



## KFO 243 Clinical Research Unit

# ELITE

## Early Immunological Determinants of Late Transplant Outcome

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**Coordinator: Prof. Edward K. Geissler, PhD – Head of Experimental Surgery**  
**Speaker: Prof. Dr. med. Hans J. Schlitt – Director of Dept. of Surgery**  
**University Hospital Regensburg**  
**Franz-Josef-Strauss-Allee 11**  
**93053 Regensburg, Germany**

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## Current Project-Related Publications August 2010 - April 2015

### Project P1:

**The role of  $\beta$ -defensins in allogeneic transplantation**

**Prof. Dr. rer. nat. Thomas Hehlgans, Immunology**

**Prof. Dr. med. Ernst Holler, Internal Medicine III, Hematology and Oncology**

1. Sporrer D, Gessner A, **Hehlgans T**, Oefner P, **Holler E**. (2015) The Microbiome and Allogeneic Stem Cell Transplantation, *Curr Stem Cell Rep* 1: 53-39.
2. **Holler E**, Butzhammer P, Schmid K, Hundsrucker C, Koestler J, Peter K, Zhu W, Sporrer D, **Hehlgans T**, **Kreutz M**, Holler B, Wolff D, **Edinger M**, Andreesen R, Levine JE, Ferrara JL, Gessner A, Spang R, Oefner PJ. (2014) Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant*. 20(5):640-5.
3. Wege AK, Huber B, Wimmer N, Männel DN, **Hehlgans T**. (2013) LT $\beta$ R expression on hematopoietic cells regulates acute inflammation and influences maturation of myeloid subpopulations. *Innate Immun*. 20(5):461-470.

4. Chai Q, Onder L, Scandella E, Gil-Cruz C, Perez-Shibayama C, Cupovic J, Danuser R, Sparwasser T, Luther SA, Thiel V, Rüllicke T, Stein JV, **Hehlgans T**, Ludewig B. (2013) Maturation of lymph node fibroblastic reticular cells from myofibroblastic precursors is critical for antiviral immunity. *Immunity*. 38(5):1013-24.
5. Barabas N, **Röhrl J**, **Holler E**, **Hehlgans T** (2013) Beta-defensins activate macrophages and synergize in proinflammatory cytokine expression induced by TLR ligands. *Immunobiology*. 2013 Jul;218(7):1005-11.
6. Harris AC, Ferrara JL, Braun TM, **Holler E**, Teshima T, Levine JE, Choi SW, Landfried K, Akashi K, Vander Lugt M, Couriel DR, Reddy P, Paczesny S (2012) Plasma biomarkers of lower gastrointestinal and liver acute GVHD. *Blood* 119:2960-3.
7. **Röhrl J**, Huber B, **Koehl GE**, **Geissler EK**, **Hehlgans T** (2012) Mouse  $\beta$ -defensin 14 (Defb14) promotes tumor growth by inducing angiogenesis in a CCR6-dependent manner. *J Immunol* 188:4931-9.
8. **Röhrl J**, **Geissler EK**, **Hehlgans T** (2012) Friend or foe: A novel role of  $\beta$ -defensins in tumor development. *Oncoimmunology* 8:1159-60.
9. Ferrara JL, Harris AC, Greenson JK, Braun TM, **Holler E**, Teshima T, Levine JE, Choi SW, Huber E, Landfried K, Akashi K, Vander Lugt M, Reddy P, Chin A, Zhang Q, Hanash S, Paczesny S (2011) Regenerating islet-derived 3-alpha is a biomarker of gastrointestinal graft-versus-host disease. *Blood* 118:6702-8.
10. Landfried K, Zhu W, Waldhier MC, Schulz U, **Ammer J**, Holler B, Wolff D, **Edinger M**, Peter K, **Kreutz M**, Andreesen R, Oefner PJ, **Holler E** (2011) Tryptophan catabolism is associated with acute GVHD after human allogeneic stem cell transplantation and indicates activation of indoleamine 2,3-dioxygenase. *Blood* 118:6971-4.
11. Gutiérrez A, **Holler E**, Zapater P, Sempere L, Jover R, Pérez-Mateo M, Schoelmerich J, Such J, Wiest R, Francés R. (2011) Antimicrobial peptide response to blood translocation of bacterial DNA in Crohn's disease is affected by NOD2/CARD15 genotype. *Inflamm Bowel Disease* 17:1641-50.

## **Project P2:**

**Interplay between receptors of innate immunity and vitamin D3 for the induction of alloreactions through antigen-presenting cells**

**Prof. Dr. med. Ernst Holler, Internal Medicine III, Hematology and Oncology**

**Prof. Dr. rer. nat. Marina Kreutz, Internal Medicine III, Hematology and Oncology**

**Prof. Dr. med. Sigrid Karrer, Dermatology**

1. Peter K, Rehli M, Singer K, Renner-Sattler K, **Kreutz M**. (2015) Lactic acid delays the inflammatory response of human monocytes. *Biochem Biophys Res Commun*. 13;457(3):412-8.
2. Krupar R, Robold K, Gaag D, Spanier G, **Kreutz M**, Renner K, Hellerbrand C, Hofstaedter F, Bosserhoff AK. (2014) Immunologic and metabolic characteristics of HPV-negative and HPV-positive head and neck squamous cell carcinomas are strikingly different. *Virchows Arch*. 465(3):299-312.
3. **Holler E**, Butzhammer P, Schmid K, Hundsrucker C, Koestler J, Peter K, Zhu W, Sporrer D, **Hehlgans T**, **Kreutz M**, Holler B, Wolff D, **Edinger M**, Andreesen R, Levine JE, Ferrara JL, Gessner A, Spang R, Oefner PJ. (2014) Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with

use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant.* 20(5):640-5.

4. Seliger C, Leukel P, Moeckel S, Jachnik B, Lottaz C, **Kreutz M**, Brawanski A, Proescholdt M, Bogdahn U, Bosserhoff AK, Vollmann-Zwerenz A, Hau P. (2013) Lactate-modulated induction of THBS-1 activates transforming growth factor (TGF)-beta2 and migration of glioma cells in vitro. *PLoS One.* 2013 Nov 1;8(11):e78935.
5. Gottfried E, Lang SA, Renner K, Bosserhoff A, Gronwald W, Rehli M, Einhell S, Gedig I, Singer K, Seilbeck A, Mackensen A, Grauer O, Hau P, Dettmer K, Andreesen R, Oefner PJ, **Kreutz M**. (2013) New aspects of an old drug--diclofenac targets MYC and glucose metabolism in tumor cells. *PLoS One* 2013 July 9;8(7):e66987.
6. Dettmer K, Vogl FC, Ritter AP, Zhu W, Nürnberger N, **Kreutz M**, Oefner PJ, Gronwald W, Gottfried E. (2013) Distinct metabolic differences between various human cancer and primary cells. *Electrophoresis.* 34(19):2836-47.
7. Moser C, Ruemmele P, Gehmert S, Schenk H, **Kreutz MP**, Mycielska ME, Hackl C, **Kroemer A**, Schnitzbauer AA, Stoeltzing O, Schlitt HJ, Geissler EK, Lang SA. (2012) STAT5b as molecular target in pancreatic cancer--inhibition of tumor growth, angiogenesis, and metastases. *Neoplasia.* 14(10):915-25.
8. Chirasani SR, Leukel P, Gottfried E, Hochrein J, Stadler K, Neumann B, Oefner PJ, Gronwald W, Bogdahn U, Hau P, **Kreutz M**, Grauer OM. (2013) Diclofenac inhibits lactate formation and efficiently counteracts local immune suppression in a murine glioma model. *Int J Cancer.* 132(4):843-53.
9. Gottfried E, **Kreutz M**, Mackensen A. (2012) Tumor metabolism as modulator of immune response and tumor progression. *Semin Cancer Biol.* 22(4):335-41.
10. Ullrich E, Bosch J, Aigner M, Voelkl S, Kroeger I, Hoffmann P, **Kreutz M**, Dudziak D, Gerbitz A. (2012) Advances in cellular therapy: 6th International Symposium on the clinical use of cellular products, March 24 and 25, 2011, Erlangen, Germany. *Cancer Immunol Immunother.* 61(3):433-43.
11. Zhu W, Stevens AP, Dettmer K, Gottfried E, Hoves S, **Kreutz M**, **Holler E**, Canelas AB, Kema I, Oefner PJ. (2011) Quantitative profiling of tryptophan metabolites in serum, urine, and cell culture supernatants by liquid chromatography-tandem mass spectrometry. *Anal Bioanal Chem.* 401(10):3249-61.
12. Gutiérrez A, Scharl M, Sempere L, **Holler E**, Zapater P, Almenta I, González-Navajas JM, Such J, Wiest R, Rogler G, Francés R (2014) Genetic susceptibility to increased bacterial translocation influences the response to biological therapy in patients with Crohn's disease. *Gut* 63(2):272-80.
13. **Kreutz M**, **Karrer S**, Hoffmann P, Gottfried E, Szeimies RM, Hahn J, **Edinger M**, Landthaler M, Andreesen R, Merad M, **Holler E** (2012) Whole-body UVB irradiation during allogeneic hematopoietic cell transplantation is safe and decreases acute graft-versus-host disease. *J Invest Dermatol* 132:179-87.
14. Hausmann M, Zeitler C, Weber A, Krebs M, Kellermeier S, Rosenstiel P, de Vallière C, Kosovac K, Fried M, **Holler E**, Rogler G (2012) MIP-3 $\alpha$  expression in macrophages is NOD dependent. *Digestion* 85:192-201.
15. Landfried K, Zhu W, Waldhier MC, Schulz U, **Ammer J**, Holler B, Wolff D, **Edinger M**, Peter K, **Kreutz M**, Andreesen R, Oefner PJ, **Holler E** (2011) Tryptophan catabolism is associated with acute GvHD following human allogeneic stem cell transplantation and indicates activation of indole-amine-2,3-dioxygenase. *Blood* 118:6971-4.

### Project P3:

#### Role of IL-13 and TGF- $\beta$ in the development of chronic rejection in solid organ transplantation

Prof. Dr. med. Stefan Fichtner-Feigl, Surgery

1. **Brunner SM**, Kesselring R, Rubner C, Martin M, Jeiter T, Boerner T, Ruemmele P, **Schlitt HJ**, **Fichtner-Feigl S**. (2014) Prognosis according to histochemical analysis of liver metastases removed at liver resection. *Br J Surg*. 101(13):1681-91.
2. Haimerl M, Verloh N, Fellner C, Zeman F, Teufel A, **Fichtner-Feigl S**, Schreyer AG, Stroszczynski C, Wiggermann P. (2014) MRI-based estimation of liver function: Gd-EOB-DTPA-enhanced T1 relaxometry of 3T vs. the MELD score. *Sci Rep*. 8;4:5621.
3. **Fichtner-Feigl S**, Kesselring R, Martin M, Obermeier F, Ruemmele P, Kitani A, **Brunner SM**, Haimerl M, **Geissler EK**, Strober W, **Schlitt HJ**. (2014) IL-13 orchestrates resolution of chronic intestinal inflammation via phosphorylation of glycogen synthase kinase-3 $\beta$ . *J Immunol*. 192(8):3969-80.
4. **Brunner SM**, **Schiechl G**, Kesselring R, Martin M, Balam S, **Schlitt HJ**, **Geissler EK**, **Fichtner-Feigl S**. (2013) IL-13 signaling via IL-13R $\alpha$ 2 triggers TGF- $\beta$ 1-dependent allograft fibrosis. *Transplant Res*. 2(1):16.
5. **Schiechl G**, **Brunner SM**, Kesselring R, Martin M, Ruemmele P, Mack M, Hirt SW, **Schlitt HJ**, **Geissler EK**, **Fichtner-Feigl S** (2013) Inhibition of innate co-receptor TREM-1 signaling reduces CD4<sup>+</sup> T cell activation and prolongs cardiac allograft survival. *Am J Transplant* 13:1168-80.
6. **Brunner SM**, Junger H, Ruemmele P, **Schnitzbauer AA**, Doenecke A, Kirchner GI, Farkas SA, Loss M, Scherer MN, **Schlitt HJ**, **Fichtner-Feigl S** (2013) Bile duct damage after cold storage of deceased donor livers predicts biliary complications after liver transplantation. *J Hepatol* Jan 12. doi:pii: S0168-8278(13)00009-3.
7. Goessmann H, Lang SA, **Fichtner-Feigl S**, Scherer MN, **Schlitt HJ**, Stroszczynski C, Schreyer AG, **Schnitzbauer AA**. (2012) Biliodigestive anastomosis: indications, complications and interdisciplinary management. *Chirurg* 83:1097-108.
8. **Brunner SM**, **Schiechl G**, Falk W, **Schlitt HJ**, **Geissler EK**, **Fichtner-Feigl S**. (2011) Interleukin-33 prolongs allograft survival during chronic cardiac rejection. *Transpl Int* 24:1027-39.
9. Kitani A, **Fichtner-Feigl S** (2010) Efficient in vivo delivery of plasmids and oligonucleotides using hemagglutinating virus of Japan envelope (HVJ-E) vector in immunological disease models. *Curr Protoc Immunol*, Chapter 10:Unit 10.17E.1-9.

### Project P4:

#### Basophils as potential modulators of humoral and cellular allo-immune responses

Prof. Dr. med. Matthias Mack, Nephrology

1. **Mack M** and Yanagita M. (2015) Origin of myofibroblasts and cellular events triggering fibrosis. *Kidney Int*. 87: 297-307.
2. Hermann FJ, Rodriguez Gomez M, Doser K, **Edinger M**, Hoffmann P, **Schiechl G**, Talke Y, Gobel N, Schmidbauer K, Bruhl H and **Mack M**. (2014) Basophils inhibit proliferation of CD4 T cells in autologous and allogeneic mixed lymphocyte reactions and limit disease activity in a murine model of graft versus host disease. *Immunology* 2014 Dec 27. [Epub ahead of print].

3. Rodriguez Gomez M, Talke Y, Hofmann C, Ketelsen I, Hermann F, Reich B, Goebel N, Schmidbauer K, Dunger N, Bruhl H, Renner K, Syed SN and **Mack M**. (2014) Basophils control T-cell responses and limit disease activity in experimental murine colitis. *Mucosal Immunol* 7:188-199.
4. Newson J, Stables M, Karra E, Arce-Vargas F, Quezada S, Motwani M, **Mack M**, Yona S, Audzevich T and Gilroy DW. (2014) Resolution of acute inflammation bridges the gap between innate and adaptive immunity. *Blood* 124:1748-1764.
5. Bischof A, Brumshagen C, Ding N, Kirchhof G, Briles DE, Gessner JE, Welte T, **Mack M** and Maus UA. (2014) Basophil expansion protects against invasive pneumococcal disease in mice. *J Infect Dis* 210:14-24.
6. Reich B, Schmidbauer K, Rodriguez Gomez M, Johannes Hermann F, Gobel N, Bruhl H, Ketelsen I, Talke Y and **Mack M**. (2013) Fibrocytes develop outside the kidney but contribute to renal fibrosis in a mouse model. *Kidney Int.* 84:78-89.
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8. **Schiechl G, Brunner SM, Kesselring R, Martin M, Ruemmele P, Mack M, Hirt SW, Schlitt HJ, Geissler EK, Fichtner-Feigl S** (2013). Inhibition of innate co-receptor TREM-1 signaling reduces CD4+ T cell activation and prolongs cardiac allograft survival. *Am J Transplant* 13:1168-80.
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10. Zigmond E, Varol C, Farache J, Elmaliah E, Satpathy AT, Friedlander G, **Mack M**, Shpigel N, Boneca IG, Murphy KM, Shakhar G, Halpern Z, Jung S (2012) Ly6C(hi) monocytes in the inflamed colon give rise to proinflammatory effector cells and migratory antigen-presenting cells. *Immunity* 37:1076-90.
11. Dhaliwal K, Scholefield E, Ferenbach D, Gibbons M, Duffin R, Dorward DA, Morris AC, Humphries D, MacKinnon A, Wilkinson TS, Wallace WA, Rooijen N, **Mack M**, Rossi AG, Davidson DJ, Hirani N, Hughes J, Haslett C, Simpson A (2012) Monocytes control second-phase neutrophil emigration in established LPS-induced murine lung injury. *Am J Respir Crit Care Med* 186:514-24.
12. London A, Itskovich E, Benhar I, Kalchenko V, **Mack M**, Jung S, Schwartz M (2011) Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. *J Exp Med* 208:23-39.
13. Kurotaki D, Kon S, Bae K, Ito K, Matsui Y, Nakayama Y, Kanayama M, Kimura C, Narita Y, Nishimura T, Iwabuchi K, **Mack M**, van Rooijen N, Sakaguchi S, Uede T, Morimoto T (2011) CSF-1-dependent red pulp macrophages regulate CD4 T cell responses. *J Immunol* 186:2229-37.
14. Rodriguez Gomez M, Talke Y, Goebel N, Hermann F, Reich B, **Mack M** (2010) Basophils support the survival of plasma cells in mice. *J Immunol* 185:7180-7185.

## Project P5:

### Role of natural killer cells in transplantation tolerance and rejection

Dr. med. Alexander Krömer, Surgery

Dr. rer. nat. Elke Eggenhofer, Experimental Surgery

Prof. Edward K. Geissler, PhD, Experimental Surgery

1. Lantow M, **Eggenhofer E**, Sabet-Baktach M, Renner P, Rovira J, **Koehl GE**, **Schlitt HJ**, **Geissler EK**, **Kroemer A**. (2015) CD27<sup>low</sup> natural killer cells prolong allograft survival in mice by controlling alloreactive CD8<sup>+</sup> T Cells in a T-bet-dependent manner. *Transplantation* 99:391-399.
2. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, Herbach N, Aichler M, Walch A, **Eggenhofer E**, Basavarajappa D, Rådmark O, Kobayashi S, Seibt T, Beck H, Neff F, Esposito I, Wanke R, Förster H, Yefremova O, Heinrichmeyer M, Bornkamm GW, **Geissler EK**, Thomas SB, Stockwell BR, O'Donnell VB, Kagan VE, Schick JA, Conrad M. (2014) Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol.* 16:1180-1191.
3. Renner P, Rovira J, Klein C, **Schlitt HJ**, **Geissler EK**, **Kroemer A**. (2014) KLRG1<sup>+</sup> natural killer cells protect against pulmonary metastatic disease by immunosurveillance. *Oncoimmunology*. 2014 Apr 8;3:e28328. eCollection 2014.
4. Sabet-Baktach M, **Eggenhofer E**, Rovira J, Renner P, Lantow M, Farkas SA, Malaisé M, Edtinger K, Shaotang Z, **Koehl GE**, Dahlke MH, **Schlitt HJ**, **Geissler EK**, **Kroemer A**. (2013) Double deficiency for ROR $\gamma$ t and T-bet drives Th2-mediated allograft rejection in mice. *J Immunol* 191:4440-4446.
5. **Eggenhofer E**, Rovira J, Sabet-Baktach M, Groell A, Scherer MN, Dahlke MH, Farkas SA, Loss M, **Koehl GE**, Lang SA, Melter M, **Schlitt HJ**, **Geissler EK**, **Kroemer A**. (2013) Unconventional ROR $\gamma$ t<sup>+</sup> T cells drive hepatic ischemia reperfusion injury. *J Immunol* 191:480-487.
6. **Eggenhofer E**, Popp FC, Mendicino M, Silber P, van't Hof W, Renner P, Hoogduijn MJ, Pinxteren J, van Rooijen N, **Geissler EK**, Deans R, **Schlitt HJ**, Dahlke MH. (2013) Heart grafts tolerized through third-party multipotent adult progenitor cells can be re-transplanted to secondary hosts with no immunosuppression. *Stem Cells Transl Med Stem Cells Transl Med* 2:595-606.
7. **Eggenhofer E**, Rovira J, Sabet-Baktach M, Groell A, Scherer MN, Dahlke MH, Farkas SA, Loss M, **Koehl GE**, Lang SA, Melter M, **Schlitt HJ**, **Geissler EK**, **Kroemer A** (2013) Unconventional ROR $\gamma$ t<sup>+</sup> T cells drive hepatic ischemia reperfusion injury. *J Immunol* 191:480-487.
8. Rovira J, Sabet-Baktach M, **Eggenhofer E**, Lantow M, **Koehl GE**, **Schlitt HJ**, Campistol JM, **Geissler EK**, **Kroemer A** (2013) A color-coded reporter model to study the effect of immunosuppressants on CD8<sup>+</sup> T-cell memory in antitumor and alloimmune responses. *Transplantation* 95:54-62.
9. **Eggenhofer E**, Benseler V, **Kroemer A**, Popp FC, **Geissler EK**, **Schlitt HJ**, Baan CC, Dahlke MH, Hoogduijn MJ (2012) Mesenchymal stem cells are short-lived and do not migrate beyond the lungs after intravenous infusion. *Front Immunol* 3:297.
10. Wege AK, Ernst W, Eckl J, Frankenberger B, Vollmann-Zwerenz A, Männel DN, Ortmann O, **Kroemer A\***, Brockhoff G\* (2011) Humanized tumor mice--a new model to study and manipulate the immune response in advanced cancer therapy. *Int J Cancer* 129:2194-2206. \*Equal senior authors

