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Institut für Pathologie

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>>> Das Wichtigste in Kürze

Liebe Leser,

auch 2016 war ein ereignisreiches Jahr für das Institut für Pathologie. In zwei Etappen konnten wir das neue «LEAN»-Histologie-Labor und die neuen Büroräumlichkeiten beziehen. Mit diesen zwei letzten grossen Umzügen wurden wir für die schwierigen, lärmigen Monate des Umbaus belohnt. Rückblickend ist es für mich erstaunlich, wie die Mitarbeiter und die Umbauteams die mit dem Umbau verbundenen Änderungen problemlos umsetzen konnten; ein herzliches Dankeschön an alle! Am Ende dieses Jahresberichts sind einige Highlights des Umbaus zusammengefasst.

Für unsere klinischen Kunden sind wir mit der Einführung von synoptischen Tumorberichten für häufige Entitäten einen wichtigen Schritt vorangegangen. Dieses aus dem Amerikanischen übernommene System der strukturierten Befundung wurde von der überwiegenden Mehrheit der Kunden sehr positiv aufgenommen und wir werden dieses System weiterverfolgen.

Für den Studentenunterricht haben wir die Makroskopiepräparate für die Kurse des 4. und 5. Studienjahres aktualisiert und den Kurs besser an die Vorlesungen angepasst.

Die Tissue Biobank Bern, welche vom Institut für Pathologie geführt wird, ist im Rahmen der SNF-geförderten Swiss Biobanking Plattform in Zusammenarbeit mit allen anderen Universitäts-Pathologien aktiv daran beteiligt, schweizweite Standards zu definieren und eine Vernetzung der unterschiedlichen Gewebebanken voranzubringen.

In der Experimentellen Pathologie wurde das Institut für Pathologie mit Frau Prof. Mirjam Schenk, Förderprofessorin der Hofschneider Stiftung, durch eine neue Forschungsgruppe auf dem Gebiet der Immunonkologie verstärkt.

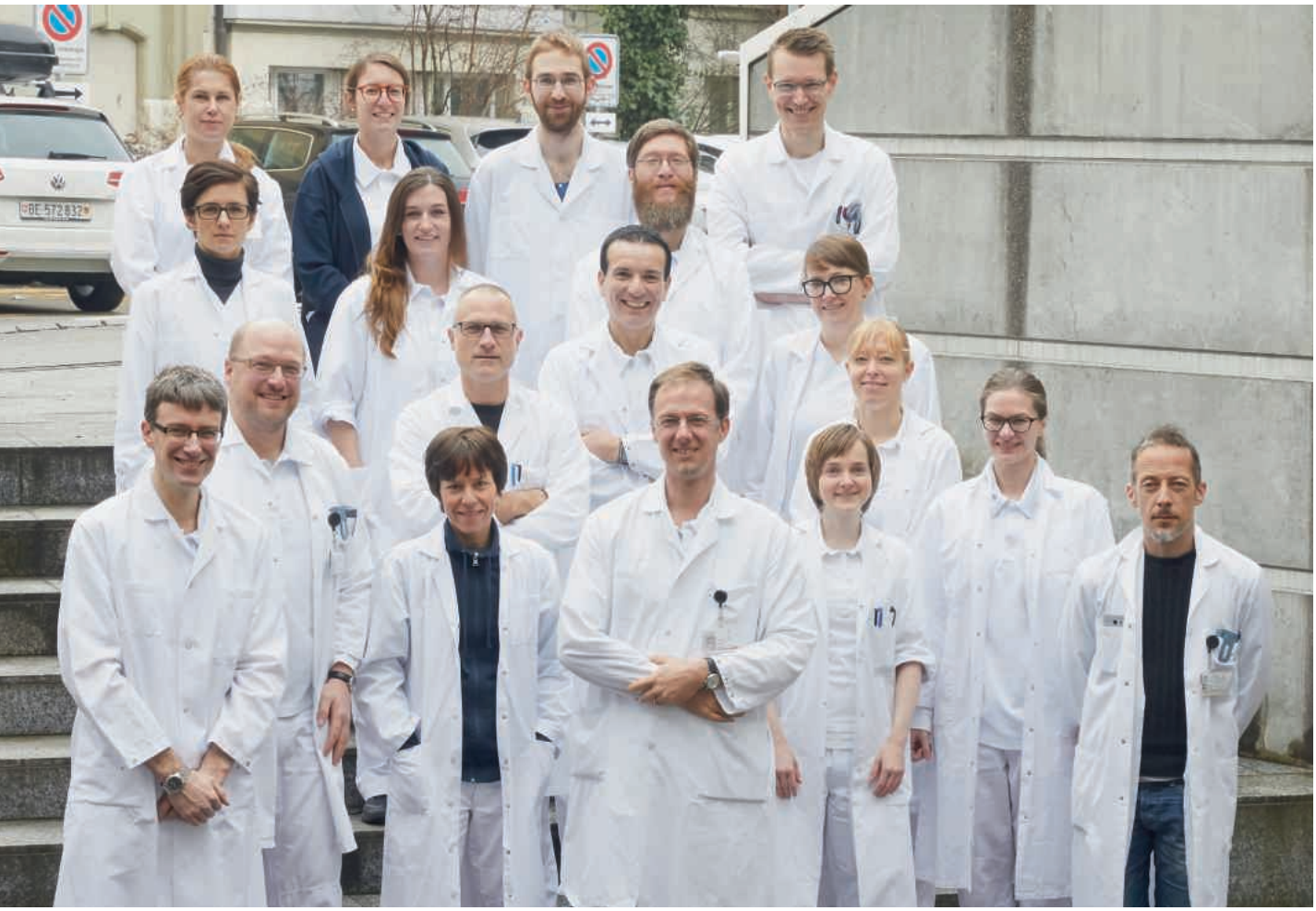
Die Arbeit geht nicht aus, die 2016 begonnene Akkreditierung wird uns auch 2017 und darüber hinaus helfen, uns weiterhin kontinuierlich zu hinterfragen und zu verbessern.

Ich wünsche Ihnen viel Vergnügen bei der Lektüre,

Ihr Aurel Perren, Direktor

Mitarbeiterinnen und Mitarbeiter des Instituts für Pathologie.

>>> Organigramm



Ärzteteam Klinische Pathologie.

Team Klinische Pathologie.

>>> Dienstleistung

1 Klinische Pathologie

Leiter: Prof. Dr. med. Alessandro Lugli

Im März 2016 konnte das neue Labor der Klinischen Pathologie, das nach dem LEAN Management System konzipiert wurde, bezogen werden. Im August 2016 erfolgte dann der Umzug für die Ärzteschaft und die Mitarbeitenden des Berichtswesens in die neuen Räumlichkeiten im zweiten Stockwerk. Der Umbau ermöglicht den drei Einheiten der Klinischen Pathologie (Ärzteschaft, Labor und Berichtswesen) optimale und kontinuierliche Arbeitsprozesse. Für das Jahr 2017 wurden auf Abteilungsebene folgende Ziele festgelegt: 1. Akkreditierung, 2. Optimierung des LEAN-Konzepts im Histopathologie- und im Immunhistochemie-Labor sowie 3. Einführung des LEAN-Konzepts im Berichtswesen.

1.1 Ärzteschaft

Die in Fachgruppen organisierte Ärzteschaft arbeitet eng mit der klinischen Kundschaft zusammen und vertritt die Pathologie an den zahlreichen wöchentlichen Tumorboards/Fallbesprechungen innerhalb des Inselspitals und in auswärtigen Spitälern. Durch die Unterstützung der Translational Research Unit (TRU) und den Besuch nationaler und internationaler Kongresse wird das Fachwissen auf dem neuesten Stand gehalten. Die 10 Assistierenden werden von 16 Fachärztinnen und Fachärzten weitergebildet.

1.2 Neuropathologie

Im Jahr 2016 untersuchte die Neuropathologie mehr als 1200 histologische Proben, darunter wurden in gut 300 Fällen intraoperative Schnellschnittuntersuchungen durchgeführt. Wir zählen damit zu den diagnostisch aktivsten Neuropathologien in der Schweiz. Der Schwerpunkt unserer Tätigkeit besteht in der Tumordiagnostik, sie 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 einschliesslich konsiliarischer Untersuchungen im Auftrag des Instituts für Rechtsmedizin 65 Hirnsektionen durch.

Die hohe Spezialisierung spiegelte sich wie in den Vorjahren in einer regen, schwerpunktmässig diagnostisch orientierten Publikationstätigkeit wider. Entsprechend dem Charakter der Neuropathologie als Schnittstelle zwischen den klinischen Neurofächern, der Labordiagnostik und der translationalen Forschung war der Fachbereich Neuropathologie auch im Jahr 2016 in zahlreichen Veranstaltungen, insbesondere in Zusammenarbeit mit Kliniken des Inselspitals, engagiert. Darüber hinaus ist das Fach Neuropathologie Teil des Neuroonkologischen Tumorzentrums und einer der Schwerpunkte der Medizinischen Allianz Bern/Basel (MBB).

1.3 Postmortale Diagnostik

Im Jahr 2016 wurden im Institut für Pathologie 146 postmortale Untersuchungen durchgeführt, inklusive neuropathologischer und pädopathologischer Untersuchungen. 55 davon waren Fälle aus dem Inselspital Bern. Nach längerer Vorbereitung wurden in der Postmortalen Diagnostik tiefgreifende Strukturänderungen, die nach dem LEAN-Prinzip erarbeitet wurden, implementiert. Neben Veränderungen in den Räumlichkeiten, die nun analog eines Operationssaals ausgestattet sind, wurden auch die Abläufe sowie die Personalbesetzung reorganisiert. So besteht z.B. das ärztliche Team aus einem Stamm von 4 FachpathologInnen, die im Turnus neben der direkten postmortalen Diagnostik auch für die Ausbildung der RotationsassistentInnen in diesem Gebiet und der Makroskopie sowie den Studentenunterricht zuständig sind. Seit Juni bieten wir zudem im Zusammenhang einer Studie zur «Implementierung der Postmortalen Diagnostik» auch die Möglichkeit an, je nach Indikation und Wunsch der Angehörigen bzw. der klinischen Kollegen postmortale Untersuchungen im Rahmen einer minimalinvasiven Diagnostik oder analog eines chirurgischen Eingriffs als postmortale operative Diagnostik durchzuführen. Diese von der Ethikkommission bewilligte Studie wird momentan noch von den Kollegen aus der chirurgischen Abteilung des Inselspitals (Leitung: PD Dr. med. Beat Schnüriger) begleitet und wird perspektivisch eine Vielzahl von nicht- oder minimalinvasiven Optionen einer postmortalen Diagnostik und Qualitätssicherung erarbeiten können.

Durch die Umstrukturierungen konnte bereits in diesem Jahr die durchschnittliche Durchlaufzeit der Autopsieberichte von über 30 auf 14 Tage bis zum abschliessenden Bericht reduziert werden. Ebenso stieg die Zahl der postmortalen Untersuchungen an Erwachsenen, inklusive auch der klassischen autoptischen Untersuchungen um 38% im Vergleich zum Vorjahr.

Laborteam Klinische Pathologie.

Team Berichtssekretariat.

1.4 Labor Histopathologie und Immunhistochemie

Der Laborumzug erfolgte durch eine sorgfältige Planungsphase und eine sehr gute Teamleistung ohne Probleme. Somit zählt das Labor der Klinischen Pathologie nun zu den modernsten in Europa und entspricht den neusten Sicherheitsstandards, was die Vorbereitungen auf die bevorstehende Akkreditierung enorm erleichtert. Die Reorganisation der Archive konnte ebenfalls erfolgreich abgeschlossen werden.

Im Jahre 2016 konnte dank dem LEAN Management System die Anzahl der Einsendungen auf 42'200 (Zuwachs: 16%) und die Probenanzahl auf insgesamt 81'700 (Zuwachs: 13%) gesteigert werden.

Die Zahl der Schnellschnittuntersuchungen konnte mit einer Durchschnittgeschwindigkeit von 20 Minuten weiter auf 2400 gesteigert werden. Auswärtige Schnellschnitte können dank dem neu eingeführten mobilen Schnellschnittfahrzeug leichter bewältigt werden.

Das Team der Immunhistochemie verarbeitete im Jahr 2016 9094 Fälle, an welchen 44'500 immunhistochemische Untersuchungen vorgenommen wurden. Zusätzlich wurden 252 native Nierenbiopsien mit je 10 Immunfluoreszenzfärbungen, 231 In-situ-Hybridisierungen (EBER) sowie 146 Fälle für die Postmortale Diagnostik verarbeitet. Aktuell stehen der Routinediagnostik 253 Primärantikörper zur Verfügung.

1.5 Berichtswesen

Im August 2016 konnte das neu eingerichtete Grossraumbüro bezogen werden, welches einen kontinuierlichen Arbeitsprozess erlaubt. Die Nähe des Berichtswesens und der Ärzteschaft im 2. Stockwerk führt zusätzlich zu einer optimalen Kommunikation. Die nächsten geplanten «Meilensteine» beinhalten die Zusammenlegung der Sekretariate Histopathologie und Zytopathologie sowie die Implementierung des LEAN-Konzeptes.

2 Molekularpathologie

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

Wissenschaftlicher Leiter: Prof. Dr. pharm. Erik Vassella
Medizinischer Leiter: PD Dr. med. et phil. Tobias Grob

Mitarbeiterinnen Molekularpathologie-Labor:
Claudia Zurbuchen, technician
Maja Neuenschwander, technician
Cornelia Schlup, technician
Brigitte Jossen, technician
Nicole Klaus, technician
Franziska Graber, technician
Sonja Gempeler, 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 den Nachweis von Mutationen, Promoter-Methylierung, Mikrosatelliteninstabilität, B- und T-Zellklonalität sowie den Nachweis spezifischer Erreger. Die Tests haben diagnostische oder prädiktive Implikation und können an Formalin-fixiertem und Paraffin-eingebettetem Gewebe durchgeführt werden. Seit dem letzten Jahr hat sich das Spektrum, jedoch nicht die Anzahl der im PCR-Labor durchgeführten Mutationsanalysen deutlich verändert. Analysen, die auf der Sequenzierung einzelner Gene beruhen, haben leicht abgenommen. Um den Faktor drei zugenommen hat hingegen das «Next-Generation Sequencing» (NGS), welches die gleichzeitige Sequenzierung ganzer Genpanels in einer einzigen Reaktion ermöglicht. Dieser Trend lässt sich so erklären, dass für den Entscheid einer zielgerichteten Therapie bei Krebspatienten der Mutationsstatus von einer immer grösser werdenden Zahl an Genen abhängt. Deutlich zugenommen hat auch die PAM50-Analyse, ein auf der Nanostring-Technologie basierender Genexpressionstest beim Mammakarzinom. Dieser Test, der das FDA-Gütesiegel trägt, erlaubt eine zuverlässige Einschätzung des Risikos von Patientinnen, Fernmetastasen zu entwickeln.

Auch die Zahl der FISH- sowie elektronenmikroskopisch durchgeführten Analysen ist seit dem letzten Jahr erneut angestiegen. Gewichtige FISH-Analysen sind der Nachweis der ALK-Translokation beim Lungenkarzinom sowie der HER2-Amplifikation beim Mammakarzinom.

Das Molekularpathologie-Labor nimmt regelmässig an Ringversuchen im Rahmen der Qualitätssicherung teil. Im letzten Jahr stand auch die Einführung der Akkreditierung an, welche uns auch in diesem Jahr beschäftigen wird. Das Molekularpathologie-Labor dient auch als Ausbildungsstätte für Assistenzärzte sowie den 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.

Mitarbeitende der Abteilung Zytopathologie.

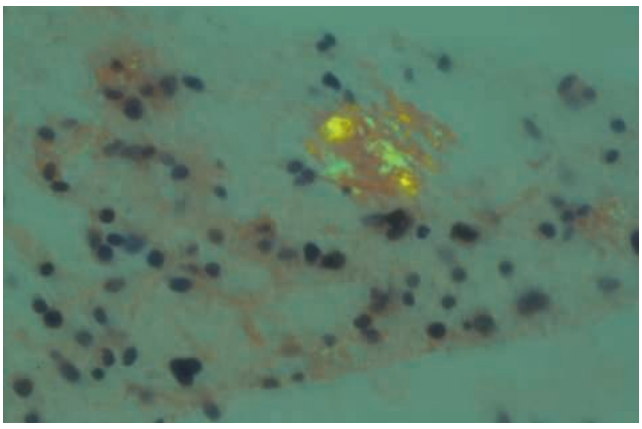
3 Klinische Zytopathologie

Leiterin: PD Dr. med. A. Schmitt Kurrer

Als schnelle, akkurate, minimalinvasive und somit kostengünstige Methode nimmt die Zytologie in einer modernen und kostenbewussten Medizin eine immer wichtigere Rolle in der Abklärung zahlreicher Krankheitsbilder ein. Vor dem Hintergrund unseres kontinuierlichen Bestrebens nach einer Optimierung der diagnostischen Prozesse und einer Stärkung der interdisziplinären Zusammenarbeit mit den klinischen Instituten des Inselspitals zugunsten des Patienten stand das Jahr 2016 unter dem Motto «Der Zytologe als Teil des Behandlungsteams». Welche Rolle spielen der Zytologe und sein Team hier?

Beispiel Amyloidoseabklärung: Seit der Gründung des Myelomzentrums am Inselspital 2016 besteht ein vermehrter Bedarf an Amyloidose-Abklärungen. Die schnellste und kostengünstigste Methode bei einer sehr guten Sensitivität von 80% ist hierfür die sogenannte «4-Quadranten-Bauchfettaspiration» (Dhingra et al., Acta Cytol. 2007 Nov-Dec;51(6):860-4). Bei dieser Untersuchung wird mit einer 18G-Kanüle an vier Stellen rund um den Bauchnabel Fettgewebe aspiriert. Das gewonnene Material wird zu einem Zellblock verarbeitet. Eine Kongorot-Färbung zeigt allfällige Amyloiddepots, welche im Polarisationsfilter eine charakteristische flaschengrüne Färbung aufweisen (siehe Abbildung). Eine genaue Typisierung des Amyloids führen wir in Zusammenarbeit mit dem Amyloid-Register des Universitätsklinikums Schleswig-Holstein in Kiel durch. Insgesamt wurden im Jahr 2016 48 Amyloidoseabklärungen in unserem Punktionsambulatorium durchgeführt.

Beispiel Abklärung Schilddrüsenknoten: Im Rahmen der 2016 gegründeten interdisziplinären Schilddrüsensprechstunde an der Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin & Metabolismus (UDEM) des Inselspitals besetzt die Zytologie ein 10%-Pensum für Feinnadelpunktionen von Schilddrüsenknoten mit direkter mikroskopischer Beurteilung der Proben im Sinne einer «rapid on-site evaluation», ROSE. Somit erhält der Patient im Normalfall eine sofortige Diagnose, sodass das weitere Vorgehen in Abhängigkeit von der Diagnose direkt mit dem Patienten besprochen und eingeleitet werden kann.



Kongo Polarisationsfilter.

4 Fachgruppen des Instituts für Pathologie der Universität Bern

Stand Dezember 2016

Dermatopathologie	
H. Dawson	031 632 99 60
Y. Banz	031 632 88 75

Endokrinopathologie	
A. Perren	031 632 32 22
M. Dettmer	031 632 99 69
A. Blank	031 632 99 01
A. Schmitt	031 632 32 48

Gastrointestinalpathologie	
A. Lugli	031 632 99 58
R. Langer	031 632 32 47
A. Blank	031 632 99 01
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
S. Berezowska	031 632 49 37
H. Dawson	031 632 99 60
V. Genitsch	031 632 99 22
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

Herz-, Gefäss- und Rheumapathologie	
Y. Banz	031 632 88 75
V. Genitsch	031 632 99 22
M. Trippel	031 632 32 76

HNO-Pathologie	
M. Dettmer	031 632 99 69
M. Wartenberg	031 632 87 54
T. Rau	031 632 87 56

Leberpathologie	
M. Montani	031 632 32 67
E. Diamantis	031 632 87 68
A. Blank	031 632 99 01

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 22
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
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
M. Wartenberg	031 632 87 54

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

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

Postmortale Diagnostik	
R. Langer	031 632 32 47
A. Blank	031 632 99 01
A. Lugli	031 632 99 58
M. Trippel	031 632 32 76

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

Molekularpathologie	
E. Vassella	031 632 99 43
T. Grob	031 632 82 37
M. Dettmer	031 632 99 69

Makropathologie	
A. Blank	031 632 99 01
M. Trippel	031 632 32 76
A. Lugli	031 632 99 58

5 Dienstleistungsstatistik

Klinische Pathologie

Histopathologie	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Anzahl Einsendungen	35'001	33'805	32'710	35'293	37'232	**42'422**
Anzahl Lokalisationen	61'693	61'015	58'795	66'420	70'286	**82'069**
Anzahl Einsendungen Schnellschnitte	–	1'220	1'472	1'673	1'647	**1'936**
Anzahl Proben Schnellschnitte	2'937	1'792	1'997	2'307	2'252	**2'454**
Autopsie						
Anzahl durchgeführte Autopsien	170	195	155	156	152	**146**
Zytopathologie						
Total Anzahl Einsendungen	–	16'946	14'237	13'788	16'043	**16'634**
Anzahl Proben Klinische Zytologie	8'849	8'218	8'361	8'418	11'582	**9'324**
Anzahl Proben Gynäkologische Zytologie	8'697	8'724	8'054	7'726	9'375	**9'869**
Total Anzahl Einsendungen Proben	16'996	16'942	16'415	16'144	20'957	**19'193**
Anzahl Zellblöcke	1'705	1'830	2'277	2'324	2'748	**2'837**
Immunhistochemie						
Anzahl Fälle (Blöcke) Diagnostik (Paraffin)	7'472	6'692	7'104	8'313	7'843	**9'094**
Anzahl Färbungen Immunfluoreszenz (Nierenbiopsien)	2'820	2'844	2'101	2'280	2'079	**2'772**
Anzahl Fälle Immunzytologie am Ausstrich	359	302	302	372	197	**158**
Anzahl Färbungen Immunzytologie am Ausstrich	777	672	586	–	240	**486**
Anzahl Färbungen Diagnostik (Paraffin)	50'535	43'436	–	52'532	47'944	**44'366**
Molekularpathologie						
Anzahl Fälle PCR-basierende Tests	1'325	1'235	1'420	1'304	1'444	**1'624**
Anzahl Fälle Lymphome	200	171	214	218	216	**221**
Anzahl Fälle Methylierungsnachweis	156	155	180	128	88	**117**
Anzahl Fälle Mutationsanalysen (EGFR, kRAS, BRAF, IH1/2 + weitere)	708	755	818	902	870	**508**
Anzahl Fälle NGS-Analysen	–	–	–	–	87	**247**
Anzahl Fälle PAM50 (Nanostring)	–	–	–	–	18	**49**
Anzahl Fälle FISH	259	206	287	554	627	**744**
Anzahl Hybridisierungen FISH	354	304	391	683	839	**981**

Tumorbank

Anzahl Einsendungen Tumorbank	803	727	831	894	1'030	**1'417**
Anzahl Eingänge TRU	–	–	166	465	457	**604**

>>> Forschung/Research

1 Research at the Institute of Pathology

Research groups Experimental Pathology
Stefan Freigang, MD
Philippe Krebs, PhD
Christoph Mueller, PhD
Mario Noti, PhD
Jean-Claude Reubi, MD
Mirjam Schenk, PhD
Mario Tschan, PhD
Erik Vassella, PhD

Research groups supported by TRU
Yara Banz, MD, PhD
Sabina Berezowska, MD
Eva Diamantis-Karamitopoulou, MD
Rupert Langer, MD
Alessandro Lugli, MD
Aurel Perren, MD, PhD
Tilman Rau, MD
Inti Zlobec, PhD

Organisational aspects

The seven research groups of the **Division Experimental Pathology** pursue their own research projects, primarily supported by extramural funding. Major pieces of equipment are shared among the experimental research groups and, upon an initial training in the appropriate use (support platforms), can be also accessed by the research personnel of the other units of the Institute of Pathology. This allows for an efficient use of the limited financial resources, but may also foster scientific collaborations within the Institute of Pathology.

The core lab of the Translational Research Unit

The Translational Research Unit (TRU) is a research facility providing tissue-based services to internal and external researchers, collaborators in the department of clinical research (DKF), Insel hospital, and other university laboratories. Our research platform performs activities for Tissue Bank Bern (TBB) and for the Comparative Pathology Platform of the University of Bern (COMPATH).

1.1 The Division of Experimental Pathology

Head: Christoph Mueller, PhD

Administrative support:
Christine Feller, 40%
Christa Hagert, 50%
Cornelia Mileto, 40%

Research activities

Thematically the research activities of the current 7 research groups in the Division of Experimental Pathology are focused on two main topics, i.e.
– immunopathology and inflammation, and
– experimental tumor pathology and tumor biology

Most 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 such as the identification of novel biomarkers for disease activity in remitting – relapsing inflammatory disorders and the development of novel vaccination strategies against solid tumors.

Personnel

Professor Jean-Claude Reubi, MD, who following his formal retirement in 2012 continued his most successful research activities in the field of peptide receptor imaging and therapy completed by the end of 2016 his research activities. We are most grateful for all his most important contributions in translational research, best evidenced by the prestigious awards received, the successful patent applications, but also by his most impressive bibliography and his bibliometric indices.

On April 1, 2016, Dr. Mirjam Schenk, PhD, started her work as an Assistant Professor, funded by the «Peter-Hans Hofschneider Stiftung Experimentelle Biomedizin» in the Division of Experimental Pathology following a most successful post-doc with Prof. Robert L. Modlin at the Department of Microbiology and Immunology, Division of Dermatology, UCLA Los Angeles (USA). In her research she will explore novel strategies for the vaccination against solid tumors, and hence, will bridge the two main research fields of our division, i.e. inflammation, and tumor biology.

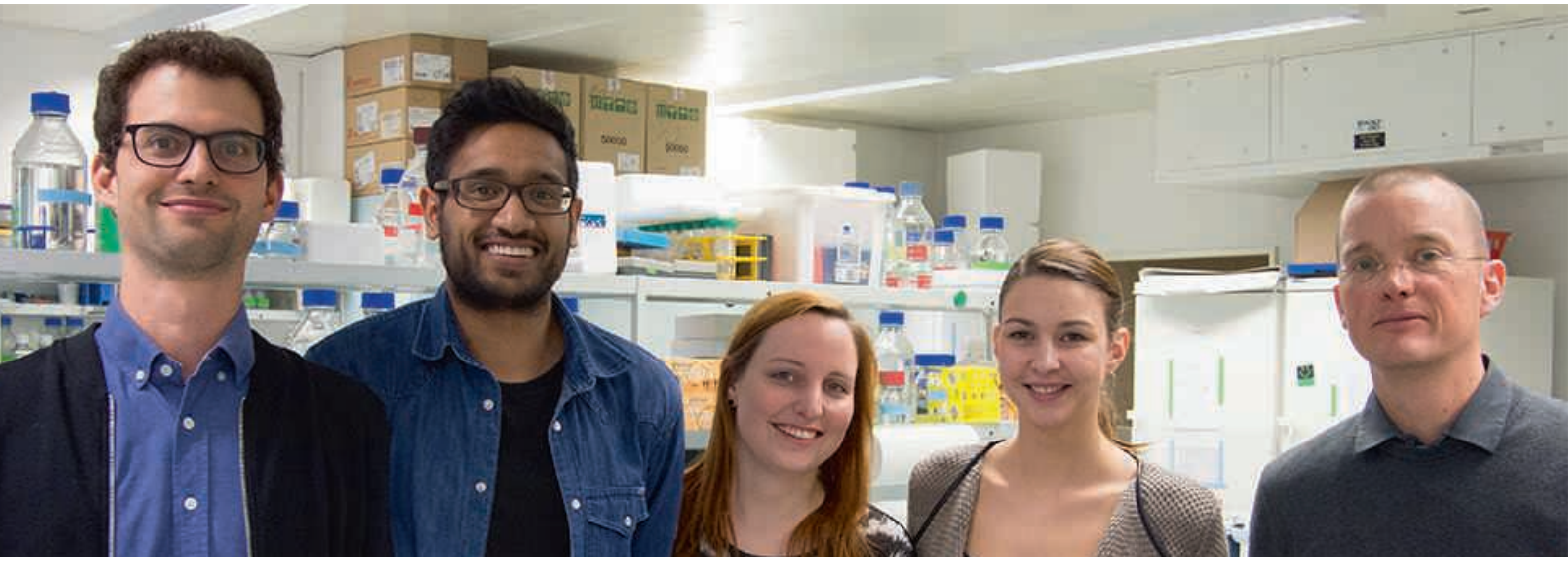
Grant support

In 2016 the amount of external funding obtained by the research groups of the Division of Experimental Pathology exceeded 3'000'000 CHF (for details see: Reports of the individual research groups).

Research infrastructure and collaborations

The research activities are well integrated on a national and international level, including the Swiss IBD cohort study. In our experimental work we can rely on facilities available at our institute, e.g. Laser Capture Microdissection, confocal microscopy, and a Nanostring® Platform for multiplexed assays for gene expression and mutation analysis, 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 also use the central mouse facility, and more recently, also the germ-free and gnotobiotic mouse facility (Clean Mouse Facility) at the Medical Faculty. In addition to these facilities, through collaborative efforts we also have access to other state-of-the-art facilities, including the metabolomics facilities at the Institute of Molecular Systems Biology, ETH Zurich (Group of Professor Uwe Sauer).

The spectrum of available and well-established technologies in the Division of Experimental Pathology includes confocal microscopy, fluorescent in situ hybridization (FISH), laser capture microdissection of FFPE, and frozen tissue sections (including immunostained FFPE tissue sections), and autoradiography of tissue sections, including a combined immunohistochemical-receptor autoradiography, but also the entire spectrum of FACS-based techniques in cell sorting and multi-color analysis. Highly sophisticated methodologies are established for the identification of miR's and their target sequences in normal, and diseased tissues, and several distinct transfection systems, including lentivirus-based transduction systems, and mRNA expression profiling from small numbers of cells and 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. Furthermore, several of our research groups have a longstanding expertise in isolating and culturing primary cells, such as immune cells, mesenchymal stromal cells, including liver sinusoidal endothelial cells, and epithelial cells from patient material, but also experimental animals. Experimental protocols for determining the functional capacities of these cell subsets ex vivo and in vitro are established and optimized.



Forschungsgruppe Stefan Freigang (Research group Stefan Freigang).

Group of Stefan Freigang, MD

Svenja Ewert, research technician
Olivier Friedli, MSc, PhD student
Marleen Hanelt, MSc, PhD student
Abilashan Sithampari, BSc, MSc student

Summary of research activities

Our research focuses on the immune recognition of lipids in inflammation and immunopathology. In particular, we study the molecular mechanisms of lipid-induced inflammation in atherosclerosis, the regulation of immune responses by products of lipid peroxidation, and the sensing of glycolipids by innate-like Natural Killer T cells.

Research activities

Project 1: Molecular mechanisms of lipid-induced inflammation

Cardiovascular diseases, particularly atherosclerosis-related diseases, remain the leading cause of death worldwide. Whereas major risk factors have been identified and provide targets for therapeutic intervention, there is still no effective treatment that directly targets the underlying inflammatory process. We have identified a novel pathway that selectively induces IL-1α-driven vascular inflammation in response to metabolic perturbation. Our study identified mitochondrial uncoupling as a metabolic signal that triggers IL-1α secretion but inhibits inflammasome activation. We are currently investigating the role of physiological mitochondrial uncoupling for inflammatory immune responses in metabolic dysfunction and microbial infection.

Project 2: Immune regulation by oxidized lipids

Another major interest of the group are products of lipid peroxidation and their immuno-regulatory properties. The exposure of cellular membranes to reactive oxygen species creates a broad range of distinct oxidized phospholipid (OxPL) species that actively modulate cellular signaling processes and influence the resulting immune response (Freigang 2016). We have previously characterized a pro-resolving activity of OxPLs that can be attributed to cyclopentenone-containing OxPLs and their respective isoprostanes (Bretscher 2015). These compounds are highly bioactive and represent promising therapeutic agents for the treatment of inflammatory diseases (Friedli 2016).

Project 3: Lipid-sensing by innate-like Natural Killer T cells

Natural Killer T (NKT) cells are a subset of innate-like T lymphocytes that recognize lipid antigens presented via CD1d. Because of their potent immunoregulatory properties, NKT cells have emerged as a promising target for cancer immunotherapy. We found that deletion of the essential autophagy gene Atg5 in antigen presenting cells augments CD1d antigen presentation in vivo (Keller 2016). These effects led to an enhanced NKT cell cytokine production upon antigen recognition and lower bacterial loads during infection with *Sphingomonas paucimobilis*. We could demonstrate that loss of Atg5 in APCs impaired the clathrin-dependent internalization of CD1d molecules via the adaptor protein complex 2 (AP2) and thereby increased the surface expression of stimulatory CD1d:glycolipid complexes. Our findings indicate that the autophagic machinery assists in the recruitment of AP2 to CD1d molecules resulting in attenuated NKT cell activation.

Internal collaborations

- Yara Banz, MD-PhD
- Christoph Mueller, PhD

External collaborations

National

- Marc Donath, MD, University of Basel, Switzerland
- Olivier Guenat, PhD, University of Bern, Switzerland
- Martin Hersberger, PhD, University Children's Hospital Zurich, Switzerland
- Jan Lünemann, MD, University of Zurich, Switzerland
- Olivier Pertz, PhD, University of Bern, Switzerland

International

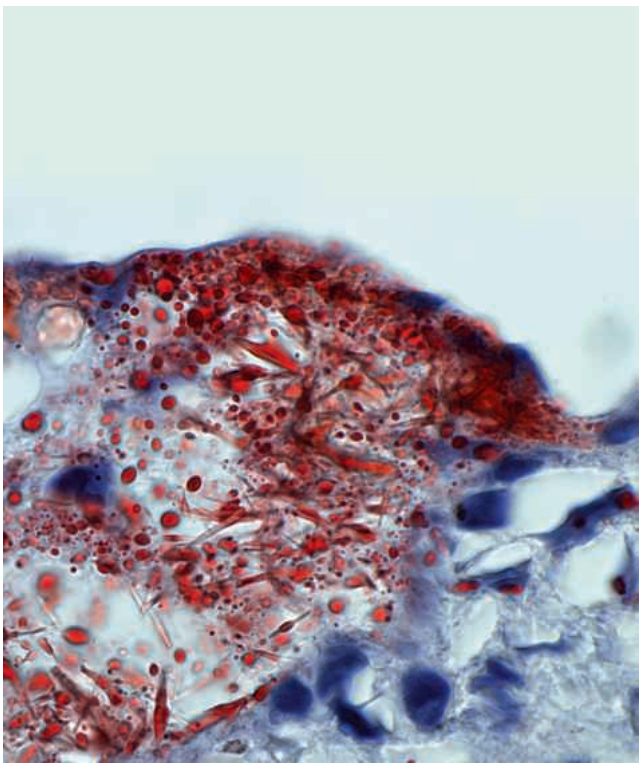
- Paul B. Savage, PhD, Brigham Young University, Provo UT, USA

Grant support

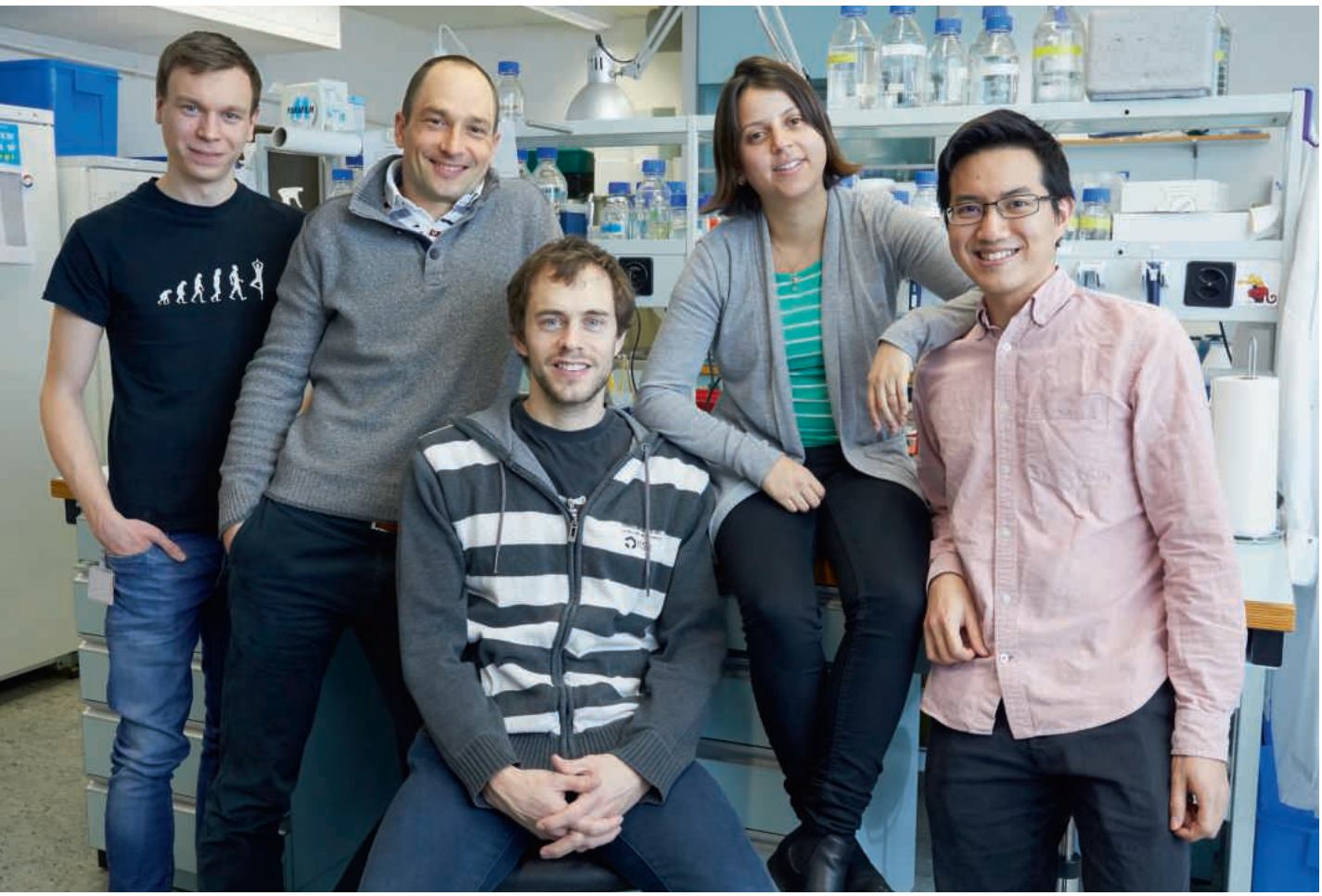
- SNF 310030_152872, S. Freigang, CHF 510'000 (2015–2017)
- SNF 316030_157702, S. Freigang, CHF 240'000 (2014–2016)
- Vontobel-Stiftung, S. Freigang, CHF 120'000 (2014–2017)
- UniBE Research Foundation, S. Freigang, CHF 15'000 (2014–2017)
- Fondation J. Dürmüller-Bol, S. Freigang, CHF 27'000 (2014–2017)
- UniBE-ID Grant, S. Freigang, CHF 150'000 (2016–2018)
- 3R Research Foundation, S. Freigang (Co-PI), O. Guenat (PI), *CHF 138'000 (2016–2017)
- Swiss Lung Liga, S. Freigang (PI), O. Guenat (Co-PI), *CHF 162'000 (2017–2019)

* Total amount of funding; funding shared by PI and Co-PI

Atherosclerosis in the aortae of mice fed a high-fat cholesterol diet. Staining with Oil Red O reveals the lipid deposits within the atherosclerotic lesions.



Cholesterol crystals: atherosclerotic lesion in the mouse heart. Needle-shaped, transparent cholesterol crystals are visible, deposits of neutral lipids are revealed by Oil Red O staining.



Forschungsgruppe Philippe Krebs (Research group Philippe Krebs).

Group of Philippe Krebs, PhD

Michael Berger, BSc, MSc student
Ludmila Cardoso Alves, MSc, PhD student
Nick Kirschke, technician
Ioannis Kritikos, BSc, MSc student
Lukas Mager, MD, PhD, postdoctoral fellow
Petra Polakova, BSc, MSc student
Regula Stuber Roos, technician, 90%
Lester Thoo Sin Lang, MSc, PhD student
Marie-Hélène Wasmer, MSc, PhD student

Research activities

Project 1: Role of cytokine signaling for myeloproliferative disease

Myeloproliferative neoplasms (MPNs) are characterized by the clonal expansion of cells from the myeloid lineage. MPNs are also associated with aberrant expression and activity of multiple cytokines. We have recently shown that IL-33 signaling is important for the development of MPN (Mager LF et al., J Clin Invest., 2015). We currently study the role of IL-33 for the progression of this disease by using mouse models and patient-derived samples.

Project 2: Role of cytokine signaling for colorectal cancer

Several genetic aberrations in key cellular pathways that underlie colon tumorigenesis have been identified. However, there is now compelling evidence that intestinal tumorigenesis is greatly promoted by chronic inflammation that follows such genetically-driven tumor-initiating events. Recently, we have shown that the IL-33 pathway contributes to intestinal tumorigenesis in humans and mice (Mertz KD, Mager LF et al., OncoImmunology, 2015, in press). We now further investigate the cellular and molecular mechanisms underlying IL-33-dependent colorectal cancer.

Project 3: Cross-talk between innate and adaptive immunity

The vertebrate immune system comprises the innate immune system, providing the first line of defense, and the adaptive immune system, which is triggered at a later stage and that is responsible for memory. In this project, we use different murine models to better understand how innate immune cells modulate adaptive immune responses in dependence on the inflammatory environment, in infectious (e.g. after infection with a pathogen) or sterile (e.g. for tumor surveillance) situations.

Internal collaborations

- Christoph Mueller, PhD
- Mario Noti, PhD
- Inti Zlobec, PhD
- Alessandro Lugli, MD
- Yara Banz, MD, PhD

External collaborations

National

- Alexandre Theocharides, MD, Division of Hematology, University Hospital Zurich, Zurich
- Guido Beldi, MD, Clinics for Visceral Surgery and Medicine, Bern
- Adrian Ochsenbein, MD, Carsten Riether, PhD, Dept. Clinical Research, University of Bern
- Andrew Macpherson, MD, Dept. Clinical Research, University of Bern
- Burkhard Ludewig, DVM, Institute of Immunobiology, Cantonal Hospital St. Gallen

International

- Kathy McCoy, PhD, University of Calgary, Calgary, Canada
- Bruce Beutler, MD, UT Southwestern Medical Center, Dallas, TX, USA
- Astrid Westendorf, PhD, Universitätsklinikum Essen, Essen, Germany

Grant support

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- SNSF, 144236, Perren/Krebs, *CHF 395'391 (2012–2016)
- Foundation Johanna Dürmüller-Bol, Krebs/Mager, CHF 20'000 (2015–2016)
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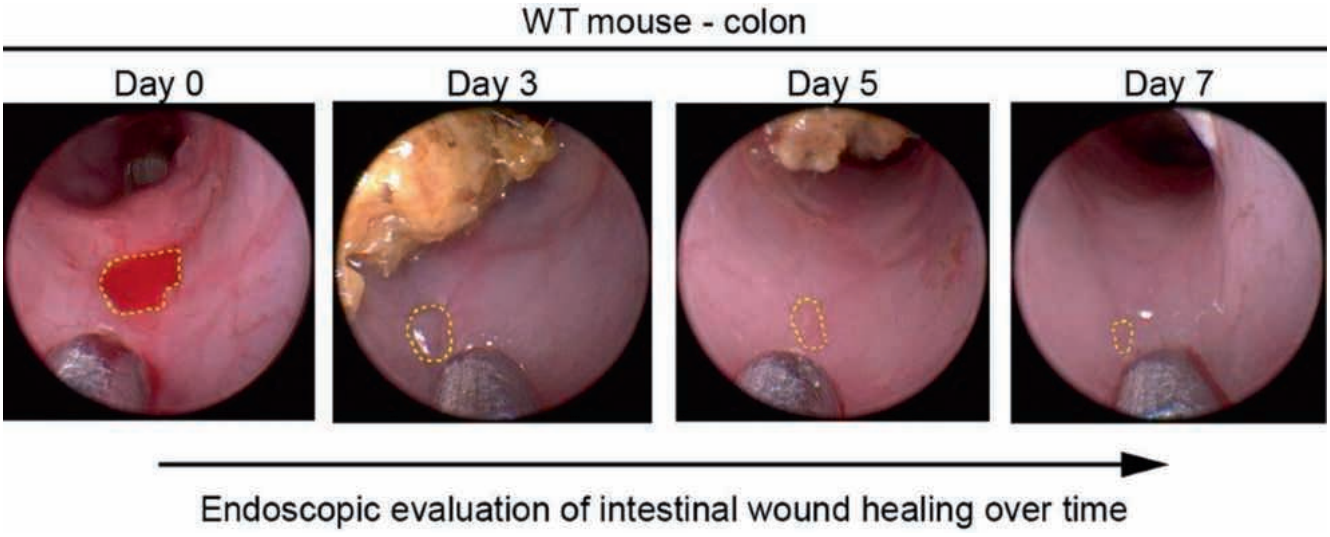
- SNSF, 163086, Philippe Krebs, CHF 525'000 (2016–2019)
- Olga Mayenfisch Foundation, Philippe Krebs, CHF 23'000 (2015–2016)
- Vontobel Foundation, Philippe Krebs, CHF 130'000 (2015–2017)
- Fondazione San Salvatore, Philippe Krebs, CHF 120'000 (2016–2017)
- Gertrud-Hagmann-Stiftung, Lukas Mager, CHF 241'566 (2015–2017)

* Total amount of funding; funding shared by PI and Co-PI



Assessment of mucosal healing in the murine intestine. A miniature forceps was used to induce injuries in the colonic mucosa of anesthetized wild-type (WT) mice. Wound-healing was then monitored by colonoscopy at the indicated time points. Lesion size was determined by normalizing the wound area (depicted by a yellow dotted line) to the diameter of the forceps (visible on the pictures).

Group of Christoph Mueller, PhD

Nadia Corazza, PhD, staff scientist/co-PI, 60%
Martin Faderl, PhD student
Kwong Chung Cheong Kwet Choy, PhD, postdoc
Silvia Rihs, technician, 90%
Leslie Saurer, PhD, staff scientist/co-PI, 60%
Alexandra Suter, technician, 60% (SIBDCS biobank)
Diego von Werdt, PhD student, since May 1, 2016
Daniel Zysset, PhD, postdoc, till October 31, 2016

Research activities

Our group has a longstanding interest in the complex immunoregulatory mechanisms that are operative in the intestinal mucosa during homeostatic conditions and the potential predispositions or events which can lead to disruption of tissue homeostasis during inflammatory conditions as in the case of inflammatory bowel diseases (Crohn's disease, ulcerative colitis). In recent years, the importance of the intestinal microflora in shaping the education of the local immune system, but also the reciprocal effects of local immune responses on the composition of the intestinal microflora have become increasingly acknowledged. Thus, we aim to link the molecular and cellular characterization of distinct immune cell subsets in the intestinal mucosa and their phenotypical and functional alterations during intestinal inflammation with concurrent analyses of the intestinal microflora and any associated metabolic changes. The molecular and cellular events that regulate the maintenance of remission vs. induction of relapse in inflammatory bowel diseases is currently one of our main research topics.

Since microbial-driven immune responses can predispose for development of tumors or even cardiovascular diseases, we have recently extended our research to other chronic inflammatory disorders (colorectal tumors and atherosclerosis). While we often use experimental mouse models to test our hypotheses, whenever possible, we validate these experimental findings using state-of-the-art technologies with patient materials, mostly archived tissue samples or biosamples obtained from the SIBDCS biobank.

Specific projects

Project 1: Molecular and cellular events that are operative during induction and resolution of chronic intestinal inflammation (Martin Faderl, MSc, Silvia Rihs, Leslie Saurer, PhD, Nadia Corazza, PhD)
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., 2016). This allows us to characterize the molecular and cellular events that are operative in the affected colonic mucosa following a timed induction of remission such as the degradation and re-establishment of the mucus layer, but also the alterations in the composition of the intestinal microbiota. Monitoring of immune parameters and associated metabolic changes complement these studies.

Taking advantage of gnotobiotic mice with a defined microbiota, we further investigate the critical effects mediated by the pathobiont *Helicobacter typhlonius* on the (intestinal) immune system leading to an accelerated onset of colitis. Intriguingly, in the presence of a gnotobiotic flora consisting of 12 commensal bacteria species (Brugiroux et al., Nature Microbiol 2016), *H. typhlonius* mediates an accelerated onset of colitis, although *H. typhlonius*-monoassociated mice fail to develop CD4 T cell mediated colitis.

Project 2: Functional plasticity of tissue-resident T cell subsets, notably in the intestinal mucosa (William Kwong, PhD, Diego von Werdt, PhD, Nadia Corazza, PhD, Silvia Rihs)
Our group has a longstanding interest in the functions exerted by conventional and unconventional intraepithelial T lymphocytes (IEL) in the intestine. Currently, we investigate the molecular mechanisms that regulate their tissue-resident phenotype and determine how functional activities of these cell subsets may differ under homeostatic versus inflammatory conditions. In particular, we are specifically looking at the role of the regulator of G protein signaling (RGS) proteins in governing IEL and tissue resident CD4 T cell functions. IEL and tissue-resident memory (TRM) cells highly express RGS1 which likely contributes to their non-circulating, tissue-resident memory phenotype. We are interested how the intestinal milieu shapes expression of RGS1 and how intestinal inflammation may potentially disrupt RGS1 expression leading to altered TRM cell responses.

Project 3: Monocyte/macrophage subsets in immunosurveillance versus inflammatory disorders: TREM-1 as an amplifier of acute and chronic inflammation (Daniel Zysset, PhD; Leslie Saurer, PhD; Silvia Rihs)
TREM-1 (Triggering Receptor Expressed on Myeloid Cells-1) is an activating innate immune receptor expressed on neutrophils and subsets of monocytes/macrophages. We recently described a critical pathogenic role for TREM-1 not only in acute inflammation, but also during chronic inflammation such as in inflammatory bowel diseases (Schenk et al., 2005, 2007). We further generated and characterized a Trem1 deficient mouse line (Weber et al., 2014). Currently, we are investigating the consequences of TREM-1-mediated signaling on the development and progression of inflammatory diseases and malignancies, including atherosclerosis and colitis-associated colorectal carcinoma.

Internal collaborations

- Stefan Freigang, MD
- Vera Genitsch, MD
- Philippe Krebs, PhD
- Mario Noti, PhD
- Mirjam Schenk PhD

External collaborations

National

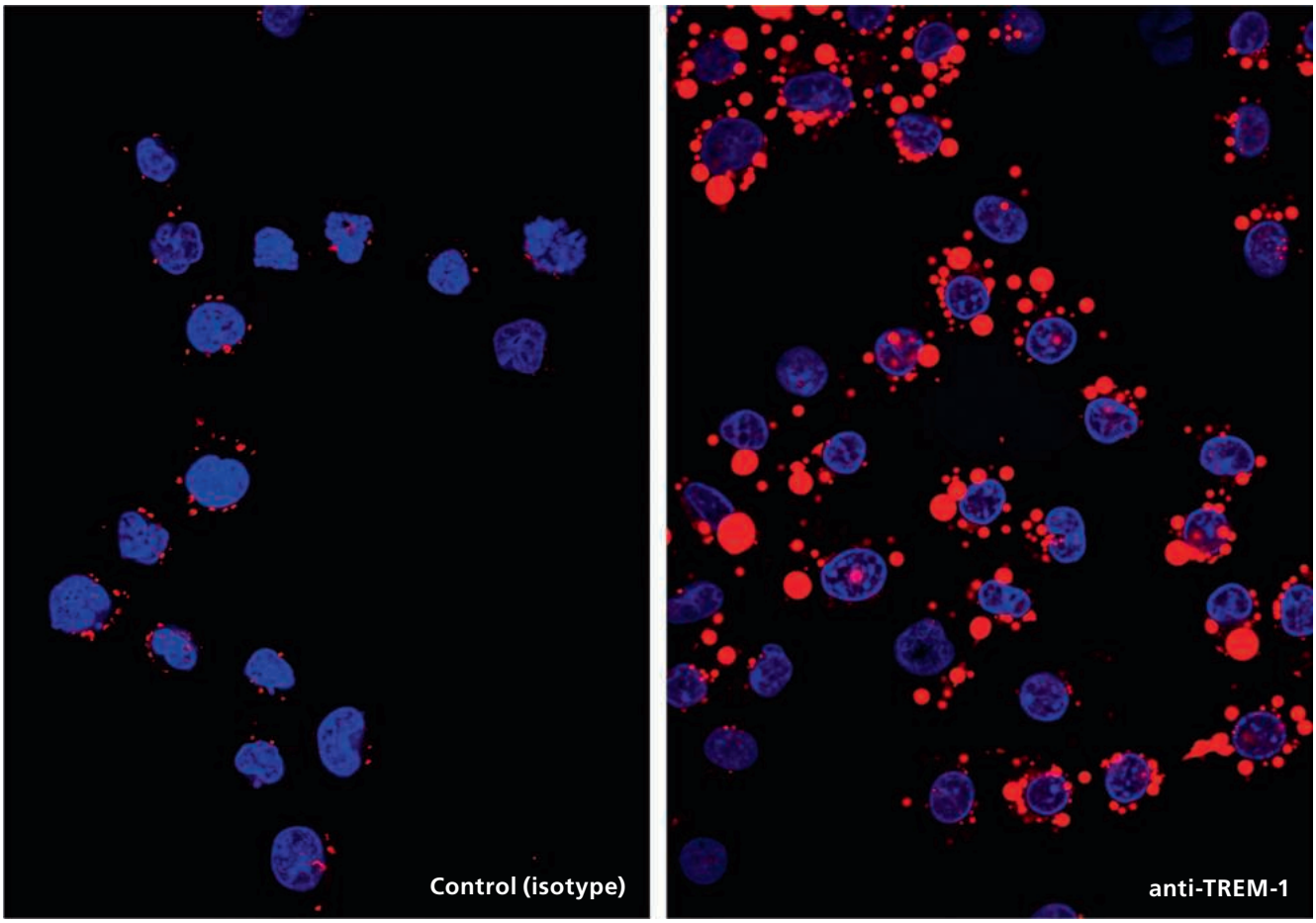
- Andrew Macpherson, MD, Department of Clinical Research, University of Bern (Sinergia)
- Wolf Hardt, PhD, Institute of Microbiology, ETH Zurich (Sinergia)
- Uwe Sauer, PhD, Institute of Molecular Systems Biology, ETH Zurich
- Walter Reith, PhD, Department of Pathology and Immunology, University of Geneva
- Gerhard Rogler, MD PhD, Division of Gastroenterology & Hepatology, University Hospital Zurich

International

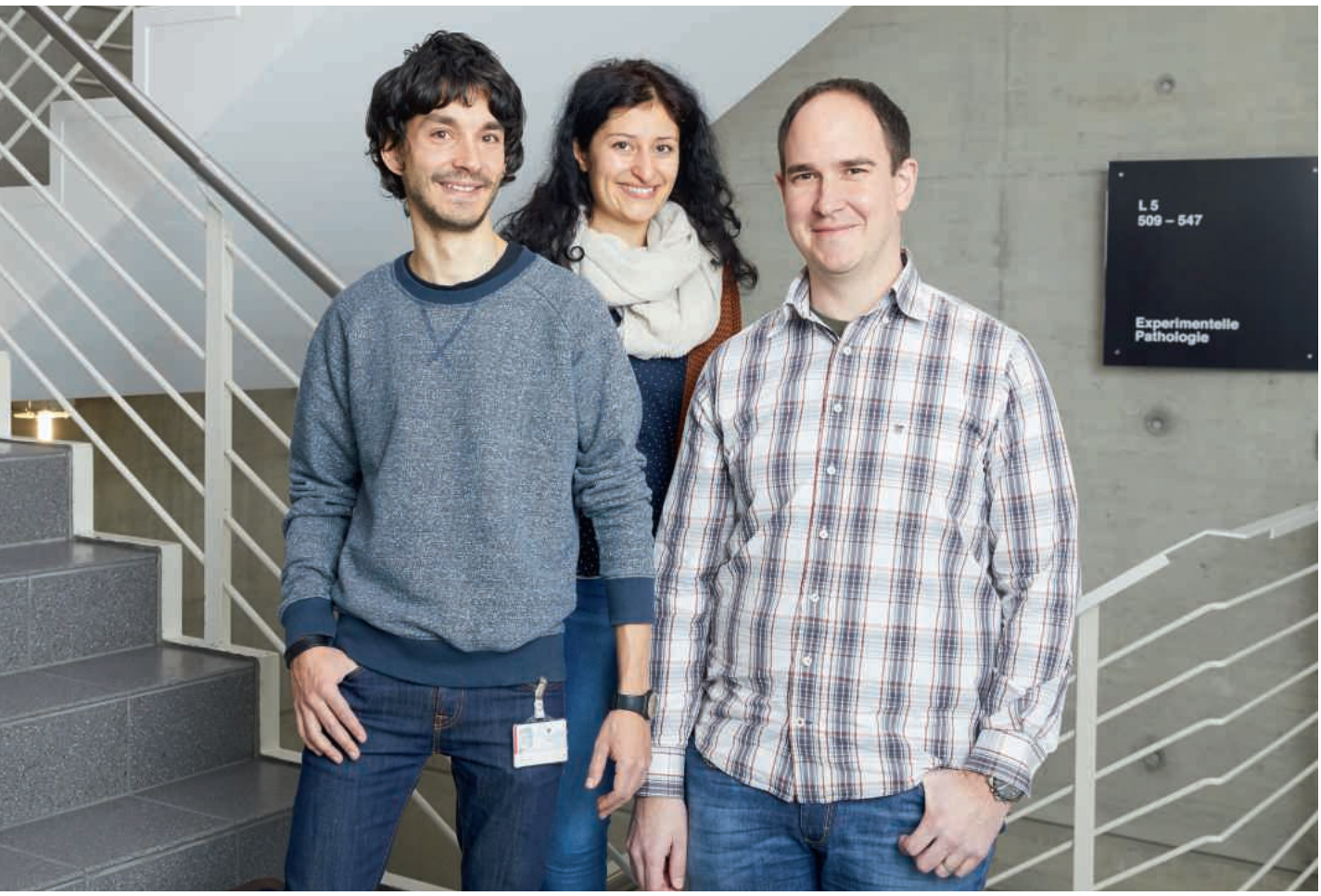
- Katrin Andreasson, MD, Stanford University Medical Center, USA
- Phil A. Beachy, PhD, Stanford University Medical Center, USA
- John Kerl, NIAID, Bethesda, MD, USA
- Bärbel Stecher, PhD, Max von Pettenkofer Institute of Hygiene and Medical Microbiology, Ludwig Maximilians University of Munich, Germany

Grant support

- SNF 310030_138392 /1, Christoph Mueller, CHF 623'000 (2011–2016)
- SNF 310030_170084, Christoph Mueller, CHF 525'000 (2016–2019)
- SNF 33CS30_134274 / 1, (SIBDCS; Co-PI), CHF 200'000 (2016–2018)
- SNF CRSII3_136286 / 1, (Sinergia; Co-PI), CHF 456'531 (2015–2017) (own share)



Activation of TREM-1 leads to an enhanced lipid uptake (red droplets) by monocytic cells, transduced with TREM-1 when cultured in the presence of 5% dyslipidemic serum from ApoE -/- mice maintained on a high fat, high cholesterol diet (right) when compared to the same cells, cultured in the same medium in the absence of TREM-1-mediated activation (left); (ORO staining, DAPI)
(Zysset et al., Nature Commun. 2016)



Forschungsgruppe Mario Noti (Research group Mario Noti, Maria Pena Rodriguez, Lukas Bäriswyl).

Group of Mario Noti, PhD

Maryam Hussain, MSc, PhD student
Maria Pena Rodriguez, MSc, technician (40%)

Research activities

Project 1: Basophils – what role play basophils in the initiation of type-2 immune responses?
Food allergies have reached pandemic proportions, with an estimated 4–8% of children and adults in westernized countries living with the daily concern that exposure to certain foods may trigger a life-threatening allergic reaction. As the public health and economic burden of food allergies continues to grow, there is an urgent need to develop new intervention strategies to prevent and treat this disease. While the effector functions mediating food allergies are well described, little is known about the early immunological events that initiate these responses. In recent studies we demonstrated that epicutaneous sensitization to food allergens on an atopic dermatitis-like skin lesion is associated with the infiltration of thymic stromal lymphopoietin (TSLP)-elicited basophils that are both necessary and sufficient for the development of food allergies (Noti et al, Nat.Med 2013; Noti et al. JACI, 2014). Employing *in vitro* and *in vivo* model systems, current research is investigating what basophil intrinsic factors promote the pathogenesis of IgE-mediated food allergies.

Project 2: Do changes in the commensal community structure alter the susceptibility to allergic inflammation?
Recent studies have highlighted that the trillions of bacteria hosting our body are not just hitchhikers, but actively communicate and contribute to the maturation of the host's immune system. Alterations in dietary habits, improved sanitary installations and limited exposure to infections associated with a Western lifestyle may significantly impact the diversity of the host's microbiota. Metagenomic sequence analyses in humans and mice have demonstrated significant changes in the composition of the gut microbiota in allergic individuals. Perturbations in this sophisticated immunehost–microbiota axis may cause uncontrolled immune responses fostering the development of chronic allergic inflammation. Employing axenic, gnotobiotic and humanized microbiota models we are currently investigating whether altered bacterial community structures associated with allergic inflammatiom are consequence or causality of disease.

Project 3: Aging – a reversible biological process?
For many people, extended lifetime goes along with poor general health associated with common inflammatory, neurodegenerative and metabolic disorders ultimately leading to a progressive decline in organ function and death. Elucidating the complex pathways controlling the rate of aging is of significant clinical importance in order to improve health and maintaining well-being throughout the life course. In a series of new studies, we are investigating how age-related changes in innate immune cell function alter the host's metabolic, immunological and physical fitness and whether targeted manipulation of innate immune cell populations in aged model organisms can promote healthy aging and increase lifespan.

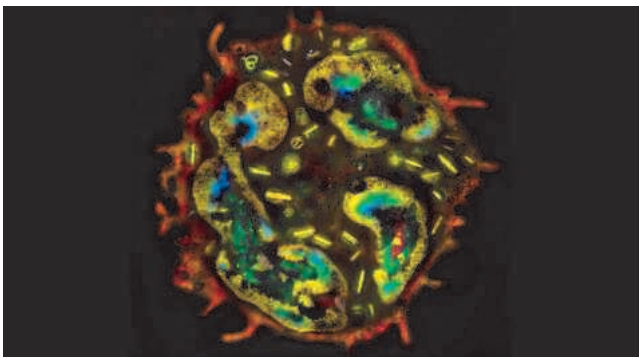
Internal collaborations
- Christoph Mueller, PhD
- Nadia Corazza, PhD
- Philippe Krebs, PhD
- Mirjam Schenk, PhD

External collaborations
National
- Alexander Eggel, PhD, Institute of Rheumatology and Immunology, University of Bern
- Carsten Riether, PhD, DKF, University of Bern
- Andrew Macpherson, PhD, and Kathy McCoy, PhD, DKF, University of Bern
- Johan Auwerx, PhD, EPFL Lausanne
- Ingrid Böhm, MD, PhD, Interventional and Pediatric Radiology, University of Bern

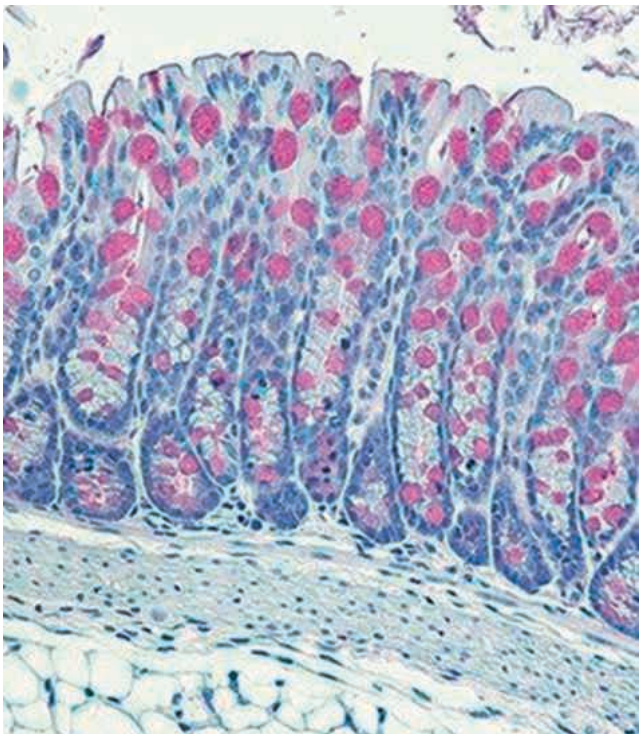
International
- David Artis, PhD, Weill Cornell University, USA
- Jonathan Spergel, MD, PhD, Childrens Hospital of Philadelphia, USA
- Brian S. Kim, MD, PhD Washington University, USA
- Thomas Brunner, PhD, Universität Konstanz, Germany
- Saul Villeda, PhD, University of California, USA

Grant Support

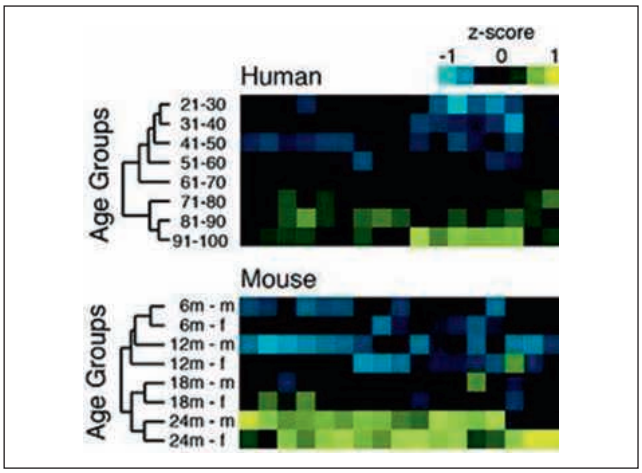
- SNF, PZ00P3_154777/1, Mario Noti, CHF 599'156 (2014–2017)
- Olga Mayenfisch Stiftung, Mario Noti, CHF 25'000 (2015–2016)
- Novartis Foundation, Mario Noti, CHF 60'000 (2015–2016)
- FreeNovation, Mario Noti, CHF 180'000 (2016–2018)



Computer-enhanced electron microscopic image of a TSLP-elicited mouse basophil.



H+E staining of mouse colon. Despite the physical separation of luminal bacteria and the mucosal immune system by a single layer of epithelial cells, the proper maturation of mucosal immune cells critically depends on microbial derived signals.



Age-related changes of immune factors in the plasma proteome of humans and mice.

Group of Jean-Claude Reubi, PhD

Beatrice Waser, technician
International collaborators

Research activities

Peptide receptor targeting of tumors is currently 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 and GIP receptors.

ad 1) Target definition includes the identification of human pathological tissues, in particular tumors, which overexpress peptide receptors. We show, for the first time, that an somatostatin receptor antagonist reveals novel indications for sst2 targeting of human cancer, including breast cancers, renal cancers, MTC, GIST and lymphomas.

ad 2) We have designed and characterized a number of new tools for peptide receptor targeting: several new GRP receptor antagonists and GLP-1 receptor antagonists.

ad 3) On the clinical side, we show the poor and probably unspecific imaging of somatostatin receptors in carotid plaques.

External collaborations

National
- E. Christ, MD, PhD, Univ. Hospital Bern
- D. Wild, MD, Univ. Hospital Basel

International
- H. Mäcke, PhD, Nucl. Med., Univ. Freiburg, Germany
- J. Rivier, PhD, Salk Institute, San Diego, CA, USA

Grant support

- Patent licence fees

Group of Mirjam Schenk, PhD

Thomas Gruber, PhD student, since June 1, 2016

Research activities

Project 1: Generation of potent cross-presenting DC for tumor immunotherapy

Only a specific subset of DC is able to present tumor antigens to CD8+ T cells in a process called cross-presentation. We aim to elucidate the mechanism(s) of cross-presentation and how this process can be manipulated in melanoma. Therefore, we are establishing models to test human monocyte derived DC as well as mouse bone marrow derived DC (BM-DC) for their ability to cross-present antigen. The knowledge of how cross-presentation is regulated *in vitro* may allow us to manipulate this process *in vivo.* Treated BM-DC will be tested in adoptive transfer as prophylactic and therapeutic treatment to established melanoma. Together, these data should identify ways to promote frequency and function of cross-presenting DC and to contribute to antitumor response in melanoma.

Project 2: Dendritic cells and their co-stimulatory properties for cytotoxic T cells in melanoma

The activation of an effective adaptive antitumor response relies mainly on presentation of tumor antigens and stimulation by DC. Despite extensive research, phenotype and function of tumor-infiltrating DC remains largely elusive and cross-presentation of tumor antigen is not well understood. We are investigating phenotype and function of TIDC and how to manipulate them *in vitro* and *in vivo* to induce a tumor- specific CTL response in melanoma. Thereby, we aim to identify ways to reprogram TIDC to present tumor antigens and activate an adaptive immune response against melanoma.

Internal collaborations

- Christoph Mueller, PhD
- Mario Noti, PhD

External collaborations

National
- Michel Gilliet, MD, Department of Dermatology, CHUV Lausanne
- Adrian Ochsenbein, MD, DKF, Oncology, Inselspital, University of Bern
- Christoph Schlapbach, MD, PhD, Department of Dermatology, Inselspital, University of Bern

International
- Robert Modlin, MD, David Geffen School of Medicine, Dermatology, UCLA, USA

Grant Support

- Stiftung experimentelle Biomedizin, CHF 763'000 (2016–2019)
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- Klinisch-Experimentelle Tumorforschung, CHF 150'000 (2016–2019)

Research group Mario P. Tschan.

Group of Mario P. Tschan, PhD

Olivia Adams, PhD student (co-supervision, Prof. R. Langer)
Magali Humbert, PhD postdoc
Félice Janser, PhD student (co-supervision, Prof. R. Langer)
Severin Mosimann, Master student (BIO)
Nicolas Niklaus, Master student (BIO)
Sarah Parejo, Master student (BIO)
Julia Parts, PhD student
Céline Krähenbühl, Master student (BMA)
Daniel Schärer, technician, 80%
Anna Schläfli, PhD, postdoc, 80%
Deborah Shan, technician
Kristin Uth, PhD student (co-supervision Prof. I. Zlobec)
Tabea Wiedmer, PhD student (co-supervision Prof. A. Perren)

Research activities

Project 1: Molecular analysis auf the autophagy pathway in AML therapy

A major interest in my laboratory is to unravel the role of Death Associated Kinase 2 (DAPK2) in acute promyelocytic leukemia (APL) therapy and autophagy. Current APL therapies such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) induced DAPK2 expression, but showed different outcomes when DAPK2 is depleted. Silencing DAPK2 results in lower autophagic activity upon ATRA treatment, whereas no impairment of autophagy was seen in ATO-treated APL cells. Inhibition of DAPK2 resulted in attenuated apoptosis during ATO treatment. To better understand the dual role of DAPK2 during ATRA and ATO therapy, we determined the DAPK2 interaction partners. Our findings indicate that two different pathways are operative in ATRA and ATO therapy, namely a p73-DAPK2-ATG5 and a DAPK2-cleaved Beclin1 pathway, respectively.

Project 2: Non-canonical autophagy during APL differentiation

Retinoids are naturally occurring vitamin A derivatives, which exert their functions via activation of nuclear retinoid acid receptor mediated gene expression. ATRA is successfully used to treat APL where it induces neutrophil differentiation of leukemic blast cells. We observed increased autophagic activity during ATRA treatment as well as impaired differentiation upon pharmacological or genetic inhibition of autophagy in APL cells. Next, we found significantly decreased expression of key autophagy genes in primary AML patients as compared to normal neutrophils. Importantly, pharmacological activation of autophagy in combination with ATRA treatment significantly boosted APL differentiation. Lastly, our data provide strong

evidence for a particular, non-canonical subtype of autophagy operative during neutrophil differentiation of APL cells. Deciphering the particular autophagy pathway active during APL differentiation is a prerequisite to develop novel differentiation therapies that are based on autophagy modulation.

Project 3: Retinoic acid therapy and autophagy in breast cancer
Pre-clinical studies showed encouraging anti-cancer effects using ATRA in breast cancer, however results in clinical settings were disappointing. We asked if autophagy is activated by ATRA and if its modulation could potentiate therapy efficiency. As a model we used the ATRA-sensitive and -resistant breast cancer cell lines, SKBR3 and MDA-MB453, respectively. We found that ATRA activates autophagy in SKBR3, but not MDA-MB453 cells. Further investigations revealed that autophagy activation depends on the presence of the retinoic acid receptor RAR. Using genetic and pharmacological approaches to inhibit autophagy, we were able to enhance ATRA toxicity. Interestingly, toxicity of ATRA partly depends on the autophagy-linked FYVE-domain-containing protein (ALFY), pointing towards a selective type of autophagy being activated by ATRA. In summary, ATRA induces autophagy in a subset of breast cancers and its inhibition represents a potential treatment strategy to enhance ATRA therapy.

Internal collaborations
- Rupert Langer, MD
- Inti Zlobec, PhD
- Aurel Perren, MD
- Erik Vassella, PhD
- Sabina Berezowska, MD

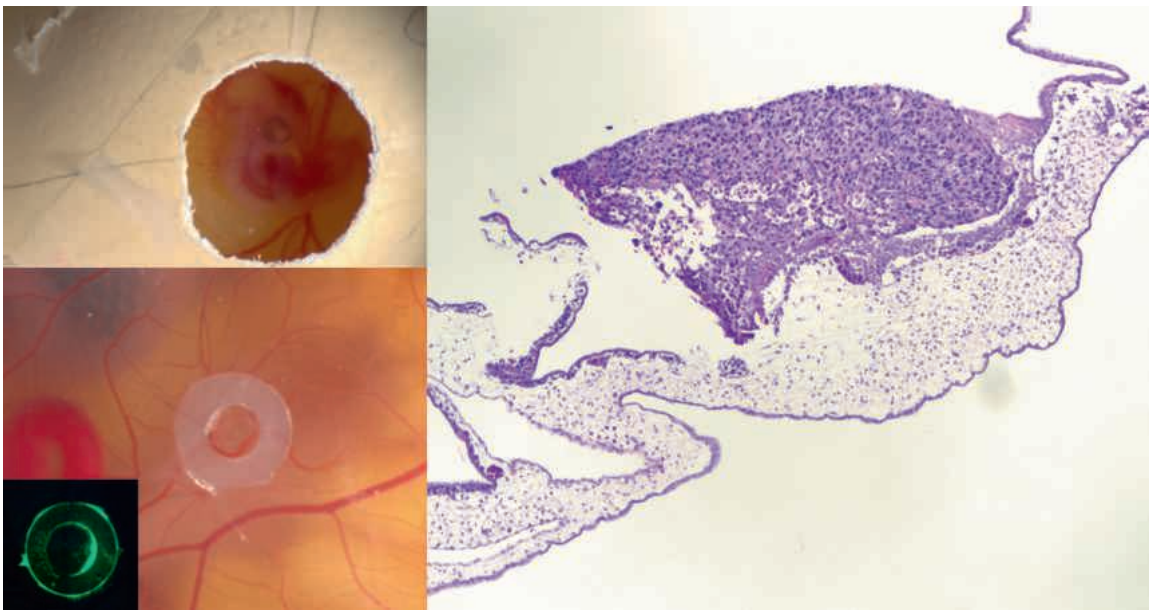
External collaborations
National
- Thomas Kaufmann, PhD, Institute of Pharmacology, University of Bern
- Volker Heussler, PhD, Institute of Cell Biology, University of Bern
- Deborah Stroka, PhD, Dpt. of Clinical Research, University of Bern
- Urban Novak, MD, Medical Oncology, University of Bern
- Jörn Dengjel, PhD, Dpt. of Biology, University of Fribourg

International
- Bruce E. Torbett, PhD, TSRI, La Jolla, CA, USA
- Sharon McKenna, PhD, Biosciencies Institute, University College Cork, Cork, Ireland
- Enrico Garattini, MD, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
- Mojgan Djavaheri-Mergny, PhD, INSERM U916 VINCO, Bordeaux Cedex, France
- Thomas Brunner, PhD, Dpt. of Biology, University of Konstanz, Germany

Grant Support

- KFS, KFS-3409-02-2014, Mario Tschan, CHF 390'000 (2014–2017)
- Giovani Ricercatori Fellowship, Mario Tschan, CHF 3'500 (2016)
- SNSF31003A_166578, Inti Zlobec, Co-PI Mario Tschan, *CHF 305'000 (2016–2019)
- Stiftung Klinische-Experimentelle Tumorforschung, Mario Tschan, CHF 81'000 (2015–2017)
- KFS-3700-08-2015, Rupert Langer, Co-PI Mario Tschan, *CHF 214'000 (2015–2017)
- UniBE Initiator Grants, Anna (Schläfli) Bill, CHF 16'150 (2016–2017)
- BKL, Anna (Schläfli) Bill, CHF 80'000 (2016–2017)

* Total amount of funding; funding shared by PI and Co-PI



Chick Chorioallantoic Membrane (CAM) Xenograft Assay for Esophageal Cancer (SK-GT-4) Cells. Top left: assessing the CAM and incubation with SK-GT-4 cells. Bottom left: growing SK-GT-4 cells on the CAM. Cells were seeded into a plastic ring for better handling. Because SK-GT-4 cells were labeled with GFP, they could also be visualized by fluorescence. Right: CAM tissues with growing SK-GT-4 cells stained with hematoxylin eosin.

Group of Erik Vassella, Dr. pharm.

Ulrich Baumgartner, PhD student
Alexander Zulliger, Master student (BIO)
Fabienne Chantal Berger, Master student (BIO)
Claudia Zurbuchen, technician
Cornelia Schlup, technician
Maja Neuenschwander, technician
Brigitte Jossen, technician
Nicole Klaus, technician
Sonja Gempeler, technician

Research Activities

microRNAs are short regulatory RNAs at the post-transcriptional level that are implicated in a wide variety of basic biological processes as well as in cancer. A global understanding of microRNA function in signaling pathways may provide insights into improving the management of cancer patients treated with targeted therapy.

To identify microRNAs implicated in EGFR signaling in NSCLC, we transduced bronchial epithelial BEAS-2B cells with retroviral vectors expressing KRAS(G12V) and monitored miRNA expression patterns by microarray analysis. Through this approach, we defined miR-29b as an important target for upregulation by mutant KRAS in non-small cell lung cancer. miR-29b conferred apoptosis resistance by targeting TNFAIP3/A20, a negative regulator of NF-κB signaling.

Surprisingly, miR-29b could confer sensitivity to intrinsic apoptosis triggered by exposure to cisplatin, a drug used widely in lung cancer treatment. Thus, miR-29b expression may tilt cells from extrinsic to intrinsic mechanisms of apoptosis. miR-19b/20b were identified as important targets for upregulation by another major branch of EGFR signaling, the PI3K/AKT pathway.

Both miRNAs are important mediators of EGFR signaling for proliferation, apoptosis and migration and confer resistance to TKI inhibitors. Interestingly, the same microRNAs were also identified in a lentiviral screen for miRNAs conferring resistance to the alkylating agent temozolomide in another tumor system, glioblastoma.

We are currently investigating the molecular mechanism of temozolomide resistance elicited by these miRNAs. Finally, another microRNA identified by this screening, miR-125b, was defined as an important regulator of TNFAIP3 (Haemmig et al. Cell, Death Disease 2014) and confers temozolomide resistance by inducing autophagy. In conclusion, microRNAs may be important regulators of targeted therapy and chemotherapy in cancer. Our results suggest that antagomirs that block the expression of endogenous microRNAs could be used in adjuvant cancer therapy.

Internal Collaborations

- Ekkehard Hewer
- Sabina Berezowska
- Mario Tschan
- Ilaria Marinoni and Aurel Perren
- Inti Zlobec
- Eva Diamantis
- Rupert Langer

External Collaborations

National

- Jean-Louis Boulay, PhD, and Luigi Mariani, MD, University Hospital, Basel
- Rolf Jaggi, PhD, DKF, Bern
- Peng Ren-Wang, PhD, and Thomas Marti, PhD, Universitätsklinik für Thoraxchirurgie
- Michael Reinert, MD, Ospedale Regionale di Lugano, Lugano

International

- Stephan Schäfer, MD, Universitätsspital Köln, Köln

Grant Support

- Bernische Krebsliga, CHF 70'000 (2014–2016)
- R'Equip 316030_164097, (2015–2016)

Team Translational Research Unit (TRU).

1.2 Translational Research Unit (TRU)

Head: Inti Zlobec, PhD

Lab administration:
Caroline Hammer, 50%

Lab technicians and research assistants:
Irene Centeno, PhD, 100%
Micha Eichmann, BSc, 20%
José Galván, PhD, 100%
Joël Kupferschmid, 40%
Patricia Ney, 80%
Liliane Schöni, 80%
Silvia Suardi, MSc, 50% COMPATH

Collaborations:
Clinical pathology division
Molecular pathology division
Cytopathology division
Experimental pathology division

www.pathology.unibe.ch/forschung/core_facilities/translational_research_unit_tru_platform/index_ger.html

Requests

TRU has processed 537 different requests over the last 12 months, an increase of 16% from 2015. Of these, 283 are oriented to research on human tissues (53%), whereas 128 (24%) are performed on animal tissues. These requests can be divided into 112 research projects carried out by internal research groups, collaborators, university/Insel researchers or external clients, and translate into an increase in the number of projects by 23% from last year.

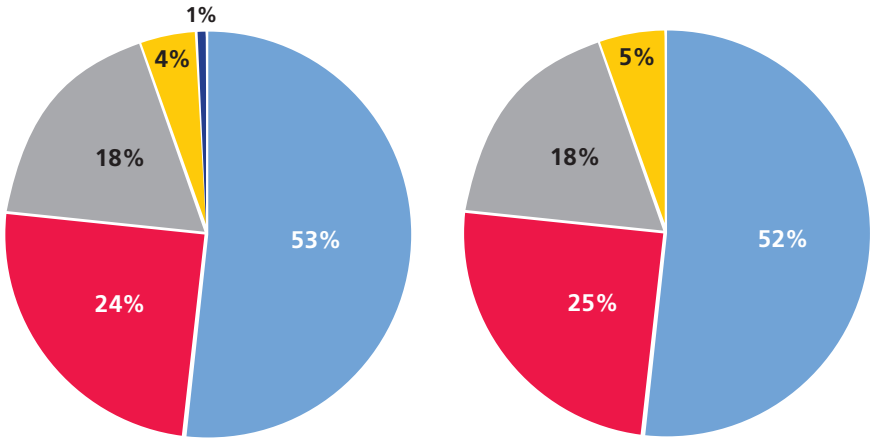
Clinical studies are numerous: 99 requests made on clinical study material were managed through TRU, a 64% increase from last year.

TRU Funding

TRU is primarily a fee-for-service facility. Third-party money funds 79% of all TRU costs and includes work performed for collaborators, external researchers as well as internal coworkers with research funding. The remaining 21% are generously provided by the institute, principally to help «start-up» projects.

Histology

Histology is the basis of TRU. Case retrievals from the archives, paraffin-embedding of tissues (done mostly by the clinical pathology division), and whole tissue sectioning for multiple downstream activities are daily business. In total, TRU has cut more than 9300 slides in the last year in addition to providing researchers with 255 tissue rolls for subsequent DNA, RNA or protein extraction. These numbers do NOT cover work performed in the context of tissue microarrays; hundreds of additional slides have been sectioned for TMA studies. Histology lab numbers are outlined below.



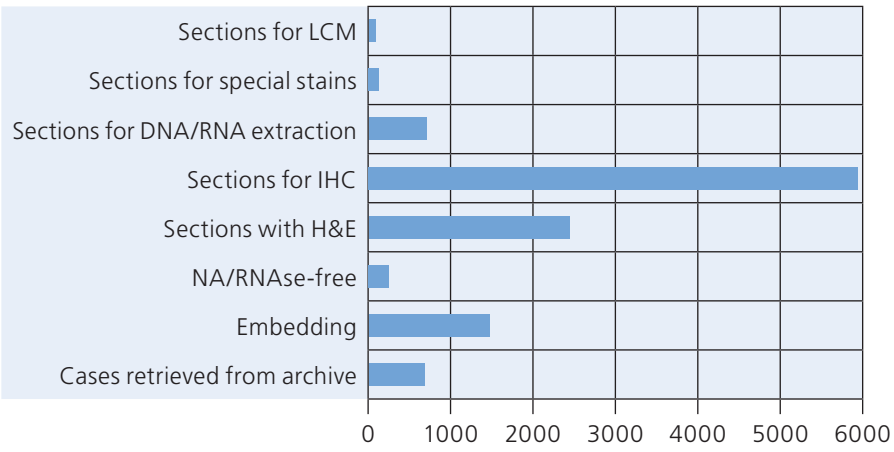
Research requests (n=537)

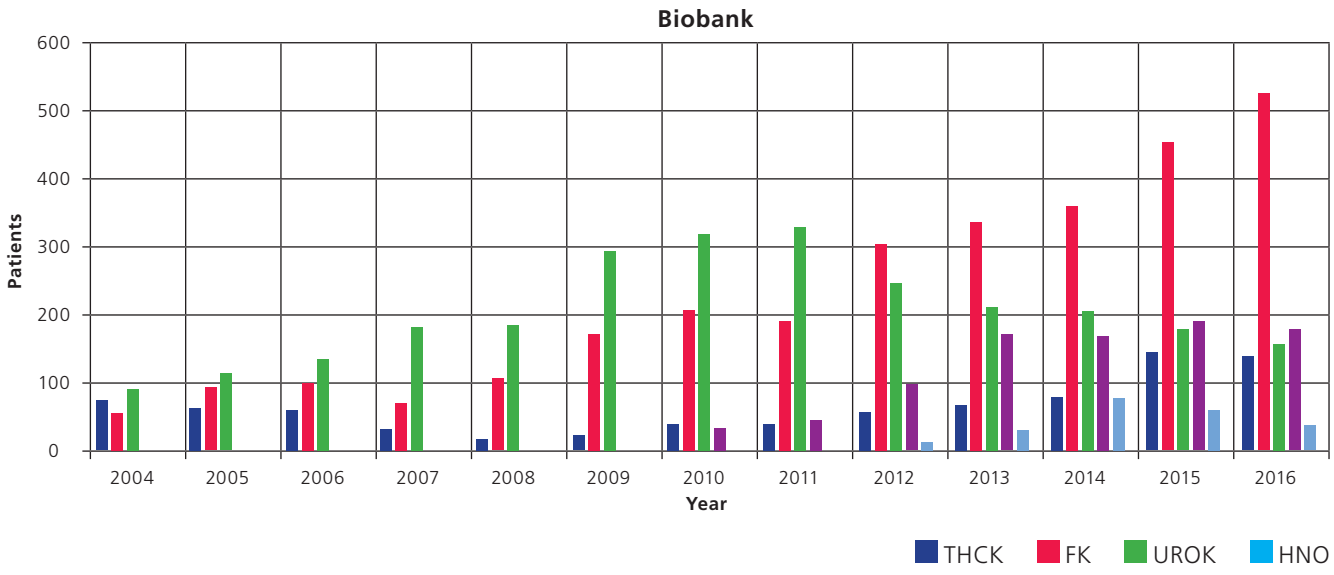
- Biobank; 23
- Diagnostics; 4
- Research; 283
- COMPATH; 128
- Clinical Studies; 99

Research projects (n=112)

- External
- Internal
- Collaboration
- Uni/Insel

Histology lab (not including preparation of TMAs)





Tissue Bank Bern (TBB)

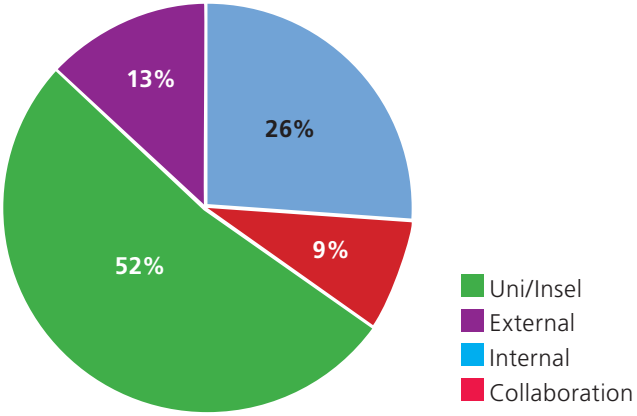
Aim of TBB is to provide the scientific community with high-quality tissue for research purposes by performing optimum tissue collection, storage and documentation. TBB is supported by the clinical pathology division and the expertise of PD Dr. Tilman Rau.

Since August 2016, TBB services are managed under TRU. TRU manages both queries and requests related to fresh frozen material and collaborative projects using tissue microarrays. 32'285 tissue samples from more than 8300 patients are currently stored in –80°C freezers in TBB. Depicted below are the changes in the number of tissue samples per year, by department stored in TBB.

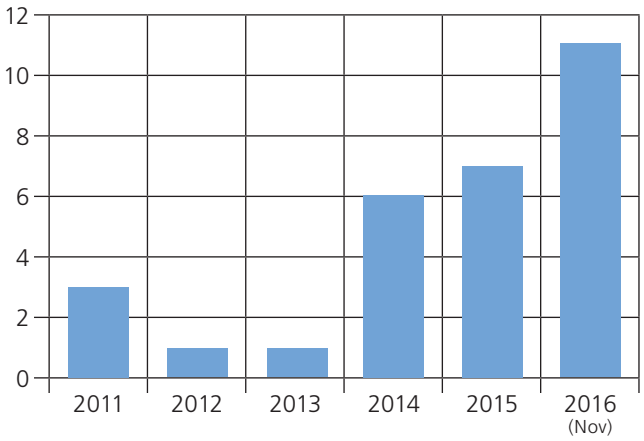
Since January to October 2016, the TBB has collected 3292 samples from 1107 cases, with the support of our clinical pathology medical and technical staff.

	Cases	Samples
Gastro	179	589
HNO	39	105
Thorax	140	484
Gyn	525	1441
Uro	159	526
Other	65	147
Total	**1107**	**3292**

Of the 26 queries by researchers answered by TBB this year, 11 have become concrete projects so far. The majority of these requests come from University of Bern and Insel research groups (52%). TBB has handed out 86 different tissue samples since January (2.6% of 1 year collection). Five prospective collections are currently being performed together with the clinical pathology laboratory, this translates into 112 samples handed out directly to researchers since January 2016.



Cryo-projects, TBB



The number of TBB projects has significantly increased over the last years, with an expected continued growth for the next years to come (see below).

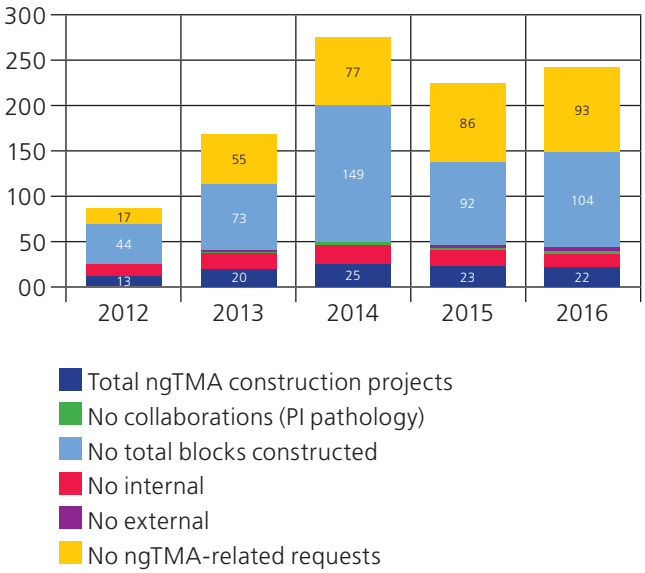
Digital pathology

next-generation Tissue Microarrays (ngTMA)

In October 2012, TRU implemented the next-generation Tissue Microarray (ngTMA) approach based on digital pathology. Since then, more than 460 ngTMA blocks have been constructed, totaling nearly 100'000 punches from 10'000 patients.

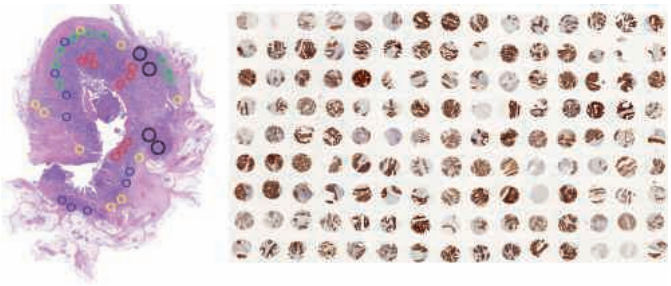
This year saw the creation of 104 ngTMA blocks (21'112 punches) constructed from 3339 digital scans. In addition, 93 different projects have used TMAs for further biomarker analysis evaluated by eye or using digital image analysis. The change in ngTMA construction projects and number of related requests is shown below. ngTMA project numbers have stabilized over time, however more collaborations and external clients are requesting ngTMA construction.

ngTMA data



Slide scanning

Slide scanning has become increasingly more important. TRU currently has access to three scanners with both brightfield and fluorescence capabilities. In addition to scans performed for construction of ngTMAs, 790 scans were made for other research purposes. Fluorescence scanning will become a support platform for the institute.



Left: Annotations on a scanned digital slide showing areas for next-generation Tissue Microarray (ngTMA) construction.
Right: Immunohistochemistry double-staining with pan-cytokeratin and CD8 on a large ngTMA.

Image analysis

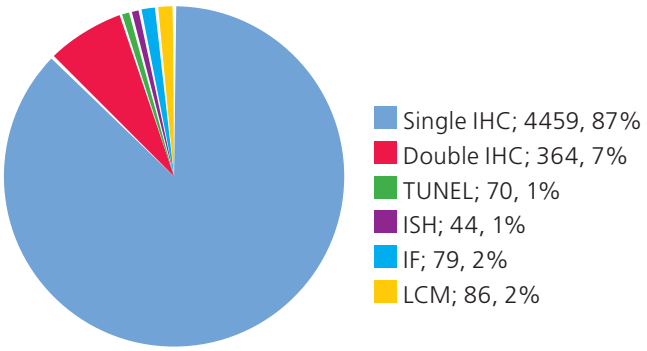
There is a huge demand and necessity for image analysis at our institute. In addition to the Definiens Tissue Studio and Developper software currently available in-house, Visiopharm software has been extensively tested and is currently being applied to numerous projects, including ngTMA and whole slide images.

Tissue visualization lab (TVL)

The main task of the TVL is the routine staining and establishment of new protocols for visualization of protein, DNA and RNA for research purposes on human and animal tissues. The TVL portfolio includes more than 350 antibodies used for immunohistochemistry or immunofluorescence, single or combination staining (e.g. double-immunohistochemistry) applied to both whole tissue sections and tissue microarrays. In addition to standard microscopy, further use of these stains include laser capture microdissection and digital image analysis.

Probes for RNA in situ hybridization are commonly tested; double-protein/RNA detection methods are used. Recently, TUNEL staining has been successfully established on both human and mouse tissues. Our work on tissue extends to cell blocks (fixed cell lines) and also blood smears, prepared together with the support of our diagnostic cytology laboratory.

TVL uses two automated immunostainers for daily work: Leica Bond Rx and Ventana Benchmark. In 2016, 60 new antibodies were tested and established in our laboratory and more than 5100 slides have been processed. Details can be found below.



Molecular analysis

The last year has seen numerous scientific questions answered using technologies such as laser capture microdissection on both fresh-frozen and formalin-fixed, pyrosequencing, next-generation sequencing and Nanostring. Many of these research projects are carried out in collaboration with the molecular pathology division.

Student support

TRU and related research groups average 12 to 13 new MD students per year. The staff of the TRU has contributed countless hours to MD Master Students' thesis and dissertation projects, not only by supporting histological aspects, but also by training students in laboratory practices and technologies. Yearly Master Symposia are organized, thus giving the students the opportunity to share their work with other students and medical doctors.

Group of Yara Banz, MD

Martina Dahinden, medical student
Simone Zwicky, medical student
Olivia Steinsiepe, medical student
Rahel Friedli, medical student

Research activities

Project 1: Investigation of the role of interleukin-33 in initiation and progression of myeloproliferative neoplasms
This will occur using basic animal models of MPN-like diseases (s. investigational work of Philippe Krebs), in a retrospective manner by investigating archived bone marrow samples and in a prospective manner in a clinical study of MPN patients.

Project 2: Investigation of the potential role of interleukin-33 in lymphomagenesis and correlation with lymphoma subtype
Furthermore we aim to study the possible correlation with the clinical presentation as well as outcome in a large cohort of lymphoma patients («lymphoma board», Inselspital Bern). Study analysis is primarily based on immunohistochemical analyses of a lymphoma Tissue Microarray (TMA) established from this patient cohort.

Internal collaborations

- Philippe Krebs, PhD
- Christian Schürch, MD

External collaborations

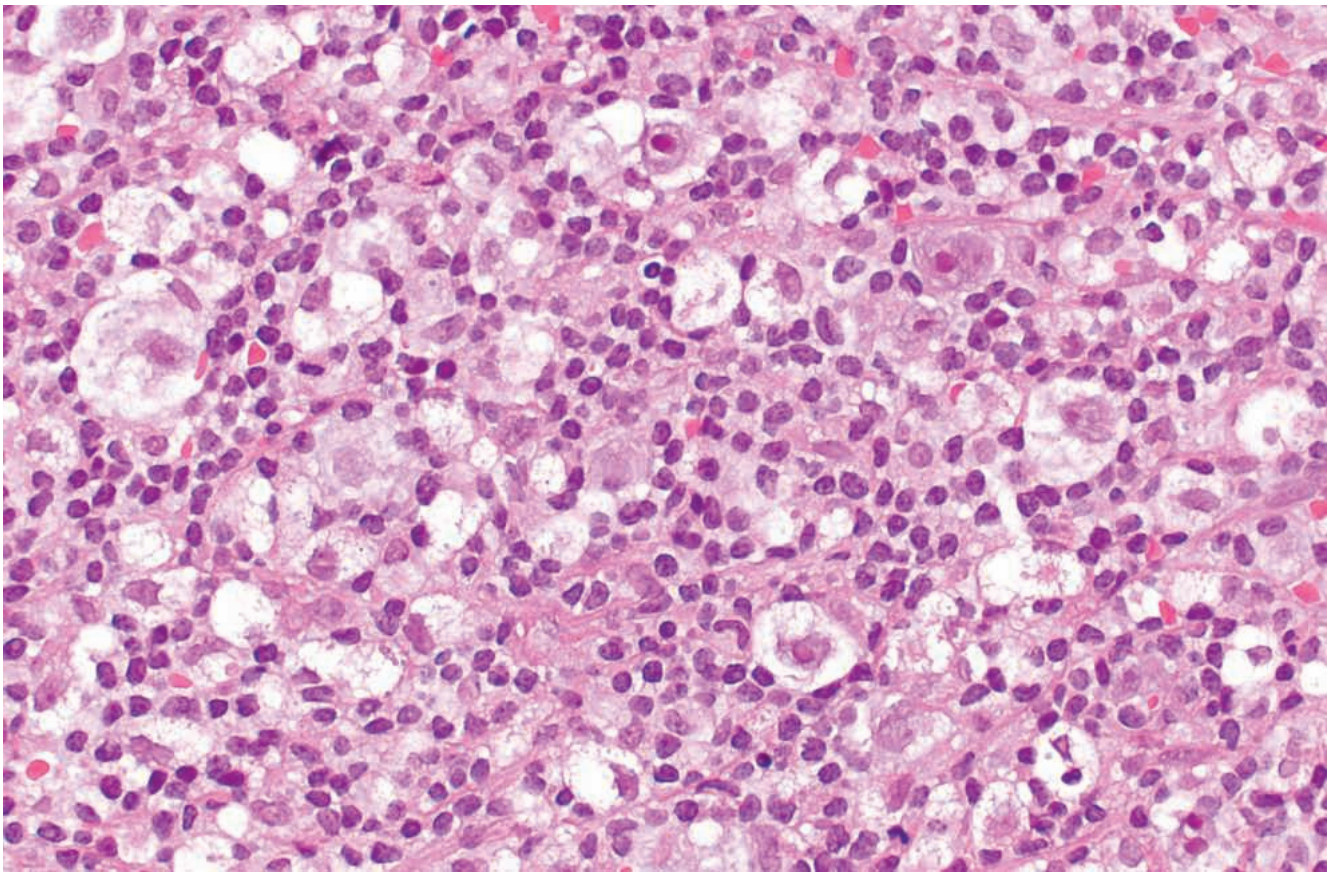
National

- Alicia Rovo, MD, Department of Hematology, University Hospital, Inselspital, Bern
- Urban Novak, Department of Oncology, University Hospital, Inselspital, Bern
- Alexander Tzankov, MD; Institute of Pathology, University of Basel
- Alexandre Theocharides, MD, Department of Hematology, University Hospital Zurich
- Robert Rieben, PhD, Department of Clinical Research, University of Bern

Grant Support

- Stiftung für klinisch-experimentelle Tumorforschung: Role of IL-33/ST2 signaling in myeloproliferative neoplasms, Yara Banz Co-PI (Ph. Krebs, PI), CHF 80'000* (2015–2015)

* Total amount of funding; funding shared by PI and Co-PI



Hochauflösendes Bild eines malignen Lymphoms (Merkmale zwischen einem klassischen Hodgkin-Lymphom und einem diffusen grosszelligen B-Zell-Lymphom.
High-resolution image of a malignant lymphoma (with features intermediate between a classical Hodgkin Lymphoma and a diffuse large B-cell Lymphoma).

Group of Sabina Berezowska, MD

Christina Neppl, MD, resident
Manuel Keller, MD student
Alexandra Kündig, MD student
Yasin Irmak, MD student
Dennis von Arx, MD student
Philipp Zens, MD student

Research activities

Project 1: Lung cancer remains the leading cause of cancer death worldwide
One of the recent significant practice-changers has been the effective therapeutic exploitation of targetable mutations, e.g. ALK-inversions. But even after clinical response on tyrosine kinase inhibitors the neoplasms will eventually develop resistance and recur. Tools to overcome those resistance mechanisms are needed for extended remission. Modulation of autophagy – the stress response and homeostasis mechanism in normal and neoplastic cells – may be one possible way to interfere with tumor cell adaptation and viability.

Our aim is therefore to characterize the role of autophagy – a druggable mechanism – in the biopathology of lung cancer, and in particular in EML4-ALK-positive NSCLC, and to map the autophagy pathway operative in resistance mechanisms to ALK inhibitors. Functional cell culture-based assays and tissue-based immunohistochemical analyses are applied.

Project 2: Very recently, lung cancer has been surprisingly shown to be amenable to immunotherapeutic approaches
Several PD-1 and PD-L1 immune checkpoint inhibitors have been approved for the treatment of patients with advanced NSCLC or are in advanced clinical studies. PD-L1 expression and tumor infiltrating lymphocytes are in the focus of many investigators. Mostly primary tumors are studies. Because 20–40% of all NSCLC patients develop brain metastases, with an associated drop in prognosis, we are interested in the characterization of cerebral metastases of lung cancer in comparison to the primary site. We conduct tissue-based research using next generation tissue micro arrays and immunohistochemistry. Hereby, one project focuses on the immunohistochemical expression of immune checkpoint marker expression and tumor infiltrating lymphocytes.

Internal collaborations

- Mario Tschan, PhD
- Erik Vassella, PhD
- Philippe Krebs, PhD
- Rupert Langer, MD

External collaborations

National
- Lukas Bubendorf, MD, and Spasenija Savic-Prince, MD, Institute of Pathology, University Hospital Basel
- Yitzhak Zimmer, PhD, University of Bern, Dept. of Clinical Research, Radiation Oncology
- Thoracic surgery research group DKF, Bern (Ralph A. Schmid, MD, Thomas M. Marti, PhD, Sean Hall, PhD, Ren-Wang Peng, PhD) www.thoraxchirurgie.insel.ch/

International
- Axel K. Walch, MD, Head, Abt. Analytische Pathologie, Helmholtz-Zentrum München, Germany

Grant support

- BKL PI, Sabina Berezowska, Co-PI Mario Tschan, CHF 32'000* (2014–2016)

* Total amount of funding; funding shared by PI and Co-PI

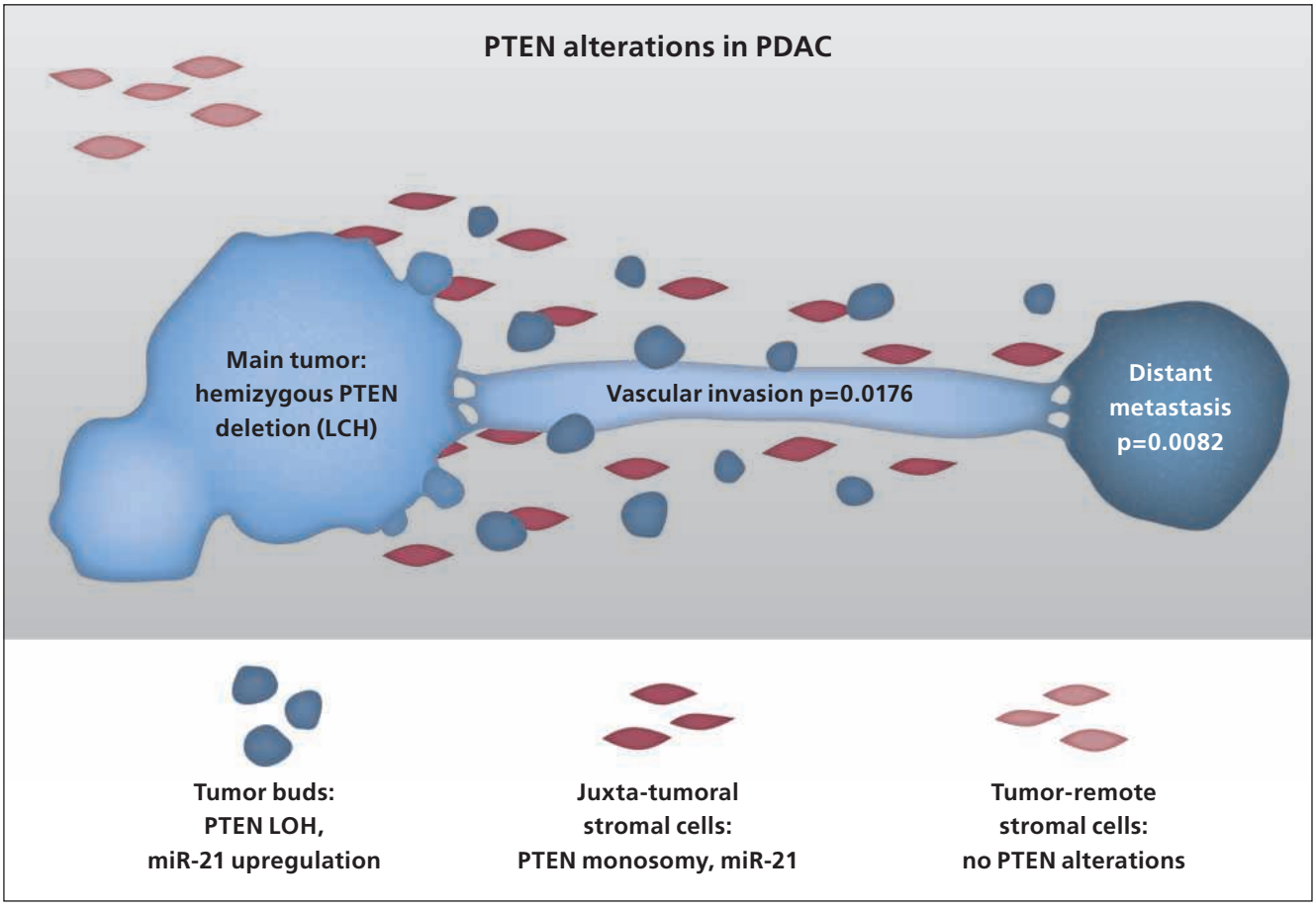
Group of Eva Diamantis-Karamitopoulou, MD

Eva Diamantis-Karamitopoulou, MD
Martin Wartenberg, MD, resident
Silvia Cibin, MD, resident
Jens Brönnimann, medical student (MD thesis)
Petra Schmid, medical student (MD thesis)

Research activities

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with rising incidence and suboptimal treatment.

Tumor microenvironment is of critical importance, both for the better understanding of the mechanisms involved in the initiation and progression of carcinogenesis as well as for improving diagnostic and therapeutic approaches. It includes invasive cancer cells, immune cells and stromal cells, consisting of cancer-associated fibroblasts, which provide a communication network via secretion of growth factors and chemokines. We could recently show that the tumor microenvironment of PDAC displays a tumor-favoring immune-cell composition, especially in the immediate environment of the tumor buds that protects budding cells, preventing their elimination by the host immune response and indicating a close interaction of the immune response with the EMT-process. However, although this interaction facilitates the survival of tumor buds, it is of itself not sufficient. There is strong evidence that also stromal cells by interacting with tumor cells are involved in pancreatic cancer progression. Our recent findings suggest that this may involve the regulation of the EMT-like tumor budding phenotype in PDAC. We could thus show that in the microenvironment of the invasive front of pancreatic cancer, tumor-budding cells are surrounded by stromal cells expressing high levels of the E-cadherin repressors SNAIL1 and ZEB1 and that this stromal cell phenotype is strongly associated with the EMT-like tumor-budding in PDAC. Moreover, we could show that PTEN loss in stromal cells, caused by PTEN genetic alterations of stromal cells (mostly monosomy of chromosome 10) and/or overexpression of miR-21, identifies a subgroup of PDACs with enhanced metastatic potential. All these results emphasize the role of the microenvironment in tumor progression and suggest close cellular interactions between EMT-like tumor budding cells and their surrounding stromal and immune cells. In more detail, we are trying to better characterize the tumor-stroma interactions taking place between the cancer-associated fibroblasts and the cancer cells, ideally represented by an aggressive cancer cell population, in form of dissociated cancer cells with EMT features, called «tumor budding cells». Our group and others have shown that tumor budding is a strong and independent prognostic factor in PDAC. However, the mechanisms that promote tumor budding are still



unknown. In this context an aim of our group is the identification and characterization of specific microRNAs in PDAC. Recent experiments in a number of cases indicate that tumor and stromal cells differentially regulate microRNAs and this correlates with the expression of proteins known to be targets of these microRNAs (manuscript submitted).

Furthermore we are interested in the detailed characterization of the peri-tumoral and intra-tumoral immune cell infiltration, especially by cytotoxic T-cells and tumor-associated macrophages (TAMs), which constitute a very important host-related factor. We could recently show that PDAC microenvironment displays a tumor-favoring immune-cell composition in the immediate environment of the EMT-type tumor-budding cells.

The general objective of our research projects is to provide information on the role of different subtypes of stromal and immune cells within the tumor microenvironment of PDAC and their impact on the EMT-process and the neoplastic progression. This will help us understand the complex cellular interactions behind phenotypic diversity within the prognostically very important area of tumor microenvironment and will provide comprehensive information on the role of each cell population of the tumor microenvironment in tumor budding and thus in neoplastic progression of pancreatic cancer from localized to metastatic disease.

Internal collaborations

- Erik Vassella, PhD
- Inti Zlobec, PhD
- Irene Centeno, PhD
- José Galván, PhD

External collaborations

National

- Beat Gloor, MD, Department of Visceral Surgery, Insel University Hospital, Bern
- Mathias Worni, MD, Department of Visceral Surgery, Insel University Hospital, Bern
- Luigi Terracciano, MD, Institute of Pathology, University of Basel
- Matthias Matter, MD, Institute of Pathology, University of Basel

International

- Prof. A. Kondi-Pafiti, University of Athens

Grant support

- Werner und Hedy Berger-Janser Stiftung zur Erforschung der Krebskrankheiten, Eva Diamantis, CHF 33'410 (2014–2016)
- Stiftung für klinisch-experimentelle Tumorforschung, Eva Diamantis, CHF 60'000 (2016–2017)

Group of Rupert Langer, MD

Group members:
Bastian Dislich, MD, PhD
Olivia Adams, PhD student (co-supervision Mario Tschan)
Ariane Janser, PhD student (co-supervision Mario Tschan)

Master students / dissertation candidates:
Monique Niklaus
Lars Guldener
Simon Nobs
Alexandra Stein
Laura Noser
Domink Arnold
Nicola Blaser
Julia Wiprechtiger
Matea Sunic

Research activities

Project 1
We are especially interested on the impact of cellular stress reactions and death mechanisms on tumor behavior and chemotherapy and resistance. In this field we are closely collaborating with Mario Tschan's group of the experimental pathology department. One focus lies on the investigation of autophagy, a cellular degradation process that has been described to play an important role not only for the maintanance of normal cellular homeostasis but also for cancer. However, the role in malignant diseases is not completely understood, since it may promote tumor death on the one hand and be beneficial for cell survival on the other hand. We are analyzing the expression of autophagy-related proteins in human biopsy and resection samples and correlate the expression patterns with clinical and pathological parameters, including tumor regression after neoadjuvant chemotherapy. The tissue analyses are complemented by functional cell line experiments that mirror the clinical scenario (i.e. treatment with conventional chemotherapeutics, but also with targeting drugs). Another interesting group of molecules are the so-called heat shock proteins (HSPs) that also play a role in cellular stress response. We are investigating a link between these two mechanisms, in specific relation to response to chemo- and targeted therapy. Here, we are focusing on Her2-targeting treatment which represents a potentially powerful therapeutic option in upper gastrointestinal malignancies. We aim at elucidating potential mechanisms for resistance to this therapy.

Project 2
A second focus of our work is the assessment of response to cytoxotic treatment based on histology. We have shown that tumor regression is a reliable prognostic factor after neoadjuvant therapy in adenocarcinomas of the upper gastrointestinal tract, and that grading of tumor regression based on histology can be considered as highly reproducible and feasible. Future studies will also encompass the histopathologic analysis of the effect of targeted treatment.

Project 3
Moreover, we are investigating morphological features with potentially prognostic impact and impact on biology such as tumor budding, inflammation (i.e. host reaction), and the role of the tumor microenvironment using several immunohistochemical markers for a more comprehensive characterization of esophageal and gastric adenocarcinomas.

Internal collaborations

- Mario Tschan, PhD
- Erik Vassella, PhD
- Inti Zlobec, PhD
- Sabina Berezowska, MD
- José Galván, PhD

External collaborations

National
- Prof. C.A. Seiler and Dr. Dino Kroell, Department of Surgery, Inselspital

International
- Dr. J. Slotta-Huspenina, Institute of Pathology, Technische Universität München, Germany
- Prof. K.F. Becker, Institute of Pathology, Technische Universität München, Germany
- Prof. A. Walch, Institute of Pathology, Helmholtz-Zentrum Neuherberg, Germany

Grant support

- Schweizerische Krebsliga KFS-3083-02-2013, Rupert Langer (PI), Mario Tschan (Co-PI), *CHF 236'000 (2013–2016)
- Schweizerische Krebsliga KFS-3700-08-2015, Rupert Langer (PI), Mario Tschan (Co-PI), *CHF 214'000 (2016–2018)
- Bernische Krebsliga, Bastian Dislich (PI), Rupert Langer, Mario Tschan (Co-PI), *CHF 60'000 (2015–2016)

* Total amount of funding; funding shared by PI and Co-PI

Group of Aurel Perren, MD

Ilaria Marinoni, PhD, senior research assistant, 80%
Anja Schmitt, MD, attending pathologist, 70%
Matthias Dettmer, MD, attending pathologist
Tabea Wiedmer, MSc, PhD student
Annunziata Di Domenico, MSc, PhD student
Dominik Nann, MD, resident (until August 2016)
Charalampos Saganas, MD, resident
Sophia Pantasis, MSc, technician
Clémence Mooser, BSc master student (BMS)
Frank Rasmus, technician in training
Renaud Maire, MSc, technician, 90%
Mirjam Franzelli, cand. med.

Research activities

Dissection of the role of DAXX and ATRX in pNET: DAXX and ATRX expression is lost in 40% of sporadic pNETs. DAXX and ATRX are involved in epigenetic regulation. We have shown that DAXX/ATRX loss predicts reduced survival and that DAXX/ATRX loss precedes ALT (Alternative Lengthening Telomeres) activation and CIN (Chromosomal Instability) along tumor progression. 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 and specifically on the epigenetic modification resulting from DAXX/ATRX loss. The possible clinical implications of our findings are then evaluated on pNETs human tissues samples.

Autophagy in pNET 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 treatments. 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 effects of combining autophagy inhibition with targeted treatments are then evaluated ex vivo on patient tumor cells.

Hypoxia in pNET: a subset of pNET show hypoxia signalling and are associated with a poor prognosis. Hypoxia leads to the upregulation of VEGF among others. As response to Sunitinib, a TKI with anti-VEGF activity approved for the therapy of metastasizing pNET, as yet cannot be predicted we aim at dissecting the mechanisms of angiogenesis and its inhibition in human pNETs as well as in pNET cell lines and the RipTAG mouse model.

Tall cell variant of papillary thyroid carcinoma (PTC): it is known that this variant of PTC is associated with an adverse outcome. These tumors respond less often to the standard treatment with radioiodine. However, the reason for this on a molecular level remains elusive. It's also not known, what defines a so-called «tall cell», the hallmark of this histopathological PTC subtype on a molecular level. These are important clinical questions that we are currently trying to answer.

Internal collaborations

- Mario Tschan, PhD
- Philippe Krebs, PhD
- Erik Vassella, PhD

External collaborations

National

- Prof. Martin Walter, Universitätsklinik für Nuklearmedizin, University of Bern
- Prof. Roche-Philippe Charles, Institut für Biochemie, University of Bern

International

- Dr. Chrissie Thirlwell, Department of Cancer Biology, Clinical Lecturer Medical Oncology, University College London, United Kingdom
- Prof. Marja Jäättelä, Head of Research Cell Death and Metabolism, Danish Cancer Society Research Center Copenhagen, Denmark
- Prof. Anne Couvelard and Dr. Jérôme Cros, Department of Pathology, Hospital Beaujon, Clichy, France
- Prof. Marianne Pavel, Head of the Neuro-Endocrine Tumor Unit, Charité Berlin, Germany
- Prof. Massimo Falconi, Surgery Departement, San Raffaele, Milan, Italy
- Prof. Luca Mastracci, Department of Surgical Science and Integrated Diagnostics (DISC), University of Genoa, Italy

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- KFS 3360-02-2014, Aurel Perren and Ilaria Marinoni (Co-Applicant), CHF 286'900 (2014–2017)
- Tumor-Forschung Bern, Ilaria Marinoni, CHF 90'000 (2015–2017)
- SNF Marie Heim-Vögtlin, Ilaria Marinoni, CHF 206'000 (2016–2018)
- Desirée and Niels Yde Foundation, Ilaria Marinoni, CHF 54'000 (2016–2019)

Group of Tilman Rau, MD

Carol Büchi, medicine student
Amanda Rohner, medicine student
Micha Eichmann, bioinformatics student

Research activities

Beyond colorectal cancer the Lynch syndrome comprises several more cancer types. Among them endometrial carcinoma reaches an up to three-fold higher detection rate than in CRC. This makes ECC to an actionable cancer type in terms of screening aspects. Taking the pre-work of genotype-phenotype correlations of CRC we transferred it to this closely related gynecological tumor type.

Project 1: ngTMA construction and immunohistochemical classification for TCGA subtypes
A cohort of n>200 endometrial carcinomas was re-classified and transferred to an ngTMA construction. Special emphasis was put on tumor heterogeneity with detection of heterogenous elements in a subgroup of cancers and consequent definition of ROIs along the tumor center as well as the invasion front. The ongoing immunohistochemical analysis is based on classical parameters like p53, hormone receptors, MMR protein expression, etc. The goal is to achieve an immunohistochemical surrogate marker panel for the TCGA-related four molecular subtypes. As a difference, the spatial resolution in different tumor areas will be accessible and precisely quantified using a DIA approach.

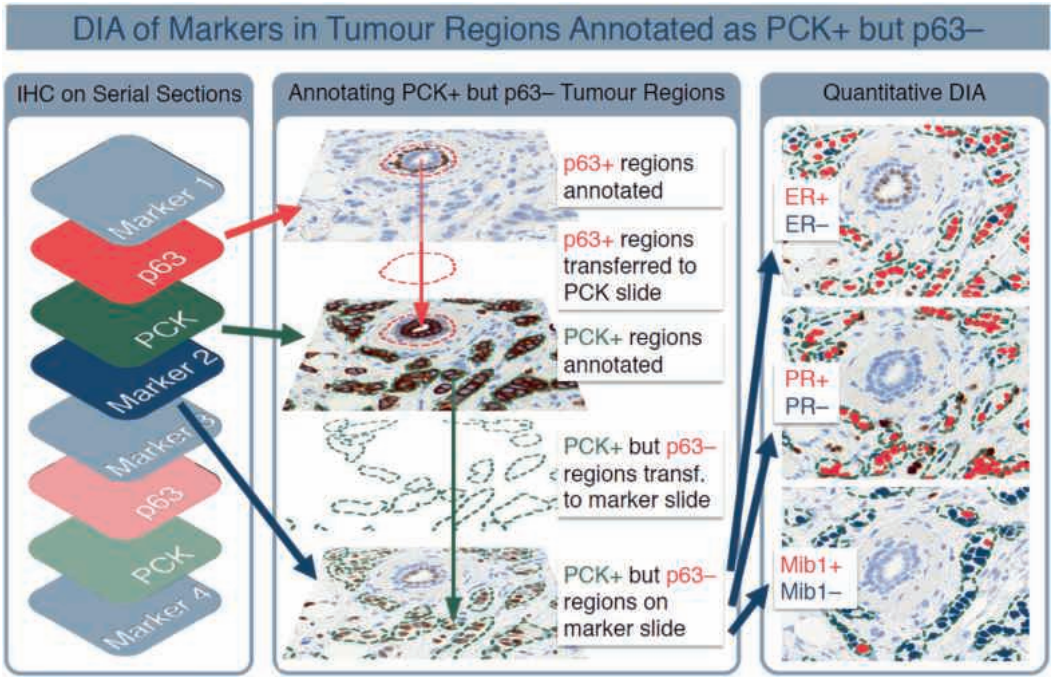
Project 2: TRU/TBB-related research of supporting character
To support the Translational Research Unit and the Tissue Bank Bern as infrastructure units of the Institute of Pathology, research projects are considered to enhance the quality of processes and methods. Two examples can be given for 2016. The retrospective analysis of cold and warm ischemia times over 12 years TBB activity led to immediate quality improvement measurements to optimize the snap freezing procedure of TBB samples. Additionally, scouting for new DIA softwares and application in clinical scenarios like a small series of borderline breast cancers was performed, compared to PAM50 results and internationally presented. Herein, the technology of virtual alignment produced a comprehensive and robust ROI selection as an innovative tool of digital pathology.

Internal collaborations

- Inti Zlobec, Prof.
- Alessandro Lugli, Prof.
- Andrea Papadia, MD
- Sara Imboden, MD
- Martin Zweifel, PD, MD

External collaborations

National
- Zsuzsanna Varga, Prof., MD, Institute of Pathology, University Hospital Zurich
- Laurence Chapatte, PhD, Clinical Research support platform, CHUV, Lausanne



Within the framework of the pilot project «Digital Pathology Sandbox» software solutions for digital histology processing are intensely evaluated and different scenarios are tested. An interesting solution for the selection of the region of interest (ROI) is offered by the software Visiopharm. In breast cancer, invasive tumor regions are defined as pan-cytokeratin-positive areas, which do not show p63-positive myoepithelia. By exact alignment of serial sections, p63-positive areas are therefore excluded from the Pan-CK area and the generated template is applied to the biomarker estrogen receptor, progesterone receptor and MIB1 as a proliferation marker.

Team Translational Research Unit (TRU).

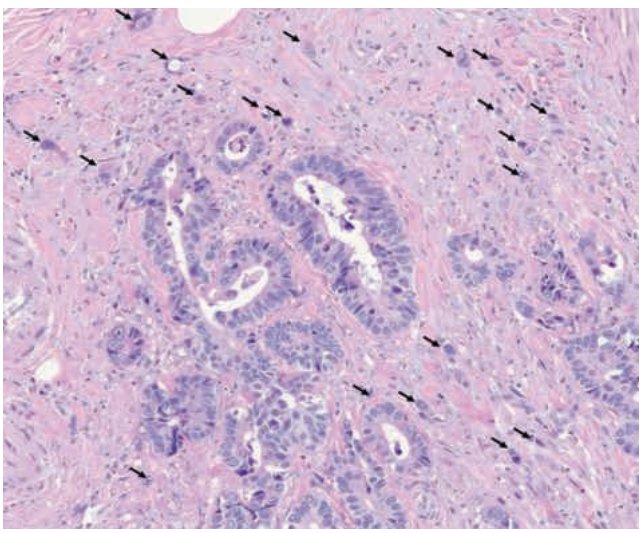
Group of Inti Zlobec, PhD, and Alessandro Lugli, MD

Group members:
Annika Blank, MD, staff pathologist
Heather Dawson, MD, staff pathologist
Monique Niklaus, MD, resident in pathology
Lena Sokol, PhD
Kristin Uth, PhD student
Stefan Zahnd, PhD student

MD thesis and dissertation students:
S. Burren
L. Christe
E. Fischer
M. Flury
J. Graule
C. Jaccard
C. Läderach
Ch. Lambert
D. Marx
S. Meyer
L. Richmond
C. Schafroth

Project 1: CDX2 – the old is new again
We have known CDX2 for years as a diagnostic marker of intestinal differentiation. But our work, stemming from 2007, shows that up to 20% of colorectal cancer have decreased expression or complete loss of CDX2 protein. CDX2 loss is associated with microsatellite instability, high-level CpG island methylation and BRAF mutation, features consistent with the serrated pathway. Our functional studies show that hypermethylation of the CDX2 promoter is a major reason for this loss and can be recovered with DNMTi treatment. Together with the group of Prof. M. Tschan, we investigate genetic and epigenetic modifications of CDX2 using CRISPR/Cas9 technology. This interesting story is the on-going work of PhD student Kristin Uth.

Project 2: Shotgun-proteomics-based protein biomarker discovery
Tissue heterogeneity has been repeatedly reported as a major source of bias in biomarker discovery over the last years, particularly for studies using whole tissue as starting material. These tissues feature a vast compilation of different cell types, thereby challenging the isolation of the signal from specific cell populations for subsequent biomarker discovery. We attempt to circumvent this problem by dissociating both fresh and formalin-fixed paraffin-embedded (FFPE) colorectal cancer tissue into single cells. Cells are labelled with vimentin (stromal cell marker) and cytokeratin (epithelial cell marker), sorted into



H&E staining of tumor budding in colorectal cancer.

distinct populations using fluorescence-activated cell sorting (FACS), and subjected to downstream shotgun-proteomics-based mass spectrometric analysis. This project, carried out by PhD student Stefan Zahnd, aims to identify new biomarkers in colorectal cancer on a proteomic level with a focus on stage II and III colorectal cancer patients.

Project 3: Clinical aspects of tumor budding in CRC
Tumor budding is defined as single cells or clusters up to four cells at the invasive front of CRC. Based on the literature, there is a strong evidence for tumor budding being an independent prognostic factor and its implementation in the daily diagnostic practice would be supportive for the patients' management in the following clinical scenarios: in malignant polyps, tumor budding is a predictor of lymph node metastases and therefore an indicator for a colonic resection; in case of the presence of tumor budding in stage II CRC, a post-operative chemotherapy should be considered and tumor budding in the pre-operative biopsies in rectal cancer would be in favor of a neo-adjuvant therapy. Our CRC research group organized in April 2016 in Bern the International Tumor Budding Consensus Conference (ITBCC) where 25 GI experts from all over the world met and agreed on an international standardized scoring system for tumor budding.

Internal collaborations
- Mario Tschan, PhD
- Erik Vassella, PhD
- Philippe Krebs, PhD
- Rupert Langer, MD
- Eva Diamantis, MD
- Matteo Montani, MD

External collaborations
National
- Luigi Terracciano, MD, Institute of Pathology, University Hospital Basel
- Laura Rubbia-Brandt, MD, Institute of Pathology, HCUG
- Daniel Inderbitzin, MD, Kantonsspital Solothurn
- Jean-François Dufour, MD, Inselspital Bern
- Visceral Surgery Department, Inselspital Bern (Drs. B. Schnüriger, G. Beldi, L. Brügger)
- Stephan Vavricka, MD, Triemli Hospital Zürich
- Giandomenica Iezzi, ZLF, University Hospital Basel

International
- Members of the International Tumor Budding Working Group (including P. Quirke, F. Bosman, and I. Nagtegaal)
- Immunoscore Collaborative Effort (immunoscore.org/) (J. Galon, F. Pagès)

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- KFS, 3294-08-2013, PI: Alessandro Lugli, CHF 233'700 (2013–2016)
- SNF, 31003A_166578, PI : Inti Zlobec, CHF 305'040 (2016–2019)
- SNF, 320030_163342, Co-PI: Inti Zlobec (PI: Chr. Bouchardy, Geneva), CHF 525'000* (2015–2018)
- Werner und Hedy Berger Janser Stiftung, PI: Inti Zlobec, CHF 145'620 (2015–2018)
- Mach-Gaensslen Foundation, PI: Inti Zlobec, CHF 39'000 (2014–ext. 2016)
- Bernese Cancer League, PI: Lena Sokol, CHF 60'000 (2015–2016)

* total amount of funding; funding shared by PI and Co-PI's

2 Akademische Grade

2.1 Akademische Grade intern

Abilashan Sithampari, MsC
Characterization of an Nrf2-dependent macrophage subset and investigation of fatty acid-induced IL-1 responses of macrophages
Hauptbetreuer: S. Freigang

Auf der Maur Priska, MsC
DAPK2 in HER2 inhibitor-induced cell death and autophagy pathways
Betreuer Patho: A. Bill
Hauptbetreuer: M. Tschan

Becker Eugenia, PhD
The impact of isotretinoin and antibiotics on microRNA/mRNA expression profiles and gut microbiota composition
Fakultät: University of Zurich
Betreuer Patho: G. Rogler
Hauptbetreuer: C. Müller

Berger Michael, MSc
Regulation of NK Cell Function During Virus Infection
Betreuer Patho: L. Cardoso Alves
Hauptbetreuer: P. Krebs

Braun Roman Othmar, PhD
Application of systems vaccinology to the veterinary field using a Toll-like receptor ligand adjuvanted liposomal vaccine targeting antigen presenting cells
Betreuer Patho: P. Krebs
Hauptbetreuer: A. Summerfield

Büchi Carol, MMed
Construction of a next-generation tissue microarray (ngTMA) of Endometrial Carcinoma
Fakultät: med. Uni Bern
Hauptbetreuer: T. Rau

Burren Sandra, Master
Evaluation von Tumor Budding in Lymphknoten und Fernmetastasen der Stadium IV Kolorektalkarzinom-Patienten
Fakultät: med. Uni Bern
Hauptbetreuer: A. Lugli

Bütler Vanessa, MD Master
The Role Of Autophagy In HER2 Amplified Esophageal Adenocarcinoma With Respect To Targeted Therapeutic Response
Betreuer Patho: O. Adams
Hauptbetreuer: M. Tschan

Canonica Katharina, MMed
Characterization and prognostic impact of macrophages in patients with colorectal cancer
Fakultät: med. Uni Bern
Hauptbetreuerin: I. Zlobec

Cuenca Miguelangel, PhD
Exploring the pathogen-commensal continuum: Cell wall auxotrophic bacteria in gnotobiotic mice
Betreuer Patho: P. Krebs
Hauptbetreuer: S. Hapfelmeier

De Niz Mariana, PhD
Imaging of malaria: conserved mechanisms of Plasmodium sequestration an virulence factor export in rodents and humans
Betreuer Patho: M. Tschan
Hauptbetreuer: V. Heussler

Filipenko Iuliia, PhD
The role of the S1P3 receptor in inflammation-associated proliferative disorders
Betreuer Patho: M. Tschan
Hauptbetreuer: A. Huwiler

Fischer Elia, MD Master Thesis
CDX2 hypermethylation in colorectal cancer
Fakultät: med. Uni Bern
Hauptbetreuerin: I. Zlobec

Frentzel Julie, PhD
Rôle et régulation de l'autophagie dans les Lymphomes Anaplasiques à Grandes Cellules ALK positifs
Betreuer Patho: M. Tschan
Hauptbetreuer: S. Giuriato

Guldener Lars, Dr. med.
Impact of peritumoral and intratumoral budding in esophageal adenocarcinomas
Fakultät: med. Uni Bern
Hauptbetreuer: R. Langer

Hostettler Isabel, PhD
Development and application of a novel screening cascade for the identification of anti-theilerial drugs
Betreuer Patho: M. Tschan
Hauptbetreuer: A. Hemphill

Irmak Yasin, MMed
Konstruktion eines Tissue Microarrays von Plattenepithel-karzinomen der Lunge mit zugehörigen Metastasen.
Fakultät: med. Uni Bern
Hauptbetreuerin: S. Berezowska

Jin Jing, PhD
PU.1-regulated autophagy genes during ATRA-induced-differentiation of acute promyelocytic leukemia (APL) cells
Hauptbetreuer: M. Tschan

Kudira Ramesh, PhD
Purinergic modulation of innate lymphoid cells during liver regeneration
Betreuer Patho: P. Krebs
Hauptbetreuer: G. Beldi

Langsch Stephanie, PhD
miR-29b is a mediator of KRAS-induced NF-kB activation in non-small cell lung cancer
Hauptbetreuer: E. Vassella

Perruzza Lisa, PhD
The purinergic P2X7 receptor at the interface between adaptive immune system and bacterial commensals in the intestine
Betreuer Patho: P. Krebs
Hauptbetreuer: F. Grassi

Rentsch Vreni, Diploma
Die Rolle von FASN in Leukämiezellen bei Akuter Promyelozytenleukämie unter ATRA-Therapie
Hauptbetreuer: M. Tschan

Schlossbauer Mathias, Dr. med.
Evaluation des Regressionsgradings nach Dworak in Kombination mit möglichen prognostischen Faktoren bei Lebermetastasen des kolorektalen Karzinoms.
Fakultät: med. FAU Erlangen (D)
Hauptbetreuer: T. Rau

Steinsiepe Olivia, MMed
The role of IL-33 in Myeloproliferative Neoplasms
Fakultät: Med Fakultät
Hauptbetreuerin: Y. Banz

Trüb Stefanie, Diploma
Die Rolle von ALFY in der ATRA induzierten Zellzytotoxizität und Autophagie bei SKBR3 Brustkrebszellen
Hauptbetreuer: M. Tschan

von Arx Dennis, MMed
Zusammenstellung eines Kollektivs und Konstruktion eines Tissue Microarrays von Lungenkarzinomen mit zugehörigen Hirnmetastasen
Fakultät: med. Uni Bern
Hauptbetreuerin: S. Berezowska

Wampfler Julian, PhD
Aberrant expression of the miRNA pathway in acute myeloid leukemia
Hauptbetreuer: M. Tschan

Wicki Simone, PhD
Regulation of cell death and innate immune signaling in mouse neutrophils
Betreuer Patho: P. Krebs
Hauptbetreuer: T. Kaufmann

Zwicky Simone, MMed
The role of IL-33 in Classical Hodgkin Lymphoma
Fakultät: Med Fakultät
Hauptbetreuerin: Y. Banz

3 Publikationen

3.1 Originalarbeiten In-House

- Adams OJ, Dislich B, Berezowska SA, Schläfli AM, Seiler CA, Kröll D, Tschan M, Langer R
  Prognostic relevance of autophagy markers LC3B and p62 in esophageal adenocarcinomas. ONCOTARGET, 7(26): 39241-55, D0: Artikel in Fachzeitschrift (IF:5.008, TC:3, MR:0.84)
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- Berezowska SA, Pöllinger A
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- Berezowska SA, Schläfli AM, Adams O, Galván Hernández JA, Bubendorf L, Prince SS, Schmid R, Gugger M, Tschan M, Langer R
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- Kölzer V, Zlobec I, Lugli A (2016) Tumor budding in colorectal cancer – ready for diagnostic practice? HUM PATHOL, 47(1): 4-19, D0: Artikel in Fachzeitschrift (IF:2.791, TC:7, MR:0.731)
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  Prognostic value of the autophagy markers LC3 and p62/SQSTM1 in early-stage non-small cell lung cancer. ONCOTARGET, 7(26): 39544-55, D0: Artikel in Fachzeitschrift (IF:5.008, TC:0, MR:0.84)
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3.3 Übrige Publikationen

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- Rau T
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- Schmitt Kurrer A, Blank A, Marinoni I, Komminoth P, Perren A
  Histopathology of NET: Current concepts and new developments. Best practice & research. Clinical endocrinology & metabolism, 30(1): 33-43, D1: Rezension (IF:0, TC:2, MR:0)
- Schmitt Kurrer A, Marinoni I, Blank A, Perren A
  New Genetics and Genomic Data on Pancreatic Neuroendocrine Tumors: Implications for Diagnosis, Treatment, and Targeted Therapies. Endocrine pathology, 27(3): 200-4, D1: Rezension (IF:0, TC:1, MR:0)
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- Simon HU, Tschan MP
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- Smit JJ, Noti M, O'Mahony L (2016) The use of animal models to discover immunological mechanisms underpinning sensitization to food allergens. Drug discovery today.
  Disease models, 17-18: 63-9, D1: Rezension
- Wohlfarth E, Berezowska SA, Pöllinger A, Geiser T, Funke M
  Trockener Husten und Leistungsknick. Swiss Medical Forum, 16(47): 1026-8, D5: Sonstiges (IF:0, MR:0)

4 Vorträge

Banz Yara
- 30.11.17, «GCA Masterclass, Apsects of Pathology», Roche GCA Symposium
- 15.12.17, Histopathologische Fallbesprechung über Vaskulitis und Myositis Experiencia Tagessymposium Rheumatologie

Berezowska Sabina
- 21.03.16, Thymome aus Sicht des Pathologen, Fortbildungsreihe der Klinik für Pneumologie und Thoraxchirurgie des Inselspitals Bern
- 23.05.16, Organization und Chair, Interdisziplinäres Mini-Symposium über UIP/IPF, Bern
- 10.12.16, PD-L1 in NSCLC, Seminar Update in PD-L1
- 26.10.16, Prognostic value of the autophagy markers LC3 and p62/SQSTM1 in early-stage non-small cell lung cancer, Laborfortbildung Thoraxchirurgie-Labor, DKF Bern

Dawson Heather
- 30.01.16, Tumor Budding – Best Buddy für das Grading kolorektaler Karzinome, Bamberger Morphologietage, Bamberg (D)
- 02.06.16, Update Tumor Budding kolorektales Karzinom, Donnerstagsfortbildung Bauchzentrum Inselspital Bern
- 17.11.16, Update Tumor Budding kolorektales Karzinom, Donnerstagsfortbildung Bauchzentrum Inselspital Bern

Freigang Stefan
- 15.01.16, Fatty acids as pro- and anti-inflammatory mediators in metabolic disease, Cardiovascular and Metabolic Research Meeting, Fribourg

Grob Tobias
- 01.07.16, Molekulare Diagnostik in der Pädopathologie, Fortbildungsreihe Pädiatrie, Inselspital Bern
- 26.08.16, Möglichkeiten der molekularen Diagnostik 2016: NGS und Co., SAKK Seminar Orphan Malignancies, Zürich
- 22.10.16, Concepts of molecular analysis: In-situ hybridization, SAMO Interdisciplinary Workshop on Molecular Analysis in Clinical Practice, Luzern
- 10.11.16, Molecular pathology of the upper gastrointestinal tract: a primer, 3rd Joint Annual Meeting of the SGPath and OEGPath, Wien

Krebs Philippe/Mager Lukas
- 16.06.16, mRNA splicing and epithelial integrity, University Hospital, Zurich
- 19.08.16, mRNA splicing and epithelial integrity, Actelion, Allschwil

Krebs Philippe
- 29.11.16, NK cell mediated regulation of adaptive immunity, University Hospital Essen, D

Langer Rupert
- 25.05.16, All you ever wanted to know about Vimentin … and never dared to ask, Seminar, IPATIMUP, Porto,
- 25.5.2016: Autophagy related Markers in tissue – lessions from esophageal and lung cancer
- 26.09.16, Recent progress in characterization of Nobelpreisin in the signaling pathway of …, XXXI International Congress of the IAP and 28th Congress of the ESP, Köln, 25–29.9.2016. Regression grading of GI cancers after neoadjuvant treatment
- 14.11.16, Tumour regression grading in digestive tumours, 7th Belgian Week of Pathology, Ghent, October 12–15, 2016, Tumour regression grading in digestive tumours

Lugli Alessandro
- 22.06.16, Postmortal Diagnostics, Interne Fortbildung, ICU, Inselspital, Bern
- 26.09.16, Leadership and LEAN Management System, Sakura Symposium, Annual Meeting of the ESP, Köln
- 27.09.16, Histological factors for outcome in GI cancers, Annual Meeting of the ESP, Köln
- 14.10.16, Leadership and LEAN Management System, Sakura Symposium, Frankfurt
- 22.10.16, Gastrointestinale Pathologie, IAP, Bonn
- 04.11.16, Results of the ITBCC, Berner Chirurgie Symposium, Inselspital, Bern
- 11.11.16, ITBCC, Annual Meeting of the Swiss and Austrian Society of Pathology, Wien
- 01.12.16, Immunoscore in a Pathology Lab based on LEAN, Melanoma Bridge, Naples
- 02.03.16, History of Pathology, Sakura Symposium, Stockholm

Magali Humbert
- 07.10.16, Dissecting the Autophagy Tumor Suppressor Pathway Network in Acute Promyelocytic Leukemia Therapy, The First Joint WGs Meeting of TRANSAUTOPHAGY COST Action CA15138, Warsaw
- 07.10.16, P73-DAPK2-ATG5 Pathway in Acute Promyelocytic Leukemia Therapy, 6th Autophagy Scientific Days organized by CFATG, Bordeaux

Müller Christoph
- 24.02.16, Induction, remission and relapse of colitis in a mouse model, Research seminar, Stanford University Medical Center, Dept of Immunology and Microbiology
- 31.03.16, A reversible mouse model of colitis in gnotobiotic mice allows to determine the immunological, microbial and metabolomic changes associated with remission of active colitis, Research seminar, La Jolla Institute of Immunology, La Jolla CA USA
- 09.08.16, Experimentelle Mausmodelle einer Kolitis: Pathogenese, Verlauf, Beurteilung und Scoring, Seminar, Animal Experimentation Committee, Bern
- 18.11.16, TREM-1 links dyslipidemia with inflammation and lipid deposition in atherosclerosis, Research seminar, Cambridge Institute of Medical Research, Cambridge University

Noti Mario
- 13.12.16, Innate immune cells in health and disease, Institute of Physiology, University of Zurich, University of Zurich
- 30.11.16, Animal models of food allergy, Annual Meeting Cost action ImpARAS, Vienna

Perren Aurel
- 18.02.16, DAXX/ATRX: ALTered telomeres as a new therapeutic gate inNETs?, ESE Basic Sciencen Course Endocrine and Neuroendocrine Cancer, Porto Portugal
- 08.03.16, Genomic and Mathematical Strategies in NET Disease Management: LungNET, Gnostic Consortium, Barcelona
- 10.03.16, Profiling in GEP-NET, ENETS, Barcelona
- 24.03.16, NET Pathology: Current standards and new trends, Post-ENETS-Kongress, Bern
- 20.04.16, Entwicklungen in der Klassifikation: eine statische Dynamik?, 4. Interdisziplinäres NET-Symposium Berlin
- 20.04.16, Führt next generation Sequenzierung zu next generation Klassifikation?, 4. Interdisziplinäres NET-Symposium Berlin
- 11.05.16, Lean Management in Pathology, Institutsweiterbildung, Tübingen, Schweiz

- 30.05.16, Current developments in classification of neurendocrine neoplasia, ECE 2016, 18th European Congress of Endocrinology, München
- 31.05.16, Tissue Biobank Bern (TBB), Eröffnung Liquid Biobank, Inselspital Bern, Schweiz
- 16.06.16, Gewebebasierte genomische Untersuchungen: Anwendung als diagnostische und prädiktive Marker in der Pathologie, Swiss MedLab 2016, SULM, Bern Expo, Schweiz
- 21.07.16, Pancreatic NET: Genetically and epigenetically diverse tumors, Seminar IPATIMUP, Portugal
- 24.08.16, Pathologische Unterschiede von GI-Lungen-Pankreas NET, Novartis, Luzern Schweiz
- 25.08.16, Biobanking Mythen und Fakten, Seminar Onkologie, Inselspital
- 23.09.16, The role of pathology in NET: To day and in the future with focus on the new WHO classification, Hot Topics in NET, Stockholm, Arlanda
- 26.09.16, What's new in New WHO, ESP/IAP XXXI International Congress of the International Academy of Pathology and 28th Congress of European Society of Pathologie, Köln, Deutschland
- 29.09.16, Diagnostic and therapeutic advances in neuroendocrine tumours, ESP/IAP XXXI International Congress of the International Academy of Pathology and 28th Congress of European Society of Pathologie, Köln, Deutschland
- 29.09.16, Hormonally active and non-active neuroendocrine tumours of the gastrointestinal tract, ESP/IAP XXXI International Congress of the International Academy of Pathology and 28th Congress of European Society of Pathologie, Köln, Deutschland
- 04.11.16, Malignancy and progression of pNETs: morphology meets molecular biology, Research Seminar UCL, London, GB
- 10.11.16, Neuroendocrine tumors of the lung: what the clinician wants to know from the pathologist -an interdisciplinary dialogue, SGPath Wien
- 12.11.16, Slide Seminar: Medullary microcarcinoma, SGPath Wien
- 18.11.16, Let's get serious in developing biomarkrs: Clinician meets pathologist!, NET Master Class. München, Deutschland
- 19.11.16, Safe practices for appendicular tumours, NET Master Class. München, Deutschland

Reubi Jean-Claude
- 12.–14.07.2016, New insights on somatostatin peptide and receptor family in tumors, International Regulatory Peptide Society, Rouen, France
- 09.–11.03.2016, Peptide Receptors as Targets in Neuroendocrine Tumors, 13th ENETS Annual Conference Barcelona 2016

Schenk Mirjam
- 01.09.16, Generation of cross-presenting dendritic cells for immunotherapy in melanoma, Institute of Pathology, Bern
- 28.09.16, Immunotherapy in melanoma: Novel DC-based strategies, BIC, Bern Immunology Club
- 02.12.16, Generation of cross-presenting dendritic cells for immunotherapy in melanoma, Symposium Stiftung Experimentelle Biomedizin, Bern

Schmitt Anja
- 12.03.16, New Genetics Data of Pancreatic Neuroendocrine Tumors: Implications for Diagnosis, Treatment, and Targeted Therapies, Endocrine Pathology Society, 2016 Annual Meeting USCAP, Seattle, USA
- 23.09.16, Ki-67 in Neuroendocrine GEP Tumours, 2. International Interdisciplinary Endocrine Surgery Conference, Recent Progress in Endocrine Surgery, Bergen, Norway
- 04.11.16, Zytologie der Schilddrüse, Curriculum der Universitätsklinik für Diabetologie, Endokrinologie, Ernährung und Metabolismus, Inselspital, Bern

Tilman Rau
- 15–17.06.2016, Gemischter Polyp des Kolorektums oder sessil serratiertes Adenom mit Dysplasien? Ein molekularpathologischer Klärungsversuch im Verbund, 44. Jahrestagung der Gesellschaft für Gastroenterologie in Bayern e.V., Straubing
- 15.12.16, Warum wir uns für den PAM50 entschieden haben. Frühes Mammakarzinom: Unklarheiten und Kontroversen, Ärztefortbildung Brustzentrum Universitätsklinik für Frauenheilkunde, Bern
- 21.05.16, Rückschlüsse aus Epigenetik und Genetik auf die Diagnostik serratierter colorektaler Läsionen, 100. Jahrestagung der Deutschen Gesellschaft für Pathologie, Berlin

Tschan Mario
- 09.09.16, Non-canonical autophagy in retinoic acid therapy?, 9th Swiss Apoptosis Meeting, Bern
- 28.09.16, ALK inhibition and autophagy responses in EML4-ALK positive NSCLC, 7th Meeting of the European Research Initiative on ALK-related malignancies (ERIA), Vienna
- 17.10.16, Autophagy in retinoic acid therapy of acute myeloid leukemia, Cancer Research Center of Toulouse (CRCT), Toulouse, France

Vassella Erik
- 23.03.16, 2nd symposium of the DCR research cluster for lung development, regeneration and disease, university of Bern, 2nd symposium of the DCR research cluster for lung development, regeneration and disease, Bern
- 19.05.16, Molecular profiling of the lung adenosquamous carcinoma: hybrid or genuine type?, 100. Jahrestagung der Deutschen Gesellschaft für Pathologie
- 07.09.16, Role of microRNAs in temozolomide resistance of g lioblastoma, Neurocentro della Svizzera Italiana

Zlobec Inti
- 10.11.16, Molecular pathology update in colorectal cancer, Annual Meeting of the Swiss and Austrian, Societies of Pathiology, Vienna
- 15.10.16, Tumor budding, Annual Meeting of the Belgian Society of Pathology, Ghent
- 26.10.16, Tumor microenvironment in colorectal cancer: application to ngTMA, Annual Meeting of the European Society of Pathology, Köln
- 25.05.16, COMPATH, Seminar Ecole Polytechnique de Lausanne, Lausanne
- 23.05.16, Application of digital pathology to the construction of high-quality tissue microarrays: the next-generation tissue microarray (ngTMA) approach, Faculty Retreat of the Swiss Cancer Center Lausanne (SCCL)
- 29.04.16, ut-offs or continuous scale for tumor budding score, International Tumor Budding Consensus Conference
- 09.03.16, Why we need to visualize, digitize and analyse the tumor microenvironment in colorectal cancer, Seminar Institute of Pathology, HUG, Geneva
- 22.01.16, Why we need to visualize, digitize and analyse tumor budding and the tumor microenvironment in colorectal cancer, Visiopharm User Group Meeting, Copenhagen

Zysset Daniel
- 06.10.16, A pro-inflammatory fine-tuner regulates atherosclerosis, Seminar, CSL Behring, Bern

5 Drittmittel

Berezowska Sabina
- Bernische Krebsliga, 28.08.14–21.01.16, EUR 32'000

Bill (Schläfli) Anna
- Bernische Krebsliga, 2016–2017, CHF 80'000
- UniBE Initiator Grants, 2016–2017, CHF 16'150

Diamantis Evanthia
- Stiftung für klinisch-experimentelle Tumorforschung, 01.05.16–31.07.18, CHF 60'000
- Werner und Hedy Berger-Janser Stiftung, 25.07.13–31.12.17, CHF 33'000

Dislich Bastian
- Bernische Krebsliga, 01.10.15–28.02.17, CHF 60'000

Freigang Stefan
- Fondation J. Dürmüller-Bol, 2014–2017, CHF 27'000
- UniBE Research Foundation, 2014–2017, CHF 15'000
- UniBE-ID Grant, 2016–2018, CHF 150'000
- Vontobel-Stiftung, 2014–2017, CHF 120'000
- SNF 310030_152872, 2015–2017, CHF 510'000
- SNF 316030_157702, 2014–2016, CHF 240'000

Freigang Stefan/Guenat Olivier
- Swiss Lung Liga, 2017–2019, CHF 162'000
- 3R Research Foundation, 2016–2017, CHF 138'000

Krebs Philippe
- Fondazione San Salvatore, 2016–2017, CHF 120'000
- Marie Curie Career Integration Grants (CIG), 2012–2017, EUR 100'000
- Olga Mayenfisch Foundation, 2015–2016, CHF 23'000
- Vontobel Foundation, 2015–2016, CHF 130'000
- SNSF 163086, 01.04.16–31.03.19, CHF 525'000

Krebs Philippe/Banz Yara
- Swiss Cancer League , 2015–2017, CHF 124'350

Krebs Philippe/Mager Lukas
- Foundation Johanna Dürmüller-Bol, 2015–2016, CHF 20'000

Langer Rupert/Tschan Mario
- Krebsforschung Schweiz, 01.04.16–30.04.18, CHF 216'000
- KFS-3700-08-2015, 2015–2017, CHF 214'000

Lugli Alessandro/Kölzer Viktor
- Krebsforschung Schweiz, Bern, 01.01.14–31.03.16, CHF 233'700

Mager Lukas
- Gertrud-Hagmann-Stiftung, 2015–2017, CHF 241'566

Marinoni Ilaria
- Desirée and Niels YDE Foundation, 01.12.16–30.11.19, CHF 50'382
- Stiftung klin.exp.Tumorforschung, 01.06.15–31.05.18, CHF 83'000
- SNF, 01.04.16–31.03.18, CHF 205'196

Mueller Christoph
- SNF 33CS30_134274 / 1, 2016–2018, CHF 200'000
- SNF CRSII3_136286 / 1, 2015–2016, CHF 456'531
- SNF 310030_138392 /1, 2011–2016, CHF 623'000
- SNF 310030_170084, 2016–2019, CHF 525'000

Noti Mario
- FreeNovation, 2016–2018, CHF 180'000
- Novartis Foundation, 2015–2016, CHF 60'000
- Olga Mayenfisch Stiftung, 2015–2016, CHF 25'000
- SNF PZ00P_154777/1, 2016–2018, CHF 599'156

Perren Aurel
- Krebsforschung Schweiz, 01.08.14–31.08.17, CHF 286'900

Perren Aurel / Krebs Philippe
- SNSF 144236, 2012–2016, CHF 395'391

Schenk Mirjam
- Hofschneider Stiftung experimentelle Biomedizin, 2016–2019, CHF 763'000
- Stiftung Klinisch Experimentelle Tumorforschung Bern, 2016–2019, CHF 150'000
- Werner Hedy Berger-Janser, 2016–2018, CHF 110'000

Schmitt Anja
- Bernische Krebsliga, 01.10.12–31.12.16, CHF 76'000

Sokol Lena/Kölzer Viktor
- Bernische Krebsliga, 01.06.15–31.05.16, CHF 60'000

Tschan Mario
- Giovani Ricercatori Fellowship, 2016–2016, CHF 3'500
- KFS KFS-3409-02-2014, 2014–2017, CHF 390'000
- Stiftung Klin. Exp. Tumorforschung, 2015–2017, CHF 81'000
- SNSF 31003A_143739, 2012–2016, CHF 390'000

Vassella Erik
- Bernische Krebsliga, 2014–2016, CHF 70'000
- R' Equip 31630_164097, 2015–2016, CHF 73'147

Zlobec Inti
- Mach-Gaensslen Foundation PI, 2014–2016, CHF 39'000
- Tumorforschung Bern, 2014–2016, CHF 30'591
- Werner und Hedy Berger Janser Stiftung, 2015–2018, CHF 145'620
- SNF CO-PI 31003A-166578/1, 2016–2019, CHF 305'040
- SNF 320030_163342, 2015–2018, CHF 525'000

6 Preise, Ernennungen, Auszeichnungen

Berezowska Sabina
- 13.04.16: Travel Grant
  6th European Lung Cancer Conference
  ESMO, Genf

Keller Manuel
- 04.12.16: Young Investigator Communication Workshop Award
  17th World Conference on Lung Cancer
  IASLC, Wien

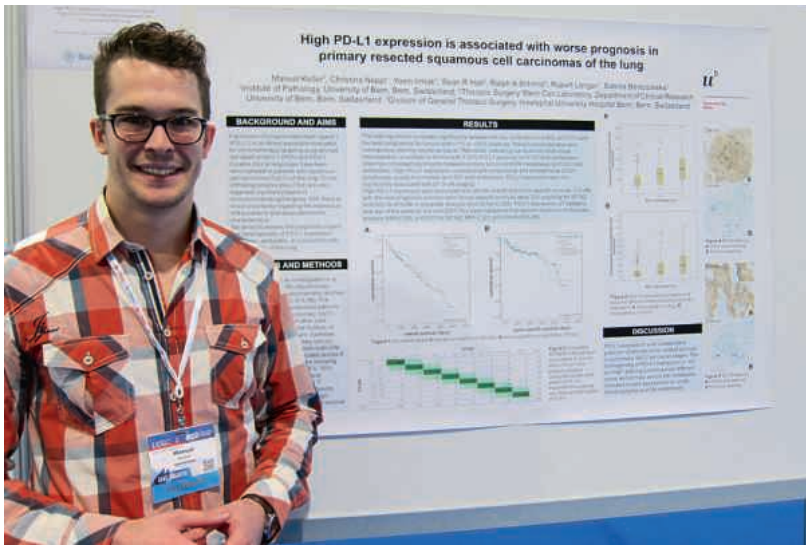
Müller Christoph
- 19.04.16: Swiss Society of Allergology and Immunology, Honorary Member
  Annual Meeting SSAI 2016
  SSAI, Montreux

Mager Lukas
- 2016: BIC prize – best paper – 2015
  Bern Immunology Club, Bern
- 2016: Dr. Lutz Zwillenberg-Preis
  University of Bern, Bern

Niklaus Monique (supervisor: Rupert Langer)
- 10.11.16: Second poster prize
  3rd joint meeting of the Swiss and Austrian Societies of Pathology 2016, Vienna
  Swiss and Austrian Societies of Pathology, Vienna

Pfizer Forschungspreis 2017.

Lutz Zwillenberg Prize, Lukas Mager.



Young Investigator Communication Workshop.

>>> Studentische Lehre

Der Einsatz der Pathologie besteht in Vorlesungen und Kursen für die Studenten der Humanmedizin, der Zahnmedizin, des Studienganges Biomedical Sciences und der Zellbiologie (Cell Biology), wo verschiedenste Vorlesungen, Kurse und Praktika über Histologie, Allgemeine und Spezielle 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 Sciences (GCB) involviert.

Die Lehrveranstaltungen 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.

Im Studiengang Humanmedizin begleitet das Fach Pathologie die Studierenden während ihrer gesamten klinischen Ausbildung vom 3. bis zum 6. Studienjahr. In dieser Zeit erhalten sie 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 «digitale Histologie-Schnittkasten» erlaubt es den Studierenden, die histologischen Schnittpräparate virtuell zu mikroskopieren, die dann später im Histologiekurs zusammen mit den jeweiligen Fachdozenten besprochen werden.

Die Grundlagen der Allgemeinen Pathologie lernen die Studierenden im letzten Jahr des Bachelor-Teils des Medizinstudiums 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 der entsprechenden wesentlichen morphologischen Veränderungen behandelt werden. Daneben ist die Pathologie auch an zahlreichen PBL-Tutoriaten des 1. bis 3. Studienjahrs beteiligt. In einem Vertiefungsseminar «Pathologie» haben die Studierenden zudem die Gelegenheit, das Tätigkeitsbild des Pathologen hautnah im Rahmen von Führungen durch das Institut kennenzulernen.

Im Masterstudiengang, hier zunächst im 4. Studienjahr (Einführungskurs 2) und im 5. Studienjahr (Schlusskurs 1) wird das erlangte Wissen 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 wöchentliche Autopsiedemonstrationen statt, in denen anhand aktueller Fallbeispiele die aktive Erarbeitung pathophysiologischer Zusammenhänge und Sequenzen verschiedenster Krankheiten im Vordergrund steht. Zudem wird unser Institut bei den Studierenden als sehr guter Ort angesehen, um im Rahmen einer Masterarbeit ersten Kontakt mit wissenschaftlichem Arbeiten zu erhalten, und auch später wird die Möglichkeit wahrgenommen, dieses in einer folgenden Dissertation fortzusetzen.

Studiengang Humanmedizin, 3. Jahr		
Vorlesungen	Kurse	Fakultativ
Allgemeine Pathologie innerhalb von Themenblöcken	Fachpraktikum	Vertiefungsseminar
	PBL (Problembasiertes Lernen)	
Studiengang Humanmedizin, 4. und 5. Jahr		
Vorlesungen	Kurse	Fakultativ
Spezielle Pathologie	Makrokurs (4. Jahr)	Masterarbeit
	Histologiekurs (4./5. Jahr)	
Vorlesungen	Autopsiedemo (4./5. Jahr)	
Studiengang Humanmedizin, 6. Jahr		
Klinisch-pathologische Konferenz, Querschnittsvorlesungen		Wahlpraktikum

Im 6. Studienjahr ist die Pathologie im Schlusskurs 2 als fachübergreifende Disziplin an mehreren interdisziplinären Vorlesungen beteiligt und behandelt auch eigene Schwerpunkte, wie die «Klinisch Pathologische Konferenz», die fest im Stundenplan verankert ist.

Studierende, die ihre Kenntnisse im Fach Pathologie vertiefen wollen oder sich für eine spätere Fachausbildung in diesem Fach interessieren, können im Rahmen des Wahlstudienjahrs 1–2 Monate auf der Pathologie verbringen. Hier durchlaufen sie 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.

Für die Studierenden der Zahnmedizin gibt es im 3. Jahr eine Vorlesungsreihe «Pathologie», in der sowohl die Allgemeine Pathologie als auch die Spezielle Pathologie einzelner wichtiger Organsysteme abgebildet ist. Im 5. Jahr werden spezielle orale Pathologien in weiteren Vorlesungen behandelt.

Studiengang Zahnmedizin Vorlesungen	
3. Jahr	**5. Jahr**
Allgemeine und Spezielle Pathologie	Spezielle Pathologie des Mund- und HNO-Bereichs

Die Mitarbeiter der Experimentellen Pathologie sind ausserdem an der Ausbildung der Studenten der philosophisch-naturwissenschaftlichen Fakultät beteiligt. Diese Lehrveranstaltungen erfolgen nach einem anderen Konzept; hier werden Kurse im Modulformat angeboten, sodass Studenten verschiedener Fächer gleiche Vorlesungsreihen besuchen.

1. Seminarreihen

- Journal Club
  (Gruppen des Instituts für Pathologie, monatlich)
- Joint Immunology Group Meeting
  (Institut für Pathologie, monatlich)
- Joint Immunology Group Meeting
  (Gruppen der Universität Bern, monatlich)
- Bern Immunology Club
  (Vorträge externer Seminargäste, monatlich)
- DKF Research Conference (monatlich)
- Bern Cancer Research Cluster (BCRC),
  (Krebsforschungsgruppen (19) der Universität Bern, wöchentlich)

2. Vorlesungsreihen im Fachgebiet Pathologie

Im Rahmen der philosophisch-naturwissenschaftlichen Fakultät werden von Dozenten des Instituts folgende Vorlesungsreihen im Modulformat angeboten und koordiniert:

2.1. General Pathology and Histology

Coordinator: Philippe Krebs

Affiliation of lecturers: Institute of Pathology und Institute of Anatomy, UniBe
Target students: BSc, MSc and PhD students in Cell Biology and Biomedical Sciences

General overview of the course:

Cellular mechanisms of pathology
Histology of normal tissue
Molecular mechanisms of pathology
Pathology of specific organ systems: – theoretical classes – practical classes

2.2. Selected Topics in Molecular Pathology

Coordinator: Erik Vassella

Affiliation of lecturers: Institute of Pathology, UniBe, DKF/Inselspital, Institute of Pathology, UniBas
Target students: BSc, MSc and PhD students in Cell Biology or Biomedical Sciences

General overview of the course:

Methods and animal models of pathology
Molecular mechanisms of pathology
Tumor biology and molecular oncology
Molecular diagnostics

2.3. Cellular and Molecular Immunology

Coordinator: Christoph Müller

Affiliation of lecturers: Institute of Pathology, DKF/Inselspital, Vetsuisse-Fakultät
Target students: BSc, MSc and PhD students in Cell Biology or Biomedical Sciences

General overview of the course:

Methods and animal models in immunology research
Specific immune cell subsets in health and disease
Molecular mechanisms of inflammation
Molecular aspects of vaccine development

3. Weitere Lehrveranstaltungen

Dozenten der Experimentellen Pathologie unterrichten zudem in Lehrmodulen, die von anderen Instituten koordiniert werden, wie im «Practical Course in Immunology» des Instituts für Zellbiologie, in Seminarveranstaltungen im Gebiet Tumorpathologie, in der Vorlesungsreihe «Blut und Abwehr» im 2. Studienjahr Medizin und im dazugehörenden Lerngruppenunterricht (PBL). Weiterhin sind Dozenten des Instituts im Rahmen von 3- bis 4-wöchigen experimentellen Praktika an der Ausbildung von Studenten der Studienrichtungen «Cell Biology» und «Biomedical Sciences» beteiligt.

>>> Weiterbildung

Ärztliche Weiterbildung im 21. Jahrhundert soll nicht nur den Nachwuchs für den Fachbereich garantieren, sondern Perspektiven schaffen, die zukunftsweisend sind. Sie soll auch dem Strukturwandel und dem jährlich steigenden Spezialisierungsdrang Rechnung tragen. Zusätzlich soll sie modern, attraktiv und motivierend, gleichzeitig aber auch bedarfsgerecht sein und die notwendigen Kompetenzen ökonomisch vermitteln. Strategisches Ziel unseres Pathologie-Weiterbildungsprogramms ist, herausragende Diagnostiker, Forscher, und für die Zukunft offene Pathologen auszubilden.

Unser Weiterbildungsprogramm stellt die klinisch orientierte Funktion der Pathologie in den Vordergrund. Es verfügt über **definierte Abschnitte (Module),** welche auch aufgrund individueller Bedürfnisse der Assistierenden unterschiedlich gestaltet werden können. So entsteht eine individuelle, zeitlich und inhaltlich flexible Struktur.

Das Modul 1 schafft einen Einblick in die Pathologie, vermittelt das Basiswissen und ist sowohl als Einstieg für Fachanwärter direkt nach dem Staatsexamen (Erstjahr-Pathologieassistenten) als auch für Assistenzärzte mit anderen Fachrichtungen, welche ein Jahr Pathologie als Fremdjahr absolvieren möchten, geeignet. Die Dauer des Moduls 1 beträgt 12 Monate und kann je nach Erfahrung und Lernkapazität verkürzt werden. Die Reihenfolge innerhalb des Moduls ist nicht vorgegeben, so kann z.B. Themenblock 1B oder 1C vor 1A absolviert werden.

Weiterbildungsmodule.

Modul 1

- **1A: Autopsie 1**
- **1B: Zuschnitt 1**
- **1C: Histo 1**

- **Mini-CEX**
- **DOPS**

12 Monate

Modul 2

- **2A: Histo 2**
- **2B: Schnellschnitte**
- **2C: Zuschnitt 2**
- **2D: Autopsie 2**
- **2E: Tumorboards**
- **2F: Spezialgebiete (KM-, Nieren-, Leberbiopsien etc., fakultativ)**

- **Mini-CEX**
- **DOPS**

36 Monate

Modul 3

- **3: Zytologie**
- **nach Bedarf Zuschnitt**
- **Tumorboards**

- **Mini-CEX**
- **DOPS**

6 Monate

Schlussprüfung:
6 Monate vor der FMH-Prüfung

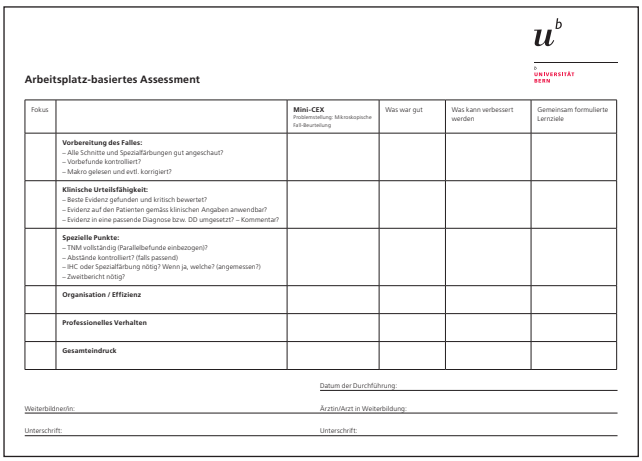
Modul 4

- **4A: Mol Path**

- **4B: Forschung**
- **TRU**
- **ExPath**

- **fakultativ**

Modul 2 mit flexiblen Untereinheiten.



Arbeitsplatz-basiertes Assessment

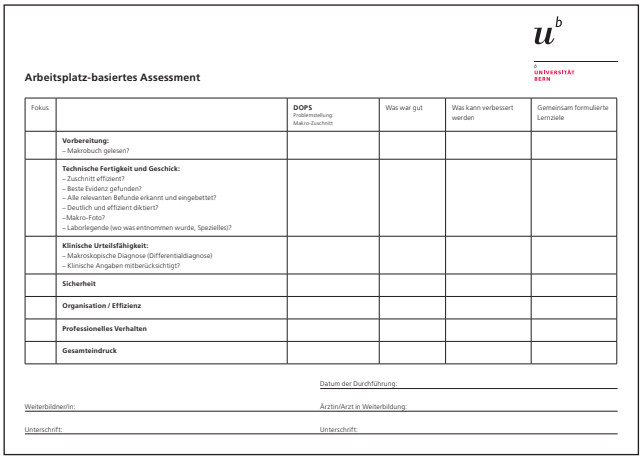
Fokus		**Mini-CEX** Problemstellung: Mikroskopische Fall-Beurteilung	Was war gut	Was kann verbessert werden	Gemeinsam formulierte Lernziele
	Vorbereitung des Falles: – Alle Schnitte und Spezialfärbungen gut angeschaut? – Vorbefunde kontrolliert? – Makro gelesen und evtl. korrigiert?				
	Klinische Urteilsfähigkeit: – Beste Evidenz gefunden und kritisch bewertet? – Evidenz auf den Patienten gemäss klinischen Angaben anwendbar? – Evidenz in eine passende Diagnose bzw. DD umgesetzt? – Kommentar?				
	Spezielle Punkte: – TNM vollständig (Parallelbefunde einbezogen)? – Abstände kontrolliert? (falls passend) – IHC oder Spezialfärbung nötig? Wenn ja, welche? (angemessen?) – Zweitbericht nötig?				
	Organisation / Effizienz				
	Professionelles Verhalten				
	Gesamteindruck				

Datum der Durchführung:

Weiterbildner/in: Ärztin/Arzt in Weiterbildung:

Unterschrift: Unterschrift:

Mini-CEX-Formular.



Arbeitsplatz-basiertes Assessment

Fokus		**DOPS** Problemstellung: Makro-Zuschnitt	Was war gut	Was kann verbessert werden	Gemeinsam formulierte Lernziele
	Vorbereitung: – Makrobuch gelesen?				
	Technische Fertigkeit und Geschick: – Zuschnitt effizient? – Beste Evidenz gefunden? – Alle relevanten Befunde erkannt und eingebettet? – Deutlich und effizient diktiert? –Makro-Foto? – Laborlegende (wo was entnommen wurde, Spezielles)?				
	Klinische Urteilsfähigkeit: – Makroskopische Diagnose (Differentialdiagnose) – Klinische Angaben mitberücksichtigt?				
	Sicherheit				
	Organisation / Effizienz				
	Professionelles Verhalten				
	Gesamteindruck				

Datum der Durchführung:

Weiterbildner/in: Ärztin/Arzt in Weiterbildung:

Unterschrift: Unterschrift:

DOPS-Formular.

Das Modul 2 stellt den Hauptkorpus der spezifischen Pathologie-Ausbildung dar und dauert 36 Monate, kann aber je nach Erfahrung und Lernkapazität verkürzt oder verlängert werden. Die Reihenfolge, der Inhalt und die Schwerpunkte können und sollen flexibel gestaltet werden. Teilnahme an klinisch-pathologischen Konferenzen und Tumorboards ebenfalls Inhalt dieses Moduls. Die Absolvierung der Themenblöcke setzt das Erfüllen der Mindestanforderungen der FMH voraus. Der Einblick in die Diagnostik von hoch spezialisierten Gebieten, wie die Knochenmark-, Nieren- und Leberbiopsien, ist prinzipiell möglich und wird je nach Interesse und Kapazitäten organisiert.

Es wird empfohlen, dass die Anmeldung für die Facharztprüfung erst nach Absolvierung aller obligatorischen Themenblöcke der Module 1 bis 3 erfolgt.

Das Modul 3 verkörpert die Ausbildung im Bereich Zytologie und kann mit dem Modul 4A (Molekularpathologie) kombiniert werden.

Das Modul 4A bietet einen Einblick in die modernen diagnostischen Methoden der Molekularpathologie, einschliesslich moderner NGS-Technologie, die für die Patienten therapierelevant sind.

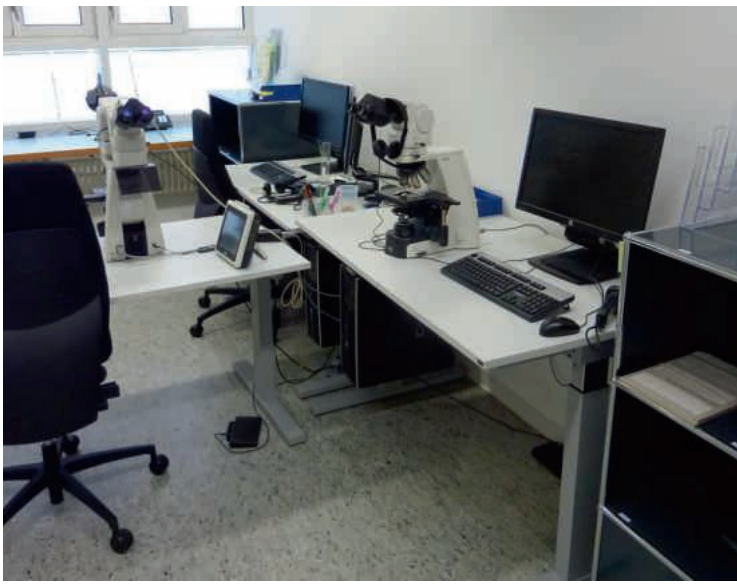
Themenblock 4B des Moduls 4 ist fakultativ, er gibt den Assistenzärzten die Möglichkeit, sich näher mit modernen Forschungsmethoden auseinanderzusetzen und an existierenden Forschungsprogrammen der Translational Research Unit und/oder der Experimentellen Pathologie teilzunehmen.

In das Weiterbildungsprogramm sind regelmässige Zwischenevaluationen (arbeitsplatzbasierte Assessments) als Etappenkontrollen integriert. Evaluationsmethoden wie Mini-CEX und DOPS werden als essenzieller Bestandteil der Weiterbildung und strukturiertes Rückmeldungsinstrument betrachtet. Aus der Zwischenbilanz erfolgt eine neue Zielvereinbarung.

Mini-CEX werden zweimal jährlich durchgeführt. Dabei wird der Assistenzarzt bei der mikroskopischen Fallabgabe, unter Beachtung folgender spezieller Punkte, beobachtet:

DOPS (ebenfalls zweimal jährlich) wird bei der makroskopischen Präparatverarbeitung eingesetzt. Dabei werden die praktischen Fertigkeiten des Assistenzarztes direkt beobachtet. Es folgt die Erteilung eines relevanten Feedbacks.

Im Institut für Pathologie der Universität Bern wird die Assistentenweiterbildung in der Routinediagnostik («sign-out») in für diesen Zweck und für die bessere Dienstleistung speziell ausgestatteten **«sign-out rooms»** durchgeführt. Diese erlauben die ungestörte Durchführung der Routinediagnostik unter optimalen Bedingungen. Zudem verstärken sie das «Team-Gefühl» zwischen Facharzt und Assistenzarzt, erhöhen die Motivation, dienen der schnelleren und besseren Dienstleistung und bieten täglich reichlich Gelegenheit für Teaching und Evaluation.



Einrichtung eines Diagnostikraums.

>>> Fortbildung

Donnerstagsseminare 2016

	Titel	Referent/-in
18.02.	Impact of regulatory T cells and infection on colitis-associated colon cancer	Prof. Dr. Astrid Westendorf Departement Infektionsimmunologie, Institut für Medizinische Mikrobiologie, Universitätsklinikum Essen
10.03.	Workshop Metabolism/Seahorse	PD Dr. St. Freigang
15.03.	Perturbing the balance between glucose and lipid metabolism by targeting Slfn2: a novel approach for treating T cell leukemia	Michael Berger, PhD The Hebrew University of Jerusalem
17.03.	The transcriptional regulator FUBP1: important for HSCs and attractive as a target for HCC therapy	Prof. Dr. Martin Zörnig Group Leader, Institute for Tumor Biology and Experimental Therapy, Frankfurt
24.03.	Adeno-Karcinoma, MANEC and NEC: different entities or a biological continuum?	Prof. Marco Volante
31.03.	Molekulares Verständnis der Entstehung neuroendokriner Pankreastumore – die Rolle der Hypoxie	PD Dr. A. Schmitt
07.04.	Infektionen mit Pilzen und Mycobakterien: vom Verdacht zur Diagnose. Möglichkeiten der Infektiologie/Mikrobiologie und Erwartungen an die Pathologie	PD Dr. Stefan Zimmerli Universitätsklinik für Infektiologie, Inselspital Bern
14.04.	A highway to the cell: cell entry routes of exosomes as a novel paradigm for therapeutic RNA delivery	PhD Nicole Meisner-Kober Novartis NIBR
21.04.	Cancer cells and stromal cells: partners in crime	Dr. Laurine Verset Hôpital Erasme, Cliniques universitaires de Bruxelles
28.04.	Epigenetics of pNET	Prof. Chrissie Thirlwell Kings College, London
26.05.	Hi-tech technical devices at the Institute	Ph. Krebs and group
02.06.	Interplay between 3q26 genes regulates glioma invasion	PD Jean-Louis Boulay Department of Biomedicine, Universität Basel
09.06.	Osteopetrose-morphologische Befunde bei seltener Knochenerkrankung	Prof. Dr. Josef Zustin Royal National Orthopaedic Hospital, Stanmore, UK
07.07.	Workshop 3D cell culture and autophagy	Prof. M. Tschan and group
25.08.	Informationsveranstaltung Support Platforms ExPath	Prof. M. Tschan
01.09.	Generation of cross-presenting dendritic cells for immunotherapy in melanoma	Mirjam Schenk, Ass.-Prof. Institut für Pathologie, Universität Bern
09.09.	Digitale Pathologie	Dr. Christian Münzenmayer Fraunhofer Institut METEAN
15.09.	Genomic characterization of basal cell carcinoma of the skin	Dr. Sergey Nikolaev, PhD Responsable de bioinformatique clinique, HUG – Hôpitaux universitaires de Genève
23.09.	The Pathologist's Role in Identifying Patients with Hypersensitivity Pneumonia	Prof. Kristine E. Konopka MD, Department of Pathology, University of Michigan

	Titel	**Referent/-in**
06.10.	Workshop Tumor Budding	Prof. I. Zlobec and group
27.10.	Histopathology in the digital age	Peter Caie School of Medicine, Medical and Biological Sciences, North Haugh, St Andrews, UK
17.11.	Deciphering dysregulated ubiquitylation in cancer: lessons learned from SPOP	Prof. Theurillat Institute of Oncology Research, Bellinzona, Department of Fundamental Oncology, University of Lausanne
08.12.	Hepatocellular adenoma: a tumor in search of a definition	Prof. Sanjay Kakar Dept of Pathology, UCSF School of Medicine, USA
15.12.	T cells in cancer: from immunotherapy to personalized vaccination	Prof. Lukas Flatz, MD Institute of Immunobiology, Kantonsspital St. Gallen, and University of Zurich

>>> Im Fokus: vom Lean Management zu einem neuen Labor

Histologielabor, Sicht vom Bereich Färben in Richtung Annahme (Bild: Athena 35).

Der Grundstein wurde im Jahr 2010 von der Institutsleitung mit der Einführung des Lean Managements in der Histologie gelegt. Dieses Instrument unterstützt die Vereinfachung von Prozessen und führte in Folge zu einem klaren Umbaukonzept. Der Neubau unterstützt heute die Abläufe im Labor und in der Diagnostik optimal. Anfänglich legte eine Biopsie von der Probeannahme bis zur Diagnose 543 Meter zurück, heute sind es lediglich noch 62 Meter. Trotz weniger Raum können wir heute mehr Proben verarbeiten. Das nationale und das internationale Interesse sind sehr gross.

Der ganze Umbau erfolgte bei laufendem Betrieb, was eine erhöhte Anforderung an die interne Planung und die Nutzer stellte. Die Nutzungsrochade erfolgte, indem die Büros im ersten Obergeschoss vor dem Baubeginn des Labors geleert wurden. Zudem wurden die Mitarbeitenden in die Etagen Erdgeschoss und drittes bis sechstes Obergeschoss verdichtet.

Nach der Fertigstellung und dem Umzug des Labors im März 2016 wurde das ehemalige Labor zum Bürotrakt für die Ärzte umgebaut.

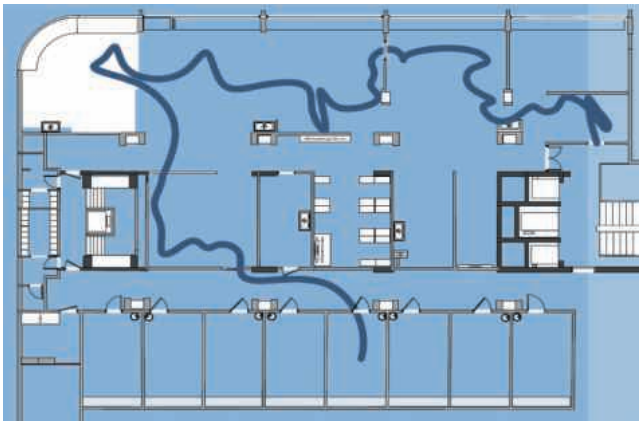
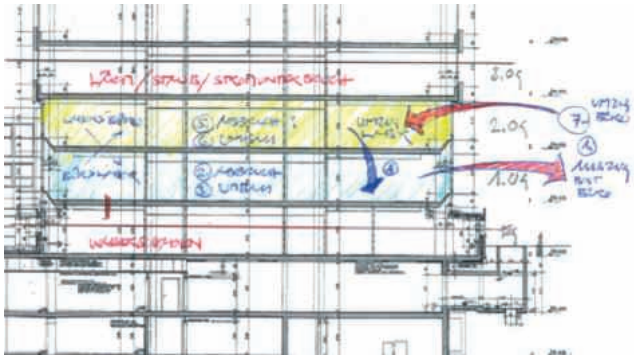


Tabelle: 62 Meter Weg für eine Probe bis zur Diagnose.



Umbau während Betrieb mit Rochaden.

Interview mit Prof. Dr. med. A. Lugli, Stellvertretender Chefarzt, Leiter Klinische Pathologie am Institut für Pathologie

Warum ein neues Labor?
Die Klinische Pathologie steht im Dienste der Patientinnen und Patienten. Folglich ist es uns sehr wichtig, speditiv richtige Diagnosen zu stellen. Um die Geschwindigkeit ohne Qualitätsverlust zu optimieren, existieren verschiedene Instrumente: Die Institutionsleitung entschied sich für das «LEAN-Management». Die Arbeitsprozesse wurden analysiert und optimiert, doch trotz guten Ergebnissen stiess man mit der bestehenden Laborinfrastruktur klar an die Grenzen.

Hat LEAN den Umbau beeinflusst?
Die Arbeitsprozesse zeigten auf, wo Mängel waren. Einschränkend waren zum Beispiel die Wände zwischen den einzelnen Laboreinheiten. Man braucht künftig keine Wände mehr, sondern Strassen. Vergleichen wir es mit der Vision eines Explorers, welcher sagt: «Ich bin sicher, dass es auf der anderen Seite des Ozeans Land gibt, aber ich muss es beweisen können, und dazu benötige ich das richtige Schiff.» Wir wussten, wohin wir wollten, aber wir hatten nicht das richtige Labor. LEAN hat uns geholfen, das Labor so zu bauen, dass wir auch in Zukunft offen und flexibel sein können. Wir haben nun viel Freiheit, sodass wir künftig weitere Optimierungen integrieren können, ohne gleich wieder umbauen zu müssen.

Was ist der Unterschied zum alten Labor?
Durch die Einzelräume im alten Labor war die Kommunikation erschwert. Das neue Labor kann man sehr gut überblicken und somit den gesamten Arbeitsprozess auf einen Blick erfassen. Kommunikation und Unterstützung sind nun viel besser möglich. Zusätzlich darf man nicht vergessen, dass der Umbau noch einen Diagnostiktrakt beinhaltet. Dieser ist meines Erachtens einmalig, denn er verfügt über sechs Diagnostikräume und ist vergleichbar mit einem OP-Trakt, welcher einen guten Service für Patientinnen und Patienten bieten kann. Vorher waren alle Ärztinnen und Ärzte im gesamten Haus verteilt. Mit dem Umbau wurde eine räumliche Nähe realisiert, wo nun die Schnittstelle von Labor und Ärzteschaft gegeben ist.

Ein Diagnostikraum.

Wie erlebten Sie als Abteilungsleiter diese Umbauphase?
Wir wurden von unserem Logistik und unserem Support sowie vom Kanton und von der Uni Bern (unsere übergeordneten Stellen) optimal unterstützt und die Mitarbeitenden wurden in der Umbauphase sehr gut begleitet.

Wie verlief der Umzug des Labors für Sie?
Ich war positiv überrascht, dass die beteiligten Mitarbeitenden sehr motiviert waren. Die Personen freuten sich, das neue Labor zu beziehen. Was extrem begrüsst wurde und immer noch wird, ist die Helligkeit des Labors. Laut vielen Besuchern sehe das Labor wie eine NASA-Station aus, was mit der Beleuchtung und der grossen Fensterfront zusammenhängt.

Wurden Ziele des LEAN-Managements erreicht?
Teilweise ja, aber wir verstehen unter Lean Management einen kontinuierlichen Verbesserungsprozess. Zurzeit optimieren wir weiter und bereiten uns auf die kommende Akkreditierung vor.

Hat der Umbau Einfluss auf Kennzahlen gehabt? Beispielsweise auf Durchlaufzeiten?
Ja, das neue Labor optimiert infrastrukturell die Durchlaufzeiten. Die Durchlaufzeiten sind jedoch so multifaktoriell, dass wir nicht den Schluss ziehen können, dass wir wegen des Umbaus schneller geworden sind, sondern dass der Umbau den Mitarbeitenden erlaubt, besser zu arbeiten. Im Vergleich zur Zeit vor «LEAN» wurden die Durchlaufzeiten und der Weg einer Gewebsprobe während der Verarbeitung verkürzt. Labor, Schnittstelle und Diagnostiktrakt sind so angeordnet, dass sie von oben wie ein «H» aussehen. Durch diese Anordnung sind wir schneller.

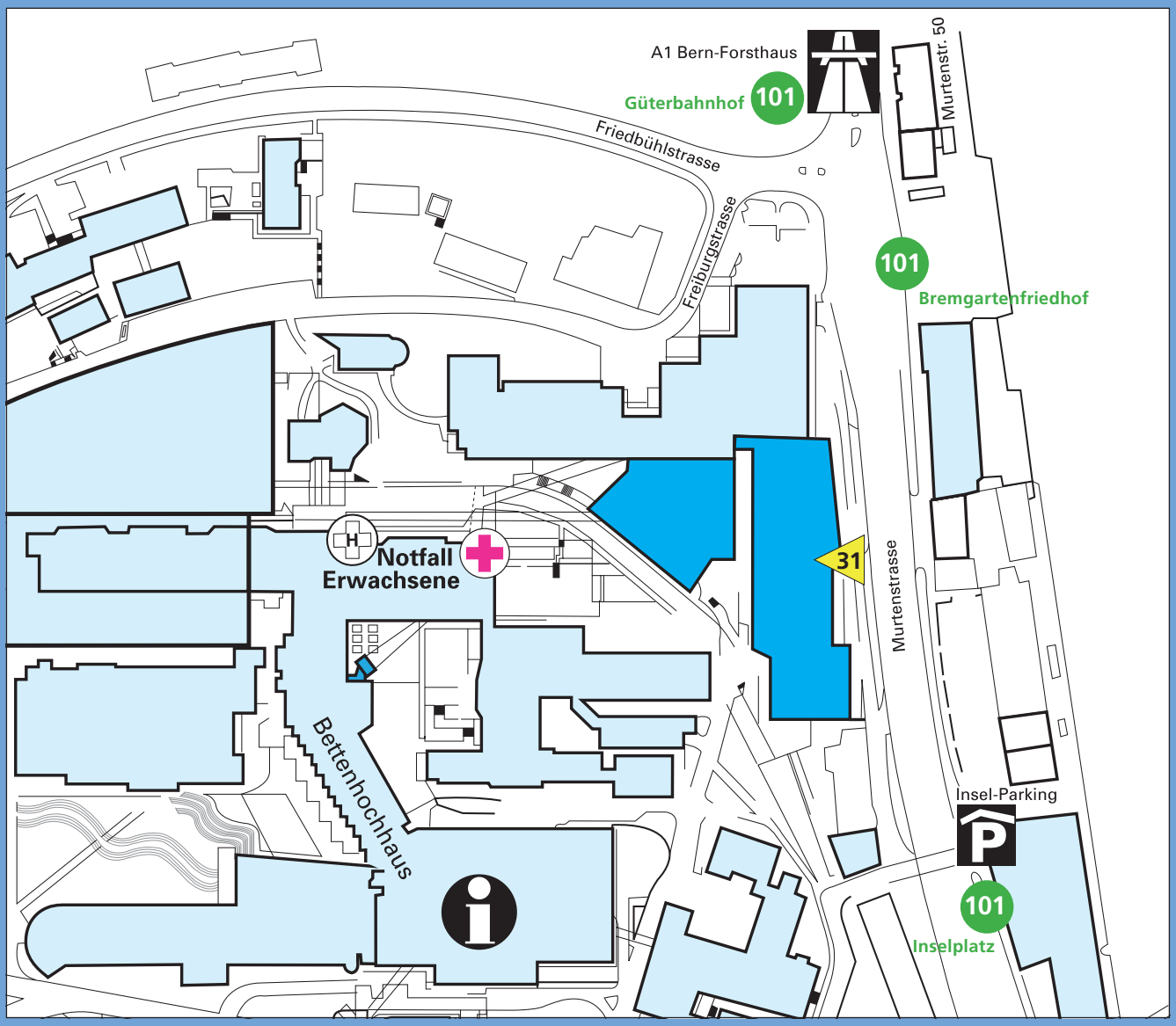
Haben Sie heute Ihr Traumlabor?
Nein, es ist zu 99% ein Traumlabor. 100% kann und darf es nie sein.

Was würden Sie Kolleginnen und Kollegen raten?
Die Grundprinzipien der Führung einhalten: Wirklich zuerst die strategische Ebene gut ausarbeiten, dann die Konklusionen auf operativer Ebene umsetzen und schlussendlich die Detailebene angehen. Leadership und Kulturwechsel sind zwei Keywords, welche man nicht unterschätzen sollte. «LEAN löst keine Probleme und ist auch keine Philosophie, LEAN ist lediglich ein Arbeitstool.»

Was sagen Sie zur «Visibility», national und international?
Diese ist enorm: Herr Perren und ich werden kontinuierlich zu Vorträgen und Kongressen eingeladen. Ich glaube, dass unsere Visibility extrem gestiegen ist, und das ist allen beteiligten Mitarbeitenden unseres Instituts besonders zu verdanken.

G. Suter, Betriebsprojektleiter

>>> Situationsplan



Universität Bern
Institut für Pathologie
Murtenstrasse 31, CH-3008 Bern
Telefon +41 31 632 32 11/12
Fax +41 31 632 49 95
www.pathology.unibe.ch