UNIVERSITÄT
BERN

Institut für Pathologie

www.pathology.unibe.ch

Jahresbericht 2021

>>> Inhalt

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>>> Das Wichtigste in Kürze

Liebe Leserin, lieber Leser

Gute Weiterbildung, Karriereförderung der Mitarbeitenden und Innovation sind zwei der strategischen Schwerpunkte des Institutes für Pathologie, auf die ich mit Ihnen etwas eingehen möchte. Ich bin stolz auf die Berufungen auf Professuren und Chefarztstellen, welche im 2021 von Ärztinnen und Ärzten angenommen wurden. Ich gratuliere Herrn Prof. Rupert Langer, neuer Ordinarius in Linz, Frau Prof. Sabina Berezowska und Herrn Prof. Ekkehard Hewer, beide Extraordinarien, Chefärztin/Chefarzt in der Pathologie der Universität Lausanne, Herrn Prof. Tilman Rau, Extraordinarius in Düsseldorf und Herrn PD Dr. Matthias Dettmer, Chefarzt der Pathologie Stuttgart! Es ist mir eine grosse Freude zu sehen, wie die «Berner Schule» sich bewährt und die Mitarbeiterinnen und Mitarbeiter sich entwickeln. Ein grosses Dankeschön auch an diejenigen, die hierbleiben und zu unserem Lehr-Umfeld aktiv beitragen. Auch unser Innovations-Potential liegt bei unseren Mitarbeitenden.

Die Digitalisierung in der Pathologie steht nun vor der Tür. Es gibt bereits erste Algorithmen basierend auf künstlicher Intelligenz, die z.B. Brustkrebs oder Prostatakrebs-Diagnosen stellen können. Im Projekt «Digitale Pathologie» haben wir 2021 begonnen, erste Diagnosen auf digitaler Basis zu stellen. Aus strategischer Sicht hat die Medizinische Fakultät und die Universität Bern ein Extraordinariat für Digitale Pathologie geschaffen. Dies Hand in Hand im Rahmen des 2020 gegründeten Center of Artificial Intelligence in Medicine der Medizinischen Fakultät der Universität Bern.

Was wird dies für den Pathologen bedeuten? Wird das Hightech Mikroskop durch eine Maus und einen Computerbildschirm ersetzt werden? Oder wird es den Pathologen überhaupt nicht mehr brauchen? Akademische Pathologinnen und Pathologen werden bei der Einführung der Digitalen Pathologie in den diagnostischen Alltag sowie in der Weiterentwicklung von Klassifikationen und Verknüpfung mit den Forschungsaktivitäten eine zentrale Rolle spielen.

Aber auch betreffend des zukünftigen Arbeitsplatzes machen wir uns Gedanken: Wir sind in Zusammenarbeit mit externen Partnern daran, einen digitalen und ergonomischen Arbeitsplatz zu entwickeln; mehr über den «Pathojet» erfahren Sie im diesjährigen Fokus am Ende des Jahresberichtes.

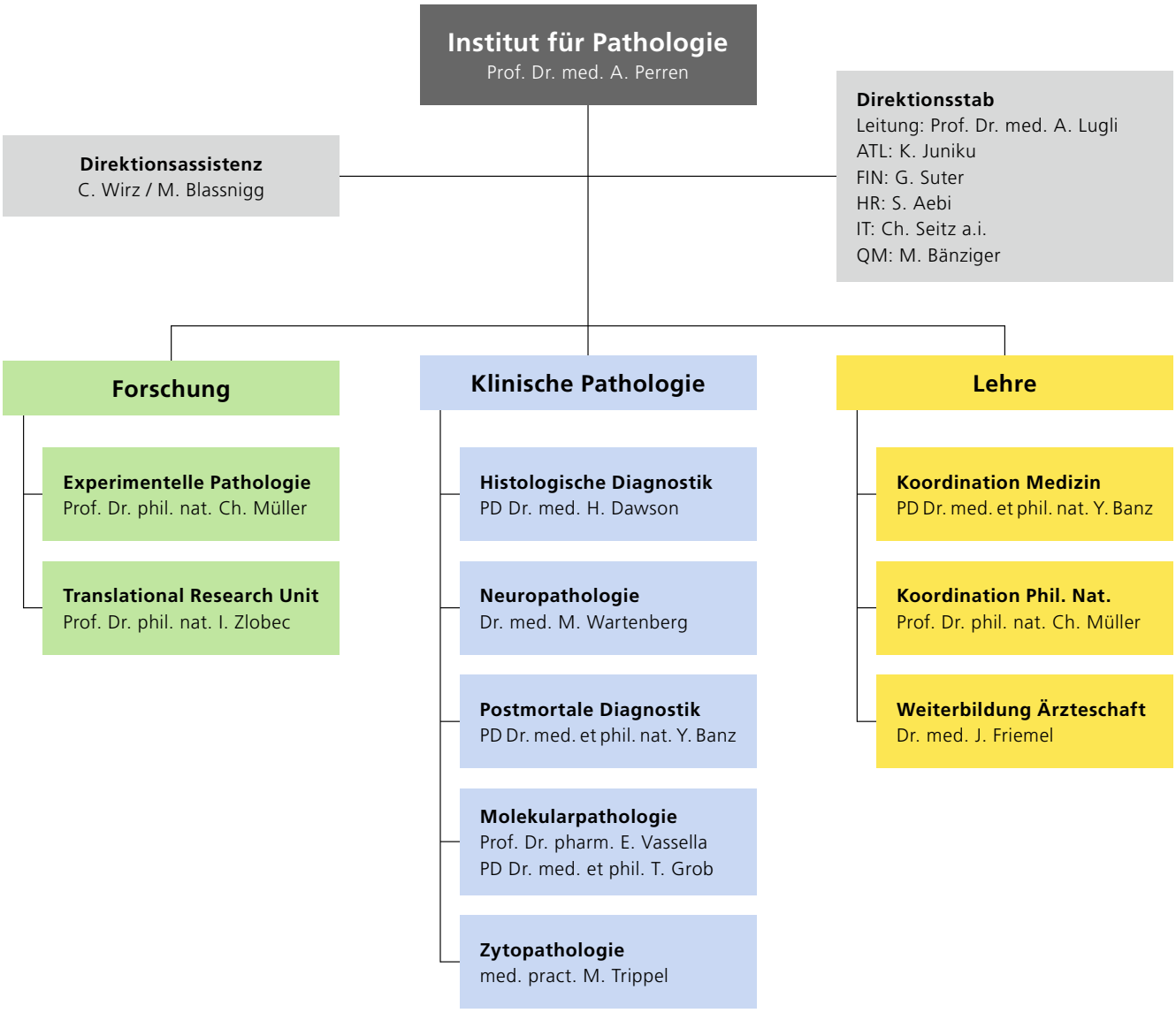
Ich wünsche Ihnen viel Freude bei der Lektüre.

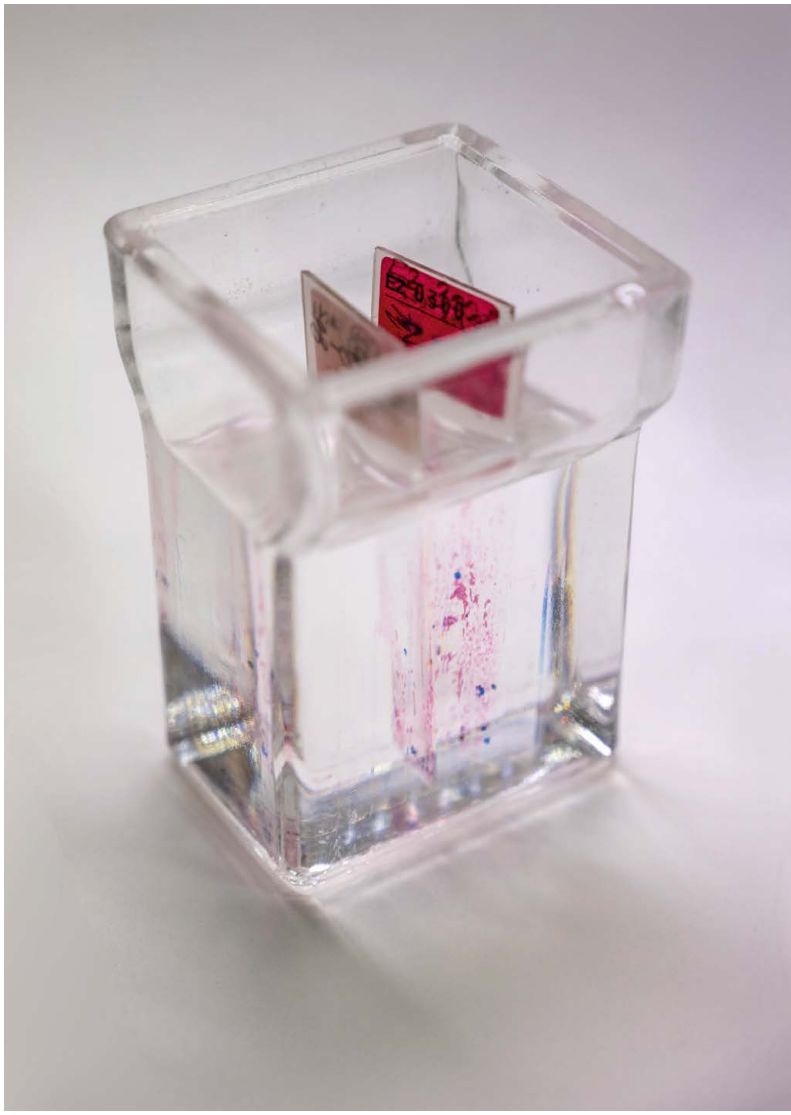
Herzliche Grüsse

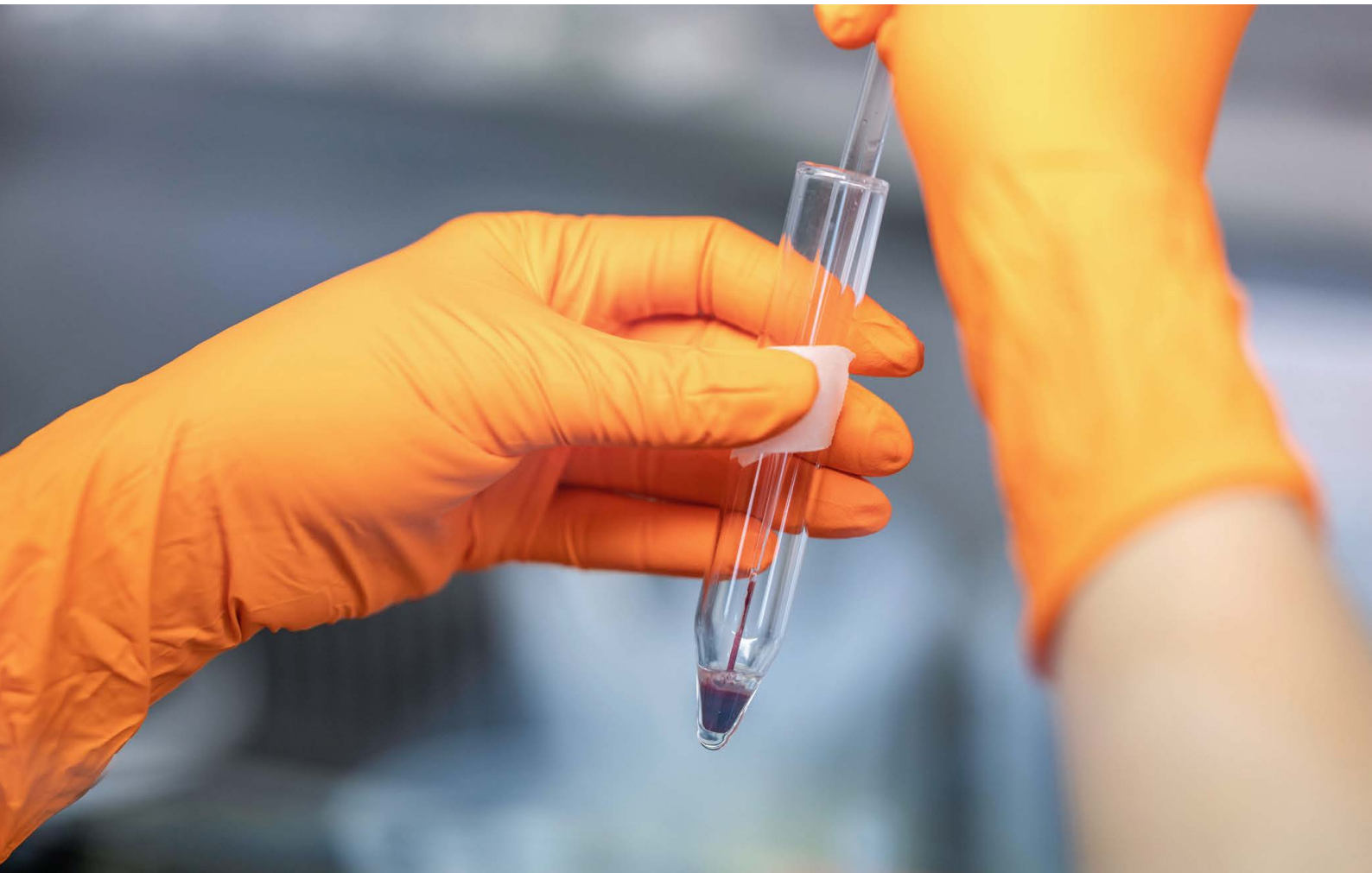
Aurel Perren, Direktor


Institut
für Pathologie
Universität Bern
31
Lehre
Diagnostik
Forschung

>>> Organigramm







>>> Dienstleistung

1 Klinische Pathologie

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

In der Klinischen Pathologie arbeiten «Ärzteschaft» und «Laborpersonal» Hand in Hand. Die Mitarbeitenden der Klinischen Pathologie arbeiten in den Bereichen der Histopathologischen Diagnostik, Zytopathologie, Postmortale Diagnostik und Molekularpathologie.

1.1 Ärzteschaft

Histologische Diagnostik (PD Dr. med. H. Dawson)
In der histologischen Diagnostik sind 18 Fachärzte und 8 Assistenzärzte tätig, welche zusammen das gesamte Spektrum der universitären Pathologie inklusive molekulare Diagnostik abdecken. Die Fachärzteschaft vertritt die Pathologie in zahlreichen interdisziplinären Tumorboards und Fallbesprechungen innerhalb des Inselspitals und externen Spitälern. Für die Ärzteschaft war auch das Jahr 2021 trotz einer gewissen sommerlichen Verschnaufpause von der Corona-Pandemie geprägt, wobei sich der neue Arbeitsalltag spürbar in den digitalen Bereich verschob. Die digitale Pathologie konnte beispielsweise so weit vorangetrieben werden, dass ein Teil der Diagnostik am Bildschirm erledigt werden kann. Um diese Prozesse zu erleichtern wurde ein Konzept eines «digitalen Schnittkastens» mit direkter Anbindung an das Laborinformationssystem erarbeitet. Zudem sind erste validierte Algorithmen zur Unterstützung der Auswertung von Biomarkern ebenfalls im Einsatz. Für das kommende Jahr sind nebst dem Ausbau der digital unterstützten Befundung weitere, nach Lean-Prinzipien gestalteten Anpassungen im Histologie-Labor inklusive Makroskopie vorgesehen, welche zum einen die Automatisierung der digitalen Diagnostik, parallel aber auch das Erstellen standardisierter synoptischer Berichte mittels Patho-Link ermöglichen werden.

Neuropathologie (Dr. Martin Wartenberg, Dr. Theoni Maragkou, Dr. Bastian Dislich)
Im Jahr 2021 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. Wir bieten ein sehr breites Spektrum an molekularen Analysen, einschliesslich Next-Generation Sequencing (NGS TSO 500) und Genom-weite Methylierungsanalyse (EPIC Array), welche hausintern im Clinical Genomics Lab des Inselspitals durchgeführt werden. In Zusammenarbeit mit dem Neuromorphologischen Labor der Neurologischen Klinik des Inselspitals wurden rund 70 Muskelbiopsien untersucht. Die postmortale Diagnostik mit über 70 Hirnsektionen. Entsprechend dem Charakter der Neuropathologie als Schnittstelle zwischen den klinischen Neurofächern, der Labordiagnostik und translationaler Forschung war der Fachbereich Neuropathologie auch im Jahr 2021 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 des SIWF und der Medizinischen Allianz Basel/Bern (MBB).

Postmortale Diagnostik (PD Dr. med. et phil. nat. Y. Banz)
2021 war auch die postmortale Diagnostik auf Grund der SARS-CoV-2 Pandemie Lage wieder diversen Herausforderungen ausgesetzt – wie natürlich viele andere Bereiche der Medizin. Die Frage wieso und wie genau eine an Covid erkrankte Person verstorben ist, beschäftigt uns immer noch. Indem wir im eingespielten Team aus Fachärzten, Assistierenden und Präparatoren dieser Frage auf den Grund gegangen sind und weiterhin gehen werden, leisten wir einen wichtigen Beitrag diese Infektionskrankheit noch besser zu verstehen, um daraus möglichst Lehren für die Zukunft zu ziehen.

Die Anzahl postmortaler Untersuchungen, inklusive neuropathologischer und pädopathologischer Untersuchungen, ist auf tiefem Niveau in etwa gleichgeblieben und liegt bei um 80 Untersuchungen. Im Kontext regelmässig stattfindender klinisch-pathologischer Konferenzen mit diversen Kliniken werden die Resultate auserwählter Untersuchungen interdisziplinär besprochen und dienen so nicht nur der eigentlichen Besprechung der Befunde, sondern auch als Weiterbildungsveranstaltung. Die Möglichkeit minimal invasiver Autopsien, welche im Institut für Pathologie angeboten werden könnten und eine valide Option darstellen, falls einer regulären Autopsie nicht zugestimmt wird, wurden 2021 leider nicht genutzt.

Die Modernisierung bzw. Digitalisierung der Lehre im Bereich der postmortalen Diagnostik (s. hierzu auch die Ausführungen im Kapitel zur studentischen Lehre) sollen in Zukunft weiter vorangetrieben und ausgebaut werden, um dem wichtigen Ziel der qualitativ hochstehenden Lehre Fachbereich der speziellen Pathologie gerecht zu werden.

Zytopathologie (med. pract. M. Trippel)
Die Zytologie ist als minimal-invasive und gleichzeitig maximal effiziente und kostengünstige Methode zukunftsweisend. Sie ist somit für die Anforderungen der modernen Medizin mit ihren immer sensitiver und spezifischer werdenden prädiktiven und prognostischen Tests ein bedeutender Partner sowohl in der gynäkologischen als auch der extra-gynäkologischen Diagnostik.

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 fortgeführt werden.

Um auch in Zukunft eine qualitativ hochstehende zytologische Diagnostik anbieten zu können, engagiert sich die Zytologie auch in der Fort- und Weiterbildung von Ärztinnen, Ärzten und von Zytotechniker/Innen.

1.2. Labor

Histologische Diagnostik (J. Ramseier)
Mit dem Umzug der Scanner ins HD-Labor erhielt die digitale Pathologie unter Berücksichtigung der LEAN-Prinzipien ihren festen Platz im Routinelabor der Histologischen Diagnostik. Nach der erfolgreichen Gerätevalidierung und der darauffolgenden Selbstkontrolle der Ärzteschaft besteht seit Oktober 2021 die Möglichkeit für jeden Facharzt einen Teil der Fälle virtuell zu erledigen.

Im Juni 2021 startete Herr Yan Hirschi als Stellvertretender Leiter in der Histologischen Diagnostik. Durch seine langjährige Erfahrung in der Pathologiebranche arbeitete er sich rasch in die Prozesse ein. Mit seinem Knowhow in der Immunhistochemie ergänzt er die Laborleitung bestens und übernahm per November 2021 die operative Leitung für diesen Prozess.

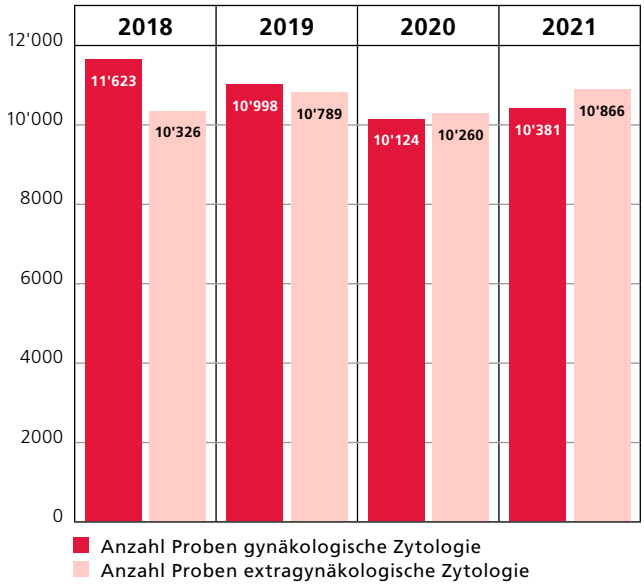
Das Q-Ziel 2021 «Einführung mitarbeiterbezogener Soll-Werte für Monitoring zentrale Routinearbeiten im HD Labor» wurde erfolgreich umgesetzt. Die Erhebung beinhaltet die Bearbeitungszeit pro Block in den Prozessen Einbetten und Mikrotomie. Erste Auswertungen zeigen deutlich, dass das erfahrungstechnisch junge Team die aus einem vergangen Projekt erhobenen Soll-Werte erreicht und teilweise sogar übertrifft. Im Laufe des Projekts wurde zudem das kontaktlose Einloggen im Pathotrac mittels personalisiertem QR Code eingeführt.

Nach einem Rückgang der Einsendungen im ersten COVID Jahr, stabilisierten sich die Einsendungen im 2021. Ende Jahr konnte sogar ein Plus von 7.9% bei den Biopsien und ein Plus von 3.7% bei den Operationspräparaten im Vergleich zu 2020 verzeichnet werden.

Zytopathologie (med. pract. M. Trippel)
Die Zytologie des Instituts für Pathologie 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.

Im Jahr 2021 untersuchten wir insgesamt 21’247 Proben mit 10’866 Proben aus der extra-gynäkologischen Zytologie und 10’381 Proben aus der gynäkologischen Zytologie.

Ein Hauptanteil der eingesandten Proben betreffen die extragynäkologische Zytologie in der die Feinnadelpunktionen aus verschiedenen Organen und Lokalisationen eine grosse Gruppe darstellen. Hier spielt auch die Herstellung der Zellblöcke eine grosse Rolle, um ergänzende immunzytochemische oder molekularpathologische Untersuchungen am eingesandten Untersuchungsmaterial durchzuführen. Neben den Proben der Feinnadelpunktionen spielen natürchlich die exfoliative Zytologie eine wichtige Rolle und auch die Anzahl der Proben der gynäkologischen Zytologie konnte sich auf stabilem Niveau halten.



Entwicklung der Einsendungen gynäkologischer und extragynäkologischer Zytologie 2018–2021.

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

Fachverantwortlicher molekulare Pathologie Prof. Dr. pharm. Erik Vassella

PD Dr. med. Tobias Grob, medizinischer Leiter molekulare Pathologie
Mitarbeiterinnen Clinical Genomics Lab

Das gemeinsam betriebene Clinical Genomics Lab unter der Leitung von Prof. Dr. Ursula Amstutz umfasst die molekulare Diagnostik der Bereiche Humangenetik, Hämatologie, Molekularpathologie und der klinischen Chemie. Gleichzeitig dient das Clinical Genomics Lab als Core Facility für Hochdurchsatzsequenzierung für die klinische Forschung und als zentrales Standbein für das Zentrum für Precision Medicine. Durch die Nutzung von Synergien und interdisziplinäre Zusammenarbeiten werden Leistung für die Patientenversorgung und die Forschung auf hohem Niveau ermöglicht.

Die Dienstleistung der Molekularpathologie im Clinical Genomics Lab ist eine Zusammenarbeit des Instituts für Pathologie und des Inselspitals. Die in diesem Fachbereich verwendeten Methoden umfasst insbesondere die Hochdurchsatz-Sequenzierung mittels TrueSightOncology (TSO) 500 Panel (Illumina) als Therapieentscheid bei soliden Tumoren. Neben der Erfassung von Mutationen aus über 500 Tumor-relevanten Genen erlaubt die Methode den Nachweis von Amplifikationen und Fusionstranskripte (insbesondere NTRK-, ALK, ROS-, FGFR2 und RET Fusionen) von Onkogenen, den Nachweis der Tumormutationslast sowie der Mikrosatelliteninstabilität, ausgelöst durch den Funktionsverlust von Mismatch-Reparaturgenen. Neben dieser Schlüsseltechnologie verwenden wir in der Routine-Diagnostik die Sanger-Sequenzierung, Pyrosequenzierung, verschiedene 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 sind weitere Analysen. Die Tests können an Formalin-fixiertem und Paraffin-eingebetteten Gewebe durchgeführt werden. Die molekulardiagnostischen Befunde werden am molekularen Tumorboard des Inselspitals besprochen.

Die Umstellung der NGS Analyse auf das TSO500 Panel hat dazu geführt, dass die Zahl der NGS Analyse im letzten Jahr um 60% zugenommen hat, was zu einer Steigerung des Umsatzes des Molekularpathologielabors um 25% führte. Neben der Diagnostik hat uns die Weiterentwicklung der Bioinformatikpipeline zur Annotation und Beurteilung (TIER System, OncoKB) der Alterationen, die mit dem TSO500 Panel erfasst wurden, beschäftigt. Diese Pipeline ist gleichzeitig eine integrierte Datenbank für annotierte Alterationen zur erleichterten Befundung und Qualitätskontrolle. Dies erlaubt uns, die NGS Befundung speditiv und mit hoher Qualität durchzuführen. Im Laufe dieses Jahres wurde zudem der Infinium Methylation EPIC Array etabliert. Dieser erlaubt die Erstellung eines Genom-weiten Methylierungsprofils von ZNS Tumoren und Sarkome als Classifier zur Unterstützung der Tumor-Diagnose. Zudem haben wir das TrueSight RNA Fusion Panel mittels Tagmentation zum Nachweis von Fusionstranskripte für die Sarkom Diagnostik etabliert. Das Prozedere der Nukleinsäureextraktion wurde vereinheitlicht; diese wird nun mittels eines Maxwell® RSC 48 Instrument (Promega) durchgeführt. Das CGL Labor steht kurz vor einer Neuakkreditierung; diese musste im Fachbereich Molekularpathologie auf Grund der Fusion mit den anderen Bereichen vorübergehend sistiert werden.

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.


Nikon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Plan Fluor
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3 Fachgruppen des Instituts für Pathologie der Universität Bern

Stand Januar 2022

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	
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
B. Dislich	031 632 71 90
A. Rodriguez	031 632 99 69

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. Stanowska	031 632 52 55
A. Marrazzini	031 632 99 01
M. Wartenberg	031 632 49 76

Leberpathologie	
M. Montani	031 632 32 67
J. Friemel	031 632 49 37
A. Mookhoek	031 632 99 20

Lungenpathologie	
A. Mookhoek	031 632 99 20
Y. Banz	031 632 88 75
T. Losmanová	031 632 31 91

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
A. Mookhoek	031 632 99 20

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
A. Safret	031 632 32 48

Molekularpathologie	
E. Vassella	031 632 99 43
T. Grob	031 664 04 78
H. Dawson	031 632 99 60
B. Dislich	031 632 71 90

4 DIR-Stab

Der Direktionsstab besteht aus den Bereichen Administrativer Support, Technischer Dienst und Logistik (ATL), Human Resources (HR), Qualitätsmanagement (QM), Informatik (IT) und Finanzen/Controlling (FIN) und unterstützt alle internen und externen Kunden des Instituts für Pathologie bei deren Aufgaben und Projekten.

Der administrative Support beinhaltet das Berichtssekretariat für die Erstellung der Berichte und Organisation der Tumorboards sowie den Support Center mit den Aufgaben interne Kundenbetreuung, Buchhaltung und Unterstützung in der Lehre. Zwecks Arbeitsprozessoptimierung gehören die Bereiche Technischer Dienst und Logistik zur ATL. Die Informatik ist strategisch auf die Digitale Pathologie und operativ auf die Infrastruktur, Support und das Patientenmanagementsystem fokussiert. Das Personalbüro ist für die personellen Anliegen der Mitarbeitenden und für die Prozesse Eintritte, Mutationen und Austritte verantwortlich, während der Bereich Finanzen/Controlling auch die Arbeitssicherheit und den Datenschutz beinhaltet.

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**	**2021**
Anzahl Einsendungen	37'232	42'422	43'607	45'491	48'601	46'372	**48'707**
Anzahl Lokalisationen	70'286	82'069	83'191	86'253	93'835	90'658	**95'500**
Einsendungen Schnellschnitte	1'648	1'936	1'761	1'784	1'831	1'770	**1'822**
Proben Schnellschnitte	2'252	2'454	2'264	2'225	2'313	2'216	**2'295**

Autopsie							
Anzahl durchgeführte Autopsien	152	146	130	134	106	99	**81**

Zytopathologie							
Anzahl Einsendungen Total	16'043	16'634	16'995	17'814	17'576	17'300	**17'038**
Anzahl Proben Klinische Zytologie	11'582	9'324	9'956	10'326	10'789	10'260	**10'856**
Anzahl Proben Gynäkologische Zytologie	9'375	9'869	10'563	11'623	10'998	10'124	**10'445**
Anzahl Proben Total	20'957	19'193	20'519	21'949	21'787	20'384	**21'301**
Anzahl Zellblöcke	2'748	2'837	3'334	3'844	4'011	4'234	**4'791**

Immunhistochemie							
Fälle (Blöcke) Diagnostik (Paraffin)	7'843	9'094	7'681	8'822	11'616	11'717	**12'788**
Färbungen Immunfluoreszenz (Nierenbiopsien)	2'079	2'772	2'464	2'010	2'486	1'980	**3'003**
Fälle Immunzytologie am Ausstrich	197	158	258	201	246	210	**154**
Färbungen Immunzytologie am Ausstrich	240	486	364	377	353	307	**204**
Färbungen Diagnostik (Paraffin)	47'944	44'366	47'597	51'971	59'249	60'913	**65'866**

Tumorbank

Einsendungen Tumorbank	1'030	1'417	1'879	1'593	1'823	2'126	**2'373**
Anzahl Projekteingänge TRU	457	604	602	738	850	640	**787**

>>> 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 & 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 appropriate use («support platforms»), can be also accessed by the research personnel of the other units of the Institute of Pathology. This allows an efficient use of the limited financial resources, 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, and 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.

Personnel

In 2021 approximately 50 persons were working in the Division of Experimental Pathology.

Grant Support

In 2021 the total amount of new external funding obtained by the research groups of the Division of Experimental Pathology was more than CHF 1.3 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) and have access to the newly established Imaging Mass Cytometry (IMC) Platform (with a Helios and a Hyperion instrument) of the DBMR, University of Bern. 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.

Group of Stefan Freigang, MD

Johanna Baumgartner, PhD student
Thi Thuy Hang Bui, PhD student
Joëlle Schläfli, MSc student
Sabrina Walthert, technician (from April 2021)

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.

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 cyclo-pentenone-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

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
- Manfred Kopf, PhD, Federal Institute of Technology Zürich (ETHZ), Switzerland
- Philippe Renaud, PhD, Dept. Chemistry and Biochemistry, University of Bern, Switzerland

International

- Hans-Christian Probst, University of Mainz, Germany
- Paul B. Savage, PhD, Brigham Young University, Provo UT, USA

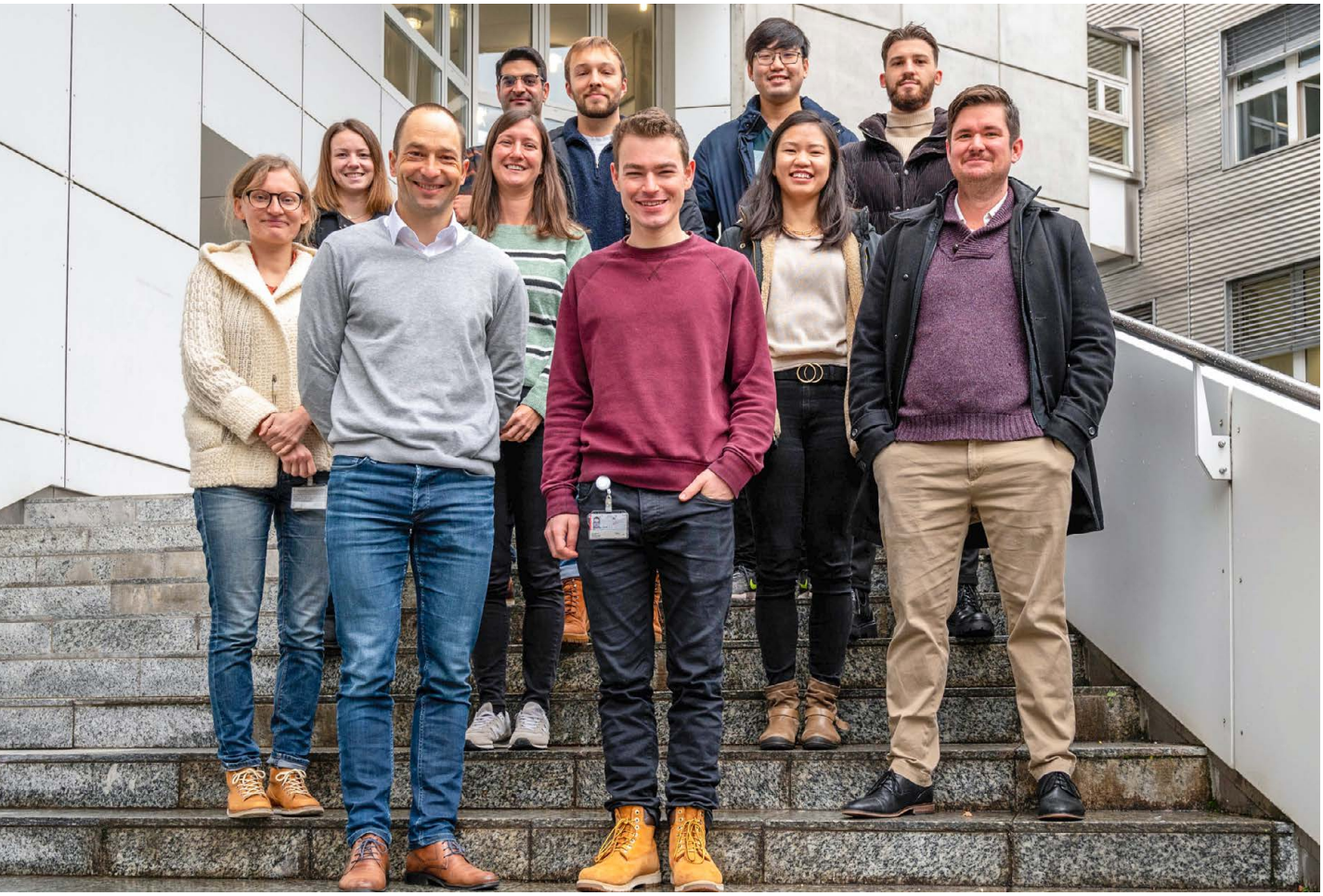
Grant Support

- Swiss National Science Foundation, S. Freigang; PI, 2020–2024, CHF 632’000
- Swiss Heart Foundation, S. Freigang; PI, 2020–2022, CHF 50’000
- UniBE 2021 PhD Fellowship, J. Baumgartner, S. Freigang, 2017–2021, CHF 90’000
- Swiss Lung Liga*, S. Freigang; PI, 2017–2021, 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

Hojjat Alizadeh Zeinabad, MSc, PhD student (visiting student from Oct 2021)
Lukas Bauer, MD doctoral student (from May 2021)
Océane Derivaz, MSc student (from July 2021)
Silvio Eugster, MSc student
Robert Gaultney, PhD, post-doc
Kristýna Hlavácková, MSc, technician 90%
Fatlind Malsiu, MSc student (from Sept 2021)
Coline Nydegger, technician, 90%
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

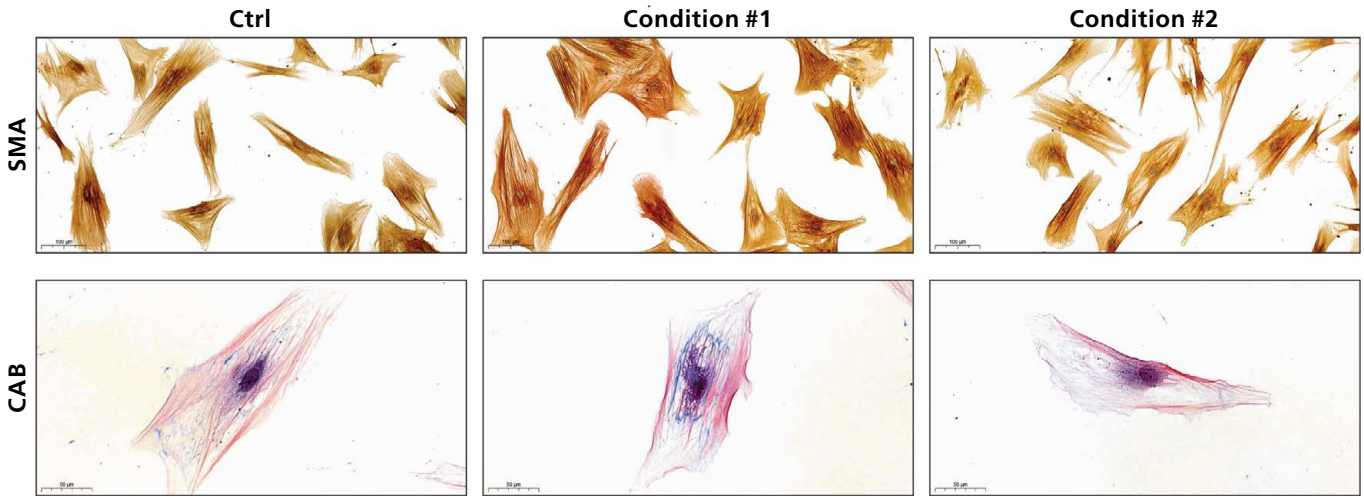
Inflammation is a driver of cancer. We have shown that IL-33 signaling is important for the development of myeloproliferative neoplasms (MPN), a type of blood cancer, and for promoting colorectal cancer (CRC) (Mager, J Clin Invest, 2015; Mertz, OncoImmunology, 2015; Pastille, Mucosal Immunol, 2019). We currently investigate the contribution of IL-33 to MPN progression and to the cellular and molecular mechanisms underlying IL-33-dependent CRC. 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 mu-



Project 1: Detection of fibrosis in human bone marrow fibroblasts. Fibroblasts were grown from patient bone marrow. After in vitro expansion, fibroblasts were cultured on chamber slides and stimulated with distinct inflammatory molecules (condition #1 or #2) or left untreated (ctrl, control). After five days, fibroblasts were fixed and stained for smooth muscle actin (SMA) or chromotrope aniline blue (CAB).

rine 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.

Project 4: Investigation of the local immune system regulation in COVID-19

The mechanisms leading to severe inflammatory lung disease in some COVID-19 patients are unknown. In this project, we will analyze the cells in the lung lavage of these patients and compare these findings with results from collaborators working on a mouse model of COVID-19. We hope so to reveal targets for COVID-19 therapy.

Internal Collaborations

- Christoph Mueller, PhD
- Inti Zlobec, PhD
- Yara Banz, MD, PhD
- Mafalda Trippel, MD

External Collaborations

National

- 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
- Nicolas Bonadies, MD; Alicia Rovó, MD; Vera U. Bacher, University Hospital of Bern

International

- Kathy McCoy, PhD, University of Calgary, Canada
- Astrid Westendorf, PhD, Universitätsklinikum 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
- 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, 2018–2021, CHF 79'554
- Swiss Lung League Project grant, P. Krebs; PI, 2018–2021, CHF 79'554
- Swiss Life; Project grant, P. Krebs; main PI, 2021–2023, CHF 20'000
- Uniscientia; Project grant, P. Krebs; main PI, 2021–2022, CHF 136'000
- Seal of Excellence Fund (SELF) UniBE; Fellowship to R. Gaultney (P. Krebs, PI) 2021–2023, CHF 128'698
- UniBE ID (Interdisciplinary) Grant, P. Krebs; main PI, 2017–2021, CHF 75'000
- Swiss Cancer Research Foundation (KFS) Project grant, P. Krebs: PI, 2017–2021, CHF 312'500

* 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% (till June 2021)
Juliana Barreto de Albuquerque, PhD, post-doc
Regina Berchtold, technician, 80%
Nadia Corazza, PhD, staff scientist/co-PI, 60% (till Feb 2021)
Antonia Ferreira, MSc
Bilgi Gungor, PhD, post-doc
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 inflammation with concurrent analyses of the intestinal microflora and the associated metabolic changes. 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 biobank of the Swiss IBD Cohort Study (SIBDCS)

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, induction of remission and repeated flares of inflammation (Brasseit et al., Mucosal Immunol 2016). In this model we monitor the composition of the intestinal microbiota during relapsing – remitting colitis and define its consequences on the metabolic profile in the feces and the host. Furthermore, we investigate how these changes influence the host immune response and vice versa. 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
- Philippe Krebs, PhD
- Mirjam Schenk, PhD

External Collaborations
National
- Andrew Macpherson, MD, Julien Limenitakis, PhD, 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

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

Grant Support
- SNF 314730_189277, Christoph Müller, 2019–2022, CHF 516'667
- SNF 33CS30_177523, SIBDCS, Christoph Müller; Co-PI, 2018–2021, CHF* 304'500
- Monique Dornonville de la Cour Stiftung, Daniel Zysset, 2018–2021, CHF 52'387
- Novarits, Juliana Barreto de Albuquerque, 2021–2022, CHF 51'182

* own share

Administrative duties
Christoph Mueller
- Chair, Program Board «Certificate of Advanced Studies in Research Management» (CAS «Forschungsmanagement»), 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) (until 31-7-2021)
- Member of the Committee on the Novo Nordisk Foundation Challenge Programme 2021/2022
- 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.

Forschungsgruppe Aurel Perren (Research group Aurel Perren).

Group of Aurel Perren, MD

Valentina Andreasi, guest PhD student (till July 2021)
Simon April, MSc, PhD student
Konstantin Bräutigam, MD, Resident
Aziz Chouchane, guest scientist
Matthias Dettmer, MD Attending Pathologist
Eva Diamantis-Karamitopoulou, guest medical doctor
Annunziata Di Domenico, post-doc (till May 2021)
Kristýna Filipová, MSc student
Philipp Kirchner, staff scientist
Renaud Maire, MSc, technician
Ilaria Marinoni, PhD, Co-PI
Viktoriia Ovcharova, MSc student Med (till April 2021)
Umara Rafiqi, MSc, PhD student
Lionel Rohner, MSc student (till April 2021)
Martin Sadowski, PhD, Senior Research Assistant
Janine Straub, MSc, Cand. Med.
Tsilla Sunier, techician
Martin Wartenberg MD, Attending Pathologist
Leonie Lara Weber, MSc student
Simona Ziaková, PhD student

Summary of Research Activities

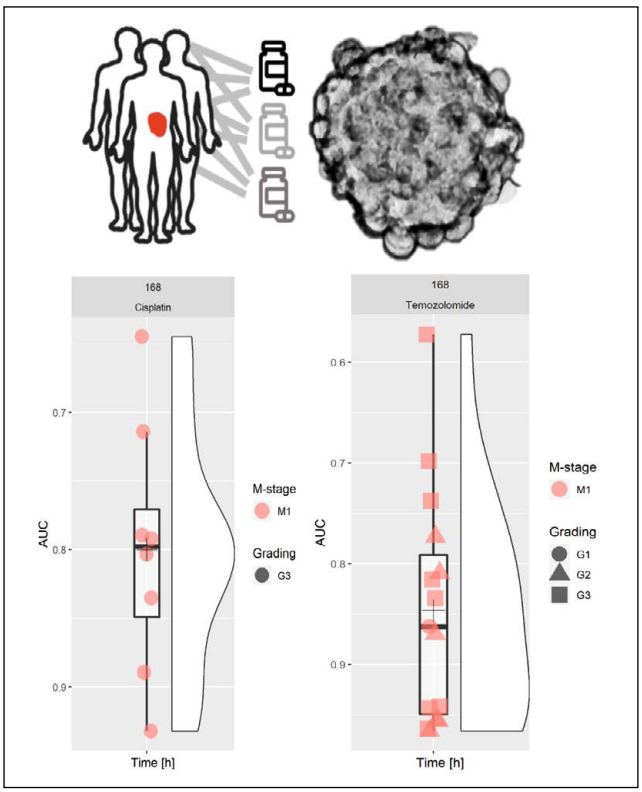
The research focus of our group is the study of endocrine tumors; notably sporadic and familial pancreatic neuroendocrine tumors (PanNETs). PanNETs are highly heterogeneous and the mechanisms leading to tumor development are still elusive. We focus on the understanding of the molecular events leading 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: 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



Project 2: Patient-derived Tumoroids from PanNET patients are utilized for in vitro pharmacotyping and molecular profiling.

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
- Corina Kim-Fuchs Universitätsklinik für Diabetologie, Endokrinologie
- Ernährungsmedizin & Metabolismus (UDEM) Inselspital, Universitätsspital

External Collaborations

National

- Beat Gloor, MD, Department of Visceral Surgery, Insel University Hospital, Bern
- Holger Moch, MD, Department of Pathology, University Hospital, Zurich
- Corina Kim-Fuchs Universitätsklinik für Diabetologie, Endokrinologie, Ernährungsmedizin & Metabolismus (UDEM) Inselspital, Universitätsspital

International

- Dr. Chrissie Thirlwell, University of Exeter school of medicine, Exter, UK
- Prof. Bertram Wiedenmann, Charité, 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), 2017–2021, CHF 70'000
- Werner und Hedy Berger-Janser Stiftung, Martin Wartenberg (PI), 2018–2021, CHF 41'587

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

Administrative duties

Aurel Perren

- Stellvertreter des Dekans Medizinische Fakultät
- Mitglied Fakultätsausschuss
- Mitglied Direktorium CCC Inselspital
- Co-Pi und Vize-Präsident Swiss Biobanking Platform (SBP)
- Vorstandsmitglied Krebsliga Bern, Ressortleiter Forschung
- Advisory Board, 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
- Mitglied Education Committee IAP. Sektion Deutschland

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

Group of Mirjam Schenk, PhD

Lukas Bäriswyl, technician (50%)
Mirela Kremenovich, PhD student
Steve Robatel, PhD student
Ivanina Biserova Mutisheva, MSc 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.

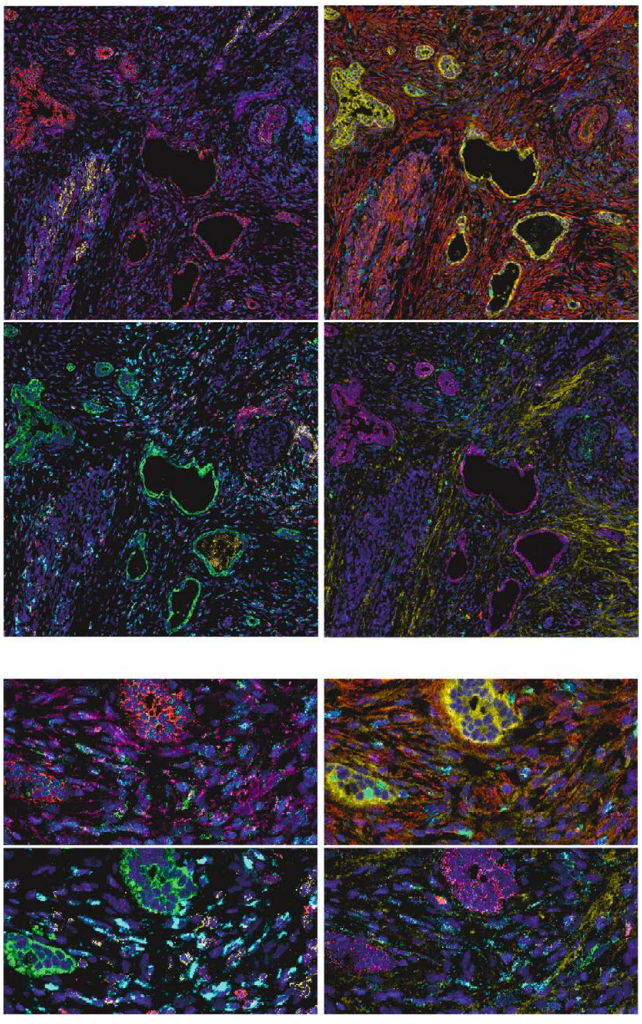
Project 2: Generation of potent cross-presenting Dendritic Cells (DC) for tumor immunotherapy

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.

Project 3: Highly multiplex, spatially resolved immuno-phenotyping of PDAC for biomarker discovery

The tumor immune microenvironment in pancreatic ductal adenocarcinoma (PDAC) is diverse, comprising various cell types that may either enhance or attenuate tumor immunity and disease progression, as well as response to therapies. It is therefore essential to dissect the immunological landscape in human PDAC tissues and to assess the correlation of various cell subsets and tumor-derived immunosuppressive factors to patient survival and other clinical parameters.

Utilizing a novel approach to perform spatially resolved multiplex immuno-histochemistry, we intend to delineate the phenotypes of tumor-infiltrating immune subpopulations in exquisite detail. Integrating these findings with transcriptomic data and tumor genotype signatures will allow us to unravel the mechanistic and prognostic relevance of certain immune markers in PDAC.



Project 3: 25-plex imaging mass cytometry (IMC) image of a human PDAC tissue section shown in four images with 6 markers each. Overview (top), zoom (bottom).

Internal Collaborations
- Martin Wartenberg, 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), 2016–2022, CHF 1.3 Mio
- San Salvatore, Mirjam Schenk (PI), 2019–2021, CHF 143’000
- Novartis , Mirjam Schenk (PI), 2021–2022, CHF 52’000

Administrative duties
- Member of the Flow Cytometry & Cell Sorting Core Facility Working Group, University of Bern
- Member of the Nomination Committee for an Associate Professorship at the Medical Faculty, University of Bern, Switzerland
- Member of the Mass Cytometry steering committee, University of Bern, Switzerland

Research group Mario P. Tschan.

Group of Mario P. Tschan, PhD

Anna Bill, PhD postdoc, 70%
Nils Bodmer, PhD student
Carmen Kalbermatter, MSc student
Deborah Krauer, technician, 80%
Rina Mehmeti, PhD student
Tanja Muralt, MSc student
Nicolas Niklaus, PhD student (till August 2021)
Ana Quirós González, MSc student
Sreoshee Rafiq, PhD student (Supervisor, Dr. M. Humbert)
Kristina Seiler, MD-PhD student (till August 2021)
Igor Tokarchuk, MD-PhD student (till July 2021)
Jun Xu, MD-PhD student (from Nov 2020)
Shun Yi, PhD student

Summary of Research Activities

Cancer Autophagy Group: My research team investigates molecular mechanisms involved in the survival of acute myeloid leukemia cells (AML). Currently, we are deciphering the function of alternative splicing, the non-metabolic functions of glycolytic enzymes and autophagy recycling pathway in AML cell survival. Additional research projects address the function of autophagy in cell migration and metastasis of breast cancer cells. All these pre-clinical studies in targeted, personalized cancer therapy are conducted in close collaboration with clinical pathologists and the Translational Research Unit.

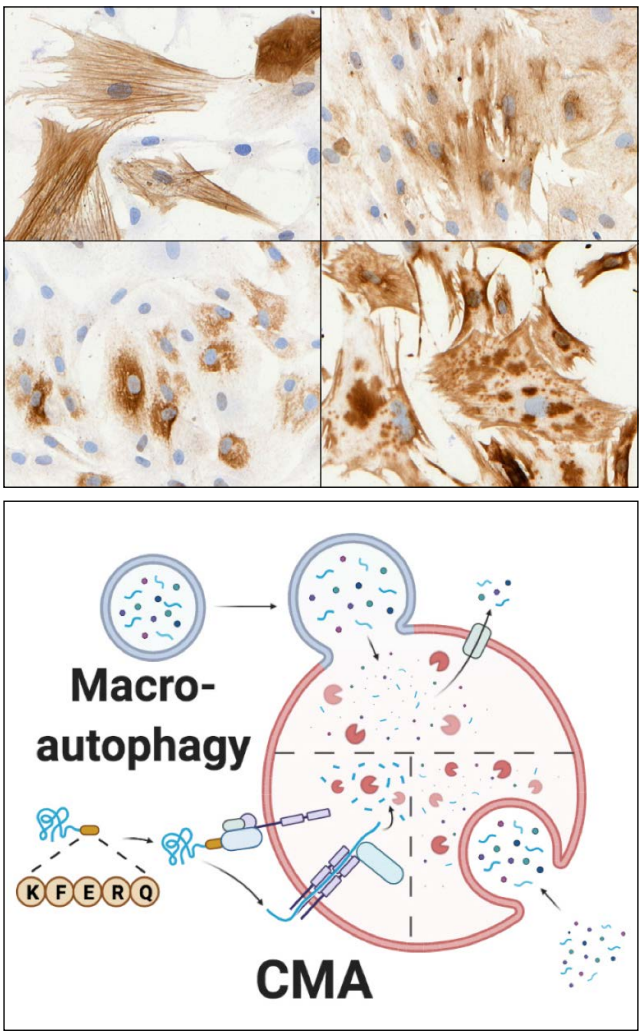
Research Activities

Project 1: Unravel the functions of autophagy in breast cancer motility

Metastasis formation accounts for the majority of deaths from breast cancer, making it imperative to better understand the mechanisms driving the metastatic cascade in order to develop therapeutic interventions to target it. We earlier discovered an oncogenic splice variant of a transcription factor and named it DMTF1β. We now show that DMTF1β promotes invasion and tumor-initiating capacity of breast cancer cells by activating autophagy. It has also been shown that inhibition of autophagy can have undesirable effects in some cancer types and induce epithelial to mesenchymal transition (EMT), one of the early steps of metastasis. Our aim is to identify breast cancer subtypes or cellular conditions in which autophagy inhibition will decrease migration, and those in which the inhibition of autophagy will promote invasiveness.

Project 2: PU.1 and alternative splicing

The transcription factor PU.1 (SPI1) plays a key role in myeloid differentiation as well as in myeloid cell survival. Aberrant low PU.1 expression contributes to an immature myeloid phenotype, e.g., acute myeloid leukemia (AML). Interestingly, two studies indicate that high PU.1 protein levels were associated with alternative splicing promoted by either direct binding to splice factors or by RNA binding. Our data indicate that PU.1



Project 1: Cancer-associated fibroblast from breast cancer patient.

controls splicing of the anti-apoptotic CFLAR (cFLIP) gene, and thereby regulates cell death during myeloid differentiation.

Project 3: Reducing FASN expression facilitates AML differentiation

Apart from glycolysis and OXPHOS, lipid metabolism is frequently reprogrammed in leukemic cells to support cellular growth. Particularly, the protein important for de novo lipid synthesis, fatty acid synthase (FASN), is frequently upregulated in tumor cells. We found that high FASN expression in acute myeloid leukemia (AML) cells is associated with an immature hematopoietic phenotype. Decreasing FASN levels by RNAi or epigallocatechin-3-gallate (EGCG) treatment, but no blocking its enzymatic function, resulted in improved response of AML cells to differentiation therapy.

Internal Collaborations

- Inti Zlobec, PhD
- Lucine Christe, 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
- Sabina Berezowska, MD, Institute of Pathology, University of Lausanne

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, Co-PIs: I. Zlobec; M. Tschan, 2020–2024, CHF* 660'000
- SNSF_31003A_173219, Mario Tschan, PI, 2017–2021, CHF 694'000
- UniBE ID grant, Co-PIs: B. Towbin; M.P. Tschan, 2021–2022, CHF* 109'000
- China Scholarship Council Fellowship, J. Xu; M. P. Tschan, PI, 2021–2024, CHF* 90'000
- Swiss Government Excellence Scholarship, Co-PIs: I. Zlobec; M.P.Tschan, 2021–2024, 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

Group of Erik Vassella, Dr. pharm.

Elham Kashani, PhD student
Massimo Maiolo, Postdoc (from Oct 2021)
Theoni Maragkou, Associate staff pathologist
Jaison Phour, technician
Elia Rossini, Master student (from Sep 2021)
Huijuan Wang, Master student (from Jul 2021)
Philipp Zens, PhD student

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: Role of serine-threonine phosphatases in temozolomide resistance of glioblastoma
We followed 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. miRNAs identified by this screen showed downregulation of serine-threonine phosphatases, which in turn caused enhanced phosphorylaton of ERK and AKT, modulated the activity of DNA repair enzymes, and thereby confer resistance to TMZ response.

Project 2: Molecular characterization of recurrent glioblastoma
Glioblastoma (GBM) is the most heterogeneous and aggressive primary brain tumors, and represents a particular challenge of therapeutic intervention. In a single-center retrospective study of 43 matched initial and post-therapeutic GBM cases with exceptionally long recurrence period, we performed whole exome sequencing in combination with mRNA and microRNA expression profiling with the aim to identify processes altered in recurrent GBM. Seven mRNAs coding for proteins implicated in Epithelial to Mesenchymal Transition (EMT) and 13 miRNAs implicated in Tumor Necrosis Factor (TNF) and Wnt signaling pathways were significantly dysregulated. To the best of our knowledge, this is the largest cohort of recurrent GBM with long-term resection intervals, that has been analyzed by multi-omics approaches 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

- Philippe Krebs
- Ilaria Marinoni and Aurel Perren

External Collaborations

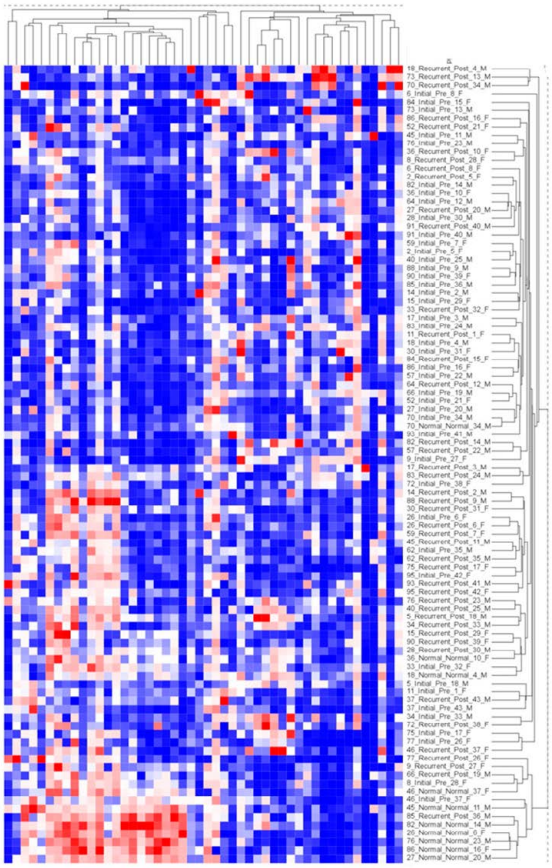
National
- Sabina Berezowska, Institut universitaire de pathologie, CHUV, Lausanne
- Iris Baumgartner, Universitätsklinik für Angiologie, Inselspital
- Markus Lüdi, Universitätsklinik für Anästhesiologie, Inselspital
- Philippe Schucht, Neuroonkologie, Inselspital

International
- Rupert Langer, Kepler Universitätsklinikum, Linz
- Pascal O. Zinn, MD, PhD, 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



Project 2: Heat map analysis of recurrent glioblastoma.

Group Translational Research Unit (TRU).

1.2 Translational Research Unit (TRU)

Head: Prof. Inti Zlobec

Lab manager: Dr. Paulina Brönnimann

Administration: Caroline Hammer (50%)

Technical and Scientific Staff:
Carmen Cardozo
Dr. Irene Centeno
Loredana Daminescu
Dr. José A. Galván
Stefan Reinhard
Fabian Wenger

Overview

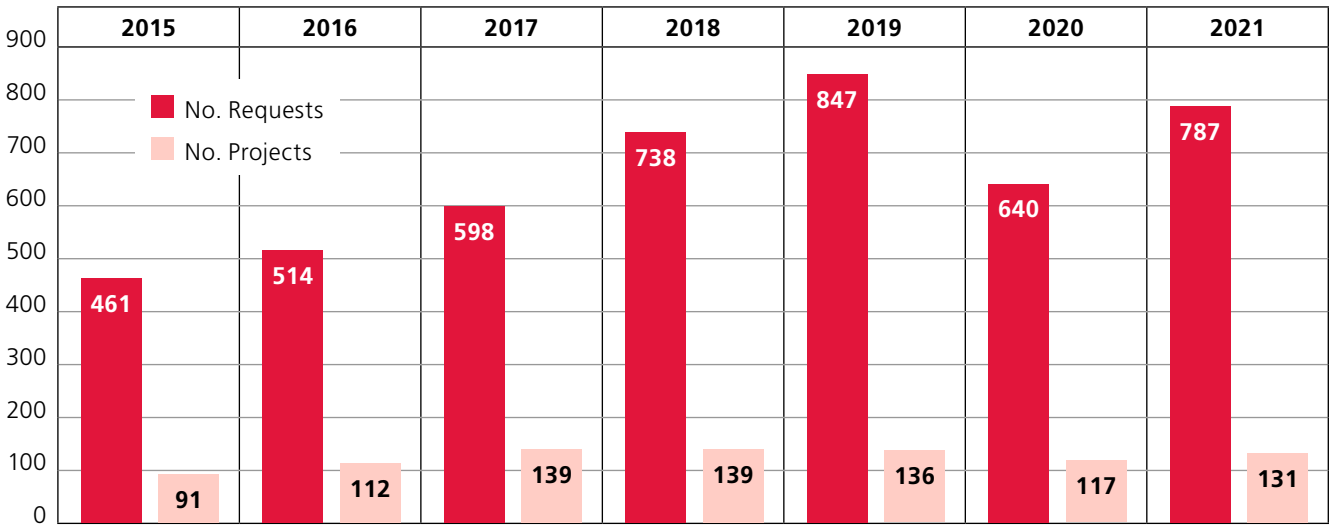
The Translational Research Unit (TRU) is a core facility of the Institute of Pathology, University of Bern. We provide tissue-based services for researchers and use innovative technologies to support translational projects conducted on human and animal tissues. We collaborate with researchers from the University of Bern, and participate in national and international projects.

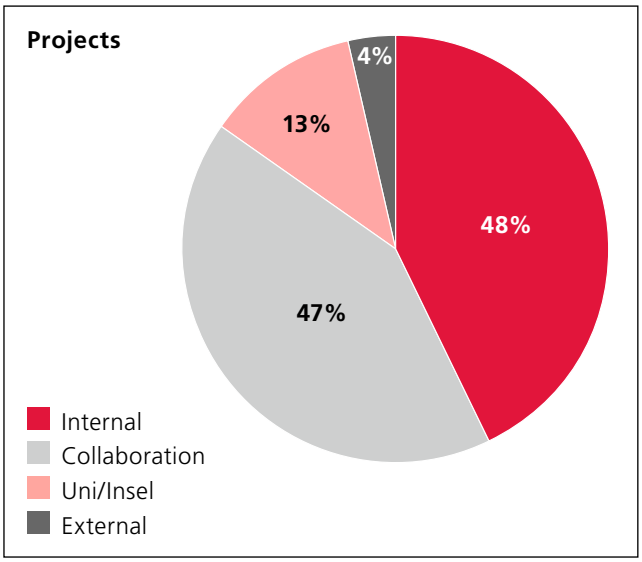
Our portfolio includes histopathology services, establishment of methods for tissue «visualization», digital pathology and image analysis, and next-generation Tissue Microarraying (www.ngtma.com). Moreover, we further support research by working together and providing access to patient material for research purposes through our certified partner biobank, Tissue Bank Bern (TBB).

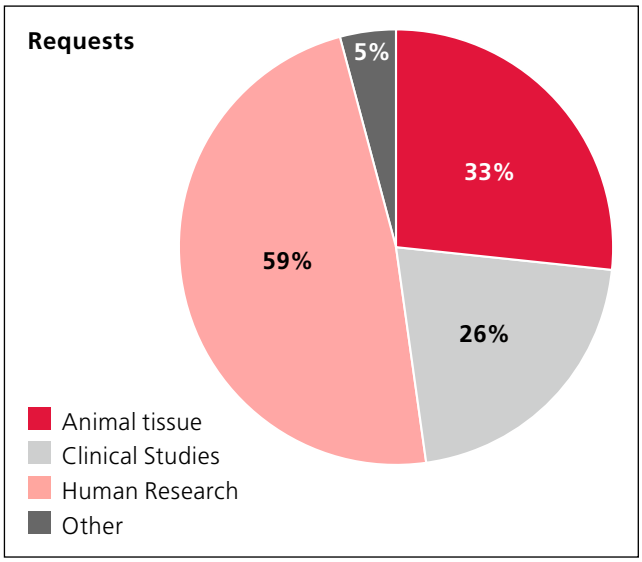
Projects and requests for services

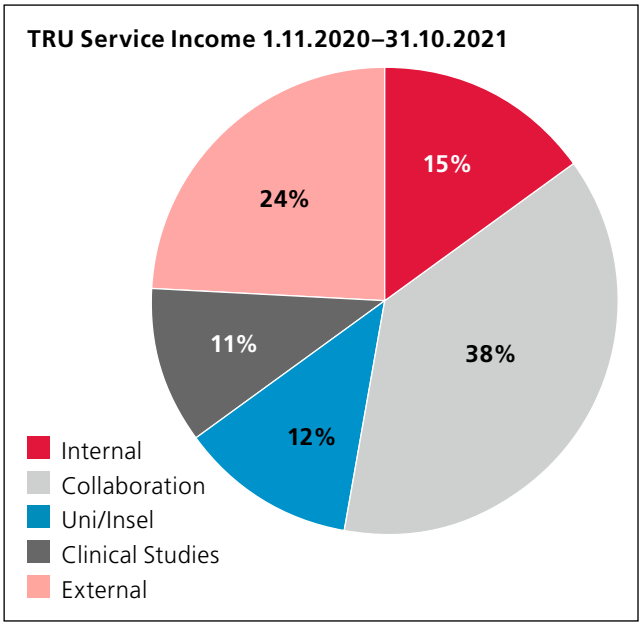
In 2021, we could support 131 projects from 787 separate requests (excluding those in TBB) indicating a positive trend comparing to year 2020 with COVID pandemic and lock-down. Of those, 48% were from internal researchers, whereas 47% were collaborations, including those with industry, and 13% were completed 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 59% human samples, 33% animal tissue and 26% clinical studies (including SAKK or trials with primary investigators at the Inselspital). The remaining are tissue-related requests.







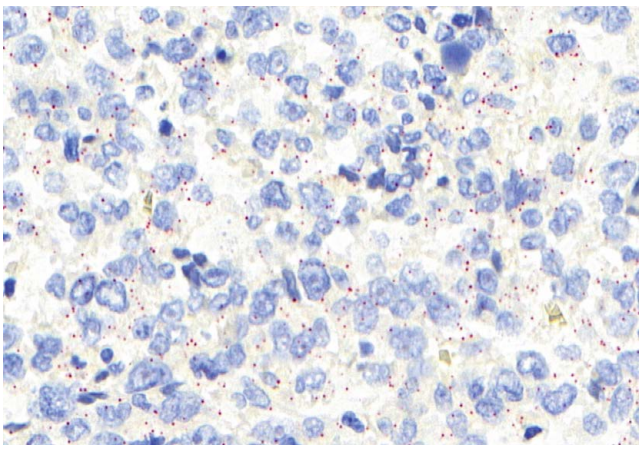


Number of projects (and associated requests) managed by TRU in 2021 and distribution of funding sources this year.

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, immunofluorescence 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 2882 (2020 n = 1905) blocks, and cut thousands of slides for H&E or special stains (n = 3788; 2020 n = 2435 slides), immunohistochemistry, TUNEL or in situ hybridization (Basescope ® Figure 2) (n = 4550; 2020 n =4936). Additionally, we have sectioned 473 frozen tissue on the cryostat.



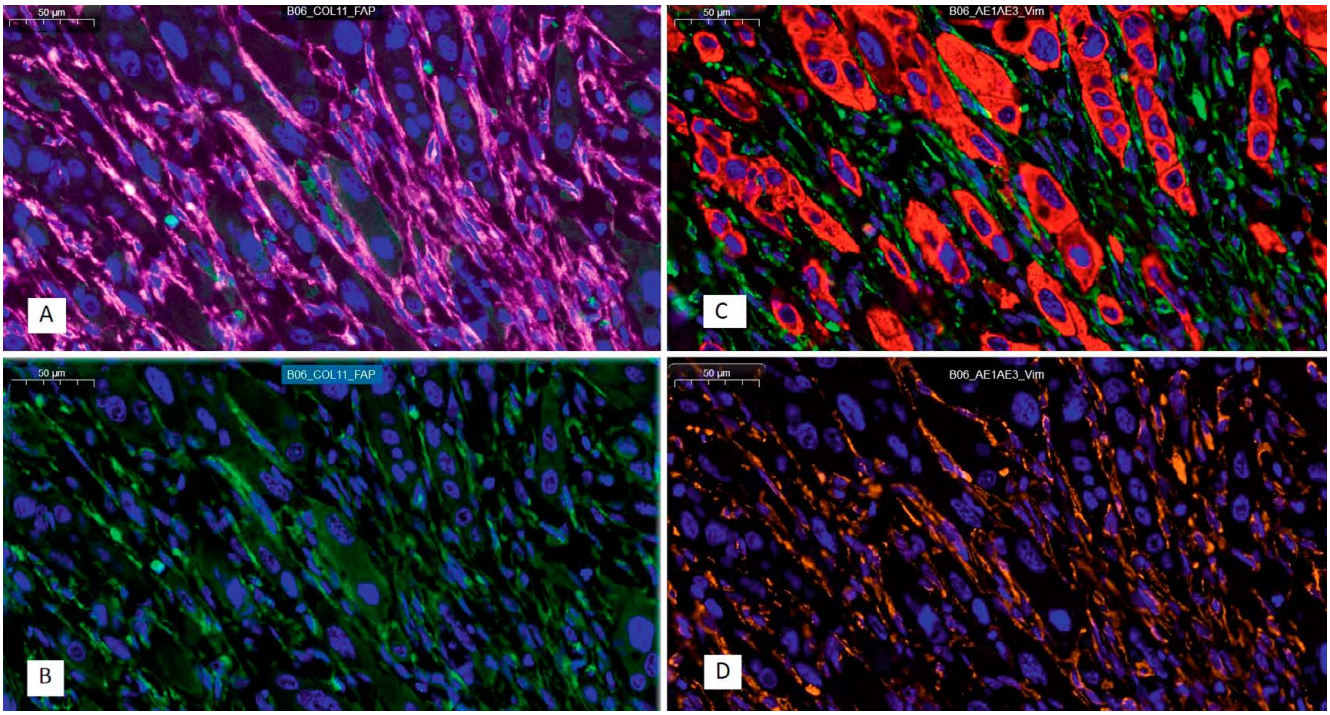
PPIB-1zz in situ Hybridization detected by Basescope® technology and Fast red as chromogen (Advanced Cell Diagnostics) in Prostate Adenocarcinoma.

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 TRU, in collaboration with Lunaphore, has received an Innosuisse grant to study the tumor microenvironment in colorectal cancer. Lunaphore's unique technology enables fast and easy multiplexed immunostaining of samples and will provide a major leap towards the quantitative and reproducible analysis of biomarkers for routine prognostic usage in clinical pathology. This project will be the first step to implement the multiplex immunofluorescence in the Institute of Pathology.

Lunaphore LabSat multiplexing technology in TRU.



Immunofluorescence staining performed on LabSat from Lunaphore.
A) FAP (pink); B) COL11 (green); C) Pan-Cytokeratin AE1 / AE3(red) and Vimentin (green); D) Vimentin (orange) in colorectal cancer.

This year, TRU has added an additional 56 new antibodies to its repertoire, and has performed 3'083 single stains, 656 double stains, 161 ISH and 94 TUNEL assays. Moreover, 52% of all slides were stained for internal researchers from the Institute of Pathology, 31% were part of collaboration projects, and 36% were performed as a service for the University/Insel researchers. In addition, about 33% 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 is 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.

In 2021, new version of CaseViewer was released under the name «Slide Viewer 2.5», where users can perform their digital annotations. The updated tool allows for copying defined annotations to multiple slides and assigning groups for annotations by color.

We have acquired an upgrate to our Panoramic P250 scanner with immunofluorescence (IF) filters. The channels included in the upgrate are: DAPI, FITC, TRITC and Cy5. The IF scanner is used for our research project using LabSat Lunaphore multiplexing device so far.

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.

Recent updates and news on our ngTMA platform can be find every time on the website: www.ngtma.com.

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, MIBI-TOF) and for assessment of intratumoral heterogeneity. This year, our ngTMAs have also been used to help develop and establish multiplexing technology at our lab by using LabSat from Lunaphore. Examination of TMAs with multiple fluorescence markers will allow us to answer numerous of scientific questions including one of our longstanding topics of interest: tumor budding in colorectal cancer.

Since it's inception in 2012, TRU has created more than 793 ngTMA blocks, totaling more than 154300 punches in recipient blocks and 4800 punches for tubes, and hence downstream molecular analysis. The number of donor blocks totals more than 20739. 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.

ngTMA®

Left: the ngTMA Grandmaster with assembled blocks; TRU staff holding tubes for DNA/RNA punches. Right top: new ngTMA logo.
Right bottom: punches that can be taken from blocks after aligning digitally annotated images using ngTMA technology.

In 2021, 26 ngTMA projects were conducted which is slightly more than in previous years. This year 59 ngTMA blocks with total 8350 punches from 1740 donorblocks were constructed and 1860 cores form 340 donor blocks were punched for downstream molecular analysis.

There were ngTMA projects to investigate Covid receptors in lung tissue in collaboration with the University Hospital Zürich or the effects of the ZIKA virus to the brain and other organs for the Stanford University in California.

Since TRU has consistently scanned each ngTMA slide after H&E or immunostaining, a massive digital archive of more than 1'000'000 spot images and several thousand whole slide images from an array of tissue types has been generated with links back to clinicopathological data. These images can now be used to train AI algorithms for prediction of clinical outcomes, molecular subtypes or other endpoints.

At TRU we always try to meet expectations of our collaborators, therefore, this year we attempted to develop frozen tissue TMA methodology. Even though more manual and tedious than ngTMAs, it could allow to perform experiments in the fields where FFPE material is not a first choice.

ngTMA was also the topic of several invited talks at various events, virtually or in-person, including the 3DHistech RX Virtual Symposium, the opening of the Center for Artificial Intelligence in medicine (CAIM), Basel Breast Cancer Research Meeting, European Association for Cancer Research-Molecular Pathology Symposium, Breakfast & Science meeting from the EPFL's Center for Biomedical Imaging, and the 1st Virtual TMA Workshop.

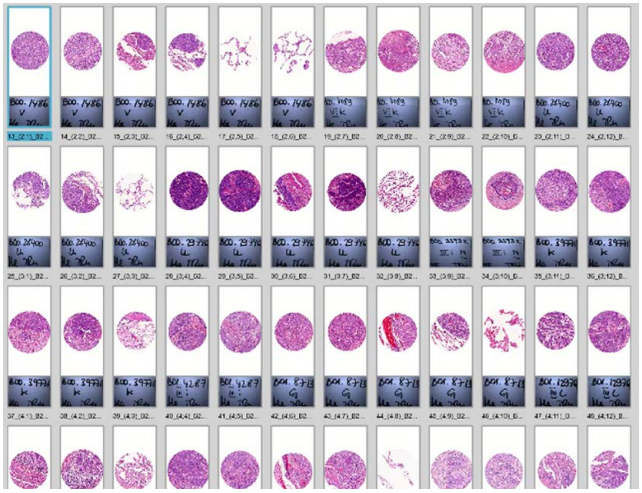
ngTMA played an important role in several research publications this year including:

- Nguyen HG, Blank A, Dawson HE, Lugli A, Zlobec I. et al. Classification of colorectal tissue images from high throughput tissue microarrays by ensemble deep learning methods. Sci Rep. 2021 Jan 27;11(1):2371. doi: 10.1038/s41598-021-81352-y. PMID: 33504830
- Burren S, Reche K, Blank A, Galvàn JA. et al. RHAMM in liver metastases of stage IV colorectal cancer with mismatch-repair proficient status correlates with tumor budding, cytotoxic T-cells and PD-1/PD-L1. Pathol Res Pract. 2021 Jul;223:153486. doi: 10.1016/j.prp.2021.153486. Epub 2021 May 18. PMID: 34051513
- Simon Leonhard April-Monn, Valentina Andreasi, Marco Schiavo Lena. et al. EZH2 Inhibition as New Epigenetic Treatment Option for Pancreatic Neuroendocrine Neoplasms (PanNENs). Cancers (Basel). 2021 Oct 7;13(19):5014. doi: 10.3390/cancers13195014. PMID: 34638497
- Rhyner Agocs G, Assarzadegan N, Kirsch R. et al. LAG-3 Expression Predicts Outcome in Stage II Colon Cancer. J Pers Med. 2021 Jul 30;11(8):749. doi: 10.3390/jpm11080749. PMID: 34442393
- Georges NDF, Oberli B, Rau TT, et al. Tumour budding and CD8+ T cells: 'attackers' and 'defenders' in rectal cancer with and without neoadjuvant chemoradiotherapy. Histopathology. 2021 Jun;78(7):1009-1018. doi: 10.1111/his.14319. Epub 2021 Apr 19. PMID: 33340423
- Guo Y, Gabola M, Lattanzio R. et al. Cyclin A2 maintains colon homeostasis and is a prognostic factor in colorectal cancer. J Clin Invest. 2021 Feb 15;131(4):e131517. doi: 10.1172/JCI131517. PMID: 33332285
- Haddad TS, Lugli A, Aherne S, et al. Improving tumor budding reporting in colorectal cancer: a Delphi consensus study. Virchows Arch. 2021 Sep;479(3):459-469. doi: 10.1007/s00428-021-03059-9. Epub 2021 Mar 1. PMID: 33650042
- Jiang S, Mukherjee N, Bennett RS et al. Rhesus macaque CODEX multiplexed immunohistochemistry panel for studying immune responses during Ebola infection. Frontiers in Immunology Accepted. In Press.
- Bräutigam K, Reinhard S, Galván JA, et al. Systematic investigation of SARS-CoV-2 receptor protein distribution along viral entry routes in humans. Respiration. Accepted. In Press

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.

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.



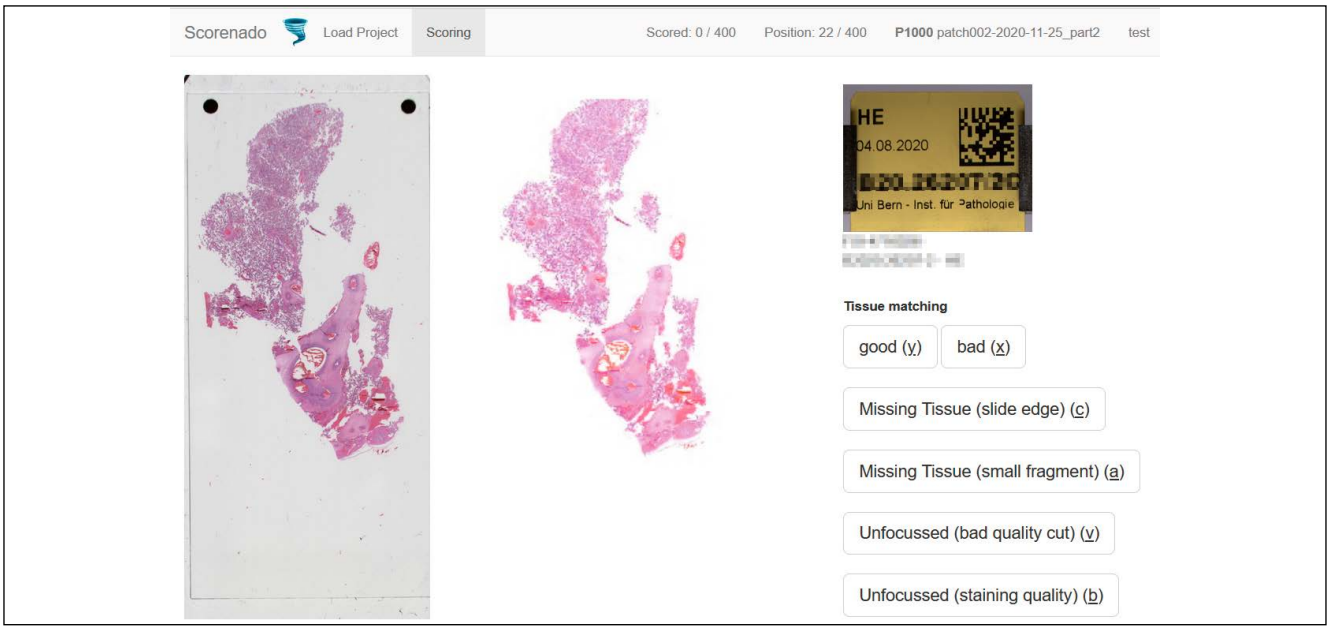
Our ngTMA facility has led to a huge number of high-quality, high-value images that can be used for training and testing different machine learning algorithms. We estimate that more than 1'000'000 images are currently available. These images include: whole slide images (WSI) that have been annotated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

So far, clinical data from 3297 patients, 354 TMAs corresponding to 102'298 spots and 3200 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 further research cohorts.

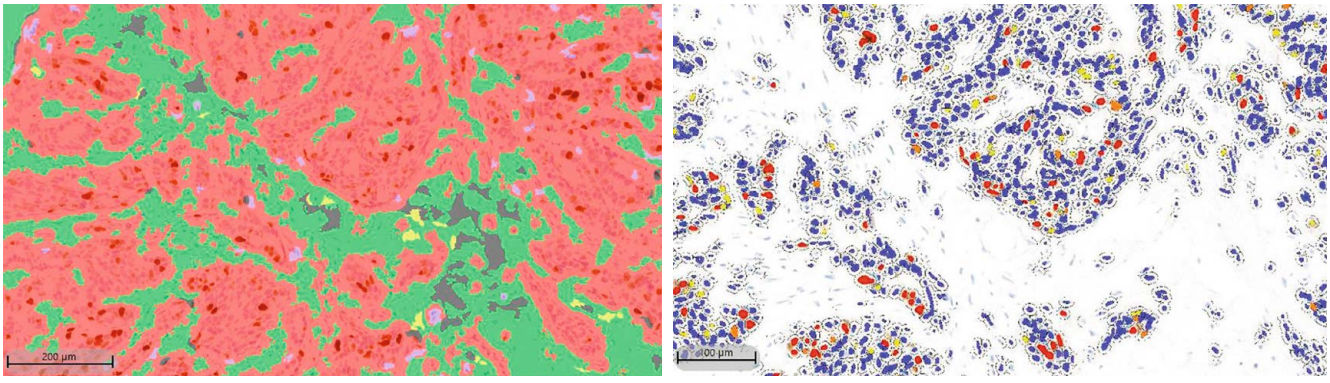
d) Digital Image Analysis

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. The current version has been redesigned to run on a public web server to allow external collaborators to score with Scorenado. Since its test launch, a total of 65 Scorenado projects, including 724 slide scans, were set up for research conducted in-house, at Insel Hospital, and at other institutes in Switzerland and abroad. Overall, 201'416 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. Scorenado was used to validate the scanners for diagnostic routine.

TRU is also supporting researchers by providing training in image analysis using the free, open-source tool QuPath. The number of high-performance computers with GPU's for digital-based image analysis was increased and consolidated into one room to facilitate access and project support for all researchers at the institute. Since summer 2021, TRU provides the Indica Labs Halo and Halo AI software including training for researchers, thanks to a collaboration we can provide up to 20 modules. This year, seven different projects could be supported. In addition, a collection of scripts facilitating image analysis in QuPath and TMA data handling was established.



Screenshot of Scorenado adapted for scanner validation in diagnostics. Allows comparing the macro image with the thumbnail to recognize unscanned areas.



Ki-67 classification in Halo. On the left the classification of the tumor areas, on the right the grading of the tumor cells according to the color intensity.

Gruppe Tissue Bank Bern (TBB).

Tissue Bank Bern (TBB)

Director: Prof. Aurel Perren

Manager and co-manager: Prof. Inti Zlobec and PD. Dr. med. Tilman Rau (until October 31st)

Lab manager: Dr. Paulina Brönnimann

Medical advisor: Dr. Aart Mookhoek

Project management and operative functions: Dr. Irene Centeno Ramos and Loredana-Ionela Daminescu

Additional members: TRU and Clinical Pathology Division staff, IT team of the 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 and Swiss Biobanking Platform standards. TBB services are, since October 2016, being performed by the Translational Research Unit (TRU) thus, personnel and resources are shared.

Workflow

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 2021, aside from providing the scientists with frozen and native material, we have increased the portfolio of customized collections, implying strong multi-institutional and cross-departmental collaboration.

We still work in close collaboration with the Angiology and HNO departments, where the bio-banking tissue is processed already in the operation theater allowing low ischemia times necessary for particular studies. This year we got the first results on the quality of these tissues, based on RNA integrity, with

REQUEST FORM	TBB ORDER PROCESSING	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

the maximum quality (RNA Integrity Number = 10) for most of the samples.

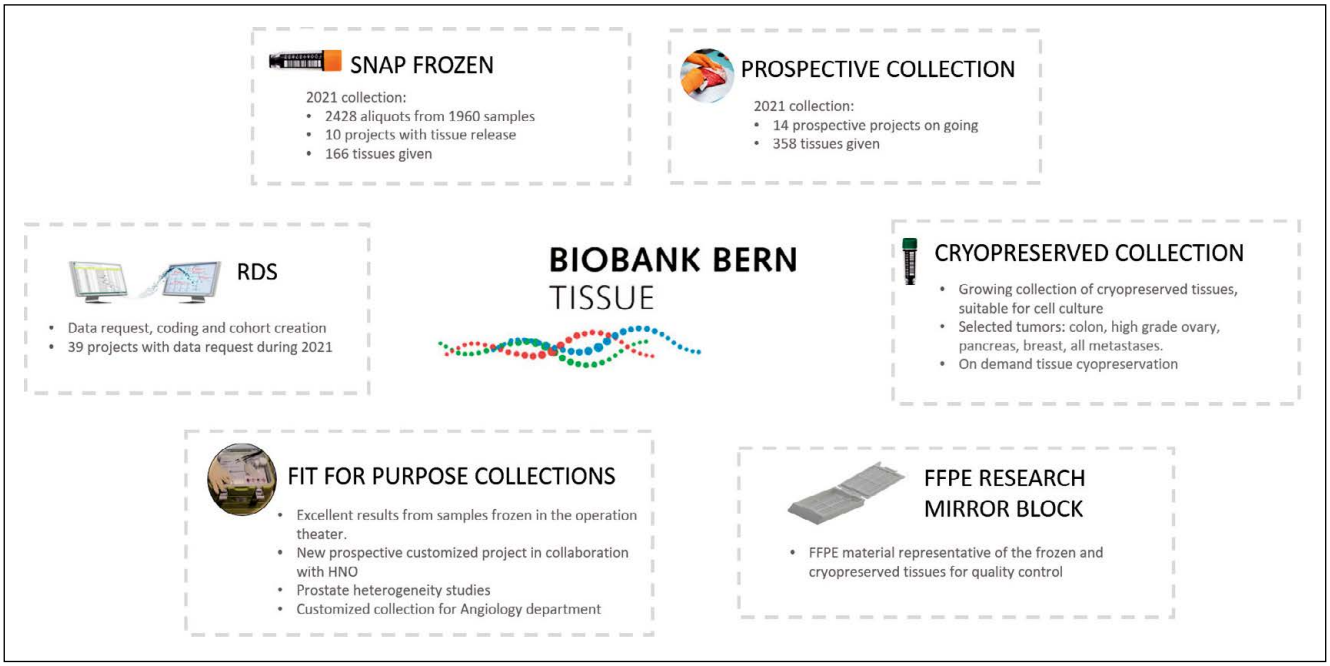
Regarding the cryopreserved collection, we slow freeze the selected tissues and store them in liquid nitrogen for experiments requiring living cells. We have 3 ongoing projects using this set-up. A representative part from the cryopreserved tissue is formalin fixed, paraffin embedded and H&E stained to assure an adequate vital tumor content before working with the cryopreserved material.

The principal on-going activities are summarised in the Figure below.

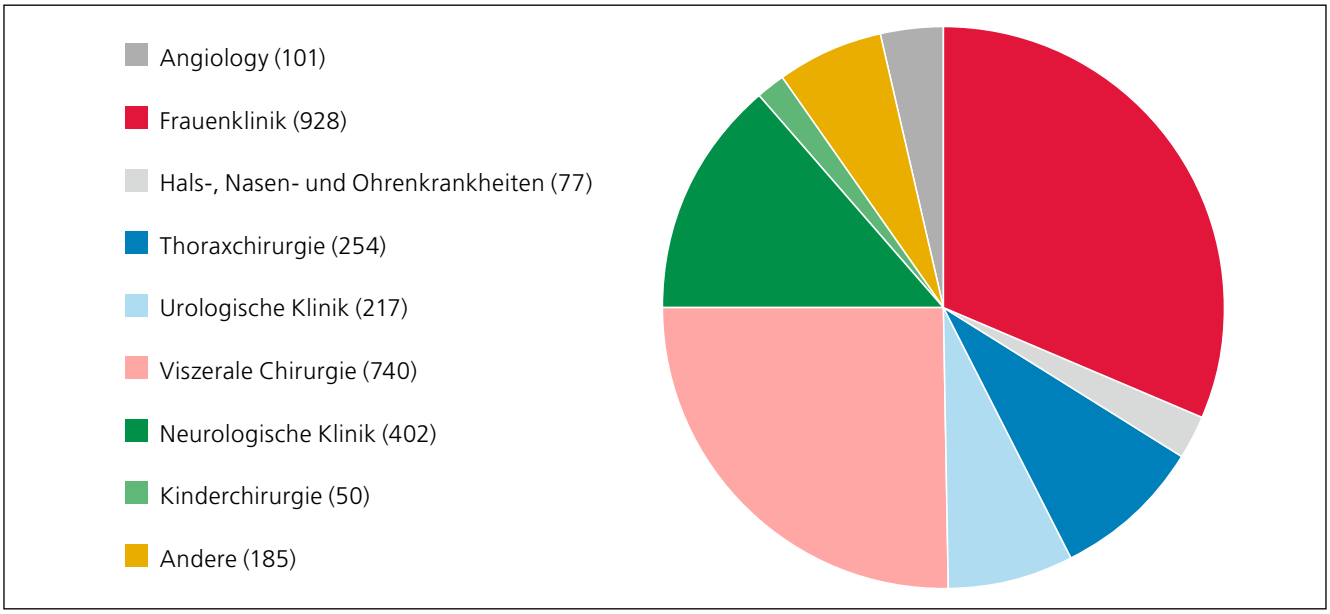
TBB institutional collection statistics

TBB markedly expanded its tissue collection reaching more than 15'000 different samples from more than 13000 patients stored in ~46'000 aliquots.

In 2021, we collected material from close to 3000 samples from different clinics that continue their important involvement in the biobank. The contribution per clinic can be found in the chart below, with the largest amount of samples deriving from the gynecology clinic, followed by the clinics of visceral surgery, neurosurgery, thoracic surgery as well as urology.



Different activities performed by TBB in 2021.



Distribution of incoming tissue specimens for biobanking.

Projects by tissue bank Bern 2021
The number of TBB projects continues to rise. In 2021, we received 63 requests for tissue and/or data.

Usage of tissue samples in 2021
During this year we have provided scientists with 166 frozen tissues (aliquots). Additionally, 358 native tissues (535 aliquots) were given in a prospective manner. The usage of frozen samples was mainly done by Inselspital/DBMR researchers, while most of the native tissue given was used by internal researchers.

Towards the best quality of service
The delivery of optimal quality tissues to researchers is one of the main aims of TBB. The standardization of the processes, documentation of pre-analytical variables and strong quality monitoring systems are essential for the development and maintenance of the highest service quality and guarantee a continual improvement. In this field, TBB accomplish the

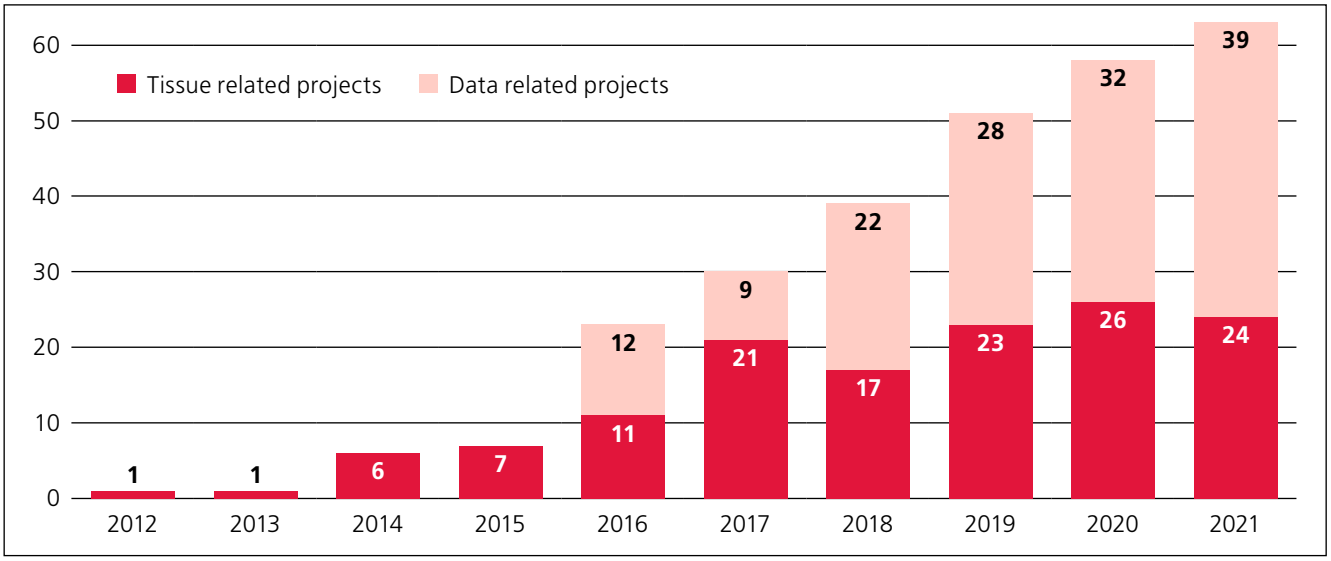
VITA
Compliance with legal and ethical standards

NORMA
Standardization of the biobanking processes

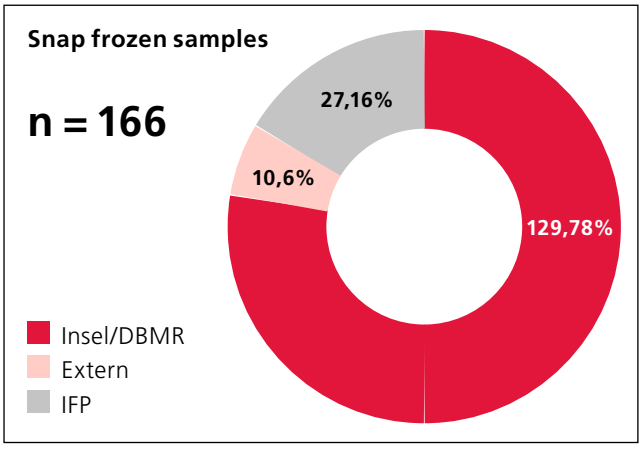
OPTIMA
Implementation of quality assurance measures of the overall biobanking system

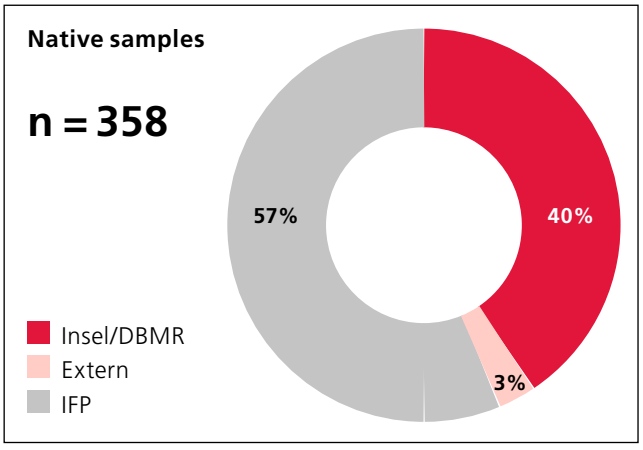
Swiss Biobanking Platform (SBP) standards, acknowledged by the acquisition of the SBP Norma and Optima label in December 2019. Additionally, the collection and storage of the TBB samples are included under the Institute of Pathology accreditation by the Swiss Accreditation Service (SAS) according to ISO 17025:2005 and ISO 15189:2013 since 21.08.2018.

TBB puts a big effort in performing Human Research Act compliant workflows as evidenced by the SBP Vita Label certificate achieved already in 2018. Additionally, TBB offers support to the biomedical research activities by facilitating compliance with best practice standards and regulatory requirements relating to ethical, legal and societal issues (ELSI).



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





Summary of tissue usage by internal, Inselspital/University of Bern (incl. DBMR) or external researchers for prospective and retrospective (frozen collection) projects in 2021.

Collection procedure of peripheral artery disease tissue samples in the surgical theatre.

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.

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

Alessandro Lugli, MD
Inti Zlobec, PhD
Heather Dawson, MD
Huu Giao Nguyen, Post-doc
Amjad Khan, PhD student
Elias Baumann, PhD student
Ana Frei, 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)
Lukas Bähler, Medicine,
Mauro Gwerder, MSc
Ibai Lertxundi, MSc
Luca Noti, Medicine
Laura Purcaro, MSc

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: Precision of risk stratification of early colorectal cancer

As colonoscopy screening programs are increasingly implemented, the detection rates of rates of early invasive colorectal cancers with submucosal invasion only (pT1 CRC) is on the rise. As such tumors are typically removed endoscopically, further patient management can include segmental resection, which includes the removal of lymph nodes to which the tumor may have spread or follow-up alone. This decision rests mainly on histopathological features associated with nodal metastases. While the risk of nodal metastases in all pT1 CRC is reported to be around 10–15%, the risk of the individual patient is highly variable and can range from 1–40%. In a large well-characterized pT1 patient cohort we aim to establish an improved risk stratification model for predicting lymph node metastasis including tumor budding and the relationship between tumor buds and certain subsets of immune cells.

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: Artificial intelligence and colorectal cancer

Our digital pathology research group focuses on aspects of budding and the tumor microenvironment (TME) from various aspects. In our Sinergia project, we explore elements of the TME and the relationship to Consensus Molecular Subtypes (CMS), using graph-based and deep-learning approaches. In a project funded by the Innosuisse we establish high-dimensional multiplexed protein analysis with the aim of learning new aspects of tumor buds within their stromal and immune contexture and relationship to patient outcome. We investigate phenotype-genotype correlations and apply state-of-the-art computational approaches for detection of specific features, such as lymphocytes. As an example of clinical utility, we are developing an in-house lymph node metastasis detection algorithm, which is currently undergoing validation and will be ready for testing in a real-life setting this year.

Internal Collaborations

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

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,
- Drs. and members of the Departments of Oncology and Visceral Surgery, Inselspital, Bern, Switzerland

International

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

Grant support

- Swiss Cancer Research, Lugli (PI), 2021–2023, CHF* 331'500
- Innosuisse, Zlobec (Co-PI), 2021–2023, CHF 450'540
- Swiss National Science Foundation, I.Zlobec (PI) / M. Tschan, 2020–2024, CHF 632'000
- Swiss National Science Foundation – SINERGIA, I.Zlobec (PI) /M. Anisimova/ MMRodriguez/B.Snjider, 2020–2024, CHF 2'875'765
- Rising Tide Foundation for Clinical Research, H. Dawson (PI), 2019–2022, CHF 108'984
- Personalized Health and Related Technologies, Co-PI Zlobec, 2018–2021, CHF 182'918
- Rising Tide Foundation for Clinical Research, I.Zlobec (PI) /JP Thiran, 2018–2021, CHF 293'8000
- Swiss Cancer League, I.Zlobec (PI) /JP Thiran, 2018–2021, CHF 361'270
- Dutch Cancer Society (Consortia grant), Co-PI Zlobec/Lugli/Dawson, 2017–2022, EUR 1'600'246
- Klinisch-experimentelle Tumorforschung, B. Dislich, 2019–2021, CHF 120'000

* 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

- Head of Translational Research Unit (TRU)
- Operative Manager of Tissue Bank Bern (TBB)
- Executive Team Member, Center for AI in Medicine (CAIM)
- Chair, IT Working Group European Society of Pathology (ESP)
- President of the Swiss Consortium for Digital Pathology (SDiPath)
- Member of the Graduate School of Cell Biology and mentor (GCB)
- Member of the Bern Center for Precision Medicine (BCPM)
- Member of the International Budding Consortium (IBC)

H. Dawson

- President of the Swiss Section of the International Academy of Pathology
- Member of the Executive Board of the Swiss Society of Molecular Pathology
- Member of the International Budding Consortium
- Member of the Swiss Association of Gastrointestinal Pathology (SAGIP)

2 Akademische Grade

MD/PhD Students

- *Storni Federico, MD / PhD*
  Development of a new therapy for peanut allergy
  Hauptbetreuer: Prof. Martin Bachmann
  Co-Advisor: Christoph Müller
- *Kristina Seiler, MD-PhD*
  Novel' non)canonical' functions' of' metabolic' enzymes' HK3' and' FASN' in' leukemic' myeloid' differentiation
  Supervisor: M. P. Tschan
  Mentor/external Reviewer: B.E. Torbett/J. Gertsch
- *Igor Tokarchuk MD-PhD*
  The impact of autophagy on breast cancer cell plasticity and viability
  Supervisor: A. Schläfli/M. P. Tschan
  Mentor/external Reviewer: T. Kaufmann/D. Stroka

PhD Students

- *Valentina Andreasi, PhD*
  Role of Chromogranin A derived fragments and other biomarkers in pancreatic neoplasms focus on neuroendocrine tumors
  Supervisor: Angelo Corti / Ilaria Marinoni
- *Paola Antonello, PhD*
  New insights in A6KR3 biology: Regulation of CXcR4/cxcL12 mediated chemotaxis of B cell lymphoma through LTB4 secretion
  Supervisor: M. Thelen
  Mentor/external Reviewer: M.P.Tschan/C. Riether
- *Johanna Baumgartner, PhD*
  Impact of OxPL/Nrf2-signaling on macrophage differentiation and function in health and disease
  Supervisor: PD Dr. Stefan Freigang
  Co-Advisor: Prof. Chirstoph Binder
  External Referee: Prof. Gerhard Krönke
  Mentor: Prof. Stephan von Gunten
- *Loic Borcard, PhD*
  Functional analysis of the role fo the neuraminidase stalk region in the balance between influenza A virus hemagglutining and neuraminidase
  Supervisor: Prof. Gert Zimmer
  Co-Advisor: Prof. Martin Schwemmle
  External Referee: Prof. Georg Herrle
  Mentor: PD Dr. Stefan Freigang
- *Martin Erhardt, PhD*
  The relevance of ceramide kinase and phospholipase A2 in in vitro models of inflammation and migration associated disorders
  Supervisor: A. Huwiler/U. Zangemeister-Wittke
  Mentor/external Reviewer: M.P.Tschan/D. Fabro
- *Hang Bui, PhD*
  Cell type-specific regulation of interleukin-1-driven inflammation
  Supervisor: PD Dr. Stefan Freigang
  Co-Advisor: Prof. Cem Gabay
  External Referee: PD Dr. Marianne Böni
  Mentor: Prof. Britta Engelhardt
- *Melle Holwerda, PhD*
  Establishment of tools to investigate the zoonotic potential of influenza D virus
  Supervisor: Prof. Ronald Dijkman
  Co-Supervisor: PD Dr. Philippe Plattet
  External Referee: Prof. Martin Schwemmle
  Mentor: PD Dr. Stefan Freigang
- *Kim Klapan, PhD*
  Evidence for lysosomal dysfunction within the epidermis in psoriasis and atopic dermatitis
  Supervisor: H.U. Simon
  Mentor/external Reviewer: M.P.Tschan/M. Bachmann
- *Nathan Leborgne, PhD*
  Role of serpins in the biology of invariant Natural Killer T cells and cathepsin G-mediated neutrophil death
  Supervisor: Prof, Charaf Benarafa
  Co-Advisor: PD Dr. Stefan Freigang
  External Referee: Prof. Marie-Chritsine Bouton
  Mentor: Prof. Thomas Kaufmann
- *Ma Lijuan, PhD*
  The role of EMT in the Alteration of Hormone Response in Enometriotic Lesions and ist Contribution to the Recurrence of Endometriosis
  Hauptbetreuer: Christoph Müller
  Mentor/external Reviewer: Prof. Dr. Michael D. Mueller
- *Alberto Mattei, PhD*
  Signaling mechanisms of non-genetic cancer drug resistance in melanoma
  Supervisor: O. Pertz
  Mentor/external Reviewer: M.P.Tschan/M. Levesque
- *Pascal Näf, PhD*
  Signaling in Steady-State Hematopoiesis and Myeloid Leukemia
  Supervisor: Prof. Dr. Adrian Ochsenbein
  Mentor: Philippe Krebs
- *Samara Naim, PhD*
  Towards understanding the physiological and pathophysiological roles of the BCL-2 family member BOK
  Supervisor: T. Kaufmann
  Mentor/external Reviewer: M. Schweizer/M.P. Tschan
- *Nicolas Niklaus, PhD*
  The versatile role of alternatively spliced DMTF1 isoforms in breast breast and prostate cancerleukemia & The function of

PU.1 in alternative splicing of CFLAR in acute myeloid leukemia
Supervisor: M. P. Tschan
Mentor/external Reviewer: G. Konstantinidou/T. Kaufmann

- *Sreoshee Rafiq, PhD*
  Lysosomes and lysosomal degradation in acute myeloid leukemia therapy
  Supervisor: M. Humbert/M. P. Tschan
  Mentor/external Reviewer: G. Konstantinidou/C. Riether
- *Olivier Pascal Schären, PhD*
  Investigation of immunogenicity and microbiota interaction of cell wall metabolite auxotrophic Salmonella
  Supervisor: Prof. Dr. Siegfried Hapfelmeier
  Co-advisor: Philippe Krebs
- *Pablo Arnold Winzer, PhD*
  Molecular changes of Neospora caninum treated with the calcium dependent protein kinase 1 inhibitor BKI-1294 and implications on the immune response
  Supervisor: Prof. Dr. Andrew Hemphill
  Mentor: Philippe Krebs

MSc Master of Science

- *Bushra Fakher, MSc*
  Involvement of miR19b in temozolomide resistance in patient derived glioblastoma stem cells
  Supervisor: Erik Vassella
- *Sophie Gund, M Sc Pharm*
  The Role of the Mitophagy Mediator NIX (BNIP3L) in DMTF1β Mediated Autophagy and Migration in Breast Cancer CellsThe Role of the Mitophagy Mediator NIX (BNIP3L) in DMTF1β Mediated Autophagy and Migration in Breast Cancer Cells
  Hauptebetreuer: M.P. Tschan
  Mentor/external Reviewer: N. Niklaus
- *Mauro Gwerder, MSc*
  Lymph node metastasis detection in lung SQC
  Hauptbetreuerin: I. Zlobec
  Mentor: C. Neppl
- *Filip Manevski, MSc*
  Comparison of CRISPR/Cas9 gene modulation systems and their effect on the expression of homeobox protein CDX2 in colorectal cancer
  Hauptbetreuer: M.P. Tschan
- *Lisa Perrig, MSc*
  Immunohistochemical Analysis of MCT1, MCT4 and PKM2 in Therapy-Naïve und Post-Therapy GBM Samples
  Supervisor: Erik Vassella
- *Laura Purcaro, MSc*
  Quality control of digital slides
  Hauptbetreuerin: I. Zlobec
- *Lionel Rohner, MSc*
  Changes in DNA methylation during pancreatic neuroendocrine tumor progression
  Supervisor: Aurel Perren/Ilaria Marinoni
- *Patricia Stegmann,* M Sc Pharm
  The Interplay of the Transcription Factor DMTF1b and the Mitophagy Receptor BNIP3 and its Effect on Autophagic Activity and Migration in Breast Cancer Cells
  HauptbetreuerM.P. Tschan
  Mentor/external Reviewer: N. Niklaus

BSc Bachelor of Science

- *Jana Annika Stritt, BSc*
  GSK126 induces cell death in PanNET cell lines
  Supervisor: Aurel Perren/Ilaria Marinoni

MD Doctor of Medicine

- *Sandra Burren, MD*
  Bedeutung der RHAMM Expression in Tumor Buds von kolorektalen Lebermetastasen
  Hauptbetreuer: Alessandro Lugli
  Mentor/external Reviewer: Annika Blank
- *Katharina Reche, MD*
  Rolle der Immunzellinfiltration bei kolorektalen Lebermetastasen in Bezug auf IMB und PMB
  Hauptbetreuer: Alessandro Lugli
  Mentor/external Reviewer: Annika Blank
- *Lynn Richmond, MD*
  Tubulin beta 3 expression in CRC upregaulated as part of tumor budding phenotype
  Hauptbetreuer: Alessandro Lugli
  Mentor/external Reviewer: Heather Dawson

Andere

- *Samuel Kuhn, Mmed*
  Lymph node metastasis detection in lung SQC
  Hauptbetreuerin: I. Zlobec
  Mentorin/external Reviewer: H. Dawson
- *David Maul, Dipl. BMA*
  Influence of DMTF1β on autophagy in breast and prostate cancer cells
  Hauptbetreuer: M.P. Tschan
  Mentor/external Reviewer: N. Niklaus

3 Publikationen

Originalarbeiten In-House

- April-Monn SL, Andreasi V, Schiavo Lena M, Sadowski MC, Kim-Fuchs C, Buri MC, Ketkar A, Maire R, Di Domenico A, Schrader J, Muffatti F, Doglioni C, Partelli S, Falconi M, Perren A, Marinoni I
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  Tumour budding and CD8+ T-cells: «attackers» and «defenders» in rectal cancer with and without neoadjuvant chemoradiotherapy.
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- Gruber T, Robatel S, Kremenovic M, Bäriswyl L, Gertsch J, Schenk M
  Cannabinoid Receptor Type-2 in B Cells Is Associated with Tumor Immunity in Melanoma. CANCERS, 13(8):
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- Vassella E, Kashani E, Zens P, Kündig A, Fung C, Scherz A, Herrmann E, Ermis E, Schmid RA, Berezowska S
  Mutational profiles of primary pulmonary adenocarcinoma and paired brain metastases disclose the importance of KRAS mutations. EUR J CANCER, 159: 227-36
- Zens P, Bello C, Scherz A, Koenigsdorf J, Pöllinger A, Schmid RA, Ochsenbein A, Neppl C, Langer R, Berezowska SA
  A prognostic score for non-small cell lung cancer resected after neoadjuvant therapy in comparison with the tumor-node-metastases classification and major pathological response.
  MODERN PATHOL, 34(7): 1333-44
- Zlobec I, Bächli M, Galuppini F, Berger MD, Dawson HE, Nagtegaal ID, Lugli A
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4 Vorträge

Philippe Krebs
- 18.–20.11.21: Cytokine-dependent regulation of myeloproliferative neoplasms, Swiss Oncology and Hematology Congress, Zurich
- 09.11.21: Analysis of coronavirus-induced lung immune response at the single-cell resolution, 10x Genomics – the Bern User Day Meeting

Magali Humbert (Group Tschan)
- 09.09.21: Concepts and Methods in Autophagy, 11th SWISS APOPTOSIS AND AUTOPHAGY MEETING

Mario Tschan
- 22.11.21: New mechanisms in AML differentiation therapy responses, Blood Research Program Research Day-2021

Inti Zlobec
- 24.03.21: Digital pathology meets molecular pathology: two sides of the same coin?, EACR-OECI Joint Virtual Conference: Molecular Pathology Approach to Cancer
- 19.03.21: Digital pathology archives: a deep learning paradise?, Opening of the Center for AI in Medicine (CAIM)
- 23.02.21: Introduction to digital pathology: the «third revolution», Science & Breaskfast seminar, Center for Biomdeical Imaging, EPFL
- 25.02.21: next-generation TMA, TMA Workshop by P. di Blasio
- 19.01.21: Digital pathology: opening new avenues for tissue-based analysis, Basel Breast Consortium
- 26.05.21: ngTMA ®: applications and integrations, 3DHistech RX Virtual Symsposium
- 08.09.21: Translation of AI toold from research into the clinic: Focus on pathology images, Africa AI Expo 2021
- 27.04.21: Introduction to digital pathology: the «third revolution», Applied Machine Learning Days (AMLD)
- 27.05.21: Introduction to digital pathology: the «third revolution», Dermatopathologie Weiterbildung Inselspital
- 18.07.21: The role of digital pathology in assessing tumour budding and tumour immune response in colorectal cancer, MSc in Artificial Intelligence for Medicine and Medical Research-Summer Trimester, University of Dublin
- 17.06.21: Multi-model assessment of tumor budding, European Congress of Digital Pathology
- 15.09.21: Application of machine learning to pathology, EMPAIA Academy
- 18.05.21: AI in breast pathology: Ki67, PathLake Masterclass University of Warwick, 2021
- 04.11.21: New molecular developments in colorectal cancer, SGPath 2021
- 30.03.21: La pathologie digitale au delà du scanner!, Webinar Telemis
- 23.09.21: Chair for : Spatial Biology: Revolutionizing Tissue Imaging and Analysis Using Spatial Profiling, DigiBase Webinar
- 01–02.12.21: Digital Pathology Course (several lectures), University of Bern

Alessandro Lugli
- 10.09.21: Tumour buds: therapeutic implicatons ?, Annual Meeting of the SGG-SGVC-SASL & SVEP, Interlaken
- 05.11.21: Immunotherapy - Side effect pathology in the GI tract: patterns and pitfalls, Annual Meeting of the SGPath, Interlaken

Christoph Müller
- 22.09.21: Tissue resident T cells: Mediators of tissue homeostasis and chronic inflammatory diseases, Universitätsklinik RIA, Fachbereich Immunologie, Inselspital Bern

Erik Vassella
- 11.11.21: NGS, Methodik und Bedeutung im klinischen Alltag, Fortbildung Medizinische Onkologie, Inselspital

A. Perren
- 26.02.21: Best abstracts: tanslational research/ Basic science, 18th Annual ENETS Conference, virtuell, Chair
- 08.03.21: ENETS 2021 aus pathologischer Sicht (highlights pathology), ENETS 2021 Kompakt, the highlights of the ENETS 2021 congress 25nd-27nd Feb. 2021
- 13.03.21: NET G3 vs NEC, NET to go, Ipsen, virtuell
- 01.–03.06.21: New histopathologic classification of NET: Current situation - and what's next, 108. Jahreskongress der Chirurgie, endokrine Chirurgie
- 01.07.21: Case discussions, Cases on Management Strategy in NETs, ESMO 23rd Word Congress on Gastrointestinal cancer
- 06.07.21: What is the origin of pancreatic endocrine tumors? Of molecular markers in precision medicine and cells of origin, New advances in medicine - Symposium Class III, Leopoldina
- 30.08.21: The 2019 classification of digestive neuroendocrine neoplasms and beyond, 33rd European Congress of Pathology
- 23.09.21: Highlights in pathology: standardization of histopathology reports according to ENETS, SwissNET
- 28.09.21: Organoide / Tumoroide sind in aller Munde: Konzept des DBMR- Organoid-Cores und konkrete Projekte an NET Tumoroiden, Gastrointestinales Tumorzentrum Zürich
- 05.11.21: What's new in endocrine pathology? Pancreas, SGPath 2021, Interlaken, Switzerland
- 16.11.21: Pancreatic Neuroendocrine Tumors: Biological and Clinical Challenges, San Raffaele Pancreas Center, Milano, Italy
- 11.12.21: IAP Tutorial, 563. Tutorial – Pankreas und Duodenum (endokrin + exokrin)
- 17.12.21: Epigenetic and metabolic progression of PanNET and potential novel treatment options?, Ap_Hp. Nord Université de Paris, Dép. de Pathologie

I. Marinoni
- 16.11.21: Translational Research:present and future, Quality and Innovation at San Raffaele Pancreas Center

Yara Banz
- 06.11.21: 559. Tutorial IAP Autopsie – Sektion des Herzen und Aspektr der Hämatopathologie, 559. Tutorial IAP Autopsie, Bonn
- 04.11.21: CAR-T cell therapy : bridging pathology and clinical practice, SGPath 87th annual congress, Interlaken
- 12.11.21: SAMO interdisciplinary Workshop on Lymphoma – diagnostic aspects of aggressive lymphomas, SAMO Workshop Lymphoma, Luzern

5 Drittmittel

R. Gaultney (fellowship)
- Seal of Excellence Fund (SELF) UniBE, 2021–2023, CHF 128'698

P. Krebs (PI)
- Swiss Life Project grant, 2021–2023, CHF 20'000
- Uniscientia Project grant, 2021–2022, CHF 136'000
- PSwiss 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, 2018–2021, CHF 79'554
- Swiss Lung League Project grant, 2018–2021, CHF 79'554
- Research Foundation (KFS) Project grant, 2017–2021, CHF 312'500

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.

P. Krebs (main PI)
- UniBE ID (Interdisciplinary) Grant, 2017–2021, CHF 75'000

M. Wartenberg (PI)
- Klin. exprimentiele Tumorforschung, 2020–2022, CHF 60'000
- Werner und Hedy Berger-Janser Stiftung, 2018–2021, CHF 41'587

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

Theoni Maragkou (PI)
- Krebsliga Bern, 2022–2023, CHF 67'500, erst ab 2022
- Stiftung für klinisch-experimentelle Tumorforschung, 2022–2023, CHF 32'500, erst ab 2022

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

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

M. Schenk (PI)
- SNF 320030_176083, 2018-2022, CHF 566'109
- Stiftung experimentelle Biomedizin, 2016–2022, CHF 1'588'000
- Wilhelm Sander Stiftung, 2019–2020, Euro 49'700
- San Salvatore, 2020–2021, CHF 143'000
- Novartis, 2021–2022, CHF 52'000

Co-PIs: I. Zlobec; M. Tschan
- SNSF_310030_197786, 2020–2024, CHF* 660'000
  * total amount of funding; funding shared I. Zlobec and M.P. Tschan

M.P. Tschan (PI)
- SNSF_31003A_173219, 2017–2021, CHF 694'000

Co-PIs: B. Towbin; M.P. Tschan
- UniBE ID Grant, 2022–2023, CHF* 109'000
  * total amount of funding; funding shared B. Towbin and M.P. Tschan

J. Xu; M. P. Tschan, PI
- China Scholarship Council Fellowship, 2021–2024, CHF 90'000

Co-PIs: I. Zlobec; M. Tschan
- Swiss Government Excellence Scholarship, 2021–2024, CHF* 90'000
  * total amount of funding; funding shared I. Zlobec and M.P. Tschan

S. Freigang (PI)
- Swiss National Science Foundation, 2020–2024, CHF 632'000
- Swiss Heart Foundation, 2020–2022, CHF 50'000
- Swiss Lung Liga, 2017–2021, CHF* 162'000
  *total amount of funding; funding shared by PI and Co-PI

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

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

Christoph Müller (Co-PI)
- SNF 33CS30_177523, SIBDCS, 2018–2021, CHF* 304'500
  *own share

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

Juliana Barreto de Albuquerque
- Novartis Foundation for Medical-Biological Research, 2021–2022, CHF 51'182

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

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

Matthias Dettmer (PI)
- Berner Krebsliga, 2017–2021, CHF 70'000

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

I. Zlobec (Co-PI)
- Innosuisse, 2021–2023, CHF 450'540
- Personalized Health and Related Technologies, 2018–2021, CHF 182'918

I.Zlobec (PI) /JP Thiran
Rising Tide Foundation for Clinical Research, 2018–2021, CHF 293'800
- Swiss Cancer League, 2018–2021, CHF 361'270

I. Zlobec, MR. Rodriguez, M. Anisimova and B. Snijder
- Swiss National Science Foundation - SINERGIA, 2020–2024, CHF 2'875'765

Co-Pi Zlobec/Lugli/Dawson
- Dutch Cancer Society (Consortia grant), 2017–2022, EUR 1'600'246

A. Lugli (PI) / M. Schürch (Co-PI)
- Swiss Cancer Research, 2021–2023, CHF* 331'500

B., Dislich
- Klin.-experimentelle Tumorforschung, 2019–2021, CHF 120'000

Magali Humbert
- Bernische Krebsliga, 2017–2021, CHF 85000

6 Preise, Ernennungen, Auszeichnungen

- Frau *Dr. Ilaria Marinoni* wurde die Venia docendi für das Fach Experimentelle Pathologie verliehen
- *Prof. Dr. P. Krebs* wird assoziierter Professor ab 1. April 2021
- *M Med José Antonio Rodriguez Calero* hat im März die Facharzt-Prüfung bestanden.
- *M Med T. Maragkou* hat im Oktober die Facharzt-Prüfung Neuropathologie bestanden.
- *Prof. Rupert Langer,* Ordinarius für Pathologie in Linz
- *Frau Prof. Sabina Berezowska,* Extraordinaria für Pathologie Universität Lausanne
- *PD Dr. Matthias Dettmer,* Chefarzt für Pathologie in Stuttgart
- *Prof. Ekkehard Hewer,* Extraordinarius für Pathologie Universität Lausanne
- *Prof. Tilman Rau,* Extraordinarius Düsseldorf

Timo Rey, EPFL
Zeiss Posterprize

Nicolas Niklaus, UNIBE
FEBS Posterprize

Jiongming Lu, MPG
Cells MDPI Posterprize

Posterpreis Jahresversammlung Life Sciences Switzerland (LS2) 19.02.2021, Online *(Gruppe Tschan)*
Nicolas Niklaus erhielt für seinen Kurzvortrag und seine Posterpräsentation «Oncogene-induced autophagy enhances migration and invasion of breast and prostate cancer cells» den FEBS Posterpreis. Seine Arbeit zeigt, dass die onkogene Spleissvariante des Transkriptionsfaktors DMTF1, welche in aggressiven Krebszellen hoch exprimiert ist, mittels Autophagie-Aktivierung die Zellmigration und -invasion antreibt.

Aktuelle Teachers of the Year
Da das vergangene Jahr so besonders war und jedes Studienjahr seine ganz eigenen Herausforderungen hatte, hatte auch jedes Studienjahr die Möglichkeit seine*n eigene*n Teacher of the Year zu wählen:
1. Jahr: PD Dr. med. Stefan Tschanz
2. Jahr: PD Dr. med. Gudrun Herrmann
3. Jahr: PD Dr. phil. nat. Franziska Suter-Riniker
4. Jahr: **PD Dr. med. Yara Banz**
5. Jahr: Dr. med. Christoph Bosshard
6. Jahr: Prof. Dr. phil. Rouven Porz

Prof. A. Angelillo-Scherrer, Head Hematology Dpt), Sreoshee Rafiq und Dr. J. Risse (SITEM).

Preis für die beste Präsentation, Forschungsprogramm Blut, Forschungstag, 22. November 2021 *(Gruppe Tschan)*
Sreoshee Rafiq hat für Ihre Präsentation «Chaperone-mediated autophagy regulation during acute promyelocytic leukemia differentiation» den Preis für die beste Studenten-Präsentation erhalten. Ihre Arbeit beschreibt, dass sich die erhöhte Aktivität einer speziellen Form der Autophagie – Chaperone-mediated autophagy (CMA) – negativ auf die Differenzierungstherapie in der Akuten Myeloischen Leukämie auswirken kann.

Posterpreis 11th Swiss Apoptosis and Autophagy Meeting (SA2M) 09.12.2021 *(Gruppe Tschan)*
Harpreet Mandhair erhielt für Ihren Kurzvortrag und Ihre Posterpräsentation «ULK complex blockade elicits NF-κB activation in GCB-DLBCL whilst augmenting cytotoxicity of Ibrutinib» den Posterpreis der Französischen Gesellschaft für Autophagie CFATG. Ihre Arbeit beschreibt, dass die Blockierung der Autophagie mittels ULK1 Inhibitoren die Wirkung von Ibrutinib bei diesem aggressiven Lymphom, trotz Aktivierung des NF-κB Signalweges, verstärken kann. Dies unterstreicht die komplexen Abläufe, wenn Autophagie-regulierende zusammen mit zytotoxischen Therapien kombiniert werden.

Seal of excellence award (26.03.2021) *(Gruppe Krebs)*
Robert Gaultney, PhD, received a Seal of excellence award for his Marie Skłodowska-Curie fellowship application (H2020-MSCA-IF-2020).

>>> Studentische Lehre

Die Universität Bern hat sich als Ziel gesetzt, ihren Ruf als Lehruniversität zu stärken (Teilstrategie 3; Strategie 2021 der Universität Bern). Dieses Ziel verfolgen wir in der studentischen Lehre am Institut für Pathologie seit Jahren. Unermüdlich setzten sich die vielen Dozierenden auch 2021 dafür ein das Fachgebiet Pathologie, die dazugehörigen Forschungsthemen und fachübergreifenden Inhalte kompetent und motivierend zu übermitteln.

Wie auch in den Vorjahren waren die Dozierenden für die Studierenden der Humanmedizin, der Zahnmedizin, des Studienganges Biomedical Sciences und der Zellbiologie (Cell Biology) im Einsatz. Dabei wurden über 100 Vorlesungen, Kurse und Praktika über Histologie, Allgemeine und Spezielle Pathologie, Molekularpathologie und Tumorpathologie von Mitgliedern des Instituts für Pathologie organisiert und angeboten.

Weiterhin betreuen viele Mitarbeitende im Institut aktiv junge Auszubildende im Studiengang PhD und MD-PhD im Kontext der Graduate School for Cellular and Biomedical Sciences (GCB). Die Lehrveranstaltungen werden von Mitarbeitenden sowohl der klinischen als auch der experimentellen Pathologie gehalten – das Thema und der Schwerpunkt des Studienganges bzw. der Veranstaltung bestimmen, ob die Veranstaltung eher durch Mitarbeitenden der Ärzteschaft oder Kolleginnen und Kollegen aus der Naturwissenschaft gehalten werden.

Zur Erleichterung vieler konnten trotz nach wie vor dominierender SARS-CoV-2 Pandemie ein Grossteil der Veranstaltungen vor Ort und in Anwesenheit der Studierenden gehalten werden. Wie wichtig und motivierend der direkte Kontakt zu den Studierenden ist, wurde vielen Dozierenden nach mehreren Monaten leerer Hörsäle stark bewusst. Die Digitalisierung, welche im Kontext unter anderem der letztjährigen Pandemiebedingten Einschränkungen den Weg in die Lehre gefunden hat, konnte erneut eingesetzt und ausgebaut werden. Die vor einem Jahr erweiterte technische Ausrüstung in allen Hörsälen im Institut konnte auch dieses Jahr zuverlässig gebraucht werden und erlaubten zusätzlich zum Frontalunterricht die Aufnahme der Kurse und Demonstration – etwas was von den Studierenden sehr geschätzt wurde.

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). Diese Vorlesungen sind in interdisziplinäre Vorlesungsveranstaltungen eingebettet, wobei die verschiedenen Themen im Kontext spezieller Themenblöcke behandelt werden. Diese theoretischen Kenntnisse werden im Rahmen der Fachpraktika Pathologie vertieft, wo die wesentlichen morphologischen Veränderungen studiert werden. Daneben ist die Pathologie auch an zahlreichen PBL Tutoriaten des 1. bis 3. Studienjahrs beteiligt. Im Vertiefungsseminar «Pathologie» haben die Studierenden zudem die Gelegenheit den Alltag des Pathologen hautnah im Rahmen von Führungen durch das Institut kennenzulernen. Glücklicherweise konnten diese Führungen 2021 wieder durchgeführt werden, sodass dieser Einblick nicht nur eine Trockenübung blieb.

Im Masterstudiengang folgt die systematische Aufarbeitung der speziellen Pathologie. Hier wird zunächst im 4. Studienjahr (Einführungskurs) sowie im 5. Studienjahr (Schlusskurs 1) organ- bzw. systembezogene Pathologie gelehrt. Anhand von theoretischen Vorlesungen und praktischen Kursen vertiefen die Studierenden ihre Kenntnisse. Wöchentlich finden nebst den virtuellen Histologiekursen auch Autopsiedemonstrationen statt, bei denen anhand aktueller Fallbeispiele die aktive Erarbeitung pathophysiologischer Zusammenhänge und Sequenzen verschiedenster Krankheiten im Vordergrund steht. Diese Kurse konnten 2021 wieder vor Ort durchgeführt werden – Kopfzerbrechen bereiten die nach wie vor tiefen Autopsiezahlen. Unsere Pflicht in der studentischen Lehre, insbesondere in der Pathologie, liegt auch in dem «hands on» übermitteln der Auswirkung verschiedenster Erkrankungen. Das Anfassen einer durch Covid-19 Erkrankung schwerst geschädigten Lunge, die makroskopische Beurteilung eines Tumors und das Erarbeiten und Erkennen krankheitsbedingter Veränderungen in den verschiedenen Organen dient dazu, das theoretische Wissen zu festigen und Engramme auf den Weg zu geben.

2021 konnten wiederum viele Studierende in verschiedensten Bereichen der Forschung im Institut ihre Masterarbeiten angehen und abschliessen – die enge Begleitung der Studierenden in diesem Kontext erlaubt auch im wissenschaftlichen Kontext dem Auftrag der Lehre gerecht zu werden. 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.

Das Wahlstudienjahrpraktikum, welches im letzten Jahr des Medizinstudiums, im 6. Studienjahr, besucht werden kann, war auch 2021 sehr gut besetzt. Den Studierenden wird angeboten, dass sie ihre Kenntnisse im Fach Pathologie vertiefen. 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-Naturwissenschaftlichen Fakultät

Die Mitarbeitenden der experimentellen und klinischen Pathologie sind auch 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 können.

1. Seminarreihen

- Bern Immunology Club, BIC
  (Vorträge externer Seminargäste, monatlich,
  seit März 2020: online)
- DBMR Research Conference (monatlich, seit März 2020: online)
- Bern Cancer Research Cluster (BCRC) – progress reports,
  wöchentlich, online
  Koordination: D. Stroka (DBMR), T. Marti (DBMR),
  M.Tschan (Pathologie)
- Bern Cancer Research Cluster (BCRC) –
  Journal Club, monatlich, online
  Koordination: D. Stroka (DBMR/UVCHM),
  M. Medova (Radio-Onkologie
- Topics in Tumor Biology
  Koordination: D. Stroka (DBMR/UVCHM),
  M.Tschan (Pathologie)

2. Vorlesungsreihen im Fachgebiet Pathologie

Zu Gunsten der phil. nat. Fakultät der UniBE werden von Dozierenden des Instituts für Pathologie 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:
- Methods and animal models of pathology
- Molecular mechanisms of pathology
- Tumor biology and molecular oncology
- Molecular diagnostics

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 (bis 31.7.2021)
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

2.4. Tumor Biology
Koordinatoren: D. Stroka (DBMR/UVCHM), Y. Zimmer (DBMR), M. Tschan (Pathologie)
Dozierende: aus dem Institut für Pathologie, Department für Biomedizinische Forschung (DBMR) und Inselspital Bern, Vetsuisse, Universität Bern.
Studierende: MSc und PhD Studierende Biomedical Sciences.

Allgemeine Übersicht:
- Cellular and molecular mechanisms of cancer biology

Studiengänge der Medizinischen Fakultät («Biomedical Sciences»)
Vorlesungsreihe im Fachgebiet Biomedizinische Wissenschaften (Study director: S. Rohr, Physiologie; Co-directors: A. Berzigotti, UVCHM, M.P. Tschan, Pathologie)

1. Tumorbiologie
Koordinator: Mario P. Tschan
Dozierende: aus dem Institut für Pathologie, Department für Biomedizinische Forschung (DBMR) und Inselspital Bern, Vetsuisse, Universität Bern.
Studierende: BSc, MSc und PhD Studierende Biomedical Sciences.

Allgemeine Übersicht:
- Cellular mechanisms of tumor development and metastasis
- Basics of proteomics and bioinformatics
- Animal and cell models

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), dem Themenblock «Blut und Abwehr» im 2. Studienjahr Medizin und dem dazu gehörenden Lerngruppenunterricht (PBL) im 2. und 3. Studienjahr. Ferner sind Dozierende des Instituts im Rahmen von 3–4–wöchigen experimentellen Praktika an der Ausbildung von Studierenden der Studienrichtung «Cell Biology» (UniBE) beteiligt.

>>> Weiterbildung

Das Institut für Pathologie der Universität Bern ist SIWF-zertifizierte Weiterbildungsstätte für das Fachgebiet Pathologie, Zytopathologie und Molekularpathologie. Die individuelle Weiterbildung wird in erster Linie täglich mit den Assistierenden in einer 1:1 Situation am Doppelmikroskop im Rahmen der Fallabgabe geleistet, dies vor allem durch die stringente Arbeitsorganisation im Diagnostikbereich, wo jeweils eine Oberärztin oder Oberarzt mit einem Assistierenden zusammenarbeitet. Zusätzlich wird die systematische Erarbeitung der organspezifischen Themengebiete durch verschiedene Weiterbildungsangebote abgedeckt. An der sogenannten strukturierten Weiterbildung beteiligen sich sämtliche Kollegen und Kolleginnen der Methoden (Molekularpathologie und Zytopathologie) bzw. der organspezifischen Fachgruppen. Die Fachgruppen sind jeweils fokussiert auf Mamma- und Gynäkopathologie, Gastrointestinalpathologie, Nephropathologie, Uropathologie, HNO-/ Ophthalmopathologie, Endokrinopathologie, Hämatopathologie, Weichteil- und Knochenpathologie, Herz-, Gefäss- und Rheumapathologie, Leberpathologie, Pankreaspathologie, Neuropathologie, Lungenpathologie, Dermatopathologie sowie Pädopathologie.

In diesem zweiten Jahr der Pandemie fanden Weiterbildungen für Ärztinnen und Ärzte praktisch ausschliesslich online oder als Hybridangebot (Präsenz mit Zertifikat) statt. Die im vergangenen Jahr vorgenommene Neuausrichtung hin zu monatlich wechselnden Themengebieten ist bei allen Mitarbeitern sehr gut angekommen und hat sich als effektiv und effizient bewährt. Einerseits ergibt sich die Möglichkeit sich über eine längere Zeit vertieft mit einem Thema zu befassen und die theoretischen Grundlagen dazu zu erarbeiten oder aufzufrischen. Das Herzstück unserer strukturierten Weiterbildung ist die Zeit zwischen 8.30 und 9.00 Uhr im Rahmen des Morgenrapports. Dort werden täglich digital verfügbare Fälle zum entsprechenden Themengebiet gezeigt. Einige Veranstaltungen, wie Molekularpathologie oder, digitale Bildanalyse, Organoide, neue Methoden zur Evaluation prädiktiver Marker sind eher theoretisch.

Komplementär zu Mikroskopie gibt es jeden Tag von 13.00 bis 13.15 Uhr eine Gelegenheit für alle Assistenten makroskopisch Präparate zu besprechen. Teilweise wird diese Zeit auch genutzt um systematisch das Vorgehen bestimmter OP-Präparate für jüngere 1. oder 2. Jahresassistenten zu erläutern. Davon profitieren sowohl die erfahrenen Assistenten (quasi als Tutoren) wie auch die jüngeren Assistenten. Ein Oberarzt/Oberärztin ist stets als Supervisor dabei.

Ein weiteres Angebot sind die monatlichen Seminare für Assistierende, bei welchen an einem Abend ein Thema vertieft besprochen wird. Diese wurden in Präsenz unter gegebenen Schutzmassnahmen durchgeführt.

Seminare für Assistierende

Monat	Referierende	Thema
Januar	Y. Banz	**Hämatopathologie: Knochenmark, Plasmozytom, T- und B-Zell Lymphome**
Februar	B. Dislich	**Orthopädische Pathologie und Knochentumoren**
März	M. Dettmer	**Molekularpathologie: Die wichtigsten diagnostisch relevanten Pathways/Mutationen**
April	M. Montani	**Gastrointestinale Pathologie: Appendix (Becherzellkarzinoid, LAMN, HAMN, usw.) + Gallenblase inkl. Makroskopie, Leber nicht neoplastisch**
Mai	A. Perren/ A. Lugli	**Immunhistochemie und Erreger Diagnostik: Für Hämatopathologie und generell: Prinzipien der IHC: was färbt Kerne, was Membranen usw., generelle Marker für z.B. verschiedene Organsysteme, Artefakte unterscheiden …**
Juni	T. Rau	**Mammapathologie: Mammakarzinom: Morphologie und Immunhistochemie**
Juli	C. Neppl	**Lungenpathologie: Nichtneoplastische Lungenerkrankungen, Zyto**
August	C. Saganas	**Makroskopie: Vorbereitung Makrokurse + Zuschnitt**
September	M. Trippel	**Pädopathologie: Foetenautopsien – Normale Histologie in den verschiedenen Phasen der Embryogenese**
Oktober	A. Rodriguez	**Prostata: Pathologie der Prostata im Alltag**
November	H. Dawson	**Dermatopathologie: Entzündliche Dermatosen und mesenchymale Tumoren, melanozytäre Läsionen**
Dezember	M. Wartenberg	**HNO: Nasennebehöhlen/Nase, Tonsillen und Dysplasie (jeweils inkl. Makroskopie)**

>>> Fortbildung

In den während des Semesters montags stattfindenden Seminaren (11:45 h–12:45 h) 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 in diesem Jahr überwiegend als online Veranstaltung durchgeführt. Zwischenzeitlich gab es erfolgreiche Hybrid-Konzepte, die für alle ein wertvolles Zusammentreffen ermöglichten. Immer in Abhängigkeit von den Entscheidungen des Bundesrates und den Vorgaben der Uni wurde mehrmals wieder auf ein reines Online Format umgestellt.

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.

Montagsseminare

Datum	Titel	Referent/-in
29.03.	**Releasing the brakes on inflammation to fight infection**	PD Dr. Stefan Freigang
03.05.	**Epigenomics of PanNETs: cell of origin and mechanisms of progression**	Dr. Ilaria Marinoni
04.05.	**Grundprinzipien des LEAN Managements**	Prof. Dr. med. Aurel Perren
01.06.	**«Near miss cases»: Schnittstelle Arzt-Labor**	PD Dr. med. Tilman Rau
21.06.	**Tissue resident T cell: Mediators of tissue homeostasis and chronic inflammatory**	Prof. Dr. phil. nat. Christoph Müller
20.09.	**Cytokine-dependent immunoregulation in cancer and pathology**	Prof. Dr. sc. Nat. Philippe Krebs
18.10.	**Engineering human NK cells for cancer immunotherapy**	Dr. Obinna Chijioke, UZH
08.11.	**Autophagy and Metabolism in AML differentiation therapy responses**	Prof. Dr. phil. nat. Mario Tschan
15.11.	**Peritoneum the forgotten organ**	Dr. Wiebke Solass, Univ. Tübingen
22.11.	**Pathologie 2030, are we still there? Chancen, Risiken und Entwicklungsfelder**	Prof. Wilko Weichert, TUM
29.11.	**Functional precision medicine by image based drug screening in human tissues**	Prof. Berend Snijder, ETH Zürich

>>> Im Fokus: Digitale Pathologie/ Pathojet/Corona

Wir digitalisieren das Institut für Pathologie!

Aber was bedeutet das für uns?
Wie sehen unserer diagnostischen Dienste, unsere Lehre und Forschung in der Zukunft aus?

Die Digitalisierung bringt Veränderungen mit sich, und Veränderungen erfordern neue Technologien, Ressourcen, Zeit und Energie sowie den unbedingten Willen, sich an eine neue Zukunft anzupassen. Dieser Prozess begann für uns vor einigen Jahren, als unsere ersten diagnostischen Objektträger digitalisiert, an Tumorboards und klinisch-pathologischen Konferenzen besprochen wurden. Im nächsten Schritt haben wir unsere intraoperativen Gefrierschnitte digitalisiert. So konnten die Pathologen ebenfalls in der Nacht Gewebe analysieren auch wenn sie nicht im Institut waren. Die Ausbildung von Assistenzärzten konnte durch die Digitalisierung der Objektträger vereinfacht werden, dies durch die gemeinsame Nutzung sowie die uneingeschränkte Verfügbarkeit. Während des Covid-19-Lockdowns ermöglichte uns die Digitalisierung, kritische Diagnosen von zu Hause aus zu erstellen. All dies veranlasste uns eine gross angelegte Umstellung für eine digitale Pathologie vorzubereiten.

Pathojet.

Dieser Veränderungsprozess ist ein kontinuierlicher und abteilungsübergreifender Prozess, der nur dank unseren Pathologen, IT-Experten, technischen Mitarbeitern und unseren externen Partner überhaupt möglich ist.

In den letzten zwei Jahren haben wir ein Konzept entwickelt, das uns in der Zukunft unterstützen wird. Aus technologischer Sicht haben wir unsere Scanning-Plattform erweitert, unsere IT-Infrastruktur erneuert und ein Bildmanagementsystem entwickelt, das unsere spezifischen Anforderungen an den diagnostischen Workflow erfüllt.
Aus klinischer Sicht haben wir unsere digitalen Diagnosen validiert und begonnen, die Integration von Bildanalyse- und Deep-Learning-Algorithmen zu erforschen, die uns bei der täglichen Arbeit unterstützen werden. Wir haben auch den ersten «PathoJet» entwickelt und patentiert, ein personalisiertes Cockpit für Pathologen, in dem digitale Diagnosen in einer völlig immersiven und ergonomischen Umgebung durchgeführt werden können.

Digitale Pathologie und künstliche Intelligenz sind für die personalisierte Medizin von grossem Nutzen. Auf digitalen Objektträgern lässt sich mit Hilfe der Bildanalyse die Expression von Biomarkern bestimmen, wodurch die Quantifizierung klinisch relevanter Merkmale wie Ki-67 bei Brustkrebspatientinnen objektiver, reproduzierbarer und besser dokumentiert wird. Wir haben die Ki-67-Expressionen mit verschiedenen Bildanalysealgorithmen eingehend untersucht und verfügen nun über ein integriertes Tool, das sofort eingesetzt werden kann. Durch Kooperationen mit der Industrie planen wir, unser Portfolio an Algorithmen im 2022 zu erweitern.

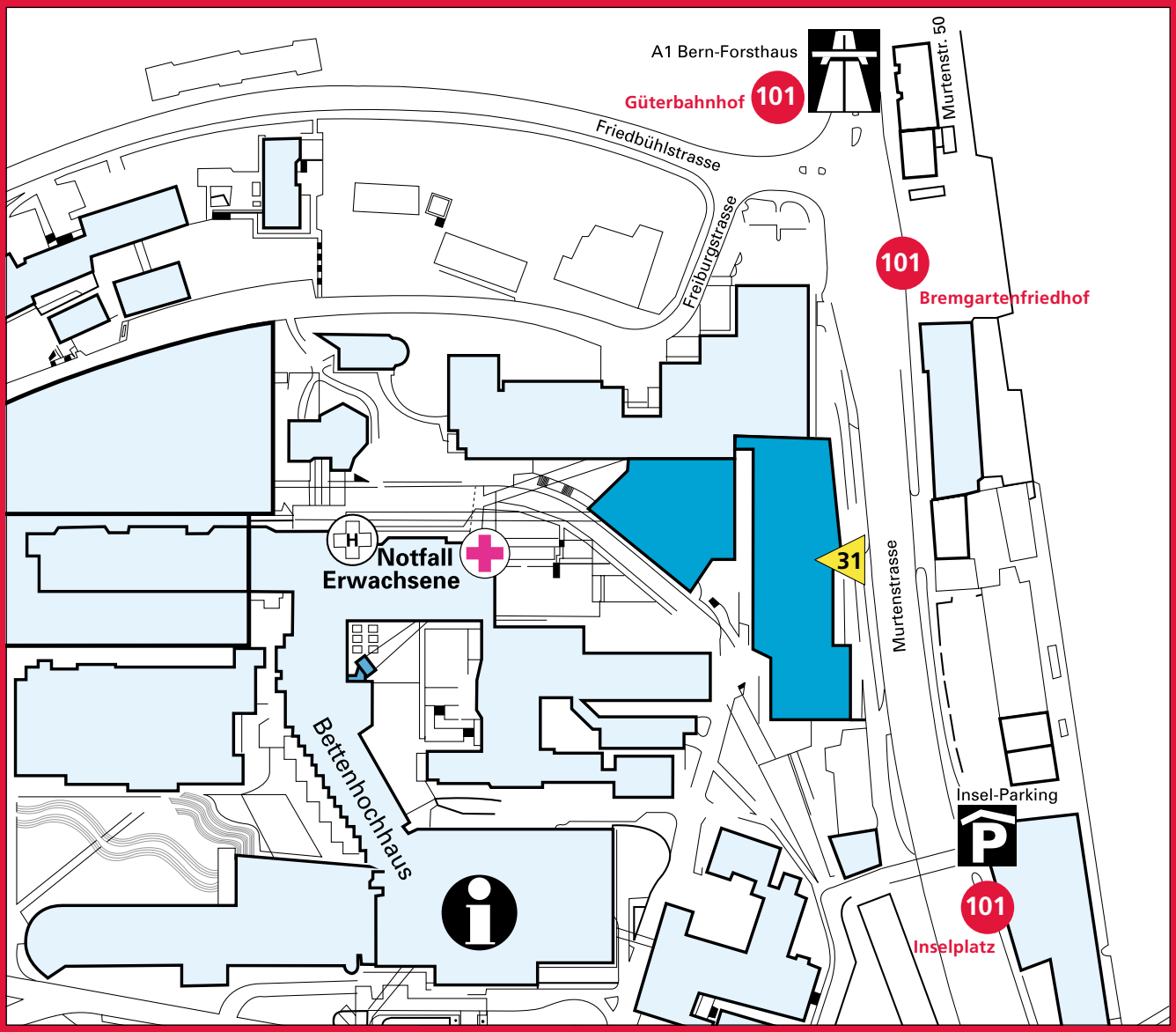
Künstliche Intelligenz kann zur Identifizierung von Charakteristiken auf digitalen Objektträgern und zur Durchführung verschiedener Bildanalyseaufgaben wie Segmentierung, Quantifizierung oder Klassifizierung von histopatholgischen Strukturen eingesetzt werden. Sie hat sich als vielversprechend erwiesen bei der Erkennung von Krebs, des Tumorgradings, der Identifizierung der ihnen zugrundeliegenden genomischen Veränderungen (MSI bei Darmkrebs), der Einteilung der Tumoren in molekulare Subtypen (z.B. CMS-Klassen) und der Vorhersage des Ansprechens auf eine zielgerichtete Therapie bei Brustkrebs unter Verwendung der digitalen H&E-Standardfärbung. Wir planen, diese Möglichkeiten weiter zu erforschen und die besten KI-Lösungen zur Ergänzung der pathologischen Diagnose zu integrieren.

Im Forschungsbereich nutzt die digitale Pathologie die Vorteile der Bioinformatik und der künstlichen Intelligenz, um neue Phänotypen zu entdecken und tiefere Einblicke in biologische Prozesse und Krankheiten zu gewinnen. Die Projekte des Instituts konzentrieren sich auf die morphomolekulare Analyse von Histopathologie-Bildern in Kombination mit Daten über die Häufigkeit, Dichte und räumlichen Muster von Zellen, um deren Interaktionen zu verstehen und sogar neue Hypothesen für weitere Experimente und Validierungen zu entwickeln. Mit dem Entstehen neuer Technologien für die hochdimensionale Proteinexpressionsanalyse gewinnt unsere Next-Generation Tissue Microarray (ngTMA®)-Plattform noch mehr an Bedeutung, da sie digitale Annotationen nutzt, um spezifische Gewebebereiche für nachgeschaltete Analysen auszuwählen.

Die Digitalisierung ist die Zukunft der Pathologie und die Zukunft ist jetzt. Mit unseren digitalen Lösungen für Diagnostik, Forschung und Lehre trägt das Institut für Pathologie dazu bei, die Pathologielandschaft in der Schweiz neu zu gestalten.

Mehr Infos unter: uniaktuell.unibe.ch (Stichwort Pathojet).

>>> Situationsplan



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