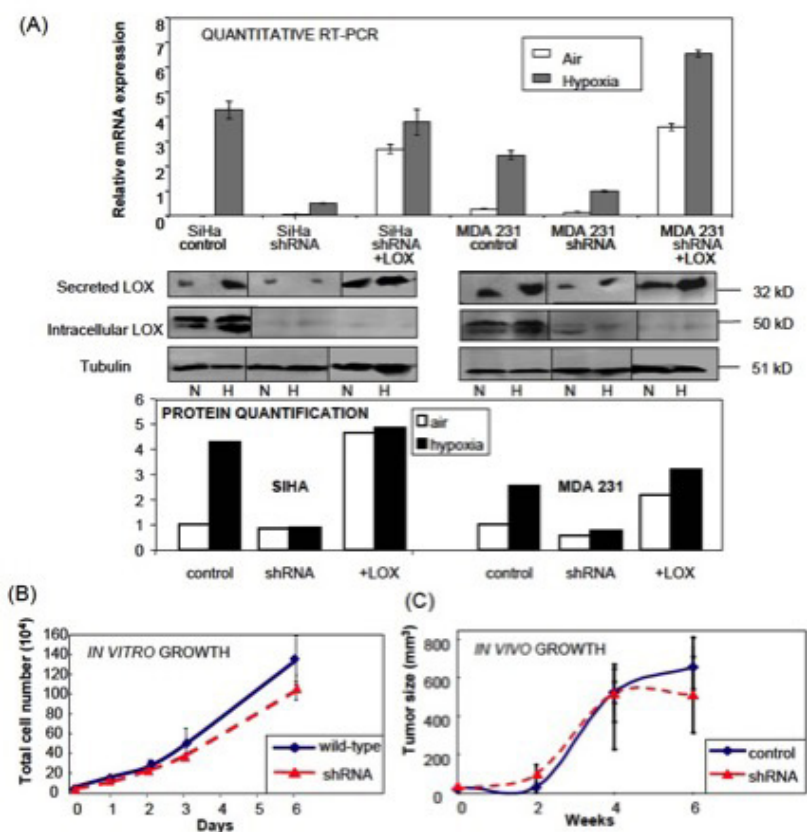
Note: Strong Levels of Similarity, susp. rotation and duplication.

Clone Detection of ROIs in Fig. 4 (C), forensicallyBeta  
Main article:



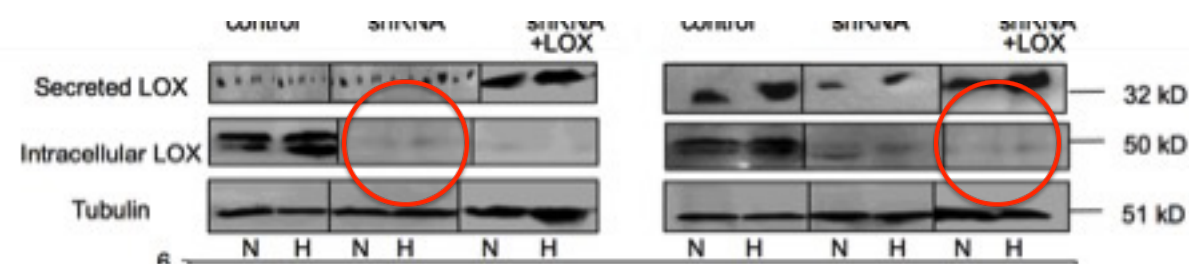
Note: Forensically clone detector without result when images are rotated.

Suppl. Fig. 4 (A)



Supplementary Figure 4: Characterization of cells expressing LOX shRNA. (A) LOX mRNA and protein expression levels were examined in cells expressing shRNA specific to LOX (shRNA) or a scrambled control sequence (control), and compared with those of shRNA cells transfected with mature LOX (+LOX). The 50 and 52kDa bands are pro-LOX, 30kDa is mature processed LOX<sup>30</sup>. (B+C) MDA231 wild-type (solid line) and LOX shRNA expressing (dashed line) growth curves. Both cell types had a similar distribution of cells in the different phases of the cell cycle with and without serum, and whether in air or hypoxia (data not shown). Data are plotted as mean  $\pm$  standard error. N=15 mice.

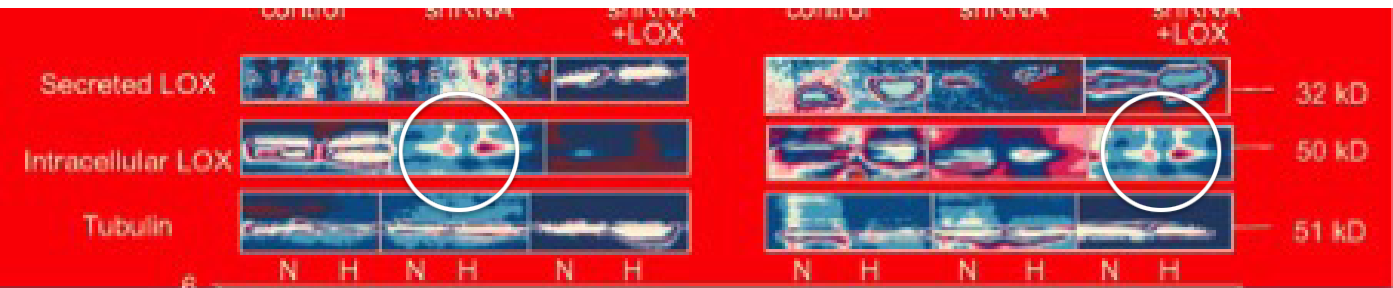
Regions of Interest (ROIs) in Fig. 4 (A)  
Supplementary:



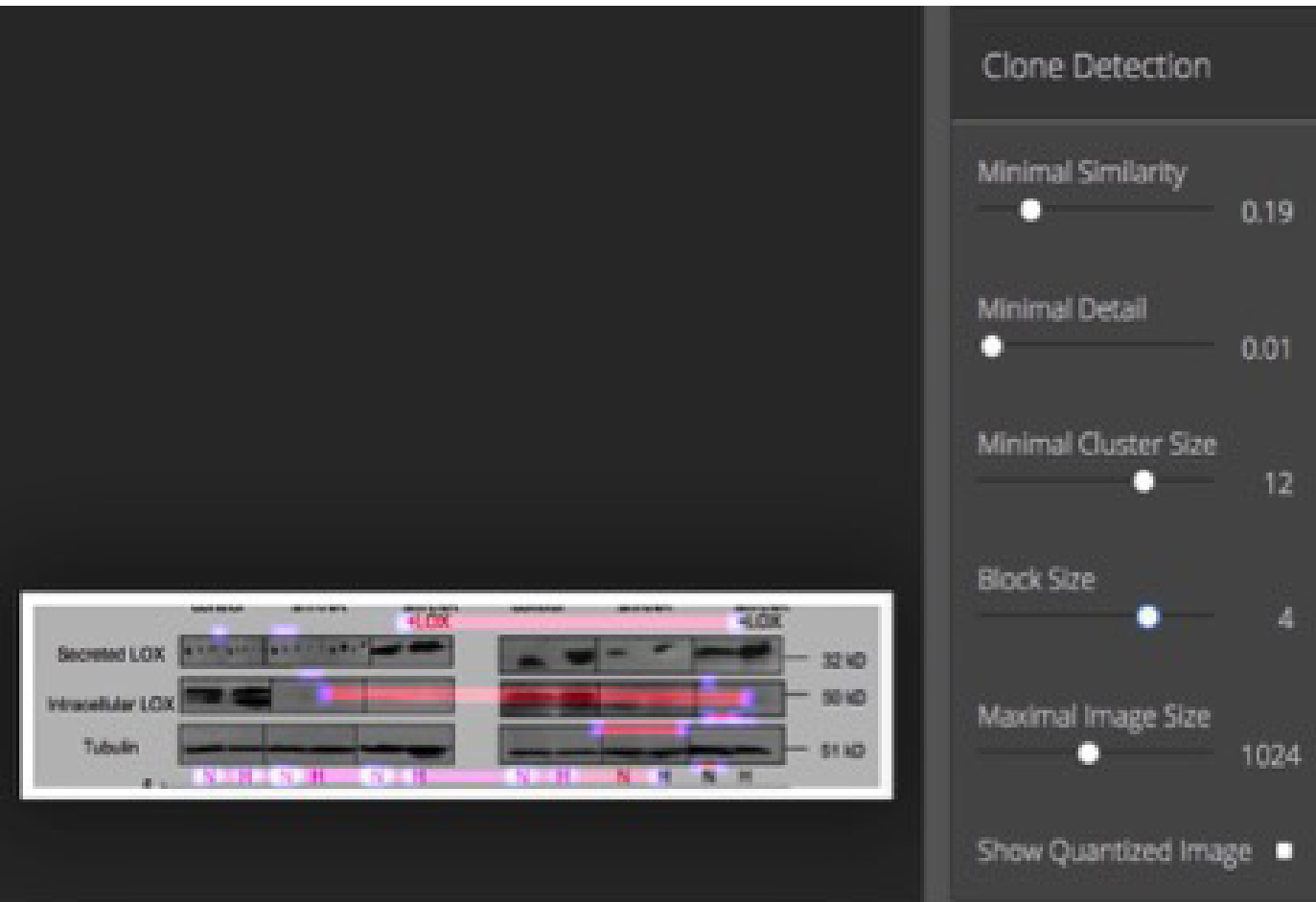
Note: Strong Levels of Similarity, susp. rotation and duplication.



Forensic Gradient Map-Analysis of ROIs in Fig. 4 (A)  
Supplementary:



Clone Detection of ROIs in Fig. 4 (a), forensicallyBeta  
Supplementary:



Note: Forensically Clone detection tool indicates obvious similarity.

Features in Dark ORI Photoshop action applied to Fig. 4 (a),  
Supplementary:

