UNIVERSITÄT
BERN

Institut für Pathologie

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Jahresbericht 2014

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>>> Editorial

Liebe Leserin, lieber Leser

Mit Freude präsentiere ich Ihnen den Jahresbericht 2014 des Instituts für Pathologie. Viele organisatorische Änderungen im Bereich der Dienstleistung konnten abgeschlossen werden. So konnten wir gegenüber unseren Kunden die angestrebte Konstanz erreichen: Unser Fachärzteteam wurde durch eigenen Nachwuchs ergänzt und die Spezialgebiete sind jetzt konstant vertreten. Im Histologielabor haben sich die neuen Prozesse nach der LEAN-Reorganisation eingespielt. Ein Höhepunkt war sicher die Anerkennung unserer Arbeit durch die Vergabe des Swiss Quality Poster Award für das Projekt der LEAN-Reorganisation. Diese externe Anerkennung für die harte Arbeit der vergangenen drei Jahre war für unser Team wichtig und zeigt uns, dass wir auf dem richtigen Weg sind. Jetzt sind eine Konsolidierung und eine Feinabstimmung das Ziel für das kommende Jahr. 2014 haben wir das LEAN-Projekt auf der Molekularpathologie abgeschlossen und neu die LEAN-Reorganisation der Abteilung Zytologie in Angriff genommen: Das Ziel hier ist eine «One-Day-Zytologie», um unseren Kunden den Geschwindigkeitsvorteil dieser noch zu wenig genutzten Methode voll anbieten zu können.

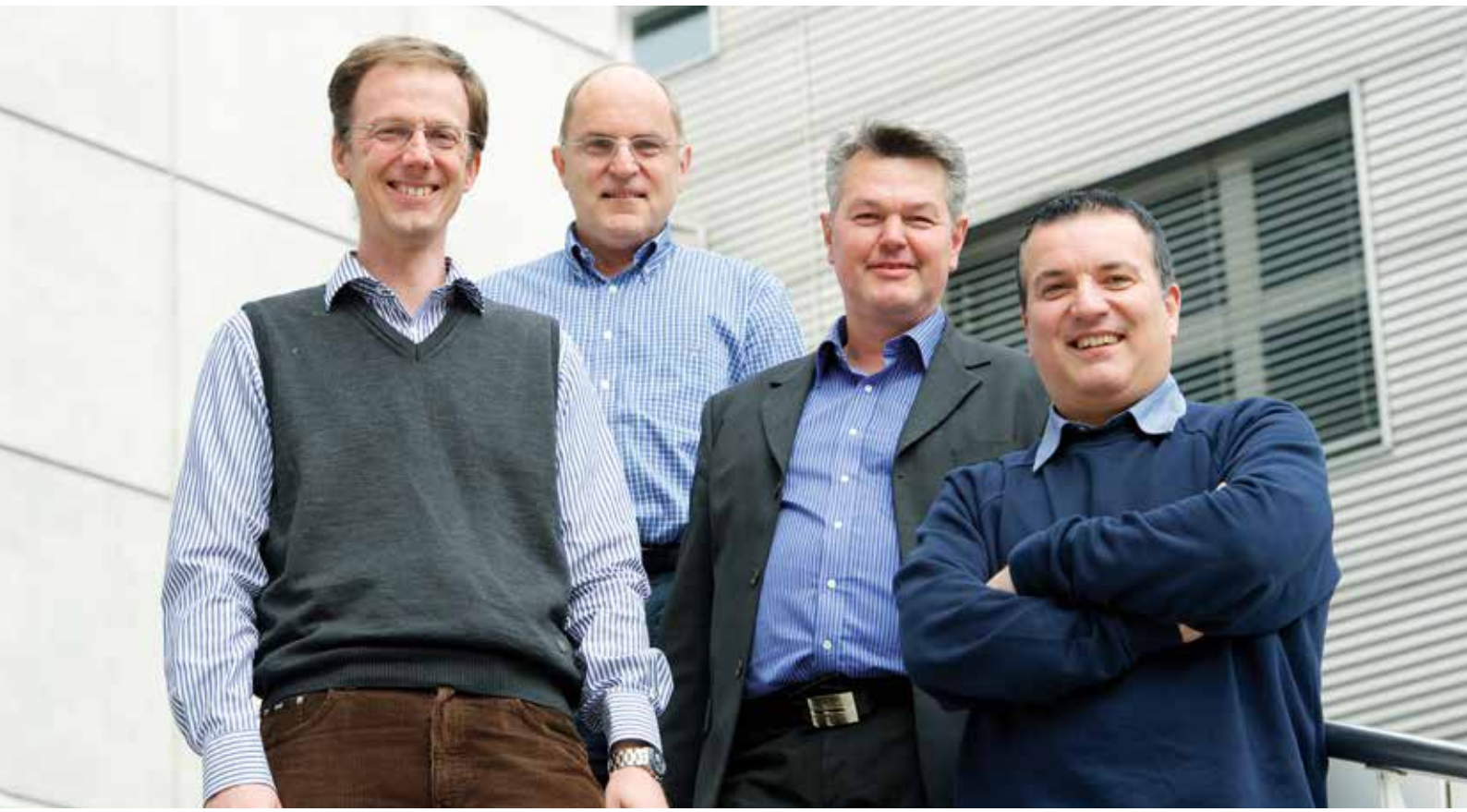
Im Bereich der Forschung beginnt sich die strategische Fokussierung auf Immunpathologie und Tumorpathologie auszuzahlen. Die Anzahl der Mitarbeiter nimmt aufgrund der erfolgreichen Drittmittelwerbung jährlich zu, sodass es in den Labors manchmal eng wird. Das Kantonale Krebsregister ist 2014 auf die volle Anzahl der Mitarbeiter angewachsen, hier verweise ich auf den eigenen Jahresbericht.

2015 wird der Konsolidierung der neuen Prozesse gewidmet, gleichzeitig können wir Mitte Jahr mit dem Umbau des Laborbereichs beginnen. Dieser Umbau wird platz- und lärmmässig eine Herausforderung für uns alle werden, wir freuen uns aber schon jetzt auf die verbesserten Räumlichkeiten.

Jetzt wünsche ich Ihnen viel Vergnügen bei der Durchsicht des Berichtes.

Herzlich

Ihr Aurel Perren



Von rechts nach links: Prof. A. Perren, Institutsleiter; Prof. Ch. Müller, PhD, Leiter Experimentelle Pathologie; G. Suter, Klinikmanager; Prof. A. Lugli, Leiter Klinische Pathologie.

Mitarbeitende des Instituts für Pathologie, Universität Bern.

>>> Organigramm

Ärzteteam Klinische Pathologie.

Team Postmortale Diagnostik.

>>> Dienstleistung

1 Klinische Pathologie

Leiter: Prof. med. Alessandro Lugli

Die Arbeitsprozesse in der Klinischen Pathologie (KPath) werden nach dem LEAN-Prinzip gestaltet und eine optimale Koordination wird durch die KPath Staff gewährleistet. Die KPath besteht aus den Einheiten Ärzteschaft, Labor Histopathologie und Immunhistochemie und Berichtswesen (Befundsekretariat und Archiv).

1.1 Ärzteschaft

Die Fachärzteschaft besteht aus 15 Fachärztinnen und Fachärzten, welche in 18 Fachgruppen, besteht jeweils aus 2 bis 6 Mitglieder eingeteilt sind. Die Fachgruppen garantieren eine optimale Kommunikation mit der klinischen Kundschaft und vertreten die Pathologie an den zahlreichen wöchentlichen und zweiwöchentlichen Tumorboards/Fallbesprechungen innerhalb des Inselspitals. Zusätzlich betätigen sich die Fachgruppen auf den Gebieten Lehre und Forschung, wobei das Fachwissen durch den Besuch nationaler und internationaler Kongresse, Analyse der aktuellen Literatur und durch Forschungstätigkeit in der Einheit «Translational Research Unit (TRU)» auf dem neuesten Stand gehalten wird.

In diesem Jahr wurde die Weiterbildung der Assistenzärztinnen und -ärzte reorganisiert und der Autopsiebetrieb gemäss LEAN-Management restrukturiert. Alle drei Bereiche der KPath werden neu durch die KPath-Ärzteschaft direkt betreut.

Für das Jahr 2015 sind folgende Projekte definiert worden:
1. Finalisierung des LEAN-Projektes in den Einheiten Labor Histopathologie und Autopsie
2. Durchführung eines LEAN-Projektes in der Einheit Berichtswesen und Archiv
3. Vorbereitung auf den bevorstehenden Umbau der Räumlichkeiten der Klinischen Pathologie

1.2 Neuropathologie

Im Jahr 2014 untersuchte der Bereich Neuropathologie knapp 1200 neurochirurgische Einsendungen. Darunter wurden in 300 Fällen intraoperative Schnellschnittuntersuchungen durchgeführt. Wir zählen damit im Hinblick auf die Tumordiagnostik zu den aktivsten Neuropathologien in der Schweiz. Aufgrund des im Schweizer Vergleich grossen Einzugsgebiets und der Ausrichtung der Neurochirurgischen Klinik des Inselspitals besteht der diagnostische Schwerpunkt in der Tumordiagnostik, umfasst jedoch das gesamte Spektrum der «Surgical Neuropathology» einschliesslich vaskulärer und pädiatrischer Neurochirurgie sowie Proben aus der Epilepsie-Chirurgie.

Hinzu kommen zahlreiche Einsendungen weiterer Disziplinen aus dem Bereich des peripheren Nervensystems. In Zusammenarbeit mit dem Neuromorphologischen Labor (Leiter: Prof. K. Rösler) der Neurologischen Klinik des Inselspitals wurden rund 70 Muskelbiopsien untersucht. Im Bereich der Postmortalen Diagnostik führten wir 93 Hirnsektionen durch.

Die hohe Spezialisierung spiegelte sich wie in den Vorjahren in zahlreichen diagnostisch orientierten Publikationen wider. Entsprechend dem Charakter der Neuropathologie als Schnittstelle zwischen den klinischen Neurofächern, der Labordiagnostik und translationaler Forschung war der Fachbereich Neuropathologie auch im Jahr 2014 in zahlreichen Veranstaltungen insbesondere mit Klinken des Inselspitals engagiert. Darüber hinaus ist das Fach Neuropathologie einer der Schwerpunkte der Medizinischen Allianz Bern/Basel (MBB).

1.3 Postmortale Diagnostik

Im Jahr 2014 wurden, ähnlich wie im Vorjahr, insgesamt 155 Autopsien durchgeführt, davon 66 für das Inselspital. Anfang des Jahres wurde begonnen, die bereits in anderen Abteilungen der Dienstleistung bereits erfolgreich umgesetzte Arbeitsplatz- und Prozessoptimierung nach dem LEAN-Prinzip durchzuführen. In diesem Rahmen wurden Räumlichkeiten neu definiert: So wurde z.B. analog zur diagnostischen klinischen Pathologie ein Diagnostikraum, in dem nicht nur die Fallerfassung, sondern auch die Falldokumentation, die Mikroskopie und die Fallabgabe stattfinden kann, eingerichtet. Weiter konnten wir einen bislang nicht zufriedenstellend genutzten Raum als Demonstrations- und Ausbildungsraum gestalten.

Neben mehreren ausgedehnten Entsorgungsaktionen wurden andererseits z.B. die Garderoben renoviert sowie auch der gesamte Innenbereich des Autopsiegebäudes. Mit diesen initialen räumlichen Veränderungen sind nun die Grundlagen für ein erfolgreiches Fortführen des LEAN-Projektes im Hinblick auf die weitere inhaltliche Optimierung der Arbeitsprozesse geschaffen worden.

Laborteam Histopathologie.

Labor Immunhistochemie.

1.4 Labor Histopathologie und Immunhistochemie

Im Jahr 2014 wurden im Labor Histopathologie für 27 219 Patienten 35 293 Einsendungen aus 66 420 Lokalisationen untersucht. Dies entspricht einem Zuwachs von 7625 Proben (13%). Die Anzahl der Schnellschnitte lag mit 1673 um 161 Fälle höher als auf dem Vorjahresniveau.

Die in den Vorjahren der nach dem LEAN-Prinzip gestalteten Prozessoptimierung (siehe auch Fokus) eingeführten Änderungen wurden nun angewandt und optimiert. Dementsprechend vergleichbar waren somit auch die durchschnittlichen Durchlaufzeiten für die Befunde, wobei mit 30 Stunden für Biopsien und 43 Stunden für Operationspräparate noch einmal eine geringe Verbesserung erzielt werden konnte. Die durchschnittliche Bearbeitungszeit für Schnellschnitte war mit 18,4 Minuten vergleichbar mit dem Vorjahr.

Die Laborleitung des Labors Histopathologie wurde 2014 neu strukturiert und besteht aus einem Laborleiter, welcher durch zwei stellvertretende Laborleiterinnen administrativ und operativ unterstützt wird. Zusätzlich leitet die Laborleitung wöchentlich die Bereichsleitungssitzungen und stellt die Weiter- und Fortbildung des Laborpersonals sicher. Der Hauptfokus für das Jahr 2015 liegt bei der Erstellung von «Standard Operating Procedures» (SOP) in allen Arbeitsprozessen des Labors.

Das Labor Immunhistochemie hat zu Beginn des Jahres neue Räumlichkeiten bezogen und sämtliche immunhistochemische Färbungen erfolgreich auf dem Leica-Bond-Färbeautomaten etabliert. Anhand von insgesamt 52 523 Färbungen, im Durchschnitt 211 pro Tag, wurden im letzten Jahr 8313 Fälle bearbeitet. Zusätzlich sind an 228 nativen Nierenbiopsien insgesamt 2280 Immunfluoreszenzfärbungen vorgenommen worden. Mit total 54 803 ist die Anzahl der immunhistochemischen Färbungen gegenüber dem Vorjahr in etwa auf gleichem Niveau geblieben.

Das Immunhistochemie-Labor hat im Verlaufe des Jahres 12 neue Primärantikörper etabliert und 2 Doppelfärbungen eingeführt. Aktuell sind 232 verschiedene immunhistochemische Färbungen, darunter 14 für die Detektion von Erregern, für die Routinediagnostik verfügbar.

1.5 Berichtswesen

Im Zuge des LEAN-Managements haben am 1. August 2014 die Sekretariate Histopathologie und Zytopathologie fusioniert. Die Zusammenarbeit der beiden Sekretariate wird nun Schritt für Schritt intensiviert und ausgebaut, so können Synergien genutzt und Auftragsschwankungen gegenseitig aufgefangen und ausgeglichen werden.

Mit einer optimierten Planung und dem gezielten Einsatz der Mitarbeiterinnen können die Arbeitsprozesse im Berichtswesen und die Durchlaufzeiten der Diagnosen in beiden Bereichen zusätzlich verbessert und verkürzt werden. Als Schnittstelle zwischen der Ärzteschaft und den Labors tragen die Sekretariate beider Bereiche einen wichtigen Teil zum reibungslosen, speditiven Arbeitsablauf bei. Im Jahre 2015 werden die Arbeitsprozesse durch ein LEAN-Projekt weiter optimiert.

Präparat wird untersucht.

Team der Molekularpathologie und der Forschungsgruppe von Prof. E. Vassella.

Mitarbeitende der Abteilung Zytopathologie.

2 Molekularpathologie

Molekularpathologie (PCR-, FISH- und EM-Labor)

Wissenschaftlicher Leiter: Prof. Dr. pharm. Erik Vassella
Medizinischer Leiter: Dr. med. Matthias Dettmer und
Prof Dr. med. Aurel Perren

Mitarbeiterinnen:
Claudia Zurbuchen, technician
Maja Neuenschwander, technician
Cornelia Schlup, technician
Brigitte Jossen, technician

In der Molekularpathologie verwenden wir die Methoden der PCR-Analyse und -Sequenzierung (PCR-Labor), Fluoreszenz-*in-situ*-Hybridisierung (FISH-Labor) sowie Elektronenmikroskopie (EM-Labor).

Das Analysenspektrum des PCR-Labors umfasst Tests im Rahmen der Lymphomdiagnostik für die Klonalitätsanalyse von B- und T-Zellen, Mikrosatelliteninstabilität, Mutationen von Tumorgenen (z.B. k-RAS, EGFR, BRAF), Heterozygotieverlust, epigenetische Veränderungen (MGMT-Promoter-Methylierung) sowie den Nachweis verschiedener bakterieller und viraler Erreger. Die Tests haben diagnostische oder prädiktive Implikation und können an Formalin-fixiertem und Paraffin-eingebettetem Gewebe durchgeführt werden. Im PCR-Labor blieb die Zahl der durchgeführten Tests in den letzten vier Jahren relativ konstant; hingegen hat die Komplexität einzelner Tests, insbesondere durch die Einführung des «Next-Generation Sequencing», stark zugenommen. Letztere Methode wurde im letzten Jahr bei 20 Fällen für diagnostische Zwecke durchgeführt, Tendenz stark ansteigend. Diese Methode wurde im Jahresbericht 2014 näher vorgestellt.

Die Zahl der im FISH-Labor durchgeführten Analysen ist in den letzten Jahren stark angestiegen; im letzten Jahr sogar um über 70 %. Gewichtige Analysen hierbei sind der Nachweis der ALK-Translokation beim Lungenkarzinom sowie der HER2-Amplifikation beim Mammakarzinom, doch auch Tests beim Non-Hodgkin-Lymphom, Magenkarzinom und Sarkom mittels FISH werden häufig durchgeführt. Die Zahl der elektronisch-mikroskopisch durchgeführten Analysen blieb weitgehend konstant.

Das Molekularpathologie-Labor nimmt regelmässig an Ringversuchen im Rahmen der Qualitätssicherung teil. Als Zielsetzung für das Jahr 2015 steht die Einführung der Akkreditierung an. Zudem sind die Etablierung weiterer Tests, z.B. BRCA-Mutationsanalyse beim serösen Ovarialkarzinom, geplant.

Das Molekularpathologie-Labor dient auch als Ausbildungsstätte für Assistenzärzte sowie für Pathologen zur Erlangung des FMH-Subtitels in Molekularpathologie. Eine Vorlesungsreihe in Molekularpathologie im Rahmen des Masterprogramms Molecular Life Sciences sowie der Graduate School wird jährlich durchgeführt.

3 Klinische Zytopathologie

Leiterin: Dr. med. A. Schmitt

Eine kundenorientierte, schnelle und qualitativ hochstehende Diagnostik des zytologischen Einsendegutes hat oberste Priorität in der Abteilung für Zytologie. Als schnelle und kostengünstige Methode konnte die Abteilung einen erneuten Anstieg der Proben im Bereich der Exfoliativzytologie und der Feinnadelpunktate (2014: 8418, 2013: 8366) sowie der Anzahl der angefertigten Zellblöcke (2014: 2324, 2013: 2277) verzeichnen. Zusätzlich wurden im Auftrag externer Kunden erstmals mehrere Feinnadelpunktionen von Lymphknoten, Schilddrüse und Weichteilen im abteilungseigenen Punktionsambulatorium durchgeführt.

Der Bedarf an zytologischer Expertise zeigte sich auch in einer regen direkten Zusammenarbeit mit spitalinternen Kunden im Rahmen der sogenannten ROSE (rapid on-site evaluation). Hierbei führt ein Zytologe vor Ort eine Schnellbeurteilung des entweder selbst mittels Feinnadelpunktion oder endoskopisch gewonnenen Materials durch.

Im stetigen Bestreben, unsere Serviceleistungen kontinuierlich zu verbessern, stand das Jahr 2014 ganz im Zeichen der Optimierung. Im Frühling startete die Abteilung mit der Reorganisation der Abläufe nach LEAN-Prinzipien. Nach einer Ist-Erhebung erfolgte zunächst die Implementierung neuer Geräte nach modernsten Standards. Eine optimale Einbindung dieser Geräte in die Arbeitsabläufe mit dem Ziel einer «same day cytology» ist derzeit in Arbeit.

Eine weitere Stärke der Abteilung neben den Bereichen Diagnostik und Dienstleistung sind Ausbildung (Zytotechnik) und Weiterbildung (Facharztsubtitel Zytologie FMH). 2014 schloss eine Schülerin der Berner Laborschule ihr Praktikum erfolgreich ab. Ein biomedizinischer Analytiker schloss nach zweijähriger berufsbegleitender Ausbildung zum Zytotechniker diese mit dem kantonal-bernischen Diplom erfolgreich ab, während eine biomedizinische Analytikerin die zweijährige berufsbegleitende Ausbildung zur Zytotechnikerin begann. Ein Pathologe bestand im Herbst 2014 erfolgreich die Prüfung für den FMH-Subtitel Zytopathologie.

4 Fachgruppen des Instituts für Pathologie der Universität Bern

Stand Januar 2015

Dermatopathologie	
Y. Banz	031 632 88 75
H. Dawson	031 632 99 60
S. Berezowska	031 632 49 37
E. Hewer	031 632 99 51

Endokrinopathologie	
A. Perren	031 632 32 22
M. Dettmer	031 632 99 69
A. Schmitt	031 632 32 48

Gastrointestinalpathologie	
A. Lugli	031 632 99 58
R. Langer	031 632 32 47
H. Dawson	031 632 99 60
E. Diamantis	031 632 87 68
M. Montani	031 632 32 67
T. Rau	031 632 87 56

Mamma- und Gynäkopathologie	
T. Rau	031 632 87 56
M. Trippel	031 632 32 76
Y. Banz	031 632 88 75
M. Montani	031 632 32 67

Hämatopathologie	
Y. Banz	031 632 88 75
A. Schmitt	031 632 32 48
E. Hewer	031 632 99 51
A. Perren	031 632 32 22

Herz-, Gefäss- und Rheumapathologie	
Y. Banz	031 632 88 75
M. Montani	031 632 32 67
V. Genitsch	031 632 99 22

HNO-Pathologie	
M. Dettmer	031 632 99 69
E. Diamantis	031 632 87 68
E. Hewer	031 632 99 51
T. Rau	031 632 87 56

Leberpathologie	
M. Montani	031 632 32 67
E. Diamantis	031 632 87 68
R. Langer	031 632 32 47

Lungenpathologie	
S. Berezowska	031 632 49 37
E. Hewer	031 632 99 51
Y. Banz	031 632 88 75

Nephropathologie	
V. Genitsch	031 632 99 01
E. Diamantis	031 632 87 68
R. Langer	031 632 32 47

Neuropathologie	
E. Hewer	031 632 99 51
S. Berezowska	031 632 49 37

Ophthalmopathologie	
A. Schmitt	031 632 32 48
E. Hewer	031 632 99 51

Pädopathologie	
M. Trippel	031 632 32 76
M. Montani	031 632 32 67
S. Berezowska	031 632 49 37

Pankreaspathologie	
E. Diamantis	031 632 87 68
M. Montani	031 632 32 67
R. Langer	031 632 32 47
A. Perren	031 632 32 22

Uropathologie	
E. Diamantis	031 632 87 68
V. Genitsch	031 632 99 22
M. Dettmer	031 632 99 69
M. Montani	031 632 32 67

Weichteil- und Knochenpathologie	
R. Langer	031 632 32 47
A. Schmitt	031 632 32 48
H. Dawson	031 632 99 60

Postmortale Diagnostik	
R. Langer	031 632 32 47
A. Lugli	031 632 99 58
E. Diamantis	031 632 87 68
Y. Banz	031 632 88 75

Zytologie	
A. Schmitt	031 632 32 48
E. Hewer	031 632 99 51
Y. Banz	031 632 88 75

5 Dienstleistungsstatistik

Klinische Pathologie

Histopathologie	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Anzahl Einsendungen	34'319	34'532	35'001	33'805	32'710	**35'293**
Anzahl Lokalisationen	58'926	59'291	61'693	61'015	58'795	**66'420**
Anzahl Proben Schnellschnitte	2'715	2'049	2'937	1'792	1'997	**2'307**
Autopsie						
Anzahl durchgeführte Autopsien	223	198	170	195	155	**156**
Zytopathologie						
Anzahl Proben Klinische Zytologie	7'670	7'844	8'849	8'218	8'361	**8'418**
Anzahl Proben Gynäkologische Zytologie	8'821	8'697	8'697	8'724	8'054	**7'726**
Anzahl Einsendungen Proben Total	16'491	16'541	16'996	16'942	16'415	**16'144**
Anzahl Zellblöcke	272	1'216	1'705	1'830	2'277	**2'324**
Immunhistochemie						
Anzahl Fälle Diagnostik (Paraffin)	7'149	6'777	7'472	6'692	7'104	**8'313**
Anzahl Färbungen Immunfluoreszenz (Nierenbiopsien)	2'808	2'712	2'820	2'844	2'101	**2'280**
Anzahl Fälle Immunzytologie am Ausstrich	681	388	359	302	302	**372**
Anzahl Färbungen Immunzytologie am Ausstrich	1'597	967	777	672	586	
Anzahl Färbungen In-situ-Hybridisierungen	87	419	576	413	478	
Molekularpathologie						
Anzahl Fälle PCR-basierende Tests	1'019	1'042	1'325	1'235	1'420	**1'304**
Anzahl Fälle Lymphome (IgH-/TCR-Rearrangement)	217	139	200	171	214	**218**
Anzahl Fälle Methylierungsnachweis	177	133	156	155	180	**128**
Anzahl Fälle Mutationsanalysen (EGFR, kRAS, BRAF, IH1/2)	343	493	708	755	818	**902**
Anzahl Fälle FISH	141	254	259	206	287	**554**
Anzahl Hybridisierungen FISH	176	328	354	304	391	**683**

Tumorbank

Anzahl Einsendungen Tumorbank	698	880	803	727	831	**894**
Unterstützte Fallprojekte (in Kollaboration mit TRU)	0	0	22	67	167	**474**

Mitarbeitende der Abteilung Experimentelle Pathologie.

Arbeit an der Zellkultur.

>>> Forschung/Research

1 Research at the Institute of Pathology

Research at the Institute of Pathology focuses on immune-driven inflammatory disorders as well as tumor biology and tumor pathology. To address specific questions in these research areas, the Division of Experimental Pathology and the Translational Research Unit work together to cover a wide range of methodological approaches including the generation and use of genetic mouse models for *in vivo* studies, the molecular and cellular characterization of distinct cell subsets *in vitro* and various tissue-based *ex vivo* analyses. With seven basic science research groups and four translational research groups the Institute of Pathology is well integrated in several local, national and international collaborations. In 2014, fifty people were working full-time on scientific research projects; moreover, twelve staff pathologists dedicated part of their working time to scientific projects. Due to the constantly increasing number of students and third-party funded research staff, labs and office space are now used to their full capacity.

1.1 The Division of Experimental Pathology

Head: Prof. Christoph Mueller, PhD

Administrative support:
Christine Feller (40%)
Christa Hagert (50%)
Martina Häusler (40%)

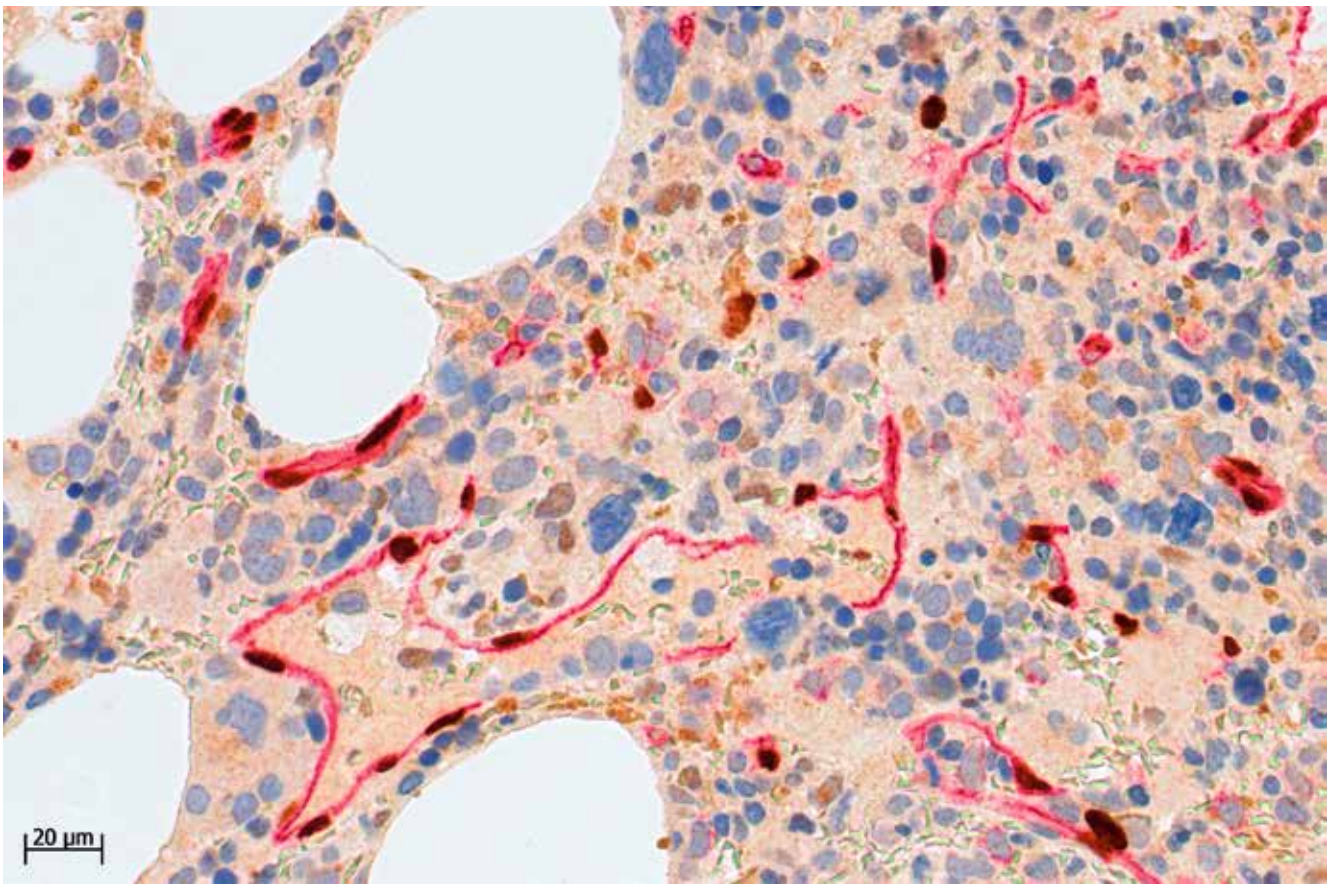
Thematically, the research activities of the currently seven research groups in the Division of Experimental Pathology are centered on two main topics:
– immunopathology and inflammation
– experimental tumor pathology and tumor biology

As of November 1st 2014, Dr. Mario Noti officially started his research activities as an Ambizione fellow of the Swiss National Science Foundation (SNSF) and junior research group leader at our Division. Here, he will continue on his successful postdoctoral work that was initiated in the lab of Prof. David Artis, U. Penn, Philadelphia. In particular, Mario Noti will be looking at the contribution of the intestinal microbiota to the pathogenesis of food allergies and eosinophilic esophagitis.

The majority of the research groups in the Division of Experimental Pathology address questions related to the fundamental aspects of cell biology and to the etiopathogenesis of neoplastic or inflammatory disorders. Nevertheless, translational aspects are also considered in our research activities. Notably, the research group of Professor Reubi is substantially financed by license fees obtained from their current patents in the field of peptide receptor targeting of tumors.

In our experimental work we can rely on facilities available at the Institute of Pathology such as laser capture microdissection and confocal microscopy (Olympus), but also on core facilities provided by the Department of Clinical Research including the FACS (cytometry) core facility, and the genomics core facility (with access to an Ion Torrent® instrument). Those two core facilities are conveniently located in the building of the Institute of Pathology. In addition, access to the microscopy center (MIC) with its instruments for confocal microscopy (including live cell imaging, and 2-photon microscopy) and to the proteomic core facility of the Medical Faculty is available. We are also part of the Interfaculty Bioinformatics Unit and are granted unrestricted access to the deep sequencing platform of the University of Bern (equipped with a Roche GS Junior and Illumina HiSeq 2000). Several of our research groups use the central mouse facility and more recently also the germ-free and gnotobiotic mouse facility (Clean Mouse Facility) at the Medical Faculty.

The spectrum of available and well-established technologies in the Division of Experimental Pathology includes confocal microscopy, including FRET analysis, fluorescent in situ hybridization (FISH), laser capture microdissection of frozen and FFPE tissue sections (including immunostained FFPE tissue sections) as well as autoradiography of tissue sections in combination with immunohistochemical stainings. Moreover, we have access to the entire spectrum of FACS-based techniques for cell sorting and multi-color analysis. Highly sophisticated methodologies are established for the identification of microRNAs and their target sequences in normal and diseased tissues; furthermore, several distinct transfection systems including lentivirus-based transduction systems and mRNA expression profiling techniques for small numbers of cells or microdissected tissues are available. The IonTorrent platform is currently used for 16S rRNA sequencing of intestinal bacteria and for the identification of the IonTorrent 50 gene cancer panel by AmpliSeq. Finally, several of our research groups have a longstanding expertise in the isolation and culture of primary cells (e.g. immune cells, epithelial cells and mesenchymal stromal cells, including liver sinusoidal endothelial cells) from experimental animals but



Immunohistochemistry showing expression of IL-33 (brown) in CD34-positive (red) endothelial cells in normal bone marrow (scale bar: 20 µm).

also from clinical material. Experimental protocols for determining the functional capacities of these cell subsets ex vivo and in vitro are continuously established and optimized.

In 2014 we were able to replace a substantial proportion of the more than 20 years old pieces of equipment and to also acquire two new cutting-edge pieces of equipment. Accordingly, supported by funds of the SNSF R'Equip programme and by the Medical Faculty a mini-endoscope suitable for the examination of small experimental animals was obtained which is now fully operative (responsible: Philippe Krebs). With additional SNSF R'Equip funds and support by the Medical faculty, a Seahorse XF° Analyzer was acquired (responsible: Stefan Freigang) which will allow us to measure the metabolic activities of cells in real-time and thereby substantially expand the spectrum of available experimental technologies. Together with the R'Equip funding, the total amount of external funding received in 2014 by the research groups of the Division of Experimental Pathology exceeded CHF 3 Mio. (mostly funded by the SNSF) which is clearly an outstanding achievement!

Honors

Jean Claude Reubi is the 2014 recipient of the «Theodor-Kocher-Vorlesung der Chirurgischen Arbeitsgemeinschaft Endokrinologie (CAEK)».

Stefan Freigang obtained the Venia legendi at the ETH Zurich, Switzerland, for the Habilitation thesis entitled «Immune recognition of lipids in inflammation and immunopathology» («Umhabilitation» subsequently approved by the Medical Faculty, University of Bern).

Teaching

Also in 2014 the Division of Experimental Pathology actively contributed to the teaching at both the Medical Faculty and the Biological Science Faculty. Teaching at the Medical faculties included tutorials in problem-based learning for lectures in general pathology for students in medicine and dentistry and lectures in the MSc course «Biomedical Sciences». Members of the Division organized several courses for undergraduate and graduate students in Cell Biology and Biomedical Sciences at the University of Bern, including courses in histology and general pathology, molecular pathology and tumor biology, a MSc course in cellular and molecular immunology, and a practical course in immunology.

Several members of the Division are actively involved in coaching PhD students from the Graduate School for Cellular and Biomedical Sciences. In 2014 the following individuals successfully completed their academic degrees at the Division of Experimental Pathology (with supervisor, co-examiner or mentor from the Division of Experimental Pathology):

Christoph Mueller
- BSc: Diego von Werdt
- MSc: Claire Micossé
  (joint project with Prof. Manfred Kopf, ETH Zurich)
- PhD (co-advisor): Kristina Ludigs, University of Lausanne

Mario Tschan
- BMA Master: Nadine Perroulaz
- PhD: Daniel Brigger, Anna Schläfli
- PhD (co-advisor): Jessica Merulla (PI: Prof. M. Molinari, IRB, Bellinzona)
- PhD (Mentor): Kei Mikami (PI: PD Dr. Y. Zimmer, Dpt. Clinical Research), Min Ma (PI: PD Dr. M. Baumgartner, VetSuisse), Olga Wiens (PI: V. Heussler, IZB), Raphael Joncourt (PI: O. Mühlemann, DCB)

Administrative duties

Several members of the Division of Experimental Pathology served in 2014 voluntarily in several profession-related functions.

Since 2013 Nadia Corazza is a member of the committee «Gleichstellung von Frauen und Männern» and was a member in one faculty search committee.

Christoph Mueller was member, or Chair, of several faculty committees in 2014, including the task force «Experimental Animal Center» and was a member of the steering committee of the program in Certified Advanced Studies (CAS) in Research Management at the University of Bern. He remained an ad hoc research council member in the SNSF «ambizione» program (Division III). He was a board member of the Swiss Society of Allergology and Immunology and member of the subcommittee «Experimental Immunology» of this society, and is also a board member of the «Stiftung für klinisch-experimentelle Tumorforschung Bern».

Mario Tschan is a member of the Interfacultary PhD Committee, which is responsible for the strategic orientation, the administration, and the quality control of the PhD program and of the Expert Committee Cell Biology, Graduate School for Cellular and Biomedical Sciences. He is a member of the «Vereinigung der Dozentinnen und Dozenten der Medizinischen Fakultät Bern» representing the interests of the lecturers at the Medical Faculty meetings. He is member of the expert commission for the Master program Biomedical Analysis.

Stefan Freigang and Philippe Krebs are also members of the Expert Commission of the Graduate School for Cellular and Biomedical Sciences of the University of Bern. Philippe Krebs is also the Biosafety Officer of the entire Institute of Pathology. In 2014 Stefan Freigang completed his training as a Radiation Safety Officer and became responsible for these duties at the Institute of Pathology in fall 2014.

Group of Stefan Freigang, MD

Olivier Friedli, PhD student
Abilashan Sithampari, MSc student
Romina Theiler, research technician

Summary of research activities

Our research focuses on the immune recognition of lipids in inflammation, microbial infection and in the pathogenesis of atherosclerosis.

Cardiovascular diseases, particularly atherosclerosis, remain the leading cause of death worldwide; they also induce substantial morbidity and health care costs. While dietary and pharmacological interventions are currently used to manage major risk factors, there is still no effective treatment that directly targets the underlying inflammatory process. We have recently characterized a novel pathway that selectively induces IL-1alpha-driven vascular inflammation and atherogenesis in response to metabolic perturbation. Our study identified fatty acid-induced respiratory uncoupling as the metabolic signal that triggers IL-1alpha secretion but simultaneously inhibits inflammasome activation. We are currently investigating the role of physiological uncoupling in the regulation of IL-1-mediated inflammation in atherosclerosis, metabolic dysfunction and microbial infection.

In addition, we study the bioactivity of the oxidized lipids that are generated during inflammatory processes. Exposure of biological membranes to reactive oxygen species creates a complex mixture of distinct oxidized phospholipid (OxPL) species. It is now increasingly recognized that such OxPL are not just byproducts of lipid peroxidation associated with inflammatory conditions or increased oxidative stress, but instead actively modulate cellular signaling processes and influence the resulting immune response. We have characterized an anti-inflammatory bioactivity of OxPL that can be attributed to a specific category of OxPL (Bretscher 2014). We show that this potent anti-inflammatory effect is mediated by the prostanoid-like OxPL component epoxycyclo-pentenone, which activates the transcription factor Nrf2 to inhibit pro-inflammatory cytokine and chemokine responses in myeloid cells in vitro and in vivo (Bretscher 2014). Based on these studies, we developed an epoxycyclopentenone-derived OxPL variant with an unprecedented anti-inflammatory bioactivity (Egger 2014). Our results provide insight to the essential structural characteristics and signaling of anti-inflammatory OxPL, and demonstrate that both are shared with endogenous, pro-resolving lipid mediators. These findings highlight the potential of targeting OxPL/Nrf2-signaling in inflammation, and suggest a novel class of highly bioactive compounds as promising therapeutic agents for the treatment of inflammatory diseases.

Internal collaborations

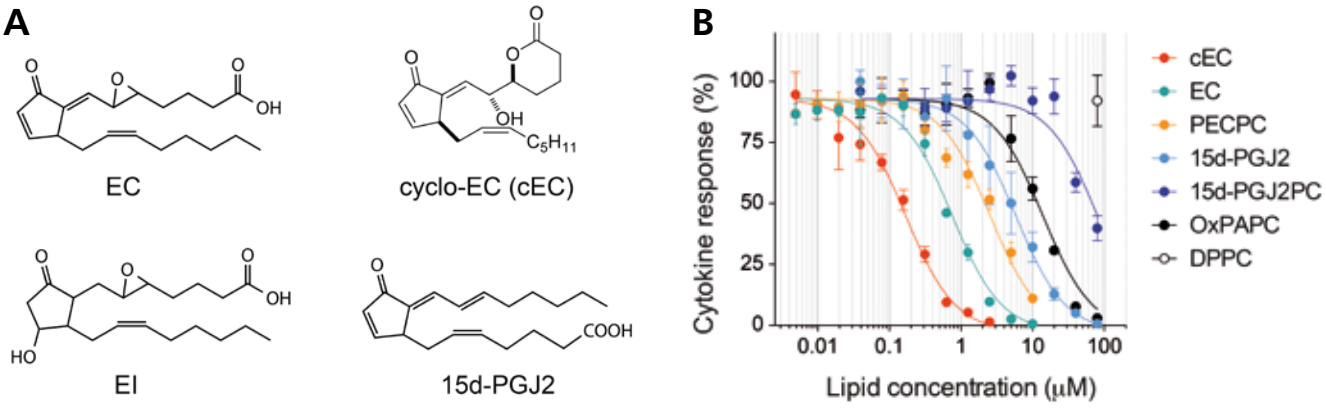
- Prof. Christoph Mueller, University of Bern, Switzerland

External collaborations

- Prof. Erick Carreira, ETH Zurich, Switzerland
- Prof. Marcus Groettrup, University of Konstanz, Germany
- Prof. Martin Hersberger, University Children's Hospital Zurich, Switzerland
- Dr. Harald Köfeler, Medical University of Graz, Austria
- Prof. Manfred Kopf, ETH Zurich, Switzerland
- Prof. Jan Lünemann, University of Zurich, Switzerland
- Prof. Paul Savage, Brigham Young University, Provo, USA

Grant support

- SNF 310030_152872, CHF 510'890
- SNF R'Equip 316030_157702, CHF 240'867
- Vontobel-Stiftung CHF 120'000
- Swiss Heart Association, CHF 70'000
- Olga-Mayenfisch-Stiftung, CHF 50'000
- Fondation Johanna Dürmüller-Bol, CHF 26'993
- UniBern Forschungsstiftung, CHF 15'000



Fatty acid cyclopentenones mediate the potent anti-inflammatory bioactivity of oxidized phospholipids.
(A) Structures of the fatty acid cyclopentenones identified in oxidized phospholipid mixtures. EI: 5,6-epoxyisoprostane E2; EC: 5,6-epoxy-isoprostane A2; cEC: synthetic anti-inflammatory epoxyisoprostane-lactone developed from EC (Bretscher et al., EMBO Mol Med. 2015); 15d-PGJ2: 15-deoxy-Δ12,14-prostaglandin J2. (B) The biological activity of indicated lipids as assessed by their ability to inhibit the TLR7-stimulated interleukin 12 secretion of bone marrow-derived dendritic cells in vitro.

Forschungsgruppe Krebs.

Group of Philippe Krebs, PhD

Ludmila Cardoso Alves, PhD student
Michael Berger, MSc student
Lukas Mager, PhD student
Regula Stuber Roos, technician
Marie-Hélène Wasmer, PhD student

Summary of research activities

Chronic inflammation of microbial etiology has been suggested as the underlying cause of several debilitating conditions, particularly in patients afflicted with inflammatory bowel disease (IBD) or certain forms of malignancies. We work along the central hypothesis that microbes, including commensals, represent a major cause for inflammation-induced immunopathology in genetically susceptible individuals. To address this issue, we use two distinct mouse mutants with defined genetic alterations affecting the hematopoietic and the radio-resistant compartment, respectively.

In particular, we aim to provide a detailed analysis of the molecular and cellular processes involved in microbe-associated pathogenesis in a model of myeloproliferative disorder and a model of IBD. The latest has also been extended to a model of colitis-associated latter colorectal cancer (CRC).

In parallel, we have also started a collaboration to assess the role in CRC of an inflammatory pathway that was recently shown to contribute to colitis development.

We anticipate that these investigations will not only extend our current knowledge on the role of microorganisms as trigger of inflammatory disorders and cancer; they may also help to develop treatment strategies with potential translation into the clinic or to define new genetic markers of disease susceptibility, thereby allowing targeted preventive care.

Another project involves an investigation of the cross-talk between innate and adaptive immune effectors for the development of adaptive immune responses in conditions of infectious versus sterile inflammation.

Internal collaborations

- Prof. Christoph Mueller, Dr. Leslie Sauer
- Prof. Aurel Perren, Dr. Ilaria Marinoni
- PD Dr. Mario Tschan
- Prof. Inti Zlobec
- Prof. Alessandro Lugli
- Dr. Mario Noti
- PD Dr. Nadia Corazza
- Dr. Viktor Kölzer
- Dr. Vera Genitsch
- Dr. Yara Banz
- Dr. Christian Schürch

External collaborations

National

- Prof. Andrew Macpherson and Prof. Kathy McCoy (Dept. Clinical Research, University of Bern)
- Prof. Adrian Ochsenbein, Dr. Carsten Riether (Dept. Clinical Research, University of Bern)
- Dr. Tobias Junt, Lab Head, Immunomodulation, Novartis Pharma AG, Postfach, CH-4002 Basel
- Dr. Kirsten D. Mertz, Institute of Surgical Pathology, University Hospital Zurich, Zurich
- Dr. Alexandre Theocharides, Division of Hematology, University Hospital Zurich and University of Zurich, Zurich

International

- Prof. Bruce Beutler, Center for Genetics of Host Defense, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, 8505, Suite NB9-202D, Dallas, TX, 75390, USA
- Prof. Daniel Popkin, Department of Dermatology, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA
- Prof. Edith Janssen & Prof. Kasper Hoebe, Division of Immunobiology, Cincinnati Children's Hospital, 2 40 Sabin Way, MLS 7021, S5.419, Cincinnati, OH 45244, USA

Grant support

- SNF (Sept. 2012–August 2015); 36 months grant: CHF 377'366
- Marie Curie Career Integration Grants (CIG), 48 months grant: € 100'000
- Stiftung für klinisch-experimentelle Tumorforschung (together with Dr. Yara Banz, 2014-2015, CHF 80'000).

Arbeit im Labor der Abteilung Experimentelle Pathologie.

Group of Prof. Christoph Mueller, PhD

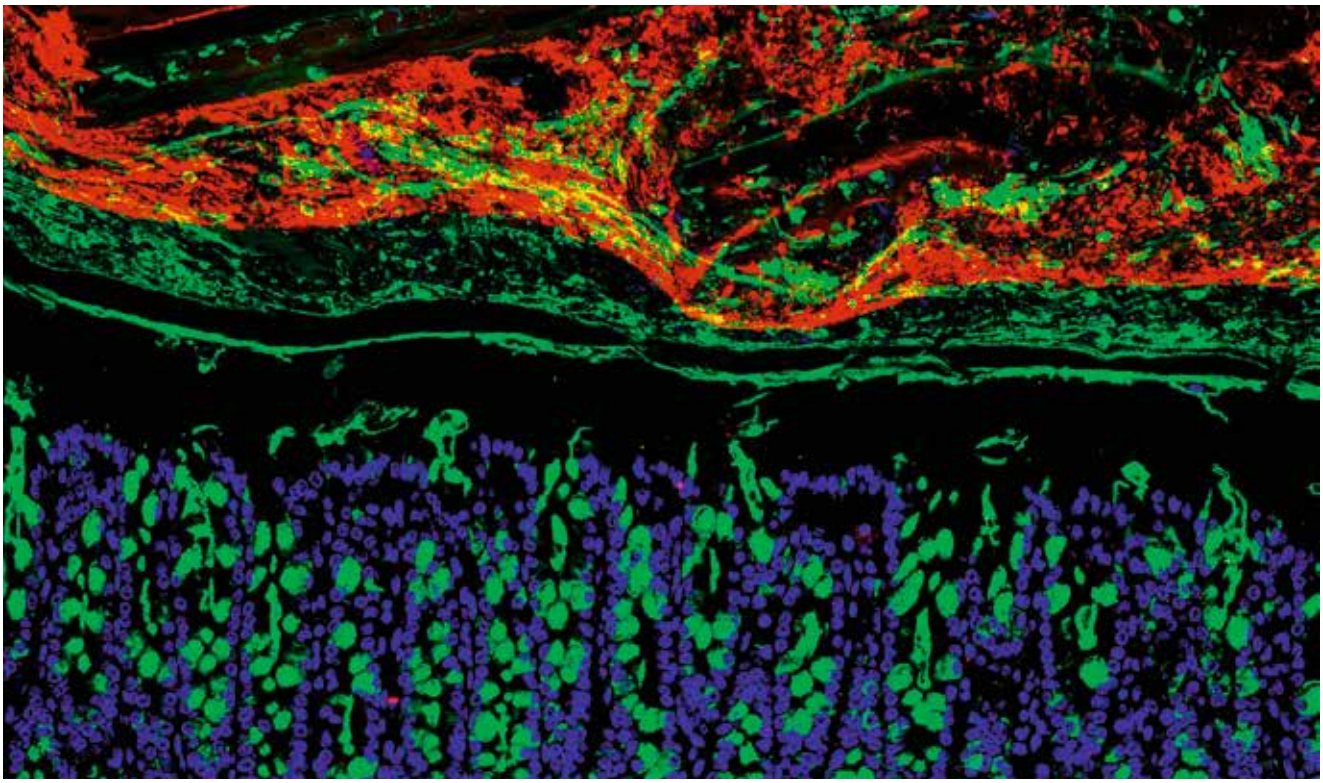
Isabella Aebi, technician (SIBDCS biobank, 40%)
Jennifer Brasseit, PhD, post-doc
Nadia Corazza, PhD, staff scientist (60%)
Martin Faderl, PhD student
Sandra Kummer, MSc student (till March, 2014)
Mario Noti, PhD, post-doc
Silvia Rihs, technician (90%)
Leslie Saurer, PhD, staff scientist (60%)
Jakub Smolar, MSc student (till March 2014)
Alexandra Suter, technician (SIBDCS biobank, 60%, from December 2014)
Diego von Werdt, MSc student
Daniel Zysset, PhD student

Summary of research activities

The intestinal mucosa is constantly exposed to a vast array of antigens. Hence, the numerous immune effector cells present within the intestinal epithelium and in the underlying lamina propria face a difficult task in mounting appropriate responses against invading pathogens while tolerating the commensal microflora and harmless antigens. It is generally accepted that aberrant immune responses against intestinal antigens in genetically predisposed individuals can lead to chronic inflammatory disorders such as seen in inflammatory bowel diseases (IBD).

The main research activities of our group are aimed at a better understanding of the immunoregulatory mechanisms that are operative in the intestinal mucosa under homeostatic conditions and the potential contribution of different immune cell subsets and inflammatory mediators to the pathogenesis of IBD. To this end, we are analysing various mouse mutants and/or transgenic lines in different models of experimental colitis. A longstanding interest lies in the improved characterization of the enigmatic CD8αα TCRαβ intestinal intraepithelial lymphocytes (IEL) that represent a major subset of mouse IEL. While under homeostatic conditions, CD8αα TCRαβ IEL are restricted to the intestinal epithelium, under inflammatory conditions these cells greatly expand and also appear at extra-intestinal sites. Besides studying their functional responses, we are currently investigating the mechanisms that lead to the migration of CD8αα TCRαβ T cells from the intestine to extra-intestinal sites with a particular focus on the regulator of G protein signaling (RGS) proteins.

In the past year, we also continued to dissect the role of innate lymphoid cells (ILC) in experimental model systems of colitis. While previous studies demonstrated a disease-promoting role for IFNg-producing ILC in innate models of colitis, our current findings employing adoptive transfer of colitogenic CD4 T cells into a lymphopenic host argue against a



Keeping bugs in check: The stratified colonic mucus layer *(stained with anti-Muc2 antibody, green)* separates luminal bacteria *(stained by FISH with eubacterial 16S rRNA specific probe, red)* from the intestinal epithelial cell layer *(DAPI stained cell nuclei, blue)*. The inner mucus layer is devoid of bacteria, while the loose outer mucus layer serves as a preferential habitat for commensal bacteria that may provide colonisation resistance. (Photomicrograph: Martin Faderl, Mario Noti.)

major contribution of these cells in colitis induction in the presence of T cells and rather point to an unanticipated important role of non-hematopoietic cells in driving disease.

A major part of research is dedicated to the investigation of mechanisms that are operative in the resolution of intestinal inflammation (Sinergia grant with the research teams of Prof. Andrew Macpherson (Gastroenterology, Bern), D. Finke (University of Basel) and W.D. Hardt (ETH Zurich). We recently established a reversible mouse model of colitis that allows for a timed and deliberate induction of remission. Indeed, shortly after remission induction a rapid clinical recovery can be observed that is followed by mucosal healing on a molecular and cellular level within a few days (Brasseit et al., *submitted*). In a continuation of the Sinergia grant (now also including Prof. U. Sauer, ETH Zurich) we will further study the dynamics of mucosal healing focusing on the distinct mutualistic interactions between host and microbial communities during induction and recovery from intestinal inflammation. To these ends, gnotobiotic mice will be used with a defined microbial consortium. The consequences of adding (or removal) of distinct bacterial species on the metabolites produced by the intestinal microbes (e.g. short-chain fatty acids) and the consequences thereof for inflammation induction, and resolution will be studied.

Our previous finding that in several models of inflammation and infection mice deficient in the immune-amplifying receptor TREM-1 (*Trem1*$^{-/-}$ mice) showed reduced immune-associated pathologies while they retained their capacity for microbial control (Weber B. et al., PLoS Pathog. 2014) has fuelled our interest in the role (as well as the prognostic and therapeutic potential) of TREM-1 in non-infectious chronic inflammatory diseases. Currently, we are investigating the function of TREM-1 in experimental models of atherosclerosis and colitis-associated cancer. With the use of a novel custom-made anti-human TREM-1 mAb that is functional on FFPE tissue specimens we further aim to substantiate our findings on the role of TREM-1 in various disease settings by extending our analyses to human tissues and making use of the state-of-art equipment and expertise that is available at the Institute of Pathology.

Internal collaborations

- Yara Banz
- Stefan Freigang
- Vera Genitsch
- Philippe Krebs
- Mario Tschan

External collaborations

International

- Bärbel Stecher, LMU, Munich, Germany
- Allan Mowat, University of Glasgow, UK

National

- Hans Acha-Orbea, University of Lausanne
- Daniela Finke, University of Basel
- Wolf Hardt, ETH Zurich
- Walter Reith, University of Geneva
- Fabienne Tacchini-Cottier, University of Lausanne
- Markus Geuking, Dept. Clinical Research, University of Bern
- Pascal Juillerat, Clinics for Visceral Surgery and Medicine, Bern
- Andrew Macpherson, Clinics for Visceral Surgery and Medicine and Dept. Clinical Research, University of Bern
- Kathy McCoy, Dept. Clinical Research, University of Bern
- Christiane Sokollik, Children's Hospital, Bern

Grant support

- SNF 310030_138392 /1, CHF 623'000 (3 years)
- SNF CRSII3_136286 / 1 (Sinergia), CHF 399'000 (3 years)
- SNF 33CS30_134274 / 1 (SIBDCS), CHF ca 65'000 (per year)
- SNF 33CS30_134274 / 1, CHF 40'000 (2 years), small nested project, to Dr. Leslie Saurer
- Bernische Krebsliga, CHF 45'000 (1 year), to Dr. Leslie Saurer
- Novartis Foundation, for medical-biological research, CHF 60'000 (to Dr. Leslie Saurer)

Group of Mario Noti, PhD

Loïc Borcard, master student (since October, 2014)

Summary of research activities

The overall research goals in the lab are to better understand the regulatory mechanisms that control immune cell homeostasis at the body's barrier surfaces.

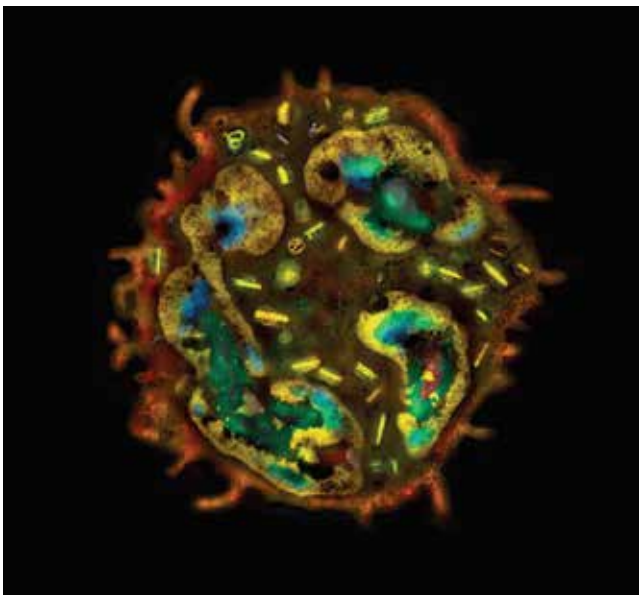
Employing models of allergic inflammation, microbial colonization and/or manipulation, current research focuses on how mammalian host genetics and signals derived from commensal microbial communities influence innate and adaptive immune responses at multiple barriers surfaces including the skin, the esophagus, the lung and the intestine.

Scientific collaborations

- Prof. David Artis, Weill Cornell University, New York, USA
- Prof. Quentin Sattentau, University of Oxford, Oxford, UK
- Prof. Andrew Macpherson and Prof. Kathy McCoy, University of Bern, Bern, Switzerland
- Prof. Bärbel Stecher, Ludwig-Maximilians-University of Munich, Munich, Germany
- Prof. Jonathan Spergel, Childrens Hospital of Philadelphia, Philadelphia, USA
- Prof. Brian Kim, Washington University, Saint Louis, USA
- Prof. Christoph Müller, University of Bern, Bern, Switzerland

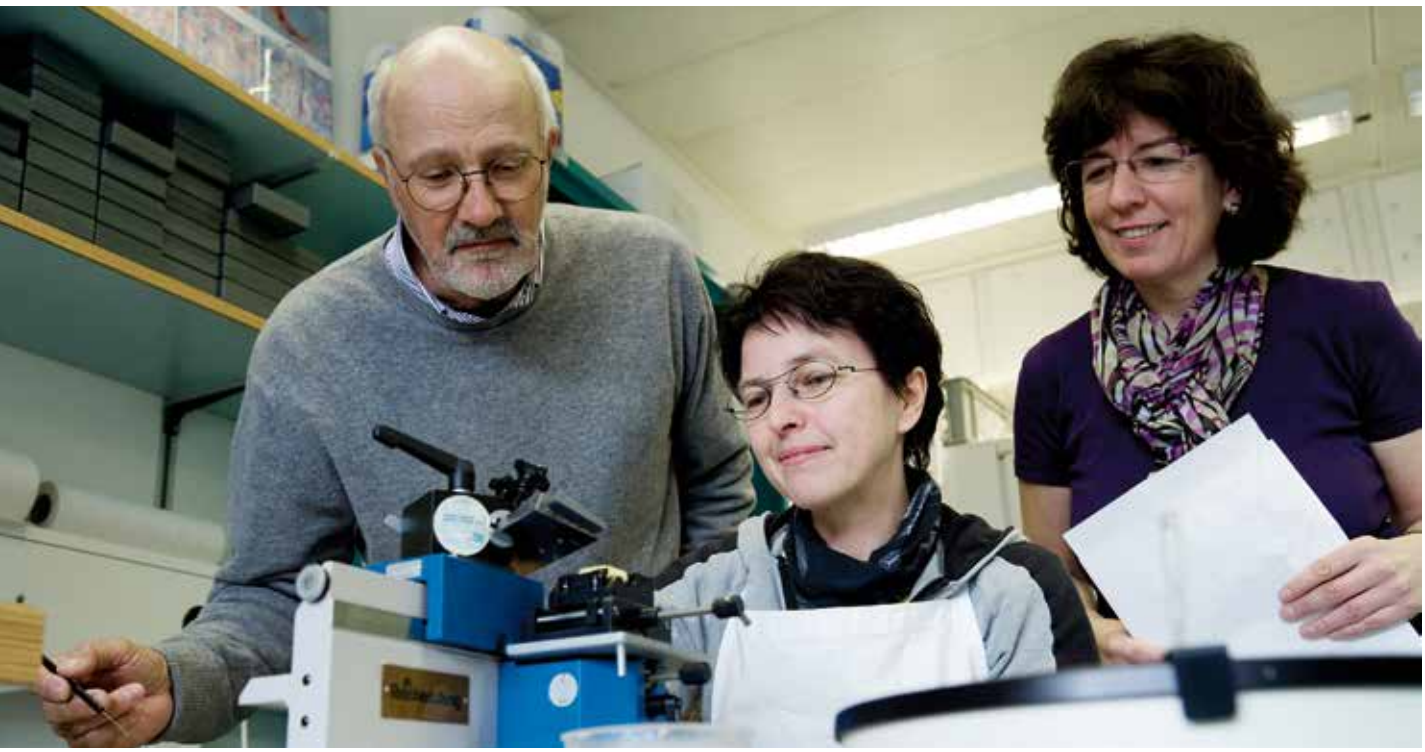
Grant support

- SNF Ambizione PZ00P3_154777/1, CHF 599'156 (3 years)



Computer-enhanced color electron micrograph of a TSLP-elicited basophil in the esophagus of a patient with eosinophilic esophagitis (EoE). Noti Mario, Elia Tait-Wojno, David Artis and the University of Pennsylvania Electron Microscopy Resource Laboratory.

Zellkultur.



Forschungsgruppe von Prof. Jean Claude Reubi.

Group of Prof. Jean Claude Reubi, MD

Beatrice Waser, technician
Meike Körner, MD, attending pathologist
International collaborators

Summary of research activities

The long-term project deals with «peptide receptor targeting of tumors». This is currently investigated at 3 different levels: 1) target definition, 2) tools, 3) clinical applications. In the reporting year, we have focused on the following peptide receptors: somatostatin receptors, gastrin-releasing peptide (GRP) receptors, GLP-1 receptors, GIP receptors.

ad 1) Target definition includes the identification of human pathological tissues, in particular tumors, which over-express peptide receptors. One of the intriguing new findings is the massive overexpression of GRP receptors very early in the prostatic carcinogenesis. This may suggest that current GRP analogs could already play a clinical role (diagnostic, radiotherapeutic) in this stage. We also show, for the first time, the immunohistochemical distribution of GLP-1 receptors in normal and diseased thyroid and pancreas, resolving a conflicting issue in the current literature. Finally, we show that a GLP-1 receptor antagonist can optimally bind to human GLP-1 targets.
ad 2) We have designed and characterized a number of new tools for peptide receptor targeting: The first pansomatostatin, ^{111}In-DOTA-LTT-SS-28, as well as other somatostatin analogs based on SS-14 backbone; several new GRP analogs with N-terminal modifications and/or PEG spacers of various lengths; new GLP-1 receptor analogs labeled with ^{64}Cu. Finally, we report on the first radiolabeled GIP receptor agonist that can successfully target GIP receptor-positive tumors in animals.
ad 3) On the clinical side, important proof of principle studies we presented: 1) PET imaging of human prostate cancer with a GRP receptor antagonist, 2) comparison of somatostatin receptor agonist versus antagonist for use in somatostatin receptor targeted therapy in NETs. We also reported on a case of disabling non-functioning pituitary adenoma successfully treated with 177Lu-DOTATOC.

Internal collaborations

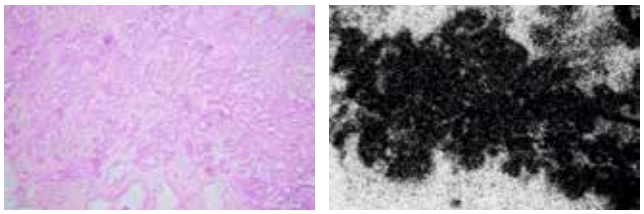
- E. Christ, Univ. Hospital Bern

External collaborations

- D. Wild, Univ. Hospital Basel
- H. Mäcke, Nucl. Med., Univ. Freiburg, D
- T. Maina, Demokritos, Athen, GR
- D. Fourmy, INSERM, Toulouse, F

Grant support

- Desirée and Niels Yde Foundation 383-12



GRP receptors in Prostate-Ca.

Forschungsgruppe von Mario Tschan.

Group of Mario P. Tschan, PhD

Olivia Adams, PhD student (co-supervision, PD Dr. R. Langer)
Priska auf der Maur, master student (BIO)
Emilly Auma, master student (BMA, since December 2014 to May 2015)
Vanessa Bütler, master student (MED)
Aladin Hamoivici, PhD student
Jing Jin, PhD student
Susanne Jutzi, master student (MED)
Julia Parts, PhD student
Daniel Schärer, master student (BMA, since December 2014 to May 2015)
Anna Schläfli, PhD postdoc
Deborah Shan, technician
Tabea Wiedmer, PhD student (co-supervision Prof. A. Perren)

Summary of research activities

Acute myeloid leukemia (AML) is characterized by an impairment of normal myeloid differentiation that leads to a clonal expansion of early immature myeloid progenitor cells. This block in differentiation is mainly caused by loss-of-function mutations in hematopoietic transcription factors that govern the orderly commitment of a cell to a particular hematopoietic lineage. Focusing on the myeloid transcription factor PU.1, we identified additional downstream targets of this transcription factor important for neutrophil differentiation including the death-associated protein kinase 2 (DAPK2) and a variety of autophagy genes. Currently, it is still in question how DAPK2 supports terminal neutrophil differentiation and function. DAPK2 may function in cell death and autophagy regulation during AML differentiation. Autophagy is a catabolic self-degradation process characterized by the formation of double-membraned autophagosomes adopted by cells to maintain cellular homeostasis during conditions of stress. In another project, we identified autophagy as an essential mechanism for AML differentiation and that combining current differentiation therapies with autophagy inducers may be beneficial for this disease. In addition, we directly linked PU.1 to glycolysis and cell survival during chemotherapy of AML cells. Lastly, we are analyzing the function of autophagy in resistance mechanisms towards different anti-cancer treatments in breast, lung and esophageal cancers. We found that combinations therapies using tyrosine kinase inhibitors or retinoic acid in combination with autophagy inhibitors increase cell death responses in a variety of cancer cell models.

DAPK2 in cell death, neutrophil differentiation and autophagy

We are currently analyzing the function of DAPK1's little brother DAPK2 (aka DRP-1) in acute myeloid leukemia (AML)

pathogenesis and neutrophil differentiation. DAPK2 lacks most of the C-terminus of DAPK1 but similar to DAPK1, it is mediating cell death in response to different stimuli such as TNF-receptor and can induce autophagy when overexpressed in 293T cells. We reported that DAPK2 is a critical downstream target of E2F1-KLF6-mediated cell death. In contrast to DAPK1 expression, which is epigenetically silenced, we demonstrated that low DAPK2 expression in AML is based on low expression of its transcriptional activators such as PU.1, CEBPA and possibly KLF6 or on transcriptional repression by the leukemic fusion protein PML-RARA in acute promyelocytic leukemia. Currently, we are investigating if DAPK2 is functional in myeloid autophagy and study its regulation by the p53 tumor suppressor family.

PU.1-dependent regulation of autophagy and cell death
In 2014, we focused on PU.1's role in cell death. We found that knocking down PU.1 significantly increased resistance to TRAIL-induced apoptosis in several AML cell lines. This resistance is associated with a marked induction of anti-apoptotic protein expression including cFLIPShort, XIAP, Bcl-2 and Mcl-1. PU.1 depleted AML cells display increased NF-κB activation providing a first explanation for the induction of the above listed antiapoptotic proteins that are regulated by NF-κB. Importantly, knocking down PU.1 significantly increased the resistance not only to TRAIL but also to anthracyclins that are used in the clinics to treat AML.

Autophagy's role in cancer therapy resistances
This is the research part where I have most in-house collaborations. In different projects we test if inhibition of autophagy enhances the effects of a variety of targeted therapies. Here I will shortly describe our research on retinoids in breast cancer therapy as an example. Many preclinical studies showed promising anticancer effects using retinoids in breast cancer. However, clinical studies were mostly disappointing possibly also due to the design of the trials and emerging resistances. We found that retinoids induce autophagic flux in human breast cancer cells and we demonstrated that the activation of autophagy depends on the retinoic acid receptor alpha. Interestingly, we found that inhibition of autophagy by depleting ATG7 in breast cancer cells resulted in significantly increased apoptosis under retinoid treatment. This suggests that inhibition of autophagy results in enhanced apoptosis, making ATRA in combination with autophagy inhibition an interesting potential treatment strategy for a selected group of breast cancer patients.

Internal collaborations
- PD Dr. Rupert Langer, Institute of Pathology
- Prof. Aurel Perren, Institute of Pathology
- Prof. Erik Vassella, Institute of Pathology
- Prof. I. Zlobec, Institute of Pathology

External collaborations
- Prof. Hans-Uwe Simon, Institute of Pharmacology, University of Bern
- Prof. Thomas Kaufmann, Institute of Pharmacology, University of Bern
- Prof. Bruce E. Torbett, TSRI, La Jolla, CA, USA
- Prof. Anne Simonsen, Dpt. of Biochemistry, University of Oslo, Norway
- Prof. Tassula Proikas-Cezanne, Department of Molecular Biology, University of Tübingen, Germany
- Dr. Nelson J. Dusetti, INSERM U1068, Marseille, France
- Prof. Gerhard Behre, Dpt. of Internal Medicine, University Hospital Leipzig, Germany
- Prof. Sharon McKenna, Biosciencies Institute, University College Cork, Cork, Ireland
- PD Dr. Philipp Jost, Dpt. of Hematology/Oncology, TUM, Munich, Germany
- Prof. Enrico Garattini, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
- Prof. Mojgan Djavaheri-Mergny, INSERM U916 VINCO, Bordeaux Cedex,France

Grant support
- SNF 31003A_143739 (2012–2015), CHF 390'000
- KFS-3409-02-2014 (2014–2016), CHF 370'000
- KLS-3360-02-2014 (2014–2016), Co-PI, CHF 287'000
- KLS-3083-02-2013 (2013–2015), Co-PI, CHF 240'000
- SNF Requip 316030_157702 Co-PI, CHF 120'000

Team der Molekularpathologie und Forschungsgruppe von Prof. E. Vassella.

Group of Prof. Erik Vassella, Dr. pharm.

Ulrich Baumgartner, PhD student
Stefan Haemmig, PhD student
Nicole Wirth, master student (since September 2014)
Stephanie Langsch, PhD student
Claudia Zurbuchen, technician
Cornelia Schlup, technician
Maja Neuenschwander, technician
Brigitte Jossen, technician

Summary of research activities

microRNAs are short regulatory RNAs at the post-transcriptional level that are implicated in a wide variety of basic biological processes including proliferation, differentiation and apoptosis. They play an important role in cancer where they act as tumor suppressing or oncogenic microRNAs. We are interested in the role of miRNAs in cell cycle control, apoptosis and drug-resistance in two tumor systems, non-small cell lung cancer (NSCLC) and gliomas. We have shown previously that miR-15a, miR-16 and miR-34a act together to induce cell cycle arrest in a synergistic and Rb-dependent manner and have identified physiologically relevant targets in NSCLC cells (Bandi et al, 2009, Bandi et Vassella 2011). In addition we showed that miR-125b, which is upregulated in glioblastomas, is significantly associated with shorter overall survival of patients treated with temozolomide. TNFAIP3 and NKIRAS2 are the most relevant targets of this miRNA. Glioblastoma cells overexpressing miR-125b showed increased NF-κB activity and, as a consequence, increased resistance TMZ. Our results provide a new mechanism of TMZ resistance in glioblastomas (Haemmig et al., 2014).

We are currently investigating miRNAs that are regulated by EGFR signaling for their role in conferring chemoresistance, apoptosis, invasion and proliferation of NSCLC cells. We identified microRNAs as effectors of kRAS signalling which are implicated in both intrinsic and extrinsic apoptosis. We confirmed the upregulation of miR-29b expression in individual clones of KRAS-transduced cells. Most strikingly, kRAS induced apoptosis resistance is at least in part due to miR-29b expression. Preliminary results suggest that miR-29b confers apoptosis resistance by inducing NF-κB activity. We are currently investigating potential targets of miR-29b. Another miRNA implicated in EGFR signalling is miR-19b, which is induced by the AKT/PKB pathway. Preliminary data suggest that this miRNA is also able to induce NF-κB activity. These projects are currently supported by the Swiss Cancer League.

In addition, we performed a lentiviral screen for miRNAs conferring temozolomide resistance in glioblastoma cell lines.

We have identified several interesting candidates and have constructed lentiviruses for overexpression in glioma cells.

Communication with host cells and stroma via microvesicles represents one pathway by which tumors can modify their surroundings to achieve a tumor-permissive environment. microRNAs can be considered as «hormones», which are released from a donor cell and shuttle via microvesicles (endosomes) to a recipient cell, where they control gene expression. In a further project that we have started very recently, we aim to assess if communication between glioma cells and microglia via microvesicle-transmitted miRNAs represents a mechanism by which tumor cells can control proliferation and apoptosis as well as chemoresistance.

In the molecular diagnostic laboratory we have established a protocol for NGS using an IonTorrent PGM. Adenosquamous carcinomas are a prime example of tumor heterogeneity. We have analyzed either components of 16 adenosquamous carcinomas using the hot spot cancer panel and showed that some tumors are of monoclonal origin while others are of biclonal origin. A manuscript is currently in preparation.

Internal collaborations

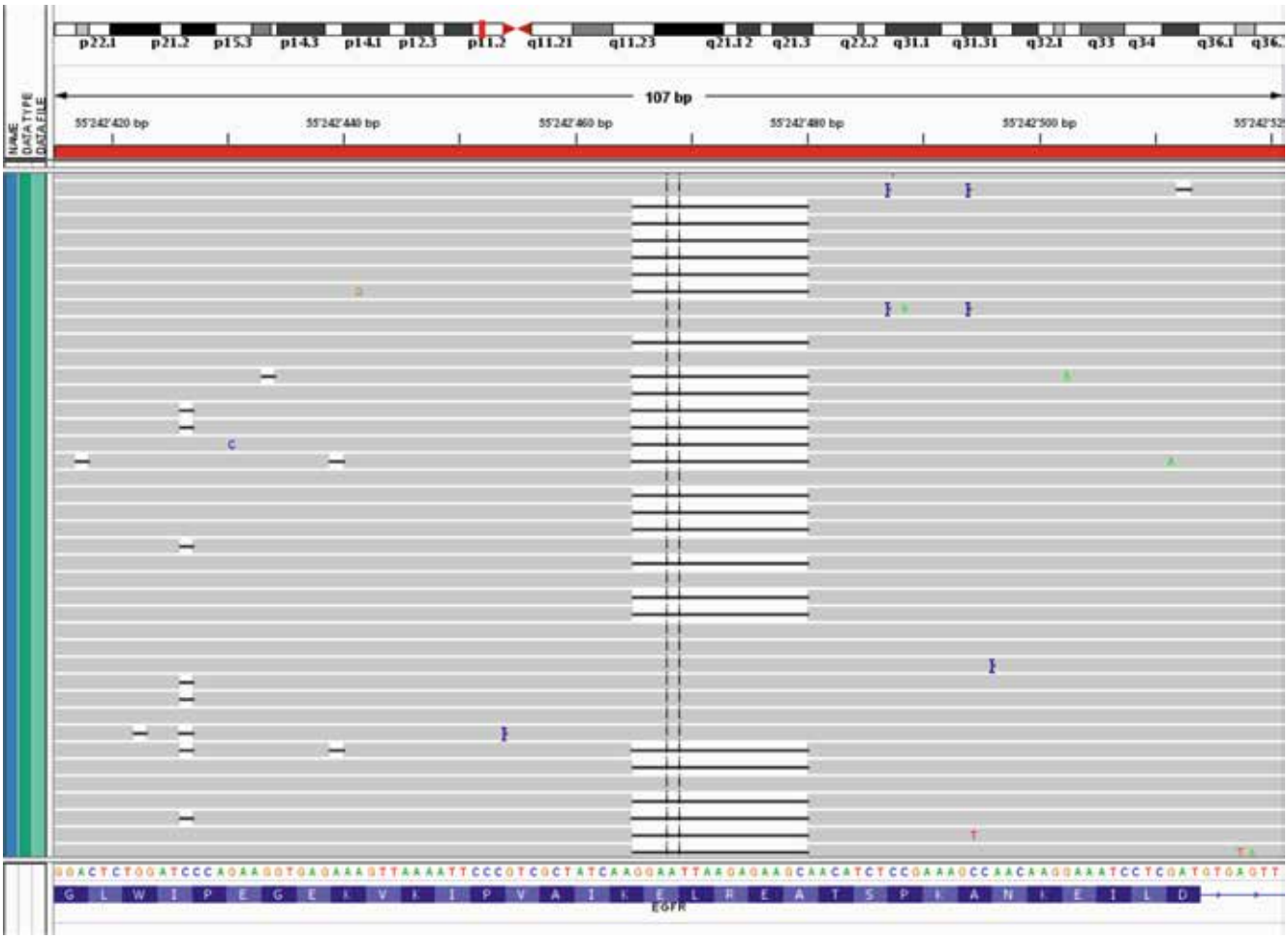
- Dr. Ekkehard Hewer, Institute of Pathology, University of Bern
- Dr. Sabina Beresowska, Institute of Pathology, University of Bern
- PD Dr. Mario Tschan, Institute of Pathology, University of Bern
- Dr. Ilaria Marinoni and Prof. Aurel Perren, Institute of Pathology, University of Bern
- Prof. Inti Zlobec, Institute of Pathology, University of Bern
- PD Dr. Eva Diamantis, Institute of Pathology, University of Bern

External collaborations

- Stephan Schäfer, Pathologie Köln
- Rolf Jaggi, DKF, Bern
- Jean-Louis Boulay and Luigi Mariani, University Hospital, Basel

Grant support

- SNF (#138129, 2012-2015, CHF 290'066)
- Krebsliga Schweiz (Project KFS-2826-08-2011, 2012–2015, CHF 204'400)
- Bernische Krebsliga



Multiple alignment of sequences within the EGFR gene obtained by next-generation sequencing which reveals a p.E746_A750delELREA deletion conferring sensititivity to tyrosine kinase inhibitors.

Team Translational Research Unit (TRU).

1.2 Translational Research Unit (TRU)

Operational Management: Prof. Inti Zlobec, PhD
Administration: Marlène Aeschlimann

TRU Technical Staff: Irene Centeno, PhD; José Galván, PhD; Caroline Hammer; Dominique Müller, PhD; Liliane Schöni

The Translational Research Unit (TRU) is a research platform that provides technical and scientific support to our medical and biological scientists, collaborators and clinical partners.

The aims of the TRU are:

To facilitate and promote translational research

The TRU provides a central laboratory, technical support, logistical support and expertise in five domains:

1. *Histology:* is the foundation of our work in TRU.
2. *Visualization:* digital pathology, immunohistochemistry, in situ hybridization and combined methods allow us to detect protein, DNA, mRNA and miRNA in tissue slides. Image analysis and automated quantification of protein expression using different software are on-going.
3. *Molecular techniques:* Laser capture microdissection, pyrosequencing (mutation and methylation analysis), MLPA, and other techniques are routinely used. Next-generation sequencing projects in collaboration with the molecular pathology division and the Inter-faculty Bioinformatics Unit are taking place.
4. *Biostatistics:* prognostic and predictive models using clinical and patient-derived endpoints are crucial for translational research. Practical biostatistics workshops are organized that focus on basic problems in pathology research.
5. *Next-generation tissue microarrays (ngTMA®):* www.ngtma.com combines histological expertise, digital pathology and automation to construct optimal tissue microarrays for both biomarker screening and targeted research questions.

Administrative support in the Translational Research Unit (TRU).

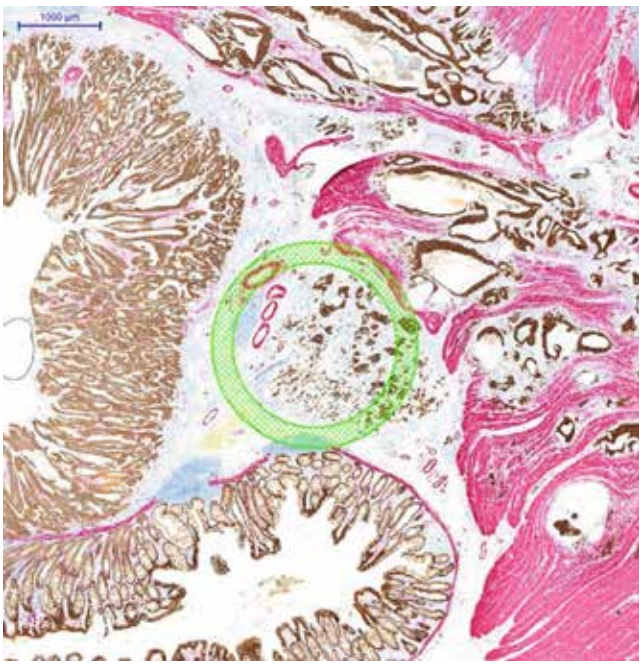
Molecular analysis in the Translational Research Unit (TRU).

To coordinate and support research projects
The TRU coordinates research projects led by our pathologists and provides additional support on issues related to ethics, material transfer agreements and data protection.

To promote interdisciplinary research and interaction with basic science
Interdisciplinary collaborations between TRU, experimental pathology research groups and collaborators in other fields are supported.

To train medical students
TRU strongly supports medical Master's students during their Thesis and Dissertation works. Students have the chance to learn laboratory techniques, digital pathology, histopathology, statistics and work with cohort data.

In addition to these research-related activities, TRU is responsible for administrating SAKK and other clinical studies involving pathologists or histopathology techniques at the Institute of Pathology.



Annotation of a digital slide double-stained for pan-cytokeratin (brown) and caldesmon (red).

Gruppe von Prof. A. Perren.

Endocrine Pathology Research Group

Group members:
Aurel Perren, MD, group leader and director
Ilaria Marinoni, PhD, senior research assistant
Anja Schmitt, MD, attending pathologist
Matthias Dettmer, MD, attending pathologist
Annika Blank, MD, resident
Laura Boos, MD, resident
Tabea Wiedmer, MSc, PhD student
Astrid Wiederkehr, BSc, master student
Sabrina Traxel, BSc, master student
Silvan Pasquinelli, cand. med.
Lea Normand, technician

Summary of research activities

The research focus of our group is the study of endocrine tumors; in particularly sporadic and familial pancreatic neuroendocrine tumors (pNETs). pNETs are rare and comprise about 3% of pancreatic tumors. They are highly heterogeneous and the mechanisms leading to tumor development are still elusive.

We focus on the understanding of the molecular events leading to pNET formation and progression as well as on the investigation of the mechanisms mediating therapy resistance and tumor aggressiveness. We integrate molecular biological (*in vitro* and *in vivo*) and clinical (human tissue based *ex vivo*) research approaches. Our scientific approach is reflected by the composition of the group members including both pathologists and biologists.

Four major projects are currently ongoing

Dissection of the role of DAXX and ATRX in pNET

DAXX and ATRX expression is lost in 40% of sporadic pNETs. We have shown that DAXX/ATRX loss predicts reduced survival and that along tumor progression DAXX/ATRX loss precedes ALT (alternative lengthening of telomeres) activation and CIN (chromosomal instability). We hypothesize that in these tumors CIN drives malignant evolution and ultimately metastasis. Yet the mechanisms by which DAXX/ATRX loss can induce genomic instability, ALT activation and tumor progression are still unknown. We focus on unraveling the mechanism underlying this new cancer-associated pathway. The possible clinical implications of our findings are then evaluated on pNETs human tissues samples.

The role of hypoxia signaling in pNET

About 10% of patients with VHL syndrome suffer from pNET. These tumors are characterized by active hypoxia signaling. We described in a subset of pNET somatic VHL alterations

that also are associated with hypoxia signaling and a poor prognosis. The underlying mechanisms are dissected on pNET cell lines with correlations to pNET tissues.

Autophagy in pNETs: biology and treatment
Autophagy plays a major role in mediating metastasis formation as well as therapy response and resistance. Pancreatic neuroendocrine tumor (pNET) patients often display primary or secondary resistance to the approved treatment.

We investigate *in vitro* and *in vivo* the role of autophagy in pNET development and in mediating therapy response and resistance. The relevance of autophagy activation in pNETs progression and the possible clinical implications are then evaluated on patient tissues.

Micro-RNAs in thyroid carcinomas
While morphologically defined subtypes of thyroid carcinomas are genetically well defined, these genetic alterations such as BRAF mutations in a subset of papillary thyroid carcinomas do not accurately predict clinical outcome and response to therapy. Using a genome wide mircoRNA screening approach in a large set of clinically well-characterized thyroid carcinomas, we dissect the potential clinical relevance as well as the functional consequences of deregulated microRNAs.

Internal collaborations
- PD Mario Tschan, Institute of Pathology, University of Bern
- Dr. Philippe Krebs, Institute of Pathology, University of Bern
- Prof. Erik Vassella, Institute of Pathology, University of Bern

External collaborations
- Prof. G. Christofori, Department of Biomedicine, University of Basel, Basel, Switzerland
- Prof. Marianne Pavel, Medizinische Klinik, Hepatologie Gastroenterologie, Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany
- Prof. Gunter Klöppel, Department of Pathology, Technical University of Munich, Munich, Germany
- Prof. Ernst-Jan Speel, Institute of Pathology Maastricht UMC, Holland
- Dr. Yuri Nikiforow, Department of Pathology, University of Pittsburg, Pittsburg, US
- PD Natalia Pellegata, Institute of Pathology, Helmholtz Zentrum, Munich, Germany
- PD Martin Anlauf, Institute of Pathology, University of Düsseldorf, Düsseldorf, Germany

Grant support
- Bernische Krebsliga Grant to Anja Schmitt Kurrer (2012–2014), CHF 80'000
- SNF Grant No. 310030_144236 to Aurel Perren (2012–2015), CHF 367'000
- KFS Grant No. 3360-02-2014. to Aurel Perren (2014–2017), CHF 286'900

Colorectal Cancer and Lower Gastrointestinal Research Group.

Colorectal Cancer and Lower Gastrointestinal Research Group

Group members:
Prof. I. Zlobec, PhD, senior research and teaching assistant
Prof. A. Lugli, MD, head clinical pathology division
Dr. T. Rau, attending pathologist
Dr. M. Montani, attending pathologist
Dr. med. V. Kölzer, MD, resident
Dr. med. H. Dawson, MD, Stv. OA
L. Sokol, PhD, post-doctoral fellow

MD students:
S. Burren, cand. med.
K. Canonica, cand. med.
M. Flury, cand. med.
J. Graule, cand. med.
M. Helbling, cand. med.
K. Hegazy, cand. med.
D. Marx, cand. med.
C. Schafroth, cand. med.

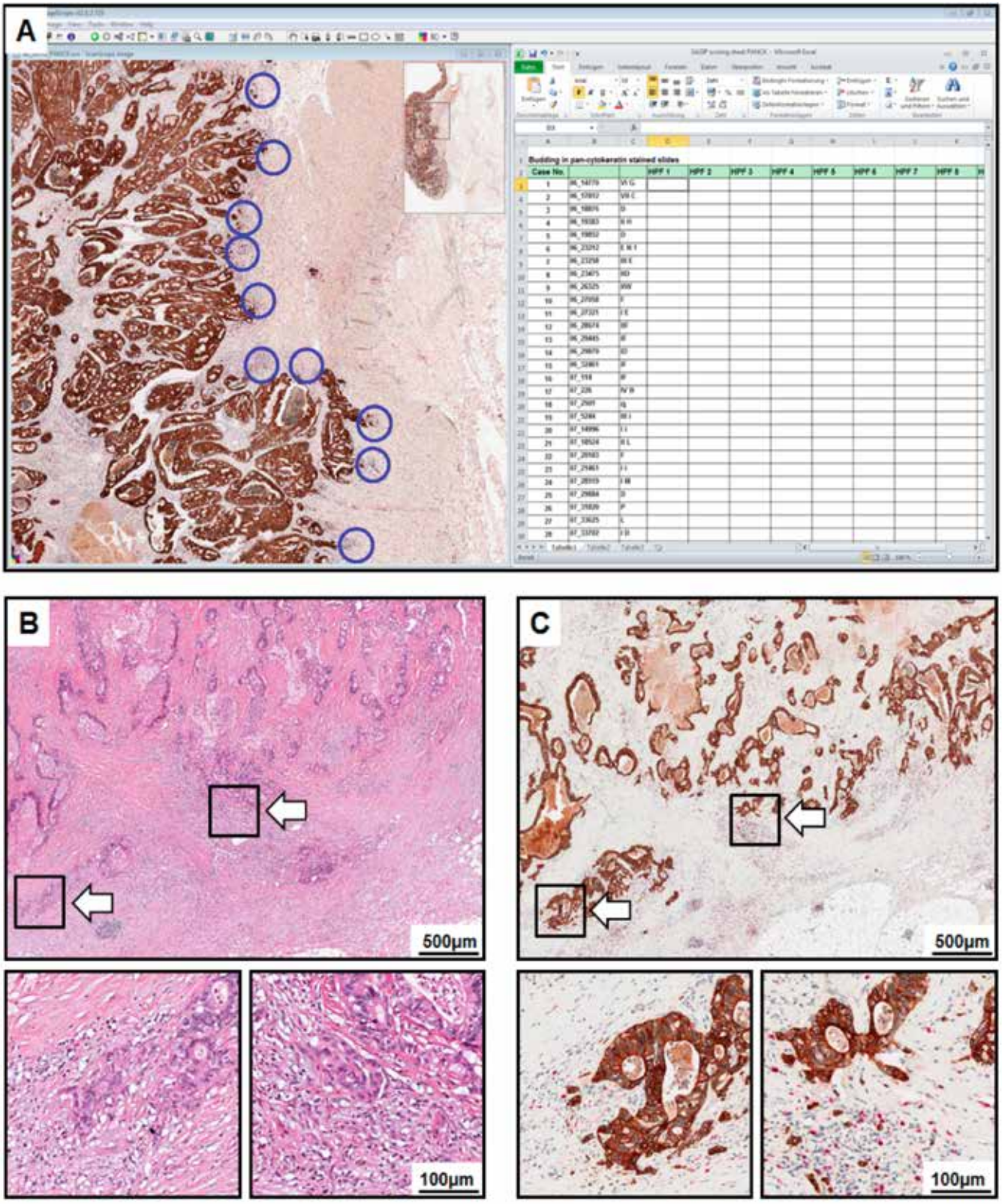
Summary of research activities

Our group takes an interdisciplinary and translational approach to study colorectal cancer, with support from our clinical partners in surgery, oncology and gastroenterology at the Insel and Tiefenau Hospitals.

Members of the group have different focuses on the following topics:

Tumor budding

Tumor buds are single cells or small cell clusters detected both in the tumor center (intratumoral budding, ITB) or at the invasive front (peritumoral budding, PTB) of colorectal cancer (CRC). Based on the literature tumor budding is associated with tumor progression and is considered an independent prognostic factor. Our research group focuses on three main aspects of tumor budding. 1. *Pathogenesis:* the aim is to characterize tumor buds on the DNA, mRNA and microRNA level, their interaction with lymphatic and blood vessels and differences in local and distant metastases, 2. *Tumor Immunology:* the aim is to investigate how tumor buds can potentially escape the immune response in the tumor microenvironment, 3. *Clinical implications of tumor budding:* Based on a national multicentric study organized by the Swiss Association of Gastrointestinal Pathology (SAGIP) a new potential scoring system (10HPF and 1HPF) using immunohistochemistry has been proposed. This scoring system will now be tested in a prospective observational study performed by the Multidisciplinary CRC Research Group. The use of a continuous scoring scale or cut-offs and the possibility to define tumor grade (G) by tumor budding are further points to be addressed.



Assessment of tumor budding in colorectal cancer.

Tumor immunology

The adaptive and innate immune responses are central for host control of colorectal carcinomas. Patients with a strong *in situ* immune reaction rarely present with lymph node or distant metastasis and benefit from a significantly improved long-term survival outcome. In our current work, we are focusing on new fields of application for the prognostic quantification of T-cell infiltration in primary colorectal cancer.

The Institute of Pathology, University of Bern is a participating center for the Immunoscore Consortium in Switzerland. Further, we are investigating mechanisms of immune evasion and immunoediting during epithelial-mesenchymal transition. By focusing on genetic regulation mechanisms of the tumor microenvironment (microRNA, CIMP, somatic mutations) and their impact on the anti-tumoral immune response we are aiming to further contribute to the detailed understanding of tumor host interaction.

Colorectal cancer pathogenesis

CDX2

Approximately 20% of all colorectal cancers arise from the so-called serrated pathway. These cancers show particular molecular changes such as BRAF mutation, CpG Island Methylator Phenotype (CIMP) and Microsatellite Instability (MSI). Our work focuses on understanding genetic aberrations, DNA methylation and protein expression profiles in these cancers and their precursor lesions. In particular, we have identified CDX2 loss as a marker of tumor progression and the hypermethylator phenotype. Current work focuses on understanding the mechanism of CDX2 loss. Together with PD Dr. Mario Tschan's group, we are planning to investigate epigenetic aspects of CDX2 regulation.

Metastasis

In collaboration with Prof. Dr. E. Vassella, we are investigating the molecular heterogeneity of colorectal cancers and their metastases using next-generation sequencing technology. In a second project, our group plans to track the progressive changes during cancer spread using human tissues allowing us to «map» molecular changes throughout metastatic dissemination and correlate these with patient outcome and response to therapies. Additionally, our work suggests that not only the carcinoma but also the surrounding tumor stroma may undergo epigenetic modifications, which may help to promote tumor progression.

Internal collaborations

Dr. Philippe Krebs, PD Dr. Mario Tschan and Prof. Erik Vassella from the Division of Experimental Research, Institute of Pathology, University of Bern as well as PD Dr. Eva Karamitopoulou, PD Dr. Rupert Langer from the Clinical Pathology Division.

External collaborations

Clinical research partners

- Prof. Dr. Daniel Inderbitzin (Tiefenauspital, Spitalnetz, Bern)
- Dr. Martin Berger
- Dr. Marion Hädrich
- Dr. Beat Schnüriger

Other research collaborators

- Immunoscore Working Group (Research Director Prof. Jerome Galon, INSERM, Paris)
- Prof. Ulrike Stein (Charité, University of Berlin)
- Prof. Iris Nagtegaal (Radboud University Medical Center, Nijmegen)
- Dr. Kristi Baker (Brigham and Women's Hospital, Boston)
- Prof. Dr. Arndt Hartmann and Prof. Dr. Regine Schneider-Stock (University of Erlangen)
- Prof. Giuseppe Masucci and Dr. Emilia Anderson (Karolinska Institutet, Stockholm)

Grant support

A. Lugli

- Swiss National Foundation (2011–2014), CHF 216'000
- Krebsliga Schweiz (2013–2015, co-applicant V. Kölzer), CHF 233'700

I. Zlobec

- Bernische Krebsliga (2011–2014), CHF 100'000
- Tumorforschung Bern (2013–2014, co-applicant E. Vassella), CHF 53'226
- Johanna-Dürmüller Bol Stiftung (2014–2015), CHF 20'000
- Mach-Gaensslen Stiftung (2014–2017), CHF 39'000
- Werner und Hedy Berger-Janser Stiftung (2015–2018), CHF 145'620

H. Dawson

- Werner und Hedy Berger-Janser Stiftung (2013–2014), CHF 26'836
- Krebsliga Schweiz (2013–2014), CHF 42'000

Neuropathology Research Group

Group members:
Ekkehard Hewer, MD, Head, Neuropathology Service
Sabina Berezowska, MD, attending pathologist

MD students:
Fabienne Brügger, cand. med.
Elsa Sartori, cand. med.

Summary of research activities

Our research interests include pathology of various types of tumors of the central and peripheral nervous system with an emphasis on gaining insights into genotype/phenotype interaction and its diagnostic implications. We also have a strong interest in neuromuscular pathology and specifically in pathology of hereditary and inflammatory myopathies.

Lung Pathology Research Group

Group Members:
Dr. Sabina Berezowska, MD, attending pathologist
Dr. Stephan Schäfer, MD, attending pathologist (until 07/2014)
Dr. Anna Schläfli, PhD, postdoc (Experimental Pathology Group Tschan)

MD students:
Luna Pescia, master student (medicine)
Yasin Irmak, master student (medicine)

Research activities

Our major research interest comprises translational research in an interdisciplinary setting. The main ongoing research projects include morphological and molecular characterization of lung cancer and metastases, and investigation of the role of autophagy in resistance mechanisms to targeted therapies. Furthermore, we participate in various basic research projects in conjunction with our collaboration partners.

Internal collaborations

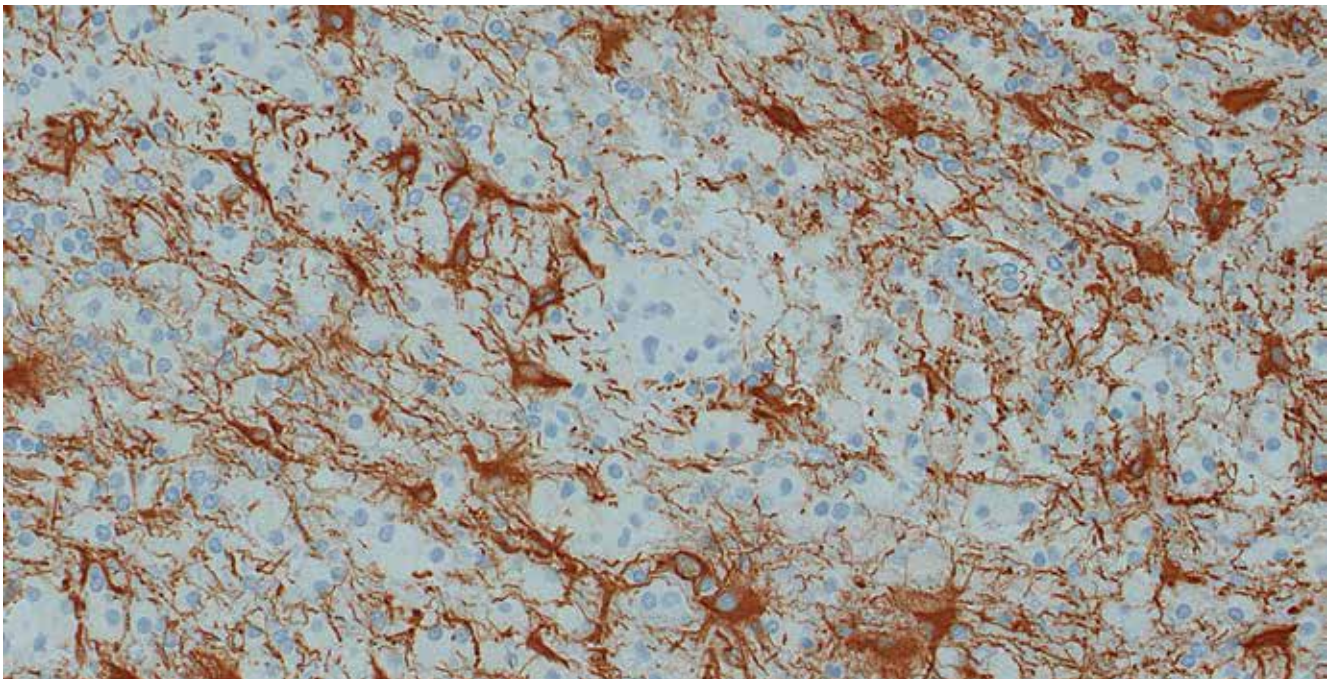
- PD Dr. Mario Tschan, Experimental Pathology, Institute of Pathology, University of Bern
- Prof. Dr. Erik Vassella, Experimental Pathology, Institute of Pathology, University of Bern
- PD Dr. Rupert Langer, Clinical Pathology, Institute of Pathology, University of Bern

External collaborations

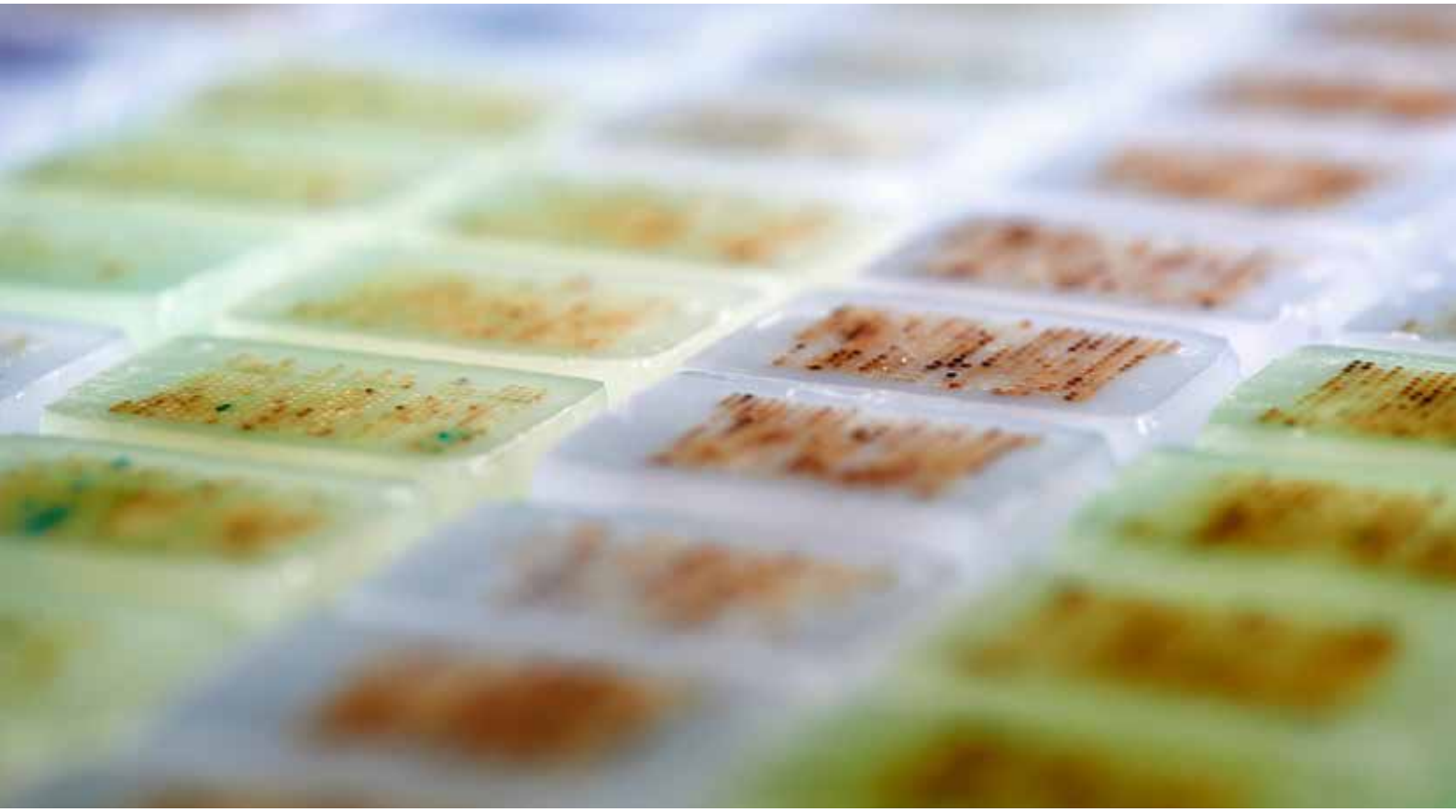
- Thoracic surgery research group DKF (Prof. Dr. R. Schmid, Dr. T. Marti, Dr. S. Hall, Dr. R. Peng, Dr. P. Dorn) thoraxchirurgie.insel.ch/de/forschungslabor/forschungsarbeit-research/
- Pulmonary Medicine (Adults) research group DKF (Prof. Dr. T. Geiser, Dr. F. Blank, Dr. M. Funke)
- Dr. Stephan Schäfer, Institute of Pathology, University of Cologne, Germany
- Prof. Dr. Lukas Bubendorf, Institute of Pathology, University of Basel, Switzerland

Grant support

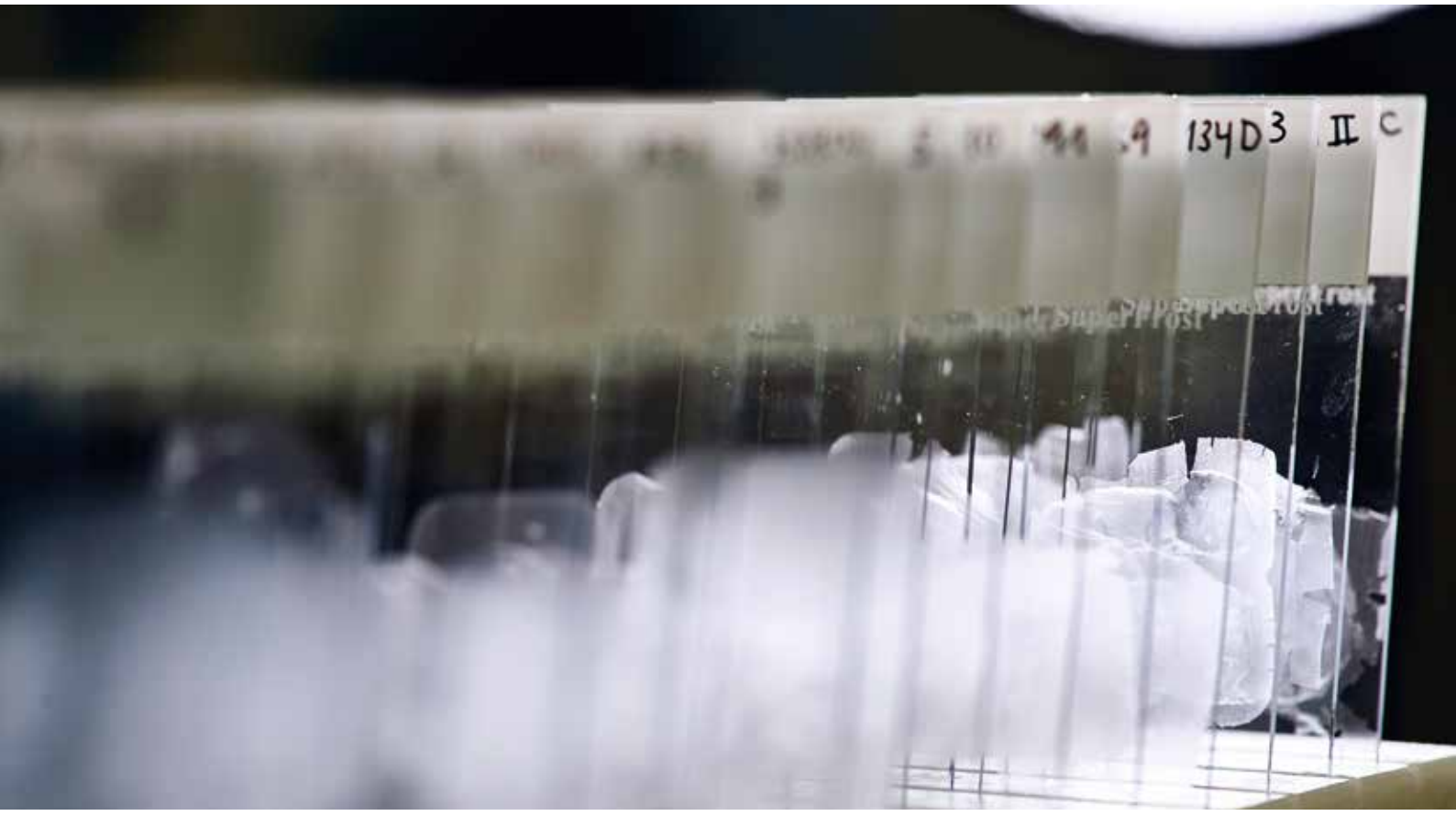
- Bernische Krebsliga Grant to Sabina Berezowska
- Bernische Krebsliga Grant to Stephan Schäfer and Erik Vassella



GFAP expression in reactive astrocytes.



next-generation Tissue Microarrays together with digital pathology are a powerful tool for studying and quantifying tissue biomarkers.



