

Aus der Chirurgischen Universitätsklinik Heidelberg

Klinik für Allgemein-, Viszeral- und Transplantationschirurgie

(Ärztlicher Direktor: Prof. Dr. med. Markus W. Büchler)

**Prolyl hydroxylase inhibition prevents graft injury  
during liver transplantation**

Inauguraldissertation

zur Erlangung des Medizinischen Doktorgrades

der Medizinischen Fakultät

der Ruprecht-Karls-Universität Heidelberg

vorgelegt von

Jun Cai

aus

Hubei

Volksrepublik China

2015

## Table of Content

---

<b>LIST OF ABBREVIATIONS.....</b>	<b>1</b>
<b>ZUSAMMENFASSUNG.....</b>	<b>3</b>
<b>1. INTRODUCTION.....</b>	<b>5</b>
<b>1.1 Liver transplantation.....</b>	<b>5</b>
<b>1.2 Ischemia and reperfusion injury in orthotopic liver transplantation.....</b>	<b>5</b>
<b>1.2.1 Ischemia and reperfusion injury.....</b>	<b>5</b>
<b>1.2.2 Pharmacological strategies to reduce ischemia and reperfusion injury during liver transplantation.....</b>	<b>7</b>
<b>1.3 Hypoxia-inducible factors and prolyl hydroxylase domain- containing enzymes.....</b>	<b>8</b>
<b>1.3.1 Hypoxia-inducible factors.....</b>	<b>8</b>
<b>1.3.2 Prolyl hydroxylase domain-containing enzymes.....</b>	<b>9</b>
<b>1.3.3 Prolyl hydroxylase domain-containing enzymes 1 deficiency protects liver from ischemia and reperfusion damage.....</b>	<b>11</b>
<b>1.4. Inhibition of prolyl hydroxylases protects organs from ischemia and reperfusion injury..</b>	<b>12</b>
<b>1.4.1 The role of hypoxia-inducible factors and prolyl hydroxylase domain-containing enzymes during ischemia and reperfusion injury.....</b>	<b>13</b>
<b>1.5. Aims of the thesis.....</b>	<b>14</b>
<b>2. MATERIALS AND METHODS.....</b>	<b>16</b>
<b>2.1 Animals.....</b>	<b>16</b>
<b>2.2. Animal models.....</b>	<b>16</b>
<b>2.2.1 Warm ischemia and reperfusion model.....</b>	<b>16</b>
<b>2.2.2 Orthotopic rat liver transplantation modle.....</b>	<b>18</b>
<b>2.2.2.1 Basic techniques and common procedures.....</b>	<b>18</b>

**Table of Content**

---

<b>2.2.2.2 Pre-surgical preparation.....</b>	<b>19</b>
<b>2.2.2.3 Donor operation.....</b>	<b>20</b>
<b>2.2.2.4 Back table graft preparation.....</b>	<b>23</b>
<b>2.2.2.5. Recipient operation.....</b>	<b>24</b>
<b>2.2.2.6 Postoperative treatment and follow-up.....</b>	<b>28</b>
<b>2.2.3 Histology.....</b>	<b>29</b>
<b>2.2.3.1 HE staining.....</b>	<b>30</b>
<b>2.3 Western Blotting.....</b>	<b>31</b>
<b>2.4 Statistics.....</b>	<b>31</b>
<b>3 RESULTS.....</b>	<b>32</b>
<b>3.1 Prolyl hydroxylase inhibitor EDHB protects against liver warm ischemia and reperfusion.....</b>	<b>32</b>
<b>3.2 The HIF-prolyl hydroxylase inhibitor EDHB protects against cold liver ischemia and reperfusion injury during orthotopic rat orthotopic liver transplantation.....</b>	<b>36</b>
<b>4 DISCUSSION AND CONCLUSIONS.....</b>	<b>38</b>
<b>5 REFERENCES.....</b>	<b>42</b>
<b>6 ACKNOWLEDGEMENTS.....</b>	<b>54</b>
<b>7 CURRICULUM VITAE.....</b>	<b>55</b>