## Project P6:

### Humoral immune reconstitution after allogeneic stem cell transplantation

Prof. Dr. med. Matthias Edinger, Internal Medicine III, Hematology and Oncology

1. Hermann FJ, Rodriguez Gomez M, Doser K, **Edinger M**, Hoffmann P, Schiechl G, Talke Y, Göbel N, Schmidbauer K, Brühl H, **Mack M**. (2014) Basophils inhibit proliferation of CD4+ T cells in autologous and allogeneic mixed lymphocyte reactions and limit disease activity in a murine model of graft versus host disease. *Immunology*. 2014 Dec 27. [Epub ahead of print].
2. Greinix HT, Kuzmina Z, Weigl R, Körmoczi U, Rottal A, Wolff D, Kralj M, Kalhs P, Mitterbauer M, Rabitsch W, **Edinger M**, **Holler E**, Pickl WF. (2015) CD19(+)CD21(low) B Cells and CD4(+)CD45RA(+)CD31(+) T cells correlate with first diagnosis of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 21(2):250-8.
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4. Schmidl C, Hansmann L, Lassmann T, Balwierz PJ, Kawaji H, Itoh M, Kawai J, Nagao-Sato S, Suzuki H, Andreesen R, Hayashizaki Y, Forrest AR, Carninci P, Hoffmann P, **Edinger M**, Rehli M; FANTOM consortium. (2014) The enhancer and promoter landscape of human regulatory and conventional T-cell subpopulations. *Blood*. 24;123(17):e68-78.
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- PG, Zhao X, Zucchelli S, Summers KM, Suzuki H, Daub CO, Kawai J, Heutink P, Hide W, Freeman TC, Lenhard B, Bajic VB, Taylor MS, Makeev VJ, Sandelin A, Hume DA, Carninci P, Hayashizaki Y. (2014) A promoter-level mammalian expression atlas. *Nature*. 27;507(7493):462-70.
6. Hofmann C, Dunger N, Doser K, Lippert E, Siller S, **Edinger M**, Falk W, Obermeier F. (2014) Physiologic TLR9-CpG-DNA interaction is essential for the homeostasis of the intestinal immune system. *Inflamm Bowel Dis*. 20(1):136-43.
  7. Hansmann L, Schmidl C, Kett J, Steger L, Andreesen R, Hoffmann P, Rehli M, **Edinger M**. (2012) Dominant Th2 differentiation of human regulatory T cells upon loss of FOXP3 expression. *J Immunol*. 1;188(3):1275-82.
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#### **Project P7:**

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#### **Project P8:**

**Project funded in 1st funding period from 2010-2013, but not continued in 2nd funding period**

**Comparing the early immunological responses of liver transplant recipients treated under a bottom-up immunosuppressive regimen utilising either CsA or Everolimus**

**Dr. Dr. James Hutchinson, Experimental Surgery**

**PD Dr. med. Andreas Schnitzbauer, Surgery**

**Professor Dr. med. Hans-Jürgen Schlitt, Surgery**