Histological tissue sections awaiting staining in the Translational Research Unit (TRU).

Pancreas Pathology Research Group

Group members:
Eva Karamitopoulou-Diamantis, MD, attending pathologist
Martin Wartenberg, MD, resident

MD students:
Jens Brönnimann, cand. med.

Summary of research activities

The main interest of the group is the study of ductal pancreatic adenocarcinoma (PDAC). In more details the group is interested in the (a) identification of molecular changes promoting Epithelial-Mesenchymal transition (EMT)- and Cancer Stem Cell (CSC)-features, (b) determination of the role of microRNAs and PTEN pathway alterations in PDAC progression and (c) identification of characteristic microRNA profiles in correlation with EMT as well as with clinical outcome, response to adjuvant therapy and survival of the patients.

Moreover, our research project is aimed at the characterization of the budding cells at a protein and gene level in order to identify a «molecular budding-promoting profile» in pancreatic cancer.

Internal collaborations

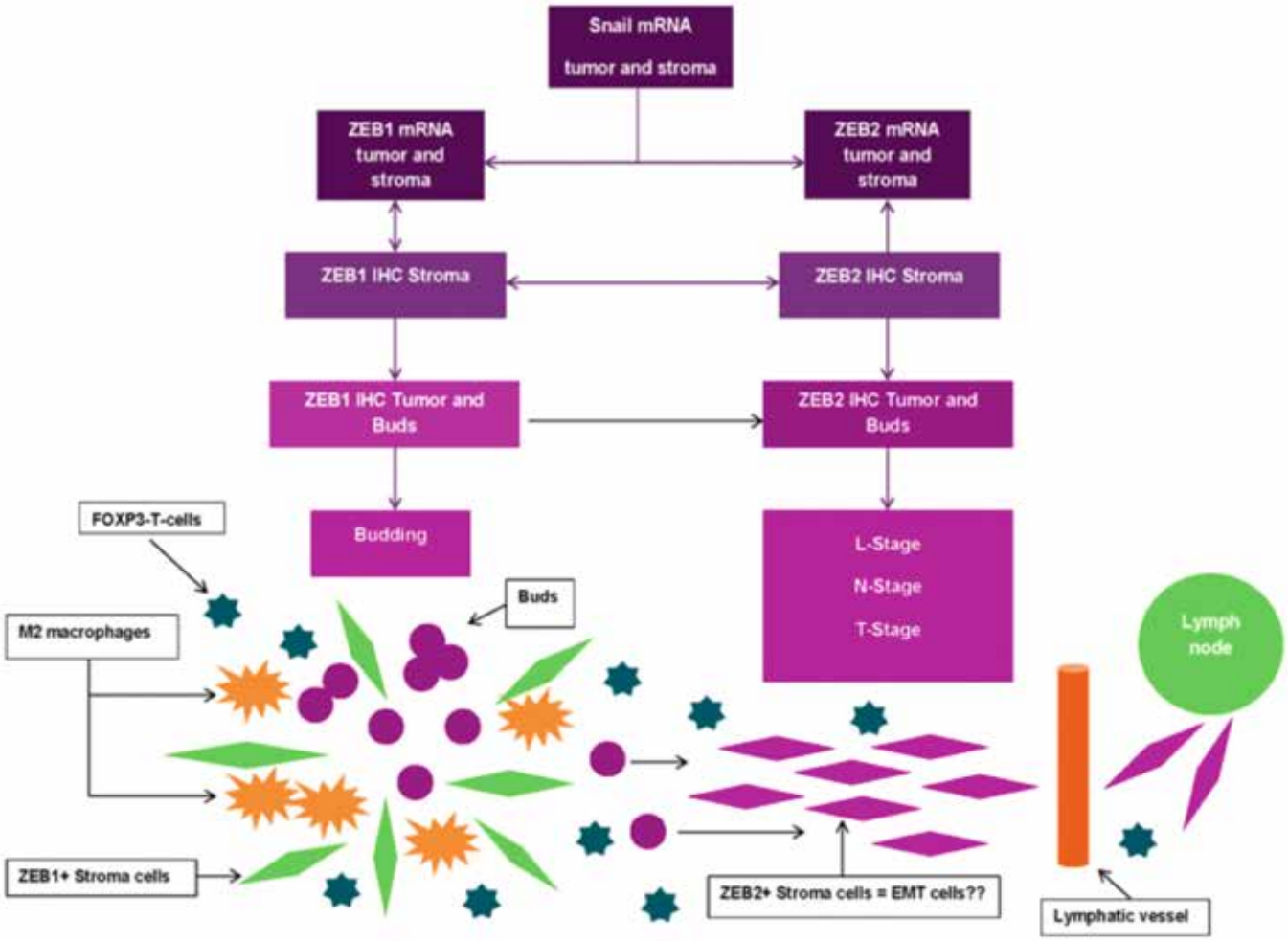
- Prof. Aurel Perren, Dr. med., Institute of Pathology, University of Bern
- Prof. Erik Vassella, Dr. pharm., Institute of Pathology, University of Bern.
- Prof. Inti Zlobec, PhD, Institute of Pathology, University of Bern

External collaborations

- Prof. Beat Gloor, MD, Department of Visceral Surgery, Insel University Hospital, Bern
- Prof. A. Kondi-Pafiti, Department of Pathology, Aretaieion University Hospital, University of Athens

Grant support

- Bernische Krebsliga, CHF 70'000
- Werner und Hedy Berger-Janser Stiftung zur Erforschung der Krebskrankheiten, CHF 33'410



Upper Gastrointestinal Research Group

Group members:
PD Dr. Rupert Langer, attending pathologist
Dr. Bastian Dislich, resident
Olivia Adams, PhD student (co-supervision with Mario Tschan)

MD students:
Lars Guldener, cand. med.
Alexandra Stein, cand. med.

Summary of research activities

We are investigating histomorphological and molecular characteristics of upper gastrointestinal tract tumors, especially esophageal carcinomas, in correlation with biological and clinical factors, treatment response (e.g. neoadjuvant chemotherapy) and patient prognosis. A special focus of our molecular studies lies on the impact of cellular stress reactions and death mechanisms including autophagy on tumor behavior and chemotherapy resistance. In this field we are closely collaborating with Mario Tschan's group of the experimental pathology department. Morphologically we are concentrating on the assessment of response to cytotoxic treatment based on histology and on the investigation of morphological features of tumors with potentially prognostic impact such as tumor budding and inflammation.

Internal collaborations

- PD. Dr. Mario Tschan, Institute of Pathology, University of Bern.
- PD Dr. Eva Diamantis, MD, Institute of Pathology, University of Bern
- Dr. Sabina Berezowska, MD, Institute of Pathology, University of Bern
- Prof Dr. Inti Zlobec, PhD Institute of Pathology, University of Bern

External collaborations

The upper gastrointestinal research group is collaborating with the departments of visceral surgery of the Inselspital Bern (Prof. Christian Seiler and Dr. Dino Kröll), the University of Heidelberg (Prof. Katja Ott) and the TU München (Prof. Marcus Feith, Dr. Ulrich Nitsche), and with working groups of the Institutes of Pathology of the Technische Universität München (Dr. Julia Slotta-Huspenina and Prof. Karl-Friedrich Becker) the Helmholtz Center München (Prof. Axel Walch) and the University of Leuven, Belgium (Prof. X. Sagaert).

Grant support

- Swiss Cancer League (2013–2015), CHF 236'000

Hematopathology and Cardiovascular Pathology

Group members (Hematopathology):
Yara Banz, MD, PhD
Christian Schürch, MD, PhD
Serena Galli, MD student
Olivia Steinsiepe, MD student
Simone Zwicky, MD student

Group members (Cardiovascular Pathology):
Yara Banz, MD, PhD
Anna-Lisa Spranger, MD student

Summary of research activities (hematopathology)

The research activities in the hematopathology group have focused on a collaborative effort with the group of Philippe Krebs in the field of chronic myeloproliferative neoplasms (MPN). The study has focused on extensive characterization of the so-called Styx mouse, an ENU-generated mutant, as a model of MPN, and the central role of interleukin-33 signaling. Whilst Philippe Krebs' group is concentrating on dissecting the molecular mechanisms and pathways behind the role of IL-33 in the disease, our aim is to investigate the IL-33 signaling in human MPN. A retrospective study of archived bone marrow samples from MPN patients in Bern and Basel is in progress to analyze the role of IL-33 in this group of diseases. Furthermore, a collaborative prospective study of MPN patients to include the analysis of bone marrow aspirates and flow cytometric analysis of peripheral blood and bone marrow in collaboration with the Department of Hematology at the University Hospital Bern has been launched.

In addition, extensive collaboration with the Tumor Immunology Research Group at the DKF to analyze CML and AML experimentally is ongoing. *In vivo* mouse models such as retroviral oncogene transduction and transplantation of bone marrow (BM) are ongoing as well as xenotransplantations of leukemia patient samples into immunocompromised mice to generate and analyze myeloid leukemias *in vivo*. Work here focuses on the role of the adaptive immune system, in particular signaling via molecules of the TNF superfamily, in the pathogenesis of myeloid leukemias. Additional models using leukemia cell lines and patient samples which are studied and manipulated *in vitro* complement these research activities.

Internal collaborations (hematopathology)

- Philippe Krebs and Lukas Mager (ExPath, Pathology Bern)

External collaborations (hematopathology)

- Carsten Riether and Adrian Ochsenbein (Tumor Immunology, Department of Clinical Research, Uni Bern)
- Urban Novak, Adrian Ochsenbein and Thomas Pabst (Oncology, Inselspital Bern)
- Peter Keller and Anne Angelillo-Scherrer (Hematology, Inselspital Bern)
- Stephan Dirnhofer and Alexander Tzankov (Pathology, University Hospital Basel)

Summary of research activities (cardiovascular pathology)

The main research activity in the cardiovascular pathology group continues to be the study of aortic pathologies in the clinical setting of aortic aneurysms and aortic dissections. The work in close collaboration with Florian Schönhoff and the team of cardiovascular surgery aims to dissect the pathologies behind aortic aneurysms and to establish a scoring system in patients with aortic aneurysms with either tricuspid (TAV) or bicuspid aortic valves (BAV) as well as Marfan syndrome for comparison. This is necessary, as standardized diagnostic criteria to assess the severity of aortic wall alterations and judge the underlying pathology are currently lacking. The experience gained and results obtained should facilitate communication with clinical colleagues, ensure a more complete and standardized work-up of surgical specimens and correctly identify and classify aortic pathologies.

Following extensive analysis of a test cohort, a large study is ongoing to validate the initial results and correlate this with clinical follow-up, genetic analyses and the study of relevant signaling pathways know to be of importance in the development of aortic aneurysms, such as TGF-beta. Whilst the study continues to include more patients in a comprehensive data base of aortic pathologies, results from the large study are currently being compiled for publication.

External collaborations (cardiovascular pathology)

- Florian Schönhoff, Thierry Carrel, Jürg Schmidli (Cardiovascular Surgery, Inselspital Bern)
- Robert Rieben (DKF, University Bern)
- Thusitha Gajanayake (University Bern)
- Christian Weisstanner and Gerhard Schroth (Neuroradiology, Inselspital Bern)

Grant support

(to Yara Banz and Philippe Krebs)

- Stiftung für klinisch experimentelle Tumorforschung Bern, 2014–2016, CHF 80'000
- Krebsliga Schweiz, 2014–2016, CHF 124'320

Medical students and their supervisors.

Medical students

TRU offers exciting opportunities to medical students looking for master thesis and dissertation projects. In 2014, eleven new master students were welcomed.

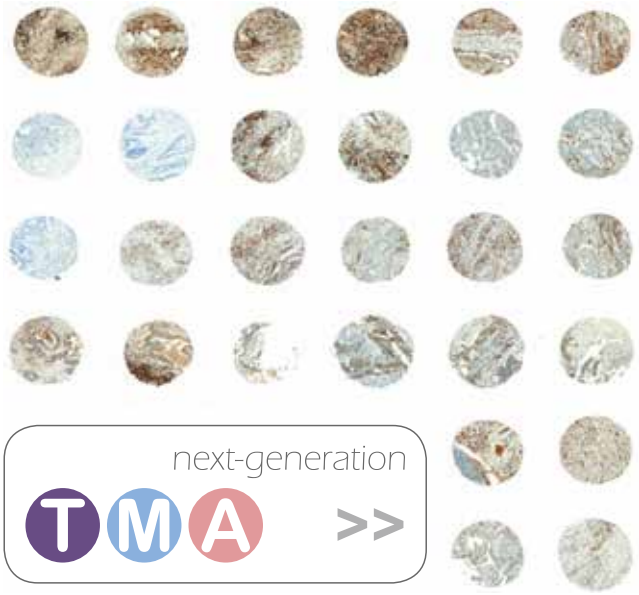
A large variety of topics are possible and may be related to:
– Preparation of a clinical cohort
– Digital pathology and quantification of protein expression
– Construction of next-generation tissue microarrays
– Microscopy and histopathology
– Investigation of diagnostic, prognostic and predictive biomarkers
– Establishment of new laboratory methods
– Molecular pathology-based projects (e.g. mutation analysis)
– Biostatistics
– Tissue biobanking

Research projects with Experimental Pathology research groups are strongly supported.

Next-generation Tissue Microarray (ngTMA)

Our ngTMA project (www.ngtma.com) was launched in October 2012 and has since received much attention nationally and internationally. ngTMA represents a new approach for the construction of tissue microarrays based on three aspects: planning and design, digital pathology expertise and automated tissue arraying.

This exciting project has led to several speaking engagements in 2014 and was recently filmed for the Journal of Visualized Experiments (J Vis Exp 2014 91: 51893, doi: 10.3791/51893).



2 Akademische Grade

2.1 Akademische Grade intern

Anna Schläfli, PhD
Retinoic acid-induced autophagy in acute myeloid leukemia and breast cancer: Implications for therapy
Fakultät: GCB, Bern
Hauptbetreuer: M. P. Tschan

Michael Berger, BSc.
The role of plasmacytoid dendritic cells (pDCs) in sterile and infectious inflammation
Fakultät: phil. nat. Uni Bern, Bern
Hauptbetreuer: P. Krebs

Claudia Läderach, MD Thesis
Construction of a next-generation tissue microarray (ngTMA) of primary breast cancer and tumor buds
Fakultät: med. Uni Bern, Bern
Betreuer Patho: I. Zlobec
Hauptbetreuer: C. Tapia

Daniel Brigger, PhD
The Regulation and Mechanism of ATRA-Induced Autophagy in Acute Myeloid Leukemia and Breast Cancer Pathology
Fakultät: GCB, Bern
Hauptbetreuer: M. P. Tschan

Fabio Hunger, Dr. med.
Hypoxia in Pancreatic Neuroendocrine Tumors
Fakultät: med. Uni Bern, Bern
Hauptbetreuer: A. Schmitt Kurrer

Jonas Heim, Master
Identification of miR-125-specific targets by affinity purification of miRNA target mRNAs
Fakultät: phil. nat. Uni Bern, Bern
Hauptbetreuer: E. Vassella

Katharina Canonica, MD Thesis
High density intratumoral and stromal CD68+ macrophages predict a favorable clinical outcome in patients with colorectal cancer
Fakultät: med. Uni Bern, Bern
Hauptbetreuer: I. Zlobec

Lucine Christe, MD Thesis
Retrospektive klinisch-pathologische Charakterisierung der kolorektalen Polypen am Institut für Pathologie der Universität Bern 2002–2013
Fakultät: med. Uni Bern, Bern
Hauptbetreuer: A. Lugli

Kristina Ludigs, PhD
On the transcriptional role of NLRC5 and the function of NLRC5-driven MHC class I expression in the immune system
Fakultät: Uni Lausanne
Betreuer Patho: C. Müller

Melina Helbling, MD Thesis
Investigation of IL-23 (p19, p40) and IL23R expression in the colorectal adenoma-carcinoma-metastasis cascade identifies a CD8 dependent role of IL23p19 on tumor progression and favorable outcome
Fakultät: med. Uni Bern, Bern
Hauptbetreuer: I. Zlobec

Claire Micossé, Master
Mechanisms of pathogenesis of imiquimod induced psoriasis
Fakultät: ETH Zürich
Betreuer Patho: C. Müller
Hauptbetreuer: Prof. M. Kopf, ETH Zürich

Nadine Perroulaz, BMA Master
Die Rolle des CEREBLON-Genes in der Entwicklung von Resistenzen gegenüber von Contergan (Lenalidomid) in der Therapie des Multiplen Myelomas
Fakultät: MEDI Fachhochschule, Bern
Hauptbetreuer: M. P. Tschan

Diego von Werdt, Bachelor
Expression of RGS1 in intra- and extraepithelial T-Cells: A marker for tissue resident T-Cells
Hauptbetreuer: C. Müller

3 Publikationen

3.1 Originalarbeiten In-House

- **Berezowska SA,** Flaig MJ, Ruëff F, Walz C, Haferlach T, Krokowski M, Kerler R, Petat-Dutter K, Horny HP, Sotlar K: Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. MODERN PATHOL, 27(1): 19-29, D0: Artikel in Fachzeitschrift (IF:6.364, TC:4, MR:0.947) [PubMed] [WoS] [DOI]
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3.2 Originalarbeiten Kollaborationen

- Aichler M, Motschmann M, Jütting U, Luber B, Becker K, Ott K, Lordick F, **Langer R,** Feith M, Siewert JR, Walch A: Epidermal growth factor receptor (EGFR) is an independent adverse prognostic factor in esophageal adenocarcinoma patients treated with cisplatin-based neoadjuvant chemotherapy. ONCOTARGET, 5(16): 6620-32, D0: Artikel in Fachzeitschrift (IF:6.627, TC:0, MR:0.92) [PubMed] [WoS]
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- Blank S, Rachakonda S, Keller G, Weichert W, Lordick F, **Langer R,** Springfeld C, Bruckner T, Becker K, Kumar R, Ott K: A retrospective comparative exploratory study on two methylentetrahydrofolate reductase (MTHFR) polymorphisms in esophagogastric cancer: the A1298C MTHFR polymorphism is an independent prognostic factor only in neoadjuvantly treated gastric cancer patients. BMC CANCER, 14(58), D0: Artikel in Fachzeitschrift (IF:3.319, TC:1, MR:0.638) [PubMed] [WoS] [DOI]
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3.3 Übrige Publikationen

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- **Dawson HAE, Kölzer V, Karamitopoulou E, Lugli A, Zlobec I:** Loss of Cdx2 Is a Potential Marker of the Serrated Pathway of Colorectal Cancer Characterized by BRAF Mutation, High-Level CpG Island Methylator Phenotype and Mismatch Repair-Deficiency. MODERN PATHOL, 27: 171A-, D3: Tagungsbeitrag (Abstract / Poster) (IF:6.364, TC:0, MR:0.947) [WoS]

- **Dawson HAE, Kölzer V, Karamitopoulou E, Lugli A, Zlobec I:** Loss of Cdx2 Is a Potential Marker of the Serrated Pathway of Colorectal Cancer Characterized by BRAF Mutation, High-Level CpG Island Methylator Phenotype and Mismatch Repair-Deficiency. LAB INVEST, 94: 171A-, D3: Tagungsbeitrag (Abstract / Poster) (IF:3.828, TC:0, MR:0.862) [WoS]
- Frei M, Buettner M, **Perren A,** Reichart P, Bornstein MM: Diagnosis and interdisciplinary treatment of a botryoid odontogenic cyst in the posterior mandible: report of a case. QUINTESSENCE INT, 45(3): 233-7, D5: Sonstiges (IF:0.728, TC:0, MR:0.171) [PubMed] [WoS] [DOI]
- **Hewer E,** Kellner-Weldon F, Abu-Isa J, **Schmitt Kurrer A:** Multiple cerebral lesions in a 60-year-old female patient with a history of liver transplantation. NEUROPATHOLOGY, 34(4): 425-7, D5: Sonstiges (IF:1.796, TC:0, MR:0.408) [PubMed] [WoS] [DOI]
- **Kölzer V, Langer R, Zlobec I, Lugli A:** Tumor budding in upper gastrointestinal carcinomas. Front Oncol, 4(216), D1: Rezension (IF:0, MR:0) [PubMed] [DOI]
- **Kölzer V, Lugli A:** The tumor border configuration of colorectal cancer as a histomorphological prognostic indicator. Front Oncol, 4(29), D1: Rezension (IF:0, MR:0) [PubMed] [DOI]
- **Langer R,** Reim D, Höfler H, Becker K: Reply to letter: «Tumor regression after neoadjuvant chemotherapy in gastric carcinoma: are there really so few responders?». ANN SURG, 259(2): e30, D5: Sonstiges (IF:7.188, TC:0, MR:1) [PubMed] [WoS] [DOI]
- Mathys J, **Vajtai I,** Vögelin E, Zimmermann DR, Ozdoba C, **Hewer E:** Desmoplastic small round cell tumor: A rare cause of a progressive brachial plexopathy. MUSCLE NERVE, 49(6): 922-7, D5: Sonstiges (IF:2.311, MR:0.524) [PubMed] [WoS] [DOI]
- Moghadamrad S, **Montani M,** De Gottardi A: Reply to: Bile salt export pump expression: Can immunohistochemistry in isolation mislead? HEPATOLOGY, 59(5): 2056-7, D5: Sonstiges (IF:11.19, TC:0, MR:0.973) [PubMed] [WoS] [DOI]

4 Vorträge

Corazza Nadia
- 13.06.14, Global Health Institute, EPFL, Lausanne

Freigang Stefan
- 26.03.14, Mitochondrial control of chronic vascular inflammation in atherosclerosis, BIC (Bern Immunology Club), Institute of Pharmacology, University of Bern
- 19.04.14, Inflammasome-independent IL-1alpha in metabolic inflammation, WIRM-VIII, World Immune Regulation Meeting, Davos
- 15.12.14, Molecular mechanisms of vascular inflammation in atherosclerosis, Kolloquium für Klinische Chemie und Biochemie, Department of Clinical Chemistry and Biochemistry, University Children's Hospital Zurich

Haimovici Aladin
- 09.12.14, PU.1 – a novel modulator of TRAIL sensitivity in myeloid leukemic cells, Swiss Apoptosis Meeting, Bern

Krebs Philippe
- 12.–13.06.2014, Cytokines and regulation of myeloproliferative neoplasms, Reunion Exp. Imm. Zurich, Institute for Exp. Imm., University Hospital Zurich,
- 04.–05.08.2014, Innate immunity as a double edged sword: Collateral damages mediated by inflammation, Visit / Seminar, Universitätsklinikum Essen, Institut für Immunologie, Essen, DE
- 06.11.14, Cytokines and regulation of myeloproliferative neoplasms, Weiter- und Fortbildungs-Seminar, Klinik für Hämatologie, Universitätsspital Zürich,
- 27.11.14, Control of adaptive immunity by pDC and NK cells, Seminar, Vetsuisse, Department of Infectious Diseases and Pathobiology, Bern
- 09.12.14, Slc15a4 – a link between lysosomal transport and innate immune receptor function, Internal Seminar, Novartis Institutes for Biomedical Research, Basel

Langer Rupert
- 07.11.14, Der histopathologische Befundbericht – mehr als nur eine HE-Färbung?, 24. Berner Chirurgie Symposium, Bern
- 08.11.14, Regression grading after chemo- or immunotherapy. Does it include immune cells?, EORTC meeting on immune therapy in gastrointestinal cancers, Mainz, Germany
- 04.12.14, Barrett – what is new?, Swiss Association of Gastrointestinal Pathology (SAGIP), Bern

Lugli Alessandro
- 27.03.14, Molecular pathology of colorectal cancer: implication for therapy, Fortbildung Departement Innere Medizin, Innere Medizin, Kantonsspital Baden, Baden (AG)
- 10.04.14, Colorectal cancer in polyps: Pathology aspects, Symposium de Gastroénterologie, Aurigen and Dianapath, Lausanne
- 10.04.14, Tumor budding in colorectal cancer: clinical approach, Symposium de Gastroénterologie, Aurigen and Dianapath, Lausanne
- 04.07.14, The immunoscore network and cancer classification, Milteny Biotec, SIDRA, SITC, EATI, 8e journées scientifiques, Paris
- 25.11.14, Tumor budding: relevance and relation to EMT, European Colon Cancer Congress, Amsterdam

Lugli Alessandro
- 06.12.14, «The implementation of the immunoscore in the daily diagnostic practice of colorectal cancer: the pathologist's point of view», Melanoma Bridge, Naples

Müller Christoph
- 21.03.14, WIRM/SSAI Meeting Davos, Davos
- 08.09.14, WHO Training Center, University of Lausanne, Davos
- 11.10.14, European Mucosal Immunology Group Meeting, Davos
- 16.04.14, Wolfsberg Immunology, PhD Student Meeting, Wolfsberg

Noti Mario
- 01.05.14, TSLP and basophils make food ahard to swallow, Fortbildungsreihe des Instituts, Biochemische Pharmakologie, Konstanz, DE
- 03.07.14, A bad alliance: TSLP and basophils team up to mediate EoE, Forbildungsreihe CSL Behring, CSL Behring, Bern

Perren Aurel
- 20.02.14, NET es sind nicht alle gleich, Deutsche Krebsgesellschaft, Berlin
- 05.03.14, The new Ethic law 2014 and the informed consent/ ENETS and SwissNET, 3rd SwissNET evening at ENETS 2014, Barcelona
- 05.03.14, Histology for NETs, 4th ENETS Postgraduate Course 2014, Barcelona
- 07.03.14, What's new in my field, 11th Annual ENETS Conference Barcelona, Barcelona
- 10.04.14, Pathologie von NET: Standards und neue Trends, Post-ENETS, Bern

- 03.07.14, La perte des gènes DAXX et ATRX est associée à une instabilité chromosomiques et réduit la survie des patients atteints de TNE GEP, 3ème NocTurNes Neuroendocrines, Paris
- 31.08.14, Do tumorigenic and signalling pathways go the same route?, 26. European Congress of Pathology, London
- 18.09.14, WHO NEN-Klassifikation 2010 - was kommt danach?, Viszeralmedizin 2014, Leipzig
- 25.09.14, Indication for surgery: Biology, WorldMEN, Wien
- 31.10.14, G3 – Poorly differentiated NET, Annual Converences of the ENETS Advisory Board, Wien
- 28.11.14, Pathology and Classification of NETs, ESMO, Leuven, Belgien
- 29.11.14, Challenges in the management of gastric, appendiceal and rectal NETs: pathology and treatment, ESMO, Leuven, Belgien
- 29.11.14, The pathologists point of view, ESMO, Leuven, Belgien
- 11.12.14, Personalized diagnosis towards more effective treatment, Swiss TPH Fall Symposium, Basel

Reubi Jean Claude
- 13.01.14, Somatostatin and its receptors: Translating science into clinical use, Guillemin Symposium, Salk Institute for Biological Studies, San Diego, CA
- 21.11.14, Somatostatin and GLP-1 receptor targeting in NET: Examples of successful translational research, Theodor-Kocher-Vorlesung, 33. Arbeitstagung der Chirurgischen Arbeitsgemeinschaft Endokrinologie (CAEK), Basel

Schläfli Anna
- 25.01.14, ALFY acts as an autophagy scaffold protein to target PML-RARA for degradation, GCB Students' Symposium 2014, Bern

Schmitt Anja
- 30.09.14, A Unicorn Among Farm Horses (Slide Seminar «Challenges in Thyroid and Pancreas Cytology»), European Congress of Cytology, Geneva

Tschan Mario P.
- 04.02.14, «Self-eating» (Autophagy) in AML Differentiation, Treffen der SAKK Leukämiegruppe, Bern
- 17.10.14, Regulation and function of autophagy in the differentiation process of acute myeloid leukemia cells, Internatjional Autophagy Conference, Toulouse, F
- 28.07.14, Autophagy and Cancer Therapy, 10th Summer School, Stein-am-Rhein
- 12.01.14, Autophagy in tumor pathology and cancer treatment resistance, Gastseminar, Bern

Wampfler Julian
- 15.05.14, «RNA binding proteins RBM38 and DND1 positively impact on AML cellular differentiation», European and Swiss Congress of Internal Medicine, Geneva

Zlobec Inti
- 20.05.14, next-generation Tissue Microarrays in Translational Research, Monday seminar, Polytechnique Fédérale de Lausanne, Institut Suisse de Recherche en Cancer (ISREC), Lausanne
- 16.09.14, Nipping colorectal cancer in the (tumor) bud: current studies and future outlook, Tuesday evening seminar, Institute of Pathology, University of Erlangen, Erlangen

5 Drittmittel

Berezowska Sabina
- Bernische Krebsliga, 01.09.14–31.12.15, CHF 32'000, Nebengesuchsteller: Mario P. Tschan

Corazza Nadia
- Novartis , 01.03.12–31.12.50, CHF 60'000, Nebengesuchsteller: C. Müller, Pathologie

Dawson Heather
- Werner und Hedy Berger-Janser Stiftung, 01.01.14–01.01.15, CHF 26'836

Diamantis Eva
- Fondation Johanna Durmüller-Bol, 01.01.13–31.12.14, CHF 20'000
- Bernische Krebsliga, 01.01.13–31.12.15, CHF 70'000
- Werner und Hedy Berger-Janser Stiftung, 01.08.13–01.08.15, CHF 33'410

Freigang Stefan
- Schweizerische Herzstiftung, 01.01.14–31.12.14, CHF 70'000
- Olga Mayenfisch, 01.04.14–31.03.15, CHF 50'000
- Stiftung Vontobel, 01.10.14–30.09.17, CHF 120'000
- UniBern Forschungsstiftung, 01.06.14–31.05.17, CHF 15'000
- Fondation Dürmüller, 25.08.14–24.08.50, CHF 26'993
- SNF, 310030_152872 / 1, 01.01.15–31.12.17, CHF 510'890
- SNF R'equip, 316030_157702 / 1, 01.12.2014–30.11.2015, CHF 120'433

Körner Meike
- Desirée and Niels YDE Stiftung, 13.06.12–12.06.14, DKK 321'078

Krebs Philippe, Banz Yara
- Stiftung für klinisch-experimentelle Tumorforschung, 01.05.14–31.12.50, CHF 80'000

Krebs Philippe
- Marie Curie Career Integration Grants, 01.01.14–31.12.17, EUR 100'000
- SNF, 310030_138188, 01.09.12–31.08.15, CHF 377'366
- SNF, 316030_145006/1, 01.09.13–31.08.14, CHF 54'000

Langer Rupert
- Krebsforschung Schweiz, Bern, 01.06.1–01.09.15, CHF 236'000, Nebengesuchsteller: Mario P. Tschan

Lugli Alessandro
- Krebsforschung Schweiz, Bern, 01.01.14–31.03.16, CHF 233'700, Nebengesuchsteller: A. Lugli
- SNF, 310030_133114/1, 06.10.10–01.03.15, CHF 216'000, Nebengesuchsteller: I. Zlobec, Pathologie; G. Iezzi, Zentrum für Lehre und Forschung, Basel; L. Terracciano, Pathologie

MacPherson Andrew, Bern
- SNF (Sinergia), 136286, 01.12.11–30.11.14, CHF 399'000, Nebengesuchsteller: C. Müller, Pathologie

Mager Lukas
- PhD Fellowship Boehringer Ingelheim Fonds, 01.05.12–15.11.14, EUR 60'000

Müller Christoph
- SNF, 310030_138392 /1, 01.11.11–31.10.15, CHF 623'000

Noti Mario
- SNF (Ambizione), PZ00P3_154777 / 1, 01.10.14–30.09.17, CHF 599'156

Ochsenbein Adrian
- Werner und Hedy Berger-Janser Stiftung, 01.06.14–31.05.17, CHF 320'000, Nebengesuchsteller: C. Schürch, C. Riether
- Mach-Gaensslen Stiftung, 01.07.14–30.06.16, CHF 77'240, Nebengesuchsteller: C. Schürch, C. Riether
- Swiss Bridge Award, 01.11.14–31.10.17, CHF 250'000, Nebengesuchsteller: C. Schürch, C. Riether

Perren Aurel
- Gewebebank, 01.06.11–31.12.50, CHF 206'213
- Krebsforschung Schweiz, 01.08.14–31.08.17, CHF 286'900

Perren Aurel, Schmitt Anja
- Bernische Krebsliga, 01.10.12–31.12.15, CHF 76'000

Perren Aurel, Dettmer Matthias
- Gertrud Hagmann Stiftung, 01.03.13–28.02.14, CHF 120'000

Perren Aurel, Marinoni Ilaria
- SNF DAXX, 310030-144236/1, 01.10.12–30.09.15, CHF 367'573

Rogler Gerhard, Uni Zürich
- SNF (SIBDCS), 33CS30_134274 /1, 01.04.11–30.06.14, CHF 482'550, Nebengesuchsteller: C. Müller, Pathologie
- SNF (SIBDCS) NEU, 33CS30_148422, 01.07.14–31.03.16, CHF 257'040, Nebengesuchsteller: C. Müller, Pathologie

Saurer Leslie
- Bernische Krebsliga, 01.10.13–30.09.15, CHF 45'000, Nebengesuchsteller: C. Müller, Pathologie
- Novartis, 01.01.14–30.04.16, CHF 60'000, Nebengesuchsteller: C. Müller, Pathologie
- SNF (small nested project), 33CS30_134274 /1, 01.11.11–31.03.14, CHF 40'000, Nebengesuchsteller: C. Müller, Pathologie

Schäfer Stephan, Vassella Erik
- Bernische Krebsliga, 01.04.14–31.07.15, CHF 35'000

Schmitt Anja
- Bernische Krebsliga, 01.10.12–31.12.15, CHF 76'000

Schürch Christian
- Swiss Life Jubiläumsstiftung, 01.03.14–28.02.15, CHF 20'000

Tschan Mario P.
- Stiftung für klinisch-experimentelle Tumorforschung, 01.02.12–30.09.14, CHF 183'000
- Cancer Research Switzerland , 08.01.14–31.07.17, CHF 369'700
- Diverse kleinere Forschungskredite, CHF 90'000
- SNF, 31003A_143739, 01.01.13–31.12.15, CHF 390'000

Vassella Erik
- Krebsforschung Schweiz, 01.04.12–31.12.15, CHF 204'400, Nebengesuchsteller: Mathias Gugger, Promed
- SNF, 31003A_138129/1, 01.04.12–31.03.15, CHF 290'066, Nebengesuchsteller: Istvan Vajtai, Pathologie Länggasse

Zlobec Inti
- Mach-Gaensslen Foundation, 01.07.2014–31.12.2015, CHF 39'000
- Johanna Dürmüller-Bol Foundation, 01.10.2014–30.04.2016, CHF 20'000
- Foundation for clinical and experimental tumor research, 01.11.2013–31.10.2014, CHF 53'226

6 Preise, Ernennungen, Auszeichnungen

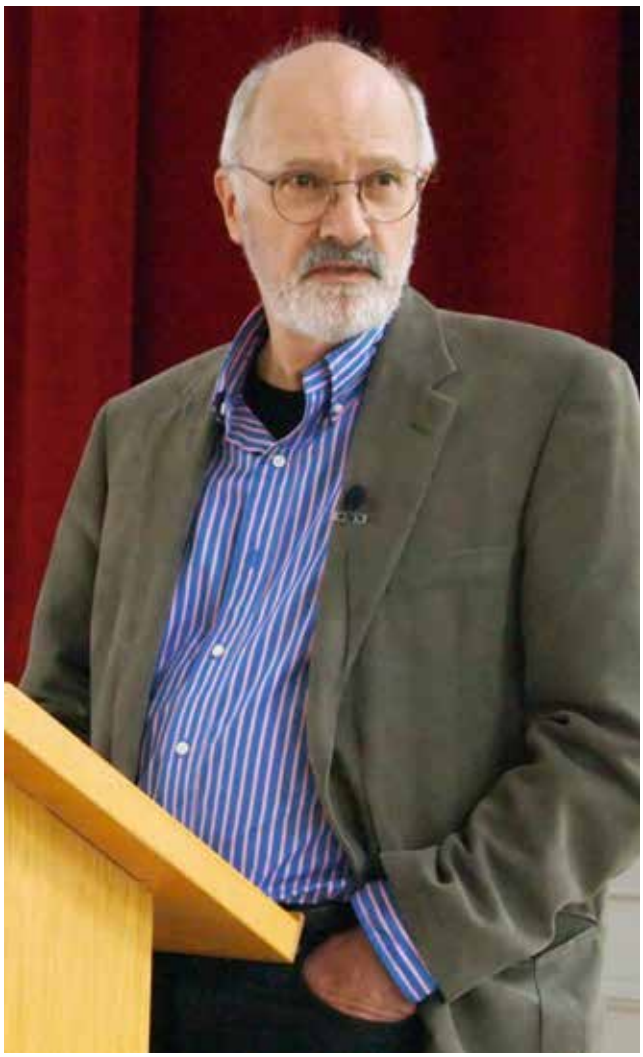
Eva Diamantis
- 11. September 2014: SIWF-Award für besonderes Engagement in der ärztlichen Weiterbildung

Jean Claude Reubi
- 21. November 2014: Theodor-Kocher-Vorlesung, 33. Arbeitstagung der Chirurgischen Arbeitsgemeinschaft Endokrinologie (CAEK), Basel

Viktor Kölzer
- 03. September 2014: George Tiniakos Award 2014 for the best scientific contribution in gastrointestinal, liver and pancreas pathology, European Society of Pathology Congress, European Society of Pathology, London, Gastrointestinale Pathologie (angegeben von Prof. Lugli)

7 Patente

Inventors: Julian Egger, Peter Bretscher, Stefan Freigang, Manfred Kopf, Erick M. Carreira
- Filed July 3, 2014, Europe EP14175553.8, CYCLIC DERIVATIVES OF EPOXYISOPROSTANOIDS AS THERAPEUTIC AGENTS



Theodor-Kocher-Vorlesung vom 21.11.2014, Prof. Jean Claude Reubi.

>>> Studentische Lehre

Das Fach Pathologie begleitet die Studierenden der Humanmedizin während ihrer gesamten klinischen Ausbildung vom 3. bis zum 6. Studienjahr. In dieser Zeit erhalten sie in Vorlesungen, Makroskopie- und Mikroskopiekursen sowie wöchentlichen Falldemonstrationen einen mehrjährigen strukturierten Unterricht, der die Kenntnisse und das Verständnis für Mechanismen, Zusammenhänge und Morphologie von Erkrankungen vermittelt. In den Kursen werden hierbei makroskopische Präparate aus unserer umfassenden Sammlung zum «Begreifen» der morphologischen Veränderungen als Lehrmittel eingesetzt. Der komplementäre Histologiekurs wurde nach zweijähriger Testphase nun komplett auf digitale Pathologie mit dem «virtuellen histologischer Schnittkasten» ausgerichtet, der wie auch in den Jahren zuvor mithilfe von Herrn Dr. Woermann, Anatomisches Institut, online zur Verfügung steht.

Die Grundlagen der Allgemeinen Pathologie lernen die Studierenden im 3. Studienjahr (Einführungskurs 1). Dies geschieht zum einen eingebettet in interdisziplinäre Vorlesungsveranstaltungen, die spezielle Themenblöcke behandeln, zum anderen im Fachpraktikum Pathologie, wo unterstützt durch die Histologie die Grundmechanismen der Pathologie und die entsprechenden wesentlichen morphologischen Veränderungen behandelt werden. Daneben ist die Pathologie auch an zahlreichen PBL-Tutoriaten beteiligt. Neu wurde 2014 auch ein Vertiefungsseminar «Pathologie» angeboten, bei dem die Studierenden die Gelegenheit hatten, das Tätigkeitsbild des Pathologen hautnah im Rahmen von Führungen durch das Institut kennenzulernen.

Im 4. Studienjahr (Einführungskurs 2) und im 5. Studienjahr (Schlusskurs 1) wird das erlangte Wissen im Sinne des Spiralkurrikulums auf die spezielle, organbezogene Pathologie angewendet. Hierbei wird ein systematisches Curriculum durchlaufen, das alle Organsysteme und ihre wichtigsten Erkrankungen abdeckt. Es besteht aus theoretischen Vorlesungen und praktischen Kursen, in denen die Studierenden sich mittels Makroskopie und Mikroskopie vertiefende Kenntnisse aktiv erarbeiten. Ergänzend finden wöchentlich Autopsiedemonstrationen statt, in denen anhand aktueller Fallbeispiele die aktive Erarbeitung pathophysiologischer Zusammenhänge und Sequenzen verschiedenster Krankheiten im Vordergrund stehen.

Im 6. Studienjahr 2014 war die Pathologie im neu reformierten Schlusskurs 2 als fachübergreifende Disziplin an mehreren interdisziplinären Vorlesungen beteiligt und behandelte auch eigene Schwerpunkte, wie die «Klinisch Pathologische Konferenz», die im Gegensatz zu den Vorjahren neu fest im Stundenplan verankert ist.

Zuletzt gibt es für Studierende, die ihre Kenntnisse im Fach Pathologie vertiefen wollen oder sich für eine spätere Fachausbildung in diesem Fach interessieren, die Möglichkeit eines 1- bis 2-monatigen Einsatzes im Rahmen des Wahlstudienjahrs. Hier durchlaufen die Wahlstudierenden ein strukturiertes Curriculum, im Rahmen dessen alle Tätigkeitsgebiete der Pathologie, wie die Autopsie, die makroskopische und histologische Diagnostik und die Zytologie, aber auch die Molekularpathologie kennengelernt werden können.

Ein weiterer Einsatz der Pathologie im universitären Lehrbetrieb bestand, wie in den Jahren zuvor, in Vorlesungen und Kursen für die Studenten der Zahnmedizin, des Studienganges Biomedical Sciences und der Zellbiologie (Cell Biology), wo verschiedenste Kurse (Histologie, Allgemeine Pathologie, Molekularpathologie und Tumorpathologie) von Mitgliedern des Instituts für Pathologie organisiert und angeboten werden. Zudem sind Mitglieder des Instituts aktiv in der Ausbildung von PhD-Studenten der Graduate School for Cellular and Biomedical Science involviert.

Die Lehrveranstaltungen sowohl für die Studierenden der Humanmedizin als auch der Fakultät für Biological Science werden von Mitarbeitern sowohl der klinischen als auch der experimentellen Pathologie gehalten, wobei je nach Thema und Schwerpunkt des Studienganges bzw. der Veranstaltung Ärzte oder Naturwissenschaftler als Dozenten fungieren.

>>> Weiterbildung

Die Ziele der internen Weiterbildung des Instituts für Pathologie der Universität Bern beinhalten die optimale Vermittlung von Wissen und das Erlangen von Kompetenzen. Die klinischen und wissenschaftlichen Fähigkeiten eines Pathologen werden dadurch gefördert, wobei das Lehrprogramm für die Assistenzärztinnen und -ärzte flexibel und individuell gestaltet wird.

Die Umsetzung dieser Ziele erfolgt durch ein modulares System mit klar definierter Struktur und regelmässigen Zwischenevaluationen in Form von mini-CEX und DOPS, welche den Bedürfnissen der Pathologie angepasst sind. Zusätzlich garantieren Diagnostikräume, welche in der Dienstleistung im Rahmen des LEAN-Management-Projekts in der Klinischen Pathologie eingeführt wurden, eine kontinuierliche und optimale Betreuung der Assistierenden durch die Fachärzteschaft.

>>> Fortbildung

Montagsseminare 2014

	Titel	Referent/-in
13.01.	New key players of cancer metastasis: identify, translate, intervene	Prof. Dr. Ulrike Stein Experimental and Clinical Research Center Charité University Medicine Berlin
20.01.	The interaction between the immune system and cancer	Maries van den Broek, Uni Zürich
27.01.	Role of IL-33/ST2 signaling in myeloproliferative neoplasms	Philippe Krebs, Yara Banz Institut für Pathologie, Universität Bern
10.02.	NAFLD – a pathology update	Prof. Pierre Bedossa, Hôpitaux Universitaires Paris Nord Val de Seine
17.02.	Androgen-Biosynthese	Prof. Christa Flück, DKF
24.02.	HFG in Biobank-Projekte – Vorstellung des Gesetzes und Fragen der Forschenden	Prof. Aurel Perren Institut für Pathologie, Universität Bern
10.03.	Towards the definition of the cellular and molecular determinants of all-trans retinoic acid anti-tumor activity in breast cancer	Prof. Enrico Garattini, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Milano
17.03.	Update in Barrett Esophagus	Prof. Jean-François Fléjou
24.03.	Protein analysis in clinical tissue specimens: problems and promises	Prof. Dr. Karl-Friedrich Becker Technische Universität München
31.03.	WIPI proteins in autophagy, health and disease	Tassula Proikas-Cezanne Eberhard Karls University Tübingen
14.04.	Death-associated protein kinase DAPK1 – a cancer gene chameleon	Regine Stock-Schneider, Universität Erlangen
28.04.	Regulation of inflammation by oxidized phospholipid signaling	Stefan Freigang Institut für Pathologie, Universität Bern
12.05.	Autophagy and Cancer Therapy	Mario Tschan Institut für Pathologie, Universität Bern
19.05.	Autophagy proteins in MHC restricted antigen presentation	Prof. Christian Münz Institute of Experimental Immunology University of Zurich
30.06.	Microbial and Metabolite Modulation of Host Immunoregulatory Responses	Dr. Liam O`Mahony, SIAF Davos
15.09.	Genomic heterogeneity and clonal evolution in solid tumors	Prof. Lukas Bubendorf Institut für Pathologie, Universität Basel
29.09.	Research in Progress	Inti Zlobec Institut für Pathologie, Universität Bern
13.10.	Hospital biobanks in the era of precision medicine	Olli Carpen, University of Turku, Finland
20.10.	Coordinated regulation of autophagy and metabolism by FOXO transcription factors	Prof. Paul Coffer University Medical Center Utrecht
27.10.	From the Lab to the Marketplace: How to benefit from University Inventions	Dr. Martin Binggeli, Unitectra Technology Transfer for the Universities of Basel, Bern and Zurich
10.11.	Trying to make sense in nonsense-mediated mRNA decay	Prof. Oliver Mühlemann Department of Chemistry & Biochemistry University of Bern
17.11.	Fighting disease by selective autophagy of aggregate-prone proteins	Prof. Anne Simonsen, PhD Dept. of Biochemistry, University of Oslo
24.11.	Mechanistic insights and therapeutic targeting of cancer hallmarks	Prof. Doug Hanahan EPFL, Lausanne
08.12.	Molecular Pathology of Gastric Cancer	Prof. Fatima Carneiro Dept of Anatomic Pathology Centro Hospitalar de São João, Porto

>>> Im Fokus

In der modernen Medizin ist die Pathologie ein fester Bestandteil des ambulanten und stationären Patientenmanagements. In der Klinischen Pathologie werden Biopsien in der präoperativen, Schnellschnitte in der perioperativen und Resektate in der postoperativen Phase zu histologischen Schnitten verarbeitet und mikroskopisch befundet. Das Produkt dieses Arbeitsprozesses, in welchem das Laborpersonal, das Ärzte- und Befundsekretariatsteam beteiligt sind, ist der Diagnosebericht. Häufig ist die mikroskopische Untersuchung der Gold-Standard bei der Diagnose von Tumoren und ausgewählten entzündlichen Erkrankungen. Eine zeitgerechte Bereitstellung der Pathologieberichte ist entscheidend, weil dieser Gold-Standard für schwerwiegende Therapie-Entscheide abgewartet wird. In der Industrie wurde zur kontinuierlichen Qualitätssteigerung das LEAN-Management System entwickelt mit den zwei Kernprinzipien: Reduktion von Leerläufen und Steigerung der «Corporate Identity» durch eine Kultur der Motivation und Förderung.

Im Jahre 2010 wurde in der Klinischen Pathologie das LEAN-Management-Modell eingeführt mit dem Ziel, die Durchlaufzeiten zu verkürzen, die Corporate Identity der eigenen Mitarbeitenden zu steigern und gleichzeitig ressourceneffizienter zu werden.

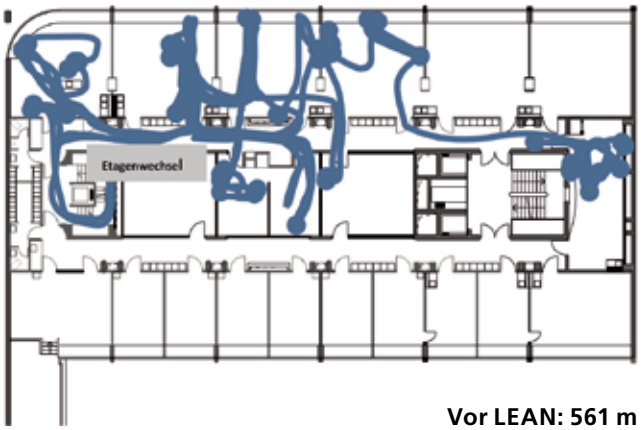
Für die operative Umsetzung des LEAN-Modells wurden folgende Massnahmen implementiert:
- Schaffung eines Führungsstabes, welcher durch einen speziell in LEAN ausgebildeten Mitarbeitenden («LEAN Officer») unterstützt wird.
- Der Arbeitsprozess wurde durch eine Raumreorganisation optimiert und kontinuierlich gestaltet (Fluss im Wertstrom) mit dem Ziel, die Wege zu verkürzen und die Liegezeiten der Gewebeproben und Operationspräparate zu reduzieren (Liegezeit = Zeit, in welcher am Präparat nicht gearbeitet wird – «waste»)
- Aufteilung des gesamten täglichen Arbeitsvolumens in mehrere kleine Einheiten, welche von allen Prozessteilnehmenden im Stundentakt bearbeitet werden («single piece workflow»).
- Aufbau eines Diagnostiktraktes, bestehend aus vier Diagnostikräumen. In jedem Diagnostikraum arbeitet ein Ärzteteam, bestehend aus einer/einem Oberärztin/Oberarzt und einer/einem Assistenzärztin/Assisstenzarzt. Alle Räume wurden kongruent mit zwei PC-Stationen, zwei Mikroskopen und Fachbüchern ausgerüstet. Diese Massnahme erlaubt eine örtliche Trennung der Diagnostik von der Lehre/Forschung.
- Jeder Arbeitsplatz in der gesamten Abteilung wurde nach dem 5S-Prinzip (Sortieren, Simplifizieren, Säubern, Standardisieren und Ständig vorhalten) reorganisiert.
- Alle eingeführten Prozesse und neu eingerichteten Arbeitsplätze wurden mit «Standards of Operation» (SOPs) definiert und mittels Erhebung von Leistungskennzahlen monitorisiert.

Durch die Implementierung dieser Massnahmen ergaben sich aus Sicht des Betriebes folgende Verbesserungen: Der Weg für ein Operationspräparat vom Zeitpunkt des Laboreinganges bis zur Diagnosestellung wurde von 561 m auf 143 m reduziert und die Liegezeiten für Operationspräparate wurden im Schnitt von 76 Stunden auf 24 Stunden (bei Gewebeeingang um 13.15 Uhr) und auf 9 Stunden (bei Gewebeeingang um 8.15 Uhr) reduziert. Zusätzlich konnten in der gesamten Abteilung 30% der Arbeitsfläche eingespart werden und durch Reduktion von Überzeiten 10% der Personalressourcen für Lehre und Forschung freigestellt werden.

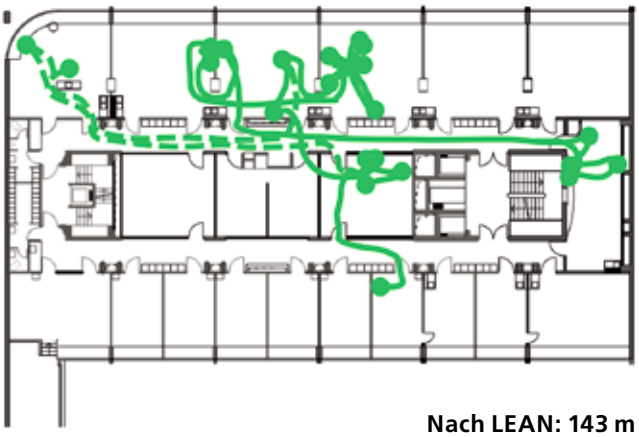
Die Durchlaufzeiten für Biopsien wurden von 68 auf 36 Stunden und für Operationspräparate von 106 auf 43 Stunden verkürzt, was aus der Sicht der Kundschaft eine deutlich bemerkbare Verbesserung darstellt.

Die LEAN-Implementierung steigerte die Ressourceneffizienz und die Kundenzufriedenheit. Folglich könnte LEAN modifiziert auch in andere Institute für Pathologie oder klinische Betriebe anderer medizinischer Fachrichtungen erfolgreich eingesetzt werden.

Das Projekt wurde mit dem Titel «Umsetzung des LEAN Management System in der Klinischen Pathologie» als Abstract beim Swiss Quality Award eingereicht und mit dem Swiss-Quality-Award-Posterpreis 2014 ausgezeichnet.

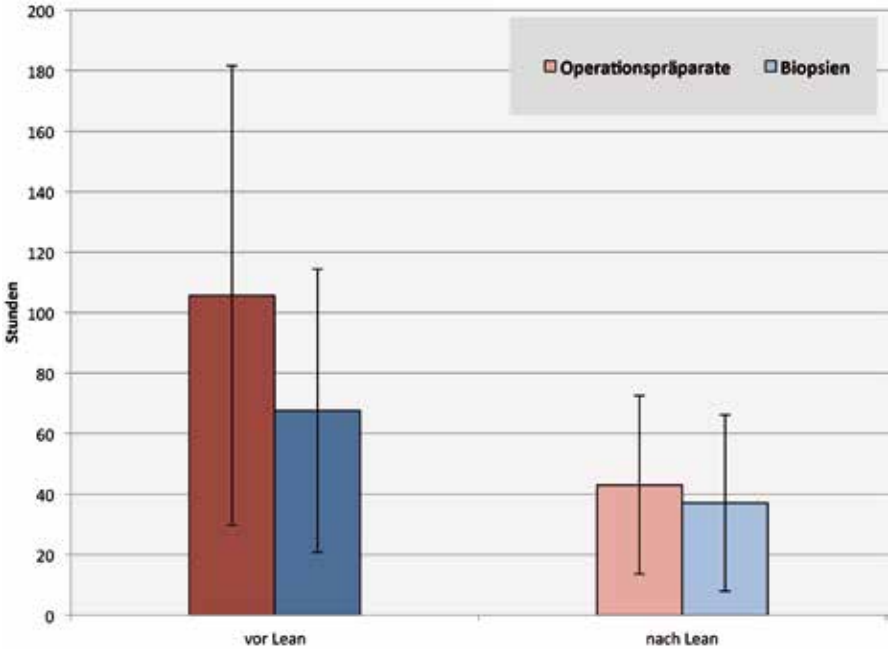


Vor LEAN: 561 m

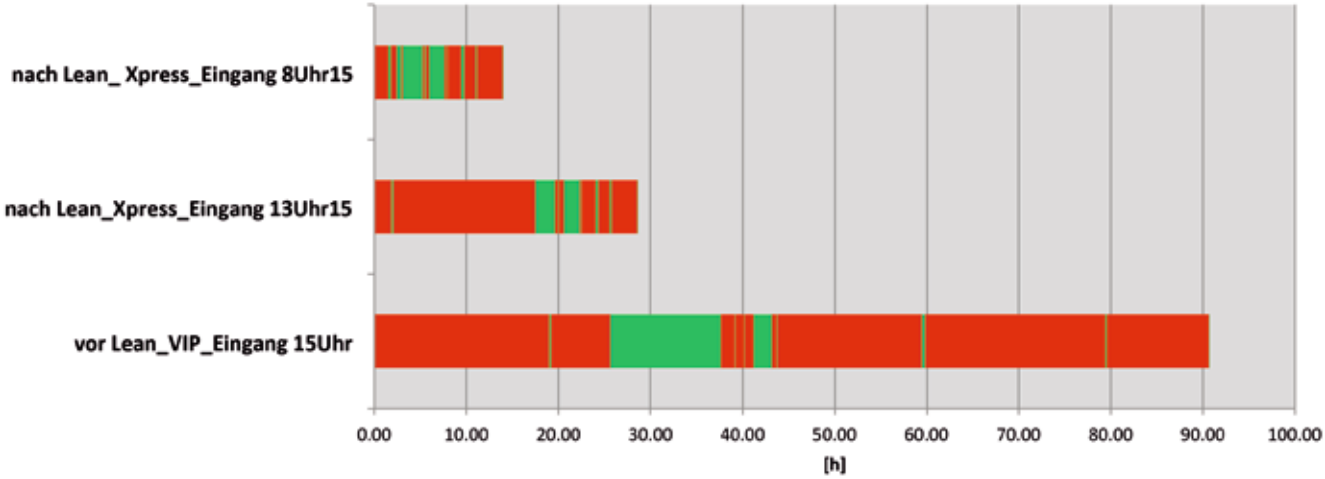


Nach LEAN: 143 m

Weg eines Operationspräparates.

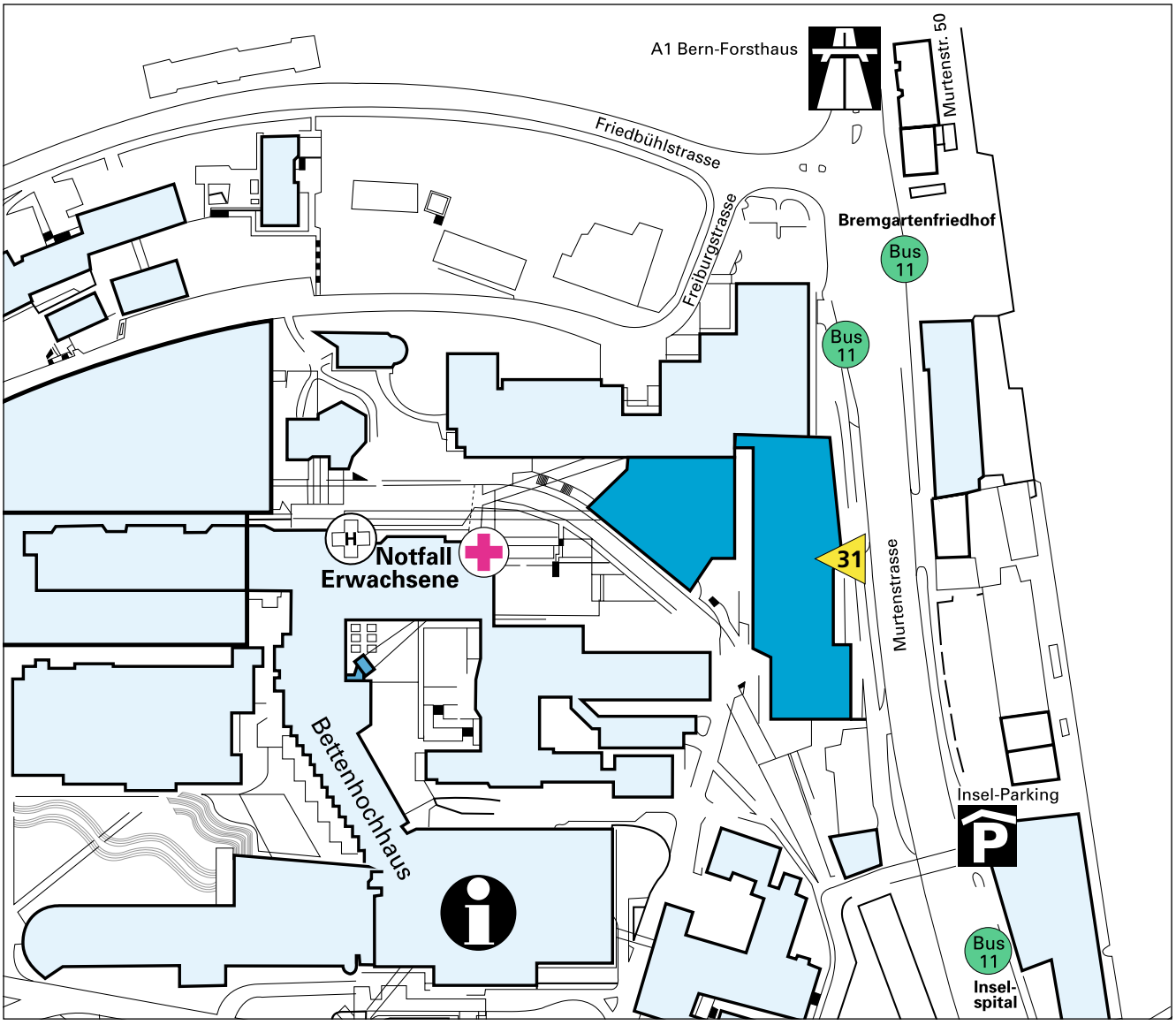


Durchlaufszeit Operationspräparate und Biopsien.



Liegezeiten (rot) nach Operationspräparaten vor und nach LEAN.

>>> Situationsplan



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