UNIVERSITÄT
BERN

Institut für Pathologie

www.pathology.unibe.ch

Jahresbericht 2020

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>>> Das Wichtigste in Kürze

Liebe Leserin, lieber Leser

Herzlich willkommen bei der Lektüre des Jahresberichtes des Instituts für Pathologie 2020! Als akademisches Zentrum sind wir besonders stolz, dass Prof. Dr. Rupert Langer auf das Ordinariat in Linz berufen wurde, und dass PD Dr. Sabina Berezowska und PD Dr. Ekkehard Hewer auf neu geschaffene Extraordinariate in Lausanne berufen wurden. Allen Dreien gratuliere ich zu diesem Erfolg.

Die bei uns in Bern entstandenen Lücken konnten wir bis 2021 mit jungen akademisch motivierten Pathologen und Pathologinnen auffüllen, wie Sie auf unserer Fachgruppenliste mit den Hauptansprechpersonen erkennen können, ein herzliches Willkommen!

Neben diesen personellen Wechseln hat auch uns die Corona-Pandemie vor grosse Herausforderungen gestellt: initial mussten wir vorübergehend bei personeller Unterbesetzung den Service an unseren Patienten aufrechterhalten, in späteren Phasen haben wir dann die Arbeit wo möglich ins Homeoffice verschoben. Dies hat zu einer Beschleunigung der Weiterentwicklung der Digitalisierung von Schnittpräparaten geführt, ein Projekt, das die Brücke zwischen Dienstleistung und Forschung schlägt.

Mit der digitalen Pathologie ist unser Institut auch im neuen Center of Artificial Intelligence in Medicine der Medizinischen Fakultät mitinvolviert. In der Forschung konnten wir 2020 einige hochrangige Publikationen veröffentlichen, in unserem Special topic am Ende des Jahresberichtes heben wir eine Übersichtsarbeit aus Nature Reviews Clinical Oncology hervor. Das Institut für Pathologie Bern wird im Bereich des «Tumor Buddings» weltweit als Zentrum wahrgenommen, was sich bereits in der hier durchgeführten Konsensuskonferenz gezeigt hat.

Obwohl wir komplett auf Fernunterricht umgestellt haben, konnten wir in der studentischen Lehre und Weiterbildung für Assistierende Kurse, Vorlesungen und Teachings aufrechterhalten. So sind auch alle unsere internen Fortbildungen inzwischen komplett auf digitale Kommunikationsmedien umgestellt.

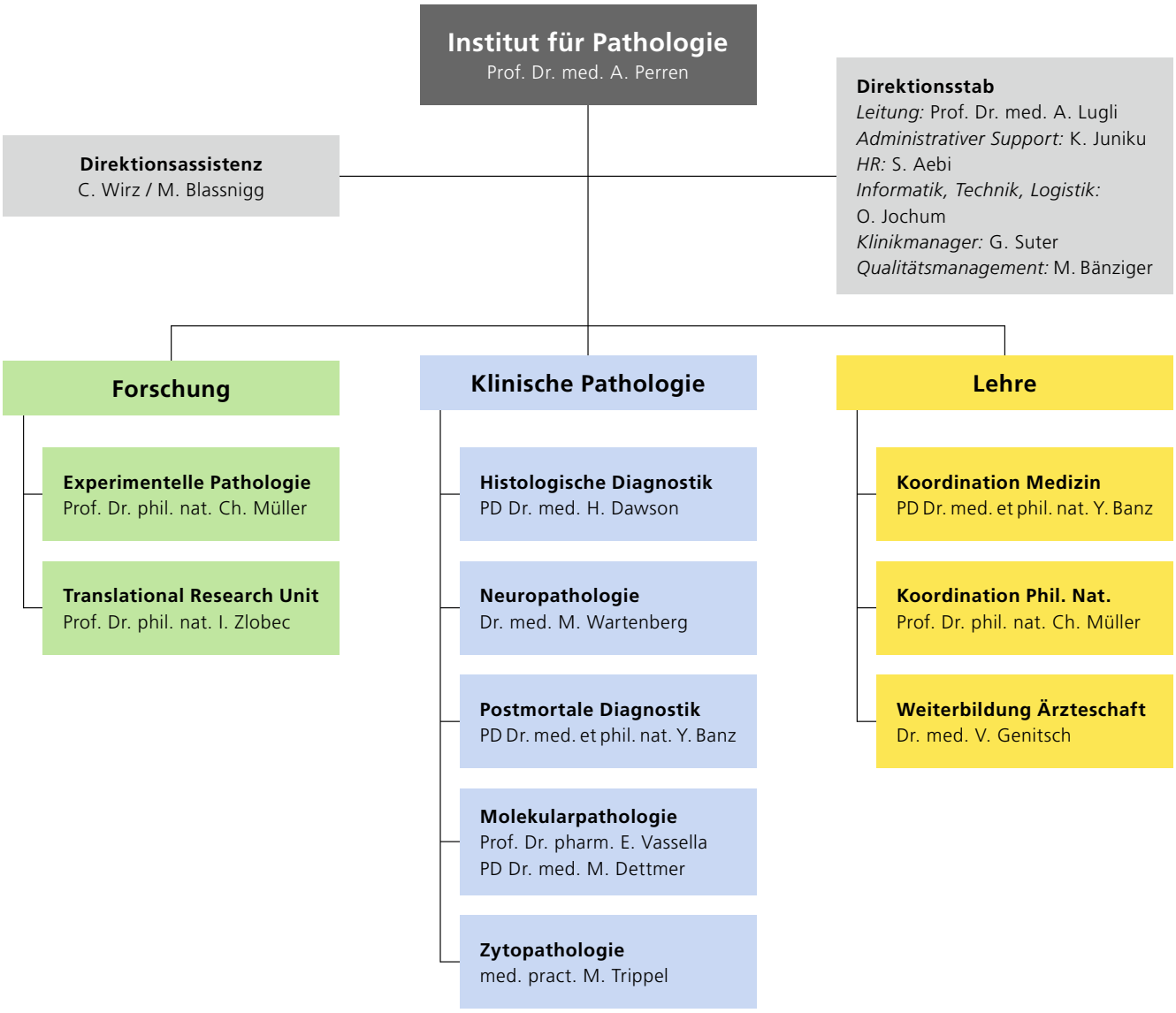
Ich hoffe wie alle, dass wir im 2021 etwas von den digitalen Medien zurück zu physischer Interaktion in allen Bereichen kommen werden und wünsche Ihnen bis dann viel Freude bei der Lektüre dieses Jahresberichts.

Herzliche Grüsse

Aurel Perren, Direktor


Diagnostik
und
Forschung

>>> Organigramm




L141
Institut für Pathologie
Klinische Pathologie

>>> Dienstleistung

1 Klinische Pathologie

Prof. Dr. med. A. Perren
Stv. Prof. Dr. med. A. Lugli

In der klinischen Pathologie arbeiten Ärzteschaft und Laborpersonal in den Bereichen Histopathologische Diagnostik (konventionelle Histologie und Immunhistochemie), Neuropathologie, Molekularpathologie, Zytopathologie und Postmortale Diagnostik.

1.1 Ärzteschaft

Histologische Diagnostik (PD Dr. med. H. Dawson)
Die Ärzteschaft besteht aus 15 Fachärztinnen und Fachärzten, welche von 8 Assistierenden unterstützt werden. 17 Fachgruppen decken das gesamte diagnostische Spektrum der Pathologie ab. An zahlreichen wöchentlichen Tumorboards/Fallbesprechungen innerhalb des Inselspitals und in auswärtigen Spitälern vertritt die Fachärzteschaft die Pathologie in der interdisziplinären Zusammenarbeit mit den Kliniken. Die Herausforderungen der Corona-Pandemie trieb die Kooperation zwischen Ärzteschaft und Informatik zur Entwicklung innovativer Tools für die digitalisierte histologische Diagnostik voran, so dass ein Teil der Diagnostik inklusive Berichterstattung komplett digital erledigt werden kann. Dies ist zugleich auch das Fundament für die geplante Implementierung weiterer digital unterstützter Prozesse wie die Biomarker-Auswertung für den diagnostischen Alltag.

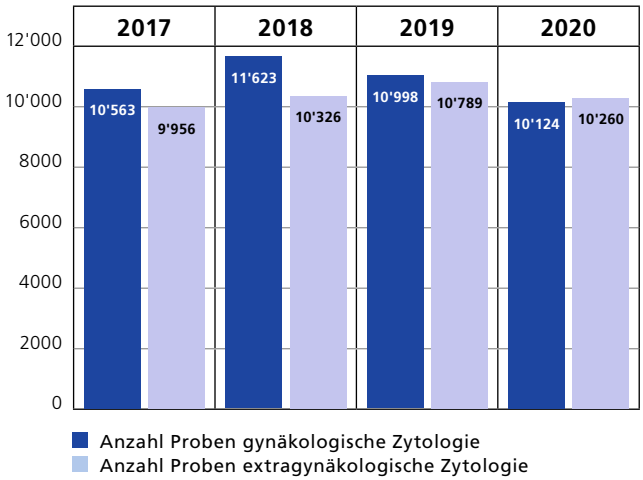
Neuropathologie (Dr. med.M Wartenberg/Dr. T. Maragkou)
Im Jahr 2020 untersuchten wir mehr als 1500 neurochirurgische und neurologische Proben, davon 350 intraoperative Schnellschnitte. Wir zählen damit weiterhin zu den diagnostisch aktivsten Neuropathologien in der Schweiz. Eine immer grössere Rolle spielt die molekulare Diagnostik von Hirntumoren, zunehmend auch die Genom-weite Methylierungsanalyse, die im Rahmen einer Kooperation mit der Neuropathologie am Universitätsspital Genf erfolgt. In Zusammenarbeit mit dem Neuromorphologischen Labor der Neurologischen Klinik des Inselspitals wurden rund 50 Muskelbiopsien untersucht. Die postmortale Diagnostik mit über 50 Hirnsektionen einschliesslich konsiliarischer Untersuchungen im Auftrag des Instituts für Rechtsmedizin ergänzt das diagnostische Spektrum. Entsprechend dem Charakter der Neuropathologie als Schnittstelle zwischen den klinischen Neurofächern, der Labordiagnostik und translationaler Forschung war der Fachbereich Neuropathologie auch im Jahr 2020 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 Basel/Bern (MBB) und des SIWF.

Postmortale Diagnostik (PD Dr. med. et phil. nat. Y. Banz)
Im Jahr 2020 wurden im Institut für Pathologie 97 postmortale Untersuchungen durchgeführt, inklusive neuropathologische und pädopathologische Untersuchungen. Die Zahlen blieben dabei trotz Einbruch im ersten und zweiten Quartal 2020 (wohl im Rahmen der SARS-CoV-2 Pandemie) in etwa stabil im Vergleich zum Vorjahr. Die SARS-CoV-2 Pandemie hat zudem den Schritt zu Zentralisierung der postmortalen Tätigkeit am Institut für Pathologie gezwungenermassen beschleunigt. Zum Schutz der Mitarbeitenden wurden nun sämtlich postmortale Untersuchungen nur noch im Institut durchgeführt, wo die persönlichen und räumlichen Schutzmassnahmen dem Sicherheitsstandard bei (potentiell) infektiösen Untersuchungen genügen. Eine direkte Interaktion mit den Anmeldenden externen Kliniken wird nach wie vor durch eine zeitnahe mündliche und schriftliche Berichtverfassung wie auch im Rahmen interdisziplinärer Fallbesprechungen gewährleistet. Die Zukunft der postmortalen Diagnostik soll weiterhin insbesondere in der Stärkung der Lehre liegen, sei es im Rahmen obengenannter klinisch-pathologischer Konferenzen als auch in der studentischen Lehre. Die Modernisierung bzw. Digitalisierung der Lehre im Bereich der postmortalen Diagnostik (s. hierzu auch die Ausführungen im Kapitel zur studentischen Lehre) soll auch in Zukunft zu diesem wichtigen Ziel beitragen.

Zytopathologie (Med. Pract. M. Trippel)
Das Jahr 2020 war auch in der Zytologie geprägt durch die herausfordernden Anpassungen im Rahmen der Covid-19/ SARS-CoV2 Pandemie bei denen die Sicherheit der Mitarbeiter bei Erhalt der hohen diagnostischen Qualität im Vordergrund stand. Im Jahr 2020 untersuchten wir insgesamt 20'384 Proben mit 10'260 Proben aus der extra-gynäkologischen Zytologie und 10'124 Proben aus der gynäkologischen Zytologie.

Die interdisziplinäre Zusammenarbeit mit der Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin & Metabolismus (UDEM) im Rahmen der interdisziplinären Schilddrüsensprechstunde und auch die gynäkologische zytologisch-histologische Korrelationstreffen mit den Klinikern der Dysplasiesprechstunde der Frauenklinik Inselspital konnten auf hohem Niveau gefestigt werden.

Ein wichtiger weiterer Grundfeiler der Zytologie ist die Fort- und Weiterbildung von ÄrztInnen und von ZytotechnikerInnen, bei welcher wir auch im Jahr 2020 viel Engagement gezeigt haben.



Entwicklung der Einsendungen gynäkologischer und extragynäkologischer Zytologie 2017–2020.

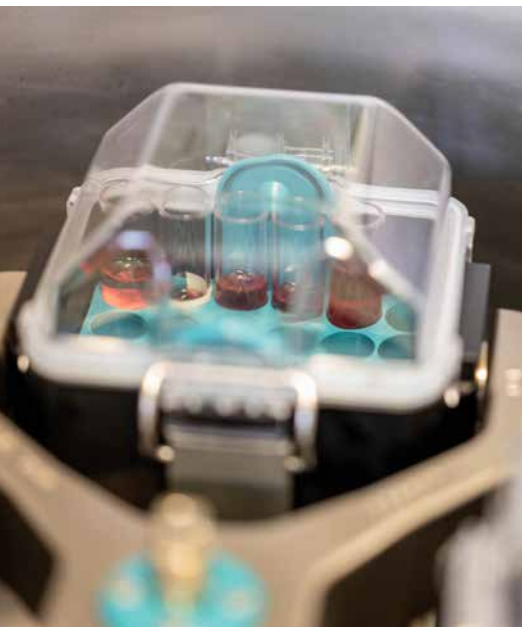
1.2. Labor

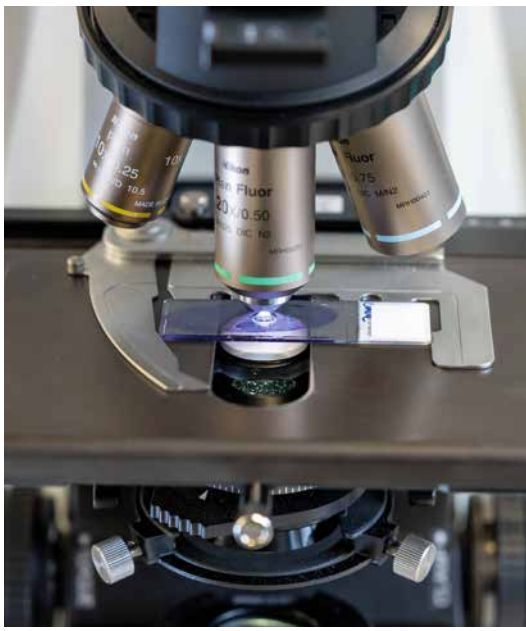
Histologische Diagnostik (J. Ramseier)
Durch die Fusion der beiden grossen K-Path Labore (Histopathologie und Immunhistochemie) entstand die Histologische Diagnostik (HD). Das neue Organigramm trat ab Juli 2020 in Kraft und ist durch die neue Aufteilung der Prozesse an die Operativen Bereiche Lean-konform.

Im ersten Quartal konnte durch die Anpassung des Entwässerungsprozesses in der Routine eine deutlich merkbaren Verbesserung der Schnittqualität in der Diagnostik erreicht werden.

Das externe Überwachungsaudit wurde auf Grund der COVID Situation digital durchgeführt. Alle angeforderten Dokumente und Resultate konnten unter anderem dank der digitalen Pathologie ohne grösseren Aufwand eingereicht werden.

Der Lockdown 2020 führte zu einem starken Rückgang der Einsendungen in diesem Zeitraum, welcher jedoch wieder zu einem grossen Teil mit der Wiederaufnahme des Normalbetriebs im Gesundheitswesen kompensiert wurde. Ende Jahr verrechnet die HD insgesamt 5% weniger Operationspräparate und 2% weniger Biopsien im Vergleich zum Vorjahr, die IHC hat mit 60913 Färbungen an 12107 Fällen ein plus von knapp 3% (Färbungen) zu verzeichnen.

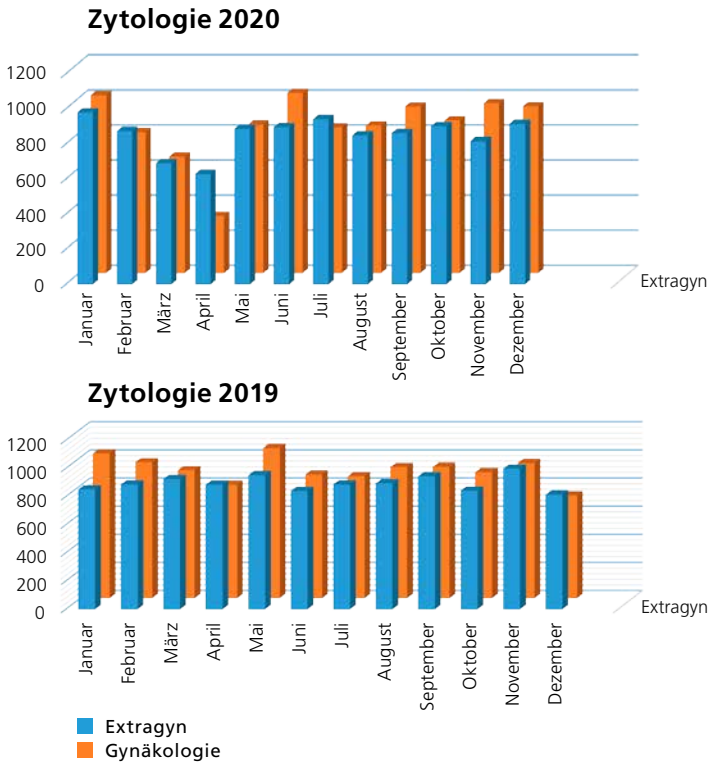




Zytopathologie (C. Baumann)
Das Jahr 2020 wurde geprägt von Covid-19/SARS-CoV2 Ereignissen. Unter diesem Aspekt standen in der Zytologie neben unseren Dienstleistungen auch die Reevaluation und Anpassungen unserer bereits hoch standardisierten und effektiven Massnahmen zur Biosicherheit im Vordergrund.

In Zusammenarbeit mit unserem Biossicherheitsbeauftragten (BSO) Prof. Dr. sc. nat. Philippe Krebs haben wir unsere Arbeitsvorschriften zur Routineverarbeitung von sämtlichen zytologischen Probematerialien erfolgreich angepasst unter Beibehaltung der hohen diagnostischen Qualität. Trotz des Rückganges der Einsendungen in den Monaten März und April 2020, blieb das eingehende zytologische Material das Jahr verteilt grundsätzlich stabil.

Die Zytologie sieht sich als Routinedienstleistungsbetrieb in dem durch kontinuierliche Verbesserungen nicht nur die Qualität gesteigert und die zeitliche Verarbeitung optimiert wurde, sondern auch mit grossen Engagement in die Ausbildung und Weiterbildung In Zytodiagnostik investiert wurde.



2 Fachverantwortung Molekularpathologie (PCR-, NGS- und FISH-Labor)

Prof. Dr. pharm. Erik Vassella, Fachverantwortlicher molekulare Pathologie

Labor: Mitarbeiterinnen Clinical Genomics Lab

Am 1. Januar 2019 wurde das Clinical Genomics Lab des Inselspital Bern als Zusammenschluss der molekularen Diagnostik der Bereiche Humangenetik, Hämatologie, Molekularpathologie und der klinischen Chemie unter der Leitung von PD Dr. med. et phil. Tobias Grob und PD Dr. Ursula Amstutz gegründet. Das interdisziplinäre Labor deckt das gesamte Spektrum der Diagnostik aus den verschiedenen Fachbereichen ab. Gleichzeitig dient das Clinical Genomics Lab als Core Facility für Hochdurchsatzsequenzierung für die klinische Forschung und dient als zentrales Standbein für das Zentrum für Precision Medicine. Durch die Nutzung von Synergien und die interdisziplinäre Zusammenarbeit werden Leistungen für die Patientenversorgung und die Forschung auf hohem Niveau ermöglicht.

Die Dienstleistung der Molekularpathologie im Clinical Genomics Lab ist eine Zusammenarbeit des Inselspital Berns und des Instituts für Pathologie. Die in diesem Fachbereich verwendeten Methoden umfassen insbesondere Hochdurchsatz-Sequenzierung, Sanger-Sequenzierung, Pyrosequenzierung, PCR-Analysen und Fluoreszenz In situ Hybridisierung. Mit diesem breiten Methodenspektrum werden prädiktive Biomarker als Therapieentscheid beim Adenokarzinom der Lunge (inklusiv EGFR T790M Liquid Biopsy), kolorektalem Karzinom, malignen Melanom, GIST, Ovarialkarzinom und Gliom abgedeckt. Genotypisierung der Blasenmole, Risikostratifizierung Mammakarzinom, Abklärung Mikrosatelliteninstabilität, B- und T-Zellklonalität, Diagnostik von Pankreaszysten sowie Nachweis spezifischer Erreger. Die Tests können an Formalin-fixiertem und Paraffin-eingebetteten Gewebe durchgeführt werden. Die molekulardiagnostischen Befunde werden am molekularen Tumorboard besprochen.

Die Schlüsseltechnologie unseres Labors ist die Hochdurchsatz-Sequenzierung. Zur Bestimmung Therapie-relevanter Biomarker wurde anfangs dieses Jahres das Oncomine Comprehensive Cancer Panel v3 verwendet, welches neben relevanten Onkogenen und Tumorsuppressorgenen auch relevante NTRK-, ALK, ROS- und RET Fusionen abdeckt. Dieses Panel wurde nun durch das TSO500 Panel ersetzt. Dieses auf der Illumina Technologie basierende Kit erlaubt neben einem erweiterten Genpanel von nun über 500 Tumor-relevanter Gene den Nachweis der Tumormutationslast sowie der Mikrosatelliteninstabilität, ausgelöst durch den Funktionsverlust von Mismatch-Reparaturgenen. Letztere Parameter können relevant für den Therapieentscheid von Immuncheckpoint-Inhibitoren sein. Das TSO500 Panel erlaubt zudem einen verbesserten Nachweis von Fusionstranskripten, da nun auch der Nachweis von RNAs mit unbekannten Fusionspartnern (z.B. FGFR oder NTRK) möglich ist.

Gegenüber den letzten zwei Jahren hat sich die Zahl der mittels Hochdurchsatz-Sequenzierung durchgeführten Analysen um 40% zugenommen. Dies wirkte sich insbesondere auf die Verwendung grösserer Genpanels aus (Zunahme um 300% im letzten Jahr und eine weitere Zunahme um 180% in diesem Jahr. Therapie-relevante Alterationen werden am molekularen Tumorboard am Inselspital besprochen, welches alle zwei Wochen stattfindet.

Gegenstand neuer Entwicklungen im Jahr 2020 war neben der Etablierung des TSO 500 Panels die Entwicklung einer eigenen Bioinformatik-Pipeline in Zusammenarbeit mit dem Bioinformatikteam der Interfaculty Bioinformatics Unit der Universität Bern. Die Annotation der nachgewiesenen Varianten erfolgt mittels OncoKB Oncology Knowledge Base. Ein weiterer Schwerpunkt war die Etablierung eines gemeinsam betriebenen Laborinformationssystems, welches gleichzeitig als Datenbank für NGS Alterationen dient. Aufgrund der Überführung der molekularen Diagnostik vom Institut für Pathologie in das CGL ist die Akkreditierung für diesen Bereich aktuell sistiert. Eine Reakkreditierung wird im Jahr 2021 erfolgen.

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

3 Fachgruppen des Instituts für Pathologie der Universität Bern

Stand April 2021

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

Endokrinopathologie	
A. Perren	031 632 32 23
J. Friemel	031 632 49 37
A. Marrazzini	031 632 99 01

Gastrointestinalpathologie	
A. Lugli	031 632 99 58
H. Dawson	031 632 99 60
B. Dislich	031 632 71 90
A. Mookhoek	031 632 99 20
M. Montani	031 632 32 67
A. Perren	031 632 32 23

Mamma- und Gynäkopathologie	
T. Rau	031 632 87 56
M. Trippel	031 632 32 76
J. Friemel	031 632 49 37
M. Montani	031 632 32 67
M. Wartenberg	031 632 49 76

Hämatopathologie	
Y. Banz	031 632 88 75
Ch. Neppl	031 632 52 03
B. Dislich	031 632 71 90

Herz-, Gefäss- und Rheumapathologie	
Y. Banz	031 632 88 75
M. Trippel	031 632 32 76
M. Montani	031 632 32 67

HNO-/Ophtalmopathologie	
O. Stanovska	031 632 52 55
M. Wartenberg	031 632 49 76
T. Rau	031 632 87 56

Leberpathologie	
M. Montani	031 632 32 67
T. Rau	031 632 87 56
A. Mookhoek	031 632 99 20

Lungenpathologie	
Ch. Neppl	031 632 52 03
Y. Banz	031 632 88 75
J. Friemel	031 632 49 37

Nephropathologie	
C. Saganas	031 632 68 55
M. Montani	031 632 32 67
A. Rodriguez	031 632 68 56

Neuropathologie	
M. Wartenberg	031 632 49 76
T. Maragkou	031 632 32 49
B. Dislich	031 632 71 90

Pädopathologie	
M. Trippel	031 632 32 76
A. Marrazzini	031 632 99 01
S. Yeginsoy	031 632 99 22

Pankreaspathologie	
M. Wartenberg	031 632 49 76
M. Montani	031 632 32 67
A. Perren	031 632 32 23

Uropathologie	
A. Rodriguez	031 632 68 56
M. Montani	031 632 32 67
C. Saganas	031 632 68 55

Weichteil- und Knochenpathologie	
H. Dawson	031 632 99 60
B. Dislich	031 632 71 90
M. Trippel	031 632 32 76

Postmortale Diagnostik und Makropathologie	
Y. Banz	031 632 88 75
B. Dislich	031 632 71 90
C. Saganas	031 632 68 55
M. Trippel	031 632 32 76
J. Friemel	031 632 49 37

Zytologie	
M. Trippel	031 632 32 76
Y. Banz	031 632 88 75
Ch. Neppl	031 632 52 03
A. Safret	031 632 32 48

Molekularpathologie	
E. Vassella	031 632 99 43
H. Dawson	031 632 99 60
B. Dislich	031 632 71 90

4 DIR-Stab

Der im Januar 2019 gegründete Direktionsstab umfasst die Bereiche Administrativer Support (AS) (Berichtssekretariat und Support Center), Human Resources (HR), Informatik, Technischer Dienst und Logistik (ITL), Klinikmanager (KM) und Qualitätsmanagement (QM) und unterstützt alle internen und externen Kunden des Instituts für Pathologie bei deren Aufgaben und Projekten.

Der administrative Support beinhaltet den Support Center mit den Aufgaben Kundenbetreuung, Buchhaltung und Unterstützung in der Lehre sowie das Berichtssekretariat für die Erstellung der Berichte und Organisation der Tumorboards. Die Hauptaufgaben Finanzen, Datenschutz und Arbeitssicherheit wurden ins Klinikmanagement integriert, während das Personalbüro für die personellen Anliegen der Mitarbeitenden und für die Prozesse Eintritte, Mutationen und Austritte verantwortlich ist. Die Informatik zusammen mit dem Technischen Dienst und der Logistik unterstützen sowohl die interne als auch die externe Kundschaft. Eine strategische Zusatzaufgabe für die Informatik beinhaltet die technischen Aspekte der «Digitale Pathologie». Das Institut für Pathologie ist seit Ende November 2017 bei der Schweizerischen Akkreditierungsstelle SAS entsprechend der Internationalen Norm ISO/IEC 17025:2017 & ISO 15189:2012 und der Schweizer Norm SN EN ISO/IEC 17025:2018 & SN EN ISO 15189:2013 als Prüflaboratorium für pathologische Diagnostik akkreditiert.

5 Dienstleistungsstatistik

Klinische Pathologie

Histopathologie	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
Anzahl Einsendungen	37'232	42'422	43'607	45'491	48'601	**46'372**
Anzahl Lokalisationen	70'286	82'069	83'191	86'253	93'835	**90'658**
Einsendungen Schnellschnitte	1'648	1'936	1'761	1'784	1'831	**1'770**
Proben Schnellschnitte	2'252	2'454	2'264	2'225	2'313	**2'216**

Autopsie						
Anzahl durchgeführte Autopsien	152	146	130	134	106	**99**

Zytopathologie						
Anzahl Einsendungen Total	16'043	16'634	16'995	17'814	17'576	**17'300**
Anzahl Proben Klinische Zytologie	11'582	9'324	9'956	10'326	10'789	**10'260**
Anzahl Proben Gynäkologische Zytologie	9'375	9'869	10'563	11'623	10'998	**10'124**
Anzahl Proben Total	20'957	19'193	20'519	21'949	21'787	**20'384**
Anzahl Zellblöcke	2'748	2'837	3'334	3'844	4'011	**4'234**

Immunhistochemie						
Fälle (Blöcke) Diagnostik (Paraffin)	7'843	9'094	7'681	8'822	11'616	**11'717**
Färbungen Immunfluoreszenz (Nierenbiopsien)	2'079	2'772	2'464	2'010	2'486	**1'980**
Fälle Immunzytologie am Ausstrich	197	158	258	201	246	**210**
Färbungen Immunzytologie am Ausstrich	240	486	364	377	353	**307**
Färbungen Diagnostik (Paraffin)	47'944	44'366	47'597	51'971	59'249	**60'913**

Tumorbank

Einsendungen Tumorbank	1'030	1'417	1'879	1'593	1'823	**2'126**
Anzahl Projekteingänge TRU	457	604	602	738	850	**640**

>>> Forschung/Research

1 Research at the Institute of Pathology

Research groups Experimental Pathology
Stefan Freigang, MD
Philippe Krebs, PhD
Christoph Mueller, PhD
Aurel Perren, MD, PhD & Ilaria Marinoni, PhD
Mirjam Schenk, PhD
Mario P. Tschan, PhD
Erik Vassella, PhD

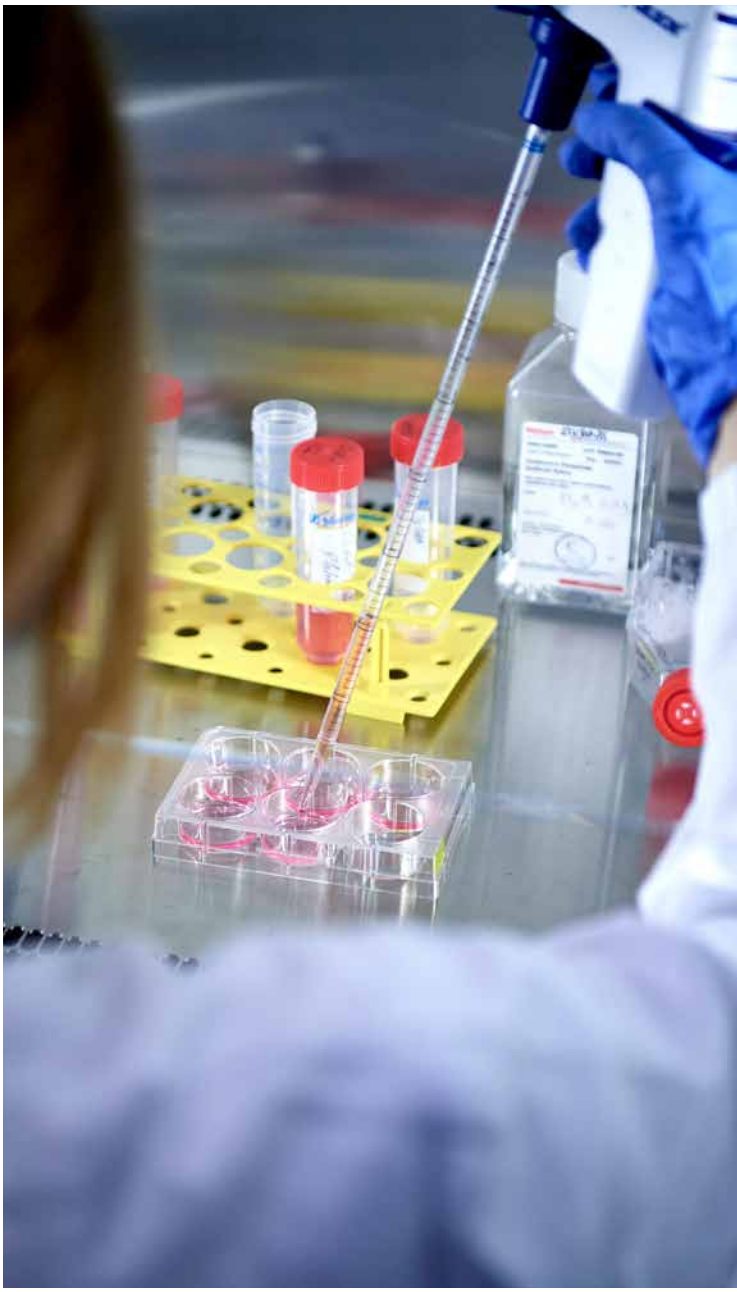
Translational Research Unit (Core Facility) (TRU)
Research groups supported by TRU
Alessandro Lugli, MD
Inti Zlobec, PhD

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 approporiate use («support platforms»), can be also accessed by the research personel of the other units of the Institute of Pathology. This allows an efficient use of the limited financial ressources, but may also foster scientific collaborations among the research staff at the Institute of Pathology.

The core lab of the Translational Research Unit

The Translational Research Unit (TRU) is a core facility specializing in tissue-based techniques. Our portfolio of services includes histology, tissue visualisation, digital slide scanning, and next-generation Tissue Microarray construction. TRU also provides support for Tissue Bank Bern and collaborates with researchers from the University, DBMR and Inselspital, as well as other researchers in Switzerland and abroad.



1.1 Division of Experimental Pathology

Head: Christoph Mueller, PhD

Research activities

Thematically the research activities of the seven 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

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 cancer and in remitting – relapsing inflammatory disorders, and the development of novel vaccination strategies against solid tumors.

The Division of Experimental Pathology also hosts the biobank of the SNSF-funded Swiss IBD cohort study (SIBDCS). At the end of 2020 more than 80'000 biosamples (serum, plasma, biopsies, DNA) from approx. 3000 patients with IBD were stored in the biobank and are made available to qualified scientists for research purposes.

Personnell

In 2020 more than 50 persons were working in the Division of Experimental Pathology.

Grant Support

In 2020 the total amount of new external funding obtained by the research groups of the Division of Experimental Pathology more than CHF 3.2 Mio (for details see: Reports of the individual research groups).

Research infrastructure and collaborations

The research activities at the Institute of Pathology are well integrated on a national and international level. In our experimental work we can both rely on facilities available at our institute, e.g. Laser Capture Microdissection, digital pathology, confocal microscopy, Cell-IQ® continuous live cell imaging and analysis system and a Nanostring® Platform for multiplexed assays for gene expression and mutation analysis, but also on core facilities provided by the Dept. of Biomedical Research, including the FACS (cytometry) core facility, and the state-of-the-art genomics core facility. 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 granted. We are also part of the Interfaculty Bioinformatics Unit and are granted unrestricted access to the Next Generation Sequencing platform of the University of Bern (equipped with an Illumina HiSeq3000, an Illumina MiSeq and an illumina NovaSeq 6000). Several of our research groups also use the central mouse facility (CAF), and the germ-free and gnotobiotic mouse facility (Clean Mouse Facility) at the Medical Faculty.

The spectrum of available and well-established technologies in the Division of Experimental Pathology includes confocal microscopy, fluorescent in situ hybridization (FISH), laser capture microdissection of FFPE and frozen tissue sections (including immunostained FFPE tissue sections), live-cell metabolic assays on a Seahorse XF Analyzer, 3D-cell cultures, 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, the assessment of autophagy, and several distinct transfection systems, including lentivirus-based transduction systems, and mRNA expression profiling from small numbers of cells and microdissected tissues are available (e.g. scRNA sequencing on the 10X Genomics platform; NanoString®analysis). Furthermore, several of our research groups have a longstanding expertise in isolating and culturing primary cells, such as immune cells, primary AML blast cells, mesenchymal stromal cells, including liver sinusoidal endothelial cells, and epithelial cells from patient material, but also from 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

Johanna Baumgartner, PhD student
Thi Thuy Hang Bui, PhD student
Nadia Oehninger, medical doctorate student
Joëlle Schläfli, MSc student (from Sep 2020)

Summary of Research Activities

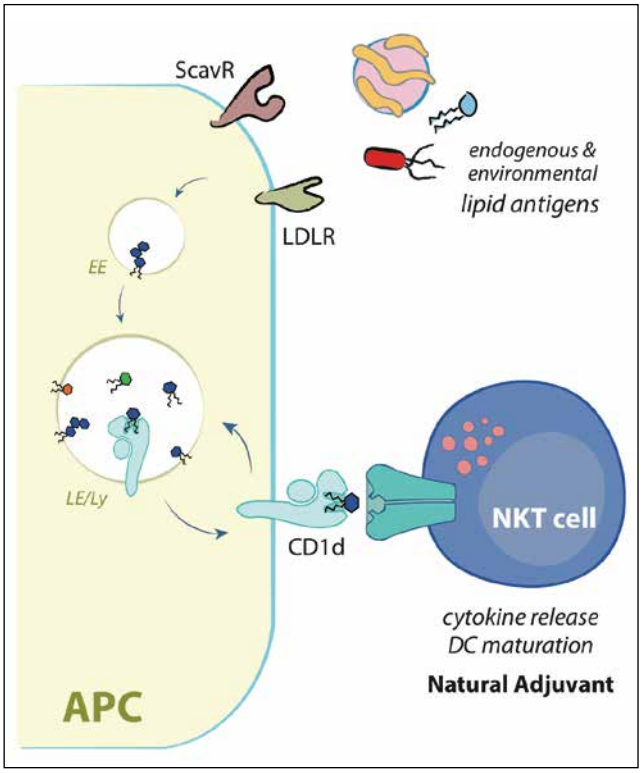
Immune recognition of lipids in inflammation and immunopathology

Lipids represent critical structural components of biological membranes as well as a significant energy source for cellular metabolism, and thus are of fundamental importance for the survival of our organism. In addition, endogenous and environmental lipids may become targets of innate and adaptive immune responses. The immune recognition of microbial and self-lipids is essential for successful anti-infectious immunity, but also contributes to chronic inflammation in metabolic disorders, such as diabetes and cardiovascular disease. Our group investigates the immune recognition of lipids in microbial infections and metabolic diseases.

Research Activities

Project 1: Glycolipid-sensing by Natural Killer T cells

Natural killer T (NKT) cells are innate-like T cells with powerful immunoregulatory functions that recognize self and microbial glycolipids presented by CD1d molecules. While the efficacy of NKT cell agonists is currently explored in the immunotherapy of infectious diseases and cancer, the mechanisms that control CD1d antigen presentation and NKT cell activation in vivo still remain incompletely understood. This project characterizes pathways linking CD1d antigen presentation to lipid metabolism, and aims to define critical effector functions of NKT cells in microbial infections.



Glycolipid-sensing by Natural Killer T cells.

Project 2: Molecular mechanisms of lipid-induced inflammation
Cardiovascular diseases, particularly atherosclerosis-related diseases, remain the leading cause of death worldwide. While first clinical trials demonstrated the beneficial effects of anti-inflammatory therapies in CVD patients, a better understanding of the molecular mechanisms of vascular inflammation will be critical to develop more effective treatment strategies. Recent advances in the field of immunometabolism generated strong interest in delineating metabolic pathways that influence macrophage responses in atherosclerosis. In this project, we study mechanisms of IL-1-driven vascular inflammation that are linked to metabolic perturbation and mitochondrial dysfunction.

Project 3: Immune regulation by oxidized lipids
Exposure of cellular membranes to reactive oxygen species creates a broad range of distinct oxidized phospholipid (OxPL) species that may actively modulate cellular signaling processes and immune responses. We have previously described cyclopentenone-containing OxPLs and their isoprostanes as pro-resolving lipid mediators. This project investigates the OxPL-signaling in myeloid cells during atherogenesis and microbial infection using functionalized lipid probes and a novel oxidative stress reporter.

Internal Collaborations
- Christoph Mueller, PhD
- Vera Genitsch, MD

External Collaborations *(printed Yearly report only)*
National
- Charaf Benarafa, PhD, Inst. of Virology and Immunology, University of Bern, Switzerland
- Marc Donath, MD, Dept. Of Biomedicine, University of Basel, Switzerland
- Cem Gabay, MD, Dept. Of Medicine, University of Geneva, Switzerland
- Olivier Guenat, PhD, ARTORG Center for Biomed. Engineering, University of Bern, Switzerland
- Georgia Konstantinidou, PhD, Inst. of Pharmacology, University of Bern, Switzerland
- Adrian Ochsenbein, MD, Dept. of Clinical Research, University of Bern, Switzerland
- Philippe Renaud, PhD, Dept. Chemistry and Biochemistry, University of Bern, Switzerland

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

Grant Support
- Swiss National Science Foundation, S. Freigang; PI, 2020–2024, CHF 632’000
- Swiss Heart Foundation, S. Freigang; PI, 2020–2021,CHF 50’000
- UniBE 2021 PhD Fellowship, J. Baumgartner, S. Freigang, 2017–2021, CHF 90’000
- University of Bern, Interdisciplinary grant*, S. Freigang; PI, 2018–2020, CHF 150’000
- Swiss Lung Liga*, S. Freigang; PI, 2017–2020, CHF 162’000

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

Administrative duties
- Member of the Expert Commission of the Graduate School for Cellular and
- Biomedical Sciences of the University of Bern
- Radiation Safety Officer for the Institute of Pathology

Forschungsgruppe Philippe Krebs (Research group Philippe Krebs).

Group of Philippe Krebs, PhD

Silvio Eugster, MSc student (from Sep 2020)
Robert Gaultney, PhD, post-doc (from Sep 2020)
Kristýna Hlavácková, MSc, technician, 90%
Coline Nydegger, technician, 90%
Lester Thoo Sin Lang, MSc, PhD student (till Sep 2020)
Wen Jie (Jeremy) Yeoh, MSc, PhD student
Vivian Vu, MSc, PhD student

Summary of Research Activities

Chronic inflammation of microbial etiology has been suggested as the underlying cause of several debilitating conditions, particularly in patients afflicted with inflammatory bowel disease (IBD) or certain types of malignancies. Our group uses mouse models and specimens from human patients to study the role of specific genes or molecular pathways for inflammation-triggered immunopathology or tumor development. We aim at a better understanding of the mechanisms underlying these pathways to possibly reveal novel therapeutic targets.

Keywords:
– Cross-talk innate / adaptive immunity
– Role of inflammation for cancer development
– Immunopathology

Research Activities

Project 1: Role of cytokine signaling for immunopathology and tumor development

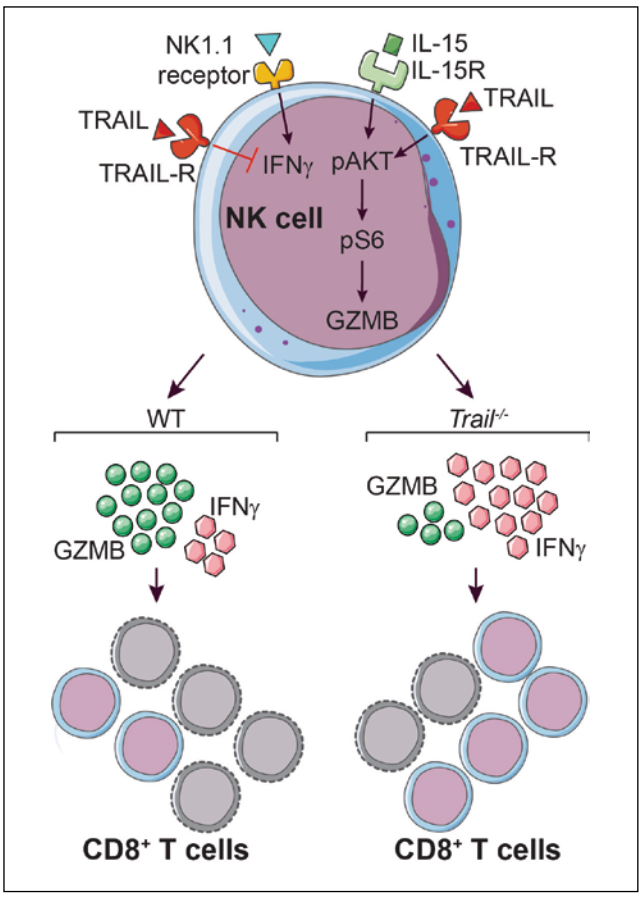
Inflammation is a driver of cancer. We have shown that IL-33 signaling is important for the development of myeloproliferative neoplasms (MPN), a type of blood cancer, and for promoting colorectal cancer (CRC) (Mager, J Clin Invest, 2015; Mertz, OncoImmunology, 2015; Pastille, Mucosal Immunol, 2019). We currently investigate the contribution of IL-33 to MPN progression and to the cellular and molecular mechanisms underlying IL-33-dependent CRC and chronic lung inflammation. For these studies, we use patient-derived samples and mouse models.

Project 2: mRNA splicing and epithelial integrity

The intestinal barrier is often disrupted during intestinal diseases, causing gut leakiness. We have recently shown that the protein ESRP1, a regulator of mRNA splicing in epithelial cells, has a critical function to maintain the integrity of the intestinal barrier (Mager et al., eLife, 2017). In this project, we further investigate how loss or reduction of ESRP1 leads to intestinal homeostasis and pathogenesis, including inflammatory bowel disease and 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; Cardoso Alves, EMBO Reports, 2020) or sterile (e.g. for tumor surveillance) situations.



TRAIL programs natural killer (NK) cells by blocking the production of inflammatory messengers (IFNγ) but promoting the formation of cell toxins (GZMB). NK cells lacking TRAIL produce more IFNγ but less GZMB, which results in greater antivirus CD8+ T cell response in infected mice (Cardoso Alves, EMBO Reports, 2020).

Internal Collaborations

- Christoph Mueller, PhD
- Inti Zlobec, PhD
- Alessandro Lugli, MD
- Yara Banz, MD, PhD
- Tilman Rau, MD

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 Res., University of Bern
- Andrew Macpherson, MD, Dept. Clinical Res., University of Bern
- Burkhard Ludewig, DVM, Institute of Immunobiology, Cantonal Hospital St.-Gallen
- Mario Noti, PhD, Department of Gastro-Intestinal Health, Immunology, Nestlé Institute of Health Sciences, Lausanne, Switzerland

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

- Swiss National Science Foundation Project grant, P. Krebs: PI, 2020–2024, CHF 632'000
- Bern Center for Precision Medicine (BCPM), P. Krebs: PI, 2020–2021, CHF 40'532
- Helmut Horten Stiftung Project grant, P. Krebs; PI, 2019–2021, CHF 130'000
- Seed money project (Swiss Confederation and ETHZ) Project grant, P. Krebs; main PI, 2019–2020, CHF 10'000
- EU / Marie Skłodowska-Curie RISE grant Project grant, P. Krebs: co-Investigator, 2018–2021, Euro* 904'500
- Bernese Lung League Project grant, P. Krebs; PI, 2018–2020, CHF 79'554
- Swiss Lung League Project grant, P. Krebs; PI, 2018–2020, CHF 79'554
- UniBE ID (Interdisciplinary) Grant, P. Krebs; main PI, 2017–2021, CHF 75'000
- Research Foundation (KFS) Project grant, P. Krebs: PI, 2017–2021, CHF 312'500
- Swiss National Science Foundation Project grant, P. Krebs: PI, 2016–2020, CHF 525'000

* total amount of funding; funding shared by PI and Co-PI; part for group Krebs is contingent on number of staff exchanges.

Administrative duties:

- Member of the Expert Commission of the Graduate School for Cellular and Biomedical Sciences of the University of Bern
- Biosafety Safety Officer for the Institute of Pathology
- Member of the Steering Committee Digital Pathology

Forschungsgruppe Christoph Mueller (Research group Christoph Mueller).

Group of Christoph Mueller, PhD

Pablo Baniclès, MSc, technician, 60%
Juliana Barreto de Albuquerque, PhD, post-doc
Regina Berchtold, technician, 80%
Nadia Corazza, PhD, staff scientist/co-PI, 60%
Antonia Ferreira, MSc student (from February 2020)
Bilgi Gungor, PhD, post-doc (from July 2020)
Alexandra Suter, technician, 60% (SIBDCS biobank) (till January 2020)
Diego von Werdt, PhD student (till February 2020)
Daniel Zysset, PhD, post-doc, 40% (till September 2020)
Beat Imhof, PhD, visiting scientist

Summary of Research Activities

Our group has a longstanding interest in the complex immunoregulatory mechanisms that are operative in the intestinal mucosa during homeostasis, and in the potential events leading to disruption of these mutualistic interactions between host and microbiome during inflammatory conditions as typically seen in inflammatory bowel diseases (Crohn's disease, ulcerative colitis). The importance of the intestinal microflora in shaping the differentiation of the local immune system, but also on 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 chronic relapsing-remitting inflammation with concurrent analyses of the intestinal microflora and the associated metabolic changes. A major focus of the ongoing research activities are tissue-resident memory T cells in the intestinal mucosa and their functional stability vs. plasticity during reversible colitis and inflammatory bowel diseases, and on the mechanisms that regulate their local differentiation and maintenance. While we often use experimental mouse models to test our hypotheses, we also validate these experimental findings using state-of-the-art technologies with patient materials obtained from the SIBDCS biobank.

Research Activities

Project 1: Changes in local immune cells during onset vs. remission vs. relapse of colitis

Understanding the mechanisms that drive remission and relapsing of intestinal inflammation is a prerequisite for treating patients with inflammatory bowel diseases. We have recently established a reversible, relapsing-remitting mouse model of colitis with reproducible onset of intestinal inflammation, with repeated flares of inflammation (Brasseit et al., Mucosal Immunol 2016). In this model we monitor the functional changes of individual T cell clones at the site of inflammation, but also in circulation during reversible colitis in mice, and corroborate these findings in patients with inflammatory bowel diseases, notably, ulcerative colitis. An ultimate goal is to identify strategies to specifically extend the remission period, or even prevent a further relapse of disease.

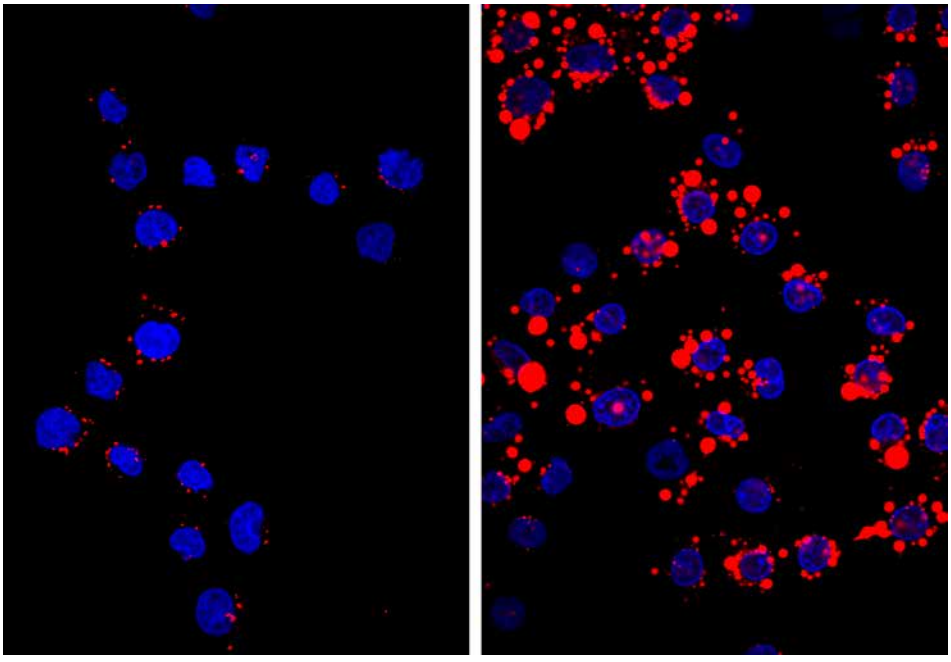
Projekt 2: TREM-1 as an amplifier of inflammation in immunosurveillance and immunopathologies
TREM-1 (Triggering Receptor Expressed on Myeloid Cells-1) is an activating innate immune receptor on neutrophils and monocytes/macrophages. We previously described a critical pathogenic role for TREM-1 not only in acute, but also in chronic inflammation, notably, in inflammatory bowel diseases (Schenk et al., J Immunol 2005, J Clin Invest 2007). We generated a Trem1-/- mouse (Weber et al. PLoS Pathog 2014) to determine the Trem1 mediated effects in the pathogenesis of atherosclerosis (Zysset et al., Nat Comms 2016) and on the development of colitis-associated colorectal carcinoma (Saurer and Zysset et al., Sci Rep 2017). Current research interests include the involvement of TREM-1 in neurological disorders, such as stroke (Liu et al., Nat Immunol 2019), neurodegenerative disorders, and in infections with intracellular pathogens such as Listeria monocytogenes.

Project 3: Functional plasticity and retention of tissue-resident TRM cells in the intestinal mucosa
Understanding the functions and the regulation of intestinal T cell subsets is one of our long-standing research objectives. Some of these T cells in the intestine represent the prototypical example of tissue-resident T cells due to their resident location at a barrier site, and their limited capacity to recirculate. Currently, we investigate the regulation of intestinal resident T cells in the protective immunity against pathogens (e.g. infection with Listeria monocytogenes), but also their contribution to the development of chronic inflammatory disorders. In particular, we investigate the molecular mechanisms that regulate their tissue-resident phenotype, and assess how distinct functional activities of this T cell subset may either result in protective immunity, or inflammatory pathologies.

Internal Collaborations
- Stefan Freigang, MD
- Vera Genitsch, MD
- Philippe Krebs, PhD
- Mirjam Schenk, PhD

External Collaborations *(printed Yearly report only)*
National
- Andrew Macpherson, MD, Department of Clinical Research, University of Bern
- Daniela Finke, MD, Department of Biomedicine, University of Basel
- Gerhard Rogler, MD PhD, Division of Gastroenterology & Hepatology, University Hospital Zurich
- Jens Stein, PhD, University of Fribourg
- Markus Britschgi, PhD, Roche Pharma Research & Early Development
- F. Hoffmann-La Roche Ltd., Basel

International
- Katrin Andreasson, MD, Neurology and Neurosciences, Stanford University Medical Center, USA
- Klaas von Gisbergen, PhD, Sanquin Research, Amsterdam, The Netherlands
- Sebastian Zundler, MD, Department of Medicine 1, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Erlangen, Germany
- John Kehrl, NIAID, Bethesda, MD, USA
- Bärbel Stecher, PhD, Max von Pettenkofer Institute of Hygiene and Medical Microbiology, Ludwig-Maximilians-University of Munich, Germany



TREM-1-activation on monocytes leads to an enhanced lipid uptake (red droplets).

Grant Support

- SNF 314730_189277, Christoph Müller, 2019–2022, CHF 516'667
- SNF 33CS30_177523, SIBDCS, Christoph Müller; Co-PI, 2018–2020, CHF* 304'500
- Monique Dornonville de la Cour Stiftung, Daniel Zysset, 2018–2021, CHF 52'387

* own share

Administrative duties

Christoph Mueller

- Chair, Program Board «Certificate of Advanced Studies in Research Management» (CAS «Forschungs-management»), University of Bern
- Member, Scientific Board, Swiss IBD Cohort Study (SIBDCS)
- Member, Executive Board, Swiss IBD Cohort Study (SIBDCS)
- Head, Biobank, Swiss IBD Cohort Study (SIBDCS)
- Member, Evaluation Committee Lutz-Zwillenberg Prize (University of Bern)
- Member, Evaluation Committee, SNSF, ambizione program
- Chair, Stiftung für klinisch-experimentelle Tumorforschung Bern
- Member, Experimental Animal Center (EAC) – Committee (University of Bern)
- Member, Research Committee, Medical Faculty
- Member of several faculty committees (appointments)

Nadia Corazza

- Member «Gleichstellungskommission», Medical Faculty, University of Bern

Alumni

Jean-Claude Reubi, MD (Prof. Dr. med. em.)

Professor Jean-Claude Reubi, MD, formally retired in 2012, but still continued in 2020 his most successful publication activities in the field of peptide receptor imaging and therapy.


EDT

Forschungsgruppe Aurel Perren.

Group of Aurel Perren, MD

Valentina Andreasi, guest PhD student
Simon April, MSc, PhD student
Konstantin Bräutigam, MD, Resident
Matthias Dettmer, MD Attending Pathologist
Eva Diamantis-Karamitopoulou, guest medical doctor
Annunziata Di Domenico, post-doc
Renaud Maire, MSc, technician
Ilaria Marinoni, PhD, Co-PI
Viktoriia Ovcharova, MSc student Med
Umara Rafiqi, MSc, PhD student
Lionel Rohner, MSc student
Martin Sadowski, PhD, Senior Research Assistant
Janine Straub, MSc, Cand. Med.
Martin Wartenberg MD, Attending Pathologist
Kristýna Filipová, MSc student

Summary of Research Activities

The research focus of our group is the study of endocrine tumors; notably sporadic and familial pancreatic neuroendocrine tumors (PanNETs). PanNETs are highly heterogeneous and the mechanisms leading to tumor development are still elusive. We focus on the understanding of the molecular events leading to PanNET formation and progression as well as on the investigation of the mechanisms mediating therapy resistance and tumor aggressiveness. We integrate molecular biological (in vitro and in vivo) and clinical (human tissue based ex vivo) research approaches.

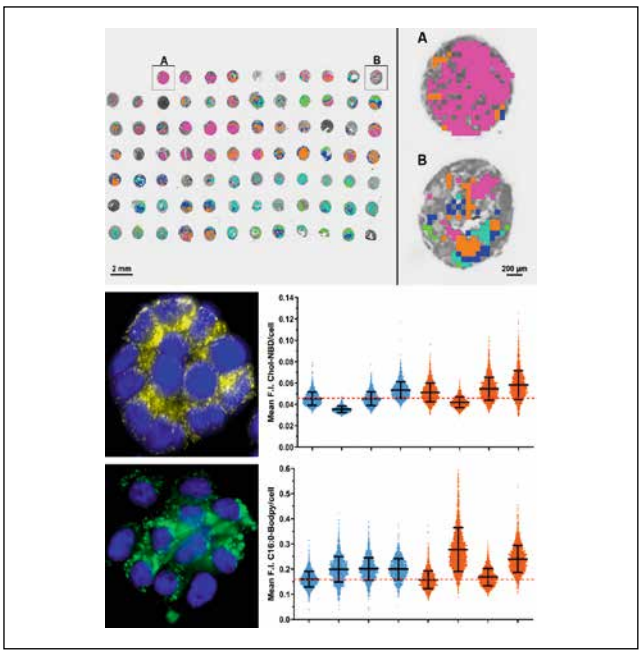
Research Activities

Project 1: Epigenetic changes in PanNETs
Almost, half of Pancreatic Neuro-endocrine Tumors (PanNETs) shows mutation in MEN1, DAXX or ATRX. All the three genes encode for proteins which are involved in epigenetic regulation. Based on DNA methylation we identified subgroups of PanNETs with: specific cell of origin, genetic background and clinical outcome. Notably, we demonstrated that MEN1/DAXX/ATRX mutated tumors originated from alpha pancreatic cells and that they have an increased risk of relapse.

We focus on understanding the epigenetic changes along PanNET progression and their impact of pathways activation.

Project 2: Precision medicine approach for PanNET treatment
Up to date, no therapy prediction based on specific molecular profile is possible for PanNET patients. We recently established patient-derived tumoroid cultures from PanNET patients which resemble features of original tumor tissue and which can be used for in vitro drug screenings. We are currently assessing the utility of PanNET tumoroids to predict patient therapy response and to identify novel epigenetic treatment options. Also, we aim at identifying specific molecular profiles through DNA sequencing, methylation- and gene expression analysis to predict therapy response in vitro and on the patients.

Project 3: Integrated Genomic and Immunophenotypic Classification of Pancreatic Cancer
By integrating immune cell background, molecular, and histomorphologic data, we describe three distinct, clinically/biologically relevant pancreatic ductal adenocarcinoma (PDAC) subtypes: «immune escape», «immune rich», and «immune exhausted». These largely correspond to previously described molecular PDAC subtypes, thus providing a recognizable morphologic substrate integrating host immune response patterns with tumor-associated factors, including molecular features and biologic behavior of the tumors. This will enable the translation of molecular findings into clinically relevant information and may provide a basis for a more successful and individualized therapeutic approach.



Project 4: Tissue mass spectrometry imaging (top) identified five metabolic subtypes of PanNET. Fluorescence microscopy simultaneously measured mitochondrial activity (middle) and lipid storage (bottom) of two PanNET cell lines (blue and orange) after treatment with various metabolic inhibitors.

Project 4: Metabolic changes in PanNET

Critical metabolic changes are early hallmarks of cancer cells. Emerging epigenetic, transcriptional and translational data suggest that PanNET cells undergo substantial metabolic reprogramming. However, the identity, functional consequences and therapeutic potential of metabolic changes in PanNET remain up until now largely unknown and untested. Our multimodal, integrated analysis of PanNET cell culture and tissue samples of various stages of tumor development by modern mass spectrometry, fluorescence microscopy and RNAseq data will delineate these metabolic and test novel therapeutic strategies.

Internal Collaborations

- Philippe Krebs, PhD
- Erik Vassella, PhD
- Inti Zlobec, PhD

External Collaborations

National

- Beat Gloor, MD, Department of Visceral Surgery, Insel University Hospital, Bern
- Holger Moch, MD, Department of Pathology, University Hospital, Zurich

International

- Dr. Chrissie Thirlwell, University of Exeter school of medicine, Exter, UK
- Prof. Bertram Wiedenmann, Charitè, University Hospital, Berlin, Germany
- Prof. Anne Couvelard and Dr. Jérôm Cros, Department of Pathology, Hospital Beaujon, Clichy, France
- Prof. Marianne Pavel, head of Endocrinology and Diabetes department, Erlangen Germany
- Prof. Massimo Falconi, Surgery Departement, San Raffaele, Milan, Italy
- Dr. med. Mauro Cives, University of Bari, Bari, Italy
- Dr. Anguraj Sadanandam, ICR, The Institute of Cancer Research, London, UK

Grant Support

- SNF 310030_188639, Aurel Perren (PI), 2020–2024, CHF 632'000
- ENETs CO-Synergy Award, Ilaria Marinoni (PI), 2019–2022, Euro 69'700
- Uniscentia, Aurel Perren (PI), 2020–2021, CHF 135'000
- KLS-4227-08-2017, Aurel Perren (PI); Ilaria Marinoni (Co-PI), 2018–2022, CHF* 395'450
- Bernische Krebsliga, Ilaria Marinoni (PI), 2018–2021, CHF 40'000
- Wilhelm Sander Stiftung, Ilaria Marinoni (PI), 2020–2021, Euro 50'000
- Berner Krebsliga, Matthias Dettmer (PI), 2017–2022, CHF 70'000

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

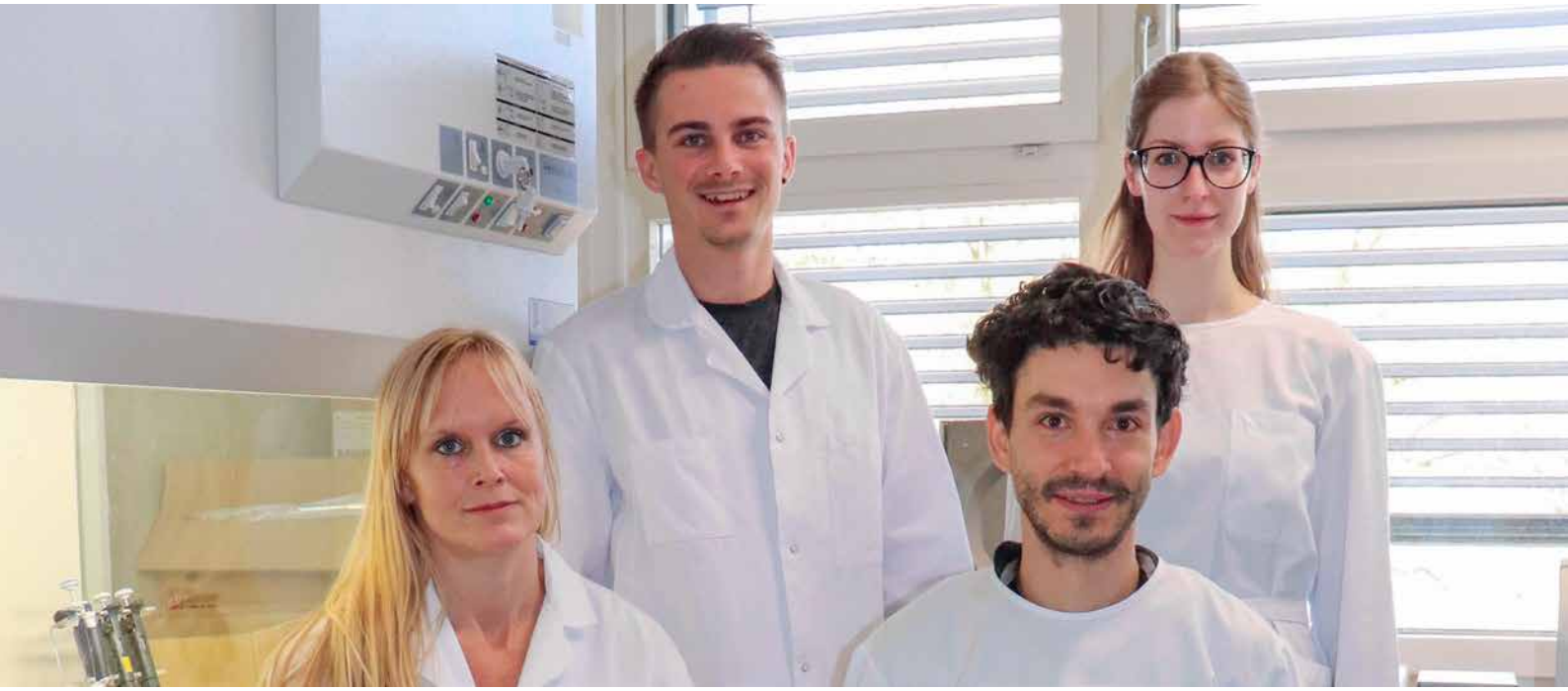
Administrative duties

Aurel Perren

- Präsidium fakultäre Kommission, Strukturkommission Genetik
- Stellvertreter des Dekans Medizinische Fakultät
- Leiter Ressourcenausschuss Medizinische Fakultät
- Mitglied Fakultätsausschuss
- Mitglied Fakultäre Strategie- und Beförderungskommission
- Mitglied Direktorium CCC Inselspital
- Co-Pi und Vize-Präsident Swiss Biobanking Platform (SBP)
- Vorstandsmitglied Krebsliga Bern, Ressortleiter Forschung
- Executive Committees –Mitglied, European Neuroendocrine Tumor Society (ENETS)
- Leiter Krebsregister Bern und Solothurn (KRBESO)
- Stiftungsrat NICER
- Vorstandsmitglied der Deutschen Gesellschaft für Pathologie (DGP)
- Mitglied Forschungskommission SkL
- Mitglied Senat SAMW
- Mitglied der Leopoldina Nationale Akademie der Wissenschaften

Ilaria Marinoni

- Member of MIC Comission University of Bern
- Member of NEXT generation committee of the European Neuroendocrine Tumor Society
- Member of European Neuroendocrine Excellence academy



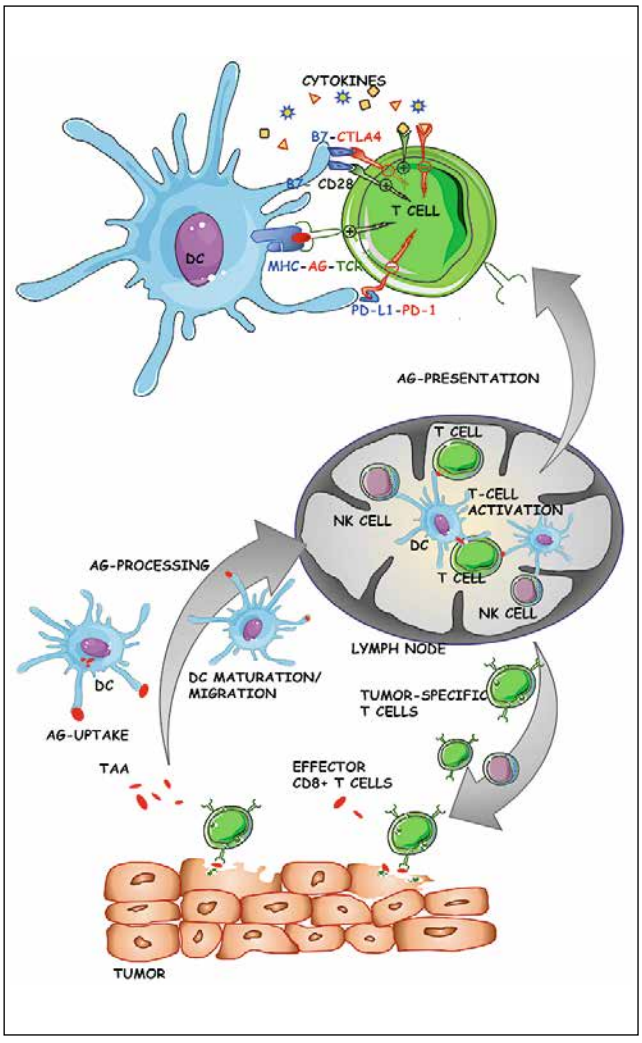
Forschungsgruppe Mirjam Schenk.

Group of Mirjam Schenk, PhD

Lukas Bäriswyl, technician (50%)
Thomas Gruber, PhD student (till May 2020)
Mirela Kremenovich, PhD student
Steve Robatel, PhD student

Summary of Research Activities

The incidence of cancer is steadily rising and presents a major public health problem in many parts of the world. A key player in preventing and controlling malignant disease is the immune system. Unfortunately, in many cancer patients anti-tumor immunity is diminished. This malfunction can be caused by improper maturation of dendritic cells (DC), which thus cannot prime and activate cells of the adaptive immune system, in particular CD8+ T lymphocytes. Cytotoxic CD8+ T lymphocytes (CTL) are essential for killing tumor cells. Using tumor-immunotherapy we aim to enhance the function of the immune system to battle cancer. Specifically, our research group aims to investigate mechanisms to induce DC that can cross-present tumor specific antigens and induce an effective anti-tumor CTL response.



Research Activities

Project 1: Dendritic cells and their co-stimulatory properties for cytotoxic T cells in melanoma

The activation of an effective adaptive anti-tumor response relies mainly on presentation of tumor antigens and stimulation by DC. Despite extensive research, the phenotypes and functions of tumor-infiltrating DC (TIDC) remain largely elusive and cross-presentation of tumor antigen is not well understood. We are elucidating the phenotypes and functions of TIDC and how to manipulate them both 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.

Project 2: Generation of potent cross-presenting Dendritic Cells (DC) for tumor immunotherapy
Only specific subsets of DC are 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-derived DC will be tested in adoptive transfer experiments as prophylactic and therapeutic treatment for established melanoma. Together, these data should identify ways to promote frequency and enhance function of cross-presenting DC and to contribute to anti-tumor response.

Internal Collaborations
- Evanthia Karamitopoulou Diamantis, MD

External Collaborations
National
- Li Tang, PhD, Institute of Bioengineering, Institute of Materials Science and Engineering EPFL, Lausanne
- Michel Gilliet, MD, Department of Dermatology, CHUV Lausanne
- Robert Hunger, MD, Department of Dermatology, Inselspital, University of Bern
- S Morteza Seyed Jafari, MD, Department of Dermatology, Inselspital, University of Bern

International
- Delphine Lee, MD, Division of Dermatology, Department of Medicine Harbor-UCLA Medical Center, Los Angeles Biomedical Research Institute

Grant Support
- SNF 320030_176083, Mirjam Schenk (PI), 2018–2022, CHF 566'109
- Stiftung experimentelle Biomedizin, Mirjam Schenk (PI), 2016-2021, CHF 1.3 Mio
- Helmut Horton, Mirjam Schenk (PI), 2019–2020, CHF 150’000
- Wilhelm Sander Stiftung, Mirjam Schenk (PI), 2019–2020, Euro 49’700
- San Salvatore, Mirjam Schenk (PI), 2019–2021, CHF 143’000
- Novartis, Mirjam Schenk (PI), 2020-2021, CHF 52’000

Administrative duties
- Member of MIC Comission University of Bern (Temporary replacement for Ilaria Marioni)
- Member of the IMC Platform Steering committee

Research group Mario P. Tschan.

Group of Mario P. Tschan, PhD

Fabienne Anderegg, BMA-Praktikantin (till April 2020)
Anna Bill, PhD postdoc, 70%
Magali Humbert, PhD postdoc (till December 2020)
Deborah Krauer, technician, 80%
Filip Manevski, Master student (BIO)
David Maul, BMA-Praktikant (from Nov 2020)
Irene Mungure, Master student (BIO) (till March 2020)
Nicolas Niklaus, PhD student
Sreoshee Rafiq, PhD student (Supervisor, Dr. M. Humbert)
Robin Schweri, Master student (BIO) (till March 2020)
Kristina Seiler, MD-PhD student
Igor Tokarchuk, MD-PhD student
Jun Xu, MD-PhD student (from Nov 2020)

Summary of Research Activities

Cancer Autophagy Group: My research team investigates molecular mechanisms involved in the pathogenesis of acute myeloid leukemias (AML). Currently, we are deciphering the function of autophagy and the transcription factor PU.1 in this disease. Additional research projects led by Magali Humbert (AML) and Anna Schläfli (Breast cancer) address the function of the autophagy recycling pathway in the resistance of hematological and solid cancers to chemotherapeutic agents and targeted therapies. All these preclinical studies in targeted, personalized cancer therapy are conducted in close collaboration with clinical pathologists and the Translational Research Unit.

Research Activities

Project 1: Function of Chaperone-Mediated Autophagy in Myeloid Leukemia Therapy

While classification of the heterogeneous blood cancer, acute myeloid leukemia (AML) improved significantly, scarce progress has been made in terms of treatment. Relapse and therapy failures remain high due to chemotherapy-resistant leukemic cells (CRLC). Our preliminary data link increased chaperone-mediated autophagy (CMA) to resistance mechanisms in differentiation therapy and an immature developmental stage of AML blasts. Therefore, we are aiming at understanding the role of CMA in the biology of AML cells and CRLC including the interaction with the microenvironment.

Project 2: Understanding the role of autophagy in retinoic acid therapy of breast cancer

Epithelial-to-mesenchymal transition (EMT) plays a key role in therapy-resistance and metastasis formation. In the present study, we therefore aim at reversing the EMT phenotype of breast cancer cells using differentiation-based therapy based on all-trans retinoic acid (ATRA). Cellular differentiation is often associated with upregulation of autophagy. Autophagy is a lysosomal degradation and recycling system and may supports cellular differentiation by removing superfluous organelles, keeping energy levels or by regulating signaling by selective removal of proteins. Therefore, we study autophagy functions during therapy-induced MET and how modulation of

autophagy can support differentiation-based therapy. Furthermore, we investigate how cancer associated fibroblasts influence cancer autophagy and therapy efficiency.

Project 3: Identification and analysis of PU.1 cell death pathways
The ETS-transcription factor PU.1 is needed throughout hematopoietic differentiation particularly by orchestrating terminal differentiation of macrophages and neutrophils. Importantly, low PU.1 expression can lead to the transformation of myeloid progenitor cells to acute myeloid leukemia (AML) blast cells. We found a new tumor suppressor function for PU.1 by supporting TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in AML cells. Currently, we are investigating how PU.1 regulates alternative splicing of anti-apoptotic genes and how this affects AML therapy responses.

Internal Collaborations
- Inti Zlobec, PhD
- Tilman Rau, MD
- Yara Banz, MD-PhD

External Collaborations
National
- Thomas Kaufmann, PhD, Institute of Pharmacology, 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
- Carsten Riether, PhD, DBMR, University of Bern

International
- Bruce E. Torbett, PhD, TSRI, La Jolla, CA, USA
- Rupert Langer, MD, Institute of Pathology and Molecular Pathology, University of Linz, Austria
- Enrico Garattini, MD, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
- Jean-Emmanuel Sarry, PhD, Centre de Recherches en Cancérologie de Toulouse - CRCT, Toulouse, France
- Sylviane Muller, PhD, CNRS UMR7242 Biotechnology and Cell Signaling, University of Strasbourg, France

Grant Support
- SNSF_310030_197786, I. Zlobec; M. Tschan; Co_PI, 2020–2024, CHF* 632'000
- Werner und Hedy Berger-Janser Stiftung, Magali Humbert, 2020, CHF 79'946
- Partenariat Hubert Curien/Germaine de Staël Funding, J.E. Sarry, Co-PI Mario Tschan, 2019–2020, CHF* 4'500
- Stiftung für klinisch-experimentelle Tumorforschung, Magali Humbert, 2018–2020, CHF 20'000
- Bernische Krebsliga, Magali Humbert, 2017–2021, CHF 85'000
- SNSF_31003A_173219, Mario Tschan, 2017–2021, CHF 693'641
- SNSF MD-PhD 03/17, Kristina Seiler; Mario Tschan; PI, 2018–2020, CHF 180'000
- UniBE international 2021, I.Tokarchuck; Mario Tschan; PI, 2018–2020, CHF 90'000

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

Administrative duties
- Member of the Interfacultary PhD Committee, Graduate School for Cellular, Biomedical Sciences (GCB)
- Chair Expert Committees Cell Biology of the GCB Graduate School
- Member of the steering board of the Master study program Biomedical Sciences at the Medical Faculty and organizer of the teaching block tumor biology for this program
- Member of the «Vereinigung der Dozentinnen und Dozenten der Medizinischen Fakultät Bern» representing the interests of UniBE lecturers at the Medical Faculty meetings
- Member of the Expert Committee for Biomedical Analysts, «Zentrum für medizinische Bildung, Höhere Fachschule»
- LS2 section autophagy, past-president
- Co-referee «assoziierte Professur» PD Dr. med. Martin Müller
- Guest editor: Special Issue «Autophagy in Cancer»

Group of Erik Vassella, Dr. pharm.

Bushra Fakher, Master student (BIO)
Elham Kashani, PhD student
Lisa Perrig, Master student (Med)
Jaison Phour, technician
Carmen Trefny, Master student (BIO) (till Mar 2020)
Miroslava Dragojlovic, BMA-Praktikantin (till May 2020)

Summary of Research Activities

MicroRNAs are short regulatory RNAs at the post-transcriptional level that are implicated in a wide variety of basic biological processes as well as in cancer. My research team is aiming at identifying microRNAs that are implicated in resistance to chemo- and targeted therapy of non-small cell lung cancer and gliomas. Our results suggest that antagomirs that block the expression of endogenous microRNAs could be used in adjuvant cancer therapy.

Research Activities

Project 1: Screening for microRNAs conferring temozolomide resistance in glioblastoma cell lines

We follow an unbiased approach for the identification of microRNAs that are most efficient at conferring resistance to the alkylating agent temozolomide in glioblastoma cells, which are the most common and most aggressive primary malignant brain tumour. To this end, glioblastoma cell lines were screened with a lentiviral microRNA library and selected for temozolomide resistance. Resistent clones were identified by next generation sequencing. We are currently investigating the molecular mechanism of temozolomide resistance elicited by these miRNAs.

Project 2: Chemoresistance mechanisms in glioblastoma

Glioblastoma is the most common and among the most aggressive primary malignant brain tumour in adults. This tumour is incurable due to its highly infiltrative growth and its intrinsic resistance to radiochemotherapy. DNA repair mechanisms play an important role in the development of resistance, but the underlying molecular mechanisms are largely unknown. We follow a translational approach for the identification of secondary mutations as well as alterations in gene expression profile, and will assess clinical-pathological characteristics of recurrent glioblastomas, which have developed resistance to radio-chemotherapy. In future, this approach may help for the development of new personalized medicine. This project is currently supported by the Swiss National Science Foundation.

Internal Collaborations

- Ekkehard Hewer
- Sabina Berezowska
- Mario Tschan
- Ilaria Marinoni and Aurel Perren
- Inti Zlobec

External Collaborations

National

- Peng Ren-Wang, PhD, and Thomas Marti, PhD, Universitätsklinik für Thoraxchirurgie
- Markus Lüdi, Universitätsklinik für Anästhesiologie
- Ekkehard Hewer and Sabina Berezowska, Institut universitaire de pathologie, Lausanne

International

- Rupert Langer, Kepler Universitätsklinikum, Linz
- Pascal Zinn, University of Pittsburgh

Grant Support

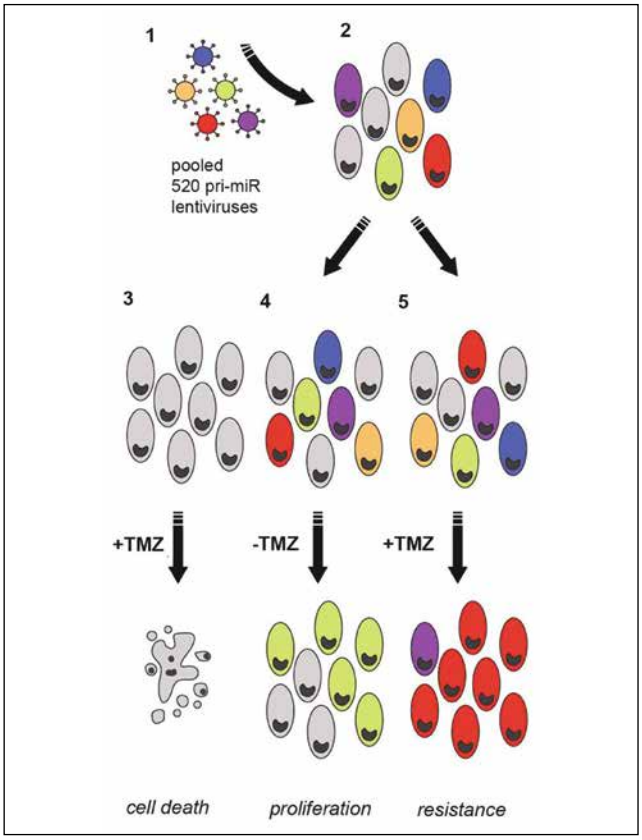
- SNF (31003A_175656), Erik Vassella; PI, 2018–2022, CHF 408'509
- SAKK 75/08 Rupert Langer, Rupert Langer; PI, Erik Vassella; Co-PI, 2018–2025, CHF 132'640
- Swiss Cancer League, Sabina Berezowska; PI, Erik Vassella; Co-PI, 2019–2022, CHF 365'500

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

Alumni

Jean-Claude Reubi, MD (Prof. Dr. med. em.)

Professor Jean-Claude Reubi, MD, formally retired in 2012, but still continued in 2020 his most successful publication activities in the field of peptide receptor imaging and therapy.



Screening for microRNAs conferring temozolomide resistance in glioblastoma cell lines.

1.2 Translational Research Unit (TRU)

Head: Inti Zlobec, PhD

Administration: Caroline Hammer (50%)

Technical and Scientific Staff:
Carmen Cardozo
Dr. Irene Centeno
Loredana Daminescu
Dr. José A. Galván
Stefan Reinhard
Sandrine Ruppen (until October)
Fabian Wenger (from November)
Dr. Magdalena Skowronska

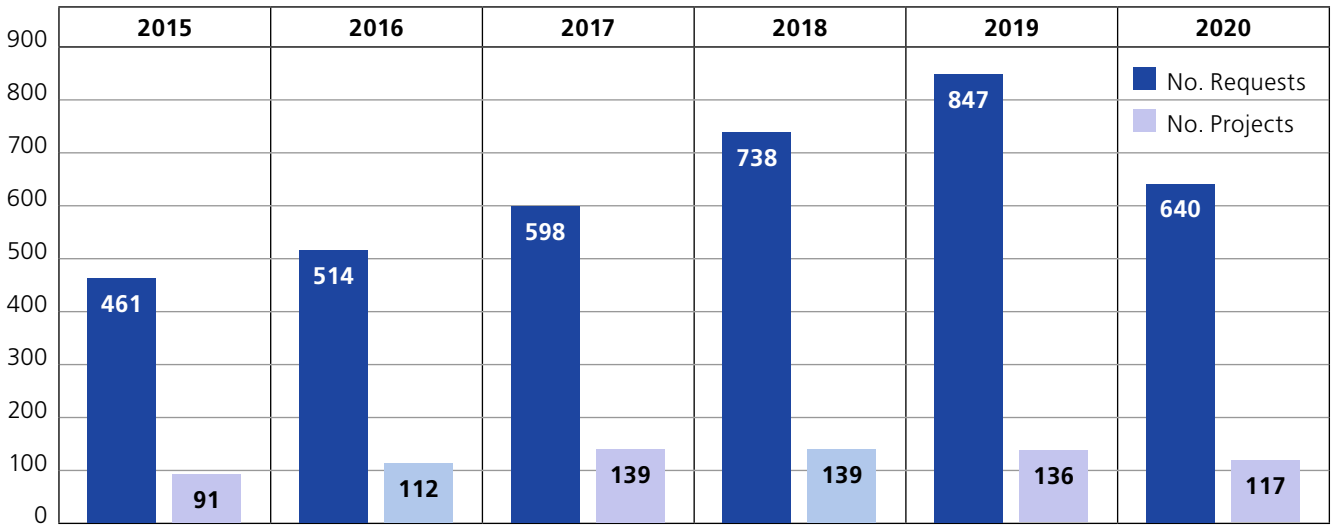
Overview

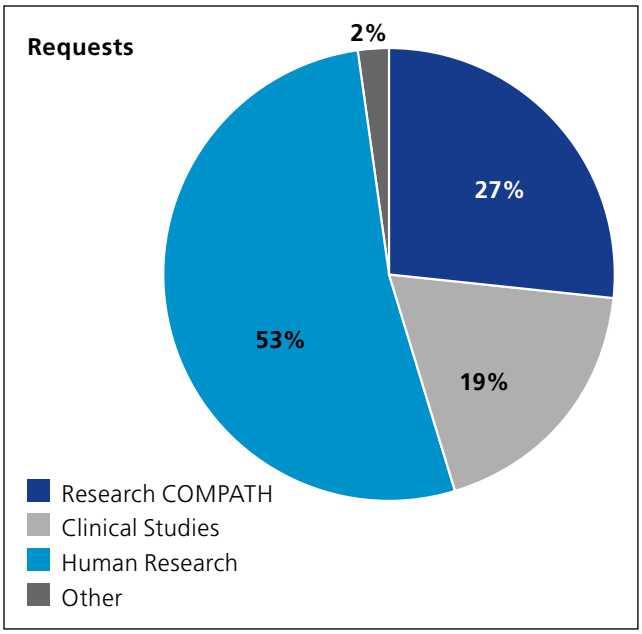
The Translational Research Unit (TRU) is a core facility of the Institute of Pathology, University of Bern. We provide tissue-based services for researchers and use innovative technologies to support translational projects conducted on human and animal tissues. We collaborate with researchers from the University of Bern, and participate in national and international projects. Our portfolio includes histopathology services, establishment of methods for tissue «visualization», digital pathology and image analysis, and next-generation Tissue Microarraying (www.ngtma.com). Moreover, we further support research by working together and providing access to patient material for research purposes through our certified partner biobank, Tissue Bank Bern (TBB).

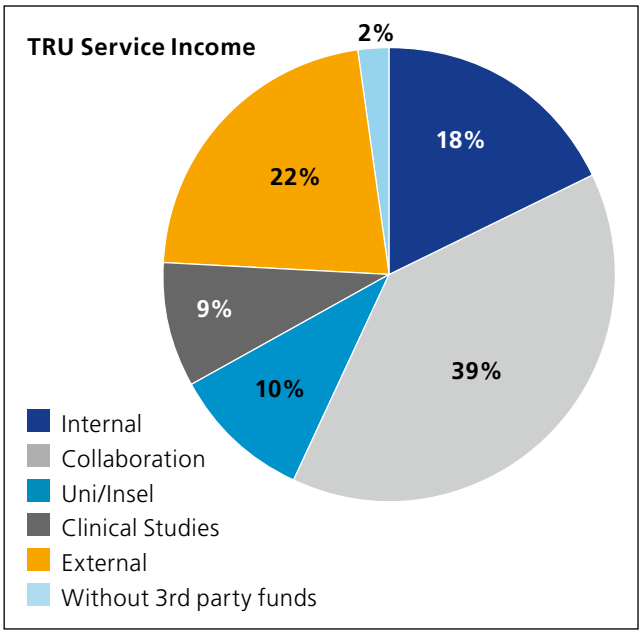
Projects and requests for services

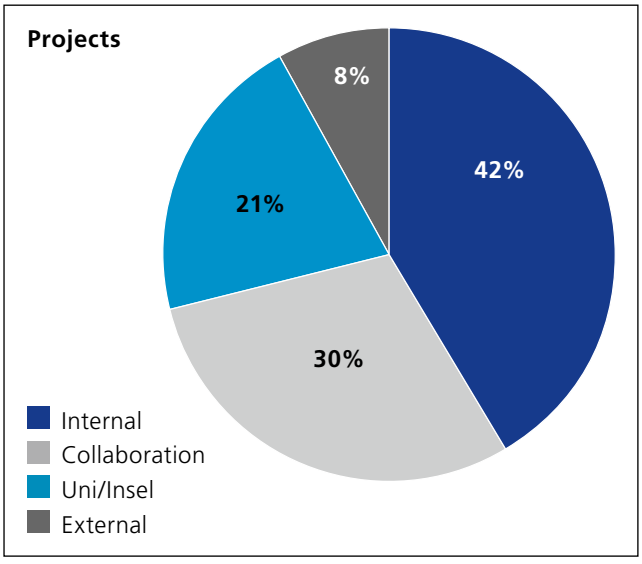
In 2020, despite the Covid-19 pandemic and closure of TRU for several months, we could still support 117 projects (169 in 2019) from 640 separate requests (excluding those in TBB). Of those, 45% were from internal researchers, whereas 23% were part of collaborations, including those with industry, and 28% were completed for researchers from the Inselspital /DBMR. The number of service requests from investigators outside of the University/hospital occurred only in a small percentage of cases (4%). TRU requests include approximately 27% animal tissue, 19% clinical studies (including SAKK or trials with primary investigators at the Inselspital). The remaining are tissue-related requests. New this year was the introduction of Selectline, a project management tool that will further help to organize requests, client lists, documentation and billing.

Sources of income vary: 98% of all of TRU's services in 2020 were funded by third party money, while the remaining 2% were sponsored by the Institute of Pathology. This institutional funding aims to cover start-up projects for our pathologists and researchers.









Number of projects (and associated requests) managed by TRU in 2020 and distribution of funding sources this year.

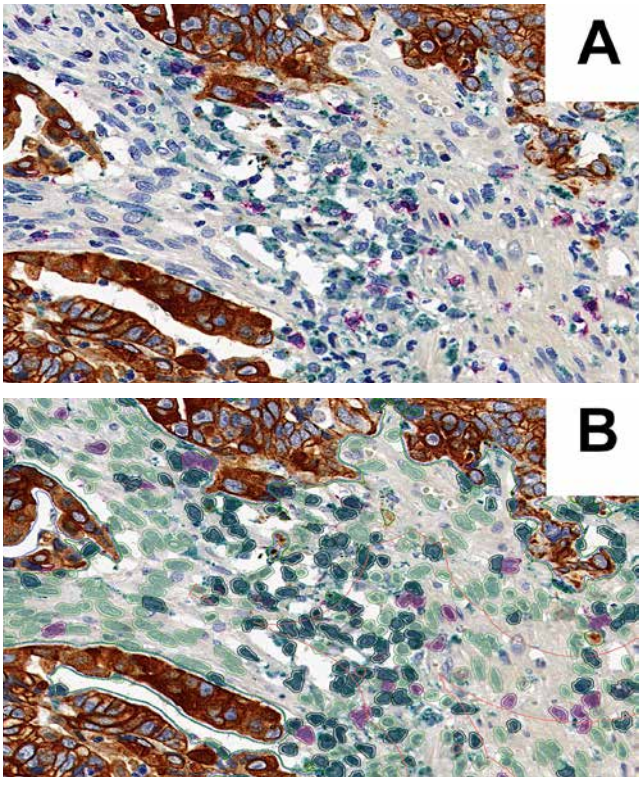
Histology services

Our lab has expertise in histology techniques and tries to personalize each research project. Sections are cut for many purposes: laser capture microdissection, DNA/RNA extraction, immunohistochemistry and other special downstream techniques (e.g. MALDI). Histology is the basis of all the work performed in TRU. This year, we have re-embedded 1905 (2019 n=2662) blocks, and cut thousands of slides for H&E or special stains (n=2435; 2019 n=3189 slides), immunohistochemistry, TUNEL or in situ hybridisation (n=3852; 2019 n=4936), empty cuts 4982 and slides requiring special DNAse/RNAse-free conditions (n=182; 2018 n=166).

Tissue Visualisation

TRU has expertise in tissue visualisation methods, including assays for immunohistochemistry (IHC), mRNA in situ hybridisation (ISH), immunofluorescence (IF), TUNEL and combinations of these. This year saw the development of multiplexed chromogenic staining (3-colors plus counterstain) tested and validated using different chromogens.

These are being used to learn about the tumor microenvironment in colorectal cancers and other disease entities by studying multiple cell types in the same tissue sections, using machine-learning algorithms. Such staining methods will pave the way for the goal of more high-dimensional multiplexing in the upcoming year.



A) PanCK (brown), CD8 (red) and CD68 (green) in colorectal cancer, B) cell detection using QuPath.

This year, TRU has added an additional 68 new antibodies to its repertoire, and has performed 3'083 single stains, 656 double stains, 102 ISH and 11 TUNEL assays. Moreover, 52% of all slides were stained for internal researchers from the Institute of Pathology, 24% were part of collaboration projects, and 23% were performed as a service for the University/Insel researchers. In addition, about 25% of all slides stained were animal tissues.

Digital pathology

Modern pathology goes hand-in-hand with digitisation. TRU has been working on digital pathology on different fronts.

a) Slide scanning

This a service used for various purposes, namely for education, to produce publication-quality images, for digital image analysis and development of artificial intelligence algorithms, for construction of next-generation Tissue Microarrays, sharing of images with research collaborators, or even archiving of slides digitally. TRU offers access to the Case Center for external users. Here, digital slides can be uploaded and viewed from outside the Institute.

b) Next-generation Tissue Microarrays (ngTMA®)

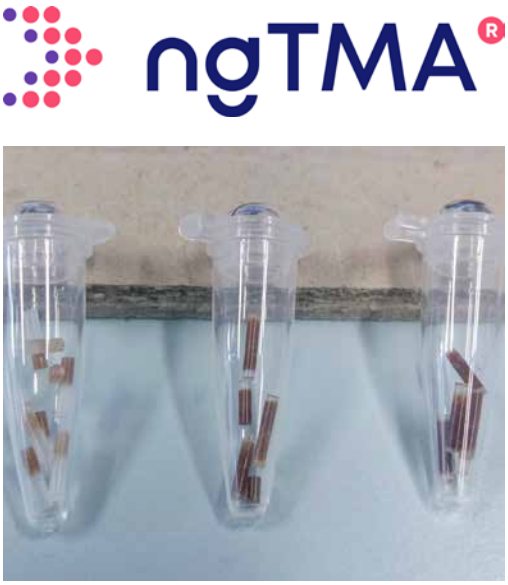
Our ngTMA facility has evolved into an internationally-recognized platform for the construction of high-quality tissue microarrays. By incorporating digital pathology and a downstream data-handling pipeline, ngTMA supports histopathology-based and computationally-driven AI research.

This year saw a more automated workflow for ngTMA from the introduction of barcode reading to the processing of TMAs into our research database Telemis or evaluation in Scorenado. We continue to work on highly complex tissue microarray projects, or involving material to be used for subsequent targeted RNA sequencing or whole exome sequencing.

In 2020, TRU launched a new website for ngTMA along with a new dynamic logo (www.ngtma.com), a Twitter account and maintains a LinkedIn page.

The demand for tissue microarrays continues to rise, in fact 2020 saw the purchase of a second tissue microarrayer for TRU, which will help us to accommodate simultaneous projects, and shorten turn-around-times.

The types of requests for ngTMA have changed over time. Originally used as a screening tool for different biomarkers, ngTMA is now employed for development of new methodologies, such as multiplexed immunofluorescence (e.g. OPAL, CODEX) and for assessment of intratumoral heterogeneity. This year, our ngTMAs have also been used to help develop machine learning algorithms using both fluorescence and chromo-



Left: the ngTMA facility, right top: new ngTMA logo, right bottom: punches that can be taken from blocks after aligning digitally annotated images using ngTMA technology.

genic staining in various tumor types, such as endometrial and colorectal cancers. Since our approach for constructing TMAs is based on digital scans, we use the instruments to punch out regions of interest marked on histological digital slides, which will undergo further molecular sequencing analysis.

Since it's inception in 2012, TRU has created more than 770 ngTMA blocks, totaling more than 145'000 punches in recipient blocks and 20'000 punches for tubes, and hence downstream molecular analysis. The number of donor blocks totals more than 19'000. The content of these donor blocks includes a large number of upper and lower gastrointestinal cancers, lung cancers, neurological tumors and endocrine (including neuroendocrine) cancers, but also sarcomas, pancreas cancers, gynecological tumors, breast cancer and urological specimens. A summary of our archive can be found on our website.

In 2020, 69% of ngTMAs constructed were for external project partners (international researchers or industry). We are proud to include the University of Stanford, University of California, Cancer Barts Institute, University of Amsterdam and Karolinska Institutet, University Hospital Zürich, Cancer Research UK and Uppsala University, Sweden among our international collaborators. On a national level, we continue our collaborations with the EPFL Lausanne, University of Basel, Inselspital and the Department for Biomedical Research (DBMR) of the University of Bern.

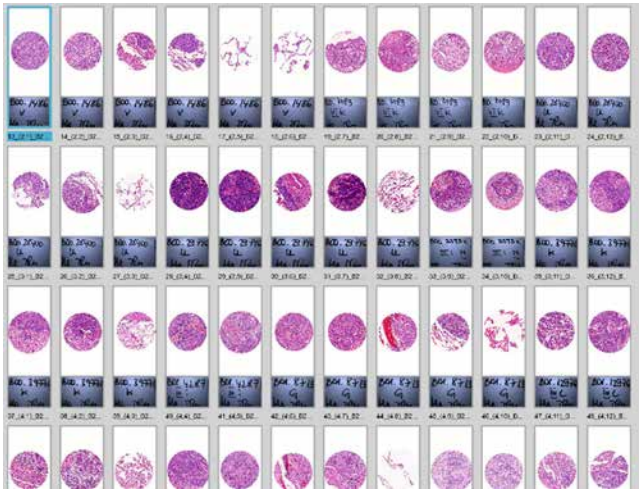
In 2020, in-person or virtual presentations of the ngTMA or related scientific projects were represented at the AACR Virtual Meeting, the 7th Digital Patholog & AI Congress: Europe, the Europe Biobank Week and the Lab Animals Course-COMPATH (University of Bern).

ngTMA played an important role in several research publications this year including:

- Rodriguez A, Gallon J, Akhoundova D, et al. The Genomic Landscape of Prostate Cancer Brain Metastases, BioRxiv https://www.biorxiv.org/content/10.1101/2020.05.12.092296v1
- Galván JA, Wiprächtiger J, Slotta-Huspenina J, et al. Immunohistochemical analysis of the expression of cancer-associated fibroblast markers in esophageal cancer with and without neoadjuvant therapy. Virchows Arch. 2020 May;476(5):725-734. doi: 10.1007/s00428-019-02714-6. Epub 2019 Dec 11. PMID: 31828432.
- Dawson H, Christe L, Eichmann M, et al. A. Tumour budding/T cell infiltrates in colorectal cancer: proposal of a novel combined score. Histopathology. 2020 Mar;76(4):572-580. doi: 10.1111/his.14006. Epub 2020 Feb 3. PMID: 31560788.
- Schürch CM, Bhate SS, Barlow GL, et al. Coordinated Cellular Neighborhoods Orchestrate Antitumoral Immunity at the Colorectal Cancer Invasive Front. Cell. 2020 Sep 3;182(5):1341-1359.e19. doi: 10.1016/j.cell.2020.07.005. Epub 2020 Aug 6. Erratum in: Cell. 2020 Oct 29;183(3):838. PMID: 32763154; PMCID: PMC7479520.
- Rau TT, Bettschen E, Büchi C, Christe L, Rohner A, Müller MD, Carlson JW,Imboden S, Zlobec I. Prognostic impact of tumor budding in endometrial carcinoma within distinct molecular subgroups. Mod Pathol. 2020 Jul 29. doi:10.1038/s41379-020-0626-9. Epub ahead of print. PMID: 32728223.
- Contat C, Ancey PB, Zangger N, Sabatino S, Pascual J, Escrig S, Jensen L,Goepfert C, Lanz B, Lepore M, Gruetter R, Rossier A, Berezowska S, Neppl C, Zlobec I, Clerc-Rosset S, Knott GW, Rathmell JC, Abel ED, Meibom A, Meylan E.Combined deletion of Glut1 and Glut3 impairs lung adenocarcinoma growth. Elife.2020 Jun 23;9:e53618. doi: 10.7554/eLife.53618. PMID: 32571479; PMCID:PMC7311173.
- Losmanová T, Janser FA, Humbert M, Tokarchuk I, Schläfli AM, Neppl C, SchmidRA, Tschan MP, Langer R, Berezowska S. Chaperone-Mediated Autophagy MarkersLAMP2A and HSC70 Are Independent Adverse Prognostic Markers in Primary ResectedSquamous Cell Carcinomas of the Lung. Oxid Med Cell Longev. 2020 Sep21;2020:8506572. doi: 10.1155/2020/8506572. PMID: 33029283; PMCID: PMC7527932.

c) Data management

Over the years, TRU has generated a huge archive of histopathology images, most labeled with histological and clinical data. These images can now be used to train AI algorithms for prediction of clinical outcomes, molecular subtypes or other endpoints.



Our ngTMA facility has led to a huge number of high-quality, high-value images that can be used for training and testing different machine learning algorithms. We estimate that more than 1'000'000 images are currently available. These images include: whole slide images (WSI) that have been annotated for subsequent TMA construction, the images of the annotated tissue areas (see left), the TMA slides themselves and, of course, different stainings that have been made on sections cut from each block.

Managing this data is however complex and many IT aspects need to be considered. Digitisation, data management and data sharing are topics of substantial importance for TRU. As such, major efforts were undertaken to develop a Human Research Act (HFG2014) compliant research database together with the company Telemis for integration of not only clinicopathological and outcome data for patients and tissue samples but also for whole slide images, and most importantly ngTMA images and related data.

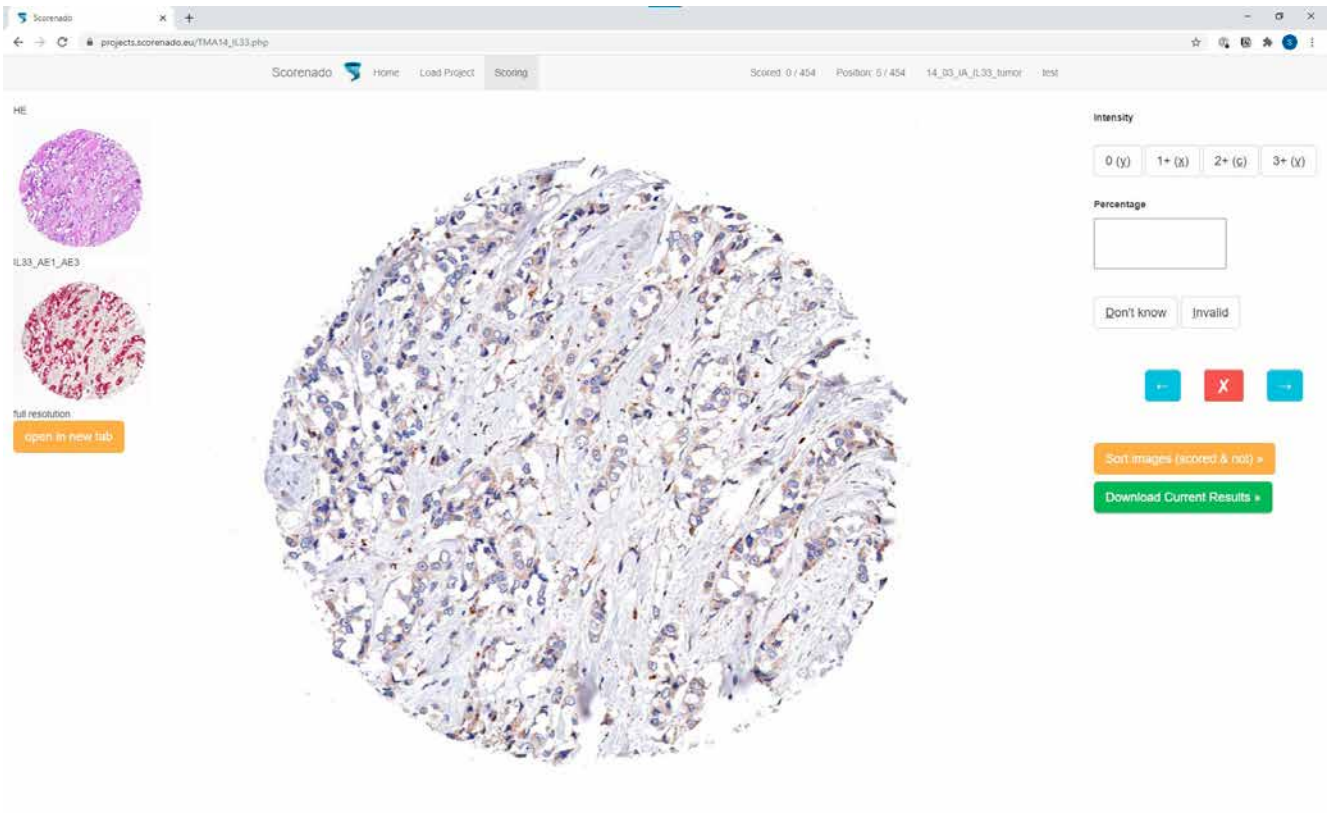
So far, clinical data from 2184 patients, 242 TMAs corresponding to 53'333 spots and 2609 whole slide images comprising seven different patient cohorts have been processed and imported into Telemis. An automated workflow is established to speed up and simplify the creation of imports to the research database. An important task for data import is in the preparatory phase of data cleaning, as such TRU helps support researchers in data preparation and are on the way to consolidate another 10 research cohorts. Enhancement of the database will continue in 2021.

d) Digital Image Analysis

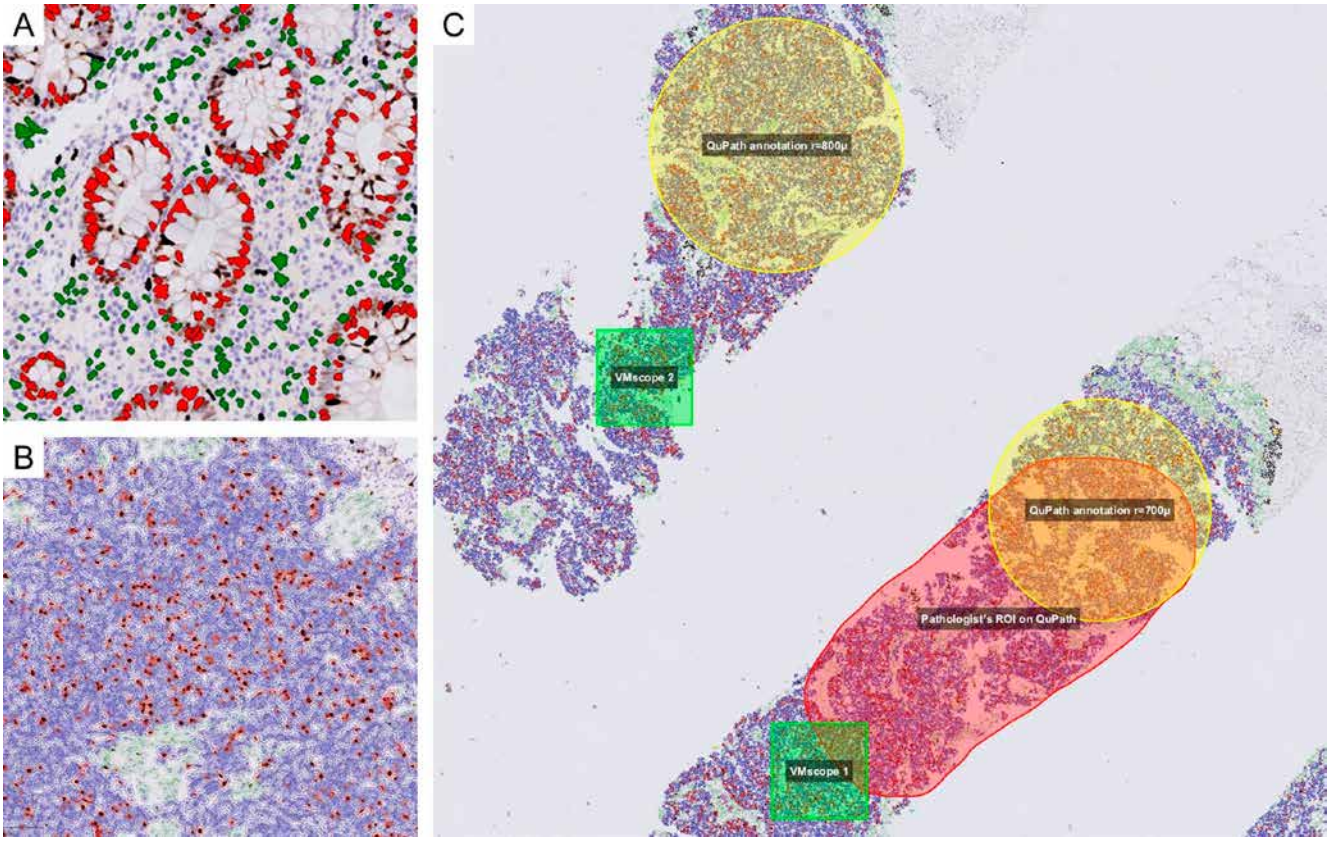
TRU provides access to «Scorenado», an efficient and user-friendly visual assessment tool for scoring TMA slide spots and other sets of images in a blinded and randomized manner. Since its test launch, a total of 53 Scorenado projects, including 615 slide scans, were set up for research conducted in-house, at Insel Hospital, and at other institutes in Switzerland and abroad. Overall, 141'456 TMA spot images or whole-tissue slide crop images have been scored with Scorenado. Project types included scoring different immunohistochemistry markers, estimating percentages of tumor positivity, counting tumor buds, and image classifications in colon, lung, breast, pancreas, and endometrium tissue.

TRU is also supporting researchers by providing training in image analysis using the free, open-source tool QuPath. This year, five different projects could be supported. In addition, a collection of scripts facilitating image analysis in QuPath and TMA data handling was established.

In addition, we have developed an open source workflow to analyze Ki-67 stained breast cancer specimens in diagnostic routine; this includes the management of the data from the scanner to the actual result. A web-app provides an overview of the status of the cases and an in-house algorithm was developed together with five pathologists in-house. TRU, together with pathologists from our Institute are carrying out comparison studies of Ki67 analysis using various machine learning tools including commercially available platforms. We work together with the digital pathology team to evaluate different deep learning algorithms, their possible integration into diagnostic routine and clinical relevance.



Screenshot of Scorenado, the spot to be scored in the middle, related spots with different staining on the left and the control unit on the right.



Comparison of different methods for detection of Ki-67 proliferation in tumor. Positive tumor cells in VM Scope (A, red) and QuPath (B, red). C shows pathologist-generated annotation (red), Qupath (yellow) and VM Scope (green).

Tissue Bank Bern (TBB)

Director: Prof. Aurel Perren

Manager and co-manager:
Prof. Inti Zlobec and PD. Dr. med. Tilman Rau

Operative functions and project management:
Dr. Irene Centeno and Dr. Magdalena Skowronska, Loredana-Ionela Daminescu

Additional members: staff of TRU and Clinical Pathology Division, IT team of Institute of Pathology.

The TBB works together with the Clinical Pathology Division at the Institute of Pathology to ensure the collection and distribution of high-quality human tissue samples conform to the Human Research Act, 2014. TBB services are, since October 2016, being performed by the Translational Research Unit (TRU) thus, personnel and resources are shared.

Workflow

The request process is simple and does not mean additional bureaucracy for the researcher. The requirements to use samples from our tissue collection include the description of the project, the type and characteristics of the requested tissue and essential information regarding the ethical approval. Our committee will evaluate each request and provide advice, if needed. The estimated timelines and processes are displayed in the picture below.

TBB activities

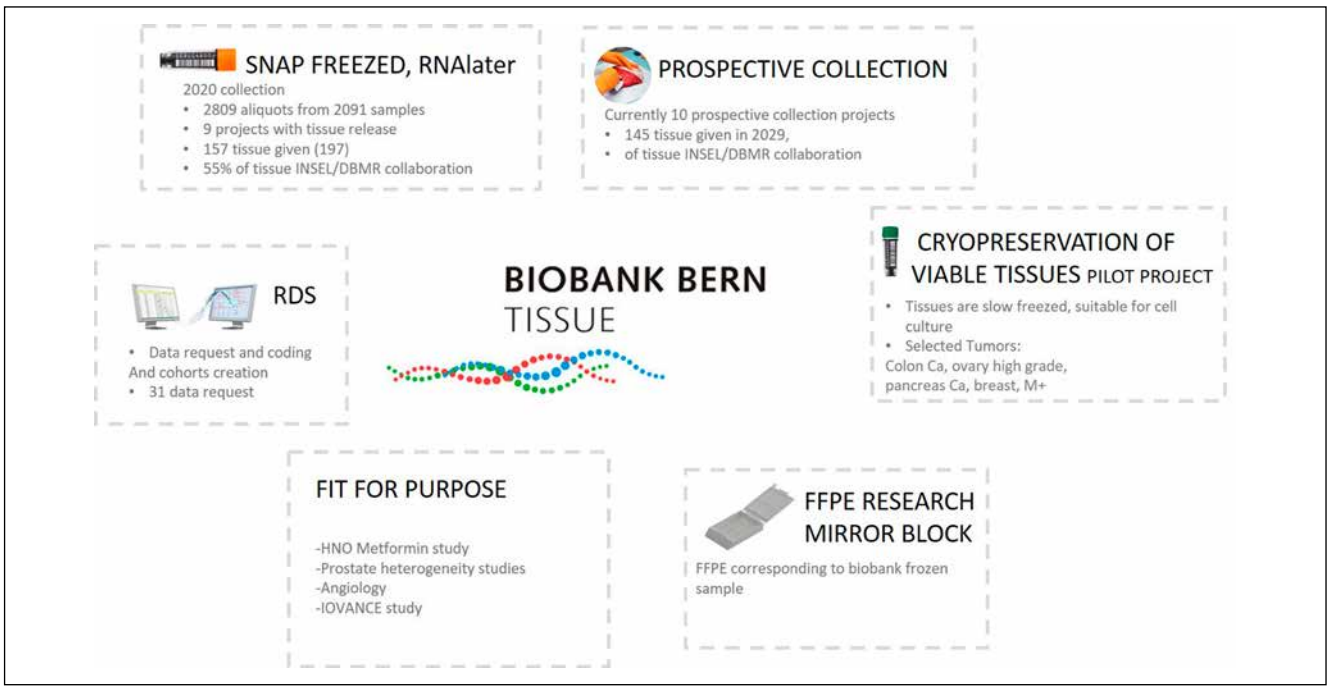
In 2020, aside from providing the scientist with frozen and native material, we have increased the portfolio of customized collections, implying strong multi-institutional and cross-departmental collaboration. Currently we closely work with the Angiology and HNO departments where we process bio-banking tissue within the operation theater allowing low ischemia times necessary for particular studies. From selected tumours, we slow freeze the tissue and store it in liquid nitrogen for experiments requiring live cells in their experimental set-up. Main on-going activities are summarised in the Figure below.

TBB institutional collection statistics

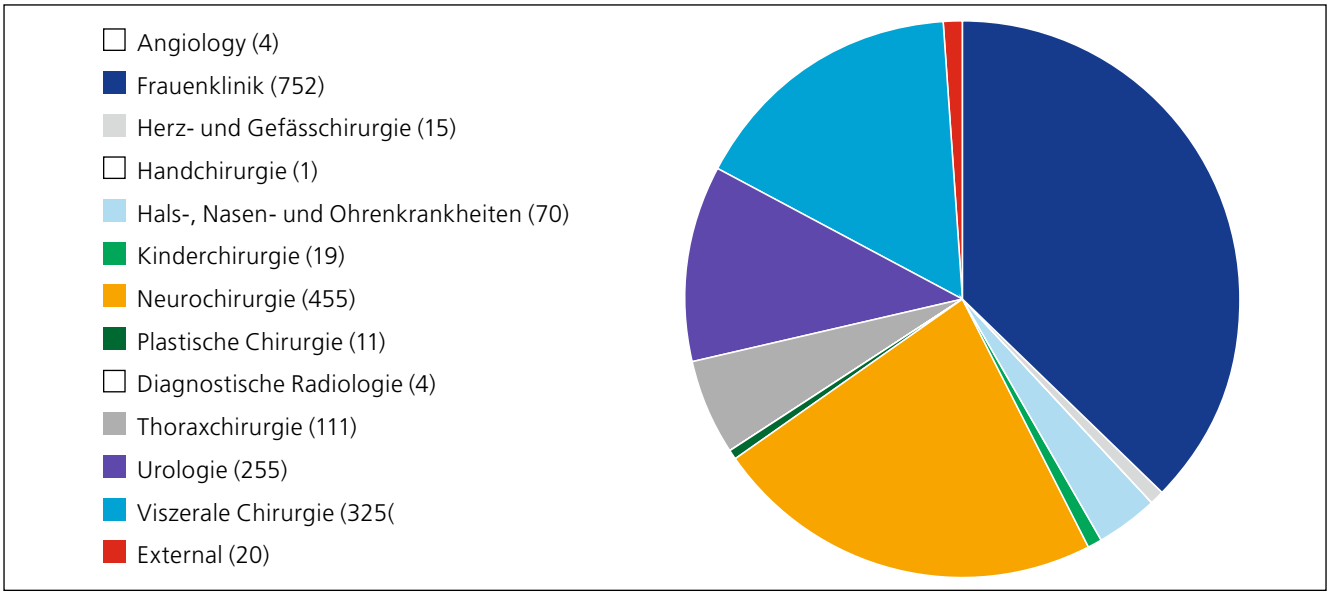
TBB markedly expanded its tissue collection reaching almost 15'000 different samples stored in ~45'000 tubes. In 2020, we collected material from ~2000 samples from different clinics that continue their important contribution to the biobank. The contribution per clinic can be found in the chart below, with the largest amount of samples deriving from the Frauenklinik (Gynecology), followed by the clinics of neurosurgery, visceral surgery and urology as well as thoracic surgery.

Below we can appreciate the coverage of pre-analytical values that are associated with tissues stored in the biobank.

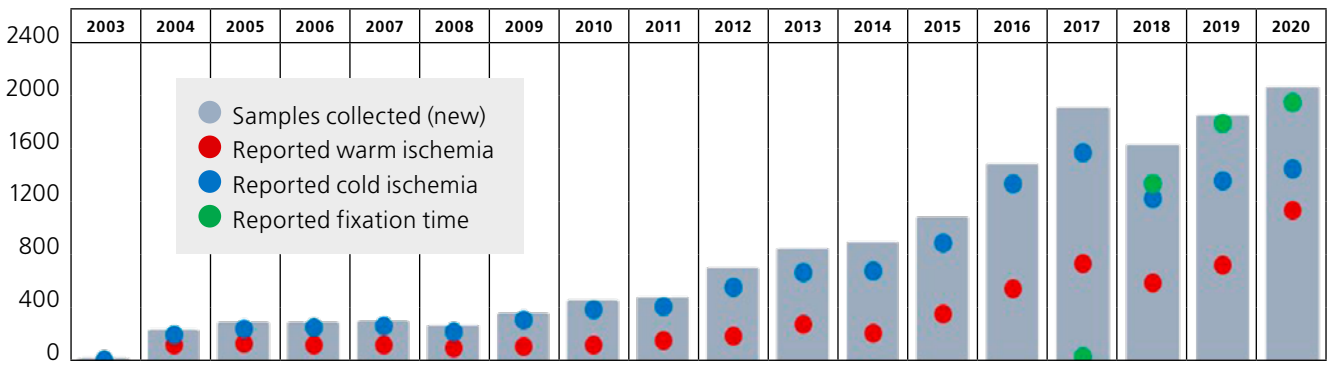
REQUEST FORM	TBB ORDER PREOCESSING	SAMPLE DELIVERY
Project description Request sample Request of data Provide ethics approval	Technical acceptance Query Clinical acceptance Consent proofing	Exit control MTA contact Material transfer to researcher
1–8 weeks	2–3 weeks	1–2 weeks



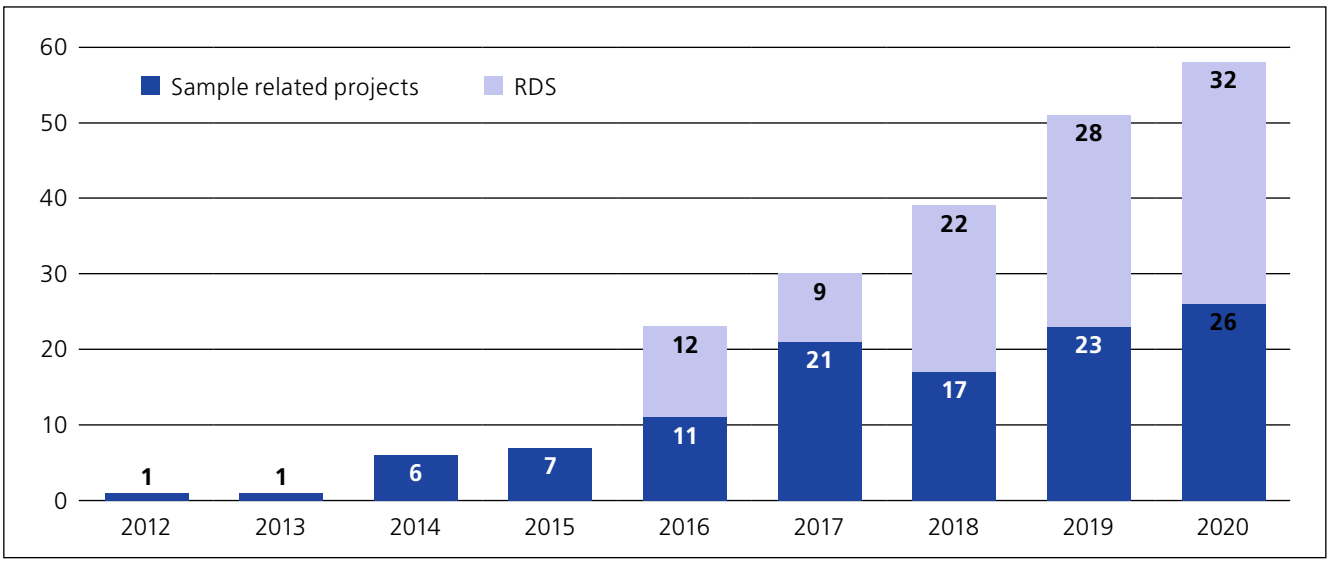
Different activities performed by TBB in 2020.



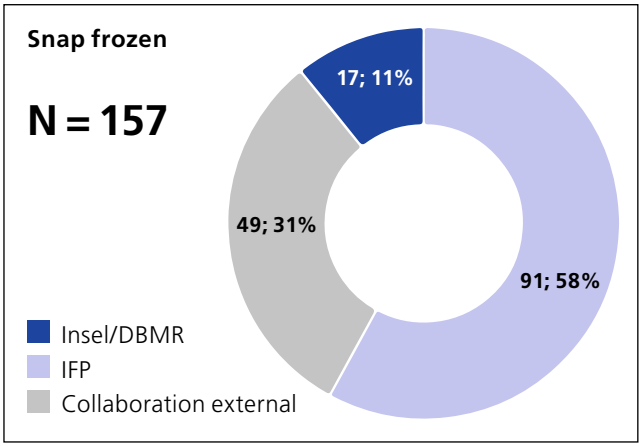
Distribution of incoming tissue specimens for biobanking.

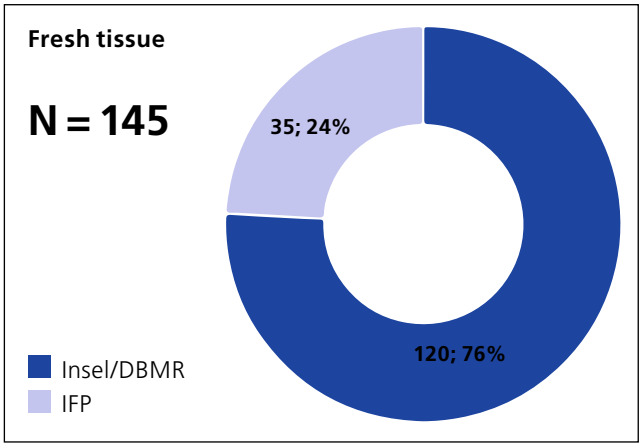


Number of collected tissue per year, with indicated coverage of pre-analytical values.



Number of TBB requests for tissues/data showing growth of usage over the last years.





Summary of tissue usage by internal, Insel Hospital or University of Bern (incl. DBMR) researchers for prospective projects and retrospective (frozen collection) in 2019.

Projects by tissue bank Bern 2020
The number of TBB projects continues to rise. In 2020, we received 58 requests for tissue and/or data.

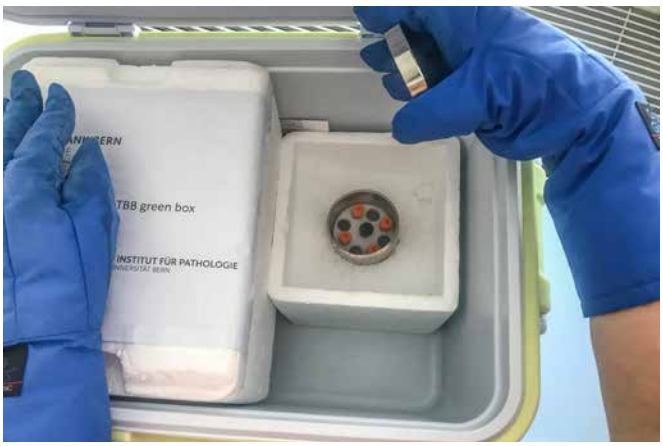
Usage of tissue samples in 2020
We have provided scientists with 157 frozen tissues, all with pathological tumour content control. Additionally, 145 tissues were given in a prospective manner.

Towards the best quality of service
The delivery of optimal quality tissues to researchers is one of the main aims of TBB. In this regard, TBB has been strongly focused on the standardization of the multiple biobanking processes together with the Swiss Biobanking Platform (SBP), including collection, transport, processing, storage and distribution of the sample as well as personnel and equipment management. TBB is rewarded with the three labels from SBP.

The collection and storage of the TBB samples are included under the Institute of Pathology accreditation by the Swiss Accreditation Service (SAS) according to ISO 17025:2005 and ISO 15189:2013 since 21.08.2018.

TBB works in compliance with Human Research Act (Humanforschungsgesetz, HFG).

Fit-for-purpose TBB Collections
Our commitment towards satisfying the requirements of the researcher is demonstrated in our enhanced procedures for customized collections. Our advanced process optimization is the result of strong simultaneous collaboration of TBB, clinics and researchers. This year we have ongoing project with



Collection procedure of peripheral artery disease tissue samples in the surgical theatre and on the right site surgery personel from the Head and Neck Surgery Clinic being trained for project based customized sample collecction.

Angiology with samples collection across different Inselspital department and Head, and Neck Surgery Clinics.

Partnerships

Excellence in biobanking is a multi-institutional and cross-departmental goal. We work in close collaboration with the Clinical Pathology division for sample acquisition; with the Insel Data Coordination Lab (IDCL) for general consent status and treatment related data management; with Liquid Biobank Bern for collaborative projects liquid-tissue and harmonisation of processes; with Krebsregister for follow-up data on cancer patients and with the Swiss Biobanking Platform for quality monitoring and process standardization. The clinics that continue to send samples for biobanking and participating actively in the implementation of «fit for purpose» collections are invaluable as are the medical doctors and technical staff of the Clinical Pathology Lab at the Institute of Pathology. Support from the IT department is of upmost importance to ensure high quality and LEAN processes.

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The TBB has been referenced in numerous articles this year:

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

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Inti Zlobec, PhD
Annika Blank, MD
Heather Dawson, MD
Felix Müller, MD
Huu Giao Nguyen, Post-doc
Amjad Khan, PhD student
Kristin Uth-Gottardi, PhD student
Linda Studer, PhD student (50%) shared Uni Fribourg (A. Fischer)
Christian Abbet, PhD student shared EPFL (JP Thiran)

Master or dissertation students (MSc or Medicine)
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Ursina Begré (MMed)
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Elia Fischer, MD
Samuel Kuhn, MD
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Jannis Wallau (MSc)
Sven Wallau (MSc)
Sandro Wanner (BMed)

Summary of research activities

Our research focuses on diagnostic, molecular and biological aspects of colorectal cancers, especially on the clinical impact of tumor budding and various components of the tumor microenvironment. We use computational approaches, including deep learning to address clinical problems, with the future aim of validation and routine implementation.

Research Activities

Project 1: The role of CDX2 in colorectal cancer
Up to 20% of colorectal cancers have decreased expression of CDX2 protein, associated with aggressive tumor features and worse patient outcome. Our work shows that CDX2 expression is affected by epigenetic changes (hypermethylation, histone deacetylation). CRISPR-Cas9 knock-outs of CDX2 in vitro are associated with reduced proflieration, increased migration and colony formation as well as other features of Epithelial-Mesenchymal Transition (EMT). These aspects are remininiscent of so-called «tumor budding». In this collaborative project with Prof. Mario Tschan, we continue to explore the role of CDX2 in EMT and tumor budding.

Project 2. Tumor budding in colorectal cancer
Our colorectal Cancer (CRC) research group organized in 2016 the «International Tumour Budding Consensus Conference (ITBCC)» which led to the implementation of tumour budding in the TNM/WHO classifications and in the NCCN (National Comprehensive Cancer Network), CAP (College of American Pathologists) and ESMO (European Society for Medical Oncology) guidelines as well. Our recent review published in Nature Reviews Clinical Oncology not only summarizes the clinical scenarios of tumour budding in CRC and other solid cancers, but also focuses on the molecular and biological aspects and the association with EMT (epithelial-mesenchymal transition) and TME (tumour microenvironment). In collaboration with the International Budding Consortium (IBC), our research is focused on the validation of the ITBCC recommendations on large colorectal cancer cohorts and further characterization of tumor buds in primary colorectal cancer and colorectal liver metastases within the tumor microenvironment. Our ultimate goal is to find targets that can be used against tumor buds in a therapeutic setting.

Project 3: The histopathology image as a new biomarker
We use machine learning applied to histopathology images to address clinically relevant problems. The project of A. Khan focuses on lymph node metastasis detection in colorectal cancer with the aim of generating an integrated diagnostic tool. G. Nguyen focuses on the development of deep learning classifiers for genotype-phenotype correlations, while work from C. Abbet and L. Studer investigates new methods for self-supervised and unsupervised learning for tissue classification and and the application of graph-based methods to provide insights into the colorectal tumor-microenvironment. We evaluate and create tools for quality control of scanned images (L. Purcaro) and collaborate with different companies and academic partners to achieve these aims.

Internal Collaborations

- Mario Tschan, PhD
- Tilman Rau, MD
- Philippe Krebs, PhD
- Bastian Dislich, MD

External collaboration

National
- Collaborators and partners in the Sinergia project: Maria Anisimova, Zürcher Hochschule für angewandte Wissenschaften, Maria Rodriguez, IBM Research, Zürich, Berend Snijder, ETH Zürich, Viktor Kölzer, Institut für Pathologie, Universitätsspital Zürich, Andreas Fischer, UniFribourg and HESO
- Jean-Philippe Thiran, EPFL, Lausanne
- Andrew Janowcyzk, CHUV, Lausanne

- Lukas Brügger, Beat Schnüriger, Peter Studer Drs. and members of the Departments of Oncology and Visceral Surgery, Inselspital, Bern, Switzerland
- Luigi Terracciano, Prof. Institute of Pathology, University Hospital Basel, Switzerland
- Gieri Cathomas, Prof. Institute of Pathology, Kantonsspital Liestal, Switzerland

International

- Prof. Iris Nagtegaal (University of Radboud, Nijmegen, Netherlands) and members of the International Tumor Budding Consensus Conference (ITBCC) and Budding Consortium

Grant support

- SNF Sinergia, I.Zlobec; M. Anisimova; MMRodriguez; B.Snjider, 2020–2024, CHF 2'875'765
- SNF, I.Zlobec; M. Tschan, 2020–2024, CHF 632'000
- Swiss Cancer League, I.Zlobec; JP Thiran, 2018–2021, CHF 361'270
- Rising Tide Foundation for Clinical Research, I.Zlobec; JP Thiran, 2018–2021, CHF 290'230
- Swiss Cancer League, M.Hediger; I.Zlobec, 2016–2020, CHF 373'600
- Rising Tide Foundation for Clinical Research, H. Dawson; A. Fischer, 2019–2022, CHF 108'984

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

Administrative duties

A. Lugli

- Vice President of the Swiss Society of Pathology (SGPath)
- Secretary of the Swiss Association of Gastrointestinal Pathology (SAGIP)
- Member of the International Budding Consortium
- Member of the ICCR Colorectal Cancer Dataset Authoring Committee

I.Zlobec

- President of the Swiss Consortium for Digital Pathology
- Organiser of the SDiPath Industry Fair, 14.01.2020, Bern, Switzerland
- Chair, Virtual Slide Seminar of the Swiss Society of Pathology, 12.06.2020, on-line
- Chair, Innovations in Lung Pathology, Joint Meeting, 07.02.2020, Bern, Switzerland
- Chair, Swiss Society of Pathology Meeting, 12.11.2020, on-line, Switzerland
- Member of the Graduate School of Cell Biology and mentor
- Executive Team Member, Center for Artificial Intelligence in Medicine
- Member of the Bern Center for Precision Medicine
- Member of The International Budding Consortium

H. Dawson

- President of the Swiss Section of the International Academy of Pathology
- Chair, Swiss Society of Pathology Meeting, 12.11.2020, on-line, Switzerland
- Member of the International Budding Consortium

2 Akademische Grade

MD/PhD Students

- *Duo Xu, MD/PhD*
  New Strategies to Target Malignant Pleural Mesothelioma.
  Hauptbetreuer/Leiter: Ralph Alexander Schmid / Ren-Wang Peng

PhD Students

- *Giuseppe Bombaci, PhD*
  Understanding the role of RNH1 in inflammation.
  Hauptbetreuer/Leiter: Ramanjaneyulu Allam
  Mentor: Stefan Freigang
- *Annunziata Di Domenico, PhD*
  Designing a pancreatic neuroendocrine tumour (PanNET) progression model based on epigenetics.
  Hauptbetreuer/Leiter: Aurel Perren/Ilaria Marinoni
- *Thomas Gruber, PhD*
  The roles of IL-32 and CB2R in tumor immunity.
  Hauptbetreuerin/Leiterin: Mirjam Schenk
- *Quentin Haas, PhD*
  The role of Siglec-7 and Siglec-9 on cytotoxic T cells.
  Hauptbetreuer/Leiter: Stephan von Gunten.
  Mentor: Philippe Krebs
- *Magdalena Hinterbrandner, PhD*
  Towards LSC eradication: Unravelling the interplay of leukemia stem cells with adaptive immune cells and the commensal microbiota.
  Hauptbetreuer/Leiter: Carsten Riether
  Mentor: Philippe Krebs
- *Alessandro Marazza, PhD*
  Lysosomal quality control of secretory proteins in mammalian cells.
  Mentor: Mario P. Tschan
- *Matteo Rossi, PhD*
  Targeting lipid metabolism in pancreatic ductal adenocarcinoma. .
  Mentor: Mario P. Tschan
- *Reto Rufener, PhD*
  New drugs against echinococcus multilocularis targeting the energy metabolism.
  Mentor: Mario P. Tschan
- *Claudia Teufel, PhD*
  mTOR-mediated regulation of group 3 innate lymphoid cell numbers and cytokine responses.
  Hauptbetreuerin/Leiterin: Daniela Finke
  External Expert: Christoph Müller
- *Lester Thoo, PhD*
  Alternative splicing modulates intestinal homeostasis and pathology.
  Hauptbetreuer/Leiter: Philippe Krebs
- *Kristin Uth-Gottardi, PhD*
  The Role of CDX2 in Colorectal Cancer.
  Hauptbetreuer/Leiter: Inti Zlobec/Mario P. Tschan
  Mentor: Torsten Ochsenreiter
- *Diego von Werdt, PhD*
  Regulator of G-protein signaling 1 (Rgs1) regulates the differentiation and function of intestinal tissue resident memory CD8 T cells.
  Hauptbetreuer/Leiter: Christoph Müller
  Co-Supervisorin: Nadia Corazza
- *Haitang Yang, PhD*
  Targeting the Mitogen-Activated Protein Kinase Signaling Cascade in KRASmutant Lung Cancer and Malignant Pleural.
  Co-Advisor: Mario P. Tschan

MSc Master of Science

- *Lisa Barbara Alfare, MSc*
  Quality assurance in pathology – Analysis of discussions of gastrointestinal cases hold by the GIPAR «Gastrointestinal Pathology Round».
  Hauptbetreuer/Leiter: Rupert Langer
  Mentorin: Heather Dawson
- *Fabienne Anderegg, MSc*
  Function of epigenetic modifiers in differentiation therapy of breast cancer.
  Hauptbetreuer/Leiter: Mario P. Tschan
- *Eva Maria Bettschen, MSc*
  Tumor budding in Endometrial Carcinoma.
  Hauptbetreuer/Leiter: Tilman Rau
- *Margaux Bringardner, MSc*
  Investigation of the contribution of SHIP1 and immune cells to bone cell lineages.
  Hauptbetreuer/Leiter: Philippe Krebs/Willy Hofstetter
- *Jana Brühlmann, MSc*
  Analyse der im real-life Setting bestimmten prädiktiven Biomarker für nicht-kleinzellige Lungenkarzinome.
  Hauptbetreuerin/Leiterin: Sabina Anna Berezowska
  Mentorin: Christina Neppl

- *Mona Vera Deppeler, MSc*
  Macro- and microscopic pathological processing of sentinel lymph nodes in endometrial cancer .
  Hauptbetreuer/Leiter: Tilman Rau
- *Simon Flückiger, MSc*
  Definition of Tumor Regression Grade and Compilation of a Tissue Microarray.
  Hauptbetreuerin/Leiterin: Vera Genitsch Gratwohl
  Mentor: Achim Fleischmann
- *Samuel Hannes Jungen, MSc*
  Comparison of multiplexed IHC versus conventional IHC using QuPath – A solution for Immunoscore?
  Hauptbetreuer/Leiter: Tilman Rau
- *Patric Jungo, MSc*
  Prognostische Faktoren diffuser Gliome.
  Hauptbetreuer/Leiter: Ekkehard Hewer
  Mentorin: A. Schmitt-Kurrer
- *Annina Rahel Leuenberger, MSc*
  Mykobakterien – wie sensitiv sind wir?
  Hauptbetreuerin/Leiterin: Sabina Anna Berezowska
  Mentorin: Christina Neppl
- *Irene Mungure, MSc*
  Linking chaperone mediated autophagy to differentiation and chemotherapy resistance in acute myeloid leukaemia.
  Hauptbetreuer/Leiter: Magali Humbert/Mario P. Tschan
- *Nicholas Munz, MSc*
  Role of miR-182-5p in Pancreatic Neuroendocrine Tumors.
  Hauptbetreuer/Leiter: Aurel Perren/Ilaria Marinoni
- *Martina Selina Ninck, MSc*
  Zusammenstellung eines Kollektivs von Resektaten rezidivierter Glioblastome incl. initialer Resektate und Konstruktion eines next-generation Tissue Microarrays.
  Hauptbetreuerin/Leiterin: Sabina Anna Berezowska
- *Iina Ruth Raass, MSc*
  Die historischen Präparate am Institut für Pathologie, Bern: Bestand, Herkunft, Erhaltungszustand und Lehreignung.
  Hauptbetreuer/Leiter: Tilman Rau
- *Nicole Andrea Schaad, MSc*
  Analyse strukturierter Tumorberichte in der Pathologie.
  Hauptbetreuer/Leiter: Sabina Anna Berezowska
  Mentor: E. Hewer
- *Robert Schweri, MSc*
  TCTP, a player in tumour reversion?
  Hauptbetreuer/Leiter: Mario P. Tschan/Torsten Ochsenreiter
- *Carmen Trefny, MSc*
  miR-19b involvement in the regulation of PP2A and apoptosis resistance in glioma cell lines.
  Hauptbetreuer/Leiter: Erik Vassella

Publikationen

Originalarbeiten In-House

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4 Vorträge

Aurel Perren
- 15.01.20: Genetik und Epigenetik bei PanNET
  Endokrinologie, Forschungsseminar, Kinderklinik Inselspital
- 02.07.20: Round Table zur neuen ESMO GEP-NEN Leitlinie
  Virtueller Roundtable, IPSEN
- 03.07.20: Models for basic research in the NET field: organoids, animal models, zebrafish
  EPC
- 10.10.20: (Molekular)Pathologie neuroendokriner Tumore
  Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie

Ilaria Marinoni
- 12–13.03.2020: Translational NET research update
  ENETs
- 07.10.20: Epigenomic of PanNETs
  Spanish group of Neuro-endocrine tumors (GETNE) XVI GETNE International Symposium

Mirjam Schenk
- 13.03.20: Research Seminar and student lecture
  Human Immunology Center of Lausanne (CHIL)
- 04.11.20: Scientific Talk / Research seminar
  Dermatology, University Hospital of Lausanne CHUV

Mario P. Tschan
- February: Short Talk
  Toulouse Oncoweek
- March: Invited Seminar
  Centre Méditerranéen de Médecine Moléculaire Speaker
- September: 2nd Swiss Autophagy Workshop
  Fribourg, Co-Organizer

Erik Vassella
- 06.02.20: Resistance mechanisms EGFR TKIs
  Swiss Molecular Tumorboard
- 06.05.20: Advisor
  Advisory Board, Bern
- 02.07.20: Melanoma with BRAF multiple driver mutations in cis
  Swiss Molecular Tumorboard

Alessandro Lugli
- 22.10.20: Role of Budding in pT1 CRC screening
  Scuola di Sanita Publica (SSP) della Regione del Veneto

Inti Zlobec
- 22.06.20: From multiplexing to artificial intelligence: new trends in tissue microarraying
  AACR Virtual Meeting
- 19.02.20: Tissue Microarraying: The Bern Experience
  3DHistech Distributor Meeting
- 03.12.20: From artificial intelligence to multiplexing: exciting avenues for next-generation Tissue Microarrays
  7th Digital Pathology & AI Congress: Europe
- 19.11.20: Tissue microarray collectives – still useful in the era of digital pathology?
  Europe Biobank Week
- 21.10.20: Digital Pathology and ngTMA
  Lab Animals Course- COMPATH

Heather Dawson
- 06.03.20: Mucinous tumors, mesotheliomas and low-grade peritoneal tumors
  Dialogue Salzburg
- 13.06.20: Case presentation
  SGPath Slide Seminar
- 29.08.20: Tried and tested – GI WHO 2019 in routine diagnostics
  SAGIP
- 21.11.20: Therapy associated pathology of the GI-Tract
  IAP Germany Course , Invited speaker and Co Organizer

5 Drittmittel

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J. Baumgartner, S. Freigang
- UniBE 2021 PhD Fellowship, 2017–2021, CHF 90'000

P. Krebs (PI)
- Swiss National Science Foundation Project grant, 2020–2024, CHF 632'000
- Bern Center for Precision Medicine (BCPM), 2020–2021, CHF 40'532
- Helmut Horten Stiftung Project grant, 2019–2021, CHF 130'000
- Bernese Lung League Project grant, 2018–2020, CHF 79'554
- Swiss Lung League Project grant, 2018–2020, CHF 79'554
- Research Foundation (KFS) Project grant, 2017–2021, CHF 312'500
- Swiss National Science Foundation Project grant, 2016–2020, CHF 525'000

P. Krebs (main PI)
- Seed money project (Swiss Confederation and ETHZ) Project grant, 2019–2020, CHF 10'000
- UniBE ID (Interdisciplinary) Grant, 2017–2021, CHF 75'000

P. Krebs (co-Investigator)
- EU / Marie Skłodowska-Curie RISE grant Project grant, 2018–2021, Euro 904'500
  (total amount of funding; funding shared by PI and Co-PI; part for group Krebs is contingent on number of staff exchanges)

Christoph Müller (PI)
- SNF 314730_189277, 2019–2022, CHF 516'667

Christoph Müller (Co-PI)
- SNF 33CS30_177523, SIBDCS, 2018–2020, CHF* 304'500
  (own share)

Daniel Zysset
- Monique Dornonville de la Cour Stiftung, 2018-2021, CHF 52'387

Aurel Perren (PI)
- SNF 310030_188639, 2020–2024, CHF 632'000
- Uniscentia, 2020–2021, CHF 135'000

Aurel Perren (PI), Ilaria Marinoni (Co-PI)
- KLS-4227-08-2017, 2018–2022, CHF* 395'450

Ilaria Marinoni (PI)
- ENETs CO-Synergy Award, 2019–2022, CHF 69'700
- Bernische Krebsliga, 2018-2019, CHF 40'000
- Wilhelm Sander Stiftung, 2020–2021, CHF 50'000

Matthias Dettmer (PI)
- Berner Krebsliga, 2017–2022, CHF 70'000

M. Schenk (PI)
- SNF 320030_176083, 2018–2022, CHF 566'109
- Stiftung experimentelle Biomedizin, 2016–2021, CHF 1'300'000
- Helmut Horton, 2019–2020, CHF 150'000
- Wilhelm Sander Stiftung, 2019–2020, Euro 49'700
- San Salvatore, 2019–2021, CHF 143'000
- Novartis, 2020–2021, CHF 52'000

Mario P. Tschan (PI)
- SNSF_31003A_173219, 2017–2021, CHF 693'641

Mario P. Tschan (Co-PI), Inti Zlobec (PI)
- SNSF_310030_197786, 2020–2024, CHF* 632'000

Mario P. Tschan (Co-PI)
- Partenariat Hubert Curien/Germaine de Staël Funding, J.E. Sarry, 2019–2020, CHF* 4'500

Magali Humbert (PI)
- Werner und Hedy Berger-Janser Stiftung, 2020, CHF 79'946
- Stiftung für klinisch-experimentelle Tumorforschung, 2018–2020, CHF 20'000
- Bernische Krebsliga, 2017–2021, CHF 85'000

Kristina Seiler, Mario Tschan (PI)
- SNSF MD-PhD 03/17, 2018–2020, CHF 180'000

I.Tokarchuck, Mario Tschan (PI)
- UniBE international 2021, 2018–2020, CHF 90'000

Erik Vassella (PI)
- SNF (31003A_175656), 2018–2022, CHF 408'509

Rupert Langer (PI), Erik Vassella (Co-PI)
- SAKK 75/08 Rupert Langer, 2018–2025, CHF 132'640

Sabina Berezowska (PI), Erik Vassella (Co-PI)
- Swiss Cancer League, 2019–2022, CHF 365'500

I.Zlobec, M. Anisimova, MMRodriguez, B.Snjider
- SNF Sinergia, 2020–2024, CHF* 2'875'765
  (total amount of funding)*

I.Zlobec (PI), M. Tschan (Co-PI)
- SNF, 2020–2024, CHF* 632'000

I.Zlobec, JP Thiran
- Swiss Cancer League, 2018–2021, CHF 361'270
- Rising Tide Foundation for Clinical Research, 2018–2021, CHF 290'230

M.Hediger, I.Zlobec
- Swiss Cancer League, 2016–2020, CHF 373'600

H. Dawson, A. Fischer
- Rising Tide Foundation for Clinical Research, 2019–2022, CHF 108'984

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

6 Preise, Ernennungen, Auszeichnungen

Eva Diamantis, Gastärztin
hat auf den 1. Mai Titel einer Titularprofessorin erhalten.

Mirjam Schenk
Venia Docendi für das Fach Experimentelle Immunologie, PD.

Antonio Rodriguez
Posterprize of German Society of Pathology 2020.
104. Jahrestagung der Deutschen Gesellschaft für Pathologie (DGP), 4.–6. Juni .


DEUTSCHE GESELLSCHAFT FÜR PATHOLOGIE E.V.
Seit 1897 – dem Leben verpflichtet

Die Deutsche Gesellschaft für Pathologie e.V. verleiht

Antonio Rodriguez
Bern, Schweiz

für die Arbeit zum Thema:

»Molekuläre Heterogeneität in Gehirnmetastasen von Prostatakarzinomen: Eine Studie Schweizweit«

den POSTER-PREIS

POSTER-PREIS DER DGP

1. September 2020, Berlin

Prof. Dr. Gustavo Baretton
Vorsitzender der DGP

Prof. Dr. med. Christoph Röcken
Stellvertretender Vorsitzender der DGP

pathologie-dgp.de

Dr. Manuel Keller:
Dies academicus 2020, Medizinische Fakultät:
2. Preis für die Dissertation «Adverse prognostic value of PD-l1 expressionin primary resected pulmonary squamous cell carcinomas and paired mediastinal lymph node metastases»

Philipp Zens
Er hat eines der 3 nach Bern (11 total Schweiz) vergebenen MD-PhD Stipendien des SNSF erhalten.
Ausserdem wurde er in der «Graduate School for Health Sciences» in Bern aufgenommen.

Simon April
11. Dezember 2020: Award for best research project & presentation, 15th Annual Meeting Swiss Stem Cell Network.

>>> Studentische Lehre

Wie in vorherigen Jahren besteht der Einsatz der Pathologie in Vorlesungen und Kursen für die Studierenden 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 wurden.

Eine Vielzahl Mitglieder des Instituts waren und sind weiterhin aktiv in der Ausbildung von PhD und MD-PhD Studierenden der Graduate School for Cellular and Biomedical Sciences (GCB) involviert. Die Lehrveranstaltungen werden von Mitarbeitenden sowohl der klinischen als auch der experimentellen Pathologie gehalten, wobei je nach Thema und Schwerpunkt des Studienganges bzw. der Veranstaltung Ärzte oder Naturwissenschaftler als Dozierende agieren.

Das Jahr 2020 in der Lehre war, wie alle Bereiche der Arbeit am Institut für Pathologie, stark geprägt durch die SARS-CoV-2 Pandemie. Die Rahmenbedingungen die sowohl auf nationaler Ebene als auch durch die Universitätsleitung gesteckt wurden, haben die studentische Lehre stark beeinflusst. Trotz den erheblichen Einschränkungen, die zeitweise die faktische Schliessung der Universität für den studentischen Unterricht zu bedeuten hatte, boten sich diverse Möglichkeiten neue, innovative, digital-gestützte Massnahmen in der Lehre durch zu setzen. Dank des unermüdlichen Einsatzes der Mitarbeitenden am Institut – sei es seitens der Dozierenden, sei es seitens der unterstützenden Domänen, konnte der studentische Unterricht nicht nur grösstenteils fortgesetzt, sondern auch innovativ ergänzt werden. Durch die erweiterte technische Ausrüstung in allen Hörsälen im Institut konnten nicht nur der Frontalunterricht sondern auch Kurse und Demonstrationen digital aufgenommen und übertragen werden.

Studiengang Humanmedizin und Zahnmedizin

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 in einen mehrjährigen strukturierten Unterricht, der die Kenntnisse und das Verständnis für Mechanismen, Zusammenhänge und Morphologie von Erkrankungen vermittelt. Die makroskopischen Kurse im 4. Studienjahr dienen dabei der Vertiefung der Inhalte der Vorlesungen und erlauben es makroskopische Präparate aus der umfassenden Sammlung zu «begreifen». Komplementär wird den Studierenden anhand eingescannter histologischer Präparate die virtuelle Mikroskopie nähergebracht und erlaubt die Besprechung weiterer wichtiger Krankheitsbilder.

Im 3. Studienjahr, dem letzten Jahr des Bachelor-Teils des Medizinstudiums werden den Studierenden die Grundlagen der allgemeinen Pathologie vermittelt (Einführungskurs 2). Diese Vorlesungen sind in interdisziplinäre Vorlesungsveranstaltungen eingebettet, wobei die verschiedenen Themen im Kontext spezieller Themenblöcke behandelt werden. Diese theoretischen Kenntnisse werden im Rahmen Fachpraktika Pathologie vertieft, wo die entsprechenden wesentlichen morphologischen Veränderungen studiert 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 – Coronabedingt mussten diese Führung 2020 virtuell durchgeführt werden anhand eines interaktiven Rundgangs. Im Masterstudiengang folgt dann die systematische Aufarbeitung der speziellen Pathologie. Hier wird zunächst im 4. Studienjahr (Einführungskurs 2) sowie im 5. Studienjahr (Schlusskurs 1) organ-/systembezogene Pathologie gelehrt. Anhand von theoretischen Vorlesungen und praktischen Kursen vertiefen die Studierenden ihre Kenntnisse. Wöchentlich finden dabei nebst den virtuellen Histologiekursen auch Autopsiedemonstrationen statt, bei denen anhand aktueller Fallbeispiele die aktive Erarbeitung pathophysiologischer Zusammenhänge und Sequenzen verschiedenster Krankheiten im Vordergrund steht. Auch diese Kurse konnten zum Teil in reduzierter Zahl vor Ort, zum Teil komplett digitalisiert gehalten werden, dank der neuen Möglichkeit zur Aufnahme von Podcasts auch im Autopsiehörsaal. Ein weiterer wichtiger Austausch mit den Studierenden findet im Rahmen der begleiteten Masterarbeiten statt, welche einen ersten Kontakt mit wissenschaftlichen Arbeiten erlauben. Die Möglichkeit im Anschluss an die Masterarbeit eine Dissertation durchzuführen wird nach wie vor rege durch die Studierenden genutzt und erlaubt es auch komplexere Projekte aufarbeiten zu können.

Auch am Ende des Medizinstudiums, im 6. Studienjahr können Studierende ihre Kenntnisse im Fach Pathologie vertiefen in Form eines Wahlstudienjahrpraktikums. Im Minimum besteht ein solches Angebot für einen Monat bis hin zu einem viermonatigen Praktikum. Während dieser Zeit wird den Studierenden ein strukturiertes Curriculum angeboten, welches ihnen erlaubt das ganze Spektrum der histopathologischen, zytopathologischen, molekularpathologischen wie auch postmortalen Diagnostik kennen zu lernen.

Dank Innovation in der Lehre, dem Aufgleisen neuer Lehrinhalte in Form von Fall-basiertem Lernen (in Form eines

Pilotprojektes), werden die 100 zusätzlichen Studierenden auch in Zukunft gut im Fachgebiet der Pathologie ausgebildet werden können. Insbesondere im Bereich der Makropathologieausbildung und der Lehre pathophysiologischer Zusammenhänge wird auf Grund der zurückgehenden Autopsien in Zukunft innovative Lehre gefördert sein.

Den Studierenden der Zahnmedizin werden im 3. Jahr sowohl die Allgemeine Pathologie, als auch die spezielle Pathologie einzelner wichtiger Organsysteme in Form einer Vorlesungsserie Pathologie vermittelt. Im 5. Studienjahr werden zudem spezielle orale Pathologien in weiteren Vorlesungen behandelt.

Studiengänge der Philosophisch-Naturwissenschaftliche Fakultät

Die Mitarbeitenden der experimentellen Pathologie sind ausserdem an der Ausbildung der Studierenden der philosophisch-naturwissenschaftlichen Fakultät (phil. nat.) beteiligt. Diese Lehrveranstaltungen werden in einem Modulformat angeboten, so dass Studierende verschiedener Fächer gleiche Vorlesungsreihen besuchen.

1. Seminarreihen

– Joint Immunology Group Meeting
  (Institut für Pathologie, monatlich, seit März 2020 aufgrund der SARS-CoV-2 Pandemie ausgesetzt)
– Bern Immunology Club, BIC
  (Vorträge externer Seminargäste, monatlich, seit März 2020: online)
– DKF Research Conference
  (monatlich, seit März 2020: online)

2. Vorlesungsreihen im Fachgebiet Pathologie

Zu Gunsten der phil. nat. Fakultät der UniBE werden von Dozierenden des Instituts folgende Vorlesungsreihen im Modulformat angeboten und koordiniert:

2.1. Allgemeine Pathologie und Histologie

Koordinator: Philippe Krebs

Dozierende: aus dem Institut für Pathologie und Institut für Anatomie, Universität Bern.

Studierende: BSc, MSc und PhD Studierende der Zell Biologie und Biomedical Sciences.

Allgemeine Übersicht:

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

Koordinator: Erik Vassella

Dozierende: aus dem Institut für Pathologie der Universität Bern und Universitätsspital Basel, Department für Biomedizinische Forschung (DBMR) und Inselspital Bern.

Studierende: BSc, MSc und PhD Studierende der Zell Biologie und Biomedical Sciences.

Allgemeine Übersicht:

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

2.3. Cellular and Molecular Immunology

Koordinator: Christoph Müller

Dozierende: aus dem Institut für Pathologie der Universität Bern, Department für Biomedizinische Forschung (DBMR) und Inselspital Bern, Vetsuisse-Fakultät.

Studierende: BSc, MSc und PhD Studierende der Zell Biologie und Biomedical Sciences.

Allgemeine Übersicht:

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

3. Weitere Lehrveranstaltungen

Dozierende der Experimentellen Pathologie unterrichten zudem in Lehrmodulen, die von anderen Instituten koordiniert werden, wie dem «Practical Course in Immunology» des Instituts für Zellbiologie (phil. nat. Fakultät), in Seminarveranstaltungen im Gebiet Tumorpathologie, in der Vorlesungsreihe «Blut und Abwehr» im 2. Studienjahr Medizin und dem dazu gehörenden Lerngruppenunterricht (PBL). Weiterhin sind Dozierende des Instituts im Rahmen von 3–4–wöchigen experimentellen Praktika an der Ausbildung von Studierenden der Studienrichtung «Cell Biology» (UniBE) und im Studiengang «Biomedical Sciences» beteiligt, der durch die Universitäten Fribourg und Bern angeboten wird.

>>> Weiterbildung

Das Institut für Pathologie der Universität Bern bietet als SIWF-zertifizierte Weiterbildungsstätte sowohl Stellen für das Fachgebiet Pathologie (8–10 Stellen), als auch Zytopathologie und Molekularpathologie (jeweils 1 Stelle), an. Ein grosser Teil dieser Weiterbildung findet während der täglichen diagnostischen Arbeit statt. Sehr wichtig ist jedoch auch die strukturierte Weiterbildung, an der sich sämtliche Kollegen und Kolleginnen des Teams beteiligen.

Wie gewohnt fanden auch in diesem Jahr täglich Weiterbildungsveranstaltungen in mikroskopischer (nach dem Morgenrapport) und makroskopischer (am Mittag anhand aktueller Präparate aus dem Zuschnitt) Pathologie für Ärztinnen und Ärzte in ihrer Assistenzzeit statt. Unser Ziel war es die Veranstaltungen in diesem Jahr neu auszurichten um die Auszubildenden in ihrer Weiterbildung noch stärker zu unterstützen. Zu Beginn des Jahres haben wir daher jeweils in Blöcken von mehreren Wochen ein Gebiet der Pathologie besprochen. Dies gab allen die Möglichkeit sich über eine längere Zeit vertieft mit diesem Thema zu befassen und die theoretischen Grundlagen dazu zu erarbeiten oder aufzufrischen.

Die Massnahmen, die wir im Rahmen der Corona-Epidemie im Verlauf des Jahres ergreifen mussten, waren dann allerdings auch für die Weiterbildung eine grosse Herausforderung. Dank digitaler Treffen konnten wir die täglich geplanten Weiterbildungsveranstaltungen nach einer kurzen Unterbrechung im Frühjahr jedoch kontinuierlich weiterführen. Theoretische Fragestellungen wurden dabei beispielweise anhand gescannter und digital mikroskopierter Schnittpräparate diskutiert.

Im Rahmen der Gesamtsituation mussten wir die Organisation jedoch gezwungenermassen auch inhaltlich umstellen und haben im Verlauf des Jahres in der Morgenfortbildung vermehrt anhand interessanter Fällen aus der täglichen Diagnostik theoretische Kenntnisse vermittelt. Das Programm war somit anders als geplant, es entstanden jedoch nichts desto trotz sehr interessante Diskussionen für alle Beteiligten anhand eines breiten Spektrums von Fällen. Daraus ergab sich auch für die Ärzte und Ärztinnen in Weiterbildung vermehrt die Möglichkeit mit Unterstützung der Fachärztinnen und Fachärzte selber mikroskopische Schnittpräparate zu präsentieren.

Die monatlichen Seminare für Assistierende, bei welchen an einem Abend ein Thema vertieft besprochen wird, konnten glücklicherweise, nach einer lediglich kurzen Unterbrechung, wie geplant weitergeführt werden.

Trotz der weiterbestehenden Pandemie bedingten Einschränkungen haben wir die Weiterbildung für das nächste Jahr wieder in nun monatlichen Themenblöcken (sowohl für die Morgenfortbildung als auch die Abendseminare) geplant und hoffen, dass die Durchführung während des gesamten Jahres möglich sein wird.

Seminare für Assistierende

Monat	Referierende	Thema
Januar	B. Dislich	**Weichteiltumoren**
Februar	T. Rau	**B3 Läsionen der Mamma**
März	A. Blank	**Leber, neoplastisch**
April	A. Perren	**Allgemeine Pathologie: Zellschaden**
Mai	E. Hewer	**Allgemeine Pathologie**
Juni	Y. Banz	**Allgemeine Pathologie: Entzündung, Gerinnung/Thrombus/Endothelschaden**
Juli	A. Lugli	**Chronisch entzündliche Darmerkrankung**
August	M. Trippel	**Adnextumoren**
September	M. Montani	**Pitfalls im Schnellschnitt**
Oktober	A. Perren	**Schilddrüse**
November	Y. Banz	**Milz**
Dezember	V. Genitsch	**Vaskulitis**

>>> Fortbildung

In den während des Semesters wöchentlich stattfindenden Seminaren gewähren uns Referenten aus dem In- und Ausland Einblicke in ein sehr breites Themenspektrum der experimentellen und klinischen Pathologie sowie anderer Fachgebiete. Diese Veranstaltungsreihe war leider besonders stark von den Einschränkungen der Corona-Pandemie betroffen, da die Anreise aus dem Ausland beinahe verunmöglicht wurde und auch der Besuch inländischer Gäste deutlich erschwert war. Diese Besuche leben, über das eigentliche Seminar hinaus, vom persönlichen Austausch, aus dem immer wieder weiterführende Zusammenarbeiten entstehen. Dennoch konnten auch in diesem Jahr äusserst interessante Referate durchgeführt werden, dies häufig dank der bestehenden digitalen Möglichkeiten.

Zudem fanden für die Mitarbeitenden des Labors der klinischen Pathologie, des Sekretariats und des Krebsregisters monatliche Fortbildungsveranstaltungen zu verschiedenen Fachbereichen der Pathologie statt, welche von den jeweiligen Fachspezialistinnen und -spezialisten gehalten wurden.

Montag- und Donnerstagsseminare

Datum	Titel	Referent/-in
23.01.	**New mechanisms regulating lymphocyte activity and their connection with cancer**	Greta Guarda, PhD Institute for Research in Biomedicine (IRB), Bellinzona
20.01.	**Pulmonary granulomatous disease-diagnostic challenges and clues**	Dr. Anja Roden Mayo Clinic in Rochester
17.02.	**Therapy-induced metabolic reprograming causes ferroptosis hypersensitivity in prostate cancer**	Martin Sadowski, PhD Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane Australia
11.05.	**Applications and challenges of single cell RNA sequencing**	Dr. rer. nat. Philipp Kirchner Humangenetisches Institut, Universitätsklinikum Friedrich-Alexander, Universität Erlangen-Nürnberg
22.06.	**3D histology of soft tissues through novel X-ray technology: a case study on idiopathic pulmonary fibrosis**	Philipp Schneider, PhD Faculty of Engineering and Physical Sciences, Bioengineering Science Research Group, University of Southampton UK
07.09.	**IBD – Beyond the Diagnosis**	Aart Mookhoek, MD PhD Fellow Gastro-intestinal Pathology at the Amsterdam UMC
19.10.	**Under the microscope: The role of ferroptosis in acquired cancer therapy resistance**	Martin Sadowski, PhD Institut für Pathologie, Universität Bern, Schweiz

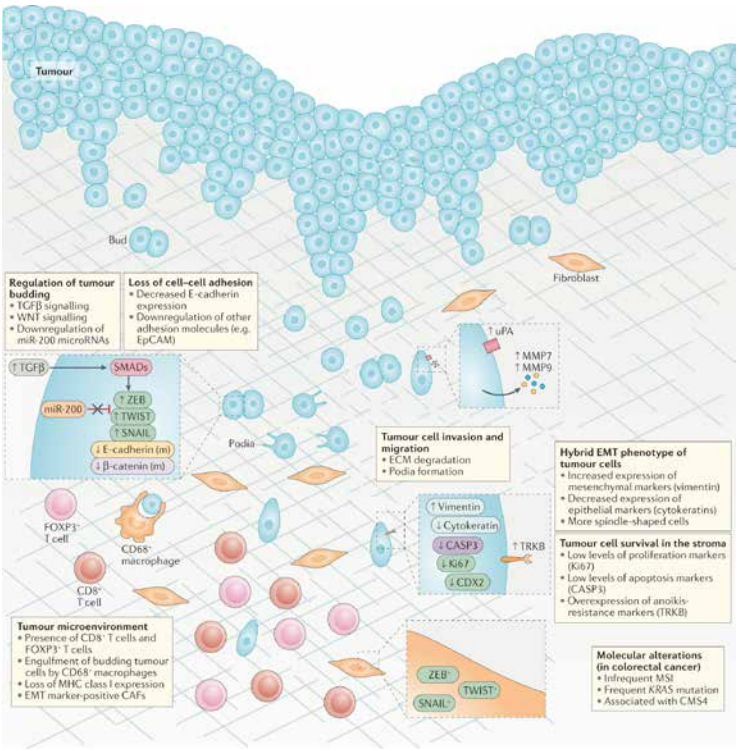
>>> Im Fokus: Tumor Budding

Seit über zehn Jahren beschäftigt sich unsere Forschungsgruppe mit dem kolorektalen Karzinom und insbesondere mit dem Phänomen des Tumor Buddings. Tumor Buds werden definiert als einzelne Tumorzellen oder Tumorzellgruppen bis zu vier Krebszellen an der Invasionsfront des kolorektalen Karzinoms. Obwohl seit vielen Jahren die starke prognostische Bedeutung dieses morphologischen Biomarkers weltweit durch zahlreiche Studien untermauert werden konnte, war dessen Implementierung in der täglichen Praxis aufgrund des Fehlens eine international anerkannte standardisierte Auswertungsmethode problematisch.

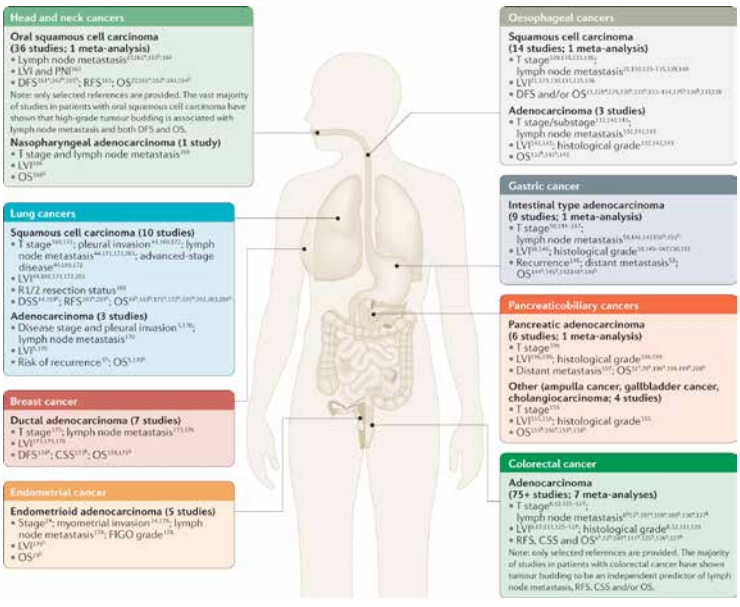
Unsere Forschungsgruppe organisierte folglich im Jahre 2016 in Bern die «International Tumour Budding Consensus Conference (ITBCC)», welche zur Implementierung von Tumor Budding in die TNM/WHO Klassifikationen sowie in den Richtlinien der NCCN (National Comprehensive Cancer Network), CAP (College of American Pathologists), ESMO (European Society for Medical Oncology) und ICCR (International Collaboration on Cancer Reporting) führte. Unterdessen ist unsere Forschungsgruppe Mitglied des IBC (International Budding Consortium), welches durch einen Grant der Dutch Cancer Society (DCS) unterstützt wird. Die Hauptziele des IBC beinhalten die Validierung der ITBCC Auswertungsmethode sowie Nützung von digitalen Methoden zur Verbesserung der Reproduzierbarkeit von Tumor Budding.

Unsere Übersichtsarbeit, welche im jahre 2020 in der Fachzeitschrift Nature Reviews Clinical Oncology veröffentlicht wurde, fasst nicht nur die klinischen Szenarien von Tumor Budding beim kolorektalen Karzinom und anderen soliden Karzinomen zusammen, sondern fokussiert ebenfalls auf die molekularen und biologischen Aspekte von Tumor Budding und deren Assoziation mit der epithelialen-mesenchymalen Transition und der Tumormikroumgebung.

Unterstützt durch mehrere Grants arbeitet unsere Forschungsgruppe am besseren Verständnis der pathogenetischen Mechanismen von Tumor Budding mit dem Ziel, eine solide Basis für eine allfäälige zukünftige Anti-Budding Therapie (ABT) zu setzen.

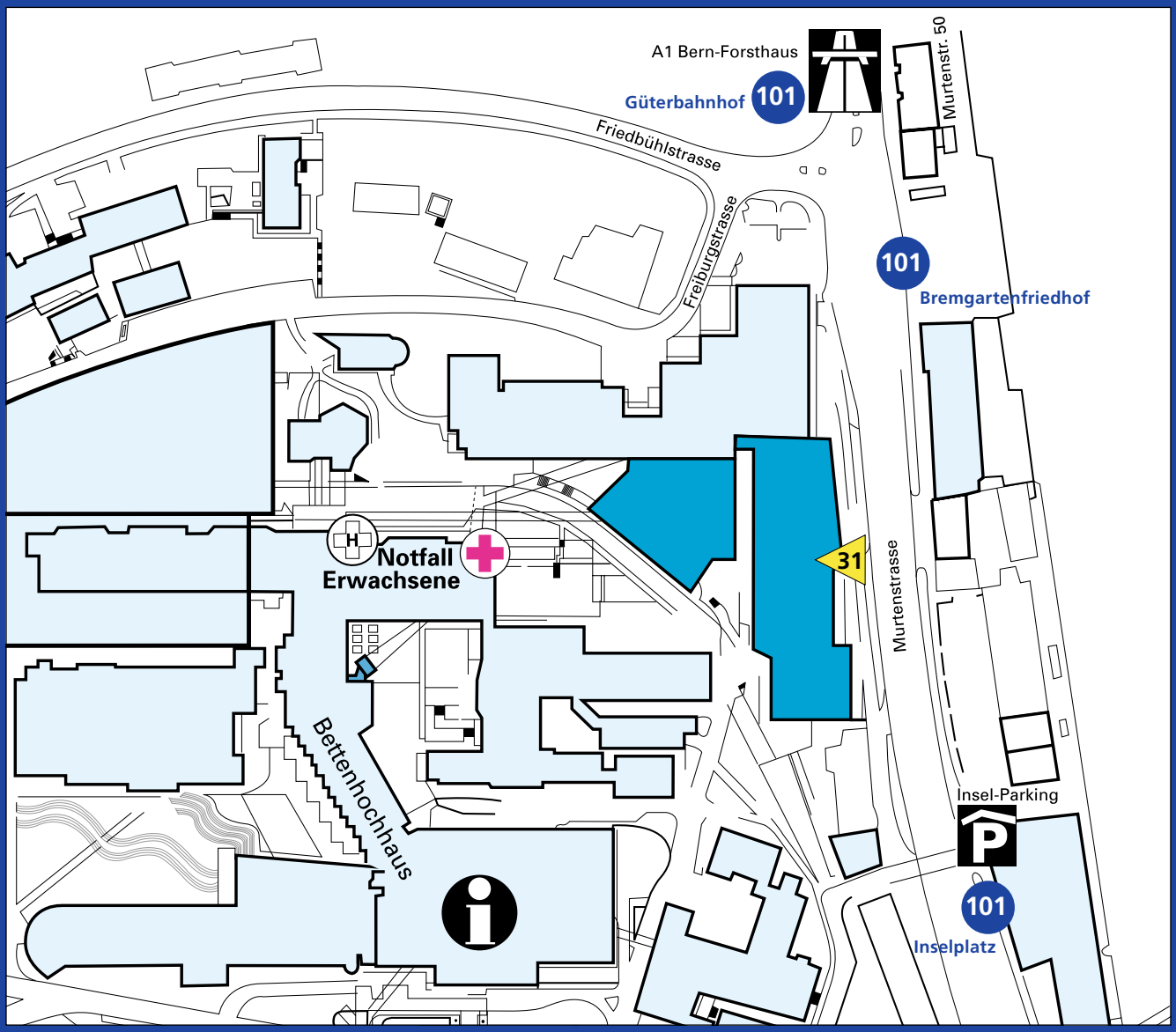


Pathogenetische Schlüsselprozesse des Tumor Budding Phänotyps (Lugli et al, Nat Rew Clin Oncol 2020).



Übersicht über die prognostische Bedeutung von Tumor Budding in unterschiedlichen Krebstypen (Lugli et al, Nat Rew Clin Oncol 2020).

>>> Situationsplan



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